Year in Review 2020
Multiple Myeloma

Rafael Fonseca, MD
Getz Family Professor of Cancer
Director for Innovation and Transformational Relationships
Interim Executive Director of the Mayo Clinic Comprehensive Cancer Center
Chair, Department of Internal Medicine
Distinguished Mayo Investigator
Mayo Clinic in Arizona
Phoenix, Arizona

RTP Year in Review 2020

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)

Courtesy of Rafael Fonseca, MD

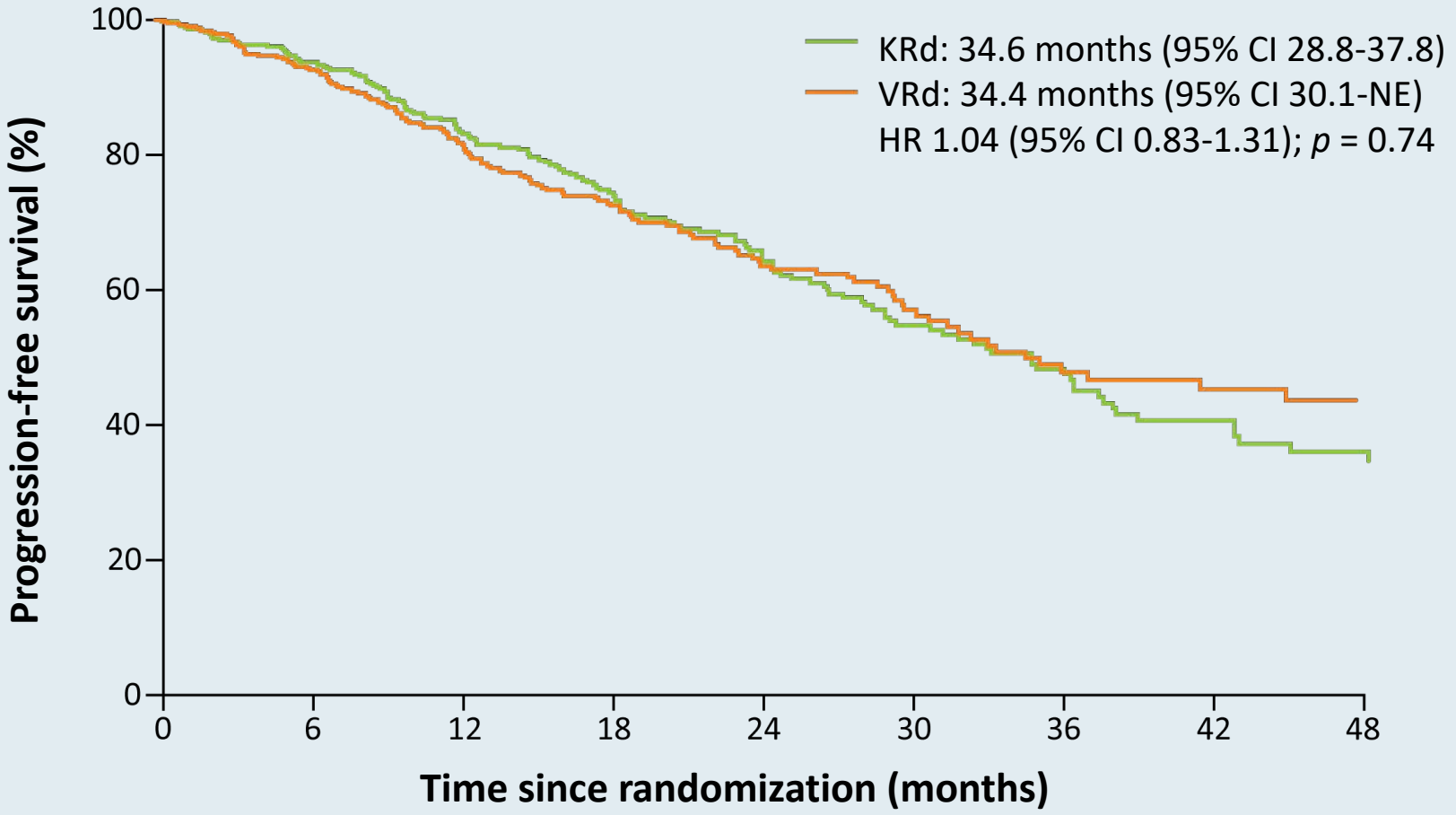
Carfilzomib or bortezomib in combination with lenalidomide and dexamethasone for patients with newly diagnosed multiple myeloma without intention for immediate autologous stem-cell transplantation (ENDURANCE): a multicentre, open-label, phase 3, randomised, controlled trial

Shaji K Kumar, Susanna J Jacobus, Adam D Cohen, Matthias Weiss, Natalie Callander, Avina K Singh, Terri L Parker, Alexander Menter, Xuezhong Yang, Benjamin Parsons, Pankaj Kumar, Prashant Kapoor, Aaron Rosenberg, Jeffrey A Zonder, Edward Faber Jr, Sagar Lonial, Kenneth C Anderson, Paul G Richardson, Robert Z Orlowski, Lynne I Wagner, S Vincent Rajkumar

***Lancet Oncol* 2020;21(10):1317-30.**

Courtesy of Rafael Fonseca, MD

ENDURANCE (E1A11): Primary PFS Endpoint (Second Interim Analysis)

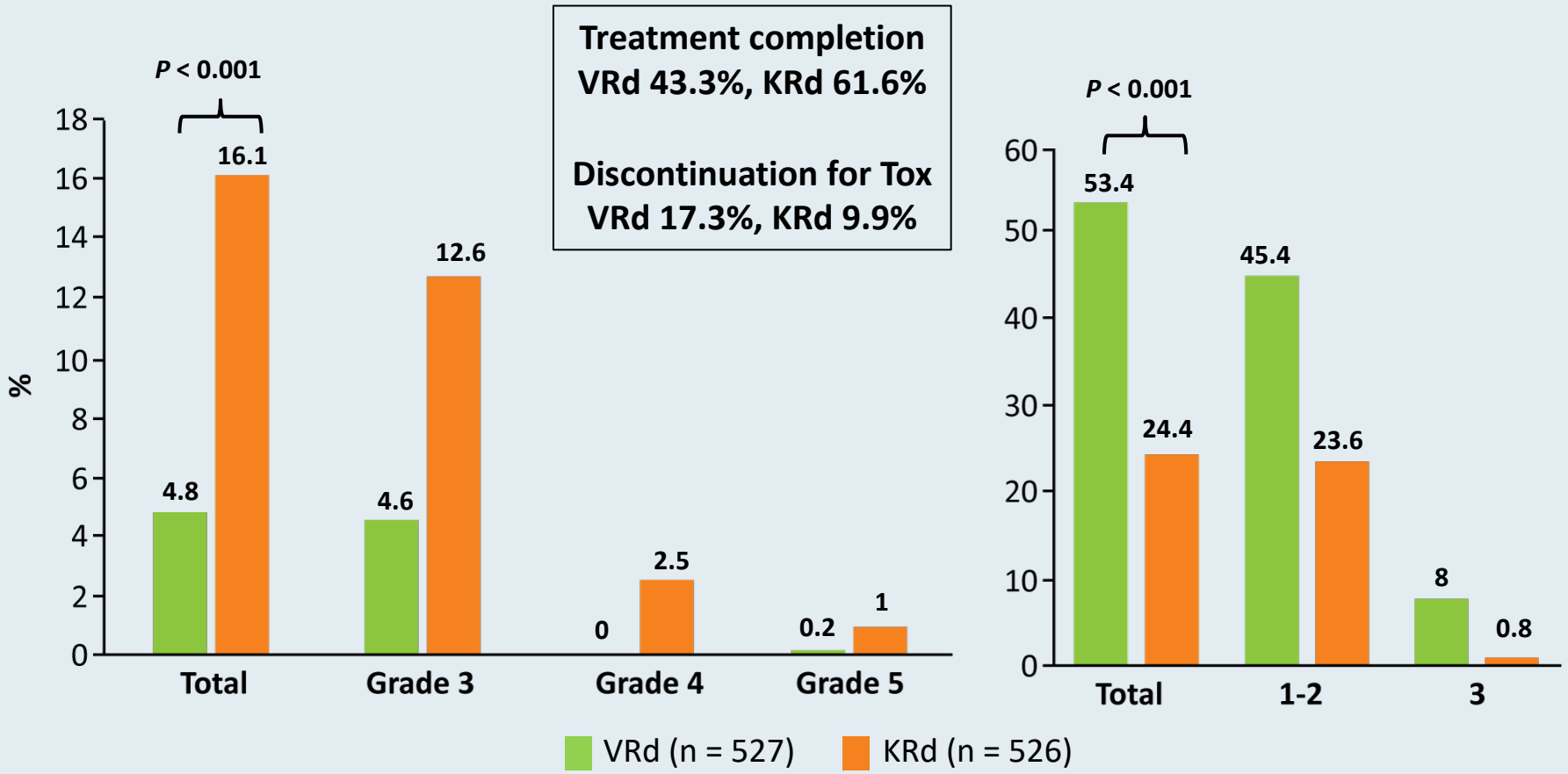


- Median OS has not been reached in either group at median follow-up of 24 months; patients will continue on long-term follow-up for overall survival

Kumar SK et al. *Lancet Oncol* 2020;21(10):1317-30.

Courtesy of Rafael Fonseca, MD

ENDURANCE (E1A11): Treatment-Emergent Adverse Events of Interest



Cardiac, pulmonary and renal

Peripheral neuropathy*

* Grades 1-2 not required reporting

Berdeja JG. ASCO 2020 Discussant.

Courtesy of Rafael Fonseca, MD

1.1 – Kumar SK et al. Carfilzomib or bortezomib in combination with lenalidomide and dexamethasone for patients with newly diagnosed multiple myeloma without intention for immediate autologous stem-cell transplantation (ENDURANCE): a multicentre, open-label, phase 3, randomised, controlled trial. Lancet Oncol. 2020 Oct;21(10):1317-1330.
Kumar S et al. 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. ASCO 2020; Abstract: LBA3. Plenary

- Impact on Patient Care and Treatment Algorithms
  - Since the primary endpoint was not met, VRd can remain a standard of care for frontline therapy of myeloma, but it is also appropriate to use KRd.
  - When using one of the two regimens one should be mindful of the trade offs in toxicity.
  - It is impossible to conclude which of the 2 regimens is better for different patient populations.
- Implications for Future Research
  - Future clinical trials looking at four drug combinations will need to address whether there is any difference in the outcomes between bortezomib and carfilzomib.
  - Predictors of drug toxicities are clearly needed.

