Welcome

participants at

Lankenau Medical Center

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Meet The Professor Program Steering Committee

Rafael Fonseca, MD
Getz Family Professor of Cancer
Chair, Department of Internal Medicine
Mayo Clinic Arizona
Scottsdale, Arizona

Ola Landgren, MD, PhD
Professor of Medicine
Chief, Myeloma Service
Department of Medicine
Memorial Sloan Kettering Cancer Center
New York, New York

Shaji K Kumar, MD
Professor of Medicine
Consultant
Division of Hematology and Blood and Marrow Transplantation
Mayo Clinic
Rochester, Minnesota

Sagar Lonial, MD
Chair and Professor
Department of Hematology and Medical Oncology
Anne and Bernard Gray Family Chair in Cancer
Chief Medical Officer
Winship Cancer Institute
Emory University School of Medicine
Atlanta, Georgia

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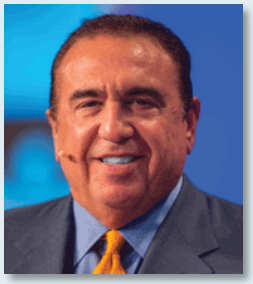
Meet The Professor Program Steering Committee

Nikhil C Munshi, MD
Professor of Medicine
Harvard Medical School
Director of Basic and Correlative Science
Associate Director, Jerome Lipper Multiple Myeloma Center
Department of Medical Oncology
Dana-Farber Cancer Institute
Boston, Massachusetts

Robert Z Orlowski, MD, PhD
Florence Maude Thomas Cancer Research Professor
Department of Lymphoma and Myeloma
Professor, Department of Experimental Therapeutics
Director, Myeloma Section
Division of Cancer Medicine
The University of Texas
MD Anderson Cancer Center
Houston, Texas

Noopur Raje, MD
Director
Center for Multiple Myeloma
Massachusetts General Hospital Cancer Center
Professor of Medicine
Harvard Medical School
Boston, Massachusetts

Nina Shah, MD
Associate Professor of Medicine
University of California
San Francisco
Division of Hematology-Oncology
San Francisco, California



Project Chair
Neil Love, MD
Research To Practice
Miami, Florida

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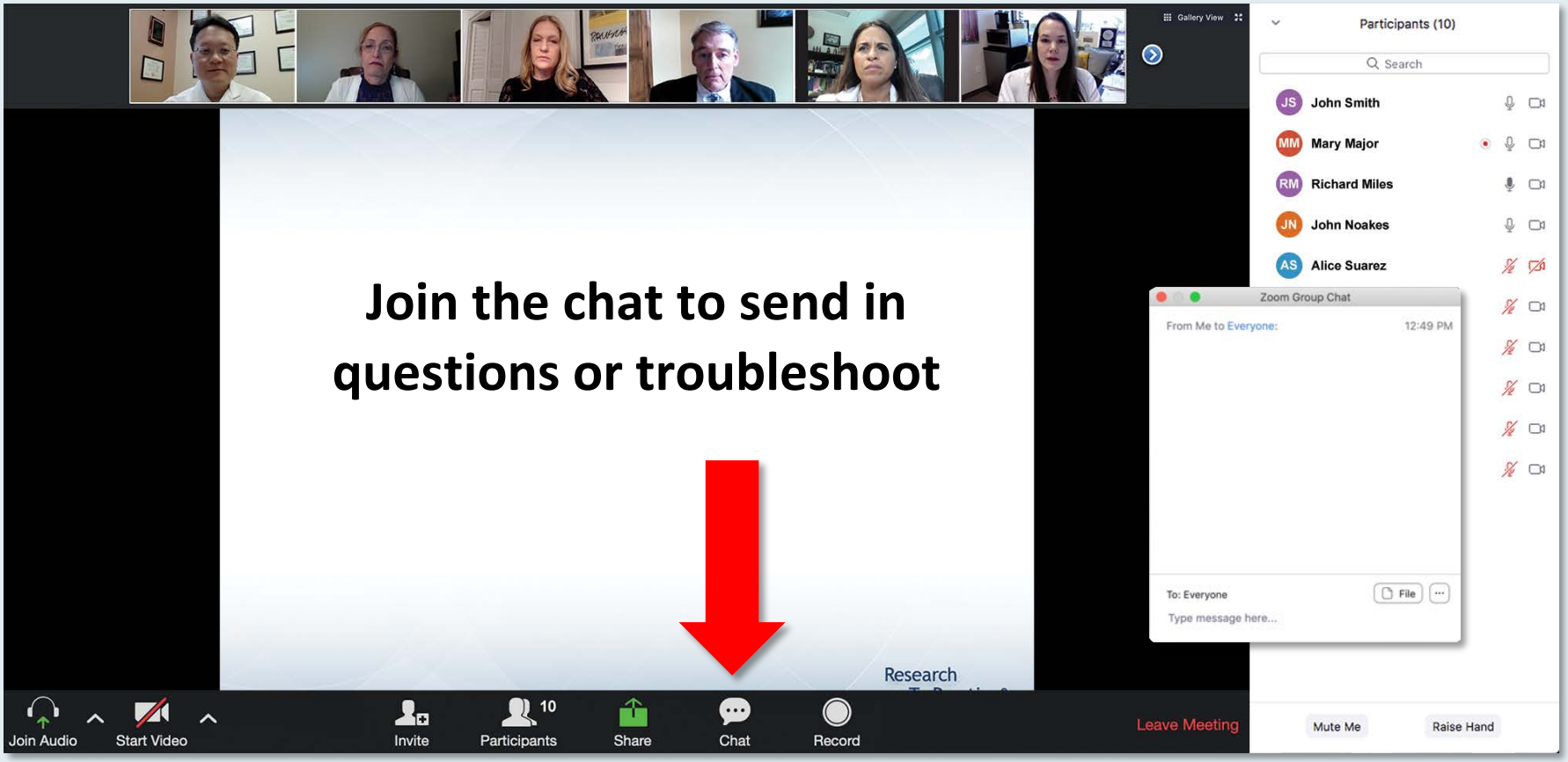
Familiarizing yourself with the Zoom interface

How to participate in the chat



Research To Practice®

Clinical Investigator Perspectives on the Current and Future Management of Multiple Myeloma

A Meet The Professor Series

Nina Shah, MD
Associate Professor of Medicine
University of California, San Francisco
Division of Hematology-Oncology
San Francisco, California

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Management of Multiple Myeloma (MM)

Module 1: Clinical Decision-Making for Patients with Newly Diagnosed MM (NDMM)

- Daratumumab-containing front-line therapy (CASSIOPEIA, MAIA, GRIFFIN)
- Minimal residual disease (MRD) testing and use in treatment decision-making
- Consolidation and maintenance therapy; emerging data with ixazomib (TOURMALINE-MM3, TOURMALINE-MM4)

Module 2: Contemporary Management of Relapsed/Refractory MM

- Data with daratumumab-containing regimens; split dosing
- Combination regimens with ixazomib (TOURMALINE-MM1)
- Recent FDA approval of selinexor and pivotal data from STORM
- Recent FDA approval of anti-CD38 isatuximab plus pomalidomide/low-dose dexamethasone and pivotal data from ICARIA-MM

Module 3: Novel Agents in Late-Stage Development

- Belantamab mafodotin (DREAMM-2)
- Clinical development of other anti-BCMA agents

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Case Presentation

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81-year-old frail woman

- Kappa light chain multiple myeloma with lytic bone lesions
  - FISH panel: Normal
  - Karyotype: Inversion 10
- Reluctant to start therapy
- RVD lite, with biochemical response (see kappa light chain levels)
  - Difficulty tolerating therapy, painful shingles despite prophylaxis
  - Significant fatigue and “mental fog” on lenalidomide
- Discontinued RVD lite, initiated daratumumab (split dose)/dexamethasone
  - Tolerating well
  - Plan to switch to subcutaneous daratumumab

Questions:

Given the fact that she had so much difficulty tolerating RVD lite, would I have been better off with the MAIA regimen for this woman? Any concerns about switching to subq daratumumab?

81-year-old frail woman
Kappa light chain levels

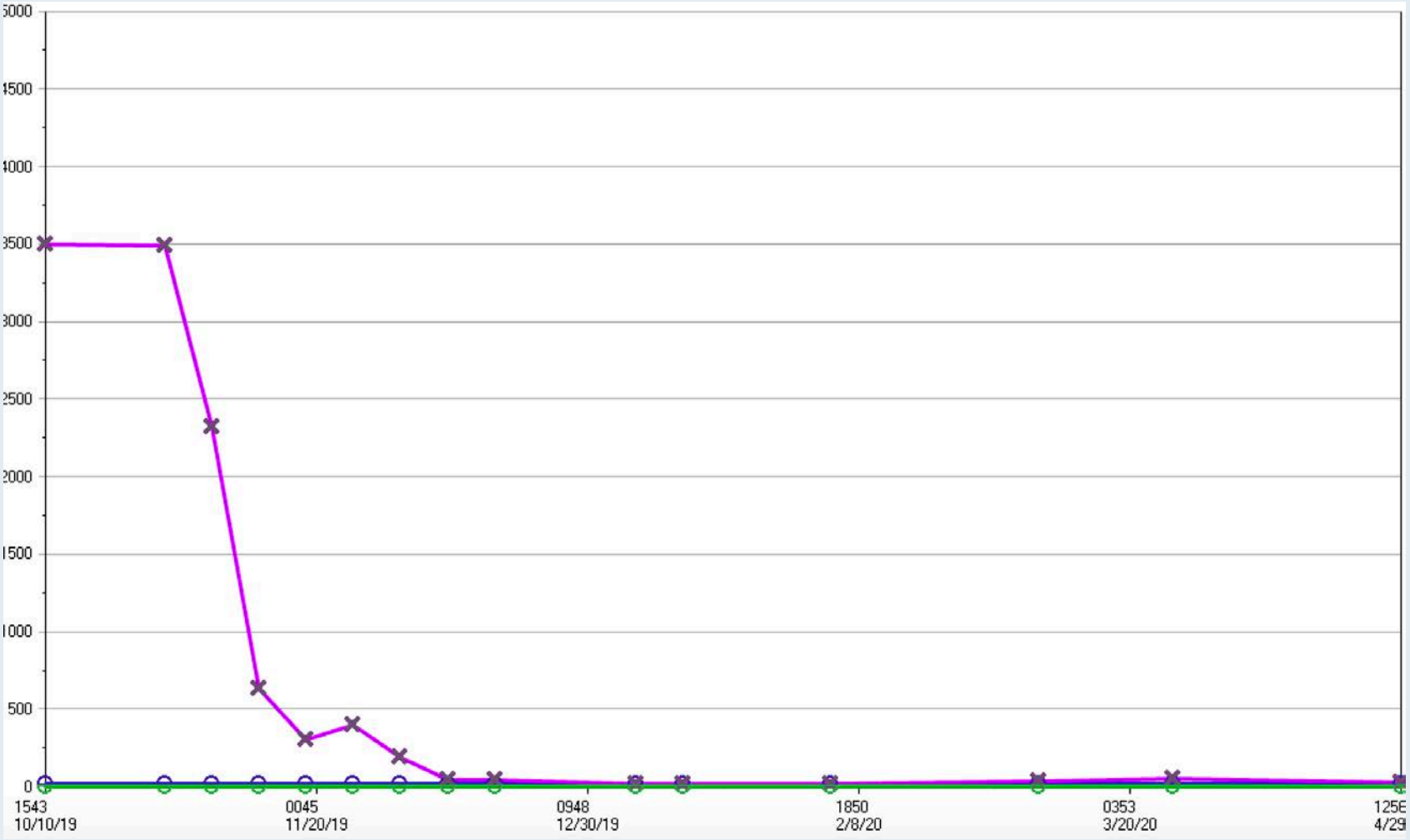
63-year-old woman with PMH of systemic lupus, depression and back pain

- T8 and L1 compression fractures → Kyphoplasty for pain relief
- ISS Stage II IgG kappa multiple myeloma (FISH: trisomy 9 and 11)
- RVD + denosumab monthly
  - Great response with normalization of light chains, resolution of M-spike after 4 cycles of RVD (see graphic)
- ASCT recommended
- COVID-19 pandemic delays stem cell collection
- One additional cycle of RVD administered
- Currently, no clinical or biochemical evidence of myeloma (see PET CT)

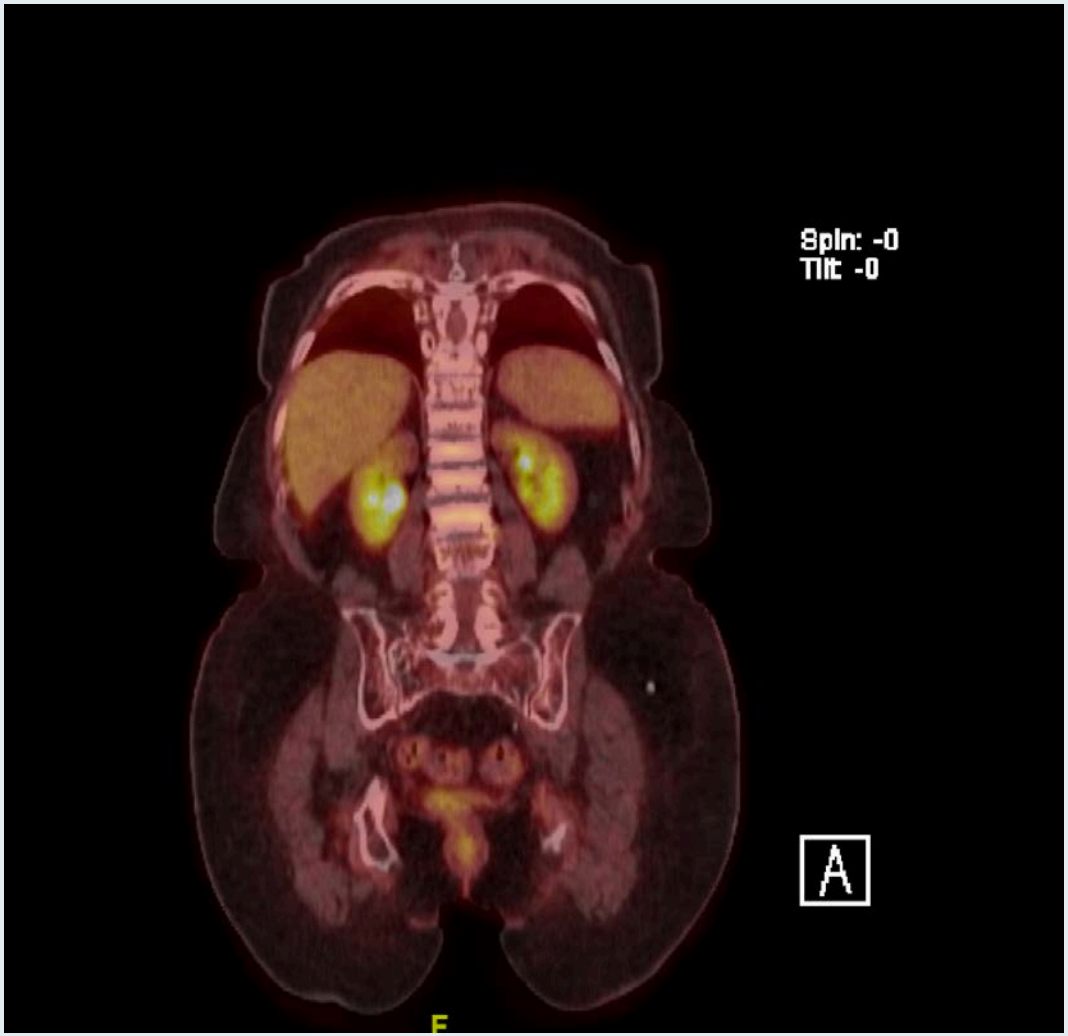
Question:

Given this lady's lupus and significant history of depression, if she were found to be MRD-negative, would maintenance lenalidomide be preferred over consolidation autologous transplant?

