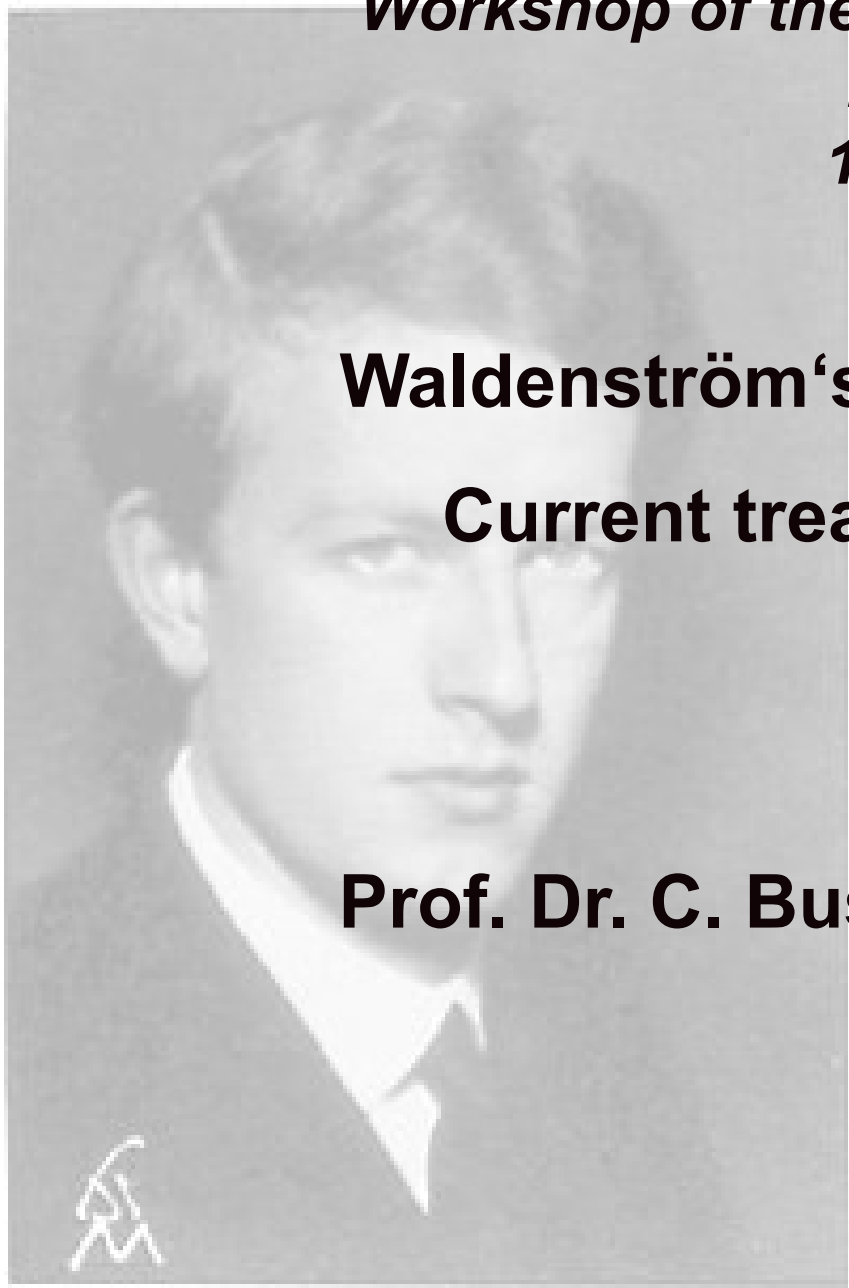

*Workshop of the Czech Myeloma Group*
*Mikulov*
*11.4.2015*

# Waldenström‘s Macroglobulinema –

# Current treatment approaches

**Prof. Dr. C. Buske**

Integratives Tumorzentrum des Universitätsklinikums
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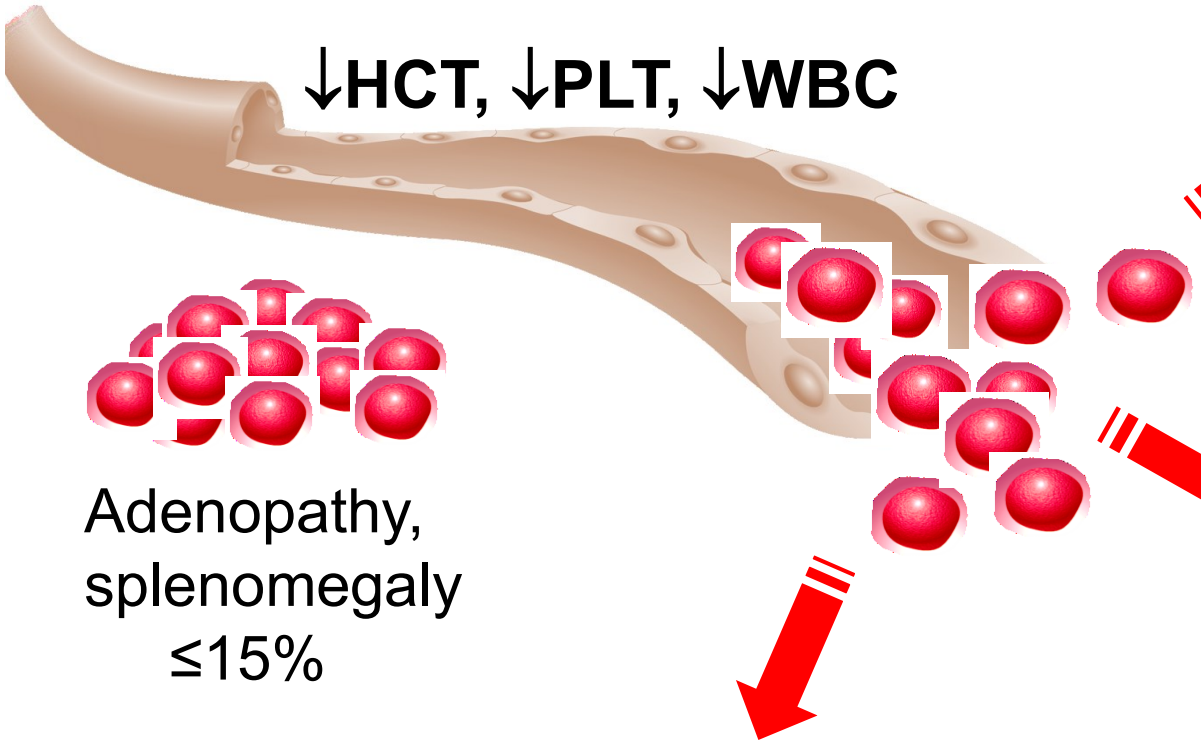
ulm university universität ulm

*Workshop of the Czech Myeloma Group*
*Mikulov*
*11.4.2015*

# Waldenström‘s Macroglobulinema – what should we know before starting treatment

# Clinicopathologic Manifestations of WM




Hyperviscosity Syndrome: Epistaxis, HA, Impaired vision >4.0 CP

Adenopathy, splenomegaly ≤15%

IgM Neuropathy (22%)
Cryoglobulinemia (10%)
Cold Agglutinemia (5%)

Fatigue, Constitutional Sxs
Cytokinemia?

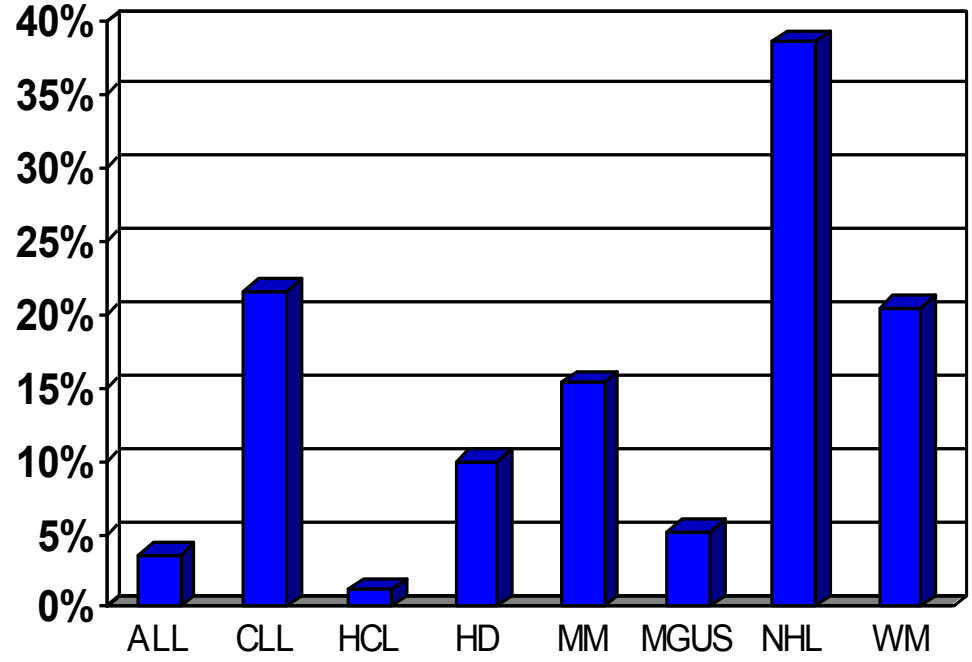
**Treon SP et al. *Cancer Treat Res.* 2008;142:211-242.**

# Genetic Predisposition

# Familial disease predisposition in WM

N=1076 consecutive patients with clinicopathological diagnosis of WM

26.1% of WM patients have a first or second degree relative with a B-cell LPD.




Distribution of B-cell LPD in relatives of 281 Familial WM patients.

Treon et al, ICML 2011.

# Waldenström's Macroglobulinemia
# - the first problem -

- **<u>WM is a rare disease (orphan disease!)</u>**

*It accounts for:*

- 1–2% of hematological neoplasms,
- with a reported age-adjusted incidence rate **of 3.4 per million among the male** population and 1.7 per million among the female population in the United States,
- **and 7.3 and 4.2 per million**, respectively, in the European standard population.

→ **Implications: no drugs approved (Ibrutinib now by the FDA), hardly any larger clinical trials, weak ‚lobby', innovations depending on drug development in other lymphomas**

# Waldenström's Macroglobulinemia
# - the second problem -

- **<u>WM is a disease of the elderly!</u>**

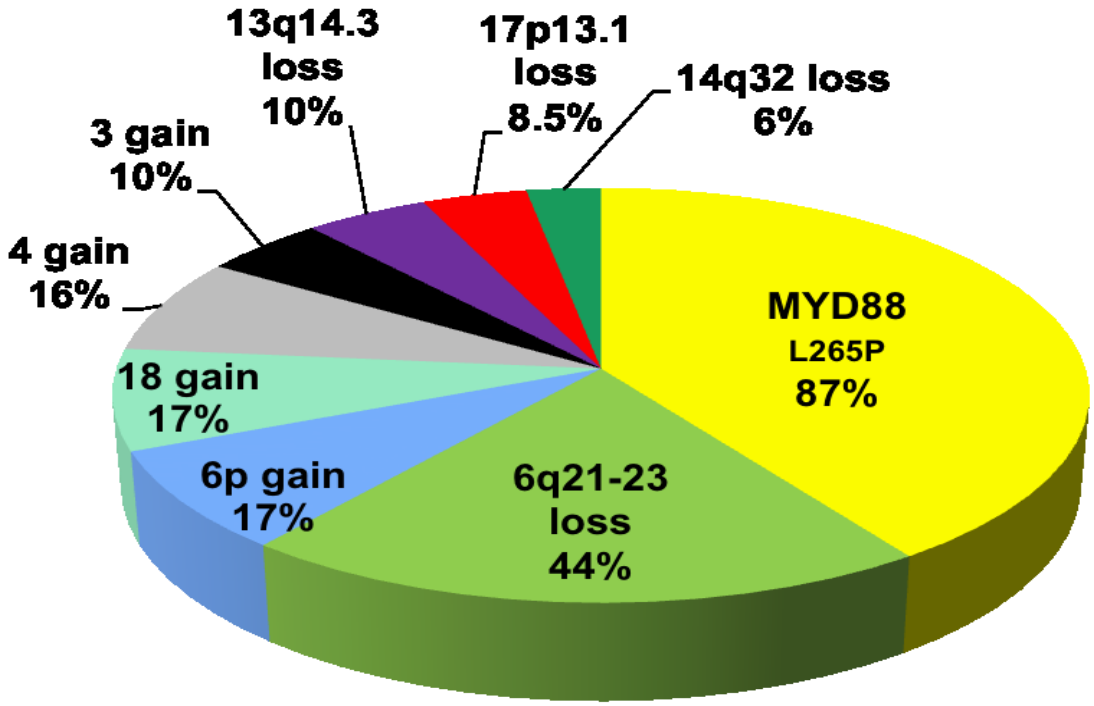
- Median age 63–68 years at diagnosis

**→ Implications: for the majority of patients dose intense approaches not feasible!**
**Eradication of lymphoma not realistic with current treatment approaches!**

# Waldenström's Macroglobulinemia
# - Molecular Biology – should we care at all?

# Molecular Abnormalities in WM

**Recurrent chromosomal abnormalities and prevalence in WM**




**Cancer implicated genes**

- r. 3 - MYD88L265P mutation
- r. 6q21-23 loss - PRDM1
- r. 17p13 loss - p53
- r. 13q14.3 loss - miRNA-15, 16
- r. 14q32 – TRAF3
- r. 4 gain - unknown
- r. 6p gain - unknown
- r. 3 gain - unknown

logica 2012; Poulain et al Clin Lymp Myel 2011(11);
Roccaro et al Blood 2009(113); Treon et al NEJM 2012(367)

# 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); Ngo & Staudt et al Nature 2011(470)

# MYD88 - a diagnostic marker

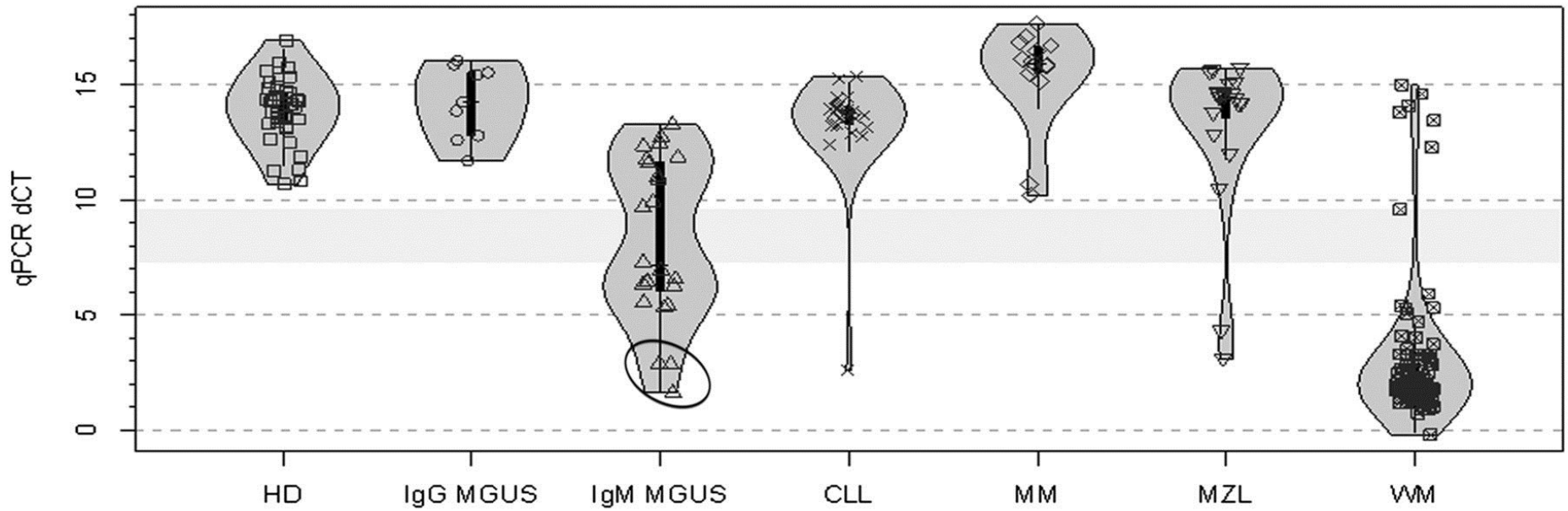
**Table 1.** MYD88 L265P expression in WM and IgM MGUS

| *Authors* | *Reference* | *Tissue* | *Method* | *MYD88 L265P positive/total number of WM patients tested, n/N (%)* | *MYD88 L265P positive/total number of IgM MGUS patients tested, n/N (%)* |
|---|---|---|---|---|---|
| Treon *et al.* | 5 | BM CD19 + | WGS/Sanger | 49/54 (91) | 2/21 (10) |
| Gachard *et al.* | 22 | BM | PCR | 21/31 (67) | ND |
| Xu *et al.* | 23 | BM CD19 + | AS-PCR | 97/104 (93) | 13/24 (54) |
| Varettoni *et al.* | 24 | BM | AS-PCR | 58/58 (100) | 36/77 (47) |
| Landgren and Staudt | 25 | BM | Sanger | | 5/9 (56) |
| Jimenez *et al.* | 26 | BM | AS-PCR | 100/117 (86) | 27/31 (87) |
| Ansell *et al.* | 27 | NA | WGS/Sanger/AS-PCR | 38/39 (97) | ND |
| Poulain *et al.* | 37 | BM CD19 + | PCR | 54/67 (80) | ND |

Abbreviations: AS-PCR, allele-specific PCR; BM, bone marrow; MYD88, myeloid differentiation factor 88; not applicable; ND, not determined; PCR, polymerase chain reaction; WGS, whole genome sequencing; WM, Waldenström's Macroglobulinemia.

