AMGEN Pfizer

Global Multiple Myeloma Academy

Global Multiple Myeloma Academy

Emerging and Practical Concepts in Multiple Myeloma

April 9–10, 2021

APTITUDE HEALTH®

Global Multiple Myeloma Academy

Welcome and Meeting Overview

Rafael Fonseca

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Faculty

Chair

Rafael Fonseca, MD
Mayo Clinic Cancer Center, USA

Majed Alahmadi, MD
King Abdulaziz Medical City, Kingdom of Saudi Arabia

Irene Ghobrial, MD
Dana-Farber Cancer Institute, USA

Mervat Mattar, MD
Cairo University, Egypt

María-Victoria Mateos, MD, PhD
University of Salamanca, Spain

Mohamad Mohty MD
Saint-Antoine Hospital and Sorbonne University, Paris, France

Keith Stewart, MD
Princess Margaret Cancer Centre, Canada

Global Multiple Myeloma Academy

Objectives of the Program

- Share key data from recent conferences that could lead to improved treatment and management for patients with myeloma
- Discuss early treatment strategies for smoldering myeloma and initial therapies for multiple myeloma
- Provide insights into the evolving role of minimal residual disease (MRD) monitoring in the management of patients with multiple myeloma
- Present the latest research on identifying multiple myeloma patients at high risk for early relapse, and management strategies for early relapse
- Discuss the benefits and limitations of current options for treating patients with multiple myeloma refractory to multiple therapeutic modalities
- Bring in the regional multiple myeloma perspective

Agenda Day 1

9 April 2021, 16.00 – 18.30 CEST / 17.00 – 19.30 AST (UTC +3)

Time (UTC +3)	Topic	Speaker
17.00 – 17.15 15 min	**Welcome and Meeting Overview** • Introduction to audience response system (ARS)	Rafael Fonseca
17.15 – 17.35 20 min	**Smoldering Multiple Myeloma** • Diagnosis, criteria, and when and how to intervene (15 min, 5-min discussion)	Irene Ghobrial
17.35 – 17.55 20 min	**Role of Minimal Residual Disease in Multiple Myeloma** • Prognostic value, clinical relevance, and MRD-driven therapeutic guidance (15 min, 5-min discussion)	Majed Alahmadi
17.55 – 18.15 20 min	**Frontline Therapy for Newly Diagnosed Transplant-Eligible Multiple Myeloma: The Role of Transplantation** • Guidelines, induction therapies, and how and when to transplant (15 min, 5-min discussion)	Mervat Mattar
18.15 – 18.35 20 min	**Optimal Use of Consolidation and Maintenance Therapy** • Evolving insights in consolidation and maintenance treatment after transplant (15 min, 5-min discussion)	Mohamad Mohty
18.35 – 18.50 15 min	**Break**	
18.50 – 19.15 25 min	**Frontline Therapy for Newly Diagnosed Transplant-Ineligible Patients** • Criteria, guidelines, and treatment choices (15 min, 10-min discussion)	Keith Stewart
19.15 – 19.30 15 min	**Session Close** • ARS questions	Rafael Fonseca

Agenda Day 2

10 April 2021, 16.00 – 19.15 CET / 17.00 – 20.15 AST (UTC +3)

Time (UTC +3)	Topic	Speaker
17.00 – 17.10 10 min	**Session Open**	Rafael Fonseca
17.10 – 17.30 20 min	**Identification and Special Considerations for High-Risk Multiple Myeloma** • Risk stratification, prognosis, and treatment choices (15 min, 5-min discussion)	María-Victoria Mateos
17.30 – 17.55 25 min	**Management of Early Relapse of Multiple Myeloma** • Definition, prognosis, and treatment choices (15 min, 10-min discussion)	Rafael Fonseca
17.55 – 18.20 25 min	**Management of Heavily Pretreated Multiple Myeloma** • Optimal use of treatment choices in relapsed/refractory multiple myeloma (excluding T-cell engagers) (15 min, 10-min discussion)	Keith Stewart
18.20 – 18.30 10 min	**Break**	
18.30 – 19.20 50 min	**New and Future Therapies for Multiple Myeloma** • Promising new developments in relapsed/refractory MM • Latest trial updates, and upcoming new strategies (including T-cell engagers) (35 min, 15-min discussion)	Irene Ghobrial
19.20 – 20.00 40 min	**Patient Case Discussion: Relapsed/Refractory Multiple Myeloma** • Treatment challenges in relapsed/refractory MM in the region (10 min) • Cases from the region will be discussed with the faculty – “tumor board approach” (30 min)	Mervat Mattar All faculty
20.00 – 20.15 15 min	**Session Close** • ARS questions	Rafael Fonseca

Global Multiple Myeloma Academy

Introduction to the Audience Response System

Rafael Fonseca

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Question 1

Which languages do you speak? (multiple choice)

a) English
b) German
c) Spanish
d) French
e) Russian
f) Mandarin
g) Modern Standard Arabic
h) Arabic dialect

Question 2

Which of the following is not part of the new criteria for treatment initiation in MM?

a) Plasma cells >60%
b) Deletion 17p
c) 2 or more lesions on an MRI
d) Extreme abnormalities in the free light chains

Question 3

Which of the following is not true in the treatment of newly diagnosed MM?

a) Deep responses are associated with better outcomes
b) VGPR is an accepted benchmark as evidence of a good response
c) Clinical trials are considering risk stratification
d) Regimens that contain daratumumab have further increased response rates
e) Maintenance prolongs overall survival for MM patients

Smoldering Myeloma

Irene Ghobrial, MD
Professor of Medicine
Lavine Family Chair for Preventative Cancer Therapies
Director of Center for Prevention of Progression (CPOP)
Director of Translational Research in Multiple Myeloma
Harvard Medical School
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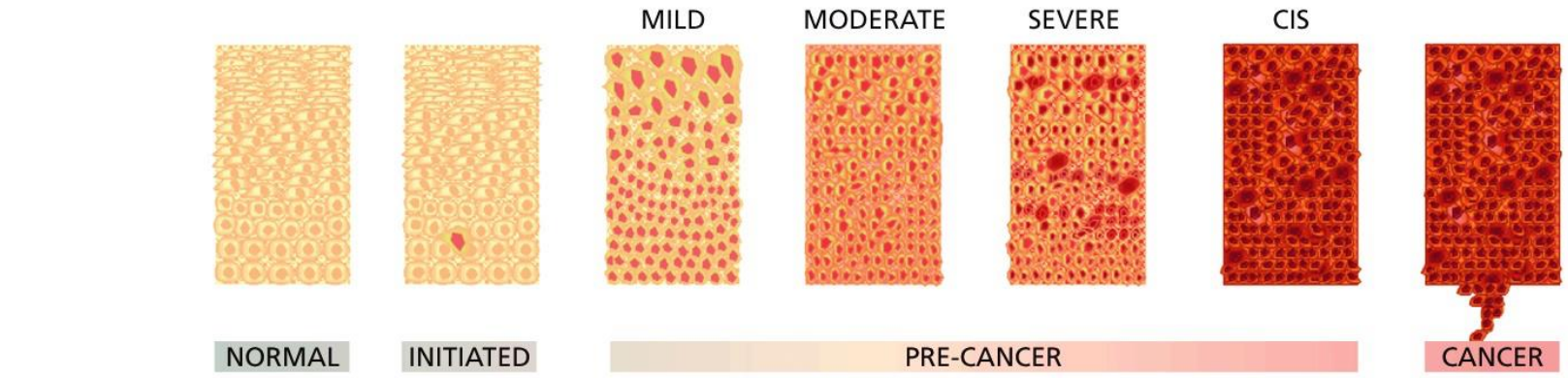
Disclosures

Research Support/PI	NA
Employee	NA
Consultant/Advisory Board	Takeda; Janssen; Celgene; Novartis; Sanofi, GSK, BMS
Major Stockholder	NA
Speakers’ Bureau	NA
Honoraria	NA

Cancer Evolution From Precursor Lesions



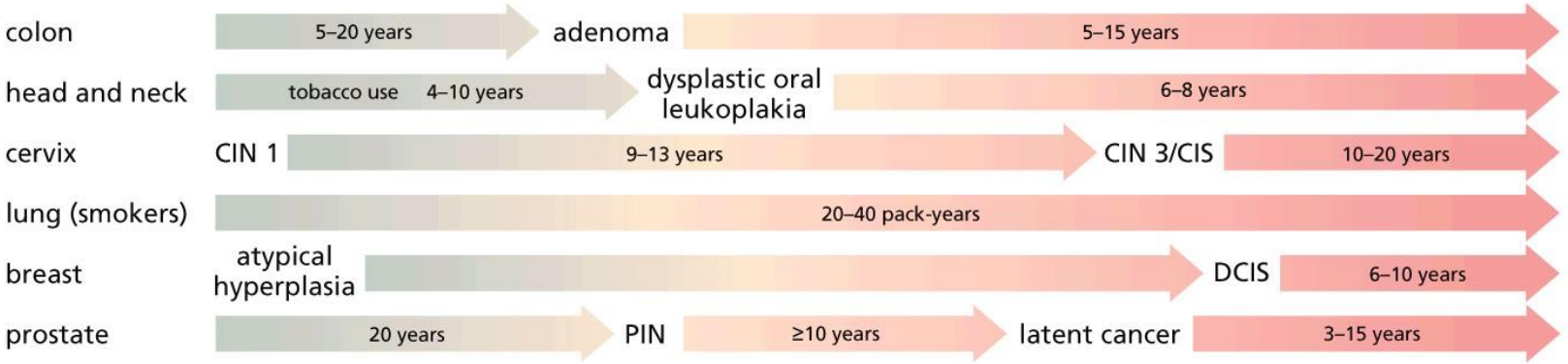
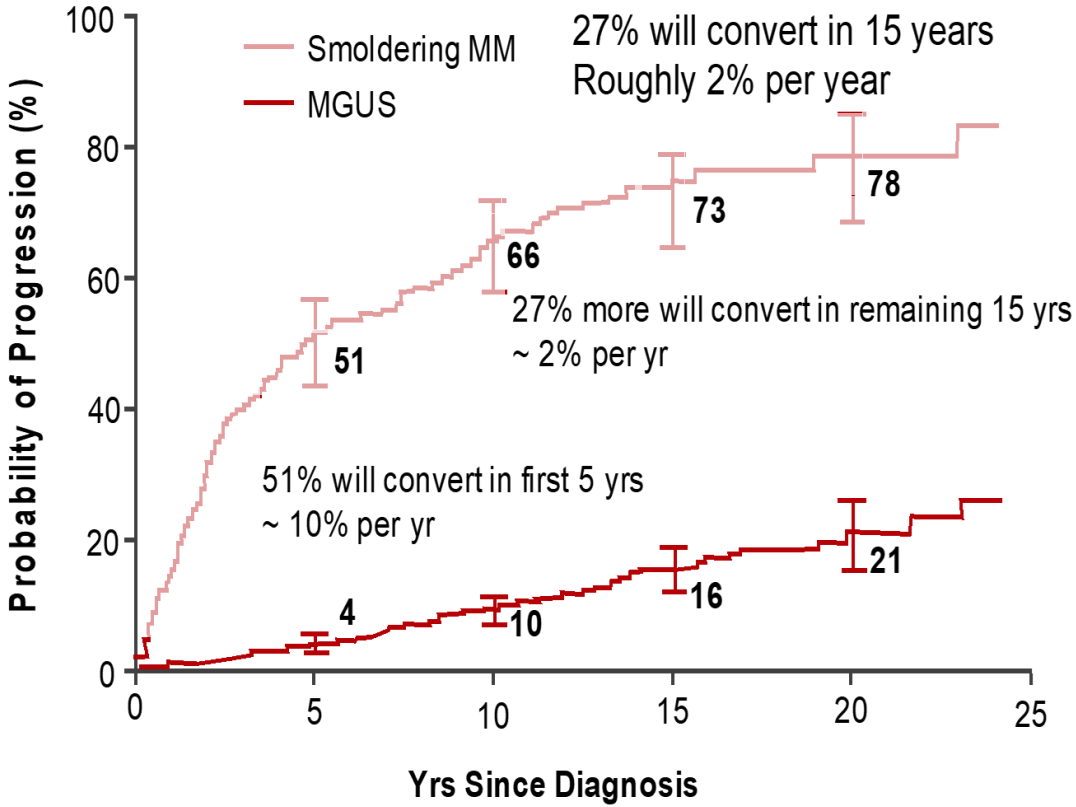


Figure 11.8a The Biology of Cancer (© Garland Science 2014)

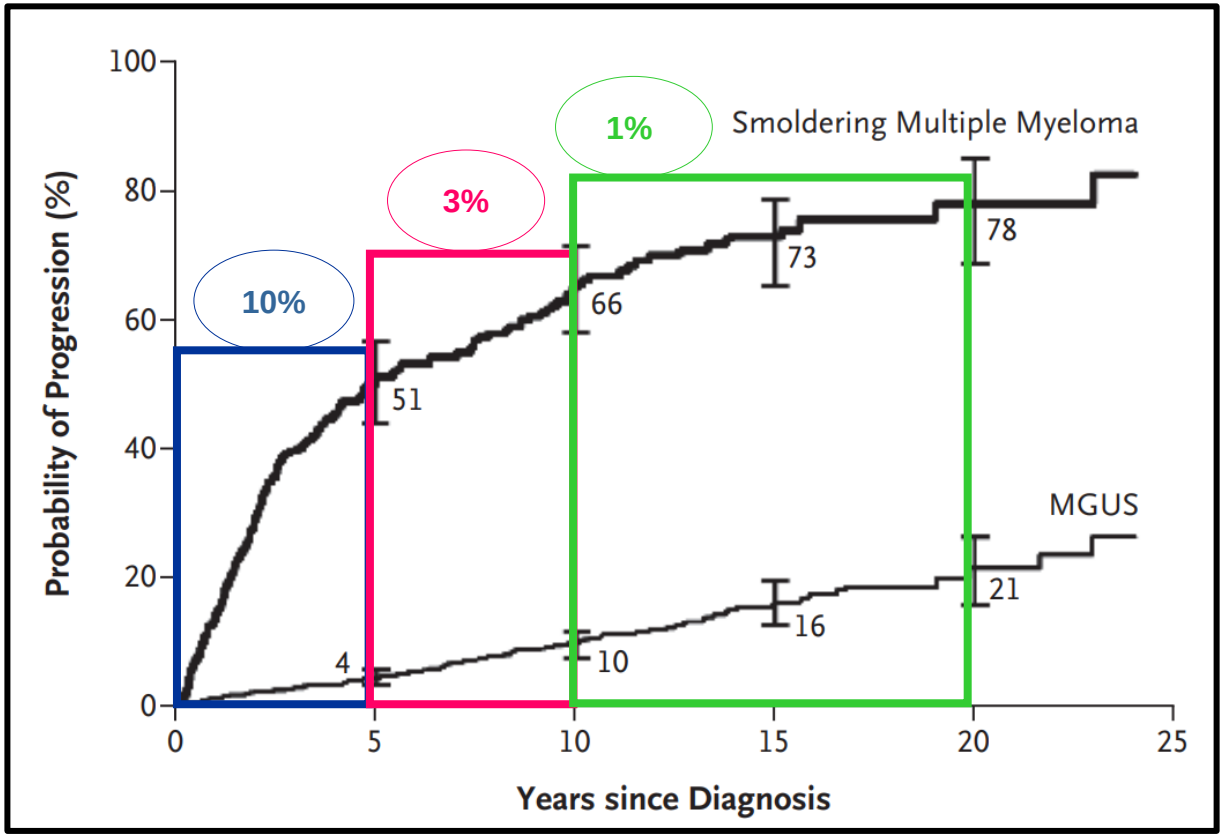
MGUS and Smoldering MM



- 3%–5% of the general population at age 50 has MGUS
- This rate is 2–3 times higher for individuals of African descent
- This rate is 2 times higher for first-degree family members of myeloma patients
- About 12 million people in the US

Kyle RA, et al. *N Engl J Med*. 2007;356:2582-2590; Greipp PR, et al. *J Clin Oncol*. 2005;23:3412-3420.

Risk of Progression of SMM to Active Disease



Can we predict high risk of progression to active disease?

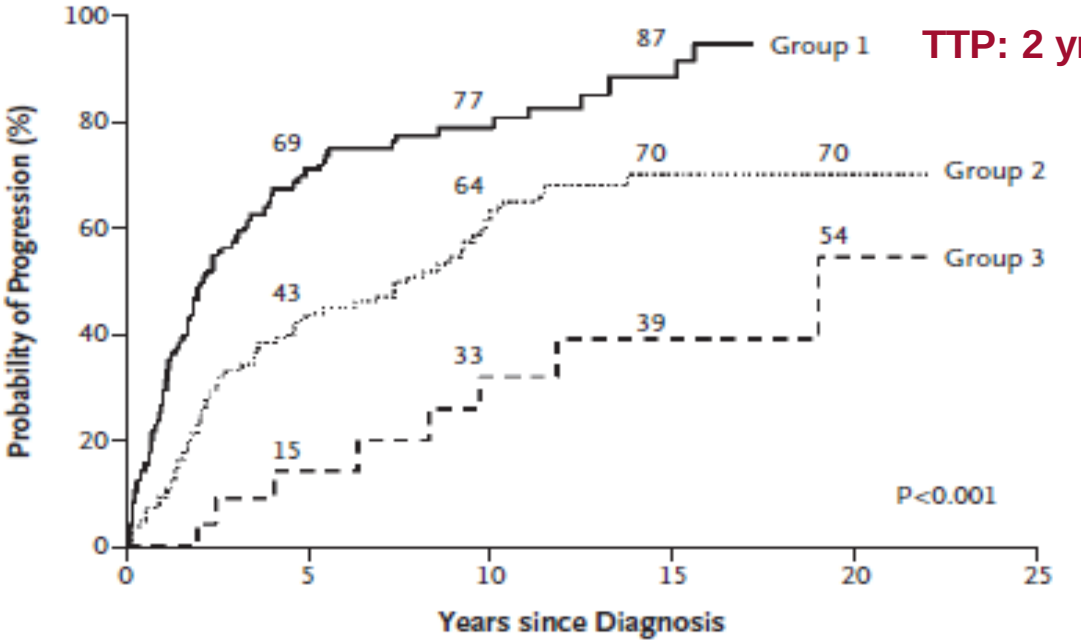
Slides courtesy of Dr San Miguel.

Kyle RA, et al. *N Engl J Med.* 2007;356:2582-2590.

Mayo Classification: PCs BM Infiltration and MC

PCBM ≥10% + MC ≥3 g/dL

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



TTP: 2 yr

TTP: 8 yr

TTP: 19 yr

Slides courtesy of Dr San Miguel.

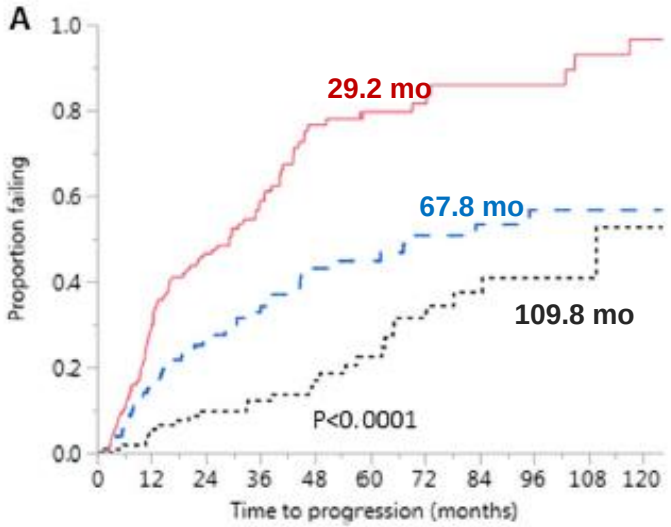
Kyle RA, et al. *N Engl J Med.* 2007;356:2582-2590.

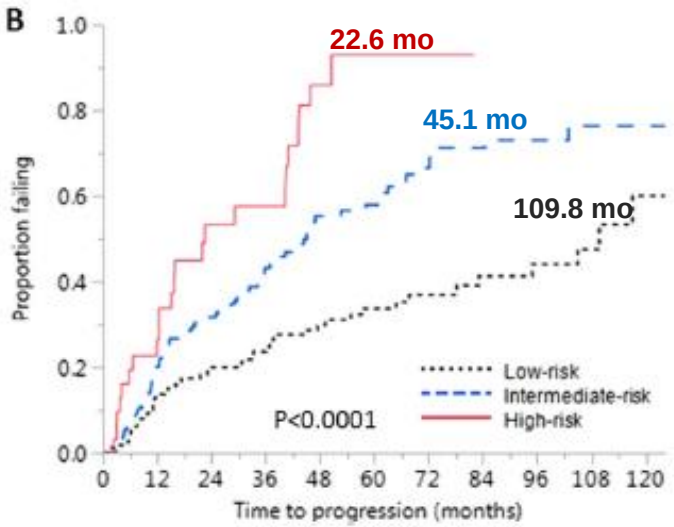
Risk Stratification of SMM: Excluding Those With MM-Defining Events (previous ultra-high-risk)

REVISED IMWG DIAGNOSTIC CRITERIA

N = 421 pts

None (low risk), 1 (intermediate risk), and ≥2 (high risk)





1. **Bone marrow-plasma cell percentage (BMPC%) >20%**
2. **Serum M-protein >2 g/dL**
3. **Serum FLC ratio >20**

1. BMPC% >10%
2. Serum M-protein >3 g/dL
3. Serum FLC ratio >8

Lakshman A, et al. *Blood Cancer J.* 2018;8:59.

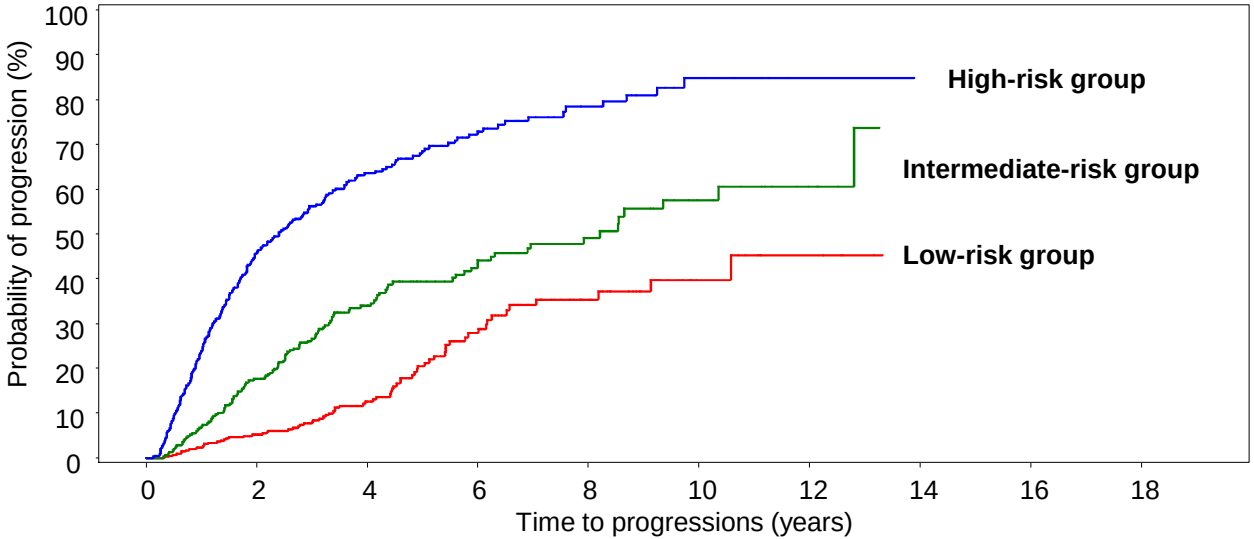
IMWG Risk-Stratification Model for SMM
(N = 2004)

- **A multicenter, retrospective study of SMM patients diagnosed since January 1, 2004**
- **Patients were included if they**
  - Had no disease progression within 6 months
  - Had baseline data from diagnosis (+/– 3 months)
  - Had follow-up ≥1 year, and
  - Did not participate in a therapeutic trial of SMM
- **To identify factors that predicted progression to myeloma through the evaluation of various clinical and laboratory factors**
  - **Univariate Cox regressions** were run for each factor to identify the possible predictors
  - Stepwise regression analysis to fit **multivariable Cox model** and significant risk factors were determined (F-test)
- **Develop a risk score to predict 2-year progression risk**

Slides courtesy of Dr San Miguel.

San Miguel J, et al. ASCO 2019. Abstract 8000.

Progression by Risk Group
(N = 1151 pts)



Characteristics included in the model

- **Serum M spike: >2 g/dL**
- **FLC ratio: >20**
- **BMPC: >20%**

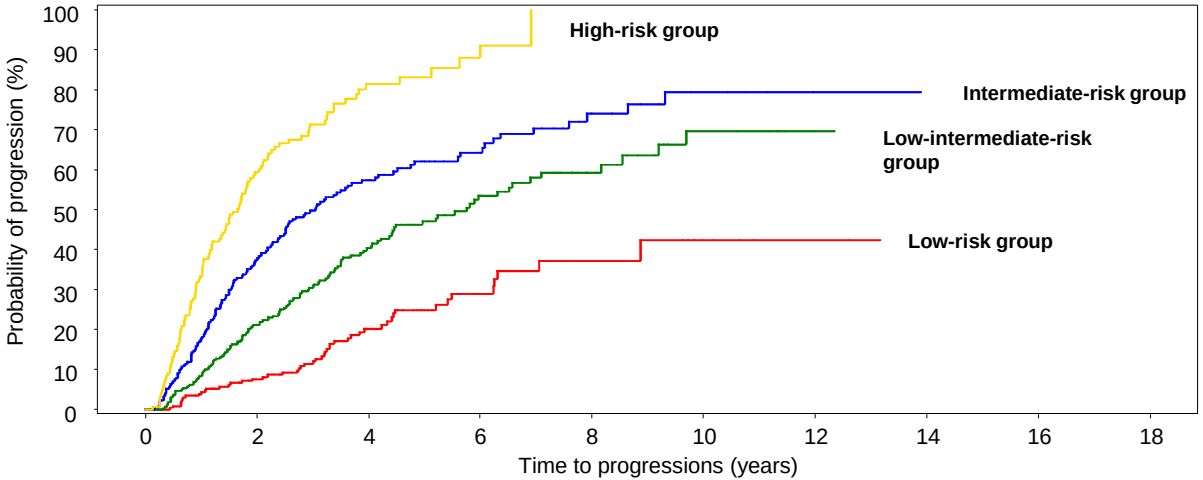
Immunoparesis and BJ proteinuria were significant in univariate

Risk-Stratification Groups	Number of Risk Factors	Hazard Ratio (95% CI) Versus Low-Risk Group	Risk of Progression at 2 Years	Number of Patients
Low-risk group	0	Reference	**5%**	**424 (37%)**
Intermediate-risk group	1	2.25 (1.68 to 3.01)	**17%**	**312 (27%)**
High-risk group	2-3	5.63 (4.34 to 7.29)	**46%**	**415 (36%)**

San Miguel J, et al. ASCO 2019. Abstract 8000.

Progression Risk Incorporating FISH

The presence of **t(4,14), t(14,16), 1q gain, or del13q** was defined as an additional risk factor



Characteristics included in the model

- **Serum M spike: >2 g/dL**
- **FLC ratio: >20**
- **BMPC: >20%**

Presence of any of the CA

Risk-Stratification Groups	Number of Risk Factors	Hazard Ratio (95% CI) Versus Low-Risk Group	Risk of Progression at 2 Years	Number of Patients
Low-risk group	0	Reference	**8%**	**232**
Low-intermediate-risk group	1	2.25 (1.62, 3.11)	**21%**	**322**
Intermediate-risk group	2	3.69 (2.68, 5.09)	**37%**	**253**
High-risk group	≥3	7.52 (5.36, 10.54)	**59%**	**145**

San Miguel J, et al. ASCO 2019. Abstract 8000.

Developing a Risk Score Tool
(N = 689)

Continuous variables categorized on the basis of clinical relevance and scores for each risk factor were assigned as relative weight. Total risk score calculated as the sum of all points for all existing risk factors.

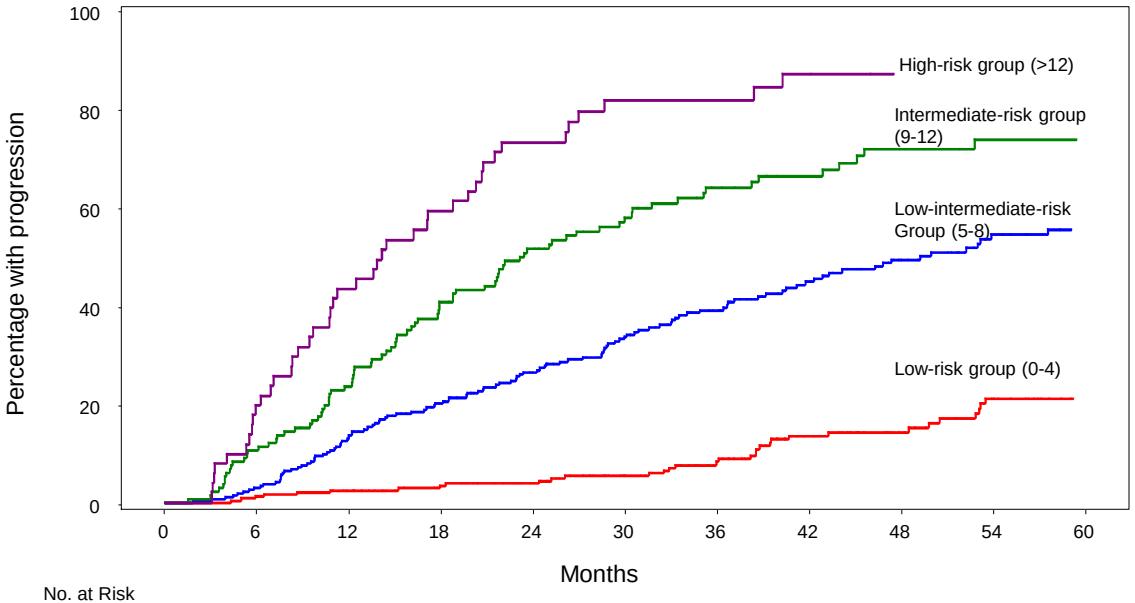
Risk Factor	Coefficient	Odds Ratio (95% CI)	*P* Value	Score
FLC Ratio				
0-10 (reference)	-	-	-	**0**
>10-25	0.69	1.99 (1.15, 3.45)	.014	**2**
>25-40	0.96	2.61 (1.36, 4.99)	.004	**3**
>40	1.56	4.73 (2.88, 7.77)	<.0001	**5**
MC (g/dL)				
0-1.5 (reference)	-	-	-	**0**
>1.5-3	0.95	2.59 (1.56, 4.31)	.0002	**3**
>3	1.30	3.65 (2.02, 6.61)	<.0001	**4**
BMPC, %				
0-15 (reference)	-	-	-	**0**
>15-20	0.57	1.77 (1.03, 3.06)	.04	**2**
>20-30	1.01	2.74 (1.6, 4.68)	.0002	**3**
>30-40	1.57	4.82 (2.5, 9.28)	<.0001	**5**
>40	2.00	7.42 (3.23, 17.02)	<.0001	**6**
FISH abnormality	0.83	2.28 (1.53, 3.42)	<.0001	**2**

Total Risk Score	Predicted Risk at 2 Years	Percentage of Sample
0	**3.2**	11.6
2	**6.2**	8.1
3	**8.5**	11.0
4	**11.6**	4.2
5	**15.7**	14.4
6	**20.8**	6.8
7	**27**	8.4
8	**34.3**	8.7
9	**42.5**	5.1
10	**51**	6.2
11	**59.5**	4.9
12	**67.5**	3.1
13	**74.6**	2.3
14	**80.5**	2.0
15	**85.4**	1.7
16+	**89.2**	1.3

689 of the original 2286 had complete data for all risk factors

San Miguel J, et al. ASCO 2019. Abstract 8000.

Risk Score to Predict Progression Risk at 2 Years



No. at Risk											
0-4	241	238	229	213	194	175	153	117	100	76	63
5-8	264	256	229	197	174	145	118	91	73	53	44
9-12	133	119	98	73	59	47	33	26	20	14	13
>12	51	41	29	21	14	9	7	5	2	2	2

Risk-Stratification Groups	Hazard Ratio (95% CI) Versus Low-Risk Group (Censored 2 Year)
0–4	**Reference**
5–8	**7.56 (3.77 to 15.2)**
9–12	**17.3 (8.63 to 34.8)**
>12	**31.9 (15.4 to 66.3)**

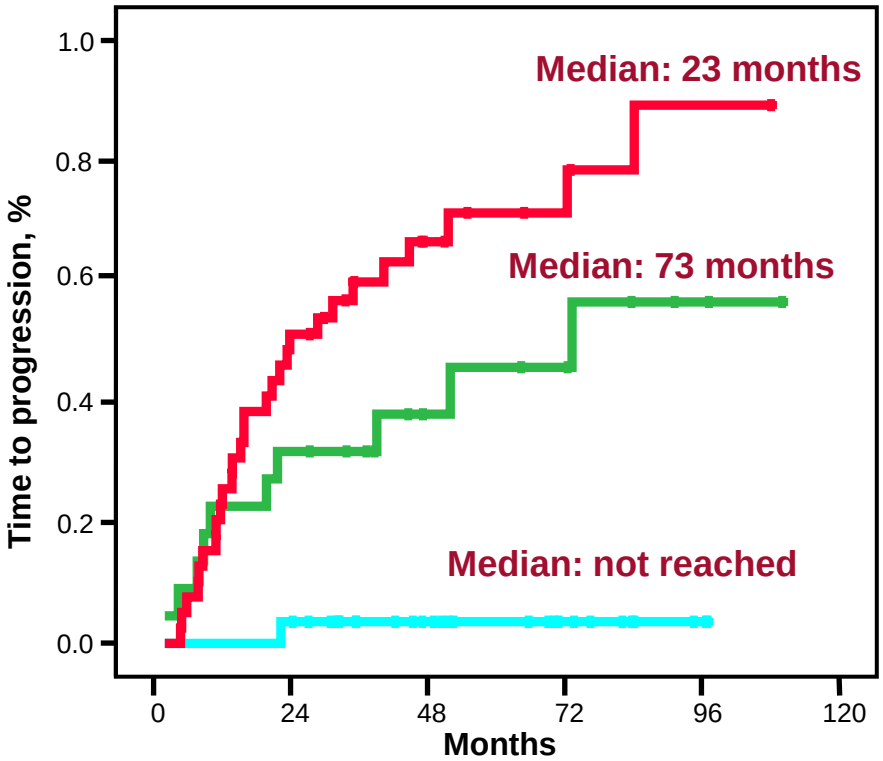
Total Risk Score	2-Year Progression n (%)
0–4	9/241 **(3.7)**
5–8	67/264 **(25.4)**
9–12	65/133 **(48.9)**
>12	37/51 **(72.6)**

Scores <5 would give a 96% NPV (4% false negative), while score >12 . . . 72% risk at 2 years

San Miguel J, et al. ASCO 2019. Abstract 8000.

Other Models: Spanish Model – PETHEMA/GEM Classification

>95% clonal PCs/total BMPCs (flow) + Immunoparesis



>95% aPC/BMPC + paresis

>95% aPC/BMPC or paresis

No adverse factors

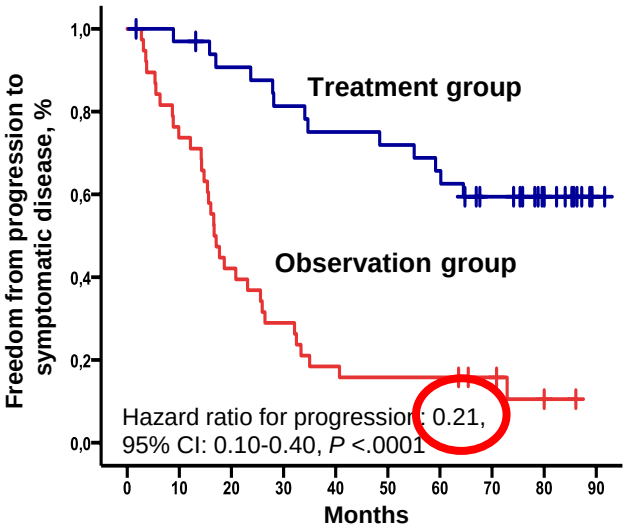
Slides courtesy of Dr San Miguel.

Pérez-Persona E, et al. *Blood.* 2007;110:2586-2592.

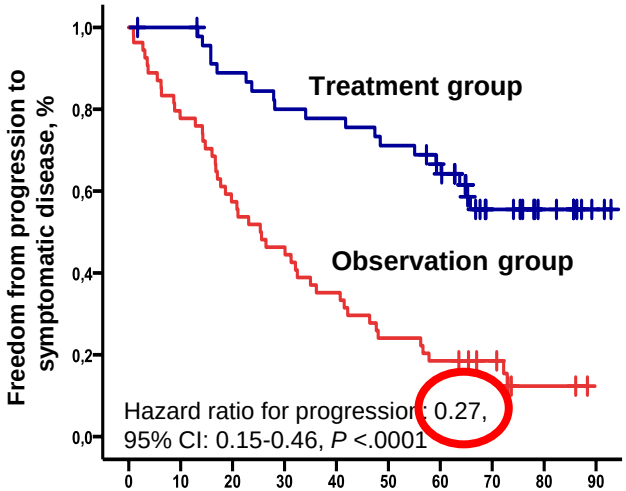
Concordance Between Mayo and Spanish Models

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

Mayo Risk Model



Spanish Risk Model



Both risk models resulted in independent prognostic factors in multivariate analysis including large number of patients with long f/u

Slides courtesy of Dr San Miguel.

Mateos MV, et al. *N Engl J Med.* 2013;369:438-447; Mateos MV, et al. *Lancet Oncol.* 2016;17:1127-1136.

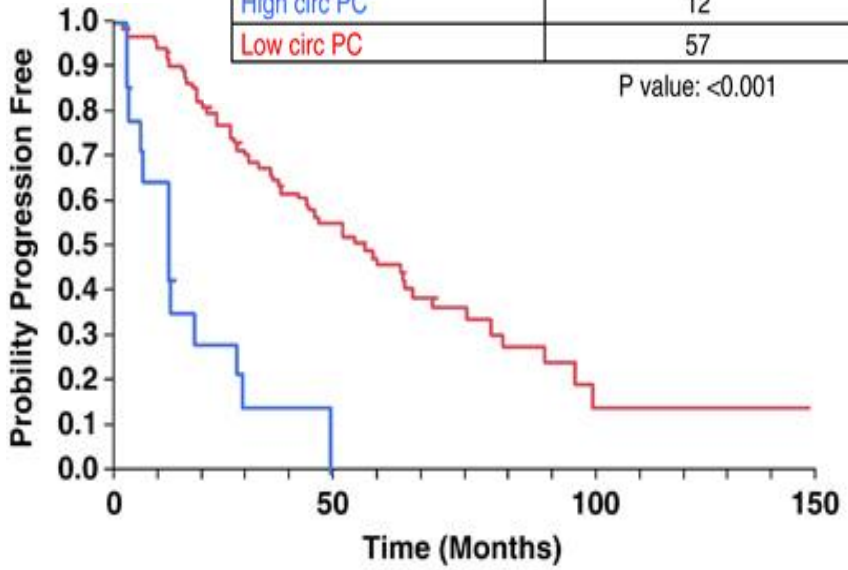
Impact of Circulating Plasma Cells (CPCs) in Smoldering MM

Immunofluorescence (n = 91)[1]

High level of circulating PCs was defined as absolute PB PCs >5 × 10(6)/L and/or >5% PCs per 100 cytoplasmic (Ig)+ (14/91 patients)

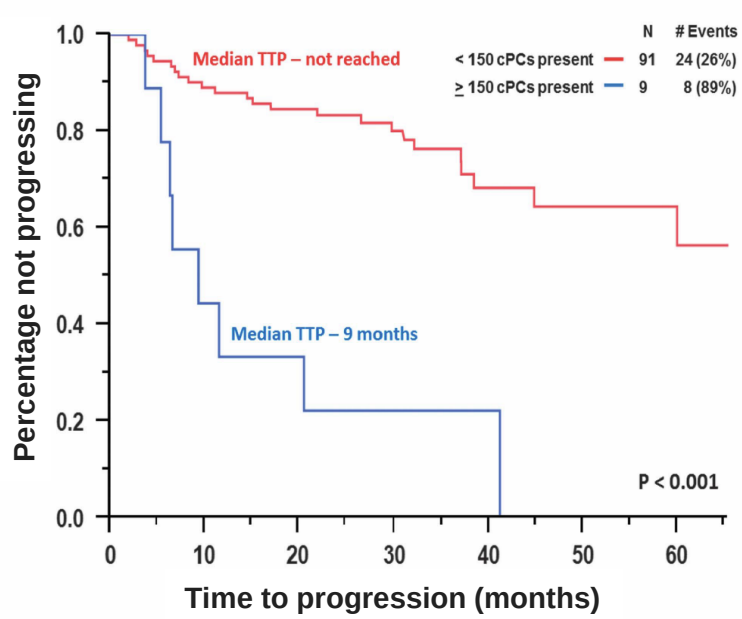
	Median TTP (months)
High circ PC	12
Low circ PC	57

P value: <0.001



Patients with high circulating PCs (14 of 91 pts; 15%) had higher risk of progression at 2 yr: 71% vs 24%; *P* = .001.

6-color flow (n = 100)[2]



TTP of patients with ≥150 cPCs was 9 months vs NR (*P* <.001).

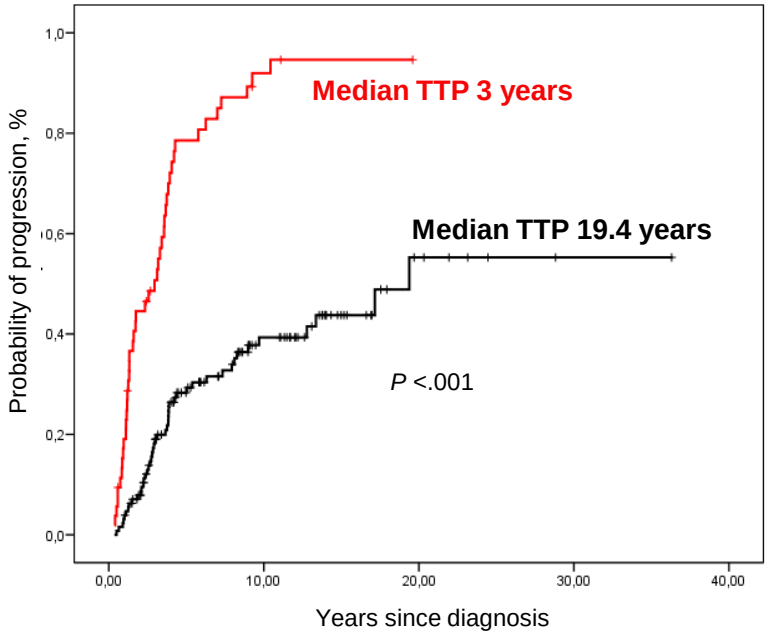
1. Bianchi G, et al. *Leukemia*. 2013;27(3):680-685;
2. Gonsalves WI, et al. *Leukemia*. 2017;31(1):130-135.

