Waldenström's Macroglobulinemia: Treatment Approach

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Primary Therapy of WM with Rituximab

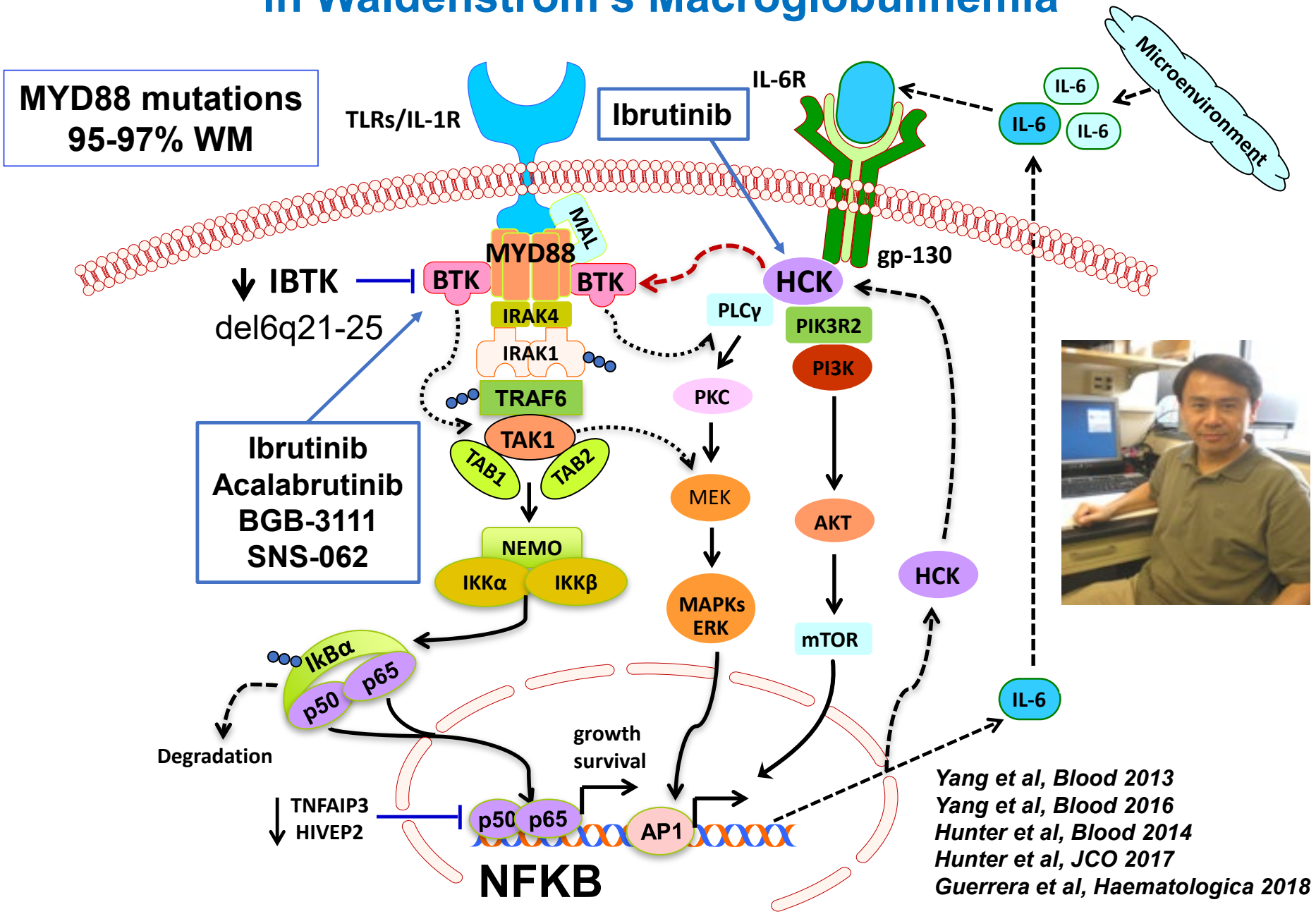
Regimen	ORR	VGPR/CR	TTP (mo)
Rituximab x 4	25-30%	0-5%	13
Rituximab x 8	40-45%	5-10%	16-22
Rituximab/thalidomide	70%	10%	30
Rituximab/cyclophosphamide i.e. CHOP-R, CVP-R, CPR, CDR	70-80%	20-25%	30-36
Rituximab/nucleoside analogues i.e. FR, FCR, CDA-R	70-90%	20-30%	36-62
Rituximab/Proteasome Inhibitor i.e. BDR, VR, CaRD	70-90%	20-40%	42-66
Rituximab/bendamustine	90%	30-40%	69

Reviewed in Dimopoulos et al, Blood 2014; 124(9):1404-11; Treon et al, Blood 2015; How I Treat WM

WM–centric toxicities with commonly used therapies

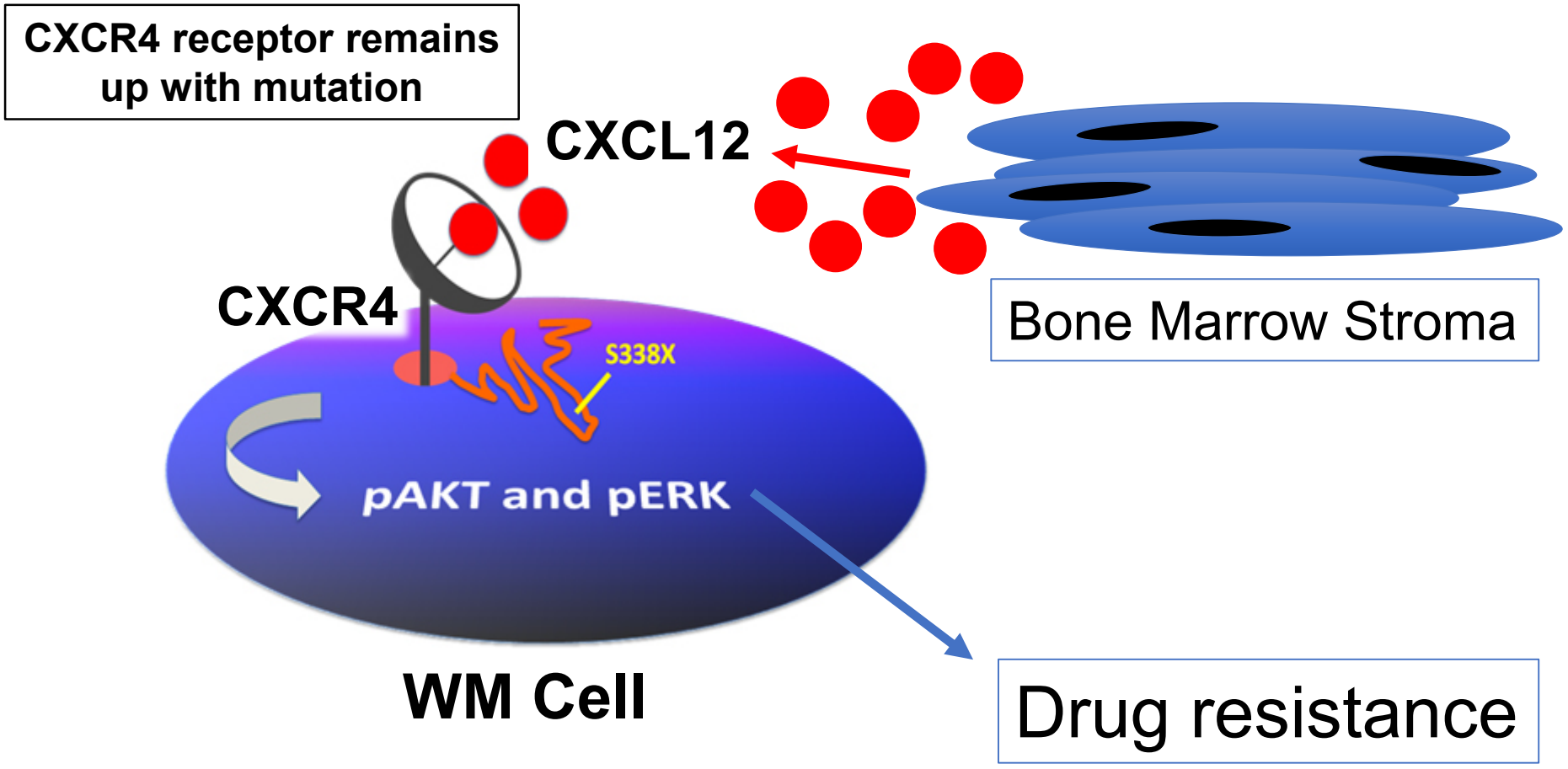
Agent	WM Toxicities
Rituximab	• **IgM flare (40-60%)->** Hyperiscosity crisis, Aggravation of IgM related PN, CAGG, Cryos. • Hypogammaglobulinemia-> infections, IVIG • Intolerance (10-15%)
Fludarabine	• Hypogammaglobulinemia-> infections, IVIG • **Transformation, AML/MDS (15%)**
Bendamustine	• Prolonged neutropenia, thrombocytopenia (especially after fludarabine) • **AML/MDS (5-8%)**
Bortezomib	• **Grade 2+3 Peripheral neuropathy (60-70%);** High discontinuation (20-60%)