Courtesy of Rafael Fonseca, MD

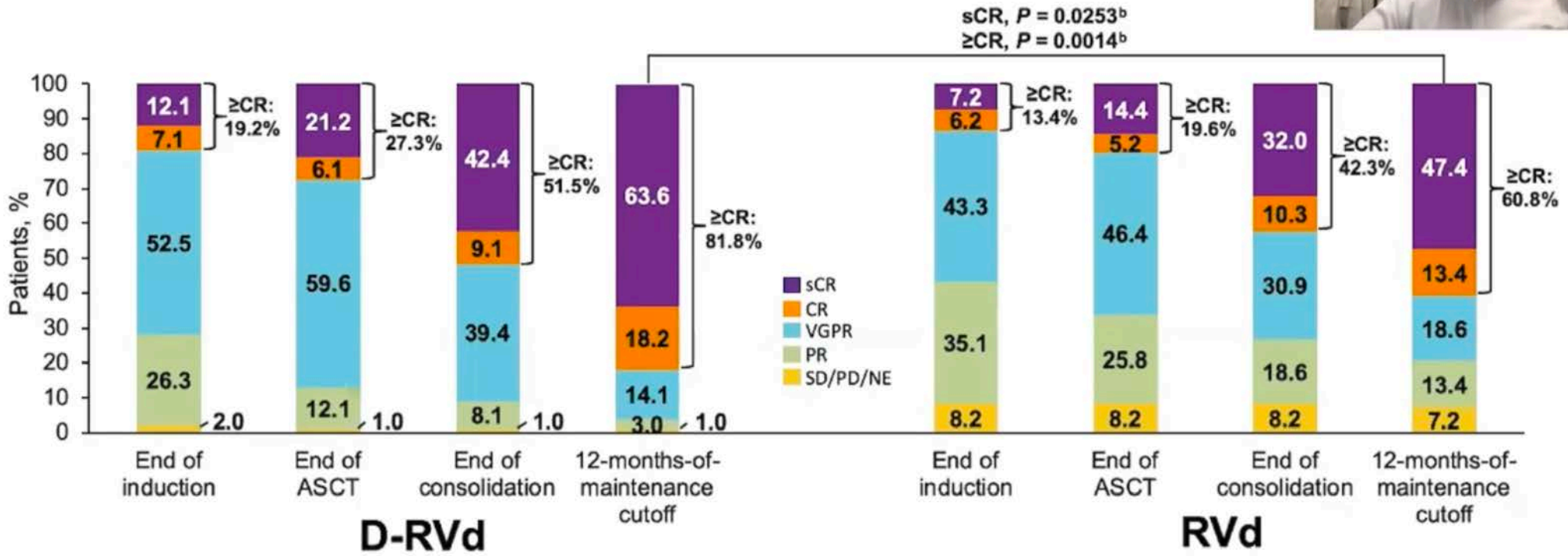
Daratumumab (DARA) plus Lenalidomide, Bortezomib, and Dexamethasone (RVd) in Patients with Transplant-Eligible Newly Diagnosed Multiple Myeloma (NDMM): Updated Analysis of Griffin after 12 Months of Maintenance Therapy

Kaufman JL et al.

ASH 2020;Abstract 549.

Courtesy of Rafael Fonseca, MD

Responses Deepened over Time[a]



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

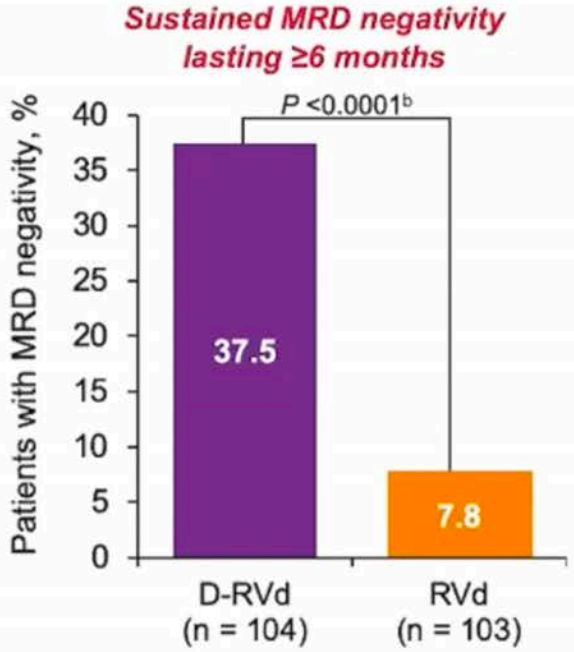
Response rates and depths were greater for D-RVd at all time points

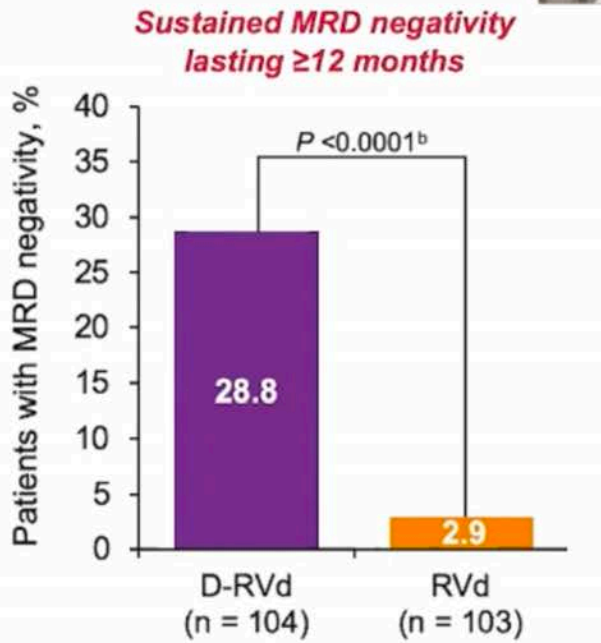
PR, partial response. SD/PD/NE, stable disease/progressive disease/not evaluable. [a]Data are shown for the response-evaluable population. [b]*P* values (2-sided) were calculated using the Cochran–Mantel–Haenszel chi-square test.

Kaufman JL et al. ASH 2020;Abstract 549.

Courtesy of Rafael Fonseca, MD

Durable MRD (10^{-5}) Negativity[a] Lasting ≥6 and ≥12 Months





- *Among patients who achieved MRD negative (10^{-5}) status, sustained MRD negativity lasting ≥12 months was noted in 30/65 (46.2%) and 3/28 (10.7%) patients*

D-RVd improved rates of sustained MRD negativity versus RVd

[a]The threshold of MRD negativity was defined as 1 tumor cell per 10^5 white cells. MRD status is based on the assessment of bone marrow aspirates by NGS in accordance with International Myeloma Working Group criteria. Median follow-up was 27.4 months, and MRD-negativity rates are among the ITT population. [b]*P* values were calculated using the Fisher's exact test.

Kaufman JL et al. ASH 2020;Abstract 549.

Courtesy of Rafael Fonseca, MD

Most Common Infections with First Onset during Maintenance Therapy (Cycles 7+)[a]

Patients, n (%)	D-RVd (D-R maintenance, n = 89)		RVd (R maintenance, n = 71)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Most common (>5%) infections				
Upper respiratory tract infection	47 (53)	4 (4)	29 (41)	2 (3)
Pneumonia	12 (13)	5 (6)	11 (15)	9 (13)
Sinusitis	9 (10)	0	7 (10)	0
Influenza	9 (10)	0	5 (7)	0
Nasopharyngitis	9 (10)	0	1 (1)	0
Urinary tract infection	8 (9)	0	1 (1)	0
Bronchitis	7 (8)	1 (1)	5 (7)	1 (1)
Cellulitis	7 (8)	1 (1)	2 (3)	1 (1)

Similar rates of any grade and grade 3/4 infections occurred for D-RVd vs RVd

[a]Any grade TEAEs that occurred in >5% of patients in either group are listed. The safety analysis population included all randomized patients who received ≥1 dose of the study treatment; analysis was according to treatment received.

Kaufman JL et al. ASH 2020;Abstract 549.

Courtesy of Rafael Fonseca, MD

Most Common Infections with First Onset during Maintenance Therapy (Cycles 7+)[a]

Patients, n (%)	D-RVd (D-R maintenance, n = 89)		RVd (R maintenance, n = 71)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Most common (>5%) infections				
Upper respiratory tract infection	47 (53)	4 (4)	29 (41)	2 (3)
Pneumonia	12 (13)	5 (6)	11 (15)	9 (13)
Sinusitis	9 (10)	0	7 (10)	0
Influenza	9 (10)	0	5 (7)	0
Nasopharyngitis	9 (10)	0	1 (1)	0
Urinary tract infection	8 (9)	0	1 (1)	0
Bronchitis	7 (8)	1 (1)	5 (7)	1 (1)
Cellulitis	7 (8)	1 (1)	2 (3)	1 (1)

Similar rates of any grade and grade 3/4 infections occurred for D-RVd vs RVd

[a]Any grade TEAEs that occurred in >5% of patients in either group are listed. The safety analysis population included all randomized patients who received ≥1 dose of the study treatment; analysis was according to treatment received.

Kaufman JL et al. ASH 2020;Abstract 549.

Courtesy of Rafael Fonseca, MD

blood

Regular Article

Blood 2020;136(8):936-45.