Smoldering Multiple Myeloma: Evolving vs Non-evolving
(N = 206)

Evolving SMM (52 [25%]): *If MC ≥30 g/L; at least 10% increase within the first 6 months from diagnosis; or if MC <30 g/L, progressive increase in MC in each of the annual consecutive measurements during 3 years*

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

- 206 patients
- Independent of Mayo criteria and immunoparesis



Evolving SMM: Median time from recognition of evolving type to symptomatic MM – 1.1 years.

- **Increased the HR for progression to 5.1**
- **Risk progression at 2 years: 45%**
- **Risk progression at 3 years: 71%**
- IgA isotype: (41.2% vs 23.8%; *P* = .02)

Slides courtesy of Dr San Miguel.

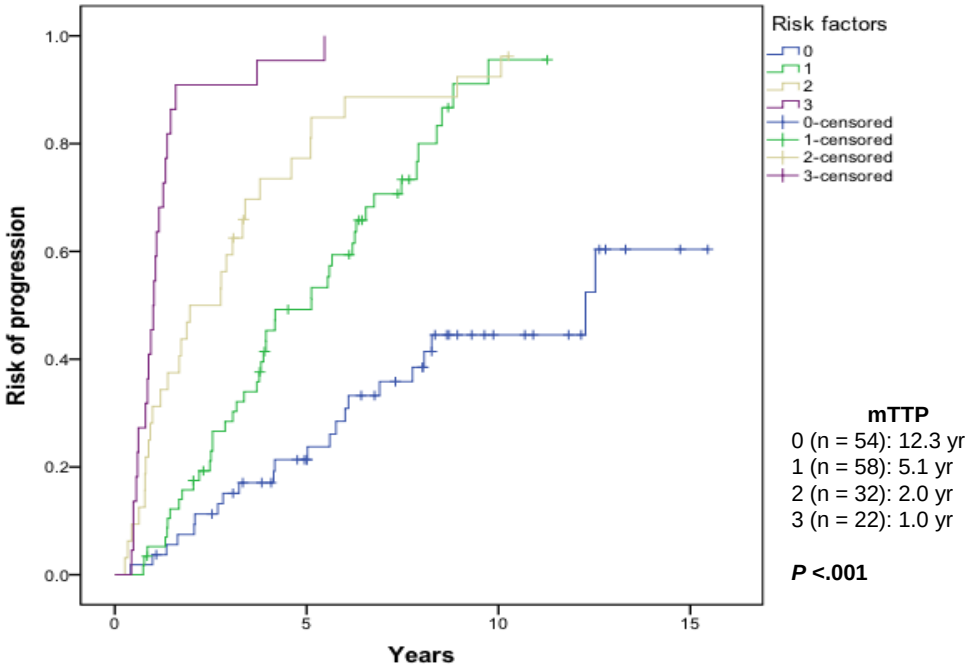
Fernández de Larrea C, et al. *Leukemia*. 2018,32:1427-1434.

Evolving Pattern of the M-Spike + eHb + BMPC

(N = 190: Mayo Clinic)

Risk factors predicting high risk:

1. **eMP** (≥10% increase in MC/Ig) within the first 6 months (only if M-protein ≥3 g/dL) and/or ≥25% increase in M/Ig within the first 12 months, with a minimum required increase of 0.5 g/dL in M-protein and/or 500 mg/dL in Ig;
2. **Evolving change in hemoglobin (eHb)** ≥0.5 g/dL decrease within 12 months of diagnosis; and
3. **BMPC** infiltration: ≥20%



The 2-year progression risk was 81.5% in individuals who demonstrated both eMP and eHb, and 90.5% in those with all 3 risk factors → ***ultra-high-risk SMM***

Slides courtesy of Dr San Miguel.

Ravi P, et al. *Blood Cancer J.* 2016;6(7):e454.

PET-CT in SMM Patients as Predictor of Progression to Symptomatic MM

	Characteristics	TTP
Zamagni E, et al[1] **120 patients**	16% had +PET (56% of them had 1 FL without osteolysis)	13 months
Dykstra B, Kumar S, et al [2] **202 patients**	41% had +PET	16 months
Siontis B, et al[3] **188 patients**	39% had +PET	21 months

Slides courtesy of Dr San Miguel.

1. Zamagni E, et al. *Leukemia.* 2016;30:417-22; 2. Dykstra B, et al. *Blood.* 2014;124:3382;
3. Siontis B, et al. *Blood Cancer J.* 2015;5:e364.

MYC and Risk of Progression in SMM

Leukemia
https://doi.org/10.1038/s41375-019-0543-4

LETTER

Multiple myeloma gammopathies

MYC dysregulation in the progression of multiple myeloma

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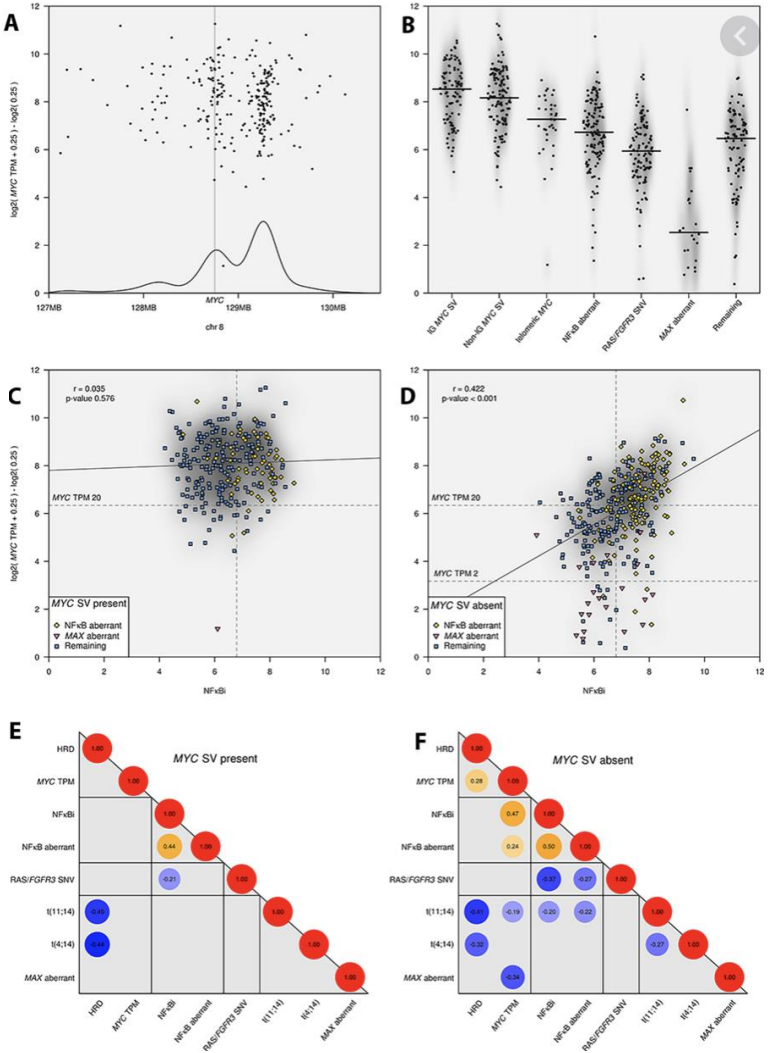
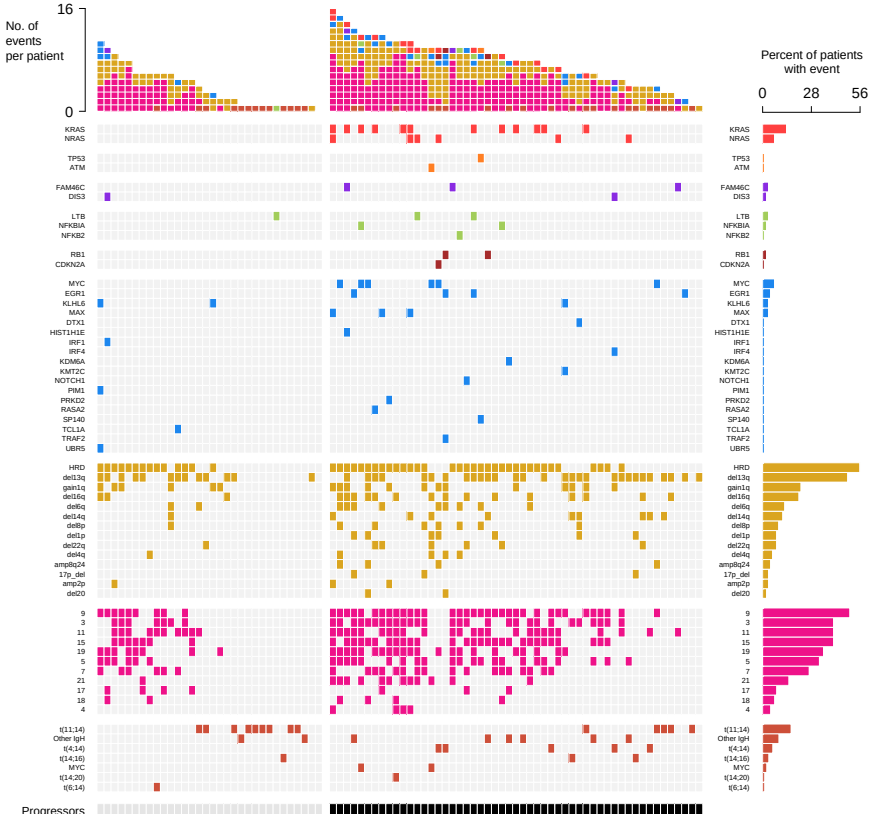


Genomic Landscape of Progressors vs Non-progressors (N = 85)

Median follow-up 6.2 yr [0.8–14.6]
Median time to progression 4 yr
61% progress

Progressors vs
Non-progressors

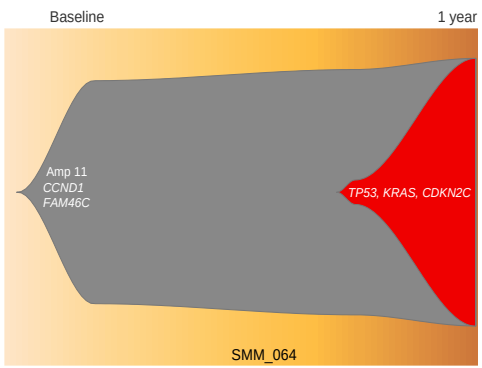


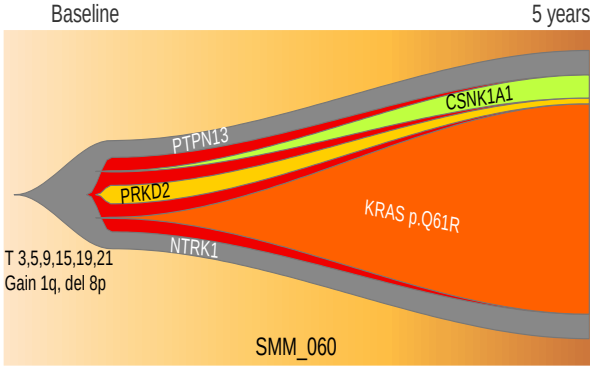
Bustoros M, et al. *J Clin Oncol.* 2020;38(21):2380-2389.

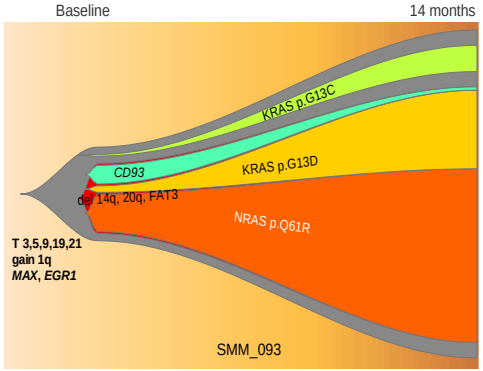
Genomic Characteristics of MGUS/SMM

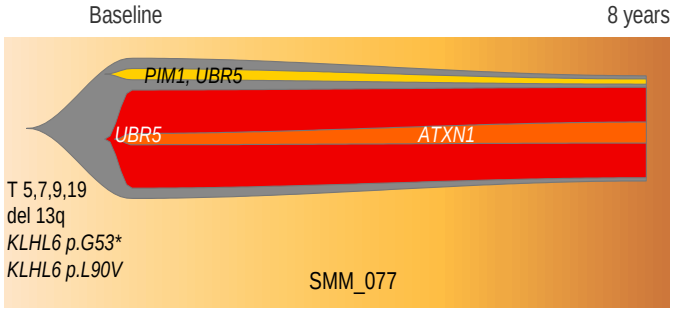
Dissecting genomic characteristics of clonal evolution from MGUS/SMM to MM and germline variants of high-risk individuals at risk of developing MGUS/SMM

Clonal Evolution of Progressed SMM Patients (n = 3) and Non-progressed Patient (n = 1)



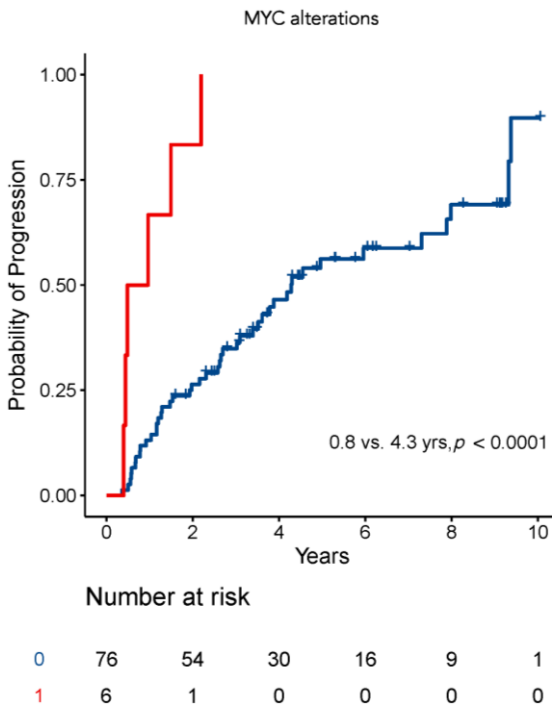


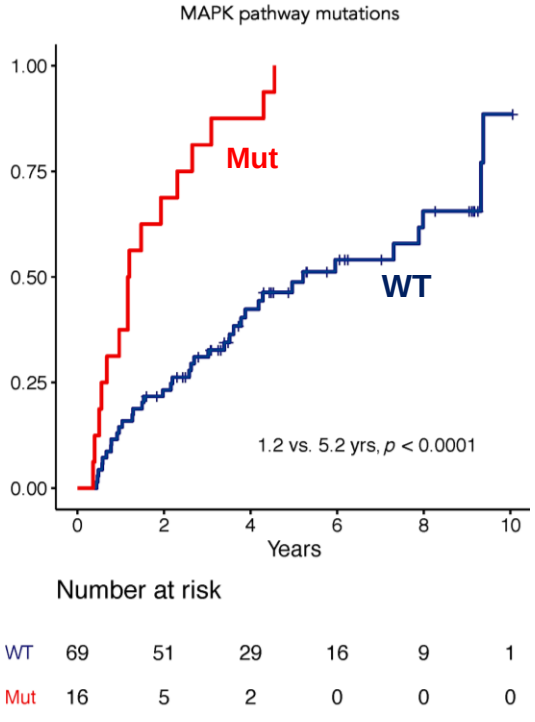


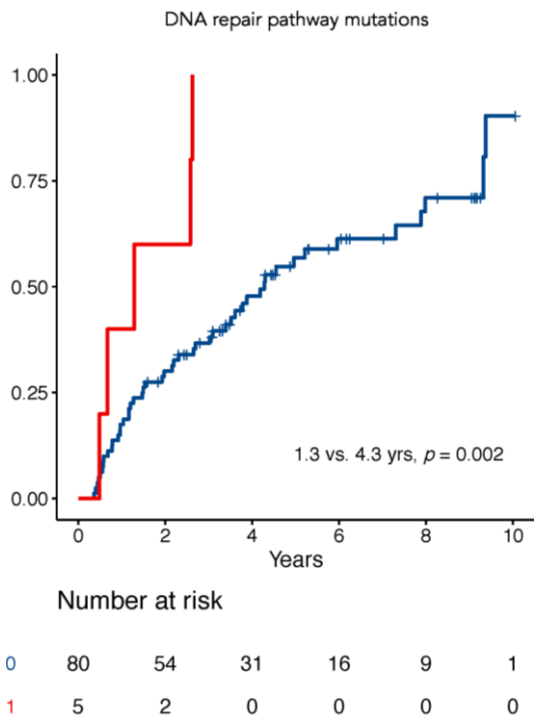


Bustoros M, et al. *J Clin Oncol.* 2020;38(21):2380-2389.

MAPK, DNA Repair, and *MYC* Predict Rapid Progression



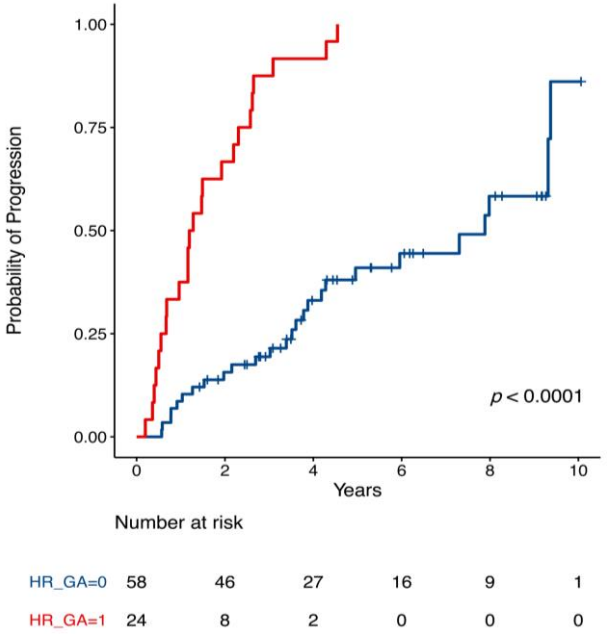




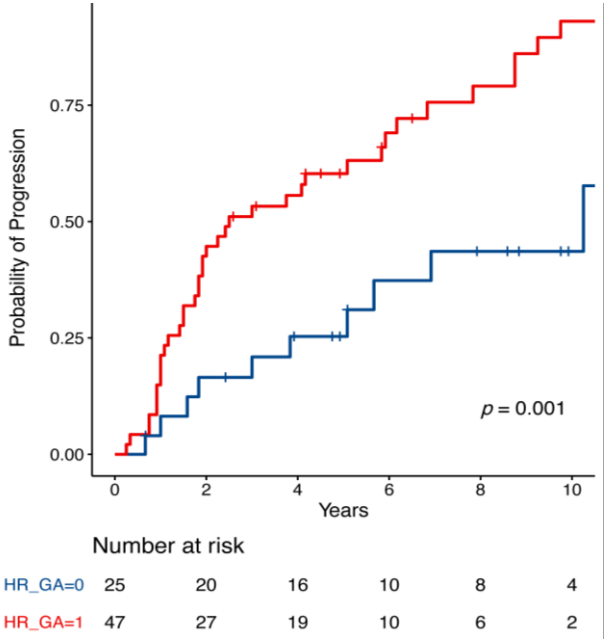
Bustoros M, et al. *J Clin Oncol.* 2020;38(21):2380-2389.

High-Risk Genomic Alterations Are Predictive in Primary and Validation Cohorts

Primary multicenter cohort
(DFCI/UK/Greece)

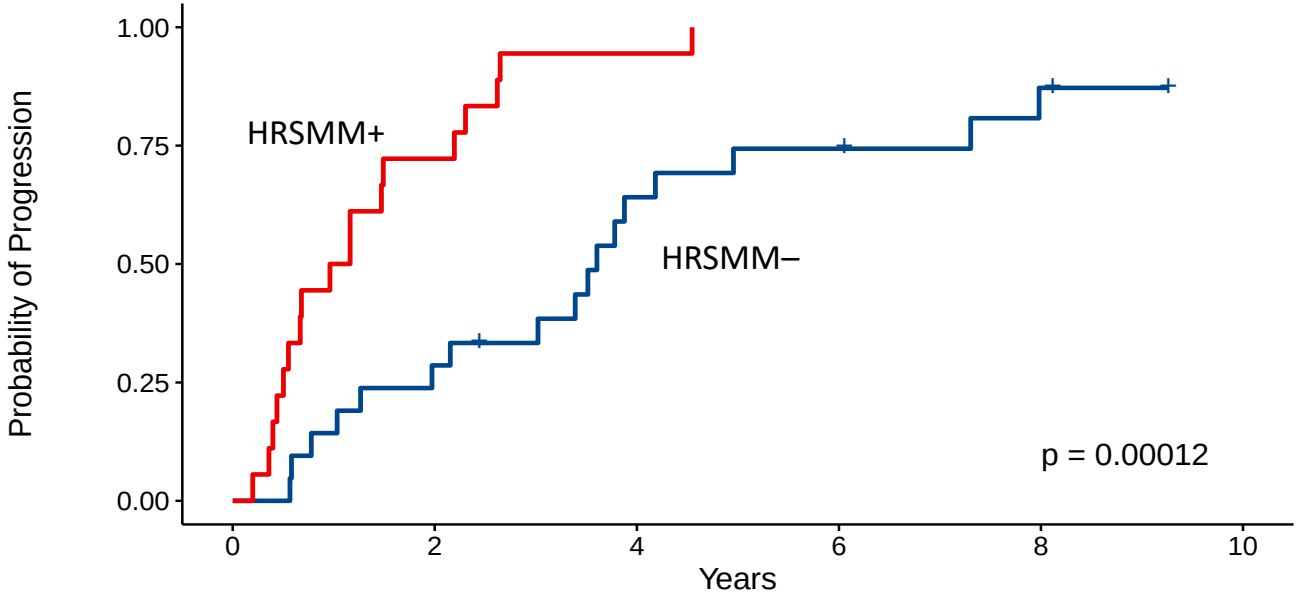


Validation cohort
(Mayo clinic)



Bustoros M, et al. *J Clin Oncol.* 2020;38(21):2380-2389.

20-2-20 High-Risk + High-Risk Genomics Progress Faster

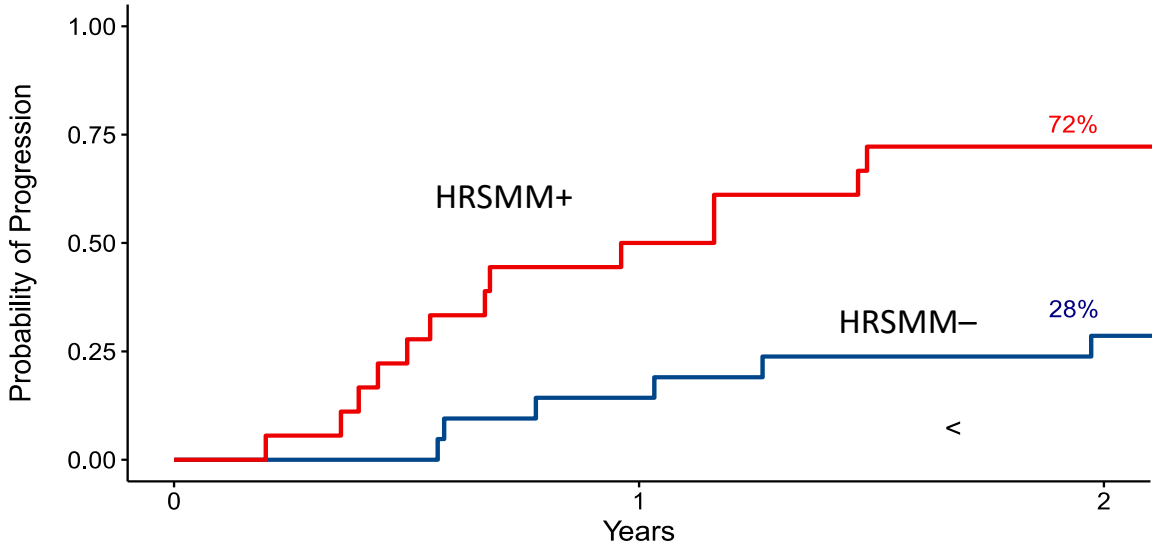


Number at risk

HR_GE=0	21	15	7	5	2	0
HR_GE=1	18	5	1	0	0	0

Bustoros M, et al. *J Clin Oncol.* 2020;38(21):2380-2389.

20-2-20 High-Risk + High-Risk Genomics Progress Faster



Number at risk

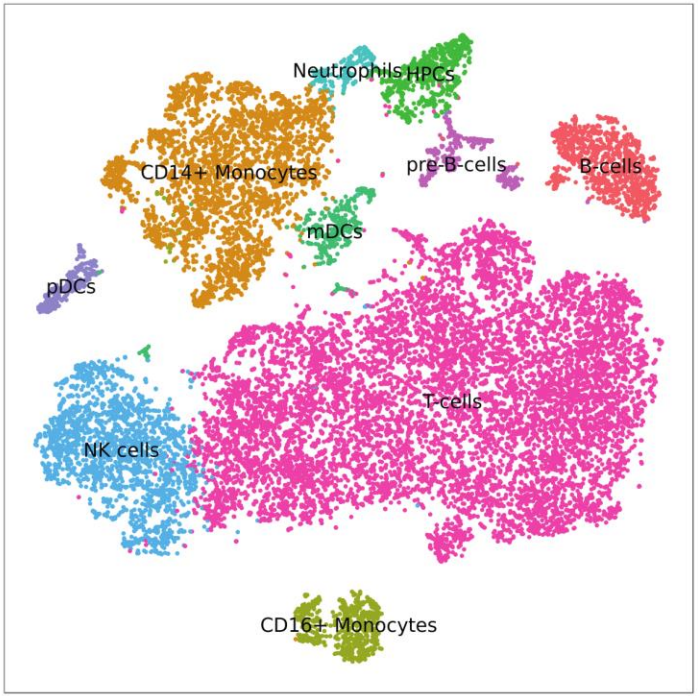
Without HR_GA	21	18	15
With HR_GA	18	9	5

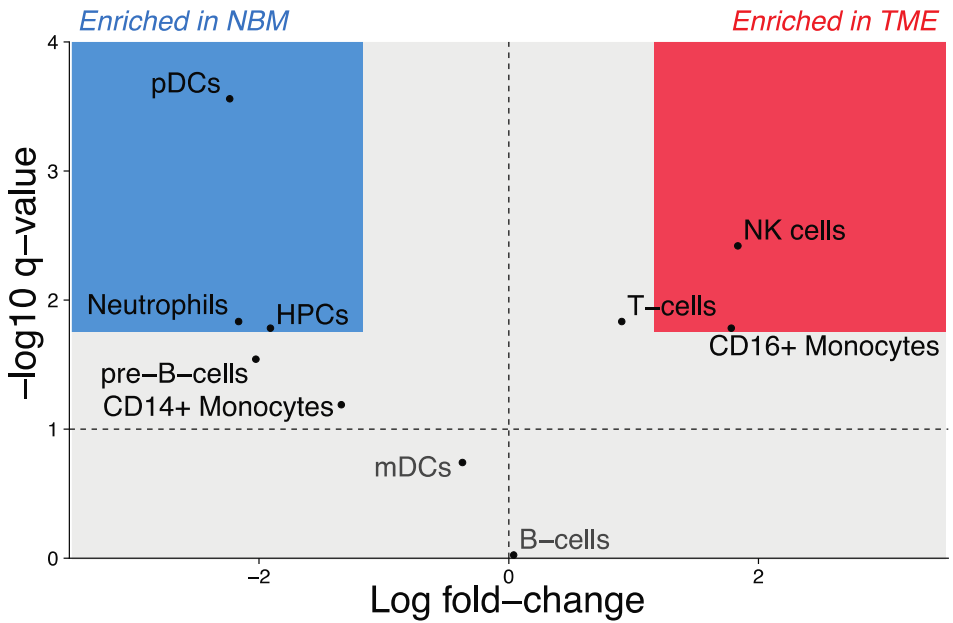
2-year probability of progression of 72% is too high and looks more like MM

Bustoros M, et al. *J Clin Oncol.* 2020;38(21):2380-2389.

Single-Cell RNA Sequencing of the Immune Cells

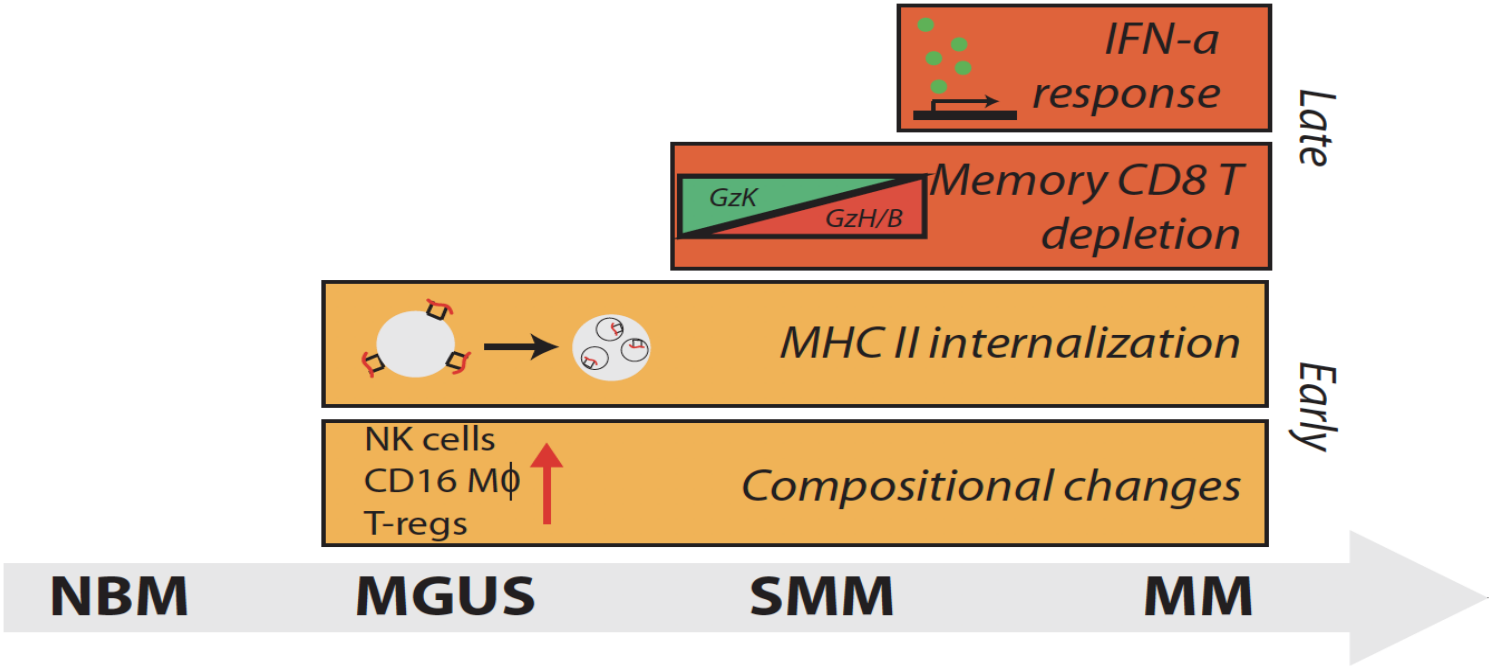
Defining the permissive tumor microenvironment in MGUS/SMM





Zavidij O, et al. *Nat Cancer.* 2020;1:493-506.

Single-Cell RNA Sequencing of the Immune Cells



Zavidij O, et al. *Nat Cancer.* 2020;1:493-506.

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DANA-FARBER CANCER INSTITUTE

We're on a mission to stop blood cancer before it starts

Help Fight Blood Cancer

JOIN THE STUDY

Enroll Now >

PCROWD is a medical research data bank.
We study blood samples and analyze data about
early phases of blood conditions that may develop into cancer.
These early conditions are called precursor conditions

pcrowd.dana-farber.org/

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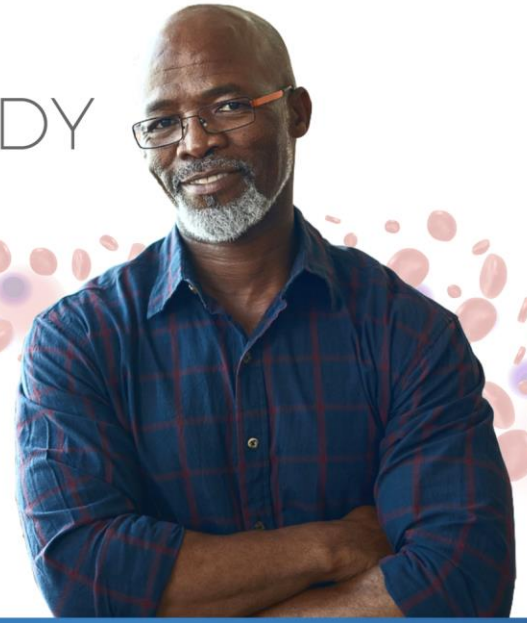
THE PROMISE STUDY

Will you join the mission to help stop myeloma before it starts?

See If You Qualify For A Free Screening



About the study

Who can join?

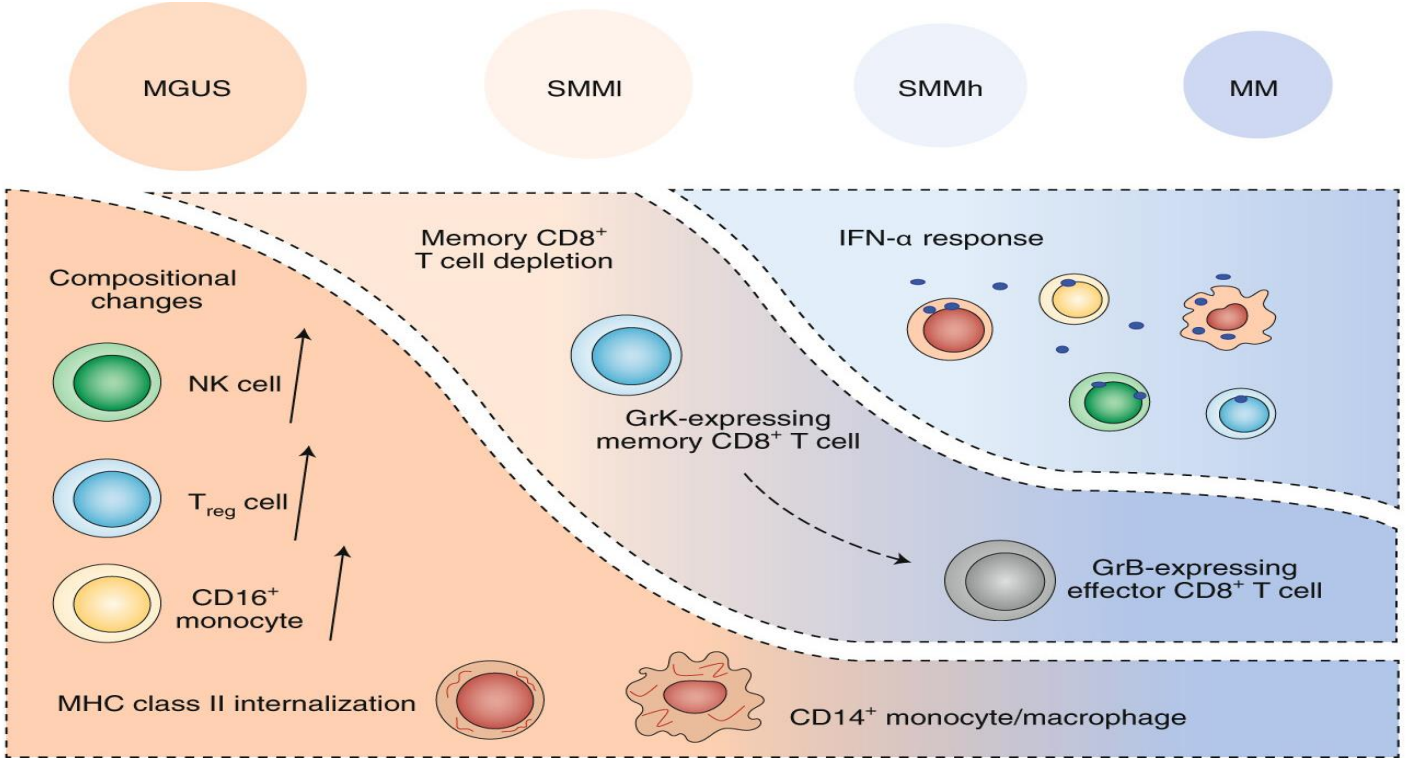
How do I join?

Got a question?
Offline

https://www.enroll.promisestudy.org

Single-Cell RNA Sequencing of the Immune Cells

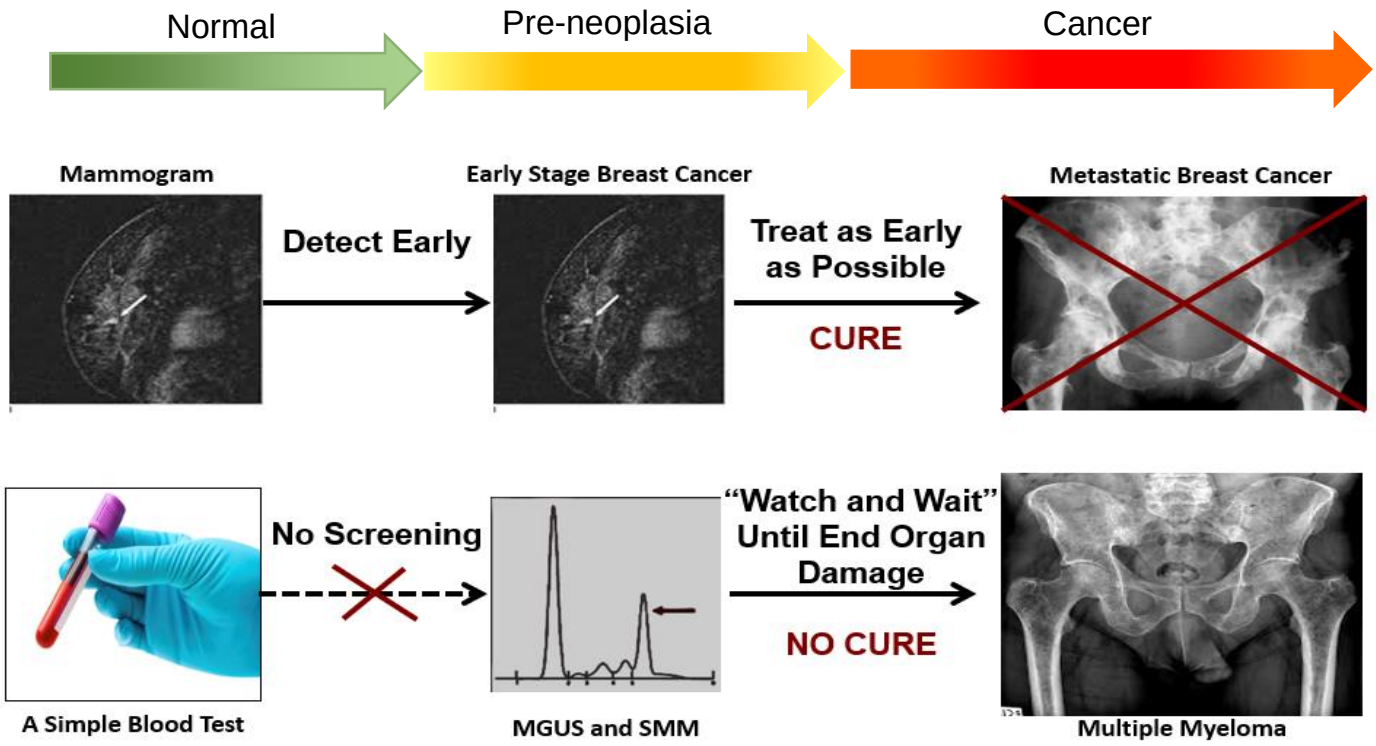
Defining the permissive tumor microenvironment in MGUS/SMM



Zavidij O, et al. *Nat Cancer.* 2020;1:493-506.

Dana-Farber Cancer Institute

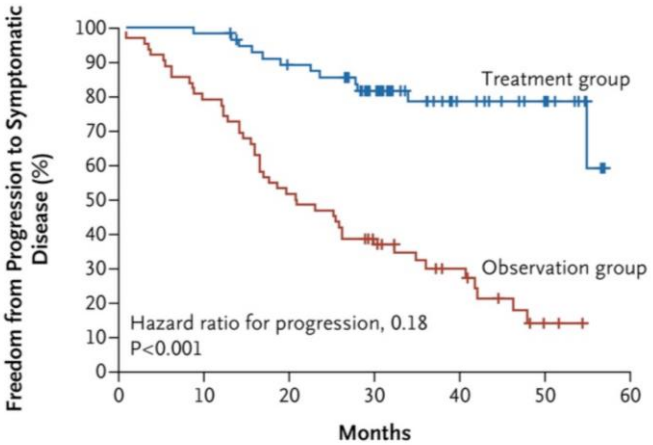
Early Screening for Cancer Detection



Therapeutic Interventions

Lenalidomide plus Dexamethasone for High-Risk Smoldering Multiple Myeloma

María-Victoria Mateos, M.D., Ph.D., Miguel-Teodoro Hernández, M.D., ilar Giraldo, M.D., Javier de la Rubia, M.D., Felipe de Arriba, M.D., Ph.D., Lucía López Corral, M.D., Ph.D., Laura Rosiñol, M.D., Ph.D., Bruno Paiva, Ph.D., Luis Palomera, M.D., Ph.D., Joan Bargay, M.D., lbert Oriol, M.D., Felipe Prosper, M.D., Ph.D., Javier López, M.D., Ph.D., ardo Olavarría, M.D., Ph.D., Nuria Quintana, M.D., José-Luis García, M.D., Joan Bladé, M.D., Ph.D., Juan-José Lahuerta, M.D., Ph.D., and Jesús-F. San Miguel, M.D., Ph.D.