63-year-old woman
Normalization of light chains



63-year-old woman
PET CT: No evidence of active disease



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74-year-old woman

- ISS Stage II IgG lambda multiple myeloma
- Lenalidomide/dexamethasone (good response) → Maintenance lenalidomide
  - Deferred ASCT
- Relapse, large plasmacytoma in the jaw
- 10/2017: Radiotherapy → Lenalidomide/ixazomib/dexamethasone → Consolidation ASCT → Maintenance ixazomib
- Currently, remains on ixazomib with no evidence of relapse
  - Worsening neuropathy causing ADL difficulties; B-12 not helpful

Questions:

- How often is peripheral neuropathy seen with ixazomib, and how is this managed?
- Would you dose reduce and discontinue if the peripheral neuropathy does not improve?
- How long would you continue the ixazomib?

74-year-old woman
No M spike and Normal Light Chains

PROTEIN ELP					
Albumin Electropho...	3.75				3.67
Alpha-1-Globulin	0.29				0.21
Alpha-2-Globulin	0.68				0.79
Gamma Globulin	0.80				0.77
Protein Beta-1	0.33				0.34
Protein BETA-2	0.26				0.22
THYROID					
TSH W/REFLEX TO FT4		5.488 *			
OTHER IMMUNOLOGY					
Kappa/Lambda Fluid...				1.500 *	
KAPPA FREE LIGHT C...				12.9	

74-year-old woman
Normal Creatinine and Calcium

ⓘ Newer results are available. Click to view them now.

Component Ref Range & Units	2mo ago (3/3/20)	2mo ago (3/3/20)	3mo ago (1/29/20)	3mo ago (1/29/20)	6mo ago (11/27/19)	6mo ago (11/27/19)
Glucose 74 - 106 mg/dL	78	78.000 R		94		98
BUN 9 - 23 mg/dL	18			21		14
AST <=34 u/l	26			27		31
Total Protein 5.7 - 8.2 G/DL	6.1		6.1 ⌄ R	6.3	6.2 R	6.2
Albumin 3.4 - 5.0 G/DL	3.7			3.8		4.3 R
Calcium 8.3 - 10.6 mg/dL	9.2			8.7		9.1
Total Bilirubin 0.3 - 1.2 mg/dL	0.6			1.3 ^		1.2
Alkaline Phosphatase 46 - 116 u/l	87			84		71
Creatinine 0.6 - 1.0 mg/dL	1.0			0.8		0.9
Sodium 136 - 145 MMOL/L	141			139		142

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74-year-old woman
Stable CBC

Ref Range & Units	2mo ago	3mo ago	6mo ago	7mo ago	8mo ago	9mo ago
WBC 4.5 - 11.0 10(3)/uL	6.0	5.7	3.1 ↓	4.2 ↓	4.8	3.6 ↓
NRBC % 0 - 5 %	0	0	0	0	0	0
RBC 4.00 - 5.20 10(6)/uL	3.98 ↓	3.54 ↓	4.26 R	4.14 R	4.03 R	4.16 R
Hemoglobin 12.0 - 16.0 G/DL	12.2	10.7 ↓	13.1	12.8	12.5	12.9
Hematocrit 33.0 - 51.0 %	38.7	35.6	41.8	40.7 R	40.2 R	41.7 R
MCV 83.0 - 98.0 CU/MIC	97.2	100.6 ↑	98.1 ↑	98.3 ↑ R	99.8 ↑ R	100.2 ↑ R
MCH 28.0 - 33.0 PG	30.7	30.2	30.8	30.9 R	31.0 R	31.0 R
MCHC 32.0 - 36.0 %	31.5 ↓	30.1 ↓	31.3 ↓	31.4 R	31.1 R	30.9 ↓ R
RDW-SD 39.0 - 46.0 CU/MIC	54.8 ↑	61.0 ↑	53.0 ↑ R	51.8 ↑ R	53.4 ↑ R	56.7 ↑ R
RDW-CV 11.6 - 14.7 %	15.3 ↑	16.7 ↑	14.6 ↑ R	14.4 R	14.4 R	15.3 ↑ R
Platelets 180 - 400 10(3)/uL	112 ↓	193	65 ↓ CM	129 ↓ R	167 R	68 ↓ R, CM
Resulting Agency	RHH	RHH	RHH	RHH	RHH	Syslink

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Audience Polling

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Currently, what is your usual pretransplant induction regimen for a 65-year-old patient with MM and no high-risk features?

1. RVD (lenalidomide/bortezomib/dexamethasone)
2. KRd (carfilzomib/lenalidomide/dexamethasone)
3. CyBorD
4. MVP, MPR or MPT (M = melphalan, P = prednisone, V = bortezomib, R = lenalidomide, T = thalidomide)
5. MVP/daratumumab
6. Rd/daratumumab
7. VTd (bortezomib/thalidomide/dexamethasone) with daratumumab
8. RVD/daratumumab
9. KRd/daratumumab
10. Other

Currently, what pretransplant induction regimen would you recommend for a 65-year-old patient with multiple myeloma (MM)?

	Standard risk	Del(17p)
 RAFAEL FONSECA, MD	KRd	RVD
 SHAJI K KUMAR, MD	RVD	RVD/daratumumab
 OLA LANDGREN, MD, PHD	KRd	KRd
 SAGAR LONIAL, MD	RVD/daratumumab	KRd
 NIKHIL C MUNSHI, MD	RVD	RVD/daratumumab
 ROBERT Z ORLOWSKI, MD, PHD	KRd	KRd
 NOOPUR RAJE, MD	RVD	KRd ± daratumumab
 NINA SHAH, MD	RVD	KRd

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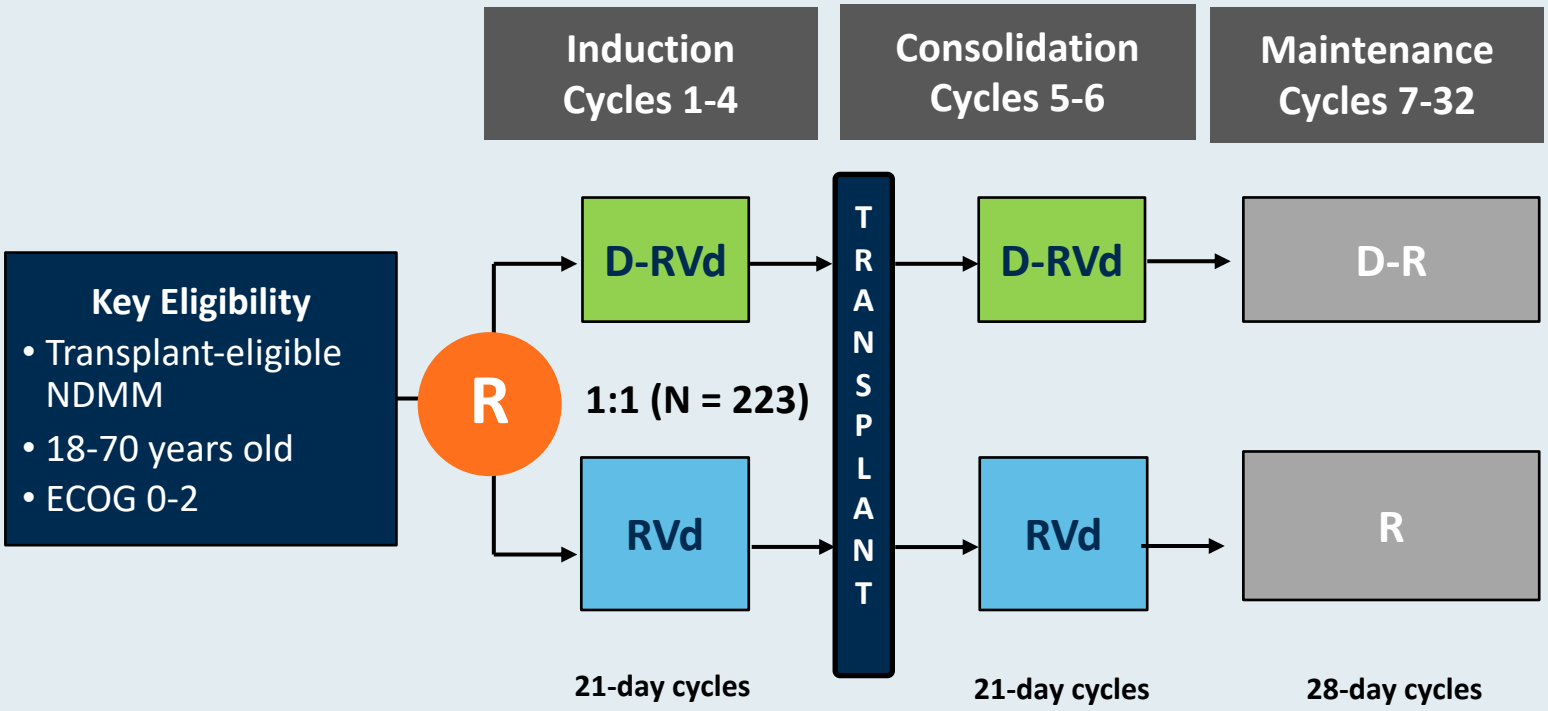
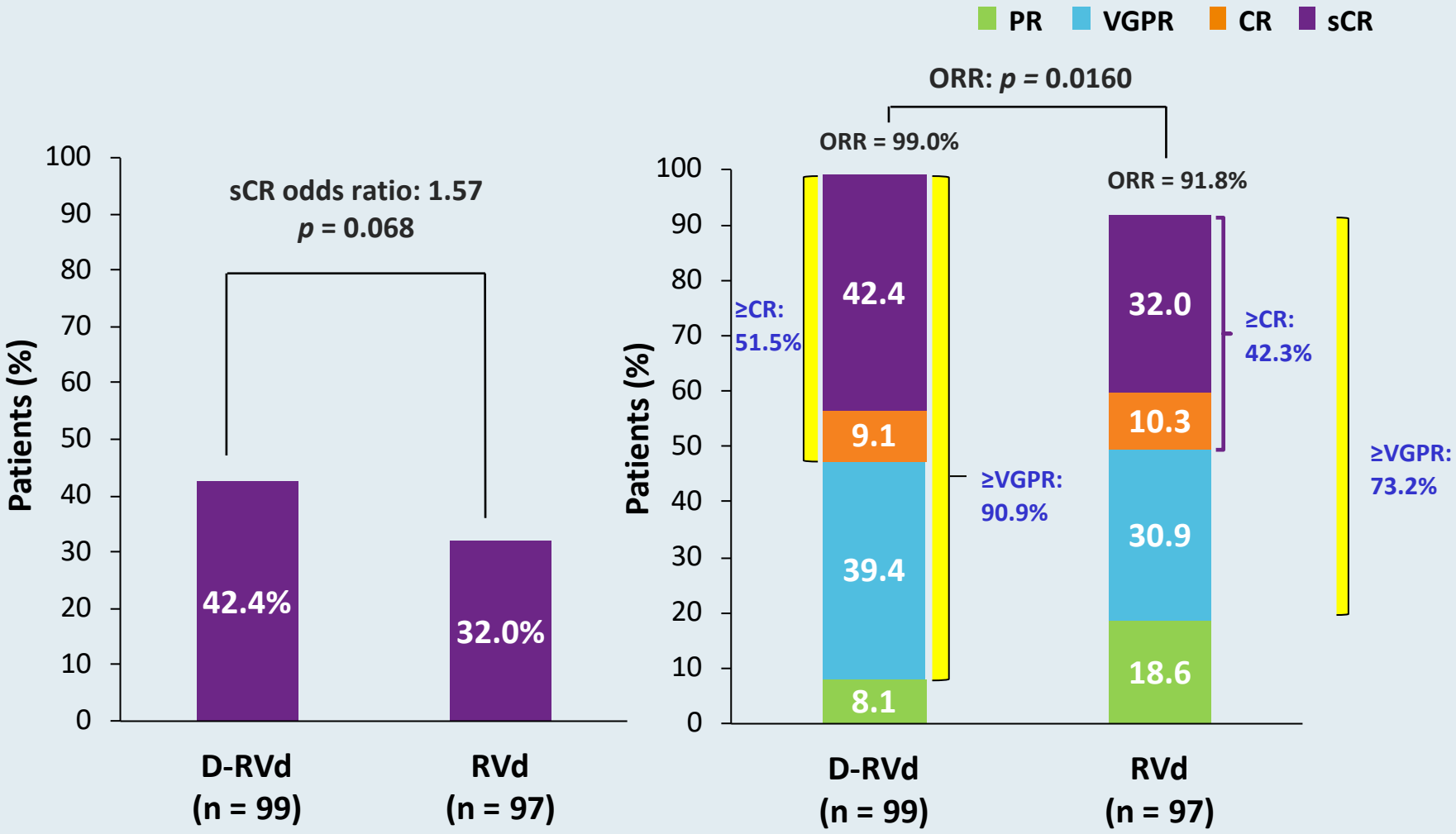
GRIFFIN Randomized Phase II Study Design



Primary endpoint: Stringent CR by end of consolidation

Voorhees P et al. IMW 2019;Abstract 906.
www.clinicaltrials.gov. Accessed January 23, 2020 (NCT02874742).

GRIFFIN Primary Endpoint: sCR at the End of Consolidation



Voorhees P et al. IMW 2019;Abstract 906.