Pro-Survival Signaling Driven by Mutated MYD88 in Waldenström's Macroglobulinemia



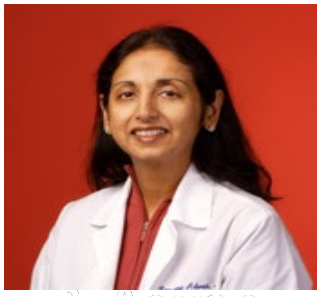
Yang et al, Blood 2013
Yang et al, Blood 2016
Hunter et al, Blood 2014
Hunter et al, JCO 2017
Guerrera et al, Haematologica 2018

Mutations in CXCR4 permit ongoing pro-survival signaling by CXCL12, the ligand for CXCR4 receptor.



CXCR4 mutations in 30-40% WM

Multicenter study of Ibrutinib in Relapsed/Refractory WM (≥1 prior therapy)



Screening

Registration

420 mg po qD Ibrutinib

Progressive Disease (PD) or Unacceptable Toxicity

Stop Ibrutinib

Event Monitoring

Stable Disease or Response Continue

Event Monitoring

✔ **MYD88, CXCR4 Mutation Status**

NCT01614821

Responses to ibrutinib are impacted by MYD88 (L265P and non-L265P) and CXCR4 mutations.

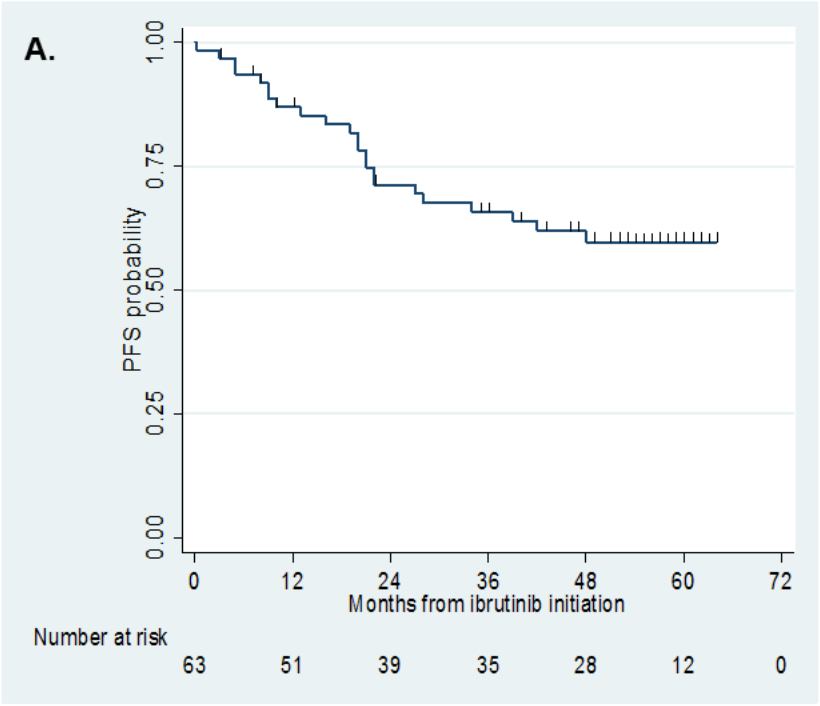
	ALL	$MYD88^{Mut}$ $CXCR4^{WT}$	$MYD88^{Mut}$ $CXCR4^{Mut}$	$MYD88^{WT}$ $CXCR4^{WT}$	P-value
N=	63	36	21	5*	
ORR	91%	100%	85.7%	60%	0.005
Major (>PR)	78%	97%	67%	0%	<0.001
VGPR	29%	44%	10%	0%	0.007
Time to Minor Response (mos.)	1.0	1.0	1.0	1.0	0.10
Time to Major response (mos.)	2.0	2.0	6.0	N/A	0.05

*2 patients at initial reporting with major responses were discovered subsequently to have MYD88 mutated disease (S243N, L265P). One patient at initial reporting was subsequently found to CXCR4 mutated disease upon genotyping of CD19-selected WM cells.