*Landgren & Tageja, Leukemia 2014*

# Real-time AS-PCR results for MYD88 L265P in samples from patients with WM, IgM MGUS, and other B-cell lymphoproliferative disorders.




Xu L et al. Blood 2013;121:2051-2058

# Real-time AS-PCR results for MYD88 L265P as a surrogate marker for tumor burden?

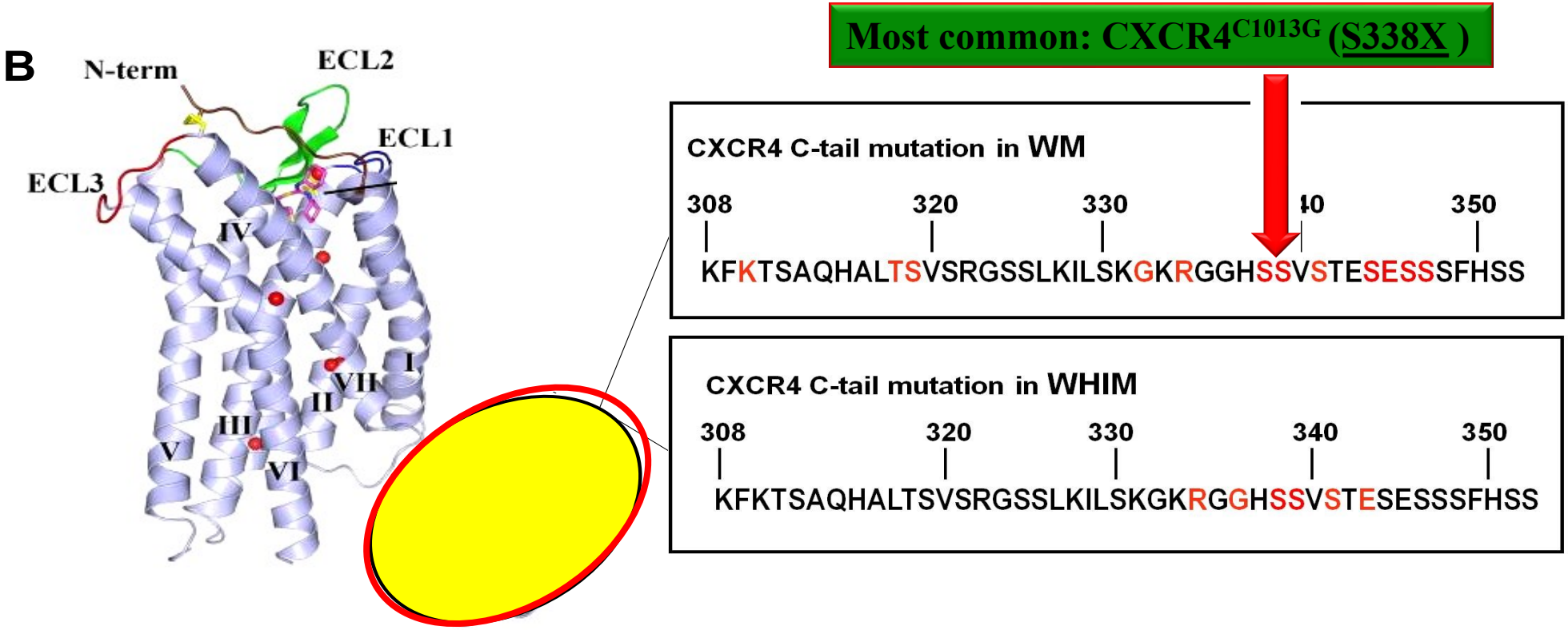
**Table 1. Comparison of MYD88 L265P before and after treatment using real-time AS-PCR in patients with WM**

| Patient | Age (years) | Gender | Treatment | Pre-/posttherapy BM involved, % | Pre-/posttherapy MYD88 L265P levels | Change in BM involved, % | Change in MYD88 L265P levels, % |
|---|---|---|---|---|---|---|---|
| A | 61 | Male | Benda-R | 70 | 78.45 | −100 | −100 |
| | | | | (negative) | (negative) | | |
| B | 44 | Male | R-CD | 90 | 60.73 | −89 | −96.33 |
| | | | | 10 | 2.23 | | |
| C | 52 | Male | R-CD | 50 | 72.12 | −90 | −73.61 |
| | | | | 5 | 19.03 | | |
| D | 59 | Male | Everolimus | 95 | 99.15 | −47 | −45.39 |
| | | | | 50 | 54.15 | | |
| E | 63 | Male | Everolimus | 90 | 96.07 | −67 | −21.03 |
| | | | | 30 | 75.87 | | |
| F | 70 | Male | Everolimus | 95 | 95.93 | −37 | −8.61 |
| | | | | 60 | 87.67 | | |
| G | 63 | Male | Everolimus | 20 | 67.93 | 25 | 12.87 |
| | | | | 25 | 76.67 | | |

Changes in expression levels for MYD88 L265P were calculated from a standard curve.
Benda-R, bendamustine and rituximab; R-CD, rituximab, cyclophosphamide, and dexamethasone.

# WHIM-like CXCR4 C-tail mutations in WM

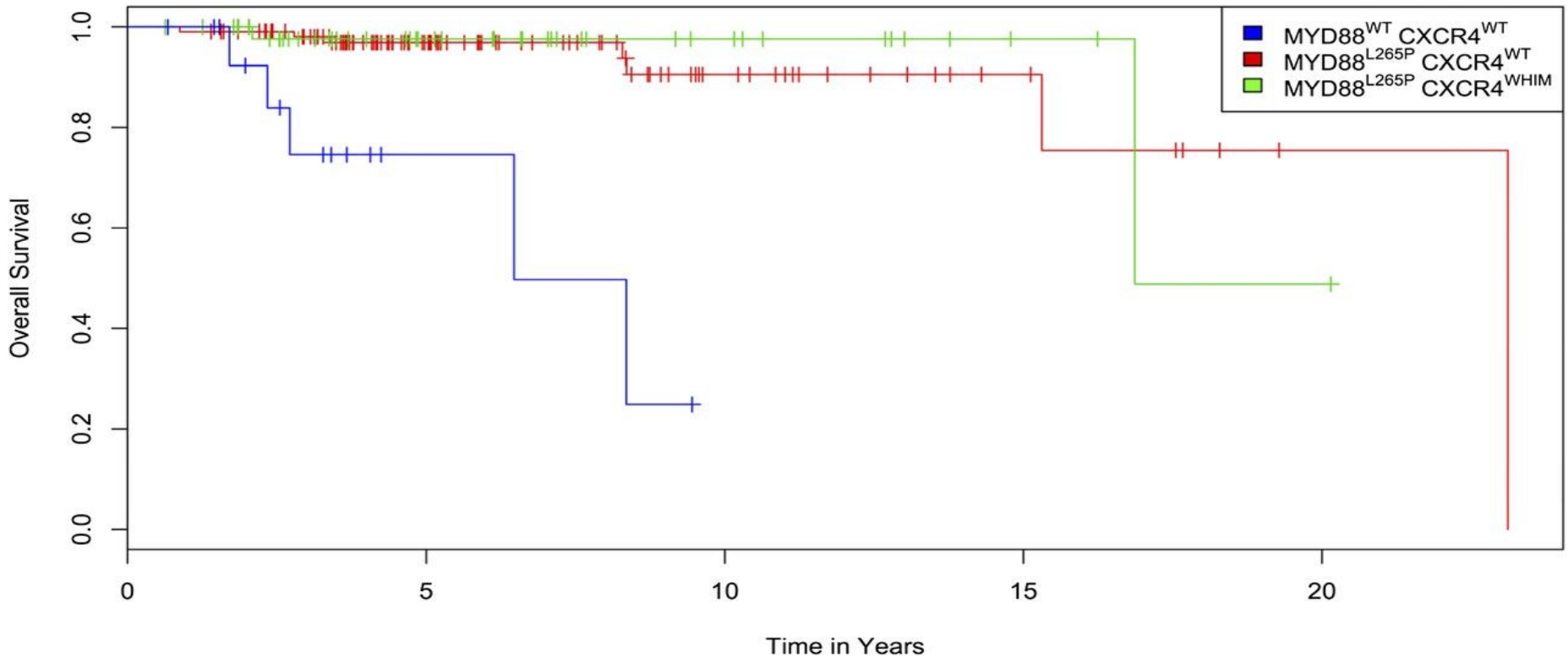
***Warts, Hypogammaglobulinemia, Infection, and Myelokathexis.***




**Somatic WHIM-CXCR4 Mutations are present in WM patients: 8/30 (27%) by WGS ; 47/152 (31%) by Sanger Sequencing.**

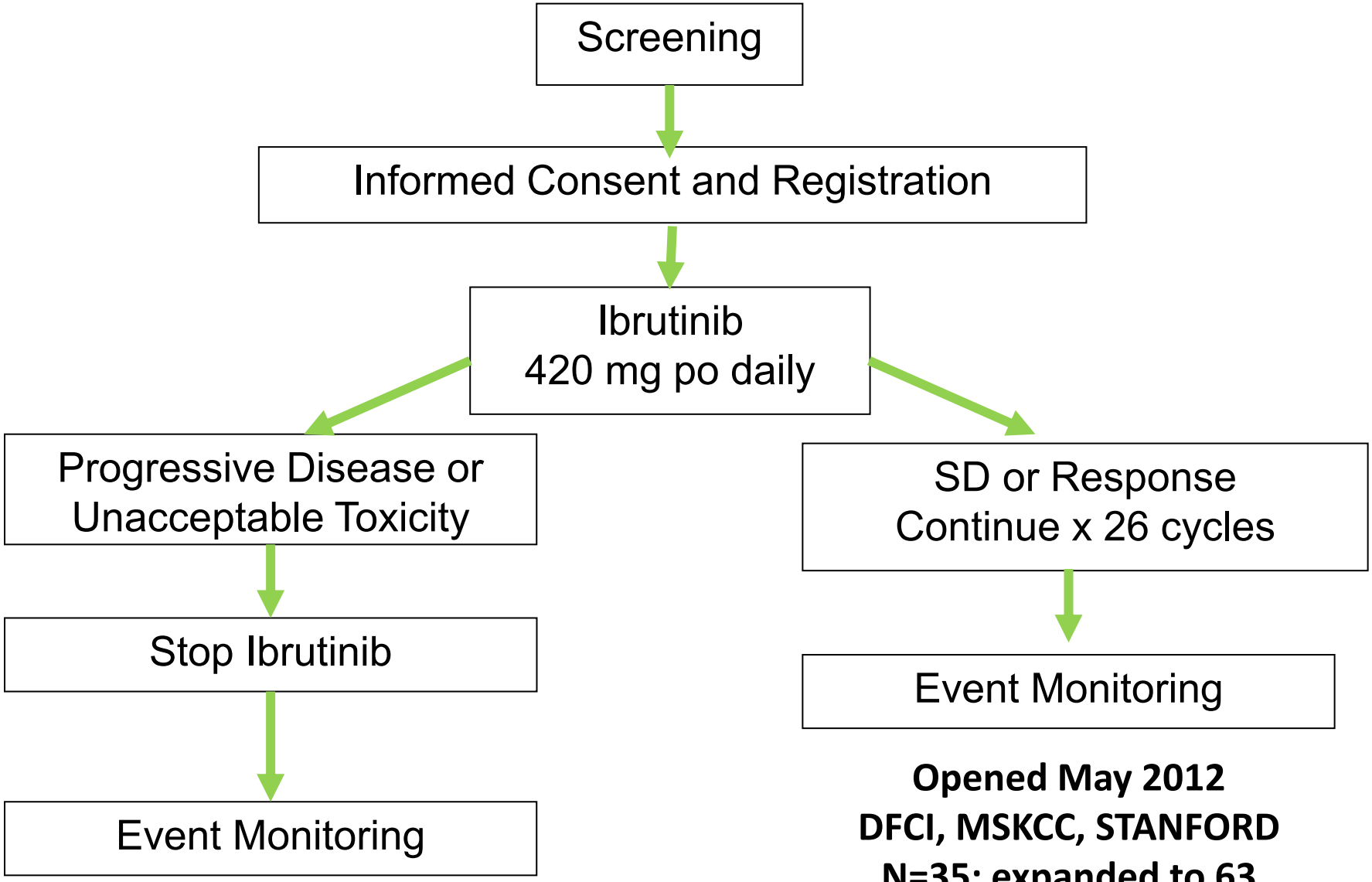
Hunter et al, JCO 2012; 30(15); Abstract 8107; Blood (Manuscript in Press)

# 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

# Phase II Study of Ibrutinib in Relapsed/Refractory WM




**Opened May 2012**
**DFCI, MSKCC, STANFORD**
**N=35; expanded to 63**

# MYD88 /CXCR4 status and Ibrutinib Major Responses

| MYD88 | N= | VGPR/PR | MR/SD/NR |
|---|---|---|---|
| L265P | 48 | 31 (65%) | 17 (35%) |
| Wild Type | 5 | 2 (40%) | 3 (60%) |

