Turin, Sept 13-14, 2018

How I treat high risk Waldenström's Macroglobulinemia?

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The first difficulty!

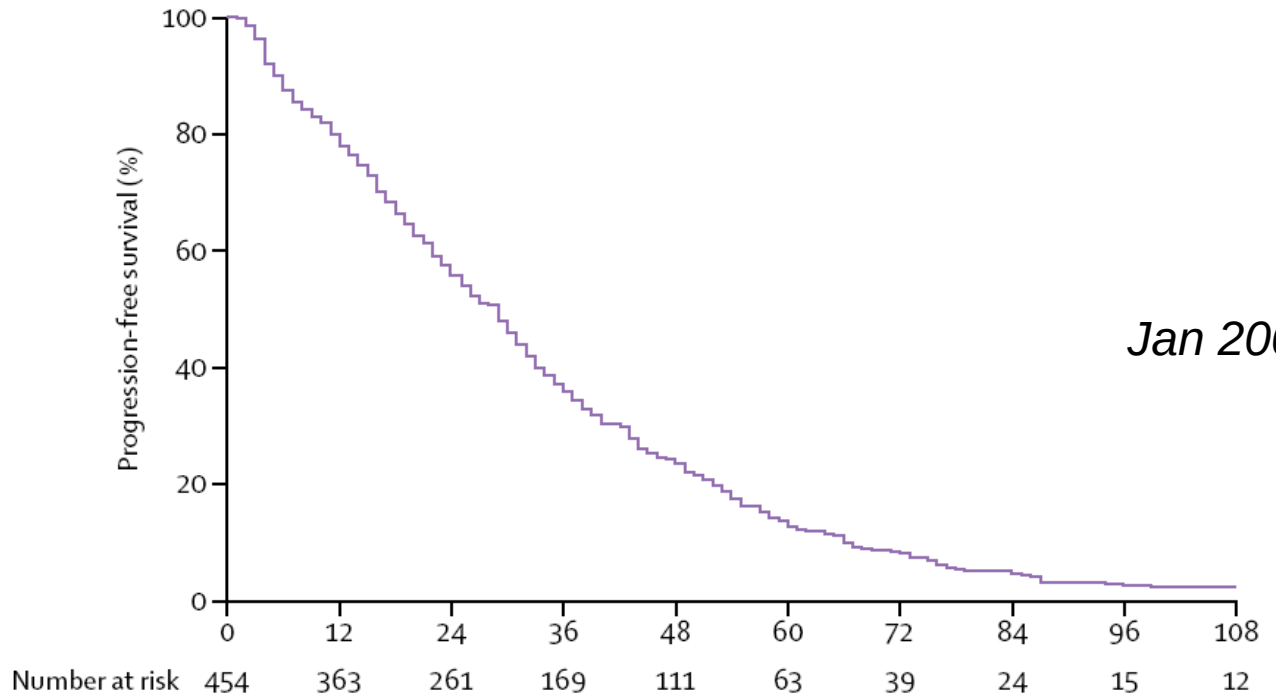
How to define high risk patients in WM!

What do we know……., WM is clinically a heterogenous disease

Treatment and outcome patterns in European patients with Waldenström's macroglobulinaemia: a large, observational, retrospective chart review

Christian Buske, Shalal Sadullah, Efstathios Kastritis, Alessandra Tedeschi, Ramón García-Sanz, Lukasz Bolkun, Xavier Leleu, Wolfgang Willenbacher, Roman Hájek, Monique C Minnema, Mei Cheng, Elizabeth Bilotti, Thorsten Graef, Meletios A Dimopoulos, on behalf of the European Consortium for Waldenström's Macroglobulinemia

PFS



Jan 2000 to Jan 2014

Lancet Haematol 2018; 5: e299–309

What do we know……., WM is clinically a heterogenous disease

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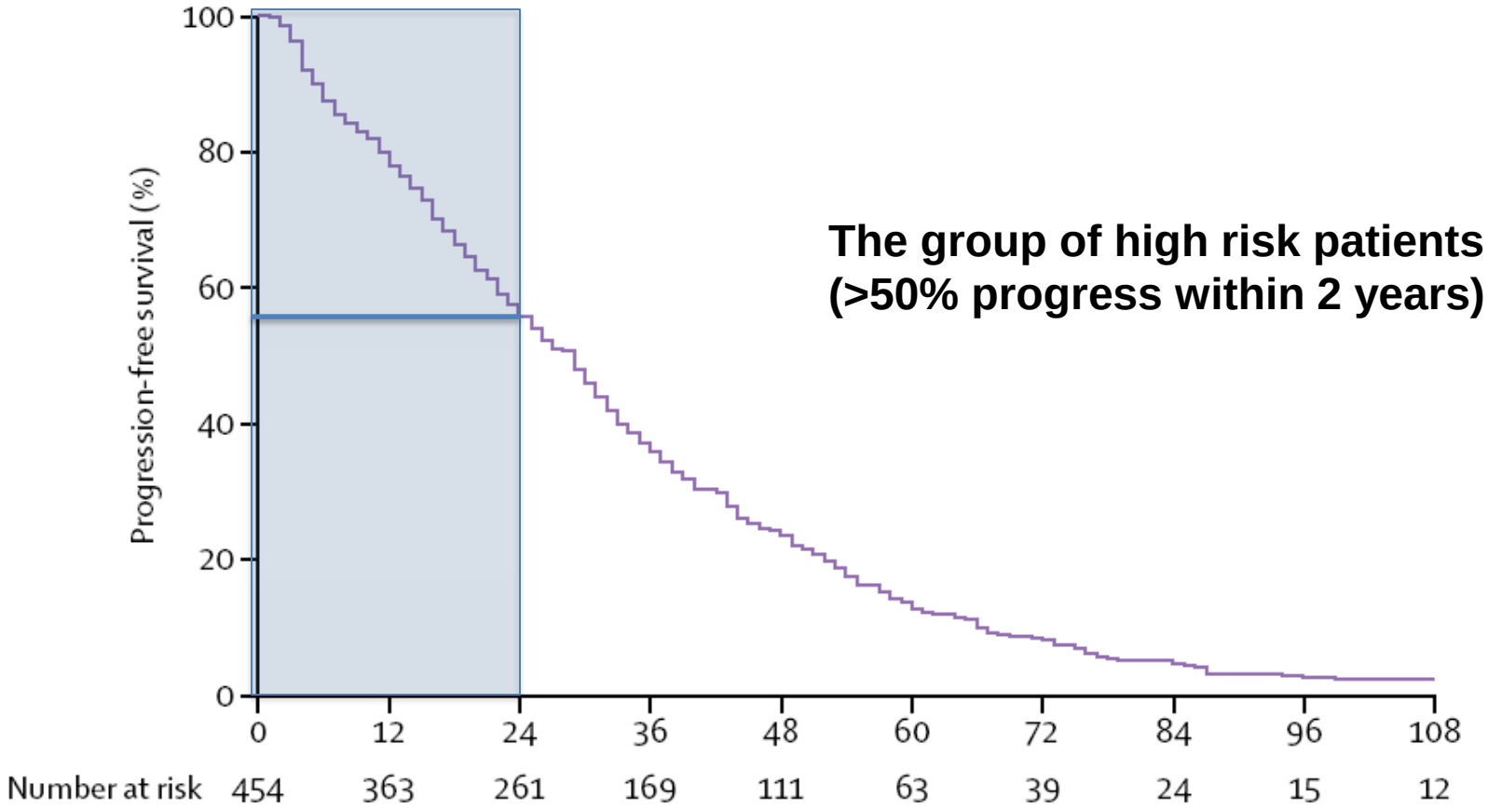

The group of high risk patients is not that small!
(>50% progress within 2 years)

Lancet Haematol 2018;
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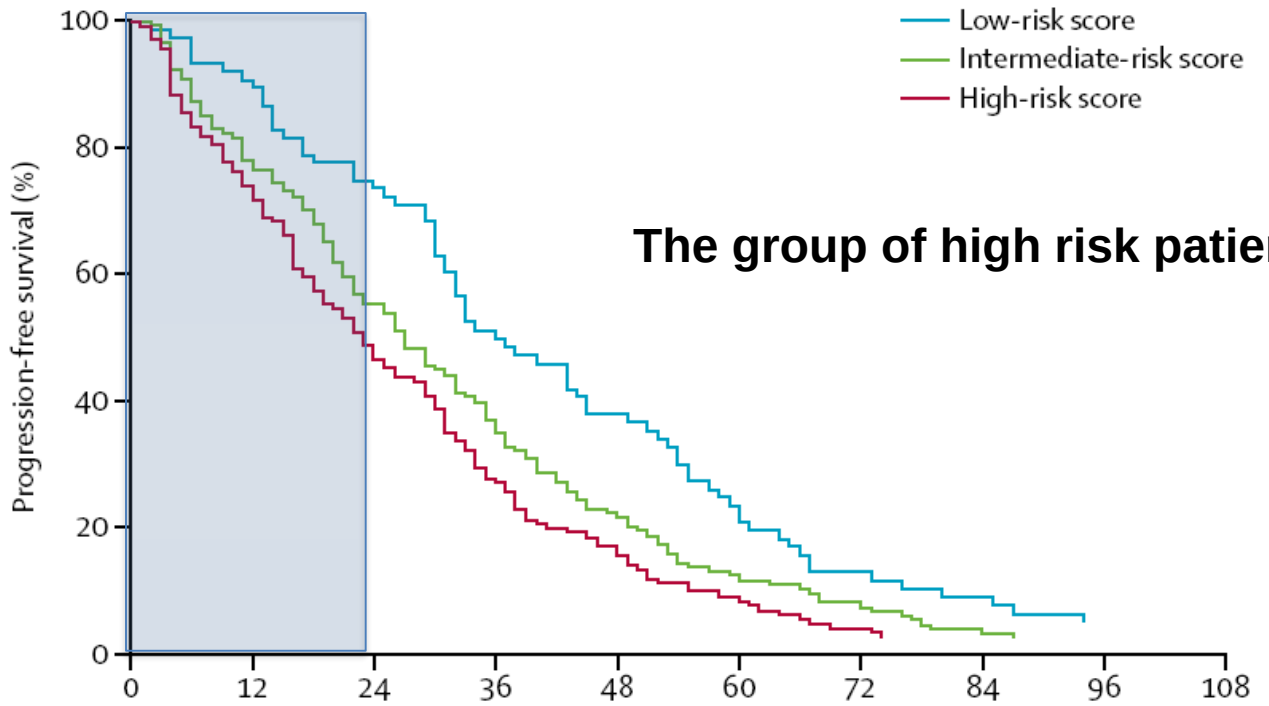
What do we know……., WM is clinically a heterogenous disease

PFS

ISSWM



The group of high risk patients is not that small!

Number at risk										
Low-risk score	76	69	57	39	29	18	10	7	.	..
Intermediate-risk score	142	111	79	53	32	18	12	6	..	..
High-risk score	139	103	68	39	24	13	6	..	..	..

Lancet Haematol 2018; 5: e299–309

What do we know……., WM is clinically a heterogenous disease

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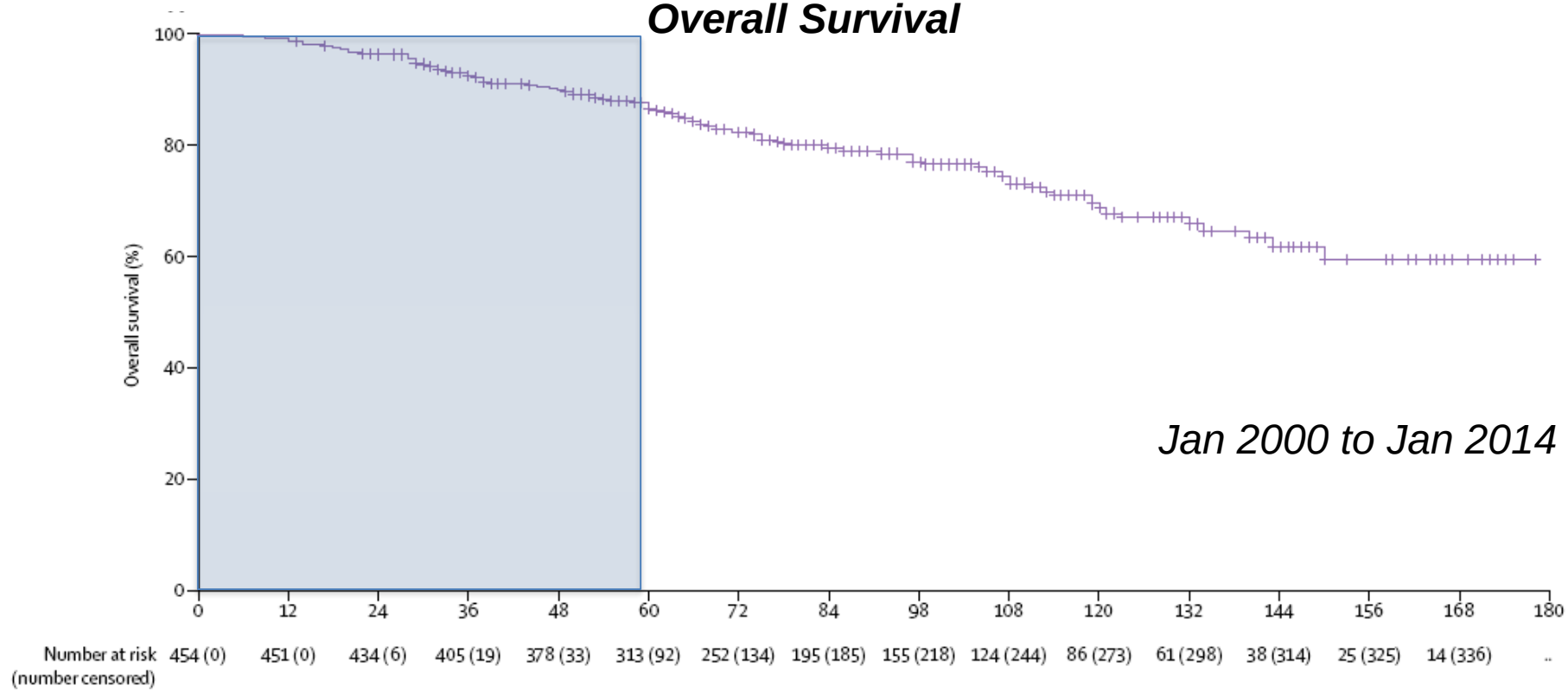
Overall Survival



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What do we know……., WM is clinically a heterogenous disease

Treatment and outcome patterns in European patients with Waldenström's macroglobulinaemia: a large, observational, retrospective chart review

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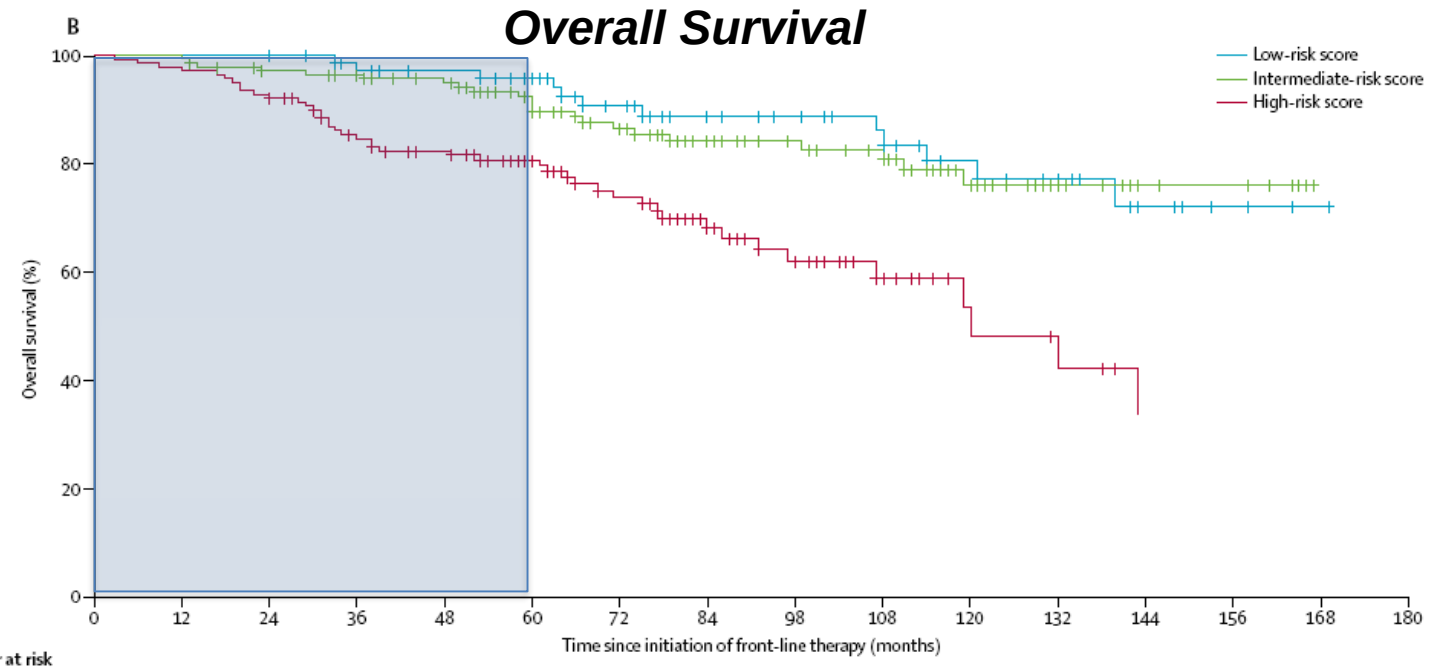


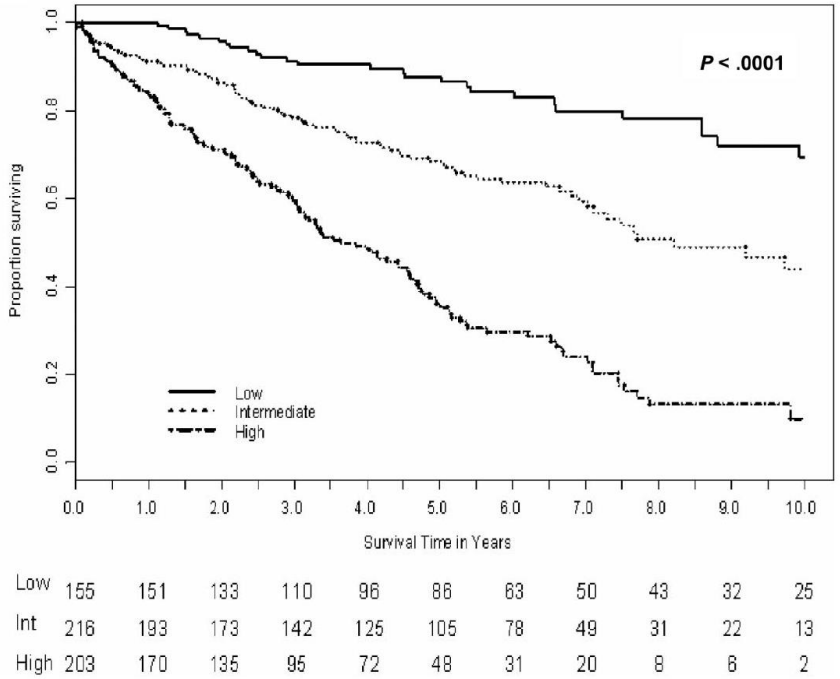
Number at risk (number censored)																
Low-risk score	76 (0)	76 (0)	76 (1)	71 (4)	67 (7)	61 (13)	50 (20)	42 (29)	37 (32)	32 (37)	25 (41)	20 (47)	12 (52)	7 (57)	5 (59)	..
Intermediate-risk score	142 (0)	142 (0)	134 (4)	129 (9)	122 (14)	101 (33)	82 (47)	63 (62)	51 (73)	46 (78)	29 (92)	18 (103)	11 (109)	10 (110)	..	..
High-risk score	139 (0)	136 (0)	129 (1)	113 (6)	103 (12)	77 (37)	60 (47)	40 (65)	28 (74)	18 (82)	10 (88)	8 (89)	..	..	..	..

Lancet Haematol 2018; 5: e299–309

Do we adapt treatment according to the ISSWM?

NO!

	Risk Score WM		
	Low	Intermediate	High
Score	0-1 (except age)	Age or 2	≥ 3
Survival	87 %	68 %	36%
Factors			
Age > 65 yrs	--	+	+
Hb ≤ 11.5 g/dl	Every factor counts as 1		
Thrombos < 100 x 10^9/l			
b_2M > 3 mg/l			
IgM > 70g/l			

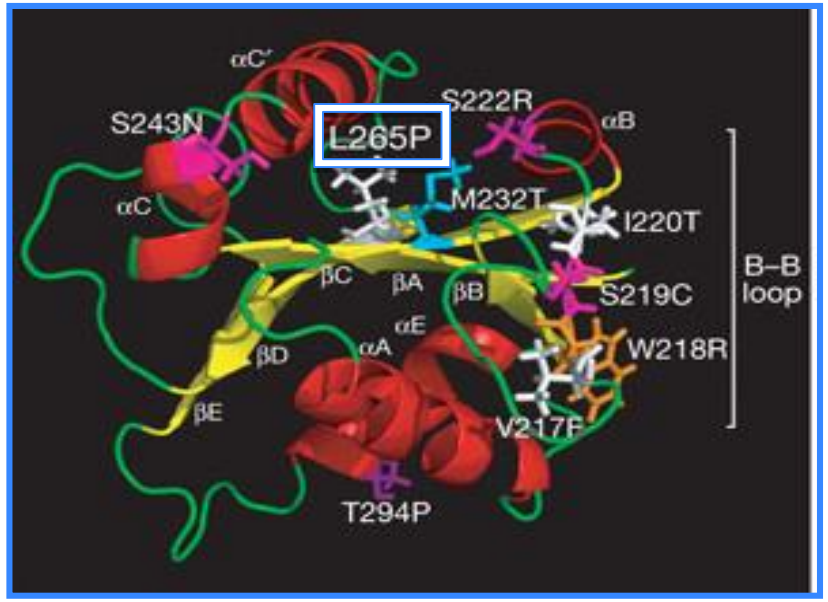


We need well defined predictive markers!

MYD88 Mutation

Treon et al

- Whole Genome Seq. of 30 WM patients, validated by Sanger Seq.
- Sanger Seq. identified $MYD88_{L265P}$ in 90% of patients (27/30 WM samples)
- 22/26 patients were heterozygous for $MYD88_{L265P}$
- 9/9 patients with familial WM carried mutant $MYD88_{L265P}$
- 2/21 patients with IgM-MGUS had $MYD88_{L265P}$ expression

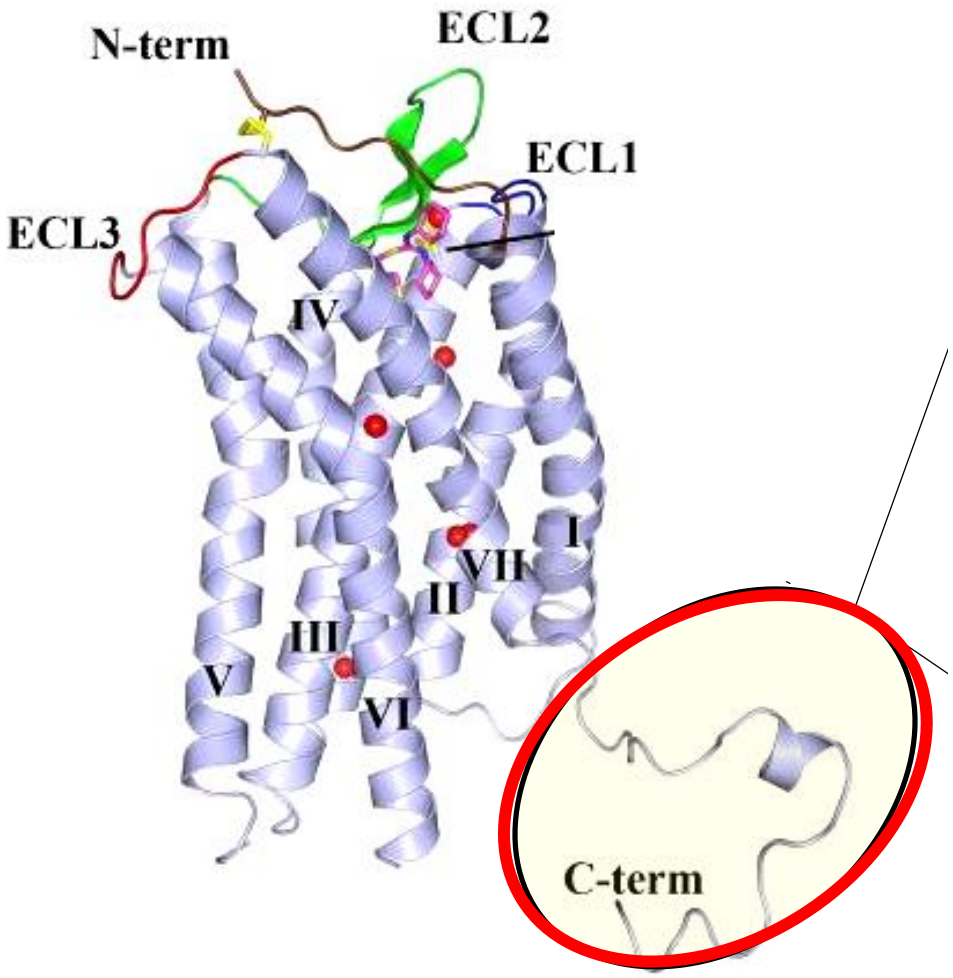


3-D structure of MY88 TIR domain

Base pair mismatch Leuc → Pro at position 265 in MYD88 coding region

Treon et al NEJM 2012; 367(9):826-33; Ngo et al Nature 2011; 470(7332):115-9

WHIM-like CXCR4 C-tail mutations in WM
Warts, Hypogammaglobulinemia, Infection, and Myelokathexis



- 30-40% of WM patients
- > 30 Nonsense and Frameshift Mutations
- Almost always occur with $MYD88^{L265P}$

Hunter et al, Blood 2013; 122: 4254; Poulain et al Clin Lymphoma Myeloma Leuk. 2011 Feb;11(1):106-8; Roccaro et al Blood 2009; 113(18):4391-402;

Waldenström's Macroglobulinemia: WM is a heterogenous disease!

Molecular Markers

Any Implications?

