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RTP satellite symposium
ASH 2017
Atlanta, Georgia

An update of available clinical research data and new treatment strategies for **Smouldering Myeloma (SMM), Amyloidosis (AL) and Waldenström's Macroglobulinemia (WM)**

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Disclosures

Advisory Committee	Amgen Inc, Celgene Corporation, Janssen Biotech Inc, Novartis, Onyx Pharmaceuticals, an Amgen subsidiary, Takeda Oncology

Case presentation 9: Dr Brenner

60-year-old woman

- 2012: IgA kappa SMM; in excellent health with a slow but progressive rise in M-spike but does not meet treatment criteria
- Patient wants to be as aggressive as possible but is unwilling to travel for a clinical trial

Case presentation 10: Dr Chen

65-year-old woman

- June 2017: AL amyloidosis diagnosed
  by excisional lymph node biopsy
  (abdominal LAD)
- Shortly after diagnosis, hospitalized for new-onset CHF with very elevated BNP and an echocardiogram consistent with cardiac amyloidosis
- Bortezomib/lenalidomide and dexamethasone x 5
  - Clinically stable
- Referred for transplant evaluation

Case presentation: Dr Morganstein

AL amyloidosis

- Management of patients with AL amyloidosis and peripheral neuropathy

Case presentation 11: Dr Matt-Amaral

76-year-old man

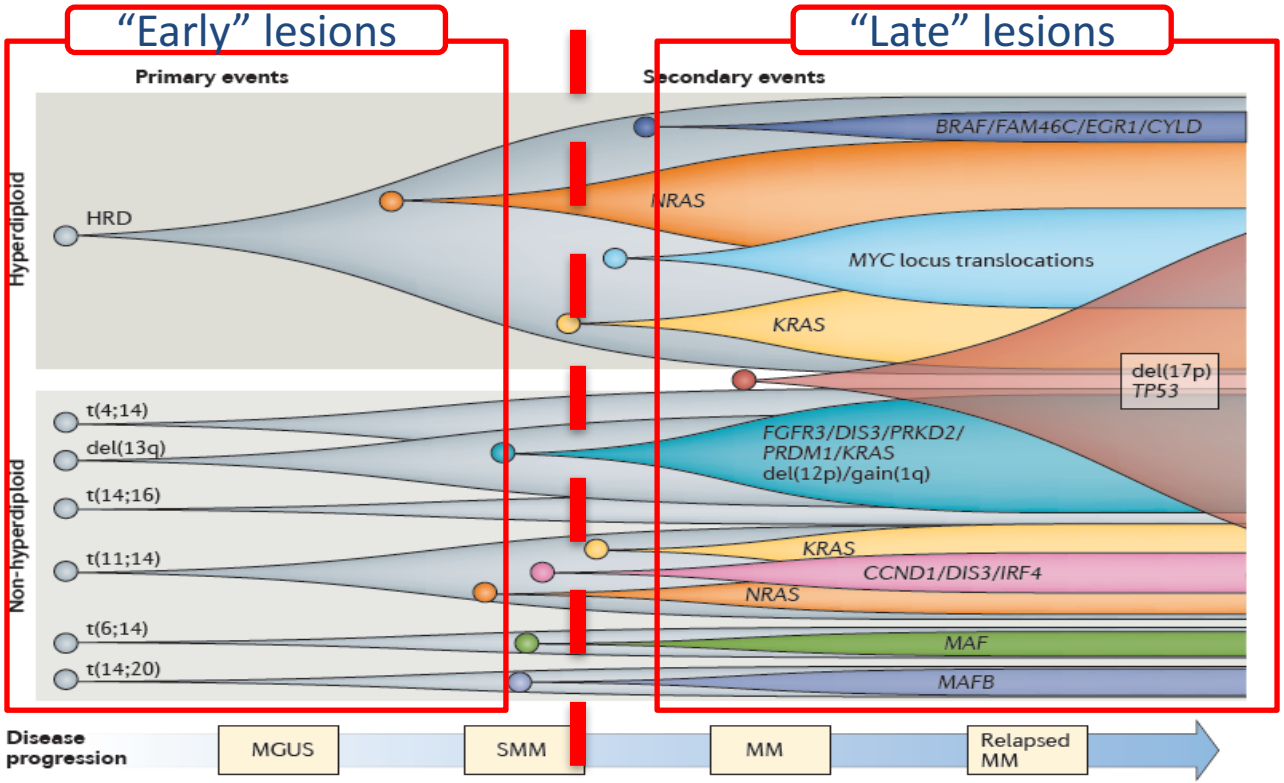
- April 2015: Diagnosed with IgM kappa WM and treated with rituximab/bortezomib/dexamethasone x 5 months
- August 2017: Completed maintenance rituximab x 2 years
  - VGPR
- Currently being observed

