*Milano 21 Aprile 2018*

# *Macroglobulinemia di Waldenstrom*

# *Terapia*

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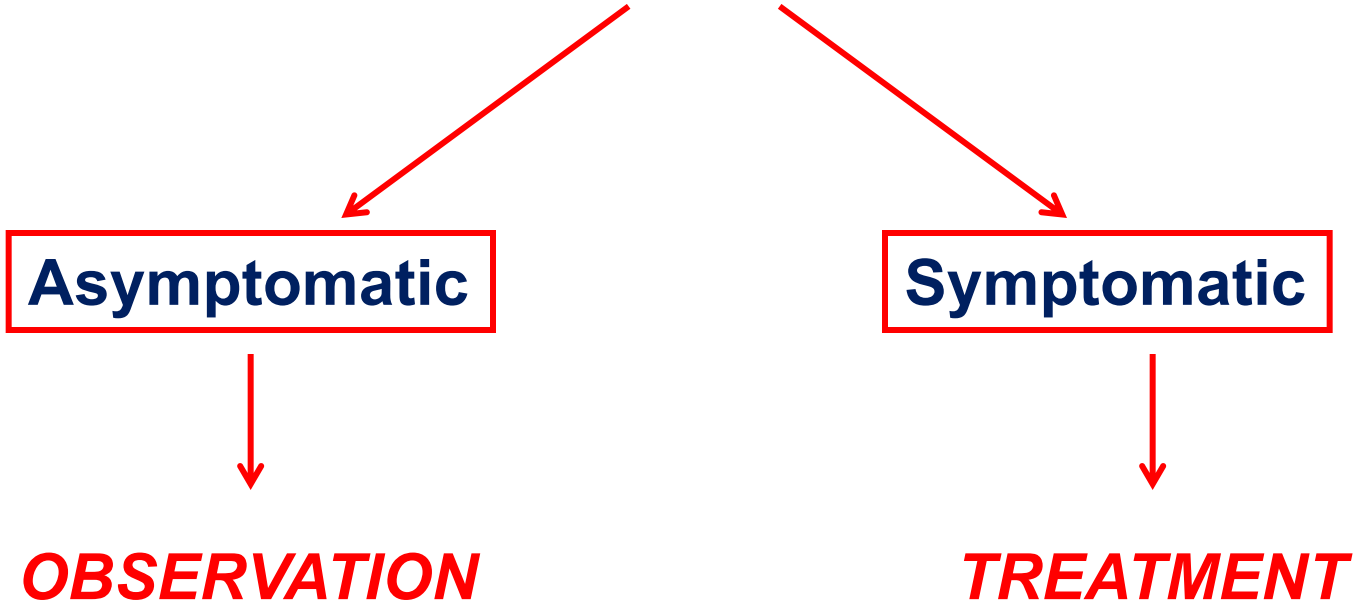
***ASST Grande Ospedale Metropoliano Niguarda***
***Milano***

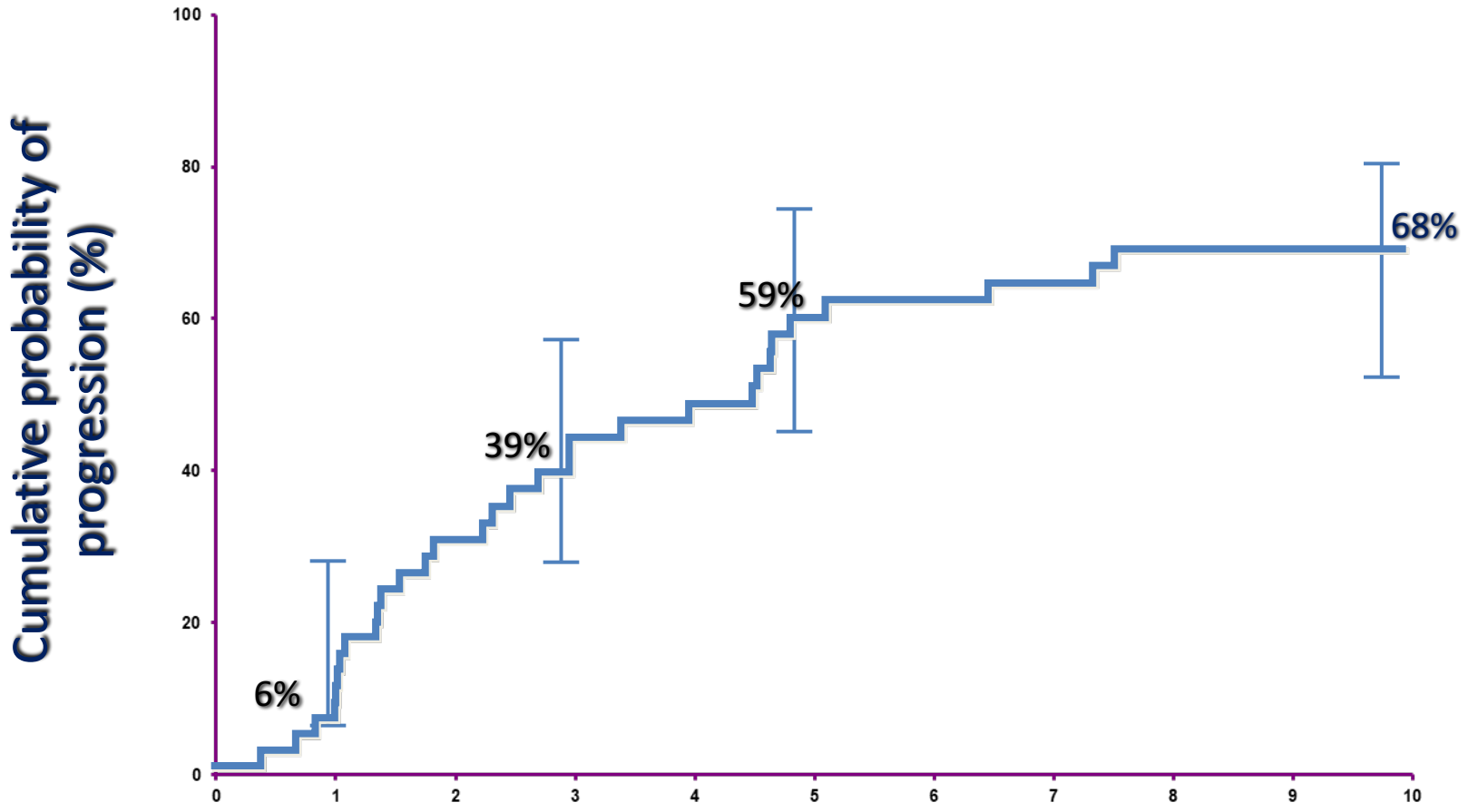
# *Management of WM patient*

- IgM monoclonal gammopathy (any level)
- Bone marrow infiltration by LPL (>10%)
  - -Intertrabecular pattern of bone marrow infiltration
  - -Specific IF: sIgM+, CD19+, CD20+, CD22+, CD79+, FMC7+, CD52+, CD5±, CD10-, CD23-, CD25+, CD27+, CD103-, CD138-




IWWM 2002-IWWM 2014

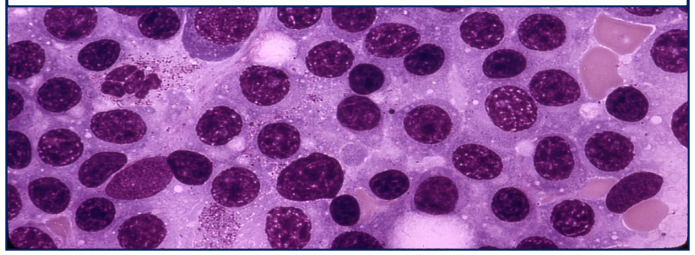
# Progression of Smoldering WM to Symptomatic WM, AL or Lymphoma




Kyle et al, 2012

# Waldenstrom's Macroglobulinemia Clinicopathological Manifestations

**Tissue infiltration by clonal cells**



*Bone Marrow Infiltration*

- Anemia
- Thrombocytopenia
- Neutropenia

*Lymphadenopathy organomegaly*

*Other organs* (GI, pulmonary, CNS)

*B symtoms*

**Morbidities mediated by the IgM monoclonal protein**

*Hyperviscosity*

*Cryoglobulinemia type I*

*Autoantibody activity*

-Cryoglobulinemia type II
-MAG, ganglioside
-cold agglutinins

*Tissue deposition*

-amyloid (light chain type)

-amorphous aggregates
Skin, GI, kidney

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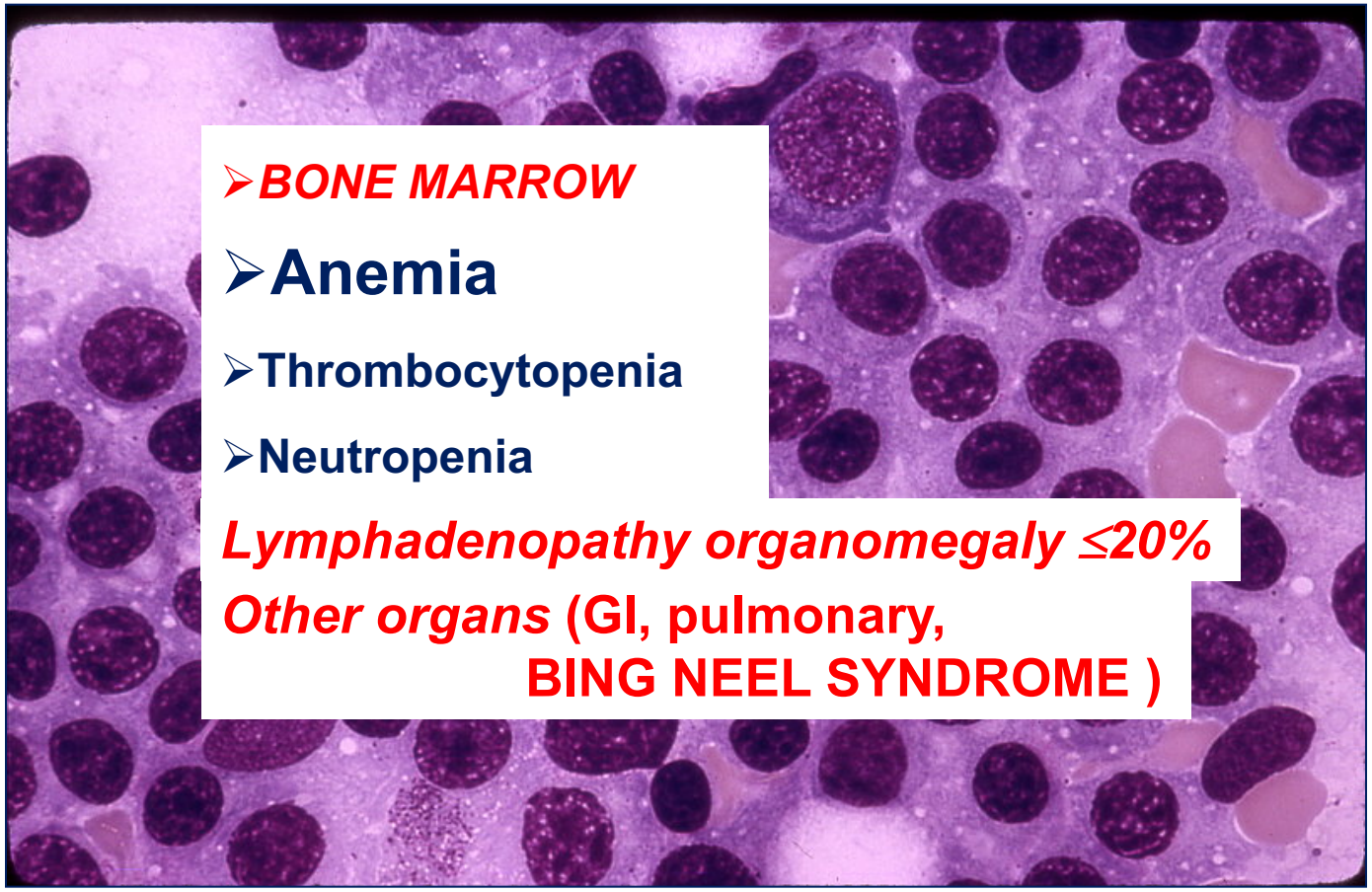

- ***BONE MARROW***
- **Anemia**
- **Thrombocytopenia**
- **Neutropenia**

***Lymphadenopathy organomegaly ≤20%***

***Other organs*** **(GI, pulmonary, BING NEEL SYNDROME )**

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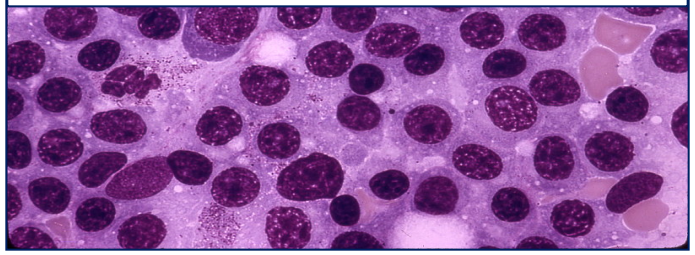

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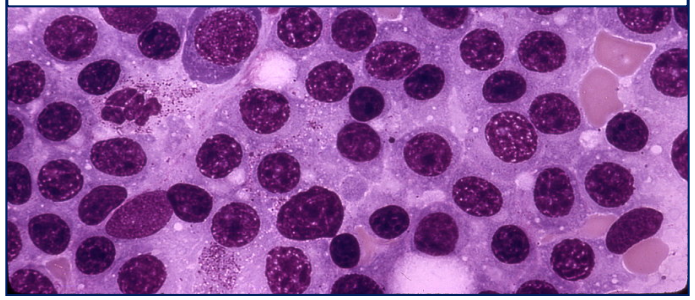

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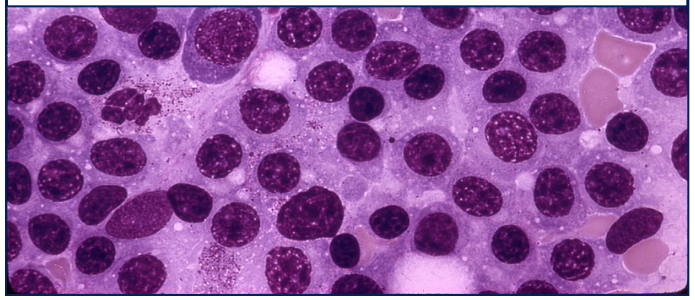
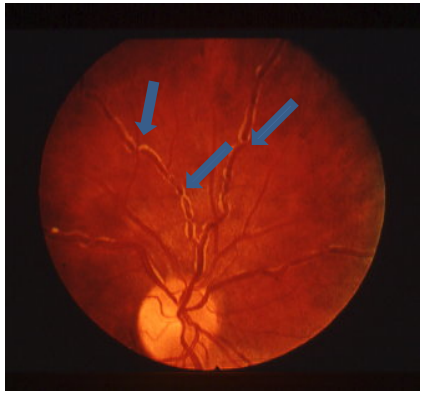


