Global Multiple Myeloma Academy

Global Multiple Myeloma Academy – Day 1

Emerging and Practical Concepts in Multiple Myeloma

June 18–19, 2021

AMGEN Pfizer Bristol Myers Squibb™

APTITUDE HEALTH®

Global Multiple Myeloma Academy

Welcome and Meeting Overview

Rafael Fonseca, MD

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Faculty

Chair

Rafael Fonseca, MD
Mayo Clinic Cancer Center, USA

Irene Ghobrial, MD
Dana-Farber Cancer Institute, USA

Vania Hungria, MD, PhD
São Germano Clinic, Brazil

Keith Stewart, MBChB, MBA
Princess Margaret Cancer Centre, Canada

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

Natalia Schütz, MD, MS
Instituto Universitario del Hospital Italiano de Buenos Aires, Argentina

Humberto Martínez Cordero, MD, MSc
National Cancer Institute, Colombia

Jorge Vela-Ojeda, MD, PhD
CMN La Raza, Mexico

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

Time (UTC –3)	Topic	Speaker
6.00 PM – 6.15 PM 15 min	**Welcome and Meeting Overview** • Introduction to audience response system (ARS)	Rafael Fonseca, MD
6.15 PM – 6.35 PM 20 min	**Smoldering Multiple Myeloma** • Diagnosis, criteria, and when and how to intervene (15 min; 5-min discussion)	Irene Ghobrial, MD
6.35 PM – 6.55 PM 20 min	**Role of Minimal Residual Disease in Multiple Myeloma** • Prognostic value, clinical relevance, and MRD-driven therapeutic guidance (15 min; 5-min discussion)	Rafael Fonseca, MD
6.55 PM – 7.15 PM 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)	Vania Hungria, MD, PhD
7.15 PM – 7.30 PM 15 min	**Break**	
7.30 PM – 7.50 PM 20 min	**Optimal Use of Consolidation and Maintenance Therapy** • Evolving insights in consolidation and maintenance treatment after transplant (15 min; 5-min discussion)	Jorge Vela-Ojeda, MD, PhD
7.50 PM – 8.15 PM 25 min	**Frontline Therapy for Newly Diagnosed Transplant-Ineligible Patients** • Criteria, guidelines, and treatment choices (15 min; 10-min discussion)	Keith Stewart, MBChB, MBA
8.15 PM – 8.30 PM 15 min	**Patient Case Discussion: Newly Diagnosed + Relapsed/Refractory Multiple Myeloma** • 10-min presentation; 5-min discussion	Eloísa Riva, MD
8.30 PM – 8.45 PM 15 min	**Session Close** • ARS questions	Rafael Fonseca, MD

Agenda Day 2

Time (UTC –3)	Topic	Speaker
6.00 PM – 6.10 PM 10 min	**Session Open**	Rafael Fonseca, MD
6.10 PM – 6.30 PM 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, MD, PhD
6.30 PM – 6.55 PM 25 min	**Management of Early Relapse of Multiple Myeloma** • Definition, prognosis, and treatment choices (15 min; 10-min discussion)	Rafael Fonseca, MD
6.55 PM – 7.20 PM 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, MBChB, MBA
7.20 PM – 7.30 PM 10 min	**Break**	
7.30 PM – 8.20 PM 50 min	**New and Future Therapies for Multiple Myeloma** • Promising new developments in relapsed/refractory MM • Latest trial updates and upcoming new strategies; focus on BCMA-directed therapies (35 min; 15-min discussion)	Irene Ghobrial, MD
8.20 PM – 9.15 PM 55 min	**Patient Case Discussion: Relapsed/Refractory Multiple Myeloma** • Cases from the region will be discussed with the faculty – “tumor board approach” • Relapsed/refractory MM, treatment challenges in the region – Natalia Schütz (Arg) – Case 1: Cristian Seehaus and Natalia Schütz (Arg) – Case 2: Ana Luiza Miranda Silva Días and Vania Hungria (Bras) – Case 3: Didier Larios Sanjuan and Humberto Martínez-Cordero (Col) – Case 4: Sofía Sánchez and Jorge Vela-Ojeda (Mex)	All faculty
9.15 PM – 9.30 PM 15 min	**Session Close** • ARS questions	Rafael Fonseca, MD

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Introduction to the Audience Response System

Rafael Fonseca, MD

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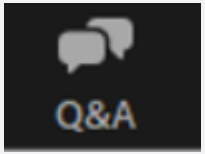
Functionality and Settings: Q&A

After each presentation, there will be 5 minutes for Q&A

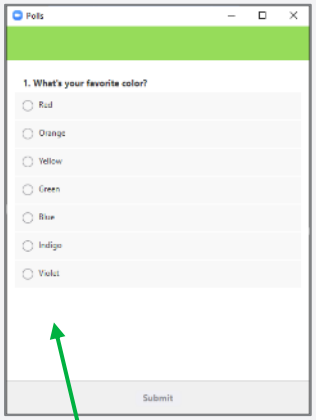
Questions can be asked via the Q&A box

> **Q&A box** – type your question in the box

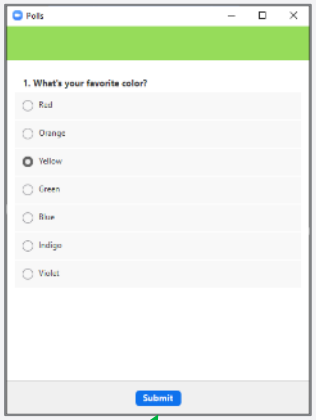


Functionality and Settings: Polling Questions

Desktop View



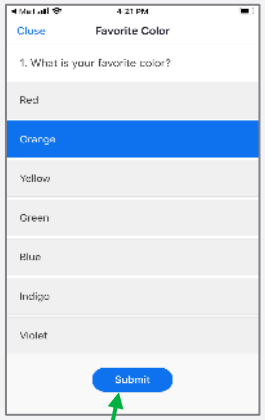
Choose Your Answer
Click on the answer (or answers if multiple choice)



Select Submit
After choosing your answer, select “Submit” to finalize

Mobile View

Choose Your Answer
Click on the answer (or answers if multiple choice)



Select Submit
After choosing your answer, select “Submit” to finalize

Question 1

In what country do you currently practice?

a) Argentina
b) Brazil
c) Canada
d) Colombia
e) Cuba
f) Mexico
g) Peru
h) Uruguay
i) Venezuela
j) Other

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) Two 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

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Smoldering Multiple Myeloma

Irene Ghobrial, MD

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Dana-Farber
Cancer Institute

Smoldering Myeloma

Irene Ghobrial, MD
Professor of Medicine
Lavine Family Chair for Preventative Cancer Therapies
Director of Center for Prevention of Progression (CPOP)
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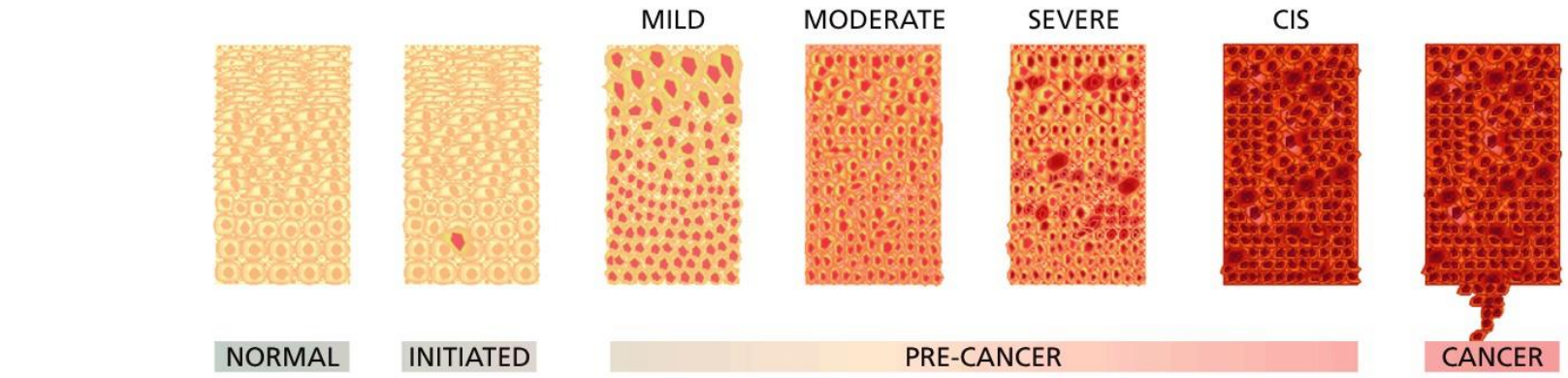
Disclosures

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



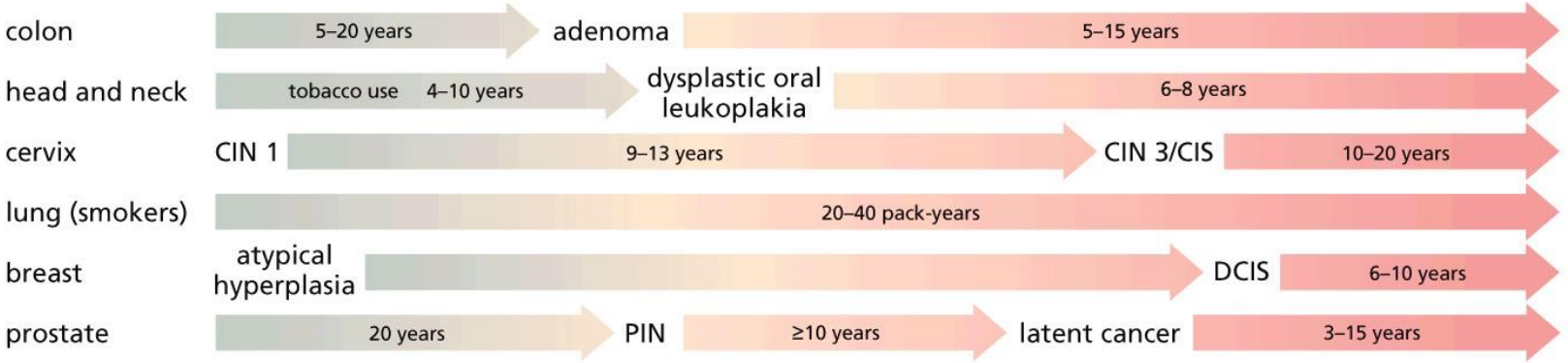
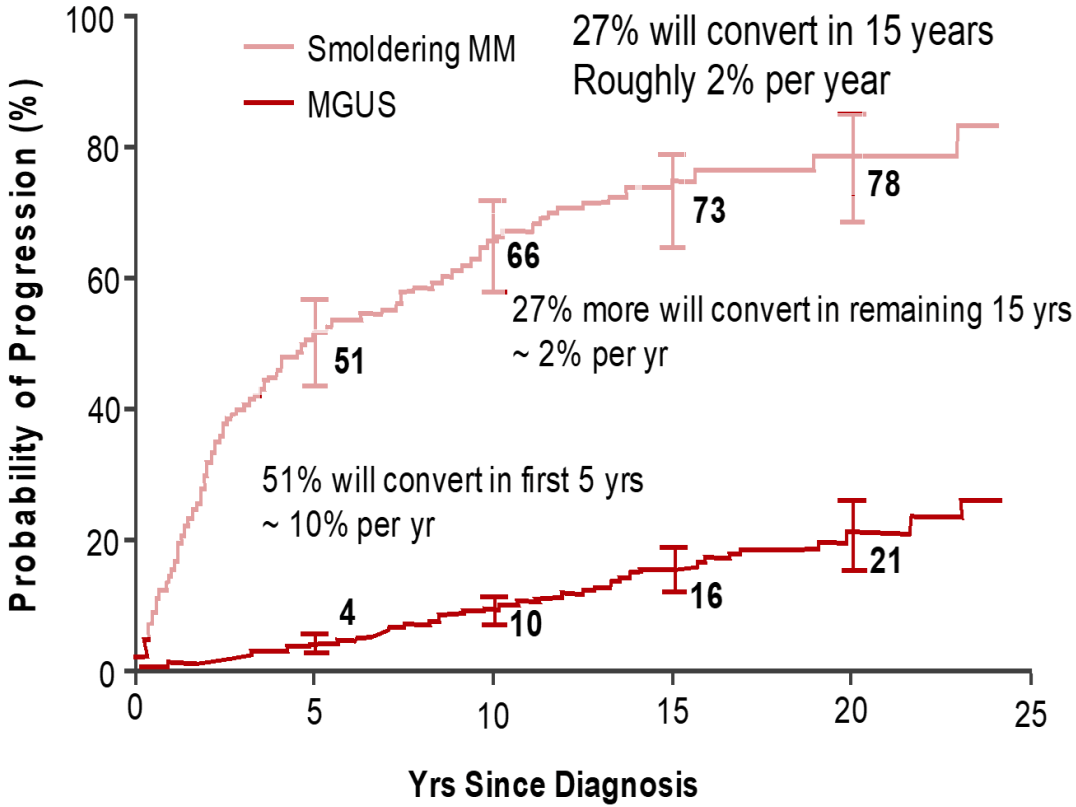


Figure 11.8a The Biology of Cancer (© Garland Science 2014)

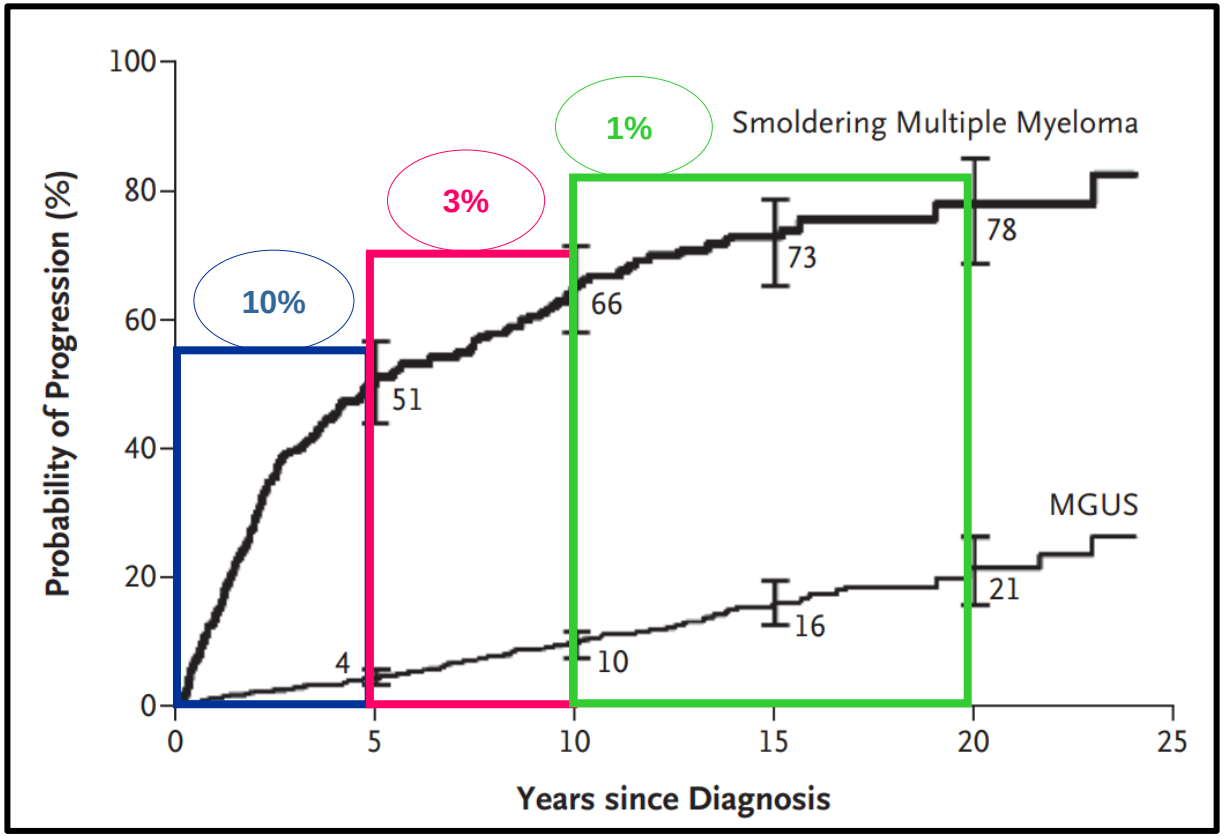
MGUS and Smoldering MM



- 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?

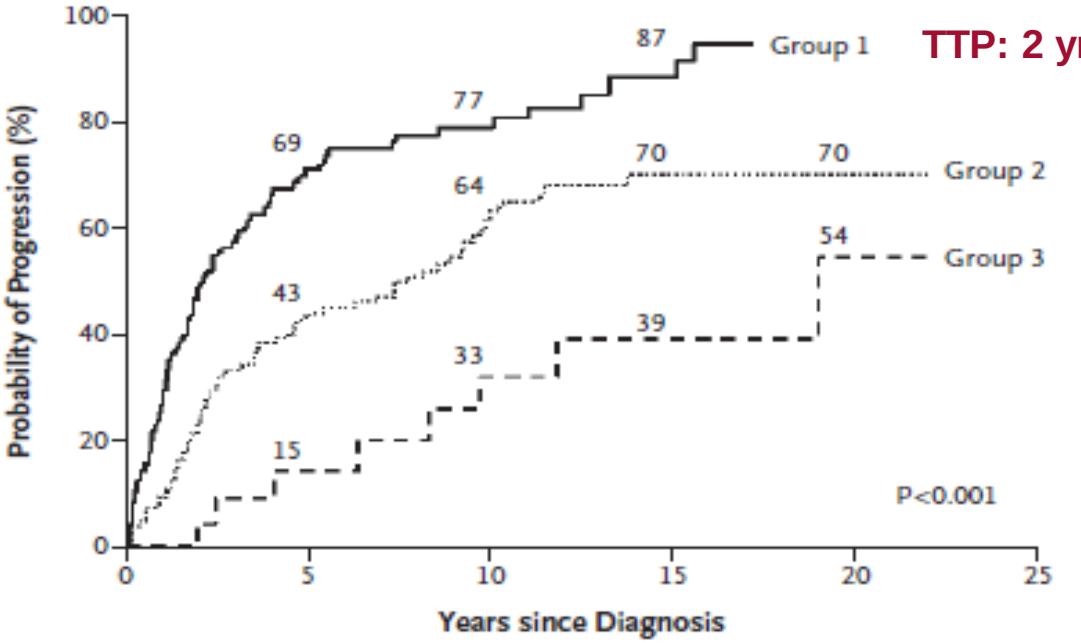
Slides courtesy of Dr San Miguel.

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.

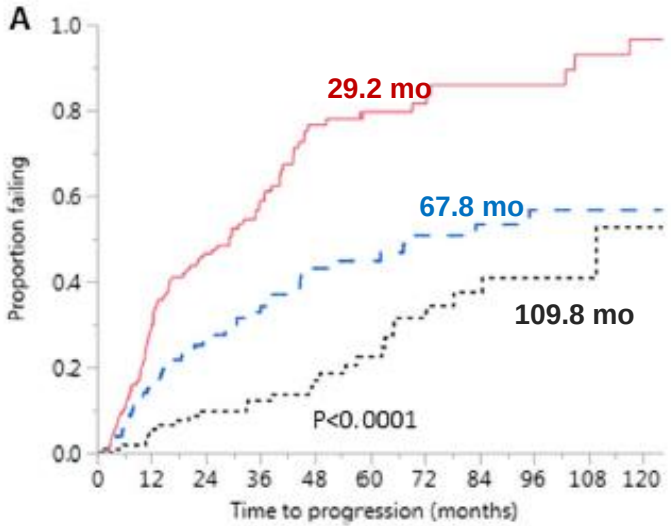
Kyle RA, et al. *N Engl J Med.* 2007;356:2582-2590.

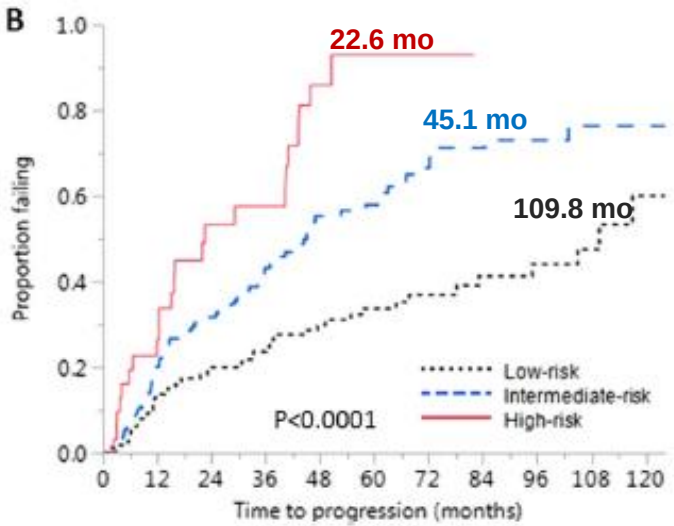
Risk Stratification of SMM: Excluding Those With MM-Defining Events (previous ultra-high-risk)

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.

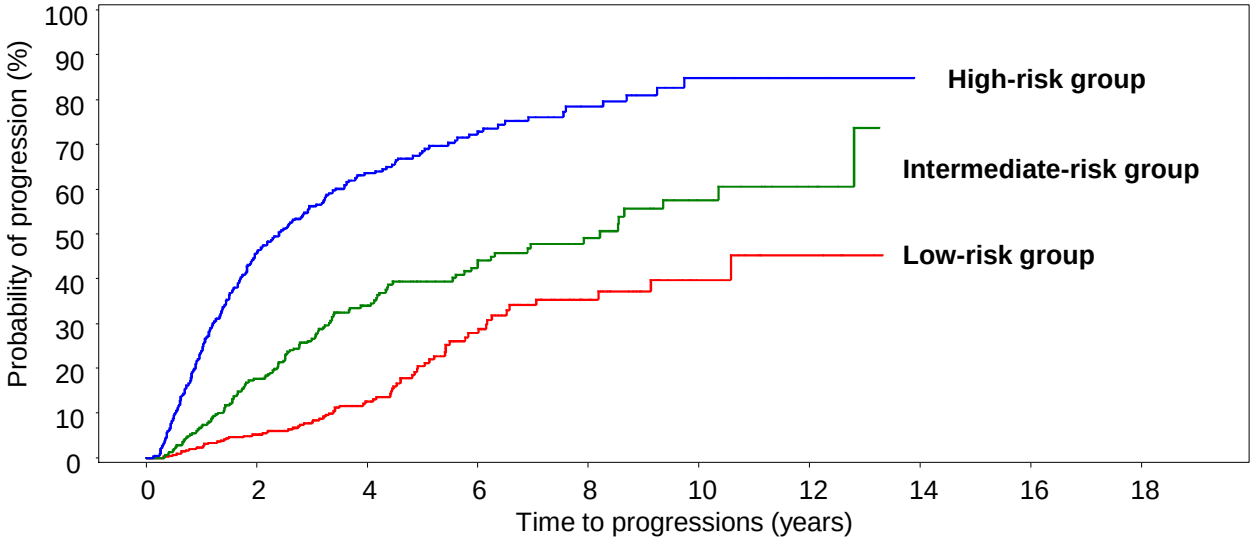
IMWG Risk-Stratification Model for SMM
(N = 2004)

- **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%**

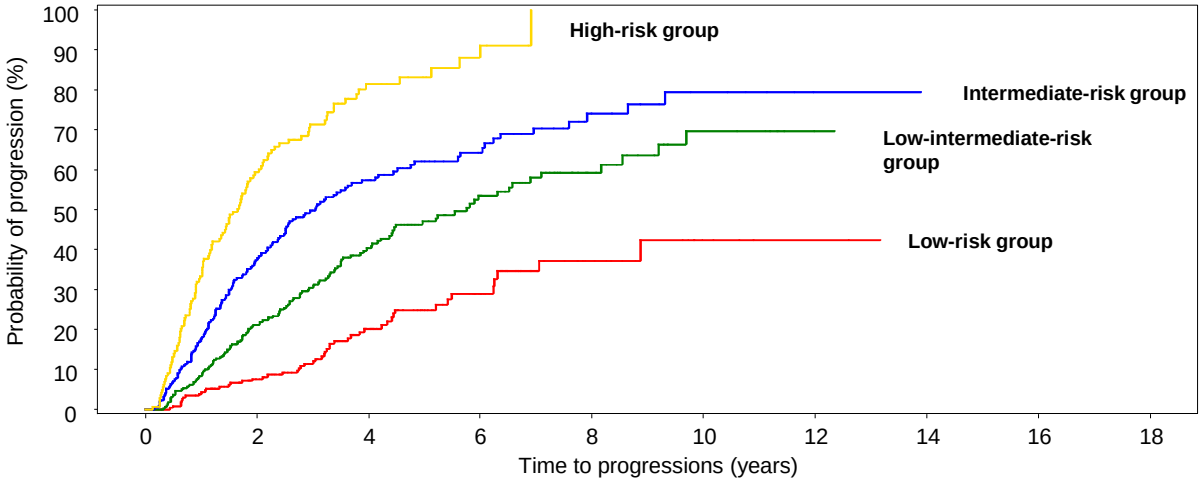
Immunoparesis and BJ proteinuria were significant in univariate

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.

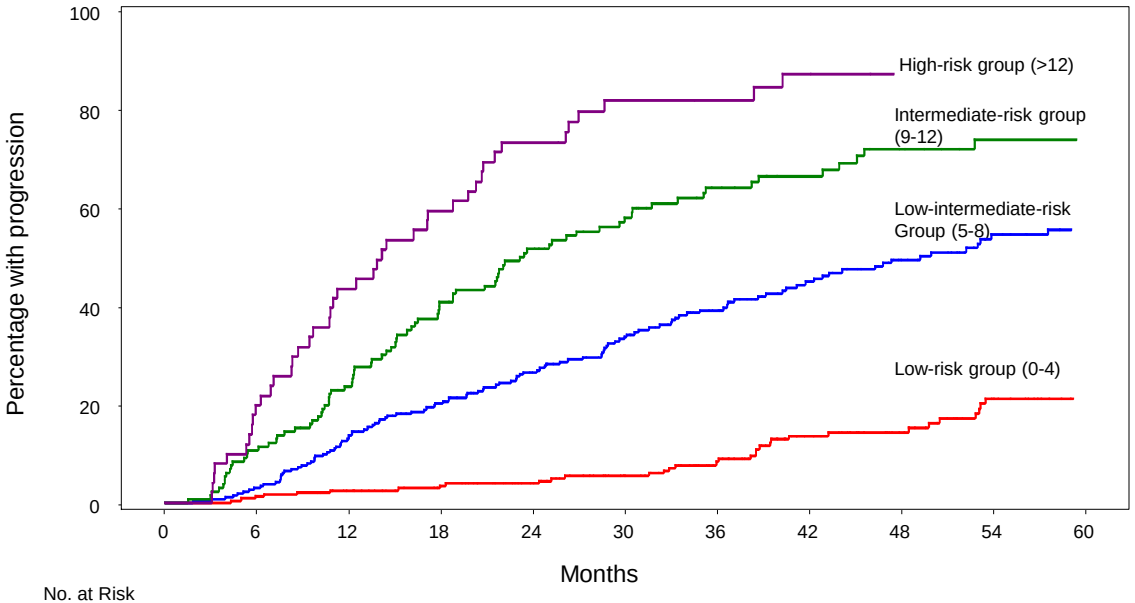
Risk Factor	Coefficient	Odds Ratio (95% CI)	*P* Value	Score
FLC Ratio				
0-10 (reference)	-	-	-	**0**
>10-25	0.69	1.99 (1.15, 3.45)	.014	**2**
>25-40	0.96	2.61 (1.36, 4.99)	.004	**3**
>40	1.56	4.73 (2.88, 7.77)	<.0001	**5**
MC (g/dL)				
0-1.5 (reference)	-	-	-	**0**
>1.5-3	0.95	2.59 (1.56, 4.31)	.0002	**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)**

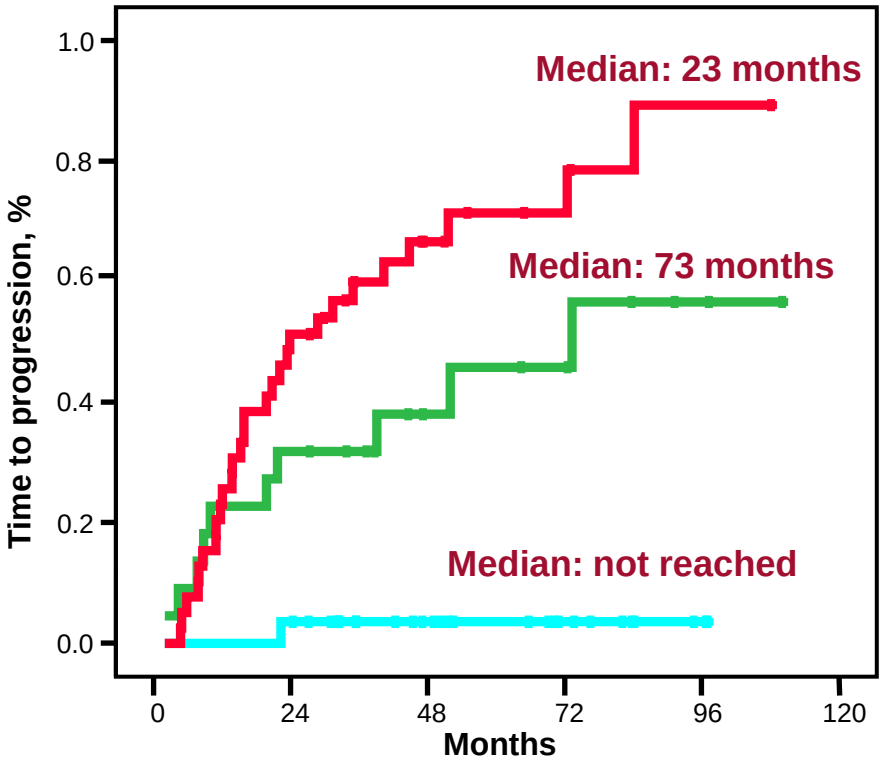
Total Risk Score	2-Year Progression n (%)
0–4	9/241 **(3.7)**
5–8	67/264 **(25.4)**
9–12	65/133 **(48.9)**
>12	37/51 **(72.6)**

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

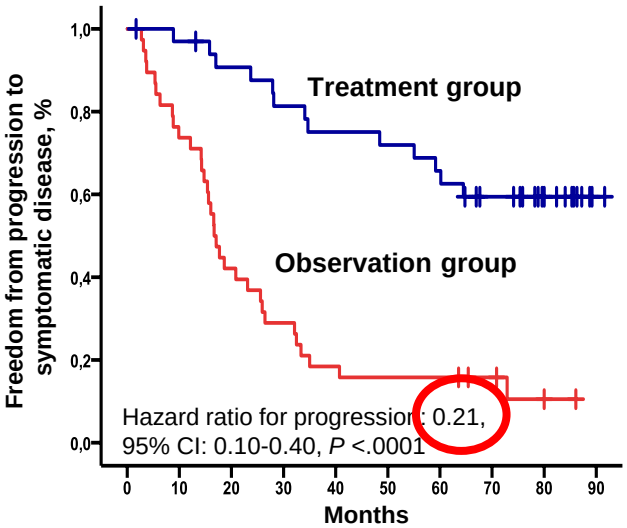
Slides courtesy of Dr San Miguel.

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

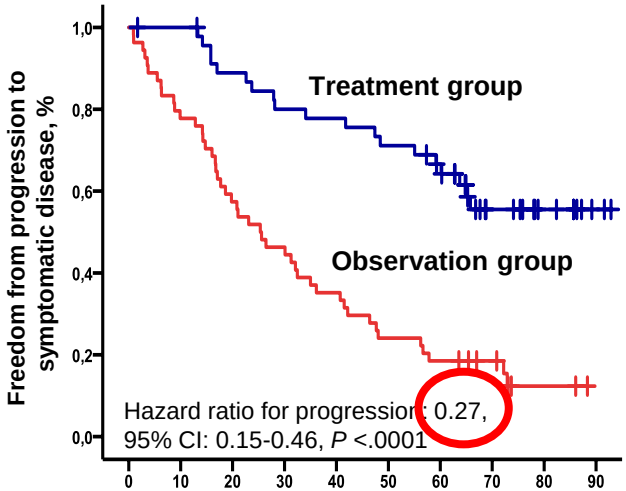
Concordance Between Mayo and Spanish Models

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.

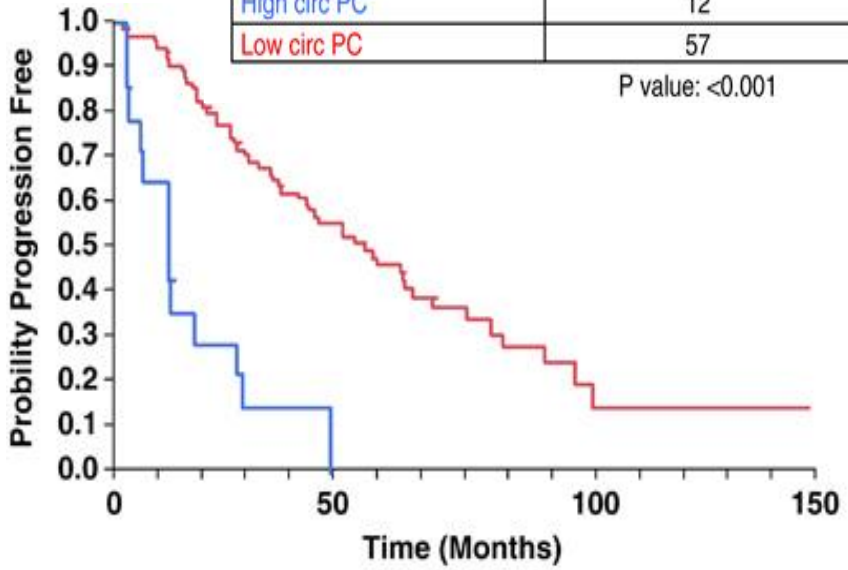
Impact of Circulating Plasma Cells (CPCs) in Smoldering MM

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)

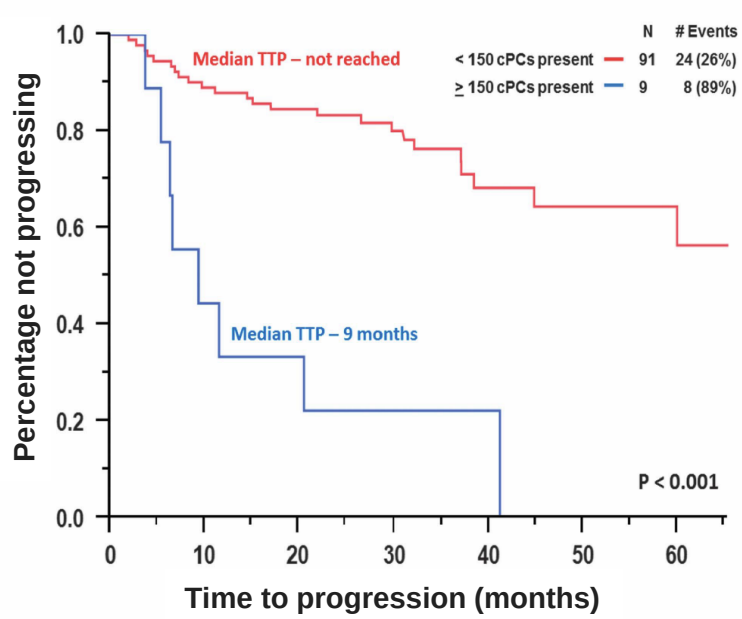
	Median TTP (months)
High circ PC	12
Low circ PC	57

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).

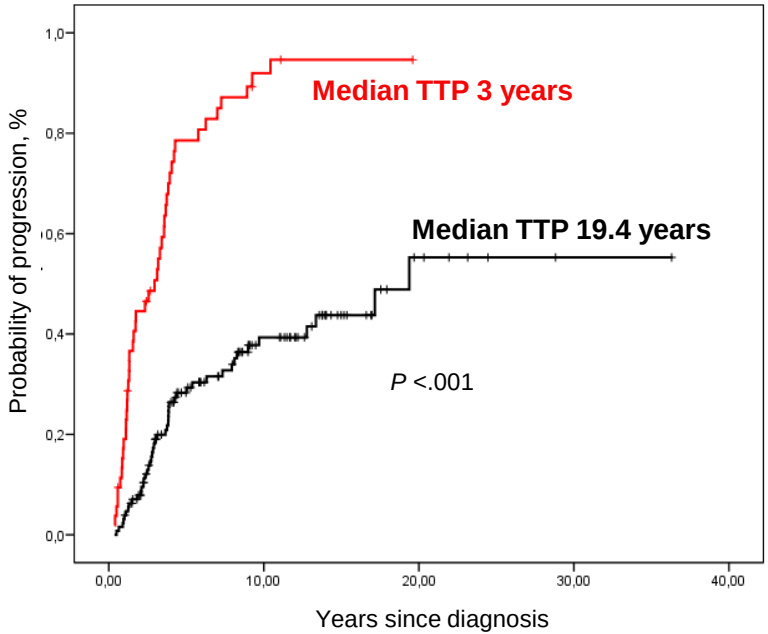
1. Bianchi G, et al. *Leukemia*. 2013;27(3):680-685;
2. Gonsalves WI, et al. *Leukemia*. 2017;31(1):130-135.

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.

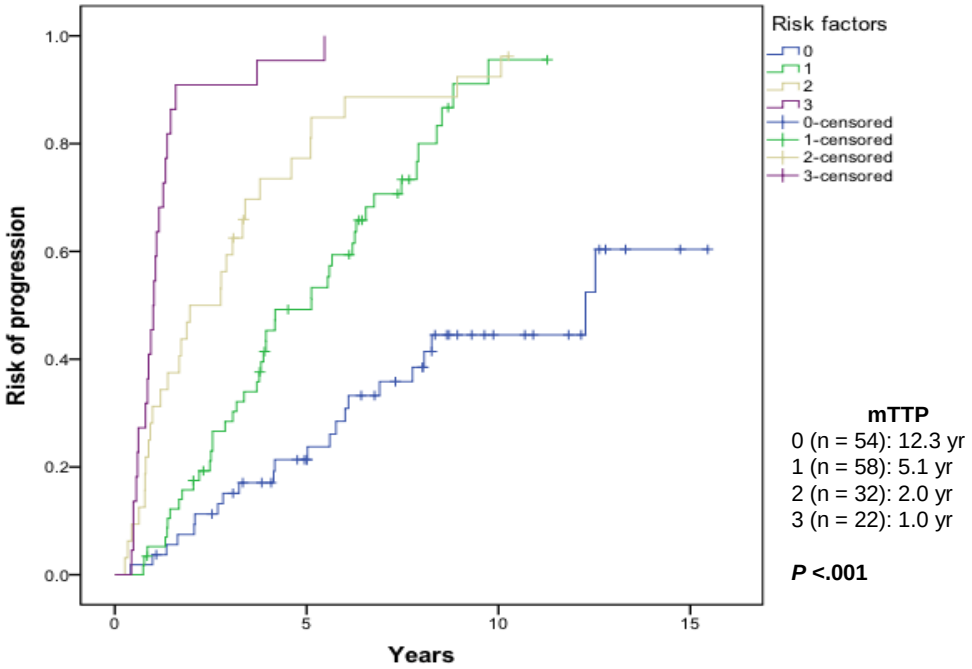
Fernández de Larrea C, et al. *Leukemia*. 2018,32:1427-1434.

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

Kristine Misund[1,2] · Niamh Keane[1,3] · Caleb K. Stein[1] · Yan W. Asmann[4] · Grady Day[1] · Seth Welsh[1] · Scott A. Van Wier[1] · Daniel L. Riggs[1] · Greg Ahmann[1] · Marta Chesi[1] · David S. Viswanatha[5] · Shaji K. Kumar[5] · Angela Dispenzieri[5] · Veronica Gonzalez-Calle[1] · Robert A. Kyle[5] · Michael O'Dwyer[3] · S. Vincent Rajkumar[5] · K. Martin Kortüm[6] · J. Jonathan Keats[7] · MMRF CoMMpass Network[8,9] · Rafael Fonseca[1] · A. Keith Stewart[1] · W. Michael Kuehl[8] · Esteban Braggio[1] · P. Leif Bergsagel[1]

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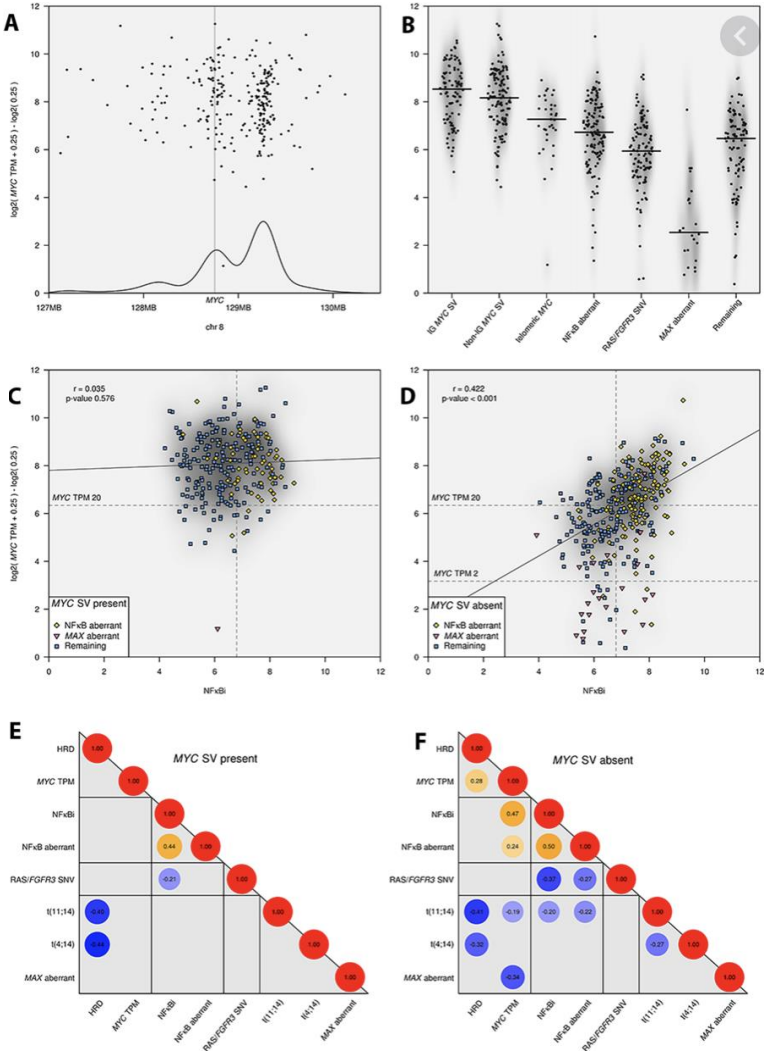
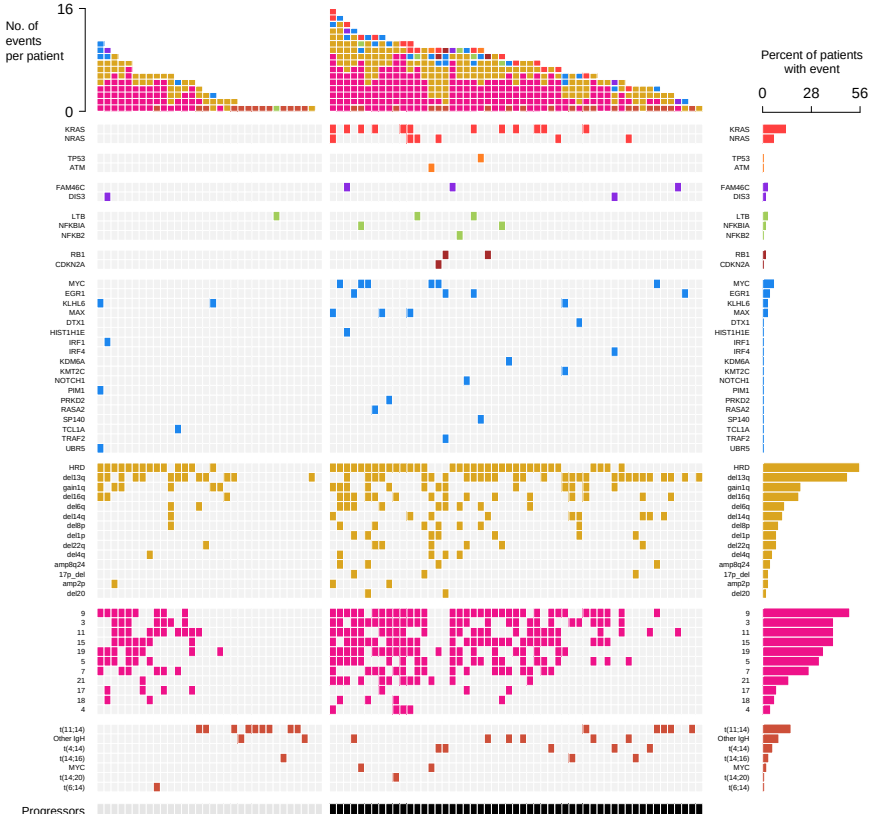


Genomic Landscape of Progressors vs Non-progressors (N = 85)

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

Progressors vs
Non-progressors

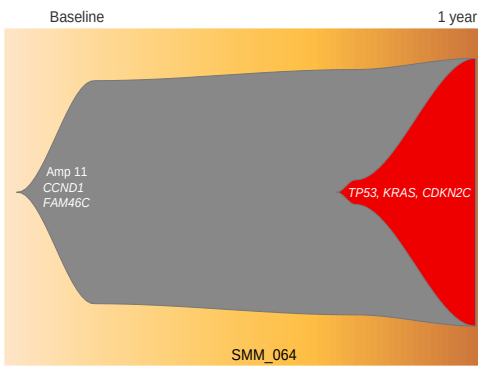


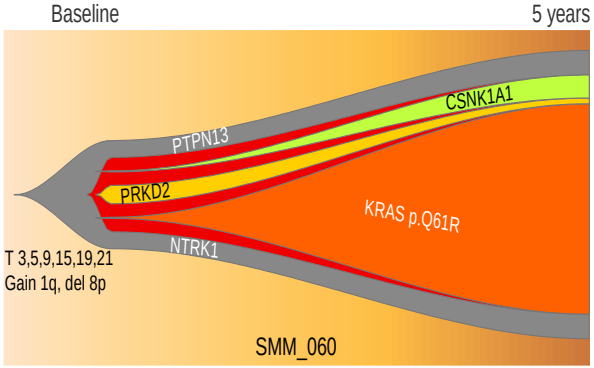
Bustoros M, et al. *J Clin Oncol.* 2020;38(21):2380-2389.