Case presentation 12: Dr Brenner

81-year-old man

- 2014: Diagnosed with WM and treated with BR with a good response
- Relapsed disease and multiple comorbidities, including atrial fibrillation on anticoagulation, DM, CAD, CRI (baseline creatinine ~3) and Parkinson's disease

Evolution of genetic aberrations in multiple myeloma



Manier S, et al Nat Rev Clin Oncol. 2016 Aug 17

2014 IMWG diagnostic criteria : a step towards earlier intervention?

Panel: Revised International Myeloma Working Group diagnostic criteria for multiple myeloma and smouldering multiple myeloma

Definition of multiple myeloma

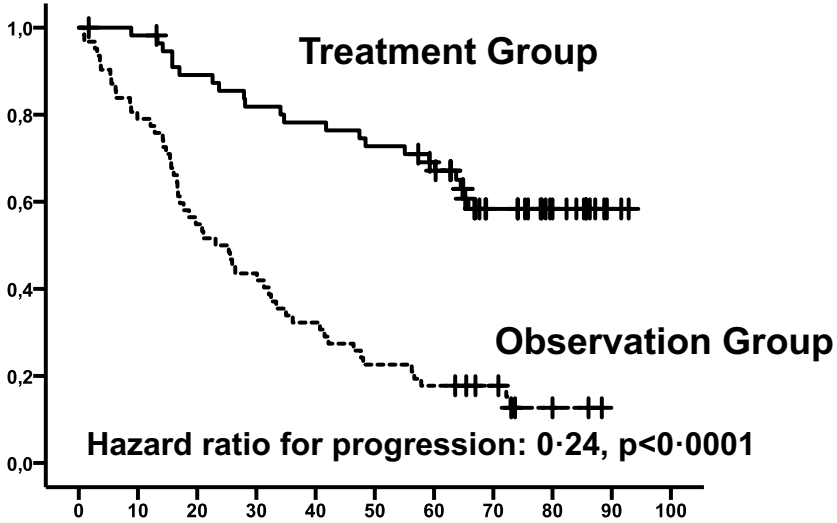
Clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma* and any one or more of the following myeloma defining events:

- Myeloma defining events:
  - Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically:
    - Hypercalcaemia: serum calcium >0·25 mmol/L (>1 mg/dL) higher than the upper limit of normal or >2·75 mmol/L (>11 mg/dL)
    - Renal insufficiency: creatinine clearance <40 mL per min† or serum creatinine >177 μmol/L (>2 mg/dL)
    - Anaemia: haemoglobin value of >20 g/L below the lower limit of normal, or a haemoglobin value <100 g/L
    - Bone lesions: one or more osteolytic lesions on skeletal radiography, CT, or PET-CT‡
  - Any one or more of the following biomarkers of malignancy:
    - Clonal bone marrow plasma cell percentage* ≥60%
    - Involved:uninvolved serum free light chain ratio§ ≥100
    - >1 focal lesions on MRI studies¶

