Updates in the Management Waldenstrom's Macroglobulinemia

HARVARD
MEDICAL SCHOOL

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Disclosures

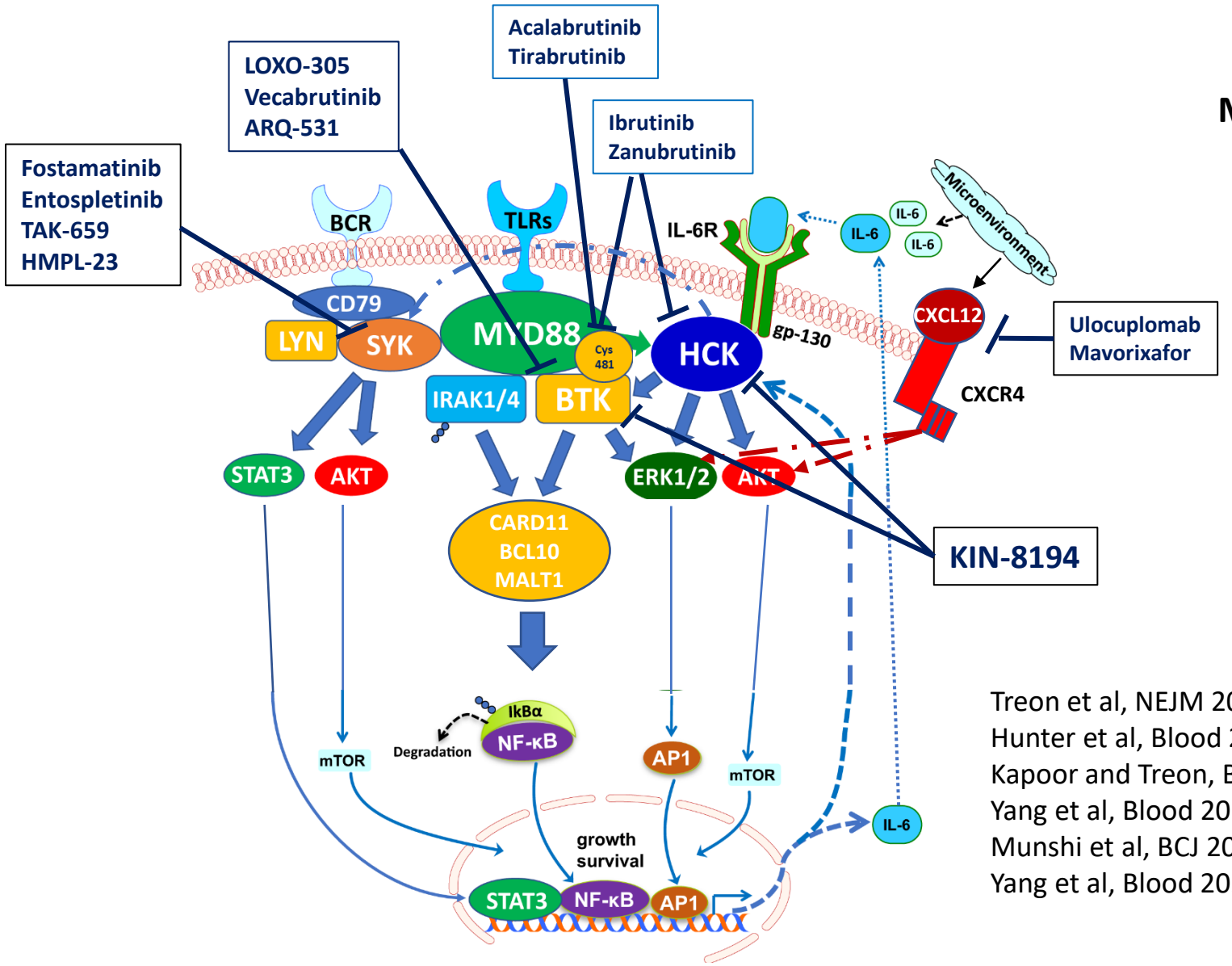
Research Support/P.I.	Abbvie/Pharmacyclics, Beigene, BMS, Eli Lilly
Consultant	Janssen, Abbvie/Pharmacyclics, Beigene, BMS

Investigational Drugs for WM:
Zanubrutinib, Acalabrutinib, Ulocuplumab, Mavorixafor, Venetoclax

Objectives

- Identify genomic subgroups in WM
- Apply targeted therapies based on genomic profiling and explain how they work for WM patients
- Manage selected therapy and the forecasted outcomes, toxicities, and duration

Pro-survival signaling triggered by mutated MYD88 and CXCR4 in WM.



Mutation Incidence in WM

MYD88: 95-97%

CXCR4: 30-40%

Treon et al, NEJM 2012

Hunter et al, Blood 2014; Xu et al, BJH 2016

Kapoor and Treon, Blood 2020; 136(18):1997-1999.

Yang et al, Blood 2013; Blood 2016

Munshi et al, BCJ 2020

Yang et al, Blood 2021 (First Edition)

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**

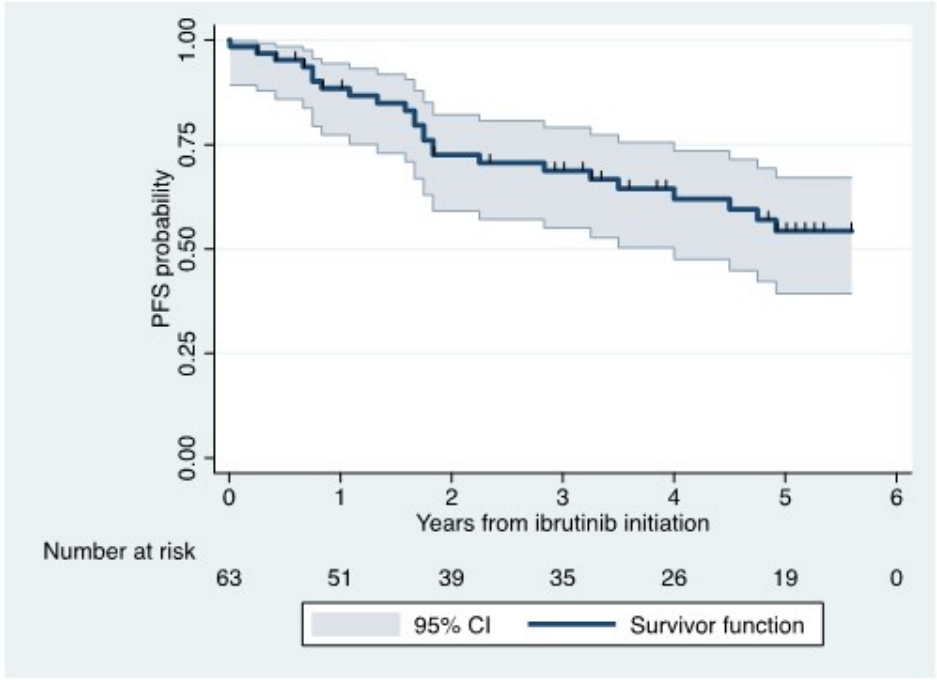
***One patient had MYD88 mutation, but no CXCR4 determination and had SD.**

Treon et al, NEJM 2015; Updated JCO 2021

Ibrutinib in Previously Treated WM: Updated PFS

All patients

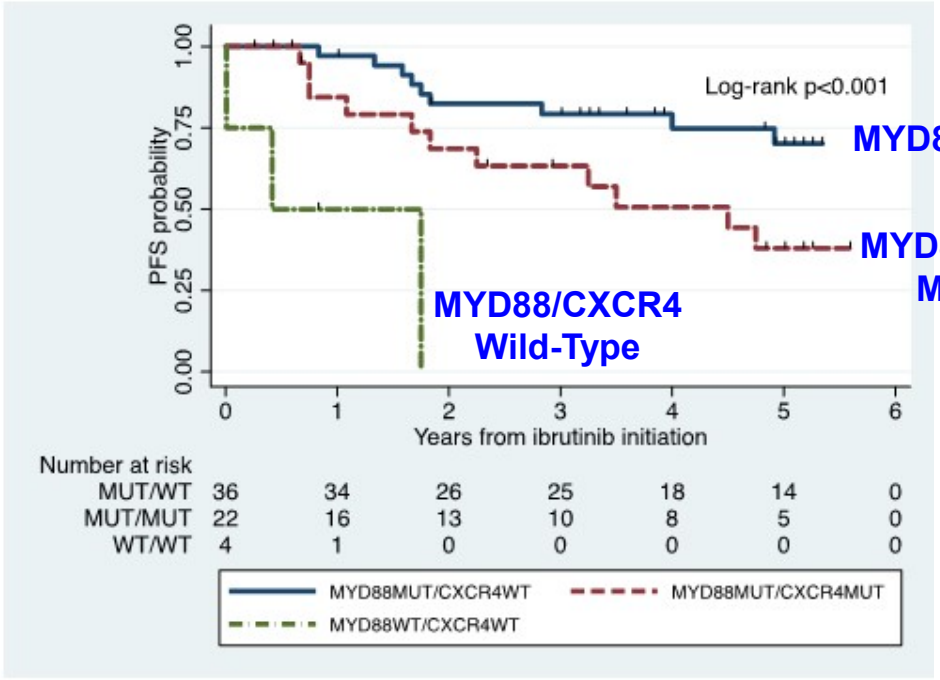
A.



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

By MYD88 and CXCR4 Mutation Status

B.