Groves et al Cancer 1998(82); Stone et al Haematologica 2011(95); Koshiol et al Arch Intern Med 2008(168); Owens et al Semin Oncol 2003(30)

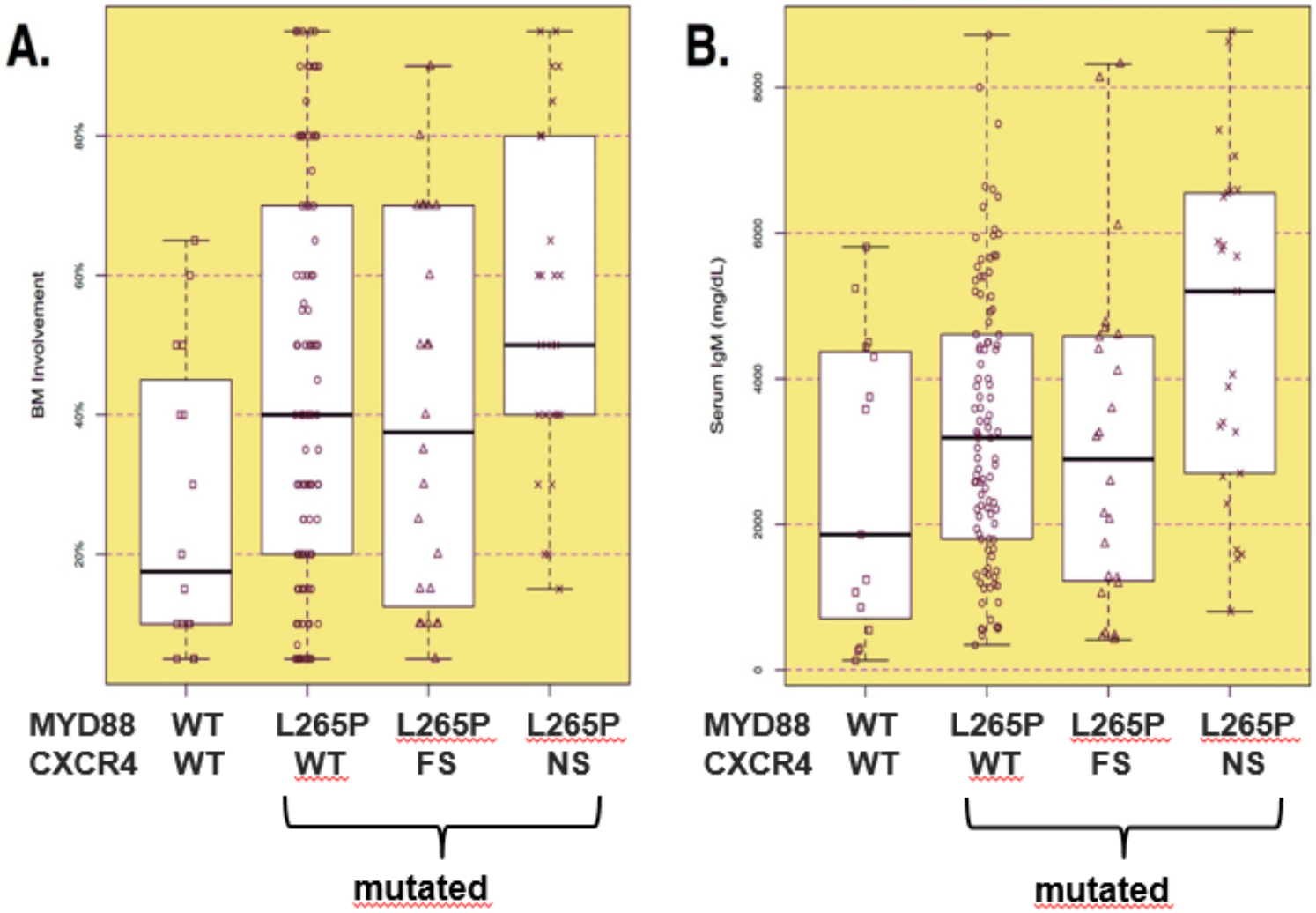
Waldenström's Macroglobulinemia: WM is a heterogenous disease!

Molecular Markers

Three groups

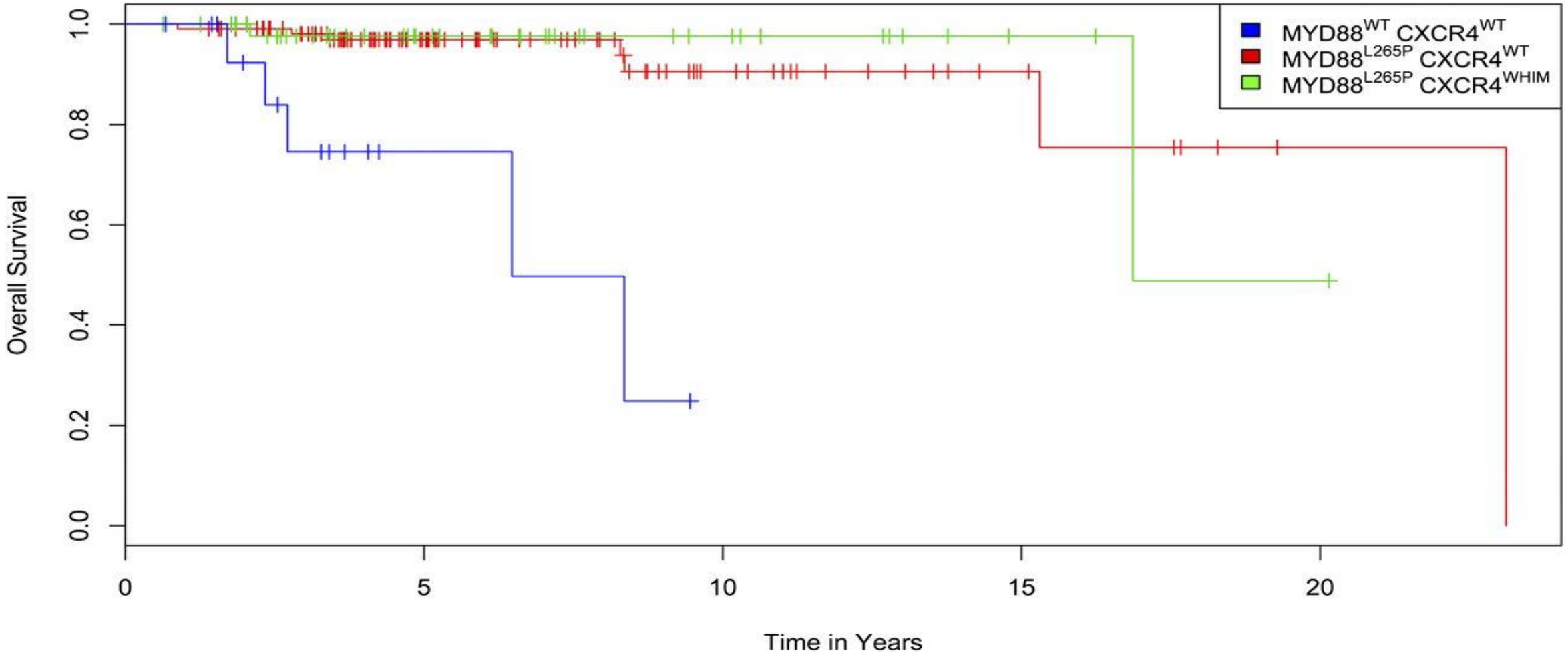
MYD88/ CXCR4	OR	VGPR/PR
+/WT		
+/+		
WT/WT		

MYD88 and CXCR4 Mutation Status Impacts Clinical Presentation of WM Patients



Treon et al, Blood 2014; 123(18):2791-6

Kaplan-Meier plot for overall survival of 175 WM patients from time of diagnosis stratified by MYD88 and CXCR4 mutation status



Treon S P et al. Blood 2014;123:2791-2796

Waldenström’s Macroglobulinemia

What about treatment?

Treatment of WM

Rituximab/Chemotherapy still a good treatmemt for many patients

.....

but Ibrutinib an important treatment option!

Ibrutinib sets the standard!

Waldenström's Macroglobulinemia

What about Ibrutinib?

What can we achieve (and what not) with Ibrutinib?

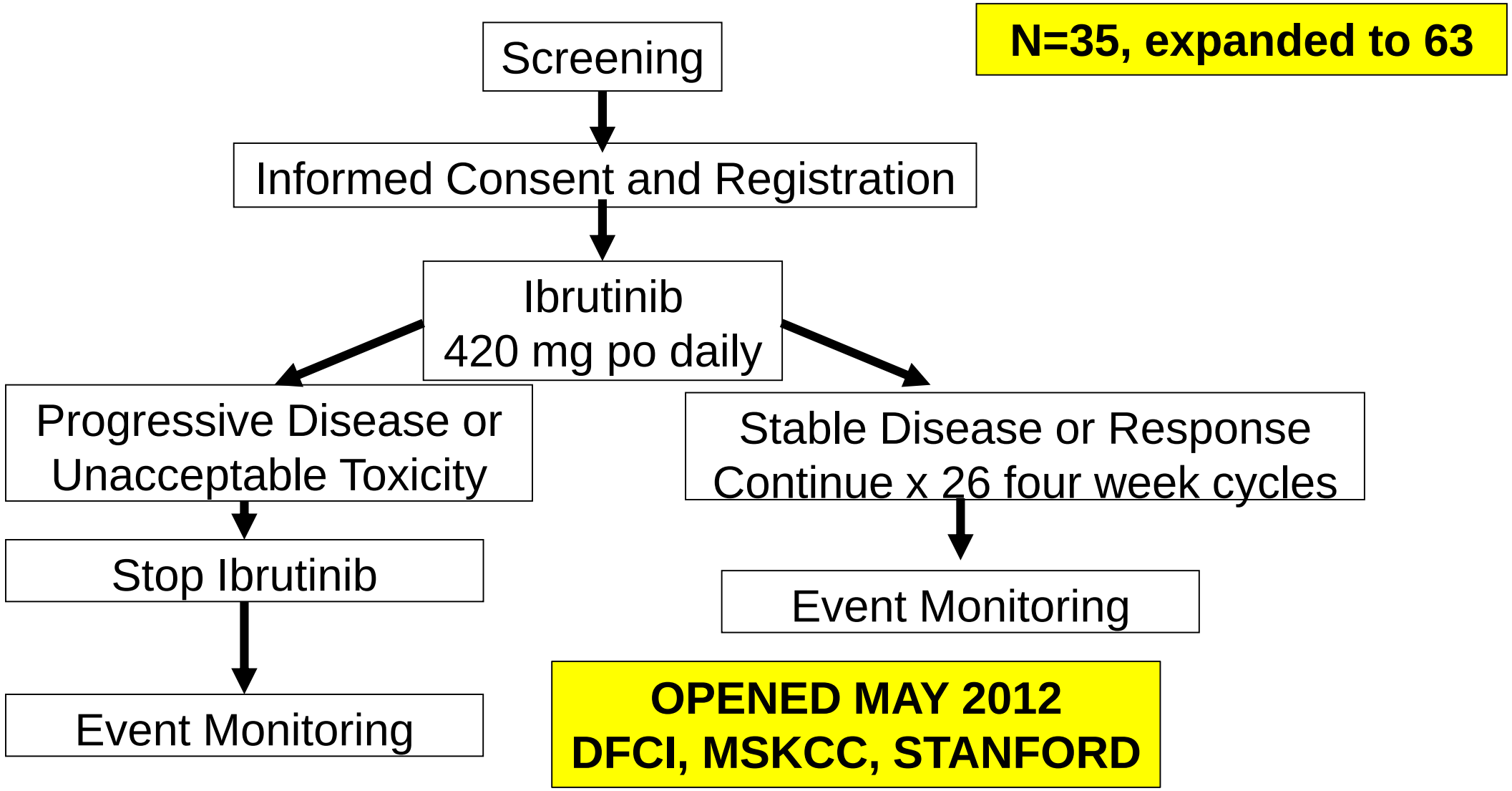
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Ibrutinib in Previously Treated Waldenström's Macroglobulinemia

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

Schema for Multicenter Phase II Study of Ibrutinib in Relapsed/Refractory WM



Treon et al., ASH 2017 (abstract 2766, poster presentation)

Clinical responses to ibrutinib: Median of 9 (range 1-18) Cycles

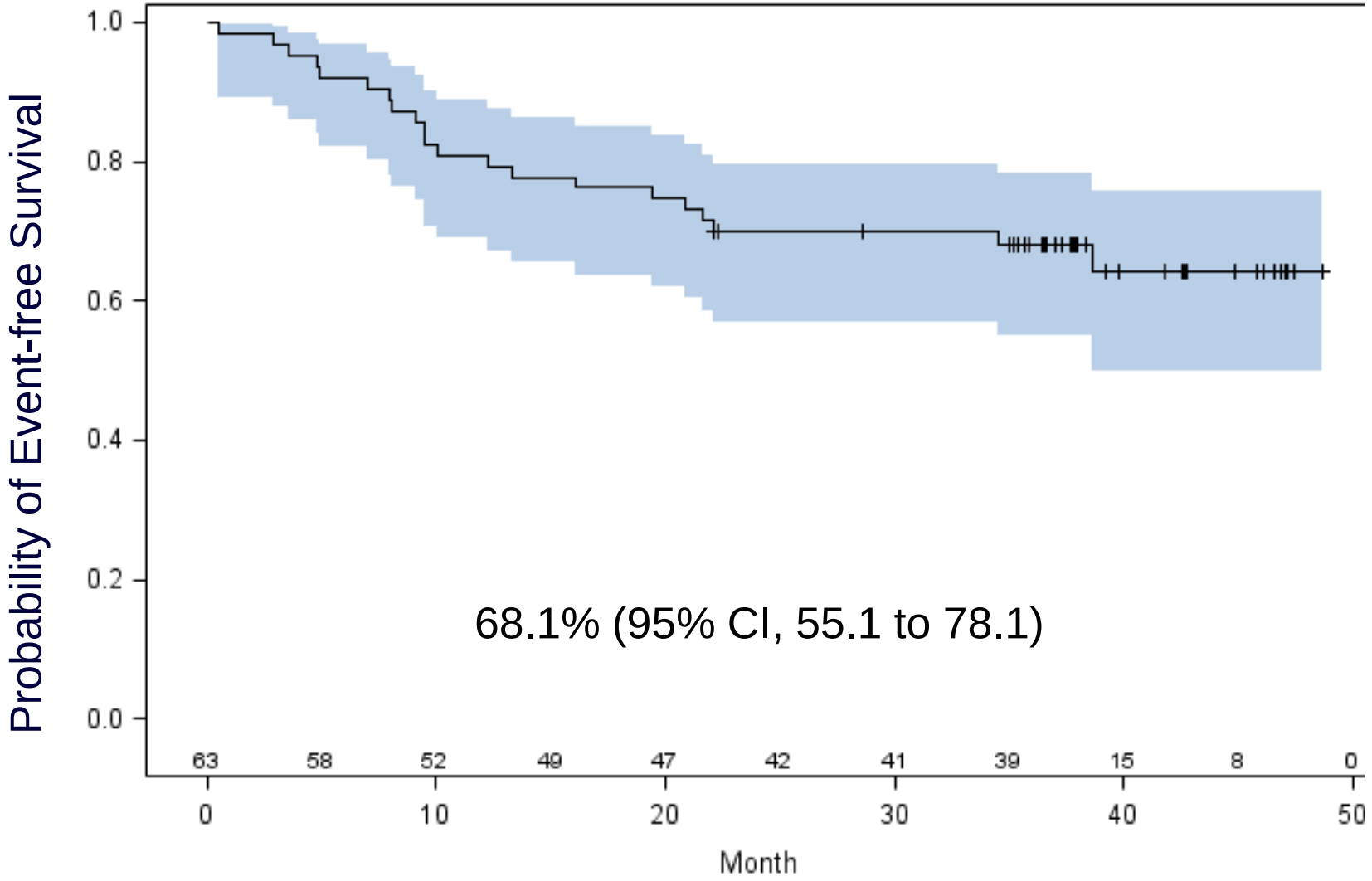
	(N= 63)	(%)
VGPR	10	15.9
PR	36	57
MR	11	17.5

Response criteria adapted from 3rd International Workshop on WM (Treon et al, BJH 2011)

ORR: 90.5% Major RR (≥ PR): 73%

Treon et al, NEJM 2015; 372(15):1430-40

Ibrutinib in Previously Treated WM: Event-free Survival



Median: 37 mo. follow-up

Treon et al, NEJM 2015; 372(15):1430-40

What do we know……., WM is clinically a heterogenous disease

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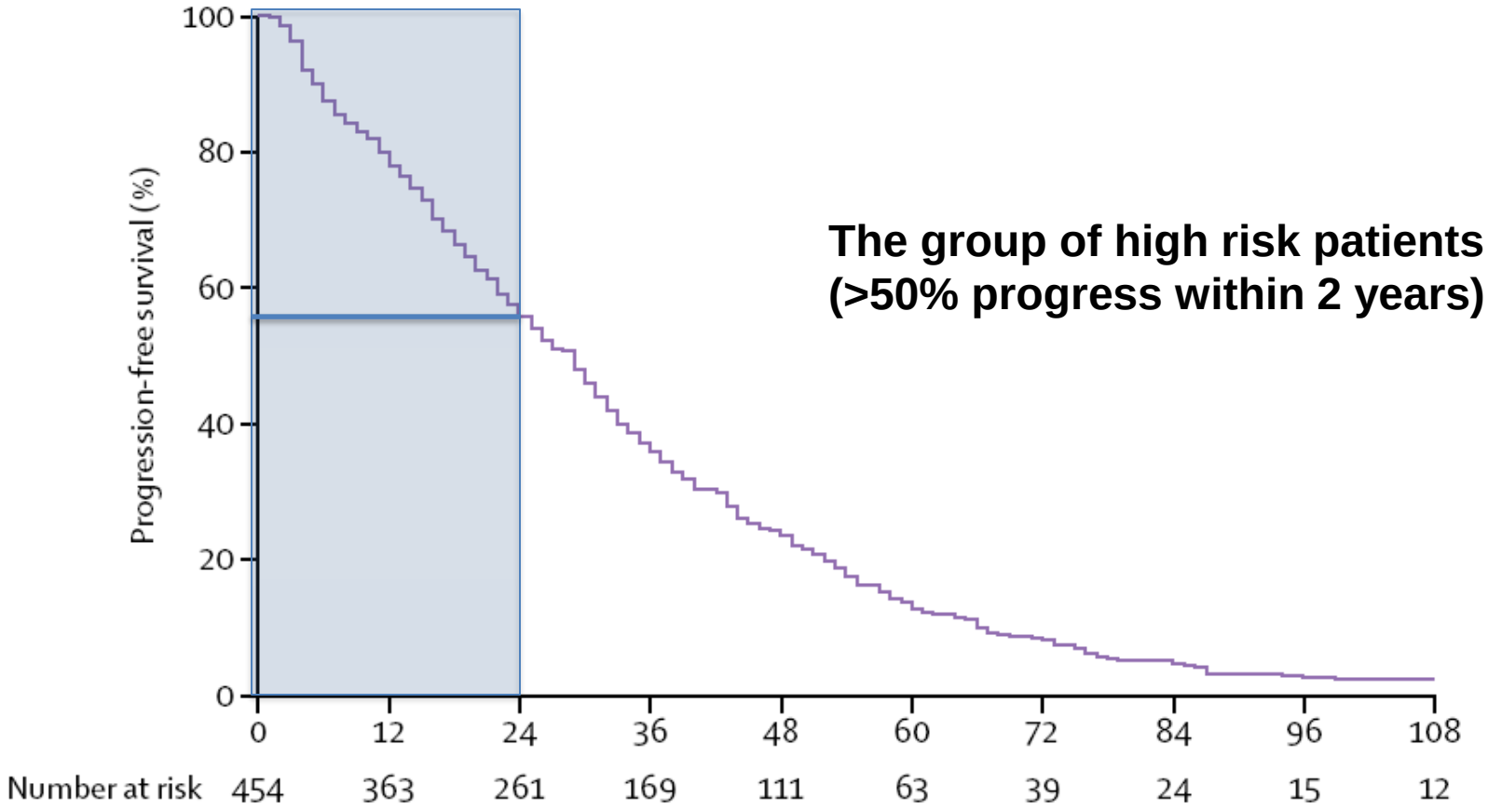


The group of high risk patients is not that small!
(>50% progress within 2 years)

Lancet Haematol 2018;
5: e299–309

The first difficulty!

How to define high risk patients in WM!

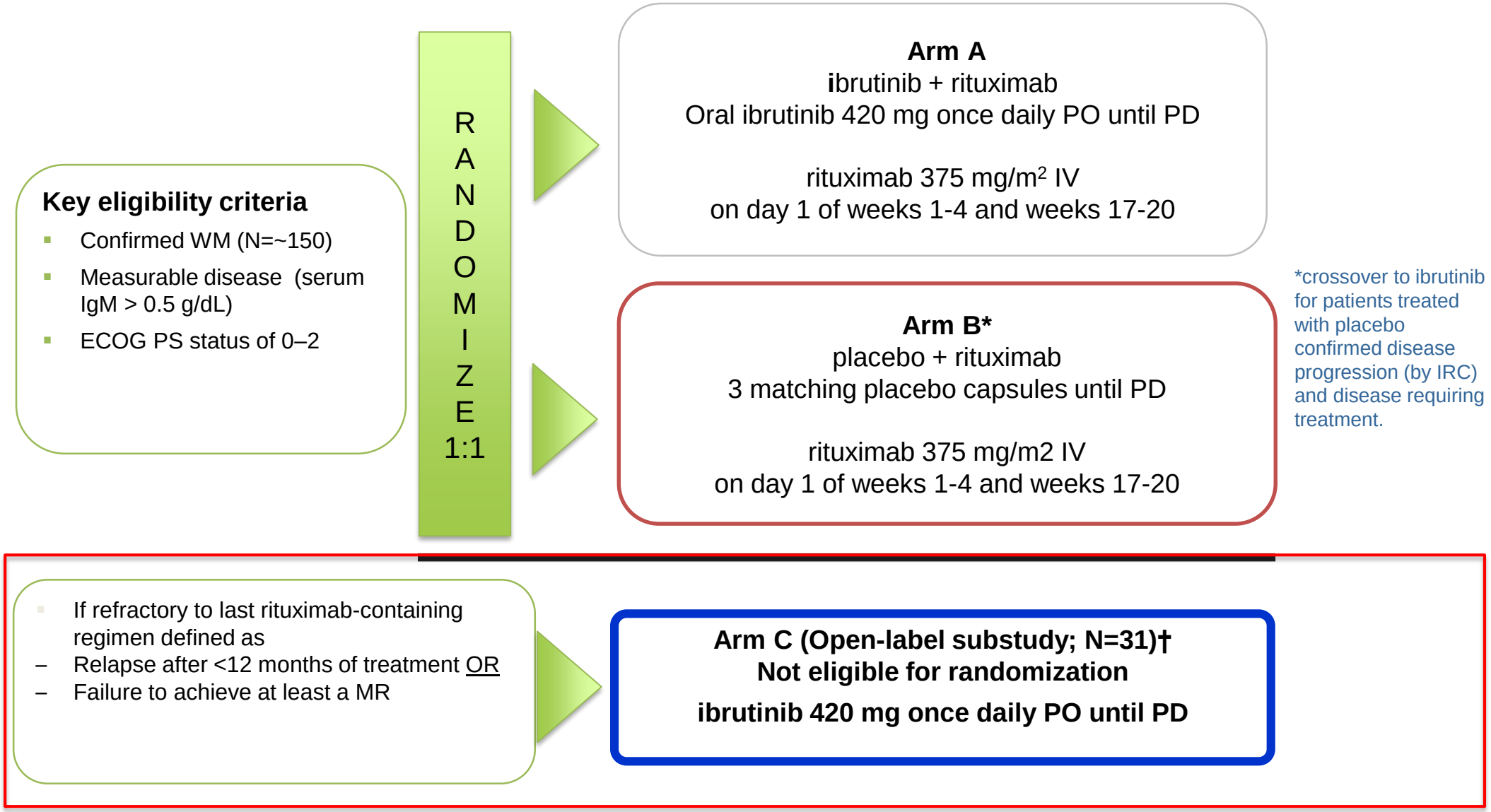
Is there at all a high risk group in the era of ibrutinib?

Treatment of WM

High risk patients =
Rituximab refractory patients?

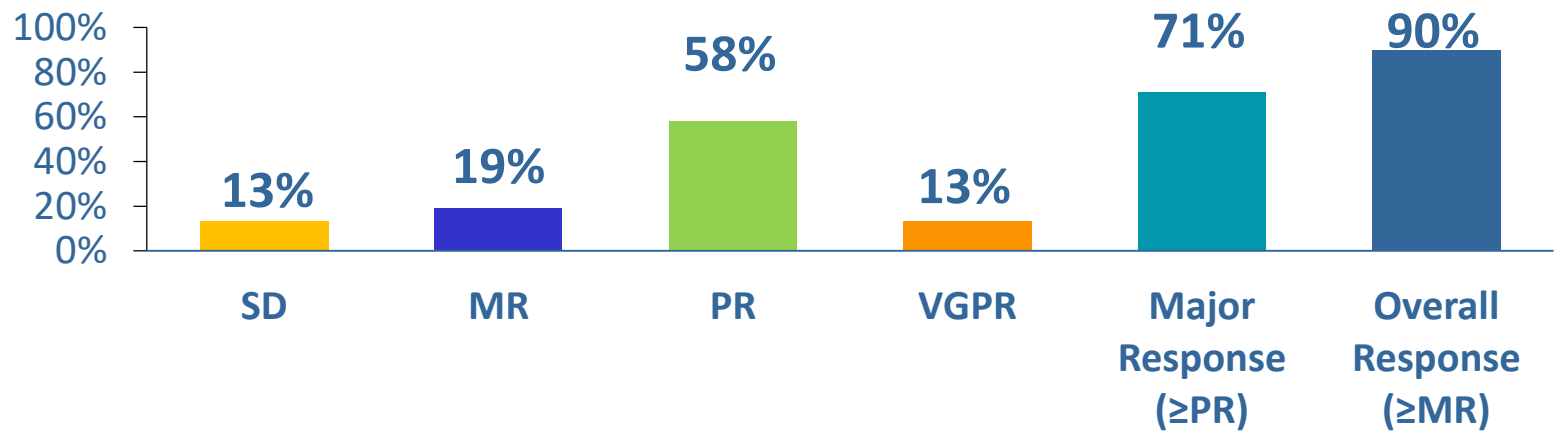
In the ibrutinib era?

