Consensus or Controversy? Investigators Discuss Clinical Practice Patterns and Available Research Data Guiding the Management of Hematologic Cancers

Multiple Myeloma

Friday, December 4, 2020
8:30 AM – 10:00 AM Pacific Time

Faculty

Rafael Fonseca, MD
Ola Landgren, MD, PhD
Nikhil C Munshi, MD
Robert Z Orlowski, MD, PhD
Edward A Stadtmauer, MD

Moderator

Neil Love, MD

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Commercial Support

This activity is supported by educational grants from AbbVie Inc, Bristol-Myers Squibb Company, GlaxoSmithKline, Karyopharm Therapeutics, Oncopeptides, Sanofi Genzyme and Takeda Oncology.

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Dr Love — Disclosures

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Dr Fonseca — Disclosures

Advisory Committee	Adaptive Biotechnologies Corporation, ONCOtracker Inc
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Dr Landgren — Disclosures

Consulting Agreements and Speakers Bureau	Amgen Inc, Bristol-Myers Squibb Company, Celgene Corporation, Janssen Biotech Inc
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Dr Munshi — Disclosures

Consulting Agreements	AbbVie Inc, Adaptive Biotechnologies Corporation, Amgen Inc, BeiGene, Bristol-Myers Squibb Company, Janssen Biotech Inc, Karyopharm Therapeutics, OncoPep, Takeda Oncology
Ownership Interest	OncoPep

Dr Orlowski — Disclosures

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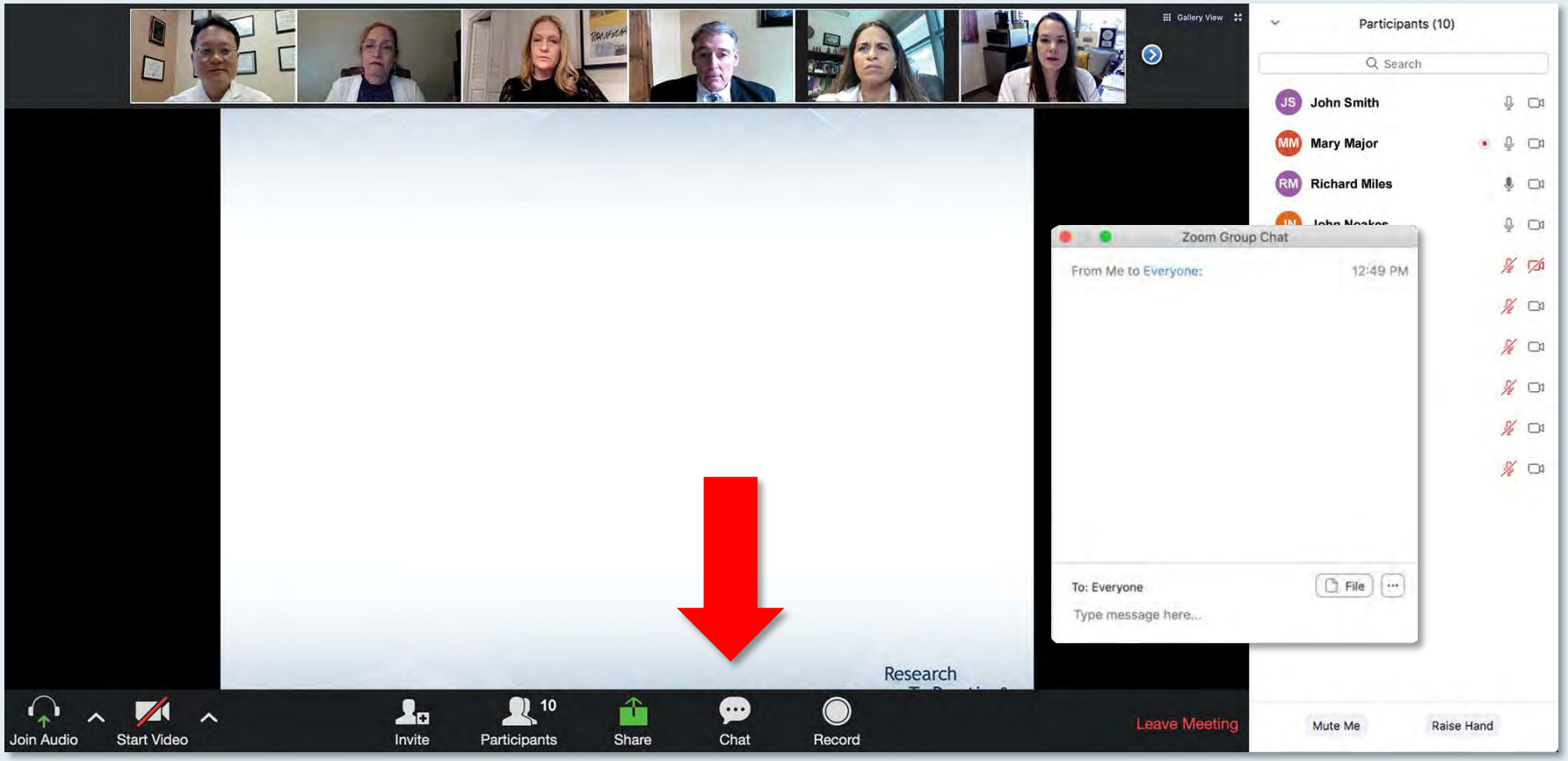
Ownership Interest	Asylia Therapeutics Inc (founder, patents, equity)

Dr Stadtmauer — Disclosures

Consulting Agreements	Amgen Inc, Celgene Corporation, Genentech, a member of the Roche Group, Janssen Biotech Inc, Sanofi Genzyme, Takeda Oncology

We Encourage Clinicians in Practice to Submit Questions



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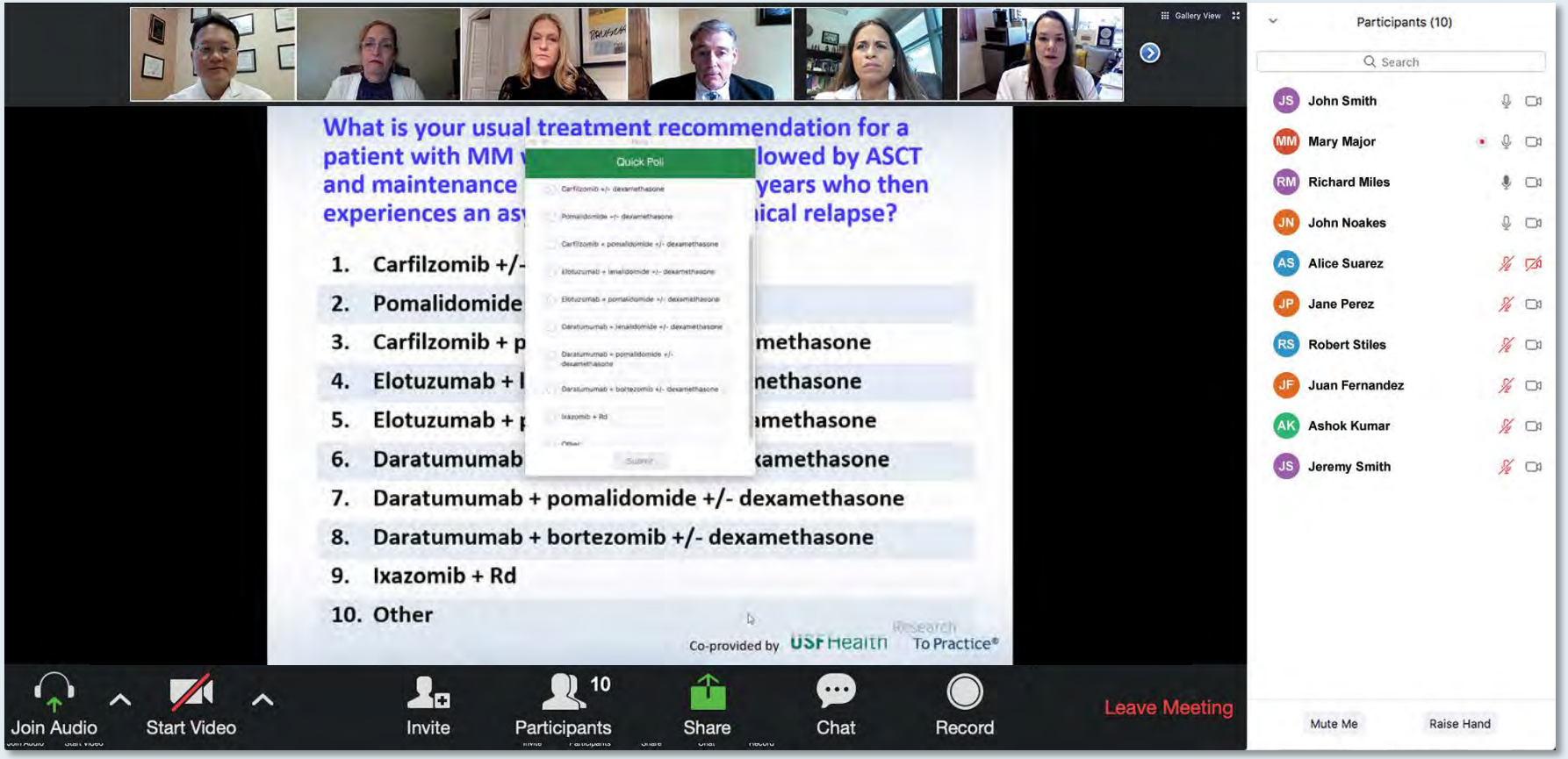

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Upcoming Webinars

Tuesday, December 8, 2020
5:00 PM – 6:00 PM ET

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Zev Wainberg, MD, MSc

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Meet The Professor: Immunotherapy and Novel Agents in Gynecologic Cancers

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Moderator

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Thank you for joining us!

CME credit information will be emailed to each participant within 3 business days.

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WITH DR NEIL LOVE

NOVEL AGENTS UNDER INVESTIGATION IN MULTIPLE MYELOMA

DR PETER VOORHEES
LEVINE CANCER INSTITUTE

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John Kuruvilla, MD
Ann S LaCasce, MD, MMSc
John P Leonard, MD
Michael E Williams, MD, ScM

Moderator

Neil Love, MD

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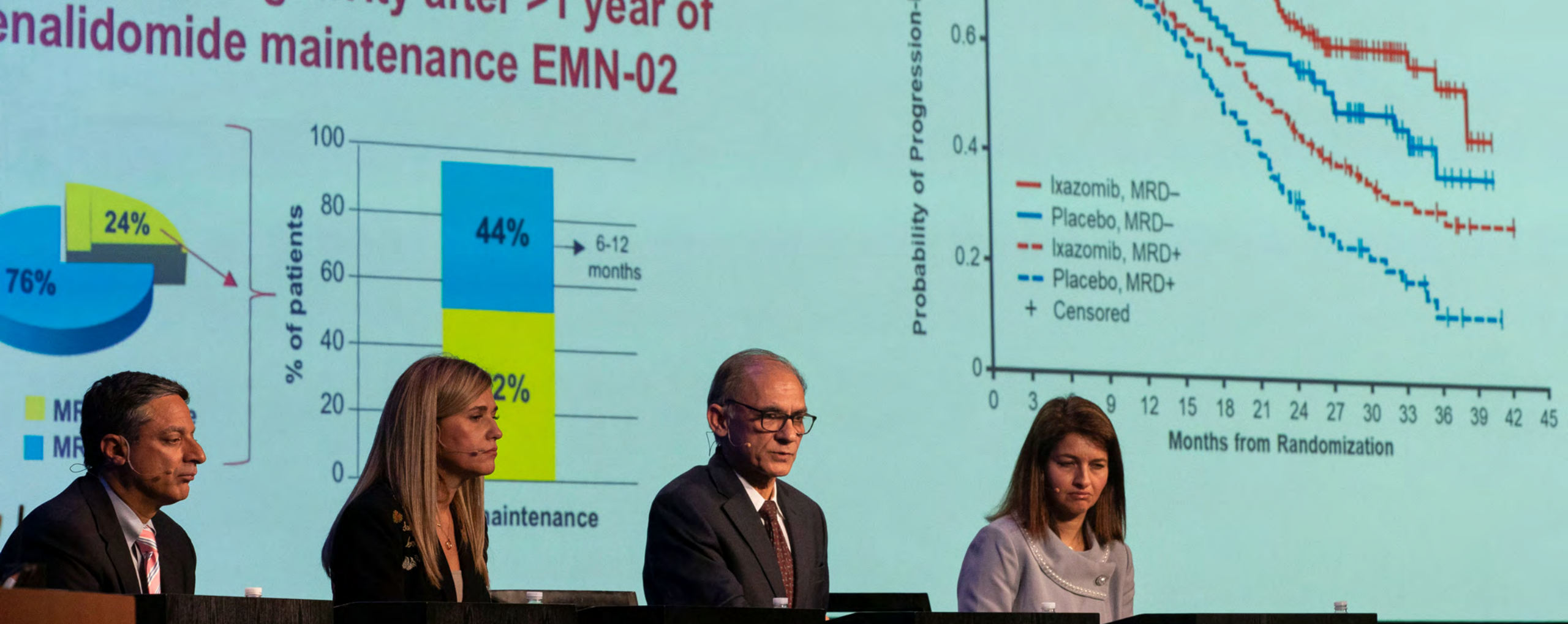
dexamethasone
alidomide
ethasone


What is your usual induction regimen for a 77-year-old patient with ISS Stage II MM who is transplant ineligible, has a creatinine level of 5 mg/dL and no high-risk features?
Lenalidomide
Rd
Bortezomib
RVd or RVd lite
KRd
CyBorD
MPV/daratumumab
Rd/daratumumab
VTd/daratumumab
3%
4%
16%
12%
1%
48%
4%
3%
4%
5%


KRd
16%
CyBorD
13%
1%
MPV/daratumumab
48%
Rd/daratumumab
4%
VTd/daratumumab
3%
4%
5%


enalidomide maintenance EMN-02
24%
76%
100
80
60
40
20
0
% of patients
44%
6-12
months
2%
aintenance
Probability of Progression-
0.6
0.4
0.2
0
Ixazomib, MRD–
Placebo, MRD–
Ixazomib, MRD+
Placebo, MRD+
+ Censored
0 3 9 12 15 18 21 24 27 30 33 36 39 42 45
Months from Randomization

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Rafael Fonseca, MD
Getz Family Professor of Cancer
Director for Innovation and
Transformational Relationships
Interim Executive Director of the Mayo
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Chair, Department of Internal Medicine
Distinguished Mayo Investigator
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Jerome Lipper Multiple Myeloma Center
Professor of Medicine
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Dana-Farber Cancer Institute
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Leader, Experimental Therapeutics Program
Leader, Myeloma Program
Sylvester Comprehensive Cancer Center
University of Miami
Miami, Florida

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

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Faculty

Edward A Stadtmauer, MD
Section Chief, Hematologic Malignancies
Roseman, Tarte, Harrow and Shaffer Families President's Distinguished Professor
University of Pennsylvania
Abramson Cancer Center of the University of Pennsylvania
Philadelphia, Pennsylvania

Moderator
Neil Love, MD
Research To Practice
Miami, Florida

Consensus or Controversy Survey Participants (in Addition to Our Faculty)

Sagar Lonial, MD
Winship Cancer Institute
Emory University School of Medicine
Atlanta, Georgia

S Vincent Rajkumar, MD
Mayo Clinic
Rochester, Minnesota

Paul G Richardson, MD
Dana-Farber Cancer Institute
Boston, Massachusetts

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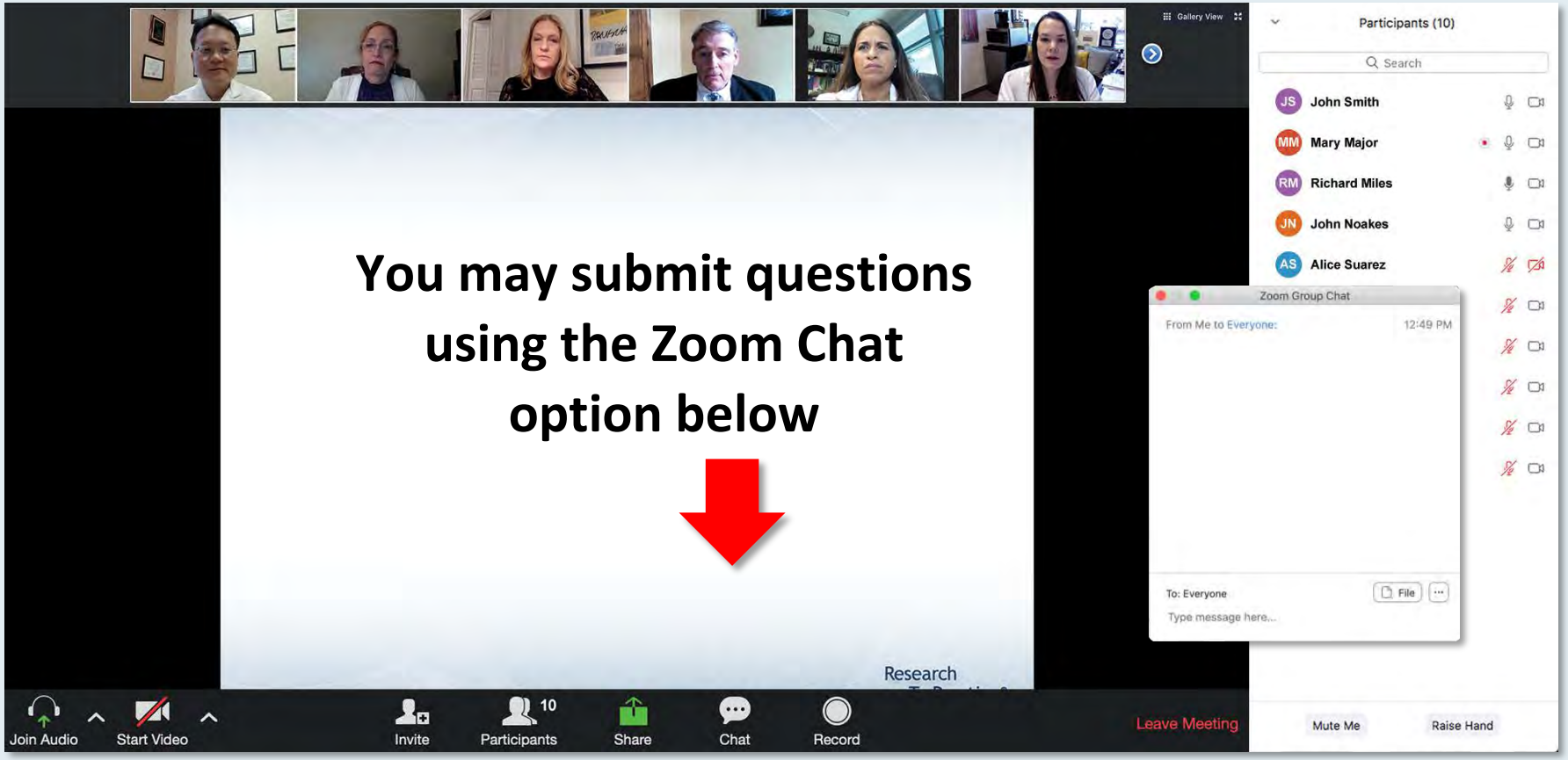

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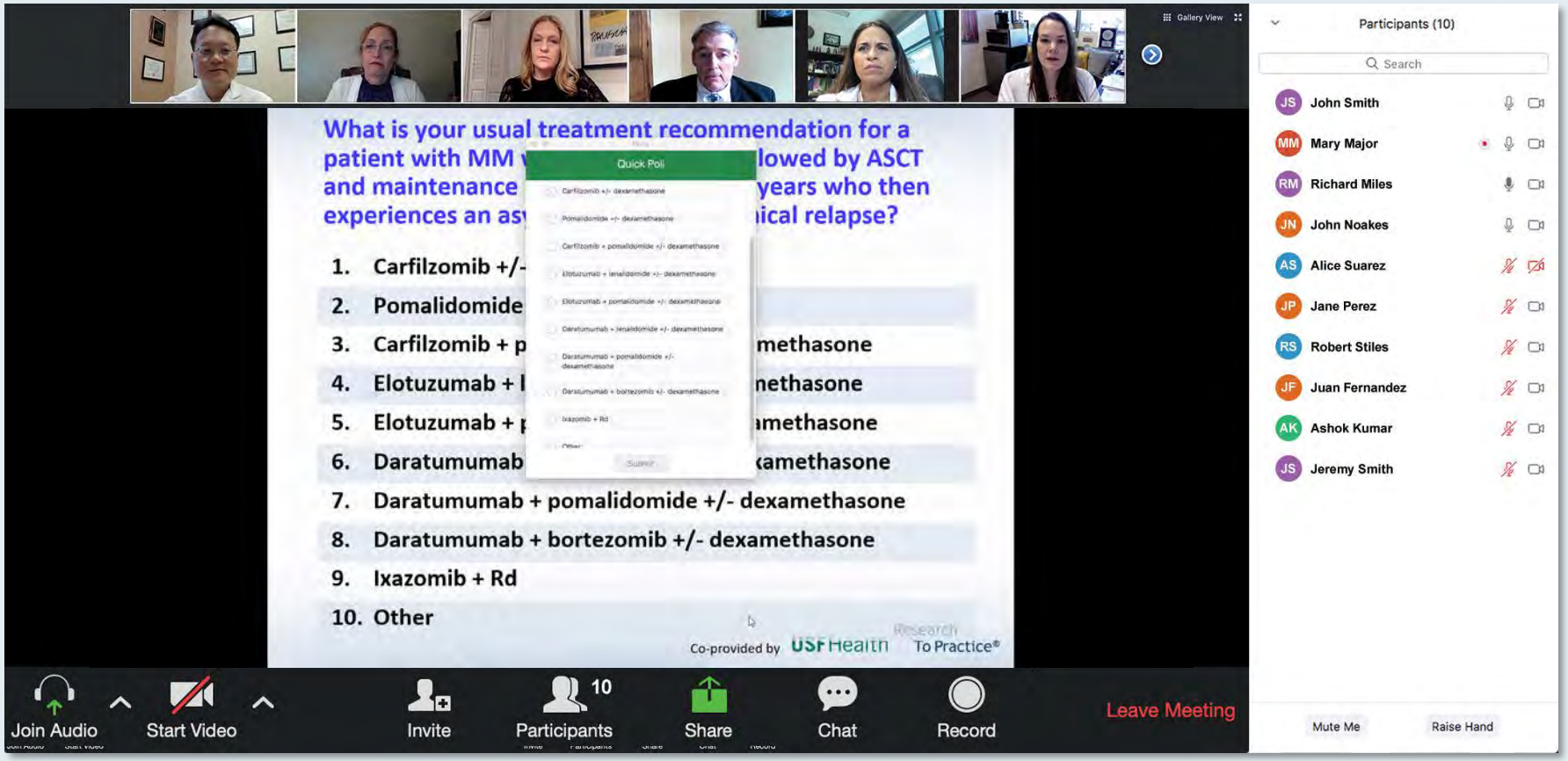

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Recent Advances in Hematologic Oncology: A 4-Part Live Webinar Series Reviewing Key Data and Presentations from the 62nd ASH Annual Meeting

Acute Myeloid Leukemia

Wednesday, January 20, 2021
5:00 – 6:00 PM ET

Faculty
Daniel A Pollyea, MD, MS
Professor Andrew H Wei, MBBS, PhD
Additional faculty to be announced

Multiple Myeloma

Wednesday, February 10, 2021
5:00 – 6:00 PM ET

Faculty
Robert Z Orlowski, MD, PhD
Edward A Stadtmauer, MD
Additional faculty to be announced

Hodgkin and Non-Hodgkin Lymphoma

Wednesday, February 3, 2021
5:00 – 6:00 PM ET

Faculty
John Kuruvilla, MD
John P Leonard, MD
Michael E Williams, MD, ScM

Chronic Lymphocytic Leukemia

Wednesday, February 24, 2021
5:00 – 6:00 PM ET

Faculty
Matthew S Davids, MD, MMSc
Additional faculty to be announced

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Presentation Library

Multiple Myeloma, Friday, December 4, 2020

Induction therapy for patients with newly diagnosed disease
Robert Z Orlowski, MD, PhD

Download Slides

Consolidation and maintenance therapy
Rafael Fonseca, MD

Download Slides

Selection and sequencing of available therapies for relapsed/ refractory disease
Nikhil C Munshi, MD

Download Slides

Chimeric antigen receptor T-cell therapy
Edward A Stadtmauer, MD

Download Slides

Other novel strategies
Ola Landgren, MD, PhD

Download Slides

Agenda

Module 1: Induction therapy for patients with newly diagnosed disease — Dr Orlowski

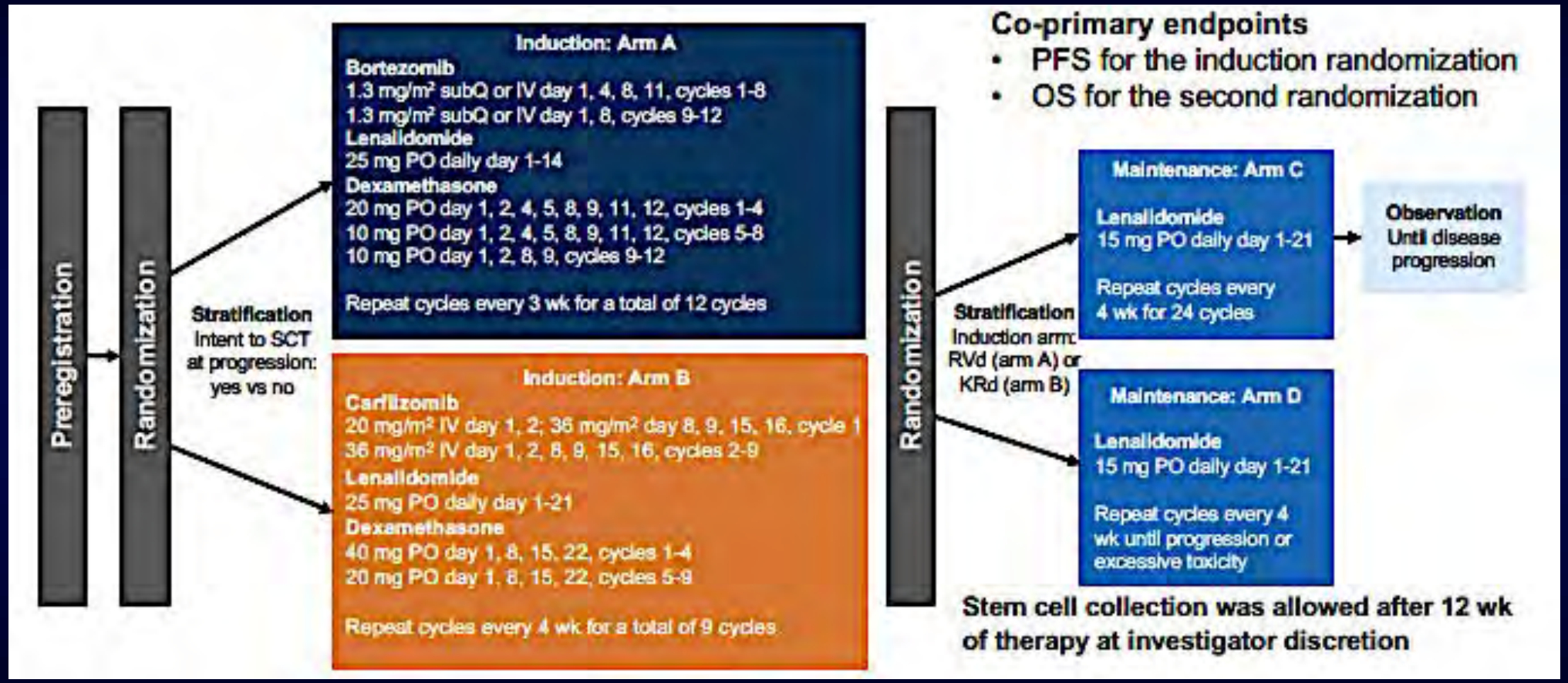
Module 2: Consolidation and maintenance therapy — Dr Fonseca

Module 3: Selection and sequencing of available therapies for relapsed/refractory disease — Dr Munshi

Module 4: Chimeric antigen receptor T-cell therapy — Dr Stadtmauer

Module 5: Other novel strategies — Dr Landgren

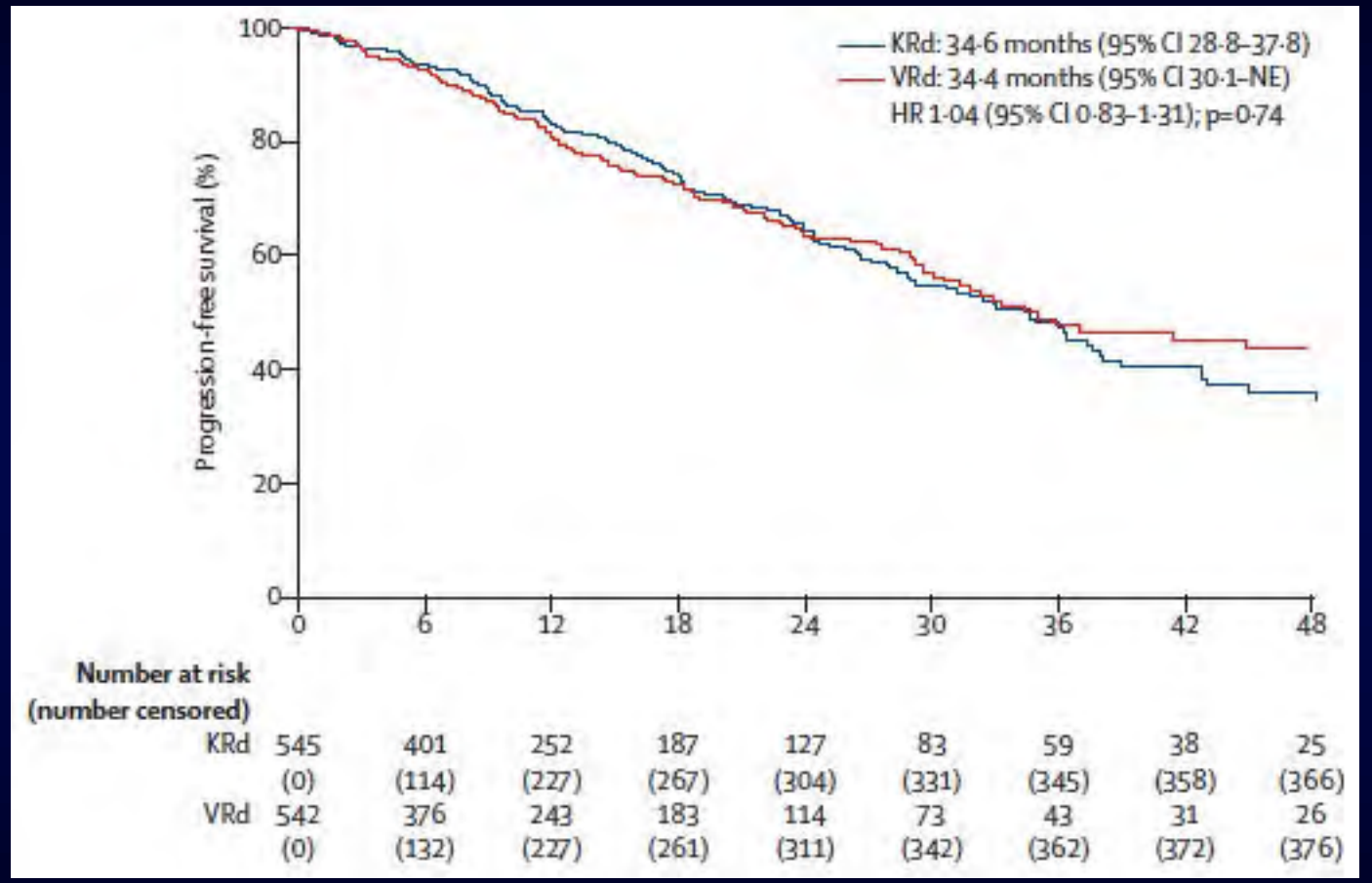
ENDURANCE Trial



Kumar, S et al. Lancet Oncol. 21: 1317, 2020.