Treon et al, NEJM 2015; Updated JCO 2021

Ibrutinib in Previously Treated WM: Adverse Events

Adverse Event	No.			
	Grade 2	Grade 3	Grade 4	Total Grades 2-4
Blood and lymphatic system disorders				
Anemia	2	1	0	3
Thrombocytopenia	1	5	2	8
Neutropenia	5	6	4	15
Febrile neutropenia	0	0	1	1
Cardiac disorders				
Atrial fibrillation	5	1	0	6
GI disorders				
Bloating	1	0	0	1
Constipation	2	0	0	2
Diarrhea	2	0	0	2
Duodenal ulcer	1	0	0	1
Gastric ulcer	1	0	0	1
Gastroesophageal reflux disease	5	0	0	5
Mucositis oral	3	0	0	3
Other	1	0	0	1
General disorders				
Edema in limbs	1	0	0	1
Infections and infestations				
Bronchial	2	0	0	2
Endocarditis	0	1	0	1
Eye	1	0	0	1
Lung	3	2	0	5
Sinusitis	1	0	0	1
Skin	3	1	0	4
Upper respiratory	1	0	0	1
Urinary tract	2	0	0	2
Procedural complications				
Postprocedure hemorrhage	1	0	0	1

Continued

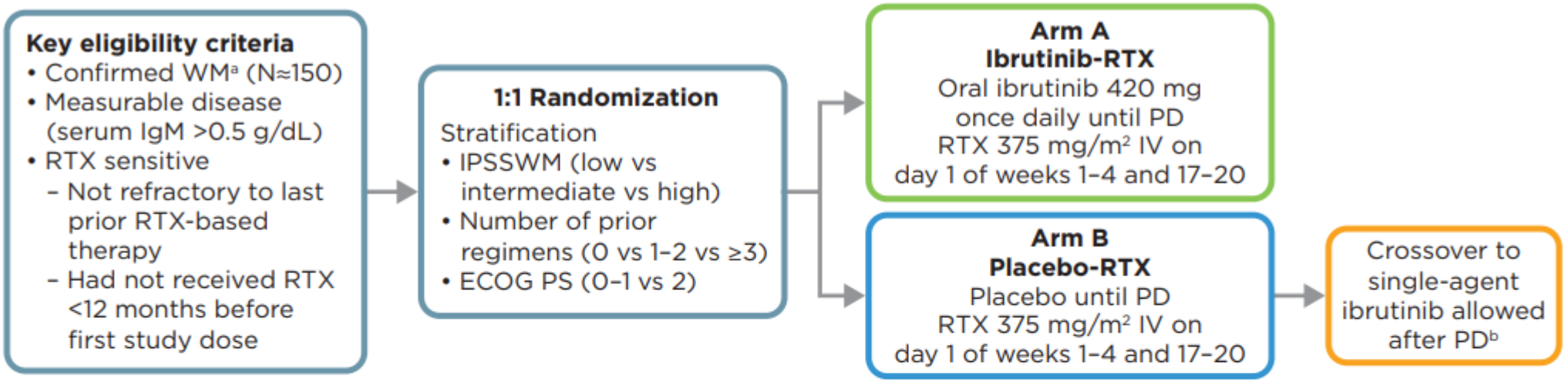
Adverse Event	No.			
	Grade 2	Grade 3	Grade 4	Total Grades 2-4
Metabolism and nutrition disorders				
Dehydration	2	0	0	2
Other	1	0	0	1
Musculoskeletal and connective tissue disorders				
Arthralgia	2	0	0	2
Myalgia	2	0	0	2
Other	2	0	0	2
Nervous system disorders				
Headache	1	0	0	1
Presyncope	1	0	0	1
Syncope	0	1	0	1
Respiratory, thoracic, and mediastinal disorders				
Cough	1	0	0	1
Epistaxis	2	0	0	2
Other	1	0	0	1
Skin and subcutaneous tissue disorders				
Pruritus	1	0	0	1
Other	2	0	0	2
Vascular disorders				
Hypertension	4	0	0	4
Hypotension	1	0	0	1

NOTE. Grade ≥ 2 adverse events deemed by investigators to be possibly, probably, or definitely associated with protocol therapy are shown. The No. of individual patients with the indicated toxicity are listed, with the highest grade toxicity shown for an individual patient. Eight patients had atrial fibrillation, including two with grade 1 events (not shown in table).

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

Treon et al, NEJM 2015; Updated JCO 2021

iNNOVATE (PCYC-1127; NCT 02165397) Study Design



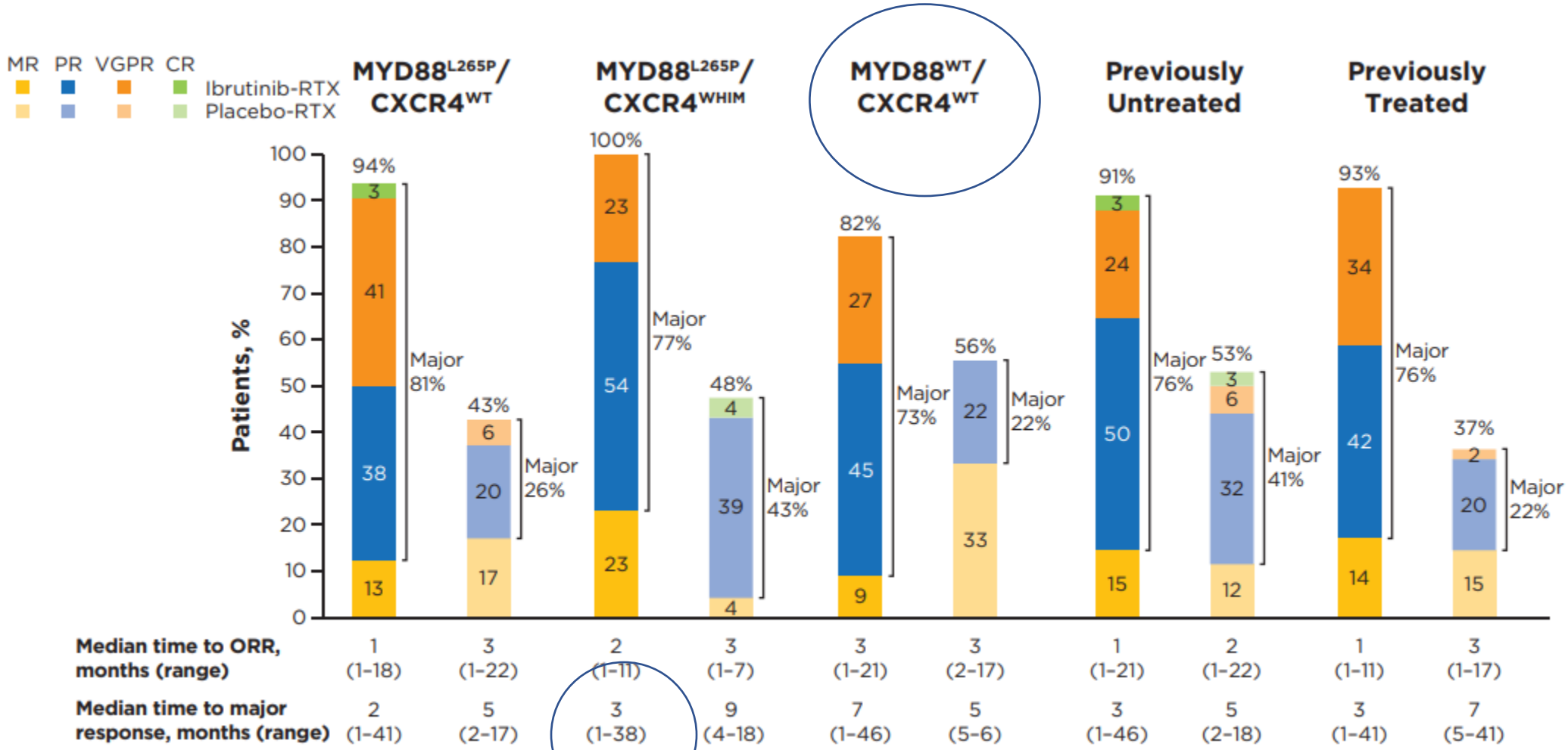
ECOG PS, Eastern Cooperative Oncology Group performance status; IPSSWM, International Prognostic Scoring System for Waldenström's Macroglobulinemia; IRC, independent review committee; IV, intravenous; PD, progressive disease.

[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 designed to assess the efficacy and safety of ibrutinib-RTX versus placebo-RTX in patients with WM
- 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

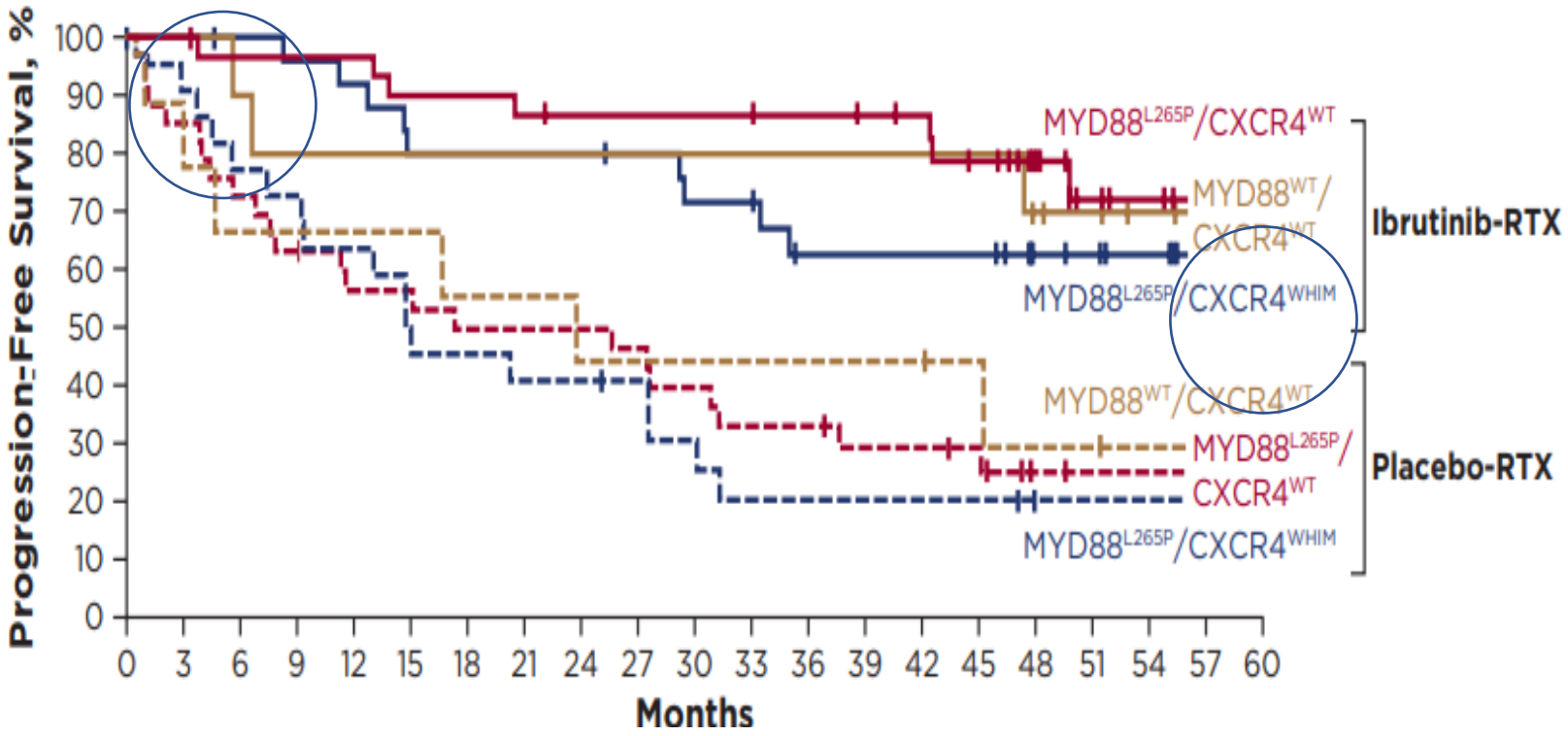
Response Rates by Genotype and Prior Treatment Status