*Hyperviscosity*

# *Hyperviscosity Syndrome (HVS)*

**observed in 15% of patients at diagnosis**

- **IgM level > 3g/dL – higher risk**
- **HVS unlikely unless > 4**
- **Viscosity levels vary between pts but correlate well with signs/sxs in the same patient**
- **Signs:**
  - **skin & mucosal bleeding,**
  - **blurred vision,**
  - **headache, dizziness, vertigo, ataxia,encephalopathy**
  - **or altered consciousness**
- **Funduscopic exam diagnostic: venous engorgement ("sausaging")**
- **Rx: plasmapheresis**



*Stone & Bogen, 2012*

# IMMEDIATE DISEASE CONTROL REQUIRED

## *PLASMAPHERESIS*

- Patients with **symptomatic hyperviscosity**

  *(bleeding, blurred vision, headache, dizziness, ataxia, encefalopathy, altered consciousness)*

- Patients with IgM **≥ 5000 mg/dL prior to Rituximab** or Ofatumumab (to avoid Rituximab-related IgM flare)

- **Patients with autoantibody syndromes that produce neuropathy or other organ dysfunction**

# *Waldenstrom's Macroglobulinemia Clinicopathological Manifestations*

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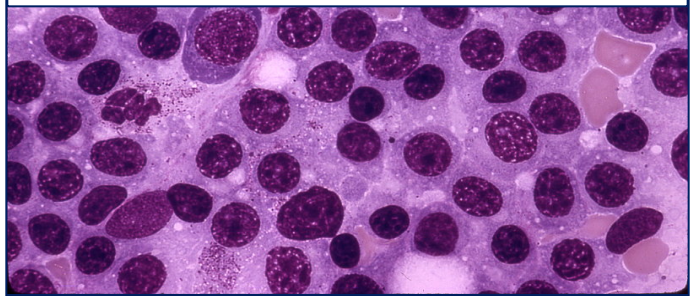

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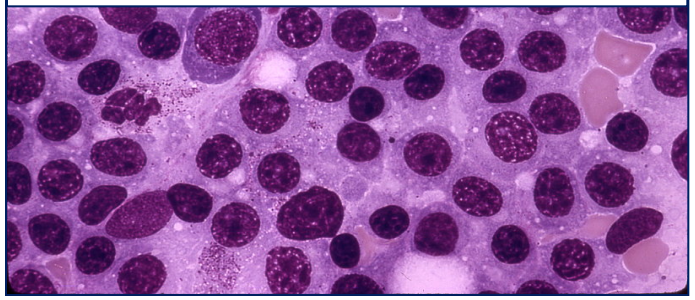
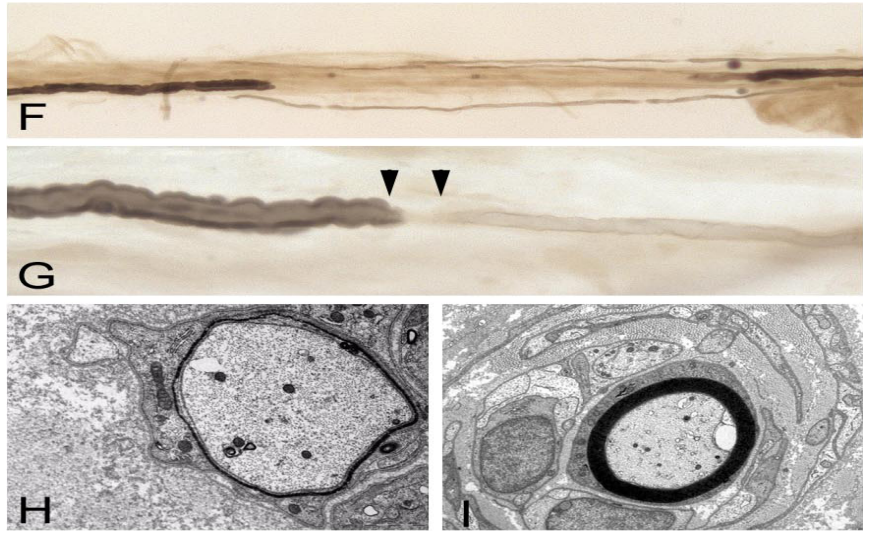


*Hyperviscosity*

*IgM neuropathy*
*~20%*

# Peripheral neuropathy

- **Autoantibodies:**
  - **Anti–myelin-associated glycoprotein (anti- MAG)**
  - **Anti-ganglioside M1**
  - **Antisulfatide**
  - **(absence of autoantibodies does not exclude the diagnosis of IgM- related neuropathy)**




- **Amyloid deposits**
- **Cryoglobulinemia**
- **Neoplastic cells infiltration**

# *Peripheral neuropathy*

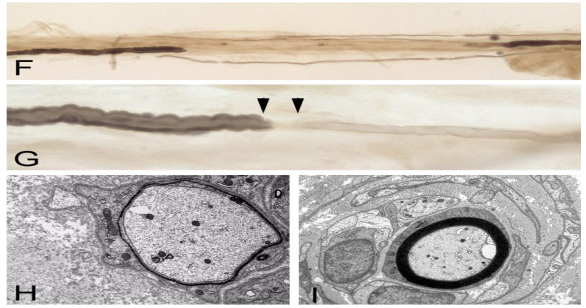
- ✓**Chronic**
- ✓**Progressive**
- ✓**distal**
- ✓**Symmetrical**
- ✓**Sensory (paresthesias, aching discomfort, dysesthesias, or lancinating pains)**

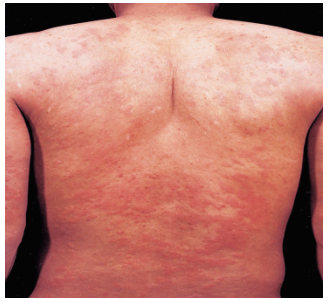
**Less common later in disease course: motor nerves involvement**

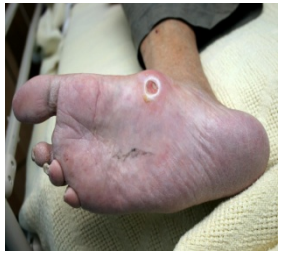
**Leg muscle atrophy in advanced stages.**

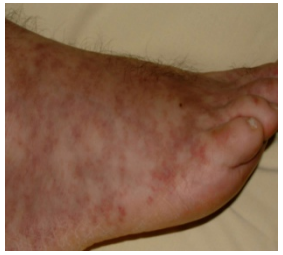
# *Waldenstrom's Macroglobulinemia Clinicopathological Manifestations*

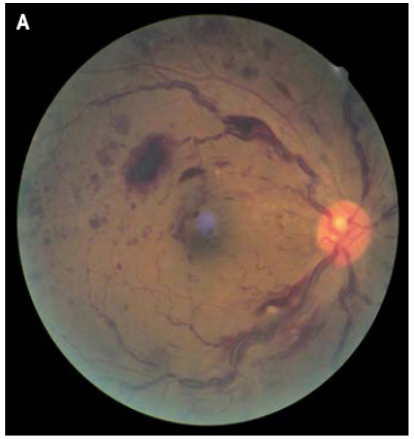
## Morbidities mediated by the IgM monoclonal protein

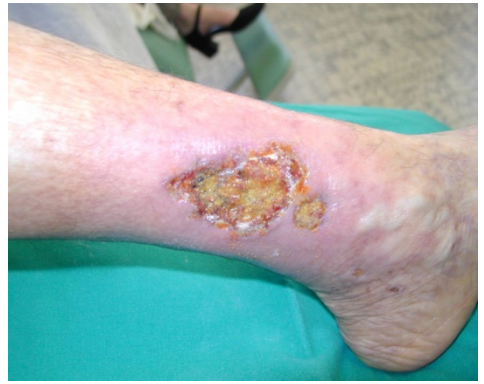




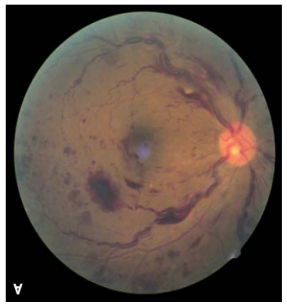


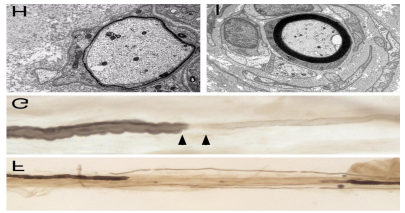


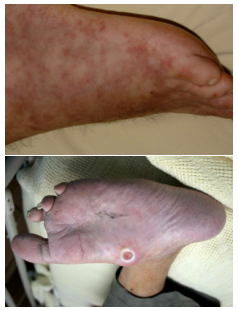



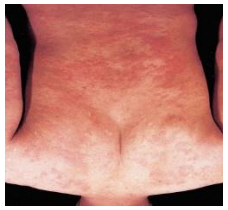
# *Considerations to be weighted in making the choice of a first line treatment*

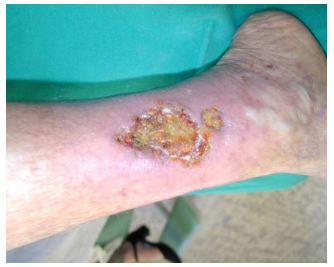
- Age, Comorbididies
- Younger patients: stem cell collection
- Disease characteristic











- Late toxicities

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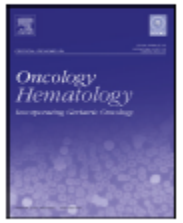


# Response rate to the treatment of Waldenström macroglobulinemia: A meta-analysis of the results of clinical trials

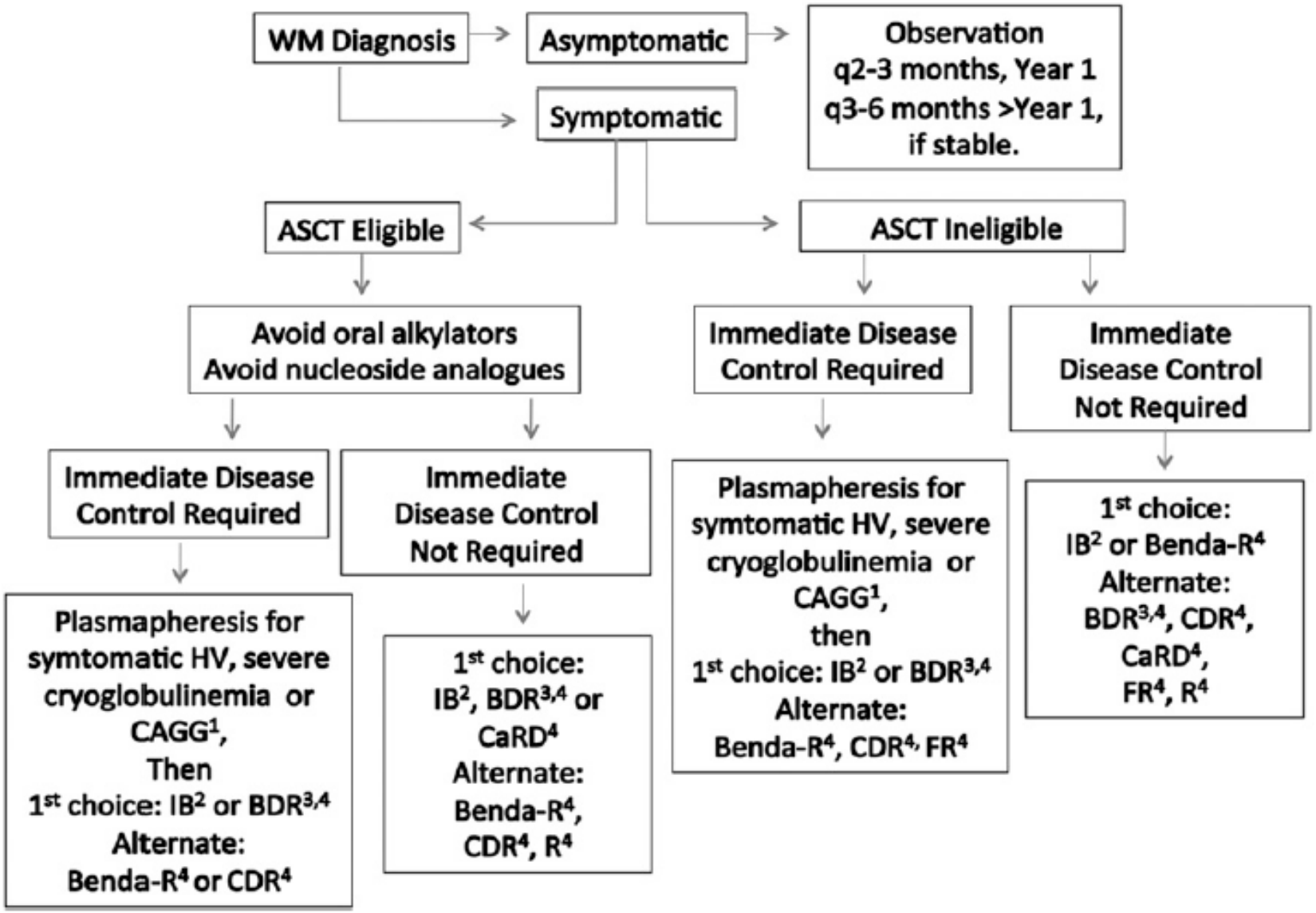
A. Santos-Lozano[a,b,*], A. Morales-Gonzalez[c], F. Sanchis-Gomar[a], C. Cristi-Montero[d,e], C. Fiuza-Luces[a], H. Pareja-Galeano[a,f], J. Martínez-López[g,h], N. Garatachea[a,i,j], A. Lucia[a,f]