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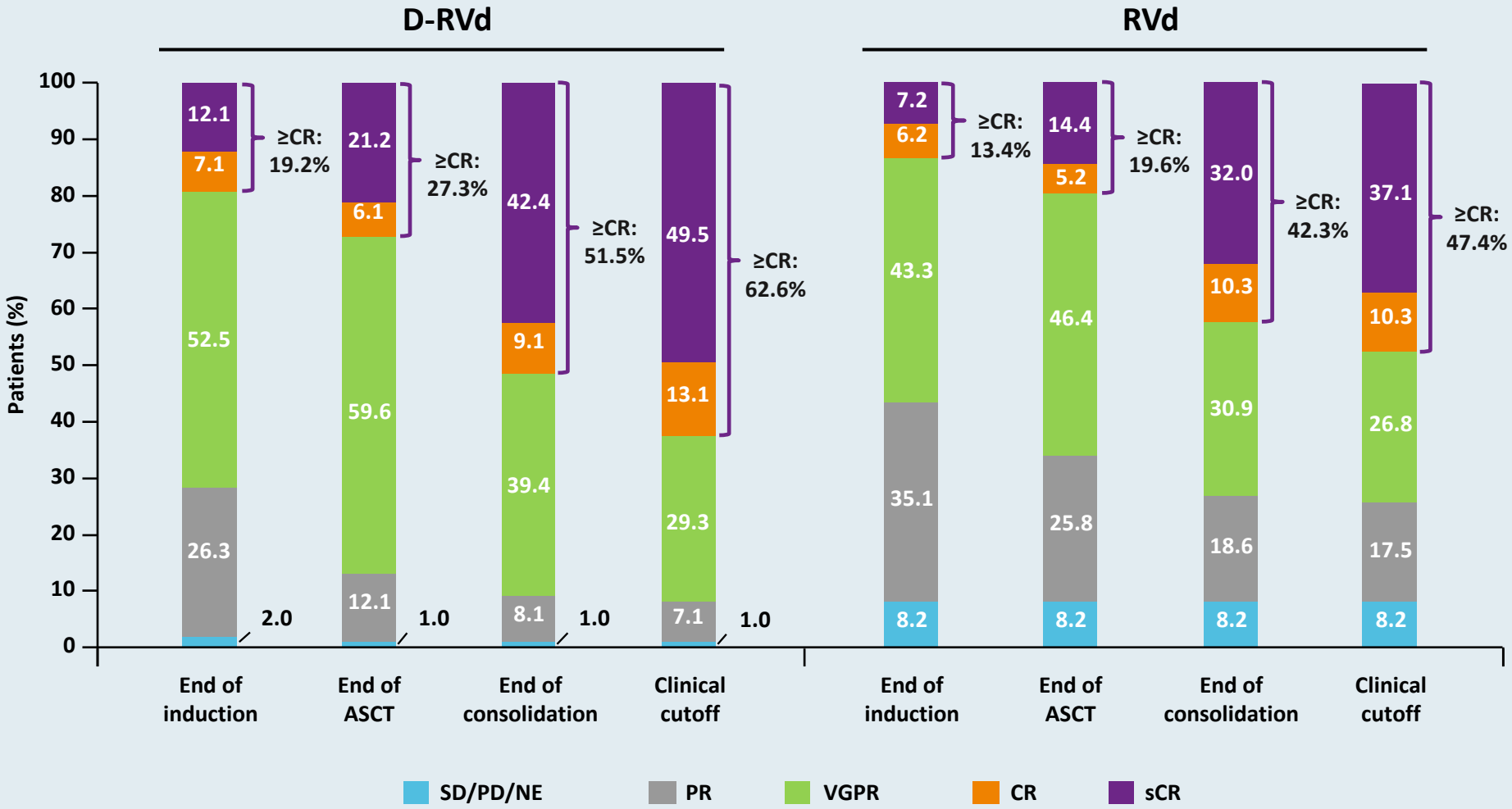
GRIFFIN: Depth of Response Over Time



Voorhees P et al. IMW 2019;Abstract 906.

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Regulatory and reimbursement issues aside, what is your preferred induction regimen for an 85-year-old patient with ISS Stage II MM who is transplant ineligible?

	Standard risk, normal renal function	Del(17p)
 RAFAEL FONSECA, MD	Rd/dara	RVD
 SHAJI K KUMAR, MD	Rd/dara	RVD lite
 OLA LANDGREN, MD, PHD	Rd/dara	RVD lite
 SAGAR LONIAL, MD	Rd/dara	RVD lite
 NIKHIL C MUNSHI, MD	Rd	RVD lite
 ROBERT Z ORLOWSKI, MD, PHD	RVD or RVD lite	RVD lite
 NOOPUR RAJE, MD	RVD or RVD lite or Rd/dara	RVD lite
 NINA SHAH, MD	RVD or RVD lite or Rd/dara	RVD lite or KRd

Dara = daratumumab

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

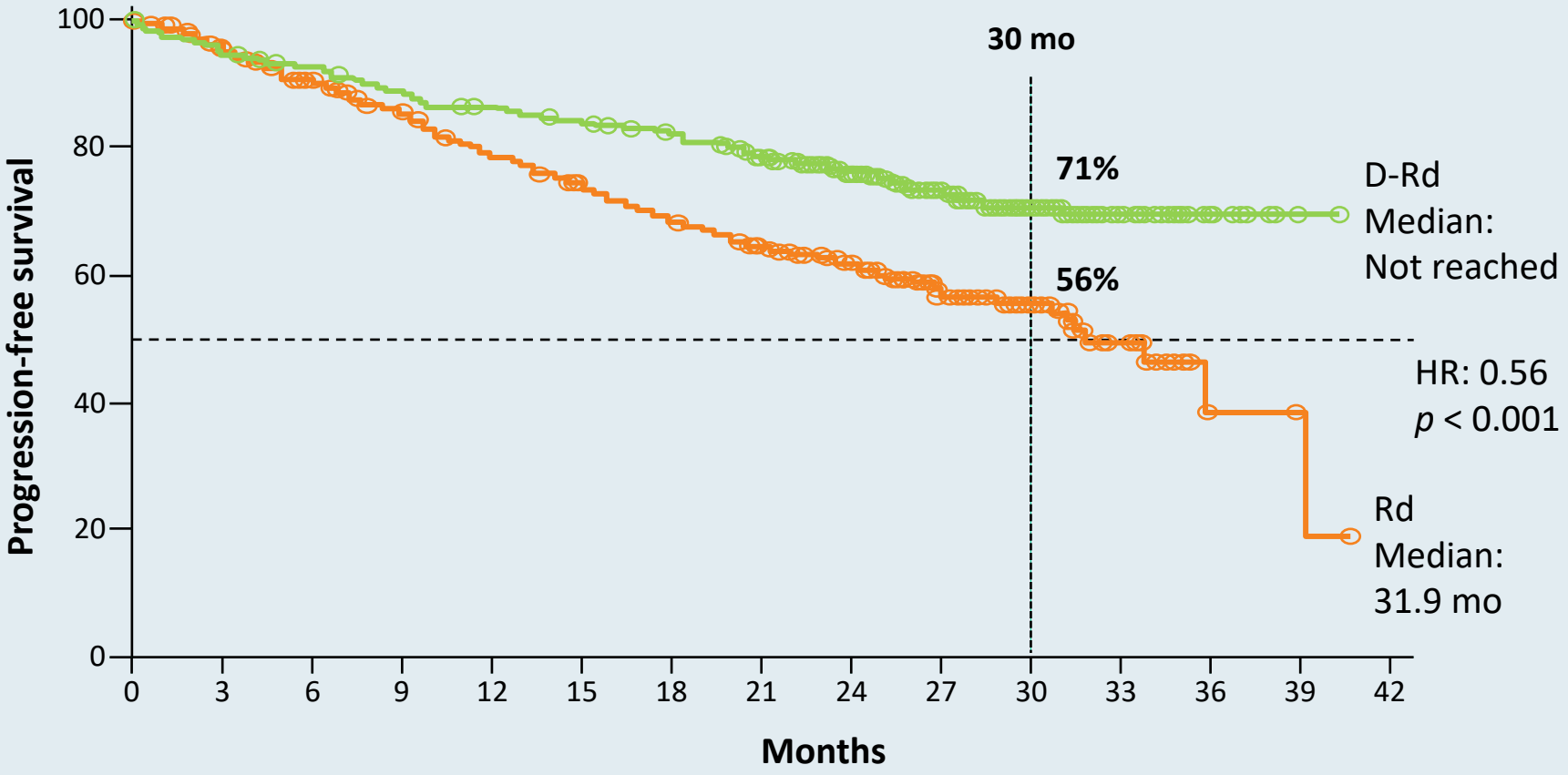
Daratumumab plus Lenalidomide and Dexamethasone for Untreated Myeloma

T. Facon, S. Kumar, T. Plesner, R.Z. Orlowski, P. Moreau, N. Bahlis, S. Basu, H. Nahi, C. Hulin, H. Quach, H. Goldschmidt, M. O'Dwyer, A. Perrot, C.P. Venner, K. Weisel, J.R. Mace, N. Raje, M. Attal, M. Tiab, M. Macro, L. Frenzel, X. Leleu, T. Ahmadi, C. Chiu, J. Wang, R. Van Rampelbergh, C.M. Uhlar, R. Kobos, M. Qi, and S.Z. Usmani, for the MAIA Trial Investigators*

N Engl J Med 2019;380(22):2104-15.

MAIA Primary Endpoint: Progression-Free Survival

NDMM Transplant Ineligible



Facon T et al. *N Engl J Med* 2019;380(22):2104-15.

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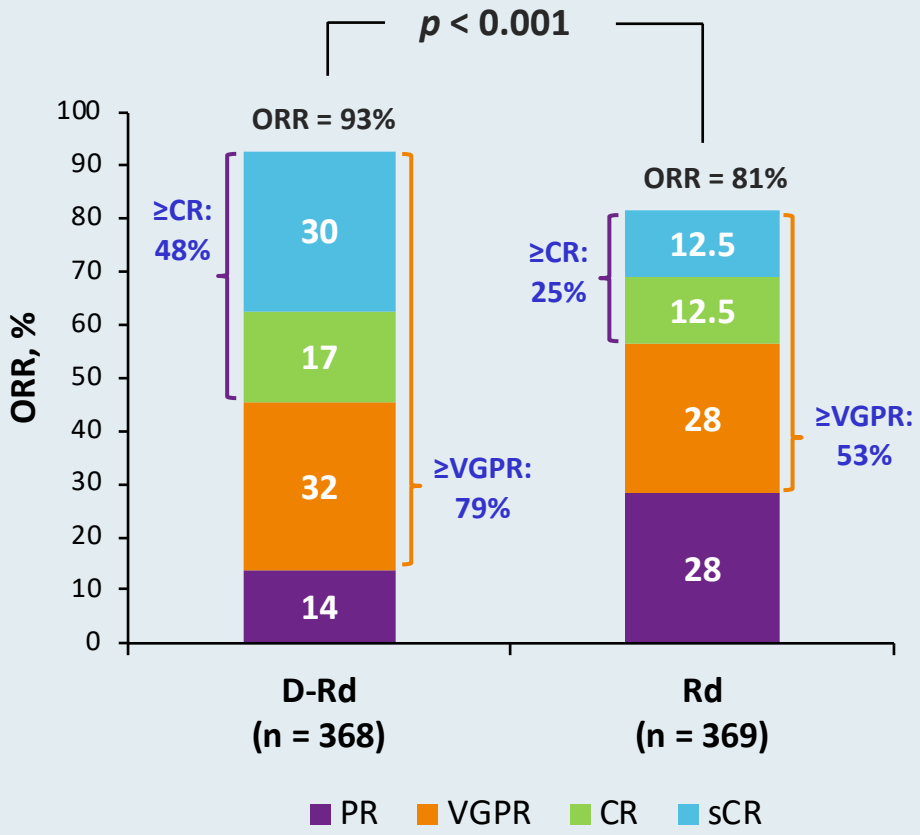
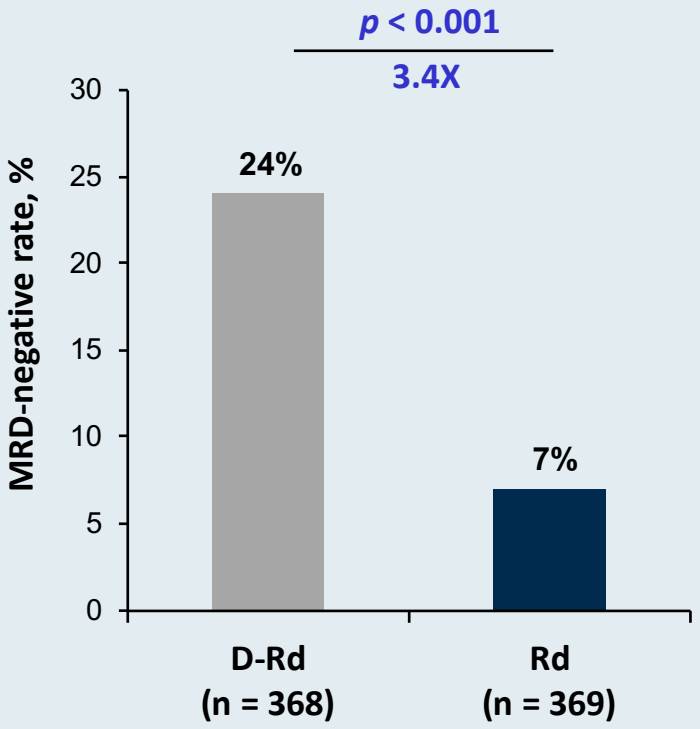
MAIA: Overall Response Rate and MRD (NGS; 10^{-5} Sensitivity Threshold) Rate





Facon T et al. *N Engl J Med* 2019;380(22):2104-15.

Are there situations in which you believe community-based oncologists/hematologists should be ordering minimal residual disease (MRD) assessment to guide treatment decision-making for patients with MM?

 RAFAEL FONSECA, MD	Yes – Pts in long-term CR or with plasmacytomas; monitoring amyloidosis
 SHAJI K KUMAR, MD	Yes – Pts with high-risk disease
 OLA LANDGREN, MD, PHD	Yes – After combination therapy; if MRD-negative, collect and store stem cells. Then go straight to maintenance
 SAGAR LONIAL, MD	No
 NIKHIL C MUNSHI, MD	Yes – Post-transplant, at CR, before and during maintenance
 ROBERT Z ORLOWSKI, MD, PHD	Yes, timing the number of induction cycles prior to stem cell collection for patients in CR
 NOOPUR RAJE, MD	No
 NINA SHAH, MD	No, I don't believe this test should be ordered in the community to make clinical decisions

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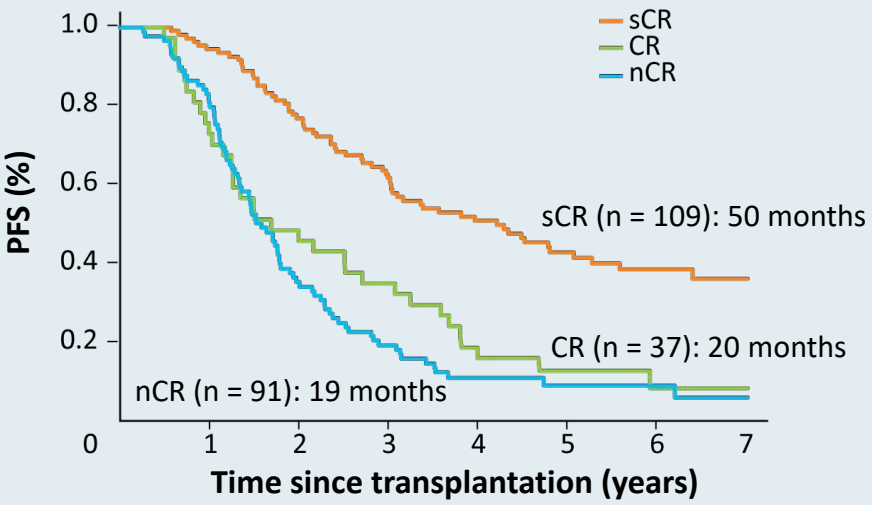
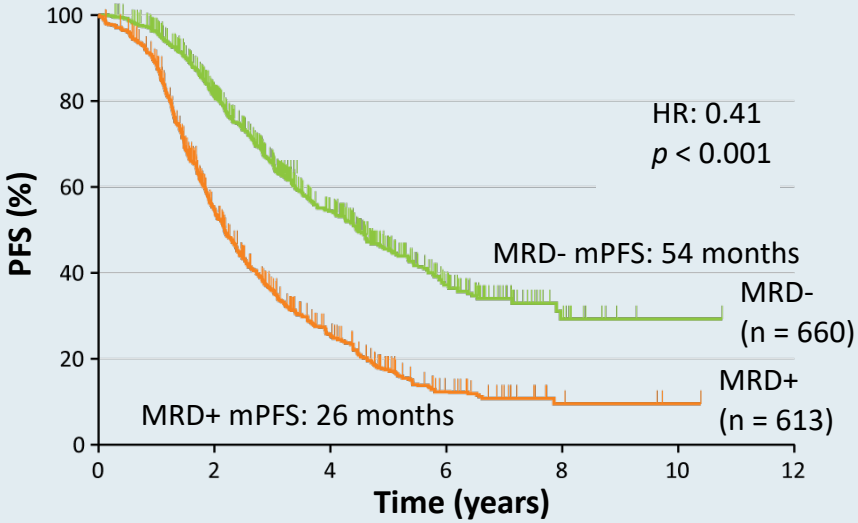
Stringent Complete Response (sCR) and MRD as a Surrogate Endpoint for PFS and OS