***p = 0.3536 Odds ratio = 2.68 95% CI 0.28-35.02***

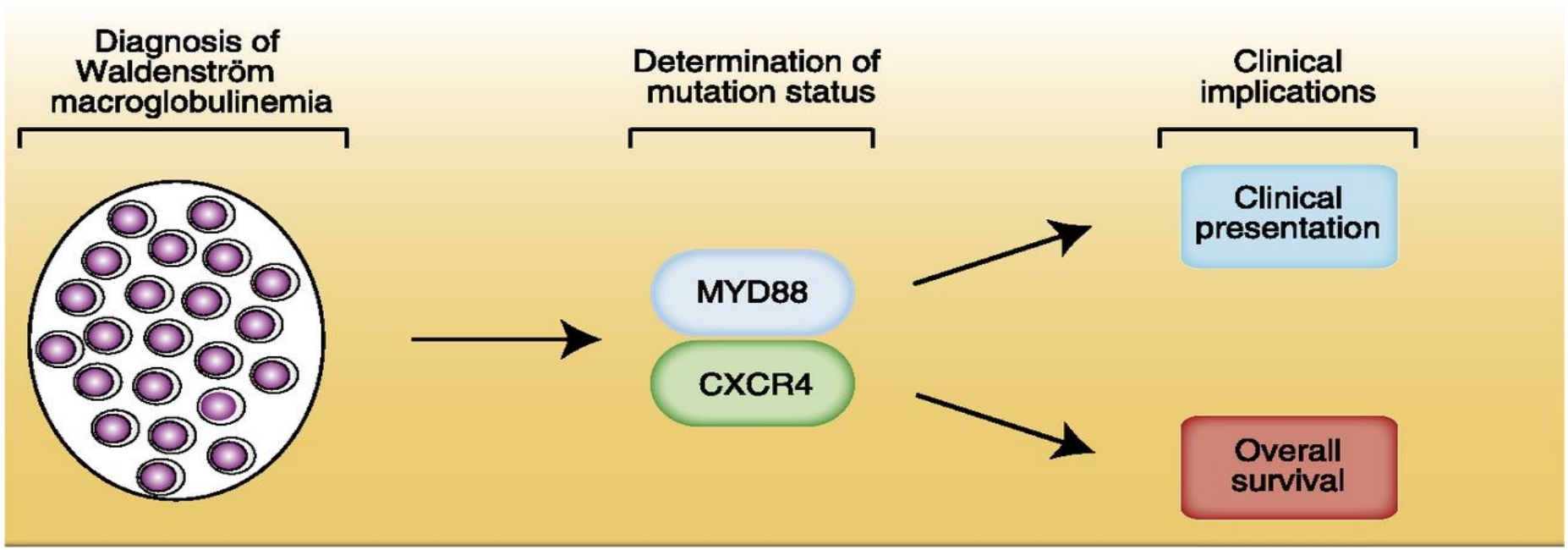
| CXCR4 | N= | VGPR/PR | MR/SD/NR |
|---|---|---|---|
| WHIM | 10 | 3 (30%) | 7 (70%) |
| Wild Type | 30 | 24 (80%) | 6 (20%) |

***p = 0.0065 Odds ratio = 0.115 95% CI 0.02-0.68***

Data Lock November 8, 2013

Treon et al, Blood 2013; 122(21): Abstract 251

# Determination of the MYD88 and CXCR4 mutation status in WM has clinical implications.




Lenz G Blood 2014;123:2750-2751

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# Waldenström‘s Macroglobulinema –

# How to treat?

Comment on Flinn et al, page 3406; and Kahl et al, page 3398; and Brown et al, page 3390

# CLL and NHL: the end of chemotherapy?

**Bruce D. Cheson** GEORGETOWN UNIVERSITY HOSPITAL

"The times they are a changin'"—Bob Dylan

In this issue of *Blood*, Flinn et al, Kahl et al, and Brown et al provide further encouragement that the possibility of a chemotherapy-free world is, indeed, a rapidly approaching reality in indolent non-Hodgkin lymphomas (NHLs), mantle cell lymphoma (MCL), and chronic lymphocytic leukemia (CLL).[1-3]

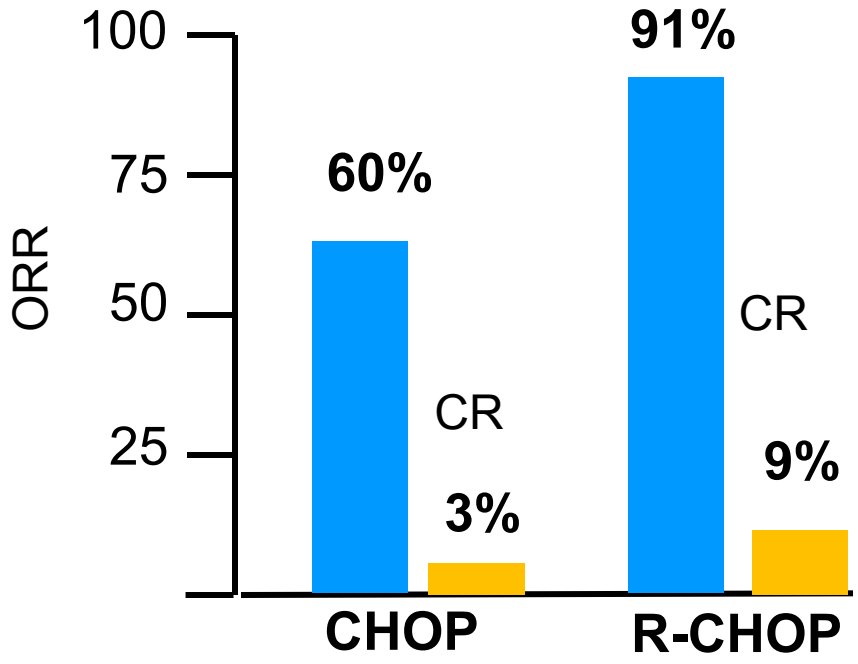

Magic Pill

# *Chemotherapy still one of the backbones In WM treatment!*

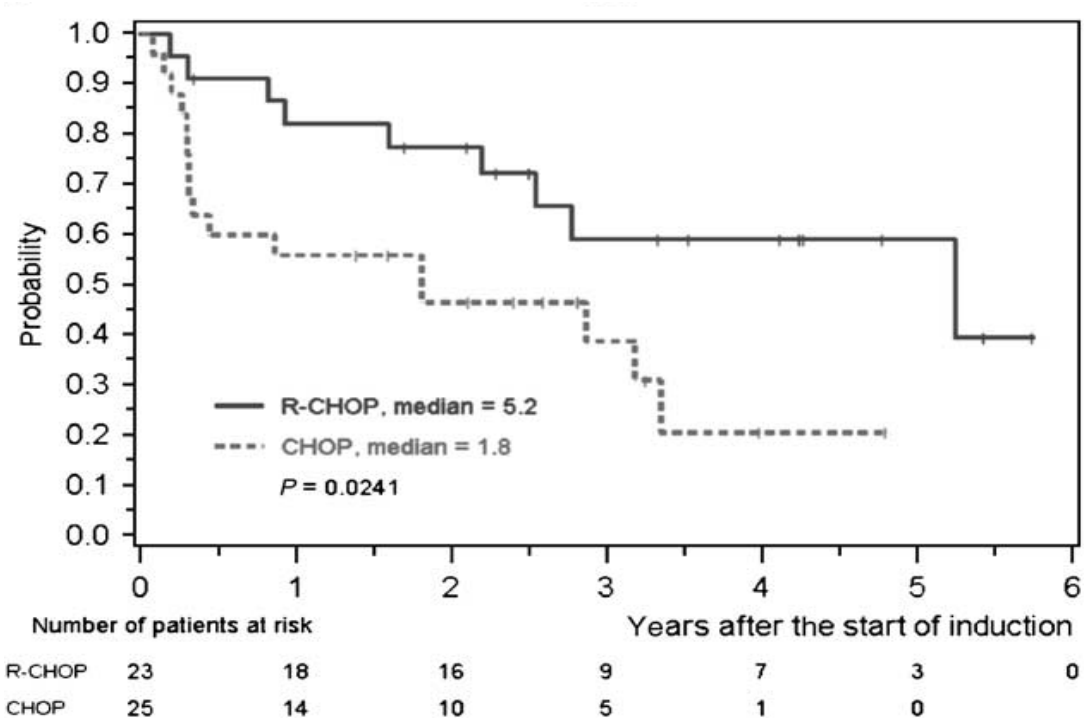
# CHOP Vs Rituximab-CHOP in WM

N=48

- CHOP: 25 pts
- R-CHOP: 23 pts

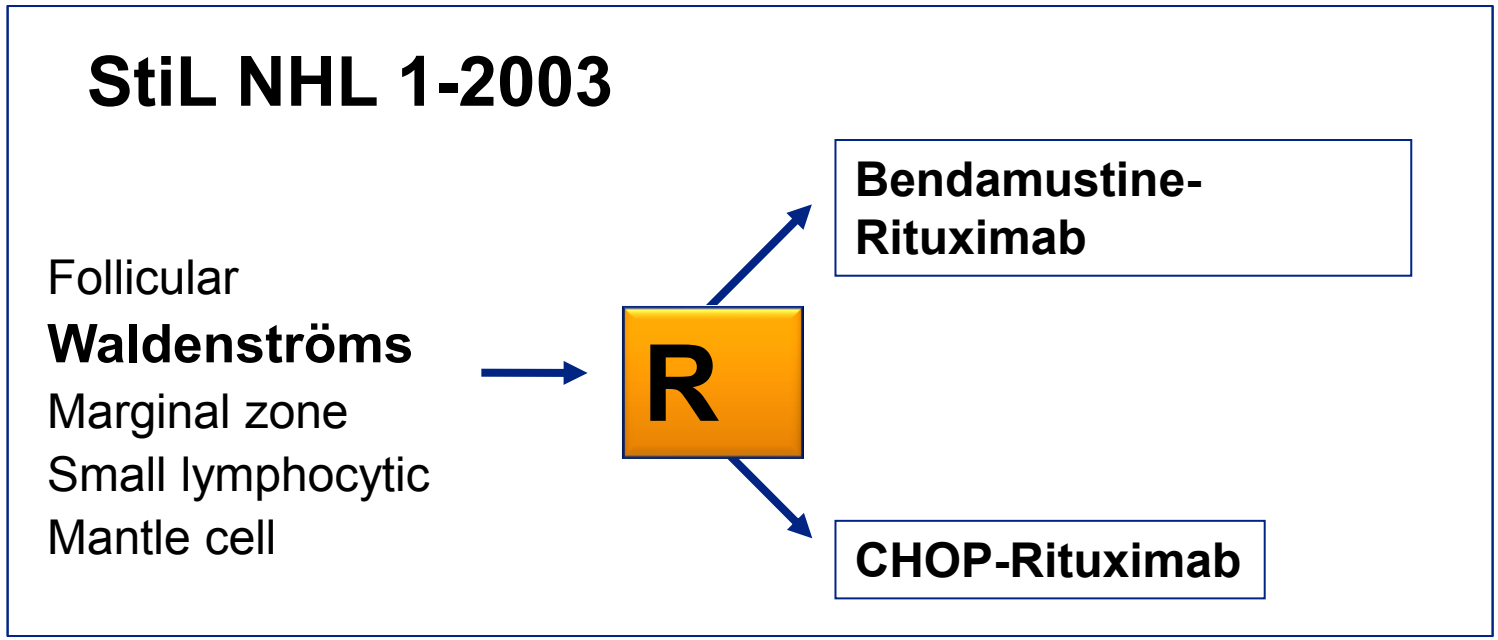



Time to treatment failure after the start of therapy for CHOP or R-CHOP




**Buske et al, Leukemia 2009**

# Bendamustine-Rituximab (B-R) vs CHOP-R




**Bendamustine 90 mg/m$^2$ day 1+2 + R day 1, max 6 cycles, q 4 wks. CHOP-R, max 6 cycles, q 3 wks.**

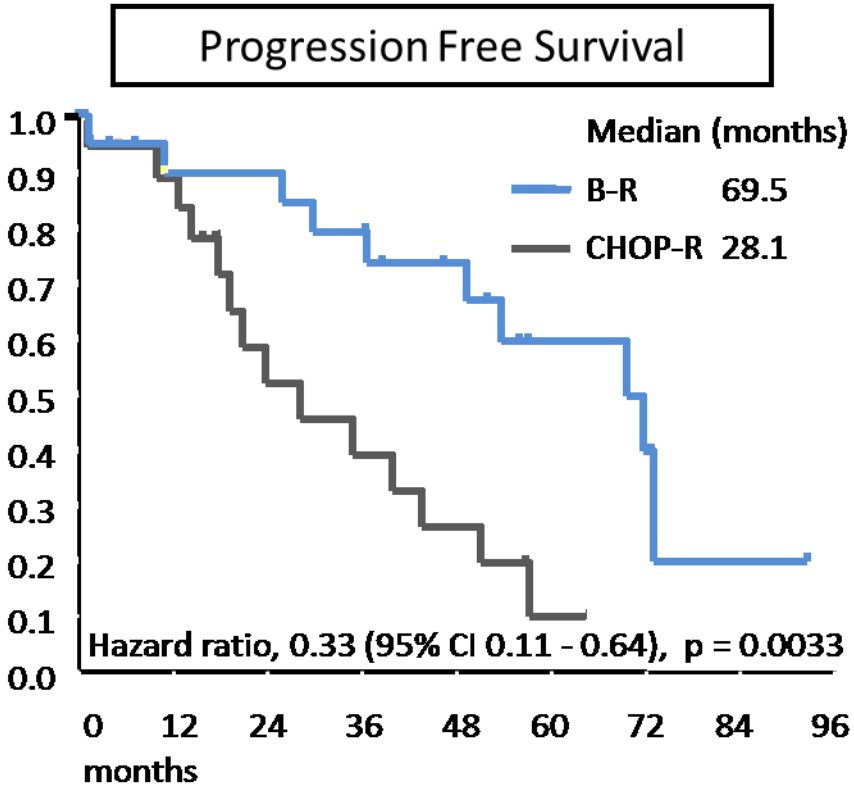
| N=41 evaluable | Benda-R (N=22) | CHOP-R (N=19) |
|---|---|---|
| Response rate | 21 (95%) | 18 (95%) |

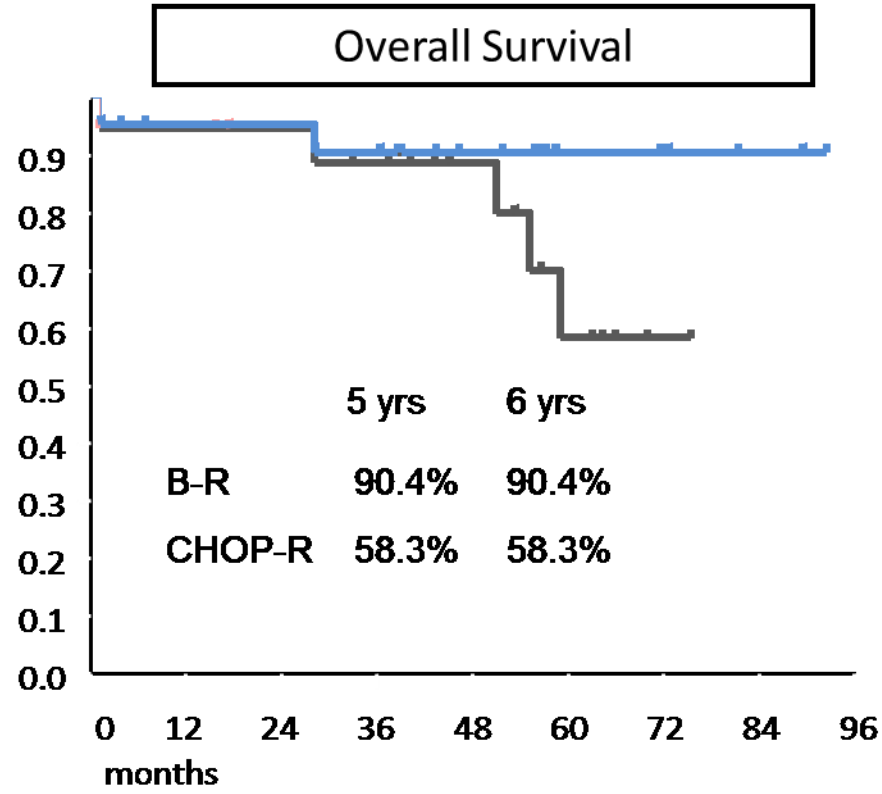
Rummel M, IMW7, Newport 2012 & Rummel et al Lancet 2013