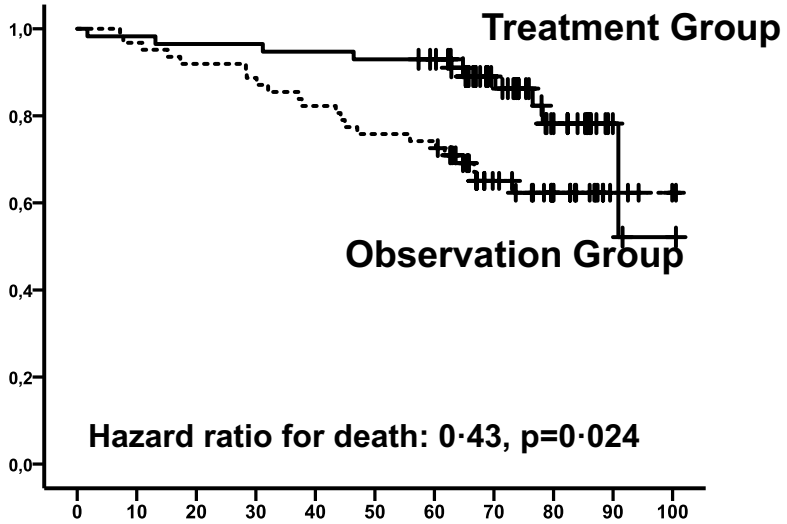
Rajkumar et al. Lancet Oncology 2014; 15: e538-48

High risk Asymptomatic (smouldering) MM
Len-dex vs observation (QuiReDex study)
(Per-protocol Patients' population) (n = 119)

Median follow-up: 75 months



Median follow-up: 75 months



Mateos MV, et al. NEJM 2013
Mateos MV, et al. Lancet Oncology 2016

Should therapy start in patients with asymptomatic myeloma?

- QuiRedex study: early intervention with LenDex in high risk SMM probably improves survival

but …

- We need additional studies to confirm benefit
- New drugs are available
- We now have tools for earlier recognition of high risk patients, means for better staging and identification of bone lesions, use of FLCs and Creatinine clearance
- Closer follow up for patients with high risk disease
  - Who are “high risk” SMM patients ? (different criteria)
- What are the goals of therapy in SMM? Delay of symptomatic disease? CR? MRD^{neg} ?
- How intensively can we aim for these targets ? (toxicity?)

Criteria for the identification of patients with SMM at high risk for progression

	2 year risk of progression
≥10% plasma cells and ≥3 g/dL of M-protein	50%[1]
≥ 20% BM plasma cells (but <60%)	48%[2,3]
One focal lesion in MRI and / or diffuse pattern	<50%[2,4]
Positive PET/CT (without osteolysis)	61%[5]
Positive PET/CT (with osteolysis)	87%[5]
Abnormal FLC ratio (>8 and <100)	<50%[2, 5,6]
95% aberrant plasma cells in Flow cytometry	<50%[7]
High risk cytogenetics	<50%[8]
Evolving increase in M-protein	~64%[3,9]
IgA SMM	<50%[9]
Evolving reduction of Hgb	~65%[3]
Increased circulating plasma cells (⩾150 cPCs)	80%[10]
Evolving reduction of Hgb and M-protein increase	81.5%[3]

[1]Kyle R et al NEJM 2007, [2]Kastritis E et al Leukemia 2013, [3]Ravi P et al BCJ 2016, [4]Hillengass J et al JCO 2010,[5]Siontis B et al BCJ 2015, [6]Dispenzieri A et al Blood 2008, [7]Perez-Persona E et al Blood 2007 ,[8]Neben K et al JCO 2013,[9]Rosinol L BJH 2003, [10]Gonsalves W et al Leukemia 2017

