What are the Novel Approaches in the Treatment of Waldenstrom's Macroglobulinemia?

VE RI TAS

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Disclosures

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Abbvie/Pharmacyclics
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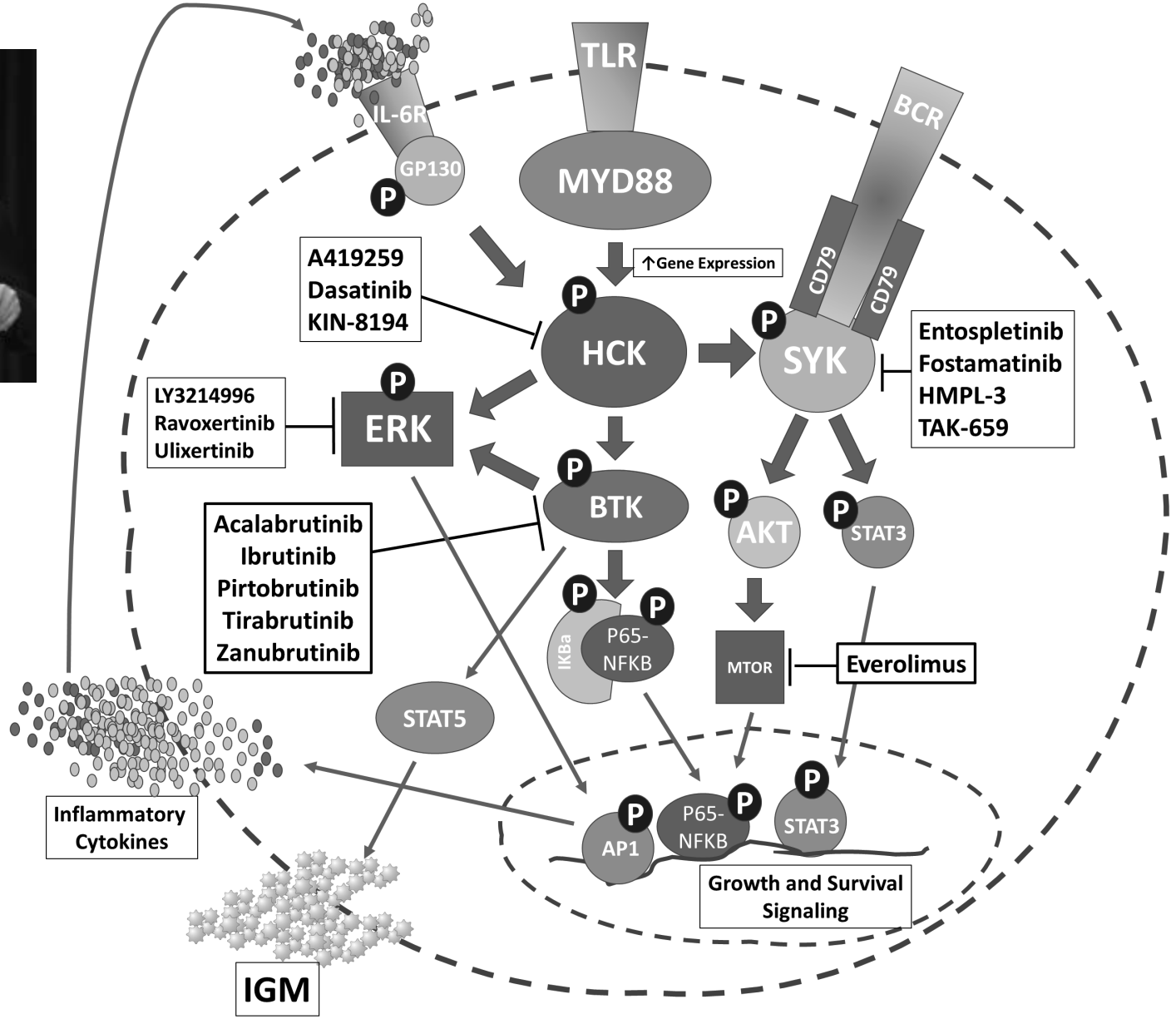
BMS
Eli Lilly
Janssen Pharmaceuticals
X4 Pharmaceuticals

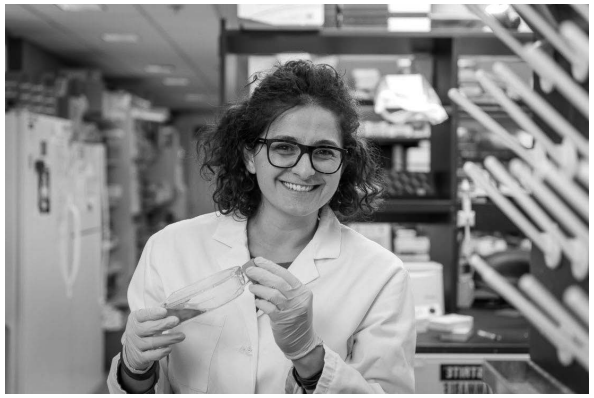
IP assigned to DFCI for MYD88, CXCR4, and IRAK and HCK and other inhibitors.

MYD88 directed pro-survival signaling in WM

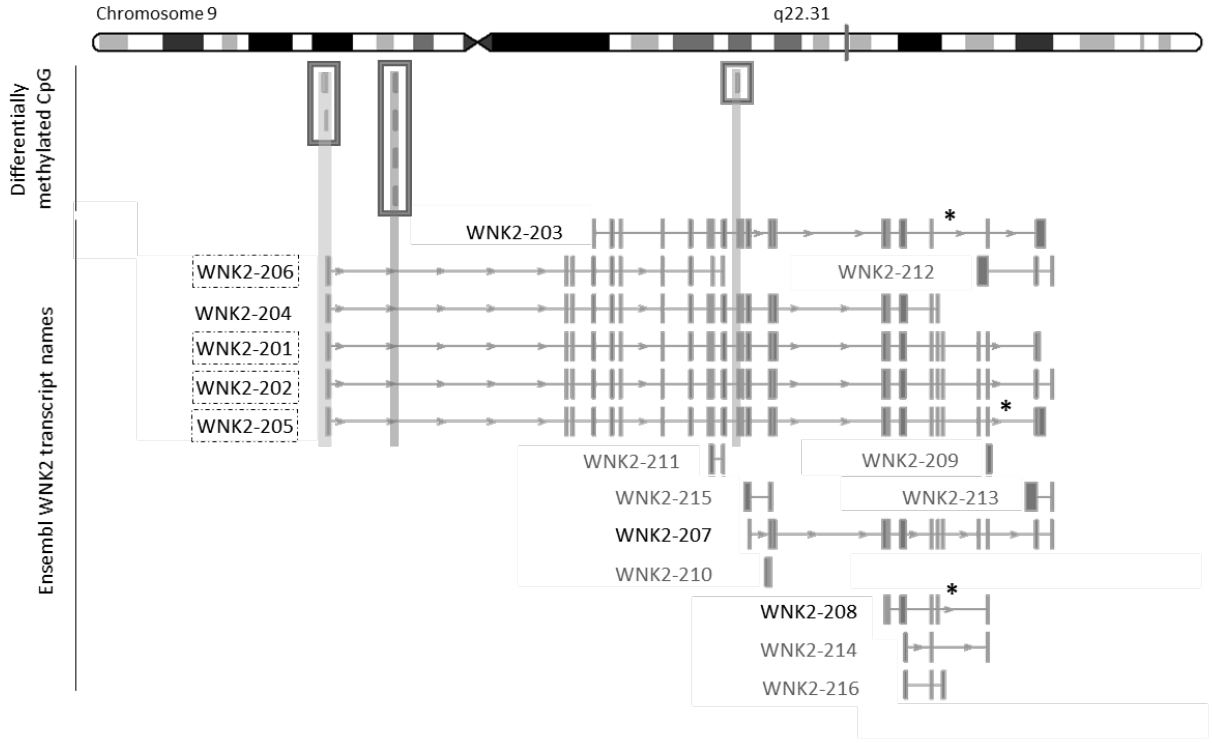


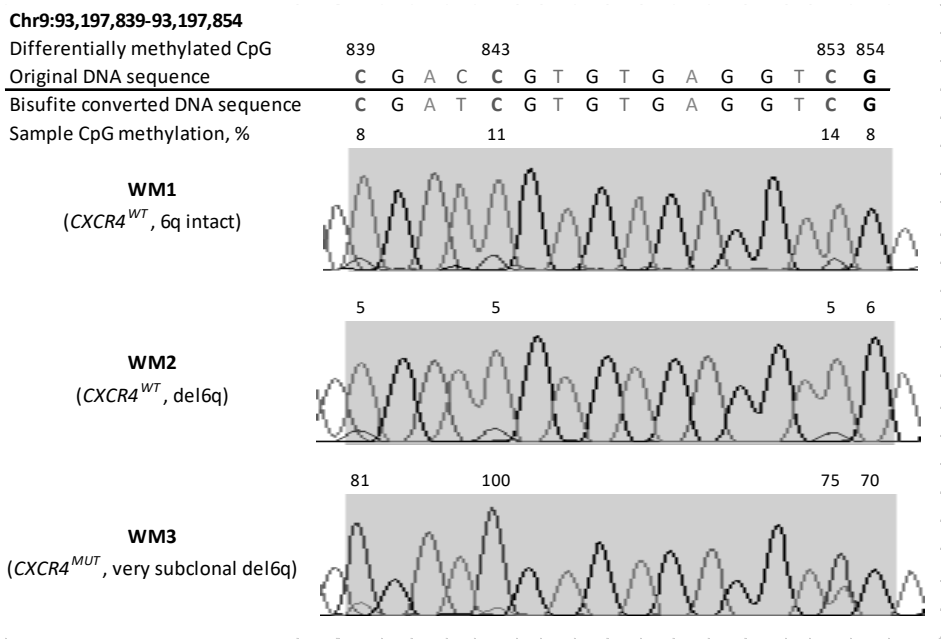
MYD88 mutations occur in 95-97% WM Patients

Treon et al, NEJM 2012
Yang et al, Blood 2013
Hodge et al, Blood 2014
Yang et al, Blood 2016
Chen et al, Blood 2018
Liu et al, Blood Adv 2020
Munshi et al, BCJ 2020
Munshi et al, Submitted.



The ERK1/2 kinase activity regulator WNK2 is suppressed due to aberrant methylation: MYD88^{Mut} CXCR4^{Mut}, MYD88^{Mut6qdel}, MYD88^{WT}

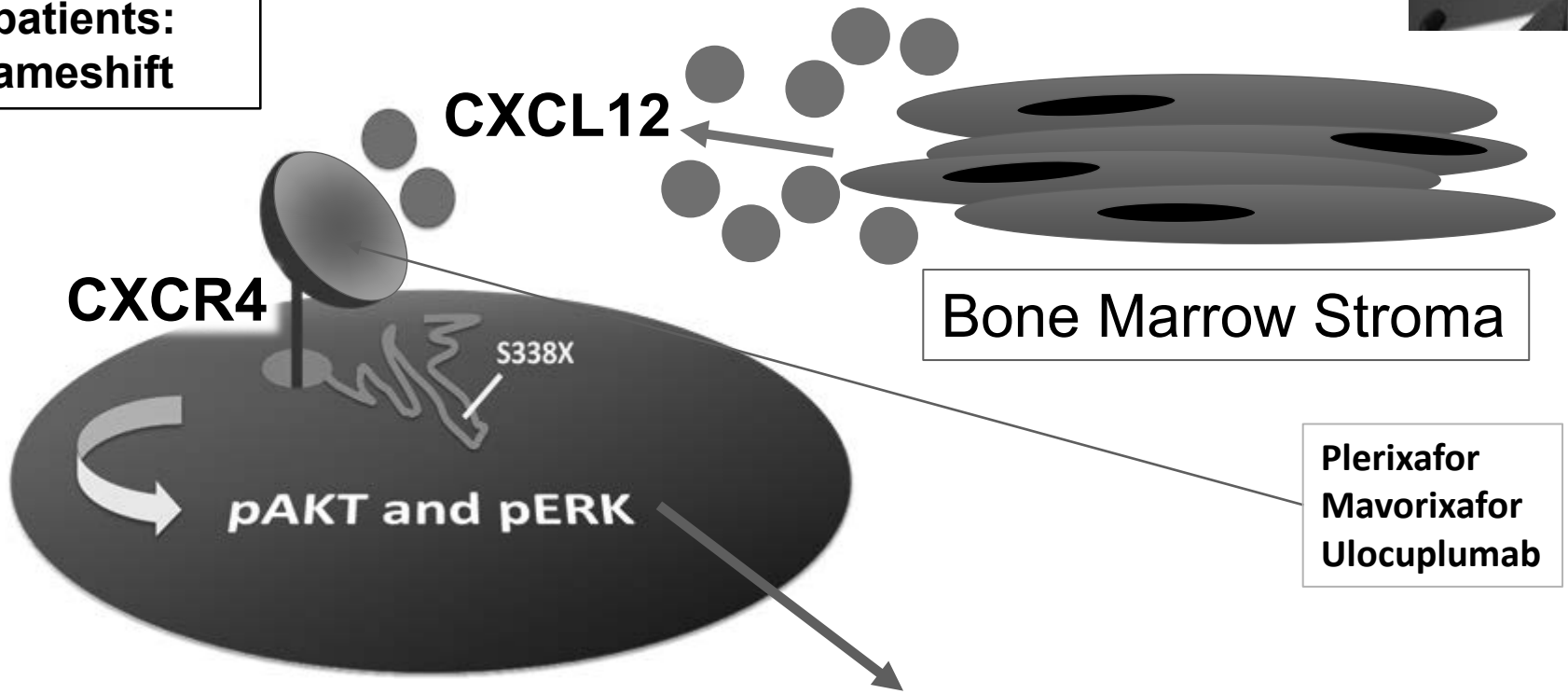




Guerrera ML et al, submitted.