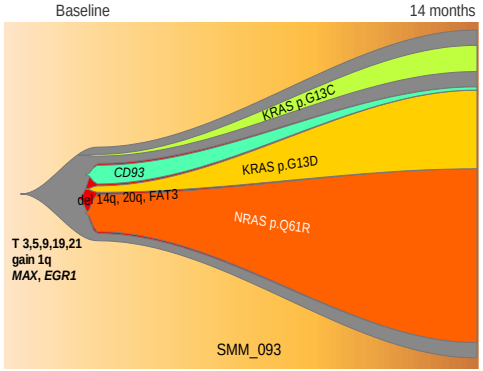
Genomic Characteristics of MGUS/SMM

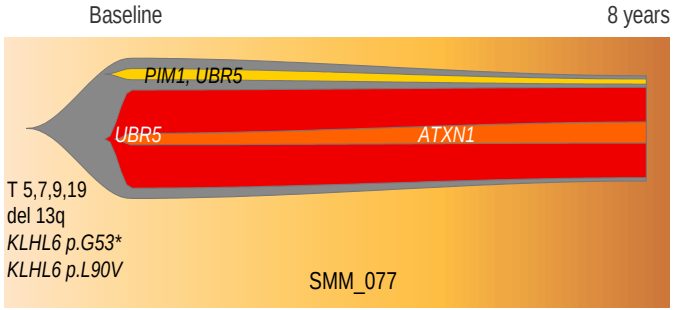
Dissecting genomic characteristics of clonal evolution from MGUS/SMM to MM and germline variants of high-risk individuals at risk of developing MGUS/SMM

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



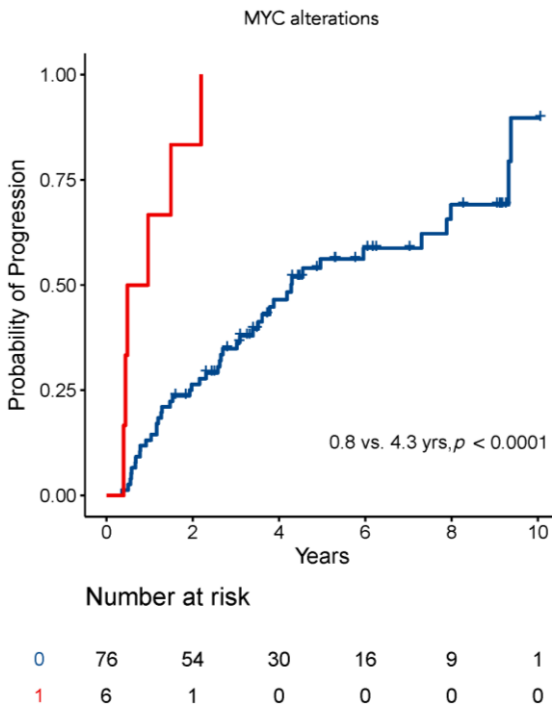


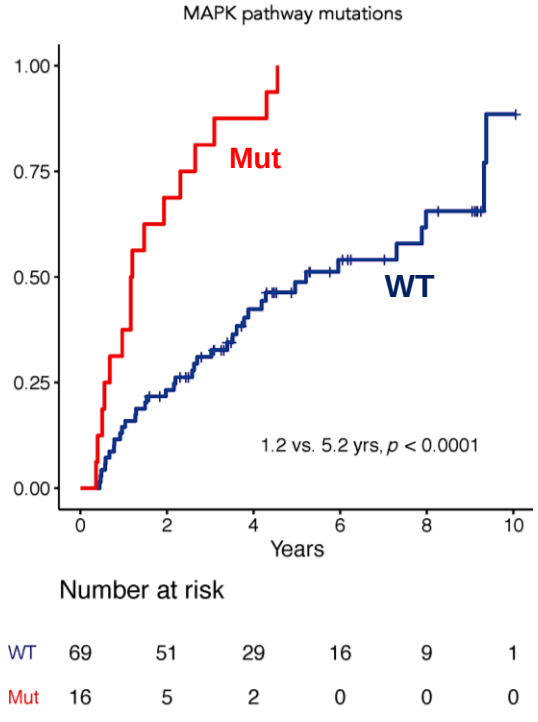


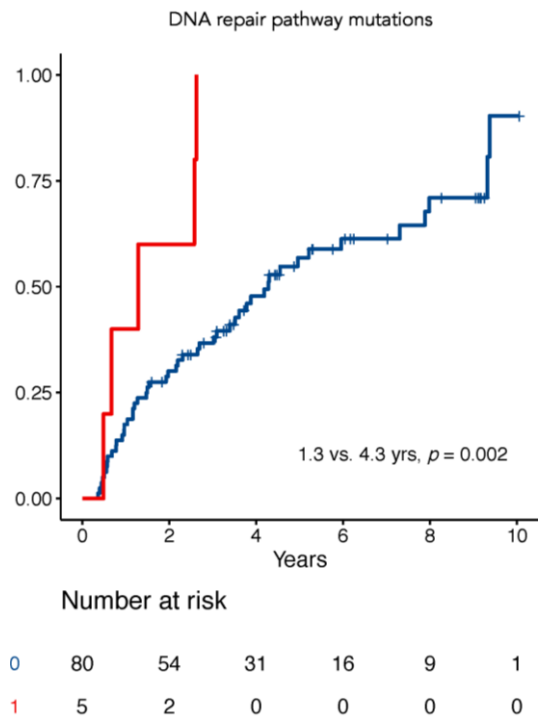


Bustoros M, et al. *J Clin Oncol.* 2020;38(21):2380-2389.

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



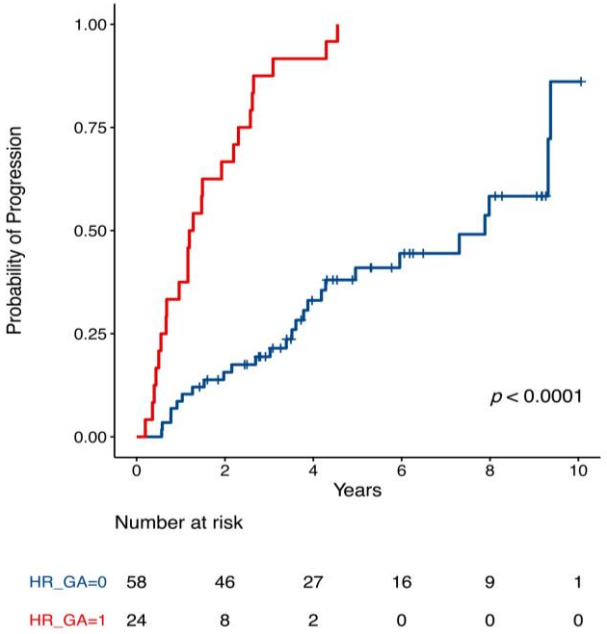




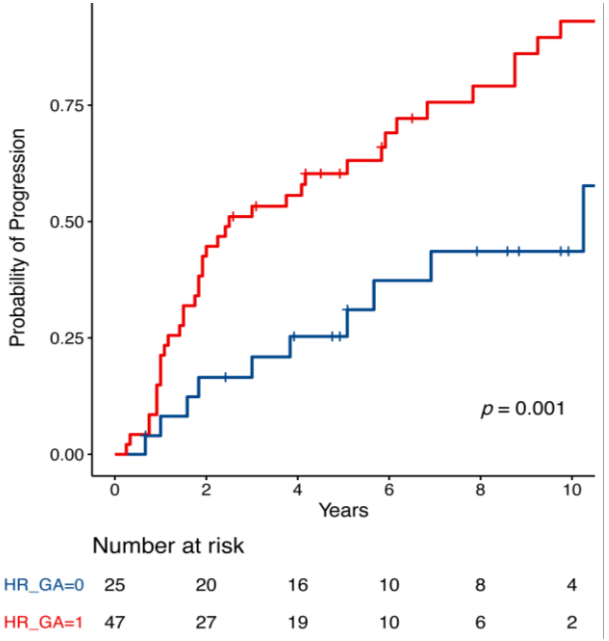
Bustoros M, et al. *J Clin Oncol.* 2020;38(21):2380-2389.

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

Primary multicenter cohort
(DFCI/UK/Greece)

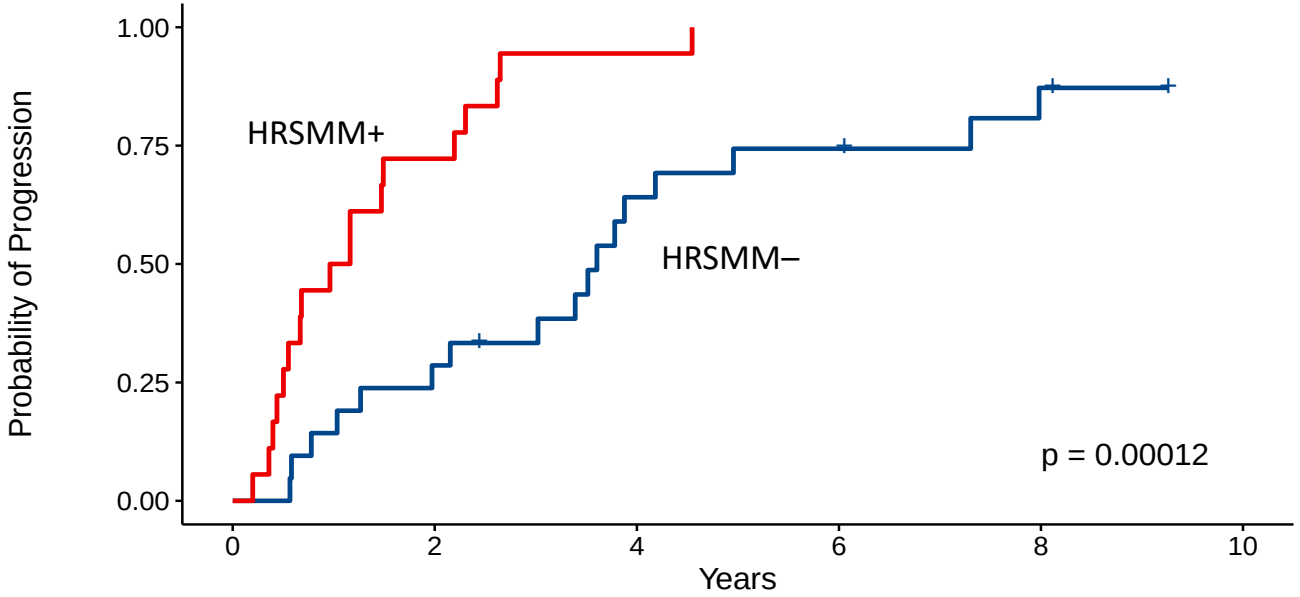


Validation cohort
(Mayo clinic)



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

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

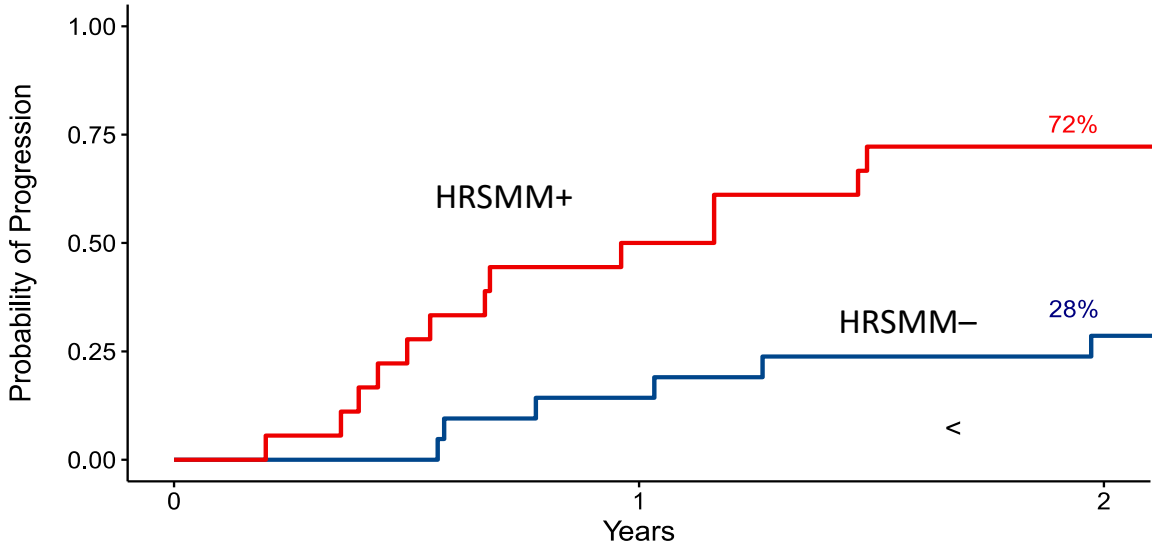


Number at risk

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

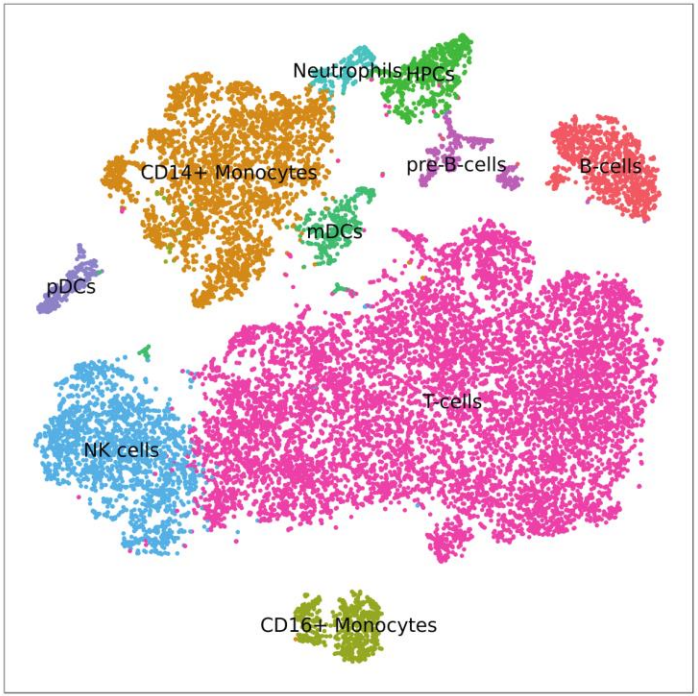
Without HR_GA	21	18	15
With HR_GA	18	9	5

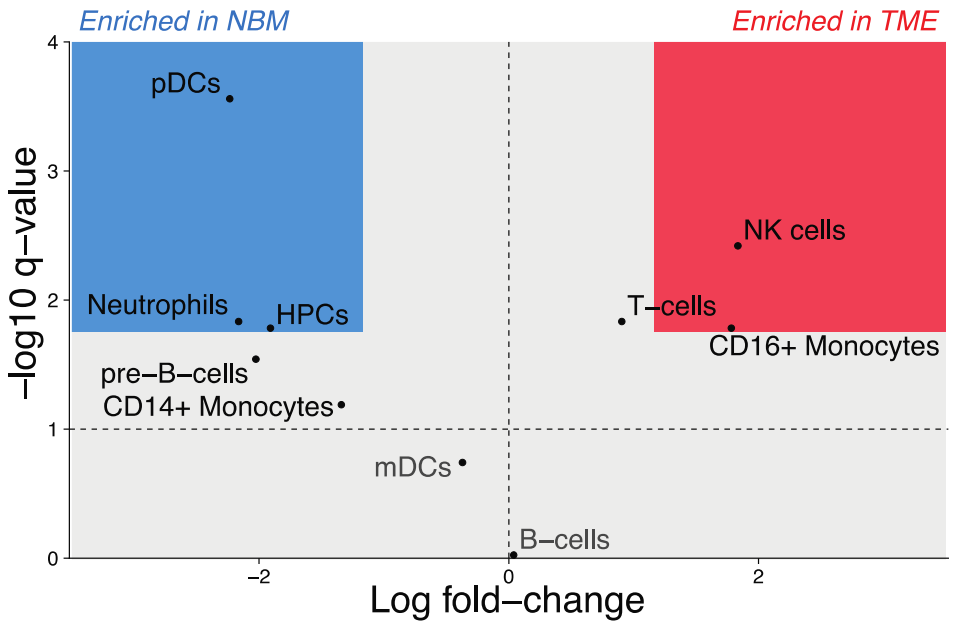
2-year probability of progression of 72% is too high and looks more like MM

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

Single-Cell RNA Sequencing of the Immune Cells

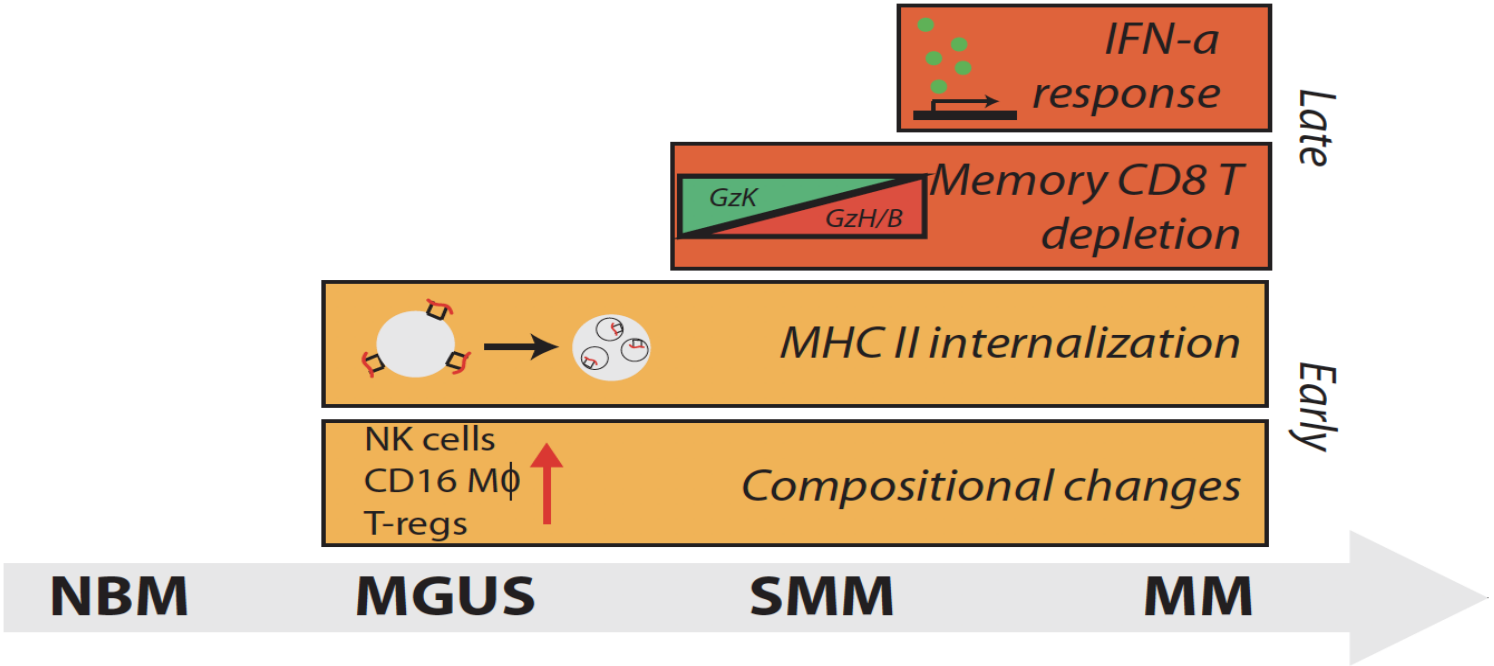
Defining the permissive tumor microenvironment in MGUS/SMM





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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early phases of blood conditions that may develop into cancer.
These early conditions are called precursor conditions

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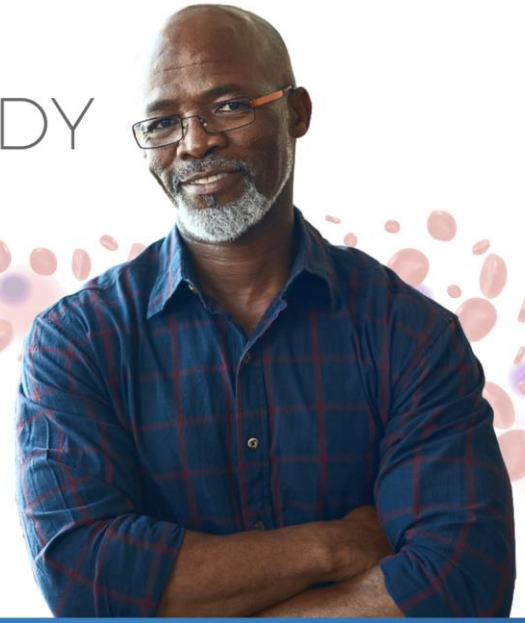
THE PROMISE STUDY

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?

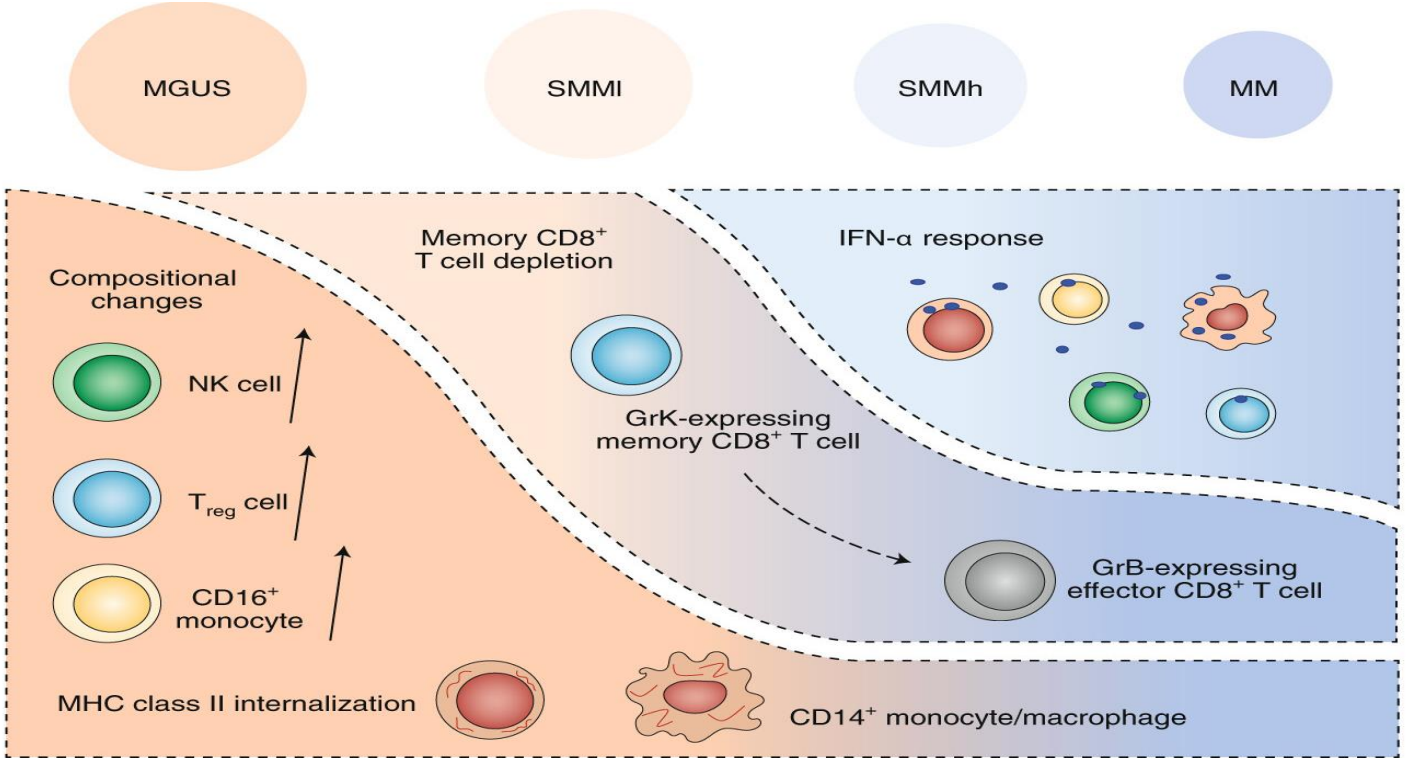
How do I join?

Got a question?
Offline

https://www.enroll.promisestudy.org

Single-Cell RNA Sequencing of the Immune Cells

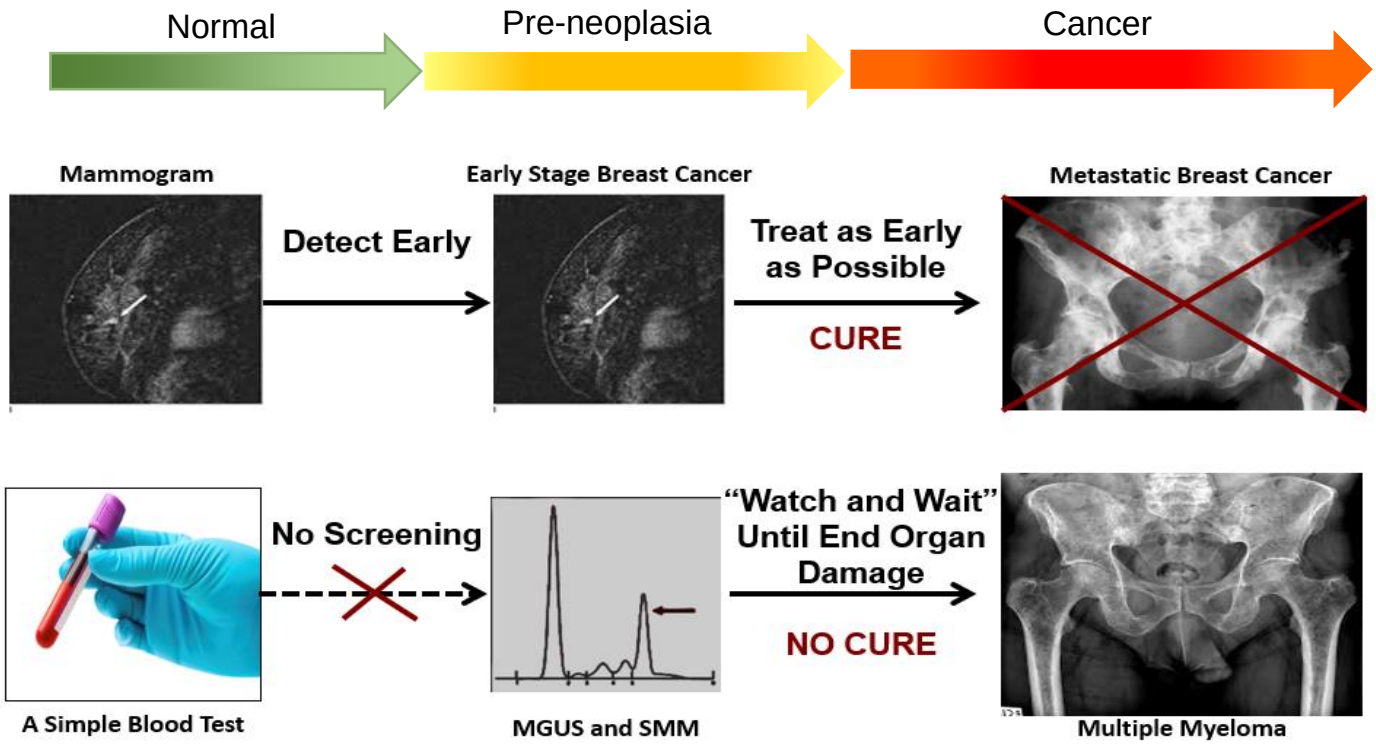
Defining the permissive tumor microenvironment in MGUS/SMM



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

Dana-Farber Cancer Institute

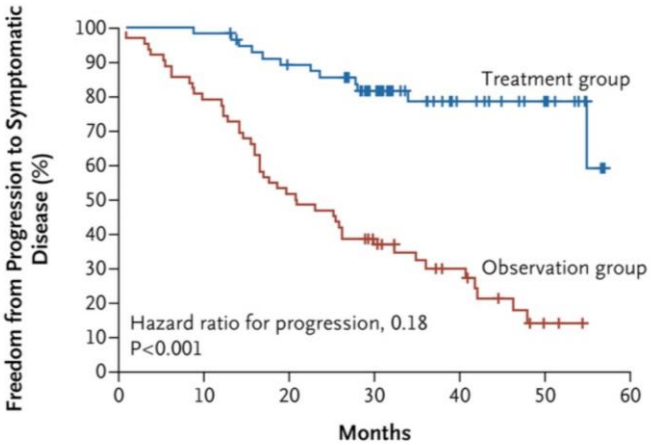
Early Screening for Cancer Detection



Therapeutic Interventions

Lenalidomide plus Dexamethasone for High-Risk Smoldering Multiple Myeloma

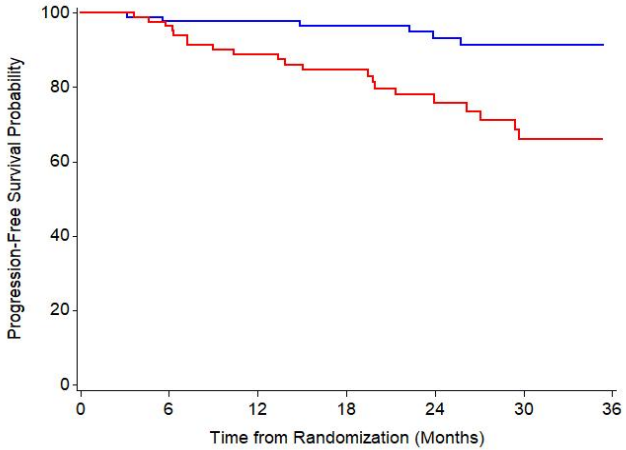
María-Victoria Mateos, M.D., Ph.D., Miguel-Teodoro Hernández, M.D., ilar Giraldo, M.D., Javier de la Rubia, M.D., Felipe de Arriba, M.D., Ph.D., Lucía López Corral, M.D., Ph.D., Laura Rosiñol, M.D., Ph.D., Bruno Paiva, Ph.D., Luis Palomera, M.D., Ph.D., Joan Bargay, M.D., lbert Oriol, M.D., Felipe Prosper, 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.

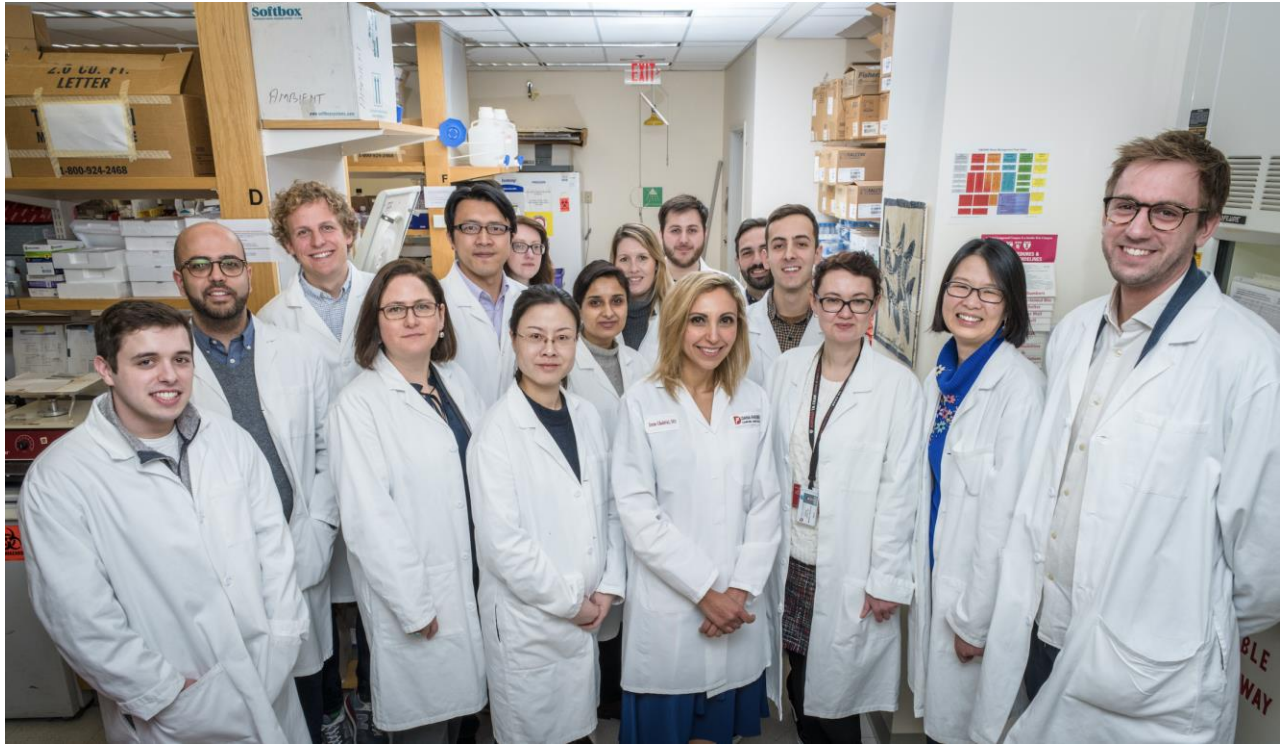
Therapeutic Interventions

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®

Global Multiple Myeloma Academy

Role of Minimal Residual Disease in Multiple Myeloma

Rafael Fonseca, MD

APTITUDE HEALTH®

MAYO CLINIC

Rafael Fonseca, MD
Interim Executive Director, Mayo Clinic Cancer Center

Multiple Myeloma

Scottsdale, Arizona

Rochester, Minnesota

Jacksonville, Florida

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Disclosures: Relaciones con la Industria

- **Consulting:** Amgen, BMS, Celgene, Takeda, Bayer, Janssen, AbbVie, Pharmacyclics, Merck, Sanofi, Kite
- **SAB:** Adaptive Biotechnologies, Caris Life Sciences (stock options)
- **Patent for FISH in MM: ~$2000/year**
- **Registered independent**
- **Believe in stem cell transplant**

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B-Cell DNA Fingerprint

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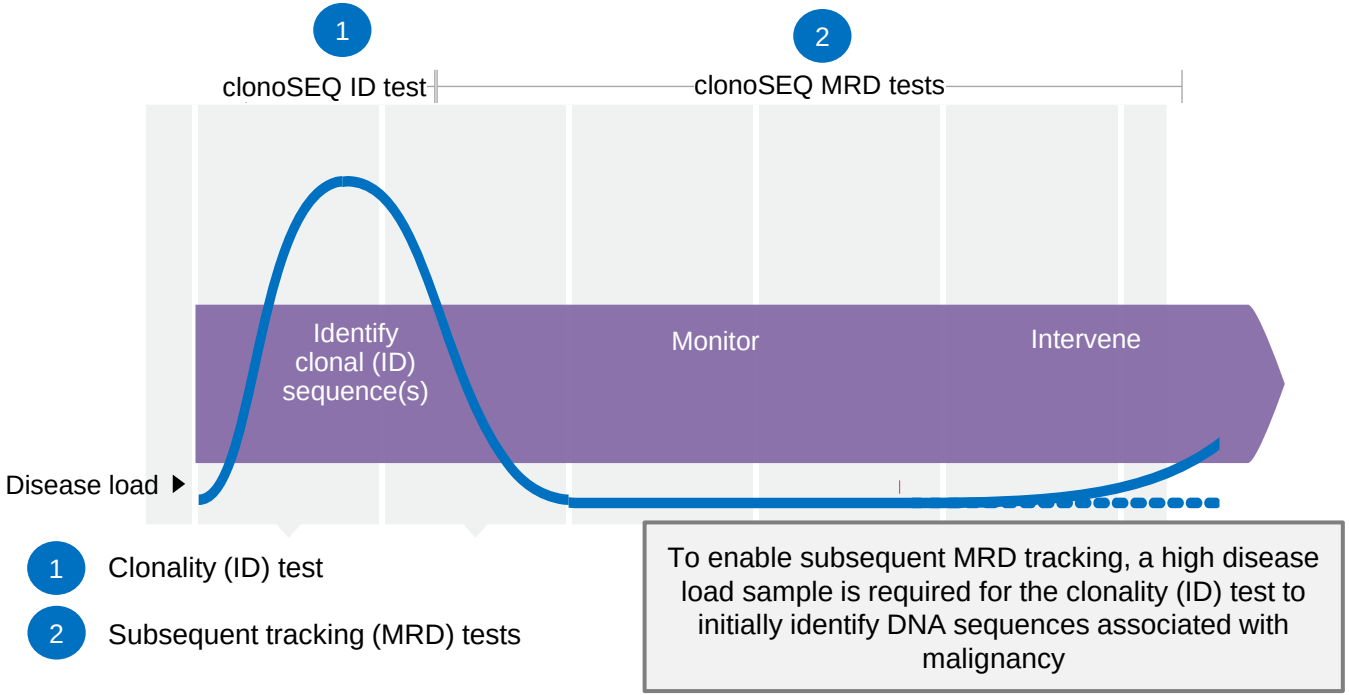
Two-Step Process: ID and Tracking



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Actionable (aka “Do”)

Scenario	Action
Can I use MRD to make clinical decisions?	Yes, and hopefully you will be convinced after this talk!
Can I use it to talk about prognosis?	Resounding yes! Critical for HR MM
If someone is still MRD+ after treatment phase, what can I do?	Consider treatment continuation? Consider a change in treatment?
Can I use MRD+ copy number results as a biomarker?	Yes! If standardized sample collections are followed, you can measure depth of the response
Can I stop treatment if someone is MRD–?	MRD is one more piece of information that informs my clinical conversation and allows decision making. We stop Rx for symptoms, labs, and time!

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What Are the “No” Answers?

Scenario	Action
Is being MRD negative synonymous with a cure?	No, as it is impossible to prove a negative. Being MRD– is the best possible response to Rx.
Is MRD status 100% determinant as we make clinical decisions?	No. It is simply more information. All clinical decisions should be made in the context of all information available for patients and physicians
Do I need to wait for phase 3 trials to see if I can use MRD in my clinical practice?	No, MRD testing is a biomarker like any other that informs clinical practice. Did we need to do phase 3 trials to start using SPEP? Or the free light chain assay?

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Fonseca, Personal.

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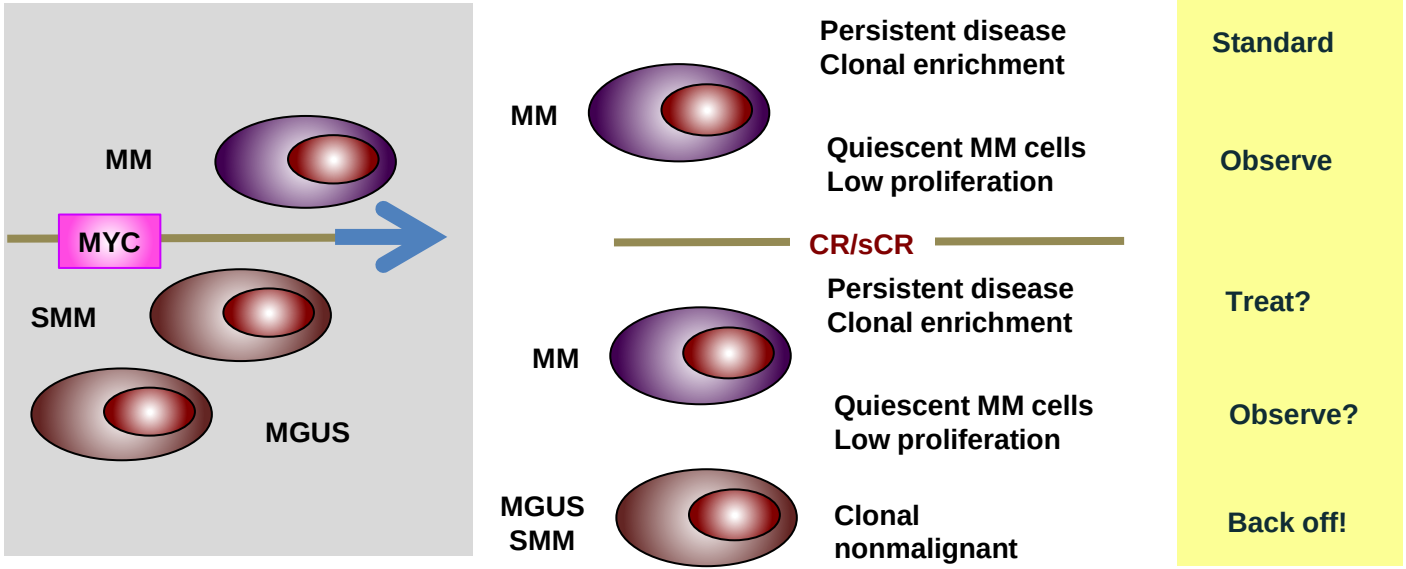
Clinical Scenarios for Using MRD

Myeloma is always preceded by MGUS. Will not address subclone principles



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Rafael Fonseca, unpublished.

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PROGNOSIS

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Meta-analysis: O. Landgren, et al

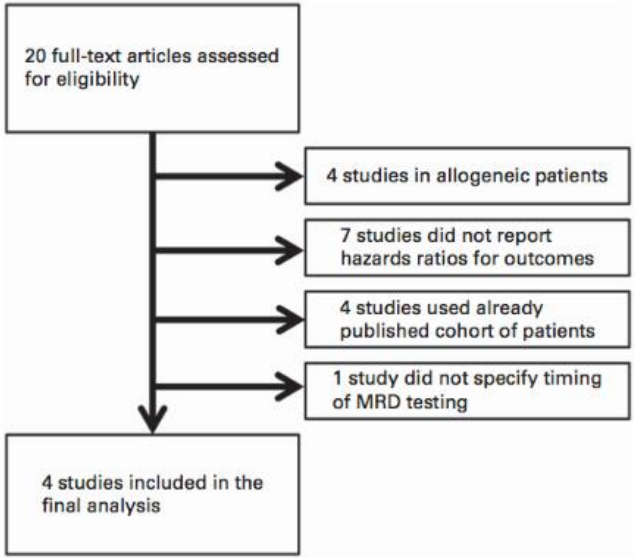
ORIGINAL ARTICLE

Role of MRD status in relation to clinical outcomes in newly diagnosed multiple myeloma patients: a meta-analysis

O Landgren[1], S Devlin[2], M Boulad[1] and S Mailankody[1]

Driven by access to better drugs, on average, newly diagnosed multiple myeloma patients have over 10 years overall survival. Using modern combination therapies—with or without the addition of high-dose melphalan and autologous stem cell transplantation—up to 80% of patients reach a complete response. As a logical and necessary step forward, clinical studies have explored strategies to detect minimal residual disease (MRD) and its correlation with clinical outcomes. In this context, MRD has been proposed as a regulatory end point for drug approval in newly diagnosed multiple myeloma. To better define the role of MRD negativity in relation to clinical outcomes, we undertook a meta-analysis including published clinical trials of newly diagnosed multiple myeloma patients. We applied a random effects model which weighted studies using the inverse–variance method. Studies were combined on the scale of the logarithm of the hazard ratio (HR) and the corresponding s.d. We found that MRD negativity (versus positivity) was associated with better PFS (HR = 0.35; 95% confidence interval (CI) 0.27–0.46; $P < 0.001$) and overall survival (HR = 0.48; 95% CI 0.33–0.70; $P < 0.001$). Our results show that MRD negativity is a strong predictor of clinical outcomes, supportive of MRD becoming a regulatory end point for drug approval in newly diagnosed multiple myeloma.

Bone Marrow Transplantation (2016) **51,** 1565–1568; doi:10.1038/bmt.2016.222; published online 5 September 2016



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Landgren O, et al. *Bone Marrow Transplant*. 2016;51:1565-1568.

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Sensitivity: Regulatory and Mathematical

Mathematical sensitivity	Cell loaded for NGS
$10^{-6.1}$	1,258,925
$10^{-6.2}$	1,584,893
$10^{-6.3}$	1,995,262
$10^{-6.4}$	2,511,886
$10^{-6.5}$	3,162.277
$10^{-6.6}$	3,981,071
$10^{-6.7}$	5,011,872
$10^{-6.8}$	6,309,573
$10^{-6.9}$	7,943,282
$10^{-7.0}$	10,000,000

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Fonseca, Personal.

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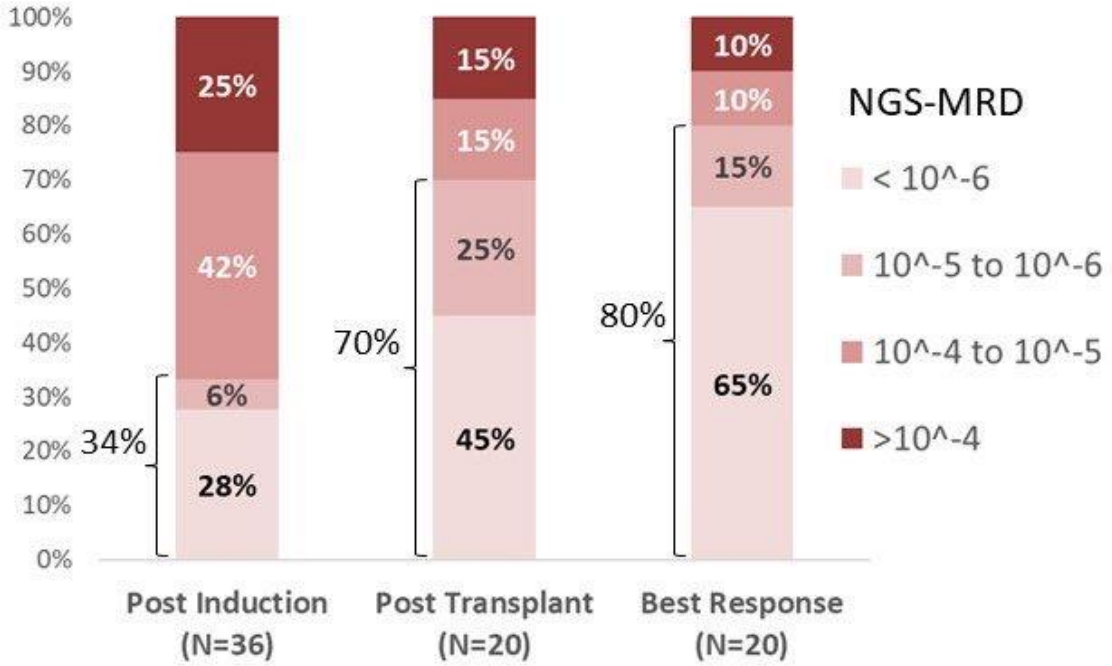
Best in Class: MASTER Trial Dara-KRD



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Costa LJ, et al. ASH 2019. Abstract 143.

