Myeloma Pathogenesis with a Focus on the Immune System

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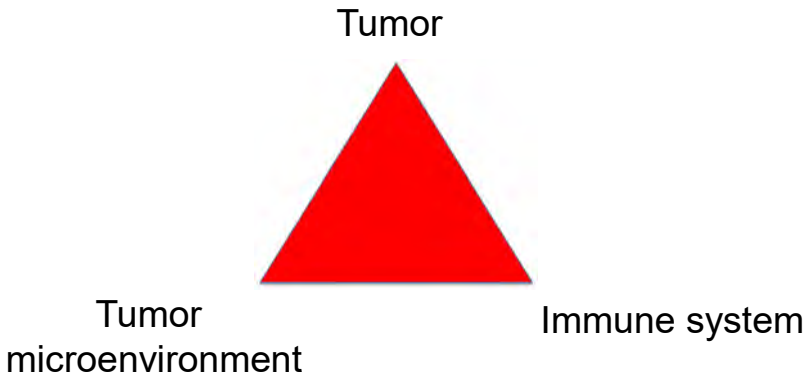
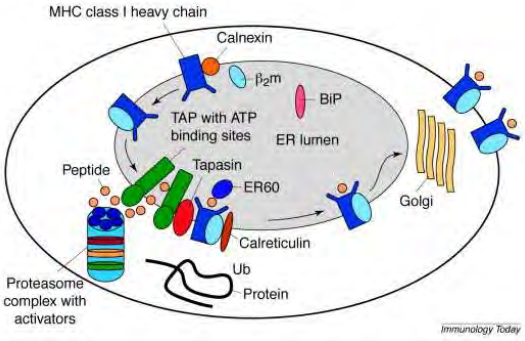
Potential Mechanisms of Immune Evasion



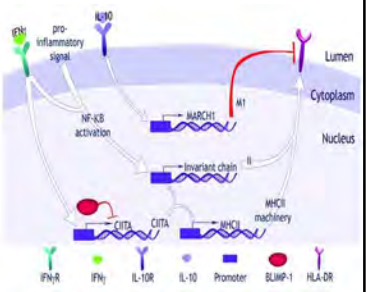
Antigen Processing Pathways

HLA Class I



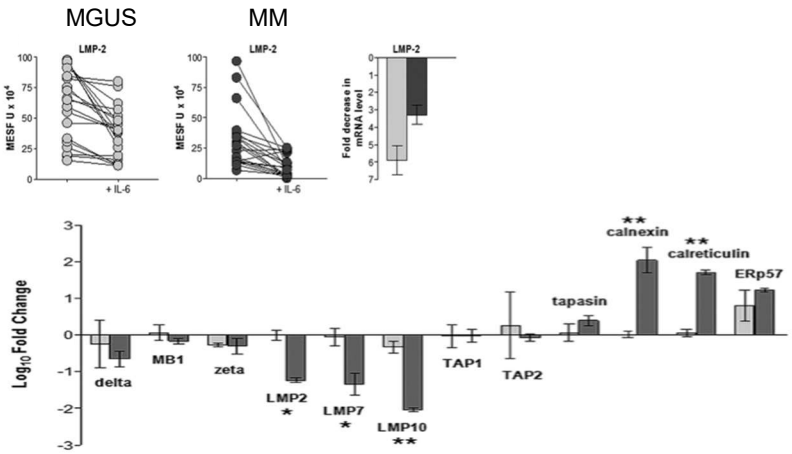
Seliger et al Imm Today: 21, 9, 2000

HLA Class II



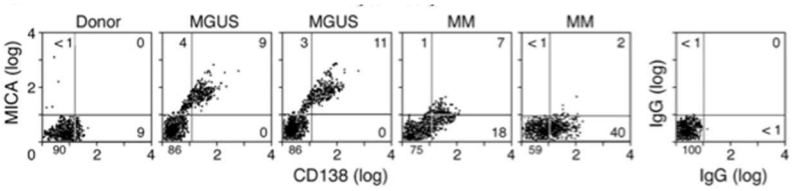
Thibodeau Oncoimm 2012

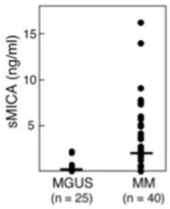
Expression of APM in MGUS and MM



Vito Racanelli et al. Blood 2010;115:1185-1193

MICA Expression

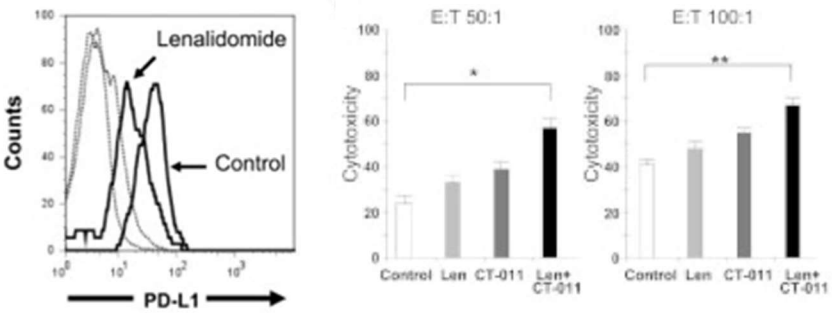




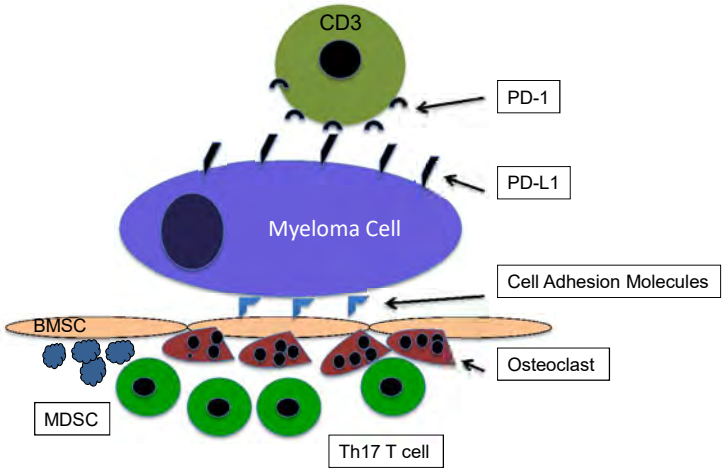
MHC Class I chain related protein A (MICA)
-NKG2D ligand
-expressed in early stage disease
-secreted with advanced MM
-sMICA suppresses effective APC cross presentation

Masahisa Jinushi et al. PNAS 2008;105:1285-1290

PD-L1 is Upregulated in MM and Modified by Lenalidomide

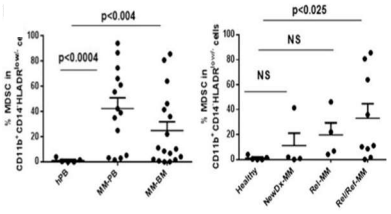


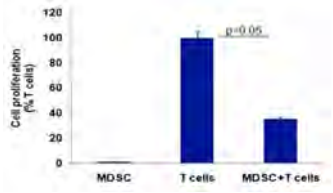
Benson et al Blood 2010 Sep 30; 116(13):



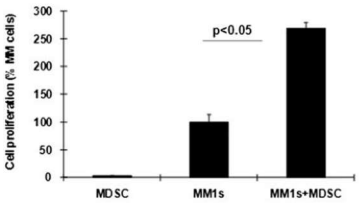
MDSCs in Myeloma

MDSC Effect on T cells



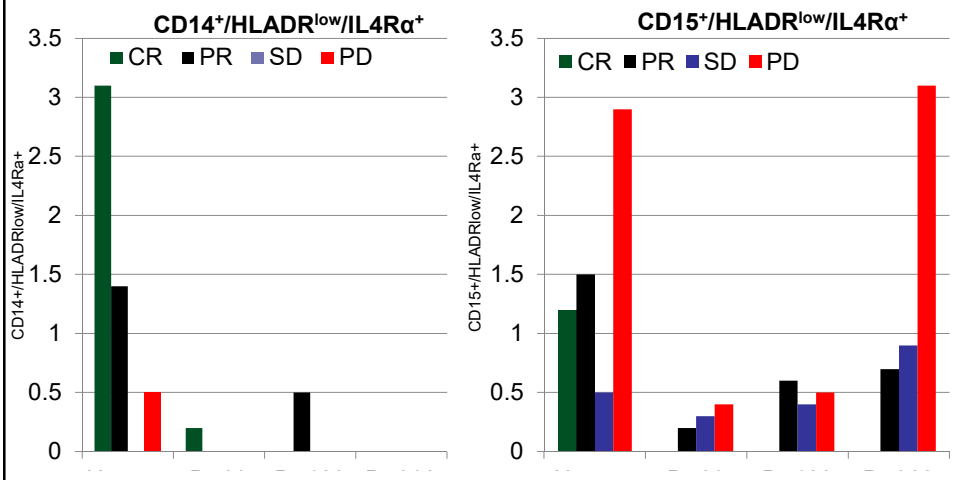


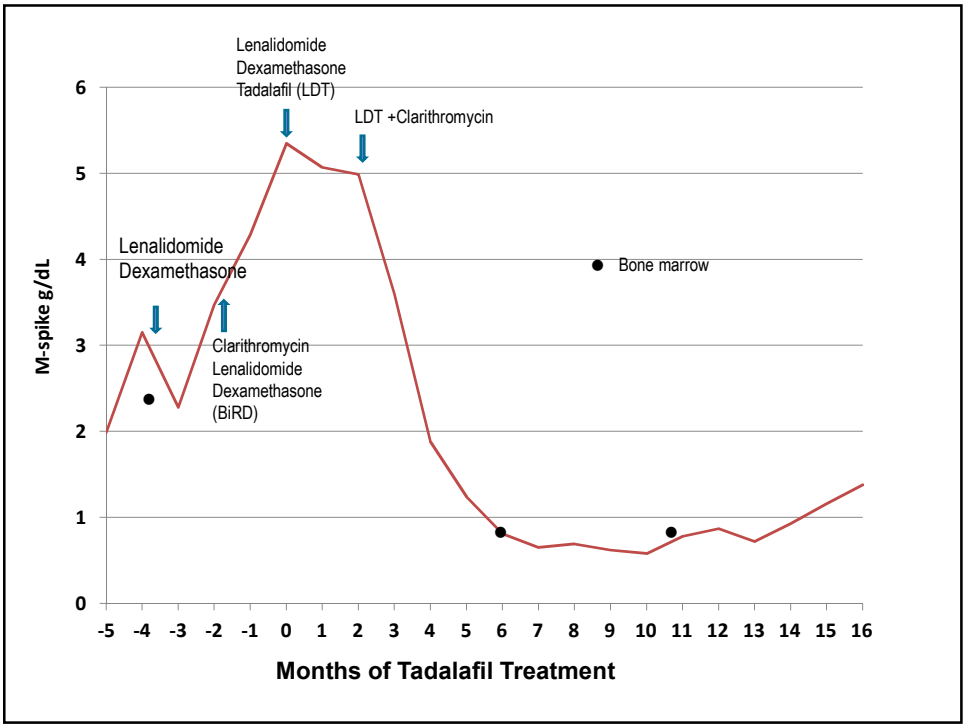
MDSC Effect on Myeloma



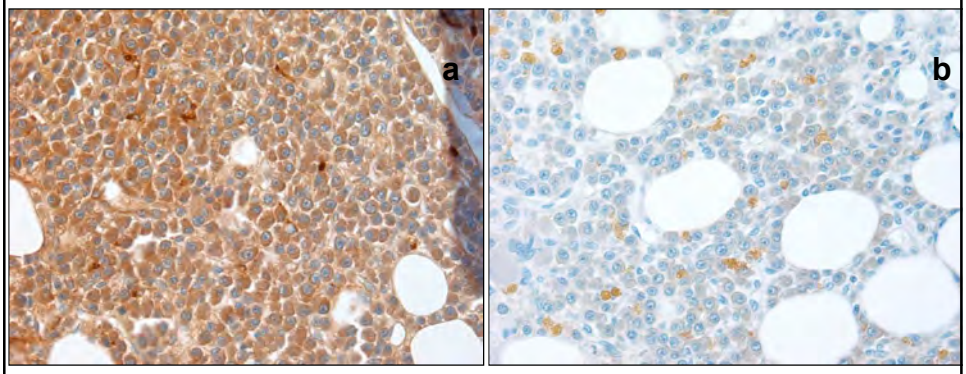
Güllü Topal Görgün et al. Blood 2013;121:2975-2987

MDSC Numbers Correlate with Clinical Responses to SCT





Effect of PDE5 Inhibition on Nitrosylation



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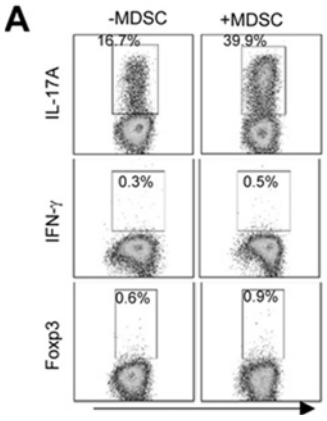
MDSCs Induce a Th17 Phenotype

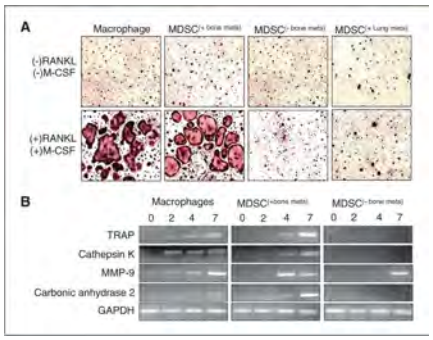


- Autoimmune disease (EAE) is associated with significant expansion of MDSCs
- MDSCs facilitate expansion of Th17 cells

YI, H JI Nov 2012

12

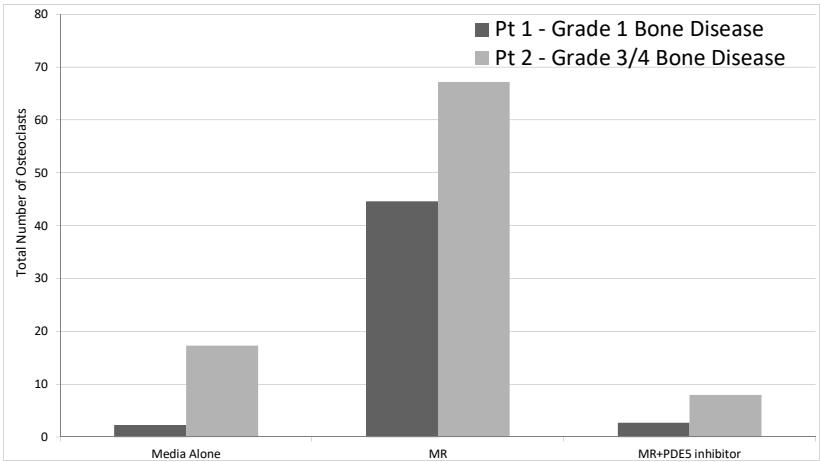
MDSCs from bone metastases induce OC differentiation

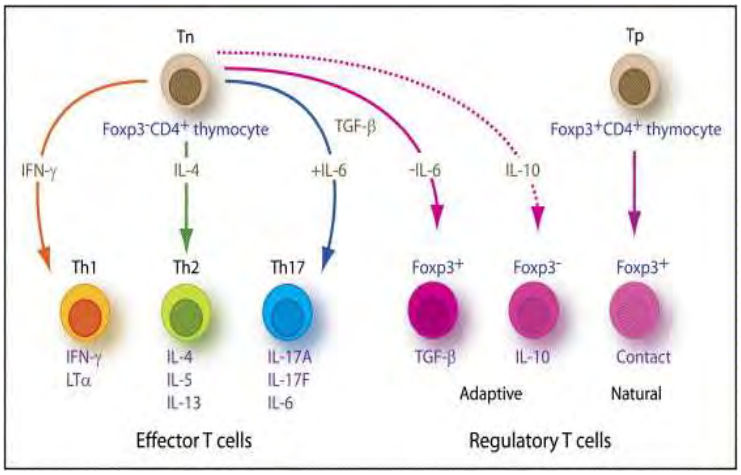


- MDSCs from active bone disease show more OC precursors
- Overexpress: iNOS, ROS, HIF1α
- Nitric oxide essential for OC differentiation

Sawant, A Cancer Res. 2013 Jan 15; 73(2): 672–682.

PDE5 Inhibitors Prevent OC Differentiation





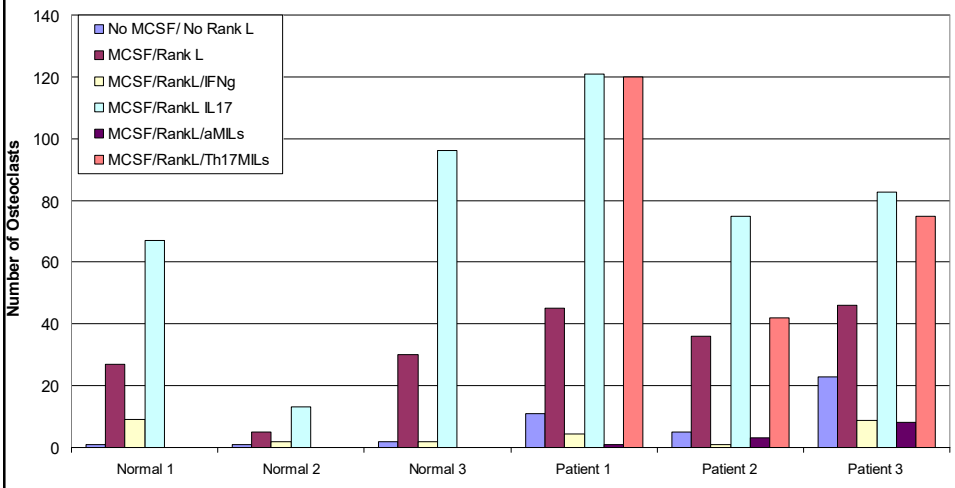
Th17 Profile of Myeloma BM Plasma

	Myeloma BM	Normal BM	Myeloma PBL	Normal PBL
TGF-β (µg/ml)	59.9	52.6	17.5	16.1
IL-6 (pg/ml)	29.6	3.7	6.5	2.3
IL-23 (pg/ml)	246.4	35.9	19.6	18
IL-17 (pg/ml)	12.2	5.1	0.4	0

Patient N= 56
Normal N=3

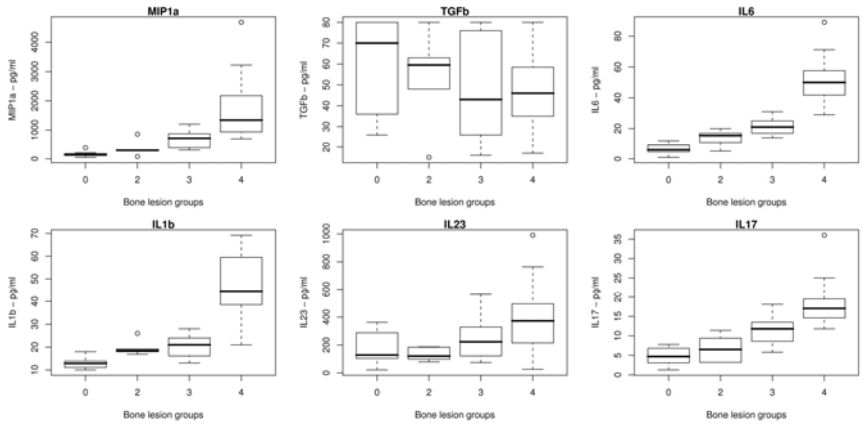
Noonan et al Blood Nov 2010

Addition of IL-17 or Th17 MILs to Osteoclast Culture Increases Outgrowth



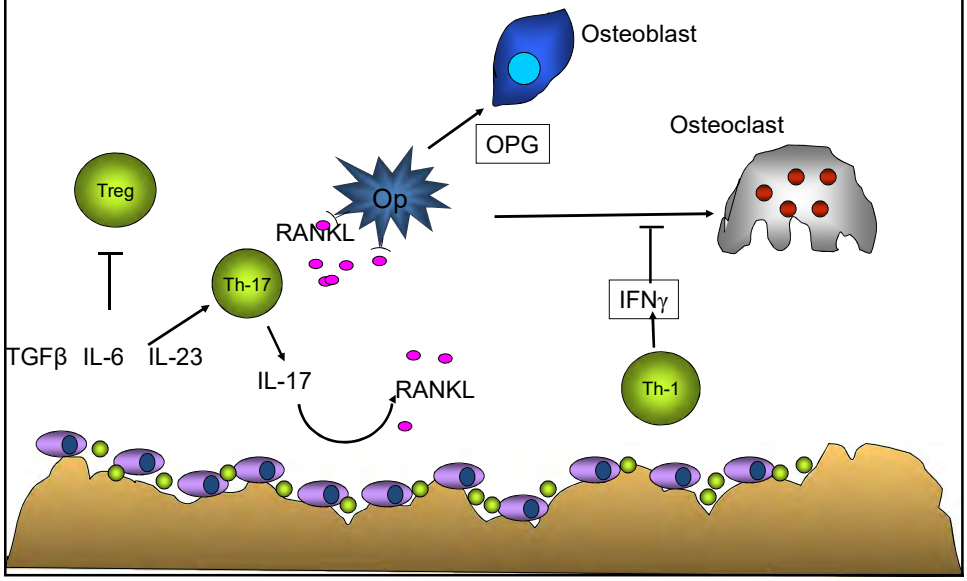
Noonan et al Blood Nov 2010

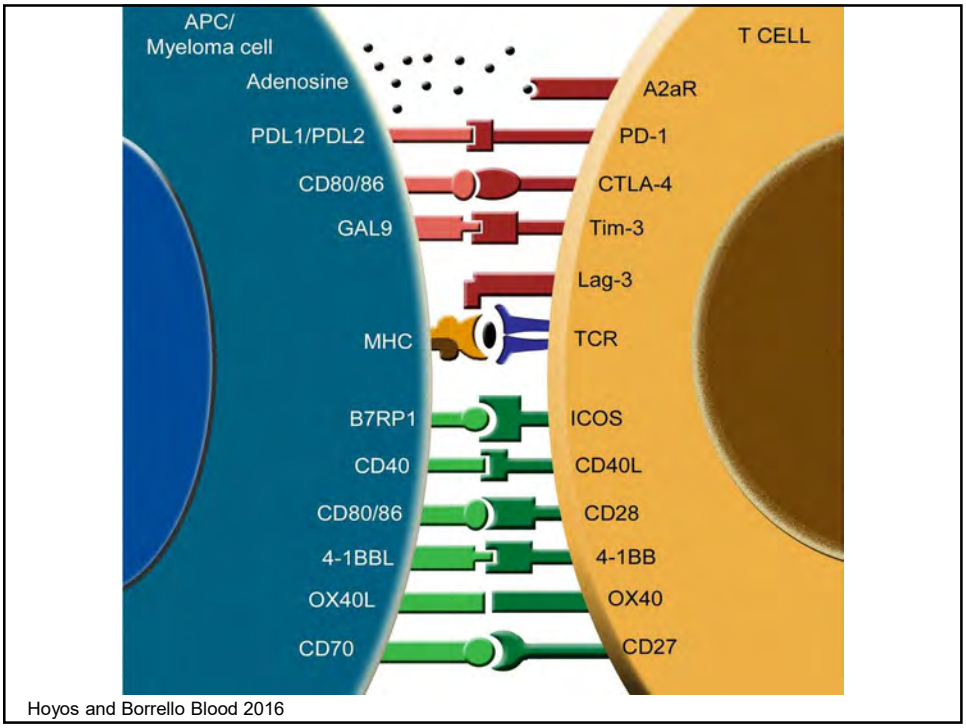
Th17 Phenotype Correlates with Lytic Bone Disease



Noonan et al Blood Nov 2010

Role of Th17 Cells in Myeloma Bone Disease

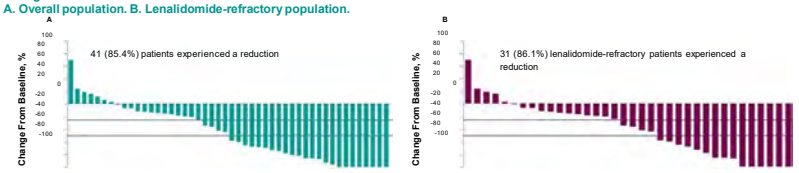




Hoyos and Borrello Blood 2016

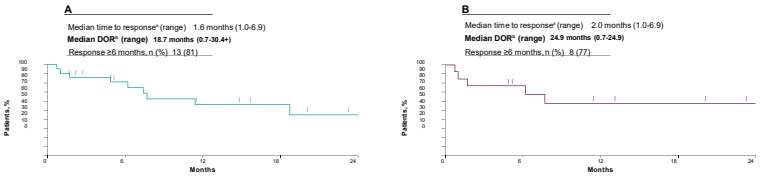
Pembrolizumab in Relapsed Myeloma

Change From Baseline in Disease Burden
A. Overall population. B. Lenalidomide-refractory population.



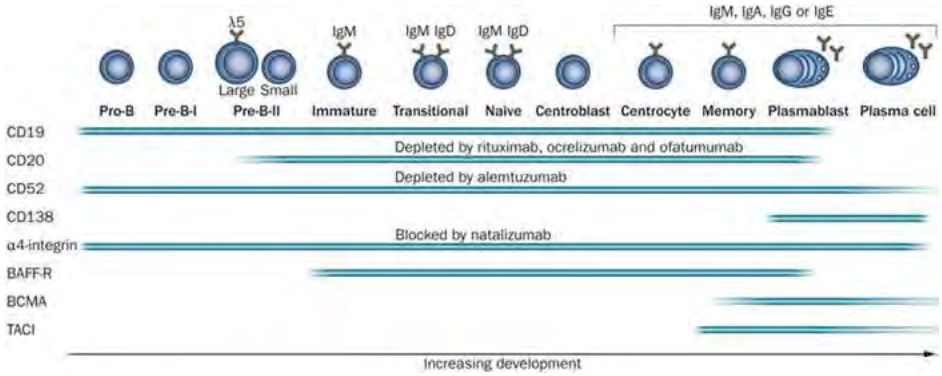
[a]12 patients were not included because they did not have ≥2 postbaseline efficacy assessments and/or had major protocol violations.

Duration of Response. A. All responders (n = 22). B. Lenalidomide-refractory responders (n = 13).

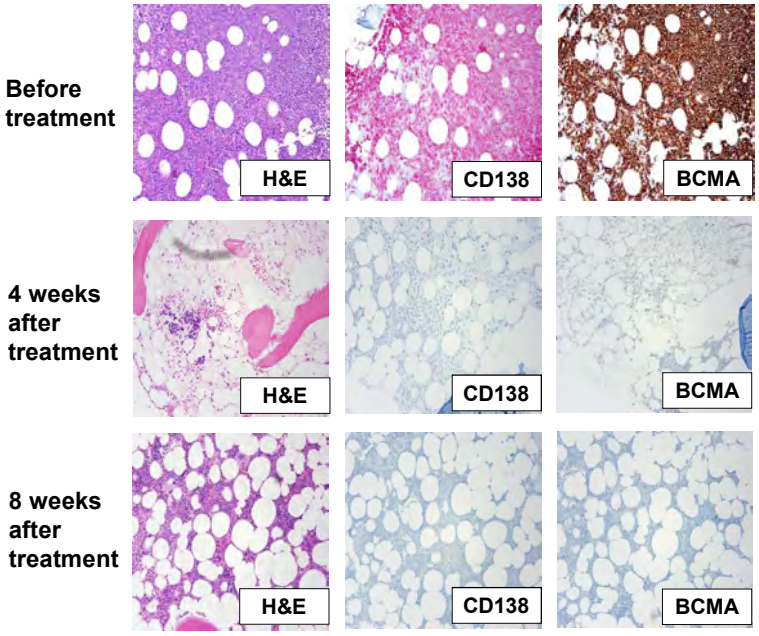


DOR, duration of response.
[a]No progressive disease at last assessment
[b]Best objective response as stringent complete response, complete response, very good partial response, or partial response
[c]From Kaplan-Meier method

Expression of Surface Markers in B cell Development



CAR-BCMA Effectively Eradicates Disease



Conclusions

- Immune suppression in tumor microenvironment in myeloma increases from MGUS to active MM
- Mechanisms of immune escape include
  - Downregulation of HLA expression
  - Dysfunction of antigen presentation
  - Increase in MDSCs
  - Development of Th17 cells
  - Increase in PD-L1 expression
  - Upregulation of PD-1 expression on T cells
- Immune therapy can show clinical benefits several of these pathways including:
  - PD-1 blockade
  - CAR-T cells targeting BCMA
  - Vaccines
  - Immunosuppressive pathways: Th17, MDSCs

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Genetics in Myeloma; The Basics

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Rochester, Minnesota

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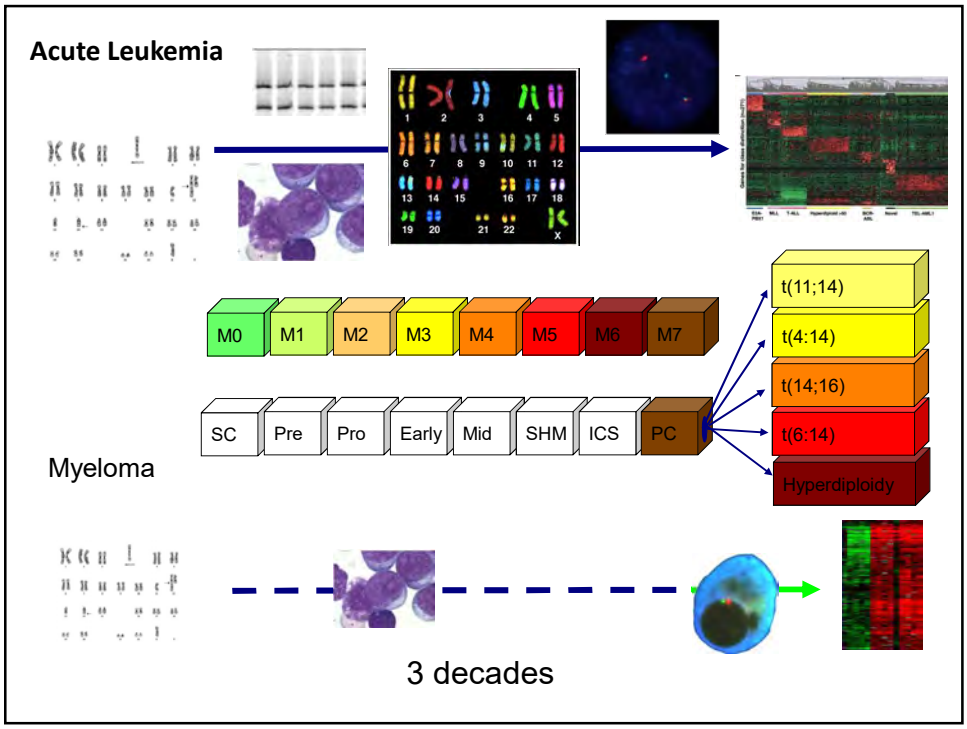
Mayo Clinic College of Medicine
Mayo Clinic Comprehensive Cancer Center

MAYO CLINIC

Disclosures

- Consulting:
  AMGEN, BMS, Celgene, Takeda, Bayer, Jansen, Novartis, Pharmacyclics, Sanofi
- Speakers Bureaus: None
- SAB: Adaptive Biotechnologies
- Patent for FISH in MM - ~$2000/year
- Registered independent – Libertarian
- Believe in stem cell transplant
- Dislike wasting your time with this slide



Methodological Evolution in Whole Genome Studies

Conventional cytogenetics

SKY

CGH

Resolution 10-20Mb

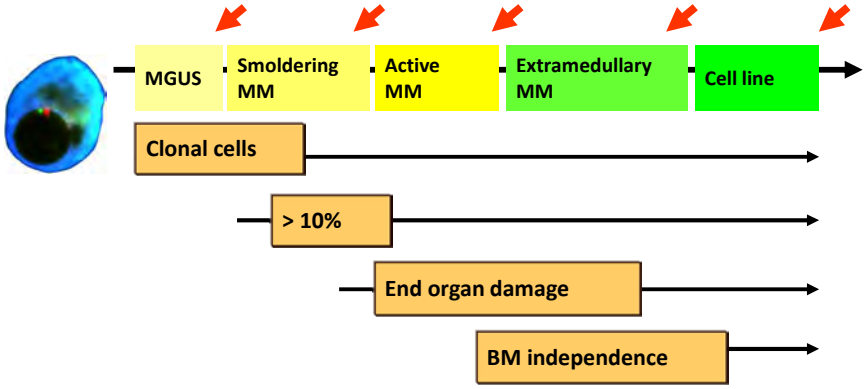
aCGH

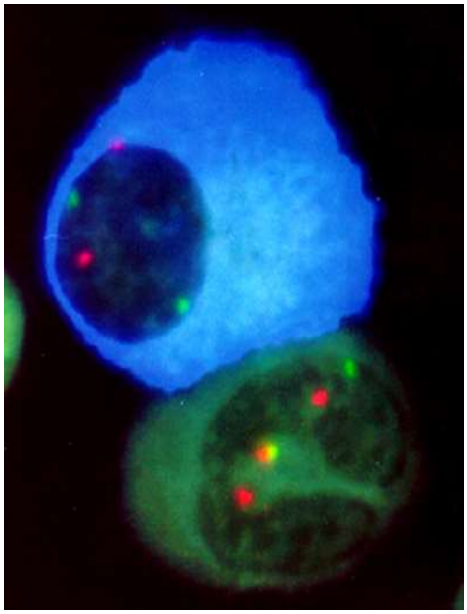
3-5Kb

Second and third generation sequencing

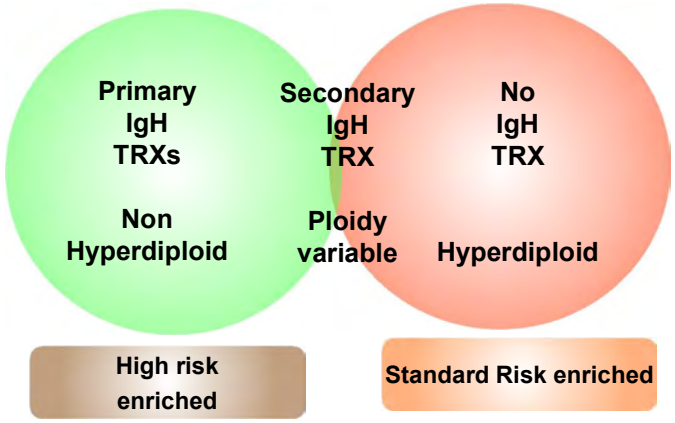
1bp

Plasma Cell Neoplasms



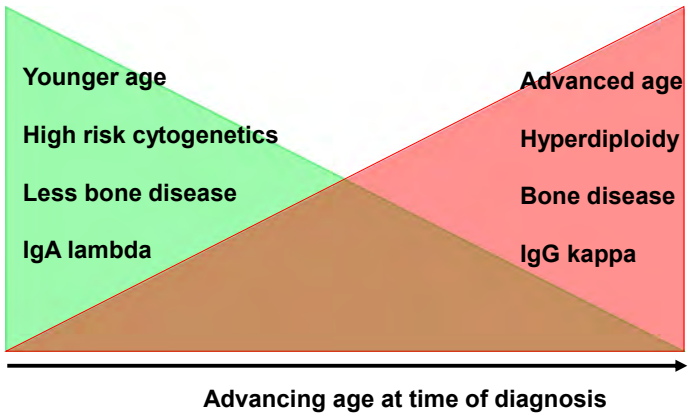


Genetic Classification of MM

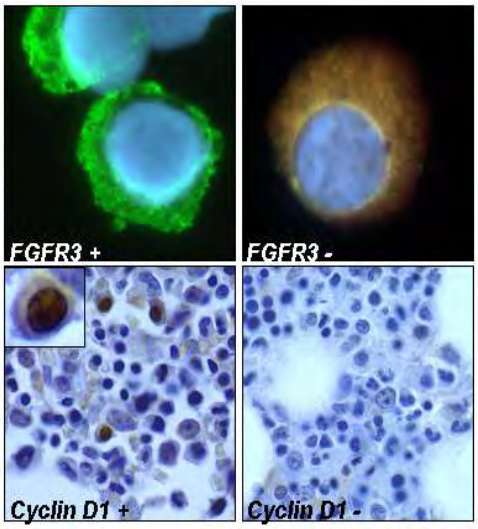


Fonseca Blood 102:2562, 2003

Inverse Relationship in MM

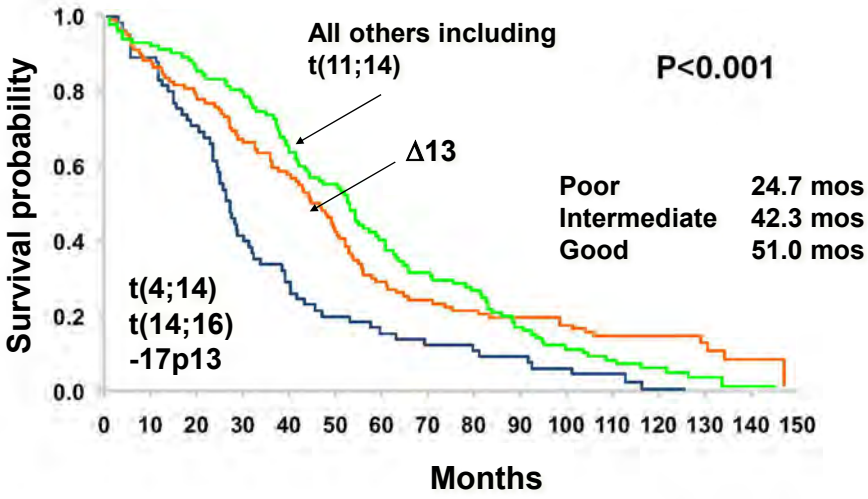


IgH Translocations



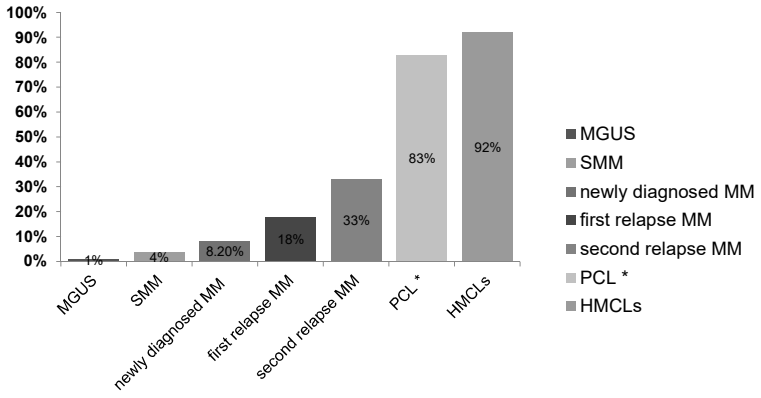
Fonseca et al *Blood* 100:1417

Molecular Prognostic Model



Fonseca et al *Blood* 101:4569, 2003

P53 deletion/mutation



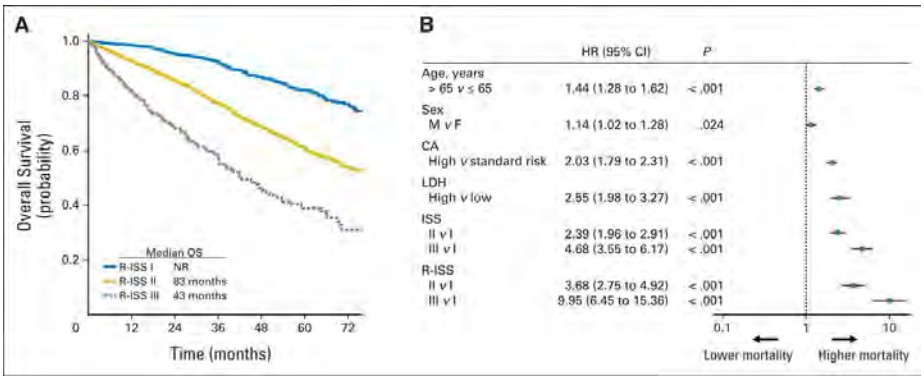
Studied 8 patients with 17p deletions at RR 7 did not have deletion at diagnosis

FISH (MGUS n=184, SMM n=116, relapsed MM n=62 and PCL n=26)
aCGH (newly diagnosed MM n=224, relapsed MM n=158 and HMCLs n=48)
p 53 mutational status was evaluated in relapsed MM (n=84) and HMCLs (n=48)

Tiedemann et al. Leukemia. 2008; 22, 1044-1052

Revised ISS Model

- **Revised system based on ISS (b2-microglobulin and albumin)**
- **Incorporates high risk cytogenetics and elevated LDH**
- **Creates model**
  - **Stage 1 Stage I ISS and cytogenetics and LDH favorable**
  - **Stage 2 The rest**
  - **Stage 3 Stage III ISS plus either high risk or high LDH**



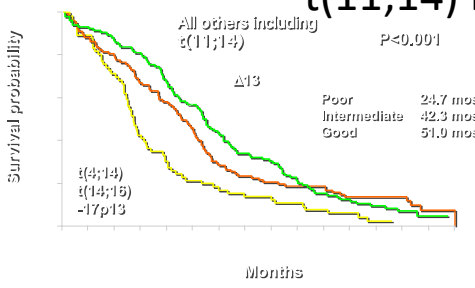
Palumbo et al JCO 33, no. 26 2863-2869

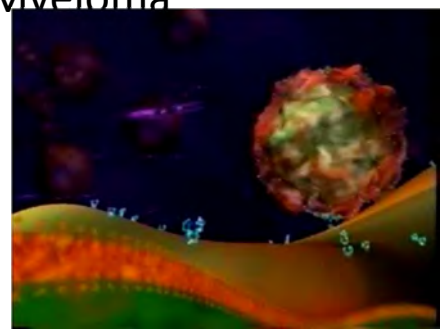
Why bother with genetics?

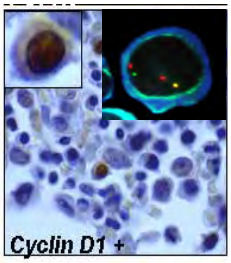
- Important for counseling
- Important for therapy selection
- Becoming predictive

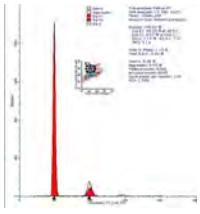
- Don't waste money on
  - Cytogenetics
  - Flow cytometry

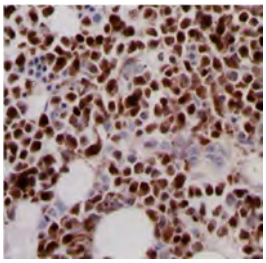
t(11;14) Myeloma



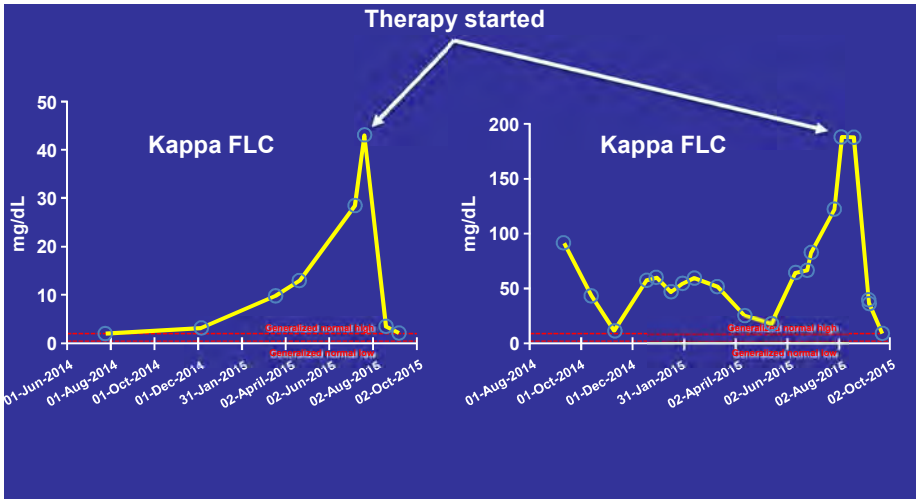




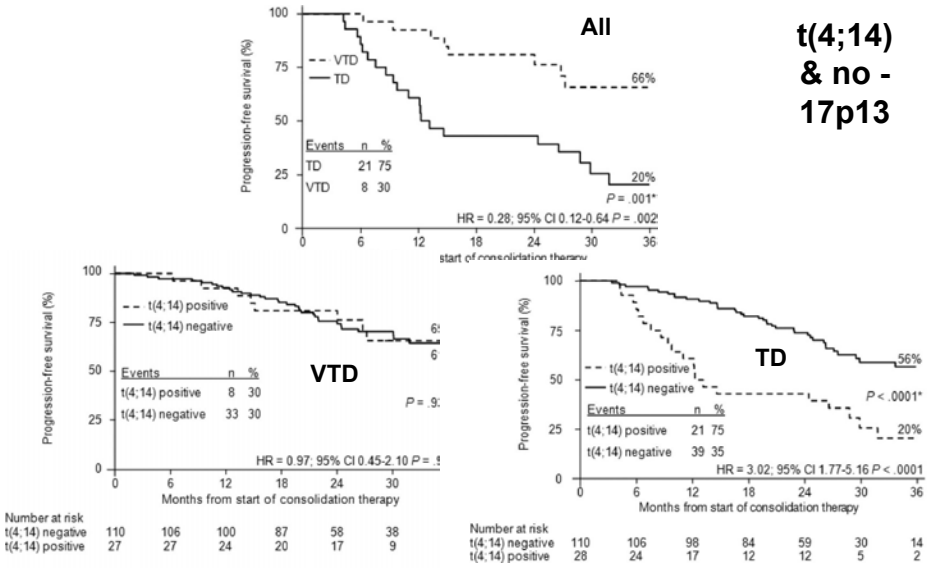




Venetoclax in t(11;14) MM

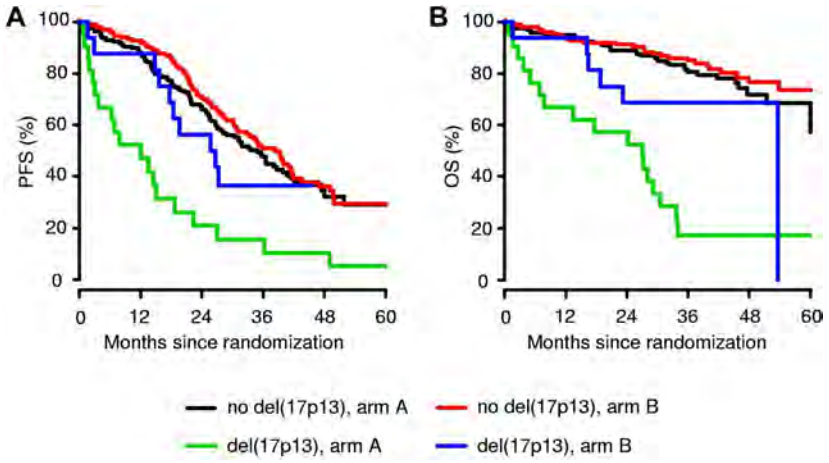


Landmark Start of Consolidation



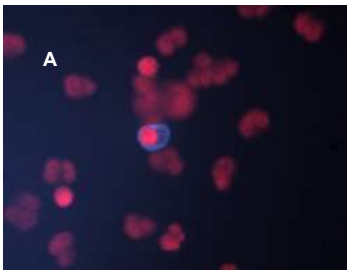
Cavo M et al. Blood 2012;120:9-19

Effects of Bortezomib on -17 MM

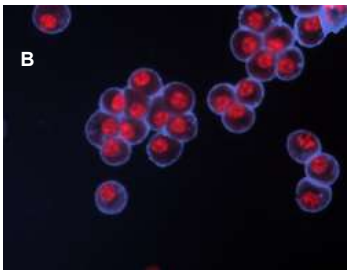


Neben K et al. Blood 2012;119:940-948

For Genomic Studies Need to Sort Cells

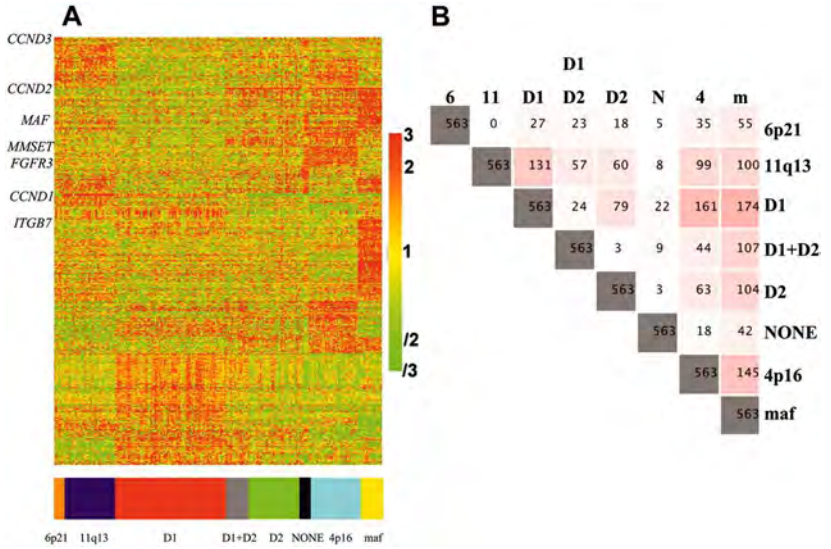


A: An ACK (ammonium chloride) lysed bone marrow from a patient with 6% lambda (AMCA) positive myeloma cells. The blue cytoplasm is AMCA conjugated Goat anti human lambda light chain. The cell nuclei were counterstained with Propidium Iodide (red).



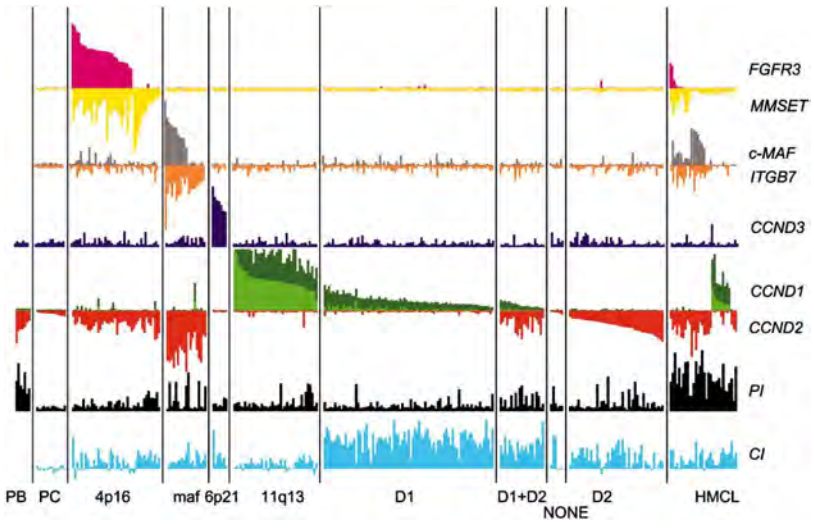
B: The same patient after CD138 bead selection using the Miltenyi autoMACS. Cells were stained with AMCA conjugated Goat anti-human lambda light chain (blue). The cell nuclei were counterstained with Propidium Iodide (red). The sample was determined to be >95% Lambda positive plasma cells.

Clustering Patterns



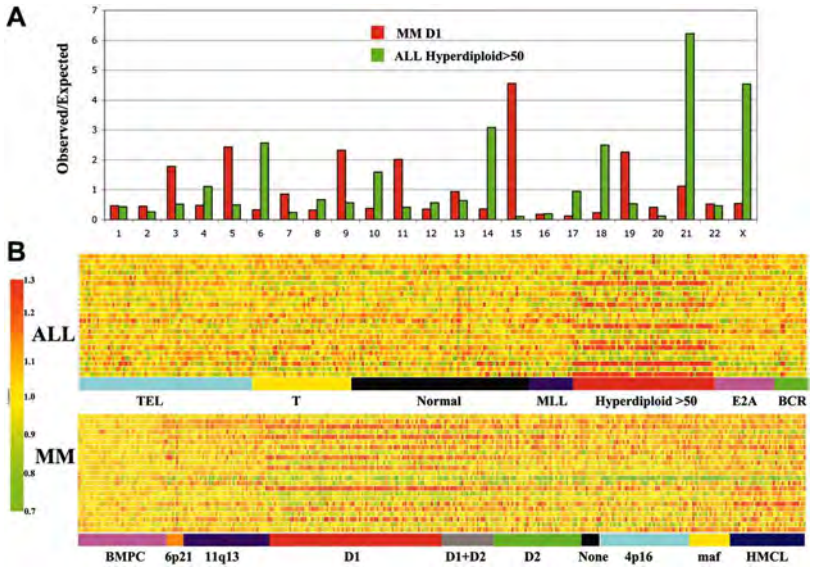
Bergsagel P L et al. Blood 2005;106:296-303

TC Classification



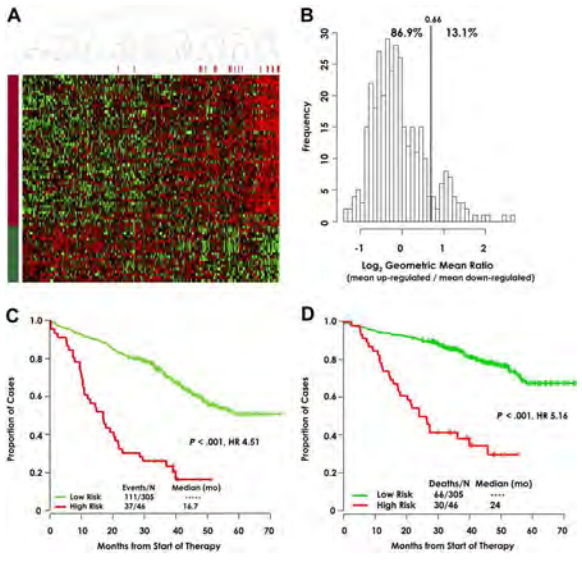
Bergsagel P L et al. Blood 2005;106:296-303

Pseudokaryotype



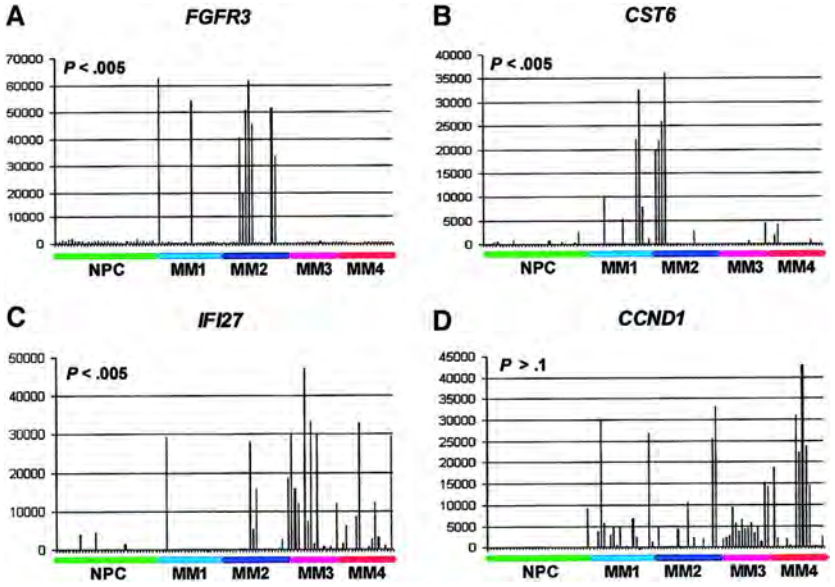
Bergsagel P L et al. Blood 2005;106:296-303

GEP signatures



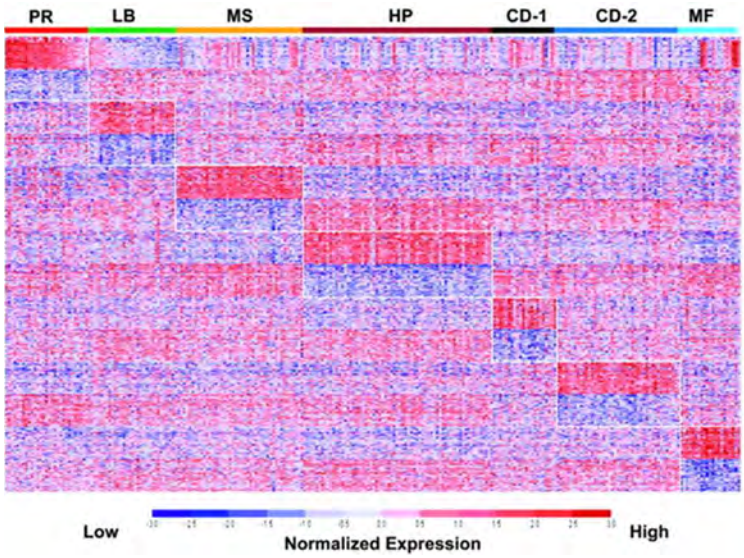
Shaughnessy et al, Blood2007, 109(6), 2276-2284

UAMS Classification



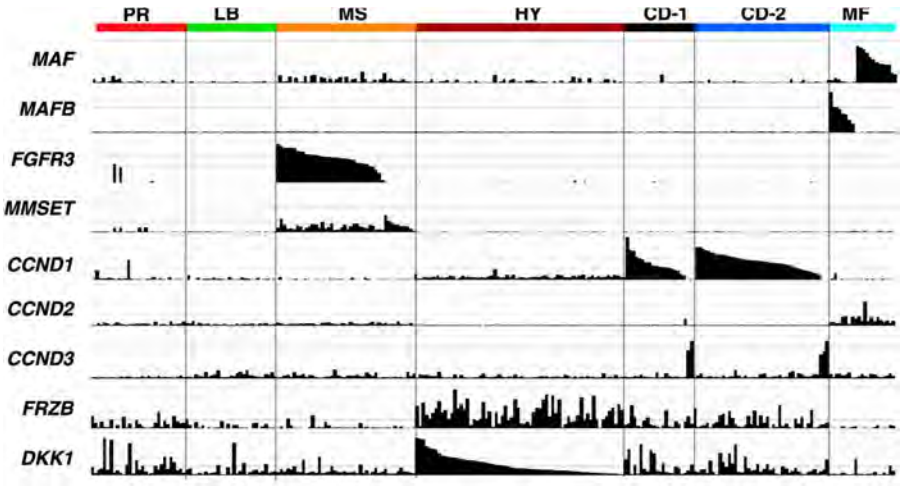
Zhan et al Blood 2002 99:1745

UAMS Classification



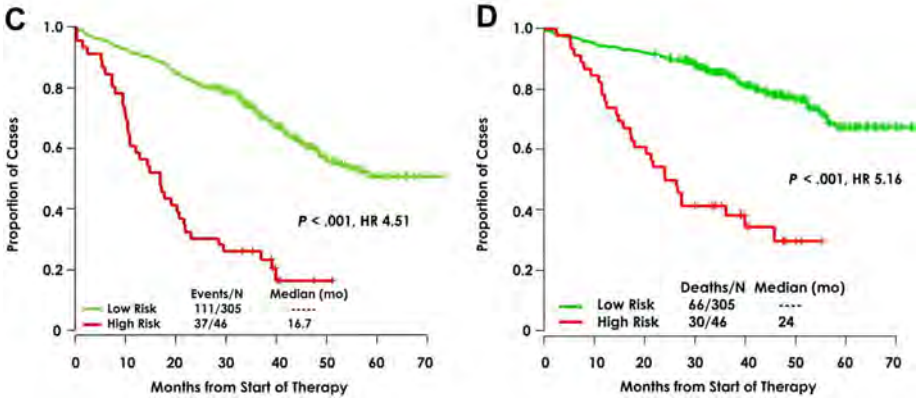
Zhan et al Blood 2006 108:2020

UAMS Classification



Zhan et al Blood 2006 108:2020

GEP signatures



Shaughnessy et al, Blood2007, 109(6), 2276-2284

MyPRS® Example MyPRS Report

The MyPRS™ (Myeloma Prognostic Risk Signature) assay is a microarray-based gene expression profile (GEP) which can be used to assist the management of patients with multiple myeloma (MM) and related disorders.

Since 2006, the 70-gene prognostic signature, developed by the University of Arkansas for Medical Sciences (UAMS) has been applied to over 4,700 patients in studies performed in 4 countries and described in 17 peer-reviewed publications[5].

MyPRS results from the analysis of an example patients' bone marrow aspirate specimen are shown below. Please contact customerservice@signalgenetics.com for information on ordering MyPRS.

Select Case Number: CL12-001876.CEL

ResultsPX Account ID	Patient MRN	Facility	Date of analysis:
client@examplehospital.com	5841265	Example Hospital	3/11/2016

Specimen Collection Date: 3/6/2016 Specimen Type: Bone Marrow Aspirate
Patient Name: Smith, J Client Name: University Healthcare Network
CD-138+ Cell Pre-Sort: 1.38%, Pre-sort Total Count: 138.3 million cells

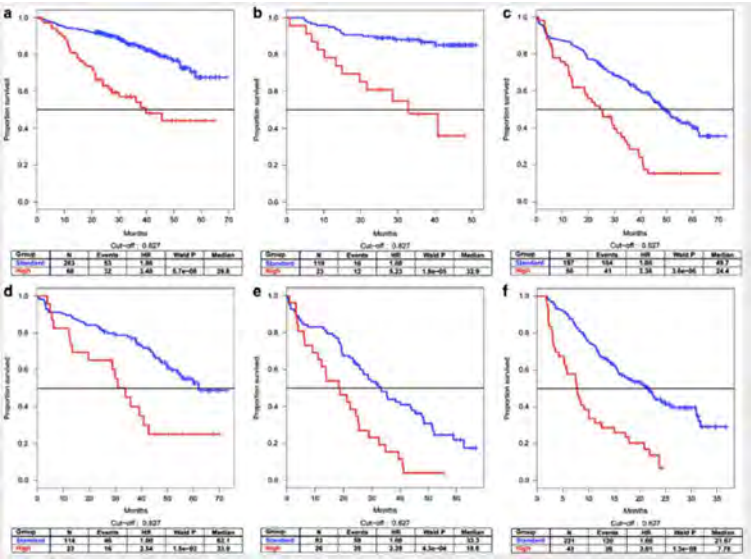
MyPRS GEP70 Risk Score Result:

LOW RISK (MyPRS Plus score<45.2)	77% Probability of being recurrence-free at 5-years*. High probability of favorable prognosis.

*TT3 independent validation series outcome data obtained from UAMS Myeloma Institute for Research and Therapy and analyzed by Signal Genetics™ on 24/6/13. These data include patients from Shaughnessy et al (2007) with updated follow-up records.

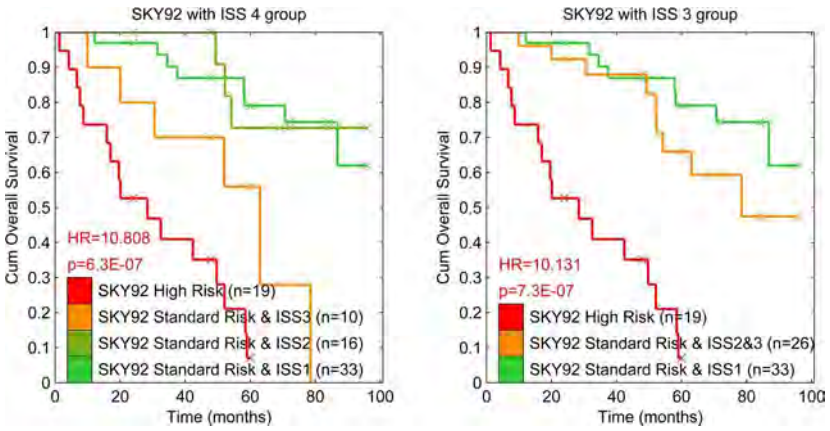
https://resultspx.signalgenetics.com/demo/myprs_demoresults.aspx

ECM92 Gene signature



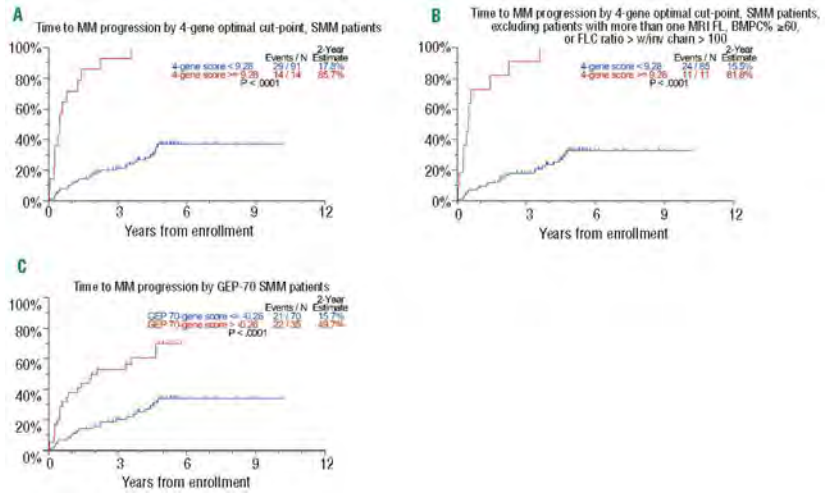
Kuiper et al *Leukemia* (2012) 26, 2406–2413

Prognostication by SKY92 + ISS



Erik van Beers et al. Blood 2015;126:5322

Progression from SMM to MM



Rashid Khan et al. Haematologica 2015;100:1214-1221

Myeloma Achilles Heel

Plasma cell biology?

Translocations?

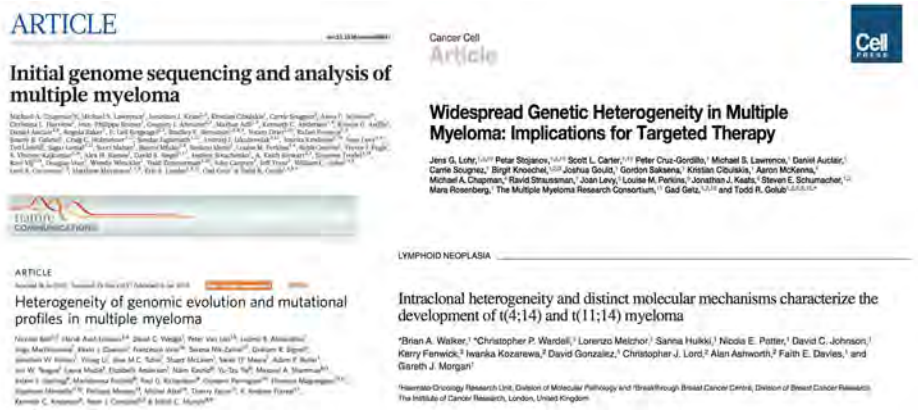
Mutations?

Progression events?

Immunology?

Microenvironment?

Publication of 1000+ MM genomes/exomes essentially defined the genetic landscape of the disease



ARTICLE

Initial genome sequencing and analysis of multiple myeloma

nature COMMUNICATIONS

ARTICLE

Heterogeneity of genomic evolution and mutational profiles in multiple myeloma

Cancer Cell

Article

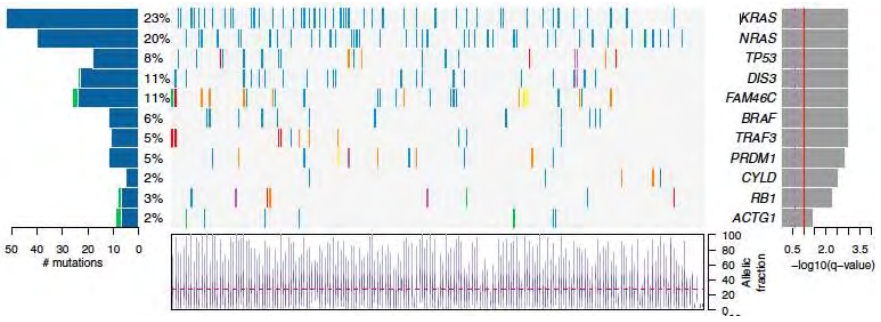
Cell

Widespread Genetic Heterogeneity in Multiple Myeloma: Implications for Targeted Therapy

LYMPHOID NEOPLASIA

Intraclonal heterogeneity and distinct molecular mechanisms characterize the development of t(4;14) and t(11;14) myeloma

Only a limited set of genes is recurrently mutated in MM



Lohr et al., Cancer Cell 2014

Pieces of the Puzzle

Future

Now

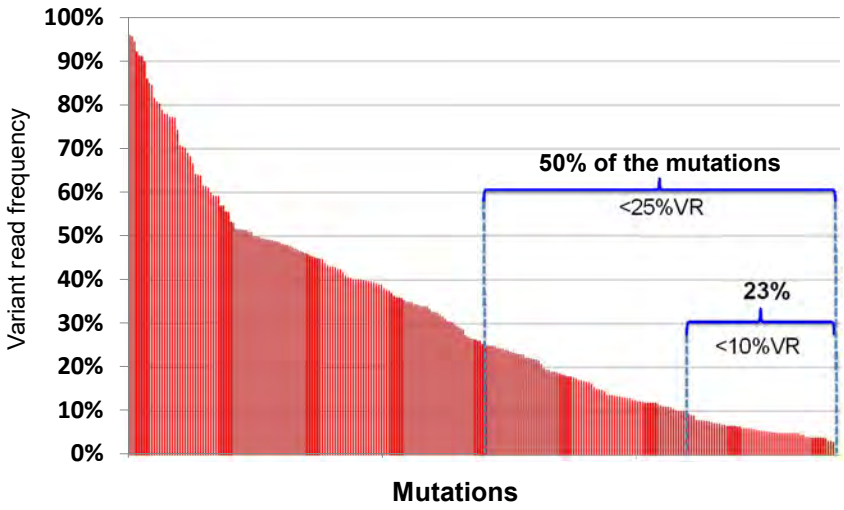
Myeloma Mutation Panel (M^3P)

- Recurrently mutated putative MM genes: *FAM46C, TP53, DIS3*
- Actionable genes: *BRAF, IDH1*
- Pathways: NF-kB, MAPK, MYC
- Drug Resistance: IMiDs, PIs, glucocorticoid
- Copy-number changes
- Biallelic deletions of TSG
- Sample purity measurement: J regions IGH, IGL-K and IGL-L →88 genes, 1327 amplicons, 373 Kb

Results to Date

- **> 600 tumor and germline samples average 658X**
- **83% have mutation - average 2 mutations/patient**
- **72 untreated del17p (p53 mutation in 28%)**
- **Braf in 9% at diagnosis and 18% at relapse**

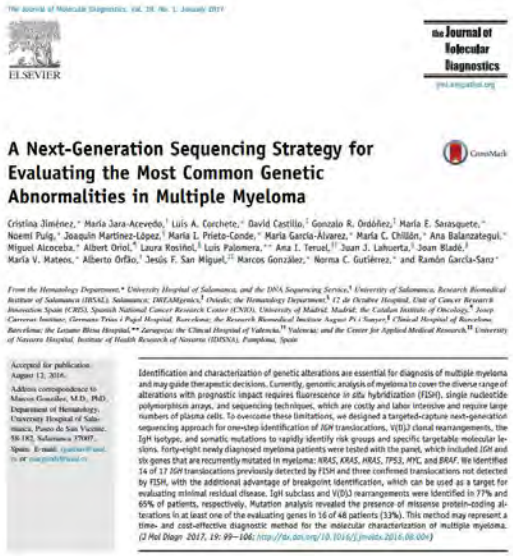
Most mutations are subclonal



Myeloma Specific Gene Mutation Panel Tracks Clonal Changes Over Time

	26.1	26.2	44.1	44.2	77.1	77.2
FAM46C				24%	92%	88%
FAT1				73%		
KRAS			28%		60%	53%
SP140	48%	37%			85%	23%
SPEN				18%		
TP53			24%	92%	82%	94%
					78%	
						88%
	Patient One		Patient Two		Patient Three	

Sequencing Approaches to Detect Genetics



ELSEVIER

the Journal of Molecular Diagnostics

A Next-Generation Sequencing Strategy for Evaluating the Most Common Genetic Abnormalities in Multiple Myeloma

Cristina Jiménez,* María Jara-Acevedo,† Luis A. Corchete,* David Castillo,‡ Gonzalo R. Ordóñez,‡ María E. Sarasquete,* Noemi Puig,* Joaquín Martínez-López,‡ María L. Prieto-Conde,* María García-Álvarez,* María C. Chillón,* Ana Balanzategui,* Miguel Alcoceba,* Albert Oriol,¶ Laura Rosiñol,‖ Luis Palomera,** Ana I. Teruel,†† Juan J. Lahuerta,‖ Joan Bladé,‖ María V. Mateos,* Alberto Orfão,† Jesús F. San Miguel,‡‡ Marcos González,* Norma C. Gutiérrez,* and Ramón García-Sanz*

From the Hematology Department, University Hospital of Salamanca, and the DNA Sequencing Service,† University of Salamanca, Research Biomedical Institute of Salamanca (IBSAL), Salamanca; DREAMgenics,‡ Oviedo; the Hematology Department,¶ 12 de Octubre Hospital, Unit of Cancer Research Innovation Spain (CRIS), Spanish National Cancer Research Center (CNIO), University of Madrid, Madrid; the Catalan Institute of Oncology,‖ Josep Carreras Institute, Germans Trias i Pujol Hospital, Barcelona; the Research Biomedical Institute August Pi i Sunyer,§ Clinical Hospital of Barcelona, Barcelona; the Lozano Blesa Hospital,** Zaragoza; the Clinical Hospital of Valencia,†† Valencia; and the Center for Applied Medical Research,‡‡ University of Navarra Hospital, Institute of Health Research of Navarra (IDISNA), Pamplona, Spain

Accepted for publication August 12, 2016.

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Identification and characterization of genetic alterations are essential for diagnosis of multiple myeloma and may guide therapeutic decisions. Currently, genomic analysis of myeloma to cover the diverse range of alterations with prognostic impact requires fluorescence *in situ* hybridization (FISH), single nucleotide polymorphism arrays, and sequencing techniques, which are costly and labor intensive and require large numbers of plasma cells. To overcome these limitations, we designed a targeted-capture next-generation sequencing approach for one-step identification of *IGH* translocations, V(D)J clonal rearrangements, the IgH isotype, and somatic mutations to rapidly identify risk groups and specific targetable molecular lesions. Forty-eight newly diagnosed myeloma patients were tested with the panel, which included *IGH* and six genes that are recurrently mutated in myeloma: *NRAS*, *KRAS*, *HRAS*, *TP53*, *MYC*, and *BRAF*. We identified 14 of 17 *IGH* translocations previously detected by FISH and three confirmed translocations not detected by FISH, with the additional advantage of breakpoint identification, which can be used as a target for evaluating minimal residual disease. IgH subclass and V(D)J rearrangements were identified in 77% and 65% of patients, respectively. Mutation analysis revealed the presence of missense protein-coding alterations in at least one of the evaluating genes in 16 of 48 patients (33%). This method may represent a time- and cost-effective diagnostic method for the molecular characterization of multiple myeloma. (*J Mol Diagn 2017, 19: 99–106; http://dx.doi.org/10.1016/j.jmoldx.2016.08.004*)

Conclusions

- Genetics can help classify MM subgroups
- Genetics have powerful prognostic implications
- Combined with standard clinical factors can best stratify patients
- Clinical tests are available
- Quality of process is critical

Institute of Biomedical Research of Salamanca

University of Salamanca

Cancer Research Center

What are the optimal imaging techniques in Myeloma?

María-Victoria Mateos
University Hospital of Salamanca
University of Salamanca
Spain

What is the role of imaging in Myeloma?