Mutated CXCR4 permits ongoing pro-survival signaling by CXCL12

CXCR4 mutations occur in 30-40% of WM patients: Nonsense and Frameshift



Hunter et al, Blood 2013; Cao et al, Leukemia 2014; Rocarro et al, Blood 2014; Cao et al, Br J Haematol. 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**

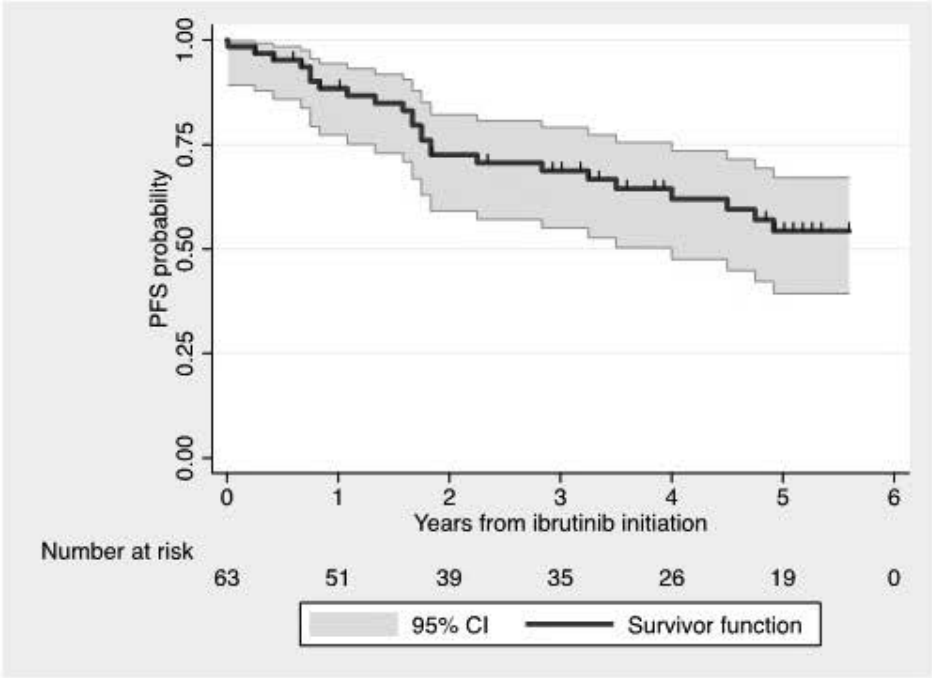
***One patient had MYD88 mutation, but no CXCR4 determination and had SD.**

Treon et al, NEJM 2015; Updated JCO 2021

Ibrutinib in Previously Treated WM: Updated PFS

All patients

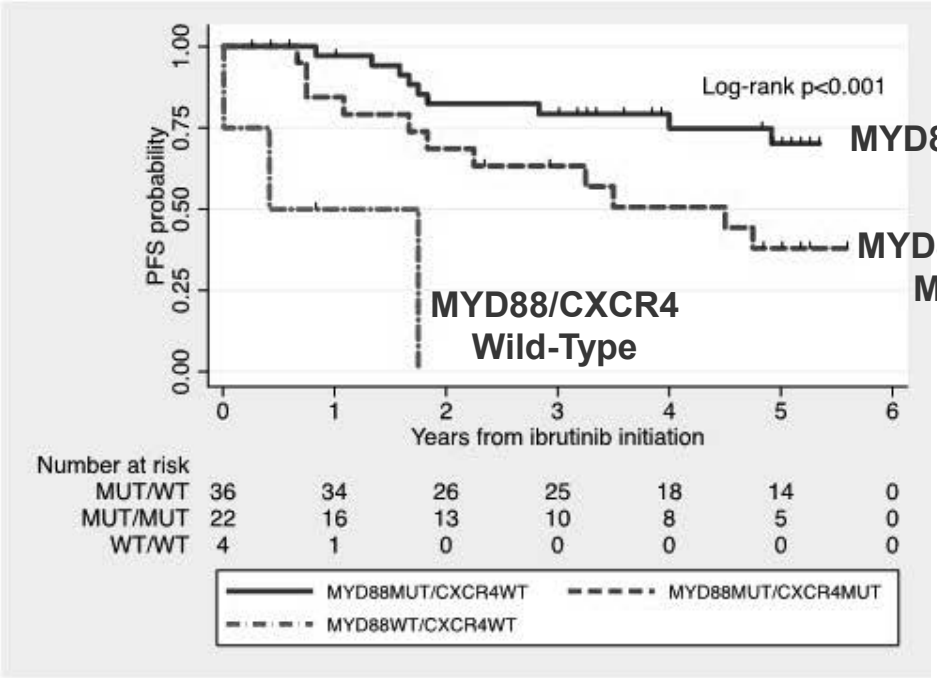
A.



5 year PFS: 54%
5 year OS: 87%

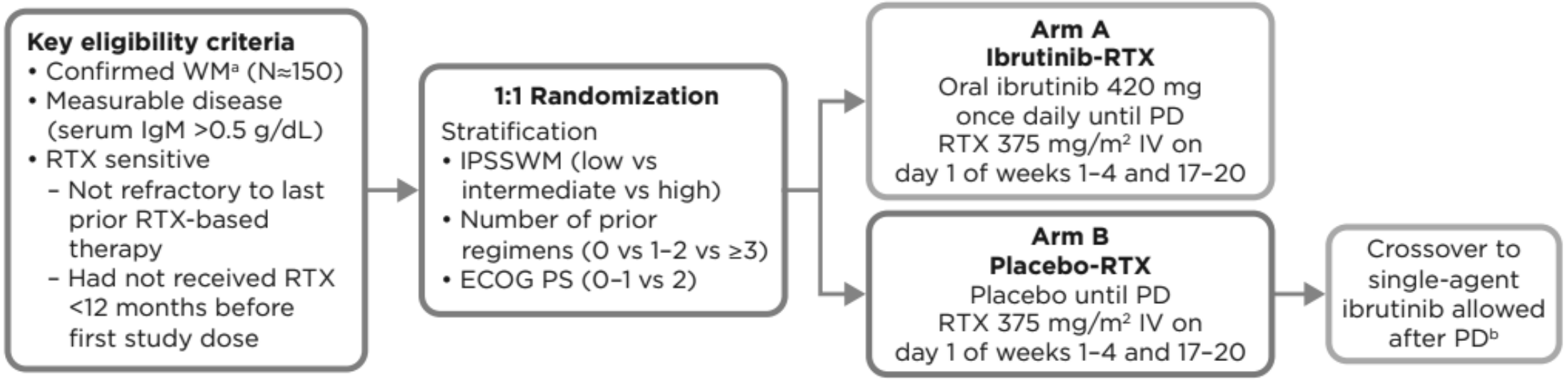
By MYD88 and CXCR4 Mutation Status

B.



Treon et al, NEJM 2015; Updated JCO 2021

iNNOVATE (PCYC-1127; NCT 02165397) Study Design



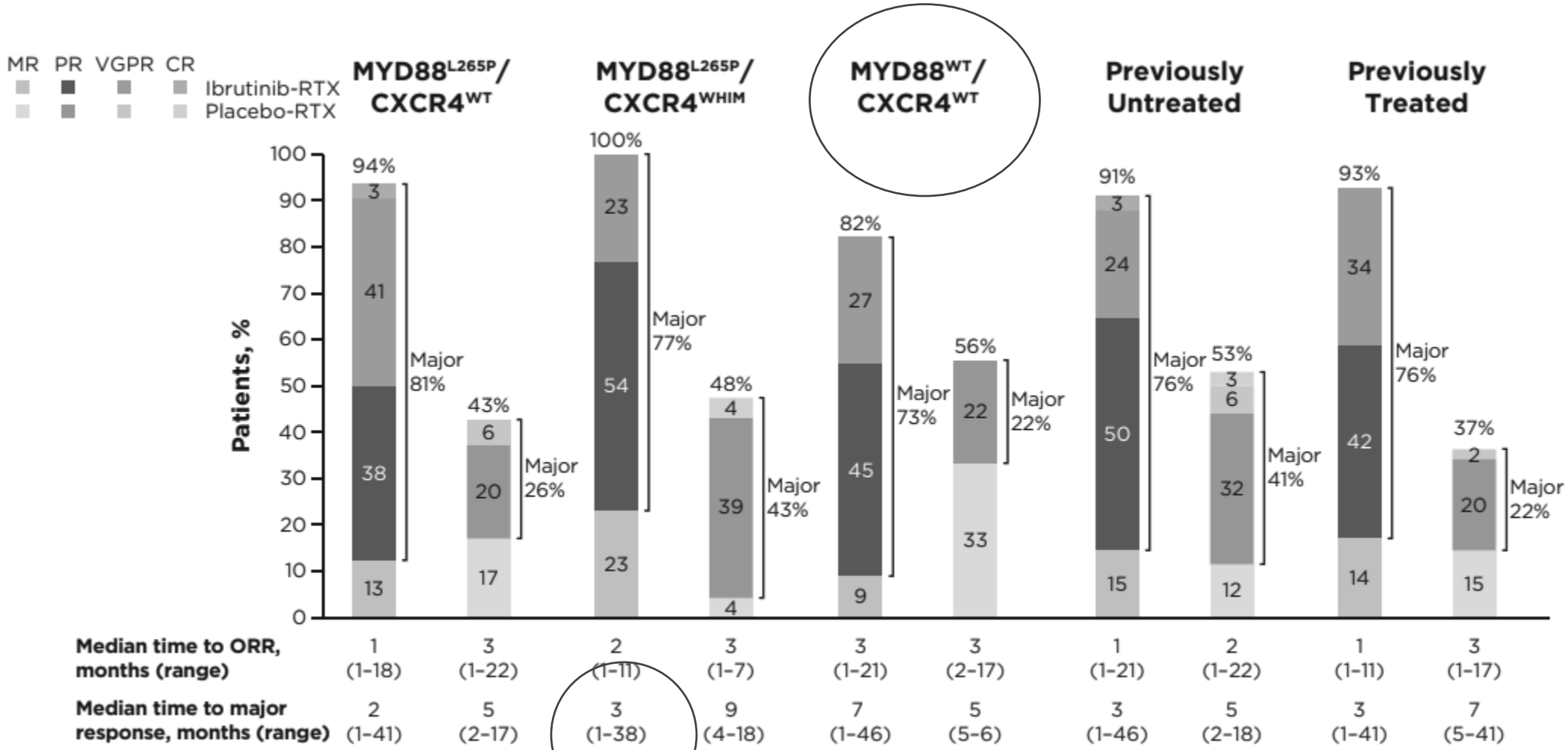
ECOG PS, Eastern Cooperative Oncology Group performance status; IPSSWM, International Prognostic Scoring System for Waldenström's Macroglobulinemia; IRC, independent review committee; IV, intravenous; PD, progressive disease.

[a]Previously untreated patients were allowed to enroll following a protocol amendment (November 2015); therefore, their enrollment started later than patients who had relapsed.
[b]Patients in the placebo-RTX arm could receive next-line single-agent ibrutinib in crossover following IRC-confirmed PD.

- iNNOVATE (PCYC-1127) was a double-blind, randomized, placebo-controlled, multicenter, international phase 3 study c assess the efficacy and safety of ibrutinib-RTX versus placebo-RTX in patients with WM (**Figure 1**).
- The primary endpoint was PFS by IRC. Secondary endpoints included response rate by IRC, time to next treatment, hemoglobin (Hgb) improvement, overall survival (OS), and safety.
- After study closure, patients without PD could continue ibrutinib in an extension program.