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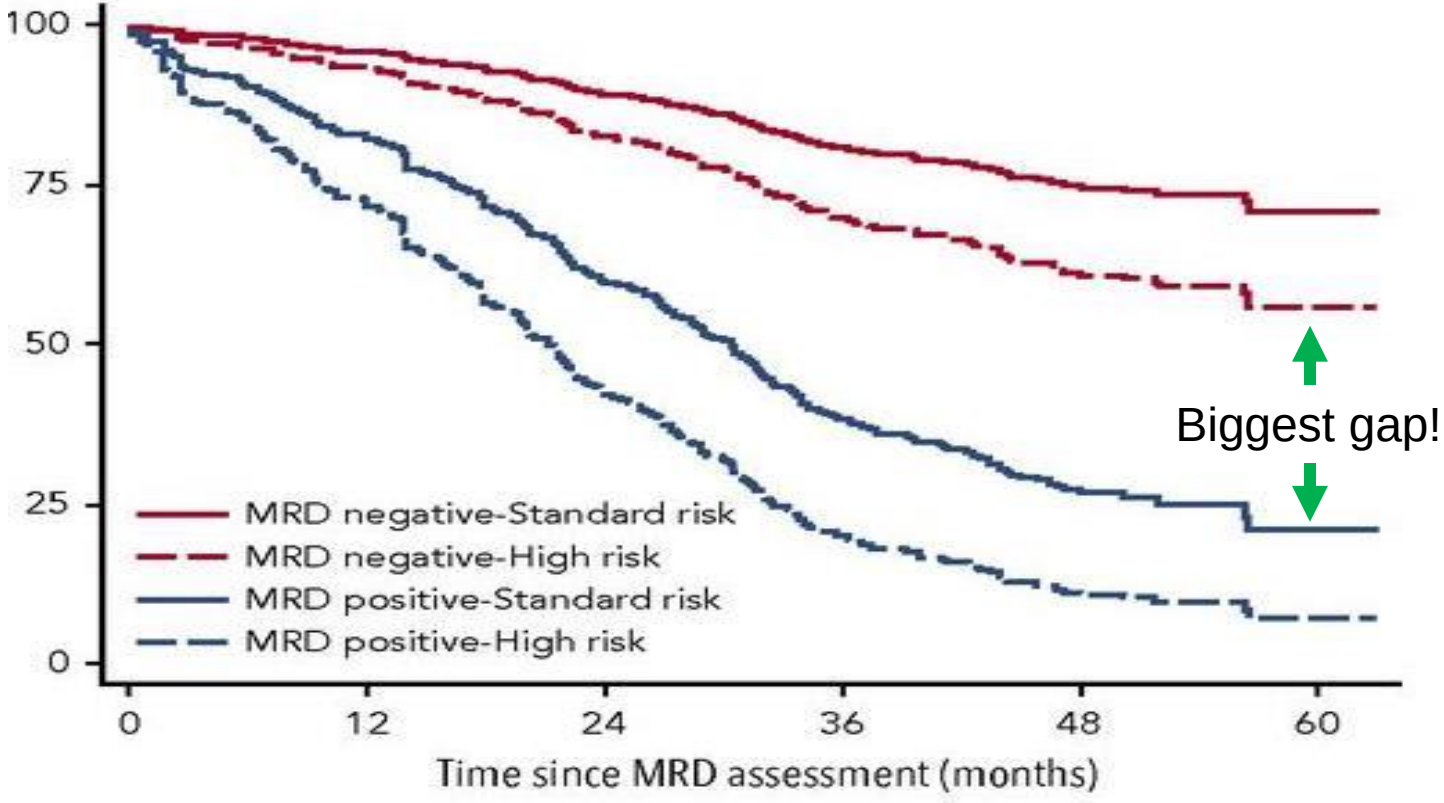
Attaining MRD– Overcomes High-Risk MM



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

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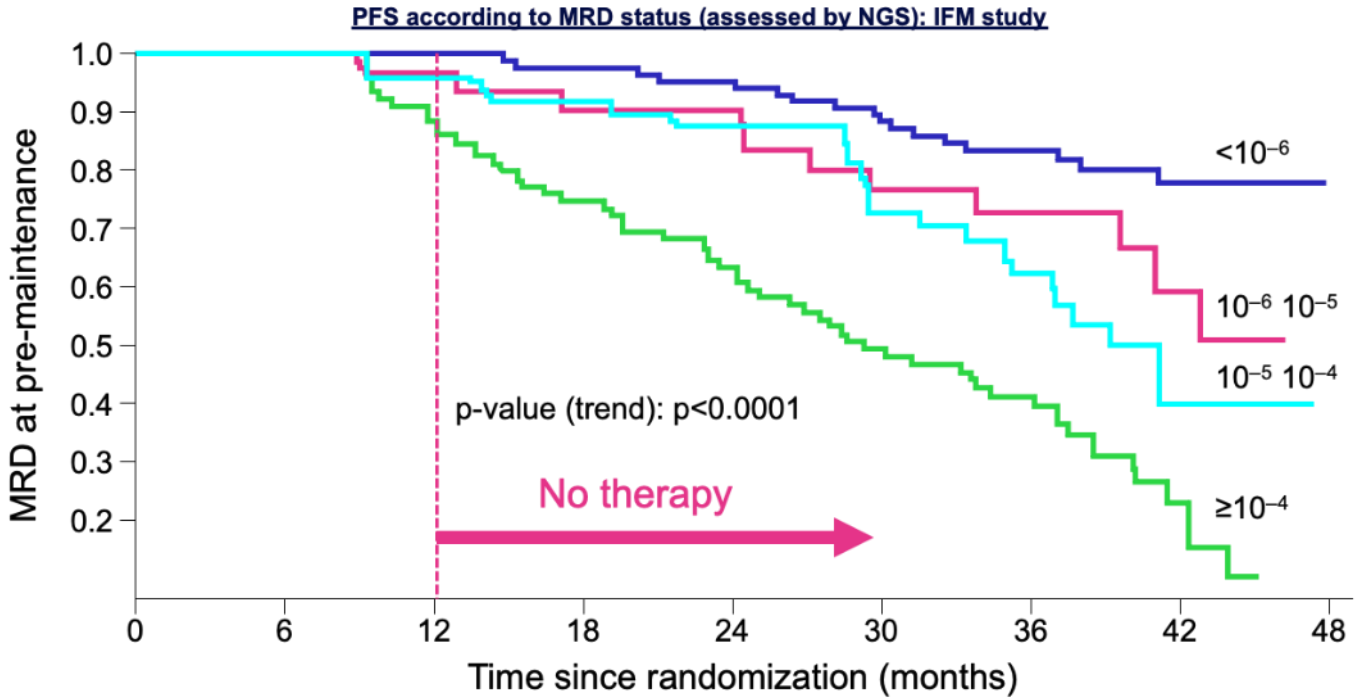
Attaining MRD– Overcomes High-Risk MM



~80 % of patients have not progressed in ~3 years despite no therapy

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

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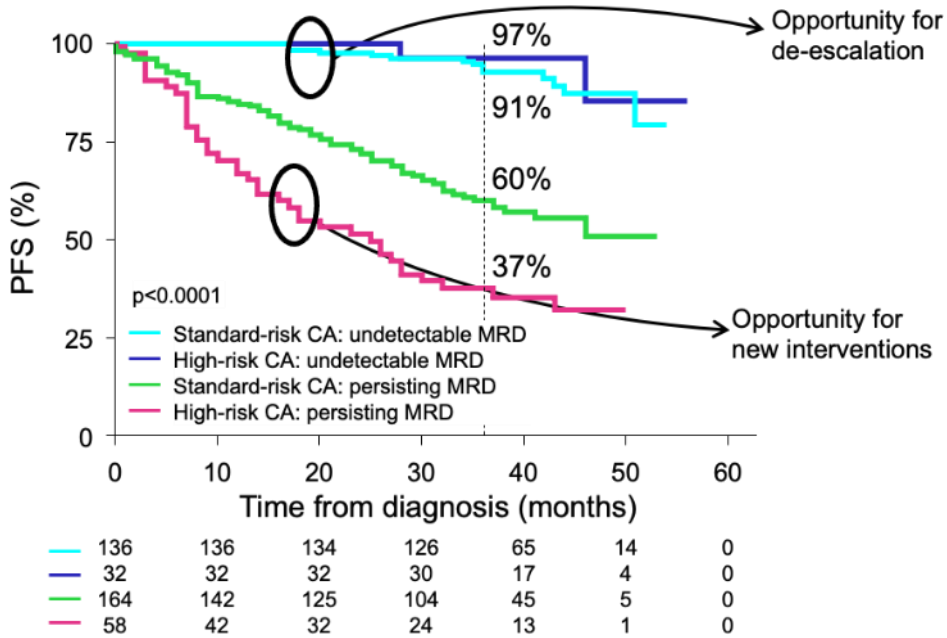
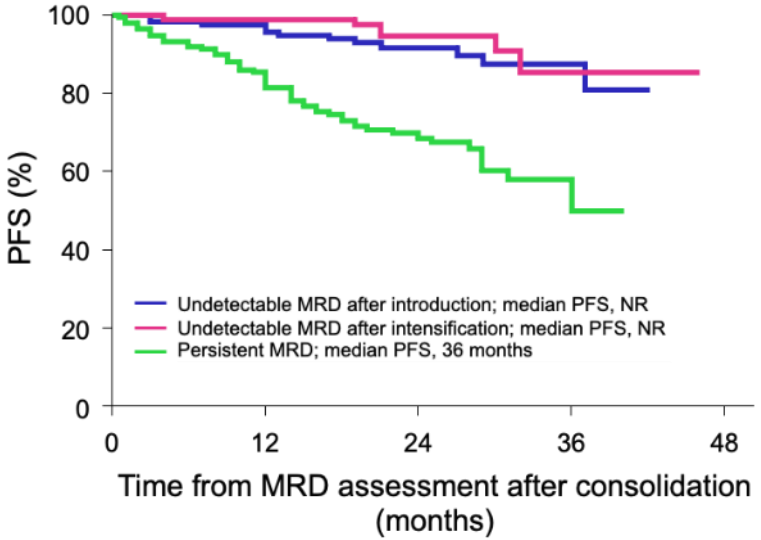
Attaining MRD– Overcomes High-Risk MM

PFS according to MRD status: PETHEMA/GEM2012 MENOS65 trial[1,2] – MRD < 2 x 10^{-6}





CA, cytogenetic abnormalities; MRD, minimal residual disease; NR, not reached; PFS, progression-free survival

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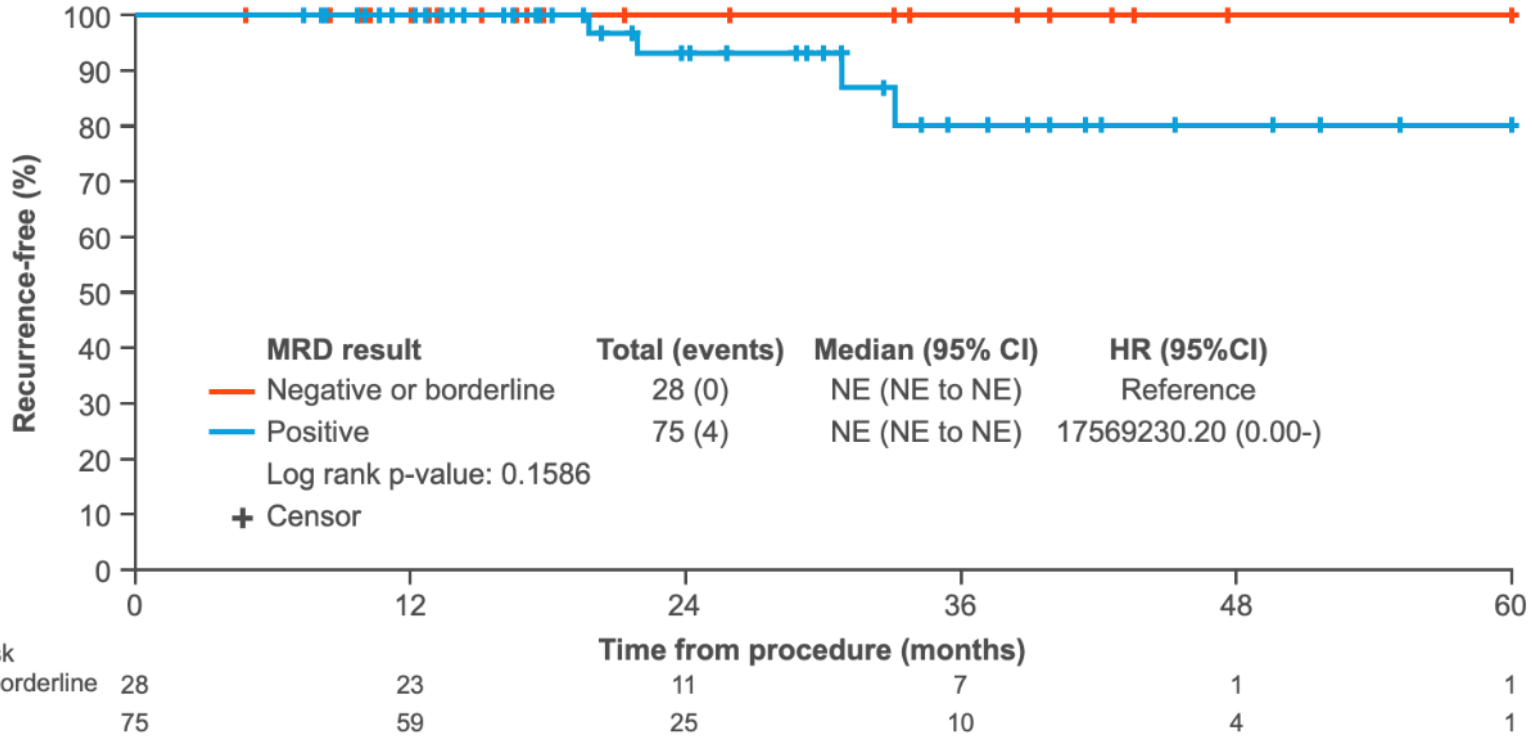
1. Paiva B, et al. *J Clin Oncol.* 2020;38:784-792; 2. Goicoechea I, et al. *Blood.* 2021;137:49-60.

MAYO CLINIC

Outcomes at Mayo Clinic in Arizona: MRD



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Gonzalez-Velez M, et al. ASH 2020. Abstract 1328.

MAYO CLINIC

High-Risk MM: Like ALL?

Test Results

Minimal Residual Disease (MRD) Status	Estimated Myeloma Molecules per Million Cells
NEGATIVE	0.0

Interpretation

The sample is NEGATIVE for the presence of myeloma gene rearrangements. Myeloma gene rearrangements were previously identified in an ID sample (December 24, 2015, Accession No. 205825). The previously identified myeloma gene rearrangements are NOT present in the current MRD sample, which is consistent with the sample being NEGATIVE for myeloma cells. The results of this test should be interpreted in the complete clinical context, including the patient's clinical presentation and current treatment regimen.

MRD Monitoring (Cellular Compartment)

Hyperdiploid: Like FL?

Test Results

Minimal Residual Disease (MRD) Status	Estimated Myeloma Molecules per Million Cells
POSITIVE	174

Interpretation

The sample is POSITIVE for the presence of myeloma gene rearrangements. Myeloma gene rearrangements were previously identified in an ID sample (November 11, 2016, Accession No. 210889). The presence of myeloma gene rearrangements is consistent with the sample being POSITIVE for myeloma cells. The results of this test should be interpreted in the complete clinical context, including the patient's clinical presentation and current treatment regimen.

MRD Monitoring (Cellular Compartment)

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MAYO CLINIC

But We Have No Data – the Magic?

American Journal of Hematology 33:86–89 (1990)

VAD-Based Regimens as Primary Treatment for Multiple Myeloma

Raymond Alexanian, Bart Barlogie, and Susan Tucker
University of Texas M.D. Anderson Cancer Center, Houston

An alternating VCAD-VAD regimen, combining vincristine-doxorubicin by continuous infusion with cyclophosphamide and pulse dexamethasone, or VAD alone, was given to 175 previously untreated patients with multiple myeloma. The response rate with primary VAD-based regimens of 55% was virtually identical to the 54% in comparable patients treated previously with similar programs by using bolus vincristine-doxorubicin. Despite responses to VAD that were more rapid in onset than any previous treatment, remission and survival times were similar. This may be due to major differences in drug sensitivity between progenitor and differentiated plasma cells. A VAD-based regimen seems better for newly diagnosed patients when rapid control of multiple myeloma is necessary.

Key words: chemotherapy for multiple myeloma, survival in multiple myeloma

Preliminary Communication

HIGH-DOSE INTRAVENOUS MELPHALAN FOR PLASMA-CELL LEUKAEMIA AND MYELOMA

T. J. McElwain R. L. Powles

Section of Medicine, Institute of Cancer Research and Royal Marsden Hospital, Downs Road, Sutton, Surrey

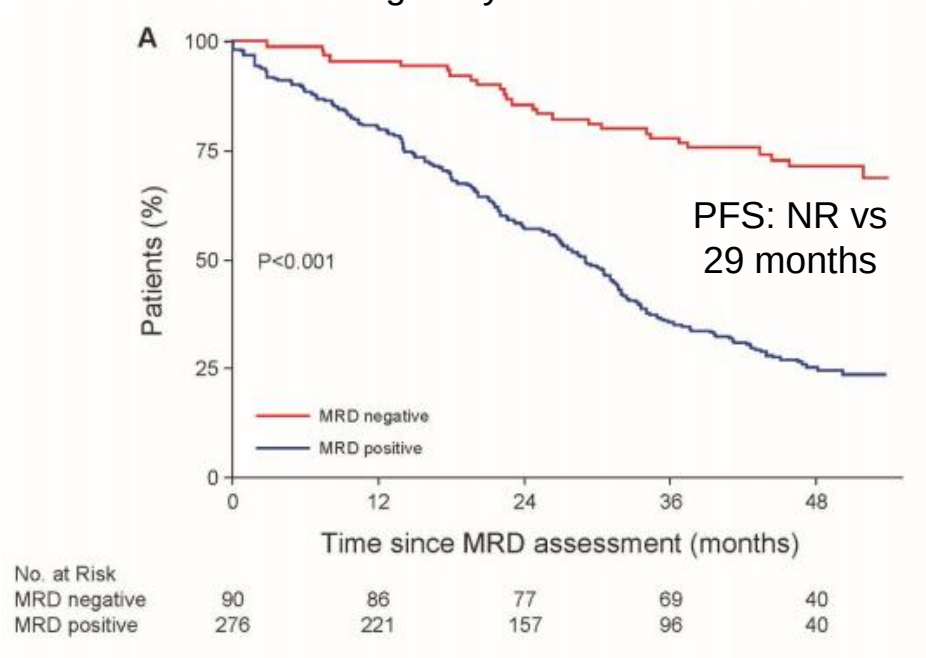
Summary 1 previously untreated patient with plasma-cell leukaemia and 8 patients with myeloma (4 previously untreated) were treated with high-dose melphalan 100–140 mg/m^2 iv. All responded to treatment. 3 of the 5 previously untreated patients achieved biochemical and bone-marrow complete remissions.

Alexanian R, et al. *Am J Hematol*. 1990;33:86-89; McElwain TJ, et al. *Lancet*. 1983;2:822-824.

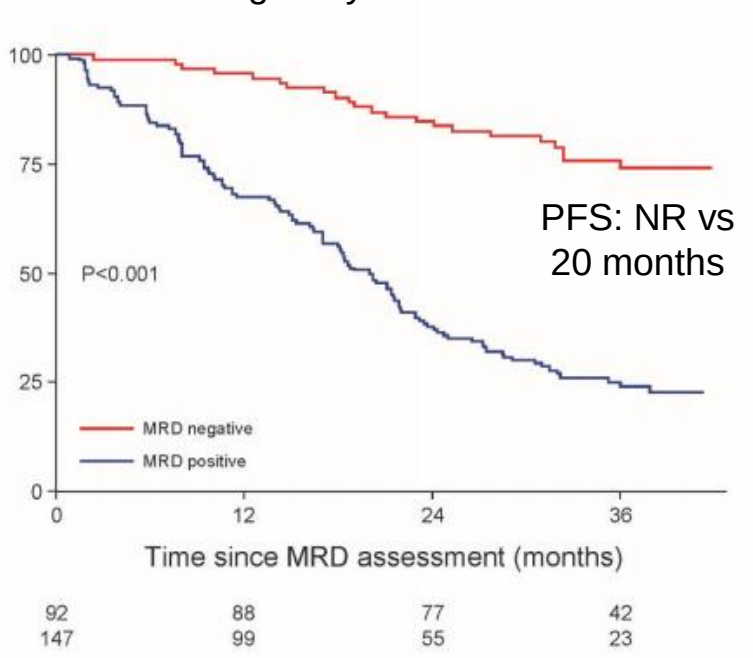
MAYO CLINIC

Outcomes by MRD

MRD negativity at the start of maintenance



MRD negativity 12 months later



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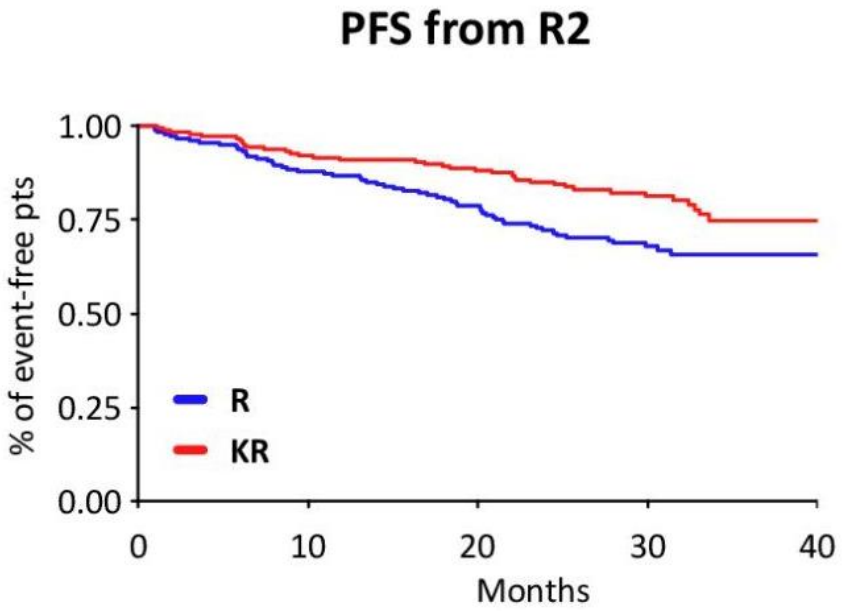
Perrot A, et al. *Blood*. 2018;132:2456-2464.

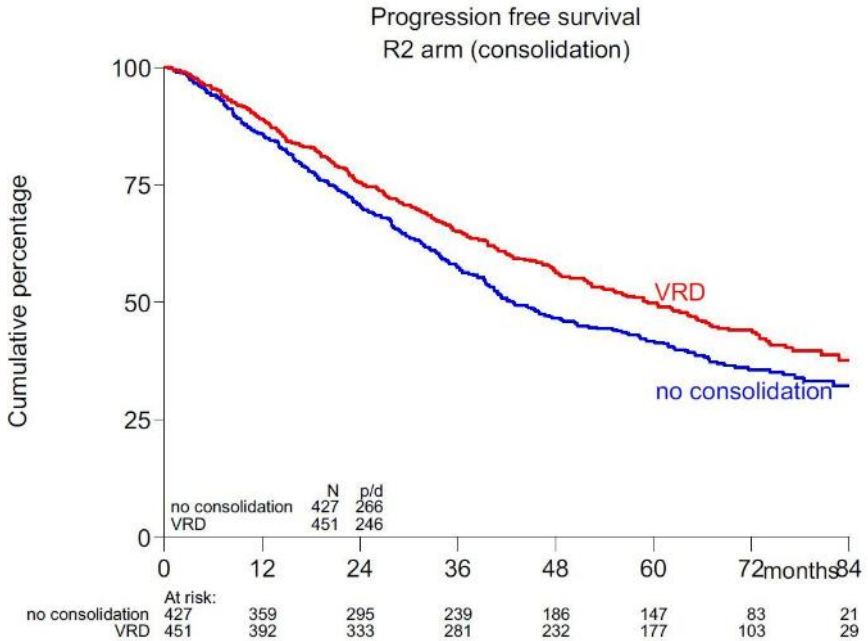
MAYO CLINIC

Consolidation Post-SCT

FORTE Trial Second Randomization KR vs R



EMN02/HO95 VRD consolidation vs maint



6-year OS was 75% (95% CI: 71-79) in the consolidation arm vs 69%

@rfonsi1, fonseca.rafael@mayo.edu

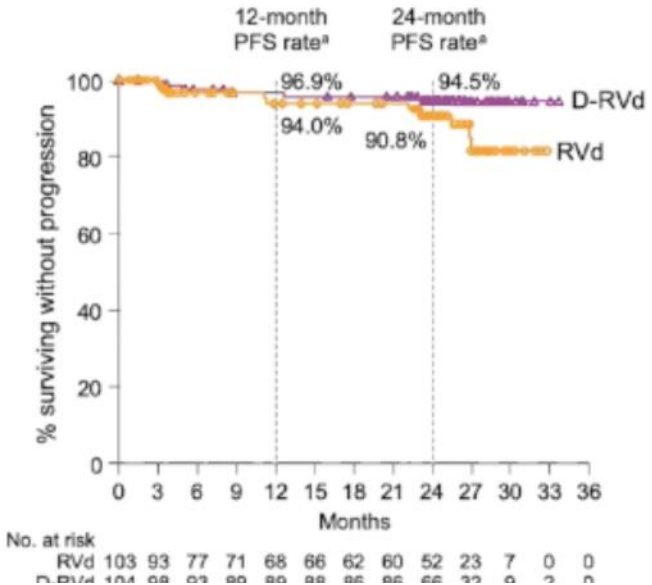
Gay F, et al. *Blood.* 2020;136(suppl 1): abstract 141; Sonneveld P, et al. *Blood.* 2020;136(suppl 1): abstract 550.

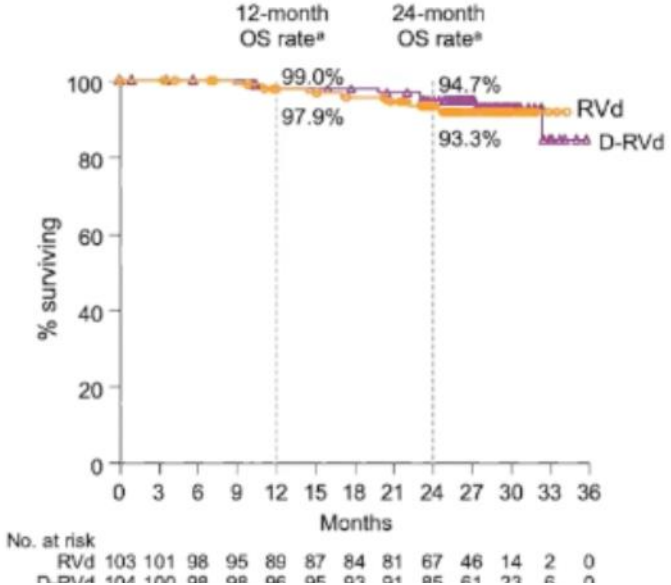
MAYO CLINIC

Update: GRIFFIN

PFS and OS in the ITT Population

- Median follow-up = 27.4 months



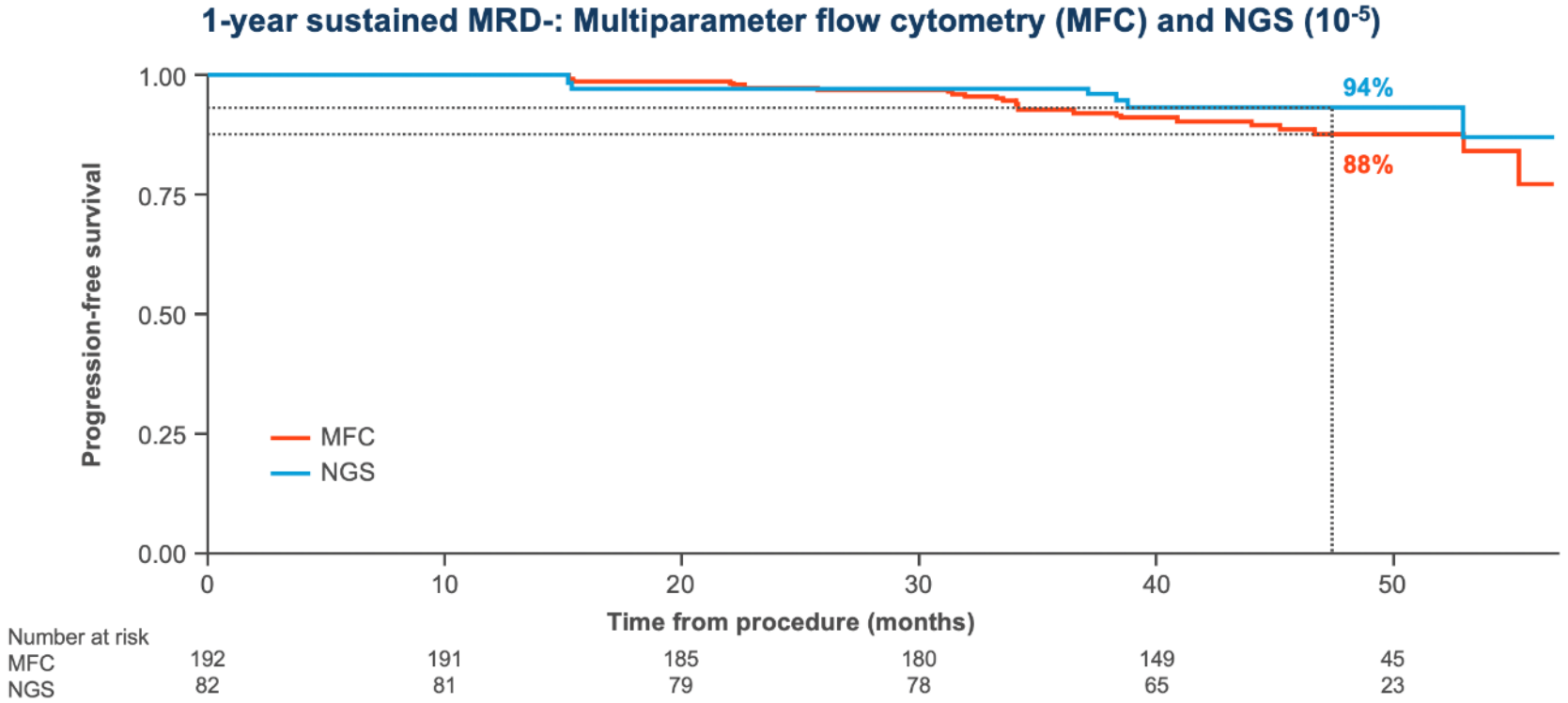


@rfonsi1, fonseca.rafael@mayo.edu

Kauffman JL, et al. ASH 2020. Abstract 549.

MAYO CLINIC

FORTE: Sustained MRD Negativity



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Gay F, et al. *Blood.* 2020;136(suppl 1): abstract 141.

MAYO CLINIC

Drive to MRD Negative

- 58 yo
- New diagnosis MM
- Induction with KRD
- Completed SCT
- Nov 2018: MRD+
  - Dara-Rd
- Aug 2019: MRD+
  - More Dara-Rd
- Feb 2020: MRD–
  - R maintenance

SAMPLE-LEVEL MRD RESULT

No Residual Sequences Detected

ESTIMATED MRD VALUE:

0 residual clonal cells (Range: 0 - 2) **

Total nucleated cells evaluated from this sample: 1,111,349

The MRD range presented above represents the 95% confidence interval for the measured number of residual clonal sequences per million nucleated cells. Details for each identified dominant sequence from this sample are provided on subsequent pages of this report.

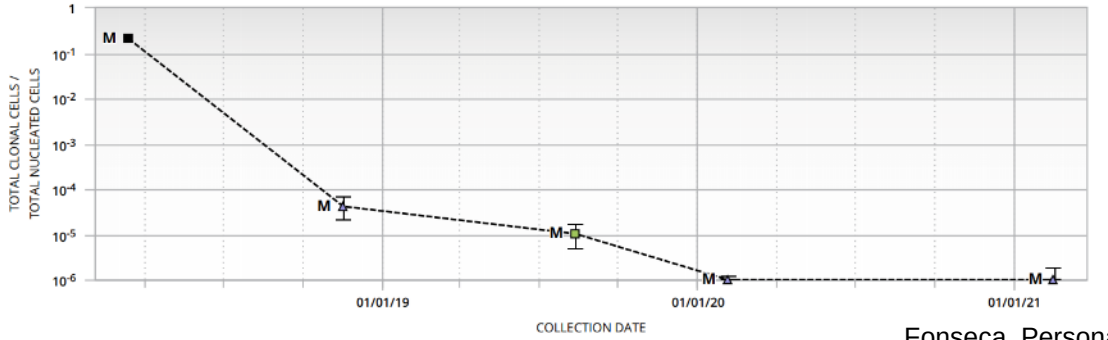
RESULTS SUMMARY

- Genomic DNA was extracted from a fresh bone marrow sample.
- The 2 dominant sequences identified in a diagnostic sample from this patient were not detected in this current sample.

** The sensitivity of this assay is directly related to the total number of cells (or cellular equivalents of genomic DNA) analyzed. There were 1,111,349 total nucleated cells evaluated from this sample.

▶ **The results obtained from this assay should always be used in combination with the clinical examination, patient medical history, and other findings.**

SAMPLE-LEVEL MRD TRACKING *(shows only the sequence determining the MRD result for each time point)*



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MAYO CLINIC

Can Also Happen With T-Cell Engagers!

SAMPLE-LEVEL MRD RESULT

No Residual Sequences Detected

ESTIMATED MRD VALUE:

0 residual clonal cells (Range: 0 - <1) **

Total nucleated cells evaluated from this sample: 3,139,577

The MRD range presented above represents the 95% confidence interval for the measured number of residual clonal sequences per million nucleated cells. Details for each identified dominant sequence from this sample are provided on subsequent pages of this report.

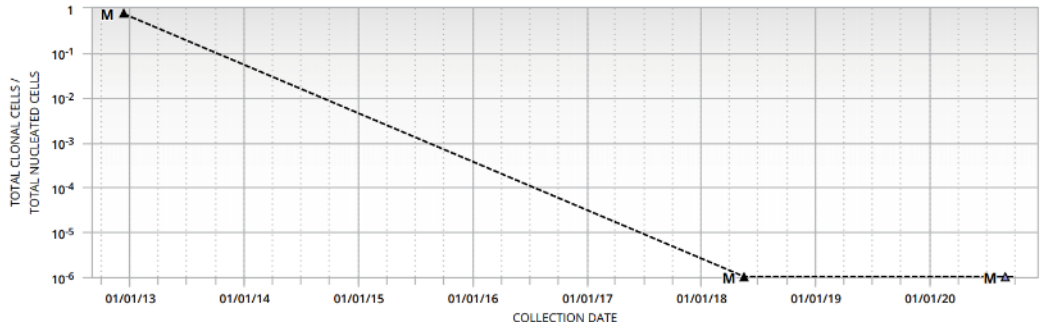
RESULTS SUMMARY

- Genomic DNA was extracted from a fresh bone marrow sample.
- The 3 dominant sequences identified in a diagnostic sample from this patient were not detected in this current sample.

** The sensitivity of this assay is directly related to the total number of cells (or cellular equivalents of genomic DNA) analyzed. There were 3,139,577 total nucleated cells evaluated from this sample.

▶ **The results obtained from this assay should always be used in combination with the clinical examination, patient medical history, and other findings.**

SAMPLE-LEVEL MRD TRACKING *(shows only the sequence determining the MRD result for each time point)*



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Fonseca, Personal.

MAYO CLINIC

Therapy Discontinuation?

SAMPLE-LEVEL MRD RESULT

No Residual Sequence Detected

ESTIMATED MRD VALUE:

0 residual clonal cells (Range: 0 - 1) **

Sequence determining MRD result: IGH Sequence A

The MRD range presented above represents the 95% confidence interval for the measured number of residual clonal sequences per million nucleated cells. Details for each identified dominant sequence from this sample are provided on subsequent pages of this report.

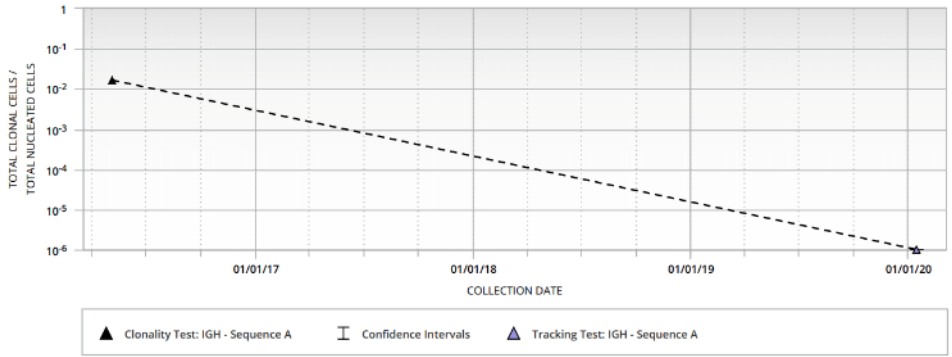
RESULTS SUMMARY

- Genomic DNA was extracted from a fresh bone marrow sample.
- The dominant sequence identified in a diagnostic sample from this patient was not detected in this current sample.

** The sensitivity of this assay is directly related to the total number of cells (or cellular equivalents of genomic DNA) analyzed. There were 2,782,146 total nucleated cells evaluated from this sample.

► **The results obtained from this assay should always be used in combination with the clinical examination, patient medical history, and other findings.**

SAMPLE-LEVEL MRD TRACKING *(shows only the sequence determining the MRD result for each time point)*



SAMPLE-LEVEL MRD RESULT

Residual Sequence Detected

ESTIMATED MRD VALUE:

<1 residual clonal cell per million nucleated cells (Range: >0 - 2) **

*** Sequence detected below Limit of Detection; frequency too low to enable consistent MRD determination across samples.*

Sequence determining MRD result: IGH Sequence B

The MRD range presented above represents the 95% confidence interval for the measured number of residual clonal sequences per million nucleated cells. Details for each identified dominant sequence from this sample are provided on subsequent pages of this report.

RESULTS SUMMARY

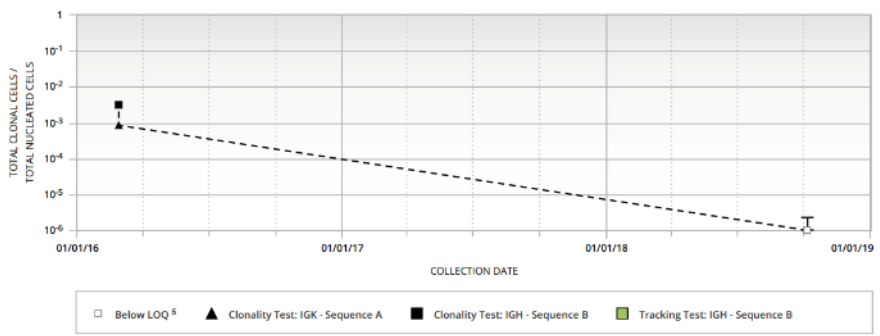
- Genomic DNA was extracted from a fresh bone marrow sample.
- 1 of the 3 dominant sequences identified in a diagnostic sample from this patient was still present in this current sample.

** The frequency of the sequence detected in this sample was too low to enable consistent determination of the presence of MRD, meaning that results could vary from sample to sample.

- There were 1,862,892 total nucleated cells evaluated from this sample.

► **The results obtained from this assay should always be used in combination with the clinical examination, patient medical history, and other findings.**

SAMPLE-LEVEL MRD TRACKING *(shows only the sequence determining the MRD result for each time point)*



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MAYO CLINIC

What Are the “No” Answers?

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Fonseca, Personal.

MAYO CLINIC

Don’t Forget the Orange Line

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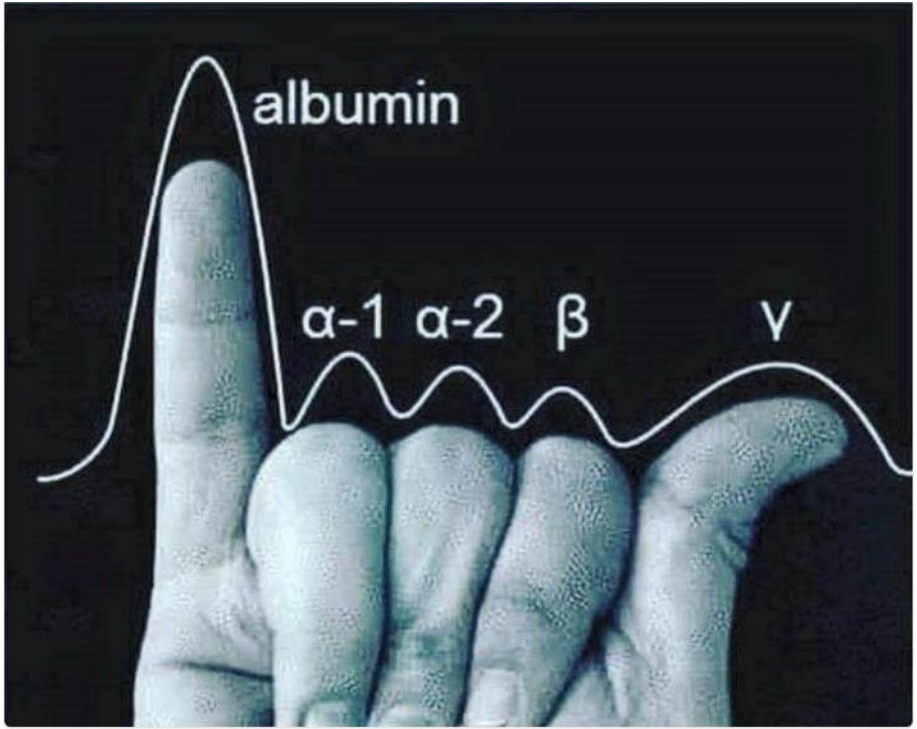
R. Fonseca, personal information.

MAYO CLINIC

Thank You!



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Global Multiple Myeloma Academy

Discussion

APTITUDE HEALTH®

Global Multiple Myeloma Academy

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

Vania Hungria, MD, PhD

APTITUDE HEALTH®

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

Vania Tietsche de Moraes Hungria

Associate Professor of Hematology at Santa Casa Medical School
Clinical Director at Clínica São Germano
São Paulo, Brazil

GBRAM
GRUPO BRASILEIRO DE MIELOMA

São Germano
Oncologia

Global Multiple Myeloma Academy

Disclosures

Honoraria: Amgen, BMS, Celgene, Janssen, Roche, Sanofi, Takeda

Agenda

- Who is a candidate for transplant?
- What is the optimal management of MM in a transplant-eligible patient?
- What are the best induction regimens for patients eligible for transplant?
- Which is the better time for transplant: upfront or at relapse?

QUESTION FOR THE AUDIENCE

In your clinical practice, what is your choice of induction regimen for patients eligible for ASCT?

a. Dara-VTd
b. Dara-VRd
c. VRd
d. VTd
e. VCd

QUESTION FOR THE AUDIENCE

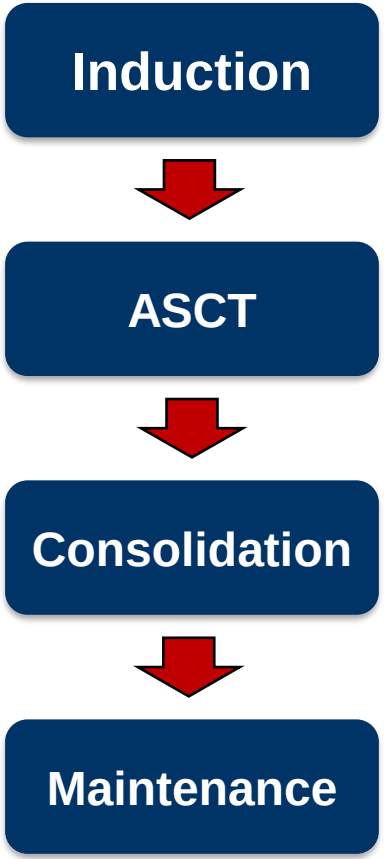
What is your opinion on transplant-eligible multiple myeloma patients?

a. Standard of care for all of them
b. Standard of care for only standard-risk patients
c. Standard of care for only high-risk patients
d. Standard of care for some of them

Newly Diagnosed Multiple Myeloma

Management of Patients Eligible for Transplant

Treatment Paradigm for Transplant-Eligible MM Patients



Therapy for ND Transplant-Eligible Multiple Myeloma

Induction

- ✓ **What is the role of induction?**
  Fast control of the disease, with low toxicity
  Achieve high response rates (MRD negativity, if possible)

- ✓ **What is the best induction regimen for patients eligible for ASCT?**
  Triplet or quadruplet regimen?

VTD is superior to VCD prior to intensive therapy in multiple myeloma: results of the prospective IFM2013-04 trial.

Moreau P, et al. *Blood.* 2016;127:2569-2574.

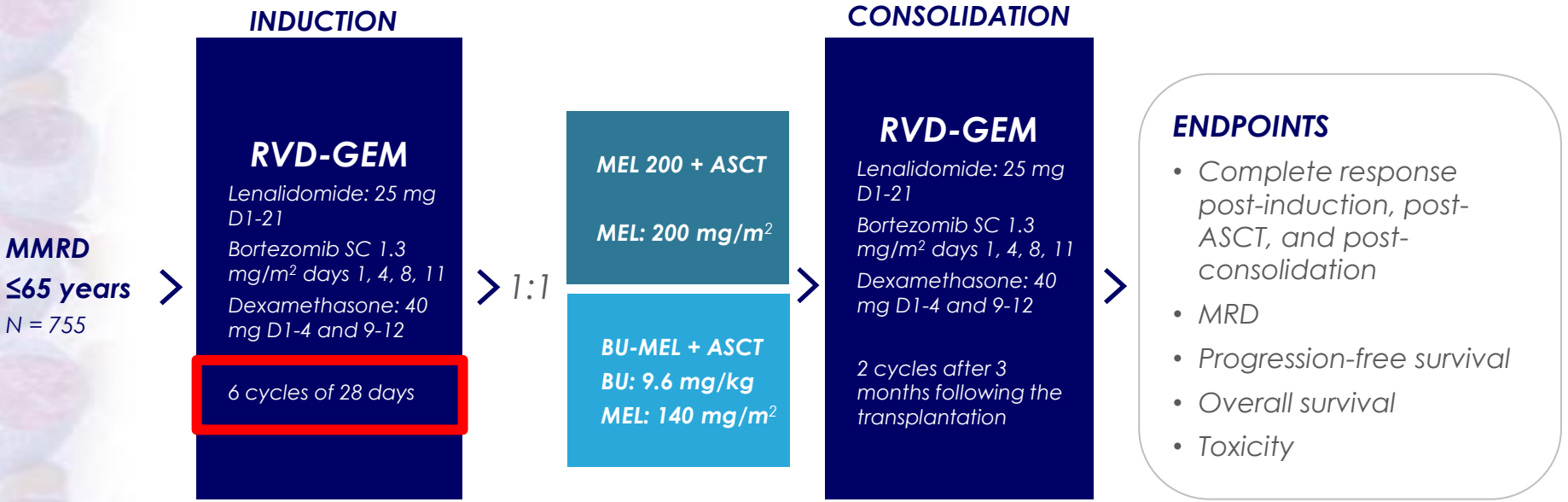
IFM2013-04 Trial: Intent-to-Treat Analysis

	VTD n = 169	VCD n = 169	*P* value
≥CR	13.0%	8.9%	.22
≥VGPR	66.3%	56.2%	.05
≥PR	92.3%	83.4%	.01

Moreau P, et al. *Blood.* 2016;127:2569-2574.

PETHEMA/GEM2012 TRIAL

Bortezomib, lenalidomide, and dexamethasone as induction therapy prior to ASCT



Rosiñol L, et al. *Blood.* 2019;134:1337-1345.