PCYC-1127 (iNNOVATE™): Study design



Dimopoulos et al, Lancet Oncol. 2017; 18(2): 241-250

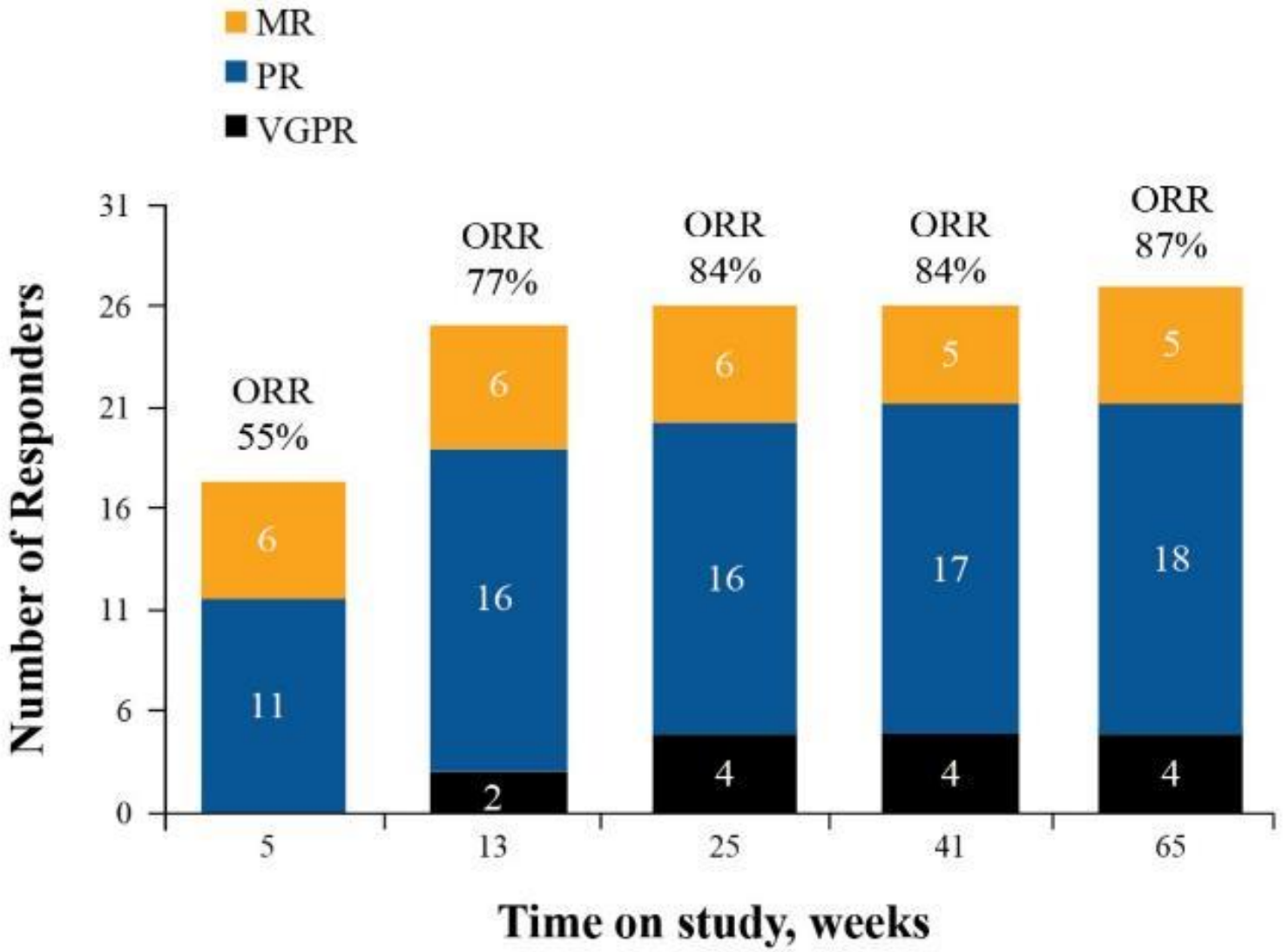
Response to single agent ibrutinib



Best Response	All (N=31)
VGPR	4
PR	18
MR	6
ORR, n (%)	28 (90)
MRR, n (%)	22 (71)

Dimopoulos et al, Lancet Oncol. 2017; 18(2): 241-250

Response to single agent ibrutinib over time



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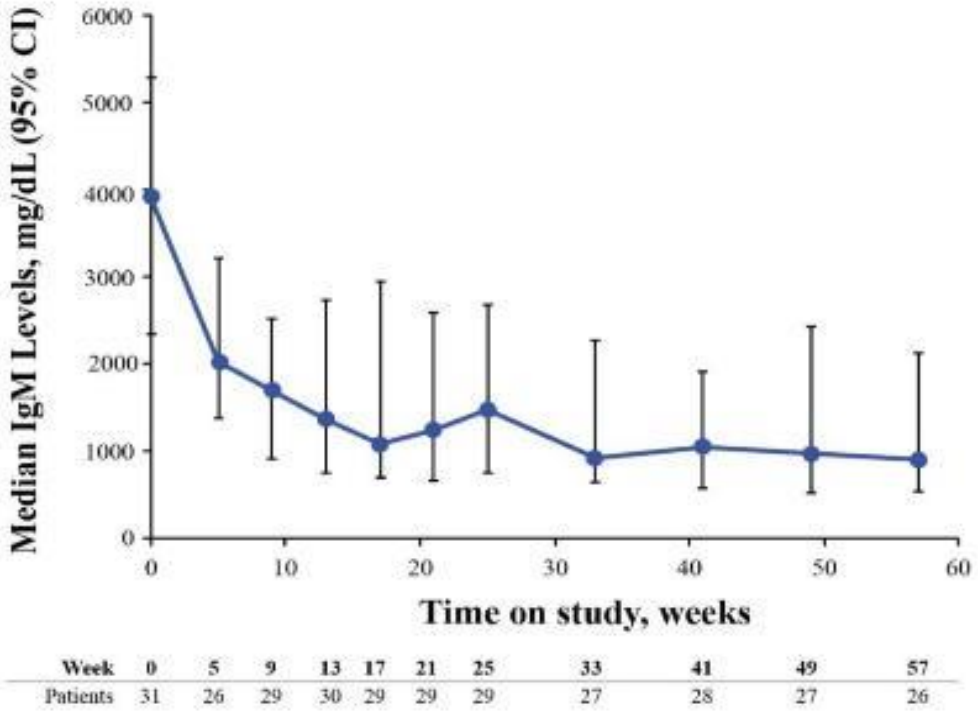
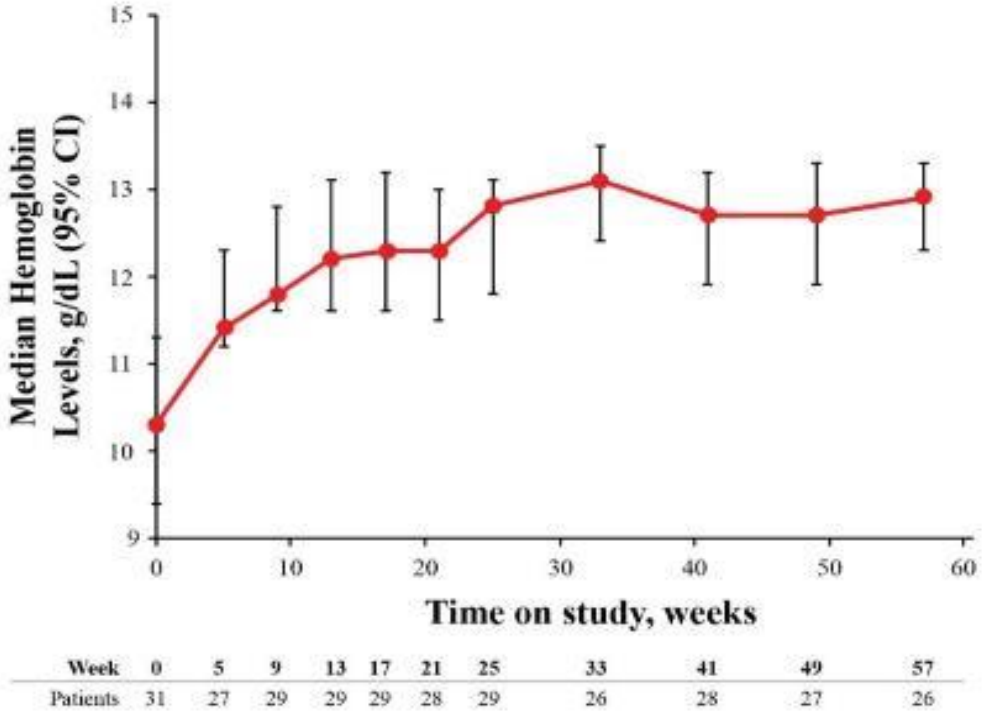
Response to single agent ibrutinib: IgM levels and hemoglobin response

Median IgM levels over time



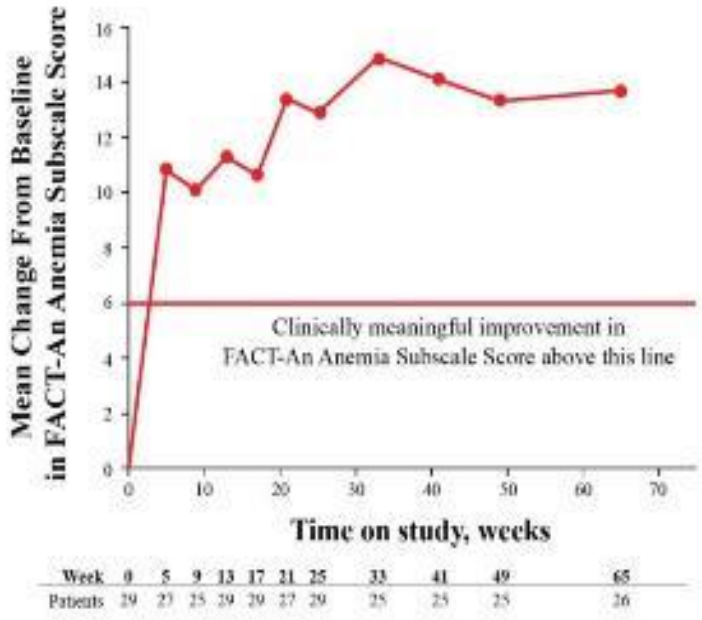
Median hemoglobin levels over time



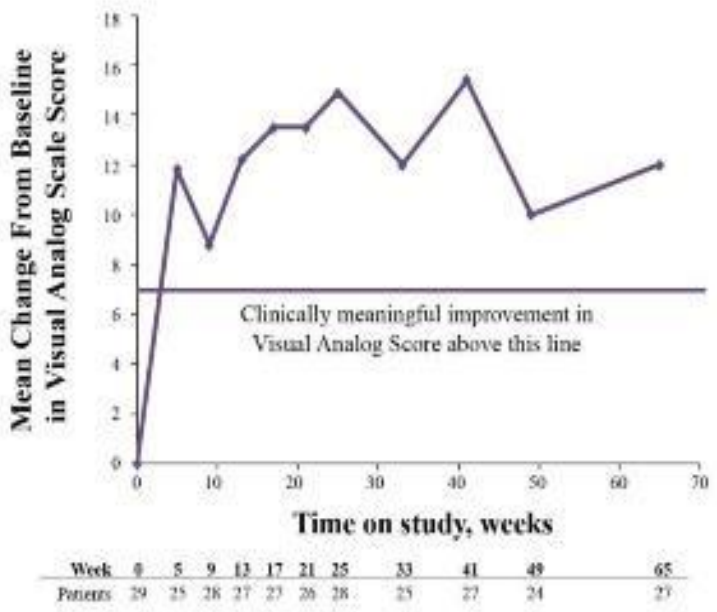
Dimopoulos et al, Lancet Oncol. 2017; 18(2): 241-250

Improvements in patient-reported outcome measurements during follow-up

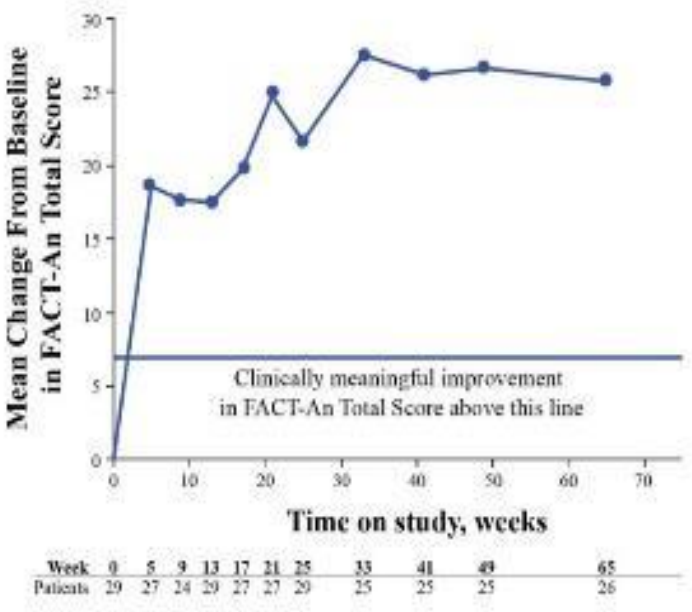
FACT-An-Anemia Subscale Score



Visual Analog Score of the EQ-5D-5L questionnaire



FACT-An total score



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Treatment of WM

High risk patients defined by the genotype?

In the ibrutinib era?

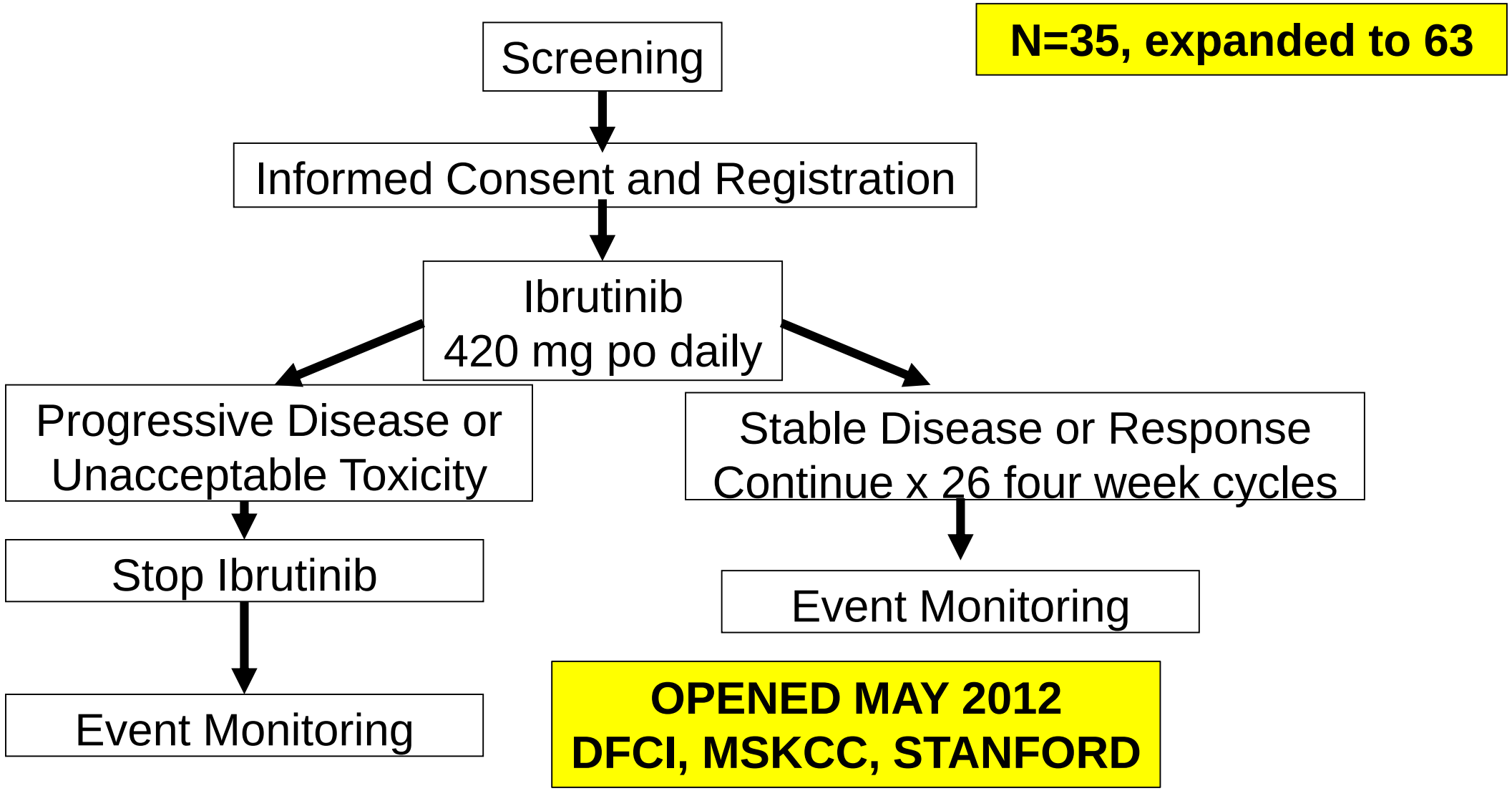
Waldenström's Macroglobulinemia: WM is a heterogenous disease!

Molecular Markers

Three groups

MYD88/ CXCR4	OR	VGPR/PR
+/WT		
+/+		
WT/WT		

Schema for Multicenter Phase II Study of Ibrutinib in Relapsed/Refractory WM



Treon et al., ASH 2017 (abstract 2766, poster presentation)

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

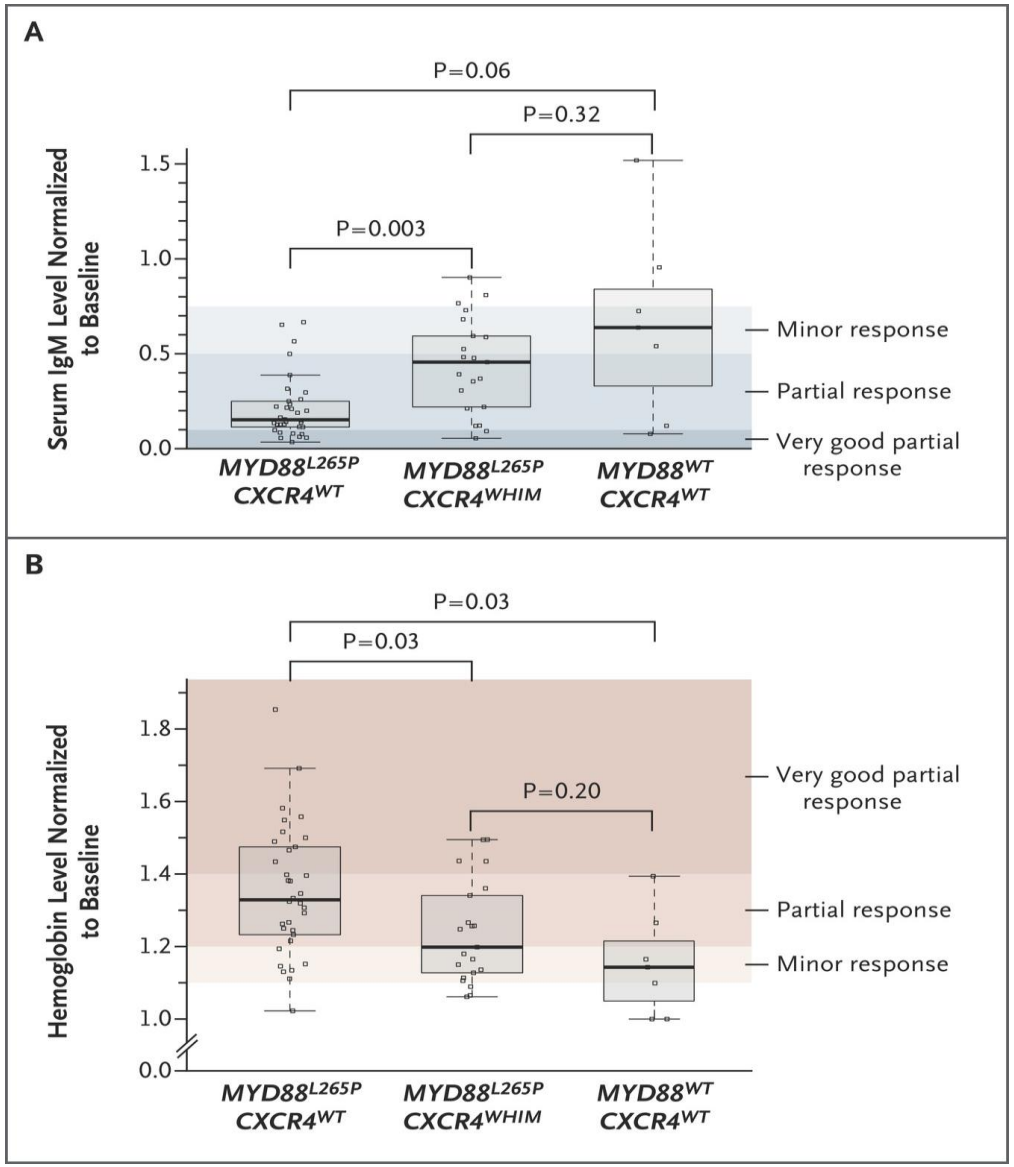
	$MYD88^{MUT}$ $CXCR4^{WT}$	$MYD88^{MUT}$ $CXCR4^{WHIM}$	$MYD88^{WT}$ $CXCR4^{WT}$	p-value
N=	36	21	5	
Overall RR	100%	85.7%	60%	<0.01
Major RR	91.7%	61.9%	0%	<0.01

2 patients subsequently found to have other MYD88 mutations not picked up by AS-PCR

Median time on ibrutinib 19.1 months

Treon et al, N Engl J Med. 2015; 372(15):1430-40; NEJM 2015; Letter, August 6, 2015.

Effect of MYD88 and CXCR4 mutation status on ibrutinib-related changes in serum IgM and hemoglobin levels



Median time on ibrutinib 19.1 months

Treon SP et al. N Engl J Med 2015;372:1430-1440

Long-Term Follow-up of Previously Treated Patients Who Received Ibrutinib for Symptomatic Waldenström's Macroglobulinemia: Update of Pivotal Clinical Trial

Steven P. Treon, Kirsten Meid, Joshua Gustine, Kurt S. Bantilan, Toni Dubeau, Patricia Severns, Guang Yang, Lian Xu, Christopher Patterson, Irene M. Ghobrial, Jacob Laubach, Zachary R. Hunter, Jorge J. Castillo, Maria L. Palomba, and Ranjana H. Advani. Dana-Farber Cancer Institute, Boston, MA; Stanford Medical Center, Palo Alto, CA; Memorial Sloan Kettering, New York, NY.

Treon et al., ASH 2017 (abstract 2766, poster presentation)

Long-term follow-up of previously treated patients who received ibrutinib for symptomatic WM: Update of pivotal clinical trial

The impact of MYD88 and CXCR4 mutation status on responses and time to at least minor (overall) and PR or better (major) responses

	All patients (n=63)	$MYD88^{MUT}$ $CXCR4^{WT}$ (n=36)	$MYD88^{MUT}$ $CXCR4^{MUT}$ (n=21)	$MYD88^{WT}$ $CXCR4^{WT}$ (n=5)	P-Value
Overall Responses (%)	90.4	100	85.7	60	0.0038
Major Responses (%)	77.7	97.2	66.6	0	<0.001
VGPR (%)	27	41.6	9.5	0	0.0114
Median Time to Minor Response or better (months)	1.0 (range 1.0-22.5)	1.0 (range 1.0-15)	1.0 (range 1.0-22.5)	1.0 (range 1.0-18)	0.1
Median Time to Major Response (months)	2.0 (range 1.0-49)	2.0 (range 1.0-49)	6.0 (range 1.0-40)	N/a	0.05

Median time on ibrutinib 46 months (0.5 – 60)

Treon et al., ASH 2017 (abstract 2766, poster presentation)

Waldenström's Macroglobulinemia

What about Ibrutinib?

What can we achieve (and what not) with Ibrutinib?

Ibrutinib as the most efficient single chemofree agent in WM –

BUT GENOTYPE DEPENDING CLINICAL ACTIVITY

We need well defined predictive markers!

The genotype paves the way……..

CXCR4 mutated and MYD88^{WT}/CXCR4^{WT} patients are „high risk“ patients in the era of ibrutinib

CXCR4 mutated and MYD88^{WT}/CXCR4^{WT} patients are „high risk“ patients in the era of ibrutinib

Approaches to improve on this!

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Phase 3 Trial of Ibrutinib plus Rituximab in Waldenström's Macroglobulinemia

M.A. Dimopoulos, A. Tedeschi, J. Trotman, R. García-Sanz, D. Macdonald, V. Leblond, B. Mahe, C. Herbaux, C. Tam, L. Orsucci, M.L. Palomba, J.V. Matous, C. Shustik, E. Kastritis, S.P. Treon, J. Li, Z. Salman, T. Graef, and C. Buske, for the iNNOVATE Study Group and the European Consortium for Waldenström's Macroglobulinemia*

This article was published on June 1, 2018, at NEJM.org.

iNNOVATE (PCYC-1127) Study Design

Key eligibility criteria

- Confirmed WM* (N≈150)
- Measurable disease (serum IgM >0.5 g/dL)
- RTX sensitive
  - Not refractory to last prior RTX-based therapy
  - Had not received RTX <12 months before first study dose

1:1 Randomization

Stratification

- IPSSWM (low vs intermediate vs high)
- Number of prior regimens (0 vs 1–2 vs ≥3)
- ECOG status (0–1 vs 2)

Arm A
ibrutinib-RTX
Oral ibrutinib 420 mg once daily until PD
RTX 375 mg/m^2 IV on
day 1 of weeks 1–4 and 17–20

Arm B
placebo-RTX
3 matching placebo capsules until PD
RTX 375 mg/m^2 IV on
day 1 of weeks 1–4 and 17–20

- **Primary Endpoint:** PFS by IRC
- **Secondary Endpoints:** Response rate, TTnT, sustained hematologic improvement, PROs, OS, safety

*Treatment-naïve patients were allowed to enroll following a protocol amendment (Nov 2015); therefore, their enrollment started later than relapsed patients.
iNNOVATE Study; ClinicalTrials.gov ID: NCT02165397

ASCO 2018, iNNOVATE WM; Dimopoulos et al.