Garcia Sanz et al, EHA Abstract EP782

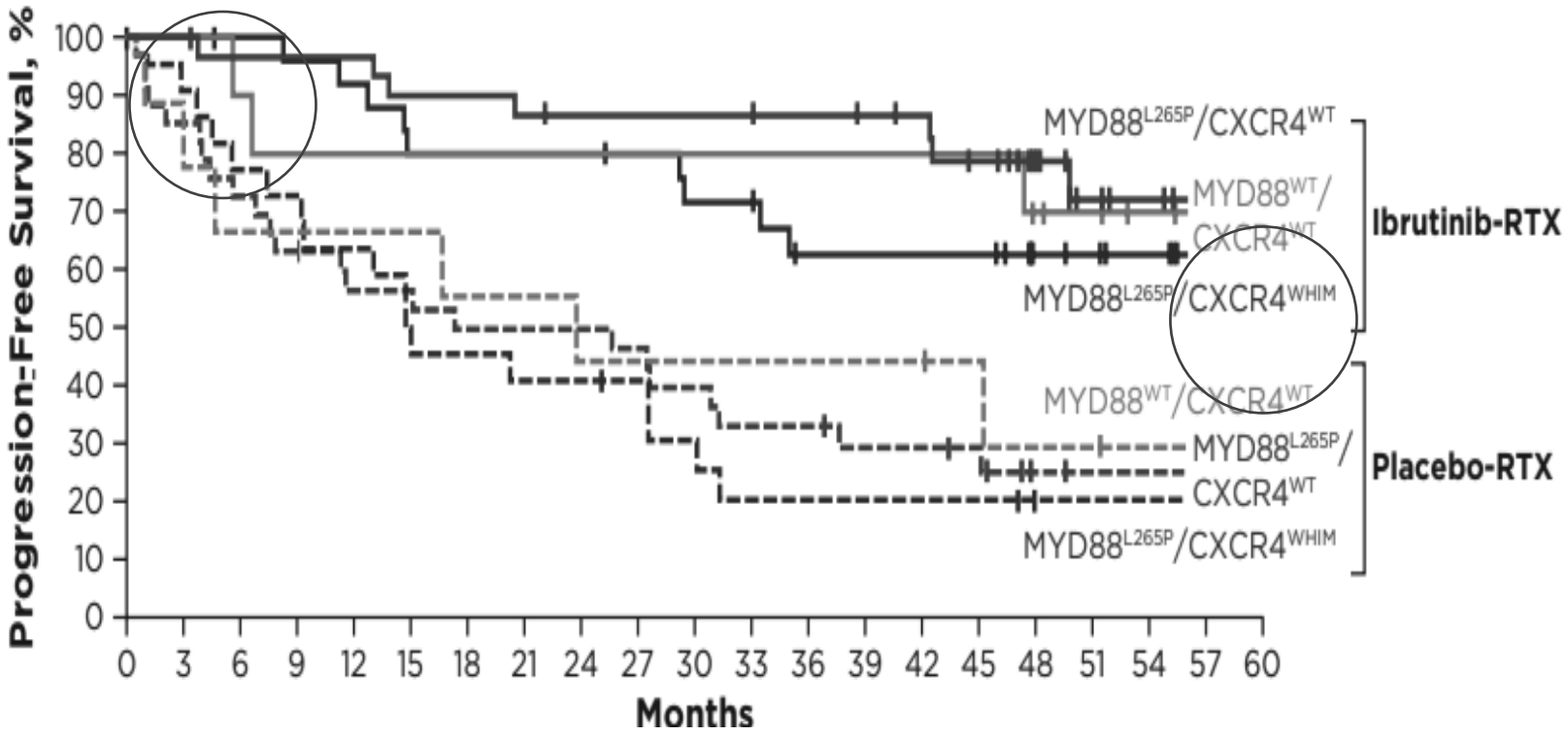
Response Rates by Genotype and Prior Treatment Status



- Higher response rates with ibrutinib-RTX were independent of genotype or prior treatment status

Garcia Sanz et al, EHA Abstract EP782

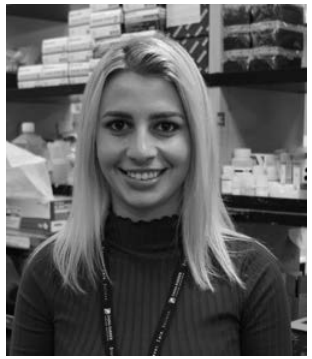
iNNOVATE: PFS by Genotype



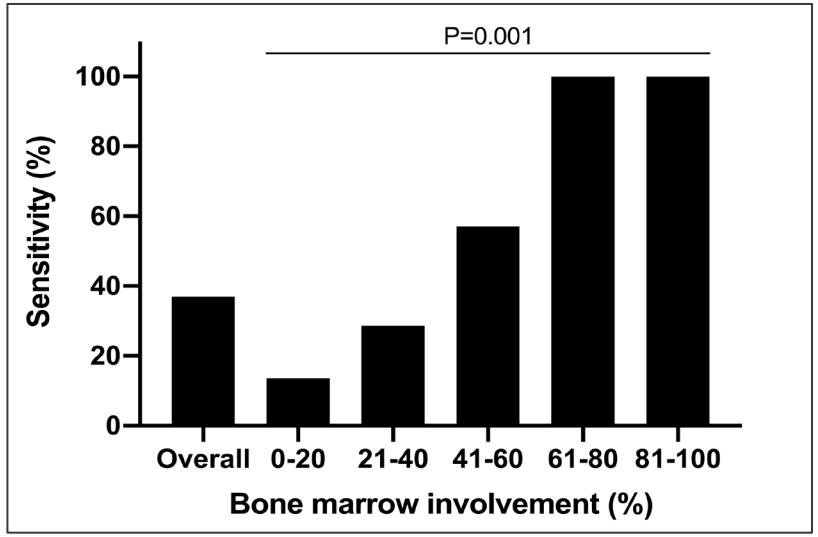
54-month PFS	Ibrutinib-RTX	Placebo-RTX
$MYD88^{Mut}/CXCR4^{WT}$	72%	25%
$MYD88^{Mut}/CXCR4^{Mut}$	63%	21%
$MYD88^{WT}/CXCR4^{WT}$	70%	30%

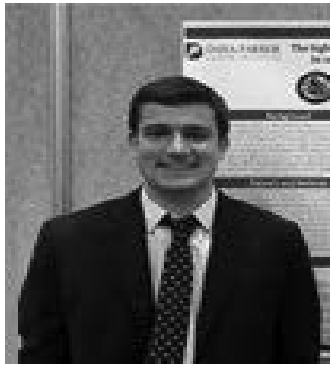
Garcia Sanz et al, EHA Abstract EP782

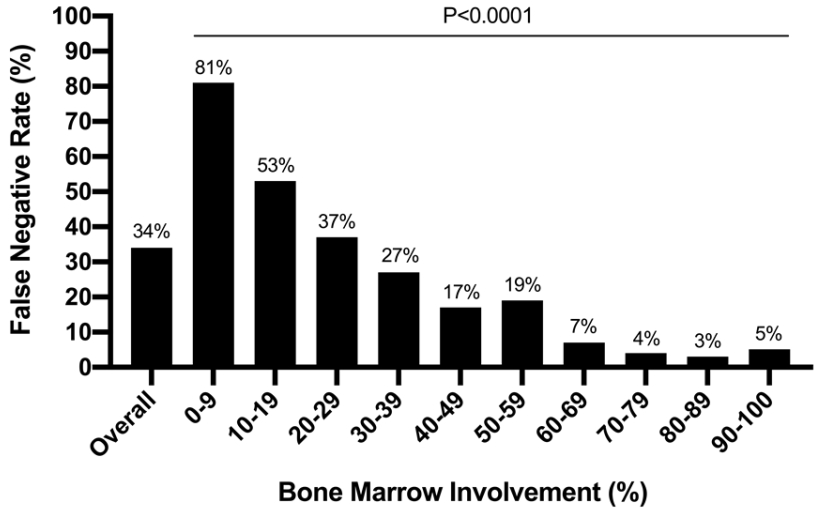
Challenges of MYD88 and CXCR4 detection in WM



	MYD88 L265P	
	AS-PCR	NGS
True Positive – no.	391	259
True Negative – no.	23	23
False Positive – no.	0	0
False Negative – no.	0	132
Concordance (κ) – %	Ref.	68 (0.19)
Sensitivity (95% CI) – %	Ref.	66 (61-71)
Specificity (95% CI) – %	Ref.	100 (83-100)
PPV (95% CI) – %	Ref.	100 (98-100)
NPV (95% CI) – %	Ref.	15 (10-22)



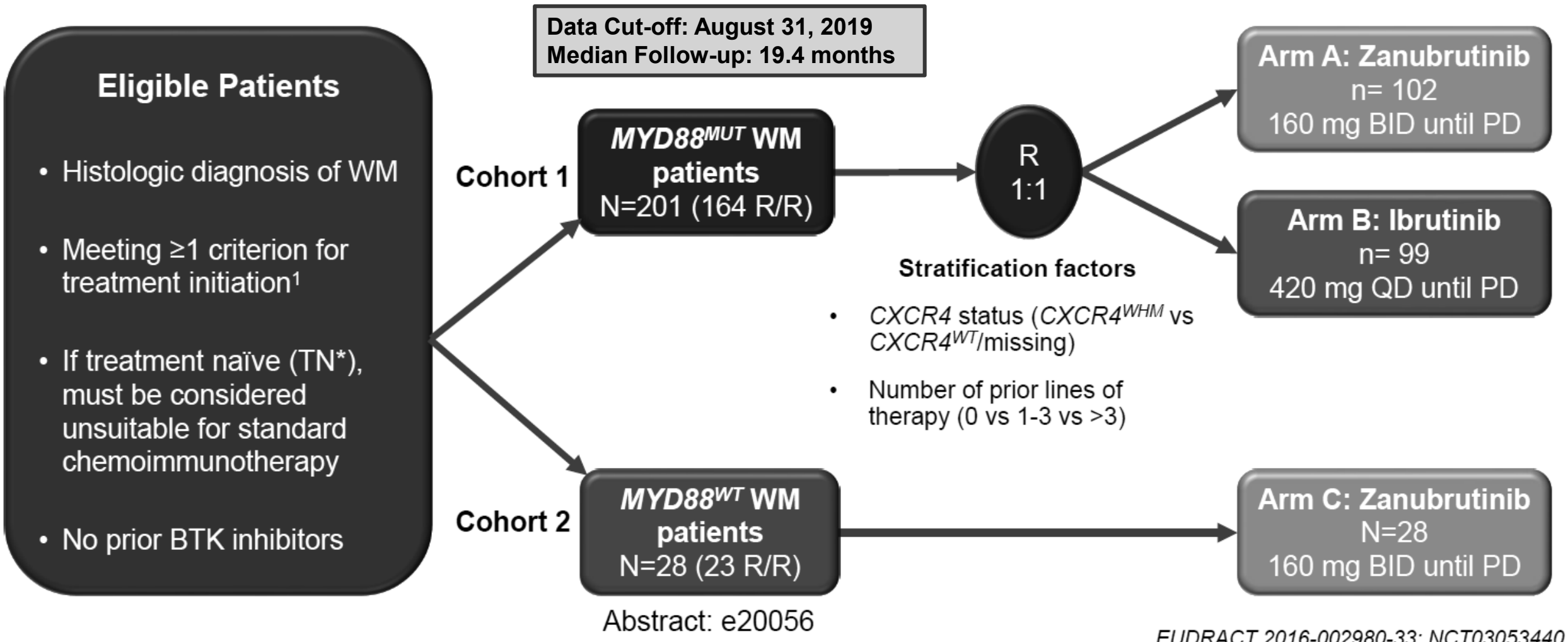




Sensitivity for mutated CXCR4 detection was 37% by NGS and unselected BM. Low BM involvement and clonality impacted detection.

Kofides et al, Hemasphere 2021; Gustine et al, BJH 2021.

ASPEN Study Design: Zanubrutinib vs Ibrutinib in *MYD88*^{MUT} WM



BID, twice daily; BTK, Bruton tyrosine kinase; 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.