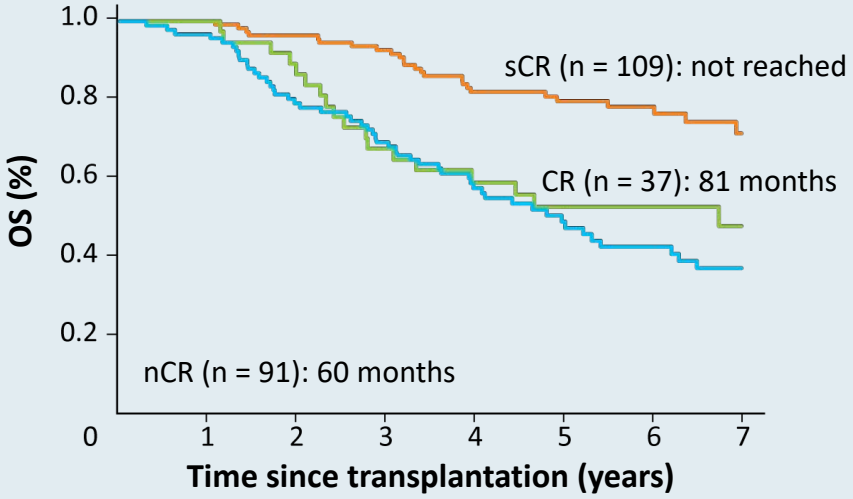
Median TTP for patients achieving CR[1]



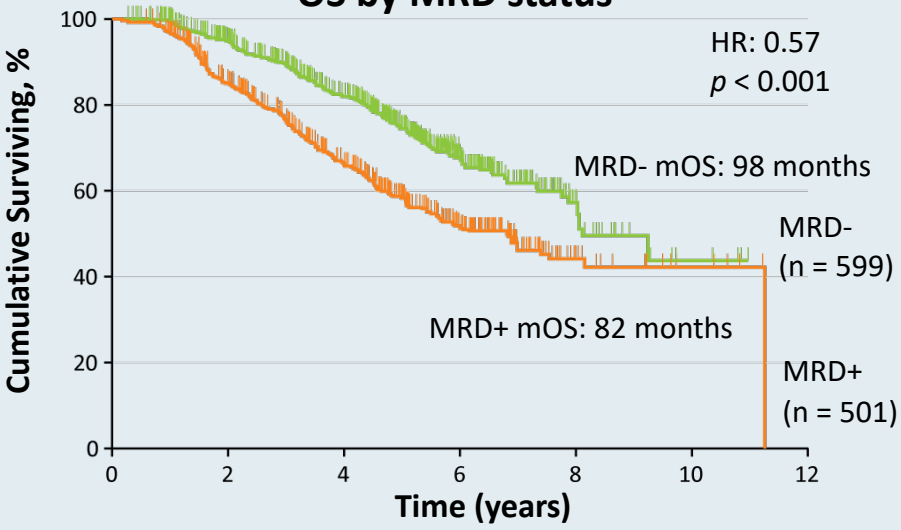
PFS by MRD status[2]



Median OS for patients achieving CR[1]



OS by MRD status[2]



1. Kapoor P et al. *J Clin Oncol* 2013;31(36):4529-35.
2. Munshi NC et al. *JAMA Oncol* 2017:3(1):28-35.

Co-provided by USF Health Research To Practice®

What is your usual recommendation for post-ASCT maintenance therapy for patients with MM who received RVD induction therapy?

	Standard-risk	Del(17p)
 RAFAEL FONSECA, MD	Lenalidomide	Len/ixa ± dex
 SHAJI K KUMAR, MD	Lenalidomide	Len/bortez ± dex
 OLA LANDGREN, MD, PHD	Lenalidomide	Lenalidomide
 SAGAR LONIAL, MD	Lenalidomide	Len/bortez ± dex
 NIKHIL C MUNSHI, MD	Lenalidomide + dex	Len/bortez ± dex
 ROBERT Z ORLOWSKI, MD, PHD	Lenalidomide	Len/ixa ± dex
 NOOPUR RAJE, MD	Lenalidomide	Len/ixa ± dex or Len/bortez ± dex
 NINA SHAH, MD	Lenalidomide	Len/K ± dex

Len = lenalidomide; ixa = ixazomib; dex = dexamethasone; bortez = bortezomib; K = carfilzomib

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VOLUME 35 · NUMBER 29 · OCTOBER 10, 2017

JOURNAL OF CLINICAL ONCOLOGY

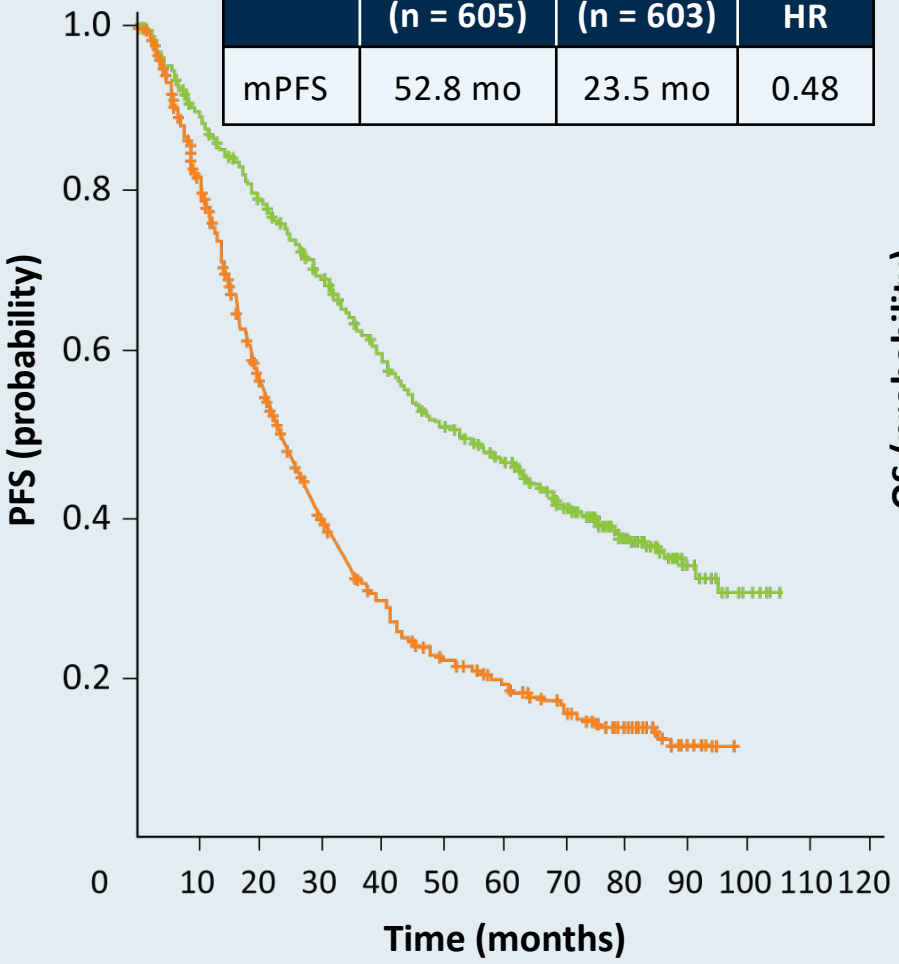
ORIGINAL REPORT

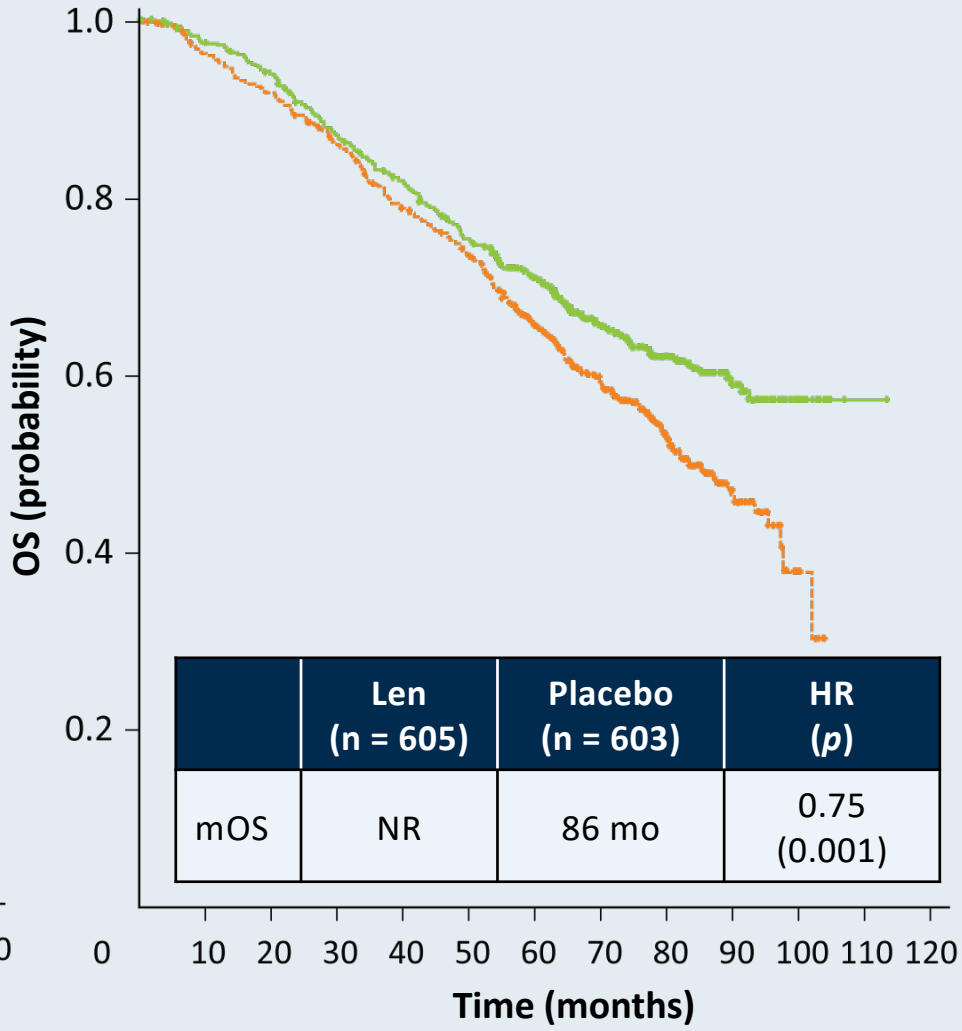
Lenalidomide Maintenance After Autologous Stem-Cell Transplantation in Newly Diagnosed Multiple Myeloma: A Meta-Analysis

Philip L. McCarthy, Sarah A. Holstein, Maria Teresa Petrucci, Paul G. Richardson, Cyrille Hulin, Patrizia Tosi, Sara Bringhen, Pellegrino Musto, Kenneth C. Anderson, Denis Caillot, Francesca Gay, Philippe Moreau, Gerald Marit, Sin-Ho Jung, Zhinuan Yu, Benjamin Winograd, Robert D. Knight, Antonio Palumbo, and Michel Attal

Survival Analyses of Lenalidomide Maintenance After ASCT in NDMM: A Meta-Analysis

	Len (n = 605)	Placebo (n = 603)	HR
mPFS	52.8 mo	23.5 mo	0.48





	Len (n = 605)	Placebo (n = 603)	HR (*p*)
mOS	NR	86 mo	0.75 (0.001)

McCarthy PL et al. *J Clin Oncol* 2017;35(29):3279-89.

Co-provided by USF Health Research To Practice®

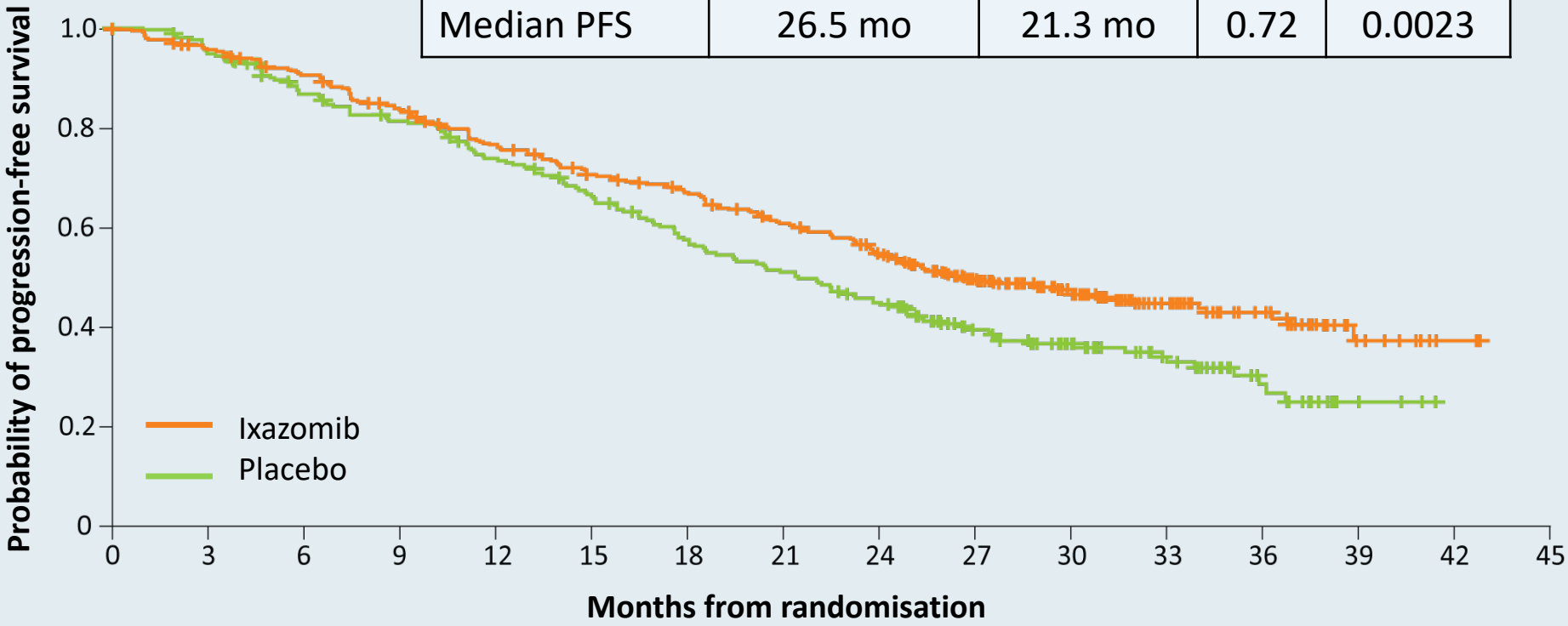
Oral ixazomib maintenance following autologous stem cell transplantation (TOURMALINE-MM3): a double-blind, randomised, placebo-controlled phase 3 trial

*Meletios A Dimopoulos, Francesca Gay, Fredrik Schjesvold, Meral Beksac, Roman Hajek, Katja Christina Weisel, Hartmut Goldschmidt, Vladimir Maisnar, Philippe Moreau, Chang Ki Min, Agnieszka Pluta, Wee-Joo Chng, Martin Kaiser, Sonja Zweegman, Maria-Victoria Mateos, Andrew Spencer, Shinsuke Iida, Gareth Morgan, Kaveri Suryanarayan, Zhaoyang Teng, Tomas Skacel, Antonio Palumbo, Ajeeta B Dash, Neeraj Gupta, Richard Labotka, S Vincent Rajkumar, on behalf of the TOURMALINE-MM3 study group**

Lancet 2019;393(10168):253-64.