Courtesy of Robert Z Orlowski, MD, PhD

ENDURANCE: PFS Data

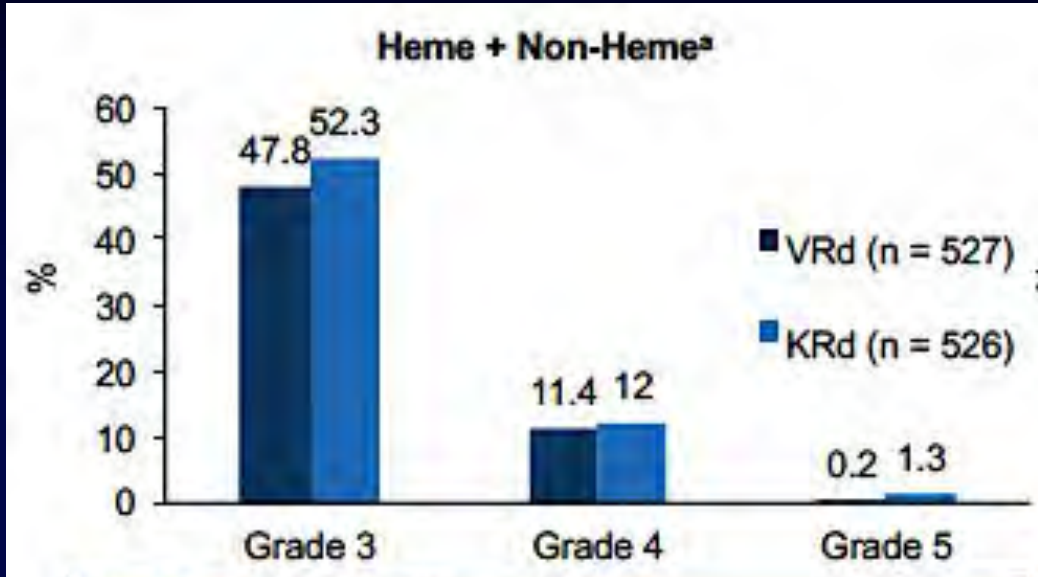


- Median PFS for patients ≥ 70 yrs
  - VRd: 37 mos (95% CI: 29-NE)
  - KRd: 28 mos (95% CI: 24-36)
- Median PFS with censoring at SCT or alternative treatment
  - VRd: 31.7 mos (95% CI: 28.5-44.6)
  - KRd: 32.8 mos (95% CI: 27.2-37.5)
- Median OS not reached in either arm (29-mo median follow-up)
  - HR: 0.98 (95% CI: 0.71-1.36; *P* = .923)
- 3-yr OS rate
  - VRd: 84% (95% CI: 80%-88%)
  - KRd: 86% (95% CI: 82%- 89%)

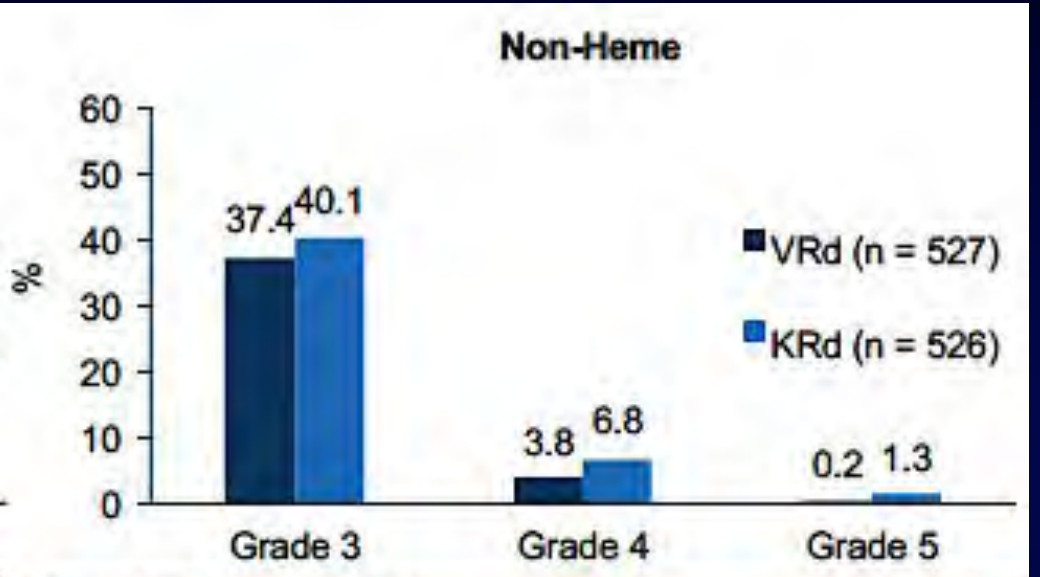
Kumar, S et al. Lancet Oncol. 21: 1317, 2020.

Courtesy of Robert Z Orlowski, MD, PhD

ENDURANCE: Adverse Events



Step 1 Treated Patients	VRd (n = 527)	KRd (n = 526)		
Rates	N (%)	N (%)	Diff KRd-RVd	Chi Square *P*
Grades 3-5	313 (59.4)	345 (65.6)	6.2	.038
(95% CI)	(55.1-63.6)	(61.3-69.6)		
Grades 4-5	61 (11.6)	70 (13.3)	1.7	.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-RVd	Chi Square *P*
Grades 3-5	218 (41.4)	254 (48.3)	6.9	.024
(95% CI)	(37.1-45.7)	(44.0-52.6)		
Grades 4-5	21 (4.0)	43 (8.2)	4.2	.004
(95% CI)	(2.5-6.1)	(6.0-10.9)		

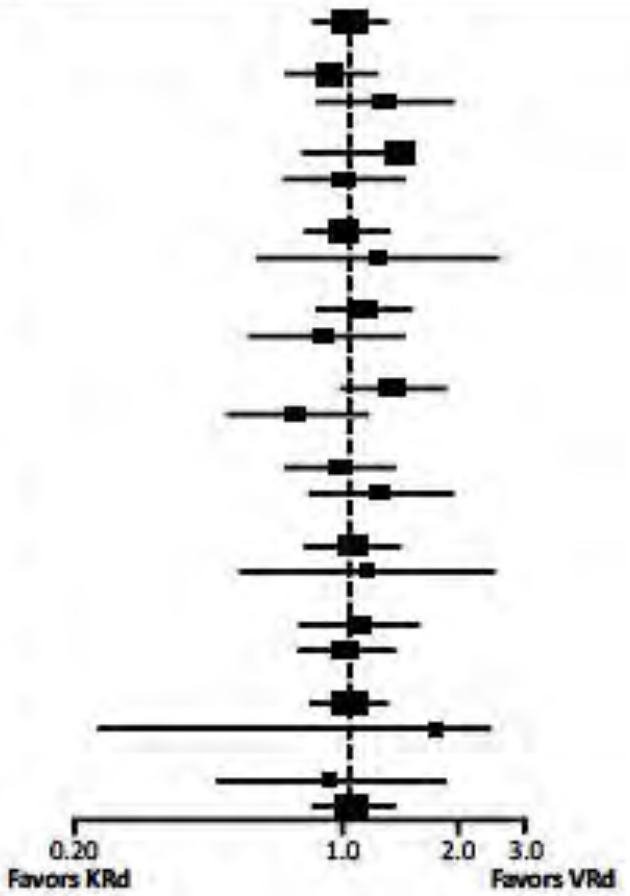
Kumar, S et al. Lancet Oncol. 21: 1317, 2020.

Courtesy of Robert Z Orlowski, MD, PhD

ENDURANCE: Subgroups

Subgroup	Patients/Events, n	Treatment HR (KRd/VRD)
Overall	1087/298	1.04 (0.83-1.31)
Age		
< 70 yrs	743/199	0.93 (0.71-1.23)
≥ 70 yrs	344/99	1.29 (0.86-1.94)
Sex		
Male	642/182	1.04 (0.77-1.39)
Female	445/116	1.01 (0.70-1.45)
Race		
White	891/254	1.02 (0.80-1.31)
Non-white	152/31	1.24 (0.60-2.56)
ISS stage		
I/II	711/186	1.14 (0.85-1.52)
III	243/71	0.90 (0.57-1.44)
Cytogenetics		
Normal	657/166	1.35 (0.99-1.64)
Abnormal	255/93	0.75 (0.50-1.15)
13q status		
Absent	534/146	0.98 (0.71-1.36)
Present	316/85	1.25 (0.81-1.94)
t(4;14) status		
Absent	770/203	1.07 (0.81-1.42)
Present	80/28	1.16 (0.54-2.47)
ECOG PS		
0	453/118	1.10 (0.77-1.59)
> 0	634/180	1.02 (0.76-1.36)
Creatinine		
< 2 mg/dL	1026/283	1.04 (0.82-1.31)
≥ 2 mg/dL	61/15	0.75 (0.23-2.42)
Measurable disease type		
Light chain MM	109/35	0.93 (0.47-1.84)
Non-light chain MM	978/263	1.05 (0.83-1.34)

*Box size adjusted for number of events



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Courtesy of Robert Z Orlowski, MD, PhD

Dara for High Risk?

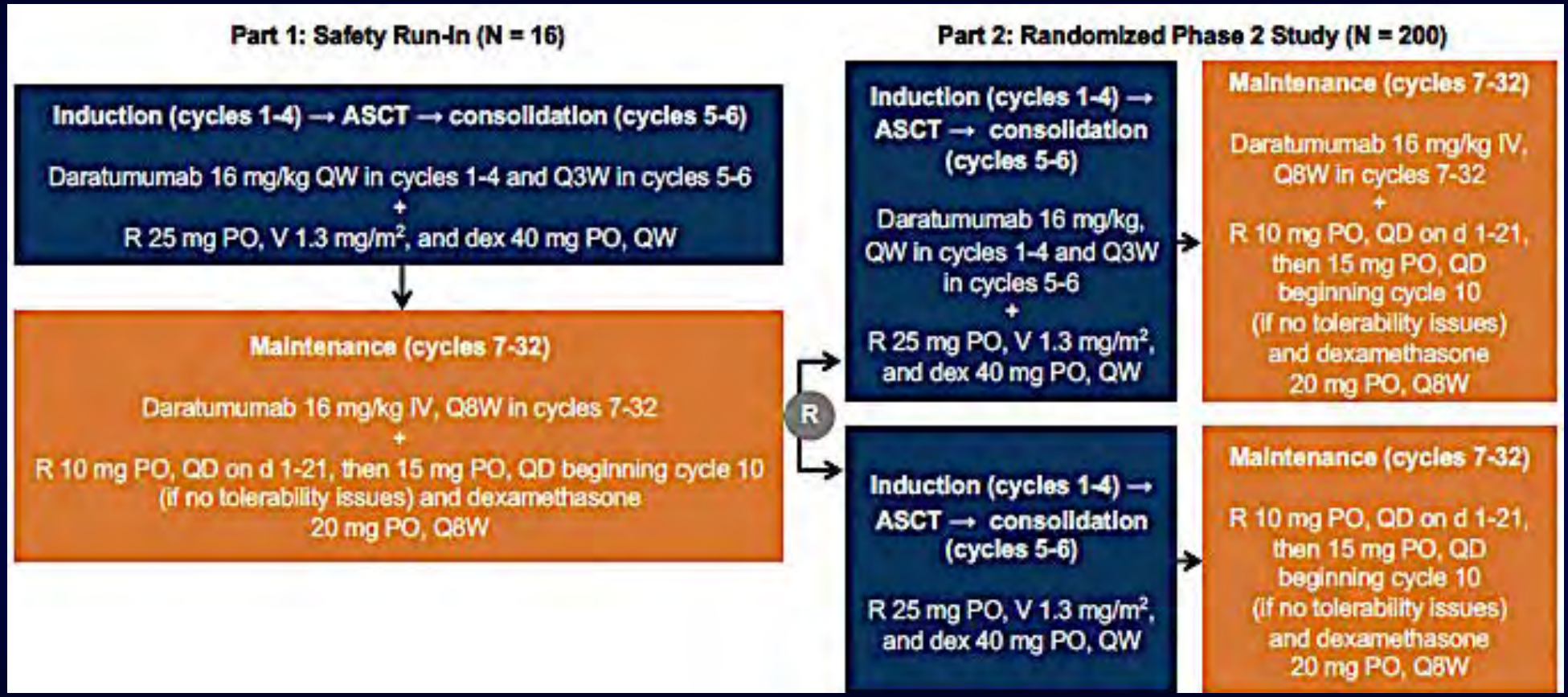
Study Name	Intervention	Control	Hazard Ratio	95% CI	p-Value
Alcyone	DaraVMP	VMP	0.78	0.43-1.42	0.42
Maia	DaraRD	RD	0.57	0.32-1.03	0.06
Cassiopeia	DaraVTD	VTD	0.67	0.35-1.29	0.23
Pooled Effect Size ($I^2$0%, Cochran's Q p = 0.77)			**0.67**	**0.47-0.95**	**0.025**
Castor	DaraVD	VD	0.41	0.21-0.83	0.01
Pollux	DaraRD	RD	0.37	0.18-0.76	0.01
Candor	DaraKD	KD	0.58	0.30-1.12	0.11
Pooled Effect Size (($I^2$0%, Cochrans Q p = 0.63)			**0.45**	**0.30-0.67**	**< 0.001**

358 NDMM patients

Giri, S et al. ASCO Abstract 8540, 2020.

Courtesy of Robert Z Orlowski, MD, PhD

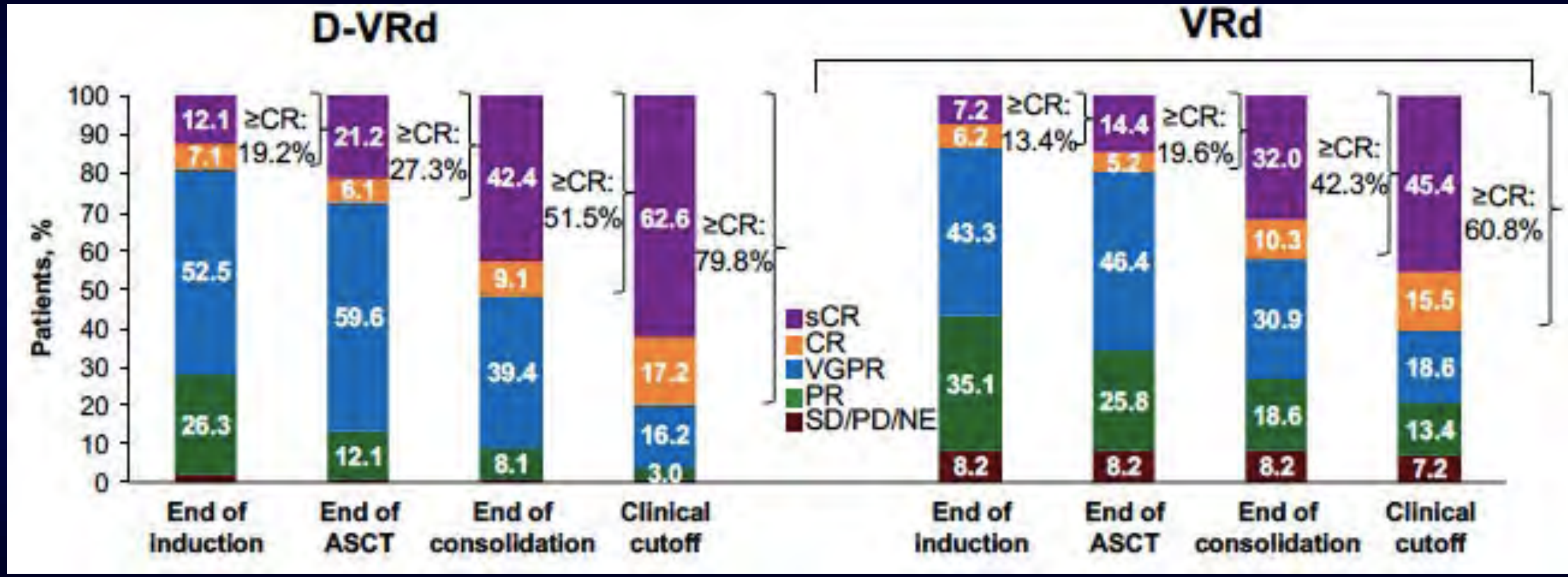
Griffin Trial



Voorhees, P et al. Blood 136: 936, 2020.

Courtesy of Robert Z Orlowski, MD, PhD

Responses Over Time



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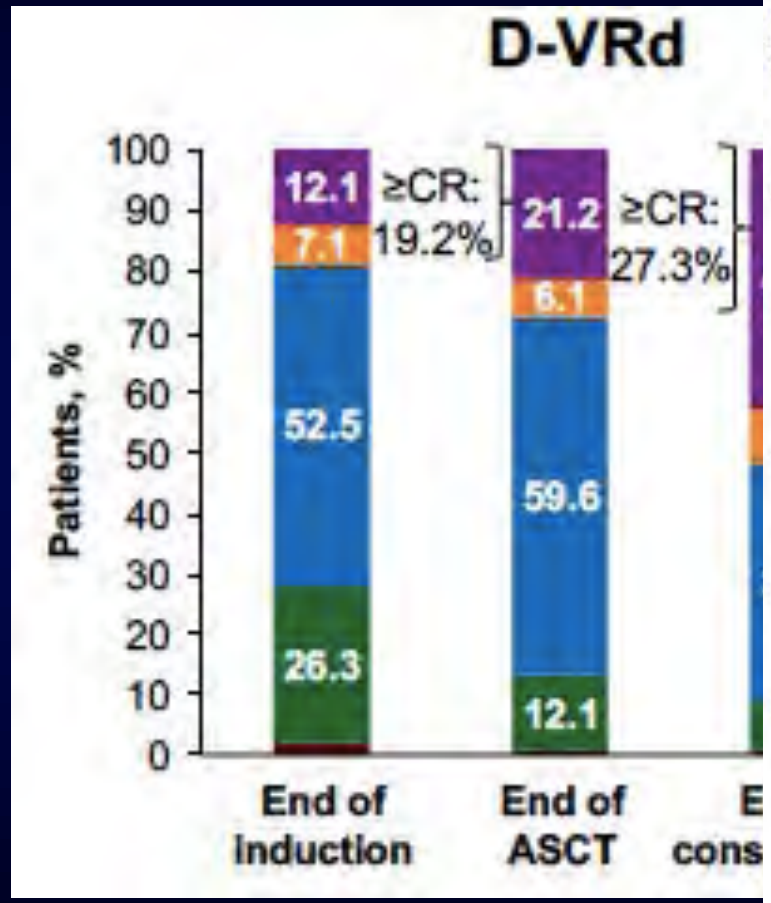
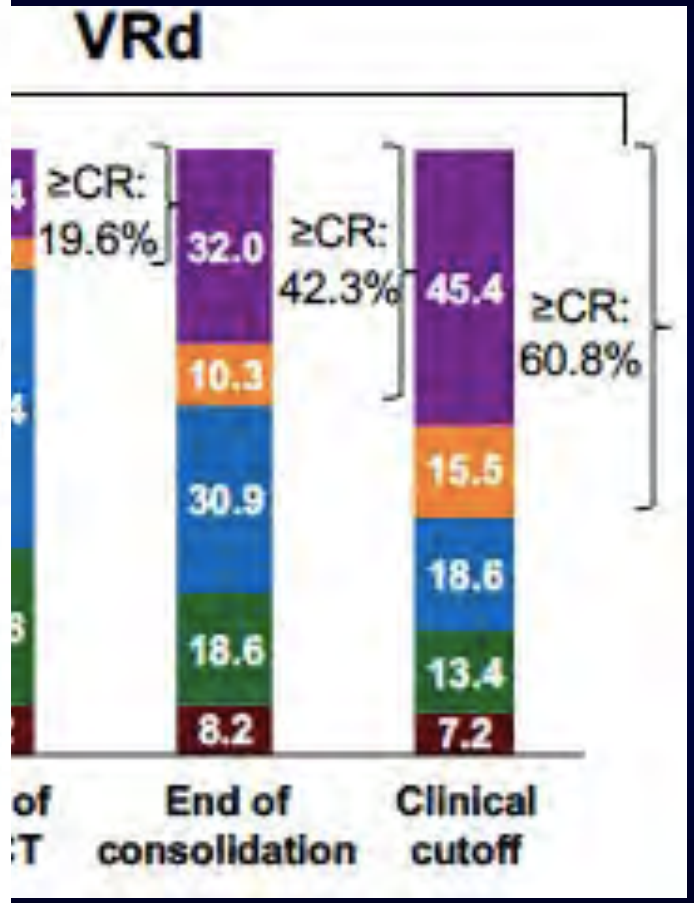
Courtesy of Robert Z Orlowski, MD, PhD

Responses Over Time



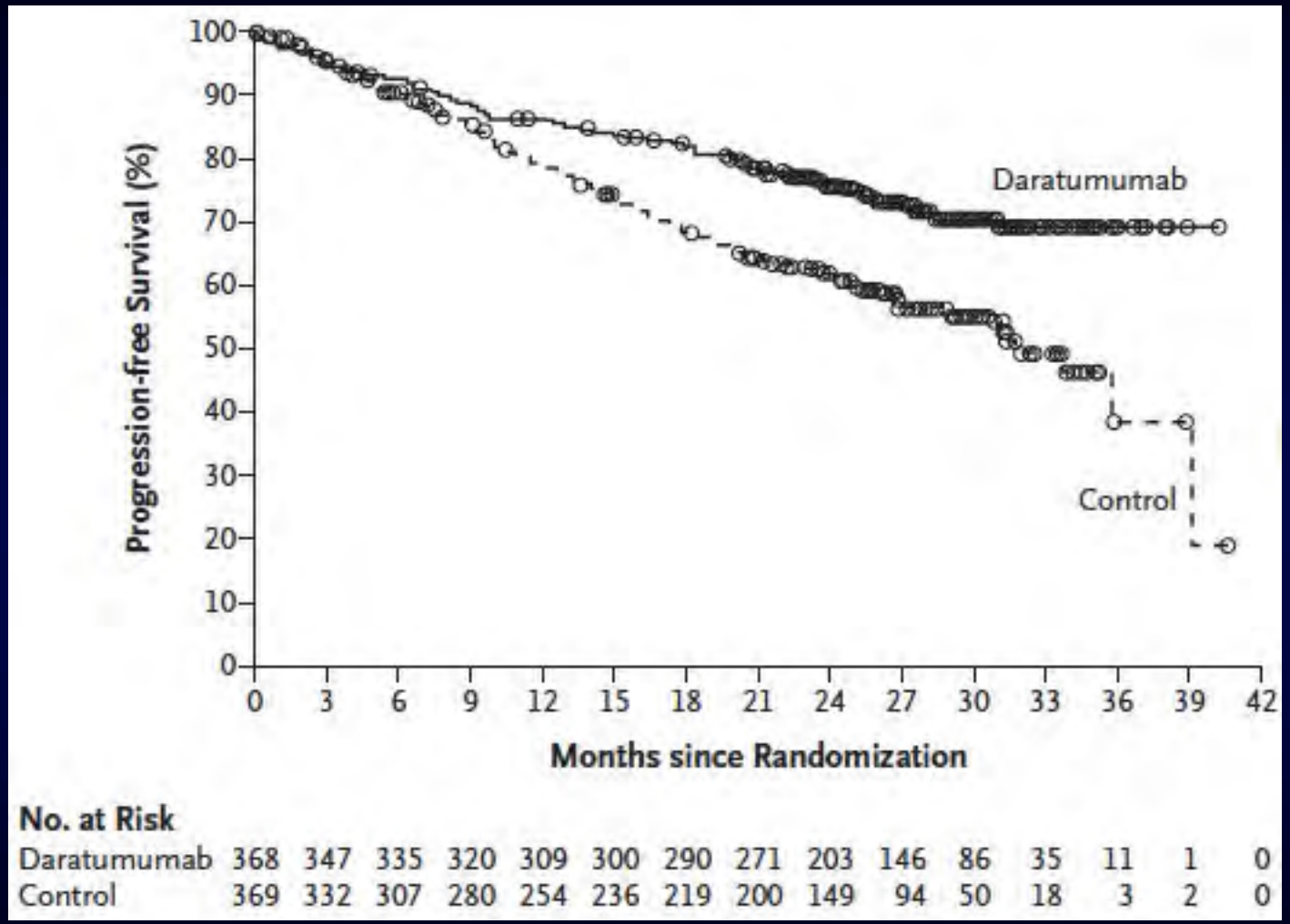
Subgroup	RVd minimal residual disease negative, n (%)	D-RVd minimal residual disease negative, n (%)	Odds Ratio (95% CI)
Sex			
Male	10/60 (16.7)	26/58 (44.8)	4.06 (1.73-9.54)
Female	11/43 (25.6)	27/46 (58.7)	4.13 (1.68-10.19)
Age			
<65 yr	16/75 (21.3)	38/76 (50.0)	3.69 (1.81-7.52)
≥65 yr	5/28 (17.9)	15/28 (53.6)	5.31 (1.57-17.97)
ISS disease stage			
I	6/50 (12.0)	25/49 (51.0)	7.64 (2.75-21.19)
II	10/37 (27.0)	20/40 (50.0)	2.70 (1.04-7.01)
III	5/14 (35.7)	8/14 (57.1)	2.40 (0.52-10.99)
Type of multiple myeloma			
IgG	11/52 (21.2)	29/55 (52.7)	4.16 (1.78-9.73)
Non-IgG	10/51 (19.6)	22/46 (47.8)	3.76 (1.53-9.26)
Cytogenetic risk			
High risk	4/14 (28.6)	6/16 (37.5)	1.50 (0.32-6.99)
Standard risk	17/83 (20.5)	45/82 (54.9)	4.72 (2.37-9.40)
ECOG PS score			
0	5/40 (12.5)	21/39 (53.8)	8.17 (2.64-25.25)
1 or 2	16/62 (25.8)	32/62 (51.6)	3.07 (1.44-6.53)



Voorhees, P et al. Blood 136: 936, 2020.

Courtesy of Robert Z Orlowski, MD, PhD

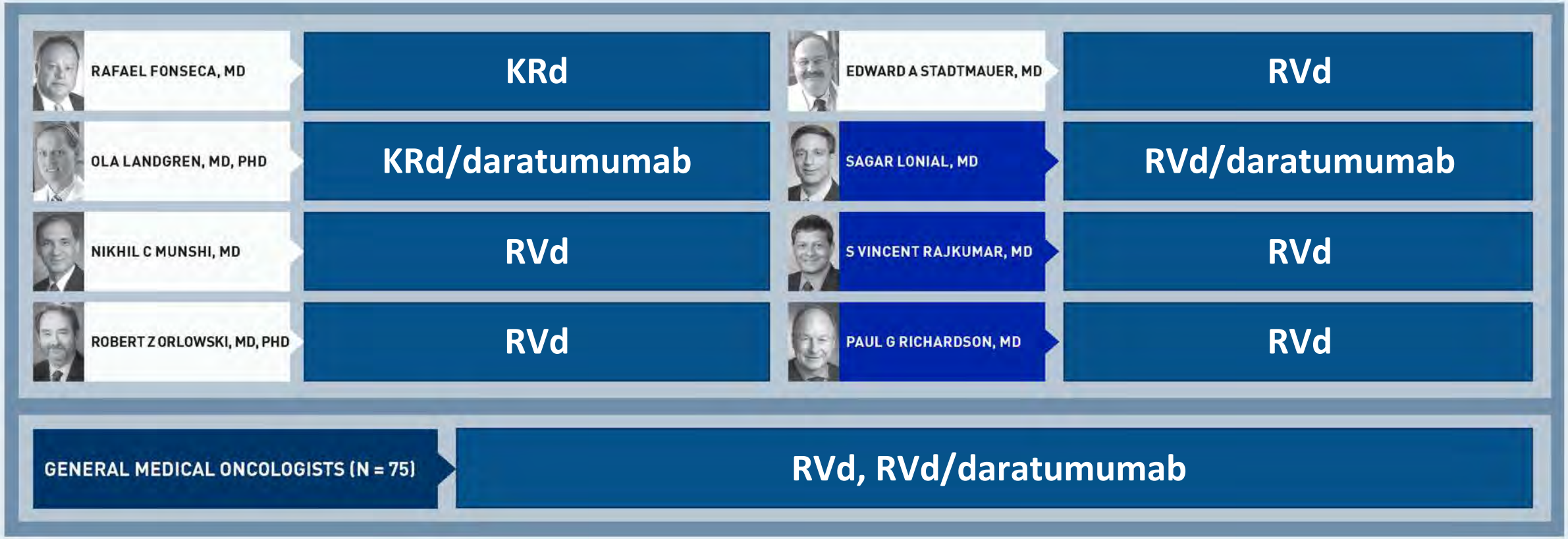
Dara/Len/dex: MAIA Data



Facon, T et al. N Engl J Med. 380: 2104, 2019.

Courtesy of Robert Z Orlowski, MD, PhD

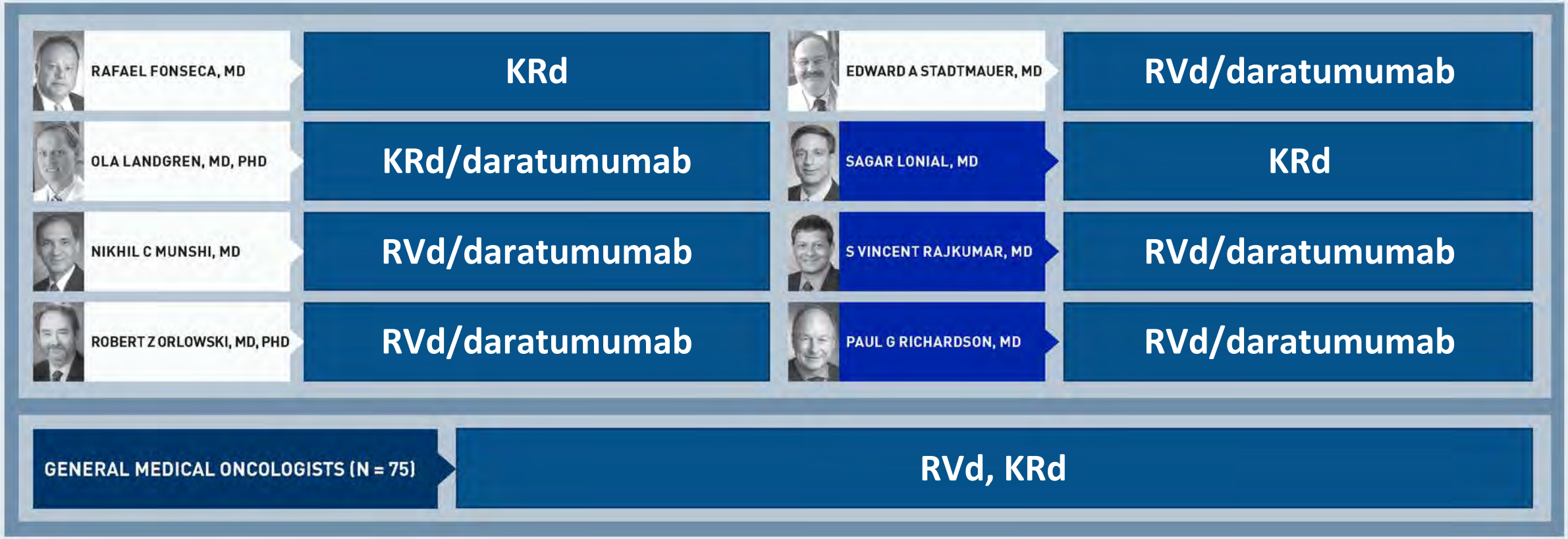
Regulatory and reimbursement issues aside, what is your preferred pretransplant induction regimen for a younger, otherwise healthy patient with MM and no high-risk features?