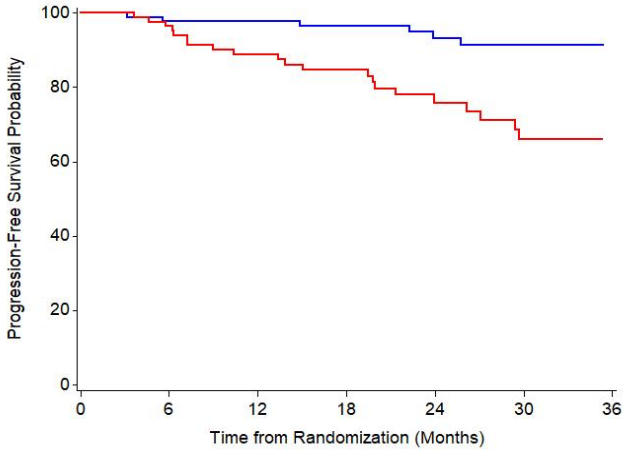


No. at Risk

Treatment group	57	57	48	38	20	14	0
Observation group	62	49	32	21	11	3	0

Randomized Trial of Lenalidomide Versus Observation in Smoldering Multiple Myeloma

Sagar Lonial, MD[1]; Susanna Jacobus, MSc[2]; Rafael Fonseca, MD[3]; Matthias Weiss, MD[4]; Shaji Kumar, MD[5]; Robert Z. Orlowski, MD, PhD[6]; Jonathan L. Kaufman, MD[1]; Abdulraheem M. Yacoub, MD[7]; Francis K. Buadi, MD[5]; Timothy O'Brien, MD[8]; Jeffrey V. Matous, MD[9]; Daniel M. Anderson, MD[10]; Robert V. Emmons, MD[11]; Anuj Mahindra, MD[12]; Lynne I. Wagner, PhD[13]; Madhav V. Dhodapkar, MBBS[1]; and S. Vincent Rajkumar, MD[5]



Numbers at Risk

Lenalidomide	90	83	81	72	55	42	35
Observation	92	77	67	56	34	26	19

Mateos M, et al. *N Engl J Med*. 2013;369:438-447; Lonial S, et al. *J Clin Oncol*. 2020;38(11):1126-1137.

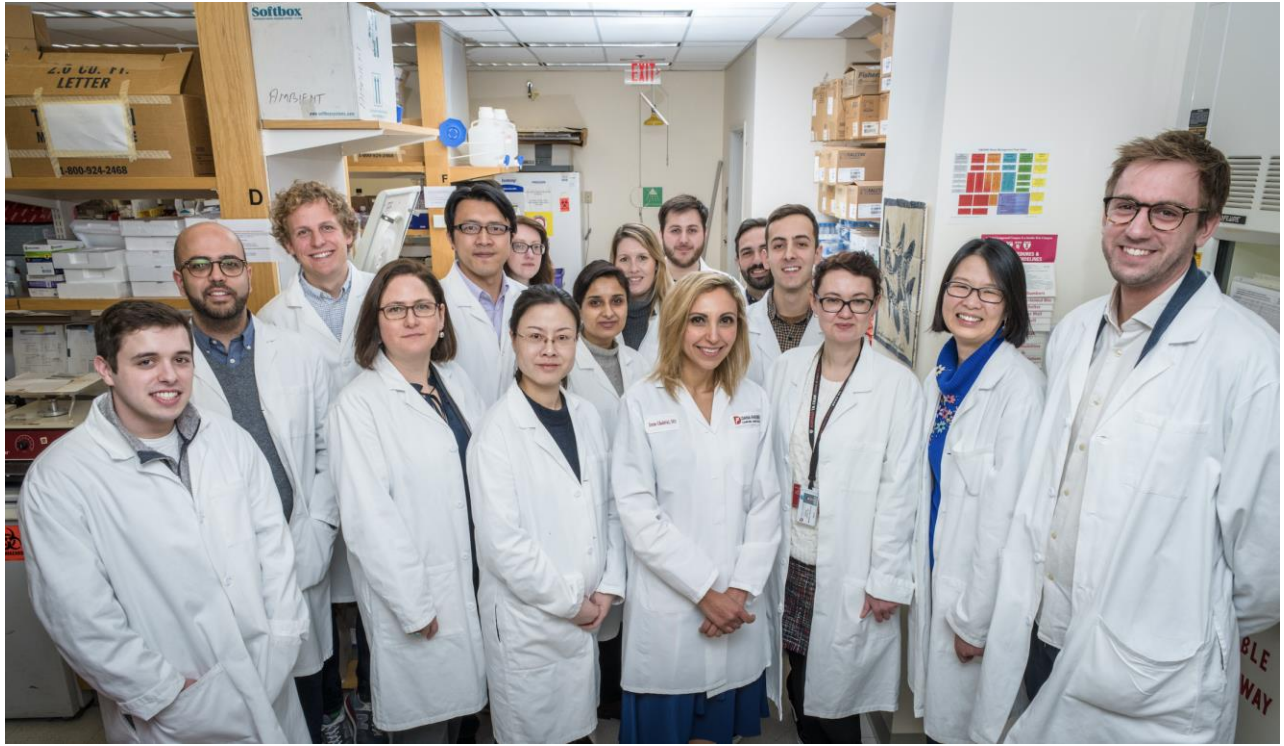
Therapeutic Interventions

Our first attempts

- Lenalidomide was the first proof of principle that early therapeutic intervention works in high-risk SMM
- Possible immune regulation
- No overall survival benefit yet
- Cannot truly predict who had benefit and who had clonal selection and tumor resistance

We need to get here

- Develop precision interception on the basis of genomic/immune profile
- Use immunotherapy early to control the clone without the need for traditional myeloma therapy
- Should we use PFS2 as a surrogate of OS?
- Identify markers of response or resistance



http://ghobriallab.danafarberdev.org/

Tim Rebbeck, Catherine Marinac, Gad Getz, Viktor Adelsteinsson, Ken Anderson, Rob Soiffer, Nikhil Munshi, Paul Richardson, Ben Ebert.
Other collaborators: Ola Landgren, Leif Bergsagel, Marta Chesi, Bruno Paiva, Jesus San Miguel.

Question 1

A 34-year-old patient comes to see you because her doctor found an M spike for an elevated protein on her routine blood work. She feels well and has no symptoms. She has no anemia, renal failure, or lesions on PET/CT scan. She has a bone marrow biopsy that shows 15% plasma cells with t(11;14) translocation. Her M spike is 1.5 g/dL and her light chain ratio is 30.

What do you want to do?

1. **She has high-risk smoldering myeloma and should go on lenalidomide and dexamethasone as therapy**
2. **She should continue on close observation for smoldering myeloma every 3 months**
3. **She has MGUS and should be seen once a year**
4. **She has high-risk smoldering myeloma but should continue observation**

Question 2

A 34-year-old patient comes to see you because her doctor found an M spike for an elevated protein on her routine blood work. She feels well and has no symptoms. She has no anemia, renal failure, or lesions on PET/CT scan. She has a bone marrow biopsy that shows 50% plasma cells with t(4;14) translocation and 17p deletion. Her M spike is 2.5 g/dL and her light chain ratio is 50 and has been increasing over the last 3 visits.

What do you want to do?

1. **She has high-risk smoldering myeloma and should go on lenalidomide and dexamethasone as therapy**
2. **She should continue on close observation for smoldering myeloma every 3 months**
3. **She has MGUS and should be seen once a year**
4. **She has high-risk smoldering myeloma and should consider a clinical trial**

Global Multiple Myeloma Academy

Discussion

APTITUDE HEALTH®

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Role of Minimal Residual Disease in Multiple Myeloma

MAJED ALAHMADI MD, FRCPC
CONSULTANT HEMATOLOGIST
KING ABDULAZIZ MEDICAL CITY-JEDDAH
ASSISTANT PROFESSOR
COLLEGE OF MEDICINE KSAU-HS

Outlines

- Why we need to assess MRD in MM?
- How to assess MRD in MM?
- What are the clinical implications of MRD in MM?

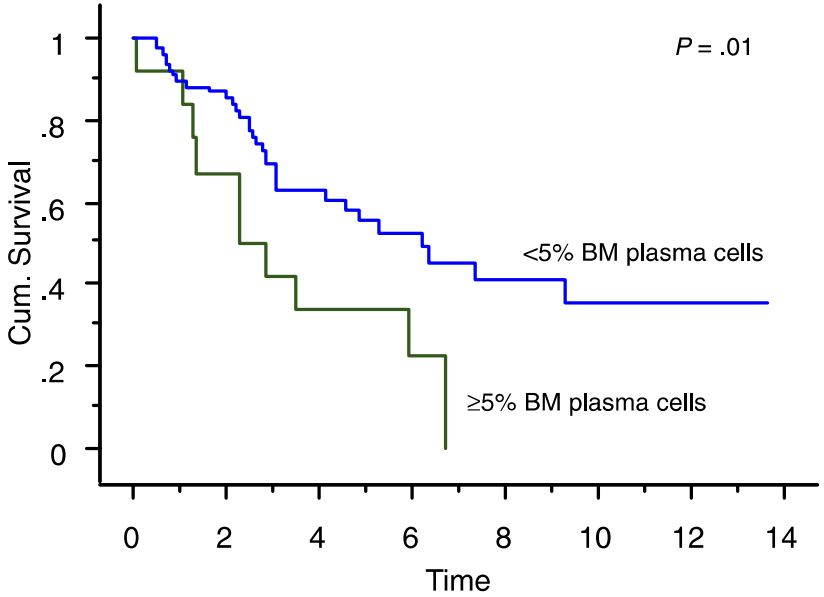
Introduction

- In the last few years, there was a significant improvement in the field of MM
  - Improved understanding of disease biology
  - Enhanced diagnostic criteria
  - Availability of sensitive and specific tools for disease prognostication
  - Increasingly effective treatment strategies
  - Enhanced supportive care

- Traditionally response assessment was made using
  - Immunological studies; SPEP and sFLC
  - Radiological studies
  - BM assessment (morphological)

But that is not enough now!

Cumulative survival



All Patients with no paraprotein & normal sFLC but either BM PC > 5% or < 5%

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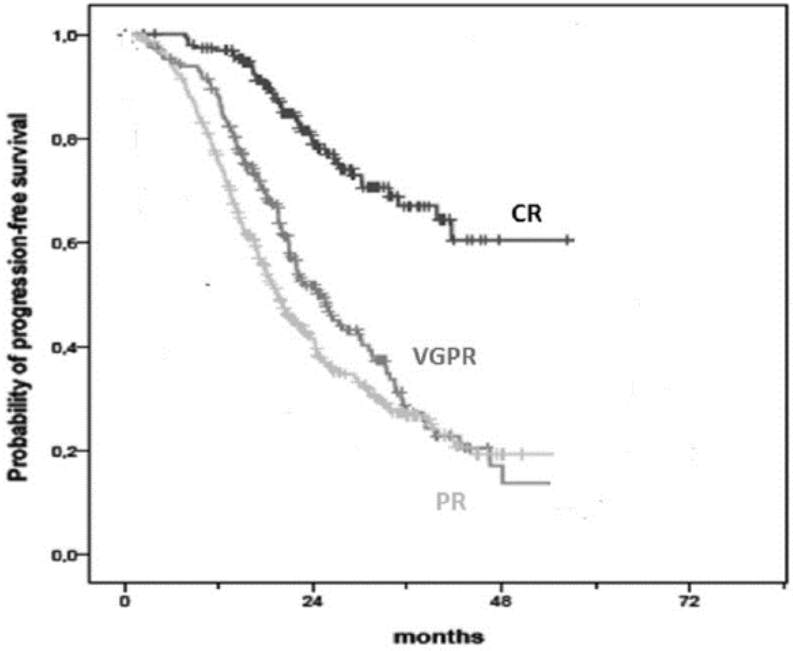
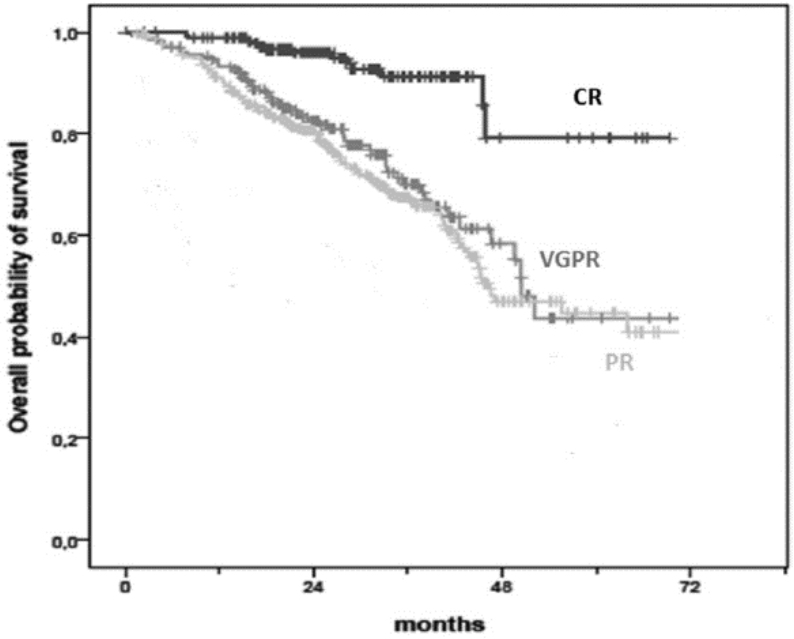
Chee CE, et al. *Blood.* 2009;114(13):2617-8

Deeper response → Better outcomes





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

MRD in MM is not a new term

- 1993 Bird et al. in Bone Marrow Transplant Journal
  - MM post allo-BMT
  - Immunoglobulin gene fingerprinting, a PCR-based technique to evaluate minimal residual disease
  - 3 patients were negative > 1 y post BMT
  - Resulted in long term disease control ?cure?

Bird JM, et al. *Bone Marrow Transplant.* 1993;12(6):651-4.

Multiparameter flow cytometric remission is the most relevant prognostic factor for multiple myeloma patients who undergo autologous stem cell transplantation

*Bruno Paiva,[1] *Maria-Belén Vidriales,[1,2] Jorge Cerveró,[1] Gema Mateo,[1,2] Jose J. Pérez,[1] Maria A. Montalbán,[3] Anna Sureda,[4] Laura Montejano,[3] Norma C. Gutiérrez,[1,2] Alfonso García de Coca,[5] Natalia de las Heras,[6] Maria V. Mateos,[1,2] Maria C. López-Berges,[1] Raimundo García-Boyero,[7] Josefina Galende,[8] Jose Hernández,[9] Luis Palomera,[10] Dolores Carrera,[11] Rafael Martínez,[12] Javier de la Rubia,[13] Alejandro Martín,[14] Joan Bladé,[15] Juan J. Lahuerta,[3] Alberto Orfao,[2,16] and Jesús F. San Miguel,[1,2] on behalf of the GEM (Grupo Español de MM)/PETHEMA (Programa para el Estudio de la Terapéutica en Hemopatías Malignas) cooperative study groups

- 4 color flowcytometry
- Assessing BM day 100 post ASCT
- Assessing these target antigens:
  - CD38/CD56/CD19/CD45, CD138/CD28/ CD33/CD38, and CD20/CD117/CD138/CD38
- Sensitivity limit of 10^{-4}

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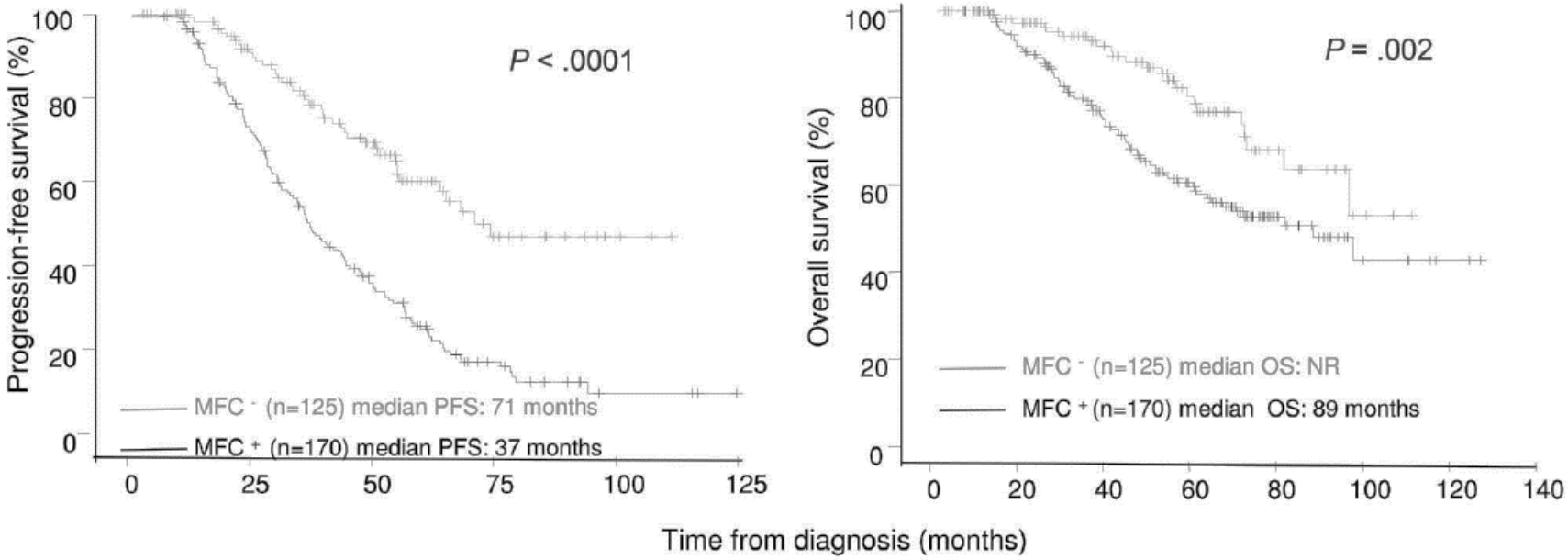
Pavia B, et al. *Blood.* 2008;112(10):4017-23.

PFS and OS for whole patient population



COLLEGE OF MEDICINE JEDDAH

Pavia B, et al. *Blood.* 2008;112(10):4017-23.

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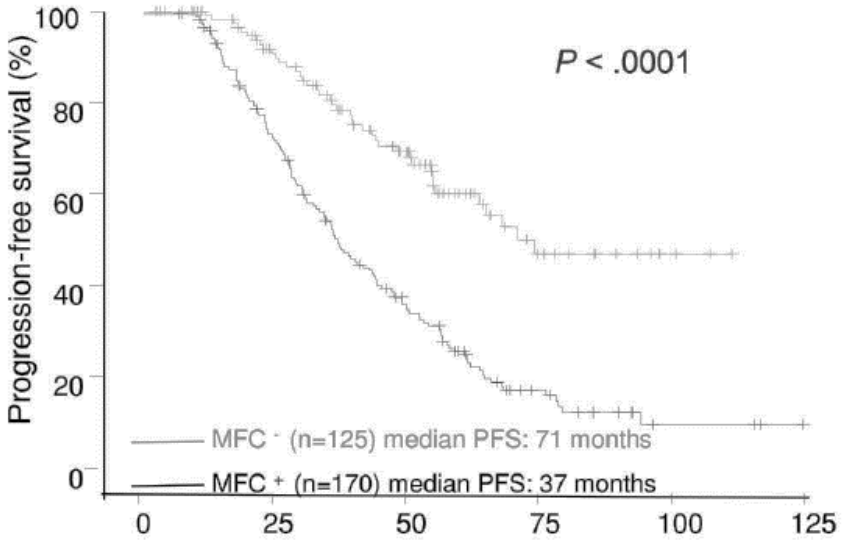

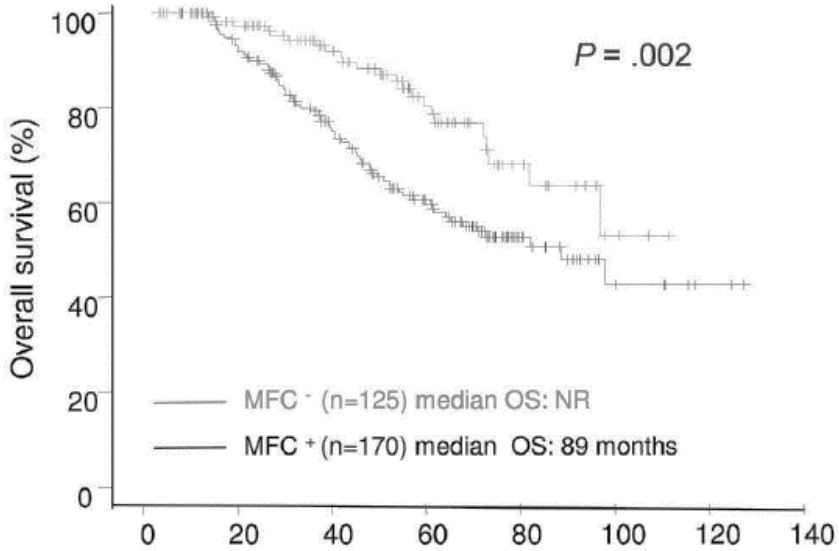

MRD negativity is the best predictor for good long-term outcomes

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Pavia B, et al. *Blood.* 2008;112(10):4017-23.

We should do better than CR in the current era

After that

So many publication about MRD in MM using so many techniques

IMWG guidelines for MRD in MM

International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma

Shaji Kumar, Bruno Paiva, Kenneth C Anderson, Brian Durie, Ola Landgren, Philippe Moreau, Nikhil Munshi, Sagar Lonial, Joan Bladé, Maria-Victoria Mateos, Meletios Dimopoulos, Efstathios Kastritis, Mario Boccadoro, Robert Orlowski, Hartmut Goldschmidt, Andrew Spencer, Jian Hou, Wee Joo Chng, Saad Z Usmani, Elena Zamagni, Kazuyuki Shimizu, Sundar Jagannath, Hans E Johnsen, Evangelos Terpos, Anthony Reiman, Robert A Kyle, Pieter Sonneveld, Paul G Richardson, Philip McCarthy, Heinz Ludwig, Wenming Chen, Michele Cavo, Jean-Luc Harousseau, Suzanne Lentzsch, Jens Hillengass, Antonio Palumbo, Alberto Orfao, S Vincent Rajkumar, Jesus San Miguel, Herve Avet-Loiseau

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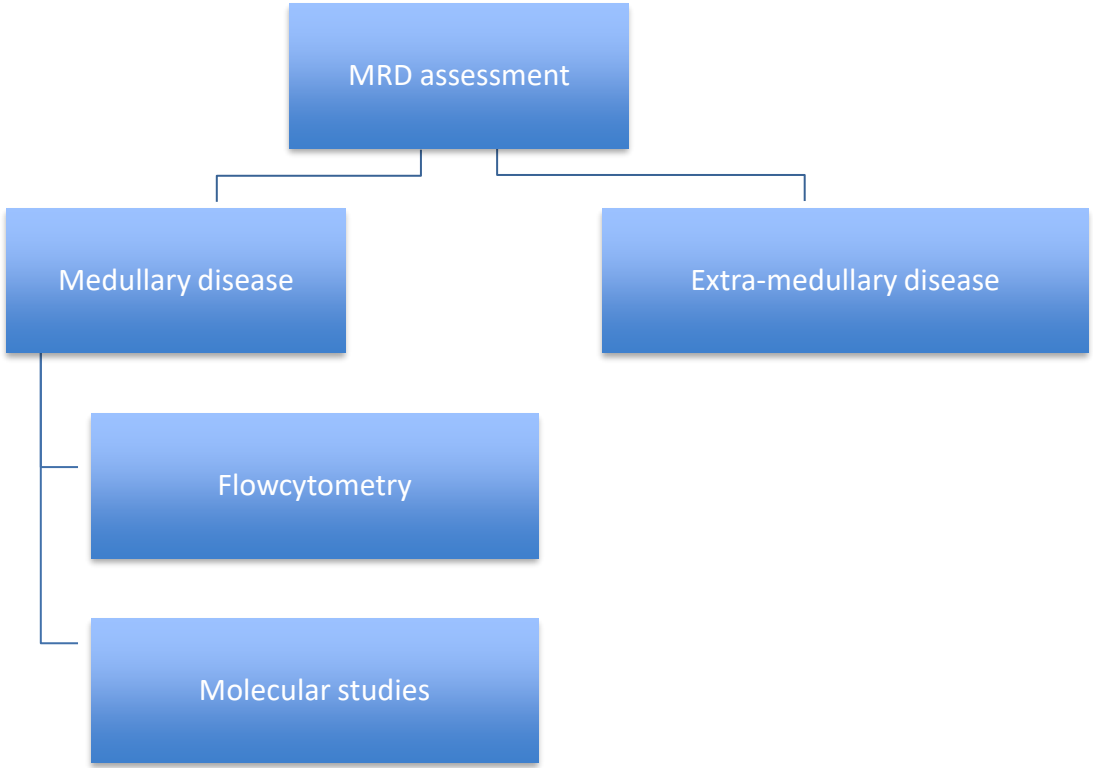
Kumar S. et al. *Lancet Oncol.* 2016;17(8):e328-e346.



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Kumar S. et al. *Lancet Oncol.* 2016;17(8):e328-e346.

Flowcytometry assessment of MRD

- Advantage of flowcytometry
  - Available
  - Rapid
  - Relatively cheap
  - Important in diagnosis, prognosis stratification and monitoring of the response of therapy
  - The role of the tumor microenvironment
  - Identification of potential therapeutic targets

Kumar S. et al. *Lancet Oncol.* 2016;17(8):e328-e346.

Flowcytometry assessment of MRD

- The most commonly used surface markers to distinguish abnormal PCs from normal ones
  - CD138, CD38, CD45, CD56, CD19, and cytoplasmic κ and λ immunoglobulin light chains
- Other markers that could be used
  - CD20, CD27, CD28, CD81, CD117, and CD200

Kumar S. et al. *Lancet Oncol.* 2016;17(8):e328-e346.

Flowcytometry assessment of MRD

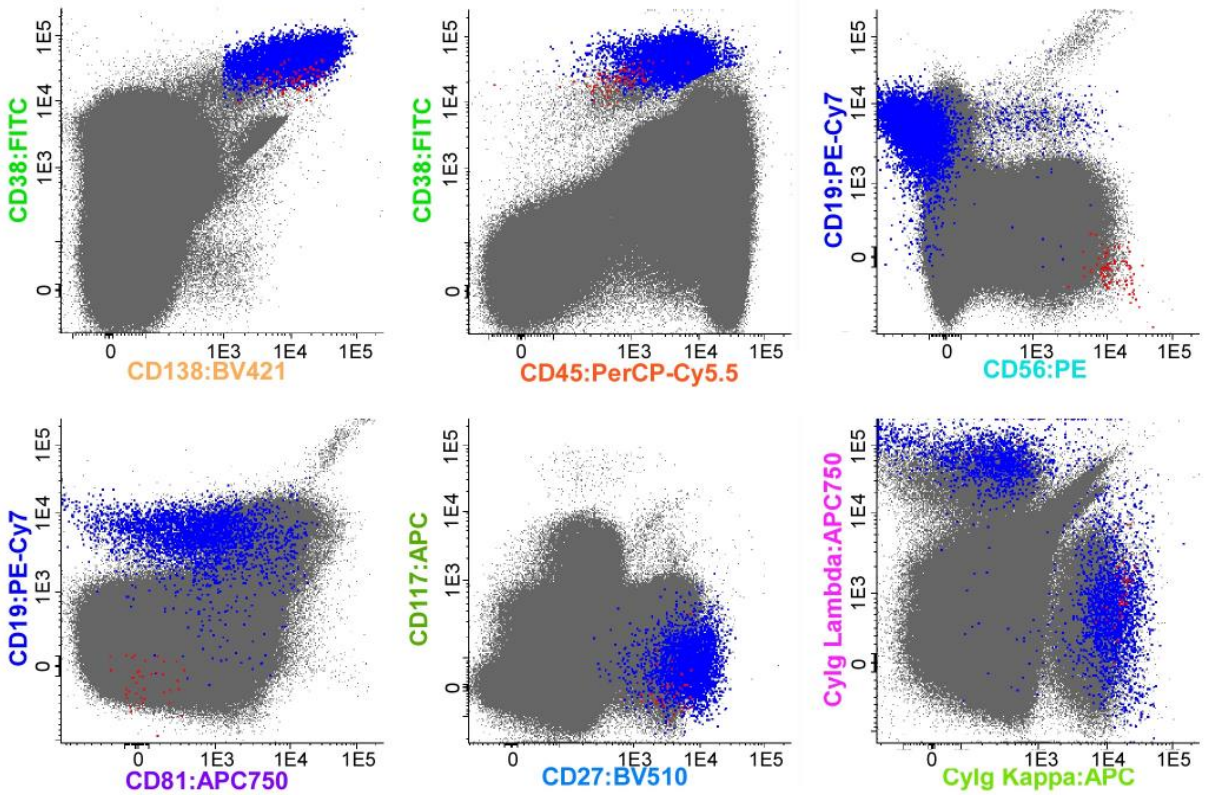
- Disadvantages
  - The heterogeneity of expression of these markers
  - Differences in the number of events studied
  - Differences in the analytical strategies used

Kumar S. et al. *Lancet Oncol.* 2016;17(8):e328-e346.

Next Generation Flowcytometry (NGF-MRD)

- EuroFlow's MFC
  - An eight-color detection method using two tubes
    - Tube 1: CD138/CD27/CD38/CD56/CD45/CD19/CD117/CD81
    - tube 2: CD138/CD27/CD38/CD56/CD45/ CD19/CyIgK/CyIgL

Burgos L and Paiva B. *Methods Mol Biol.* 2018;1792:15-34



COLLEGE OF MEDICINE JEDDAH

Personal communication from Dr Alahmadi.

IMWG definition of MRD negativity by flowcytometry

- Flow MRD-negative
  - Absence of phenotypically aberrant clonal plasma cells by NGF on bone marrow aspirates using the EuroFlow standard operation procedure for MRD detection in multiple myeloma (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells or higher

Romano A. et al. *Front Oncol.* 2019:9:699.

Trial	Disease status and treatment	N	MRD negative	Outcomes
Paiva et al.[1]	Newly diagnosed MM from GEM2000*. MRD day 100 after ASCT	295	125 (42%)	PFS (median 71 months vs 37 months; p<0·001) and OS (median not reached vs 89 months; p=0·002)
Rawstron et al.[2]	MRC IX trial, ASCT cohort	397	246 (62%)	Median PFS for MRD +ve 15·5 months vs 28·6 months for MRD -ve (p<0·001). Median OS of 59·0 months in MRD+ve vs 80·6 months in MRD -ve (p=0·02)
	MRC IX trial, no ASCT cohort	245	37(15%)	MRD-positive associated with non-significantly inferior PFS (median 7·4 months vs 10·5 months, p=0·1)
Puig et al.[3]	GEM2000*and GEM2005MENOS65† trials	102	52 (51%)	MRD-negative patients had longer PFS, both in intensively treated patients (median 45 months vs 27 months, p=0·02) and in non-intensively treated patients (not reached vs 27 months; p=0·002)
Sarasquete et al.[4]	MM post ASCT in CR	24	13 (53%)	Improved PFS for MRD-negative patients (median 27 months vs 10 months; p=0·05)

1. Pavia B, et al. *Blood* 2008; 112: 4017–23;
2. Rawtson AC, et al. *J Clin Oncol* 2013; 31: 2540–47;
3. Puig N, et al. *Leukemia* 2014; 28: 391–97;
4. Sarasquete ME, et al. Haematologica 2005; 90: 1365–72.

Molecular assessment of MRD

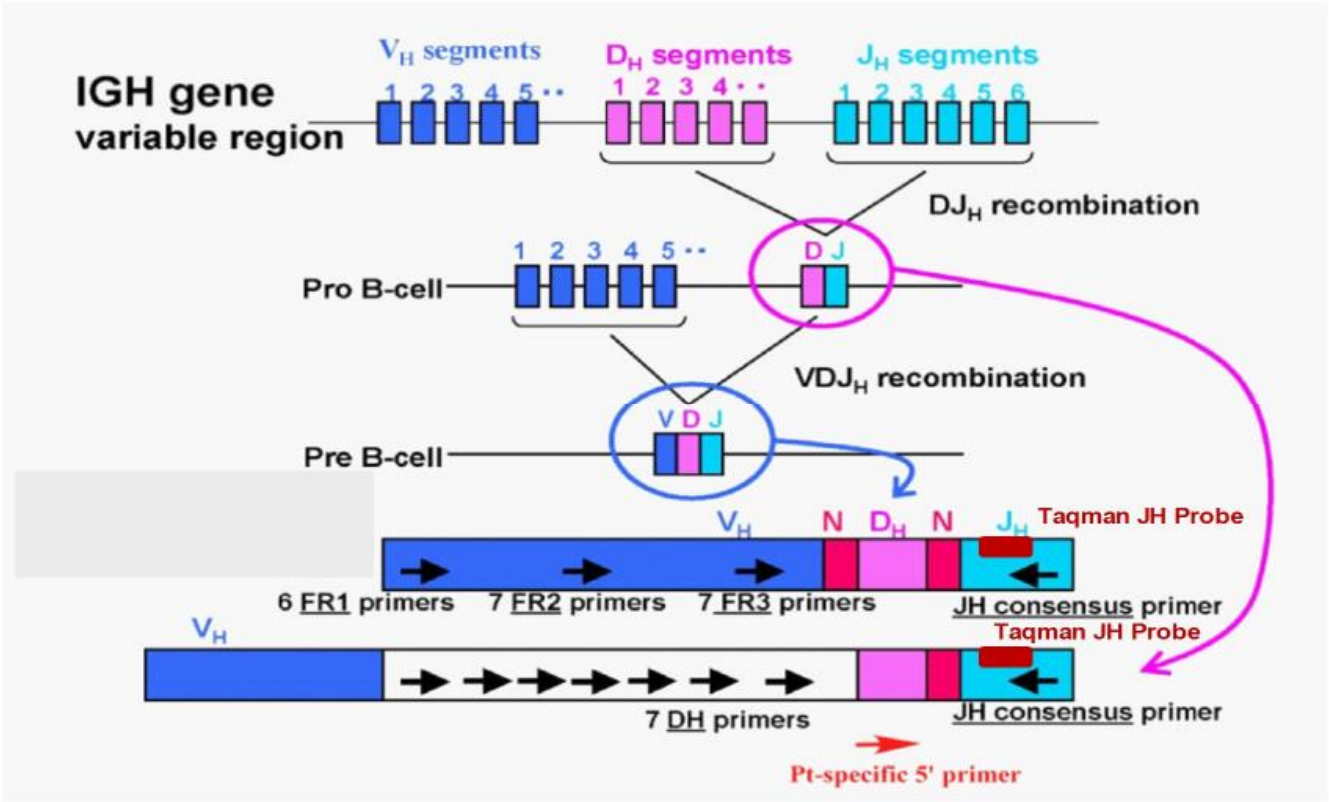
- Either by using
  - Allele-specific oligonucleotide real-time quantitative PCR (ASO-qPCR)
  - Next-generation sequencing

Romano A. et al. *Front Oncol.* 2019:9:699.

Molecular assessment of MRD

- ASO-qPCR
  - Uses allele-specific oligonucleotide real-time quantitative PCR (ASO-qPCR)
  - Target plasma-cell-specific immuno- globulin heavy chain (*IGH*) gene rearrangements
  - Allows the detection of very low levels of multiple myeloma plasma cells
  - Sensitivity that can detect one in 10^5 cells

Romano A. et al. *Front Oncol.* 2019:9:699.



Personal communication from Dr Alahmadi.

Molecular assessment of MRD

- Next-generation sequencing
  - Mostly with LymphoSIGHT platform
    - Uses sets of multiple primers for the amplification and sequencing of immunoglobulin gene segments

Romano A. et al. *Front Oncol.* 2019:9:699.

Trial	Disease status and treatment	N	MRD negative	Outcomes
Puig et al.[1]	GEM2000 and GEM05 trials	103 (170)	47%	MRD-negative patients had significantly longer PFS (median 54 months vs 27 months; p=0·001)
Putkonen et al.[2]	Patients with MM who had achieved a CR/near CR after ASCT	37	57%	Low/negative-MRD after ASCT resulted in longer PFS (median 70 vs 19 months; p=0·003)
Ladetto et al.[3]	Four cycles of bortezomib, thalidomide, and dexamethasone consolidation after ASCT	112	18%	Improved PFS; 100% vs 77% at 6 months detected by allele-specific oligonucleotide qPCR [p=0·02]
Martinelli et al.[4]	Patients who achieved a complete response following ASCT	50	27%	MRD-negative patients had a significantly lower relapse rate (41% vs 16%; p<0·05) and longer PFS (median 35 months vs 110 months; p<0·005)

1. Puig N, et al. *Leukemia* 2014; 28: 391–97;
2. Putkonen M. et al. *J Haematol* 2010; 85: 416–23;
3. Ladetto M, et al. *J Clin Oncol* 2010; 28: 2077–84;
4. *Martinelli G, et al. J Clin Oncol* 2000; 18: 2273–81.

	Allele-specific oligonucleotide qPCR	MFC	*VDJ* sequencing
Applicability	60–70%	Nearly 100%	≥90%
Need for baseline sample	Yes, requires production of patient-specific probes	Not required; abnormal plasma cells can be identified in any sample by their distinct immunophenotypic pattern *vs* normal plasma cells	Baseline samples required for identification of the dominant clonotype; alternatively, a stored sample from a time point with detectable disease can be used to define baseline status
Sample requirements	<1 million cells	>5 million cells	<1 million cells; higher numbers improve sensitivity
Sample processing	Can be delayed; can use both fresh and stored samples	Needs assessment within 24–48 h; requires a fresh sample	Can be delayed; can use both fresh and stored samples
Sample quality control	Not possible. Additional studies required	Immediate with global bone marrow cell analysis	Not possible. Additional studies required
Sensitivity	≥1 in 10^5	≥1 in10^5	≥1 in 10^5
Information regarding sample composition	No further information available	Detailed information available on leucocyte subsets and their relative distribution	Information about immunoglobulin gene repertoire of B cells in the studied patient samples
Turnaround and complexity	Labour intensive; requires the development of patient-specific primers/probes; can take several days	Can be done in a few hours; automated software available	Can take several days for turnaround; requires intense bioinformatics support. Use of local laboratories could speed up this limitation
Standardisation	Has been done for other diseases (EuroMRD), can be done for myeloma as well	Standardised by the EuroFlow consortium	In process
Availability	Wide*	Most hospitals with four-colour flow cytometry. Eight or more-colour flow cytometry requires more experienced centres/laboratories. Many laboratories have adopted the EuroFlow laboratory protocols and use the EuroFlow MRD tubes	So far limited to one company/platform

*Globally, about 60 MRD laboratories are EuroMRD members and participate twice per year in the external quality assurance rounds. MFC=multiparametric flow cytometry. MRD=minimal residual disease.

Table 3: **Comparison of different bone marrow minimal residual disease assessment techniques**

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Kumar S. et al. *Lancet Oncol.* 2016;17(8):e328-e346.

	NGF	NGS
Applicability (% cases)	99%	~90%
Sensitivity	2–4 × 10^{-6}	10^{-6}
Time to result	2–3 h	≥7days
Number of cells required	2 × 10^{7}	2–3 × 10^{6}
Need for fresh sample	Yes (within 24 h)	No
Need for diagnostic sample	No	Yes
Quantitative	Yes	Yes
Intrinsic quality control for hemodilution	Yes	No
Cell characterization	Yes	No
Molecular characterization	No	Yes
Availability	Wide	Limited
Reproducibility among centers	High	Not reported
Harmonization	Yes	Not reported
Cost	+	++

Personal communication from Dr Alahmadi.

Extramedullary disease

- PET-CT
- MRI
  - Both are good in detecting extra-medullary disease on presentation
  - But which one is better in evaluating MRD status?

Kumar S. et al. *Lancet Oncol.* 2016;17(8):e328-e346.

VOLUME 35 · NUMBER 25 · SEPTEMBER 1, 2017

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

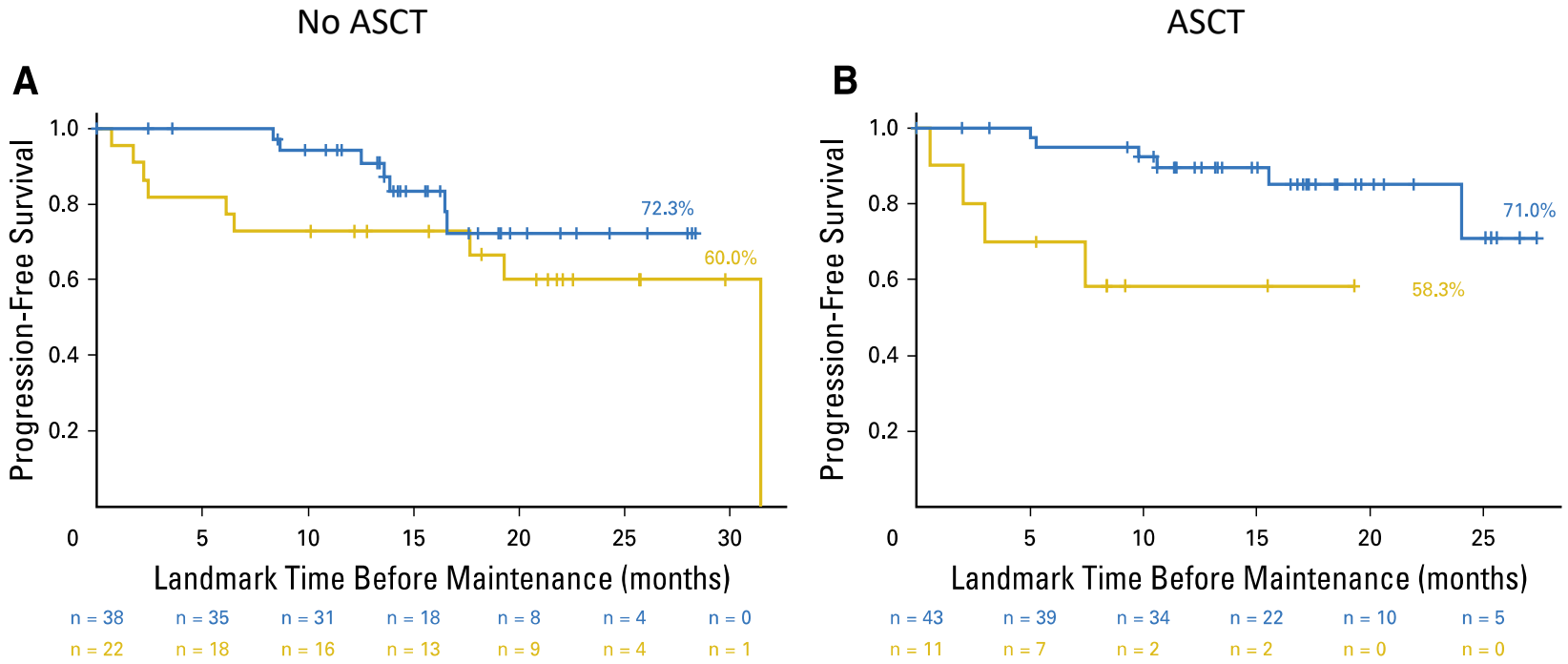
Prospective Evaluation of Magnetic Resonance Imaging and [^{18}F]Fluorodeoxyglucose Positron Emission Tomography-Computed Tomography at Diagnosis and Before Maintenance Therapy in Symptomatic Patients With Multiple Myeloma Included in the IFM/DFCI 2009 Trial: Results of the IMAJEM Study

Philippe Moreau, Michel Attal, Denis Caillot, Margaret Macro, Lionel Karlin, Laurent Garderet, Thierry Facon, Lotfi Benboubker, Martine Escoffre-Barbe, Anne-Marie Stoppa, Kamel Laribi, Cyrille Hulin, Aurore Perrot, Gerald Marit, Jean-Richard Eveillard, Florence Caillon, Caroline Bodet-Milin, Brigitte Pegourie, Veronique Dorvaux, Carine Chaleteix, Kenneth Anderson, Paul Richardson, Nikhil C. Munshi, Herve Avet-Loiseau, Aurelie Gaultier, Jean-Michel Nguyen, Benoit Dupas, Eric Frampas, and Françoise Kraeber-Bodere

IMAJEM study

- They looked at the data from the IFM 2009 trial in both ASCT and non-ASCT group
- Conclusion was
  - MRI and PET/CT are comparable in detection of bony lesions upon diagnosis
  - Negative PET-CT post therapy is associated with better PFS and OS

Moreau P. et al. *J Clin Oncol.* 2017;35(25):2911-2918.



