Waldenström Macroglobulinemia: The Burning Questions

IWMF Ed Forum May 2017

Morie Gertz MD, MACP

Are my kids going to get this?

- Familial seen in approximately 5–10% of all CLL patients and can be associated with earlier age of diagnosis, more female prevalence, and increased incidence of other lymphoproliferative disorders (LPD), such as non-Hodgkin Lymphoma. 6 per 100,000 persons per year

WM/LPL #2144 controls 8279

Relative risk of lymphoproliferative malignancies and MGUS among first-degree relatives of LPL/WM patients

	Risk among first-degree relatives								
	Relatives of LPL pts only			Relatives of WM pts only			Relatives of LPL/WM pts combined		
	Pts	Co	RR (95% CI)*	Pts	Co	RR (95% CI)*	Pts	Co	RR (95% CI)*
LPL/WM	4	1	16.6 (1.7-162.2)	6	1	24.0 (2.9-201.1)	10	2	20.0 (4.1-98.4)
Non-Hodgkin lymphoma	15	26	2.3 (1.2-4.3)	28	32	3.5 (2.1-5.8)	43	58	3.0 (2.0-4.4)
Chronic lymphocytic leukemia	7	6	4.8 (1.6-14.1)	9	13	2.7 (1.1-6.5)	16	19	3.4 (1.7-6.6)
Hodgkin lymphoma	3	2	5.9 (1.0-36.0)	1	19	0.2 (0.0-1.5)	4	21	0.8 (0.3-2.2)
Multiple myeloma	6	11	2.2 (0.8-5.9)	5	16	1.2 (0.4-3.3)	11	27	1.6 (0.8-3.2)
MGUS	2	1	8.1 (0.7-90.6)	3	3	4.0 (0.8-20.0)	5	4	5.0 (1.3-18.9)

RR indicates relative risk; CI, confidence interval; LPL, lymphoplasmacytic lymphoma; WM, Waldenström macroglobulinemia; MGUS, monoclonal gammopathy of undetermined significance; Pts, patients; and Co, controls.

*All estimates were adjusted for sex of first-degree relative.

Familial Waldenstrom's macroglobulinemia and relation to immune defects, autoimmune diseases, and haematological malignancies - A population-based study from northern Sweden

Lena Brandefors, Eva Kimby, Kristina Lundqvist, Beatrice Melin & Jack Lindh

DOI:
http://dx.doi.org/10.3109/0284186X.2015.1096019

PUBLISHED ONLINE:
11 November 2015

Table 1 of 3

Table I. Characteristic of 12 families with WM, MM and/or IgM MGUS identified through Swedish and Regional Lymphoma Registry and the Swedish Cancer Registry (1997–2011).

Family ID	Number of affectedFamily members	Diagnosis	Gender and age at diagnosis	Relations of affected family members	Reported autoimmune disease	Reported haematological disease among relatives
A	3	**WM**, WM†, IgM MGUS	M76, M?, M48	**Siblings, parent**-child	–	–
B	4	**WM**, WM†, IgG MGUS, monoclonal FLC/s	F52, M?, F33, F80	**First cousins, parent**-child, siblings	RA[b], Hypothyroidism, psoriasis, MS	CML
C	2	**WM**, WM	F29, F66	Parent-**child**	–	–
D	3	WM, WM, IgM MGUS	F62, M?, M52	**Siblings**	Hypothyroidism[c], PMR	
E	2	**WM,WM**	M84, F85	**Siblings**	AHA[a]	Acute leukemia
F	2	**WM**, IgM MGUS	M49, F80	Parent-**child**	ALS	–
G	3	**WM**, MM†, IgG MGUS	F80, M78, F80	**First cousin, siblings**	PMR[a]	Hodgkin's Lymphoma
H	4	**WM**, WM†, IgM MGUS, IgM MGUS	F50, M78, F? F68	Parent-**child, niece, first cousin**	Hypothyroidism[a], ITP[a] PMR[c], Bechterew's disease[d]	–
I	4	**WM**, IgM MGUS, IgM MGUS, IgG MGUS	M66, M63, F72, F60	**Siblings**	RA[b], Systemic connective tissue disease[d]	Follicular[c] Lymphoma
J	2	**WM**, MM†	M71, M66	**First cousin**	Psoriasis, Psoriatic Arthritis, Arthritis of undetermined significance	–
K	2	**WM, WM**	F73, M 85	**Siblings**	–	–
L	2	**WM**, MM	F69, F65	**Siblings**	Sjogren's syndrome[b] Hypothyroidism[a]	Indolent B-cells lymphoma
Total 12					In 9/12 families	In 5/12 families

12/56 patients had a family member affected

My opinion

- first degree relatives can have a serum protein electrophoresis beginning at age 50 repeated every 2 years

How long will I live?