**46 studies (corresponding to a total of 1409 patients)**

*IN CONCLUSION PTS WITH WM SHOW A BETTER RR TO COMBINATION THERAPY THAN MONOTHERAPY*

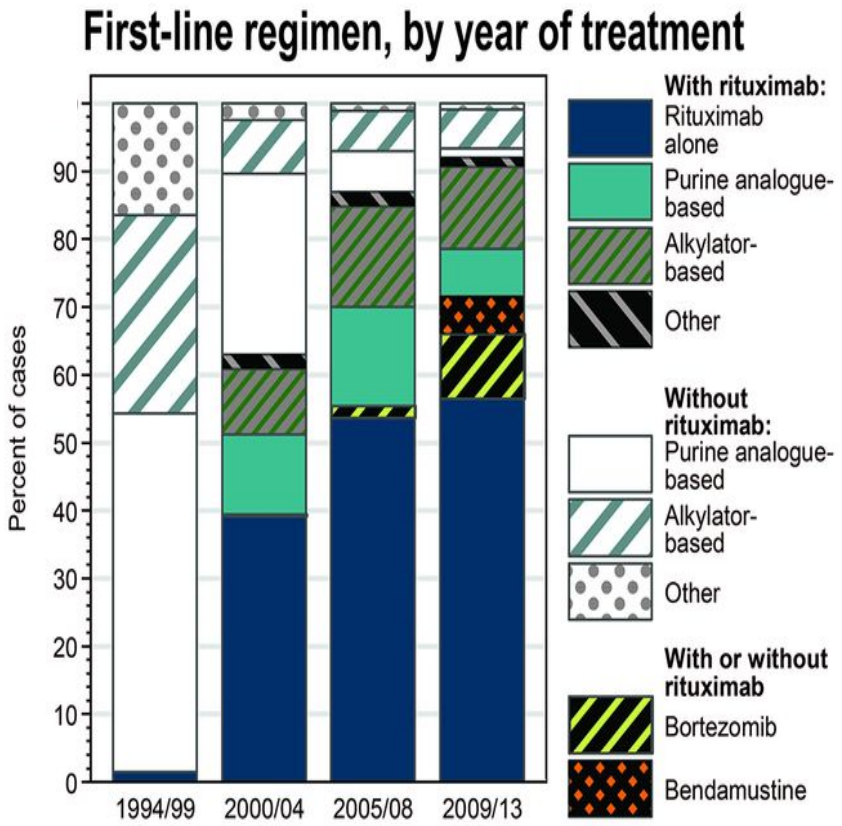
- **effect of the different therapies on VGPR could not be assessed** (3 studies reported VGPR) Tedeschi 2012; Treon.,2014, 2009
- **Impossible to perform a meta-analysis on PFS: heterogeneity in reporting results**
  - ***mean time PFS*** (Zinzaniet 1995; Case 1991)
  - ***median time PFS*** (with range at different follow-up times) Betticheret 1997; Leblond 2013; Treon 2014, 2008, 2009,2005; Agathocleous , 2010; Dimopoulos, 2002, 2003;Fenchel, 1995; Foran , 1999; Thalhammer-Scherreret , 2000; Van Den Neste , 2004
  - ***mean duration of response*** (Leblondet al., 2001; Hellmann et al., 1999)
  - ***median duration of response*** (Leblond et al., 2001; Peinert et al., 2010)
  - ***time to progression*** Dimopoulos , 2005, 2004, 2002; Betticher , 1997;Treon, 2005; Dhodapkar, 2003
  - ***% of PFS patients atdifferent follow-up times*** Ghobrial , 2010; Dimopoulos, 2007. 1994; Tedeschi, 2012; Gertz et, 2009, 2004;Anagnostopoulos, 2006; Delannoy , 1994; Treon et 2005; Rummel , 2013
  - **PFS data not reported** Buske , 2009; Fridrik, 1997; Henselet, 2005; Rabascio, 2010; Delannoy, 1994; Laszlo 2010; Van Den Neste, 2000

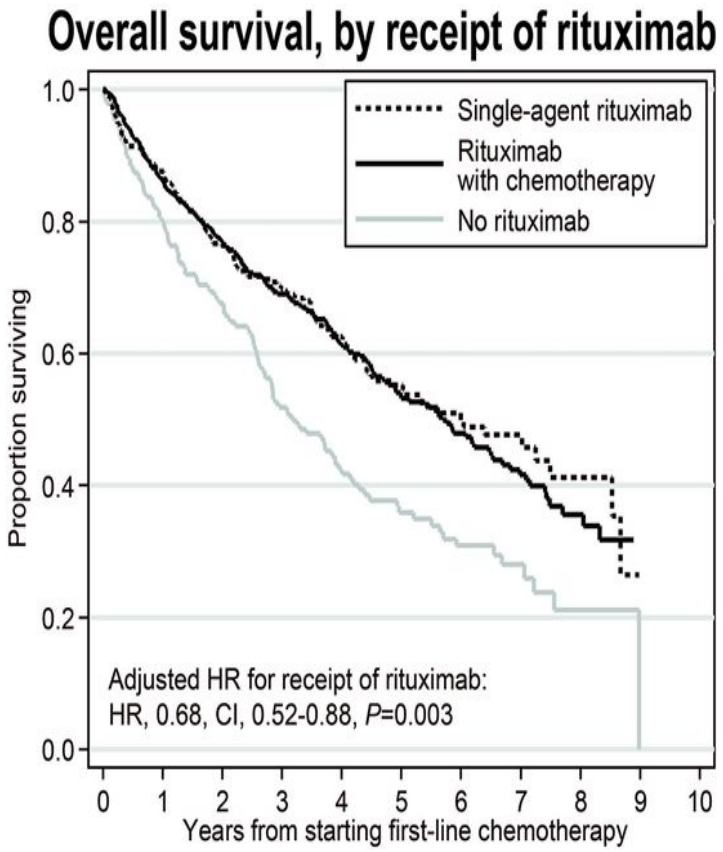
# *Guide to primary therapy for WM : Treon 2015*



# *Standard first line treatment for medically fit pts*

## RITUXIMAB COMBINATIONS



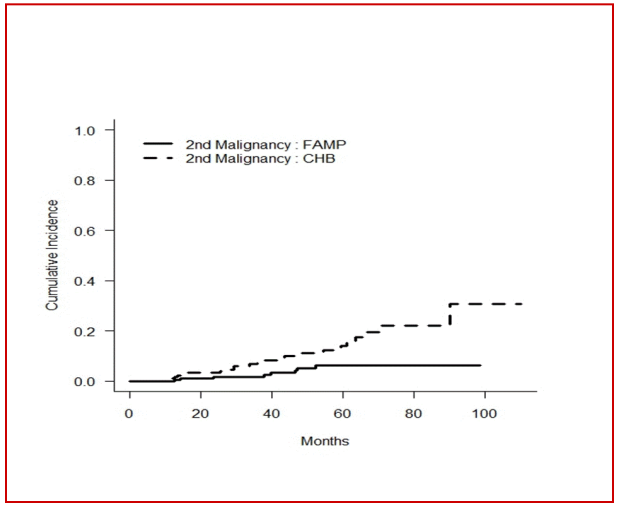
# *First line treatment: what should we avoid*

- AVOID ORAL ALKYLATORS
- AVOID PURINE ANALOGUES
- AVOID VINCRISTINE (anthraciclynes not necessary)

# First line treatment: avoid oral alkylators

## *PHASE III randomized trial: Fludarabine vs Chlorambucil*

- **Fludarabine by oral route**:
  -safe in WM patients,
  -more effective than CHB: ORR 47.8% *vs* 38%
  -significantly better duration of response and OS
- **For the first time a front-line treatment shows a significant impact on overall survival in WM**
- **In the CHB arm, @ 6 yrs statistically** higher number of second malignancies (20.6% vs 3.7%).




Leblond et al, JCO 2013

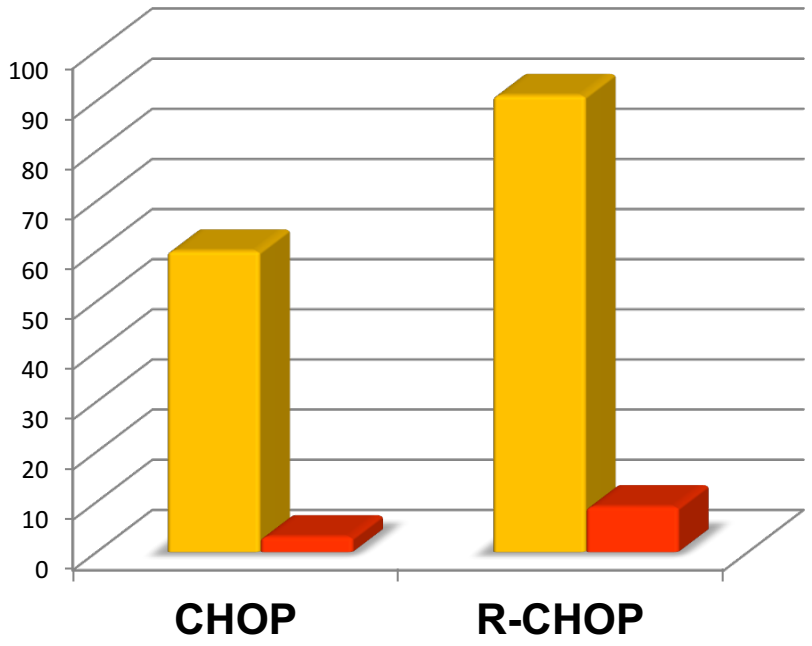
# First line treatment: avoid purine analogues

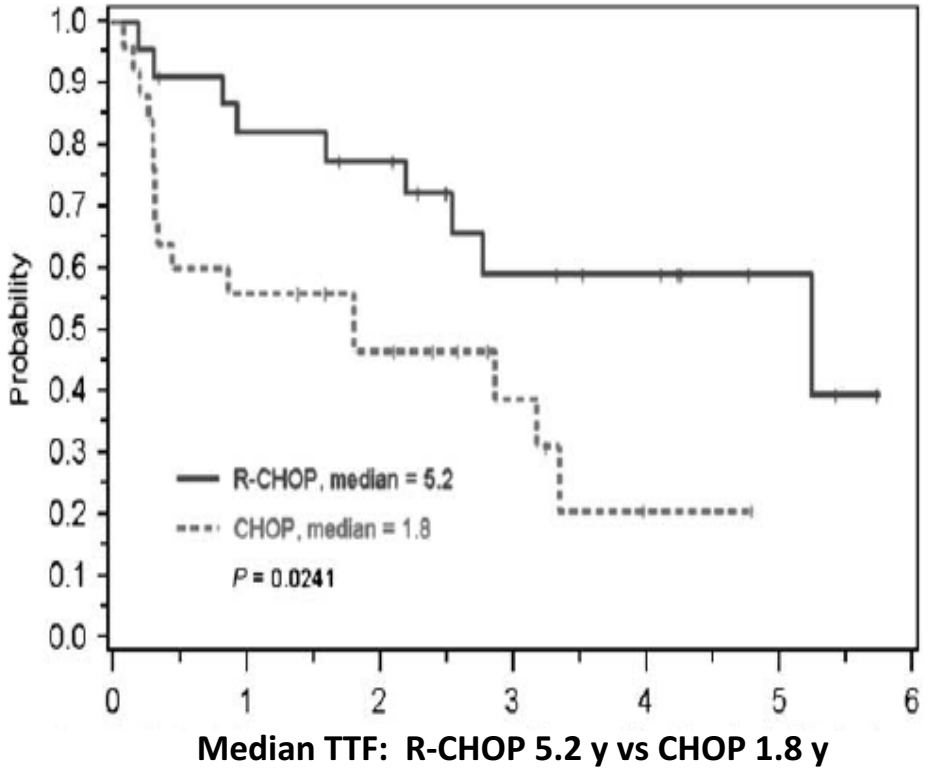
| Combination | N° pts | naive | ORR | Major | CR | TTP | Ref |
|---|---|---|---|---|---|---|---|
| R Fludarabine | 43 | 63% | 95% | 86% | 4% | 51 m | Treon 2008 |
| R Flu Cy | 43 | 65% | 79% | 74% | 11% | 50 m | Tedeschi A 2012 |

- ✓*Immunosuppression*
- ✓*Myelosuppression*
- ✓*Impact on stem cell collection*
- ✓*Potential secondary malignancy risks*

# First line treatment: avoid VCR, anthracycline

## Rituximab with CHOP in Lymphoplasmocytic lymphoma




**Median TTF: R-CHOP 5.2 y vs CHOP 1.8 y**

- ✓ *neuropathy from vincristine*
- ✓ *febrile neutropenia*
- ✓ *hospitalization*

**Buske et al Leukemia 2009**

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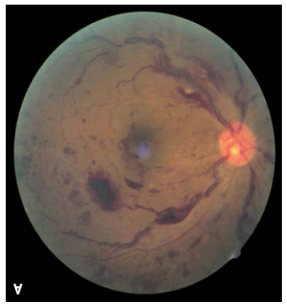
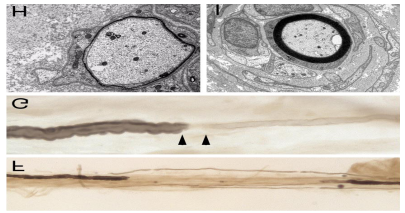
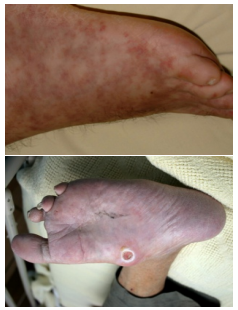
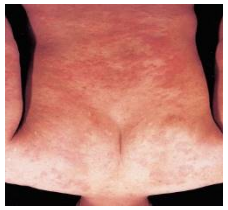
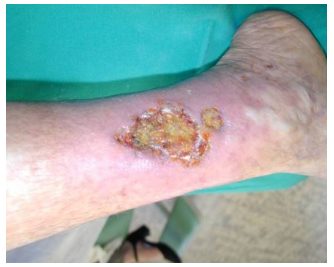










- Late toxicities

# *First line treatment choice*

- **Age, Comorbididies**
- **Younger patients: stem cell collection**
- **Disease characteristic**
- **Late toxicities**

**DRC: Dexamethasone Cyclophosphamide Rituximab**

**BR: Bendamustine Rituximab**

*Ibrutinib: no reimbursement*

*Bortezomib: only R/R*

VOLUME 25 · NUMBER 22 · AUGUST 1 2007

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

# Primary Treatment of Waldenström Macroglobulinemia With Dexamethasone, Rituximab, and Cyclophosphamide

*Meletios Athanasios Dimopoulos, Athanasios Anagnostopoulos, Marie-Christine Kyrtsonis, Konstantinos Zervas, Constantinos Tsatalas, Garyfallia Kokkinis, Panagiotis Repoussis, Argyris Symeonidis, Souzana Delimpasi, Eirini Katodritou, Elina Vervessou, Evriliki Michali, Anastasia Pouli, Dimitra Gika, Amalia Vassou, Evangelos Terpos, Nikolaos Anagnostopoulos, Theophanis Economopoulos, and Gerasimos Pangalis*

| Drugs | dose | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|---|
| Dexamethasone iv | 20 mg | ♦ | | | | |
| Rituximab iv | 375 mg sqm | ♦ | | | | |
| Cyclophosphamide PO | 200 mg sqm | ♦ | ♦ | ♦ | ♦ | ♦ |

