# Welcome participants at UH Seidman Cancer Center

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

## *A Meet The Professor Series*


**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

**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
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Anne and Bernard Gray Family Chair in Cancer
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Emory University School of Medicine
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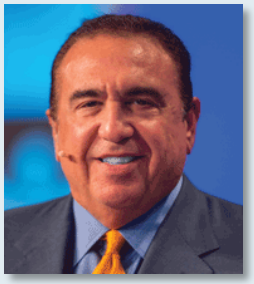
# *Meet The Professor* Program Steering Committee

**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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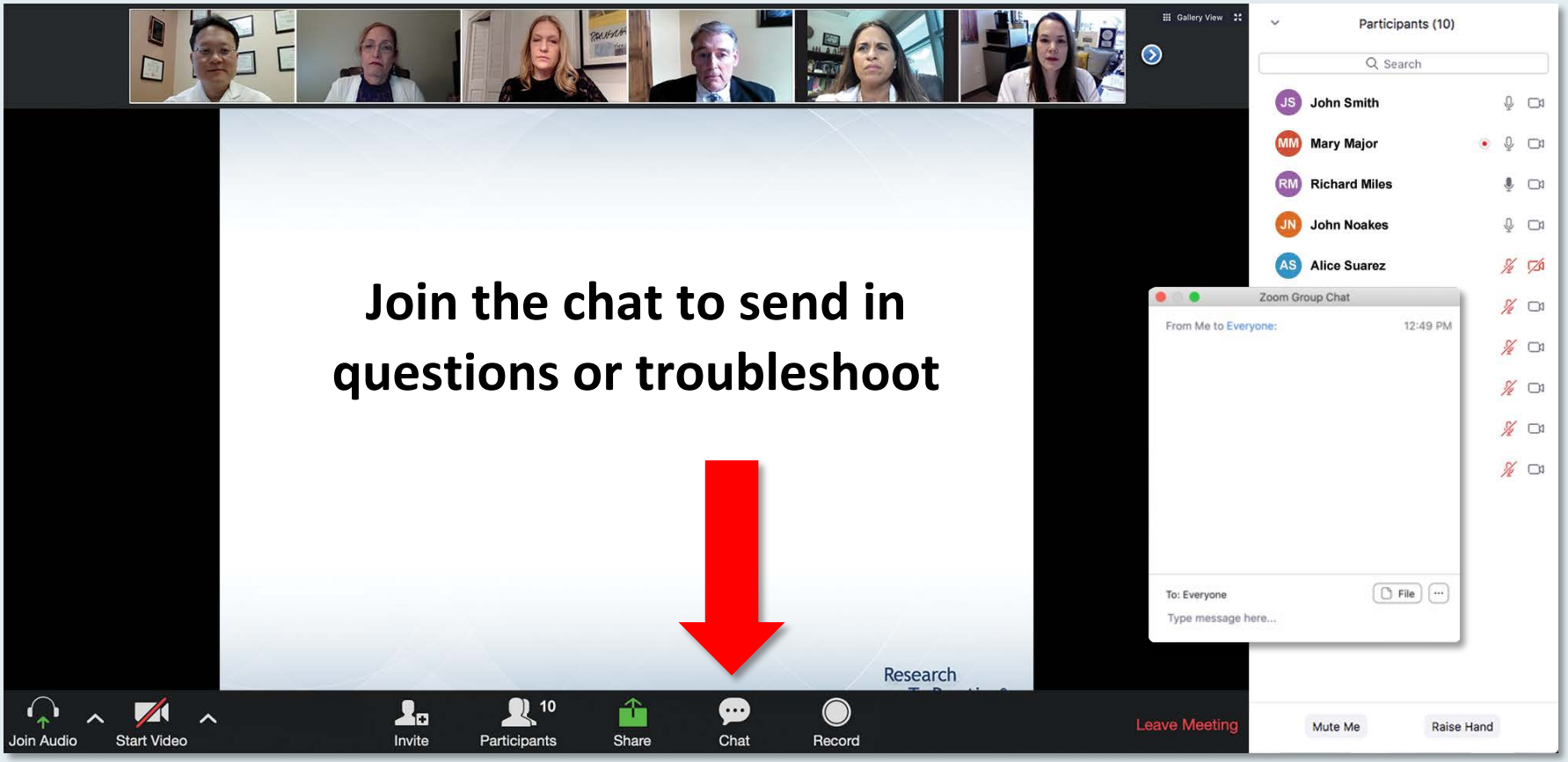
# Familiarizing yourself with the Zoom interface

## How to participate in the chat




Research To Practice®

# 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)
- Recent relevant datasets

## 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
- Recent relevant datasets

## Module 3: Novel Agents in Late-Stage Development

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

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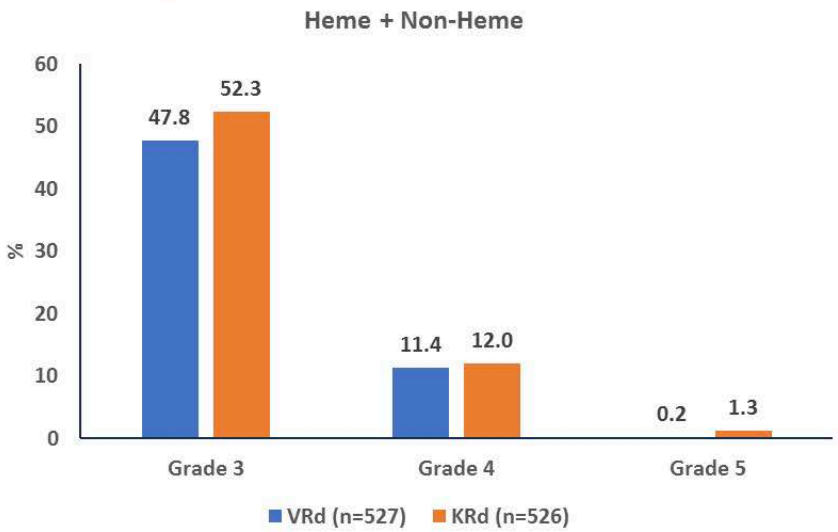
# Recent Relevant Datasets

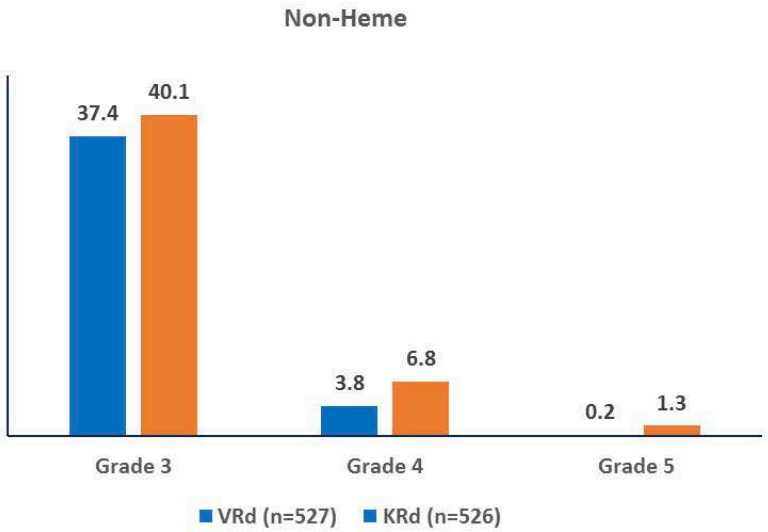
# Carfilzomib, Lenalidomide, and Dexamethasone (KRd) versus Bortezomib, Lenalidomide, and Dexamethasone (VRd) for Initial Therapy of Newly Diagnosed Multiple Myeloma (NDMM): Results of ENDURANCE (E1A11) Phase III Trial

Kumar S et al.

ASCO 2020;Abstract LBA3. (Plenary)

# ENDURANCE (E1A11): Treatment-Related AEs




*Grade 3 heme not required reporting

| Step 1 Treated Patients | VRd (n=527) | KRd (n=526) | | |
|---|---|---|---|---|
| Rates | N (%) | N (%) | Diff KRd-VRd | chisq p-value |
| Grades 3-5 | 313 (59.4) | 345 (65.6) | 6.2 | 0.038 |
| (95% CI) | (55.1-63.6) | (61.3-69.6) | | |
| Grades 4-5 | 61 (11.6) | 70 (13.3) | 1.7 | 0.394 |
| (95% CI) | (9.0-14.6) | (10.5-16.5) | | |

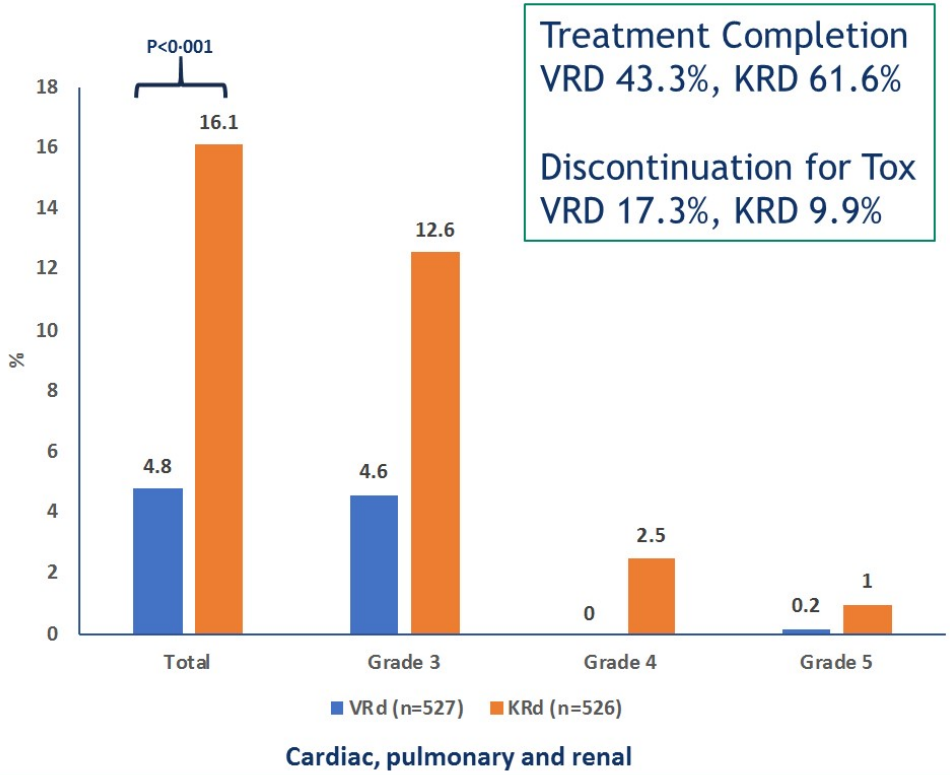
| Step 1 Treated Patients | VRd (n=527) | KRd (n=526) | | |
|---|---|---|---|---|
| Rates | N (%) | N (%) | Diff KRd-VRd | chisq p-value |
| Grades 3-5 | 218 (41.4) | 254 (48.3) | 6.9 | 0.024 |
| (95% CI) | (37.1-45.7) | (44.0-52.6) | | |
| Grades 4-5 | 21 (4.0) | 43 (8.2) | 4.2 | 0.004 |
| (95% CI) | (2.5-6.1) | (6.0-10.9) | | |





Kumar S et al. ASCO 2020;Abstract LBA3.

