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

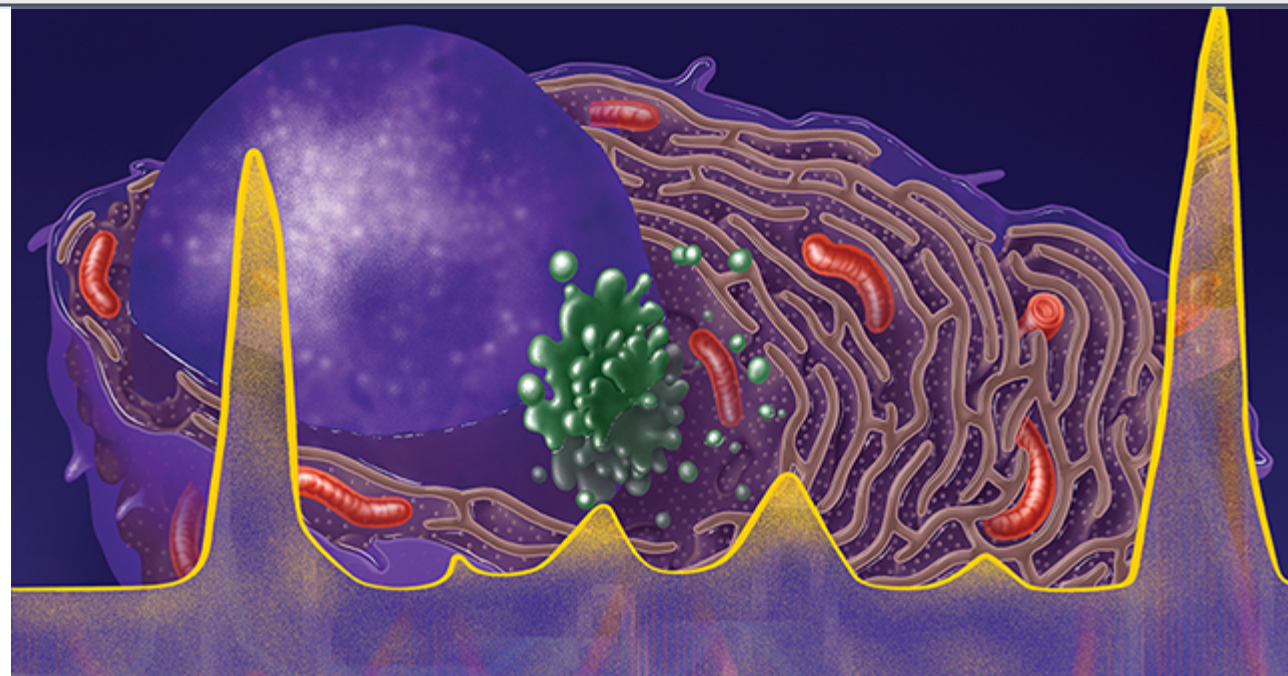
PURDUE UNIVERSITY

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

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Associate Director, Myeloma Program
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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

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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:

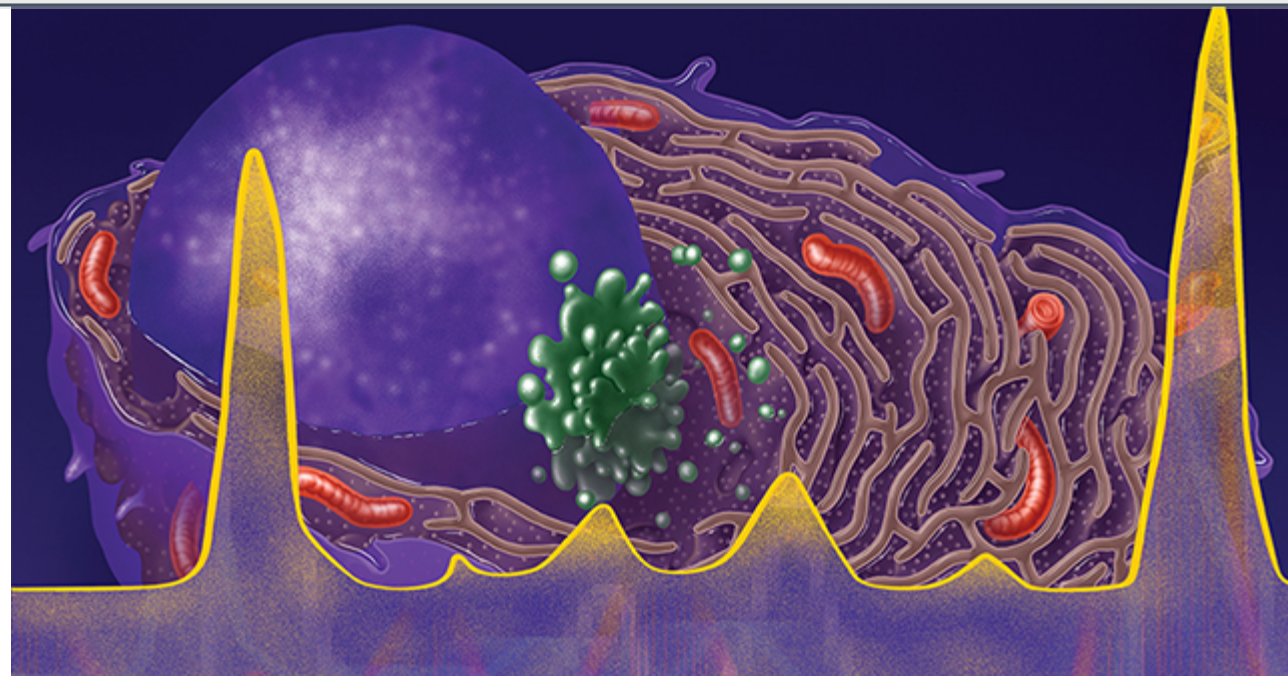
- Initiate treatment for appropriate patients based on an accurate diagnosis of monoclonal gammopathy of undetermined significance, smoldering MM, or active MM
- Create individualized treatment strategies for patients with newly diagnosed MM through consideration of the available clinical data as well 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

The Current Therapeutic Landscape for Relapsed or Refractory MM: Which Combinations to Use and When?

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



Faculty

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

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

Patient Case Example

- A 72-year-old male otherwise healthy presented with back pain and fatigue
  - X-ray showed multiple compression fracture at L4 and L5
- Labs:
  - Hemoglobin: 9.5 g/dL
  - Total protein: 11 g/dL
  - LC_{Kappa}: 1200 mg/L
  - β_2M: 3.8 mg/L
  - Creatinine: 1.2 mg/dL
  - SPEP → M-prot: 4.2 g/dL
  - LC_{lamba}: 5 mg/L
  - LDH: 250 U/L (199 ULN)
  - Calcium: 10.6 mg/dL
  - IFE → IgG kappa
  - k/l ratio: 240
  - Alb: 3.7 g/dL
- Imaging: PET/CT scan showed multiple hypermetabolic lytic lesions, no extramedullary disease noted
- Bone marrow biopsy: 75% kappa-restricted plasma cells, FISH: 1q21 gain, t(4;14)

Patient Case Example, Continued

- He was treated with bortezomib/lenalidomide/dexamethasone (RVd) for 6 cycles and achieved a VGPR
- He was considered a transplant candidate and underwent ASCT
- 3-month response: sCR (serum immunofixation and SPEP were negative, normal sFLC, < 5% PC, IHC negative] *BUT* he was MRD-positive
- He received continuous RVd for maintenance therapy for 21 months until follow-up showed increasing light chain (kappa 150 mg/L, lambda 5 mg/L; ratio: 30), but he remained asymptomatic

In your current clinical practice, which of the following treatment options would you choose?

Expert Recommendations	
Brian G.M. Durie, MD	Daratumumab/carfilzomib/dexamethasone Daratumumab/pomalidomide/dexamethasone Carfilzomib/pomalidomide/dexamethasone
Shaji Kumar, MD	Daratumumab/pomalidomide/dexamethasone
Thomas G. Martin, MD	Daratumumab/pomalidomide/dexamethasone
Philippe Moreau, MD	Unsure
S. Vincent Rajkumar, MD	Daratumumab/bortezomib/dexamethasone
Jesus San-Miguel, MD	Daratumumab/carfilzomib/dexamethasone Daratumumab/pomalidomide/dexamethasone Carfilzomib/pomalidomide/dexamethasone

Slide credit: clinicaloptions.com

Patient Case Example, Continued

- The patient was treated with daratumumab/pomalidomide/dexamethasone (DPd) and after 2 cycles, achieved a VGPR (immunofixation positive)
- He continued DPd, with reduction in pomalidomide and dexamethasone due to side effects
- At 9 months, he experienced increasing light chain values (kappa 50 mg/L, lambda 2.5 mg/L; ratio: 20) and developed symptomatic femur pain
  - MRI shows large bone lesions with ST component
  - PET shows no other lesions

In your current clinical practice, which of the following treatment options would you choose next?

