Myeloma: 2020 Update

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MAYO CLINIC

No conflicts to disclose

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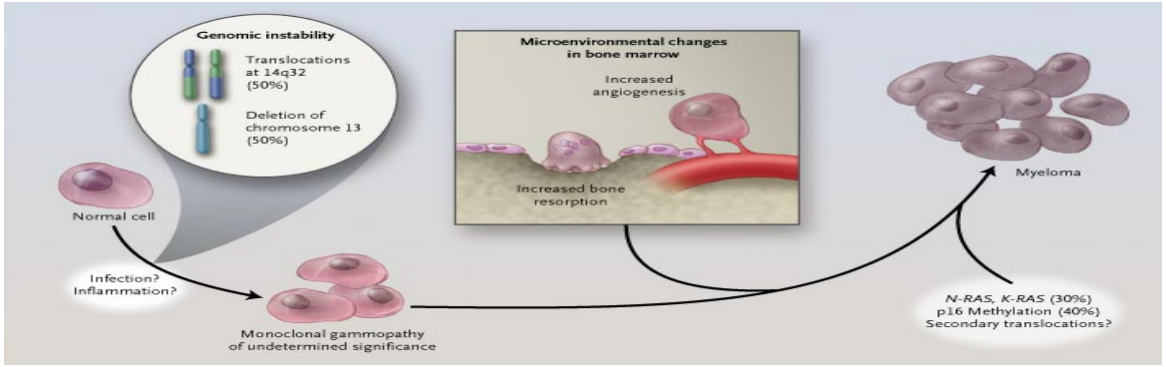
Previous Disease Definitions

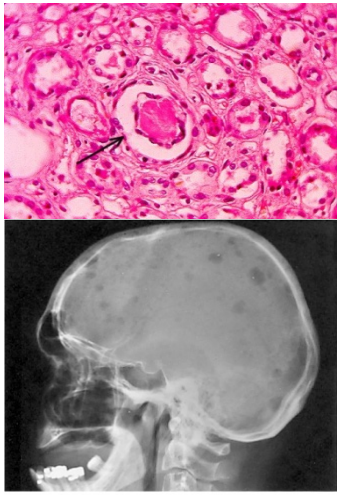
MGUS	SMM	MM

- <10% BMPC AND
- <3gm/dL M protein AND
- No CRAB

- ≥10% BMPC OR
- ≥3 gm/dL M protein AND
- No CRAB

- Clonal PCPD
- CRAB





CRAB= Hypercalcemia, renal failure, anemia, or lytic bone lesions attributable to a clonal plasma cell disorder

Rajkumar SV. Cecil Textbook of Medicine, 26th Edition, 2020

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Revised IMWG Criteria

MGUS	SMM	MM
• <10% BMPC AND • <3 gm/dL M protein AND • No MDE	• ≥10%-60% BMPC OR • ≥3 gm/dL S. M protein OR • ≥500 mg/24h Ur. M protein AND • No MDE	• PCPD, AND • 1 or more MDE • CRAB • ≥60% BMPC • ≥100 FLC ratio • >1 MRI focal lesion

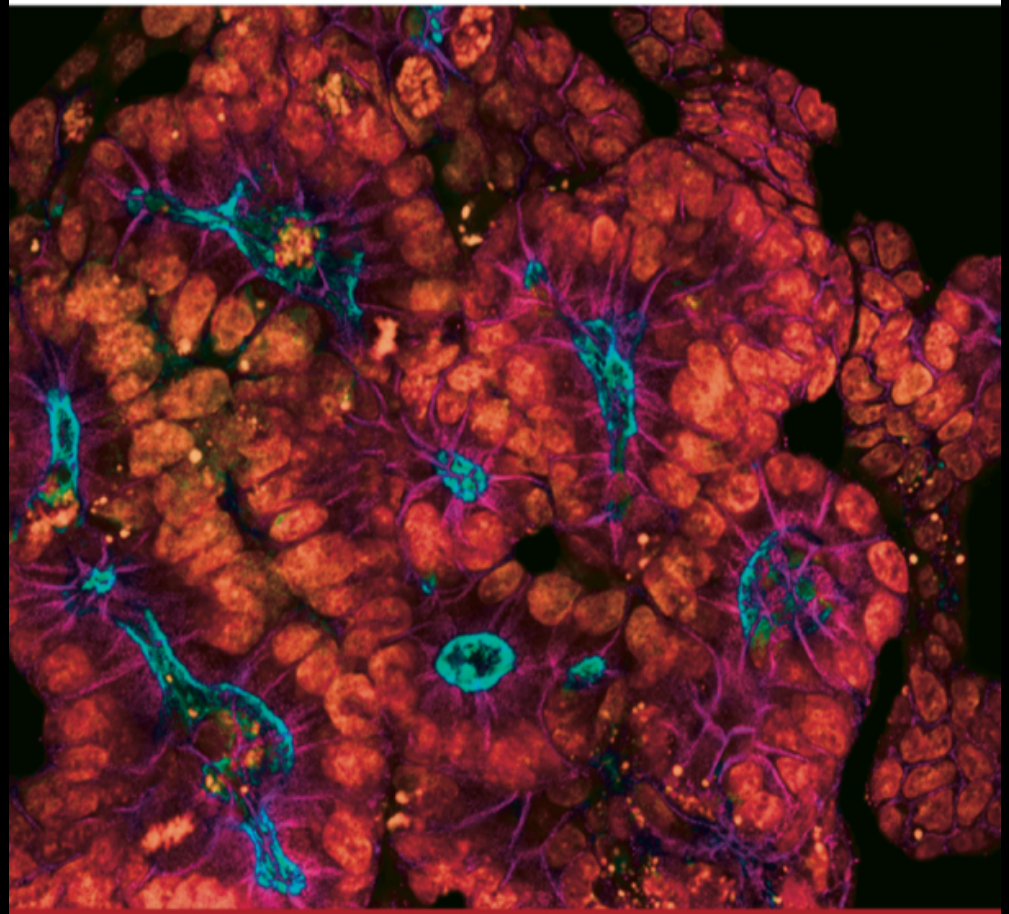
Rajkumar SV, Dimopoulos M, Palumbo A, et al. Lancet Oncol. 2014;15(12):e538-e548.

MDE, myeloma-defining events

nature REVIEWS

July 2018 volume 15 no. 7
www.nature.com/reviews

CLINICAL ONCOLOGY



THE MULTIPLE MYELOMAS
Cytogenetic-based classification to guide therapy

Effective and sustainable drug development
Can high drug prices be tackled?

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Myeloma Classification and Risk-Stratification

High-Risk

- t(14;16) (C-MAF)
- t(14;20) (MAF-B)
- t(4;14) (FGFR3/MMSET)
- del (17p)
- gain (1q)

Standard-Risk

- Trisomies
- t(11;14) (CCND1)
- t(6;14) (CCND3)

Kumar S, et al. Blood. 2012;119:2100-2105

mSMART 3.0: Risk Stratification of Active MM

High-Risk Myeloma

- FISH
  - t(4;14)
  - t(14;16)
  - t(14;20)
  - Del 17p
  - 1q gain

- Double-Hit Myeloma = Any 2 high risk abnormalities
- Triple-Hit Myeloma = 3 or more high risk abnormalities

Standard-Risk Myeloma

All others including:

- Trisomies
- t(11;14)
- t(6;14)

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INITIAL THERAPY

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SWOG VRd vs Rd

Randomization
N = 525
Newly diagnosed MM

Stratification:
- ISS (I, II, III)
- Intent to transplant @ progression (yes/no)

Eight 21-day Cycles of VRd

Bortezomib 1.3/mg^2 IV
Days 1, 4, 8, and 11
Lenalidomide 25 mg/day PO
Days 1-14
Dexamethasone 20 mg/day PO
Days 1, 2, 4, 5, 8, 9, 11, 12

Six 28-day Cycles of Rd

Lenalidomide 25 mg/day PO
Days 1-21
Dexamethasone 40 mg/day PO
Days 1, 8, 15, 22

After induction; Both arms recevied Rd Maintenance Until PD, Toxicity or Withdrawal

Durie BGM, et al. ASH 2015

NCI National Clinical Trials Network
a National Cancer Institute program

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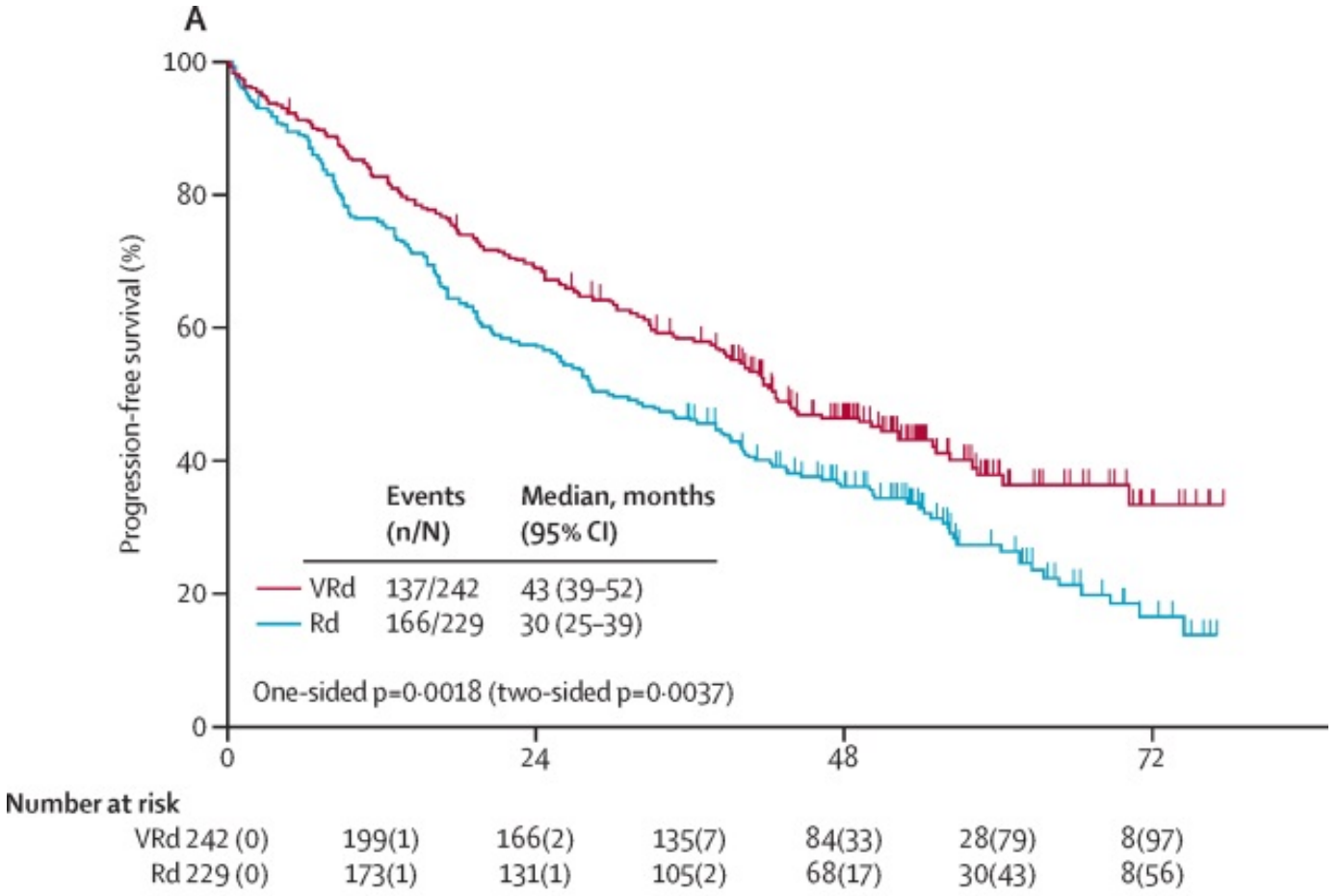
S0777 Trial: VRd vs Rd

Progression-free Survival



Durie et al. The Lancet 2017 389, 519-527DOI: (10.1016/S0140-6736(16)31594-X)