Bortezomib, Lenalidomide, and Dexamethasone as Induction Therapy Prior to Autologous Transplant in Multiple Myeloma

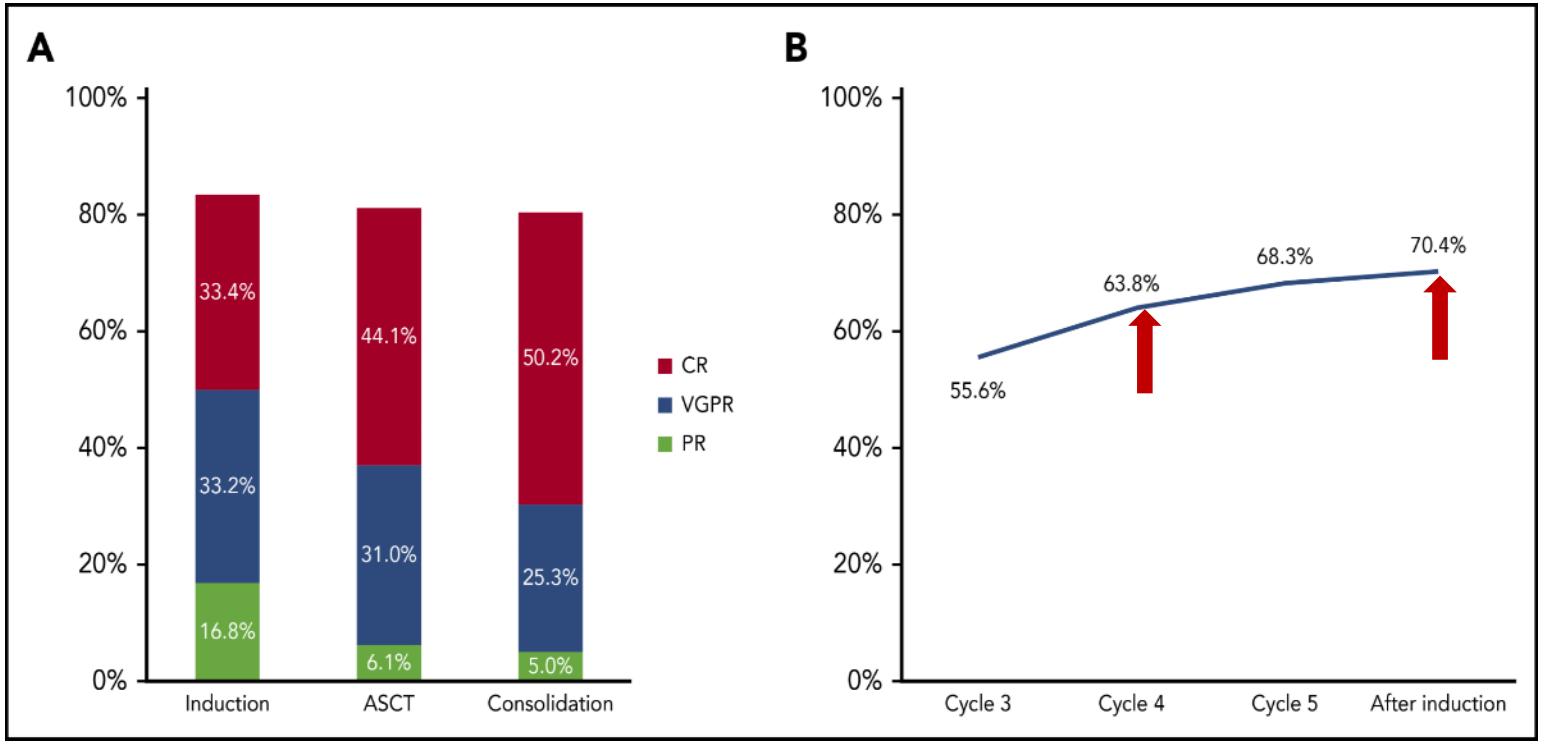
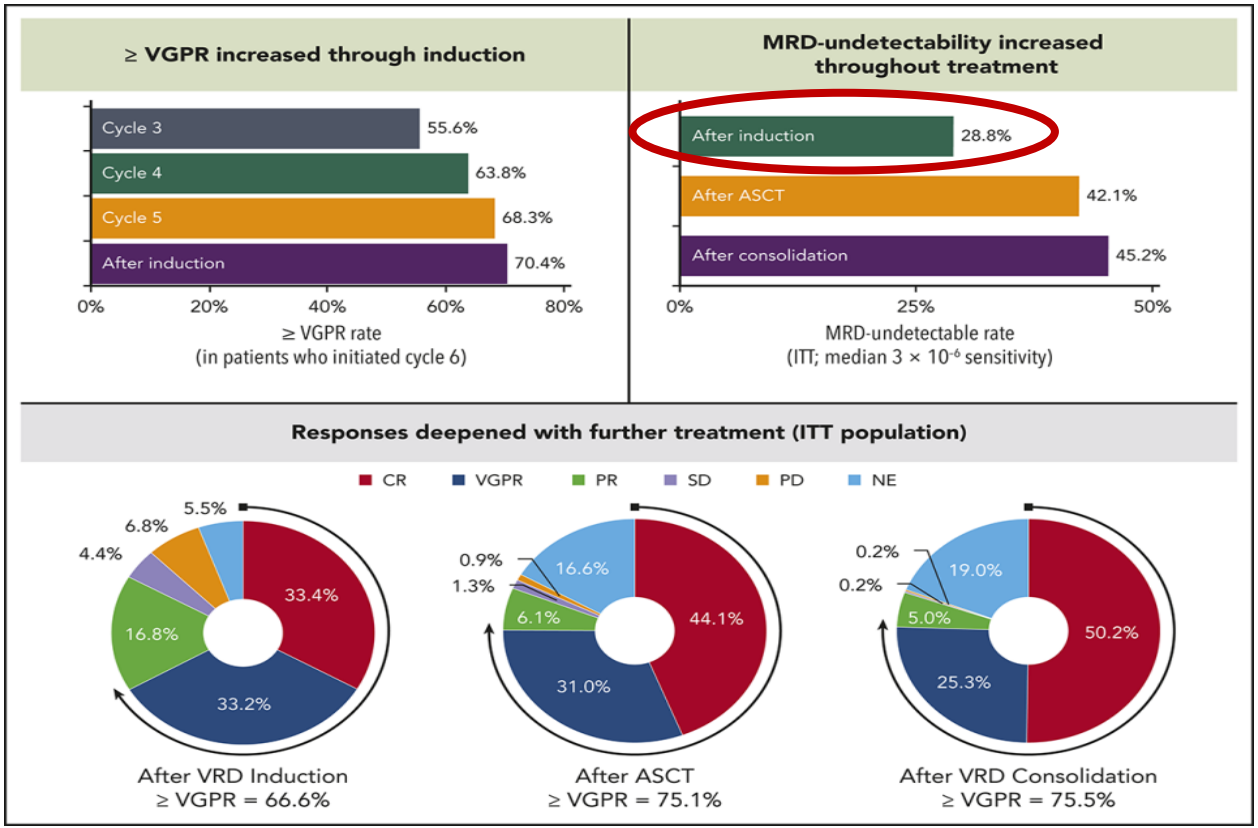


Figure Legend: *Response. (A) Response rates in the ITT population (N = 458). (B) Rates of VGPR or better throughout induction in the 426 patients who initiated cycle 6.*

American Society of Hematology
Helping hematologists conquer blood diseases worldwide

Rosiñol L, et al. *Blood.* 2019;134:1337-1345.

Bortezomib, Lenalidomide, and Dexamethasone as Induction Therapy Prior to Autologous Transplant in Multiple Myeloma



American Society of Hematology
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Rosiñol L, et al. *Blood.* 2019;134:1337-1345.

VTD vs VRD

Bortezomib-Lenalidomide-Dexamethasone vs Bortezomib-Thalidomide-Dexamethasone Induction: Integrated Analysis of Randomized Controlled Trials in Transplant-Eligible Newly Diagnosed Multiple Myeloma

Figure 4. ≥ VGPR and MRD-Negative Rates After Induction and ASCT in the GEM Studies[a]

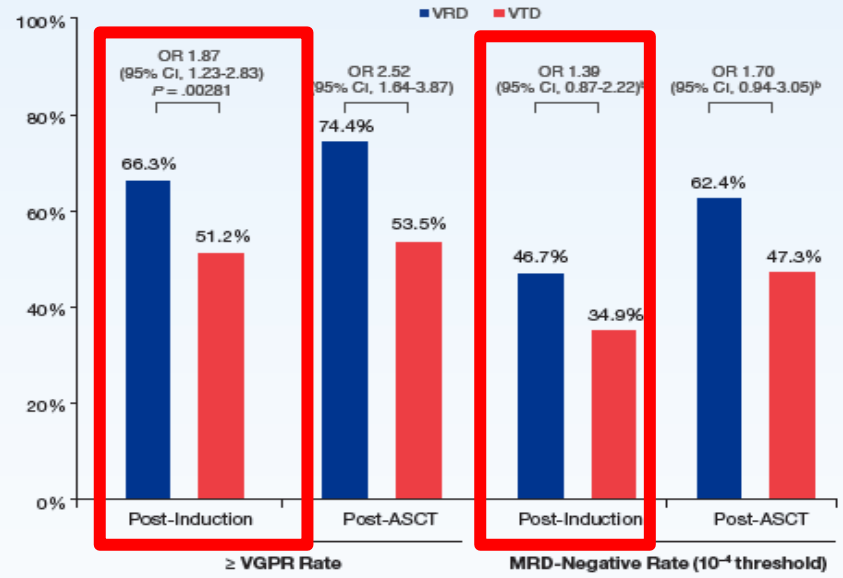
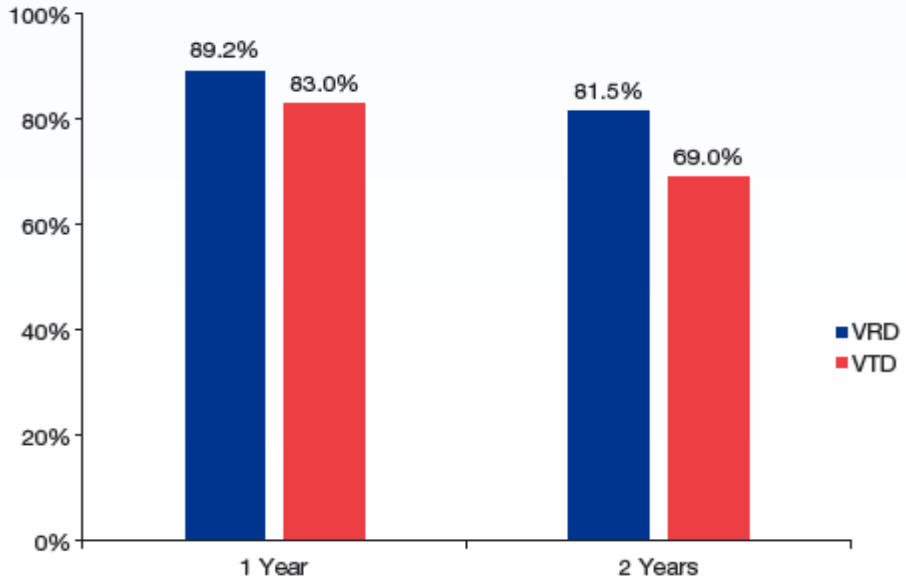


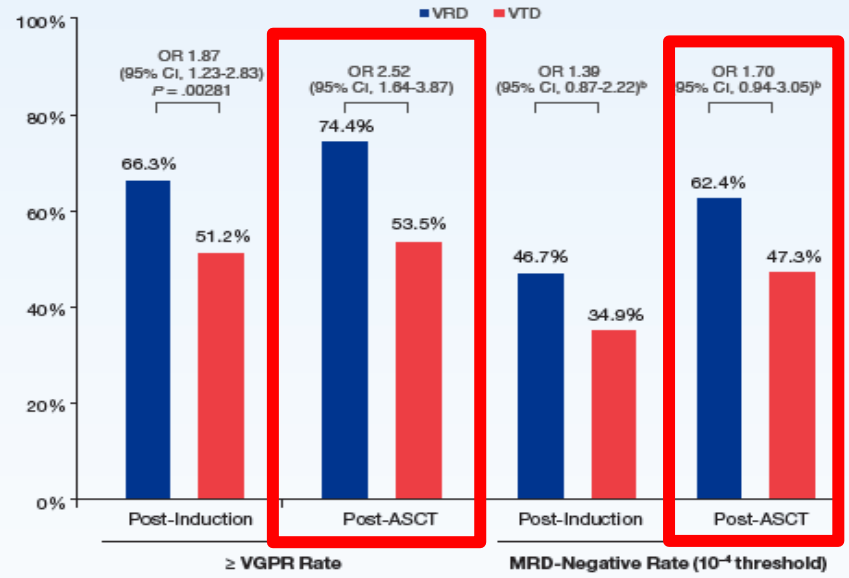
Figure 5. Event-Free PFS in the GEM Studies



Rosiñol L, et al. EHA 2019. Poster PF594.

Bortezomib-Lenalidomide-Dexamethasone vs Bortezomib-Thalidomide-Dexamethasone Induction: Integrated Analysis of Randomized Controlled Trials in Transplant-Eligible Newly Diagnosed Multiple Myeloma

Figure 4. ≥ VGPR and MRD-Negative Rates After Induction and ASCT in the GEM Studies[a]



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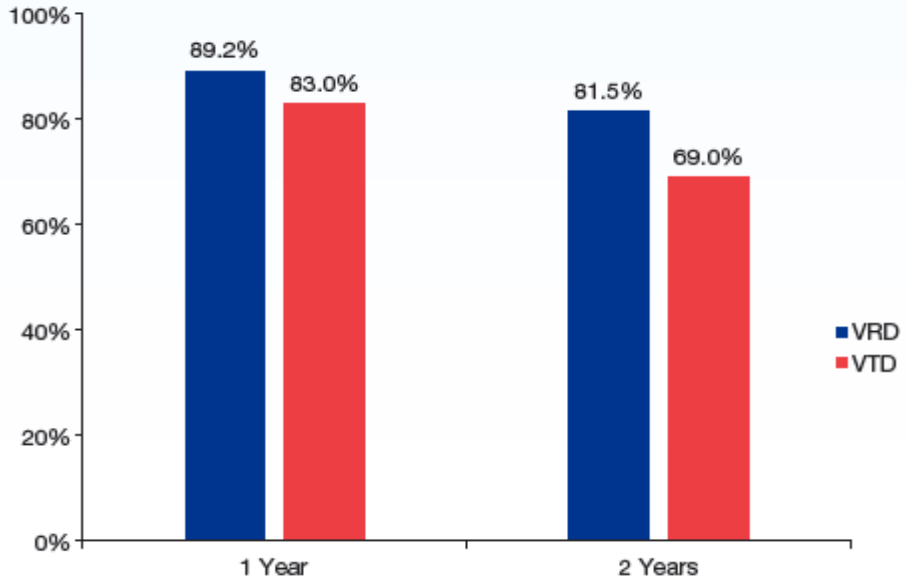


Therapy for ND Transplant-Eligible Multiple Myeloma

Induction

- ✓ **What is the role of induction?**

  Fast control of the disease, with low toxicity

  Achieve high response rates (MRD negativity, if possible)

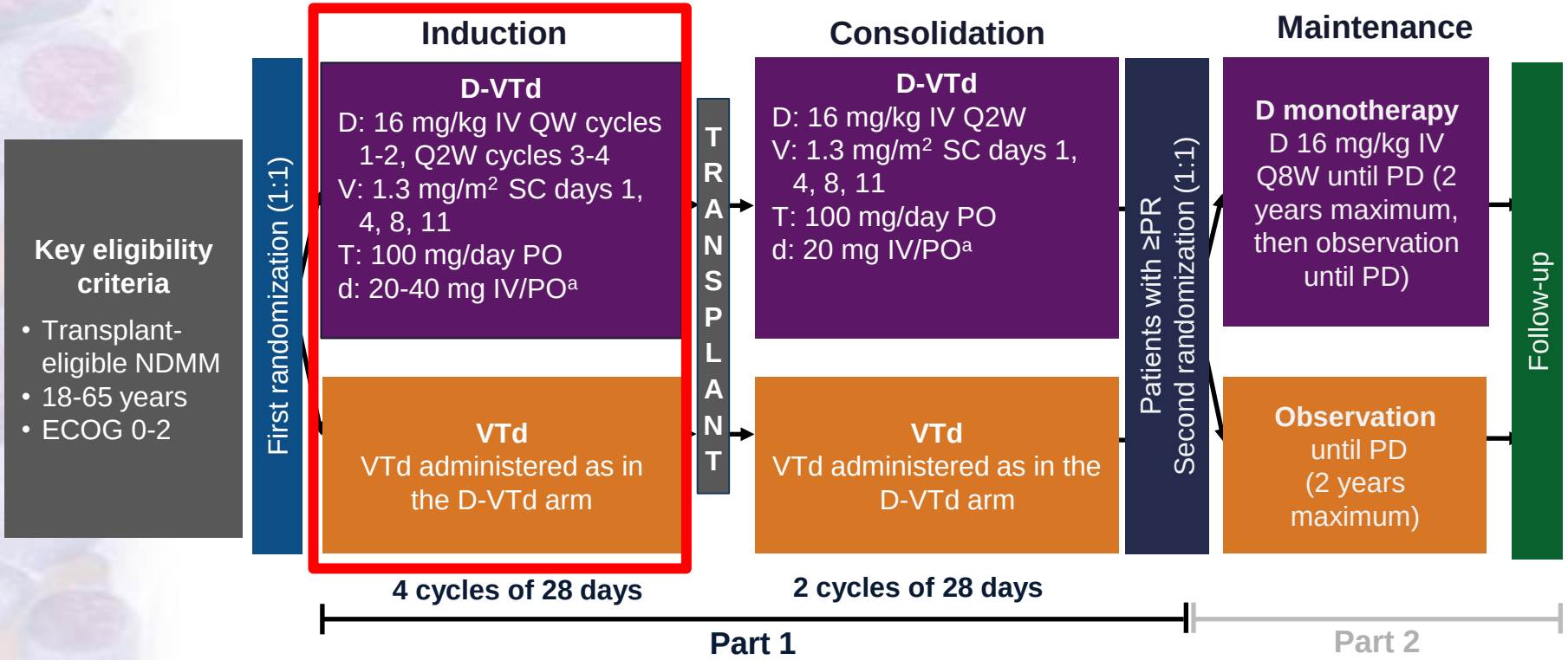
- ✓ **What is the best induction regimen for patients eligible for ASCT?**

Triplet or quadruplet regimen?

3 drugs + monoclonal antibody?

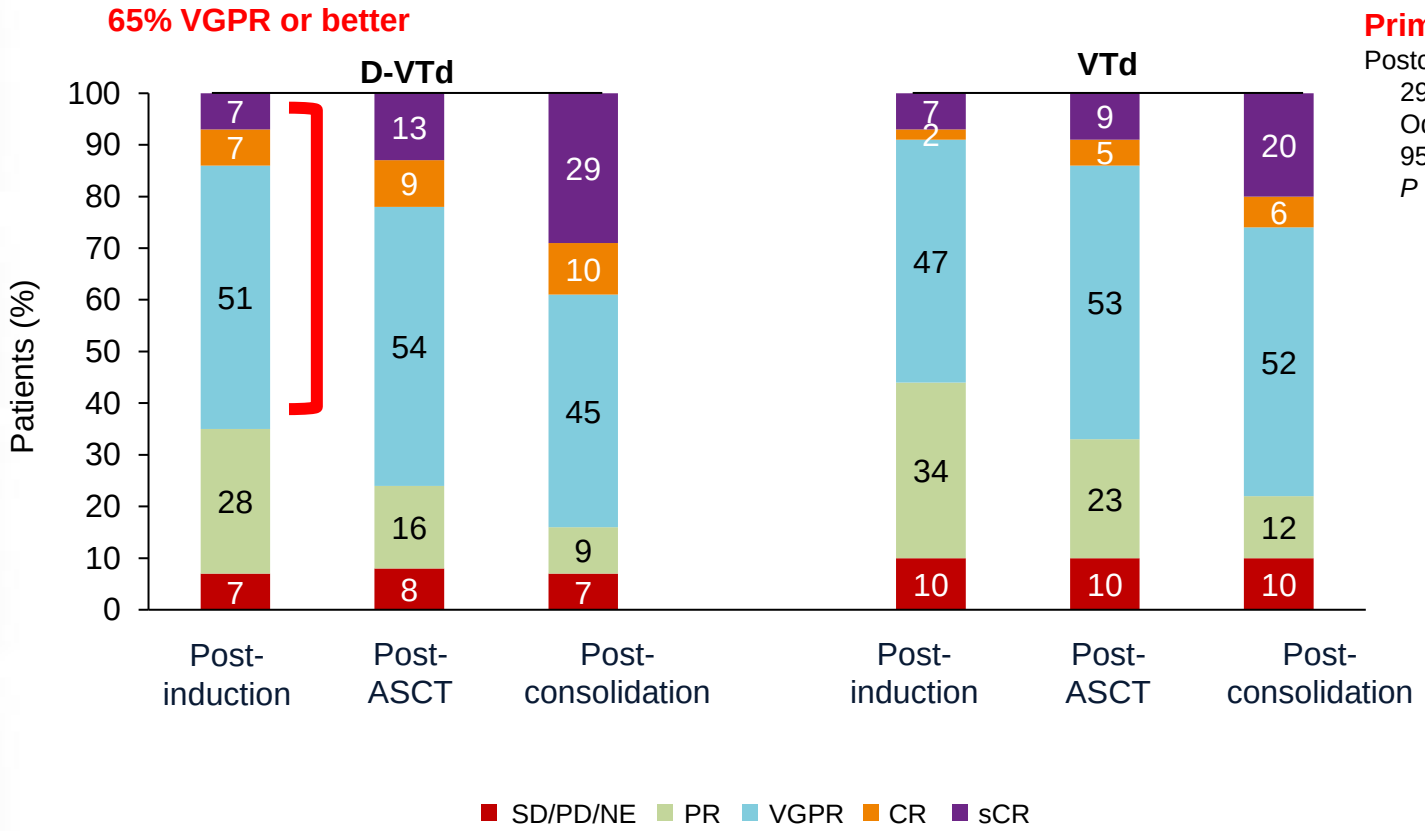
CASSIOPEIA Study Design

Phase III study of D-VTd vs VTd in transplant-eligible NDMM (N = 1,085); 111 sites from 9/2015 to 8/2017



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

Efficacy: Response Rates Over Time



Primary endpoint

Postconsolidation sCR

29% D-VTd vs 20% VTd

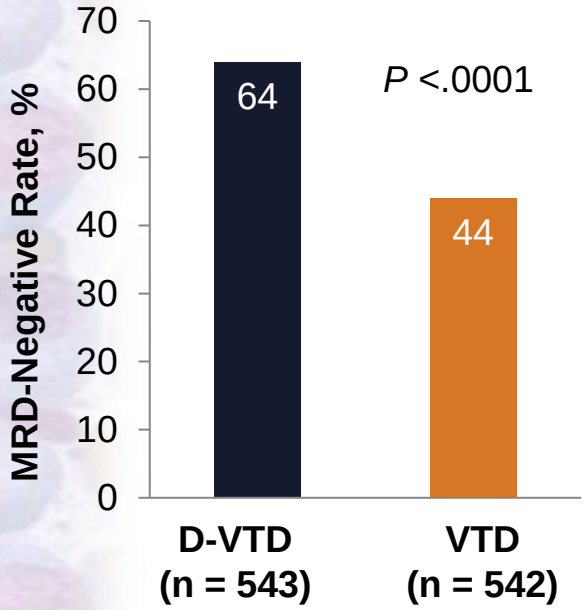
Odds ratio, 1.60;

95% CI, 1.21-2.12;

P = .0010

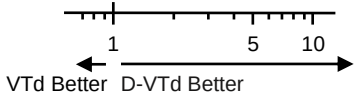
Moreau P, et al. *Lancet*. 2019;394:29-38.

Efficacy: MRD (Flow Cytometry; 10^{-5})



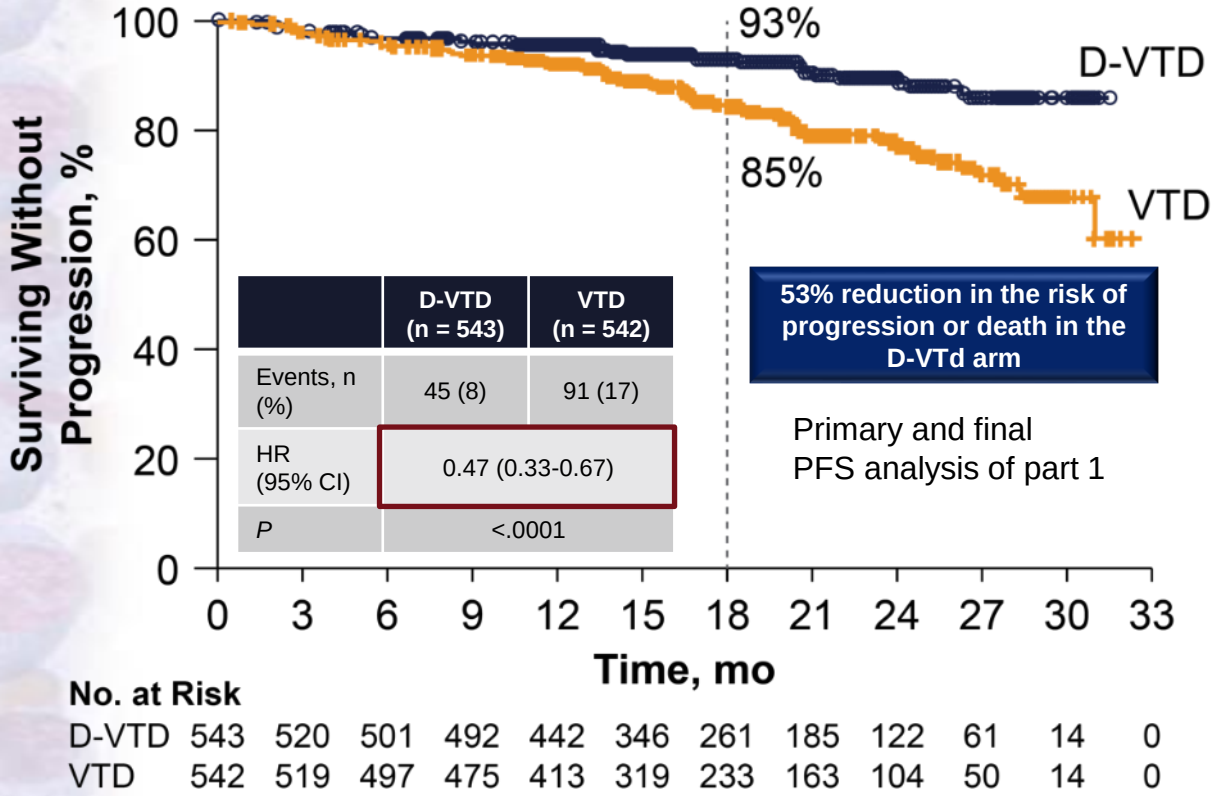
D-VTd superior across all subgroups, including high-risk cytogenetics and ISS stage III

Subgroup	VTd	D-VTd	Odds Ratio (95% CI)
	Minimal residual disease negative, n (%)		
Sex			
Male	131 (41)	192 (61)	2.22 (1.62–3.05)
Female	105 (47)	154 (68)	2.37 (1.62–3.48)
Age			
<50 years	38 (42)	56 (68)	2.84 (1.53–5.28)
≥50 years	198 (44)	290 (63)	2.19 (1.68–2.85)
Site			
IFM	204 (45)	287 (64)	2.16 (1.65–2.81)
HOVON	32 (38)	59 (65)	3.05 (1.65–5.65)
ISS disease stage			
I	103 (45)	137 (67)	2.48 (1.68–3.67)
II	96 (41)	155 (61)	2.21 (1.54–3.18)
III	37 (46)	54 (64)	2.14 (1.15–4.00)
Cytogenetic profile at trial entry			
High risk	38 (44)	49 (60)	1.88 (1.02–3.46)
Standard risk	197 (43)	296 (64)	2.35 (1.80–3.07)
Baseline creatinine clearance			
>90 mL/min	139 (44)	205 (62)	2.07 (1.51–2.84)
≤90 mL/min	97 (43)	141 (67)	2.64 (1.79–3.89)
Baseline hepatic function			
Normal	216 (43)	310 (65)	2.40 (1.85–3.10)
Impaired	20 (48)	36 (57)	1.47 (0.67–3.21)
Type of multiple myeloma			
IgG	122 (39)	201 (61)	2.43 (1.77–3.34)
Non-IgG	59 (49)	61 (66)	2.00 (1.15–3.50)
ECOG performance status			
0	112 (44)	172 (65)	2.39 (1.68–3.41)
≥1	124 (44)	174 (63)	2.17 (1.55–3.04)



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

Efficacy: PFS From First Randomization



	D-VTD (n = 543)	VTD (n = 542)
Events, n (%)	45 (8)	91 (17)
HR (95% CI)	0.47 (0.33-0.67)	
P	<.0001	

53% reduction in the risk of progression or death in the D-VTd arm

Primary and final PFS analysis of part 1

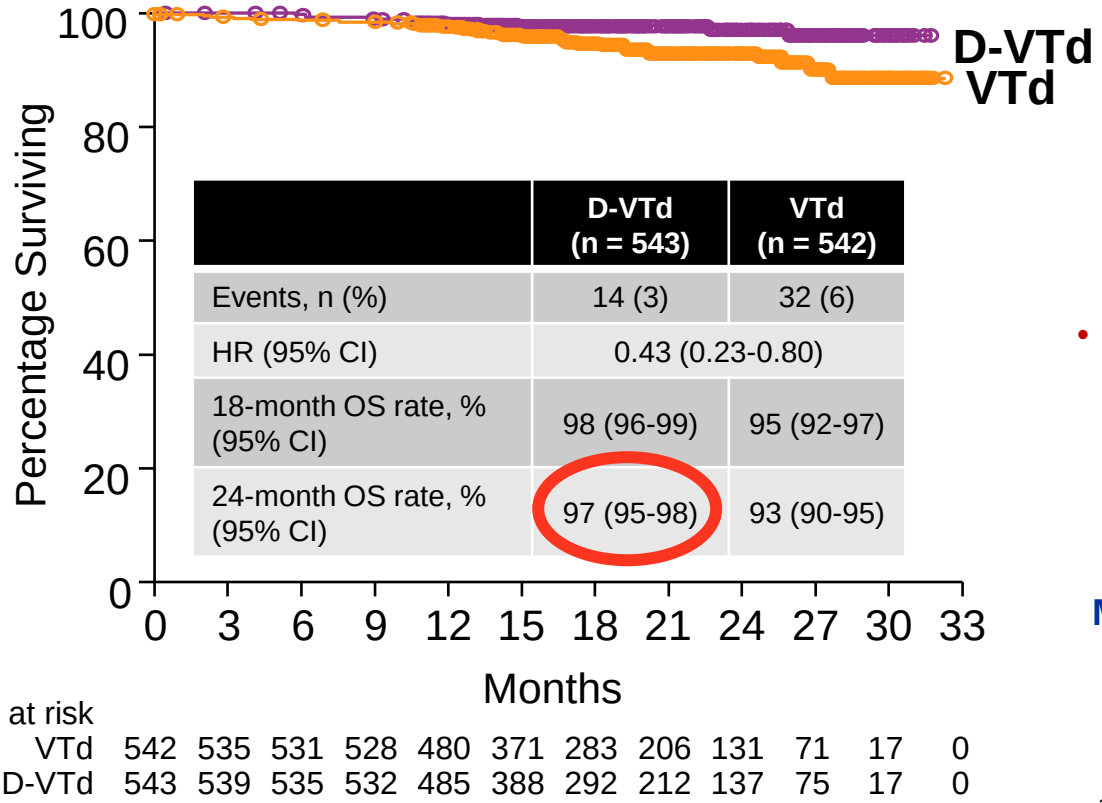
- **Median (range) follow-up: 18.8 (0.0-32.2) months[1]**

- **UPDATED[2]**
  Median (range) follow-up: 44.5 months
  Dara-VTd: not reached
  VTd: 51.5 months

HR: 0.58 (95%CI 0.47-0.72)
P<0.0001

1. Moreau P, et al. *Lancet*. 2019;394:29-38.
2. Moreau P, et al. ASCO 2021.

Efficacy: OS



	D-VTd (n = 543)	VTd (n = 542)
Events, n (%)	14 (3)	32 (6)
HR (95% CI)	0.43 (0.23-0.80)	
18-month OS rate, % (95% CI)	98 (96-99)	95 (92-97)
24-month OS rate, % (95% CI)	97 (95-98)	93 (90-95)

No. at risk												
VTd	542	535	531	528	480	371	283	206	131	71	17	0
D-VTd	543	539	535	532	485	388	292	212	137	75	17	0

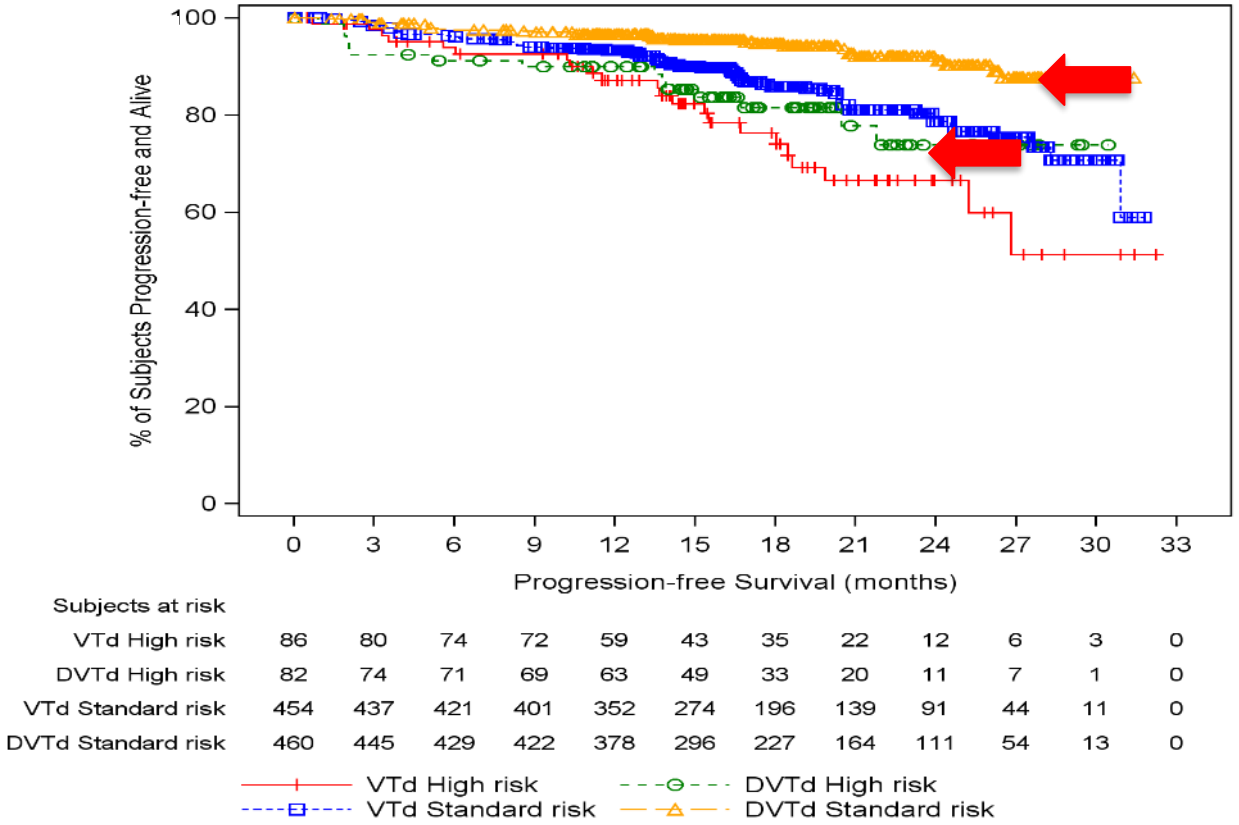
OS data are immature after median follow-up of 18.8 months[1]

- **UPDATED[2]**
  Median (range) follow-up: 44.5 months
  D-VTd: 41 deaths
  VTd: 73 deaths

Median OS was not reached in either treatment arm

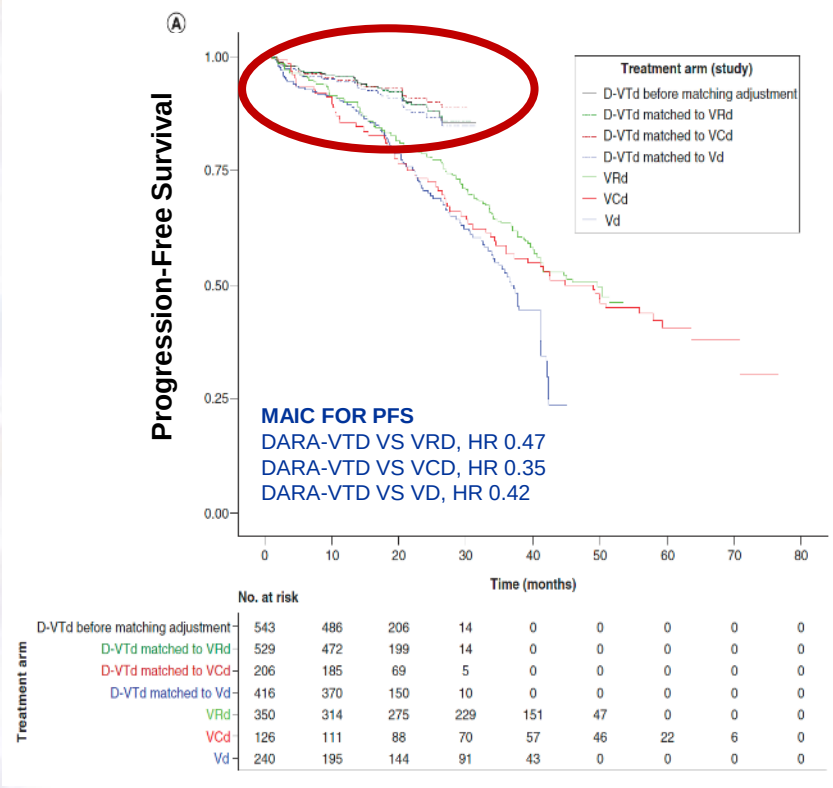
1. Moreau P, et al. *Lancet*. 2019;394:29-38.
2. Moreau P, et al. ASCO 2021.

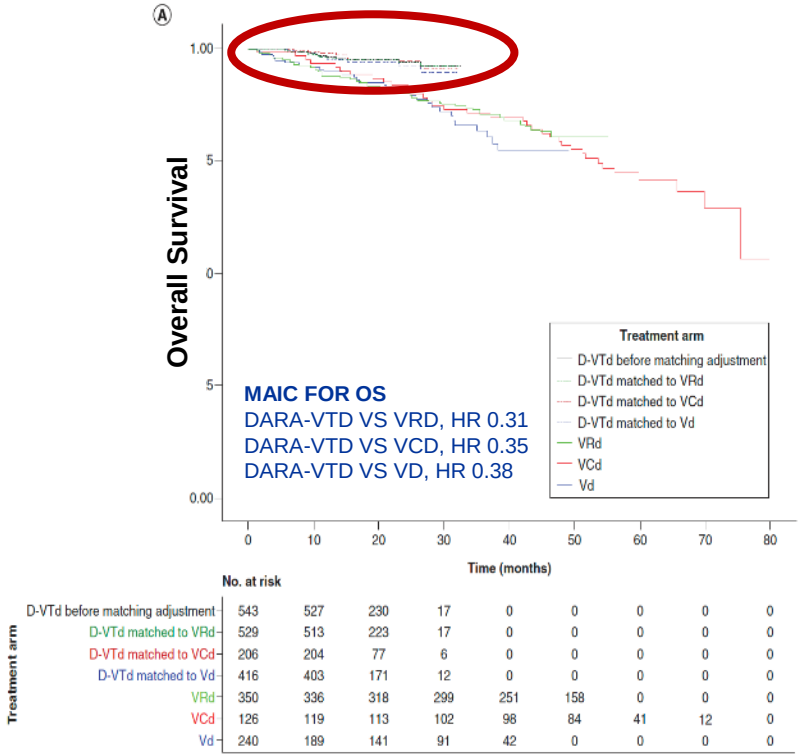
CASSIOPEIA: PFS According to Risk Status



Moreau, Sonneveld, Avet-Loiseau. Unpublished data.

Frontline Daratumumab-VTd vs SOC in ASCT-Eligible MM: Matching-Adjusted Indirect Comparison (MAIC)

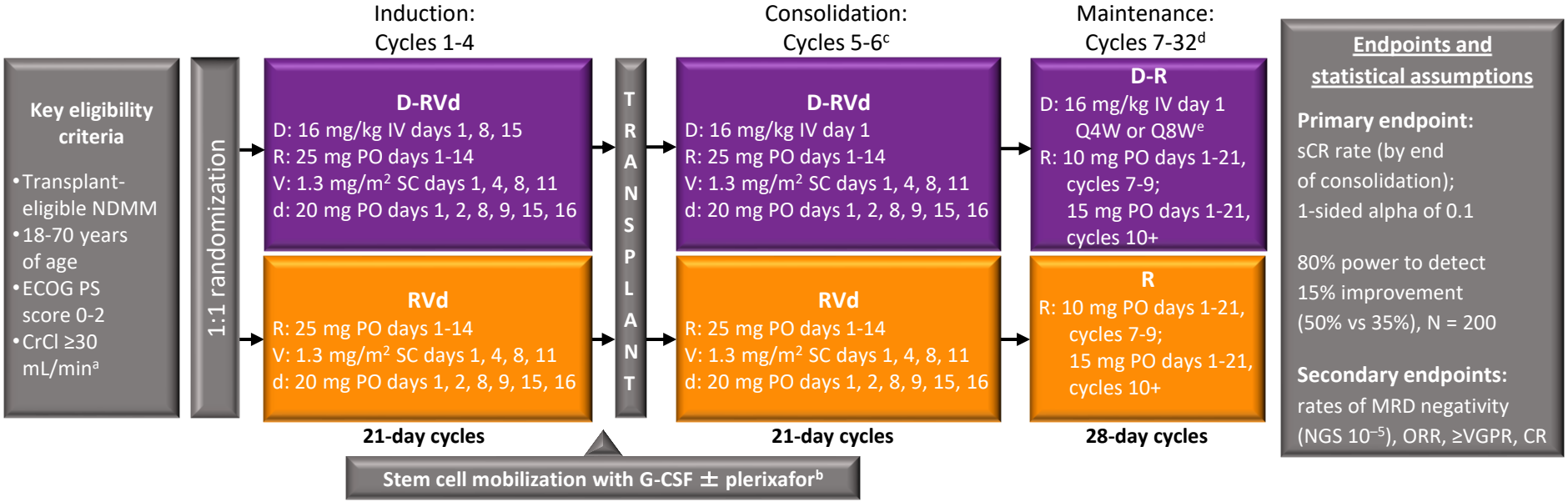




Moreau P, et al. *Immunotherapy.* 2021;13:143-154.

GRIFFIN: Randomized Phase II

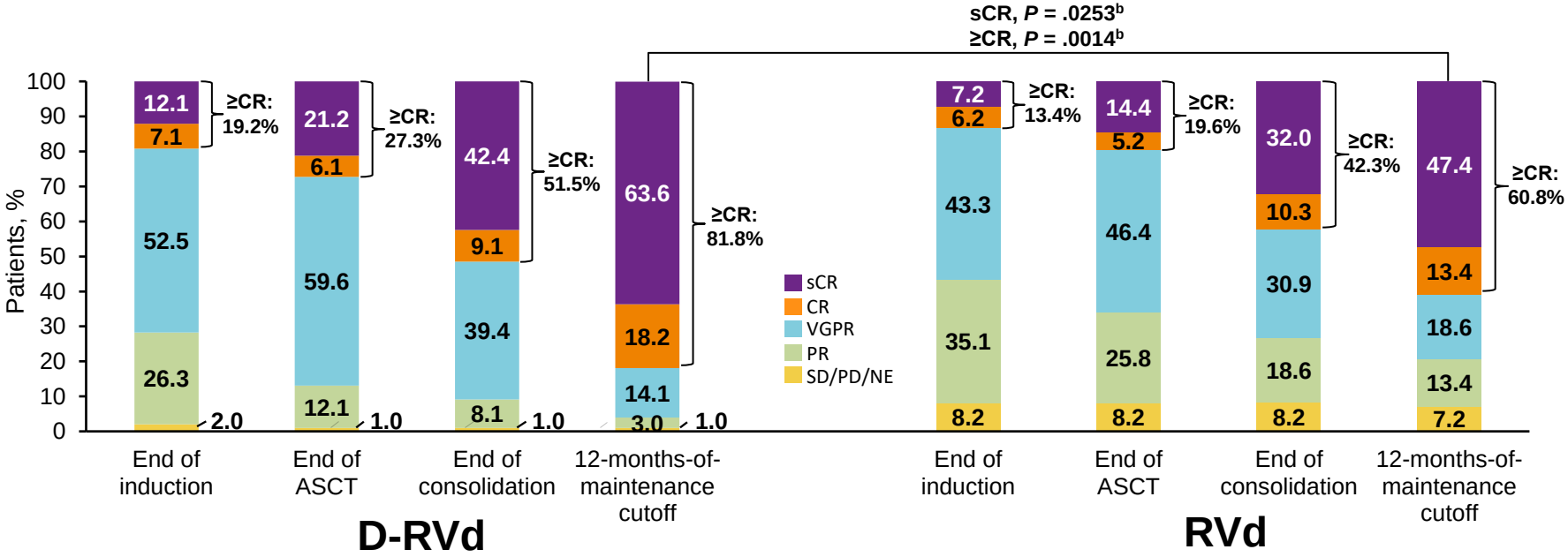
Phase II study of D-RVd vs RVd in transplant-eligible NDMM, 35 sites in the United States, with enrollment between December 2016 and April 2018



ECOG PS, Eastern Cooperative Oncology Group performance status; CrCl, creatinine clearance; IV, intravenous; PO, oral; G-CSF, granulocyte colony-stimulating factor; Q4W, every 4 weeks; Q8W, every 8 weeks; NGS, next-generation sequencing; ORR, overall response rate; VGPR, very good partial response; CR, complete response. [a]Lenalidomide dose adjustments were made for patients with CrCl ≤50 mL/min. [b]Cyclophosphamide-based mobilization was permitted if unsuccessful. [c]Consolidation was initiated 60 to 100 days posttransplant. [d]Patients who complete maintenance cycles 7 to 32 may continue single-agent lenalidomide thereafter. [e]Protocol Amendment 2 allowed for the option to dose daratumumab Q4W, on the basis of pharmacokinetic results from study SMM2001 (NCT02316106).

Voorhees P, et al. ASH 2019. Abstract 691. Oral presentation.

Responses Deepened Over Time[a]



- *Results for end of induction, ASCT, and consolidation are based on a median follow-up of 13.5 months at the primary analysis*
- *Median follow-up at 12-months-of-maintenance therapy cutoff was 27.4 months*

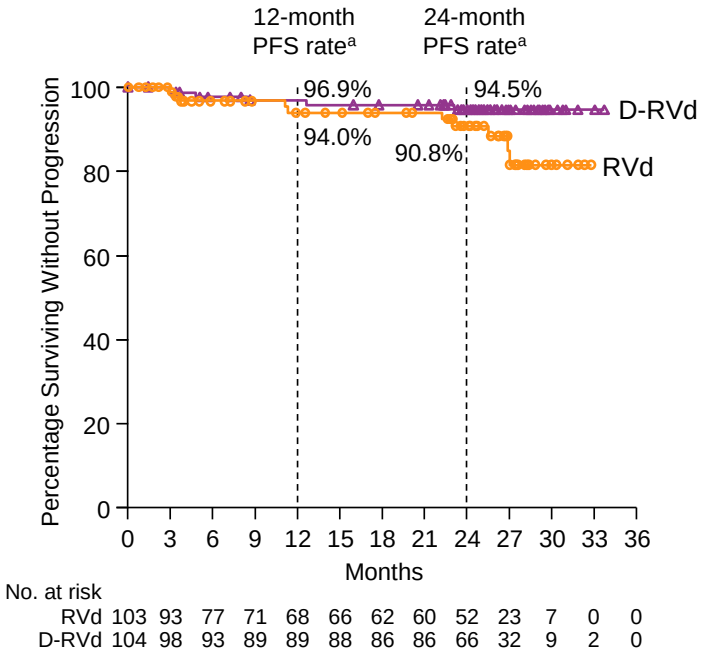
Response rates and depths were greater for D-RVd at all time points

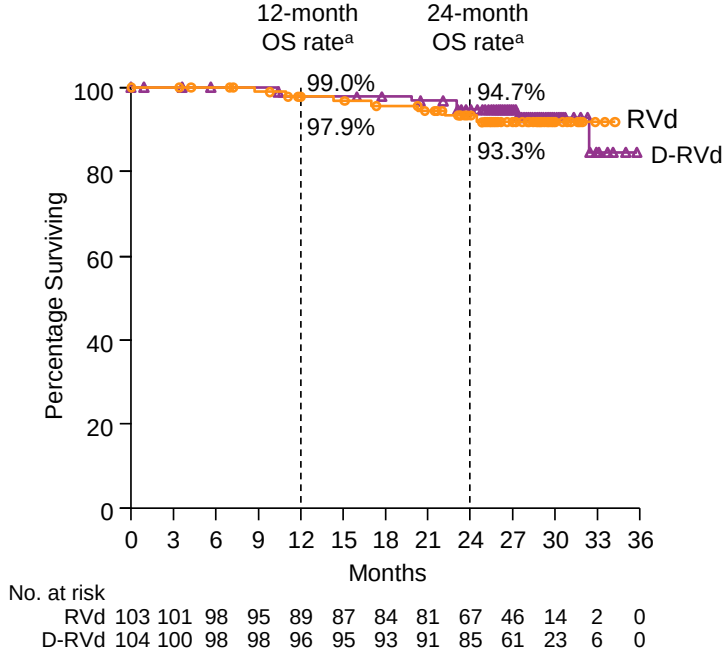
PR, partial response. SD/PD/NE, stable disease/progressive disease/not evaluable. [a]Data are shown for the response-evaluable population. [b]*P* values (2-sided) were calculated using the Cochran-Mantel-Haenszel chi-square test.

Voorhees P, et al. ASH 2019. Abstract 691. Oral presentation.