30-month PFS in -ve PET vs +ve PET: 78.7% v 56.8%

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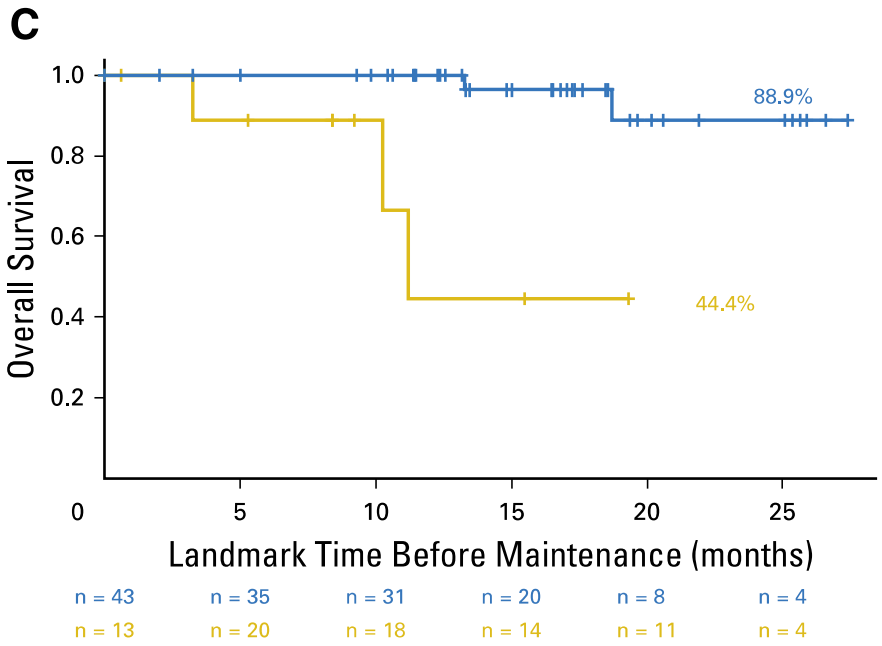
Moreau P. et al. *J Clin Oncol.* 2017;35(25):2911-2918.



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Moreau P. et al. *J Clin Oncol.* 2017;35(25):2911-2918.

- Based on IMWG guidelines
  - Radiological MRD negativity is defined as disappearance of every area of increased tracer uptake found at baseline PET/CT

Kumar S. et al. *Lancet Oncol.* 2016;17(8):e328-e346.

Noninvasive Molecular Monitoring in Multiple Myeloma Patients Using Cell-Free Tumor DNA

A Pilot Study

Giulia Biancon,*† Silvia Gimondi,*† Antonio Vendramin,† Cristiana Carniti,* and Paolo Corradini*†

- Circulating tumor DNA as a surrogate maker for the BM MRD status with no need for BM biopsy.

COLLEGE OF MEDICINE JEDDAH

Biancon G. et al. *J Mol Diagn.* 2018;20(6):859-870.

Table 1 Summary of recent phase III studies which reported outcomes associated with MRD status

Study	Patient population	MRD methodology (sensitivity)	Outcome
ALCYONE. Mateos et al. [34]	TI ND randomized to D-VMP vs VMP	NGS (10^{-5})	Quadruplet therapy improved MRD negativity rate. MRD negativity associated with superior PFS.
IFM2009; Attal et al. [35]	TE ND receiving RVD induction randomized to consolidation with ASCT/RVD vs RVD followed by R maintenance	MFC (10^{-4})	Higher rate of MRD negativity in transplant arm. MRD negativity associated with superior PFS.
IFM2009; Perrot et al. [36]	TE ND receiving RVD induction randomized to consolidation with ASCT/RVD vs RVD followed by R maintenance	NGS (10^{-6})	Higher rate of MRD negativity in transplant arm. MRD negativity associated with superior PFS and OS.
MAIA; Facon et al. [37]	TI ND randomized to DRd vs RD	NGS (10^{-5})	Triplet therapy improved MRD negativity rate. MRD negativity associated with superior PFS.
Myeloma XI; de Tute et al. [38]	TE and TI ND receiving R maintenance	MFC (4×10^{-5})	Lenalidomide maintenance increases rate of MRD negativity. MRD negativity associated with superior PFS.
Gambella et al. [39]	ND receiving R maintenance	ASO-RQ-PCR (10^{-5}) and MFC (10^{-4} to 10^{-5}).	Lenalidomide maintenance increases rate of MRD negativity. MRD negativity associated with superior PFS.
CASTOR. Spencer et al. [40]	RR receiving DVd vs Vd	NGS (10^{-5}, 10^{-6})	Triplet therapy improved MRD negativity rate. MRD negativity associated with superior PFS.
POLLUX. Dimopoulos et al. [41]	RR receiving DRd vs Rd	NGS (10^{-5}, 10^{-6})	Triplet therapy improved MRD negativity rate. MRD negativity associated with superior PFS.

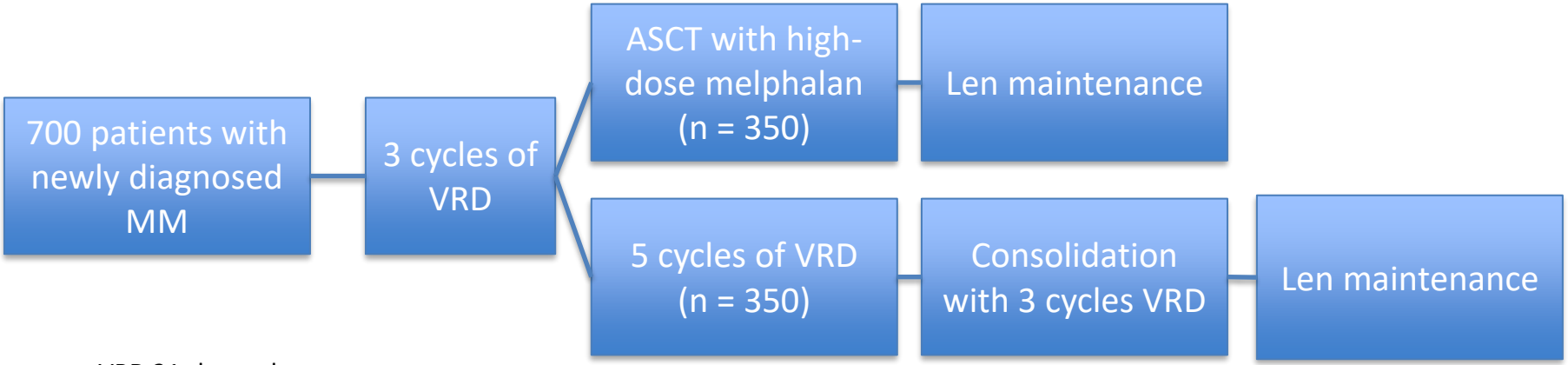
CR, 10^{-5}, 10^{-6} OR EVEN DEEPER?

- Newer modalities of therapy ➡ deeper responses
- For now, 10^{-5} but that might get change

EARLY, DELAYED OR NO ASCT FOR TRANSPLANT ELIGIBLE PATIENTS?

IFM 2009

IFM 2009



VRD 21-day cycle:

- Lenalidomide: 25mg days 1-14
- Bortezomib: 1.3mg/m^2 IV days 1,4,8 and 11.
- Dexamethasone: 20mg on days 1, 2, 4, 5, 8, 9, 11, and 12

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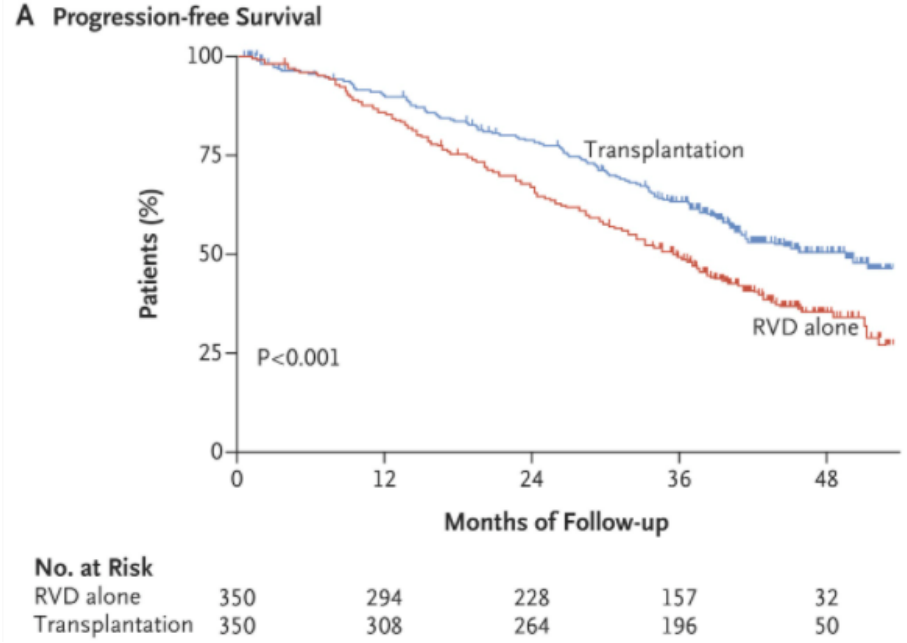
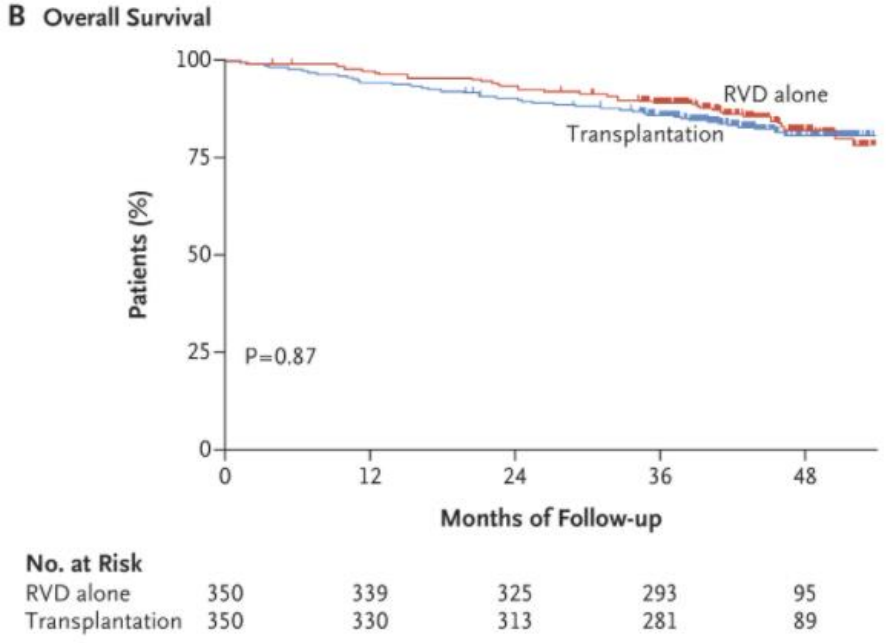
Attal M. et al. *N Engl J Med.* 2017;376:1311-1320.

Kaplan-Meier curves for PFS and OS





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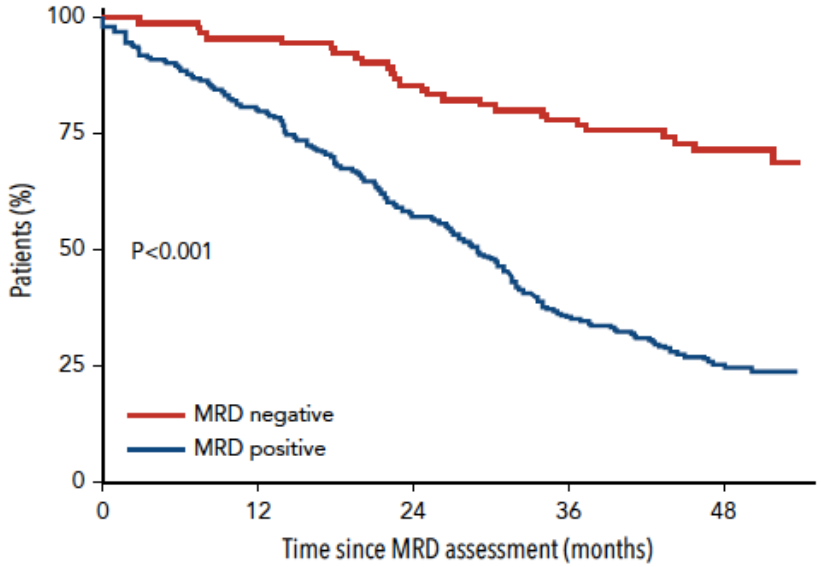
Attal M. et al. *N Engl J Med.* 2017;376:1311-1320.

PFS by MRD status



- IFM 2009
- Induction VRD followed by ASCT vs VRD
- MRD 10^{-6}
- PFS:
  - MRD –ve: NR
  - MRD +ve: 29 months

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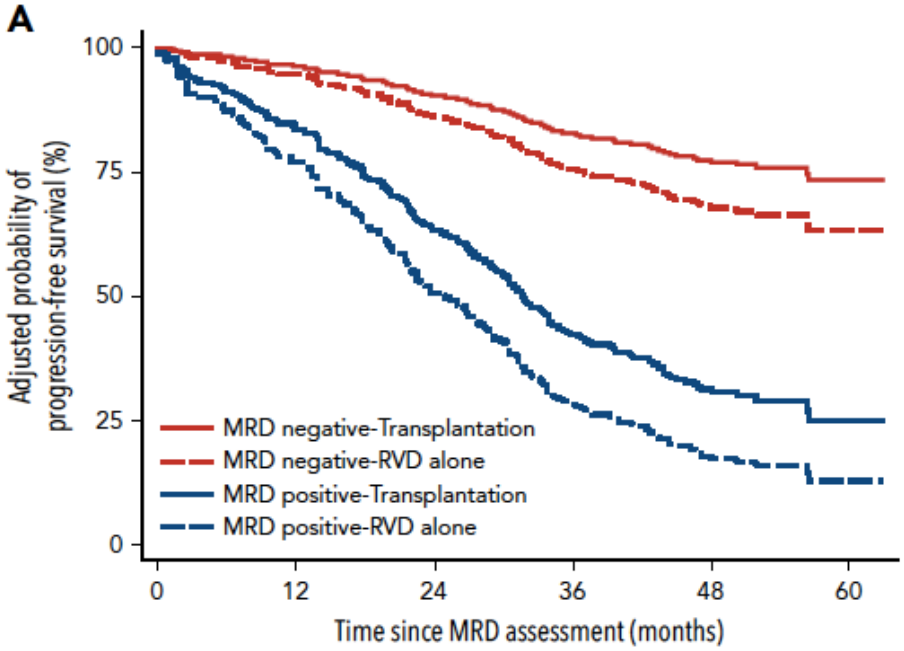
Perrot A, et al. *Blood*. 2018;132(23):2456-2464.

Probability of PFS by MRD status and treatment group



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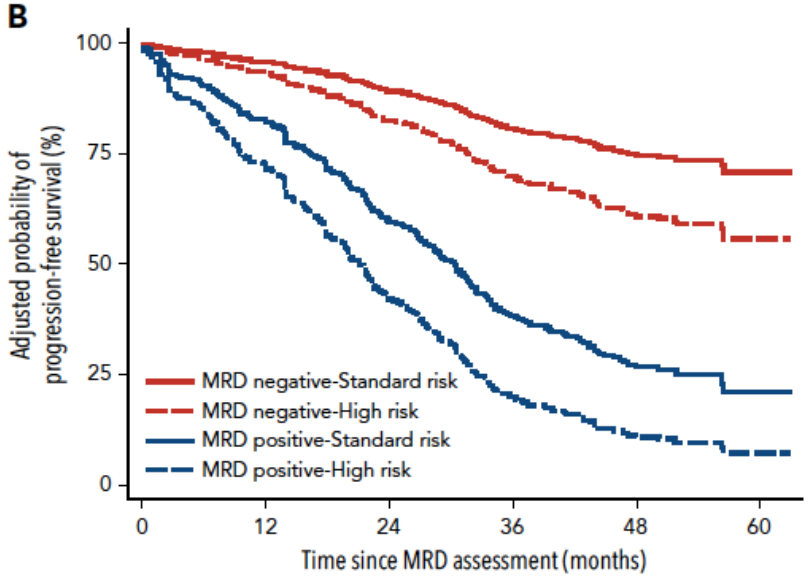
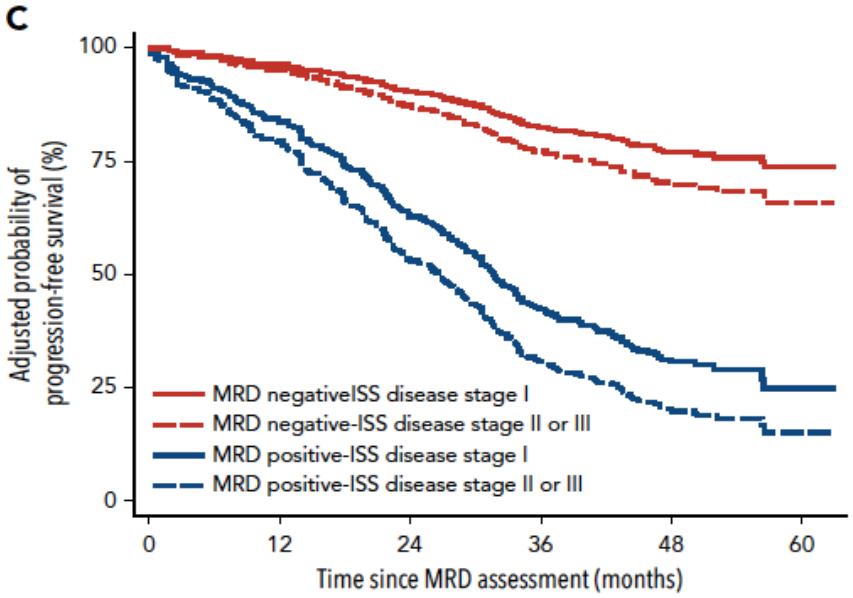
Attal M. et al. *N Engl J Med.* 2017;376:1311-1320.

Probability of PFS by MRD status and cytogenetic risk status or ISS disease stage

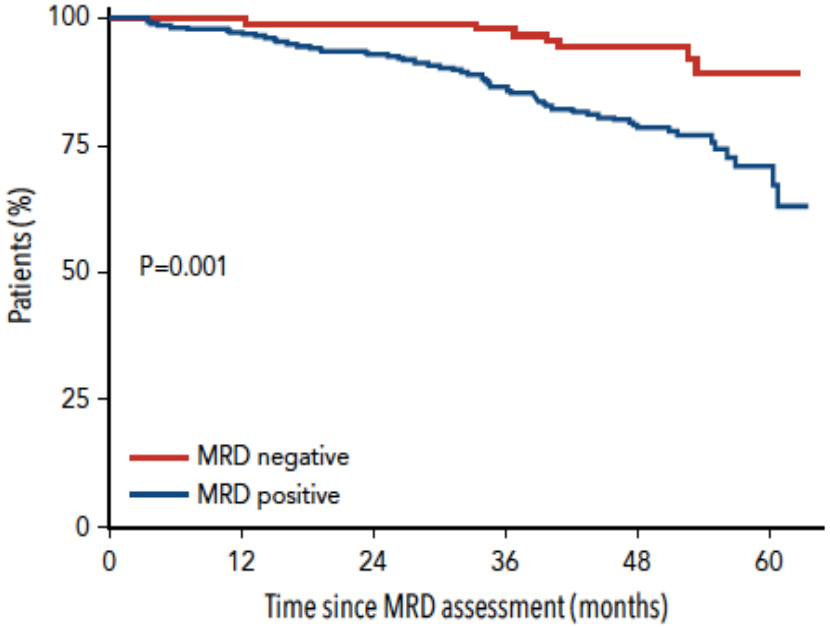




COLLEGE OF MEDICINE JEDDAH

Attal M. et al. *N Engl J Med.* 2017;376:1311-1320.

OS by MRD status



- 4-years OS
  - MRD –ve: 94%
  - MRD +ve: 79%

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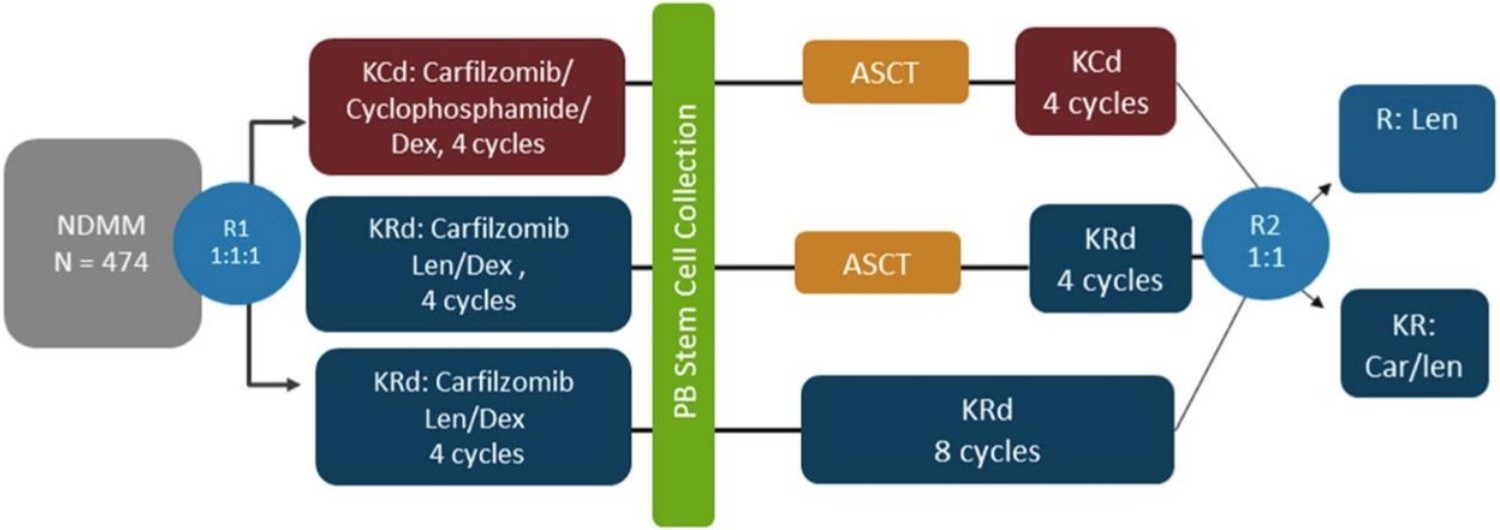
Attal M. et al. *N Engl J Med.* 2017;376:1311-1320.

FORTE trial



Comparable in patient who achieved MRD 10^{-6} either they were treated with KRD +ASCT vs KRD 12 cycles with no ASCT

Gay F, et al. *J Clin Oncol.* 2019;15_suppl 8002-8002.

- Offer ASCT to all ASCT eligible vs ASCT if no deep MRD –ve achieved?
- MRD driven approach?

NEED FOR CONSOLIDATION AFTER ASCT?

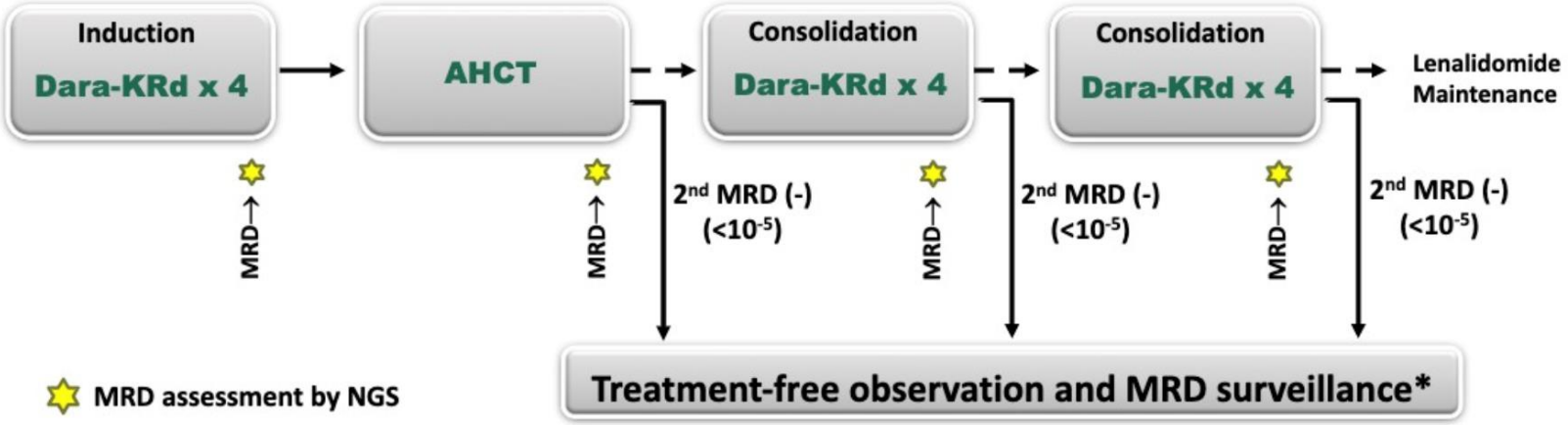
- Consolidation post ASCT improves the response achieved
- Clinical significance is debatable

Ladetto M, et al. *J Clin Oncol.* 2010;28(12):2077-84.

Treatment

Dara-KRd

- Daratumumab 16 mg/m^2 days 1,8,15,22 (days 1,15 C 3-6; day 1 C >6)
- Carfilzomib (20) 56 mg/m^2 Days 1,8,15
- Lenalidomide 25 mg Days 1-21
- Dexamethasone 40mg PO Days 1,8,15,22



*24 and 72 weeks after completion of therapy

MASTER trial

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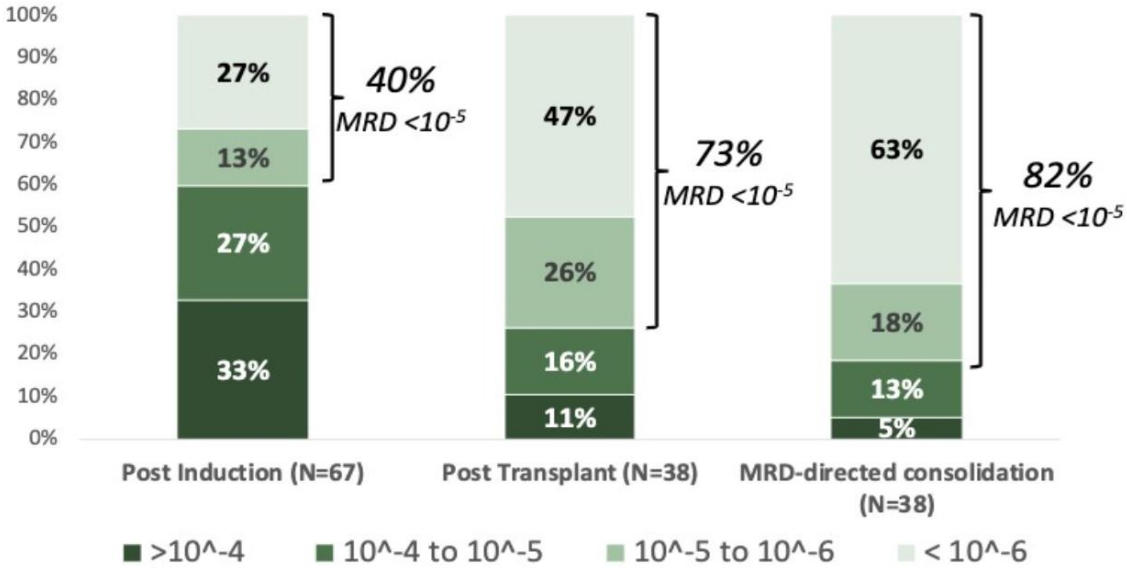
Costa L, et al. Abstract #635. ASH 2019

Best MRD response by phase of therapy

- MRD trackable by NGS clonoSEQ® in 78/81 patients (96%)
- 100% of datapoints obtained in patients with trackable MRD

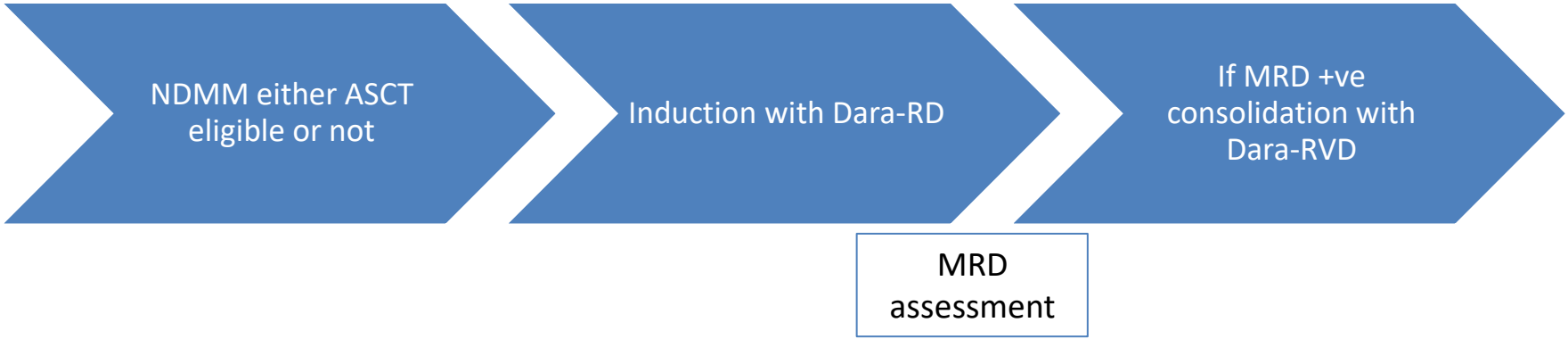


MASTER trial

COLLEGE OF MEDICINE JEDDAH

Costa L, et al. Abstract #635. ASH 2019

Ongoing trial NCT04140162



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ClinicalTrials.gov Identifier: NCT04140162

WHAT IS THE OPTIMAL DURATION OF MAINTENANCE THERAPY?

Continuous until disease progression

Might prolong PFS

Fixed duration then stop

Using MRD driven strategy for the proper duration of maintenance

Ongoing trials

- NCT04108624 (MRD2STOP)
  - MM pts on single agent maintenance
  - MRD driven cessation of maintenance

- NCT04221178
  - MRD driven maintenance therapy cessation

ClinicalTrials.gov Identifier: NCT0410824 and NCT04221178

MRD driven de-escalation or stopping therapy

ID	Therapy	MRD driven decision
NCT02969837	NDMM Elo-KRd as initial therapy	All with receive Elo-KRD for 12 cycles and then: MRDneg: Elo-Rd maintenance until PD MRDpos: Elo-KRd for 6 more cycles and then Elo-Rd maintenance until PD
NCT04071457 (DRAMMATIC)	1100 patients post ASCT	Subcu Dara-R vs R alone: After 2 years of maintenance with each arm: MRD pos >10^{-6}: Continue with assigned treatment MRD neg (10^{-6}): Randomization to either stop or continue assigned treatment for up to 7 years

ClinicalTrials.gov Identifier: NCT02969837 and NCT04071457

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Global Multiple Myeloma Academy

Frontline Therapy for Newly Diagnosed Transplant-Eligible Multiple Myeloma: The Role of Transplantation

Mervat Mattar

APTITUDE HEALTH®

Newly Diagnosed Transplant-Eligible Myeloma

Mervat Mattar, MD

Professor, Clinical Hematology,

Faculty of Medicine,

Cairo University

Points of Discussion

- Myeloma local incidence
- Myeloma aim of therapy in 2021
- Myeloma first-line therapy guidelines
- When to transplant
- How to transplant
- Single vs tandem transplant
- Myeloma local transplant experience

Myeloma in Egypt

Egypt
Source: Globocan

Incidence, Mortality and Prevalence by cancer site

	New cases				Deaths				5-year prevalence (all ages)	
Cancer	Number	Rank	(%)	Cum.risk	Number	Rank	(%)	Cum.risk	Number	Prop. (per 100 000)
Liver	27 895	1	20.7	4.01	26 523	1	29.8	3.84	28 977	28.32
Breast	22 038	2	16.4	5.04	9 148	2	10.3	1.89	61 160	120.79
Bladder	10 655	3	7.9	1.60	6 170	3	6.9	0.79	26 986	26.37
Non-Hodgkin lymphoma	7 305	4	5.4	0.91	4 078	5	4.6	0.49	19 096	18.66
Lung	6 538	5	4.9	0.97	5 817	4	6.5	0.86	7 116	6.95
Leukaemia	5 231	6	3.9	0.58	3 858	6	4.3	0.49	14 274	13.95
Prostate	4 767	7	3.5	1.26	2 227	10	2.5	0.18	10 523	20.35
Brain, central nervous system	4 499	8	3.3	0.49	3 686	7	4.1	0.44	11 470	11.21
Colon	3 430	9	2.5	0.45	1 910	11	2.1	0.23	7 687	7.51
Stomach	3 353	10	2.5	0.43	2 631	9	3.0	0.32	4 400	4.30
Pancreas	2 987	11	2.2	0.43	2 841	8	3.2	0.41	2 702	2.64
Ovary	2 787	12	2.1	0.67	1 839	12	2.1	0.47	6 854	13.54
Thyroid	2 661	13	2.0	0.30	472	22	0.53	0.05	7 913	7.73
Kidney	2 208	14	1.6	0.27	1 105	14	1.2	0.11	5 717	5.59
Corpus uteri	1 694	15	1.3	0.47	350	23	0.39	0.08	5 041	9.96
Oesophagus	1 571	16	1.2	0.23	1 531	13	1.7	0.22	1 718	1.68
Larynx	1 552	17	1.2	0.23	1 061	15	1.2	0.15	3 980	3.89
Rectum	1 512	18	1.1	0.18	807	16	0.91	0.09	3 565	3.48
Hodgkin lymphoma	1 396	19	1.0	0.13	483	21	0.54	0.03	3 757	3.67
Cervix uteri	1 320	20	0.98	0.31	744	17	0.84	0.19	3 189	6.30
Lip, oral cavity	1 319	21	0.98	0.15	544	20	0.61	0.05	3 239	3.17
Gallbladder	941	22	0.70	0.14	688	18	0.77	0.10	1 148	1.12
Multiple myeloma	736	23	0.55	0.11	649	19	0.73	0.09	1 658	1.62
Salivary glands	393	24	0.29	0.05	150	26	0.17	0.02	1 099	1.07
Mesothelioma	337	25	0.25	0.04	307	24	0.34	0.04	401	0.39
Anus	289	26	0.21	0.04	135	28	0.15	0.02	697	0.68
Testis	273	27	0.20	0.05	48	32	0.05	0.01	962	1.86
Nasopharynx	260	28	0.19	0.03	160	25	0.18	0.01	689	0.67
Hypopharynx	220	29	0.16	0.03	136	27	0.15	0.02	340	0.33
Vulva	219	30	0.16	0.06	111	29	0.12	0.03	573	1.13
Oropharynx	202	31	0.15	0.03	69	31	0.08	0.01	487	0.48
Melanoma of skin	190	32	0.14	0.03	75	30	0.08	0.01	509	0.50
Vagina	80	33	0.06	0.02	35	33	0.04	0.01	196	0.39
Kaposi sarcoma	70	34	0.05	0.01	24	34	0.03	0.00	182	0.18
Penis	10	35	0.01	0.01	4	35	0.00	0.00	27	0.05
All cancer sites	134 632	-	-	16.27	89 042	-	-	10.94	278 165	271.8

The Global Cancer Observatory. Accessed 27 March 2021.

217 Egyptian Myeloma Patients

Factor	Number of patients	Percentage
Bodily pains	152	70
Splenomegaly	15	7
Lymphadenopathy	6	3
Hyperviscosity symptoms	22	10
Residence in rural areas	130	60
Smoking	98	45
Sex (male/female)	128, 89	59, 41
Age group (years)		
<40	8	4
40–49	20	9
50–59	85	39
60–69	82	38 %
70–79	20	9
≥80	2	1
Immunoglobulin electrophoresis:		
Light chain	26	12
Ig G myeloma	158	73
Ig M myeloma	11	5
Ig A myeloma	22	10
Kappa chain	151	70
Lambda chain	65	30
Hypercalcemia	86	40
Anemia (HB<10 g/dl)	206	95
Creatinine>1.5 mg/dl	65	30

Elhusseiny N, et al. *Ann Hematol.* 2014;93(1):141-145.

217 Egyptian Myeloma Patients

Factor	Number of patients	Percentage
Bodily pains	152	70
Splenomegaly	15	7
Kappa chain	151	70
Lambda chain	65	30
Hypercalcemia	86	40
Anemia (HB<10 g/dl)	206	95
Creatinine>1.5 mg/dl	65	30

38% between 50–59 yr

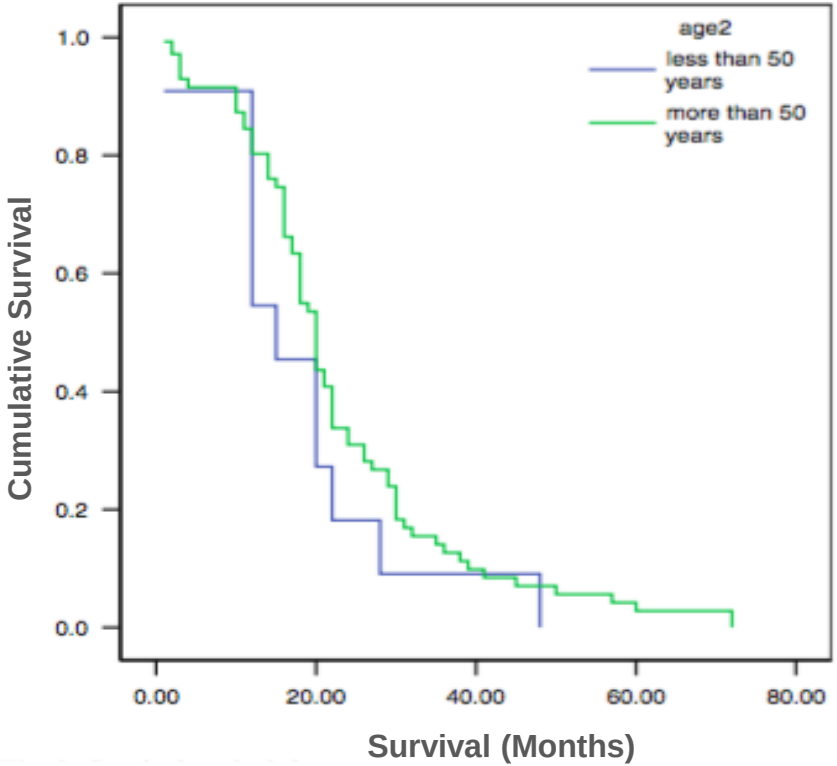
39% between 60–69 yr

M > F

IgG kappa

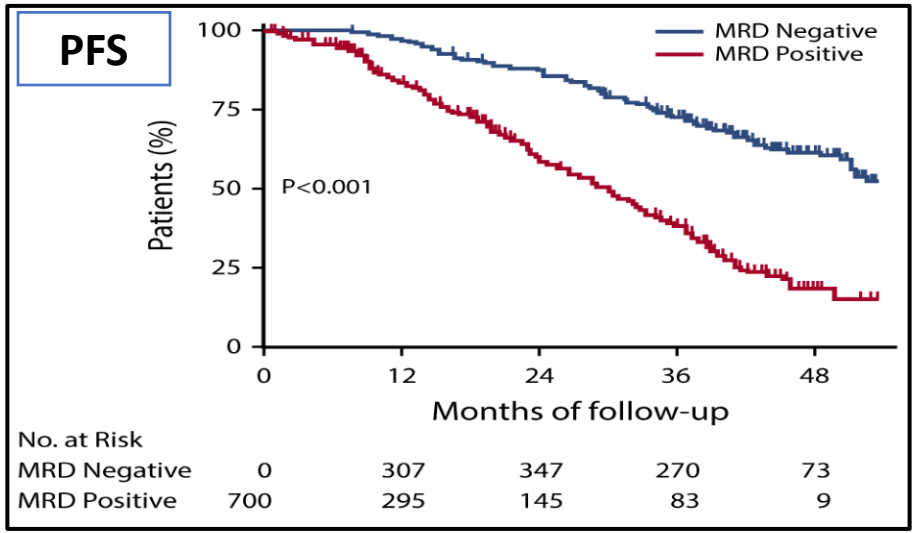
Elhusseiny N, et al. *Ann Hematol.* 2014;93(1):141-145.

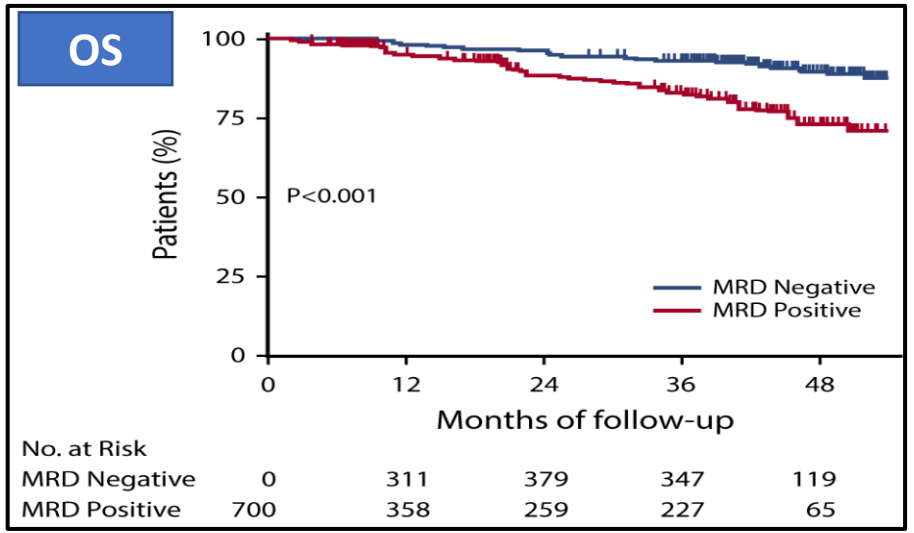
217 Egyptian Myeloma Patients: OS by Age



Elhusseiny N, et al. *Ann Hematol.* 2014;93(1):141-145.