- Precise identification of bone disease, as sign of **organ damage and need to start treatment**
- Identification of sites of **extra-medullary disease** (total body techniques)
- Differential diagnosis between localized disease **(BSP)** and systemic disease **(MM)**
- Correct identification of sites of bone disease at risk of complications (fractures, neurological complications) (MRI gold standard)
- **Correct follow up of the patients after treatment**

Zamagni E. et al, BJH 2012

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Zamagni E. et al, BJH 2012

ACTIVE MYELOMA: the CRAB CRITERIA

Myeloma-related end organ damage due to the plasma cell proliferative process

- **C:** Calcium levels increased
- **R:** Renal insufficiency
- **A:** Anemia
- **B:** Bone lesions, osteolytic or osteoporosis

X-ray was the standard of care for bone lesions detection

Rajkumar V. et al., Lancet Oncology 2014

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

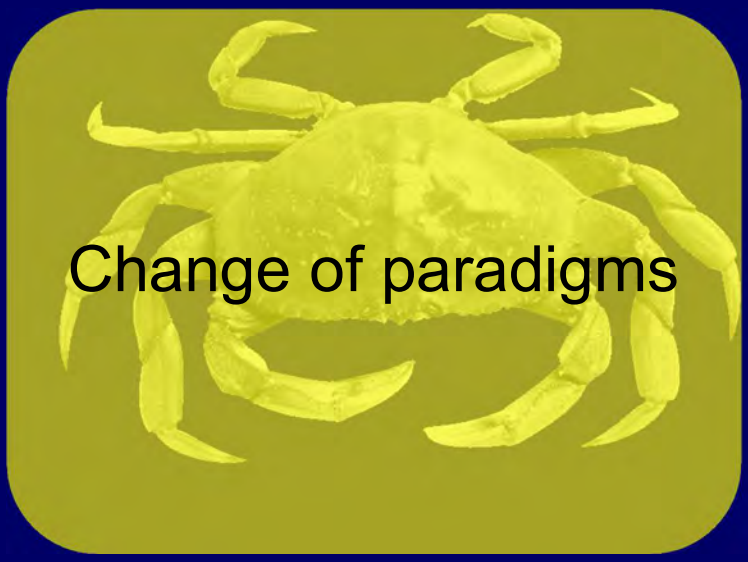
International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma

S Vincent Rajkumar, Meletios A Dimopoulos, Antonio Palumbo, Joan Blade, Giampaolo Merlini, Maria-Victoria Mateos, Shaji Kumar, Jens Hillengass, Efstathios Kastritis, Paul Richardson, Ola Landgren, Bruno Paiva, Angela Dispenzieri, Brendan Weiss, Xavier LeLeu, Sonja Zweegman, Sagar Lonial, Laura Rosiñol, Elena Zamagni, Sundar Jagannath, Orhan Sezer, Sigurdur Y Kristinsson, Jo Caers, Saad Z Usmani, Juan José Lahuerta, Hans Erik Johnsen, Meral Beksac, Michele Cavo, Hartmut Goldschmidt, Evangelos Terpos, Robert A Kyle, Kenneth C Anderson, Brian G M Durie, Jesus F San Miguel

This International Myeloma Working Group consensus updates the disease definition of multiple myeloma to include validated biomarkers in addition to existing requirements of attributable CRAB features (hypercalcaemia, renal failure, anaemia, and bone lesions). These changes are based on the identification of biomarkers associated with near inevitable development of CRAB features in patients who would otherwise be regarded as having smouldering multiple myeloma. A delay in application of the label of multiple myeloma and postponement of therapy could be detrimental to these patients. In addition to this change, we clarify and update the underlying laboratory and radiographic variables that fulfil the criteria for the presence of myeloma-defining CRAB features, and the histological and monoclonal protein requirements for the disease diagnosis. Finally, we provide specific metrics that new biomarkers should meet for inclusion in the disease definition. The International Myeloma Working Group recommends the implementation of these criteria in routine practice and in future clinical trials, and recommends that future studies analyse any differences in outcome that might occur as a result of the new disease definition.

www.thelancet.com/oncology Vol 15 November 2014

Rajkumar V. et al., Lancet Oncology 2014

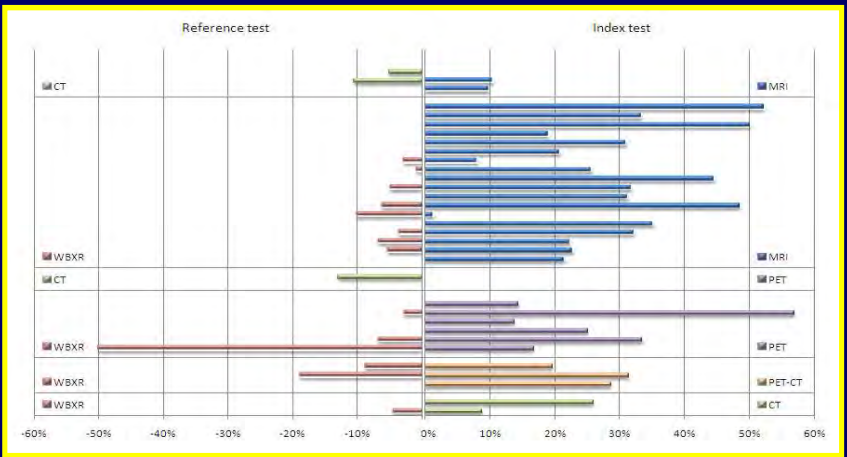


International Myeloma Working Group updated Criteria for the diagnosis of Multiple Myeloma

- **Definition of myeloma bone disease (CRAB):clear evidence of one or more sites of osteolytic bone destruction (at least 5 mm or more in size) seen on CT, WBLDCT, PET/CT, regardless of weather they can be visualized on skeletal radiography or not**
- If doubt lesions on CT or PET/CT: close follow-up every 3-6 months and/or biopsy of the lesion
- Oseoporosis per se in the absence of lytic lesions is not sufficient for CRAB

Rajkumar V. et al., Lancet Oncology 2014

Systematic review
New imaging techniques had a higher detection rate as compared to WBXR*



* Except for ribs and skull

Regelink JC et al. BJH 2013;162:50-61.

MRD supersedes CR
and could meet some of the key requirements for a surrogate endpoint such as:

- move the PFS of patients in remission from 3–5 years to 8–10 years
- independence from treatment
- predict different outcomes upon different MRD-negative rates
- useful in all patient subgroups
- reliable and widely available techniques, inside and outside the BM

San Miguel J. EHA 2016

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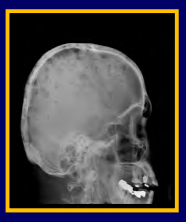
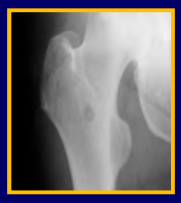
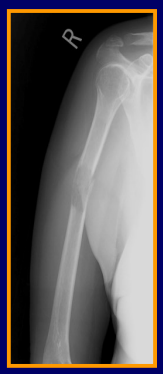
    - >1 focal lesions on MRI studies‖

Rajkumar V. et al., Lancet Oncology 2014 IMWG, BJH 2003

Is conventional radiography "the gold standard" for depicting myeloma osteolytic lesions in 2016?







- Lytic lesions are visible only if at least 30%-50% of trabecular substance is lost
- Unable to identify small osteolytic lesions (planar technique)
- Low sensitivity in the spine
- Unable to distinguish between osteoporotic vertebral fractures and MM related ones
- It cannot be used for the assessment of response to treatment

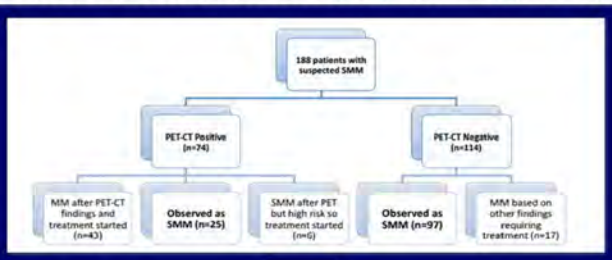
Frequent underestimation of MM bone disease

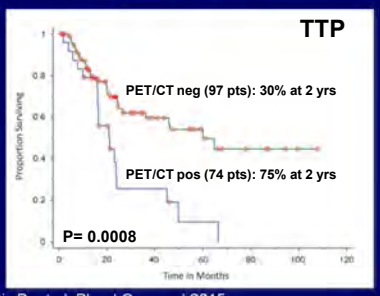
Zamagni E. et al, BJH 2012 Pianko et al, Clin Canc Res 2014

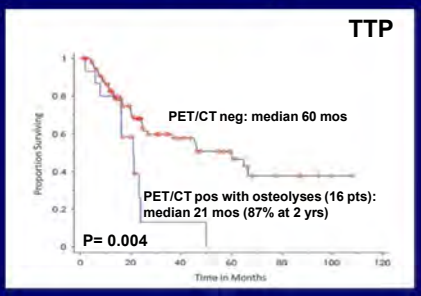
ORIGINAL ARTICLE

Positron emission tomography-computed tomography in the diagnostic evaluation of smoldering multiple myeloma: identification of patients needing therapy

B Siontis[1], S Kumar[2], A Dispenzieri[2], MT Drake[3], MQ Lacy[2], F Buadi[2], D Dingli[2], P Kapoor[2], W Gonsalves[2], MA Gertz[2] and SV Rajkumar[2]



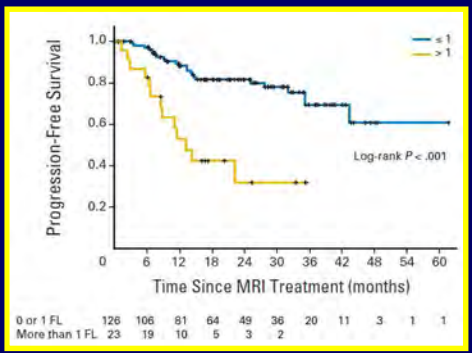




Siontis B. et al, Blood Cancer J 2015

Prognostic value of WBMRI: biomarker of malignancy

- 149 patients
- FL in 28%
- >1 focal lesion in 15% [23 patients]
- 9/23 would have been missed by axial examination only
- median PFS 13 months vs not reached



Hillengas et al. JCO 2010;28:1606-10

Prognostic value of WBMRI

ORIGINAL ARTICLE

Predictive value of longitudinal whole-body magnetic resonance imaging in patients with smoldering multiple myeloma

Table 2. Multivariate analysis

Variable	*HR*	*95% CI*	*P-value*
1st MRI ⩾2 FL	2.24	0.84–5.98	0.108
MRI-PD	***14.1***	***5.06–39.3***	***<0.001***
M-Protein ⩾20 g/l	***1.05***	***1.01–1.09***	***0.022***
1st MRI ⩾2 FL	2.90	0.45–18.6	0.260
MRI-PD	***10.4***	***2.57–42.0***	***0.001***
aPC/BMPC⩾95%	***6.40***	***1.36–30.2***	***0.020***

Abbreviations: aPC, aberrant plasma cells; BMPC, bone marrow plasma cells; CI, confidence intervals; FL, focal lesions; HR, hazard ratio; MRI, magnetic resonance imaging; MRI-PD, radiological progressive disease. Multivariate analysis for serum M-Protein and aPC/BMPC ⩾95% at initial MRI as well as radiological progressive disease (MRI-PD) for progression into symptomatic MM. P-values are derived from Wald-test in Cox proportional hazard analysis. Bold and italic numbers represent significant findings.

Newer imaging techniques: are all of them similar?

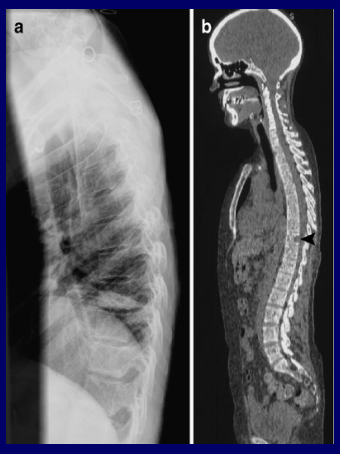
- **Morphological:** assessing bone destruction
  - **WB-MDCT-LDCT, CT** part of PET/CT
- **Functional**: assessing bone marrow infiltration and disease metabolism
  - **ASSIAL MRI- WBMRI (DCE-MRI, DWI-MRI), PET/CT**

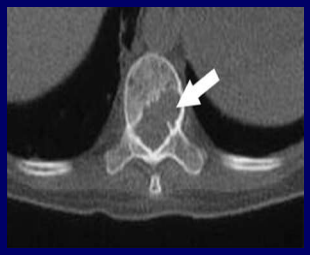
ROLE OF NEWER IMAGING TECHNIQUES

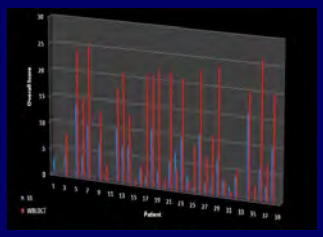
- **MORPHOLOGICAL**: assessing bone destruction
  - WB-MDCT-LDCT, CT part of PET/CT
- **FUNCTIONAL**: assessing bone marrow infiltration and disease metabolism
  - ASSIAL MRI- WBMRI (DCE-MRI, DWI-MRI), PET/CT

- **Active MM**
  - **at diagnosis:** staging and prognosis
  - **after treatment: evaluation of treatment response**
- **Early stage/smoldering MM**

Whole-Body Low-Dose CT: more sensitive than Conventional Radiography

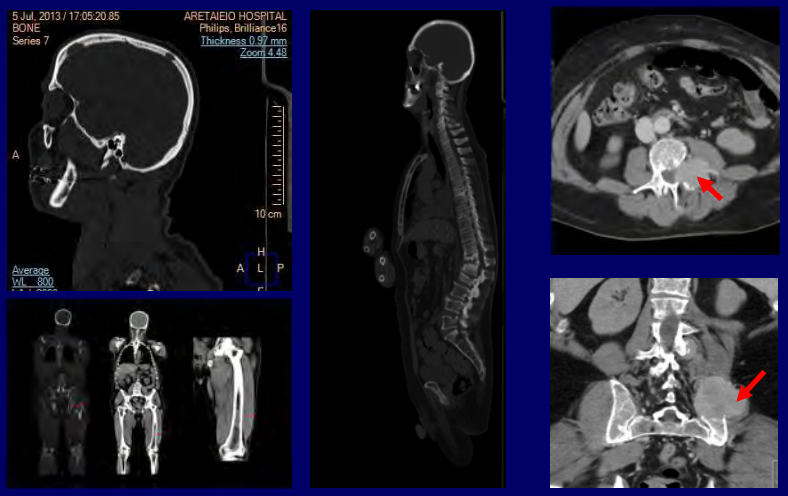






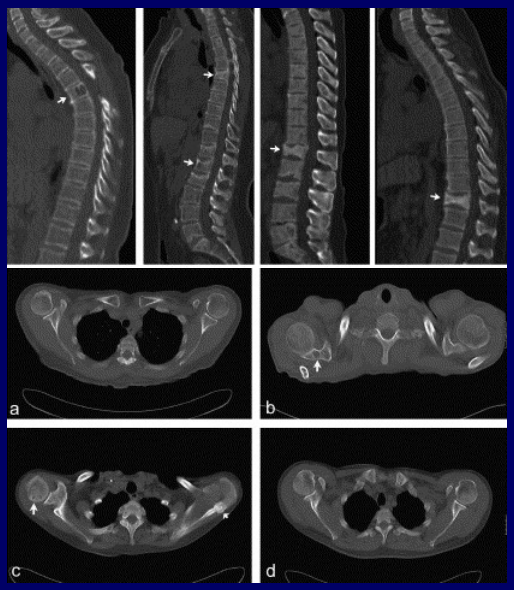
Gleeson et al. Skeletal Radiol 2009;38:225-36

Whole-Body Low-Dose CT: more sensitive for all bones



- Fast scanning time, low radiation dose (3,3-7 msV), high resolution images
- Demonstration of extra-osseus findings

WHOLE BODY LOW-DOSE MULTIDETECTOR ROW-CT (WB-LDCT)



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- Demonstration of extra-osseus findings

Horger M., EJ Radiol, 2004
Hur J., J Comput Assist Tomogr, 2007

Shortt CP et al, Sem Musculoskel Radiology 2010
Ippolito D. et al, Eur J Radiol 2013

Wolf MB et al, Eur Journal Radiology 2014
Pianko MJ et al, Clin Canc Res 2014

WBLDCT vs WBXR for the lytic lessions detection in MM

Study	Study design	N° pts	Reference test	Key findings

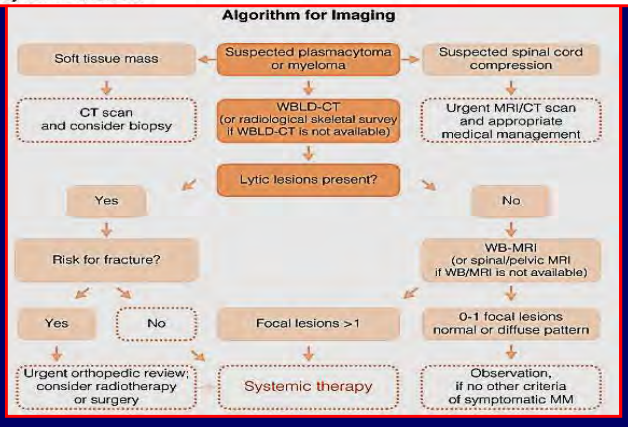
	Kropil et al. (14)				Princewill et al. (16)			
	WBLDCT (# detected)	WBXR (# detected)	Ratio of detection (WBLDCT#/ WBXR#)	P	WBLDCT (# detected)	WBXR (# detected)	Ratio of detection (WBLDCT#/ WBXR#)	P
Total skeleton	247	120	2.06	Not reported	968	248	3.90	<0.001
Skull	7	1	7.00	Not reported	94	86	1.09	0.02
Spine	69	15	4.60	<0.001	241	49	4.92	<0.001
Thoracic cage (ribs and sternum)	60	29	2.07	<0.001	222	3	74.00	<0.001
Pelvis and flat bones	61	24	2.54	<0.001	240	36	6.67	<0.001
Long bones and extremities	46	47	0.98	Not reported	171	74	2.31	<0.001

WBLDCT > WBXR, in particular in the axial skeleton. **63%** pts up-staged with WBLDCT, **23%** pts neg at WBXR and pos at WBCT

Princewill Pianko MJ et al. Clin Cancer Res 2014 Cancer Invest 2013		51	WBXR	WBLDCT > WBXR 61% of the pts up-staged with WBLDCT

European Myeloma Network Guidelines for the Management of Multiple Myeloma-related Complications

Evangelos Terpos,[1*] Martina Kleber,[2,3*] Monika Engelhardt,[2*] Sonja Zweegman,[4] Francesca Gay,[5] Efstathios Kastritis,[1] Niels W.C.J. van de Donk,[6] Benedetto Bruno,[5] Orhan Sezer,[7] Annemiek Broijl,[8] Sara Bringhen,[5] Meral Beksac,[9] Alessandra Larocca,[5] Roman Hajek,[10] Pellegrino Musto,[11] Hans Erik Johnsen,[12] Fortunato Morabito,[13] Heinz Ludwig,[14] Michele Cavo,[15] Hermann Einsele,[16] Pieter Sonneveld,[4] Meletios A. Dimopoulos,[1] and Antonio Palumbo[5] on behalf of the European Myeloma Network



WBLD-CT is the novel standard procedure for the diagnosis of lytic disease in patients with MM (grade 1A)
Conventional radiography can also be used if WBLD-CT is not available

Terpos E. et al., Haematologica 2015

International Myeloma Working Group updated Criteria for the diagnosis of Multiple Myeloma

- **Definition of myeloma bone disease (CRAB):clear evidence of one or more sites of osteolytic bone destruction (at least 5 mm or more in size) seen on CT, WBLDCT, PET/CT, regardless of weather they can be visualized on skeletal radiography or not**
- If doubt lesions on CT or PET/CT: close follow-up every 3-6 months and/or biopsy of the lesion
- Oseoporosis per se in the absence of lytic lesions is not sufficient for CRAB

Rajkumar V. et al., Lancet Oncology 2014

PET/CT vs WBXR OR MRI in Multiple Myeloma

- 7 studies PET ± CT vs WBXR: 6/7 PET showed more lytic lesions with the exception of the skull
- Identification of extra-medullary disease

- ***CT part of PET/CT is valid for assessing bone destruction***
- ***PET/CT is the functional assessment for disease metabolism***

Van Lammeren-Venema D et al., Cancer 2011

PET/CT vs WBXR OR MRI in Multiple Myeloma

- 18 studies, 798 patients
- 7 studies PET ± CT vs WBXR: 6/7 PET showed more lytic lesions with the exception of the skull
- 5 studies PET ± CT vs MRI spine and/or pelvis: 4/5 MRI was superior in detecting myeloma bone disease, especially in case of diffuse bone infiltration
- 1 study PET/CT vs WBMRI: concordant in 80% cases
- Identification of extra-medullary disease

- ***CT part of PET/CT is valid for assessing bone destruction***
- ***PET/CT is the functional assessment for disease metabolism***

Van Lammeren-Venema D et al., Cancer 2011

Role of ^{18}F-FDG PET/CT in the diagnosis and management of multiple myeloma and other plasma cell disorders: a consensus statement by the International Myeloma Working Group

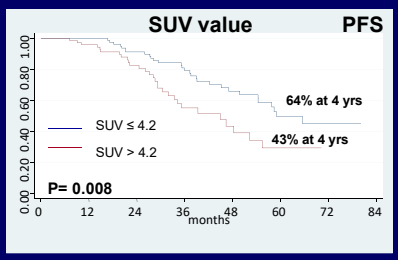
Michele Cavo, Evangelos Terpos, Cristina Nanni, Philippe Moreau, Suzanne Lentzsch, Sonja Zweegman, Jens Hillengass, Monika Engelhardt, Saad Z Usmani, David H Vesole, Jesus San-Miguel, Shaji K Kumar, Paul G Richardson, Joseph R M Bihael, Fernando Leal da Costa, Meletios Athanasios Dimopoulos, Chiara Zingaretti, Niels Abildgaard, Hartmut Goldschmidt, Robert Z Orlowski, Wee Joo Chng, Hermann Einsele, Sagar Lonial, Bart Barlogie, Kenneth C Anderson, S Vincent Rajkumar, Brian G M Durie, Elena Zamagni

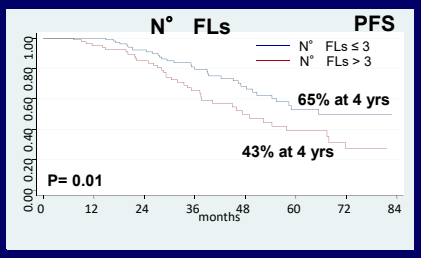
	Grade
Active multiple myeloma	
^{18}F-FDG PET/CT should be considered as part of the initial investigations in patients with newly diagnosed multiple myeloma because it provides information useful for prognostication and allows to more carefully assess the bulk of the disease, particularly in patients with extramedullary sites of the disease; assessing the bulk of the disease with ^{18}F-FDG PET/CT also applies to patients with relapsed or refractory multiple myeloma	B
In patients with newly diagnosed multiple myeloma, with or without EMD, and more than three focal lesions, ^{18}F-FDG PET/CT identifies subgroups of patients with unfavourable outcomes; controversies exist about the prognostic role of SUV_{max}	B
^{18}F-FDG PET/CT is now the preferred technique for evaluating and monitoring response to therapy; metabolic changes assessed by ^{18}F-FDG PET/CT provide an earlier evaluation of response compared with MRI	A
^{18}F-FDG PET/CT should be coupled with sensitive bone marrow-based assays as part of minimal residual disease detection inside and outside the bone marrow	B

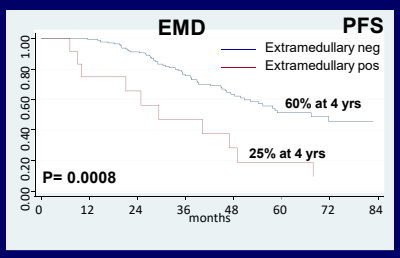
Cavo M et al, Lancet Oncology 2017

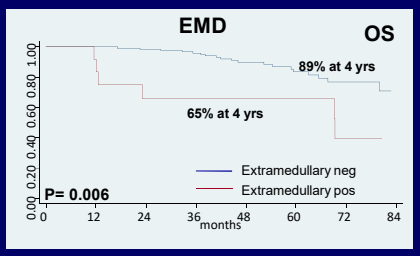
Prognostic value of PET/CT at diagnosis in NDMM transplant-candidates

N° OF FLs, SUV VALUE, EMD









Zamagni E. et al, Blood 2011

How to proceed in the clinic with a NDMM patient?

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- **Oseoporosis per se in the absence of lytic lesions is not sufficient for CRAB**

Rajkumar V. et al., Lancet Oncology 2014

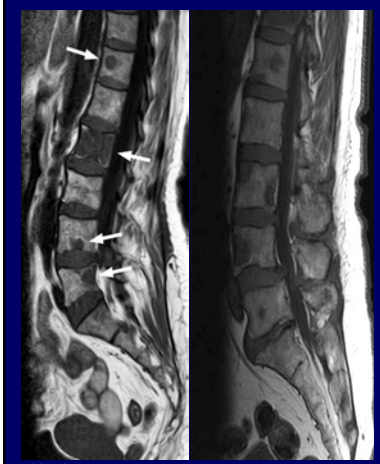
Magnetic Resonance Imaging

- MRI is a non-invasive technique which provides detailed information about bone marrow involvement
  - patterns: focal, diffuse, variegated, normal
  - discriminates normal vs myeloma marrow infiltration (osteoporotic vs malignant fractures)
- A WB-MRI (or MRI of the spine and pelvis) is mandatory in all patients with a presumed diagnosis of solitary plasmacytoma and in patients with smoldering MM
- It provides accurate illustration of spinal cord and/or nerve root compression, soft tissue extension, avascular necrosis

Terpos et al. J Clin Oncol 2011;29:1907-15

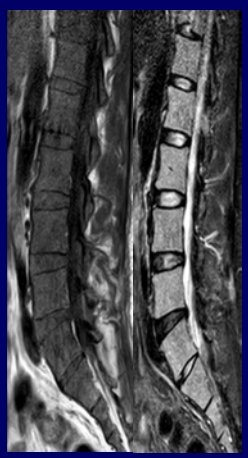
MRI patterns in MM

Focal lessions: 40% of NDMM

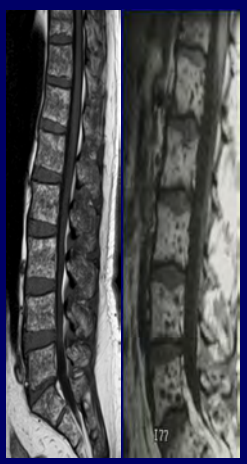


52% of 267 patients with normal skeletal survey had focal lesions on MRI

Diffuse pattern: 20%



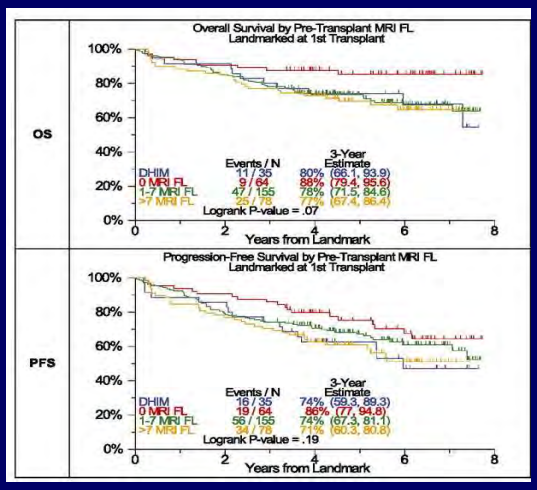
Variegated pattern: 4%



Moulopoulos & Koutouilidis. Bone Marrow MRI (Springer) 2015

Walker et al. J Clin Oncol 2007;25:1121-8

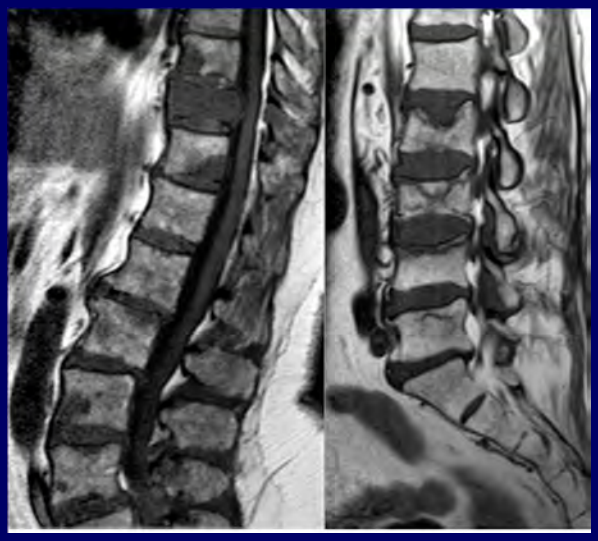
Prognostic value of MRI focal lesions at diagnosis



Usmani et al. Blood 2013;121:1819-23

Magnetic Resonance Imaging

due to myeloma osteoporotic



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Terpos et al. J Clin Oncol 2011;29:1907-15

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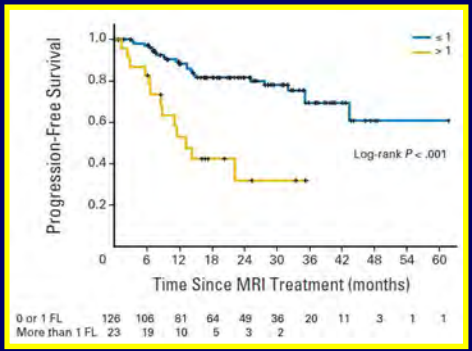

Hillengas et al. JCO 2010;28:1606-10

Imaging techniques at diagnosis in Myeloma

	WBLDCT	PET/CT	MRI
PROS	• Sensitivity and specificity • CT-guided biopsy, surgery, RT planning • Can depict EMD, BM involvement, lytic lesions • **Rapid acquisition time, low radiation dose (3-5 mSV)** • **Intermediate cost**	• Sensitivity and specificity • Optimal to assess **EMD** • Can depict lytic lesions (CT part) • **Can assess tumor burden and disease metabolism** • **Prognostic significance of FLs and SUV**	• Sensitivity and specificity • **No radiation** • **Gold standard for detection of diffuse BM involvement** • Optimal for CNS imaging • Gold standard for differential diagnosis between osteoporotic and pathological fractures • Can depict EMD (WBMRI) • Prognostic significance of FLs
CONS	• Sub-optimal for diffuse BM involvement • **Few data/unclear prognostic significance of lesion number**	• **Sub-optimal for diffuse BM involvement** • High cost , availability • Radiation dose intermediate (10 mSV)	• Imaging time (in particular axial) • **No detection of lytic lesions: not enough to define end organ damage (MDE)** • High cost , availability

How to proceed in the clinic with a NDMM patient?

- **Order of preference:**
  - **PET/CT: the CT part is valid for lytic lesions detection and PET can be useful to evaluate the response to treatment**
  - **WBLDCT: valid for lytic lesions**
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- **If doubt lesions on CT or PET/CT: close follow-up every 3-6 months and/or biopsy of the lesion**
- **Oseoporosis per se in the absence of lytic lesions is not sufficient for CRAB**
- **MRI: mandatory in solitary plasmacytoma, SMM, spinal cord compression,..**

Rajkumar V. et al., Lancet Oncology 2014

What is the role of imaging in Myeloma?

- Precise identification of bone disease, as sign of **organ damage and need to start treatment**
- Identification of sites of **extra-medullary disease** (total body techniques)
- Differential diagnosis between localized disease **(BSP)** and systemic disease **(MM)**
- Correct identification of sites of bone disease at risk of complications (fractures, neurological complications) (MRI gold standard)
- **Correct follow up of the patients after treatment: Metabolic response to treatment**

Zamagni E. et al, BJH 2012

Axial MRI or DWI-WBMRI vs WBXR in Multiple Myeloma

•Detection of FLs: MRI 74%, WBXR 56%; 52% patients with normal WBXR had FLs at MRI [1]

•WBMRI detected higher number of lesions in 37% of the patients; 18% patients WBXR negative, WBMRI positive [2]

•Clear superiority of axial MRI and WBMRI in: spine, pelvis, sternum and ribs ($P < 0,001$)

•Axial MRI equally effective as PET/CT in detecting FLs ($P= 0,33$)[3]

•Role of DWI-WBMRI in detecting the diffuse pattern[4,5]

….but no detection of lytic lesions

[1] Walker B et al, JCO 2007
[2] Narquin S. et al., Diagnostic and Interv Imaging 2013
[3] Moreau P et al, ASH 2015
4. Koutoulidis V et al, Radiology 2016
5, Pawlyn C, Haematologica 2016

bjh research paper

Comparison of modern and conventional imaging techniques in establishing multiple myeloma-related bone disease: a systematic review

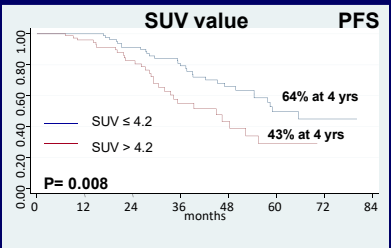
COMPARISON OF PET, PET/CT, MRI OR CT vs WBXR AT STAGING

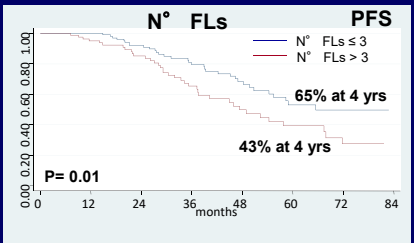
- 32 directly comparison studies, prospective and retrospective, 1661 patients
- Index test vs reference standard: detection rate
- Quality assessment of diagnostic studies
- All index tests had sensitivity above 0,9 as compared to WBXR (low false negative). Fewer additional lesions detected by PET/CT and MRI as compared to WBLDCT WBLDCT can replace WBXR
- Modern imaging techniques detected fewer lesions in the skull

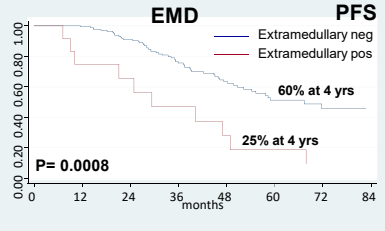
Regelink J. et al., BJH 2013

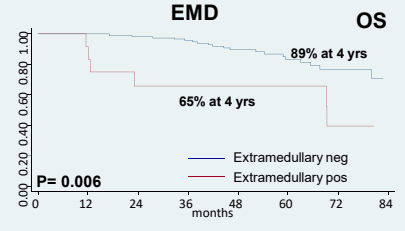
PROGNOSTIC VALUE OF PET/CT AT DIAGNOSIS IN ASCT CANDIDATES

N° OF FLs, SUV VALUE, EMD









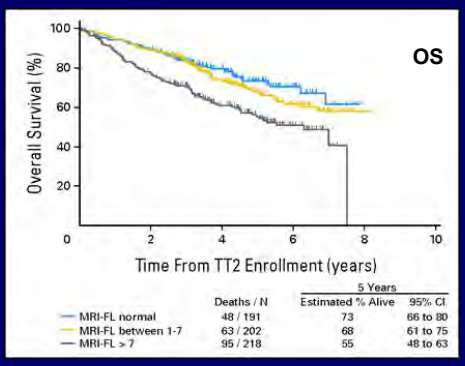
Zamagni E. et al, Blood 2011

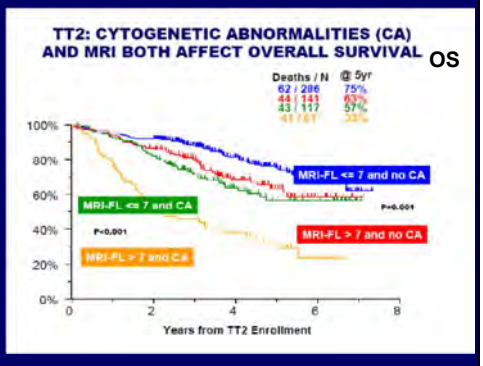
PROGNOSTIC VALUE OF PET/CT AT STAGING

- Several independent series of patients ASCT candidates, correlating with MRI findings, standard prognostic factors and molecular features of PCs[1,2,3,4]
- Small group of patients non ASCT eligible (retrospective study) [5]
- Series of patients pre- ALLO SCT (retrospective study) [6]
- Re-staging at relapse (retrospective studies) [7,8]

[1] Zamagni E. et al, Blood 2011
[2] Bartel. TB et al, Blood 2009
[3] Waheed S et al, Haematologica 2012
[4] Usmani S.Z. et al, Blood 2013
[5] Zamagni E. et al, Clin Canc Res 2015
[6] Patriarca F. et al, Biol BMT 2015
[7] Lapa C. et al, Oncotarget 2014
[8] Derlin T. et al, EJNM Mol Imag 2011

PROGNOSTIC VALUE OF MRI AT DIAGNOSIS[1,2,3,4,5]

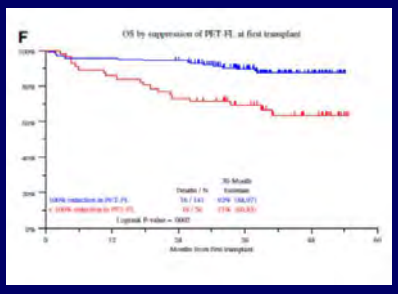


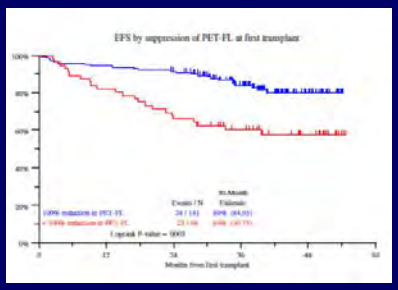


- Correlation between diffuse MRI pattern and high-risk cytogenetics (CA) [3]
- Correlation between MRI FLs and CRP, LDH, ISS [4]
- Identification of a group of pts with very high-risk disease (CA+MRI) [3,4]
- MRI prognostic scoring system (combining diffuse and focal infiltration pattern)[5]

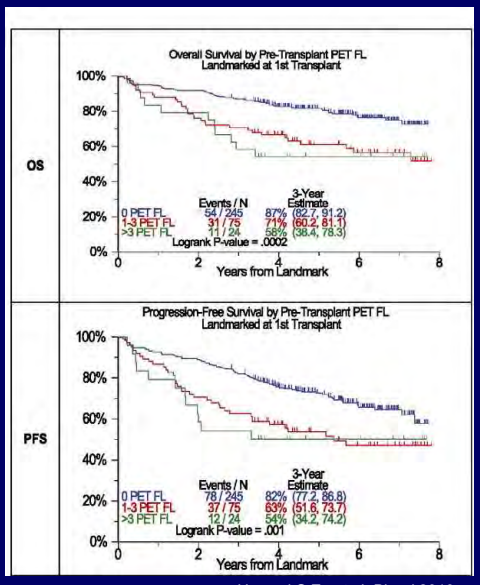
[1]Moulopoulos L.A. et al, Annals Oncology 2005
[2]Mouolopulos L.A. et al, Leukemia 2010
[3]Moulopoulos L.A. et al, AJH 2012
[4]Walker R. et al, JCO 2007
[5]Mai EK. et al, Haematologica 2015

Prognostic value of PET-CT after induction and before ASCT



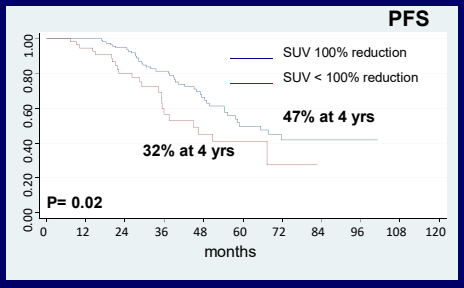


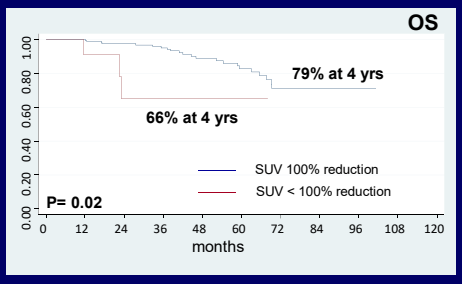
Bartel. TB et al, Blood 2009



Usmani S.Z. et al, Blood 2013

Prognostic value of PET/CT after ASCT





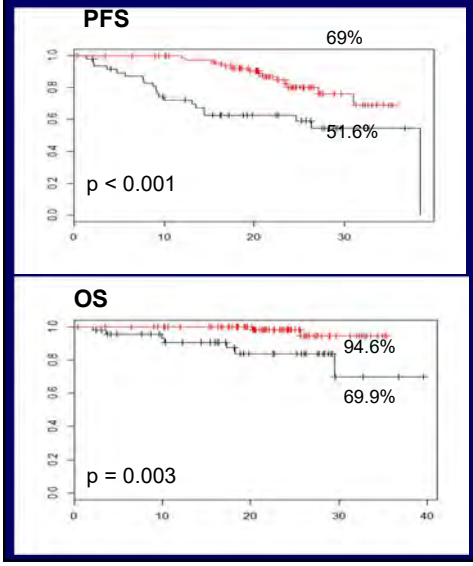
Zamagni E. et al, Blood 2011

Multivariate analysis

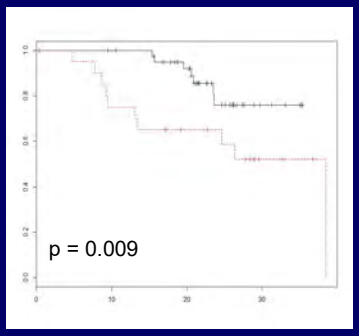
VARIABLES	HAZARD RATIO (95% CI)	P VALUE
TTP		
Extramedullary disease	15. 43 (4.11-57.95)	0.000
del (17p) ± t(4;14)	1.86 (1.12-3.49)	0.05
Not complete FDG PET suppression	1.82(1.19-3.77)	0.01
PFS		
Extramedullary disease	5. 93 (2.27-15.51)	0.000
del (17p) ± t(4;14)	1.90 (1.09-3.32)	0.023
Not complete FDG PET suppression	1.89 (1.06-3.35)	0.030
OS		
Relapse	9.35 (2.79-31.31)	0.000

Prognostic value of PET-CT normalisation before maintenance (62% normalised): IMF/DFCI trial

RVD x 4 c →ASCT



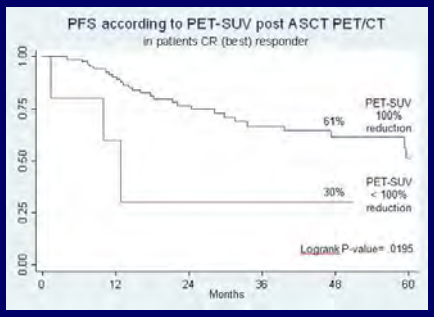
PFS in Arm A: RVD x 8 cycles



Moreau P. et al, JCO 2017

PET/CT MRD monitoring in CR patients

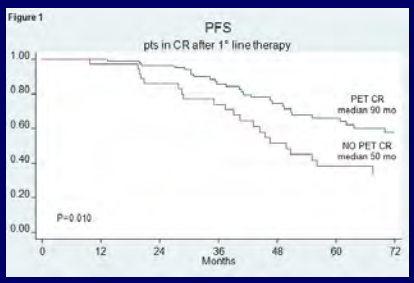
ASCT candidates (192 pts)

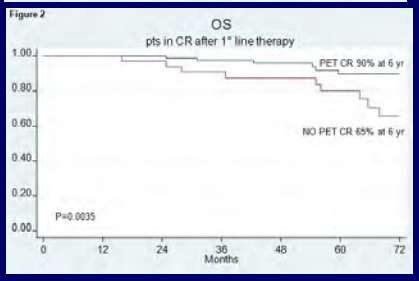


Zamagni E. et al, Blood 2011

- 70% PET-CR, 40-50% biochemical CR
- **25-30%** of the patients in conventionally-defined CR had PET/CT still positive

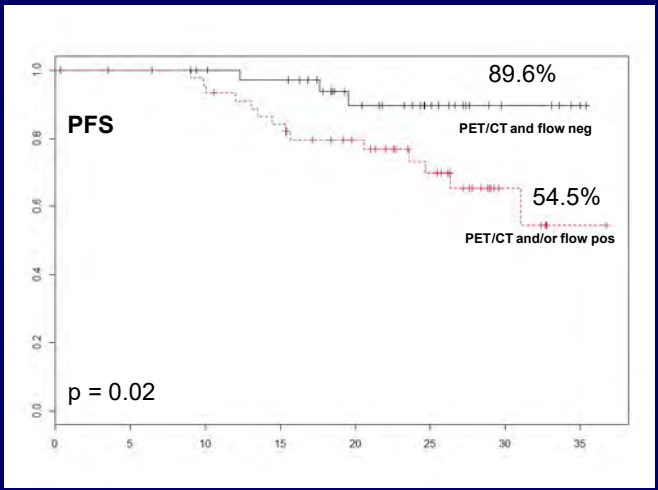
ASCT eligible and not-eligible (189 pts)





Zamagni E. et al, Clin Canc Res 2015

PET-CT and Flow-MRD monitoring before maintenance
IMF/DFCI



86/134 evaluated by both PET/CT and flow

47,7% both negative

Moreau P. et al, JCO2017

IMAGING TECHNIQUES AFTER TREATMENT

	PET/CT	MRI
PROS	• Specificity • Earlier post-therapy changes • Prognostic significance in CR patients (MRD monitoring) and complementarity with MFC • Good correlation with biochemical response	• High sensitivity in detecting diffuse BM infiltration • Pathological fractures assessment • Functional MRI protocols (DWI and DCE): quantification of structural and functional changes of tissues, related to cellular density and perfusion
CONS	• Lack of standardization • Applicability in 75% of the patients • Availability, cost	• False positive: FLs can persist years after therapy • Lack of standardization • No data about prognostic value in CR • Preliminar experience on functional methods • Availability, cost

Zamagni E. et al, BJH 2012
Hillengass J. et al, Leuk and Lymphoma 2013
Mesguich C et al, EJR 2014
Giles SL, Radiology 2014
Moreau et al, ASH 2015

New response criteria: IMWG 2016

Standard IMWG Response criteria[6]	*sCR (stringent complete response)*	CR as defined below PLUS Normal FLC ratio[10] AND Absence of clonal cells in bone marrow biopsies by immunohistochemistry (κ/λ ratio ≤4:1 or ≥1:2 for κ and λ patients, respectively, after counting ≥100 PCs)[7]
	CR (complete response)	Negative immunofixation on the serum AND urine AND[11] Disappearance of any soft tissue plasmacytomas AND <5% plasma cells in bone marrow aspirates (If cellular MRD is to be performed, the first BM aspirate should be sent to MRD and morphological evaluation is not mandatory)

	Response subcategory	Response criteria [1]
IMWG MRD negativity criteria (Requires CR as defined below)	*Sustained MRD negative*	MRD negative in the marrow (Next-generation flow or Next-generation sequencing) and by imaging as defined below, confirmed one year apart.[2] Subsequent evaluations can be used to further specify the duration of negativity (e.g., MRD negative @ 5 years etc)
	Flow MRD-negative	Absence of phenotypically aberrant clonal plasma cells by next-generation flow cytometry[4] on bone marrow aspirates using the EuroFlow standard operation procedure for MRD detection in MM (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells or higher
	Sequencing MRD negative	Absence of clonal plasma cells by next generation sequencing on bone marrow aspirates in which presence of a clone is defined as less than 2 identical sequencing reads obtained after DNA sequencing of bone marrow aspirates using the Lymphosight® platform (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells[5] or higher
	Imaging+ MRD-negative	MRD negative as defined by Next-generation flow or Next-generation sequencing **PLUS** Disappearance of every area of increased tracer uptake found at baseline or a preceding PET/CT[3]

Role of ^{18}F-FDG PET/CT in the diagnosis and management of multiple myeloma and other plasma cell disorders: a consensus statement by the International Myeloma Working Group

Michele Cavo, Evangelos Terpos, Cristina Nanni, Philippe Moreau, Suzanne Lentzsch, Sonja Zweegman, Jens Hillengass, Monika Engelhardt, Saad Z Usmani, David H Vesole, Jesus San-Miguel, Shaji K Kumar, Paul G Richardson, Joseph R Mikhael, Fernando Leal da Costa, Meletios-Athanassios Dimopoulos, Chiara Zingaretti, Niels Abildgaard, Hartmut Goldschmidt, Robert Z Orlowski, Wee Joo Chng, Hermann Einsele, Sagar Lonial, Bart Barlogie, Kenneth C Anderson, S Vincent Rajkumar, Brian G M Durie, Elena Zamagni

Table 6: Recommendations for use of 18F-FDG PET/CT in MM

Recommendation	Grade
Active MM:	
18F-FDG PET/CT can be considered as part of the initial workup in patients with newly diagnosed MM since it provides information useful for prognostication and allows to more carefully assess the bulk of the disease, particularly in patients with extramedullary sites of the disease. This latter indication for use of 18F-FDG PET/CT applies also to patients with relapsed/refractory MM	B
In newly diagnosed MM, EMD and >3 FLs on 18F-FDG PET/CT identify subgroups of patients with unfavorable outcomes, particularly those who are candidates to receive upfront ASCT. Controversies exist about the prognostic role of SUV_{max}	B
18F-FDG PET/CT is by now the preferred technique for evaluating and monitoring response to therapy. Metabolic changes assessed by 18F-	A

Lancet Oncology 2017

PROGNOSTIC VALUE OF PET/CT AFTER TREATMENT

Study	Study design	N° pts	Treatment	PFS	OS	Cox reg
Bartel Blood 2009	P	239	TT3	PET-CR pre ASCT	PET-CR pre ASCT	Yes
Zamagni Blood 2011	P	192	Thal-dex + double ASCT	PET SUV post induction and PET-CR post ASCT	PET-CR post ASCT	Yes
Usmani Blood 2013	P	302	TT3	PET FLs (3) day +7	PET FLs (3) day +7	Yes
Dimitrakopoulou-Strauss Clin Nucl Med 2009	P	19	CHT	SUV during CHT	/	/
Eliott EJH 2011	R	56	Various (CHT, ASCT, novel agents)	PET-CR post therapy	/	/
Fonti Caldarella C. et al, Int J Mol Imaging 2012 J Nucl Med 2012	R	47	Novel agents + ASCT in 19 pts	MTV post therapy	MTV post therapy	/

PROGNOSTIC VALUE OF PET/CT AFTER TREATMENT

3 independent prospective series of patients (US, Italy, France)

- Before ASCT (day 7 CHT, post-induction, at first ASCT)[1,2,4]
- After ASCT[3]
- Before maintenance[4]

TO ASSESS MRD

- PFS and OS difference PET pos vs neg in CR patients[3,7] (retrospective study, 282 pts) and complementary with MFC[4]
- No stratification of CR patients[5] (US study, 45 pts)

[1] Bartel. TB et al, Blood 2009
[2] Usmani S.Z. et al, Blood 2013
[3] Zamagni E. et al, Blood 2011
[4] Moreau P. et al, ASH 2015
[6] Korde N, JAMA Oncol 2015
[7] Zamagni E. et al, Clin Canc Res 2015

Prognostic value of MRI after treatment

Standard axial MRI or WBMRI

- Late response after ASCT[1] (US study, axial MRI)
- 100 pts after ASCT[2] (Germany, WBMRI)

FUNCTIONAL WBMRI: DWI and DCE

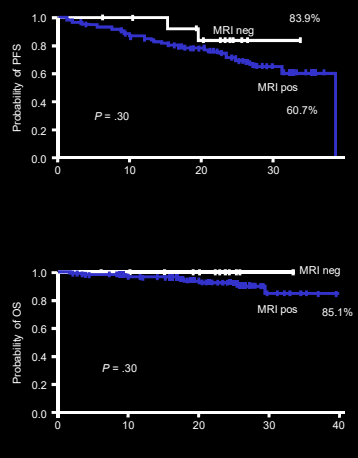
Independent experiences on small series of patients (Germany, UK, France)

- 30 pts after CHT or ASCT: good correlation with clinical response[3] (France, DCE)
- 26 pts after ASCT: feasibility of the technique[4] (UK, DWI)
- 27 pts after treatment: correlation of DCE and DWI MRI and with clinical response[5,6]
- iTIMM prospective trial DWI-WBMRI vs PET/CT in newly diagnosed MM

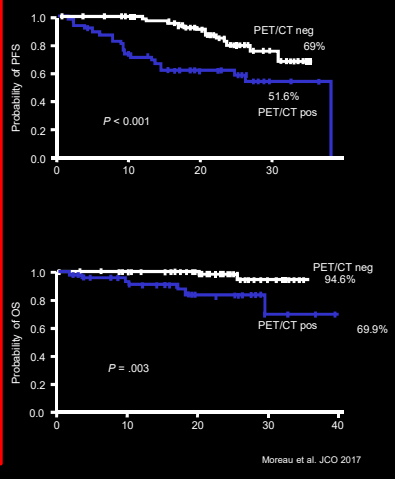
[1] Walker R. et al, JCO 2007
[2] Hillengass J. et al, Haematologica, 2012
[3] Lin C et al, Radiology 2010
[4] Giles SL. et al, Radiology 2014
[5] Bourillon C et al, Radiology 2015
[6] Dutoit JC et al, Eur J Radiol 2016

IMAJEM Secondary Endpoint: Prognostic Impact Before Maintenance

Negative MRI (11% of pts) not predictive of survival

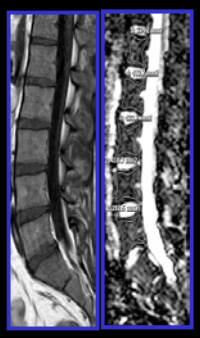


Negative PET/CT (62% of pts) associated with improved PFS, OS

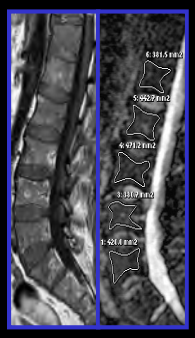


Moreau et al. JCO 2017

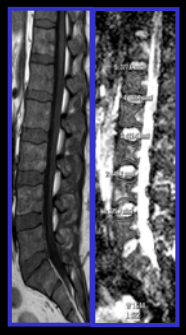
MRI- Diffusion Weighted Imaging



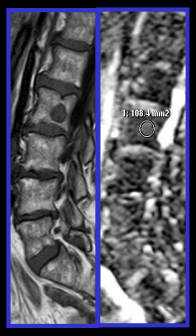
Normal MRI pattern of a 41 year-old male patient with 25% BM infiltration, mean ADC: 0.322 x 10^{-3} mm^2/sec)



Normal MRI pattern in a 77 year–old male patient with anemia and BM infiltration 25%, mean ADC: 0.496 x 10^{-3} mm^2/sec



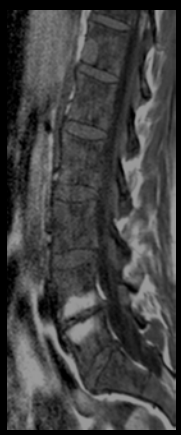
Diffuse MRI pattern of a 54 year–old male patient with 44% BM infiltration (mean ADC: 0.803 x 10^{-3} mm^2/sec)



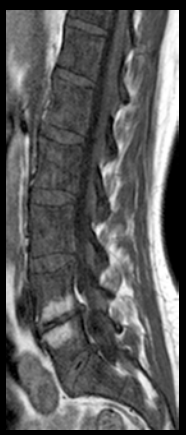
Focal MRI pattern of a 55 years-old female patient with 40% BM infiltration, max ADC: 0.778 x 10^{-3} mm^2/sec

Terpos et al. ASH 2015;abstract 4178 (poster presentation)

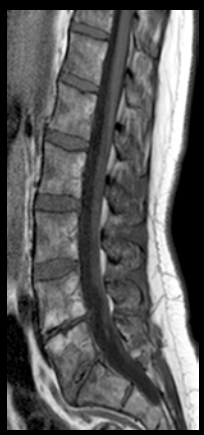
Can ADC predicts for response?



Pre RX ADC: 0.904x$10^{-3}$$mm^2$/sec



6 weeks post Rx-ADC: 0.560 x $10^{-3}$$mm^2$/sec



6 months post Rx-ADC: 0.400 x 10^{-3} mm^2/sec

Terpos, Dimopoulos, Moulopoulos et al. unpublished data

OPEN ISSUES

- Quality of many studies hampered by a poor description of selection and execution criteria
- Major inconsistency in methodology between studies
- Need to define standardized criteria for imaging definitions and positivity cut-off

Zamagni E. et al, BJH 2012
Regelink JC et al, BJH 2013

Pianko MJ et al, Clin Canc Res 2014
Mesguich C et al, EJR 2014

IMAGING SUB-STUDY OF EMN-02

- PET/CT performed:
  - Baseline
  - After induction treatment (within 10 days)

Table-1: Five-point Deauville Criteria.

Score 1	No uptake
Score 2	Uptake $\leq$ mediastinum
Score 3	Uptake $\geq$ mediastinum $<$ liver
Score 4	Uptake moderately increased above liver at any site
Score 5	Markedly increased uptake at any site including new sites of disease

* Defined as max score between Fs, BMs and EMs

Zamagni E. et al, ASH 2016

STANDARDIZATION PROJECT

- **Definition of criteria for FDG-PET/CT interpretation:**
  - Descriptive criteria, scored with the 5-point scale Deauville criteria for lymphomas
  - Positivity cut-off to be defined a posteriori
  - IMPeTUs vs prognosis: simplification of descriptive criteria and correlation with outcomes, according to prognostic evaluation of each parameter

Lesion type	Site	Number of lesions (x)	Grading
Diffuse	Bone marrow[a]		Deauville five-point scale
Focal (F)	Skull (S)	x = 1 (no lesions)	Deauville five-point scale
	Spine (SP)	x = 2 (1 to 3 lesions)	
	Extraspinal (ExP)	x = 3 (4 to 10 lesions)	
		x = 4 (>10 lesions)	
Lytic (L)		x = 1 (no lesions)	
		x = 2 (1 to 3 lesions)	
		x = 3 (4 to 10 lesions)	
		x = 4 (>10 lesions)	
Fracture (Fr)	At least one		
Paramedullary (PM)	At least one		
Extramedullary (EM)	At least one	N/EN (nodal/extranodal)[b]	Deauville five-point scale

[a] "A" if hypermetabolism in limbs and ribs

[b] For nodal disease (N): *C* cervical, *SC* supraclavicular, *M* mediastinal, *Ax* axillary, *Rp* retroperitoneal, *Mes* mesenteric, *In* inguinal; For extranodal disease (EN): *Li* liver, *Mus* muscle, *Spl* spleen, *Sk* skin, *Oth* other

FDG-PET/CT PARAMETERS AND CONCORDANCE AMONG REVIEWERS

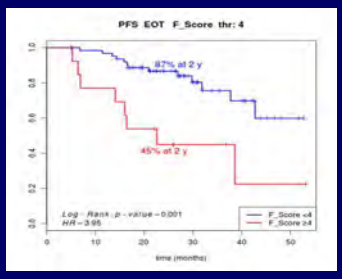
	score 2			score 3			score 4*			score 5		
	BM	Fs	EM	BM	Fs	EM	BM	Fs	EM	BM	Fs	EM
Staging	-0.01	0.51	0.05	0.32	0.52	0.05	**0.50**	**0.53**	**0.51**	0.34	0.50	0.00
Post Ind	-0.04	0.46	0.34	0.24	0.46	0.24	**0.38**	**0.45**	**0.22**	1.00	0.38	0.00
EOT	-0.03	0.51	0.42	0.22	0.59	0.42	**0.41**	**0.50**	**0.49**	1.00	0.31	0.45

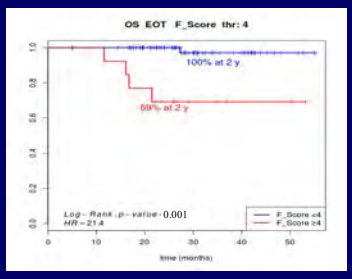
Krippendorff's alpha coefficient (> 0.5 as reference)

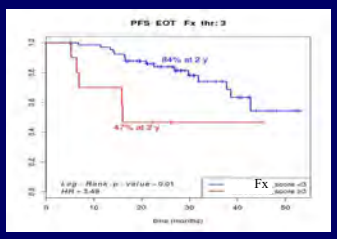
* Defined as > liver uptake (SUVmax 3.5)

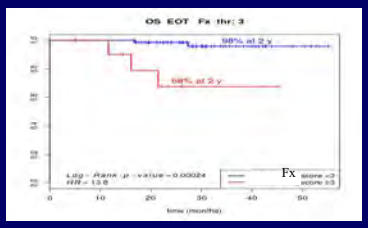
Zamagni E. et al, ASH 2016

PFS AND OS ACCORDING TO PRE-MAINTENANCE FDG-PET/CT:
Focal lesions (score ≥ 4) and number (Fx > 3)









Zamagni E. et al, ASH 2016

UNIIVARIATE ANALYSIS OF PRE-MAINTENANCE FDG-PET/CT PARAMETERS AFFECTING PFS

	HR	lower .95	upper .95	p-value
BM_Score thr:2	1,00	1,00	1,00	0,51
BM_Score thr:3	1,33	0,56	3,13	0,52
BM_Score thr:4	2,17	0,49	9,61	0,31
BM_Score thr:5	1,00	1,00	1,00	0,62
Fx thr:2	2,31	0,96	5,51	0,06
Fx thr:3	3,49	1,26	9,64	0,02
Fx thr:4	3,35	0,75	14,88	0,11
F_Score thr:2	4,03	1,62	10,02	0,00
F_Score thr:3	3,65	1,51	8,85	0,00
F_Score thr:4	3,95	1,63	9,55	0,00
F_Score thr:5	24,16	2,51	232,30	0,01
EMD	4,27	1,24	14,68	0,02
Global score thr:2 (no BM)	4,28	1,66	11,07	0,00
Global score thr:3 (no BM)	3,81	1,53	9,46	0,00
Global score thr:4 (no BM)	3,65	1,54	8,69	0,00
Global score thr:5 (no BM)	2,67	0,62	11,60	0,19

Zamagni E. et al, ASH 2016

FUTURE STEPS

•Validation of the criteria in independent series of patients (FORTE GIMEMA trial) and cross-validation with french IMAJEM study (IFM 2009 trial)

•Definition, by combined analysis of IMPeTUs and CASSIOPET, of 3 interpretative criteria:

- FLs at diagnosis
- High BM uptake
- PET CR

Italian Myeloma criteria for Pet Use

IMPeTUS

International Myeloma criteria for Pet Use

Open issues

•How to incorporate imaging into risk-stratification at diagnosis (for both smoldering and symptomatic MM) and imaging- MRD after treatment; what is the optimal follow-up with PET ?

•What to do with persistent focal lesions after systemic therapy? What is the precise biology of persistent FLs?

•Novel biomarkers for PET/CT (C-methionine[1,2],C-acetate[3],C-choline[4,5,6],MM specific tracers)

•Newer techniques (PET/MRI)

[1]Dankerl A. et al, Radiology 2007

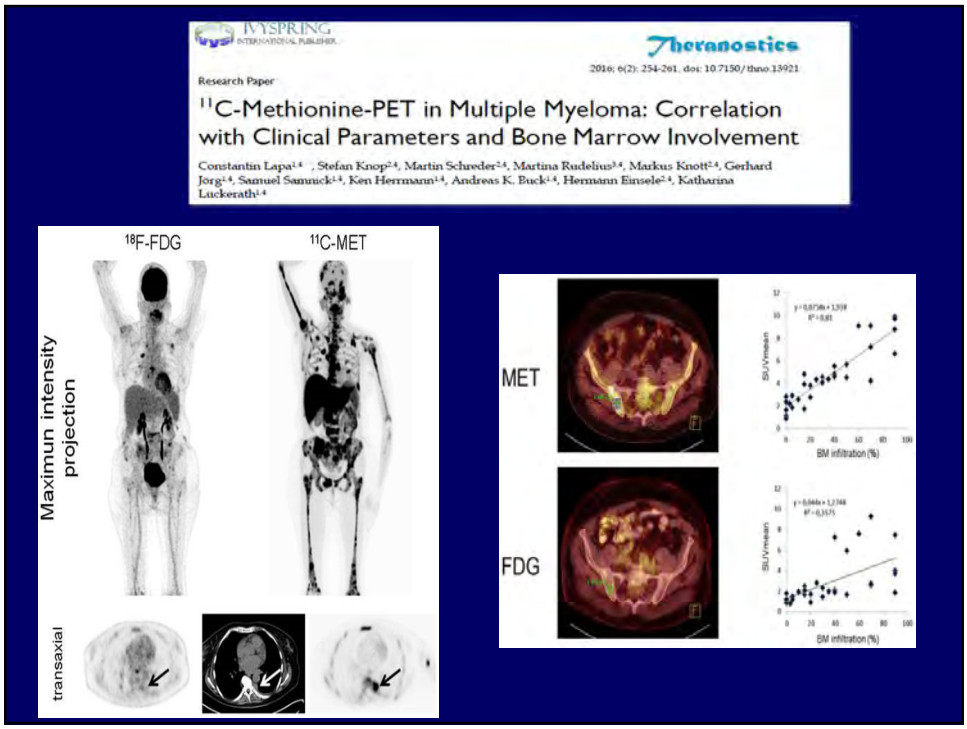
[2] Lapa C et al, Theranostics 2016

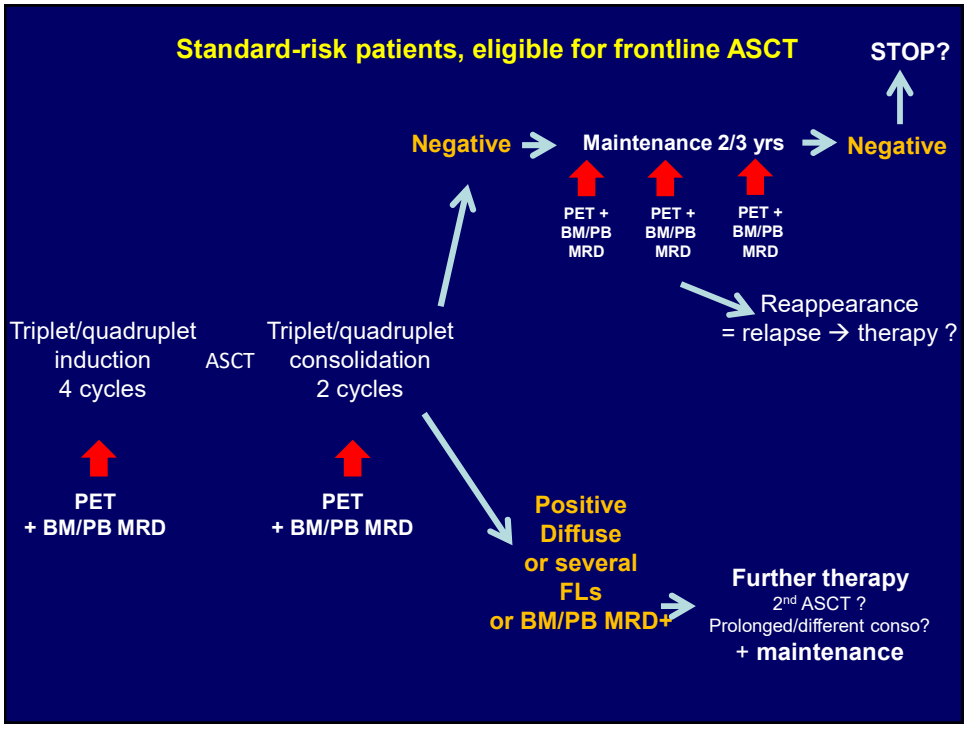
[3]Nakamoto Y. et al, Eur J Nucl Med Mol Imaging 2013

[4] Lin C. et al, Eur J Nucl Med Mol Imaging 2014

[5] Nanni C et al, World J Surgery Oncology 2007

[6] Cassou-Mounat T, Eur J Nucl Med Mol Imaging 2016


IVYSPRING INTERNATIONAL PUBLISHER
Theranostics
2016; 6(2): 254-261. doi: 10.7150/thno.13921
Research Paper
11C-Methionine-PET in Multiple Myeloma: Correlation with Clinical Parameters and Bone Marrow Involvement
Constantin Lapa, Stefan Knop, Martin Schreder, Martina Rudelius, Markus Knott, Gerhard Jörg, Samuel Samnick, Ken Herrmann, Andreas K. Buck, Hermann Einsele, Katharina Luckerath
18F-FDG
11C-MET
Maximun intensity projection
transaxial
MET
FDG
SUVmean
BM infiltration (%)


Standard-risk patients, eligible for frontline ASCT
STOP?
Negative
Maintenance 2/3 yrs
Negative
PET + BM/PB MRD
PET + BM/PB MRD
PET + BM/PB MRD
Reappearance = relapse → therapy ?
Triplet/quadruplet induction 4 cycles
ASCT
Triplet/quadruplet consolidation 2 cycles
PET + BM/PB MRD
PET + BM/PB MRD
Positive Diffuse or several FLs or BM/PB MRD+
Further therapy
2nd ASCT ?
Prolonged/different conso?
+ maintenance

CONCLUSION

- **Newer imaging techniques** have proved reliable tools in the staging and as predictors of outcome in MM patients, both in early stage and active disease and should be used in the work-up of patients
- **PET/CT and DWI-MRI** are the favorite techniques for assessing and monitoring response to therapy and are becoming complementary investigation tools for detecting minimal residual disease, going beyond the conventionally defined CR level
- **Comparative studies** between PET/CT and functional MRI are warranted
- **Implementation of prospective clinical trials** with newer imaging techniques will help to adress several issues, standardize the interpretation of the results and optimize the use of these promising tools

How to Perform an Appropriate Protein Screening and Decisions on Follow-up

Joan Bladé
Unidad de Amiloidosis y Mieloma
ICMHO, Hospital Clínic, Barcelona

Santiago de Chile, 11 de Agosto, 2017

Concept

- Clonal proliferation of mature B lymphocytes (plasma cells and/or lymphoplasmocytoid cells) resulting in a monoclonal production of an homogenous immunoglobulin (M component).

Classification

1. **Multiple myeloma (MM) and variants**
   - Smoldering myeloma
   - Plasma cell leukemia
   - Osteosclerotic myeloma (POEMS)
   - Non-secretory myeloma
   - Solitary plasmacytoma (bone or extramedullary)
2. **Waldenström`s Macroglobulinemia (WM)**
3. **Immunoglobulin light chain amyloidosis or primary amyloidosis (AL)**
4. **MG of undetermined significance (MGUS)**

Incidence

1. MM → 4-5 new cases/100.000 person
2. WM → 0.5 new cases/100.000 person
3. AL → 1 new case/100.000 person
4. MGUS
   - Patients >50 years-old → 3%
   - Patients >70 years-old → 5%

MM. Diagnostic

	MGUS	SMM	MM
BMPC (%)	<10 and	≥10 and/or	≥10*
M-protein (g/L)	<30	≥ 30	Any
Symptoms	No	No	Yes**

*Clonal
**Hypercalcemia, renal failure, anemia, bone lytic lesions, recurrent bacterial infections and/or extramedullary plasmocytomas

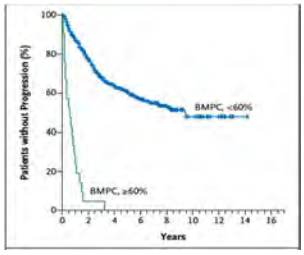
Indicators of Increasing Disease and/or End-organ Dysfunction MM-related (**CRAB**)

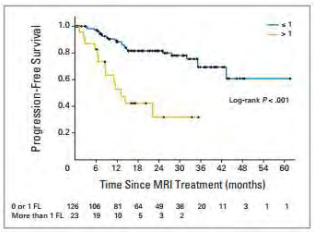
- Hyper**C**alcemia (> 11.5 mg/dL)
- **R**enal failure (↑ serum creatinine by ≥ 2 mg/dL)
- **A**nemia (↓ Hb by > 2 g/dL or < 10 g/dL)
- Increase (> 50% and at least 1 cm) in size of existing **B**one lesions or plasmacytomas
- Other: hyperviscosity, development of new soft tissue plasmacytomas or bone lesions

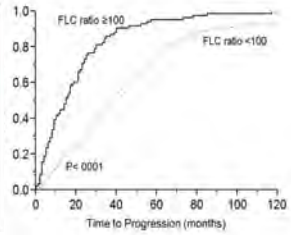
*Rajkumar *et al*, Blood 2011; 117: 4691-5.

Ultra-High Risk Smoldering Myeloma

(>80% at 2 years)







BMPC ≥ 60%

Median TTP: 7 months

Rajkumar SV et al; NEJM, 2011

> 1 FOCAL LESIONS IN MRI

Median TTP: 13 mos.

Hillengass J et al; JCO, 2011

sFLC RATIO ≥ 100

Median TTP: 15 mos.

Larsen JT et al; Leukemia, 2012

Rajkumar *et al*, Lancet Oncol 2014

Multiple Myeloma Workup

1. Complete blood count and differential; peripheral blood smear
2. Chemistry screen, including creatinine, calcium, LDH, beta2-microglobulin
3. Serum protein electrophoresis and immunofixation
3. Serum immunoglobulins (nephelometric quantification)
4. Measurement of serum free light chain (FLC)
5. 24-hour urine collection for electrophoresis and immunofixation
6. Bone marrow aspirate: morphology, immunophenotype and cytogenetics by FISH (13q, t(11;14); t(4;14); t(14;16); 17p)
7. Radiologic skeletal survey

---

10. CT and/or MRI if clinically needed
11. PET/CT in patients with suspected extramedullary disease

IMWG definition of measurable disease and recommended measurements

Definitions of measurable disease
Response criteria to all categories of response except CR are aplicable only to patients who have “measurable” disease defined by at least one of the following measurements:
– Serum M-protein ≥ 10 g/L – Urine M-protein ≥ 200 mg/24h – Involved FLC level ≥ 100 mg/L plus an abnormal FLC ratio
Measurement of the M-protein
– Serum M-protein: quantitated using densitometry on SPEP, unless than SPEP is unrelaible, which should be explicitly reported – Urine M-protein: quantitated using 24h-UPEP only – Patients with “measurable disease” should be followed monthly by both SPEP and UPEP for response assessment while on therapy

IMWG Uniform Response Criteria

sCR	CR as defined below plus normal FLC ratio plus absence of bone marrow clonal plasma cells
CR	Negative IF on serum and urine, disappearance of any soft-tissue plasmacytomas and <5% BMPC
VGPR	≥ 90% serum M-protein decrease and urine M-protein <100 mg/24h
PR	≥50% serum M-protein reduction plus ≥90% urine M-protein decrease or to <200 mg/24hrs plus ≥50% reduction in the size of soft-tissue plasmacytomas

IMGW criteria for disease progression

Increase of ≥25% from lowest level in one or more of the following*:

- – Serum M-protein (the absolute increase must be ≥ 5 g/L)
- – Urine M-protein (the absolute increase must be ≥200 mg/24hrs)
- – Bone marrow plasma cell percentage (the absolute increase must be ≥ 10%)
- – Development of new bone lesions or soft-tissue plasmacytomas or definite increase in the size of existing bone lesions or soft-tissue plasmacytomas
- – Development of hypercalcemia (corrected serum calcium >11.5 mg/dL) attributed to the plasma cell disorder

Modified from Durie et al (Leukemia 2006; 20:1467-1473)
*All categories of progression require two consecutive assessments made at any time
**For progressive disease, serum M-protein increases of > 10 g/L are sufficient to define progression if the starting serum M-component was ≥ 50 g/L

Monitoring of Patients under Active Therapy

Induction and/or Maintenance

Before every cycle

- CBC, chemistry including serum EP and 24-hours protein urine excretion with EP
- If EP negative → serum and urine IF and, if negative, bone marrow aspirate in order to confirm CR

Follow-up in Patients with Multiple Myeloma Off-Therapy

After conventional therapy: (patients with stable response)	After HDT/SCT:
– First year: every 2 months – Beyond first year: every 3 months – Beyond 5 years: every 4 months	– First 6 months: every 2 months – Two first years: every 3 months – From 2 to 5 years: every 4 months – Beyond 5 years: every 6 months

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Patients with asymptomatic relapse or PD*

– After conventional therapy: every 2 months

– After HDT/SCT: every 3 months

* Unless abrupt PD

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Lab work-up during follow-up off therapy

1. Complete blood count and chemistry
2. Serum total protein and EF
3. 24-hours urine protein measurement with EF
4. Serum and urine immunofixation and serum FLC every 2 visits only in patients in CR
5. Bone marrow aspirate and/or imaging techniques only when clinically indicated
   - Bone marrow: unexplained cytopenias (medullary progression, MDS)
   - Imaging: bone or extramedullary progression

Oligoclonal Bands

1. Monoclonal protein ≠ original
2. In patients in CR (ASCT, novel therapies)
3. Faint small bands in the gamma region, usually non-quantifiable
4. More frequent: IgG-k, IgG-λ, IgM (k or λ), k or λ light chains, rarely IgA
5. Frequently multiple and fluctuating
6. Never show a significant increase
7. Tipically persistent all along the CR duration and their disappearance usually precedes relapse

Is it time to implement minimal residual disease (MRD) in multiple myeloma management?

Jesus San-Miguel
Universidad de Navarra

1st IMS workshop, Santiago de Chile 11-12 August 2017

Disclosures

Research Support/P.I.	NA
Employee	NA
Consultant	NA
Major Stockholder	NA
Speakers Bureau	NA
Honoraria	NA
Scientific Advisory Board	NA

What should be the goal of treatment in MM?

To search for an appropriate balance between treatment efficacy, toxicity & costs

- To eradicate the all tumor cells
- To achieve and maintain the best possible response

- *MGUS signature: <10% of patients may achieve a functional cure with persistent clonal cells*
  - *Persistent MGUS-like clones after therapy* [1,2]
  - *Immune surveillance of residual clones* [3,4]

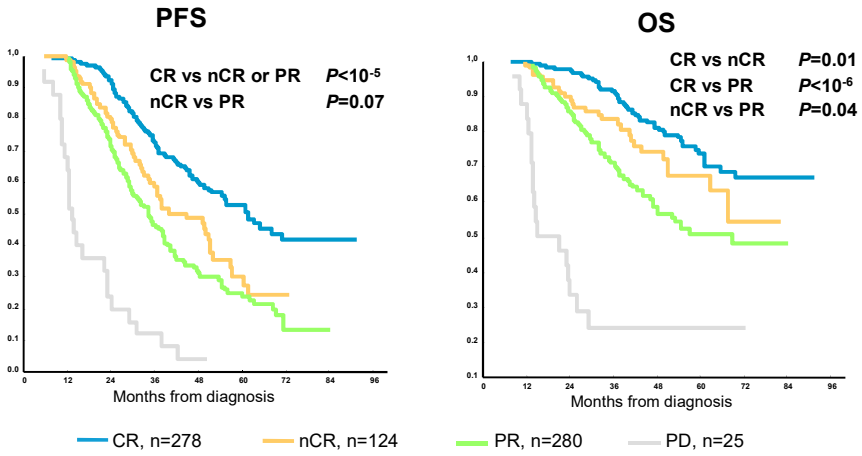
1. Zhan F, et al. Blood. 2007;109:1692-700
2. Paiva B, et al. Leukemia. 2013;27:2056-61
3. Pessoa de Magalhães RJ, et al. Haematologica. 2013;98:79-86
4. Bryant C, et al. Blood Cancer J. 2013;3:e148

Evidence supporting this statement

CR a surrogate marker for survival

The better the quality of the response the longer the survival

Clinical impact of CR in transplant-eligible MM

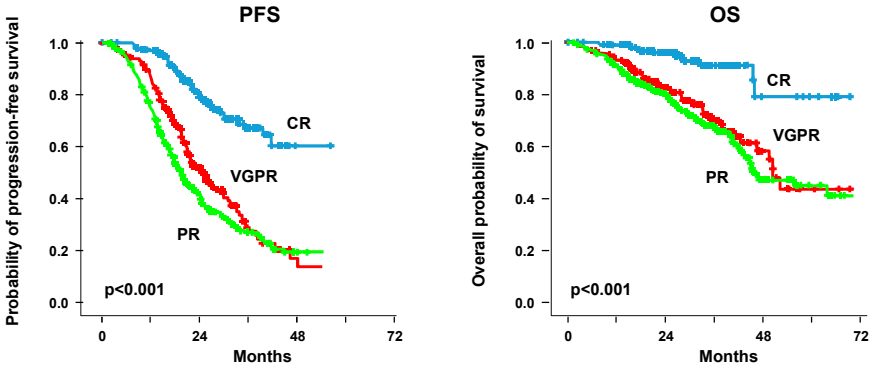


	CR	nCR	PR	PD
Median PFS, months	61	40	34	13
Median OS, months	NR	NR	61	15

Lahuerta JJ et al. J Clin Oncol 2008;26:5775–5782

Clinical impact of CR in elderly MM

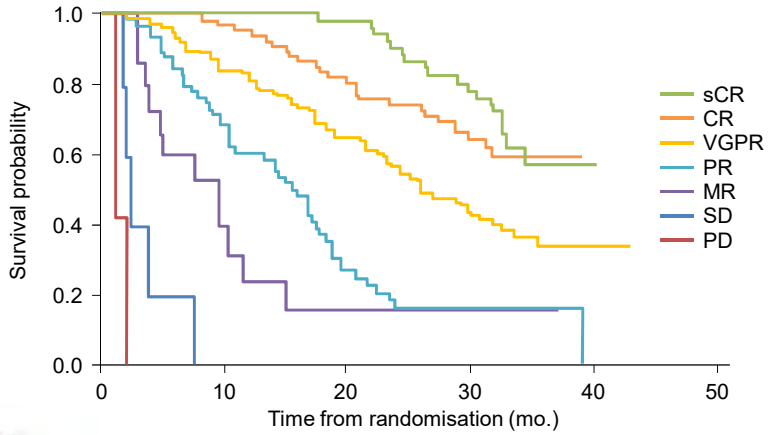
- Retrospective analysis: 3 randomized European trials of GIMEMA and HOVON groups (n=1175)
- First-line treatment: MP (n=332), MPT (n=332), VMP (n=257), VMPT-VT (n=254)



Significant benefit also seen when analysis is restricted to patients >75 years old

Gay F et al. Blood 2011;117:3025-3031

Clinical impact of CR in relapsed/refractory MM



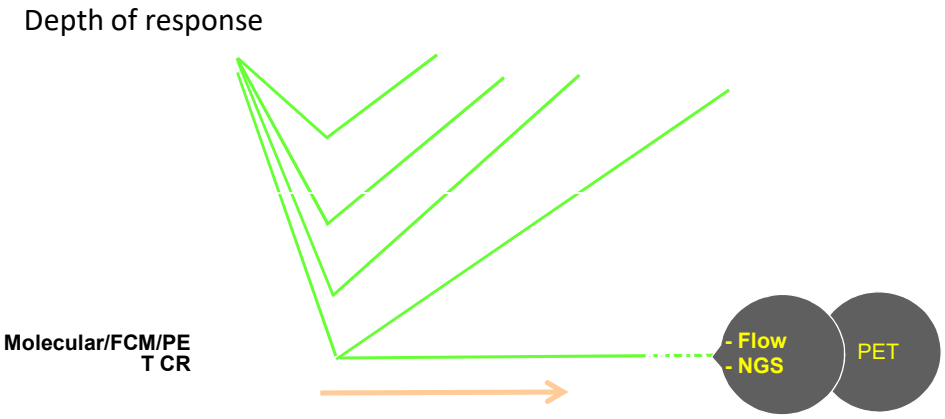
Suppl. to Stewart AK, et al. N Engl J Med. 2015;372:142–52

CR criteria in MM are suboptimal

- **Negative Immunofixation & < 5% PC in BM**

More sensitive techniques are needed…
MRD Techniques

Which level of response should be measured?