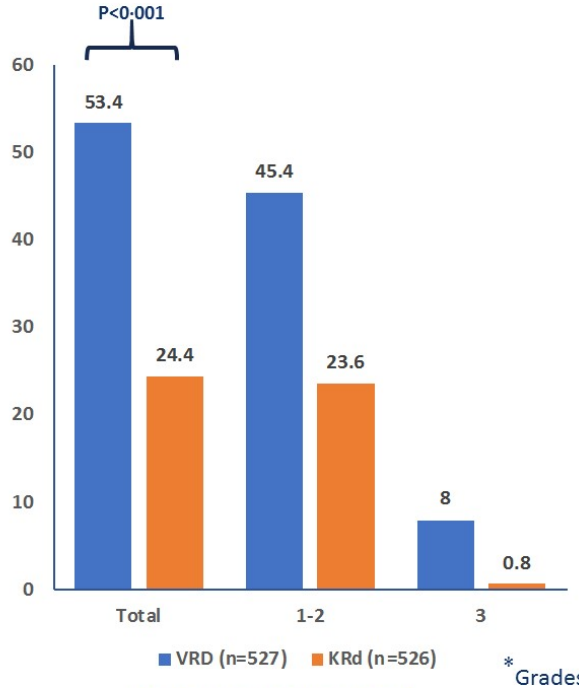
# ENDURANCE (E1A11): TEAEs of Interest




Cardiac, pulmonary and renal

Treatment Completion
VRD 43.3%, KRD 61.6%

Discontinuation for Tox
VRD 17.3%, KRD 9.9%




Peripheral neuropathy*

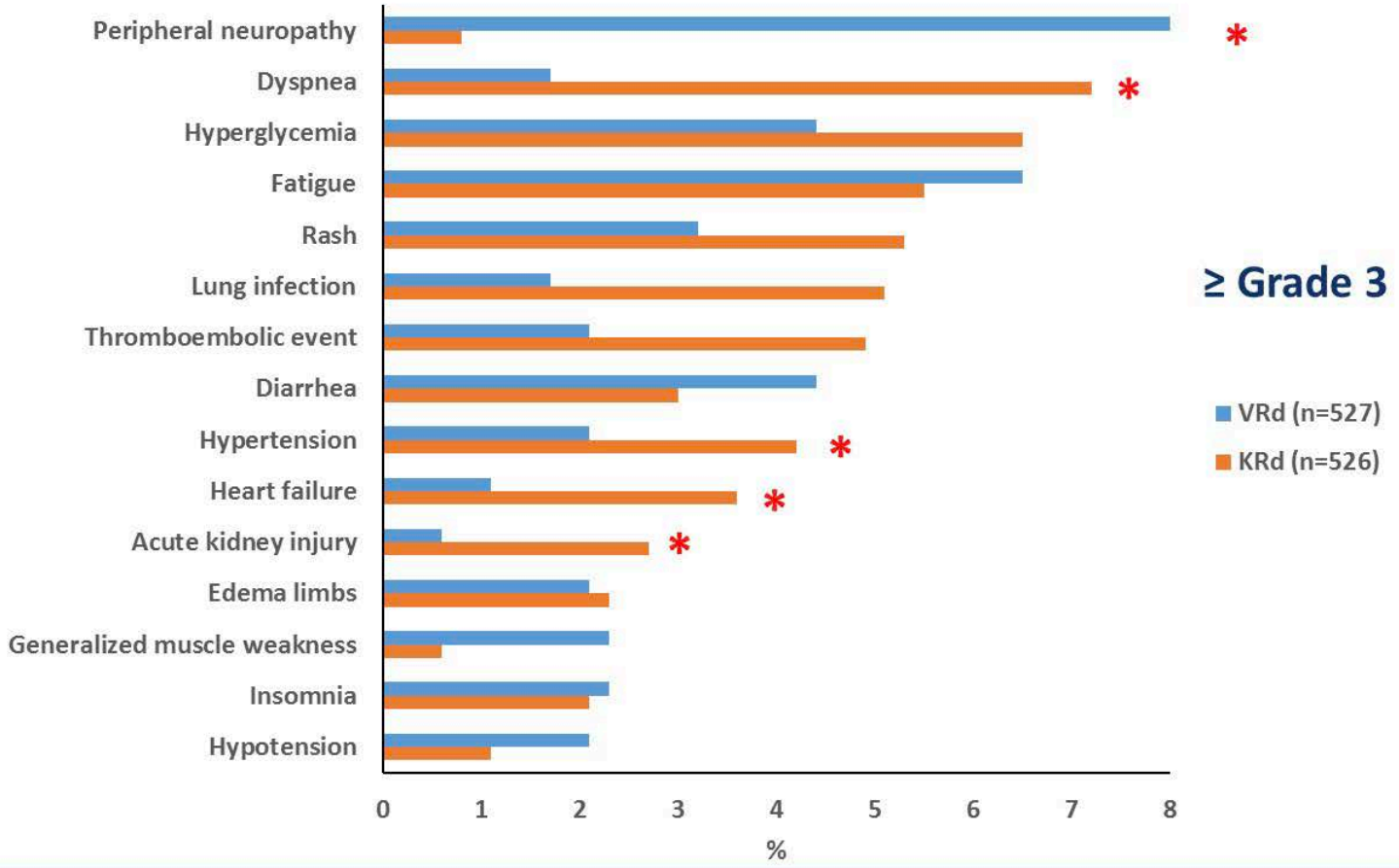
*Grades 1-2 not required reporting





Berdeja JG. ASCO 2020 Discussant.

# ENDURANCE (E1A11): Treatment-Related AEs (≥2%)








Kumar S et al. ASCO 2020;Abstract LBA3.

# Primary Analysis of the Randomized Phase II Trial of Bortezomib, Lenalidomide, Dexamthasone with/without Elotuzumab for Newly Diagnosed, High-Risk Multiple Myeloma (SWOG-1211)

Usmani SZ et al.

ASCO 2020;Abstract 8507.

# Depth of Response to Isatuximab, Carfilzomib, Lenalidomide, and Dexamethasone (Isa-KRd) in Front-Line Treatment of High-Risk Multiple Myeloma: Interim Analysis of the GMMG-CONCEPT Trial

Weisel K et al.

ASCO 2020;Abstract 8508.

# 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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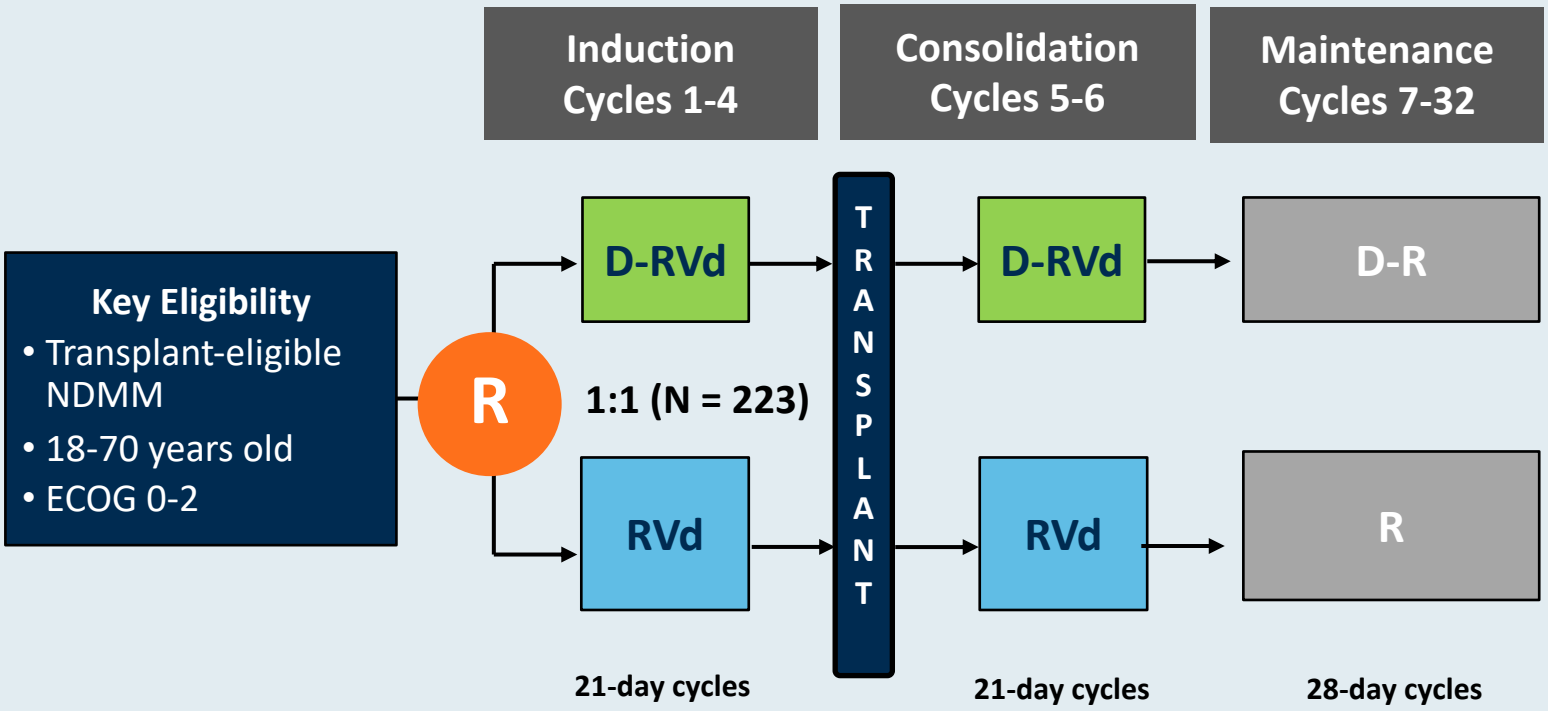
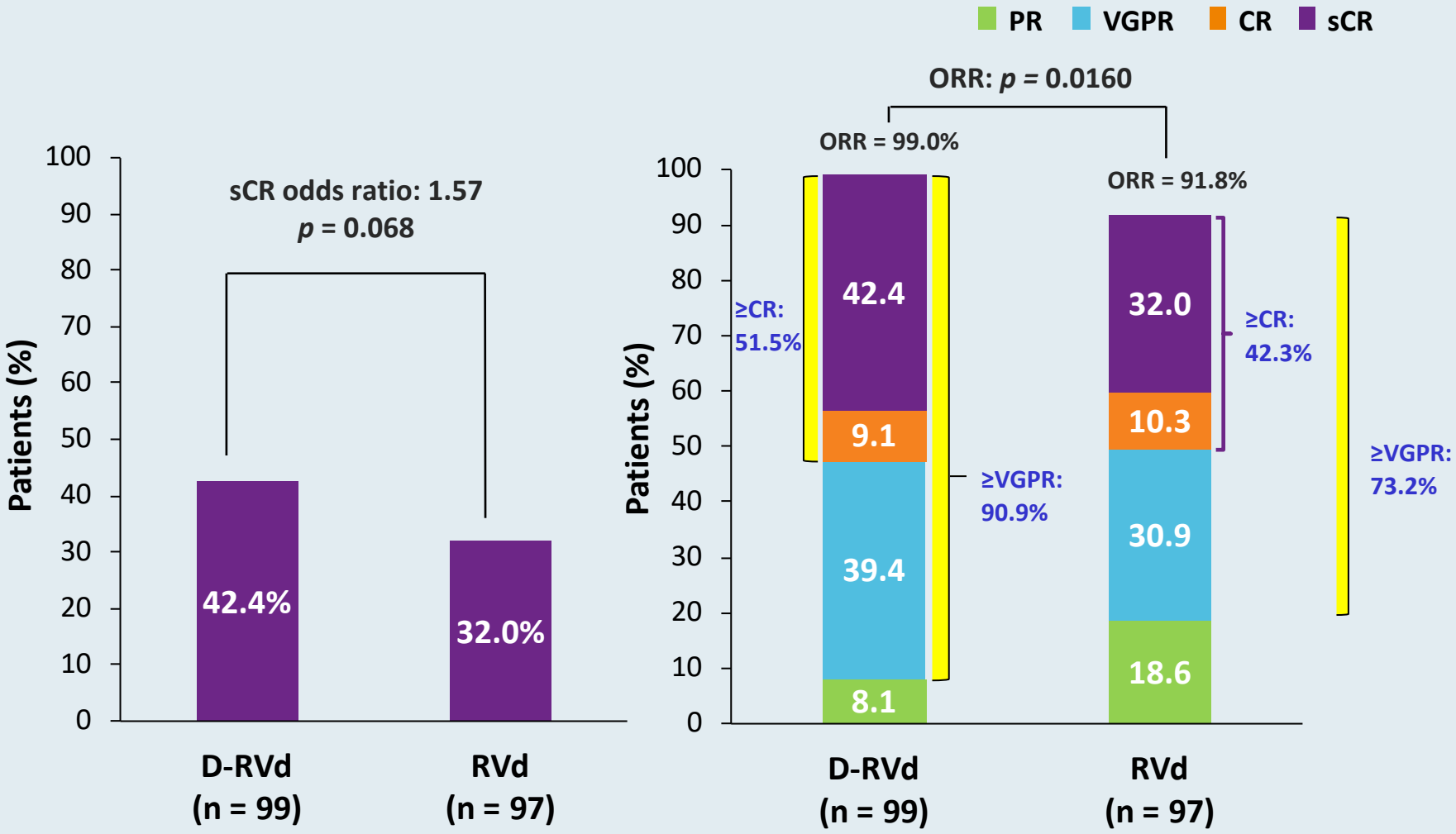
# GRIFFIN Randomized Phase II Study Design