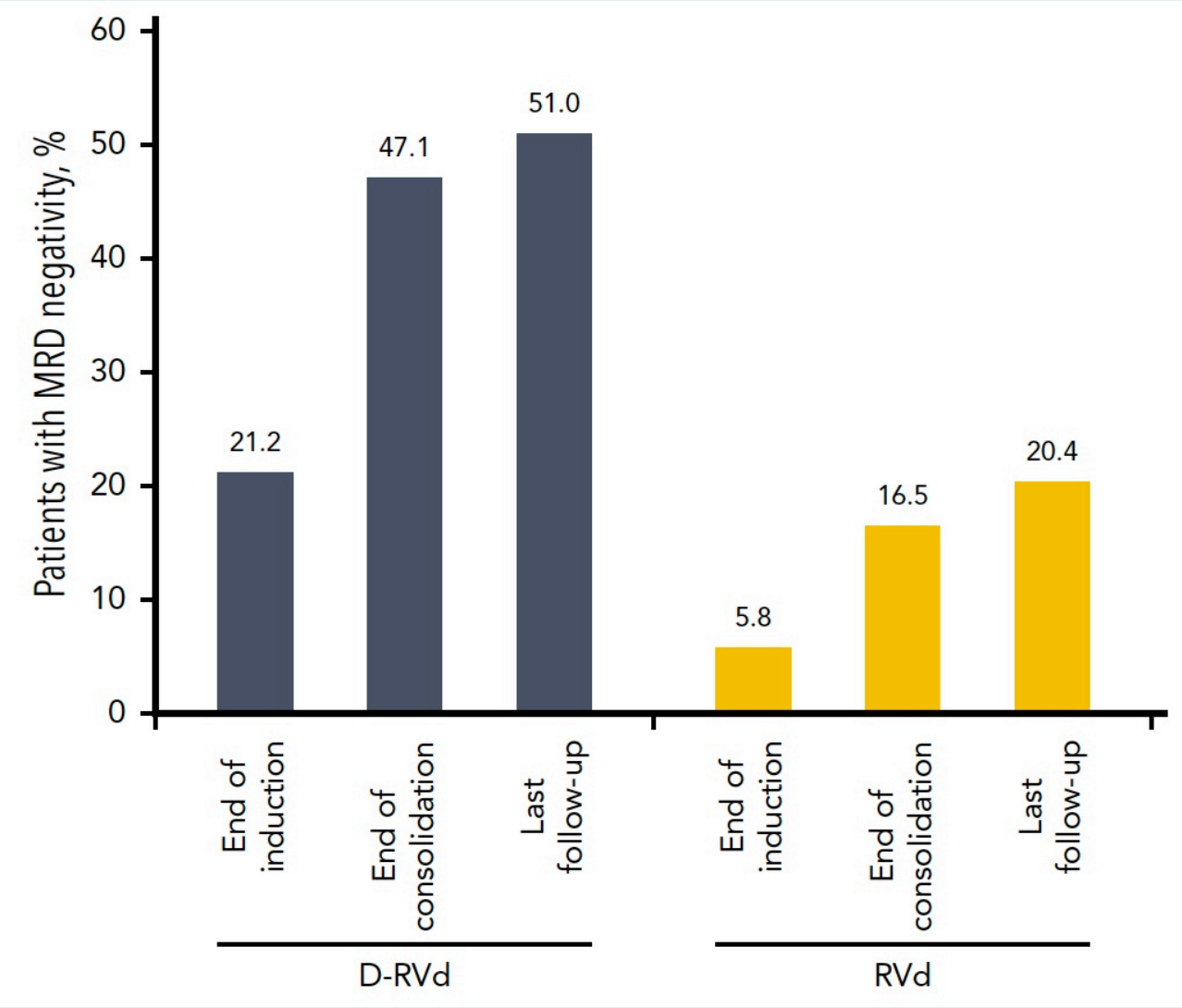
CLINICAL TRIALS AND OBSERVATIONS

Daratumumab, lenalidomide, bortezomib, and dexamethasone for transplant-eligible newly diagnosed multiple myeloma: the GRIFFIN trial

Peter M. Voorhees,[1] Jonathan L. Kaufman,[2] Jacob Laubach,[3] Douglas W. Sborov,[4] Brandi Reeves,[5] Cesar Rodriguez,[6] Ajai Chari,[7] Rebecca Silbermann,[8] Luciano J. Costa,[9] Larry D. Anderson Jr,[10] Nitya Nathwani,[11] Nina Shah,[12] Yvonne A. Efebera,[13] Sarah A. Holstein,[14] Caitlin Costello,[15] Andrzej Jakubowiak,[16] Tanya M. Wildes,[17] Robert Z. Orlowski,[18] Kenneth H. Shain,[19] Andrew J. Cowan,[20] Sean Murphy,[21] Yana Lutska,[21] Huiling Pei,[22] Jon Ukropec,[23] Jessica Vermeulen,[24] Carla de Boer,[24] Daniela Hoehn,[21] Thomas S. Lin,[21] and Paul G. Richardson,[3] for the GRIFFIN Trial Investigators

Courtesy of Rafael Fonseca, MD

Summary of Response Rates and MRD Negativity (10^{-5}) Rates Over Time



- MRD negativity (10^{-5}) rates in the intent-to-treat population by the end of induction therapy, end of consolidation and last follow-up
- All MRD data are from the analysis with a median follow-up of 22.1 months
- MRD was evaluated at baseline, first evidence of suspected CR or sCR, at the end of induction and consolidation, and after 12 and 24 months of maintenance, regardless of response (per protocol amendment 2)

Voorhees PM et al. *Blood* 2020 Aug 20;136(8):936-45.

Courtesy of Rafael Fonseca, MD

1.2 – Kaufman JL et al. Daratumumab (DARA) Plus Lenalidomide, Bortezomib, and Dexamethasone (RVd) in Patients with Transplant-Eligible Newly Diagnosed Multiple Myeloma (NDMM): Updated Analysis of Griffin after 12 Months of Maintenance Therapy. ASH 2020;Abstract 549. Voorhees PM et al. Daratumumab, lenalidomide, bortezomib, and dexamethasone for transplant-eligible newly diagnosed multiple myeloma: the GRIFFIN trial. Blood. 2020 Aug 20;136(8):936-945.

- Impact on Patient Care and Treatment Algorithms
  - Four drug combinations have a superior response rate compared to triplets.
  - Dara-VRD is a safe regimen for the frontline treatment of myeloma.
  - The level of MRD negativity is unprecedented.
  - There should be no further use of cyclophosphamide if lenalidomide is available.

- Implications for Future Research
  - It will be important to know whether carfilzomib should replace bortezomib in four drug combinations.
  - It will be important to know if four drug combinations will lead to treatments that can omit stem cell transplant.

Courtesy of Rafael Fonseca, MD

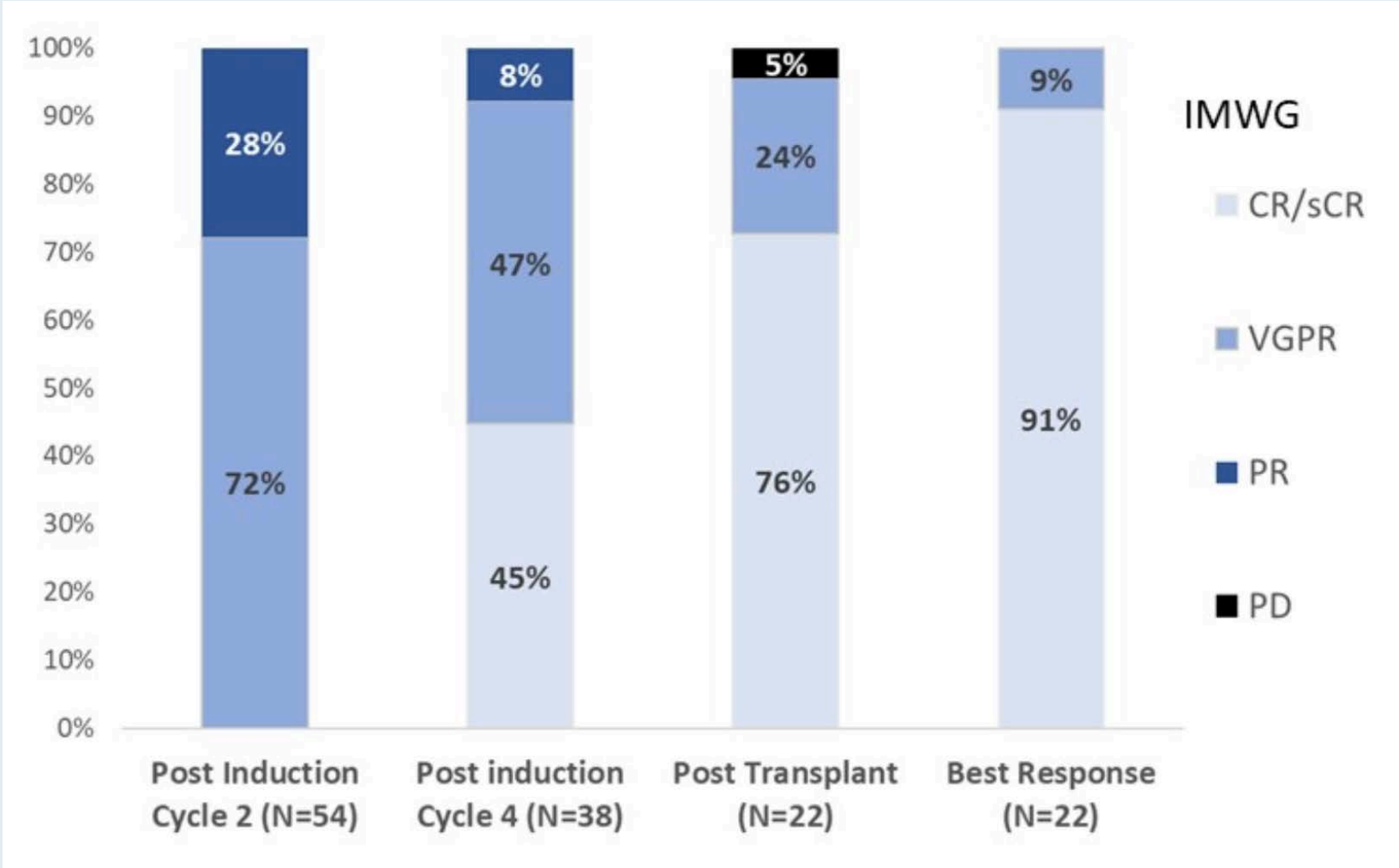
Daratumumab, Carfilzomib, Lenalidomide and Dexamethasone (Dara-KRd) Induction, Autologous Transplantation and Post-Transplant, Response-Adapted, Measurable Residual Disease (MRD)-Based Dara-KRd Consolidation in Patients with Newly Diagnosed Multiple Myeloma (NDMM)

Costa LJ et al.