- 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



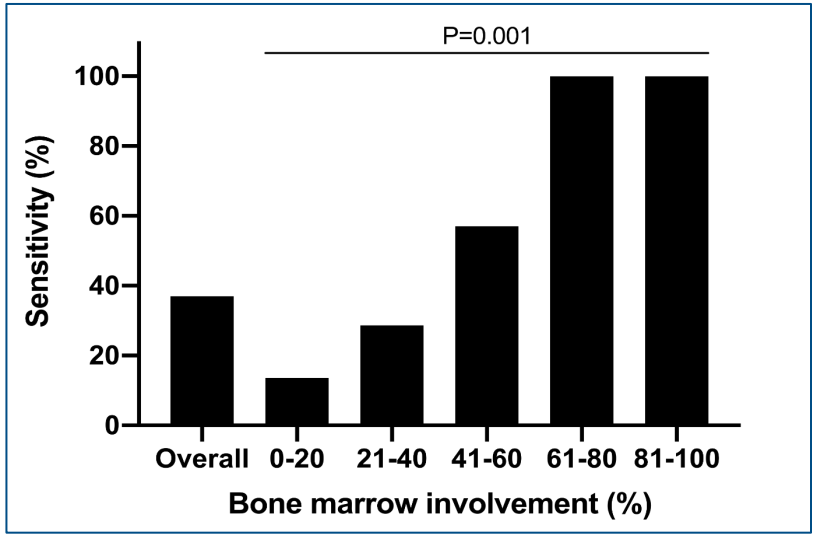
54-month PFS	Ibrutinib-RTX	Placebo-RTX
$MYD88^{Mut}/CXCR4^{WT}$	72%	25%
$MYD88^{Mut}/CXCR4^{Mut}$	63%	21%
$MYD88^{WT}/CXCR4^{WT}$	70%	30%

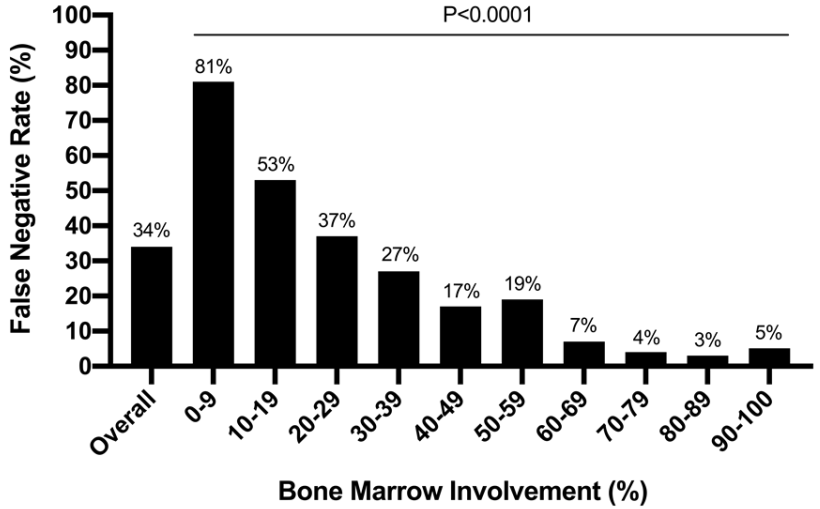
Mutated (Mut); Wild-Type (WT); RTX (Rituximab)

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 (in press).

iNNOVATE: Adverse Events Associated with Ibrutinib-Rituximab

Garcia Sanz et al, EHA Abstract EP782

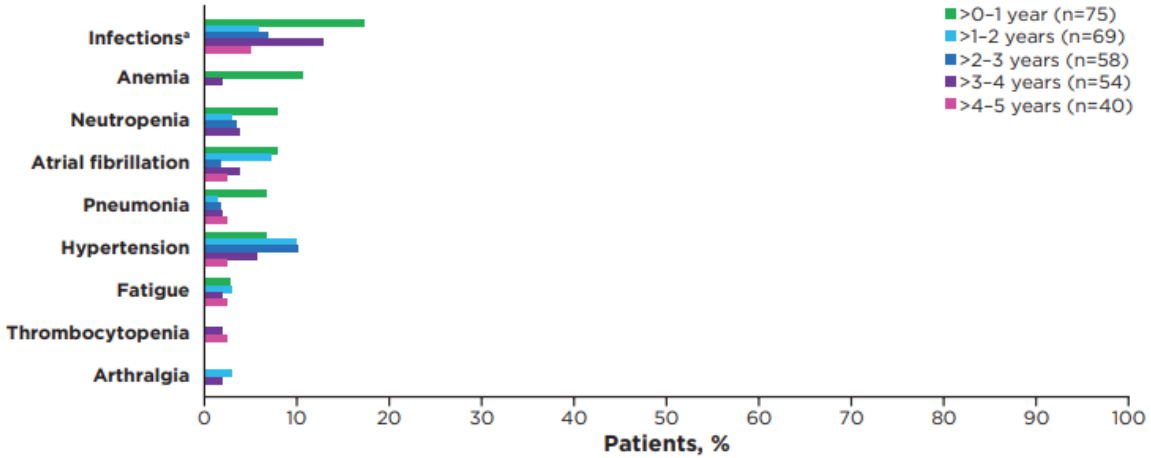
Table 4. Safety Summary

Prevalence	Ibrutinib-RTX	
	Year 3–4 (n=54)	Year 4–5 (n=40)
AE leading to ibrutinib dose reduction, n (%)	6 (11)	2 (5)
AE leading to ibrutinib discontinuation, n (%)	2 (4)	2 (5)
Death due to TEAE, n (%)	0	1 (3)[a]
Major hemorrhage, n (%)	0	0
Most common TEAEs, n (%)		
Diarrhea	6 (11)	1 (3)
Arthralgia	8 (15)	5 (13)
Hypertension	9 (17)	4 (10)

TEAE, treatment-emergent adverse event.
Treatment ended for the placebo-RTX arm; safety data for this arm has been previously reported.[3]
[a]One patient in the ibrutinib-RTX arm died due to pneumonia; this AE was not considered related to study drug.

- With 63 months of overall follow-up, ibrutinib-RTX maintained a manageable safety profile (**Table 4**).
- 88% of AEs that led to an ibrutinib dose reduction resolved following dose reduction.

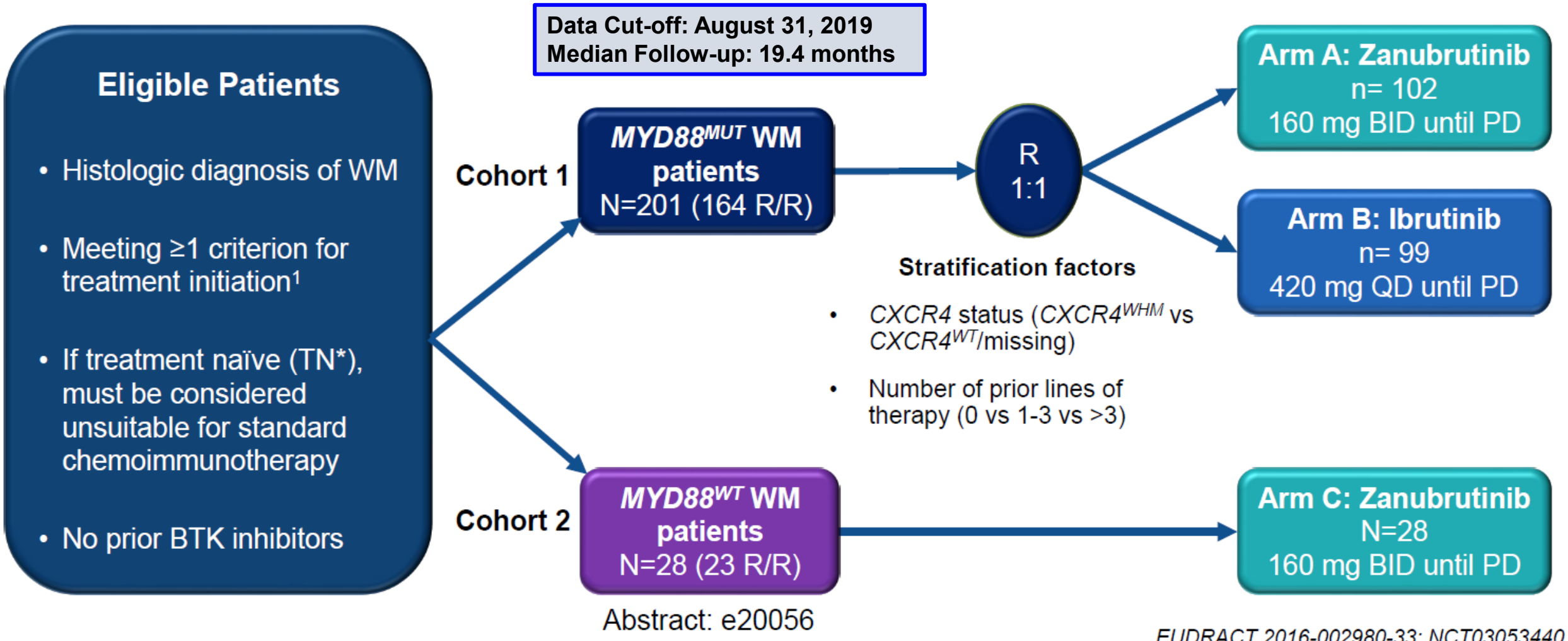
Figure 10. Prevalence of Grade ≥3 AEs of Clinical Interest by Yearly Interval



[a]Combined terms.

- The prevalence of grade ≥3 AEs of clinical interest with ibrutinib-RTX generally decreased over time (**Figure 10**).
- 12 patients presented with grade 3/4 atrial fibrillation, and 9 (75%) remained on treatment; no other ibrutinib discontinuations due to common (≥10%) grade 3/4 AEs occurred.

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.