**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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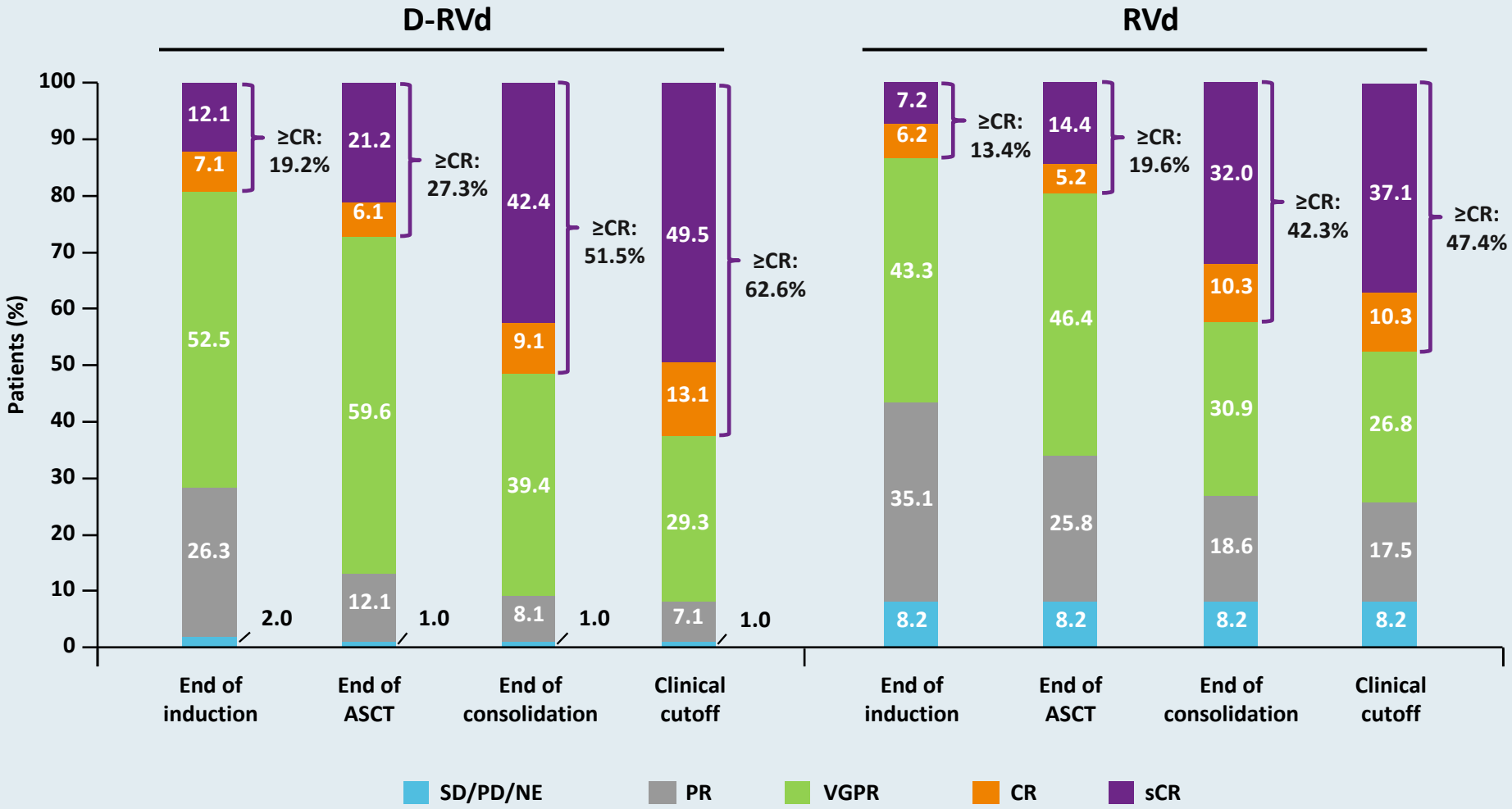
# GRIFFIN: Depth of Response Over Time




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

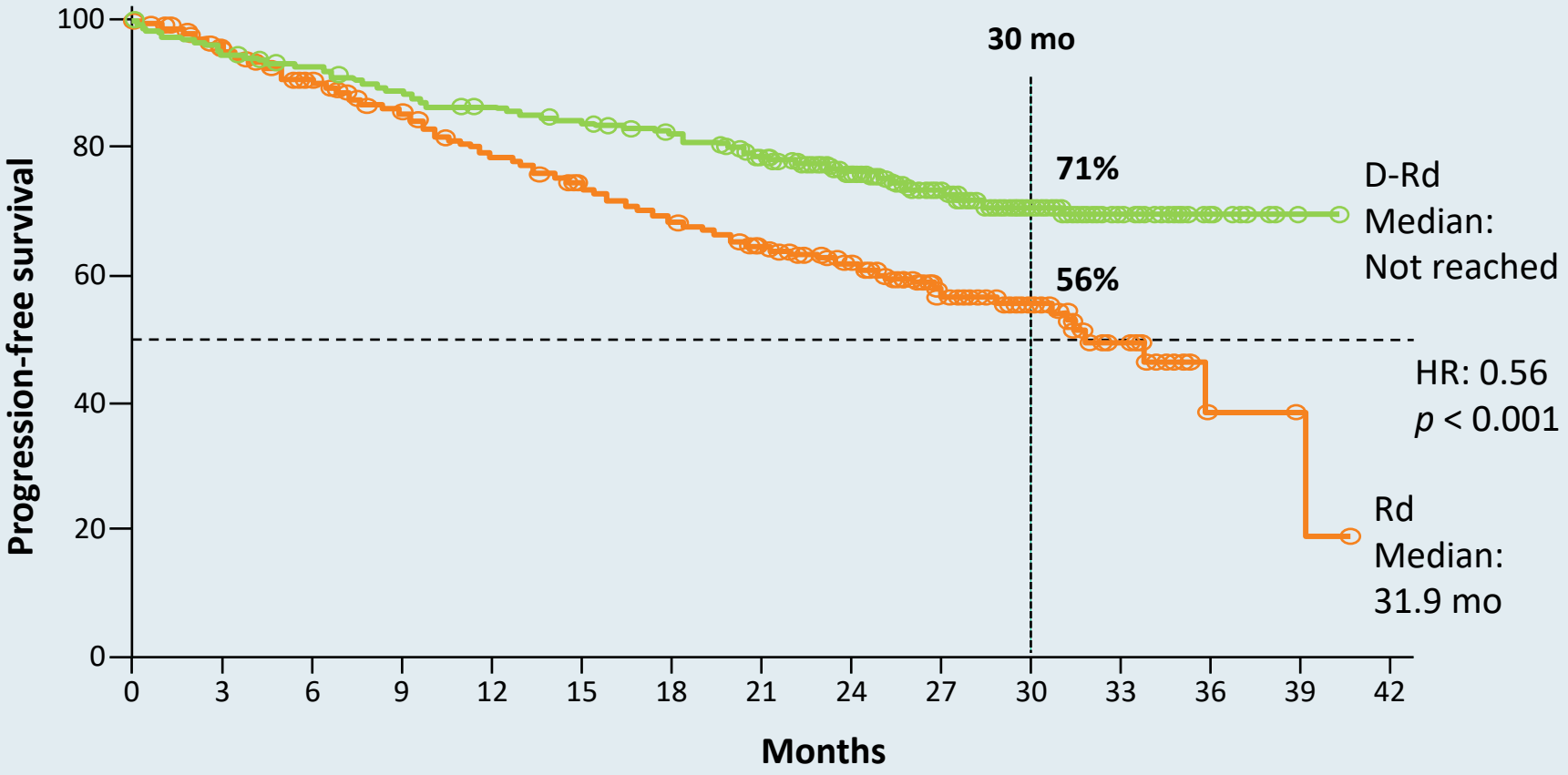
# Daratumumab plus Lenalidomide and Dexamethasone for Untreated Myeloma