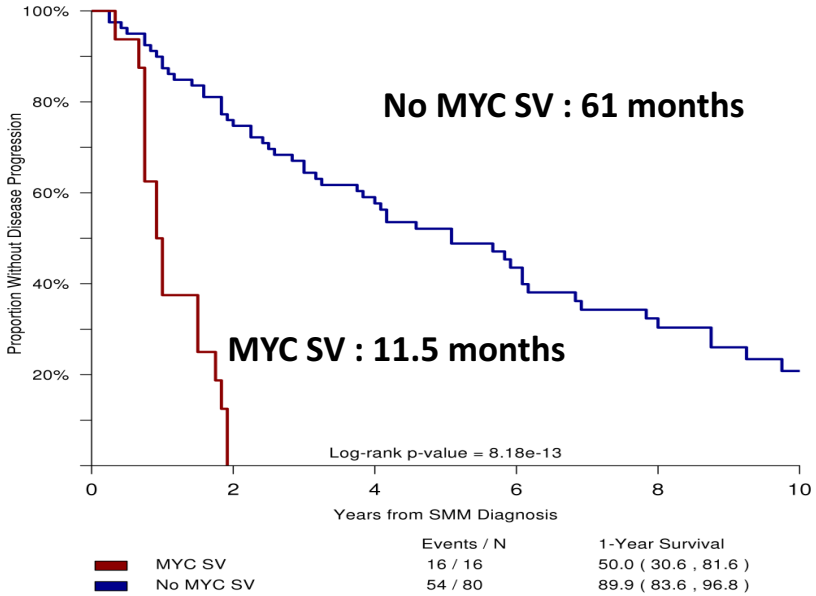
Smouldering Multiple Myeloma: Who are “High risk” patients ?

MYC Translocations Identified By Sequencing Panel in Smoldering Multiple Myeloma Strongly Predict for Rapid Progression to Multiple Myeloma

N=128 patients (32 MGUS) not progressing after 10 years.

SMM with MYC structural variants (SV) TTP of 11.5 vs 61 month; p<0.0001.

Multivariate analysis : MYC SV an independent variable for progression to MM (hazard ratio=7, 95% confidence interval 3.6-13.7, p=0.00001).



***Niamh Keane N et al ASH 2017* Abstract #393**

Original Investigation

Treatment With Carfilzomib-Lenalidomide-Dexamethasone With Lenalidomide Extension in Patients With Smoldering or Newly Diagnosed Multiple Myeloma

8 cycles KRd Combination Therapy

Carfilzomib 20/36 mg/m^2, day 1, 2, 8, 9, 15, 16

Lenalidomide 25 mg/day, day 1-21

Dexamethasone 20/10 mg, day 1,2, 8,9,15,16,22,23

SD or better?

24 cycles Rev Extended Dosing

Lenalidomide 10 mg/day, day 1-21

- Each cycle is 28 days
- Stem cell harvest after ≥4 cycles of CRd for patients <70-75 yrs
- C1D1/2 – Carfilzomib dose is 20 mg/m^2
- C1- 4 – Dex dose is 20 mg, C5- 8 – Dex dose is 10 mg

Response after	2 cycles	8 cycles	20 cycles	Overall
Best Response, No. (%)				
CR or sCR	1 (8)	8 (73)	3 (100)	12 (100)
nCR	0	3 (27)	0	0
VGPR	5 (42)	0	0	0
PR	6 (50)	0	0	0
SD	0	0	0	0
Best Overall Response,				
At least nCR	1 (8)	11 (100)	3 (100)	12 (100)
At least VGPR	6 (50)	11 (100)	3 (100)	12 (100)
ORR, at least PR	12 (100)	11 (100)	3 (100)	12 (100)

Korde N et al al JAMA Oncol 2015

New treatment paradigms in AL amyloidosis

1. Reduction or elimination of toxic light chains is the primary goal
    1. Deeper responses → better outcomes
    2. Faster responses → better outcomes

2. Strategies to enhance fibril absorption or degradation
    1. Monoclonal antibodies targeting amyloid fibrils

Treatment of AL amyloidosis

- Standard of care: Bortezomib combos →VGPR/CR~ 50%
- Risk adapted therapy

Low risk (Mayo stage 1)	Intermediate risk (Mayo stage 2 & 3A)	High risk (Mayo stage 3B)
ASCT in eligible patients or CyBorD /VCD or BMDex	CyBorD/VCD or BMDex or ASCT in eligible patients	Low dose Bortezomib regimens