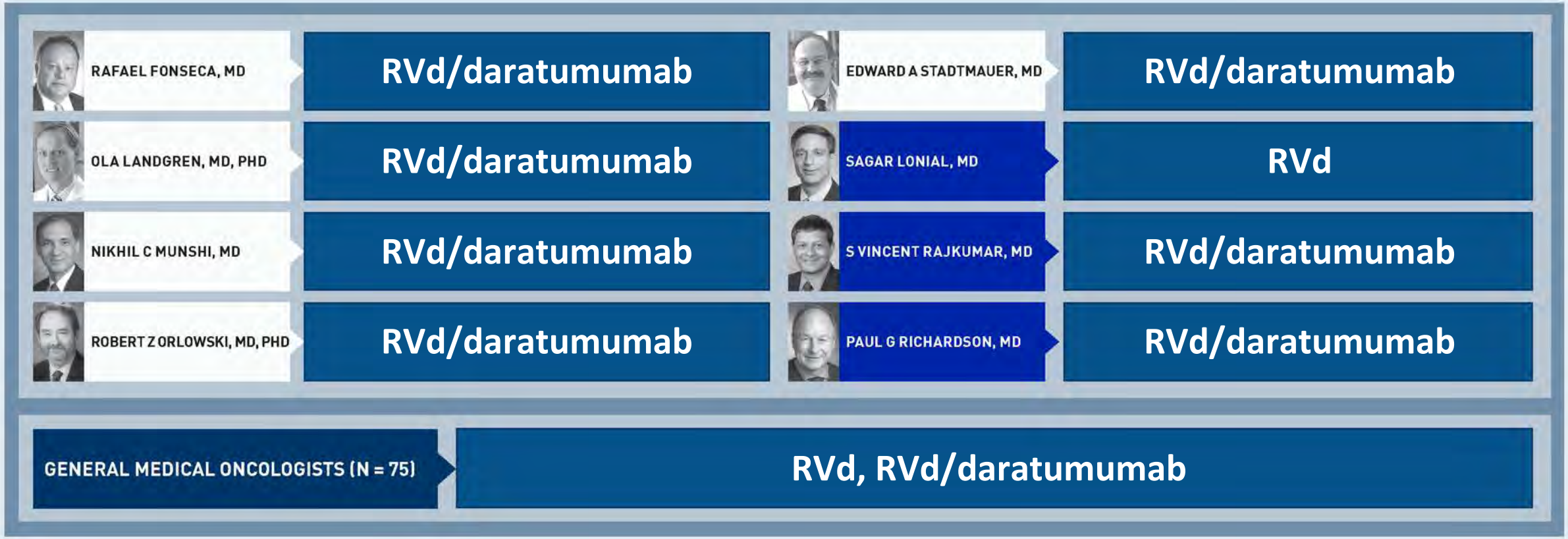
Regulatory and reimbursement issues aside, what is your preferred pretransplant induction regimen for a younger, otherwise healthy patient with MM and del(17p)?

1. RVd
2. KRd
3. CyBorD
4. Rd/daratumumab
5. RVd/daratumumab
6. KRd/daratumumab
7. MPV/daratumumab
8. Other

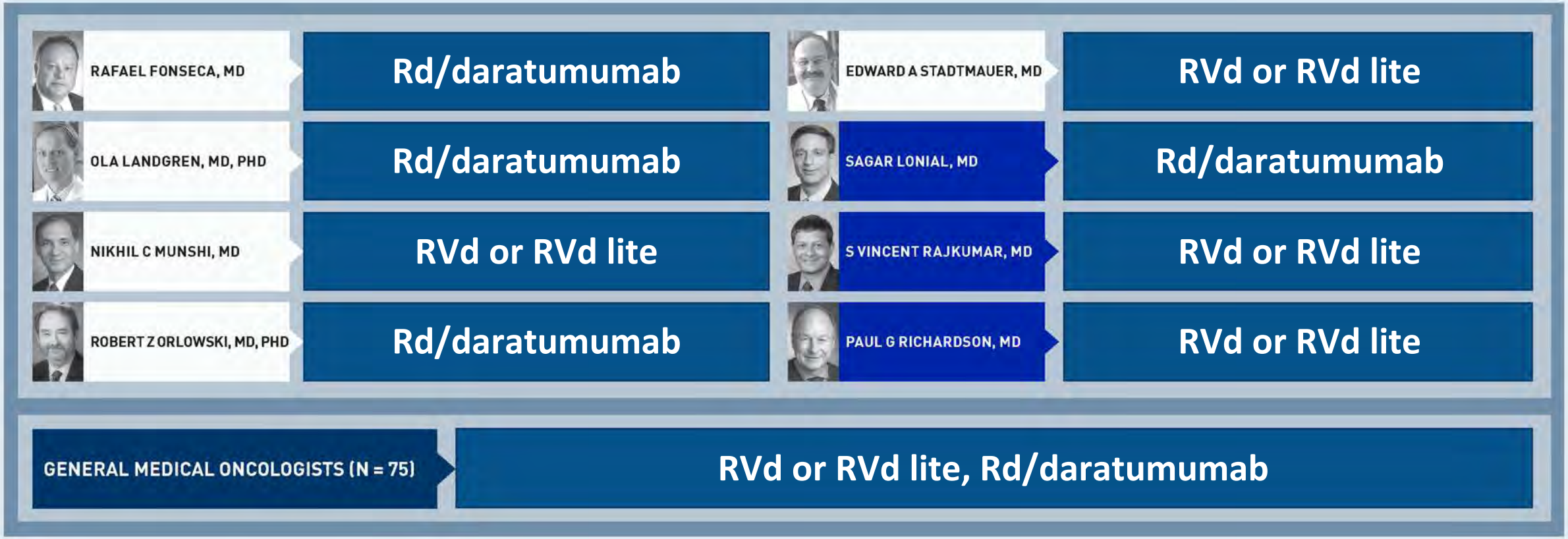
Regulatory and reimbursement issues aside, what is your preferred pretransplant induction regimen for a younger, otherwise healthy patient with MM and del(17p)?



Regulatory and reimbursement issues aside, what is your preferred pretransplant induction regimen for a 65-year-old patient with MM and del(17p) and a history of NYHA Class II congestive heart failure?



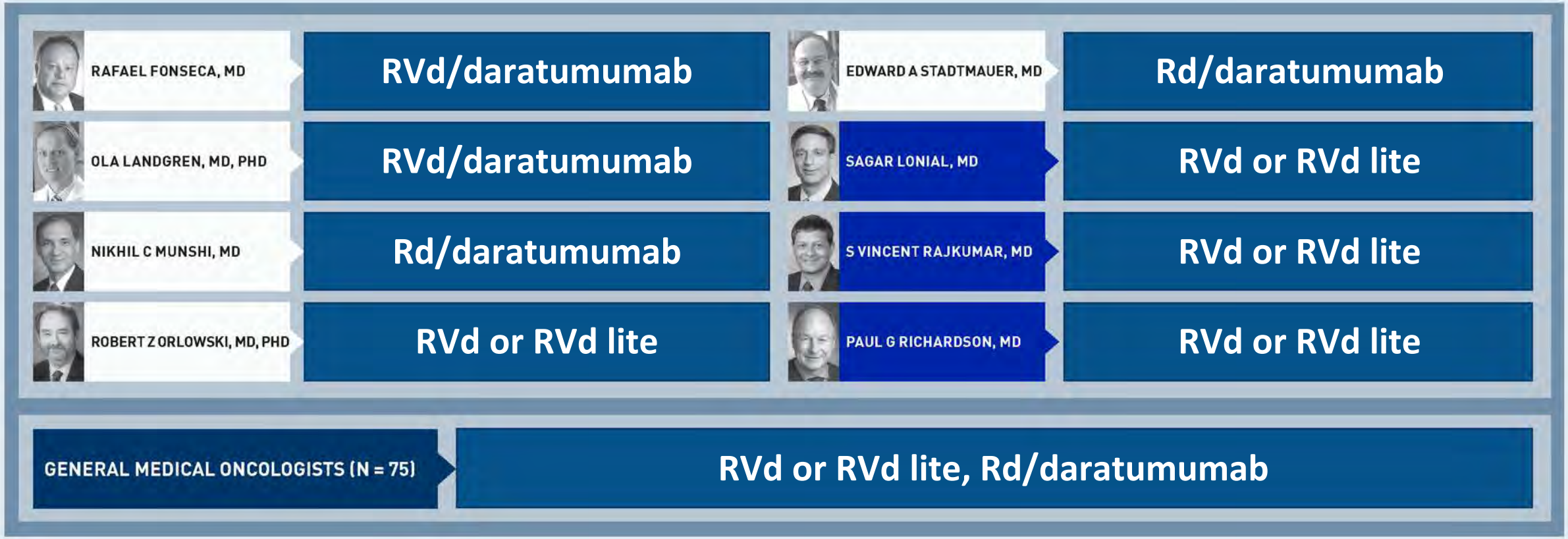
Regulatory and reimbursement issues aside, what is your preferred induction regimen for an otherwise healthy 80-year-old patient with MM and no high-risk features who is transplant ineligible with normal renal function?



Regulatory and reimbursement issues aside, what is your preferred induction regimen for an 80-year-old patient with MM who is transplant ineligible with normal renal function and del(17p)?

1. Rd
2. RVd or RVd lite
3. KRd
4. CyBorD
5. MPV/daratumumab
6. Rd/daratumumab
7. VTd/daratumumab
8. Other

Regulatory and reimbursement issues aside, what is your preferred induction regimen for an 80-year-old patient with MM who is transplant ineligible with normal renal function and del(17p)?

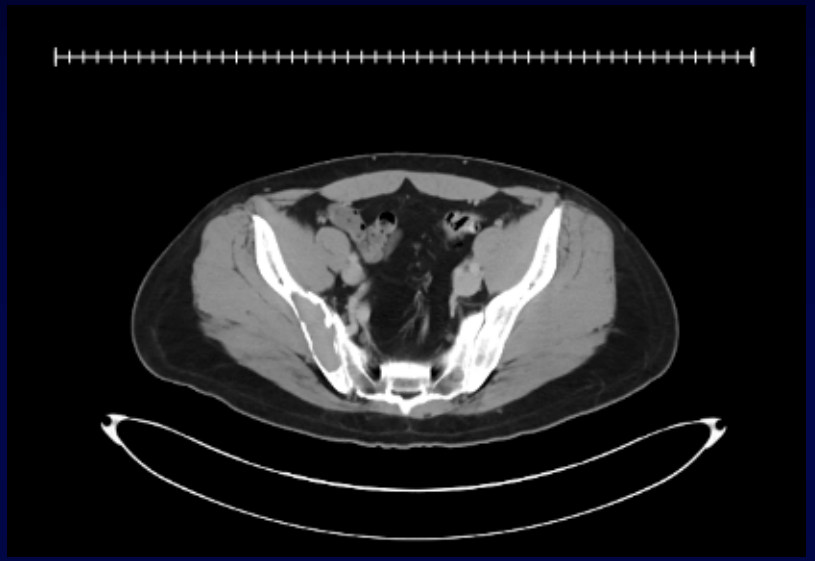


Regulatory and reimbursement issues aside, what is your preferred induction regimen for an otherwise healthy 80-year-old patient with MM and no high-risk features who is transplant ineligible with a creatinine of 3.5 mg/dL (previously 1.2 mg/dL)?

 RAFAEL FONSECA, MD	Rd/daratumumab	 EDWARD A STADTMAUER, MD	CyBorD
 OLA LANDGREN, MD, PHD	CyBorD	 SAGAR LONIAL, MD	VTd/daratumumab
 NIKHIL C MUNSHI, MD	CyBorD	 S VINCENT RAJKUMAR, MD	CyBorD
 ROBERT Z ORLOWSKI, MD, PHD	RVd or RVd lite	 PAUL G RICHARDSON, MD	RVd or RVd lite
GENERAL MEDICAL ONCOLOGISTS (N = 75)	CyBorD, RVd or RVd lite		

Case Presentation – Dr Orlowski: A 65-year-old man with newly diagnosed high-risk myeloma; del(17p)

- 65 yo M p/w pelvic pain & fatigue
- Initial labs show anemia (Hgb 8.8)
- Imaging shows a pelvic lytic lesion
- Bone marrow 56% PCs, FISH del 17p
- Induction with VRd
- Followed by ASCT with BuMel preparative regimen
- Post-ASCT maintenance with ixazomib/lenalidomide



Courtesy of Robert Z Orlowski, MD, PhD

Agenda

Module 1: Induction therapy for patients with newly diagnosed disease — Dr Orlowski

Module 2: Consolidation and maintenance therapy — Dr Fonseca

Module 3: Selection and sequencing of available therapies for relapsed/refractory disease — Dr Munshi

Module 4: Chimeric antigen receptor T-cell therapy — Dr Stadtmauer

Module 5: Other novel strategies — Dr Landgren

MAYO CLINIC

MRD Controversies

- Flow versus NGS
- Can be used to stop therapy
  - Long term CR - maintenance
  - Test for it
    - If positive – maybe stay on Rx?
    - If negative – more confidently stop?
- Explore for VGPR
- We did not ask for Phase 3 trials to use sFLC

@rfonsi1, fonseca.rafael@mayo.edu

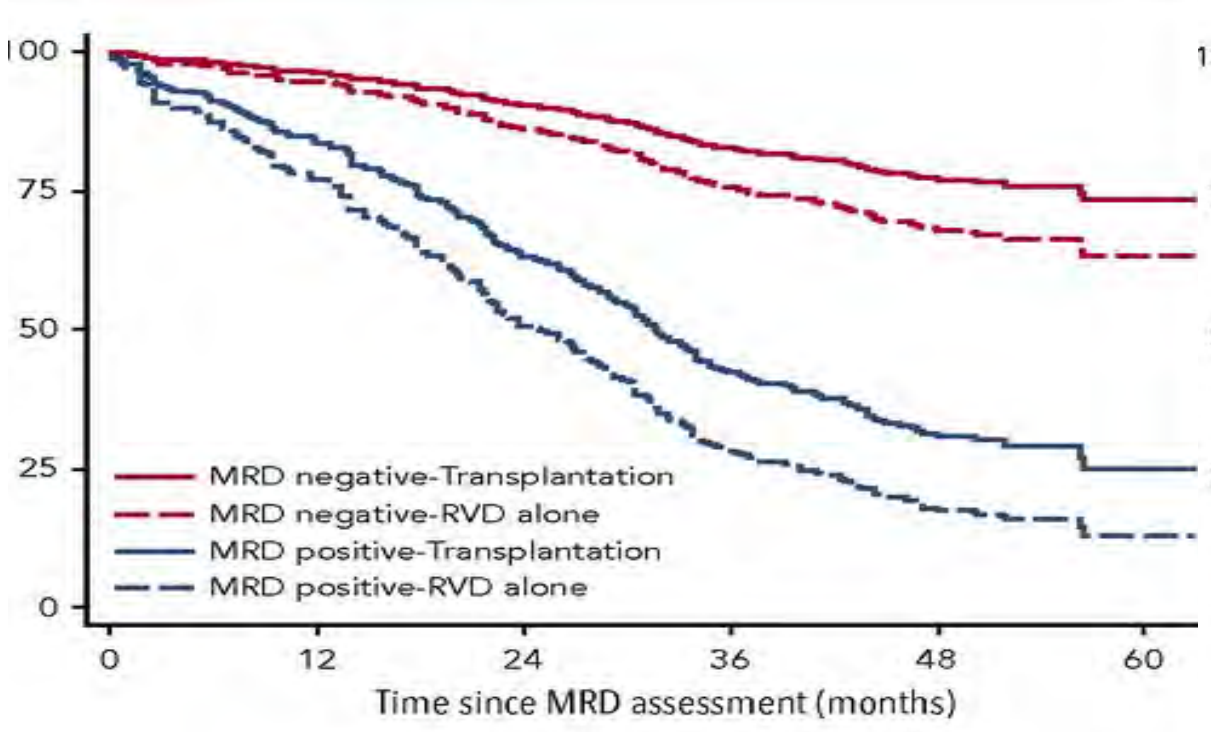
Courtesy of Rafael Fonseca, MD

R Fonseca, personal information

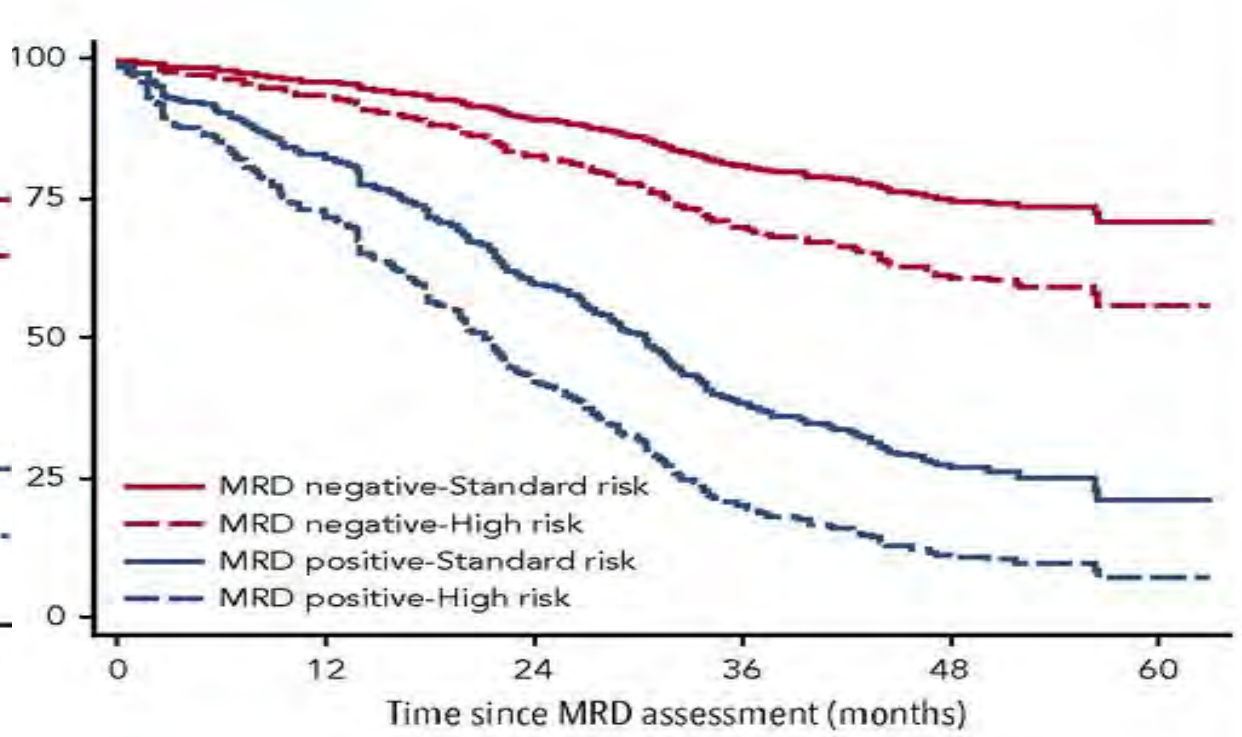
MAYO CLINIC

Outcomes by MRD

MRD Status and SCT vs not



MRD Status and Risk status



@rfonsi1, fonseca.rafael@mayo.edu

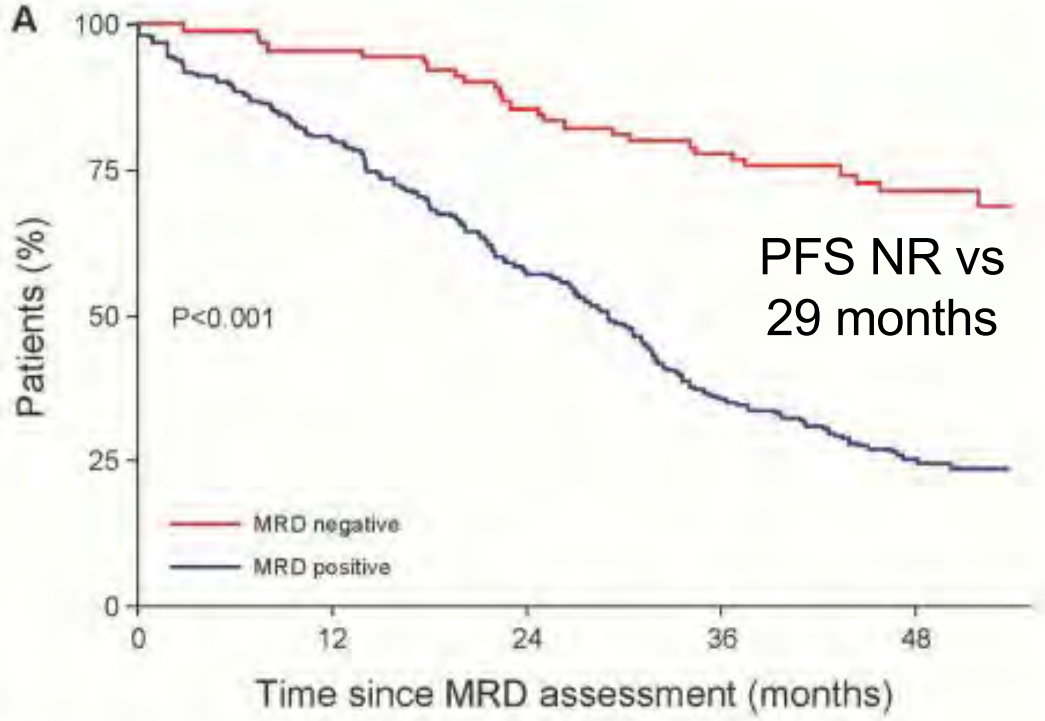
Courtesy of Rafael Fonseca, MD

Aurore Perrot et al. Blood 2018;132:2456-2464

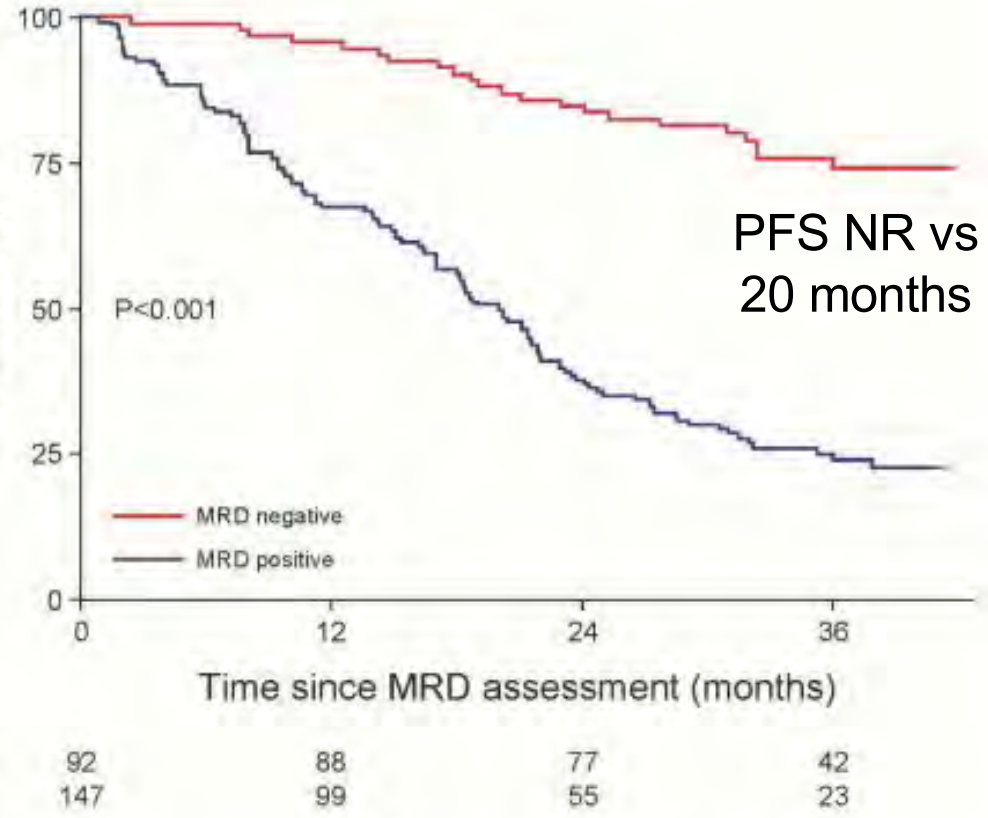
MAYO CLINIC

Outcomes by MRD

MRD Negativity at the start of maintenance



MRD Negativity 12 months later



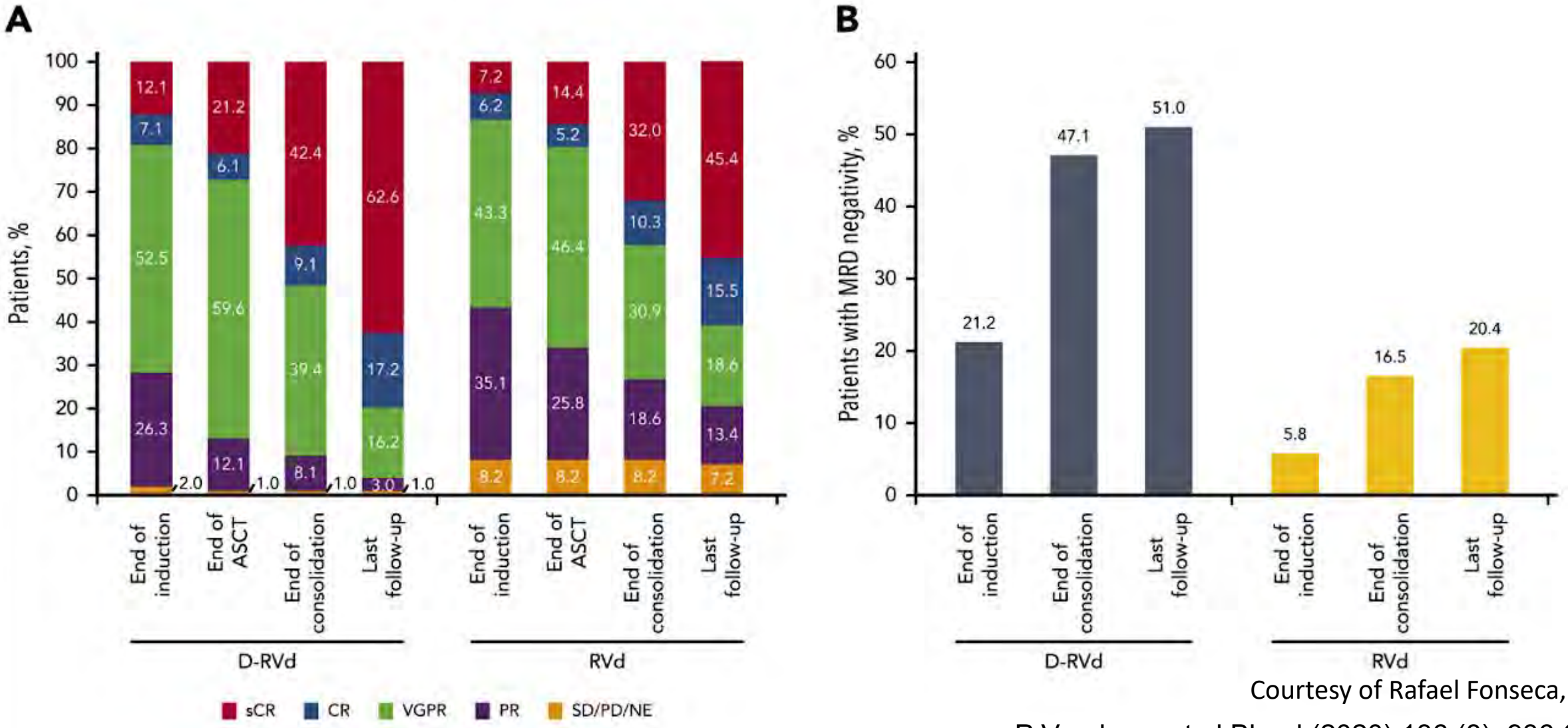
@rfonsi1, fonseca.rafael@mayo.edu

Courtesy of Rafael Fonseca, MD

Aurore Perrot et al. Blood 2018;132:2456-2464

MAYO CLINIC

GRIFFIN Trial of Dara-RVd for Newly Diagnosed MM: ORR and MRD (10^{-5})

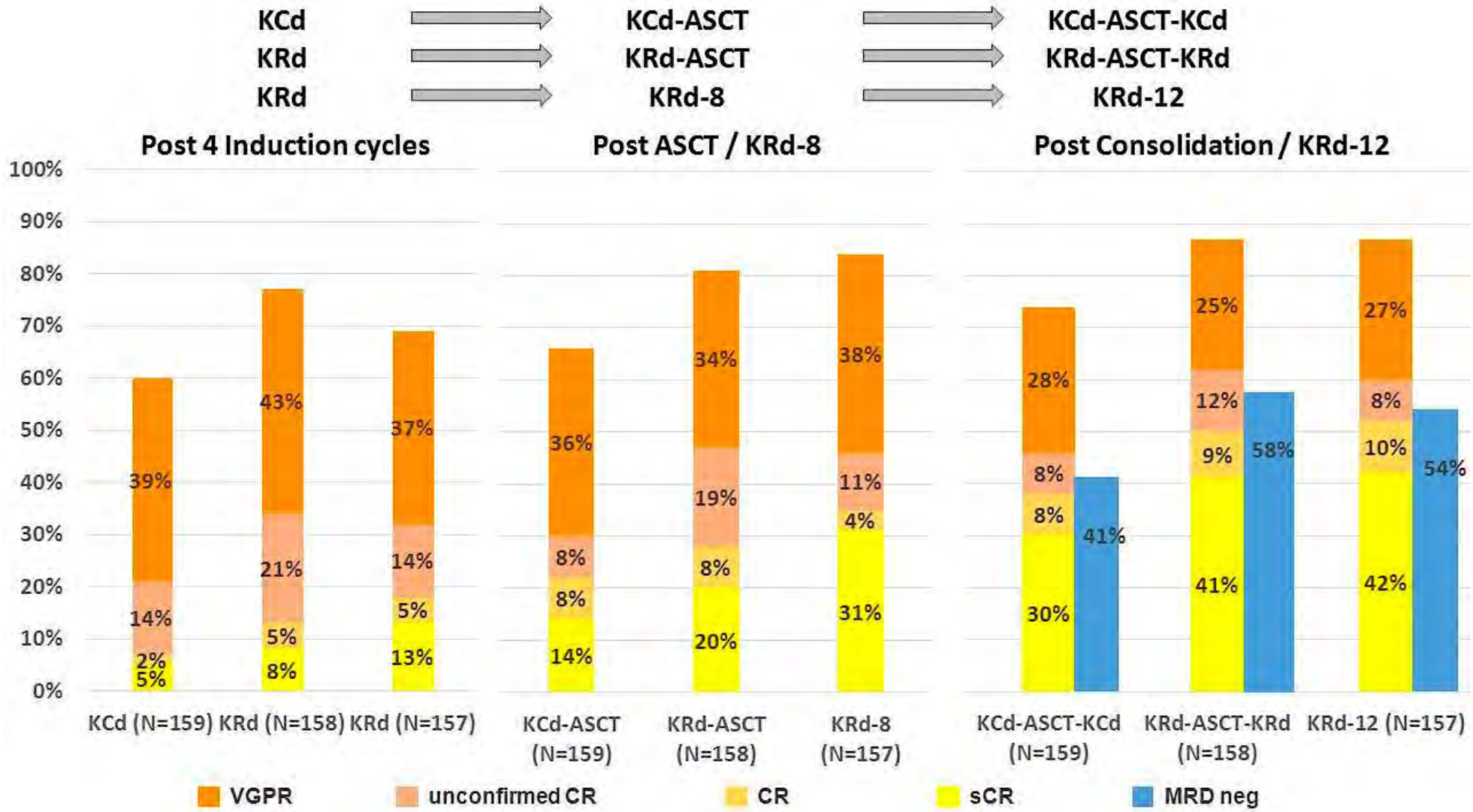


Courtesy of Rafael Fonseca, MD

P Voorhees et al Blood (2020) 136 (8): 936-945.