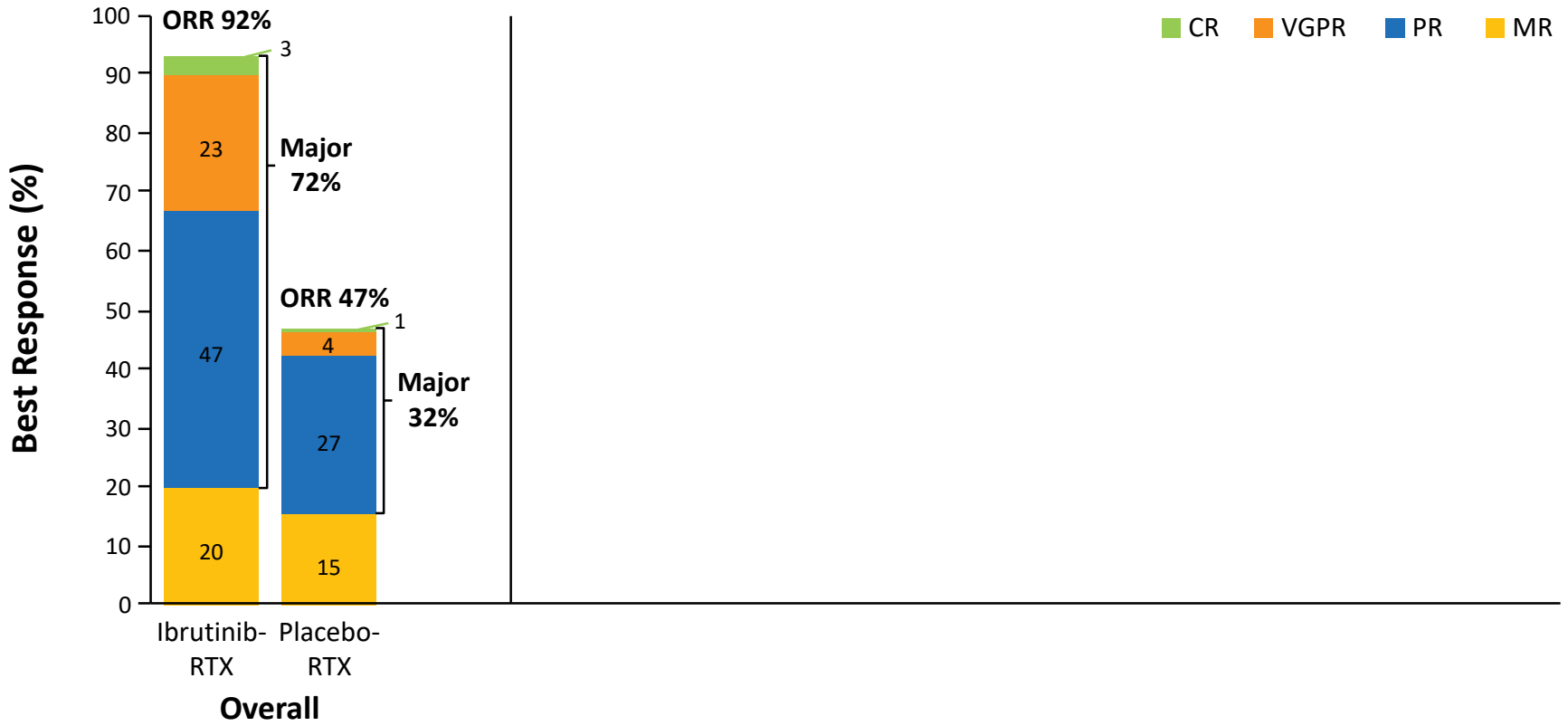
Demographics and Clinical Characteristics Were Balanced at Baseline

Characteristic at Randomization	Ibrutinib-RTX (n = 75)	Placebo-RTX (n = 75)
Median age, years (range)	70 (36–89)	68 (39–85)
Age ≥75 years, n (%)	30 (40)	20 (27)
Male sex, n (%)	45 (60)	54 (72)
IPSSWM, n (%)		
Low	15 (20)	17 (23)
Intermediate	33 (44)	28 (37)
High	27 (36)	30 (40)
Baseline hemoglobin ≤11 g/dL, n (%)	44 (59)	50 (67)
Baseline serum IgM ≥50 g/L, n (%)	17 (23)	15 (20)
Disease-related symptoms, n (%)		
Fatigue	42 (56)	49 (65)
Constitutional symptoms*	19 (25)	29 (39)
Hyperviscosity	9 (12)	10 (13)
Extramedullary disease, n (%)	59 (79)	60 (80)
Adenopathy	56 (75)	58 (77)
Splenomegaly	9 (12)	18 (24)
Number of prior systemic therapies, n (%)		
0	34 (45)	34 (45)
1–2	34 (45)	36 (48)
≥3	7 (9)	5 (7)

*Constitutional symptoms included night sweats, weight loss, and fever.

ASCO 2018, iNNOVATE WM; Dimopoulos et al.

Higher Response Rates* Were Observed With Ibrutinib-RTX

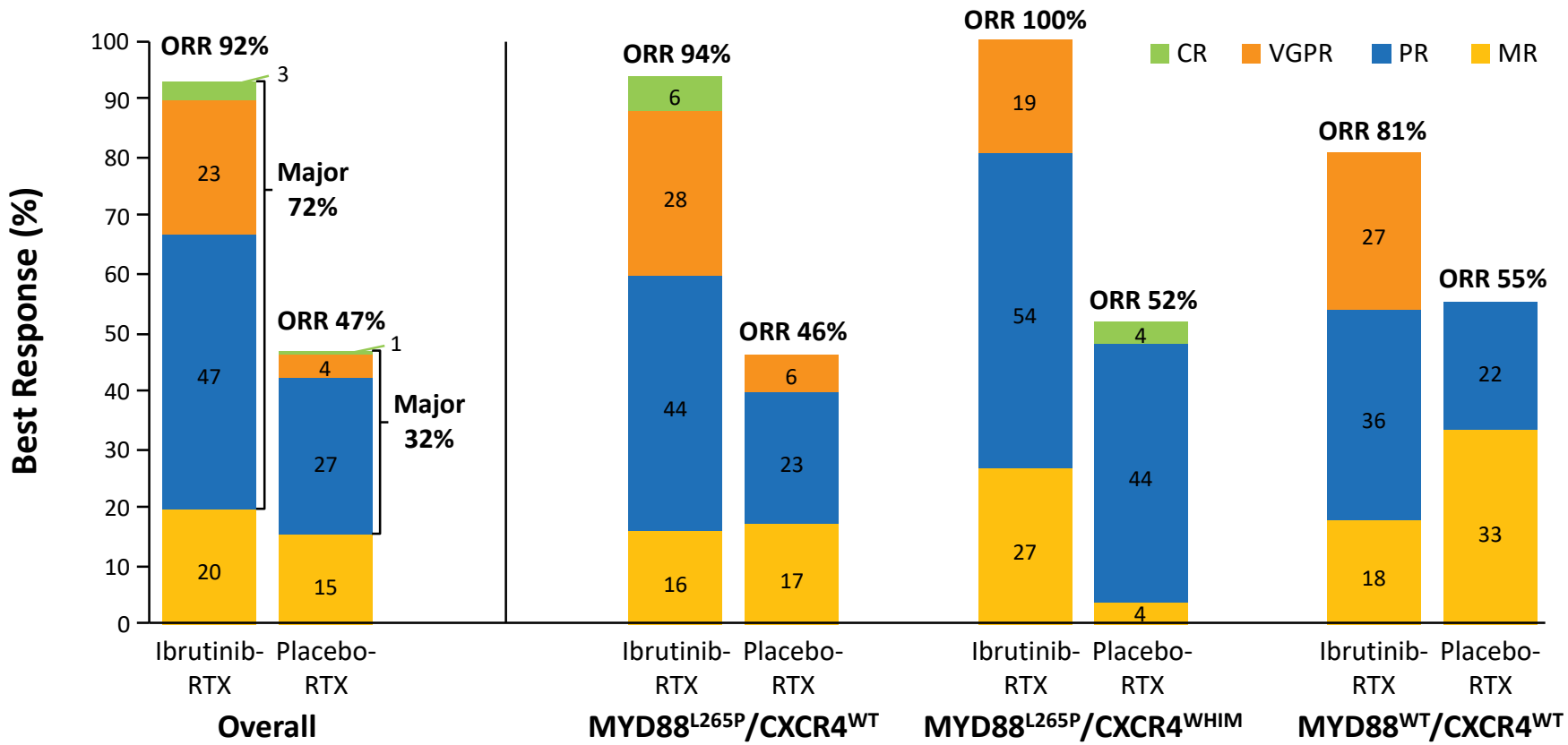


- **Overall, ibrutinib-RTX vs placebo-RTX:**
  - **Major response (≥PR) rate: 72% vs 32%; *P* <0.0001**
  - **Overall (≥MR) response rate: 92% vs 47%; *P* <0.0001**

*Following modified 6th IWWM Response Criteria (NCCN 2014); required two consecutive assessments.

ASCO 2018, iNNOVATE WM; Dimopoulos et al.

Higher Response Rates* Were Observed With Ibrutinib-RTX



- **Proportion of patients with genetic subtype†, ibrutinib-RTX vs placebo-RTX:**
  - **$MYD88^{L265P}/CXCR4^{WT}$: 46% vs 52%**
  - **$MYD88^{L265P}/CXCR4^{WHIM}$: 38% vs 34%**
  - **$MYD88^{WT}/CXCR4^{WT}$: 16% vs 13%**

*Following modified 6th IWWM Response Criteria (NCCN 2014); required two consecutive assessments.

†Proportion of patients calculated after excluding patients for whom data were missing or unknown (ibrutinib-RTX: n = 6; placebo-RTX: n = 8).

ASCO 2018, iNNOVATE WM; Dimopoulos et al.

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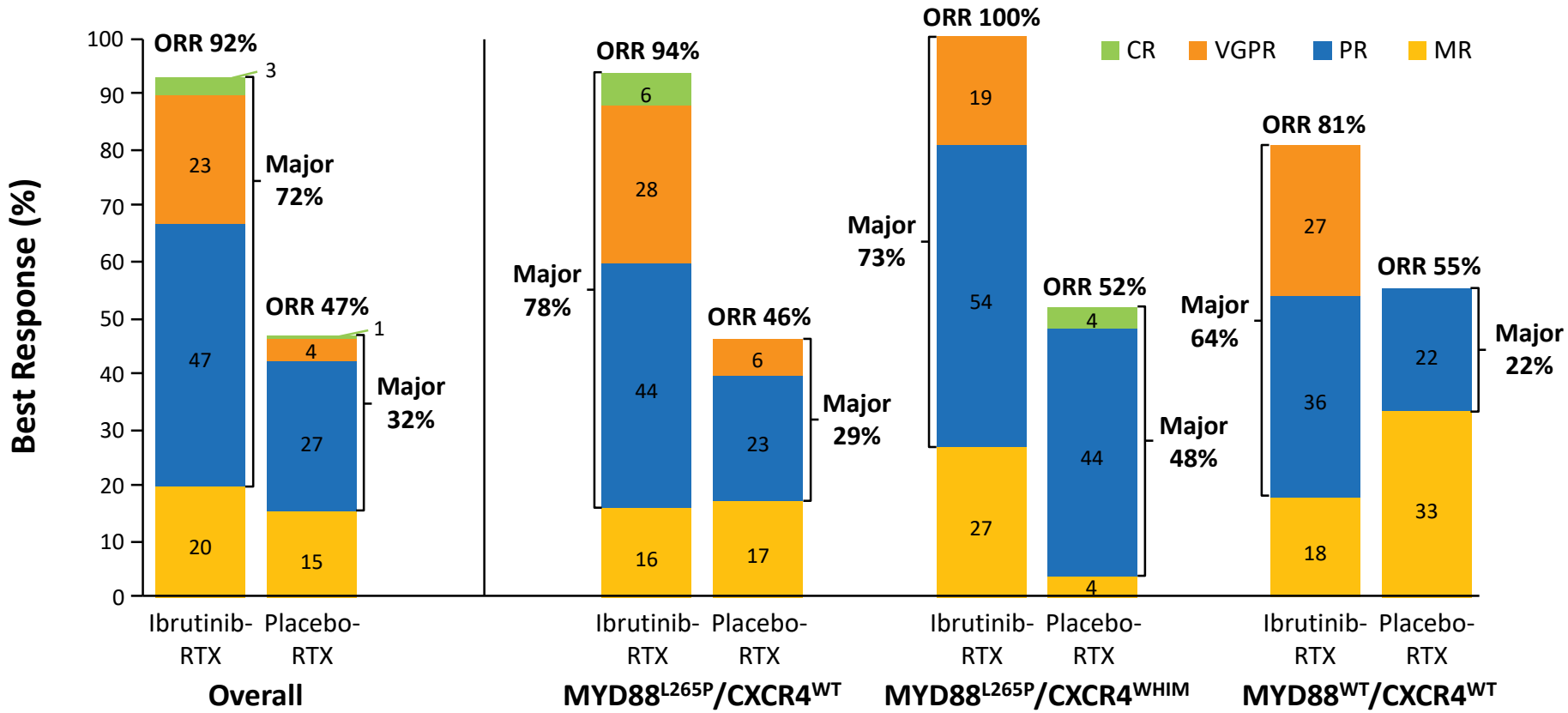

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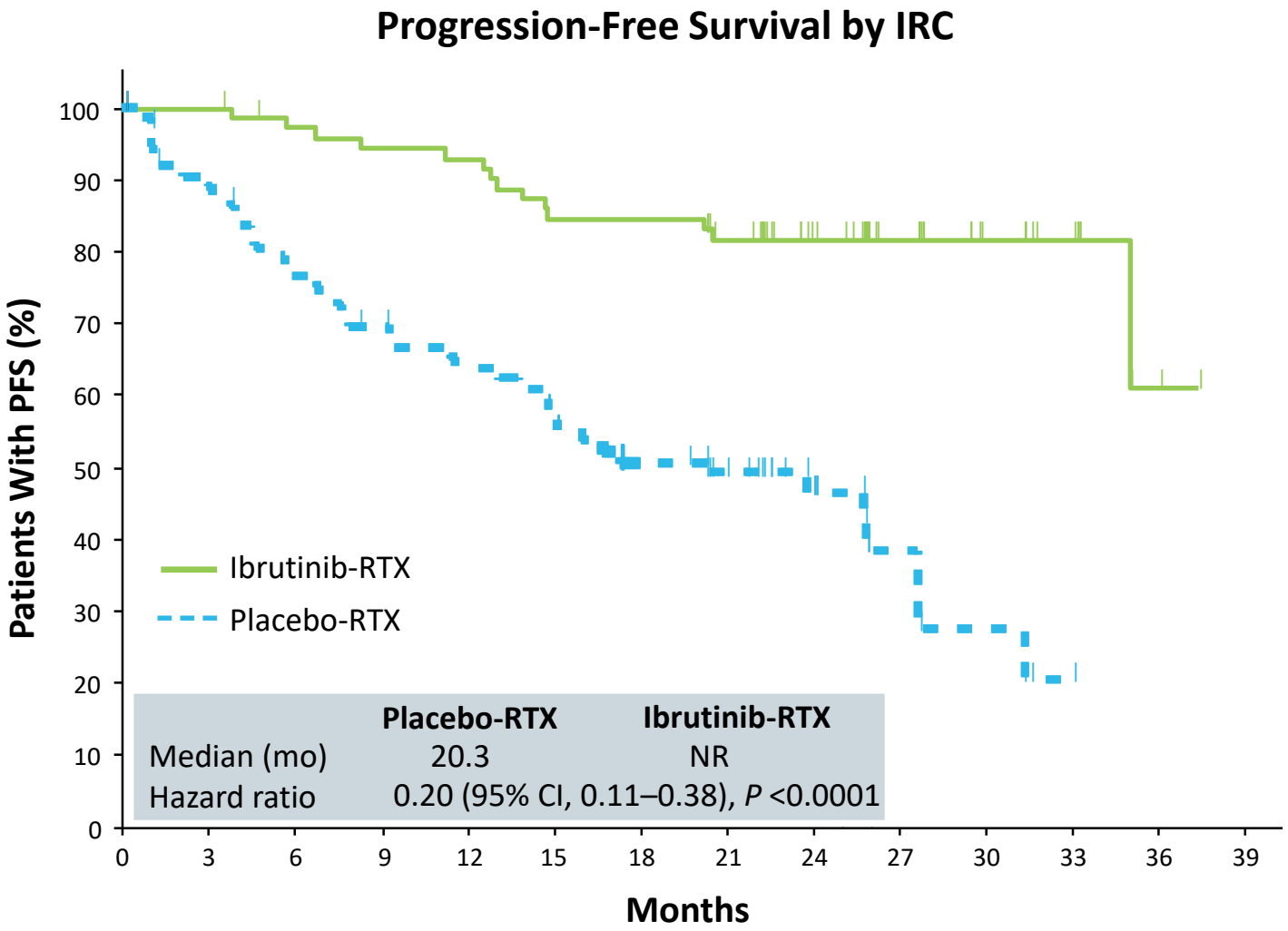
ASCO 2018, iNNOVATE WM; Dimopoulos et al.

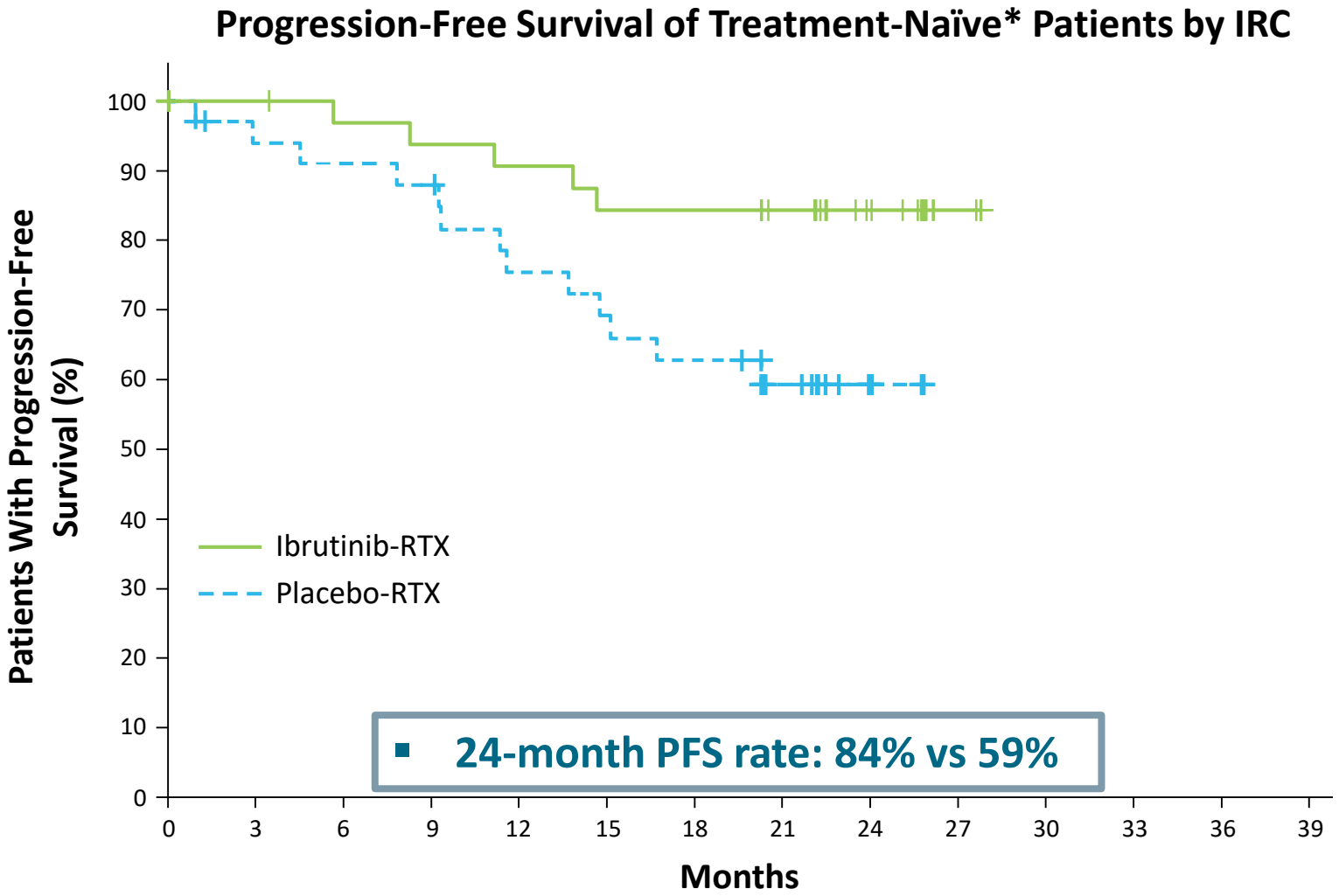
Progression-Free Survival Was Prolonged With Ibrutinib-RTX



- **30-month PFS rate at a median follow-up of 26.5 months: 82% vs 28%**
- **Consistent with IRC assessment, investigator-assessed PFS yielded a hazard ratio of 0.218 (*P* <0.0001)**

ASCO 2018, iNNOVATE WM; Dimopoulos et al.

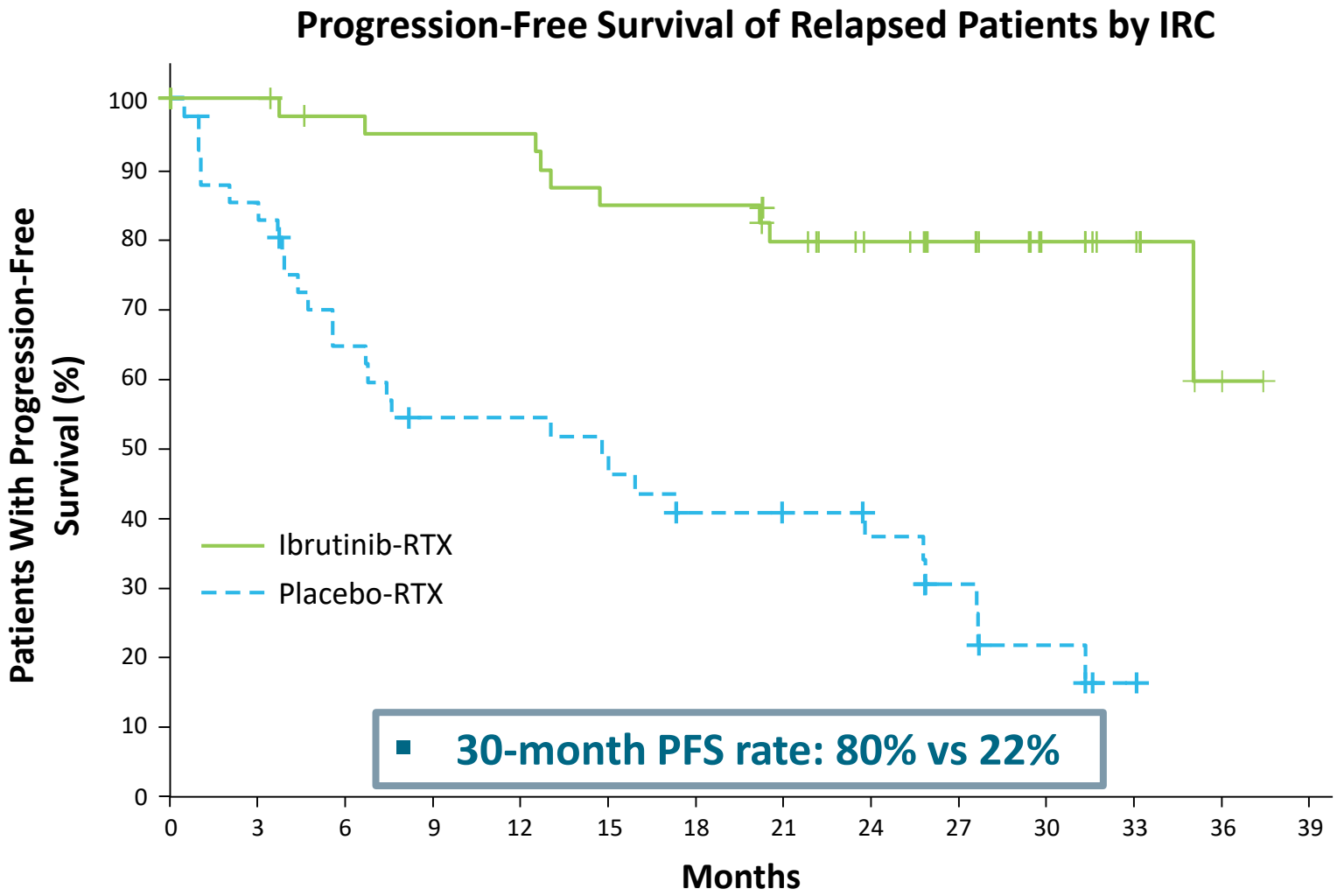
Progression-Free Survival: Treatment-Naïve Patients



*This patient population was allowed to enroll following a protocol amendment (Nov 2015); therefore, their enrollment started later than relapsed patients.

ASCO 2018, iNNOVATE WM; Dimopoulos et al.

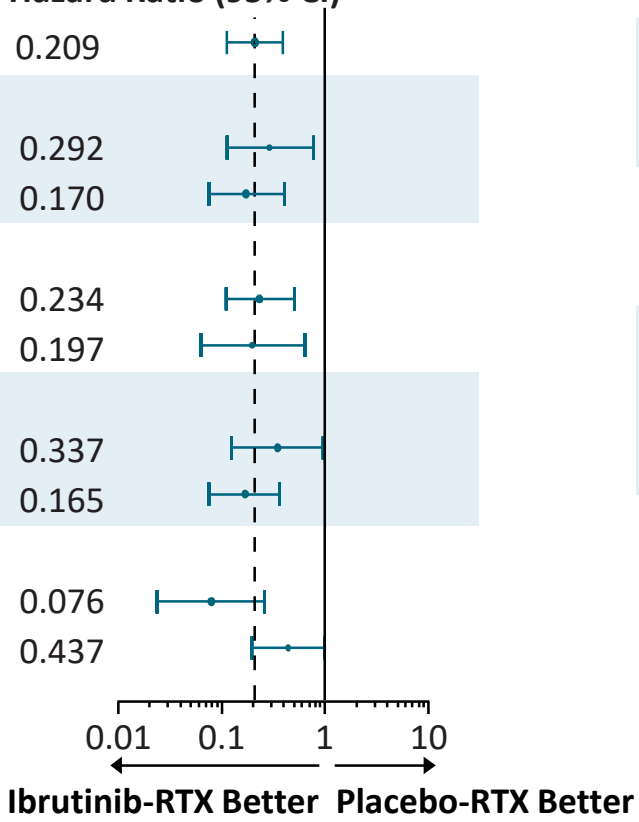
Progression-Free Survival: Relapsed Patients

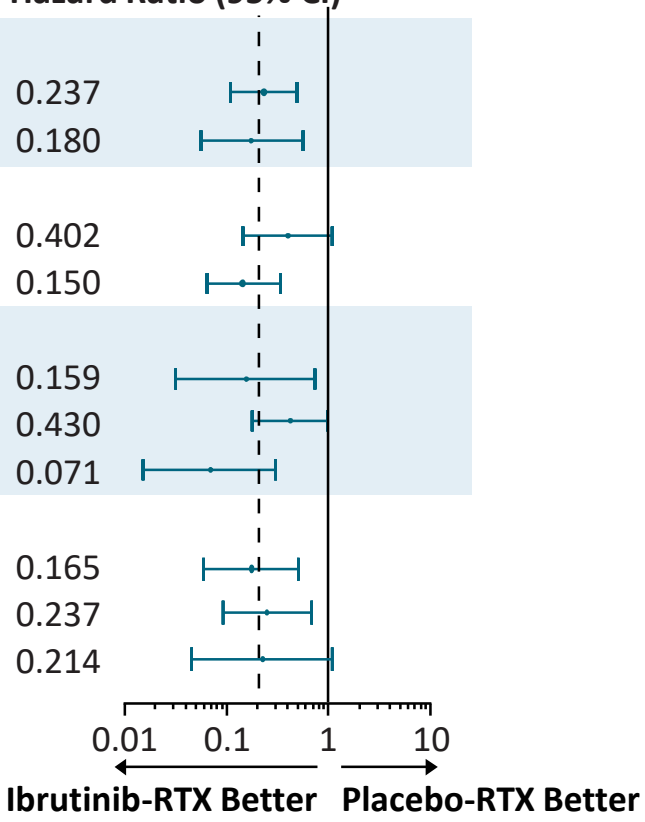


ASCO 2018, iNNOVATE WM; Dimopoulos et al.