- Since I began practice the survival has more than doubled
- Half of patients with symptomatic WM succumb to the disorders associated with old age
- New drugs are being developed at a rapid pace
  - **Oprozomib**, IMO-8400, Lenalidomide & **everolimus** combinations, **carfilzomib**, bendamustine, **ibrutinib**
- The danger of medians
  - Height across populations & income

Everolimus

- Active as a single agent
- Active with bortezomib
- Rise in triglycerides
- Consistent with >5 years of use

oprozomib

- Oral proteosome inhibitor
- Not neurotoxic given 2 days a week
- Impressive activity as a single agent
- Nausea and diarrhea managed with a new extended release formulation

What can I do to live longer

- Life style
- Activity
- Nutrition
- Obesity & Chemotherapy
  - clear standards or dosing guidelines are unable to be made for the obese population
- Frailty
  - may be predictive of decreased cancer-independent survival

Obesity and cancer

- 26% increase in men 10 % increase in women
- 5 ft 8 in at 164 pounds
- These numbers apply at weight at 196 about 35 pounds overweight
- High levels of insulin like growth factor and adipokine as well as changes in male and female hormones

What are the risks of Imaging (X-rays)

- We are all exposed to radiation daily 0.01 millisieverts
- Chest X ray 0.1 mS
- Mammogram 0.4
- CT abdomen & Pelvis 10 mS
- PET CT 25mS
- Estimated exposure at Fukushima 2011 average 10

Australian study 2013

- 680000 children that had CT imaging
- Comparator 10,000,000 children no CT
- Scanned children 45 cancers/10000 over 10 yrs
- Unscanned 39 cancers/10000 over 10 yrs
- Scanned children had a 24% rise in cancer risk
- Each additional scan increased risk 16%

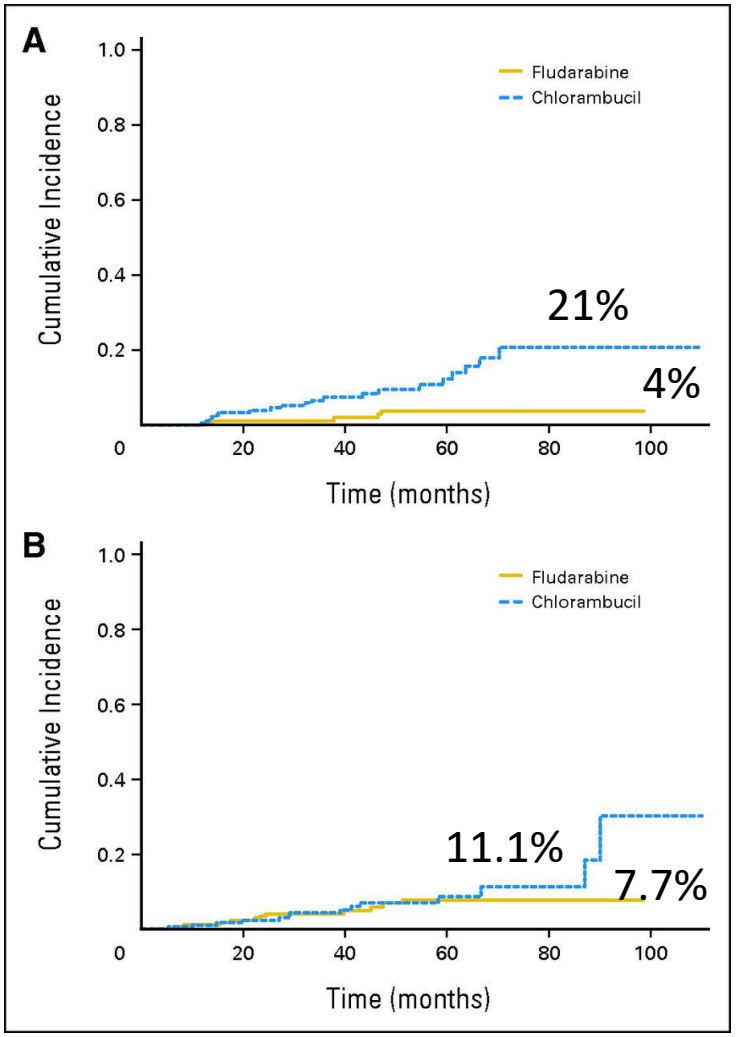
Moral

- Try to minimize imaging and ask how essential it is

Will my WM transform into something worse?

- Richter's Transformation
  - tumor cells of DLBCL are clonally identical to those of WM/LPL.
  - occur in 6% of patients with WM
  - Role of nucleoside analogs
- MDS
  - Role of chemotherapy and DNA damage 1-3%

Cumulative incidence of (A) secondary malignancies and (B) high-grade lymphomas.



Leblond V et al. JCO 2013;31:301-307

Will I be Disabled?

- Fortunately the overwhelming majority of patients have complications limited to their blood counts and problems of the lymph nodes liver & spleen are much less common
- Neuropathy
  - Not therapy related
- Renal Complications/amyloidosis
- Cryoglobulinemia

What are the complications that can be seen?

