Provided by Purdue University and developed in partnership with Clinical Care Options, LLC and the International Myeloma Foundation.

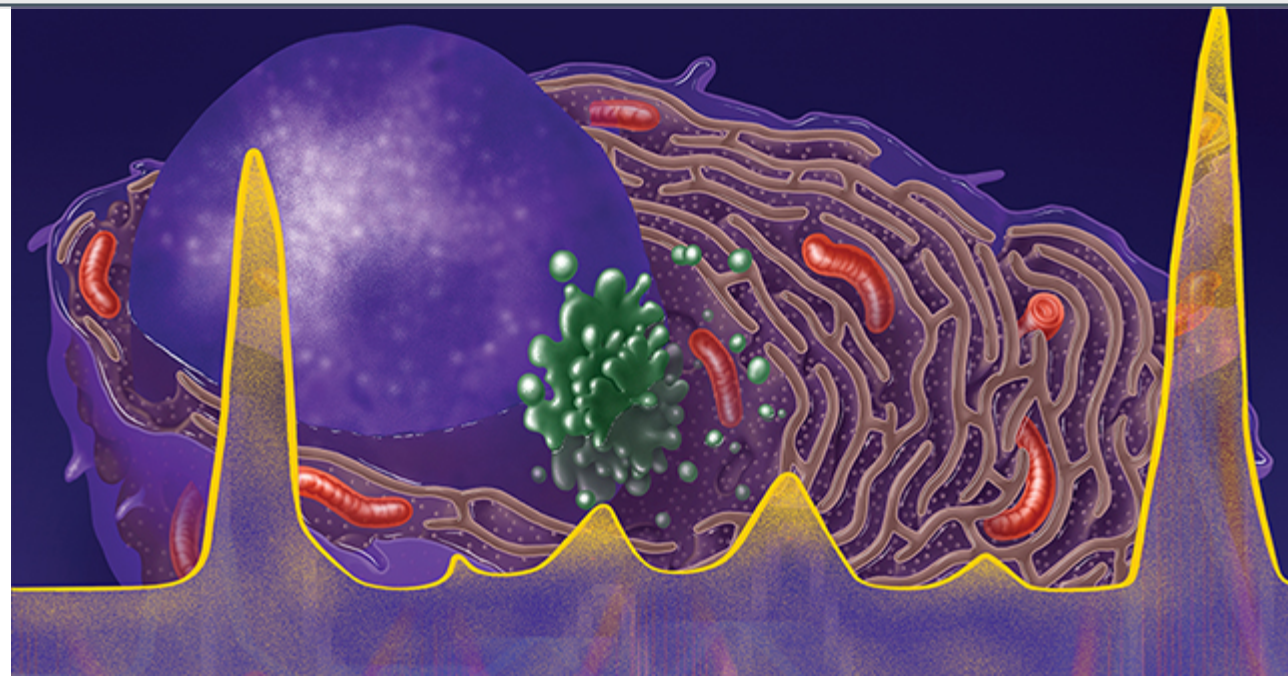
PURDUE UNIVERSITY

INTERNATIONAL MYELOMA FOUNDATION

CCO LIVE

Approaches To Achieve the Best Possible Outcomes in Myeloma

Friday, December 6, 2019
1:00 PM – 4:00 PM
Orlando, Florida



Supported by educational grants from Celgene Corporation, Janssen Biotech, Inc., administered by Janssen Scientific Affairs, LLC, Karyopharm Therapeutics Inc., Oncopeptides, Takeda Oncology, and The Binding Site.

Friday Satellite Symposium preceding the 61st ASH Annual Meeting & Exposition.

Program Chair and Moderator

Brian G.M. Durie, MD
Medical Director, AMyC
Co-Chair Myeloma Committee, SWOG
Chairman, International Myeloma Foundation
Specialist in Multiple Myeloma and Related Disorders
Cedars-Sinai Outpatient Cancer Center
Los Angeles, California

Brian G.M. Durie, MD, has disclosed that he has received consulting fees from Amgen, Celgene, Johnson & Johnson, and Takeda.

Faculty

Shaji Kumar, MD
Department of Hematology
Mayo Clinic
Rochester, Minnesota

Shaji Kumar, MD, has disclosed that he has received consulting fees paid to his institution from AbbVie, Amgen, Celgene, Genentech, Janssen, Kite, MedImmune, Merck, and Takeda and funds for research support from AbbVie, Amgen, Bristol-Myers Squibb, Celgene, Janssen, Kite, MedImmune, Merck, Novartis, Roche/Genentech, Sanofi, and Takeda.

Faculty

Thomas G. Martin, MD
Clinical Professor of Medicine
Associate Director, Myeloma Program
University of California, San Francisco Medical Center
San Francisco, California

Thomas G. Martin, MD has disclosed that he has received consulting fees from Legend Biotech and funds for research support from Amgen, Johnson & Johnson – Janssen, Sanofi, and Seattle Genetics.

Faculty

Philippe Moreau, MD
Professor of Clinical Hematology
Head, Hematology Department
University Hospital Hôtel-Dieu
Nantes, France

Philippe Moreau, MD, has disclosed that he has received consulting fees from AbbVie, Amgen, Celgene, Janssen, and Takeda.

Faculty

S. Vincent Rajkumar, MD
Edward W. and Betty Knight Scripps Professor of Medicine
Mayo Clinic
Rochester, Minnesota

S. Vincent Rajkumar, MD, has no real or apparent conflicts of interest to disclose.

Faculty

Jesús F. San-Miguel, MD, PhD
Director of Clinical and Translational Medicine
Universidad de Navarra
Pamplona, Spain

Jesús F. San-Miguel, MD, PhD, has disclosed that he has received consulting fees from Amgen, Bristol-Myers Squibb, Celgene, Janssen, Merck Sharp & Dohme, Novartis, Roche, Sanofi, and Takeda.

Learning Objectives

At the conclusion of this activity, participants should be able to:

- Initiate treatment for appropriate patients based on an accurate diagnosis of monoclonal gammopathy of undetermined significance, smoldering MM, or active MM
- Create individualized treatment strategies for patients with newly diagnosed MM through consideration of the available clinical data as well as risk assessment, age, comorbidities, and patient preferences
- Select safe and effective maintenance therapy for patients with MM based on risk and response to induction therapy
- Evaluate the efficacy and safety of combination regimens to individualize therapeutic strategies for patients with MM at first relapse
- Plan appropriate treatment strategies using all available agents and classes to provide efficacious combination therapies to heavily pretreated patients with relapsed/refractory MM
- Employ novel agents and clinical trial participation as part of clinical care strategies for MM

Agenda

- Diagnosis and Risk Stratification of Plasma Cell Disorders - ***Jesús F. San-Miguel, MD, PhD***
- Evolution of Upfront Therapy for the Transplantation-Ineligible Patient - ***Shaji Kumar, MD***
- Upfront Therapy for the ASCT-Eligible Patient: Advances in Induction, ASCT, Consolidation, and Maintenance Therapy - ***Philippe Moreau, MD***
- The Current Therapeutic Landscape for Relapsed or Refractory MM: Which Combinations to Use and When? - S***. Vincent Rajkumar, MD***
- Future Directions: A New Era of Promising Treatments for MM - ***Thomas G. Martin, MD***
- Proposed 2020 treatment algorithms for MM