Improved Progression-Free Survival Was Observed Across Prespecified Subgroups

Subgroup	No. of Patients	Hazard Ratio (95% CI)
All patients	150	0.209
Age		
<65	58	0.292
≥65	92	0.170
Gender		
Male	99	0.234
Female	51	0.197
Prior treatment history		
Previously untreated	68	0.337
Previously treated	82	0.165
Baseline IgM		
<40 g/L	94	0.076
≥40 g/L	56	0.437
Baseline hemoglobin		
≤11 g/dL	94	0.237
>11 g/dL	54	0.180
Baseline β2-microglobulin		
≤3 mg/L	42	0.402
>3 mg/L	108	0.150
IPSSWM at screening		
Low	32	0.159
Intermediate	61	0.430
High	57	0.071
Genotype		
$MYD88^{L265P}/CXCR4^{WT}$	67	0.165
$MYD88^{L265P}/CXCR4^{WHIM}$	49	0.237
$MYD88^{WT}/CXCR4^{WT}$	20	0.214

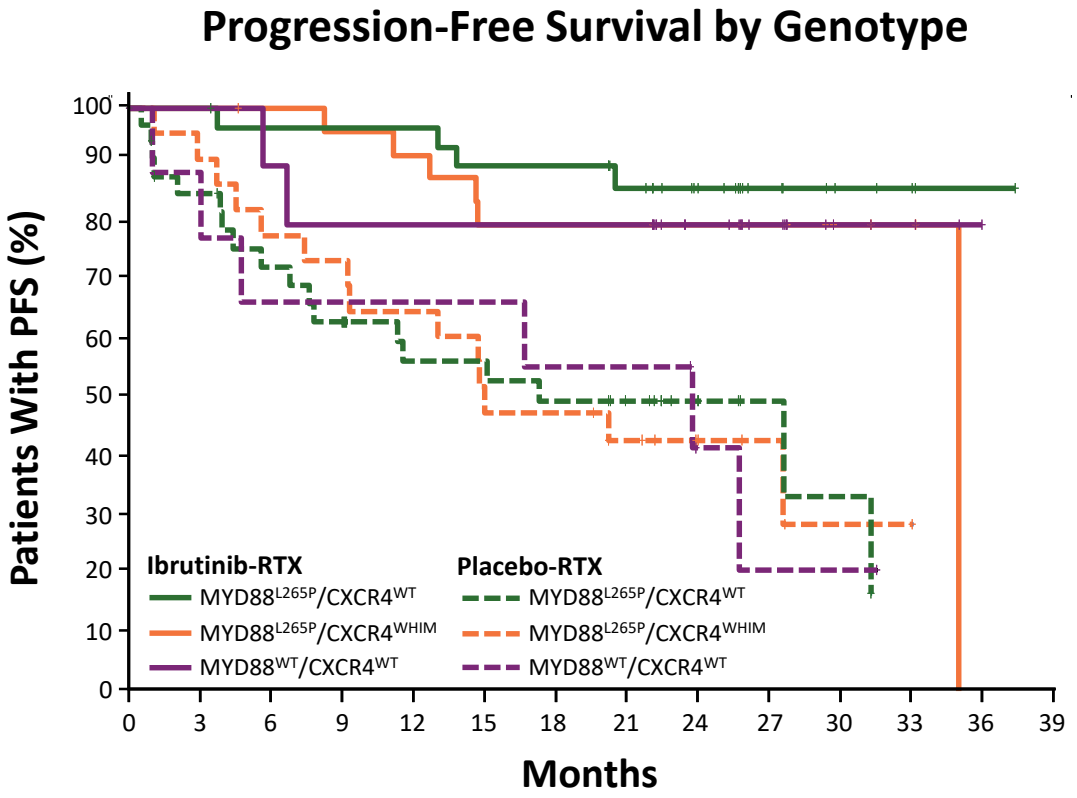


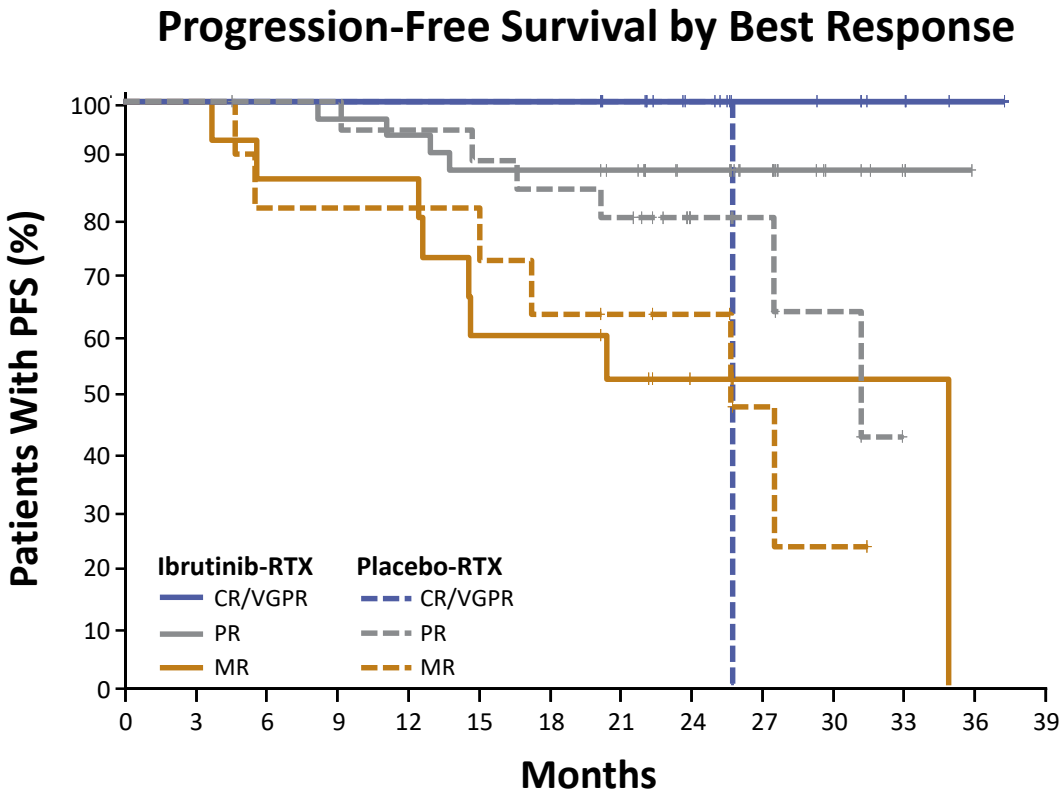


- **Of note, improved PFS was seen in treatment-naïve patients, relapsed patients, and independent of MYD88/CXCR4 genotype**

ASCO 2018, iNNOVATE WM; Dimopoulos et al.

Progression-Free Survival by Genotype and Depth of Response

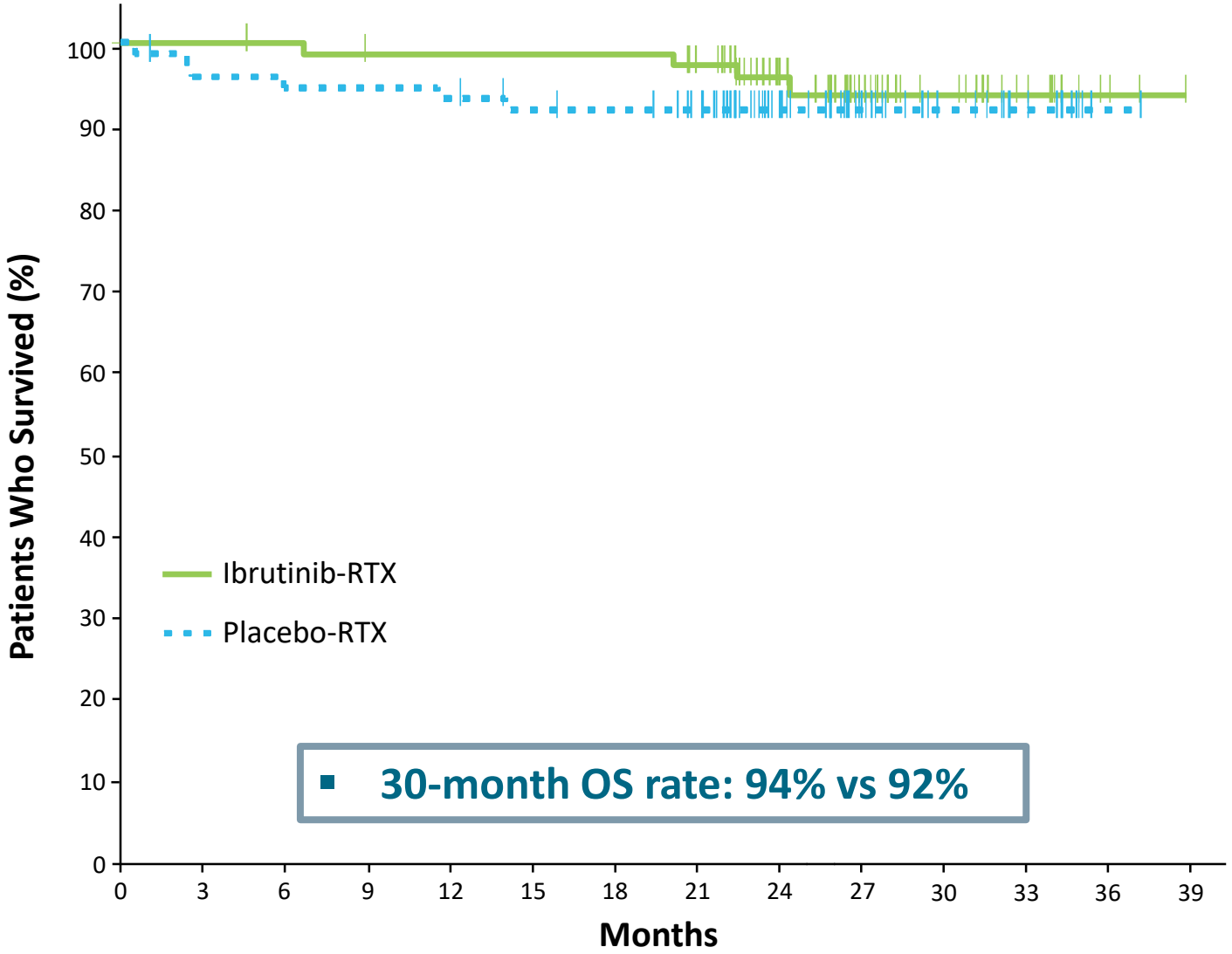




- Improved PFS observed across different MYD88/CXCR4 genotypes with ibrutinib-RTX
- No notable difference in observed PFS between PR and VGPR/CR with ibrutinib-RTX

ASCO 2018, iNNOVATE WM; Dimopoulos et al.

Overall Survival



- 30-month OS rate: 94% vs 92%

- 30 patients in the placebo-RTX arm crossed over to single-agent ibrutinib
- At a median follow-up of 26.5 months,
  - 4 deaths on ibrutinib-RTX
  - 6 deaths on placebo-RTX

ASCO 2018, iNNOVATE WM; Dimopoulos et al.

Treatment of WM

What comes next?

Improving Ibrutinib (Ibrutinib as a backbone)!

→ ***Rituximab/Ibrutinib – Yes, iNNOVATE***
→ ***Rituximab/Ibrutinib/Proteasome inhibitor?***

Primary therapy of WM with carfilzomib, rituximab, dexamethasone (CaRD)

Induction Cycle 1 q21 Days

Days 1, 2, 8, 9: Carfilzomib 20 mg/m^2 IV; dex 20 mg IV

Days 2, 9: Rituximab 375 mg/m^2

Induction Cycles 2-6 q21 Days

Days 1, 2, 8, 9: Carfilzomib 36 mg/m^2 IV; dex 20 mg IV

Days 2, 9: Rituximab 375 mg/m^2

Maintenance Cycles 1-8 q2 Months

Days 1, 2: Carfilzomib 36 mg/m^2 IV; dex 20 mg IV

Day 2: Rituximab 375 mg/m^2

Primary endpoints: ORR, TTP, neuropathy incidence

Treon et al Blood 2014; 124(4):503-510

Carfilzomib, rituximab and dexamethasone (CaRD)

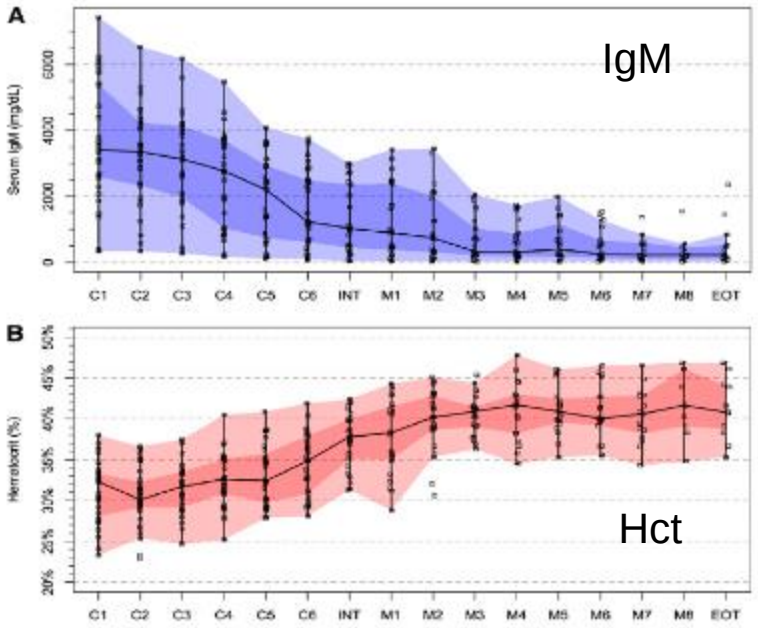
- N=31 patients (28 previously untreated; 3 rituximab, chemo & PI naïve)
- Reasons for treatment initiation:
  - anemia (n = 30)
  - extramedullary disease (n = 5)
  - hyperviscosity (n = 4)
  - IgM-related PN (n = 3)

- 29/30 patients had $MYD88^{L265P}$
- 11/30 patients had $CXCR4^{WHIM}$

Treon et al Blood 2014; 124(4):503-510

Response to CaRD

	N	(%)
ORR	**27**	**87.1%**
Major Response (≥PR)	**21**	**67.7%**
CR	**1**	**3.2%**
VGPR	**10**	**32.2%**
PR	**10**	**32.2%**
MR	**6**	**19.3%**
Non-Response	**4**	**13%**



- Median time to ≥MR: 2.1 months, median time to best response: 12.81 months
- **$CXCR4^{WHIM}$ status: did not affect ORR, ≥PR rate**
- N=9 patients underwent prophylactic pretherapy plasmapheresis, which included 4 patients for whom omission of rituximab occurred for ≥1 cycle.
- "IgM flare" associated with rituximab observed in 5 /22 (22.7%) patients

Treon et al Blood 2014; 124(4):503-510

European Consortium for Waldenström‘s Macroglobulinemia
ECWM - Trials 2018

Trials
First Line

ECWM-1 (Phase III)
DRC versus Bortezomib-DRC
European, over 60 centers
recruiting

ECWM-2 (Phase II)
B-Rituximab/Ibrutinib
European
30 centers

ECWM-3 (Phase III)
Carfilzomib/Ibrutinib vs Ibrutinib
European
60 centers

Relapse

ECWM-3 (Phase III)
Carfilzomib/Ibrutinib vs Ibrutinib
European
60 centers

ECWM-R2 Phase II;
Hovon, Greece
Ixazomib/Rituximab/Dex

ECWM-R3
Phase II; France
Idelalisib/GA101

http://www.ecwm.eu/clinical_trials/__Clinical-Trials.html

ECWM-2 - Quartal III 2018
first line WM – single arm phase II

Key eligibility criteria

- Confirmed WM (N=53)
- Measurable disease
  (serum IgM > 0.5 g/dL)
- In need of treatment
- ECOG PS status of 0–2
- Genotyped for MYD88/CXCR4

Treatment

Induction

- Bortezomib SC 1.6/m^2 d1,8,15 cycle 1-6
- Rituximab 375 mg/m2 IV cycle 1, 1400 SC cycle 1-6
- Ibrutinib 420 mg PO continuously

Maintenance

- Rituximab 1400 SC every 2nd month x 12
- Ibrutinib 420 mg PO continously

http://www.ecwm.eu/clinical_trials/__Clinical-Trials.html

Treatment of WM

What comes next?

After Ibrutinib relapse!

→ ***ABT-199***

DANA-FARBER CANCER INSTITUTE

HARVARD MEDICAL SCHOOL

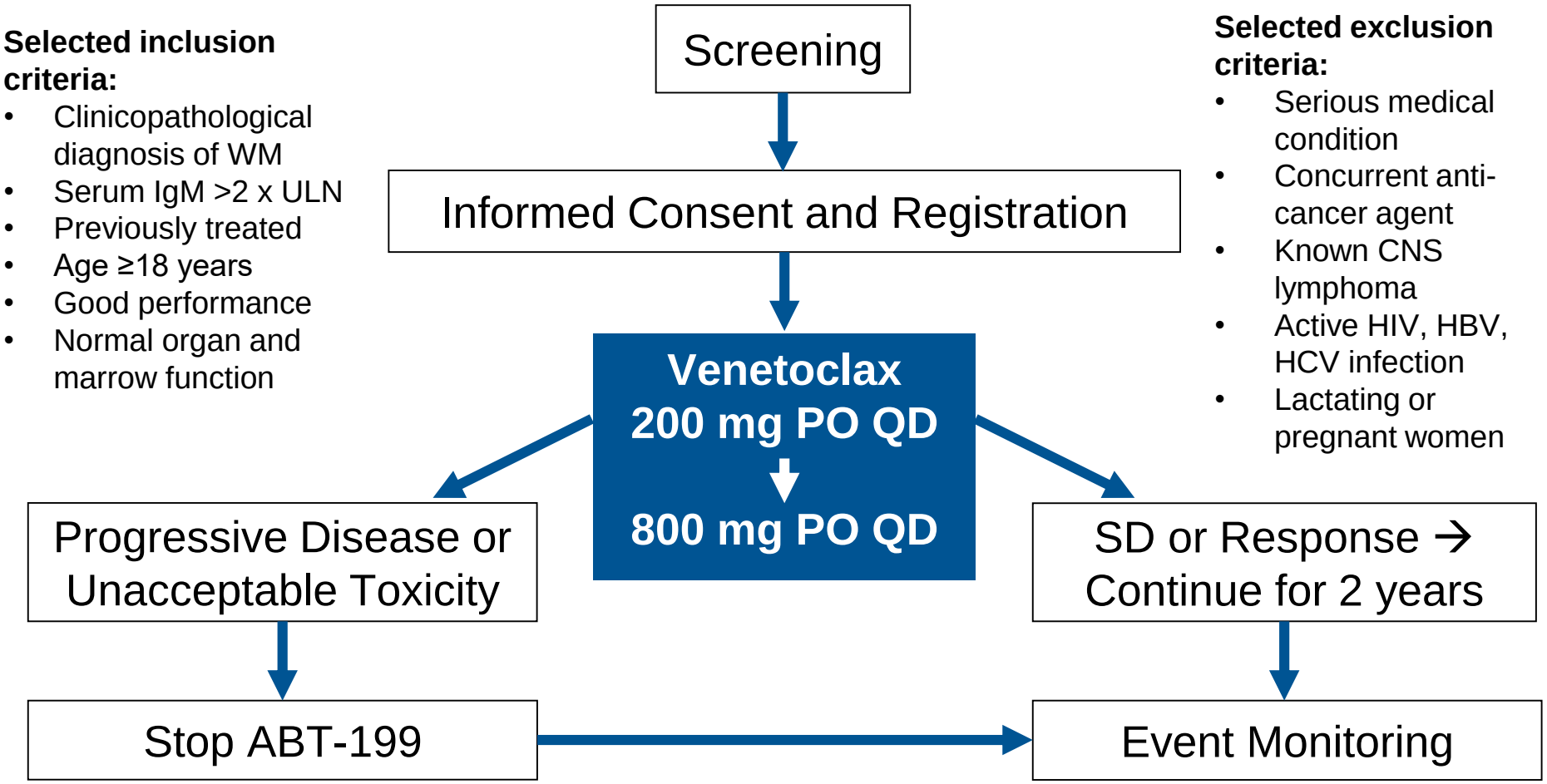
Phase II Study of Venetoclax in Previously Treated Waldenstrom Macroglobulinemia


Castillo JJ, Gustine J, Meid K, Dubeau T, Allan J, Furman R, Siddiqi T, Advani R, Lam J, Hunter Z, Yang G, Davids M, Treon SP

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:

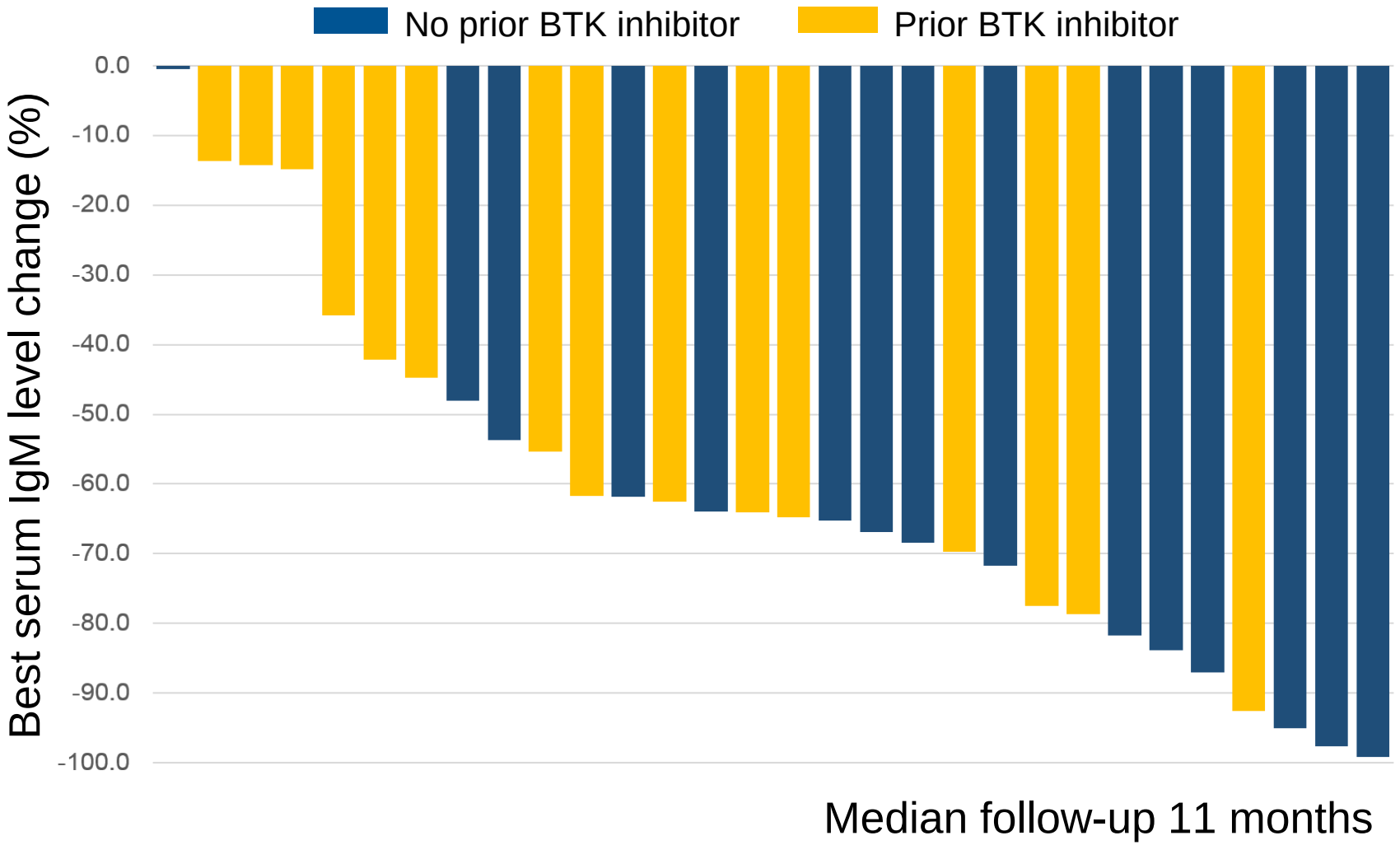
- Serious medical condition
- Concurrent anti-cancer agent
- Known CNS lymphoma
- Active HIV, HBV, HCV infection
- Lactating or pregnant women

www.clinicaltrials.gov: NCT02677324

Phase II Study of Venetoclax in Previously Treated WM

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%)

Phase II Study of Venetoclax in Previously Treated WM



Median follow-up 11 months

Phase II Study of Venetoclax in Previously Treated WM

Response	Number (%)
Overall (≥Minor)	26 (87%)
Major (≥Partial)	22 (74%)
Very good	5 (17%)
Partial	17 (57%)
Minor	4 (13%)
Stable	4 (13%)

Phase II Study of Venetoclax in Previously Treated WM

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

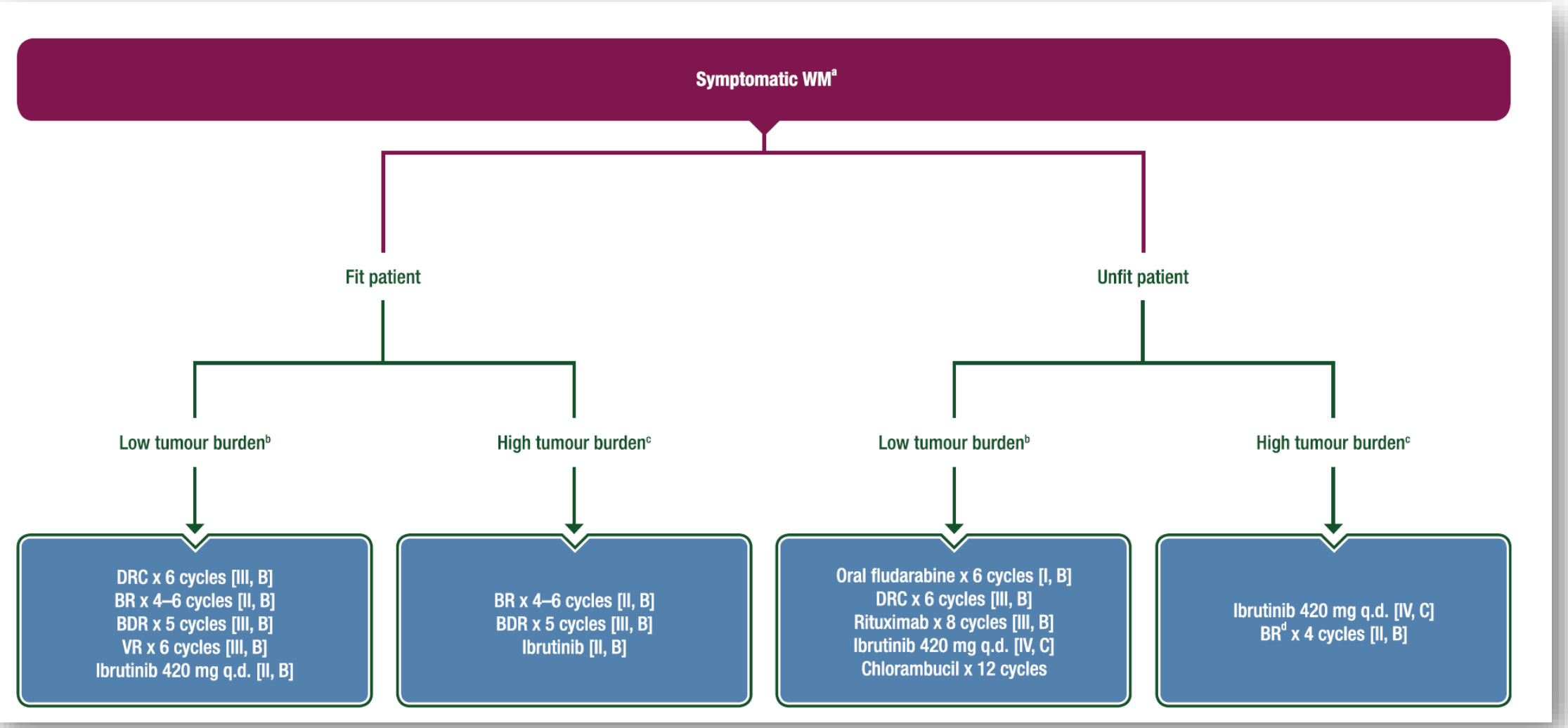
1 patient had progressive disease at 9 months (MYD88, CXCR4, TP53)