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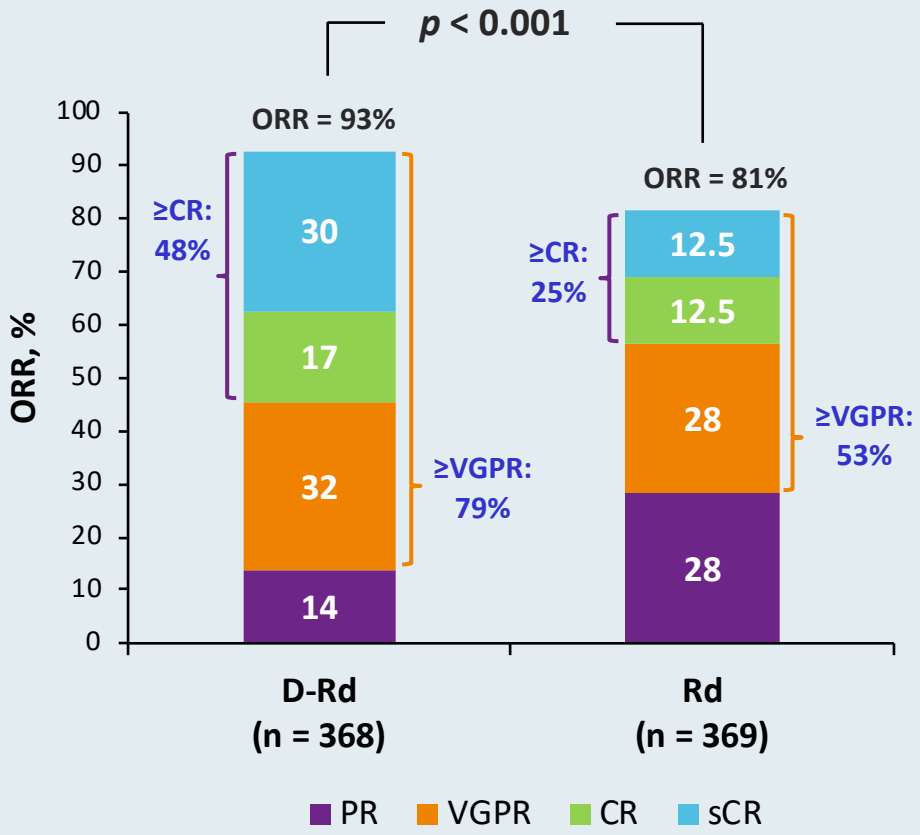
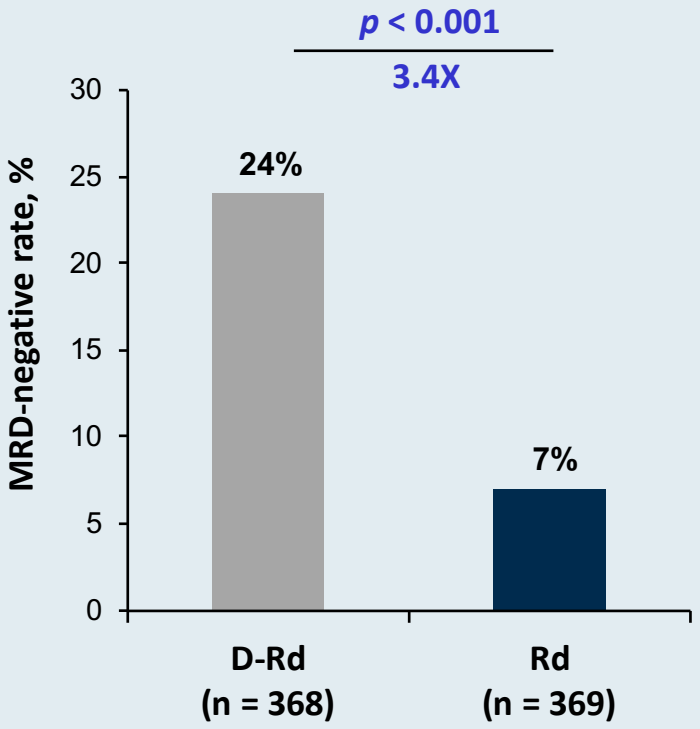
# MAIA: Overall Response Rate and MRD (NGS; $10^{-5}$ Sensitivity Threshold) Rate




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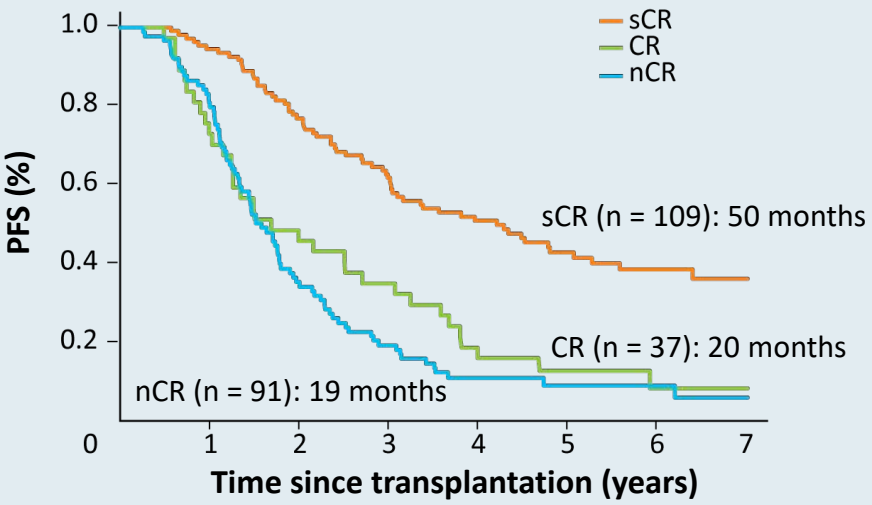
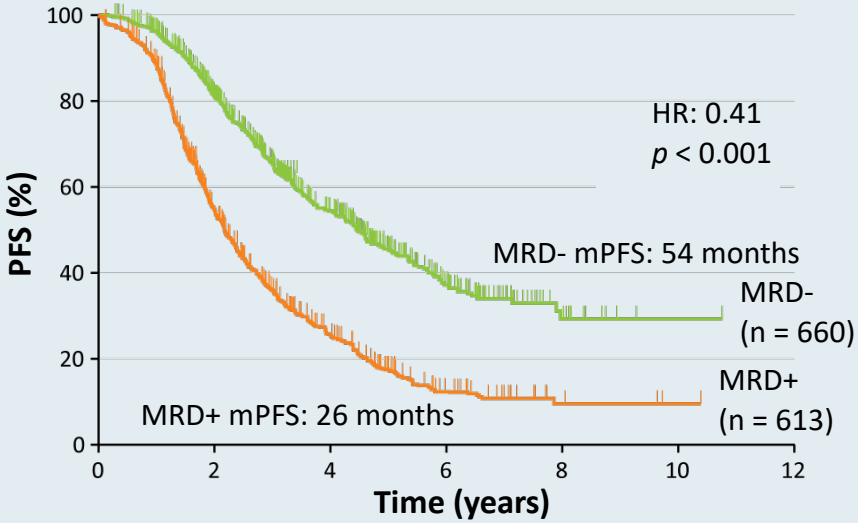
# Stringent Complete Response (sCR) and MRD as a Surrogate Endpoint for PFS and OS

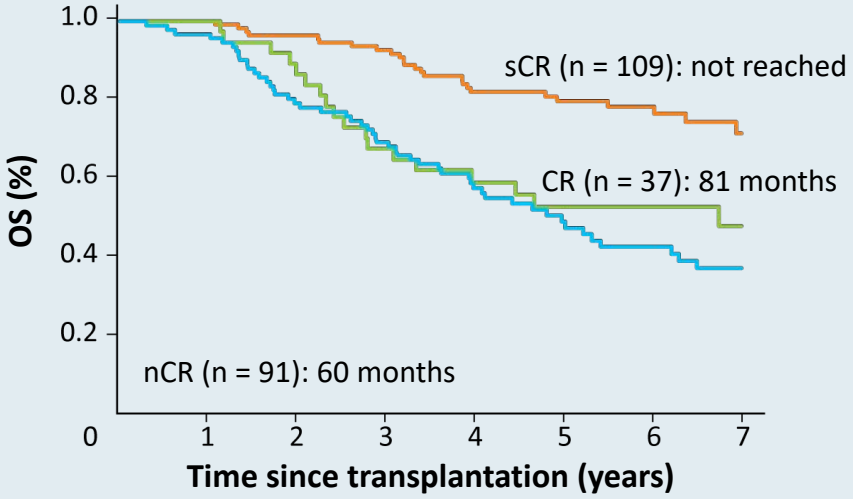
## Median TTP for patients achieving CR[1]



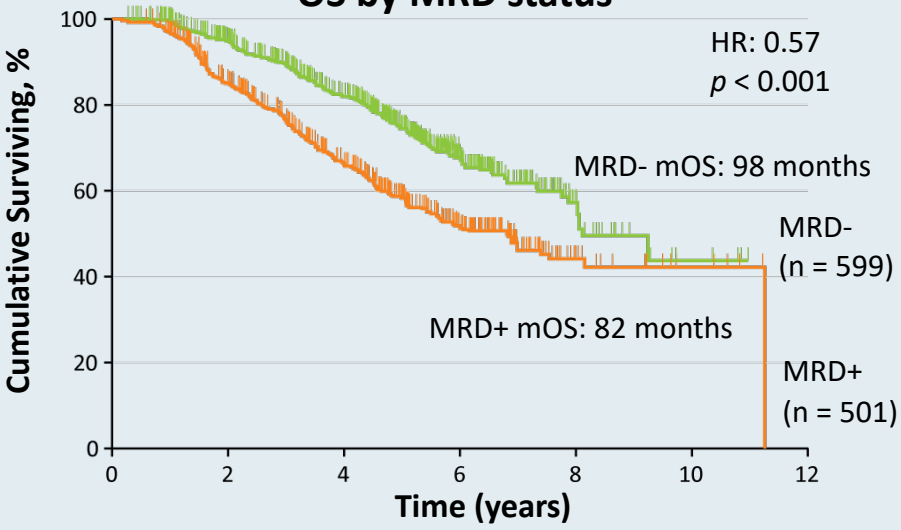

## PFS by MRD status[2]




## 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.



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# 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

Co-provided by USF Health Research To Practice®

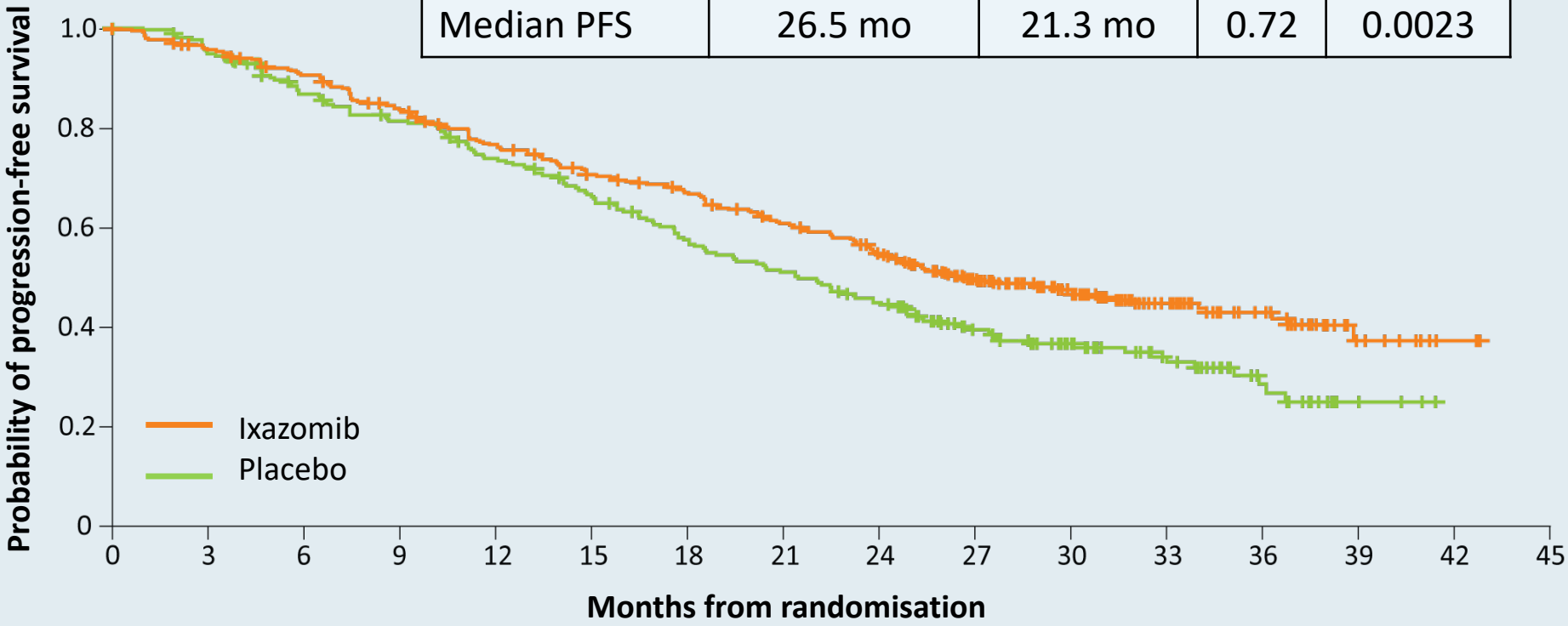
# Oral ixazomib maintenance following autologous stem cell transplantation (TOURMALINE-MM3): a double-blind, randomised, placebo-controlled phase 3 trial

*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.