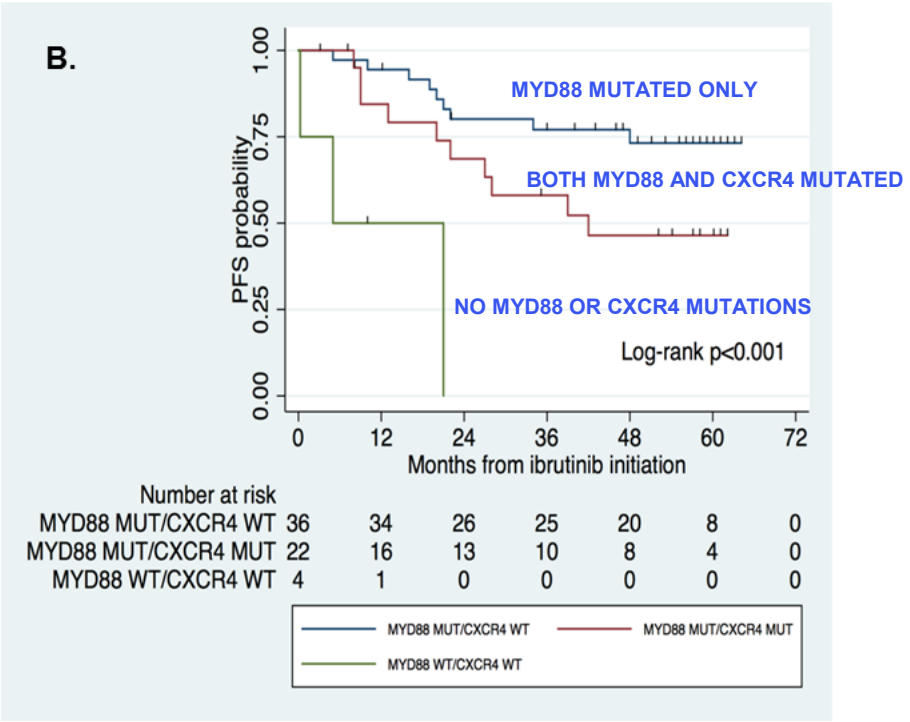
Treon et al, EHA 2018

Ibrutinib in Previously Treated WM: Updated PFS

All patients



MYD88 and CXCR4 Status

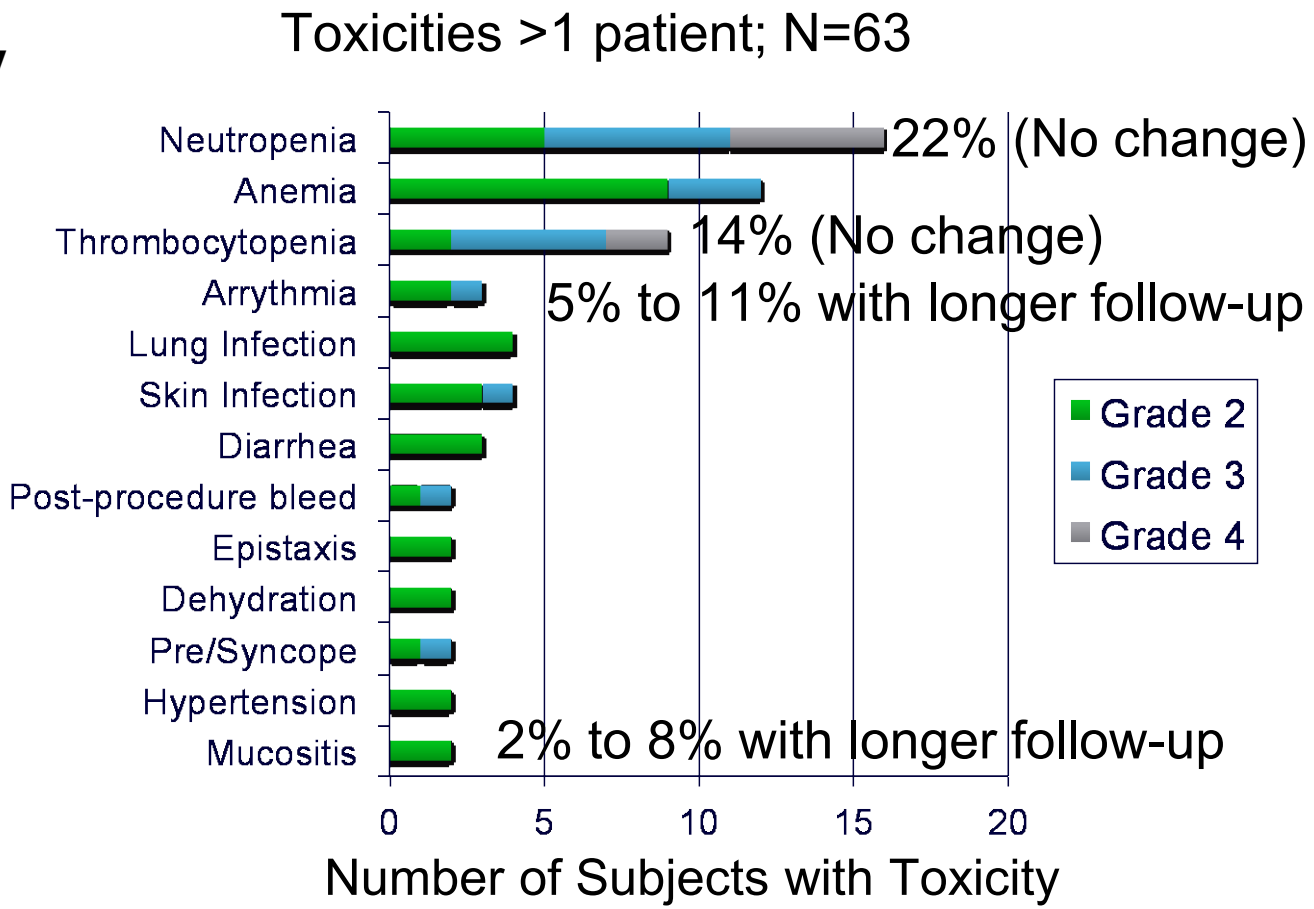


5 year PFS: 60% (95% CI 46-71%).

Treon et al, EHA 2018

Ibrutinib Related Adverse Events in previously treated WM patients

Original Study

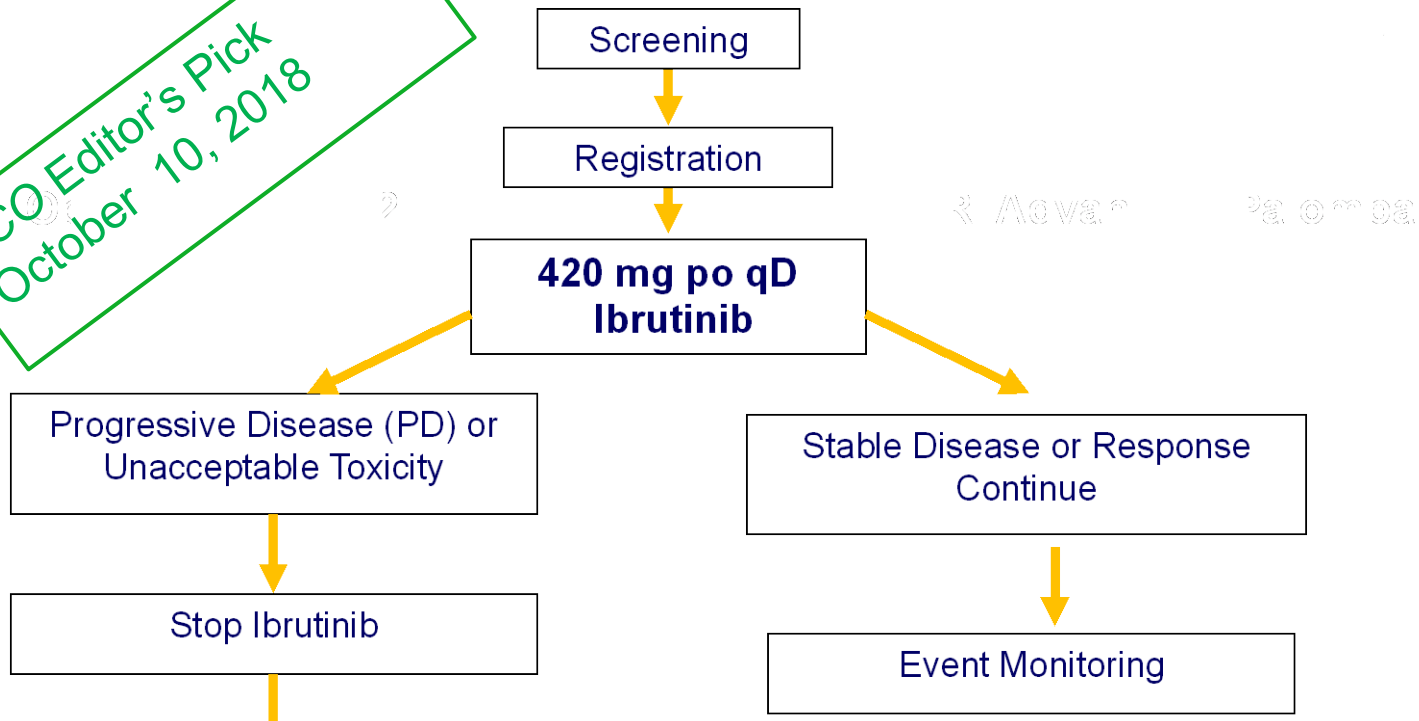


Update on Adverse Events (Grade ≥2) in ≥5% of patients: Neutropenia (22%); Thrombocytopenia (14%), Pneumonia (9%); GERD (8%); Hypertension (8%); anemia (6%); and skin infection (5%). Seven patients (11%) had atrial arrhythmia [Grade 1 (n=1); Grade 2 (n=5); Grade 3 (n=1)], and 6 continued ibrutinib following medical management.