PFS and OS in the ITT Population

Median follow-up = 27.4 months



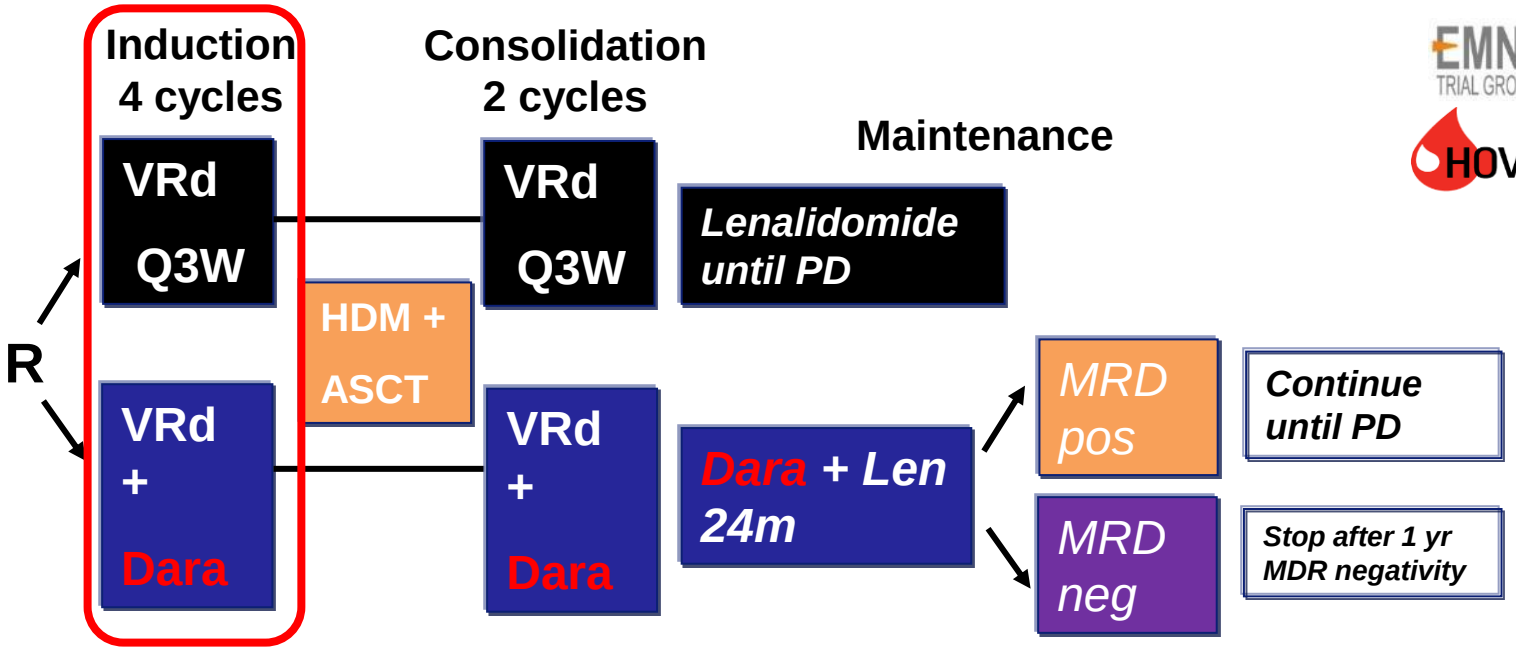


Median PFS and OS were not reached for D-RVd and RVd

OS, overall survival. [a]Kaplan-Meier estimate.

Voorhees P, et al. ASH 2019. Abstract 691. Oral presentation.

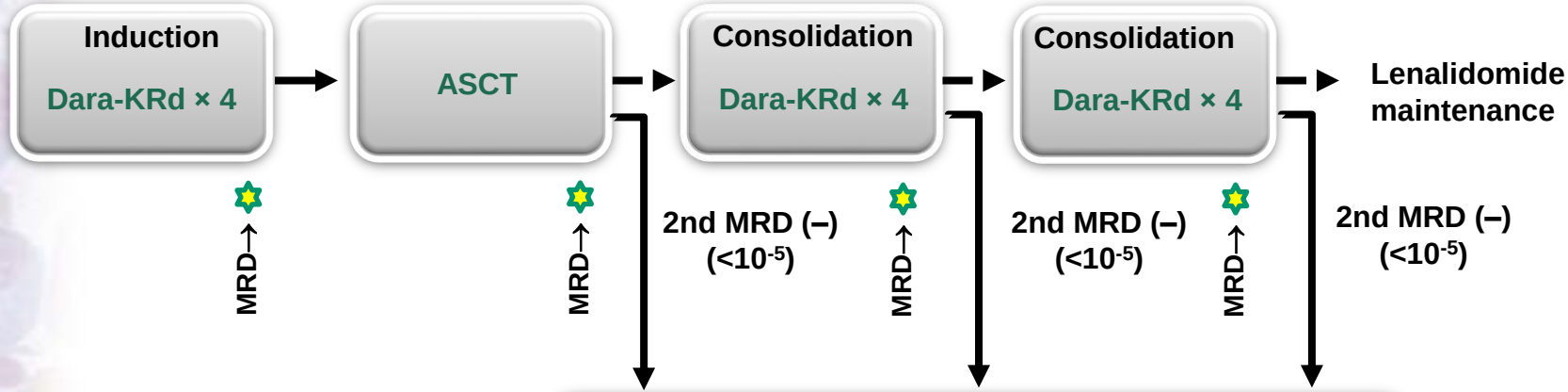
Daratumumab-VRd in ASCT-Eligible NDMM: *EMN017/HOVON158/MMY3014 Registration Trial*



- Primary endpoint: PFS
- Secondary endpoint: MRD 10^{-5} by NGS after consolidation
- Patients: NDMM, 18-70 yr, n = 640

PERSEUS; PI, P. Sonneveld.

MASTER Trial: Daratumumab + KRd: *Risk-Adapted, MRD-Guided Therapy*



Dara-KRd

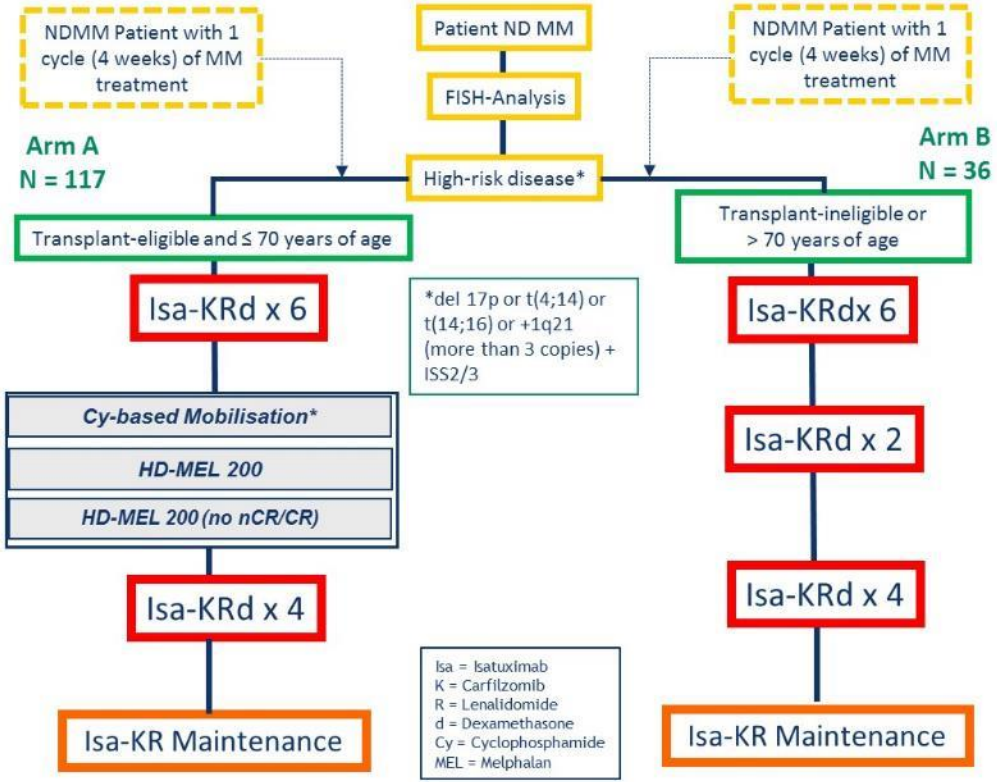
- Daratumumab 16 mg/m^2 days 1, 8, 15, 22 (days 1,15 C 3-6; day 1 C >6)
- Carfilzomib (20) 56 mg/m^2 days 1, 8, 15
- Lenalidomide 25 mg days 1-21
- Dexamethasone 40 mg PO days 1, 8, 15, 22

MRD assessment by NGS

First Risk-Adapted Therapy Trial for Newly Diagnosed Patients (the MASTER trial)

Costa L, et al. ASH 2019. Abstract 860.

Study Design – GMMG CONCEPT (NCT03104842)



Isa-KRd Induction
Cycle 1

Isatuximab	10 mg/kg	day 1, 8, 15, 22
Carfilzomib	20 mg/m²	day 1, 2
Carfilzomib	36 mg/m²	day 8, 9, 15, 16
Lenalidomide*	25 mg	day 1-21
Dexamethasone**	40 mg*	day 1, 8, 15, 22
28-day-cycle		

Isa-KRd Induction
Cycle 2-6

Isatuximab	10 mg/kg	day 1, 15
Carfilzomib	36 mg/m²	day 1, 2, 8, 9, 15, 16
Lenalidomide**	25 mg	day 1-21
Dexamethasone***	40 mg*	day 1, 8, 15, 22
28-day-cycle		

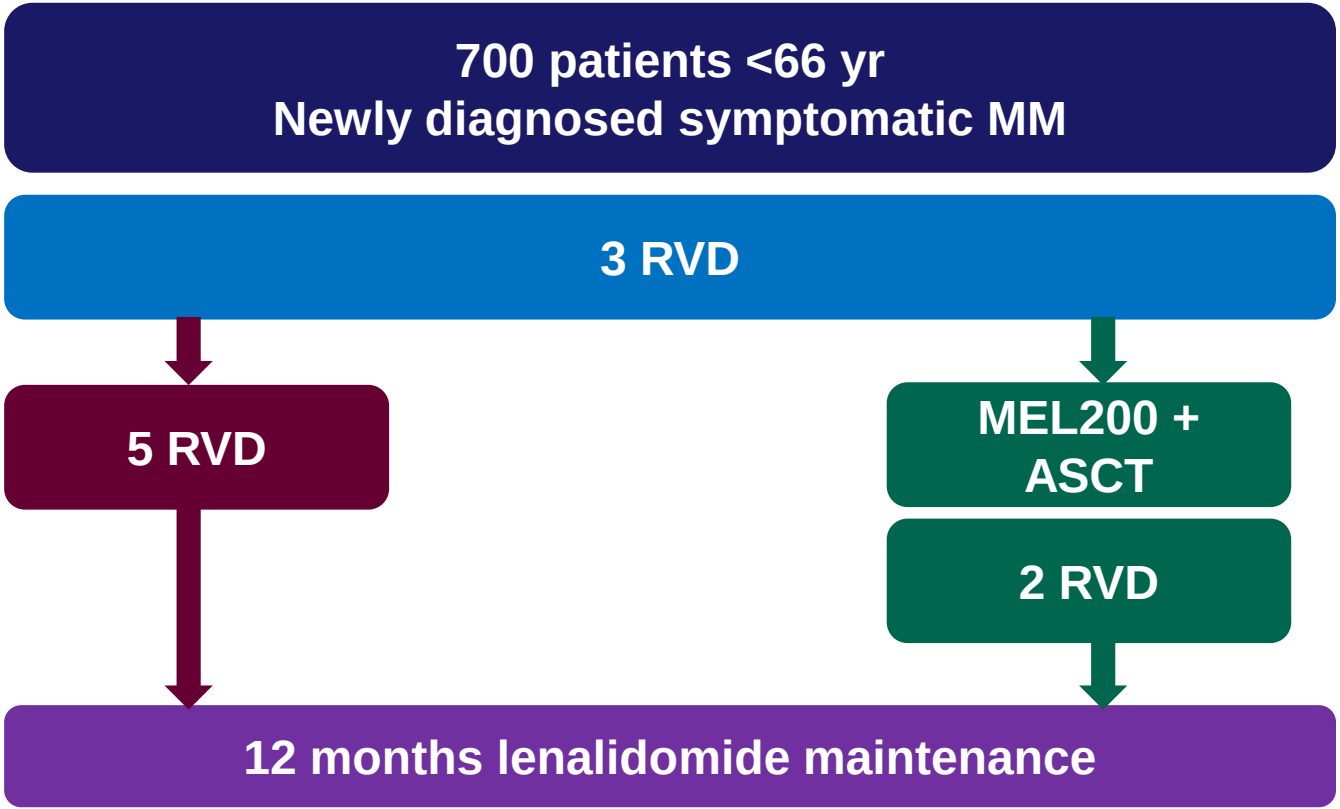
* Cy-based mobilisation was moved in an amendment to the time after 3 induction cycles
**Dose adaption of lenalidomide according to renal function
***20 mg in patients ≥75 years

Therapy for ND Transplant-Eligible Multiple Myeloma

ASCT

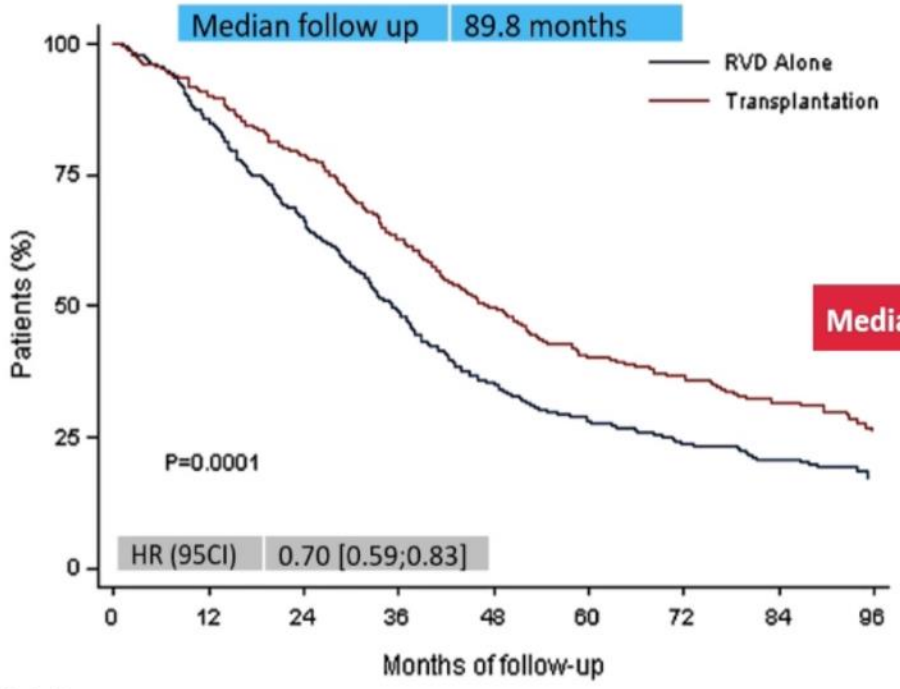
- ✓ **What is the best time for transplant?**
  Upfront or at relapse?

IFM DFCI 2009 Trial



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

Updated PFS (primary endpoint)



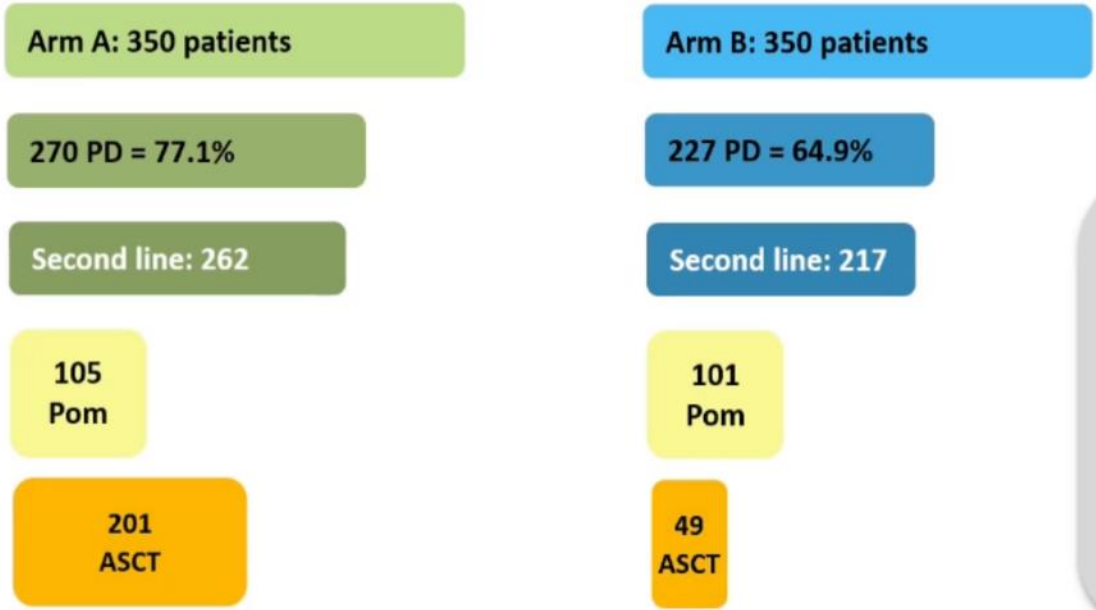
Median PFS 47.3 months (Transplantation, arm B)

Median PFS 35 months (RVD alone, arm A)

30% reduction in the risk of progression or death in patients receiving transplant

Perrot A, et al. ASH 2020. Oral presentation.

Relapse regimens

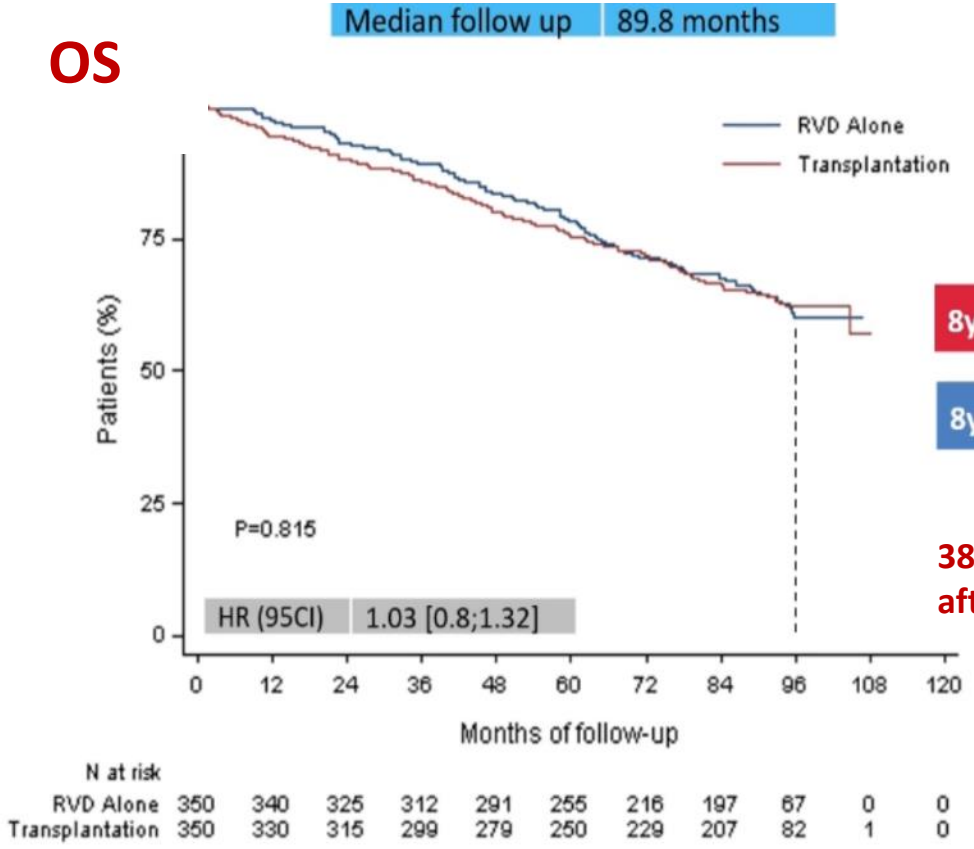


- 40 and 46% of patients who initiated a second line received pomalidomide
- Only 14 and 12 patients received carfilzomib and daratumumab-based regimens
- Others regimens: anthracyclines, alkylants, bendamustine

38% of the patients in arm B didn't need a second line
23% of the patients who relapsed and needed a second line in arm A didn't received a transplant

Perrot A, et al. ASH 2020. Oral presentation.

OS



8y-OS 62.2% (Transplantation, arm B)

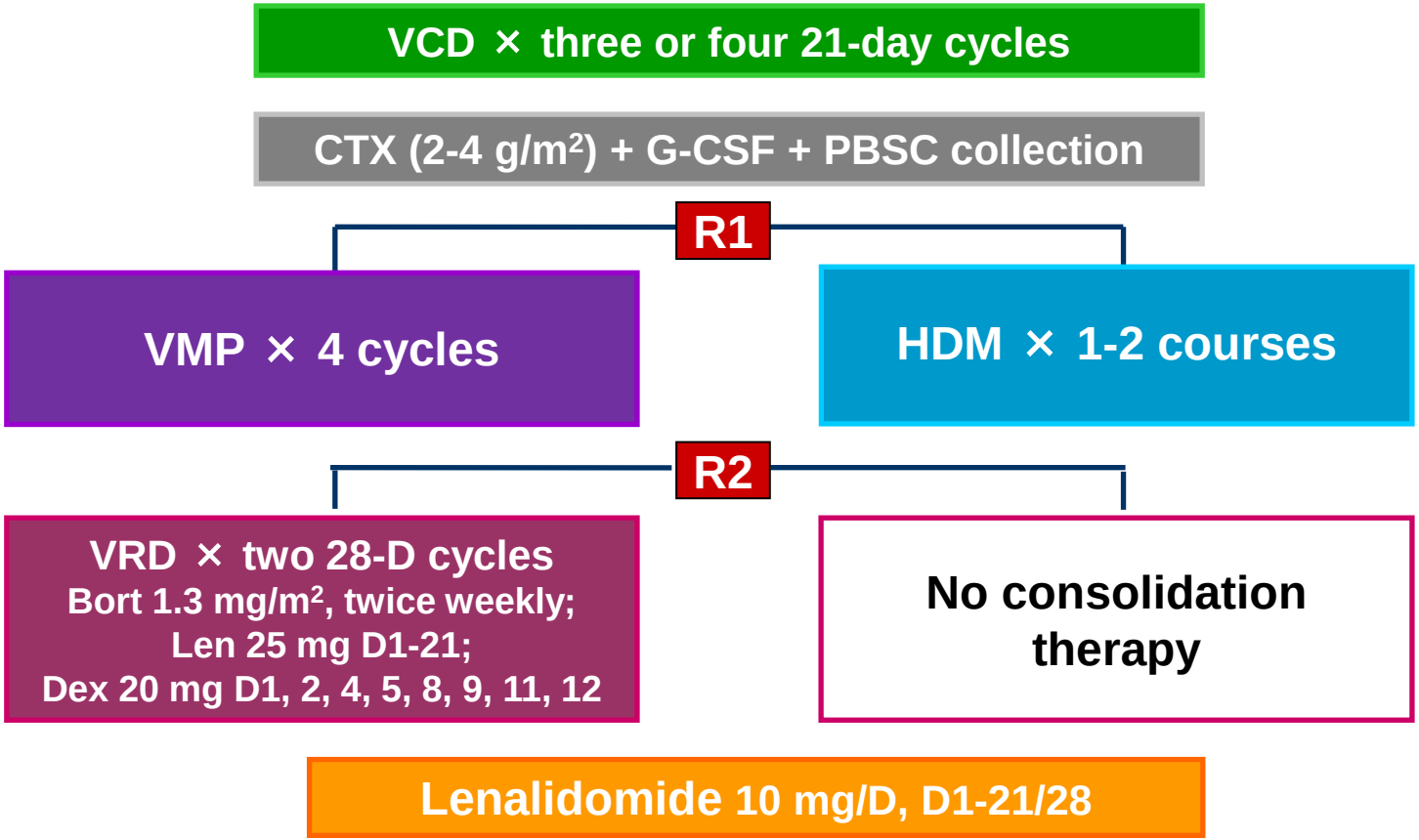
8y-OS 60.2% (RVD alone, arm A)

38% of patients in arm B/ASCT did not relapse after 8 years of follow-up

More than 60% of the patients in the two arms are alive after 8 years of follow-up

Perrot A, et al. ASH 2020. Oral presentation.

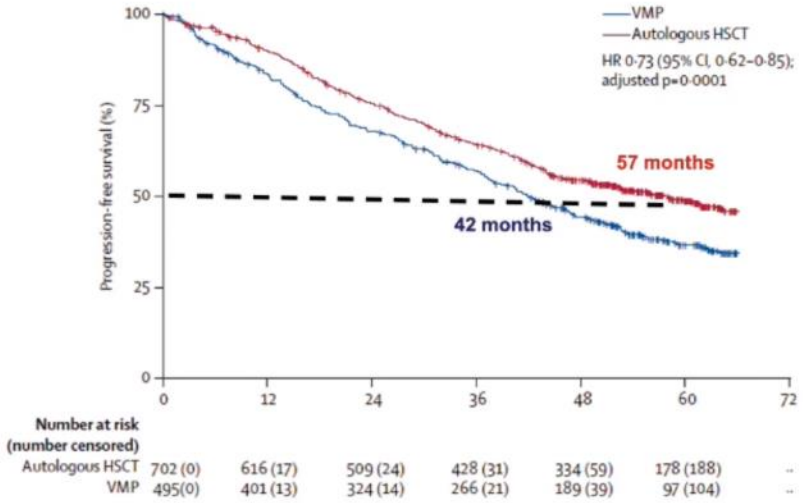
EMN02/HO95 MM Trial: Study Design

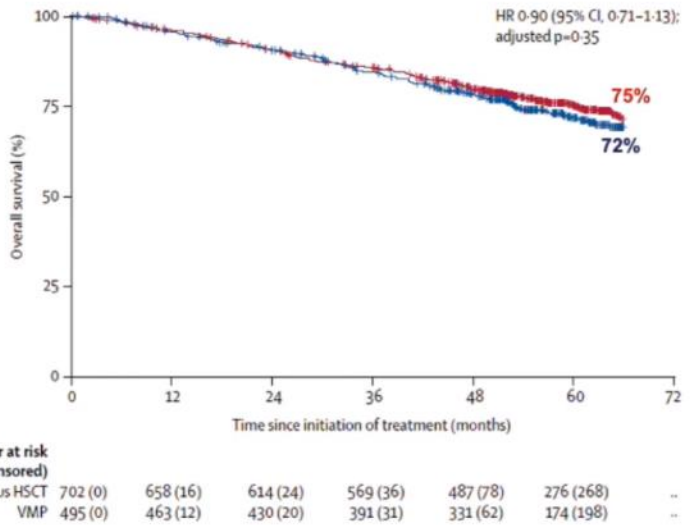


Cavo M, et al. *Lancet Haematol.* 2020;7:e456-e468.

EMN02/HO95

Outcome analyses (median follow-up: 60.5 months)

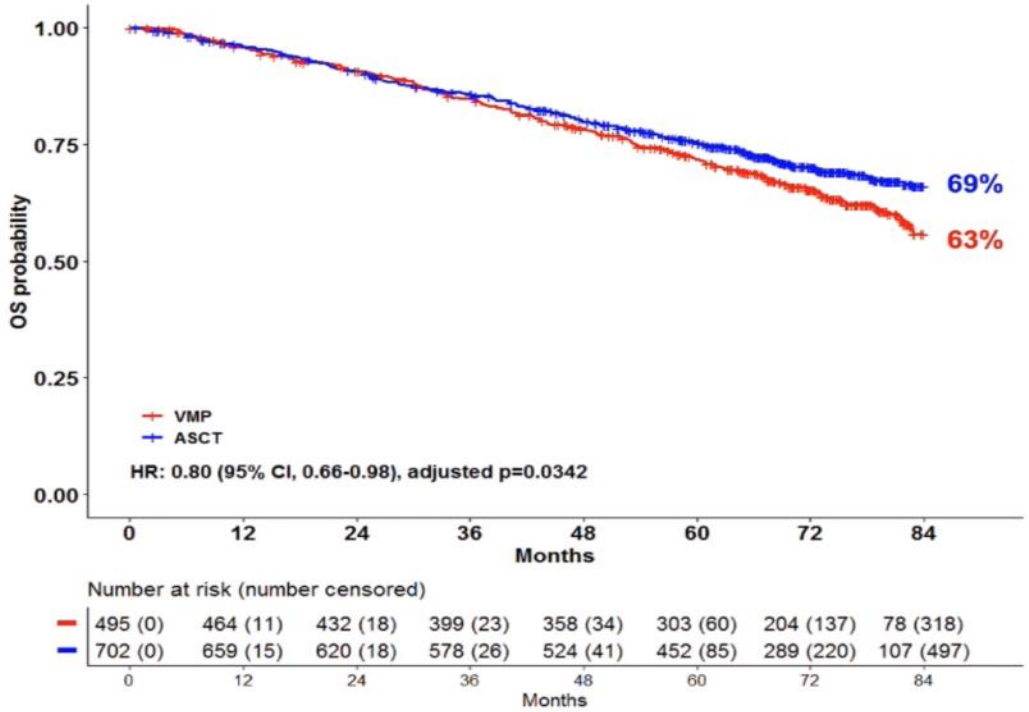




Cavo M, et al. *Lancet Haematol.* 2020;7:e456-e468.

EMN02/HO95

Overall survival (extended follow-up: 75 months)

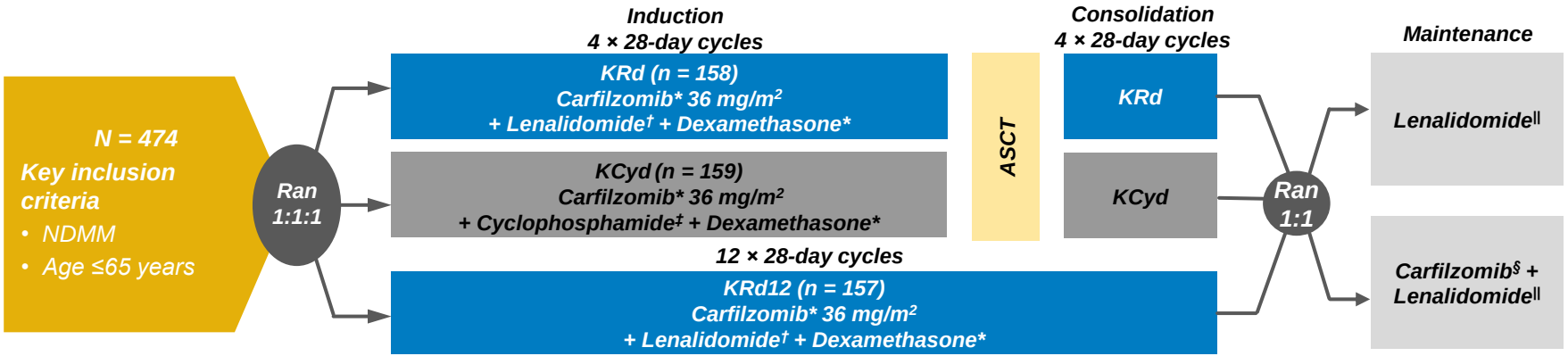


Cavo M, et al. ASH 2020. Abstract 142.

FORTE Trial: Study Design[1-3]

KRd-ASCT, KRd12, or KCyd-ASCT in NDMM: PFS and OS Analysis

- *The FORTE study previously demonstrated that KRd with or without ASCT led to deep responses and improved outcomes vs KCyd with ASCT in patients with NDMM[1,2]*
- *This study evaluated PFS of 3 induction and 2 maintenance therapies in patients with NDMM[3]*
- *The efficacy in different subgroups of patients and safety of the maintenance phase was also evaluated[3]*



Primary endpoint: *PFS*
Select secondary endpoints: *OS, safety*

*Carfilzomib and dexamethasone 20 mg administered on days 1, 2, 8, 9, 15, and 16. †Lenalidomide 25 mg administered on days 1–21. ‡Cyclophosphamide 300 mg/m² administered on days 1, 8, and 15. §Carfilzomib administered at 36 mg/m² on days 1, 2, 15, and 16, subsequently amended to 70 mg/m² on days 1 and 15 for up to 2 years. ‖Lenalidomide administered at 10 mg on days 1–21 every 28 days until progression.
ASCT, autologous stem cell transplant; KCyd, carfilzomib, cyclophosphamide, dexamethasone; KR, carfilzomib, lenalidomide; KRd, carfilzomib, lenalidomide, dexamethasone; KRd12, 12 cycles of KRd; NDMM, newly diagnosed multiple myeloma; OS, overall survival; PFS, progression free survival; R, lenalidomide; Ran, randomized.

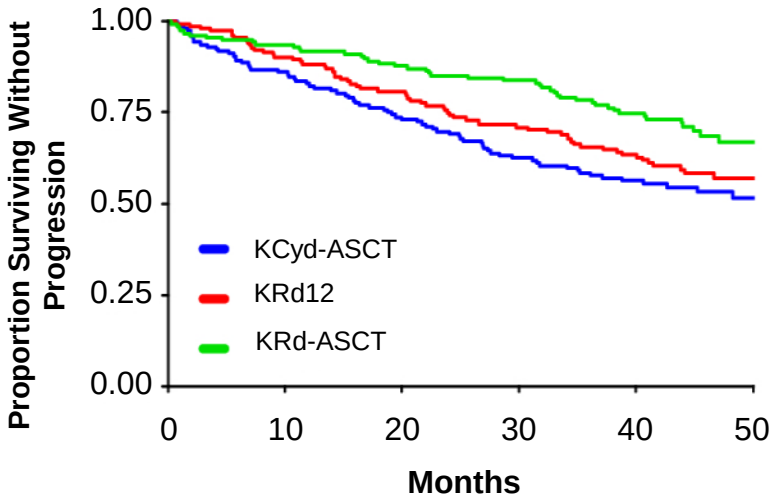
1. Gay F, et al. Presented at: ASCO Annual Meeting; May 31–June 4, 2019; Chicago, IL. Abstract 8002. 2. Gay F, et al. Presented at: 24th Congress of the EHA; June 13−16, 2019; Amsterdam, The Netherlands. Abstract S872. 3. Gay F, et al. Presented at 62nd ASH Annual Meeting and Exposition; Dec 5–8, 2020; Virtual. Abstract 141.

Efficacy: Induction*

FORTE Trial (KRd-ASCT, KRd12, or KCyd-ASCT in NDMM): PFS and OS Analysis

PFS From First Randomization

Median follow-up 45 mo



Median PFS: NR

Median PFS: 57 months

Median PFS: 53 months

	HR	*P*
KRd-ASCT vs KCyd-ASCT	0.53	<.001
KRd-ASCT vs KRd12	0.64	.023
KRd12 vs KCyd-ASCT	0.82	.262

Treatment	3-Year OS, %
KRd-ASCT	90
KRd12	90
KCyd-ASCT	83

Treatment with KRd-ASCT significantly improved PFS

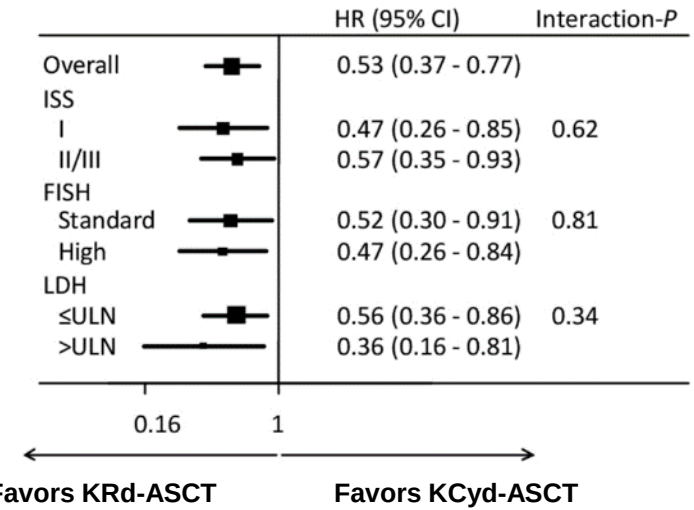
*Data cutoff June 30, 2020; median follow-up 45 mo.
ASCT, autologous stem cell transplant; FISH, fluorescence in situ hybridization; H, high; HR, hazard ratio; ISS, International Staging System; KCyd, carfilzomib, cyclophosphamide, dexamethasone; KRd, carfilzomib, lenalidomide, dexamethasone; KRd12, 12 cycles of KRd; L, low; LDH, lactate dehydrogenase; NR, not reached; OS, overall survival; PFS, progression-free survival; R1, first randomization.
Gay F, et al. Presented at 62nd ASH Annual Meeting and Exposition; Dec 5–8, 2020; Virtual. Abstract 141.

Data, comments, and/or conclusions on this slide are based on the congress abstract and represent authors' findings and views that are independent of Amgen.

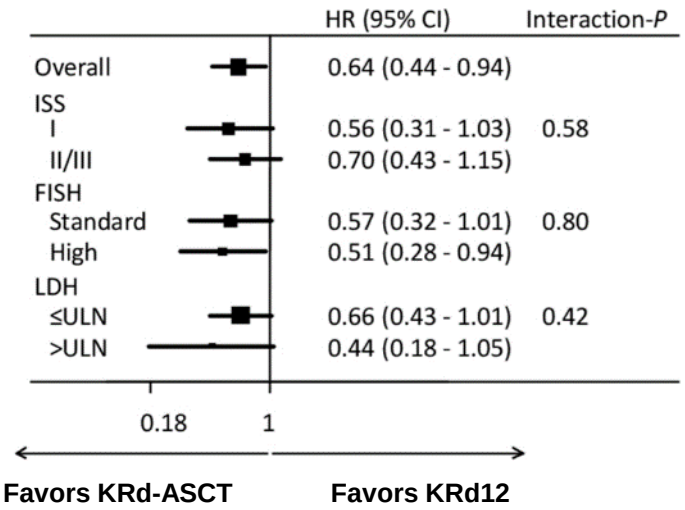
Efficacy: Induction*

FORTE Trial (KRd-ASCT, KRd12, or KCyd-ASCT in NDMM): PFS and OS Analysis

PFS From R1: KRd-ASCT vs KCyd-ASCT



PFS From R1: KRd-ASCT vs KRd12



PFS benefit with KRd-ASCT treatment was observed in most subgroups compared with both KRd12 and KCyd-ASCT

*Data cutoff June 30, 2020; median follow-up 45 mo.

ASCT, autologous stem cell transplant; FISH, fluorescence in situ hybridization; HR, hazard ratio; ISS, International Staging System; KCyd, carfilzomib, cyclophosphamide, dexamethasone; KRd, carfilzomib, lenalidomide, dexamethasone; KRd12, 12 cycles of KRd; LDH, lactate dehydrogenase; OS, overall survival; PFS, progression-free survival; R1, first randomization; ULN, upper limit of normal.

Gay F, et al. Presented at 62nd ASH Annual Meeting and Exposition; Dec 5–8, 2020; Virtual. Abstract 141.

Conclusions

Conclusions

- ✓ ***Young patients:*** ASCT upfront remains standard of care
- ✓ ***Induction:***

  Three-drug–based combo

  VRd > VTd > VCd

  KRd?

  Three drugs + monoclonal antibody (D-VTd is approved)

  Number of cycles for induction: 4 to 6 cycles

- ✓ ***Conditioning regimen:*** Mel 200 is the standard of care

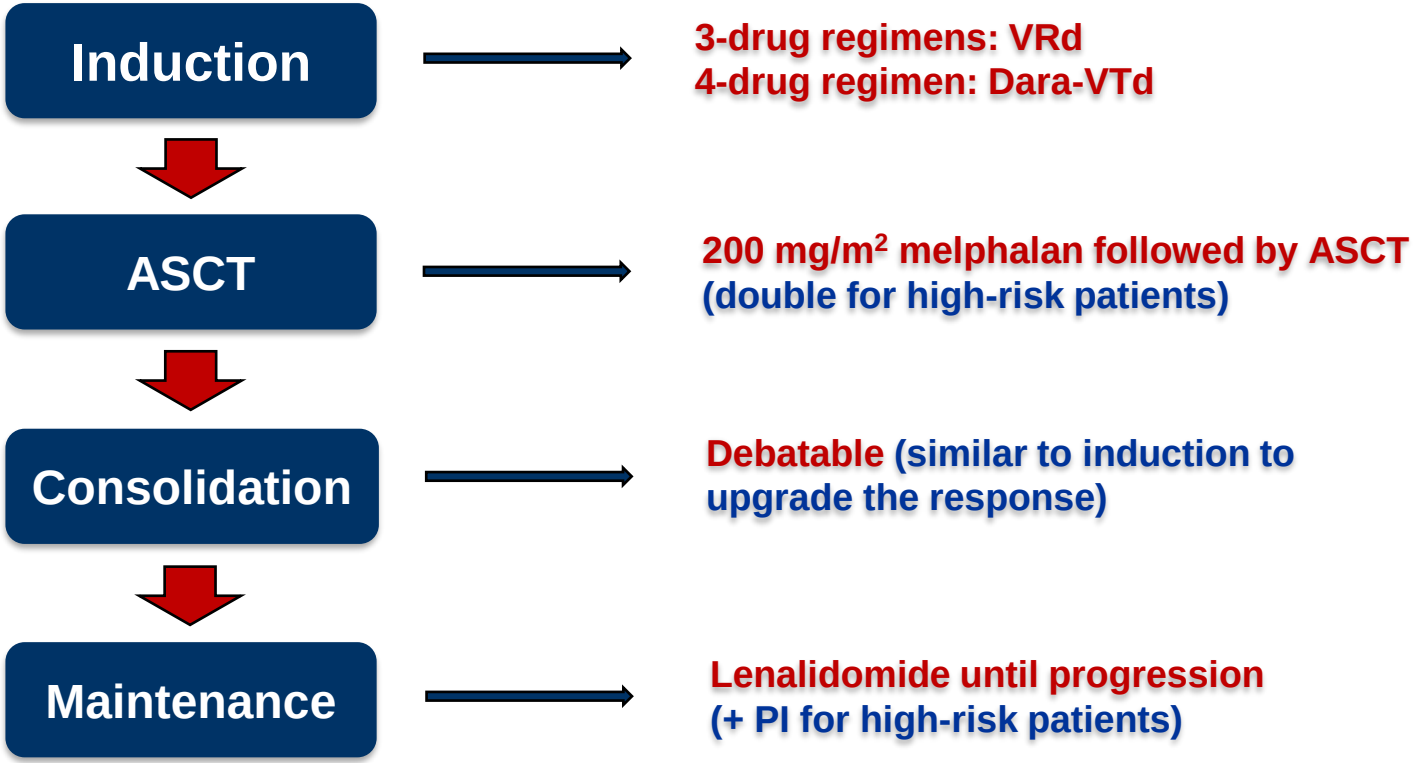
QUESTION FOR THE AUDIENCE

Provided that you had access, what do you think would be the best choice for the induction regimen for patients eligible for ASCT? **[repeated question]**

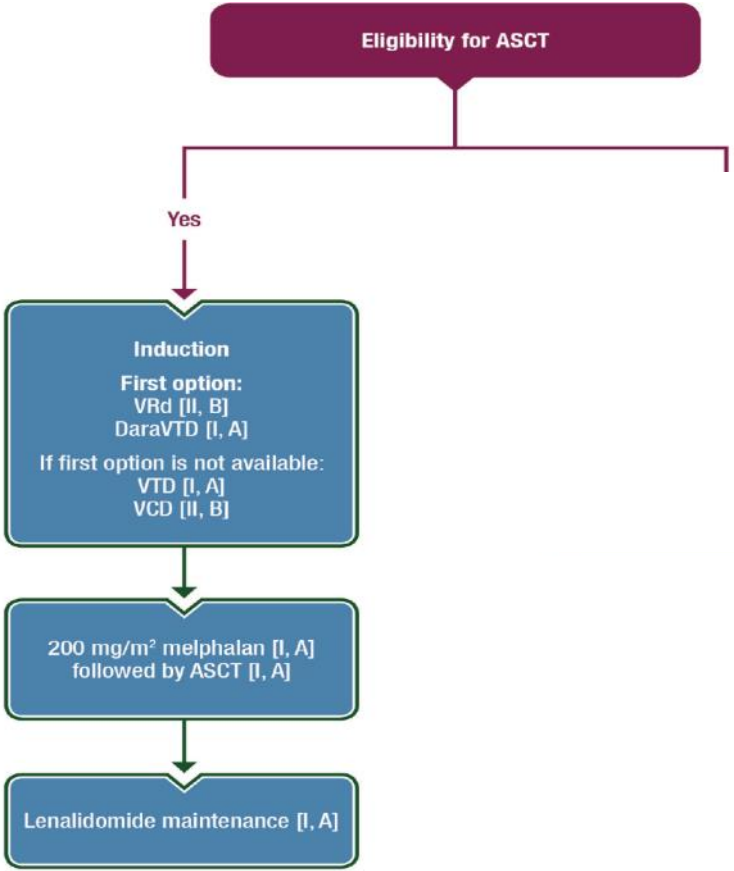
a. Dara-VTd
b. Dara-VRd
c. VRd
d. VTd
e. VCd

Treatment Paradigm for Transplant-Eligible MM Patients

My current opinion for private patients in Brazil



EHA-ESMO Guideline 2021



Dimopoulos MA, et al. *Ann Oncol.* 2021;32:309-322.