# Case Presentation

Co-provided by USF Health Research To Practice®

# Case (from the practice of Ehsan Malek, MD)

- **Adding monoclonal antibody to induction triplet, SWOG (Elo/VRD), German trial (ISA/KRD), GRIFFIN Dara/VRD, Cassiopeia (DaraVTD)**
- 58 y/o newly diagnosed 17p stage III myeloma, transplant-eligible, normal renal function

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- Data with daratumumab-containing regimens; split dosing
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## Module 3: Novel Agents in Late-Stage Development

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

Co-provided by USF Health Research To Practice®

# Recent Relevant Datasets

# First-in-Human Phase I Study of the Novel CELMoD Agent CC-92480 Combined with Dexamethasone (DEX) in Patients (pts) with Relapsed/Refractory Multiple Myeloma (RRMM)

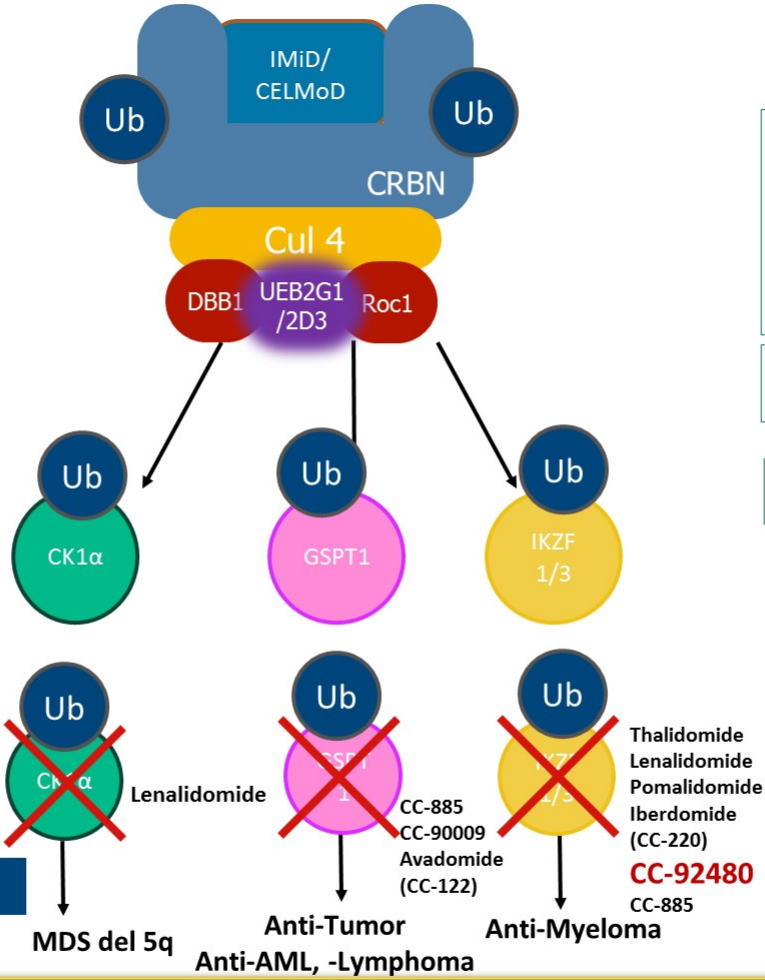
Richardson PG et al.

ASCO 2020;Abstract 8500.

Co-provided by USF Health Research To Practice®

# CC-92480/Dexamethasone Combined with Bortezomib or Daratumumab or Carfilzomib

| IMiD® | Indication |
|---|---|
| Thalidomide | Erythrema nodosum<br>Erythrema leprosum<br>Multiple Myeloma |
| Lenalidomide | Mantle Cell Lymphoma<br>Multiple Myeloma<br>Myelodysplastic Syndrome (5q-) |
| Pomalidomide | Multiple Myeloma<br>Kaposi Sarcoma |



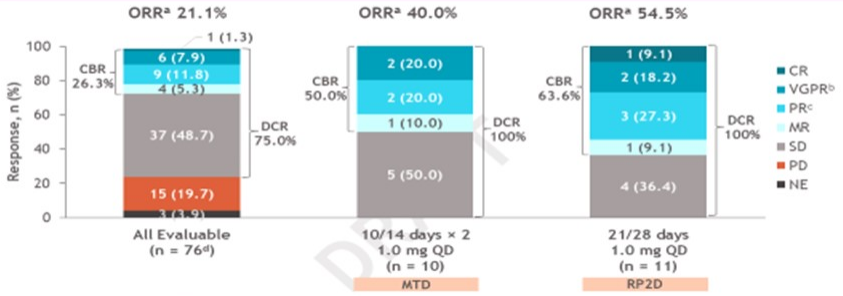

Abbreviations: CK1a: casein kinase 1a;
CELMods: Cereblon E3 Ligase Modulation Drugs;
CRL4: cullin-4 RING E3 ligase;
CRBN: Cereblon; CNS: Central Nervous System;
CUL4: Cullin-4; DDB1: DNA damage-binding protein 1;
GSPT1: G1 To S Phase Transition 1;
IKZF1: Ikaros zinc-finger protein 1;
IKZF3: Aiolos zinc-finger protein 3;
IMiDs: Immunomodulatory Drugs;
MDS: Myelodysplastic Syndrome;
Roc1: Ring finger protein;
UB: Ubiquitination
UBE2G1/2D3: Ubiquitin-conjugating enzymes

| Clinical Trials | CELMoDs® |
|---|---|
| Multiple Myeloma<br>Diffuse Large B-Cell Lymphoma<br>CNS Lymphoma<br>Glioblastoma<br>Hepatocellular Carcinoma<br>Chronic Lymphocytic Leukemia | CC-122 |
| Multiple Myeloma<br>Systemic Lupus Erythematosus | CC-220 |
| Acute Myeloid Leukemia | CC-90009 |
| Multiple Myeloma | CC-92480<br>Indisulam<br>Eisai |
| Acute Myeloid Leukemia?<br>(in vitro) | CC-885 |


Holstein et al, Next-Generation Drugs. Targeting the Cereblon Ubiquitin Ligase. JCO 2018
Lu G et al eLife 2018
Gandhi AK et al Br J Haem 2014
Krönke J et al Science 2014
Hansen JD et al J Med Chem 2020
Uehara, T. et al Nat Chem Biol 2017

# CC-92480/Dexamethasone Combined with Bortezomib or Daratumumab or Carfilzomib

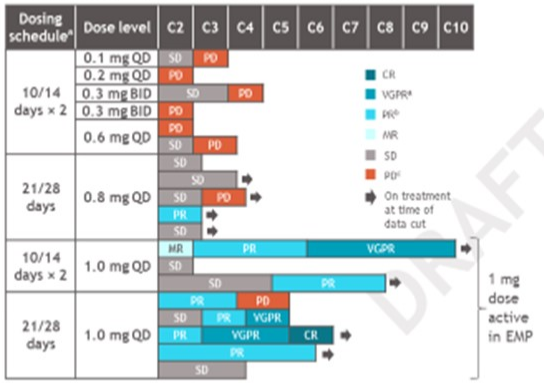
## Response




- At the RP2D 1.0 mg QD 21/28 days, 7 out of 11 patients were triple class-refractory[e]
  - 1 patient had CR, 1 VGPR, 2 PR, and 1 MR

## Responses in Patients With Extramedullary Plasmacytomas

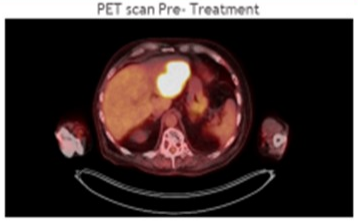
- Only patients on continuous schedules are shown



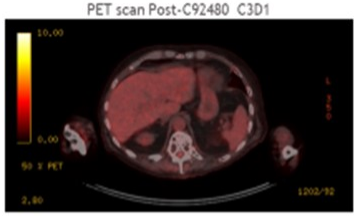

[a] 1 patient in the 21 /28 1.0 mg cohort had an unconfirmed VGPR as of the data cutoff date.
[b] 1 patient in the 21 /28 0.8 mg cohort had an unconfirmed PR as of the data cutoff date.
[c] 1 patient in the 21 /28 0.8 mg cohort had an unconfirmed PD as of the data cutoff date.

CI, confidence interval; CR, complete response; EMP, extramedullary plasmacytomas; MR, minimal response; PD, progressive disease; PET, positron emission tomography; PR, partial response; SD, stable disease; VGPR, very good partial response.

PET scan Pre- Treatment



PET scan Post-C92480 C3D1





- Future:
- NDMM and RRMM: Phase 1/2 of CC-92480 with dexamethasone in combination with bortezomib ***or*** daratumumab ***or*** carfilzomib NCT03989414
- Mitigating hematologic toxicity
- Role in the context of lenalidomide, pomalidomide, iberdomide

  Optimal combination therapy

  Induction, maintenance, salvage

## DLTs by Dose Level

| | Dosing schedule | Dose level | Patients, n | DLTs |
|---|---|---|---|---|
| Continuous | 10/14 days × 2 | 0.1 mg QD | 3 | - |
| | | 0.2 mg QD | 4 | 1 patient (neutropenia) |
| | | 0.3 mg QD | 4 | - |
| | | 0.6 mg QD | 8 | 1 patient (pneumonitis) |
| | | 1.0 mg QD | 10 | 2 patients (neutropenia; febrile neutropenia) |
| | 21/28 days | 0.8 mg QD | 12 | - |
| | | 1.0 mg QD | 11 | 3 patients (neutropenia; febrile neutropenia; sepsis) |
| Intensive | 3/14 days × 2 | 0.2 mg BID | 4 | - |
| | | 0.4 mg BID | 3 | - |
| | | 0.8 mg BID | 4 | - |
| | 7/14 days × 2 | 0.8 mg BID | 3 | - |
| | | 1.6 mg QD | 5 | 1 patient (febrile neutropenia) |
| | | 2.0 md QD | 5 | 2 patients (pneumonitis; increased ALT, neutropenia, and thrombocytopenia) |

- MTD was determined at 1.0 mg QD for both 10/14 days × 2 and 21/28 days schedules

ALT, alanine transaminase; BID, twice daily; DLT, dose-limiting toxicity; MTD, maximum tolerated dose; QD, once daily.





PRESENTED BY: Philip McCarthy

# Weekly Selinexor, Bortezomib, and Dexamethasone (SVd) versus Twice Weekly Bortezomib and Dexamethasone (Vd) in Patients with Multiple Myeloma (MM) After One to Three Prior Therapies: Initial Results of the Phase III BOSTON Study

Dimopoulos MA et al.

ASCO 2020;Abstract 8501.