TOURMALINE-MM3 Primary Endpoint: Progression-Free Survival (ITT)

	Ixazomib (n = 395)	Placebo (n = 261)	HR	*p*-value
Median PFS	26.5 mo	21.3 mo	0.72	0.0023



Dimopoulos MA et al. *Lancet* 2019;393(10168):253-64.

TOURMALINE-MM4 Trial of Ixazomib as First-Line Maintenance Therapy Met Primary Endpoint for MM Not Treated with Stem Cell Transplantation

Press Release – November 08, 2019

"The randomized, Phase 3 TOURMALINE-MM4 study met its primary endpoint of progression free survival (PFS). The trial evaluated the effect of single-agent oral ixazomib as a first line maintenance therapy versus placebo in adult patients diagnosed with multiple myeloma not treated with stem cell transplantation. TOURMALINE-MM4 is the first industry sponsored Phase 3 trial to explore the concept of 'switch' maintenance, the use of medicines not included in initial induction therapy, in this setting."

https://pipelinereview.com/index.php/2019110872810/Small-Molecules/Phase-3-Trial-of-NINLAROTM-ixazomib-as-First-Line-Maintenance-Therapy-Met-Primary-Endpoint-in-Multiple-Myeloma-Patients-not-treated-with-Stem-Cell-Transplantation.html

Co-provided by USF Health Research To Practice®

Management of Multiple Myeloma (MM)

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- Minimal residual disease (MRD) testing and use in treatment decision-making
- Consolidation and maintenance therapy; emerging data with ixazomib (TOURMALINE-MM3, TOURMALINE-MM4)

Module 2: Contemporary Management of Relapsed/Refractory MM

- Data with daratumumab-containing regimens; split dosing
- Combination regimens with ixazomib (TOURMALINE-MM1)
- Recent FDA approval of selinexor and pivotal data from STORM
- Recent FDA approval of anti-CD38 isatuximab plus pomalidomide/low-dose dexamethasone and pivotal data from ICARIA-MM

Module 3: Novel Agents in Late-Stage Development

- Belantamab mafodotin (DREAMM-2)
- Clinical development of other anti-BCMA agents

Co-provided by USF Health Research To Practice®

Case Presentation

Co-provided by USF Health Research To Practice®

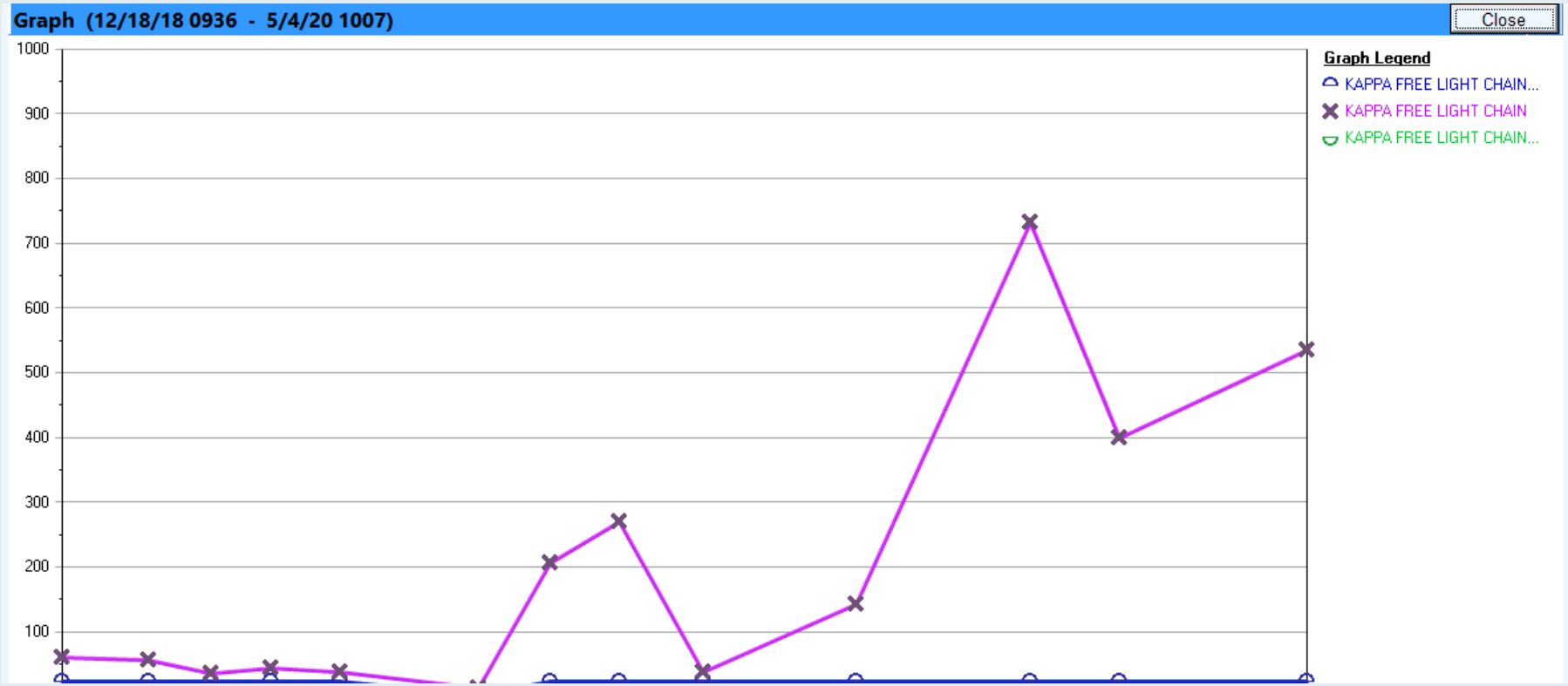
80-year-old transplant-ineligible man

- ISS Stage III IgG kappa multiple myeloma, with multiple lytic bone lesions
  - FISH: deletion 17p
- RVD
  - On and off lenalidomide intermittently past 2 years due to fatigue and rash
- Progressive disease: Increasing kappa light chain level (see graph), new bone lesions and concurrent myocardial infarction
  - Placement of 2 coronary artery stents
  - Recovering well

Question:

What regimen should he receive given his history of cardiac disease and poor tolerance of lenalidomide?

80-year-old transplant-ineligible man
Increasing light chains



Audience Polling

Co-provided by USF Health Research To Practice®

What is your usual treatment recommendation for a patient with MM who receives RVD followed by ASCT and maintenance lenalidomide for 1.5 years who then experiences an asymptomatic biochemical relapse?

1. Carfilzomib +/- dexamethasone
2. Pomalidomide +/- dexamethasone
3. Carfilzomib + pomalidomide +/- dexamethasone
4. Elotuzumab + lenalidomide +/- dexamethasone
5. Elotuzumab + pomalidomide +/- dexamethasone
6. Daratumumab + lenalidomide +/- dexamethasone
7. Daratumumab + pomalidomide +/- dexamethasone
8. Daratumumab + bortezomib +/- dexamethasone
9. Ixazomib + Rd
10. Other

What is your usual treatment recommendation for a patient with MM who receives RVD followed by ASCT, who experiences asymptomatic biochemical relapse after …

	1.5 years of maintenance lenalidomide	3 years of maintenance lenalidomide
 RAFAEL FONSECA, MD	Dara/pom ± dex	Dara/pom ± dex
 SHAJI K KUMAR, MD	Dara/pom ± dex	Dara/pom ± dex
 OLA LANDGREN, MD, PHD	Dara/pom ± dex	Dara/pom ± dex
 SAGAR LONIAL, MD	Dara/pom ± dex	Dara/pom ± dex
 NIKHIL C MUNSHI, MD	Dara/pom ± dex	Elo/pom ± dex
 ROBERT Z ORLOWSKI, MD, PHD	Dara/pom ± dex	Ixazomib + Rd
 NOOPUR RAJE, MD	Dara/pom ± dex Carfilzomib/pom ± dex if high risk	Pom ± dex or dara/pom ± dex
 NINA SHAH, MD	Dara/pom ± dex	Dara/pom ± dex

Dara = daratumumab; pom = pomalidomide;
Elo = elotuzumab

Co-provided by USF Health Research To Practice®

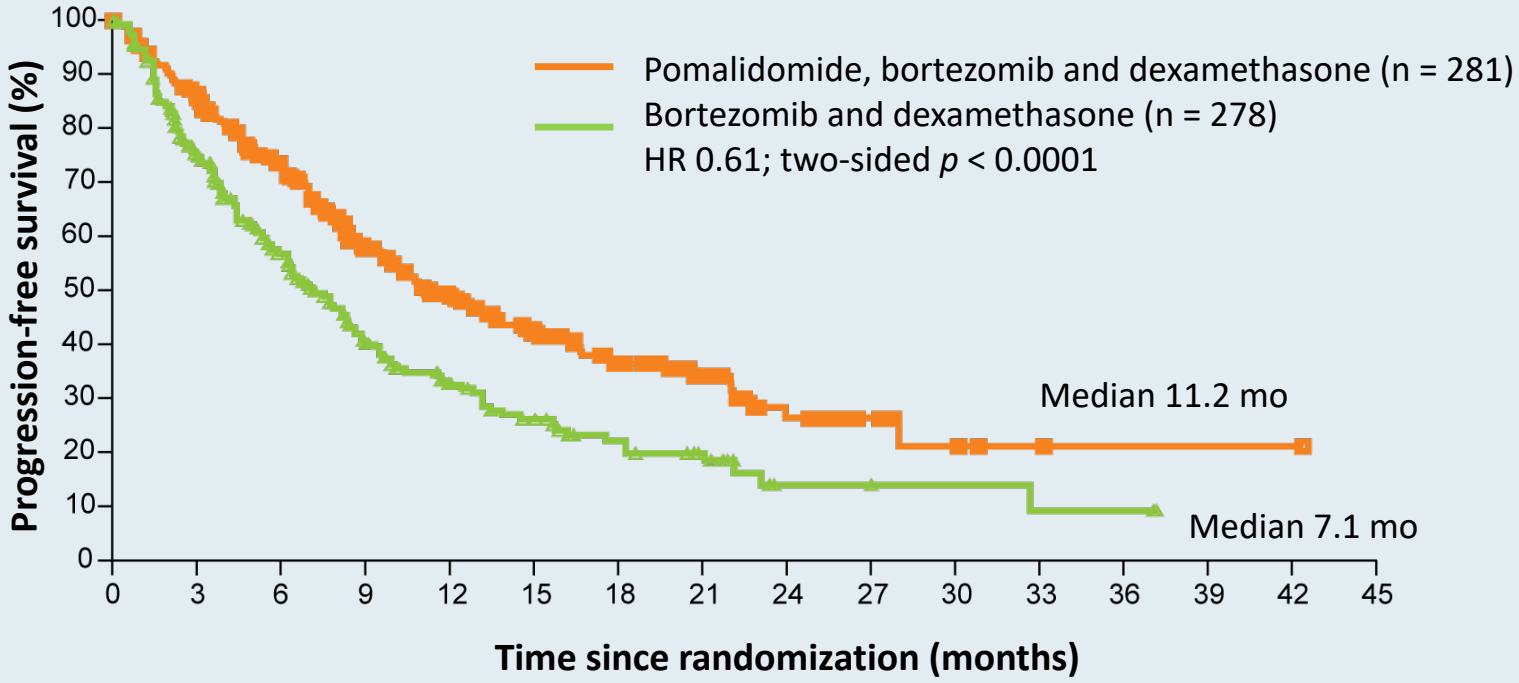
What is your usual treatment recommendation for a patient with MM and del(17p) treated with induction therapy followed by ASCT and maintenance RVD for 1.5 years who then experiences symptomatic relapse?

	Induction RVD	Induction KRd
 RAFAEL FONSECA, MD	K/pom ± dex or Dara/pom ± dex	Dara/pom ± dex
 SHAJI K KUMAR, MD	K/pom ± dex	Dara/pom ± dex
 OLA LANDGREN, MD, PHD	K/pom ± dex	K/pom ± dex
 SAGAR LONIAL, MD	Dara/pom ± dex	Dara/pom ± dex
 NIKHIL C MUNSHI, MD	K/pom ± dex	Dara/pom ± dex
 ROBERT Z ORLOWSKI, MD, PHD	K/pom ± dex	K/pom ± dex
 NOOPUR RAJE, MD	K/pom ± dex	CAR-T therapy
 NINA SHAH, MD	Dara/pom ± dex	Dara/pom ± dex

Co-provided by USF Health Research To Practice®

OPTIMISMM: Phase III Trial of Pomalidomide with Bortezomib and Dexamethasone in Relapsed/Refractory MM

All patients with 1-3 prior lines of therapy (including 2 or more cycles of lenalidomide)



Median PFS	Pom-bort/dex	Bort/dex	HR (*p*-value)
Refractory to lenalidomide (n = 200; 191)	9.5 mo	5.6 mo	0.65 (0.0008)
Refractory to lenalidomide and 1 prior line of treatment (n = 64; 65)	17.8 mo	9.5 mo	0.55 (0.03)

Richardson PG et al. *Lancet Oncol* 2019;20(6):781-94.

Co-provided by USF Health Research To Practice®

Daratumumab-Based Regimens for Relapsed and/or Refractory MM

	POLLUX[1] Dara-Rd vs Rd	CASTOR[2] Dara-Vd vs Vd
Prior therapies	**Bortezomib: 84%** **Len/Thal: 18%/43%** **IMiD + PI: 44%**	**Bortezomib: 65%** **Len/Thal: 42%/49%** **IMiD + PI: 48%**
Median lines prior Tx	**1 (range: 1-11)**	**2 (range: 1-10)**
Median PFS (mo) – ITT **(n = 569; 498)**	**NR vs 17.5** HR 0.41, $p < 0.0001$	**16.7 vs 7.1** HR 0.31, $p < 0.0001$
Median PFS (mo) – prior Bort **(n = 479; 326)**	**NR vs 17.5** HR 0.40, $p < 0.0001$	**12.1 vs 6.7** HR 0.35
Median PFS (mo) – prior Len **(n = 100; 209)**	**NR vs 18.6** HR 0.32, $p = 0.0008$	**9.5 vs 6.1** HR 0.38

NR = not reached

[1] Dimopoulos MA et al. *Haematologica* 2018;103(12):2088-96;
[2] Spencer A et al. *Haematologica* 2018;103(12):2079-87.

Co-provided by USF Health Research To Practice®

FDA Approval of Subcutaneous Daratumumab (Daratumumab and Hyaluronidase-fihj) for Newly Diagnosed or Relapsed/Refractory MM

Press Release – May 1, 2020

"On May 1, 2020, the Food and Drug Administration approved daratumumab and hyaluronidase-fihj for adult patients with newly diagnosed or relapsed/refractory multiple myeloma. This new product allows for subcutaneous dosing of daratumumab."