ASH 2019;Abstract 860.

Courtesy of Rafael Fonseca, MD

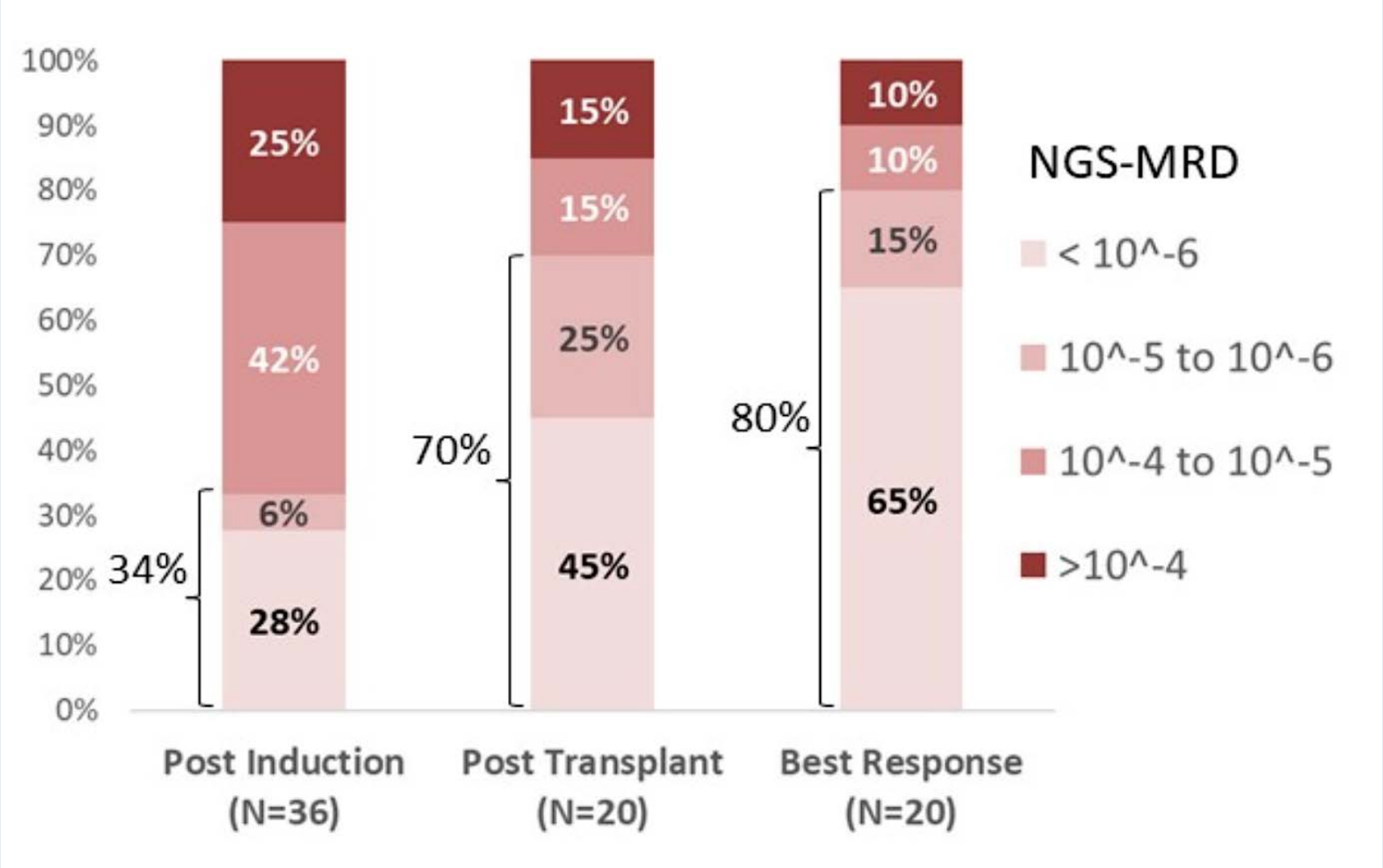
Responses Over Time



Costa LJ et al. *ASH* 2019;Abstract 860.

Courtesy of Rafael Fonseca, MD

MRD-Negative Remissions



Costa LJ et al. *ASH* 2019;Abstract 860.

Courtesy of Rafael Fonseca, MD

1.3 – Costa LJ *et al; MASTER trial investigators.* Daratumumab, carfilzomib, lenalidomide and dexamethasone (Dara-KRd) induction, autologous transplantation and post-transplant, response-adapted, measurable residual disease (MRD)-based Dara-KRd consolidation in patients with newly diagnosed multiple myeloma (NDMM). ASH 2019; Abstract 860.

- Impact on Patient Care and Treatment Algorithms
  - When this combination becomes approved this will be one of the options for frontline treatment of multiple myeloma.
  - The level of response and MRD negativity is the highest reported so far.
  - Adapting therapy based on the level of the response is an interesting approach for selected patients.
- Implications for Future Research
  - The future of myeloma induction is with 4 drugs. Will it include other agents such as bispecific antibodies?
  - The long-term outcomes need to be reported to understand the implications of MRD.
  - Future clinical trials should test whether stem cell transplant can be omitted.

Courtesy of Rafael Fonseca, MD

Articles

Lancet 2020;395(10218):132-41.

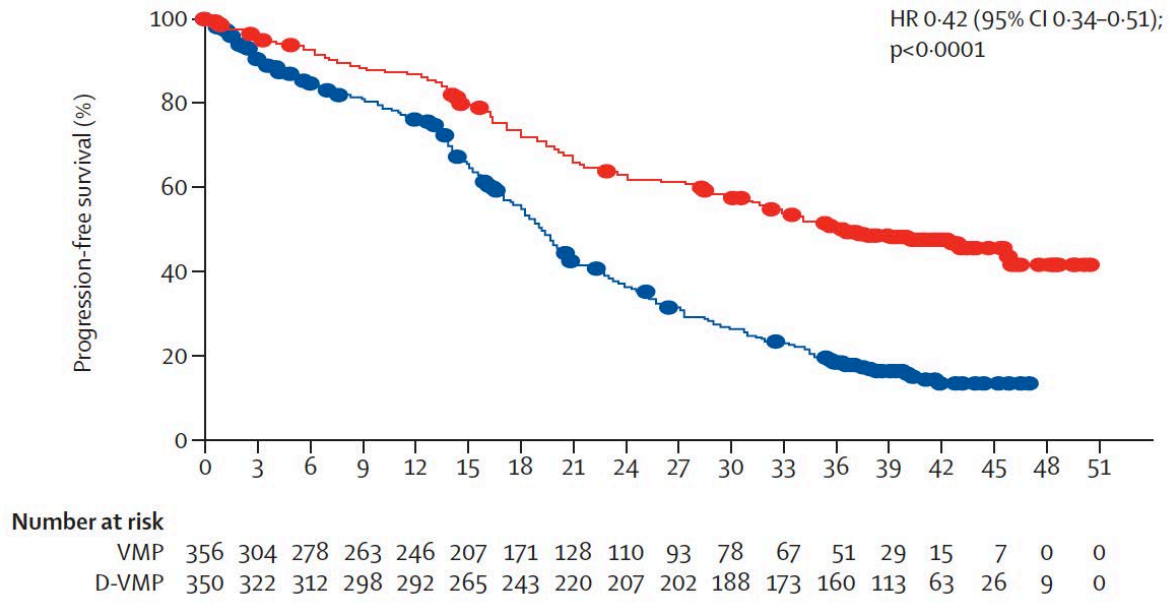
Overall survival with daratumumab, bortezomib, melphalan, and prednisone in newly diagnosed multiple myeloma (ALCYONE): a randomised, open-label, phase 3 trial

Maria-Victoria Mateos, Michele Cavo, Joan Blade, Meletios A Dimopoulos, Kenshi Suzuki, Andrzej Jakubowiak, Stefan Knop, Chantal Doyen, Paulo Lucio, Zsolt Nagy, Ludek Pour, Mark Cook, Sebastian Grosicki, Andre Crepaldi, Anna Marina Liberati, Philip Campbell, Tatiana Shelekhova, Sung-Soo Yoon, Genadi Iosava, Tomoaki Fujisaki, Mamta Garg, Maria Krevvata, Ying Chen, Jianping Wang, Anupa Kudva, Jon Ukropec, Susan Wroblewski, Ming Qi, Rachel Kobos, Jesus San-Miguel

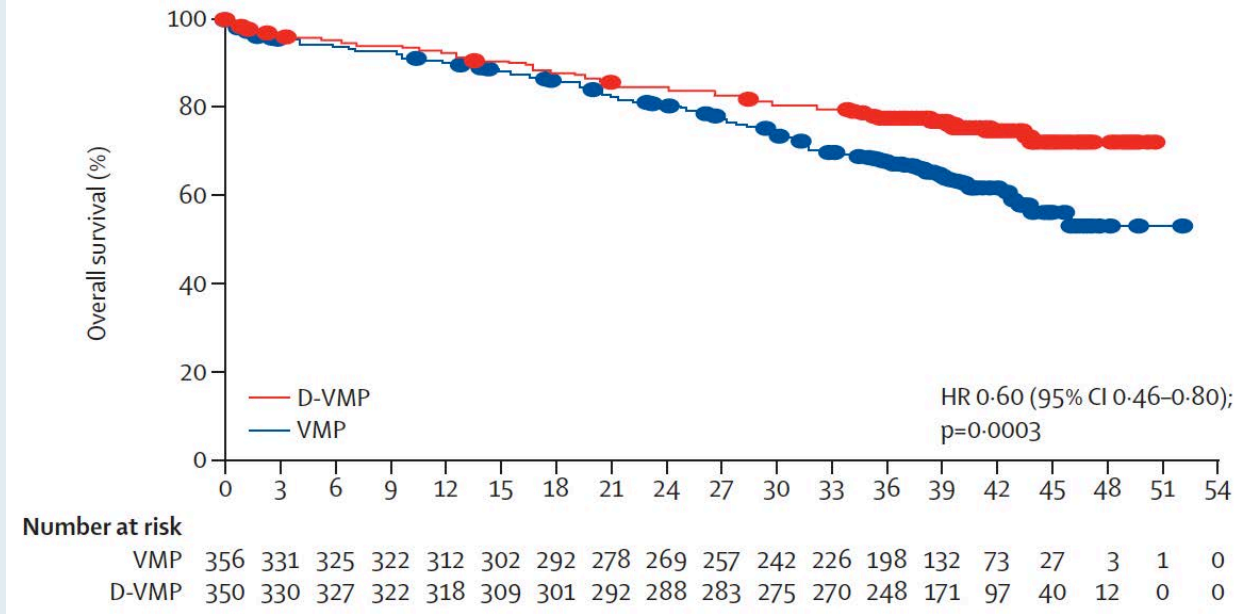
Courtesy of Rafael Fonseca, MD

ALCYONE: PFS and OS Analyses (Median Follow-up 40.1 months)

PFS



Interim OS Analysis



Mateos MV et al. *Lancet* 2020;395(10218):132-41.