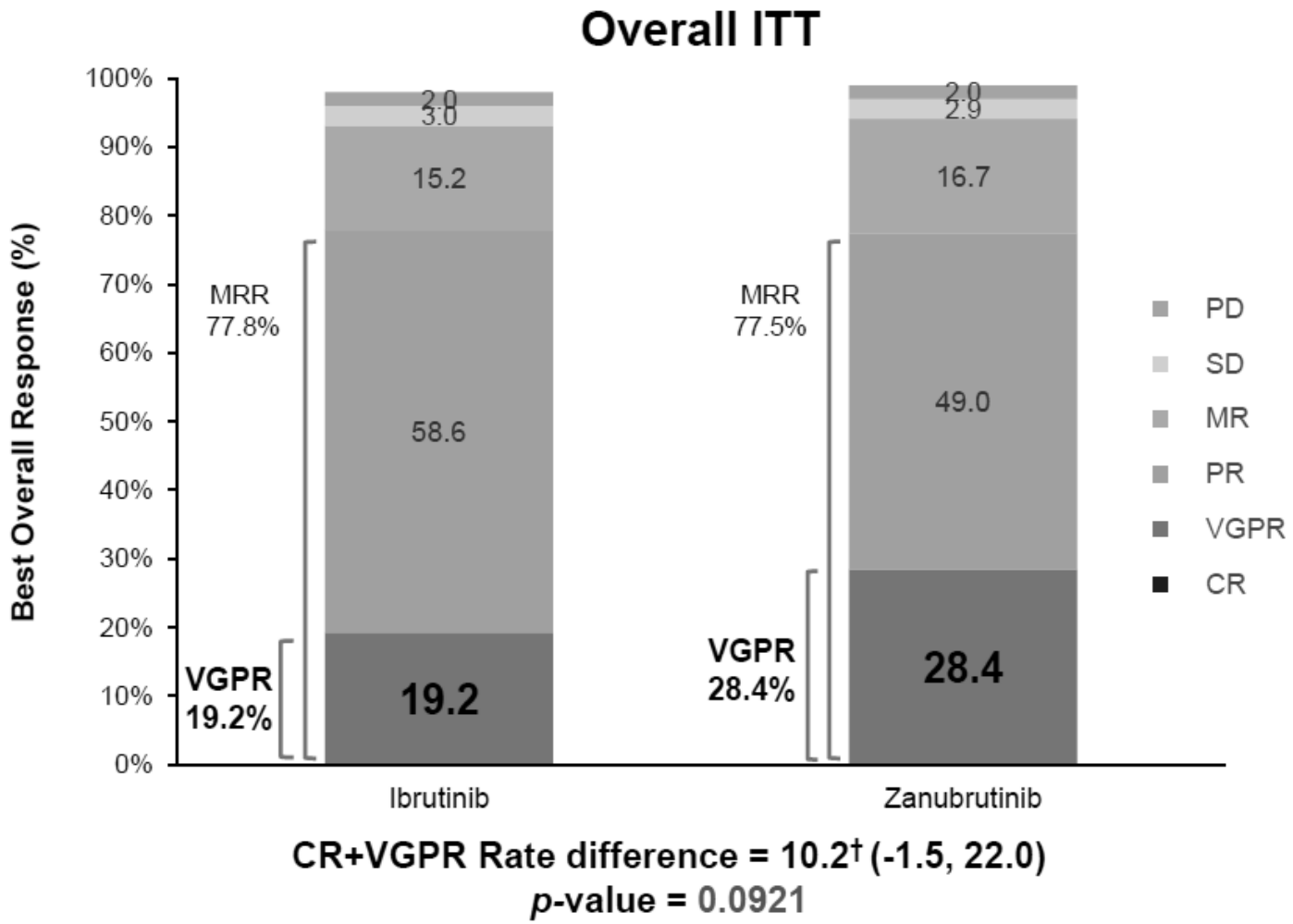
*Up to 20% of the overall population.

1. Dimopoulos MA, et al. *Blood*. 2014;124:1404-1411.

Tam et al, Blood 2020

ASPEN: Efficacy – Response by IRC (Data cutoff: 31 August 2019)

- Superiority in CR+VGPR rate compared to ibrutinib in relapsed/refractory population (primary study hypothesis) was not significant*



***CXCR4 mutated patients had lower VGPR responses in both arms in post-hoc analysis using NGS:**

	Mut	WT
Zanu	(18% v.	34%)
Ibru	(10% v.	24%)

CR, complete response; IRC, independent review committee; ITT, intention-to-treat; MRR, major response rate; MR, minor response; ; ORR, overall response rate; PD, progressive disease; PR, partial response; R/R, relapsed/refractory; SD, stable disease; VGPR, very good PR.
Overall concordance between Independent review and investigators = 94%
* All other *P* values are for descriptive purposes only. †Adjusted for stratification factors and age group.

Tam et al, Blood 2020

ASPEN: AE Categories of Interest (BTKi Class AEs)

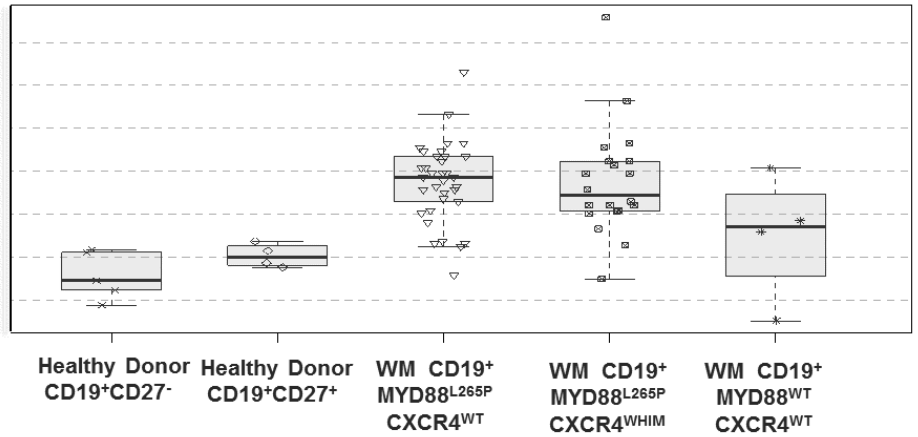
AE *Categories*, n (%) (pooled terms)	All Grades		Grade ≥ 3	
	Ibrutinib (n = 98)	Zanubrutinib (n = 101)	Ibrutinib (n = 98)	Zanubrutinib (n = 101)
Atrial fibrillation/ flutter†	**15 (15.3)**	2 (2.0)	4 (4.1)	0 (0.0)
Diarrhea (PT)	**31 (31.6)**	21 (20.8)	1 (1.0)	3 (3.0)
Hemorrhage	**58 (59.2)**	49 (48.5)	8 (8.2)	6 (5.9)
Major hemorrhage[a]	9 (9.2)	6 (5.9)	8 (8.2)	6 (5.9)
Hypertension	17 (17.3)	11 (10.9)	**12 (12.2)**	6 (5.9)
Neutropenia[b]†	13 (13.3)	**30 (29.7)**	8 (8.2)	**20 (19.8)**
Infection	66 (67.3)	67 (66.3)	19 (19.4)	18 (17.8)
Second Malignancy	11 (11.2)	12 (11.9)	1 (1.0)	2 (2.0)

Higher AE rate in bold blue with ≥ 10% difference in any grade or ≥ 5% difference in grade 3 or above.
No tumor lysis syndrome was reported. Opportunistic infection ibrutinib (n=2), zanubrutinib (n=1).
AE, adverse event; BTKi, Bruton tyrosine kinase inhibitor; PT, preferred term.
[a]Defined as any grade ≥ 3 hemorrhage or any grade central nervous system hemorrhage.
[b]Including PT terms of neutropenia, neutrophil count decreased, febrile neutropenia, agranulocytosis, neutropenic infection and neutropenic sepsis.
† Descriptive two-sided *P*-value < 0.05.