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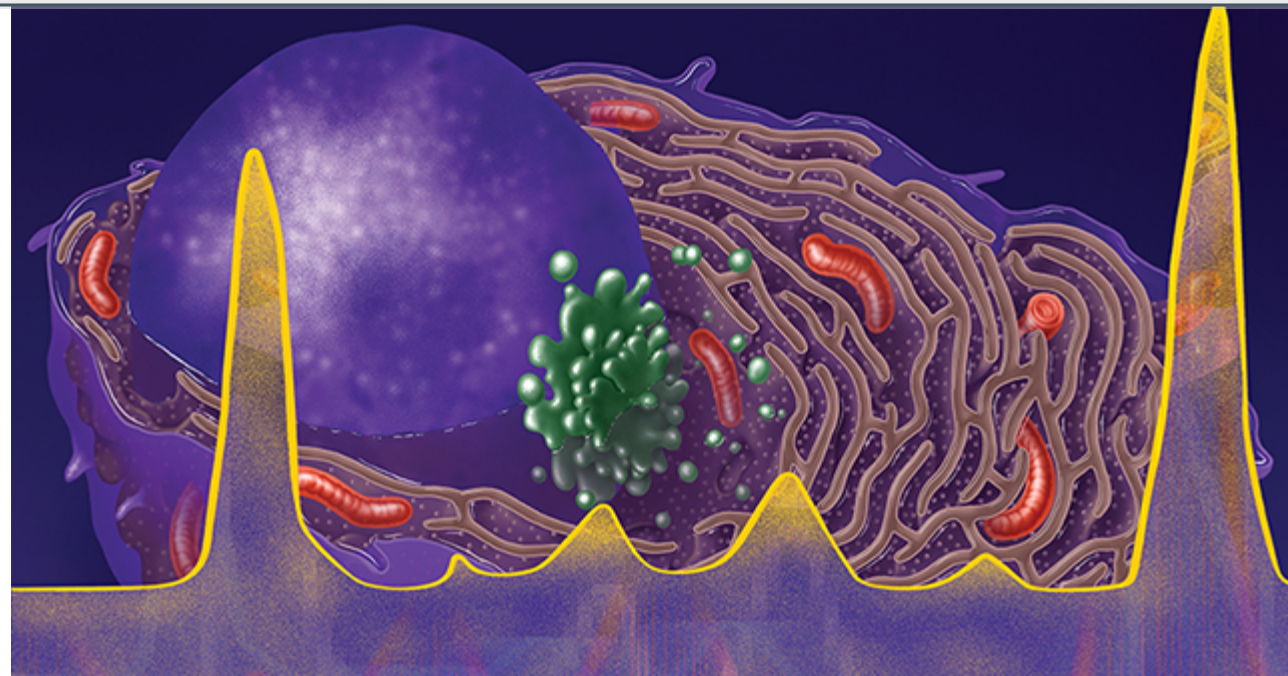
Case Discussion 2—Evolution of Upfront Therapy for the Transplantation-Ineligible Patient

Shaji Kumar, MD
Department of Hematology
Mayo Clinic
Rochester, Minnesota



Faculty

Shaji Kumar, MD
Department of Hematology
Mayo Clinic
Rochester, Minnesota

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Patient Case Example

- A 75-year-old male presented with increasing back pain that was associated with radiculopathy involving the right lower extremity
- MRI showed multiple enhancing destructive lesions in the lumbar spine, sacrum, pelvis, right iliac bone, destructive lesion in L1 vertebra and L3 vertebra
- Initial lab evaluation showed elevated total protein at 10, and creatinine of 1.4
- Additional workup showed:
  - Hemoglobin: 12.0 g/dL
  - Calcium: normal
  - Serum M-spike: 3.2 g/dL, IgG kappa
  - IgG: 3350 mg/dL
  - FLC: kappa 655 mg/L, lambda 4.3 mg/L
  - Bone marrow plasma cells: 60%
  - β_2-microglobulin: 6.9 µg/mL
  - Albumin: 3.6 g/dL
  - Plasma cell FISH: trisomy 7, 11, 14
  - Conventional cytogenetics: normal

In your current clinical practice, which of the following would you recommend for initial therapy?

Expert Recommendations	
Brian G.M. Durie, MD	Bortezomib/lenalidomide/dexamethasone
Shaji Kumar, MD	Bortezomib/lenalidomide/dexamethasone
Thomas G. Martin, MD	Bortezomib/lenalidomide/dexamethasone Daratumumab/lenalidomide/dexamethasone (*once SQ dara available*)
Philippe Moreau, MD	Lenalidomide/dexamethasone
S. Vincent Rajkumar, MD	Bortezomib/lenalidomide/dexamethasone
Jesus San-Miguel, MD	Daratumumab/bortezomib/melphalan/prednisone (*already approved*) Daratumumab/lenalidomide/dexamethasone (*not yet approved*)

Slide credit: clinicaloptions.com

Evolution of Upfront Therapy for the ASCT-Ineligible Patient

Shaji Kumar, M.D.
Professor of Medicine
Chair, Myeloma, Amyloid, Dysproteinemia Group
Mayo Clinic

Scottsdale, Arizona

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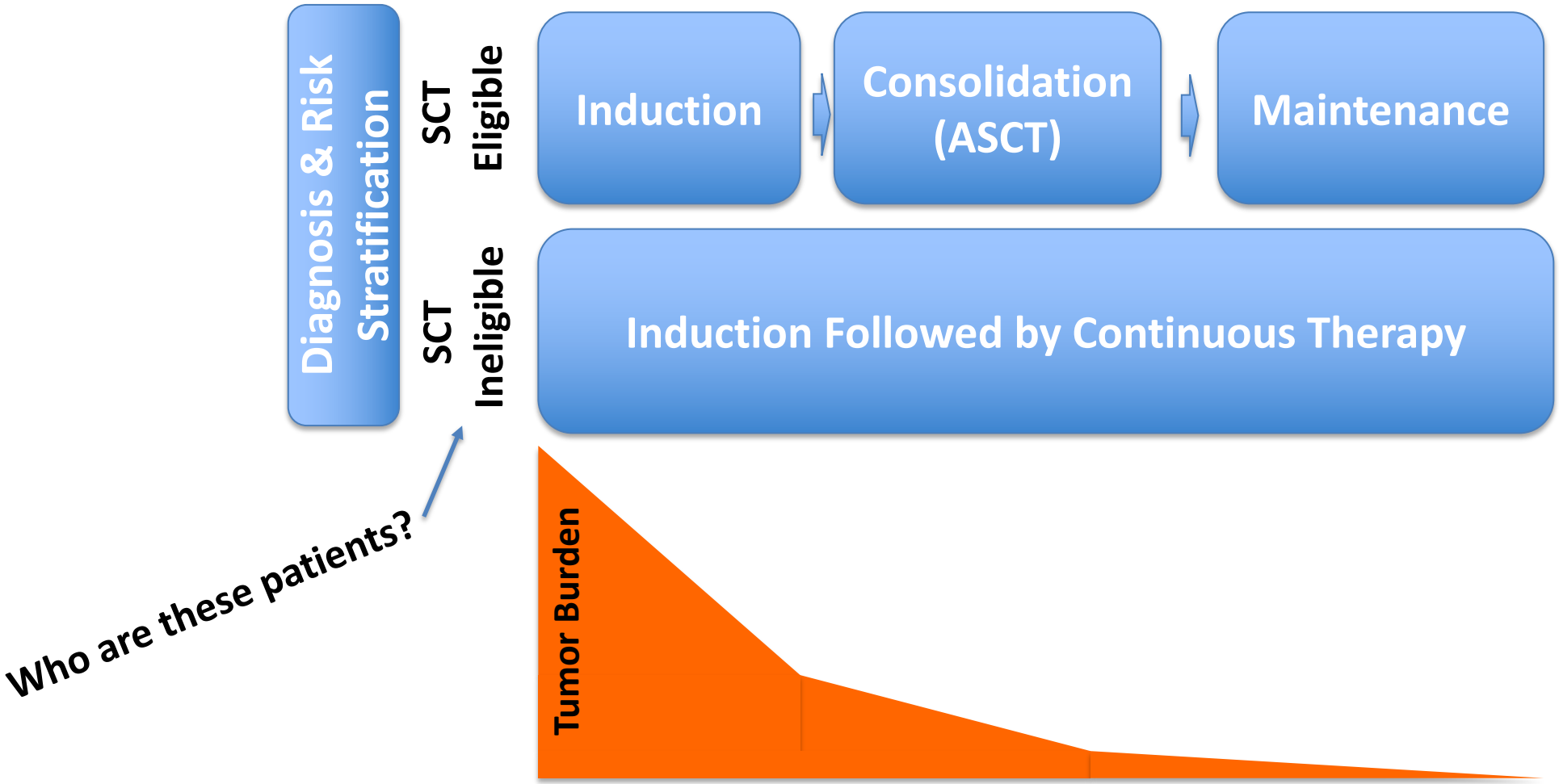
Jacksonville, Florida