## 72 pts Toxicity

**89% of pts completed the expected 6 courses**

| Percentage of pts affected | | | | | |
|---|---|---|---|---|---|
| *Toxicity grade* | *0* | *1* | *2* | *3* | *4* |
| Neutropenia | 66 | 15 | 10 | 7 | 2 |

***20 infections:*** **1 infection related death**

**9 requiring hospitalization**

**10 treated on an outpatient basis**

Dimopoulous et al 2007; Kastritis et al Blood 2015

# First line treatment: DRC

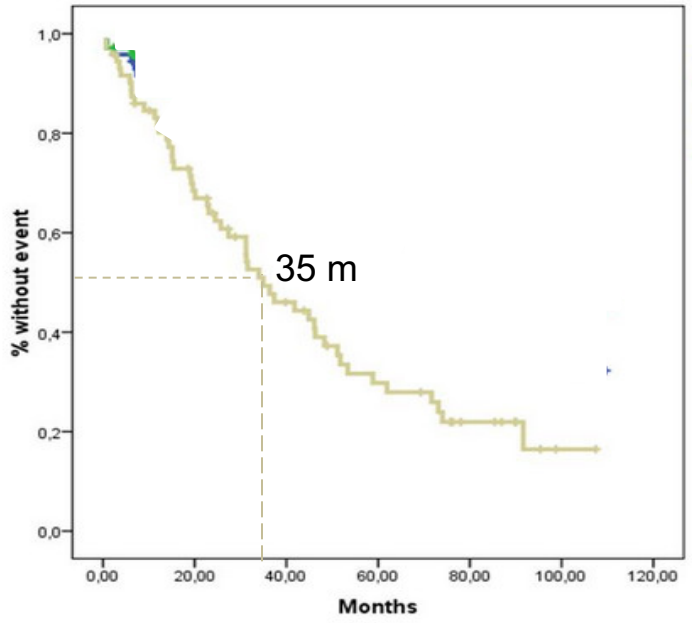
**Response**

- **CR 7 %**
- **PR 67 %**
- **MR 9 %**

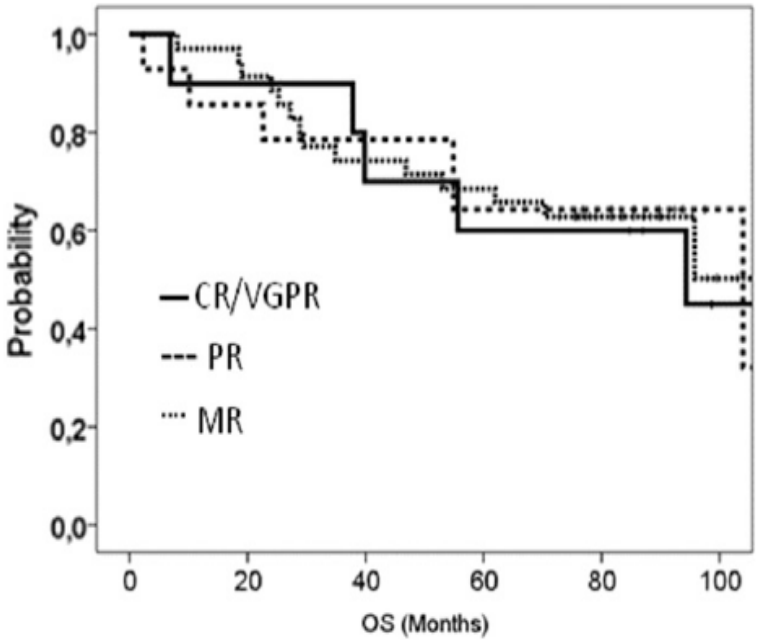
**Time to NextTreatment**

**51 m**

**Progression Free Survival**




**Overall Survival**




Dimpopoulous et al 2007; Kastritis et al Blood 2015

# First line treatment: DRC

Median time to 50% reduction of serum monoclonal protein
4.1 m (range, 0.7 to 14 months)

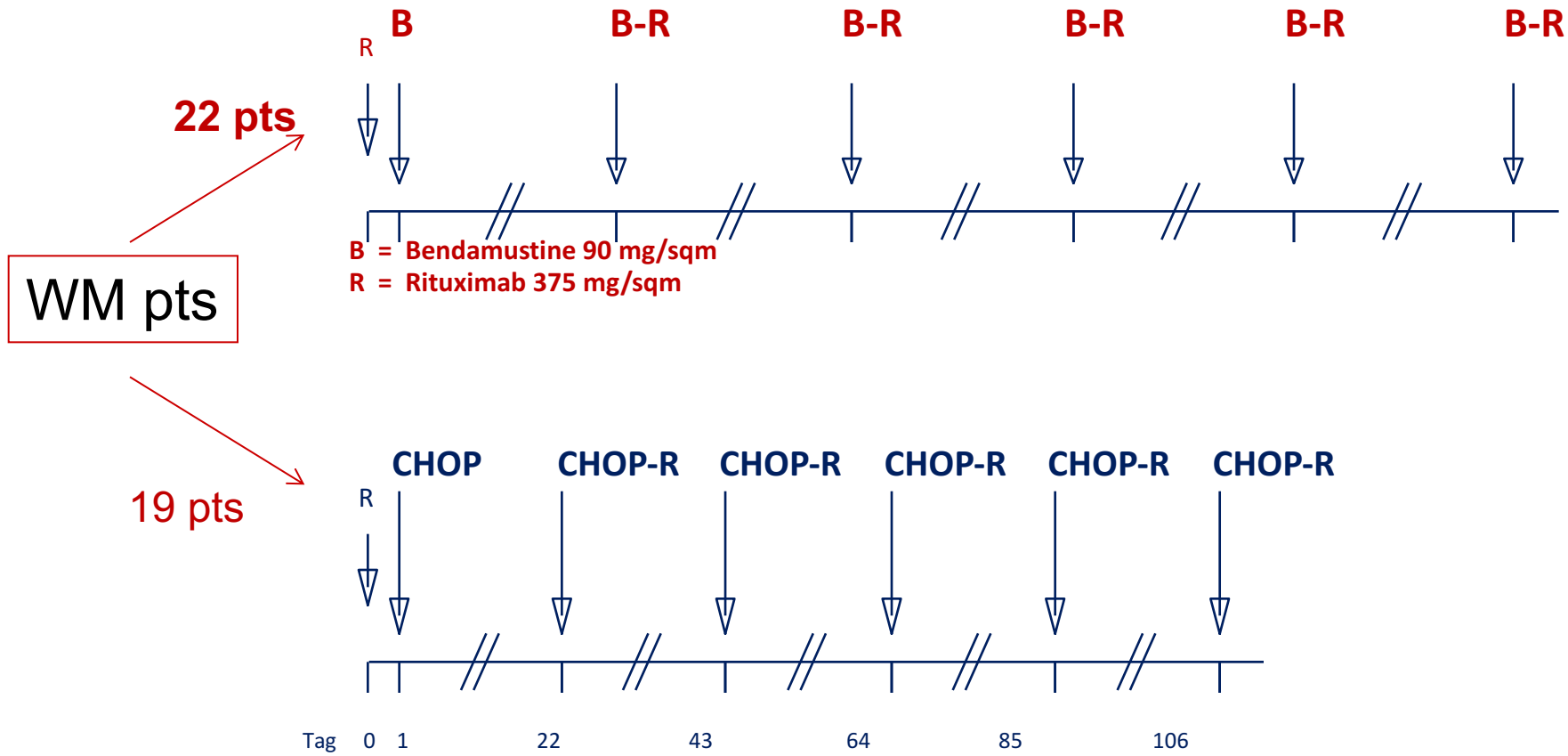
To be considered:

- Immediate disease control not required
- elderly
- Cytopenia
- Autoantibodies (neuropathy)

# Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial

Lancet 2013; 381: 1203–10

Mathias J Rummel, Norbert Niederle, Georg Maschmeyer, G Andre Banat, Ulrich von Grünhagen, Christoph Losem, Dorothea Kofahl-Krause, Gerhard Heil, Manfred Welslau, Christina Balser, Ulrich Kaiser, Eckhart Weidmann, Heinz Dürk, Harald Ballo, Martina Stauch, Fritz Roller, Juergen Barth, Dieter Hoelzer, Axel Hinke, Wolfram Brugger, on behalf of the Study group indolent Lymphomas (StiL)




| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| CHOP | | day | 1 | 22 | 43 | 64 | 85 | 106 |
| Rituximab | 375 mg/m² | day | 0 | 22 | 43 | 64 | 85 | 106 |

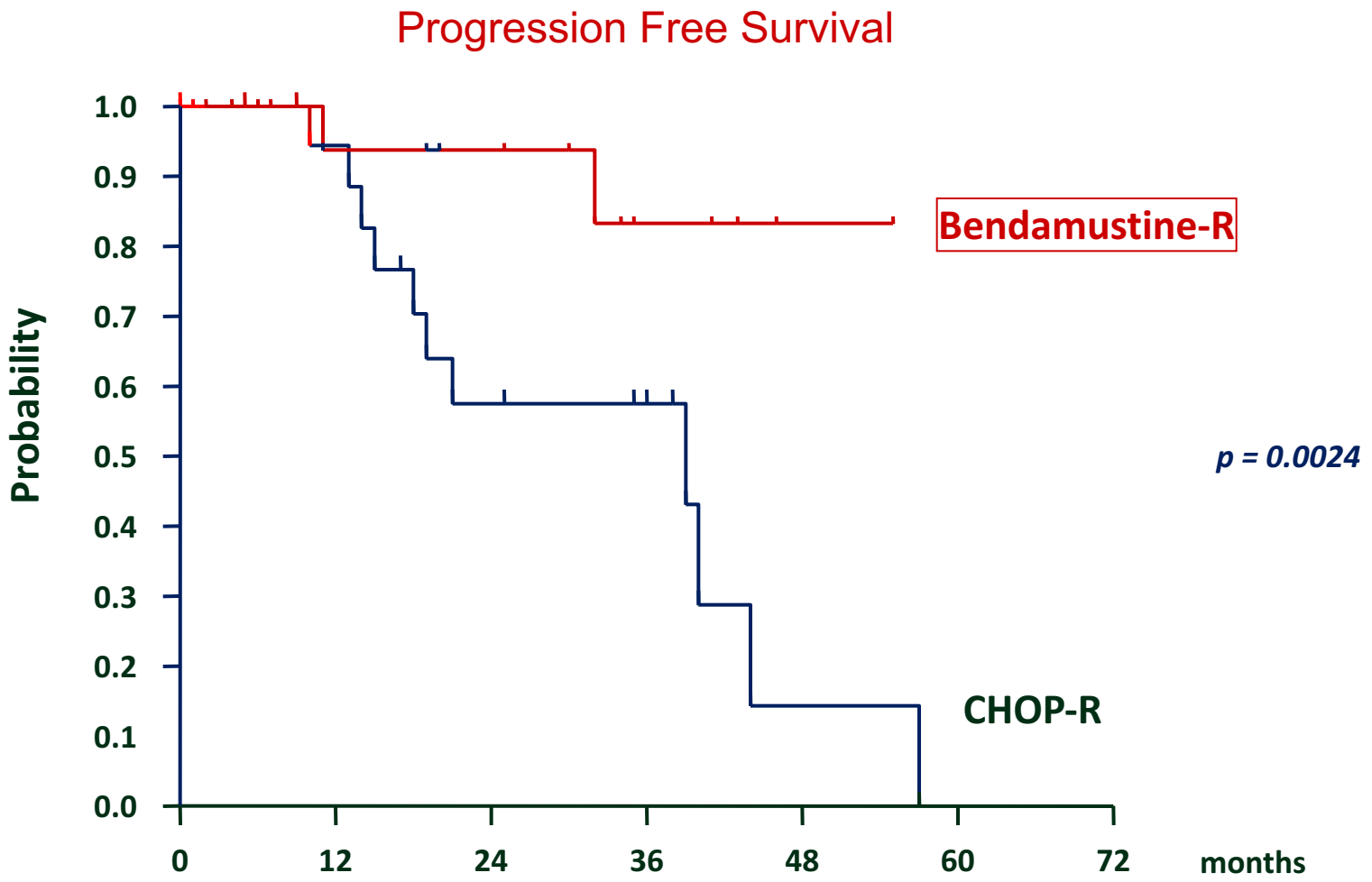
Rummel et al 2013

# First line treatment: Bendamustine Rituximab

| | Bendamustine Rituximab | CHOP Rituximab |
|---|---|---|
| Response rate | 96% | 94% |
| Disease Relapse | 9% | 41% |
| Deaths | 4% | 6% |
| Leucocytopenia 3/4 | 12% | 38% |
| G-CSF | 4% | 20% |
| Infections | 27% | 41% |
| Neuropathy (any grade) | 2% | 9% |
| Waldenstrom Neuropathy (any grade) | 1% | 3% |

Rummel et al IWWM 2014

# First line treatment: Bendamustine Rituximab




Rummel et al IWWM 2014

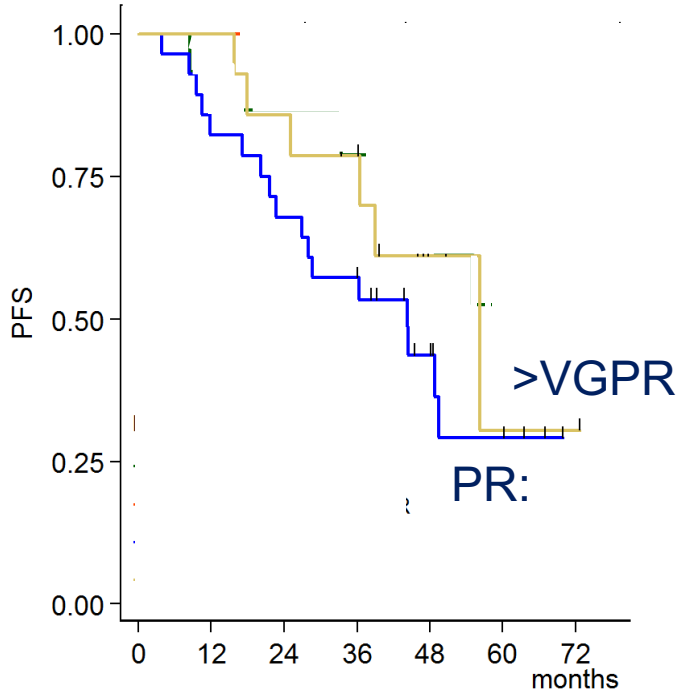
# Salvage treatment Bendamustine Rituximab