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)

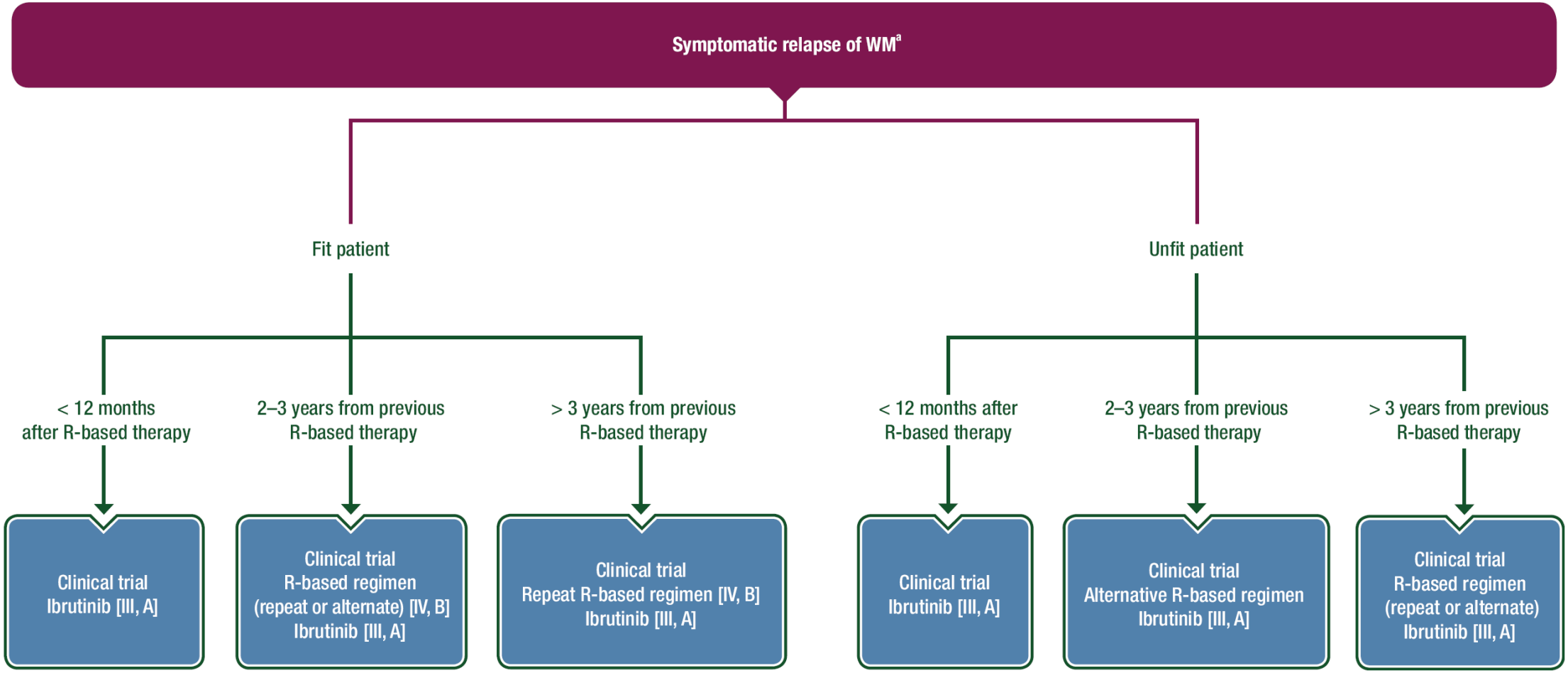
Laboratory TLS (n=1). No IgM flare. No deaths.

Therapeutic Algorithm – ESMO Guidelines 2018



Kastritis E,…. ,Buske C on behalf of the ESMO Guidelines Committee

Therapeutic Algorithm – ESMO Guidelines 2018



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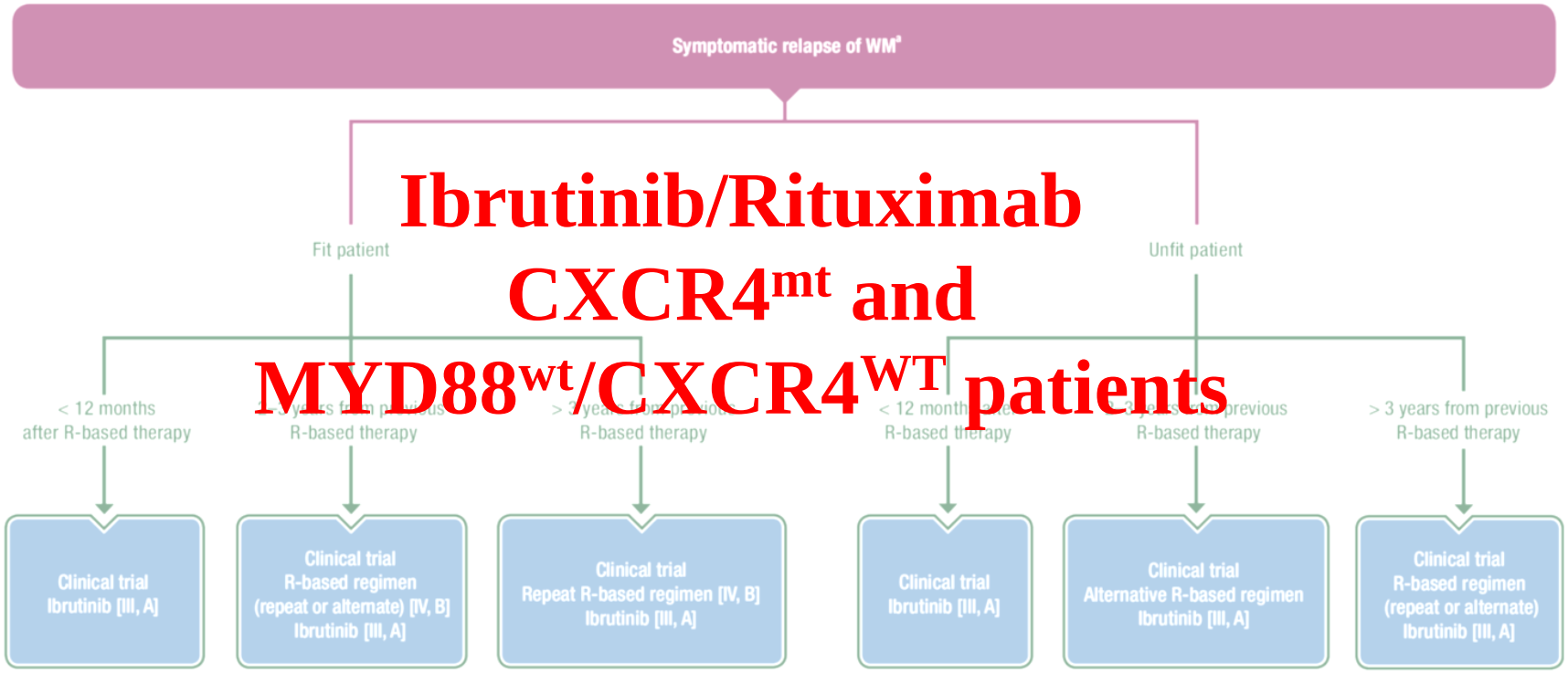

Ibrutinib/Rituximab
$CXCR4^{mt}$ and
$MYD88^{wt}/CXCR4^{WT}$ patients

Kastritis E,…. ,Buske C on behalf of the ESMO Guidelines Committee

European Consortium for Waldenström´s Macroglobulinemia

CLINICAL INTERGROUP
PATHOLOGY PANEL
RESEARCH
CLINICAL TRIALS
MEMBERS

DATES

07.12.2013 - 10.12.2013
ASH 2013
New Orleans

12.06.2014 - 15.06.2013
EHA 2014
Milano

CLINICAL INTERGROUP

Clinical Intergroup

The ECWM is based on a clinical intergroup connecting all major clinical national study groups such as:

- BNLI
- Czech Myeloma Group
- FIL Italian Intergroup
- FCGCLLWM Group
- GLSG/OSHO
- Greek Myeloma Study Group
- HOVON
- Nordic Lymphoma Group
- Portuguese Lymphoma Study Group

http://www.ecwm.eu

Many thanks!

Treatment of WM

Rituximab/Chemotherapy still a good therapy for many patients

European Consortium for Waldenström‘s Macroglobulinemia
ECWM - Trials 2017

Trials
First Line

ECWM-1 (Phase III)
DRC versus Bortezomib-DRC
European, over 60 centers
recruiting

R2W (ECWM-2)(Phase II)
BCR versus FCR
UK , 27 centers
Finished recruitment

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B-Rituximab/Ibrutinib
Germany, France, Greece
60 centers

Relapse

ECWM-R1 (Phase III, iNNOVATE):
Rituximab + Placebo vs Rituximab plus Ibrutinib
Global, 59 centers
Activation in Europe Dec 2014

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ECWM-R3
Phase II; France
Idelalisib/GA101

ECWM-R4
Phase II GA101/CD38 mAb

http://www.ecwm.eu/clinical_trials/__Clinical-Trials.html

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Phase II; France
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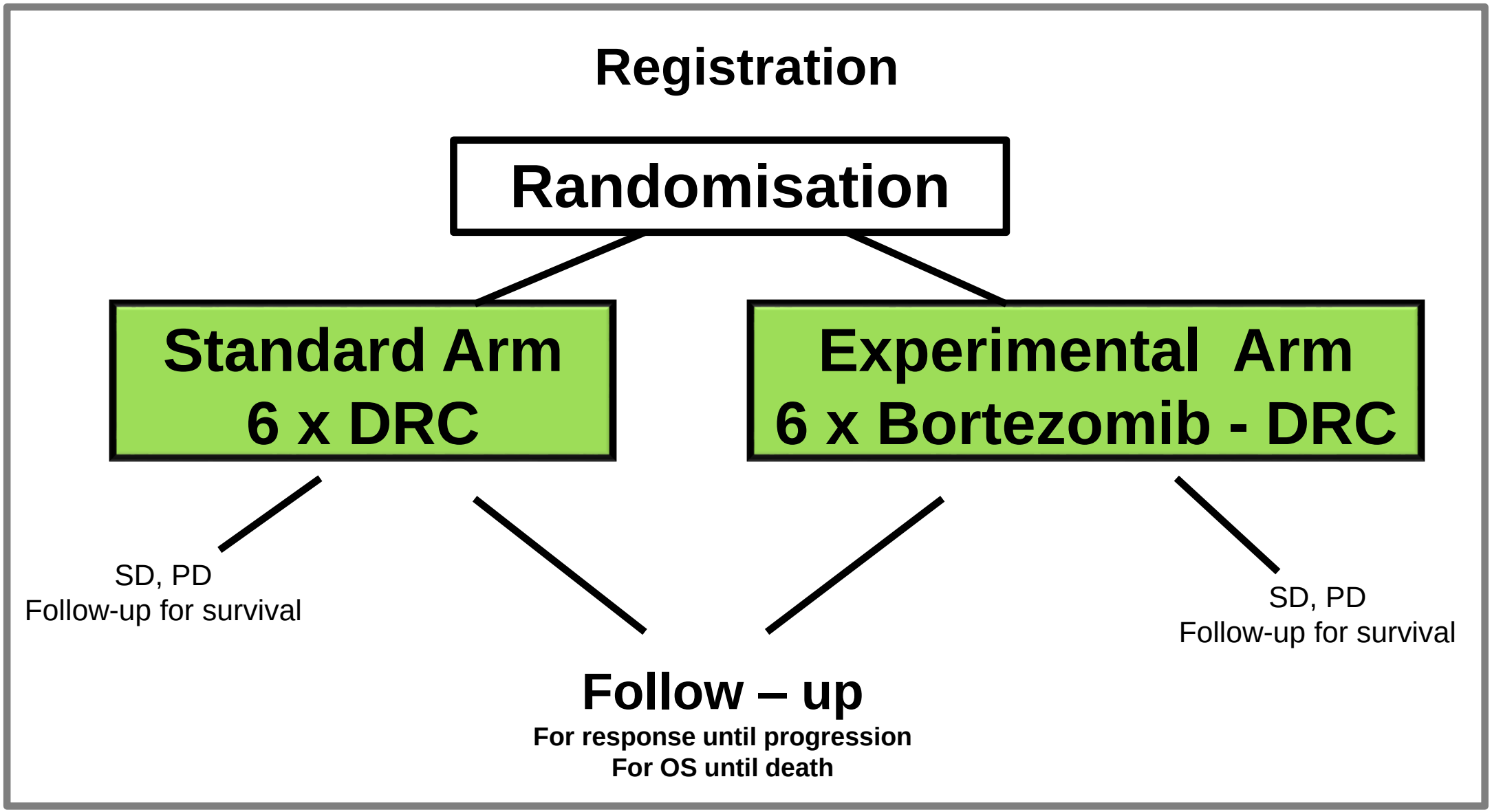
ECWM-R4
Phase II GA101/CD38 mAb

http://www.ecwm.eu/clinical_trials/__Clinical-Trials.html

ECWM-1 first line WM



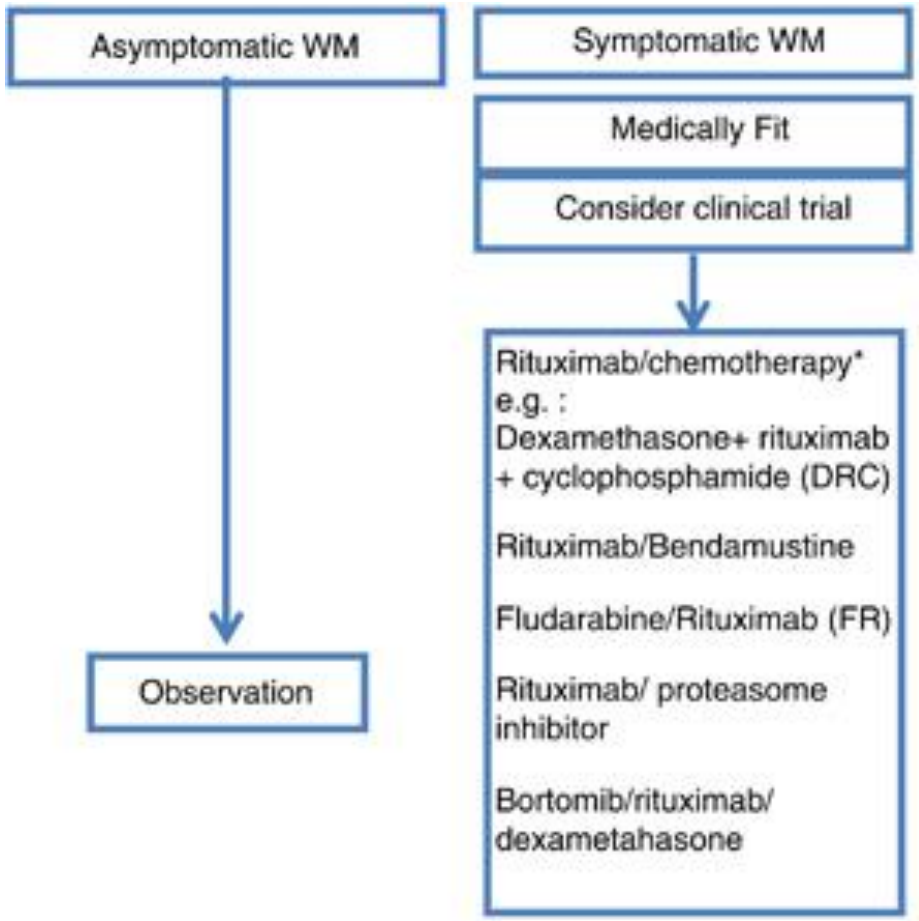
http://www.ecwm.eu/clinical_trials/__Clinical-Trials.html

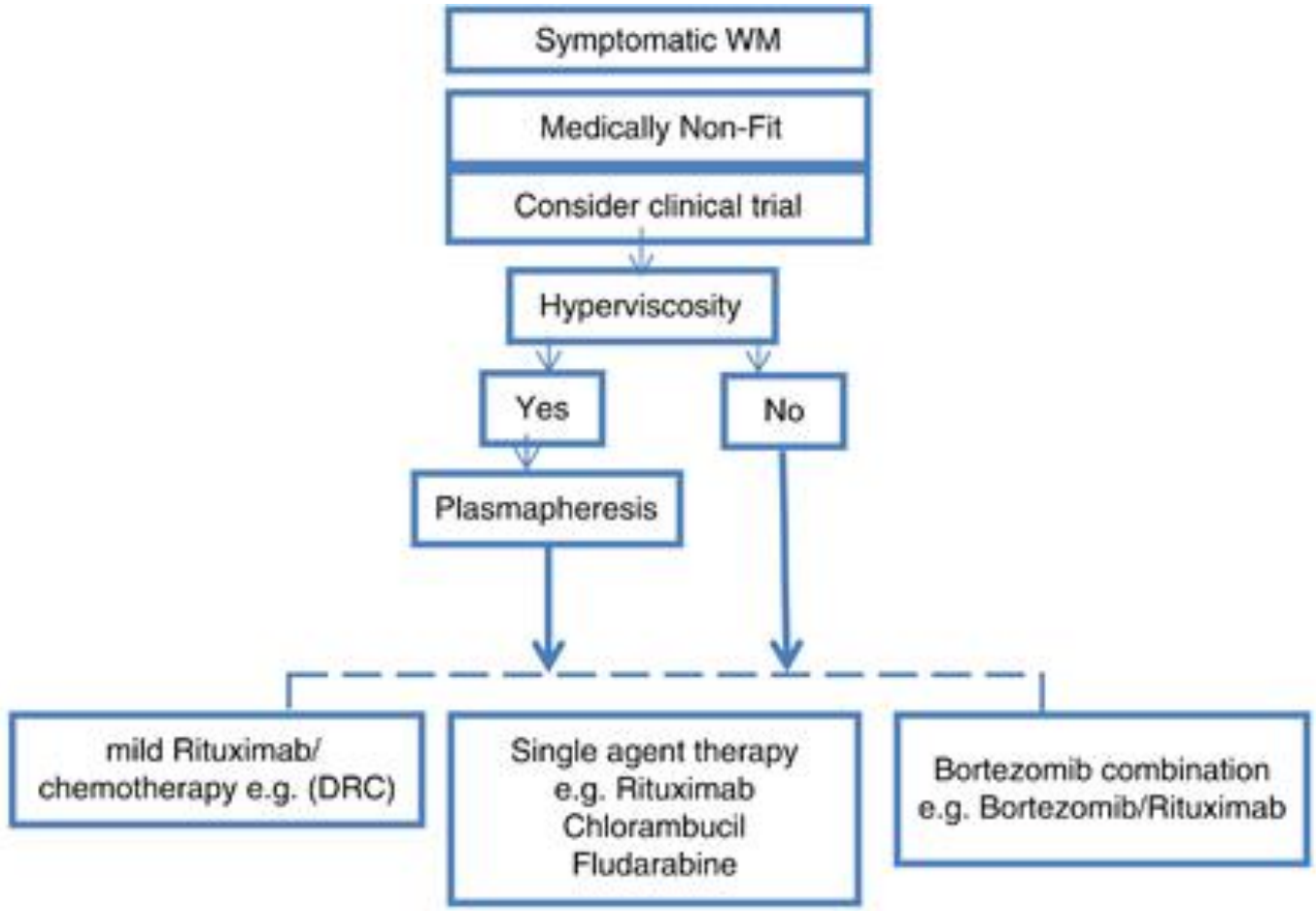
Study ECWM-1 - Status

- Study activated in: Germany, France, Greece, Portugal, Spain, Sweden, Czech Republic
- Patients randomized: 191 (April 2017)