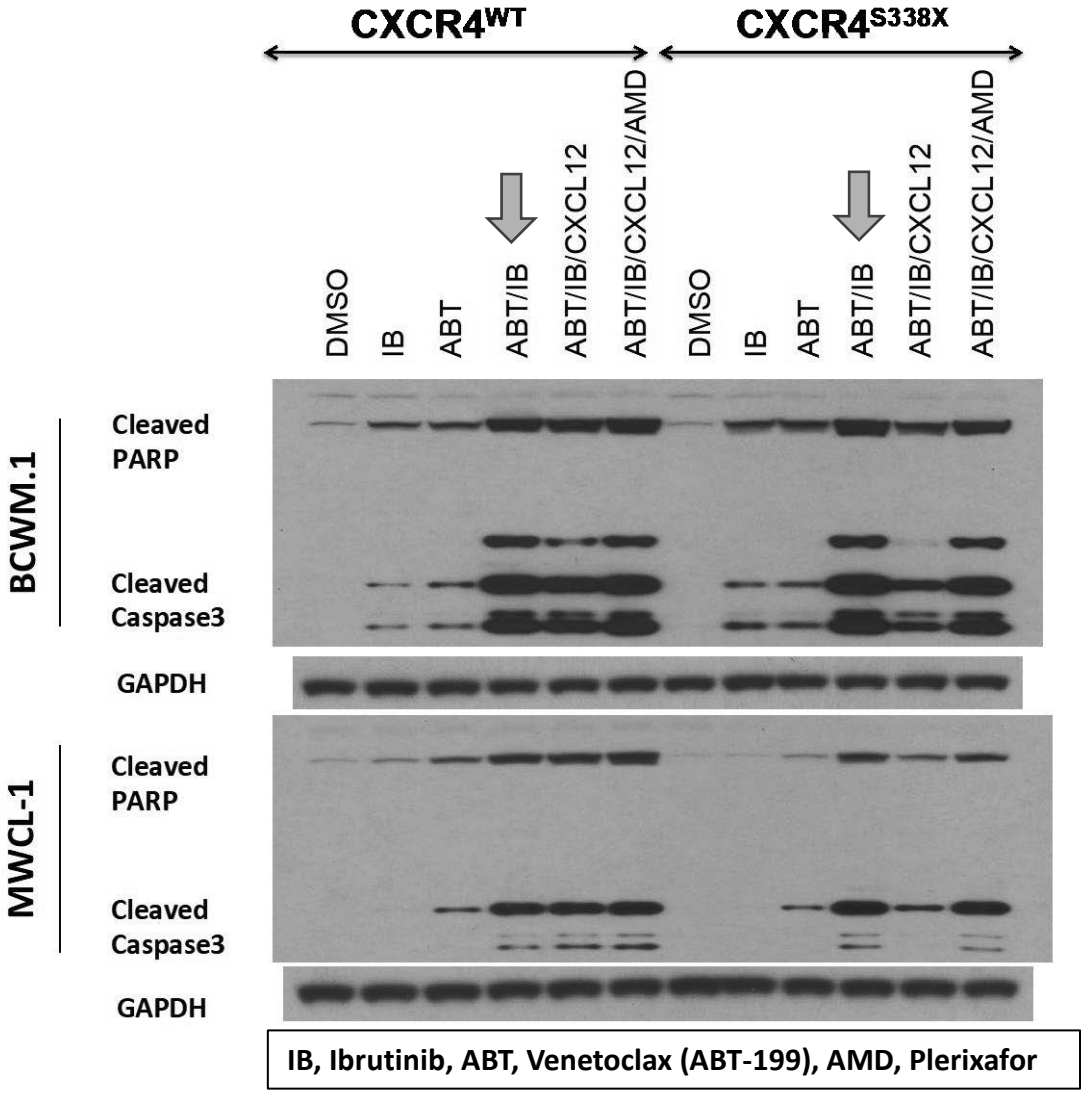
Tam et al, Blood 2020

Targeting BCL2 in Waldenstrom's Macroglobulinemia with Venetoclax

Higher BCL2 levels in MYD88 mutated WM

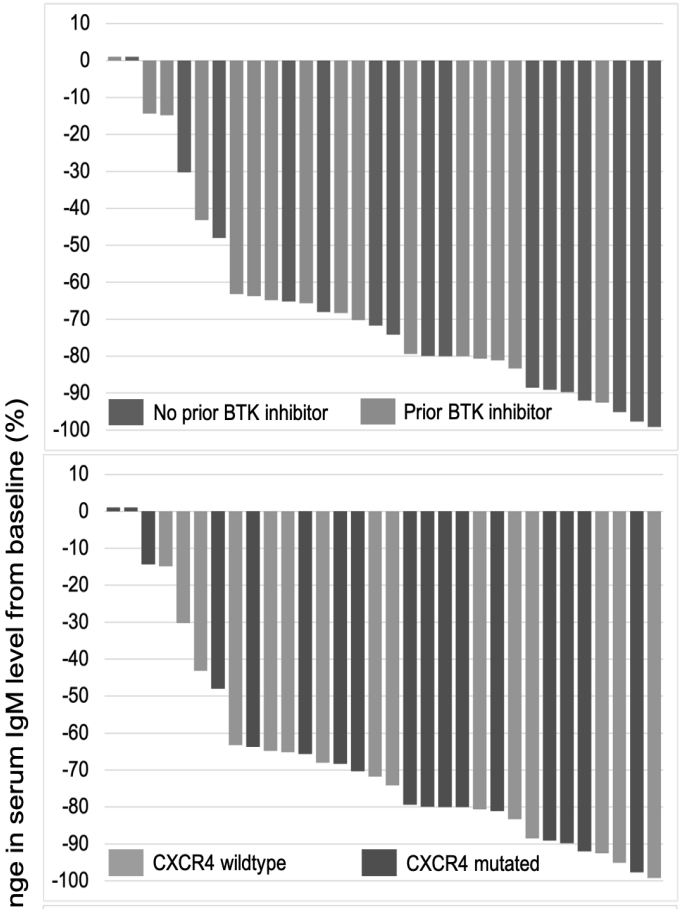


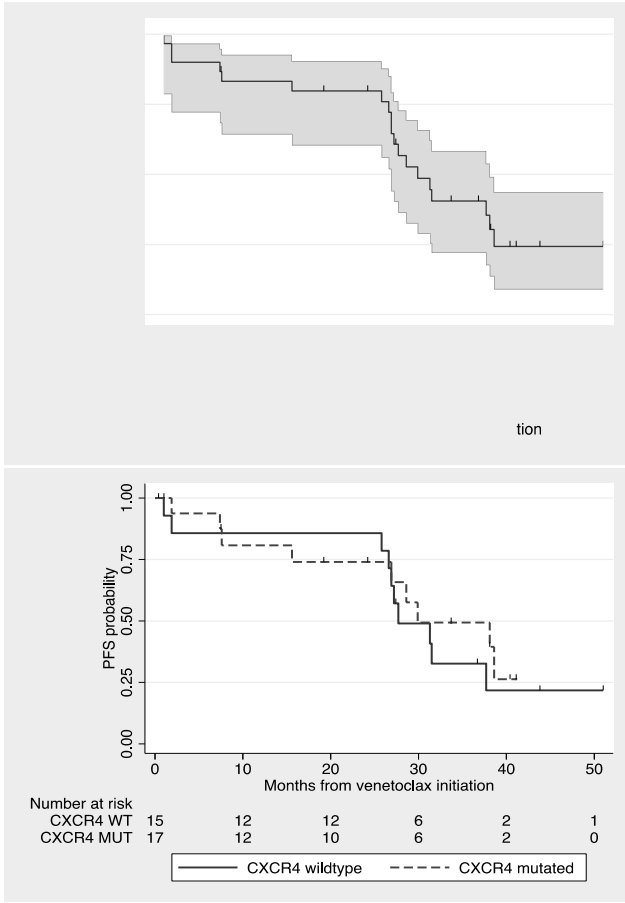
Cao et al, BJH 2015; 168(5): 701–7.



IB, Ibrutinib, ABT, Venetoclax (ABT-199), AMD, Plerixafor

Phase II Study of Venetoclax in Previously Treated WM





ORR: 84%; Major RR: 81%

Median PFS: 30 months

Clinical trials.gov: NCT02677324

Castillo et al, 17th IMW 2019; Manuscript submitted.

Ibrutinib/Venetoclax in Treatment Naïve WM

24 months

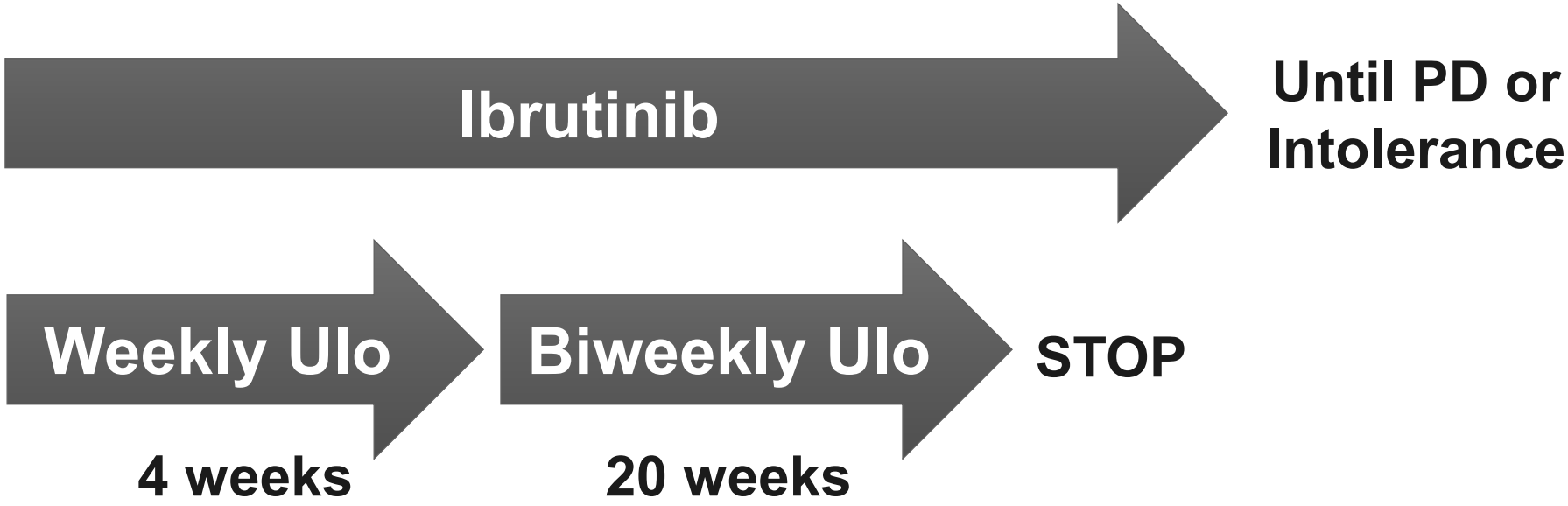
Ibrutinib 420 mg/day x 4 weeks	Ibrutinib 420 mg/day Add Venetoclax 100 mg/day week 5 200 mg/day week 6 400 mg/day weeks 7,8	Ibrutinib 420 mg/day And Venetoclax 400 mg/day	Observation
4 weeks	**4 weeks**	**22 months**	**Follow to PD or off study**

Jorge Castillo, PI (DFCI)

CLINICALTRIALS.GOV: NCT04273139

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

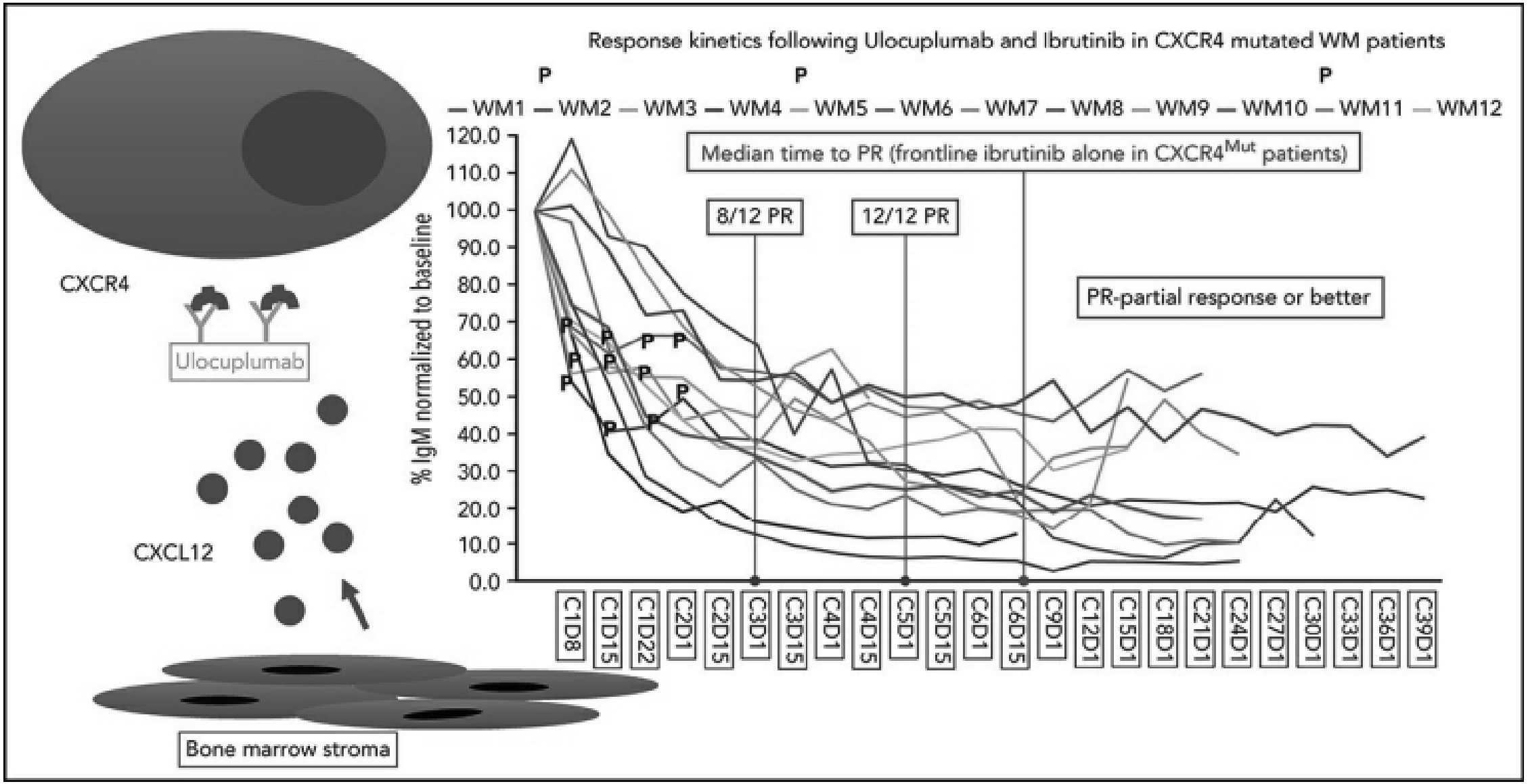
Schema



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

Treon et al, Blood 2021.

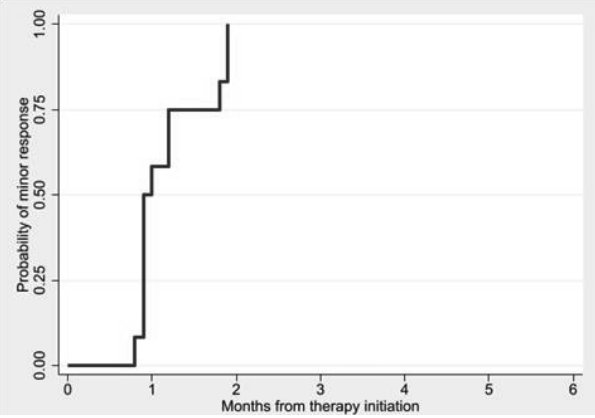
ClinicalTrials.gov Identifier: NCT03225716



Treon et al, Blood 2021

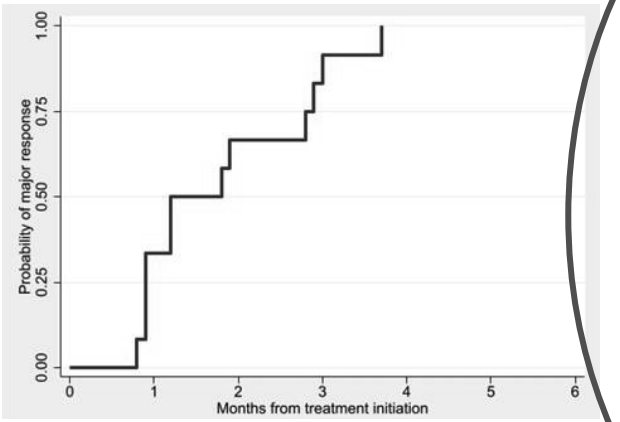
Response and PFS Data/Ibrutinib plus Ulo