THANK YOU!!!

hungria@dialdata.com.br

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Discussion

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Break

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Optimal Use of Consolidation and Maintenance Therapy

Jorge Vela-Ojeda, MD, PhD

APTITUDE HEALTH®

Optimal Use of Consolidation and Maintenance Therapy

Jorge Vela Ojeda, MD, PhD
Head of Hematology Department
La Raza Medical Center
IMSS, Mexico City

Consolidation Treatment in Multiple Myeloma

- Consolidation treatment is generally a short-term treatment (2–4 cycles of combination therapies) given after ASCT
- The aim is to improve the depth of response obtained with the previous treatment phases, before maintenance therapy, in order to prolong PFS
- Although many trials support the use of consolidation to maintain response achieved after induction therapy and to improve patient survival, prolonged exposure to new drugs might increase toxicities

Consolidation Treatment in Multiple Myeloma

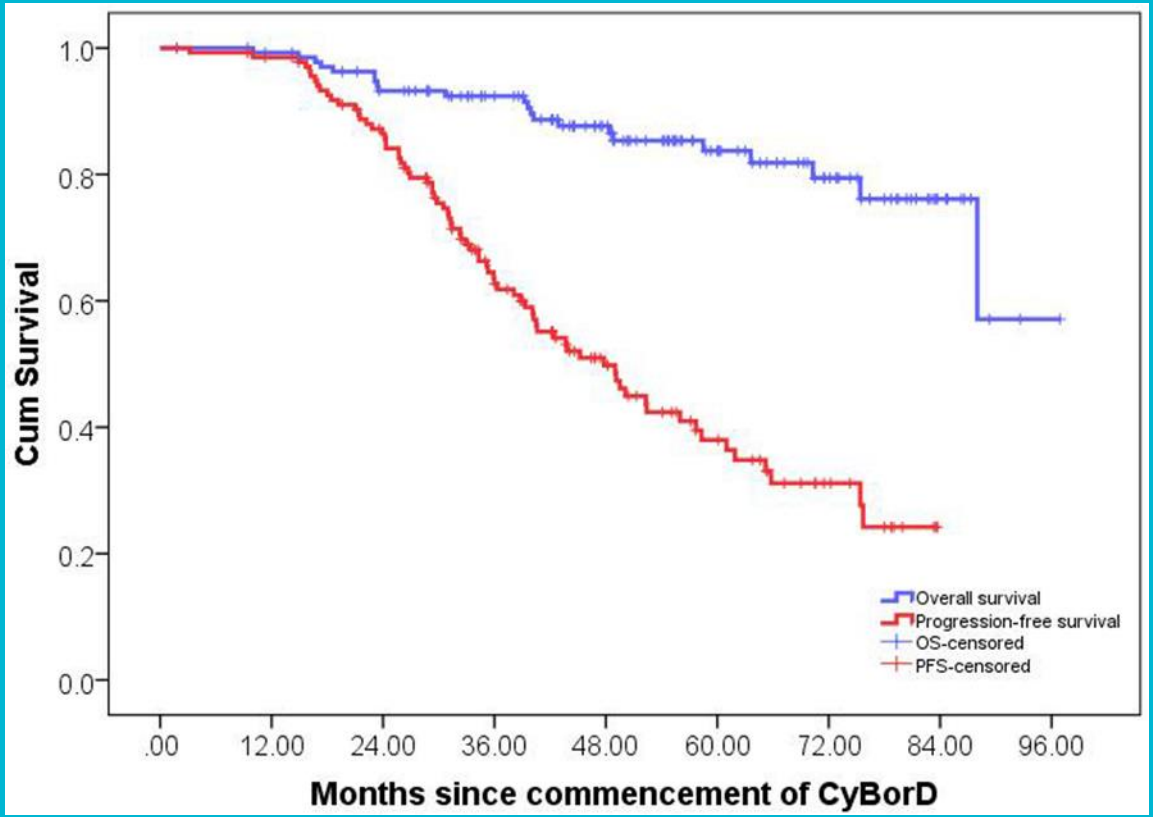
Table 1. Studies of Post-ASCT Novel Agent–Based Consolidation Therapy: Impact on Outcomes

Reference	Type of Trial	Treatment Scheme	No. of Patients	Response Rate	EFS or PFS	OS
Bortezomib-based						
Cavo[7]	Phase III	VTD *v* TD consolidation	160 *v* 161	CR/nCR pre consolidation: 63% *v* 55% (*P* = NS) CR/nCR post consolidation: 73% *v* 61% (*P* = .020)	3-yr PFS 60% *v* 48% *P* = .042	3-yr OS 90% *v* 88% *P* = NS
Mellqvist[28]	Phase III	Bortezomib consolidation *v* no consolidation	187 *v* 183	≥VGPR pre consolidation: 40% *v* 39% (*P* = NS) ≥VGPR post consolidation: 71% *v* 57% (*P* = .009)	Median PFS 27 m *v* 20 m *P* = .05	3-yr OS 80% *v* 80% *P* = NS
Leleu[29]	Retrospective comparison	VTd consolidation *v* no consolidation	121 *v* 96	CR post consolidation: 52% *v* 30% (*P* = .001)	Median TTP not reached *v* 25 m (*P* = .005)	4-yr OS 84% *v* 91% *P* = NS
Ladetto[30]	Phase II	VTD consolidation	39	CR pre VTD: 15% CR post VTD: 49%	Median PFS 60 m	3-yr OS 89%
Lenalidomide-based						
Attal[31]	Phase III	Len consolidation + Len maintenance *v* Len consolidation + placebo	307 *v* 307	CR pre consolidation: 58% CR post consolidation: 69% *P* <.001	NR after consolidation	NR after consolidation
Roussel[32]	Phase II	RVD consolidation	31	sCR/CR pre VRD: 42% sCR/CR post VRD: 48%	NR	NR

Abbreviations: VTD, bortezomib, thalidomide, dexamethasone; TD, thalidomide, dexamethasone; CR, complete response; nCR, near complete response; PFS, progression-free survival; OS, overall survival; ns, not significant; VGPR, very good partial response; VTd, bortezomib, thalidomide, low dose dexamethasone; TTP, time to progression; Len, lenalidomide; NR, not reported; VRD, bortezomib, lenalidomide, dexamethasone sCR, stringent complete response; VRD, bortezomib, lenalidomide, dexamethasone.

Cavo M, et al. *Semin Oncol.* 2013;40:610-617.

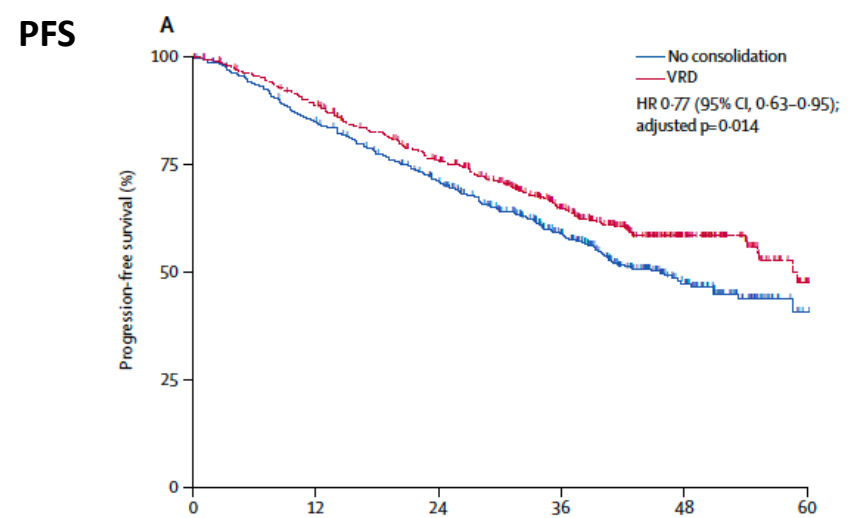
CyBorD Consolidation Treatment in Multiple Myeloma



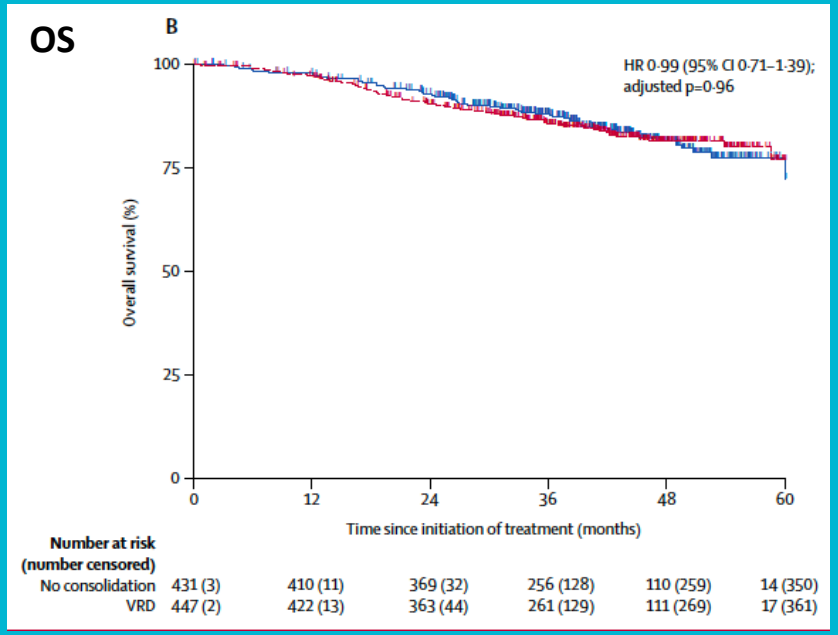
Ting Tan SA, et al. *Blood*. 2020;136(suppl 1): abstract 33.

VRD Consolidation Therapy vs No Consolidation

PFS

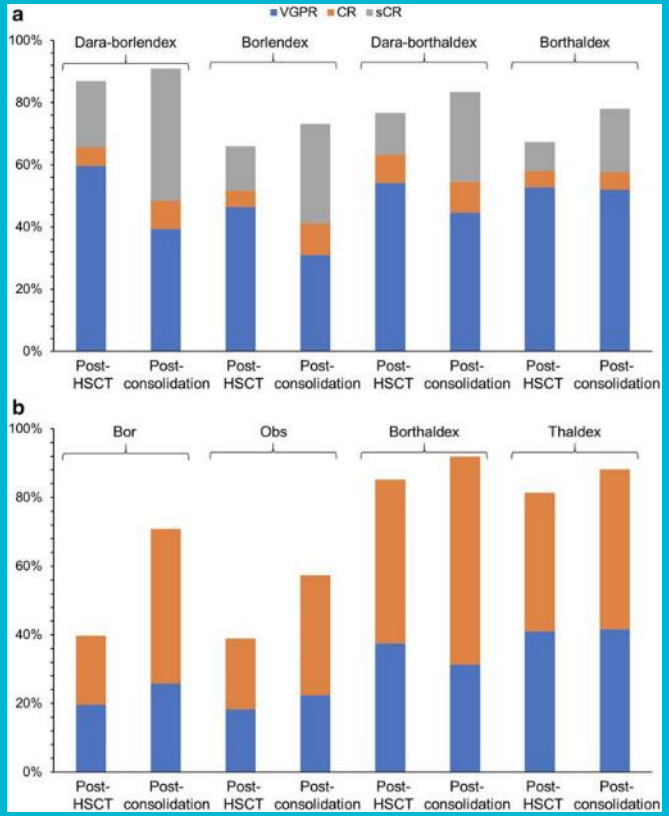


OS



Cavo M, et al. Lan*cet Haematol*. 2020;7:e456-e468.

Responses After Auto-HSCT and Consolidation for Different Comparisons: A Systematic Review



Gagelmann N, et al. *Ann Hematol*. 2021;100:405-419.

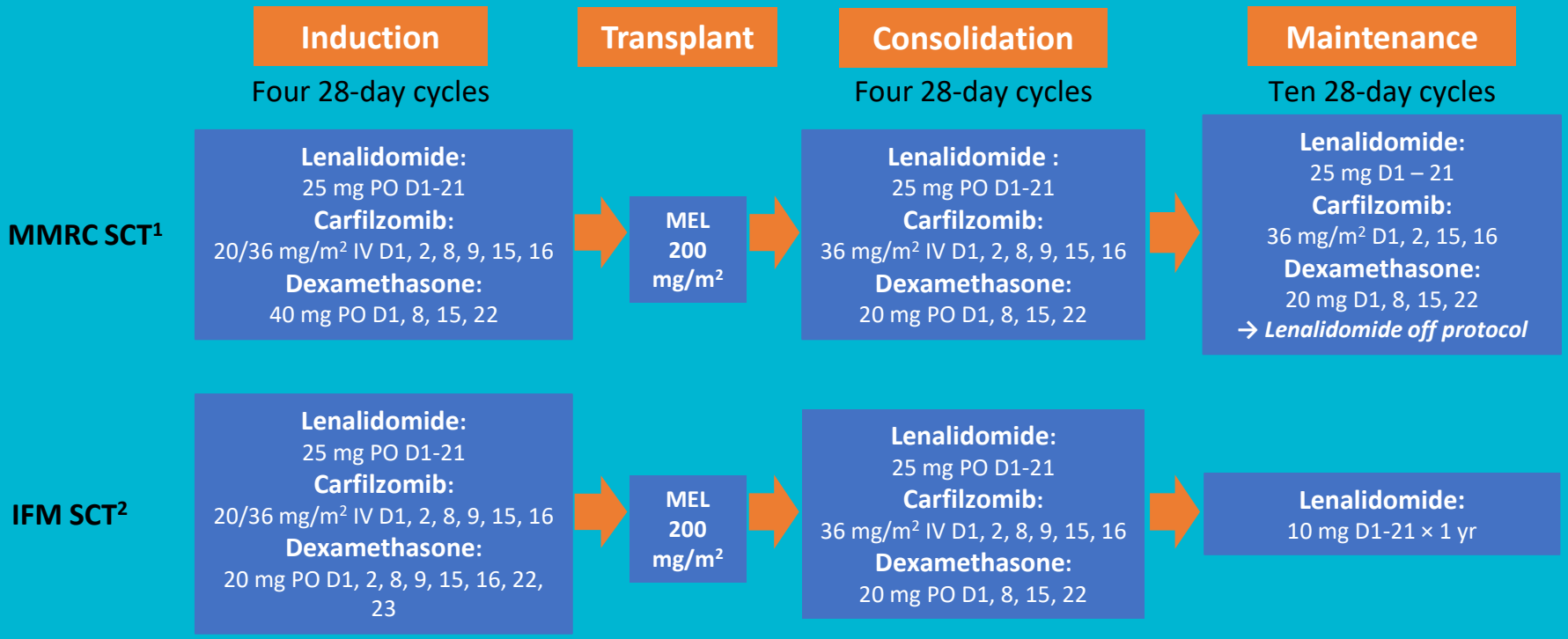
Consolidation Treatment in High-Risk Multiple Myeloma

Table 3 Outcome in high-risk multiple myeloma

Study	Regimen	Definition of high-risk MM	Outcome
Cavo et al. [18], Tacchetti et al. [35]	Borthaldex	ISS stage III	OS: HR, 0.52 ($P = 0.06$)
		t(4;14) and/or del(17p)	PFS/OS: HR, 0.45 ($P < 0.001$)/0.57 ($P = 0.03$)
Sonneveld et al. [42], Cavo et al. [22]	Borlendex	del(17p) and/or t(4;14) and/or t(14;16)	PFS: HR, 1.06
Stadtmauer et al. [27], Hari et al. [43]	Borlendex	Presence of high beta 2-microglobulin (> 5.5 mg/L) or cytogenetics (t(4;14), t(14;20), t(14;16), del(17p), del(13) detected by standard cytogenetics only, or aneuploidy)	5-y OS: 76% (66–84) vs. 62% (52–69); 5-y PFS: 37% (26–48) vs. 32% (24–40)
Moreau et al. [28]	Dara-borthaldex	ISS stage III	sCR/PFS: OR, 1.07 (0.54–2.12)/HR, 0.66 (0.32–1.39)
		t(4;14) and/or del(17p)	sCR/PFS: OR, 0.83 (0.42–1.66)/HR, 0.67 (0.35–1.30)
Voorhees et al. [29]	Dara-borlendex	ISS stage III	sCR/MRD−: 1.56 (0.34–7.14)/0.42 (0.09–1.92)
		t(4;14) and/or del(17p) and/or t(14;16)	sCR/MRD−: 1.92 (0.34–11.11)/0.67 (0.14–3.13)

Gagelmann N, et al. *Ann Hematol*. 2021;100:405-419.

KRd for Newly Diagnosed MM: Phase II Trials



1. Zimmerman TM, et al. ASH 2016. Abstract 675; 2. Moreau P, et al. ASH 2016. Abstract 1142.

KRd for Newly Diagnosed MM: Phase II Results

Outcome, %	Post-induction		Post-ASCT		Post-consolidation	
	MMRC SCT[1] (n = 76)	IFM SCT[2] (n = 46)	MMRC SCT[1] (n = 71)	IFM SCT[2] (n = 42)	MMRC SCT[1] (n = 70)	IFM SCT[2] (n = 42)
MRD neg by flow	NR	63	NR	81	86	89
MRD neg by NGS					64	59
CR/sCR	16	25.5	27	45	67	69
≥VGPR	73	83.5	90	88	91	92.5

MMRC SCT trial[1]

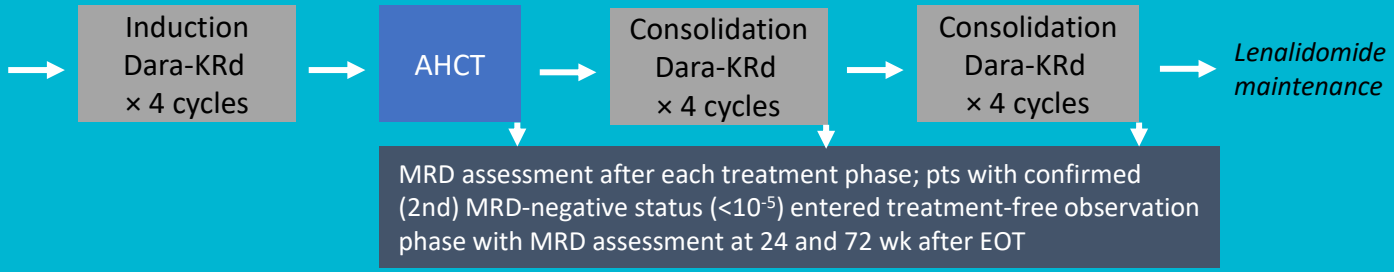
- 3-yr PFS in standard-risk vs high-risk MM: 89% vs 80%
- 3-yr OS: 96% vs 94%

1. Zimmerman TM, et al. ASH 2016. Abstract 675; 2. Moreau P, et al. ASH 2016. Abstract 1142.

MASTER: Study Design

- Multicenter, single-arm phase II trial

Untreated* patients with NDMM and measurable disease, ECOG PS 0-2, CrCl ≥40 mL/min, without significant cardiopulmonary disease or current/prior malignancy (N = 81)†

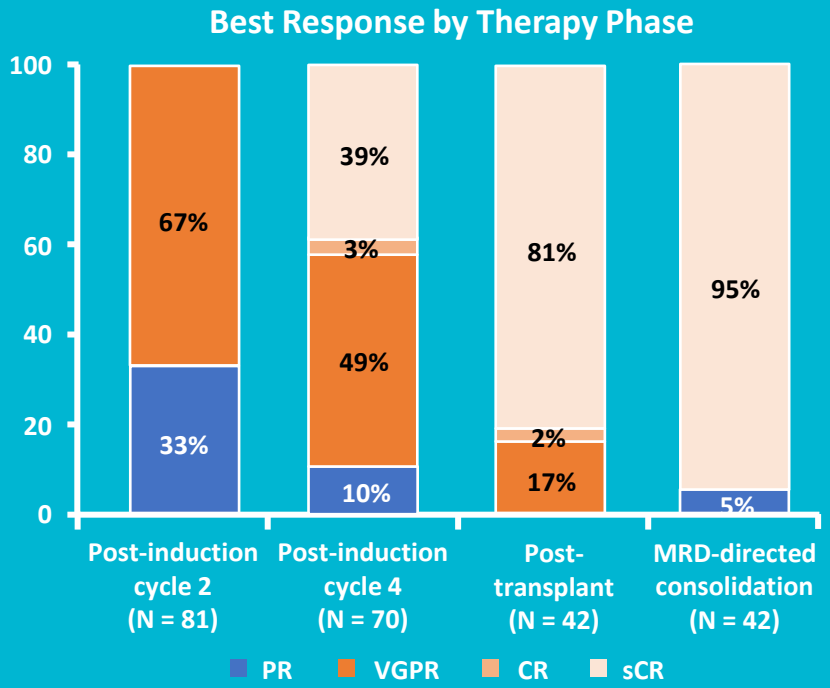


Dara-KRd dosing: daratumumab 16 mg/m² on days 1, 8, 15, 22 (days 1, 15 of cycles 3-6; day 1 cycle >6); carfilzomib 56 mg/m² days 1, 8, 15; lenalidomide 25 mg days 1-21; dexamethasone 40 mg PO days 1, 8, 15, 22. *One VCD cycle permitted. †Planned recruitment N = 123.

- Primary endpoint: MRD-negative remission (<10^{-5}) on NGS assay in pts receiving induction, AHCT, and response-adapted consolidation
- Secondary endpoints: safety, imaging frequency plus remission, MRD status post-AHCT, IMWG response, loss of MRD negativity in pts with no maintenance therapy
- Exploratory endpoint: MRD-negative rates on NGS assay (threshold <10^{-6})

Costa L, et al. ASH 2019. Abstract 860.

MASTER: Best Response by Treatment Phase

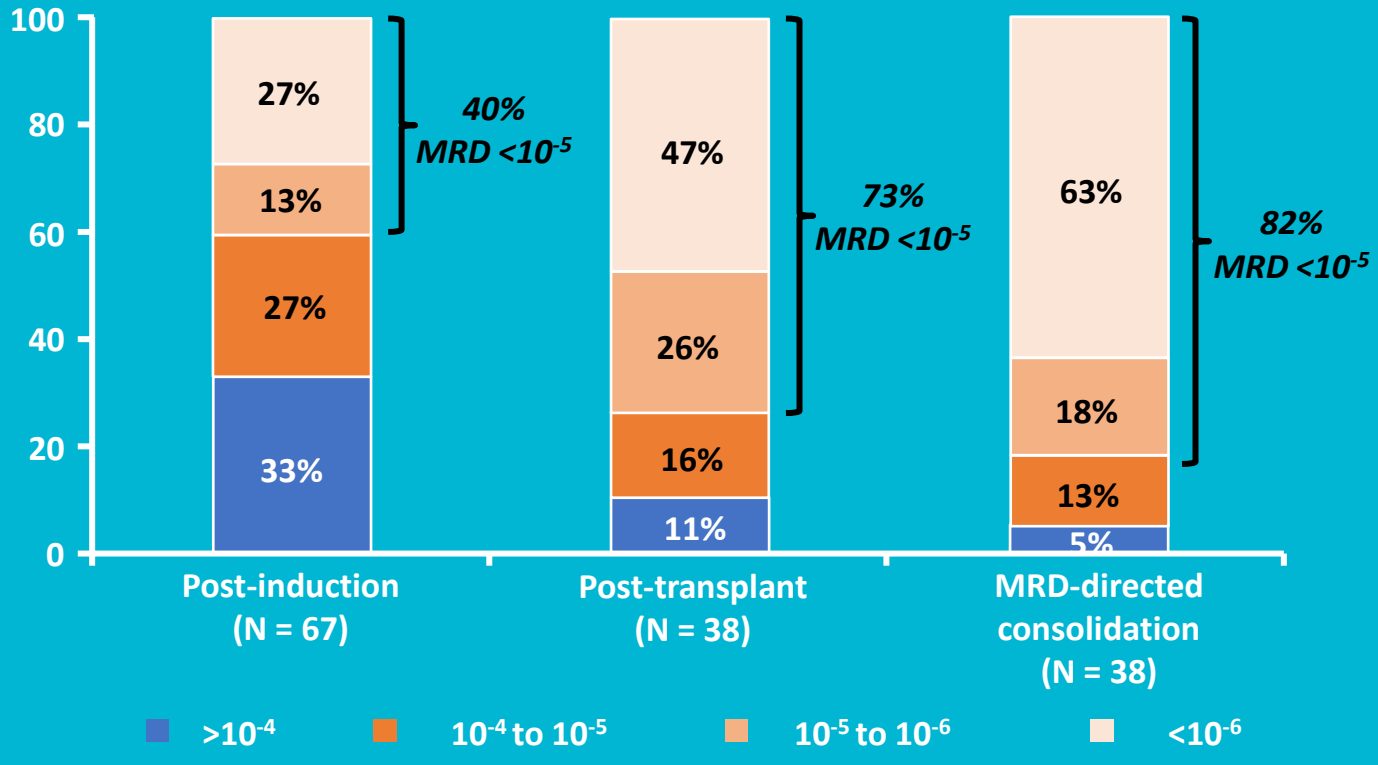


sCR, % (n)	Post-induction	Post-transplant	MRD-Based Consolidation
All patients	39 (70)	81 (42)	95 (42)
Standard-risk patients	44 (50)	79 (29)	97 (29)
High-risk patients [t(4;14), t(14;16), or del17p]	25 (20)	85 (13)	91 (13)

- n = 27 (n= 19 standard risk, n = 7 high risk) achieved MRD-negative status and entered observation phase; no relapse or MRD positivity at median follow-up of 4.9 months

Costa L, et al. ASH 2019. Abstract 860.

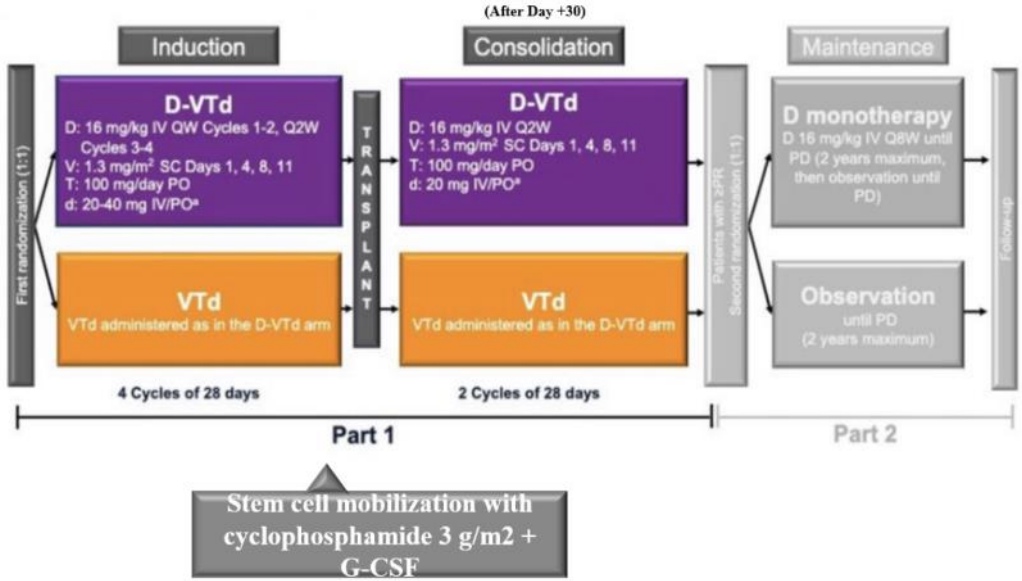
MASTER: MRD Response by Treatment Phase



Costa L, et al. ASH 2019. Abstract 860.

Phase III CASSIOPEIA Trial: VTD ± Daratumumab in NDMM in SCT Eligible

- 1,085 NDMM
- ASCT eligible
- Median age 58 (22-65)
- ECOG 0-2
- GFR ≥40 mL/min
- Transaminases<2.5xULN
- 16% were high risk t(4;14) or del17p



Primary end point:
-sCR rate after consolidation

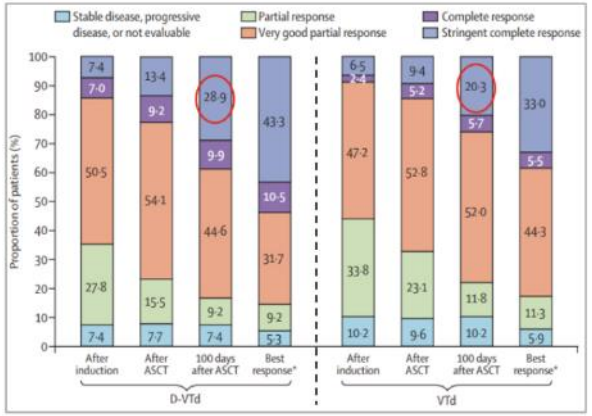
Secondary outcomes:
-ORR
-PFS
-OS
-MRD (NGF/NGS 10^{-5})
-Duration of response

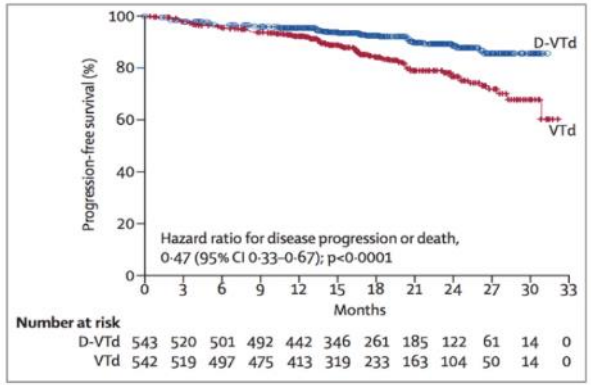
Moreau, et al. *Lancet.* 2019;394:29-39.

CASSIOPEIA: VTD ± Daratumumab Efficacy

sCR + CR: 53.8% vs 38.5%

sCR rate 29% vs 20% (P=0.001)



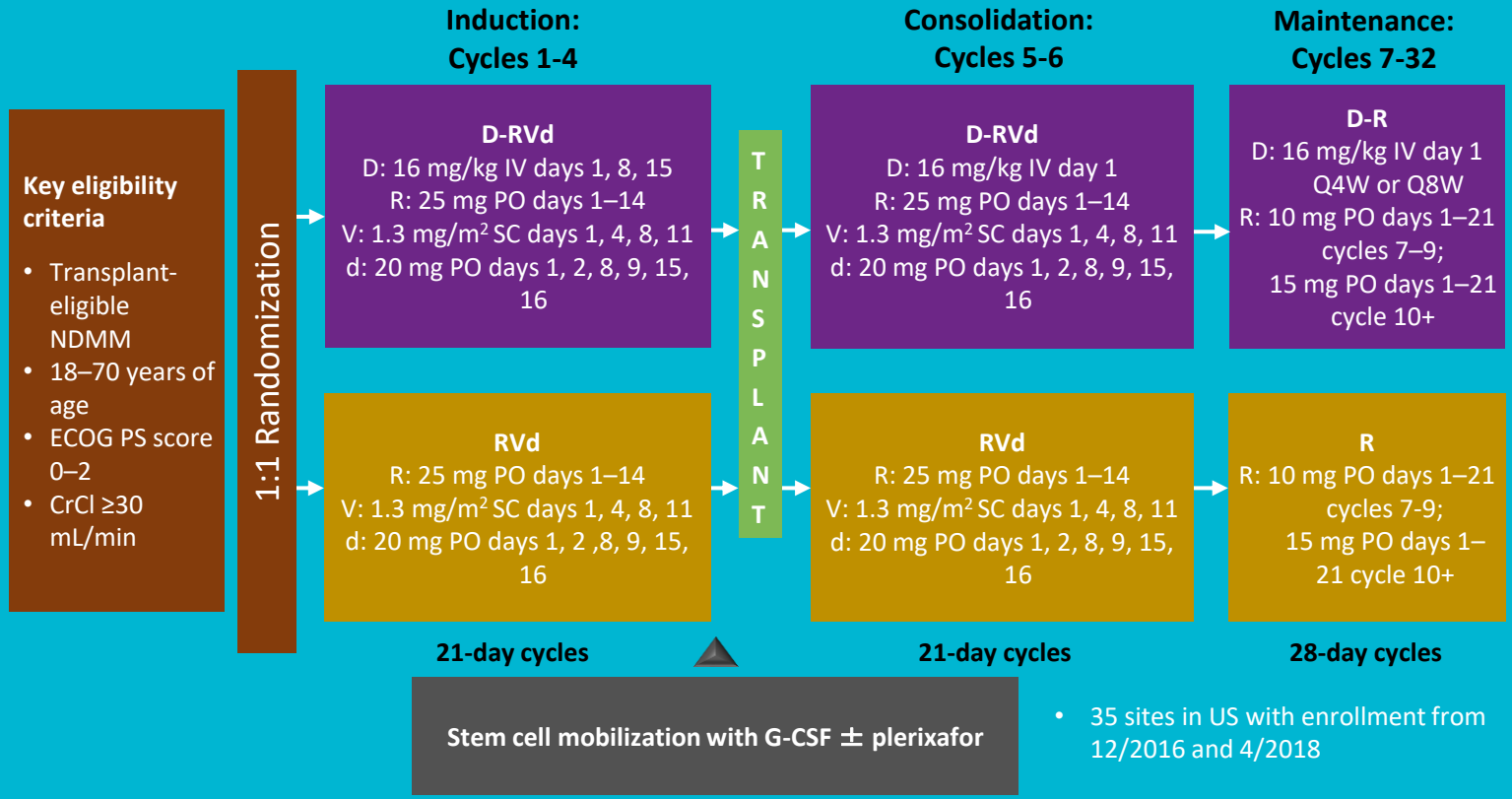


MRD-negative rates after ASCT:

Arm	NGF (P<.0001)	NGS (P<.0001)
D-VTd	64%	57%
VTD	44%	37%

Moreau, et al. *Lancet.* 2019;394:29-39.

Randomized Phase II GRIFFIN Study: RVd + Daratumumab in ASCT-Eligible Patients[1]



Endpoints and statistical assumptions

Primary endpoint:
sCR rate (by end of consolidation);
1-sided alpha of 0.1

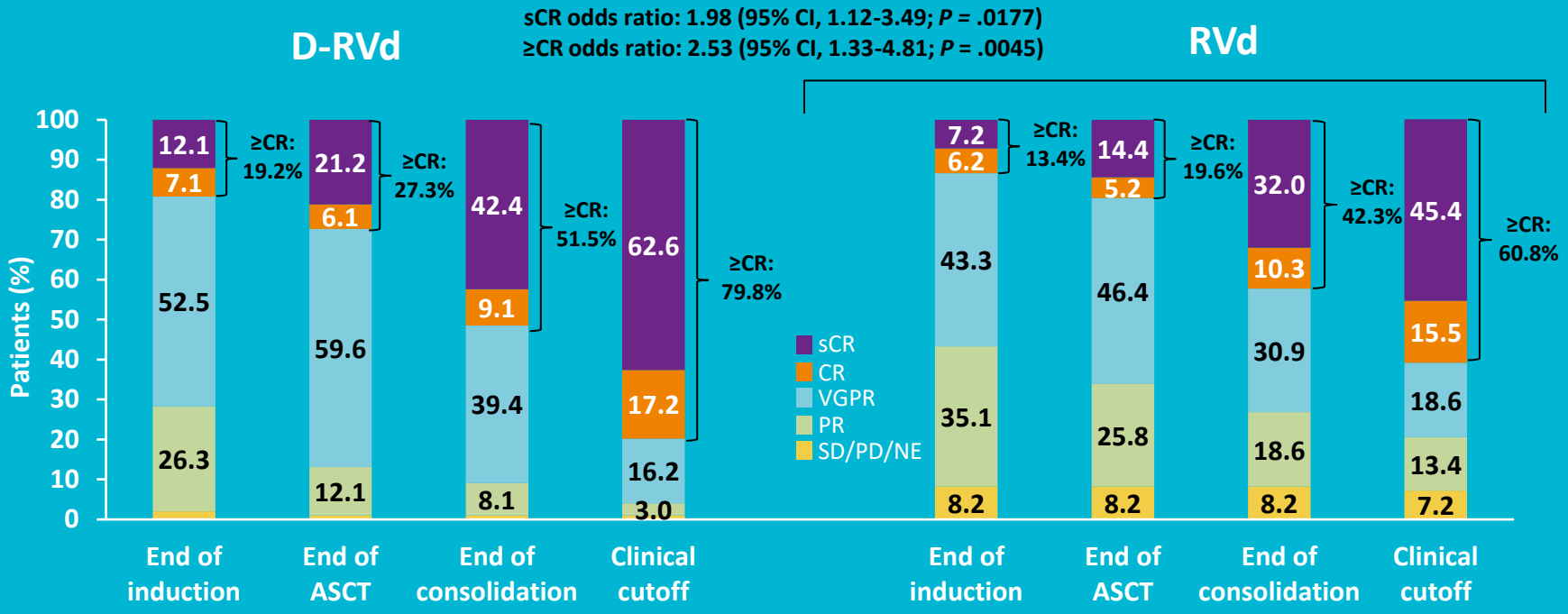
80% power to detect 15% improvement
(50% vs 35%), N = 200

Secondary endpoints:
rates of MRD negativity (measured by clonoSEQ; NGS 10^{-5}), CR, ORR, ≥VGPR

- 35 sites in US with enrollment from 12/2016 and 4/2018

Voorhees PM, et al. *Blood*. 2020;136:936-945.

GRIFFIN: Responses Deepened Over Time



Response rates and depths were greater for D-RVd at all time points

Voorhees PM, et al. *Blood*. 2020;136:936-945.

Post-consolidation MRD Negativity

MRD-Negative Status (10^{-5}),* n (%)	D-RVd	RVd	Odds Ratio (95% CI)	*P* Value†
In ITT population				
MRD negative regardless of response	46/104 (**44.2**)	15/103 (**14.6**)	4.70 (2.38-9.28)	<.0001
MRD negative with CR or better	30/104 (**28.8**)	10/103 (**9.7**)	3.73 (1.71-8.16)	.0007
In patients achieving CR or better	30/51 (**58.8**)	10/41 (**24.4**)	4.65 (1.76-12.28)	.0014
In patients who received ASCT	45/94 (**47.9**)	14/78 (**17.9**)	4.31 (2.10-8.85)	<.0001

D-RVd improved MRD negativity (10^{-5}) rates at the end of consolidation

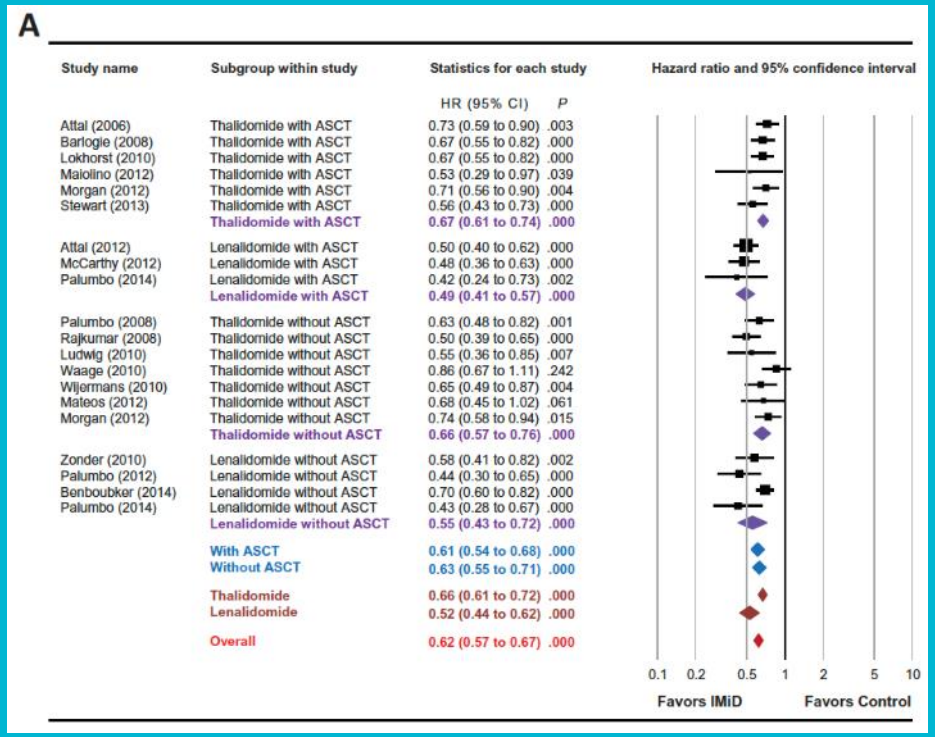
*The threshold of MRD negativity was defined as 1 tumor cell per 10^5 white cells. MRD status is based on assessment of bone marrow aspirates by next-generation sequencing in accordance with International Myeloma Working Group criteria. MRD assessments occurred in patients who had both baseline (with clone identified/calibrated) and post-baseline MRD (with negative, positive, or indeterminate result) samples taken (D-RVd, n = 71; RVd, n = 55). Patients with a missing or inconclusive assessment were considered MRD positive. †*P* values were calculated from the Fisher's exact test.

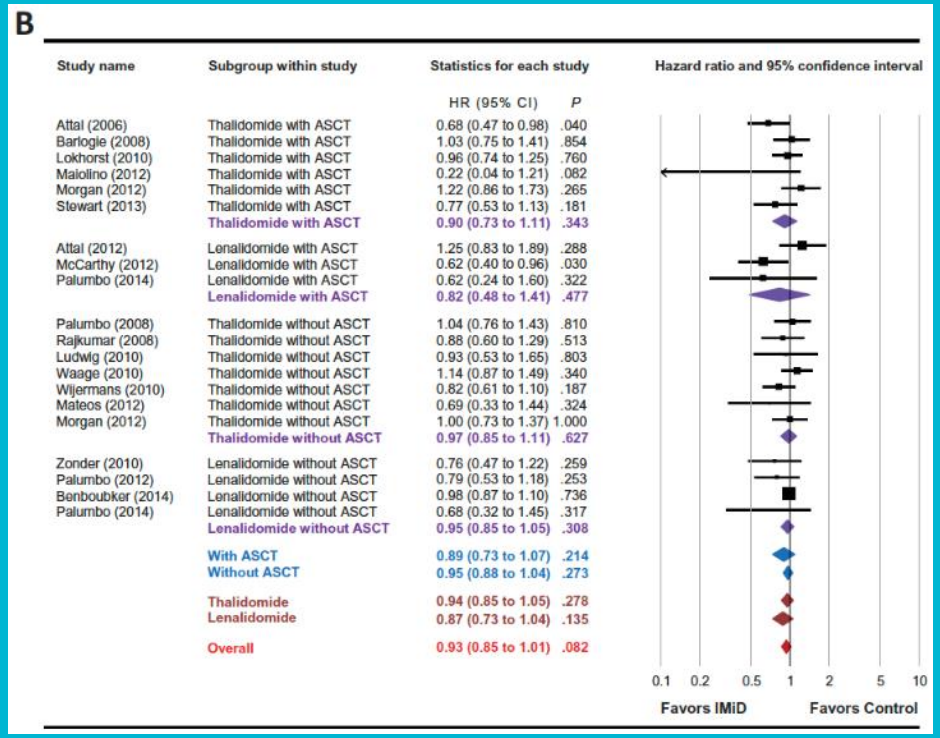
Quality of Evidence in Post-transplant Maintenance Therapy

	Lenalidomide	Bortezomib	Ixazomib
Phase III trials	CALGB [55] IFM [56] GIMEMA [50] Myeloma XI [57]	HOVON-65/GMMG-HD4* [74, 75] PETHEMA^ [77]	TOURMALINE-MM3 [81]
Meta-analyses	McCarthy et al [58] Gay et al^ [80]	Gay et al^ [80]	
Observational studies	Connect registry [59]		
Retrospective studies		Mayo Clinic Analysis [78] Duke University analysis [84] GMMG trials [79]	

Morè S, et al. *Expert Rev Hematol*. 2020;13:351-362.

IMiDs as Maintenance in Myeloma





Wang Y, et al. *J Natl Cancer Inst*. 2016;108:djv342.

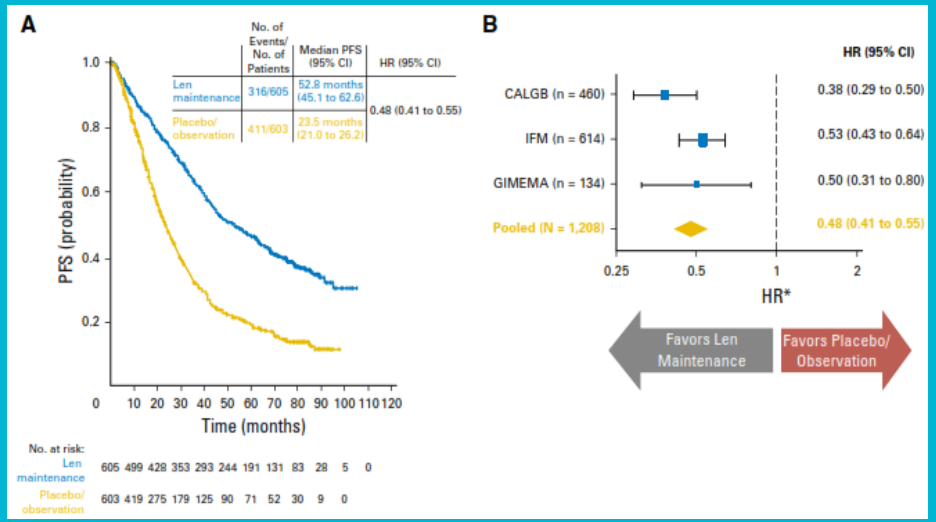
Table 2. Summary of four phase III trials exploring lenalidomide maintenance post ASCT.

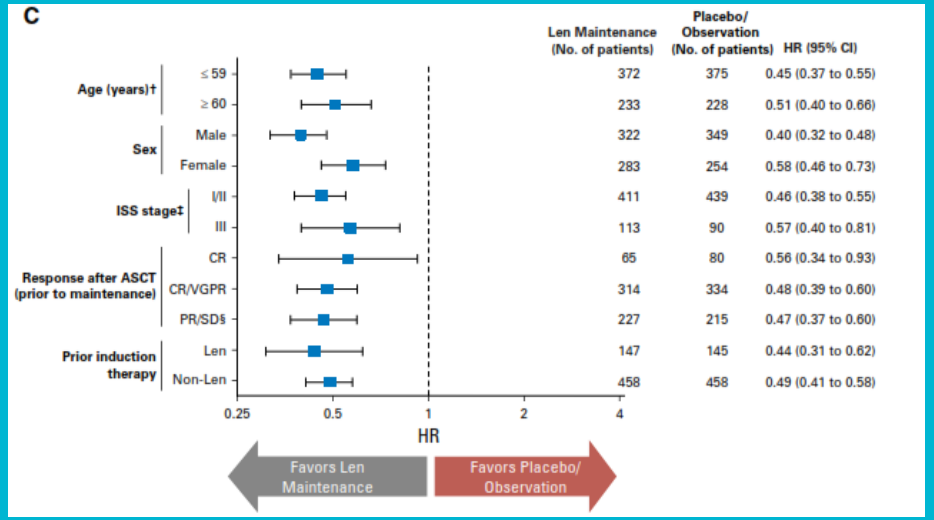
Study	No patients	Maintenance schedule	Follow-up (median)	PFS/TTP (median)	OS
CALGB 100104 [55]	460	L 10 mg/day first 3 monts, 15 mg after 3 months if tolerated vs placebo until PD	91 months	57.3 (L) vs 28.9 (P) months; HR 0.57; $p < 0.0001$	113.8 (L) vs 84.1 months; HR 0.61; $p = 0.0004$ (5-yr 76% vs 64%)
IFM 2005–02 [56]	614	L 10 mg/day first 3 months, 15 mg after 3 months if tolerated vs placebo, until PD	45 months	41 (L) vs 23 (P) months; HR 0.50; $p < 0.001$	4-yr OS 73% (L) vs 75% (P); HR 1.25; $p = 0.29$
GIMEMA [50]	251	L 10 mg days 1–21 (28 days cycle) vs observation, until PD	79.5 months	41 (L) vs 21.6 (Obs) months; HR 0.44; $p < 0.001$	3-yr OS 88% (L) vs 79.2% (Obs); HR 0.64; $p = 0.14$
Myeloma XI [57]	1248	L 25 mg/day (10 mg after amendment) vs observation, until PD	31 months	57 (L) vs 30 (Obs) months; HR 0.46; $p < 0.0001$	3-yr 87.5% (L) vs 80.2% (Obs); HR 0.87; $p = 0.15$

L, lenalidomide; P, placebo; Obs, observation

Morè S, et al. *Expert Rev Hematol*. 2020;13:351-362.

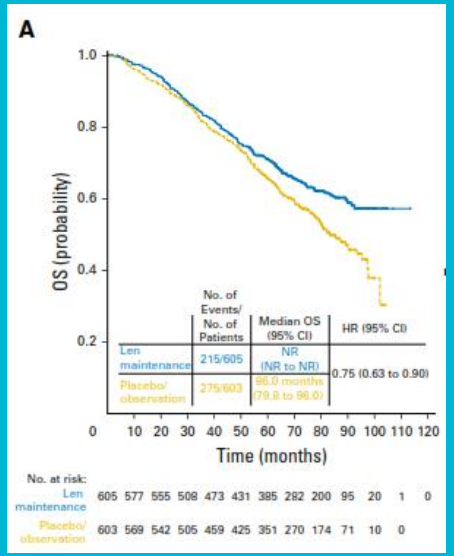
Lenalidomide Maintenance: PFS

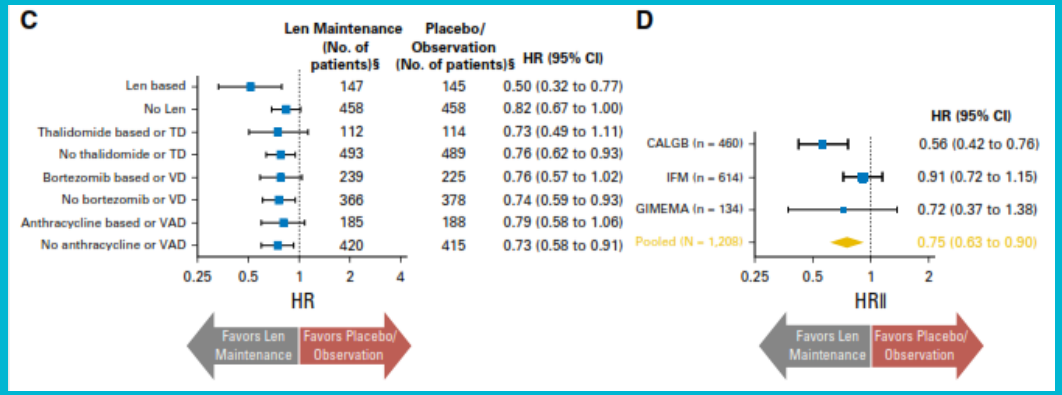


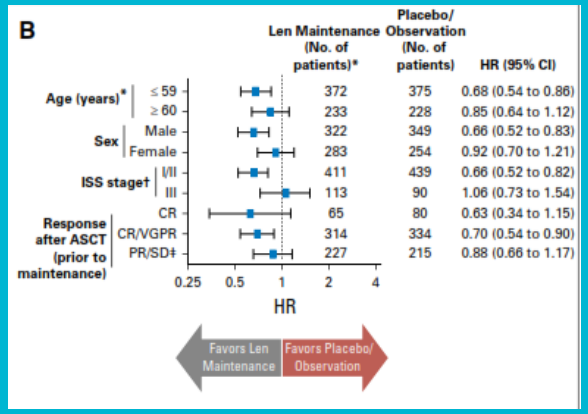


McCarthy PL, et al. *J Clin Oncol*. 2017;35:3279-3289.