Expert Recommendations	
Brian G.M. Durie, MD	Clinical trial targeting BCMA
Shaji Kumar, MD	Clinical trial targeting BCMA
Thomas G. Martin, MD	Carfilzomib/pomalidomide/dexamethasone Clinical trial targeting BCMA (*if extrameduallary/non-secretory disease allowed*)
Philippe Moreau, MD	Unsure
S. Vincent Rajkumar, MD	Carfilzomib/pomalidomide/dexamethasone
Jesus San-Miguel, MD	Clinical trial targeting BCMA

Slide credit: clinicaloptions.com

Patient Case Example, Continued

- Patient was treated with carfilzomib/pomalidomide/dexamethasone (KPd)
- He achieved stable disease (stable sFLC values) for 4 cycles then a repeat PET shows “2 new lesions”

In your current clinical practice, which of the following treatment options would you choose next?

Expert Recommendations	
Brian G.M. Durie, MD	Clinical trial targeting BCMA
Shaji Kumar, MD	Clinical trial targeting BCMA
Thomas G. Martin, MD	All of the above
Philippe Moreau, MD	Unsure
S. Vincent Rajkumar, MD	Clinical trial targeting BCMA
Jesus San-Miguel, MD	Clinical trial targeting BCMA

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Selection of Regimen

- Timing of the relapse
- Response to prior therapy
- Aggressiveness of the relapse
- Performance status

The Data

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Approval Data for Early Relapse Options

- Carfilzomib
- Ixazomib
- Daratumumab
- Elotuzumab

New Drug + Rd versus Rd

Rajkumar SV. 2019

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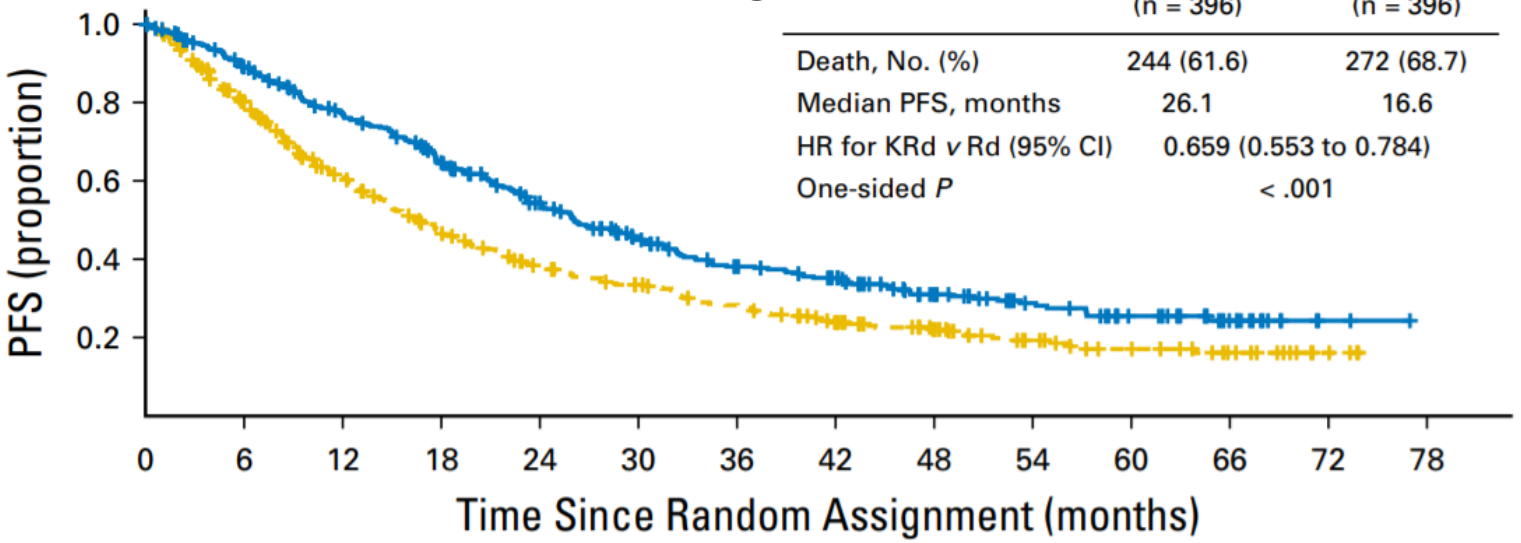
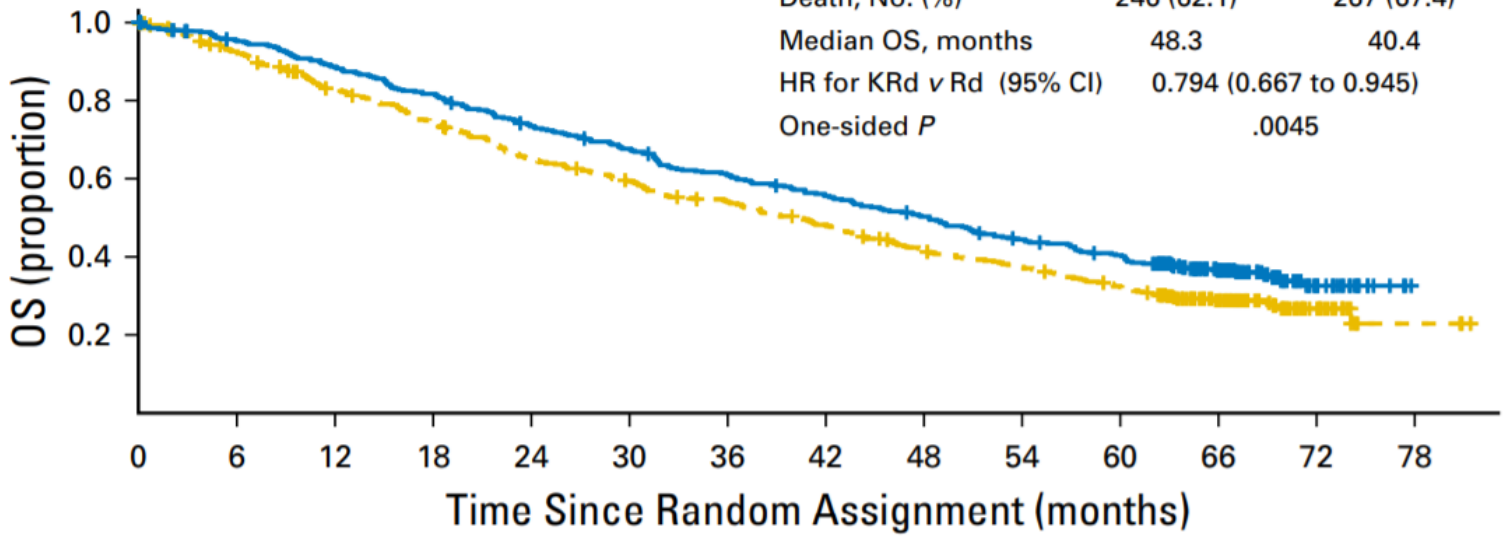
Carfilzomib Rd vs Rd: ASPIRE Trial

PFS



	KRd (n = 396)	Rd (n = 396)
Death, No. (%)	244 (61.6)	272 (68.7)
Median PFS, months	26.1	16.6
HR for KRd *v* Rd (95% CI)	0.659 (0.553 to 0.784)	
One-sided *P*	< .001	

OS



	KRd (n = 396)	Rd (n = 396)
Death, No. (%)	246 (62.1)	267 (67.4)
Median OS, months	48.3	40.4
HR for KRd *v* Rd (95% CI)	0.794 (0.667 to 0.945)	
One-sided *P*	.0045	

Siegel. JCO. 2018;36:728.