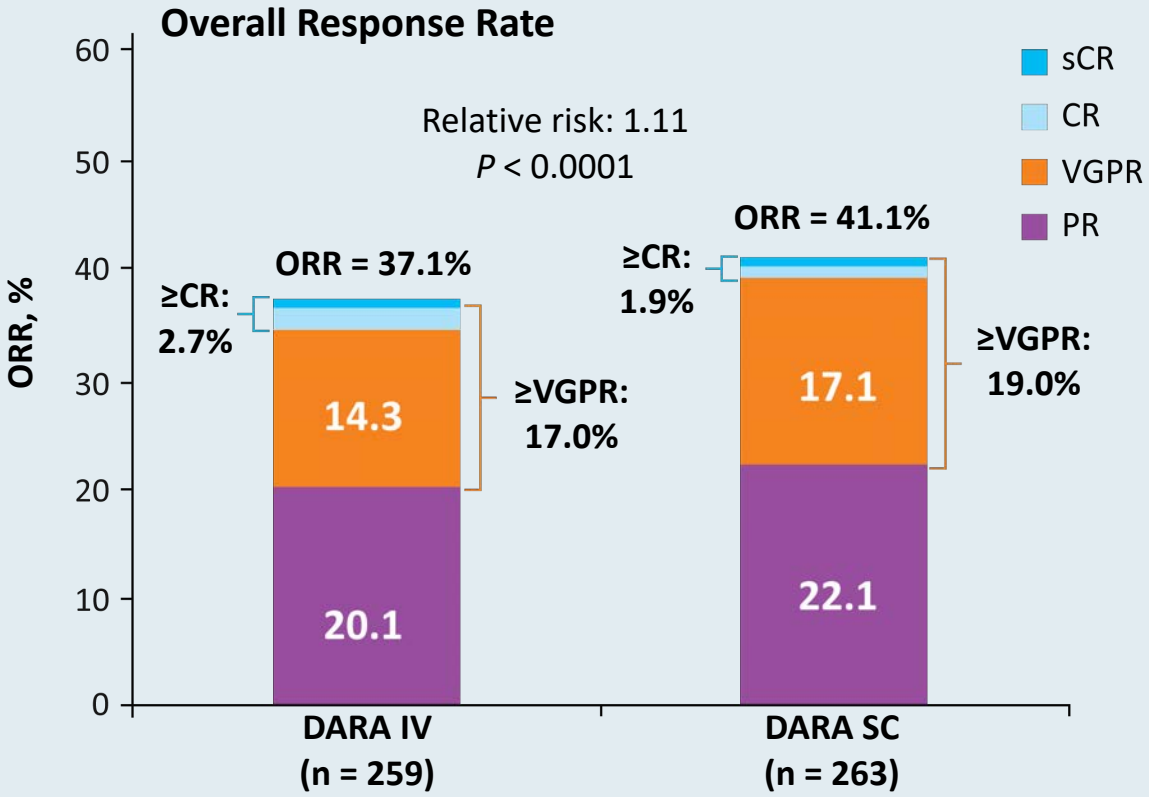
Daratumumab and hyaluronidase-fihj is approved for certain indications that intravenous daratumumab had previously received.

Efficacy of daratumumab and hyaluronidase-fihji (monotherapy) was evaluated in COLUMBA (NCT03277105), an open-label noninferiority trial randomly assigning 263 patients to daratumumab and hyaluronidase-fihj and 259 to intravenous daratumumab.

https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-daratumumab-and-hyaluronidase-fihj-multiple-myeloma

Co-provided by USF Health Research To Practice®

COLUMBA: Phase III Noninferiority Trial of Subcutaneous (SC) versus Intravenous (IV) Daratumumab for Relapsed or Refractory MM



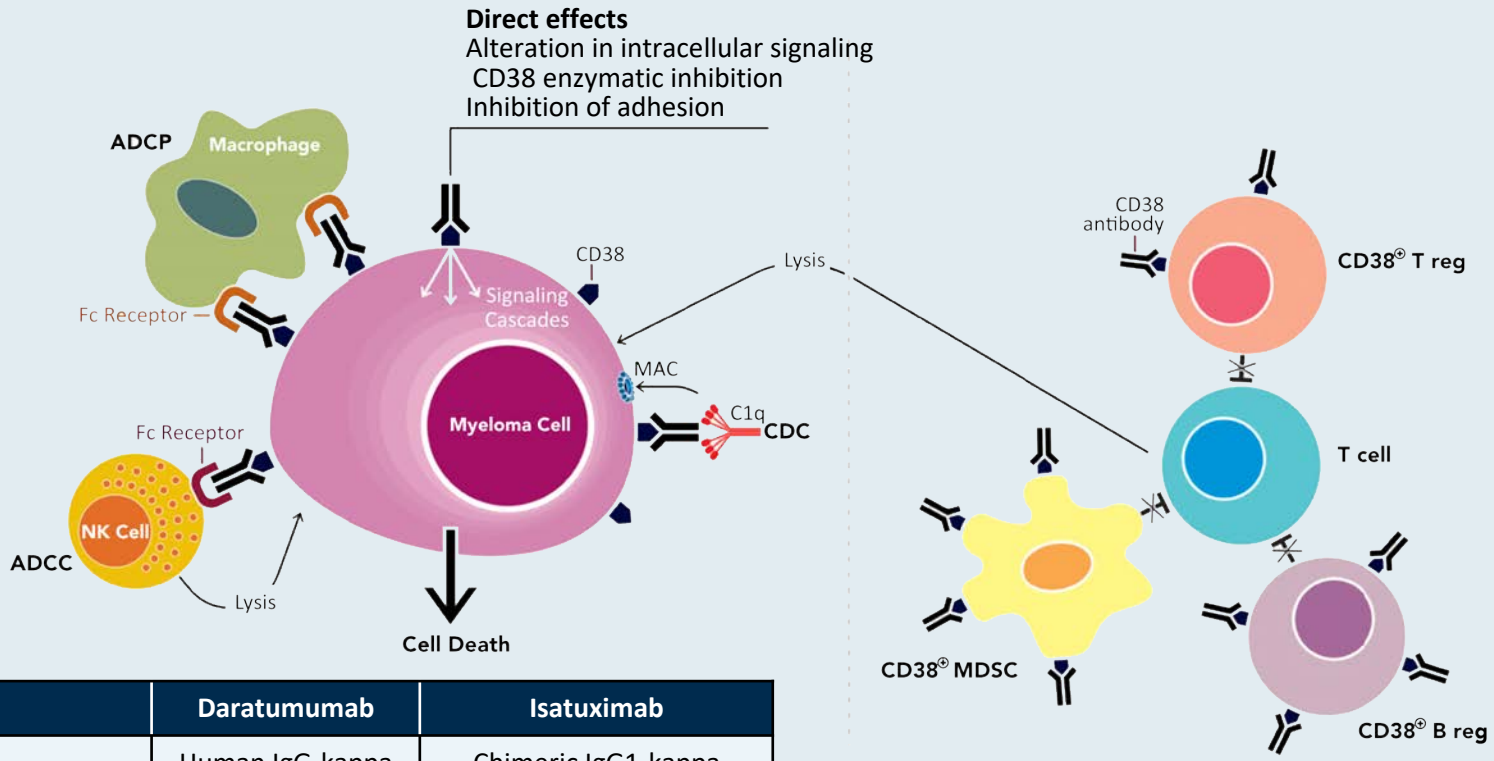
	DARA IV (n = 258)	DARA SC (n = 260)	Odds ratio (*p*-value)
Rate of infusion-related reactions	34.5%	12.7%	0.28 (<0.0001)

Mateos M-V et al. ASCO 2019;Abstract 8005.

Anti-CD38 Antibodies: Mechanism of Action, Structural and Pharmacologic Similarities and Differences

Fc-dependent immune effector mechanisms and direct effects

Immunomodulatory effects



Mechanism of action	Daratumumab	Isatuximab
Origin, isotype	Human IgG-kappa	Chimeric IgG1-kappa
CDC	+++	+
ADCC	++	++
ADCP	+++	Not determined
PCD direct	—	++
PCD cross linking	+++	+++
Modulation ectoenzyme function	+	+++

van de Donk NWCJ et al. *Blood* 2018;131(1):13-29.

Co-provided by USF Health Research To Practice®

FDA Approves New Therapy for Patients with Previously Treated Multiple Myeloma

Press Release – March 02, 2020

Today, the US Food and Drug Administration approved isatuximab-irfc, in combination with pomalidomide and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor.

The FDA approved isatuximab-irfc based on the results of a clinical trial involving 307 patients with relapsed and refractory multiple myeloma who had received at least two prior therapies, including lenalidomide and a proteasome inhibitor.

Patients who received isatuximab-irfc in combination with pomalidomide and low-dose dexamethasone showed improvement in PFS with a 40% reduction in the risk of disease progression or death compared to patients who received pomalidomide and dexamethasone. These patients also had an overall response rate of 60.4%. In comparison, the patients who only received pomalidomide and low-dose dexamethasone had an overall response rate of 35.3%.

https://www.fda.gov/news-events/press-announcements/fda-approves-new-therapy-patients-previously-treated-multiple-myeloma

Co-provided by USF Health Research To Practice®

A 65-year-old man who initially received RVD → ASCT followed by maintenance lenalidomide has received multiple regimens for relapsed disease, including daratumumab, and is now refractory to PIs and IMiDs. *Regulatory and reimbursement issues aside*, what would you generally consider for the next line of therapy?

 RAFAEL FONSECA, MD	BCMA-directed CAR-T therapy
 SHAJI K KUMAR, MD	Belantamab mafodotin
 OLA LANDGREN, MD, PHD	Belantamab mafodotin
 SAGAR LONIAL, MD	Belantamab mafodotin
 NIKHIL C MUNSHI, MD	BCMA-directed CAR-T therapy
 ROBERT Z ORLOWSKI, MD, PHD	BCMA-directed CAR-T therapy
 NOOPUR RAJE, MD	BCMA-directed CAR-T therapy
 NINA SHAH, MD	BCMA-directed CAR-T therapy

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Management of Multiple Myeloma (MM)

Module 1: Clinical Decision-Making for Patients with Newly Diagnosed MM (NDMM)

- Daratumumab-containing front-line therapy (CASSIOPEIA, MAIA, GRIFFIN)
- Minimal residual disease (MRD) testing and use in treatment decision-making
- Consolidation and maintenance therapy; emerging data with ixazomib (TOURMALINE-MM3, TOURMALINE-MM4)

Module 2: Contemporary Management of Relapsed/Refractory MM

- Data with daratumumab-containing regimens; split dosing
- Combination regimens with ixazomib (TOURMALINE-MM1)
- Recent FDA approval of selinexor and pivotal data from STORM
- Recent FDA approval of anti-CD38 isatuximab plus pomalidomide/low-dose dexamethasone and pivotal data from ICARIA-MM

Module 3: Novel Agents in Late-Stage Development

- Belantamab mafodotin (DREAMM-2)
- Clinical development of other anti-BCMA agents

Co-provided by USF Health Research To Practice®

Case Presentation

Co-provided by USF Health Research To Practice®

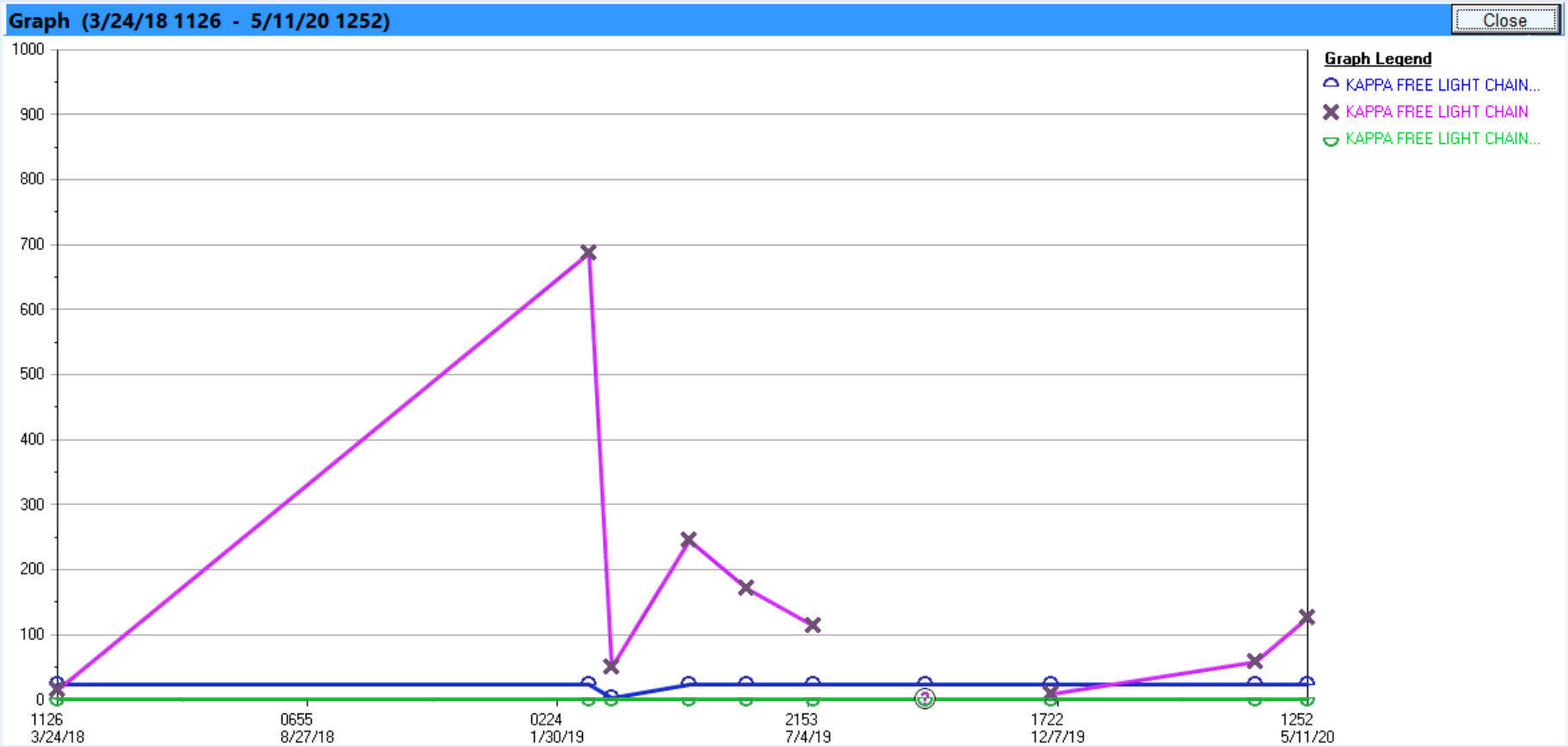
77-year-old woman

- 2007: Diagnosed with IgG kappa multiple myeloma
- Induction thalidomide-based regimen → ASCT
- Over the years, multiple lines of therapy, including RVD and carfilzomib/dexamethasone
  - Carfilzomib discontinued due to the cardiac issues
- Ixazomib/dexamethasone → PD → Pomalidomide/daratumumab/dex
- Winter 2018: New bone lesions → 2nd ASCT (tolerates well, good response)
- Currently, disease progression with a new bone lesion in the sternum (see PET) and increasing light chains (see light chain).