Multiple Myeloma Aim of Therapy: MRD?





Gandolfi S, et al. *Blood.* 2018;132(11):1114-1124.

Myeloma Risk-Stratification

Table 1. Revised International Staging System

Prognostic factor	Criteria
ISS stage	
I	Serum β_2-microglobulin <3.5 mg/L, serum albumin ≥3.5 g/dL
II	Not ISS stage I or III
III	Serum β_2-microglobulin ≥5.5 mg/L
CA by iFISH	
High risk	Presence of del(17p) and/or translocation t(4;14) and/or translocation t(14;16)
Standard risk	No high-risk CA
LDH	
Normal	Serum LDH below the upper limit of normal
High	Serum LDH above the upper limit of normal
A new model for risk stratification for MM	
R-ISS stage	
I	ISS stage I and standard-risk CA by iFISH and normal LDH
II	Not R-ISS stage I or III
III	ISS stage III and either high-risk CA by iFISH or high LDH

	High risk	Standard risk
FISH abnormalities	t(4;14), t(14;16), t(14;20), del(17/17p), gain(1q)	All others including: FISH: t(11;14), t(6;14)

Palumbo A, et al. *J Clin Oncol.* 2015;33(26):2863-2869; Sonneveld P, et al. *Blood.* 2016;127(24):2955-2962.

MAYO CLINIC

mSMART 3.0: Classification of Active MM

High-Risk

- High Risk genetic Abnormalities [a,b]
  - t(4;14)
  - t(14;16)
  - t(14;20)
  - Del 17p
  - p53 mutation
  - Gain 1q
- RISS Stage 3
- High Plasma Cell S-phase[c]
- GEP: High risk signature

- Double Hit Myeloma: Any 2 high risk genetic abnormalities
- Triple Hit Myeloma: 3 or more high risk genetic abnormalities

Standard-Risk[a]

All others including:

- Trisomies
- t(11;14)[d]
- t(6;14)

[a] Trisomies may ameliorate
[b] By FISH or equivalent method
[c] Cut-offs vary
[d] t(11;14) may be associated with plasma cell leukemia

Dispenzieri et al. Mayo Clin Proc 2007;82:323-341; Kumar et al. Mayo Clin Proc 2009 84:1095-1110; Mikhael et al. Mayo Clin Proc 2013;88:360-376. v14 //last reviewed August 2018

MAYO CLINIC

mSMART 3.0: Classification of Active MM

High-Risk

- High Risk genetic Abnormalities [a,b]
  - t(4;14)
  - t(14;16)
  - t(14;20)
  - Del 17p
  - p53 mutation
  - Gain 1q
- RISS Stage 3
- High Plasma Cell
- GEP: High risk sig

- Double Hit Myeloma: Any 2 high risk genetic abnormalities
- Triple Hit Myeloma: 3 or more high risk genetic abnormalities

Standard-Risk[a]

All others including:

- Trisomies
- t(11;14)[d]
- t(6;14)

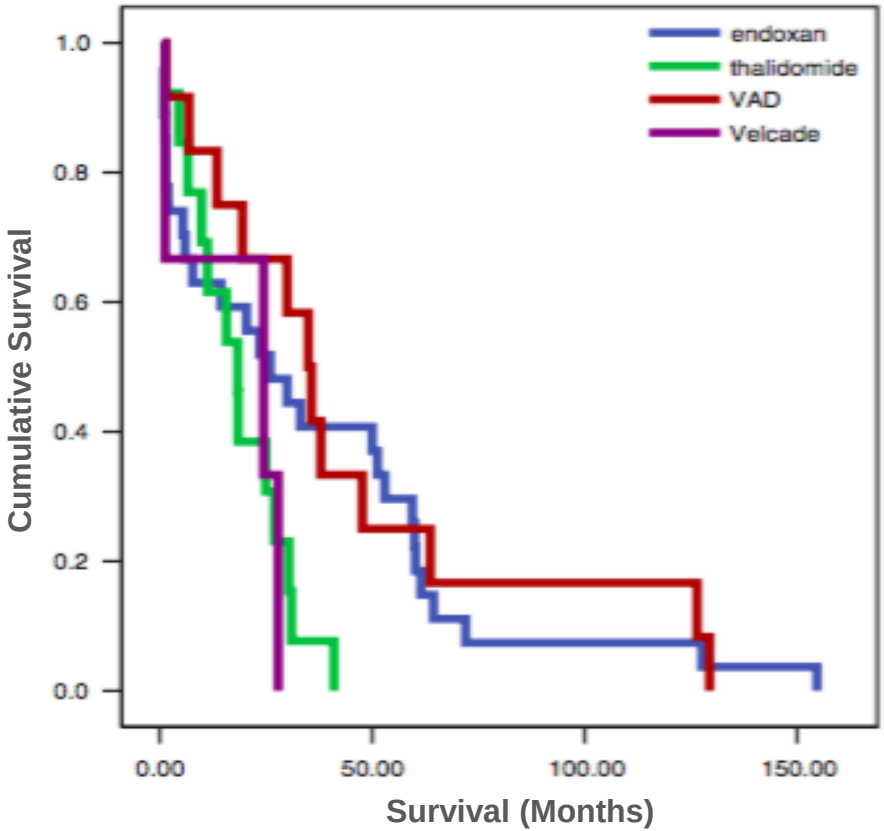
✓**Rapidly responding but early relapsing patients**
Extramedullary disease

[a] Trisomies may ameliorate
[b] By FISH or equivalent method
[c] Cut-offs vary
[d] t(11;14) may be associated with plasma cell leukemia

Dispenzieri et al. Mayo Clin Proc 2007;82:323-341; Kumar et al. Mayo Clin Proc 2009 84:1095-1110; Mikhael et al. Mayo Clin Proc 2013;88:360-376. v14 //last reviewed August 2018

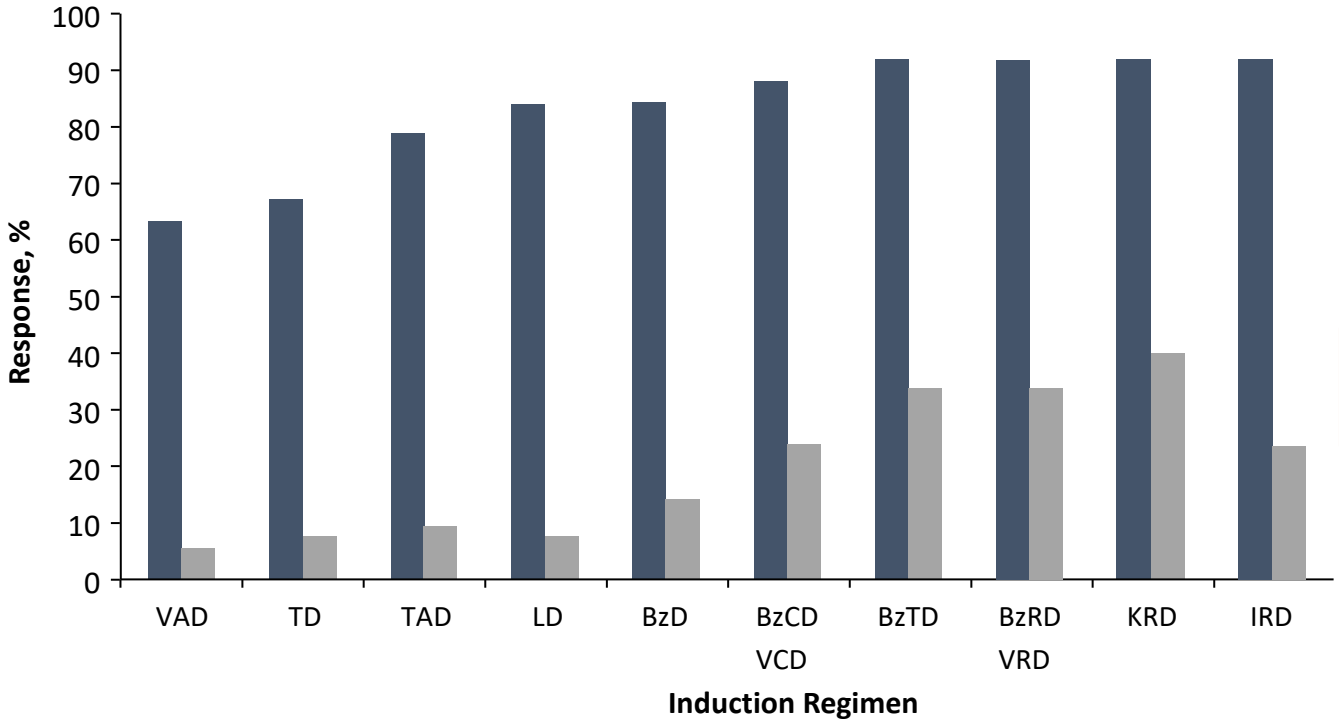
First-Line Therapy

217 Egyptian Myeloma Patients: OS by Regimen



Elhusseiny N, et al. *Ann Hematol.* 2014;93(1):141-145.

Triplet Myeloma Therapy: Response to Induction

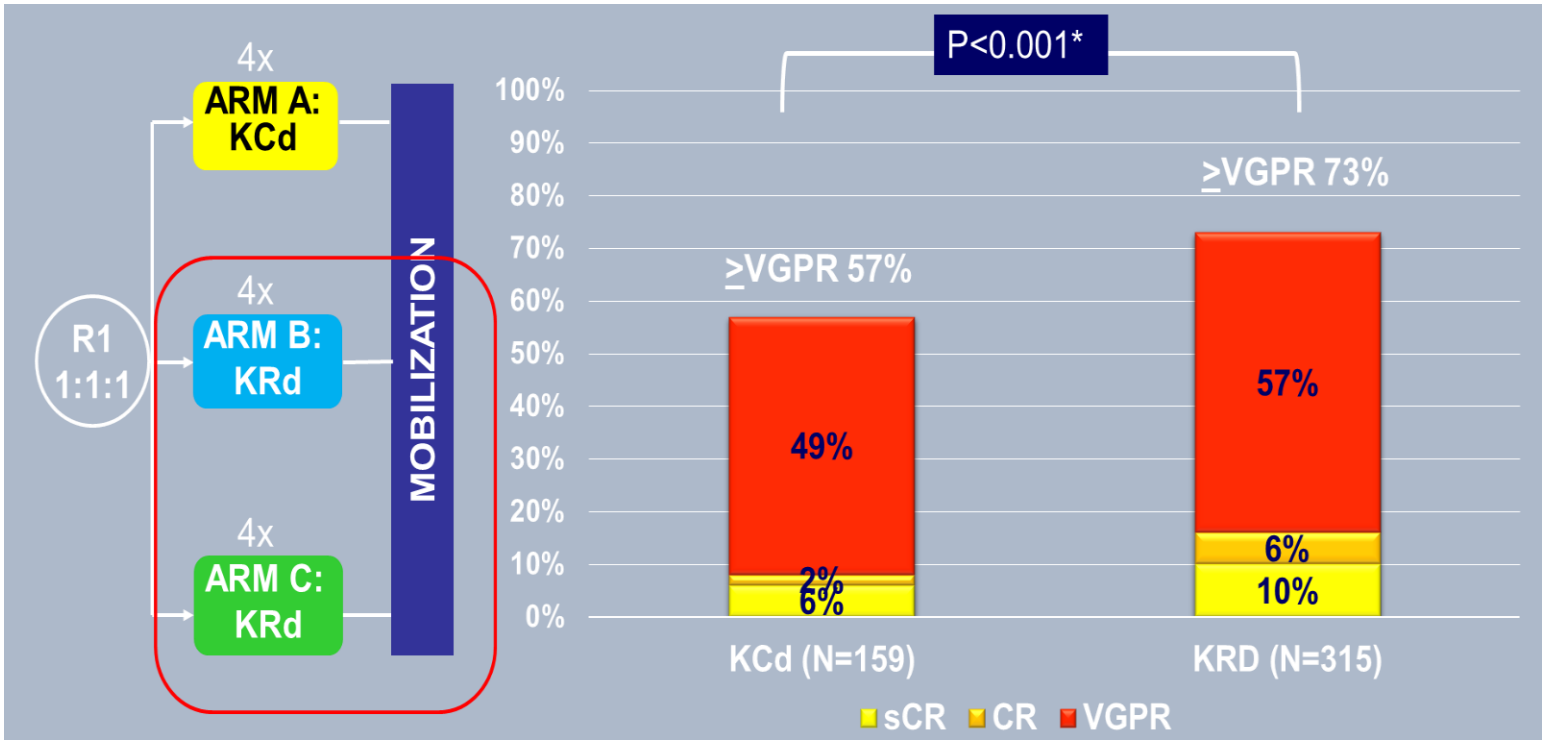


This translates into prolonged PFS

Adapted from: How I treat MM in younger patients. Stewart K, Richardson P, San Miguel JF. *Blood*. 2009;114:5436-5443.

KRd vs KCd Induction Phase (FORTE Trial)

Endpoint 1: VGPR Rate With KRd vs KCd Induction – ITT Analysis

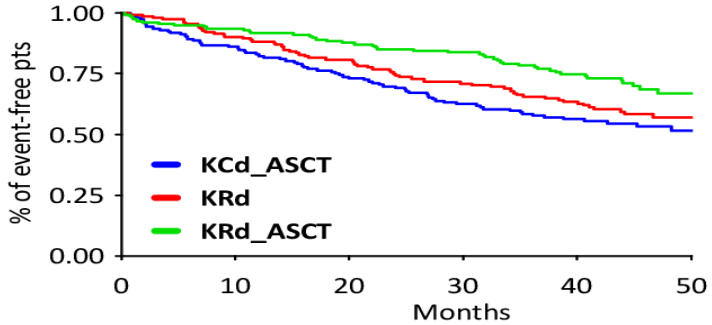


R1, randomization 1; KCd, carfilzomib, cyclophosphamide, dexamethasone; KRd, carfilzomib, lenalidomide, dexamethasone; sCR, stringent complete response; CR, complete response; VGPR, very good partial response; FISH, fluorescence in situ hybridization. *Adjusted for International Staging System Stage, FISH analysis, and age.

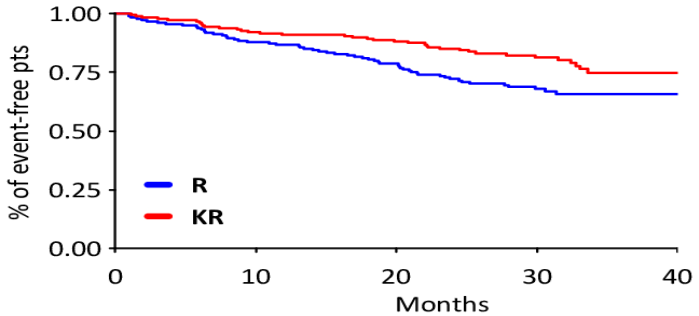
Gay F, et al. ASCO 2017. Abstract 8002.

FORTE Trial: NDMM Survival

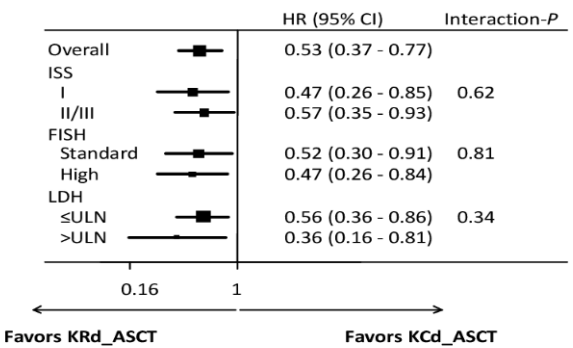
PFS from R1



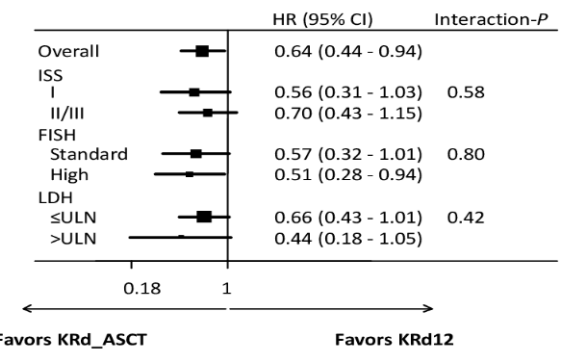
PFS from R2



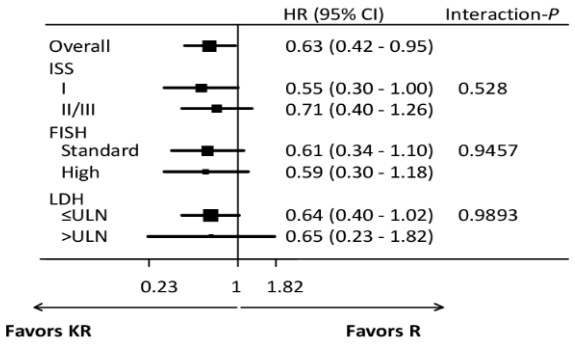
PFS from R1: KRd_ASCT vs KCd_ASCT subgroup analyses



PFS from R1: KRd_ASCT vs KRd12 subgroup analyses



PFS from R2: KR vs R subgroup analyses



PFS, progression-free survival; R1, first randomization (induction treatment); R2, second randomization (maintenance treatment); pts, patients; K, carfilzomib; C, cyclophosphamide; R, lenalidomide; d, dexamethasone; KRd12, 12 cycles of KRd; ASCT, autologous stem cell transplantation; HR, hazard ratio; *P*, *P* value; ISS, International Staging System stage; FISH, fluorescence in situ hybridization; LDH, lactate dehydrogenase; ULN, upper limit of normal.

Gay F, et al. ASH 2020. Abstract 141.

Quadruplet Combinations in TE-NDMM

Dara-VTD (CASSIOPEIA) and Dara-VRD (GRIFFIN) Trials

CASSIOPEIA study (D-VTD vs VTD)

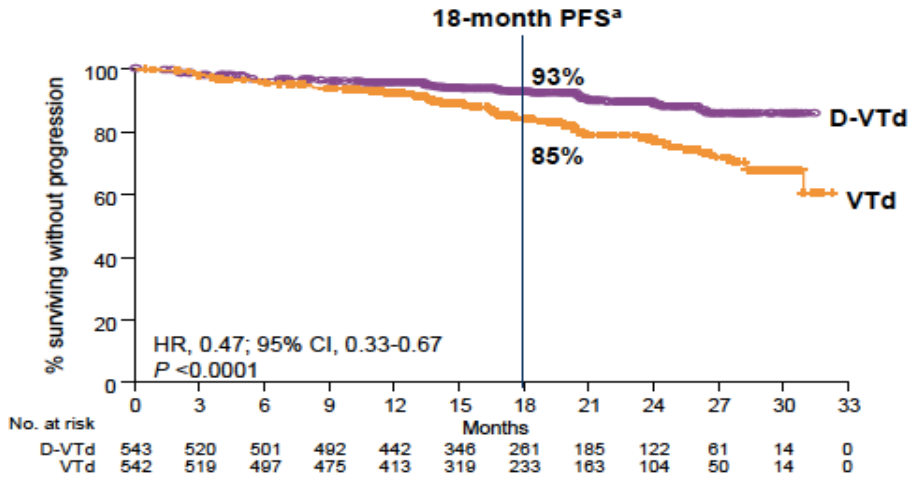
4× D-VTD + ASCT (Mel) + 2× D-VTD – Dara vs Obs

D-VTD vs VTD (post-conso)
>CR 39% vs 26% *(P = .001)*

MRD (10^{-5}) neg in CR: D-VTD 34% vs 20% *(P <.0001)*

Median FUP 18.8 months

PFS



Moreau P, et al. *Lancet*. 2019;394(10192):29-38.

GRIFFIN study (D-VRD vs VRD)

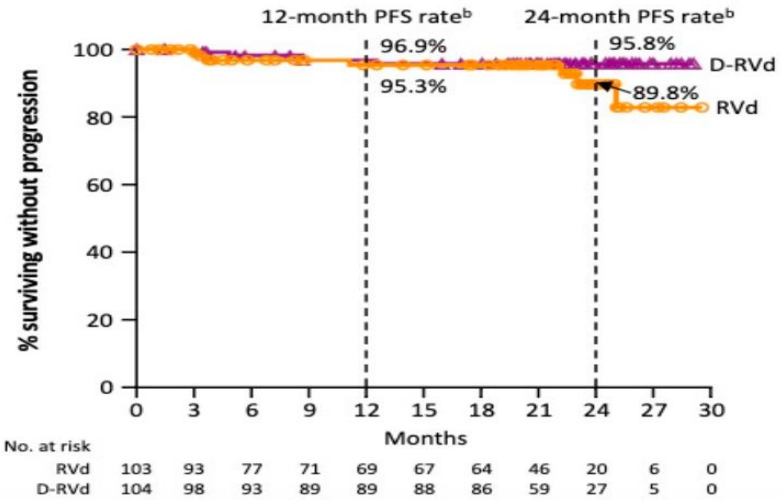
4× D-VRD + ASCT (Mel) + 2× D-VRD

D-VRD vs VRD (at cutoff date)
>CR 51.5% vs 42.3%

MRD (10^{-5}) neg in CR: D-VRD 62.2% vs 32.2%

Median FUP 21.1 months

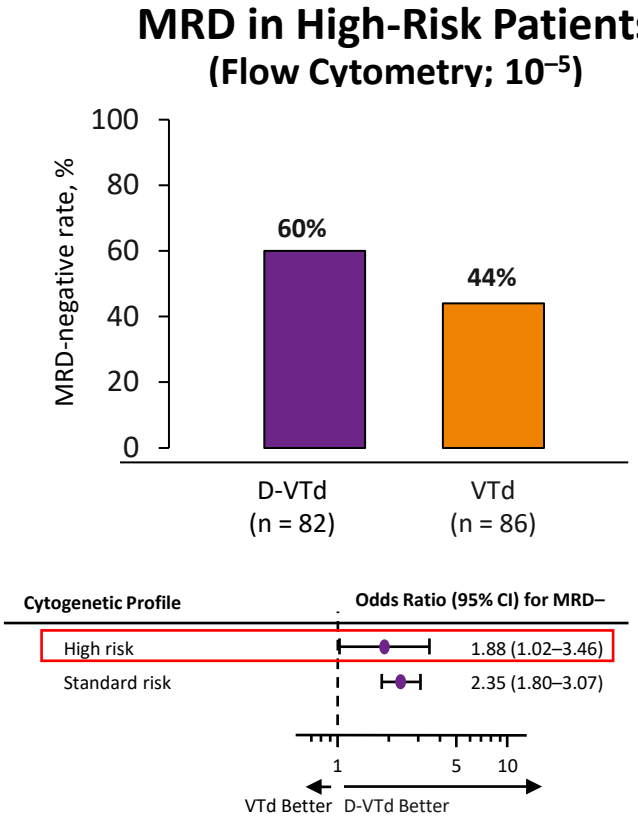
PFS

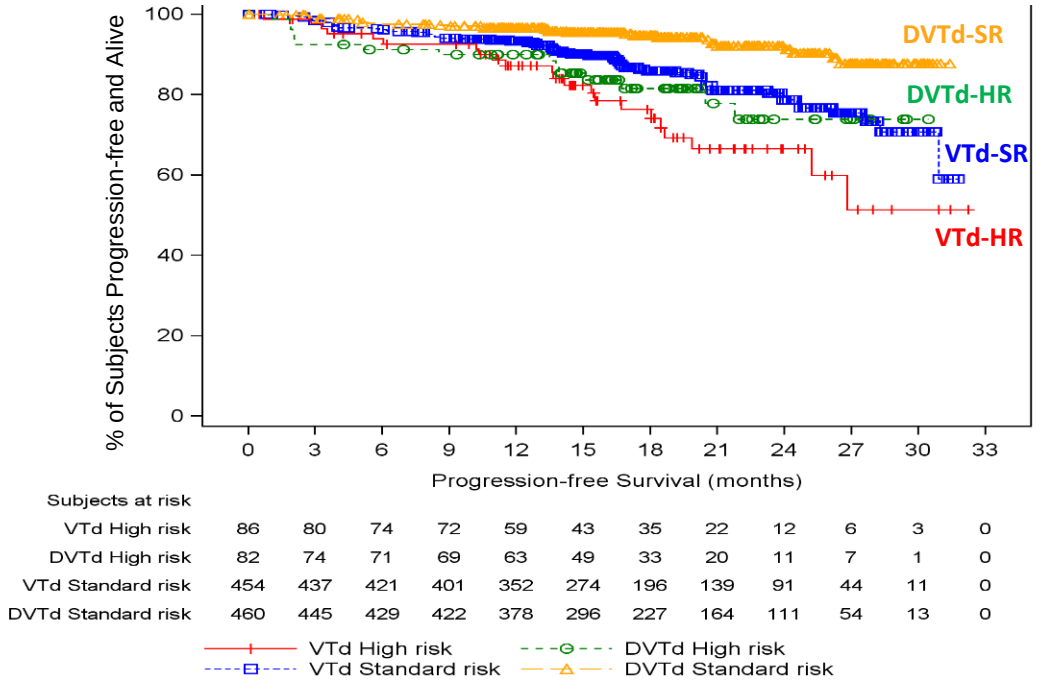


Voorhees P, et al. ASH 2019. Oral presentation.

Dara-VTD vs VTD as Induction and Consolidation in TE NDMM:

Results From the Phase 3 CASSIOPEIA Trial (n = 1085) – HR Subgroups



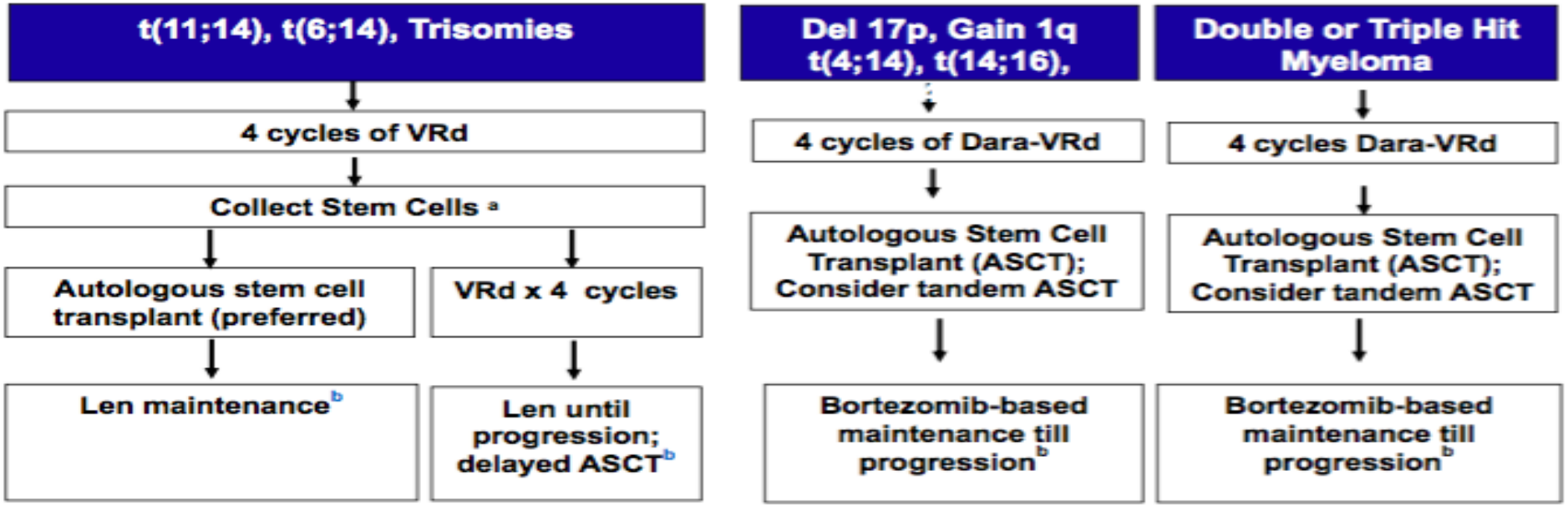


Moreau P, et al *Lancet*. 2019;394(10192):29-38; Avet-Loiseau H, et al. International Myeloma Workshop. Boston, MA; September 2019.

MAYO CLINIC

mSMART – Off-Study

Transplant Eligible

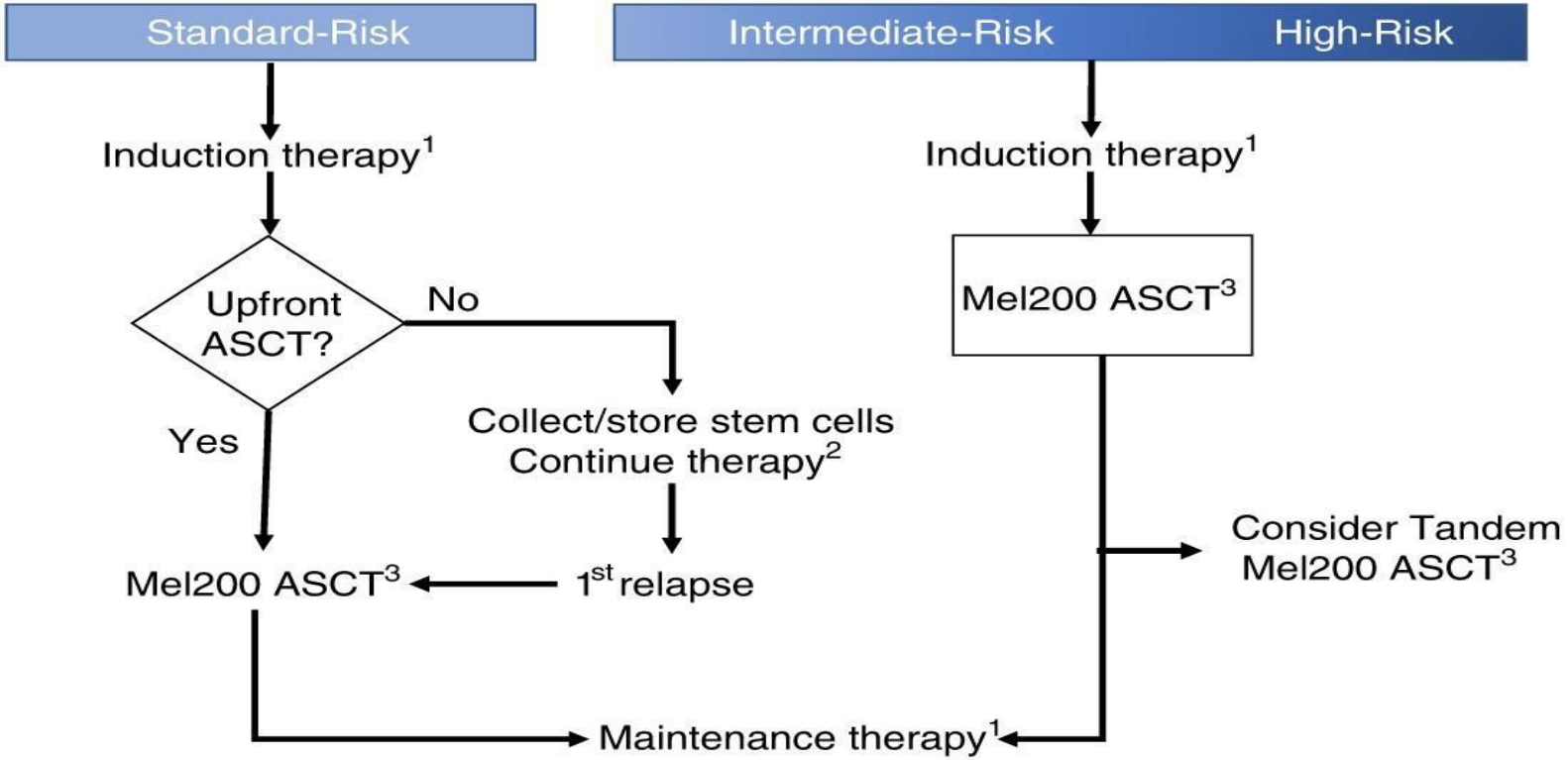


[a] *If age >65 or > 4 cycles of VRd, consider mobilization with G-CSF plus cytoxan or plerixafor;* [b] *Duration usually until progression based on tolerance*

VRd, Bortezomib, lenalidomide, dexamethasone; Dara, daratumumab

Dispenzieri et al. Mayo Clin Proc 2007;82:323-341; Kumar et al. Mayo Clin Proc 2009 84:1095-1110; Mikhael et al. Mayo Clin Proc 2013;88:360-376. v19 //last reviewed Feb 2021

Newly Diagnosed MM



[1]Refer to newly diagnosed MSMART algorithm [2]Eventually transition to maintenance therapy

[3]For Age >70 or CrCl<30 ml/min, consider use Mel140 mg/m2

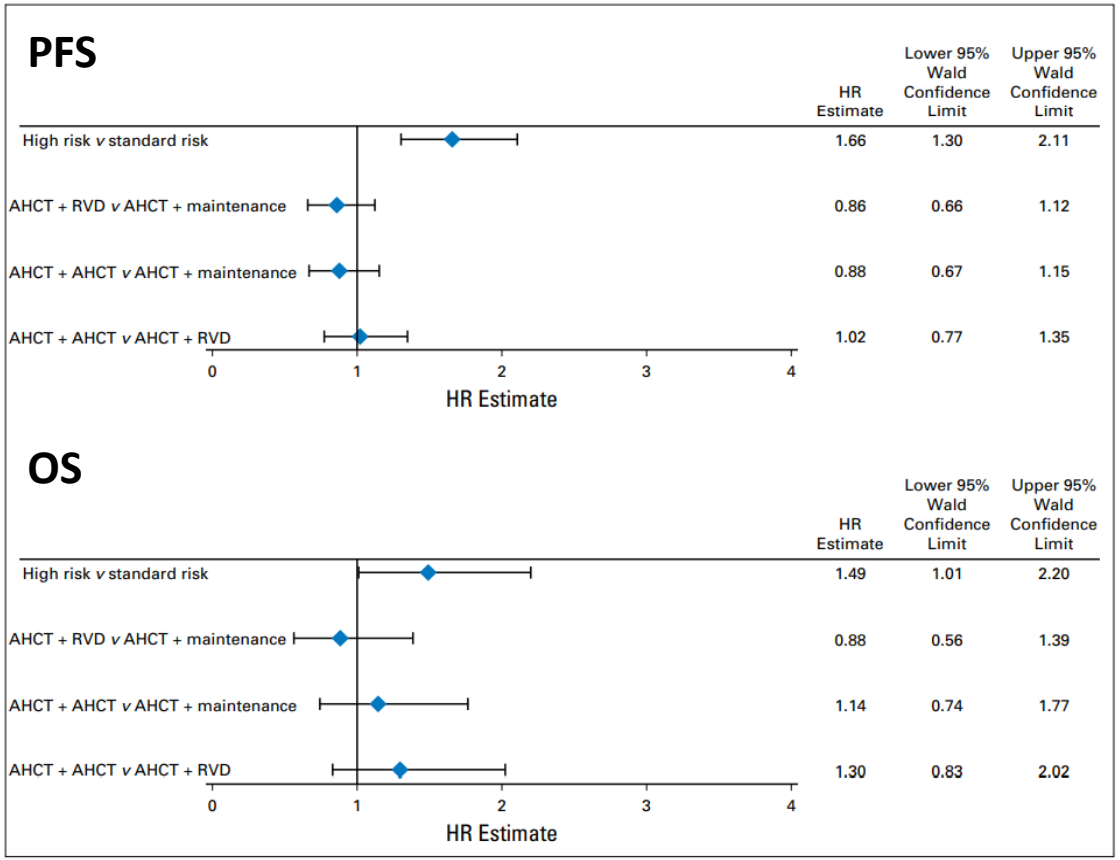
Gonsalves M, et al. *Bone Marrow Transplant.* 2019;54:353-367.

Myeloma: Early vs Late ASCT

		Early	Late	*P*
Pooled analysis of 2 trials (n = 529)[1,2]	4-year PFS	44%	26%	<.001 (HR 0.53)
	4-year OS	84%	70%	<.001 (HR 0.51)
GIMEMA MM-RV-209 . . . Rd-MPR vs Rd-Mel200 (2nd rand: +/– maint) EMN MM-RV-441 . . . Rd-CRD vs Rd-Mel200 (2nd rand: R vs RP maint)				
IFM-DFCI 2009 trial[3]	4-year PFS	47%	35%	<.001 (HR 0.69)
	4-year OS	83%	81%	NS
RVD × 8 + ASCT at relapse vs RVD × 3 + ASCT (Mel200) + RVD × 2				
EMN02/HO95[4]	3-year PFS	65%	57%	.001 (HR 0.73); high risk 0.53
	3-year OS	86.3%	84.6%	NS
Induction VCD × 3–4 => VMP intensive vs ASCT => VRD conso vs no conso => R maint				

1. Palumbo A, et al. *N Engl J Med*. 2014;371(10):895-905; 2. Gay F, et al. *Lancet Oncol*. 2015;16(16):1617-1629;
3. Attal M, et al. *Blood*. 2015;126: abstract 391. Presented at ASH 2015; 4. Cavo M, et al. *Blood*. 2016;128: abstract 673. Presented at ASH 2016.

Myeloma: Tandem vs Single Transplant



Stadtmauer EA, et al. *J Clin Oncol.* 2019;37(7):589-597.

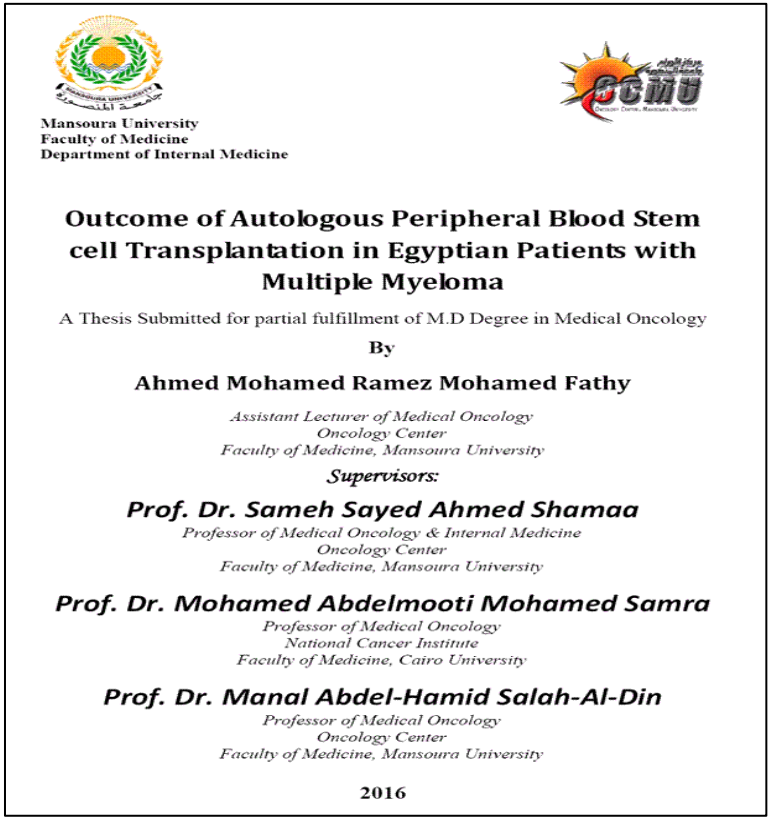
Patient Transplant Eligibility
HCT-Specific Comorbidity Index

Comorbidity	Definitions of comorbidities included in the new HCT-CI	HCT-CI weighted scores
Arrhythmia	Atrial fibrillation or flutter, sick sinus syndrome, or ventricular arrhythmias	**1**
Cardiac‡	Coronary artery disease, § congestive heart failure, myocardial infarction, or EF ≤50%	**1**
Inflammatory bowel disease	Crohn disease or ulcerative colitis	**1**
Diabetes	Requiring treatment with insulin or oral hypoglycemics but not diet alone	**1**
Cerebrovascular disease	Transient ischemic attack or cerebrovascular accident	**1**
Psychiatric disturbance†	Depression or anxiety requiring psychiatric consult or treatment	**1**
Hepatic, mild‡	Chronic hepatitis, bilirubin >ULN to 1.5× ULN, or AST/ALT >ULN to 2.5× ULN	**1**
Obesity†	Patients with a body mass index >35 kg/m^2	**1**
Infection†	Requiring continuation of antimicrobial treatment after day 0	**1**
Rheumatologic	SLE, RA, polymyositis, mixed CTD, or polymyalgia rheumatica	**2**
Peptic ulcer	Requiring treatment	**2**
Moderate/severe renal‡	Serum creatinine >2 mg/dL, on dialysis, or prior renal transplantation	**2**
Moderate pulmonary‡	DLCO and/or FEV_1 66%-80% or dyspnea on slight activity	**2**
Prior solid tumor‡	Treated at any time point in the patient's past history, excluding nonmelanoma skin cancer	**3**
Heart valve disease	Except mitral valve prolapse	**3**
Severe pulmonary‡	DLCO and/or FEV_1 ≤65% or dyspnea at rest or requiring oxygen	**3**
Moderate/severe hepatic‡	Liver cirrhosis, bilirubin >1.5× ULN, or AST/ALT >2.5× ULN	**3**

Sorror ML, et al. *Blood.* 2005;106(8):2912-2919.

Auto Transplant Among 140 Egyptian Myeloma Patients (2008–2014)

- Overall response: 85.7%
- CR: 61.4%
- TRM: 5.7%
- 5-year OS: 80.9%
- 5-year PFS: 26.2%



Mansoura University
Faculty of Medicine
Department of Internal Medicine

Outcome of Autologous Peripheral Blood Stem cell Transplantation in Egyptian Patients with Multiple Myeloma

A Thesis Submitted for partial fulfillment of M.D Degree in Medical Oncology

By

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Supervisors:

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Prof. Dr. Manal Abdel-Hamid Salah-Al-Din
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Oncology Center
Faculty of Medicine, Mansoura University

2016

Myeloma Treatment: Future Perspectives

	Induction	HDM+ASCT	Mobilization	Tandem ASCT	Consolidation	Maintenance
Until recently	VCD/VTD	Yes	Cy + G-CSF	No consensus	VTD/VRD	Lenalidomide for 1 year
Current standard	VRD	Yes	G-CSF +/- Cy Prelixafor for bad mobilizers	For high risk	No standard	Lenalidomide until progression
Future perspective	DARA-VRD DARA-KRD	For selected patients? High risk/MRD+	G-CSF +/- Cy +/- hrTPO Prelixafor for bad mobilizers	High risk/MRD+	No standard	Lenalidomide + PI (Ixazomib) for high risk patients

THANK YOU


يوم التوعية
لمرضي الهودجكن والمايلوما المتعددة
في عصر كوفيد 19
أستاذ دكتور
مرفت مطر
دكتور
إبراهيم أحمد قنصوة
دكتور
مروة صلاح
دكتور
محمد سعيد
الجمعة 26 مارس 2021
1:30 عصرا الي 3:30 عصرا

Questions for Newly Diagnosed Transplant-Eligible Myeloma

Mervat Mattar, MD

Professor, Clinical Hematology,

Faculty of Medicine,

Cairo University

Question 1

What are the high-risk chromosomal abnormalities in myeloma?