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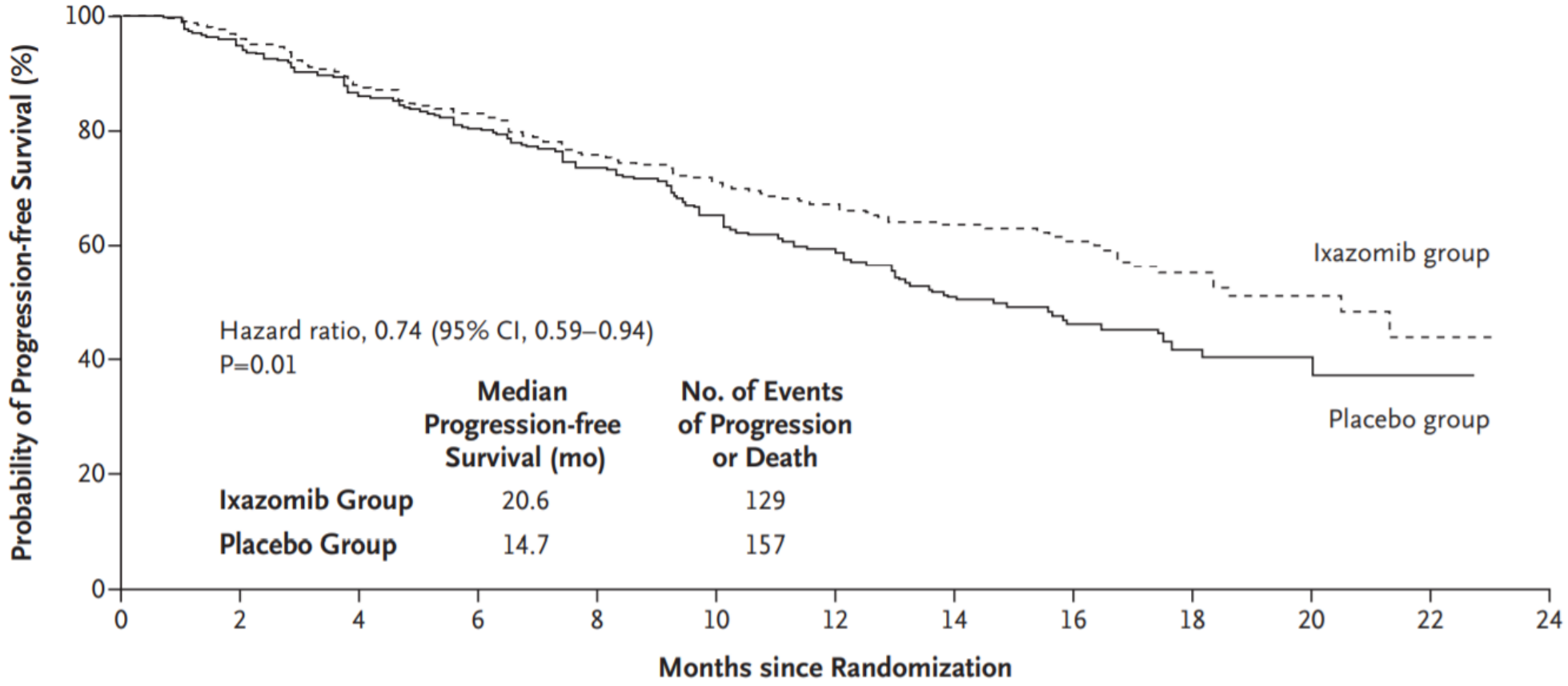
Ixazomib-Rd vs Rd: TOURMALINE-MM1 Trial



No. at Risk

Ixazomib group	360	345	332	315	298	283	270	248	233	224	206	182	145	119	111	95	72	58	44	34	26	14	9	1	0
Placebo group	362	340	325	308	288	274	254	237	218	208	188	157	130	101	85	71	58	46	31	22	15	5	3	0	0

Moreau. NEJM. 2016;374:1621.

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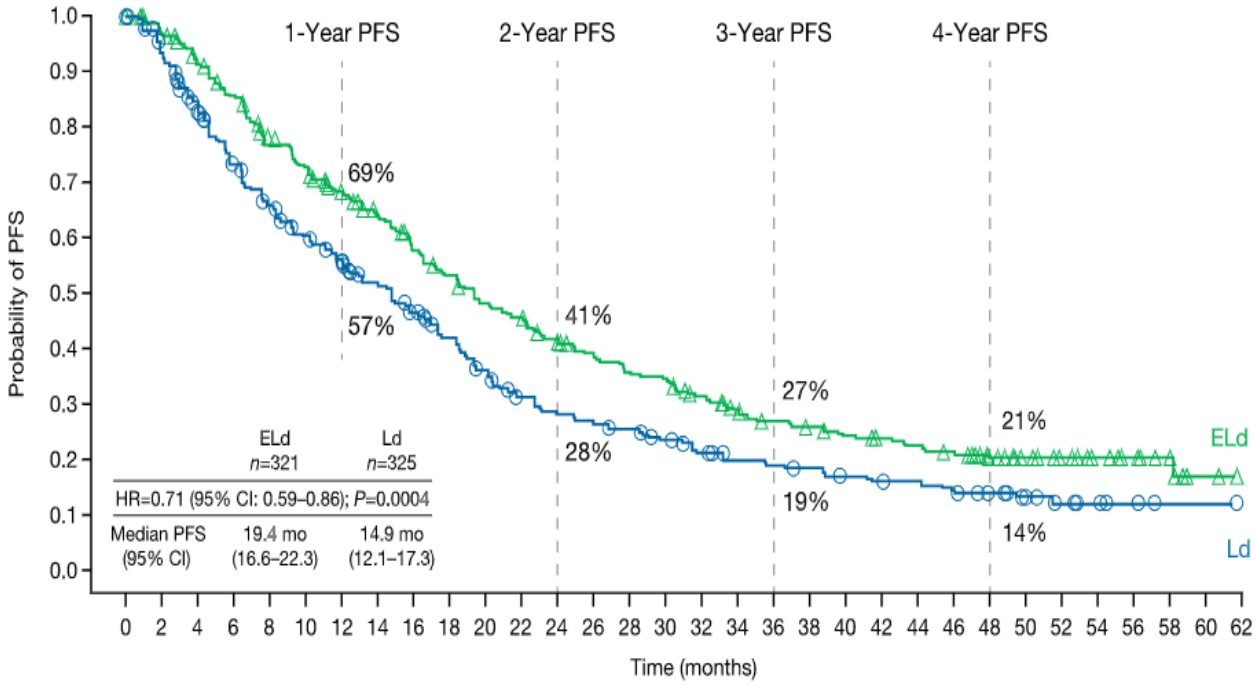
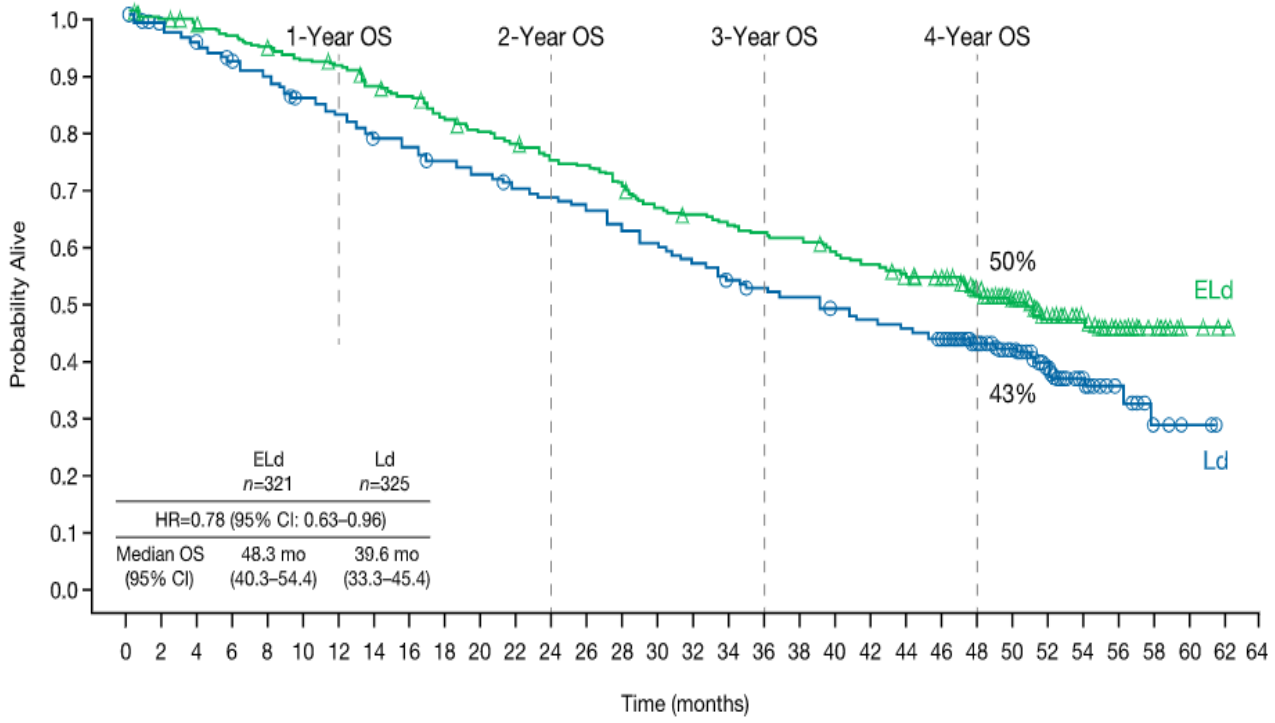
Elotuzumab Rd vs Rd: ELOQUENT-2 Trial

PFS



OS



Dimopoulos. Cancer. 2018;124:4032.