Myeloma Treatment Paradigm



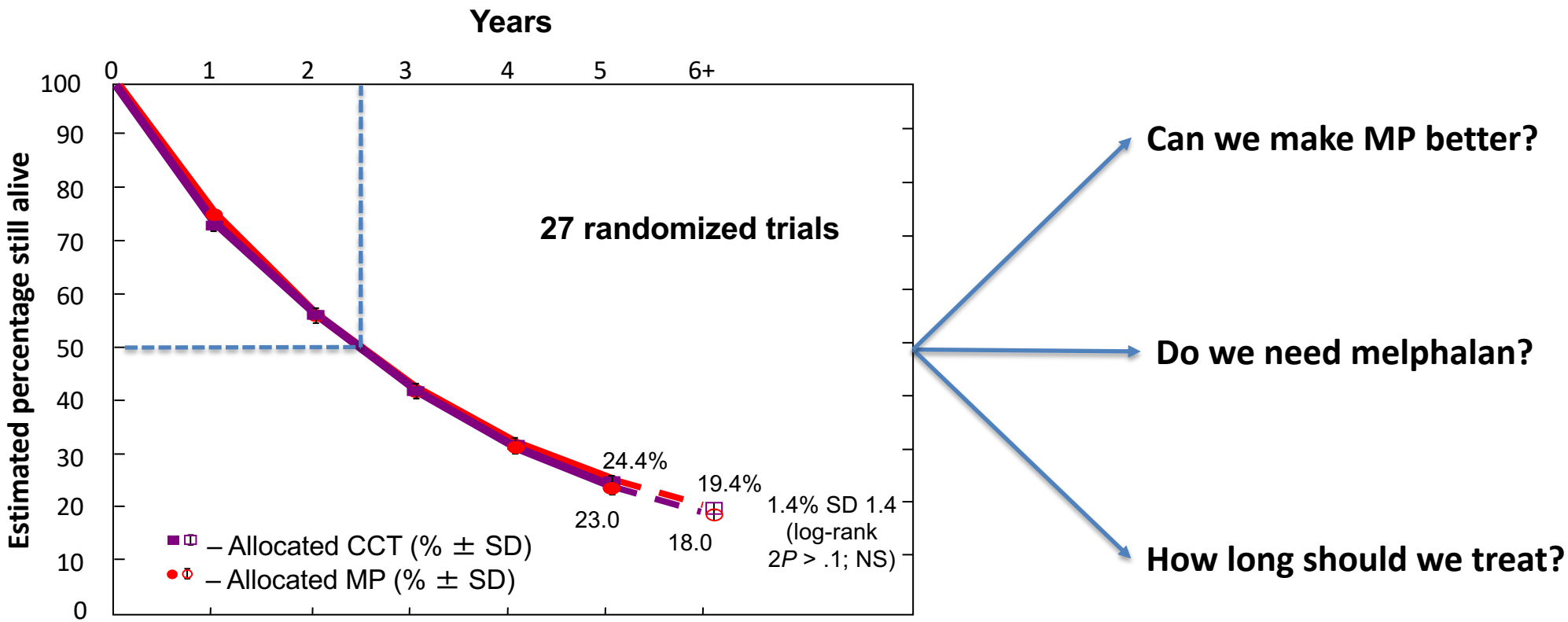
Transplant Eligibility…Who? When?

- Has been primarily based on age…patients included in the initial trials
  - Presence of comorbidities…ability to tolerate the procedure
  - Functional status…frailty
  - Access to healthcare
  - Increasingly patient choice as more options arrive
- Decision made at time of diagnosis → decision regarding initial Rx
  - Less of an issue now as treatment approaches converge

Why Is Age an Important Issue?

- Comorbidities
  - Hypertension, ischemic heart disease, diabetes
  - Renal insufficiency
  - Osteoporosis
  - Psychological issues
- Frailty
- Altered drug metabolism
- Limited social support, financial issues
- Limited independence/mobility

The Start: Melphalan + Prednisone



Can we make MP better?

Do we need melphalan?

How long should we treat?

Myeloma Trialists' Collaborative Group. *J Clin Oncol.* 1998;16;12:3832

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CAN WE IMPROVE MP?

MP vs MPT

	GIMEMA[1,2]	IFM 99-06[3]	IFM 01-01[4]	Nordic[5]	HOVON[6]
Median PFS, months					
MP	15	18	19	14	11
MPT	22	28	24	15	15
P value	0.0004	< 0.0001	0.001	NS	< 0.002
Median OS, months					
MP	48	33	29	32	31
MPT	45	52	44	29	40
P value	NS	0.0006	0.028	NS	0.05

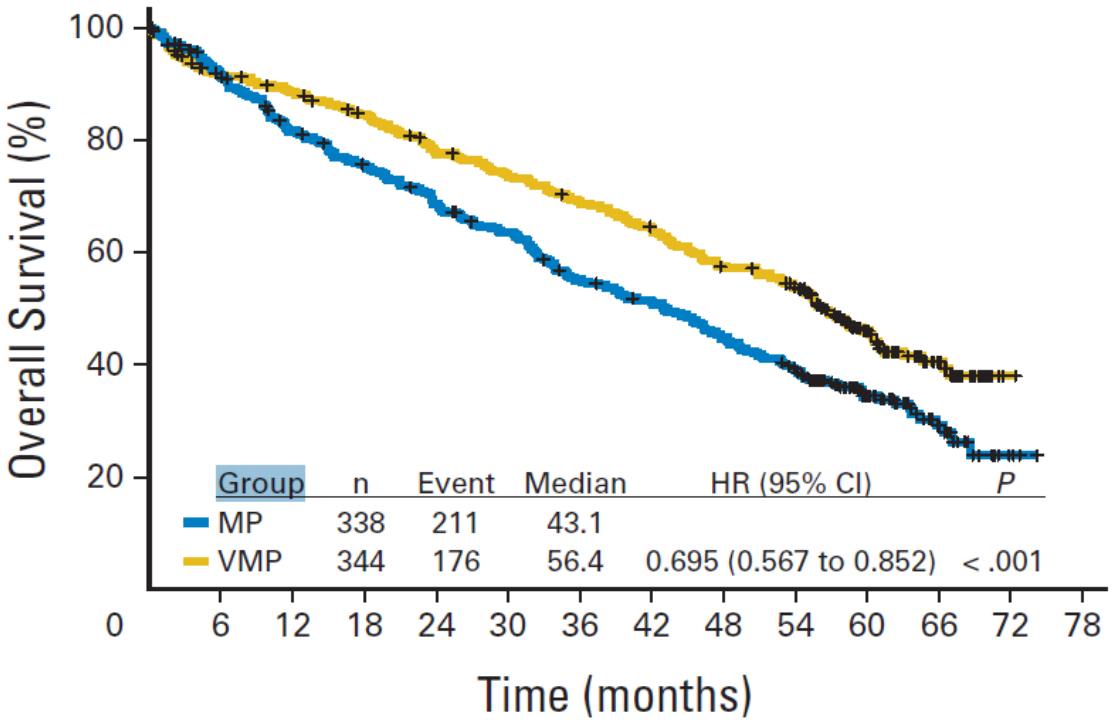
‡ Significant.