# 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<br>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

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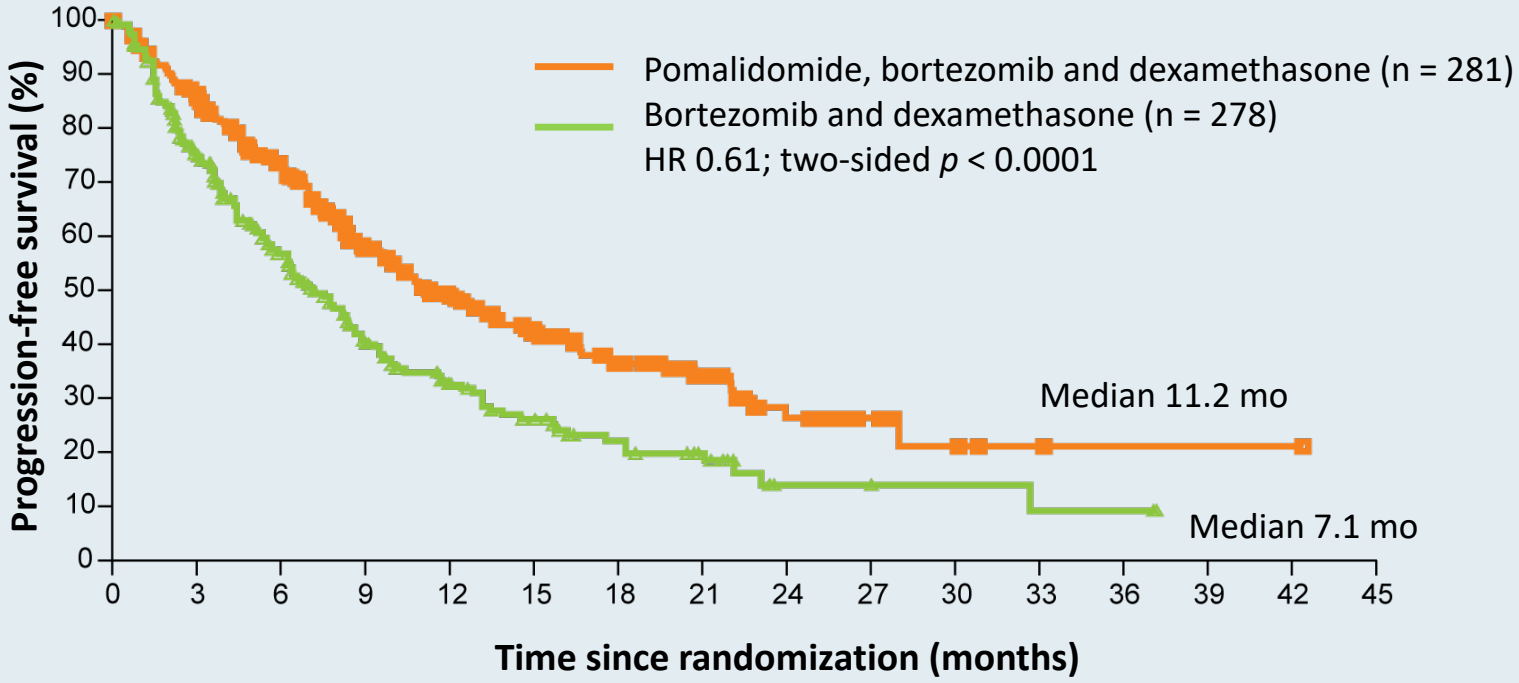
# OPTIMISMM: Phase III Trial of Pomalidomide with Bortezomib and Dexamethasone in Relapsed/Refractory MM

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

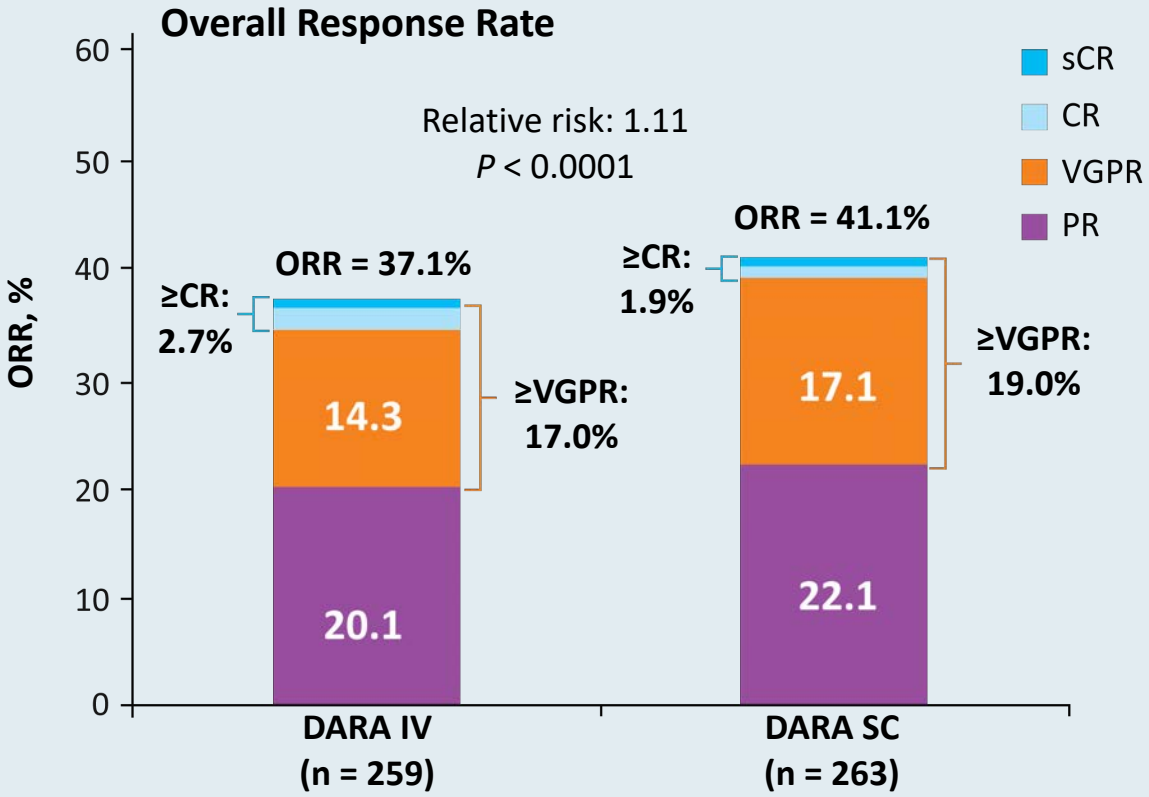
Daratumumab and hyaluronidase-fihj is approved for certain indications that intravenous daratumumab had previously received.

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



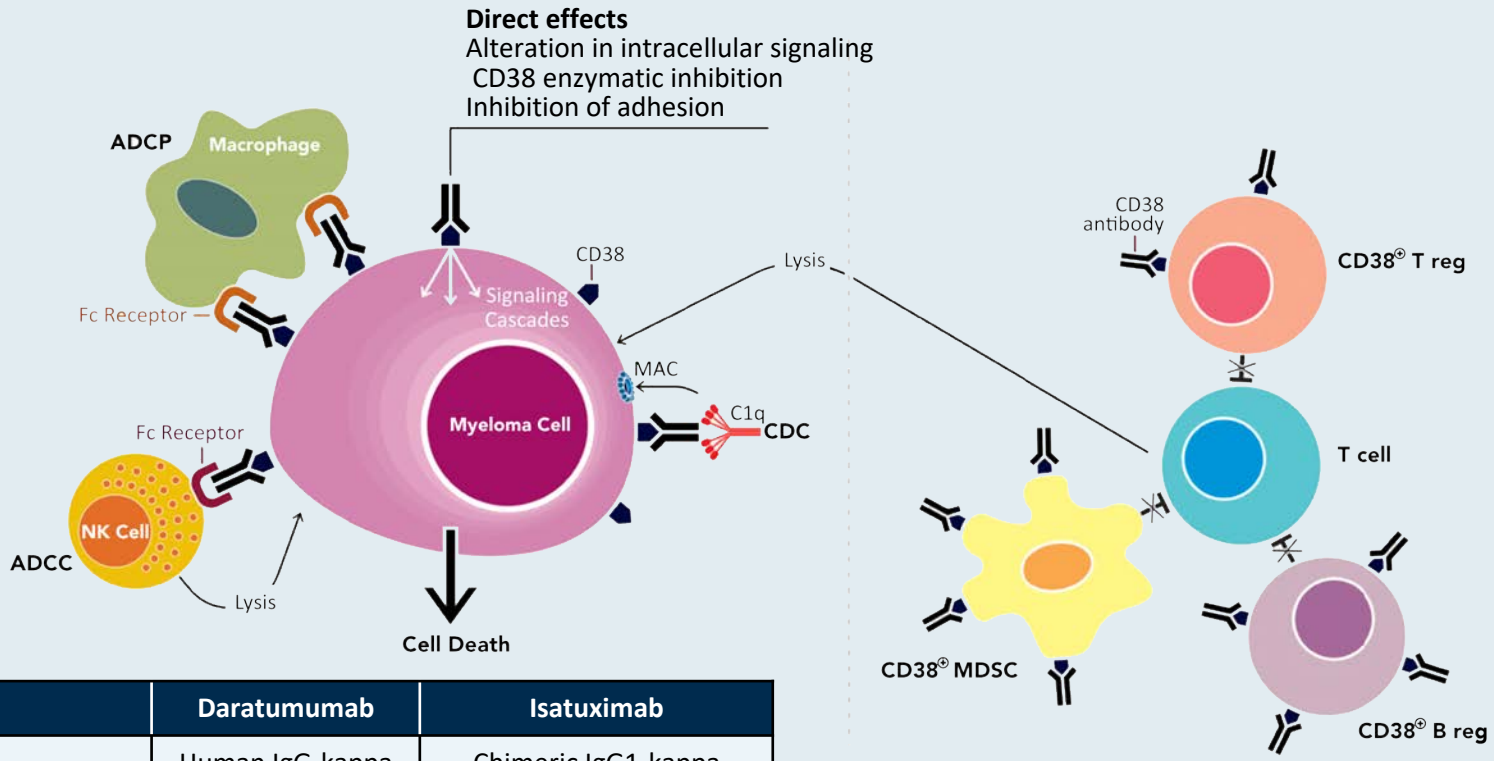

| | DARA IV (n = 258) | DARA SC (n = 260) | Odds ratio (*p*-value) |
|---|---|---|---|
| Rate of infusion-related reactions | 34.5% | 12.7% | 0.28 (<0.0001) |

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®

# Case Presentation

Co-provided by USF Health Research To Practice®

# Case (from the practice of Ehsan Malek, MD)

- **Early intervention in high risk smoldering myeloma (E3A06 trial, Lonial: PI).**
- 68 y/o Caucasian woman with IgG Kappa smoldering myeloma, 40% light-chain restricted plasma cells in bone marrow biopsy, 1q gain, M-spike 1.2 gr/dL, Light chain ratio: 44, normal renal function, no anemia or bony lesions. M spike through last year increased; 1.2>1.6>1.9>2.5 gr/dL and Cr: 1.2>1.3>1.3>1.4. When is the optimal time for treatment?

# 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)
- Recent relevant datasets

## 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
- Recent relevant datasets

## Module 3: Novel Agents in Late-Stage Development

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

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# Recent Relevant Datasets

# DREAMM-6: Safety and Tolerability of Belantamab Mafodotin in Combination with Bortezomib/Dexamethasone in Relapsed/Refractory Multiple Myeloma (RRMM)

Nooka AK et al.