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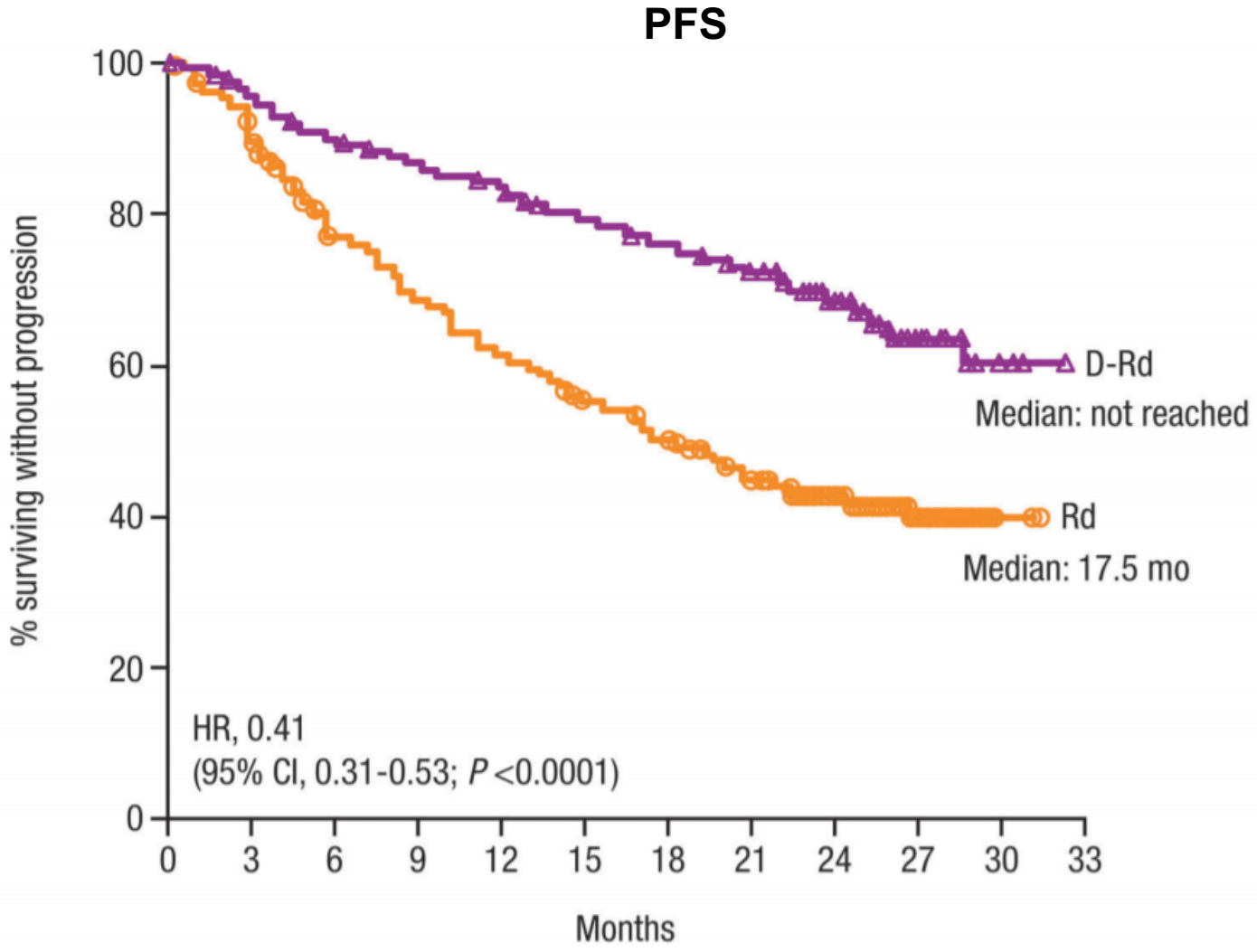
Daratumumab Rd vs Rd: POLLUX Trial



Dimopoulos. Haematologica. 2018;103:2088.

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Approval Data for Early Relapse Options

- Panobinostat
- Daratumumab

New Drug + Vd versus Vd

Rajkumar SV. 2019

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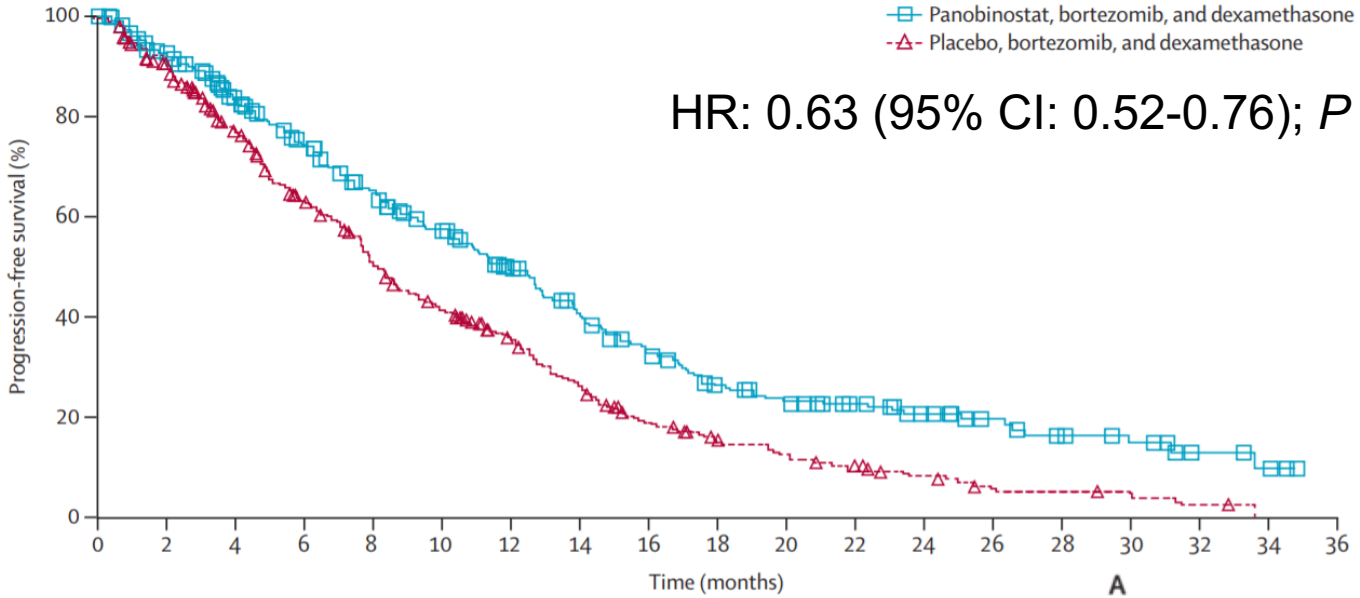
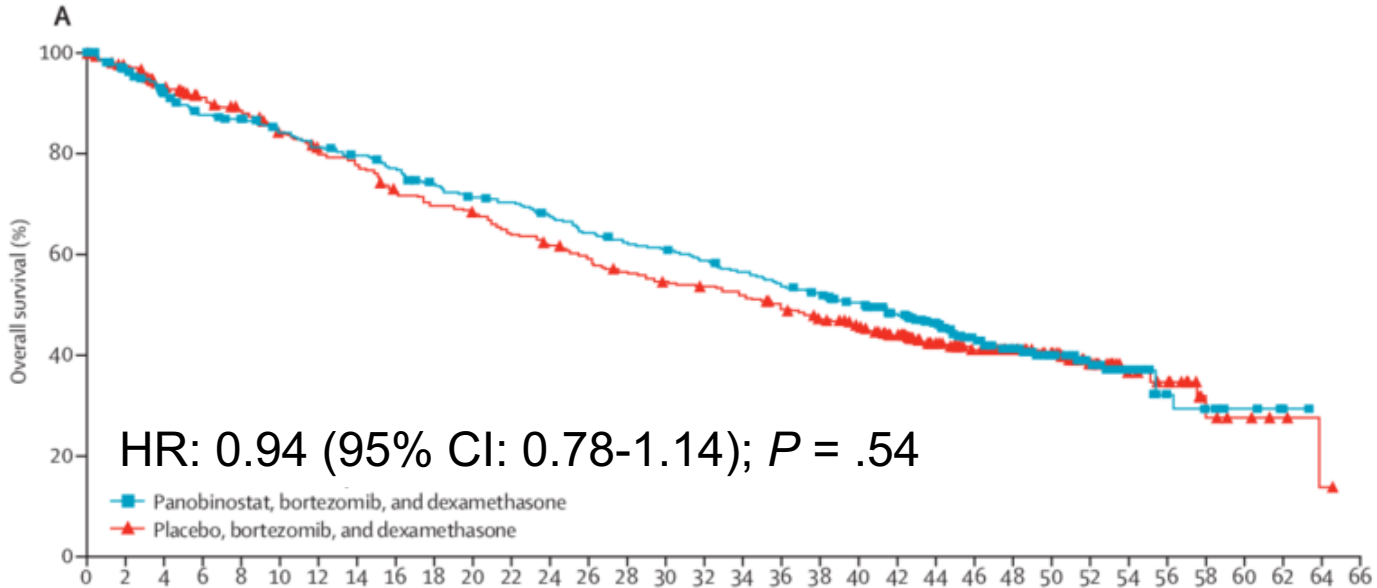
Panobinostat-Vd vs Vd: PANORAMA-1 Trial



HR: 0.63 (95% CI: 0.52-0.76); *P* < .0001



HR: 0.94 (95% CI: 0.78-1.14); *P* = .54

San Miguel. Lancet Haematol. 2016;3:e50.