http://www.ecwm.eu/clinical_trials/__Clinical-Trials.html

Treatment Algorithms – WM
First line

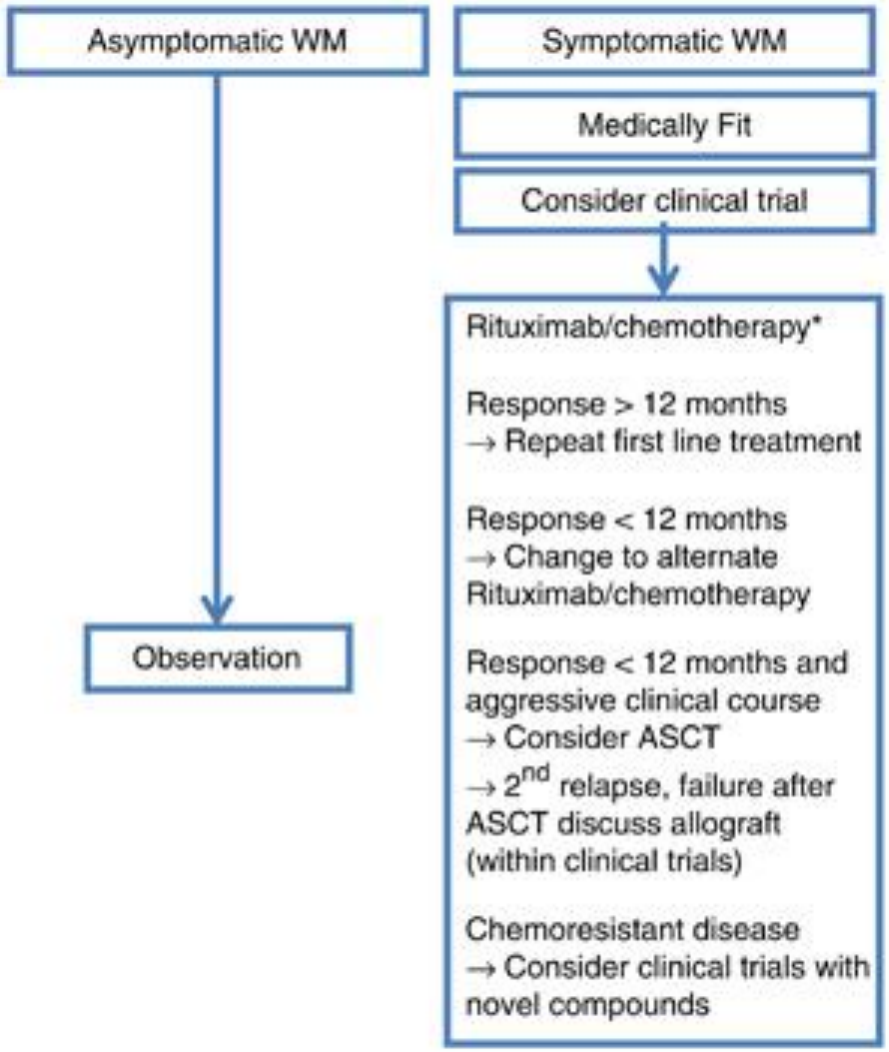


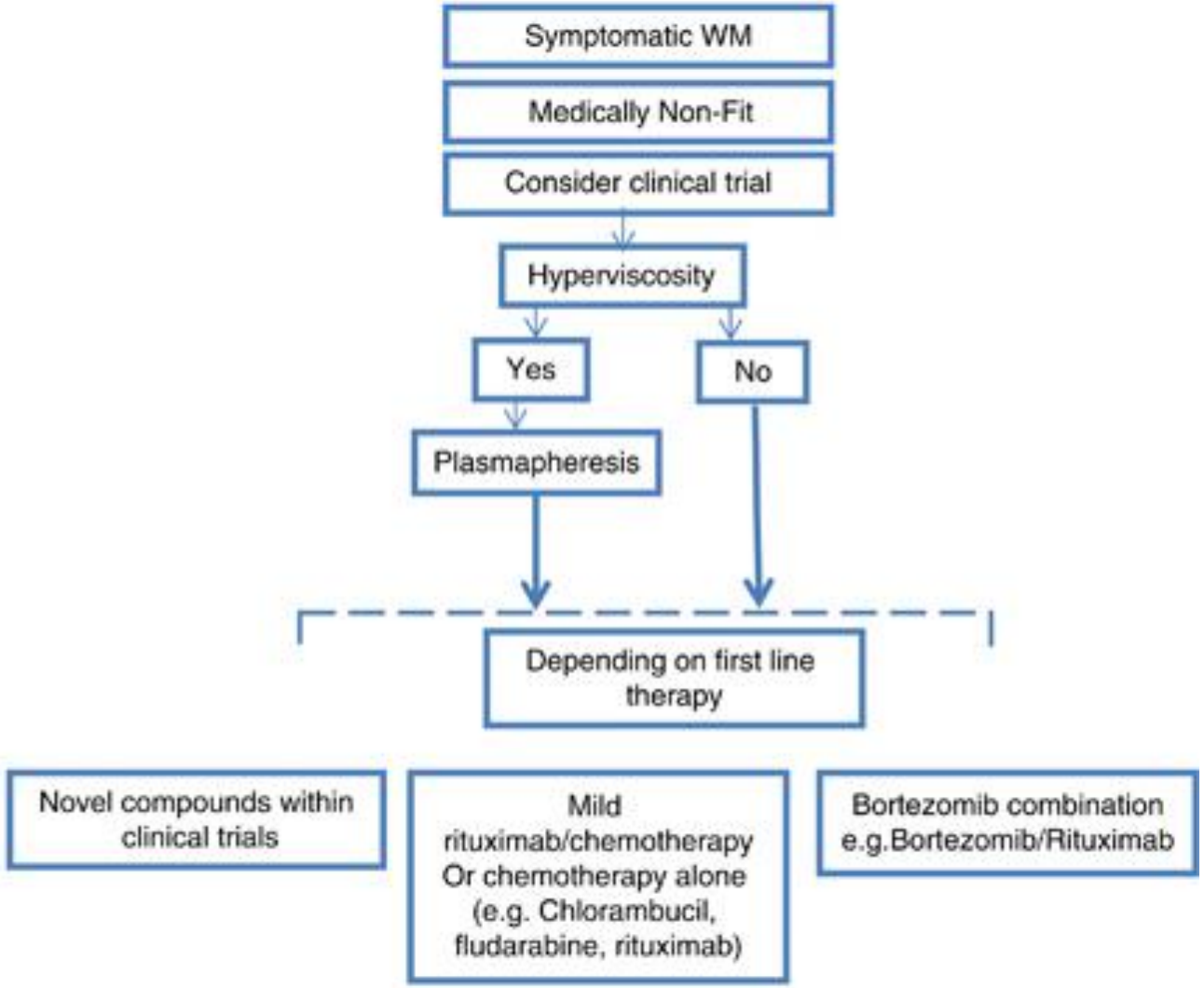


*In case of hyperviscosity consider plasmapheresis before Rituximab application

Buske et al., Ann Oncol 2-013; 24(Supplement 6): vi155–vi159

Treatment Algorithms – WM
Relapse





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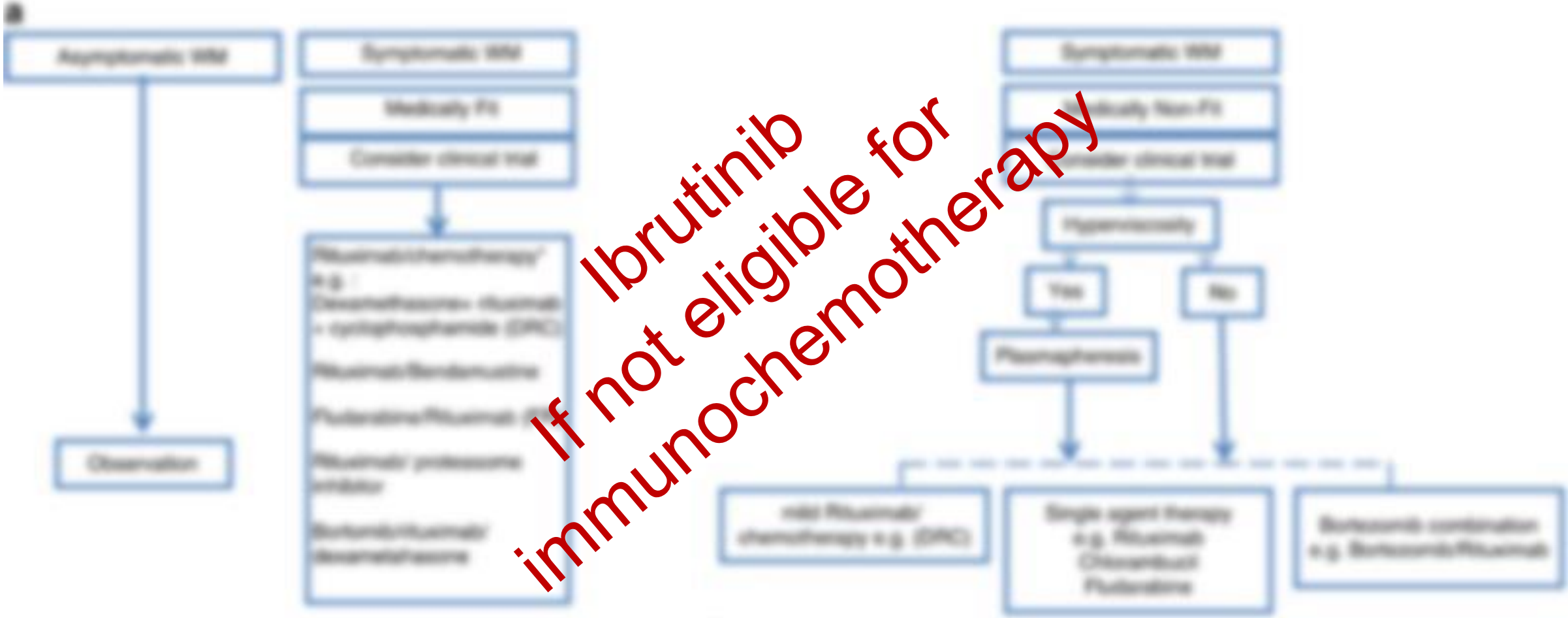
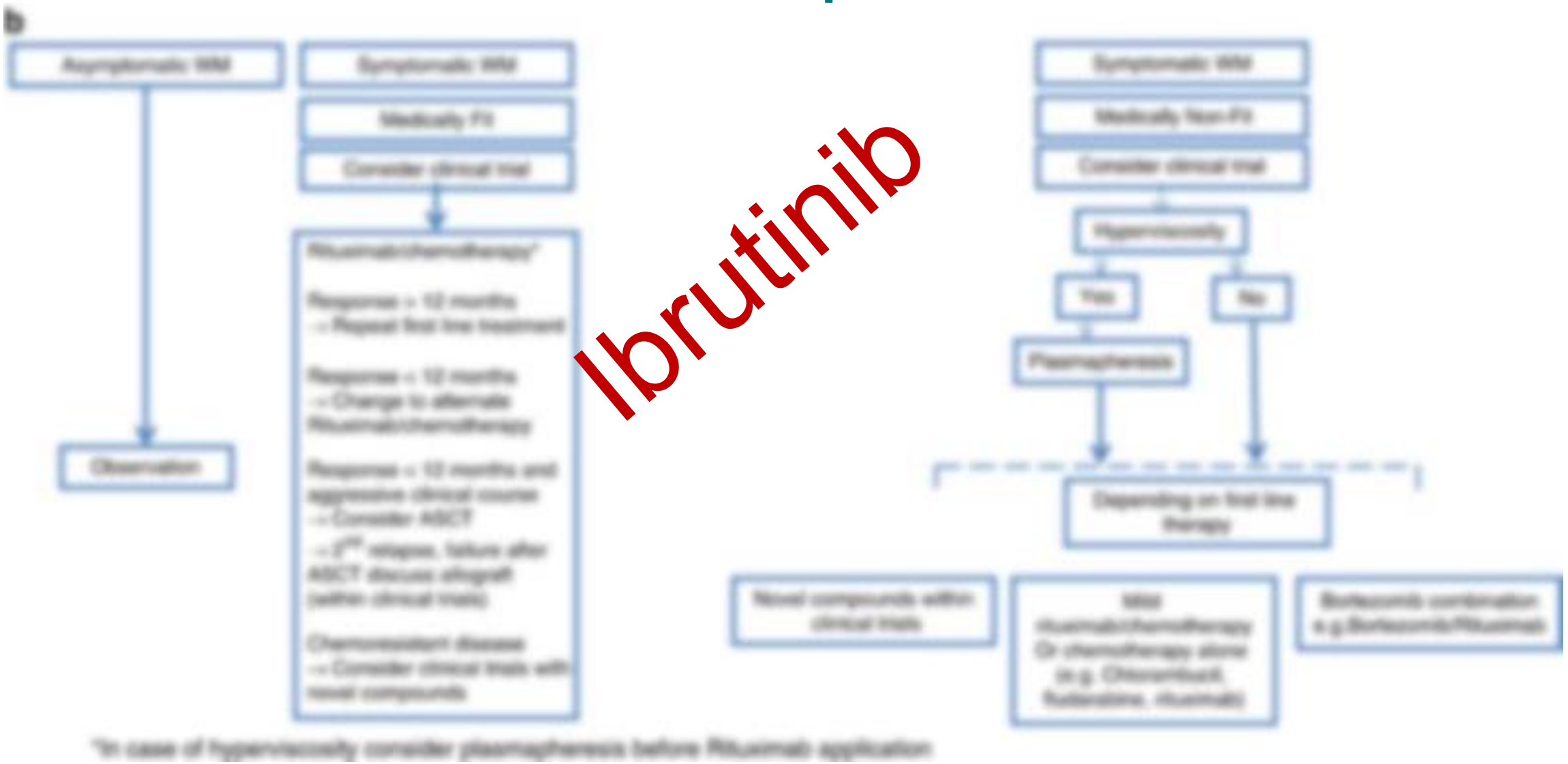
Treatment Algorithms – WM
First line



Ibrutinib
If not eligible for
immunochemotherapy

Buske et al., Ann Oncol 2-013; 24(Supplement 6): vi155–vi159

Treatment Algorithms – WM
Relapse



Buske et al., Ann Oncol 2-013; 24(Supplement 6): vi155–vi159

Modified Response and Progression Criteria for Investigator Assessment

Category	Response Criteria*
Complete response (CR)	• Serum IgM values in the normal range • Disappearance of monoclonal protein by immunofixation (Note: Reconfirmation of CR status is required with a second immunofixation at any time point) • No histological evidence of bone marrow involvement • Complete resolution of lymphadenopathy†/splenomegaly‡ if present at baseline
Very good partial response (VGPR)	• At least 90% reduction of serum IgM from baseline or serum IgM values in normal range • Reduction in lymphadenopathy†/splenomegaly‡ if present at baseline
Partial response (PR)	• At least 50% reduction of serum IgM from baseline • Reduction in lymphadenopathy†/splenomegaly‡ if present at baseline
Minor response (MR)	• At least 25% but less than 50% reduction of serum IgM from baseline
Stable disease (SD)	• Not meeting criteria for CR, VGPR, PR, MR, or progressive disease
Progressive disease (PD)	At least one of the following: • A ≥25% increase in serum IgM with a total increase of at least 500 mg/dL from nadir§ • Confirmation of the initial IgM increase is required when IgM is sole criterion for PD • Appearance of new lymph nodes >1.5 cm in any axis, ≥50% increase from nadir in sum of product of diameters of one or more node, or ≥50% increase in longest diameter of a previously identified node >1 cm in short axis • Appearance of new splenomegaly or ≥50% increase from nadir in enlargement of the spleen • Appearance of new extranodal disease • New or recurrent involvement in bone marrow • New symptomatic disease (based on presence of malignant pleural effusion, Bing Neel syndrome, amyloidosis or light chain deposition disease, or other paraprotein-mediated disorder

*Primary activity evaluations are based on independent review committee evaluations. †A target lesion is defined as a lymph node with a long axis >1.5 cm or a short axis >1.0 cm. ‡Splenomegaly is defined as the longest cranial-caudal measurement of the spleen >13 cm. § Nadir for serum IgM is defined as the lowest serum IgM value obtained at any time from baseline with the exception that serum IgM levels post-g will not be considered for up to 35 days.

ASCO 2018, iNNOVATE WM; Dimopoulos et al.

The BTK Inhibitor, BGB-3111, is Tolerable and Highly Active in Patients with Waldenström Macroglobulinemia: Interim Data From an Ongoing Phase 1 First-in-Human Trial

Constantine S Tam[1,2], Judith Trotman[3,4], Stephen Opat[5,6], Paula Marlton[7], Gavin Cull[8], David Simpson[9], David Gottlieb[4,10], Matthew Ku[11], David Ritchie[1,2,12], Emma Verner[3], Sumita Ratnasingam[5], Mary Ann Anderson[2,12], Peter Wood[7], Mark Kirschbaum[13], Lai Wang[13], Ling Xue[13], Eric Hedrick[13], John F Seymour[1,2], Andrew W Roberts[2,12]

[1]Peter MacCallum Cancer Center, East Melbourne, Victoria, Australia, [2]University of Melbourne, Parkville, Victoria, Australia, [3]Concord Repatriation General Hospital, Concord, Australia, [4]University of Sydney, Australia, [5]Monash Health, Clayton, Victoria, Australia, [6]Monash University, Clayton, Victoria, Australia, [7]Princess Alexandra Hospital and University of Queensland, Brisbane, Australia, [8]Sir Charles Gairdner Hospital, Perth, Western Australia, Australia, [9]North Shore Hospital, Auckland, New Zealand , [10]Westmead Hospital, Westmead, Australia, [11]Austin Health, Heidelberg, Victoria, Australia, [12]Melbourne Health, Parkville, Victoria, Australia, [13]BeiGene, Beijing, China

Tam et al., Blood 2015; abstract 832

Efficacy Summary (n=32)

	Total
Median follow-up (range)	9.6 months (3.0- 24.7 months)
Best Response (n=32)	
CR	0
VGPR	11 (34%)
PR	14 (44%)
MR	5 (16%)
SD	2 (6%)
IgM reduction (median, %)	32.5 g/L to 4.0 g/L (88%)
Hemoglobin Change (median)	10.3 g/dl to 13.6 g/dl
Lymphadenopathy Reduction by CT (#pts, range)	12/12 (9-100%)

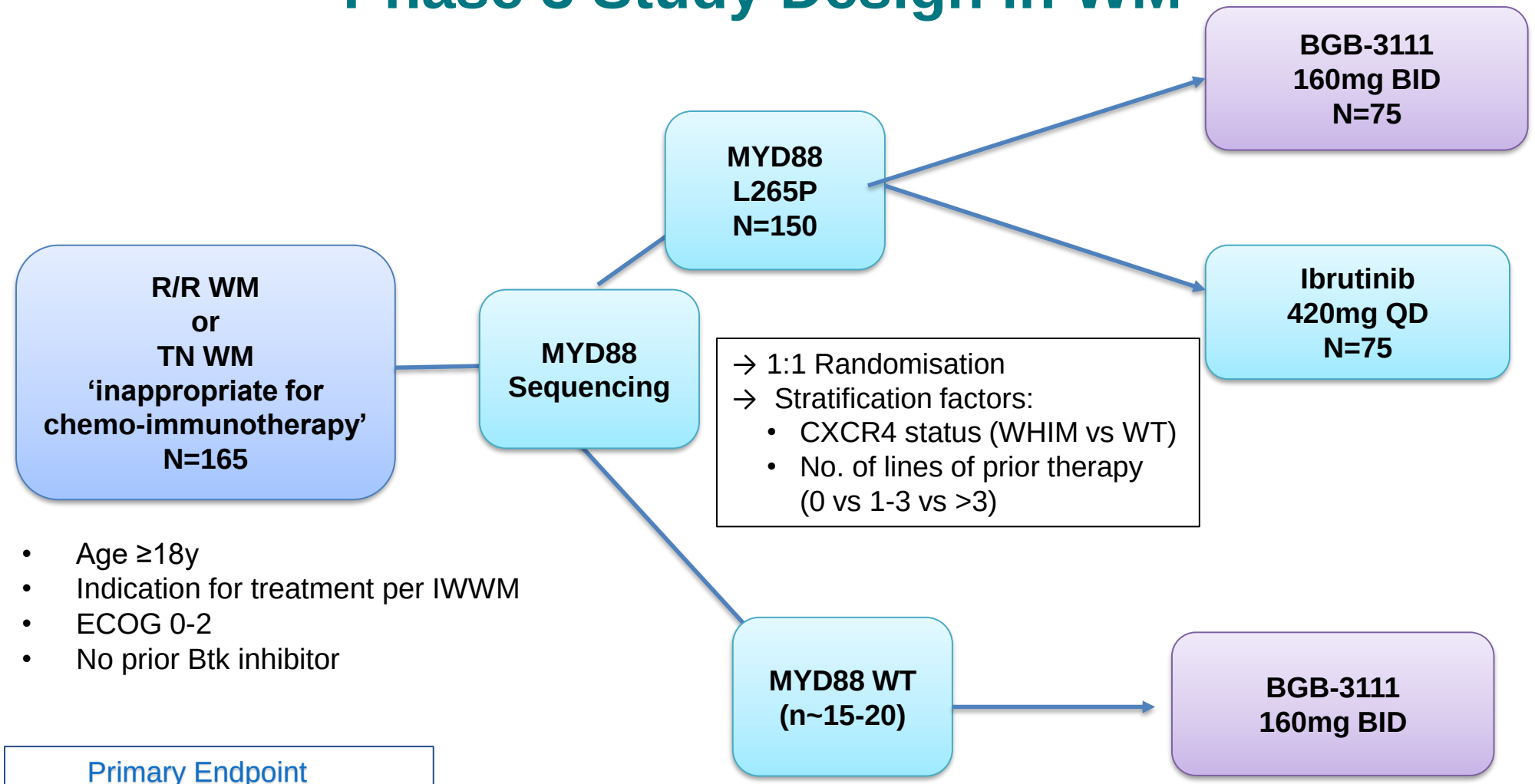
78%*

94%**

* Major response rate
** Overall response rate

Tam et al., Blood 2015; abstract 832

Phase 3 Study Design in WM



- Age ≥18y
- Indication for treatment per IWWM
- ECOG 0-2
- No prior Btk inhibitor

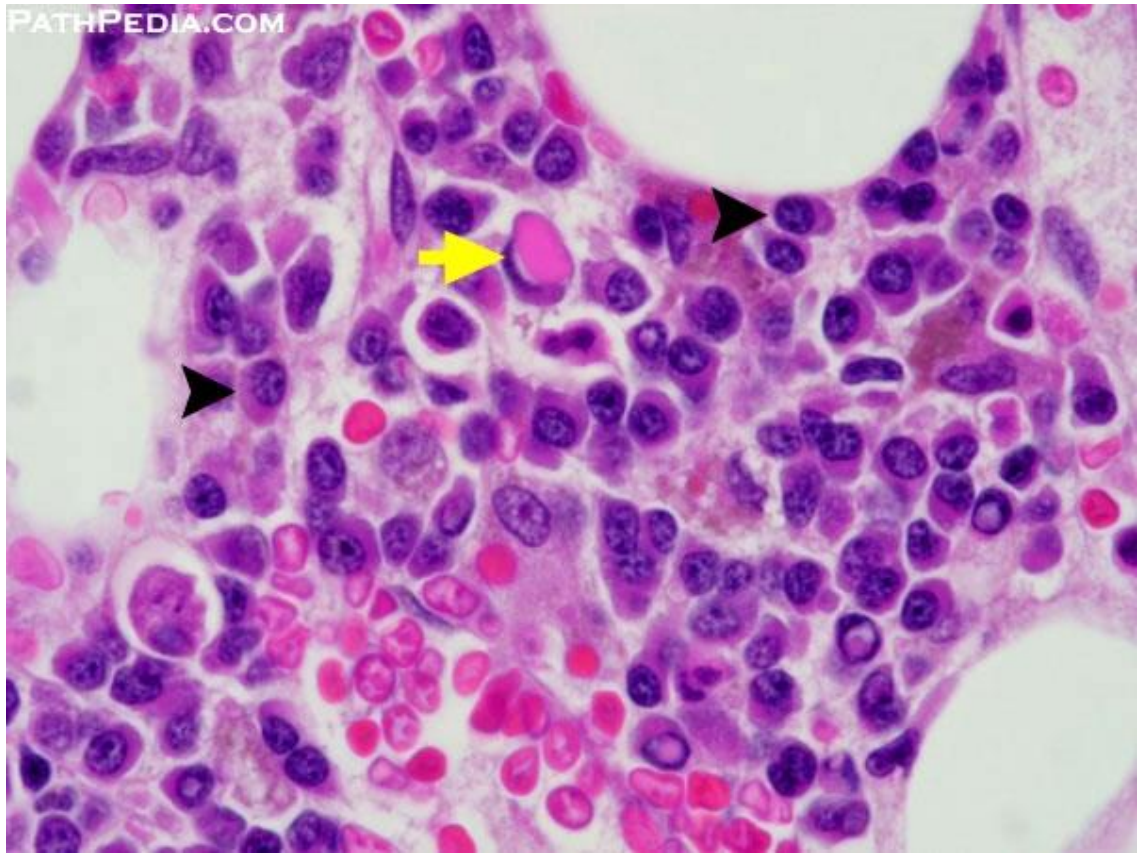
Primary Endpoint
- CR/VGPR rate

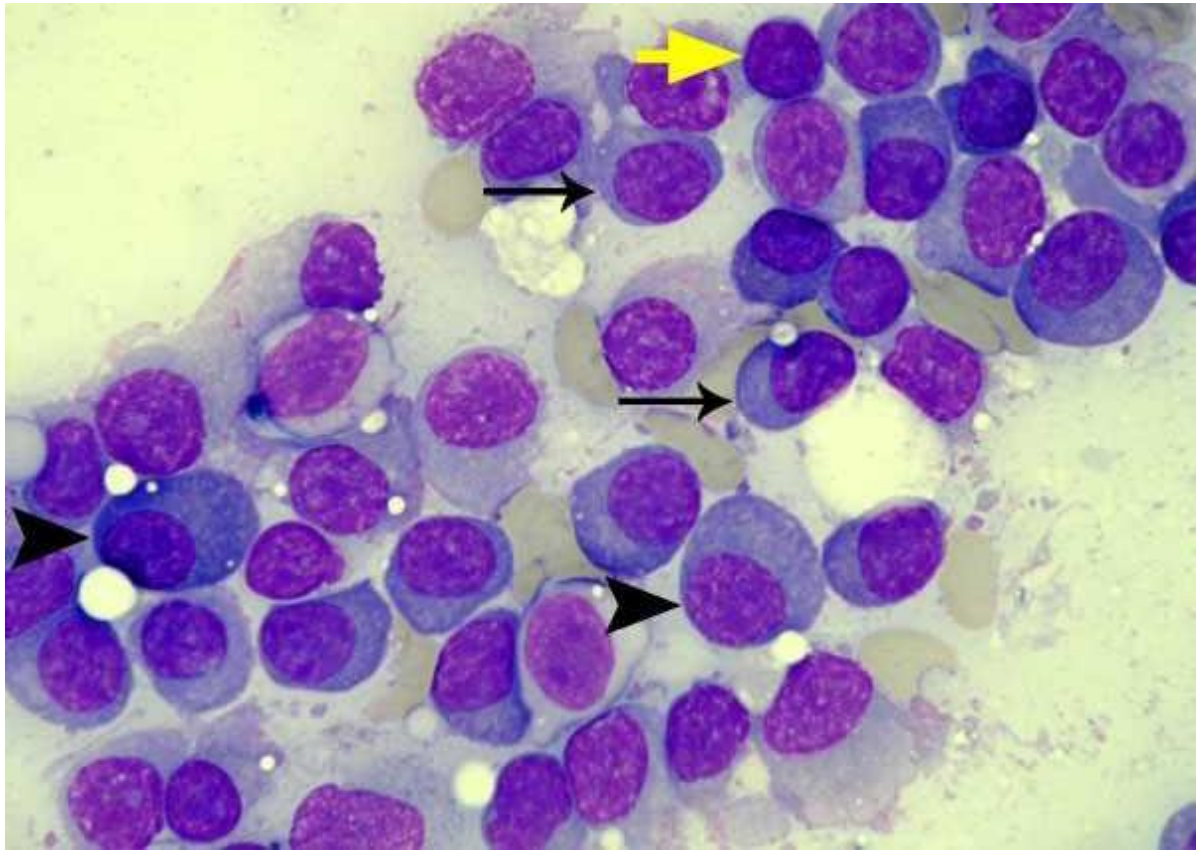
Secondary Endpoint
- MRR (≥PR)
- PFS
- Duration of response
- Symptom resolution

Safety Endpoints
- Incidence, timing and severity of AE
- Incidence of AE of special interest (Afib, bleeding, diarrhea
- Incidence, severity and timing of AE leading to discontinuation

Exploratory Endpoints
- Major RR in MYD88 WT
- OS
- Time to next treatment
- Identification of resistance markers

Why this – WM consists of two cellular populations!

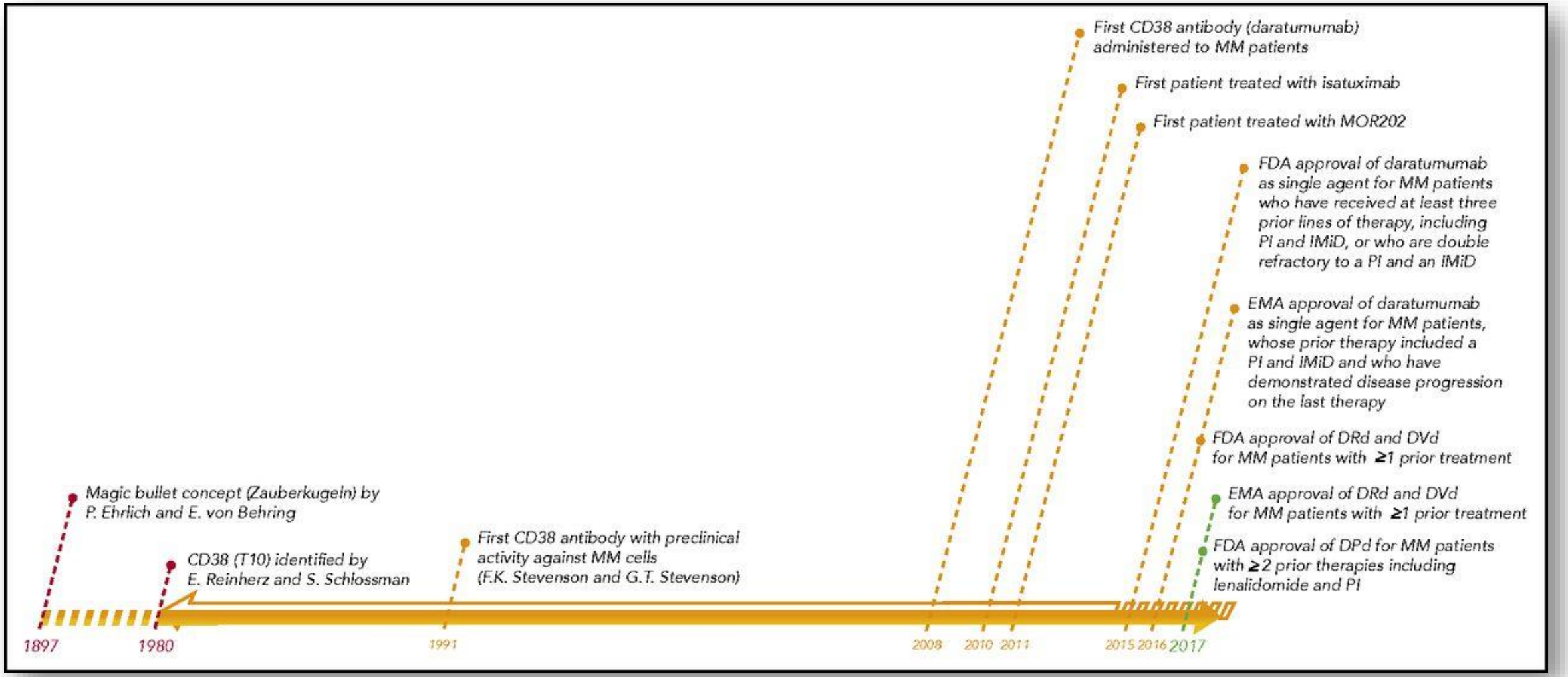




CD20^{+} lymphoid population <u>and</u> CD20^{-} CD38^{+} plasmacytic population!