# B-R vs CHOP–R as First-Line Treatment

## (subanalysis of the StiL NHL1 study in WM patients)

| B-R | CHOP-R |
|---|---|
| N= 22 | N=19 |



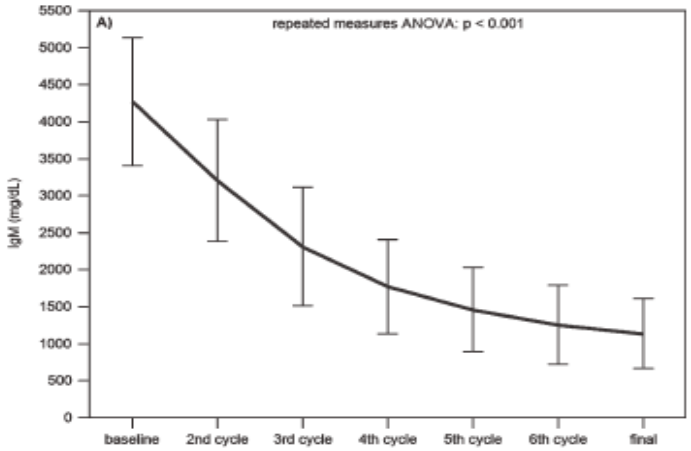

Rummel et al Lancet 2013

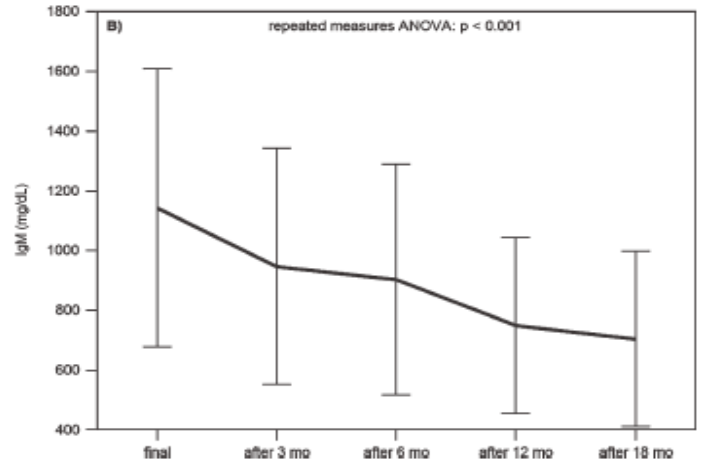
# FCR in previously untreated or pretreated patients

**ORR was 79%**

**An improvement of the quality of responses was observed during follow-up**

***Toxicity was significant***




No. of Patients (%)

| Response | End of Treatment | Best Response During Follow-Up |
|---|---|---|
| Overall response rate | 34 (79) | 34 (79) |
| Major response | 32 (74.4) | 33 (76.7) |
| Complete remission | 5 (11.6) | 8 (18.6) |
| Very good partial remission | 9 (20.9) | 6 (13.9) |
| Partial remission | 18 (41.8) | 19 (44.1) |
| Minor response | 2 (4.6) | 1 (2.3) |
| Stable disease | 4 (9.3) | 4 (9.3) |
| Progressive disease/failure | 1/4 (11.6) | 1/4 (11.6) |

Tedeschi et al Cancer 2012

# De-escalating chemotherapy!

# Phase II study of DRC regimen in patients with previously untreated symptomatic WM

- Dexamethasone 20mg IV day 1
- Rituximab 375 mg/m2 day1
- Cyclophosphamide po 100 mg/m$^2$ bid on days 1 to 5 (total dose 1000 mg/m$^2$)

• DRC courses q 21 days X 6 courses
• Patients without PD observed without treatment.

**N=72**

CR = 7%
PR = 67%
MR = 9%
**ORR = 83%**
SD = 8%
PD = 8%

**Median time to 50% IgM reduction was 4.1 months (range, 0.7-14)**

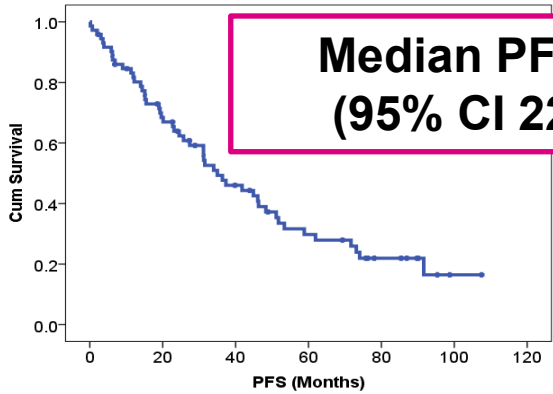
**IgM flare in 32%, ≥25% IgM increase in 11%**

***Dimopoulos et al J Clin Oncol 2007***

# DRC : long follow up

**(Median follow up for patients still alive <u>>7 years</u>)**

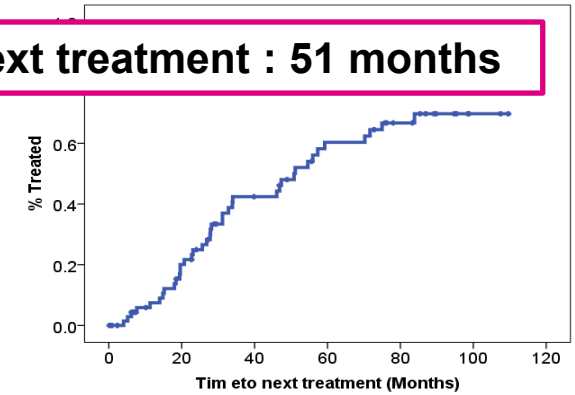
## PFS



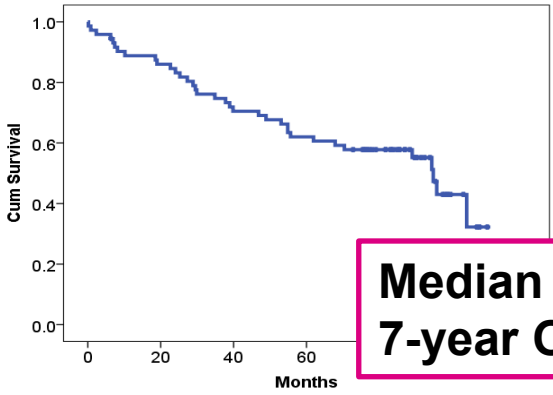

**Median PFS: 35 months**
**(95% CI 22-48 months)**

## Time to next treatment

**Median Time to next treatment : 51 months**

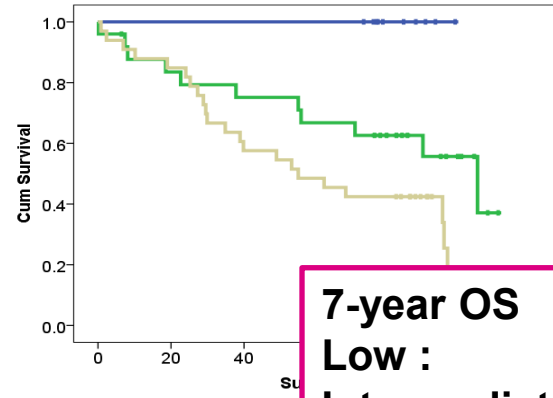



## Overall survival




**Median OS : 95 months**
**7-year OS 58%**

## Overall survival per ISSWM




**7-year OS**

| | |
|---|---|
| **Low :** | **100%** |
| **Intermediate:** | **63%** |
| **High :** | **42%** |

***Dimopoulos et al ASH 2012***

# DRC : long follow up
# Second line therapy

**40 (55%) patients have received second line treatment**

| | | N=40 | Response (MR or better) |
|---|---|---|---|
| Rituximab-based (70%) | Rituximab-alone | 7 (17.5%) | 23 (82%) |
| | DRC | 11 (27.5%) | |
| | Rituximab+other agents | 10 (25%) | |
| Non-Rituximab (30%) | Alkylating agents | 5 (12.5%) | 8 (67%) |
| | Nucleoside analogs | 4 (10%) | |
| | Bortezomib | 2 (5%) | |
| | HDT | 1 (2.5%) | |

Dimopoulos et al ASH 2012

# DRC – Toxicities

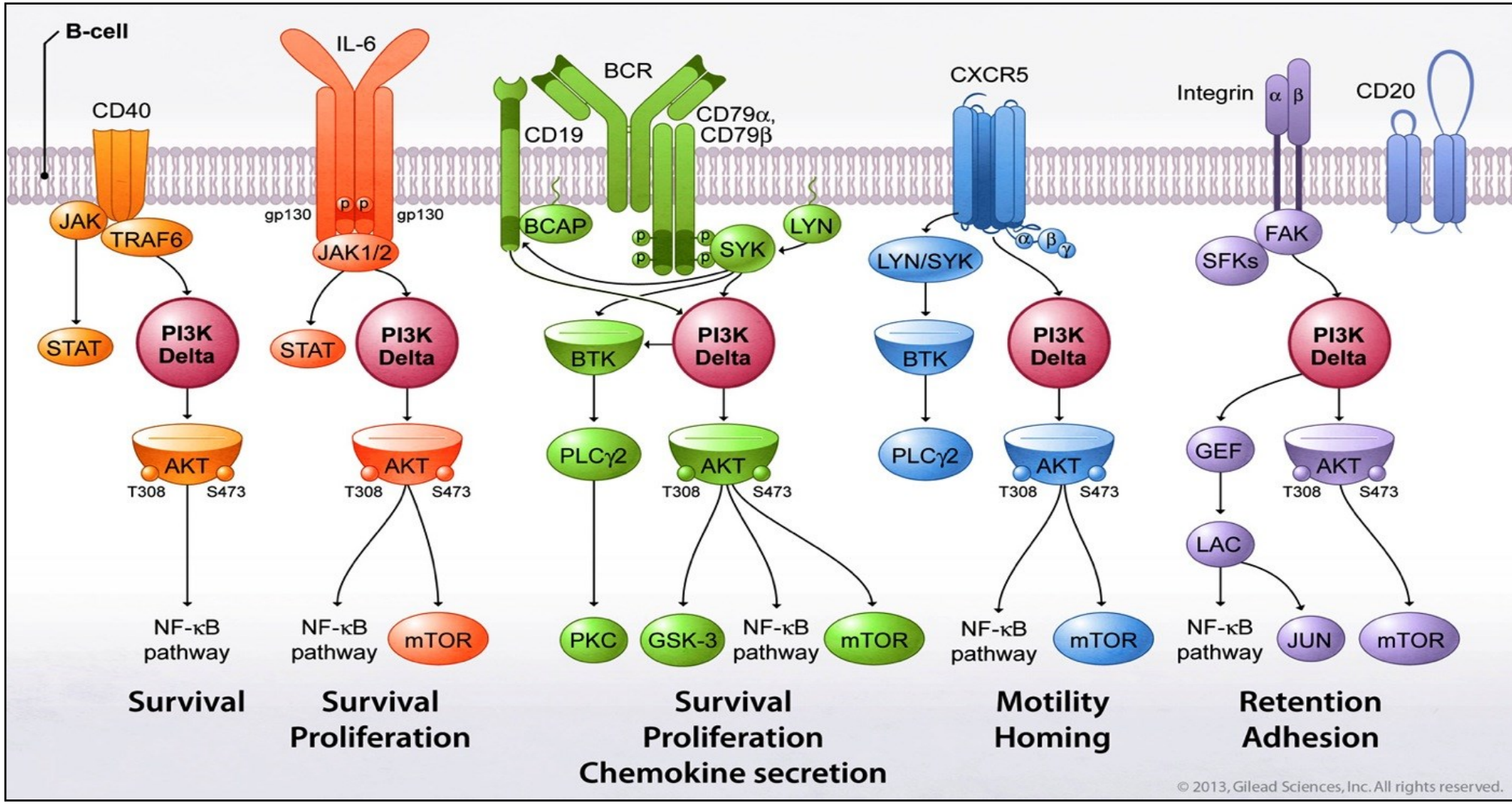
**Table 2.** Toxicity of Treatment With DRC (percentage of patients affected)

| 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***

# Searching the Magic Pill in WM



# How can we improve….. ‘novel agents’?

1. Thalidomid
2. Lenalidomid
3. Bortezomib
4. Ixazomib
5. Enzastaurin
6. Ibrutinib
7. Idelalisib

# Bortezomib/Rituximab

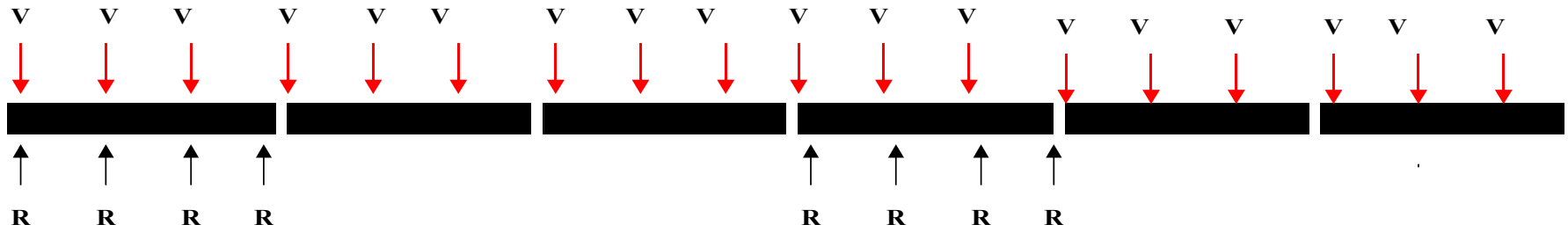
VOLUME 28 · NUMBER 8 · MARCH 10 2010

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

# Phase II Trial of Weekly Bortezomib in Combination With Rituximab in Relapsed or Relapsed and Refractory Waldenström Macroglobulinemia

*Irene M. Ghobrial, Fangxin Hong, Swaminathan Padmanabhan, Ashraf Badros, Meghan Rourke, Renee Leduc, Stacey Chuma, Janet Kunsman, Diane Warren, Brianna Harris, Amy Sam, Kenneth C. Anderson, Paul G. Richardson, Steven P. Treon, Edie Weller, and Jeffrey Matous*




1 cycle =28 days

---V Bortezomib 1.6 mg/m $^2$ days 1, 8, 15 q 28 days x 6 cycles

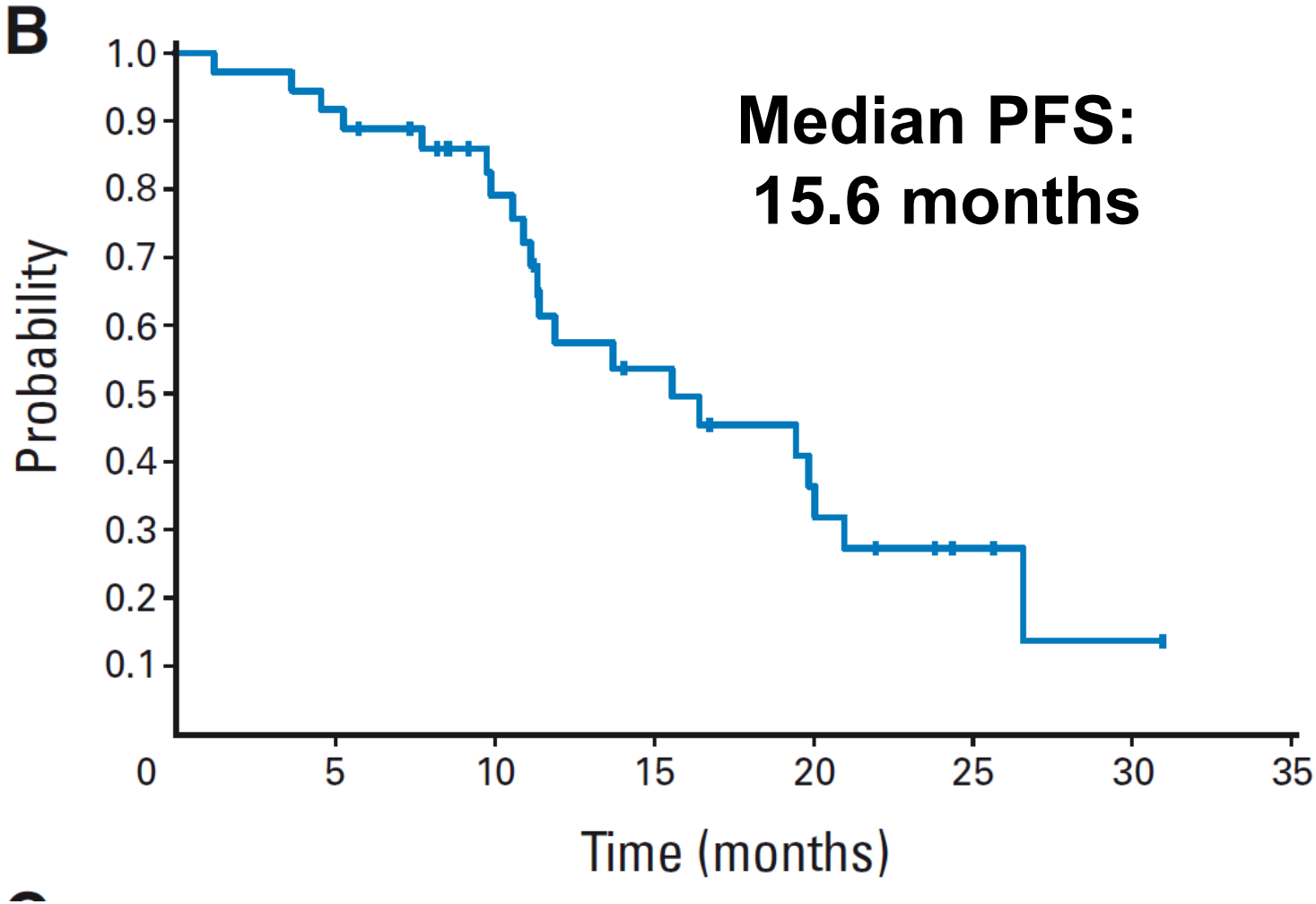
---R Rituximab 375 mg/m $^2$ days 1, 8, 15, 22 on cycles 1 and 4