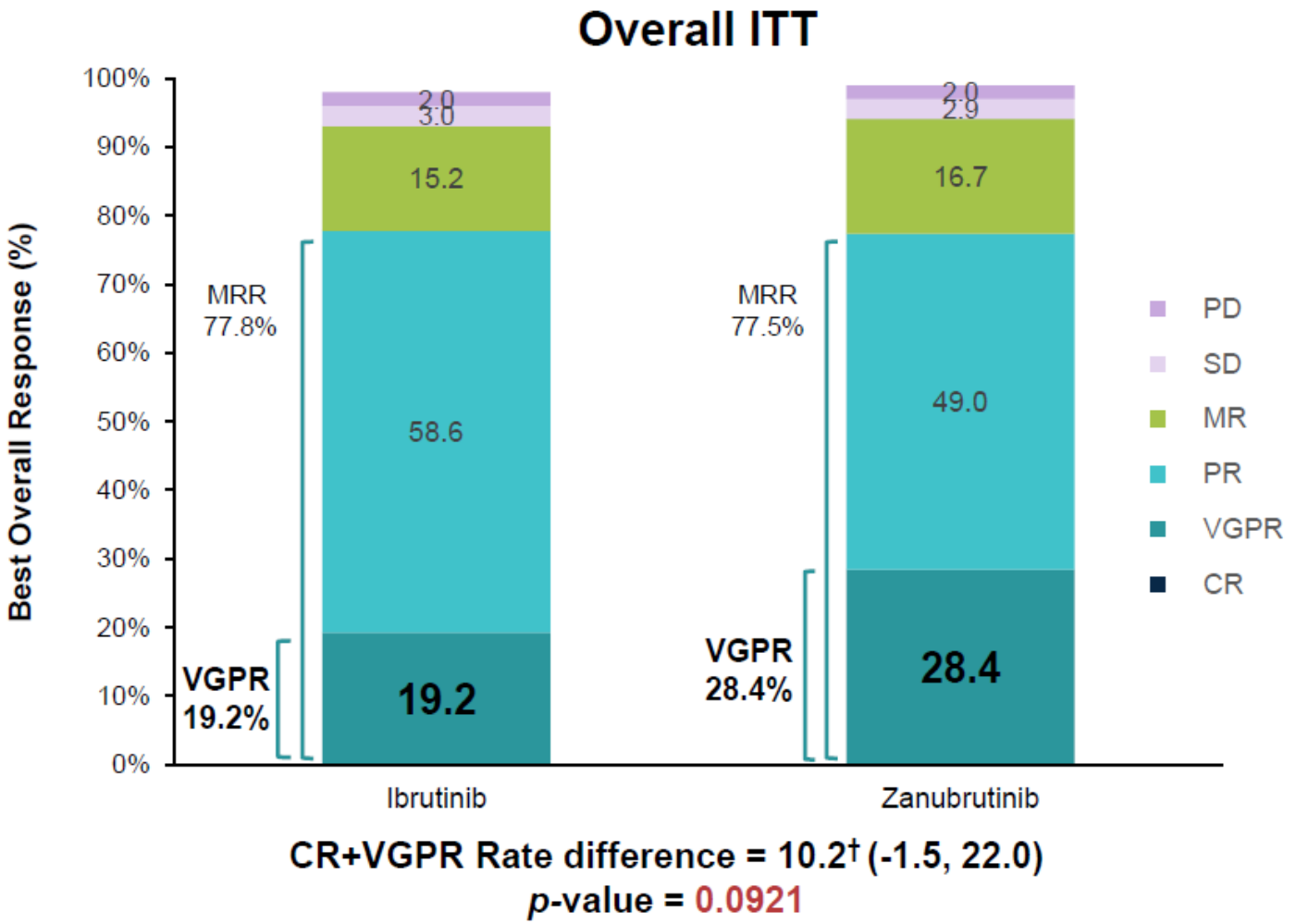
*Up to 20% of the overall population.

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.

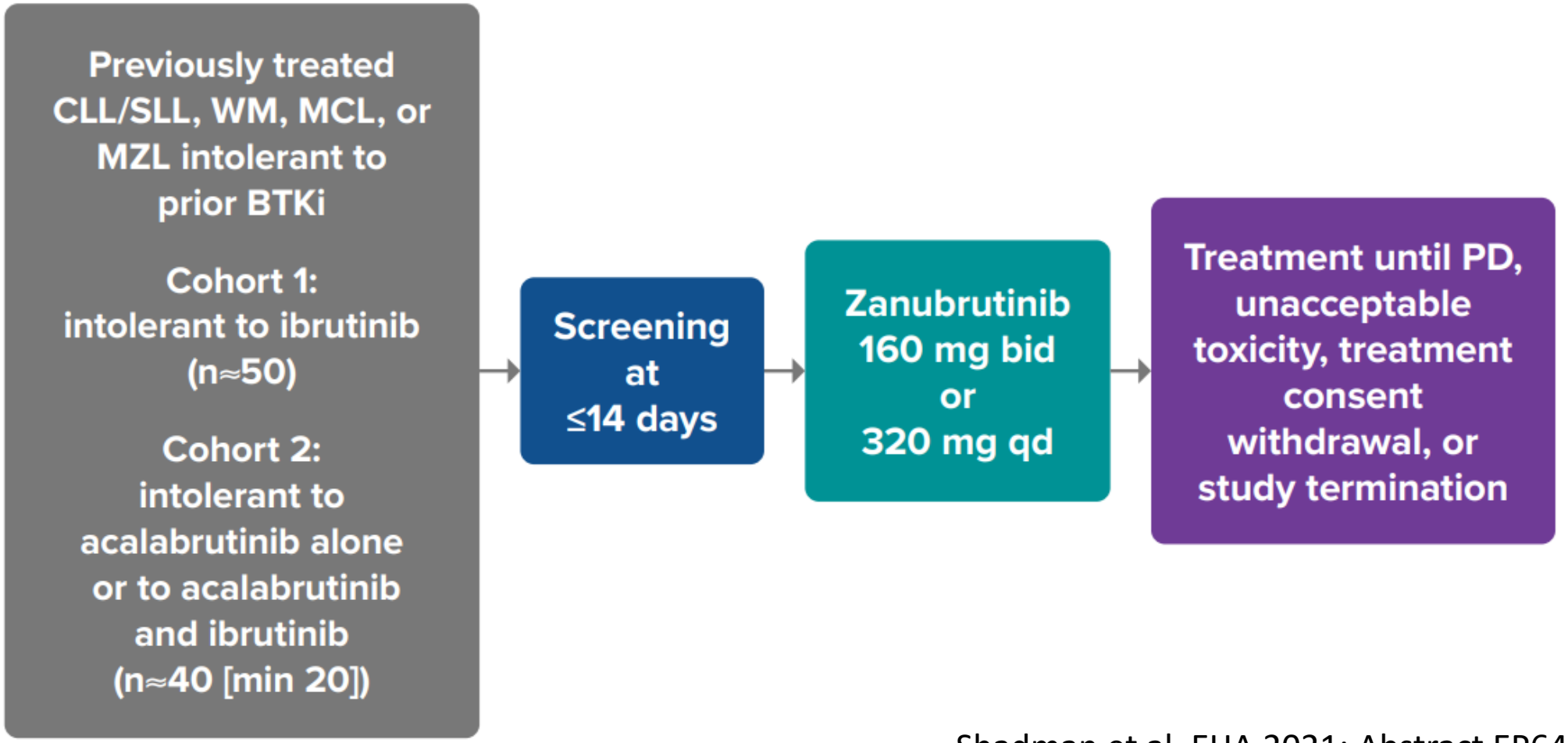
Tam et al, Blood 2020

Additional AEs of Special Interest

Safety Analysis Population	Zanubrutinib (n=204), n (%)		Ibrutinib (n=207), n (%)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Cardiac disorders[a]	28 (13.7)	5 (2.5)	52 (25.1)	14 (6.8)
Atrial fibrillation and flutter (key 2º endpoint)	**5 (2.5)**	**2 (1.0)**	**21 (10.1)**	**4 (1.9)**
Hemorrhage	73 (35.8)	6 (2.9)	75 (36.2)	6 (2.9)
Major hemorrhage[b]	6 (2.9)	6 (2.9)	8 (3.9)	6 (2.9)
Hypertension	34 (16.7)	22 (10.8)	34 (16.4)	22 (10.6)
Infections	122 (59.8)	26 (12.7)	131 (63.3)	37 (17.9)
Neutropenia[c]	58 (28.4)	38 (18.6)	45 (21.7)	31 (15.0)
Thrombocytopenia[c]	19 (9.3)	7 (3.4)	26 (12.6)	7 (3.4)
Secondary primary malignancies	17 (8.3)	10 (4.9)	13 (6.3)	4 (1.9)
Skin cancers	7 (3.4)	3 (1.5)	10 (4.8)	2 (1.0)

AE, adverse events. All events are of any grade unless otherwise specified.
[a] Cardiac disorders leading to treatment discontinuation: zanubrutinib 0 patients and ibrutinib 7 (3.4%) patients.
[b] Includes hemorrhages that were serious or grade ≥3 or CNS hemorrhages of all grades.
[c] Pooled terms including neutropenia, neutrophil count decreased, and febrile neutropenia; thrombocytopenia and platelet count decreased.

PRELIMINARY RESULTS OF A PHASE 2 STUDY OF ZANUBRUTINIB IN PATIENTS WITH PREVIOUSLY TREATED B CELL MALIGNANCIES INTOLERANT TO IBRUTINIB/ACALABRUTINIB



Shadman et al, EHA 2021; Abstract EP642

Patient Demographics and Baseline Characteristics

Characteristics	Cohort 1 (n=57)	Cohort 2 (n=7)	Total (N=64)
Indication			
CLL	38 (66.7)	4 (57.1)	42 (65.6)
WM	9 (15.8)	1 (14.3)	10 (15.6)
SLL	6 (10.5)	0 (0)	6 (9.4)
MCL	2 (3.5)	1 (14.3)	3 (4.7)
MZL	2 (3.5)	1 (14.3)	3 (4.7)
Age, median (range), y	71 (49-91)	71 (65-76)	71 (49-91)
Male, n (%)	30 (52.6)	5 (71.4)	35 (54.7)
ECOG PS 0, n (%)	33 (57.9)	4 (57.1)	37 (57.8)
No. of prior therapy regimens, median (range)	1 (1-12)	3 (2-5)	2 (1-12)
Prior BTKi, n (%)			
Ibrutinib monotherapy	50 (87.7)	5 (71.4)[a]	55 (85.9)
Ibrutinib combination therapy	8 (14.0)[b]	0 (0)	8 (12.5)
Acalabrutinib monotherapy	NA	7 (100)	7 (10.9)
Time on most recent prior BTKi, median (range), mo	9.7 (1.1-73.7)	2.1 (0.5-26.8)	9.2 (0.5-73.7)
On-study zanubrutinib dosing regimen			
160 mg bid	35 (61.4)	5 (71.4)	40 (62.5)
320 mg qd	22 (38.6)	2 (28.6)	24 (37.5)

Data cutoff: 01 Mar 21.