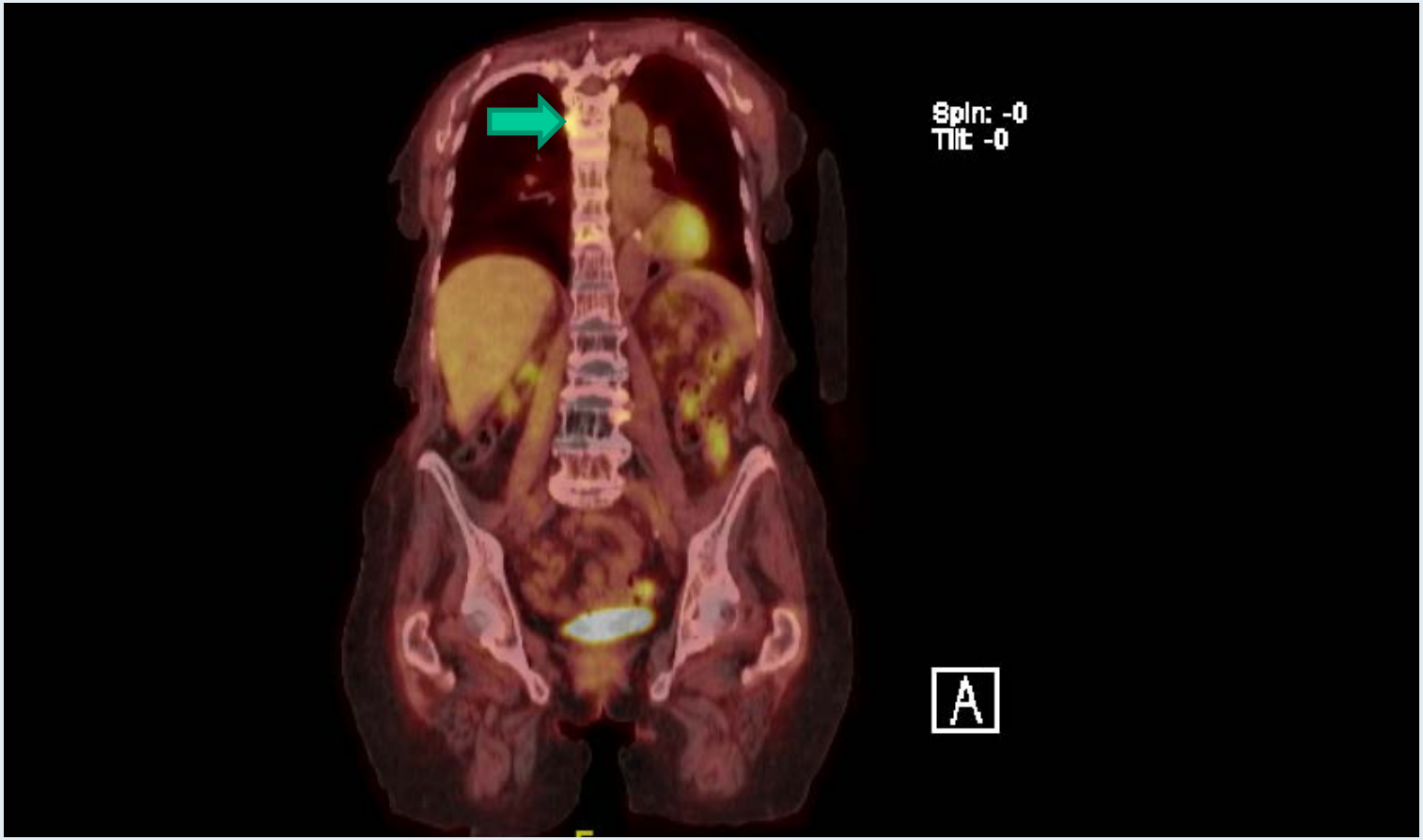
Question:

How should this patient be treated? Selinexor? Clinical trial with BiTE? CAR T?

77-year-old woman
Increasing light chains



77-year-old woman
New sternal lesion



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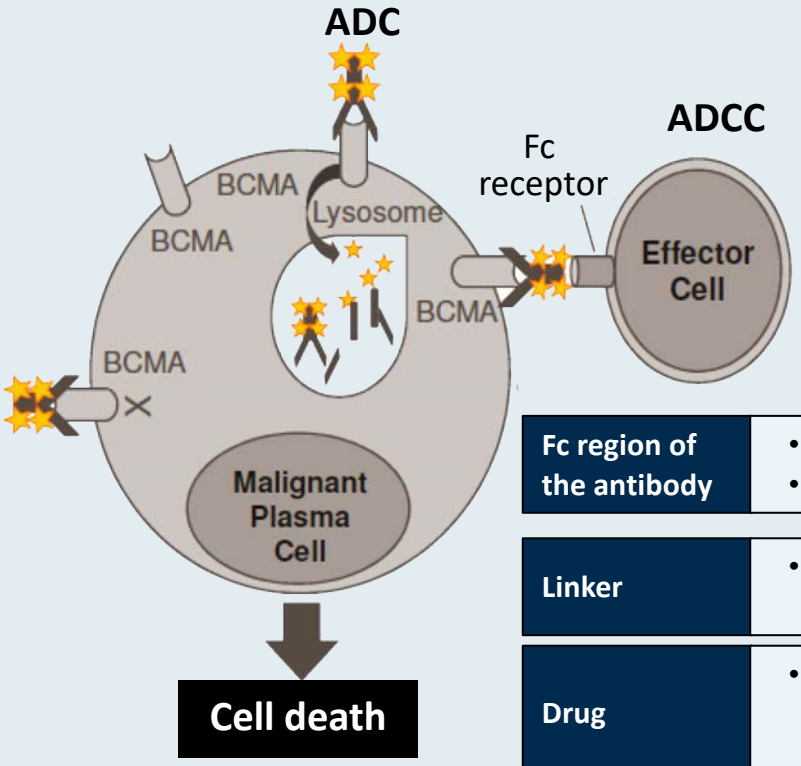
Belantamab Mafodotin: Anti-BCMA Antibody-Drug Conjugate

- B-cell maturation factor (BCMA) expression is restricted to B cells at later stages of differentiation and is required for survival of plasma cells
- BCMA is broadly expressed at variable levels on malignant plasma cells
- Belantamab mafodotin is a humanized, afucosylated IgG1 anti-BCMA antibody conjugated to microtubule disrupting agent MMAF via a stable, protease-resistant maleimidocaproyl linker



Fc region of the antibody	• **Target specific** • **Enhanced ADCC**
Linker	• **Stable in circulation**
Drug	• **MMAF (non cell permeable, highly potent auristatin)**

Mechanisms of action:
- ADC mechanism
- ADCC mechanism
- Immunogenic cell death
- BCMA receptor signaling inhibition

Tai YT et al. *Blood* 2014;123(20):3128-38.

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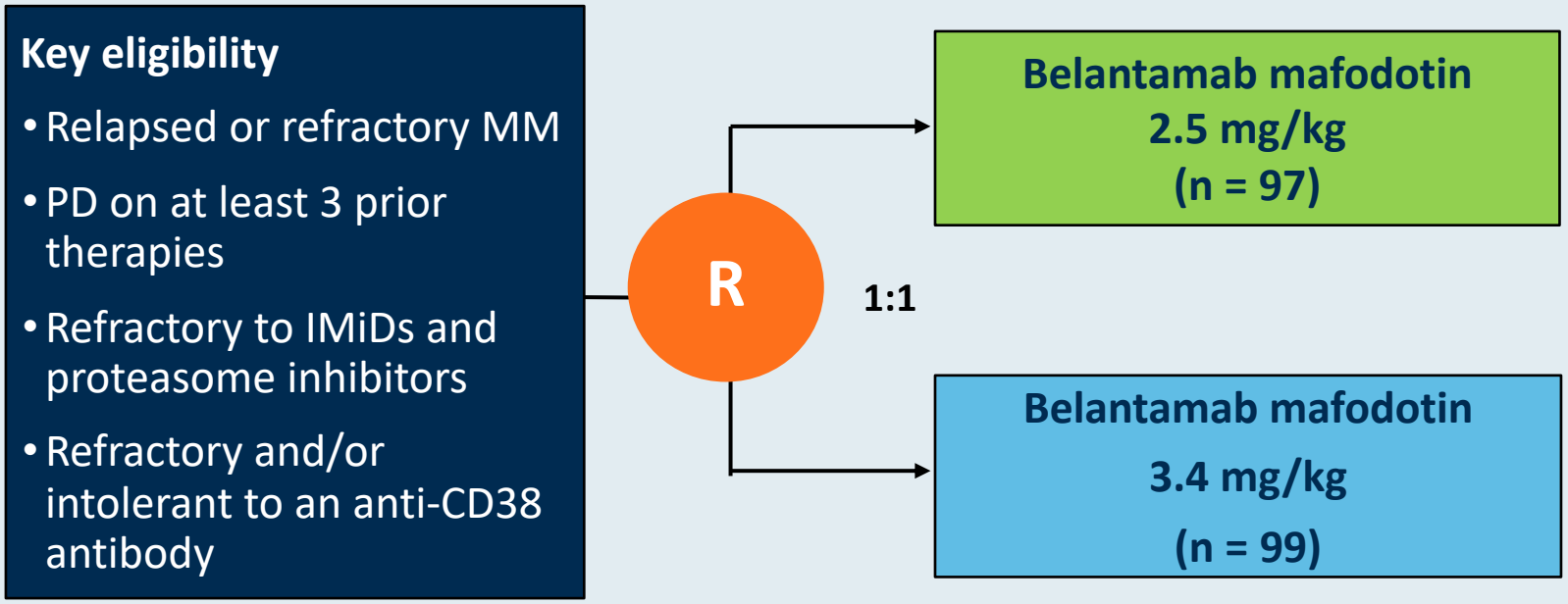
DREAMM-2 Randomized Phase II Study Design



Primary endpoint: Overall response in the intent-to-treat population as determined by an independent review committee

Lonial S et al. *Lancet Oncol* 2020;21(2):207-21.

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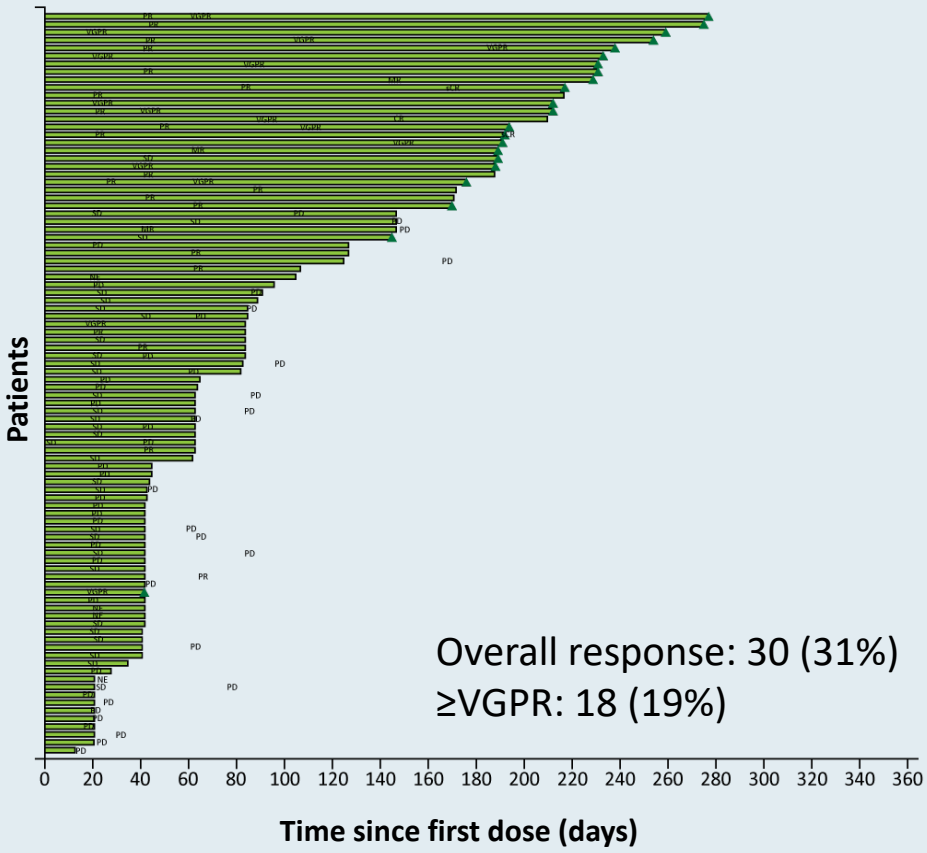
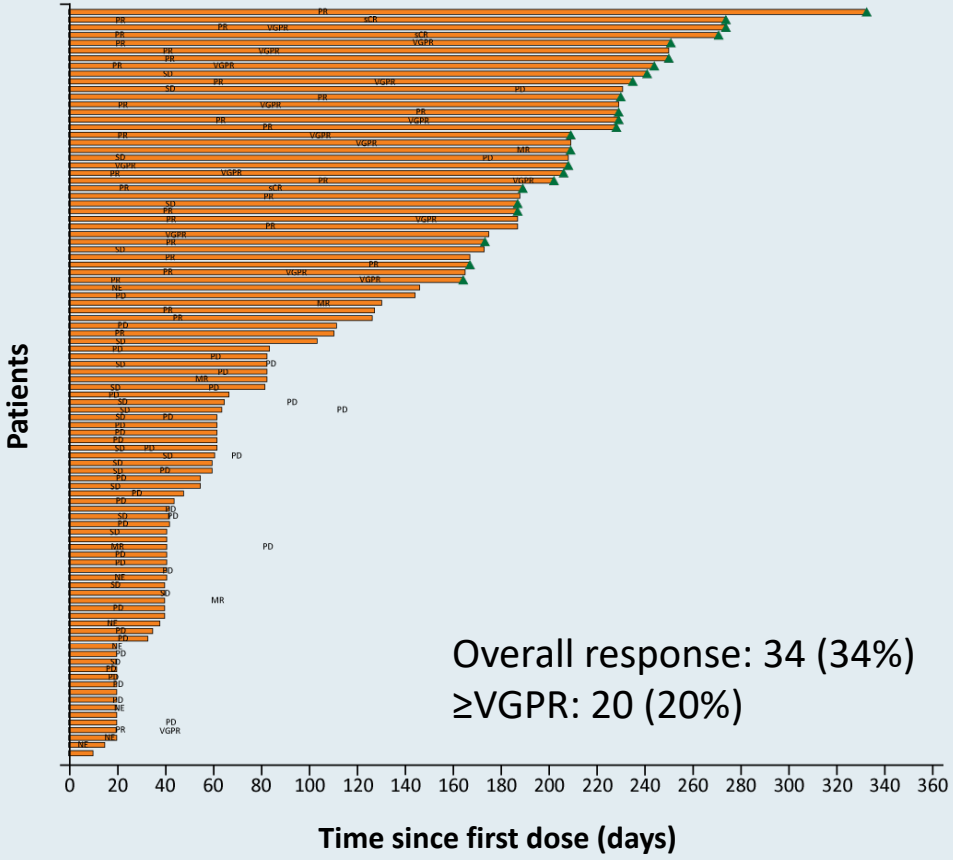
DREAMM-2: Response and Duration of Response

2.5 mg/kg



Overall response: 30 (31%)
≥VGPR: 18 (19%)