# BR – Response Rates

**Table 2.** Response Measured by M Spike and Using IgM Measured by Nephelometry

| Response | M Spike | | IgM by Nephelometry | |
|---|---|---|---|---|
| | No. | % | No. | % |
| CR | 1 | 3 | 2 | 5 |
| nCR | 1 | 3 | NA | |
| PR | 17 | 46 | 21 | 57 |
| MR | 11 | 30 | 9 | 24 |
| SD | 4 | 11 | 2 | 5 |
| PD | 1 | 3 | 1 | 3 |
| Unevaluable | 2 | 5 | 2 | 5 |
| CR + nCR + PR + MR* | 30 | 81 | 32 | 87 |
| CR + nCR + PR† | 19 | 51 | 23 | 62 |

# BR – Progression Free Survival



# Toxicities

**Table 3.** Summary of Treatment-Related (possible, probably, definitely) Adverse Events in > 10% of Patients (N = 37)

| Toxicity | Grade 1 to 2 | | Grade 3 to 4 | | Grade 5 | |
|---|---|---|---|---|---|---|
| | No. | % | No. | % | No. | % |
| Hematologic | | | | | | |
| Hemoglobin | 30 | 81 | 4 | 11 | | |
| Leukocytes | 19 | 51 | 5 | 14 | | |
| Lymphopenia | 3 | 8 | 9 | 24 | | |
| Neutrophils | 11 | 30 | 6 | 16 | | |
| Thrombocytopenia | 14 | 37 | 5 | 13 | | |
| Gastrointestinal | | | | | | |
| Diarrhea | 14 | 37 | | | | |
| Constipation | 4 | 11 | | | | |
| Nausea | 11 | 30 | | | | |
| Vomiting | 4 | 11 | | | | |
| Infections | | | | | | |
| Infection, conjunctivitis | 6 | 16 | | | | |
| Infection, respiratory | 3 | 8 | | | 1 | 3 |
| Herpes Zoster reactivation | 4 | 11 | | | | |
| Electrolytes and liver function studies | | | | | | |
| Hyponatremia | 4 | 11 | | | | |
| Hyperglycemia | 16 | 43 | | | | |
| Alkaline phosphatase | 6 | 16 | | | | |
| AST | 6 | 16 | | | | |
| Neurologic/pain/others | | | | | | |
| Peripheral neuropathy | 15 | 41 | 2 | 5 | | |
| Muscle pain | 4 | 11 | | | | |
| Fatigue | 25 | 68 | | | | |
| Dizziness | 4 | 11 | | | | |
| Allergic reaction | 11 | 30 | | | | |

# European Consortium for WM
# ECWM-1 study

## Efficacy of first line Dexamethasone, Rituximab and Cyclophosphamide (DRC) +/- Bortezomib for patients with Waldenström's Macroglobulinaemia (ECWM-1)

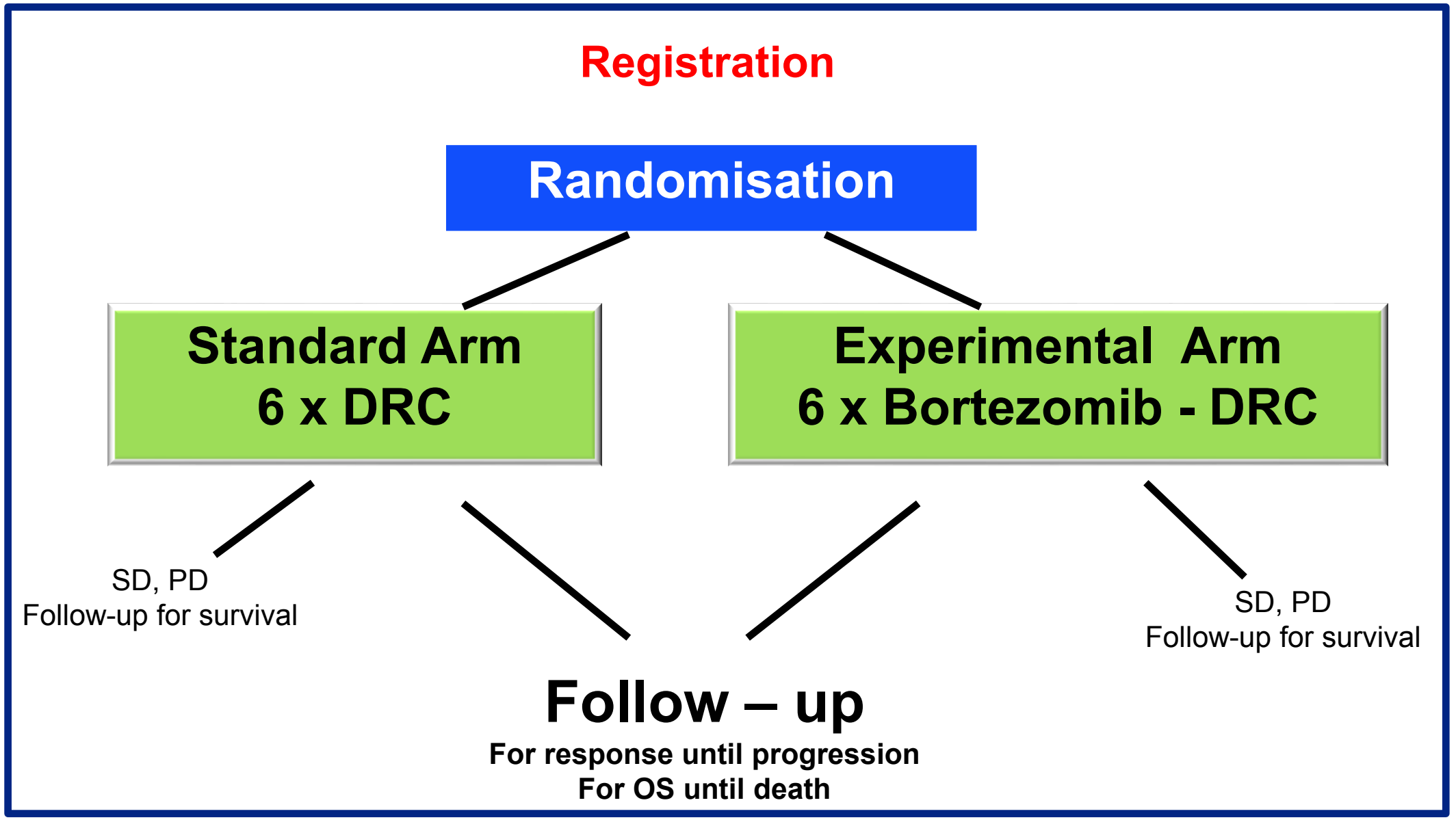
## -a multicenter, open, two-arm, open label, randomized phase III trial

| | |
|---|---|
| Patient recruitment | 384 patients based on the statistical analysis plan |
| Number of study centers | Approximately 100 |
| Duration of recruitment | Approximately 3.3 years |
| Involved study groups | 11 European Study groups |


Clinicaltrials.gov : NCT01788020

# *ECWM-1*

**first line WM**

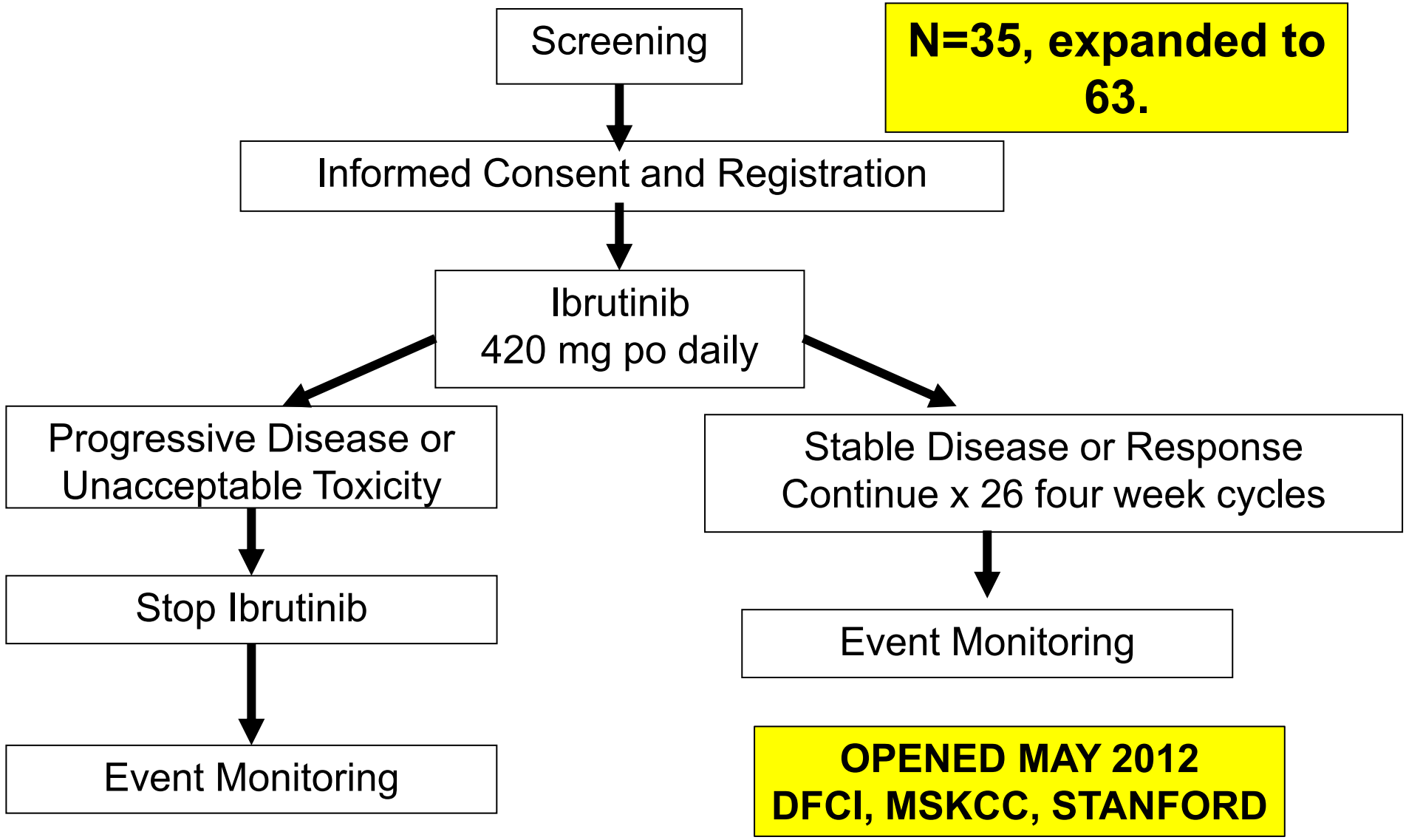


# Phase II Study of the Bruton's Tyrosine Kinase (Btk) Inhibitor Ibrutinib in Waldenstrom's Macroglobulinemia

**Steven P. Treon**

**Dana-Farber Cancer Institute**

# SCHEMA FOR MULTICENTER PHASE II STUDY OF IBRUTINIB IN RELAPSED/REFRACTORY WM



# Clinical Responses to Ibrutinib

## Median of 9 (range 1-18) Cycles

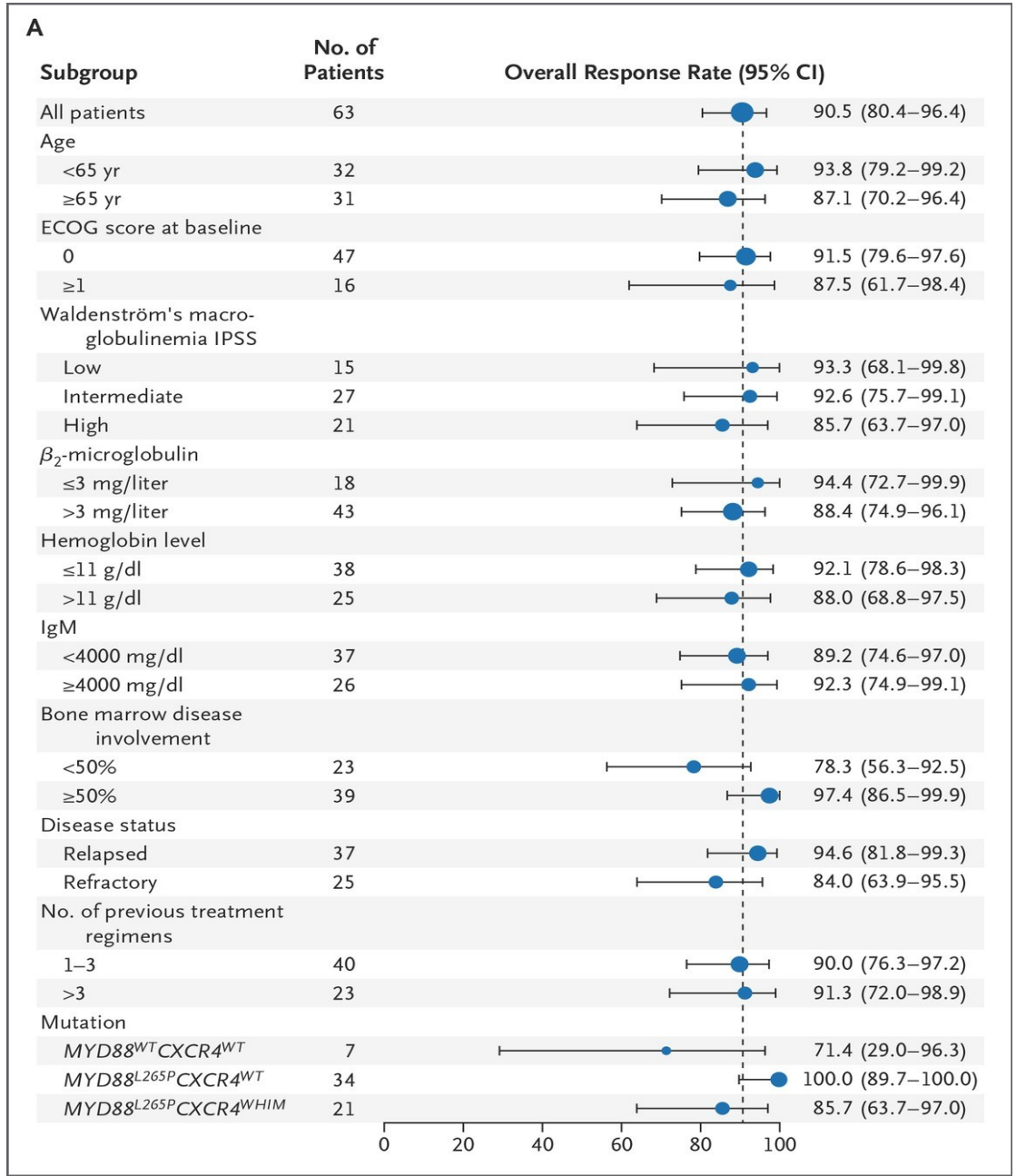
| | (N= 63) | (%) |
|---|---|---|
| VGPR | 10 | 15.9 |
| PR | 36 | 57 |
| MR | 11 | 17.5 |