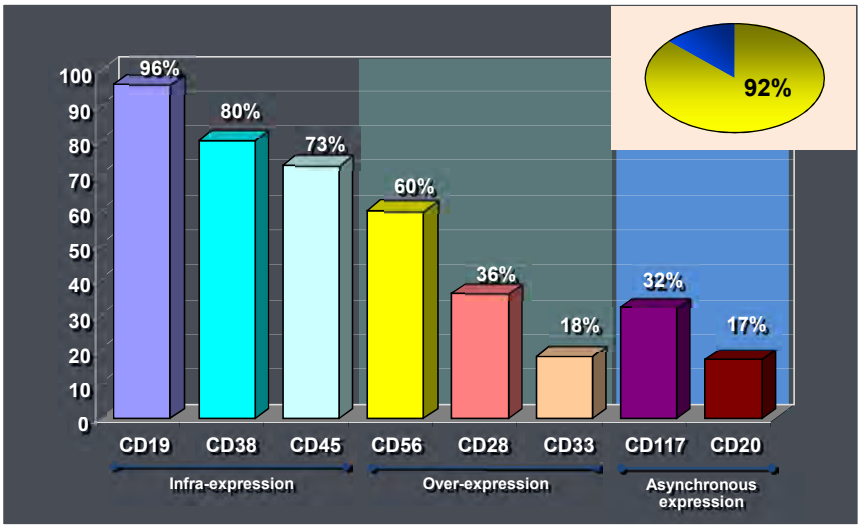
More sensitive techniques are needed…..

Multiparametric Flow Cytometry

Critical analysis on the value of

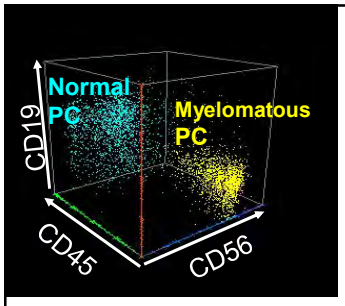
MRD versus CR

Incidence of phenotypically aberrant MM-PC (N= 915)



Mateo G et al. J Clin Oncol; 2008;26:2737-44.

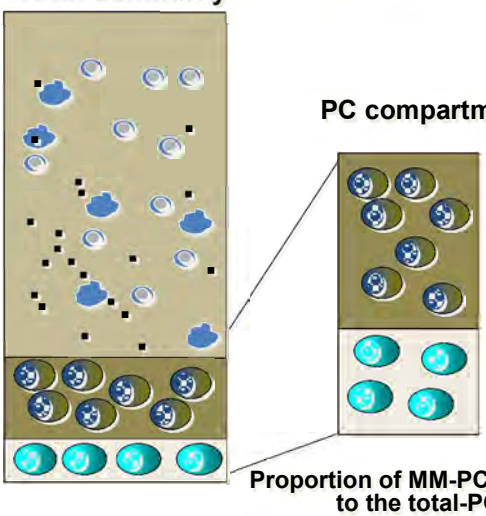
MRD:parameters analyzed



Distinction between myelomatous & normal PC

Total cellularity

PC compartment



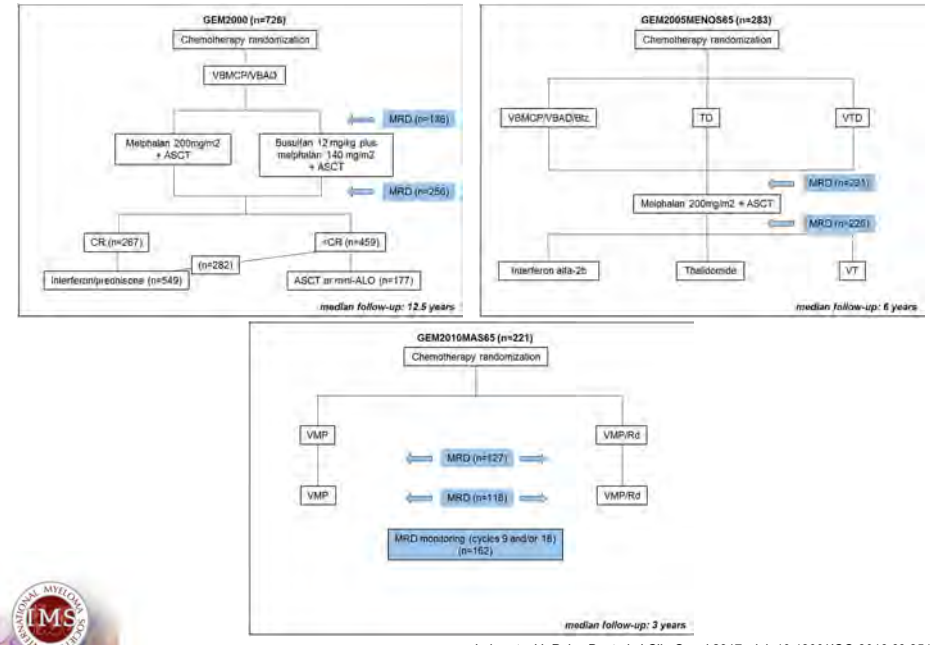
% myelomatous PC
% MM-PC
% normal PC % N-PC

Proportion of MM-PC referred to the total-PC

%MM-PC/ total-PC

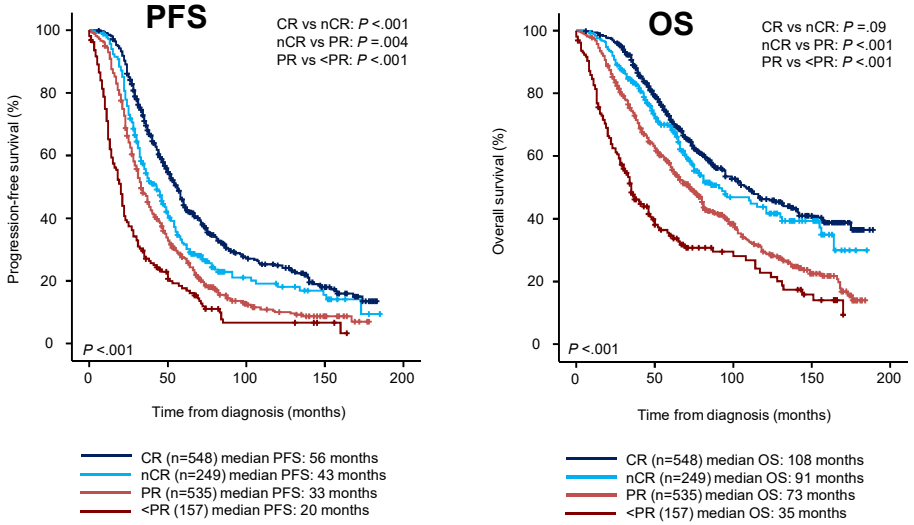
San Miguel JF et al Blood; 2002; 99:1853-6.

Critical analysis on the value of CR and MRD



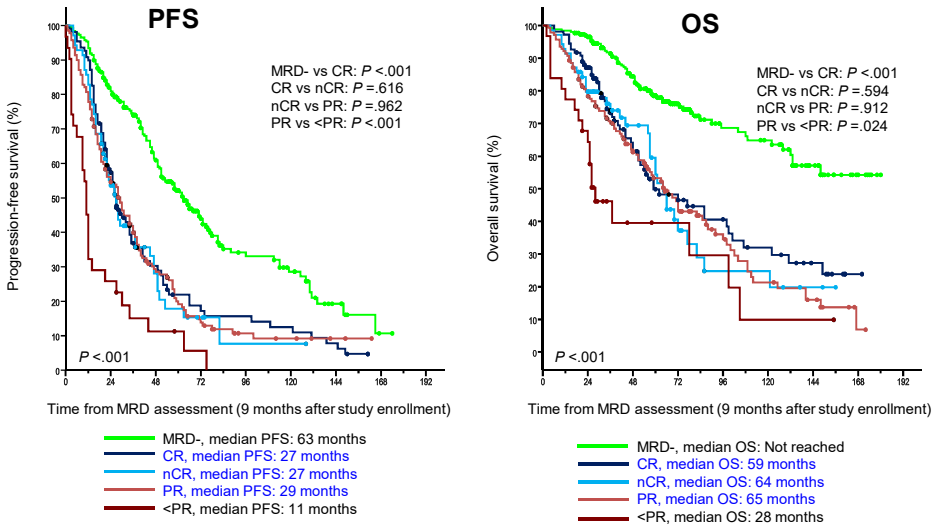
Lahuerta JJ, Paiva B, et al. J Clin Oncol 2017; *doi: 10.1200/JCO.2016.69.2517.*

Patients attaining CR experience prolonged PFS and OS…but…



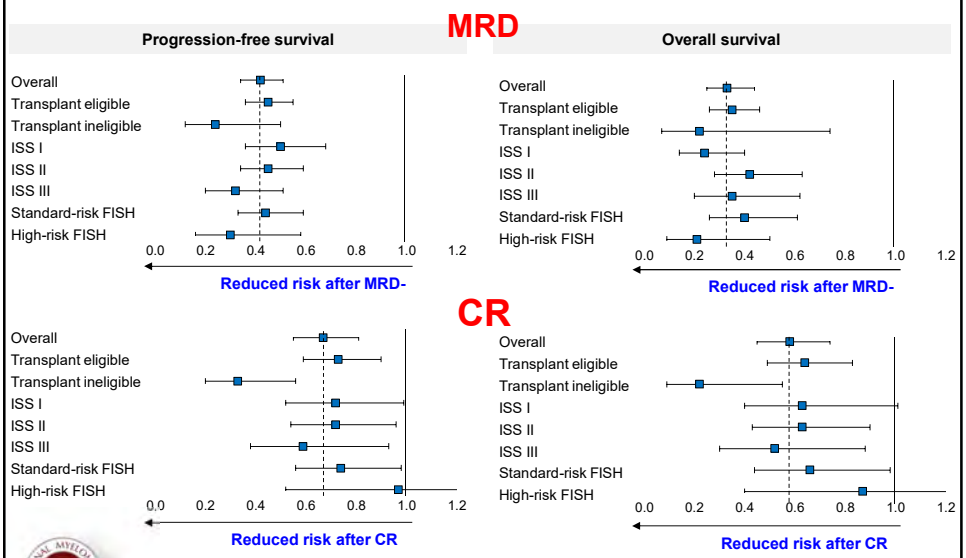
GEM2000, GEM2005MENOS65, GEM2005MAS65, GEM2010MAS65

The true value of CR relies in the MRD status, and CR w/o MRD is no better than PR



Lahuerta JJ, Paiva B, et al. J Clin Oncol 2017; *doi: 10.1200/JCO.2016.69.2517.*

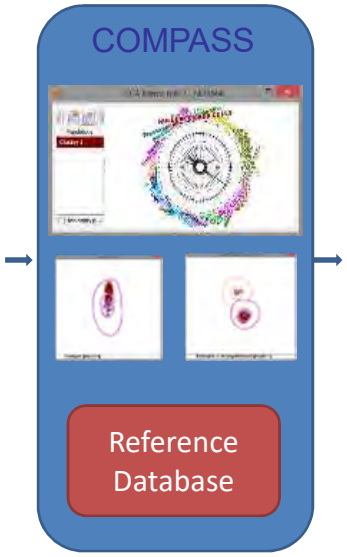
MRD vs CR across MM patient' subgroups



Lahuerta JJ, Paiva B, et al. J Clin Oncol 2017; *doi: 10.1200/JCO.2016.69.2517.*

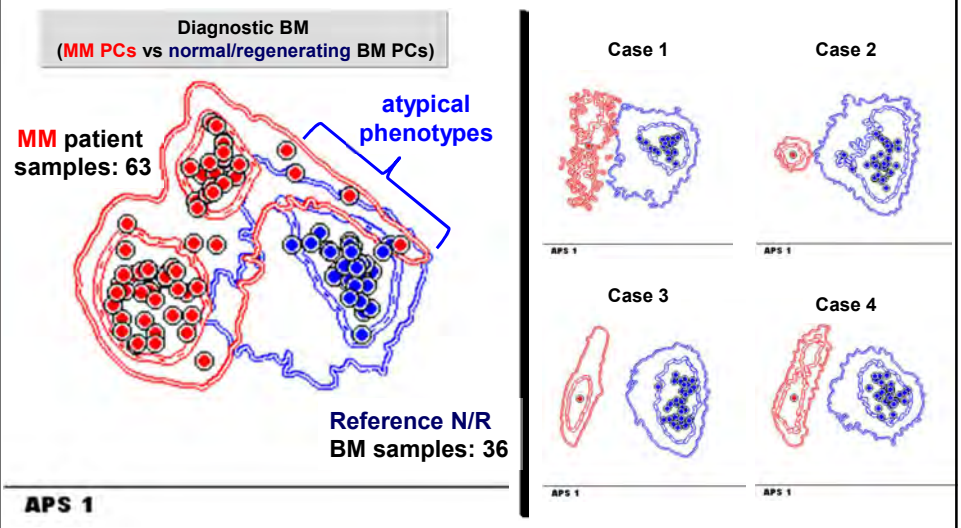
Next generation Flow-MRD monitoring in MM

*An **optimized** 2-tube 8-color monoclonal antibody panel was constructed **after five rounds of design-evaluation-and-redesign**. Additionally, a bulk-lysis sample preparation procedure was established for acquisition of **≥10^7 cells/patient**, and novel software tools for **automated analysis***



Flores-Montero J, et al. Leukemia. 2017. doi: 10.1038/leu.2017.29

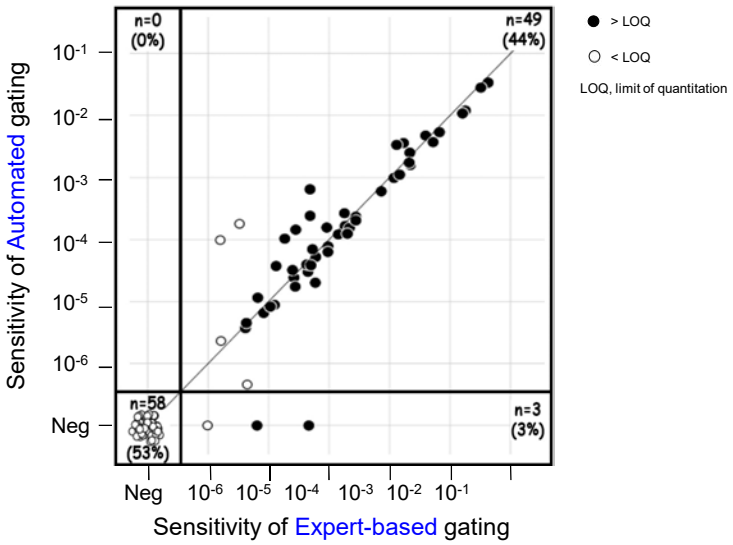
Next generation Flow-MRD monitoring in MM
- applicable to all patients -



New software: Principal component analysis: clusters

Flores-Montero J, et al. Leukemia. 2017. doi: 10.1038/leu.2017.29

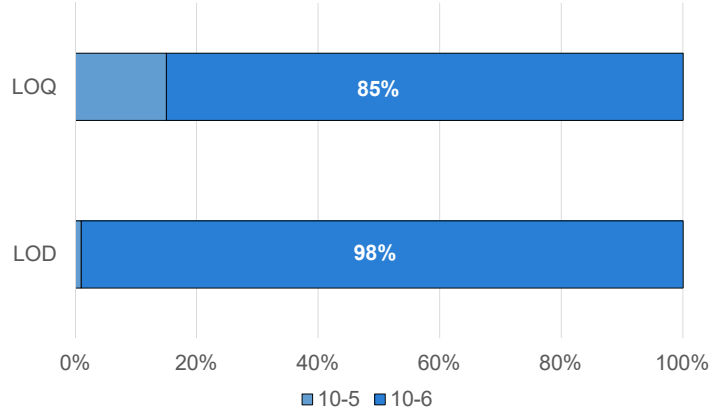
NGF expert (manual) vs automated analysis



TIME OF DATA ANALYSIS (automated vs expert-based analysis):
8h 52m vs. 19h 39m (4m 50s vs. 10m 43s/case)

Flores-Montero J, et al. Leukemia. 2017. doi: 10.1038/leu.2017.29

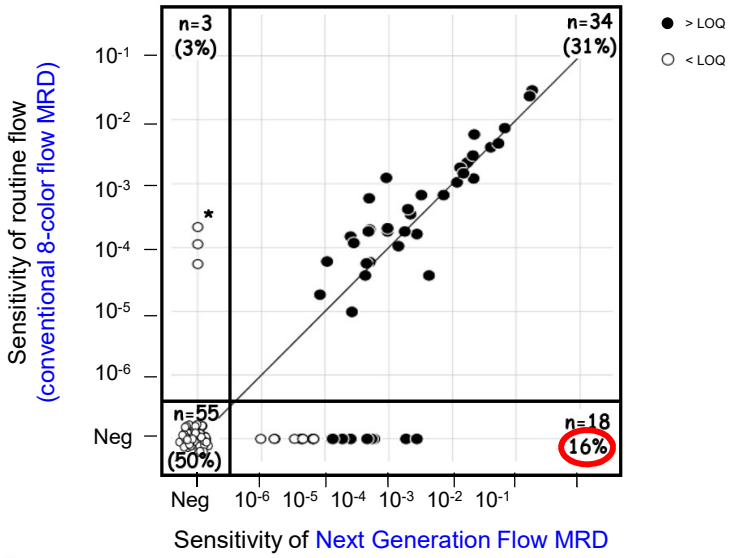
NGF reaches 10^{-6} sensitivity in the vast majority of MM patients (GEM2012MENOS65)



LOQ (level of quantitation) : 50 cells / total nucleated viable cells
LOD (level of detection): 20 cells / total nucleated viable cells

Flores-Montero J, et al. Leukemia. 2017. doi: 10.1038/leu.2017.29

NGF vs 2nd generation flow



* 2 samples proven polyclonal by Cylg staining

Flores-Montero J, et al. Leukemia. 2017. doi: 10.1038/leu.2017.29

Next generation Flow-MRD monitoring in MM

ADVANTAGES

- World-wide availability
- High applicability: 100%
- Fast for clinical decisions (<4h)
- Relatively simple
- Quantitative (% myeloma PCs)
- high-sensitivity ($3x10^{-6}$)
- Assessment of non-PC BM cell compartments: sample QC
- Standardized (EuroFlow)
- Cost (250 euro/sample)

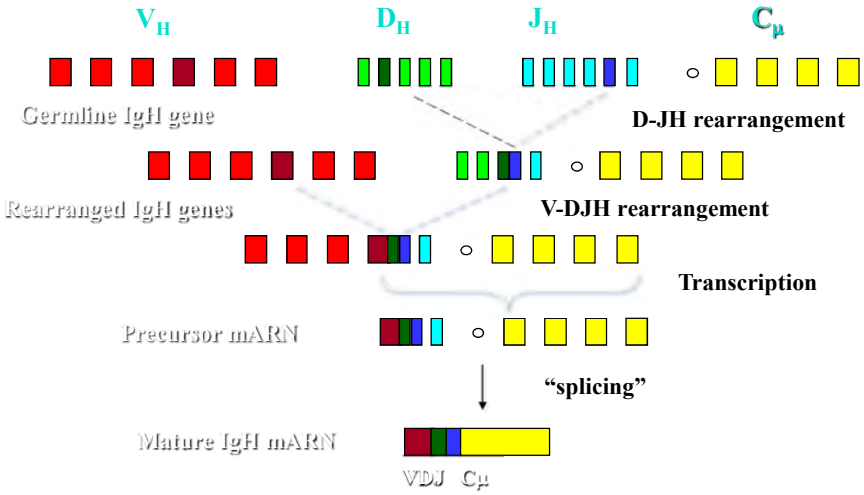
LIMITATIONS (?)

- Fresh (<48h) samples required
- ~~Less sensitive than molecular methods~~
- ~~Lack of standardization~~
- Heterogeneous BM infiltration or extramedullary disease

Achieving a Global Standard for MRD Testing

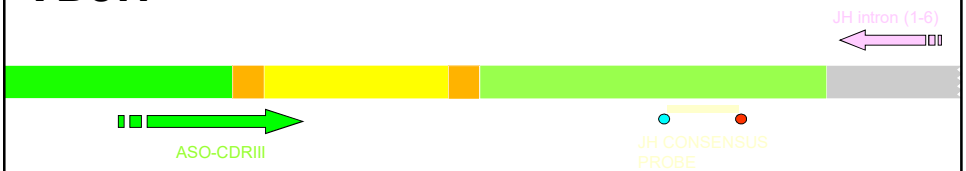
Over 40 laboratories in 16 countries have implemented NGF

Immunoglobulin heavy (IgH) chain gene rearrangement

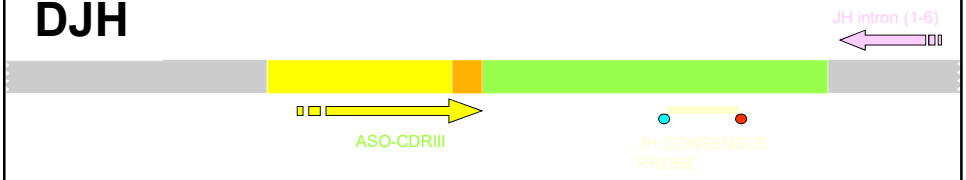


REAL-TIME strategy for *IGH* rearrangements

VDJH*

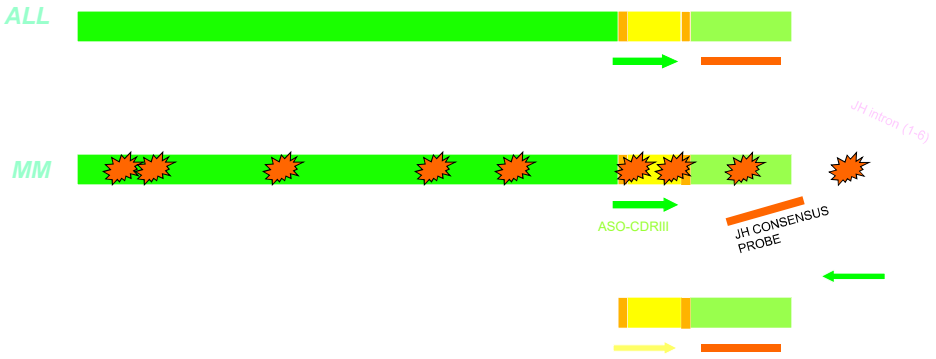


DJH



Verhagen et al, Leukemia 2000; 14:1426

PITFALS FOR THE RQ-PCR CONSENSUS IN MM



MM: Somatic Mutations in VDJH: 100% (invalid for consensus primers), while in DJH 12%

Gonzalez et al Leukemia 2003, Hematologica 2005

1.Use several targets: VDJH, DJH, Kde, 2.*Clone PCR products* (time & labor consuming)

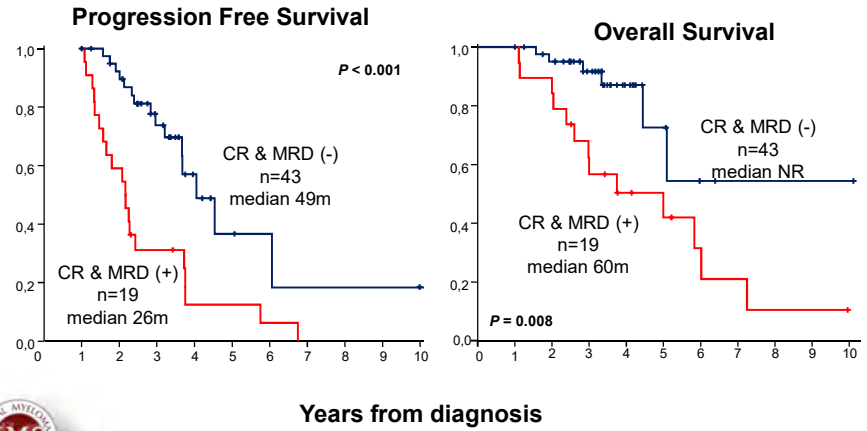
3.Design patient-specific primers, both forward and reverse *4. Design patient-specific probes* (expensive)

Prognostic value of MRD evaluation by PCR (Qualitative & semi-Q) in MM

Author	Context	Sensitivity	N	MRD Status	PFS	OS
Corradini JCO 1999	QL ASO-PCR Auto/Allo	10^{-6}	29	20 positive 9 negative	55% 78%	NR
López-Pérez et al Leukemia 2000	QL cons-PCR Auto, apheresis	10^{-3}-10^{-4}	27	12 positive 11 negative	20 m* 40 m	20%* 86%
Martinelli JCO 2000	QL ASO-PCR Auto/Allo	10^{-6}	44	32 positive 12 negative	65%* 93%	NR
Corradini Blood 2003	QL ASO-PCR Allo	10^{-6}	48	16 positive 19 mixed 13 negative	0% 33% 100%	NR
Ladetto et al, JCO, 2010	QL Nested-PCR VTP Post-Auto	10^{-6}	39	33 positive 6 negative	66% 100%	NR
Terragna et al, ASH 2010	QL Nested-PCR VTD vs. TD post-auto	NR	67	27 positive 60 negative	NR NR	VTD: 67% TD: 52%
López-Pérez et al Leukemia 2000	Semi-QT FL-PCR Auto, apheresis	10^{-3}-10^{-4}	23	14 positive 13 negative	19 m* 39 m	28%* 81%
Bakkus BJH 2004	Semi-QT PCR LDM Auto	10^{-6}	59	38 >0,015% 22 <0.015%	16 m* 64 m	NR
Martínez-Sánchez et al BJH 2008	Semi-QT FL-PCR	10^{-3}-10^{-4}	53	25 positive 28 negative	28%* 68%	68% 86%
Puig et al Leukemia 2014	QL ASO-PCR	10^{-6}	103	55 positive 48 negative	27m 54m	

MRD monitoring using ASO-PCR

31% of the patients in conventionally-defined CR had positive MRD by ASO-PCR



Puig N, et al. Leukemia. 2014;28(2):391-7

MRD monitoring using ASO-PCR

PROS

- Highly-specific detection of clonality
- Sensitivity (10^{-6})
- Detection of putative CSCs
- Reproducibility among centers
- Does not require immediate sample processing
- Standardized (EuroMRD)

CONS

- Limited applicability (~60%)
- Limited value in patients with patchy BM infiltration and/or extramedullary disease
- Does not measure subclonal dynamics
- No assessment of sample quality
- Requires diagnostic sample
- Turnaround time & time consuming
- Cost (increased by baseline sample)

MRD monitoring using NGS

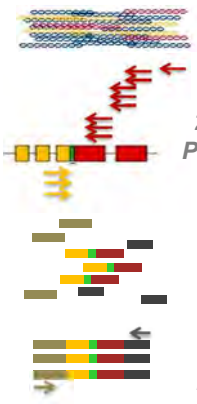
Commercial

Adaptive SEQUENTA

immunoSEQ™ Amplify Discovery

invivoscribe

Home-made



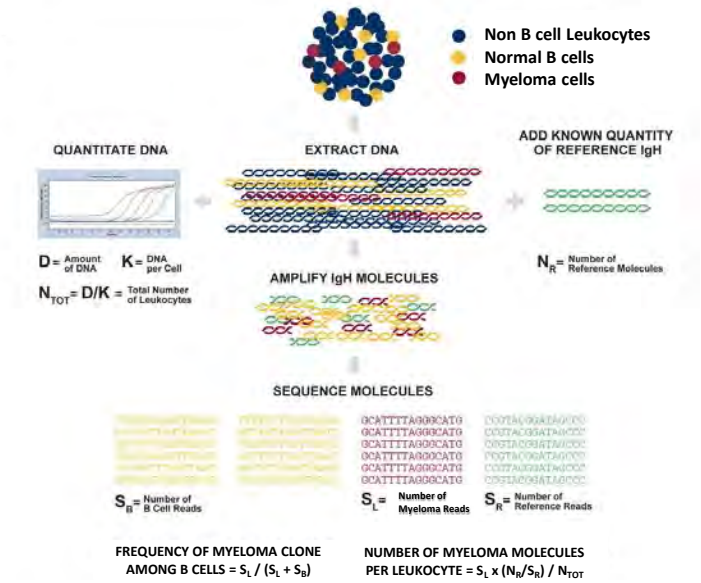
1. Extraction and quantification of gDNA (qPCR)

*2. VDJ, DJ,KDEL etc. PCR amplification with **Biomed 2 primers***

3. Ligation with barcodes

4. Sequencing, Ion Proton Platform

The LYMPHOSIGHT™ Platform



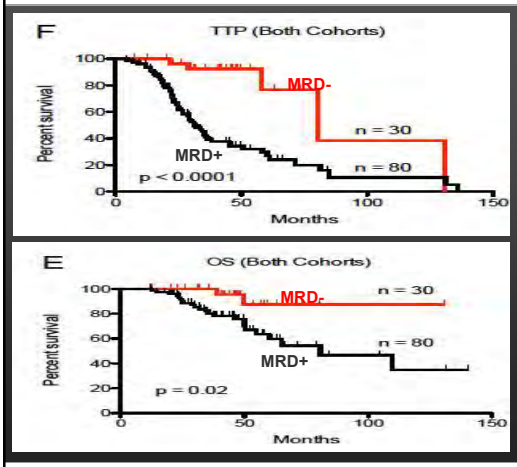
MRD monitoring by NGS

high-sensitivity and superior applicability compared to ASO-PCR

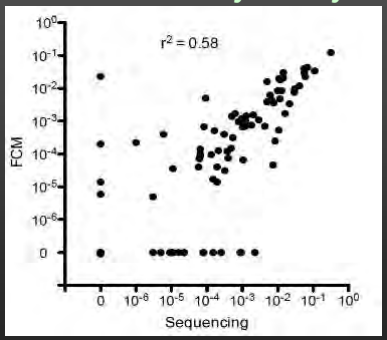
Deep sequencing of rearranged BCR genes **(Lymphosight™)**

N 133 cases in CR or VGPR (sensitivity ≥10^{-5}), GEM00,05,10;

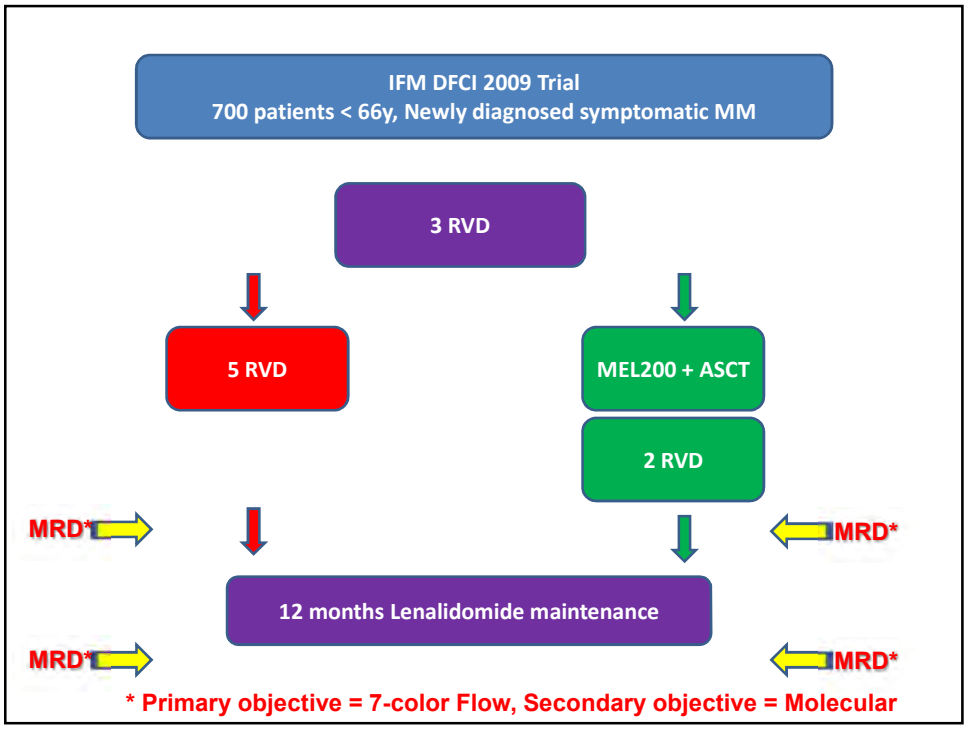
Detection of myeloma-specific gene rearrangements in diagnostic samples of 91% patients: High Applicability



NGS vs. Flow cytometry

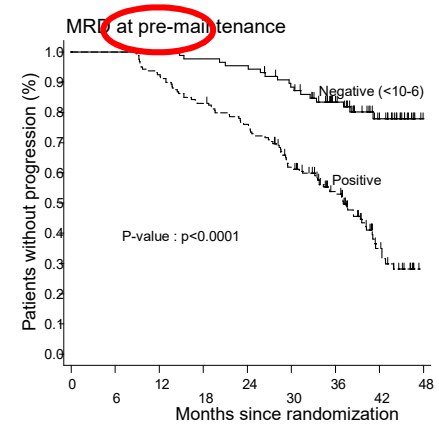


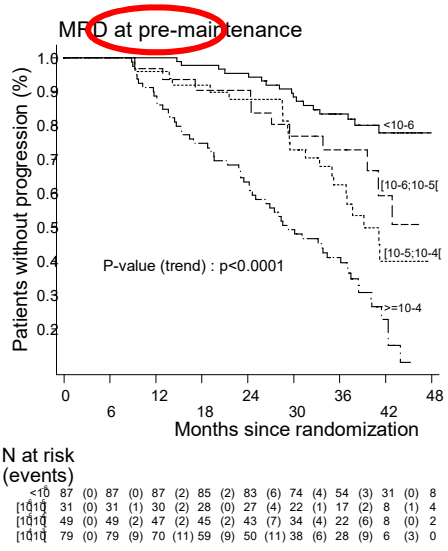
Martinez-Lopez et al , Blood. 2014 May 15;123(20):3073-9



MRD monitoring using NGS

Deep sequencing of rearranged BCR genes

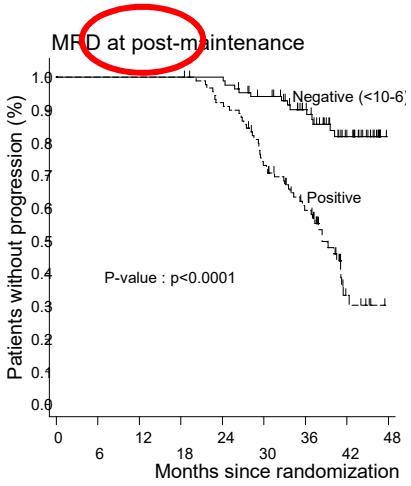




Avet-Loiseau H, et al. Blood 2015;126: abstract 191

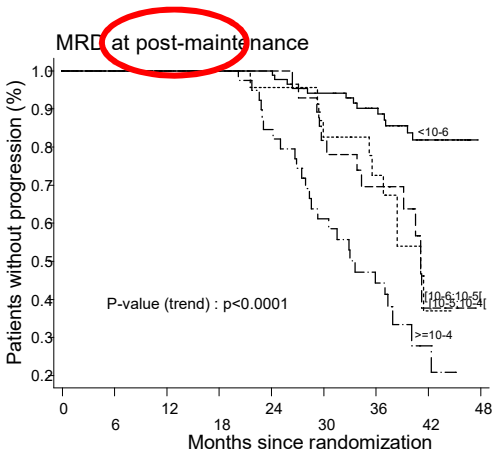
MRD monitoring using NGS

Deep sequencing of rearranged BCR genes



N at risk (events)

MRD neg (<10^{-5})	80	(0)	86	(0)	86	(0)	86	(0)	86	(5)	77	(3)	61	(5)	36	(0)	10			
MRD positive	92	(0)	92	(0)	92	(0)	92	(7)	83	(17)	64	(11)	45	(13)	11	(1)	5			



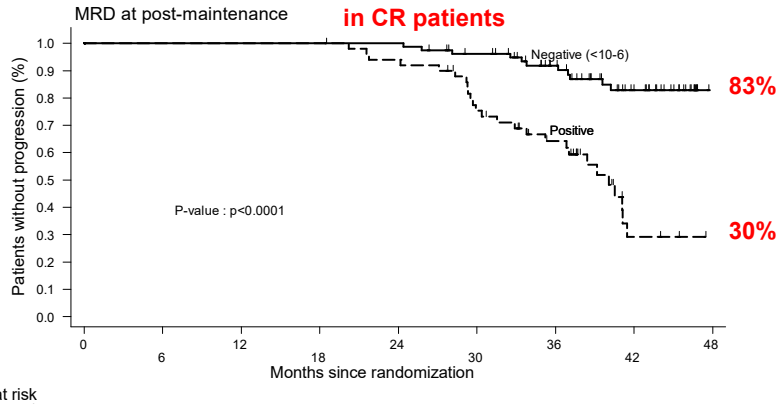
N at risk (events)

<10^{-6}	86	(0)	86	(0)	86	(0)	86	(0)	86	(5)	77	(3)	61	(5)	36	(0)	10			
[10^{-6};10^{-5}[	29	(0)	29	(0)	29	(0)	29	(0)	28	(5)	22	(3)	16	(4)	4	(1)	1			
[10^{-5};10^{-4}[	23	(0)	23	(0)	23	(0)	23	(1)	22	(3)	19	(2)	14	(5)	3	(0)	2			
[10^{-4};10[	40	(0)	40	(0)	40	(0)	40	(6)	33	(9)	23	(6)	15	(4)	4	(1)	2			

Avet-Loiseau H, et al. Blood 2015;126: abstract 191

MRD monitoring by NGS redefines the concept of CR in myeloma

39% of the patients in conventionally-defined CR had positive MRD by NGS



N at risk (events)

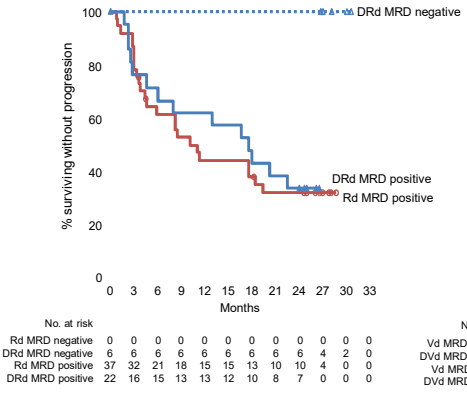
MRD neg (<10^{-5})	80	(0)	80	(0)	80	(0)	80	(0)	80	(3)	73	(3)	57	(5)	33	(0)	9
MRD positive	51	(0)	51	(0)	51	(0)	51	(3)	47	(9)	36	(5)	26	(9)	6	(0)	3

Avet-Loiseau H, et al. Blood 2015;126: abstract 191

Dara+ Lena-dex (POLLUX) & Dara+ Bort-dex (CASTOR) :

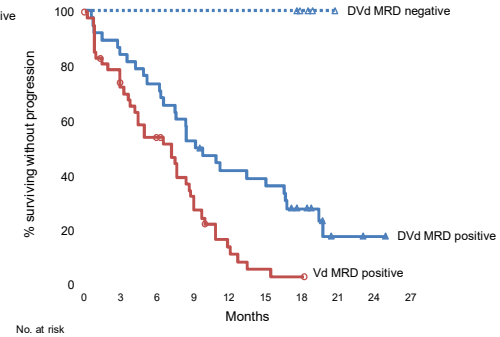
PFS according to MRD in Patients of High Cytogenetic Risk Status (10^{-5})

Pollux



No. at risk												
Rd MRD negative	0	0	0	0	0	0	0	0	0	0	0	0
DRd MRD negative	6	6	6	6	6	6	6	6	4	2	0	
Rd MRD positive	37	32	21	18	15	15	13	10	10	4	0	0
DRd MRD positive	22	16	15	13	13	12	10	8	7	0	0	0

CASTOR



No. at risk											
Vd MRD negative	0	0	0	0	0	0	0	0	0	0	
DVd MRD negative	6	6	6	6	6	6	3	0	0	0	
Vd MRD positive	51	32	23	13	4	2	1	0	0	0	
DVd MRD positive	38	32	28	20	15	14	8	2	1	0	

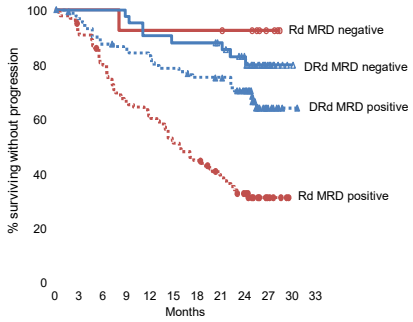
High-risk patients treated with DARA who were MRD negative remained progression free

[a]Percentage of patients within a given risk group and treatment arm.

Dara+ Lena-dex (POLLUX) & Dara+ Bort-dex (CASTOR) :

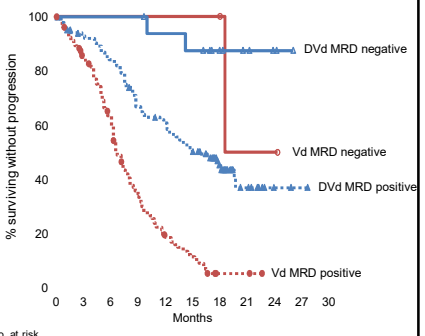
PFS according to MRD in Patients of Standard Cytogenetic Risk Status (10^{-5})

Pollux



No. at risk												
Rd MRD negative	13	13	13	12	12	12	12	12	11	4	0	0
DRd MRD negative	42	42	42	41	38	37	37	35	26	8	1	0
Rd MRD positive	100	91	79	65	60	51	44	35	25	6	0	0
DRd MRD positive	91	86	78	75	73	69	65	64	50	11	1	0

CASTOR



No. at risk											
Vd MRD negative	3	3	3	3	3	3	3	1	1	0	0
DVd MRD negative	17	17	17	17	15	14	9	6	3	0	0
Vd MRD positive	132	103	76	41	22	13	2	2	0	0	0
DVd MRD positive	106	93	84	66	59	49	27	9	2	1	0

[a]Percentage of patients within a given risk group and treatment arm.

MRD supersedes CR

and could met some of the key requirements for a surrogate endpoint such as:

- move the PFS of patients in remission from 3-5 years to 8-10 years
- independence from treatment
- predict different outcomes upon different MRD-negative rates
- useful in all patient' subgroups
- reliable and widely available techniques

IMWG Criteria for MRD in Multiple Myeloma

	Response subcategory	Response criteria
IMWG MRD negativity criteria (Requires CR as defined below)	Sustained MRD negative	MRD negative in the marrow (Next-generation flow or Next-generation sequencing) and by imaging as defined below, confirmed one year apart. Subsequent evaluations can be used to further specify the duration of negativity (e.g., MRD negative @ 5 years etc)
	Imaging MRD-negative	MRD negative as defined below (Next-generation flow or Next-generation sequencing) PLUS Disappearance of every area of increased tracer uptake found at baseline or a preceding PET/CT[3]
	Flow MRD-negative	Absence of phenotypically aberrant clonal plasma cells by next-generation flow cytometry[4] on bone marrow aspirates using the EuroFlow standard operation procedure for MRD detection in MM (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells or higher
	Sequencing MRD negative	Absence of clonal plasma cells by next generation sequencing on bone marrow aspirates in which presence of a clone is defined as less than 2 identical sequencing reads obtained after DNA sequencing of bone marrow aspirates using the Lymphosight® platform (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells[5] or higher

Kumar SK, et al. *Lancet Oncology*. In press.

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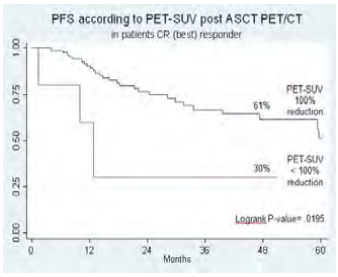
Kumar SK, et al. *Lancet Oncology*. In press.

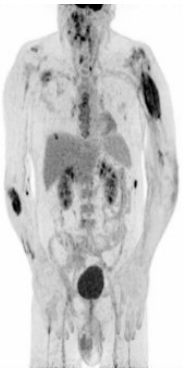
Predictive value of PET/CT after treatment in MM patients: The concept of PET CR

ASCT candidates (192 pts)

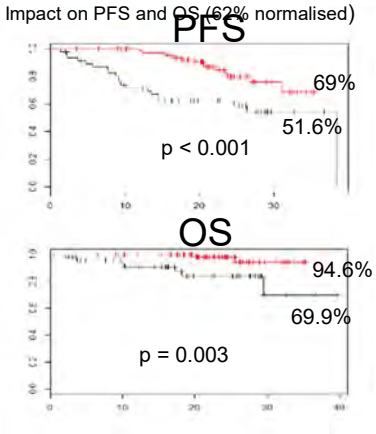


3m post-ASCT: Complete FDG suppression at PET/CT ……Longer PFS & OS

Zamagni E. et al, Blood 2011;118(23):5989
Zamagni E, et al. Clin Cancer Res 2015;21(19):438

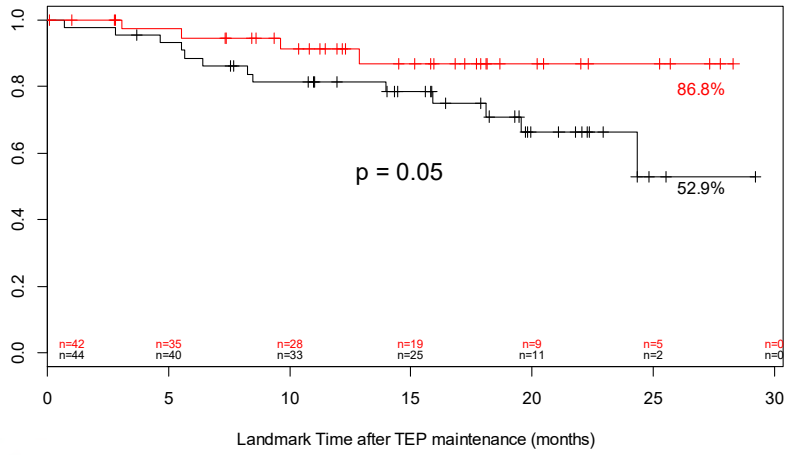


IFM 2009: PET-CT normalisation before maintenance
Impact on PFS and OS (62% normalised)



Moreau P, et al. Blood 2015 126:395

PFS for patients with negative PET-CT and negative MRD by flow cytometry before maintenance (48%) vs others (52%)*



*Total: 86 Patients

Moreau et al. ASH2015; JCO 2017 in press

Individual features of currently available techniques to monitor MRD

	NGF	ASO-PCR	NGS	PET/CT
Applicability	~100%	60-70%	~90%	~100%*
Reproducibility	High	High	Not reported	Moderate at MRD
Availability	High	Intermediate	Limited	Intermediate
Diagnostic sample	Important but not mandatory	Mandatory	Mandatory	Important but not mandatory
Time	2-3 hours	≥5 days (follow-up)	≥7 days	2-hours
Cost per sample	~350 USD	~500 USD (follow-up)	~700 USD	~2.000 USD
Sensitivity	10^{-5} – 10^{-6}	10^{-5} – 10^{-6}	10^{-6}	High (4 mm)
Quantitative	Yes	Yes	Yes	Yes
Fresh sample	Needed	Not needed	Not needed	NA
Patchy sample	Impacts	Impacts	Impacts	No impact
Global cell characterization	Yes	No	No	No
Standardization	Ongoing (EuroFlow)	Yes, (EuroMRD)	Not reported (Adaptive) Ongoing (EuroMRD)	No

Paiva B, Van Dongen JJ, Orfao A. Blood. 2015;125(20):3059-3068

New Sensitive tests for diagnosis, prognosis and to monitor treatment efficacy

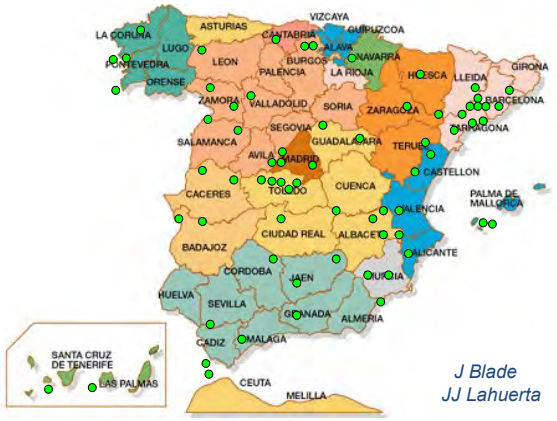
- Myeloma Diagnosis and monitoring can not remain in the **Paleolithic era** (….morphology and conventional Radiology)
- In MM you need to evaluate MRD **inside and outside** the BM
- New techniques require **standardization** (Precaution for treatment decisions…!!)
- There are **singular MM subtypes** ('rapid responders but early relapsing' or with 'MGUS profile'): in these the standard response criteria do not correlate with outcome

New Sensitive tests for diagnosis, prognosis and to monitor treatment efficacy (II)

- New techniques are **expensive**…. MRD follow-up study (1200 $), PET (1300$)…….but compare this with the costs of just one additional cycle of novel drugs (sometimes no needed)……
- MRD techniques will contribute both to a better **definition of response** and to **monitor the efficacy** of intensification and maintenance therapies…may be critical **to tailor treatment** to avoid both under & over treatments
- But….Please do not forget **Standard techniques**

Grupo Español de Mieloma (GEM)

Hospitales
Clínico de Barcelona
12 Octubre (Madrid)
Clínico de Salamanca
Clínico de San Carlos (Madrid)
Hospital de Badalona
Clínico de Asturias
Fr. Peset (Valencia)
Universitario de Canarias
Rio Ortega (Valladolid)
Cínico de Zaragoza
Hospital General de Jerez
Ramón y Cajal (Madrid)
Morales Meseguer (Murcia)
La Fe (Valencia)
C.U. de Navarra
Galdakao (Vizcaya)
Clínico de Valladolid
Sant Pau (Barcelona)
Arnau Vilanova (Lérida)
Universitario de Santiago
General Universitario de Valencia
Universitario de Getafe (Madrid)
Insular de las Palmas
H. de La Princesa (Madrid)
Severo Ochoa (Madrid)
Juan XIII (Tarragona)
Toledo
Gandia (Valencia)
Vall D´Hebrón (Barcelona)
San Jorge (Huesca)
Verge de la Cinta (Tortosa)
Alarcos (Ciudad Real)
Mataró (Madrid)
Juán Canalejo (Coruña)
Ferrol



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JJ Lahuerta

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Salamanca: A. Orfao *Mv Mateos; E Ocio; N. Gutierrez; R Garcia-Sanz,* Flores-Montero J
Navarra: *B. Paiva, P Maiso, P. Rodriguez, MJ Calasanz, F Prosper*

HOSPITAL UNIVERSITARIO DE SALAMANCA

IBSAL Instituto de Investigación Biomédica de Salamanca

University of Salamanca

MGUS & Smouldering Myeloma:

María-Victoria Mateos
University Hospital of Salamanca- IBSAL
Salamanca. Spain

DISCLOSURES OF COMMERCIAL SUPPORT

Name of Company	Research support	Employee	Consultant	Stockholder	Speaker's Bureau	Advisory Board	Other
Janssen					x	x	
Celgene	x				x	x	
Amgen					x	x	
Takeda					x	x	

Objectives

- What is Smouldering Myeloma?
- Diagnosis of Smouldering Myeloma and differential diagnosis with other plasma cell disorders
- Why do we call it “Smouldering” Myeloma?
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Smouldering MM: diagnostic criteria

Study	M Protein (g/dl)	Bone Marrow Plasma Cells (%)
Kyle and Greipp, 1980	≥ 3	≥ 10
Alexanian et al, 1988	> 2	
Wisloff et al, 1991	IgA > 1,5; IgG > 3	
Facon et al, 1995		
Weber et al, 1[illegible]		-
C[illegible]	[illegible] IgG 3.6-6.9	>10
	[illegible] chain proteinuria > 1 g/24h	
Ro[illegible] [illegible], 2003&	≥ 3	≥ 10
IMWG, 2003∞	≥ 3	≥ 10

*Either diagnostic criterion is acceptable, &Both diagnostic criteria are required, ∞Either or both diagnostic criteria are acceptable

On the basis of a series of six patients who met the criteria for multiple myeloma (MM) but whose disease did not have an aggressive course and they did not progress

Smouldering MM: diagnostic criteria

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Alexanian et al, 1988	> 2	-
Wisloff et al, 1991	IgA > 1,5; IgG > 3	-
Weber et al, 1997	> 2,5	-
Facon et al, 1995	-	>15
Cesana et al, 2002*	IgA 2.1-4.9; IgG 3.6-6.9 Light chain proteinuria > 1 g/24h	>10
Rosiñol et al, 2003&	≥ 3	≥ 10
IMWG, 2003∞	≥ 3	≥ 10

**Either diagnostic criterion is acceptable*
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Clinical Case

- 52 years-old man
- Asymptomatic.
- Routine analysis
- **Elevated total serum proteins (10.2 g/dL) with normal albumin**
- Hemogram and biochemistry normal

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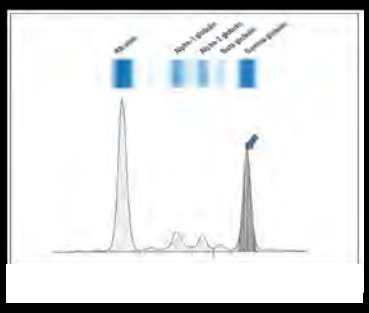

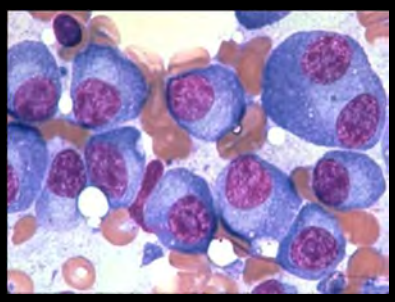

Smouldering MM: diagnostic criteria

	Smouldering Multiple Myeloma (SMM)
Monoclonal component	≥ 3 g/dL serum
	AND/OR
Bone Marrow Plasma Cells (%)	10-60%
	AND
Mieloma-defining event [a]	Absent

a) Myeloma Related Organ or Tissue Impairment (end organ damage) related to Plasma cell proliferative process: anemia with 2 g/dL below the normal level or <10 g/dL, or serum calcium level >10 mg/L (0.25 mmol/L) above normal or >110 mg/dL (2.75 mmol/L), or lytic bone lesions or osteoporosis with compressive fractures, or renal insuficiency (creatinine >2 mg/dL or 173 mmol/L),[CRAB: Calcium increase, Renal impairment, Anemia and Bone lesion] or symptomatic hyperviscosity,, amyloidosis or recurrent bacterial infections (>2 episodes in 12 m).
b) For symptomatic multiple myeloma, a minimum level of M-component or BM plasma cell infiltration (although usually it is >10%, is not required, provided than this two features coexists with the presence of end organ damage

Rajkumar SV et al. Lancet Oncology 2014

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MGUS/SMM/MM: diagnostic criteria

	Monoclonal Gammopathy of uncertain significance (MGUS)	Smouldering Multiple Myeloma (SMM)	Symptomatic Multiple Myeloma
Monoclonal component	< 3 g/dL serum	≥ 3 g/dL serum	Present (*serum/urine*)
	AND	AND/OR	AND
Bone Marrow Plasma Cells (%)	< 10%	10-60%	> 10%[b]
	AND	AND	AND
Myeloma-defining event	Absent	Absent	Present

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)
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Rajkumar SV. Lancet Oncology 2014

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	AND	AND	AND
Mieloma-defining event	Absent	Absent	Present

Concomitant diseases that can mimic MM:
-Increase of serum Cr due to diabetes or hypertension
-Anemia due to idon-vitamin deficiency, chronic disease,..
-Diffuse osteoporosis
-Hyperparatiroidism
-Single asymptomatic bone lesion

Rajkumar SV. Lancet Oncology 2014

Recommended work up at 3 months in patients with MGUS/smouldering MM

- Medical History and physical examination
- Hemogram
- Creatinine and calcium values
- Protein studies

  - Total serum protein and serum electrophoresis (serum M-protein)
  - 24-h urine protein electrophoresis (urine M-protein)
  - Serum and urine immunofixation
  - Serum free light chain mesurement (FLC ratio)

If results show stabilization of the disease, diagnosis of MGUS/SMM is confirmed

Mateos MV et al. Current hematologic malignancy reports. 2013; 8(4): 270-6

MGUS: 3 subtypes

Tumor load

Aymptomatic; low-risk of progression	Asymptomatic; high-risk of progression	Symptomatic
Non-IgM MGUS	SMM	MM
IgM MGUS	SWM	WM
Light-chain MGUS	Idiopathic Bence Jones proteinuria	Light-chain MM

time

5.3% of population older than 70 yrs present a MGUS

Recommended work up at baseline in patients with MGUS

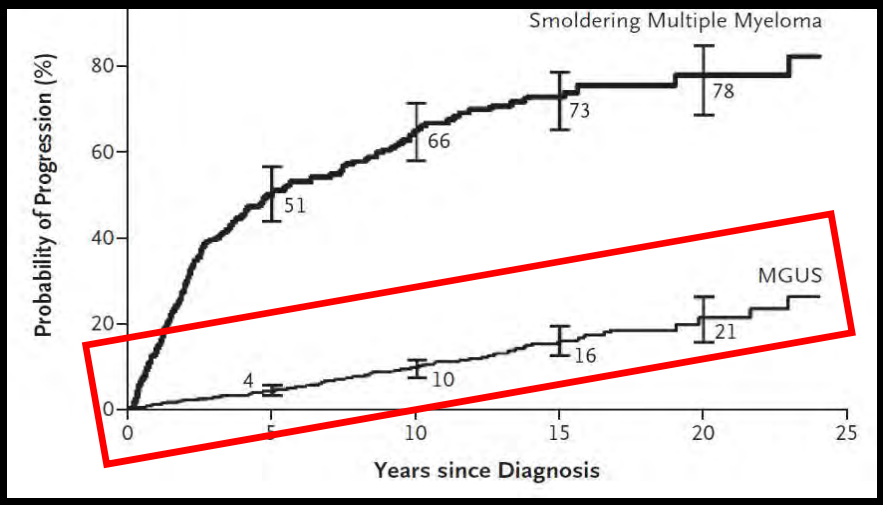
- **Medical History and physical examination**
- **Hemogram**
- **Creatinine and calcium values**
- **Protein studies**

  - Total serum protein and serum electrophoresis (serum M-protein)
  - 24-h urine protein electrophoresis (urine M-protein)
  - Serum and urine immunofixation
  - **Serum free light chain mesurement (FLC ratio)**

- **Bone Marrow aspirate+/- biopsy***
- **Bone lesions evaluation***

- For IgG MGUS with M-protein <1.5 g/dL, bone marrow and skeletal survey are not necessary
- For IgM MGUS, bone marrow and CT are recommended to detect MW or NHL

MGUS: Risk of progression to MM

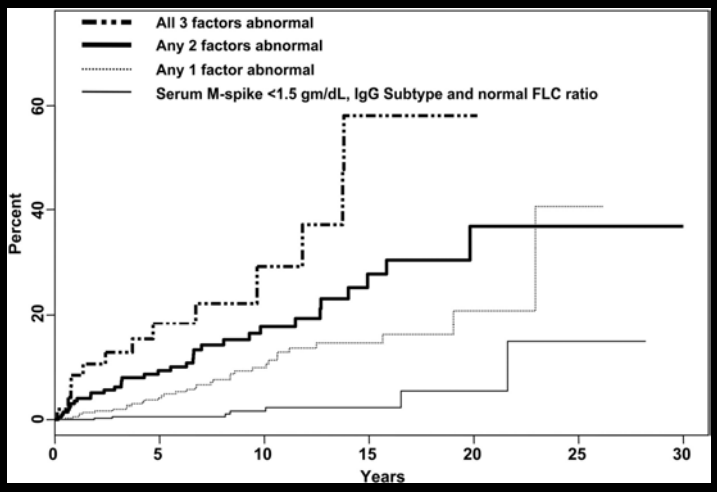


Is possible to evaluate the risk of progression?

Kyle NEJM 2007

1. Predictive factors: combinations

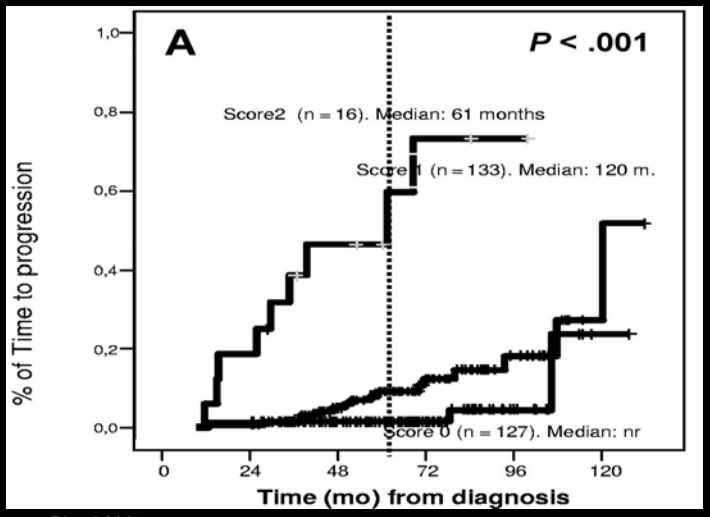
- non IgG MGUS
- M-protein ≥ 15 g/L
- Abnormal serum kappa/lambda FLC ratio



Rajkumar Blood 2005

2. Predictive factors: combinations

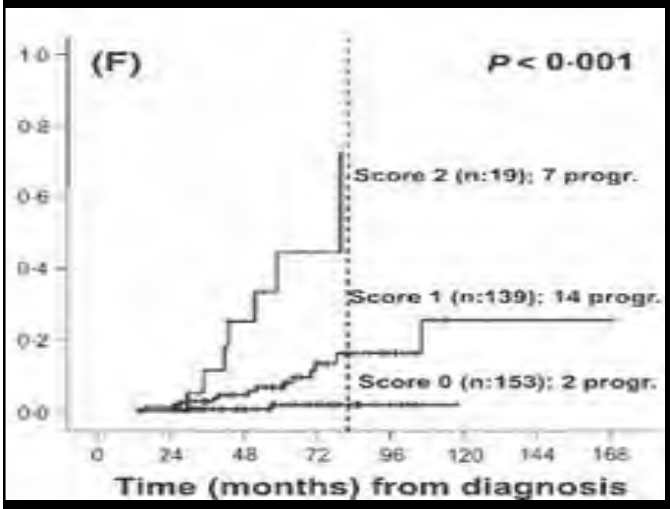
-DNA aneuploidy
-Multiparameter flow cytometry of bone marrow plasma cells
(≥95% aberrant BM plasma cells)



Pérez-Persona Blood 2007

3. Predictive factors: combinations

-Evolution of monoclonal component
-Multiparameter flow cytometry of bone marrow plasma cells
(≥95% aberrant BM plasma cells)



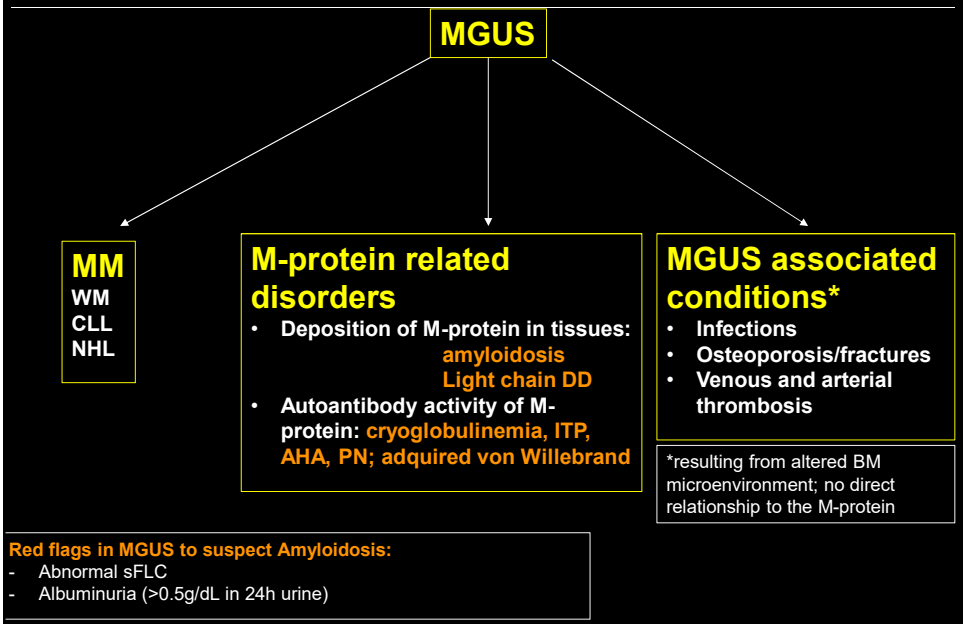
Pérez-Persona BJH 2010

MGUS: Management

- **Management should be risk-adapted**
- **Low risk MGUS (IgG/<1.5 g/dL/normal FLC): if stable 6 months after dx confirmation→ every 2 to 3 years**
- **Intermediate/high risk MGUS should be followed annually**

Kristinsson et al. reported significantly better OS in patients with MM who had prior knowledge of MGUS than in those without prior knowledge (median survival, 2.8 years versus 2.1 years, respectively; P = 0.01), suggesting that earlier treatment of MM leads to improved survival

MGUS: Special considerations



MGUS

- **MGUS is one of the most common premalignant disorders**
  - Malignant transformation
  - Symptoms related to the M-protein
  - Symtoms due to cytokines produced by plasma cell clone
  - Symtoms related to the plasma cell clone
- **Better biomarkers for predicting progression are needed**
- **Treatment of high-risk patients ?**

MGUS prevalence

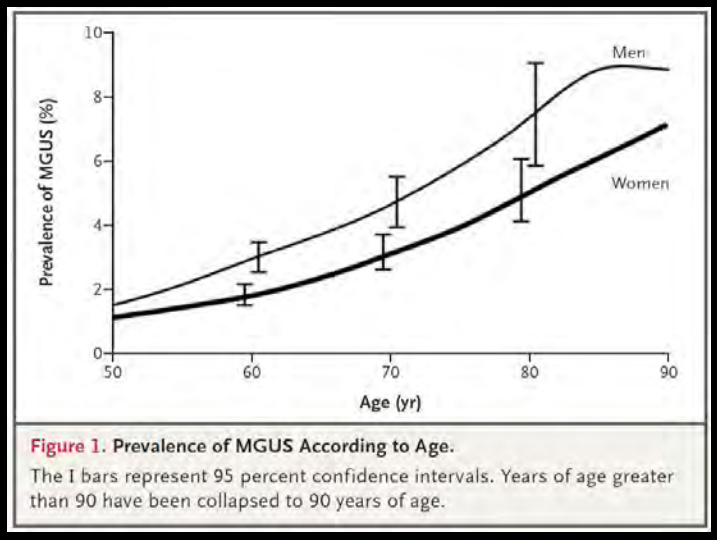


Figure 1. Prevalence of MGUS According to Age.
The I bars represent 95 percent confidence intervals. Years of age greater than 90 have been collapsed to 90 years of age.

Kyle NEJM 2006

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)
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    - 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¶

Subgroup of SMM patients that require be treated

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

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  - 24-h urine protein electrophoresis (urine M-protein)
  - Serum and urine immunofixation
  - Serum free light chain mesurement (FLC ratio)*
- Bone Marrow aspirate+/- biopsy*
- Skeletal survey/Low-dose CT/PET-CT
- MRI of the spine and pelvis/ Whole-body MRI*

*Required to identify ultra high risk SMM->MM

Mateos MV et al. Current hematologic malignancy reports. 2013; 8(4): 270-6.

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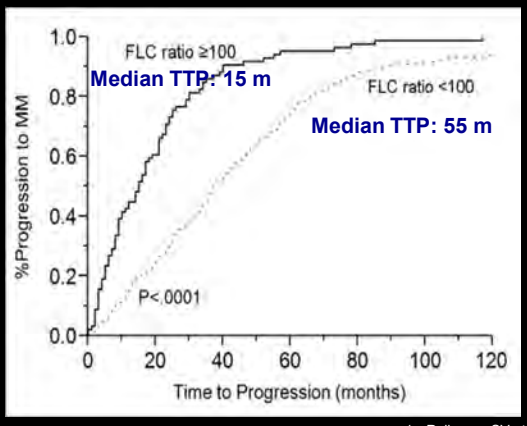
Ultra-high risk SMM: Serum involved/uninvolved free-light chain (FLC) Ratio

N= 586 patients



1. Rajkumar SV et al. N Engl J Med 2011; 365:474-475
2. Kastritis E, et al. Leukemia. 2013 Apr;27(4):947-53
3. Waxman AJ, et al. J Clin Oncol 32:5s, 2014 (suppl; abstr 8607)

Multiple Myeloma: Serum involved/uninvolved free-light chain (FLC) Ratio

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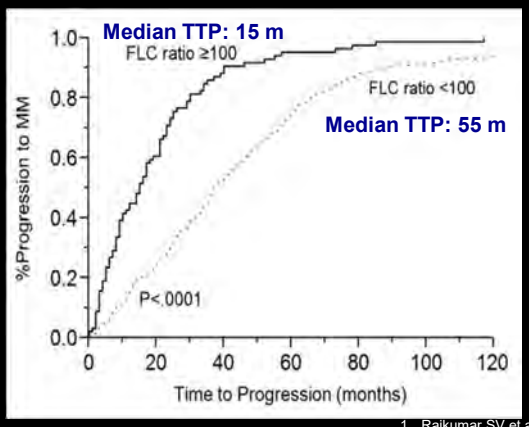

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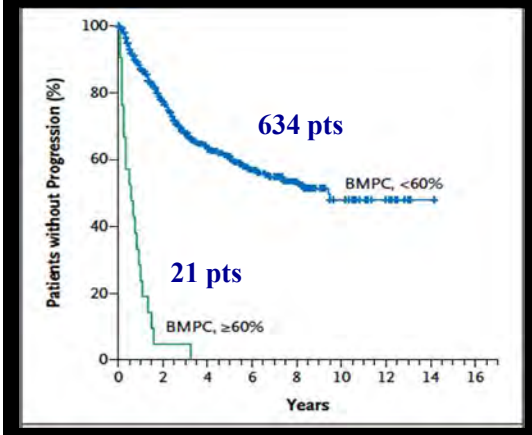
Ultra-high risk SMM: Plasma Cells in the Bone Marrow at baseline

N= 655 patients



"In these patients (3.2%), median TTP was 7m and 95% of them progressed to symptomatic MM within 2y" [1]

1. Rajkumar SV et al. N Engl J Med 2011; 365:474-475
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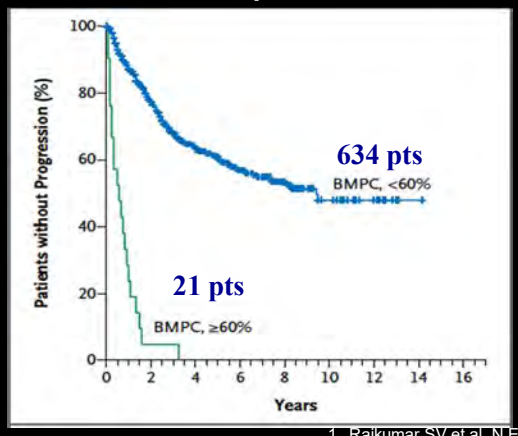

1. Rajkumar SV et al. N Engl J Med 2011; 365:474-475
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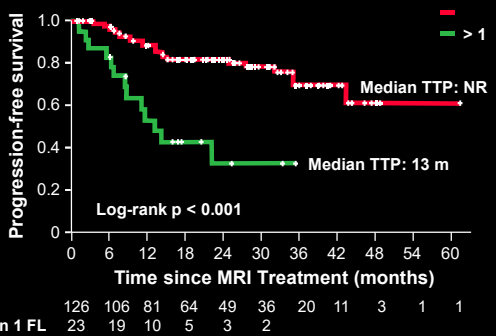
Smouldering Multiple Myeloma: Whole MRI

149 patients with asymptomatic MM
Whole MRI: 28% of pts: Focal lesions



***> 1** Focal lesion plus diffuse pattern → adverse prognosis*

1. Hillengass J, et al. J Clin Oncol 2010;28:1606-1610
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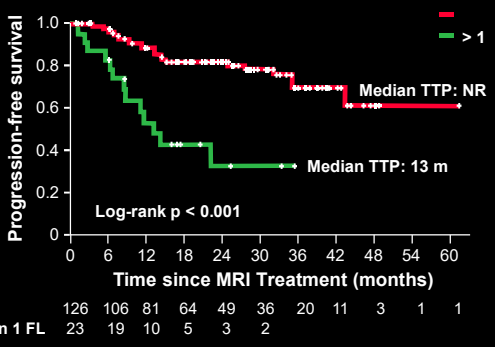

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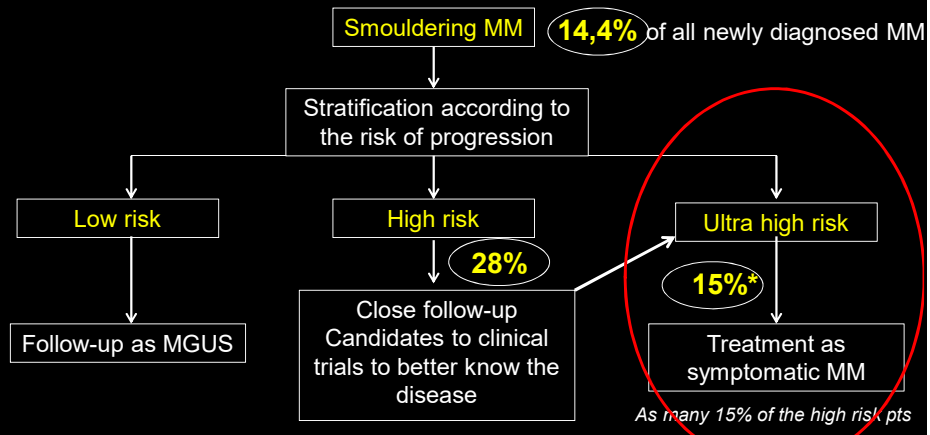
Smouldering Multiple Mieloma

What is the frequency of new MM according to the new definition?

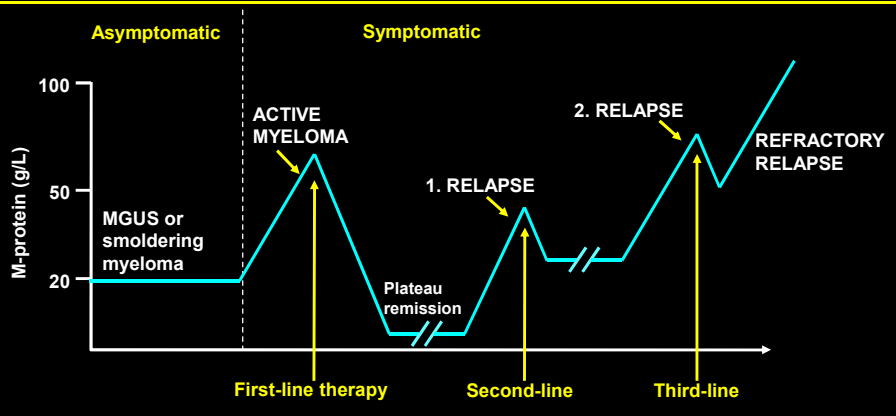


Using the World population as reference, the age standardized incidence of smouldering multiple myeloma is 0.44 per 100.000, and high-risk disease 0.14 per 100.000

Kristinsson S et al. NEJM 2013

What is the next step?
What happens with the other SMM patients?

Natural History of MM



Myeloma is always preceeded by MGUS or Smoldering Mieloma and is key to know the risk of progression to myeloma

MGUS, monoclonal gammopathy of undetermined significance

Why do we call it “smouldering”?