Courtesy of Rafael Fonseca, MD

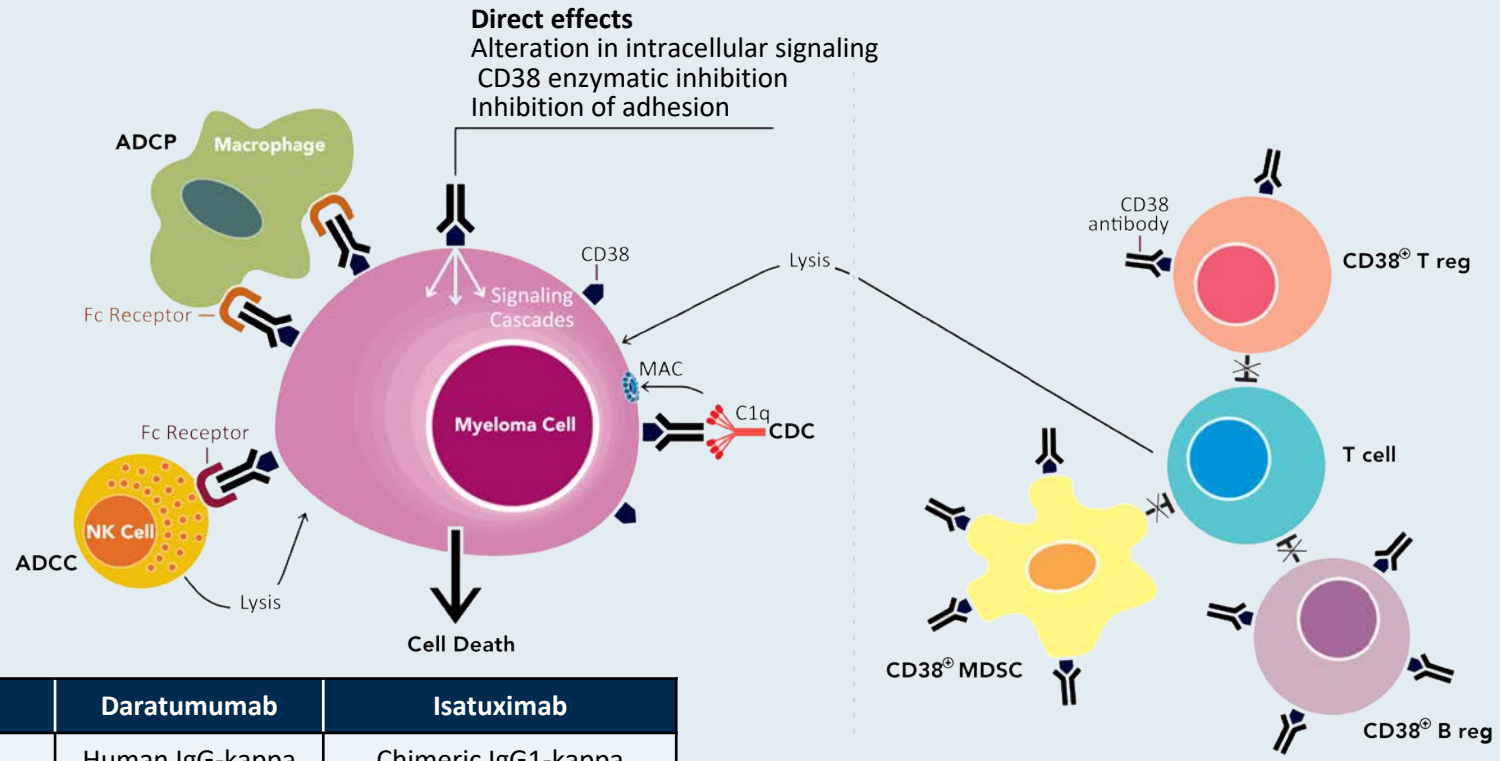
1.4 – Mateos MV et al. Overall survival with daratumumab, bortezomib, melphalan, and prednisone in newly diagnosed multiple myeloma (ALCYONE): a randomised, open-label, phase 3 trial. Lancet. 2020 Jan 11;395(10218):132-141.

- Impact on Patient Care and Treatment Algorithms
  - While this regimen will not be used much in the United States it provides excellent outcomes from a global perspective.
  - The outcomes reported are almost as good as what is reported with MAIA.
  - These outcomes can be achieved without an IMID.
- Implications for Future Research
  - This combination needs to be explored in the setting of renal failure.
  - This combination needs to be explored in patients who cannot tolerate an IMID.
  - This combination is likely to be tested by pharmaco-economists given its affordability

Courtesy of Rafael Fonseca, MD

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.

Courtesy of Rafael Fonseca, MD

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.

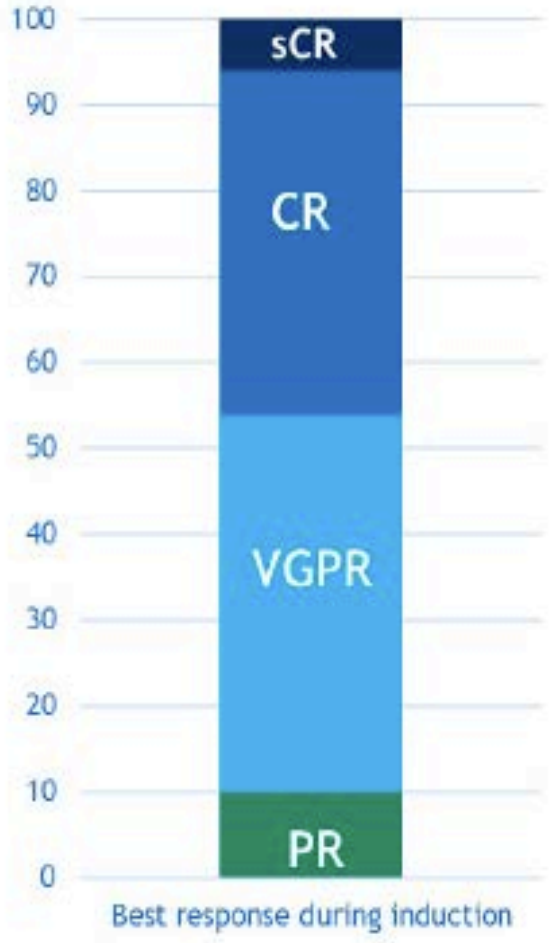
ASCO 2020;Abstract 8508.

Courtesy of Rafael Fonseca, MD

GMMG-CONCEPT: Best response to therapy, 6 induction cycles

All evaluable patients: n = 50

- Overall response rate (ORR, ≥ PR): 100%
- ≥ VGPR : 90%; CR/sCR: 46%
  - Arm A: 41/46 ≥ VGPR
  - Arm B: all (n = 4) VGPR
- Arm A: MRD-assessment in 33 patients during induction
  - 20 patients MRD negative
  - 11 patients MRD positive
  - 2 not assessable



Weisel K et al. ASCO 2020;Abstract 8508.

Courtesy of Rafael Fonseca, MD

1.6 – Weisel K et al. 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. ASCO 2020; Abstract 8508. Oral, HoD

- Impact on Patient Care and Treatment Algorithms
  - These are very interesting results with long duration of disease control in this patient population.
  - High-risk patients should continue to receive proteasome inhibitors.
  - Isatuximab is an appropriate monoclonal antibody for the treatment of these patients.
- Implications for Future Research
  - Will it be better to start with carfilzomib or with an IMID in the relapsed and refractory setting?
  - If carfilzomib is better, does the subcutaneous route of daratumumab matter as much?