ASCO 2020;Abstract 8502.

# Idecabtagene Vicleucel (ide-cel; bb2121), A BCMA-Targeted CAR T-Cell Therapy, in Patients with Relapsed and Refractory Multiple Myeloma (RRMM): Initial KarMMa Results

Munshi NC et al.

ASCO 2020;Abstract 8503.

# Update of CARTITUDE-1: A Phase Ib/II Study of JNJ-4528, A B-cell Maturation Antigen (BCMA)-Directed CAR-T-Cell Therapy, in Relapsed/Refractory Multiple Myeloma

Berdeja JG et al.

ASCO 2020;Abstract 8505.

# Orvacabtagene Autoleucel (orva-cel), A B-cell Maturation Antigen (BCMA)-Directed CAR T Cell Therapy for Patients (pts) with Relapsed/Refractory Multiple Myeloma (RRMM): Update of the Phase 1/2 EVOLVE Study (NCT03430011)

Mailankody S et al.

ASCO 2020;Abstract 8504.

# ASCO 2020: 3 BCMA CAR T Studies

## Characteristics Summary

| | KarMMa: idecabtagene vicleucel (n=128) | EVOLVE: orvacabtagene autoleucel (n=62) | CARTITUDE-1: JNJ-4528 (n = 29) |
|---|---|---|---|
| Age | 61 (33-78) | 61 (33-77) | 60 (50-75) |
| High Risk Cytogenetics, % | 35 | 41* | 27 |
| Tumor Burden in BM, % | >50% PC = 51 | — | ≥60% PC = 24 |
| Extramedullary PCs, % | 39 | 23 | 10 |
| Median prior lines of therapy | 6 (3-16) | 6 (3-18) | 5 (3-18) |
| Triple refractory, % | 84 | 94 | 86 |
| Bridging therapy, % | 88 | 63 | 79 |
| Unique properties | Human BCMA, 4-1BB, CD3z | Modified spacer, CD4:CD8 enriched for CM | Median cell dose **0.72x10$^6$** cells/kg<br>2 BCMA single chain antibodies |

PRESENTED AT: 2020 ASCO ANNUAL MEETING #ASCO20



PRESENTED BY: Krina Patel MD MSc

* Included +1q21

# ASCO 2020: 3 BCMA CAR T Studies

## Safety

| | KarMMa | EVOLVE | CARTITUDE-1 |
|---|---|---|---|
| ↓ANC ≥G3, % | 89 | 90 | 100 |
| ↓plts ≥G3, % | 52 | 47 | 69 |
| CRS: all, ≥G3,% | 84, 6 | 89, 3 | 93, 7 |
| Med. time to CRS, duration, days | 1 (1-12)<br>5 (1-63) | 2 (1-4)<br>4 (1-10) | 7 (2-12)<br>4 (2-64) |
| ICANS: all, ≥G3,% | 17, 3 | 13, 3 | 10, 3 |
| HLH/MAS, % | -- | 5 | ? 7 (lfts) |
| Infections: all, ≥G3 % | 69, -- | 40, 13 | --, 19 |
| Toci/steroid/ anakinra use, % | 52/15/0 | 76/52/23 | 79/21/21 |

? This was not listed at MAS/HLH, I am just speculating → could this have been early MAS

## Efficacy

| | KarMMa (n = 128) | EVOLVE (n = 62) | CARTITUDE-1 (n = 29) |
|---|---|---|---|
| ORR, % | 73 (66-81) | 92 | 100 |
| sCR/CR, % | 33 | 36 | 86 |
| MRD neg ≥$10^{-5}$, % (of evaluable) | 94 | 84 | 81 |
| PFS/DoR, months | 8.8/10.7 | NR* | NR** |
| Screened<br>Apheresed<br>Treated | 150<br>140<br>128 | -- | 35<br>35<br>29 |

* 300 x10^6 cell dose cohort (lowest) = PFS 9.3 months, other med F/U = 8.8 and 2.3 month
** 9 mo PFS = 86%

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PRESENTED BY: Krina Patel MD MSc

Patel K. ASCO 2020 Discussant

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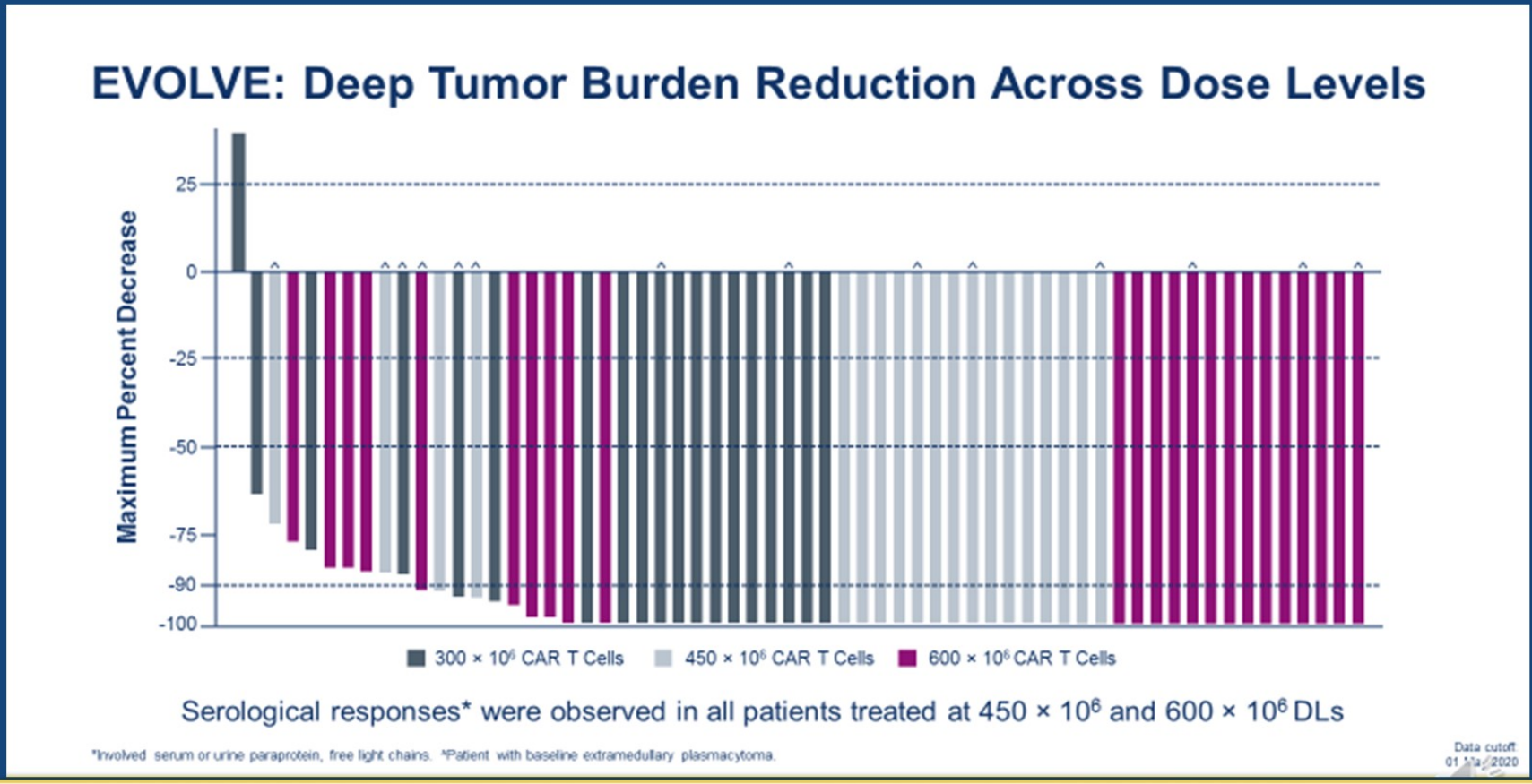
# EVOLVE BCMA CAR T Study

## Look at that waterfall!

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PRESENTED BY: Krina Patel MD MSc

Patel K. ASCO 2020 Discussant

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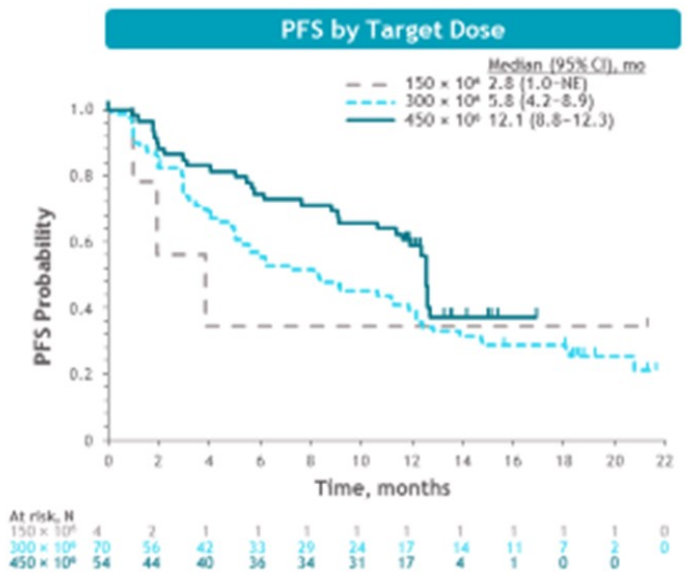
# Idecabtagene Vicleucel BCMA CAR T Study

## Progression free survival with a single cell infusion!

### Progression-Free Survival

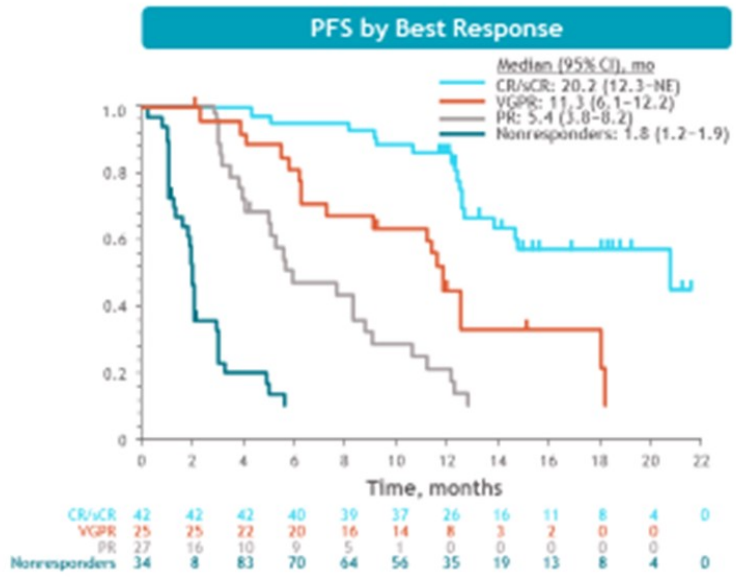
KarMMa™

**PFS by Target Dose**




- PFS increased with higher target dose; median PFS was 12 mo at 450 × $10^6$ CAR+ T cells

**PFS by Best Response**




- PFS increased by depth of response; median PFS was 20 mo in patients with CR/sCR

Data cutoff: 14 Jan 2020. NE, not estimable; PFS, progression-free survival.

