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ESMO Clinical Practice Guidelines

Waldenström Macroglobulinemia Discussion Clinical Case Presentation

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Disclosures

Honoraria from Roche, Janssen, Pharmacyclics

Research funding from Roche, Janssen

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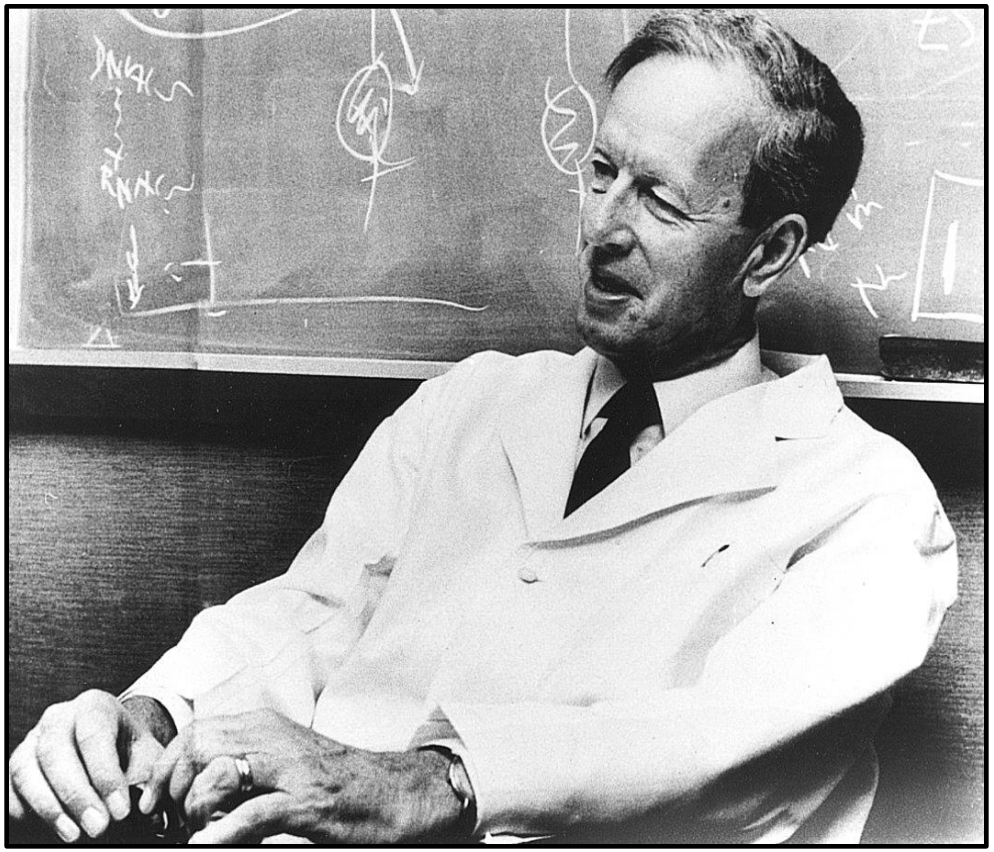
Waldenström Macroglobulinemia (WM)

- First identified in 1944 by Swedish physician, Jan G. Waldenström

- Observations based on 2 patients presenting with:
  - Lymphadenopathy
  - Nasopharyngeal bleeding
  - Increased blood viscosity
  - Infiltration of bone marrow by neoplastic B-cells



Jan G. Waldenström, MD

Waldenström J Acta Medica Scandinaviva 1944

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Case Report

2002: 51 years

- Arterial hypertension, BP=160/90 mmHg, systolic BP: sometimes 190 mmHg
- IgM kappa “MGUS” (no marrow assessment)
- Hb=12.7 g/dL, WBC=6.2 10^9/L, PMN=3.16 10^9/L, Platelet=289 10^9/L, IgM concentration: 9g/L

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Case Report (continued)

May 2011:

- Epistaxis, No other symptoms
- No lymph nodes
- Hb=10.2 g/dL, WBC=3.7 10^9/L, PMN=2.07 10^9/L, Platelet=198 10^9/L
- SEP: β2-globulin: 11.3 g/L; IgM concentration: 60.9 g/L; β2-microglobulin: 2.4 mg/L

  FLC kappa: 300 mg/L, lambda: 6.59 mg/L
- Bone marrow biopsy:

  diffuse lymphoid infiltration (>80%)

  CD20 positive

  MYD88 (L265P) positive (posterior assessment)

  Trisomy 4, del(6q)

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Case Report (continued)

May 2011 (continued)

- Cryoglobulin: positive, high titer, preventing the identification of the type
- Fundoscopic:

  February 2011 (at this time done at home for arterial hypertension): central retinal hemorrhages, tortuous blood vessels

  Adjust treatment of arterial hypertension → good control of BP

  May 2011: small blot-like retinal hemorrhages, tortuous blood vessels with venous sausaging

June 2011:

- Hb=9.1 g/dL, Platelet=214 10^9/L, WBC=3.9 10^9/L, PMN=1.99 10^9/L

Q 1: Please indicate indisputable criteria for initiating therapy in May 2011

1. Epistaxis
2. *Fundoscopic abnormalities*
3. Anemia
4. *IgM concentration*
5. none

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LPL/ Waldenström's macroglobulinemia - Start of Therapy –

Consensus Panel Recommendation

-- not be based on IgM level per se
-- recurrent fever, night sweats, fatigue due to anemia
-- weight loss
-- presence of progressive symptomatic lymphadenopathy or splenomegaly
-- presence of anemia (Hb ≤ 10 g/dL) or platelet count ≤ 100 x 10^9/L
-- symptomatic sensorimotor peripheral neuropathy
-- systemic amyloidosis, renal insufficiency or symptomatic cryoglobulinemia
-- hyperviscosity syndrome

Q 2: Please indicate the ISSWM subgroup

1. Low
2. Intermediate
3. High

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International Prognostic Index WM (ISSWM)

	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			

Q 2: Please indicate the ISSWM subgroup

1. Low (Score 1 → Hb)
2. Intermediate
3. High

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Response Criteria?

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Initial Therapy

DRC regimen (Dexamethasone, Rituximab, Cyclophosphamide) is initiated

	Date	Hb (g/dL)	IgM (g/L)
1st cycle DRC	25/06/2011	9.1	66.4
6th cycle DRC	05/12/2011	11.7	19.4
Best response	22/05/2013	13.6	6

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Response Criteria in WM

Response category	Definition
Complete response (CR)	Absence of serum monoclonal IgM protein by immunofixation Normal serum IgM level Complete resolution of extramedullary disease, i.e., lymphadenopathy and splenomegaly if present at baseline Morphologically normal bone marrow aspirate and trephine biopsy
Very good partial response (VGPR)	Monoclonal IgM protein is detectable ≥90% reduction in serum IgM level from baseline* Complete resolution of extramedullary disease, i.e., lymphadenopathy/splenomegaly if present at baseline No new signs or symptoms of active disease
Partial response (PR)	Monoclonal IgM protein is detectable ≥50% but<90% reduction in serum IgM level from baseline* Reduction in extramedullary disease, i.e., lymphadenopathy/splenomegaly if present at baseline No new signs or symptoms of active disease
Minor response (MR)	Monoclonal IgM protein is detectable ≥25% but<50% reduction in serum IgM level from baseline* No new signs or symptoms of active disease
Stable disease (SD)	Monoclonal IgM protein is detectable <25% reduction and <25% increase in serum IgM level from baseline* No progression in extramedullary disease, i.e., lymphadenopathy/splenomegaly No new signs or symptoms of active disease
Progressive disease (PD)	≥25% increase in serum IgM level* from lowest nadir (requires confirmation) and/or progression in clinical features attributable the disease

*Sequential changes in IgM levels may be determined either by M protein quantitation by densitometry or total serum IgM quantitation by nephelometry.