Courtesy of Rafael Fonseca, MD

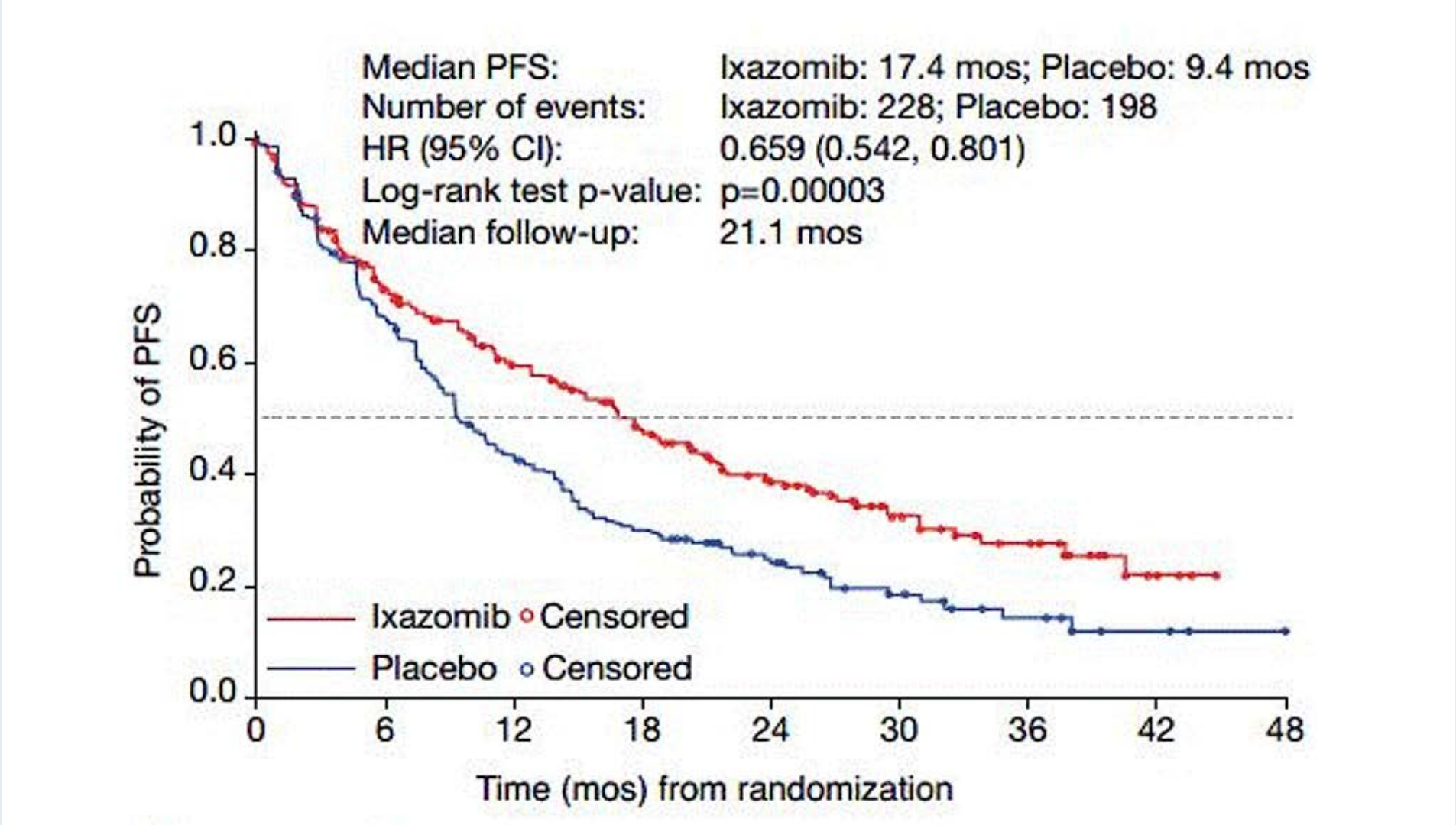
Ixazomib vs Placebo as Post-Induction Maintenance Therapy in Newly Diagnosed Multiple Myeloma (NDMM) Patients (pts) Not Undergoing Autologous Stem Cell Transplant (ASCT): Phase 3 TOURMALINE-MM4 Trial

Dimopoulos M et al.

EHA 2020;Abstract S200.

Courtesy of Rafael Fonseca, MD

TOURMALINE-MM4: Progression Free Survival



Dimopoulos M et al. EHA 2020;Abstract S200.

Courtesy of Rafael Fonseca, MD

2.1 – Dimopoulos M et al. Ixazomib vs placebo as post-induction maintenance therapy in newly diagnosed multiple myeloma (NDMM) patients (pts) not undergoing autologous stem cell transplant (ASCT): Phase 3 TOURMALINE-MM4 trial. EHA 2020; Abstract S200. Oral

- Impact on Patient Care and Treatment Algorithms
  - Ixazomib is a new option for maintenance treatment of elderly patients.
  - While the drug does not have this same durability of response as lenalidomide it may be helpful in selected subsets.
  - Maintenance is better than no maintenance.
- Implications for Future Research
  - Additional studies of maintenance with oral medications are needed, in particular ixazomib in combination with lenalidomide.

Courtesy of Rafael Fonseca, MD

Subcutaneous Daratumumab + Cyclophosphamide, Bortezomib, and Dexamethasone (CyBorD) in Patients with Newly Diagnosed Light Chain (AL) Amyloidosis: Primary Results from the Phase 3 ANDROMEDA Study

Kastritis E et al.

EHA 2020;Abstract LBA2604.

Courtesy of Rafael Fonseca, MD

ANDROMEDA: Efficacy summary of daratumumab + CyBorD versus CyBorD for AL amyloidosis

Efficacy	Daratumumab + CyBorD (n = 195)	CyBorD (n =193)	Hazard or odds ratio	*p*-value
Overall Hematologic Response	92%	77%	NR	NR
CR	53%	18%	5.10	<0.0001
≥VGPR	79%	49%	NR	NR

"The addition of DARA to CyBorD was superior to CyBorD alone, resulting in deeper and more rapid hematologic responses and improved clinical outcomes with an acceptable safety profile. DARA-CyBorD therapy resulted in improved MOD-PFS and substantially higher organ responses in newly diagnosed AL amyloidosis pts."

Kastritis E et al. EHA 2020. Abstract LBA2604.

Courtesy of Rafael Fonseca, MD

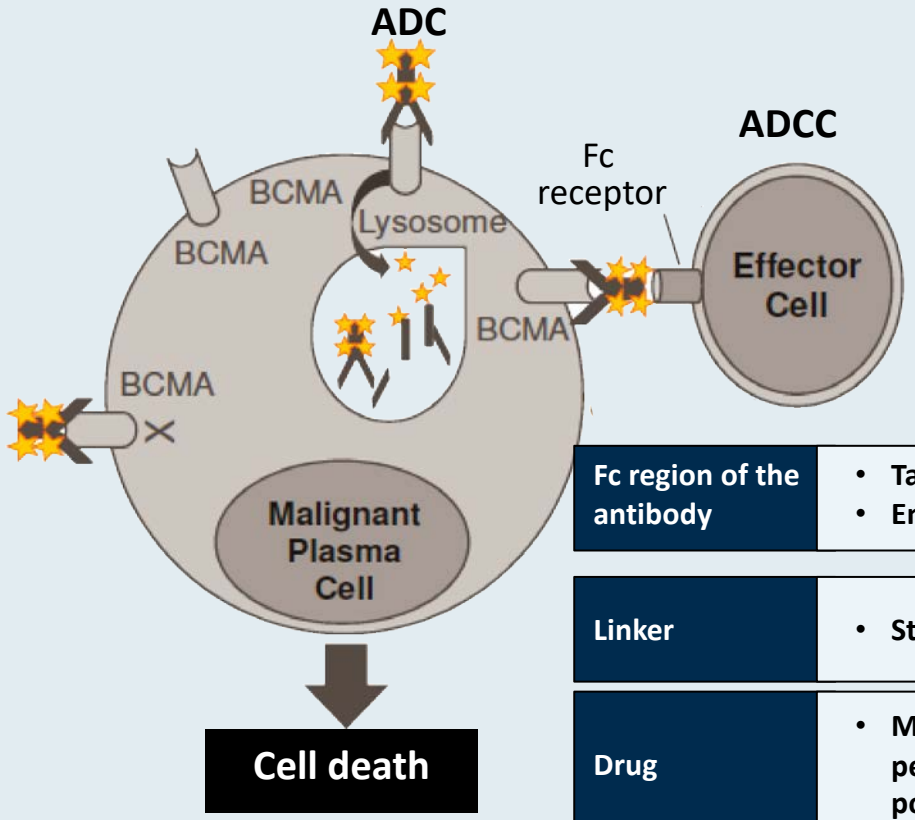
1.5 – Kastritis E et al. Subcutaneous daratumumab + cyclophosphamide, bortezomib, and dexamethasone (CyBorD) in patients with newly diagnosed light chain (AL) amyloidosis: Primary results from the phase 3 ANDROMEDA study. EHA 2020; Abstract LB2604. Late Breaking

- Impact on Patient Care and Treatment Algorithms
  - The combination results in the highest level of response reported so far for AL amyloidosis.
  - The combination is well tolerated and leads to a high rate of complete response.
  - This is the new standard of care for patients not transplanted.
- Implications for Future Research
  - Can this replace stem cell transplant?
  - Is there value in stem cell transplant for patients who achieve a CR?
  - Can venetoclax replace cyclophosphamide in patients with t(11;14)?

Courtesy of Rafael Fonseca, MD

Belantamab Mafodotin: Anti-BCMA Antibody-Drug Conjugate

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



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

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

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

Courtesy of Rafael Fonseca, MD

DREAMM-2: Single-Agent Belantamab Mafodotin (Belamaf) in Patients with Relapsed/Refractory Multiple Myeloma (RRMM) – 1-Year Outcomes By Prior Therapies

Lonial S et al.

ASH 2020;Abstract 1417.

Courtesy of Rafael Fonseca, MD

DREAMM-2: Efficacy Outcomes

	Patients with 3-6 prior therapies (n = 47)	Patients with ≥7 prior therapies (n = 50)
ORR, % (97.5% CI)	34 (19.3-51.4)	30 (16.5-46.6)
Median DoR (95% CI estimates), months	11.0 (4.2-NR)	13.1 (4.0-NR)
Probability of DoR ≥6 months, % (95% CI estimates)	63 (31-83)	73 (44-89)
Median PFS (95% CI estimates), months	2.9 (1.5-5.7)	2.2 (1.2-3.6)
Probability of PFS at 6 months, % (95% CI estimates)	35 (20-50)	30 (17-43)

CI = confidence interval; DoR = duration of response; NR = not reached; ORR = overall response rate; PFS = progression-free survival

Lonial S et al. ASH 2020;Abstract 1417.

Courtesy of Rafael Fonseca, MD

3.1 – Lonial S et al. DREAMM-2: Single-Agent Belantamab Mafodotin (Belamaf) in Patients With Relapsed/Refractory Multiple Myeloma (RRMM) – 1-Year Outcomes by Prior Therapies. ASH 2020;Abstract 1417.

- Impact on Patient Care and Treatment Algorithms
  - Belantamab is an effective agent capable of inducing responses in patients with relapsed and refractory multiple myeloma.
  - It has single agent activity.
  - Careful monitoring of the ocular toxicity is imperative.
- Implications for Future Research
  - Combinatorial approaches need to be urgently studied in the setting.
  - At which line of therapy to use belantamab remains an open question but likely will start at the 2nd or 3rd relapse?