Monoclonal Gammopathy of uncertain significance (MGUS)

Smouldering Myeloma (SMM)

Multiple Myeloma (MM)

Transition from MGUS/SMM to MM

- Expansion of altered clones already present in MGUS patients

  López Corral et al. Leukemia 2012

- Branching model→ Key molecular events leading to disease evolution→ distinct patterns of driver mutations

  Walker et al. Nature Reviews Cancer 2012

- Differences in inmune surveillance

  Dosani et al. Blood Cancer J. 2015

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- Branching model → Key molecular events leading to disease evolution → distinct patterns of driver mutations

  Walker et al. Nature Reviews Cancer 2012

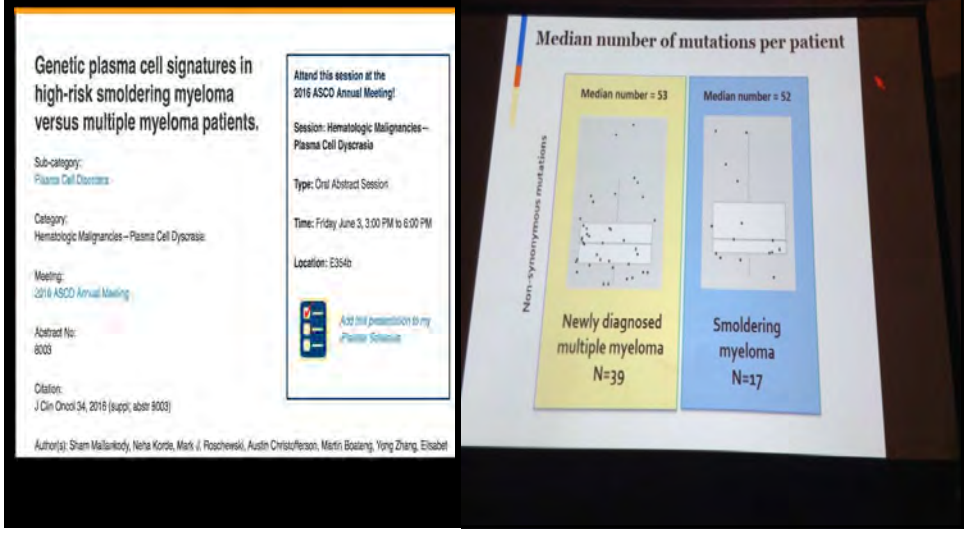
- Differences in inmune surveillance

  Dosani et al. Blood Cancer J. 2015

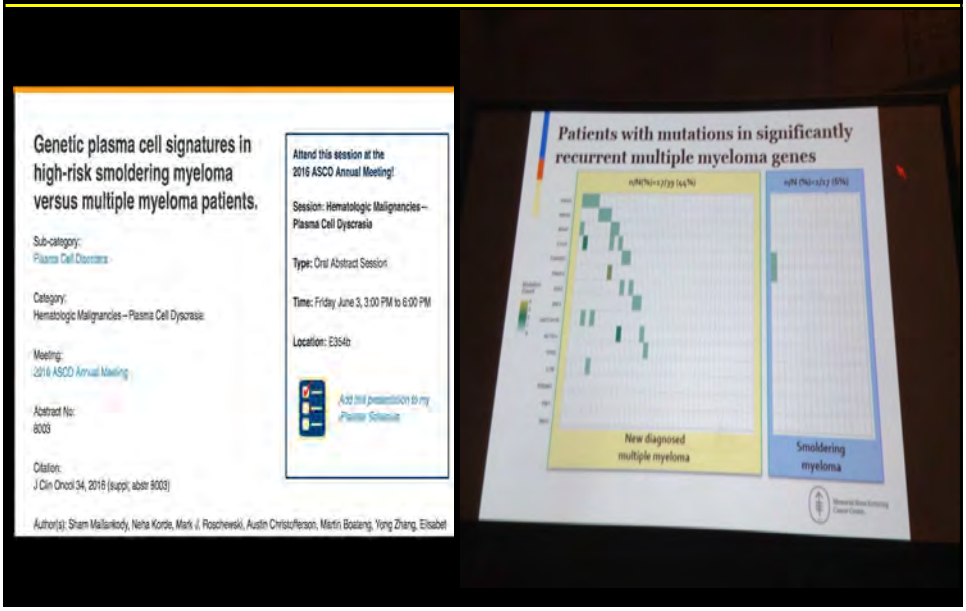
We do not know the key mechanism of transition

MGUS, monoclonal gammopathy of undetermined significance

Transition from MGUS/SMM to MM



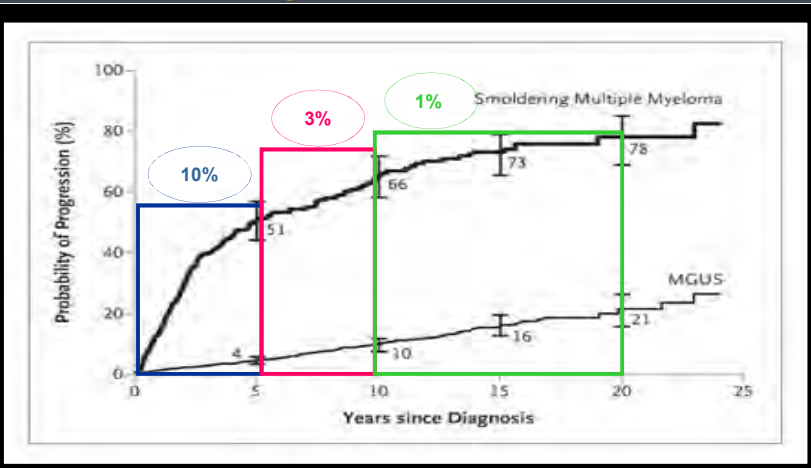
Transition from MGUS/SMM to MM



Objectives

- What is Smouldering Myeloma?
- Diagnosis of Smouldering Myeloma and differential diagnosis with other plasma cell disorders
- Why do we call it “Smouldering” Myeloma?
- What is the mechanism of transition from SMM to MM?
- What is the risk of progression to Myeloma?
- Is it possible to evaluate the individual risk of progression to Myeloma?
- What is the optimal management for Smouldering Myeloma patients?

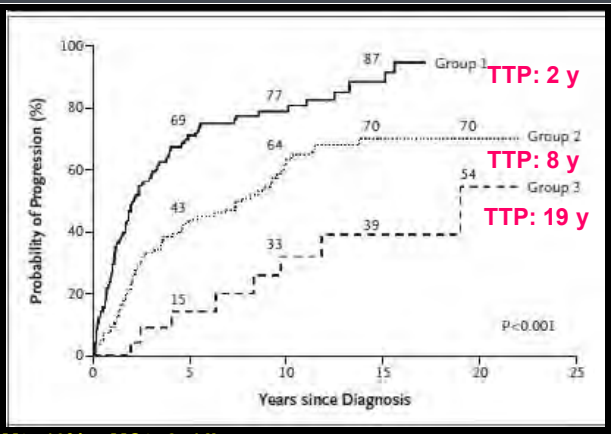
MGUS/Smouldering Multiple Myeloma: Risk of progression to active disease



According to the heterogeneity in the risk of progression to MM, we have to identify the individual risk for each new SMM patient.

Kyle R. N Engl J Med 2007; 356:2582-90

Mayo risk model: PCs BM infiltration and Serum M-component level



TTP: 2 y

TTP: 8 y

TTP: 19 y

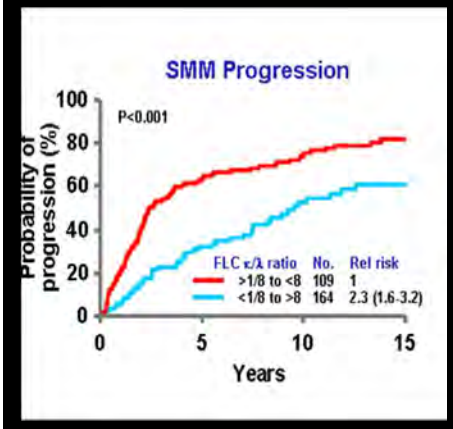
50% risk at 2 yrs

Group 1: *PCBM ≥ 10% + MC ≥ 3g/dl*
Group 2: *PCBM ≥ 10% + MC < 3g/dl*
Group 3: *PCBM < 10% + MC ≥ 3g/dl*

Kyle R. N Engl J Med 2007; 356:2582-90

Smouldering Multiple Myeloma: serum immunoglobulin free-light chain (FLC) ratio (n:273)

Serum FLC ratio <0.125 or > 8

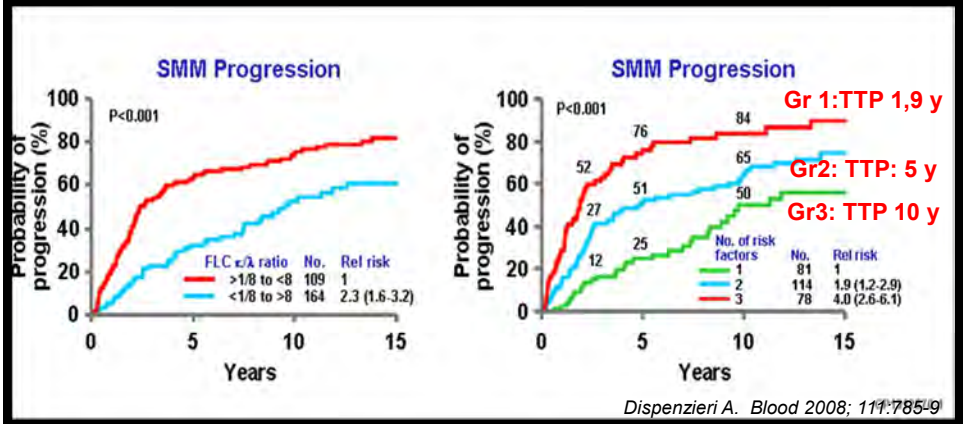


Dispenzieri A. Blood 2008; 111:785-9

Mayo Clinic model: serum immunoglobulin free-light chain (FLC) ratio (n:273)

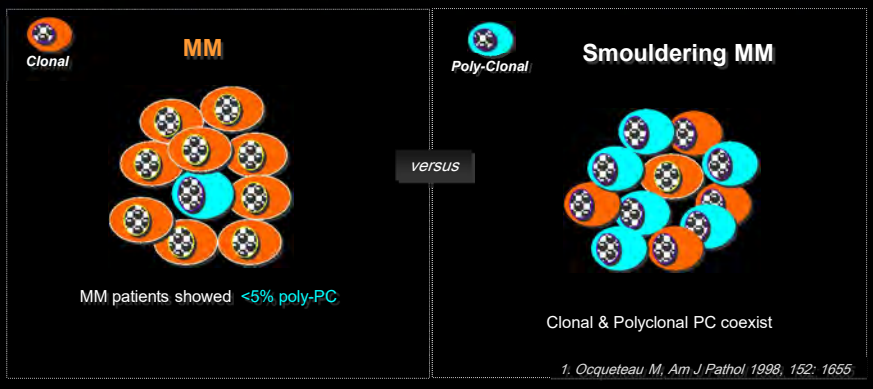
Serum FLC ratio <0.125 or > 8

PCsBM Infiltration ≥ 10%
Serum M protein ≥ 3 g/dL
Serum FLC ratio <1/8 or >8



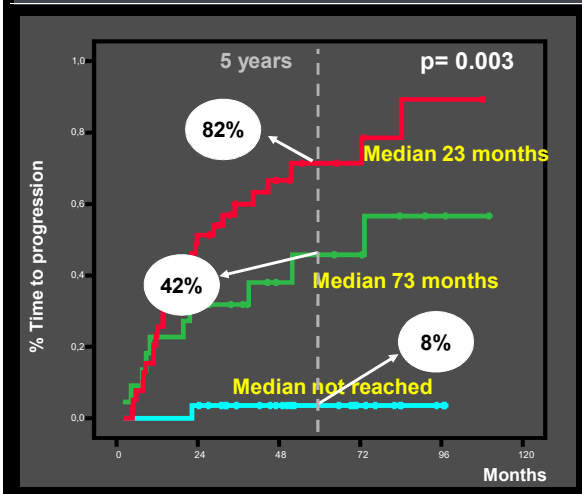
Dispenzieri A. Blood 2008; 111:785-9

Spanish Model: Analysis of the PC compartment by flow cytometry



Immunoparesis: Low levels of uninvolved immunoglobulins
>25% of the lowest level for each immunoglobulin

Spanish model: Aberrant PCs by immunophenotype plus immunoparesis



>95% aPC/BMPC + paresis
n= 39 (28 progr.)

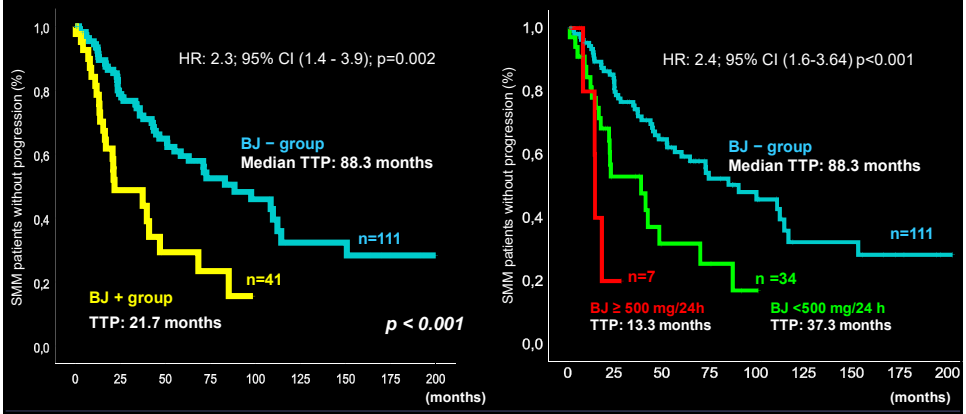
50% risk at 2 yrs

>95% aPC/BMPC or paresis
n= 22 (10 progr.)

No adverse factors
n= 28 (1 progr.)

Pérez E. Blood 2007; 110:2586-92

BJ proteinuria in SMM as a predictor marker of progression to symptomatic MM



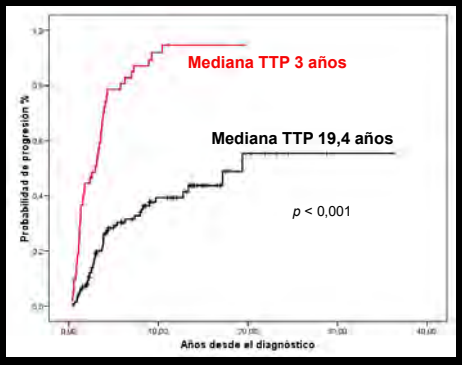
•Risk of progression at 2 years in BJ + group: 51%
•Risk of progression at 18 months in SMM BJ ≥ 500 mg/24 h : 80%

González- Calle V et al. Leukemia 2016

Evolution pattern of the M-spike: evolving vs nonevolving (n:207)

Evolving SMM (52 (25%)): **at least 10% increase within the first 6 months from diagnosis when M-Protein was ≥30 g/L or progressive increase in M-Protein in each of the annual consecutive measurements during a period of 3 years in patients with an initial MP < 30 g/L**

Non-evolving (75%): **Stable serum M-protein until progression occurs**



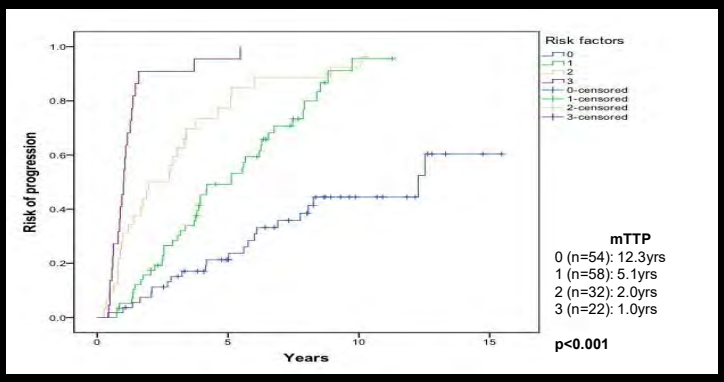
Evolving SMM

- Risk progression at 2 years: 45%
- Risk progression at 5 years: 78%
- IgA isotype: (41,2% frente a 23,8%, p=0,02)

Fernández Larrea C et al. ASH 2014

Evolution pattern of the M-spike + eHb + BMPC: (n:190)

Risk factors predicting high risk: 1) eMP as Larrea et al.; 2) eHb: decrease of ≥ 0.5g/dL Hb within 12m of diagnosis; and 3) BMPC infiltratation : ≥20%



SMM with eMP and eHb (with or without BMPC ≥20% had >80% risk of progression to MM within 2 years of diagnosis→ ultra high risk SMM

Ravi et al. ASCO 2016

Del(17p), t(4;14), and +1q21 predict progression from smouldering to symptomatic MM (n=248)

- del(17p13), t(4;14), +1q21 showed significant impact on TTP

	TTP	P
All pts	4.9 years	
+1q21 versus no gain of 1q21	3.7 years 5.3 years	0.013
del(17p13) versus no del(17p13)	2.7 versus 4.9 years	0.019
t(4;14) versus no t(4;14)	2.9 versus 5.2 years	0.021
HD versus NHD	3.9 versus 5.7 years	0.036

- Multivariate analysis: t(4;14), +1q21, HD, reduction of uninvolved immunoglobulins and risk score defined by Kyle et al. as independent factors for adverse outcome
- Conclusion: specific chromosomal aberrations drive transition from asymptomatic to symptomatic disease

Neben et al. JCO 2013; October 21 Epub ahead of print

Primary molecular cytogenetic abnormalities and risk of progression in SMM (n=351)

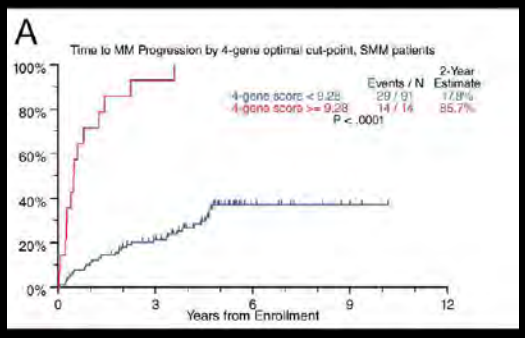
- del(17p13), t(4;14), trisomies showed significant impact on TTP

Cytogenetic abnormalities	TTP
High-risk subgroup	
t(4;14), del(17p)	24 months
Intermediate-risk subgroup	
Trisomy (ies) withouth IgH translocation	34 months
Standard/low-risk subgroup	
T(11;14), other, or no abnormalities	55 months/NR

Rajkumar SV. Leukemia 2013; 27(8): 1738-44

Gene Expression Profiling of purified CD138+ tumor cells in SMM (n: 105)

The validated 70-gene model (GEP-70) identified SMM patients with GEP70>-0.26 with a 51% of progression risk at 2 yrs.

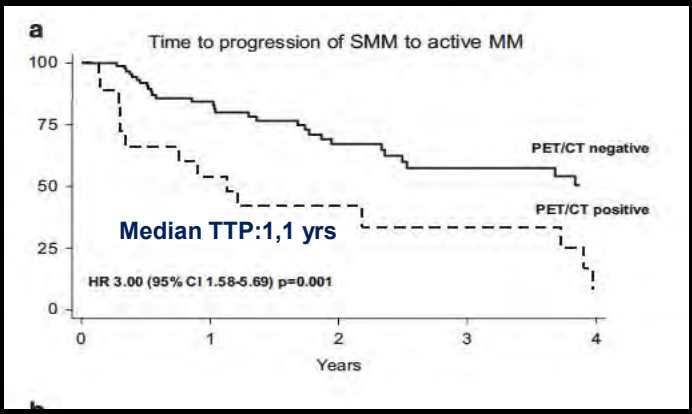


A gene signature derived from 4 genes at an optimal binary cut-point of 9.28, identified 14 patients (13%) with a 2-year therapy risk of 85.7%

Dhodapkar MV et al. Blood 2013
Khan RC et al. Haematologica 2015

PET-CT in SMM patients as predictor of progression to symptomatic MM (n: 120)

16% of patients had PET positive: 56% of them had 1 FL with a median PET SUV of 4.45 and no osteolysis was observed.

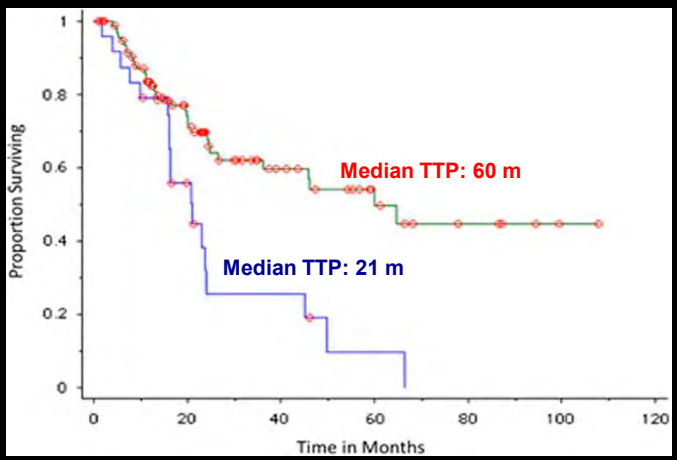


Relative risk of skeletal progression was 3.0 (95% CI 1.3-12, P= 0.013)

Zamagni E et al. Leukemia 2016

Smouldering Multiple Myeloma: PET/CT (n:188)

Positive PET/CT: 39% of the patients



Siontis B et al. Blood Cancer J 2016

Smouldering Multiple Myeloma: Risk models

Identification of high risk SMM→ 50% of progression risk at 2y

- ***Mayo Clinic:*** ≥10% clonal plasma cell bone marrow infiltration, and ≥30g/L of serum M-protein, and serum-free light ratio >0.125 or <8
- ***Spanish:*** ≥95% of aberrrant plasma cells measured by flow plus >25% decrease in one or both uninvolved immunoglogulins
- ***Heidelberg:*** Tumor mass defined by Mayo risk model plus t(4;14)/del17p/gains of 1q/
- ***Japanese:*** Beta 2-microglobulin ≥ 2.5 mg/L plus M-protein increment rate > 1 mg/dL/day
- ***SWOG:*** serum M-protein ≥2 g/dL plus involved free light chain >25 and GEP >-0.26 (71% of risk progression at 2 yrs)
- ***PENN:*** **≥ 40% clonal PCBM infiltration plus sFLC ratio ≥ 50 plus Albumin □ 3.5 mg/dL (81% of risk at 2 yrs)**
- ***Czech & Heidelberg:*** immunoparesis plus serum M-protein ≥ 2.3 g/dL plus involved/uninvolved sFLC > 30 **(81% of risk at 2 yrs)**
- ***Barcelona:*** evolving pattern plus serum M-protein ≥ 3 g/dL plus immunoparesis **(80% of risk at 2 yrs)**

Each model appears to identify patients at high risk, with some but not complete overlap

Smouldering Multiple Myeloma: Risk models

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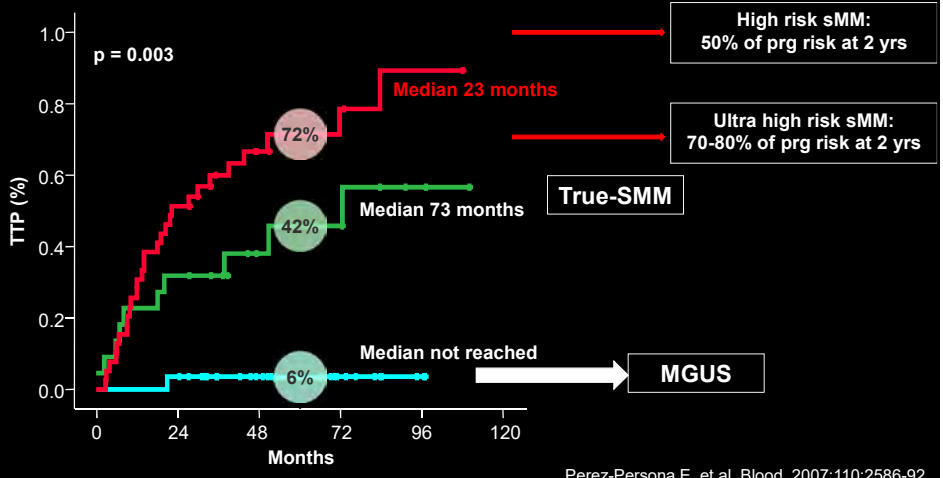
Smouldering MM: Heterogeneous disease



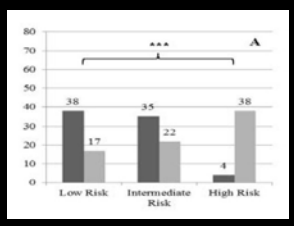
Perez-Persona E, et al. Blood. 2007;110:2586-92.

Disagreement between smoldering myeloma risk models

Distribution of 77 SMM patients using both the Mayo and Spanish models. Overall agreement 22/77 (28.6%)

	PETHEMA low, n	PETHEMA mid, n	PETHEMA high, n
Mayo low, n	11	15	12
Mayo mid, n	6	7	22
Mayo high, n	0	0	4

Significant disagreement between models (p<0.0001)

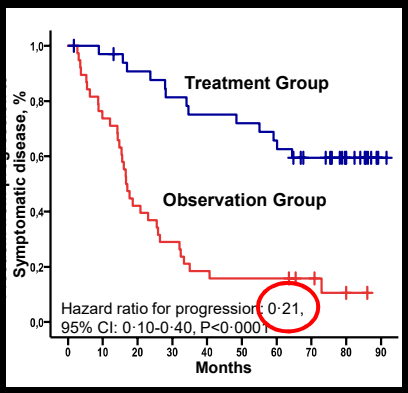


Cherry et al. *Leuk Lymphoma 2013*

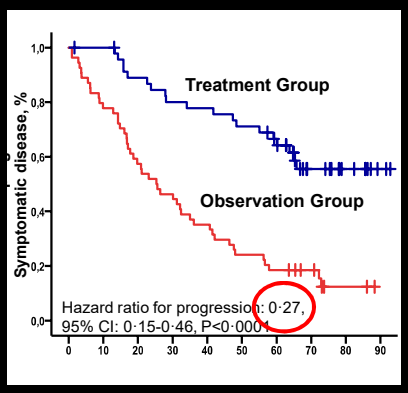
Concordance between Mayo and Spanish model

Len-dex vs no treatment: TTP to active disease (n = 119)

Mayo Risk model



Spanish Risk model



Mateos MV et al. Data unpublished

What is the next step?
What happens for the other SMM patients?

How to proceed once patients are stratified according to the risk?

Smouldering Multiple Myeloma: Management

- Management should be risk-adapted
- Low risk SMM should be followed as MGUS-like pts: annually
- Intermediate risk SMM should be followed as true SMM pts: every 6 months
- Ultra high-risk should be considered MM and be treated
- High-risk SMM can benefit from early treatment

Low and Intermediate risk Smouldering Multiple Myeloma

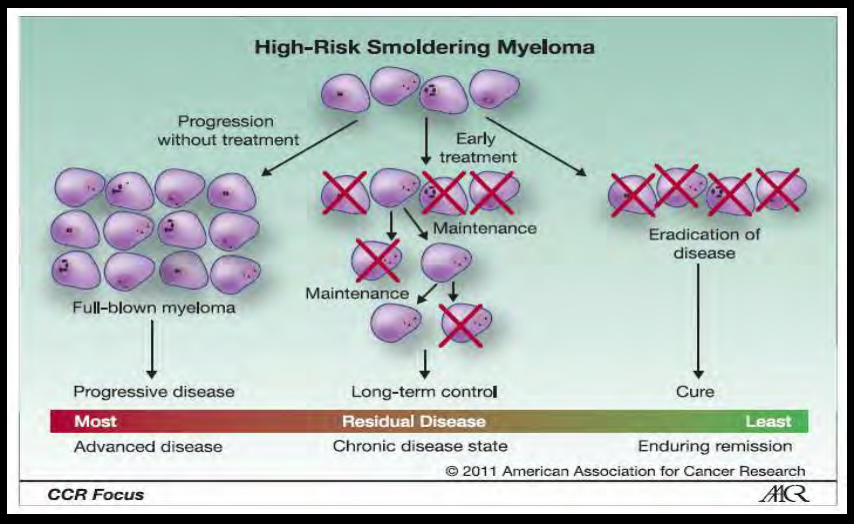
What is the optimal work-up to do?

- Medical History and physical examination
- Hemogram
- Creatinine and calcium values
- Protein studies
  - Total serum protein and serum electrophoresis (serum M-protein)
  - 24-h urine protein electrophoresis (urine M-protein)
  - Serum and urine immunofixation
  - Serum free light chain mesurement (FLC ratio)
- Bone Marrow aspirate+/- biopsy Only if suspect of active disease
- Skeletal survey/Low-dose CT/PET-CT PET-CT annually for intermediate risk?
- MRI of the spine and pelvis/ Whole-body MRI Repeat at 6 months if one focal lession was present.

Smouldering Multiple Myeloma: Management

- Management should be risk-adapted
- **Low risk SMM** should be followed as MGUS-like pts: annually
- **Intermediate risk SMM** should be followed as true SMM pts: every 6 months
- **Ultra high-risk** should be considered **MM** and be treated: new biomarkers will be in the future incorporated to the MM definition
- **High-risk** SMM can benefit from early treatment

Treatment goals for high-risk smouldering myeloma



Landgren et al, *Clin Cancer Research 2011*

Smouldering Multiple Myeloma: Management

Agents	ORR (%)	TTP	OS	Reference
Early MP* vs Deferred MP	52 55	No benefit	No benefit	Hjorth M, et al. Eur J Haematol. 1993 Grignani G, et al. Br J Cancer. 1996 Riccardi A, et al. Br J Cancer. 2000
Thal+Zol vs Zol**	37 0	No benefit	No benefit	Witzig TE, et al. Leukemia 2013
Bisphosphonates***vs observation	0	No benefit	No benefit	Martin A, et al. Br J Haematol. 2002 D'arena et al. Leuk Lymphoma. 2011 Musto P, et al. Cancer. 2008

**Abandon: No differences in survival and potential risk of secondary leukemias*
***Low efficacy&high rates of discontinuation due to PN*
****Skeletal related events lower in the bisphosphonate groups* ***(39% vs 73% and 55% vs 78%)***

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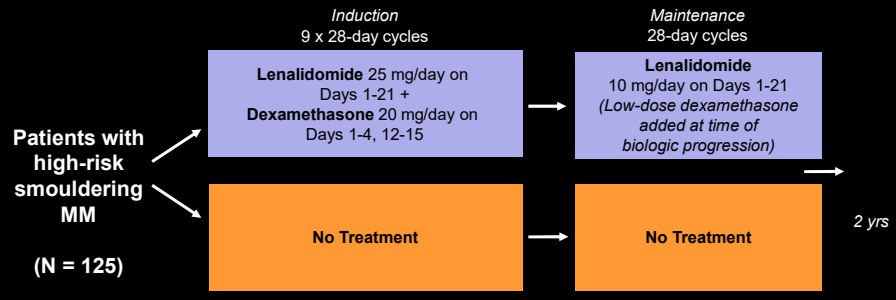
Low, intermediate and high risk patients were included

**Abandon: No differences in survival and potential risk of secondary leukemias*
***Low efficacy&high rates of discontinuation due to PN*
****Skeletal related events lower in the bisphosphonate groups* ***(39% vs 73% and 55% vs 78%)***

QuiRedex: Study Design

- Multicenter, open-label, randomized phase III trial



In both arms, blood counts, biochemical analysis (including creatinine and calcium) and serum/urine levels of MC were performed monthly. Skeletal survey was performed during the screening phase and thereafter only if clinical symptoms emerged.

High-risk was defined according to the Mayo and/or Spanish models

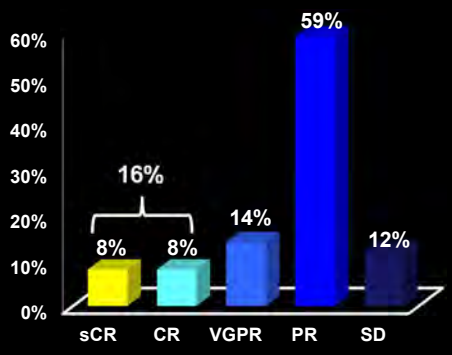
Mateos MV, et al. NEJM 2013; 369:438-47

Lenalidomide + Dex: response rate

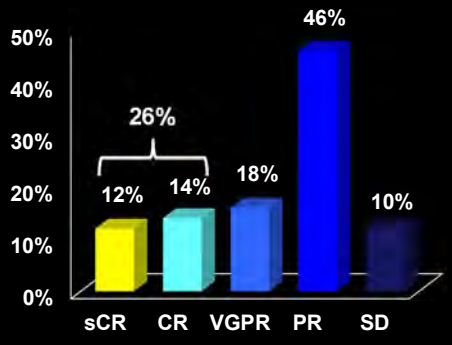
On ITT (n = 57) Median number of induction cycles: 9 (range 1–9)

***ORR: 80%; sCR: 7%, CR: 7%; VGPR: 11%; PR: 65%;* SD: 21%**

After 9 induction cycles (n = 51)



After a median of 15 maintenance cycles (2-41) (n=50)



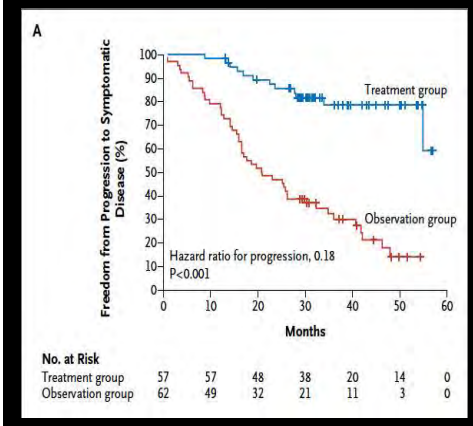
*IMWG criteria.

Mateos MV, et al. NEJM 2013; 369:438-47

Len-dex vs no treatment: TTP to active disease (n = 119)

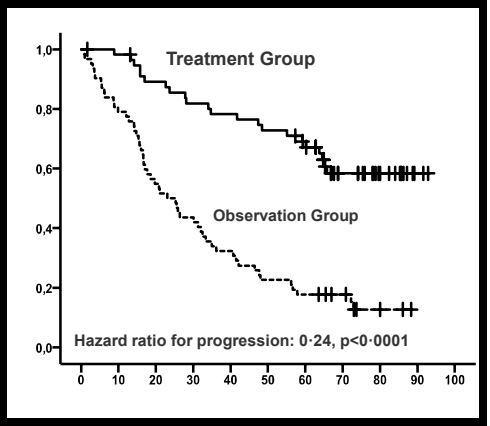
Per-protocol Patients population

Median follow-up: 40 m



Mateos MV, et al. NEJM 2013

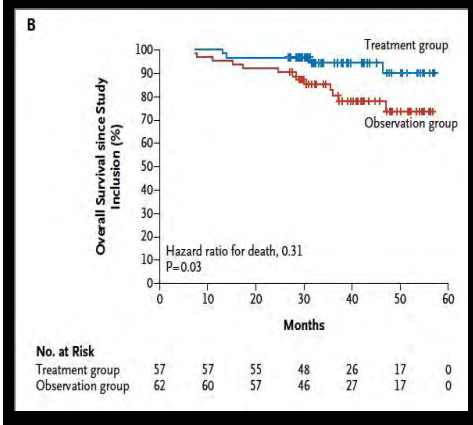
Median follow-up: 75 m



Mateos MV, et al. Lancet Oncology 2016: accepted for publication

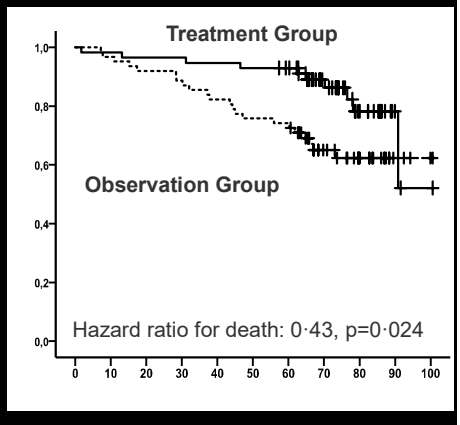
Len-dex vs no treatment: OS from inclusion (n = 119)

Median follow-up: 40 m



Mateos MV, et al. NEJM 2013

Median follow-up: 75 m



Mateos MV, et al. Lancet Oncology 2016: accepted for publication

Len-dex: biological progressions (n:57 pts)

15 biological progressions during maintenance therapy

Dex was added according to the protocol

(20 mg 4 days)

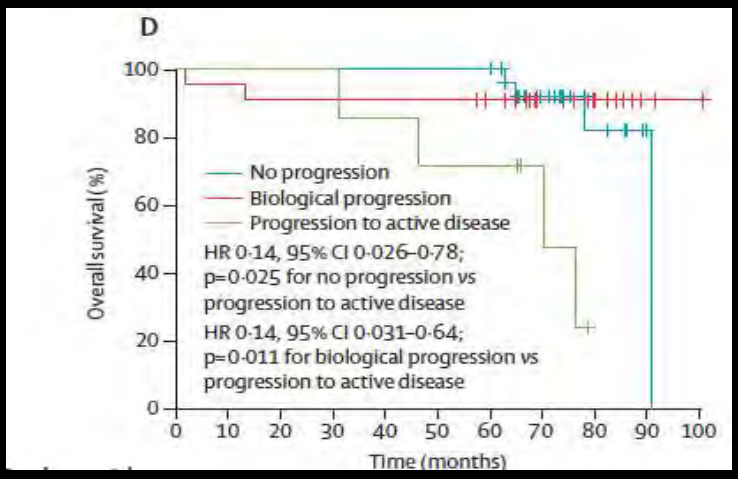
- **3 pts achieved PR and 12 stabilized their disease**
  - **5 finally progressed to Myeloma**
  - **10 pts remain in stable disease and five of them with len 10 mg plus 20 mg dex for 4 days**

Why this pre-emptive strategy only for the experimental arm?
What was the benefit of this pre-emptive strategy?

Mateos MV, et al. Lancet Oncology 2016: accepted for publication

Len-dex vs no treatment: OS according to the type of progression (n = 119)

Median follow-up: 75 m



Mateos MV, et al. Lancet Oncology 2016: accepted for publication

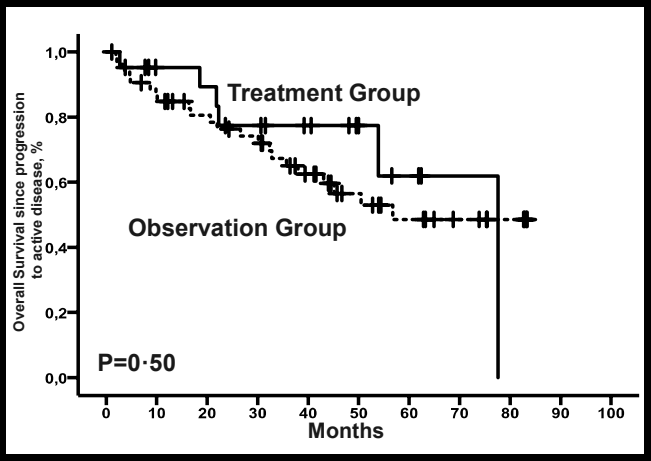
What about rescue therapies?

Subsequent therapy	Lenalidomide-dex (n=22)	Observation (n=53)
PI-based combinations	13 (59%)	23 (43%)
IMiD's-based combinations	3 (14%)	8 (15%)
PI-IMiD's-based combinations	2 (9%)	16(30%)
Conventional chemotherapy	4 (18%)	6 (11%)
	4 pts (18%) received ASCT	15 pts (28%) received ASCT

Mateos MV, et al. Lancet Oncology 2016: accepted for publication

Len-dex vs no treatment: OS from progression to active disease (n = 119)

Median follow-up: 75 months



Early treatment does not induce more resistant relapses

Mateos MV, The Lancet Oncology 2016: accepted for publication

QuiRedex: toxicity profile during induction (n:125)

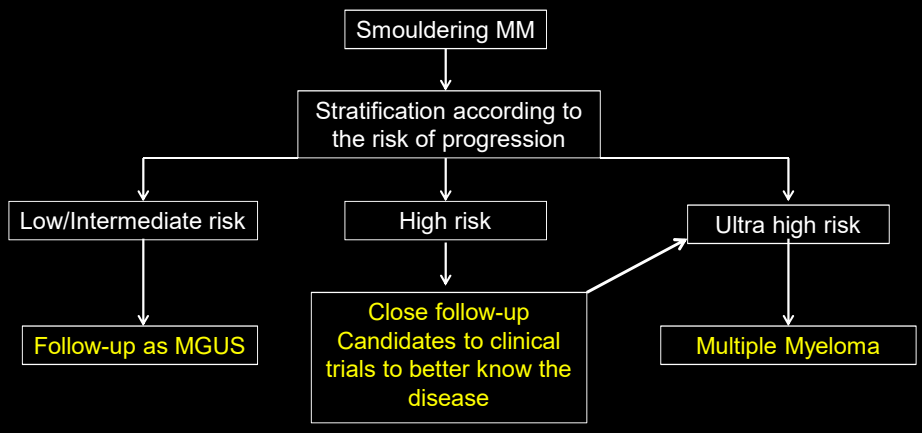
	Len-dex arm (n:62)		Abstention arm (n:63)
	G1	G2	G1-2
Anemia	11 (20%)	4 (7%)	2 (4%)
Neutropenia	3 (6%)	8 (14%)	
Thrombopenia	6 (11%)	1 (2%)	
Asthenia	6 (11%)	5 (9%)	6 (11%)
Constipation	4 (7%)	6 (11%)	1 (2%)
Diarrhea	9 (17%)	4 (7%)	2 (4%)
Rash	12 (23%)	6 (11%)	
Infection*	19 (35%)	6 (11%)	14 (26%)
DVT**	1 (2%)	2 (4%)	
SPM -Hematologic -Non hematolog	1 patient (PV) 5 patients*		1 patient (MDS)

*3 prostate cancers, 1 breast cancer and 1 cervical epidermoid carcinoma

The cumulative risk of developing a second primary malignancy at 7 years was 12% (95% CI 0á31–11) in the treatment group and 3% (0–4) in the observation group (p=0.070).

Mateos MV, et al. Lancet Oncology 2016: accepted for publication

Smouldering Multiple Myeloma



- **Though there is not any drug approved for SMM, it is dificult and "almost unethical" not offering treatment NOW to high risk SMM**
- **What is the most appropriate treatment?**

High-risk Smouldering Multiple Myeloma

- Len-dex is effective as early treatment, with benefit in TTP to active disease and also in OS
- Numerous clinical trials with several drugs are currently ongoing in this group of patients:
  Elotuzumab, daratumumab, Elo-Rd, KRd, ….

Current Studies in High-Risk Smouldering MM

- Biomarker study of elotuzumab (phase II)[2]
- Siltuximab (anti IL6) or no treatment (phase II)[3]
- Biomarker study of BHQ880 (anti DKK1) (phase II)[4]: *Data presented at ASH2012: no antitumor effect but anabolic activity*
- Lenalidomide or observation (phase III)[1]
- Elotuzumab-Lenalidomide-dex
- Daratumumab single agent at different doses (Centaurus trial)
- Carfilzomib, lenalidomide, and dexamethasone (phase II)[5]:

1. ClinicalTrials.gov. NCT01169337.
2. ClinicalTrials.gov. NCT01441973.
3. ClinicalTrials.gov. NCT01484275.
4. ClinicalTrials.gov. NCT01302886.
5. ClinicalTrials.gov. NCT01572480.

Phase II trial for high-risk SMM: Carfilzomib/Revlimid/dex

Study open for high-risk smouldering myeloma pts ≥18 years old

8 cycles KRd Combination Therapy

Carfilzomib 20/36 mg/m²,
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?

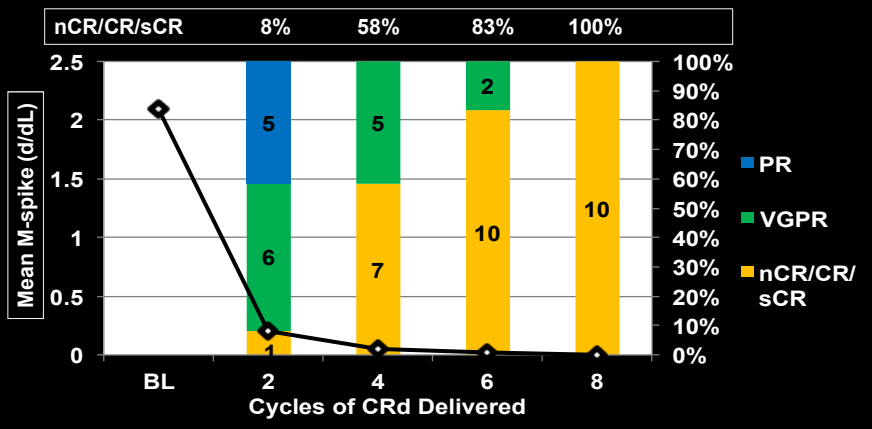
24 cycles Rev Extended Dosing

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/m²
- C1- 4 – Dex dose is 20 mg, C5- 8 – Dex dose is 10 mg

Landgren, et al. *ASH2014: abstract 4746*

Response rates in relation to cycles of KRd



11/12 (92%) are MRD negative by 8-color flow cytometry of the bone marrow

Landgren, et al. *ASH2014: abstract 4746*

Curative Estrategia Smouldering Alto Riesgo (CESAR trial) (n:90)

Induction 6 cycles of KRd

MRD

ASCT (melphalan 200)

MRD

Consolidation (2 cycles of KRd)

MRD

Maintenance (Len-dex for 2yrs)

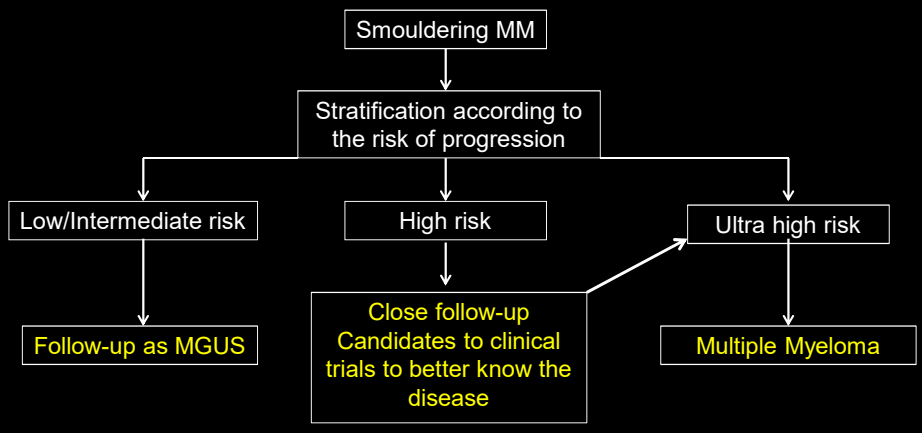
MRD

Primary objective: To evaluate the proportion of patients in sustained immunophenotypic response at 5 years

Hypothesis: At least 50% of patients will achieve the objective

20 centers

Smouldering Multiple Myeloma



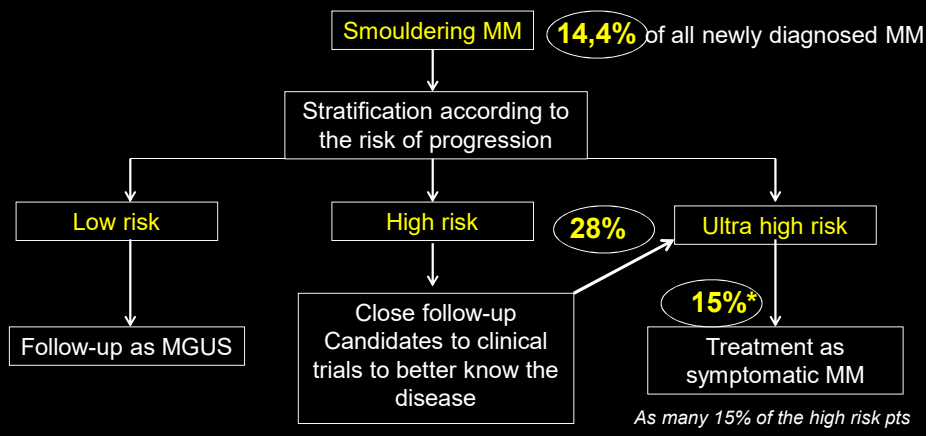
- **In the near future, new biomarkers will be validated and more SMM patients will be considered as Myeloma and patients will be treated as patients with active disease**

Smouldering Multiple Myeloma: Summary

- **The standard of care remains observation until progression to active disease**
- **The results of the studies would support to plan early treatment in patients at high risk of progression to MM**
- **Len-dex is effective as early treatment, with benefit in TTP to active disease and also in OS**
- **Numerous clinical trials with several drugs are currently ongoing in this group of patients**

These results support to change the current treatment paradigm for this patient population
Early treatment for high risk SMM patients

Smouldering Multiple Myeloma



Using the World population as reference, the age standardized incidence of smouldering multiple myeloma is 0.44 per 100.000, and high-risk disease 0.14 per 100.000

Kristinsson S et al. NEJM 2013

Acknowledgments

- **Investigators of the Spanish Myeloma Group: JF San Miguel**
- **Salamanca Myeloma Team:** N Gutiérrez, EM Ocio, N Puig, R García-Sanz, M Garayoa

How I treat newly diagnosed transplant eligible patients with multiple myeloma

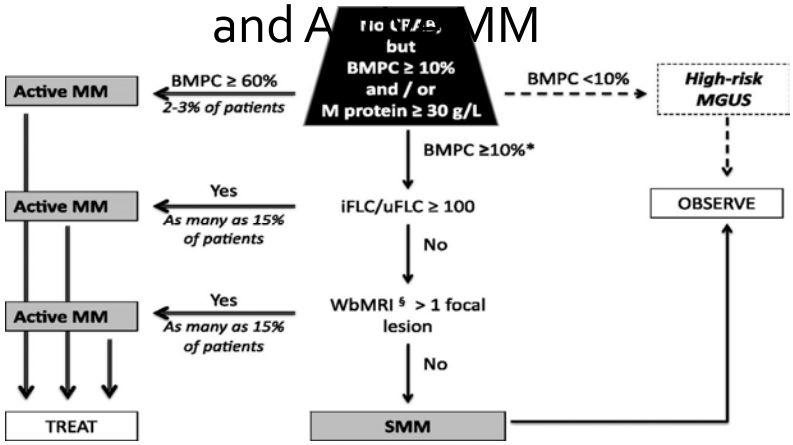
Sergio Giralt MD
Melvin Berlin Family Chair in Myeloma Research
Professor of Medicine, Weill Cornell Medical College
Chief Attending, Adult BMT Service
Memorial Sloan Kettering Cancer Center

Start with the basics

Case Presentation: MJ

- MJ is a 50 year old female who on routine PE was found with a total elevated serum protein 10.5 gm/lt and a hemoglobin of 11 gm/dl.
- Further work up reveals
- SPEP shows IgG 4,700 mg/dL and kappa 5,200 mg/dL
- M spike 4.2 g/dL
- 24-hour urine was normal < 0.16 g/24 hours
- β_2-microglobulin normal 1.6 mg/L
- Bone marrow biopsy showed 60% plasma cells; normal cytogenetics, no IgH translocations. DECREASED IRON STAINS
- Bone survey showed mild osteopenia

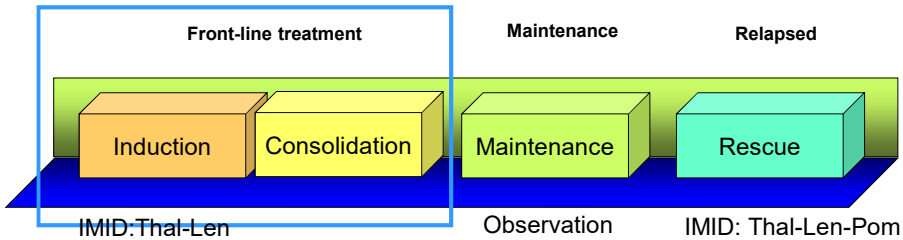
Algorithm for Reclassifying SMM and A[illegible]MM



- *Consider including patients with the following FISH: deletion 17p, t(4;14), and 1q21 gains as active MM; this population could account for as many as 30% of SMM patients. §Consider using more than 1 fluorodeox.

Dispenzieri A et al. Blood 2013;122:4172-4181. ©2013 by American Society of Hematology

Multiple Myeloma Treatment Lines[a]



IMID:Thal-Len
Proteosome Inhibitor: Bor-Car-Ixa
Steroids: Dex-Pred
Alkylator: Cyclo-Mel
Anthracycline: LipoDox-Dox
SCT

Observation
IMID: Thal-Len
Proteosome Inh: Bor
Steroids: Dex-Pred

IMID: Thal-Len-Pom
Proteosome Inh: Bor-Ca
Steroids: Dex-Pred
Alkylators: Mel-Cy-Bend
Investigational

[a]Transplant eligible patients.
Bor = bortezomib; Dex = dexamethasone; Dox = doxorubicin; Thal = thalidomide; Len = lenalidomide; SCT = stem-cell transplant; Pred = prednsione; Lipo/Dox = liposomal doxorubicin.
NCCN Clinical Practice Guidelines v2.2014.

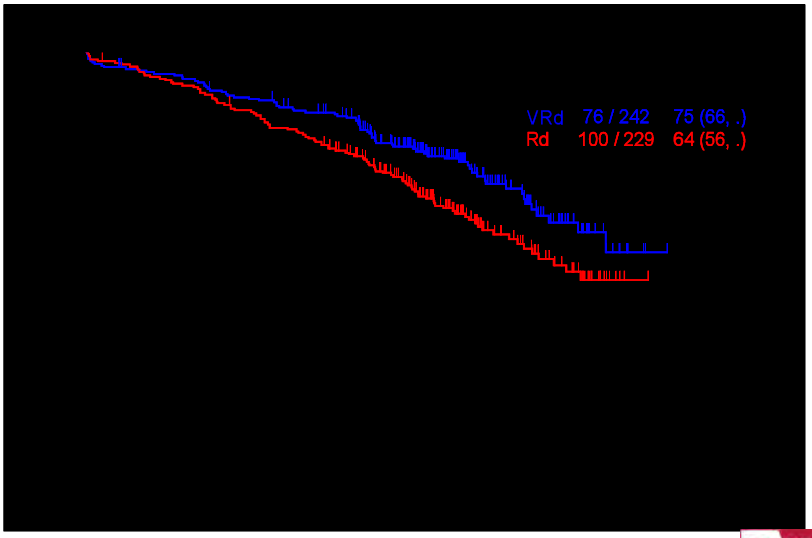
SWOG ASH 2015 Confirmed Response*: RVd Versus Rd (Durie et al)

	RVd	Rd
CR	15.7%	8.4%
VGPR	27.8%	23.4%
PR	38%	39.7%
ORR (PR or better)	81.5%	71.5%
SD	15.7%	24.3%
SD or better	97.2%	95.8%
PD or Death	2.8%	4.2%

*Assessable patients

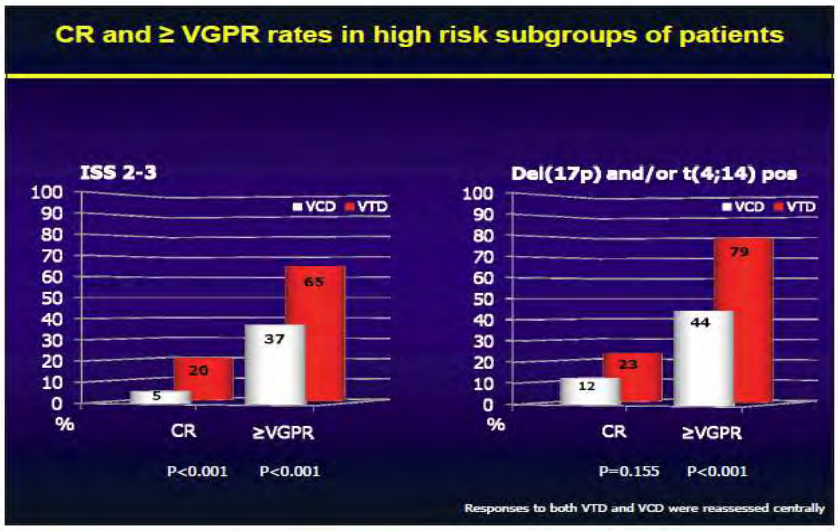
Durie B, et al. *Blood.* 2015;126: Abstract 25.

SWOG ASH 2015: Overall Survival By Assigned Treatment Arm

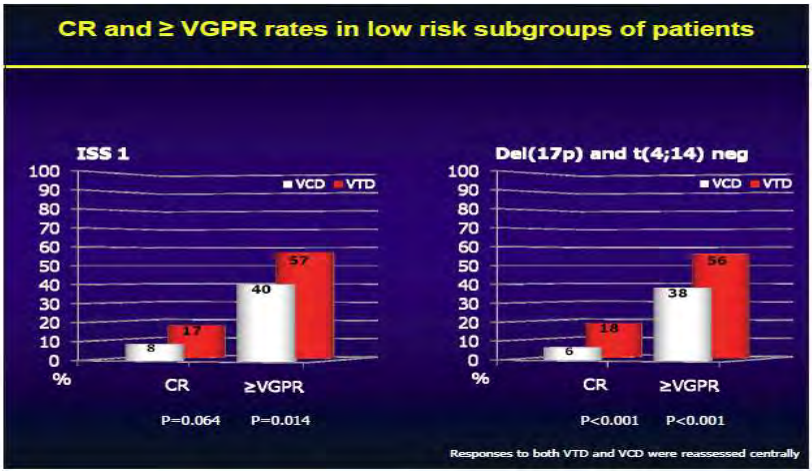


Durie B, et al. *Blood.* 2015;126: Abstract 25.

Optimal Induction Therapy High Risk Patients. Cavo et al ASH 2014



Optimal Induction Therapy Low Risk Patients. Cavo et al ASH 2014



677 Trends in Pre- and Post-Transplant Therapies Prior to First Autologous Hematopoietic Cell Transplantation Among Patients with Multiple Myeloma in the United States, 2004-2014

D'Souza et al ASH 2016

Figure 1A

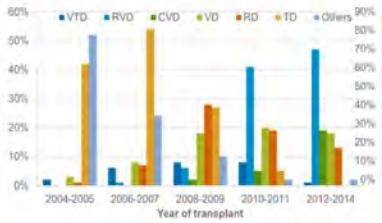
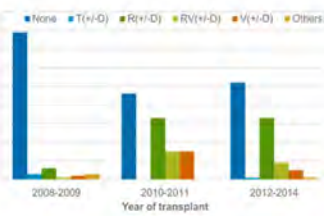
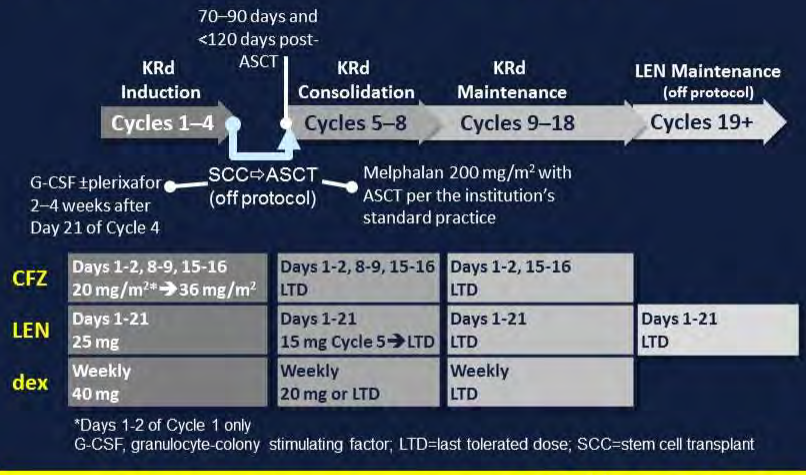


Figure 1B



Newer regimens
KRD
KRD – Dara
IXA RD

Treatment Schema – 28-day Cycle

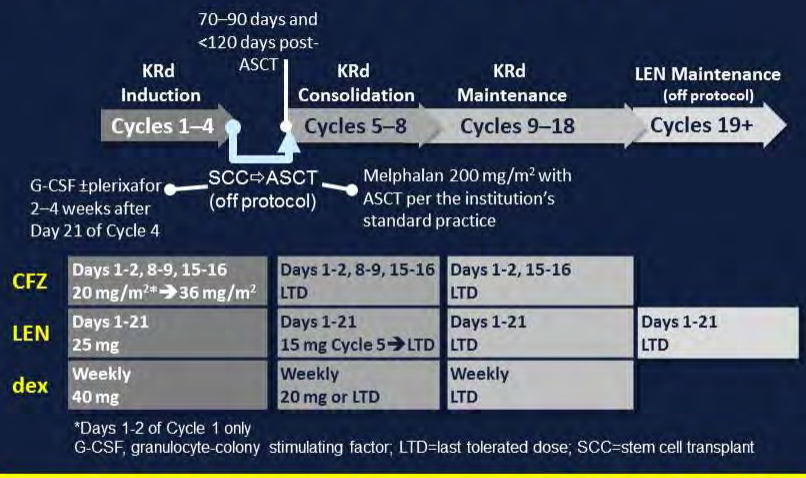


CFZ	Days 1-2, 8-9, 15-16 20 mg/m²*→36 mg/m²	Days 1-2, 8-9, 15-16 LTD	Days 1-2, 15-16 LTD	
LEN	Days 1-21 25 mg	Days 1-21 15 mg Cycle 5→LTD	Days 1-21 LTD	Days 1-21 LTD
dex	Weekly 40 mg	Weekly 20 mg or LTD	Weekly LTD	

*Days 1-2 of Cycle 1 only
G-CSF, granulocyte-colony stimulating factor; LTD=last tolerated dose; SCC=stem cell transplant

KRd+ASCT considered promising: improvement of ***sCR at the end of 8 cycles*** from historical rate of ***30% for KRd without transplant*** to ***50% for KRd+ASCT***

Treatment Schema – 28-day Cycle



CFZ	Days 1-2, 8-9, 15-16 20 mg/m²*→36 mg/m²	Days 1-2, 8-9, 15-16 LTD	Days 1-2, 15-16 LTD	
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G-CSF, granulocyte-colony stimulating factor; LTD=last tolerated dose; SCC=stem cell transplant

KRd+ASCT considered promising: improvement of ***sCR at the end of 8 cycles*** from historical rate of ***30% for KRd without transplant*** to ***50% for KRd+ASCT***

Daratumumab (DARA) in Combination with Carfilzomib, Lenalidomide, and Dexamethasone (KRd) in Patients (pts) With Newly Diagnosed Multiple Myeloma (MMY1001): an Open-label, Phase 1b Study

Andrzej Jakubowiak,[1] Ajai Chari,[2] Sagar Lonial,[3] Brendan Weiss,[4] Raymond L. Comenzo,[5] Kaida Wu,[6] Nushmia Z. Khokhar,[6] Jianping Wang,[7] Parul Doshi,[6] Saad Z. Usmani[8]

[1]University of Chicago Medical Center, Chicago, IL; [2]Tisch Cancer Institute, Mount Sinai School of Medicine, New York, NY, USA; [3]Department of Hematology and Medical Oncology, Winship Cancer Institute, Emory University, Atlanta, GA, USA; [4]Abramson Cancer Center and Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA; [5]Division of Hematology/Oncology, John C. Davis Myeloma and Amyloid Program, Tufts Medical Center, Boston, MA; [6]Janssen Research & Development, LLC, Spring House, PA, USA; [7]Janssen Research & Development, LLC, Raritan, NJ, USA; [8]Levine Cancer Institute/Carolinas HealthCare System, Charlotte, NC, USA.

Study Design

Eligibility/Treatment

- NDMM
- Transplant eligible and non-eligible
- Treatment duration: ≤13 cycles or until elective discontinuation for ASCT
- No clinically significant cardiac disease; echo required at screening

Dosing Schedule (28-d cycles)

Daratumumab:

- Split dose: 8 mg/kg Days 1-2 of Cycle 1
- 16 mg/kg QW on Cycles 1-2, Q2W on Cycles 3-6, and Q4W thereafter

Carfilzomib:

- 20 mg/m^2 C1D1
- Escalated to 70 mg/m^2 C1D8+; weekly (Days 1, 8, 15)

Lenalidomide:

- 25 mg; Days 1-21 of each cycle

Dexamethasone: 40 mg/week[a]

Endpoints

Primary

- Safety, tolerability

Secondary

- ORR, duration of response, time to response, IRR

Exploratory

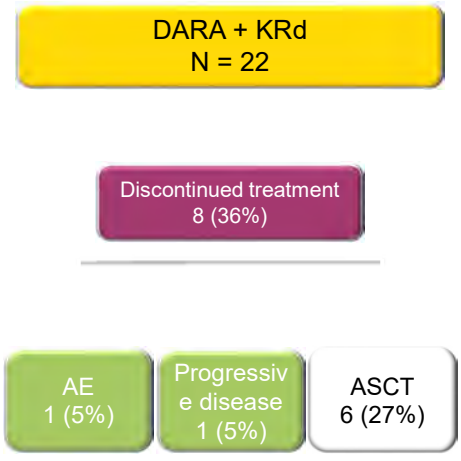
- PFS

Baseline Demographics

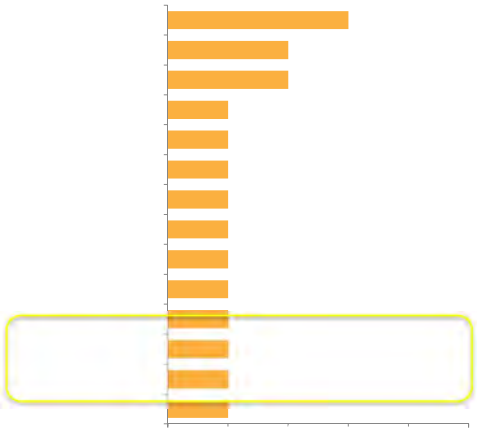
Characteristic	DARA + KRd (N = 22)
Age, years, n (%)	
Median (range)	59.5 (34-74)
<65	15 (68)
65 - <75	7 (32)
Gender, n (%)	
Male	12 (55)
Female	10 (46)
Race, n (%)	
White	19 (86)
African American	1 (5)
American Indian or Alaska Native	1 (5)
Not reported	1 (5)
ECOG score, n (%)	
0	12 (55)
1	9 (41)
2	1 (5)

Patient Disposition

- Median follow-up:
  10.8 (range, 4.0-12.5) months
- Median number of treatment cycles:
  11.5 (range, 1.0-13.0)
- Except for 3 patients, all escalated to carfilzomib 70 mg/m^2 by C2D1
  - 1 discontinued treatment before C2D1
  - 1 dose reduction to 56 mg/m^2 at C2D1
  - 1 escalated to 70 mg/m^2 at C3D8



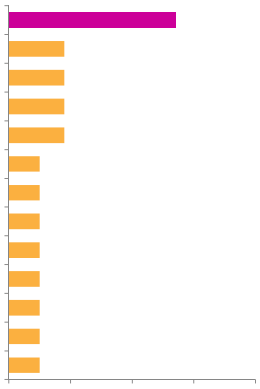
Serious TEAEs (N = 22)



Consistent with previous reports from KRd studies

Infusion Times and Reactions (N = 22)

Infusion Times	
Infusion	**Median (range) infusion time, h**
First	
C1D1	**4.15 (4.0-6.0)**
C1D2	**4.15 (3.9-6.0)**
Second	**4.18 (3.6-7.1)**
Subsequent	**3.38 (1.4-6.1)**

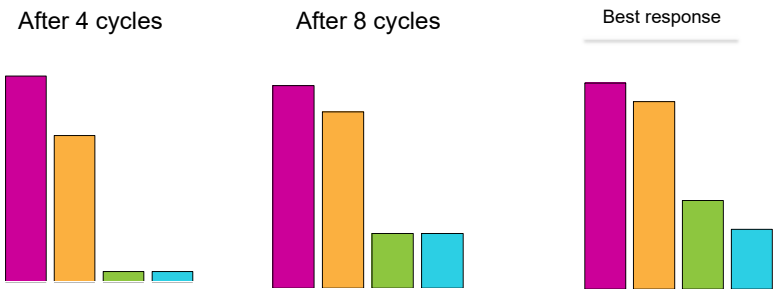


- No grade 3/4
- Occurrence
  - First infusion: 5 (23%) patients
  - Second infusion: 1 (5%) patient
  - Subsequent infusions: 1 (5%) patient

Lower rates of IRRs observed with split first dosing

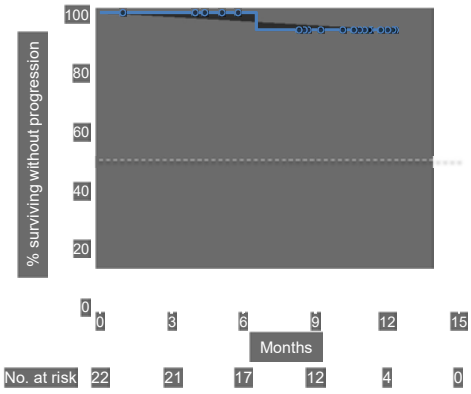
Response Rate[a,b]

- Median number of treatment cycles: 11.5 (range, 1.0-13.0



Depth of response improved with duration of treatment

PFS



- Median follow-up: 10.8 (range, 4.0-12.5) months
- Overall survival = 100

12-month PFS rate[a] = 94%

Stem Cell Harvest and ASCT[a]

- Median number of $CD34^+$ cells collected from patients: 10.4 x 10^6 cells/kg (n = 19)
- Median 5 treatment cycles prior to stem cell harvest

Patient	Stem cell mobilization	Total $CD34^+$ cells ($x10^6$/kg body weight)	Treatment cycle at ASCT	Best response[b]
1	Plerixafor and Filgrastim	30	9	sCR
2	Plerixafor and Filgrastim	12	5	VGPR
3	Plerixafor and Filgrastim	28	4	VGPR
4	Filgrastim	38	4	VGPR
5	Plerixafor and	10.4	5	VGPR
6	Filgrastim	6.5	4	VGPR

Stem cell yield is consistent with previous KRd studies

[a]Per protocol, patients who continued to ASCT discontinued study treatment.
[b]Best response among patients who elected ASCT.

Presented by: Andrzej Jakubowiak

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Lenalidomide-Ixazomid Dexa (RID) NDMM EHA 2017

	Richardson et al	Kumar et al	Dimopoulos et al
Ixazomib dose	3.0-3.7 Twice Weekly	1.6-3.8 Weekly	4.0 mg weekly CTX 300/400 mg/m2 1-8-15
N	40 (did not proceed to HCT)	42 (did not proceed to HCT)	70 non transplant eligible
ORR	93%	80	
CR+VGPR	68%	63%	
CR	32%	32%	
Median PFS	24.9 m	25 m	56% at 2 years
% Discontinuing due to AE Most Common	NS Rash and Neutropenia	NS Rash and Neutropenia	24% Neutropenia

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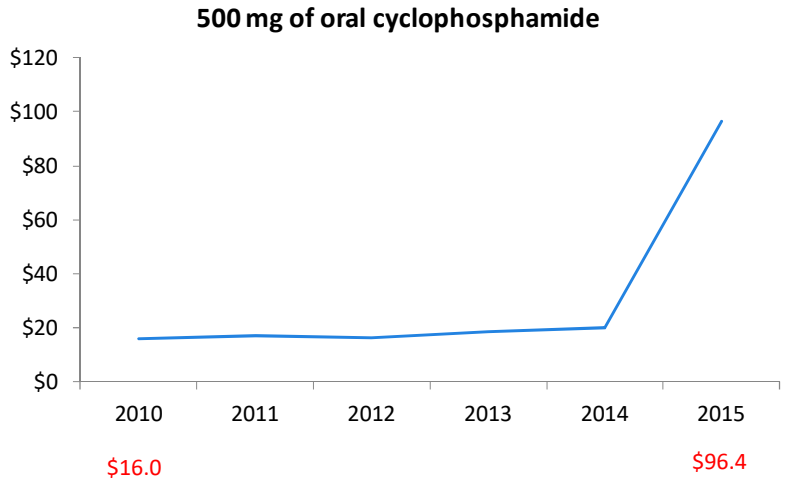
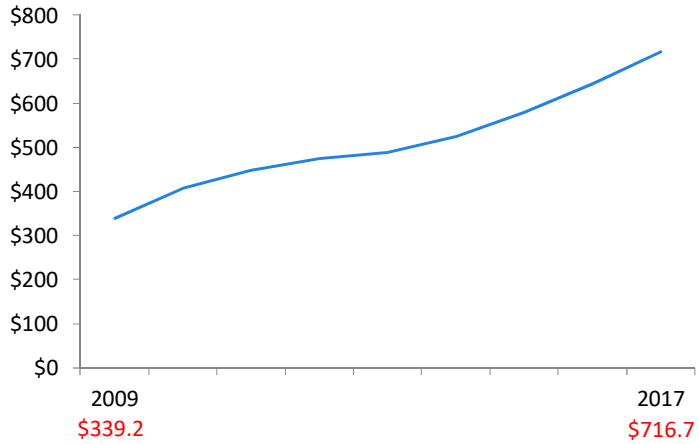
Are drug prices increasing over time: Oral cyclophosphamide



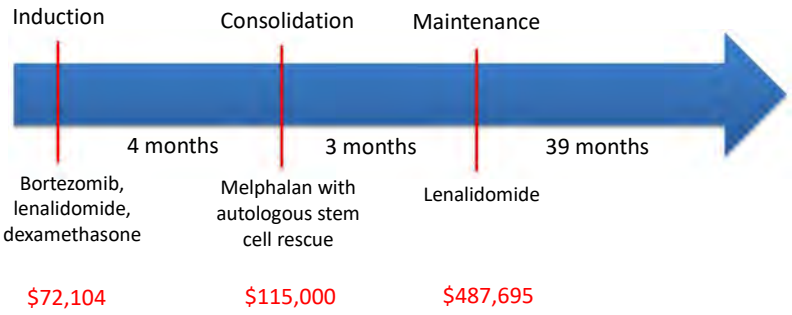
Medicare Part B average sales price (ASP).

Are drug prices increasing over time: Lenalidomide



Average wholesale price (AWP) from Redbook online.

Do high drug prices harm societies: Multiple Myeloma



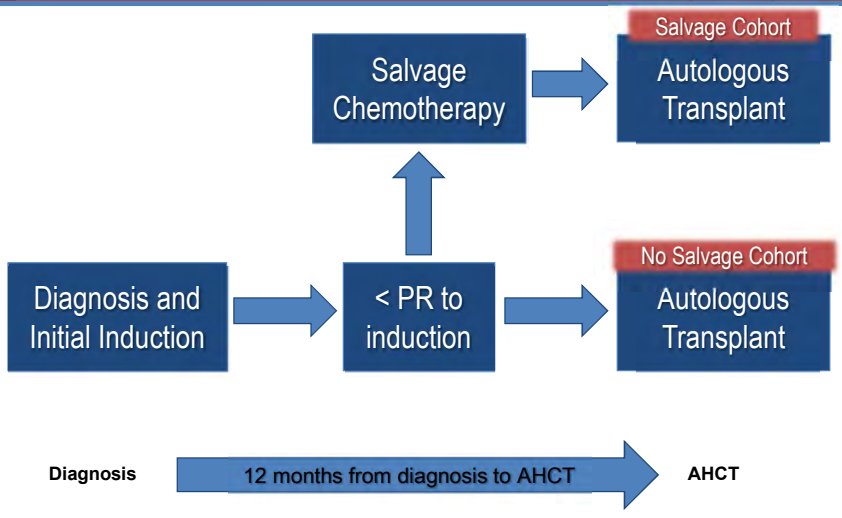
Optimal induction for Latin America

- Most cost effective approach to achieve a major response VGPR or greater
- CY-BOR-D x 4
- If no VGPR after 4 cycles consider
  - RVD x 4

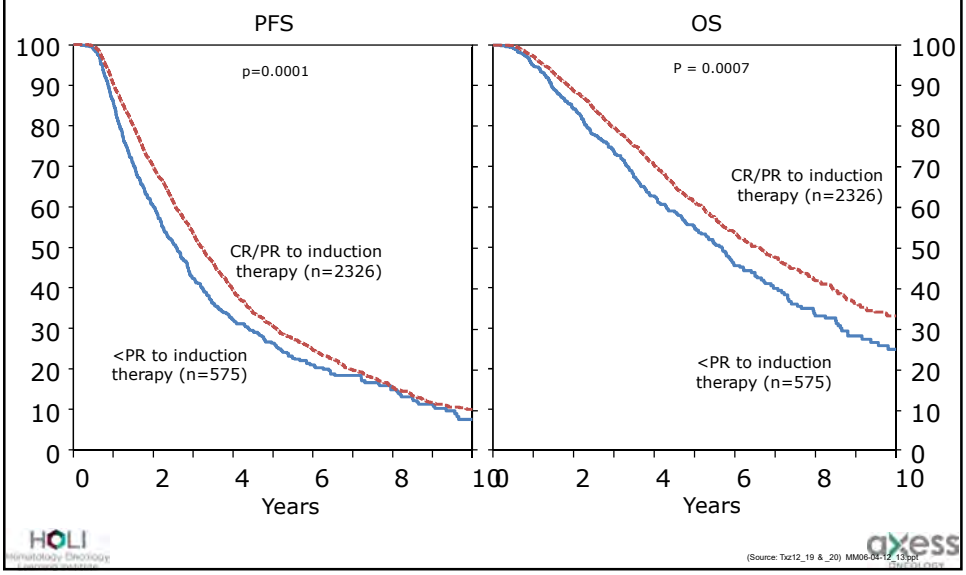
- Effect of Pre-transplant Salvage Therapy Prior to Autologous Transplant (AHCT) in Patients Not Responding to Initial Induction for Multiple Myeloma (MM)

CIBMTR Study MM06-04

- Methods

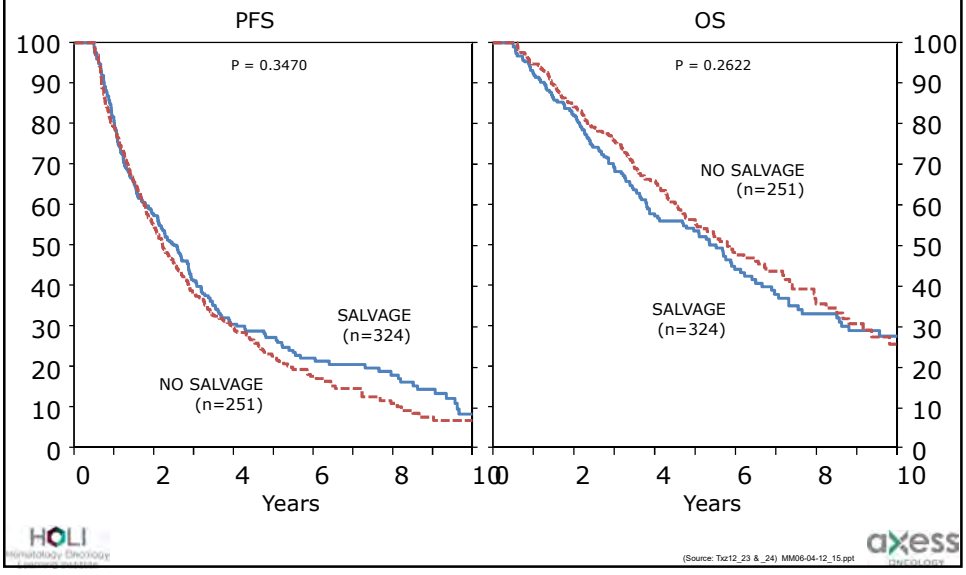


- Probability of Survival, based on Response to Initial Chemotherapy



(Source: Txz12_19 &_20) MM06-04-12_13.ppt

- Outcomes with/without Pre-AHCT Salvage



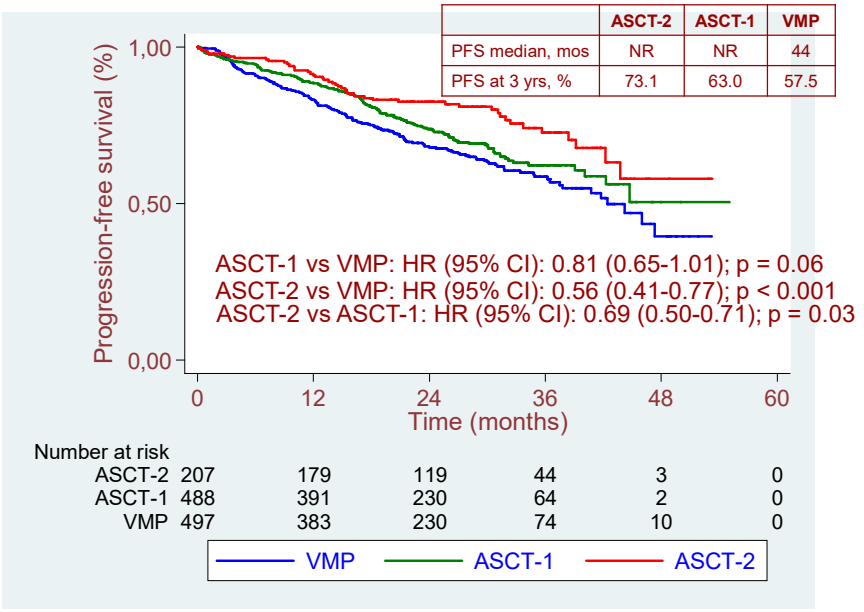
(Source: Txz12_23 &_24) MM06-04-12_15.ppt

CONSOLIDATION = CONTROVERSY

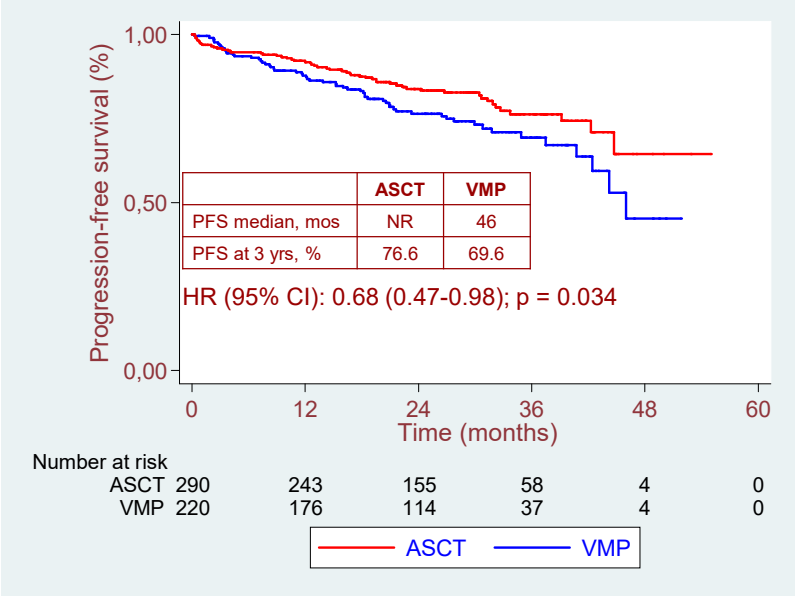
991 Upfront Single Versus Double Autologous Stem Cell Transplantation for Newly Diagnosed Multiple Myeloma: An Intergroup, Multicenter, Phase III Study of the European Myeloma Network (EMN02/HO95 MM Trial)

Cavo et al.