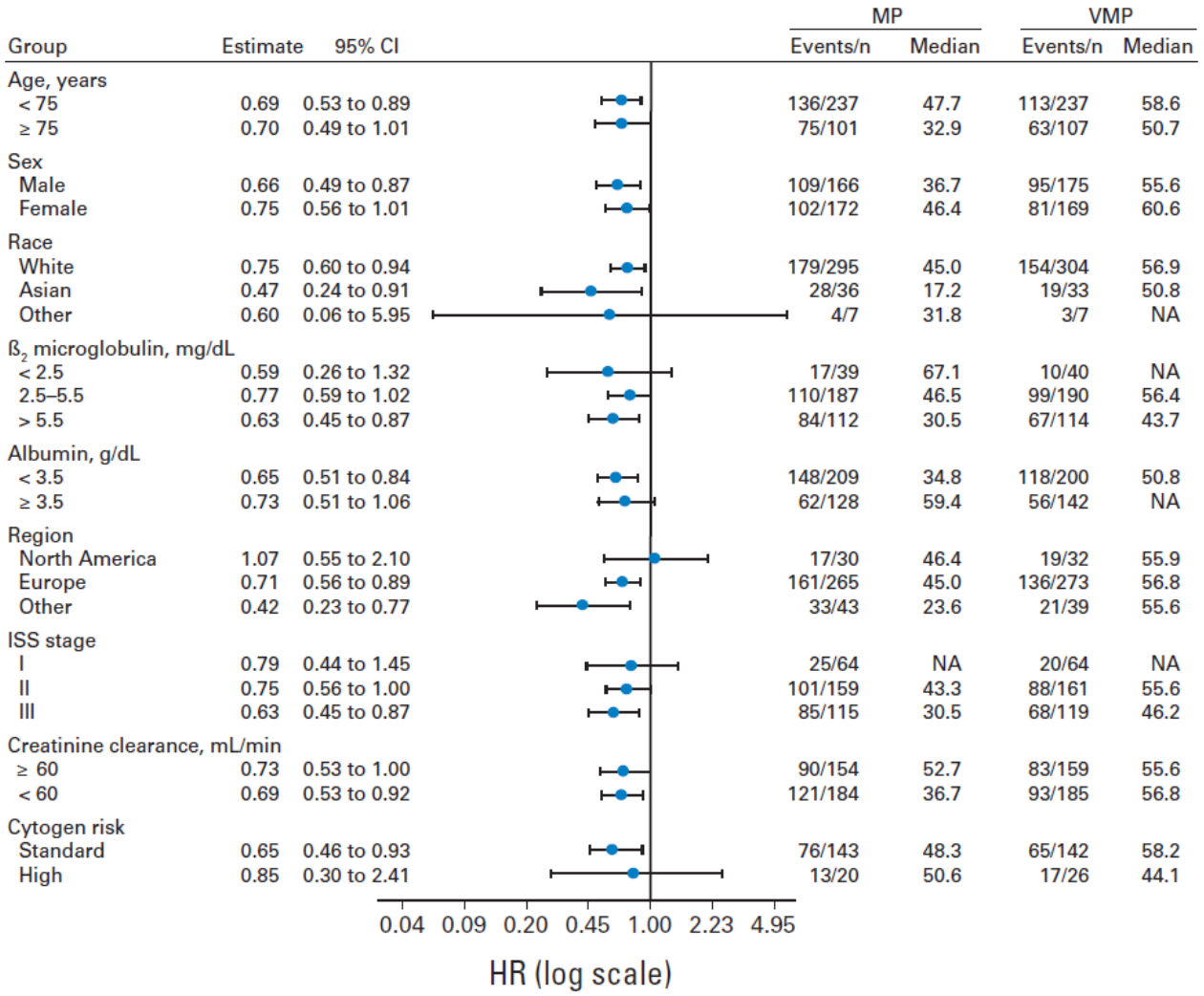
In 4 of 5 studies, MPT was superior to MP in terms of PFS

In 2 of 5 studies, MPT was superior to MP in terms of OS

1. Palumbo A, et al. Lancet. 2006;111:825-31. 2. Palumbo A, et al. Blood. 2008;112:3107-14. 3. Facon T, et al. Lancet. 2007;370:1209-18. 4. Hulin C, et al. J Clin Oncol. 2009;27:3664-70. 5. Waage A, et al. Blood. 2010;116:1405-12. 6. Wijermans P, et al. J Clin Oncol. 2010;28:3160-6.

VISTA Trial: MPV vs MP





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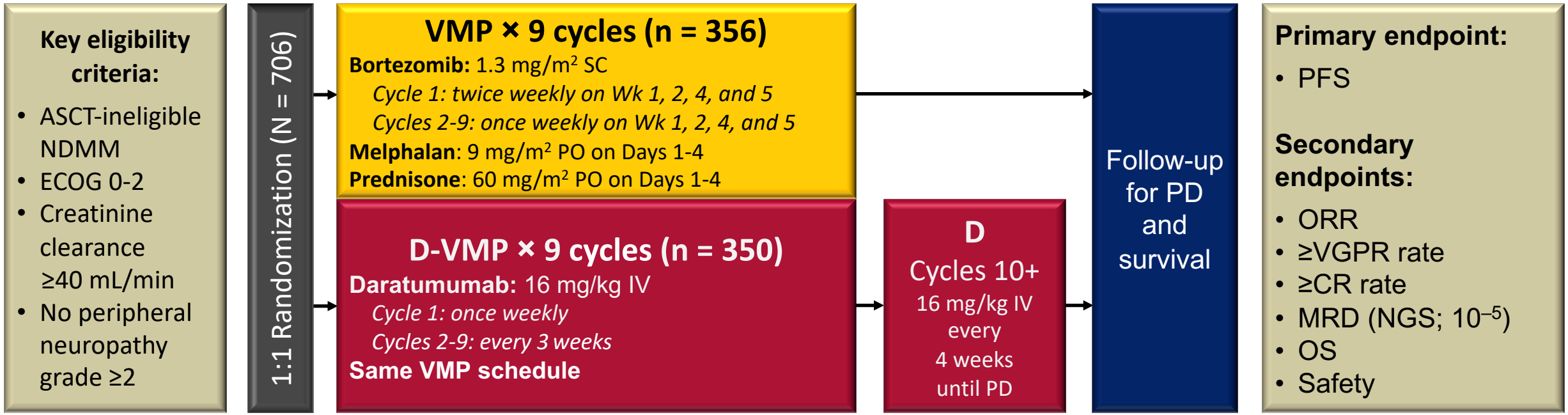
San Miguel et al. JCO 2013;31:448-455

ALCYONE: Dara-VMP vs VMP



Stratification factors

- ISS (I vs II vs III)
- Region (EU vs other)
- Age (<75 vs ≥75 years)

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

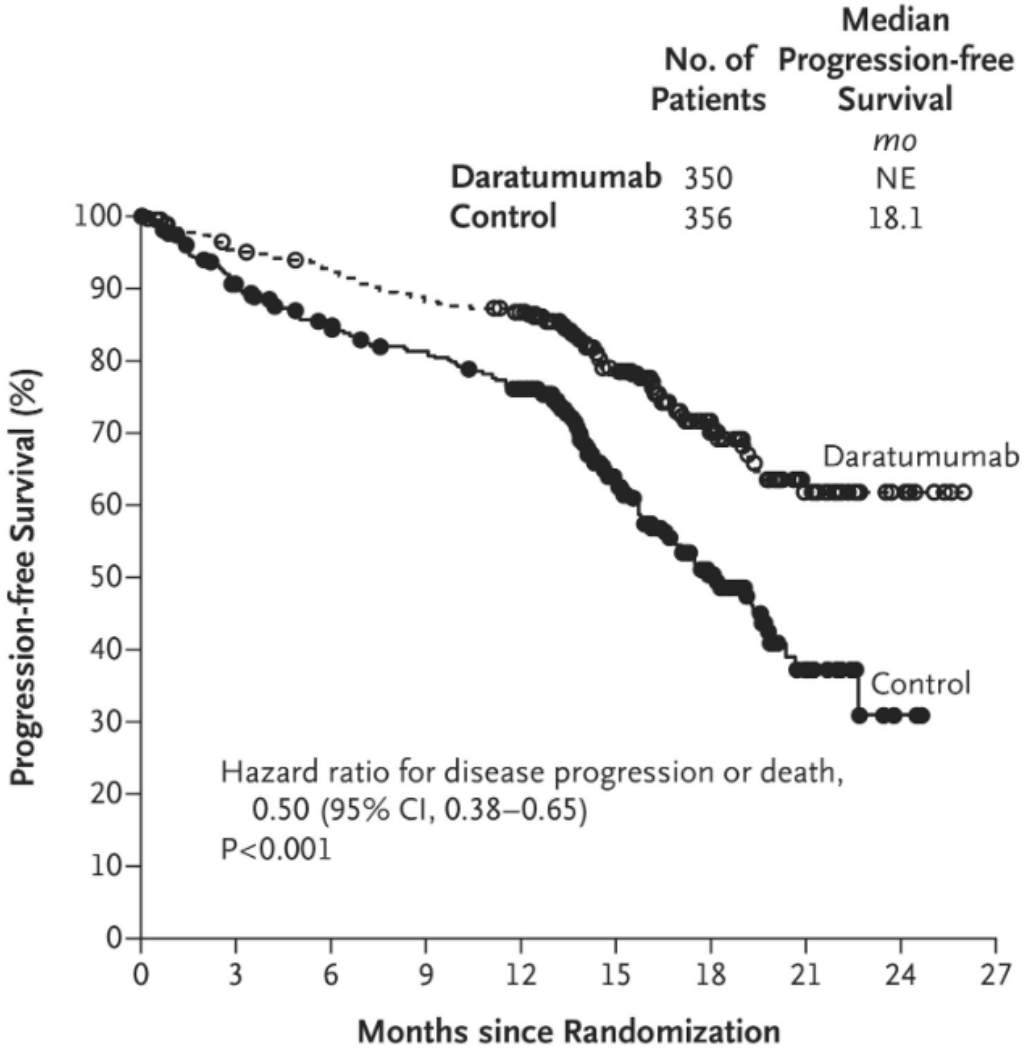
Statistical analyses

- 360 PFS events: 85% power for 27.6% lower risk of disease progression or death
- Interim analysis: ~231 PFS events