Courtesy of Rafael Fonseca, MD

DREAMM-6: Safety, Tolerability, and Clinical Activity of Belantamab Mafodotin (Belamaf) in Combination with Bortezomib/Dexamethasone (BorDex) in Relapsed/Refractory Multiple Myeloma (RRMM)

Popat R et al.

ASH 2020;Abstract 1419.

Courtesy of Rafael Fonseca, MD

DREAMM-6: Clinical Activity

"Response was evaluable in all patients; ORR was 78% (95% CI 52.4-93.6), with very good partial response (VGPR) in 9 (50%) and PR in 5 (28%) patients. One (6%) patient had minimal response, and 3 (17%) patients had stable disease. Clinical benefit rate was 83% (95% CI 58.6-96.4). After a median of 18.2 weeks (range 6.0-46.4 weeks) on treatment, median DoR was not reached."

Courtesy of Rafael Fonseca, MD

DREAMM-6: Overview of Adverse Events

Patients with AE, n (%)	Belamaf 2.5 mg/kg SINGLE + BorDex (N = 18) [Parts 1 and 2]
AEs related to study treatment	18 (100)
Grade 3/4 AE	16 (89)
AEs leading to permanent discontinuation of a study treatment	5 (28)
AEs leading to permanent discontinuation of belamaf	0
AEs leading to dose reductions	13 (72)
Corneal events	7 (39)
Thrombocytopenia	6 (33)
AEs leading to dose interruption/delay	18 (100)
Corneal events	15 (83)
Thrombocytopenia	7 (39)
Any SAE	12 (67)
Fatal SAE	0
SAEs related to study treatment	5 (28)

Popat R et al. ASH 2020;Abstract 1419.

Courtesy of Rafael Fonseca, MD

3.2 – Popat R et al. DREAMM-6: Safety, Tolerability, and Clinical Activity of Belantamab Mafodotin (Belamaf) in Combination with Bortezomib/Dexamethasone (BorDex) in Relapsed/Refractory Multiple Myeloma (RRMM). ASH 2020;Abstract 1419.

- Impact on Patient Care and Treatment Algorithms
  - Belantamab can be safely combined with other anti-myeloma therapies.
  - The profile of toxicity is acceptable for the combination although the corneal toxicity remains a challenge.
  - In patients who are intolerant to IMIDs this provides a new alternative.
- Implications for Future Research
  - Additional combinations of this antibody, with other anti-myeloma therapies need to be explored.
  - This antibody needs to be combined with other T-cell engaging agents.
  - If the corneal toxicity can be mitigated this agent could replace “naked” antibodies in the front-line setting.

Courtesy of Rafael Fonseca, MD

Articles

Lancet Haematol 2020;7(5):e370-80.

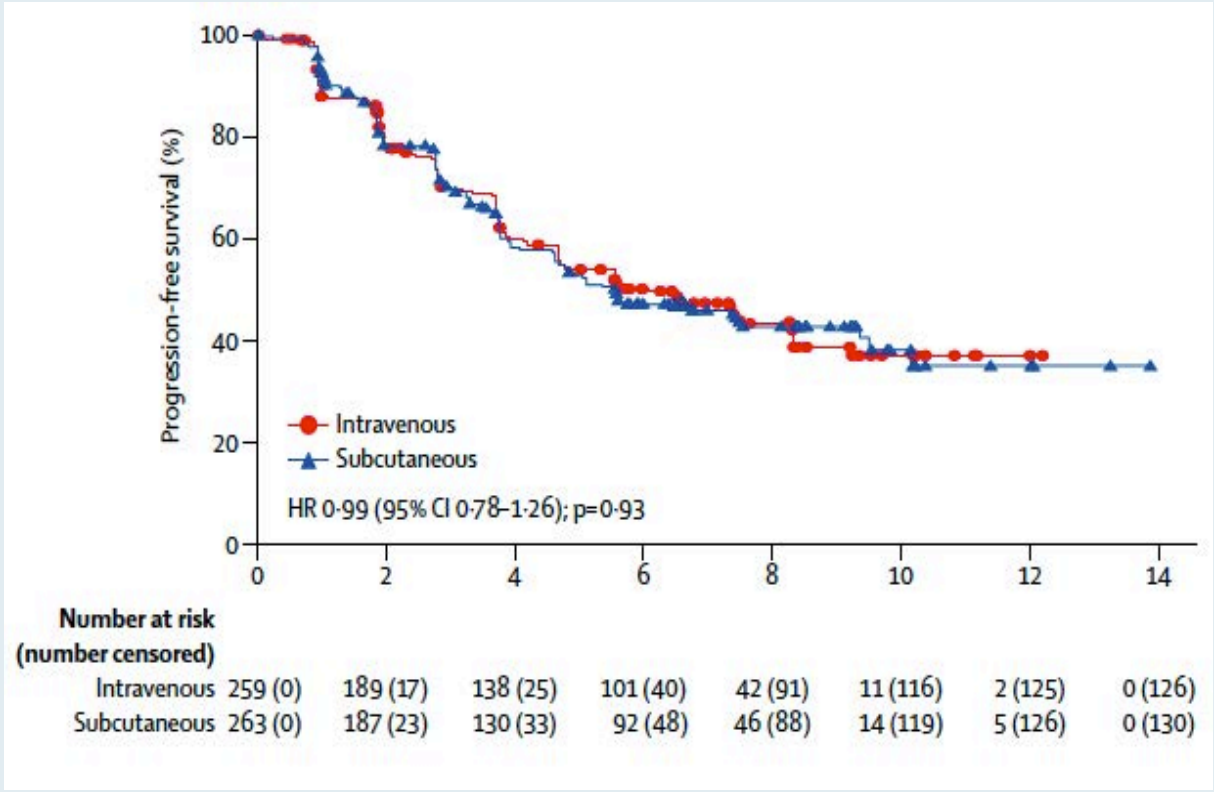
Subcutaneous versus intravenous daratumumab in patients with relapsed or refractory multiple myeloma (COLUMBA): a multicentre, open-label, non-inferiority, randomised, phase 3 trial

Maria-Victoria Mateos, Hareth Nahi, Wojciech Legiec, Sebastian Grosicki, Vladimir Vorobyev, Ivan Spicka, Vania Hungria, Sibirina Korenkova, Nizar Bahlis, Max Flogegard, Joan Bladé, Philippe Moreau, Martin Kaiser, Shinsuke Iida, Jacob Laubach, Hila Magen, Michele Cavo, Cyrille Hulin, Darrell White, Valerio De Stefano, Pamela L Clemens, Tara Masterson, Kristen Lantz, Lisa O'Rourke, Christoph Heuck, Xiang Qin, Dolly A Parasrampuria, Zhilong Yuan, Steven Xu, Ming Qi, Saad Z Usmani

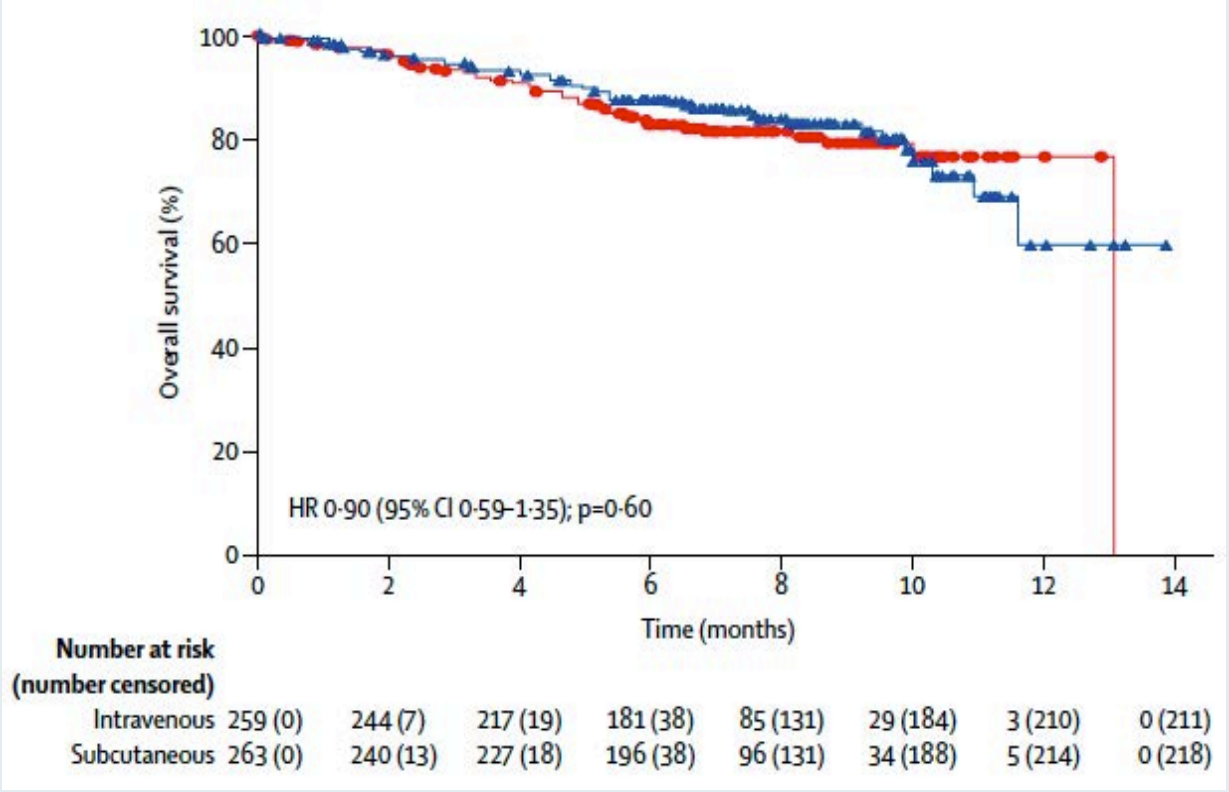
Courtesy of Rafael Fonseca, MD

COLUMBA: PFS and OS Analyses (Median Follow-up 7.5 months)

Progression-free Survival



Overall Survival



Mateos MV et al. *Lancet Haematol* 2020;7(5):e370-80.