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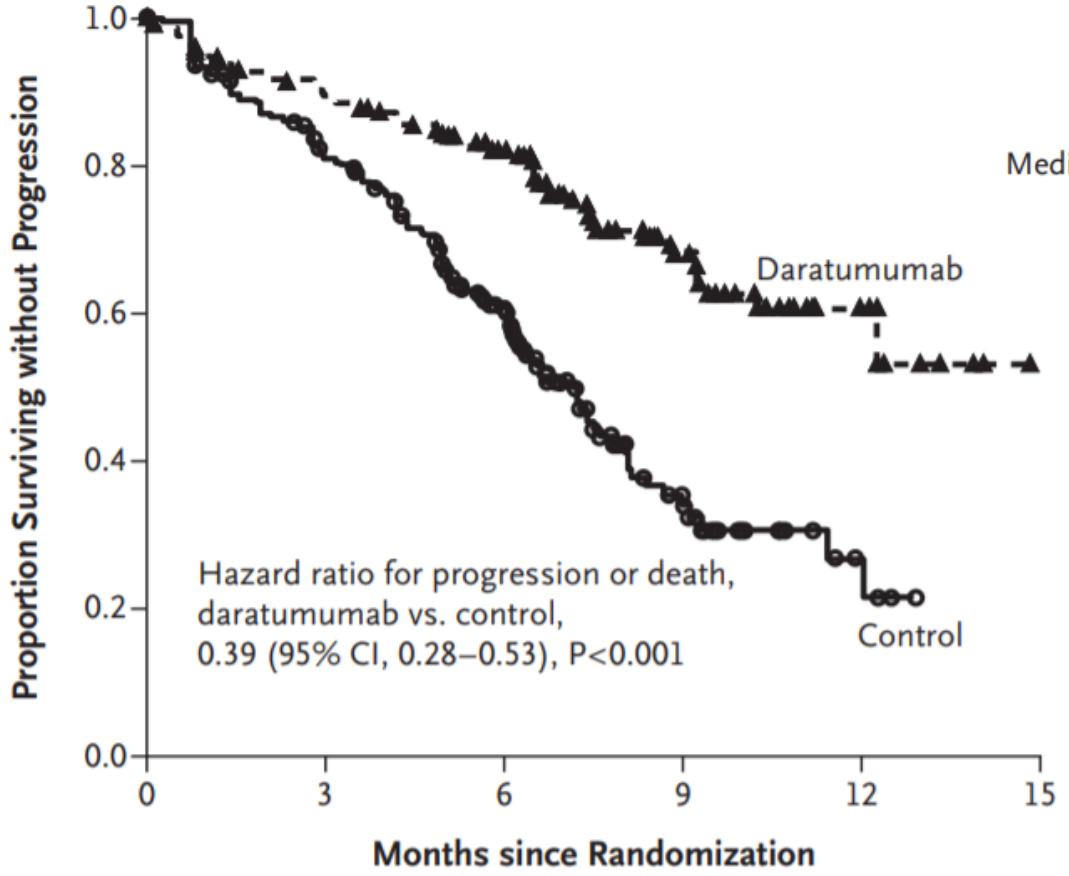
Daratumumab-Vd vs Vd (PFS): CASTOR Trial



	Daratumumab Group (N=251)	Control Group (N=247)
Median progression-free survival (mo)	NE	7.2

No. at Risk						
Daratumumab group	251	215	146	56	11	0
Control group	247	182	106	25	5	0

Palumbo. NEJM. 2016;375:754.

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Trial	CR, %	Median PFS, Mos	HR for PFS (95% CI)	*P* Value
Len-based regimens				
TOURMALINE-MM1			0.74 (0.59-0.94)	0.01
• Lenalidomide/dexamethasone	7	14.7		
• Ixazomib/lenalidomide/dexamethasone	12	20.6		
ELOQUENT-2			0.70 (0.57-0.85)	< 0.001
• Lenalidomide/dexamethasone	7	14.9		
• Elotuzumab/lenalidomide/dexamethasone	4	19.4		
ASPIRE			0.69 (0.57-0.83)	< 0.001
• Lenalidomide/dexamethasone	14	17.6		
• Carfilzomib/lenalidomide/dexamethasone	32	26.3		
POLLUX			0.37 (0.27-0.52)	< 0.001
• Lenalidomide/dexamethasone	19	18.4		
• Daratumumab/lenalidomide/dexamethasone	43	NR		
Bortezomib-based regimens				
PANORAMA1			0.63 (0.52-0.76)	< 0.001
• Bortezomib/dexamethasone	6	8.1		
• Panobinostat/bortezomib/dexamethasone	11	12.0		
CASTOR			0.39 (0.28-0.53)	< 0.001
• Bortezomib/dexamethasone	9	7.2		
• Daratumumab/bortezomib/dexamethasone	19	NR		

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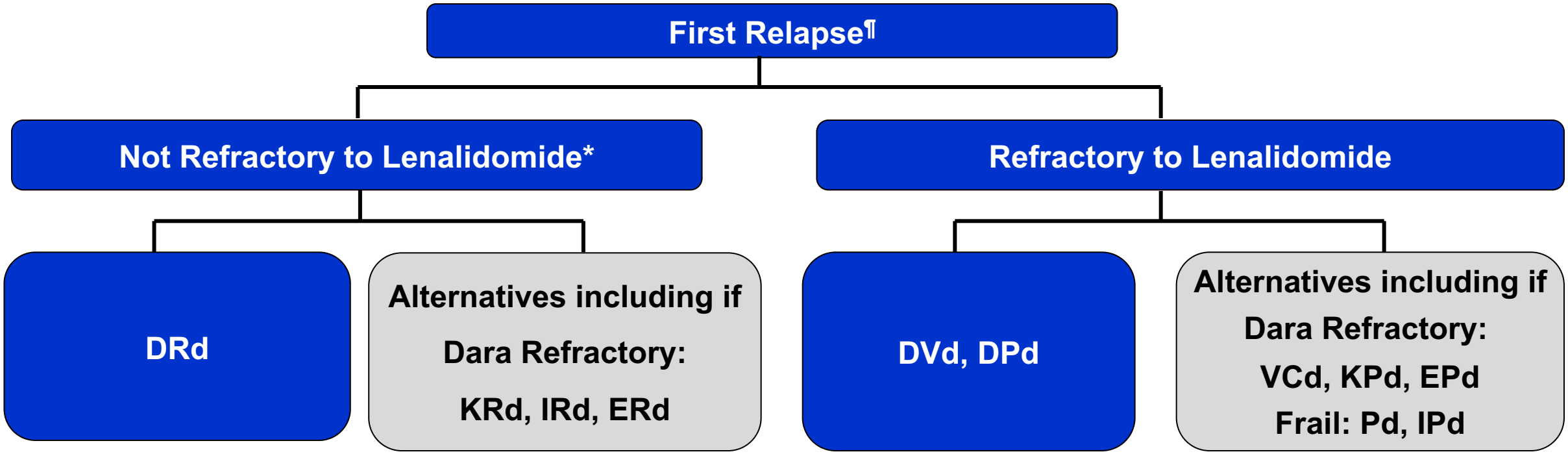
Myeloma: First Relapse



*Relapse occurring while off all therapy, or while on small doses of single-agent lenalidomide, or on bortezomib maintenance

¶ Consider salvage auto transplant in eligible patients

Rajkumar. NEJM. 2016;375:1390.