MAYO CLINIC

KRd in Newly Dx MM: Summary (Forte Trial)



Courtesy of Rafael Fonseca, MD

Gay F, et al. ASH 2018

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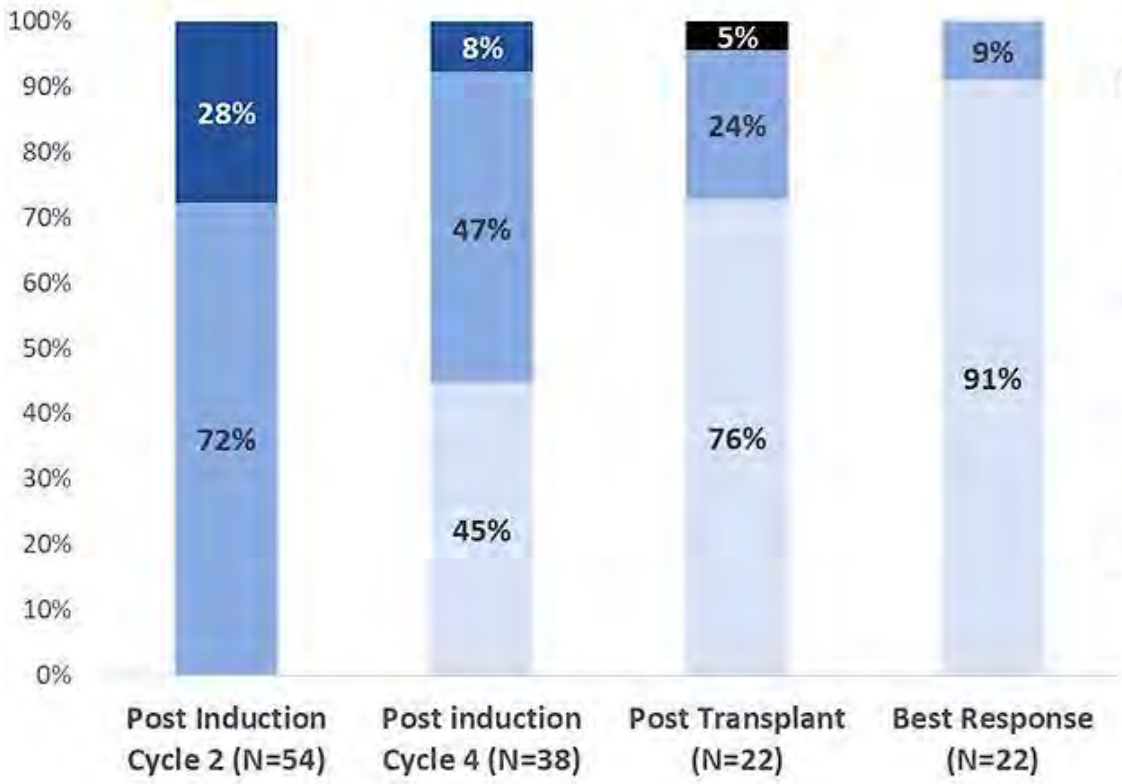
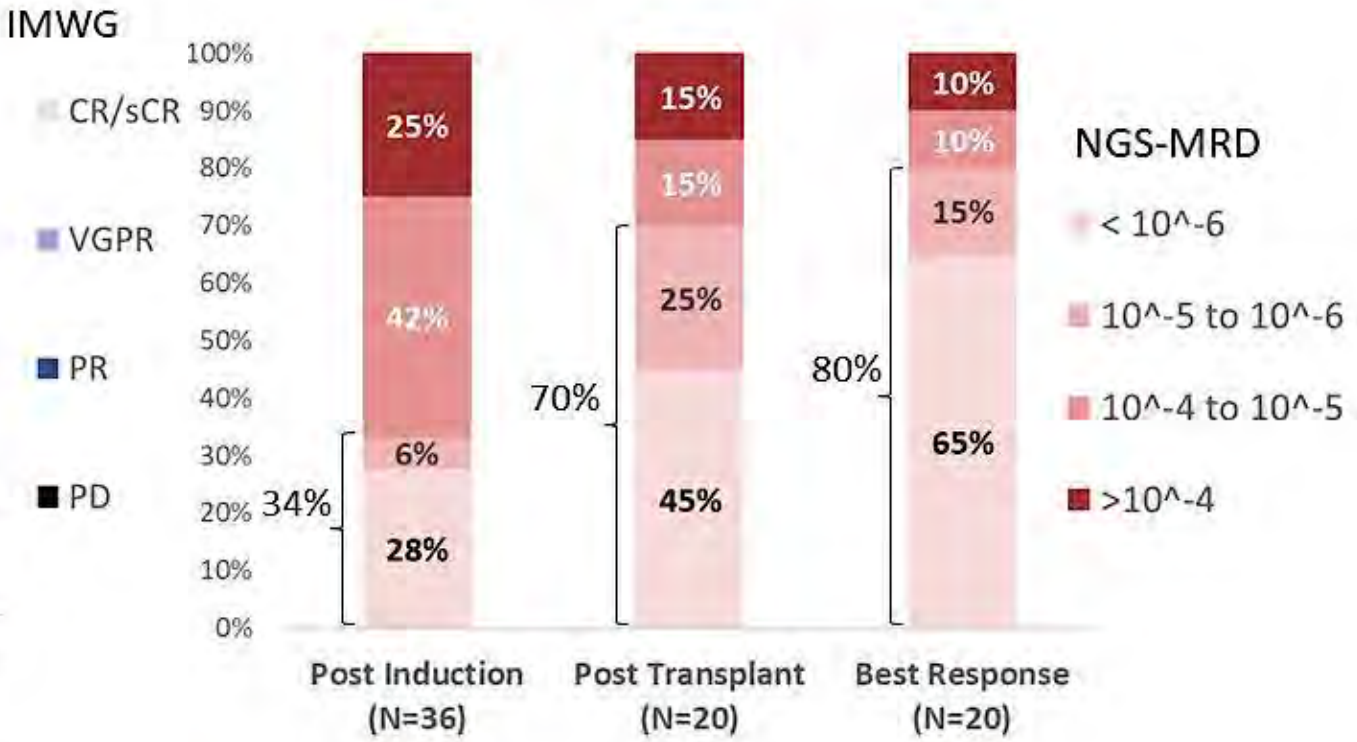
MAYO CLINIC

MASTER Trial: Dara-KRD in Newly Diagnosed MM





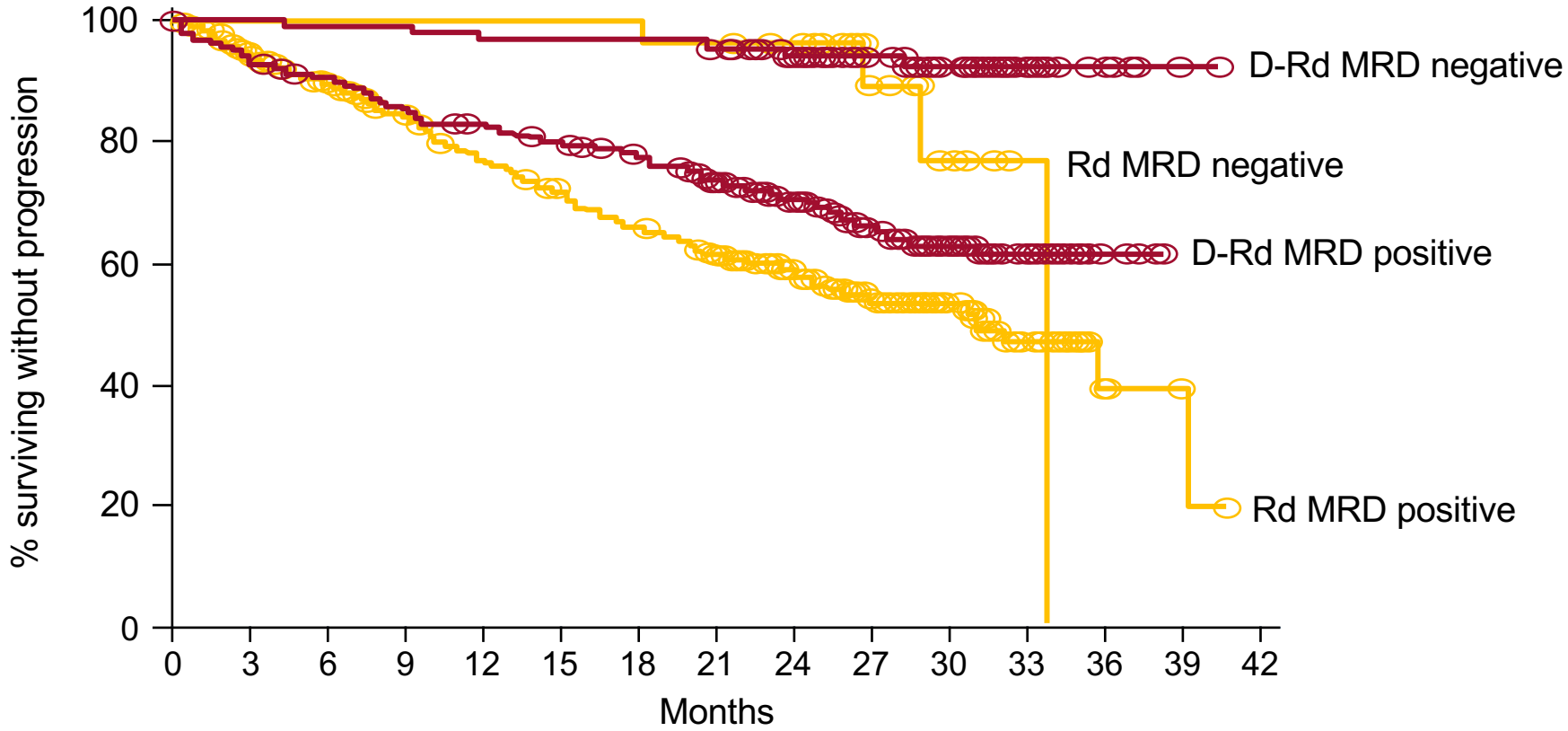
@rfonsi1, fonseca.rafael@mayo.edu

Courtesy of Rafael Fonseca, MD

Costa et al. ASH 2019

MAYO CLINIC

MAIA: PFS by MRD Status



No. at risk															
Rd MRD negative	27	27	27	27	27	27	27	25	21	12	5	1	0	0	0
D-Rd MRD negative	89	89	88	88	86	86	86	84	70	55	33	12	5	1	0
Rd MRD positive	342	305	280	253	227	209	192	175	128	82	45	17	3	2	0
D-Rd MRD positive	279	258	247	232	223	214	204	187	133	91	53	23	6	0	0

- **>3-fold higher MRD negativity achieved with D-Rd**

@rfonsi1, fonseca.rafael@mayo.edu

Courtesy of Rafael Fonseca, MD

What is your usual recommendation for post-ASCT maintenance in patients with MM and no high-risk features who received RVD induction therapy?

 RAFAEL FONSECA, MD	Lenalidomide	 EDWARD A STADTMAUER, MD	Lenalidomide
 OLA LANDGREN, MD, PHD	Lenalidomide	 SAGAR LONIAL, MD	Lenalidomide
 NIKHIL C MUNSHI, MD	Lenalidomide	 S VINCENT RAJKUMAR, MD	Lenalidomide
 ROBERT Z ORLOWSKI, MD, PHD	Lenalidomide	 PAUL G RICHARDSON, MD	Lenalidomide
GENERAL MEDICAL ONCOLOGISTS (N = 75)	Lenalidomide, Lenalidomide + dexamethasone		

What is your usual recommendation for post-ASCT maintenance in patients with MM and del(17p) who received RVD induction therapy?

 RAFAEL FONSECA, MD	Lenalidomide/ixazomib	 EDWARD A STADTMAUER, MD	Lenalidomide
 OLA LANDGREN, MD, PHD	Lenalidomide (KRd as induction)	 SAGAR LONIAL, MD	Carfilzomib/ lenalidomide/dex
 NIKHIL C MUNSHI, MD	Bortezomib/ lenalidomide/dex	 S VINCENT RAJKUMAR, MD	Lenalidomide/bortezomib
 ROBERT Z ORLOWSKI, MD, PHD	Lenalidomide/bortezomib	 PAUL G RICHARDSON, MD	Lenalidomide/bortezomib

GENERAL MEDICAL ONCOLOGISTS (N = 75)	Lenalidomide, Lenalidomide + dexamethasone

Outside of a clinical trial setting, have you ordered or would you order an MRD assay to inform the decision regarding maintenance therapy?

 RAFAEL FONSECA, MD	I haven't and would not	 EDWARD A STADTMAUER, MD	I have
 OLA LANDGREN, MD, PHD	I have	 SAGAR LONIAL, MD	I haven't and would not
 NIKHIL C MUNSHI, MD	I have	 S VINCENT RAJKUMAR, MD	I have
 ROBERT Z ORLOWSKI, MD, PHD	I haven't and would not	 PAUL G RICHARDSON, MD	I have
GENERAL MEDICAL ONCOLOGISTS (N = 75)	I haven't and would not		

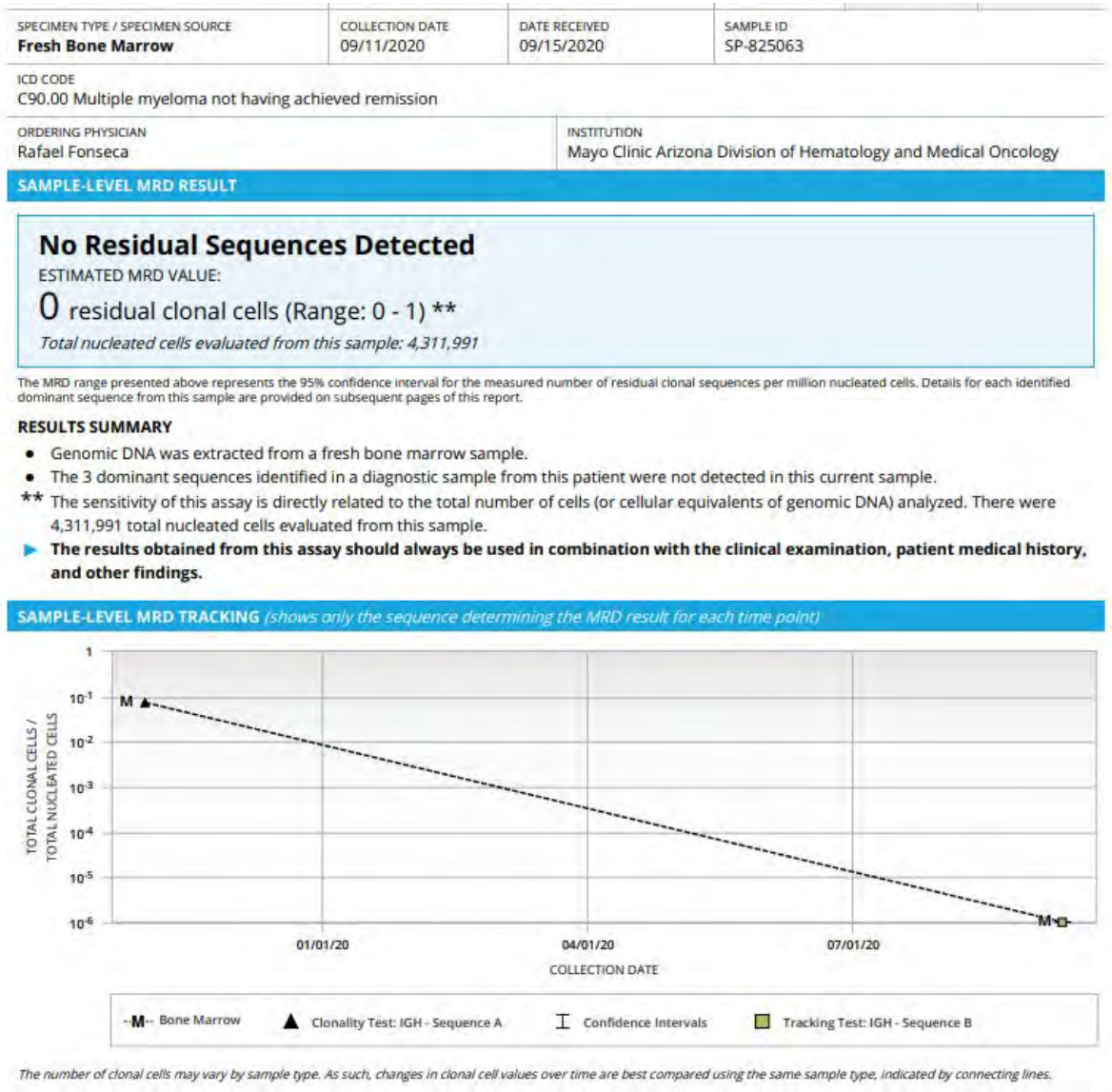
Outside of a clinical trial setting, have you ordered or would you order an MRD assay to inform the decision regarding autotransplant after induction treatment?

1. I haven’t and would not
2. I haven’t but would for the right patient
3. I have

Outside of a clinical trial setting, have you ordered or would you order an MRD assay to inform the decision regarding treatment in the postinduction autotransplant setting?

Case Presentation – Dr Fonseca: A 53-year-old man with newly diagnosed myeloma

- 53 yo male
- New diagnosis MM
- Induction with KRD
- Completed SCT
- Recovered and comes for day 100



SPECIMEN TYPE / SPECIMEN SOURCE	COLLECTION DATE	DATE RECEIVED	SAMPLE ID
Fresh Bone Marrow	09/11/2020	09/15/2020	SP-825063

ICD CODE
C90.00 Multiple myeloma not having achieved remission

ORDERING PHYSICIAN
Rafael Fonseca

INSTITUTION
Mayo Clinic Arizona Division of Hematology and Medical Oncology

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: 4,311,991

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 4,311,991 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)*

The number of clonal cells may vary by sample type. As such, changes in clonal cell values over time are best compared using the same sample type, indicated by connecting lines.

@rfonsi1, fonseca.rafael@mayo.edu

Courtesy of Rafael Fonseca, MD

Case Presentation – Dr Fonseca: A 58-year-old man with newly diagnosed myeloma

- 58 yo male
- New diagnosis MM
- Induction with KRD
- Completed SCT
- 11/2018 MRD+
  - Dara-Rd
- Aug 2019 MRD+
  - More Dara-Rd
- Feb 2020 MRD-
  - R maintenance

ICD CODE
C90.00 Multiple myeloma not having achieved remission

ORDERING PHYSICIAN
Rafael Fonseca

INSTITUTION
Mayo Clinic Arizona Division of Hematology and Medical Oncology

SAMPLE-LEVEL MRD RESULT

No Residual Sequences 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.

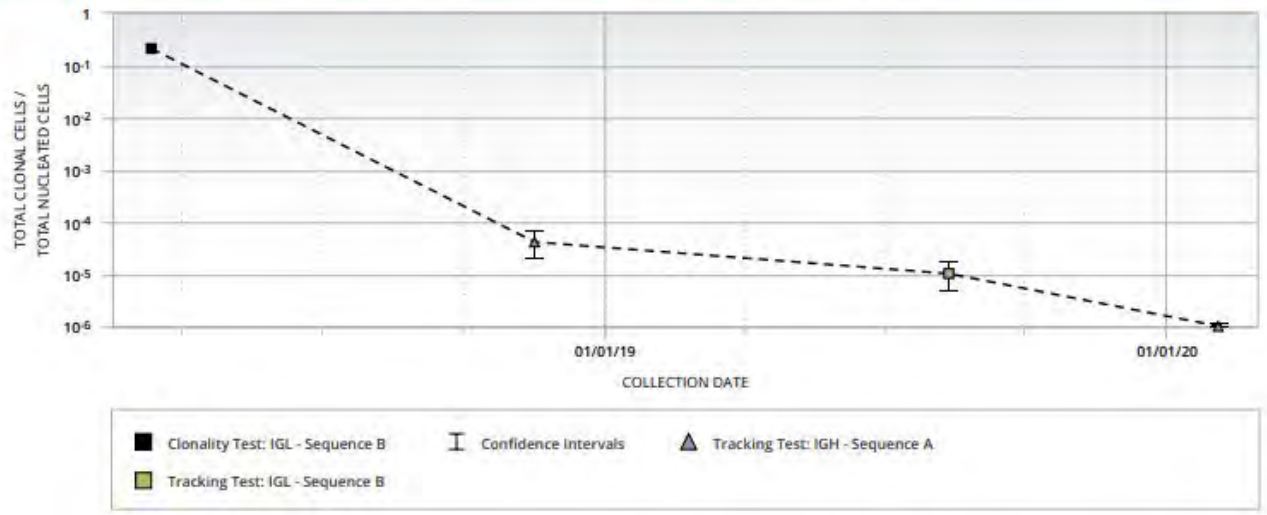
RESULTS SUMMARY

- Genomic DNA was extracted from a fresh bone marrow sample.
- The 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 1,678,265 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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Courtesy of Rafael Fonseca, MD

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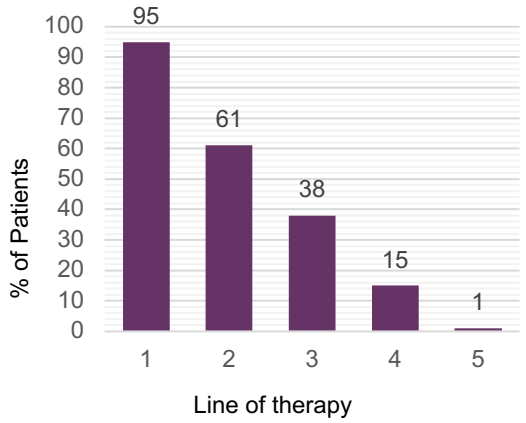
Module 4: Chimeric antigen receptor T-cell therapy — Dr Stadtmauer

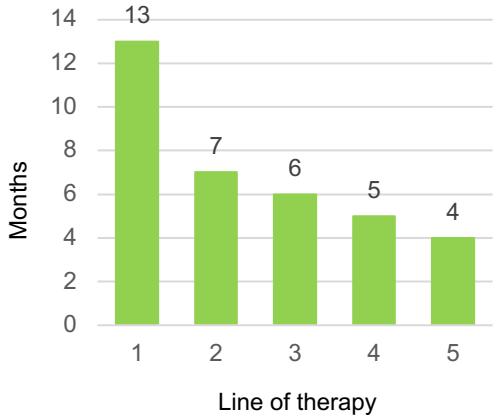
Module 5: Other novel strategies — Dr Landgren

Initial Treatment is Best Chance For Deep and Durable Remissions

Attrition
% of Patients Able to Get Nth Line of Therapy



Diminishing Returns
Median Duration of Nth Line of Therapy



- Attrition: high risk & frail elderly patients in particular will not live to Nth relapse
- Response rates and duration diminish with each successive line of therapy
- Early use of efficacious regimens to achieve *and sustain remissions* critical

Courtesy of Nikhil C Munshi, MD

Yong K et al. *Br J Haematol.* 2016;175(2):252-264.

Indications for Retreatment

- Patients with asymptomatic rise in M-protein (biochemical relapse) can be observed to determine the rate of rise and nature of the relapse
- Clinical relapse: direct indicators of increasing disease with end organ dysfunction (MDE)
- Significant paraprotein relapse: Accelerated Doubling of the M-component in two consecutive measurements separated by < 2 months; OR
- High levels of free light chain with renal presentation
- High risk cytogenetics with biochemical progression

Courtesy of Nikhil C Munshi, MD

Rajkumar SV et al Blood. 2011 May 5;117(18):4691-5.

Factors to Consider for Treatment Selection

Disease related Factors

- Nature of relapse
- Risk stratification
- Disease burden
- R-ISS staging

1. Nooka AK, et al. Blood. 2015;125:3085-3099.
2. Palumbo A, et al. N Engl J Med. 2011;364:1046-1060.
3. Palumbo A, et al. Blood. 2011;118:4519-4529.
4. Orlowski RZ, Lonial S. *Clin Cancer Res.* 2016;22:5443.

Treatment related Factors

- Previous therapy
- Regimen-related toxicity
- Depth and duration of previous response, tumor burden at relapse
- Retreatment with previous therapies

1. Nooka AK, et al. Blood. 2015;125:3085-3099.
2. Palumbo A, et al. N Engl J Med. 2011;364:1046-1060.
3. Palumbo A, et al. Blood. 2011;118:4519-4529.

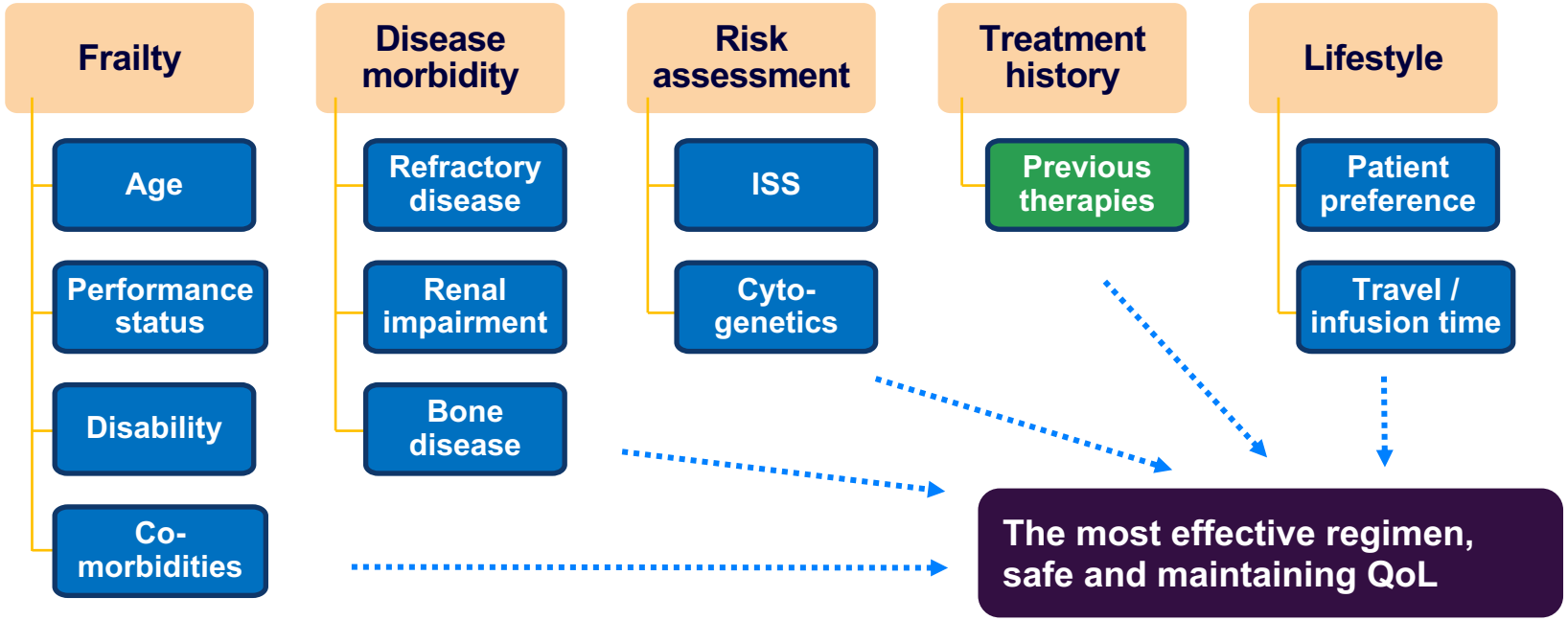
Patient related Factors

- Renal insufficiency:
- Hepatic impairment Comorbidities and frailty
- Patient preferences

1. Nooka AK, et al. Blood. 2015;125:3085-3099.
2. Palumbo A, et al. N Engl J Med. 2011;364:1046-1060.
3. Palumbo A, et al. Blood. 2011;118:4519-4529.

Courtesy of Nikhil C Munshi, MD

Disease and Patient-based Factors Influencing the Treatment Decision-making at the Relapsed Setting



- Choice of PI- or IMiD-based partner depends on prior treatment
- Nearly all phase 3 studies show triplets perform better than doublets
- Cross trial comparisons should not be done

Clegg A et al. Lancet 2013;381:752–762; Handforth C et al. Ann Oncol 2015;26:1091–1101; Chen X et al. Clin Interv Aging 2014;9:433–441; Palumbo A et al. Blood 2015;125:2068–2074; Jhaveri D et al. Haematologica 2016;101:1–881 (Abstract E1312); Sonneveld P et al. Leukemia 2013;27:1959–1969; Faiman BM et al. Clin J Oncol Nurs 2011;15:66–76; Miceli TS et al. Clin J Oncol Nurs 2011;15:9–23; Greipp PR et al. J Clin Oncol 2005;23:3412–3420; Binder M et al. Haematologica 2016;101:P665; Merz M et al. Haematologica 2016;101:P650; Chng WJ et al. Leukemia 2016;30:1071–1078; Chung TH et al. PLoS One 2013;20:e66361; Sonneveld P et al. Leukemia 2013;27:1959–1969; Ramsenthaler C et al. BMC Cancer 2016;16:427; Williams LA et al. J Clin Oncol 2016;34:e18127; Ramasamy K et al. Haematologica 2017;102:E1457.