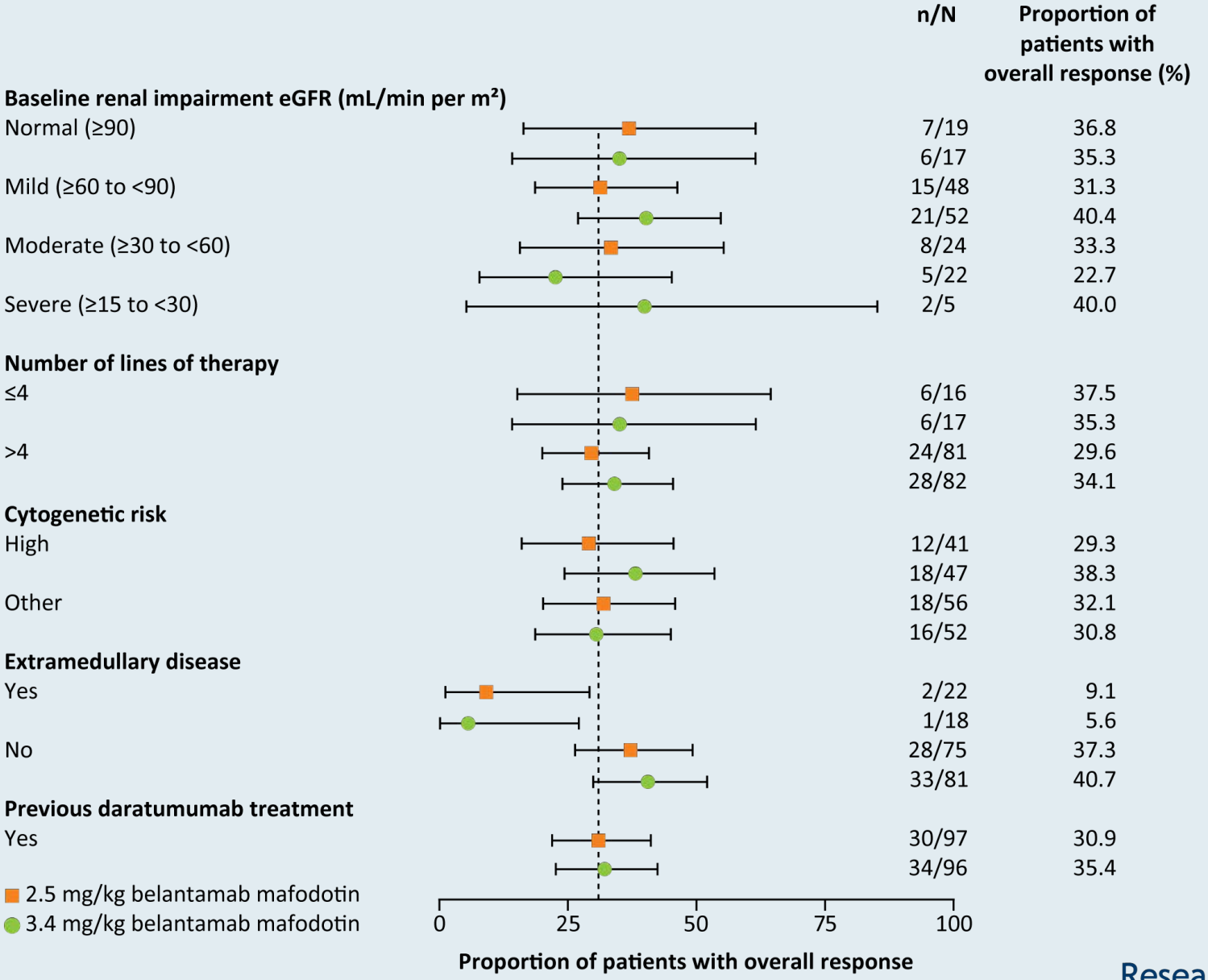
3.4 mg/kg



Overall response: 34 (34%)
≥VGPR: 20 (20%)

Lonial S et al. *Lancet Oncol* 2020;21(2):207-21.

DREAMM-2: Overall Response in Select Patient Subgroups



Lonial S et al. *Lancet Oncol* 2020;21(2):207-21.

DREAMM-2: Select Adverse Events

Adverse events (AEs) of special interest, any grade	Belantamab mafodotin 2.5 mg/kg (n = 95)	Belantamab mafodotin 3.4 mg/kg (n = 99)
Thrombocytopenia	35%	59%
Infusion-related reactions	21%	16%
Corneal events	71%	75%
Drug-related serious AEs		
Infusion-related reactions	3%	2%
Pyrexia	6%	5%
Sepsis	2%	2%
Pneumonia	4%	12%

Lonial S et al. *Lancet Oncol* 2020;21(2):207-21.

A patient with MM should be in similar physical condition to that appropriate for ASCT to be a suitable candidate for BCMA-targeted CAR T-cell therapy.

 RAFAEL FONSECA, MD	Disagree
 SHAJI K KUMAR, MD	Agree
 OLA LANDGREN, MD, PHD	Agree
 SAGAR LONIAL, MD	Agree
 NIKHIL C MUNSHI, MD	Agree
 ROBERT Z ORLOWSKI, MD, PHD	Agree
 NOOPUR RAJE, MD	Agree
 NINA SHAH, MD	Agree

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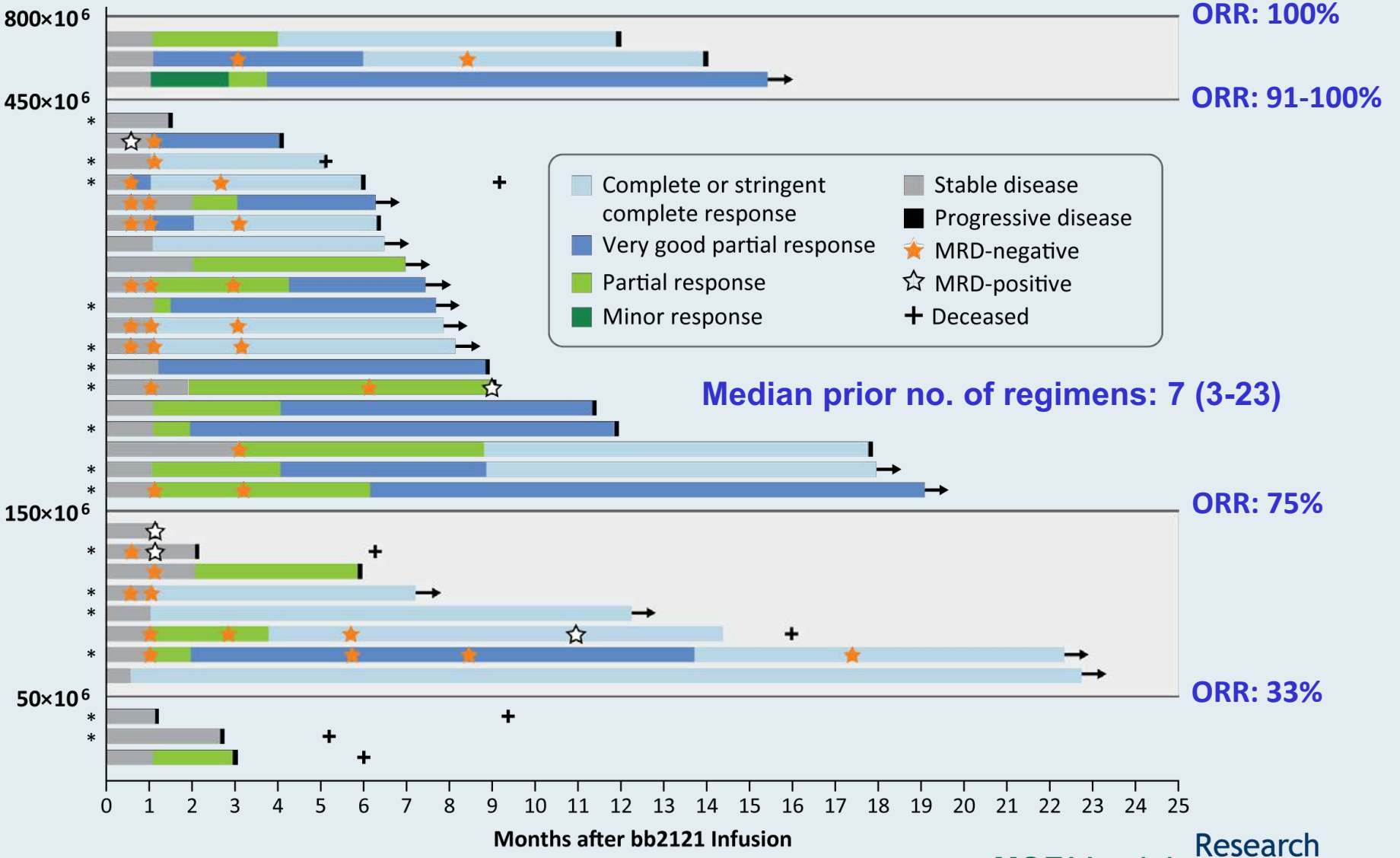
In general, when do you refer patients for possible inclusion in trials of BCMA-targeted CAR T-cell therapy?

 RAFAEL FONSECA, MD	Refractory to all drugs
 SHAJI K KUMAR, MD	Triple-class refractory
 OLA LANDGREN, MD, PHD	Per protocol eligibility criteria
 SAGAR LONIAL, MD	Few treatment options, slow relapse to wait the time to get cells
 NIKHIL C MUNSHI, MD	Having received PI, IMiD and anti-CD38 antibody in combination and disease progressing
 ROBERT Z ORLOWSKI, MD, PHD	Multiply relapsed/refractory setting; more recently in earlier settings based on trial availability
 NOOPUR RAJE, MD	As early as possible
 NINA SHAH, MD	After failure of 3rd-line treatment

Tumor Response According to Dose of Chimeric Antigen Receptor-Positive (CAR+) T Cells



Raje N et al. *N Engl J Med* 2019;380(18):1726-37.

Pivotal Phase II KarMMa Study of bb2121 (Ide-cel) in R/R MM Meets Primary and Key Secondary Endpoints

Press Release – December 6, 2019

"On 6th December 2019, it was announced that the phase II KarMMA study met its primary endpoint of overall response rate (ORR) and key secondary endpoint of complete response (CR) rate. The KarMMA study is investigating idecabtagene vicleucel (ide-cel, also known as bb2121), in patients with relapsed/refractory multiple myeloma (RRMM). Ide-cel is a chimeric antigen receptor (CAR) T-cell therapy targeting B-cell maturation antigen (BCMA)."

CAR T-cell dose	150 x 10^6	300 x 10^6	450 x 10^6	150 – 450 x 10^6
N	4	70	54	128
ORR	50%	68.6%	81.5%	73.4%
CR/stringent CR	25%	28.6%	35.2%	31.3%
Median DoR	—	9.9 mo	11.3 mo	10.6 mo
Median PFS	—	5.8 mo	11.3 mo	8.6 mo

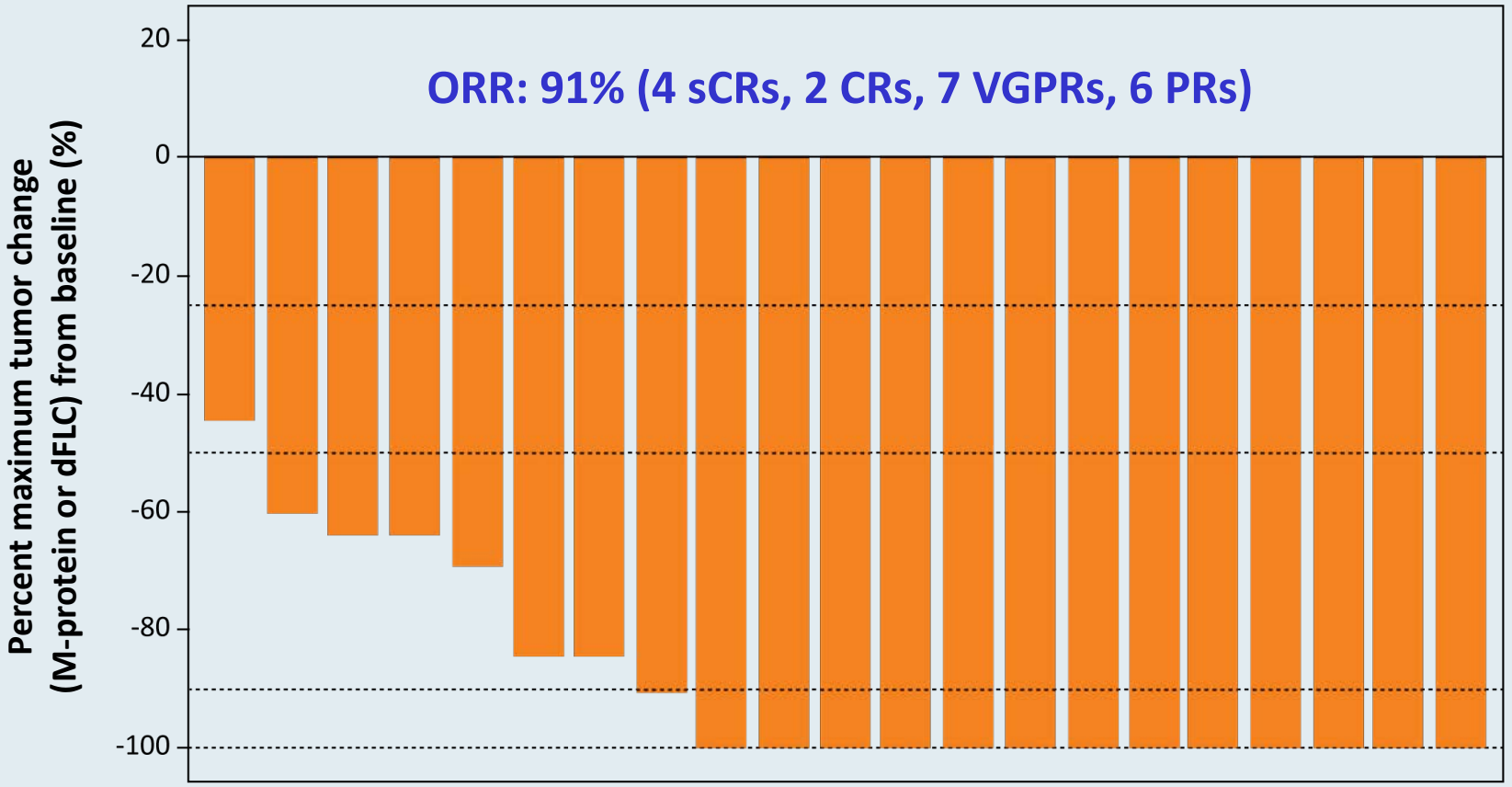
https://multiplemyelomahub.com/medical-information/update-from-the-karmma-study-of-car-t-cell-product-bb2121-ide-cel

Co-provided by USF Health Research To Practice®

CARTITUDE-1: A Phase Ib/II Study of JNJ-4528 in R/R MM

Median prior lines of treatment: 5 (range: 3-16)

Maximum Reduction in Tumor Burden from Baseline in Response-Evaluable Patients (n = 21)



Madduri D et al. ASH 2019;Abstract 577.

Thank you for joining us!

CME credit information and slides will be emailed to each participant later today.

Co-provided by USF Health Research To Practice®

Clinical Investigator Perspectives on the Current and Future Management of Multiple Myeloma

A Meet The Professor Series

Nina Shah, MD
Associate Professor of Medicine
University of California, San Francisco
Division of Hematology-Oncology
San Francisco, California

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WITH DR NEIL LOVE

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