71pts

*45 pts (63%):*
Bendamustine 90 mg/sqm d 1,2; Rituximab 375 mg/sqm d 1

*26 pts (37%)*
Bendamustine 70 (50) mg/sqm d 1,2 Rituximab 375 mg/sqm d 1

| | |
|---|---|
| Overall Response Rate: | 81% |
| CR+VGPR: | 23% |
| PR: | 52% |
| mR: | 6% |




Tedeschi et al 2015

# Salvage treatment Bendamustine Rituximab

| | N° (%) on 71 pts | N° (%) on 361 courses |
|---|---|---|
| Neutropenia G 3/4* | 25 (36) | 47 (13) |
| Anemia G 3/4 | 6 (9) | 11 (3) |
| PLTpenia G 3/4 | 6 (9) | 11 (3) |
| Dose reduction | 10 (15) | 14 (4) |
| Treatment delay | 28 (39) | 36 (10) |

| | |
|---|---|
| FUO: | 14 episodes in 11 pts (15%) |
| INFECTIONS: | 14 in 10 pts (14%) |
| *Major* | *5 (4 pneumonia; 1 fatal sepsis)* |
| *Minor* | *9 ( 4 HZ, 4 upper respiratory tract, 1 oral candidiasis)* |

Tedeschi et al 2015

# First line treatment Bendamustine Rituximab

Treatment  well tolerated even in elderly patients

To consider:

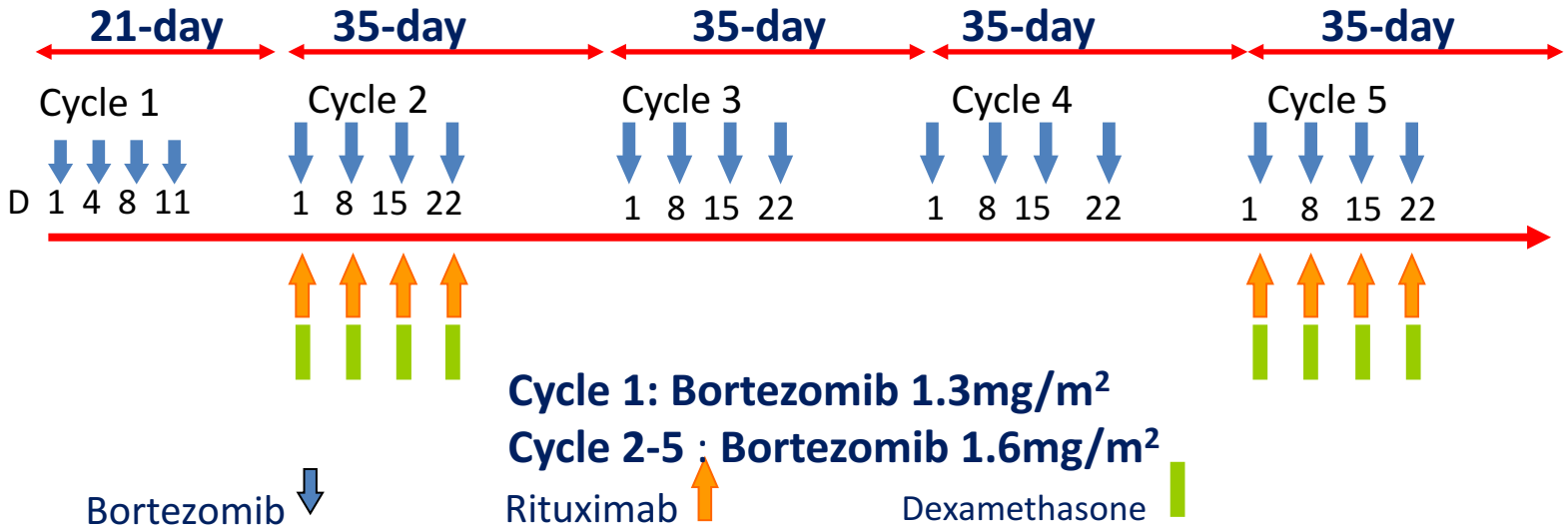
-Immediate disease control required

- Bulky disease

BLOOD, 7 NOVEMBER 2013 • VOLUME 122, NUMBER 19

# Primary therapy of Waldenström macroglobulinemia (WM) with weekly bortezomib, low-dose dexamethasone, and rituximab (BDR): long-term results of a phase 2 study of the European Myeloma Network (EMN)

Meletios A. Dimopoulos,[1] Ramón García-Sanz,[2] Maria Gavriatopoulou,[1] Pierre Morel,[3] Marie-Christine Kyrtsonis,[4] Eurydiki Michalis,[5] Zafiris Kartasis,[6] Xavier Leleu,[7] Giovanni Palladini,[8] Alessandra Tedeschi,[9] Dimitra Gika,[1] Giampaolo Merlini,[8] Efstathios Kastritis,[1] and Pieter Sonneveld[10]



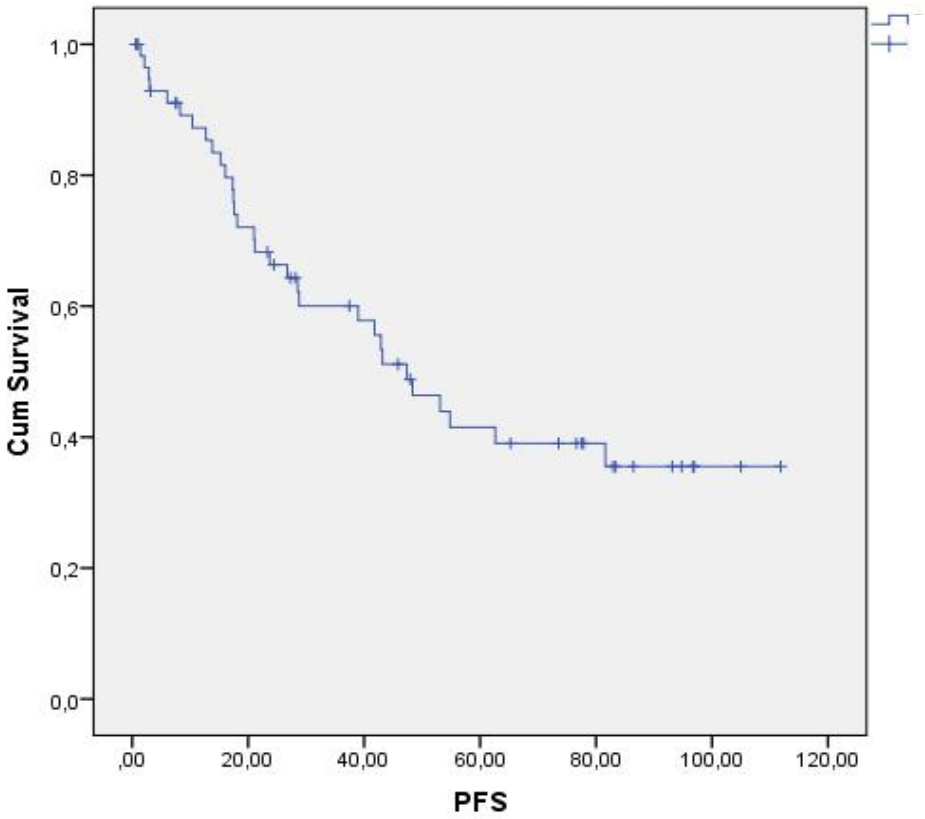

*Dimopoulous 2013 and in press 2016*

# Bortezomib Rituximab Dexamethasone first line treatment

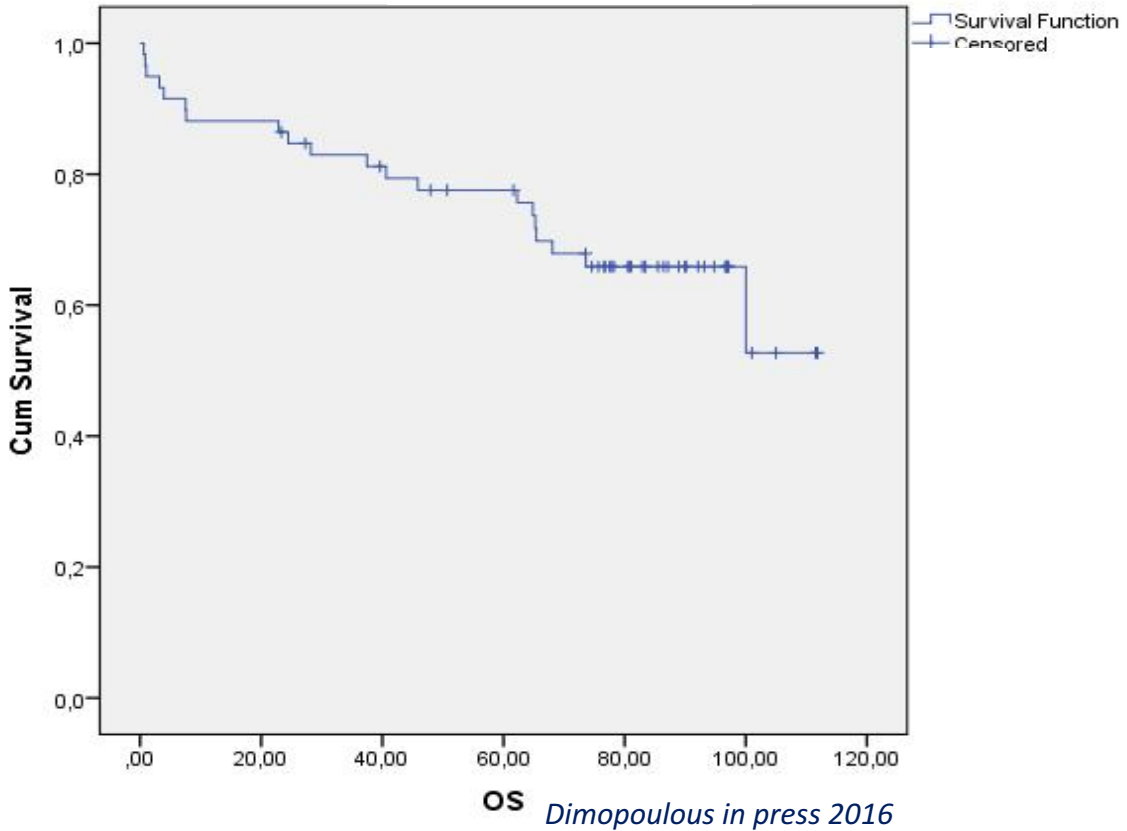
**ORR: 85 % →** **CR: 3%**
**VGPR: 7%**
**PR: 58%**
**mR: 17%**

**Median follow up: 86 months**

**Progression Free Survival**




**Overall Survival**




*Dimopoulous in press 2016*

# Bortezomib Rituximab Dexamethasone first line treatment

- High ORR: 85-96%
- Follow-up :

  Dimopoulous et al 2016 weekly schedule 5 courses: median PFS 42 m

  Treon et al 2015 d1,4,8,11;n8 courses: TTP 5.5 y, Estimated 5-y PFS: 57%
- Low rate of haematological toxicity
- Rapid IgM reduction: median time to response 1.4 m
- Major concern:

  Neurotoxicity need of dose reductions/discontinuation

  Weekly bortezomib: associated with less neuropathy

*Treon et al 2009,2015*
*Ghobrial et al 2010*
*Dimopoulous 2013, 2016*

# Salvage treatment in WM

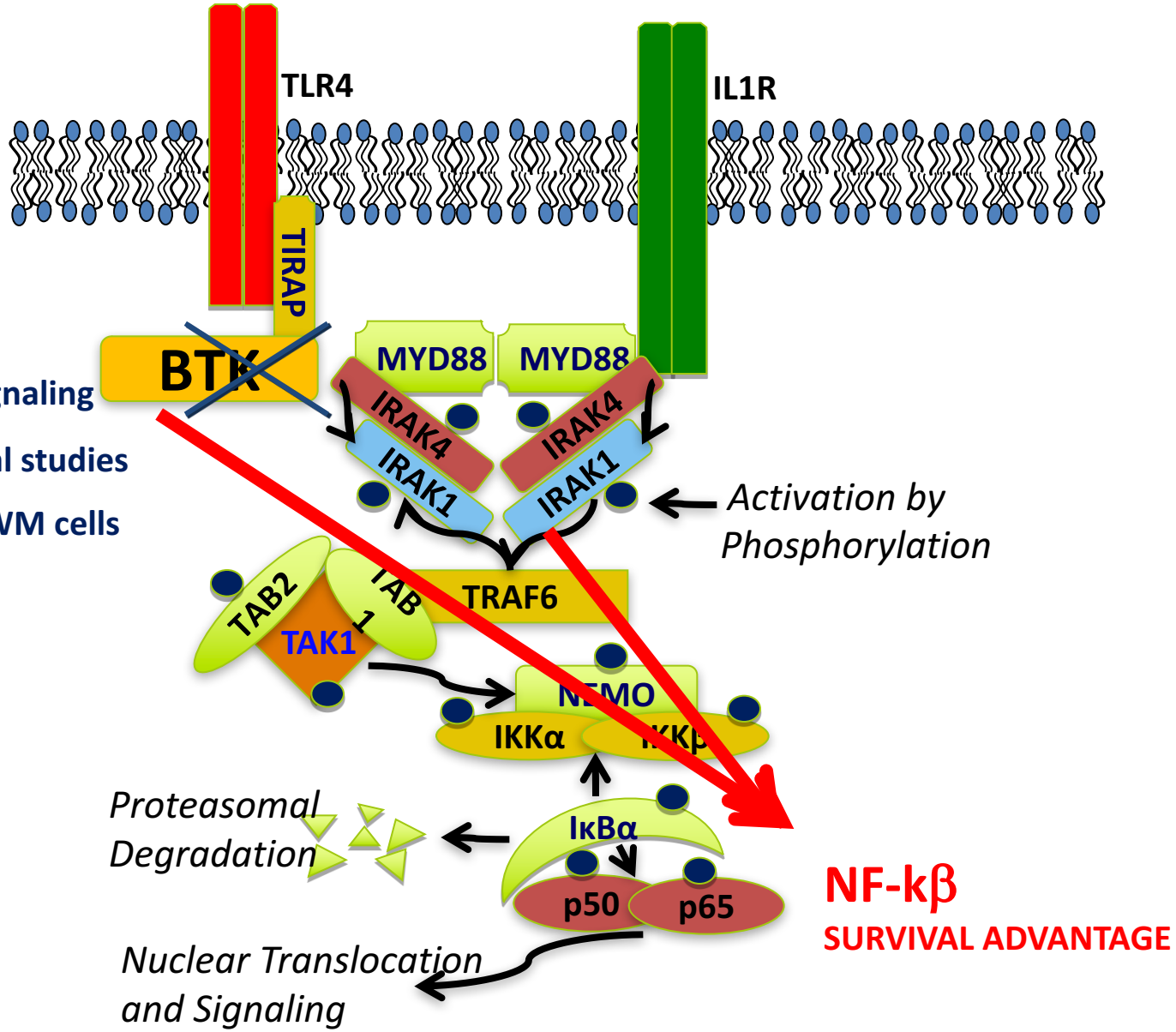
| | F-R<br>*Treon 2009* | *2CdA-R*<br>*Laszlo 2010* | *FCR*<br>*Tedeschi 2015* | B-R<br>*Tedeschi 2015* | B-R<br>*Treon 2011* | *Bortezomib-R*<br>*Ghobrial 2010* |
|---|---|---|---|---|---|---|
| N° pts | 16 | 13 | 37 | 71 | 24 | 37 |
| Median previous Tx | 1 | 1 | 1 | 1 | 2 (1-9) | 2 (1-5) |
| ORR | 93.8 | 81% | 81% | 80% | 79% | 81% |
| Major R | 81.3% | - | 80% | 74% | 79% | 52% |
| Tx discontinuation for toxicity | *21%*<br>1st line or > | 17%<br>1st line or > 4 courses | 29% | 14% | 30% | 12% |
| Median Follow-up | 40.1 m | NE in R/R | 51 m | 19 m | 7.5 m | 14 m |
| TTP median | 38.4 m | - | NR | NR | 13.2 m | 16.4 m |