Courtesy of Nikhil C Munshi, MD

Therapeutic Advances in Multiple Myeloma

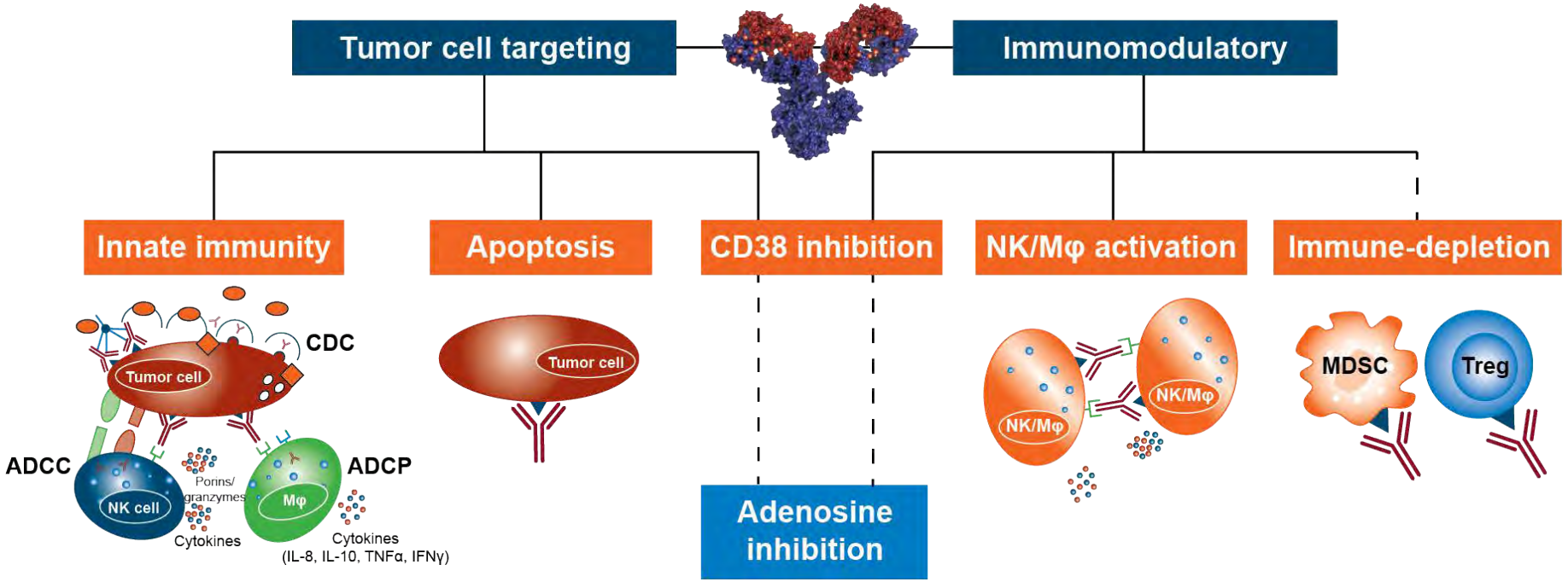
- ~~11~~ 12 new Agents in last 15 years:
- Proteasome inhibitors: bortezomib, Carfilzomib, Ixazomib
- Immunomodulator: thalidomide, lenalidomide, pomalidomide
- HDAC inhibitor: Panobinostat
- Monoclonal antibodies: elotuzumab, daratumumab Isatuximab, Belantamab mafodotin
- Exportin inhibitor: Selinexor
- Alkylating Agent: bendamustine
- Existing older agents: melphalan, dexamethasone. cyclophosphamide, anthracycline, etoposide
- Near approval: Ide-cel, Cilta-cel, melflufen, venetoclax, BCMA-bispecifics

- 2-, 3-, 4-drug combinations - effective in relapsed/refractory myeloma

Courtesy of Nikhil C Munshi, MD

Isatuximab: Mechanism of Action

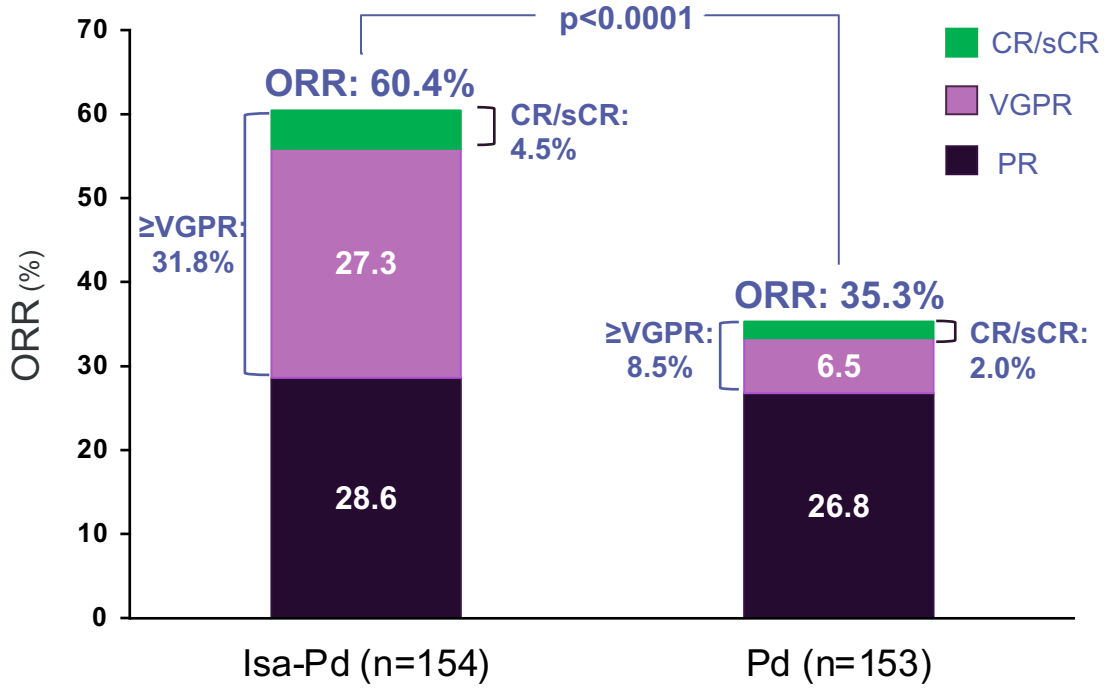
- Active in combination studies in R/R MM



- **Effective combinations**
  - **ICARIA-MM – Isa Pd**
  - **IKEMA – Isa Kd**

Courtesy of Nikhil C Munshi, MD

ICARIA-MM: Significant Improvement in Response with Isa-Pd Compared to Pd



Median time to 1st response: Isa-Pd 35 days vs Pd 58 days

True CR rate in Isa-Pd underestimated because of isatuximab interference with M-protein measurement

	Isa-Pd (n=154)	Pd (n=153)
nCR, %	15.6	3.3

MRD negativity at 10^{-5} (ITT): 5.2% for Isa-Pd vs 0% for Pd

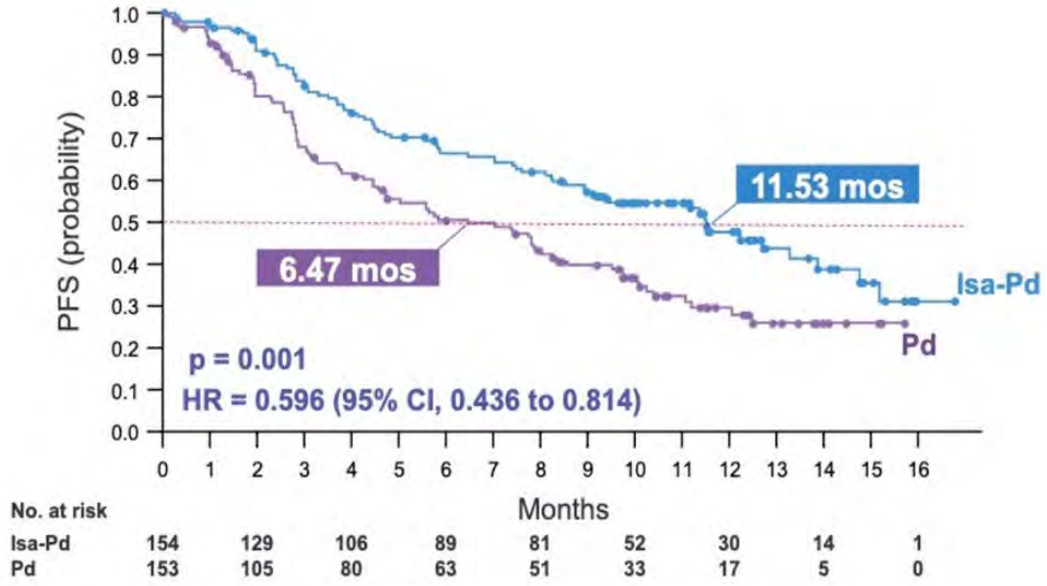
Addition of Isa to Pd resulted in significant improvement in overall and depth of response

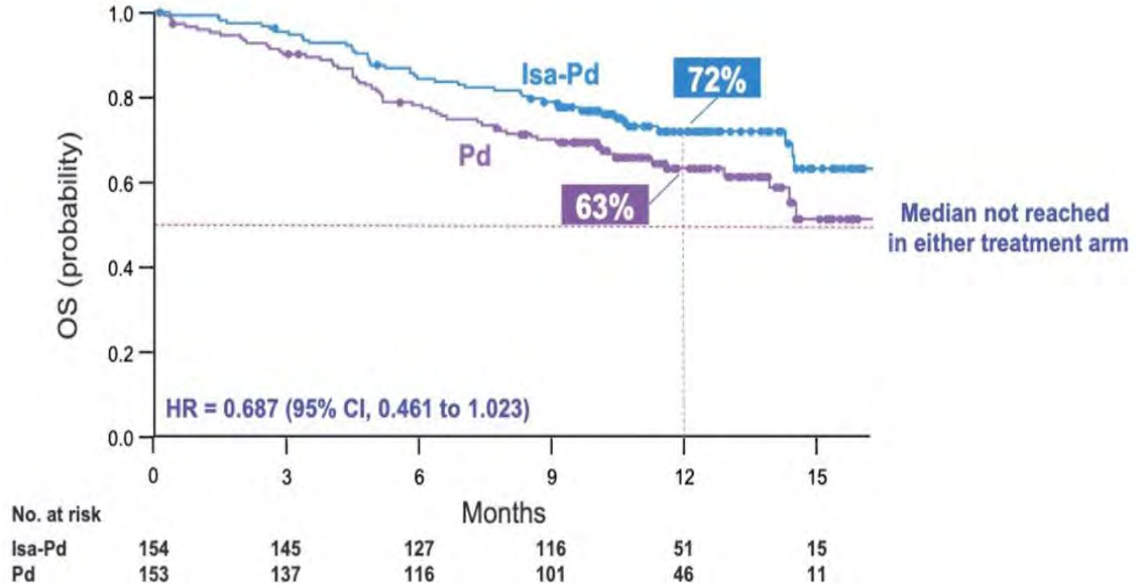
Data cut-off 11 Oct, 2018
CR complete response; d, dexamethasone; IRC, Independent Review Committee; Isa, isatuximab; ITT, intent-to-treat; MRD, minimal residual disease; nCR, near complete response; ORR, overall response rate; P, pomalidomide; PR, partial response; sCR, stringent complete response; VGPR, very good partial response
*All criteria for a complete response were met except that immunofixation remained positive [Richardson PG, et al. *N Engl J Med.* 2003;348(26):2609-2617]

Courtesy of Nikhil C Munshi, MD

ICARIA-MM: Significant Improvement in Survival with Isa-Pd Compared to Pd

- 307 patients, after a median number of 3 lines, 95% len-refractory
- Significant and clinically meaningful improvement in PFS; consistent across subgroups



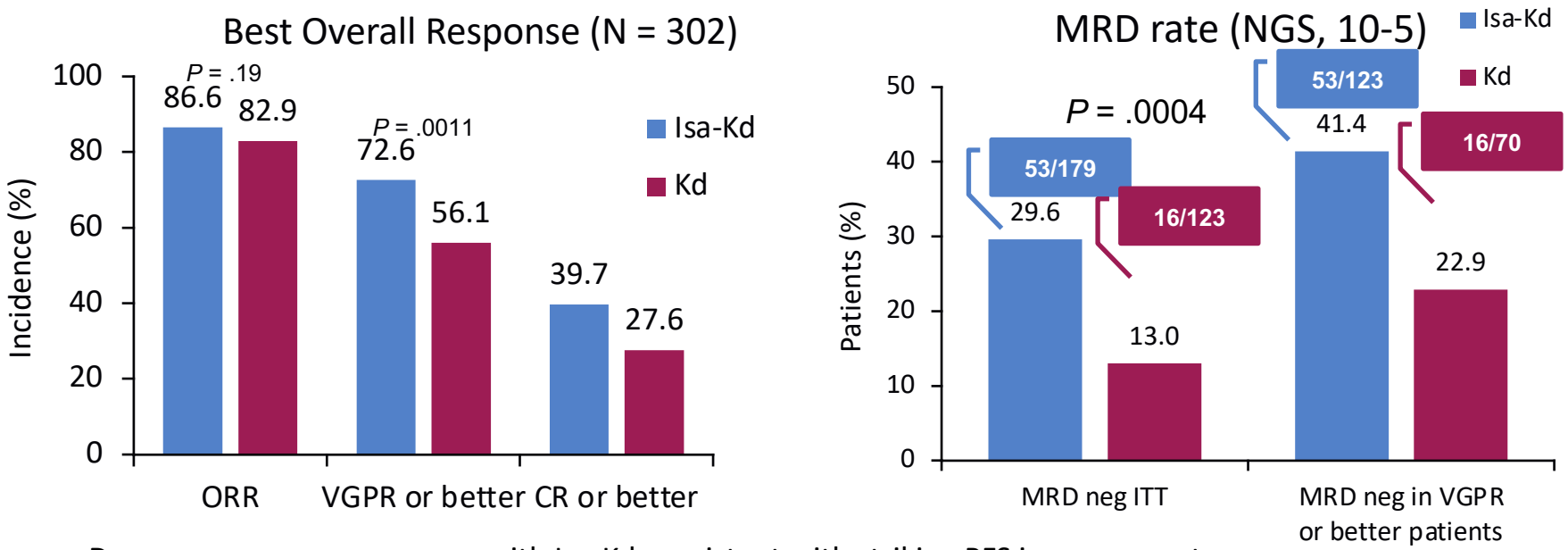


CI, confidence interval; HR, hazard ratio; IRC, independent review committee; OS, overall survival; PFS, progression-free survival; Isa-Pd, isatuximab-pomalidomide-dexamethasone; Pd, pomalidomide-dexamethasone.

Richardson P et al. Lancet. 2019;394(10214):2096-2107.

Courtesy of Nikhil C Munshi, MD

IKEMA: Carfilzomib/Dexamethasone ± Isatuximab: Response

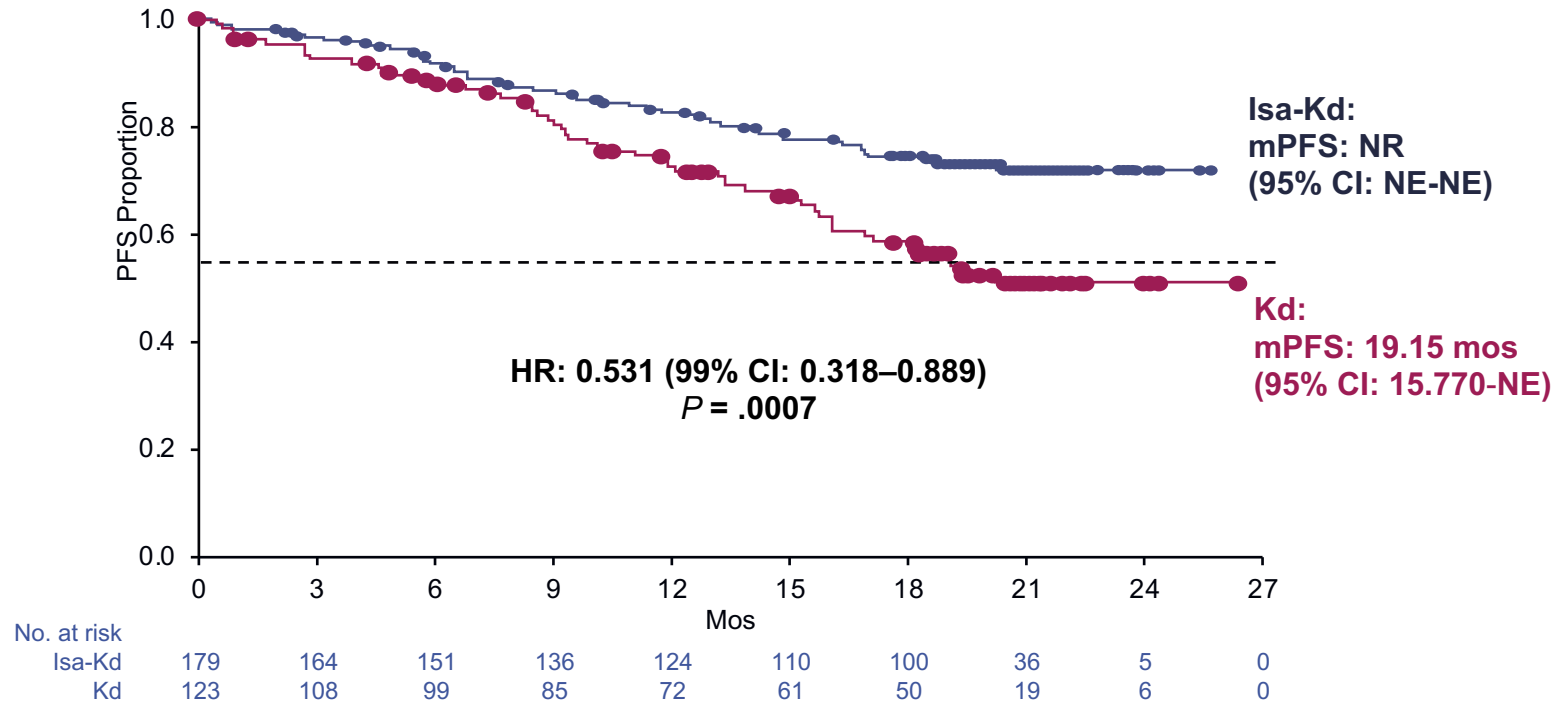


- Deeper responses were seen with Isa-Kd consistent with striking PFS improvement
- MRD negativity rate with Isa-Kd was approximately 30% in ITT population

Courtesy of Nikhil C Munshi, MD

Moreau. EHA 2020. Abstr LB2603.

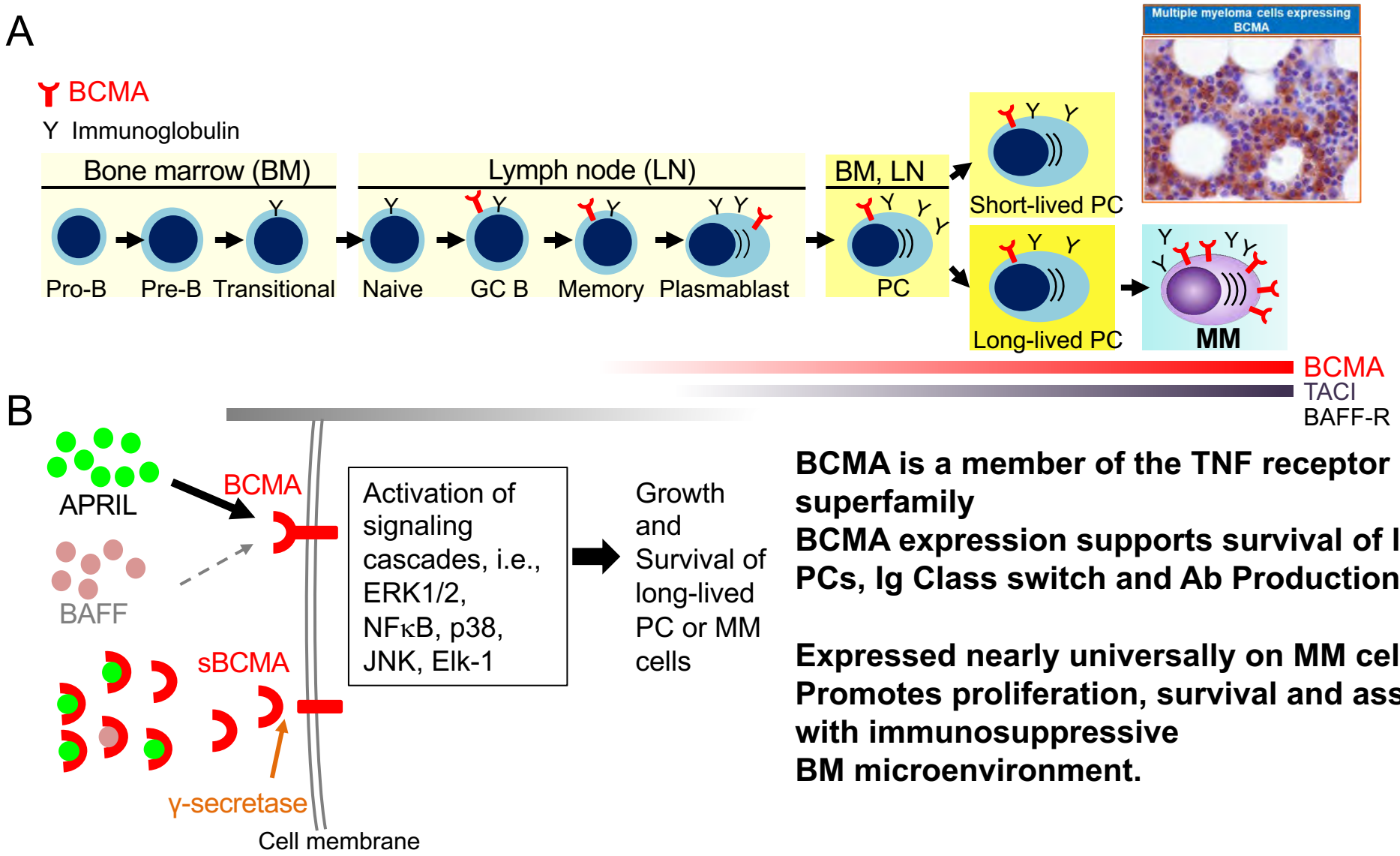
IKEMA: Isa-Kd Showed Improvement in PFS vs Kd : 47% Reduction of Risk



Moreau. EHA 2020. Abstr LB2603.

Courtesy of Nikhil C Munshi, MD

B-Cell Maturation Antigen (BCMA)
A Promising Target in Multiple Myeloma



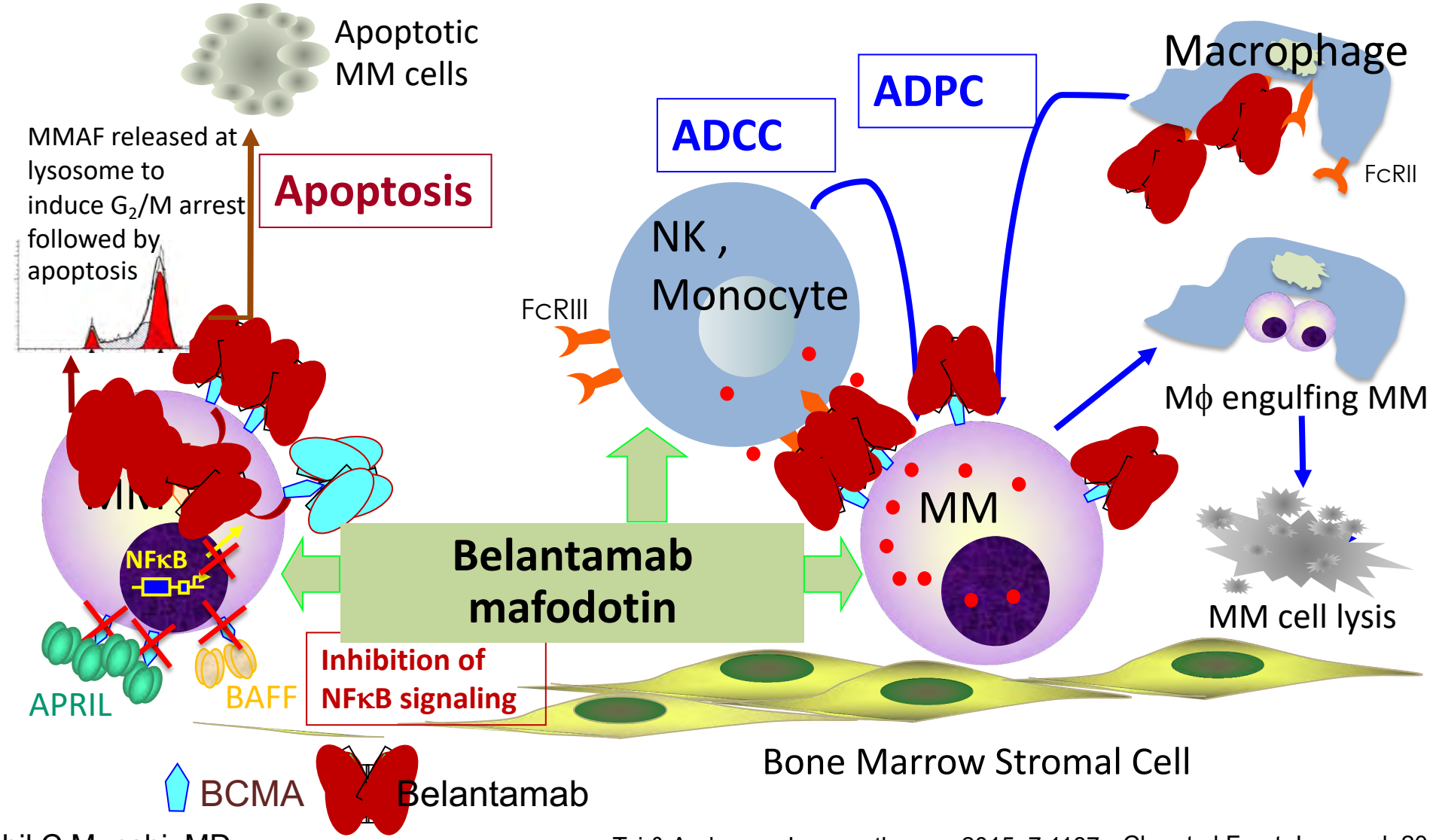
BCMA is a member of the TNF receptor superfamily
BCMA expression supports survival of long-lived PCs, Ig Class switch and Ab Production

Expressed nearly universally on MM cells
Promotes proliferation, survival and associated with immunosuppressive BM microenvironment.

Courtesy of Nikhil C Munshi, MD

Cho et al Front. Immunol. 2018. 01821

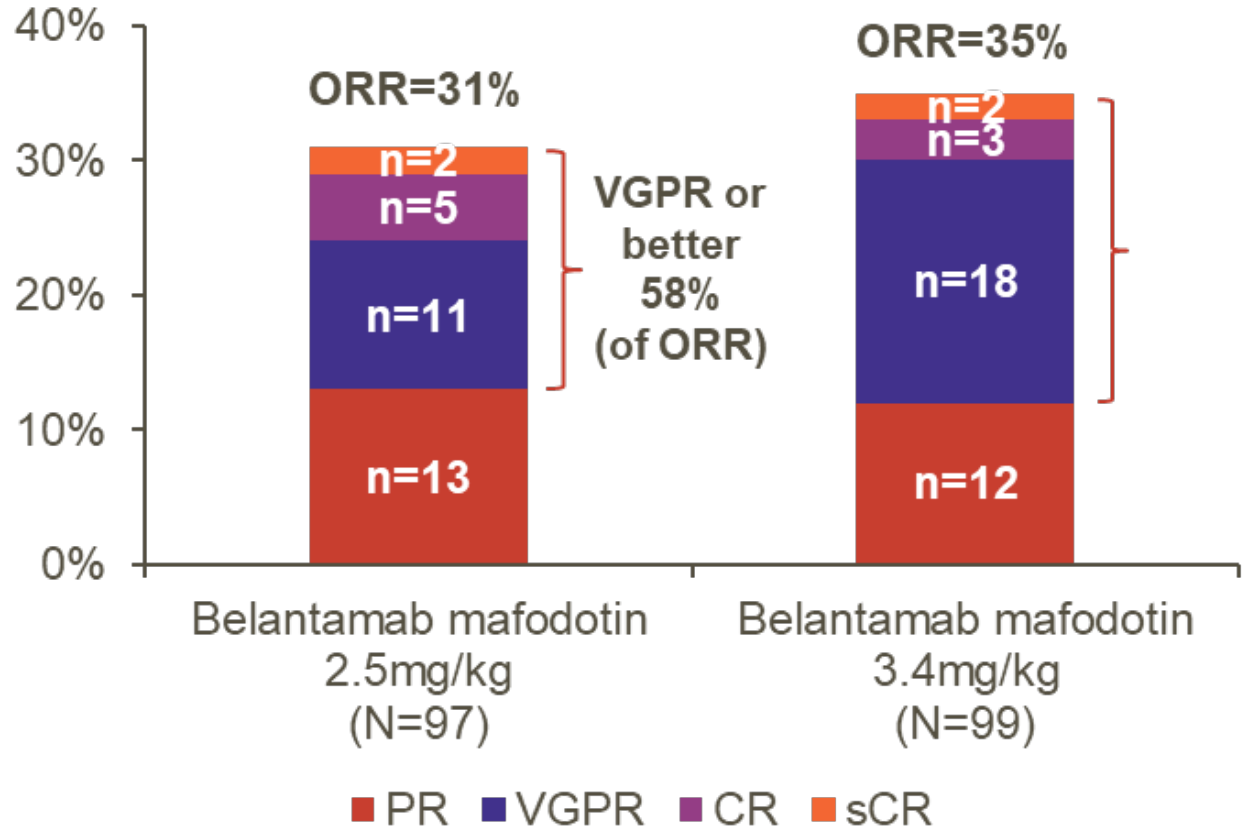
Belantamab mafodotin - a BCMA Auristatin Immunotoxin Induces Strong Anti-MM Effects via multiple MOAs



Courtesy of Nikhil C Munshi, MD Tai et al Blood 2014 123:3128 Tai & Anderson Immunotherapy 2015 ;7:1187 Cho et al Front. Immunol. 2018. 01821

Belantamab mafodotin: Overall response

DREAMM-2 13-month follow-up



1. Lonial S et al. *Lancet Oncol.* 2020;21(2):207-221. **2.** Lonial S et al. Poster presented at: American Society of Clinical Oncology Annual Meeting;. Poster 436.

Courtesy of Nikhil C Munshi, MD

Belantamab mafodotin: Common adverse events Keratopathy and Thrombocytopenia

DREAMM-2

Adverse events*	Any grade, n (%)		Grades ≥ 3, n (%)	
	2.5mg/kg n=95	3.4mg/kg n=99	2.5mg/kg n=95	3.4mg/kg n=99
Any event	93 (98)	99 (100)	80 (84)	83 (84)
Keratopathy (MECs) - changes to the superficial corneal epithelium	68 (72)	76 (77)	44 (46)	42 (42)
Thrombocytopenia	36 (38)	56 (57)	21 (22)	32 (32)
Anemia	NR	NR	20 (21)	27 (27)
Neutropenia	NR	NR	10 (11)	17 (17)
Pneumonia	NR	NR	6 (6)	11 (11)

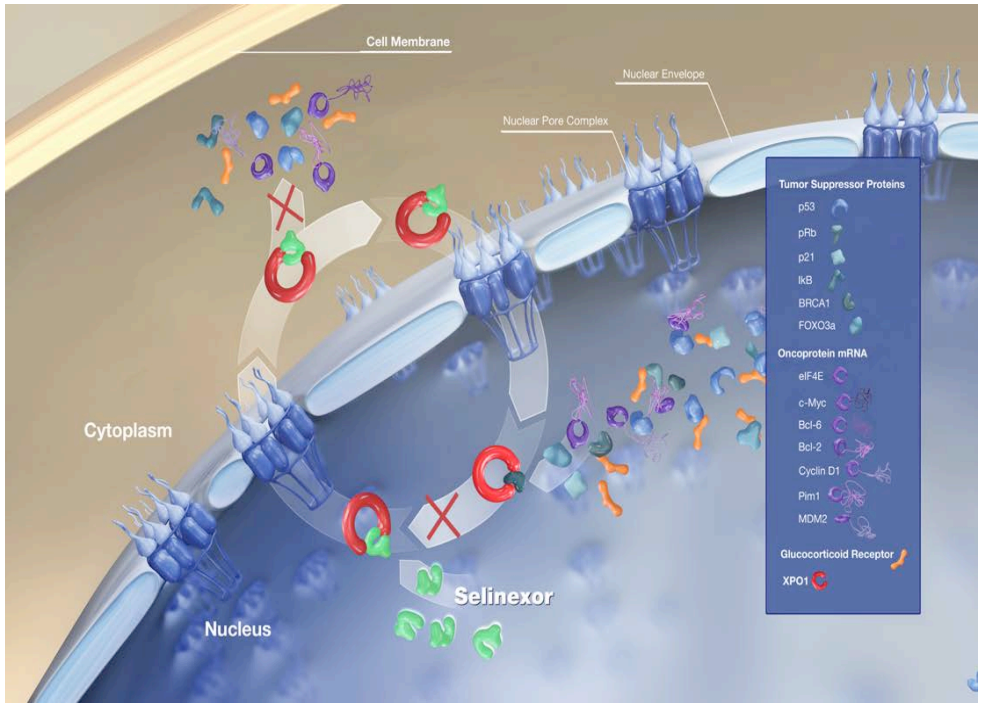
1. Lonial S et al. *Lancet Oncol.* 2020;21(2):207-221. **2**. Lonial S et al. Poster presented at: American Society of Clinical Oncology Annual Meeting;. Poster 436.