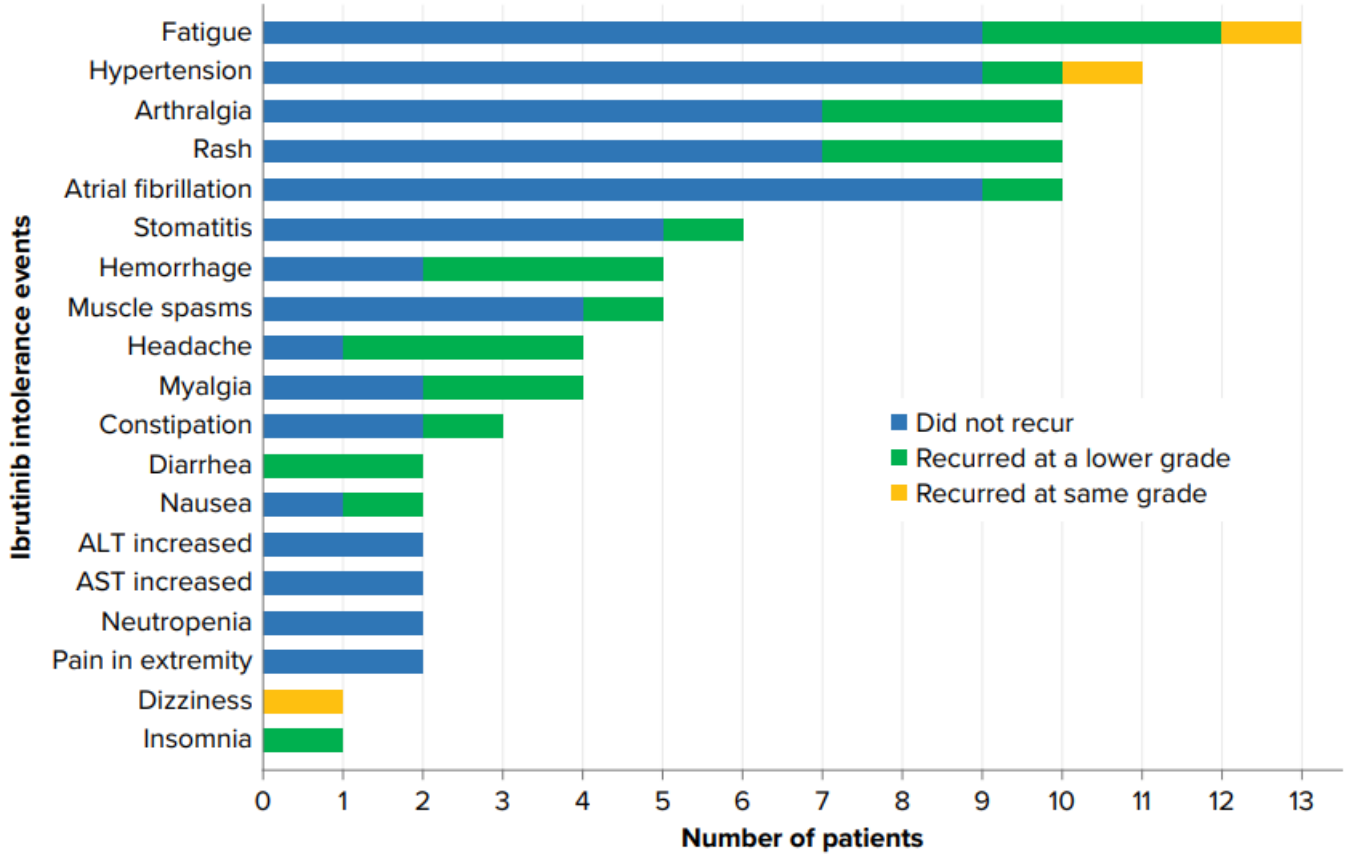
BTKi, Bruton tyrosine kinase inhibitor; bid, twice daily; CLL, chronic lymphocytic leukemia; ECOG PS, Eastern Cooperative Oncology Group performance status; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; NA, not applicable; qd, once daily; SLL, small lymphocytic leukemia; WM, Waldenström macroglobulinemia.

[a] Five patients had both prior ibrutinib and acalabrutinib therapies.

[b] One patient received ibrutinib combination therapy followed by ibrutinib monotherapy.

Shadman et al, EHA 2021; Abstract EP642

Recurrence of Ibrutinib Intolerance Events on Zanubrutinib



Data cutoff: 01 Mar 21.
ALT, alanine aminotransferase; AST, aspartate transaminase.
[a] Intolerance events occurring in ≥2 patients or recurring in ≥1 patient shown here.

- 86/115 ibrutinib intolerance events (75%) did not recur
  - Of the 29 recurrent ibrutinib intolerance events, 26 (90%) recurred at a lower severity, and 3 (10%) at the same severity

Shadman et al, EHA 2021; Abstract EP642

REGULAR ARTICLE

blood advances

Zanubrutinib for the treatment of MYD88 wild-type Waldenström macroglobulinemia: a substudy of the phase 3 ASPEN trial

Meletios Dimopoulos,[1] Ramon Garcia Sanz,[2] Hui-Peng Lee,[3] Marek Trneny,[4] Marzia Varettoni,[5] Stephen Opat,[6,7] Shirley D'Sa,[8] Roger G. Owen,[9] Gavin Cull,[10,11] Stephen Mulligan,[12] Jaroslaw Czyz,[13,14] Jorge J. Castillo,[15,16] Marina Motta,[17] Tanya Siddiqi,[18] Mercedes Gironella Mesa,[19] Miquel Granell Gorrochategui,[20] Dipti Talaulikar,[21] Pier Luigi Zinzani,[22,23] Elham Askari,[24] Sebastian Grosicki,[25] Albert Oriol,[26] Simon Rule,[27] Janusz Kloczko,[28] Alessandra Tedeschi,[29] Christian Buske,[30] Veronique Leblond,[31] Judith Trotman,[32,33] Wai Y. Chan,[34] Jan Michel,[35] Jingjing Schneider,[34] Ziwen Tan,[36] Aileen Cohen,[34] Jane Huang,[34] and Constantine S. Tam,[37-40] for the ASPEN investigators

	N=	%
ORR	23	81%
Major (PR or better)	13	50%
VGPR	7	27%

N=28

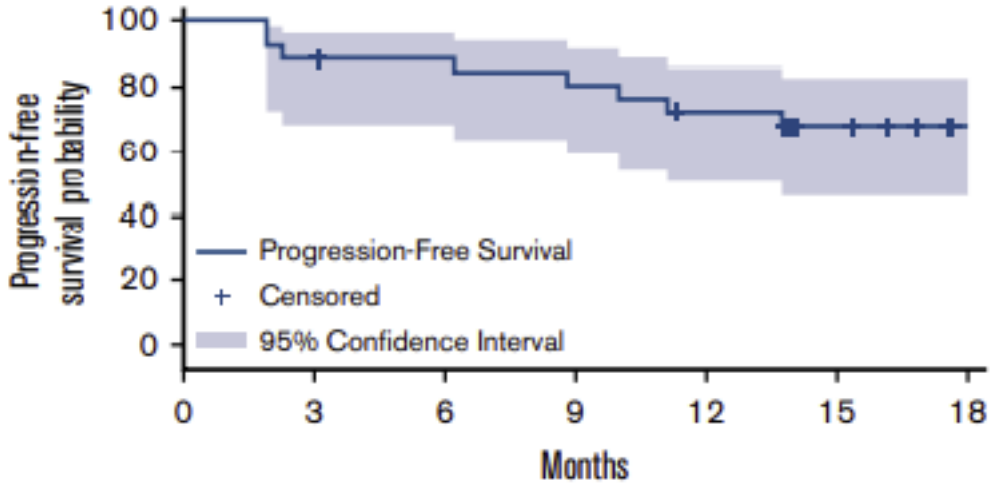
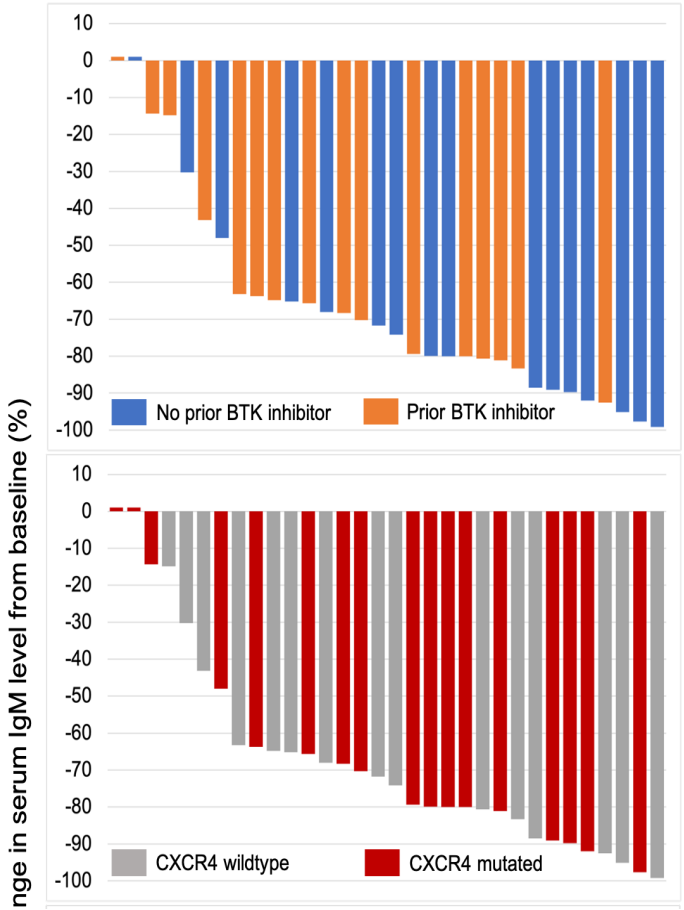
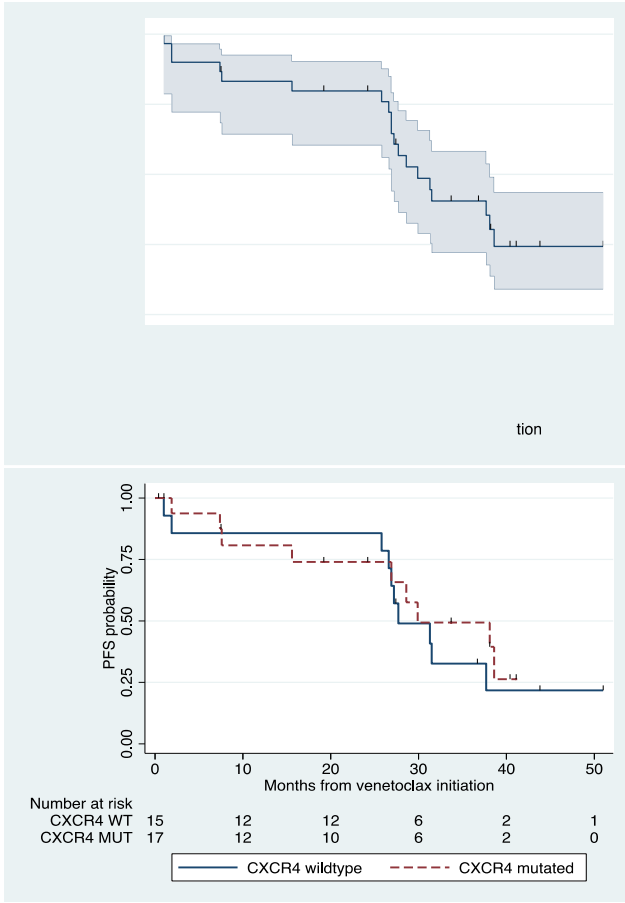


Table 1. Baseline demographic and disease characteristics

Characteristic	Treatment-naïve (n = 5)	Relapsed/refractory (n = 23)	Overall (N = 28)
Bone marrow involvement, n (%)	4 (80)	22 (96)	26 (93)
Median percent tumor cells (min, max)	13 (0, 70)	25 (0, 90)	23 (0, 90)