Best response

sometimes very delayed

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If we have to treat….., which treatment would we choose?

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Case Report - Initial Therapy

1. DRC regimen (Dexamethasone, Rituximab, Cyclophosphamide) is initiated

	Date	**Hb (g/dL)**	**IgM (g/L)**
1st cycle DRC	25/07/2011	9,1	66,4
6th cycle DRC	05/12/2011	11,7	19,4
Best response	22/05/2013	13,6	6

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Treatment Concepts in Waldenstrom‘s Macroglobulinemia

Published Data

a. Chemotherapy alone

-- alkylating agents

-- purine analogues

b. Rituximab alone

c. Rituximab plus Chemotherapy

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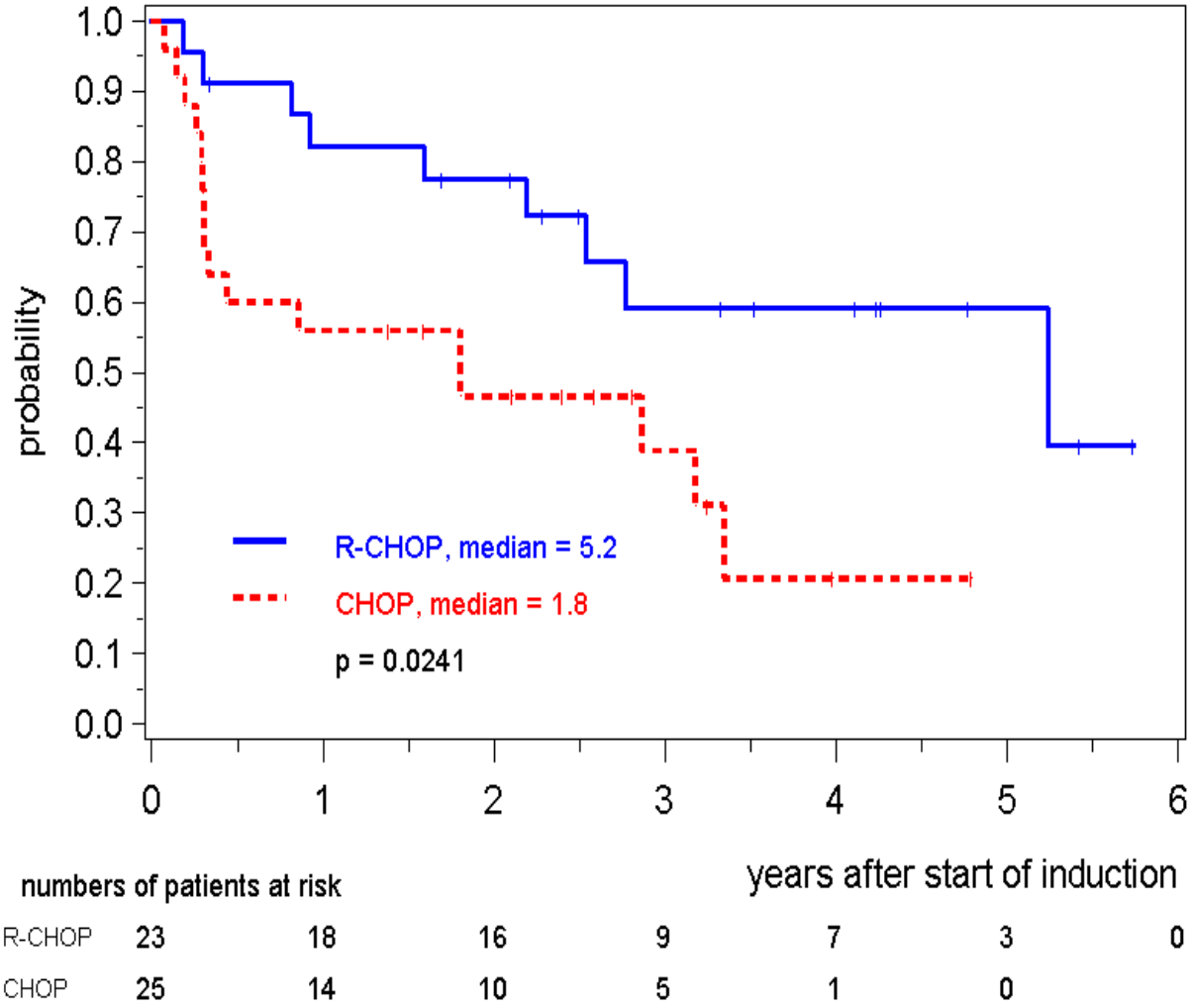
CHOP vs. R-CHOP in WM
- TTF -



Buske et al., Leukemia 2009

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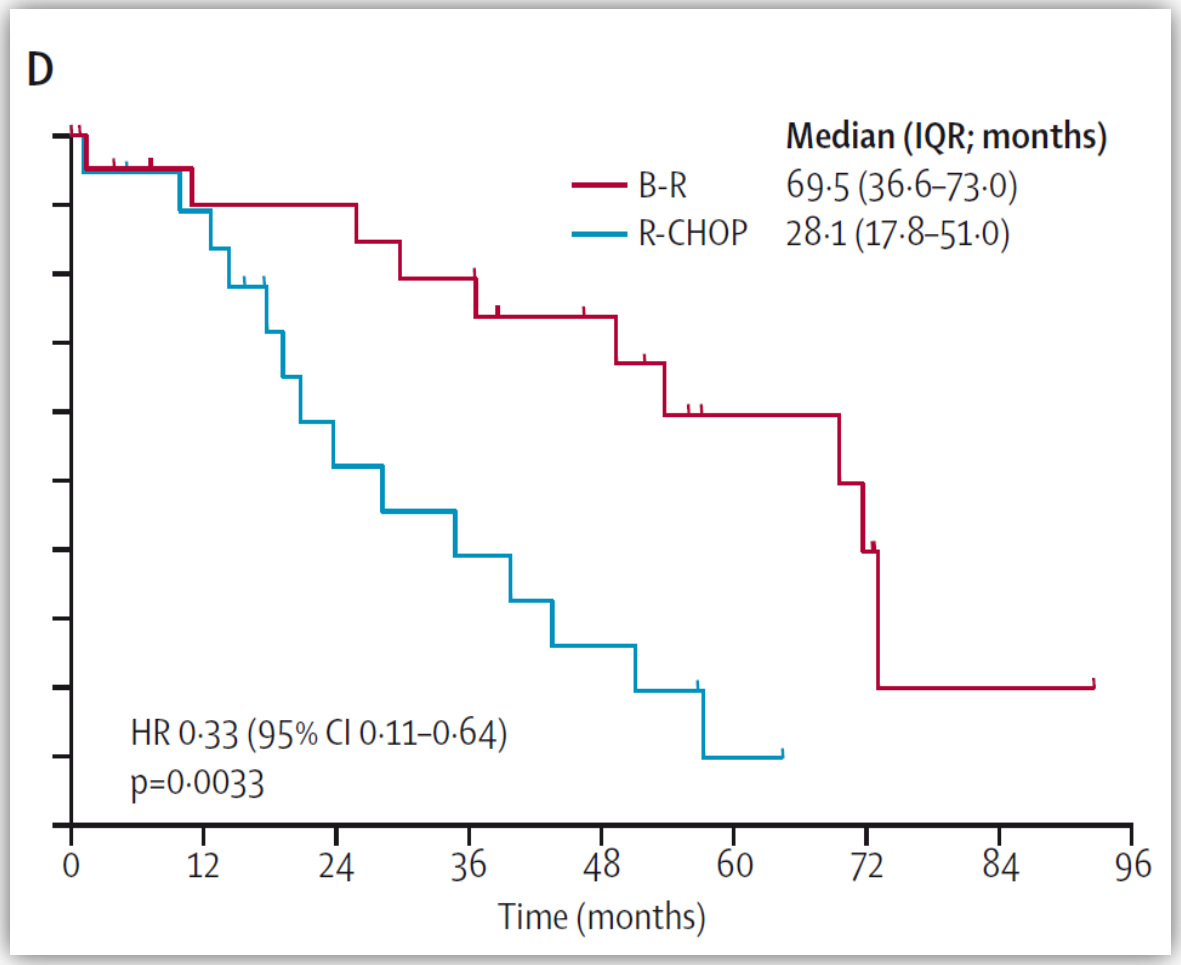
PFS Waldenström