Courtesy of Nikhil C Munshi, MD

Targeting XPO-1

Selinexor approved for use in pts with RRMM who have received four prior therapies (including pts refractory to two proteasome inhibitors or IMiDs and an anti-CD38 antibody)

Selinexor is an oral XPO-1 inhibitor that induces nuclear retention and activation of TSPs and the GR in the presence of steroids, and suppresses oncoprotein expression[1]

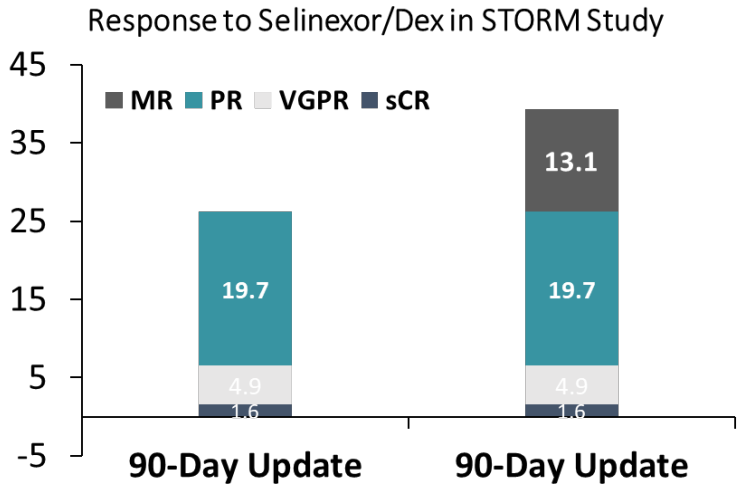


Courtesy of Nikhil C Munshi, MD

[1]Schmidt et al., Leukemia, 2013, [2]Tai et al., Leukemia, 2013, [3]Argueta et al., Oncotarget, 2018 [4]Turner et al, 2017 unpublished

Targeting Nuclear Transport
Selinexor

- Inhibits XPO1
  - XPO1 is the major nuclear export protein
  - XPO1 is overexpressed in MM
- Results of STORM Study
  - N = 122; median 7 prior treatments
  - 86% refractory to bortezomib, carfilzomib, lenalidomide, pomalidomide, and daratumumab
  - mDOR = 4.4 months
  - Associated with hematologic and GI toxicity
    - Aggressive supportive care needed

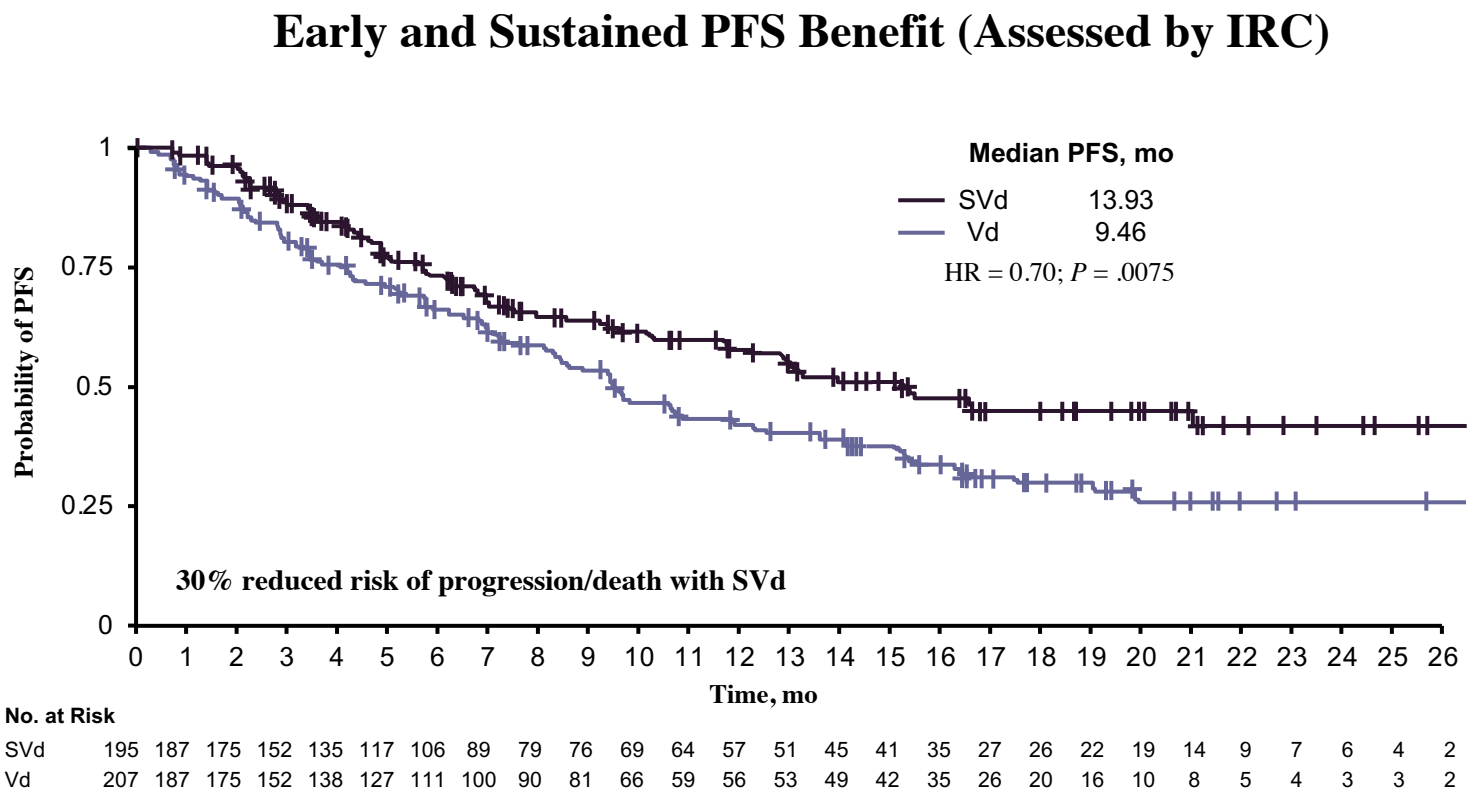


FDA-Approved July 2019
In combination with Dex in adults with RRMM after ≥ 4 prior therapies (≥ 2 PIs, ≥ 2 immunomodulatory drugs, and an anti-CD38 antibody)

- Chari A, et al. *N Engl J Med.* 2019;381:727-738.

Courtesy of Nikhil C Munshi, MD

Phase 3 BOSTON Trial: Selinexor Plus Vd in RRMM



Courtesy of Nikhil C Munshi, MD

Conclusions

- Select from daratumumab-, elotuzumab-, and isatuximab-based triplets
- No solid data to support a specific sequence or preference for one agent over another
- Data from high-risk subgroups show that they benefit, but not as much as standard risk
- Possibility that proteasome inhibitor-based triplets may have a greater benefit in high-risk

Courtesy of Nikhil C Munshi, MD

Conclusions

- Exciting novel approaches in pipeline, including both small molecules and new immunotherapies (S. Jagannath)
  - SINE, BCL2, MCL1 inhibitors
  - BiTEs, bispecific antibodies
- Immunotherapies such as CAR T-cells are showing impressive activity in the relapsed and refractory setting
  - Challenges remain, including toxicity, manufacturing time, and cost
- Due to earlier use of novel agents, relapsed and especially refractory disease is becoming more challenging to manage
- Better use of our current drugs in new combinations can have efficacy even if these agents were given previously
- Novel(er) drugs available on clinical trials offer the possibility of new mechanisms of action and may overcome prior drug resistance

Courtesy of Nikhil C Munshi, MD

What is your usual treatment recommendation for a 65-year-old patient with MM treated with RVD → ASCT and maintenance lenalidomide for 1.5 years who then experiences asymptomatic biochemical relapse?

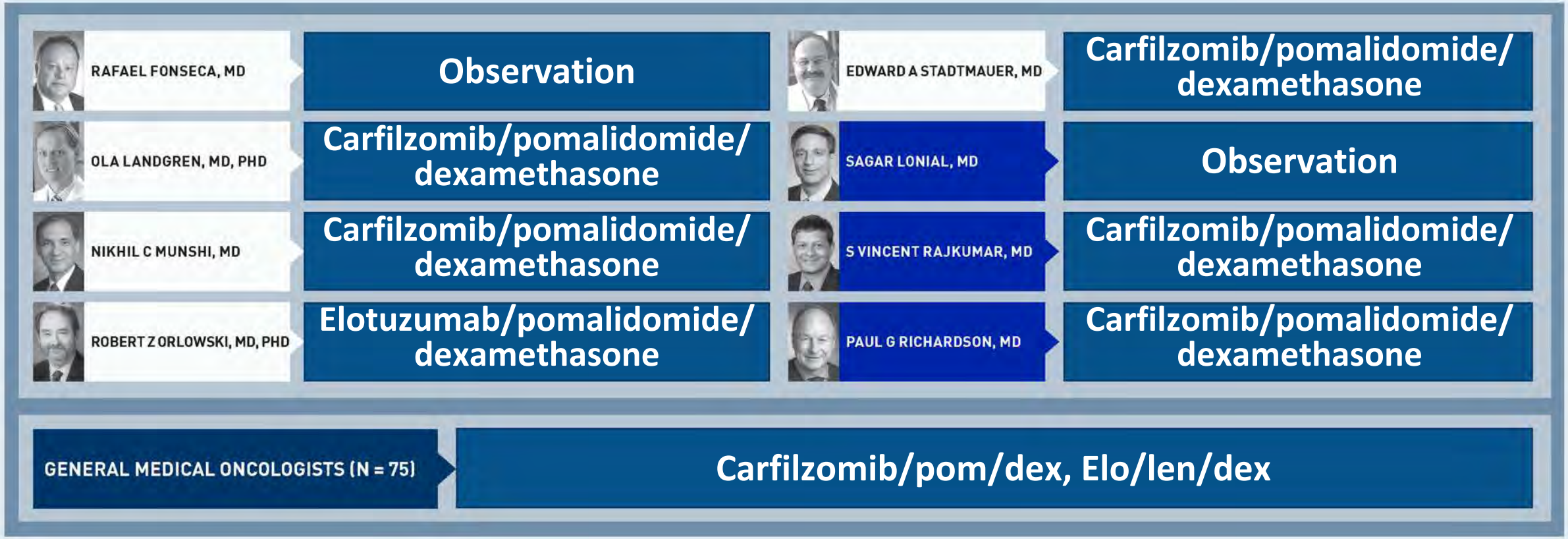
1. Carfilzomib + dexamethasone (dex)
2. Pomalidomide + dex
3. Carfilzomib + pomalidomide + dex
4. Elotuzumab + lenalidomide + dex
5. Elotuzumab + pomalidomide + dex
6. Daratumumab + lenalidomide + dex
7. Daratumumab + pomalidomide + dex
8. Other

What is your usual treatment recommendation for a 65-year-old patient with MM treated with RVD → ASCT and maintenance lenalidomide for 1.5 years who then experiences asymptomatic biochemical relapse?

 RAFAEL FONSECA, MD	Observation	 EDWARD A STADTMAUER, MD	Daratumumab/ lenalidomide/dex
 OLA LANDGREN, MD, PHD	Daratumumab/ pomalidomide/dex	 SAGAR LONIAL, MD	Observation
 NIKHIL C MUNSHI, MD	Elotuzumab/ lenalidomide/dex	 S VINCENT RAJKUMAR, MD	Daratumumab/ pomalidomide/dex
 ROBERT Z ORLOWSKI, MD, PHD	Daratumumab/ pomalidomide/dex	 PAUL G RICHARDSON, MD	Elotuzumab/ lenalidomide/dex

GENERAL MEDICAL ONCOLOGISTS (N = 75)	Dara/len/dex, Elo/len/dex

What is your usual treatment recommendation for a 65-year-old patient with MM treated with RVD/daratumumab → ASCT and maintenance lenalidomide/daratumumab for 1.5 years who then experiences an asymptomatic biochemical relapse?



Which of the following agents would you generally use first for a patient with relapsed MM who has experienced disease progression on multiple prior therapies, including daratumumab, proteasome inhibitors and IMiDs?

1. Isatuximab
2. Selinexor
3. Belantamab mafodotin
4. BCMA-directed CAR T-cell therapy
5. I would not recommend any of these

Which of the following agents would you generally use first in a patient with relapsed MM who has experienced disease progression on multiple prior therapies, including daratumumab, proteasome inhibitors and IMiDs?

 RAFAEL FONSECA, MD	BCMA-directed CAR T-cell therapy
 OLA LANDGREN, MD, PHD	BCMA-directed CAR T-cell therapy
 NIKHIL C MUNSHI, MD	BCMA-directed CAR T-cell therapy
 ROBERT Z ORLOWSKI, MD, PHD	BCMA-directed CAR T-cell therapy
 EDWARD A STADTMAUER, MD	Belantamab mafodotin
 SAGAR LONIAL, MD	Belantamab mafodotin
 S VINCENT RAJKUMAR, MD	Belantamab mafodotin
 PAUL G RICHARDSON, MD	Selinexor
GENERAL MEDICAL ONCOLOGISTS (N = 75)	BCMA-directed CAR T-cell therapy, Belantamab mafodotin

Who performs eye examinations for your patients with MM receiving belantamab mafodotin?

1. Optometrists
2. Ophthalmologists
3. I do not recommend regular eye examinations for my patients receiving belantamab mafodotin
4. I have not administered belantamab mafodotin to a patient with MM
5. Other

Who performs eye examinations for your patients with MM receiving belantamab mafodotin?

 RAFAEL FONSECA, MD	Ophthalmologist	 EDWARD A STADTMAUER, MD	Ophthalmologist
 OLA LANDGREN, MD, PHD	Ophthalmologist	 SAGAR LONIAL, MD	Ophthalmologist
 NIKHIL C MUNSHI, MD	Ophthalmologist	 S VINCENT RAJKUMAR, MD	Optometrist
 ROBERT Z ORLOWSKI, MD, PHD	Ophthalmologist	 PAUL G RICHARDSON, MD	Ophthalmologist

Case Presentation – Dr Munshi: A 61-year-old woman with multiple regimen-refractory myeloma

61-year-old lady with IgG λ multiple myeloma, with amp 1q

- VRd x 5 with minimal response (45% reduction) → changed to CyBorD with PR
- Autologous cell stem cell transplant →
- Relapsed 4 months post ASCT
- – Carfilzomib/cyclophosphamide/dexamethasone.
  - – Response 3 months
- - Daratumumab/pomalidomide/dexamethasone
  - – Response 4 months
- Multiple lines of therapy with initial response with quick subsequent relapse
- **What would be the next line of therapy?**

Courtesy of Nikhil C Munshi, MD

Case Presentation – Dr Munshi: A 62-year-old man with disease relapse after ASCT

- **62-year-old male in good physical condition. Presented for evaluation of recent fatigue and shortness of breath. Labs are as follows**
  - M-spike, IgG kappa: 6.1 g/dL
  - Beta-2-microglobulin: 9.8 mg/dL
  - Bone marrow aspirate: 90% plasma cells
  - FISH: t(11;14)

  - Hemoglobin: 7.8 g/dL
  - Calcium: 9.0 mg/dL
  - Creatinine 1.5 mg/dL
  - Albumin: 2.6 g/dL
  - Skeletal survey: Diffuse lytic lesions

- VRd →ASCT → lenalidomide maintenance x 24 mo. → PD
- **What are his options at first relapse?**

Courtesy of Nikhil C Munshi, MD

Agenda

Module 1: Induction therapy for patients with newly diagnosed disease — Dr Orlowski

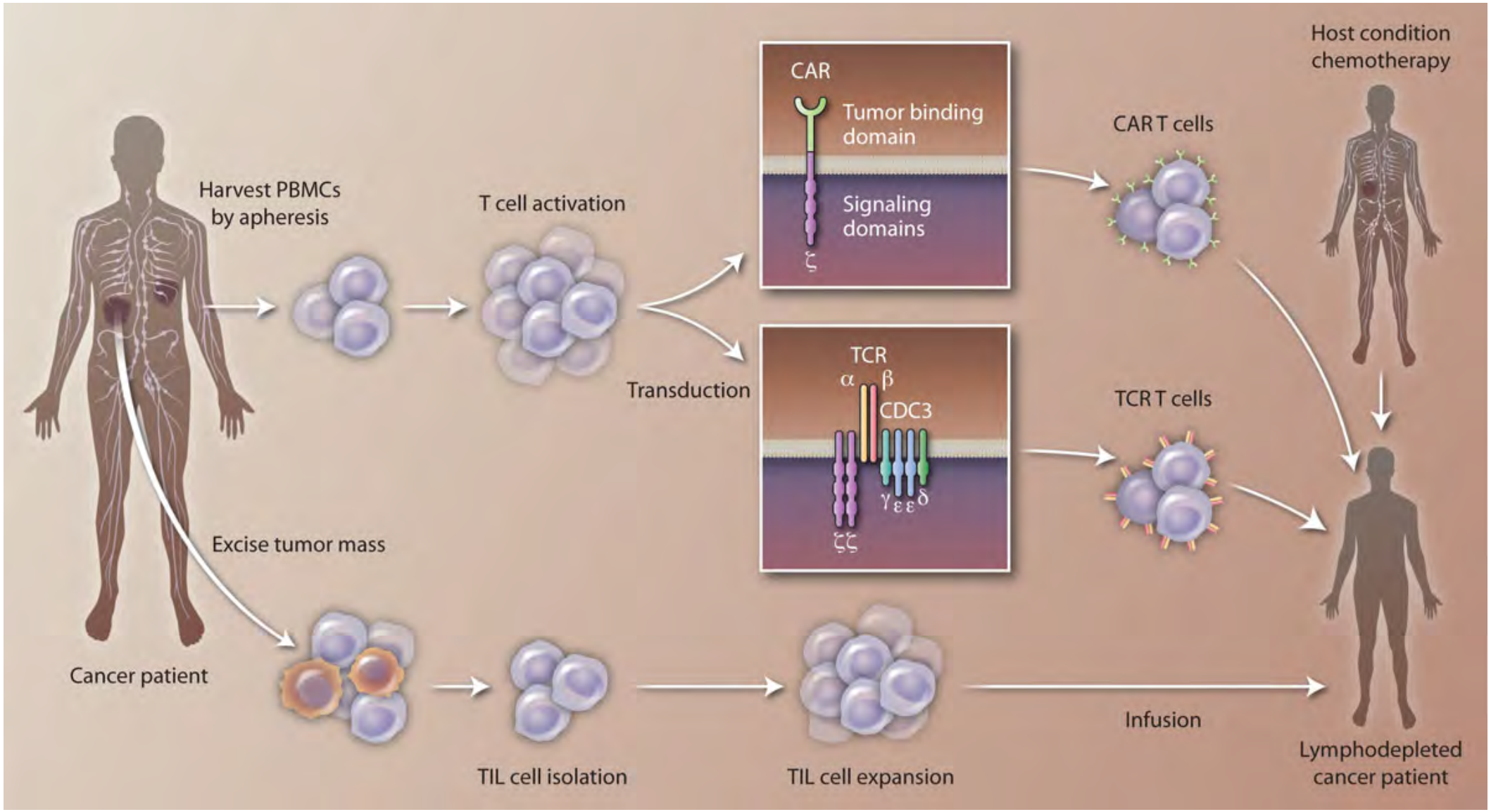
Module 2: Consolidation and maintenance therapy — Dr Fonseca

Module 3: Selection and sequencing of available therapies for relapsed/refractory disease — Dr Munshi

Module 4: Chimeric antigen receptor T-cell therapy — Dr Stadtmauer

Module 5: Other novel strategies — Dr Landgren

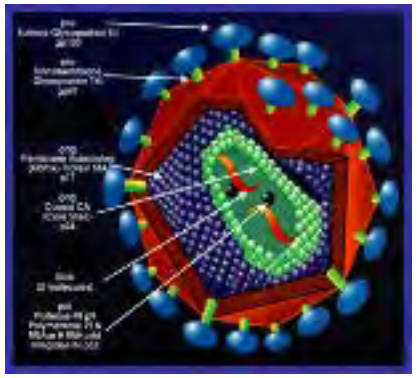
Adoptive T-cell therapy (three major approaches)



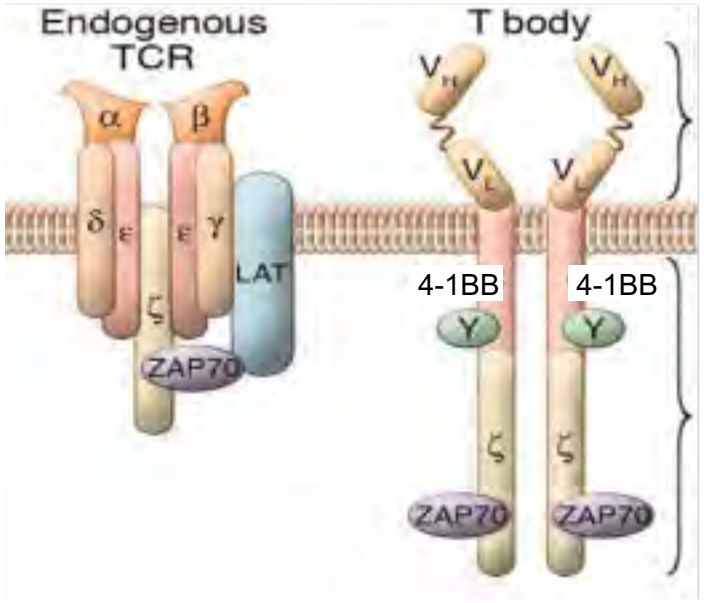
June et al *Sci Trans Med 2015*

Courtesy of Edward A Stadtmauer, MD

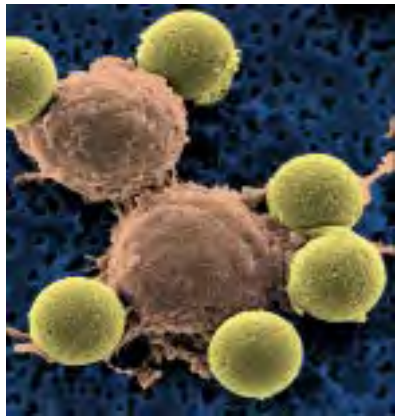
CAR for Plasma Cell Malignancy:
Autologous T Cells Transduced w/ Anti-BCMA Receptor Spliced to CD3 zeta and 4-1BB Signaling Domains



Lentiviral vector to deliver construct



CD3-z and 4-1BB signaling domains augments proliferation and survival

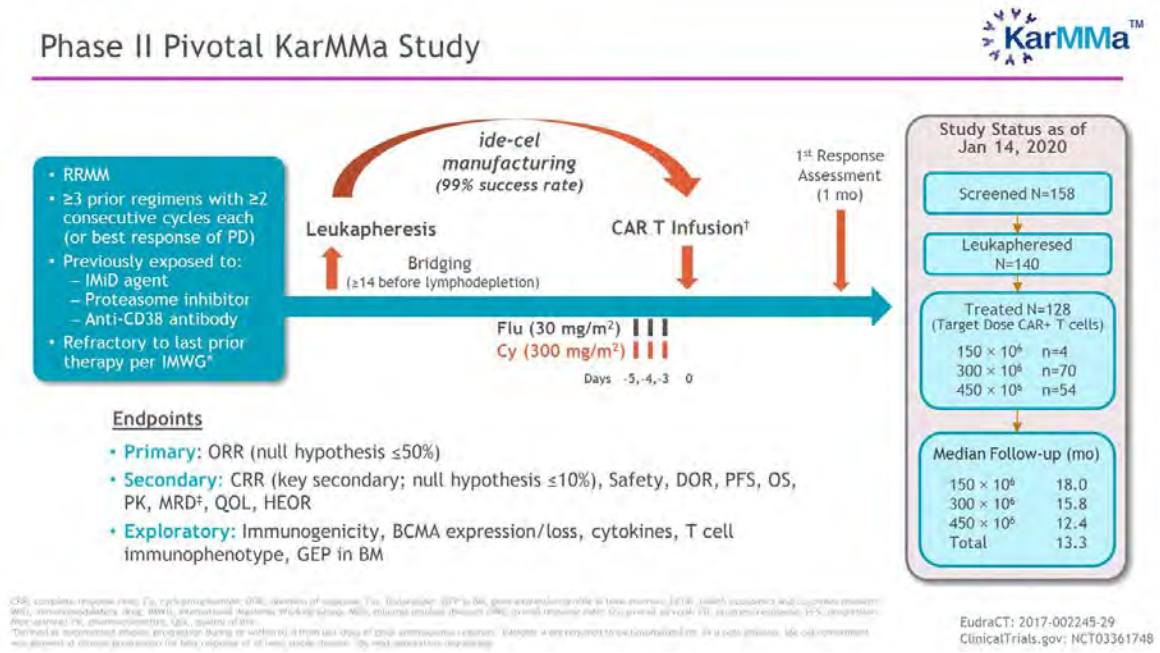


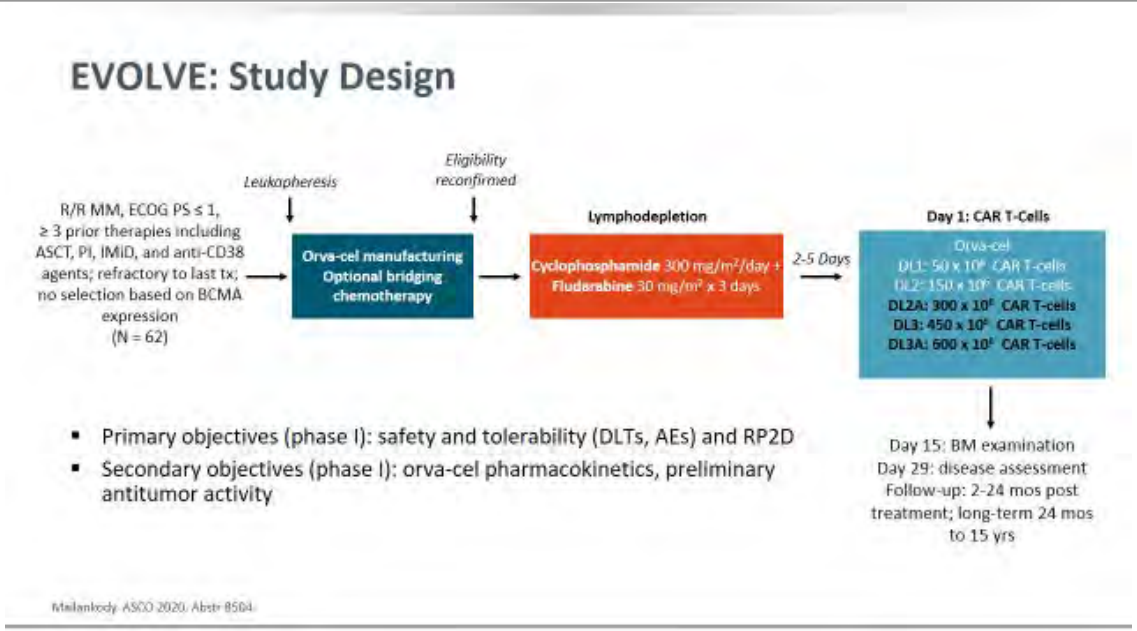
Anti-CD3/anti-CD28 mab coated bead stimulation (artificial DC) Expands the cells

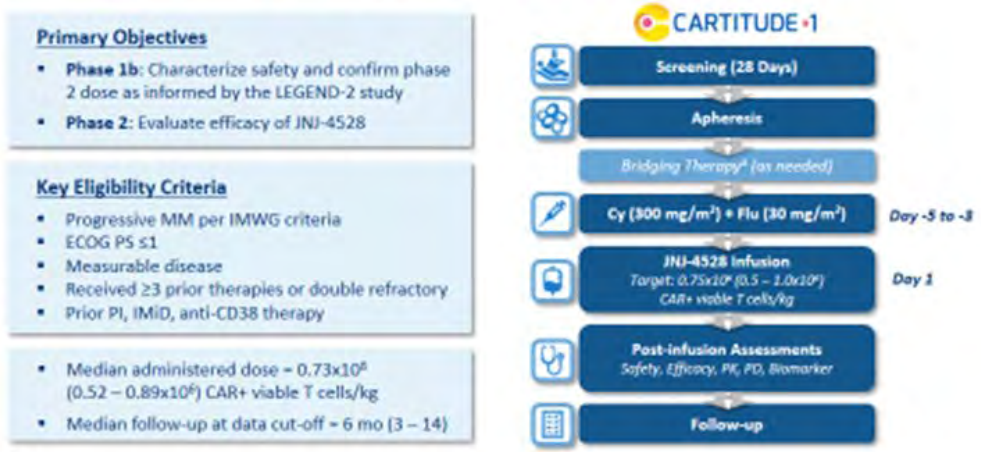
Adapted from: Maus MV, et al. Blood. 2014;123:2625-35.