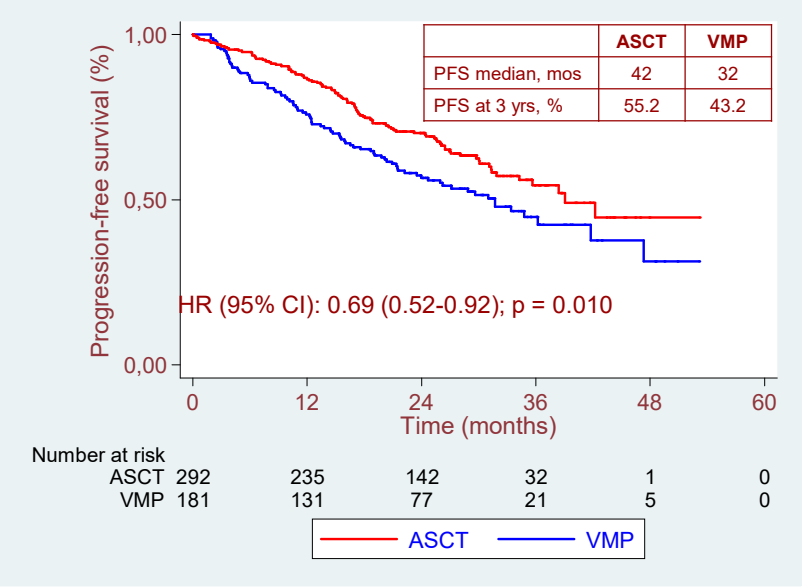
PFS by Randomization to ASCT-1 or ASCT-2



PFS by cytogenetics (standard risk)



PFS by cytogenetics (high risk)



	ASCT	VMP
PFS median, mos	42	32
PFS at 3 yrs, %	55.2	43.2

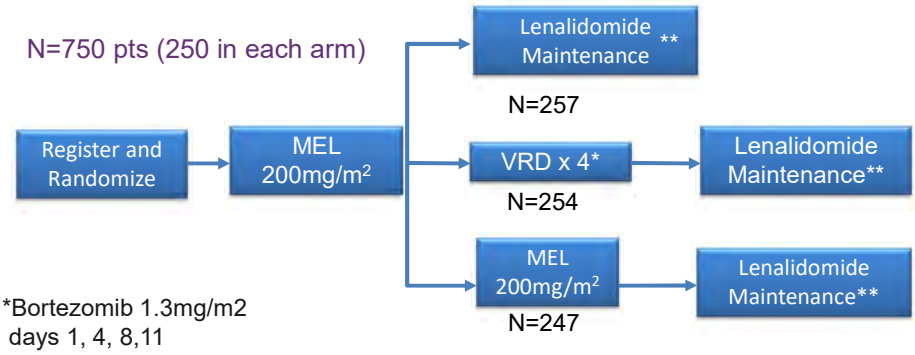
Primary Results from the Randomized Prospective Phase III Trial of the Blood and Marrow Transplant Clinical Trials Network

(BMT CTN 0702 – STaMINA Trial)

NCT#01109004

Autologous Hematopoietic Cell Transplant (AHCT), with and without Consolidation (with Bortezomib, Lenalidomide (Len) and Dexamethasone) and Len Maintenance versus Tandem AHCT and Len Maintenance for Up-Front Treatment of Patients with Multiple Myeloma

BMT CTN 0702 Stem Cell Transplantation for Multiple Myeloma Incorporating Novel Agents: SCHEMA



*Bortezomib 1.3mg/m2
days 1, 4, 8,11
Lenalidomide 15mg days 1-15
Dexamethasone 40mg
days 1, 8, 15
Every 21 days

**Lenalidomide x 3years :
10mg/d for 3 cycles , then 15 mg/d
Amendment in 2014 changed
Lenalidomide maintenance until
disease progression after report of
CALGB 100104

BMT CTN 0702: Regimens prior to Transplant

	Auto/Auto (N=247)		Auto/RVD (N=254)		Auto/Maint (N=257)	
	N	%	N	%	N	%
Initial Therapy						
Bort/Len/Dex	141	57.1	134	52.8	143	55.6
Cy/Bort/Dex	33	13.4	35	13.8	40	15.6
Len/Dex	24	9.7	28	11.0	22	8.6
Bort/Dex	28	11.3	32	12.6	32	12.5
Other	21	8.5	25	9.8	20	7.8

Bort, bortezomib; Cy, cyclophosphamide; Dex, dexamethasone; Len, lenalidomide

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Compliance with each interventic

	Auto/Auto (N=247)		Auto/RVD (N=254)		Auto/Maint (N=257)	
	N	%	N	%	N	%
Received 2nd Intervention						
No	79	32.0	30	11.8	-	-
Yes	168	68.0	224	88.2	-	-
Started maintenance						
No	41	16.6	43	16.9	14	5.4
Yes	206	83.4	211	83.1	243	94.6

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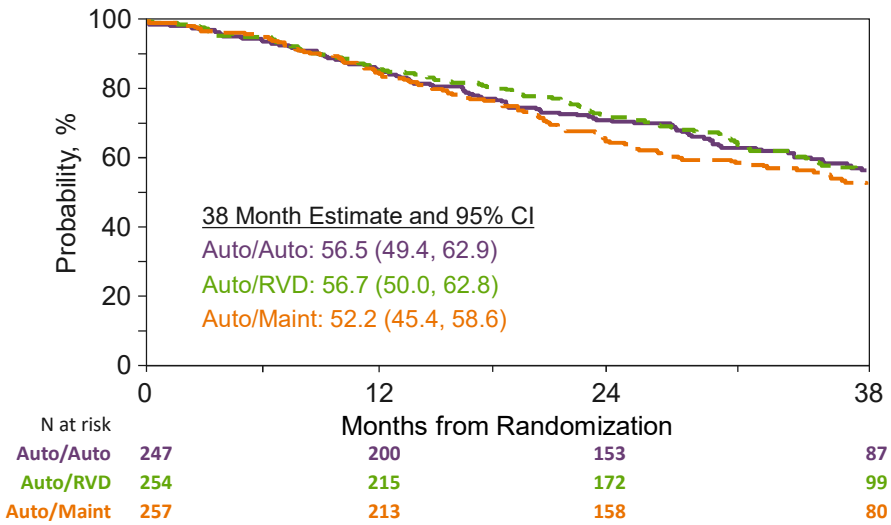
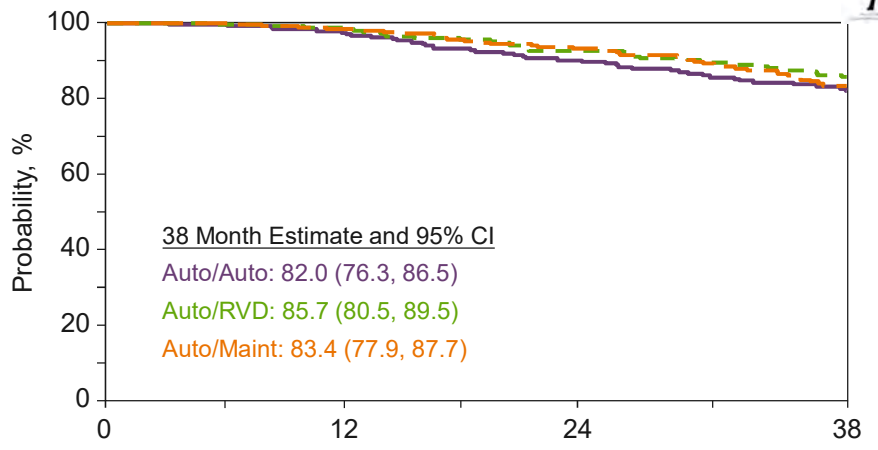
Primary Endpoint: Progression-free Survival



326

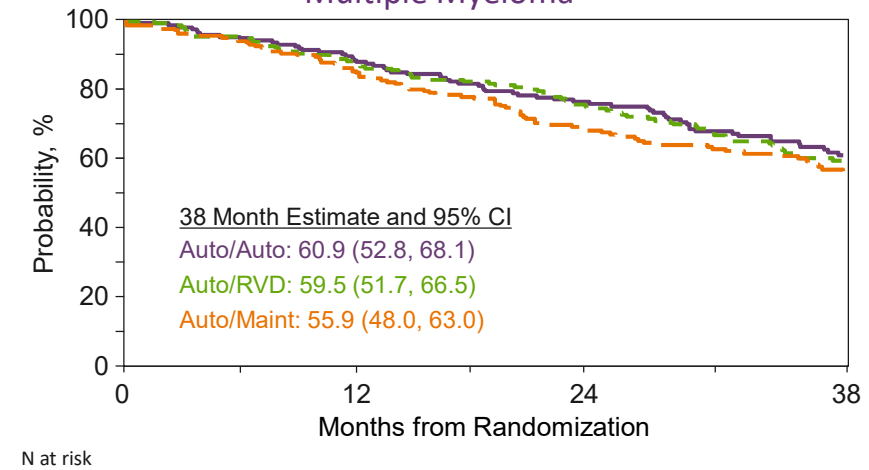
Overall Survival



N at risk				
Auto/Auto	247	231	204	147
Auto/RVD	254	246	229	166
Auto/Maint	257	247	227	148

327

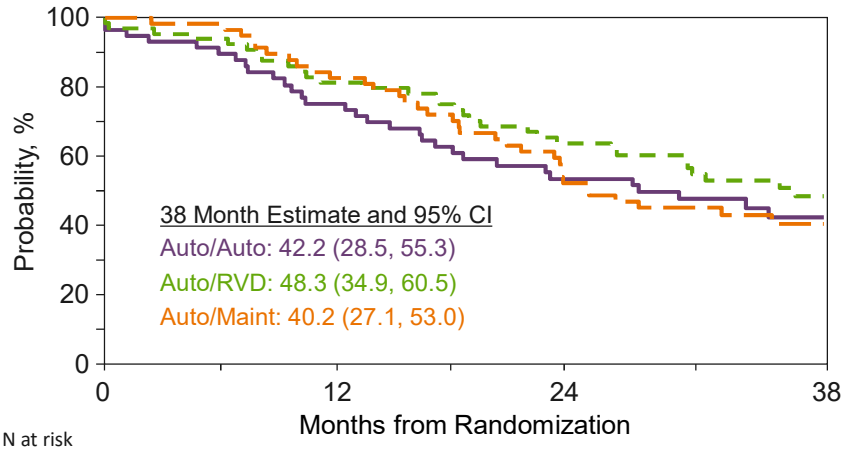
Progression-free Survival – Patients with Standard Risk Multiple Myeloma



N at risk				
Auto/Auto	190	158	125	73
Auto/RVD	189	163	134	81
Auto/Maint	198	166	125	64

328

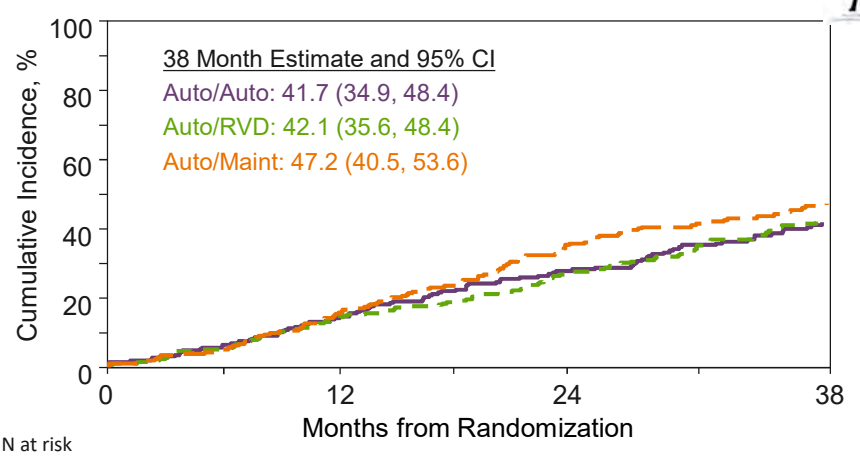
Progression-free Survival – Patients with High Risk Multiple Myeloma



N at risk				
Auto/Auto	57	42	28	14
Auto/RVD	65	52	38	18
Auto/Maint	59	47	33	16

329

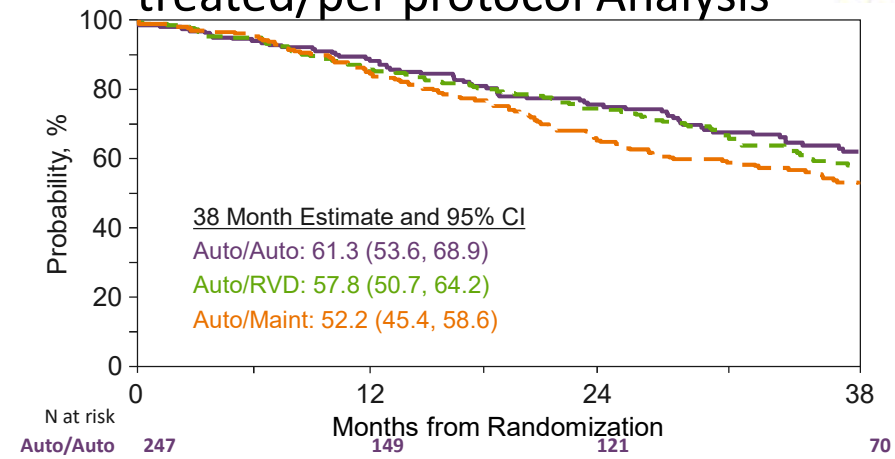
Multiple Myeloma Progression



N at risk				
Auto/Auto	247	200	153	87
Auto/RVD	254	215	172	99
Auto/Maint	257	213	158	80

330

Progression-Free Survival – as treated/per protocol Analysis



N at risk				
Auto/Auto	247	149	121	70
Auto/RVD	254	195	160	91
Auto/Maint	257	212	157	79

331

Conclusion

- In the era of thalidomide analogues and proteasome inhibitors used in the initial therapy for myeloma (in this study >90% either, >50% both) and the use of prolonged maintenance therapy with lenalidomide, post transplant consolidation with cycles of RVD or a second transplant do not produce incremental PFS benefit.

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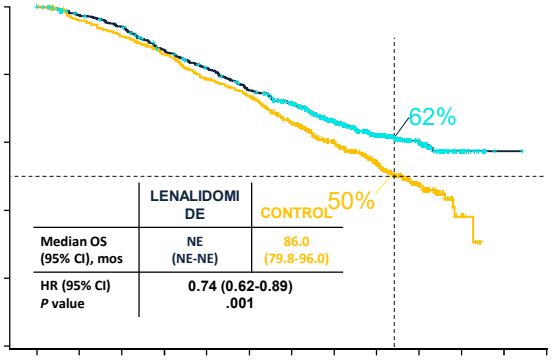
Lenalidomide Maintenance After High-Dose Melphalan and Autologous Stem Cell Transplant in Multiple Myeloma: A Meta-Analysis of Overall Survival

Michel Attal,[1] Antonio Palumbo,[2] Sarah A. Holstein,[3] Valérie Lauwers-Cances,[1] Maria Teresa Petrucci,[4] Paul Richardson,[5] Cyrille Hulin,[6] Patrizia Tosi,[7] Kenneth C. Anderson,[5] Denis Caillot,[8] Valeria Magarotto,[9] Philippe Moreau,[10] Gerald Marit,[11] Zhinuan Yu,[12] Philip L. McCarthy[13]

Overall Survival: Median Follow-Up of 80 Months



All SPMs After Randomization

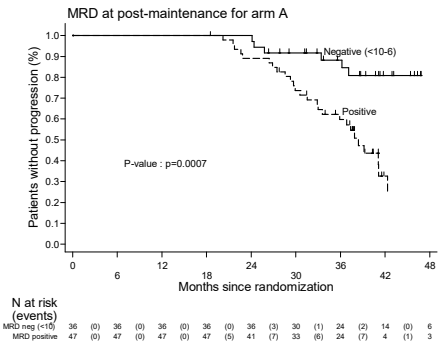
SPMs, n[b]	CALGB[a]		IFM		GIMEMA	
	LEN (n = 224)	Placebo (n = 221)	LEN (n = 306)	Placebo (n = 302)	LEN (n = 56)	No MNTC (n = 79)[c]
Hematologic	15	8	21	9	0	0
AML[d]	7	0	6	3	–	–
MDS	4	4	4	3	–	–
B-cell malignancy	4	3	11	2	–	–
Other	0	1	1	1	–	–
Solid tumors	17	10	21	13	5	2

[a]SPMs in placebo arm include those that occurred after crossover. [b]Patients who experienced > 1 SPM (eg, 2 types of SPMs) or > 1 episode of an SPM are counted once in each SPM category. This analysis includes SPMs before and after PD. [c]In the GIMEMA-RV-MM-PI-209 study, the no maintenance arm includes patients eligible for the maintenance phase without any dose of LEN maintenance. [d]Includes AML and MDS to AML.

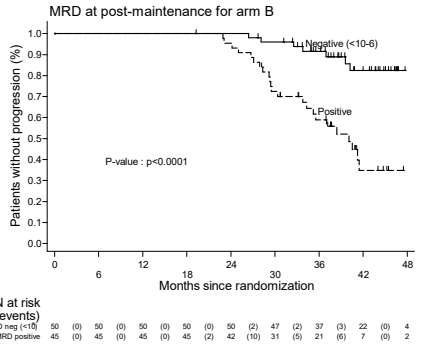
AML, acute myeloid leukemia; LEN, lenalidomide; MDS, myelodysplastic syndromes; MNTC, maintenance; SPMs, second primary malignancy.

IFM/DFCI 2009 ~ PFS according to MRD Post Maintenance

RVD Arm



Transplant Arm



Avet-Loiseau H, et al *Blood*. 2015;126: Abstract 191.

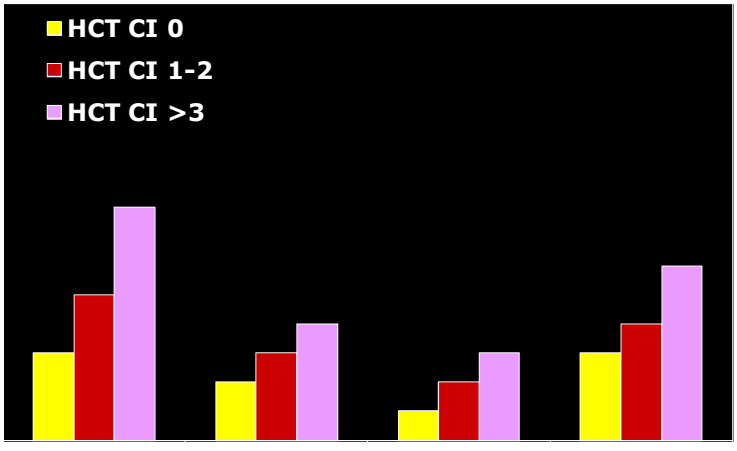
Transplant Eligibility in Older Patients

Community Dwelling, Healthy
Age 82

Community Dwelling, Frail
Ages 19, 82, 23

Community Dwelling, Typical
Institutionalized, Frail
Ages 84,81

100-Day Mortality by HCT-CI After Autologous Hematopoietic Cell Transplantation According to Performance Score and Disease Indication



CLINICAL TRIALS AND OBSERVATIONS

Geriatric assessment predicts survival and toxicities in elderly myeloma patients: an International Myeloma Working Group report

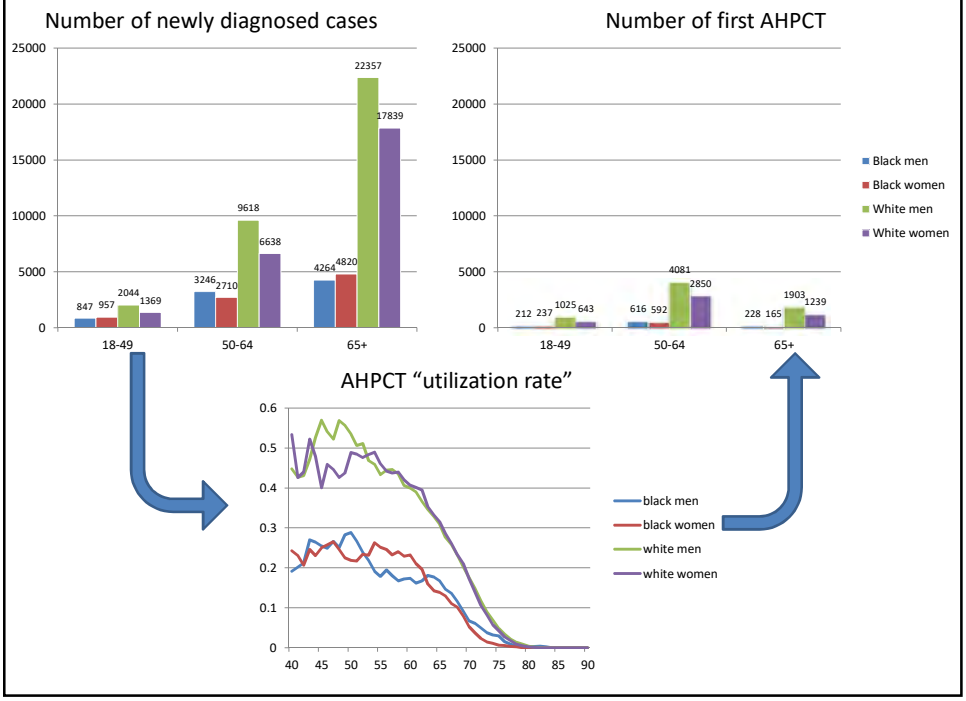
Antonio Palumbo,[1] Sara Bringhen,[1] Maria-Victoria Mateos,[2] Alessandra Larocca,[1] Thierry Facon,[3] Shaji K. Kumar,[4] Massimo Offidani,[5] Philip McCarthy,[6] Andrea Evangelista,[7] Sagar Lonial,[8] Sonia Zweegman,[9] Pellegrino Musto,[10] Evangelos Terpos,[11] Andrew Belch,[12] Roman Hajek,[13] Heinz Ludwig,[14] A. Keith Stewart,[15] Philippe Moreau,[16] Kenneth Anderson,[17] Hermann Einsele,[18] Brian G. M. Durie,[19] Meletios A. Dimopoulos,[11] Ola Landgren,[20] Jesus F. San Miguel,[21] Paul Richardson,[22] Pieter Sonneveld,[23] and S. Vincent Rajkumar[4]

Table 2. The final Cox regression model

	HR (95% CI)	P	Score
Age, y			
≤75	1	—	0
76-80	1.13 (0.76-1.69)	.549	1
>80	2.40 (1.56-3.71)	<.001	2
ADL			
>4	1	—	0
≤4	1.67 (1.08-2.56)	.020	1
IADL			
>5	1	—	0
≤5	1.43 (0.96-2.14)	.078	1
CCI			
≤1	1	—	0
≥2	1.37 (0.92-2.05)	.125	1
ISS			
I	1	—	—
II	2.37 (1.38-4.09)	.002	—
III	3.21 (1.85-5.58)	<.001	—
Chromosome abnormalities			
Favorable	1	—	—
Unfavorable	1.79 (1.23-2.60)	.002	—
Missing	1.13 (0.69-1.83)	.036	—
Therapy			
Proteasome inhibitors	1	—	—
Lenalidomide	0.74 (0.50-1.11)	.142	—

HRs and relative risks are for OS in patients with the factors as compared with those without the factors. The model was adjusted for ISS, chromosome abnormalities, and therapy. Unfavorable profile defined as t(4;14) or t(14;16) or del17p13.

AIC = 1748.918; Harrell C index = 0.7069.



1190 Significant Differences in Stem Cell Transplant Utilization Rates (STUR) of Autologous Hematopoietic Cell Transplant (AHCT) in Multiple Myeloma (MM) Based on Ethnicity without Differences in Efficacy. a CIBMTR Report. D'Souza et al.

Table 1. Stem cell Transplant utilization rate estimate

Year	Hispanic (95%CI)	Non-Hispanic White (95%CI)	Non-Hispanic Black (95%CI)
2008	8.6 (7.9 -9.4)%	22.6 (21.8 -23.9)%	12.2 (11.4 -13.0)%
2009	9.8 (9.0 -10.7)%	26.6 (25.7 -27.5)%	13.2 (12.4 -14)%
2010	11.9(10.9-13.0)%	29.4(28.4-30.4)%	15.7(14.8-16.8)%
2011	11.4(10.6-12.4)%	34 (32.9 -35.1)%	18.2(17.1-19.3)%
2012	14.2(13.1-15.4)%	35.4(34.3-36.6)%	19(18-20.2)%
2013	16.9(15.6 -18.3)%	37.8 (35.5 -38)%	20.5(19.4-21.8)%

Table 2. Outcomes of AHCT in MM by ethnicity (values are expressed as probabilities with 95% confidence intervals)

Outcome	**H** (N=1933)	**NHW** (N=18046)	**NHB** (N=4123)	p-value
TRM				0.4
100 days	0.6 (0.3-1)%	0.9 (0.7-1)%	0.6 (0.4-0.9)%	0.2
1 year	2 (2-3)%	3(2-3)%	3 (2-3)%	0.7
PFS				1.0
1-year	82 (80-84)%	83 (82-83)%	82 (81-83)%	0.3
2-year	66 (64-68)%	66 (65-67)%	66 (64-67)%	0.9
3-year	54 (51-56)%	53 (52-54)%	54 (52-55)%	0.8
OS				0.1
1-year	94 (93-95)%	94 (93-94)%	94 (94-95)%	0.3
2-year	86 (85-88)%	86 (85-86)%	86 (85-87)%	0.7
3-year	80 (77-82)%	77 (77-78)%	79 (77-80)%	0.05

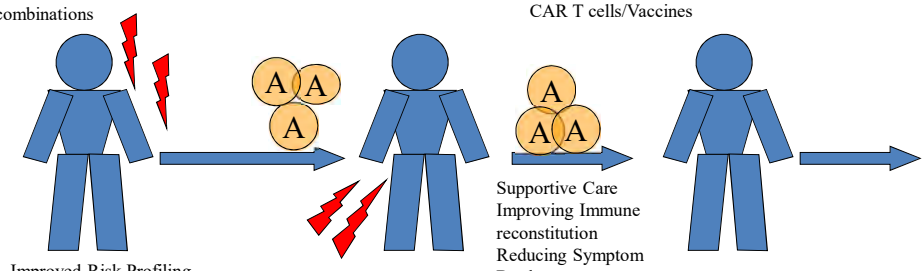
Future Directions in Myeloma and HCT

Pre HCT Therapy
Improved induction
Carfilzomib/Daratumumab combinations

Graft Engineering to Enhance Immune Recovery

Post Transplant Cellular & Immune Therapies

CAR T cells/Vaccines



Improved Risk Profiling
Response and Risk Adapted Therapy

Prep Regimen
Novel combinations
Melflufen
Radio-immune-conjugates

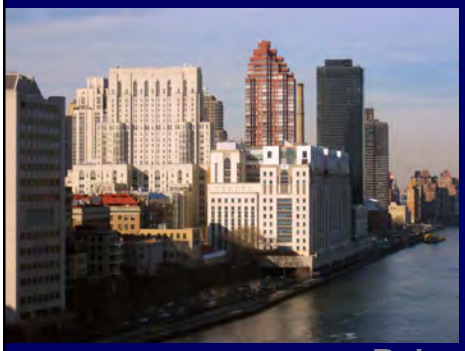
Supportive Care
Improving Immune reconstitution
Reducing Symptom Burden

Relapse Prevention
Drugs
Antibodies
ImIDS
PIs
Cells/Vaccines
WT1
Car T cells
Myeloma DC vaccine

Frontline Treatment for MM Transplant Eligible

- Current standard is
  - Triple induction (ImID,PI, steroids)
  - Single high dose melphalan auto HCT
  - Maintenance lenalidomide
- HCT severely underutilized in United States
- Risk Stratification is still NOT STANDARD
- However…
  - Patients with high risk features reasonable to explore
    - IMID/PI maintenance
  - Tandem auto or auto/allo HCT
- MRD Directed therapy not yet standard but all roads point towards that destination

Treatment of the Fit/Older MM Patient



Myelomacenter.org
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Disclosures for Ruben Niesvizky

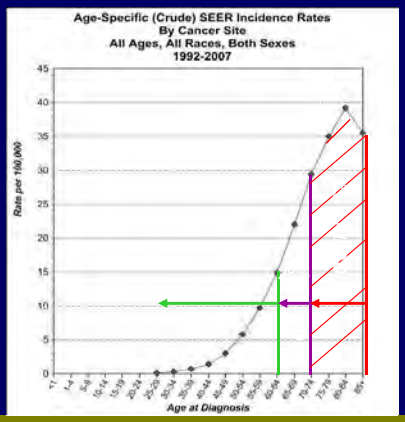
In compliance with ACCME policy, following disclosures to the session audience:

Research Support/P.I.	**Celgene, Takeda, Amgen, Janssen, BMS**
Employee	**N/A**
Consultant	**Celgene, Takeda, Amgen, Janssen, BMS**
Major Stockholder	**N/A**
Honoraria	**N/A**
Speakers Bureau/Scientific Advisory Board	**N/A**

The Elderly Patient

The median age at diagnosis is 70 years

- **Nearly half of multiple myeloma patients are considered elderly**
- **Traditionally the definition of elderly based on transplant eligibility (European and North American trials)**
  - **Patients under 65 years of age, 35%**
  - **Older patients from 65 to 75 years of age, 28%**
  - **Elderly patients over 75, 37%**

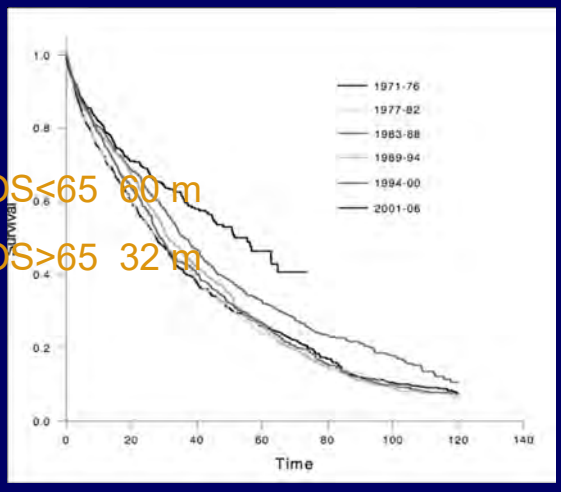


Palumbo A, et al. *Hematology Am Soc Hematol Educ Program.* 2009:566-577.; Ferlay J, et al. GLOBOCAN 2002 Cancer Incidence, Mortality and Prevalence Worldwide. IARC CancerBase No. 5 Version 2.0. Lyon: IARC Press; 2004.; Ries LAG, et al. National Cancer Institute. SEER Cancer Statistics Review. Source: SEER 13. Accessed August 24, 2010 at: http://seer.cancer.gov/faststats

Survival as a Function of Era

Median OS<65 60 m

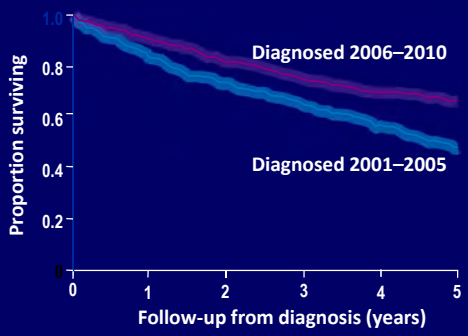
Median OS>65 32 m



Kumar et al Blood 2007

Continued Improvement in Survival Since the Introduction of Novel Agents

- Survival improved over time, particularly in patients aged > 65 years (p = 0.001)
- 1,056 patients grouped into 2001–2005 and 2006–2010 cohorts



Survival	2001–2005	2006–2010	p
Median OS, years	4.6	NR	0.001
1-year survival, %	83	90	
5-year estimated OS, %			
Overall	48	66	
> 65 years	31	56	0.001
< 65 years	63	73	NS

Kumar SK, et al. Blood. 2012;120:[abstract 3972]. Updated data presented at ASH 2012.

Individualized Treatment in Older Patients with Multiple Myeloma

- Biology of the Disease
  - FISH and ploidy
  - GEP
  - Others
- Host
  - Comorbidities
  - Functional status
- Therapeutics and Toxicology
  - Response and dose modifications
- Psychosocial Aspects
  - Access to care and social support

Individualized Treatment in Older Patients with Multiple Myeloma

- Biology of the Disease
  - FISH and ploidy
  - GEP
  - Others
- Host
  - Comorbidities
  - Functional status
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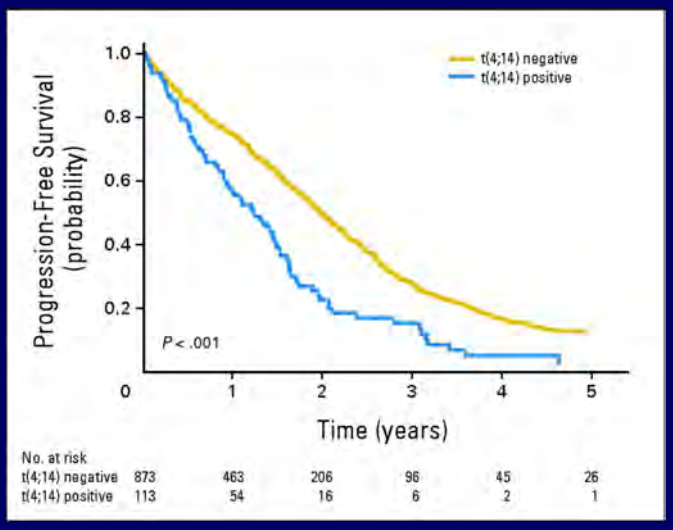
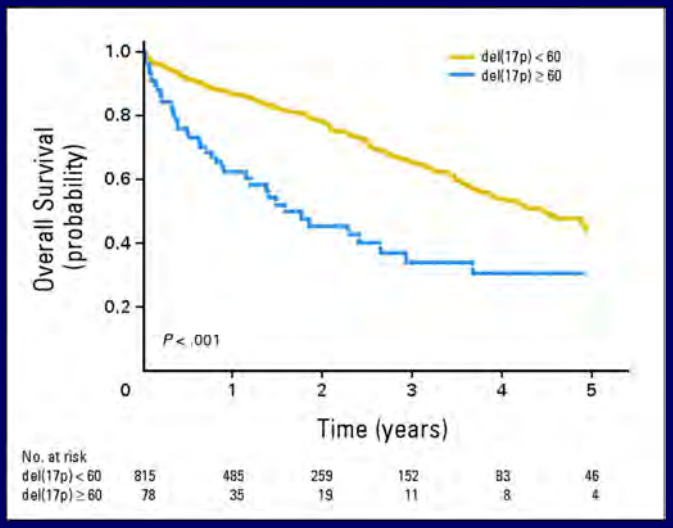
  - Response and dose modifications
- Psychosocial Aspects
  - Access to care and social support

Progression-free survival curves according to presence of t(4;14).



Hervé Avet-Loiseau et al. JCO 2013;31:2806-2809

Overall survival curves according to presence of del(17p).



Hervé Avet-Loiseau et al. JCO 2013;31:2806-2809

JOURNAL OF CLINICAL ONCOLOGY ASCO

Individualized Treatment in Older Patients with Multiple Myeloma

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2-Year Mortality Rate for Persons Age 70 Years and Older

- 8% if fully independent
- 14% if dependent in IADL
- 27% if dependent in ADL
- >40% if institutionalized

Reuben. *Am J Med*. 1992;93:663.

Comorbidity Is a Key Factor in Survival

Age-Comorbidity Score	N	Actual 10-Year Survival (%)
0-1	369	97-99
2	136	87
3	109	79
4	42	47
5	29	34

Charlson et al. *J Chronic Dis*. 1987;40:373.

Aspecto	Método	Conclusión Clínica y Proporcionalidad
Funcional	Motilidad, Desempeño físico, Fatiga,	Inversamente or Directamente supervivencia
Psiquiátrico	HADS	Directamente proporcional a la morbilidad psiquiática
Social	MOS 3MS	Inversamente or Directamente supervivencia
Nutrición	NMA	Supervivencia
Co-morbilidad	Formula calculada	Supervivencia

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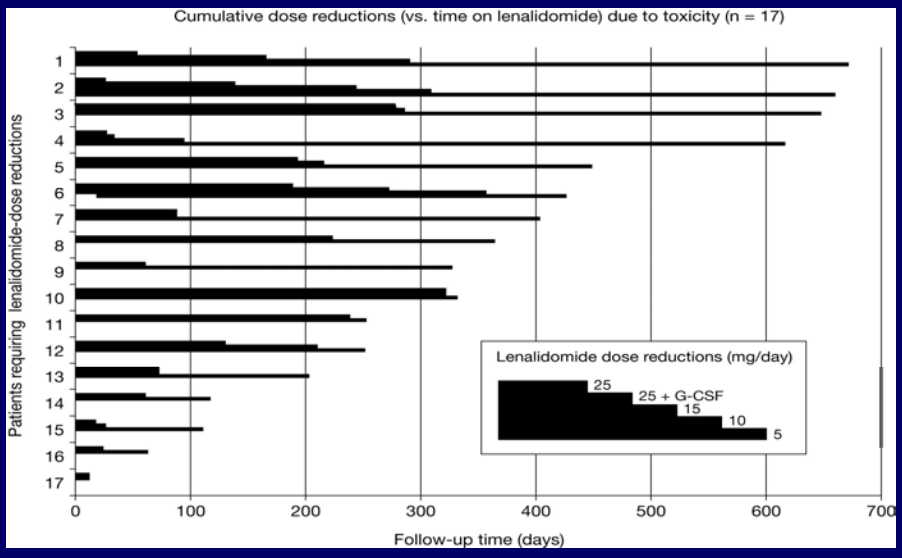
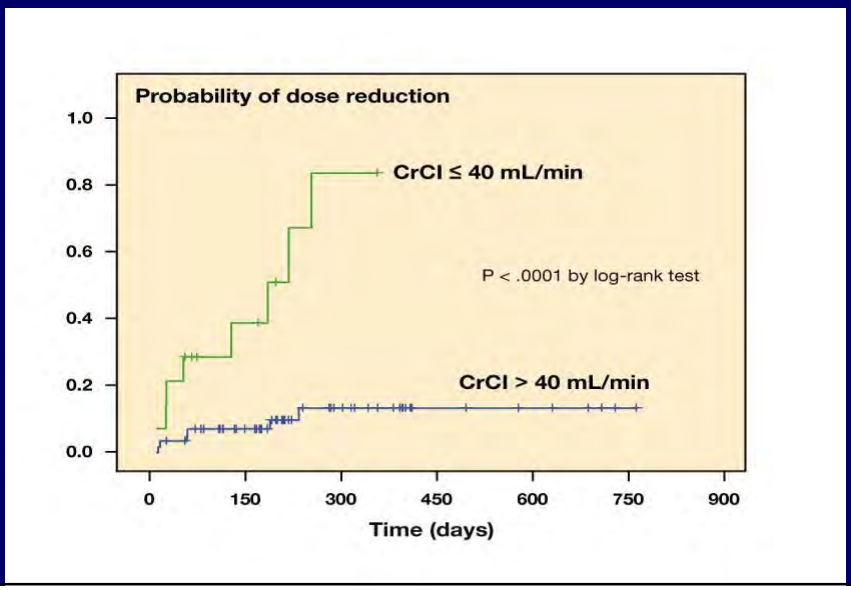
P450 CYP
Renal Clearance

Toxicity: Myelosuppression

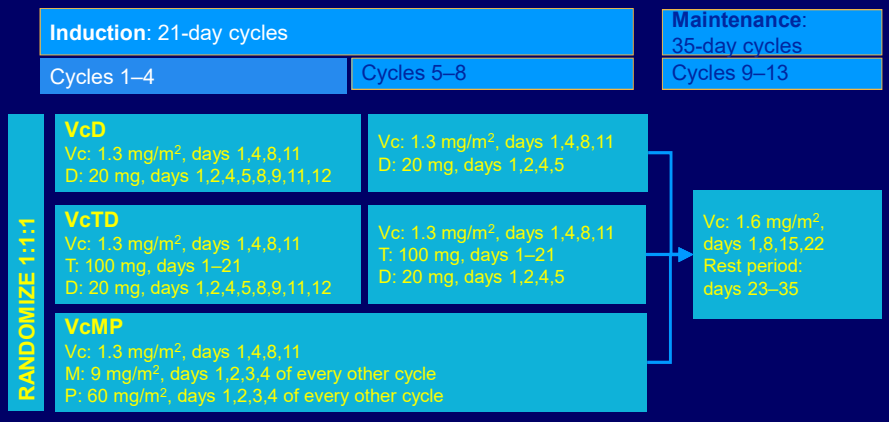


Br J Haematology 138, 640–643, 2007

Toxicity: Myelosuppression

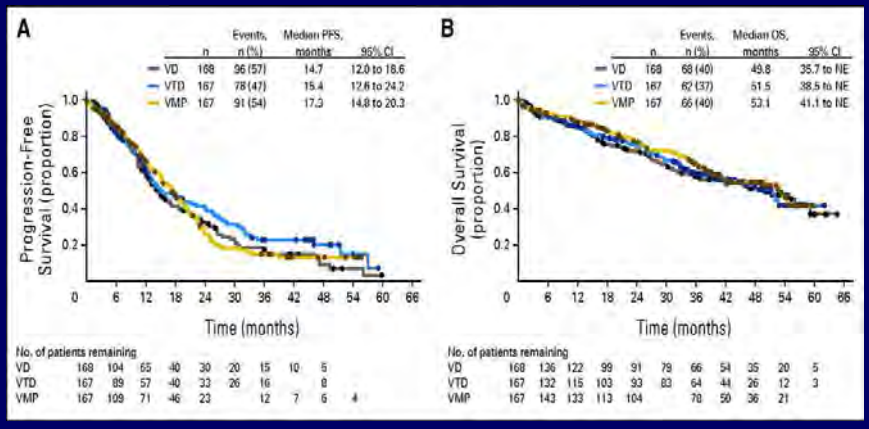


UPFRONT protocol



Niesvizky et al. JCO doi:10.1200/JCO.2014.58.7618

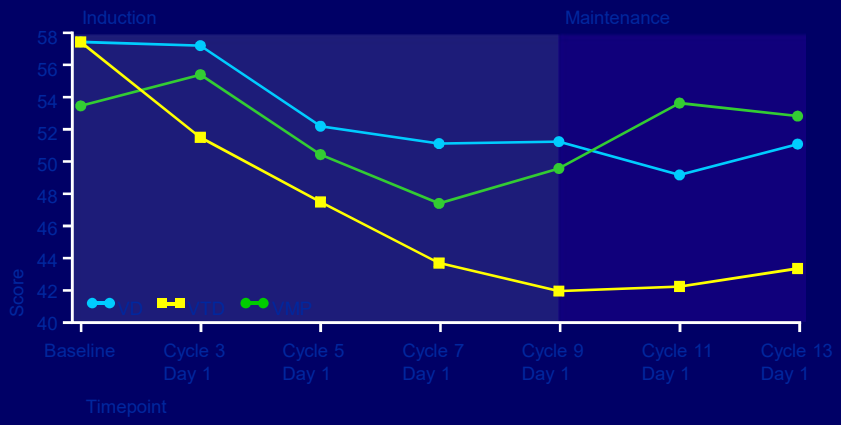
UPFRONT protocol: **(A) progression-free survival (PFS) and (B) overall survival (OS) in the intent-to-treat population.**



Niesvizky et al. JCO doi:10.1200/JCO.2014.58.7618

JOURNAL OF CLINICAL ONCOLOGY ASCO

Patient-reported QoL (mean global health status score by treatment arm)



- In all three treatment arms, there was a trend for decreasing QoL during induction, followed by an improvement/stabilization in QoL during maintenance
- There was a trend for poorer QoL in the VTD vs. VD and VMP arms

UPFRONT QoL poster (Niesvizky et al., ASH 2011, abstract 1864)

Once-weekly administration of bortezomib as a strategy to improve tolerability

Study details	Grade ¾ GI toxicity	Grade 3/4 peripheral neuropathy	Discontinuation due to AE
VISTA: VMP[1-3] Bortezomib twice-weekly	20%	14%	34%
(GIMEMA)[4] Bortezomib once-weekly	-	5%	17%
(PETHEMA/GEM)[5] Bortezomib once-weekly	7%	7%	12%†

†Discontinuations due to SAEs

1. San Miguel et al. NEJM 2008;359:906
2. San Miguel et al. NEJM 2008;359:906; Supplementary Appendix
3. Mateos et al. J Clin Oncol 2010;28:2259-66
4. Palumbo et al. JCO 2010; 28:5101-09
5. Mateos et al. Lancet Oncol 2010;11:934-41

Once-weekly administration of bortezomib as a strategy to maintain/improve the efficacy

Study details	CR+PR	CR	PFS	3 yrs-OS
VISTA: VMP[1-3] Bortezomib twice-weekly	71%	30%	TTP:24 m	68%
Modified VISTA[4] (GIMEMA) Bortezomib once-weekly VMPT→VT VMP	 90% 81%	 42% 24%	 37 m 27 m	 85% 80%
Modified VISTA[5] (PETHEMA) Bortezomib once-weekly VMP vs VTP→VT vs VP	 80%	 23%→42%	 31 m	 70%

1. San Miguel et al. NEJM 2008;359:906
2. San Miguel et al. NEJM 2008;359:906; Supplementary Appendix
3. Mateos et al. J Clin Oncol 2010;28:2259-66
4. Palumbo et al. J Clin Oncol 2010;28:5101-9
5. Mateos et al. Lancet Oncol 2010;11:934-41

Bortezomib IV versus SC

222 relapsed and/or refractory MM patients. Bz is given at conventional dose and scheme

	Bortezomib IV (n=73)	Bortezomib SC (n=145)
Primary endpoint: response after 4/8cycles (single agent bortezomib or +/-dex))		
ORR	42%/52%	42%/52%
CR	8%/12%	6%/10%
TTP	9·4 m	10·4 m

	Bortezomib IV		Bortezomib SC	
	All grades	Grade ≥3	All grades	Grade ≥3
Periph Neurop	53%	16%	38%	6%
				P=0·04 and 0·03

No diferences in pharmakokinetics studies

Moreau *et al*. Lancet Oncology 2011; 12(5): 431-40
Arnulf B et al. Haematologica 2012: Epub ahead of print

Individualized Treatment in Older Patients with Multiple Myeloma

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Survival

QOL

Regular Article

CLINICAL TRIALS AND OBSERVATIONS

Geriatric assessment predicts survival and toxicities in elderly myeloma patients: an International Myeloma Working Group report

Antonio Palumbo,[1] Sara Bringhen,[1] Maria-Victoria Mateos,[2] Alessandra Larocca,[1] Thierry Facon,[3] Shaji K. Kumar,[4] Massimo Offidani,[5] Philip McCarthy,[6] Andrea Evangelista,[7] Sagar Lonial,[8] Sonja Zweegman,[9] Pellegrino Musto,[10] Evangelos Terpos,[11] Andrew Belch,[12] Roman Hajek,[13] Heinz Ludwig,[14] A. Keith Stewart,[15] Philippe Moreau,[16] Kenneth Anderson,[17] Hermann Einsele,[18] Brian G. M. Durie,[19] Meletios A. Dimopoulos,[11] Ola Landgren,[20] Jesus F. San Miguel,[21] Paul Richardson,[22] Pieter Sonneveld,[23] and S. Vincent Rajkumar[4]

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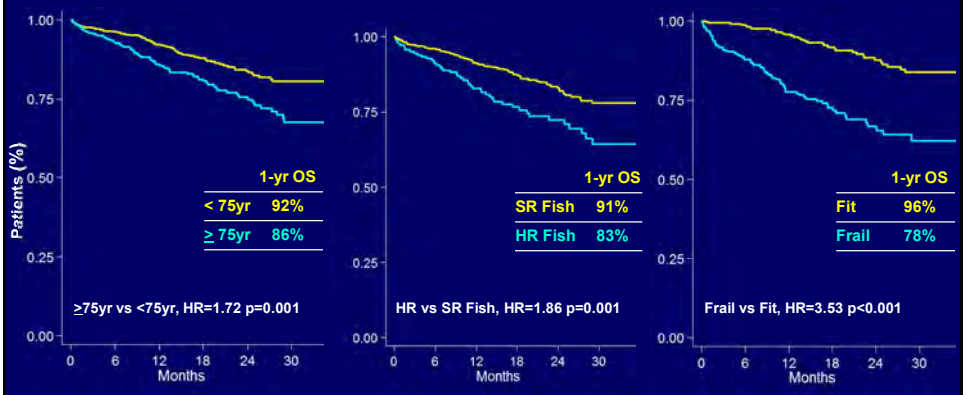
March 26, 2015; Blood: 125 (13)

Frailty Index

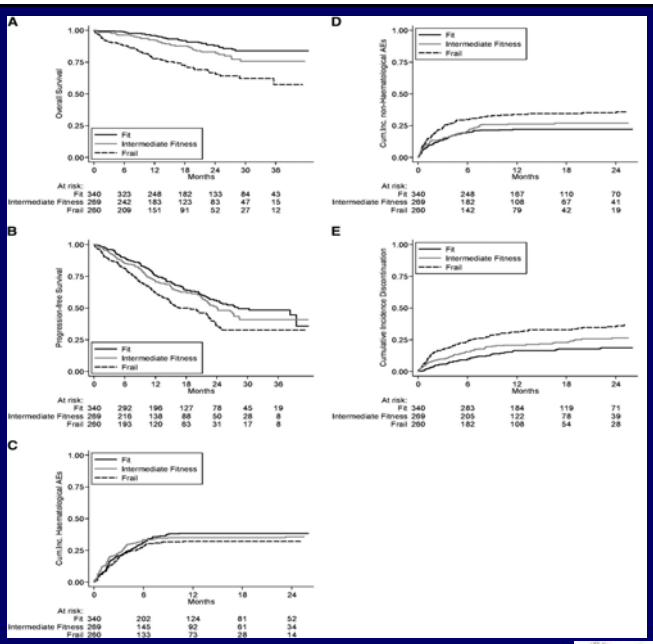
Variable		HR (CI 95%)	P	SCORE
AGE	Age <75 years	1	-	0
	Age 75-80 years	1.37 (0.93-2.03)	0.114	1
	Age >80 years	2.75 (1.81-4.18)	<0.001	2
CHARLSON INDEX	Charlson ≤1	1	-	0
	Charlson ≥2	1.6 (1.07-2.39)	0.021	1
ADL SCORE	ADL >4	1	-	0
	ADL≤4	1.76 (1.14-2.71)	0.01	1
IADL SCORE	IADL >5	1	-	0
	IADL≤5	1.53 (1.03-2.27)	0.036	1

ADDITIVE TOTAL SCORE	PATIENT STATUS
0	FIT
1	UNFIT
≥2	FRAIL

Overall Survival

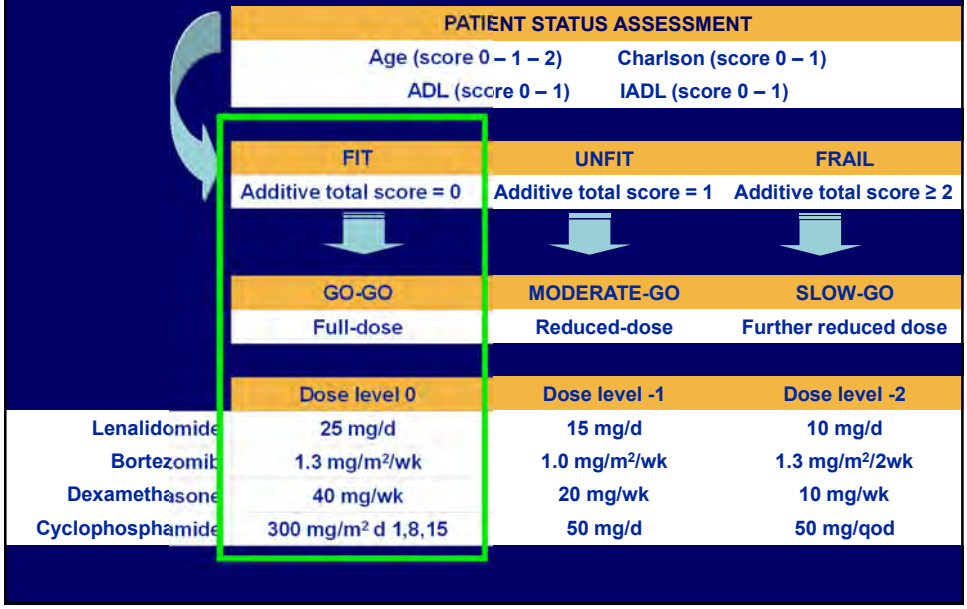


Fit defined as: score=0 Frail defined as: score≥2
HR Fish: presence of t(4;14) or t(14;16) or del 17q13



Antonio Palumbo et al. Blood 2015;125:2068-2074

Proposed Management: Palumbo et a



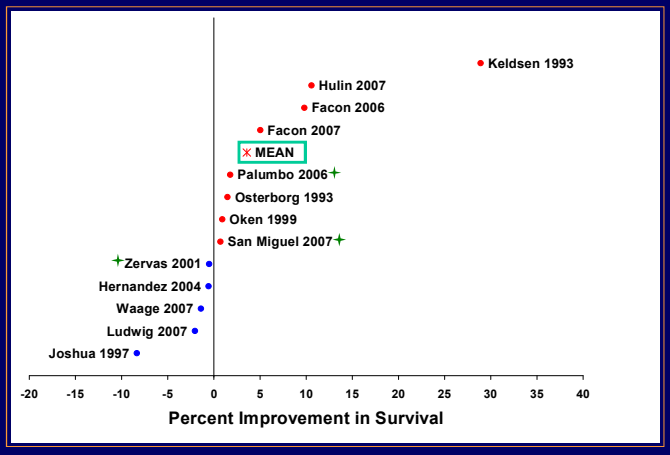
The Older Fit Patient

Therapeutic Considerations:

Is CR/MRD the goal?

CR in non-transplant setting

van de Velde et al. Haematologica 2007



Mean = 3.6%		
ΔCR/nCR	OS	ΔOS
+10%	35m	+12.6m
+10%	50m	+18m

Median not available, OS calculated from 2yr (San Miguel), 3yr (Palumbo) and 5yr (Zervas) esti

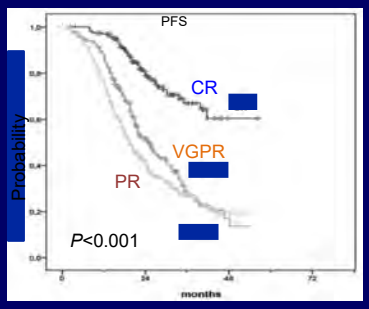
- Medline/OVID search from 1980 – Mar 2008
- 13 studies (4396 patients) meeting the criteria: randomized comparative trials in newly diagnoses MM reporting CR or CR/nCR and survival (either median survival or survival rate)
- Percent improvement in survival for each percent increase in the CR/nCR rate was calculated for each study

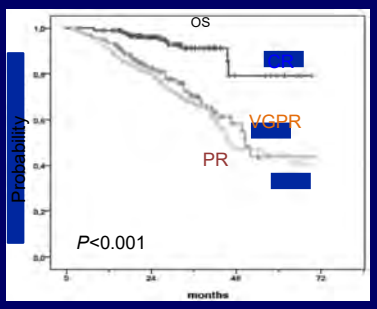
- 5 of 13 studies failed to show association: primarily due to the confounding effect of a therapy that generates high CR and is simultaneously too toxic
- Two polarizing impact of a therapy on survival (higher CR leading to longer survival vs higher toxicity leading to shorter survival) confounds analysis

Hematologic CR correlates with long-term PFS and OS in elderly patients treated with novel agents

- Retrospective analysis: 3 randomized European trials of GIMEMA and HOVON groups (N=1175)
- First-line treatment

  MP (n=332), MPT (n=332), VMP (n=257), VMPT-VT (n=254)

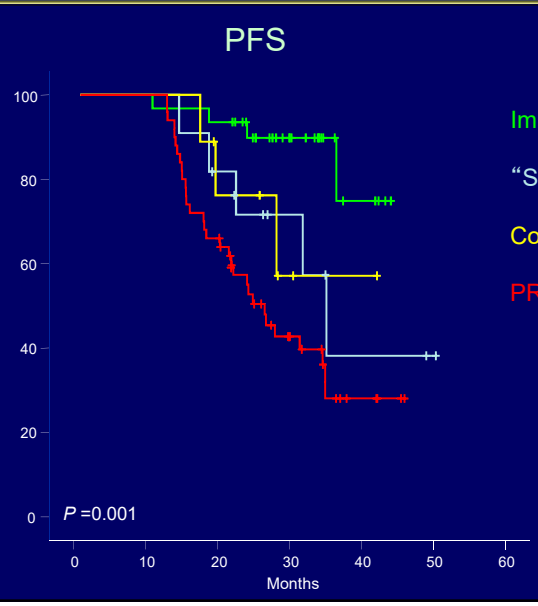




- Significant benefit also seen when analysis is restricted to patients >75 years old

Gay *et al. Blood* 2011; 117(11):3025-31

The better the quality of the response the longer the survival (Immunophenotypic CR): GEM2005>65y



Immunophenotypic CR	90% at 3y
"Stringent CR"	38% at 3y
Conventional CR	57% at 3y
PR (≥70% reduction)	28% at 3y

Paiva et al; J Clin Oncol. 2011;29(12):1627-33.

The Older Fit Patient

Therapeutic Considerations:

Is CR/MRD the goal?

Is Transplant the way?

Two Fridas

Older Patients: To Transplant or Not

- Performance status and/or functional status
- Cardiac function
- Pulmonary function
- Liver function
- Infectious disease
- Psychosocial support
- Patient goals and preferences

AuPBSC Transplants Age ≥60 yrs at time of HCT

YEARS	94-95	96-97	98-99	00-01	02-03	04-05	P_{trend}
Number of patients	39	127	179	529	955	1337	
OS d100 95%CI	92 (82-98)	94 (90-98)	94 90-97)	97 (95-98)	97 (96-98)	98 (97-99)	0.45
OS 12 month post tx	73 (57-86)	79 (71-85)	84 (78-90)	92 (90-93)	92 (90-93)	91 (90-93)	<.001

McCarthy PL et al *Biol Blood Marrow Transplant* ***19***:1116–1123.

Cost-Effectiveness of Autologous Hematopoietic Stem Cell Transplantation for Elderly Patients with Multiple Myeloma using the Surveillance, Epidemiology, and End Results–Medicare Database

Gunjan L. Shah [1,*], Aaron N. Winn [2,3], Pei-Jung Lin [2], Andreas Klein [4], Kellie A. Sprague [4], Hedy P. Smith [4], Rachel Buchsbaum [4], Joshua T. Cohen [2], Kenneth B. Miller [4], Raymond Comenzo [4], Susan K. Parsons [4,5]

Biology of Blood and Marrow Transplantation
Volume 21, Issue 10

Table 2
Median Monthly Cost

	Transplantation	Nontransplantation
Living more than 2 years	n = 234	n = 180
First year after diagnosis*	$8337	$2607
Middle years	$2435	$2088
Last year	$8114	$6809
Living less than 2 years	n = 36	n = 90
Monthly†	$13,106	$6756

Total cost of care per month during each time frame. Significant differences were seen only in the first year after diagnosis for patients living longer than 2 years and monthly for those living less than 2 years.
* $P < .001$.
† $P = .013$.

Age Is Not a Prognostic Variable With Autotransplants for Multiple Myeloma

By D.S. Siegel, K.R. Desikan, J. Mehta, S. Singhal, A. Fassas, N. Munshi, E. Anaissie, S. Naucke, D. Ayers, D. Spoon, D. Vesole, G. Tricot, and B. Barlogie

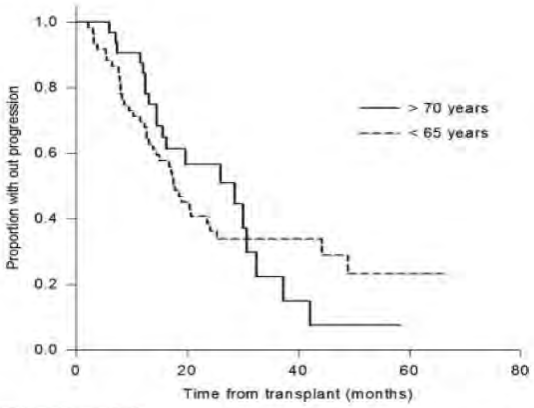
Multiple myeloma (MM) typically afflicts elderly patients with a median age of 65 years. However, while recently shown to provide superior outcome to standard treatment, high-dose therapy (HDT) has usually been limited to patients up to 65 years. Among 550 patients with MM and a minimum follow-up of 18 months, 49 aged ≥65 years were identified (median age, 67; range, 65 to 76 years). Their outcome was compared with 49 younger pair mates (median, 52; range, 37 to 64 years) selected among the remaining 501 younger patients (<65 years) matched for five previously recognized critical prognostic factors (cytogenetics, β_2-microglobulin, C-reactive protein, albumin, creatinine). Nearly one half had been treated for more than 1 year with standard therapy and about one third had refractory MM. All patients received high-dose melphalan-based therapy; 76% of the younger and 65% of the older group completed a second transplant ($P = .3$). Sufficient peripheral blood stem cells to support two HDT cycles (CD34 > 5 × 10^6/kg) were available in 83% of younger and 73% of older patients ($P = .2$). After HDT, hematopoietic recovery to critical levels of granulocytes (>500/μL) and of platelets (>50,000/μL) proceeded at comparable rates among younger and older subjects with both first and second HDT. The frequency of extramedullary toxicities was comparable. Treatment-related mortality with the first HDT cycle was 2% in younger and 8% among older subjects, whereas no mortality was encountered with the second transplant procedure. Comparing younger/older subjects, median durations of event-free and overall survival were 2.8/1.5 years ($P = .2$) and 4.8/3.3 years ($P = .4$). Multivariate analysis showed pretransplant cytogenetics and β_2-microglobulin levels as critical prognostic features for both event-free and overall survival, whereas age was insignificant for both endpoints ($P = .2/.8$). Thus, age is not a biologically adverse parameter for patients with MM receiving high-dose melphalan-based therapy with peripheral blood stem cell support and, hence, should not constitute an exclusion criterion for participation in what appears to be superior therapy for symptomatic MM.

Autologous stem cell transplantation in elderly multiple myeloma patients over the age of 70 years

Ashraf Badros, Bart Barlogie, Eric Siegel, Christopher Morris, Raman Desikan, Maurizio Zangari, Athanasios Fassas, Elias Anaissie, Nikhil Munshi and Guido Tricot *Myeloma and Transplantation Research Center, University of Arkansas for Medical Sciences, Little Rock, AR, USA*

Autologous stem cell transplantation in patients of 70 years and older with multiple myeloma: Results from a matched pair analysis

Shaji K. Kumar,* David Dingli, Martha Q. Lacy, Angela Dispenzieri, Suzanne R. Hayman, Francis K. Buadi, S. Vincent Rajkumar, Mark R. Litzow, and Morie A. Gertz



American Journal of Hematology
Volume 83, Issue 8, pages 614–617, August 2008

demonstrating median overall survival for the two antation.

ORR 97%
CR 42%

ORIGINAL ARTICLE

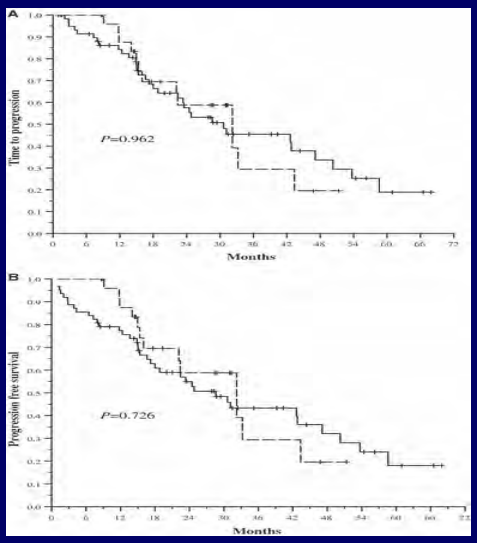
ThaDD plus high dose therapy and autologous stem cell transplantation does not appear superior to ThaDD plus maintenance in elderly patients with *de novo* multiple myeloma

Massimo Offidani[1], Pietro Leoni[1], Laura Corvatta[2], Claudia Polloni[1], Silvia Gentili[1], Agnese Savini[1], Francesco Alesiani[2], Marino Brunori[2], Massimo Catarini[2], Giuseppe Visani[2], Arduino Samori[2], Maurizio Burattini[2], Riccardo Centurioni[2], Mauro Montanari[1], Paolo Fraticelli[2], Miriana Ruggieri[2], Sadia Falcioni[2], Piero Galieni[2]

[1]Clinica di Ematologia Azienda Ospedaliero-Universitaria, Ospedali Riuniti di Ancona, Ancona; [2]Marche Myeloma Network (GEMaMM), Ancona, Italy

European Journal of Haematology
Volume 84, Issue 6, pages 474–483, June 2010

ThaDD plus high dose Mel vs ThaDD plus maintenance in elderly patients with *de novo* multiple myeloma

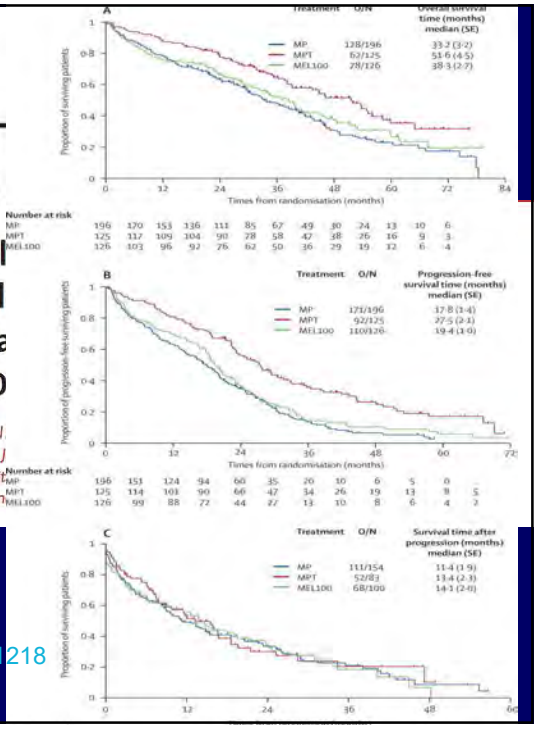


European Journal of Haematology
Volume 84, Issue 6, pages 474-483, 11 MAR 2010 DOI: 10.1111/j.1600-0609.2010.01418.x
http://onlinelibrary.wiley.com/doi/10.1111/j.1600-0609.2010.01418.x/full#f3

THE LANCET

Melphalan and prednisone pl
melphalan and prednisone al
autologous stem cell transpla
multiple myeloma (IFM 99–0

Thierry Facon, Jean Yves Mary, Cyrille Hulin, Lotfi Benboubker, Michel
Carine Chaleteix, Mamoun Dib, Laurent Voillat, Hervé Maisonneuve, J
Philippe Casassus, Jérôme Jaubert, Henry Jardel, Chantal Doyen, Brigit
Claire Mathiot, Hervé Avet-Loiseau, on behalf of the Intergroupe Fran



MP: 12 months
MPT: 12 months
VAD, hi D CTX, Mel 100/m2 x 2
Volume 370, Issue 9594, 2007, 1209–1218

CLINICAL TRIALS AND OBSERVATIONS

Bortezomib induction, reduced-intensity transplantation, and lenalidomide consolidation-maintenance for myeloma: updated results

Francesca Gay,[1] Valeria Magarotto,[1] Claudia Crippa,[2] Norbert Pescosta,[3] Tommasina Guglielmelli,[4] Federica Cavallo,[1] Sara Pezzatti,[5] Samantha Ferrari,[2] Anna Marina Liberati,[6] Stefania Oliva,[1] Francesca Patriarca,[7] Massimo Offidani,[8] Paola Omedé,[1] Vittorio Montefusco,[9] Maria Teresa Petrucci,[10] Nicola Giuliani,[11] Roberto Passera,[12] Giuseppe Pietrantuono,[13] Mario Boccadoro,[1] Paolo Corradini,[9] and Antonio Palumbo[1]

Induction PAD *four 21-day courses*	Transplant MEL100 *two courses*	Consolidation Len-Pdn *four 28-day courses*	Maintenance Len *until progression*

	PAD	PAD+ MEL	PAD+MEL+Len Pr	+ Len maint
CR	12%	78%	48%	53%
VGPR	43%	43%	32%	29%
PR	33%	17%	14%	13%
SD	11%	6%	5%	4%
PD	0	0		

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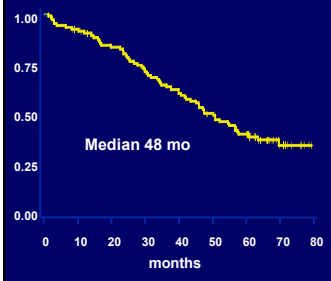
August 22, 2013; Blood: 122 (8)

Sequential approach
NDMM patients

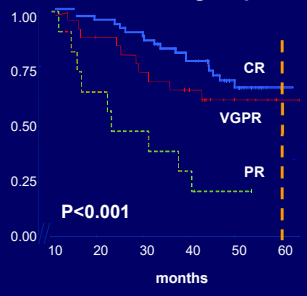
Induction PAD *four 21-day courses*	→	Transplant MEL100 *two courses*	→	Consolidation Len-Pdn *four 28-day courses*	→	Maintenance Len *until progression*

Median follow-up 66 months **Median age 70 years**

PFS



PFS according response



OS according response

Gay F, et al. Gr. Emat. Milan 19 November 2012

PAD, bortezomib-pegylated doxorubicin-dexamethasone; MEL100, Melphalan100 mg/m²; Len-Pdn, lenalidomide-prednisone; Len, lenalidomide; PFS, progression-free survival; OS, overall survival; CR, complete response; VGPR, very good partial response; PR, partial response; NDMM, newly diagnosed multiple myeloma

The Older Fit Patient

Therapeutic Considerations:

Is CR/MRD the goal?

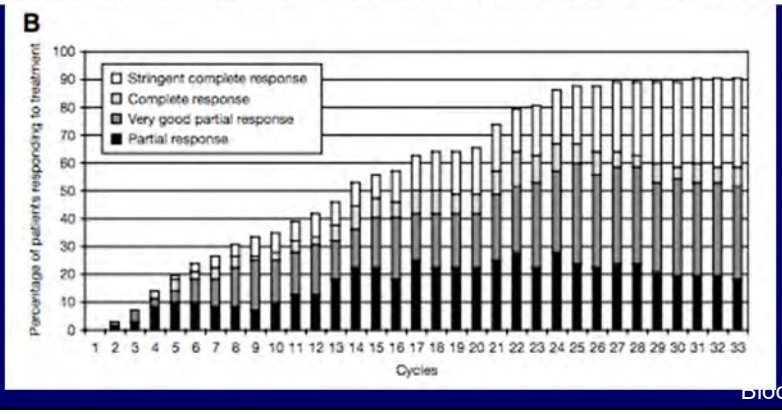
Is transplant the way?

Is continued treatment best?