Median Time to Minor Response



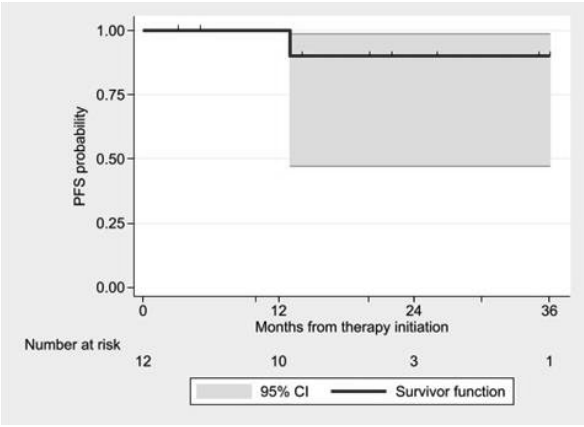
0.9 (95% CI 0.9-1.8) months

Median Time to Minor Response



1.2 (95% CI 0.9-2.8) months

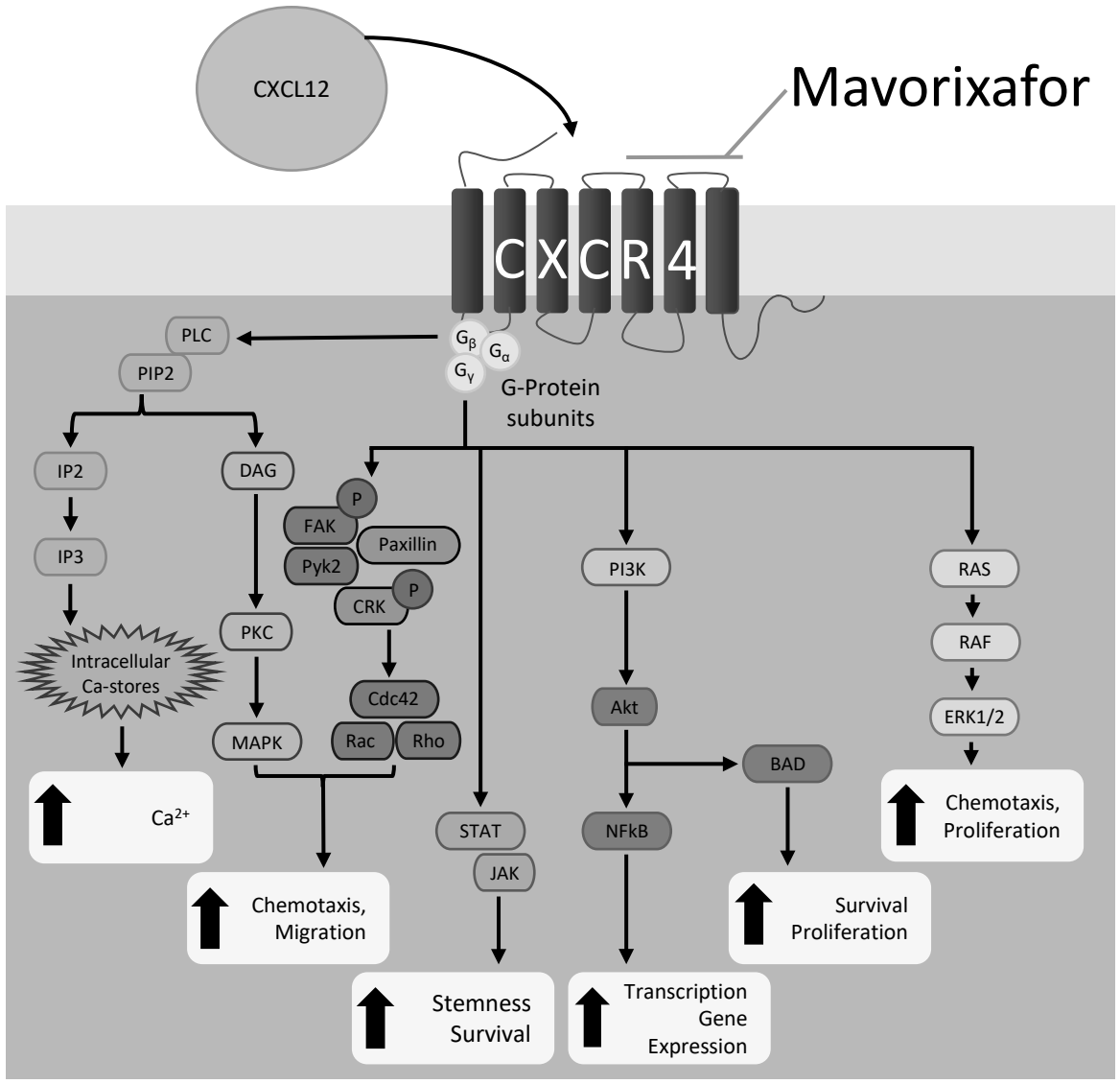
Median Time to PFS

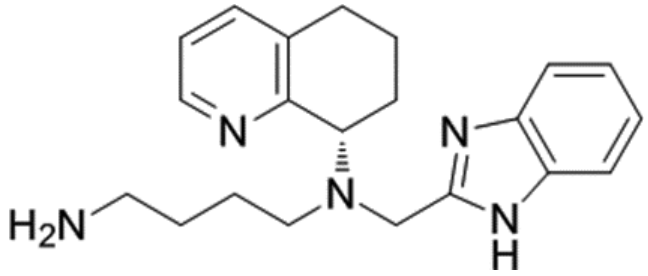


2-year 90% estimated

Treon et al, Blood 2021

Mavorixafor in combination with ibrutinib in CXCR4 mutated WM

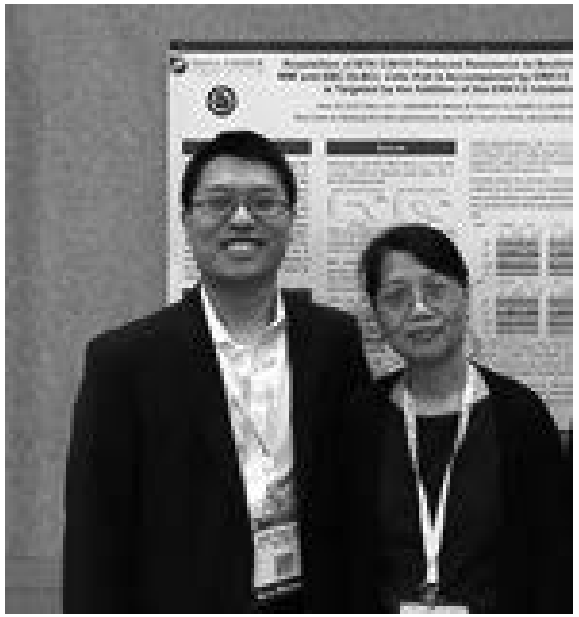


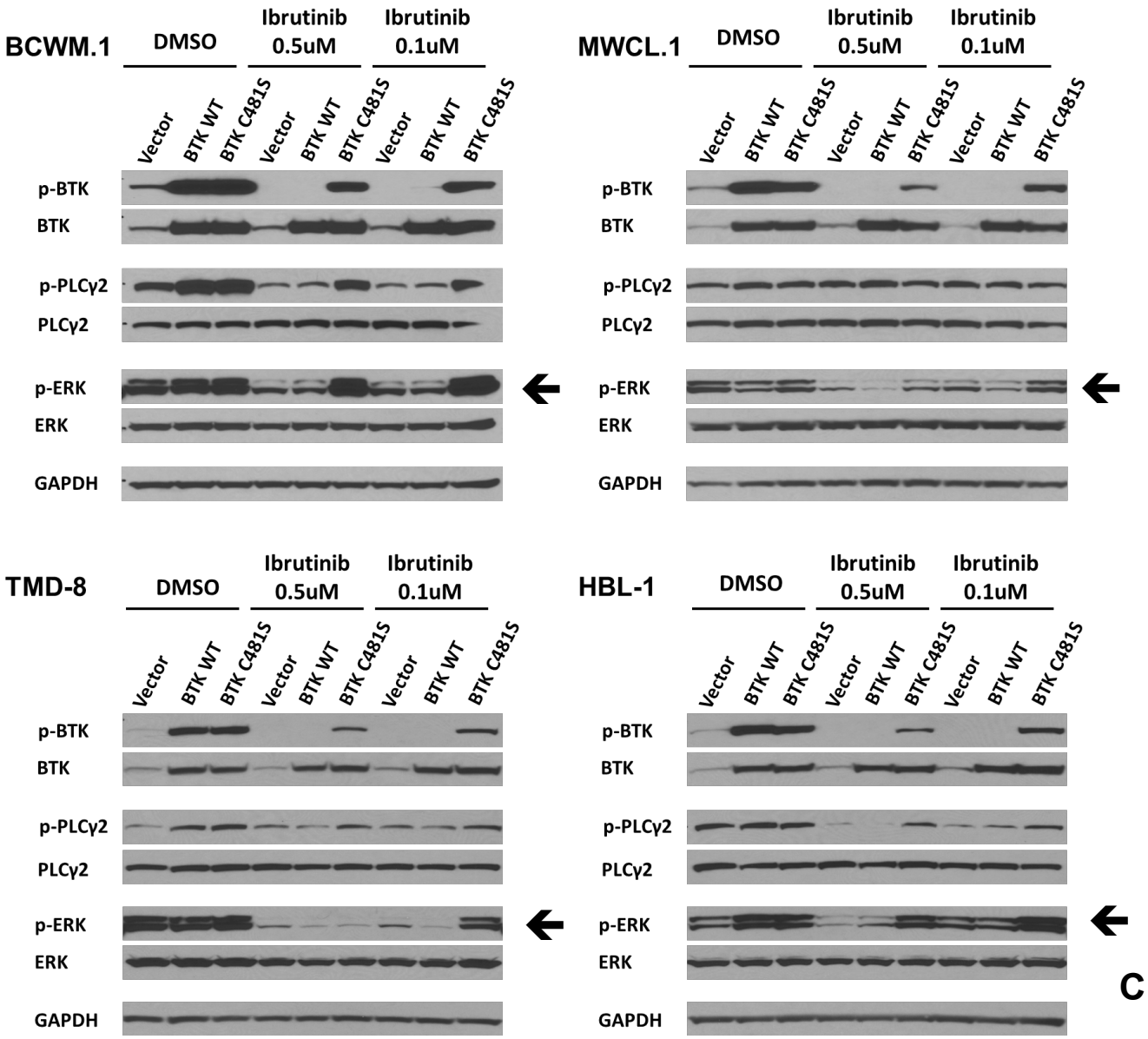


- Non-competitive, allosteric, small molecule antagonist of CXCR4
- Orally Bioavailable; mean $t_{1/2}$ of ~23 hours
- High volume of distribution

ClinicalTrials.gov:NCT04274738

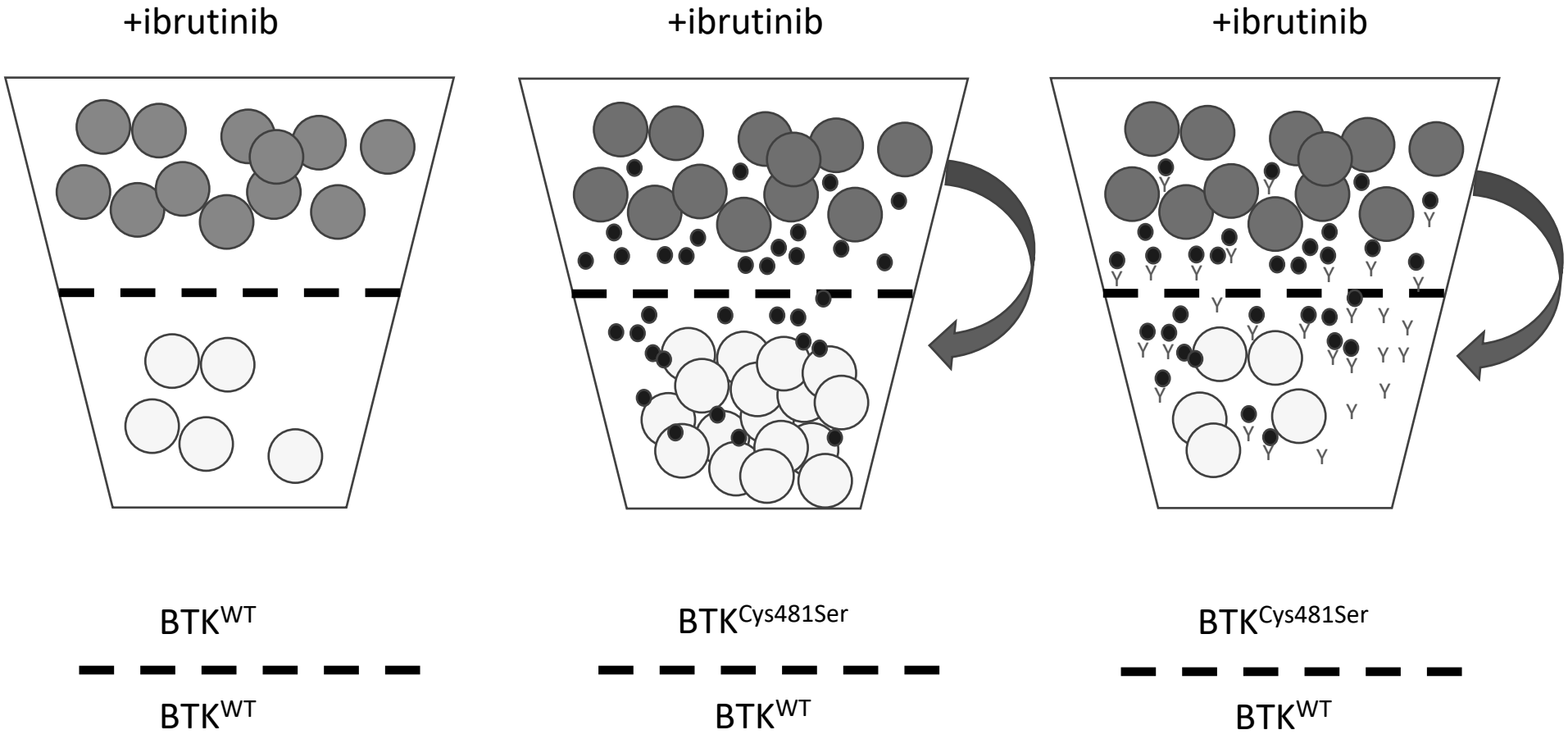
$BTK^{Cys481Ser}$ expressing cells displayed persistent activation of BTK and ERK1/2 following ibrutinib treatment.