Rummel et al., Lancet 2013

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De-escalating treatment?

DRC

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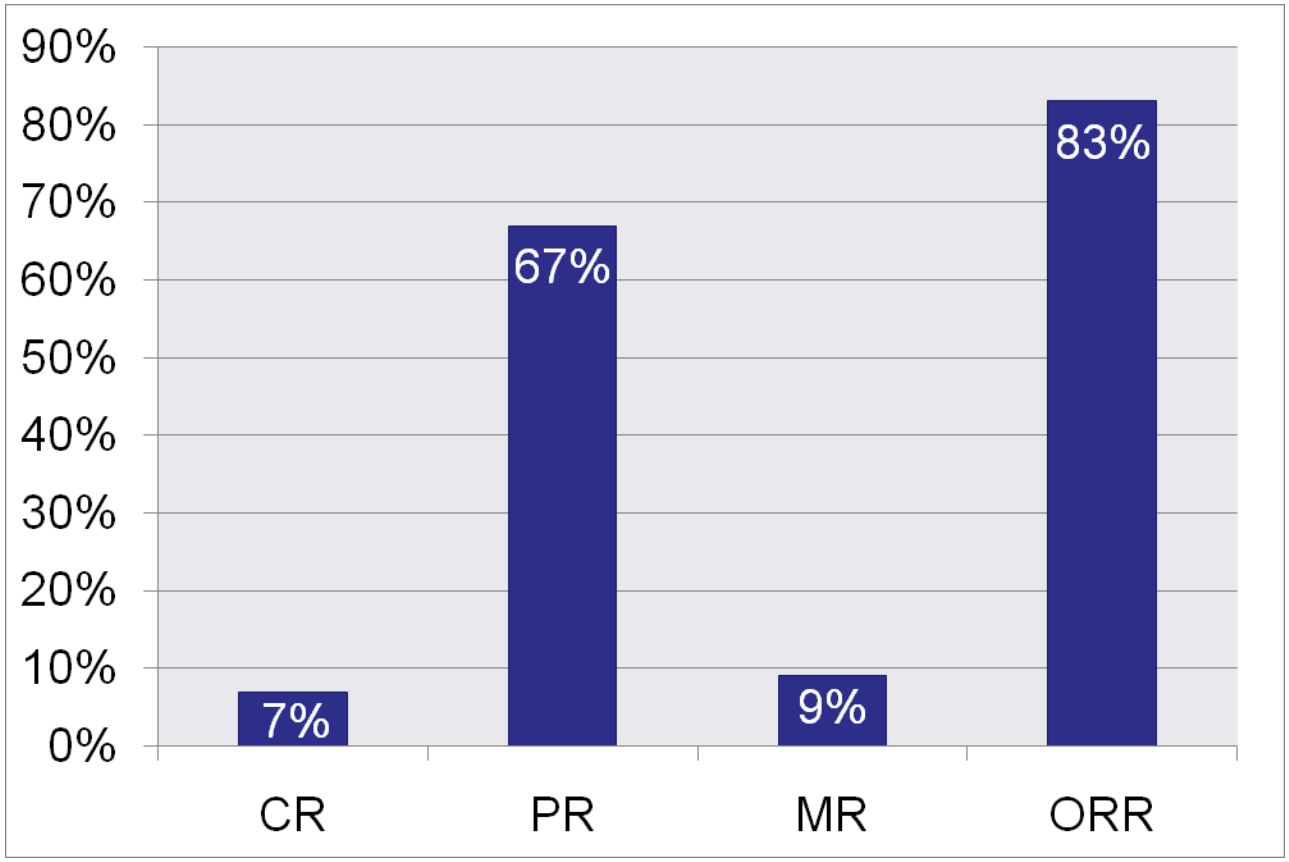
Results
Response to DRC