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

**ORR: 90.5%  Major RR (≥ PR): 73%**

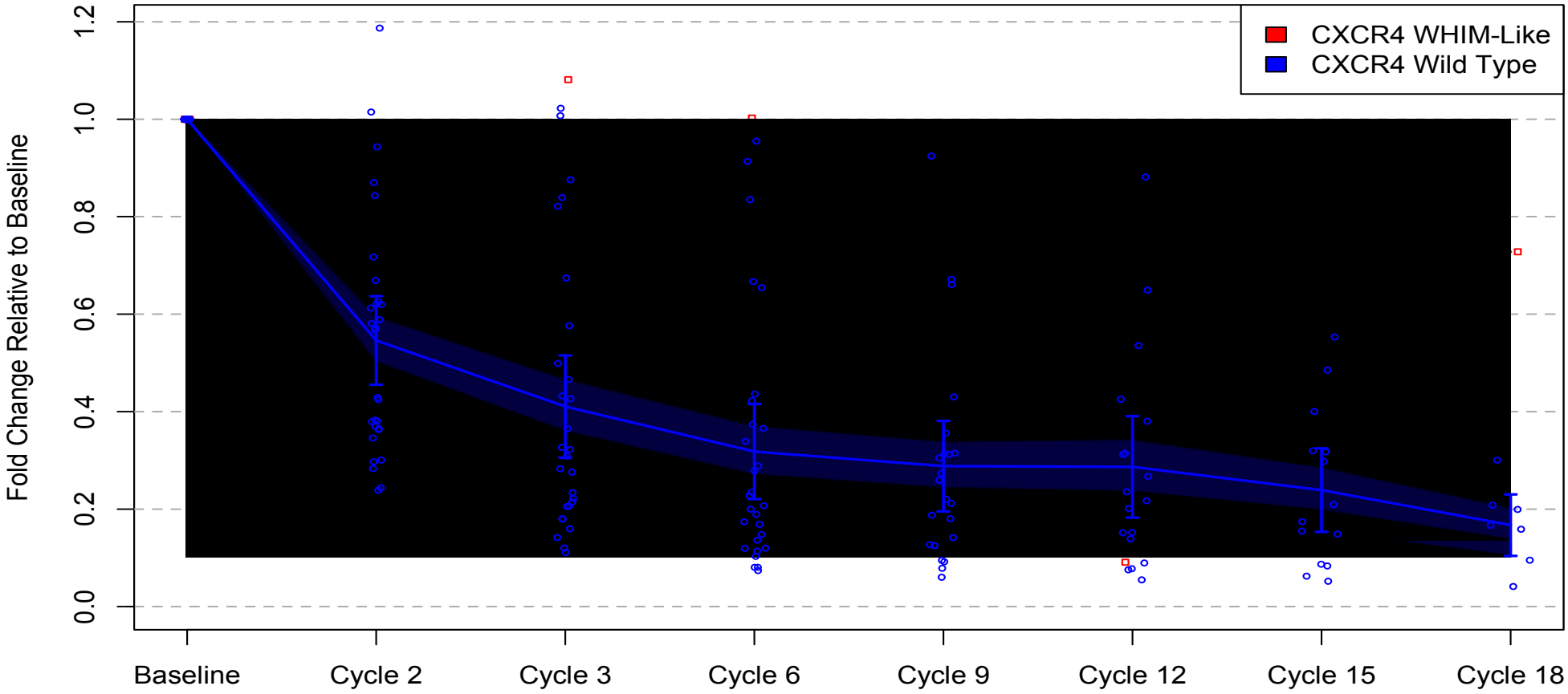
***Treon et al, NEJM 2015***

# Subgroup Analyses of Responses.




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

# Serial changes in serum IgM levels following Ibrutinib Stratified by CXCR4 status

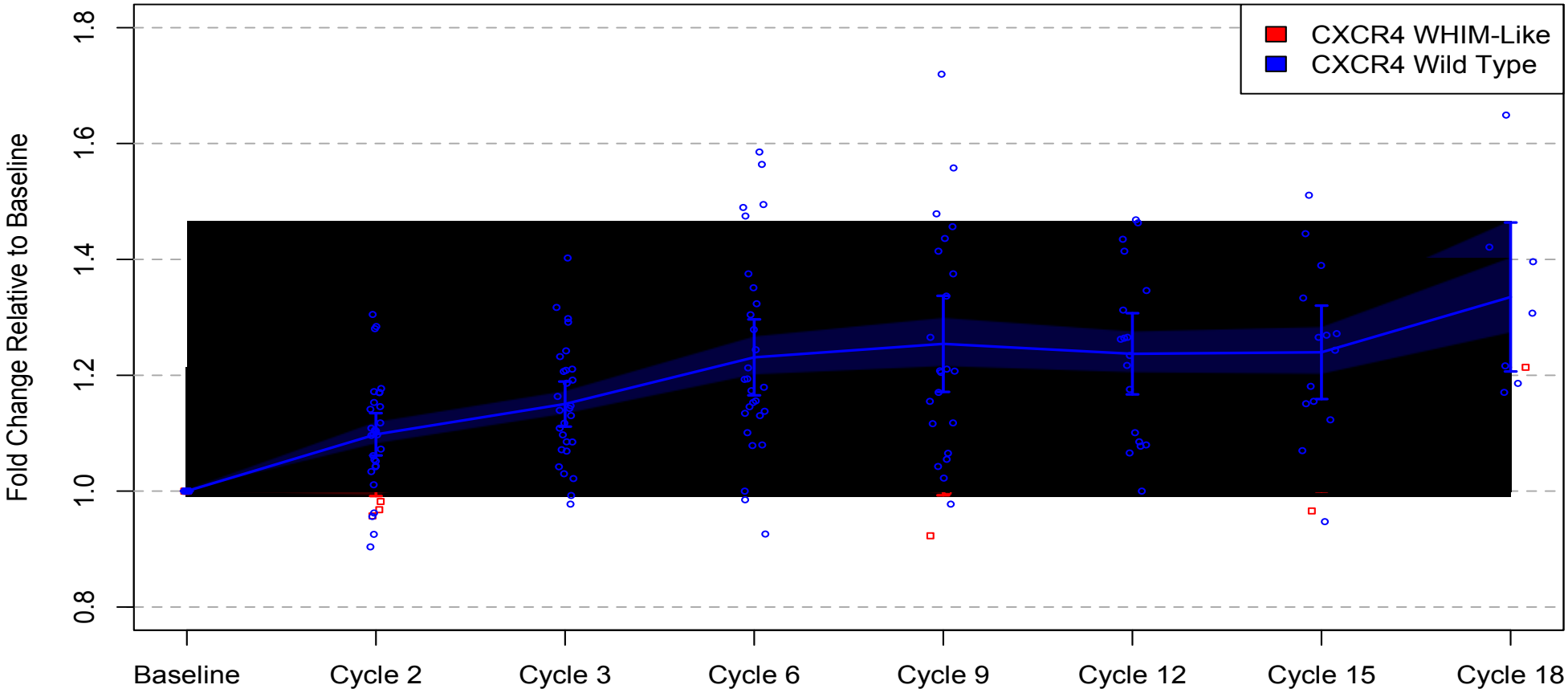



Serum IgM Mean Fold Change and Standard Error of the Mean by Cycle

ANOVA p-values: Mutation Status = 1.88e-10 Therapy Cycle = 2.63e-36 Interaction effect = 8.93e-02

Treon et al, Blood 2013; 122(21): Abstract 251

# Serial Hemoglobin levels following Ibrutinib Stratified by CXCR4 status

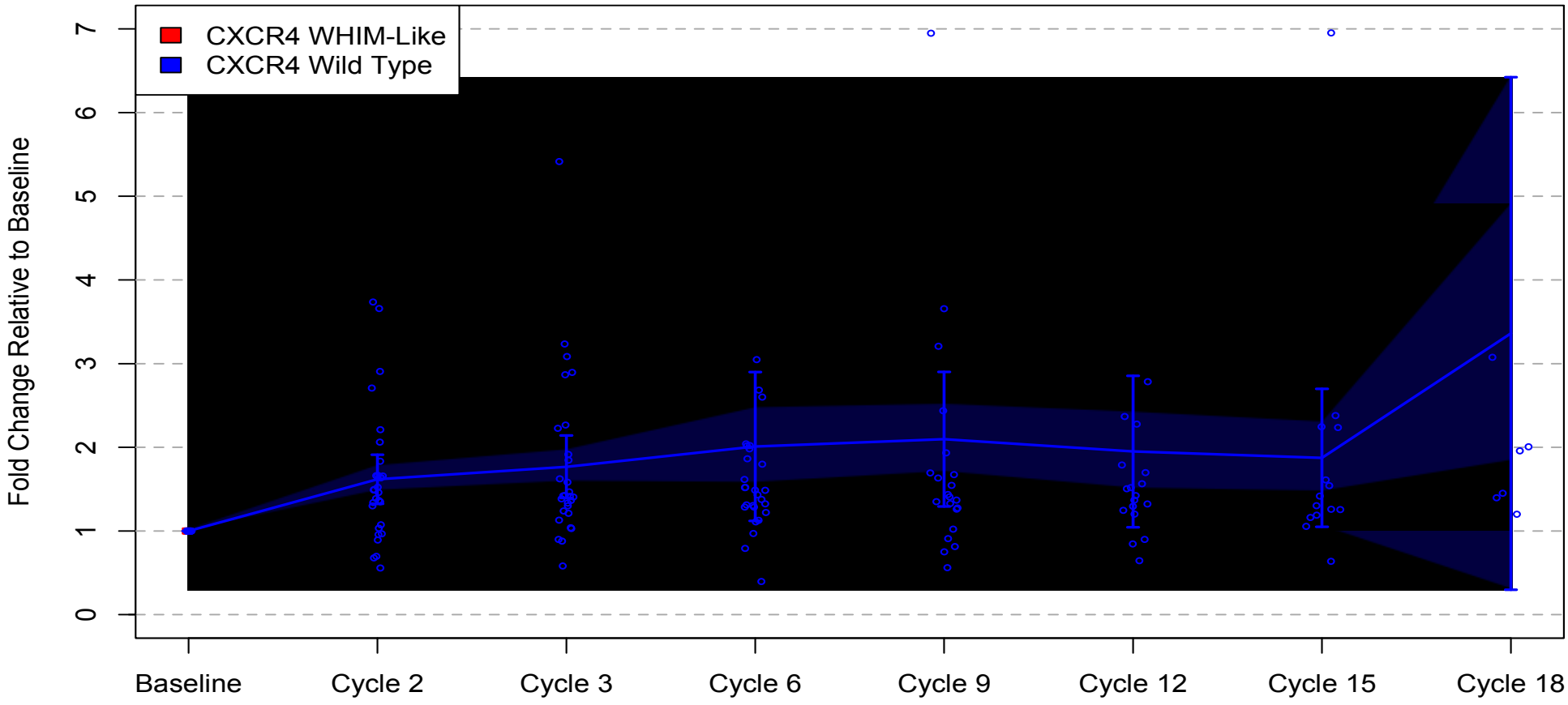



Hb Mean Fold Change and Standard Error of the Mean by Cycle

ANOVA p-values: Mutation Status = 9.75e-07 Therapy Cycle = 8.13e-16 Interaction effect = 8.64e-02

Treon et al, Blood 2013; 122(21): Abstract 251

# Serial Peripheral Lymphocyte Counts following Ibrutinib Stratified by CXCR4 status

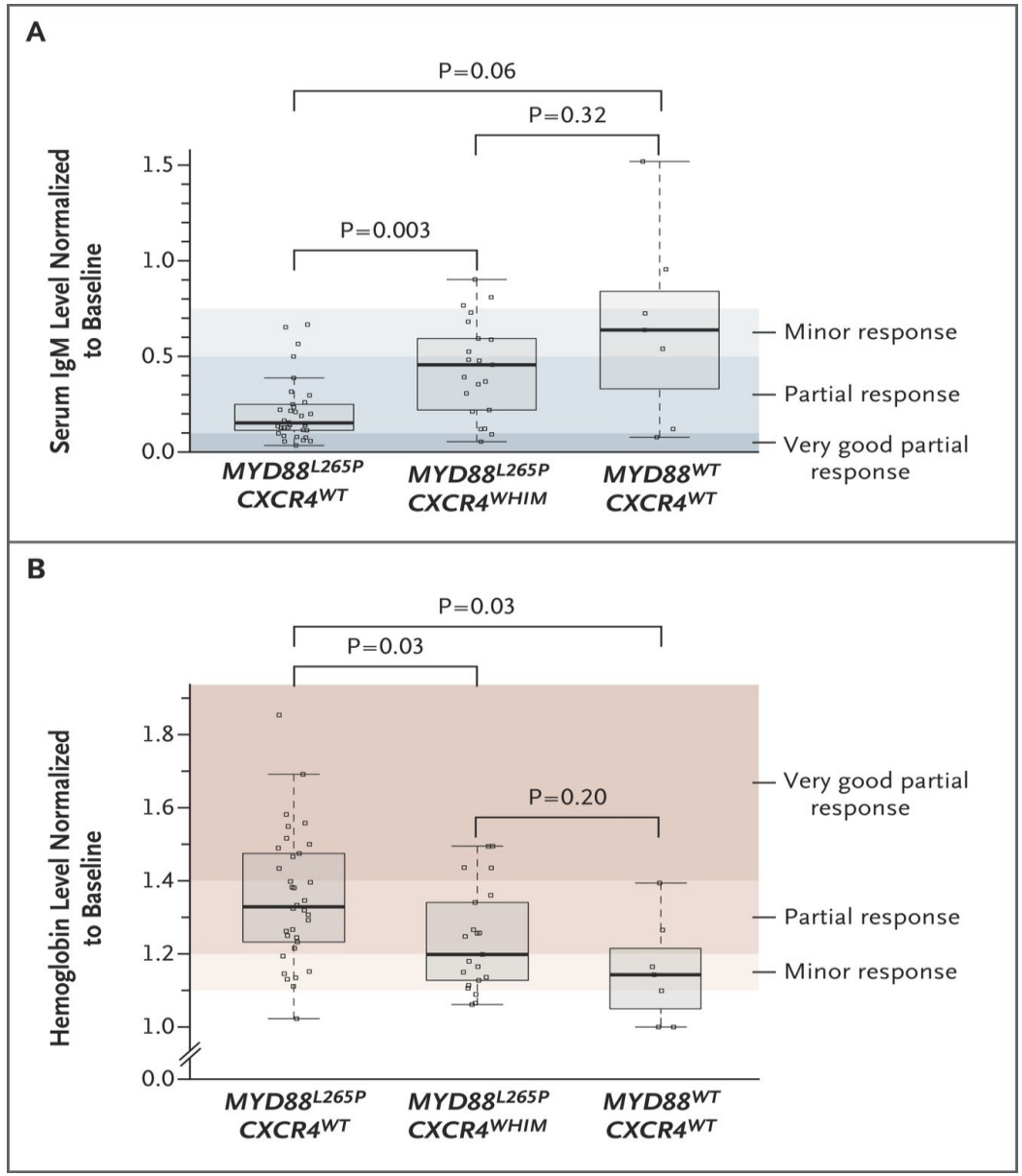



Absolute Lymphocyte Count Mean Fold Change and Standard Error of the Mean by Cycle