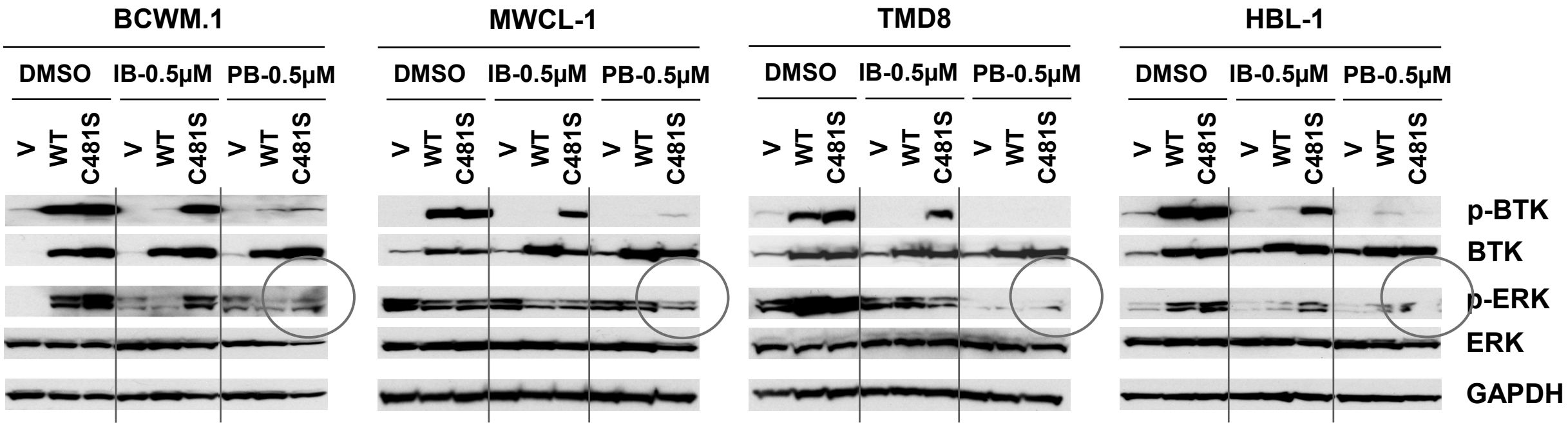
Chen et al, *Blood* 2018

$BTK^{Cys481Ser}$ mutated clones release cytokines that protect BTK^{WT} clones from ibrutinib triggered cytotoxicity



Chen et al, Blood 2018

Pirtobrutinib-a non-covalent BTK-Inhibitor Suppresses p-BTK and p-ERK1/2 in Ibrutinib Resistant BTK^{Cys481Ser} Expressing Cells

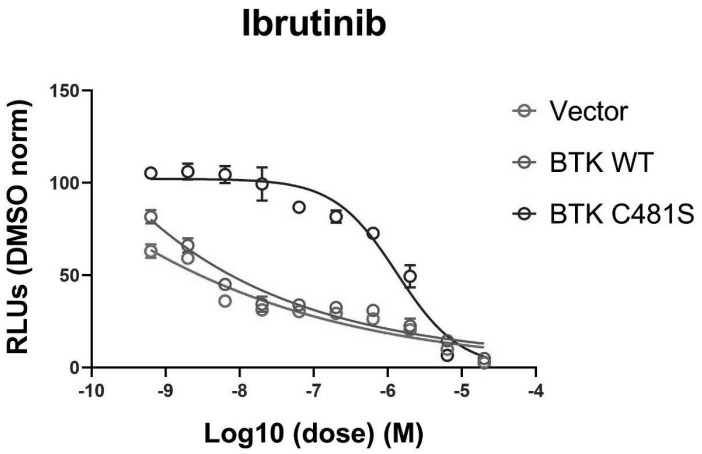


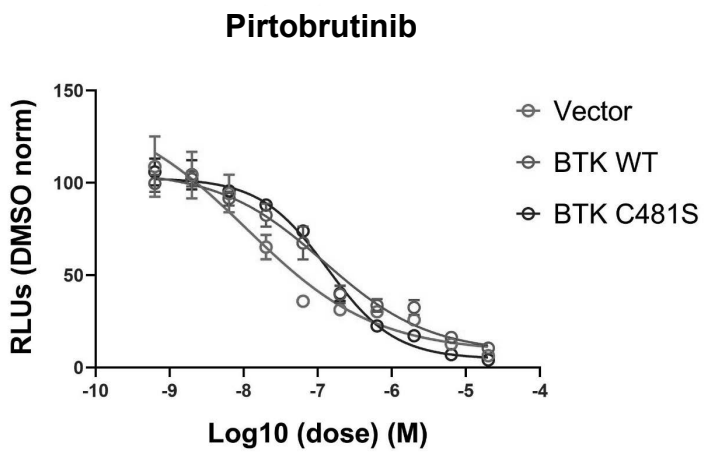
V-vector only; WT-BTK wild-type; C481S-BTK Cys481Ser mutant;
IB, ibrutinib; PB, pirtobrutinib

Munshi et al, Submitted

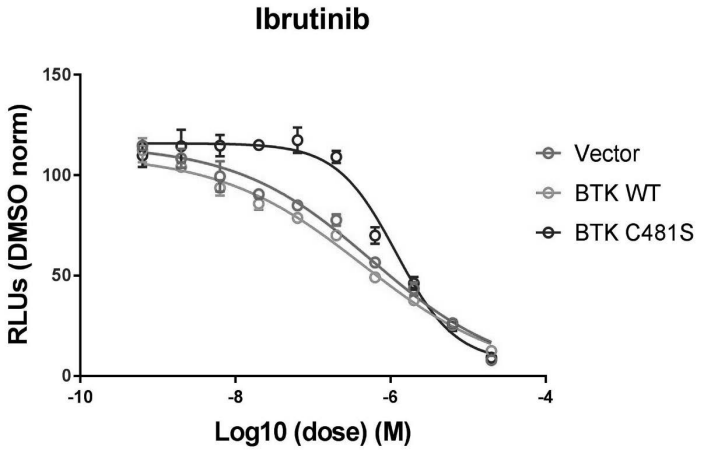
Pirtobrutinib Overcomes Ibrutinib Resistance Related to BTK^{Cys481Ser}

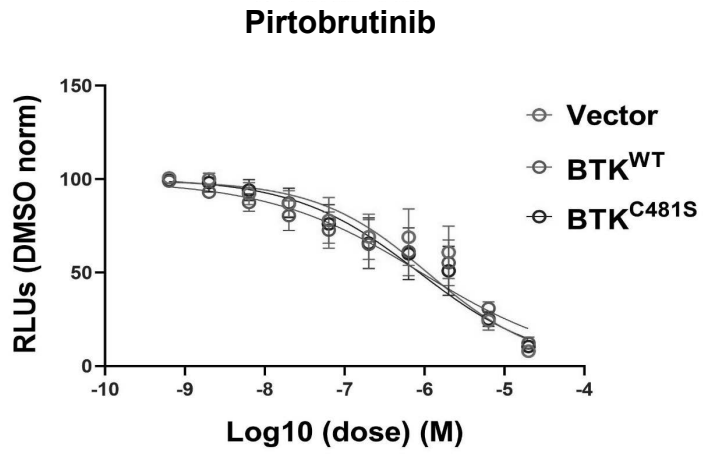
TMD8





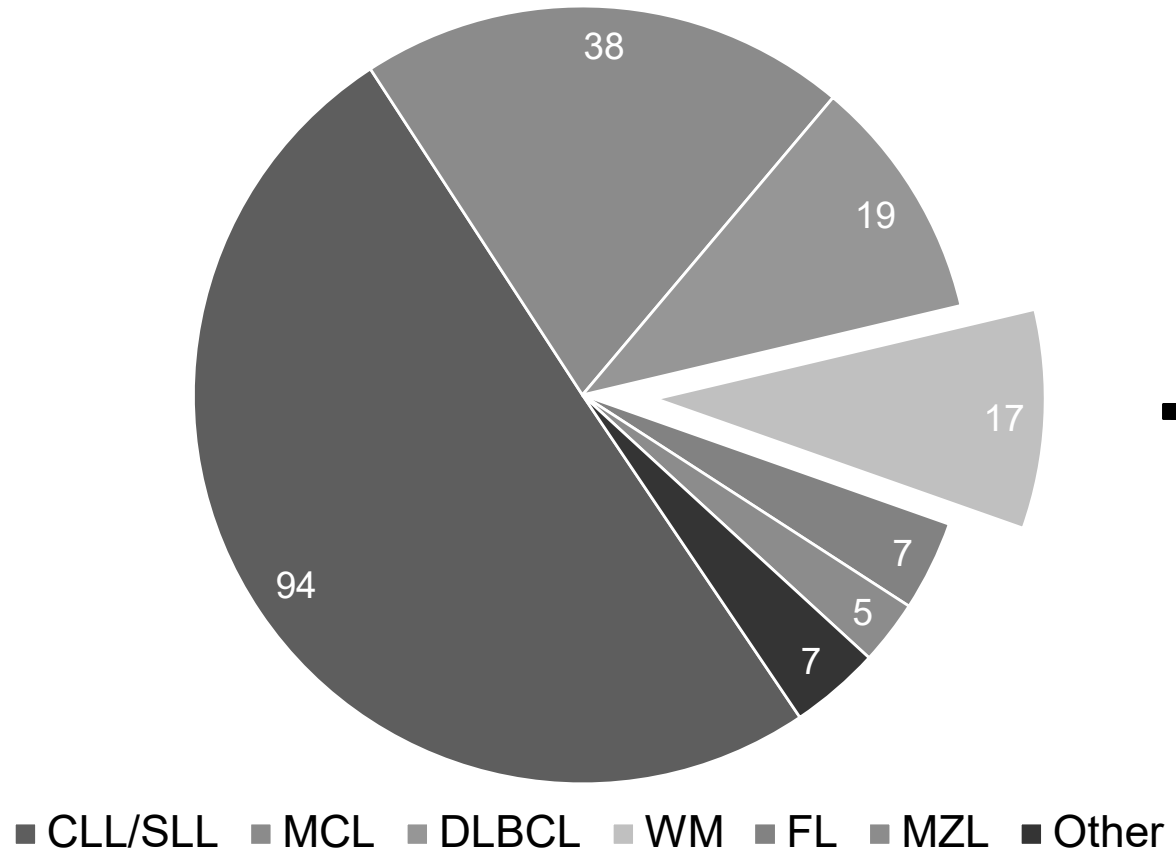
BCWM.1





Munshi et al, submitted

Pirtobrutinib in Previously Treated Mantle Cell Lymphoma, Waldenström's Macroglobulinemia, and Other NHLs: Phase 1/2 BRUIN Study.