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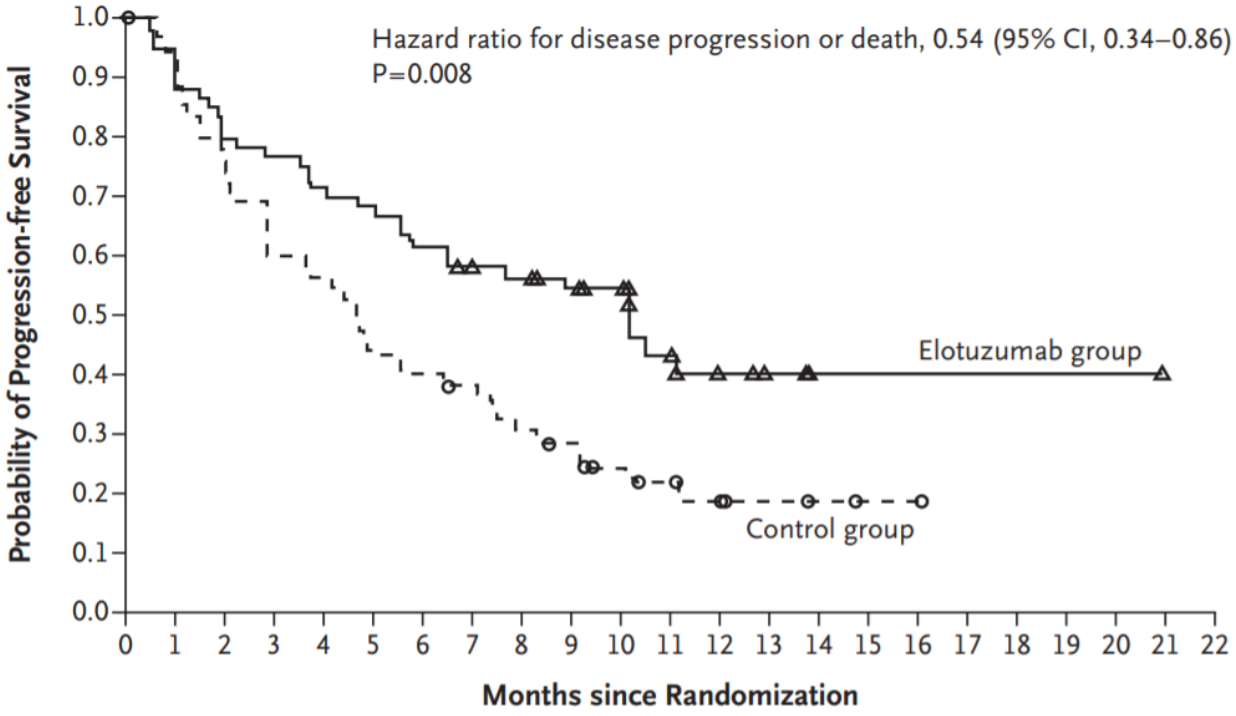
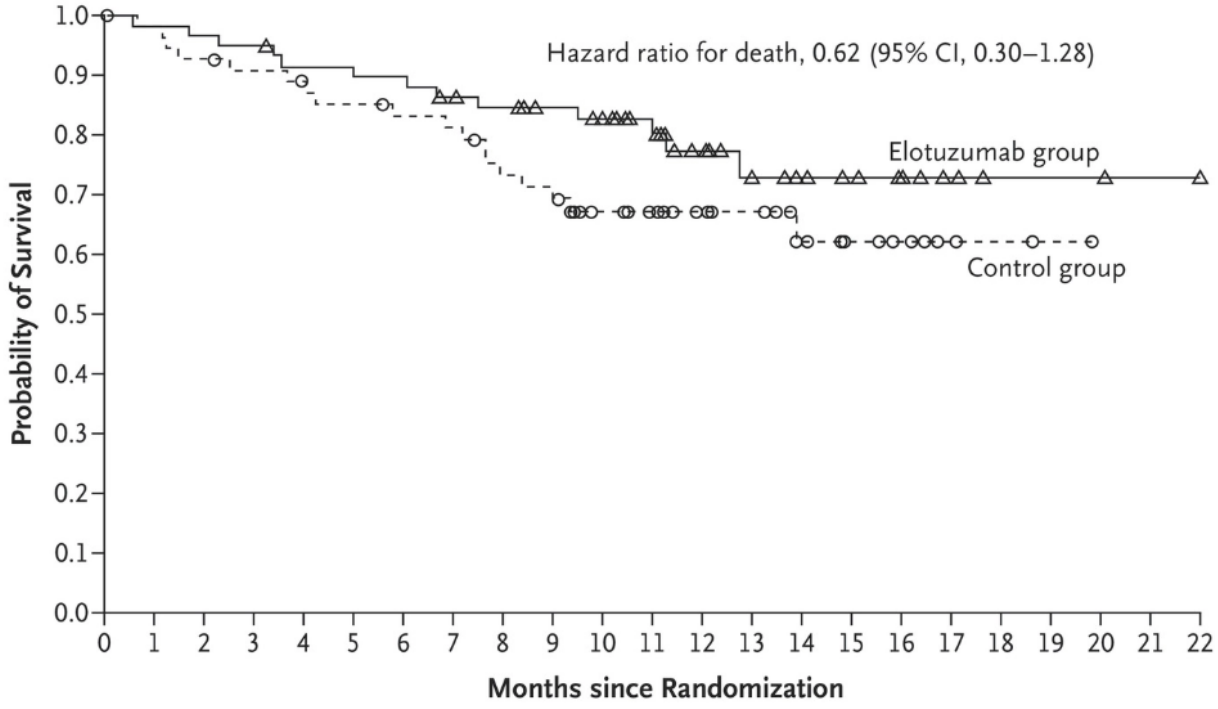
Elotuzumab-Pd vs Pd: ELOQUENT-3

PFS



OS



Dimopoulos. NEJM. 2018;379:1811.

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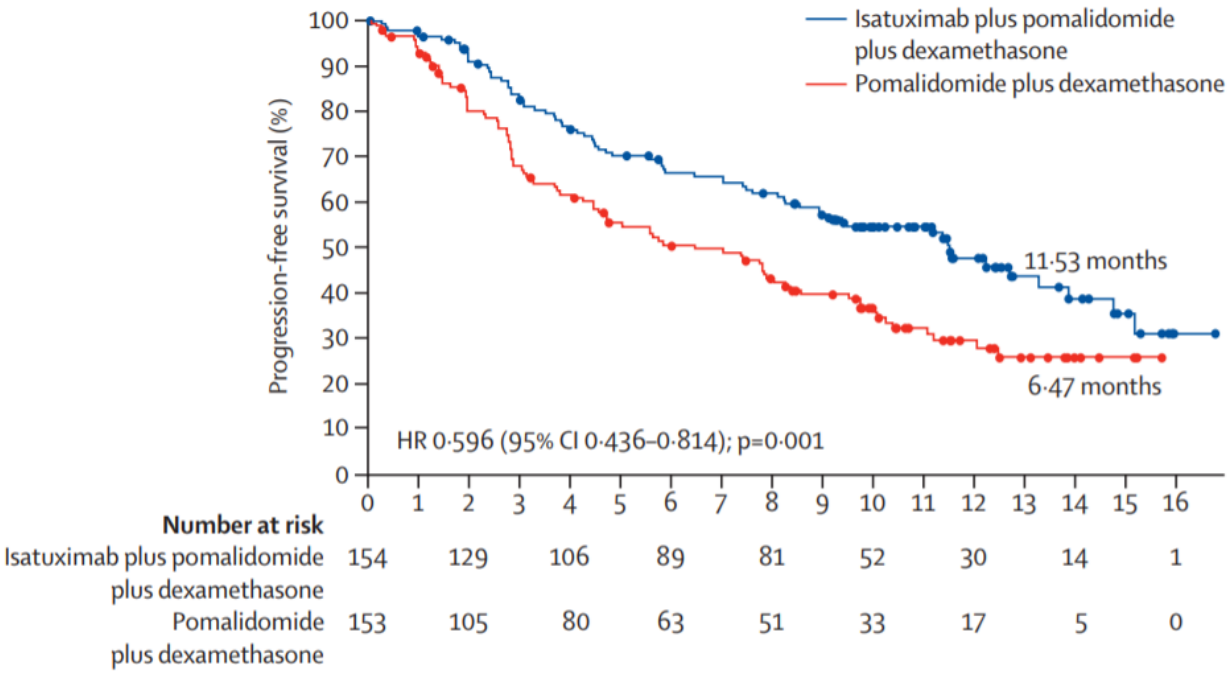
Isatuximab-Pd vs Pd (PFS and OS): ICARIA Trial