12

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Patel K. ASCO 2020 Discussant

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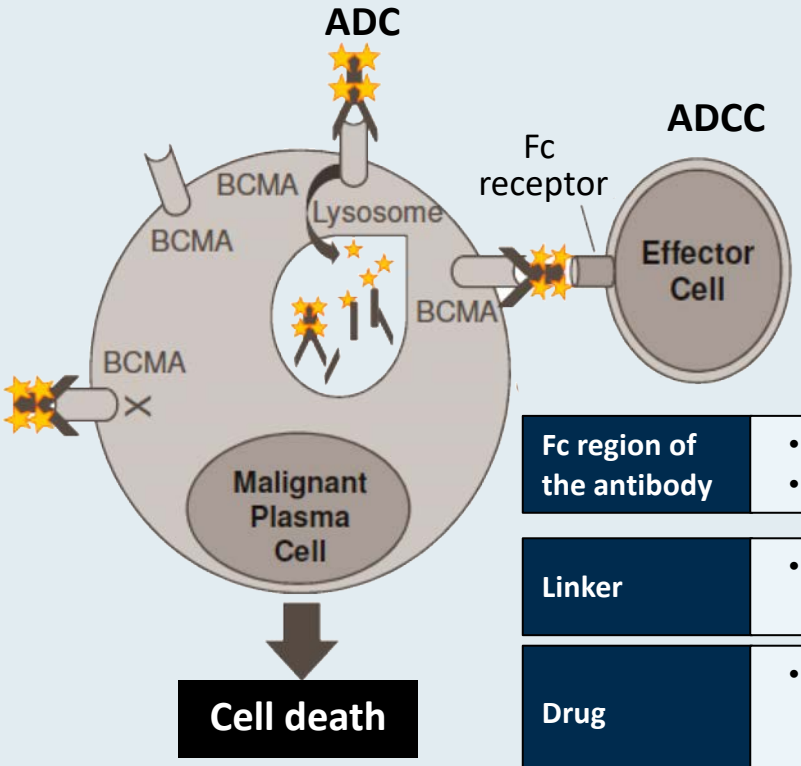
# Belantamab Mafodotin: Anti-BCMA Antibody-Drug Conjugate

- 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



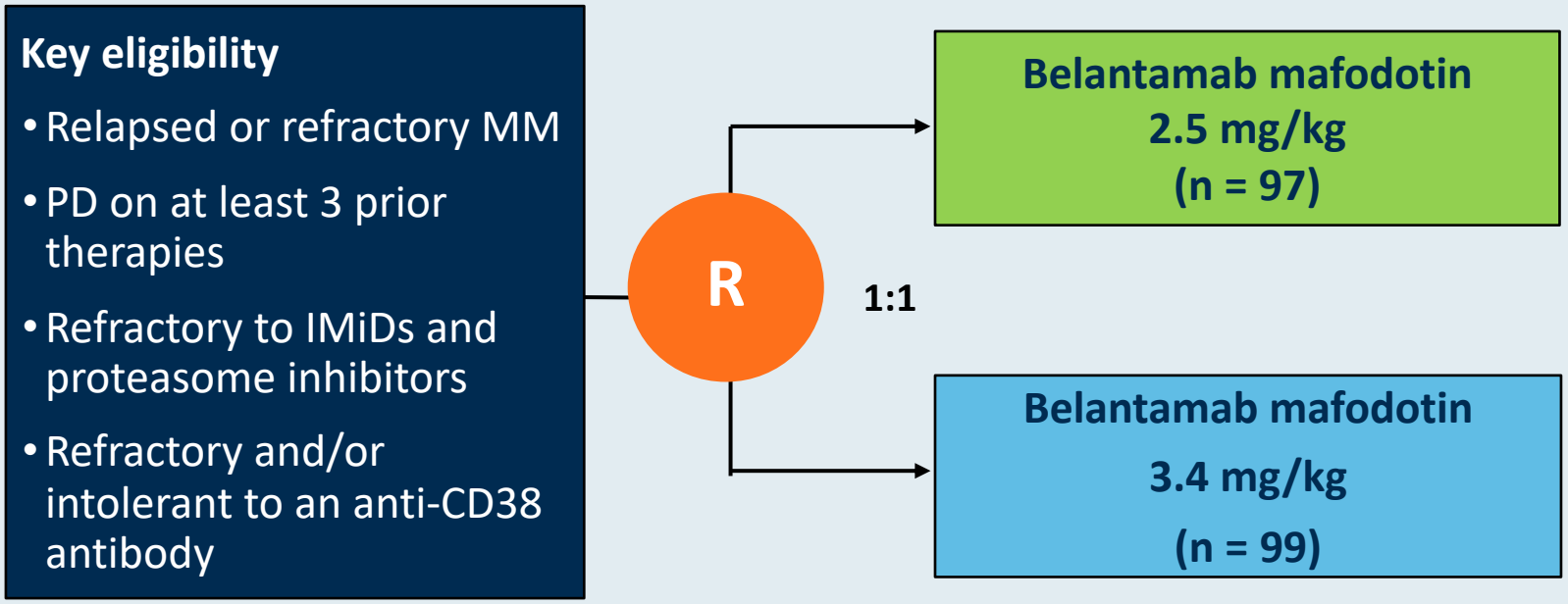

| | |
|---|---|
| **Fc region of the antibody** | • **Target specific**<br>• **Enhanced ADCC** |
| **Linker** | • **Stable in circulation** |
| **Drug** | • **MMAF (non cell permeable, highly potent auristatin)** |

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

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

Co-provided by USF Health Research To Practice®

# 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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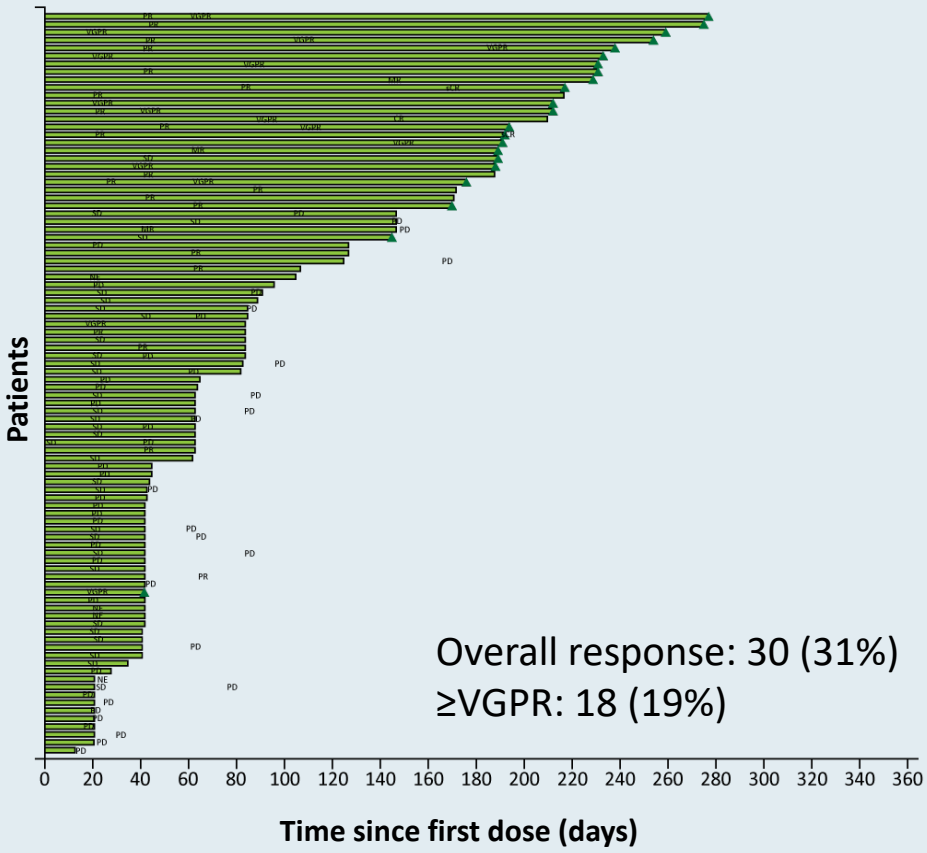
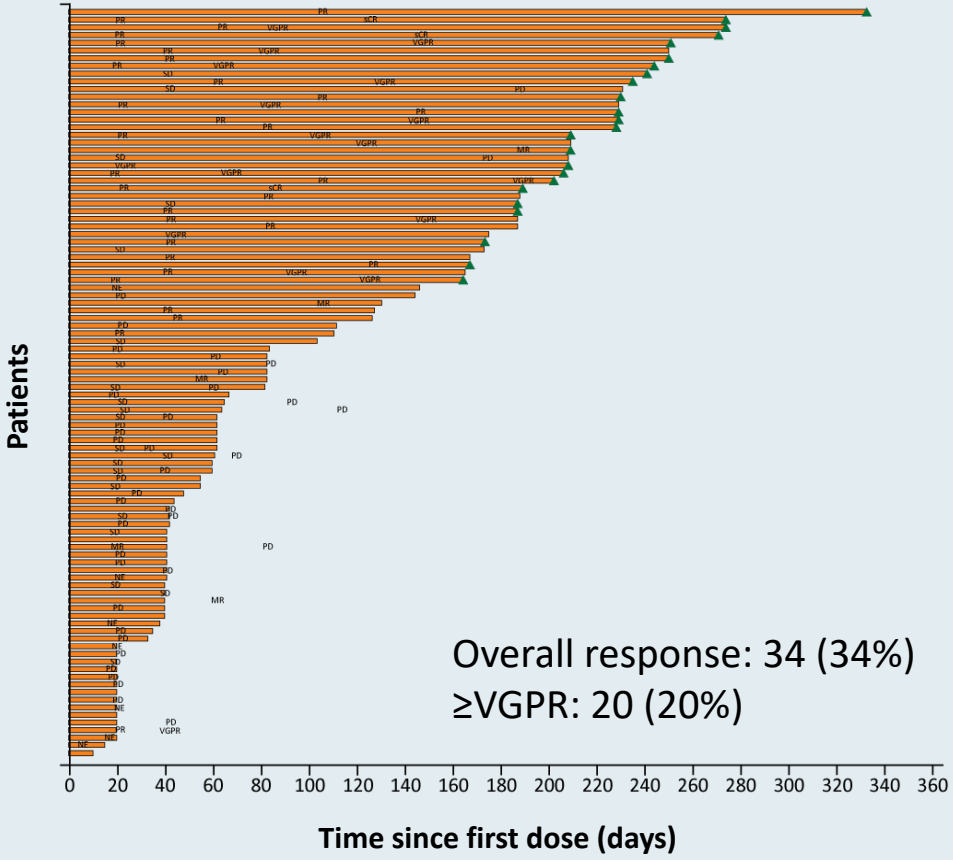
# DREAMM-2: Response and Duration of Response

## 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: 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.

# 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 |

# Case Presentation

Co-provided by USF Health Research To Practice®

# Case (from the practice of Ehsan Malek, MD)

- **Late relapse/refractory myeloma: BOSTON trial (Isatuximab/Vel/Dex), DREAM trial (Belantamab+Velcade), New generation IMiDs (CC92480), Ide-Cel BCMA CAR T, CARTITUDE**

- 48 y/o Caucasian female, IgG kappa, standard risk R-ISS stage II Multiple Myeloma: VRD (x4) → PR, KRD (x4) → VGPR, auto-SCT → CR, KR maintenance. She relapsed after 14 months of being on KR, Dara/Pom → VGPR, 8 months later had relapse, enrolled on BCMA CAR T-cell trial → CR, relapsed 11 months after. Normal renal function, ECOG:1, 50% plasma cell burden, BCMA+, CD38+ on bone marrow biopsy. What are the options?

*Thank you for joining us!*

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

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

## *A Meet The Professor Series*

**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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