- 15 evaluable for efficacy
- 60% previously exposed to covalent BTK inhibitors
- ORR 60%
  - 1 VPGR
  - 4 PR
  - 4 MR

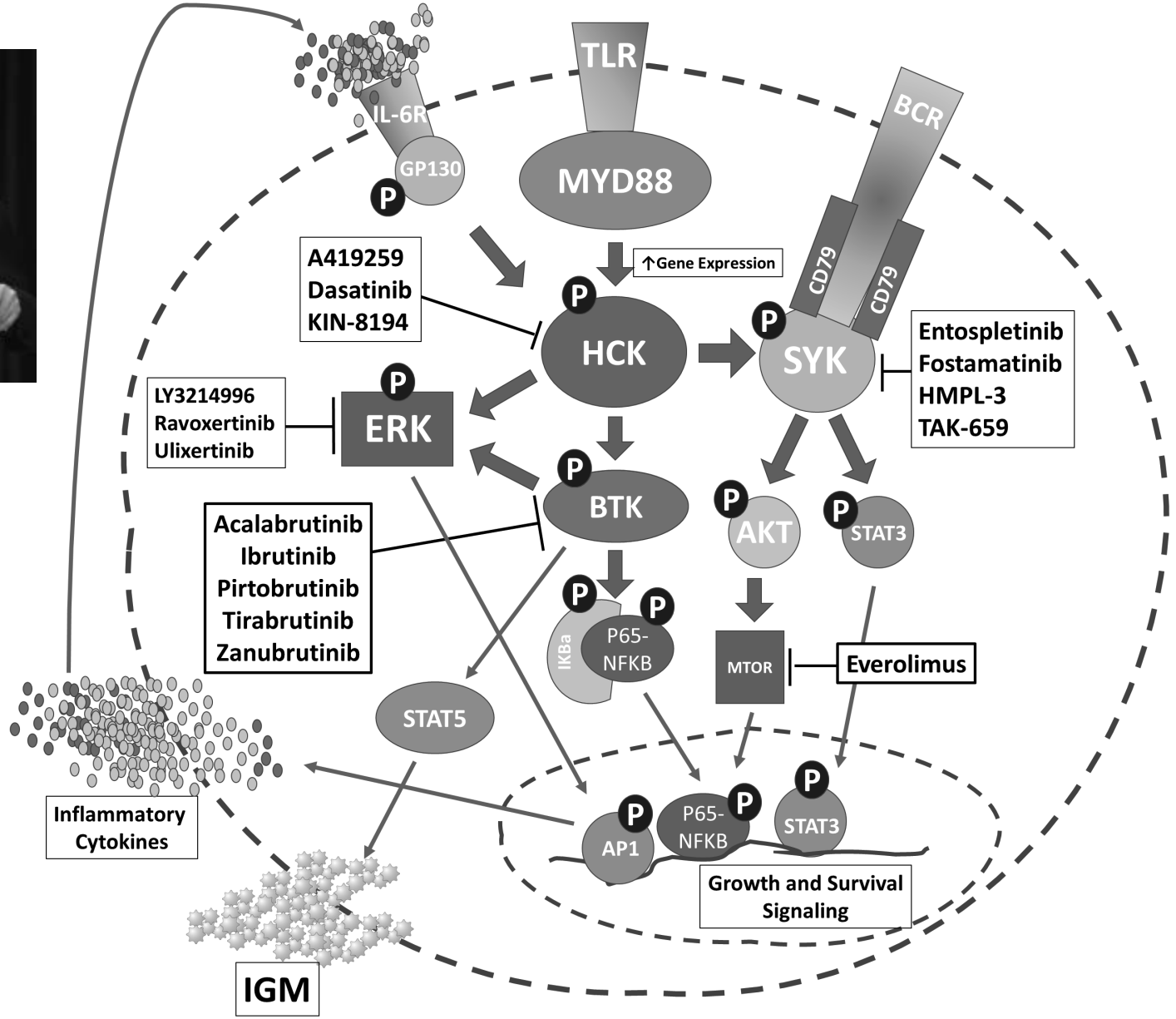
Wang et al. ASH 2020

Trial Design

- Single-arm, open-label phase II study
- Multicenter: DFCI/MGH, MSKCC, Mayo, SCCA, Stanford, Colorado Cancer Center.
- Pirtobrutinib at 200 mg orally QD on 28-day cycles
- Dose reduction allowed for toxicity.
- Participants will continue pirtobrutinib until PD or toxicity and will be followed for up to 2 years after completion of 48 cycles of treatment or until death.

Jorge Castillo, PI (DFCI)
Shayna Sarosiek, Co-Inv. (DFCI)

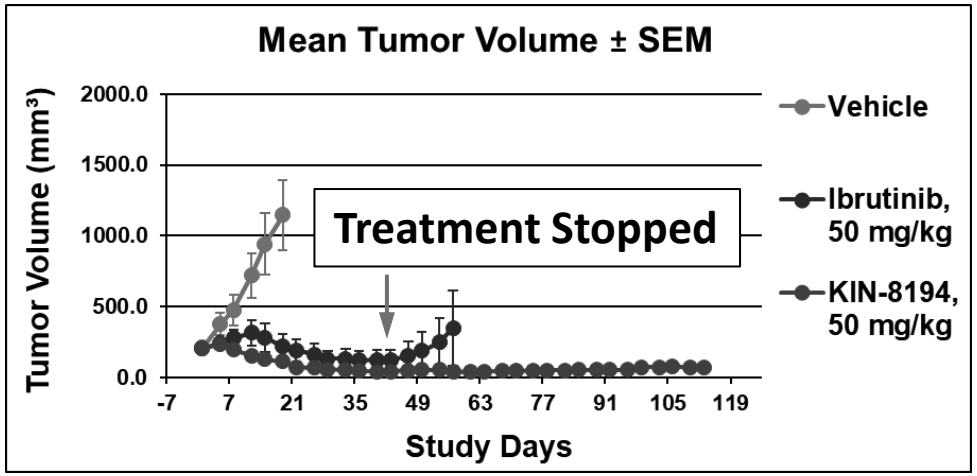
MYD88 directed pro-survival signaling in WM

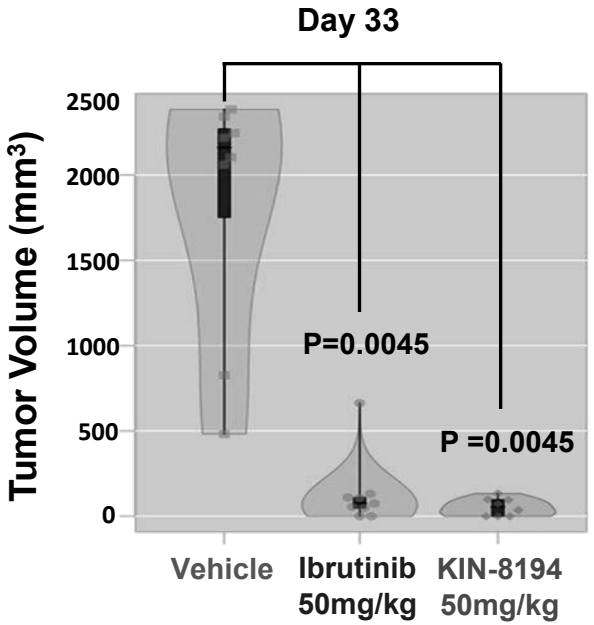


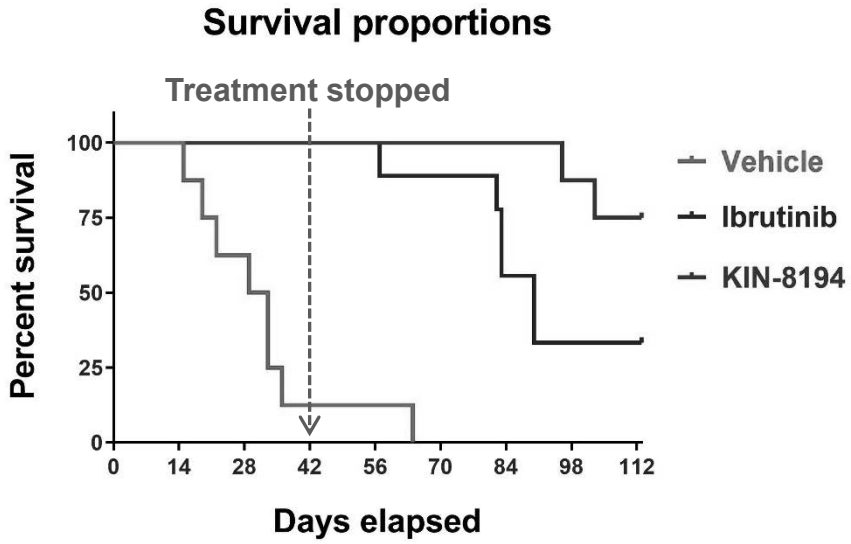
MYD88 mutations occur in 95-97% WM Patients

Treon et al, NEJM 2012
Yang et al, Blood 2013
Hodge et al, Blood 2014
Yang et al, Blood 2016
Chen et al, Blood 2018
Liu et al, Blood Adv 2020
Munshi et al, BCJ 2020
Munshi et al, Submitted.

Development of a dual HCK/BTK Inhibitor: KIN-8194
Efficacy Studies in BTK wild-type TMD8 xenografted mice





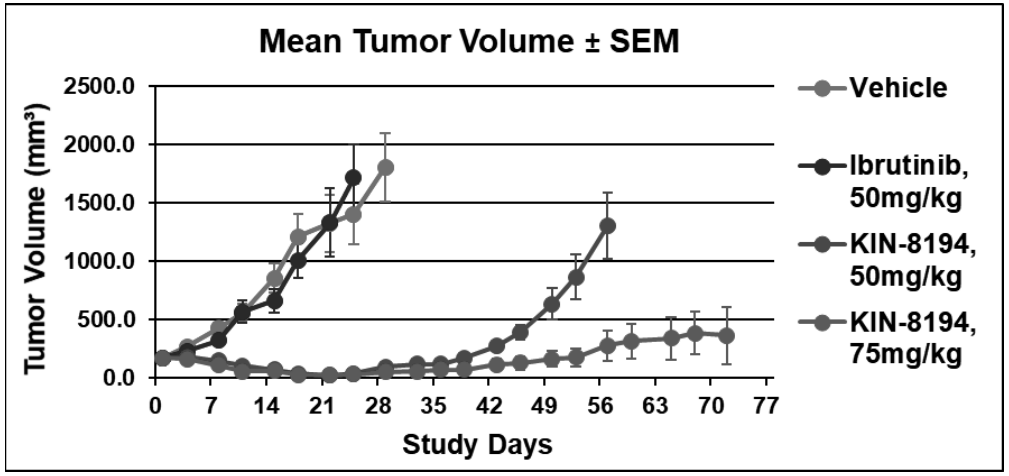


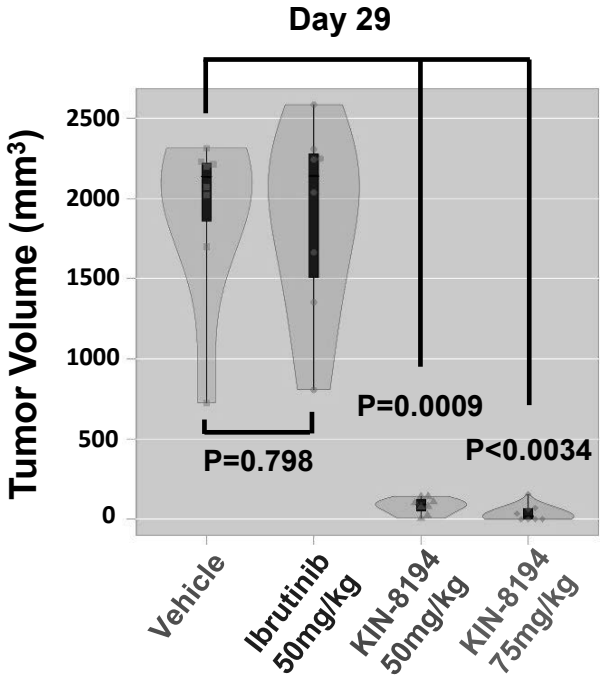
Median Survival	Vehicle	Ibrutinib (50mg/kg)	KIN-8194 (50mg/kg)
(days)	31	90	Undefined

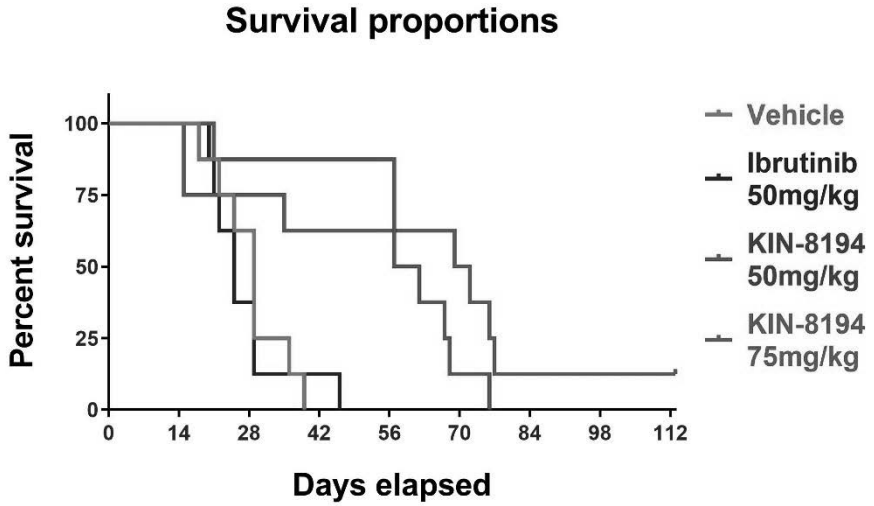
Log-rank (Mantel-Cox) test, P<0.0001

Yang et al, Blood 2021

Development of a dual HCK/BTK Inhibitor: 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

11th International Workshop for Waldenstrom's Macroglobulinemia

Madrid, October 6-8, 2022

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