- Can the activity of Bortezomib regimens improve further?
  - Faster responses
  - Deeper responses
  - Sustained responses

IMiDs for AL amyloidosis

Regimen	No (% 1st Line)	HR (CR)	Organ Resp.	Common SAEs	100-d mortal.	PFS / OS (y)
CTD *Wechalekar 2007*	75 (41%)	74% (21%)	27%	Sedation Fluid retention	4%	1.7 / 3.4
RD+ *Dispenzieri 2007* *Sanchorawala 2007*	22 (41%) 34(9%)	41% 67% (21%)	23% 21%	Neutropenia, Fatigue	18% 3%	1.6 / - - /-
RCd# *Kastritis 2012* *Kumar 2012* *Cibeira 2015*	37(65%) 35 (69%) 28 (100%)	55%(8%) 77%(11%) 46%(25%)	22% 29% 46%	Neutropenia Fatigue	19% ~10% 36%	10 mos / 1.5 y 7.4 mos/~3y 54%@2y /59%@2y
Mdex-R *Moreau 2010*	26 (100%)	58% (23%)	50%	Neutropenia, Fatigue	-	@2y 54% / 81%
PomDex *Dispenzieri 2012* *Palladini 2013*	33 (0)	48% (3%)	15%	Neutropenia	3%	1.2 / 2.3

New Treatments for AL amyloidosis: unmet needs

- Enhanced activity in order to achieve faster and deeper responses, especially in high risk patients

- Safety: Patients with AL are vulnerable to toxicities (cardiac toxicity , neurotoxicity, GI toxicity)

- Durability of responses

Daratumumab in AL amyloidosis retrospective data

- Daratumumab in AL amyloidosis: rapid activity, no cardiac toxicity, no myelotoxicity

– N=25 consecutive **previously treated AL patients**

– 72% cardiac involvement

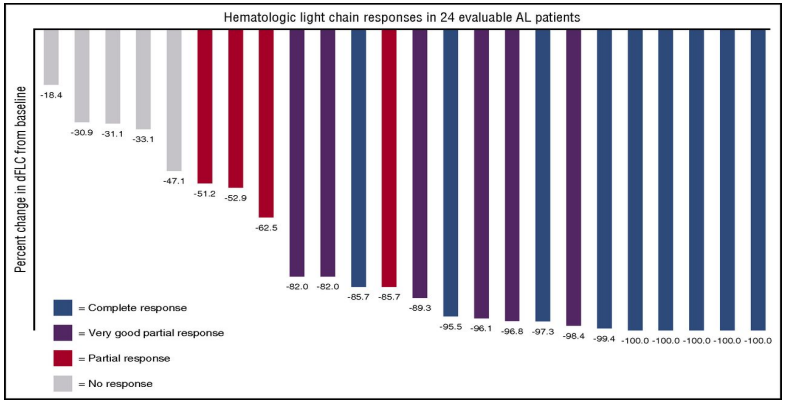
– median: 3 prior lines

– Daratumumab standard dose and schedule

– HemORR : 76% (CR: 36%, VGPR: 24%).

– Median time to response: 1 month.

– no Gr3- 4 IRRs ; Gr1-2: 15/24 patients.



Kaufman GP et al Blood 2017

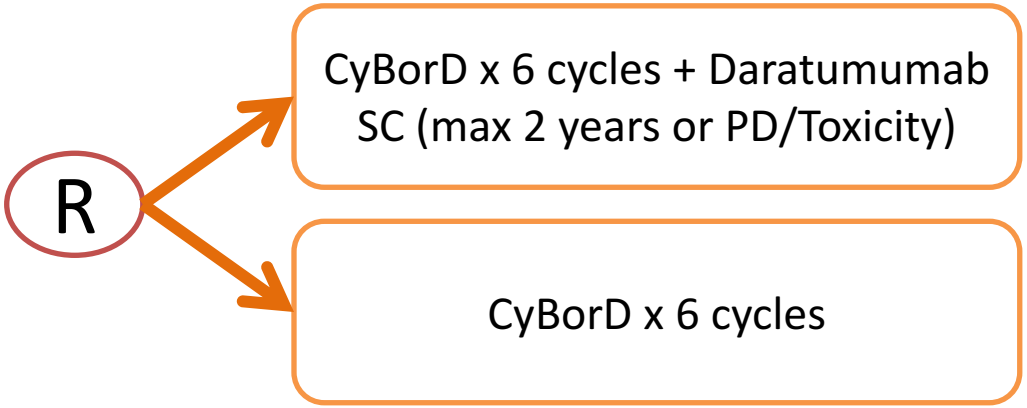
Daratumumab in AL amyloidosis: Phase 2 data