Classification	No.	%
Monoclonal gammopathy of undetermined significance (MGUS)	242	56 Ratio MGUS:WM=4:1
Waldenström's macroglobulinemia (WM)	71	17
Lymphoma (LY)	28	7
Chronic lymphocytic leukemia (CLL)	21	5
Primary amyloidosis (AL)	6	1
Lymphoproliferative disease (LP)	62	14
Total	430	100

The spectrum of IgM monoclonal gammopathy in 430 cases

	MGUS	WM	LY	CLL	AL	LP	Total
Palpable liver (%)	11	25	32	48	33	29	19
Palpable spleen (%)	6	20	29	62	17	34	17
Lymphaden opathy (%)	3	17	43	67	0	39	16

Five percent of all patients had a peripheral neuropathy; more than half the cases occurred in patients with MGUS.

Viscosity in WM

	MGUS	WM	LY	CLL	AL	LP
No. of patients						
Tested	40	**51**	6	3	1	24
>4.0 cP	0	**15**	0	0	0	2[‡]
>1.8 cP	16	46	3	2	1	18
Viscosity (cP)						
Median	1.7	2.8	1.8	1.9	2.0	2.0
Range	1.0–2.9	1.2–14.8	1.3–2.8	1.8–2.8	2.0	1.2–6.5

Should I be tested for MYD88 L256P?

- **MYD88 is not currently part of the diagnostic criteria**
- **MYD88- may be less ibrutinib responsive**
- **Therapy as yet is not determined by MYD88 status**
- **Does not distinguish WM from IgM MGUS**

What are the Triggers for initiating therapy?

Second International Workshop on Waldenström's Macroglobulinemia agreed that initiation of therapy was appropriate for patients with constitutional symptoms such as **fever, night sweats, fatigue due to anemia, or weight loss**. The presence of **progressive, symptomatic lymphadenopathy or splenomegaly** provided additional reasons to begin therapy. The presence of anemia with a **hemoglobin value of 10 g/dL or lower or a platelet count lower than 100 × 10^9/L** due to marrow infiltration also justified treatment. Certain complications such as **hyperviscosity syndrome, symptomatic sensorimotor peripheral neuropathy, systemic amyloidosis, renal insufficiency, or symptomatic cryoglobulinemia** may also be indications for therapy

Mayo Clin Proc. 2010 Sep;85(9):824-33.

What should I monitor when I see my Provider?

Watch & Wait; Prior Rx

- Hb
- Platelets
- M-Spike
- IgM
- ± Free light Chain
- Monitoring of liver spleen & lymph node size

On Active Rx

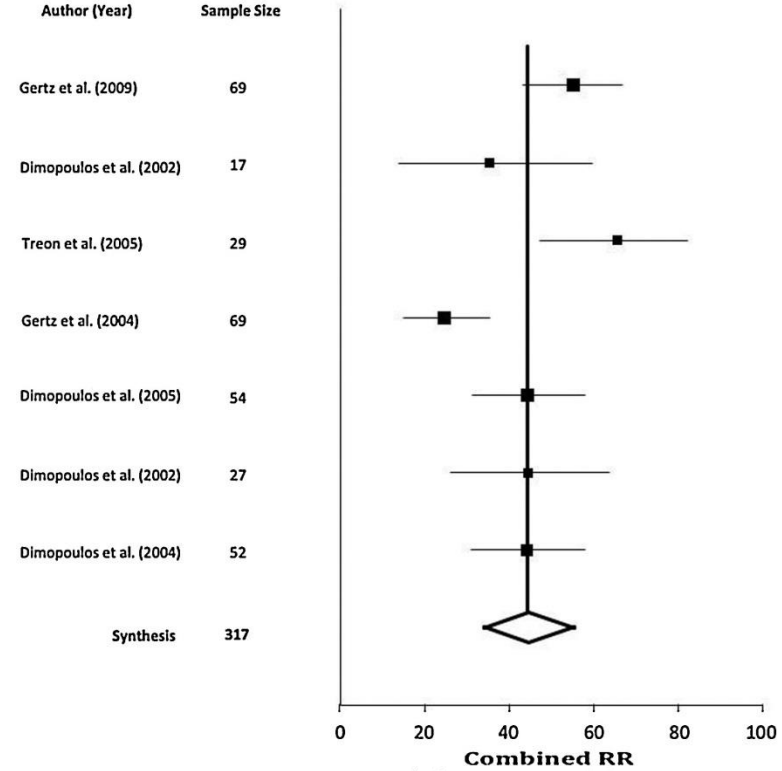
- The key monitoring metric should be driven by why therapy was initiated and corroborated by indirect measures of WM including IgM & M spike

Note bone marrow is not part of my routine monitoring schedule

Is Rituxan alone a good therapy?