A) t(11;14)

B) t(6;14)

C) 17p-

D) t(14;16)

E) Both C and D

Question 2

How many first-line therapy cycles are usually advised before ASCT?

A) 1 cycle KRD

B) 3 cycles RD

C) 2 cycles Dara-VRD

D) 4 cycles of proteasome inhibitor/IMiD/Dex

Global Multiple Myeloma Academy

Discussion

APTITUDE HEALTH®

Global Multiple Myeloma Academy

Optimal Use of Consolidation and Maintenance Therapy

Mohamad Mohty

APTITUDE HEALTH®

“Optimal use of consolidation and maintenance therapy in multiple myeloma”

Prof Mohamad MOHTY
Clinical Hematology and Cellular Therapy Dept
Sorbonne University
Hôpital Saint-Antoine
Paris, France

Disclosures (relevant to this talk)

I have the following relationships to disclose:

1. Employment/leadership position/advisory role: No
2. Stock ownership or options: No
3. Patent royalties/licensing fees: No
4. Honoraria: *Adaptive Biotechnologies, Amgen, BMS, Celgene, Janssen, Takeda, Novartis, Sanofi*
5. Manuscript fees: No
6. Research funding: *Celgene, Janssen, Sanofi*
7. Subsidies or donations: No
8. Endowed departments by commercial entities: No
9. Gifts and others: No
10. Off-label use: This presentation may include discussion of off-label use of some drugs.

Aims of consolidation or maintenance therapy

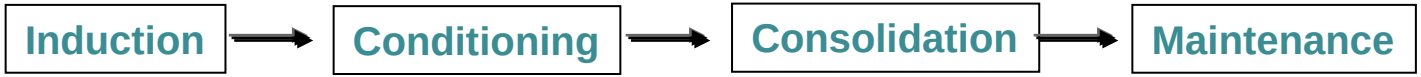
Consolidation

- Improve response/induce deeper response following therapy
  - By administering treatment for a limited period

Maintenance

- Maintain response achieved following therapy
  - By administering a gentle treatment for a prolonged period
  - **Long-term safety is a major issue**

Reduce the risk of relapse
Extend PFS AND OS

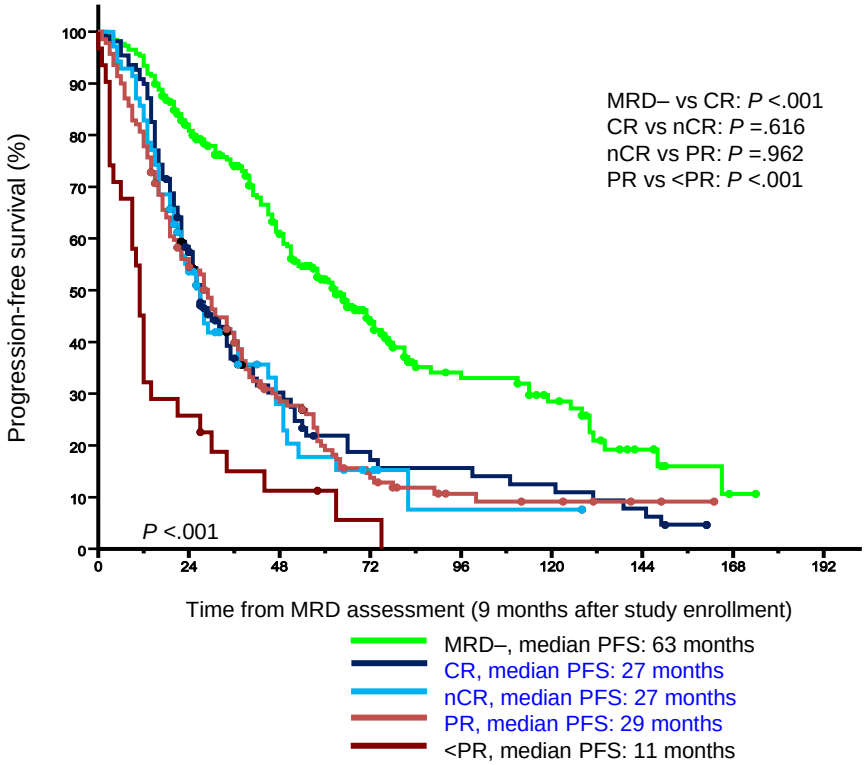


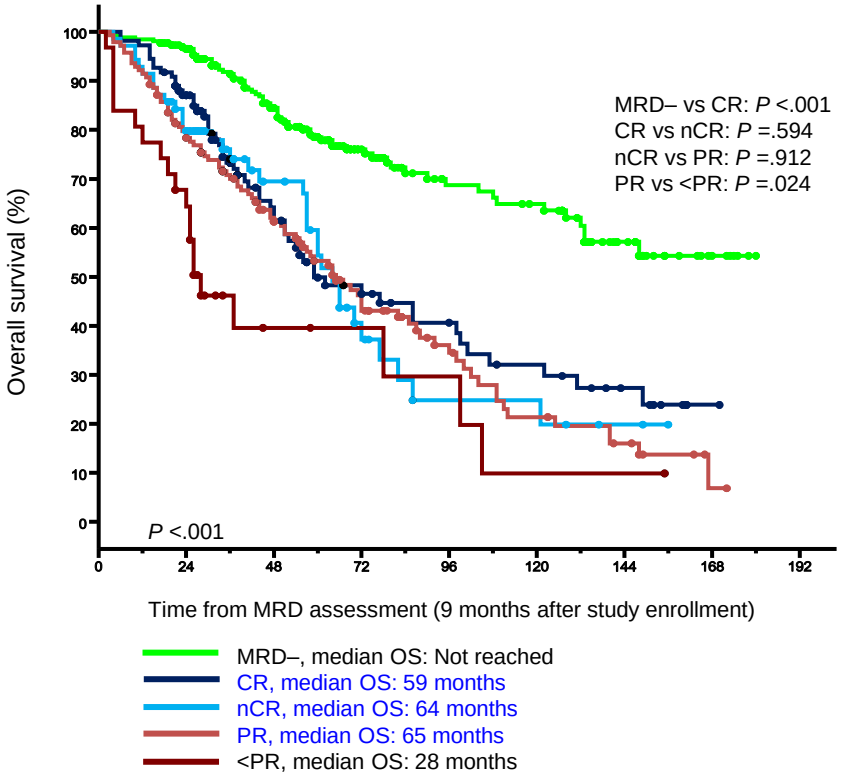
Why do we need consolidation and/or maintenance?

Only achieving MRD negativity prolongs patient survival

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

Data were analyzed from 609 patients who were enrolled in the GEM (Grupo Español de Mieloma) 2000 and GEM2005MENOS65 studies for transplant-eligible MM and the GEM2010MAS65 clinical trial for elderly patients with MM who had minimal residual disease (MRD) assessments 9 months after study enrollment. Median follow-up of the series was 71 months.



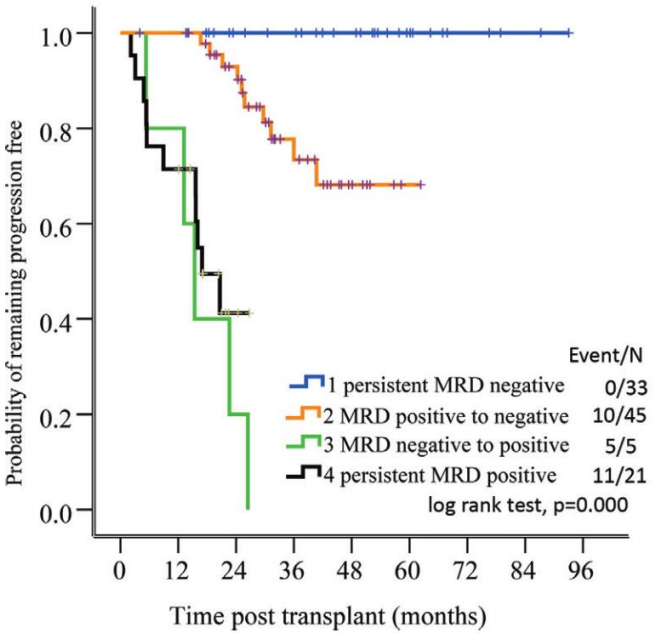


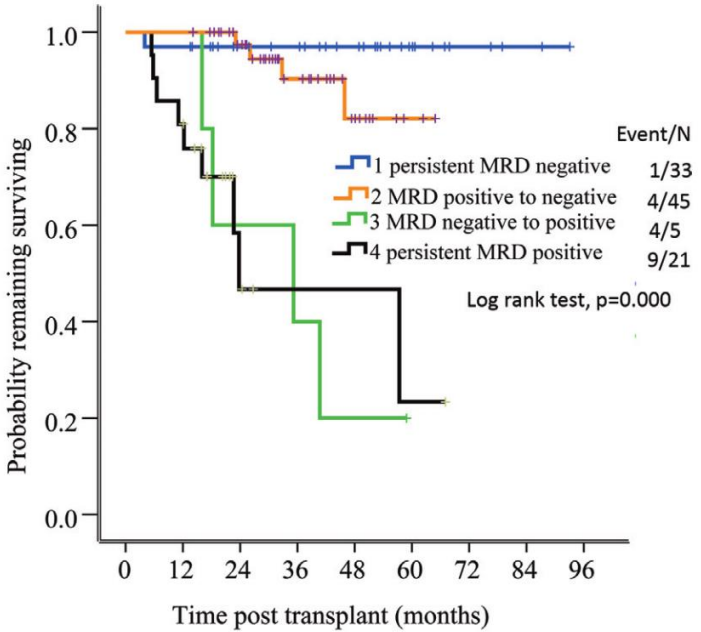
CR, complete remission; nCR, near-CR; MRD, minimal residual disease; PFS, prolonged progression-free; PR, partial remission

Lahuerta JJ, Paiva B, et al. *J Clin Oncol*. 2017;35(25):2900-2910.

24 months of sustained MRD negativity identifies patients with very low risk of disease progression

Flow MRD was monitored in 104 consecutive patients with MM after induction and at the 3rd, 6th, 9th, 12th,18th, and 24th months post-transplant; 4 MRD evolution patterns were revealed.





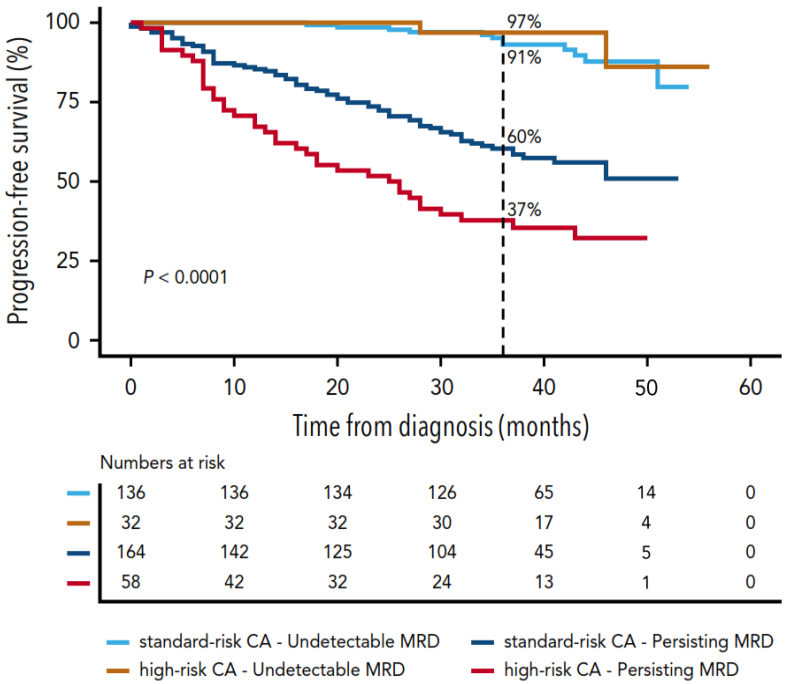
Time to progression (TTP) and overall survival (OS) were compared among the 4 MRD evolution patterns. The TTP for MRD evolution patterns 1 to 4 were not reached, not reached, 15.4±2.4 months, and 16.9±3.0 months, respectively; the corresponding OS were not reached, not reached, 35.2±18.6 months, and 23.8±15.0 months, respectively.

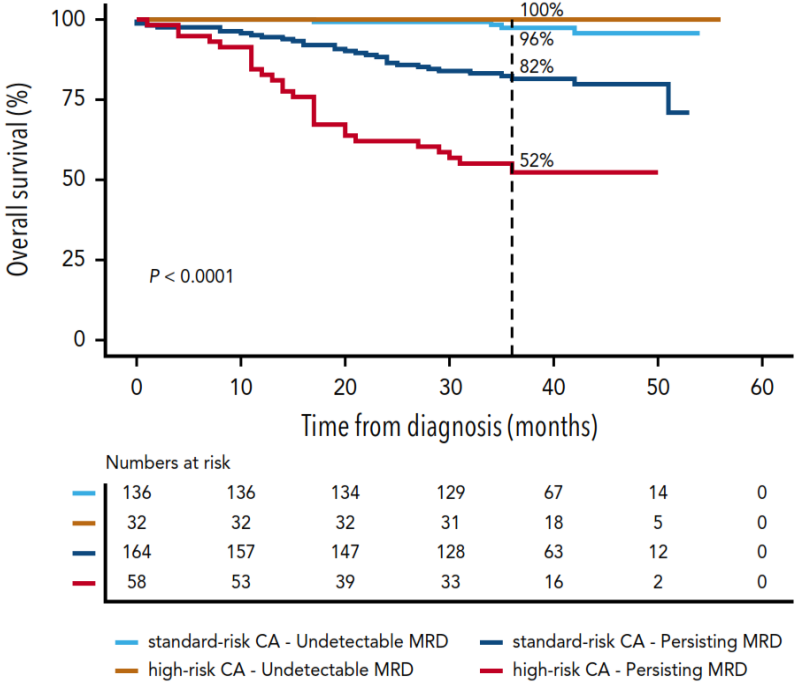
Gu J, et al. *Biol Blood Marrow Transplant*. 2018;24(12):2568-2574.

Achieving undetectable MRD overcomes the dismal prognosis of transplant-eligible patients with high-risk cytogenetics

Next-generation flow (NGF) cytometry was used to evaluate measurable residual disease (MRD) in MM patients with standard- vs high-risk CAs (n = 300 and 90, respectively) enrolled in the PETHEMA/GEM2012MENOS65* trial, and to identify mechanisms that determine MRD resistance in both patient subgroups (n = 40).

*Open-label, phase 3 study that included 458 patients who received 6 induction cycles of bortezomib, lenalidomide, and dexamethasone (VRD); underwent autologous stem cell transplantation (ASCT) conditioned with busulfan-melphalan or melphalan-200 (high-dose therapy [HDT]); and received 2 consolidation cycles of VRD.





CA, cytogenetic abnormality.

Goicoechea I, et al. *Blood*. 2021;137(1):49-60.

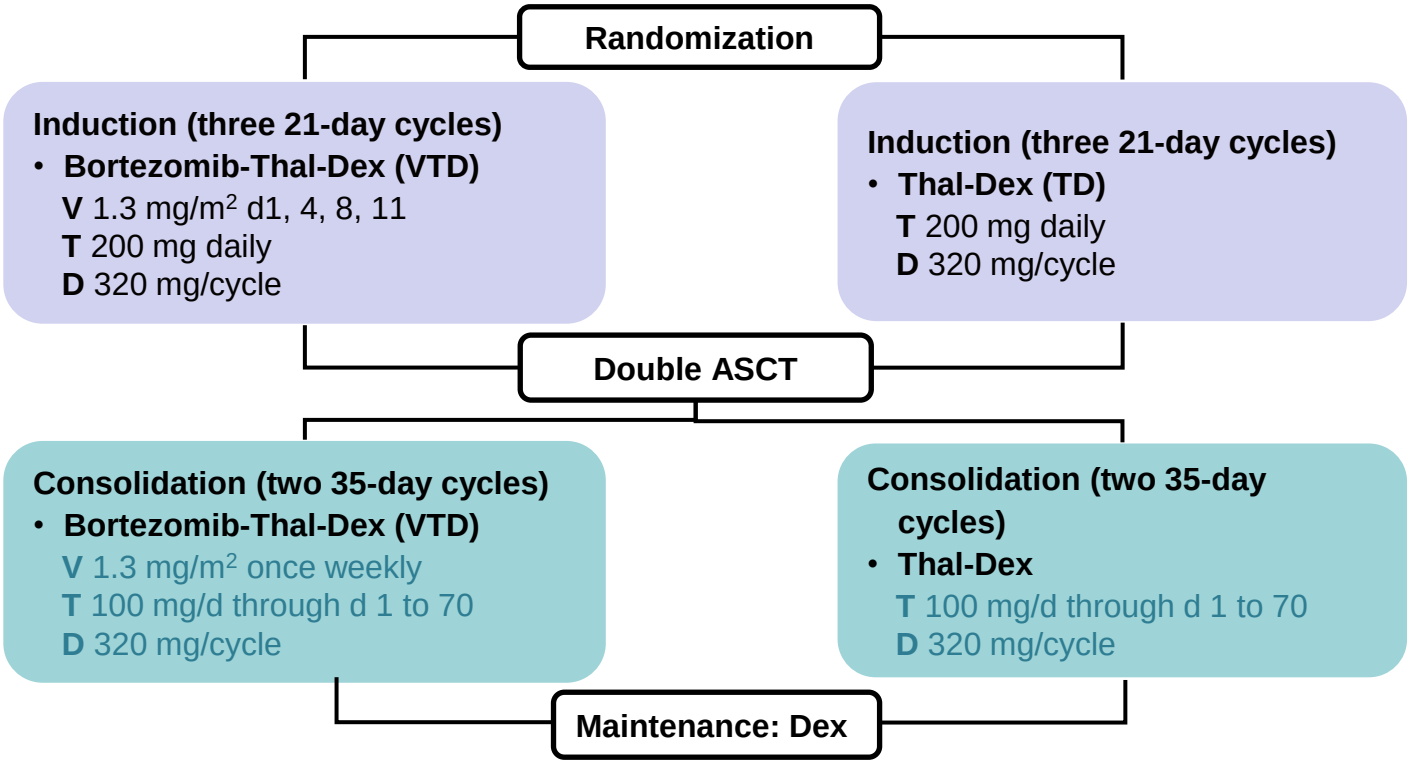
Impact of consolidation after high-dose therapy?

Consolidation therapy leads to upgraded responses

Agent/regimen	Duration of treatment	Response:	Prior to consolidation	After consolidation
Thal/dex[1] (phase 3) n = 161	Two 35-day cycles	CR:	40.4%	46.6%
Lenalidomide[2] (phase 3) n = 577	Two 28-day cycles	≥VGPR:	58%	69%
Bortezomib[3] (phase 3) n = 187	21 weeks	≥nCR:	20.1%	45.1%
VTD[1] (phase 3) n = 160	Two 35-day cycles	CR:	48.7%	60.6%
VTd[4] (retrospective study) n = 121	Two 21-day cycles	CR:	33%	52%
VTD[5] n = 39	Four 35-day cycles	CR: Mol. CR:	15% 3%	49% 18%
VRD[6] (phase 2) n = 39	Two 21-day cycles	CR + sCR:	42%	48%

1. Cavo et al. *Blood*. 2012;120(1):9-19; 2. Attal et al. *N Engl J Med*. 2012; 366:1782-1791; 3. Mellqvist et al. *Blood*. 2013;121(23):4647-4654; 4. Leleu et al. *Leukemia*. 2013;27(11):2242-2244; 5. Ladetto et al. *J Clin Oncol*. 2010;28(12):2077-2084; 6. Roussel et al. *J Clin Oncol*. 2014;32(25):2712-2717.

Phase III: VTD vs TD as induction and consolidation (GIMEMA study)



Cavo et al. *Lancet*. 2010;376(9758):2075-2085.

Phase III: VTD vs TD (GIMEMA study)
Impact of consolidation therapy

Per-protocol analysis: 321 patients			
	VTD	**TD**	***P***
CR before consolidation	48.7%	40.4%	.131
CR post-consolidation	60.6%	46.6%	.012
Upgrade to CR post-consolidation	30.5%	16.7%	.029
Landmark analysis from start of consolidation (30 months median follow up)			
3-yr PFS	60%	48%	.042

- Frequency of grade 3/4 AEs comparable in both groups
  - 10.6% VTD, 9.3% TC
- PN with VTD: 0.6%
- Skin rash, DVT: 0.6% in each group
- VTD arm: patients received 93% of planned doses of bortezomib and thal

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

Achieving molecular remission with VTD consolidation following transplant (GIMEMA study)

n = 66 with ≥nCR after ASCT, treated with 2 cycles VTD or TD

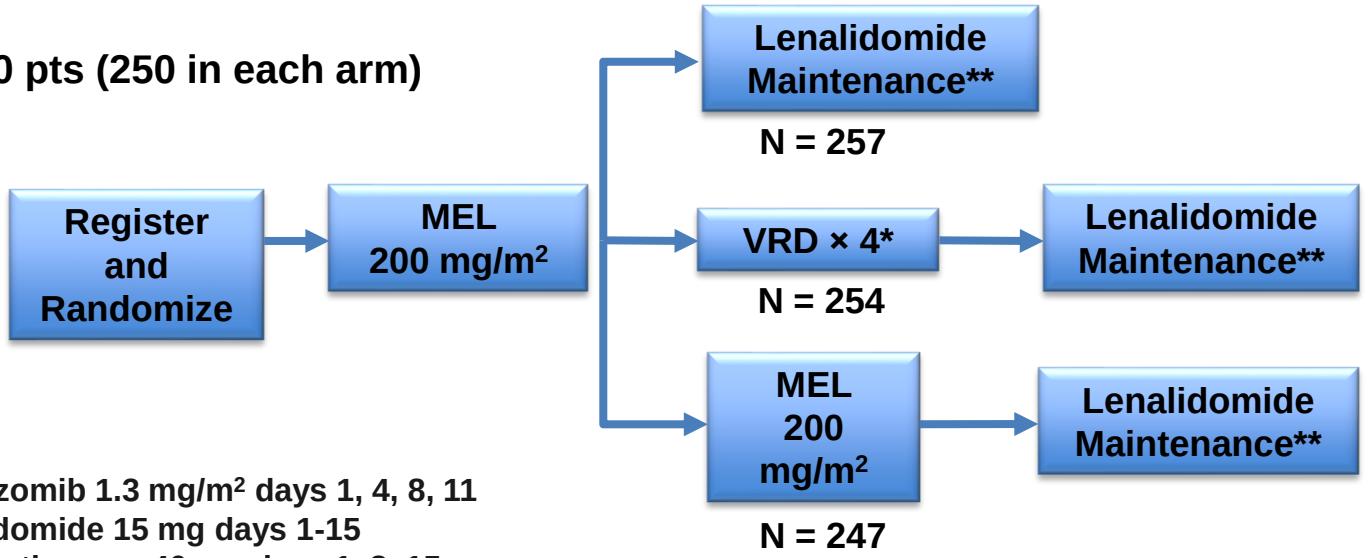
Efficacy (n = 66)	VTD	TD	*P*
Pre-consolidation (day 0) PCR negativity	39%	31%	.062
Post-consolidation (day +70) PCR negativity	64%	48%	.007
Reduction in tumor burden post-consolidation (day +70) (real-time quantitative PCR)	Median 5-log reduction	Median 1-log reduction	.05

VTD consolidation significantly reduced tumor burden compared with TD as detected by PCR

Terragna et al. *Blood*. 2010;116(21): abstract 861 (oral presentation).

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

N = 750 pts (250 in each arm)

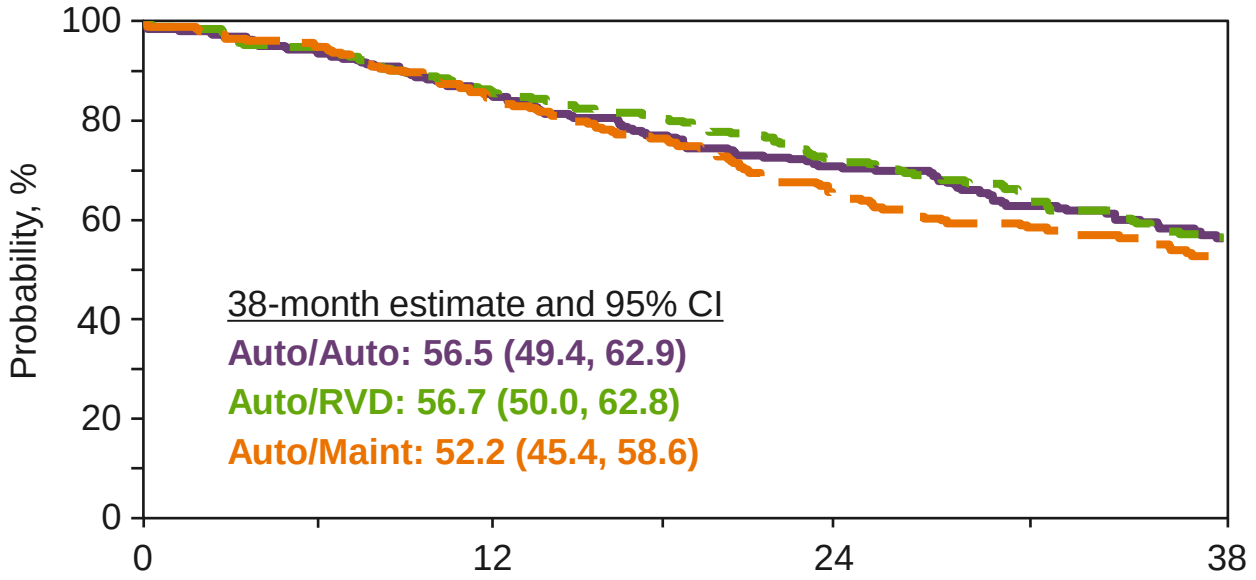


*Bortezomib 1.3 mg/m² days 1, 4, 8, 11
Lenalidomide 15 mg days 1-15
Dexamethasone 40 mg days 1, 8, 15
Every 21 days

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

Stadtmauer et al. *J Clin Oncol*. 2019;37(7):589-597.

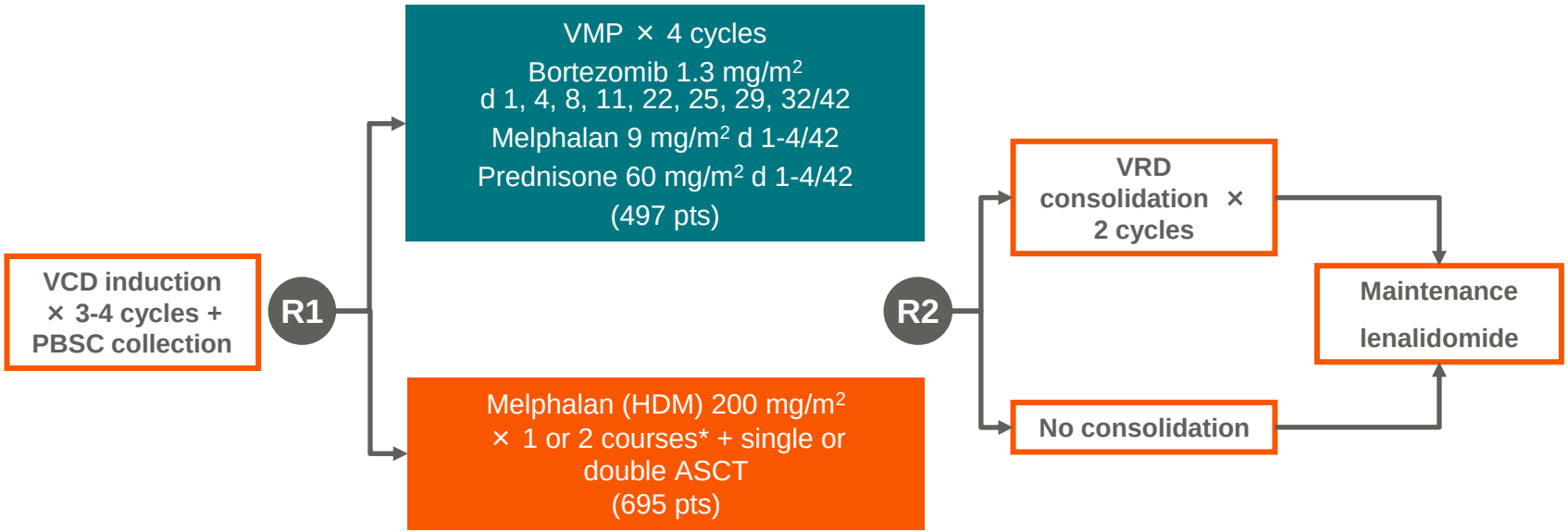
STAMINA trial primary endpoint: Progression-free survival



No. at risk				
Auto/Auto	247	200	153	87
Auto/RVD	254	215	172	99
Auto/Maint	257	213	158	80

Stadtmauer et al. *J Clin Oncol*. 2019;37(7):589-597.

EMN02/HO95 MM Study: Design



Stratification factor: ISS I vs II vs III

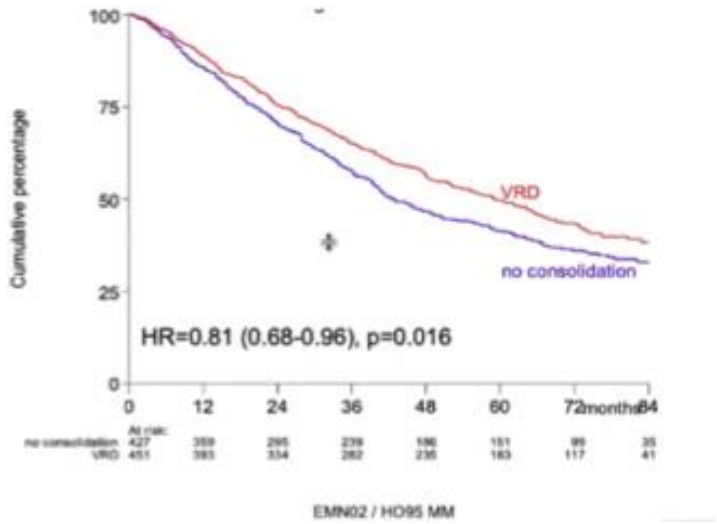
***Randomization to VMP or HDM was 1:1 in centers with a fixed single ASCT policy**

Randomization to VMP or HDM-1 or HDM-2 was 1:1:1 in centers with a double ASCT policy

Cavo M, et al. ASH 2017. Abstract 397 (oral presentation).

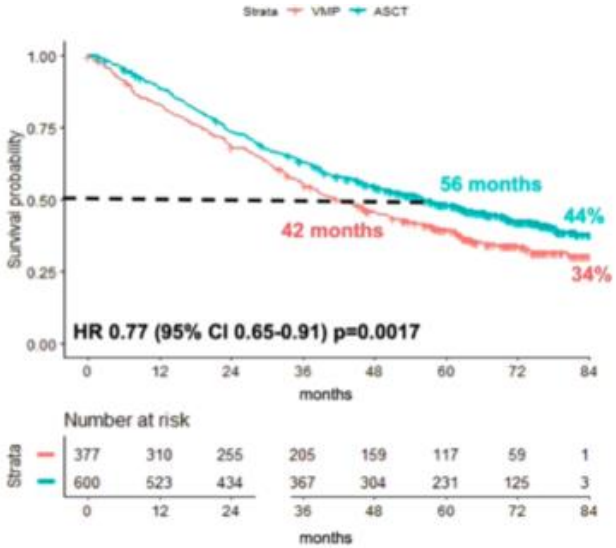
EMN02/HO95: PFS after consolidation and maintenance

PFS2 in patients with VRD vs no consolidation



Consolidation with VMP improves PFS and is independent of prior intensification

PFS2 following lenalidomide maintenance



PFS was significantly extended with lenalidomide maintenance in patients assigned to ASCT vs VMP

ASCT, autologous stem cell transplant; CI, confidence interval; HDM, high-dose melphalan; HR, hazard ratio; IQR, interquartile range; OS, overall survival; PFS, progression free survival; VCD, bortezomib, cyclophosphamide, dexamethasone; VMP, bortezomib, melphalan and prednisolone

Sonneveld et al. ASH 2020. Abstract 550 (oral presentation).

Cavo et al. ASH 2020. Abstract 142 (oral presentation).

Impact of maintenance therapy after auto-SCT

Phase 3 studies of thalidomide maintenance therapy after ASCT

	N	Maintenance vs No Maintenance	
		EFS or PFS	OS
Attal et al[1]	597	3-year EFS 52% vs 36%**	4-year OS 87% vs 77%*
Barlogie et al[2]	668	5-year EFS 56% vs 44%**	8-year OS 57% vs 44%*
Spencer et al[3]	243	3-year PFS 42% vs 23%**	3-year OS 86% vs 75%
Lokhorst et al[4]	535	Median 22 m vs 34 m**	Median 60 m vs 73 m
Morgan et al[5]	492	Median 30 m vs 23 m**	3-year OS 75% vs 80%
Stewart et al[6]	332	Median 28 m vs 17 m*	4-year OS 68% vs 60%

*, p≤0.05; **, p≤0.01.

1. Attal M, et al. *Blood*. 2006;108:3289-3294; 2. Barlogie B, et al. *Blood*. 2008;112:3115-3121; 3. Spencer A, et al. *J Clin Oncol*. 2009;27:1788-1793; 4. Lokhorst, et al. *Blood*. 2010;115:1113-1120; 5. Morgan G, et al. *Blood*. 2012;119(1):7-15; 6. Stewart, et al. ASH 2010.

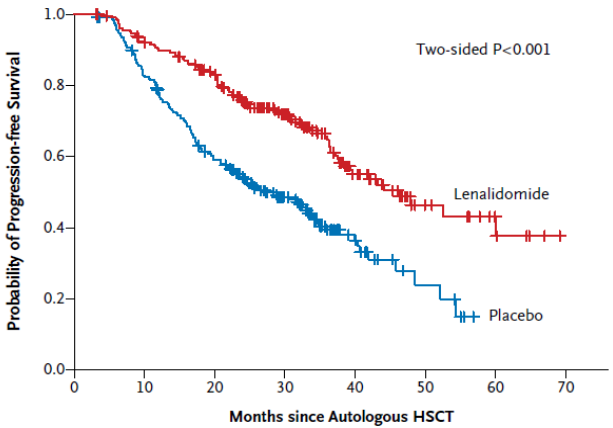
Phase 3 studies of thalidomide maintenance therapy after ASCT

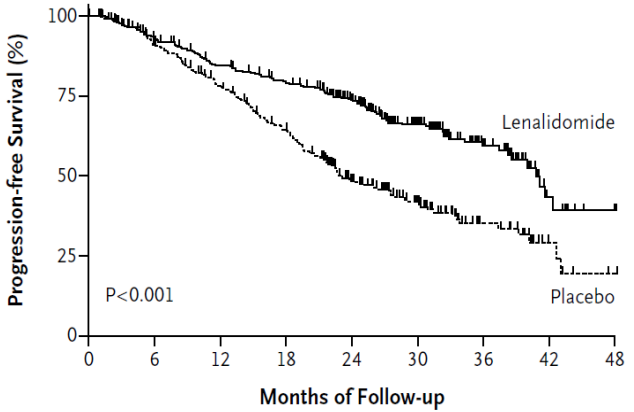
Induct With Thal	Improved OS	Survival After Relapse
No[1]	Yes, at 29 m; No at 5.7 yr	Similar in all groups
No[2]	Yes (3-year follow-up)	Similar in all groups
Yes[3]	Yes (7.2-year follow-up)	Reduced OS after thal exposure
Yes[4]	No	Reduced OS after thal exposure
Yes[5]	No	Reduced OS after thal exposure
Yes[6]	No	Not reported

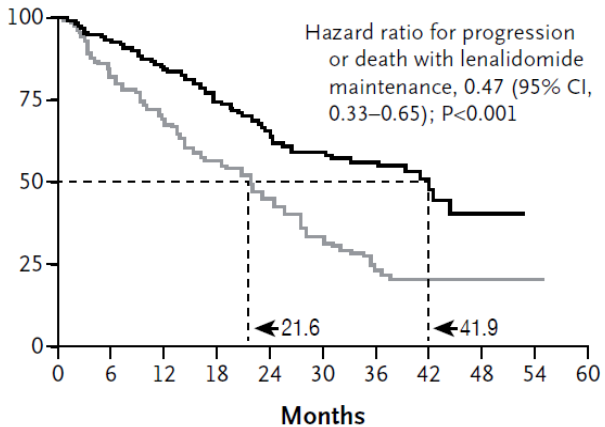
1. Attal M, et al. *Blood*. 2006;108:3289-3294; 2. Spencer A, et al. *J Clin Oncol*. 2009;27:1788-1793; 3. Barlogie, et al. *N Engl J Med*. 2006;354:1021-1030; *Blood*. 2008;112:3115-3121; *J Clin Oncol*. 2010;28:1209-1214; 4. Lokhorst, et al. *Blood*. 2010;115:1113-1120; 5. Morgan G, et al. *Blood*. 2012;119(1):7-15; 6. Stewart, et al. *Blood* 2010;116(21): Abstract 39.

Phase 3 studies of thalidomide maintenance therapy after ASCT

PFS



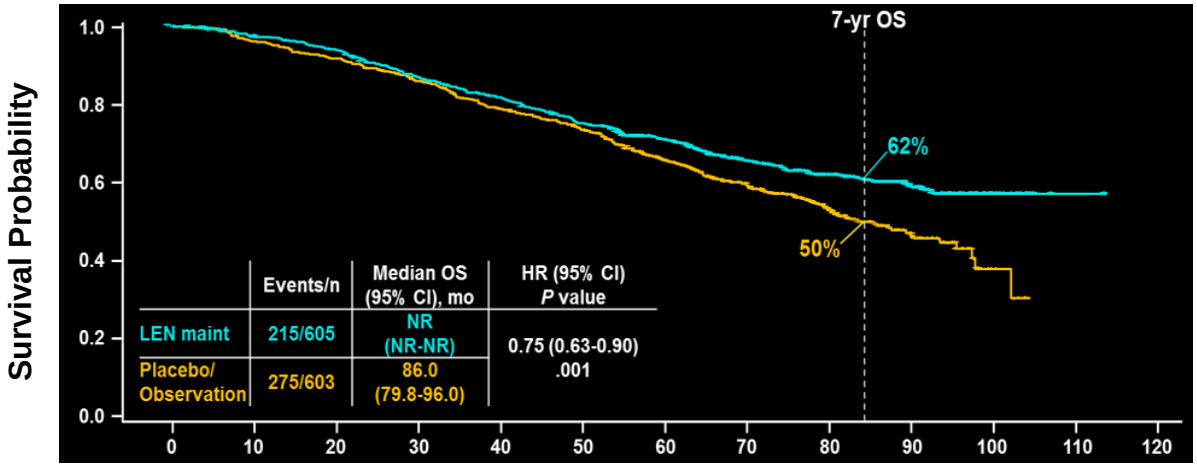




1. Attal M, et al. *N Engl J Med.* 2012;366(19):1782-1791; 2. McCarthy PL, et al. *N Engl J Med.* 2012;366(19):1770-1781; 3. Palumbo A, et al. *N Engl J Med.* 2014;371(10):895-905.

Overall survival: median follow-up of 80 months

There is a 25% reduction in risk of death, representing an estimated 2.4-year increase in median survival (March 2015 data cutoff)[a]



No.at Risk													
LEN maint	605	577	555	508	473	431	385	282	200	95	20	1	0
Placebo/ Observation	603	569	542	505	459	425	351	270	174	71	10	0	

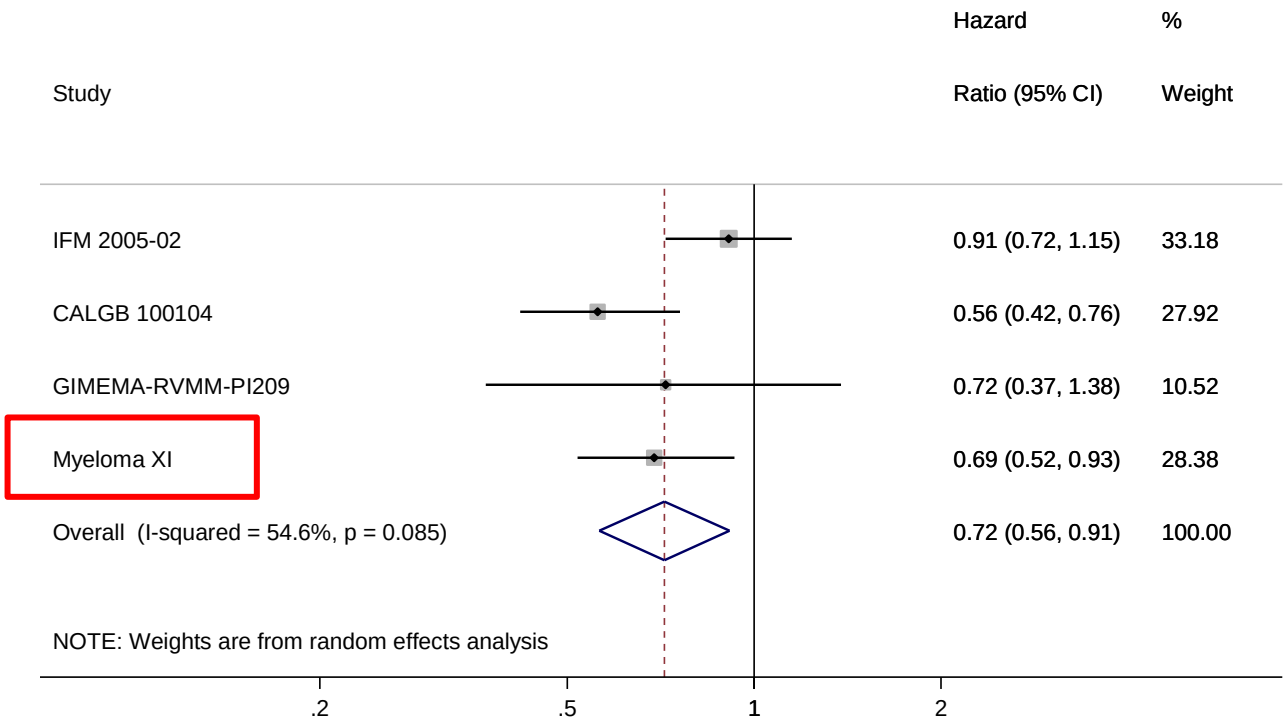
[a]Log-rank test and Cox model stratified by study to assess impact of lenalidomide maintenance on overall survival. Median for lenalidomide treatment arm was extrapolated to be 115 months based on median of the control arm and HR (median, 86 months; HR = 0.75).