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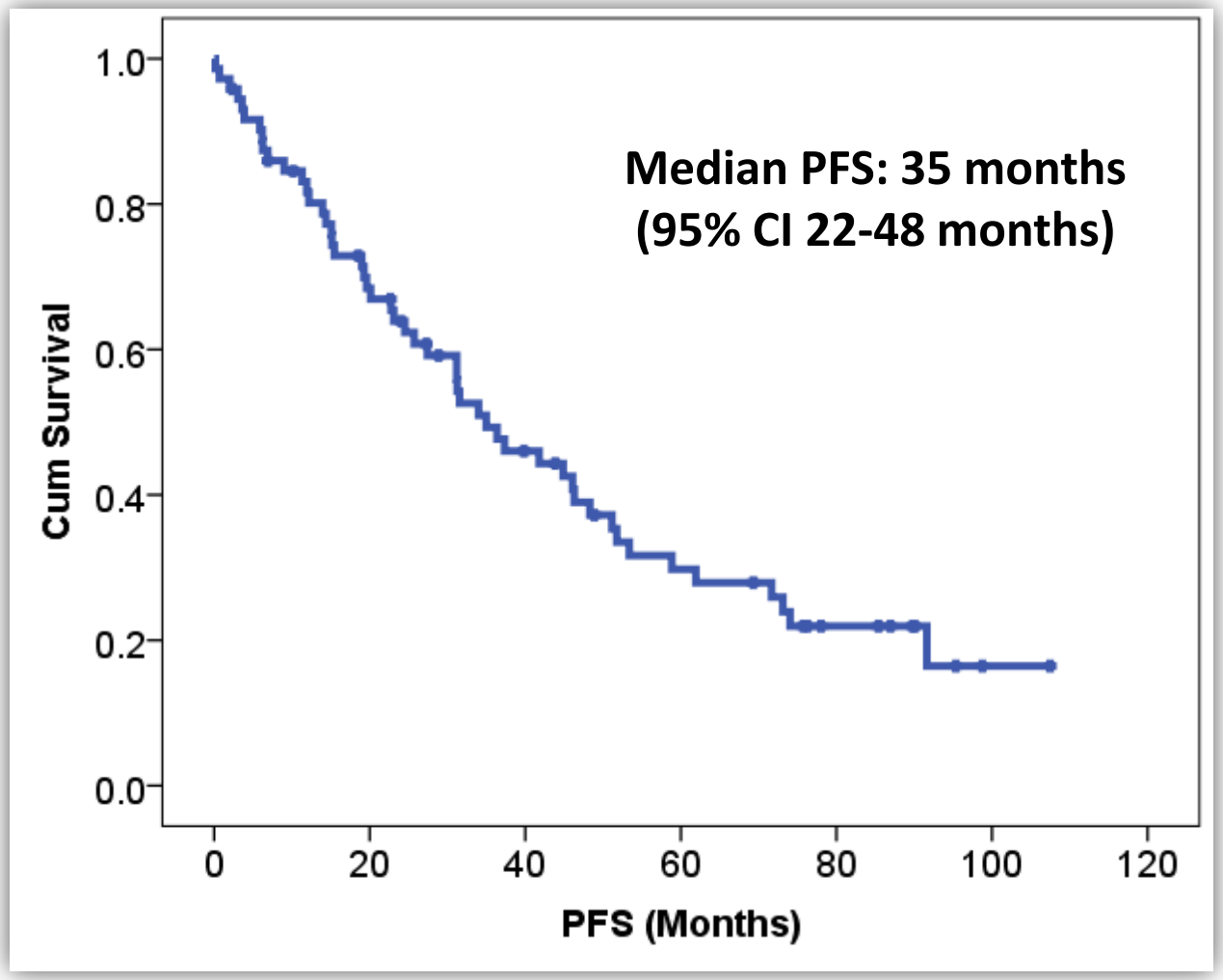
Progression Free Survival



Median follow up for patients still alive is 87 months (range 73-110 months)

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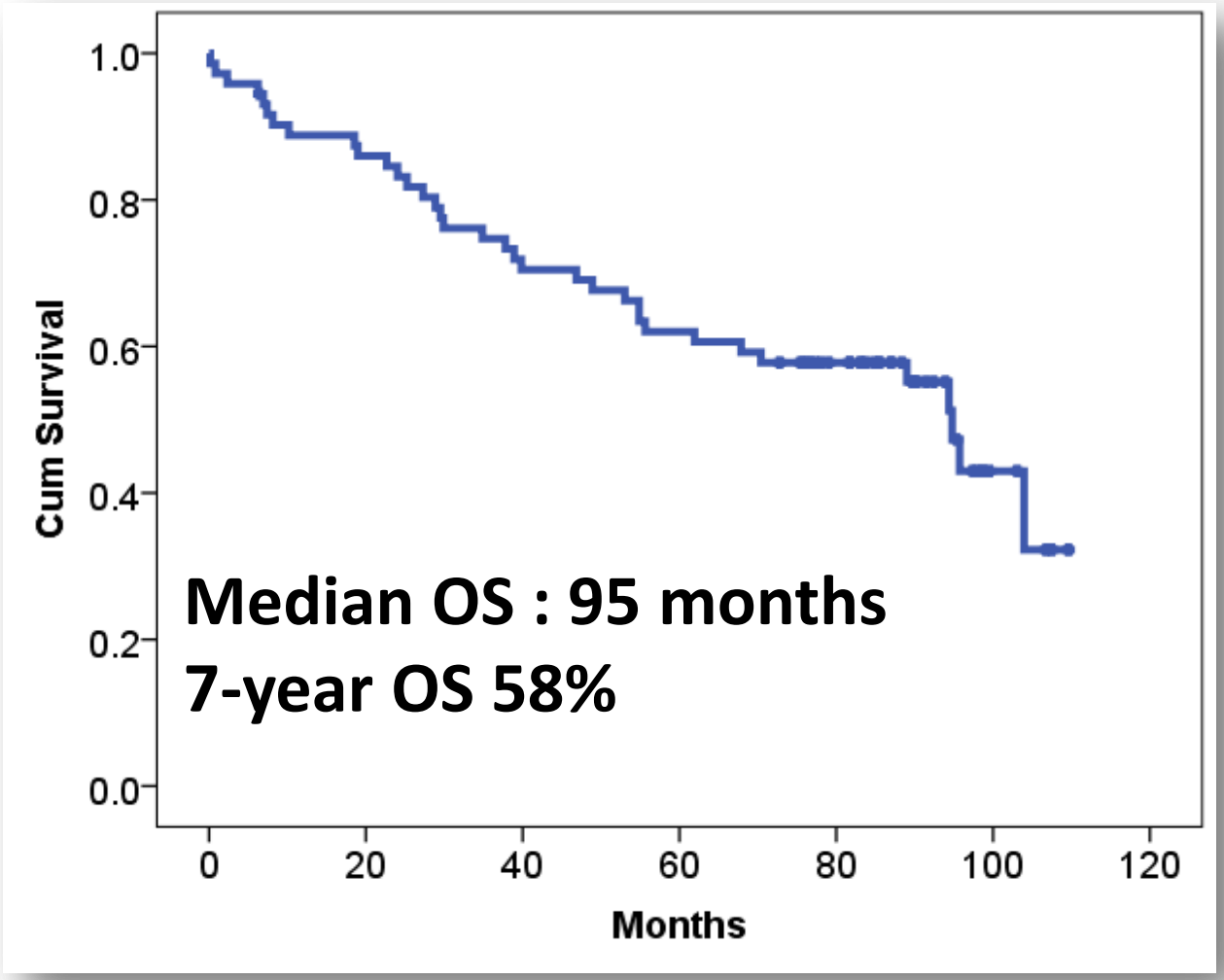
Overall Survival



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DRC – Toxicities

Table 2. Toxicity of Treatment With DRC (percentage of patients affected)

Toxicity	Grade 0	1	2	3	4
Neutropenia	66	15	10	7	2
Thrombocytopenia	93	7	0	0	0
Nausea/vomiting	62	25	13	0	0
Chills/fever	84	12	4	0	0
Headache	81	15	2	2	0
Hypotension	94	2	0	4	0
Alopecia	78	18	4	0	0

Abbreviation: DRC, dexamethasone, rituximab, and cyclophosphamide.

Dimopoulos et al., JCO 2007

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How can we improve….. ‘novel agents’?