# Ibrutinib in WM

**IBRUTINIB**

**Blocks IkBa and NFKB p65 signaling**

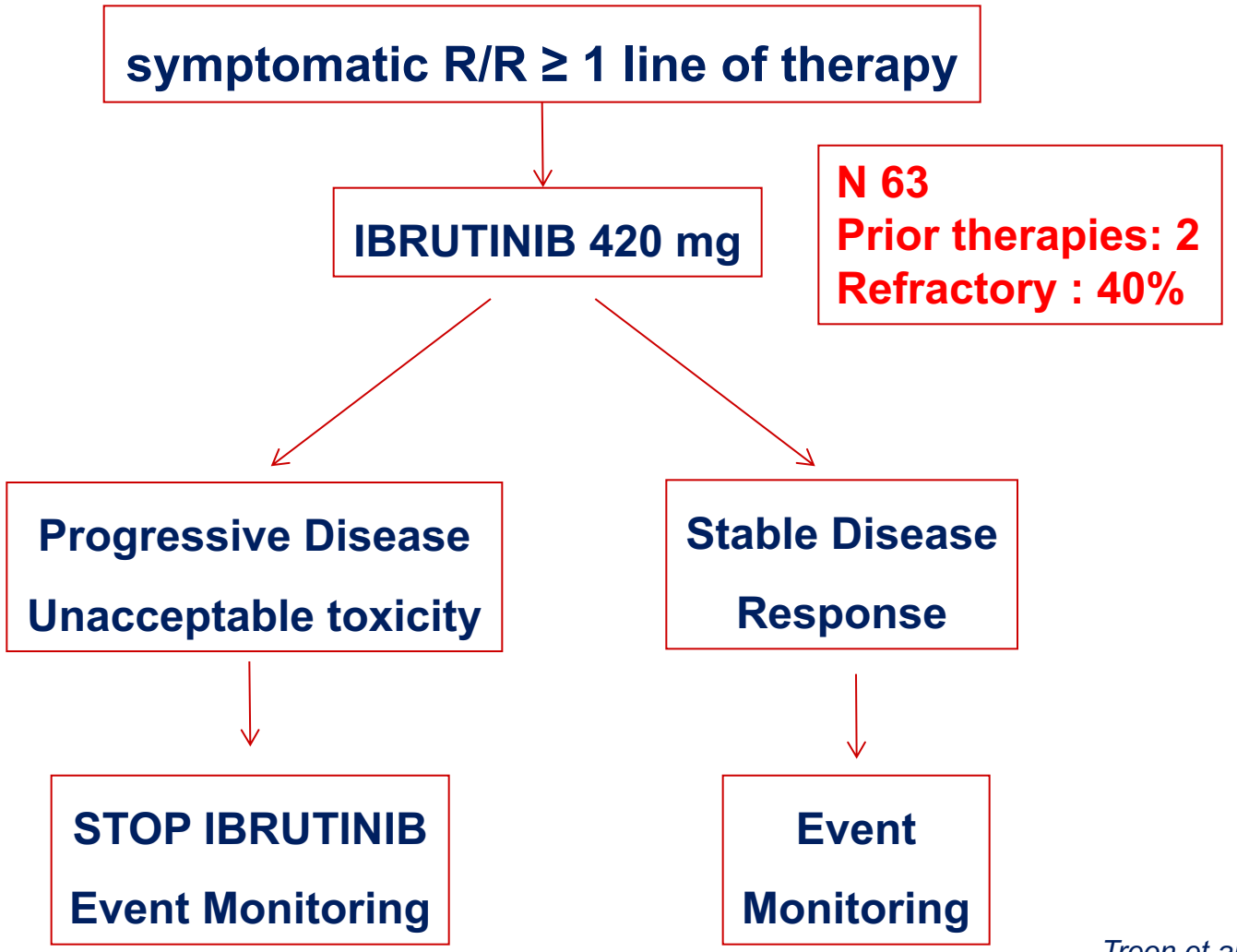
**Induce apoptosis In preclinical studies of MYD88 L265P expressing WM cells**



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# Ibrutinib in Previously Treated Waldenström's Macroglobulinemia