Lenalidomide Maintenance: OS

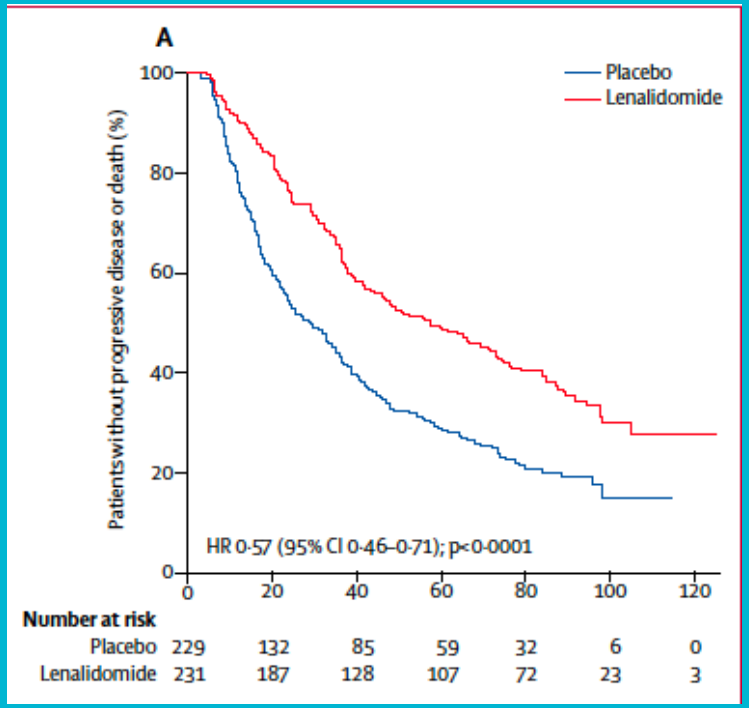


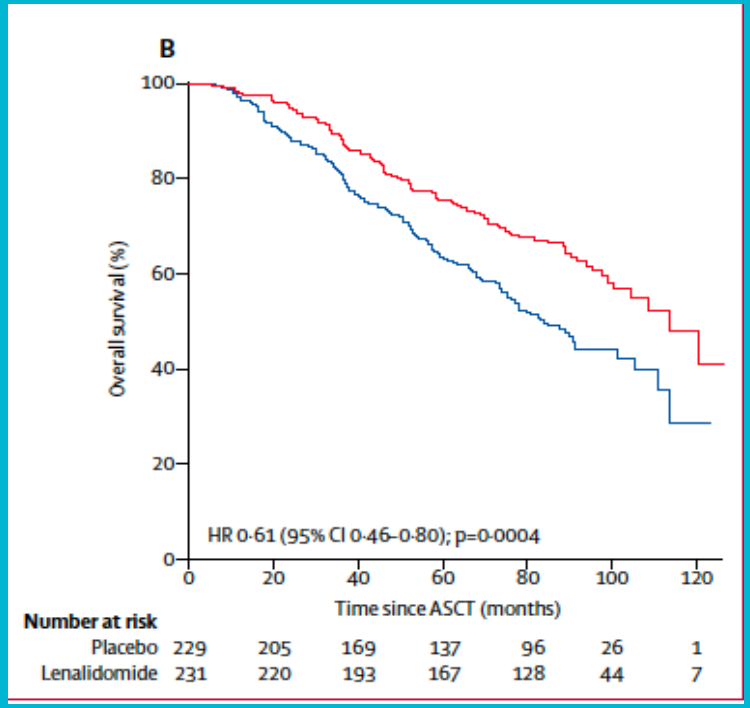




McCarthy PL, et al. *J Clin Oncol*. 2017;35:3279-3289.

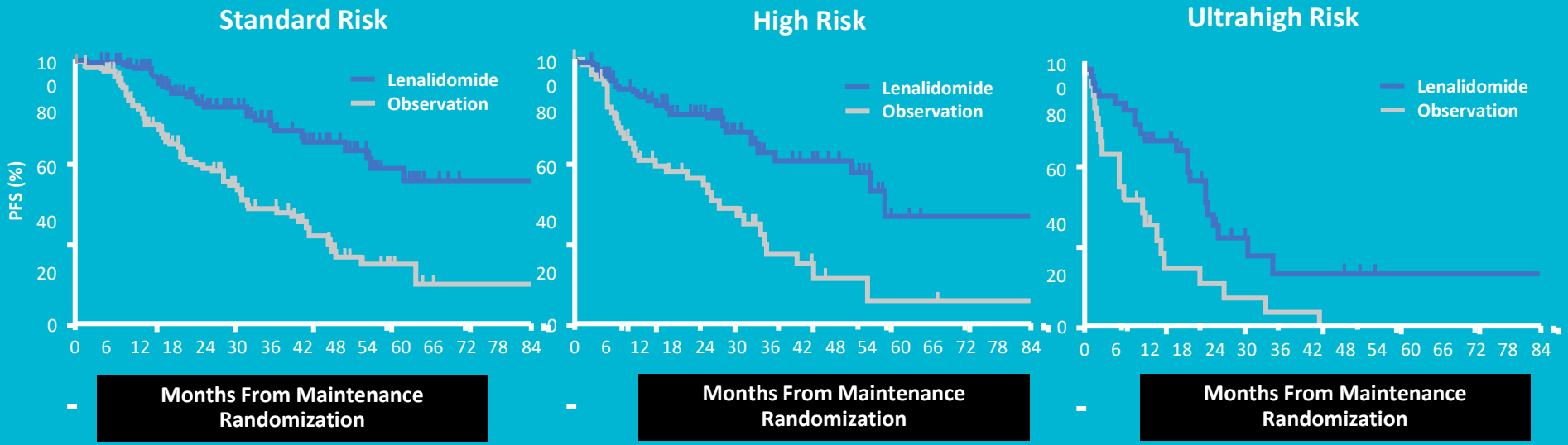
Lenalidomide Maintenance





Holstein SA, et al. *Lancet*. 2017;4:E431-E442.

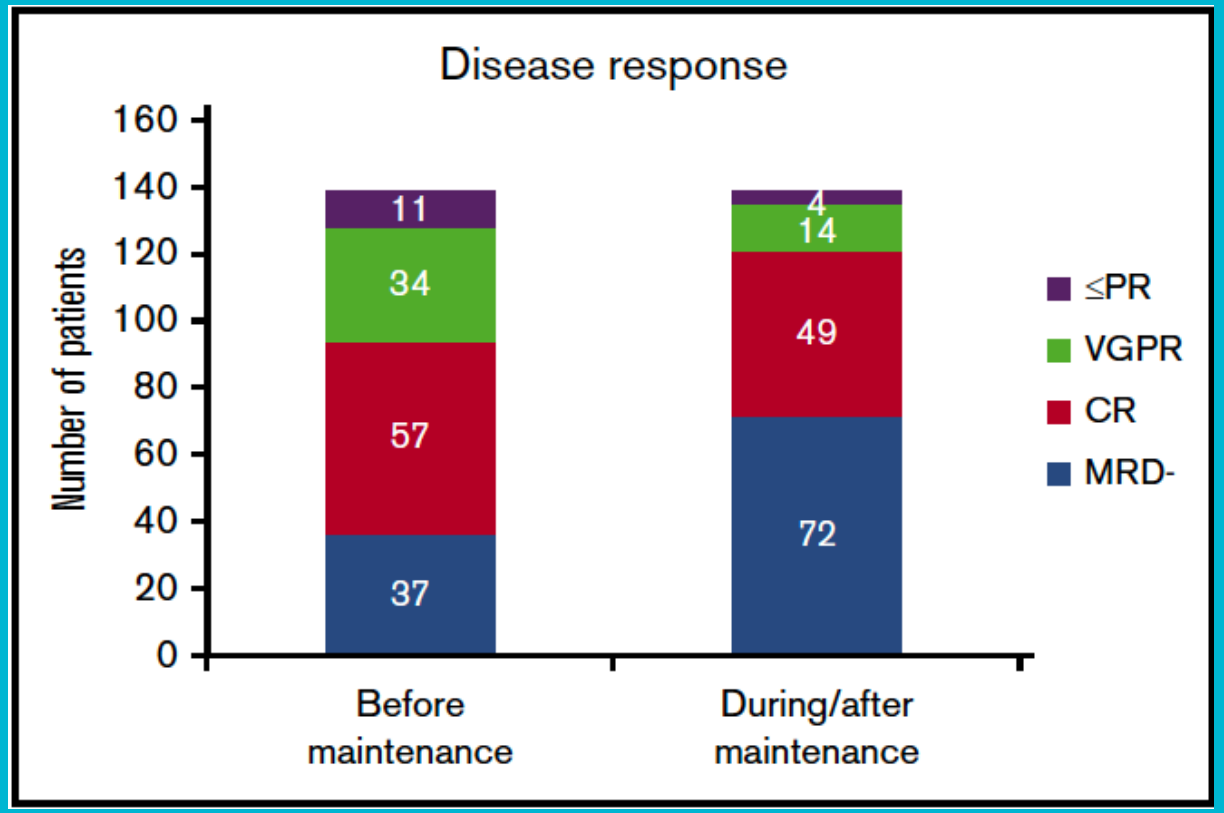
Phase III Myeloma XI Trial: PFS With Len Maintenance in ASCT-Eligible Patients by Cytogenetic Risk



- High risk: presence of either t(4;14), t(14;16), t(14;20), del 17p, or gain 1q
- Ultrahigh risk: presence of more than 1 of these lesions
- Standard risk: absence of these lesions

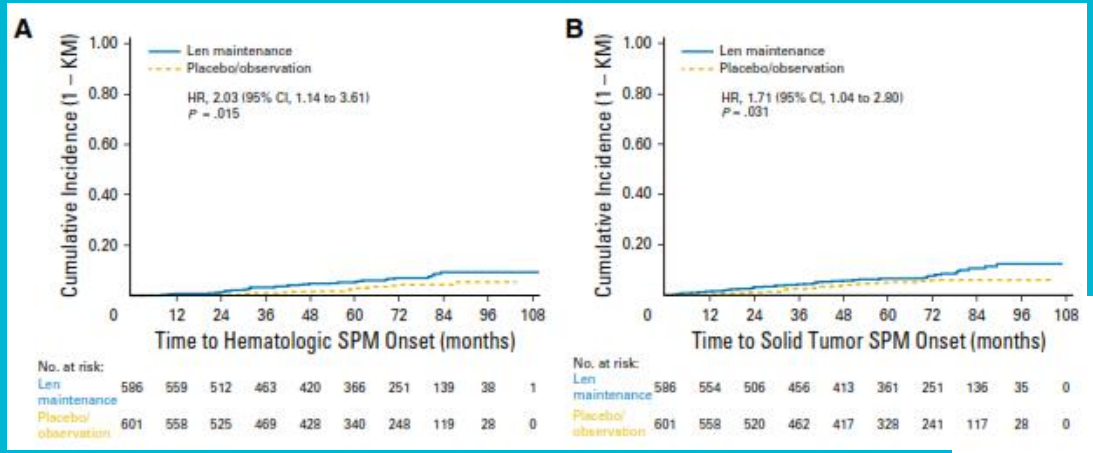
Jackson GH, et al. *Lancet Oncol*. 2019;20:57-73.

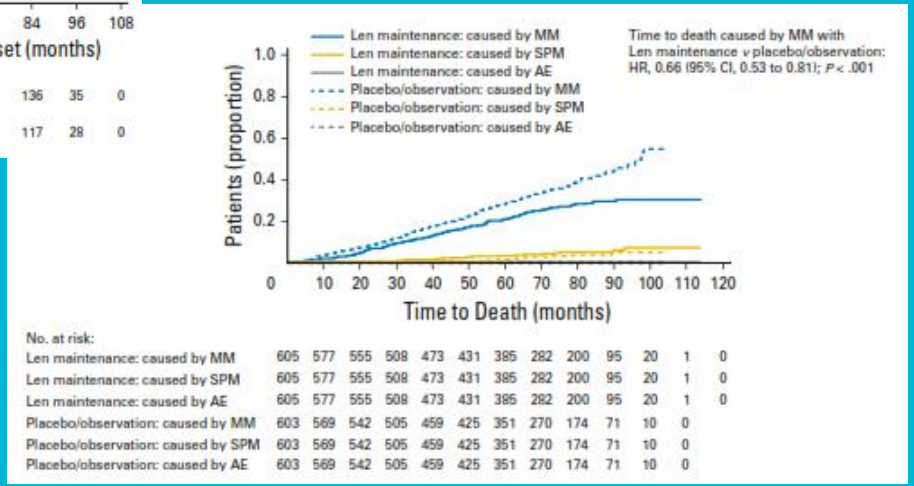
Comparison of Response Status at the Beginning of Lenalidomide Maintenance and at Maximal Response



Alonso R, et al. *Blood Adv.* 2020;4:2163-2171.

Second Malignancies

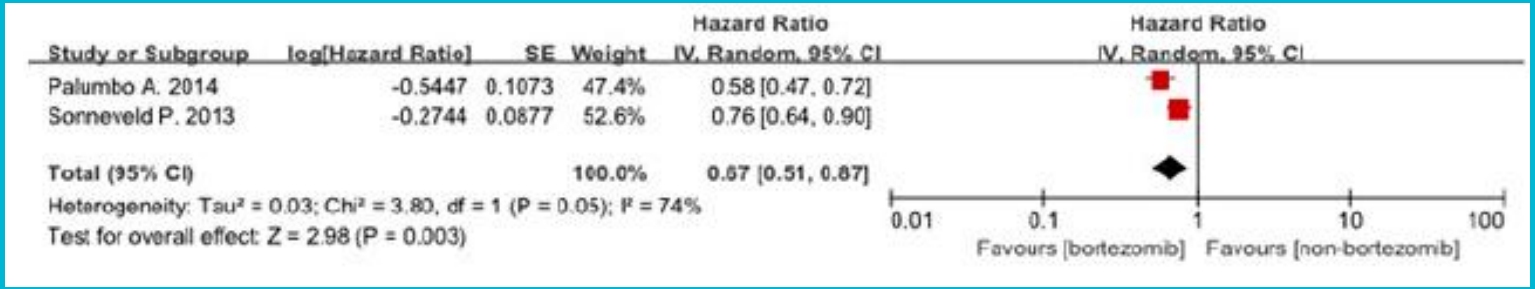




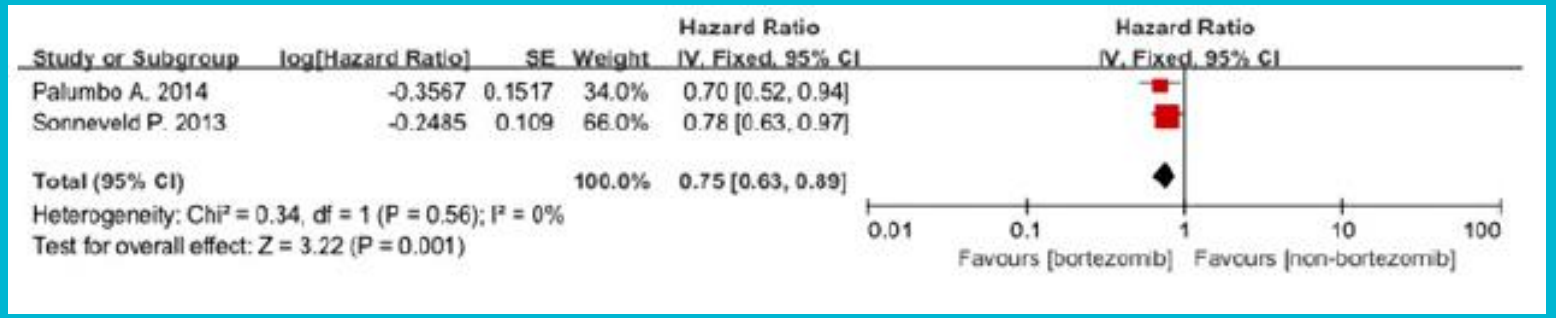
McCarthy PL, et al. *J Clin Oncol*. 2017;35:3279-3289.

Pooled Hazard Ratios of PFS and OS Comparing Bortezomib Maintenance Therapy Arm With Non-Bortezomib Maintenance Therapy Arm

PFS



OS



Sun CY, et al. *Biosci Rep*. 2017;37:BSR20170304.

Lenalidomide vs Bortezomib as Maintenance Therapy

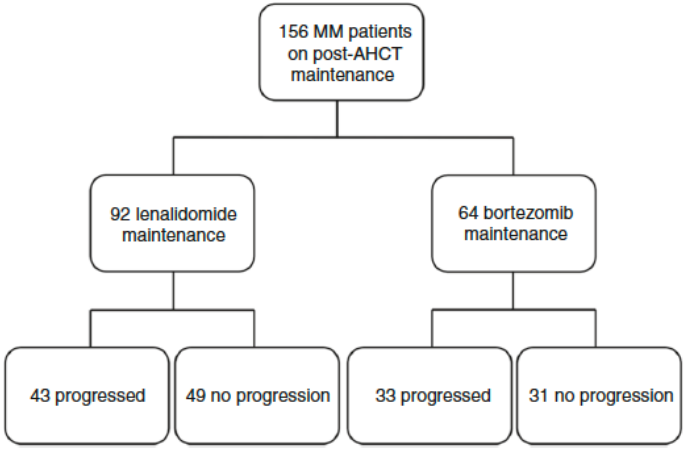


Fig. 1 CONSORT flow diagram

Table 3 Median time to progression by cytogenetic risk

FISH risk	Lenalidomide	Bortezomib	*p*-Value
Standard, months	26.9 (10.8–54.3) ($n = 24$)	25.7 (10.9–66.6) ($n = 18$)	0.80
Intermediate/ high, months	27.5 (9.8–58.1) ($n = 13$)	24.1 (9.8–48.0) ($n = 15$)	0.47

FISH fluorescence in situ hybridization

Huang J, et al. *Bone Marrow Transplant*. 2018;53:701-707.

TOURMALINE-MM3: Study Design

- Multicenter, double-blind, randomized phase III trial

Stratified by induction regimen (PI without IMiD vs IMiD without PI vs PI + IMiD), ISS disease stage (I vs II or III), and post-ASCT response (CR vs VGPR vs PR)

Adult patients with newly diagnosed MM; documented local cytogenetics/ FISH prior to transplant; ≥PR after induction with a PI and/or an IMiD followed by melphalan 200 mg/m^2 + single ASCT within 1 yr of beginning therapy, ECOG PS ≤2
(N = 656)

Maintenance

Ixazomib 3 mg on days 1, 8, and 15 for cycles 1-4, then 4 mg on days 1, 8, and 15 for cycles 5-26
(n = 395)

Placebo on days 1, 8, and 15
(n = 261)

Maximum 26 cycles, PD, or toxicity

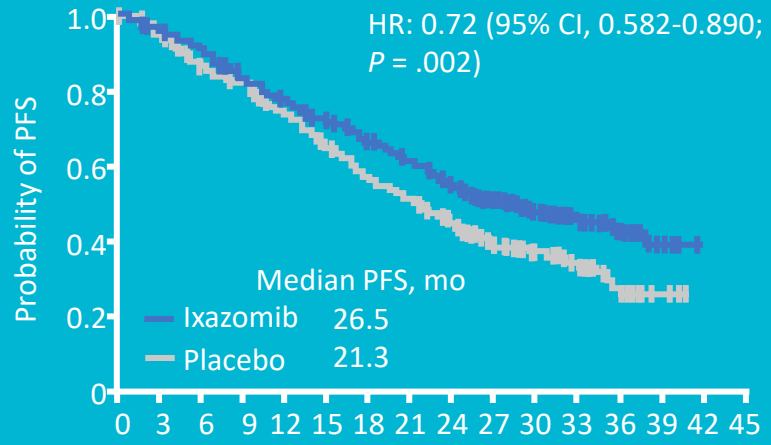
*28-day cycles; after 4 cycles, patients were eligible for dose escalation from 3 mg to 4 mg.

- Primary endpoint: PFS by IRC review
- Secondary endpoint: OS

Dimopoulos MA, et al. ASH 2018. Abstract 301.

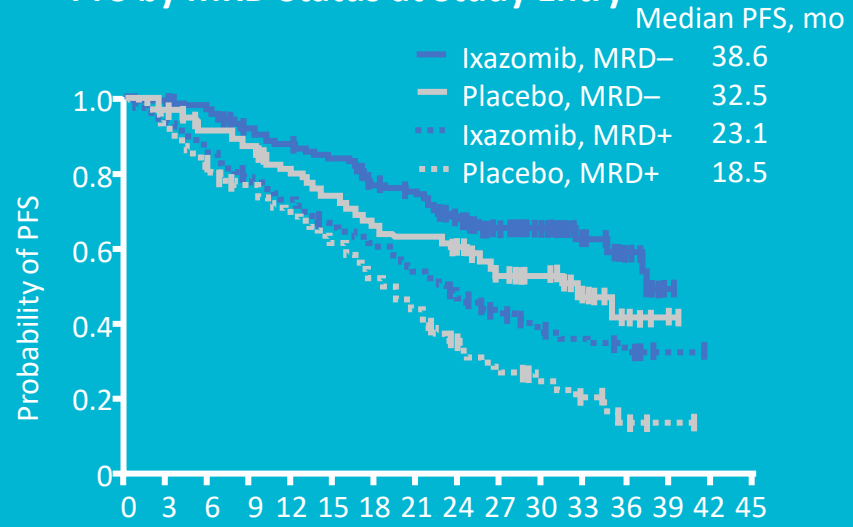
TOURMALINE-MM3: PFS

PFS: Overall (Primary Endpoint)



Patients at Risk, n															
Ixazomib	395	363	340	311	279	255	238	213	187	135	93	56	35	9	3	0
Placebo	261	238	210	195	174	153	130	117	100	69	46	32	15	3	0	0

PFS by MRD Status at Study Entry



Patients at Risk, n															
Ixazomib, MRD–	117	111	107	99	92	88	84	77	69	54	41	26	17	3	0	0
Ixazomib, MRD+	75	72	66	64	56	51	46	42	41	30	21	17	7	2	0	0
Placebo, MRD–	225	204	188	170	152	134	124	109	93	64	43	25	15	4	2	0
Placebo, MRD+	139	123	106	94	85	75	62	53	38	22	15	9	4	1	0	0

- At median follow-up of 31 mo, median OS not reached in either treatment arm

Dimopoulos MA, et al. ASH 2018. Abstract 301.

Table 4. Ongoing trials studying proteasome inhibitors in maintenance therapy.

Trial	Stage	Maintenance regimen	Identifier
Carfilzomib			
Evaluation of the safety and efficay of carfilzomib combined with cyclophosphamide and dexametahsone (CCyd) or lenalidomide and dex (CRd) followed by ASCT or 12 cycles of carfilzomib combined with dex and len for patients eligible for ASCT with newly diagnosed multiple myeloma (FORTE)	II	Lenalidomide vs lenalidomide plus carfilzomib until PD	NCT02203643
Carfilzomib/cyclophosphamide/dexametahsone with maintenance carfilzomib in multiple myeloma (Cardamon)	II	Carfilzomib for 18 months	NCT02315716
Trial of carfilzomib, lenalidomide, dexamethasone versus lenalidomide alone after ASCT for multiple myeloma	III	Lenalidomide vs carfilzomib, lenalidomide, dexamethasone for 36 months	NCT2659293
Ixazomib			
Safety and efficacy of a triplet combination of MLN9708, lenalidomide and dexamethasonne in the initial management of multiple myeloma (IFM2013-06)	II	Ixazomib for 12 months	NCT01936532
Phase II study if IRD (ixazomib, lenalidomide, dexamethasone) post ASCT followed by maintenance ixazomib or lenalidomide for multiple myeloma	II	Ixazomib vs lenalidomide until PD	NCT02253316
Alternating ixazomib citrate and lenalidomide as maintenance therapy after stem cell transplant in treating patients with multiple myeloma	II	Ixazomib alternate with lenalidomide for 24 months	NCT02619682
Ixazomib plus lenalidomide plus dexamethasone for newly diagnosed myeloma patients	II	Ixazomib plus lenalidomide in high-risk; lenalidomide in standard risk until PD	NCT03376672
Trial studying maintenance treatment with lenalidomide and dexamethasone versus lenalidomide, dexamethasone and MLN9708 after ASCT in patients with newly diagnosed multiple myeloma	III	Lenalidomide plus dexametahsone *vs* ixazomib, lenalidomide, dexametahsone for 24 months in MRD- and 5 yr in MRD+	NCT02406144
Testing the addition of ixazomib to lenalidomide in patients with evidence of residual multiple myeloma, OPTIMUM trial	III	Ixazomib plus lenalidomide *vs* lenalidomide until PD	NCT03941860

Morè S, et al. *Expert Rev Hematol*. 2020;13:351-362.

Elotuzumab + Len-Dex Maintenance in MM: Study Design

- Phase II trial

Pts with ASCT within 18 mo of starting induction therapy for NDMM, with ≤2 previous lines of therapy, ECOG PS 0-2, and able to start therapy within 60-210 days of ASCT ($N_{planned}$ = 100)

→ Elotuzumab + Lenalidomide + Dexamethasone (n = 68)

Elotuzumab dosing
- In first 28 pts: 10 mg/kg IV QW C1-C2, then 10 mg/kg Q2W in C3-6, then 20 mg/kg Q4W C7+
- In next 40 pts: 10 mg/kg IV QW C1-C2, then 20 mg/kg Q4W C3+

Lenalidomide dosing
- 10 mg/day in C1-C3, then 15 mg/day at physician's discretion* in C4+

Dexamethasone dosing
- Pts <75 yr of age: 28 mg PO 3-24 hr preinfusion C1-C2 only, then 4-10 mg IV preinfusion
- Pts ≥75 yr of age: 8 mg PO 3-24 hr preinfusion C1-C2 only, then 4-10 mg IV preinfusion

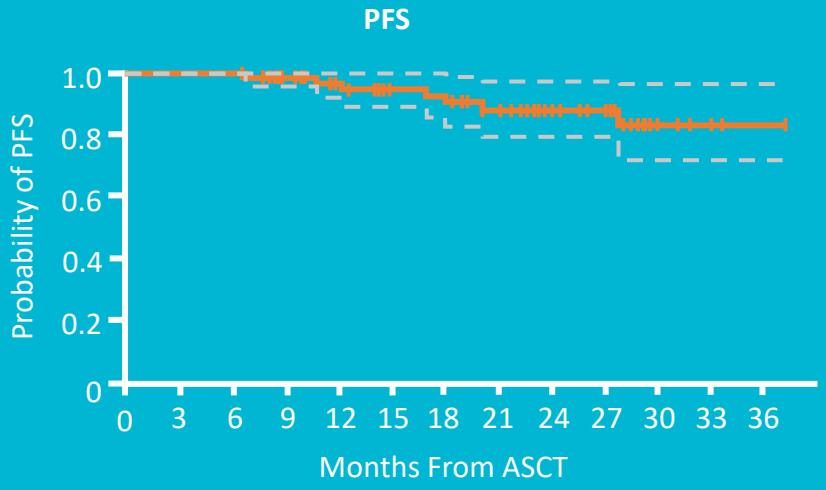
Pts receive prophylaxis for herpes zoster and DVT per IMWG guidelines

*Dose increased if no significant cytopenias and no nonhematologic toxicity grade >1.

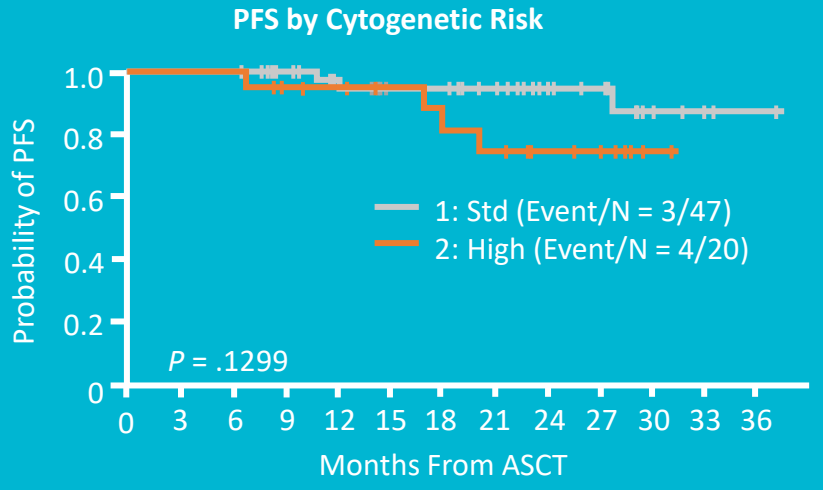
- Primary endpoint: PFS
- Secondary endpoints: ORR, OS, safety, SPM

Thomas SK, et al. ASH 2017. Abstract 840.

Elotuzumab + Len-Dex Maintenance in MM: PFS



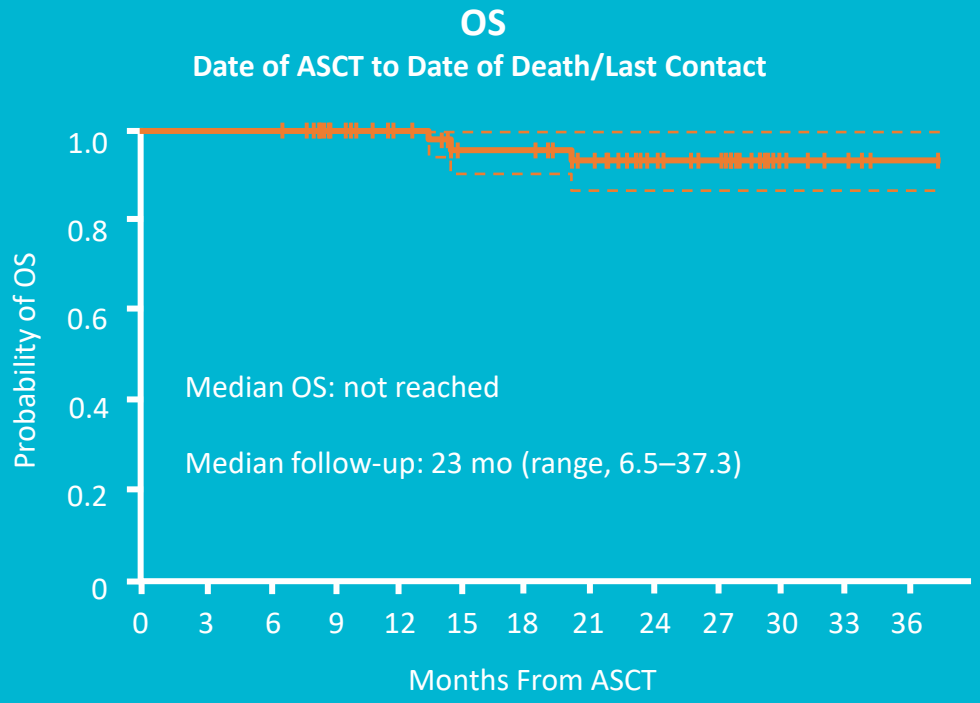
- Median follow-up: 23 mo (range, 6.5-37.3)
- Median PFS not reached
  - **2-yr estimated PFS: 88%**



- Disease progression occurred in 6 pts
  - 3 with high-risk cytogenetics
  - 3 with standard-risk cytogenetics
- 1 death occurred in pt with high-risk cytogenetics in VGPR

Thomas SK, et al. ASH 2017. Abstract 840.

Elotuzumab + Len-Dex Maintenance in MM: OS

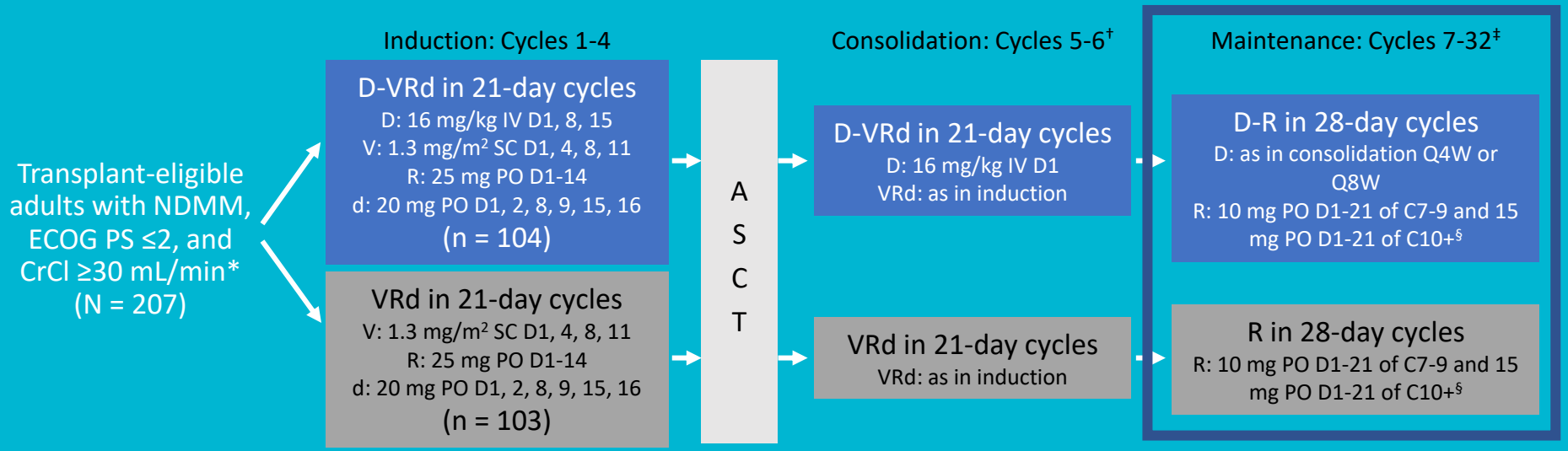


- 3 pt deaths
  - PD while on salvage therapy (n = 2)
  - Acute encephalopathy with refractory status epilepticus on study (in VGPR) (n = 1)

Thomas SK, et al. ASH 2017. Abstract 840.

GRIFFIN Maintenance Phase Update: Study Design

- Multicenter, open-label, randomized phase II trial



*Lenalidomide dose was adjusted in patients with CrCl ≤50 mL/min. †Consolidation began 60-100 days after transplantation. ‡Patients completing maintenance phase were permitted to continue single-agent lenalidomide. §15 mg administered only If tolerable.

- Primary endpoint: sCR by end of consolidation with 1-sided $\alpha = .1$
- Secondary endpoints: MRD, CR, ORR, ≥VGPR

Kaufman JL, et al. ASH 2020. Abstract 549.

GRIFFIN Maintenance Phase Update: Depth of Response Over Time

Depth of Response	D-VRd				VRd			
	End of Induction	End of ASCT	End of Consolidation	12 Months of Maintenance Cutoff	End of Induction	End of ASCT	End of Consolidation	12 Months of Maintenance Cutoff
sCR	12.1	21.2	42.4	63.6*	7.2	14.4	32.0	47.4*
CR	7.1	6.1	9.1	18.2*	6.2	5.2	10.3	13.4*
VGPR	52.5	59.6	39.4	14.1	43.3	46.4	30.9	18.6
PR	26.3	12.1	8.1	3.0	35.1	25.8	18.6	13.4
SD/PD/NE	2.0	1.0	1.0	1.0	8.2	8.2	8.2	7.2

*P = .0253 for comparison of sCR for D-VRd vs VRd. P = .0014 for comparison of ≥CR.

- Median follow-up at 12-mo maintenance therapy cutoff: 27.4 mo
  - Entered maintenance phase: 87% D-VRd vs 68% VRd; discontinued during maintenance phase: 12% D-VRd vs 17% VRd
- End of induction, ASCT, consolidation data are from primary analysis (median follow-up: 13.5 mo)

Kaufman JL, et al. ASH 2020. Abstract 549.

Table 2. Ongoing phase III trials of maintenance after ASCT.

Study	NCT Number	Maintenance
Antibody-based		
Cassiopeia	NCT02541383	**Daratumumab** versus observation
Auriga	NCT03901963	**Daratumumab**-Lenalidomide versus Lenalidomide
SWOG1803/BMT CTN 1706		**Daratumumab**-Lenalidomide versus Lenalidomide
GMMG-HD7	NCT03617731	**Isatuximab**-Lenalidomide versus Lenalidomide
GMMG-HD6	NCT02495922	**Elotuzumab**-Lenalidomide versus Lenalidomide
Proteasome inhibitor-based		
ATLAS	NCT02659293	**Carfilzomib**-Lenalidomide-Dexamethasone versus Lenalidomide
GEM2014MAIN	NCT02046144	**Ixazomib**-Lenalidomide versus Lenalidomide

Merz AMA, et al. *Expert Rev Anticancer Ther.* 2019;19:889-898.

Conclusions

- Currently, there is controversy in recommending consolidation therapy following ASCT, but recent results using novel agents are in favor of this modality
- Lenalidomide maintenance therapy until progression or intolerance is the current approved standard of care in patients who undergo ASCT
- An increased risk of SPMs is associated with lenalidomide maintenance following ASCT, although their benefits in terms of PFS and OS are better than the risk of this complication
- Bortezomib and ixazomib are other excellent choices for maintenance therapy, including patients with high risk
- Future trials will also assess the role of second-generation novel agents, such as carfilzomib, pomalidomide, elotuzumab, daratumumab, and bendamustine as maintenance therapy, either alone or in combination

Global Multiple Myeloma Academy

Discussion

APTITUDE HEALTH®

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Frontline Therapy for Newly Diagnosed Transplant-Ineligible Patients

Keith Stewart, MBChB, MBA

APTITUDE HEALTH®

CURE
EVOLVE
CONNECT
COMFORT

Treatment of Newly Diagnosed Transplant-Ineligible Multiple Myeloma

Keith Stewart, MBChB, MBA
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

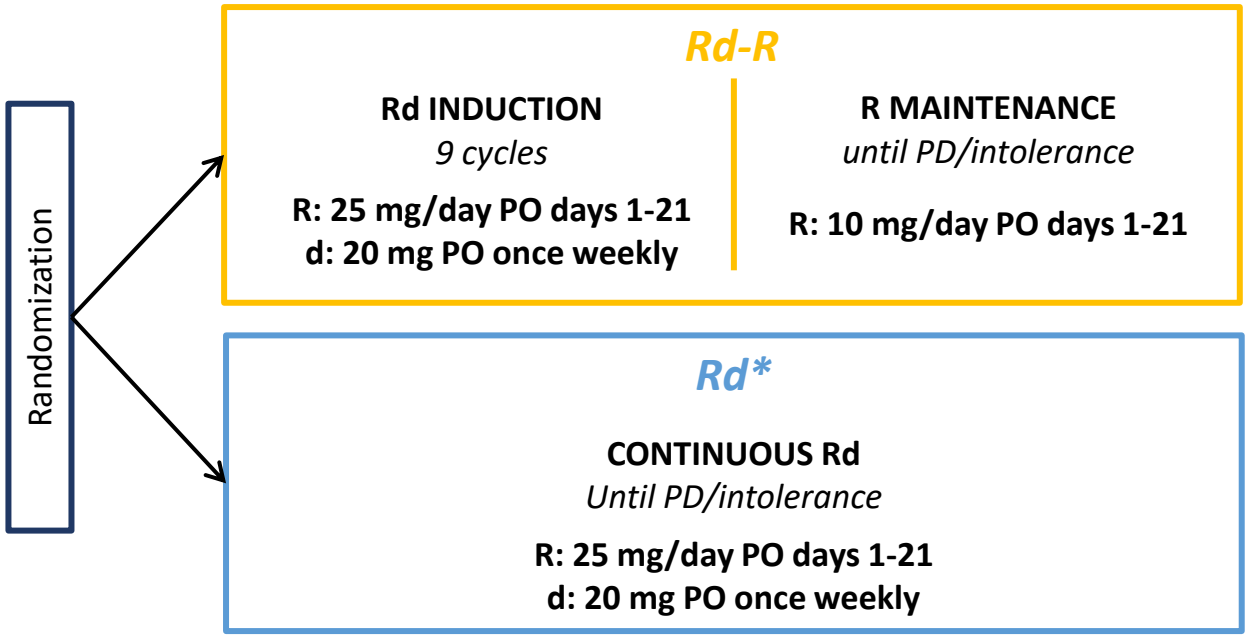
Dose/Schedule-Adjusted Rd-R vs Continuous Rd for elderly, intermediate-fit, newly diagnosed multiple myeloma patients

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]



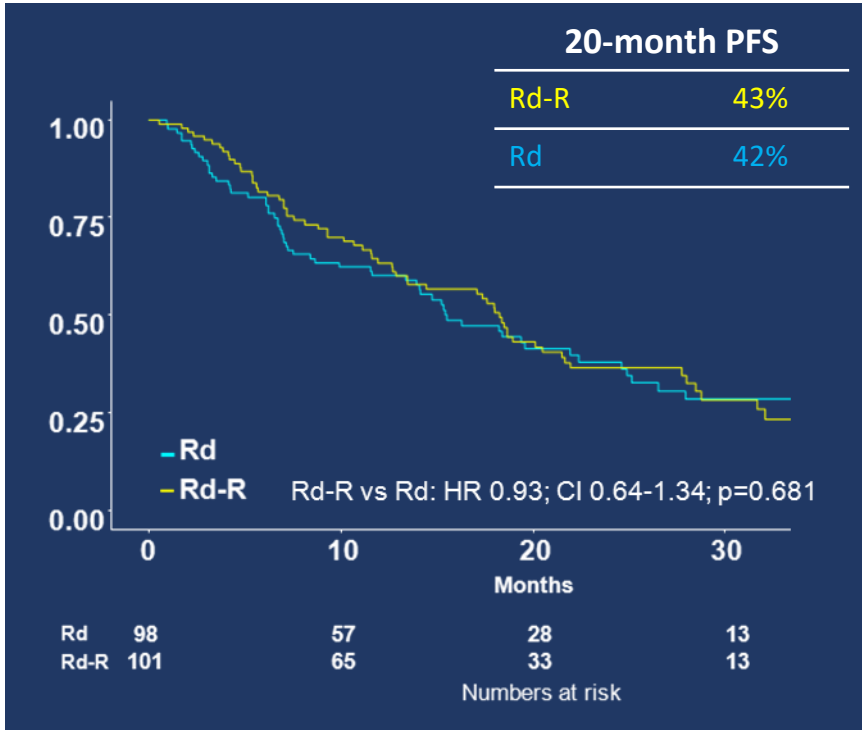
*The dose and schedule of continuous Rd was the one adopted in patients >75 years in the FIRST trial.[2]

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

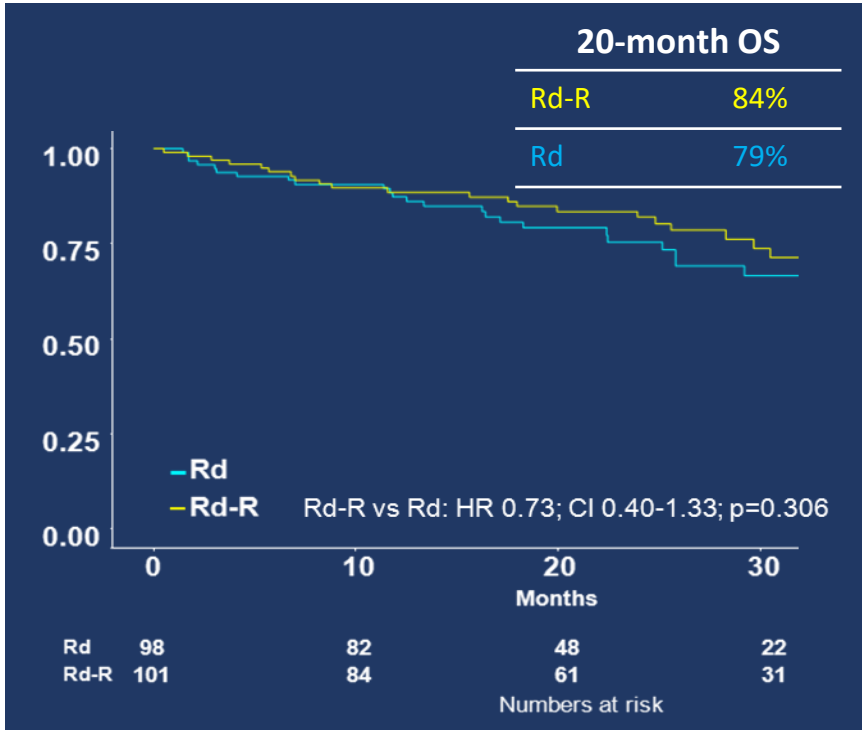
1. Larocca A, et al. *Blood.* 2021. doi: 10.1182/blood.2020009507; 2. Hulin C, et al. *J Clin Oncol.* 2016;34(30):3609-3617.

Rd vs Rd-R: PFS and OS

Progression-Free Survival



Overall Survival

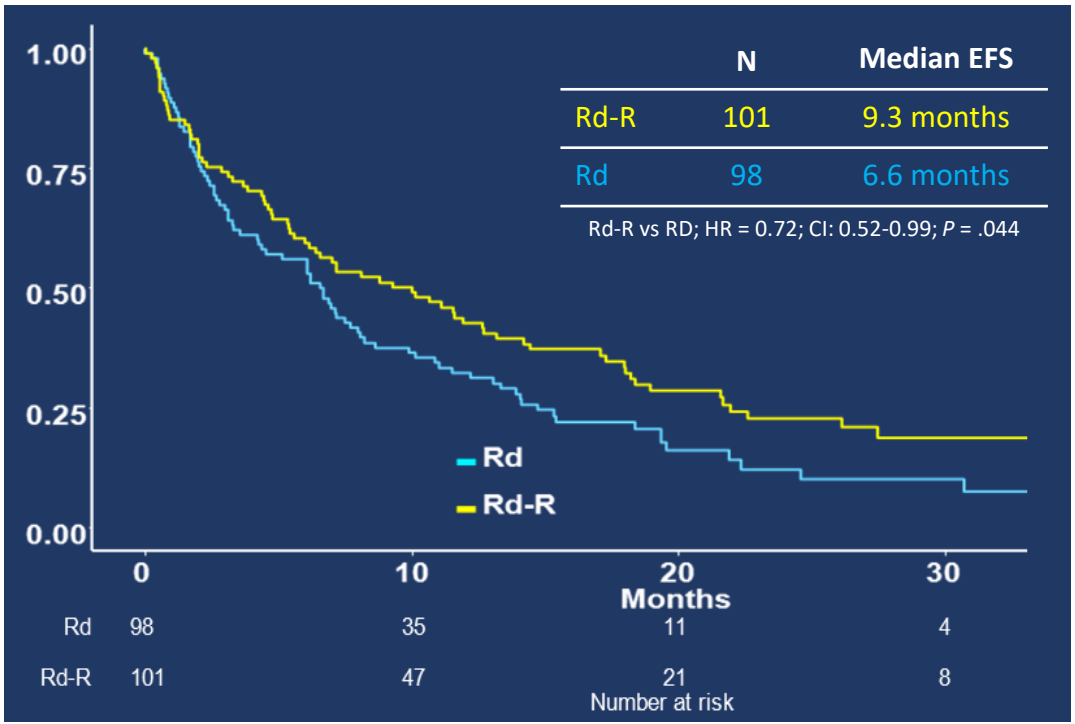


R, lenalidomide; d, dexamethasone; PFS, progression-free survival; OS, overall survival.