Phase II Study of Venetoclax in Previously Treated WM





ORR: 84%; Major RR: 81%

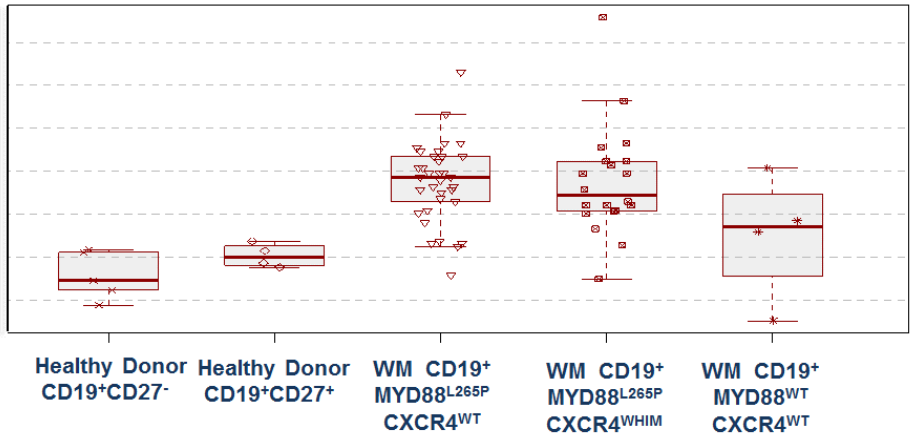
Median PFS: 30 months

Clinical trials.gov: NCT02677324

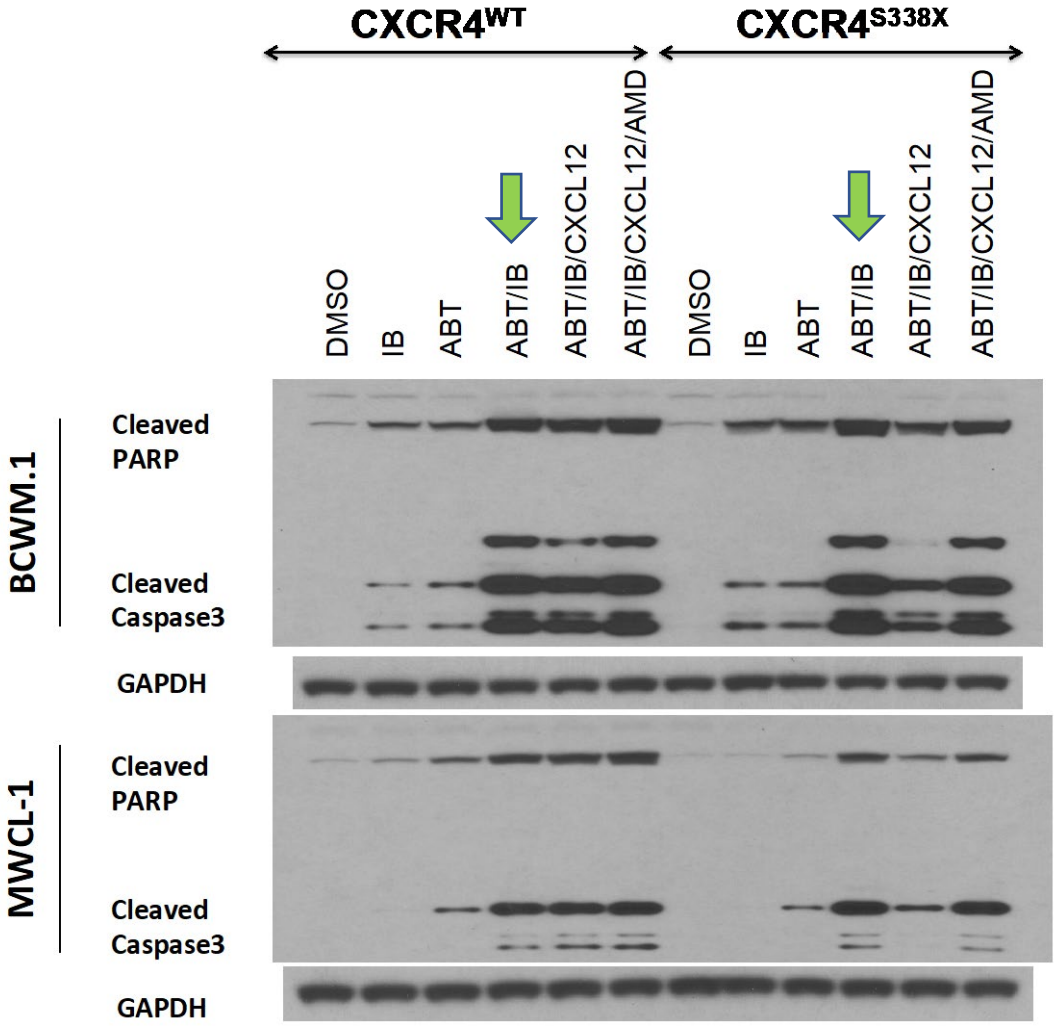
Castillo et al, 17th IMW 2019; Manuscript submitted.

Venetoclax (ABT-199) Augments Ibrutinib-induced Apoptosis

Higher BCL2 levels in MYD88 mutated WM



Cao et al, BJH 2015; 168(5): 701–7



Ibrutinib and Venetoclax in Treatment Naïve WM

24 months

Ibrutinib
420 mg/day
x 4 weeks

4 weeks

Ibrutinib
420 mg/day
Add Venetoclax
100 mg/day week 5
200 mg/day week 6
400 mg/day weeks 7,8

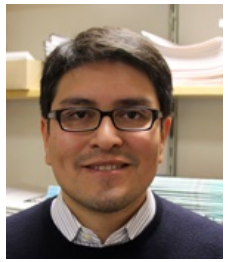
4 weeks

Ibrutinib
420 mg/day
And
Venetoclax
400 mg/day

22 months

Observation

Follow to PD or off study

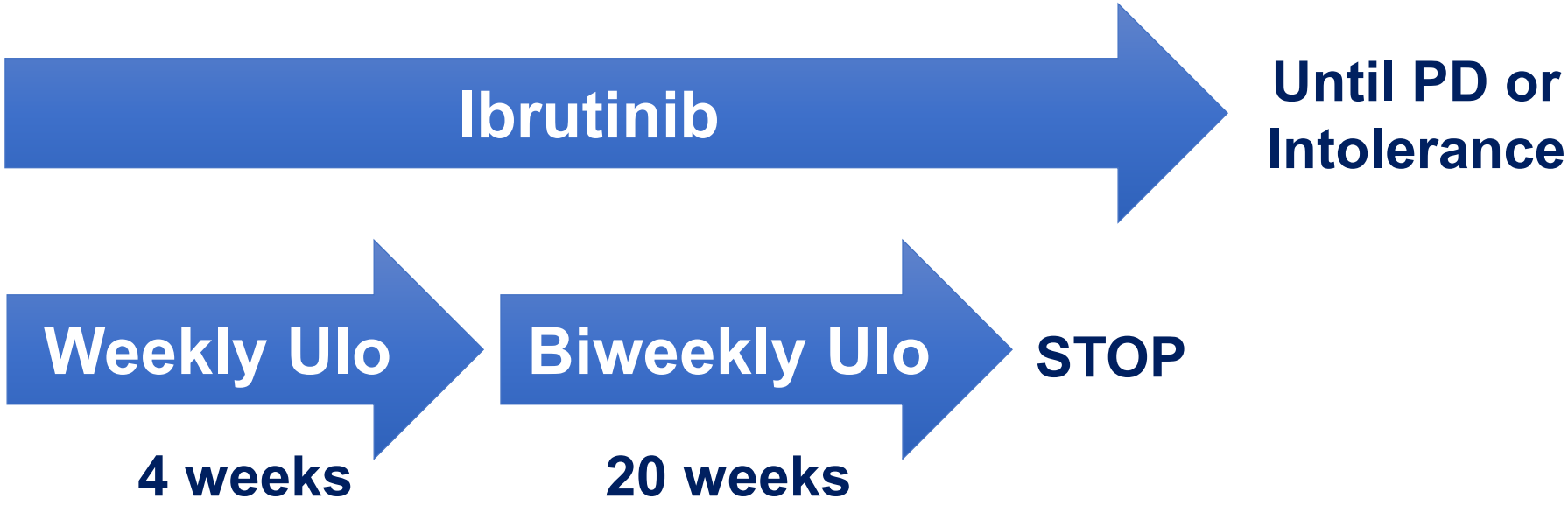


Jorge Castillo, PI (DFCI)

CLINICALTRIALS.GOV: NCT04273139

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

Schema

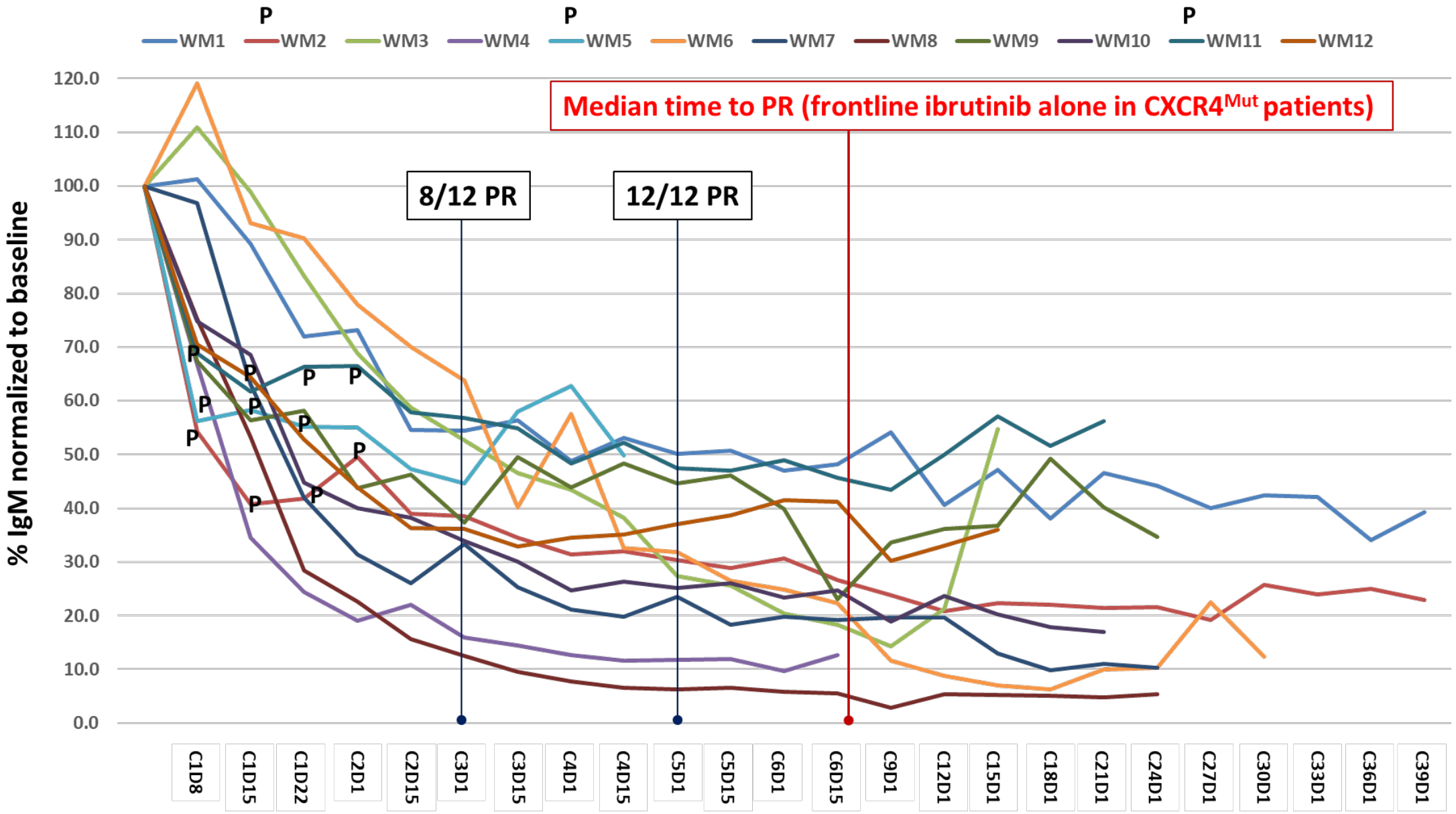


Dose Level	Ibrutinib	Ulocuplumab Cycle 1	Ulocuplumab Cycles 2-6
Level 1 –Starting dose	420mg PO DQ	400 mg weekly	800 mg every other week
Level 2	420mg PO DQ	800 mg weekly	1200 mg every other week
Level 3	420mg PO DQ	800 mg weekly	1600 mg every other week

Treon et al, Blood 2021.