BiRD (Biaxin [clarithromycin]/Revlimid [lenalidomide]/dexamethasone) combination therapy results in high complete- and overall-response rates in treatment-naive symptomatic multiple myeloma

Ruben Niesvizky,[1] David S. Jayabalan,[1,2] Paul J. Christos,[3] Jessica R. Furst,[1] Tara Naib,[1] Scott Ely,[2] Jessica Jalbrzikowski,[1] Roger N. Pearse,[1] Faiza Zafar,[1] Karen Pekle,[1] April LaRow,[1] Richard Lent,[2] Tomer Mark,[1] Hearn J. Cho,[1] Tsiporah Shore,[1] Jeffrey Tepler,[1] John Harpel,[1] Michael W. Schuster,[1] Susan Mathew,[2] John P. Leonard,[1] Madhu Mazumdar,[3] Selina Chen-Kiang,[2] and Morton Coleman[1]

[1]Center of Excellence for Lymphoma and Myeloma, Division of Hematology and Medical Oncology, Department of Medicine, [2]Department of Pathology, and [3]Division of Biostatistics and Epidemiology, Department of Public Health, Weill-Cornell Medical College, New York Presbyterian Hospital-Cornell Medical Center, New York, NY



Blood 2008

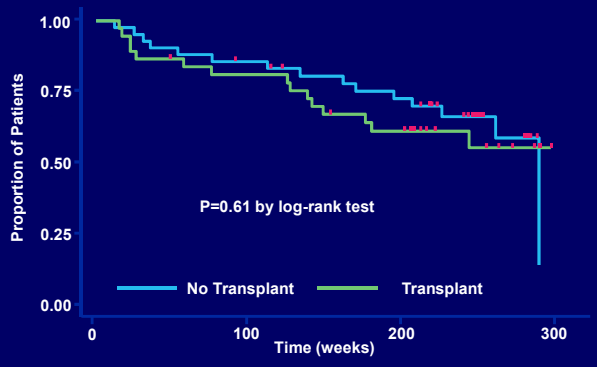
blood
Leading the world in reporting basic and applied hematology research
JOURNAL OF THE AMERICAN SOCIETY OF HEMATOLOGY

BiRd (clarithromycin, lenalidomide, dexamethasone): an update on long-term lenalidomide therapy in previously untreated patients with multiple myeloma

Adriana Rossi,[1] Tomer Mark,[1] David Jayabalan,[1,2] Paul Christos,[3] Faiza Zafar,[1] Karen Pekle,[1] Roger Pearse,[1] Selina Chen-Kiang,[2] Morton Coleman,[1] and Ruben Niesvizky[1]

Blood. 2013;121(11):1982-1985)

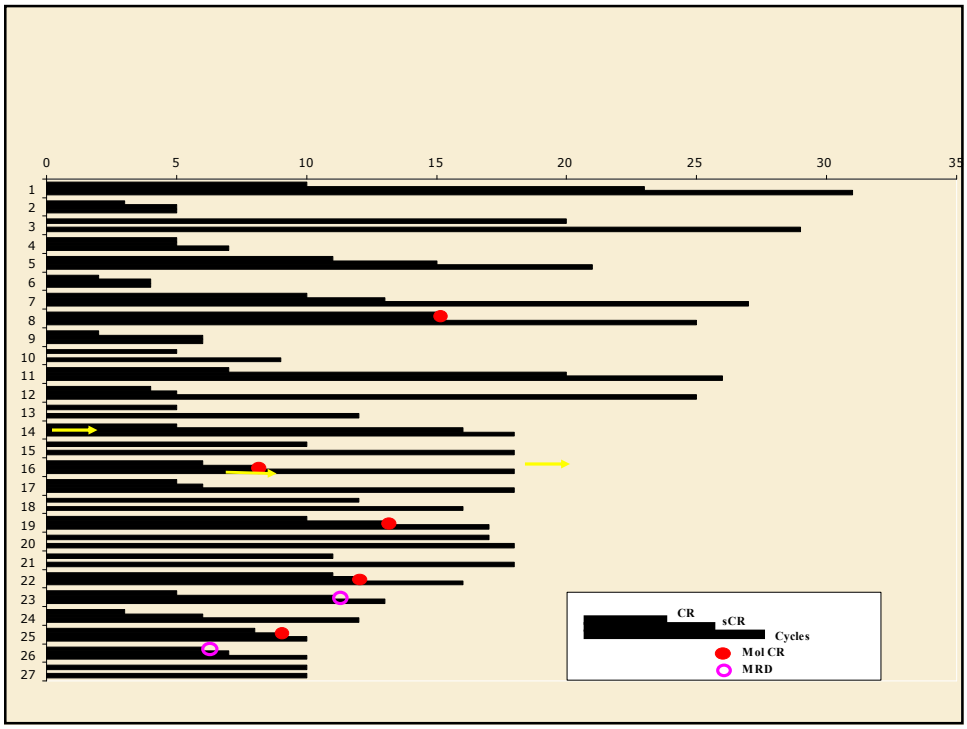
Progression-Free Survival is not Affected by Transplant After Lenalidomide



No Transplant:
N=36 patients, 15 progressions
Median PFS = 307.9 weeks (95% CI 207 - NR)
5-year PFS = 60.7% (95% CI = 41.5% - 75.2%)

Transplant:
N=32 patients, 15 progressions
Median PFS = 259.4 weeks (95% CI 146.9 - NR)
5-year PFS = 48.0% (95% CI = 27.5% - 65.8%)

Rossi et al, Blood 2013 Jan 8 Epub


0
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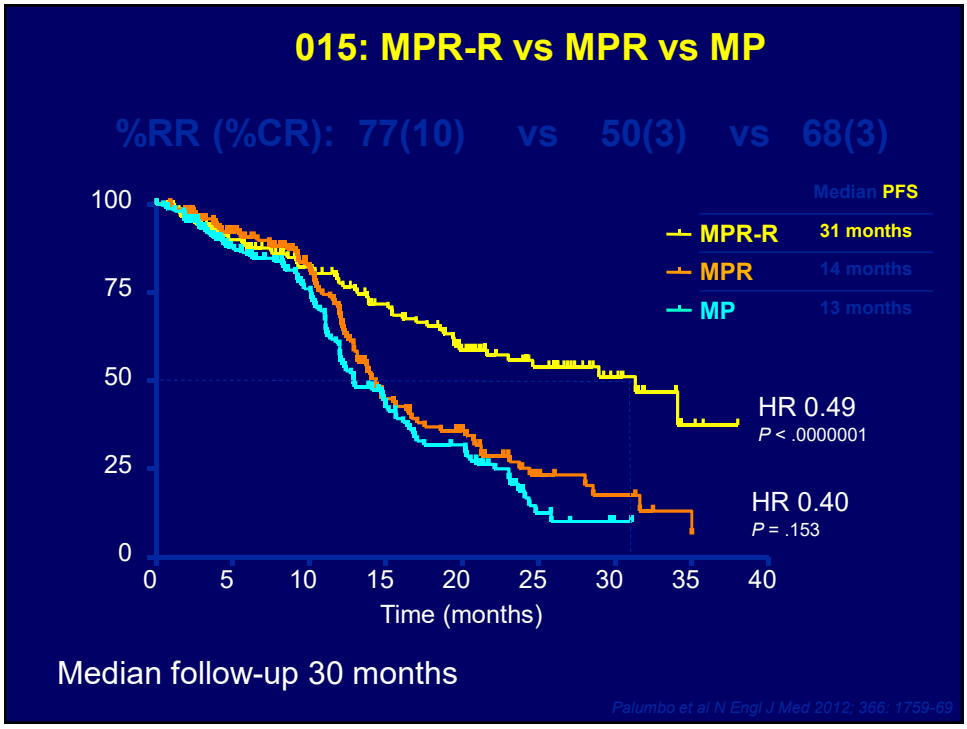
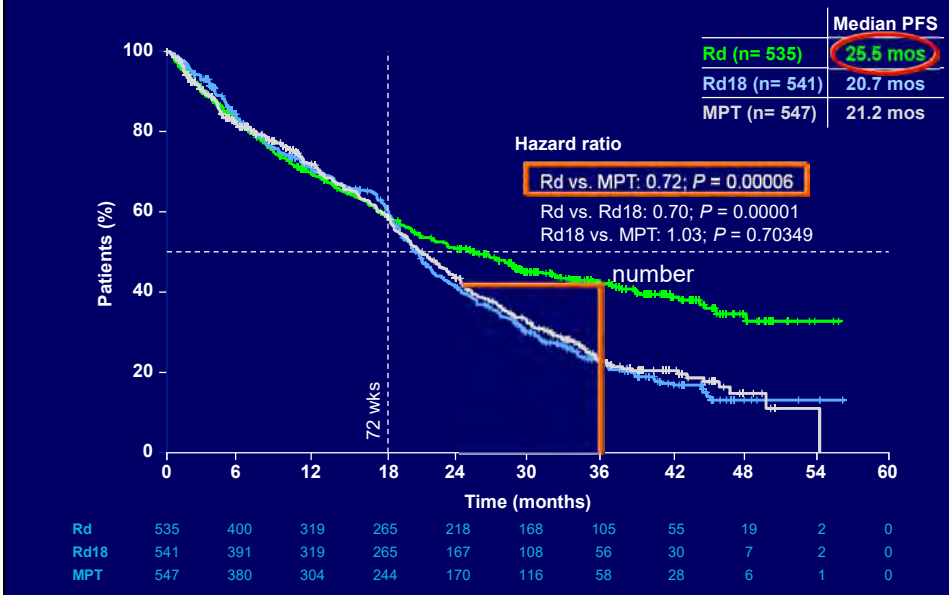
CR
sCR
Cycles
Mol CR
MRD


015: MPR-R vs MPR vs MP
%RR (%CR): 77(10) vs 50(3) vs 68(3)
Median PFS
MPR-R 31 months
MPR 14 months
MP 13 months
100
75
50
25
0
0
5
10
15
20
25
30
35
40
Time (months)
HR 0.49
P < .0000001
HR 0.40
P = .153
Median follow-up 30 months
Palumbo et al N Engl J Med 2012; 366: 1759-69

FIRST Trial: Final PFS

Continuous Rd ⬇ the risk of PFS events (PD or death) by 28% vs. MPT

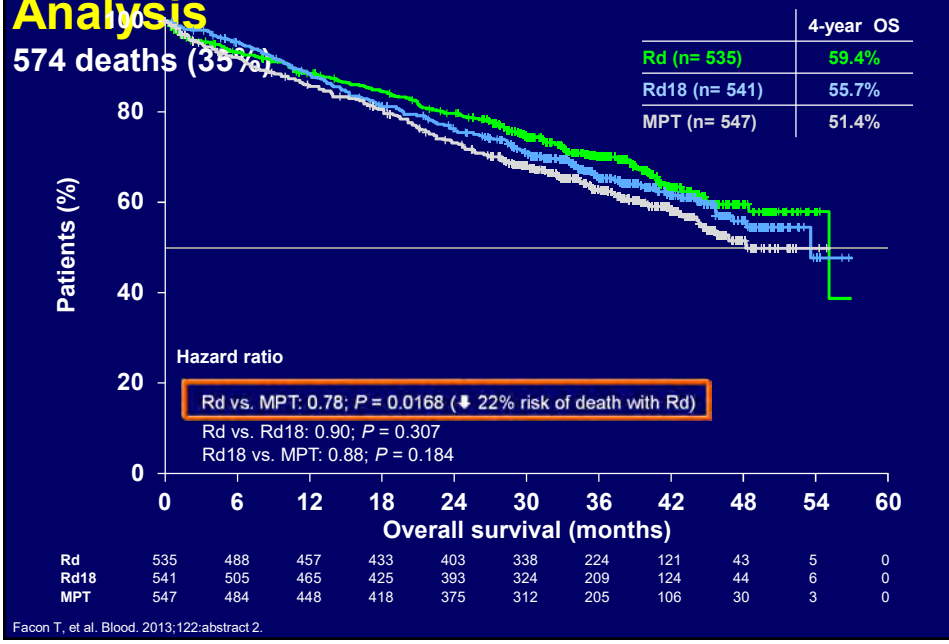


mos, months; MPT, melphalan, prednisolone, thalidomide; PFS, progression-free survival; Rd, Lenalidomide plus low-dose dexamethasone.

Facon T, et al. Blood. 2013;122:abstract 2.

FIRST Trial: Overall Survival Interim Analysis[398]

574 deaths (35%)



Facon T, et al. Blood. 2013;122:abstract 2.

The Older Fit Patient

Therapeutic Considerations:

Is CR/MRD the goal?

Is transplant the way?

Is continued treatment best?

Can novel drugs improve outcome?

A Phase 2 Study of Modified Lenalidomide, Bortezomib, and Dexamethasone (RVD lite) in Transplant-Ineligible Multiple Myeloma Patients

Induction (cycles 1-9)
Repeat q35 days × 9 cycles

Lenalidomide 15 mg po days 1-21
Bortezomib 1.3 mg/m^2 on days 1, 8, 15, 22
Dexamethasone 25 mg po days 1, 2, 8, 9, 15, 16, 22, 23 (patients =75 years old)
Dexamethasone 25 mg po days 1, 8, 15, 22 (patients >75 years old)

↓

Consolidation (cycles 10-15)
Repeat q28 days × 6 cycles

Lenalidomide 15 mg po days 1-21 (or last tolerated dose as of cycle 9)
Bortezomib 1.3 mg/m^2 sc on days 1, 15 (or last tolerated dose as of cycle 9)

↓

Maintenance (cycle 16 until progression)
Repeat q28 days until disease progression

Lenalidomide 10 mg po days 1-21 (or last tolerated dose as of cycle 15)

Elizabeth O'Donnell et al ASH 2014

Response after 4 cycles (%) (n=30)	
ORR (≥PR)	27 (90.0)
CR	5 (16.7)
VGPR	11 (36.7)
PR	11 (36.7)
SD	3 (10.0)
VGPR or better	16 (53.3)

Fatigue	9 (26.5)	7 (20.6)	1 (2.9)	17 (50.0)
Peripheral sensory neuropathy	7 (20.6)	6 (17.6)	1 (2.9)	14 (41.2)
Hypophosphatemia	1 (2.9)	.	11 (32.4)	12 (35.3)
Edema limbs	11 (32.4)	.	1 (2.9)	12 (35.3)
Rash maculo-papular	3 (8.8)	4 (11.8)	4 (11.8)	11 (32.4)
Insomnia	3 (8.8)	5 (14.7)	1 (2.9)	9 (26.5)
Depression	5 (14.7)	3 (8.8)	.	8 (23.5)
Diarrhea	7 (20.6)	1 (2.9)	.	8 (23.5)
Constipation	5 (14.7)	2 (5.9)	.	7 (20.6)
Dysgeusia	5 (14.7)	2 (5.9)	.	7 (20.6)
Hyperglycemia	4 (11.8)	2 (5.9)	1 (2.9)	7 (20.6)
Psychiatric disorders	2 (5.9)	3 (8.8)	2 (5.9)	7 (20.6)
Skin and subcutaneous tissue disorders	5 (14.7)	1 (2.9)	.	6 (17.6)

Ph1/2 CMP: Study Design

blood

Study population

- Newly diagnosed symptomatic MM
- >65 years old
- Karnofsky PS ≥60%
- ECOG 0-2
- Creatinine clearance >30 mL/min
- Neutrophils ≥1000/mm^3
- Platelets ≥50,000/mm^3

Carfilzomib
30 min IV 20/27, 20/36, or 20/45 mg/m^2
D1, 2, 8, 9, 22, 23, 29, 30

Melphalan
9 mg/m^2 PO D1-4

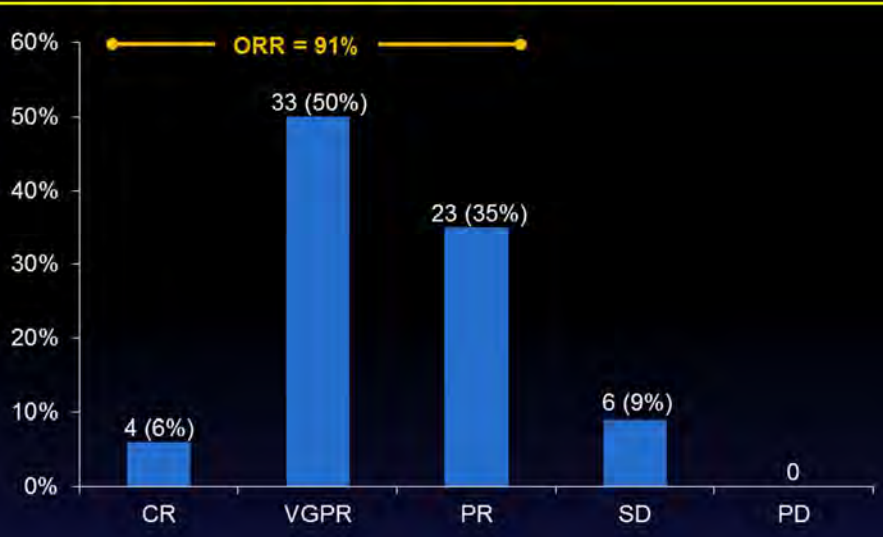
Prednisone
60 mg/m^2 PO D1-4

42-day cycles

Primary endpoint: MTD
Secondary endpoints: Toxicity, RR, PFS, OS

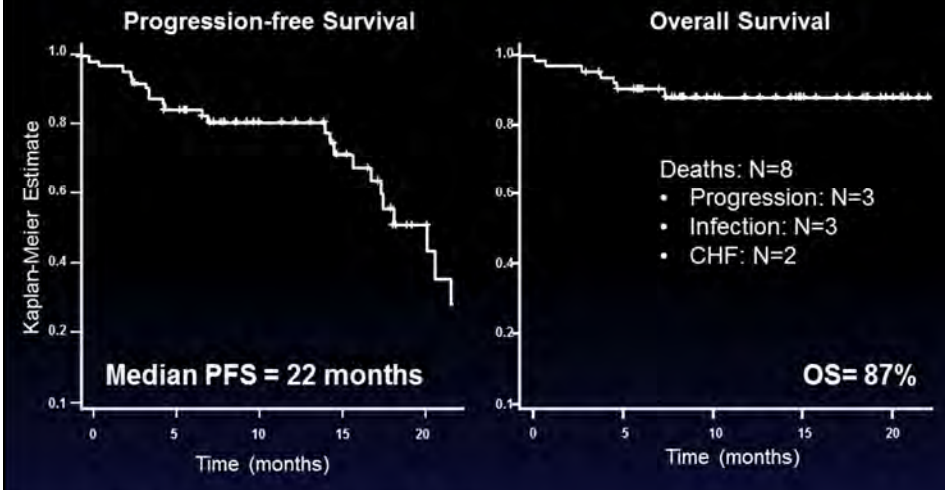
Moreau P, et al. EHA 2013. Abstract P224 (poster presentation); Touzeau C, et al. ASCO 2013. Abstract 8513 (oral presentation).

Ph1/2 CMP: Response Rates



Moreau P, et al. EHA 2013. Abstract P224 (poster presentation); Touzeau C, et al. ASCO 2013. Abstract 8513 (oral presentation).

Ph1/2 CMP: Survival*
Median follow-up 12 months, N=68



*Interpretation of time to event endpoints are limited in a single arm trial

Moreau P, et al. EHA 2013. Abstract P224 (poster presentation); Touzeau C, et al. ASCO 2013. Abstract 8513 (oral presentation).

A phase 1/2 study of carfilzomib in combination with lenalidomide and low-dose dexamethasone as a frontline treatment for multiple myeloma

Jakubowiak, et al Blood, 2011

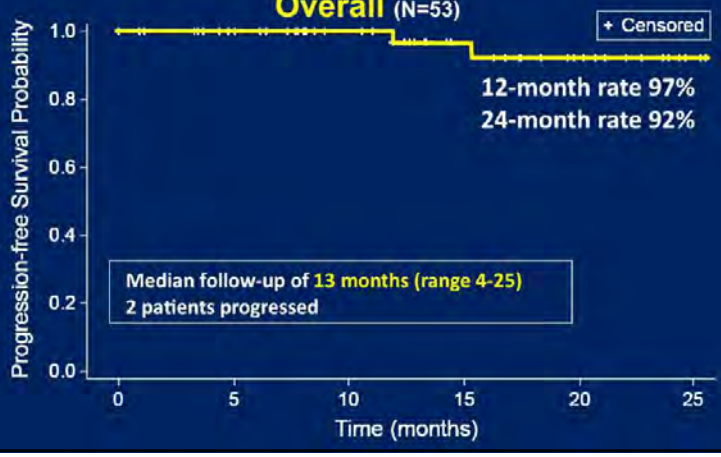
CR 42%
≥VGPR 62%

Progression-free Survival

≥65 years (N=23)

All patients progression-free and all alive after median follow-up 13 months (range 6–25)

Overall (N=53)



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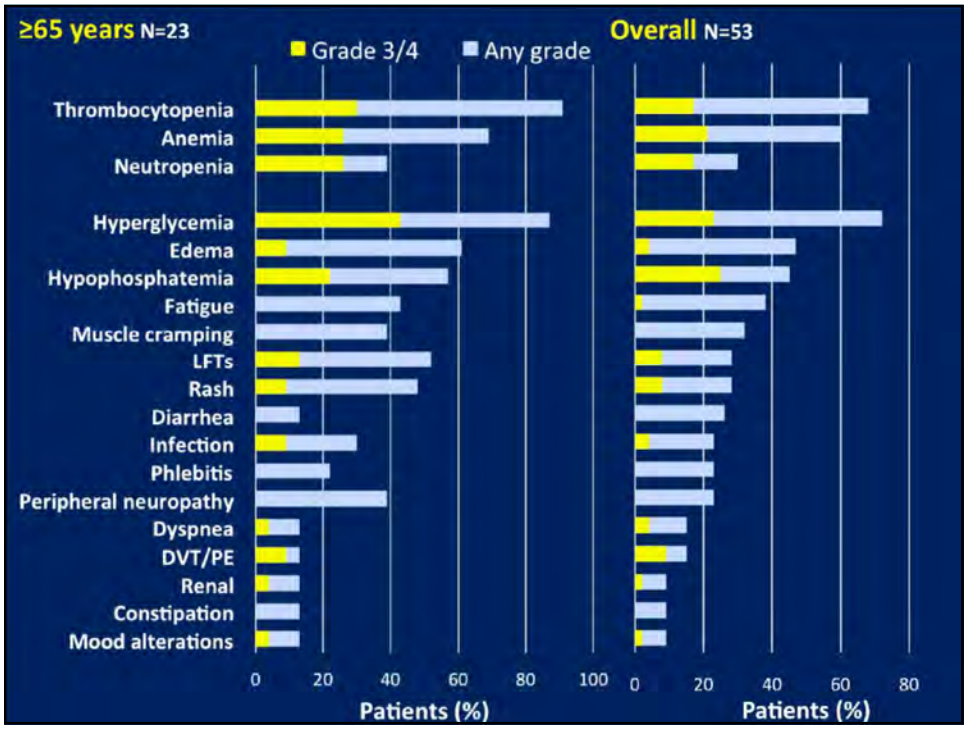
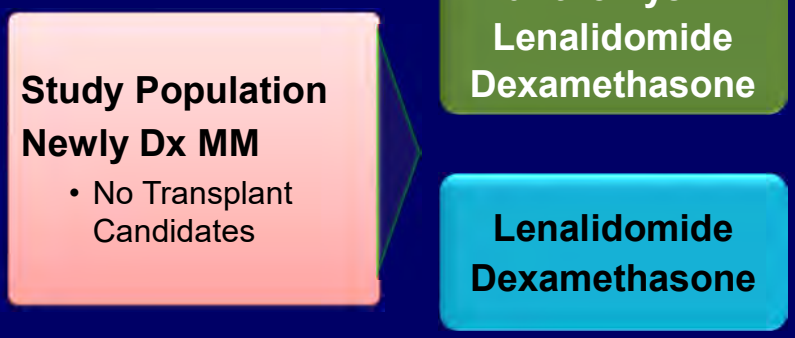


LANDSCAPE

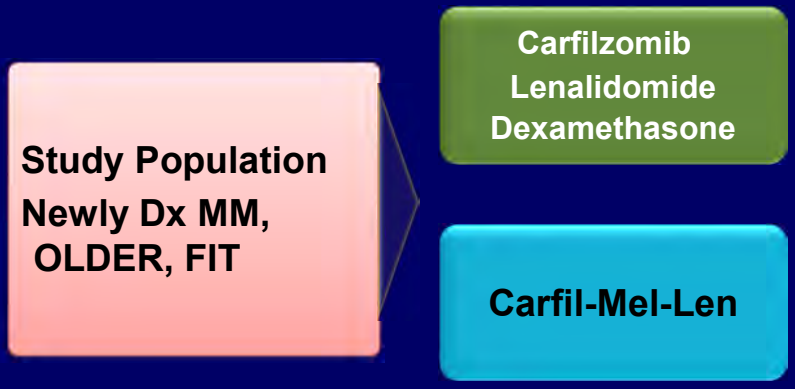
	Regimen		OS	PFS	TTP		
Fit	Mel 100 x2-RP x4 Con-Rev maint		63@5	47			
Unfit -Frail	MPR-R		70@3	31			
	RD-R		59@4	25.5			
	CMP			22			
	VMP vista		56		24		
	VMP upfront		53.1	17.3			
	VTD upfront		51.5	15.4			
	VD upfront		49.8	14.7			
	MPR			14			
	CRD			*92% at 24 m			

CLARIDEX : Phase III Trial of Clarithomycin + Lenalidomide + Dex



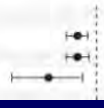
- Primary endpoint: PFS, OS

Other Potential Studies : Randomized Carfilzomib Rev Dex vs Carfil induction MEL + Lenalidomide maint



- Primary endpoint: PFS, OS

Subgroup	Daratumumab Group	Control Group	Daratumumab Group	Control Group	Hazard Ratio (95% CI)
	no. of progression events or deaths/total no.		*median progression-free survival (mo)*		
Age					
<65 yr	24/133	55/140	NE	18.4	0.40 (0.24–0.65)
65–74 yr	26/124	43/108	NE	NE	0.40 (0.24–0.67)
≥75 yr	3/29	18/35	NE	11.4	0.11 (0.02–0.51)
ISS disease stage					



The Older Fit Patient

Therapeutic Considerations:

Is CR/MRD the goal? YES

Is transplant the way? Can be

Is continued treatment best? YES

Can novel drugs improve outcome? YES

Collaborators

Myelomacenter.org

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Karen Pekle
Arthur Perry
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Selina Chen-Kiang, PhD
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Joseph Lane MD
Paul Christos

Institute of Biomedical Research of Salamanca

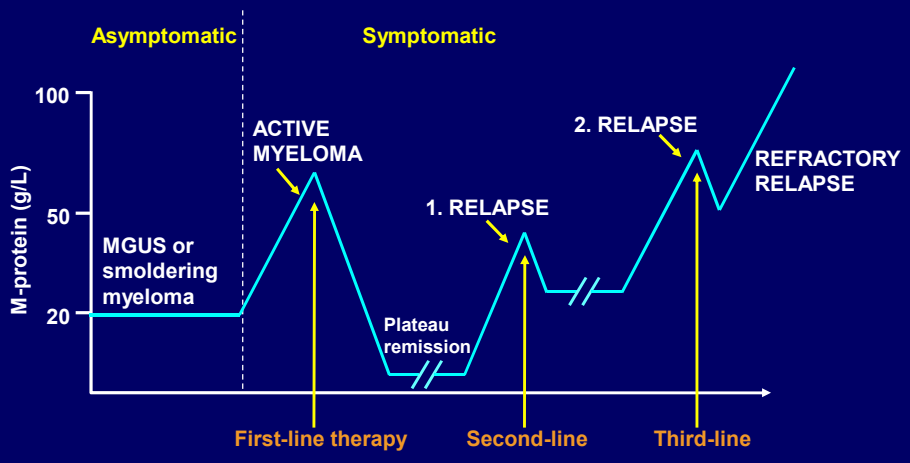
University of Salamanca

Cancer Research Center

Tratamiento del MM en recaída

Enrique M. Ocio
University Hospital & Cancer Research Center
University of Salamanca
Spain

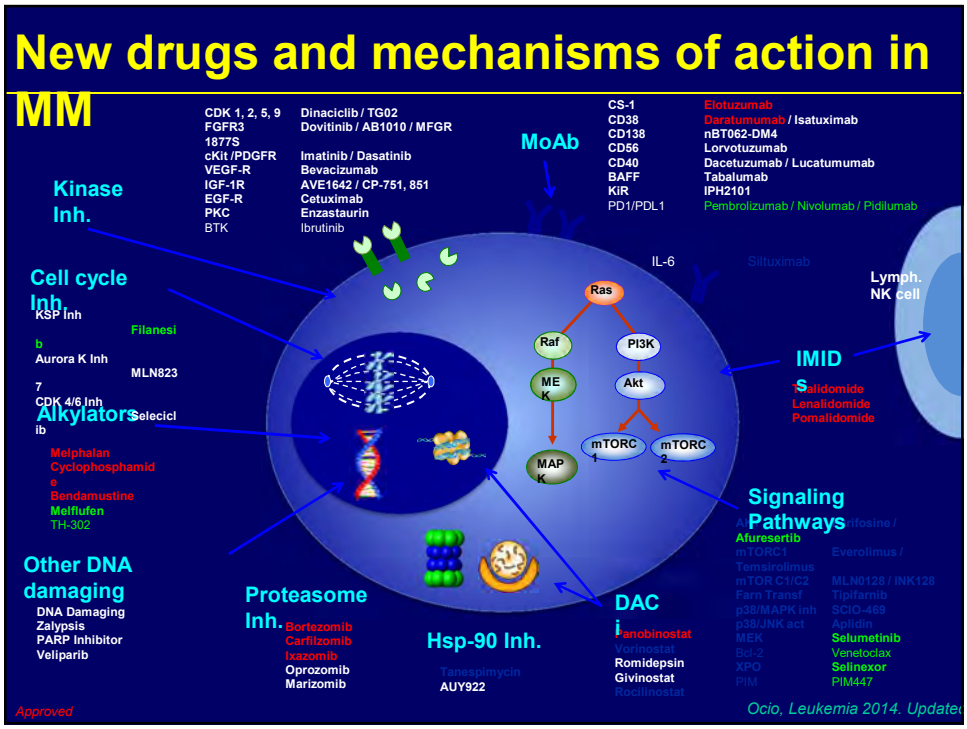
Natural History of MM patients



Strategies at the moment of progression of the disease are necessary

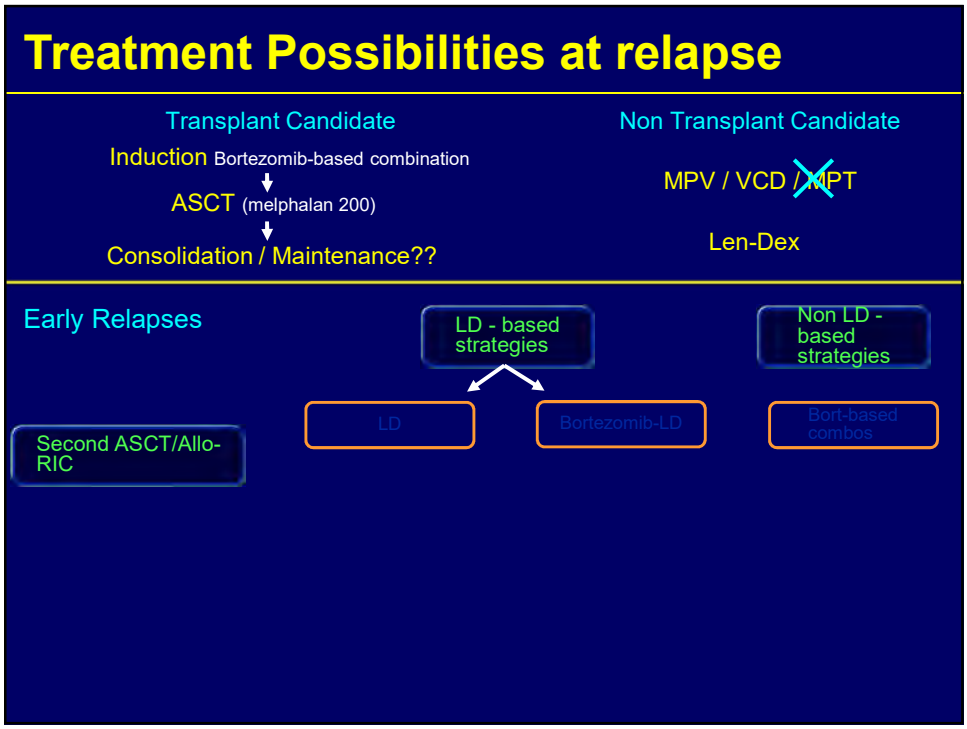
MGUS, monoclonal gammopathy of undetermined significance

New drugs and mechanisms of action in MM



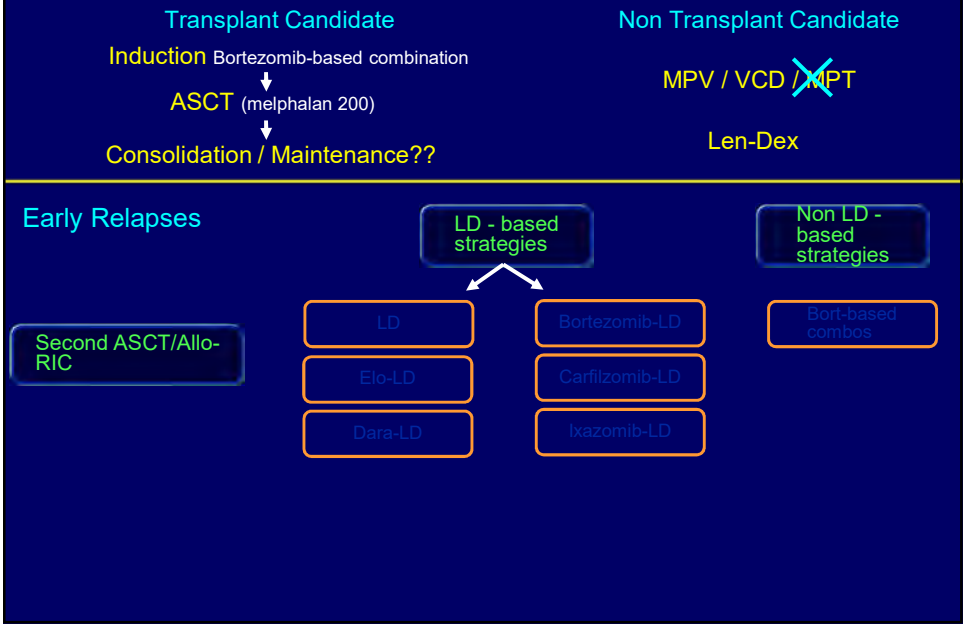
Which options do we have in early relapses?

Treatment Possibilities at relapse

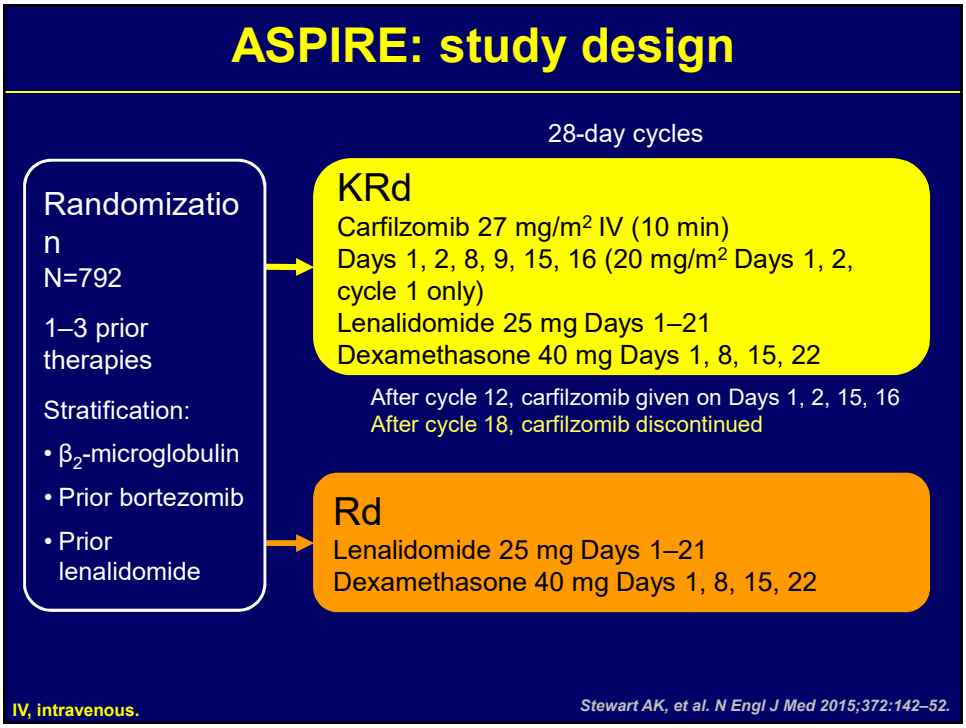


Is Len-Dex still a standard for early relapses?

Treatment Possibilities at relapse



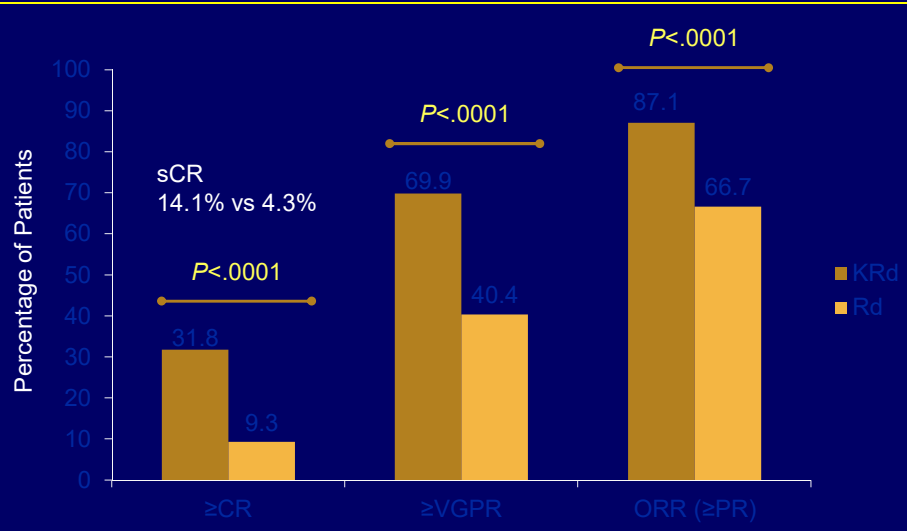
ASPIRE: study design



IV, intravenous.

Stewart AK, et al. N Engl J Med 2015;372:142–52.

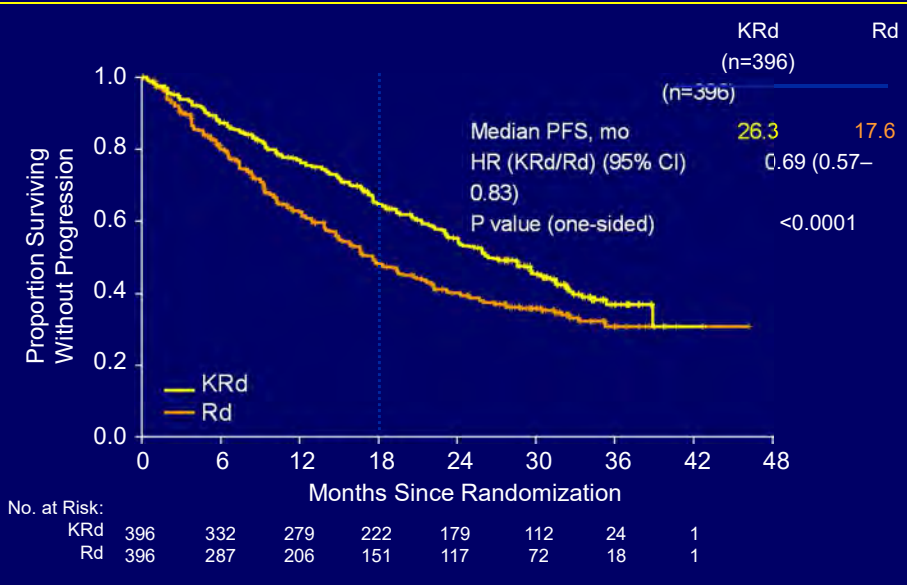
ASPIRE: Response (Secondary Endpoint)



- Median duration of response was 28.6 months in the KRd group and 21.2 months in the Rd group

Stewart AK, et al. N Engl J Med 2015;372:142–52.

ASPIRE: PFS (Primary Endpoint) *(ITT n=792)*



Stewart AK, et al. N Engl J Med 2015;372:142–52.

TOURMALINE-MM1

Phase 3 study of weekly oral ixazomib plus lenalidomide-dexamethasone

Global, double-blind, randomized, placebo-controlled study design

N=722

Randomization

1:1

Ixazomib + Lenalidomide + Dexamethasone
Ixazomib: 4 mg on days 1, 8, and 15
Lenalidomide: 25 mg* n dys 1-21
Dexamethasone: 40 mg on days 1, 8, 15, 22

Repeat every 28 days until progression, or unacceptable toxicity

Placebo + Lenalidomide + Dexamethasone
Placebo: on days 1, 8, and 15
Lenalidomide: 25 mg* on days 1-21
Dexamethasone: 40 mg on days 1, 8, 15, 22

Stratification:
- Prior therapy: 1 vs 2 or 3
- ISS: I or II vs III
- PI exposure: yes vs no

Primary endpoint:
- PFS

Key secondary endpoints:
- OS
- OS in patients with del(17p)

Response and progression (IMWG 2011 criteria[1]) assessed by an independent review committee (IRC) blinded to both treatment and investigator assessment

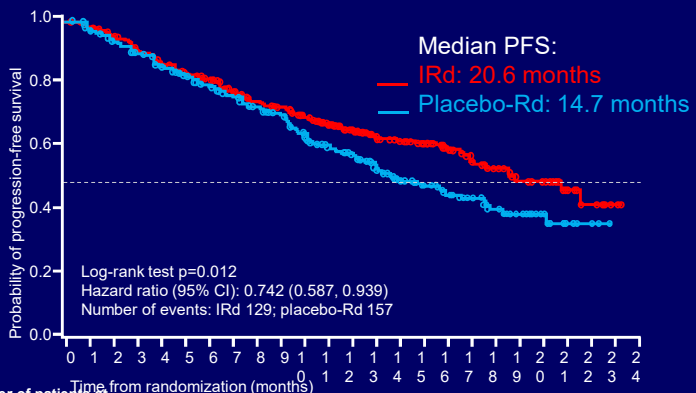
*10 mg for patients with creatinine clearance ≤60 or ≤50 mL/min, depending on local label/practice

1. Rajkumar S, et al. Blood 2011;117:4691–5.

Moreau P et al. NEJM 2016;374(17):1621-34

TOURMALINE-MM1

Final PFS analysis



Number of patients at risk:																									
IRd	360	345	332	315	298	283	270	248	233	224	206	182	145	119	111	95	72	58	44	34	26	14	9	1	0
Placebo-Rd	362	340	325	308	288	274	254	237	218	208	188	157	130	101	85	71	58	46	31	22	15	5	3	0	0

Median follow-up: ~15 months

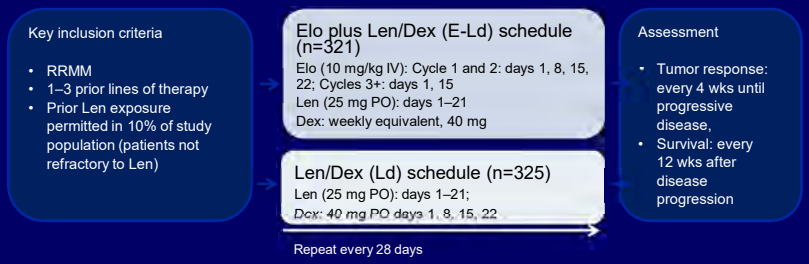
A significant, 35% improvement in PFS with IRd vs placebo-Rd

Interim OS analysis @ 23 months of FU: 81 and 90 deaths in ixazomib and placebo, respectively

Moreau P, ASH 2015 Abst 727

Eloquent-2: Elo + Ld vs Ld
Study Design

- Open-label, randomized, multicenter, phase 3 trial (ELOQUENT-2)

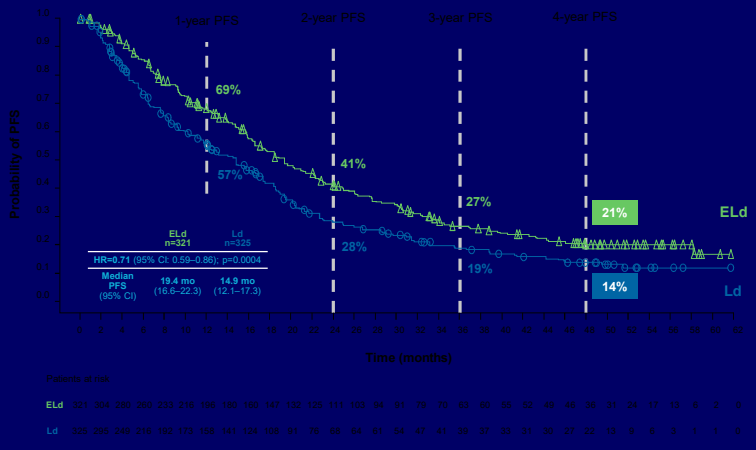


- Endpoints:
  - Co-primary: PFS and ORR
  - Other endpoints: overall survival (data not yet mature); duration of response, quality of life, safety
- All patients received premedication to mitigate infusion reactions prior to Elo administration

Lonial S, et al. N Engl J Med 2015; 373(7):621–31.

ELOQUENT-2: 4-Year Follow-up

Progression-Free Survival – All Randomized Patients



A 29% reduction in the risk of progression or death and a relative improvement of 50% in the PFS rate (21% vs 14%) were observed with ELd vs Ld

POLLUX: Study Design

Multicenter, randomized (1:1), open-label, active-controlled phase 3 study

Key eligibility criteria

- RRMM
- ≥1 prior line of therapy
- Prior lenalidomide exposure, but not refractory
- Patients with creatinine clearance ≥30 mL/min

Stratification factors

- No. prior lines of therapy
- ISS stage at study entry
- Prior lenalidomide

RANDOMIZE 1:1

DRd (n = 286)

Daratumumab 16 mg/kg IV
- Qw in Cycles 1-2, q2w in Cycles 3-6, then q4w until PD

R 25 mg PO
- Days 1-21 of each cycle until PD

d 40 mg PO
- 40 mg weekly until PD

Rd (n = 283)

R 25 mg PO
- Days 1-21 of each cycle until PD

d 40 mg PO
- 40 mg weekly until PD

Cycles: 28 days

Primary endpoint
- PFS

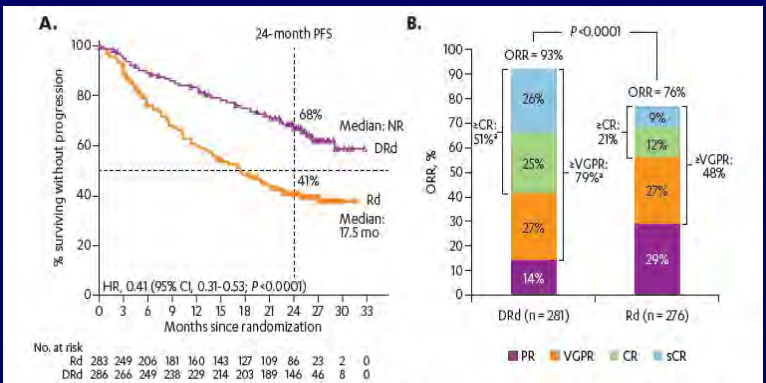
Secondary endpoints
- TTP
- OS
- ORR, VGPR, CR
- MRD
- Time to response
- Duration of

Statistical analyses
- 295 PFS events: 85% power for 7.7 month PFS improvement
- Interim analysis: ~177 PFS events

Pre-medication for the DRd treatment group consisted of dexamethasone 20 mg[a], paracetamol, and an antihistamine

[a]On daratumumab dosing days, dexamethasone was administered 20 mg premed on Day 1 and 20 mg on Day 2; RRMM, relapsed or refractory multiple myeloma; ISS, international staging system; R, lenalidomide; DRd, daratumumab/lenalidomide/dexamethasone; IV, intravenous; qw, once weekly; q2w, every 2 weeks; q4w, every 4 weeks; PD, progressive disease; PO, oral; d, dexamethasone; Rd, lenalidomide/dexamethasone; TTP, time to progression; MRD, minimal residual disease

Pollux: Dara-Rd vs Rd. Updated Efficacy

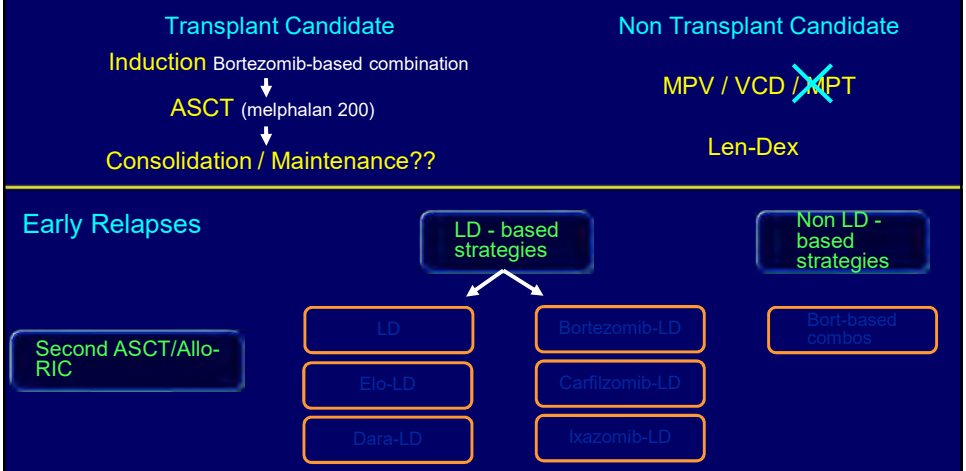


PFS, progression-free survival; ITT, intent-to-treat; ORR, overall response rate; DRd, daratumumab/lenalidomide/dexamethasone; Rd, lenalidomide/dexamethasone; HR, hazard ratio; CI, confidence interval; NR, not reached; CR, complete response; VGPR, very good partial response; PR, partial response; sCR, stringent complete response.

[a]P<0.0001 for DRd versus Rd.

Dimopoulos, NEJM 2016 & Bahlis N, et al. EHA 2017

Treatment Possibilities at relapse



Len-Dex alone should not probably be considered the standard for first relapses any more

Which PI-based possibilities do we have?

Treatment Possibilities at relapse

Transplant Candidate

Induction Bortezomib-based combination

↓

ASCT (melphalan 200)

↓

Consolidation / Maintenance??

Non Transplant Candidate

MPV / VCD / ~~MPT~~

Len-Dex

Early Relapses

Second ASCT/Allo-RIC

LD - based strategies

- LD
- Elo-LD
- Dara-LD
- Bortezomib-LD
- Carfilzomib-LD
- Ixazomib-LD

Non LD - based strategies

- Bort-based combos
- Panob-BD
- Kd
- Dara-BD

ENDEAVOR: Study design

Randomization 1:1

N=929

Stratification:

- Prior proteasome inhibitor therapy
- Prior lines of treatment
- ISS stage
- Route of V administration

Kd

Carfilzomib 56 mg/m^2 IV

Days 1, 2, 8, 9, 15, 16 (20 mg/m^2 days 1, 2, cycle 1 only)

Infusion duration: 30 minutes for all doses

Dexamethasone 20 mg

Days 1, 2, 8, 9, 15, 16, 22, 23

28-day cycles until PD or unacceptable toxicity

Vd

Bortezomib 1.3 mg/m^2 (V bolus or subcutaneous injection)

Days 1, 4, 8, 11

Dexamethasone 20 mg

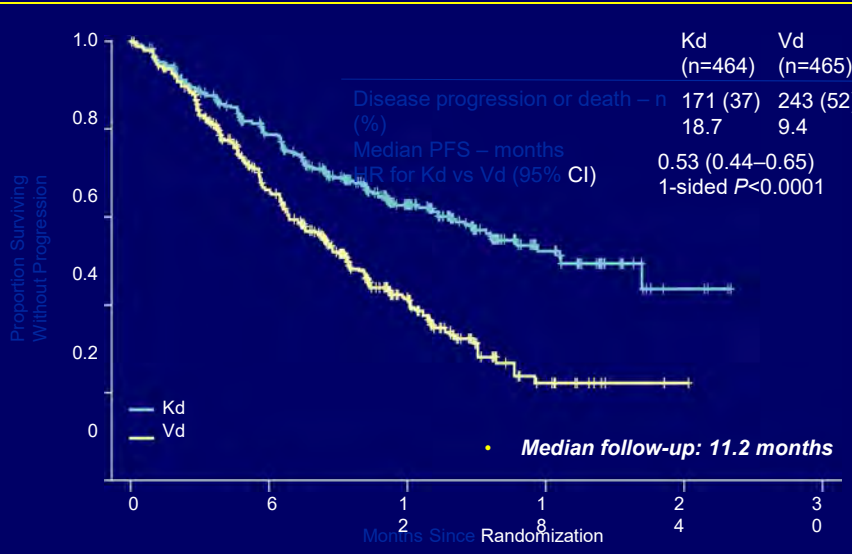
Days 1, 2, 4, 5, 8, 9, 11, 12

21-day cycles until PD or unacceptable toxicity

ISS, International Staging System; IV, intravenous; Kd, carfilzomib and dexamethasone; PD, progressive disease; Vd, bortezomib and dexamethasone; V, bortezomib.

434

Primary End Point: Progression Free Survival



	Kd (n=464)	Vd (n=465)
Disease progression or death – n (%)	171 (37)	243 (52)
Median PFS – months	18.7	9.4
HR for Kd vs Vd (95% CI)	0.53 (0.44–0.65)	
	1-sided *P*<0.0001	

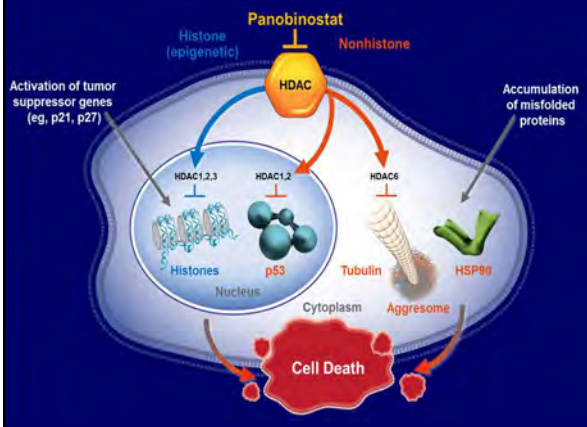
CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; Kd, carfilzomib and dexamethasone; PFS, progression-free survival; Vd, bortezomib and dexamethasone.

Intent-to-Treat Population

Dimopoulos ASCO & EHA 2015

MoA of DACi

Pan-DACi, such as panobinostat, inhibit a broad range of deacetylase enzymes that target both histone and nonhistone proteins involved in oncogenesis[1]



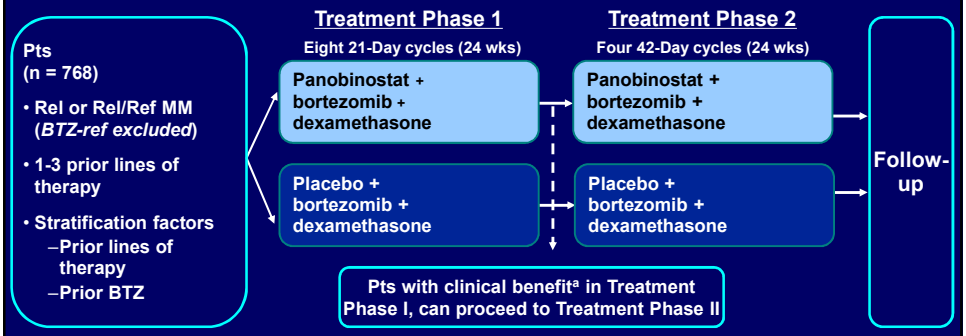
Pan-DACi inhibit growth and promote death of myeloma cells through inhibition of HDAC enzymes:

- Histone proteins, which are implicated in epigenetic dysregulation, resulting in activation of tumor suppressor genes[2-4]
- Nonhistone proteins, which promote toxic accumulation of misfolded proteins, leading to cell stress[2,5,6]

1. Farydak (panobinostat) [package insert]. East Hanover, NJ: Novartis; 2014. 2. Atadja P, et al. Cancer Lett. 2009;280:233-241. 3. Mannava S, et al. Blood. 2012;119:1450-1458. 4. Kalushkova A, et al. PloS One. 2010;5:e11483. 5. Catley L, et al. Blood. 2006;108:3441-3449. 6. Glozak MA and Seto E. Oncogene. 2007;26:5420-5432.

PANORAMA 1 Study Design

Randomized, Double-Blind, Phase 3 Study in Relapsed or Relapsed and Refractory MM



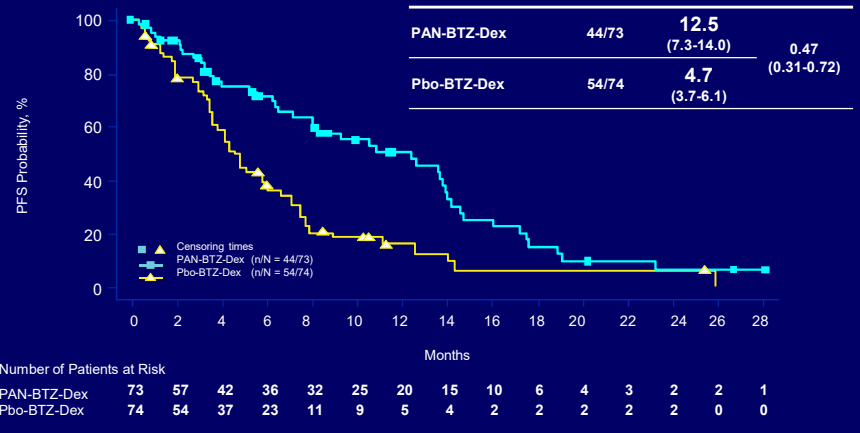
- **Primary endpoint: PFS (per modified EBMT criteria; confirmed by IRC)[1,2]**
- **Key secondary endpoint: OS**
- **Other secondary endpoints: ORR, nCR/CR rate, DOR, TTR, TTP, QoL, and safety**

Study conducted at 215 centers across 34 countries

[a] Achieving ≥ no change according to modified EBMT criteria (SD or better)

1. Blade J, et al. *Br J Haematol*. 1998;102:1115-1123
2. Richardson PG, et al. *N Engl J Med*. 2003; 348:2609-2617

Panorama 1: Prior BTZ + IMiDs ≥ 2 Prior Lines



- Among the subgroup of patients previously treated with BTZ and an IMiD with ≥ 2 prior lines of therapy the difference in median PFS benefit was 7.8 months

Einsele et al. EHA 201

Panorama 1: Toxicity

Median time on treatment of 152 days (3-411) for Panobinostat + Bort + Dex
vs 187 days (3-443) for the control arm

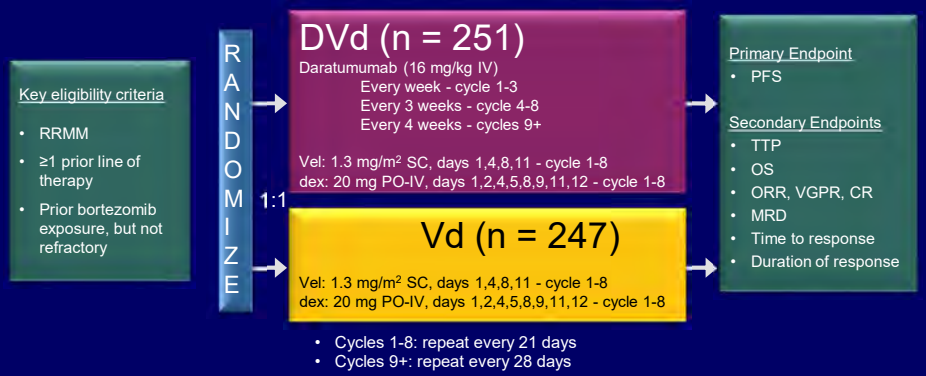
33% of pts discontinued treatment due to AEs *(vs 17% in the control arm)*

	PAN-BTZ-Dex (n = 381)		Pbo-BTZ-Dex (n = 377)	
Preferred term – %	**All grades**	**Grade 3/4**	**All grades**	**Grade 3/4**
Diarrhea	68.2	25.5	41.6	8.0
Peripheral neuropathy[a]	60.6	17.6	67.1	14.6
Asthenia/fatigue	57.0	23.9	40.6	11.9
Nausea	36.2	5.5	20.7	0.5
Peripheral edema	28.6	2.1	19.1	0.3
Decreased appetite	28.1	3.1	12.5	1.1
Constipation	26.8	1.0	32.6	1.1
Pyrexia	26.0	1.3	14.9	1.9
Vomiting	25.7	7.3	13.0	1.3
Cough	21.3	1.0	18.6	0
Thrombocytopenia	97.6	67.4	83.5	31.4

San Miguel, Lancet Oncology 201

CASTOR: Study Design

Multicenter, randomized, open-label, active-controlled phase 3 study

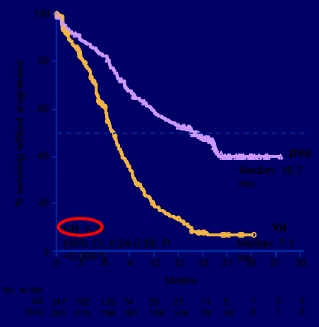


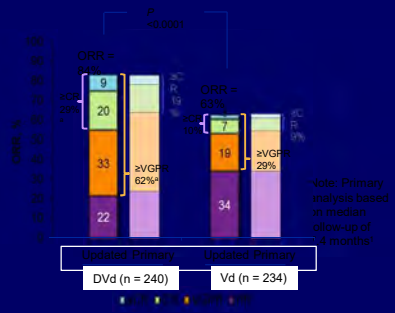
- Cycles 1-8: repeat every 21 days
- Cycles 9+: repeat every 28 days

Daratumumab IV administered in 1000 mL to 500 mL; gradual escalation from 50 mL to 200 mL/min permitted

RRMM, relapsed or refractory multiple myeloma; DVd, daratumumab/bortezomib/dexamethasone; IV, intravenous; Vel, bortezomib; SC, subcutaneous; dex, dexamethasone; PO, oral; Vd, bortezomib/dexamethasone; PFS, progression-free survival; TTP, time to progression; ORR, overall response rate; VGPR, very good partial response; CR, complete response; MRD, minimal residual disease.

Castor: Dara-Vd vs Vd Updated Efficacy: ITT





Duration of response: 18.9 months for DVd versus 7.6 months for Vd

- 69% reduction in risk of progression for DVd versus Vd
- 9.6-month improvement in median PFS for DVd versus Vd
- Responses continue to deepen

HR, hazard ratio; CI, confidence interval; PR, partial response; sCR, stringent complete response
1. Palumbo A, et al. *N Engl J Med*. 2016;375:754-766.
*P <0.0001 for DVd versus Vd

Palumbo et al, NEJM 2016. Weisel et al, EHA 2017

Treatment Possibilities at relapse

Transplant Candidate

Induction Bortezomib-based combination

↓

ASCT (melphalan 200)

↓

Consolidation / Maintenance??

Non Transplant Candidate

MPV / VCD / ~~MPT~~

Len-Dex

Early Relapses

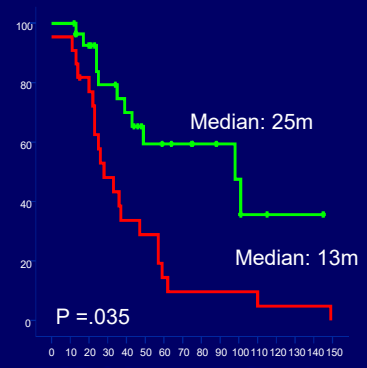
- Second ASCT/Allo-RIC
- LD - based strategies
  - LD
  - Elo-LD
  - Dara-LD
  - Bortezomib-LD
  - Carfilzomib-LD
  - Ixazomib-LD
- Non LD - based strategies
  - Bort-based combos
  - Panob-BD
  - Kd
  - Dara-BD

Is it possible and important to achieve MRD- in RRMM?

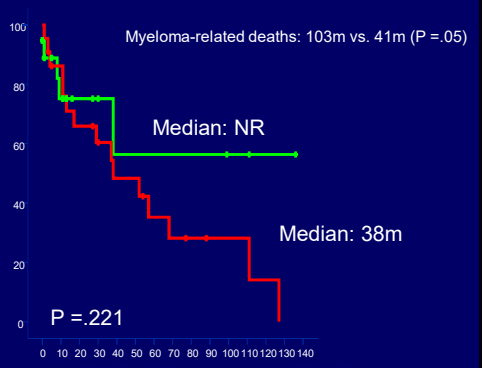
MRD monitoring by 4-color flow: R/R patients

- 43 patients in CR after salvage therapy (81% treated w/o novel agents; 63% received SCT)

TTP



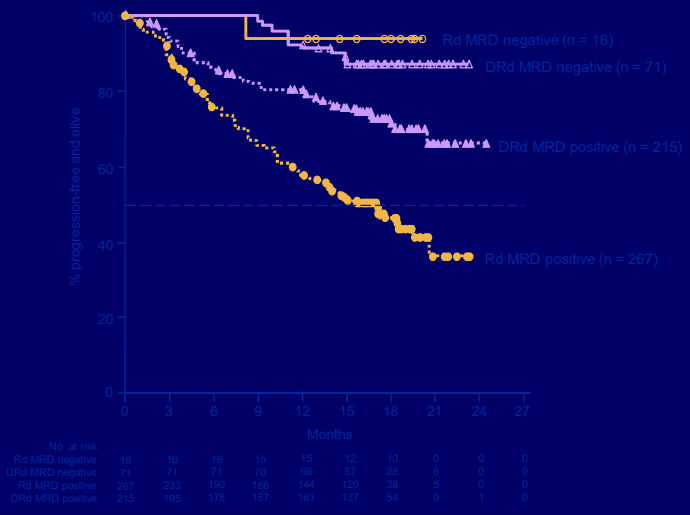
OS



Flow CR (n=20)
MRD positive

Paiva B. et al. Haematologica 2015; 100(2); median f/up: 16 months

PFS: MRD Status (10^{-5})

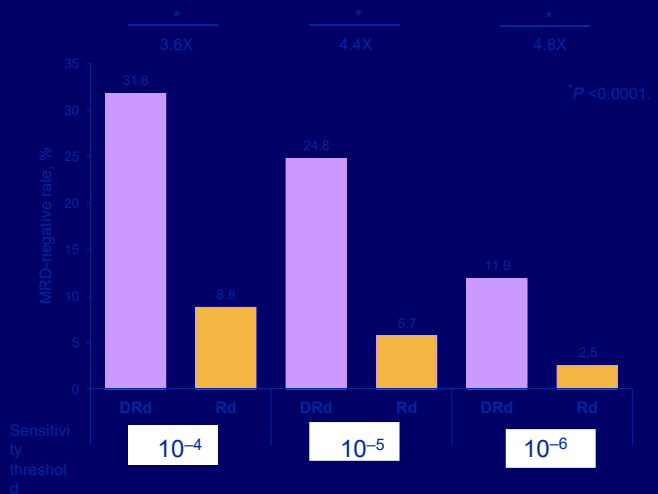


MRD negativity is associated with better outcomes

Intent to treat population

Usmani SZ, et al. ASH 2016. Abst.1151

MRD-negative Rate



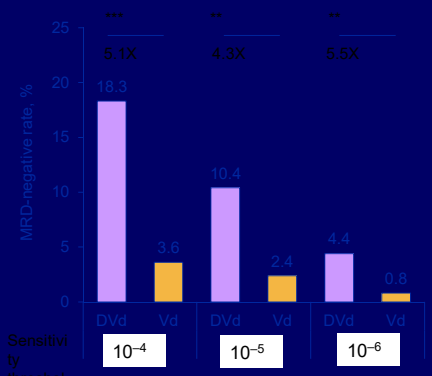
MRD-negative rates were >3-fold higher at all thresholds

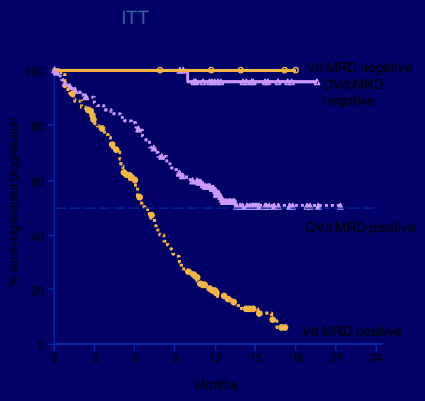
Intent-to-treat population
P values are calculated using likelihood-ratio chi-square test.

Usmani SZ, et al. ASH 2016. Abst.1151

Castor: Dara-Vd vs Vd. Outcomes by MRD rates

ITT (N = 498)





- MRD was evaluated by ClonoSEQ-NGS-based assay in a central lab at three sensitivity thresholds, for patients with suspected CR and also for patients who maintain CR at C9 and C15

MRD-negative rates for DVd were ≥3-fold higher across all thresholds
MRD negativity is associated with better outcomes

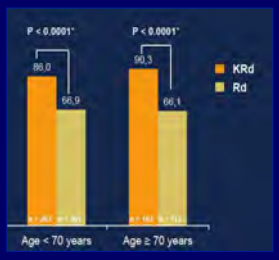
***P <0.0001, * P=0.011, NS, not significant.
P values calculated using likelihood-ratio chi-square test.
MRD-negativity rate = proportion of patients with negative MRD test results at any time during treatment.

Mateos M, et al. Presented at ASH 2016 (Abstract 1150), oral

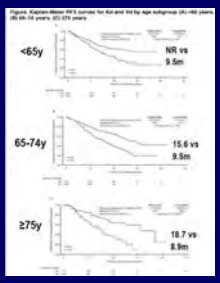
Would advanced age modify our strategy?

Would advanced age modify our strategy?

Aspire

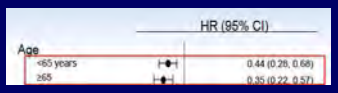


Endeavor



Castor

Pollux



Eloquent

Panorama

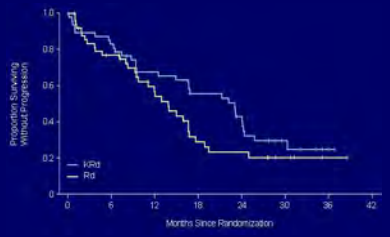
Tourmaline

What if the patient has adverse cytogenetics?

ASPIRE: KRd vs Rd in RMM

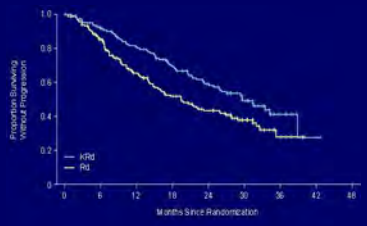
Subgroup analysis in HR patients: PFS

High-risk group



	KRd (n=48)	Rd (n=52)
PFS, median months	23.1	13.9
Hazard ratio (95% CI)	0.70 (0.43–1.16)	

Standard-risk group



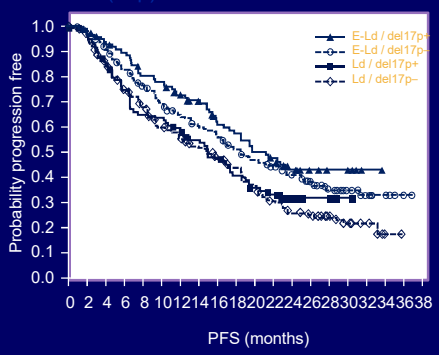
	KRd (n=147)	Rd (n=170)
PFS, median months	29.6	19.5
Hazard ratio (95% CI)	0.66 (0.48–0.90)	

The high-risk group: t(4;14) or t(14;16) or with del(17p) in ≥60% of plasma

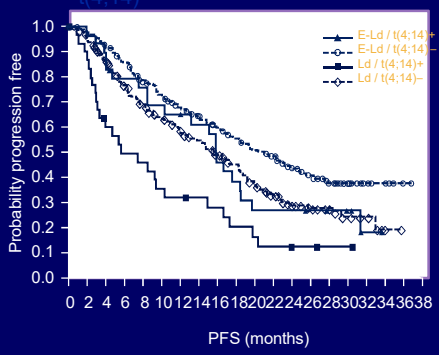
Avet Loiseau H, ASH 2015 Abst

Eloquent-2: Elo-Rd vs Rd
PFS of Patients with or without del(17p) and/or t(4:14)

del(17p)



t(4;14)



E-Ld / del17p+ (events: 50/102), median (95% CI): 21.19 (16.62, NE)
E-Ld / del17p– (events: 123/213), median (95% CI): 18.46 (15.84, 22.77)
Ld / del17p+ (events: 61/104), median (95% CI): 14.92 (10.61, 18.50)
Ld / del17p– (events: 142/218), median (95% CI): 14.85 (11.86, 18.43)

E-Ld / t(4;14)+ (events: 21/30), median (95% CI): 15.84 (8.41, 18.46
E-Ld / t(4;14) – (events: 152/285), median (95% CI): 20.34 (17.28, 2
Ld / t(4;14)+ (events: 25/31), median (95% CI): 5.55 (3.09, 10.25)
Ld / t(4;14)– (events: 178/290), median (95% CI): 15.74 (13.04, 18.5

NE = not estimated

Lonial S, et al. ASCO 2015; abstract 8508

Tourmaline-MM1: I-Rd vs Placebo-Rd in RMM

Subgroup analysis in HR patients: PFS

	ORR, %		≥VGPR, %		≥CR, %		Median PFS, months		
	IRd	Placebo-Rd	IRd	Placebo-Rd	IRd	Placebo-Rd	IRd	Placebo-Rd	HR
All patients	78.3*	71.5	48.1*	39	11.7*	6.6	20.6	14.7	0.742*
Standard-risk patients	80	73	51	44	12	7	20.6	15.6	0.640*
All high-risk patients	79*	60	45*	21	12*	2	21.4	9.7	0.543
Patients with del(17p)†	72	48	39	15	11*	0	21.4	9.7	0.596
Patients with t(4;14) alone	89	76	53	28	14	4	18.5	12.0	0.645

*p<0.05 for comparison between regimens. †Alone or in combination with t(4;14 or t(14;16).
Data not included on patients with t(14:16) alone due to small numbers (n=7).

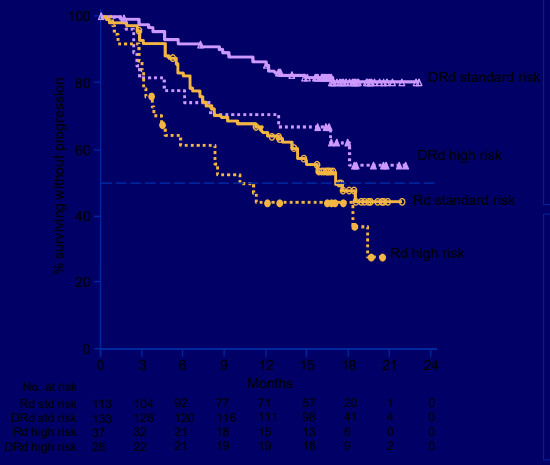
- Median OS was not reached in either arm
- In the IRd arm, median PFS in high-risk patients was similar to that in the overall patient population and in patients with standard-risk cytogenetics

Cut-off values: del(17p) >5%; t(4;14) and t(14;16) >3%

Moreau P, ASH 2015 Abst 727

Pollux: Dara-Rd vs Rd. PFS by Cytogenetic Risk[a]

- Comparable results in 1 to 3 prior lines population



High risk	DRd n = 25	Rd n = 37
Median PFS, mo	NR	10.2
HR (95% CI)	0.44 (0.19-1.03)	
P value	0.0475	
	n = 27	n = 36
ORR, %	85	67
P value	NS	

Standard risk	DRd n = 133	Rd n = 113
Median PFS, mo	NR	17.1
HR (95% CI)	0.30 (0.18-0.49)	
P value	<0.0001	
	n = 132	n = 111
ORR, %	95	82
P value	0.0020	

DRd improves outcomes regardless of cytogenetic risk but benefits the most standard risk patients

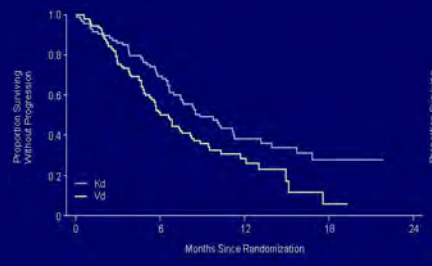
NR: not reached; NS: not significant
[a]Cytogenetic risk-evaluable analysis set. High-risk patients had any of t(4;14)

Usmani SZ, et al. Presented at ASH 2016 (Abstract 1151), oral

Endeavor: Carfilzomib-Dex vs Bortezomib-Dex in RMM

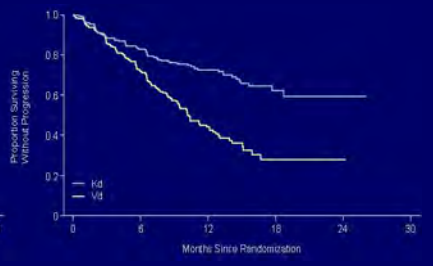
Subgroup analysis in HR patients: PFS

High-risk group



	Kd (n=97)	Vd (n=113)
PFS, median months (95% CI)	8.8 (6.9–11.3)	6.0 (4.9–8.1)
Hazard ratio (95% CI)	0.646 (0.453–0.921)	

Standard-risk group

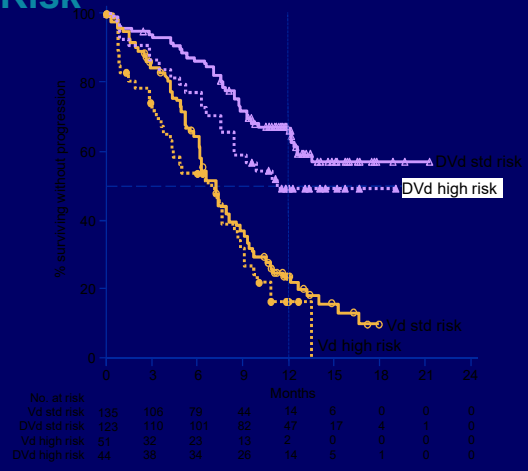


	Kd (n=284)	Vd (n=291)
PFS, median months (95% CI)	NE (18.7–NE)	10.2 (9.3–12.2)
Hazard ratio (95% CI)	0.439 (0.333–0.578)	

High-risk patients: t(4;14) or t(14;16) in >10% or del(17p) in ≥20% of

Chng WJ, ASH 2015 Abst 30

Castor: Dara-Vd vs Vd. PFS by Cytogenetic Risk[a]



High risk[b]	DVd n = 44	Vd n = 51
Median PFS, mo	11.2	7.2
HR (95% CI)	0.49 (0.27-0.89)	
P value	0.0167	
	n = 44	n = 47
ORR, %	82	62
P value	0.039	

Standard risk	DVd n = 123	Vd n = 135
Median PFS, mo	NR	7.0
HR (95% CI)	0.29 (0.20-0.43)	
P value	<0.0001	
	n = 118	n = 131
ORR, %	85	64
P value	0.0003	

DVd improves outcomes regardless of cytogenetic risk

NR, not reached.
[a]ITT/Biomarker risk-evaluable analysis set.
[b]Central next-generation sequencing. High-risk patients had any of t(4;14), t(14;16),

Mateos M, et al. Presented at ASH 2016 (Abstract 1150), oral

Efficacy of novel combinations based on cytogenetic risk

PFS	High Risk				St Risk			
	Exp	Control	Dif.	HR	Exp	Control	Dif.	HR
Aspire[1] K-Rd vs Rd	23.1	13.9	9.2	0.70 (0.43–1.16)	29.6	19.5	10.1	0.66 (0.48–0.90)
Tourmaline[2] IRd vs Rd	21.4	9.7	11.7	0,543	20.6	15.6	5	0.640
Eloquent 2[3] Elo-Rd vs Rd 17p	21.19	14.92	6.27	-	18.46	14.85	3.61	-
Eloquent 2[3] Elo-Rd vs Rd t(4;14)	15.84	5.55	10.29	-	20.34	15.74	4.6	-
Pollux[4] Dara-Rd vs Rd	NR	10.2	-	0.44 (0.19-1.03)	NR	17.1	-	0.30 (0.18-0.49
Endeavor[5] Kd vs Bd	8.8	6	2,8	0.646 (0.453–0.921)	NE	10.2	-	0.439 (0.333–0.578)
Castor[6] Dara-Bd vs Bd	11.2	7.2	5	0.49 (0.27-0.89)	NR	7.0	-	0.29 (0.20-0.43)

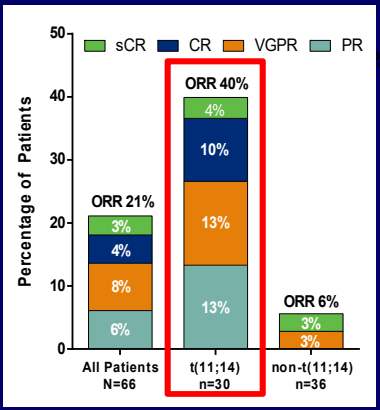
1. The high-risk group: t(4;14) or t(14;16) or with del(17p) in >60% of plasma cells
2. Cut-off values: del(17p) >5%; t(4;14) and t(14;16) >3%
4, 6. High-risk patients had any of t(4;14), t(14;16), or del17p.
5. High-risk patients: t(4;14) or t(14;16) in ≥ 10% or del(17p) in ≥ 20% of screened PC

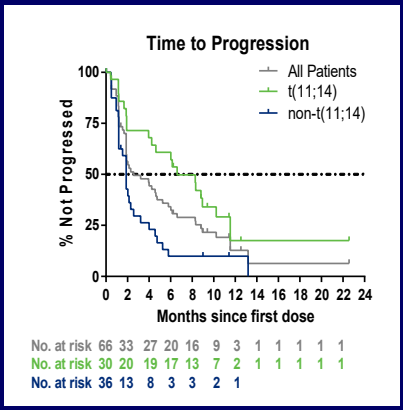
1. Avet Loiseau H, ASH 2015 Abst 73
2. Moreau P, ASH 2015 Abst 727
3. Lonial S, ASCO 2015; Abst. 8508
4. Usmani SZ, ASH 2016, Abst.
5. Chng WJ, ASH 2015 Abst 30
6. Mateos M, ASH 2016, Abst.