Courtesy of Rafael Fonseca, MD

3.3 – Mateos MV, et al. Subcutaneous versus intravenous daratumumab in patients with relapsed or refractory multiple myeloma (COLUMBA): a multicentre, open-label, non-inferiority, randomised, phase 3 trial. Lancet Haematol. 2020 May;7(5):e370-e380.

- Impact on Patient Care and Treatment Algorithms
  - Subcutaneous daratumumab is as effective as intravenous.
  - Every patient who starts daratumumab should be started on the subcutaneous administration.
  - The subcutaneous administration is safer with a lower incidence of reaction.
- Implications for Future Research
  - All future clinical trials of daratumumab need to be conducted with the subcutaneous formulation.
  - Future trials are likely to test self administration of medications such as daratumumab.

Courtesy of Rafael Fonseca, MD

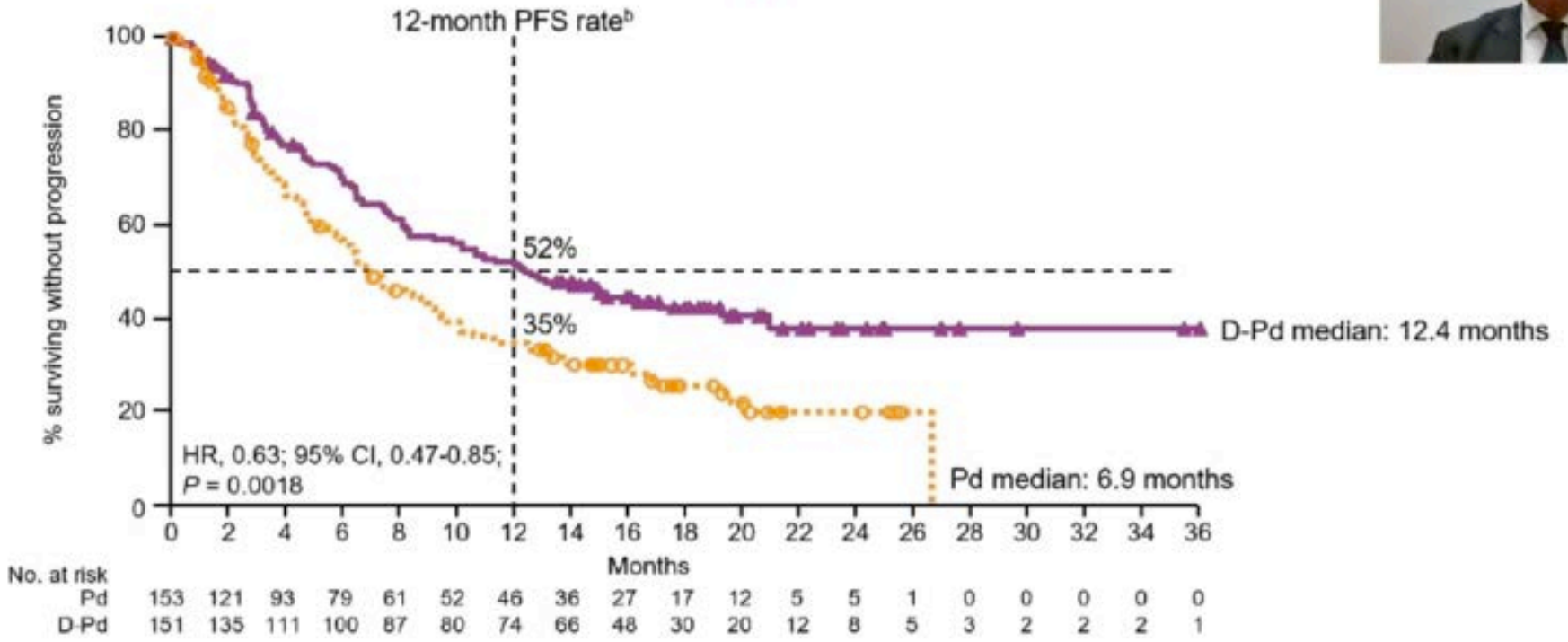
Apollo: Phase 3 Randomized Study of Subcutaneous Daratumumab Plus Pomalidomide and Dexamethasone (D-Pd) versus Pomalidomide and Dexamethasone (Pd) Alone in Patients (Pts) with Relapsed/Refractory Multiple Myeloma (RRMM)

Dimopoulos MA et al.

ASH 2020;Abstract 412.

Courtesy of Rafael Fonseca, MD

PFS at a Median Follow-up of 16.9 Months[a]



- Median PFS among patients refractory to lenalidomide was 9.9 months for D-Pd and 6.5 months for Pd

Addition of DARA SC to Pd improved PFS, with a 37% reduction in the risk of progression or death

HR, hazard ratio; CI, confidence interval. [b]Intent-to-treat population. [a]Kaplan–Meier estimate.

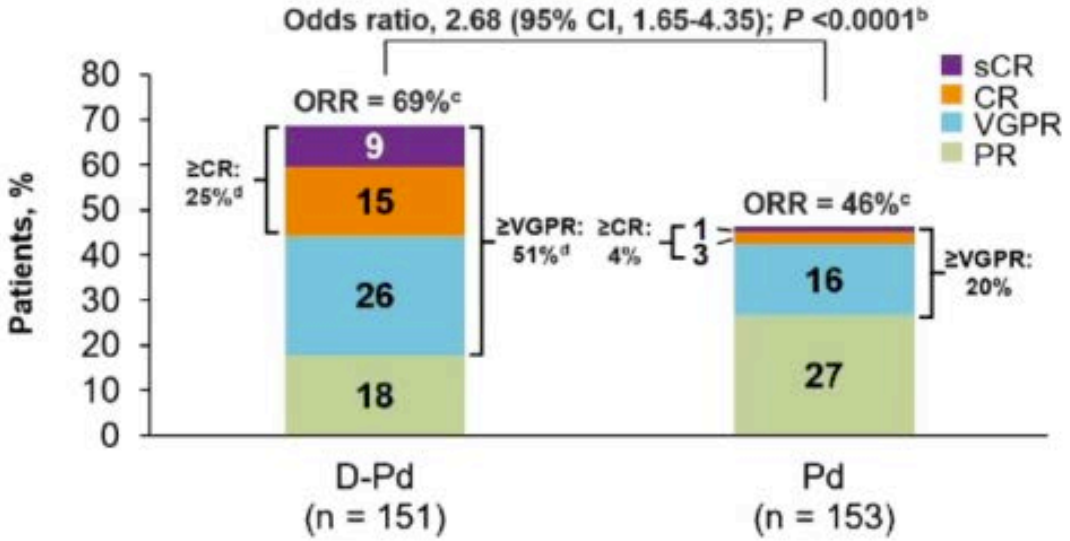
American Society *of* Hematology

Dimopoulos MA et al. ASH 2020;Abstract 412.

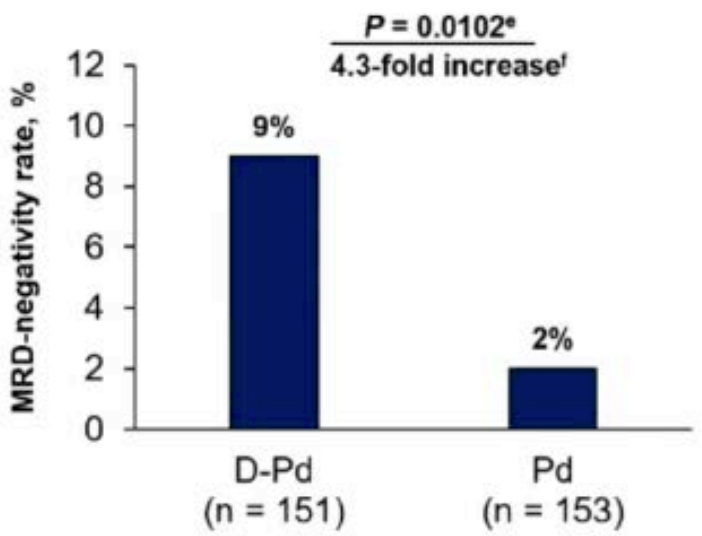
Courtesy of Rafael Fonseca, MD

Depth of Response[a]

Hematologic response



MRD negativity



ORR, ≥VGPR rate, ≥CR rate, and MRD-negativity rate were significantly higher with D-Pd versus Pd

PR, partial response; IMWG, International Myeloma Working Group; ITT, intent-to-treat. [a]Responses were assessed by computer algorithm in accordance with IMWG recommendations and included patients in the ITT population. [b]*P* value was calculated from the 2-sided Cochran–Mantel–Haenszel chi-square test, stratified for ISS stage (I, II, III) and number of lines of prior therapy (1, 2-3, ≥4). [c]Values may not add to total due to rounding. [d]*P* <0.0001. [e]*P* value (2-sided) was calculated using the Fisher's exact test. [f]Non-rounded values are 8.6% and 2.0%.

Dimopoulos MA et al. ASH 2020;Abstract 412.

Courtesy of Rafael Fonseca, MD

3.4 – Dimopoulos MA et al. Apollo: Phase 3 Randomized Study of Subcutaneous Daratumumab Plus Pomalidomide and Dexamethasone (D-Pd) Versus Pomalidomide and Dexamethasone (Pd) Alone in Patients (Pts) with Relapsed/Refractory Multiple Myeloma (RRMM). ASH 2020;Abstract 412.

- Impact on Patient Care and Treatment Algorithms
  - Although the combination of daratumumab, pomalidomide and dexamethasone remains a good option for relapsed and refractory myeloma, the durability of response was lower than expected.
  - This regimen is effective, but caution needs to be exercised in patients with extensive prior IMID use (*e.g.*, maintenance).
  - In patients with aggressive disease, it might be preferable to combine daratumumab with carfilzomib.
- Implications for Future Research
  - Understanding which patients are refractory to IMiDs remains a major gap in myeloma translational research.
  - Four drug combinations should be studied in the setting of relapsed and refractory myeloma.

Courtesy of Rafael Fonseca, MD