Courtesy of Edward A Stadtmauer, MD

BCMA Directed CAR T Studies: ASH 2019, ASCO 2020







Similar approach in 3 studies:

R/R MM
Steady state T cell collection
CY/FLU lymphodepletion
Single infusion

BCMA Directed CAR T Studies: ASH 2019, ASCO 2020

Response Rates

	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) 5 (1-63)	2 (1-4) 4 (1-10)	7 (2-12) 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

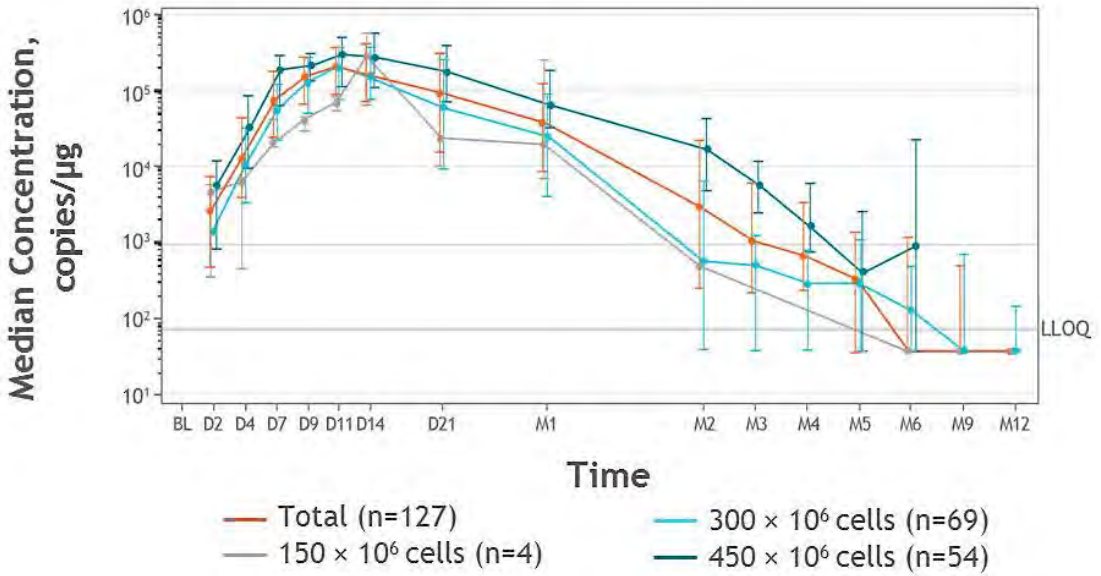
	KarMMa (n = 128)	EVOLVE (n = 62)	CARTITUDE-1 (n = 29)
ORR, %	73 (66-81)	92	100
sCR/CR, %	33	36	86
MRD neg ≥10^{-5}, % (of evaluable)	94	84	81
PFS/DoR, months	8.8/10.7	NR*	NR**
Screened Apheresed Treated	150 140 128	--	35 35 29

Presented By Krina Patel at ASCO 2020

Courtesy of Edward A Stadtmauer, MD

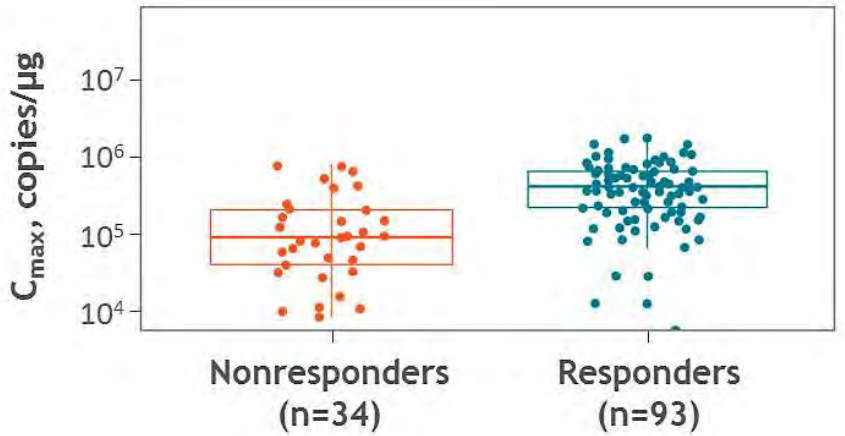
CAR+ T Cell Expansion, Persistence, and Peak Exposure

CAR+ T Cell Expansion and Persistence



	Mo 1	Mo 3	Mo 6	Mo 9	Mo 12
Evaluable patients, n	118	100	49	27	11
Patients with detectable vector, n (%)	117 (99)	75 (75)	29 (59)	10 (37)	4 (36)

Peak Vector Copies in Responders (≥PR) vs Nonresponders (<PR)



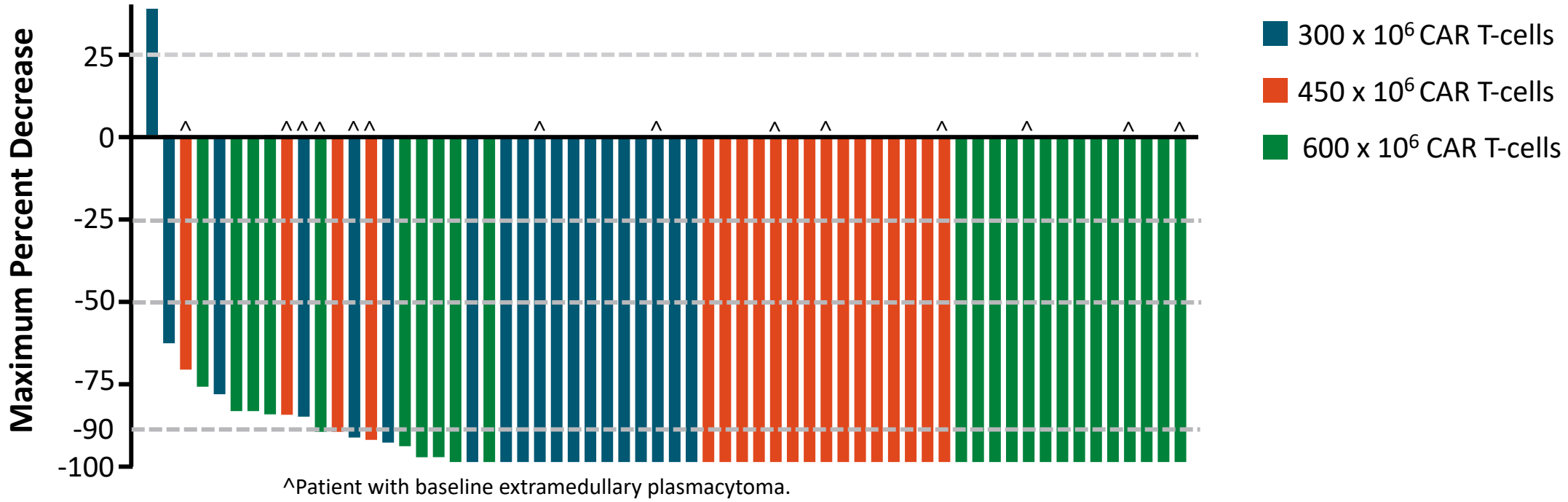
- Median peak CAR+ T cell expansion was at 11 d
- Median expansion increased at higher target doses with overlapping profiles
- Peak exposure higher in responders than nonresponders
- Durable persistence was observed up to 1 y

Data cutoff: 19 April 2019. Pharmacokinetic (PK) analysis population (N=127). One patient died on day 4 and had no evaluable PK samples and was therefore excluded. Error bars represent interquartile range. BL, baseline; C_{max}, maximum concentration; LLOQ, lower limit of quantitation; M, month.

Munshi, ASCO 2020, Abstract 8503

Courtesy of Edward A Stadtmauer, MD

EVOLVE: Tumor Burden Reduction According to Dose



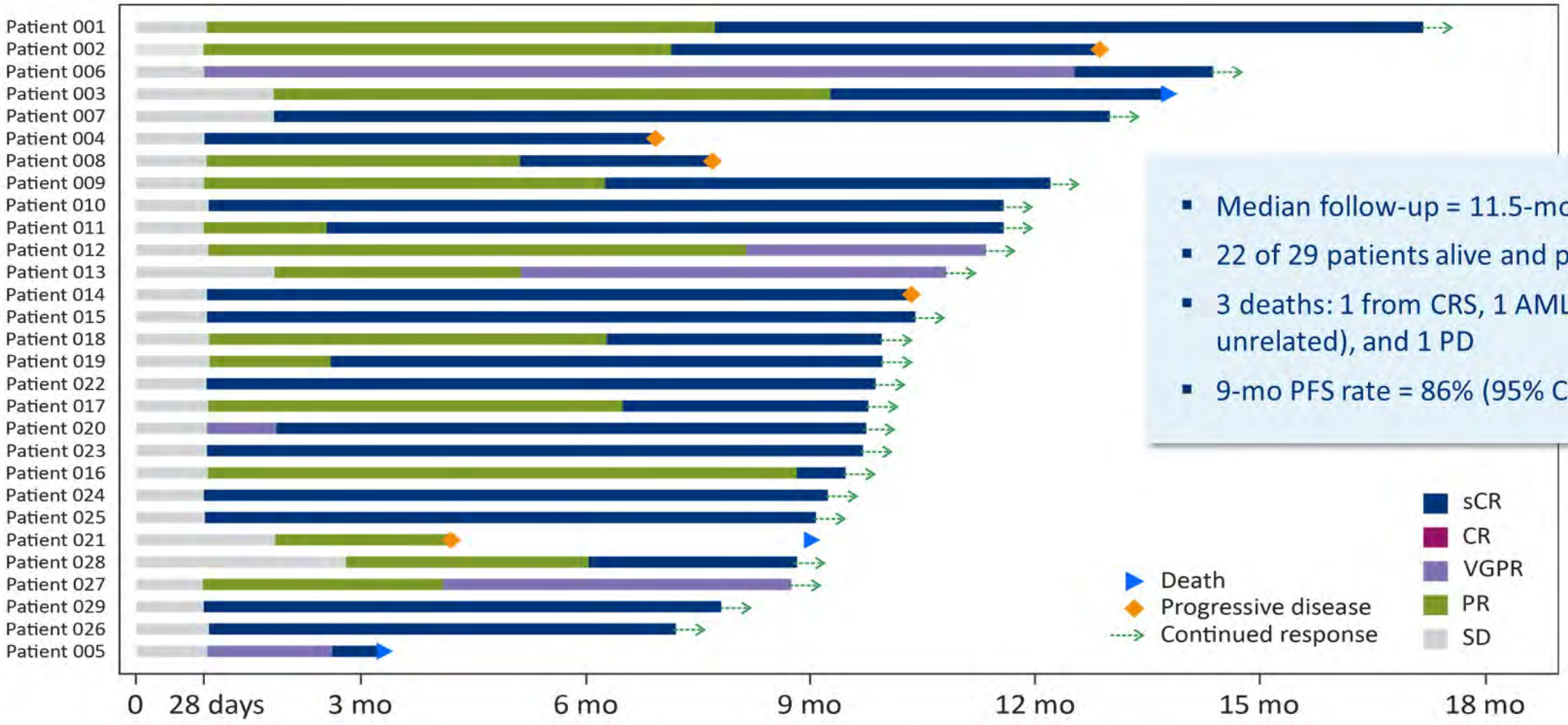
^Patient with baseline extramedullary plasmacytoma.

- Serologic responses (serum or urine paraprotein, free light chains) were observed in all patients treated at 450 x 10^6 and 600 x 10^6 dose levels
- Orva-cel activity not impacted by high baseline sBCMA
  - 12/12 patients achieved ≥ PR; 8/12 ≥ VGPR

Mailankody. ASCO 2020. Abstr 8504.

Courtesy of Edward A Stadtmauer, MD

CARTITUDE-1: Duration of Response



- Median follow-up = 11.5-mo (3 – 17)
- 22 of 29 patients alive and progression-free
- 3 deaths: 1 from CRS, 1 AML (treatment unrelated), and 1 PD
- 9-mo PFS rate = 86% (95% CI, 67 – 95)

AML=acute myeloid leukemia (biphenotypic); PD=progressive disease; PFS=progression-free survival

Courtesy of Edward A Stadtmauer, MD

Presented By Jesus Berdeja at TBD

Why not more durable responses?

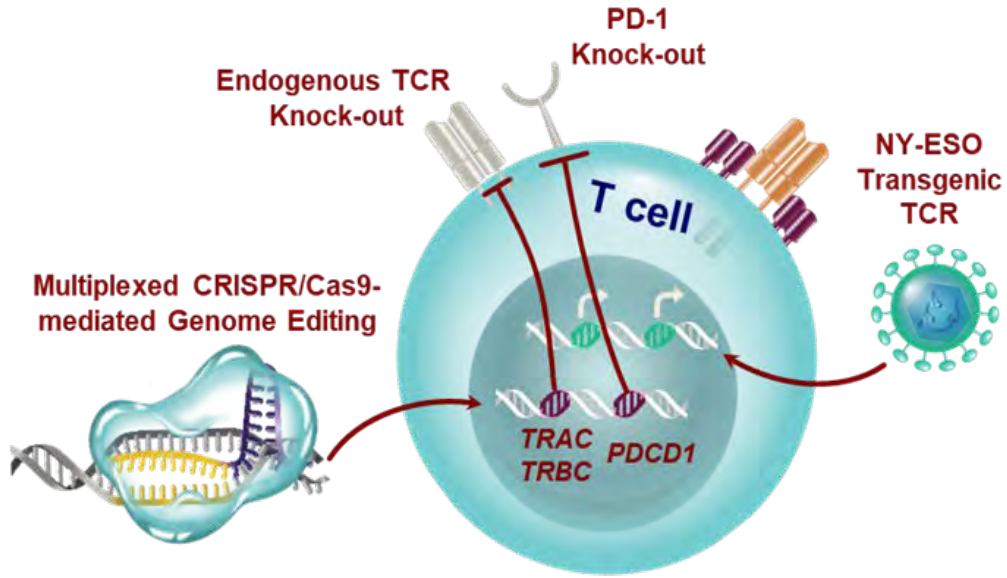
- **CAR-intrinsic factors**
  - Binding affinity, epitopes
  - Tonic signaling
  - Co-stimulation
- **T-cell intrinsic factors**
  - Pre-manufacturing
  - Post-manufacturing
  - Post-infusion
- **Tumor-intrinsic factors**
  - Myeloma cell
  - Microenvironment
- **Other**
  - Lymphodepletion regimen?

Courtesy of Edward A Stadtmauer, MD

Cohen et al, J Clin Invest 2019; Brudno et al, J Clin Oncol 2018; Wang et al, ASH 2019, #1909

Manufacturing NYCE T cells: *Multiplexed Genomic Editing*

- Autologous T cells
- Anti-CD3/CD28 bead stimulation
- Electroporation with ribonucleoprotein (RNP) complexes:
  TRAC/*TRBC*/*PDCD1* gRNAs + Cas9 Protein
- Transduction with NY-ESO-1 TCR lentiviral vector
- Expansion of engineered T cells



Cell Product Release Criteria

- Viability: ≥ 70%
- NY-ESO TCR Transduction Efficiency (Vβ8 Flow Cytometry): ≥ 2%
- NY-ESO TCR Transduction Efficiency (WPRE qPCR): ≥ 0.02 - ≤ 5 Avg. copies / cell
- Residual Beads: ≤ 100 beads / 3 x 10^6 cells
- Endotoxin Content: ≤ 3.5 EU / mL
- Microbial Contamination: Negative
- Long-term Culture: No growth in the presence of IL-2 (no cell transformation)
- Replication Competent Lentivirus (VSV-G): < 50 Avg. copies / µg DNA
- *TRAC, TRBC, PDCD1* Disruption: Detectable
- Residual Cas9 Protein: Decreasing concentration from Day 0 to cell harvest

Stadtmauer *et al, Science,* 2020

Courtesy of Edward A Stadtmauer, MD

Conclusions (NYCE T Cells Study)

- Generation of multiplexed genetic engineering of autologous T cells expressing NY-ESO-1 TCR and CRISPR/Cas9 gene edited to eliminate endogenous TCR and PD-1 (NYCE T cells) is feasible
- Three patients with advanced cancer have safely received NYCE T cells after lymphodepletion
- Engineered T cells expand, survive and persist long-term in patients
- Best overall response achieved after NYCE T cell infusion to date is stable disease
- May allow for engineering of off-the-shelf allogeneic CAR T cells

Courtesy of Edward A Stadtmauer, MD

What's Happening in 2020 for Engineered T cells for Myeloma?

- **Anti-BCMA CAR registration trials in rel/ref MM**
  - Not perfect, still lots of relapses within 1 year, but remarkable responses in R/R MM without other options
  - Ongoing ph 1/2 for next-gen CAR products

- **CAR T cells against CD38, SLAMF7 (CS1), GPRC5D, NY-ESO-1**
  - These are all reasonable targets, but much more limited experience

- **Anti-BCMA CAR trials for less-heavily treated patients**
  - 1-3 priors
  - Post-induction in hi risk
    - CART-BCMA +/- CART-19
  - Post-autoSCT
    - ASCT + CAR T in High Risk or Poor Response

Courtesy of Edward A Stadtmauer, MD

What's Happening in 2020 for Engineered T cells for Myeloma?

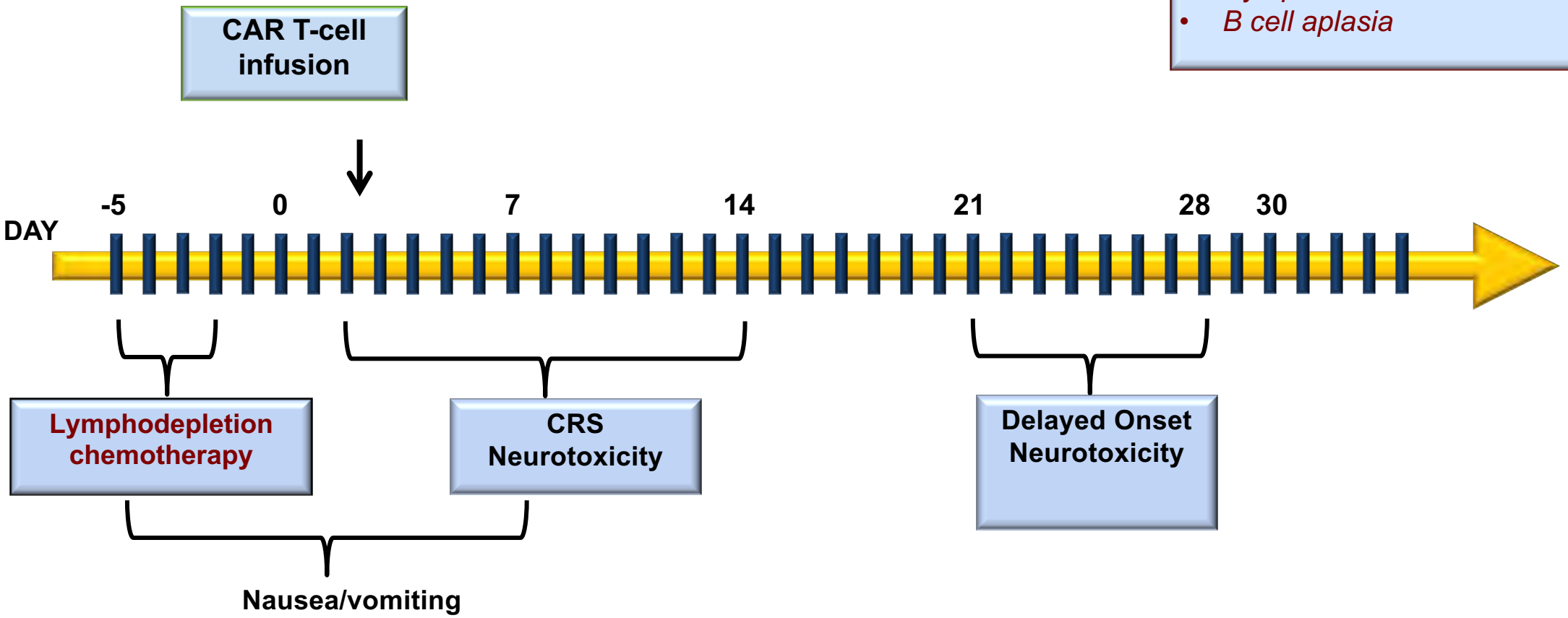
- **Anti-BCMA CAR combo trials**
  - Other CAR T cells, IMiDs, checkpoint inhibitors

- **Gene-edited T cells**
  - "Off-the-shelf" allogeneic CAR T cells
  - PD-1 deficient, endogenous TCR edited T cells (*Science* 2020)

Courtesy of Edward A Stadtmauer, MD

CAR-T Toxicities Timeline

Adverse Events > Day 30:
- *Infection*
- *Cytopenias*
- *B cell aplasia*



Brudno JN, et al. Blood. 2016;127:3321-30. Neelapu SS, et al. Nat Rev Clin Oncol. 2018; 15:47-62.

Courtesy of Edward A Stadtmauer, MD

CAR T-Cell Toxicity/Treatments

Cytokine Release Syndrome

Cause:
Activation/expansion of CAR T-cells increased levels of cytokines (IL-6, IL-15, INF-γ, GM-CSF, others)

Onset: variable; 1 to 3 days CD28; 3 to 5 days 4-1BB

Duration: 3 to 5 days

Risk: variable up to 30% grade 3

- Disease burden
- Peak CAR T-cell levels
- Pre-treatment and peak cytokine levels

Neurotoxicity

Cause:
Mechanism less understood

- High CSF: blood cytokine levels
- CAR-positive and CAR-negative T-cells in CSF

Onset: 5 to 7 days; later than CRS

Duration: 5 to 10 days

- Fully reversible except in cases of fatal cerebral edema

Risk: variable, up to 40% grade 3

- Disease burden
- Peak CAR T-cell levels
- Early and high-grade CRS
- Pre-treatment and peak cytokine levels
- DIC

- Santomasso B, et al. *Am Soc Clin Oncol Educ Book.* 2019;39:433-444.

Courtesy of Edward A Stadtmauer, MD

ASTCT Consensus Grading of CRS

CRS Parameter*	Grade 1	Grade 2	Grade 3	Grade 4
Fever#†	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C
		With		
Hypotension#	None	Not requiring vasopressors	Requiring one vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
		And/ or‡		
Hypoxia#	None	Requiring low-flow nasal cannula^ or blow-by	Requiring high-flow nasal cannula^, facemask, non-rebreather mask, or Venturi mask	Requiring positive pressure (eg: CPAP, BiPAP, intubation and mechanical ventilation)

#Not attributable to any other cause

†In patients who have CRS then receive tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity

‡CRS grade is determined by the more severe event

^Low-flow nasal cannula is ≤ 6 L/min and high-flow nasal cannula is > 6 L/min

*Organ toxicities associated with CRS may be graded according to CTCAE v5.0 but they do not influence CRS grading

Lee et al. *Biol Blood Marrow Transplant*, 2019 Apr;25 (4):625-638

Courtesy of Edward A Stadtmauer, MD

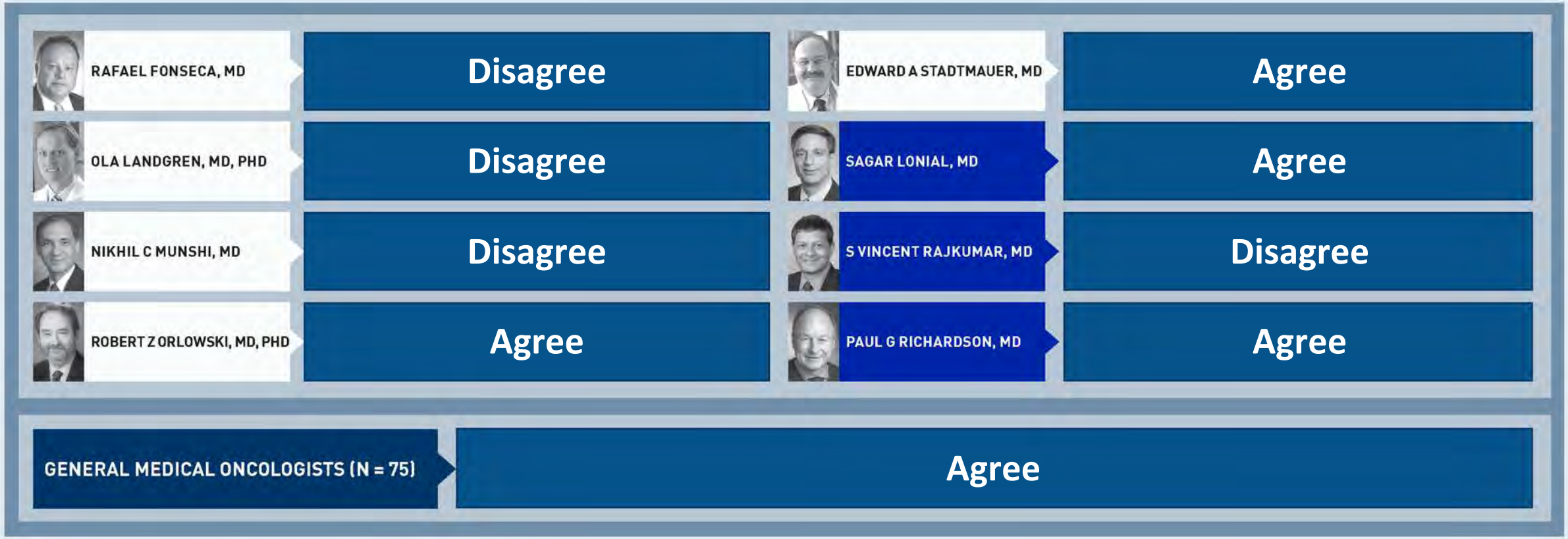
What do you currently believe is the optimal point at which chimeric antigen receptor (CAR) T-cell therapy should be administered in MM?

 RAFAEL FONSECA, MD	At first relapse
 OLA LANDGREN, MD, PHD	At first relapse
 NIKHIL C MUNSHI, MD	At third relapse
 ROBERT Z ORLOWSKI, MD, PHD	At second relapse
 EDWARD A STADTMAUER, MD	After third relapse
 SAGAR LONIAL, MD	At third relapse
 S VINCENT RAJKUMAR, MD	After third relapse
 PAUL G RICHARDSON, MD	At third relapse
GENERAL MEDICAL ONCOLOGISTS (N = 75)	At third relapse, At second relapse

A patient with MM should be in adequate physical condition to undergo ASCT in order to be a suitable candidate for BCMA-targeted CAR T-cell therapy.

1. Agree
2. Disagree
3. I don’t know

A patient with MM should be in adequate physical condition to undergo ASCT in order to be a suitable candidate for BCMA-targeted CAR T-cell therapy.



How would you compare the risk of cytokine release syndrome and CNS toxicity with BCMA-targeted CAR T-cell therapy to that with the CD19-targeted CAR T-cell therapy that is approved in lymphoma and acute lymphocytic leukemia?

 RAFAEL FONSECA, MD	The risk is greater with CD19 CAR T
 OLA LANDGREN, MD, PHD	The risk is greater with CD19 CAR T
 NIKHIL C MUNSHI, MD	The risk is greater with CD19 CAR T
 ROBERT Z ORLOWSKI, MD, PHD	The risk is greater with CD19 CAR T
 EDWARD A STADTMAUER, MD	The risk is about the same
 SAGAR LONIAL, MD	The risk is greater with CD19 CAR T
 S VINCENT RAJKUMAR, MD	The risk is greater with CD19 CAR T
 PAUL G RICHARDSON, MD	The risk is greater with CD19 CAR T

GENERAL MEDICAL ONCOLOGISTS (N = 75)	Risk is about the same, Greater with BCMA-targeted CAR T

Case Presentation – Dr Stadtmauer: A 55-year-old man with multi-regimen refractory myeloma

- 55-year-old man with a heavily treated IgA lambda MM manifested by bone marrow plasmacytosis, lytic bone lesions, serum and urine monoclonal protein and an 11;14 translocation
- VRD → HD melphalan and autologous stem cell transplant → VRd maintenance therapy for 2 years → VGPR
- Progressed and received following regimens: Cy-Pom-Dex → VPD → bendamustine, daratumumab → Dara-Rev-Dex → Car-Pom-Pred with biochemical progression.
- Enrolled on a BCMA directed CAR T protocol, underwent steady-state harvest. Did not require bridging therapy. Successful manufacturing, fludarabine/cyclophosphamide lymphodepleting therapy followed by infusion of target dose of CAR T cells 5/6/19.

Courtesy of Edward A Stadtmauer, MD

Case Presentation – Dr Stadtmauer: A 55-year-old man with multi-regimen refractory myeloma (continued)

- On D+ 2 had fevers to 103, rigors, hypotension, desaturations to 83%, and altered mental status of lethargy. Ferritin slightly increased to 480 with CRP significantly increased to 13.
- Empirically started on cefepime and was given tocilizumab x1 dose (CRS was thought to be more likely etiology of his symptoms).
- Transferred to the MICU for worsening mental status. Persistent profound agitated delirium. Neuro workup included LP, CT and MRI which were unrevealing for a source of his agitation and as such his agitation was thought to be due to neurotoxicity.
- Started on dexamethasone 10 mg q6h. Anakinra (D+4 - D+11) for CRS treatment and heavily
- Intubated for airway protection (D+3 - D+12)

Courtesy of Edward A Stadtmauer, MD

Case Presentation – Dr Stadtmauer: A 55-year-old man with multi-regimen refractory myeloma (continued)

- D+12
  - Hgb 10.4, WBC 20.4, platelet 99,000
  - Ferritin of 184, CRP of 0.30
  - SPEP shows an M-spike of 2.1 g/dl (decreased from 2.8) IgA 1,856 (decreases from 2,416).
  - CT scan of his head → no evidence of an acute process, and numerous bone lesions in his skull.
- D+22 Neurologic symptoms resolved. Performance status improved rapidly. Discharged D +28
- D+60 IgA 323
- PD 11.9 months later (IgA 667) started Car-Pom-Dex →NR
- Enrolled on a BCMA bispecific Ab protocol. Well tolerated without neurotoxicity. PR.
- May 2020 IgA 287 → high-dose melphalan 200 mg/m^2 and autologous transplantation. D+ 75 IgA 179
- +4 months from his salvage stem-cell transplant in remission and started on maintenance Elo-Rev-Dex

Courtesy of Edward A Stadtmauer, MD

Agenda

Module 1: Induction therapy for patients with newly diagnosed disease — Dr Orlowski

Module 2: Consolidation and maintenance therapy — Dr Fonseca

Module 3: Selection and sequencing of available therapies for relapsed/refractory disease — Dr Munshi

Module 4: Chimeric antigen receptor T-cell therapy — Dr Stadtmauer

Module 5: Other novel strategies — Dr Landgren

RTP
RESEARCH
TO PRACTICE

Targeting Bcl-2 for the treatment of multiple myeloma

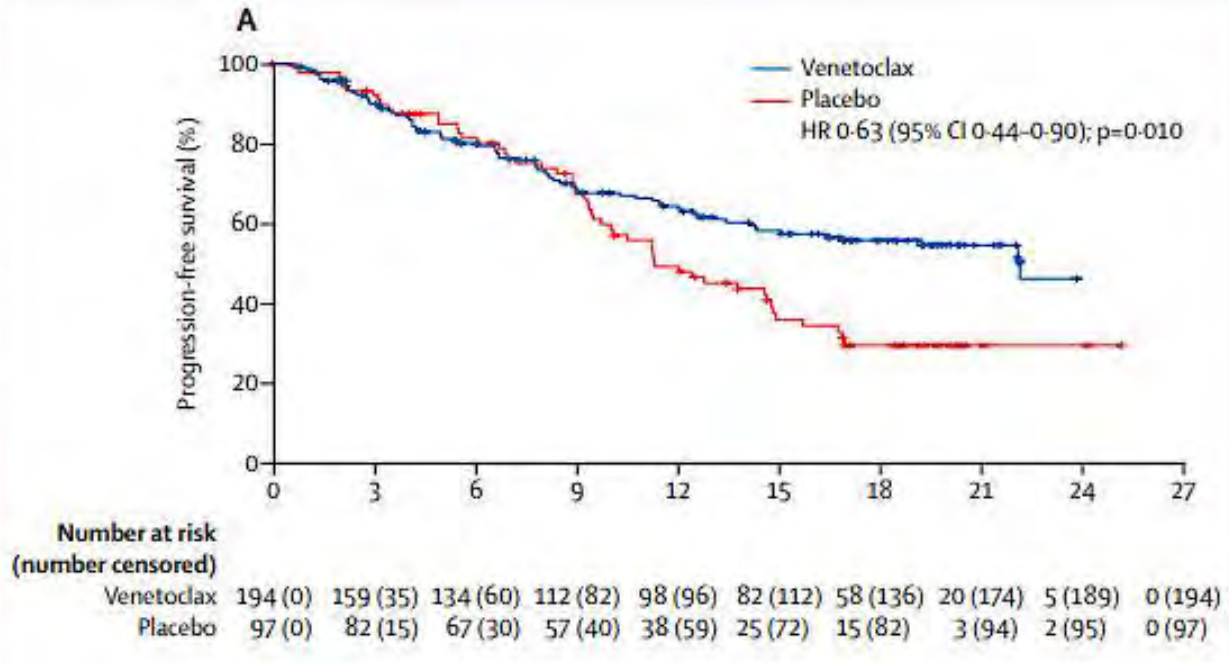
- Overexpression of anti-apoptotic proteins are hallmarks of cancer
- Tumor cell proliferation is regulated through interactions between anti-apoptotic (Mcl-1, Bcl-2 and Bcl-xL) and pro-apoptotic (Bax and Bak) members
- Subset of myeloma cells with high Bcl-2 expression and low Mcl-1 expression commonly found in CCND1 subset, characterized by the presence of the translocation (11;14)
- Venetoclax binds to Bcl-2 and Bcl-x_L but not to Mcl-1. It induces apoptosis by displacing proapoptotic BH3-only proteins (Bim and Puma) from Bcl-2, leading to caspase-dependent cell death