PFS



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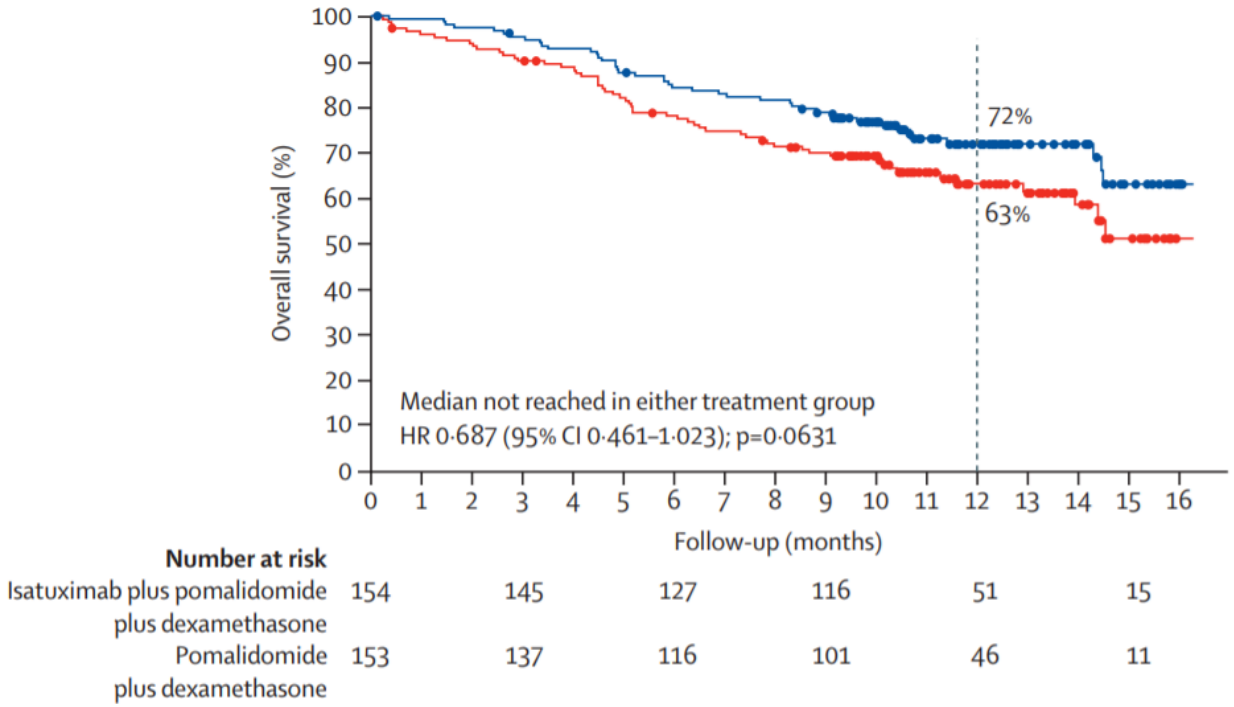

Attal. Lancet. 2019 [Epub ahead of print]

icariamm

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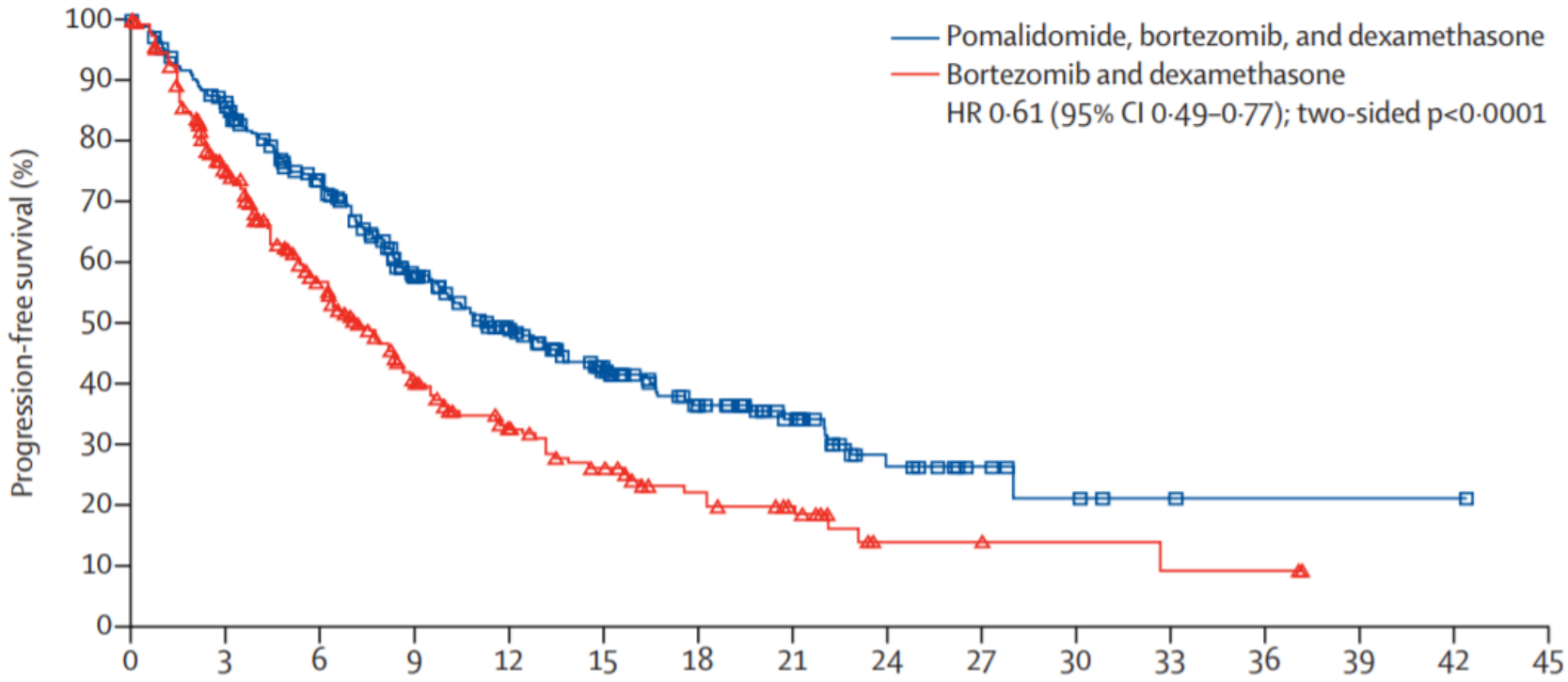
PVd vs Vd (PFS): OPTIMISMM Trial



Number at risk (number censored)																
Pomalidomide, bortezomib, and dexamethasone	281 (0)	233 (11)	182 (28)	128 (46)	94 (62)	67 (76)	47 (88)	28 (105)	13 (115)	7 (121)	4 (123)	2 (125)	1 (126)	1 (126)	1 (126)	0 (127)
Bortezomib and dexamethasone	278 (0)	176 (39)	112 (63)	66 (79)	42 (92)	30 (96)	20 (102)	14 (106)	4 (113)	4 (113)	3 (114)	2 (114)	2 (114)	0 (116)	0 (116)	0 (116)

Richardson. Lancet Oncol. 2019;20:781.