ANOVA p-values: Mutation Status = 1.17e-03 Therapy Cycle = 3.68e-02 Interaction effect = 7.88e-01

Treon et al, Blood 2013; 122(21): Abstract 251

# Effect of *MYD88* and *CXCR4* Mutation Status on Ibrutinib-Related Changes in Serum IgM and Hemoglobin Levels.

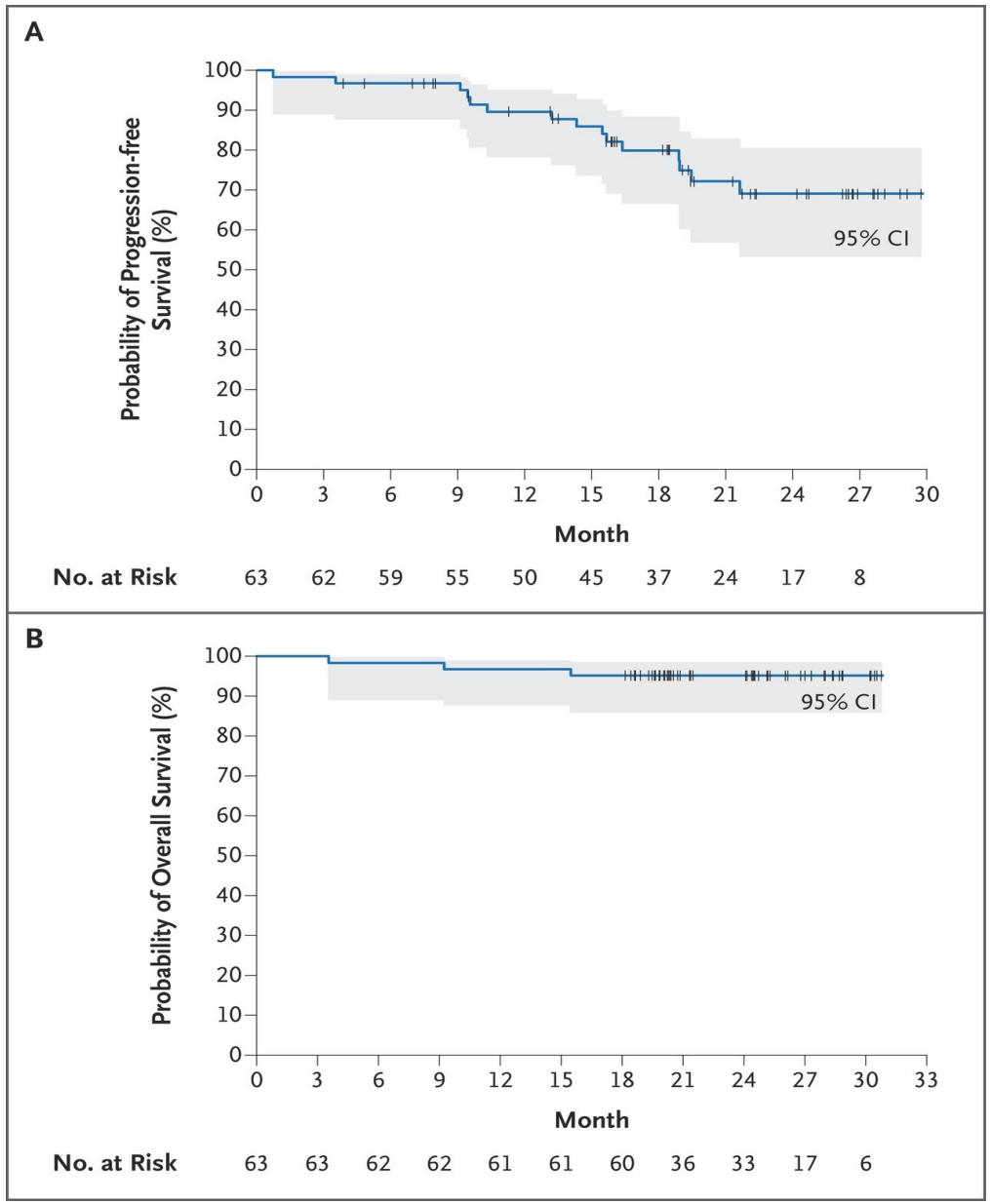



Treon SP et al. N Engl J Med 2015;372:1430-1440

# MYD88 /CXCR4 status and Ibrutinib Responses

| MYD88/ CXCR4 | OR | VGPR/PR |
|---|---|---|
| +/- | 100 % | 91.2% |
| +/+ | 85.7 % | 61.9% |
| -/- | 71.4% | 28.6% |

# Kaplan–Meier Curves for Progression-free and Overall Survival.




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

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

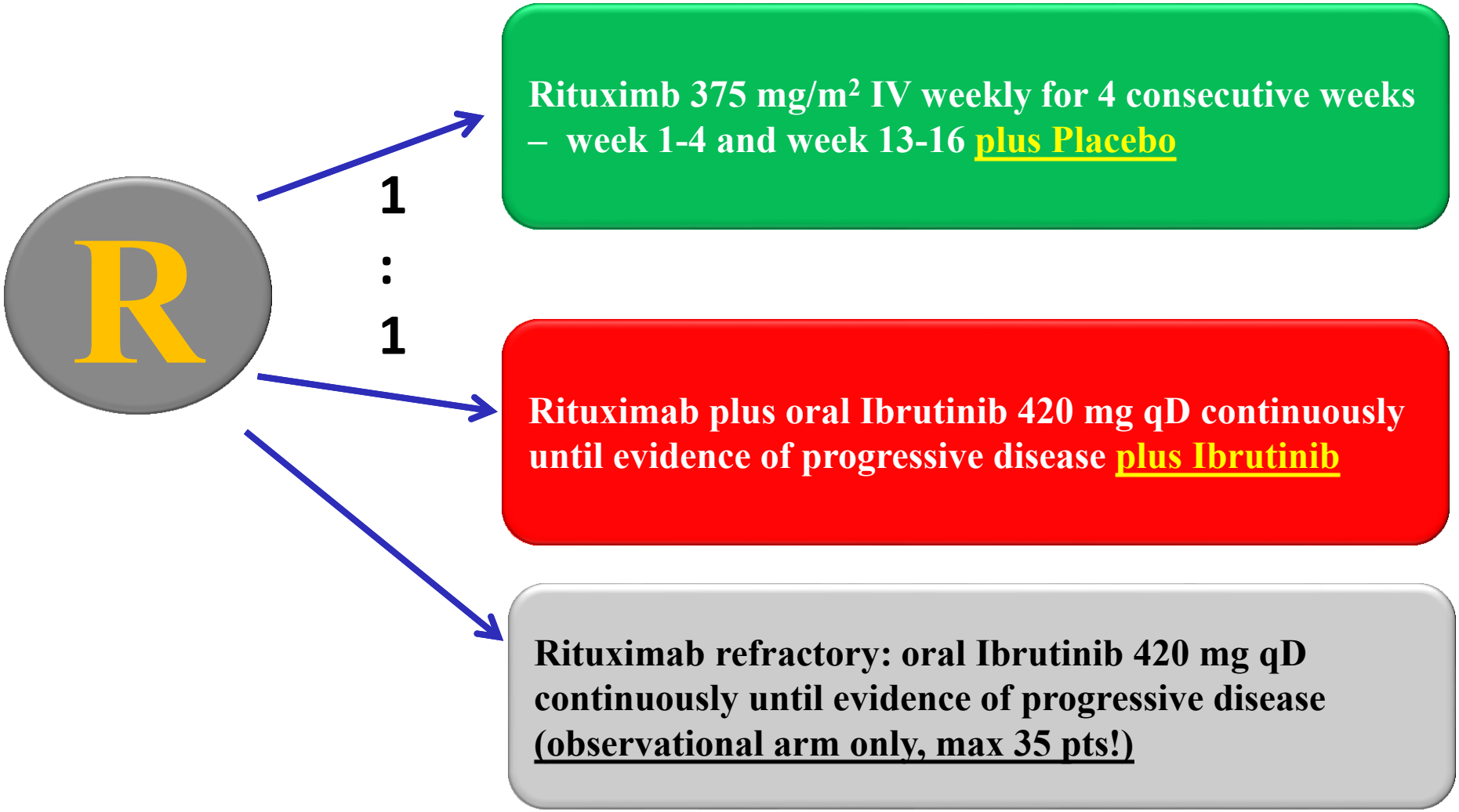
| ADVERSE EVENT | ≥GRADE 2 | GRADE 3 | GRADE 4 |
|---|---|---|---|
| THROMBOCYTOPENIA | 6 (17.1%) | 3 (8.6%) | 0 (0.0%) |
| NEUTROPENIA | 6 (17.1%) | 2 (5.7%) | 1 (2.8%) |
| HEMATOMA | 1 (2.9%) | 0 (0.0%) | 0 (0.0%) |
| EPISTAXIS | 1 (2.9%) | 0 (0.0%) | 0 (0.0%) |
| STOMATITIS | 1 (2.9%) | 1 (2.9%) |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

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

## ECWM-R1

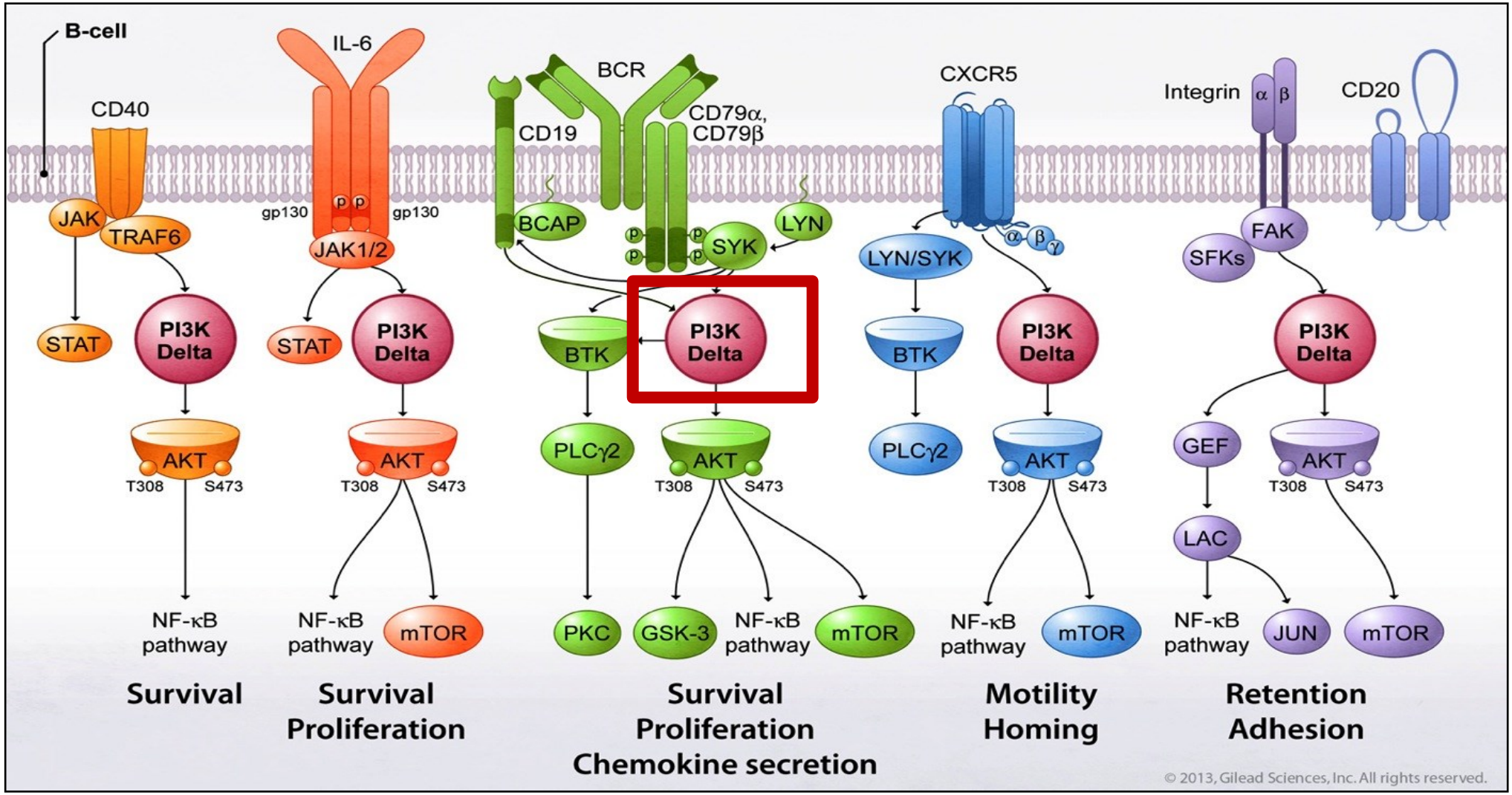
European Waldenström's Macroglobulinemia Consortium

# ECWM-R1 / Relapse




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

# PI3Kδ Inhibition Impacts Multiple Critical Pathways in iNHL



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

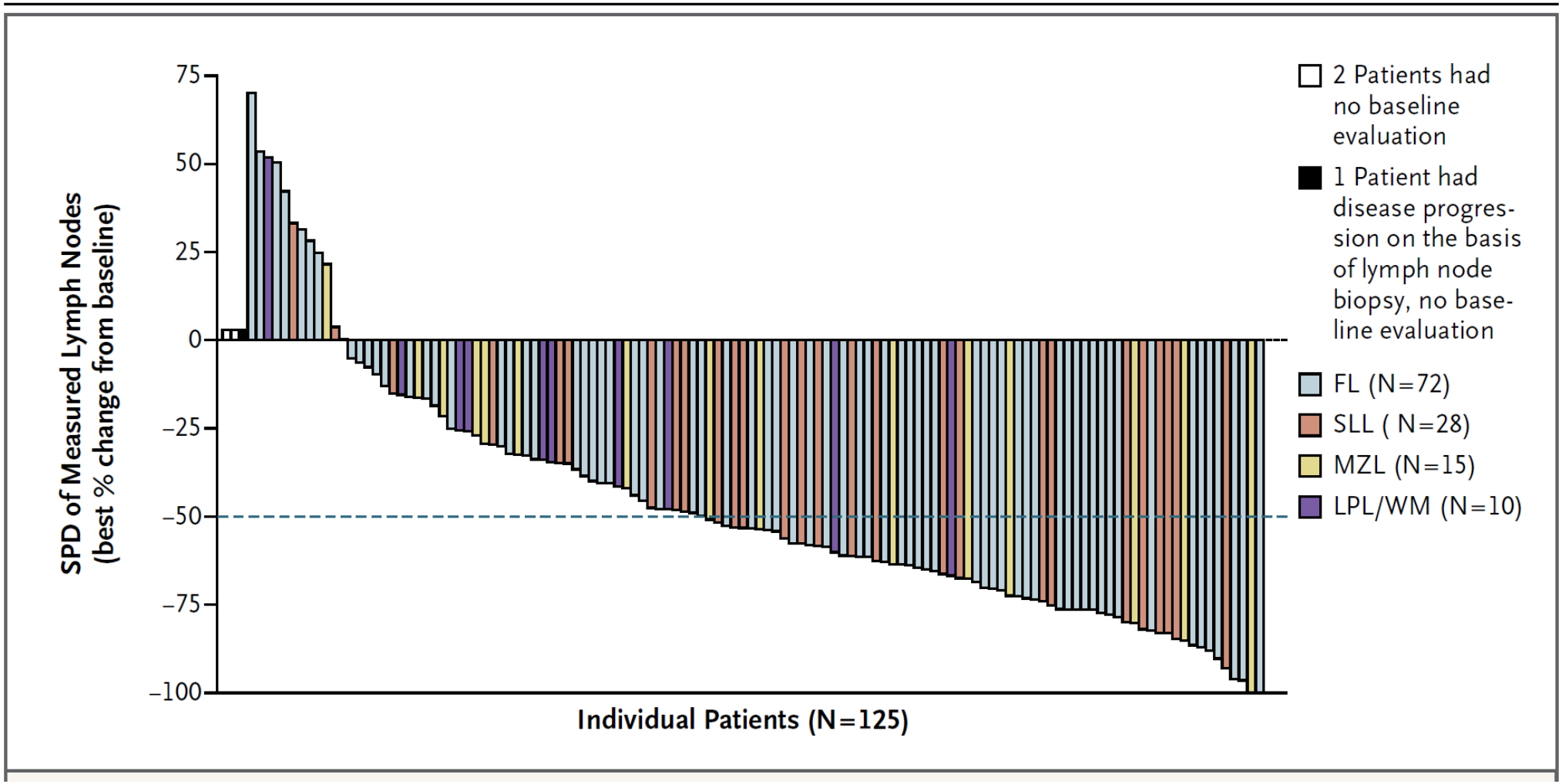
# PI3Kδ Inhibition by Idelalisib in Patients with Relapsed Indolent Lymphoma

Ajay K. Gopal, M.D., Brad S. Kahl, M.D., Sven de Vos, M.D., Ph.D., Nina D. Wagner-Johnston, M.D., Stephen J. Schuster, M.D., Wojciech J. Jurczak, M.D., Ph.D., Ian W. Flinn, M.D., Ph.D., Christopher R. Flowers, M.D., Peter Martin, M.D., Andreas Viardot, M.D., Kristie A. Blum, M.D., Andre H. Goy, M.D., Andrew J. Davies, M.R.C.P., Ph.D., Pier Luigi Zinzani, M.D., Ph.D., Martin Dreyling, M.D., Dave Johnson, B.S., Langdon L. Miller, M.D., Leanne Holes, M.B.A., Daniel Li, Ph.D., Roger D. Dansey, M.D., Wayne R. Godfrey, M.D., and Gilles A. Salles, M.D., Ph.D.