- N=69 strictly defined WM
- Four doses of rituximab
- 50% fall in IgM in 19 (28%)
- 25-50% fall in IgM in 17 (25%)
- >25% reduction in IgM 36/69=52%
  - Chlorambucil single agent reduction of IgM >50%-39%
  - Fludarabine 48% (second cancers 3.7%)
- Single agent R produces **inferior** response rates compared with combinations (44% 7 studies 317 patients vs 73% for combinations 700 patients)

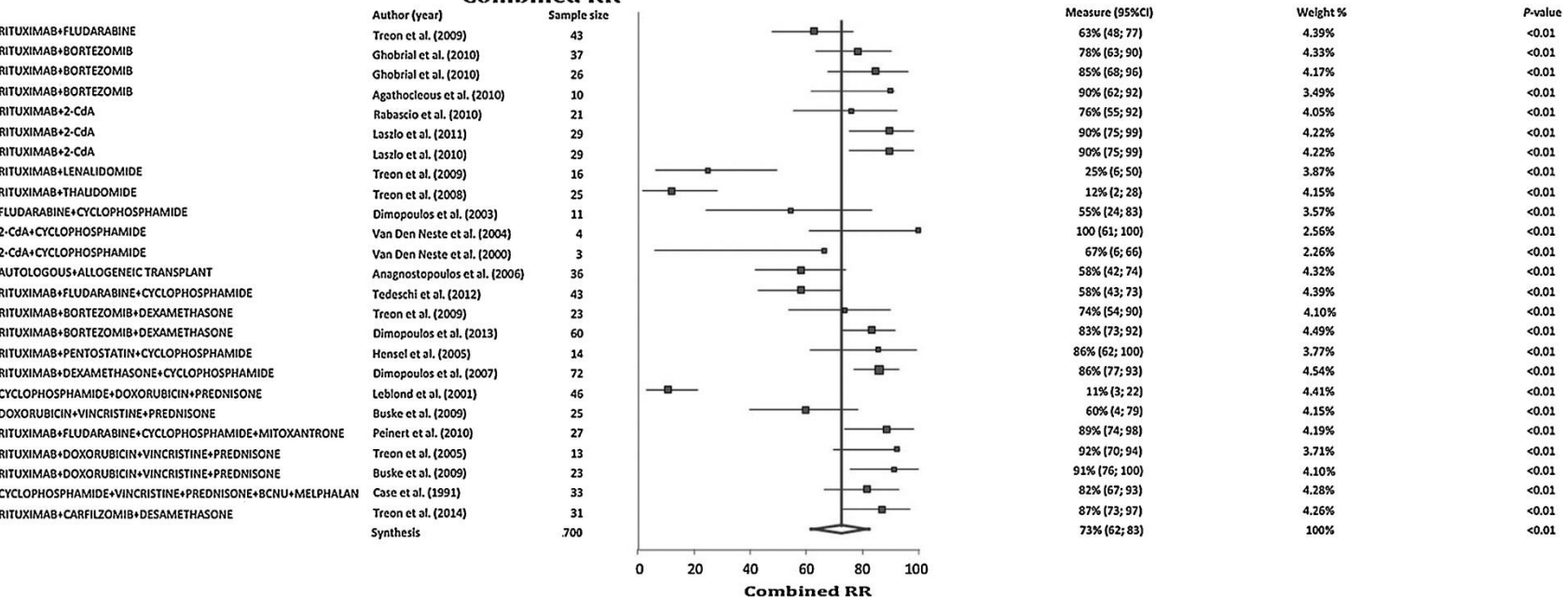
J Clin Oncol. 2013 Jan 20;31(3):301-7; Brit J Haem in press 2015



R alone

[Critical Reviews in Oncology/Hematology Volume 105](), September 2016, Pages 118–126

Combinations



How deep a response do I need?

- Controversial and debates on depth of response are ongoing
- Unclear that adding new therapies to deepen response after a plateau has been achieved is indicated and its not part of my practice

Should I get a second opinion?

In Multiple Myeloma centers that averaged > 10.6 patients / year (Canada)
Had significantly better outcomes than facilities caring for fewer patients

JCO V34 : 7suppl abs 284

What's the deal with maintenance Rituximab

- Observational study R maint associated with improved outcomes but more frequent infections. No quality of life measure done
- In a survey performed in the Netherlands WM maintenance was recommended by 23% and actually used for their last patient in 8.5%-
- The National Institute for Health and Clinical Excellence (NICE) considered it impossible to draw firm conclusions regarding the clinical effectiveness of the intervention -2013

Results in FL

Table 2. Trials evaluating maintenance rituximab in patients with untreated follicular lymphoma

Study	No.	Induction regimen	Maintenance schedule	PFS or EFS (MR versus observation)	OS (MR versus observation)
Hochster *et al.* [11]	387	CVP	Four weekly doses every 6 months for 2 years	64%* vs 33% (3 years)	91% vs 86% (3 years)
Martinelli *et al.* [19]	202	R alone	Single dose at 3, 5, 7 and 9 months	24 months* vs 13 months	Difference not statistically significant
Ardeshna *et al.* [21]	720	R alone	Single dose every 2 months for 2 years	79% reduction in the risk of progression with MR*	Not reported
Salles *et al.* [13]	1217	R-CVP, R-CHOP or R-FCM	Single dose every 2 months for 2 years	74.9%* vs 57.6% (3 years)	Not significantly different between the two arms
Foa *et al.* [40]	545	Various R based regimens	Single dose every 2 months for 2 years	Not reported	Not reported
Vitolo *et al.* [25]	242	R-FND	Single dose every 2 months for four doses	80% vs 68% (2 years)	No data available

CVP, cyclophosphamide, vincristine, prednisone; CHOP, cyclophosphamide, adriamycin, vincristine, prednisone; FCM, fludarabine, cyclophosphamide, mitoxantrone; FND, fludarabine, mitoxantrone, dexamethasone; MR, maintenance rituximab; OS, overall survival; PFS, progression-free survival; R, rituximab.
*Statistically significant value.