HR, hazard ratio; maint, maintenance; NR, not reached; OS, overall survival.

McCarthy PL, et al. *J Clin Oncol*. 2017;35:3279-3289.

Transplant-eligible meta-analysis

Demonstrates improved OS with maintenance lenalidomide



Attal M, et al. *N Engl J Med*. 2012;366:1782-1791.
McCarthy PL, et al. *N Engl J Med*. 2012;366:1700-1781.
Palumbo A, et al. *N Engl J Med*. 2014;371:895-905.
McCarthy PL, et al. *J Clin Oncol*. 2017;35(29):3279-3289.
Jackson G, et al. ASH 2017. Abstract 436.

What we know today for transplant-eligible patients with MM: Maintenance with lenalidomide

Maintenance

ESMO Guidelines 2017[1]
Lenalidomide maintenance is EMA-approved for the treatment of adult patients with newly-diagnosed MM who have undergone ASCT

Lenalidomide

Study details	n	Treatment	PFS	OS
Meta-analysis[2] Median follow-up: 80 months	605 603	Induction → ASCT → lenalidomide daily (or D 1–21/28) until progression Placebo/observation	52.8 mo 23.5 m HR (95% CI) 0.48 (0.41 to 0.55)	Not reached 86.0 mo; *P* = .001
MYELOMA XI[3] Median follow-up: 30.6 months	730 518	Transplant eligible: CTD or CRD → ASCT → lenalidomide D 1–21/28 until progression	56.9 mo 30.1 mo; *P* <.0001	87.5% 80.2%; *P* = .0130

1. Moreau P, et al. *Ann Oncol*. 2017;28(suppl 4):iv52-iv61; 2. McCarthy PL, et al. *J Clin Oncol.* 2017;35:3279-3289; 3. Jackson G, et al. ASH 2017. Abstract 436 (oral presentation).

What we know today for transplant-eligible patients with MM: Maintenance with bortezomib

Bortezomib

Study details*	n	Treatment	PFS	OS
HOVON 65 MM/GMMG-HD4[1,2] Median follow-up: 96 months (overall trial)	413 414	PAD × 3 → HDM → bortezomib every 2 weeks for 2 years VAD × 3 → HDM → thalidomide daily for 2 years	34 mo 28 mo; *P* <.001	48% 45%; *P* = .24
PETHEMA/GEM[3] Median follow-up: 58.6 months (from maintenance start)	91 88 92	TV (thal daily, 1 cycle bortezomib every 3 mo) for 3 years Thal (daily for 3 years) Interferon-α2b (3×/week for 3 years)	50.6 mo 40.3 mo 32.5 mo; *P* = .03	Not significantly diffferent between arms

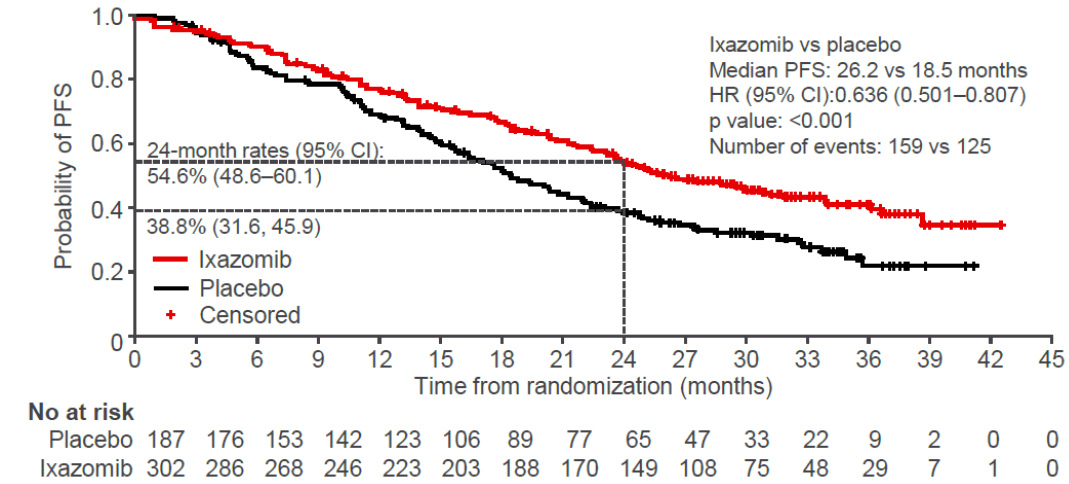
*Bortezomib administered at 1.3 mg/m^2 IV in both studies.

1. Goldschmidt H, et al. *Leukemia*. 2018;32(2):383-390; 2. Sonneveld et al. ASH 2015. Abstract 27 (oral presentation); 3. Rosiñol et al. *Leukemia*. 2017;31(9):1922-1927.

New findings in transplant-eligible MM: Ixazomib maintenance

TOURMALINE-MM3 phase III study update: Ixazomib maintenance post-ASCT

PFS in patients with a response of VGPR or PR at study entry, by treatment arm



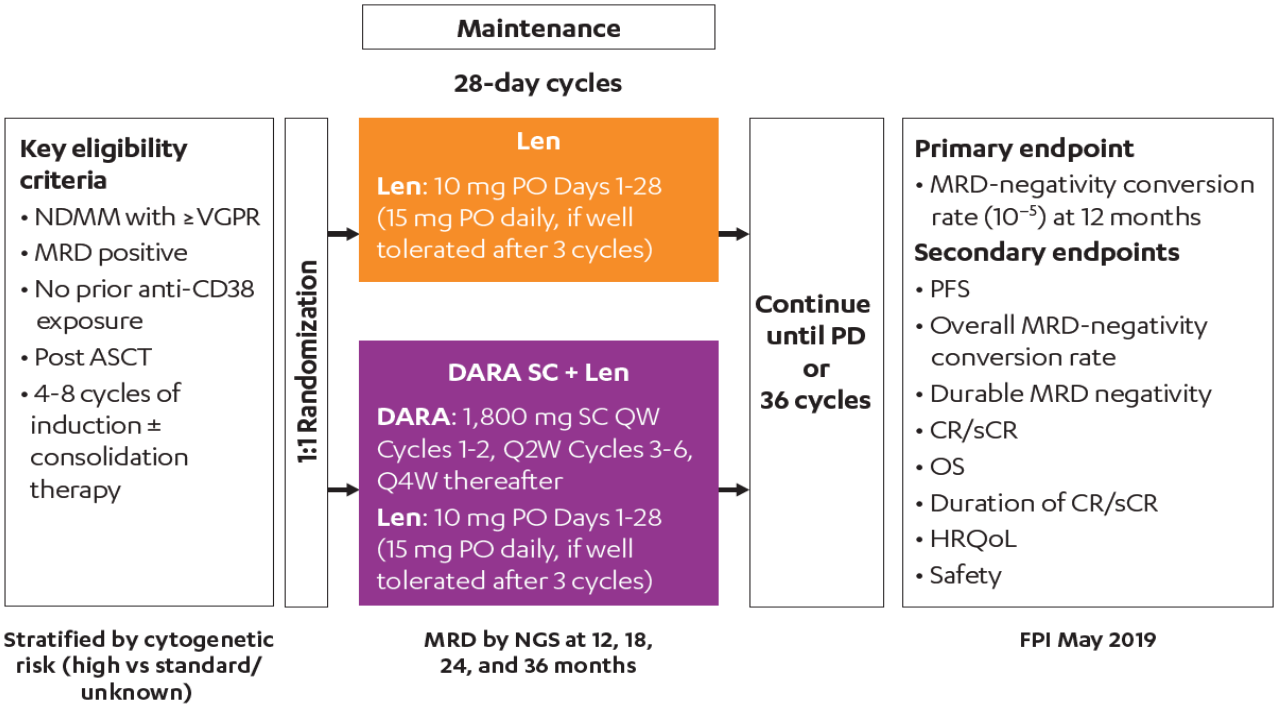
- Median follow-up of 30.9 months for ixazomib and 31.3 months for placebo

Post-ASCT maintenance with ixazomib resulted in a significantly higher rate of deepening response vs placebo among patients with VGPR/PR at study entry

Goldschmidt H, et al. EHA 2019. Abstract PS1382 (poster presentation).

AURIGA phase III study: Design

Objective: to evaluate the conversion rate to MRD negativity after maintenance treatment with DARA SC plus Len vs Len alone in patients with NDMM who are MRD positive after ASCT



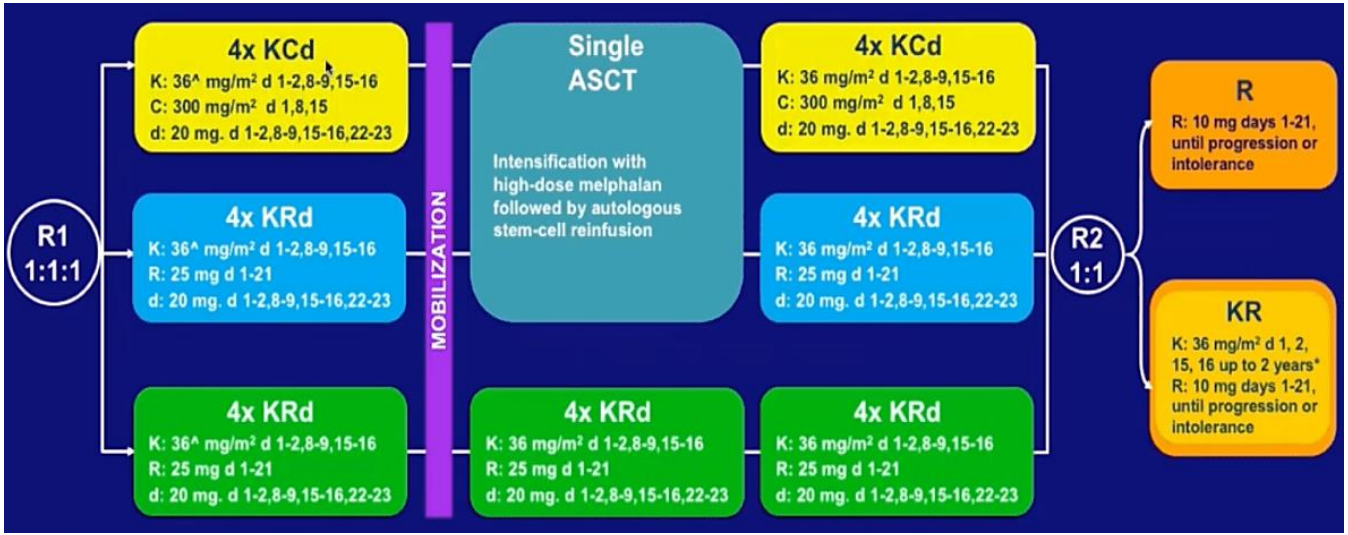
NDMM, newly diagnosed multiple myeloma; VGPR, very good partial response; MRD, minimal residual disease; ASCT, autologous stem cell transplant; Len, lenalidomide; PO, oral; DARA SC, daratumumab subcutaneous; QW, weekly; Q2W, every 2 weeks; Q4W, every 4 weeks; NGS, next-generation sequencing; PD, progressive disease; PFS, progression-free survival; CR, complete response; sCR, stringent complete response; OS, overall survival; HRQoL, health-related quality of life; FPI, first patient in.

Shah et al. ASH 2019. Abstract 1829.

Combining both modern consolidation and maintenance?

FORTE: Design and patients

474 NDMM transplant eligible patients <65 years old



Median age of patients

Randomization 1	KCd_ASCT N = 159	KRd_ASCT N = 158	KRd12 N = 157
Median age, years (IQR)	57 (52-62)	57 (52-62)	57 (51-62)
Randomization 2	**KR N = 178**	**R N = 178**	
Median age, years (IQR)	56 (52-62)	57 (51-52)	

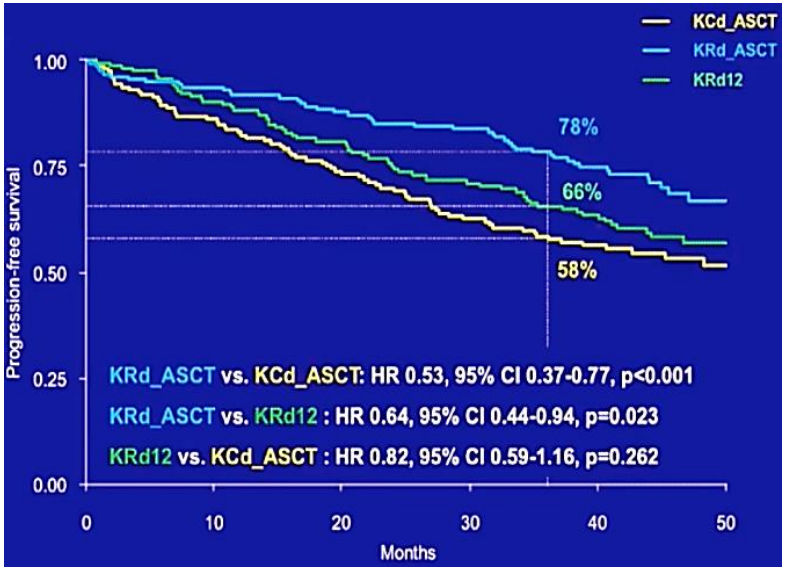
^200 mg² on days 1-2, cycle 1 only. Carfilzomib 70 mg/m² days 1, 15 every 28 days up to 2 years for patients that have started maintenance treatment from 6 months before the approval of Amendment 5.0 onward. ASCT, autologous stem cell transplant; IQR, interquartile range; K, carfilzomib; C, cyclophosphamide; NDMM, newly-diagnosed MM; R, lenalidomide; R1, first randomization (induction and consolidation); R2, second randomization (maintenance).

Gay et al. ASH 2020. Abstract 141 (oral presentation).

FORTE: PFS after consolidation and maintenance

3-year PFS after consolidation

Median follow-up: 45 months (40-49 months)

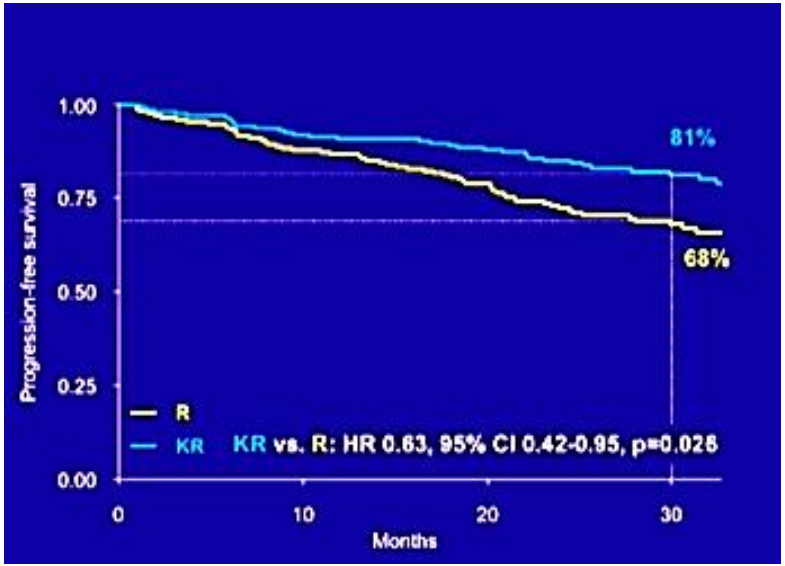


- Sustained MRD negativity (MFC at a sensitivity of 10^{-5})
- KRd_ASCT 68%, KRd12 54%, KCd_ASCT 45%, P<0.001

KRd_ASCT significantly prolonged PFS vs KRd and KCd_ASCT

30-month PFS

Median follow-up: 31 months (26-36 months)



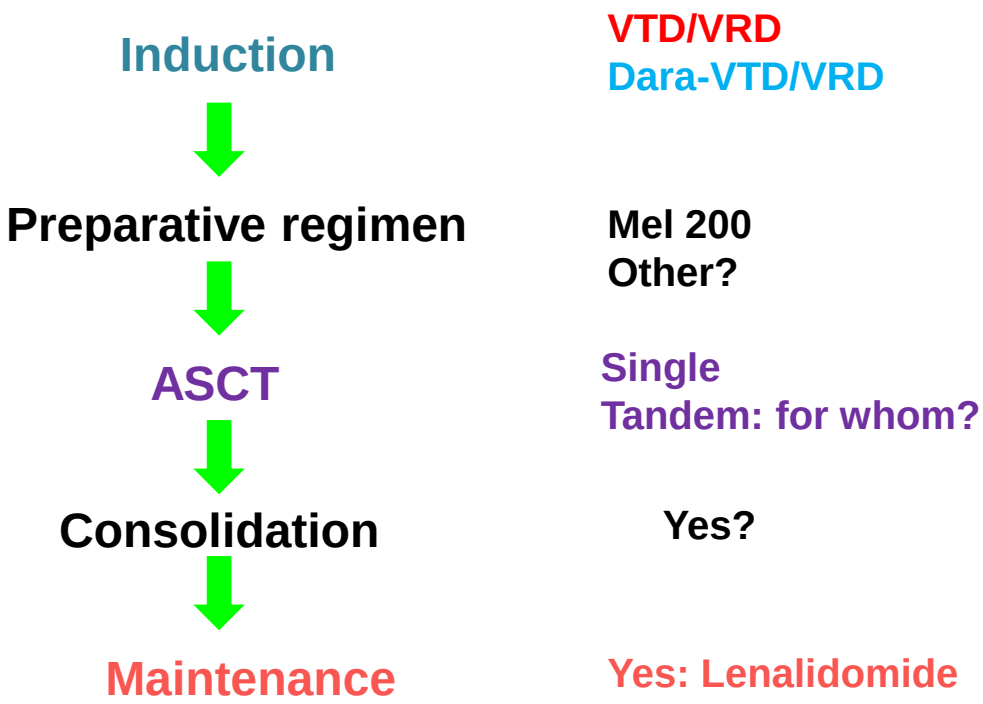
- Rate of conversion from MRD+ to MRD– (MFC at a sensitivity of 10^{-5}): KR 46%, R 32%; *P* = .04
- No KR discontinuations; 4 patients on KR and 1 patient on R had secondary malignancies
- 27% of patients on KR had ≥1 extra hematological AE vs 15% of patients on R (*P* = .012)

KR significantly prolonged PFS vs R

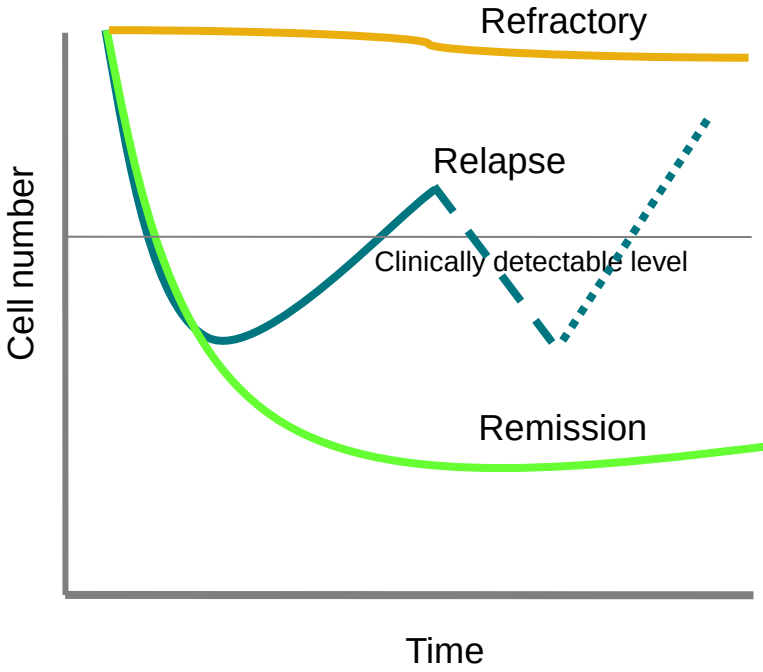
ASCT, autologous stem cell transplant;; CI, confidence interval; HR, hazard ratio; KRd carfilzomib, cyclophosphamide, dexamethasone; KRd, carfilzomib, lenalidomide dexamethason; MRD, minimal residual disease; MFC, multiparameter flow cytometry; PFS, progression-free survival; R, lenalidomide.

Gay et al. ASH 2020. Abstract 141 (oral presentation).

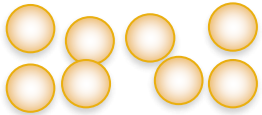
Strategy for treating newly diagnosed myeloma patients: Intensive approach



Multiple myeloma: The search for a cure?

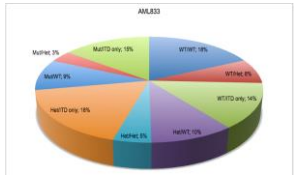


- Homogeneous resistant



- Heterogeneous

- Homogeneous sensitive



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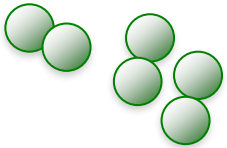

“Consolidation/ Maintenance”?

Global Multiple Myeloma Academy

Discussion

APTITUDE HEALTH®

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Break

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Frontline Therapy for Newly Diagnosed Transplant-Ineligible Patients

Keith Stewart

APTITUDE HEALTH®

Treatment of Newly Diagnosed Transplant-Ineligible Multiple Myeloma

Keith Stewart, MBChB
Professor of Medicine
Director, Princess Margaret Cancer Centre
Toronto

Which of the following has not shown significant improvement in PFS?

A. VRd vs Rd

B. IRd vs Rd

C. Dara-Rd vs Rd

D. VMP-Dara vs VMP

E. Rd vs MPR

Treatment of Non–Transplant-Eligible Myeloma, Newly Diagnosed

REASONABLE OPTIONS (frailty, comorbidity, availability, geography all considerations)

- Rd
- CyborD
- RVd
- RVd-lite
- Daratumumab, lenalidomide, dexamethasone
- Daratumumab + VMP

RESEARCH ARTICLE | MARCH 19, 2021

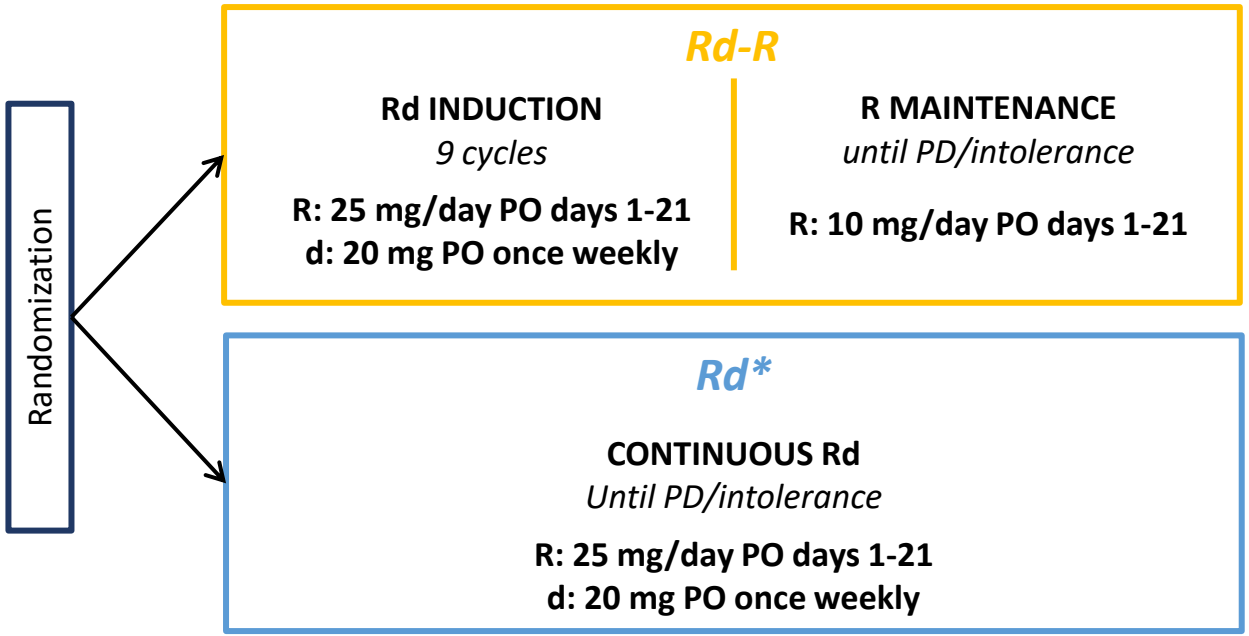
Dose/Schedule-Adjusted Rd-R vs Continuous Rd for elderly, intermediate-fit, newly diagnosed multiple myeloma patients

Clinical Trials & Observations

Alessandra Larocca , Francesca Bonello , Gianluca Gaidano , Mattia D'Agostino , Massimo Offidani , Nicola Cascavilla , Andrea Capra , Giulia Benevolo , Patrizia Tosi , Monica Galli , Roberto Marasca , Nicola Giuliani , Annalisa Bernardini , Elisabetta Antonioli , Delia Rota Scalabrini , Claudia Cellini , Alessandra Pompa , Federico Monaco , Francesca Patriarca , Tommaso Caravita , Paolo Corradini , Paola Tacchetti , Mario Boccadoro , Sara Bringhen

Study Design
Rd vs Rd-R

199 intermediate-fit patients have been enrolled and could be evaluated[1]



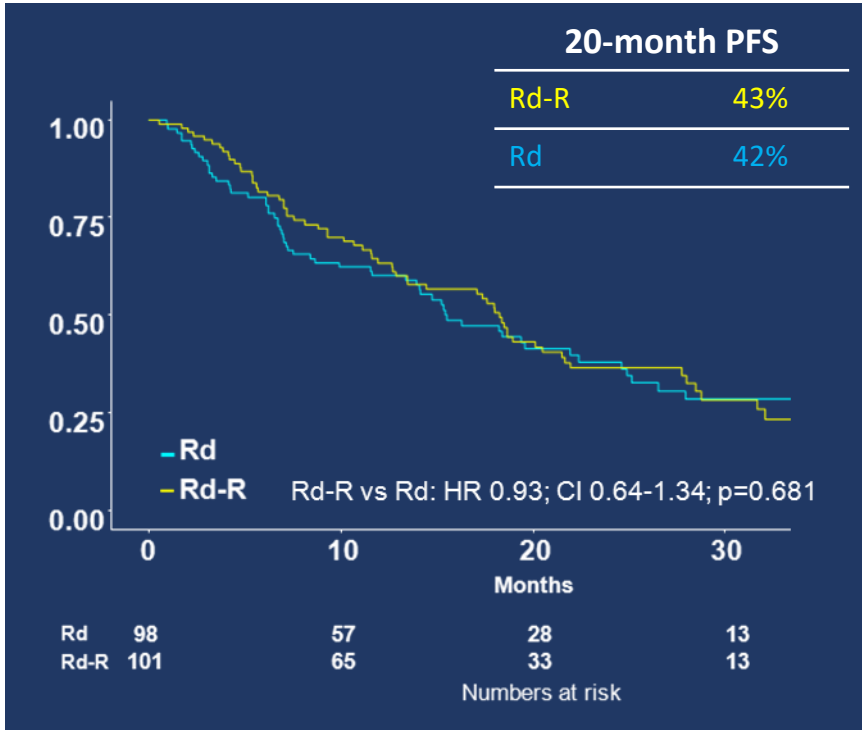
*The dose and schedule of continuous Rd was the one adopted in patients >75 years in the FIRST trial.[2]

R, lenalidomide; d, dexamethasone; PO, orally; PD, progressive disease.

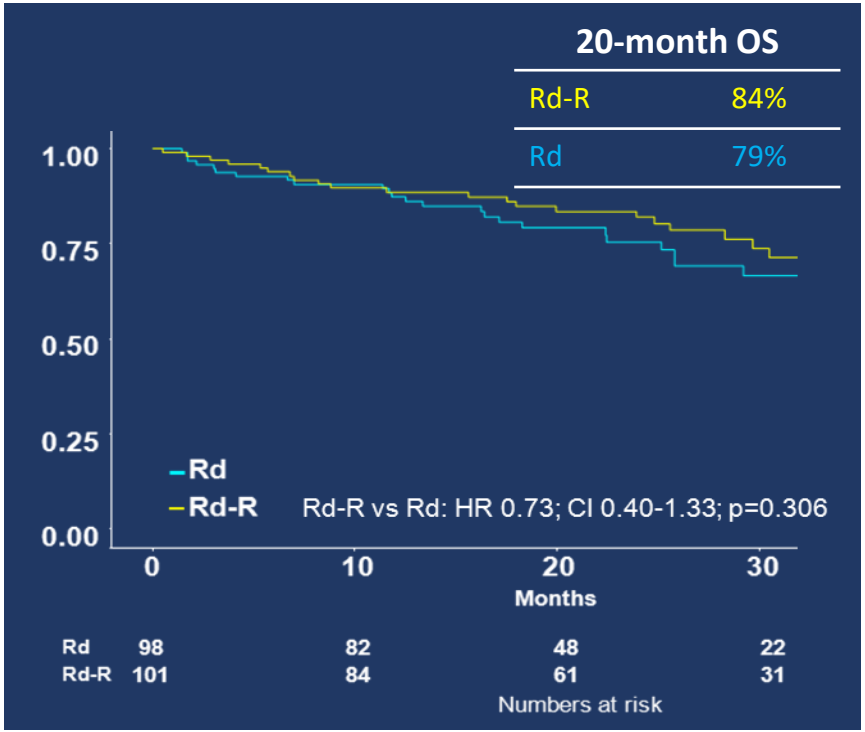
1. Larocca A, et al. *Blood.* 2021. doi: 10.1182/blood.2020009507; 2. Hulin C, et al. *J Clin Oncol.* 2016;34(30):3609-3617.

Rd vs Rd-R: PFS and OS

Progression-Free Survival



Overall Survival

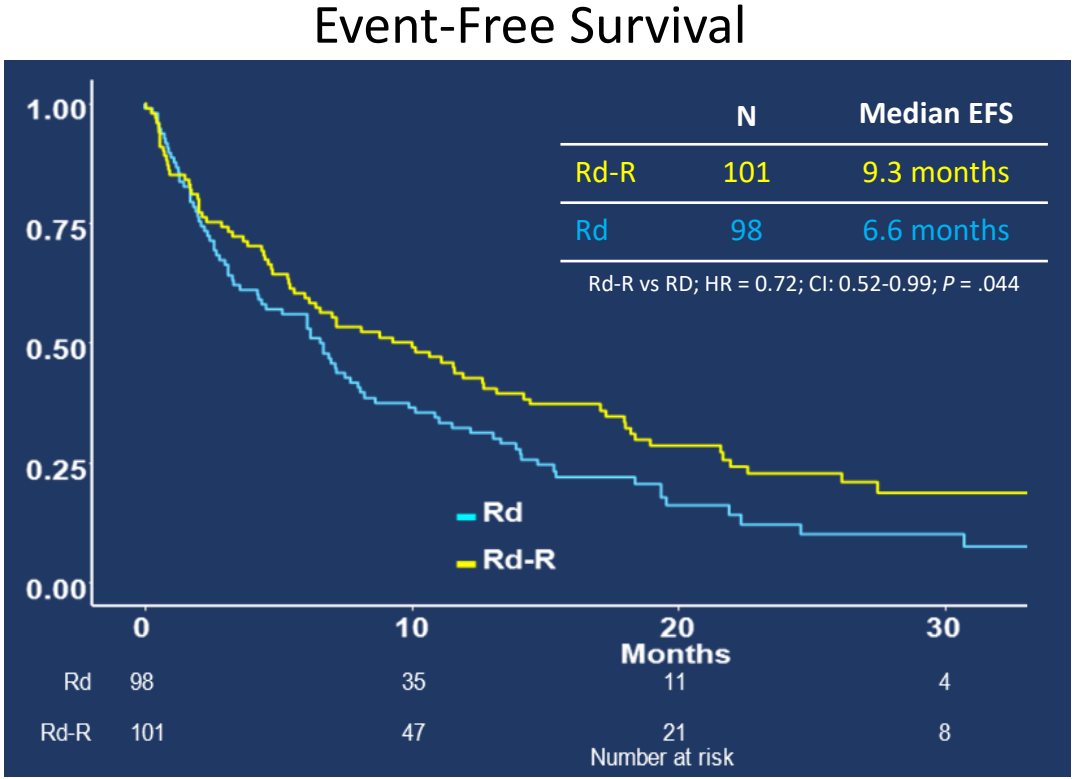


R, lenalidomide; d, dexamethasone; PFS, progression-free survival; OS, overall survival.

Larocca A, et al. *Blood.* 2021. doi: 10.1182/blood.2020009507.

Rd vs Rd-R: Event-Free Survival

Median follow-up 25 months



Primary endpoint: event-free survival (EFS)

Definition of the event[a]

- Hematologic grade 4 AEs
- Non-hematologic grade 3-4 AEs, including SPM
- Discontinuation of lenalidomide therapy
- Disease progression
- Death for any cause

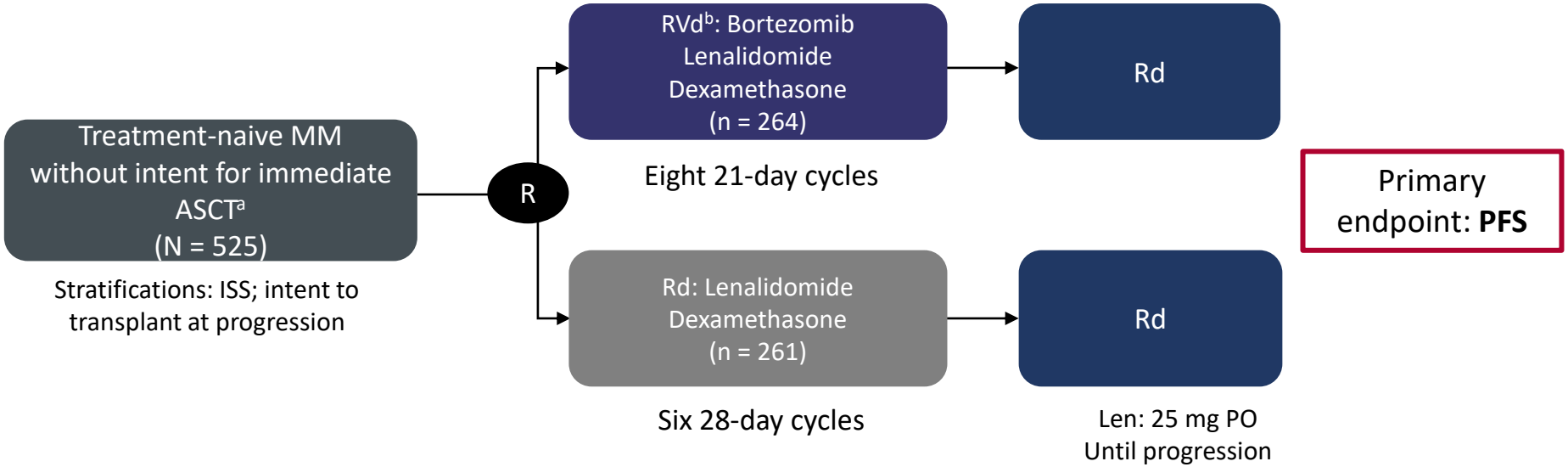
[a]Related to study drugs.

R, lenalidomide; d, dexamethasone; EFS, event-free survival; AEs, adverse events; SPM, second primary malignancy.

Larocca A, et al. *Blood.* 2021. doi: 10.1182/blood.2020009507.

SWOG S0777: Study Design

VRd vs Rd



[a]All patients received aspirin (325 mg/d). [b]Patients received HSV prophylaxis.
High-risk cytogenetics included: t(4;14), t(14;16), or del(17p); preliminary data from 316 patients.
Durie BGM, et al. ASH 2018. Abstract 1992; Durie BGM, et al. *Lancet*. 2017;389:519-527.

Updated Response Assessment

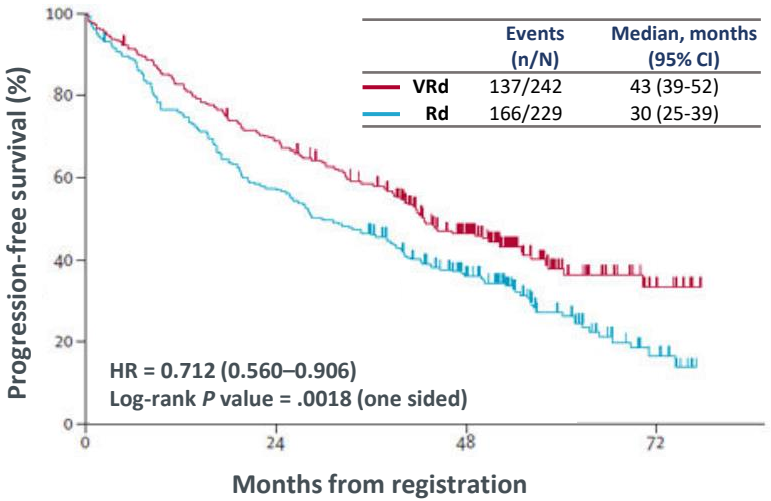
	Response, n (%)	
	RVd (n = 215)	Rd (n = 207)
CR	52 (24.2)	25 (12.1)
VGPR	109 (50.7)	85 (41.1)
≥VGPR	(74.9)	(53.2)
PR	33 (15.3)	53 (25.6)
ORR	194 (90.2)	163 (78.8)
SD	15 (7.0)	34 (16.4)
PD or death	6 (2.8)	10 (4.8)

Durie BGM, et al. ASH 2018. Abstract 1992.

SWOG S0777: PFS and OS

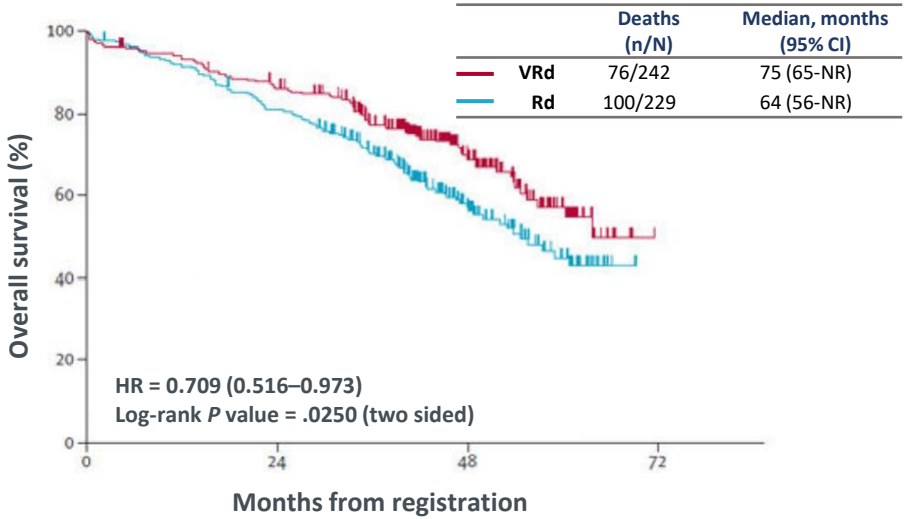
Progression-Free Survival

By assigned treatment arm



Overall Survival

By assigned treatment arm



Triplet is better than a doublet

Durie BGM, et al. *Lancet*. 2017;389:519-527.

SWOG S0777: Overall Survival

Based on current eligibility (N = 460)

	Deaths/N	Median, mo
Rd	125/225	69 (59-88)
VRd	102/235	NR
	P = .0114	

VRd: 55% OS at 7 years

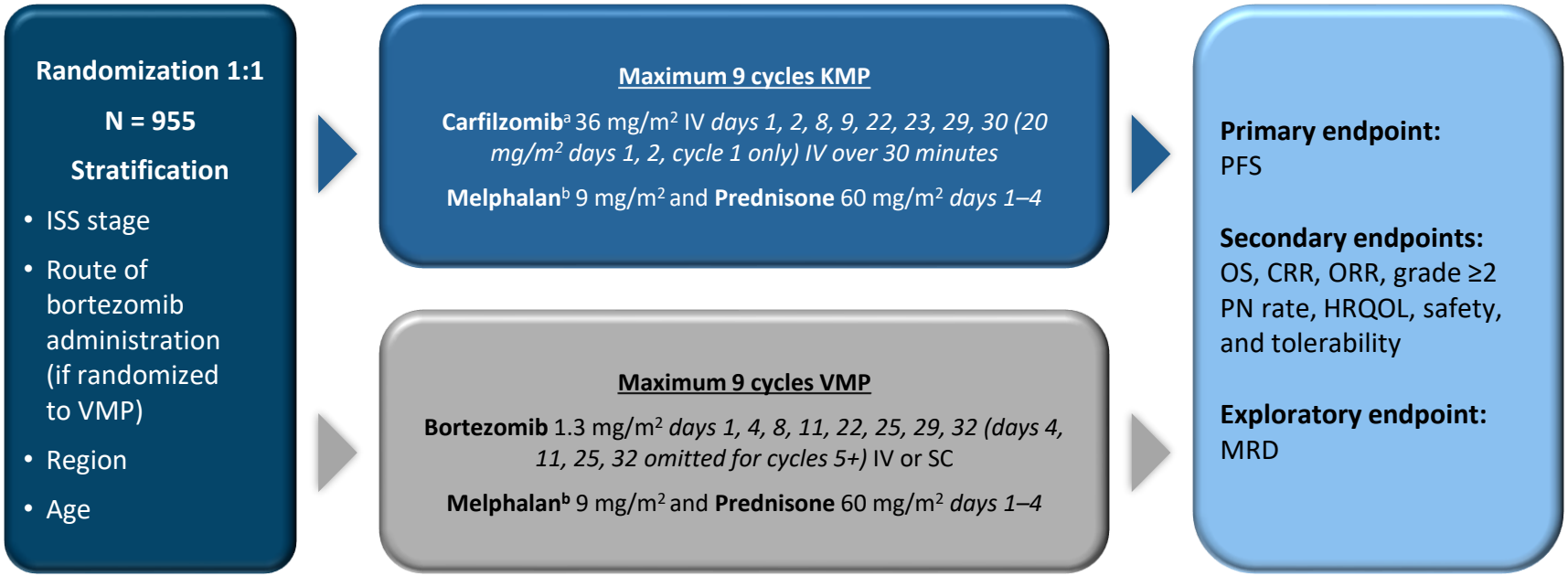
Durie BGM, et al. ASH 2018. Abstract 1992.