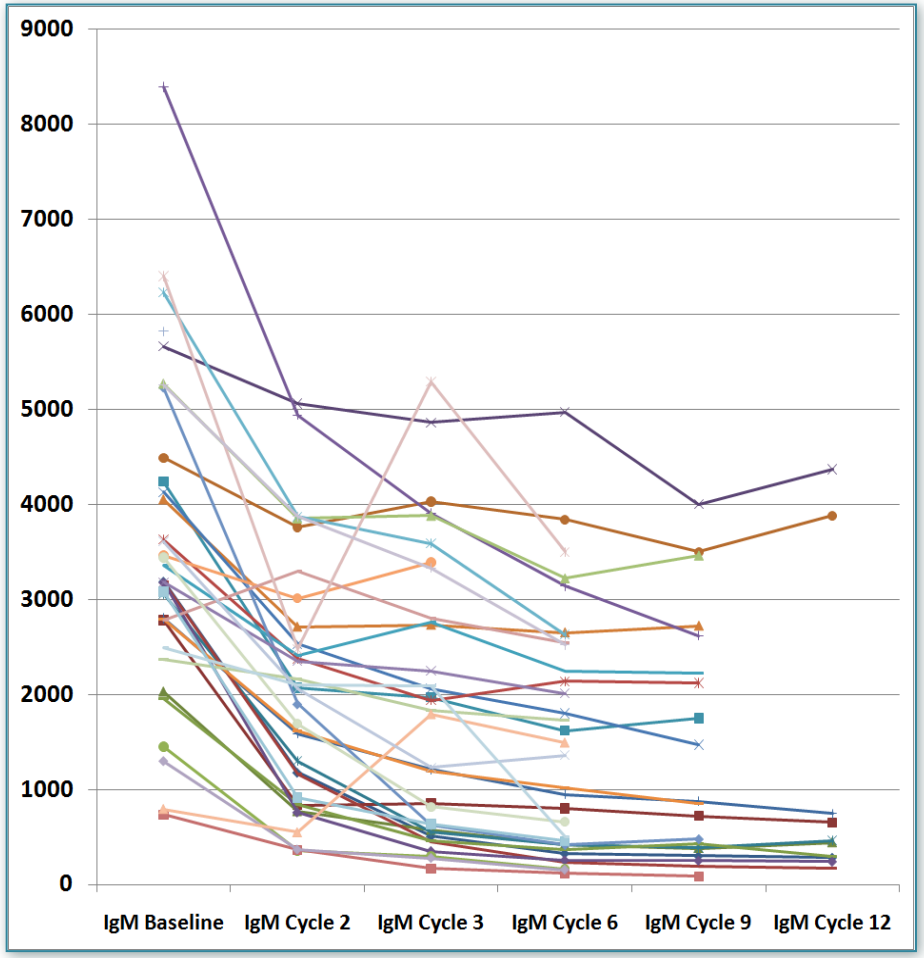



*Treon et al NEJM 2015*

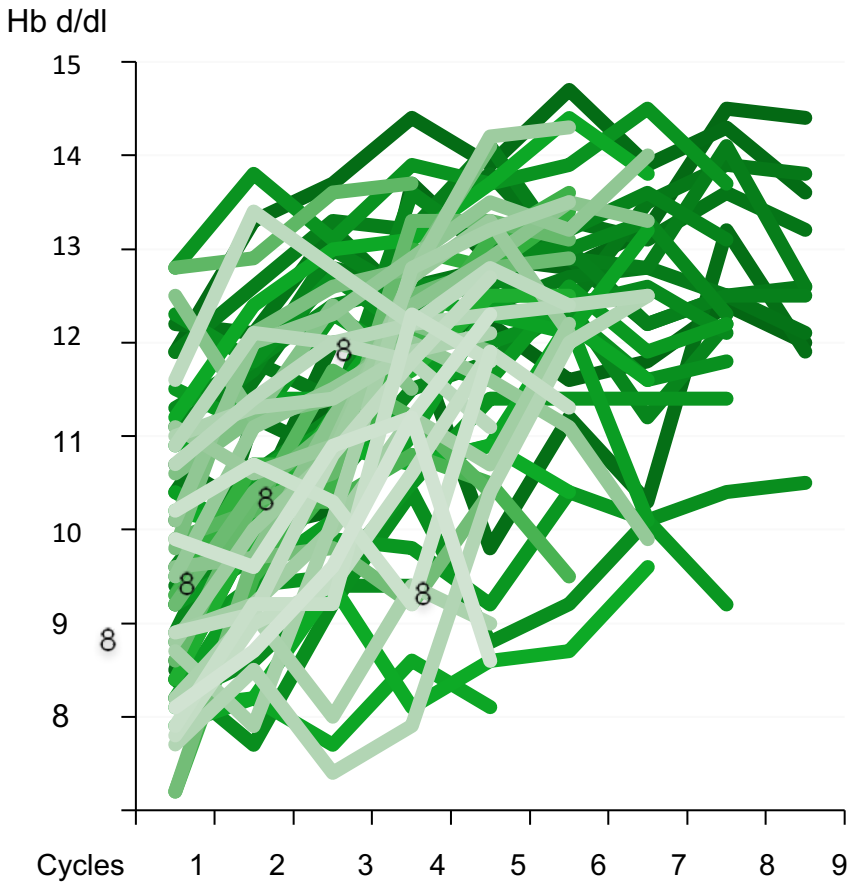
# Ibrutinibin WM: IgM levels and Hb

*Serial Serum IgM Levels Following Ibrutinib*

Median time to Response = 4 weeks

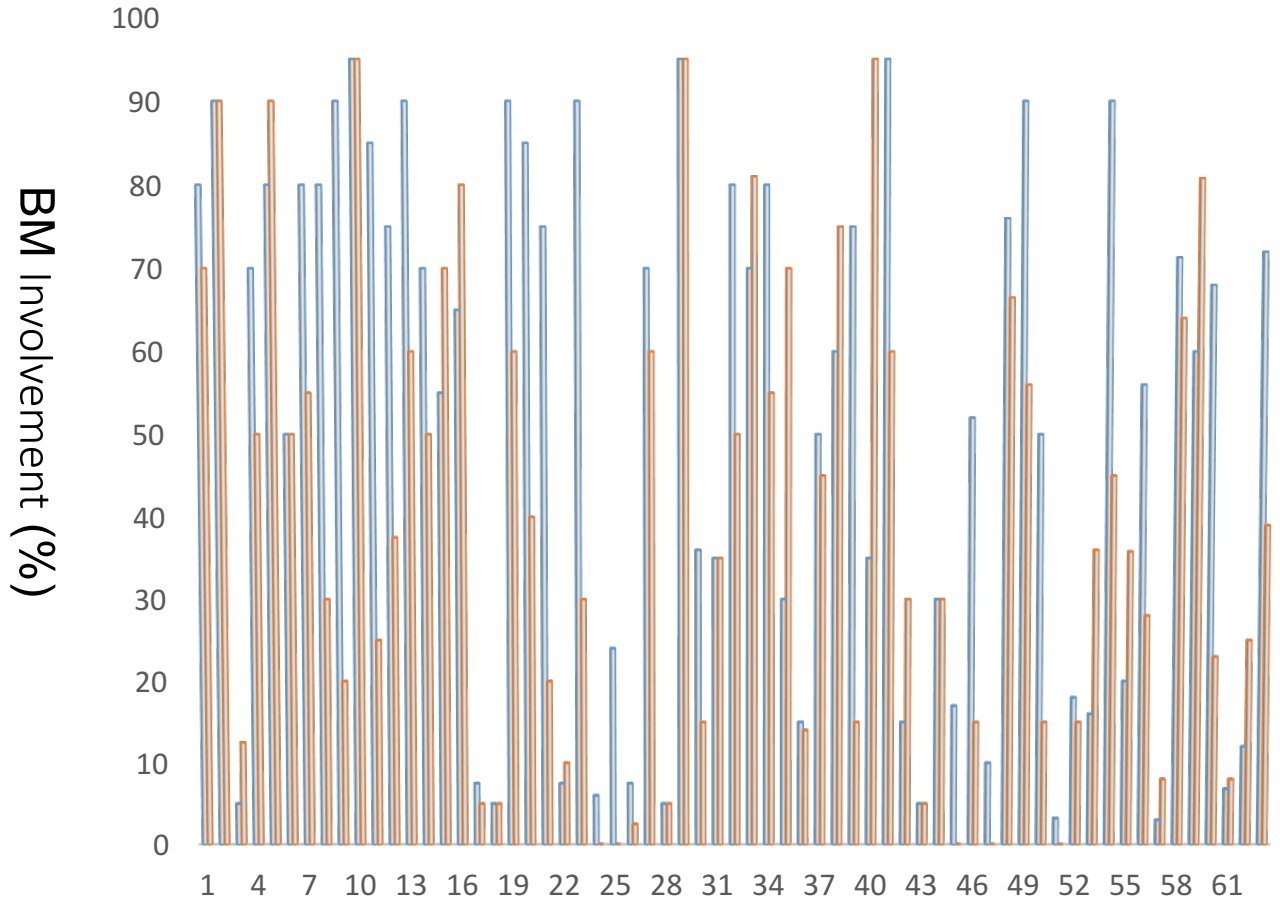



*Hemoglobin Response*



# Ibrutinibin WM: IgM levels and Hb

At Best Response 60% to 25%; p< 0.01



# Ibrutinibin WM: Response

**Response after a median duration of: 19.1 (range 0.5-29.7) months**

| Response | N° pts |
|---|---|
| CR | 0 |
| VGPR | 10 |
| PR | 36 |
| mR | 11 |

**MRR 73%**

**ORR 90.5%**

**Median time to at least a:**

**- mR 4 weeks**

**- PR 8 weeks**

***EXTRAMEDULLARY DISEASESE***

**68% decreased or resolved adenopathy**

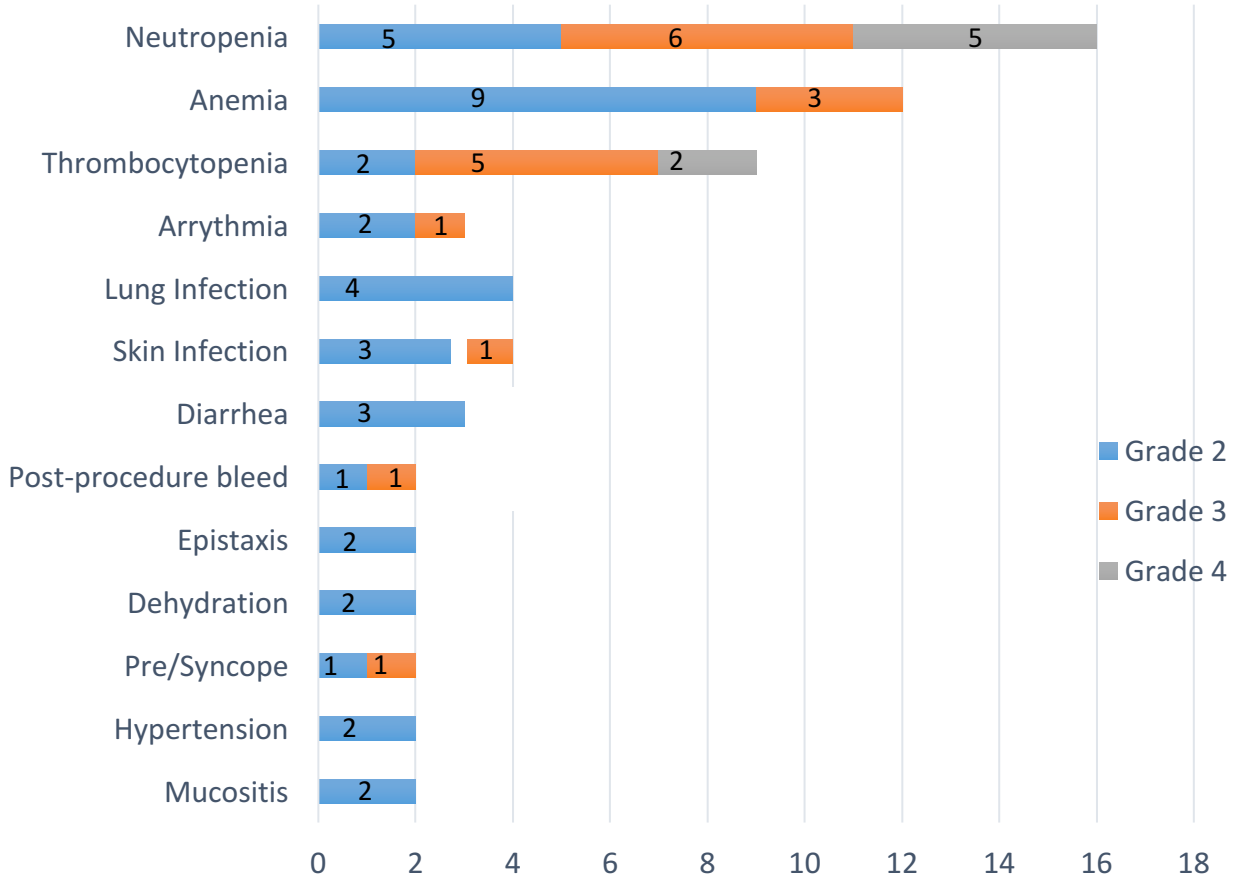
**57% decreased splenomegaly**

***PERIPHERAL NEUROPATHY***

**9/9 improvement or stabilization**

Treon et al NEJM 2015

# Ibrutinib Related Adverse Events



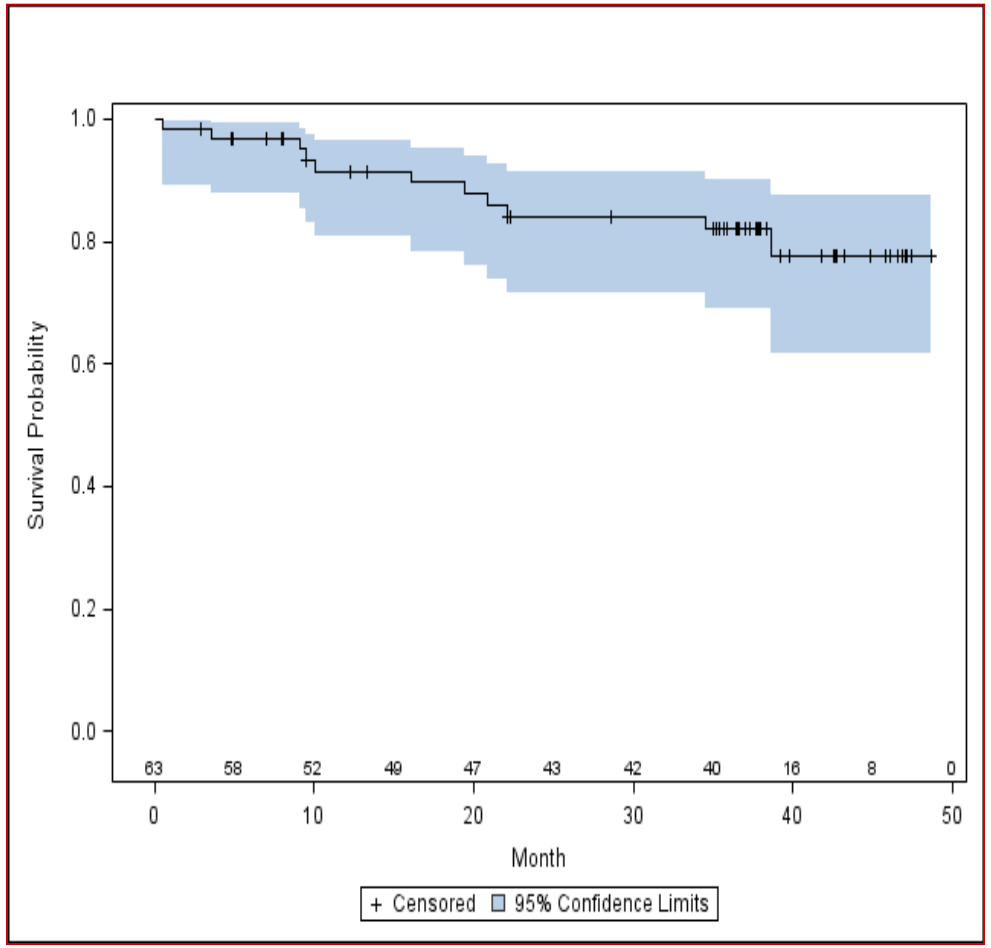

*Number of Subjects with Toxicity*

*Treon et al NEJM 2015*

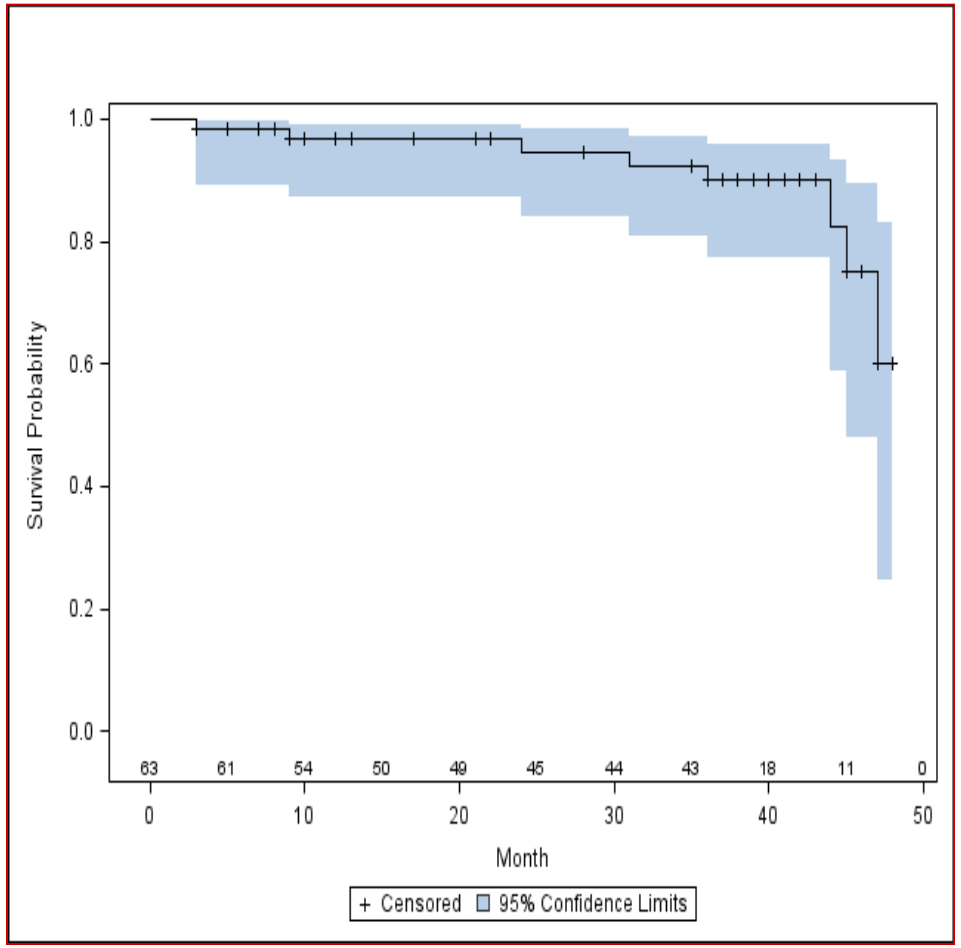
# Ibrutinib in WM: long term follow-up

## Median follow-up 37 months

### Progression-free survival



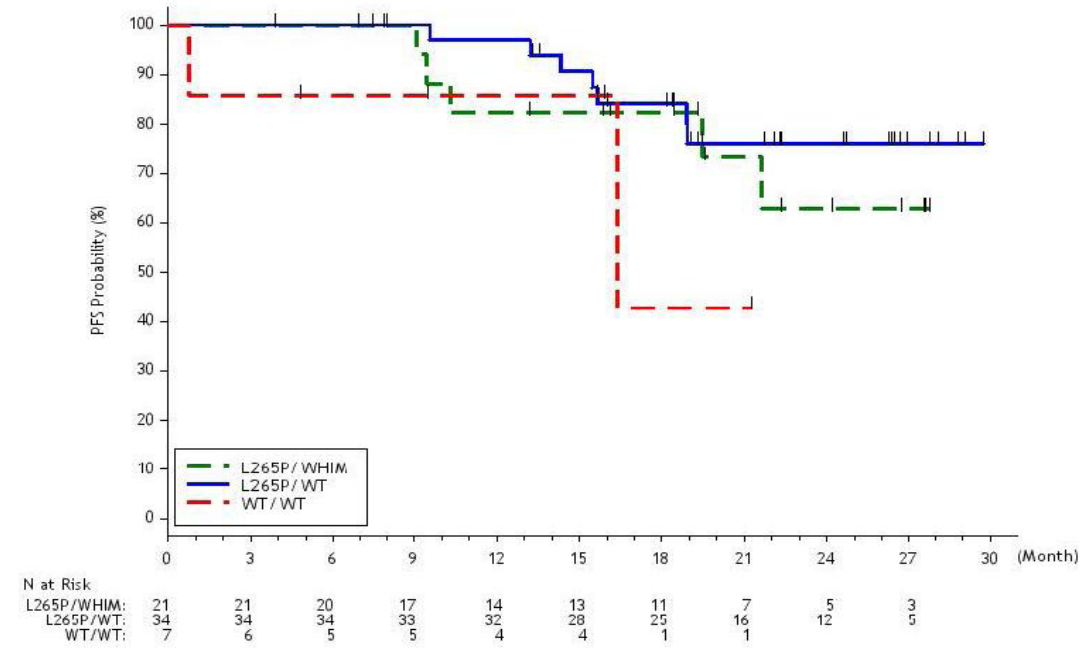

### Overall survival




*Treon et al NEJM 2015, Palomba et al IWWM 2016*

# Ibrutinibin WM: efficacy according to biological features

| | $MYD88^{L265P}$ $CXCR4^{WT}$ | $MYD88^{L265P}$ $CXCR4^{WHIM}$ | $MYD88^{WT}$ $CXCR4^{WT}$ | P value |
|---|---|---|---|---|
| N | 34 | 21 | 7 | |
| ORR | 100% | 85.7% | 71.4% | <0.01 |
| Major RR | 91.2% | 61.9% | 28.6% | <0.01 |