#2739

Bendamustin-Rituximab Induction Followed by Observation or Rituximab Maintenance for Newly Diagnosed Patients with Waldenström's Macroglobulinemia: Results From an ongoing Prospective, Randomized, Multicenter Study (StiL NHL 7-2008 –MAINTAIN-; ClinicalTrials.gov Identifier: NCT00877214)

Mathias J. Rummel, MD, Christian Lerchenmüller, MD, Richard Greil, MD, Martin Görner, Manfred Hensel, MD, Erik Engel, Ulrich Jaeger, MD, Friedhelm Breuer, Bernd Hertenstein, Otto Prummer, MD, PhD, Christian Buske, MD, Juergen Barth, Alexander C. Burchardt, MD and Wolfram Brugger

Background:

Treatment for Waldenström's Macroglobulinemia (WM) typically consists of rituximab in combination with nucleoside analogs with or without alkylating agents or with cyclophosphamide-based therapies or cyclophosphamide and dexamethasone (1, 2). In addition, combination treatments including bortezomib, thalidomide, lenalidomide and bendamustine have been shown to have activity in WM.

Bendamustine has demonstrated durable responses in previously treated patients with WM both as monotherapy and in combination with rituximab (3).

In addition, a recent observational study suggests improved clinical outcomes following maintenance rituximab therapy in patients with WM who responded to induction treatment that consisted of a rituximab-containing regimen (4).

We initiated a multicenter, prospective, randomized phase III trial to investigate the impact of adding rituximab maintenance following B-R first-line induction. The trial includes patients with WM, marginal zone, small lymphocytic and mantle cell lymphomas (ClinicalTrials.gov Identifier: NCT00877214).

The trial is currently ongoing and we present first and preliminary results of the induction phase for patients with WM.

Methods:

Treatment consists of a maximum of 6 cycles of B-R (bendamustine 90 mg/m², rituximab 375 mg/m²) administered every 28 days plus 2 cycles of rituximab every 4 weeks.

Responding patients (≥ PR) are eligible for further treatment and are/will be randomized to observation or 2 years of rituximab maintenance every two months. The primary endpoint is PFS.

Results:

From April 2009 to July 2012, 57 centers included a total of 162 patients with newly diagnosed WM with a median age of 67 years (31% < 60 years, 69% > 60 years). At baseline/inclusion/screening, the following median values were recorded: β2-Microglobulin 3.3 mg/L, hemoglobin 10.1 g/dL, and IgM 2110 mg/dL (max. 13400 mg/dL).

The trial is currently ongoing, and we report results for 116 evaluable patients who have completed the induction phase (data cut-off Aug 2012): 43 women (37%) and 73 men (63%). 100 patients have responded to B-R leading to an overall response rate (ORR) of 86%. At the time of response evaluation, the median Hb was 12.6 g/dl and the median IgM was 380 mg/dl (Table 1).

No uncommon toxicities were observed during B-R induction.

To date, 90 patients have undergone randomization after completing the induction phase: 43 to observation and 47 to maintenance. Recruitment and randomization are ongoing. No results can be reported from the maintenance part of the trial.

Conclusion:

Initial results of our trial confirm that for patients with Waldenström's Macroglobulinemia, induction treatment with B-R is efficacious and has a manageable safety profile. The role of rituximab maintenance in this disease is under investigation.

Study details	
Title	StiL Study NHL 7-2008: Prospective Randomized Multicenter Study in First-line Treatment of Advanced progredIeNT Follicular And Other IndoleNt and Mantle Cell Lymphomas (MAINTAIN)
ClinicalTrials.gov Identifier:	NCT00877214
Study type	Multicenter, prospective, randomized, Phase III
Treatment	
Induction	Maximum of 6 cycles of B-R Bendamustine 90 mg/m² Rituximab 375 mg/m² administered every 28 days plus 2 cycles of rituximab every 4 weeks.
Maintenance	Randomization to Observation or 2 years of rituximab maintenance, 375 mg/m², every two months
Included Patients from 04/2008 to 8/2012	162 (recruitment ongoing)
Evaluable patients	116 43 women [37%] 73 men [63%]
Randomized patients (following completion of the induction phase)	90 43 observation 47 maintenance
Values @ baseline/inclusion/screening	
Median age	67 years 31% < 60 years 69% > 60 years
β2-Microglobulin	3.3 mg/L
Hemoglobin	10.1 g/dL
IgM	2110 mg/dL (max. 13400 mg/dL)
Values @ the time of response evaluation	
Overall Response Rate	86 %
Hemoglobin	12.6 g/dL
IgM (median)	380 mg/dL

Table 1: Overview of study details and preliminary results

Primary Completion Date:April 2017

References:

1. Gertz MA. Am J Hematol. 2012 May;87(5):503-10.
2. Treon SP. Blood. 2009 Sep 17;114(12):2375-85.
3. Treon SP, et al. Clin Lymphoma Myeloma Leuk. 2011 Feb;11(1):133-5
4. Treon S, et al. Br J Haematol 2011;154(3):357-62

Studiengruppe indolente Lymphome

Consensus for Newly Diagnosed Waldenström Macroglobulinemia

- IgM MGUS (<10% lymphoplasmacytic infiltration)
- Asymptomatic/smoldering Waldenstrom's
- Hemoglobin ≥11 g/dL
- Platelets ≥120 x 10^9/L

- Hemoglobin <11 g/dL or symptomatic
- Platelets <120 x 10^9/L
- IgM-related neuropathy
- WM-associated hemolytic anemia
- Symptomatic cryoglobulinemia

- Bulky Disease
- Profound cytopenias –
  - Hemoglobin ≤10 g/dL
  - Platelets <100 x10^9/L
- Constitutional symptoms
- Hyperviscosity symptoms

Hyperviscosity symptoms

Yes

No

Plasmapheresis

Observation

Single Agent Rituximab*

(1 cycle; no maintenance therapy)
*plasmapheresis if hyperviscosity develops with treatment

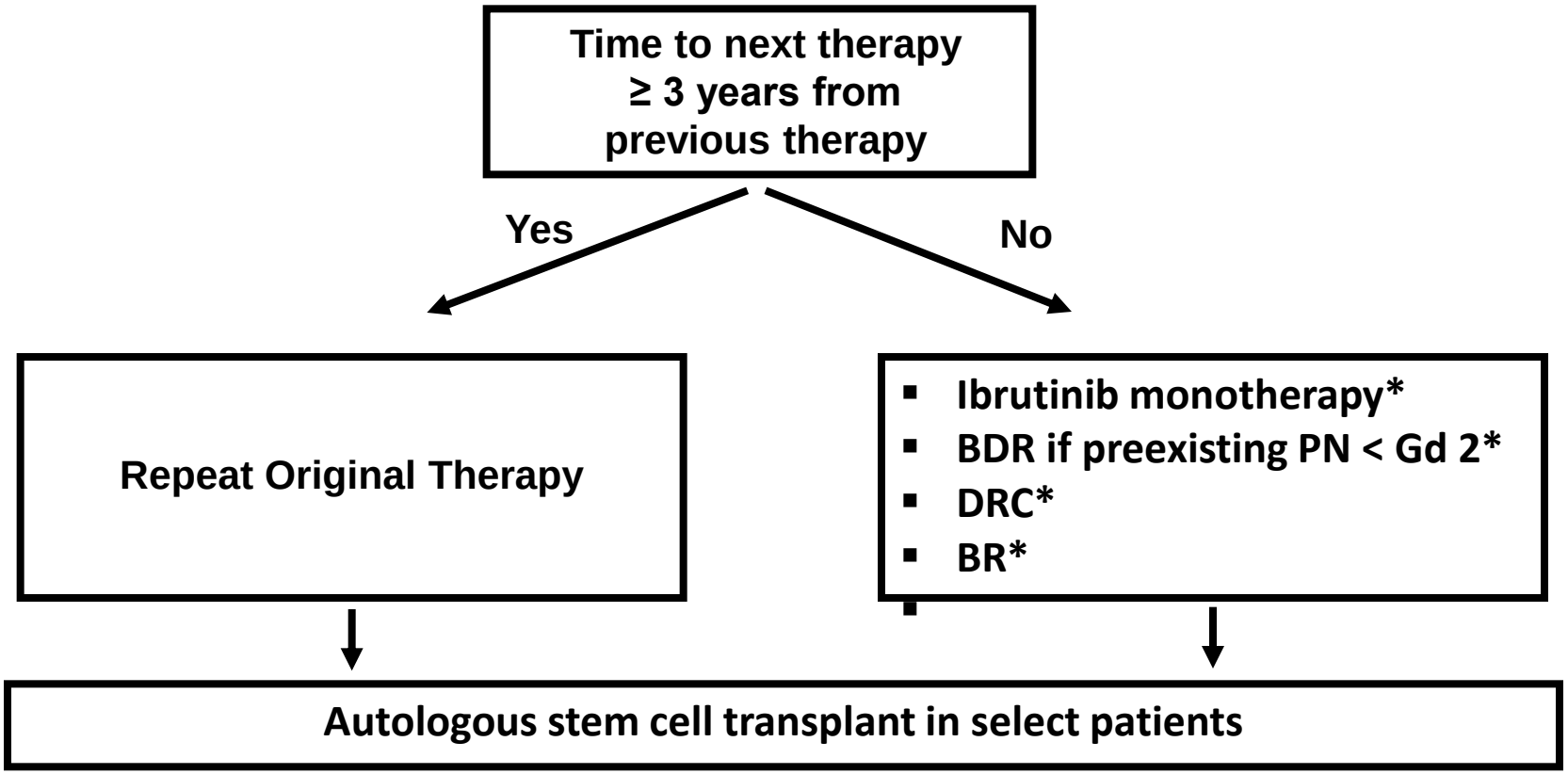
Bendamustine + Rituximab (BR)* x 4-6 cycles
No rituximab maintenance therapy

Harvest stem cells if ≤ 70 years and potential autologous stem cell transplantation candidate in future

*__Dexamethasone + Rituximab +Cyclophosphamide (DRC)*__x 6 cycles is an alternative if the disease burden is low

v4 Revised March 2015

Waldenström Macroglobulinemia Consensus for Off-Study Salvage Therapy



DRC = Dexamethasone + Rituximab + Cyclophosphamide; BR = Bendamustine + Rituximab; BDR = Bortezomib (weekly), Dexamethasone + Rituximab; PN= peripheral neuropathy

* If not previously used.