Bodet L, et al. *Blood*. 2011 Oct 6;118(14):3901-3910

Courtesy of Ola Landgren, MD, PhD

Venetoclax in combination with bortezomib and dexamethasone in patients with relapsed or refractory multiple myeloma (BELLINI)

- Venetoclax, bortezomib and dexamethasone have shown encouraging clinical efficacy with acceptable safety and tolerability in phase 1 trial
- 291 patients (1-3 prior lines) randomized to receive venetoclax (n=194) or placebo (n=97), with bortezomib and dexamethasone
- At median follow-up of 18.7 months, median progression-free survival (PFS) was 22.4 versus 11.5 months favoring venetoclax; p=0.010



- Prespecified sub-analysis of t(11;14) patients (N=35) show median PFS not reached versus 9.5 months in venetoclax versus placebo group; similarly, sub-analysis of patients with high Bcl-2 expression (qPCR) levels (N=98) show median PFS of 22.4 versus 9.9 months, respectively

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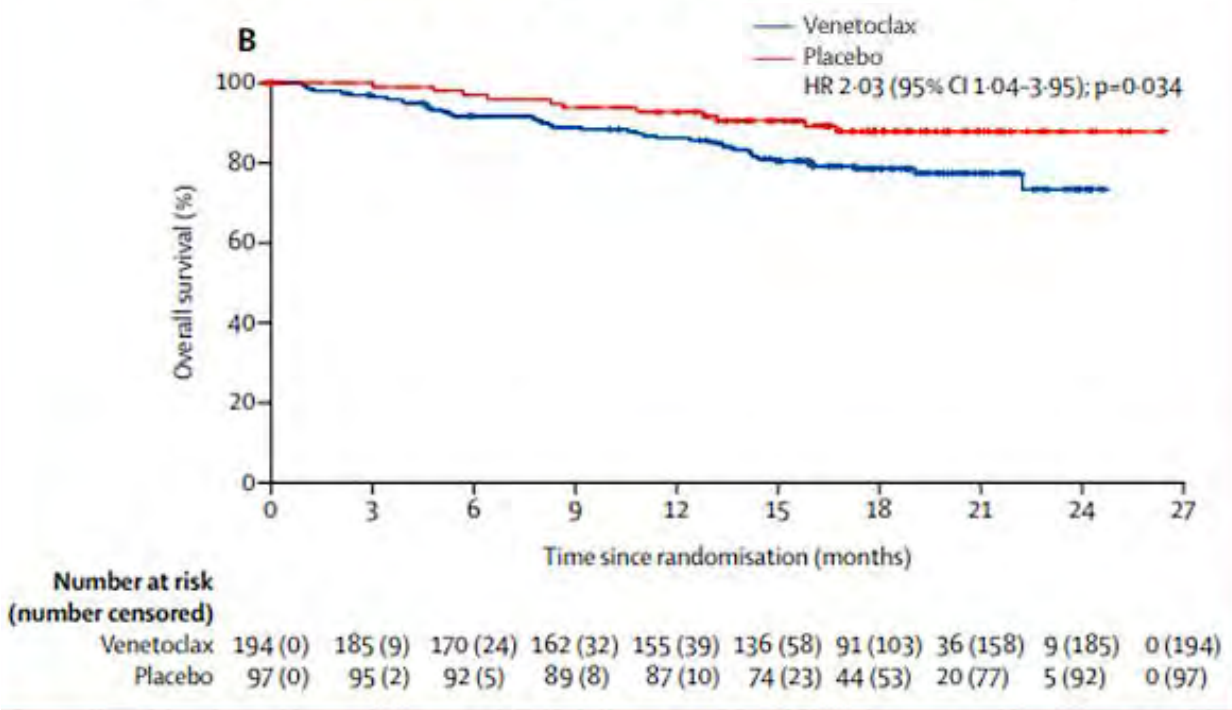
Kumar S, et al. *Lancet Oncology*. 2020 Oct 29;S1470-2045

Courtesy of Ola Landgren, MD, PhD

Venetoclax in combination with bortezomib and dexamethasone in patients with relapsed or refractory multiple myeloma (BELLINI)

- However, excess death was found; in safety analysis population, 21% and 11% of pts in the venetoclax and placebo group died, respectively
- 8/13 of treatment-emergent deaths (within 30 days of last dose) in the venetoclax group were infections, including 5 patients who died from sepsis/septic shock and 3 who died from pneumonia
- In venetoclax group, excess mortality primarily seen in patients without t(11;14)



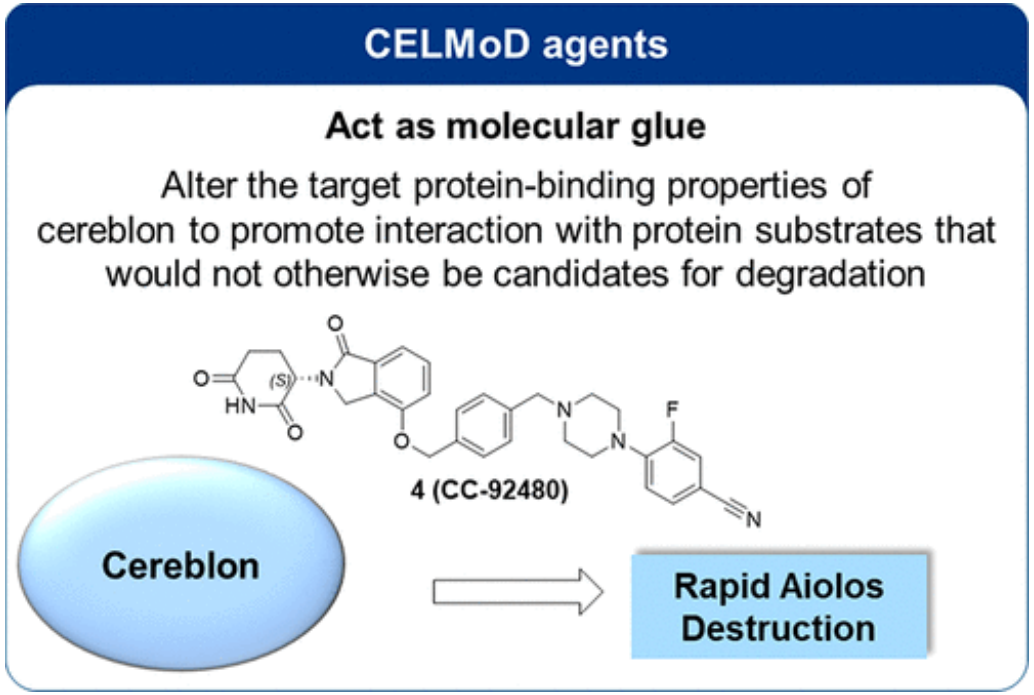
- Authors speculate venetoclax combination may select aggressive malignant clones? Or, treatment-induced immunosuppression may cause susceptibility to life-threatening infections? Or, other explanation(s)?

Kumar S, et al. *Lancet Oncology*. 2020 Oct 29;S1470-2045

Courtesy of Ola Landgren, MD, PhD

Cereblon E3 ligase modulators (CELMoDs)

- CC-92480 binds to cereblon, thereby affecting the ubiquitin E3 ligase activity, and targeting certain substrate proteins for ubiquitination…
- … this induces proteasome-mediated degradation of certain transcription factors, some of which are transcriptional repressors in T cells…
- … this leads to modulation of the immune system, including activation of T lymphocytes; and antiproliferative effects and induction of apoptosis in myeloma cells



Hansen JD, et al. *J Med Chem*. 2020 Jul 9;63(13):6648-6676;

Courtesy of Ola Landgren, MD, PhD

Phase I trial supports CC-92480 for heavily pretreated multiple myeloma

- Patients received escalating doses of CC-92480 + dexamethasone. Parallel dosing schedules: more continuous with 4-day or 7-day breaks *vs.* intensive with longer breaks in a 28-day cycle

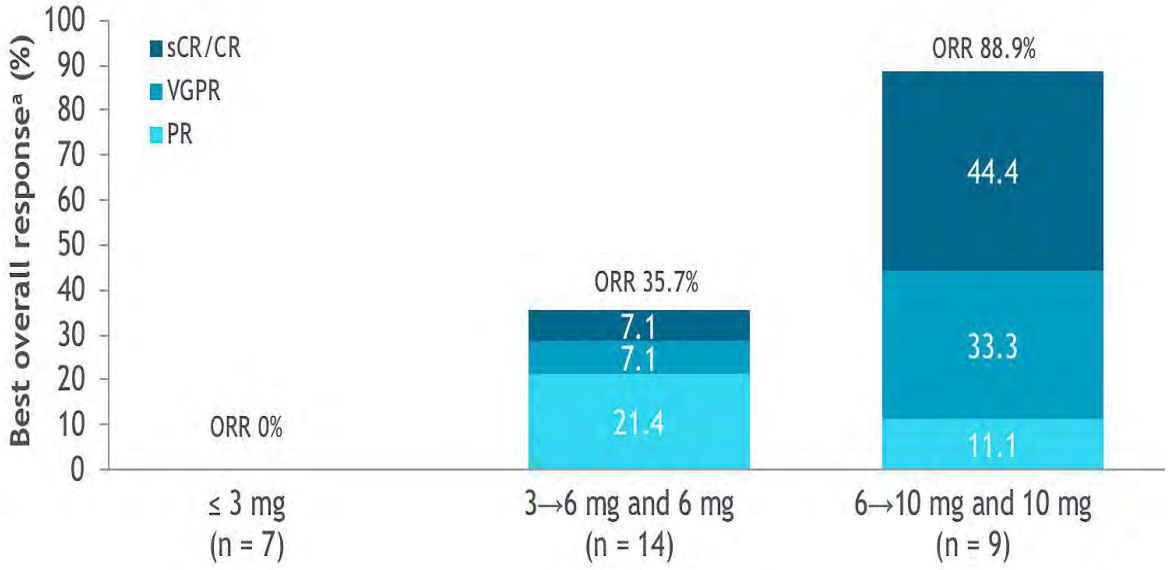
- 66 patients received CC-92480 plus dexamethasone; median 6 (range 2-13) prior therapies. Prior therapies: proteasome inhibitors (100%), lenalidomide (97%), pomalidomide (92%), high-dose melphalan (76%). About 50% were considered triple-class refractory

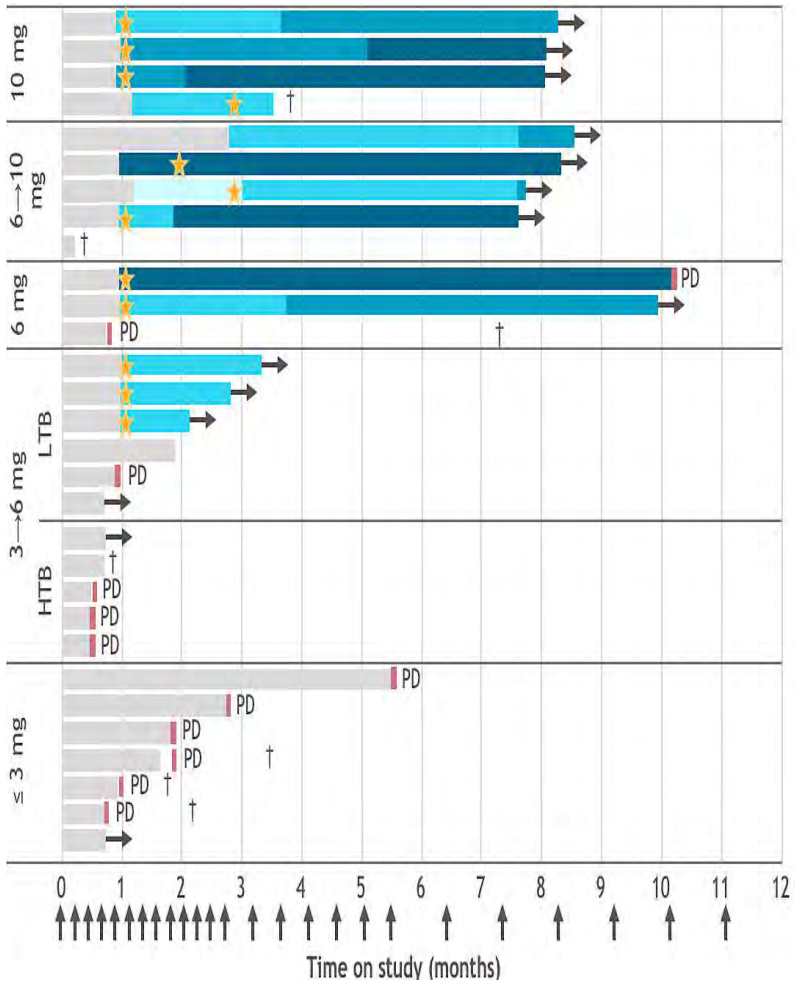
- About 30% of patients remained on CC-92480. Of 51 patients who discontinued treatment, main cause was progressive disease (n=39), withdrawal (n=5), death (n=5), and adverse events (AEs; n=1). No deaths related to CC-92480

Richardson PG, et al. *EHA 2020* (abstract S208)

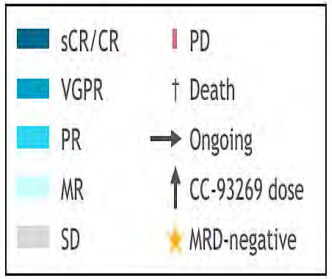
Courtesy of Ola Landgren, MD, PhD

Bi-specific BCMA/CD3 for the treatment of multiple myeloma: CC-93269: efficacy





- Median time to first response was 4.1 weeks (range 4.0-13.1)
- 11 of 13 responses are ongoing
- 5 of 30 (16.7%) patients achieved an MRD-negative sCR/CR
  - 12 of 13 (92.3%) responding patients achieved MRD negativity (≤ $1/10^5$) in the bone marrow on or before C4D1 by Euroflow[a]



In all patients (N=30), 43% ORR and 17% sCR/CR; among patients receiving 10 mg (N=9), 89% ORR and 44% sCR/CR

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Costa L, et al. *EHA 2020* (abstract S205)

Courtesy of Ola Landgren, MD, PhD

Bi-specific BCMA/CD3 for the treatment of multiple myeloma: teclistamab: study design

Key Objectives

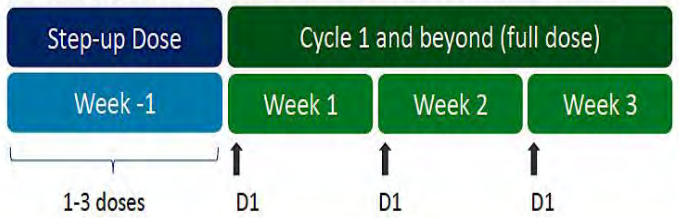
- Part 1: Identify RP2D
- Part 2: Safety and tolerability
- Antitumor activity, PK, PD

Key Eligibility Criteria

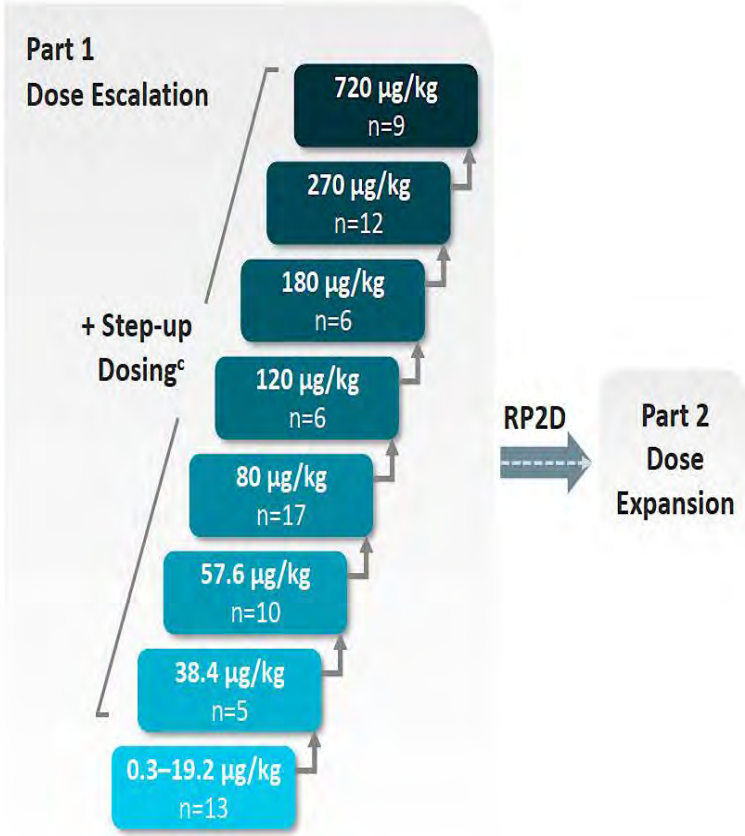
- Measurable MM
- RR or intolerant to established MM therapies
- Hb ≥8 g/dL, platelets[a] ≥75x10^9/L, ANC ≥1.0x10^9/L
- No prior BCMA-targeted therapy

Intravenous Dosing

- Initial Q2W dosing switched to weekly ± step-up dosing
- Pre-medications[b] limited to step-up doses and 1st full dose



- **Results from Part 1 intravenous dose escalation are presented**



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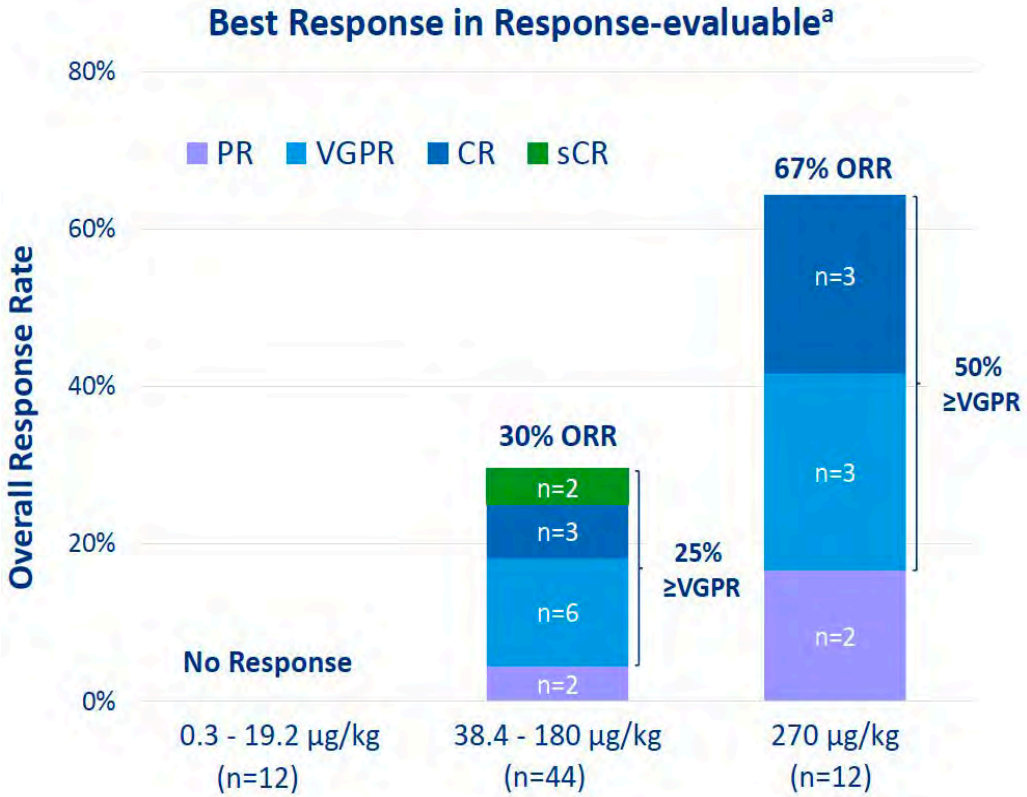
Mateos MV, et al. *EHA 2020* (abstract S206)

Courtesy of Ola Landgren, MD, PhD

Bi-specific BCMA/CD3 for the treatment of multiple myeloma: teclistamab: prior therapies and efficacy

Characteristic	Total (N = 78)
Prior lines of therapy, median (range)	6 (2–14)
Triple-class exposed, n (%)[c]	72 (92)
Penta-drug exposed, n (%)[d]	51 (65)
Refractory status, n (%)	
Carfilzomib	48 (62)
Pomalidomide	56 (72)
Anti-CD38[e]	68 (87)
Triple-class refractory[c]	62 (80)
Penta-drug refractory[d]	32 (41)
Refractory to last line of therapy,[f] n (%)	67 (86)



- At 270 µg/L. 7/8 responders were triple class refractory; 5/8 were penta-refractory.
- 4/5 evaluable patients were MRD neg at 10^{-6}
- 2/2 evaluable patients maintained MRD neg for 5m (VGPR) and 14m (CR)

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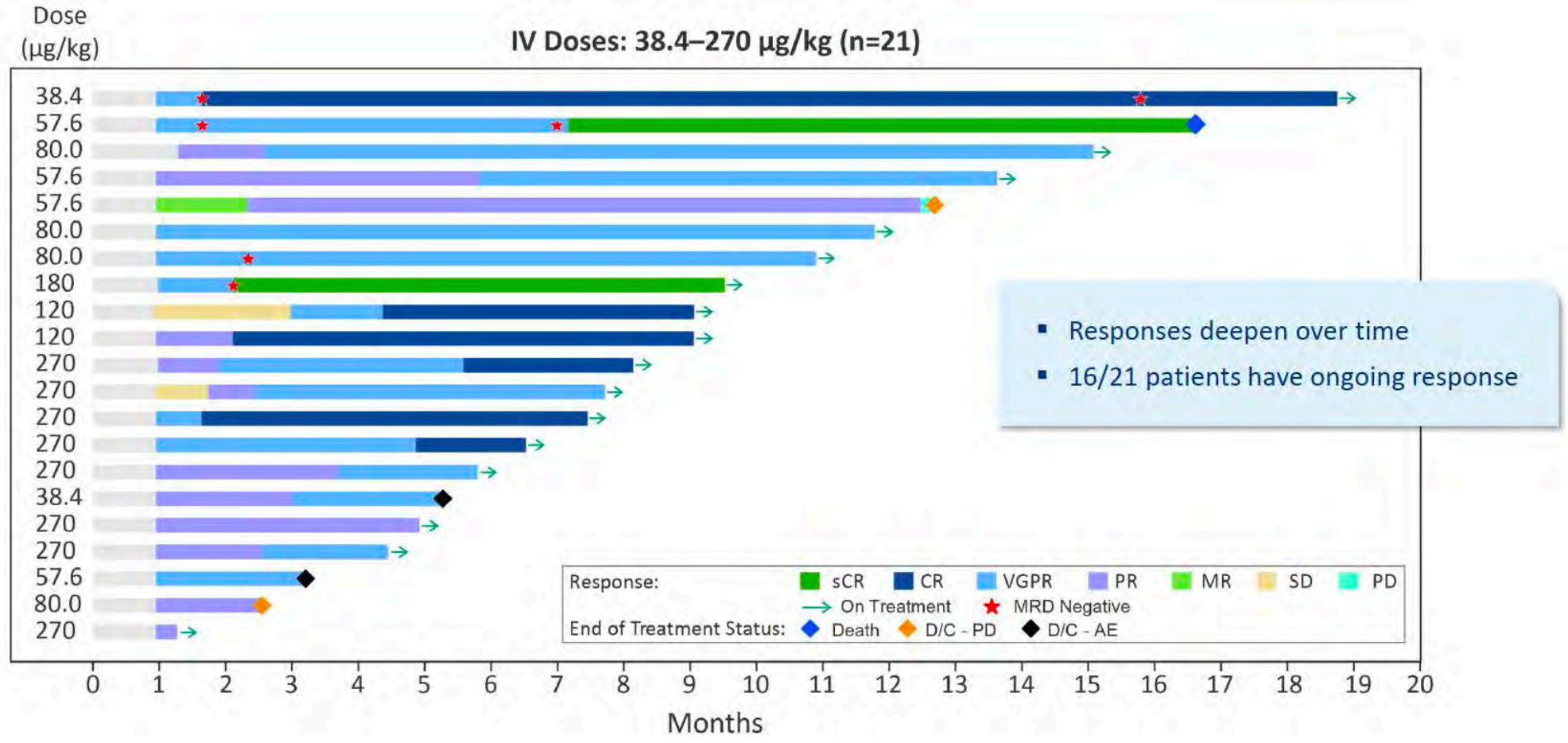
Mateos MV, et al. *EHA 2020* (abstract S206)

Courtesy of Ola Landgren, MD, PhD

Bi-specific BCMA/CD3 for the treatment of multiple myeloma: teclistamab: duration of response



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Mateos MV, et al. *EHA 2020* (abstract S206)

Courtesy of Ola Landgren, MD, PhD

Bispecific antibodies in development for the treatment of multiple myeloma

Target	Agent	Type	Comments	Clinical trials no.*
BCMA	AMG 420 (BI 836909)	BiTE	7 of 10 (70%) ORR in phase 1 expansion at MTD; single-agent phase 1b/2 ongoing	NCT02514239, NCT03836053
BCMA	PF-06863135	Bispecific	Single-agent phase 1	NCT03269136
BCMA	JNJ-64007957	Bispecific	Single-agent phase 1	NCT03145181
BCMA	TNB-383B	Bispecific	Single-agent phase 1	NCT03933735
BCMA	REGN5458	Bispecific	Single-agent phase 1	NCT03761108
BCMA	CC-93269 (EM901)	Bispecific	Single-agent phase 1	NCT03486067
BCMA	AMG 701	Bispecific	Single-agent phase 1	NCT03287908
BCMA	AFM26	Bispecific	CD16 × BCMA, targets NK cells, preclinical	
BCMA	HPN217	Bispecific	Preclinical	
BCMA	EM801	Bispecific	Preclinical	
CD38	AMG 424	Bispecific	Single-agent phase 1	NCT03445663
CD38	GBR 1342	Bispecific	Single-agent phase 1	NCT03309111
FcRH5	BFCR4350A	Bispecific	Single-agent phase 1	NCT03275103
GPRC5D	JNJ-64407564	Bispecific	Single-agent phase 1	NCT03399799

Cohen A. *ASH 2019* (Educational session)

Courtesy of Ola Landgren, MD, PhD

Melflufen: a novel peptide-drug conjugate that rapidly delivers cytotoxic payload into tumor cells

- HORIZON single arm study (N=95), melflufen + low-dose dex in pts refractory to pom and/or daratumumab. Pts must have received ≥2 prior lines. ORR primary endpoint.
  - 30% ORR: 1 pt achieved sCR, 11% VGPR, and 18% PR. Median PFS: 4 months
  - Treatment-related grade 3/4 AEs were reported in 68 pts (72%), most commonly (>20%) neutropenia (55%), thrombocytopenia (52%), and anemia (26%). The most common treatment-related nonhematologic grade 3/4 AE was pneumonia (3%)

Richardson PG, et al. *EHA 2019* (abstract S1605)

Courtesy of Ola Landgren, MD, PhD

Melflufen: a novel peptide-drug conjugate that rapidly delivers cytotoxic payload into tumor cells

- OCEAN, randomized, global, Phase III study evaluating the efficacy and safety of melflufen + dexamethasone *versus* pomalidomide + dexamethasone
  - Eligible patients cannot be primary refractory, they should have received 2-4 prior lines of therapy; patients refractory to both their last line of therapy and lenalidomide within 18 months of randomization

Table 1. OCEAN study dose schedule.

Group	Drug	Dose	Schedule (/28-day cycle)
Arm A	Melflufen	40 mg IV	Day 1
	Dexamethasone	40 mg oral tablets†	Days 1, 8, 15 and 22
Arm B	Pomalidomide	4 mg oral capsule	Days 1–21 (inclusive)
	Dexamethasone	40 mg oral tablets†	Days 1, 8, 15 and 22

†The dexamethasone dose will be reduced to 20 mg for patients aged ≥75 years. In the USA only, oral dexamethasone may be substituted with IV dexamethasone at the investigator's discretion.

IV: Intravenous.

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Schjesvold F, et al. *Future Oncol.* 2020 Apr;16(11):631-641

Courtesy of Ola Landgren, MD, PhD

Are there situations in which you would attempt to use venetoclax outside a trial setting for relapsed/refractory MM?

1. Yes
2. Yes, but only for patients with t(11;14) or high Bcl-2 expression
3. No

Are there situations in which you would attempt to use venetoclax outside a trial setting for relapsed/refractory MM?

 RAFAEL FONSECA, MD	Yes, only in t(11;14) or high Bcl-2
 OLA LANDGREN, MD, PHD	Yes, only in t(11;14) or high Bcl-2
 NIKHIL C MUNSHI, MD	Yes, only in t(11;14) or high Bcl-2
 ROBERT Z ORLOWSKI, MD, PHD	Yes, only in t(11;14) or high Bcl-2
 EDWARD A STADTMAUER, MD	Yes, only in t(11;14) or high Bcl-2
 SAGAR LONIAL, MD	Yes, only t(11;14)
 S VINCENT RAJKUMAR, MD	Yes, only in t(11;14)
 PAUL G RICHARDSON, MD	Yes, only in t(11;14) or high Bcl-2
GENERAL MEDICAL ONCOLOGISTS (N = 75)	Yes, only in t(11;14) or high Bcl-2

Reimbursement and regulatory issues aside, at what point, if any, would you attempt to access venetoclax for a patient with MM and t(11;14)?

 RAFAEL FONSECA, MD	First line	 EDWARD A STADTMAUER, MD	Second line or third line
 OLA LANDGREN, MD, PHD	Beyond third line	 SAGAR LONIAL, MD	Second line
 NIKHIL C MUNSHI, MD	Third line	 S VINCENT RAJKUMAR, MD	Beyond third line
 ROBERT Z ORLOWSKI, MD, PHD	Second line	 PAUL G RICHARDSON, MD	Second line
GENERAL MEDICAL ONCOLOGISTS (N = 75)	Beyond third line, Second line		

A woman in her early 60s with multiple myeloma and t(11;14) who has received multiple prior lines of therapy

- S/p VRd → ASCT → maintenance lenalidomide for NDMM
  - Significant peripheral neuropathy
- Disease recurrence → Daratumumab/pomalidomide → PD
- Carfilzomib/lenalidomide → PD
- BCMA-targeted CAR T-cell therapy, with response duration < 1 year and rapid pace of disease progression
  - BMB: 80% plasma cells; t(11;14)
- Disease debulking with DCEP and steroid
  - BMB: 40% plasma cells
- 2nd cycle of DCEP
  - BMB: 20% plasma cells
- Carfilzomib (20 mg/m^2 → 56 mg/m^2)/dexamethasone
  - Venetoclax added in starting with lowest-dose and increased to 800 mg/m^2
- Currently, 1 year later patient has a complete response

Consensus or Controversy? Investigators Discuss Clinical Practice Patterns and Available Research Data Guiding the Management of Hematologic Cancers

Chronic Lymphocytic Leukemia

Friday, December 4, 2020
12:00 PM – 1:30 PM Pacific Time

Faculty

Paul M Barr, MD
Matthew S Davids, MD, MMSc
Kerry Rogers, MD
Tanya Siddiqi, MD
Professor Dr Stephan Stilgenbauer

Moderator

Neil Love, MD

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Thank you for joining us!

CME credit information will be emailed to each participant within 3 business days.

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