1. Thalidomid
2. Lenalidomid
3. Bortezomib
4. Enzastaurin
5. Ibrutinib

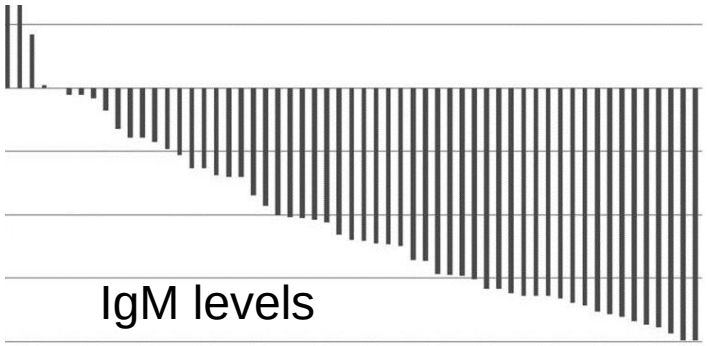
Case Report - Outcome…

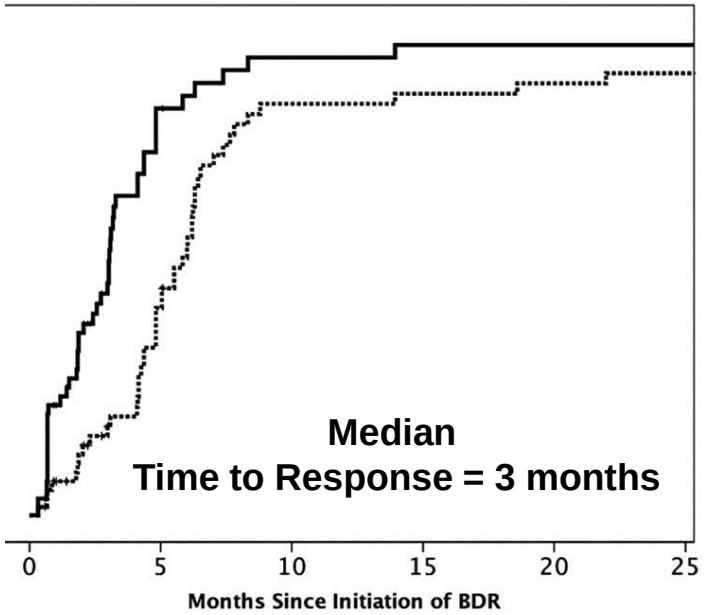
1. Plasmapheresis from December 5-11, 2013,
2. December 16, 2013: fever, blood culture staphylococcus lugdunensis despite Augmentin® (amoxicillin/clavulanate potassium)
3. Endocarditis with abscess of aortic valve
4. Cardiac surgery
5. February 20, 2014: asthenia, no lymph node,
    1. Hb=7.4 g/dL, platelet=130 $10^9/mm^3$, WBC=2.47 $10^9/mm^3$, PMN =1.16 $10^9/mm^3$

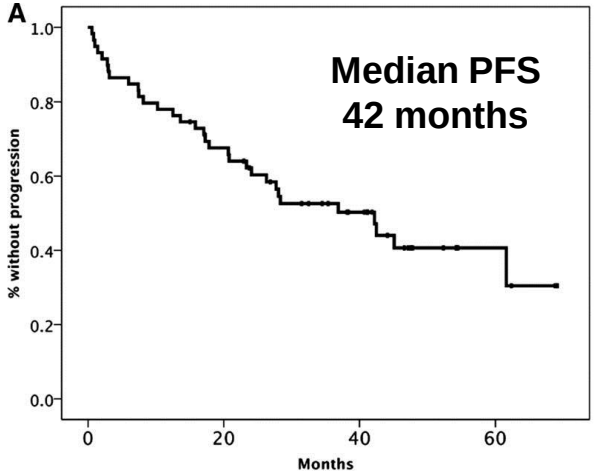
2. BDR

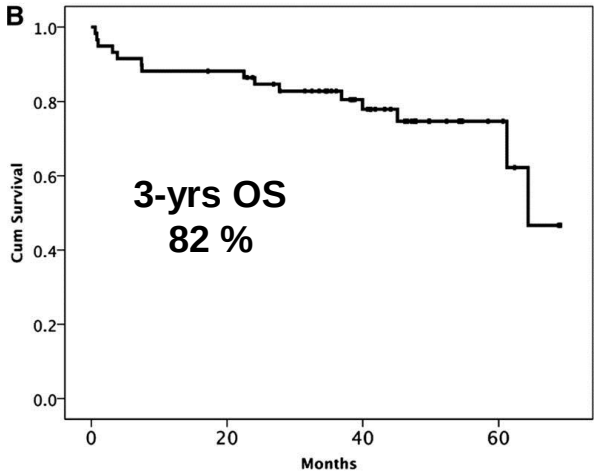
Date	SEP: M-spike (g/L)	IgM conc (g/L)	Viscosity (cSt)	Protein (g/L)	comment
02/04/2014	13,5	84,6		104	
16/04/2014	16	90,1	4,14	102	
22/04/2014	13,8	56,13	2	79	
07/05/2014		52,26	2,03	95	
28/05/2014	12,2	49,24	1,88	83	No cryoglobulin
25/06/2014	4,8	43,54		88	