How about Ibrutinib?

- 1 prior treatment
- Intended therapy consisted of 420 mg of oral ibrutinib daily for 2 years.

Efficacy
• Response rate: 61.9% (95% CI: 48.8, 73.9) • Partial response: 50.8% • Very good partial response: 11.1% • Median duration of response: not reached (range, 2.8+ - 18.8+ months)

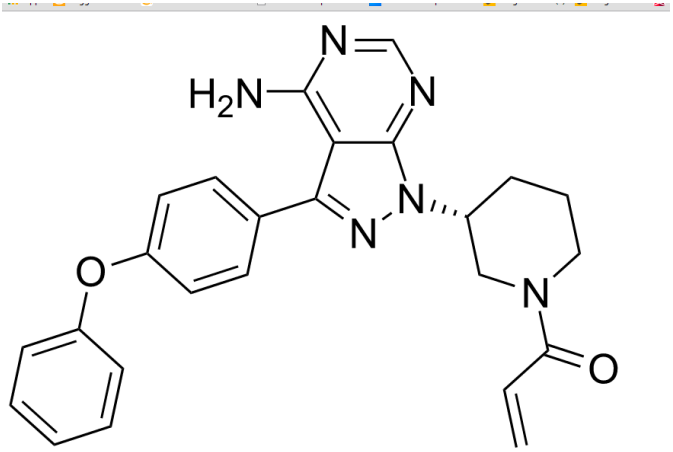
- a median time to response of 4 weeks. Median IgM 3610 to 1340. Hb 10.5 to 12.6

Ibrutinib

- MYD 88 status did not impact response
- CXCR4 WT major response of 77% CXCR4-WHIM response 30%
- Mutated WHIM had less benefit in IgM level and Hb improvement
- Neutropenia 19% thrombocytopenia 14%

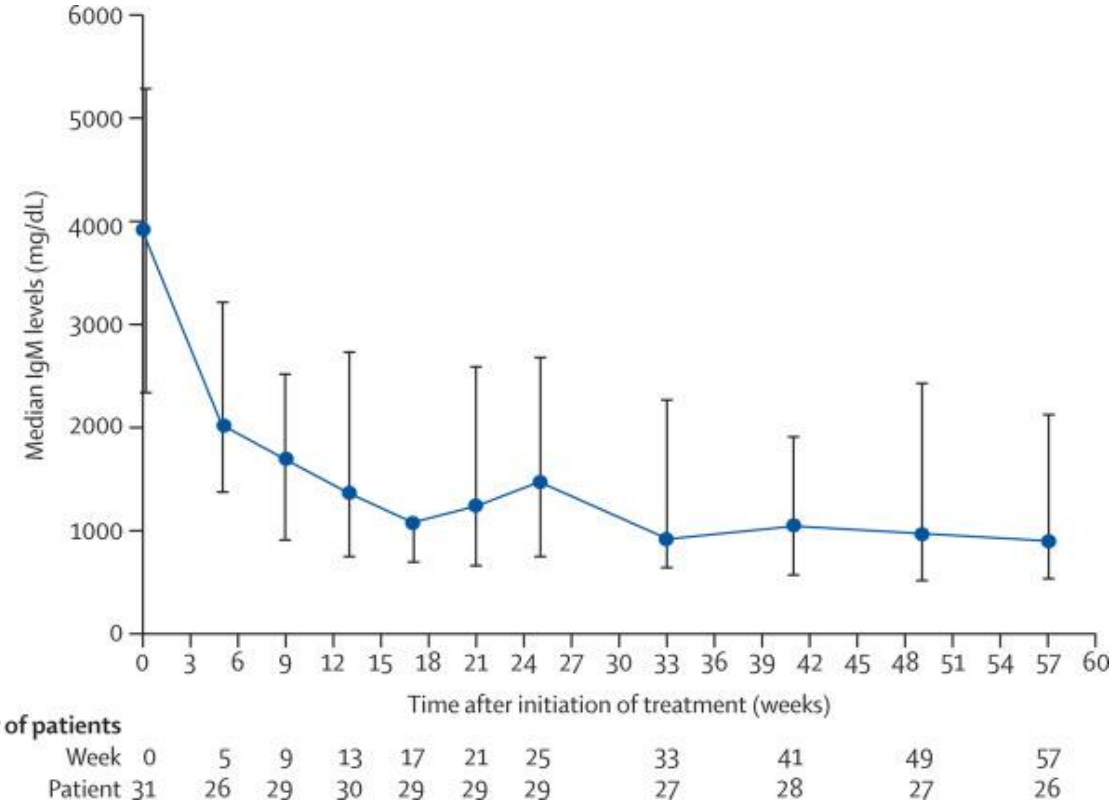
Ibrutinib

- FDA Breakthrough Therapy Designation
- FDA approved Mantle Cell 11/13 & CLL 2/14
- Diarrhea & Platelets **atrial fibrillation**
- Rash Swelling Joint Pain
- Bleeding, pneumonia
- Final approval Jan 29, 2015