Can we use biomarkers to predict sensitivity to a given combination?

Venetoclax monotherapy

n= 66 pts. Median of 5 prior lines. 79% refractory to last line; 61% double refractory to Btz & Len





Higher ORR (88% vs 20%) in t(11;14) with a high BCL2:BCL2L1 ratio

Main toxicities are thrombocytopenia (26% G3-4) and neutropenia (21% G3-4)

Serious AEs: pneumoniae (8%) and sepsis (5%)

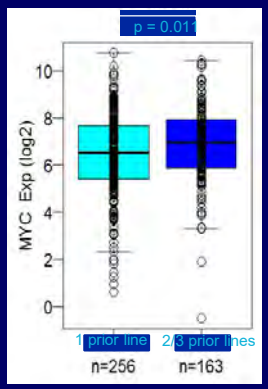
30-1200 mg oral admon (MTD: 1200 mg)

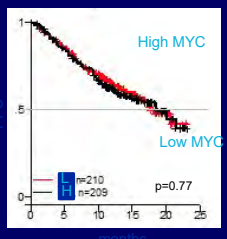
Kumar, et al. Presented at ASH 2016 (Abstract 977), oral presentation

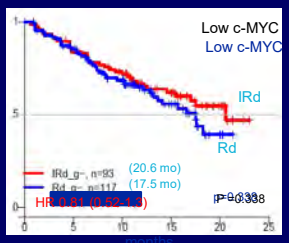
c-myc expression influences response to Ix-RD

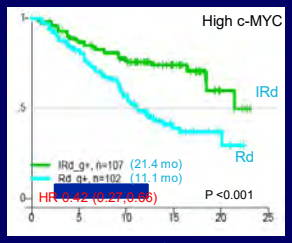
RNAseq data available for 58% (419/722) of enrolled patients

MYC, Median









Patients with 1 prior line that include SCT do not benefit from IRD irrespective of MYC expression.

Hypothesis of enrichment of more immature PC (CD19^{++}, CD81^{++})

Only pts with 2-3 prior lines or 1 prior line non including SCT and high MYC benefit from IRD

Di Bacco et al ASH 2016 Abst 243

Strategies at relapse: How to make the right choice?

Type of relapse

Efficacy of previous treatments

Cytogenetics

Convenience of administration

Toxicity of previous treatments

Cost

Further options

Biomarkers

Strategies at relapse: How to make the right choice?

1. Does this patient require treatment?
   - Symptomatology; Significant Paraprotein Relapse; Aggresive Presentation at diagnosis

2. Is he candidate to ASCT at relapse
   - If previous ASCT DOR>18-24 m; Comorbidities; Patient's consent; Availability of HSC; …

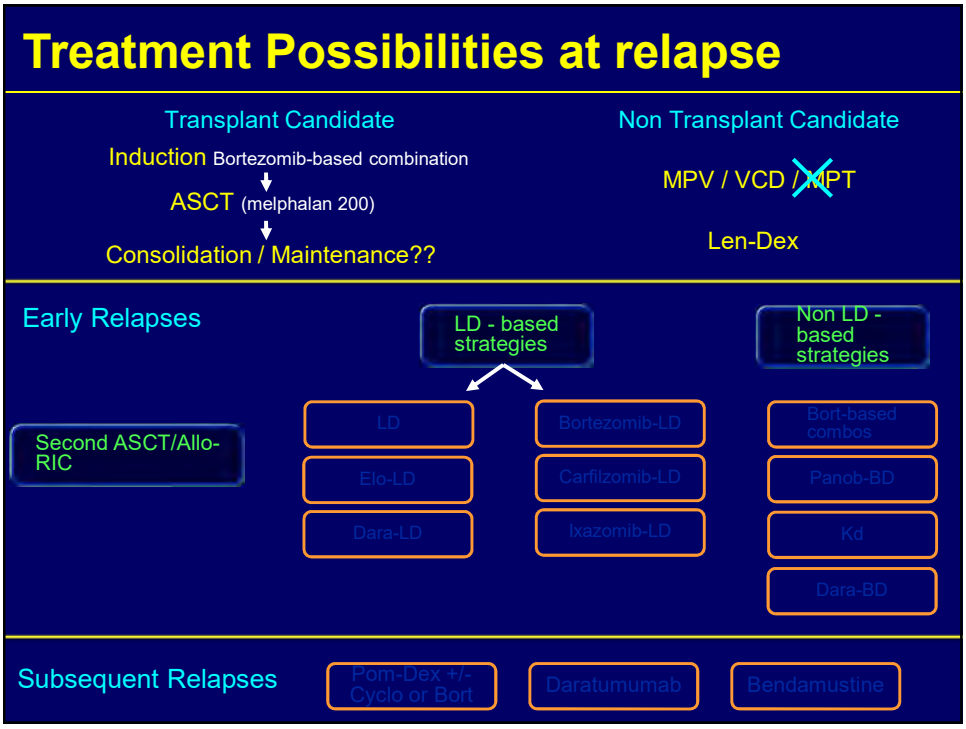
3. Which were the prior regimens: Efficacy and toxicity?

Candidate to Len-Dex based		Candidate to Non Len-Dex based	
K-Rd	I-Rd	Bd retr.	Panob-Bd
Elo-Rd	Dara-Rd	Kd	Dara-Bd

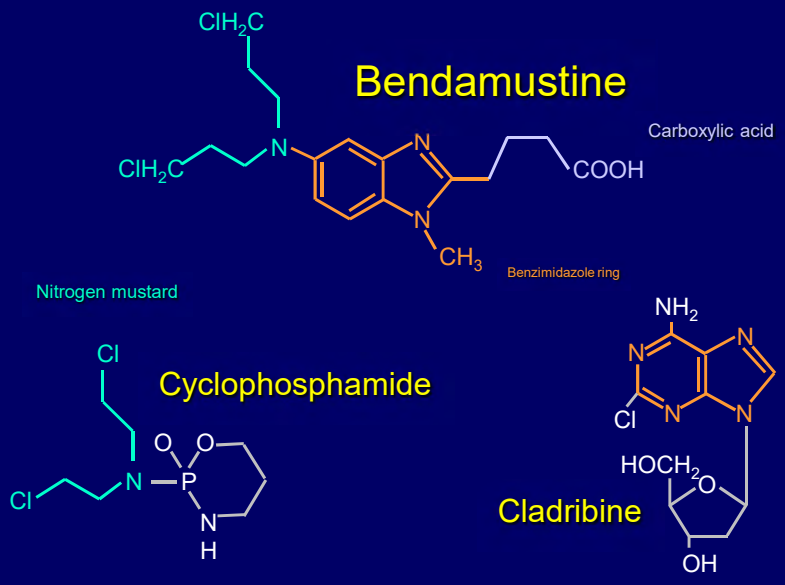
4. Factors to take into consideration
   - Aggresive rel. (more potent) … K-Rd; Dara-Rd
   - 1 prior line … K-Rd; Dara-Bd; Kd
   - Preference for oral … I-Rd
   - High risk cytog. … K-Rd; I-Rd; Elo-Rd; Dara-Vd, Dara Rd
   - Indolent relapses (>3.5 y TFI) … Elo-Rd;
   - > 1 prior lines … K-Rd; Panob-Bd
   - Prior PI refr. … Elo-RD; Dara-Rd; K-Rd, I-Rd

Which options do we have in late relapses?

Treatment Possibilities at relapse



Bendamustine: an old-new drug



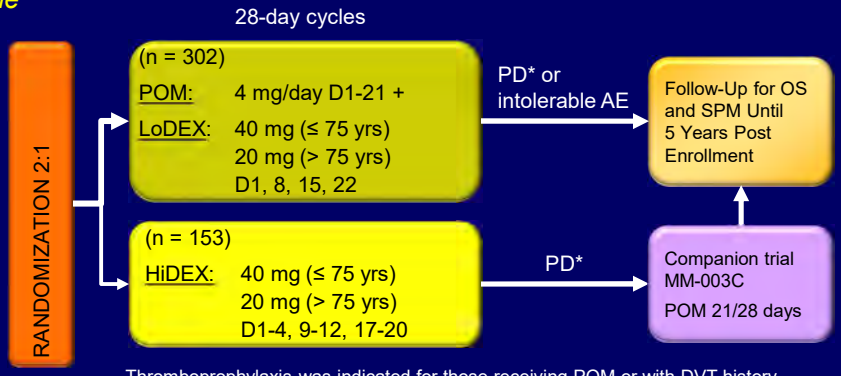
Bendamustine in R/R MM

- Single agent[1] (31 patients relapsing HDT) ORR: 31% (7% CR, 24% PR); PFS: 6m
- Benda-Bort[2] (40 patients *6 prior lines*) ORR: 27% (2% CR, 5% VGPR, 21%PR)
- Benda-Bortz-Dex[3] (40 patients *4 prior lines*) ORR: 72% (25% VGPR, 47%PR)
- Benda-Bort-Dex[4] (79 patients *2 prior lines*) ORR: 61% (15% CR, 20% VGPR, 25% PR)
- Benda-Bort-Dex[5] (73 patients *elderly 1st rel.*) ORR: 70% (14% CR, 16% VGPR, 40% PR)
- Benda-Bort-Dex[6] (75 patients *1 prior line*) ORR: 72% (16% CR, 19% VGPR, 37% PR)
- Benda-Bort-Pred[7] (78 patients *2 prior lines*) ORR: 69% (17% nCR,13% VGPR, 40% PR)
- Benda-Thal-Pred[8] (28 patients *2 prior lines*) ORR: 86% (14% CR, 18% VGPR, 50% PR)
- Benda-Thal-Dex[9] (23 patients *3 prior lines*) ORR: 26% (4% CR, 22% PR)
- Benda-Thal-Dex[10] (66 patients *R/R to 2 prior lines*) ORR: 46%
- Benda-Len-Dex[11] (29 patients *3 prior lines*) ORR: 52% (24% VGPR, 28% PR)
- Benda-Len-Dex[12] (41 patients *3 prior lines*) ORR: 50% (11% CR, 7% VGPR, 32% PR)

1. Knop et al. Hematologica 2005, 90:1287
2. Berenson. BJH 2013
3. Hrusowsky et al ASH 2007 Abstract 4851
4. Ludwig H. Blood 2013
5. Rodon, ASH 2013. Abstract 1971
6. Offidani, Blood Cancer J 2013
7. Pönisch et al. J Cancer Res Clin Oncol 2013
8. Pönisch et al. BJH 2008,
9. Grey-Davies E. BJH 2012
10. Schey, ASH 2013. Abstract 286
11. Lentzsch. S. Blood 2012
12. Pozzi, ASH 2013. Abstract 3222

MM-003 Design: POM + LoDEX vs HiDEX

455 pts Refractory MM Pts Who Have Failed BORT and LEN & refr to last line



Thromboprophylaxis was indicated for those receiving POM or with DVT history

Stratification

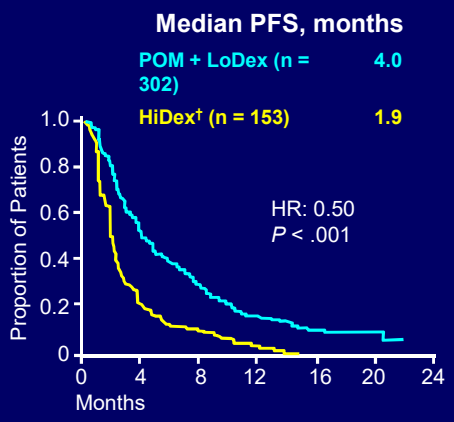
- **Age (≤ 75 vs > 75 yrs)**
- **Number of prior Tx (2 vs > 2)**
- **Disease population**

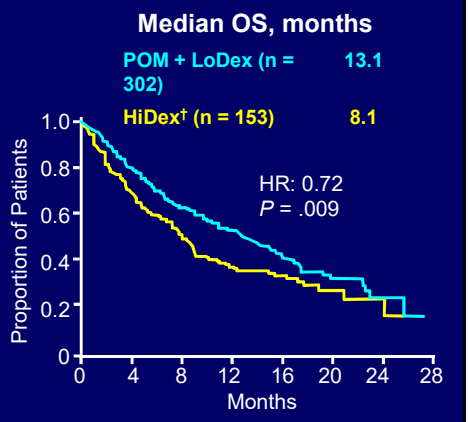
- Len: Prior (100%); Refr (93%)
- Btz: Prior (100%); Refr (78%)

San Miguel, Lancet Oncology 2013

MM-003 Final Analysis: Pomalidomide/ LoDex vs HiDex: PFS and OS

ORR (≥ PR): 31% vs 10%; (≥ MR): 39% vs 16%

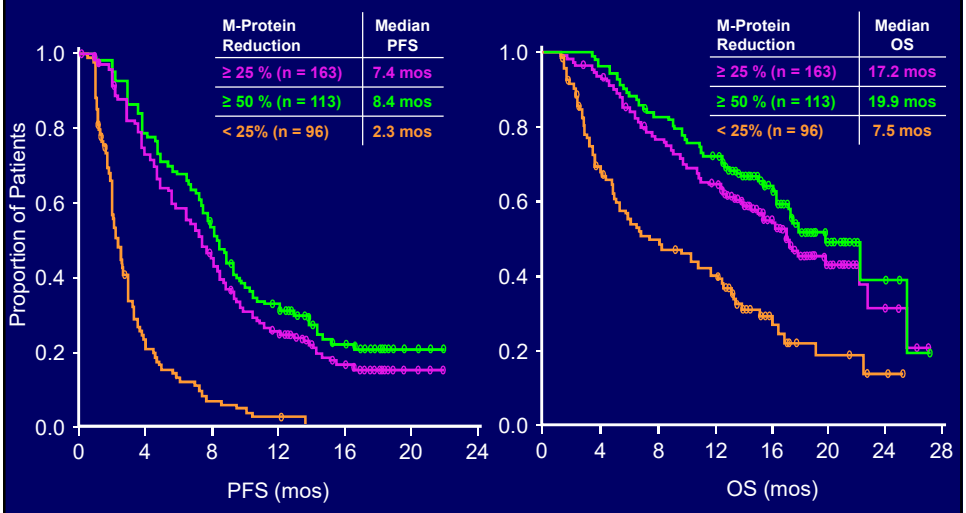




*Primary endpoint.
†85 pts (56%) on the HiDex arm received subsequent POM.

San Miguel, Lancet Oncology 2013

PFS and OS by M-Protein Reduction: Patients Assigned to POM



Patients achieving ≥ MR attain a significant survival benefit

San Miguel J, et al. Patient Outcomes by Prior Therapies and Depth of Response: Analysis of MM-003, a Phase 3 Study Comparing Pomalidomide + Low-Dose Dexamethasone (POM + LoDEX) vs High-Dose Dexamethasone (HiDEX) in Relapsed/Refractory Multiple Myeloma (RRMM). Oral presentation at: American Society of Hematology. 2013; December 7-10; New Orleans, LA.

Future Pom-Dex combinations

	POM + Vd[1]	K + POMdex[2]	Ixa + POMdex[3]	Dara + POMdex[4]
Study phase	1	1/2	1/2	1
Prior lines of therapy, n	1–4		1–5 including PI and Len	≥2 (2–13)
Refractory to Len, n (%)	All patients were Len-refractory	40 (87)	32 (100); 25 (100)	87 (89)
Refractory to PI, n (%)	All pts were PI-exposed (but not refractory)	NR	20 (63); 15 (60)*	74 (76)
ORR, %	65	84	44	71
Median (range) DOR	7.4 (4.4–9.6) months	NR	56 (28-160) months	NR
Median PFS, months	NR	12.9	NR	6-month rate = 66%

*bortezomib; †MTD: POM 4 mg + BORT (IV or SC) 1.3 mg/m² + LoDex 20 mg (10 mg for patients >75 years); ‡MTD: Carfilzomib 27 mg/m² QZW + POM 4 mg D1–21 + Dex 40/20 mg QW

D, day; Dex, dexamethasone; DOR, duration of response; IMiD, Immunomodulatory drug; Len, lenalidomide; NR, not reported; ORR, overall response rate; PI, proteasome inhibitor; PFS, progression-free survival

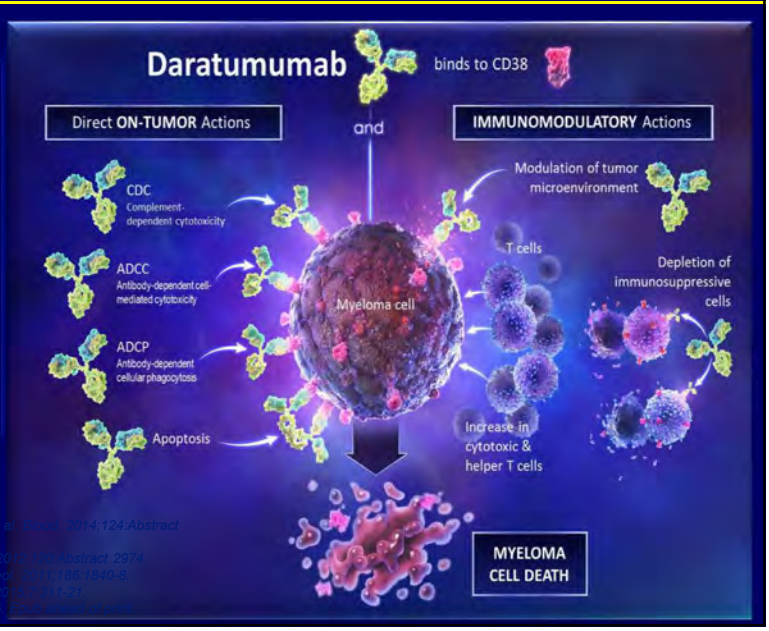
1.Richardson et al. EHA 2016; P653; 2. Rosenbaum et al. ASH 2015 (Abstract 8007); 3. Krishnan et al. ASCO 2016 (Abstract 8008), oral presentation; 4. Chari et al. ASH 2015 (Abstract 508); oral presentation

- Pomalidomide combinations at ASH 2016
  - Cyclo-D; Marizomib; Carfilzomib; Ixazomib; Daratumumab; MOR202; Isatuximab; Pembrolizumab; Filanesib; Selinexor; ACY-247

Chari A, et al. ASH 2016. Abst 453; Spencer et al, ASH 2016 Abs. 3326; Bringhen et al, ASH 2016 Abs. 1145; Kumar et al, ASH 2016 Abs. 3327; Nooka AK, et al. ASH 2016. Abst 492; Raab et al. ASH 2016 Abst 1157; Richardson, et al. ASH 2016. Abst 2123; Badros A, et al. ASH 2016. Abst 490; Ocio et al. ASH 2016 Abst 4503; Chen et al. ASH 2016. Abst 3330; Niesvizky R, et al. ASH 2016. Abst 3307

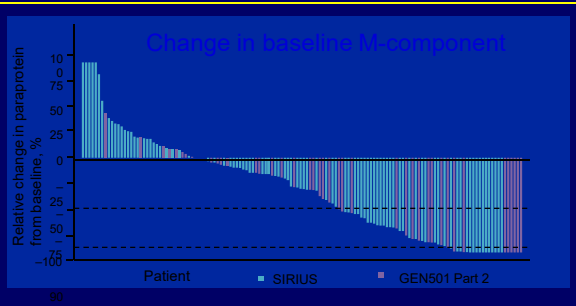
Daratumumab (Anti-CD38): Background

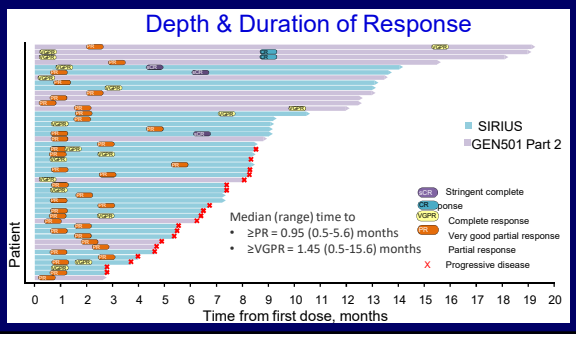
- Human CD38 IgGκ monoclonal antibody
- Direct and indirect anti-myeloma activity[1-5]
- Depletes CD38+ immunosuppressive regulatory cells[5]
- Promotes T-cell expansion and activation[5]

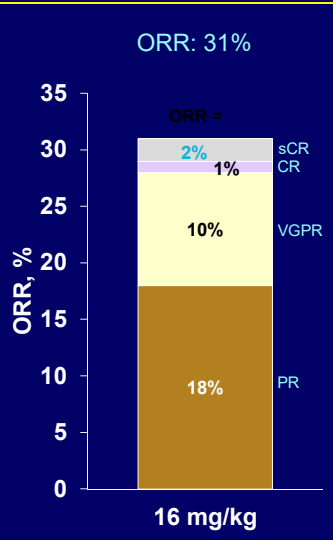


1. Lammerts van Bueren J, et al. Blood. 2014;124:Abstract 3474.
2. Jansen JMH, et al. Blood. 2012;120:Abstract 2974.
3. de Weers M, et al. J Immunol. 2011;186:1840-8.
4. Overdijk MB, et al. MAbs. 2012;4:405-21.
5. Krejcik J, et al. Blood. 2016;

Daratumumab (Anti-CD38) in MM: GEN501 & Sirius



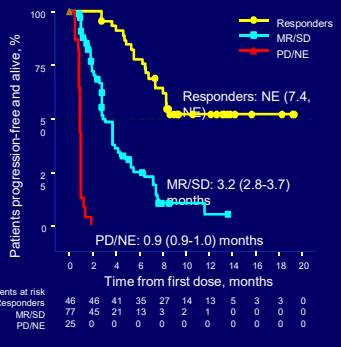




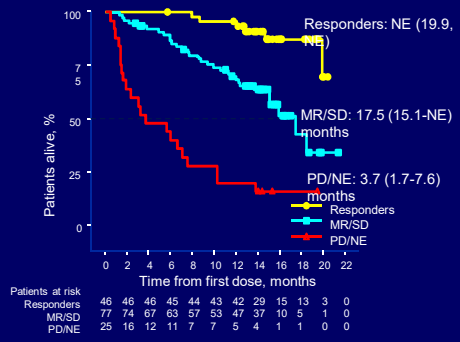
Usmani S. ASH 2015. Abs. 29

Daratumumab (Anti-CD38) in MM: GEN501 & Sirius

Progression-free survival



Overall Survival



- **For the combined analysis, median OS = 19.9 (95% CI, 15.1-NE) months**
- **1-year overall survival rate = 69% (95% CI, 60.4-75.6)**

Usmani S. ASH 2015. Abs. 29

PAVO: Study Design

Phase 1b, open-label, multicenter, dose-finding, proof of concept study

Key eligibility criteria
- RRMM with measurable disease
- ≥2 prior lines of treatment
- Not received anti-CD38 therapy

Group 1 (n = 8)
DARA: 1,200 mg
rHuPH20: 30,000 U

→

Group 2[a] (n = 45)
DARA: 1,800 mg
rHuPH20: 45,000 U

Primary endpoints
- C_{trough} of DARA at Cycle 3/Day 1
- Safety

Secondary endpoints
- ORR
- CR
- Duration of response
- Time to response

Dosing schedule
- Approved schedule for IV
- 1 Cycle = 28 days

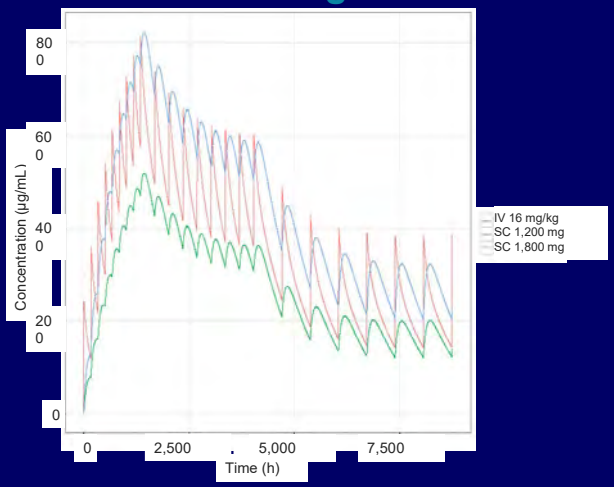
Infusion time
- 1,200 mg: 20-min infusion (60 mL)
- 1,800 mg: 30-min infusion (90 mL)

Pre-[b]/post-infusion medication
- Acetaminophen, diphenhydramine, montelukast, and methylprednisolone

RRMM, relapsed or refractory multiple myeloma; QW, weekly; Q2W, every 2 weeks; Q4W, every 4 weeks; C_{trough}, trough concentration; DRR, overall response rate; CR, complete response; PK, pharmacokinetic
[a]Group 2 comprises 4 distinct cohorts, each treated with DARA 1,800 mg and rHuPH20 45,000 U; C_{trough} on Cycle 3/Day 1 in Group 1 supported dose selection for Group 2. The study evaluation team reviewed safety after Cycle 1 and PK after Cycle 3/Day 1 for each cohort.
[b]Administered 1 hour prior to infusion.

Usmani S, et al. Presented at ASH 2016 (Abstract 1149), oral

Simulation of Mean Concentration-Time Profiles of DARA Following SC and IV Dosing[a]



- Similar C_{max} for SC 1,800 mg versus IV 16 mg/kg overall
- Lower C_{max} for SC 1,800 mg during the initial weekly administration
- Higher C_{trough} for SC 1,800 mg versus SC 1,200 mg

C_{max}, peak plasma concentration
[a]Dosing schedule is QW in Cycles 1 to 2, Q2W in Cycles 3 to 6, and Q4W thereafter

Usmani S, et al. Presented at ASH 2016 (Abstract 1149), oral

Safety

- AE profile of DARA-PH20 was consistent with IV DARA
- No treatment discontinuations due to TEAEs were observed in the 1,800-mg
- **IRRs**

	1,200 mg n = 8	1,800 mg n = 45
IRR, % (n)	**13** (1)	**24** (11)
Chills	**13** (1)	**9** (4)
Pyrexia	**0** (0)	**9** (4)
Pruritus	**0** (0)	**4** (2)
Dyspnea	**13** (1)	**0** (0)
Flushing	**0** (0)	**2** (1)
Hypertension	**0** (0)	**2** (1)
Hypotension	**0** (0)	**2** (1)
Nausea	**0** (0)	**2** (1)
Non-cardiac chest pain	**13** (1)	**0** (0)
Oropharyngeal pain	**0** (0)	**2** (1)
Paresthesia	**0** (0)	**2** (1)
Rash	**0** (0)	**2** (1)
Sinus headache	**0** (0)	**2** (1)
Tongue edema	**0** (0)	**2** (1)
Vomiting	**0** (0)	**2** (1)
Wheezing	**0** (0)	**2** (1)

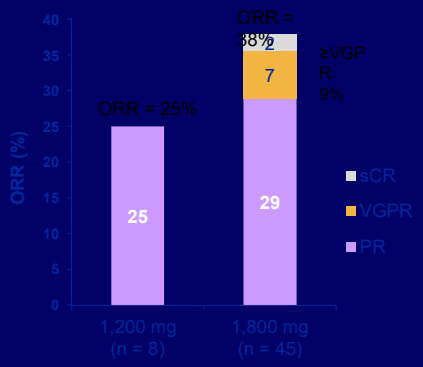
- All IRRs in the 1,800-mg group were grade 1 or 2
- One grade 3 IRR of dyspnea in the 1,200-mg group
- No grade 4 IRRs were observed
- All IRRs occurred during or within 4 hours of the first infusion
- No IRRs occurred during subsequent infusions in either group
- Abdominal wall SC tolerated

Low IRR incidence and severity with DARA SC

Usmani S, et al. Presented at ASH 2016 (Abstract 1149), oral

ORR

Response	1,200 mg n = 8	1,800 mg n = 45
ORR, % (n)	**25** (2)	**38** (17)
sCR	**0** (0)	**2** (1)
CR	**0** (0)	**0** (0)
VGPR	**0** (0)	**7** (3)
PR	**25** (2)	**29** (13)
MR	**13** (1)	**11** (5)
SD	**50** (4)	**38** (17)
PD	**13** (1)	**13** (6)



- Responses to DARA-PH20 were observed across both groups

Deeper responses were observed in the 1,800-mg group

Response-evaluable set.
sCR, stringent complete response; VGPR, very good partial response; PR, partial response; MR, minimal response; SD, stable disease; PD, progressive disease.

Usmani S, et al. Presented at ASH 2016 (Abstract 1149), oral

Conclusions

- Identify Biochemical relapses → Does this patient require treatment?
- Early relapses (1-3 prior):
  - Len-Dex substituted by K-Rd; Elo-Rd; I-Rd; Dara-Rd;
  - Non Len-Dex combinations: Kd; Panob-Bd and Dara-Bd
- Late relapses (>2-3): Bendamustine, Pom-Dex; Daratumumab
- Probably the problem has changed
  - What else can I prescribe to this patient? → How should I choose?
    - Based on: Efficacy & Tox of prev. Tx; Type of Relapse; Age; Cost; Cytogenetics
- Continue including patients in clinical trials so in the next 10 years

Amyloidosis: "Under-diagnosed disorder"

Joan Bladé
Amyloidosis and Myeloma Unit
Hospital Clinic of Barcelona

Santiago de Chile, 12 de Agosto, 2017

Concept of Amyloidosis

- Group of “rare” diseases characterized by extracellular deposition of amyloid fibrils (Congo red +) in organs and tissues

Pathogenesis

Increased synthesis, specific mutations or aging of autologous proteins (amyloidogenic precursor proteins)

Conformational changes and aggregation forming amyloid fibrils (Congo-red positive)

Deposition of amyloid fibrils in tissues cause functional damage of involved organs, and eventually (if untreated) leads to death

Types of Amyloidosis

Can be classified according to:

- Localized versus systemic
- Acquired versus hereditary
- Different amyloidogenic precursor proteins

Most Common Forms of Systemic Amyloidosis **99%**

Precursor protein	Main synthesizing organ	Amyloid type
Ig Light chain	**Bone marrow**	**Ig LC amyloidosis = AL amyloidosis** **75%**
Serum amyloid A protein	Liver	Secondary (reactive) amyloidosis = AA amyloidosis
Wild type transthyretin	Liver	Senile systemic amyloidosis (SSA) = wild type ATTR amyloidosis
Mutated transthyretin	Liver	Hereditary ATTR amyloidosis = hereditary ATTRV30M amyl.
Mutated apolipoprotein A1	Liver, GI tract	Hereditary AApoAI amyloidosis

Localized Amyloidosis

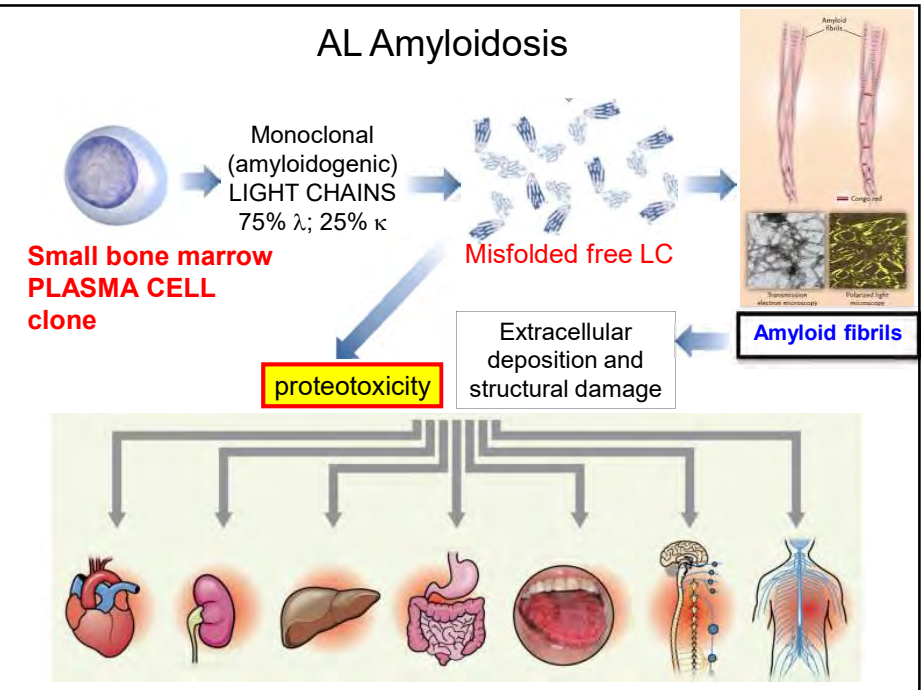
- Local formation and deposition of light chain (AL) amyloid fibrils, confined to a single site (WITHOUT an underlying systemic plasma cell disorder)
- Sites:
  - tracheo-bronchial tree (upper resp tract, nasopharynx),
  - urinary tract (bladder),
  - skin and nails,
  - GI tract,
  - Others (lymph nodes, orbit, …)
- Treatment: LOCAL, if needed (surgery, laser, RDT…)
- Low risk of progression to systemic AL amyloidosis

Light Chain Amyloidosis (AL Amyloidosis)

Epidemiology

- Incidence: 4-10 patients/million/year
- Aprox. one-fifth as common as multiple myeloma
- Median age at diagnosis: 64 years
  (<5% of patients are < 40 years-old)
- Male predominance: 2/3 of patients (referral bias?)
- Median survival (untreated patients): 10-14 months

AL Amyloidosis



Merlini & Stone, Blood. 2006

Monoclonal Gammopathy

- M protein by electrophoresis (moderate size): 50%
- M protein by immunofixation: 90-95%
- Isotype:
  - 32% IgG
  - 24% Bence-Jones
  - 10% IgA,
  - 5% IgM
  - 1% IgD
- Light chain isotype: LAMBDA (75%)
- Bone marrow plasma cell infiltration: 5-10%
  (>20% in about ¼ patients)
- No CRAB

Main clinical manifestations

- Fatigue and anorexia (weight loss)
- Organ involvement
  - Kidney, 70-80%
  - Heart, 50-70%
  - Liver, 20%
  - Peripheral / autonomic neuropathy, 20%/15%
  - Gastrointestinal, 8% (only 1% symptomatic)
  - Soft tissue, 12%

Renal involvement (70-80%)

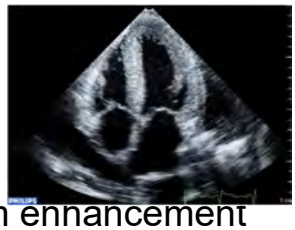
- Glomerular proteinuria evolving to overt nephrotic syndrome (hypercholesterolemia, edema)
- Less frequently renal failure progressing to ESRD
  - Serum creatinine > 2 mg/dL in 20% patients

Cardiac involvement (50-70%)

- Restrictive cardiomyopathy
- Congestive heart failure
- Arrhythmias (syncope or sudden death)
- Rarely angina or infarction
- Elevation of cardiac biomarkers
  (NT-proBNP, troponin T or I)

Cardiac involvement (50-70%)

- ECG: low voltages +/- pseudoinfarct pattern
- Echo: LV concentric hypertrophy
  - Thickening of LV and RV walls, interventricular and interatrial septa (>12 mm)
  - "Granular sparkling"
  - Normal LV ejection fraction (reduced in advanced disease)



- Cardiac MR: late gadolinium enhancement

Liver involvement (20%)

- Hepatomegaly

  (Amyloid infiltration versus congestive heart failure in patients with cardiac amyloidosis)
- Elevated alkaline phosphatase
- Rarely elevated bilirubin

  (bilirubin > 5 mg/dL ➡ survival <1 month)
- Kappa clones more frequently found (30-40%)

Nervous system involvement

Peripheral neuropathy (PN) (20%)

- Symmetric distal sensori(motor) PN
- Seldom isolated (2%) in contrast with PN in ATTR-V30M

Autonomic neuropathy (15%)

- Postural hypotension
- Impotence
- Bowel dysfunction (severe diarrhea to constipation)

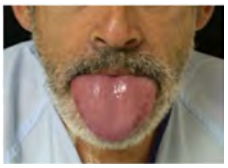
GI involvement

- Bleeding (due to vascular fragility and loss of vasomotor responses to injury)
- Gastroparesis
- Malabsorption
- Constipation
- Intestinal pseudo-obstruction (dysmotility)

Other clinical manifestations (I)

- Periorbital purpura (15%)

- Macroglossia (10%)
- Submandibular swelling
- Hoarse or weak voice
- Dry mouth
- Jaw claudication



Other clinical manifestations (II)

- Carpal tunnel syndrome (25%)
- Factor X deficiency (10-15%)
- Muscular pseudohypertrophy, articular deposits, shoulder pad sign
- Splenomegaly (5%)
  - Hyposplenism in 25% of patients
- Pulmonary/pleural involvement (<5%)

Diagnosis

1. Clinical suspicion:
   - ⇨ Any clinical manifestation
   - ⇨ Serum and/or urine M component
2. Confirmatory biopsy:
   - ⇨ Amyloid deposition (Congo Red +)
   - ⇨ Typing by immunohistochemistry (k or λ LC)
3. Gold-standard of congophilic deposits typing: Proteomics (LMD/MS)

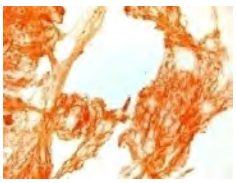
Cohen AD, Comenzo RL. ASH 2010.

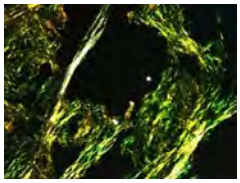
Serum Free Light Chain (FLC)

- Ig FLC is the precursor of amyloid
- FLC assay (Freelite)
- Role in diagnosis: Abnormal FLC in 90% of patients
- Role in disease monitoring:
  - "Measurable" by M-protein in 25% of patients
  - "Measurable" by FLC in >50% of patients
- Independent prognostic value

Proving systemic amyloid deposition

Diagnosis of amyloidosis relies on Congo red staining of tissue biopsy



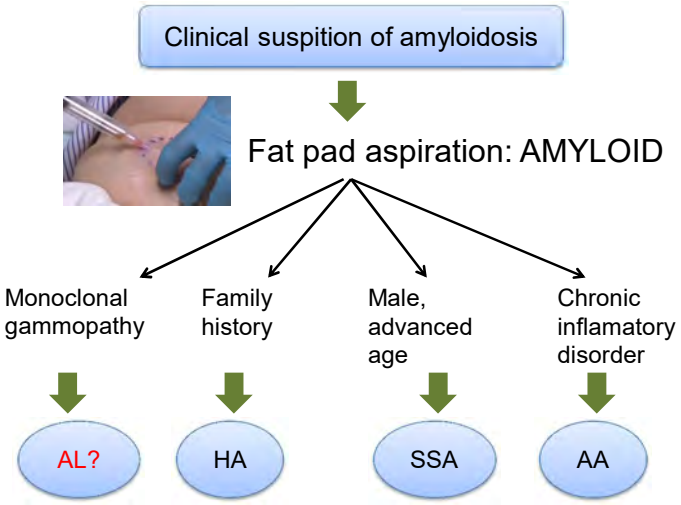


- Tissue of choice: **abdominal fat** (sensitivity 88%)
- **If negative** → labial minor **salivary glands** (S: 58%) or **rectum**
- **If negative** → **involved organ** (kidney, liver, heart,…)

  (hemorrhagic risk!!)

Courtesy of Dr. Merlini

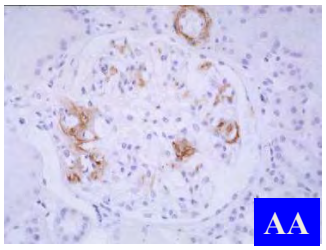
Differential Diagnosis

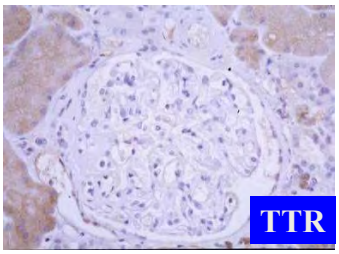


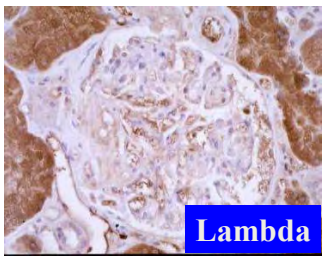
Treatment Approaches in Systemic Amyloidosis

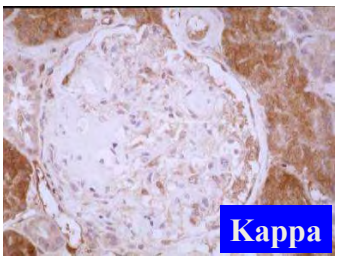
Amyloid type	Treatment options
AL amyloidosis	Chemotherapy
AA amyloidosis	Treatment of underlying disease
Senile systemic amyloidosis (SSA)	Treatment of heart failure, heart Tx
Hereditary ATTR amyloidosis	Liver Tx
Hereditary AApoAI amyloidosis	Liver Tx

Typing by immunohystochemistry







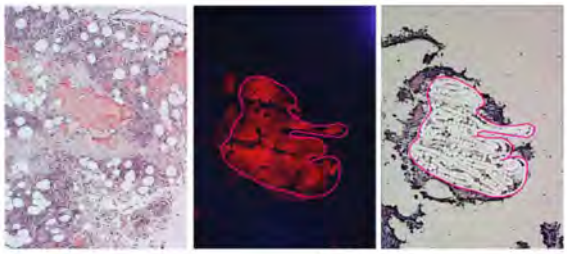


Cortesía Dr. Solé

Classification of amyloidosis by laser microdissection and mass spectrometry based proteomic analysis in clinical biopsy specimens

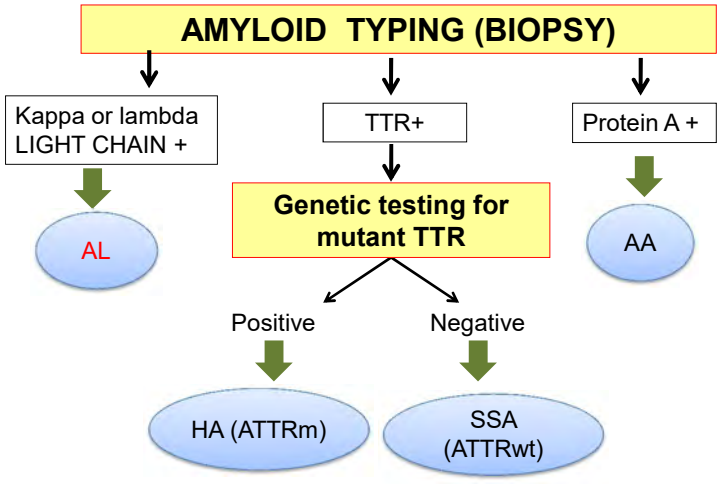
Julie A. Vrana1, Jeffrey D Gamez1, Benjamin J. Madden2, Jason D. Theis1, H. Robert Bergen III2 and Ahmet Dogan1

1 Department of Laboratory Medicine and Pathology, 2 Mayo Proteomics Research Center, Mayo Clinic, Rochester MN 55905

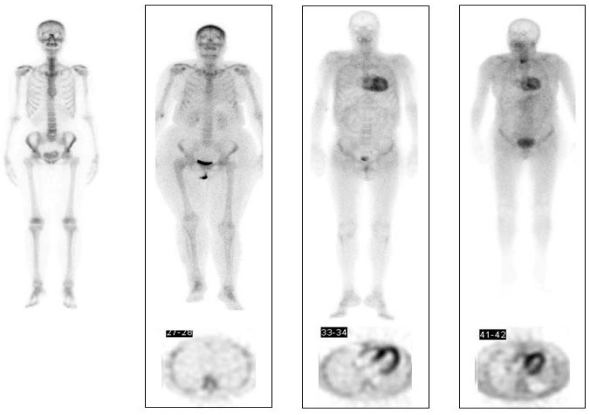


Blood 2009, 114:4957-4959

# Accession	MW	Control	1	2	3	4
1 ALBU_HUMAN	69 kDa		100% (36)	100% (35)	100% (36)	100% (35)
2 APOE_HUMAN	36 kDa		100% (19)	100% (17)	100% (18)	100% (17)
3 VTNC_HUMAN	54 kDa		100% (13)	100% (13)	100% (17)	100% (14)
4 KAC_HUMAN	12 kDa		100% (7)	100% (6)	100% (7)	100% (6)
5 APOA4_HUMAN	45 kDa		100% (15)	100% (19)	100% (17)	100% (13)
6 SAMP_HUMAN	25 kDa		100% (8)	100% (9)	100% (9)	100% (9)
7 C4BP_HUMAN	67 kDa		100% (11)	100% (10)	100% (12)	100% (10)
8 HBB_HUMAN	16 kDa		100% (4)	100% (8)	100% (9)	100% (7)
9 CLUS_HUMAN	52 kDa		100% (10)	100% (7)	100% (8)	100% (8)
10 CO6A3_HUMAN	344 kDa		100% (6)	100% (13)	100% (17)	100% (10)
11 APOA1_HUMAN	31 kDa		100% (7)	100% (5)	100% (9)	100% (7)
12 CO9_HUMAN	63 kDa		100% (5)	100% (5)	100% (5)	100% (7)
13 TRFE_HUMAN	77 kDa		100% (7)	100% (6)	100% (9)	100% (4)
14 HBA_HUMAN	15 kDa			100% (4)	100% (4)	100% (4)
15 CO3_HUMAN	187 kDa		100% (3)	100% (4)	100% (8)	100% (5)



Gammagrafía ^{99m}Tc-DPD



Control AL TTR TTR

Perugini et al, J Am Coll Cardiol 2005

Looking for Organ Involvement

- Thorax X-ray
- ECG and echocardiogram
- Holter (suspected arrhythmia)
- Cardiac MR (unclear echo)
- Skeletal survey (bone pain)
- Electrophysiological studies (suspected polyneuropathy)
- GI endoscopic study (suspected GI involvement)

AL Prognosis

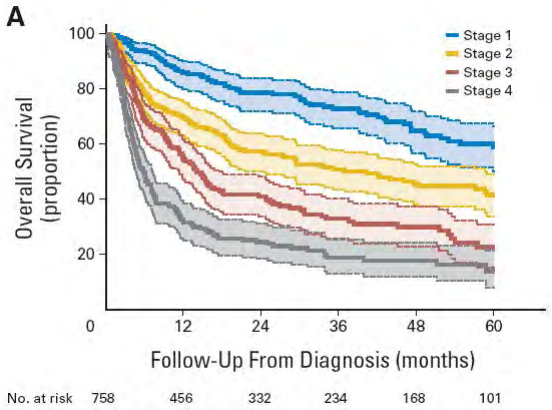
- Cardiac involvement → cardiac biomarkers
- Tumor burden → serum free light chains
- Response to therapy

Revised Prognostic Staging System (I)

Kumar et al, JCO 2012 (Mayo Clinic)

- N: 810 newly AL
- **Prognostic factors for OS**
  - FLC-diff ≥ 180 mg/L
  - cTnT ≥ 0.025 ng/mL
  - NT-proBNP ≥ 1800 pg/mL

Revised Prognostic Staging System (II)



Median OS:

- I: 94 mos.
- II: 40 mos.
- III: 14 mos.
- IV: 5,8 mos.

Hem Response (HR) Evaluation

	Gertz et al, 2005
CR	Negative serum and urinary immunofixation Normal FLC ratio BMPC <5%
PR	If serum M protein >5 g/L → 50% ↓ If urinary M protein > 100 mg/day → 50% ↓ If iFLC > 100 mg/L → 50% ↓
SD	No CR, PR or progression

	Palladini et al, 2012
aCR	= ¿BM needed?
VGPR	**dFLC* <40 mg/L**
PR	**dFLC* decrease >50%**
SD	No response

* Baseline dFLC must be ≥50 mg/L

Cardiac Response Evaluation

	Gertz et al, 2005	Palladini et al, 2012
Response	↓ IVSd (≥ 2 mm) or ↑ EF (20%) or ↓ NYHA (2 classes) No ↑ in diuretic use No ↑ in wall thickness	**NT-proBNP* ↓ >30% and >300 ng/L** NYHA class response (2 classes)
Progression	↑ IVSd (2 mm) ↑ NYHA (1 grade) with a ↓ EF of ≥ 10%	**NT-proBNP* ↑ >30% and >300 ng/L** **cTn (I or T) ↑ >33%** EF ↓ by 10% or more

* If baseline level of NT-proBNP > 650 ng/L

Important: prognostic value of NT-proBNP at 3 and 6 months; prognostic value of cTn only at 6 months after start of therapy

Renal Response Evaluation

	Gertz et al, 2005	Palladini et al, 2014** (at 6 months)
Response	– ≥ 50% ↓ (at least 0.5 g/day) of 24-hr urine protein* – Serum creat and creatCl must not worsen by 25% over baseline	– ≥ 30% ↓ of 24-hr urine protein or below 0.5 g/24h – No renal progression
Progression	– ≥ 50% ↑ of 24-hr urine protein to at least 1g/day – or ≥ 25% worsening of serum creat or creatCl	– ≥ 25% worsening of eGFR

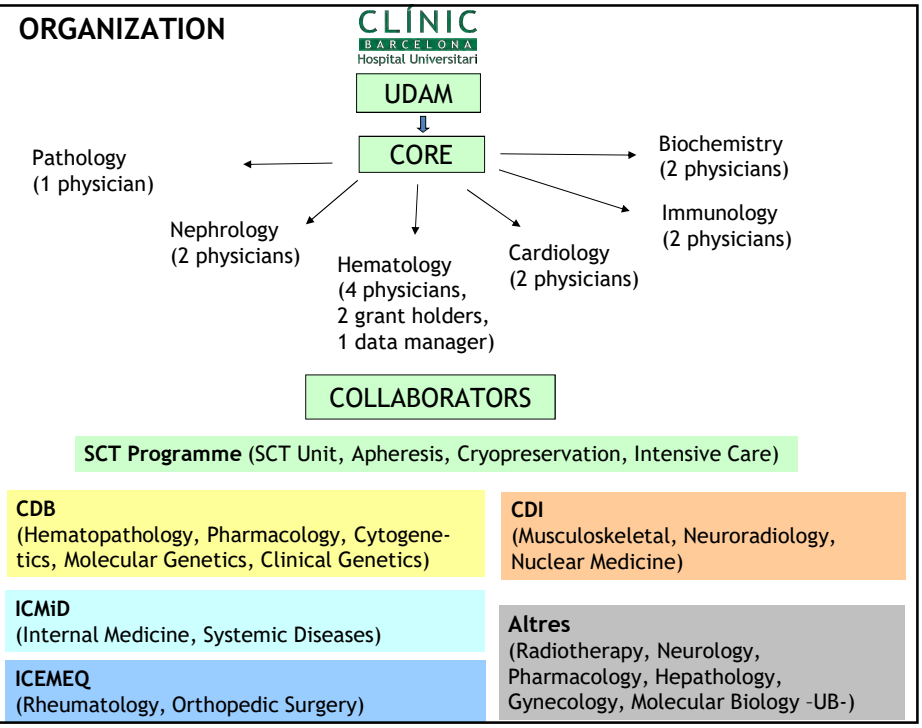
* If baseline level 24-hr urine protein > 0.5 g/day

** Palladini et al, Blood 2014;124:2325-32. N= 461 (validation cohort: 271).

Take-Home Message

- Most important: **early diagnosis**
  - ➡ early initiation of the most effective therapy

ORGANIZATION



Institute of Biomedical Research of Salamanca

University of Salamanca

Cancer Research Center

Macroglobulinemia de Waldenström

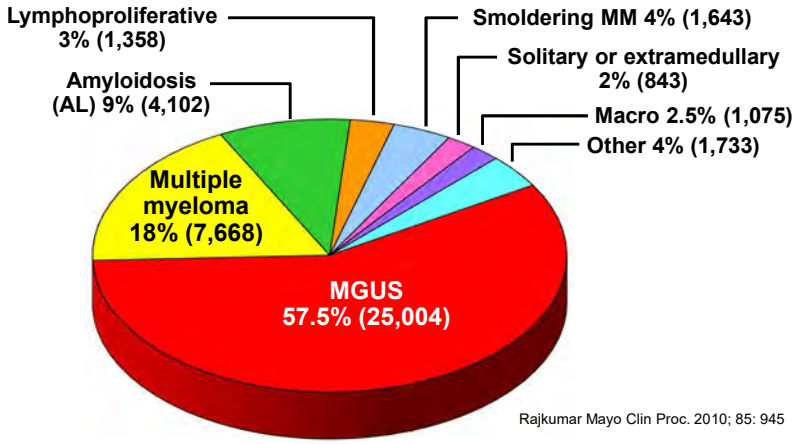
Enrique M. Ocio
University Hospital & Cancer Research Center
University of Salamanca
Spain

Gammapatías monoclonales

- Enfermedades de Células Plasmáticas
  - Variantes de Mieloma
    - Mieloma Sintomático
      - Mieloma Sintomático variante con Amiloidosis
      - Mieloma Sintomático variante con Enfermedad de Cadenas Ligeras Sistémica
    - Mieloma Indolente ("Indolent")
    - Mieloma Quiescente ("Smoldering")
    - Mieloma Osteosclerótico (Síndrome POEMS)
    - Leucemia de Células Plasmáticas
    - Mieloma no Secretor
  - Gammapatía Monoclonal de Significado Incierto (GMSI)
  - Plasmocitomas
    - Plasmocitoma Solitario del Hueso
    - Plasmocitoma Extramedular
- Otras Enfermedades Inmunosecretoras
  - Macroglobulinemia de Waldenström (Inmunocitoma)
  - Enfermedad de Cadenas Pesadas (ECP)
    - ECP gamma
    - ECP alfa
    - ECP alfa con enfermedad inmunoproliferativa del intestino delgado
    - ECP mu
  - Enfermedades de depósito de Inmunoglobulinas
    - Enfermedad de Cadenas Ligeras Sistémica
    - Amiloidosis Primaria

Distribution of monoclonal gammopathies
Mayo Clinic 1960–2007

N = 40,426



Rajkumar Mayo Clin Proc. 2010; 85: 945

Macroglobulinemia de Waldenström

Baja frecuencia
- 6% of todas la gammapatías monoclonales
- 2-5 casos/mill/año (GEM, 3'1) 2500 casos/año en Europa

Edad avanzada
- Mediana: 71. Masculino/Femenino: 2:1

Historia Natural
- Enfermedad indolente, supervivencia media: 11 años
- 1/3 muere por otras causas; 2/3 mueren de MW

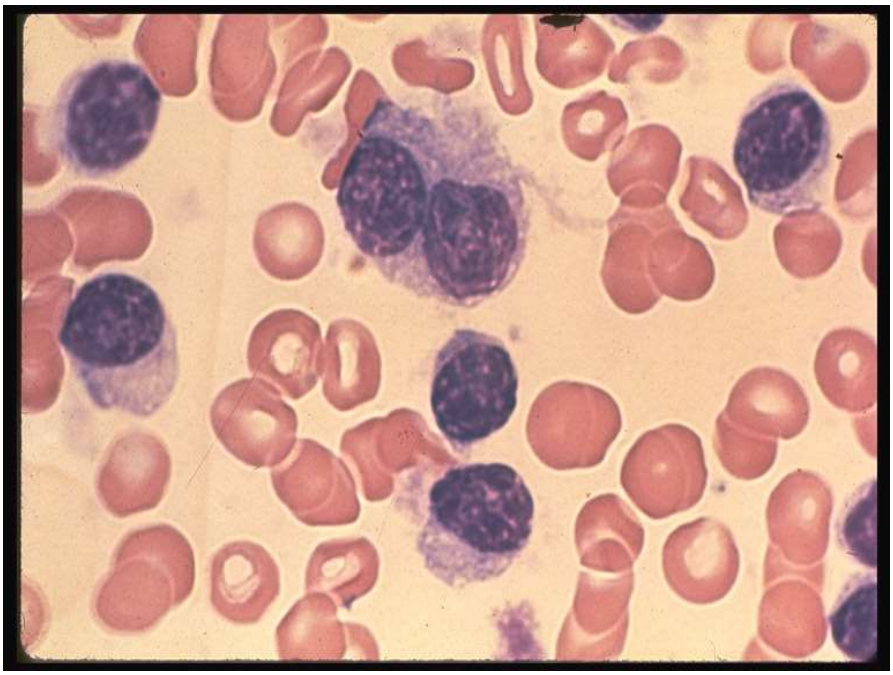
Tratamiento eficaz

Interés biológico

Definición de MW

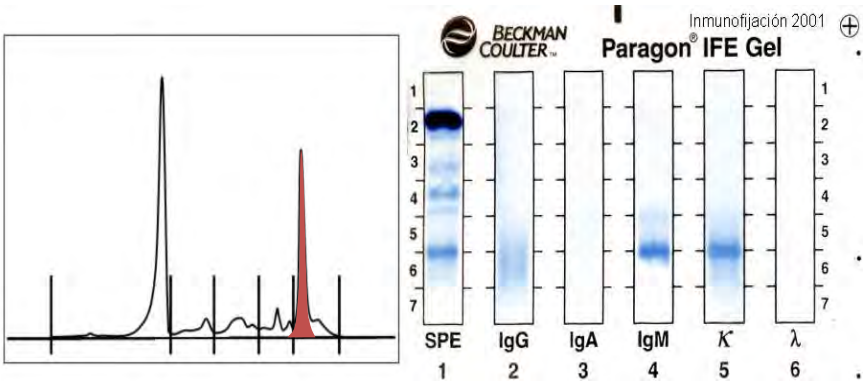
- Trastorno linfoproliferativo raro caracterizado primariamente por infiltración de médula ósea y presencia de componente monoclonal IgM.

- El trastorno patológico subyacente en la MW es el linfoma linfoplasmocítico tal y como lo define las clasificaciones OMS [(WHO) World Health Organization] y REAL (Revised European-American Lymphoma).



Protein Electrophoresis

Immunofixation



Clasificación de Gammapatías IgM

	Proteína monoclonal IgM[1]	Infiltración medular[2]	Síntomas atribuibles a la IgM	Síntomas atribuibles a infiltración[3]
MW Sintomática	+	+	+ (4)	+ (4)
MW Asintomática	+	+	–	–
Trastorno tipo IgM[5]	+	–	+	–
GMSI IgM	+	–	–	–

1) No se precisa un umbral de concentración de IgM para distinguir GMSI de MW, aunque la concentración de IgM raramente supera los 3 g/dL en la GMSI; 2) Si un paciente tiene infiltración medular inequívoca por linfoma linfoplasmocítico, tiene MW; si no hay evidencias, se considerará GMSI. Sin embargo, hay pacientes con evidencias equívocas de infiltración de MO: ej. detección de células B clonales por citometría de flujo o PCR sin evidencias morfológicas de infiltración; o infiltrados equívocos de MO sin estudios confirmatorios de clonalidad. En tanto no haya más datos, estos pacientes se clasifican como GMSI 3) Los síntomas atribuibles a infiltración tumoral incluyen: síntomas constitucionales, citopenias y organomegalias. 4) Se requiere la presencia de uno o ambos grupos de síntomas. (5) Población de pacientes que tienen síntomas atribuibles a la proteína monoclonal IgM, pero no tienen evidencias de células tumorales. Ej: crioglobulinemia sintomática, amiloidosis o fenómenos autoinmunes tales como isquemia periférica y crioaglutininemia. Estos pacientes son un grupo clínicamente distinto y se propone el término "trastornos relacionados con IgM"

Owen et al, Sem Hematol 2003, 30:110-115

BIOPSIA ÓSEA OBLIGATORIA

Essential evaluation of patients with Waldenström Macroglobulinaemia (WM)

Evaluation
- History and physical examination
- Include familial history for WM and other B-cell lymphoproliferative disorders
- Include funduscopic examination
- Review of systems

Laboratory studies
- Complete blood count
- Complete metabolic panel
- Serum immunoglobulin levels (IgA, IgG, IgM)
- Serum and urine electrophoresis with immunofixation
- Serum beta-2-microglobulin level

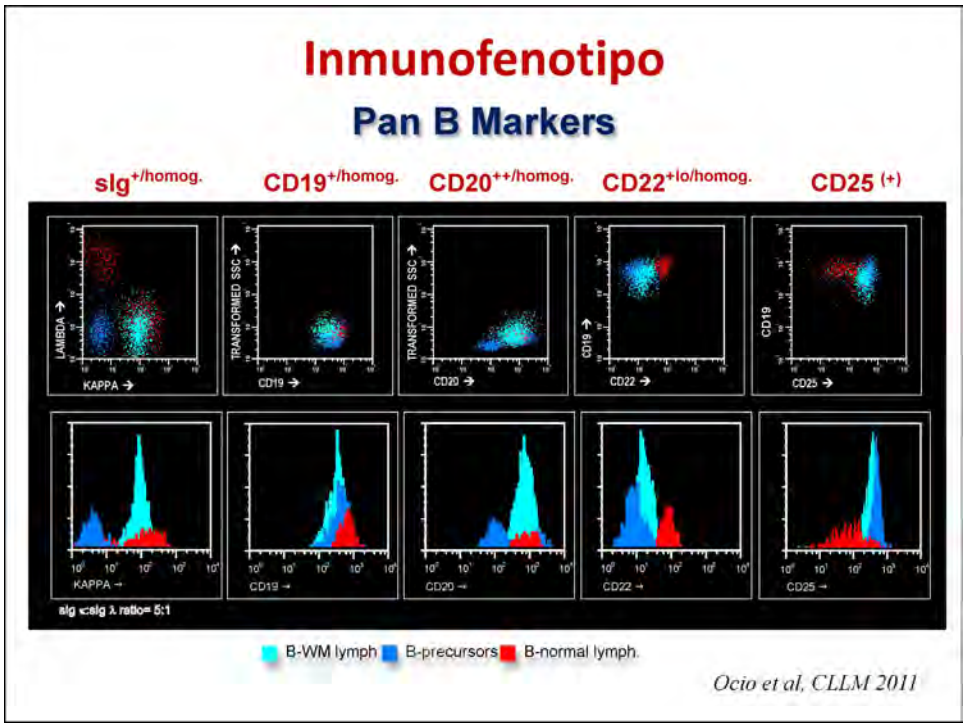
If clinically indicated
- Cryoglobulins
- Cold agglutinin titre
- Serum viscosity
- Screening for von Willebrand disease
- 24-h urine protein quantification

Bone marrow aspiration and biopsy Immunohistochemistry
- Flow cytometry
- Testing for MYD88 L265P gene mutation

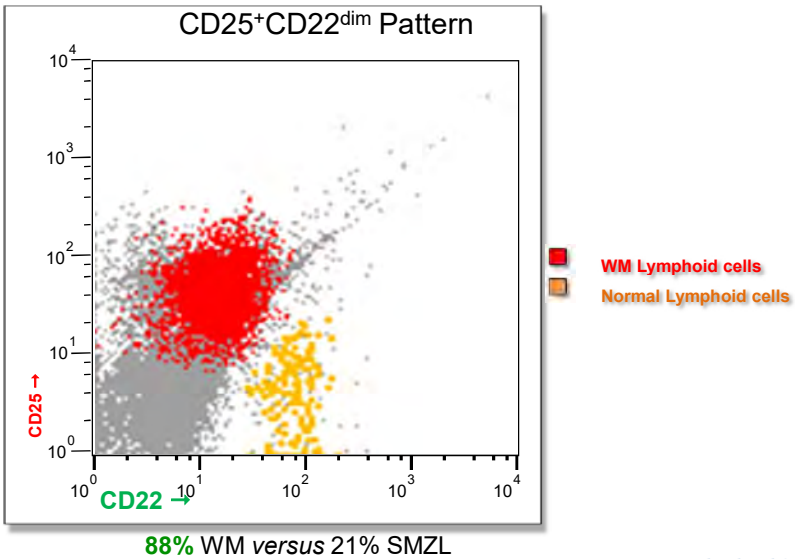
Computerized tomography scans of the chest, abdomen and pelvis with intravenous contrast
- In patients being considered for therapy

Castillo JJ, Garcia-Sanz R, E Hatjiharissi, et al. Br J Haematol 2016, 175, 77–86

Son útiles el inmunofenotipo y las alteraciones citogenéticas y/o moleculares?



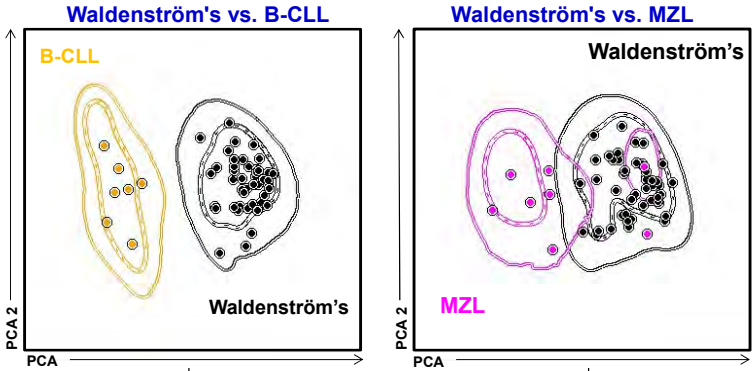
Antigenic combinations useful for differential diagnosis



88% WM *versus* 21% SMZL

Paiva et al, Blood 2015

Flow cytometry contributes to distinguish between WM and B-CLL or MZL



Parameter	Significance
LAIR1 ↓	23.64
CD79b ↑	22.44
sIgM ↑	19.07
CD27 ↓	11.22
CD5 ↓	10.49

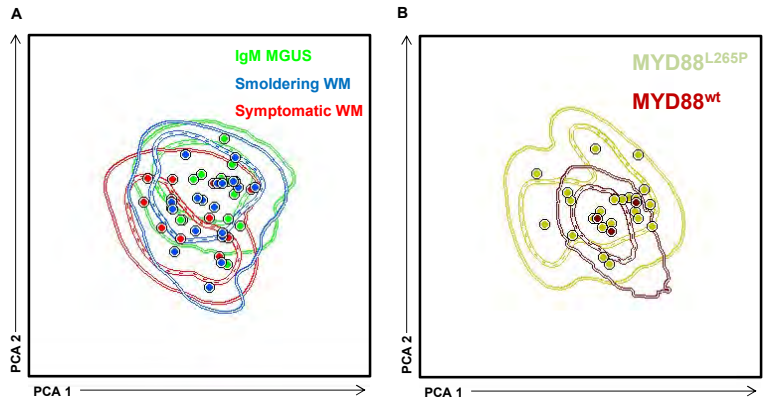
BMPCs polyclonal in B-CLL

Parameter	Significance
LAIR1 ↓	33.72
sIgM ↑	25.25
CD79b ↑	23.52
CD27 ↓	14.79
CD11c ↓	13.29

BMPCs polyclonal in MZL

Paiva et al, Blood 2015; 125:2370-80.

Waldenström's Macroglobulinemia MYD88L^{265P} and MYD88^{WT} are indistinguishable by immunophenotyping

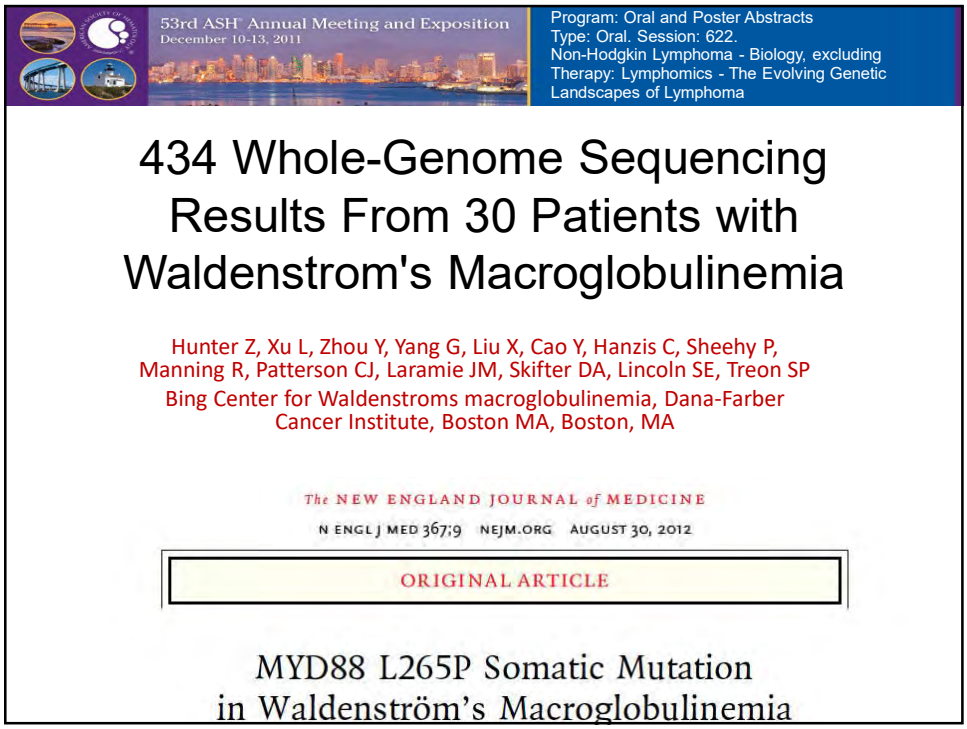


Paiva et al, Blood 2015; 125:2370-80.

Cytogenetic Abnormalities in WM

	Schop 2002	Ocio 2006	Fonseca 2006	Chang 2004	Nguyen-Khac 2010 N=132
Deletion of 6q21	42%	33%	47%	-	22%
Deletion of 13q14	16%	3%	-	9%	13%
Deletion of 17p23*	15%	7%	-	9%	8%
IgH translocations	0%	13%	2%	14%	3%
Deletion of 11q22	-	-	-	-	8%
Trisomy 4	-	-	-	-	8%
Trisomy 12	-	-	-	-	3%
Complex Karyotype (25/79)	-	-	-	-	32%
Trisomy 18	-	-	-	-	11%

** Poor prognosis*



Whole genome sequencing in WM

- Paired malignant (WM LPC) and normal (CD19-depelted PBMC) cell genomes from **10 WM** patients were sequenced
- Genome from BM LPC alone were sequenced for additional **20 WM** patients
- Results were validated by Sanger sequencing and included a cohort of WM, IgM MGUS , MM patients and healthy donors

Zachary Hunter ASH 2011, 434a

Results

Tumor and normal genomes were both sequenced to an average of 66X (range 60-91X) coverage of mapped individual reads. The average gross mapped yield for these genomes was 186.89 (range 171.56-262.03 Gb).

Acquired copy number changes were common:

- Losses: chromosome 6q (13/30; 43%),
- Gains:
  - –chromosome 4 (7/30; 23%)
  - –6p (3/30; 10%)
- Large regions of CNLOH were observed in 9/30 (30%) of patients occurring in chromosomes 1, 2, 3, 5, 9, 11, 17, 21, and X.

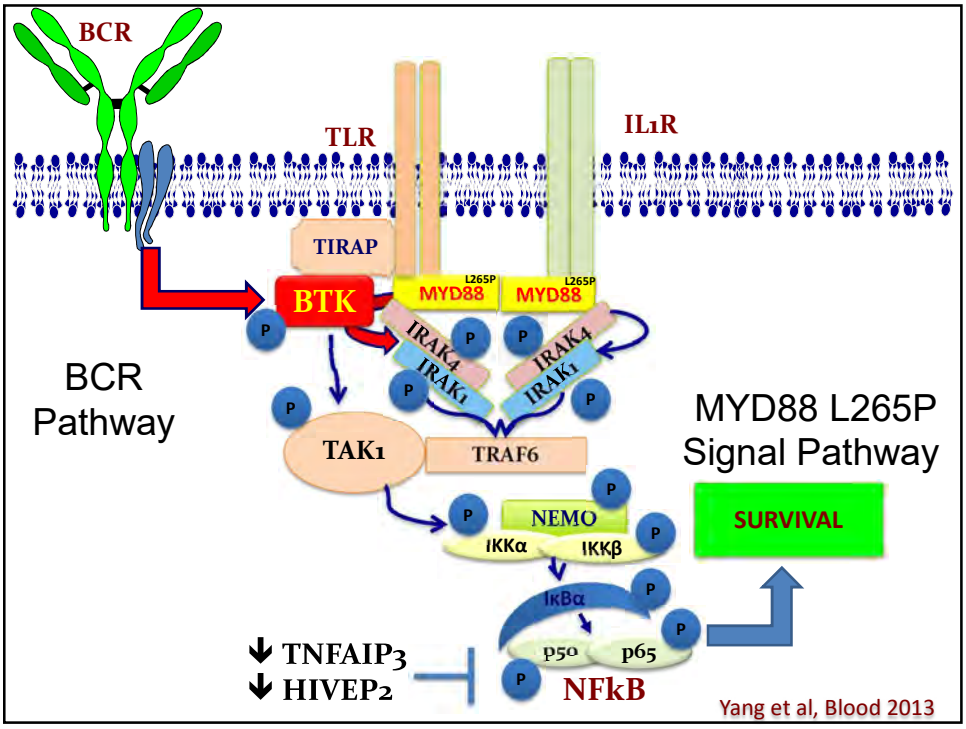
Results

Involved Gene	Frequency
Myeloid differentiation primary response (MYD88) gene (38182641 in chromosome 3p22.2): 265 leucine → proline (L265P)	26/30 (86.7%) 4/26 (15%) Homozygous, due to CNLOH
Transporter 2, ATP-binding cassette, sub-family B (TAP2) gene	7/30 (23%)
Chemokine (C-X-C motif) receptor 4 (CXCR4) gene	6/30 (20%)
Low density lipoprotein receptor-related protein 1B (LRP1B) gene	5/30 (17%)
Mesothelin (MSLN) gene	4/30 (13%)
AT rich interactive domain 1A (ARID1A)	3/30 (10%)
Histone cluster 1, H1e (HIST1H1E)	3/30 (10%)
Rap guanine nucleotide exchange factor 3 (RAPGEF3)	3/30 (10%)

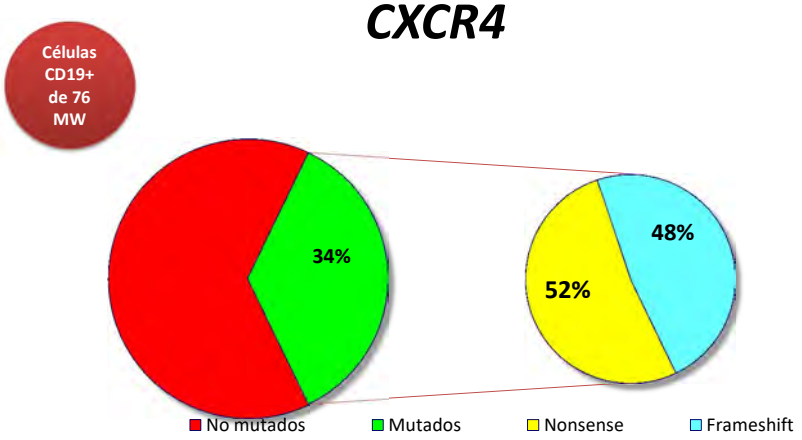
MYD88 L265P mutation in B-cell LPD

Entity	N	MYD88 L265P	
Waldenström's Macroglobulinemia	117	101	(86%)
IgM MGUS	31	27	(87%)
Non-CG Diffuse Large Cell Lymphoma	48	9	(19%)
Marginal Zone Lymphomas	14	3	(21%)
B-CLL (18 with IgM M-component)	39	0	(0%)
Hairy cell Leukemia	36	0	(0%)
Lymphoplasmocytic lymphoma	9	0	(0%)
Multiple Myeloma (3 IgM)	24	0	(0%)
MGUS IgG/IgA	25	0	(0%)
Healthy volunteers	38	0	(0%)

Jiménez et al, Leukemia 2013

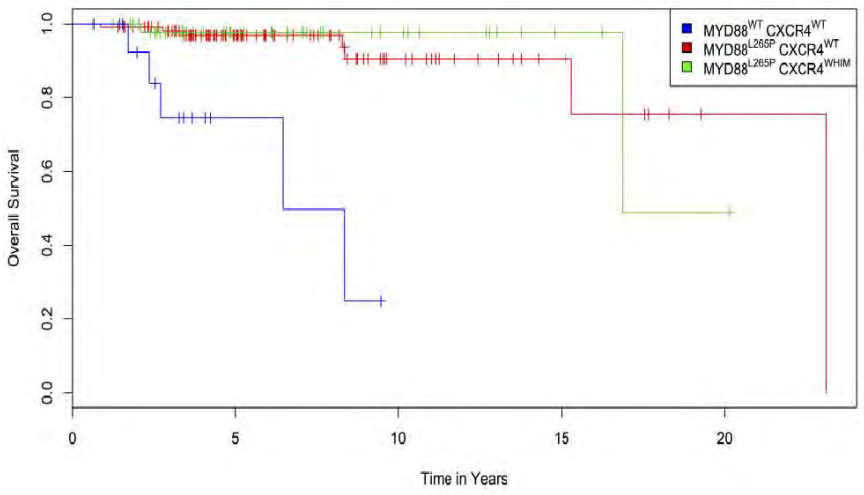


Incidencia de mutaciones de *CXCR4*



Jiménez et al, ASH 2015

Overall Survival is Inferior with MYD88^{WT} Genotype in WM



HR 10.54 (95% CI 2.40-46.2; p=0.002)

540

Existe algún índice pronóstico en MW?