BDR – rapidly acting and effective









Dimopoulos M A et al. Blood 2013;122:3276-3282

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

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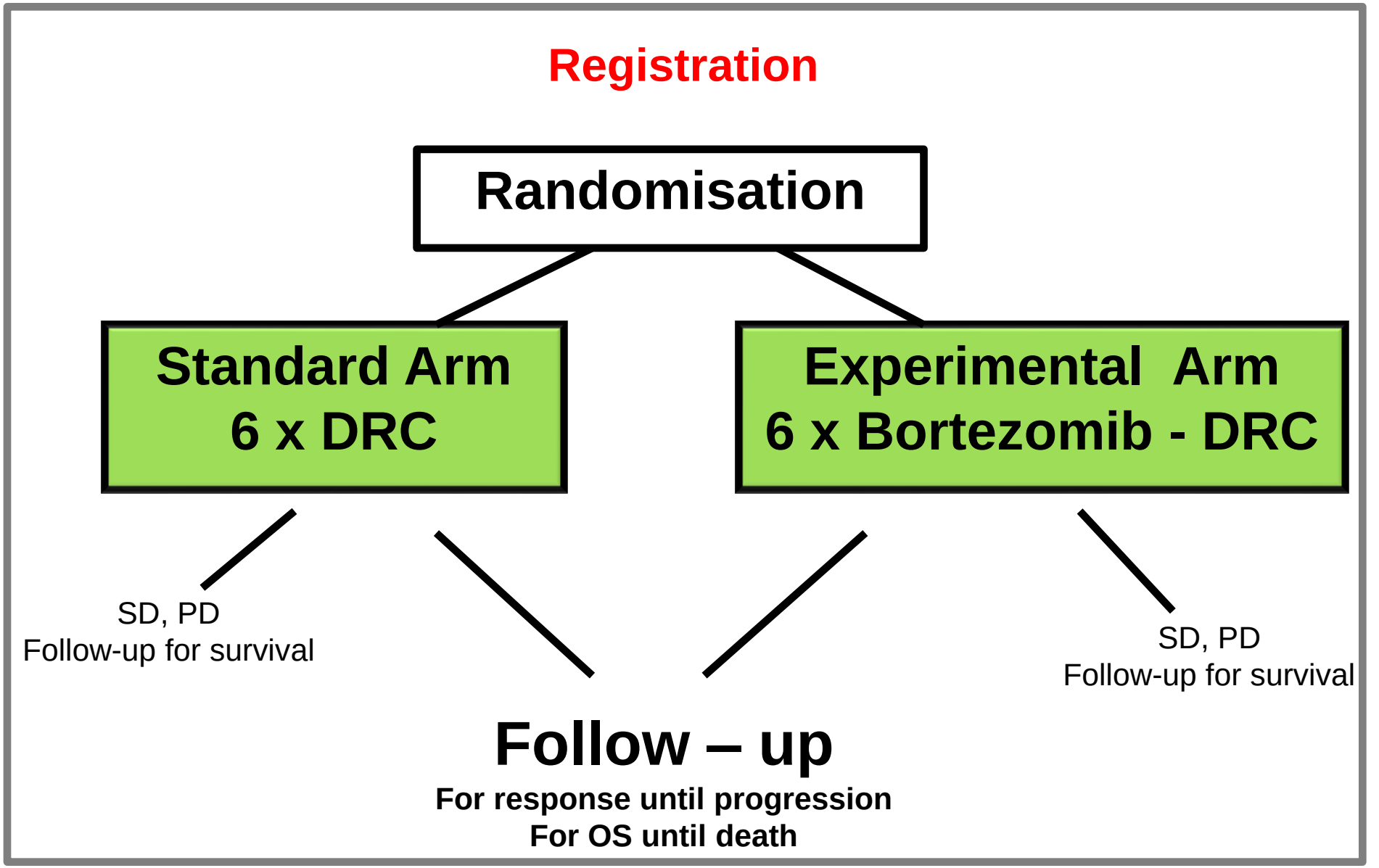
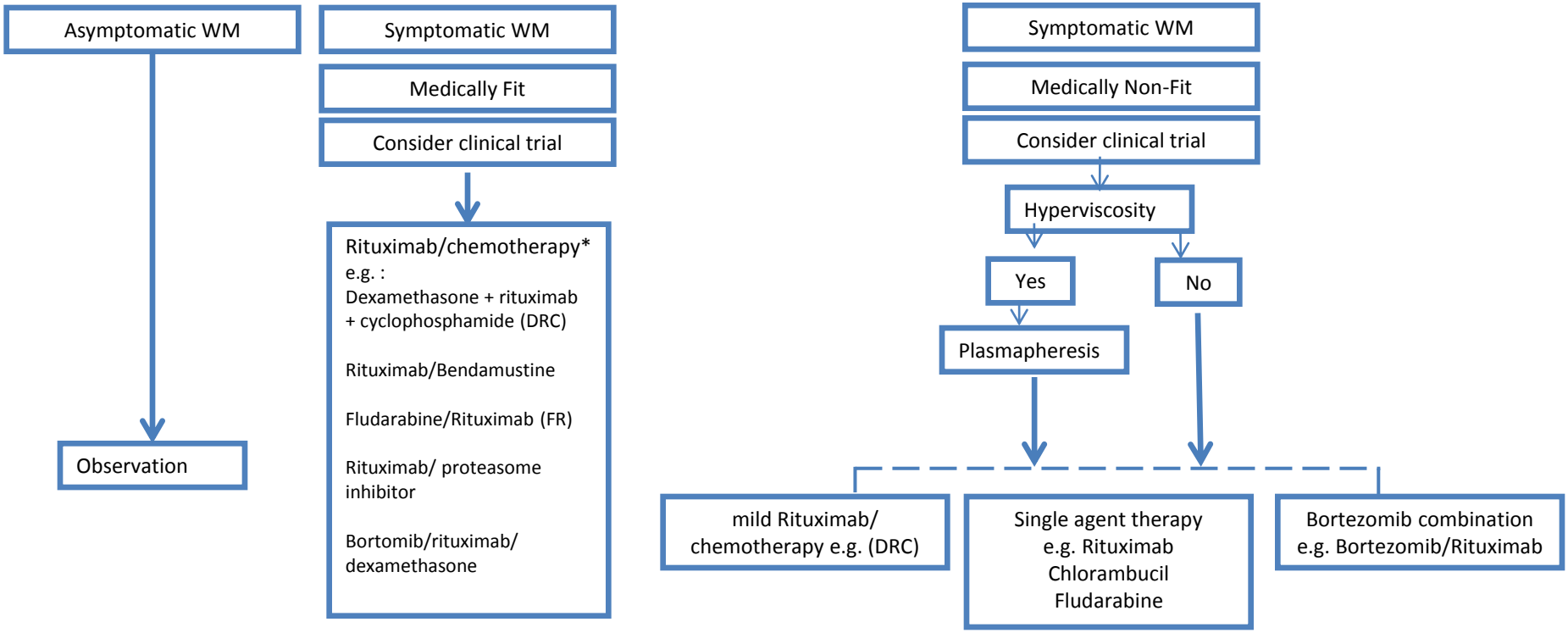
Study Flow



Treatment Algorithms - WM

Newly diagnosed WM



* In case of hyperviscosity consider plasmapheresis before Rituximab application

Buske et al., ESMO Guidelines, 2014

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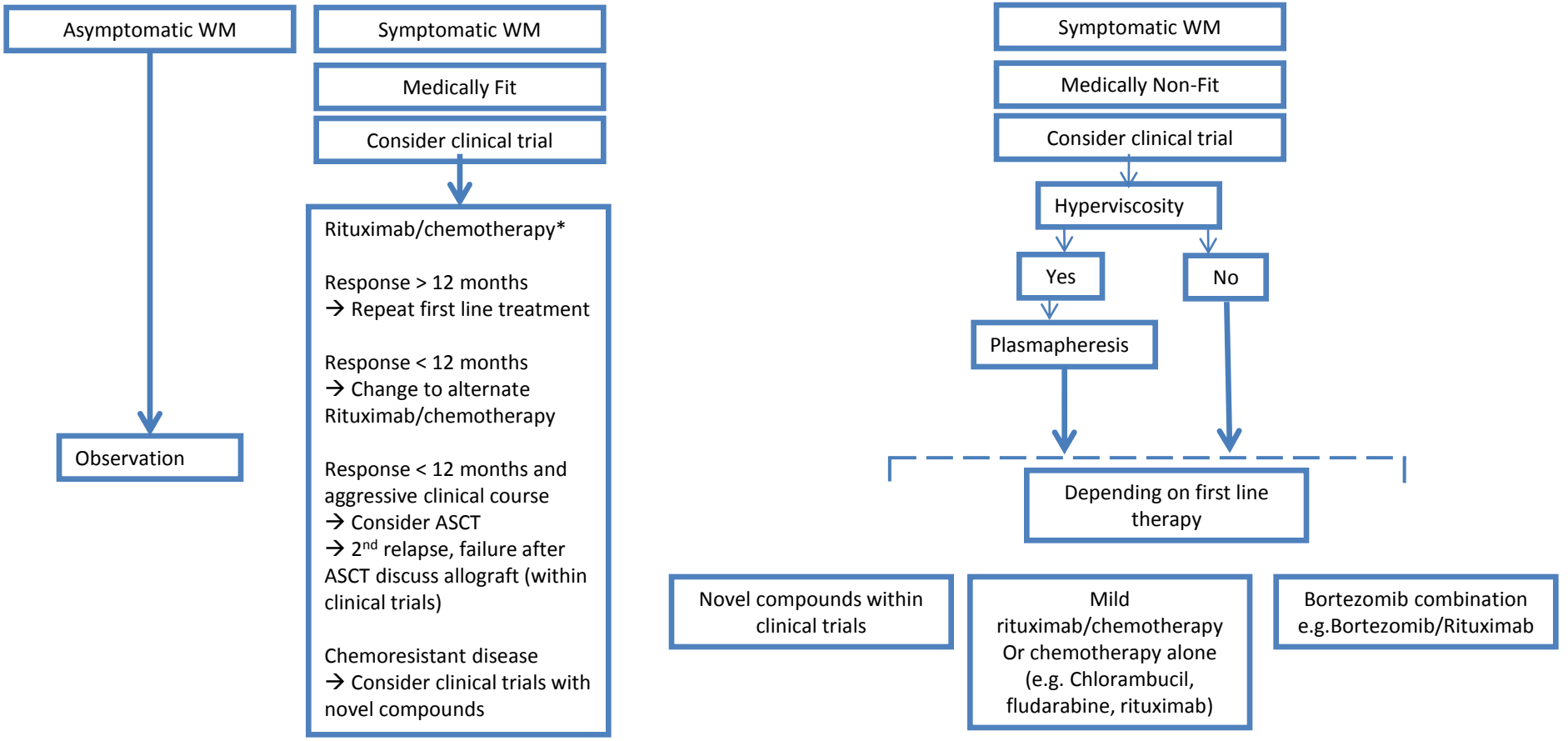
Treatment Algorithms - WM