	V Sanchorawala et al #507	M Russel et al #508
Number of patients	8	30 (24 evaluable)
Cardiac AL	100%	60%
Prior therapies	3 (1-6)	2.5 (1-5)
Prior HDM/ASCT	6 (75%)	NR
IMiDs	5 (62.5%)	46%
PIs	7 (87.5%)	93%
ORR	7 (87.5%)	63%
CR / VGPR	- / 6 (75%)	4 (17%) / 7 (29%)
Toxicity	IRR Gr1-2: 25%	IRR Gr1-2: 33%

- Daratumumab given IV
- Highly active as monotherapy , Safe and tolerable
- Selected patients (R/R AL) able to receive multiple lines of therapy prior to Dara
- Cannot extrapolate these results for newly diagnosed AL patients

Daratumumab in AL amyloidosis: Phase 3 study in newly diagnosed AL (stage 1-3A)

Previously untreated AL patients with measurable disease
Mayo stage I-IIIA (IIIB excluded)



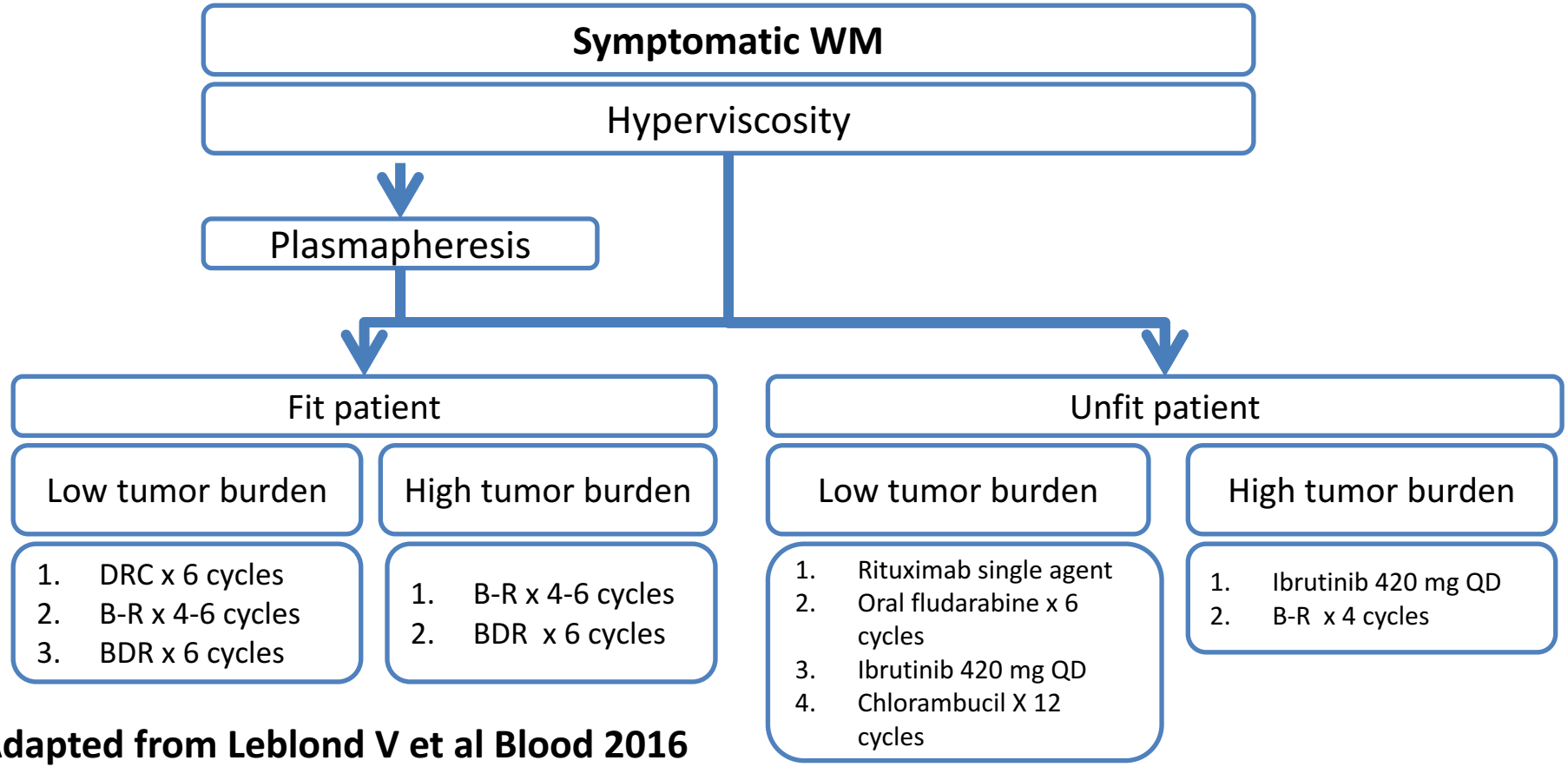
Primary Outcome: Overall Complete Hematologic Response