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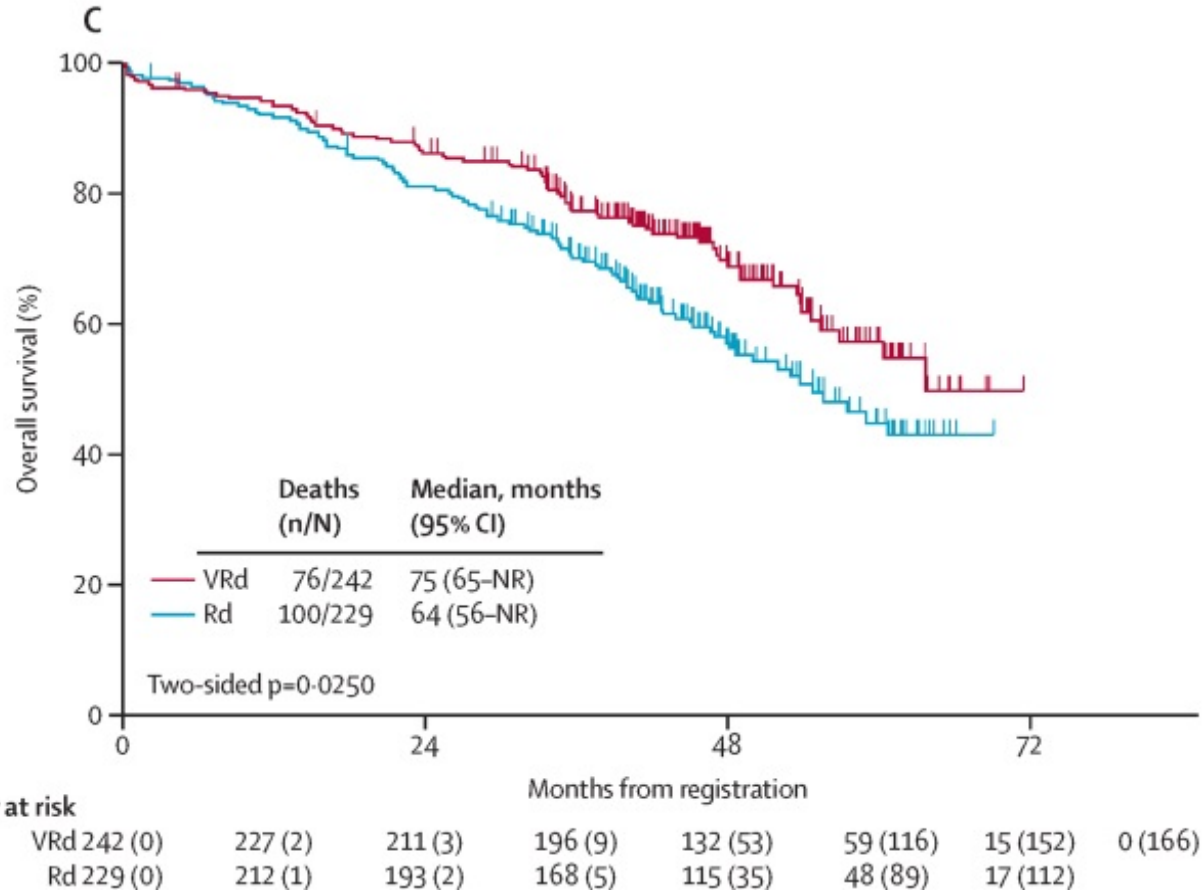
S0777 Trial: VRd vs Rd

Overall Survival



Durie et al. The Lancet 2017 389, 519-527DOI: (10.1016/S0140-6736(16)31594-X)

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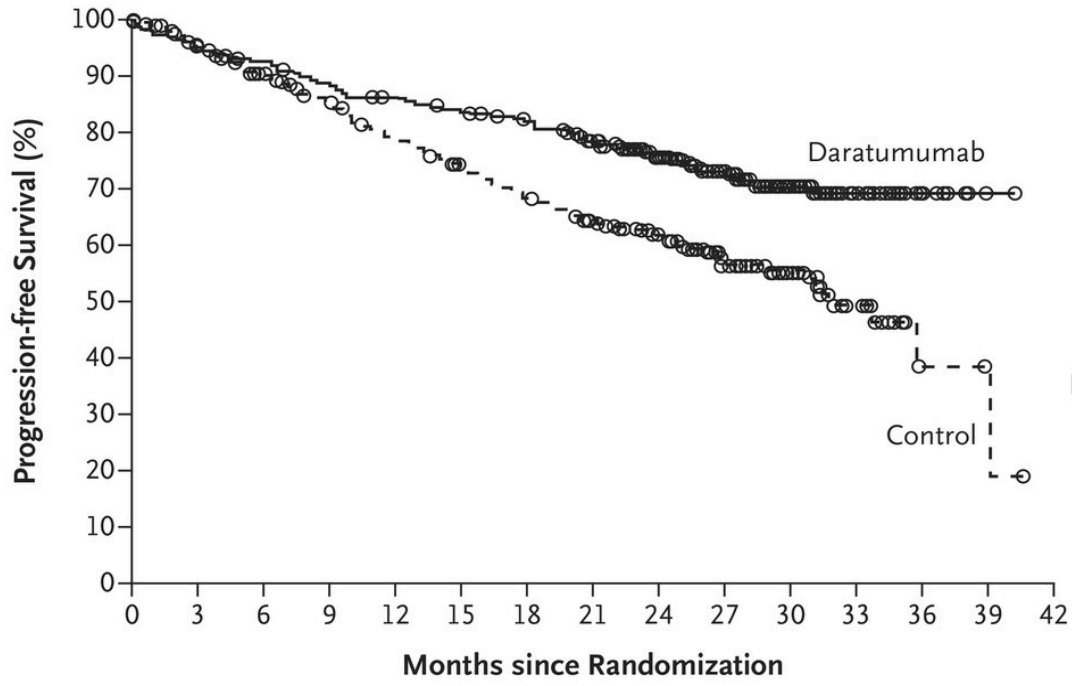
Dara-Rd vs Rd (MAIA trial)
Progression-Free Survival



	No. of Patients	Median Progression-free Survival
		mo
Daratumumab	368	Not reached
Control	369	31.9

Hazard ratio for disease progression or death, 0.56 (95% CI, 0.43–0.73)
P<0.001

No. at Risk

Daratumumab	368	347	335	320	309	300	290	271	203	146	86	35	11	1	0
Control	369	332	307	280	254	236	219	200	149	94	50	18	3	2	0

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

The NEW ENGLAND JOURNAL of MEDICINE

MENU

nature REVIEWS CLINICAL ONCOLOGY

News & Views | Published: 08 March 2019

HAEMATOLOGICAL CANCER

MAIA under the microscope — bringing trial design into focus

Prashant Kapoor & S. Vincent Rajkumar ✉

Nature Reviews Clinical Oncology (2019) | Download Citation ↓

Using the example of the recently reported phase III MAIA trial, we emphasize herein the requirement to dig deeper into trial designs and end points to determine their appropriateness for the questions at hand and to assess whether a benefit in terms of the primary end point — even if statistically significant and seemingly clinically meaningful — is sufficient to warrant a change in clinical practice.

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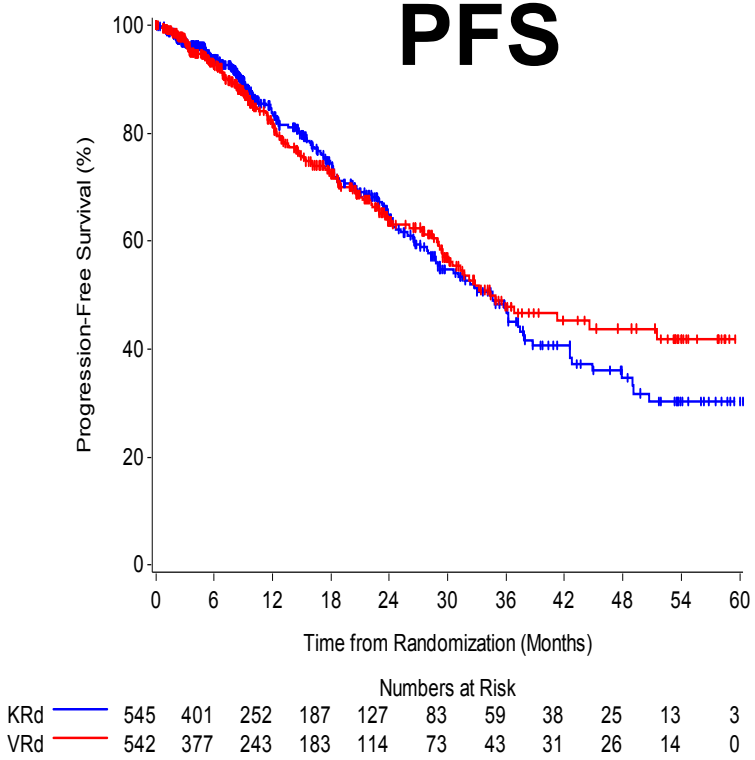
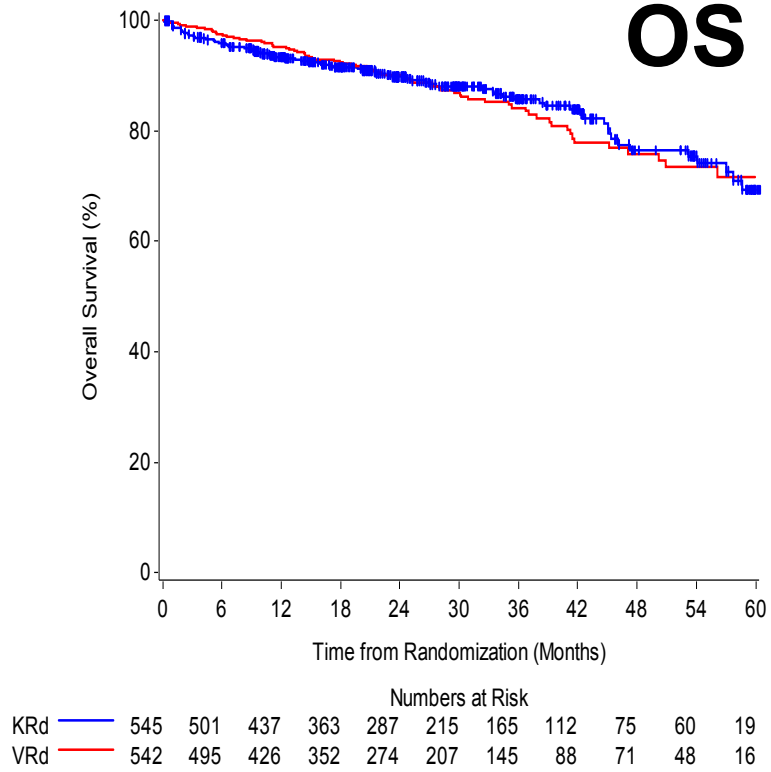
KRd vs VRd (ENDURANCE TRIAL)