MAYO CLINIC

Mateos M-V et al. N Engl J Med 2018;378:518-528

ALCYONE: Dara-VMP vs VMP



Variable	Daratumumab Group (N=350)	Control Group (N=356)
Overall response		
No. with response	318	263
Rate — % (95% CI)	90.9 (87.3–93.7)	73.9 (69.0–78.4)
Best overall response — no. (%)		
Complete response or better	149 (42.6)	87 (24.4)
Stringent complete response‡	63 (18.0)	25 (7.0)
Complete response	86 (24.6)	62 (17.4)
Very good partial response or better	249 (71.1)	177 (49.7)
Very good partial response	100 (28.6)	90 (25.3)
Partial response	69 (19.7)	86 (24.2)
Stable disease	20 (5.7)	76 (21.3)
Progressive disease	0	2 (0.6)
Response could not be evaluated	12 (3.4)	15 (4.2)
Negative status for minimal residual disease — no. (%)§	78 (22.3)	22 (6.2)

MAYO CLINIC

Mateos M-V et al. N Engl J Med 2018;378:518-528

859 Daratumumab Plus Bortezomib, Melphalan, and Prednisone Versus Bortezomib, Melphalan, and Prednisone in Patients with Transplant–Ineligible Newly Diagnosed Multiple Myeloma: Overall Survival in Alcyone

Program: Oral and Poster Abstracts
Type: Oral
Session: 653. Myeloma: Therapy, excluding Transplantation: Improving the Outcomes of Newly Diagnosed Multiple Myeloma
Hematology Disease Topics & Pathways:
Diseases, antibodies, Adult, Biological, multiple myeloma, Therapies, Study Population, Plasma Cell Disorders, Lymphoid Malignancies

Monday, December 9, 2019: 4:30 PM
Hall E2, Level 2 (Orange County Convention Center)

Maria-Victoria Mateos[1], *Michele Cavo*[2*], *Joan Bladé, MD, PhD*[3], *Meletios A. Dimopoulos, MD*[4], *Kenshi Suzuki, MD, PhD*[5], *Andrzej Jakubowiak, MD, PhD*[6], *Stefan Knop*[7*], *Chantal Doyen, MD*[8], *Paulo Lucio, MD, PhD*[9*], *Zsolt Nagy, MD, PhD*[10*], *Ludek Pour, MD*[11*], *Mark Cook, MBChB, PhD*[12], *Sebastian Grosicki, MD, PhD*[13], *Andre H Crepaldi, MD*[14*], *Anna Marina Liberati*[15], *Philip Campbell, MBBS, FRACP, FRCPA*[16], *Tatiana Shelekhova*[17*], *Sung-Soo Yoon, MD, PhD*[18], *Genadi Iosava, MD*[19*], *Tomoaki Fujisaki, MD, PhD*[20*], *Mamta Garg, MD, FRCP, FRCPath*[21*], *Maria Krevvata, PhD*[22*], *Jianping Wang*[23*], *Anupa Kudva, MD*[23*], *Jon Ukropec, PhD*[24], *Susan Wroblewski, PhD*[22*], *Rachel Kobos, MD*[23] *and Jesus San-Miguel, MD, PhD*[25]

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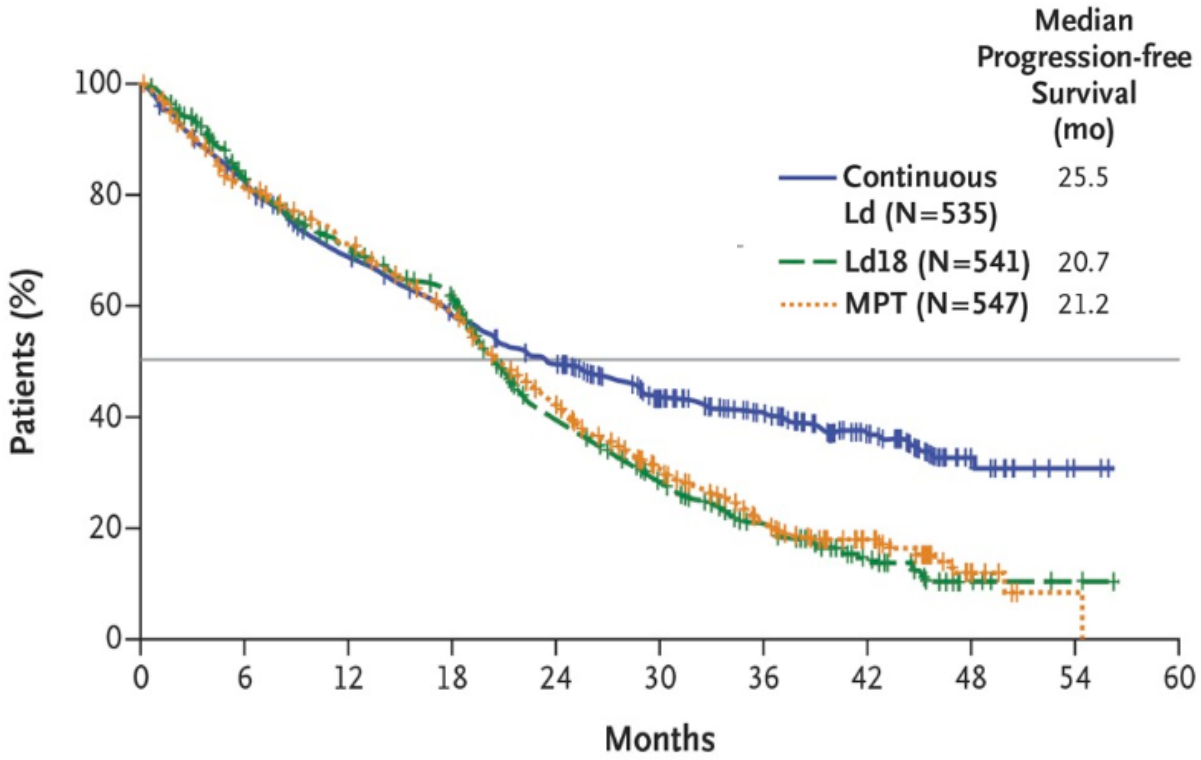
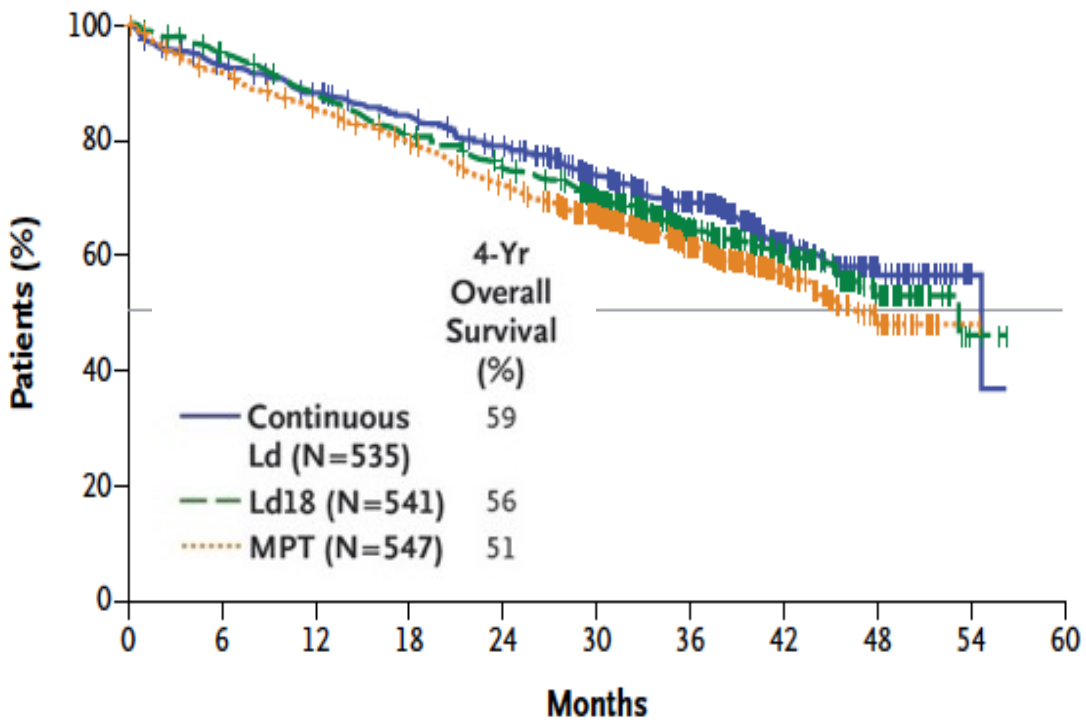
DO WE NEED MELPHALAN?