Modified RVD ("RVD-lite") for Elderly/Frail

- Dosing
  - Lenalidomide 15 mg days 1–21 of a 35-day cycle
  - Bortezomib 1.3 mg/m^2 weekly days 1, 8, 15, 22
  - Dexamethasone 20 mg twice weekly for pts ≤75 yr and days 1, 8, 15, 22 for pts >75 yr
- 53 patients treated
- Median age of patients: 72 years
- iORR: 90% (10 CR, 14 VGPR, 12 PR, 4 SD)
- Toxicities manageable
  - Grade ≥3 toxicities included hypophosphatemia in 15 (31%) and rash in 5 (10%) pts
  - Fatigue most common, in 31/49 (63%) patients, mostly grade 1–2
  - Peripheral neuropathy of any grade was reported in 21/49 (43%) pts including grade 1 (11, 22%), 2 (9, 18%), and 3 (1, 2%)

O'Donnell EK, et al. ASH 2015. Abstract 4217.

CLARION: Study Design



[a]Carfilzomib was administered for 2 weeks out of 3 twice per cycle.

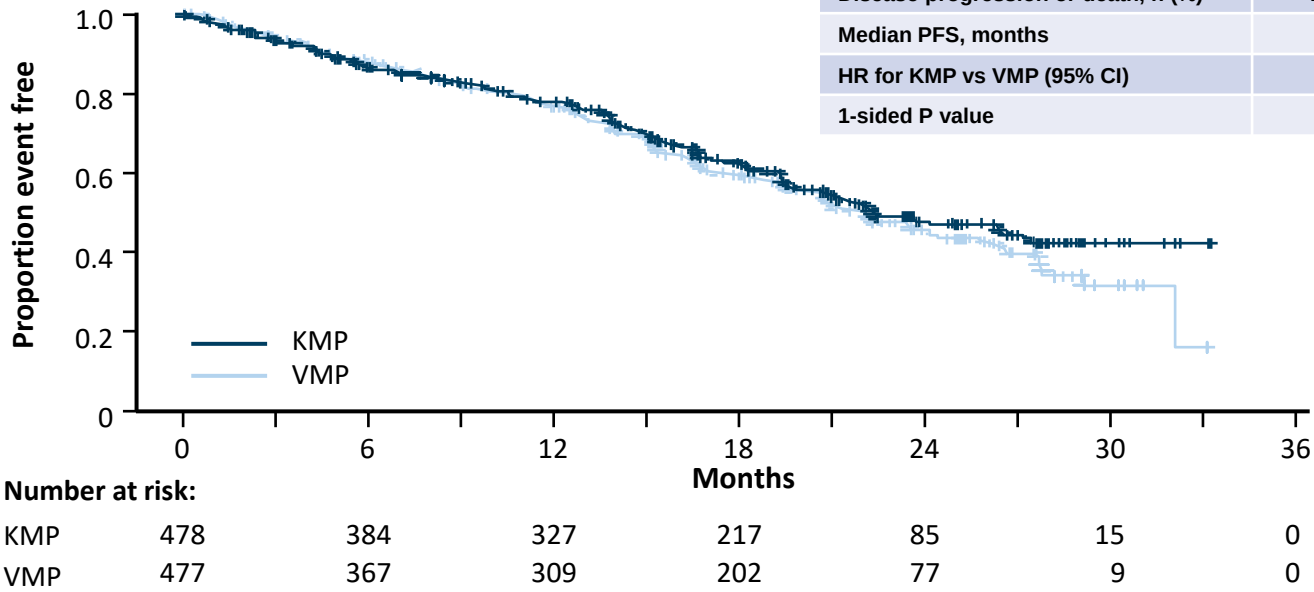
[b]Melphalan dose was 7 mg/m² if age was >75 years or CrCl was 30 to < 50 mL/min; 5 mg/m² if CrCl was 15 to <30 mL/min.[1]

CRR, complete response rate; CrCl, creatinine clearance; HRQOL, health-related quality of life; ISS, International Staging System; IV, intravenous; KMP, carfilzomib, melphalan, prednisone; MRD, minimal residual disease; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PN, peripheral neuropathy; SC, subcutaneous; VMP, bortezomib, melphalan, prednisone.

Facon T, et al. Presented at: 16th International Myeloma Workshop; New Delhi, India; March 1-4, 2017.

Primary Endpoint: Progression-Free Survival

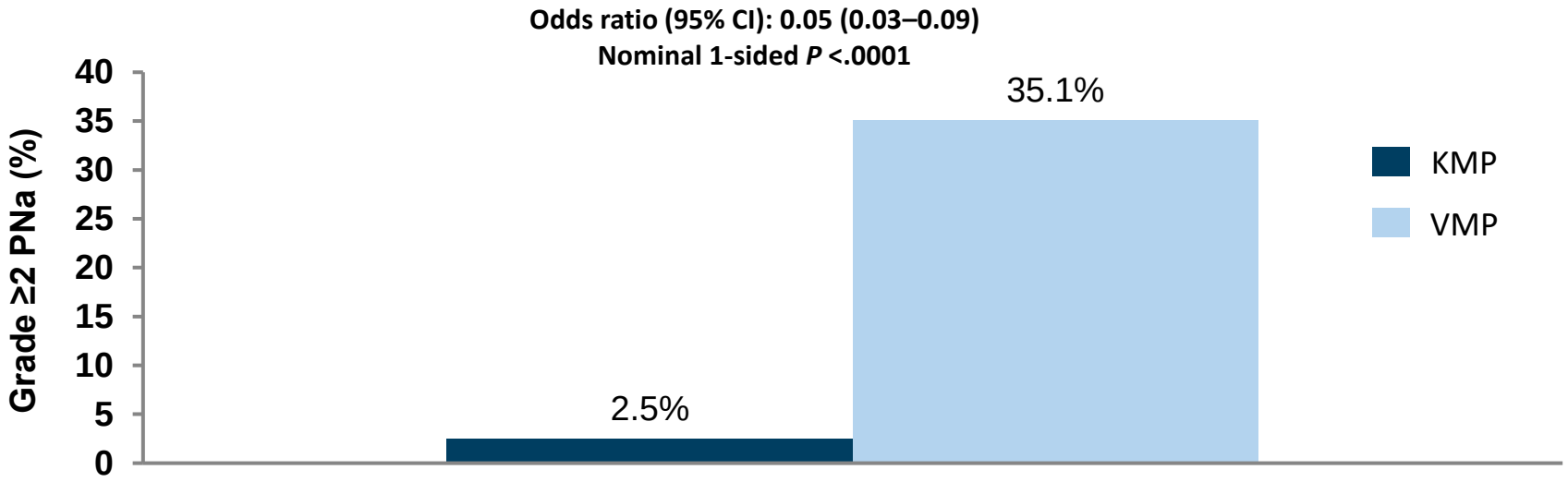
	KMP (n = 478)	VMP (n = 477)
Disease progression or death, n (%)	207 (43.3)	214 (44.9)
Median PFS, months	22.3	22.1
HR for KMP vs VMP (95% CI)	0.91 (0.75–1.10)	
1-sided P value	.16	



- Median follow-up time: 22.2 months for KMP and 21.6 months for VMP
- The absence of PFS difference was consistent across subgroups

HR, hazard ratio; KMP, carfilzomib, melphalan, prednisone; PFS, progression-free survival; VMP, bortezomib, melphalan, prednisone.
Facon T, et al. Presented at: 16th International Myeloma Workshop; New Delhi, India; March 1-4, 2017.

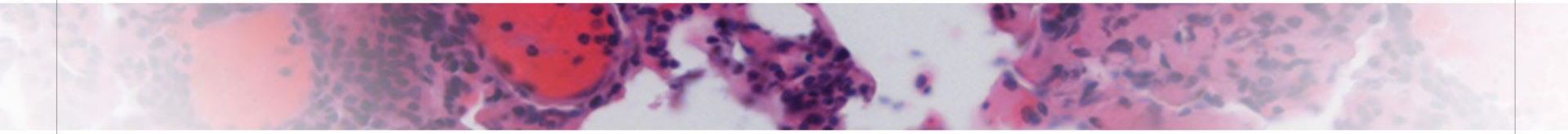
Secondary Endpoint: Grade ≥2 Neuropathy



- Among patients in the VMP group, 69% received subcutaneous bortezomib throughout their treatment

[a]Standardized MedDRA Query Narrow Search for peripheral neuropathy.
KMP, carfilzomib, melphalan, prednisone; MedDRA, Medical Dictionary for Regulatory Activities; PN, peripheral neuropathy; VMP, bortezomib, melphalan, prednisone.
Facon T, et al. Presented at: 16th International Myeloma Workshop; New Delhi, India; March 1-4, 2017.

American Society *of* Hematology
Helping hematologists conquer blood diseases worldwide



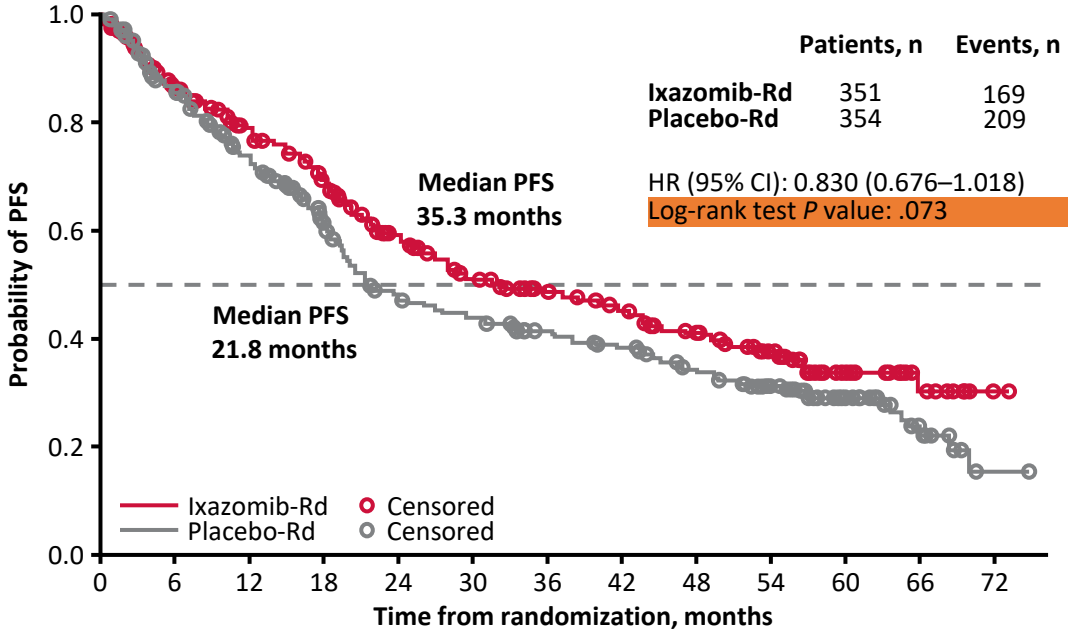
The Phase 3 TOURMALINE-MM2 Trial: Oral Ixazomib, Lenalidomide, and Dexamethasone vs Placebo-Rd for Transplant-Ineligible Patients with Newly Diagnosed Multiple Myeloma

Thierry Facon,[1] Christopher P. Venner,[2] Nizar J. Bahlis,[3] Fritz Offner,[4] Darrell J. White,[5] Lotfi Benboubker,[6] Sophie Rigaudeau,[7] Philippe Rodon,[8] Sung-Soo Yoon,[9] Kenshi Suzuki,[10] Hirohiko Shibayama,[11] Xiaoquan Zhang,[12] Godwin Yung,[12] Robert M. Rifkin,[13] Philippe Moreau,[14] Sagar Lonial,[15] Shaji K. Kumar,[16] Paul G. Richardson,[17] and S. Vincent Rajkumar[16] on behalf of the TOURMALINE-MM2 study group

[1]Centre Hospitalier Universitaire (CHU) Lille, Service des Maladies du Sang, University of Lille, Lille, France; [2]Division of Medical Oncology, Cross Cancer Institute, University of Alberta, Edmonton, AB, Canada; [3]Division of Hematology and Oncology, Charbonneau Cancer Research Institute, University of Calgary, Calgary, AB, Canada; [4]Hematology, Department of Internal Medicine, Ghent University Hospital, Ghent, Belgium; [5]QEII Health Sciences Center and Dalhousie University, Halifax, NS, Canada; [6]Service d'Hématologie et Thérapie Cellulaire, Hôpital Bretonneau, Centre Hospitalier Régional Universitaire (CHRU), Tours, France; [7]Department of Clinical Hematology, Centre Hospitalier Versailles, Le Chesnay, France; [8]Unité d'Hématologie et d'Oncologie, Centre Hospitalier Périgueux, Périgueux, France; [9]Department of Internal Medicine, Seoul National University Hospital, Seoul, South Korea; [10]Department of Hematology, Japanese Red Cross Medical Center, Tokyo, Japan; [11]Department of Hematology and Oncology, Osaka University Graduate School of Medicine, Suita, Japan; [12]Millennium Pharmaceuticals, Inc., Cambridge, MA, USA, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited; [13]Rocky Mountain Cancer Centers/US Oncology Research, Denver, CO, USA; [14]Department of Hematology, University Hospital Hôtel Dieu, University of Nantes, Nantes, France; [15]Department of Hematology and Medical Oncology, Winship Cancer Institute, Emory University, Atlanta, GA, USA; [16]Division of Hematology, Department of Internal Medicine, Mayo Clinic, Rochester, MN, USA; [17]Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA

Electronic poster presentation at the virtual 62nd Annual Meeting of the American Society of Hematology (ASH), December 5–8, 2020.
For questions or comments please contact Professor Thierry Facon: Thierry.FACON@CHRU-LILLE.FR.

Ixazomib-Rd vs Placebo-Rd: PFS



Patients at risk, n

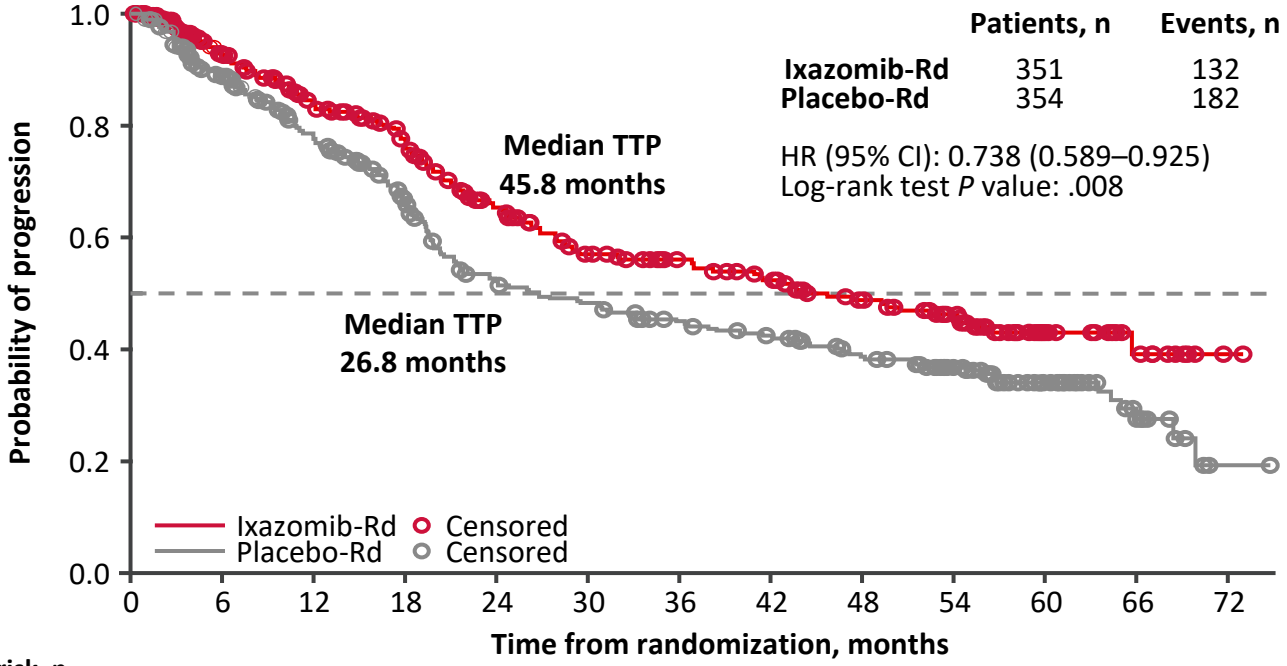
Ixazomib-Rd	351	261	220	187	147	120	107	96	81	64	28	10	1
Placebo-Rd	354	273	225	174	132	121	106	98	82	63	35	16	1

- Median follow-up for PFS: 53.3 vs 55.8 months in ixazomib-Rd and placebo-Rd arms, respectively
- Median DOT: 20 cycles in each arm
  - 54% of patients in the ixazomib-Rd arm and 54% in the placebo-Rd arm entered cycle 19
  - Relative dose intensity for all agents was similar between arms

Data cutoff: December 2, 2019.
DOT, duration of treatment; HR, hazard ratio.

Facon T, et al. ASH 2020. Oral presentation 551.

Longer TTP With Ixazomib-Rd vs Placebo-Rd

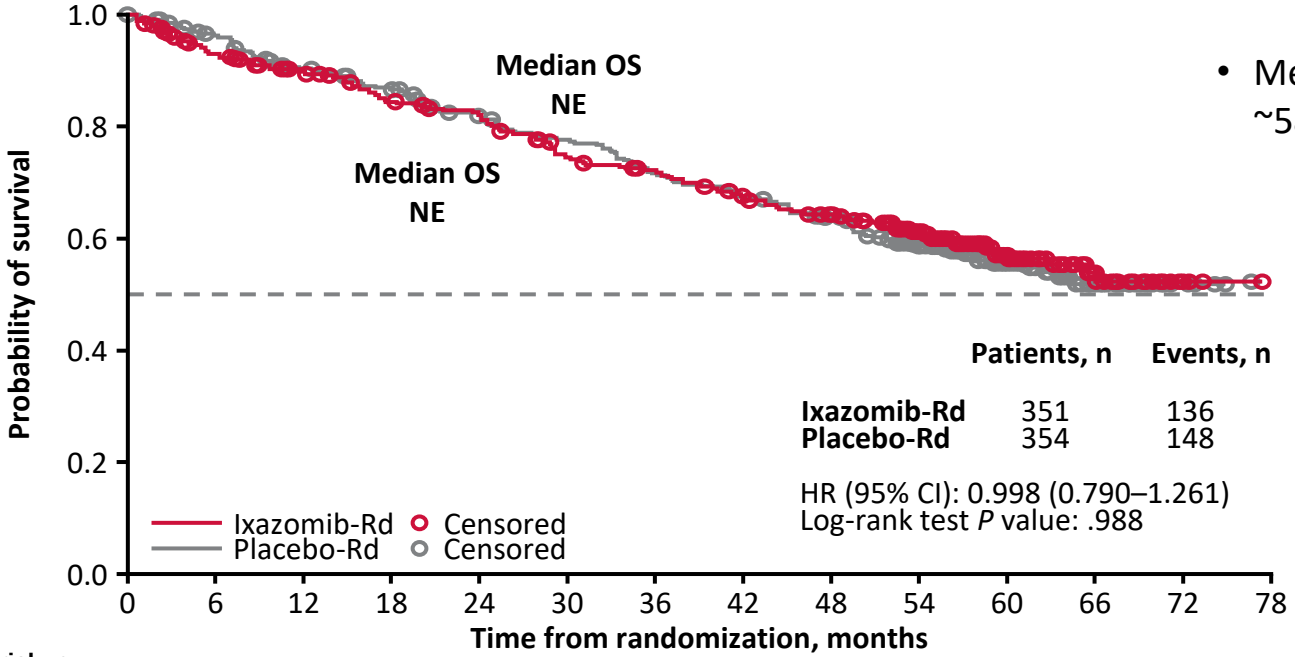


Patients at risk, n

Ixazomib-Rd	351	260	218	187	147	119	107	96	80	64	28	10	1
Placebo-Rd	354	272	224	174	132	121	106	97	82	63	35	16	1

Facon T, et al. ASH 2020. Oral presentation 551.

Median OS Not Reached in Either Arm



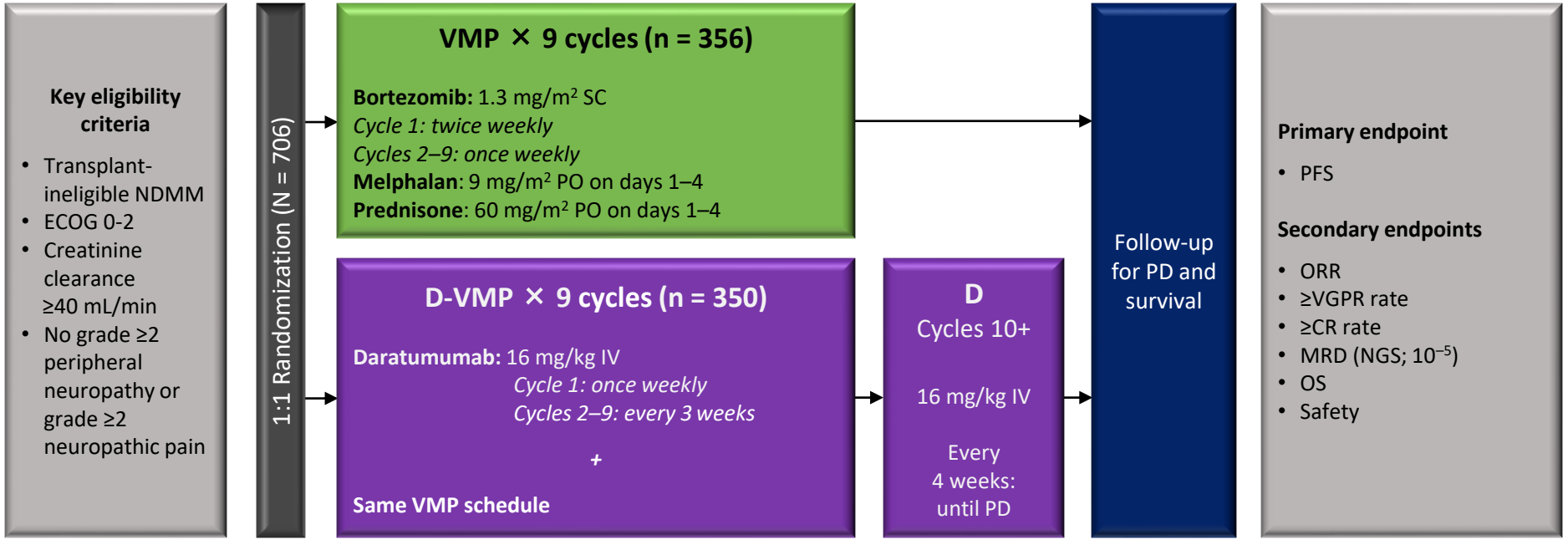
Patients at risk, n

Ixazomib-Rd	351	316	296	274	262	235	225	208	194	151	79	36	4
Placebo-Rd	354	334	310	294	271	256	236	222	204	158	83	43	7

- Median follow-up for OS: ~58 months

Facon T, et al. ASH 2020. Oral presentation 551.

ALCYONE: Study Design



Stratification factors

- ISS (I vs II vs III)
- Region (EU vs other)
- Age (<75 vs ≥75 years)

- Cycles 1-9: 6-week cycles
- Cycles 10+: 4-week cycles

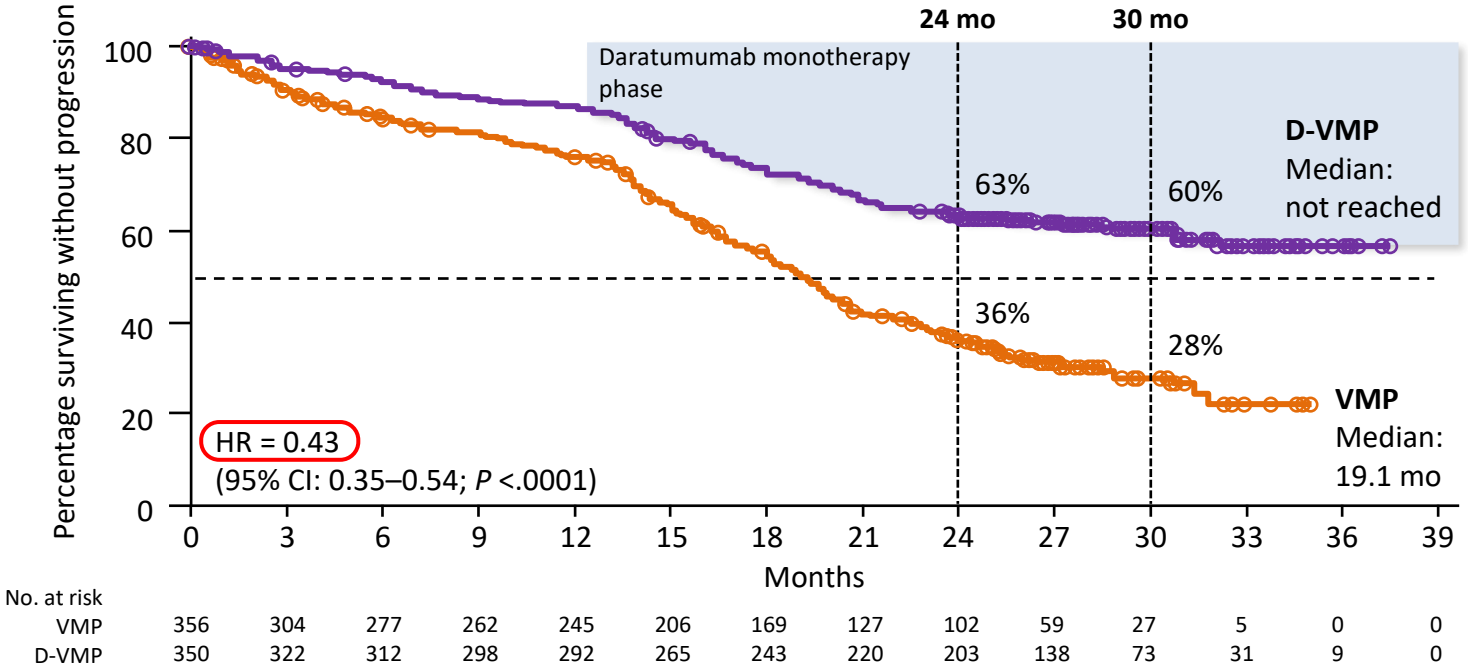
Statistical analyses

- 360 PFS events: 85% power for 8-month PFS improvement

Mateos MV, et al. *N Engl J Med.* 2018;378(6):518-528.

ALCYONE: PFS

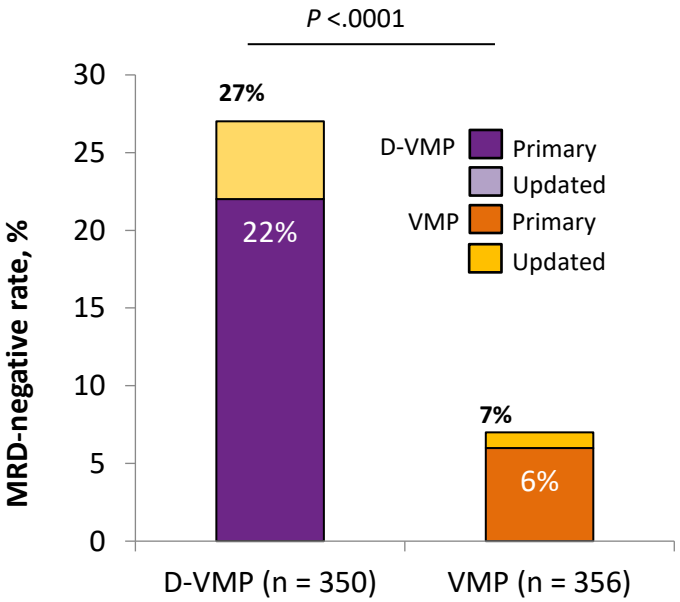
- Median (range) follow-up: 27.8 (0–39.2) months

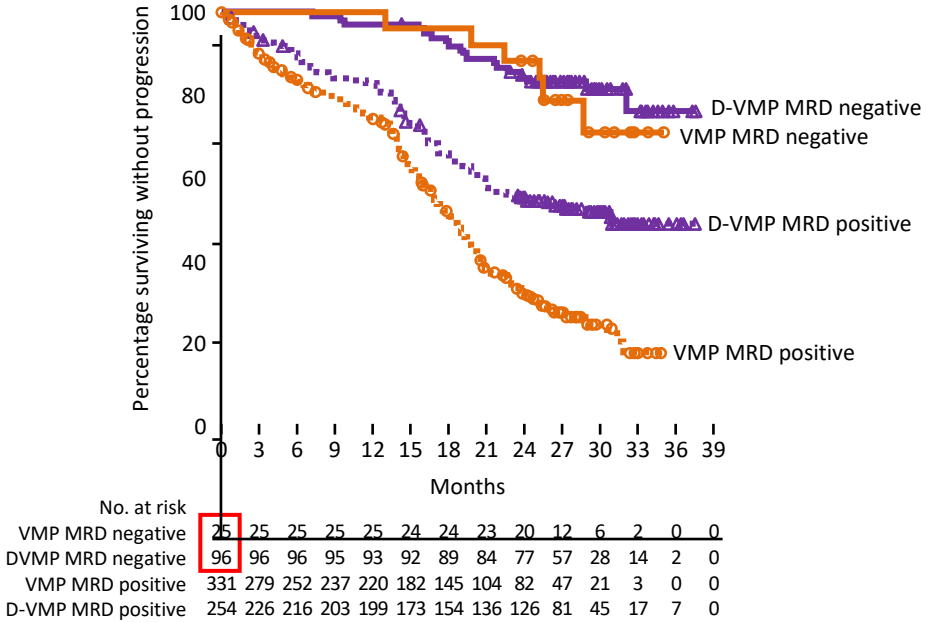


Mateos MV, et al. *N Engl J Med.* 2018;378(6):518-528.

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

- Median (range) follow-up: 27.8 (0–39.2) months

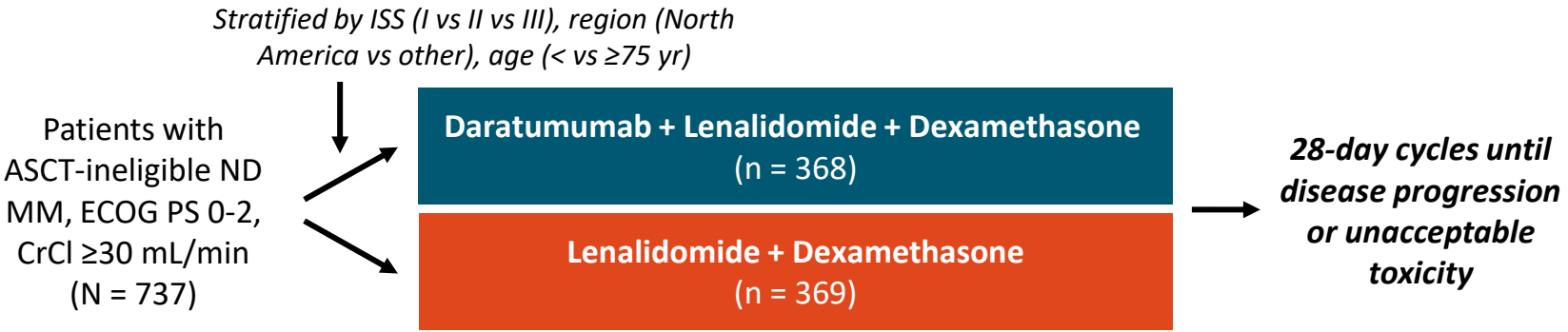




Mateos MV, et al. *N Engl J Med.* 2018;378(6):518-528.

MAIA: Study Design

- Multicenter, open-label, randomized phase III trial



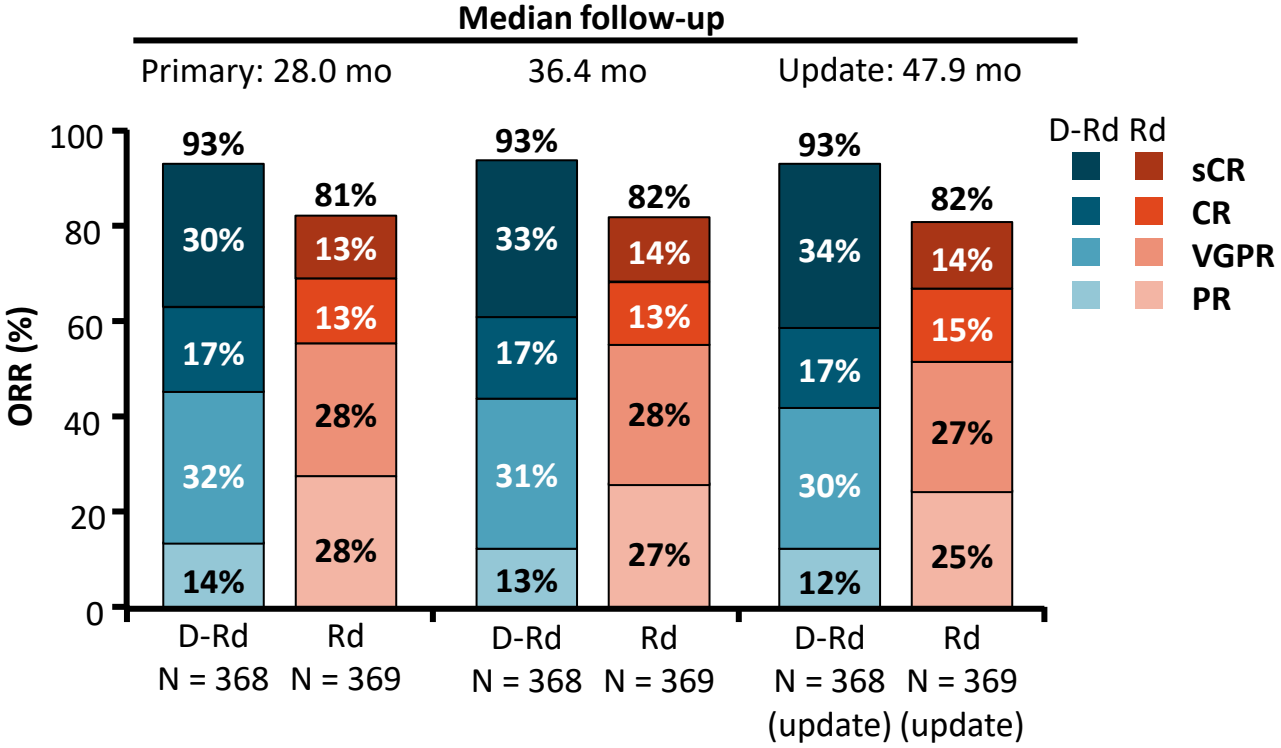
Dosing: daratumumab, 16 mg/kg IV (QW cycles 1-2, Q2W cycles 3-6, Q4W cycle 7+); lenalidomide, 25 mg QD PO on days 1-21; dexamethasone 40 mg QW PO or IV

- Primary endpoint: PFS
- Secondary endpoints: TTP, CR/sCR, MRD by NGS (10^{-5}), PFS2, OS, ORR, safety

Kumar SK, et al. ASH 2020. Abstract 2276. Reproduced with permission.

MAIA: ORR

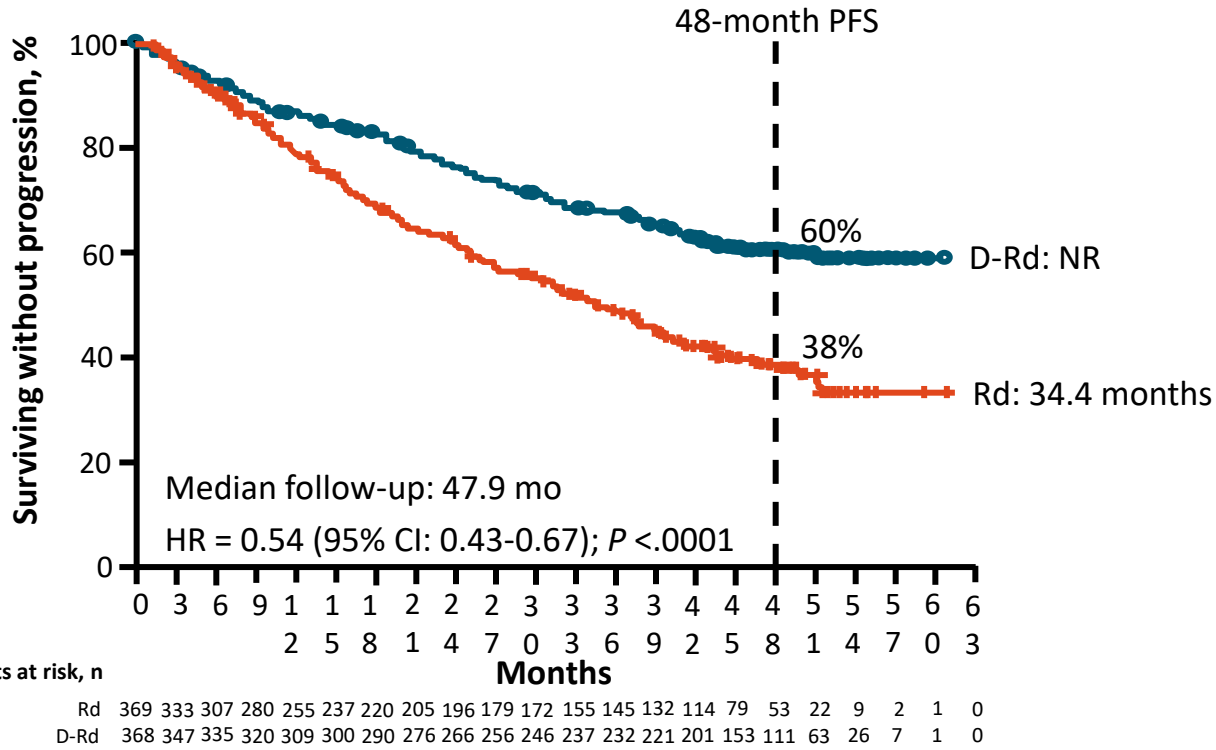
ITT population



- Rates of ≥CR and ≥VGPR higher, responses deeper with D-Rd vs Rd
- Median DOR: NR with D-Rd vs 44.3 mo with Rd

Kumar SK, et al. ASH 2020. Abstract 2276. Reproduced with permission.

MAIA: PFS



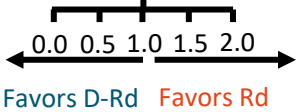
PFS Event	D-Rd	Rd
Median PFS, mo	NR	34.4
PFS rate, %		
• 12 mo	86.2	78.4
• 24 mo	76.0	61.6
• 36 mo	67.4	48.4

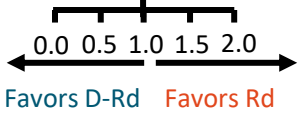
- Risk of progression or death reduced 46% with D-Rd vs Rd
- PFS benefit evident across all subgroups, except among small set with reduced hepatic function
  - Median PFS in high-risk subgroup: 45.3 mo with D-Rd vs 29.6 mo with Rd

Kumar SK, et al. ASH 2020. Abstract 2276. Reproduced with permission.

MAIA: Subgroup Analysis of PFS

	Rd		D-Rd		HR (95% CI)
	n/N	Median	n/N	Median	
Sex					
Male	103/195	32.3	78/189	NE	0.60 (0.45-0.81)
Female	96/174	354	63/179	NE	0.47 (0.34-0.65)
Age					
<75 yr	105/208	37.5	71/208	NE	0.50 (0.37-0.68)
≥75 yr	94/161	31.4	70/160	NE	0.58 (0.43-0.79)
Race					
White	179/339	34.5	127/336	NE	0.54 (0.43-0.67)
Other	20/30	30.4	14/32	NE	0.55 (0.28-1.09)
Region					
North America	57/102	30.4	42/101	NE	0.53 (0.36-0.80)
Other	142/267	36.9	99/267	NE	0.54 (0.41-0.69)
Baseline renal function (CrCl)					
>60 mL/min	117/227	37.4	75/206	NE	0.53 (0.40-0.71)
≤60 mL/min	82/142	29.7	66/162	NE	0.53 (0.38-0.73)
Baseline hepatic function					
Normal	186/340	33.8	125/335	NE	0.50 (0.40-0.63)
Impaired	13/29	35.1	16/31	29.2	1.06 (0.51-2.21)
ISS staging					
I	39/103	51.2	28/98	NE	0.60 (0.37-0.97)
II	92/156	29.7	61/163	NE	0.46 (0.34-0.64)
III	68/110	24.2	52/107	42.4	0.59 (0.41-0.85)
Type of MM					
IgG	117/231	38.7	91/225	NE	0.67 (0.51-0.88)
Non-IgG	49/760	23.5	26/74	NE	0.36 (0.22-0.58)
Cytogenic risk at study entry					
High risk	28/44	29.6	23/48	45.3	0.57 (0.33-1.00)
Standard risk	153/279	34.4	99/271	NE	0.48 (0.38-0.62)
ECOG PS score					
0	68/123	39.6	42/127	NE	0.45 (0.31-0.67)
1	92/187	35.1	72/178	NE	0.61 (0.45-0.84)
≥2	39/53	23.5	27/63	NE	0.52 (0.31-0.85)





Kumar SK, et al. ASH 2020. Abstract 2276. Reproduced with permission.

Clinical Take-Homes: Induction Therapy

Transplant-Ineligible Patients

- VRD-lite and Rd remain standards
- Daratumumab + Rd is a new entrant
- Other daratumumab-based combinations (eg, VMP-Dara) are FDA approved and incorporated into treatment guidelines on the basis of phase III evidence
- **Future:** Rd-daratumumab (subQ)
- **Long-term future:** Introduction of venetoclax and T-cell engagers?

When using Rd as induction in an elderly patient, which of the following statements is true?

A. Full-dose lenalidomide 25 mg continuous provides the best outcomes

B. Dexamethasone 20 mg weekly until progression provides optimal results

C. Fixed-duration therapy is recommended to avoid second primary malignancies

D. Lenalidomide 10 mg is recommended after fixed-duration lenalidomide and dexamethasone

E. Lenalidomide should not be used if creatinine clearance is less than 45

Global Multiple Myeloma Academy

Discussion

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Session Close – Audience Response Questions

Rafael Fonseca

APTITUDE HEALTH®

Question 1

Which statements are true for the treatment of myeloma?

a) There is a high rate of attrition (loss)

b) Several drug trials show that 2 drugs can be as good as 3 in terms of efficacy

c) Myeloma is a heterogeneous disease with increased rates of *p53* abnormalities with progression

d) All of the above

e) A and C

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Question 2

Which of the following is not true in the treatment of newly diagnosed MM?

a) Deep responses are associated with better outcomes
b) VGPR is an accepted benchmark as evidence of a good response
c) Clinical trials are considering risk stratification
d) Regimens that contain daratumumab have further increased response rates
e) Maintenance prolongs overall survival for MM patients

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