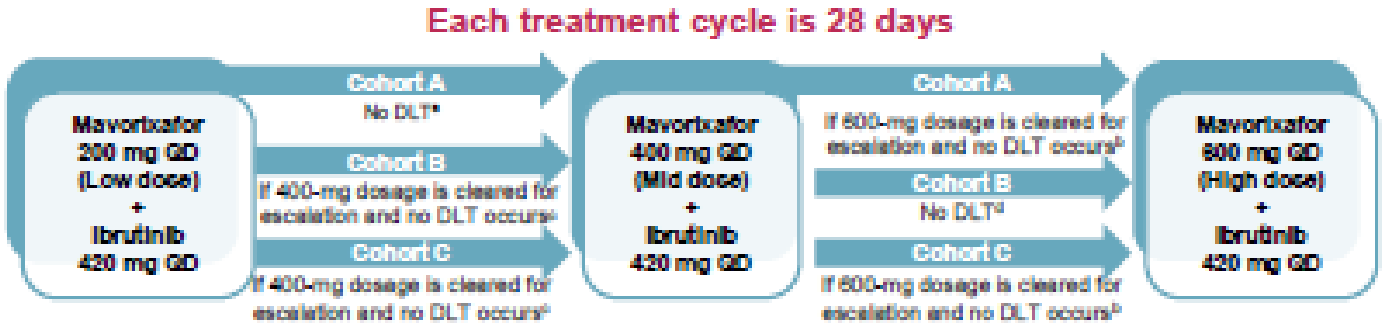
ClinicalTrials.gov Identifier: NCT03225716

Kinetics of response following Ulocuplumab and Ibrutinib in CXCR4 mutated WM patients

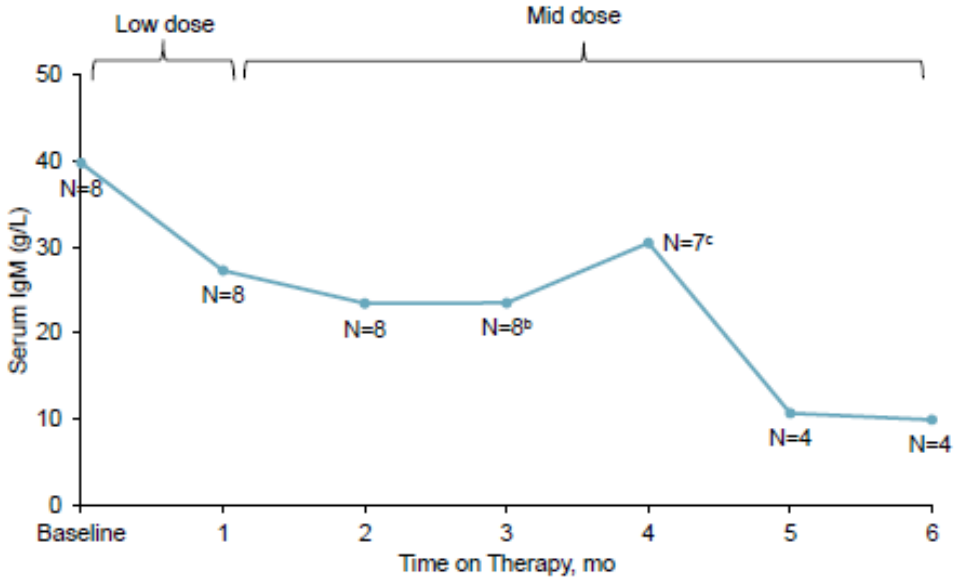


Treon et al, Blood 2021 (online)

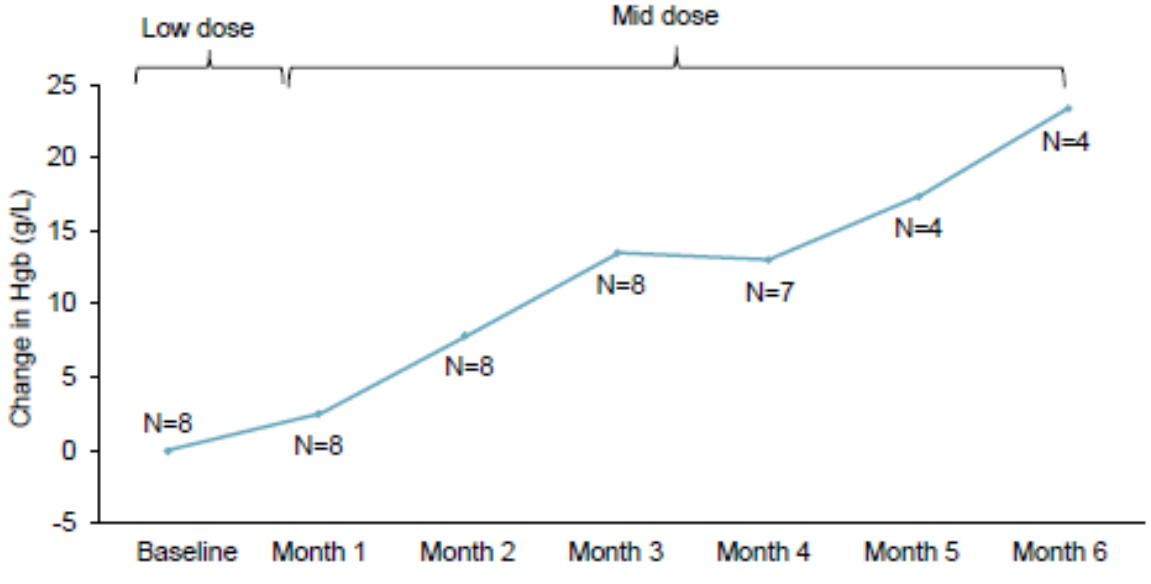
PRELIMINARY CLINICAL DATA FROM A PHASE 1B STUDY OF MAVORIXAFOR AND IBRUTINIB IN PATIENTS WITH WALDENSTRÖM'S MACROGLOBULINEMIA WITH MYD88 AND CXCR4 MUTATIONS



sIGM



Hemoglobin



Treon et al, EHA 2021 Abstract EP784

Acquired Resistance in WM Patients on Ibrutinib

Targeted next-generation sequencing for MYD88, CXCR4, BTK, PLCG2, CARD11, LYN.

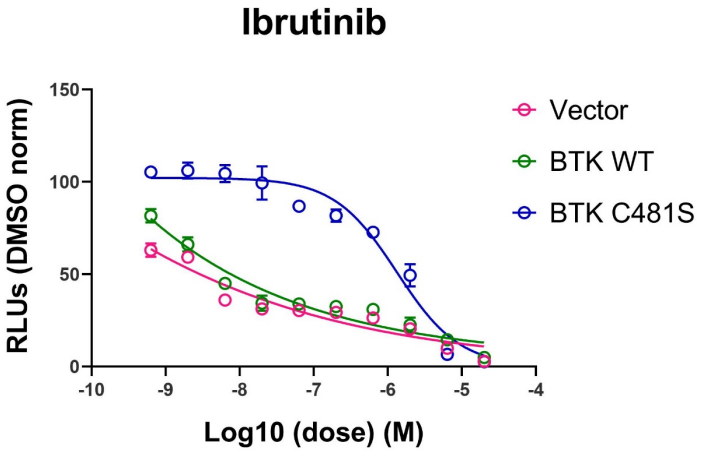
Patient*	L265P positive cells with BTK C481R$^{T>C}$	L265P positive cells with BTK C481S$^{T>A}$	L265P positive cells with BTK C481S$^{G>C}$	L265P positive cells with BTK C481Y$^{G>A}$	L265P positive cells with PLCG2 Y495H$^{T>C}$	L265P positive cells with CARD11 L878F$^{C>T}$
WM1	None	None	None	None	None	None
WM2	**32.4%**	**6.6%**	**5.8%**	**1.0%**	None	None
WM3	**0.3%**	**34.4%**	**6.5%**	**0.3%**	None	**0.2%**
WM4	None	None	None	None	None	None
WM5	None	None	None	None	None	None
WM6	None	None	**10.3%**	None	**11.9%**	None

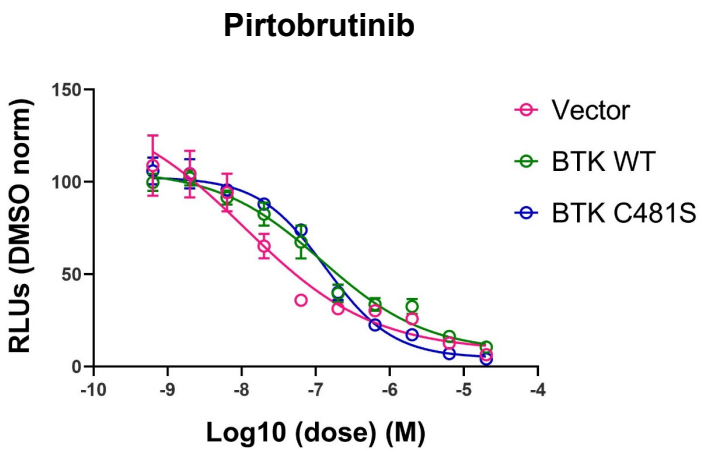
All patients were MYD88 mutated. WM2, WM3, WM6 are CXCR4 WHIM mutated.