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

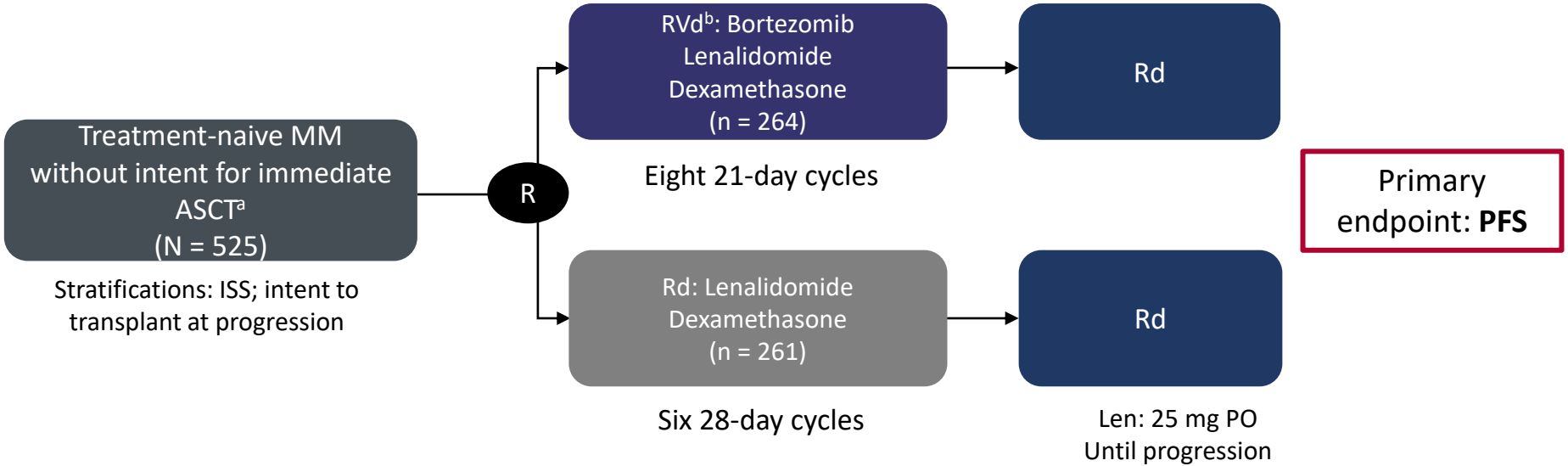
[a]Related to study drugs.

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

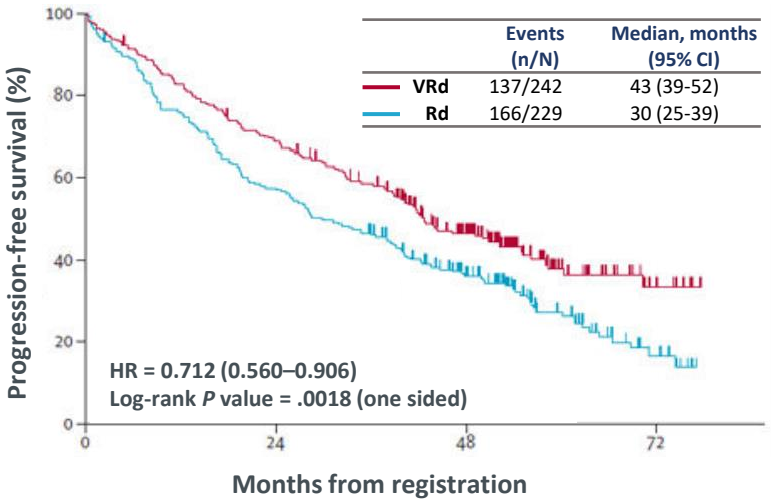
	Response, n (%)	
	RVd (n = 215)	Rd (n = 207)
CR	52 (24.2)	25 (12.1)
VGPR	109 (50.7)	85 (41.1)
≥VGPR	(74.9)	(53.2)
PR	33 (15.3)	53 (25.6)
ORR	194 (90.2)	163 (78.8)
SD	15 (7.0)	34 (16.4)
PD or death	6 (2.8)	10 (4.8)

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

SWOG S0777: PFS and OS

Progression-Free Survival

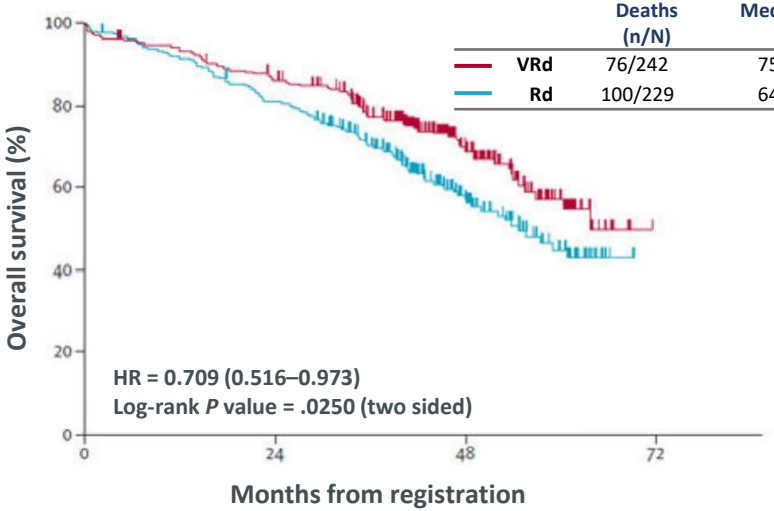
By assigned treatment arm



	Events (n/N)	Median, months (95% CI)
VRd	137/242	43 (39-52)
Rd	166/229	30 (25-39)

Overall Survival

By assigned treatment arm



	Deaths (n/N)	Median, months (95% CI)
VRd	76/242	75 (65-NR)
Rd	100/229	64 (56-NR)

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

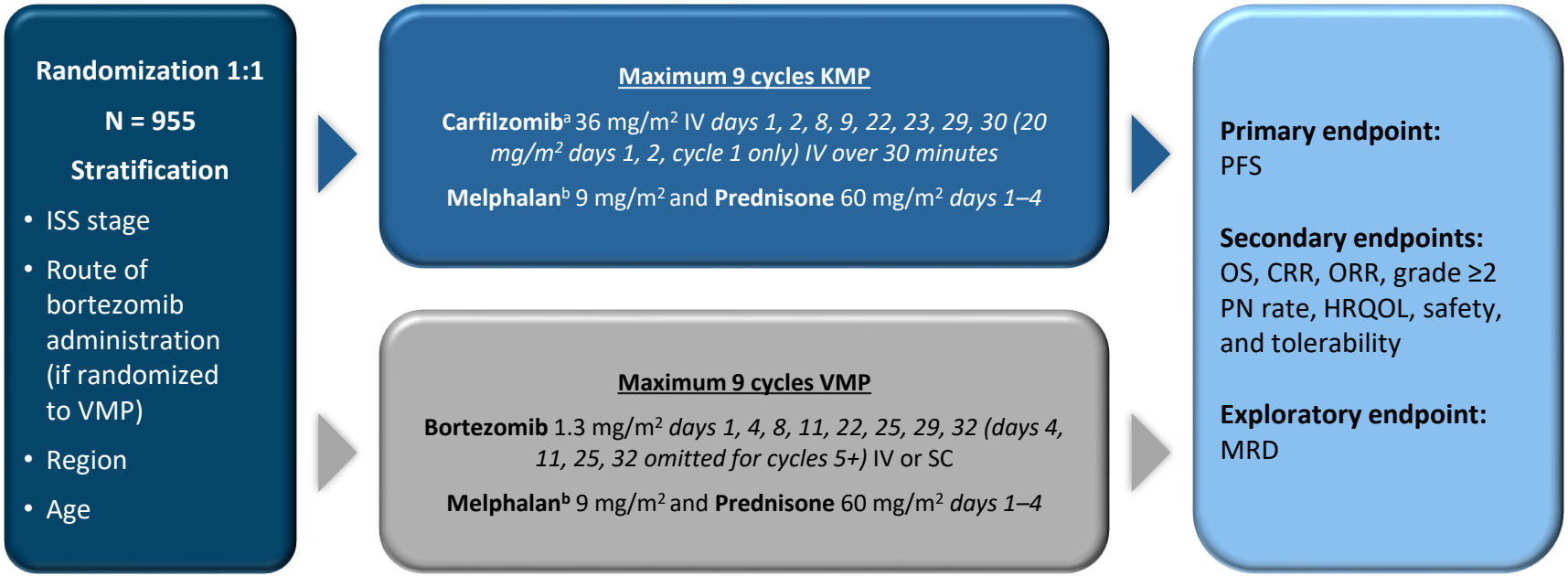
Durie BGM, et al. ASH 2018. Abstract 1992.

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 yr
- iORR: 90% (10 CR, 14 VGPR, 12 PR, 4 SD)
- PFS: 41.9 months
- Toxicities manageable
  - Peripheral neuropathy of any grade was reported in 61%

O'Donnell EK, et al. ASH 2015. Abstract 4217; O'Donnell EK, et al. *Blood*. 2019;134(suppl 1):3178-3178.

CLARION: Study Design



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

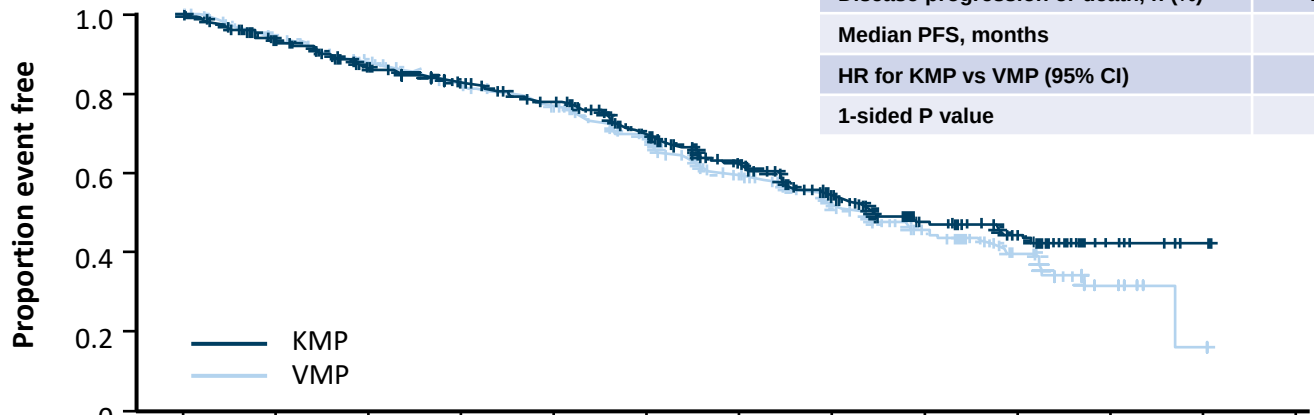
[b]Melphalan dose was 7 mg/m² if age was >75 years or CrCl was 30 to < 50 mL/min; 5 mg/m² if CrCl was 15 to <30 mL/min.[1]

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	



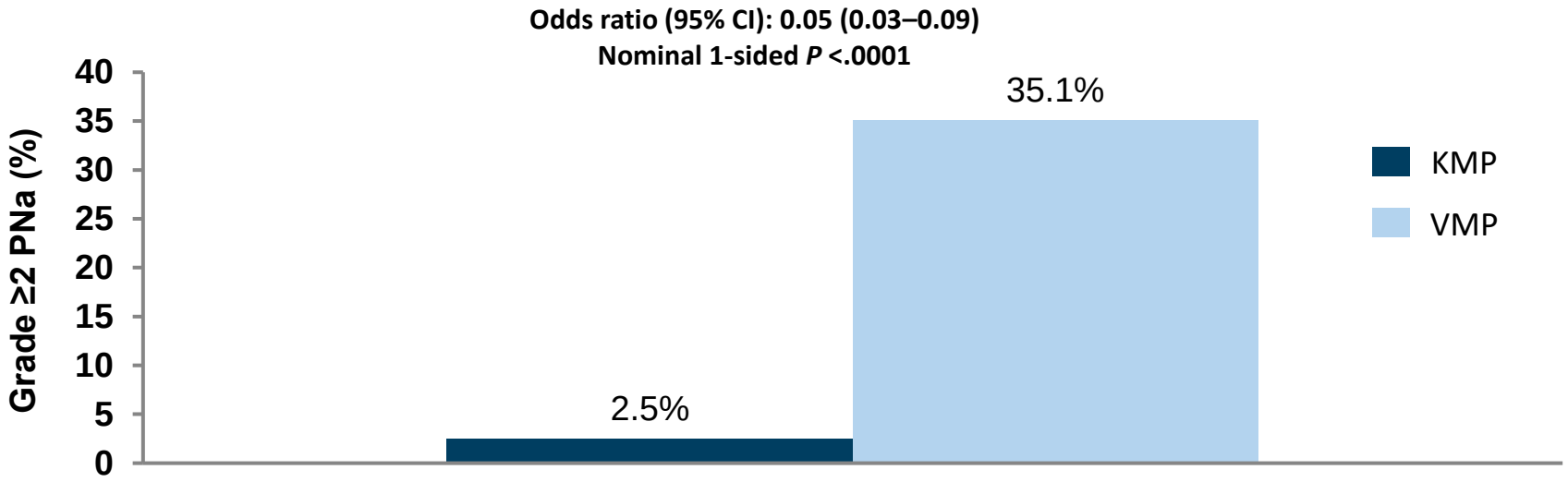
Number at risk:

KMP	478	384	327	217	85	15	0
VMP	477	367	309	202	77	9	0

- 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.

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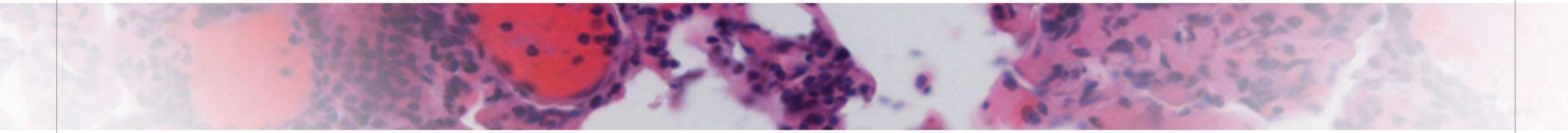


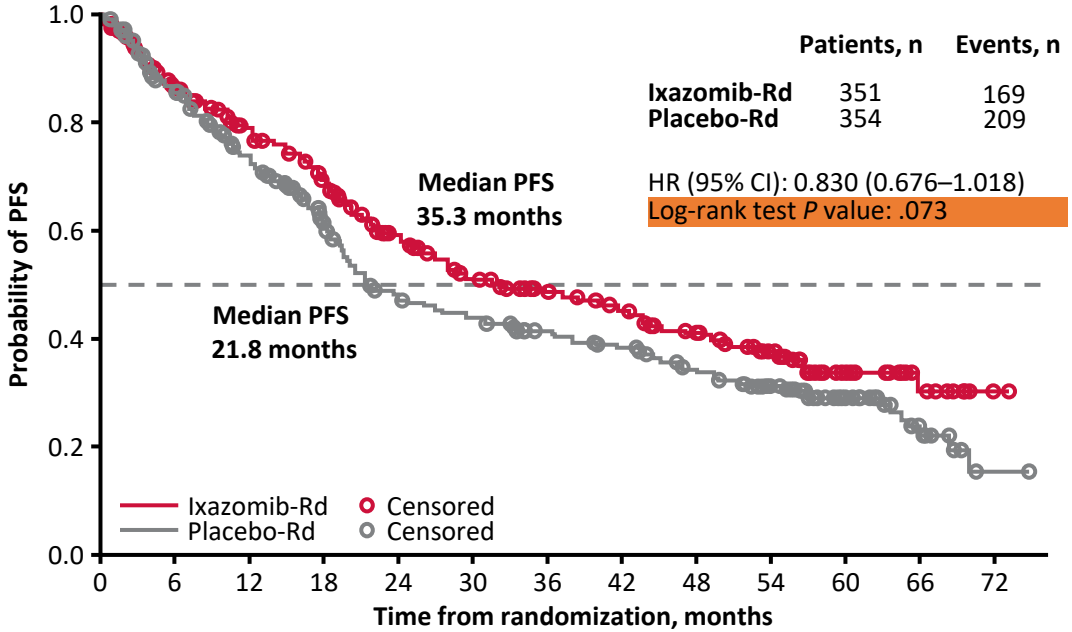
The Phase 3 TOURMALINE-MM2 Trial: Oral Ixazomib, Lenalidomide, and Dexamethasone vs Placebo-Rd for Transplant-Ineligible Patients with Newly Diagnosed Multiple Myeloma

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

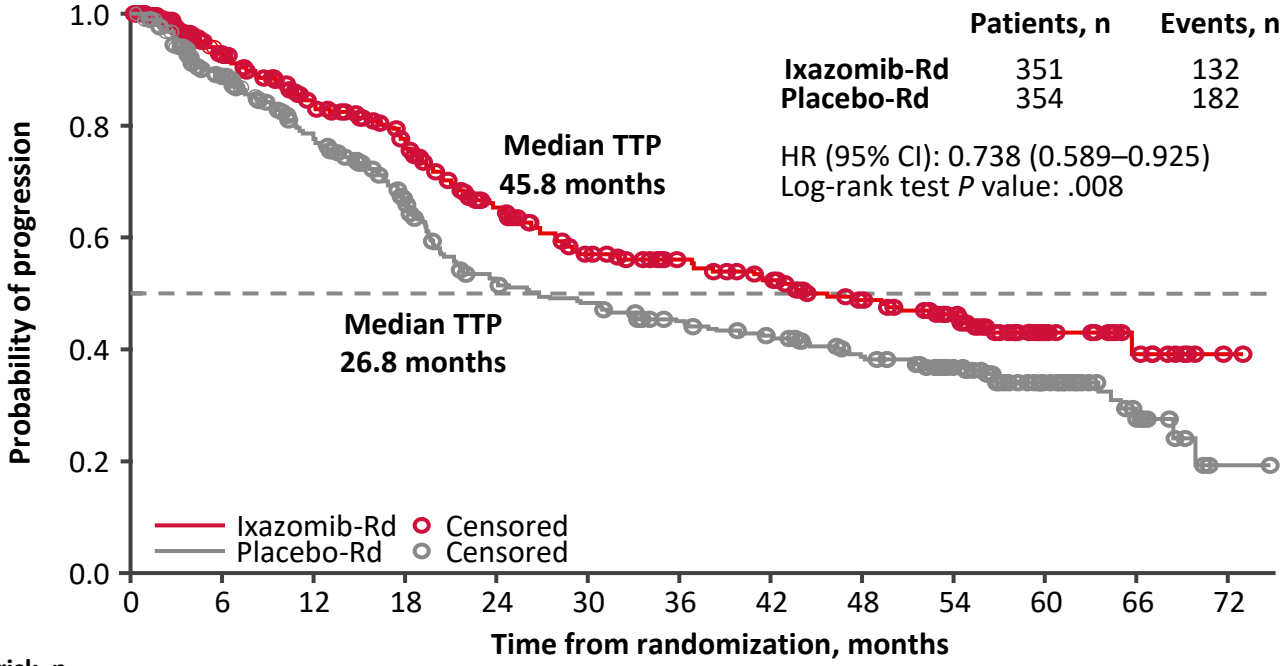
Ixazomib-Rd	351	261	220	187	147	120	107	96	81	64	28	10	1
Placebo-Rd	354	273	225	174	132	121	106	98	82	63	35	16	1

- 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

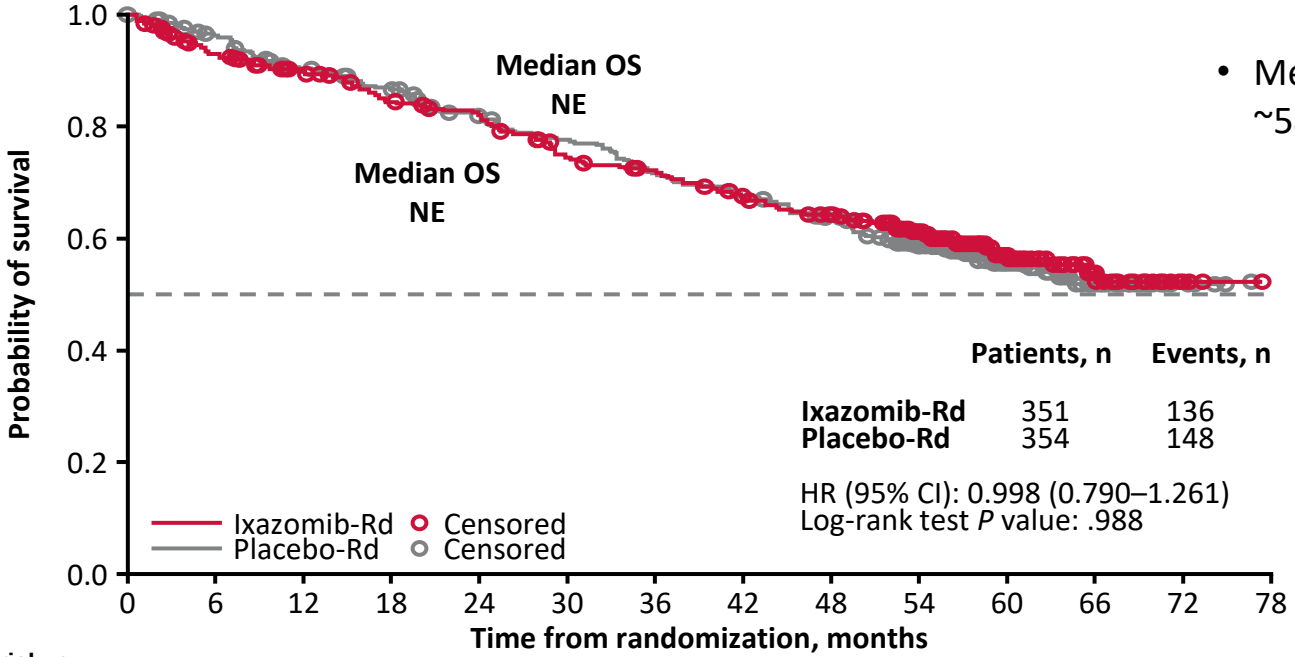


Patients at risk, n

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



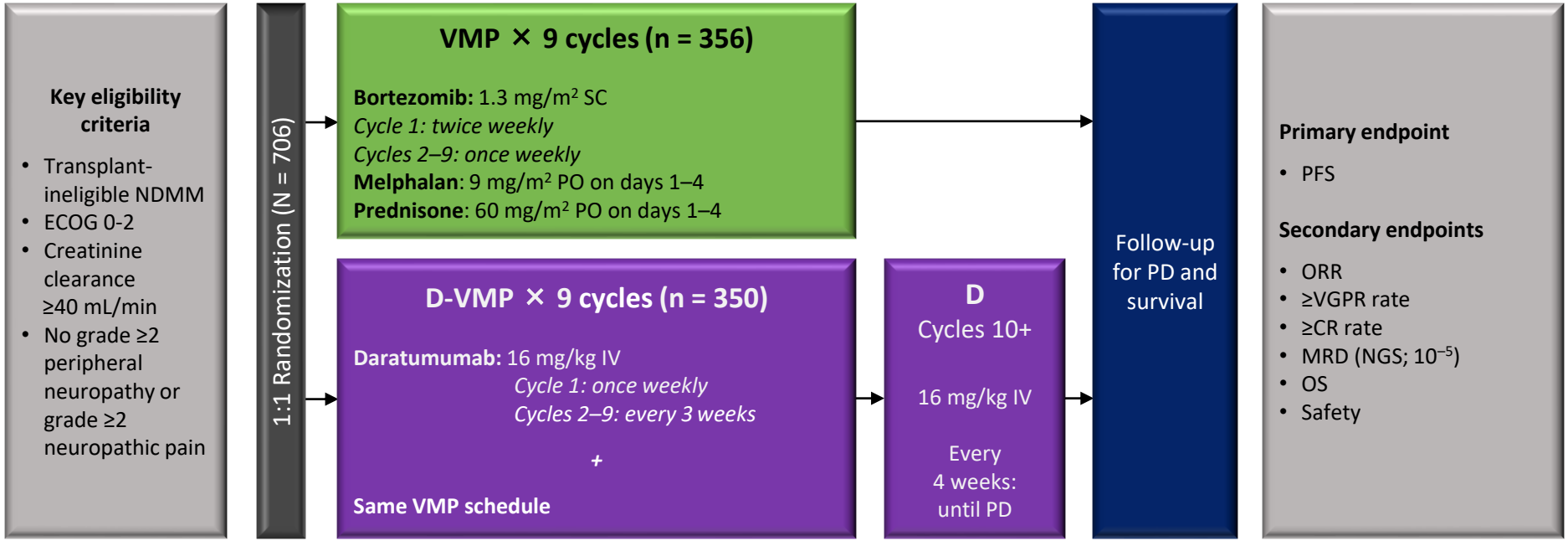
Patients at risk, n

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)

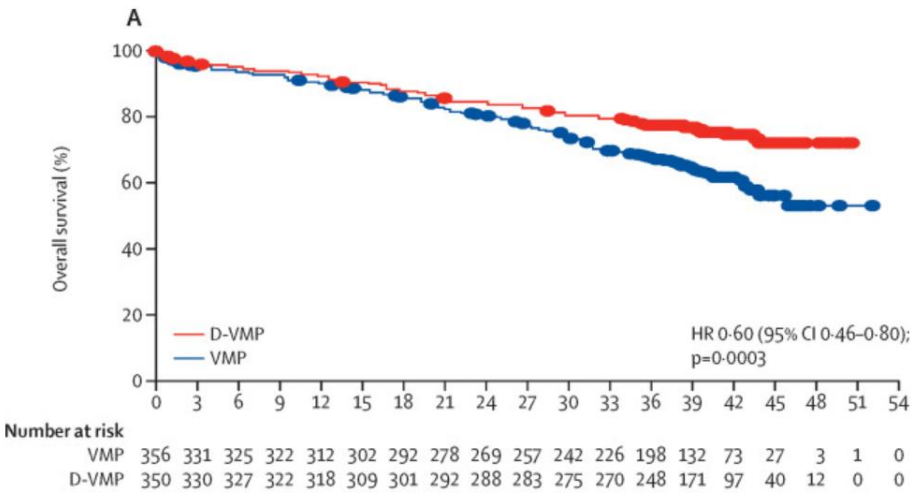
- Cycles 1-9: 6-week cycles
- Cycles 10+: 4-week cycles

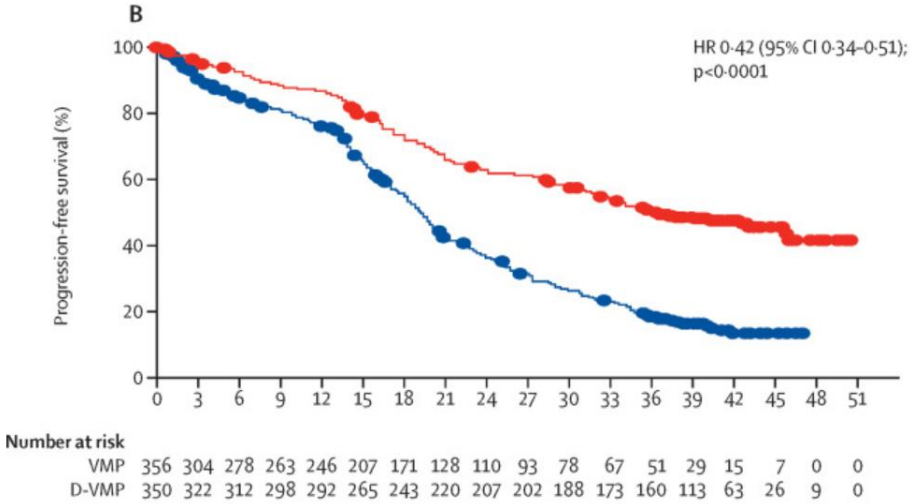
Statistical analyses

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

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

ALCYONE

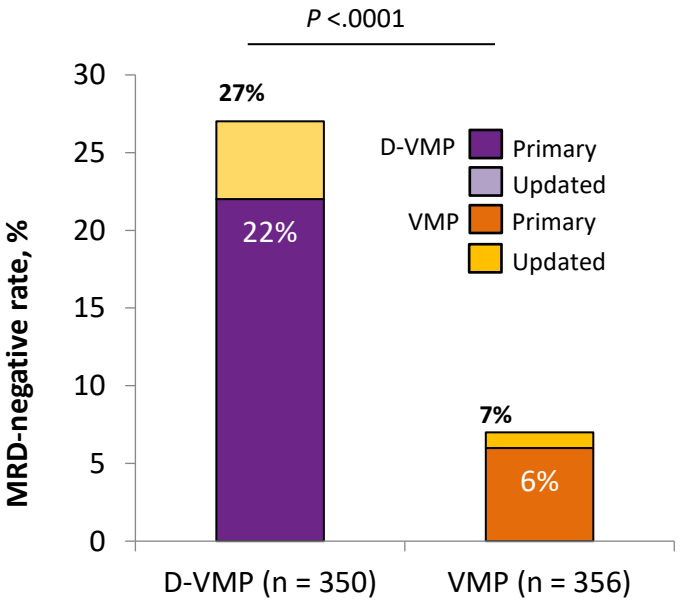


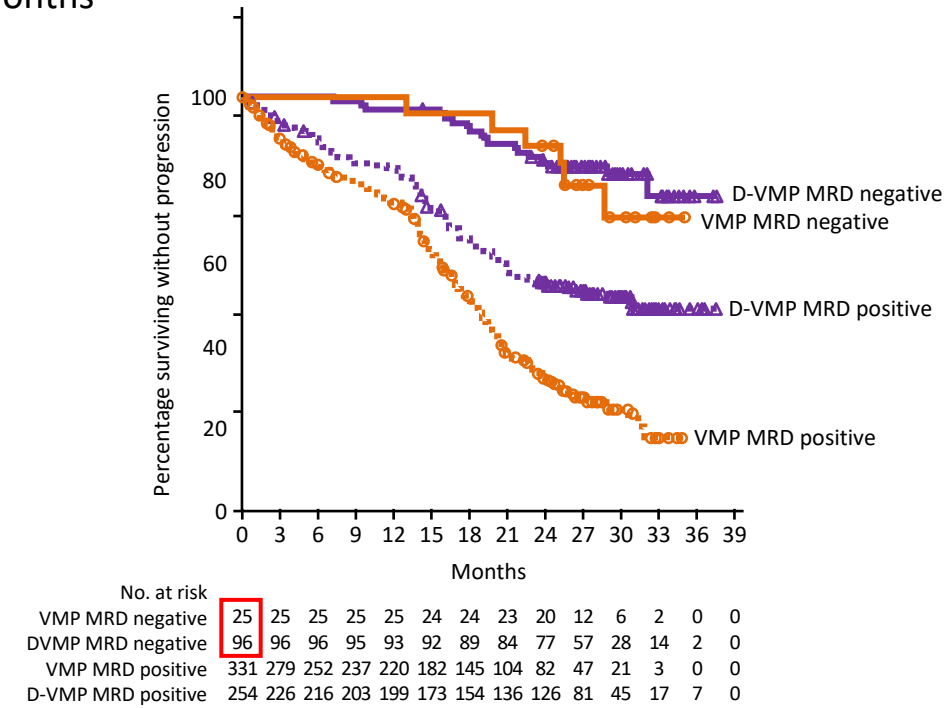


Mateos MV, et al. *Lancet.* 2020 Jan 11;395(10218):132-141.

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

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

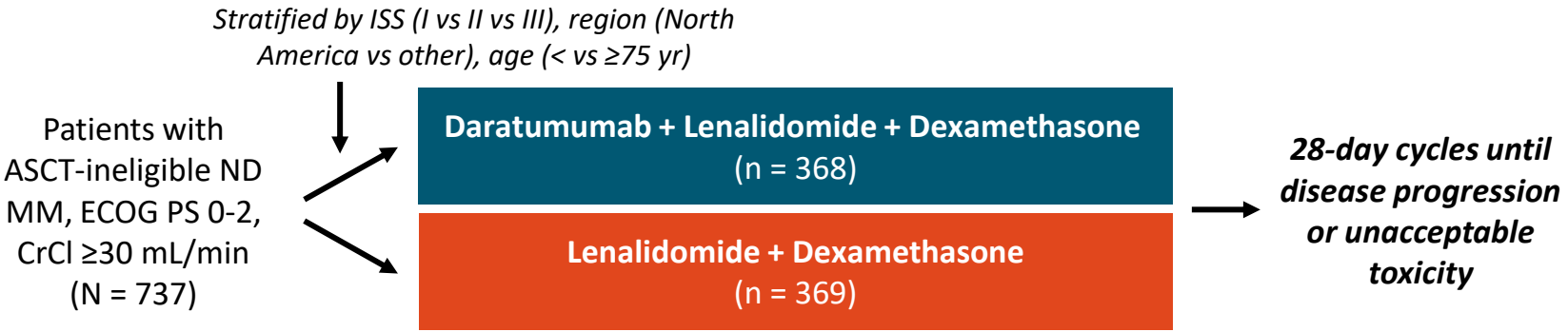




Mateos MV, et al. *N Engl J Med.* 2018;378(6):518-528.

MAIA: Study Design

- Multicenter, open-label, randomized phase III trial



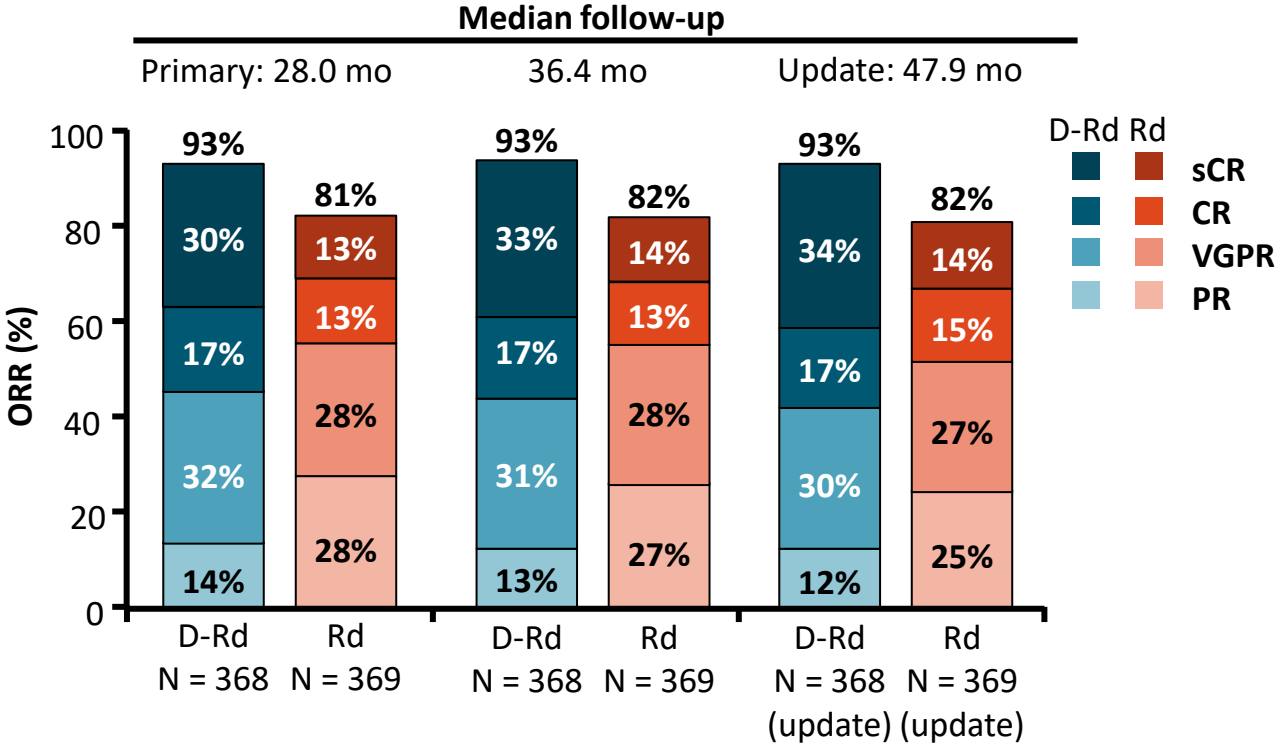
Dosing: daratumumab, 16 mg/kg IV (QW cycles 1-2, Q2W cycles 3-6, Q4W cycle 7+); lenalidomide, 25 mg QD PO on days 1-21; dexamethasone 40 mg QW PO or IV

- 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

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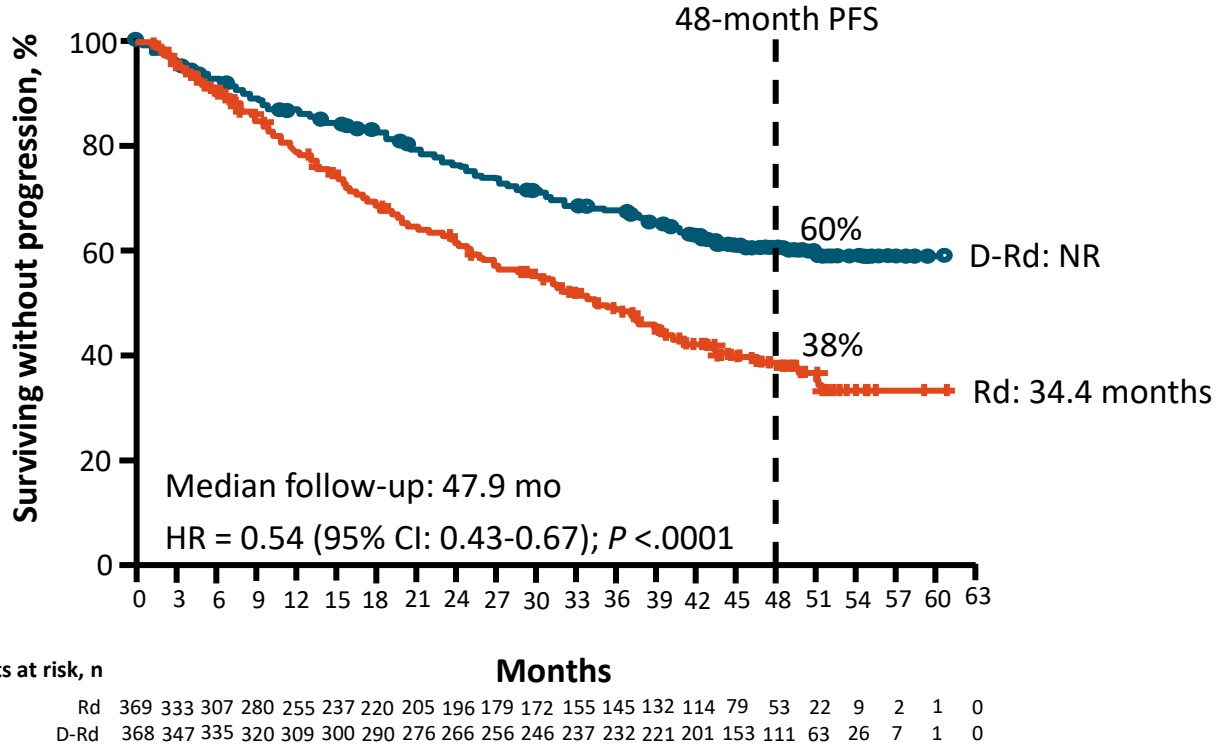
MAIA: PFS



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

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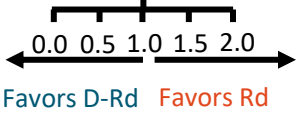
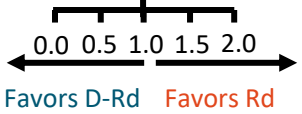
MAIA: Subgroup Analysis of PFS

	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)





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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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Patient Case Discussion: Newly Diagnosed + Relapsed/Refractory Multiple Myeloma

Eloísa Riva, MD

Hospital de Clínicas,

Montevideo, Uruguay

APTITUDE HEALTH®

Patient History and Frontline Therapy

- 48 y/o male, previously healthy. Engineer
- Feb 2019: bone pain and anemia
  - Blood tests: Hb 8 g/dL, no CPC. Creatinine 2.3 mg/dL. Calcium 12 mg/dL. Alb 3.8 g/dL. LDH elevated. B2 microglobulin 5770 mg/dL. MC 5.2 g/dL, IgG lambda. Immunoparesis
  - Urine test: 24h proteinuria 2 g. Lambda+
  - Bone marrow biopsy: 80% clonal plasma cells. t(14;16)+
  - Imaging: spine-pelvic MRI multiple lytic lesions on thoracic and lumbar spine

- MM IgG lambda, IIIB, RISS III, t(14;16)+

How do you treat young, high-risk MM patients?

a) VRd plus tandem ASCT plus bortezomib maintenance

b) Dara-VRd plus ASCT plus bortezomib maintenance

c) KRD

d) Dara-KRd

e) Other?

Patient History and Frontline Therapy

- Frontline therapy
  - VRD × 6, achieving VGPR
  - Tandem autologous SCT (08/2019 and 01/2020)
  - Bortezomib maintenance

Relapsed/Refractory Setting

3 months post-second aSCT

- Asymptomatic
- VGPR. MC 0.3 g/dL. sFLC kappa 12 and lambda 50 mg/L
- Bone marrow 5% plasma cells
- No proteinuria

5 months post-transplantation

- Numb sensation over his left chin spreading into his left lower anterior teeth
- Mild masticatory impairment
- No infection or local trauma. No dental surgery
- MRI imaging (head and neck): no abnormalities

6 months post-transplantation

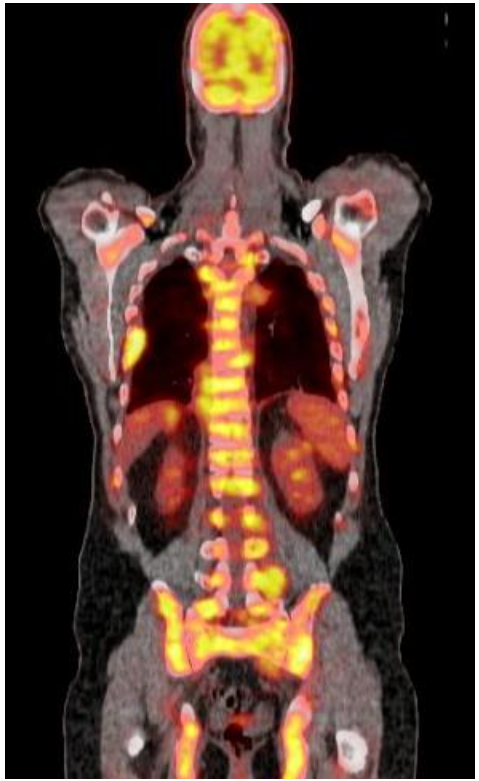
- Bone pain, dysarthria, and weakness. Masticatory impairment plus dysphagia
- 5-kg loss
- Exam: disorientation, bradypsychia, and dysarthria. Left hemitongue atrophy. Posterior right pillar palsy. Palpable tumor in the 7th left costal arch of 5 cm
- Hb 7 g/dL, Plt 20000/Ul, no CPC
- Creatinine 2.8 mg/dL, Ca 14 mg/dL
- MC 0.5 (lambda) and 0.3 g/dL (IgG lambda)
- sFLC kappa 9.7 mg/L, lambda 4470 mg/L
- B2 microglobulin 59 mg/dL. LDH × 3VN. Alb 2.3 g/dL
- BM: 70% clonal plasma cells. CG/FISH: no abnormalities

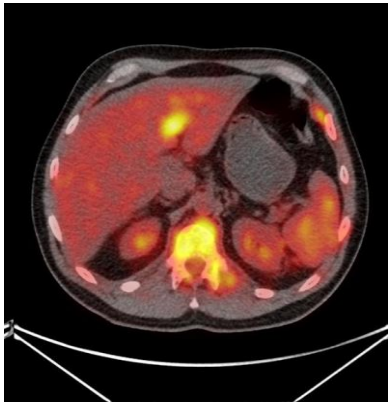
Imaging at Relapse

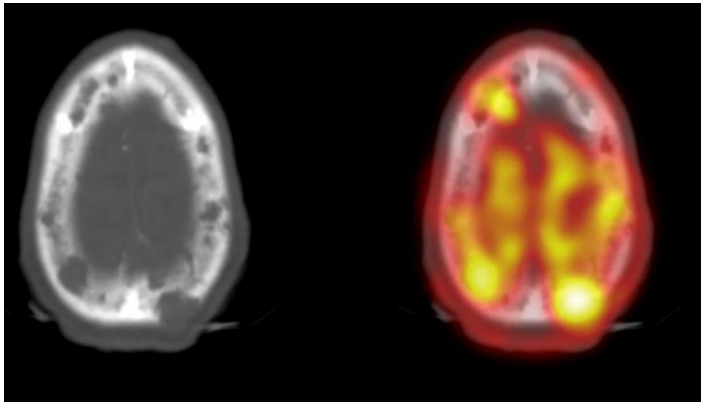
- Brain MRI: multiple lytic lesions on skull cap and base, with dural enhancement. Clivus involvement by a soft tissue component with intracranial extension and dural thickening with a slight mass effect in the temporal lobe

- LP+ immunophenotype: no infiltration, no infection (bacterial, virus, TBC, and fungal)

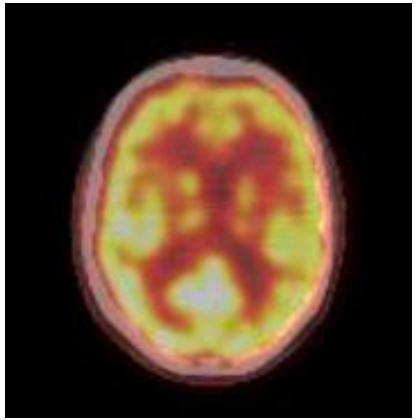
18-FDG PET-CT

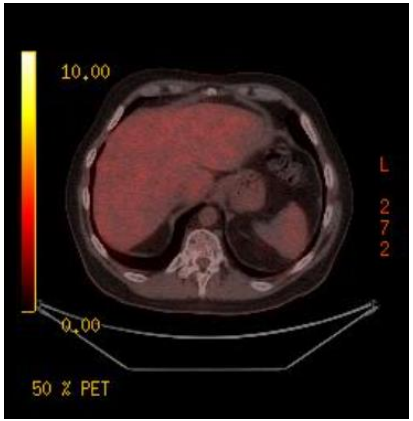






Dr Eloísa Riva. Montevideo, Uruguay





Dr Eloísa Riva. Montevideo, Uruguay

Treatment in the Relapsed/ Refractory Setting

- Second-line therapy
- Jul 2020: Cyc-dex followed by HCVAD-MA plus bw it mtx/cytarabine
  - TLS. Dialysis (2)
  - Partial clinical improvement. FLC lambda 340 mg/L. Creatinine 1.1 mg/dL. Calcium 8 mg/dL
- Sep 2020: daratumumab-pomalidomide-dexamethasone
  - CR at 2 months
  - CR at 7 months of therapy
  - Complete resolution of neurologic symptoms. Mild hemitongue atrophy
  - Hb 12 g/dL, PLT 76000/Ul, PEF and IFE–, sFLC normal
  - 18-FDG PET-CT: Unchanged lytic lesions. No abnormal masses. Complete metabolic regression

Points for Discussion

50 y/o MM IgG lambda, RISS 3, t(14;16)+. VRd × 6, tandem ASCT, bortezomib maintenance. Early aggressive relapse. HCVAD-MA followed by DPd. CR 7 months.

a) How do you treat aggressive MM relapse?

b) What is the role of allogeneic SCT?

c) Would MRD status define change of therapy?

d) What would you choose as next treatment?

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Session Close – Audience Response Questions

Rafael Fonseca, MD

APTITUDE HEALTH®

Question 1

Which of the following is not part of the new criteria for treatment initiation in MM? **[repeated question]**

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

Question 2

Which of the following is not true in the treatment of newly diagnosed MM? **[repeated question]**

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

Thank You!

- Please complete the **evaluation survey** that will be sent to you via chat
- The meeting recording and slides presented today will be shared on the www.globalmmacademy.com website

THANK YOU!

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Emerging and Practical Concepts in Multiple Myeloma

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