Treon et al, EHA 2018

Ibrutinib Monotherapy in Symptomatic Treatment Naive WM

JCO Editor's Pick
October 10, 2018



✔ **MYD88, CXCR4 Mutation Status**

NCT02604511

Treon et al, JCO 2018

Time to and depth of response to ibrutinib are impacted by CXCR4 mutations.

	All Patients	MYD88^{MUT} CXCR4^{WT}	MYD88^{MUT} CXCR4^{MUT}	P-value
N=	30	16	14	N/A
Overall Response Rate-no. (%)	30 (100%)	16 (100%)	14 (100%)	1.00
Major Response Rate-no. (%)	25 (83%)	15 (94%)	10 (71%)	0.16
Categorical responses				
Minor responses-no. (%)	5 (17%)	1 (6%)	4 (29%)	0.16
Partial responses-no. (%)	19 (63%)	10 (63%)	9 (64%)	1.00
Very good partial responses-no. (%)	6 (20%)	5 (31%)	1 (7%)	0.18
Median time to response (months)				
Minor response (≥Minor response)	1.0	0.9	1.7	0.07
Major response (≥Partial response)	1.9	1.8	7.3	0.01

Data cutoff: Jan. 22, 2018

Median f/u: 14.6 (range 1.8-21.6 months)

Treon et al, JCO 2018

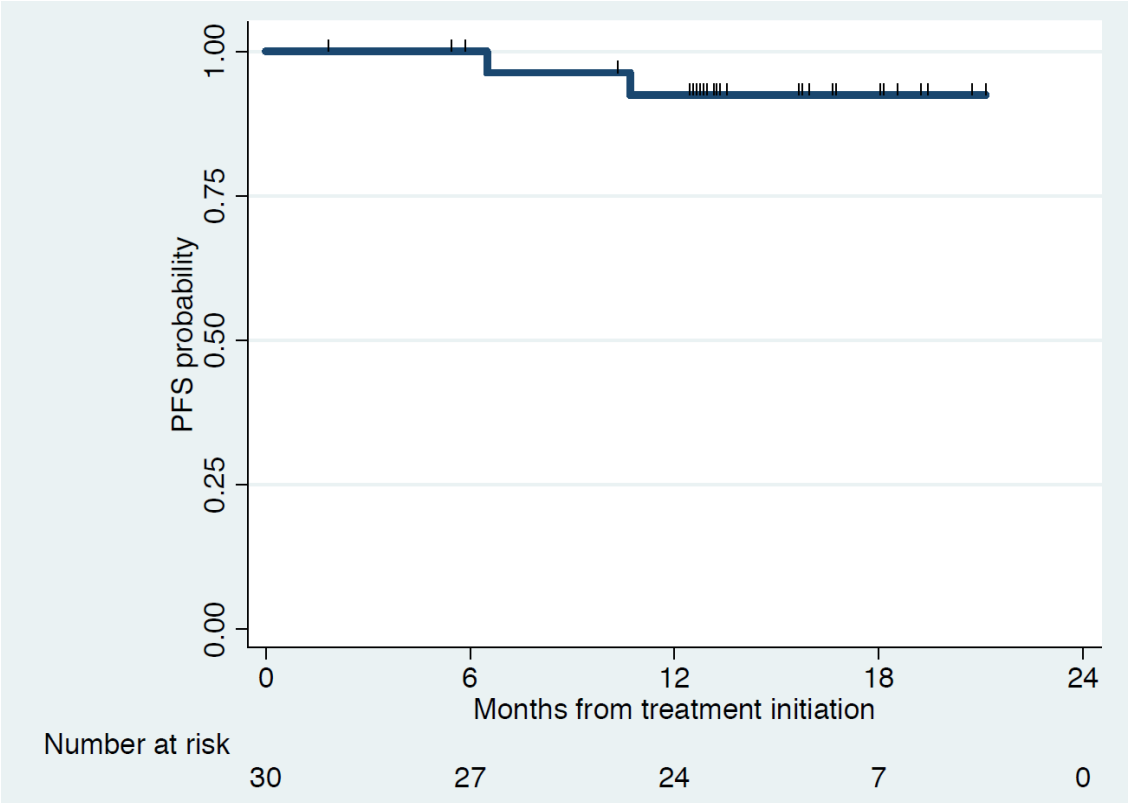
Adverse Events (≥5%)

Event or Abnormality	Grade 2	Grade 3	Grade 4	Total Grades 2-4
Arthralgia	2 (7%)	0 (0%)	0 (0%)	2 (7%)
Atrial fibrillation	3 (10%)	0 (0%)	0 (0%)	3 (10%)
Bruising	2 (7%)	0 (0%)	0 (0%)	2 (7%)
Hypertension	2 (7%)	2 (7%)	0 (0%)	4 (13%)
Neutropenia	2 (7%)	0 (0%)	0 (0%)	2 (7%)
Upper respiratory infection	2 (7%)	0 (0%)	0 (0%)	2 (7%)
Urinary tract infection	2 (7%)	0 (0%)	0 (0%)	2 (7%)

- Minimal hematological toxicity
- Median serum IgA levels decreased from 62 to 39 mg/dL; p=0.04
- Median serum IgG levels declined from 563 to 462; p=0.003
- Afib medically managed in 2 patients who continue on treatment; cardiac ablation for one patient with left atrial enlargement off treatment.