Relapsed WM



* In case of hyperviscosity consider plasmapheresis before Rituximab application

Buske et al., ESMO Guidelines, 2014

Many thanks!

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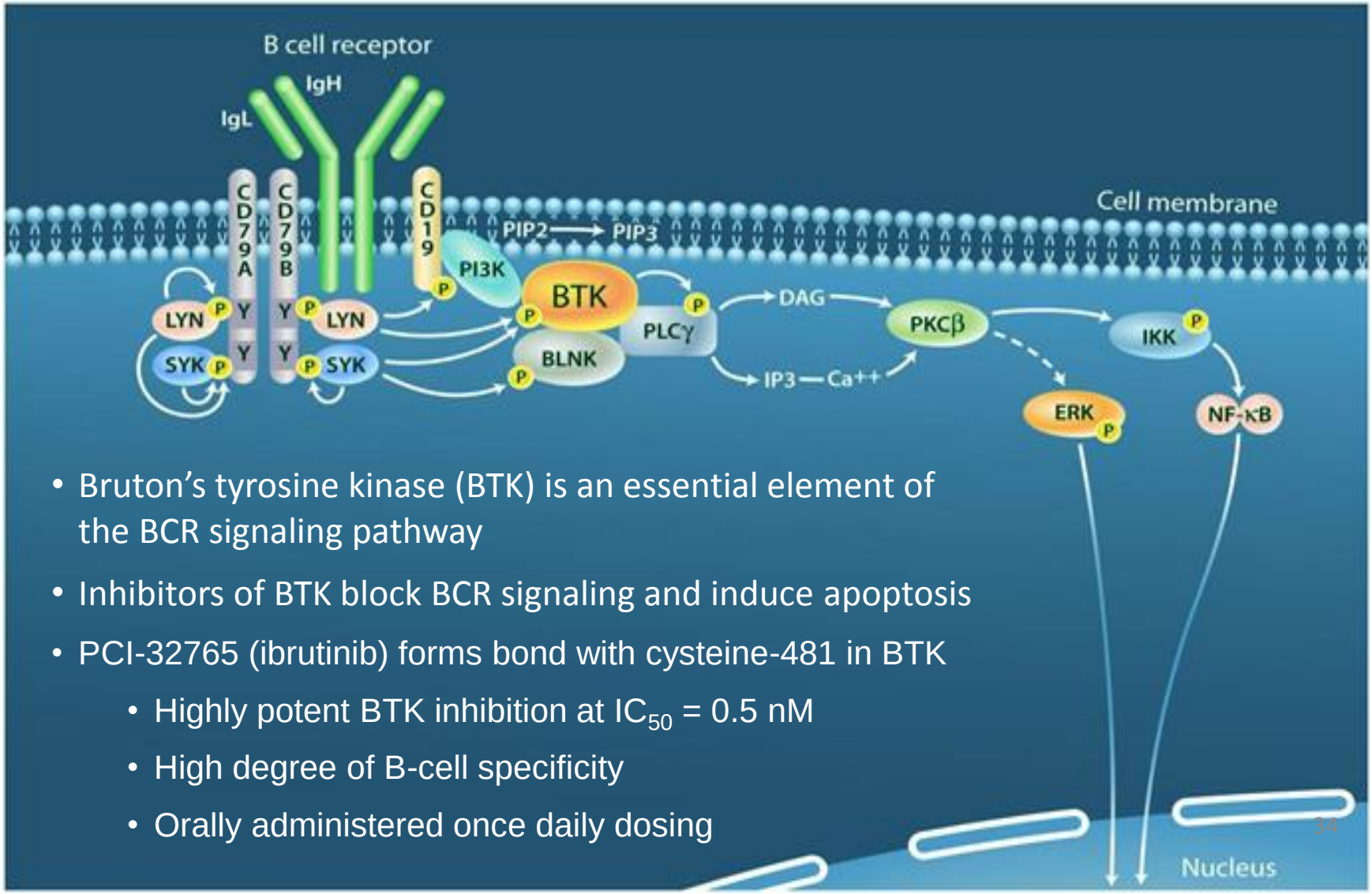
Bruton's Tyrosine Kinase (BTK): A Critical Kinase for Lymphoma Cell Survival and Proliferation



- Bruton's tyrosine kinase (BTK) is an essential element of the BCR signaling pathway
- Inhibitors of BTK block BCR signaling and induce apoptosis
- PCI-32765 (ibrutinib) forms bond with cysteine-481 in BTK
  - Highly potent BTK inhibition at IC_{50} = 0.5 nM
  - High degree of B-cell specificity
  - Orally administered once daily dosing