PFS



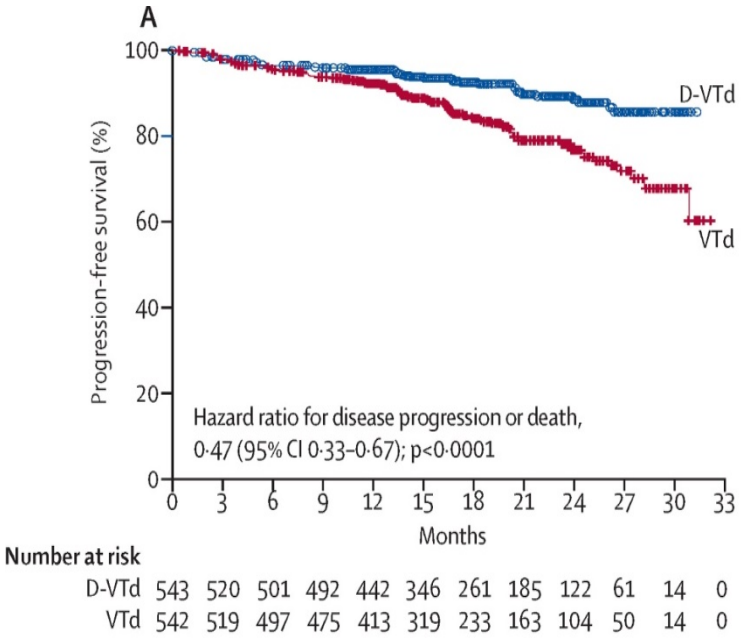
OS

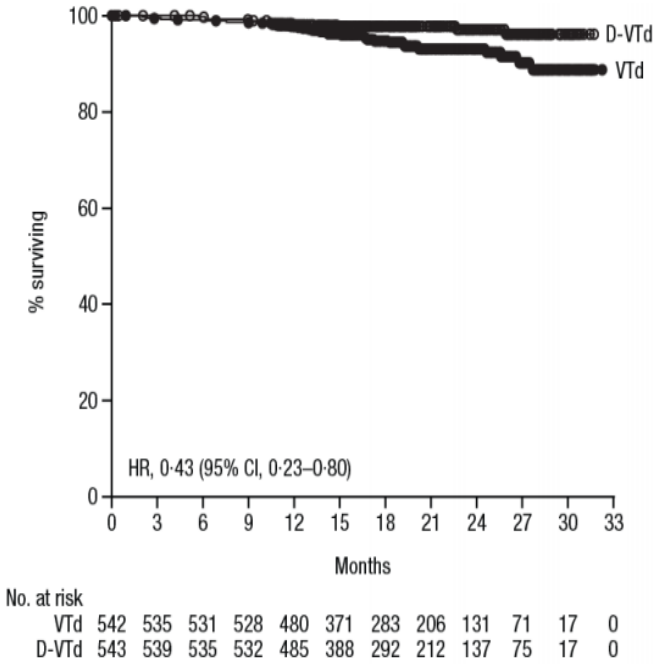


Kumar S. ASCO 2020

MAYO CLINIC

CASSIOPEIA TRIAL: Dara-VTd vs VTd Quadruplets as Initial Therapy

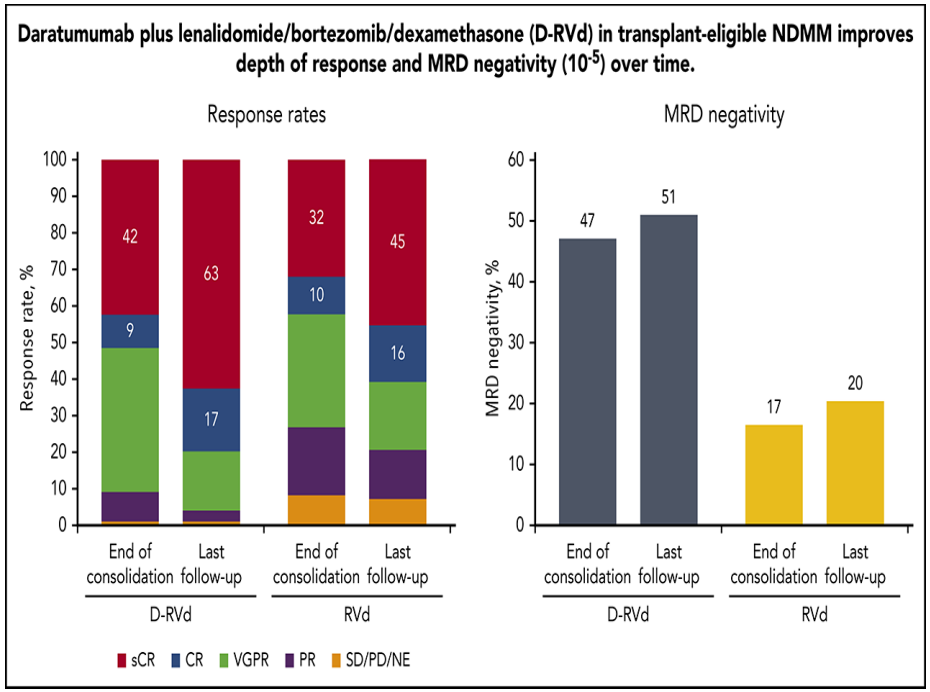


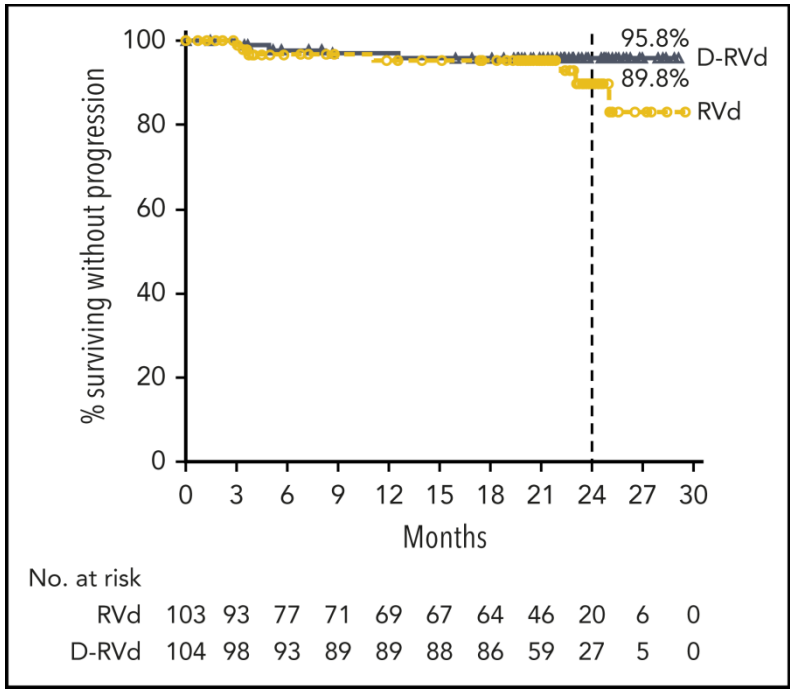


The Lancet 2019 394, 29-38DOI: (10.1016/S0140-6736(19)31240-1)

MAYO CLINIC

Daratumumab-VRd for transplant-eligible newly diagnosed myeloma: GRIFFIN trial





Voorhees PM, et al. the GRIFFIN trial, Blood, 2020,

American Society of Hematology
Helping hematologists conquer blood diseases worldwide

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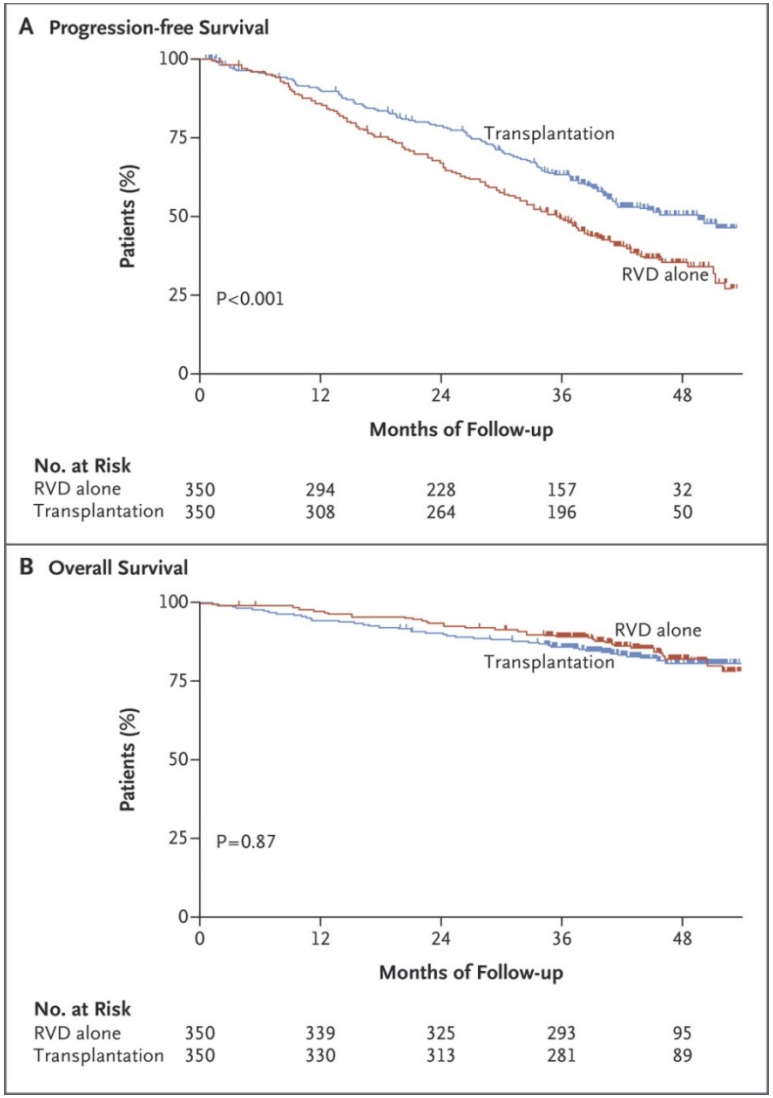

Attal M et al. N Engl J Med 2017;376:1311-1320.

IFM 2005 Trial

Early vs Delayed Transplant

Progression-free Survival and Overall Survival with ASCT in Myeloma

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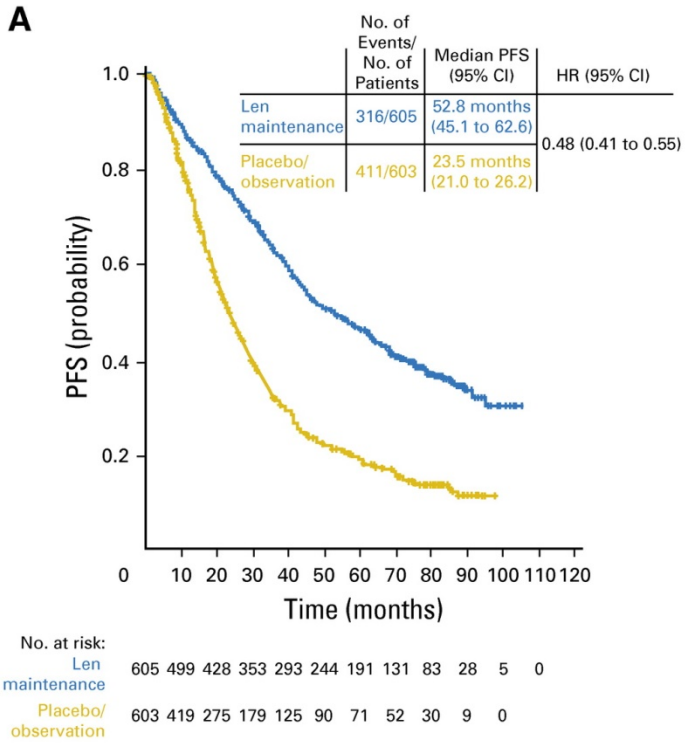
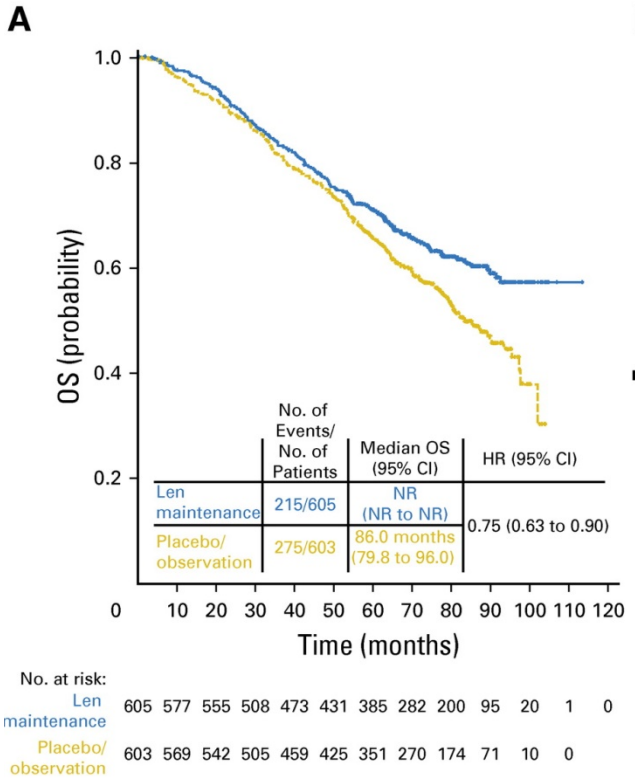
Lenalidomide Maintenance Meta-analysis
PFS and OS





Published in: Philip L. McCarthy; et al. JCO 2017, 35, 3279-3289.
DOI: 10.1200/JCO.2017.72.6679

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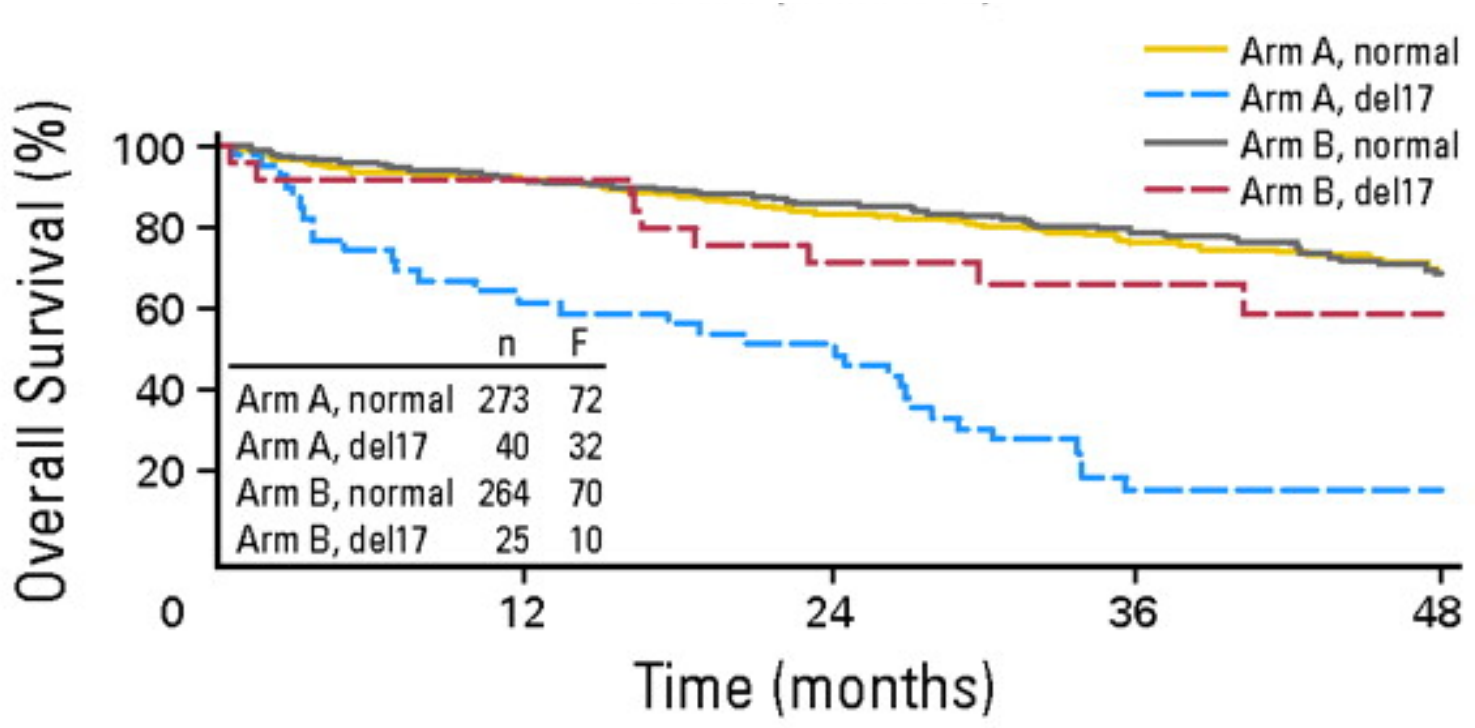
PAD vs VAD: OS according to del(17p)