Treon et al, JCO 2018

Ibrutinib Monotherapy in Frontline WM: PFS



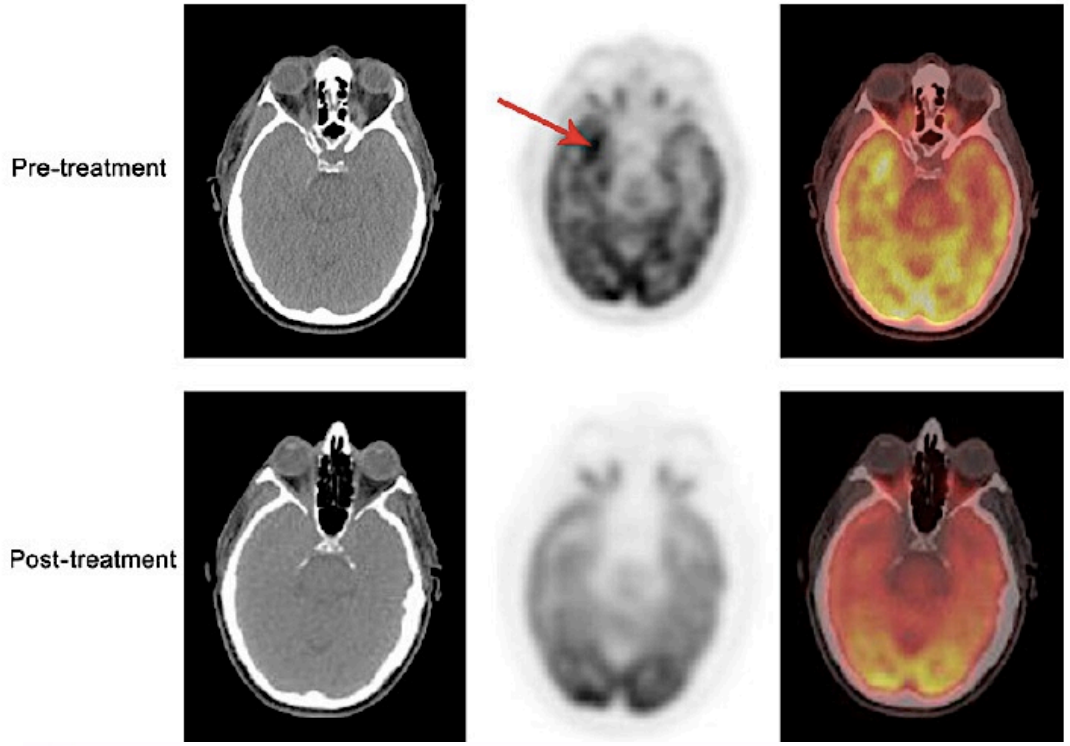
18 mo: PFS 92%;
All patients alive.

PD patients were both CXCR4 mutated.

Data cutoff: Jan. 22, 2018 Median f/u: 14.6 (range 1.8-21.6 months)

Treon et al, JCO 2018

Ibrutinib (560 mg/day) induced response in a WM patient with Bing Neel Syndrome



Study Day	Time post-dose (h)	Ibrutinib (nM)		
		CSF	Plasma	%CSF/Plasma
Day 1	0	BLQ	BLQ	NA
	2	34	1133	3·0
1 Month	3	16	463	3·5
4 Months	2·5	7	318	2·2

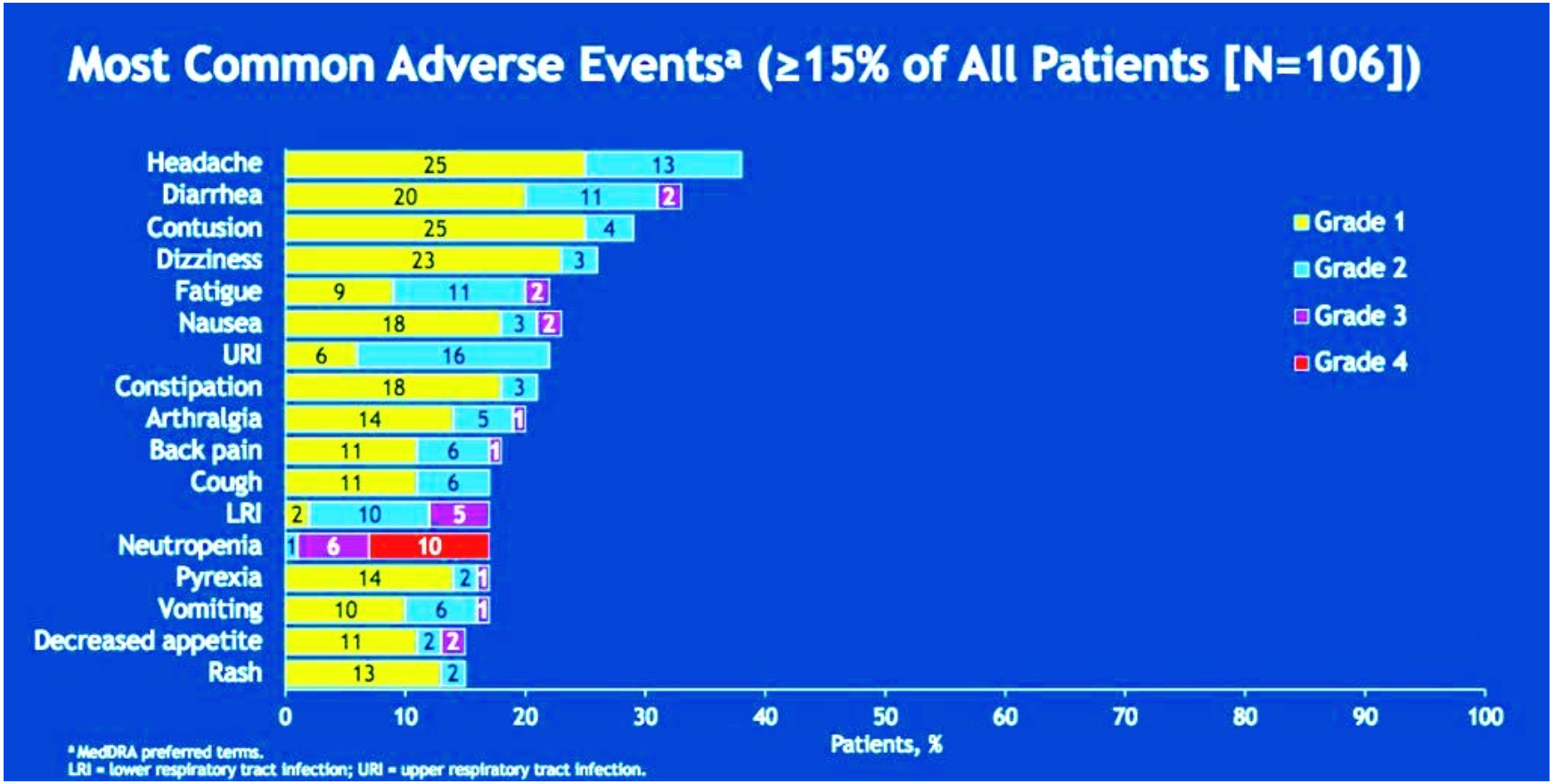
Mason et al, BJH 2016

Acalabrutinib (ACP-196) in Treatment Naïve and Previously Treated WM

	TN (n=14)	R/R (n=92)
ORR (≥ minor response [MR]), n (%)	13 (93)	86 (94)
95% CI	66, 100	86, 98
Major response rate (≥ partial response [PR])	11 (79)	72 (78)
95% CI	49, 95	68, 86
Complete response	0	0
Very good PR	1 (7)	29 (32)
PR	10 (71)	43 (47)
MR	2 (14)	14 (15)
24-mo rate, % (95% CI)		
DOR	90 (47, 99)	84 (73, 90)
PFS	90 (47, 99)	82 (72, 88)
OS	92 (54, 99)	89 (80, 94)

Owen et al, ASCO 2018; EHA 2018

Acalabrutinib in WM



Atrial fibrillation occurred in 3 pts (1 Gr 3). Bleeding events occurred in 57% of pts; 4 events were Gr 3/4: There were 5 Gr 5 events: pneumonia, glioblastoma multiforme, esophageal carcinoma, myocardial ischemia, and intracranial hematoma.