Xu et al, Blood 2017

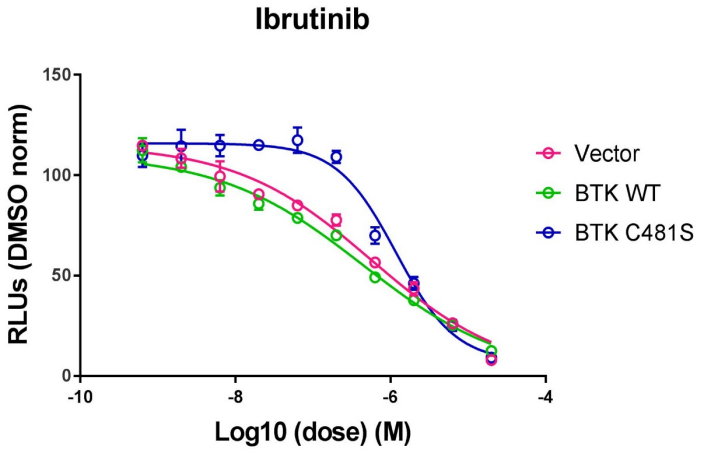
Pirtobrutinib Overcomes Ibrutinib Resistance Caused by BTK^{Cys481Ser}

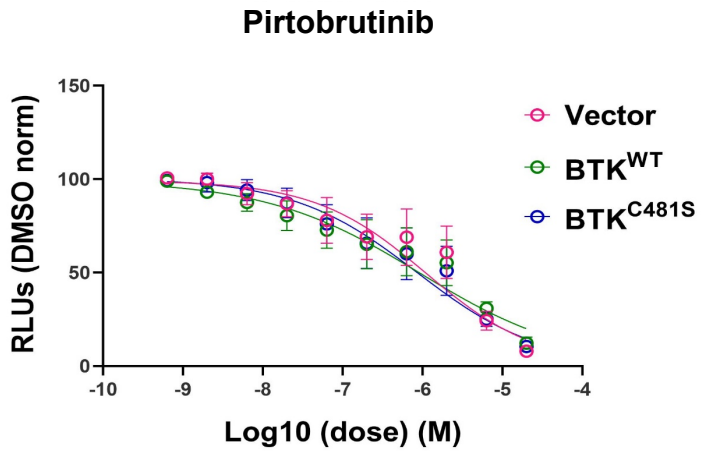
TMD8





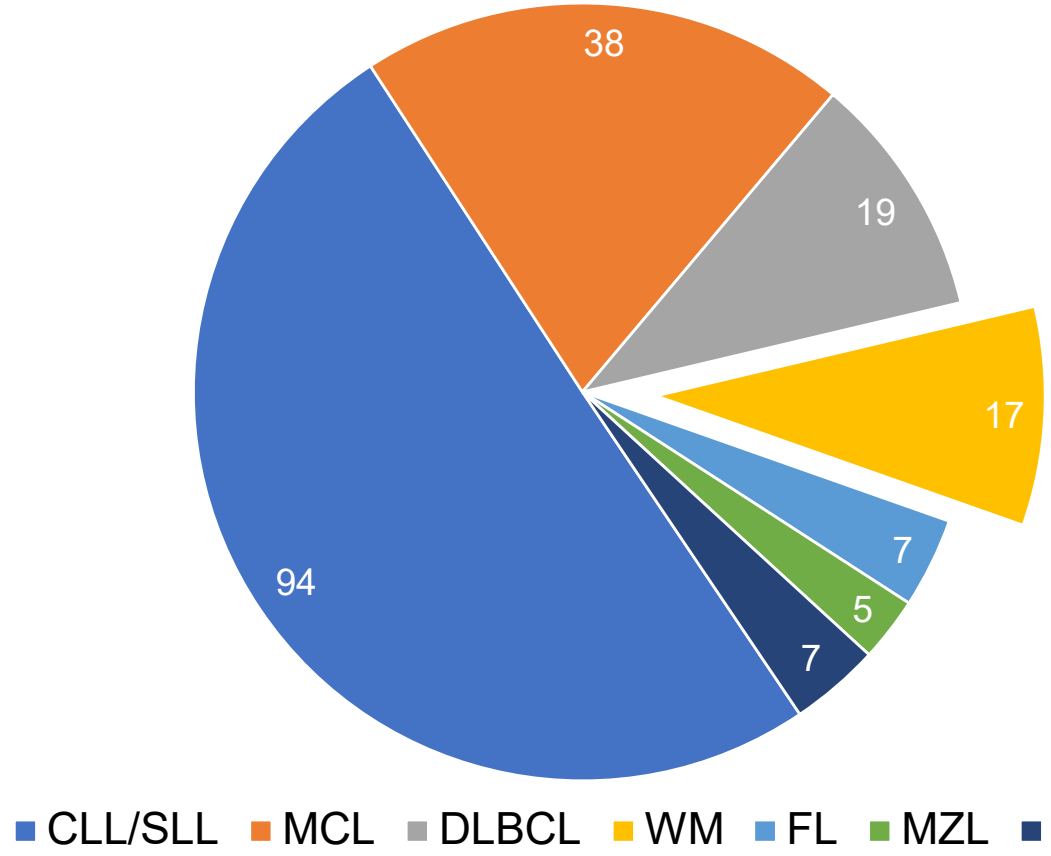
BCWM.1





Munshi et al, ASH 2021 (submitted)

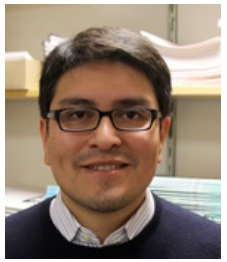
LOXO-305, A Next Generation, Highly Selective, Non-Covalent BTK Inhibitor in Previously Treated Mantle Cell Lymphoma, Waldenström's Macroglobulinemia, and Other Non-Hodgkin Lymphomas: Results from the Phase 1/2 BRUIN Study



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

Wang et al. ASH 2020

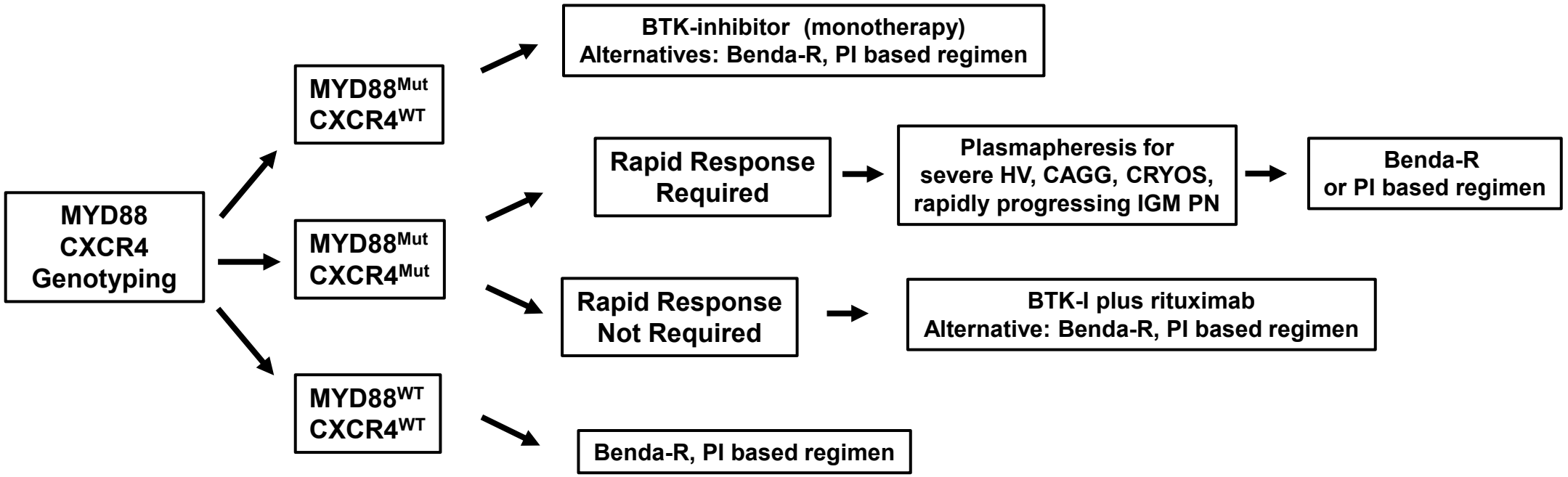
Trial Design



Jorge Castillo, PI (DFCI)

- 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.

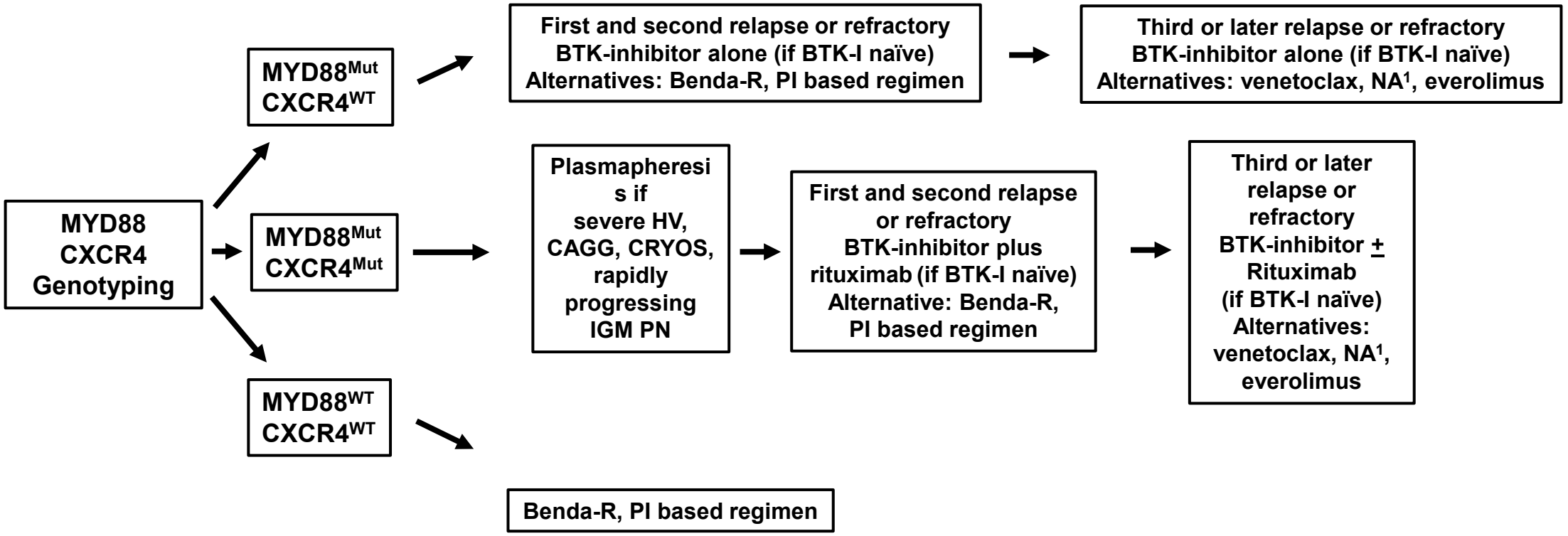
Genomic Based Treatment Approach to Symptomatic Treatment Naïve WM



- Rituximab should be held for serum IgM ≥4,000 mg/dL
- Benda-R for bulky adenopathy or extramedullary disease.
- PI 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 patients responding to rituximab based regimens.

Treon et al, JCO 2020; 38:1198-1208

Genomic Based Treatment Approach to Symptomatic Relapsed or Refractory WM



- **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.**

Treon et al, JCO 2020; 38:1198-1208