RD (Continuous or 18 Cycles) vs MPT

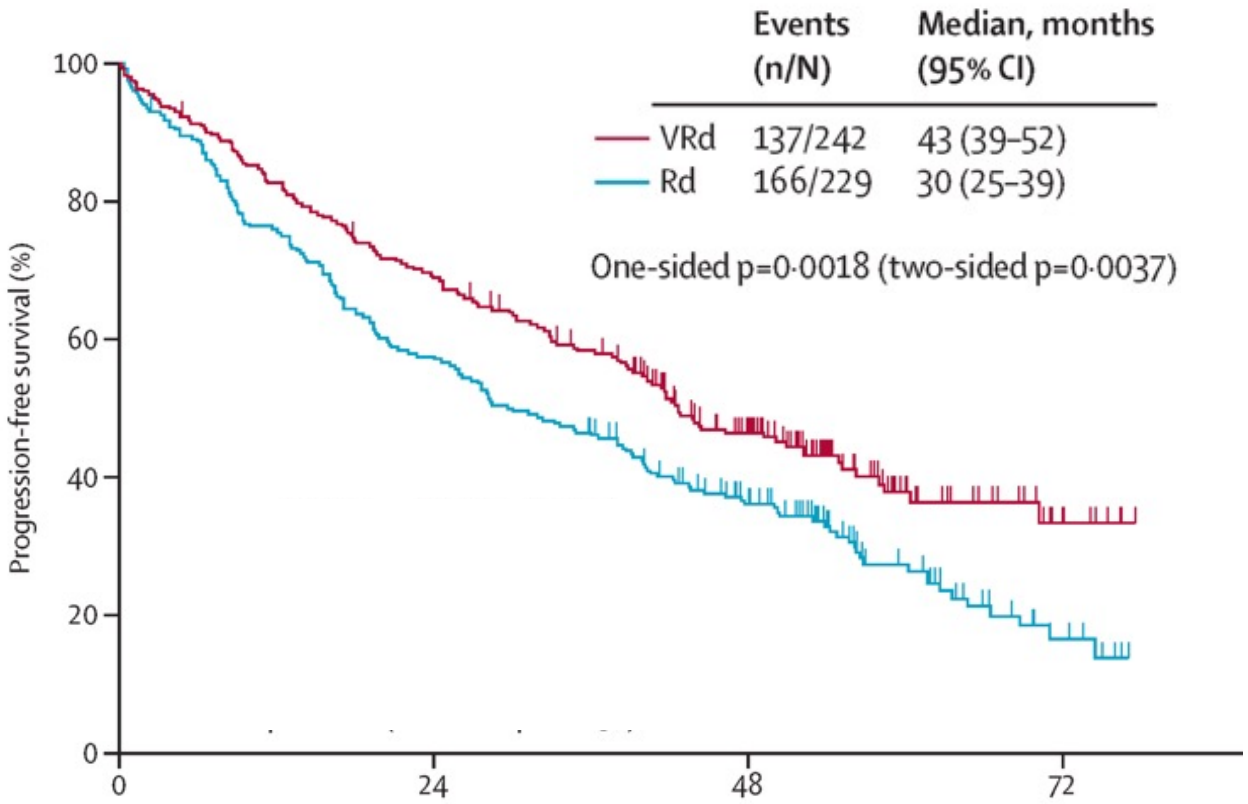


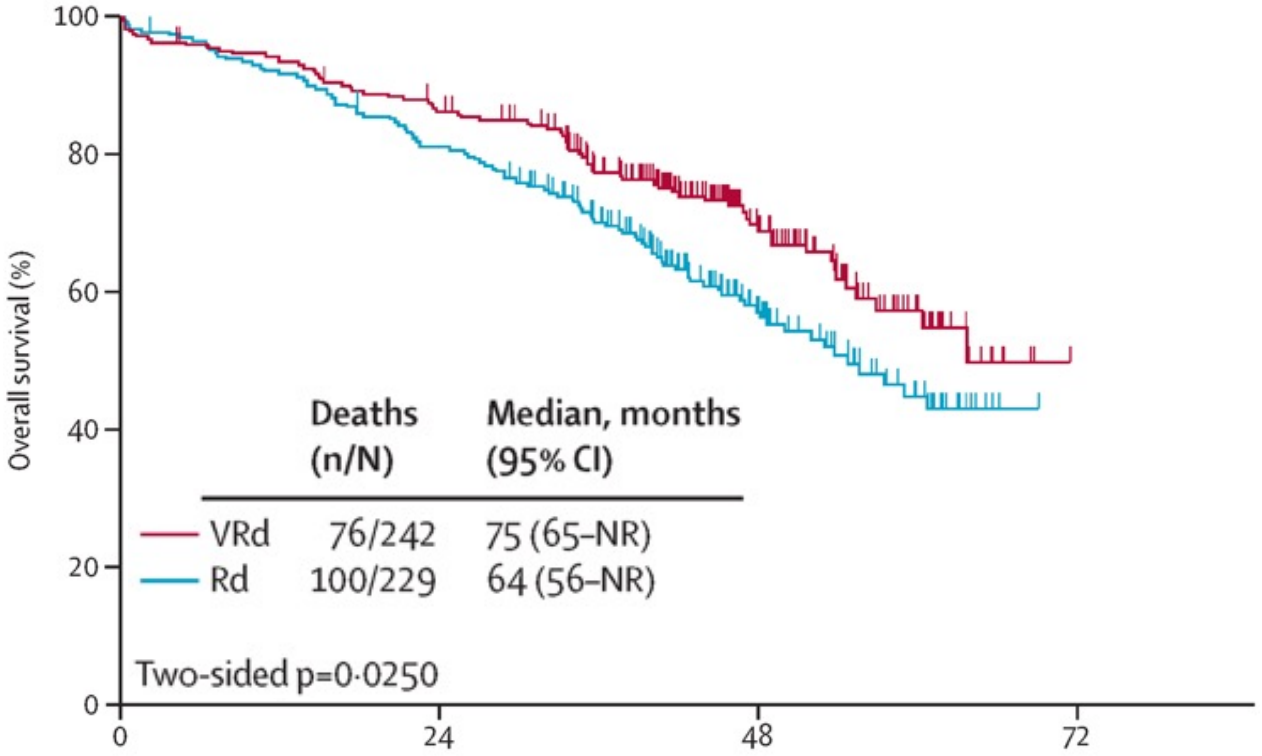


Benboubker et al. N Engl J Med 2014;371:906-17.

MAYO CLINIC

S0777: VRd vs Rd





Durie et al. Lancet 2017;389:519–527.