Owen et al, ASCO 2018; EHA 2018

Zanubrutinib in WM

Best response, n (%)	OVERALL (n=51)	By *MYD88* Status			
		MYD88^{L265P}/ *CXCR4*^{WT} (n=25)	*MYD88*^{L265P}/ *CXCR4*^{WHIM} (n=5)	*MYD88*^{WT} (n=6)	Unknown Status (n=15)
ORR	47 (92)	23 (92)	5 (100)	5 (83)	14 (93)
MRR	41 (80)	21 (84)	4 (80)	3 (50)	13 (87)
VGPR	**22 (43)**	**14 (56)**	**2 (40)**	**1 (17)**	**5 (33)**
PR	19 (37)	7 (28)	2 (40)	2 (33)	8 (53)
MR	6 (12)	2 (8)	1 (20)	2 (33)	1 (7)
SD	4 (8)	2 (8)	0	1 (17)	1 (7)

Phase I/II Data
51 patients out of 67 evaluable for efficacy
Genotyping unknown for many patients
91% PFS at 1 year

Trotman et al, EHA 2018

Zanubrutinib in WM

Adverse Event	N=67		Adverse Event	N=67	
	All Gr %	Gr 3-4 %		All Gr %	Gr 3-4 %
Petechiae/purpura/ contusion	37		Gastroesophageal reflex disease	10	
Upper respiratory tract infection	34		Neutropenia	10	6.0
Constipation	18		Rash	10	
Diarrhea	18	1.5	Basal cell carcinoma	9.0	3.0
Cough	13		Hypertension	9.0	3.0
Anemia	12	7.5	Squamous cell carcinoma	6.0	3.0
Back pain	12	3.0	**Atrial fibrillation/flutter**	6.0	
Epistaxis	12		Pyrexia	4.5	3.0
Headache	12	1.5	Pneumonia	4.5	3.0
Nausea	12		Actinic keratosis	4.5	3.0
Urinary track infection	12		**Major hemorrhage***	**3.0**	**3.0**

Trotman et al, EHA 2018

iNNOVATE Study in WM

Treatment Naïve + Previously Treated

45 centers in 9 countries

1:1 Randomization
N = 150

ARM A: ibrutinib 420mg
+ Rituximab 375mg/m² x 8 infusions
(weeks 1,2,3,4,17,18,19, and 20)

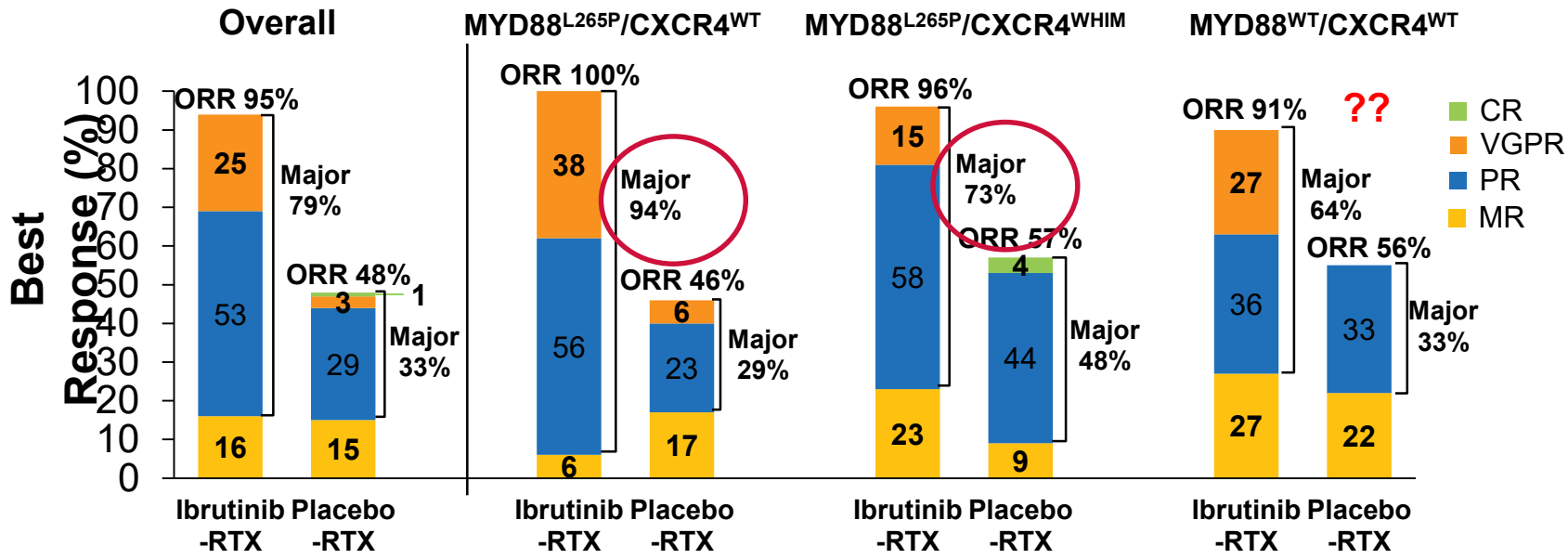
ARM B: Placebo
+ Rituximab 375mg/m² x 8 infusions
(weeks 1,2,3,4,17,18,19, and 20)