ELSEVIER

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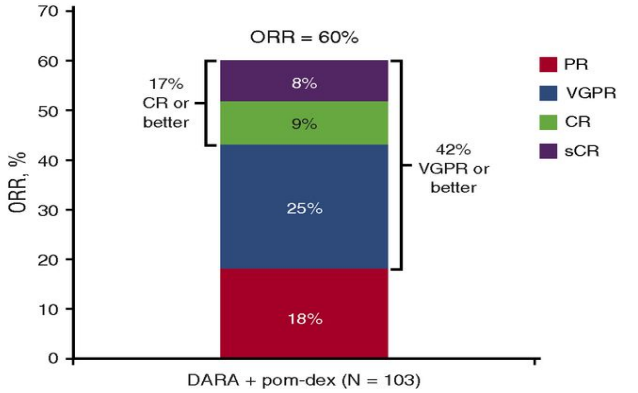
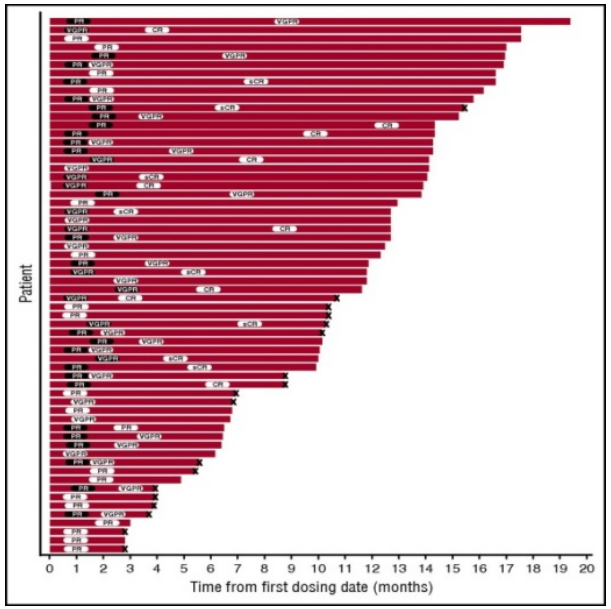
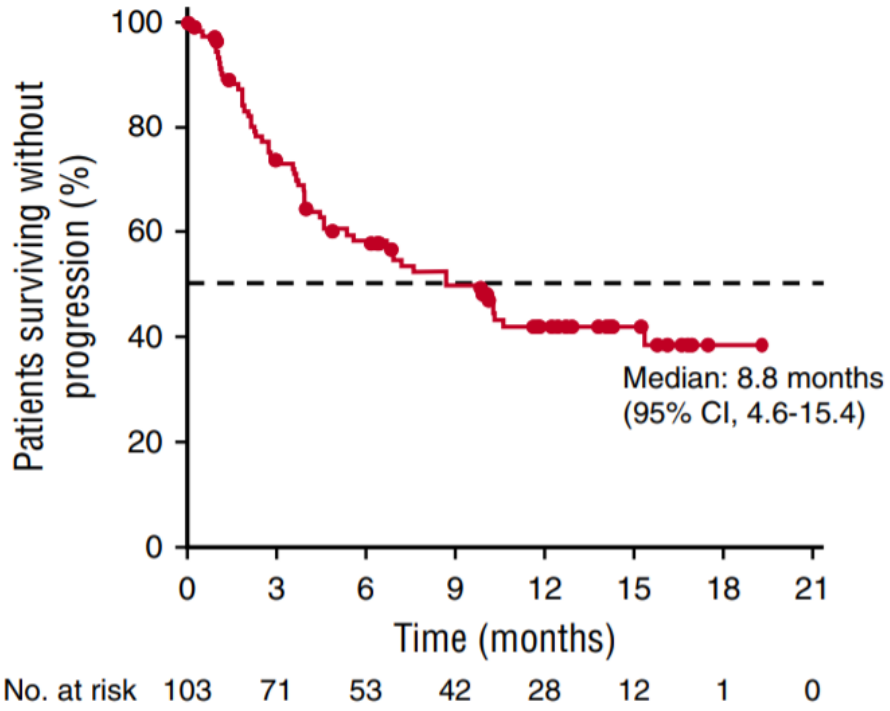
Daratumumab-Pom-Dex: Phase II Trial (n = 103)





PFS



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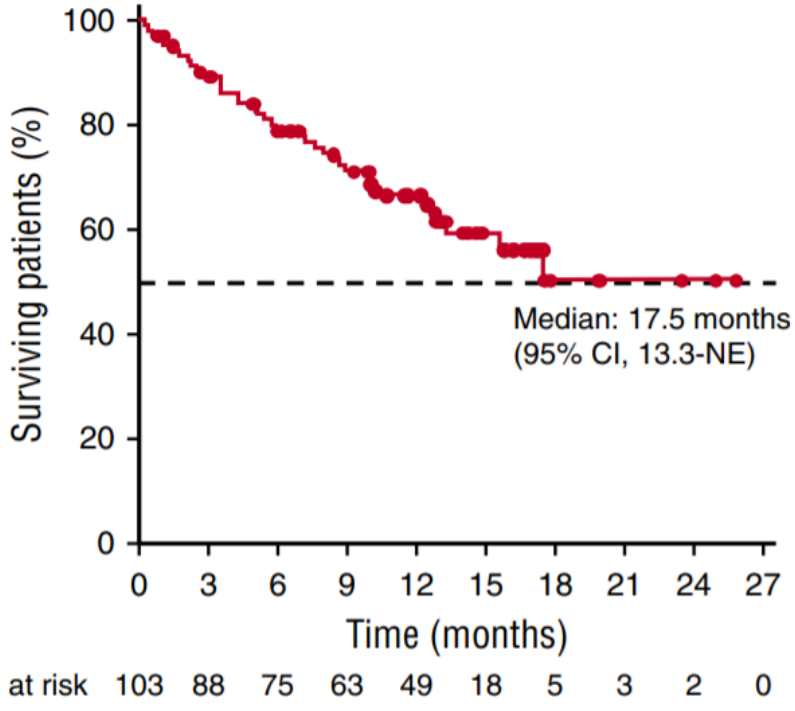

Chari. Blood. 2017;130:974.

blood

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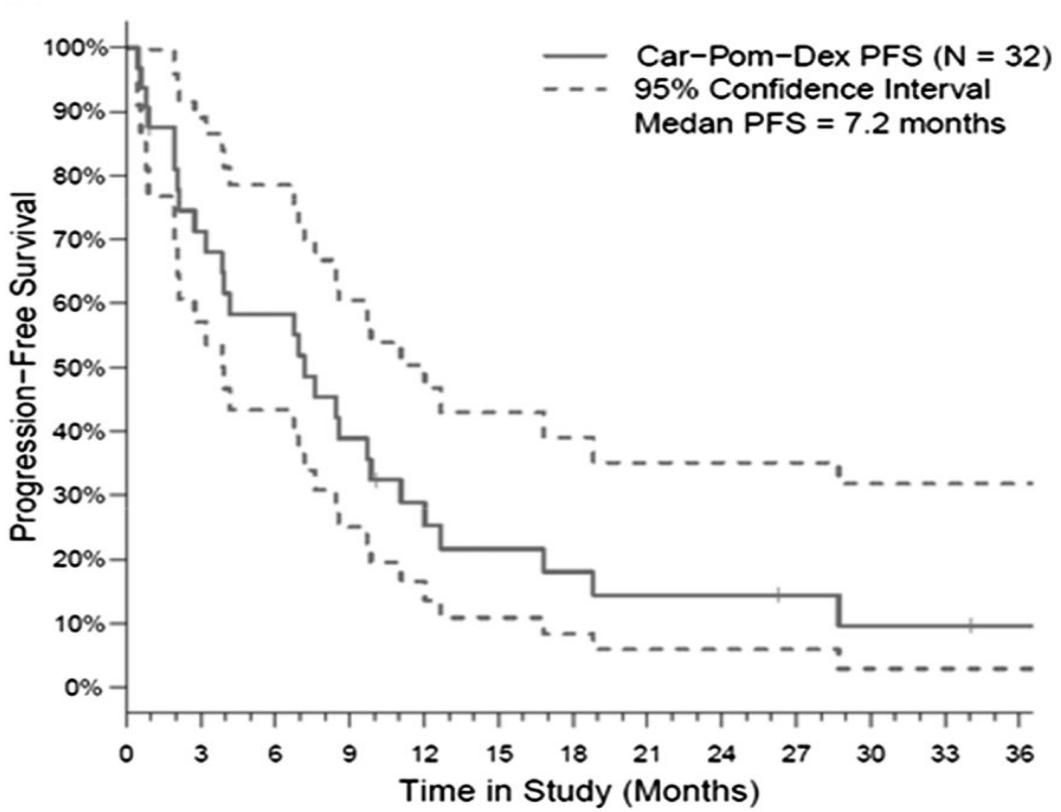
Carfilzomib-Pom-Dex: Phase I Trial (N = 32)

Response Category, n (%)	All Evaluable Patients (N = 32)
ORR	16 (50)
VGPR	5 (16)
PR	11 (34)
MR	5 (16)
SD	8 (25)
PD	3 (9)



Shah. Blood. 2015;126:2284.

blood

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Principles

- Prefer triplets
- At least two new drugs
- Consider transplant in eligible patients
- Clinical Trials

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Myeloma: Second or Higher Relapse

First-Relapse Options

- Any first relapse options that have not been tried

(2 new drugs; triplet preferred)

Additional Options

- VDT-PACE like anthracycline containing regimens
- Melphalan
- Selinexor
- Bendamustine-based regimens
- Adding Panobinostat
- Quadruplet regimens

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Active Drugs in Multiple Myeloma

Old Drugs

- Alkylators
- Steroids
- Interferon
- Anthracyclines

Older Drugs (2003-2007)

- Bortezomib
- Thalidomide
- Lenalidomide
- Liposomal doxorubicin

Recently Approved Drugs (2013-2019)

- Carfilzomib
- Pomalidomide
- Ixazomib
- Daratumumab
- Panobinostat
- Elotuzumab
- Selinexor

Future Drugs

- CAR-Ts
- Belantamab mafodotin (GSK2857916)
- AMG 420/ AMG701
- Isatuximab
- Iberdomide (CC-220)
- Venetoclax
- Melflufen
- Filanesib
- LGH 447
- Dinaciclib
- Oprozomib
- Marizomib

Rajkumar SV. 2019