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RVD Lite

Induction (cycles 1–9)
Repeat q35 days × 9 cycles

Lenalidomide 15 mg po days 1–21
Bortezomib 1·3 mg/m^2 sc* days 1, 8, 15, 22
Dexamethasone 20 mg po days 1, 2, 8, 9, 15, 16, 22, 23 (patients ≤75 years)
Dexamethasone 20 mg po days 1, 8, 15, 22 (patients >75 years)

Consolidation (cycles 10–15)
Repeat q28 days × 6 cycles

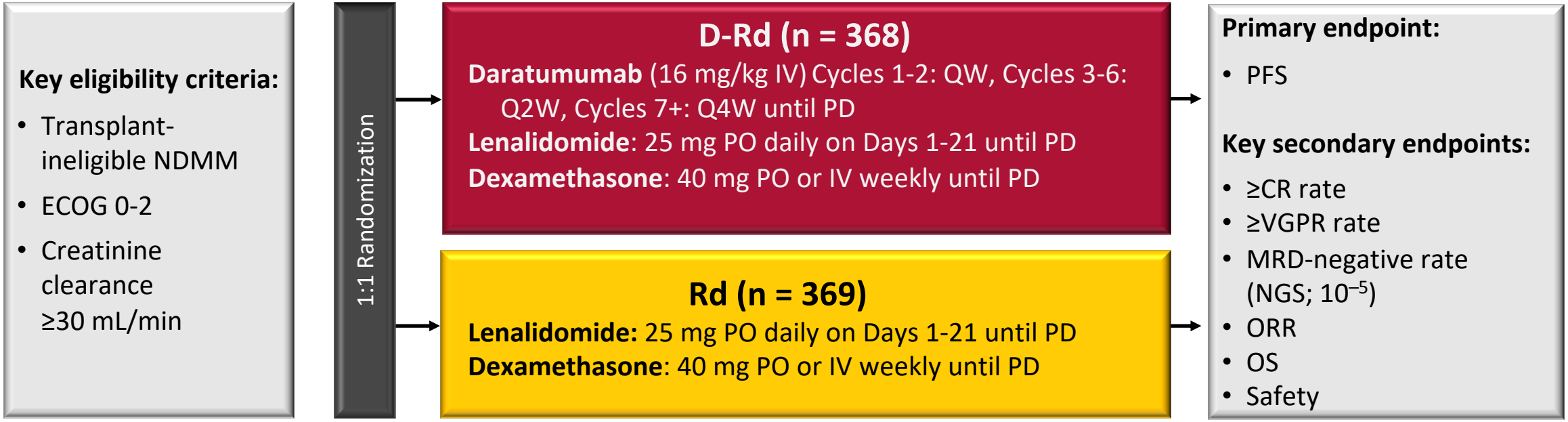
Lenalidomide 15 mg po days 1–21 (or last tolerated dose as of cycle 9)
Bortezomib 1·3 mg/m^2 sc on days 1, 15 (or last tolerated dose as of cycle 9)

	Patients	
	Total = 50	%
Best overall response		
Stringent complete response	6	12
Complete response	16	32
Very good partial response	11	22
Partial response	10	20
Minimal response	1	2
Stable disease	3	6
Not evaluable*	3	6
Overall response rate	43	86
Very good partial response or better	33	66

* The first 10 patients received bortezomib intravenously for cycle 1 only followed by subcutaneous administration. Subsequent patients received bortezomib subcutaneously.

O'Donnell EK, et al. Br J Haematol. 2018;182:222-230.

MAIA: Daratumumab Len-Dex vs Len Dex



Cycle: 28 days

- Phase 3 study of D-Rd vs Rd in transplant-ineligible NDMM (N = 737)

Facon T et al. N Engl J Med 2019;380:2104-2115

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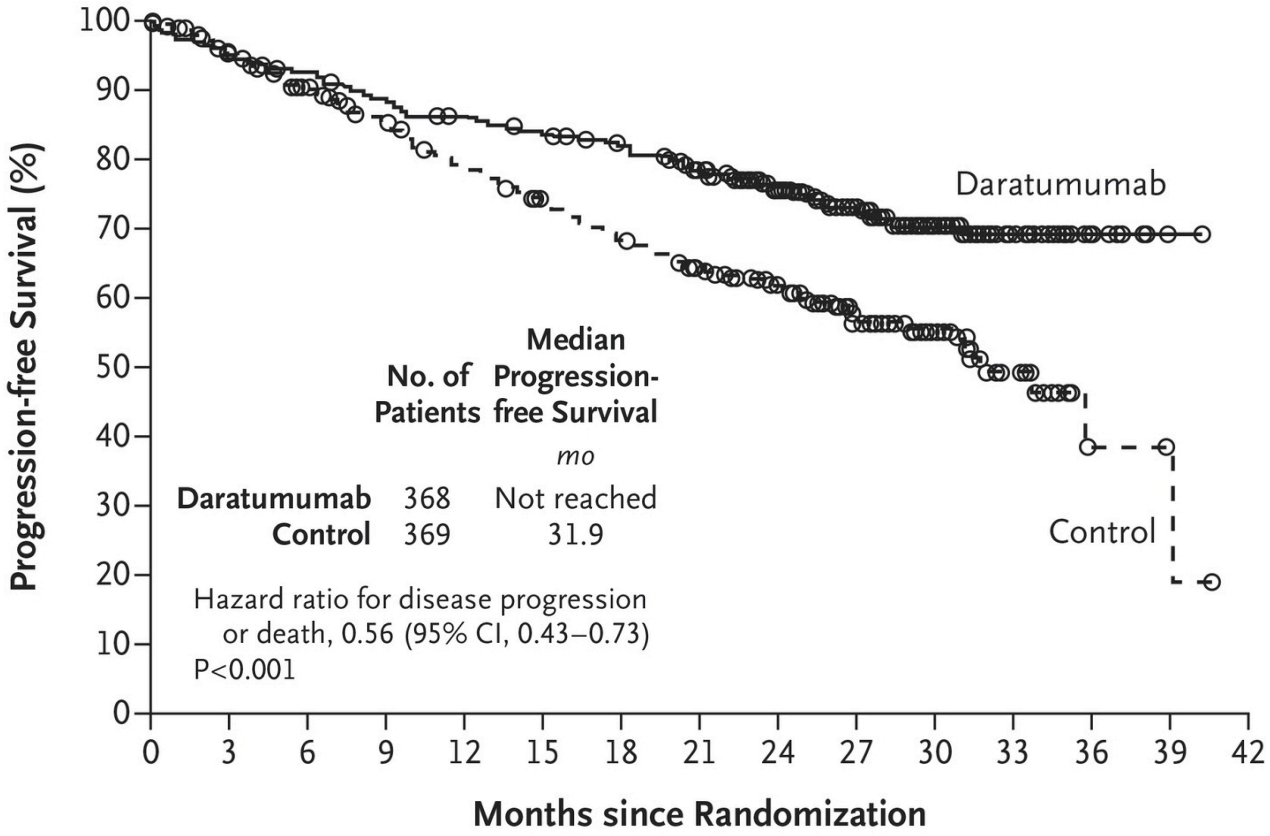
MAIA: Daratumumab+Rd vs Rd



Variable	Daratumumab Group (N=368)	Control Group (N=369)
Overall response — no. (% [95% CI])	342 (92.9 [89.8–95.3])	300 (81.3 [76.9–85.1])
Best overall response — no. (%)		
Complete response or better	175 (47.6)	92 (24.9)
Stringent complete response‡	112 (30.4)	46 (12.5)
Complete response	63 (17.1)	46 (12.5)
Very good partial response or better	292 (79.3)	196 (53.1)
Very good partial response	117 (31.8)	104 (28.2)
Partial response	50 (13.6)	104 (28.2)
Stable disease	11 (3.0)	56 (15.2)
Progressive disease	1 (0.3)	0
Response could not be evaluated	14 (3.8)	13 (3.5)
Negative status for minimal residual disease — no. (%)§	89 (24.2)	27 (7.3)