N=31

ARM C: ibrutinib 420mg
Subjects considered
refractory to prior rituximab

ABC patients genotyped for MYD88 and CXCR4

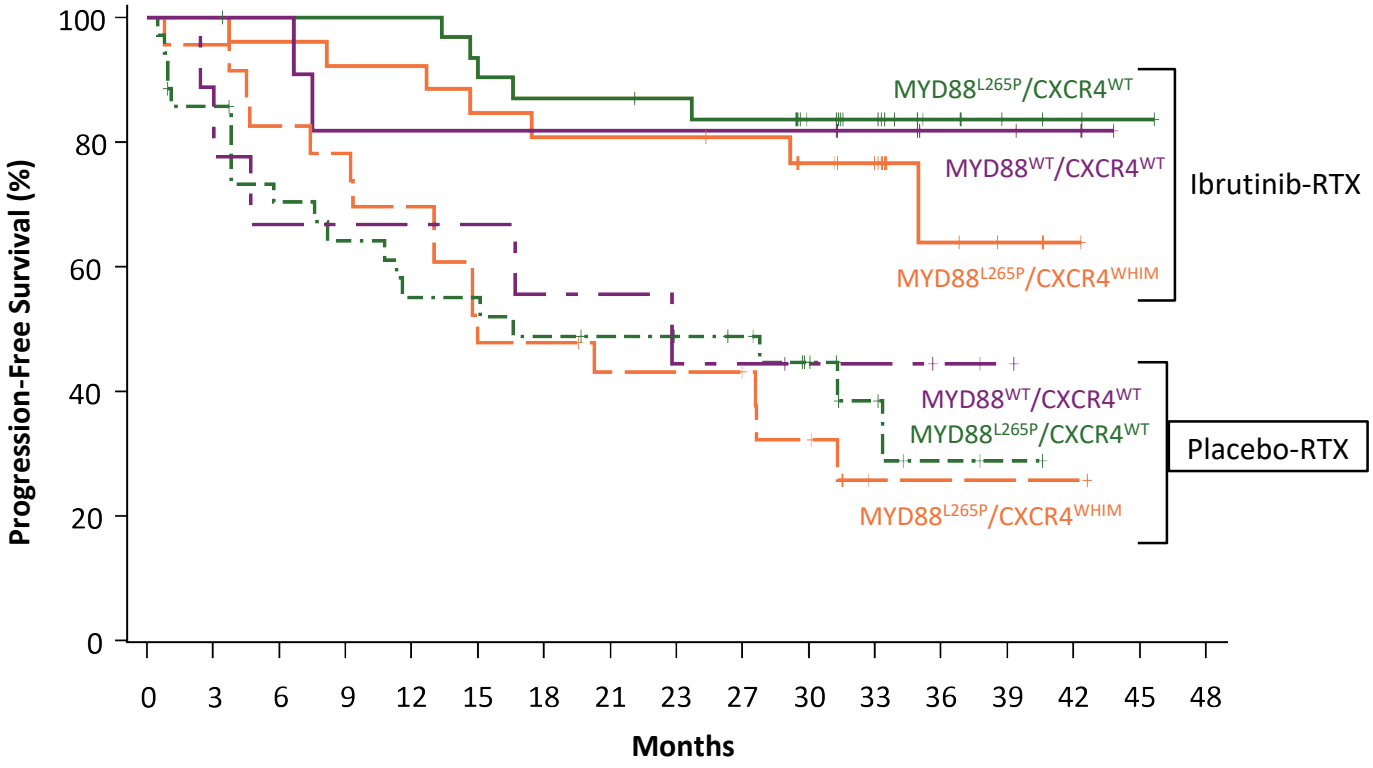
Responses in Innovate AB Study: Update



	Overall		MYD88L265P/CXCR4WT		MYD88L265P/CXCR4WHIM		MYD88WT/CXCR4WT	
	Ibrutinib -RTX	Placebo -RTX	Ibrutinib -RTX	Placebo -RTX	Ibrutinib -RTX	Placebo -RTX	Ibrutinib -RTX	Placebo -RTX
Median time to ≥PR, months (range)	2 (1–28)	6 (2–26)	2 (1–28)	5 (2–17)	3 (1–19)	11 (4–18)	6 (1–17)	6 (5–26)
Median time to ≥MR, months (range)	1 (1–18)	3 (1–24)	1 (1–18)	3 (1–24)	1 (1–11)	3 (1–8)	2 (1-17)	3 (2–17)

Busket et al, ASH 2018

Progression-Free Survival Benefit With Ibrutinib-RTX Independent of MYD88/CXCR4 Genotype



- **Improved PFS across all genotypes with ibrutinib-RTX**
- **36-month PFS rates**
  - **$MYD88^{L265P}/CXCR4^{WT}$: 84% vs 29%**
  - **$MYD88^{L265P}/CXCR4^{WHIM}$: 64% vs 26%**
  - **$MYD88^{WT}/CXCR4^{WT}$: 82% vs 44%**

Innovate AB Data: Busket et al, ASH 2018.

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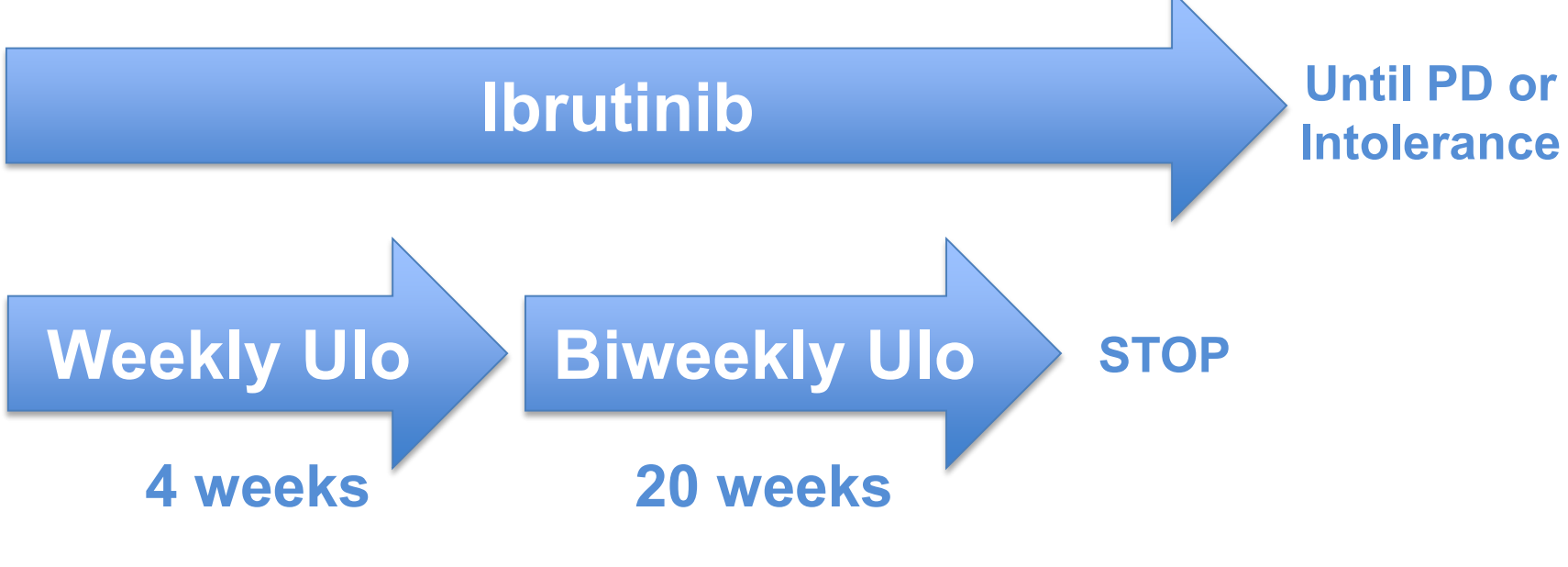
fighting blood cancers

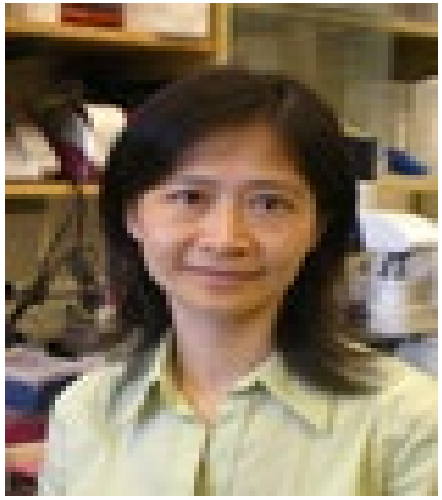
Phase I/II Trial of Ulocuplumab and Ibrutinib in CXCR4 mutated patients with symptomatic WM