Sonneveld P et al. JCO 2012;30:2946-2955

JOURNAL OF CLINICAL ONCOLOGY

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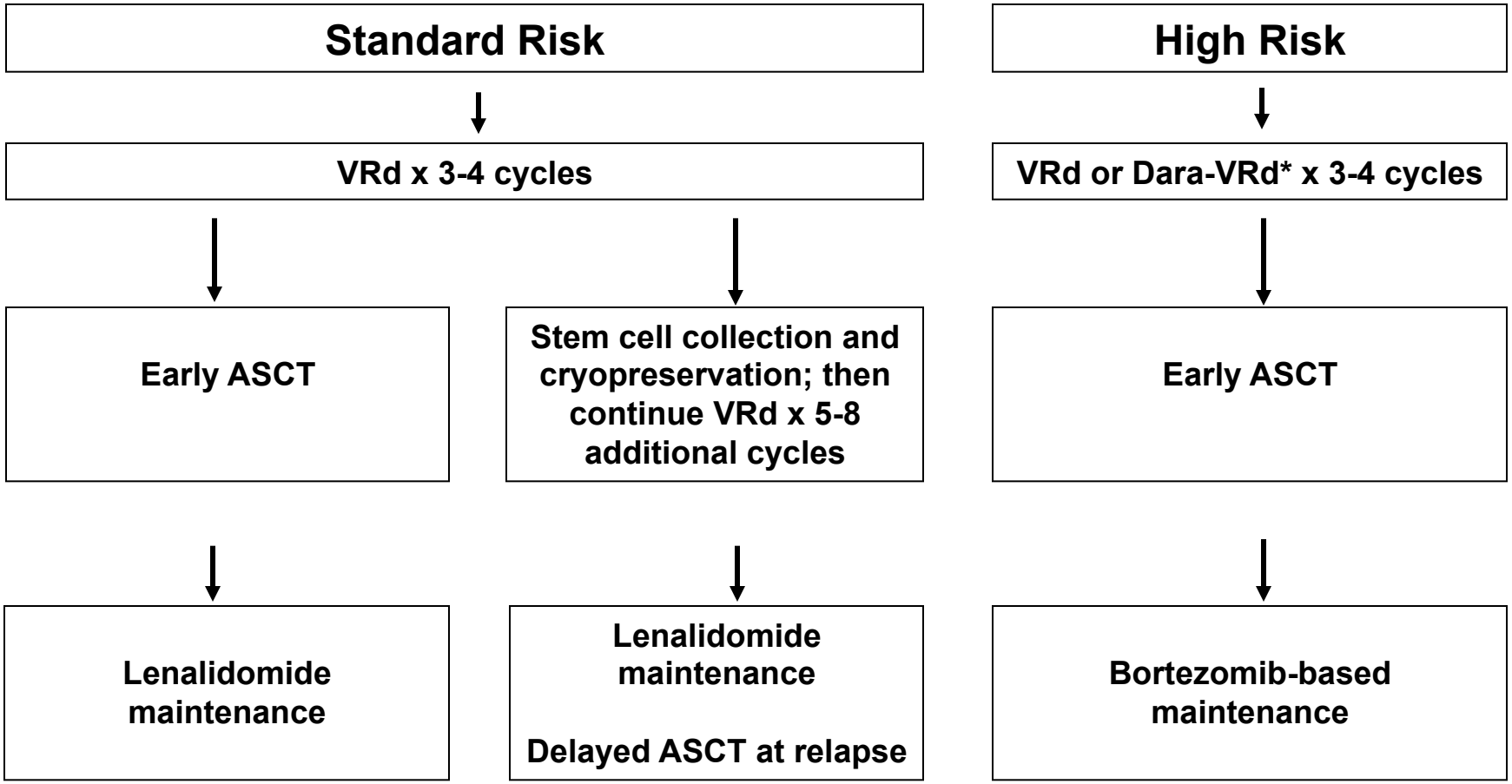
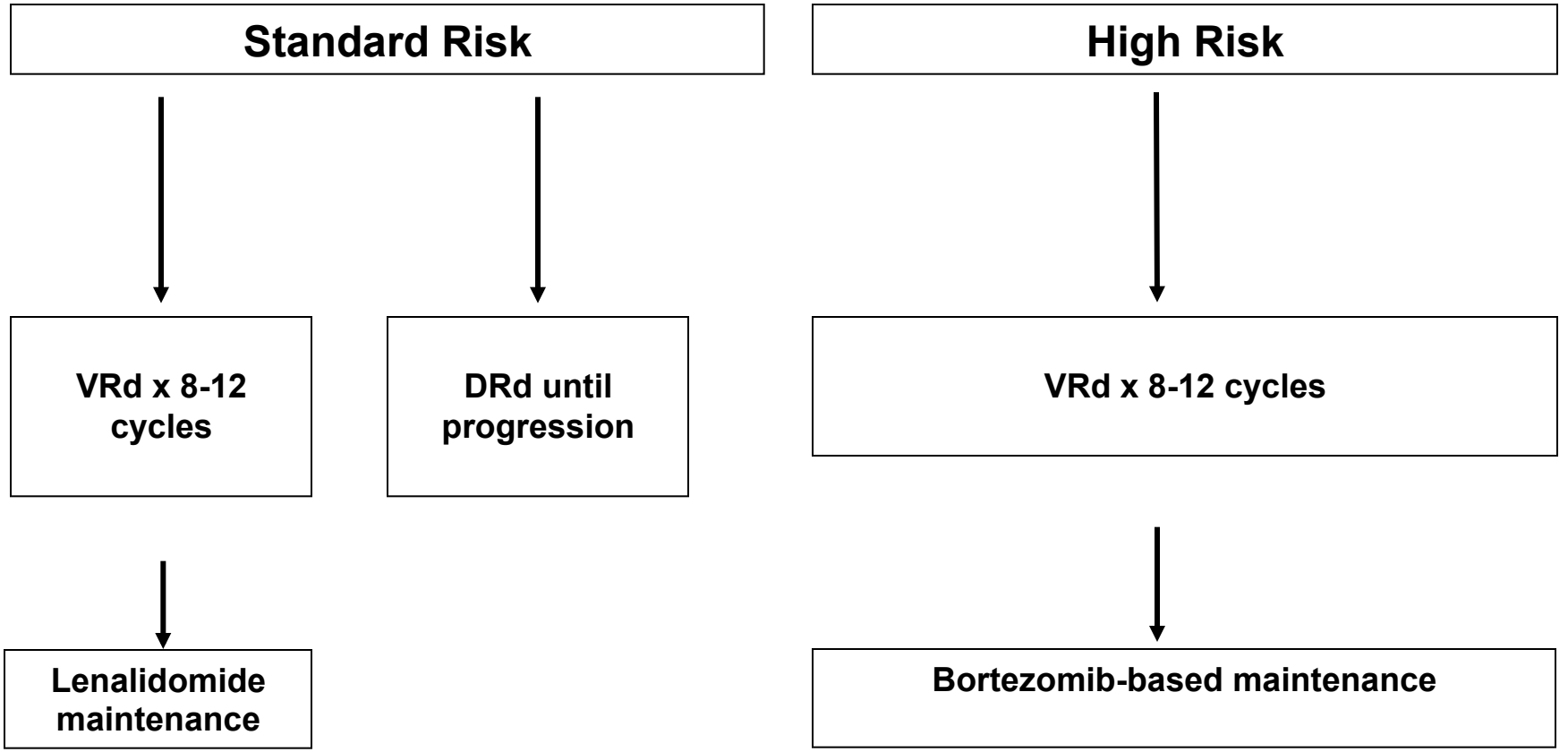
Newly Diagnosed Myeloma: Transplant Eligible



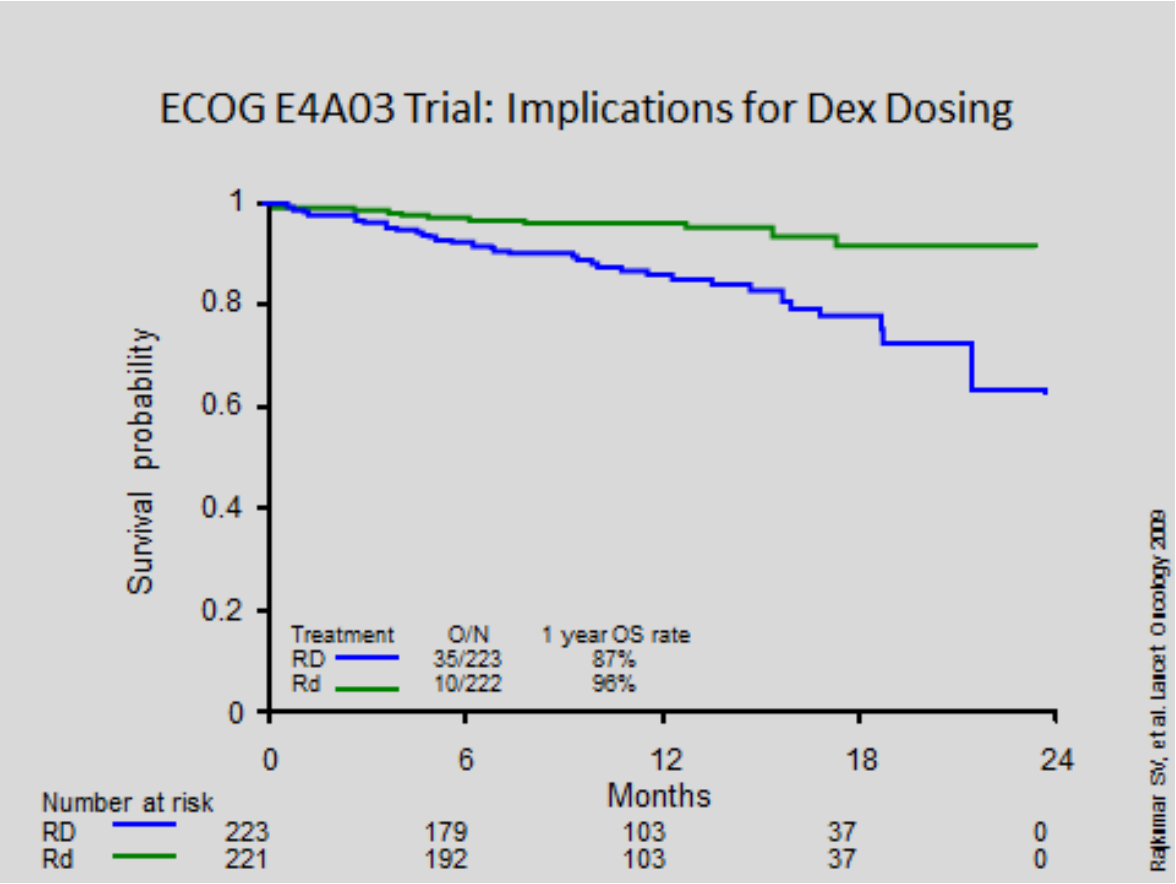
Rajkumar SV. Blood Cancer J. 2020

MAYO CLINIC

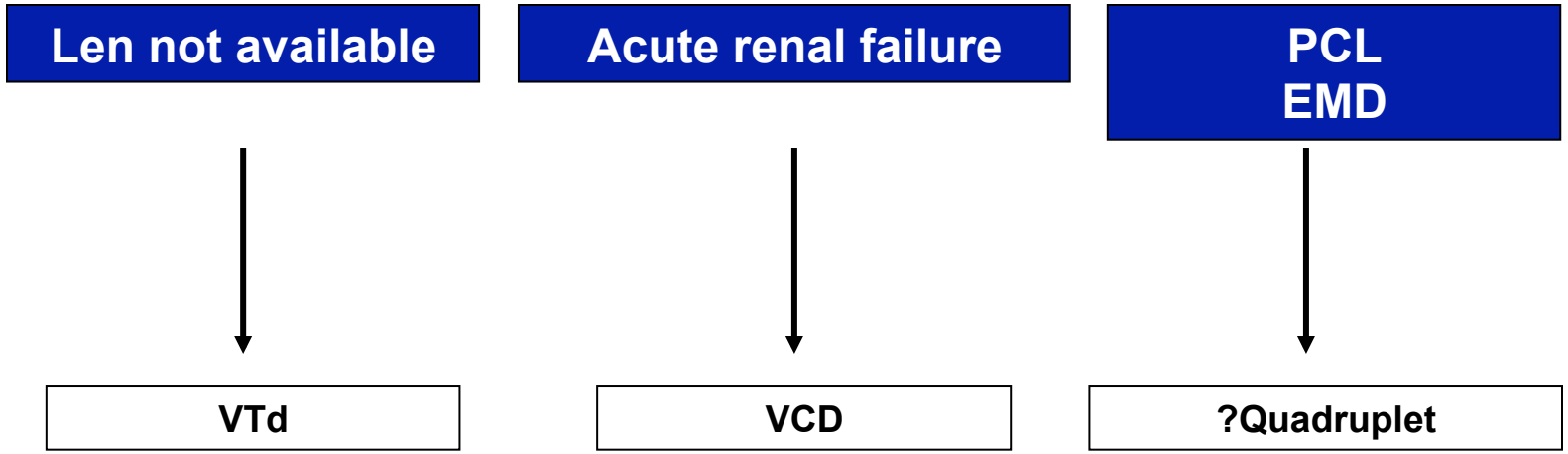
Newly Diagnosed Myeloma: Transplant Ineligible