Facon T et al. N Engl J Med 2019;380:2104-2115

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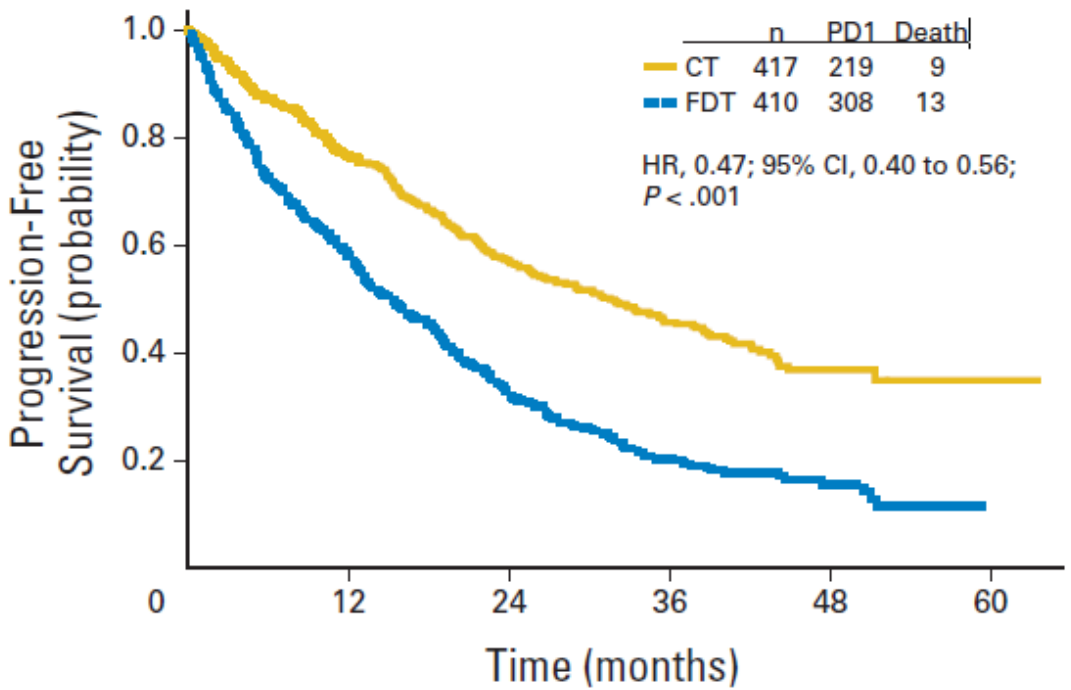
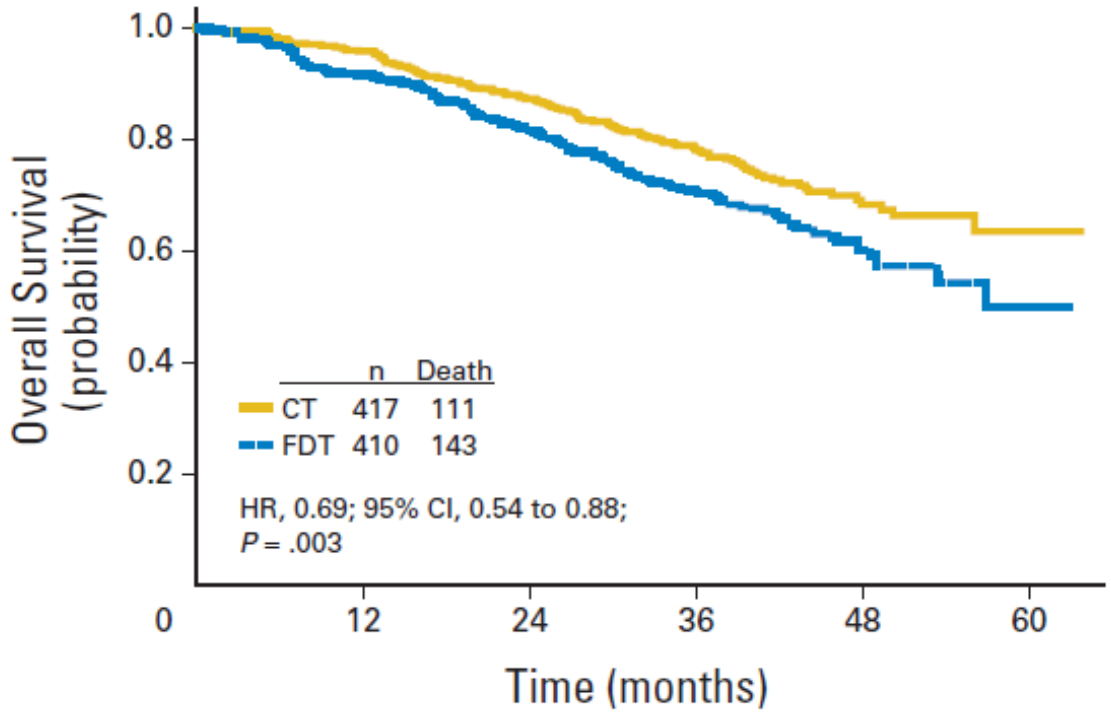
Continuous Therapy vs Fixed Duration





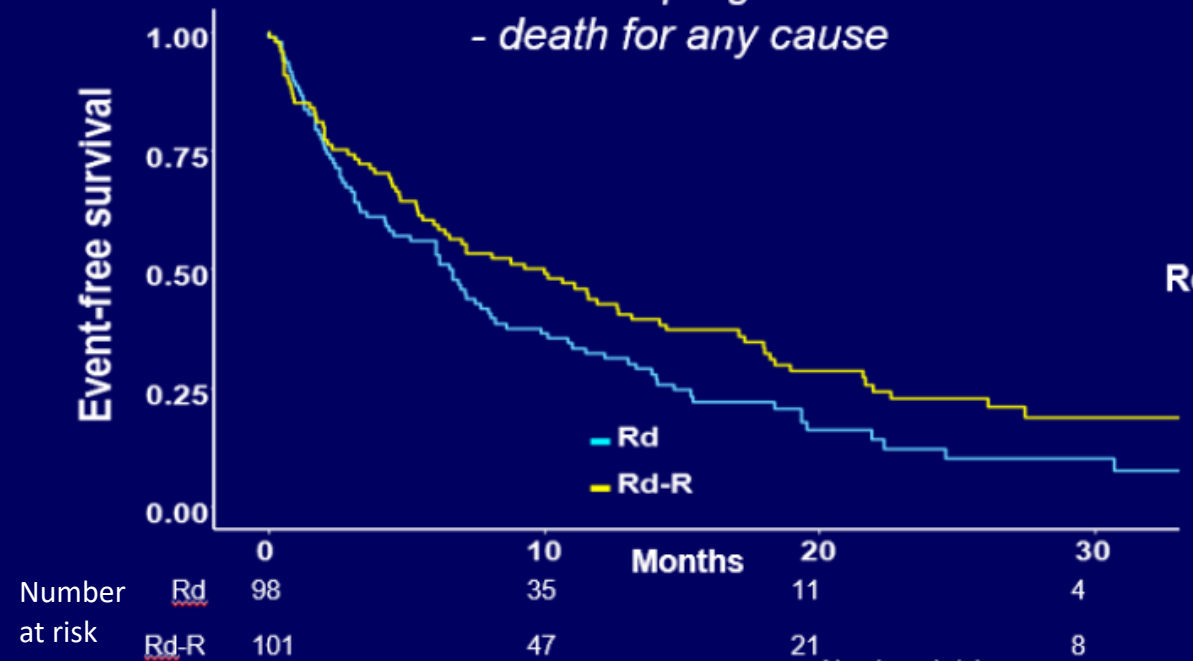
MAYO CLINIC

Palumbo A et al. J Clin Oncol. 2015;33:3459-66.

Shorter Duration of Dex

Primary endpoint: Event-free Survival (EFS)

Definition of the event:- hematologic grade 4 AEs*
- non-hematologic grade 3-4 AEs including SPM
- discontinuation of lenalidomide therapy
- disease progression
- death for any cause



	N	Median EFS
Rd-R	101	9.3 months
Rd	98	6.6 months

Rd-R vs Rd: HR 0.72; CI 0.52-0.99; p=0.044

Larocca et al. ASH 2018.[abstract 355].

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Duration of Therapy

- Ongoing debate
- Improves PFS, effect on OS not consistent
- Increased toxicity, especially long term
- Quality-of-life impact
- Cost of care

Conclusions

- Melphalan not necessary as part of initial therapy
- VRd or Dara-Rd are preferred regimens for initial therapy
- VRd for high-risk patients
- Rd in elderly, frail patients
- Continuous therapy until progression, if well tolerated, is reasonable
- Dose modifications for age and frailty important
- Early discontinuation of dexamethasone important
- Careful monitoring for toxicity important

MAYO CLINIC

kumar.shaji@mayo.edu

THANK YOU