# Phase 2 Idelalisib Monotherapy in Refractory iNHL (Study 101-09)


- **Primary endpoint:**
  - Overall Response Rate (ORR)
- **Secondary endpoints:**
  - Duration of Response (DOR)
  - Progression Free Survival (PFS)
  - Overall Survival (OS)
  - Safety
  - Quality of life

# Study 101-09 Waterfall Plot Lymph Node Response



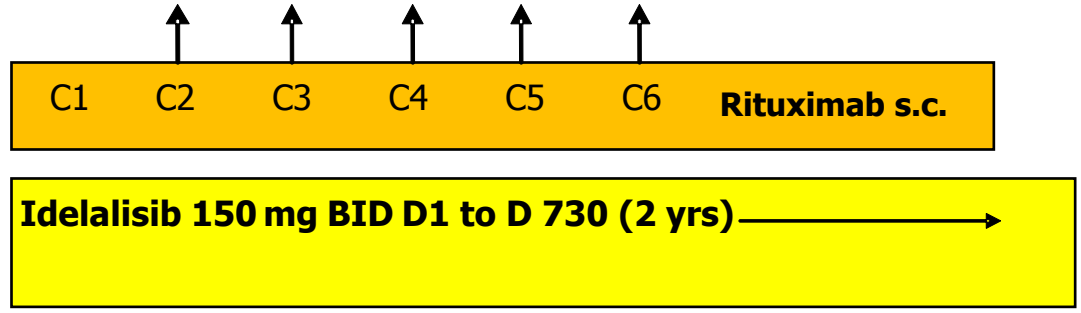

- 90% had improvement in lymphadenopathy
- 57% had ≥50% decrease from baseline

Table 2.1.1.4: Overall Response Rate (ORR) - by Disease
ITT Analysis Set

| | FL (N=72) | SLL (N=28) | WM (N=10) | MZL (N=15) | Total (N=125) |
|---|---|---|---|---|---|
| Independent Review Committee (IRC) | | | | | |
| Assessments Best Overall Response Rate (%) | | | | | |
| Complete Response | 6 ( 8.3%) | 0 | 0 | 1 ( 6.7%) | 7 ( 5.6%) |
| Partial Response | 33 ( 45.8%) | 17 ( 60.7%) | 7 ( 70.0%) | 6 ( 40.0%) | 63 ( 50.4%) |
| Minor Response | 0 | 0 | 1 ( 10.0%) | 0 | 1 ( 0.8%) |
| Stable Disease | 24 ( 33.3%) | 10 ( 35.7%) | 1 ( 10.0%) | 7 ( 46.7%) | 42 ( 33.6%) |
| Progressive Disease | 8 ( 11.1%) | 0 | 1 ( 10.0%) | 1 ( 6.7%) | 10 ( 8.0%) |
| Not Evaluable | 1 ( 1.4%) | 1 ( 3.6%) | 0 | 0 | 2 ( 1.6%) |
| Missing | 0 | 0 | 0 | 0 | 0 |
| ORR (%) [a] | 39 ( 54.2%) | 17 ( 60.7%) | 8 ( 80.0%) | 7 ( 46.7%) | 71 ( 56.8%) |
| 95% CI (%) [b] | 42 - 66 | 40.6 - 78.5 | 44.4 - 97.5 | 21.3 - 73.4 | 47.6 - 65.6 |
| Investigator Assessments Best Overall Response Rate (%) | | | | | |
| Complete Response | 5 ( 6.9%) | 0 | 0 | 2 ( 13.3%) | 7 ( 5.6%) |
| Partial Response | 37 ( 51.4%) | 16 ( 57.1%) | 7 ( 70.0%) | 4 ( 26.7%) | 64 ( 51.2%) |
| Minor Response | 0 | 0 | 1 ( 10.0%) | 0 | 1 ( 0.8%) |
| Stable Disease | 21 ( 29.2%) | 10 ( 35.7%) | 1 ( 10.0%) | 9 ( 60.0%) | 41 ( 32.8%) |
| Progressive Disease | 8 ( 11.1%) | 2 ( 7.1%) | 1 ( 10.0%) | 0 | 11 ( 8.8%) |
| Not Evaluable | 1 ( 1.4%) | 0 | 0 | 0 | 1 ( 0.8%) |
| Missing | 0 | 0 | 0 | 0 | 0 |
| ORR (%) [a] | 42 ( 58.3%) | 16 ( 57.1%) | 8 ( 80.0%) | 6 ( 40.0%) | 72 ( 57.6%) |
| 95% CI (%) [b] | 46.1 - 69.8 | 37.2 - 75.5 | 44.4 - 97.5 | 16.3 - 67.7 | 48.4 - 66.4 |
| Agreement (%) [c] | 76.4 | 96.4 | 100 | 93.3 | 84.8 |

# *ECWM-R3*
## relapsed WM

An Open Label non-randomized Phase II Study exploring “outpatient chemo-free” treatment association with Idelalisib + subcutaneous rituximab in Patients with relapsed/refractory Waldenstrom’s Macroglobulinemia (WM)




Primary end point: PFS (from 15 months to 30 months; 50 pts)

Start Q2 2015

*Sponsor ECWM/French CLL/WM Intergroup*

# *European Consortium for Waldenström's Macroglobulinemia*

# ECWM - Trials 2014/2015


## *Trials*
## *First Line*

***ECWM-1 (Phase III)***
**DRC versus Bortezomib-DRC**
**European, 80 centers**
**recruiting**

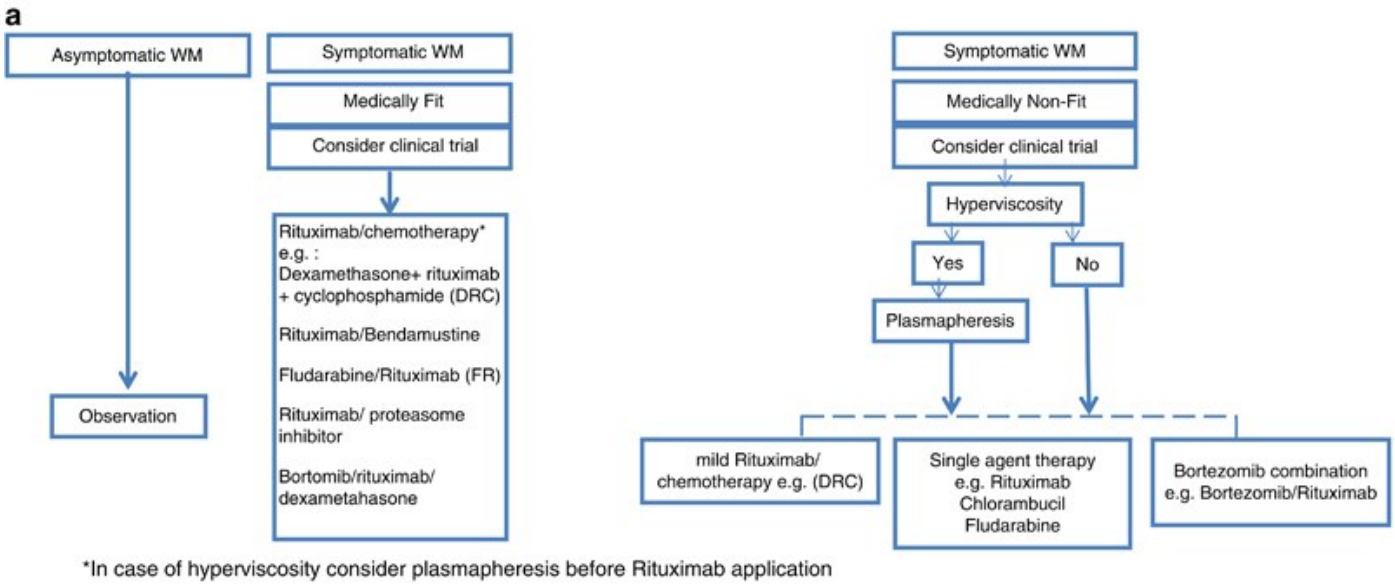
## *Relapse*

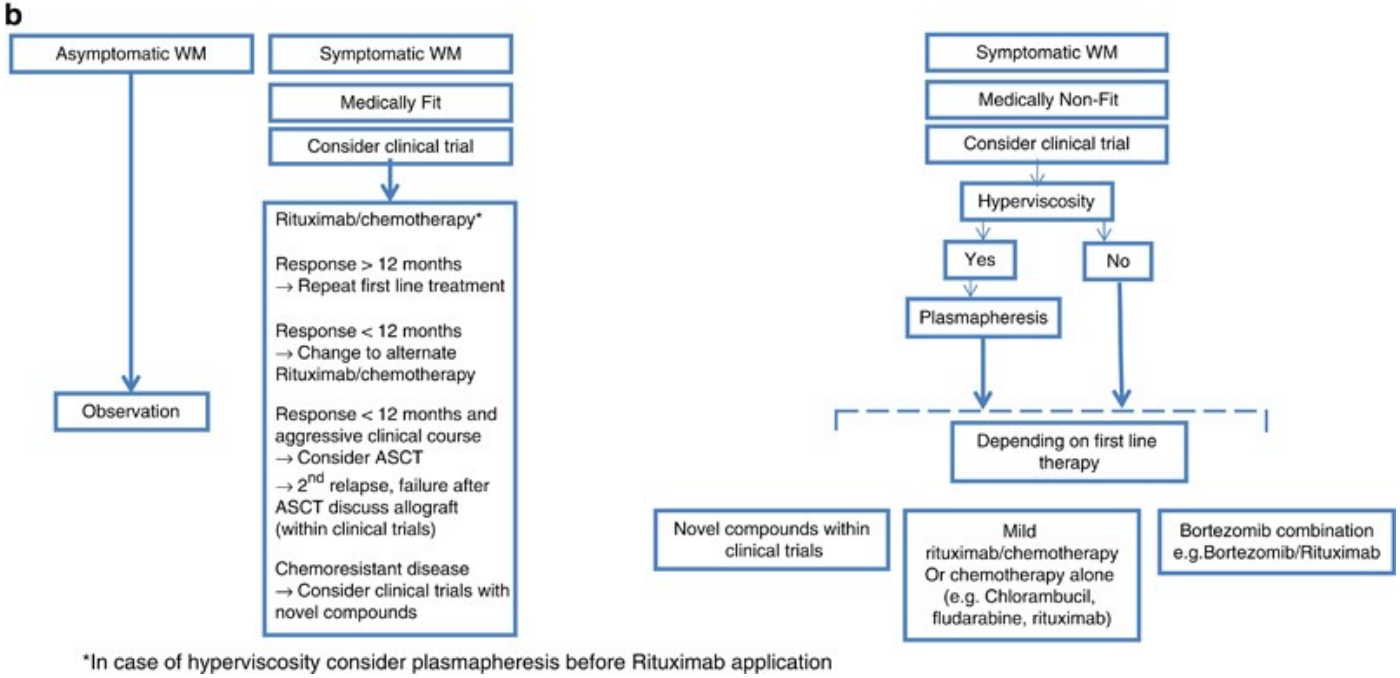
***ECWM-R1 (Phase III):***
**Rituximab + Placebo vs Rituximab plus Ibrutinib**
**Global, 59 centers**
**Activation in Germany Nov/Dec 2014**

***ECWM-R2***
**Ixazomib/Rituximab/Dexa**

***ECWM-R3***
**Idelalisib/Rituximab**

# Treatment Algorithms - WM




***ESMO Guidelines***

***Buske et al., 2014***

# *Indolent B - NHL*
# *Hopefully a bright future*

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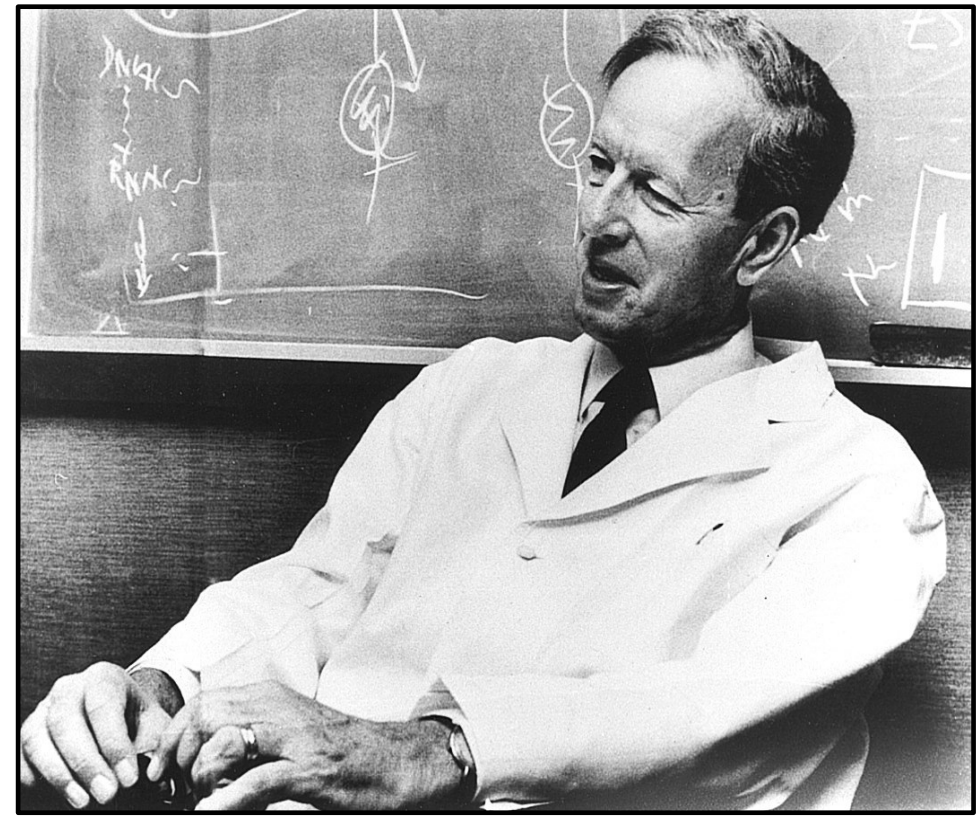

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# Many Thanks!