Rajkumar SV. Blood Cancer J. 2020


ECOG E4A03 Trial: Implications for Dex Dosing
Survival probability
1
0.8
0.6
0.4
0.2
0
Treatment
O/N
1 year OS rate
RD
35/223
87%
Rd
10/222
96%
0
6
12
18
24
Months
Number at risk
RD
223
179
103
37
0
Rd
221
192
103
37
0
Rajkumar SV, et al. Lancet Oncology 2008

Initial Therapy: Special Settings



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RELAPSED MYELOMA

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Active Drugs in Multiple Myeloma

Old Drugs

- Alkylators
- Steroids
- Interferon
- Anthracyclines

Drugs approved 2003-2007

- Bortezomib
- Thalidomide
- Lenalidomide

Active Drugs 2013-2020

- Carfilzomib
- Ixazomib
- Pomalidomide

- Daratumumab
- Isatuximab

- Panobinostat

- Elotuzumab

- Selinexor

- Belantamab

Rajkumar SV. 2020

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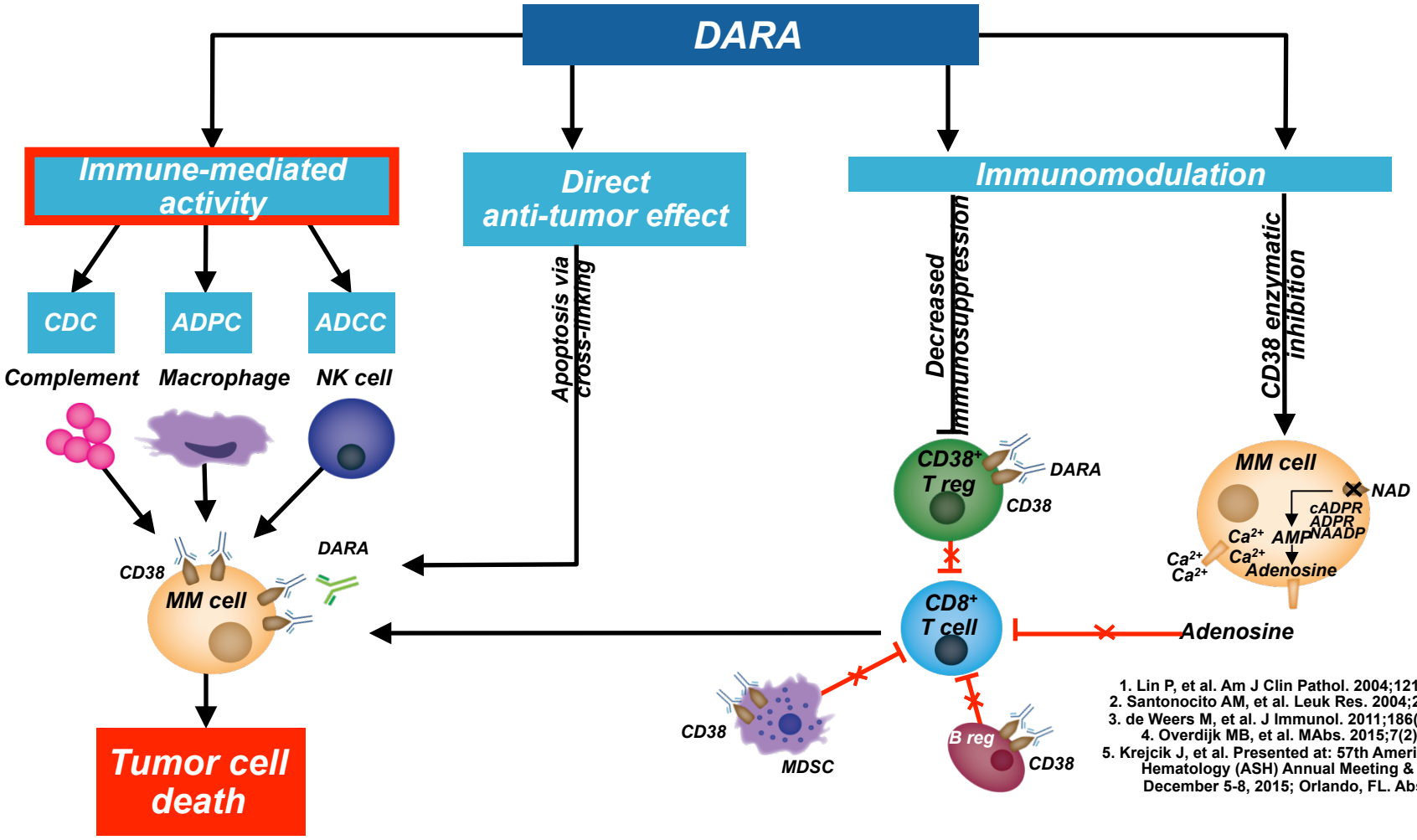
Daratumumab: Anti CD38 MoAb



1. Lin P, et al. Am J Clin Pathol. 2004;121(4):482-488.
2. Santonocito AM, et al. Leuk Res. 2004;28(5):469-477.
3. de Weers M, et al. J Immunol. 2011;186(3):1840-1848.
4. Overdijk MB, et al. MAbs. 2015;7(2):311-321.
5. Krejcik J, et al. Presented at: 57th American Society of Hematology (ASH) Annual Meeting & Exposition; December 5-8, 2015; Orlando, FL. Abstract 3037.

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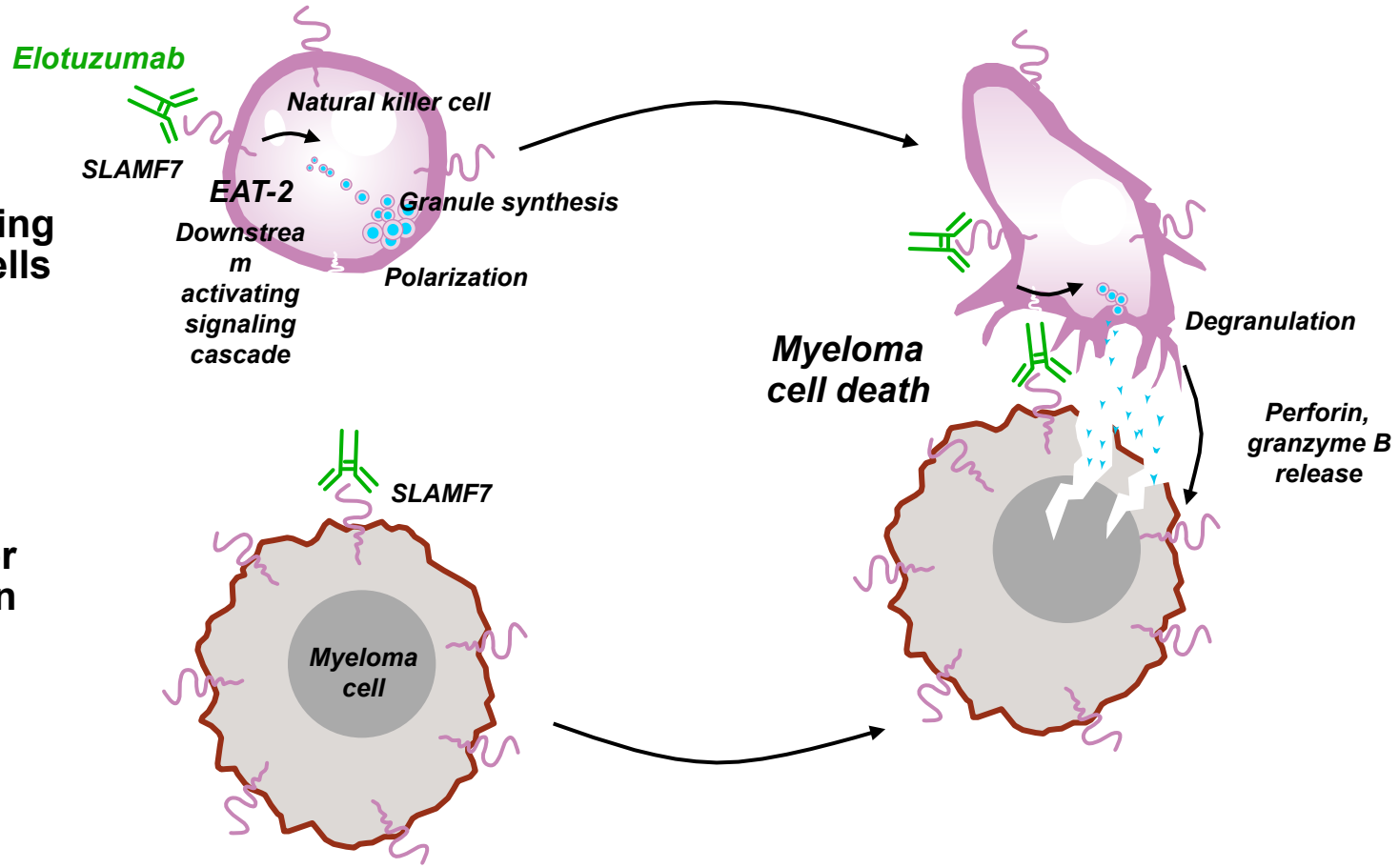
Elotuzumab: Anti SLAMF7 MoAb

A **Directly activating natural killer cells**

B **Tagging for recognition (ADCC)**



i ED et al. Clin Cancer Res 2008;14:2775–84; 2. Collins SM et al. Cancer Immunol Immunother 2013;62:1841–9.
DCC=antibody-dependent cell-mediated cytotoxicity; SLAMF7=signaling lymphocytic activation molecule F7

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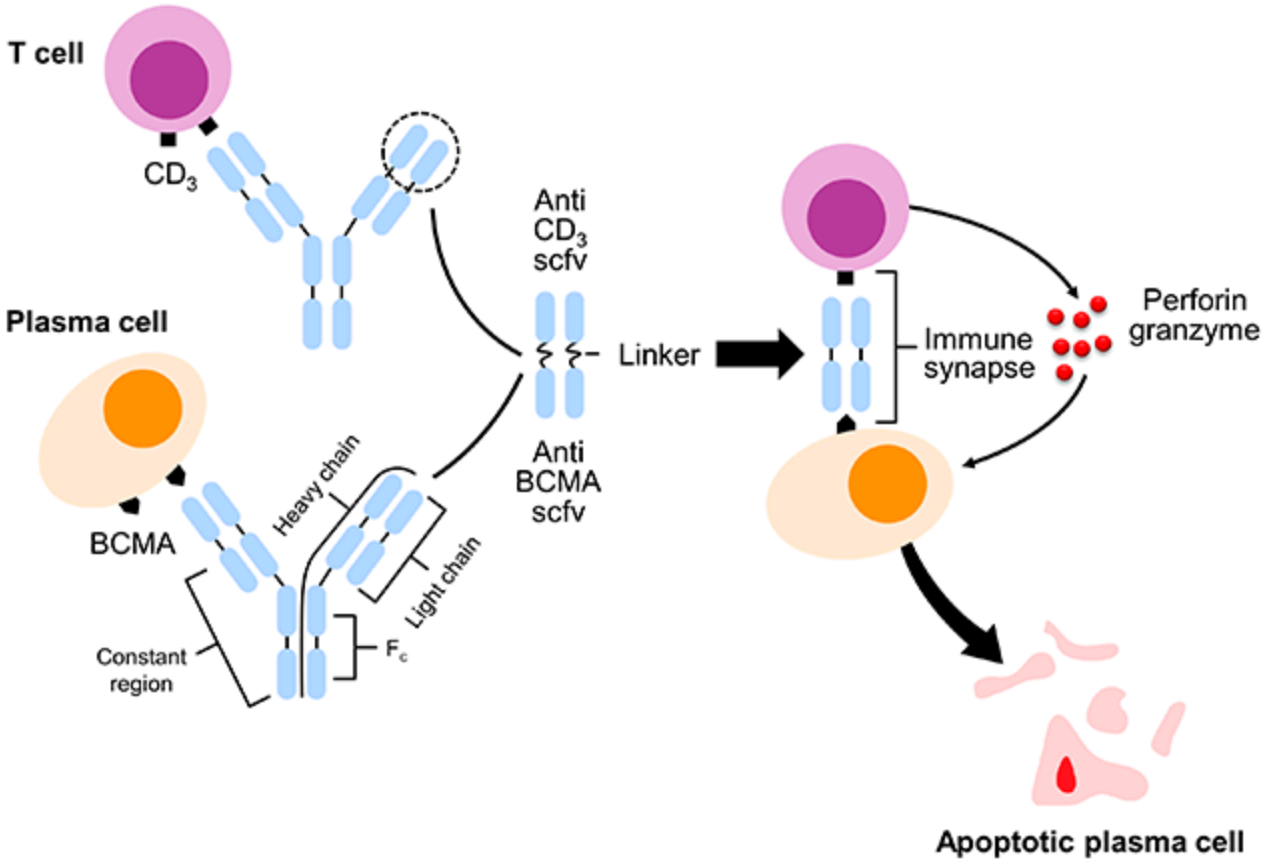
BiTE: Belantamab



Kumar S, Rajkumar SV. J Clin Oncol 2020

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Selection of Regimen

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

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Most Recently Approved Drugs