Prognosis: Uni/Multivariate analyses: n=587

Characteristics	No of patients	Median survival	95%CI	p value
• Age				
≤ 65	254	141	120-153	
> 65	333	56	49-63	<0.0001
• B2M (mg/L)				
≤ 3	251	122	103-141	
> 3	326	63	55-83	<0.0001
• Hemoglobin (g/L)				
≤ 11.5	381	123	110-179	
> 11.5	205	72	62-84	<0.0001
• Platelets (109/L)				
≤ 100	54	51	32-59	
> 100	531	90	83-116	<0.0001
• Absolute neutrophil count (109/L)				
≤ 1.5	53	46	27-74	
> 1.5	512	89	80-103	0.0018
• Serum monoclonal protein (g/L)				
< 70	541	90	82-110	
> 70	43	49	37-62	0.0016
• Serum albumin (g/L)				
< 35	197	79	55-89	
> 35	354	106	92-137	0.0012

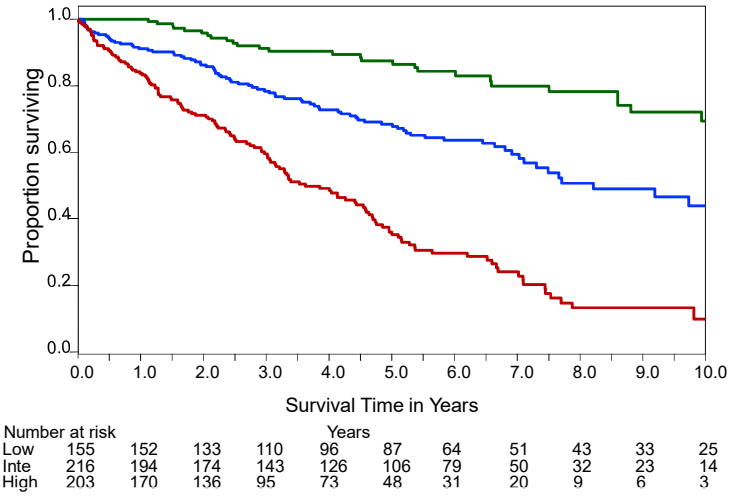
Morel et al, Blood 2009;113:4163-4170

The Prognostic Index: ISSWM

Stratum	Score	Total	Failed	Median	0.95lcl	0.95ucl
Low	0 or 1 (except age)	155 (27%)	38	142.5	120.3	195.7
Intermediate	Age>65 or 2	216 (38%)	87	98.6	81.7	137.2
High	>2	203 (35%)	134	43.5	36.6	55.1

Morel et al, Blood 2009;113:4163-4170

The Prognostic Index: ISSWM

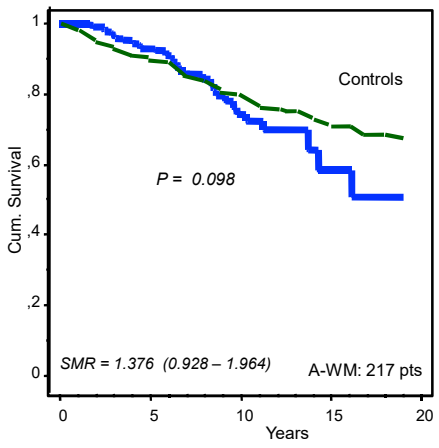


Blood 2009;113:4163-4170

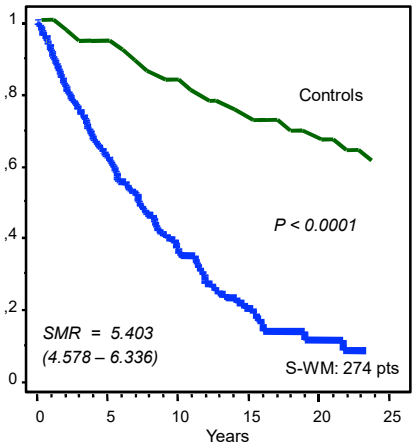
Cómo lo trato?

Supervivencia Global

MW Asintomática



MW sintomática



Morel et al, IMWG 2009

Treatment Criteria: Symptomatic disease

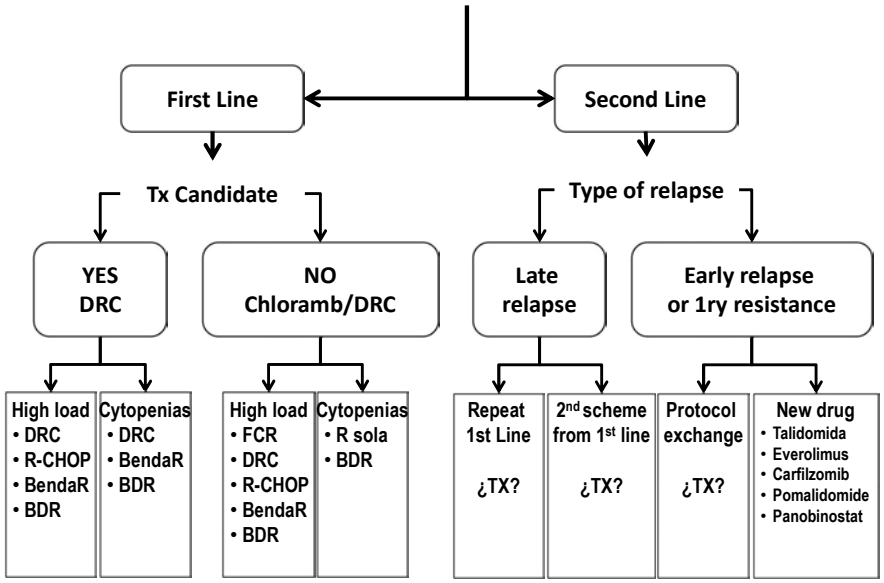
1. Recurrent fever, night sweats, weight loss, fatigue
2. Hyperviscosity
3. Lympadenopathy which is either symptomatic or bulky (≥5cm in maximum diameter)
4. Symptomatic hepatomegaly and/or splenomegaly
5. Symptomatic organomegaly and/or organ or tissue infiltration
6. Peripheral neuropathy due to WM
7. Symptomatic cryoglobulinemia
8. Cold agglutinin anemia
9. Immune hemolytic anemia and/or thrombocytopenia
10. Nephropathy related to WM
11. Amyloidosis related to WM
12. Hemoglobin ≤10g/dL
13. Platelet count $<100 \cdot 10^9$/L

Kyle et al. Semin.Oncol 2003; 30: 116-120

Therapeutic options

- ✓ Alkylators
  - Chlorambucil & prednisone
  - Chlorambucil continuous
  - Chlorambucil intermittent
  - COP
  - Melphalan & prednisona
- ✓ Polychemotherapy:
  - CHOP, M2, VAD
- ✓ Purine analogs
  - 2-Chloro-deoxi-adenosine
  - Fludarabine
  - 2-Deoxicoformicin
- ✓ Monoclonal Antibodies
  - Anti-CD20
  - Anti-CD52, Anti-CD22
- ✓ Proteasome inhibitors
  - Bortezomib
  - Cafilzomib
- ✓ IMiDs
- ✓ BTK inhibitors
- ✓ Transplant
  - Autologous
  - Alogeneic

WALDENSTRÖM MACROGLOBULINEMIA TREATMENT



Tratamiento de la macroglobulinemia de Waldenström
RESUMEN

Regimen	CR+PR	PFS	DR	OS
Alquilantes	40-70%	60 m	45 m	>5 años
Fludarabina sola	50%	40 m	45 m	>5 años
Rituximab solo	30%	46 m	72 m	>5 años
Combo Análogos purinas	85-90%	45 m		>5 años
R-CHOP	83%	62 m		>5 años
CHOP	64%	18 m		>5 años
CDR	83%	35 m		>5 años
BendaR	96%	69 m		>5 años
BDR	91%	45 m	66 m	>5 años

Comparative Outcomes Following CP-R, CVP-R, and CHOP-R in Waldenström's Macroglobulinemia

Leukothea Ioakimidis,[1] Christopher J. Patterson,[1] Zachary R. Hunter,[1] Jacob D. Soumerai,[1] Robert J. Manning,[1] Barry Turnbull,[2] Patricia Sheehy,[1] Steven P. Treon[1,3]

	N	ORR	CR	Comments
CHOP-R	23	96%	17%	Higher IgM (*P* = 0.015)
CVP-R	16	88%	12%	-
CP-R	19	95%	0%	↓ neutropenic fever and neuropathy

62 | Clinical Lymphoma & Myeloma March 2009

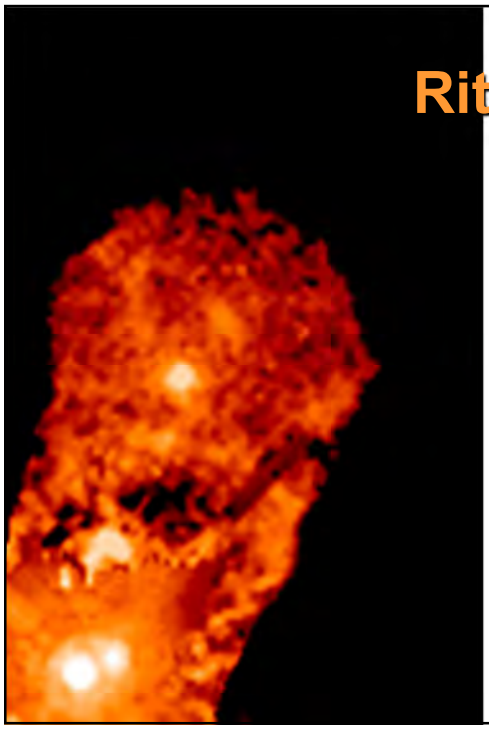
Waldenström's Macroglobulinemia Treament in Previously untreated patients

Anti-CD20

and…

1. Alkylating agents
2. Nucleoside analogues

3. Immunomodulatory agents (IMiDs)
4. Bortezomib

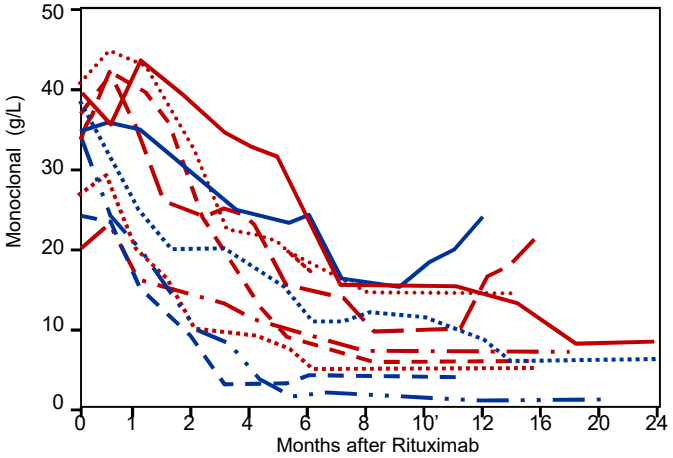


Rituximab in WM

Flare

flamme

Treatment of newly diagnosed patients with Rituximab: IgM Flare



15-30 days after treatment,
increase by ≥ 25% in 50-73%, may persist up to 4 m.
Associated with decreased response rate

Dimopoulos et al JCO, 2002,
Treon et al Ann Oncol, 2004,
Ghobrial et al Cancer 2004

DRC regimen

- Dexamethasone 20 mg IV day 1
- Rituximab 375 mg/m^2 IV day 1
- Cyclophosphamide 100 mg/m^2 PO BID days 1-5 (total dose 1000 mg/m^2)

DRC courses are repeated every 21 days for 6 courses

Dimopoulos J Clin Oncol 2007; Kastritis Blood 2016

DRC regimen

- N=72
- CR = 7%
- PR = 67%
- MR = 9%
- SD = 8%
- PD = 8%

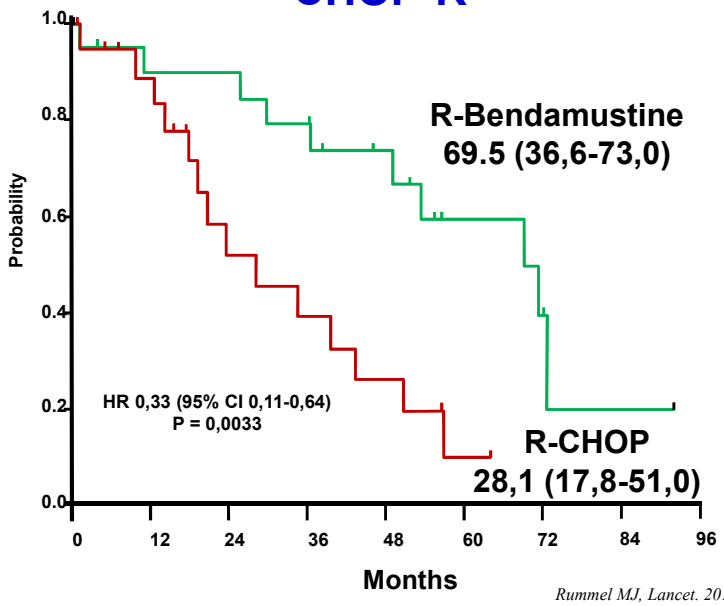
ORR = 83%

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

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

Dimopoulos J Clin Oncol 2007; Kastritis Blood 2016

Progression Free Survival for WM: B-R vs. CHOP-R

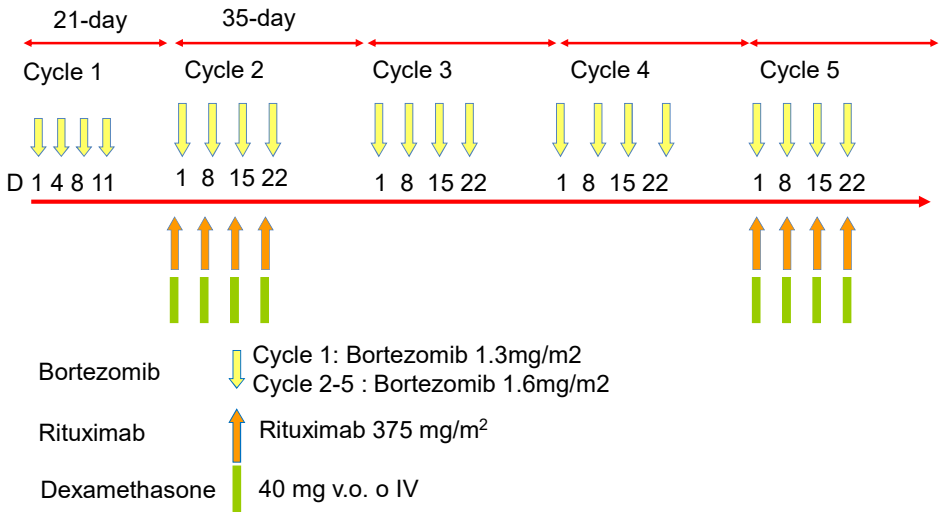


Rummel MJ, Lancet. 2013, 6736: 61763-2

Bortezomib in WM

	Autores	n	Ciclos	Asoc	RP	RAC
Tratados	**Dimopoulos et al., Haematologica 05**	10	6	No	60%	0%
	Chen et al., JCO 07	27	6	No	44%	0%
	Treon et al., CCR 07	27	6	No	48%	0%
	Ghobrial et al, JCO 10	37	6	R	87%	5%
No tratados	**Treon et al., JCO 2009***	23	6	RD	96%	22%
	Dimopoulos, Blood 2013*	59	6	RD	85%	10%

European Myeloma Network Multicenter Protocol



Dimopoulos et al Blood 2011; Gavriatopoulos et al, Blood 2016

CaRD

- Induction
  - Carfilzomib IV,
    - 20 mg/m^2, infused over 20 minutes (cycle 1 only)
    - 36 mg/m^2 infused over 30 minutes (for cycles 2 and beyond)
  - Dexamethasone IV, 20 mg, given on days 1-2 & 8-9
  - Rituximab, 375 mg/m^2, days 2 and 9

  Every 21 days for 6 cycles

- Maintenance (for stable disease or better), 8 weeks later:
  - Carfilzomib IV, 36 mg/m^2, D1 & D2
  - Dexamethasone IV, 20 mg, D1 & D2
  - Rituximab, 375 mg/m2, D2 only

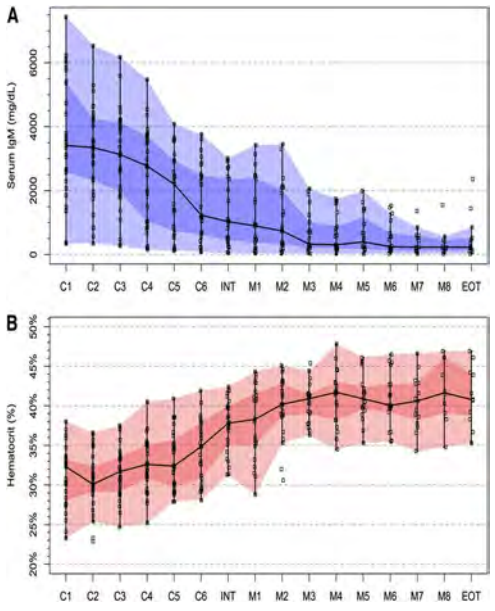
  Every 8 weeks for 8 cycles.

Treon et al, *Blood*. 2014;124:503-510)

CaRD regimen (1st-2nd line, no prior PI)

- N=31
- CR = 1
- VGPR = 10
- PR = 10
- MR = 6)
- NR = 4

ORR = 87%



PI: proteasome inhibitor; CR: complete response; VGPR: Very good partial response; Partial Response; MR: minor response; NR: no response.

Treon et al Blood 2014

CaRD, toxicitity

Table 2. Adverse events possibly, probably, or definitely associated with protocol therapy

Toxicity type	Any grade	Grade 1	Grade 2	Grade 3	Grade 4
Anemia	3 (9.7%)	0 (0%)	2 (6.5%)	1 (3.2%)	0 (0%)
Arthralgia	3 (9.7%)	3 (9.7%)	0 (0%)	0 (0%)	0 (0%)
Azotemia	3 (9.7%)	1 (3.2%)	2 (6.5%)	0 (0%)	0 (0%)
Cardiomyopathy	1 (3.2%)	0 (0%)	0 (0%)	1 (3.2%)	0 (0%)
Chest pain (non-cardiac)	1 (3.2%)	0 (0%)	1 (3.2%)	0 (0%)	0 (0%)
Dyspepsia	1 (3.2%)	1 (3.2%)	0 (0%)	0 (0%)	0 (0%)
Fatigue	2 (6.5%)	1 (3.2%)	1 (3.2%)	0 (0%)	0 (0%)
Hyperglycemia	31 (100%)	7 (22.6%)	17 (54.8%)	7 (22.6%)	0 (0%)
Hyperamylasemia	8 (25.8%)	7 (22.6%)	1 (3.2%)	0 (0%)	0 (0%)
Hyperbilirubinemia	9 (29.0%)	7 (22.6%)	2 (6.5%)	0 (0%)	0 (0%)
Hyperkalemia	1 (3.2%)	1 (3.2%)	0 (0%)	0 (0%)	0 (0%)
Hyperlipasemia	17 (54.8%)	4 (12.9%)	8 (25.8%)	5 (16.1%)	0 (0%)
Hypokalemia	1 (3.2%)	1 (3.2%)	0 (0%)	0 (0%)	0 (0%)
Insomnia	2 (6.5%)	1 (3.2%)	1 (3.2%)	0 (0%)	0 (0%)
Infusion reaction (rituximab)	7 (22.6%)	1 (3.2%)	6 (19.4%)	0 (0%)	0 (0%)
Mucositis	2 (3.2%)	2 (3.2%)	0 (0%)	0 (0%)	0 (0%)
Neutropenia	11 (34.8%)	7 (22.6%)	1 (3.2%)	2 (6.5%)	1 (3.2%)
Peripheral neuropathy	6 (19.4%)	5 (16.1%)	1 (3.2%)	0 (0%)	0 (0%)
Rash	9 (29.0%)	6 (19.4%)	3 (9.7%)	0 (0%)	0 (0%)

2956 Ixazomib, Dexamethasone and Rituximab in previously untreated patients with Waldenstrom Macroglobulinemia (Castillo JJ)

Phase II

Induction: six 4-week cycles

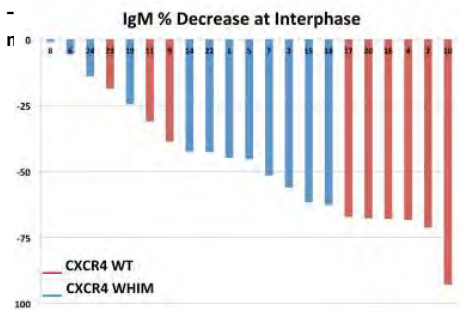
Ixazomib 4 mg 1, 8 , 15
Dexamethasone 20 mg 1,8,15
Rituximab 375 mg/m2 IV 1

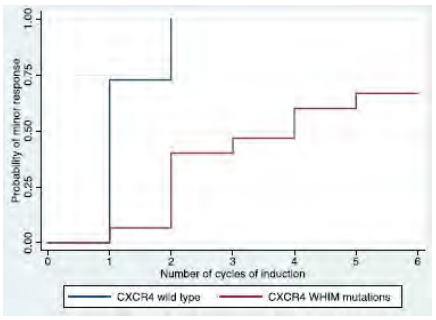
Maintenance: Six 8-week cycles

Characteristic	Patients (N=26)
Age at WM diagnosis – yr	63 (46-81)
Age of treatment initiation – yr	65 (46-82)
Hemoglobin – g/dL	10.2 (6.9-13.2)
Serum IgM – mg/dL	5,068 (653-7,650)
Bone marrow involvement - %	55 (5-95)
Lymphadenopathy – no. (%)	46 (12)
Splenomegaly	12 (3)
MYD88 L265P	100 (26)
CXCR4 WHIM	58 (15)
Nonsense	67 (10)
Frameshift	33 (5)
Criteria for treatment initiation – no. (%)	13 (48.1)
Anemia	1 (3.8)
Symptomatic splenomegaly	7 (27)
Hyperviscosity	4 (15.4)
Peripheral neuropathy	5 (19.2)
Constitutional symptoms	1 (3.8)
IgM >6,000 mg/dL	1 (3.8)
Pancytopenia	

2956 Ixazomib, Dexamethasone and Rituximab in previously untreated patients with Waldenstrom Macroglobulinemia (Castillo JJ)

Results: (of the 16 patients completed induction)
-Median Time To Response : 8 weeks
-ORR : 80% (VGPR 5%, PR 45%, MR 30%)
-The median time to Minor Response in CXCR4mut was 4 cycles vs 1 cycle en CXCR4wt
-Major response (VGPR+PR) were observed in 40% CXCR4mut patients vs 55% CXCR4wt

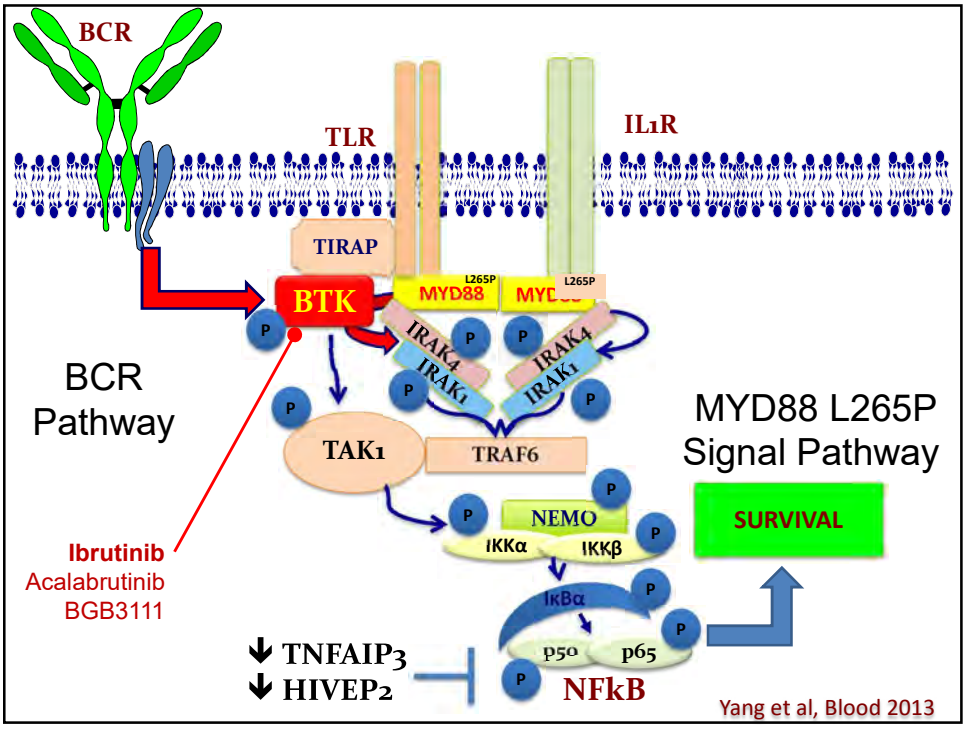




Conclusion: IDR active,well tolerated, no PN. CXCR4 mutation affect time /dept of response

Waldenström's Macroglobulinemia Treatment in Previously treated patients

- **"Late" Relapses after initial response (>12 months)**
  - Same prior line or another 1st line protocol
- **"Early" relapses after initial response, and primary or secondary relpases:**
  - Switch for another first line
  - "Conventional" Lymphoma strategy:
    - Polychemotherapy (plus R): CHOP, CAP, VBCMP y VAD
    - Trasplant: Auto or Alo
  - New therapies ("experimental"):
    - Bortezomib, IMiDs, Alemtuzumab, Bendamustine...
    - Everolimus
    - Carfilzomib
    - Pomalidomide
    - Panobinostat



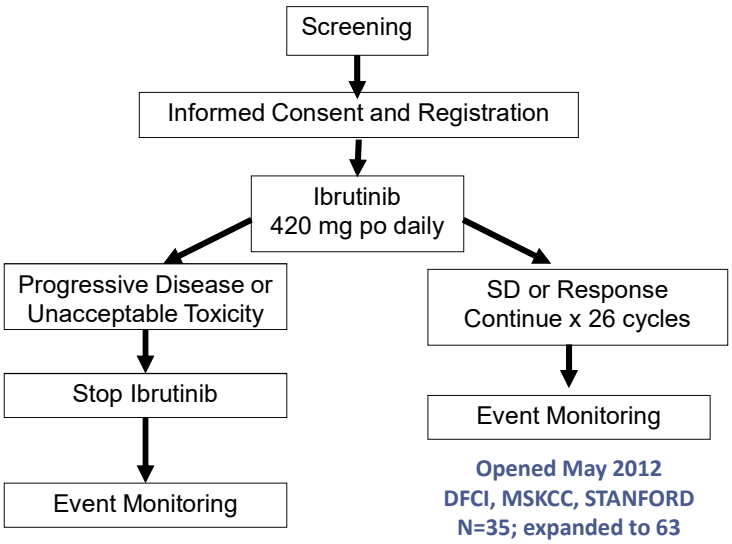
Ibrutinib in Previously Treated Waldenstrom's Macroglobulinemia

Steven P. Treon, Christina Tripsas, Kirsten, Diane, Guarav Varma, Rebecca Green, Kimon Argyropoulos, Guang Yang, Yang Cao, Lian Xu, Christopher J. Patterson, Scott Rodig, James L. Zehnder, Jon C. Aster, Nancy Lee Harris, Sandra Kanan, Irene Ghobrial, Jorge Castillo, Jacob Laubach, Zachary R. Hunter, M. Lia Palomba, and Ranjana Advani.

Dana-Farber Cancer Institute
Memorial Sloan-Kettering Cancer Center
Stanford University Medical Center

Treon et al NEJM, 2015

Phase II Study of Ibrutinib in Relapsed or Refractory WM

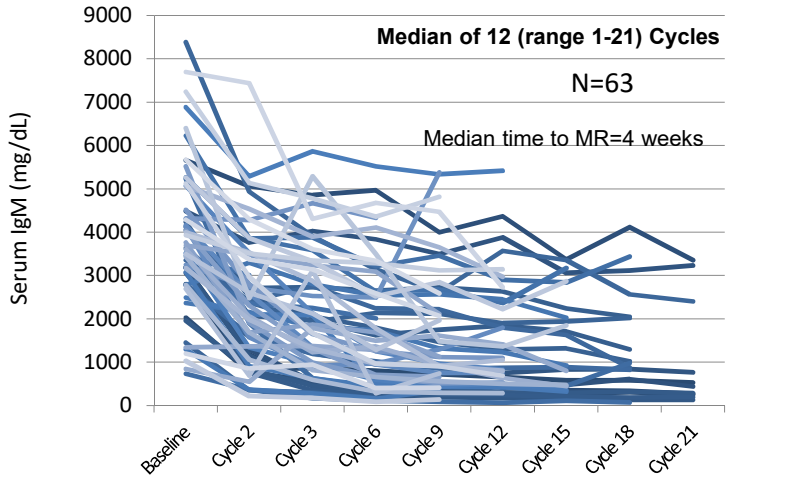


Baseline Characteristics for Study Participants (n=63)

Characteristic	Median	Range
Age (yrs)	63	44-86
Male/Female	48/15	N/A
Prior therapies	2	1-8
Hemoglobin (mg/dL)	10.5	8.2-13.8
Platelet (k/uL)	214	24-459
Serum IgM (mg/dL)	3,610	735-8,390
B_2M (mg/dL)	3.9	1.3-14.2
BM Involvement (%)	70	3-95
Adenopathy >1.5 cm	37 (58.7%)	N/A
Splenomegaly >15 cm	7 (11.1%)	N/A

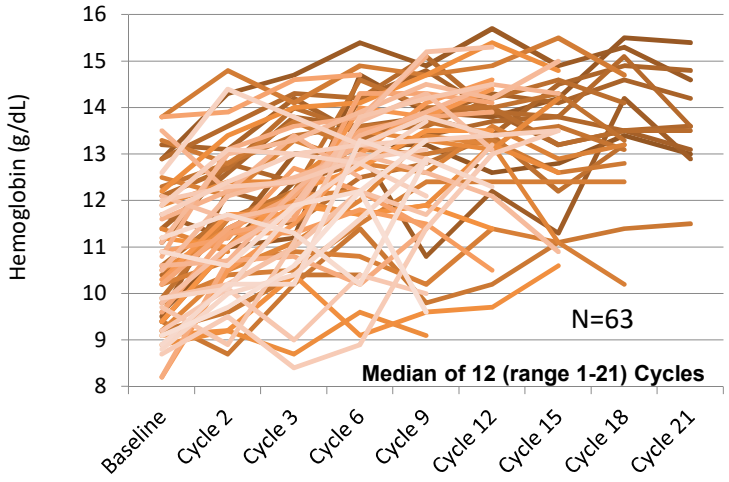
Serial Serum IgM Levels Following Ibrutinib

Best IgM Response: 3,610 to 915 mg/dL; p<0.0001



Serial Hemoglobin Levels Following Ibrutinib

Best Hemoglobin Response: 10.5 to 13.5; p<0.0001



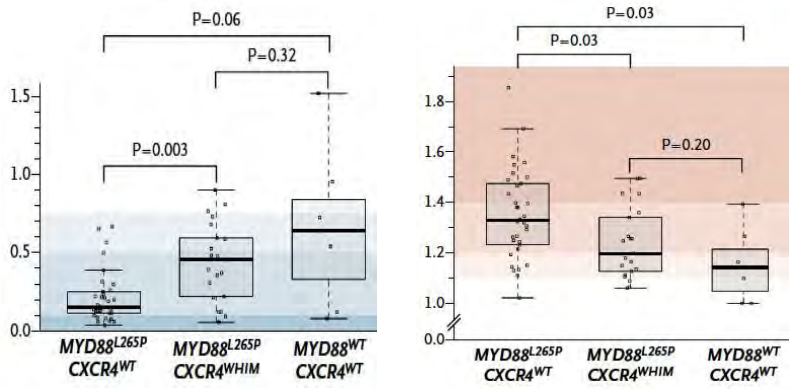
Best Clinical Responses to Ibrutinib

Median of 12 (range 1-21) Cycles

	(N=63)	(%)
VGPR	9	14
PR	34	54
MR	12	19
SD	7	11
Non-Responder	1	2

ORR: 87% Major RR (≥PR): 68%

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



573

Responses to ibrutinib are impacted by MYD88 (L265P and non-L265P) and CXCR4 mutations.

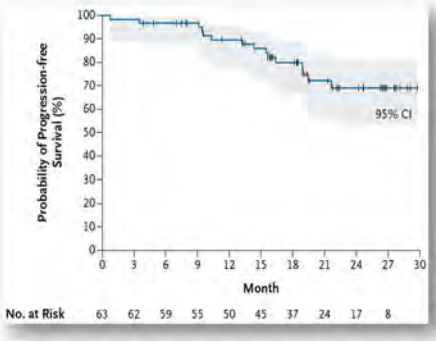
	MYD88^{MUT} CXCR4^{WT}	MYD88^{MUT} CXCR4^{WHIM}	MYD88^{WT} CXCR4^{WT}	p-value
N=	36	21	5	
Overall RR	100%	85.7%	60%	<0.01
Major RR	91.7%	61.9%	0%	<0.01

2 patients subsequently found to have other MYD88 mutations not picked up by AS-PCR

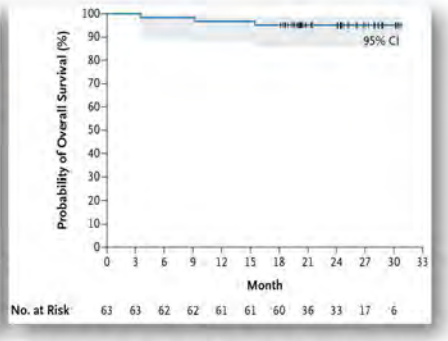
Treon et al, N Engl J Med. 2015; 372(15):1430-40; NEJM 2015; Letter, August 6, 2015.

Progression-free and overall survival for 63 previously WM patients treated with ibrutinib.

PFS



OS



Treon et al, N Engl J Med. 2015; 372(15):1430-40.

Ibrutinib Related Adverse Events

	Grade 2	Grade 3	Grade 4	Total Grade 2-4
Blood and lymphatic system disorders				
Anemia	9 (14.3%)	3 (4.8%)	0 (0%)	12 (19.0%)
Neutropenia ★	5 (7.9%)	6 (9.5%)	5 (7.9%)	16 (25.4%)
Thrombocytopenia ★	2 (3.2%)	5 (7.9%)	2 (3.2%)	9 (14.3%)
Cardiac disorders				
Atrial fibrillation ★	2 (3.2%)	1 (1.6%)	0 (0%)	3 (4.8%)
Sinus tachycardia	1 (1.6%)	0 (0%)	0 (0%)	1 (1.6%)
Gastrointestinal disorders				
Diarrhea	3 (4.8%)	0 (0%)	0 (0%)	3 (4.8%)
Gastroesophageal reflux disease	1 (1.6%)	0 (0%)	0 (0%)	1 (1.6%)
Mucositis oral	2 (3.2%)	0 (0%)	0 (0%)	2 (3.2%)
Infections and infestations				
Febrile neutropenia	0 (0%)	0 (0%)	1 (1.6%)	1 (1.6%)
Endocarditis infective	0 (0%)	1 (1.6%)	0 (0%)	1 (1.6%)
Lung infection	4 (6.3%)	0 (0%)	0 (0%)	4 (6.3%)
Sinusitis	1 (1.6%)	0 (0%)	0 (0%)	1 (1.6%)
Skin infection	3 (4.8%)	1 (1.6%)	0 (0%)	4 (6.3%)
Urinary tract infection	1 (1.6%)	0 (0%)	0 (0%)	1 (1.6%)
Injury, poisoning and procedural complications				
Postoperative hemorrhage ★	1 (1.6%)	0 (0%)	0 (0%)	1 (1.6%)
Metabolism and nutrition disorders				
Dehydration	2 (3.2%)	0 (0%)	0 (0%)	2 (3.2%)
Musculoskeletal and connective tissue disorders				
Arthralgia	1 (1.6%)	0 (0%)	0 (0%)	1 (1.6%)
Nervous system disorders				
Presyncope	1 (1.6%)	0 (0%)	0 (0%)	1 (1.6%)
Syncope	0 (0%)	1 (1.6%)	0 (0%)	1 (1.6%)
Respiratory, thoracic and mediastinal				
Epistaxis ★	2 (3.2%)	0 (0%)	0 (0%)	2 (3.2%)
Cough	1 (1.6%)	0 (0%)	0 (0%)	1 (1.6%)
Skin and subcutaneous tissue disorders				
Pruritus	1 (1.6%)	0 (0%)	0 (0%)	1 (1.6%)
Folliculitis	1 (1.6%)	0 (0%)	0 (0%)	1 (1.6%)
Rash	1 (1.6%)	0 (0%)	0 (0%)	1 (1.6%)
Skin Peeling	1 (1.6%)	0 (0%)	0 (0%)	1 (1.6%)
Vascular disorders				
Hematoma ★	0 (0%)	1 (1.6%)	0 (0%)	1 (1.6%)
Hypertension	2 (3.2%)	0 (0%)	0 (0%)	2 (3.2%)
Hypotension	1 (1.6%)	0 (0%)	0 (0%)	1 (1.6%)

Data Lock February 28, 2014

★ More common in pts ≥ 2 prior therapies [576]

Single-Agent Ibrutinib in Rituximab-Refractory Patients with Waldenström's Macroglobulinemia: Results From a Multicenter, Open-Label Phase 3 Substudy (iNNOVATE™)

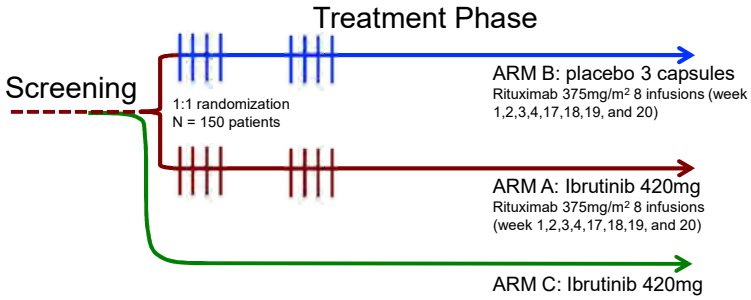
Dimopoulos, MA, Trotman J, Tedeschi A, Matous JV, Macdonald D, Tam C, Tournilhac O, Ma S, Oriol A, Heffner LT, Shustik C, García-Sanz R, Cornell RF, Fernández de Larrea C, Castillo JJ, Granell M, Kyrtsonis MC, Leblond V, Symeonidis A, Kastritis E, Singh P, Li J, Graef T, Bilotti E, Treon S, Buske C, on behalf of the iNNOVATE™ Study Group and the European Consortium for Waldenström's Macroglobulinemia (ECWM).

Dimopoulos Lancet Oncol. 2017 Feb;18(2):241-250

Innovate: Study design

Randomization will be stratified using the following stratification:

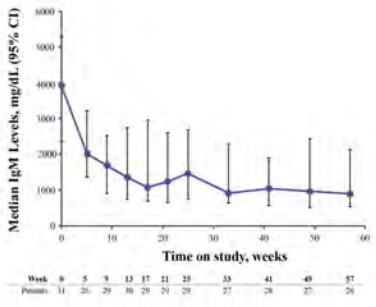
a) WM IPSS assessed at Screening (Low vs. Intermediate vs. High)
b) Number of prior systemic treatment regimens (0, 1-2 vs. ≥3)
c) ECOG status (ECOG 0-1 vs. 2)

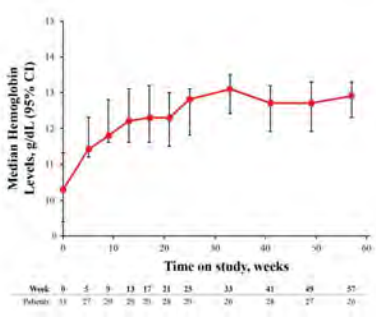


ARM C: To allow treatment of subjects considered refractory to prior Rituximab

Dimopoulos et al EHA, 2015

iNNOVATE (Arm C): Response to therapy

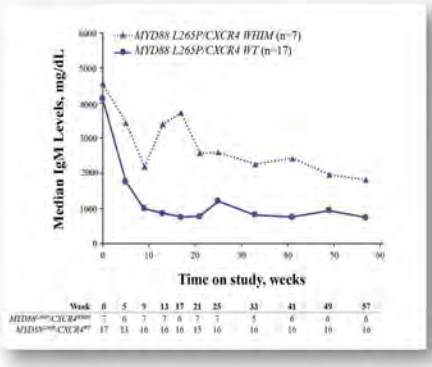


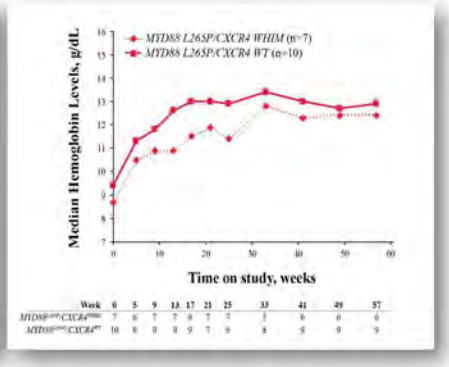


Best Response	All* (N=31)	MYD88^{L265P}/CXCR4^{WT†} (n=17)	MYD88^{L265P}/CXCR4^{WHIM} (n=7)
VGPR	4	3	0
PR	18	11	5
MR	6	1	2
ORR§, n (%)	28 (90)	15 (88)	7 (100)
MRR**, n (%)	22 (71)	14 (82)	5 (71)
18-month PFS, %	86	94	86
18-months OS, %	97	100	100

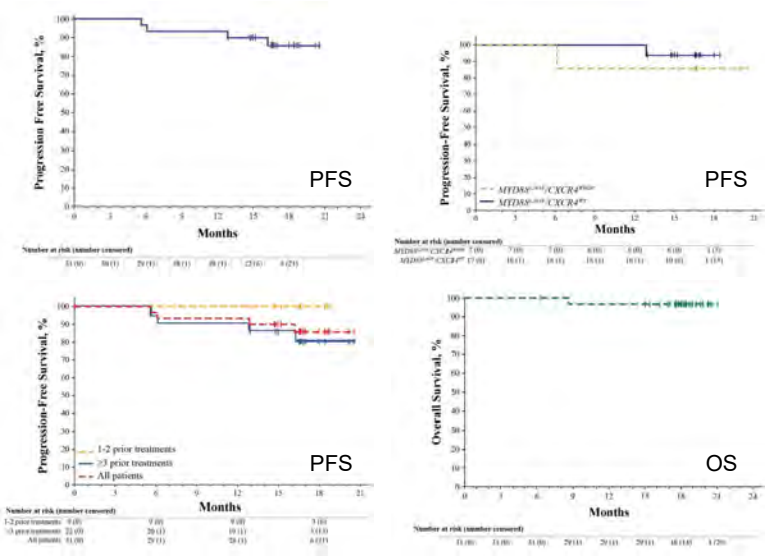
iNNOVATE (Arm C)

Response to therapy according to mutational status

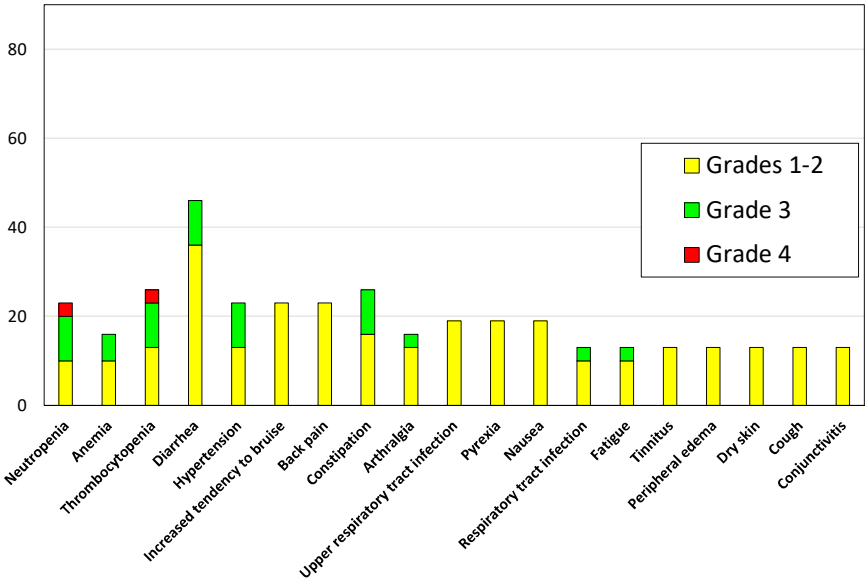




iNNOVATE (Arm C): Survival



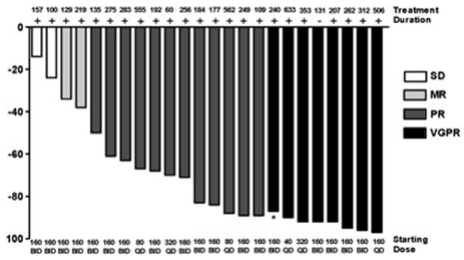
iNNOVATE (Arm C): Toxicity



ASH2016: #1216 High Major response Rate, Including VGPR, in Patients with Waldenstrom Macroglobulinemia (WM) treated with the Highly Specific BTK inhibitor Bgb-3111:Expansion Phase Results from ongoing Phase I Study (Tam CS)

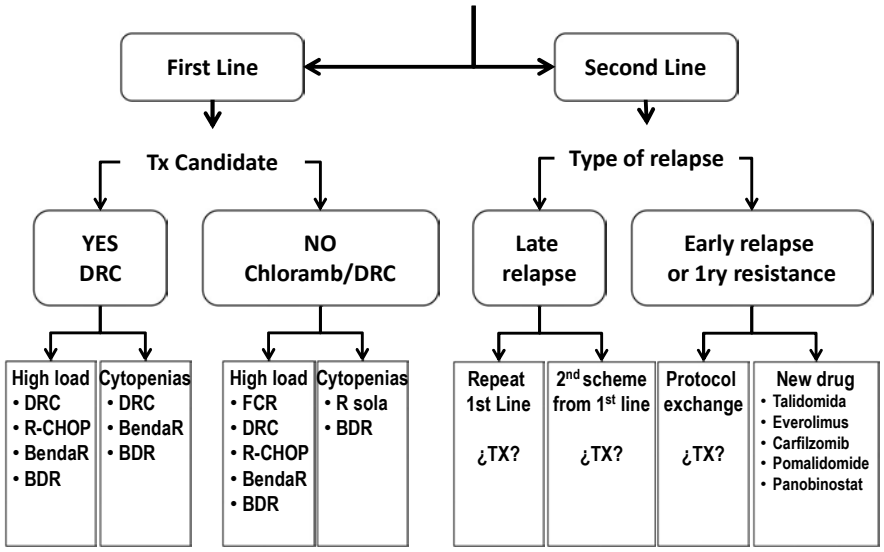
Introduction: BGB-3111 irreversible BTK inhibitor with greater selectivity and superior bioavailability
Phase I (6 ptes) 40,80,160,320 mg and **Phase 2** (25 ptes) 160, 320 mg; **24 evaluable for response**
Major Response 83% (**VGPR 33%,** PR 50%)
AE´s (1/2). Respiratory infection 25%, diarrhea 25% and nausea 21%

Age (median, range)	66 (49-79)
ECOG PS	
0	7
1	17
2	0
Number of prior therapies (n)	
0	1
1-3	21
>3	2
Types of prior therapy (n, %)	
Rituximab	21 (88%)
Alkylating agents	20 (83%)
Corticosteroids	17 (71%)
Fludarabine	7 (29%)
ASCT	2 (8%)
Refractory to prior therapy* (n, %)	13 (54%)

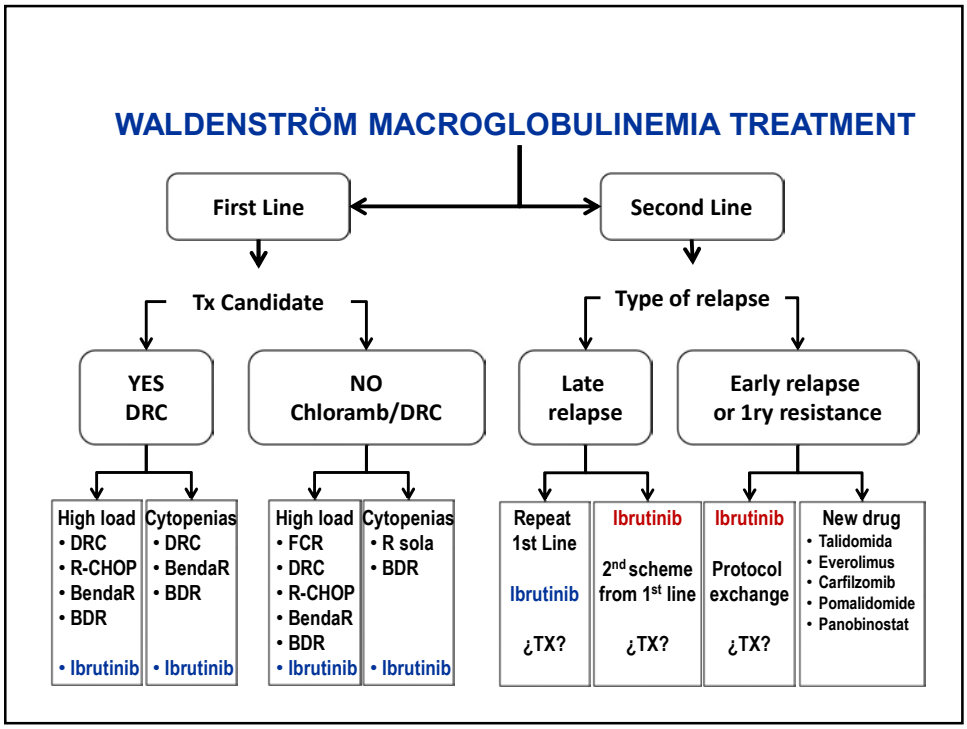


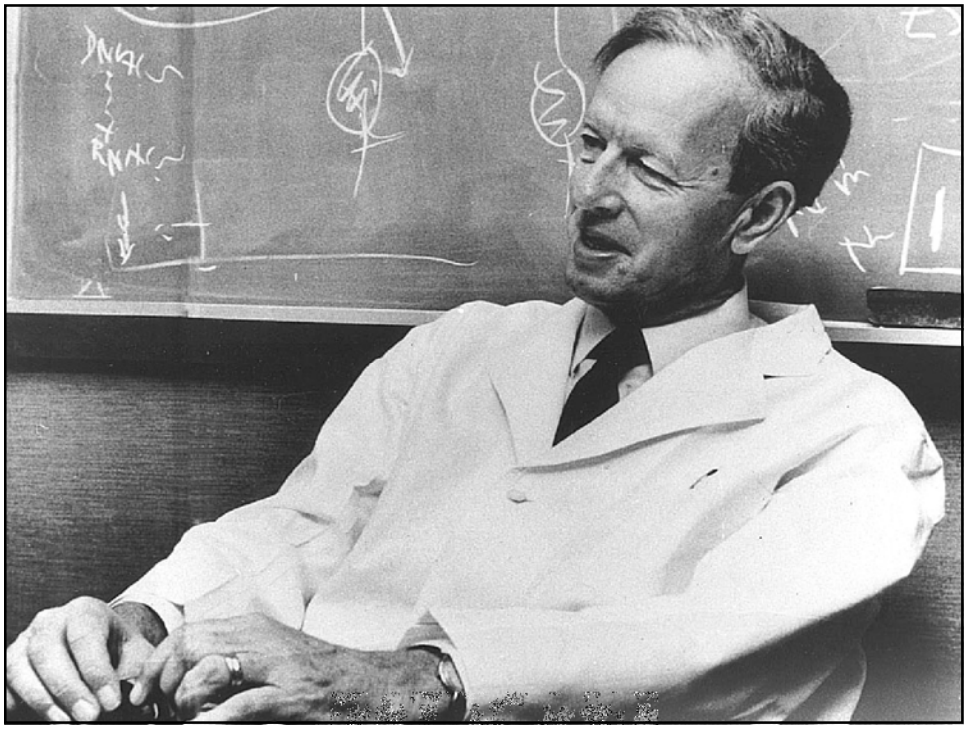
Conclusions: BGB-3111 is well tolerated and highly active in WM. Te depth and quality of response, warrant a randomized comparison against Ibrutinib

WALDENSTRÖM MACROGLOBULINEMIA TREATMENT



WALDENSTRÖM MACROGLOBULINEMIA TREATMENT





TREATMENT OF DISEASE COMPLICATIONS

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disclosures

- Research funding from the following:
  - Abbvie, Amgen, Bluebird, BMS, Celgene, Janssen, Novartis, Takeda, Teva

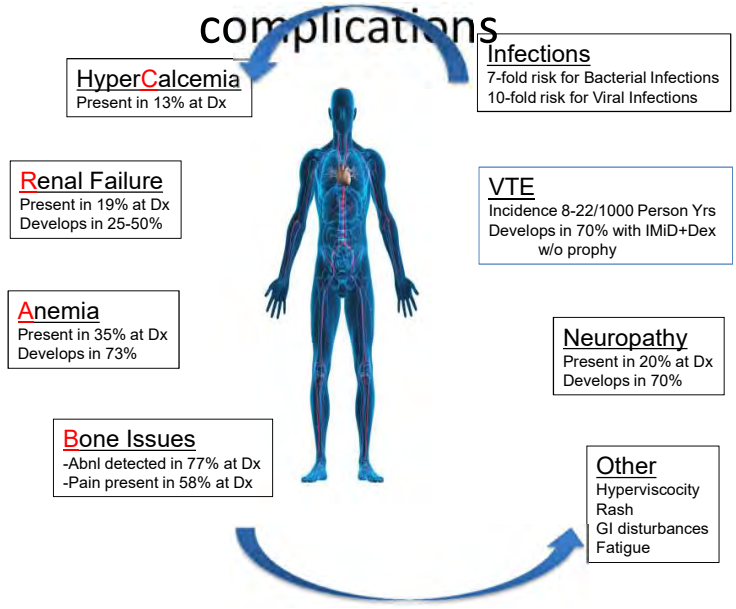
AIMS

- Identify complications due to MM and its treatments
- Review standard recommendations for prevention of complications
- Recommended management of complications related to MM itself
- Review standard recommendations for management of treatment-related complications

Case: Presentation

- A 69-yr-old man presents with low back pain, fatigue
- Physical examination: T 36.4˚, BP 186/79 mm Hg, P 75/min, R 20/min
- Laboratory assessments
  - Hb 9.6 g/dL
  - Serum creatinine 2.35 mg/dL
  - Calcium 11.9 mg/dL
  - IgG 3800 mg/dL, IgA 43 mg/dL, IgM 9 mg/dL
  - SPEP – 3gm/dL abnormal protein, IFE IgGk
  - SFKLC 200 mg/dL
  - β_2-microglobulin 6.9 mg/L
  - Albumin 3.2 g/dL
  - LDH 200 nl
- Skeletal survey: small lytic lesions spine and pelvis, compression fracture at T12
- Bone marrow biopsy: 70% k-restricted plasma cells

MM-Related and/or treatment-related complications

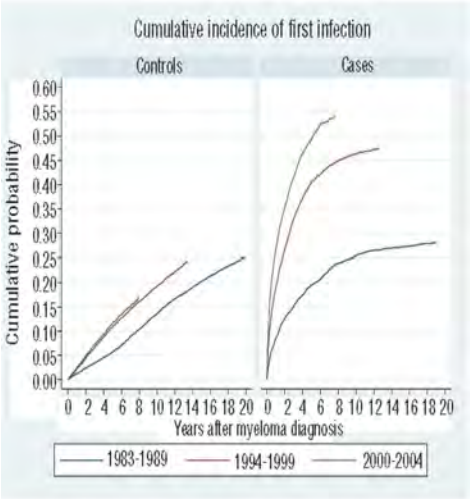


Immunosuppression in mm

- MM leads to multifactorial humoral and cellular immune dysfunction
- Anti-myeloma therapy is immunosuppressive
  - PIs can suppress T cell function
    - Grade 3 /4 infections in 35% of newly dx pts reported in VRD arm in SWOG S0777 trial
  - Lenalidomide and pomalidomide can cause neutropenia in >25% patients
    - Grade 3 /4 infections in 29% newly dx pts on len/dex reported by FIRST trial
  - Dexamethasone is pan-immmunosuppressive
- Pts often are elderly and have comorbidities that further increase risk

Tete et al. Front Immunol 2014. Dhodapkar et al. Lancet 2007. Benboubker et al. NEJM 2014. Dimopoulos et al. NEJM 2007. San Miguel et al. Lancet Oncol 2013. Rajkumar et al. Lancet Oncol 2010. Yee et al. ERJ-M 2016. Berges et al. Immunology 2008

Population-Based Swedish Study:
Cumulative incidence of first infection over time in myeloma patients and their matched controls.



Take home points:
-7-fold risk of bacterial infection
-10-fold risk of viral infection
-Infectious risk greatest during 1st yr dx
-Infections account for 20% early mortality
highest risk first 2-4 mos of treatment

-Bacterial infections predominate during the first weeks of initial therapy
-Viral infections, often due to reactivation and most common during PI/Dex treatment

Cecilie Blimark et al. Haematologica 2015;100:107-113

recommendations

- Infection prophylaxis
  - Pts should remain up to date on appropriate vaccinations
    - Yearly influenza recommended
    - Pneumovax recommended though unclear benefit but if done should be done at time of best disease control
    - Live vaccines should be avoided
  - VZV prophylaxis when receiving PIs, monoclonal abs, during ASCT recovery period is recommended with acyclovir or similar agents
  - Antibacterial prophylaxis with mixed results
    - Not routinely recommended
    - Consider in high risk patients at initial dx 2-3 mos
    - Consider with lenalidomide/pomalidomide therapy during 1st 3 mos
  - Use of IVIG is controversial
    - Consider in pts with hypogammaglobunemia and recurrent infections
  - Consider use of G-CSF in treatment induced neutropenia or neutropenic fever

Terpos et al: Haematologica 2015. Anderson et al: J Natl Compr Cancer Netw 2016. Chanan-Khan et al: JCO 2008. Lonial et al: NEJM 2015. Oken et al: Am J Med 1996. Vesole et al: Leukemia 2012. Chapel et al: Lancet 1994. Musto et al: BJH 1995. Aapro et al: EurJCan 2011.

Bone disease: scope of problem

- Osteolytic bone disease is present in up to 80% of pts at dx
- Increased osteoclast activity leads to skeletal-related events (SREs)
  - Vertebral CF
  - Other pathologic fractures
  - Spinal Cord Compression

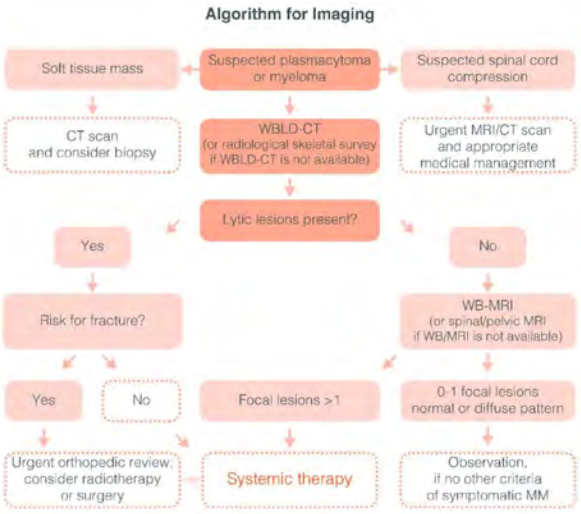
Terpos et al: Ann Oncol 2005. Kyle et al: Mayo Clin Proc 2003.

imaging

- Skeletal Survey (WBXR)
  - Current standard technique for detection of lytic lesions, widely available
- WBLD-CT
  - More sensitive and accurate than WBXR and easy to perform where available
  - Used more and more in parts of the world as a replacement for WBXR
- WB-MRI
  - now indicated as part of the definition of active MM
    - >1 focal lesion by MRI is a MM-defining
  - depicts bone marrow involvement
- PET/CT – May be substituted for MRI as above
  - May correlate better with response to therapy
  - May be useful in MRD evaluation

Dimopoulos et al: Leukemia 2009. Hillengass et al: JCO 2010. Kastritis et al: Leukemia 2014. Zamagni et al: Blood 2011. Spinnato et al: EurJRadiol 2012. Derlin et al: Eur Radiol 2013. Walker et al: JCO 2007. Waheed et al: Haematologica 2013.

EMN Guidelines: Algorithm for imaging in multiple myeloma (MM).



Evangelos Terpos et al. Haematologica 2015;100:1254-1266

Bisphosphonate use

- Pamidronate and zoledronic acid (ZA)have been found to reduce SREs in Phase III studies
- IV ZA >>> PO Clodranate
  - Reduced SREs
  - Improved OS by 10 mos in MM pts with lytic lesions
  - Effects continued beyond 2 yrs but unknow if all depths of remission benefitted equally
- No study has shown superiority of ZA over pamidronate but a meta-analysis showed a survival advantage to ZA over placebo

Berenson et al: NEJM 1996. Berenson et al: Cancer 2001. Morgan et al: Lancet 2010. Morgan et al: Blood 2012. Mhaskar et al: CDSR 2012.

Side effects of bisphosphanates

- Acute phase reactions
- Hypocalcemia
- Hypophosphatemia
- Renal impairment
- Osteonecrosis of the jaw (ONJ)

Terpos et al: JCO 2013. Berenson et al: JClinPharmacol 1997; Dimopoulos et al: Haematologica 2006.

EMN/IMWG Recommendations for bone health

- ZA 4mg over 15-30 min or pam 90mg over 2-4 h IV q3-4wks
  - All MM pts with CrCl >30 mL/min and osteolytic lesions
  - Continue ZA past 2 yrs though unclear if benefit continues for pts in ≥ VGPR, pam unclear benefit past 2 yrs
- Calcium po 600mg/d; vitamin D2 400 IU/d
  - 60% of MM pts are Vitamin D deficient, yearly levels recommended
- Adjust ZA for renal fx, hold until crcl within 10% baseline
  - hold for crcl < 30. HD ok if no expectation of recovery
- ONJ more common with ZA, after invasive dental procedures, and associated with prolonged use of ZA
  - Try to have dental clearance and extractions/traumatic procedure prior to initiating bisphosphonates
  - IMWF recommend holding for 90 days pre and post invasive dental procedure

Terpos et al: Haematologica 2015. Terpos et al JCO 2013.

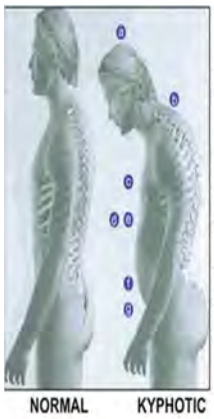
Bone pain treatment

- Radiotherapy for solitary plasmacytoma, symptomatic SC compression, severe uncontrolled pain or prevention of pathologic fx
  - 3000 cGy in 10-15 fx usually sufficient
  - Can lead to delays of systemic therapy
  - Can adversely affect stem cell mobilization
- Vertebroplasty vs Kyphoplasty
- Surgery – rare
  - For pathologic fractures of long bones
  - Restore spinal stability
  - [illegible]pinal

Niesvizky et al: J Natl Compr Canc Netw 2010. Christoulas et al: Expert Rev Hematol 2009.
Drake MT. Oncology (Williston Park) 2009. Terpos et al: JCO 2013. Webb et al: Br J Pharmacol 2014.

VERTEBROPLASTY VS KYPHOPLASTY

PROCEDURE	ADVANTAGES	DISADVANTAGES
Vertebroplasty	Faster surgery and less post op pain due to smaller trocar	Cement leakage, vertebral height restoration is questionable; however, some studies show similar height restoration
Kyphoplasty	Less cement leakage, restoration of height to vertebral body preventing kyphosis at that level	Similar post op outcomes to vertebroplasty procedure while costing 20 times more and requiring overnight stay



a. Height loss
b. Upright posture becomes impossible
c. Pulmonary volume loss due to anterior wedging of the spine
d. 12 rib rests on the iliac crest
e. Narrowed gab between ribs and ilium
f. Protruding abdomen
g. Distension, constipation, early satiety, eructation

Berenson et al: Lancet Oncol 2011. Bhargava et al: JCO 2009

Renal impairment – Defined as GFR < 60mL/min

- Present in 19% of pts at dx
- Develops in 25-50% at some point in disease course
- Pathophysiology is complex
  - Principal renal mechanism is cast nephropathy
    - Direct consequence of high serum concentration of SFLC
  - Direct deposition of light chains as in LCDD or amyloidosis
- Other offending conditions
  - Hypercalcemia
  - Dehydration
  - Nephrotoxic medications

Kebler et al: Eur J Haematol 2009. Dimopoulos et al: Leukemia 2008. Hutchison et al: Nat Rev Nephrol 2011.

Management

- MM patient with RI should be considered an emergency
- Interventions should include
  - Hydration +/- urine alkalization
  - treatment of hypercalcemia
  - prompt anti-myeloma therapy
  - Use of plasma exchange, standard dialysis, high cut off dialyzers are reasonable when available but have not been proven to definitive impact course and thus not recommended as standard at this time

Burnette et al: NEJM 2011. Clark et al: Am J Nephrol 2008. Heyne et al: Am J Hematol 2012. Zannetti et al: Am J Hematol 2015.

Antimyeloma therapy in pts with renal impairment - frontline

- Bortezomib-based combinations have been shown to be most effective in reversing renal insufficiency and are the treatment of choice.
  - BTZ-based therapy may even overcome negative prognostic effect of RI (HOVON-65 trial)
- Bortezomib/Dex + Thalidomide (VTD) or cyclophosphamide (CyBorD) or doxorubicin (PAD) do not require dose-adjustments and should be 1st line
- In elderly patients also consider bortezomib, melphalan, prednisone (VMP)
- Lenalidomide can be used as long as the recommended adjustments for degree of RI are followed

Dimopoulos et al: JCO 2010. Dimopoulos et al: Leukemia 2013. Scheid et al: Haematologica 2014. Dimopoulos et al: CID 2016. Facon et al: Lancet Oncol 2016.

Antimyeloma therapy in pts with renal impairment – transplant

- High dose melphalan and ASCT can be performed safely in patient with RI, including on dialysis
- Traditionally melphalan dose has been reduced to 140mg/m2 in patients with RI
- Recent analysis by the CIBMTR reported improved outcomes and no worse toxicity in patients with mild-moderate RI (CcCl > 30mL/min) when treated with melphalan 200mg/m2

Badros et al: EJH 2004. Knudsen et al: EJH 2005. Lee et al: BMT 2004. Raab et al: Haematologica 2006. Sweiss et al: BMT 2016. Mahindra et al: ASH 2

Other Antimyeloma therapies in pts with renal impairment

- Pomalidomide
  - No need to adjust, at least with CrCl >30mL/min
- Elotuzumab
  - No need to adjust even on HD
- Carfilzomib
  - No need to adjust
- Daratumumab
  - No data but likely safe?
- Bendamustine
  - no need to adjust
- Ixazomib
  - needs adjustment only for pts with CrCl <30 mL/min or on HD

Weisel et al. Haematologica2016; Berdeja et al. CLML 2016; Quach et al. CCP 2017; Ponish et al. JCRCO 2013; Gupta et al. BJH 2016.

Case 2: Presentation

- 57-yr-old man diagnosed with MM
- Was started on
  - Bortezomib
    - 1.3 mg/m^2 IV on Days 1, 4, 8, 11
  - Thalidomide
    - 100 mg PO on Days 1-21
  - Dexamethasone
    - 40 mg PO on day of and day following btz
- After cycle 2, M-spike had decreased to 0.3 g/dL, but noted numbness, burning, stabbing sensation feet and legs

PERIPHERAL NEUROPATHY: RISK FACTORS AND GENERAL CONSIDERATIONS

COMMON PROBLEM AT BASELINE DUE TO CO-MORBIDITIES AND MM AND EVENTUALLY FROM

General Considerations

- Endocrine disorders
  - Hypothyroidism
  - Diabetes
- Nutritional disease
- Connective tissue disease
- Vascular disease
- Medications
- Herpes zoster
- Most common symptoms
  - Sensory deficits
  - Neuropathic pain

Disease- and Treatment-Related Factors

- Hyperviscosity syndrome
- Hypergammaglobulinemia
- Incidence of peripheral neuropathy at diagnosis: 20%
- Up to 75% of pts on therapy
- Incidence of grade 3/4 CIPN with novel agents
  - Bortezomib: 6% to 22%
    - ↓ with wkly vs twice-weekly dosing
    - ↓ with SC administration
  - Thalidomide: 3% to 23%
    - ↑ with higher doses and prolonged therapy, often permanent
  - Carfilzomib: < 2%

Gleason C, et al. J Natl Compr Cancer Netw. 2009;7:971-979. Palumbo A, et al. J Clin Oncol. 2014;32:587-600. Kurtin S, et al. J Adv Pract Oncol. 2013;4:307-321. Siegel D, et al. Haematologica. 2013;98:1753-1761. Richardson et al: Leukemia 2012. Delforge et al: Lancet Oncol 2010.

Thalidomide VS Bortezomib

PN and associated symptoms

- Thalidomide
  - Affects larger myelinated axons
    - Cumulative
    - Dose-dependent
    - Mostly irreversible
  - Autonomic dysfunction
    - Dizziness
    - Orthostasis
  - Tremor
    - Reversible with dose adjustment/discontinuation
- Bortezomib
  - Affects small myelinated and unmyelinated fibers
    - Hyperesthesia
    - Neuralgia
    - Altered temperature sensation
    - Reversible if intervene early
  - Autonomic dysfunction

Richardson et al: Leukemia 2012. Delforge et al: Lancet Oncol 2010. Delforge et al: Blood 2017

PN management

- Careful attention with pts on therapy
  - Prompt dose reductions for thalidomide
  - Bortezomib – SQ dosing, weekly dosing , dose reduction
    - Randomized trial IV vs SQ dosing
      - all grade PN decreased from 53% to 38%
      - grade 3 and 4 PN decreased from 16% to 6%.
- Treat neuropathic pain (ref)
  - Analgesics
  - Calcium channel blockers (e.g. gabapentin, pregabalin)
  - Serotonin-norepinephrine reuptake inhibitors
  - Tricyclic antidepressants (e.g. amitriptyline)
  - Acetyl-L-carnatin and alpha lipoic acid have shown activity in chemo-induced PN but no prospective analyses

Richardson et al: Leukemia 2012. Tempescul et al: Hematologica 2015. Delforge et al: Blood 2017. Jordan et al: J Neurooncol 2015

Venous Thromboembolism (Vte)

- MM patients at higher risk due to several factors specific to disease and treatments
- Incidence VTE is 8-22/1000 person years
- Highest risk during first 4 months of treatment
- Incidence increases by up to 70% with IMiDs+Dex in absence of anticoagulation
- A randomized study with lenalidomide-based therapy established benefit of thromboprophylaxis with both ASA and enoxaparin
  - The incidence of VTE was
    - 2.3% in patients on aspirin 100mg/day
    - 1.2% in pts on enoxaparin 40mg/day

De Stefanis et al: Semin Thromb Hemost 2011. Dimopoulos et al: Leukemia 2011.
Dimopoulos et al: Leukemia 2014. Palumbo et al: Leukemia 2008. Larocca et al: Blood 2012.

Imwg risk factor assessment and prophylaxis recommendations

RISK FACTORS

Palumbo A, et al. Leukemia. 2008;22:414-423.

Treatment-related	Patient-specific	Myeloma-specific
IMiDs	Age	Active/uncontrolled Disease
High-dose Dexamethasone	Previous VTE	Hyperviscocity
Erythropoietin	Infection	
Anthracyclines	Surgical Procedure	
Multiagent chemotherapy	Cardiovascular Co-morbs	
	Immobilization	
	Inherited thrombophilia	
	Central venous catheter	
	Recommendations for thromboprophylaxis	
Risk factor	**Number of risk factors**	**Therapy**
Treatment-specific	≥ 1	LMWH or warfarin
Patient-specific	1	ASA
Myeloma-Specific	1	ASA
Patient or myeloma-specific	≥ 2	LMWH or warfarin

Risk Assessment for VTEs in Pts Receiving IMiD-based Therapy

- VTE prophylaxis for individual risk factors (eg, age or obesity) or myeloma-related risk factors (eg, immobilization or hyperviscosity)
  - If ≤ 1 risk factor present, aspirin 81-325 mg/day
  - If ≥ 2 risk factors present, LMWH (equivalent to enoxaparin 40 mg/day) or full-dose warfarin (target INR: 2-3)
- VTE prophylaxis for myeloma therapy–related risk factors (eg, high-dose dexamethasone, IMiDs, doxorubicin, multiagent chemotherapy)
  - LMWH (equivalent to enoxaparin 40 mg/day) or full-dose warfarin (target INR: 2-3)

Palumbo A, et al J Clin Oncol. 2014;32:587-600.
Palumbo A, et al. Leukemia. 2008;22:414-423.

anemia

- Present in almost 75% of all newly dx pts and universally in relapsed disease
- Causes multifactorial both disease specific and treatment-induced
- Renal insufficiency common

Kyle et al: Mayo Clin Proc 2003. Willan et al: Clin Interv Aging 2016. Silvestris et al: Blood 2002. Birgegard et al: EurJH 2006.

Management of anemia

- PRBC transfusion for rapid restoration
- Erythropoiesis-stimulating agents (ESAs)(Erythropoietin and darbepoetin)
  - No clear guidelines for use in MM
  - Conflicting study results in patients with MM
    - Vista, subanalysis, revealed no inferior outcome with ESA use in MM but small subset
  - ASH and ASCO recommends ESA use at lowest possible dose to avoid transfusions

Mhaskar et al: JNCCN 2010. Baz et al: Acta Haematol 2007. Katodritou et al: Ann Hematol 2008. Richardson et at: BJH 2011

ESA-use considerations

- Important potential side-effects
  - Increase thromboembolic complications
  - HTN
  - Possible increased mortality
- Consider use in patients with
  - Persistent hgb <10 or who are transfusion dependent
  - Ruled out other reversible causes such as iron/B12 def
  - Target hgb should be no more than 12 g/dL
- ESA use remains controversial

Lyman et al: Cancer 2006. Niesvizky et al: JNCCN 2010. Baz et al: Acta Haematol 2007.
Katodritou et al: AmJHematol 2008. Richardson et at: BJH 2011

CArdiotoxicity

- Mechanism unclear
  - Direct endothelial effects, Sarcomeric protein turnover inhibition are hypotheses
- Thought to be a class effect for PIs
  - Cardiac failure Gr 3 or higher
    - Vd 3%, IxaRd 3%, KRd 7%, Kd 6%
  - HTN Gr 3 or higher
    - Vd 3%, IxaRd 3%, KRd 4%, Kd 9%
- Carfilzomib most concerning
  - All grade dyspnea 25%, HTN 15%,
  - In absence of other cardiac risk factors, severe cardiac failure ~5%
- Additional risk factors
  - Other cardiotoxic agents, mediastinal XRT, cardiac amyloid, high dose steroids

Subedi et al: Ann Hematol 2014. Kumar et al: Blood 2016. Rosenthal et al: Blood Cancer J 2016. Hasinoff et al: Cardiovasc Toxicol 2016.
Moreau et al: Lancet Oncol 2011. Stewart et al: NEJM 2015. Dimopoulos et al: Lancet Oncol 2016. Moreau et al: NEJM 2016. Danhof et al: EJH 2016.

Carfilzomib Cardiac-directed management

- Prior to starting therapy
  - Scree for cardiovascular risk factors
  - HTN and other cardiovascular issues should be optimally controlled prior to starting
- During treatment
  - Regular clinical surveillance
  - Good BP control
  - Serial echo, BNP are of uncertain benefit
- If cardiac failure develops
  - Discontinue use
  - Detailed cardiac evaluation and treatment
  - Once cardiac function restored
    - If individual risk-benefit favorable consider restarting carfilzomib
    - Consider dose reduction

Rosenthal et al: Blood Cancer J 2016. Russell et al: Blood 2015. Mikhael: CLML 2016.

Suggested Empiric Age-Adjusted Dose Reduction in Pts With Myeloma

Agent	Younger Than 65 Yrs	65-75 Yrs	Older Than 75 Yrs
Dexamethasone	40 mg/day on Days 1-4, 15-18 q4w ***or*** Days 1, 8, 15, 22 q4w	40 mg/day on Days 1, 8,1 5, 22 q4w	20 mg/day on Days 1, 8, 15, 22 q4w
Melphalan	0.25 mg/kg on Days 1-4 q6w	0.25 mg/kg on Days 1-4 q6w ***or*** 0.18 mg/kg on Days 1-4 q4w	0.18 mg/kg on Days 1-4 q6w ***or*** 0.13 mg/kg on Days 1-4 q4w
Cyclophosphamide	300 mg/day on Days 1, 8, 15, 22 q4w	300 mg/day on Days 1, 8, 15 q4w ***or*** 50 mg/day on Days 1-21 q4w	50 mg/day on Days 1-21 q4w ***or*** 50 mg/day QOD on Days 1-21 q4w
Thalidomide	200 mg/day	100 mg/day ***or*** 200 mg/day	50 mg/day to 100 mg/day
Lenalidomide	25 mg/day on Days 1-21 q4w	15-25 mg/day on Days 1-21 q4w	10-25 mg/day on Days 1-21 q4w
Bortezomib	1.3 mg/m^2 bolus on Days 1, 4, 8, 11 q3w	1.3 mg/m^2 bolus on Days 1, 4, 8, 11 q3w ***or*** on Days 1, 8, 15, 22 q5w	1.0- 1.3 mg/m^2 bolus on Days 1, 8, 15, 22 q5w

Palumbo A, et al. N Engl J Med. 2011;364:1046-1060.

Treatment-related complications and recommendations (Adapted from emn recs)

Complication	Treatment	AE grade	Dosing Recommendations	Management
Neutropenia	Len-based	Gr 2/3 w infection or Gr 4	None if expected to improve or 25-50% dose reduction	GCSF until neutrophil recovery
Anemia	All	Gr 2-4 (hgb <10 g/dL)	None if expected to improve or 25-50% dose reduction	Consider ESA use
Renal	Len	CrCl 30-60 mL/min CrCl < 30 mL/min, no HD CrCl < 30 mL/min, yes HD	10 mg QD 15 mg QOD 5 mg QD	Correct other associated factors: dehydration, hypercalcemia, hyperuricemia, other nephrotoxic meds
Neuropathy	Thal-based	Gr 2 Gr 3-4	50% dose reduction Discontinue until Gr 1 then restart at 50% dose	Monitor carefully Consider symptomatic treatment
	Bor-based	Gr 1 with pain or Gr 2 Gr 2 with pain or Gr 3 Gr 4	Switch to SQ from IV; Switch to weekly dosing Dose reduce from 1.3 to 1.0 to 0.7 mg/m2 Hold and resume when Gr 1 or less Recs as in lower grade but dose reduction rec Discontinue use	Monitor carefully Consider symptomatic treatment
VTE	Thal/Len	All grades	Temporary discontinuation and full anticoagulation	Reevaluate for retreatment

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THANK YOU