Ibrutinib for patients with rituximab-refractory Waldenström's macroglobulinaemia (iNNOVATE): an open-label substudy of an international, multicentre, phase 3 trial

	All* (N=31)	MYD88 (Leu265Pro)/CXCR4 (wild type; n=17)†	MYD88 (Leu265Pro)/CXCR4 (WHIM; n=7)
Very good partial response	4 (13%)	3 (18%)	0
Partial response	18 (58%)	11 (65%)	5 (71%)
Minor response	6 (19%)	1 (6%)	2 (29%)
Overall response (%)	28 (90%)	15 (88%)	7 (100%)
Major response (%)	22 (71%)	14 (82%)	5 (71%)



Median IgM levels of patients treated with ibrutinibError bars denote 95% CI.

Meletios A Dimopoulos, Judith Trotman, Alessandra Tedeschi, Jeffrey V Matous, David Macdonald, Constantine Tam, Olivier Tournilhac, Shuo Ma, Albert Oriol, Leonard T Heffner, Chaim Shustik, Ramón García-Sanz, Robert F Cornell, Carlos Fernández de Larrea, Jorge J Castillo, Miquel Granell, Marie-Christine Kyrtsonis, Veronique Leblond, Argiris Symeonidis, Efstathios Kastritis, Priyanka Singh, Jianling Li, Thorsten Graef, Elizabeth Bilotti, Steven Treon, Christian Buske

null, 2016, Available online 10 December 2016

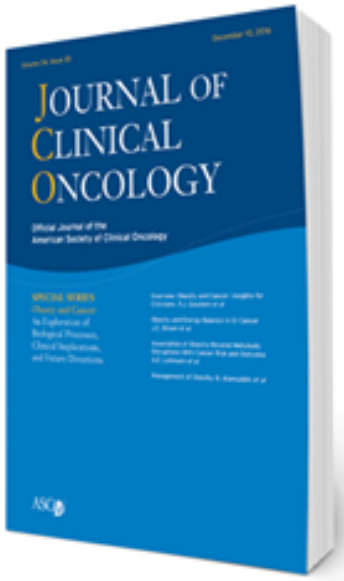
http://dx.doi.org/10.1016/S1470-2045(16)30632-5

Carfilzomib

- Combined with rituximab and dexamethasone in NDWM.
- The overall response rate was 87%, with 36% having at least a very good partial response.
- At 2 years, 65% were progression free. The peripheral neuropathy rate and cardiomyopathy rates were both 3%.

JOURNAL OF CLINICAL ONCOLOGY
Official Journal of the American Society of Clinical Oncology

Obesity and Cancer: An Exploration of Biological Processes, Clinical Implications and Future Directions



Given the obesity epidemic that is occurring in most of the developed and developing world, the association of obesity and cancer has become increasingly important. The risk of many types of cancers is higher in overweight/obese individuals and there is growing evidence that obesity is also associated with poor outcomes of several cancers.

This *JCO* Special Series issue reviews associations of obesity with many common cancers, discusses the impact of obesity on cancer treatment, and reviews approaches to management of obesity.

Share your thoughts on this issue
@JCO_ASCO


Sweets
Fats
Protein/Dairy
Carbohydrates
Daily Physical Activity
Fruits
Vegetables
Mayo Clinic Healthy Weight Pyramid™

Health and insulin levels

- Levels linked to obesity and are driving by intake of simple sugars (glucose, sucrose)-partially measured by glycemic index
- FDA provides sugar information on almost all products
- Butter 0 g An egg 0.4 g
- Oatmeal Cherrios 1 g
- Kix 3 g
- Apple Jacks 12 g
- Granola 13 g

- Twinkie 19g
- Unsweetened OJ 20g
- Yogurt 26 g (Strawberry-flavored original Yoplait yogurt, 99 percent fat free)
- Snickers bar, at 30 g of sugar
- Coke 12 oz 33 g (RDA 36g men less for women)
- **Craisins 40 g**

Cream filled and sugar filled.

Twinkies Snack Cakes
1 Twinkie
Sugars, total: 19g
Calories, total: 145
Calories from sugar: 74

2 Twinkies (1 package)
Sugars, total: 37g
Calories, total: 290
Calories from sugar: 148

One donut, one sugar cube.

Donettes, Powdered Sugar
6 Donuts (85g)
Sugars, total: 23g
Calories, total: 340
Calories from sugar: 92

Yoplait Yogurt, Strawberry
6 oz Container
Sugars, total: 27g
Calories, total: 170
Calories from sugar: 108

1 sugar cube = 4.0g