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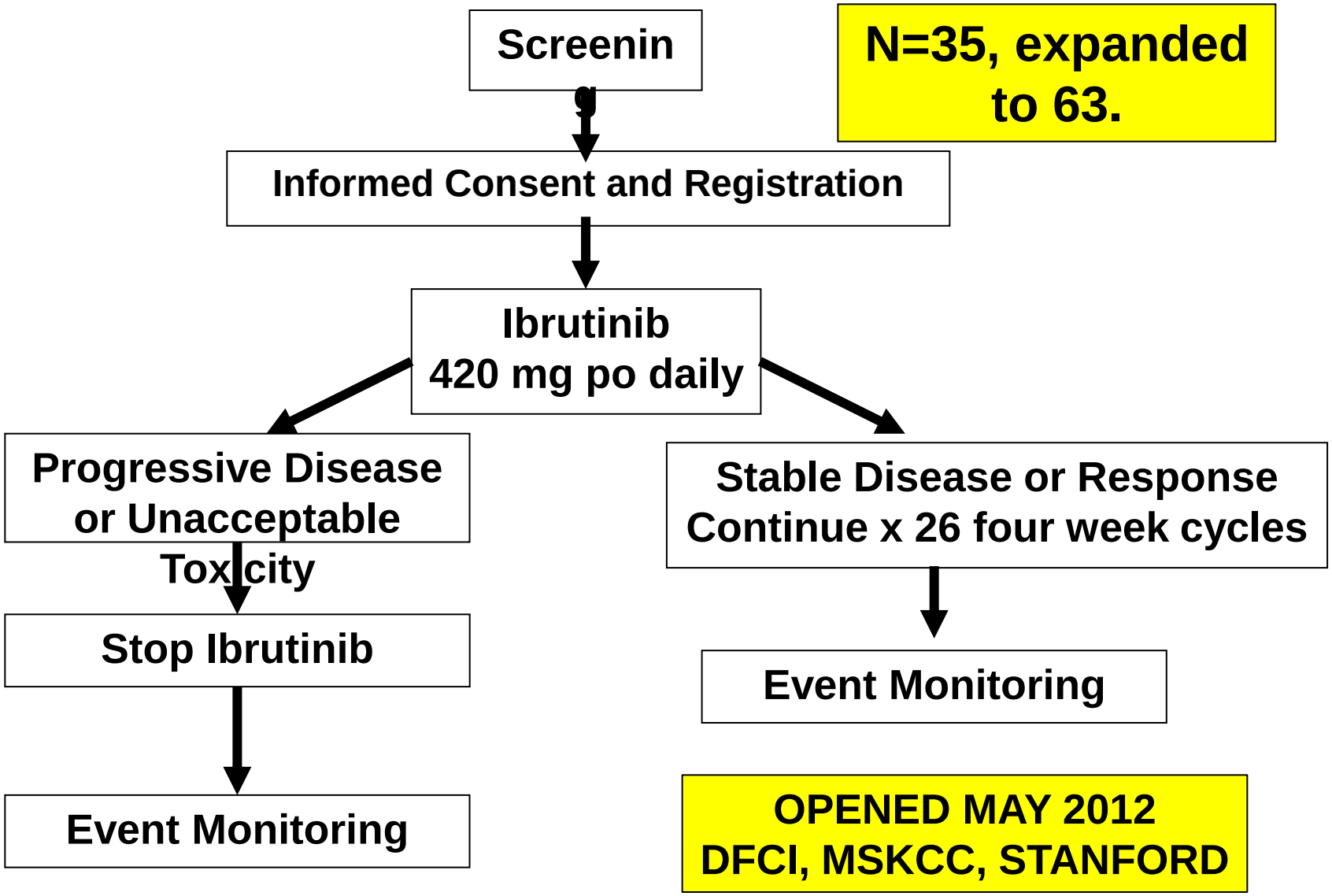
MULTICENTER PHASE II STUDY OF IBRUTINIB IN RELAPSED/REFRACTORY WM



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BEST CLINICAL RESPONSES TO IBRUTINIB
(≥6 CYCLES; N=35)

Data Lock June 3, 2013

	(n=)	(%)
VGPR	4	11.4
PR	19	54.3
MR	6	17.1
SD	5	14.3
NON-RESPONDER	1	2.9

ORR: 83% MAJOR RR (≥ PR): 66%

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POSSIBLY, PROBABLY, OR LIKELY RELATED (N=35)

ADVERSE EVENT	≥GRADE 2	GRADE 3	GRADE 4
THROMBOCYTOPENIA	6 (17.1%)	3 (8.6%)	0 (0.0%)
NEUTROPENIA	6 (17.1%)	2 (5.7%)	1 (2.8%)
HEMATOMA	1 (2.9%)	0 (0.0%)	0 (0.0%)
EPISTAXIS	1 (2.9%)	0 (0.0%)	0 (0.0%)
STOMATITIS	1 (2.9%)	1 (2.9%)	1 (2.9%)
ATRIAL FIBRILLATION	1 (2.9%)	1 (2.9%)	0 (0.0%)

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A randomized phase III study of Ibrutinib p.o. versus extended Rituximab i.v. therapy in patients with previously treated WM

ECWM-R1

European Waldenström's Macroglobulinemia Consortium

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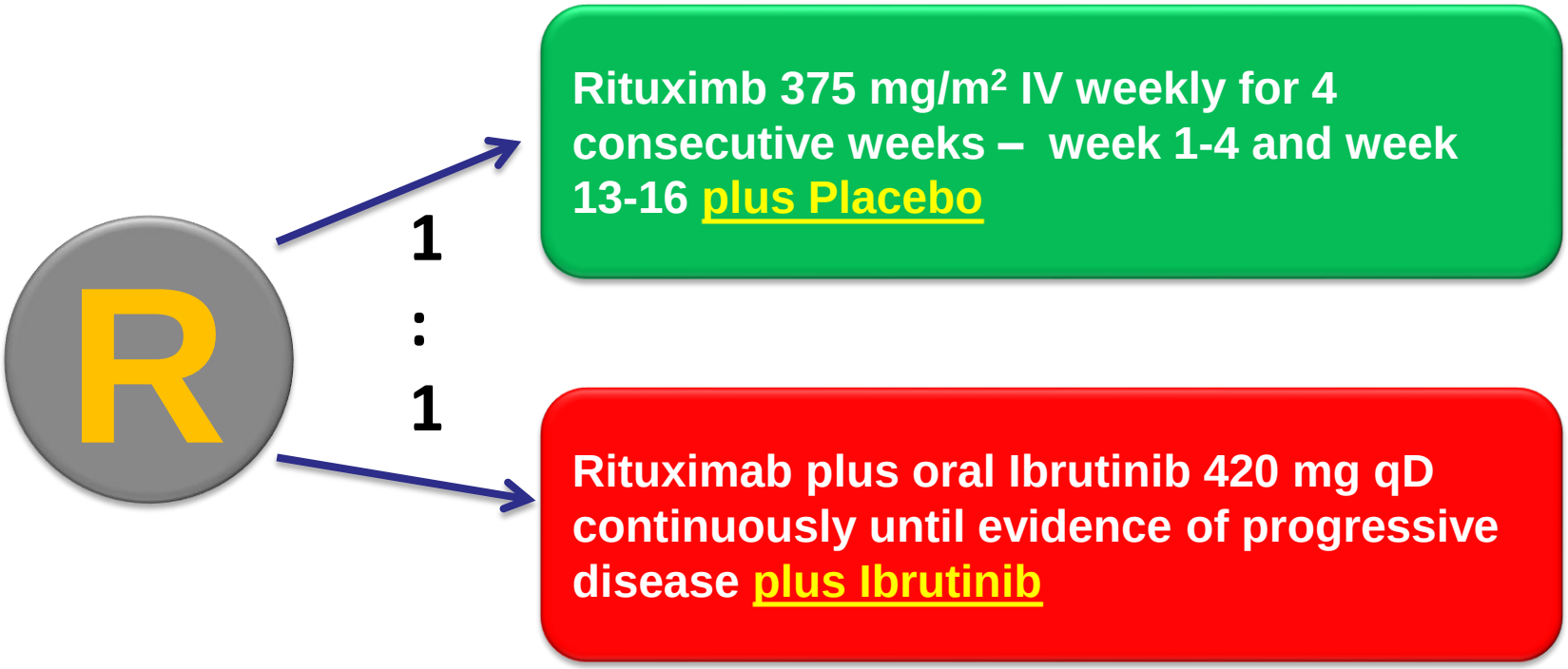
ECWM-R1 / Relapse



Crossover: Patients who are randomized in the rituximab arm and demonstrate progressive disease, will be allowed to receive ibrutinib