- Carfilzomib
- Ixazomib
- Daratumumab
- Elotuzumab
- Panobinostat

3 vs 2 trials

New Drug plus doublet (Rd or Vd) versus Doublet

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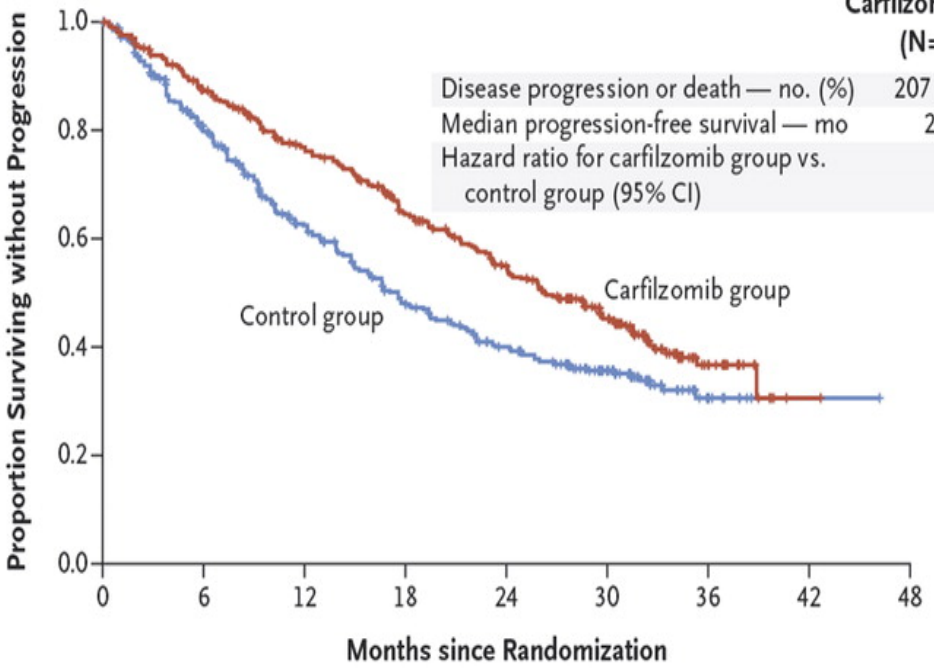
Carfilzomib Rd vs Rd (PFS): Aspire Trial

A



	Carfilzomib Group (N=396)	Control Group (N=396)
Disease progression or death — no. (%)	207 (52.3)	224 (56.6)
Median progression-free survival — mo	26.3	17.6
Hazard ratio for carfilzomib group vs. control group (95% CI)	0.69 (0.57–0.83)	

P=0.0001

No. at Risk								
Carfilzomib group	396	332	279	222	179	112	24	1
Control group	396	287	206	151	117	72	18	1

Stewart AK, et al. *N Engl J Med.* 2015;372(2):142-152.

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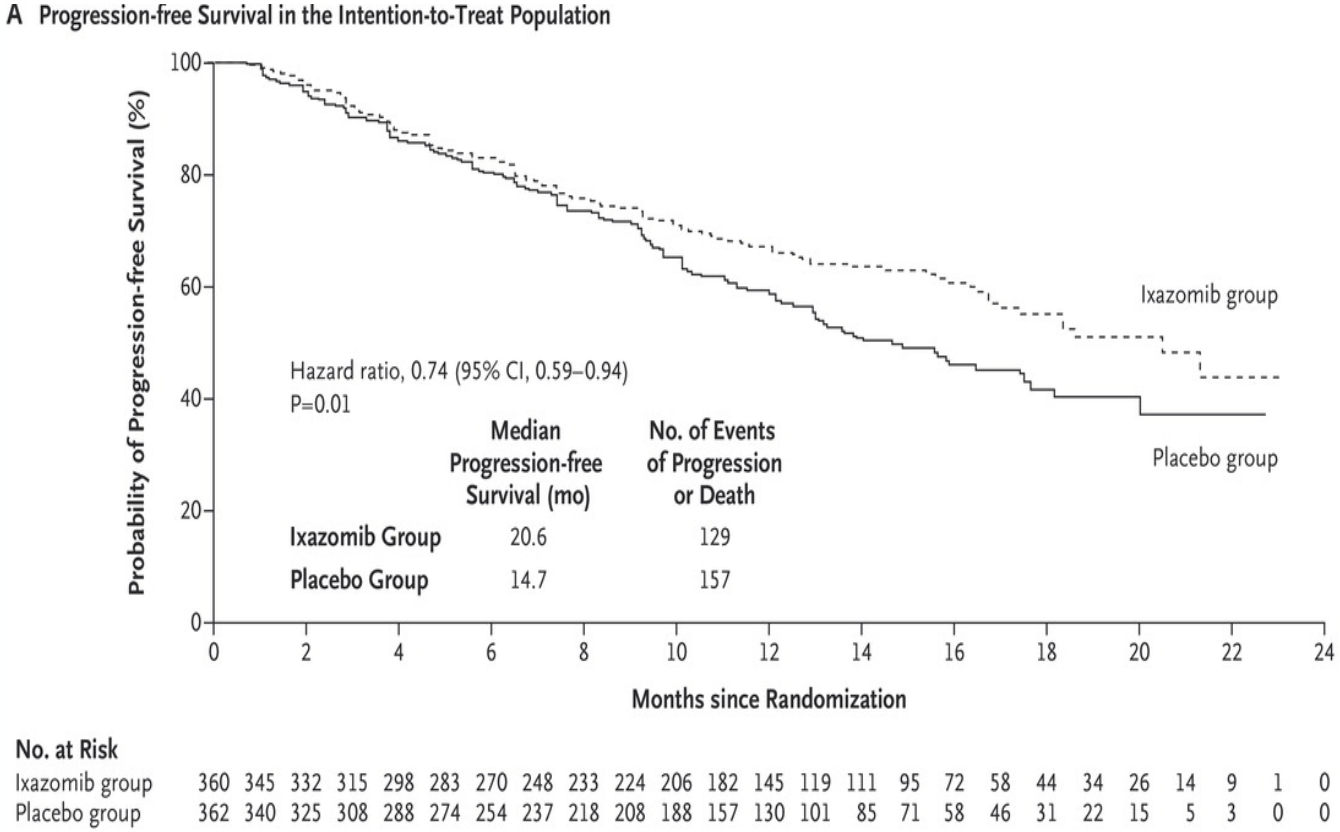
Ixazomib-Rd vs Rd (PFS): Tourmaline Trial



Moreau P et al. N Engl J Med 2016;374:1621-1634.

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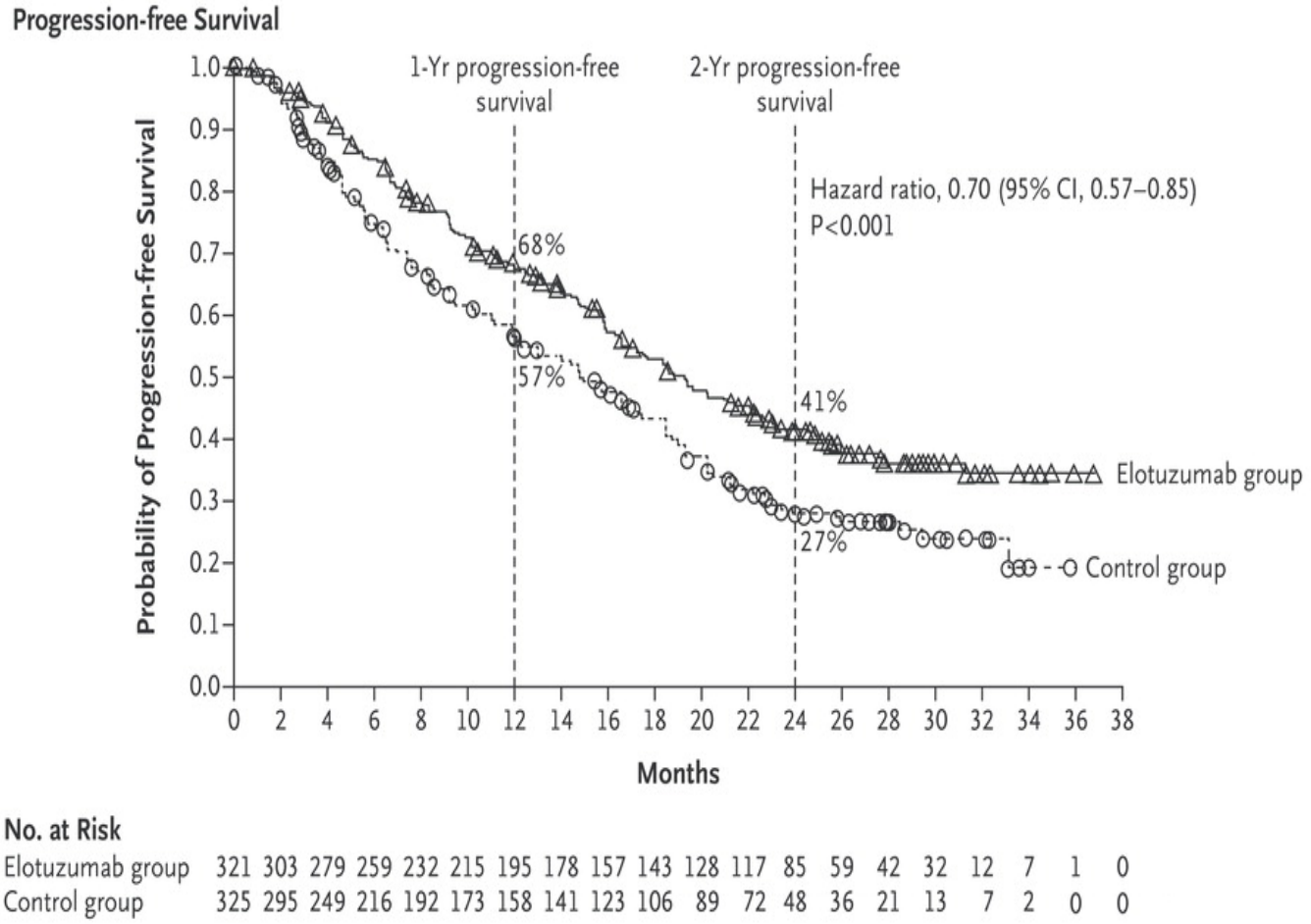
Elotuzumab Rd vs Rd (PFS): Eloquent-2 Trial



Lonial S et al. N Engl J Med 2015;373:621-631.

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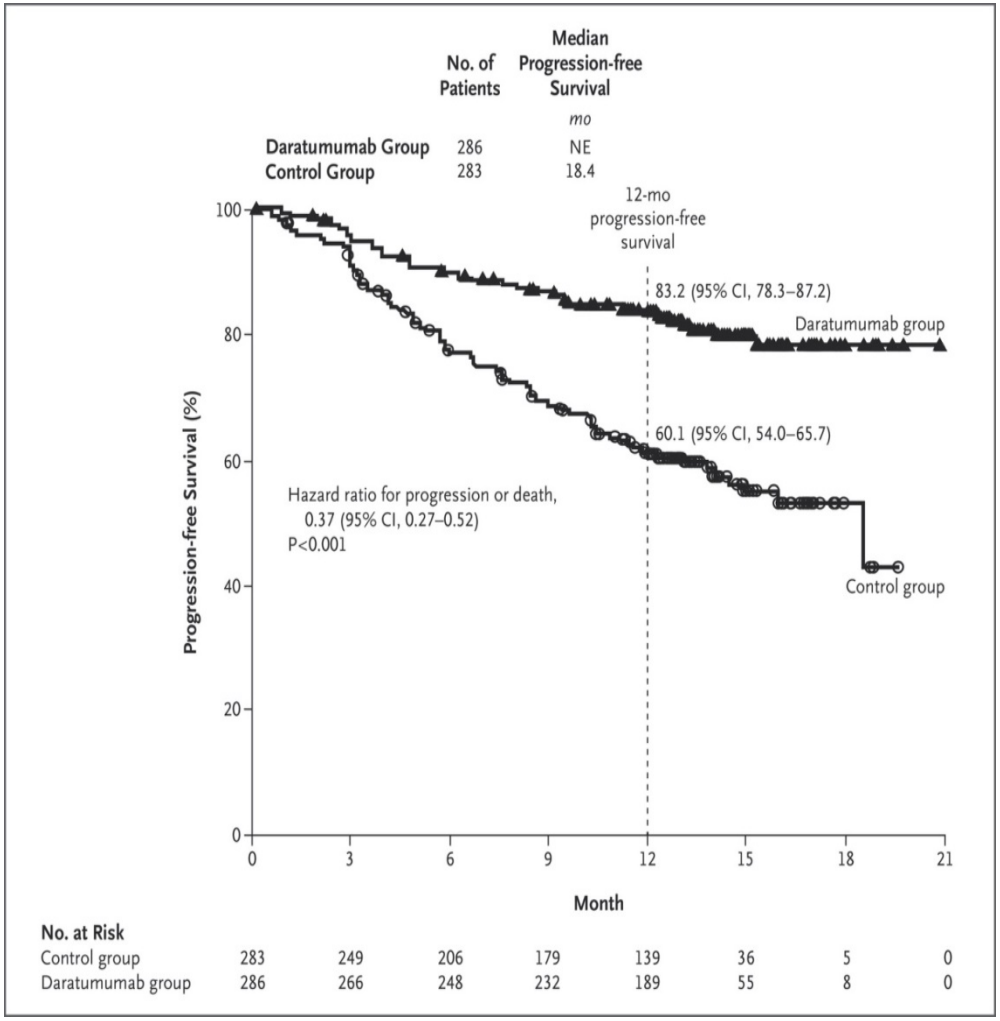
Daratumumab Rd vs Rd (PFS): POLLUX Trial



Dimopoulos MA et al. N Engl J Med 2016;375:1319-1331.