Schema

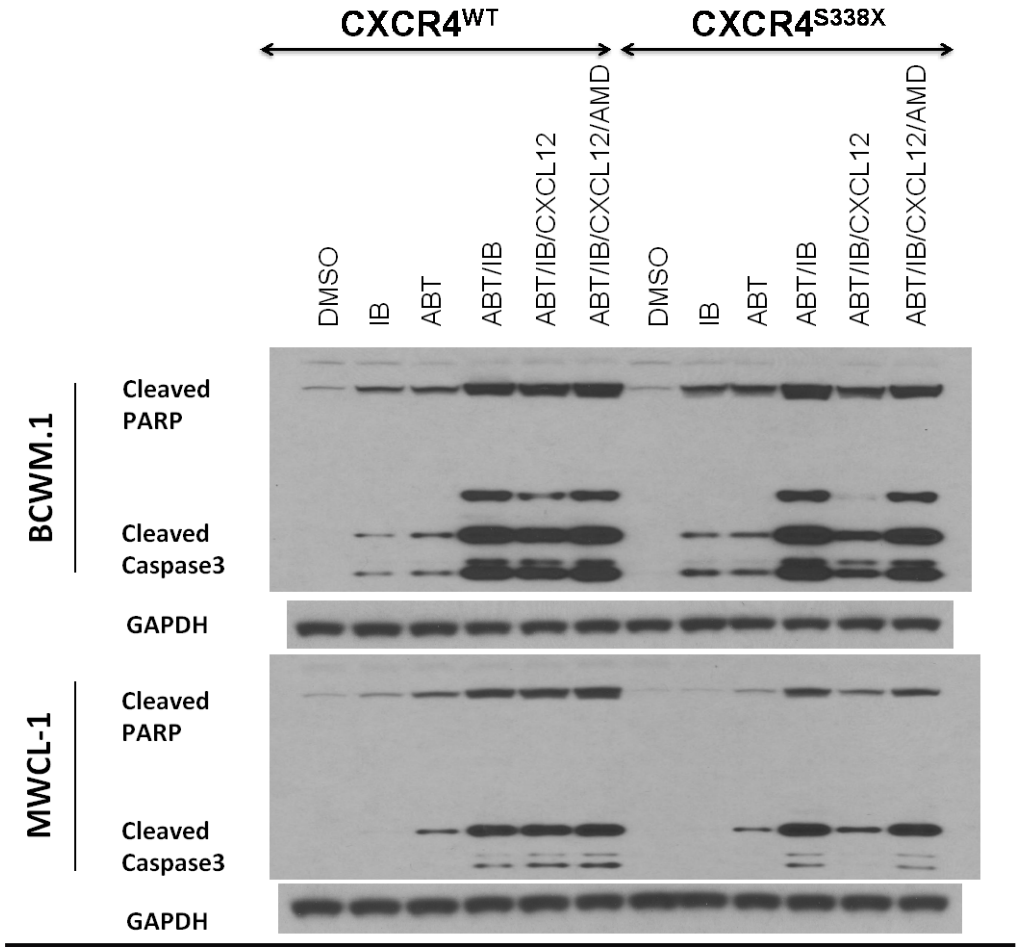


Dose Level	Ibrutinib	Ulocuplumab Cycle 1	Ulocuplumab Cycles 2-6
Level 1 –Starting dose	420mg PO DQ	400 mg weekly	800 mg every other week
Level 2	420mg PO DQ	800 mg weekly	1200 mg every other week
Level 3	420mg PO DQ	800 mg weekly	1600 mg every other week

ClinicalTrials.gov Identifier: NCT03



Venetoclax (ABT-199) impacted by CXCR4 mutation



Cao et al, BJH 2015

Phase II Study of Venetoclax in Previously Treated WM

Selected inclusion criteria:

- Clinicopathological diagnosis of WM
- Serum IgM >2 x ULN
- Previously treated
- Age ≥18 years
- Good performance
- Normal organ and marrow function

Selected exclusion criteria:

- Serious medical condition
- Concurrent anti-cancer agent
- Known CNS lymphoma
- Active HIV, HBV, HCV infection
- Lactating or pregnant women

Screening

↓

Informed Consent and Registration

↓

Venetoclax
200 mg PO QD
↓
800 mg PO QD

Progressive Disease or Unacceptable Toxicity → Stop ABT-199

SD or Response → Continue for 2 years → Event Monitoring

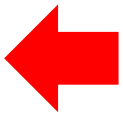
www.clinicaltrials.gov: NCT02677324

Castillo et al. EHA 2018

Phase II Study of Venetoclax in Previously Treated WM

Baseline characteristics

Characteristic	Number (%)
Age, years	66 (39-80)
Male sex	17 (57%)
Previous treatments	2 (1-10)
Prior BTK inhibitors	15 (50%)
MYD88 L265P	30 (100%)
CXCR4 mutations	16 (53%)
Serum IgM level (mg/dl)	3,543 (642-7,970)
Hemoglobin level (g/dl)	10.6 (6.4-13.5)
Platelet count (K/ul)	222 (7-445)
Lymphadenopathy	9 (30%)
Splenomegaly	6 (20%)



Castillo et al. EHA 2018

Phase II Study of Venetoclax in Previously Treated WM

Response	No prior ibrutinib (n=15)	Prior ibrutinib (n=15)	CXCR4 WT (n=14)	CXCR4 MUT (n=16)
Overall	14 (93%)	12 (80%)	12 (86%)	14 (87%)
Major	13 (87%)	9 (60%)	9 (86%)	13 (63%)
Very good	4 (27%)	1 (7%)	4 (29%)	1 (7%)
Partial	9 (60%)	8 (53%)	8 (57%)	9 (56%)
Minor	1 (7%)	3 (20%)	0 (0%)	4 (25%)
Stable	1 (7%)	3 (20%)	2 (14%)	2 (13%)

Median follow-up: 11 months

1 patient had progressive disease at 9 months (MYD88, CXCR4, TP53)

Castillo et al. EHA 2018

Phase II Study of Venetoclax in Previously Treated WM

Adverse Event, N (%)	Grade 1	Grade 2	Grade 3	Grade 4	All Grades
Neutropenia	2 (7)	4 (14)	6 (21)	3 (10)	15 (52)
Anemia	1 (3)	5 (17)	2 (7)	0	8 (28)
URI	2 (7)	0	1 (3)	0	3 (10)
Nausea	9 (31)	4 (14)	0	0	13 (48)
Headache	2 (7)	3 (10)	0	0	5 (17)
diarrhea	4 (14)	1 (3)	0	0	5 (17)
Chills	2 (7)	1 (3)	0	0	3 (10)
Constipation	2 (7)	1 (3)	0	0	3 (10)
Mucositis oral	2 (7)	1 (3)	0	0	3 (10)
Muscle Cramps	1 (3)	1 (3)	0	0	2 (7)

Laboratory TLS (n=1). No IgM flare. No deaths.

Castillo et al. EHA 2018

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)

Approach to Frontline Therapy of Symptomatic WM

Hyperviscosity, Severe Cryos, CAGG, PN➔ Plasmapheresis

MYD88 Mutated/No CXCR4 mutation

No bulky disease, no contraindications➔ Ibrutinib (if available)

Bulky disease ➔ Benda-R +Ibrutinib and Rituximab

Amyloidosis ➔ Bortezomib/Dex/Rituximab (BDR)

IgM Peripheral Neuropathy ➔ Rituximab ± Alkylator

MYD88 Mutated/CXCR4 mutation +Ibrutinib and Rituximab

Same caveats as above

If immediate response needed, either BDR or Benda-R

MYD88 Wild-Type

✓non-L265P MYD88 mutations

BDR > Benda-R

- **Hold Rituximab until IgM <4000 mg/dL or empiric pheresis is performed.**
- **Consider Maintenance Rituximab**
- **Consider Ofatumumab if R intolerant.**

Hunter et al, JCO 2017; LeBlond IWWM10

Salvage Therapy of Symptomatic WM

Consider repeat primary therapy if response >2 years

MYD88 Mutated/No CXCR4 mutation
Same caveats as primary therapy

+Venetoclax for pts previously exposed to IB

MYD88 Mutated/CXCR4 mutation
Same caveats as primary therapy
If immediate response needed, either BDR or Benda-R

MYD88 Wild-Type
Same caveats as primary therapy
✓non-L265P MYD88 mutations

- **Everolimus >2 prior therapies**
- **Nucleoside analogues (non-ASCT candidates)**
- **ASCT in multiple relapses, chemosensitive disease**

Hunter et al, JCO 2017