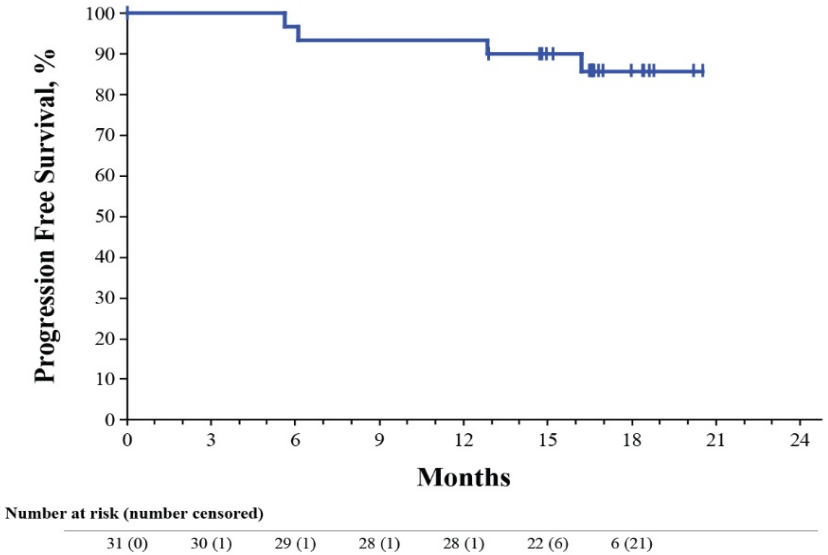

*Treon et al NEJM 2015, Palomba et al IWWM 2016*

# Single-Agent Ibrutinib in Rituximab-Refractory WM Results From a Multicenter, Open-Label Phase 3 Substudy (iNNOVATE™)

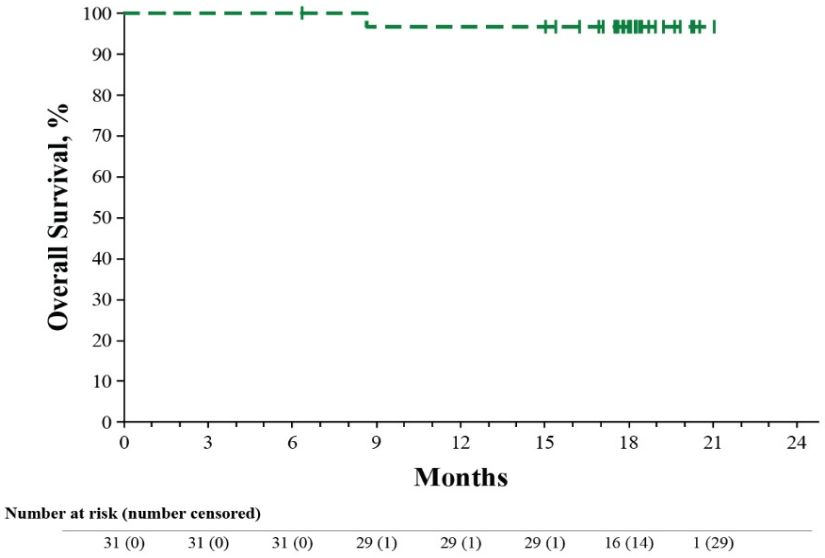
## ARM C

31 pts median of 4 prior therapies, 71% having ≥3 prior therapies

### Progression-free survival




### Overall survival

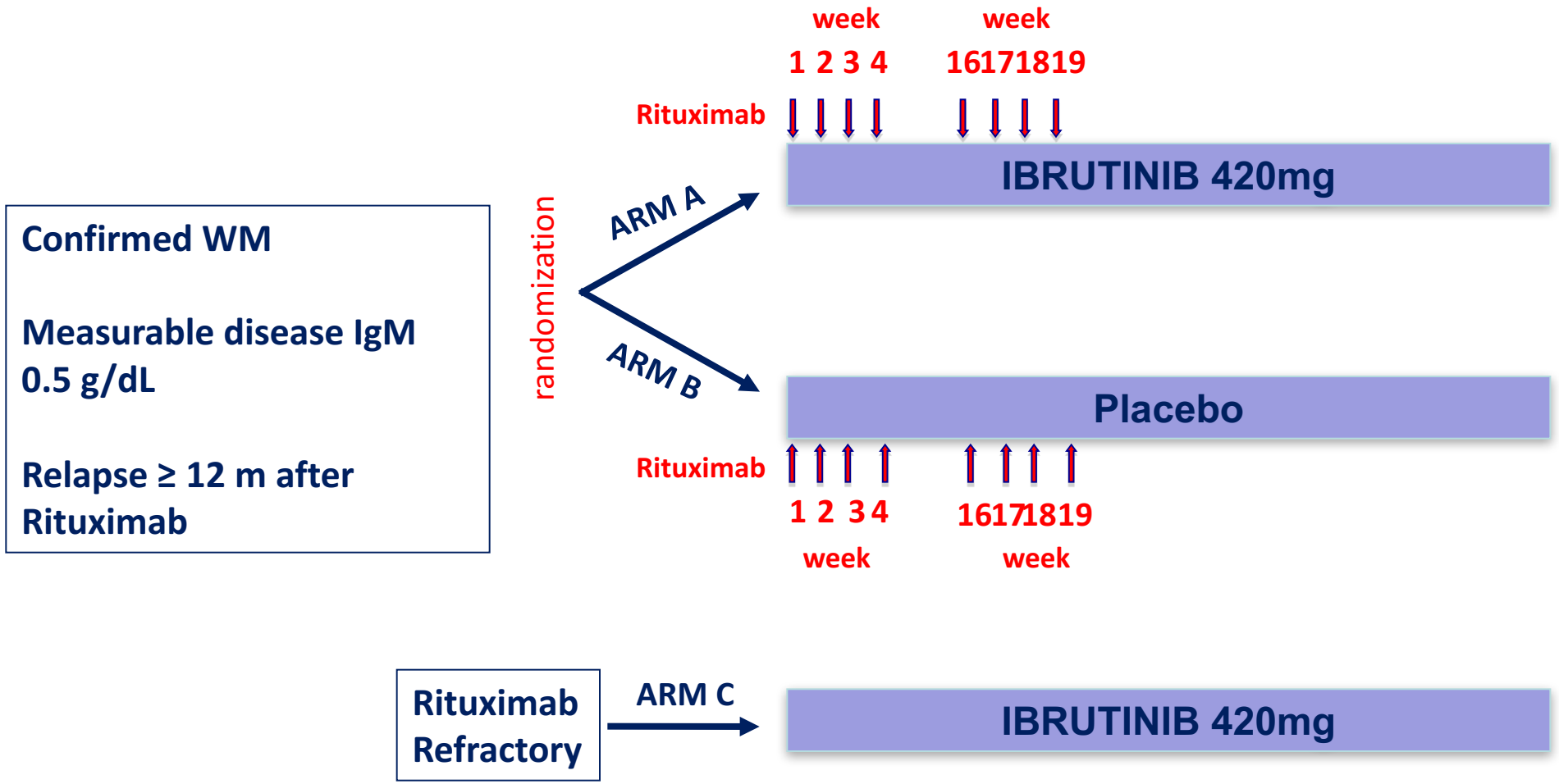



Dimopoulos Lancet Oncol 2017

# PROTOCOLLI APERTI
# OSPEDALE NIGUARDA

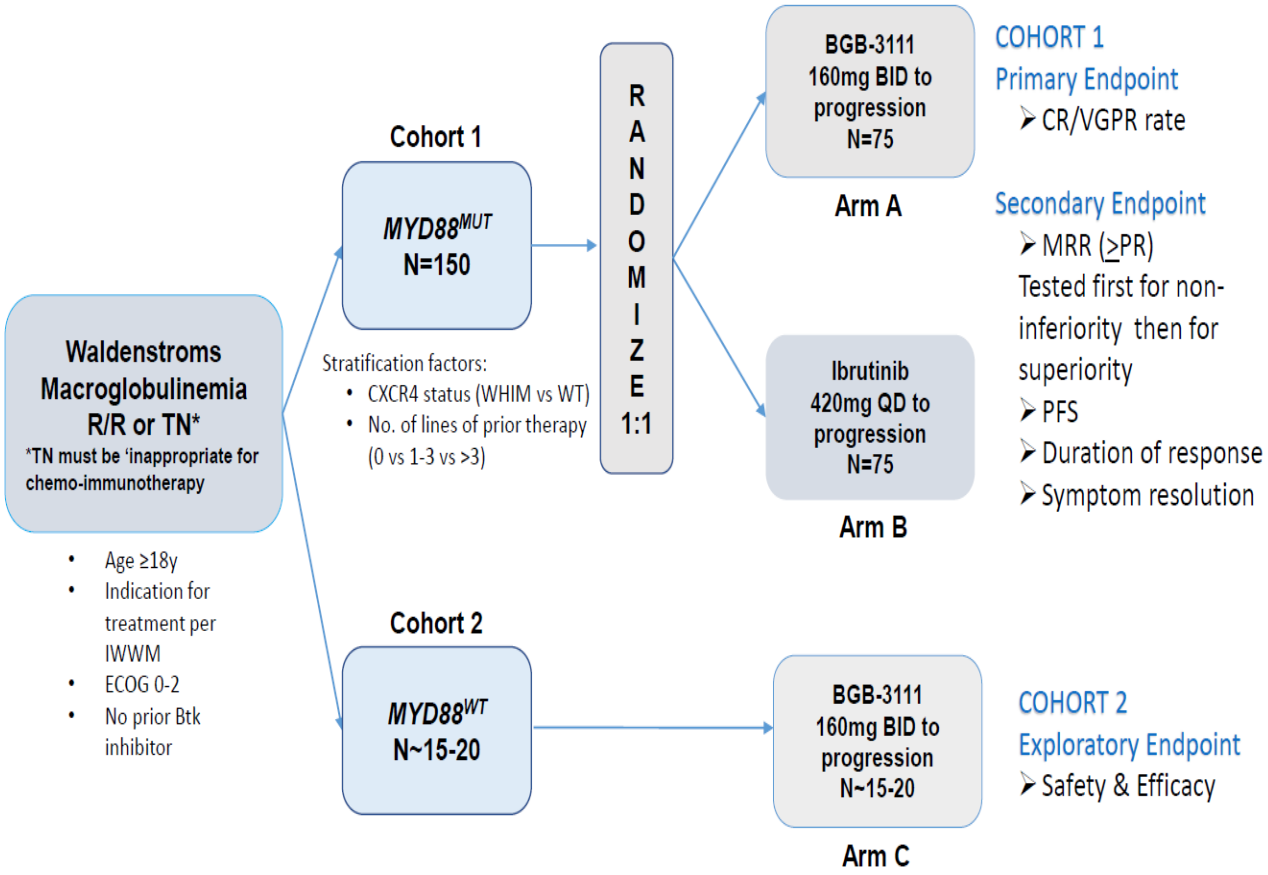
# International Multicenter, Open-Label Phase 3 (iNNOVATE™) rituximab placebo *versus* rituximab ibrutinib

## *Study Deisgn*

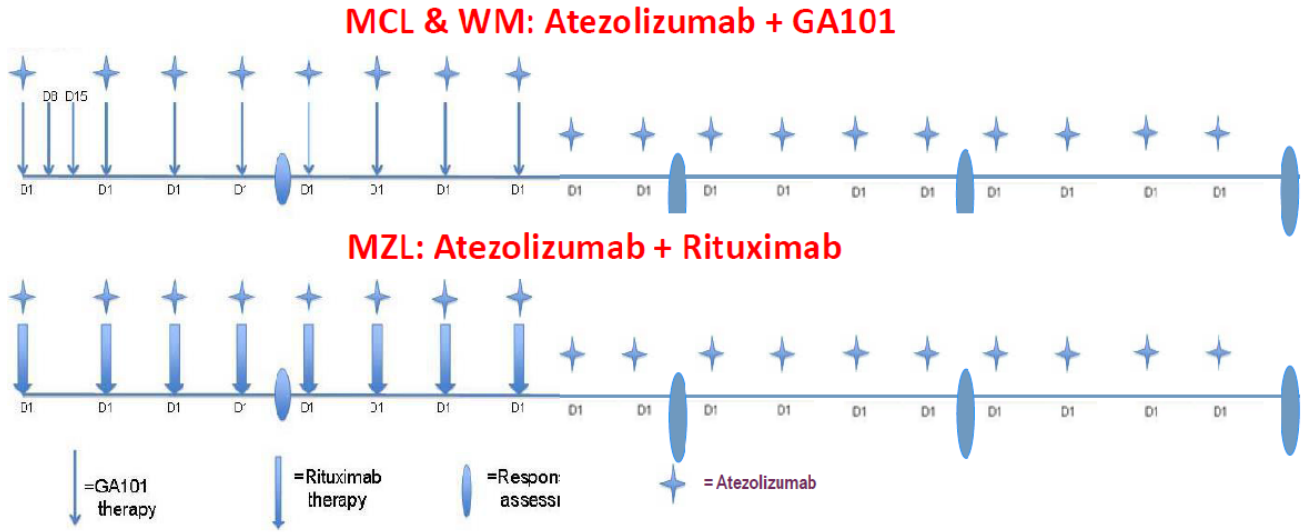


# BGB-3111-MW-302

A Phase 3, Randomized, Open-Label, Multicenter Study Comparing the Efficacy and Safety of the Bruton's Tyrosine Kinase (BTK) Inhibitors BGB-3111 and Ibrutinib in Subjects with Waldenström's Macroglobulinemia (WM)



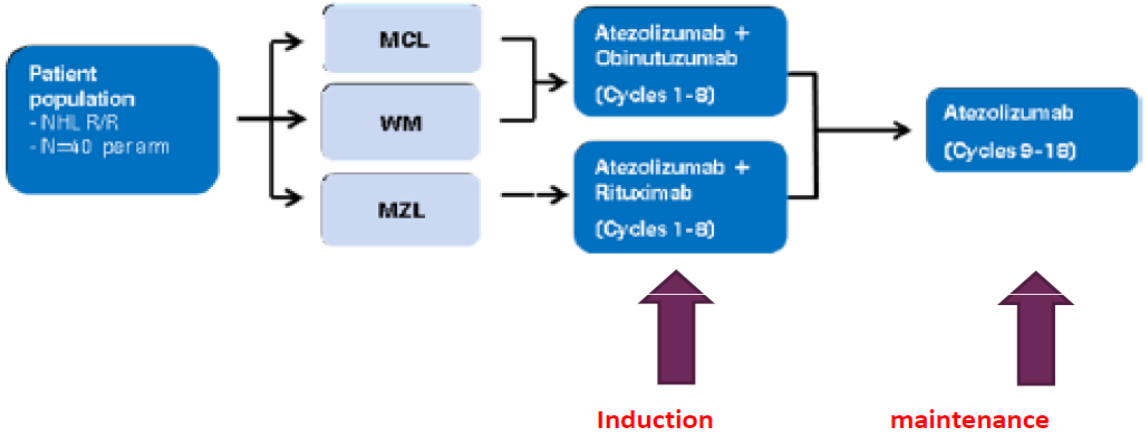
# A PHASE II STUDY EXPLORING THE SAFETY AND EFFICACY OF ATEZOLIZUMAB ADMINISTERED IN COMBINATION WITH OBINUTUZUMAB OR RITUXIMAB ANTI-CD20 THERAPY IN PATIENTS WITH RELAPSED/REFRACTORY MANTLE CELL LYMPHOMA, MARGINAL ZONE LYMPHOMA AND WALDENSTRÖM MACROGLOBULINEMIA




Sites will prospectively choose

CHOP for 6 or 8 cycles

Cycle length: 3 weeks




# Ricerca Clinica