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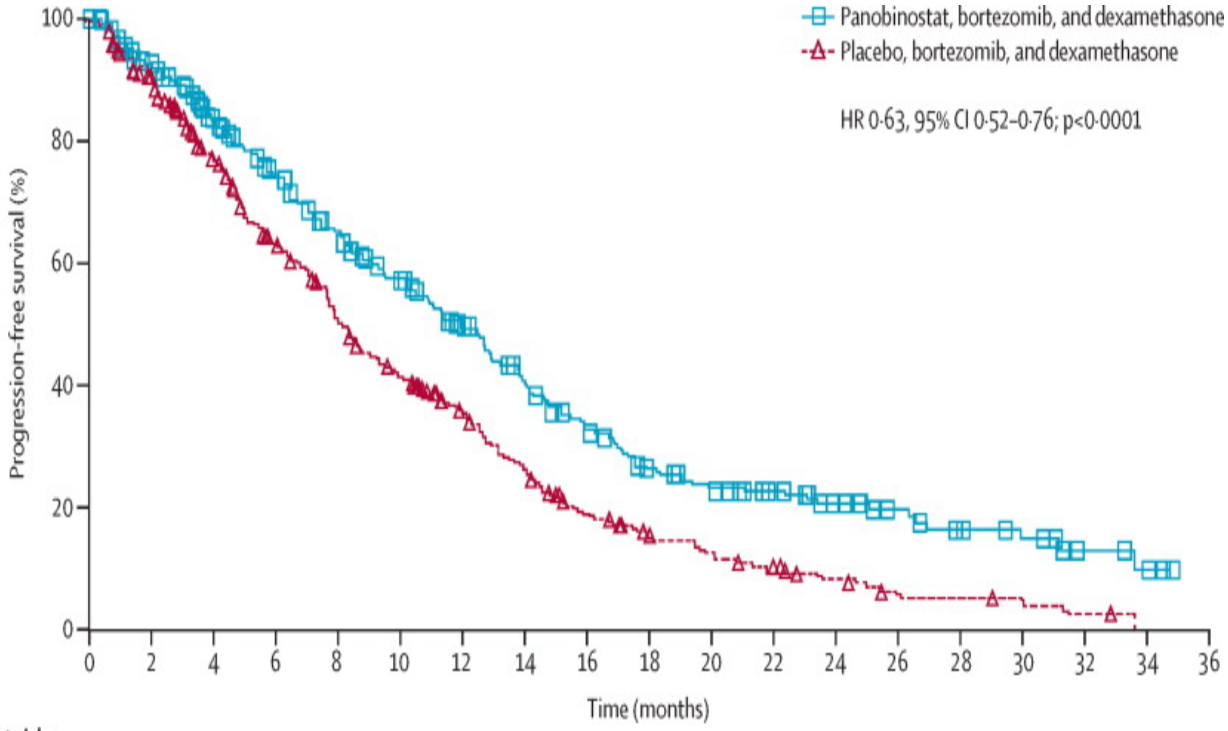
Panobinostat-Vd versus Vd(PFS): Panorama 1 Trial



Number at risk																			
Panobinostat, bortezomib, and dexamethasone	387	288	241	202	171	143	113	89	69	52	44	35	26	18	13	10	5	3	0
Placebo, bortezomib, and dexamethasone	381	296	235	185	143	114	89	64	42	32	24	18	12	5	5	3	2	0	0

San Miguel JF, et al. *Lancet Oncol.* 2014;15(11):1195-1206.

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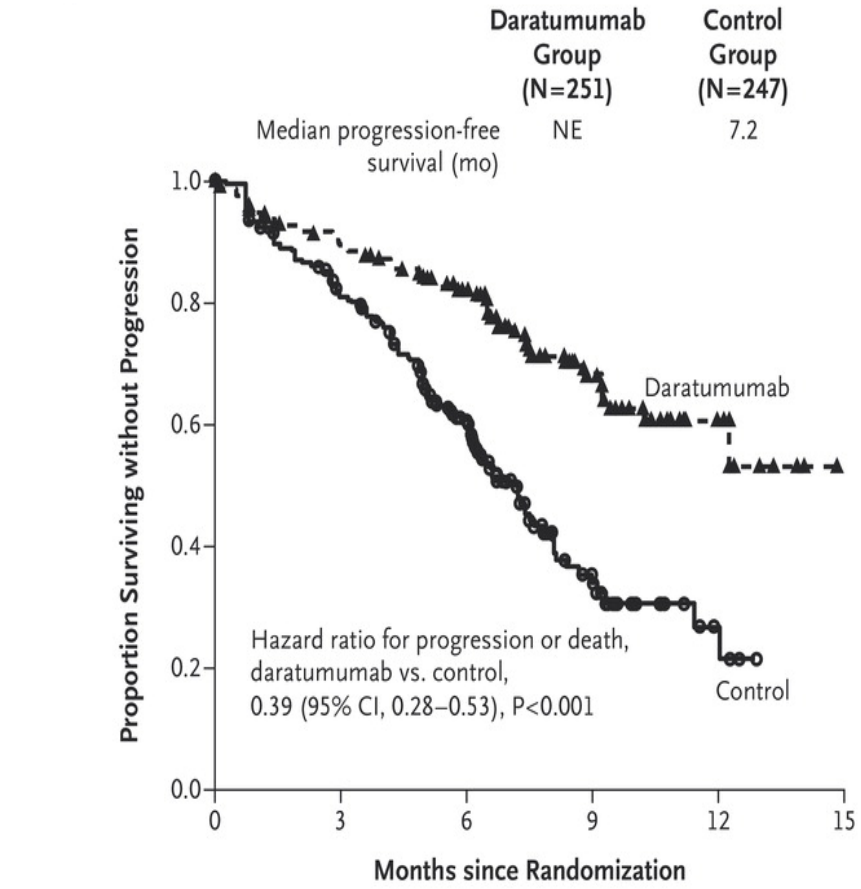
Daratumumab-Vd versus Vel (PFS): CASTOR Trial



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

Palumbo A et al. N Engl J Med 2016;375:754-766.

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Table 1. Results of New Regimens for the Treatment of Relapsed Multiple Myeloma.*

Trial and Regimen†	Complete Response	Median Progression-free Survival	Hazard Ratio for Disease Progression or Death (95% CI)	P Value
	% of patients	*mo*		
Lenalidomide-based regimen				
TOURMALINE-MM1[6]			0.74 (0.59–0.94)	0.01
Lenalidomide–dexamethasone	7	14.7		
Ixazomib–lenalidomide–dexamethasone	12	20.6		
ELOQUENT-2[7]			0.70 (0.57–0.85)	<0.001
Lenalidomide–dexamethasone	7	14.9		
Elotuzumab–lenalidomide–dexamethasone	4	19.4		
ASPIRE[4]			0.69 (0.57–0.83)	<0.001
Lenalidomide–dexamethasone	14	17.6		
Carfilzomib–lenalidomide–dexamethasone	32	26.3		
POLLUX[10]			0.37 (0.27–0.52)	<0.001
Lenalidomide–dexamethasone	19	18.4		
Daratumumab–lenalidomide–dexamethasone	43	NR		
Bortezomib-based regimen				
PANORAMA1[5]			0.63 (0.52–0.76)	<0.001
Bortezomib–dexamethasone	6	8.1		
Panobinostat–bortezomib–dexamethasone	11	12.0		
CASTOR[9]			0.39 (0.28–0.53)	<0.001
Bortezomib–dexamethasone	9	7.2		
Daratumumab–bortezomib–dexamethasone	19	NR		

Rajkumar SV, Kyle RA. N Engl J Med 2016;375:1390-1392.

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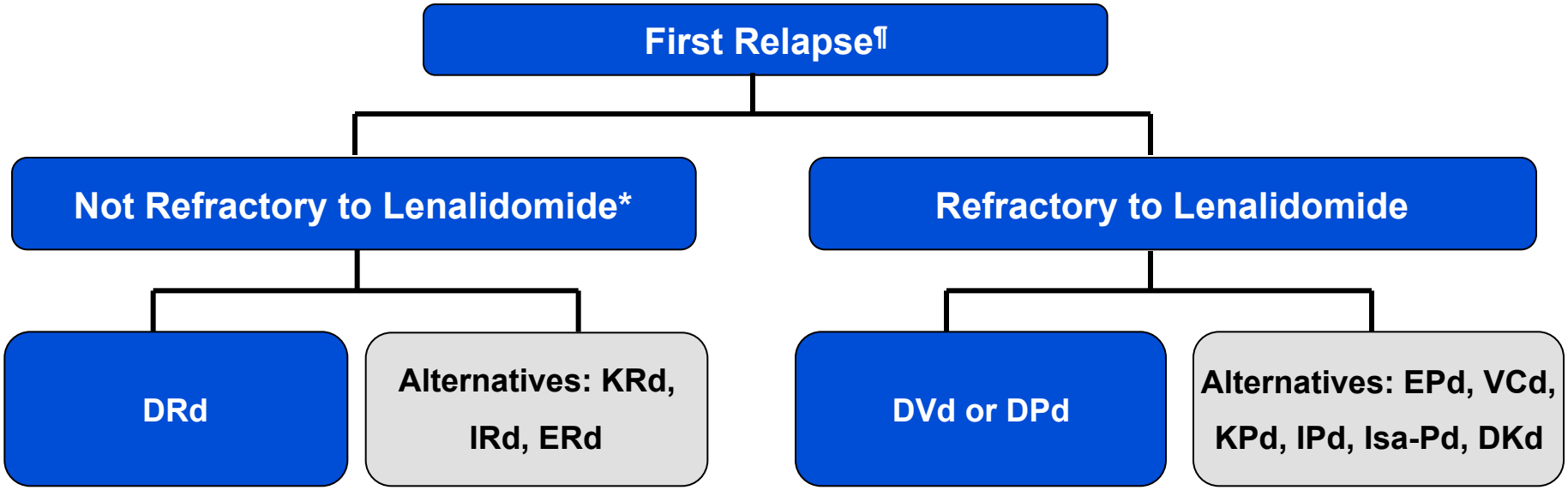
Myeloma: First Relapse



*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 SV, Kyle RA. Progress in Myeloma: A Monoclonal Breakthrough. N Engl J Med 2016;375:1390-1392

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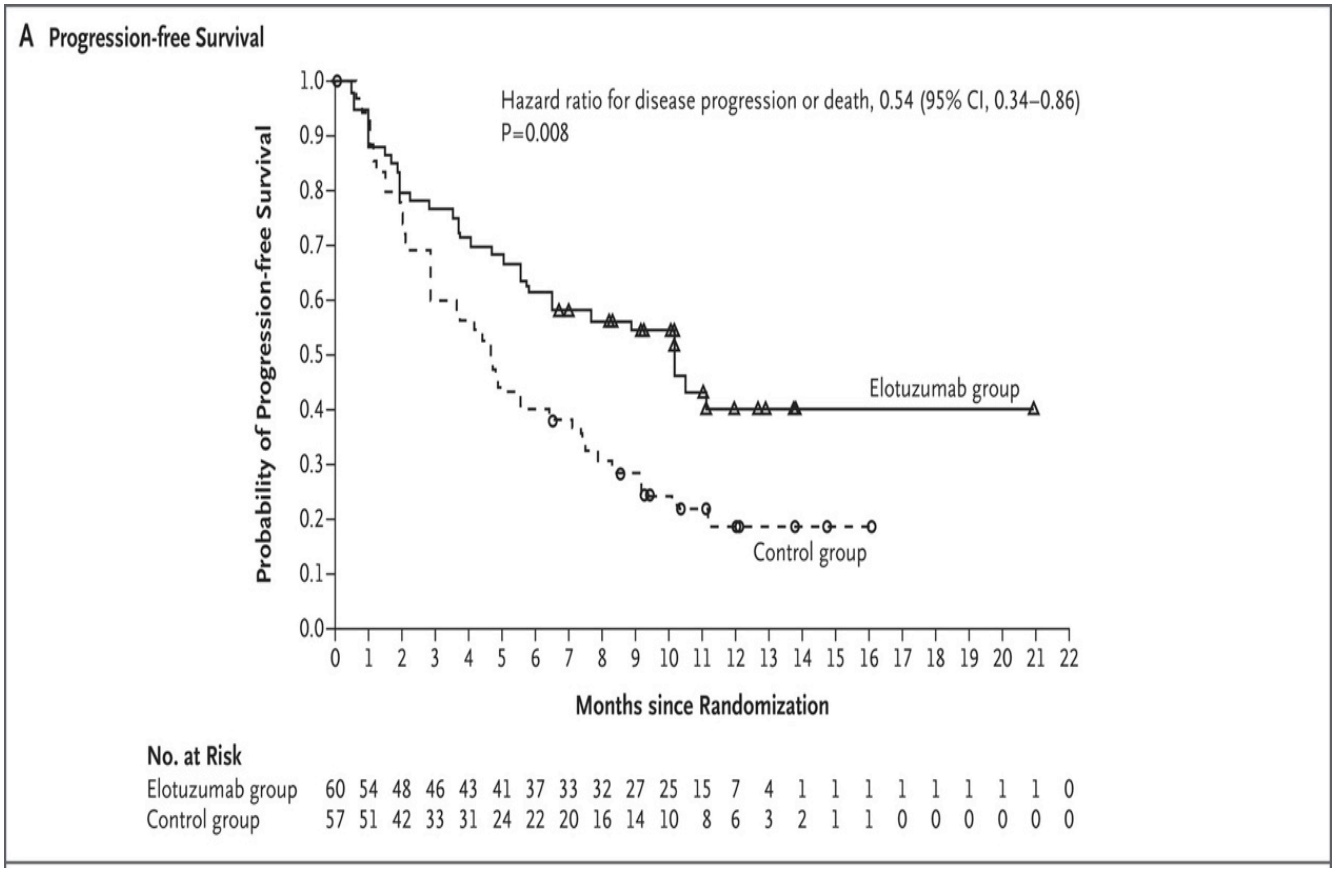
Elotuzumab-Pd vs Pd (PFS)



Dimopoulos MA, et al. N Engl J Med 2018;379:1811-1822.