Personal communication

History of CD38 antibodies



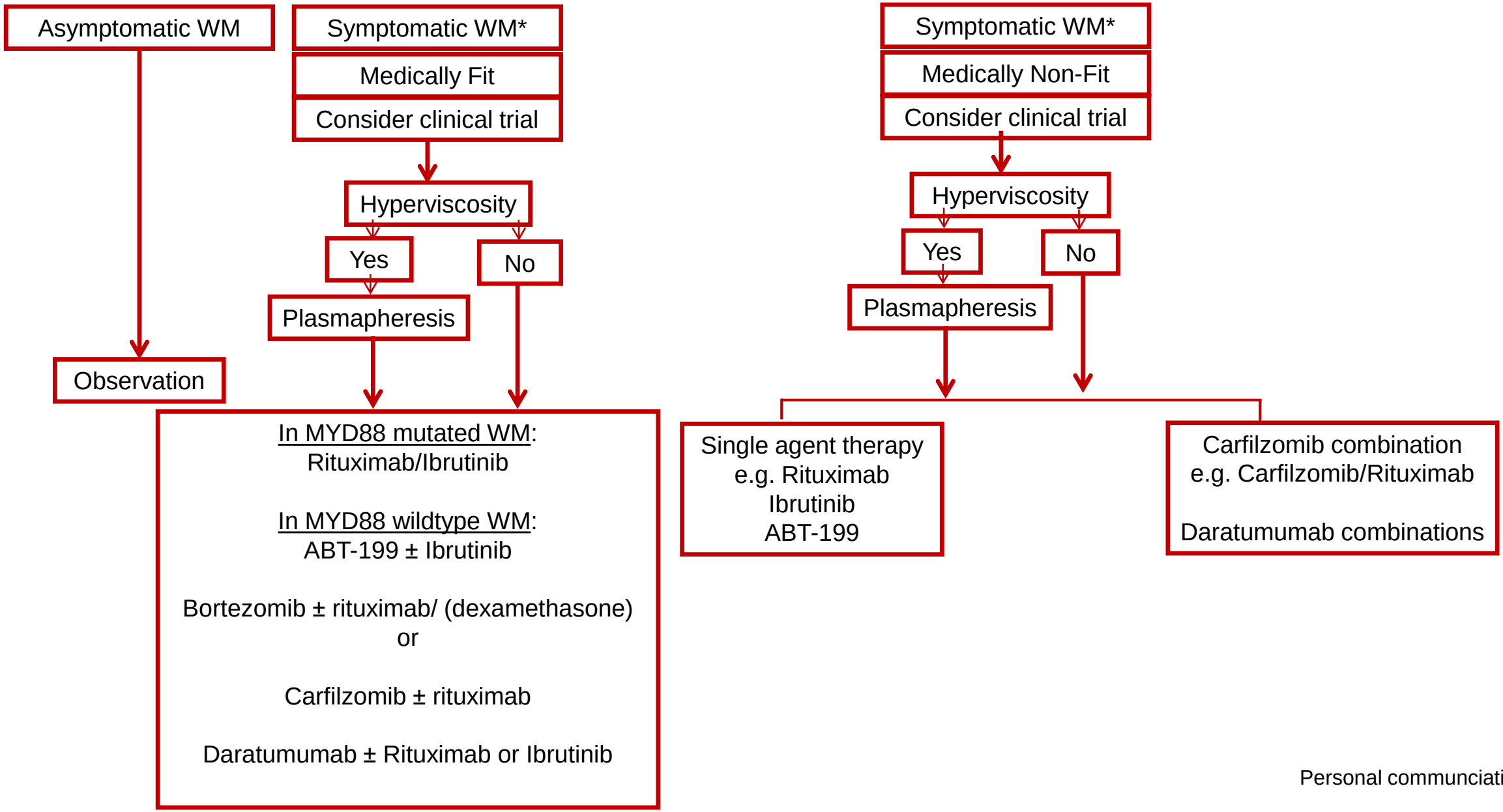
Niels W. C. J. van de Donk et al. Blood 2018;131:13-29

Ulocuplumab (BMS-936564 / MDX1338): a fully human anti-CXCR4 antibody induces cell death in chronic lymphocytic leukemia mediated through a reactive oxygen species-dependent pathway

Manoj K. Kashyap[1], Deepak Kumar[1], Harrison Jones[1], Carlos I. Amaya-Chanaga[1], Michael Y. Choi[1], Johanna Melo-Cardenas[1], Amine Ale-Ali[1], Michelle R. Kuhne[3], Peter Sabbatini[4], Lewis J. Cohen[4], Suresh G. Shelat[4], Laura Z. Rassenti[2], Thomas J. Kipps[1,2], Pina M. Cardarelli[3] and Januario E. Castro[1,2]

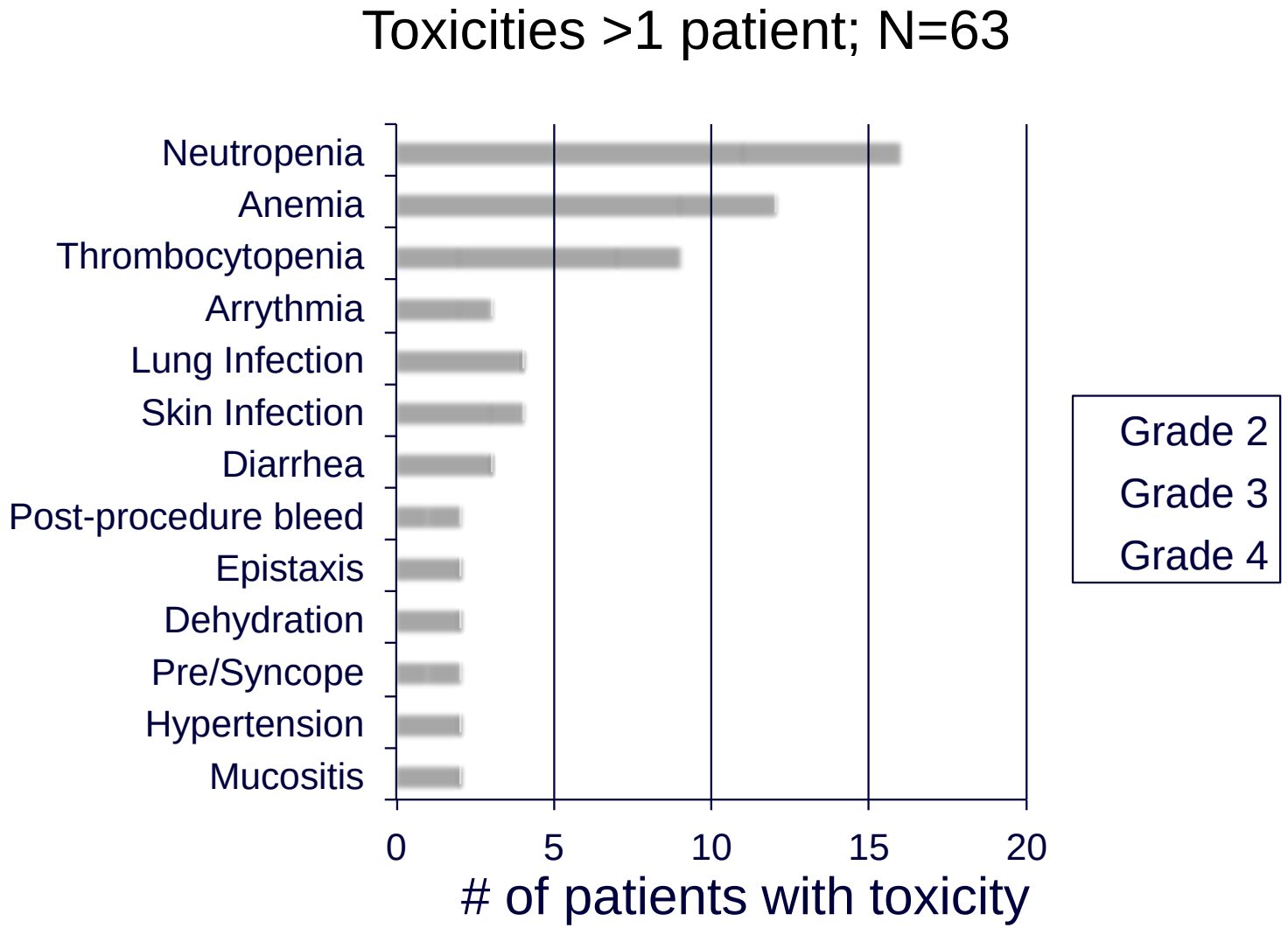
Kashyap et al., Oncotarget 2016; 7(3): 7(3):2809-22

WM treatment in 5 years?



Personal communciation

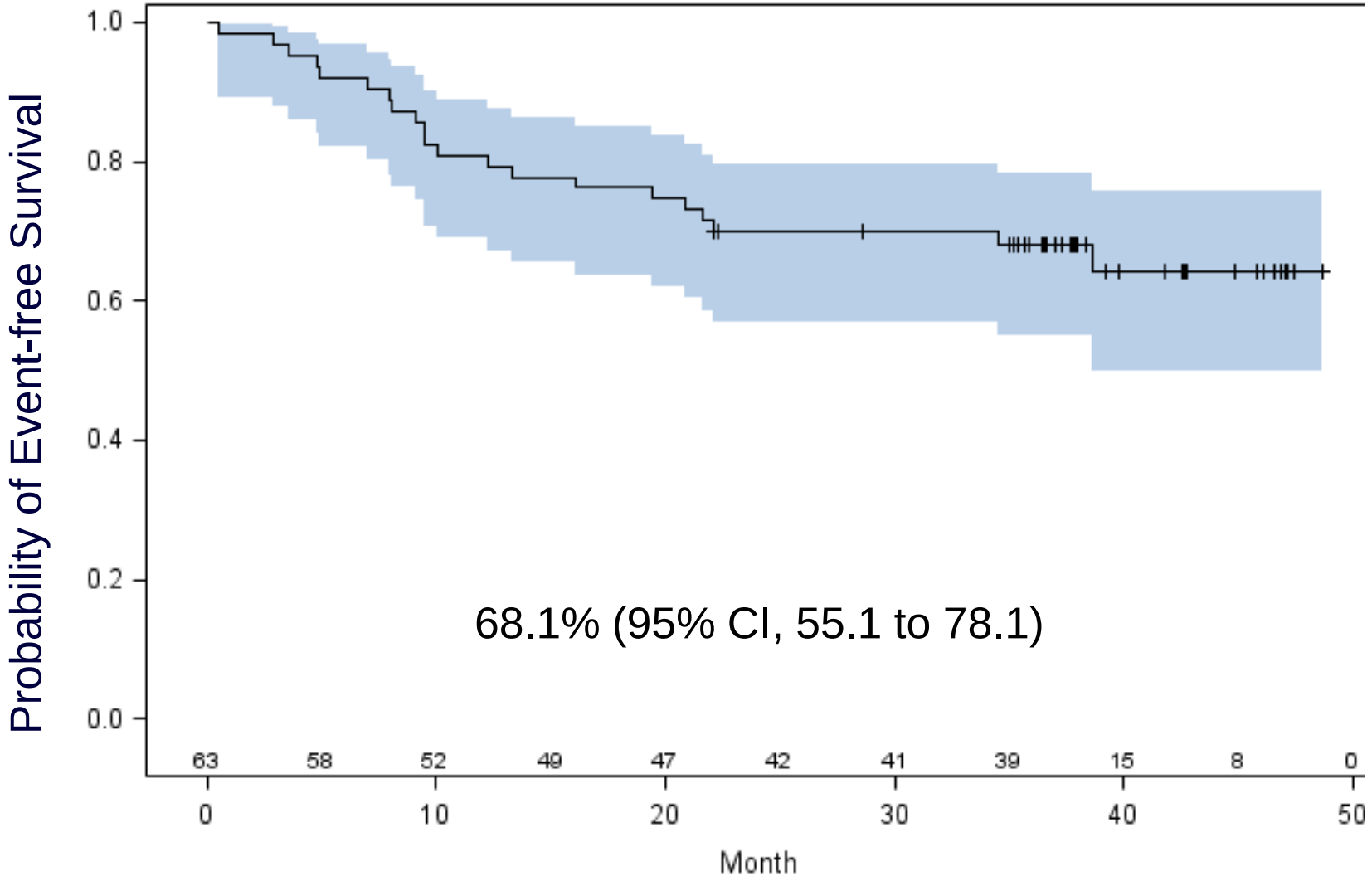
Ibrutinib-related adverse events in previously treated WM patients



- No impact on IGA and IGG immunoglobulins

Treon et al, NEJM 2015; 372(15):1430-40; Gustine et al, Am J Hematol. 2016 Jun;91(6):E312-3

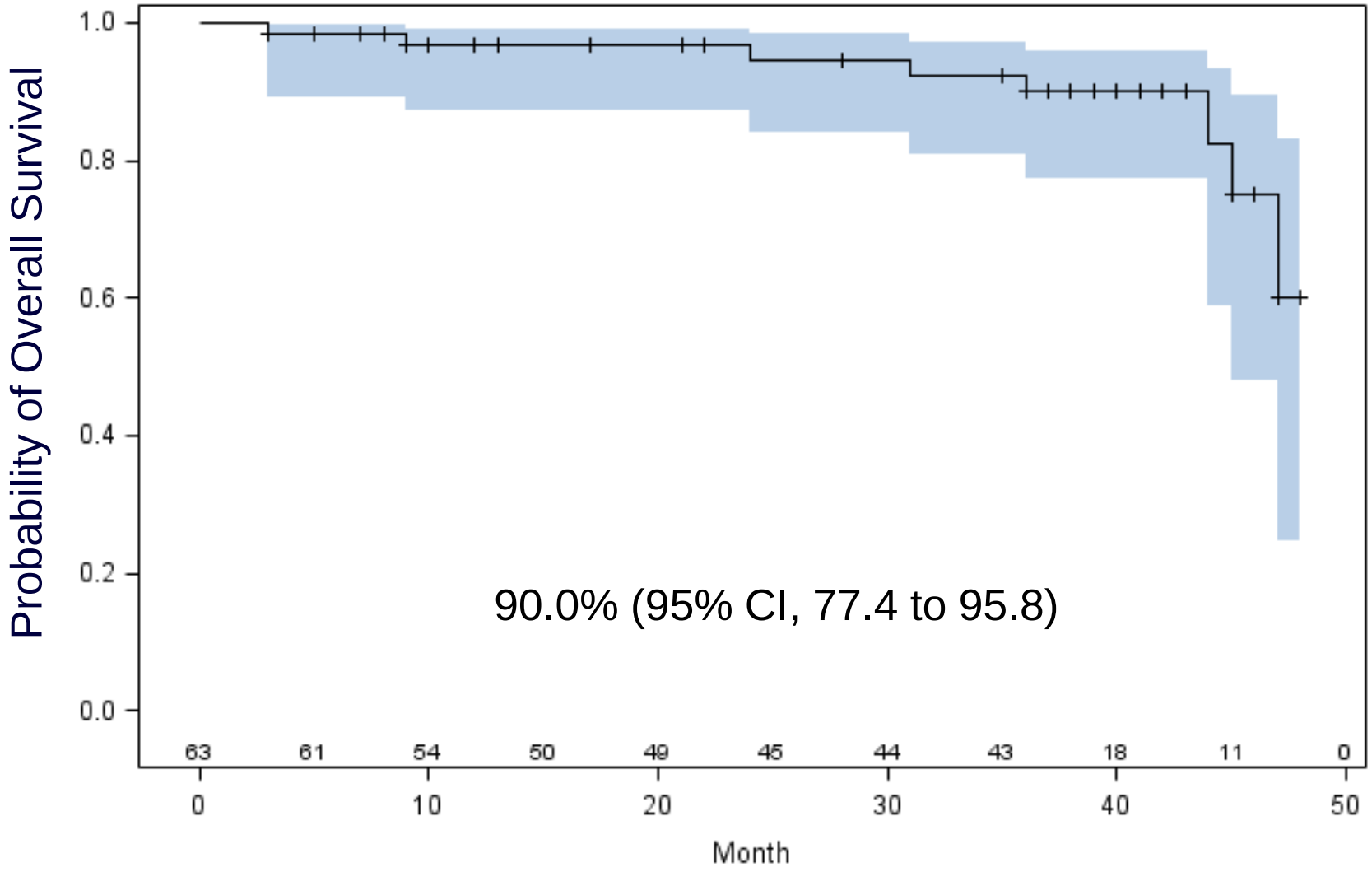
Ibrutinib in Previously Treated WM: Event-free Survival



Median: 37 mo. follow-up

Treon et al, NEJM 2015; 372(15):1430-40

Ibrutinib in Previously Treated WM: Overall Survival



Median: 37 mo. follow-up

Treon et al, NEJM 2015; 372(15):1430-40

Hematologic toxicity

	Grades 1-2	Grade 3	Grade 4	Total Gr 3/4
Neutropenia	3 (10)	3 (10)	1 (3)	13%
Anemia	3 (10)	2 (6)	0	6%
Thrombocytopenia	4 (13)	1 (3)	1 (3)	6%

Dimopoulos et al, Lancet Oncol. 2017; 18(2): 241-250

Non-hematologic toxicity (>10%)

	Grade 1-2	Grade 3	Grade 4
Diarrhea	11 (36)	2 (6)	0
Hypertension	4 (13)	3 (10)	0
Increased tendency to bruise	7 (23)	0	0
Back pain	7 (23)	0	0
Constipation	5 (16)	1 (3)	0
Arthralgia	4 (13)	1 (3)	0
Upper respiratory tract infection	6 (19)	0	0
Pyrexia	6 (19)	0	0
Nausea	6 (19)	0	0
Respiratory tract infection	3 (10)	1 (3)	0
Fatigue	3 (10)	1 (3)	0
Tinnitus	4 (13)	0	0
Peripheral edema	4 (13)	0	0
Cough	4 (13)	0	0
Conjunctivitis	4 (13)	0	0

Dimopoulos et al, Lancet Oncol. 2017; 18(2): 241-250

Infectious complications

	Grade 1-2	Grade 3	Grade 4
Upper respiratory tract infection	6 (19)	0	0
Pyrexia	6 (19)	0	0
Respiratory tract infection	3 (10)	1 (3)	0
Pneumonia	1 (3)	1 (3)	0
Paronychia	1 (3)	1 (3)	0
Cellulitis	1 (3)	1 (3)	0
Aspergillus infection	0	1 (3)	0

Grade 3-4 infections : 15%

Dimopoulos et al, Lancet Oncol. 2017; 18(2): 241-250

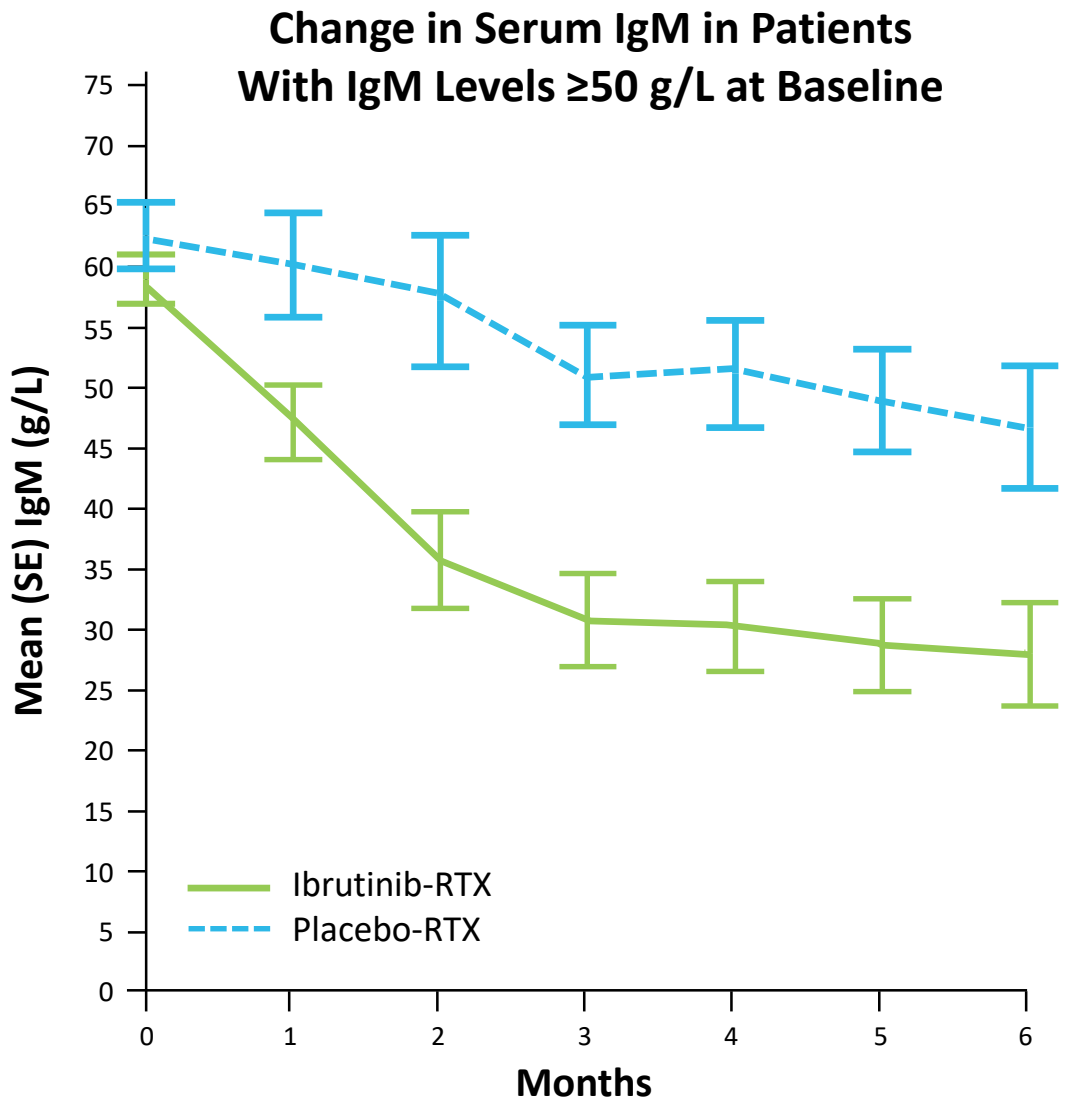
Patient Disposition

	Ibrutinib-RTX (n = 75)	Placebo-RTX (n = 75)
Received study treatment, n (%)	75 (100)	75 (100)
Discontinued ibrutinib/placebo, n (%)		
Progressive disease	7 (9)	33 (44)
AE	4 (5)	3 (4)
Withdrawal by patient	6 (8)	7 (9)
Investigator decision	2 (3)	6 (8)
Discontinued RTX early, n (%)		
Progressive disease	0	6 (8)
AE	2 (3)	9 (12)
Withdrawal by patient	3 (4)	4 (5)
Investigator decision	0	3 (4)

- **93% of patients on ibrutinib-RTX completed RTX treatment vs 71% on placebo-RTX**

ASCO 2018, iNNOVATE WM; Dimopoulos et al.

More Rapid Decline in IgM With Ibrutinib-RTX



- Rapid decline in median IgM in patients with IgM ≥50 g/L at baseline
  - At week 9, mean IgM reduced 39% from baseline with ibrutinib-RTX
- No plasmapheresis with ibrutinib-RTX vs 12 patients with placebo-RTX during the course of treatment

ASCO 2018, iNNOVATE WM; Dimopoulos et al.

Safety Profile of Ibrutinib-RTX Was Similar to the Known Profiles of Each Agent

	Ibrutinib-RTX (n = 75)		Placebo-RTX (n = 75)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
AEs*, n (%)	75 (100)	45 (60)	75 (100)	46 (61)
Infusion-related reactions	32 (43)	1 (1)	44 (59)	12 (16)
Diarrhea	21 (28)	0	11 (15)	1 (1)
Anemia	14 (19)	8 (11)	22 (29)	13 (17)
Hypertension	14 (19)	10 (13)	4 (5)	3 (4)
Asthenia	12 (16)	0	19 (25)	2 (3)
Atrial fibrillation	11 (15)	9 (12)	2 (3)	1 (1)
Fatigue	10 (13)	2 (3)	20 (27)	1 (1)
Tumor flare	6 (8)	0	35 (47)	2 (3)

- **Median time on treatment**
  - **Ibrutinib-RTX: 25.8 months (range, 1.0–37.2)**
  - **Placebo-RTX: 15.5 months (range, 0.4–34.3)**
- **Ibrutinib-RTX: 55% of atrial fibrillation occurred in patients ≥75 years of age**

*The events listed are AEs of any grade that occurred in ≥25% of patients in either treatment group and for which the frequency differed between treatment groups by ≥5% or grade ≥3 AEs that occurred in ≥10% of patients in either treatment group, unless otherwise noted.

ASCO 2018, iNNOVATE WM; Dimopoulos et al.

No Unexpected Toxicities Were Reported

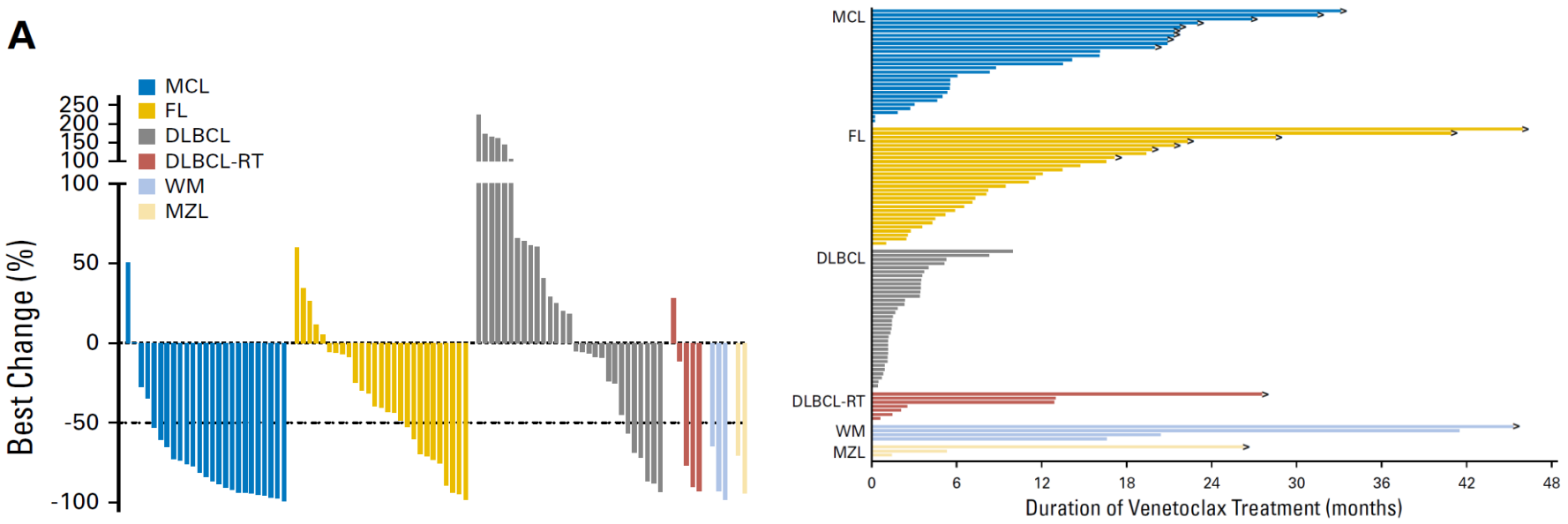
Serious AE, n (%)	Ibrutinib-RTX (n = 75)	Placebo-RTX (n = 75)
Any serious AE*	32 (43)	25 (33)
Pneumonia	6 (8)	2 (3)
Atrial fibrillation	5 (7)	1 (1)
Respiratory tract infection	3 (4)	0
Anemia	2 (3)	0
Arthralgia	2 (3)	0
Congestive cardiac failure	2 (3)	0
Fall	2 (3)	0
Gastroenteritis	2 (3)	0
Myocardial ischemia	2 (3)	0

- **Major hemorrhage: 4% in each arm**
  - **Anticoagulant/antiplatelet medication use**
    - **Ibrutinib-RTX: 43%**
    - **Placebo-RTX: 36%**
- **3 Grade 5 AEs occurred on placebo-RTX (intracranial hemorrhage, nervous system disorder, and not specified)**

*The events listed are serious AEs that occurred in ≥2% of patients in either treatment group.

ASCO 2018, iNNOVATE WM; Dimopoulos et al.

Phase I First-in-Human Study of Venetoclax in Patients With Relapsed or Refractory Non-Hodgkin Lymphoma



Davids J Clin Oncol 2016