Secondary Outcomes : Major Organ Deterioration Progression-Free Survival (MOD-PFS), Progression-Free Survival (PFS), Organ Response Rate (OrRR), Overall Survival (OS), QOL measurements, Time to Next Treatment (TNT), Hematologic VGPR, Time to CR, VGPR, Duration of CR, Time to Organ Response, Duration of Organ Response

CyBorD: dexamethasone (40 mg PO or IV, followed by cyclophosphamide (300 mg /m^2 PO or IV), then bortezomib (1.3 mg/m^2 SC) weekly on Days 1, 8, 15, 22 in every 28-day cycle for a maximum of 6 cycles.

ClinicalTrials.gov Identifier: NCT03201965

Treatment of Waldenström's Macroglobulinemia



Adapted from Leblond V et al Blood 2016

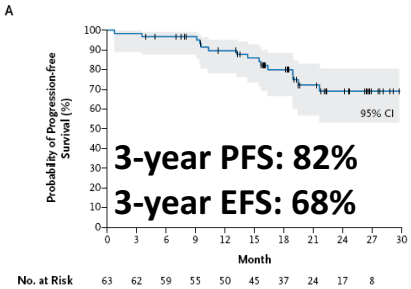
Ibrutinib in the treatment of Waldenström's Macroglobulinemia

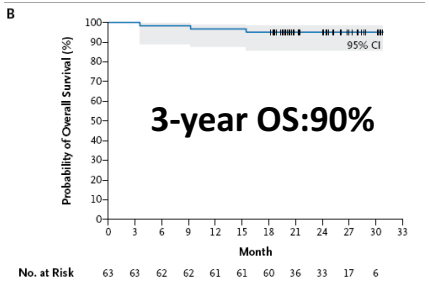
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Ibrutinib in Previously Treated Waldenström's Macroglobulinemia

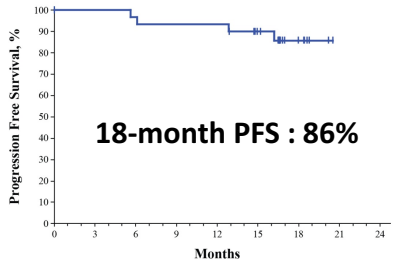
Steven P. Treon, M.D., Ph.D, Christina K. Tripsas, M.A., Kirsten Meid, M.P.H., Diane Warren, B.S., Gaurav Varma, M.S.P.H., Rebecca Green, B.S., Kimon V. Argyropoulos, M.D., Guang Yang, Ph.D., Yang Cao, M.D., Lian Xu, M.S., Christopher J. Patterson, M.S., Scott Rodig, M.D., Ph.D., James L. Zehnder, M.D.,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

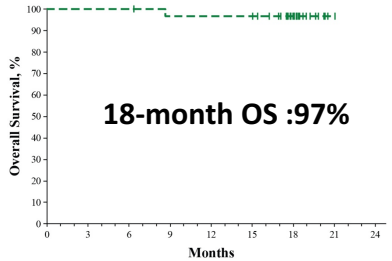




Ibrutinib for patients with rituximab-refractory Waldenström's macroglobulinaemia (iNNOVATE): an open-label substudy of an international, multicentre, phase 3 trial

*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, on behalf of the iNNOVATE Study Group and the European Consortium for Waldenström's Macroglobulinemia**





Treon SP et al NEJM 2015

Dimopoulos MA et al Lancet Oncol 2017

Treatment of Waldenström's Macroglobulinemia

- Ibrutinib is a new standard of care for patients with relapsed WM and especially for rituximab refractory patients

- Several open questions:
  - What is the role of ibrutinib in newly diagnosed patients?
  - What is the optimal duration of therapy? Is continuous therapy feasible ?
  - What ibrutinib-containing combinations can be used to improve efficacy (deeper responses) and limit duration of therapy ?
  - What are the treatment options after ibrutinib failure?

Treatment of Waldenström's Macroglobulinemia

PCYC-1127 (iNNOVATE™) Study Design

Key eligibility criteria

- Confirmed WM (N=~150)
- Measurable disease (serum IgM > 0.5 g/dL)
- ECOG PS status of 0–2

RANDOMIZE 1:1

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

Arm B*
placebo + rituximab
3 matching placebo capsules until PD
Rituximab 375 mg/m2 IV
on day 1 of weeks 1-4 and weeks 17-20

*crossover to ibrutinib for patients treated with placebo confirmed disease progression (by IRC) and disease requiring treatment.

- If refractory to last rituximab-containing regimen defined as
  - Relapse after <12 months of treatment OR
  - Failure to achieve at least a MR

Arm C (Open-label substudy; N=31)
Not eligible for randomization

ibrutinib 420 mg once daily PO until PD

Ibrutinib Discontinuation in Waldenström Macroglobulinemia: Etiologies, Outcomes, and IgM Rebound

- N=189 WM patients received ibrutinib → 51 (27%) discontinued ibrutinib.
- Ibrutinib discontinued due to
  - PD in 27 patients (53%)
  - toxicity in 29%
  - non-response in 10%
  - miscellaneous in 8%
- IgM rebound after ibrutinib discontinuation: 37/51 patients (73%)
- 6 patients (16%) required plasmapheresis.
- 38/51 (76%) received salvage therapy - ORR to salvage: 73%
- Regimens used after ibrutinib: anti-CD20+alkylator (ORR: 16/22; 73%), PI(4/5; 80%), NAs (2/2; 100%), BCL2 inhibitor (3/5; 60%), other (2/5; 40%).
- Median OS following discontinuation of ibrutinib was 32 months.

Gustine J et al ASH 2017 **Abstract #802**

Ibrutinib Is Highly Active As First Line Therapy in Symptomatic Waldenström's Macroglobulinemia

- N=30 patients with newly diagnosed WM (median age 67)
- All patients expressed $MYD88^{L265P}$ - 14 (47%) had a $CXCR4^{mut}$.
- ORR: 96.7% , ≥PR: 80%, VGPR: 17% - No CRs
- Median follow-up: 8.1 months, two patients PD, both $CXCR4^{mut}$
- Three patients (10%) had treatment-related atrial arrhythmia
- $CXCR4^{mut}$ associated with delays in ibrutinib response

(ClinicalTrials.gov number, NCT02604511).

Treon SP et al ASH 2017 **Abstract #2767**