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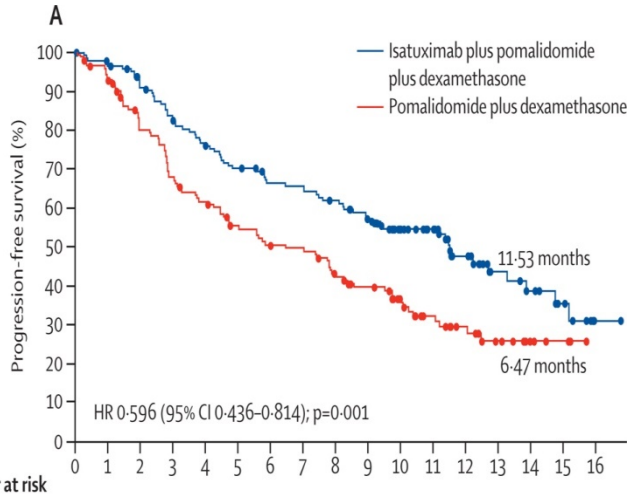
ICARIA Trial: Isatuximab-Pd versus Pd

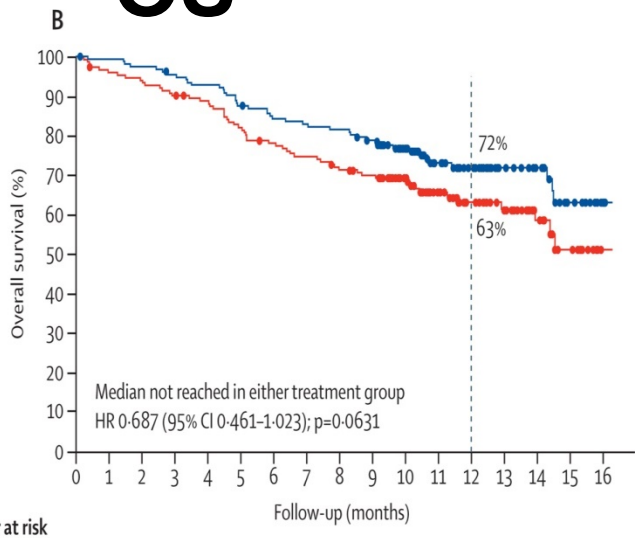
icaria mm

PFS



Number at risk									
Isatuximab plus pomalidomide plus dexamethasone	154	129	106	89	81	52	30	14	1
Pomalidomide plus dexamethasone	153	105	80	63	51	33	17	5	0

OS



Number at risk						
Isatuximab plus pomalidomide plus dexamethasone	154	145	127	116	51	15
Pomalidomide plus dexamethasone	153	137	116	101	46	11

ELSEVIER

Attal M, et al. *The Lancet* 2019 DOI: (10.1016/S0140-6736(19)32556-5)

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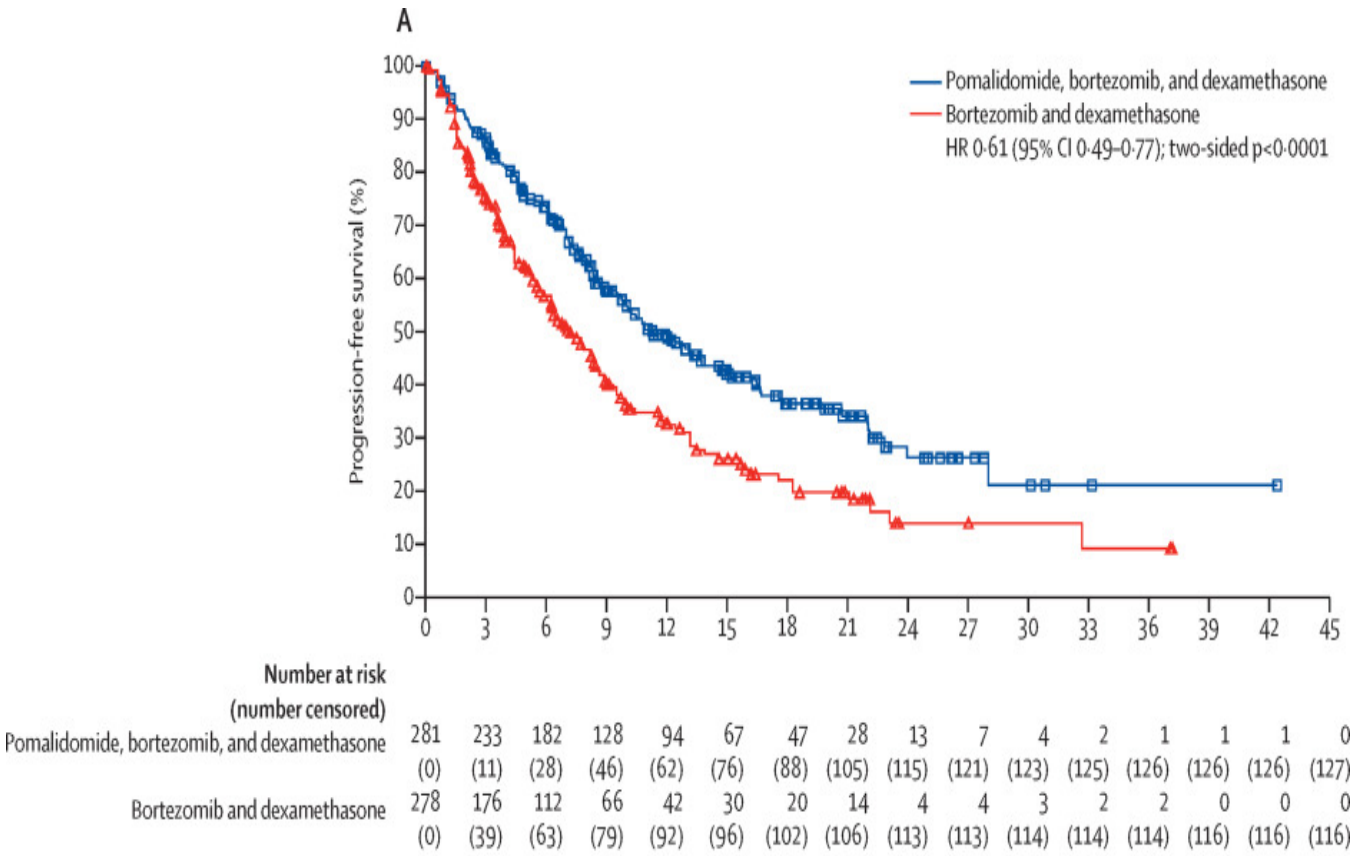
OPTIMISMM Trial: PVd vs Vd



ELSEVIER

Richardson P, et al. The Lancet Oncology
Volume 20, Issue 6, June 2019, Pages 781-794

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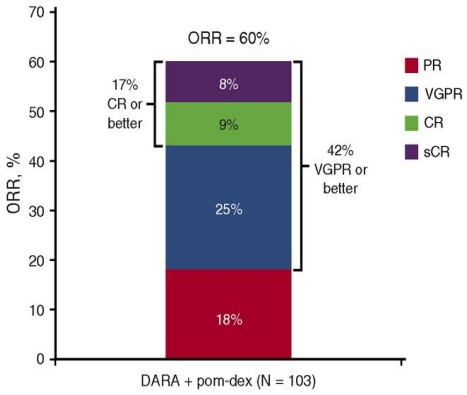
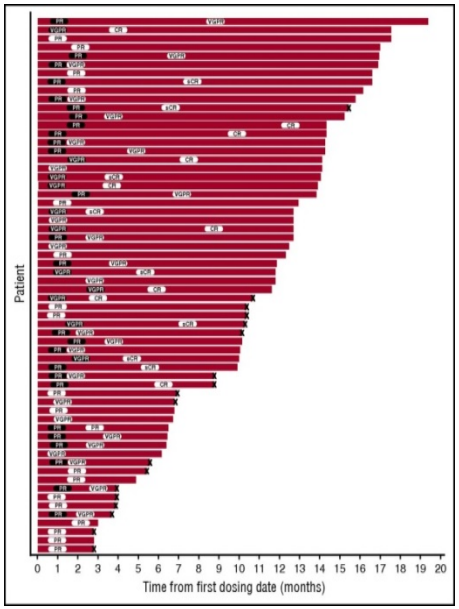
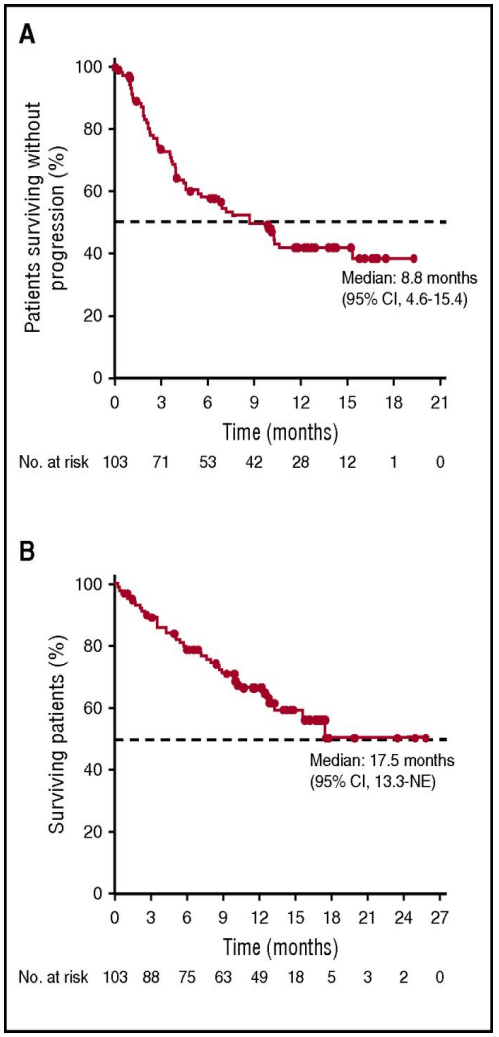
Daratumumab-Pom-Dex (Phase II) n=103







Chari et al. Blood 2017;130:974-981

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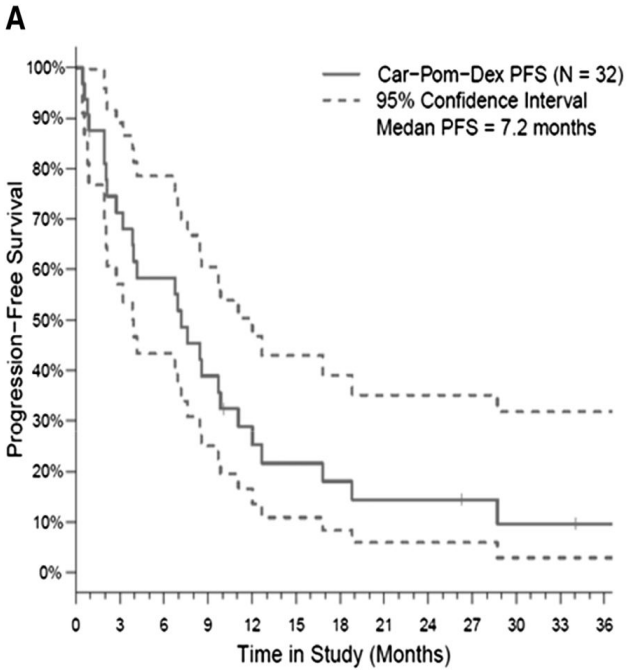
Carfilzomib-Pom-Dex

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 JJ, et al. Blood 2015 126:2284-2290

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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

- Belantamab
- VDT-PACE like anthacycline containing regimens
- Venetoclax (only t11;14)
- Melphalan
- Bendamustine-based regimens
- Adding Panobinostat
- Selinexor
- Quadruplet regimens

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Active Drugs in Multiple Myeloma

Old Drugs	Older Drugs (2003-2007)	Active Drugs (2013-2020)	Future Drugs
▪ Alkylators ▪ Steroids ▪ Interferon ▪ Anthracyclines	▪ Bortezomib ▪ Thalidomide ▪ Lenalidomide ▪ Liposomal doxorubicin	▪ Carfilzomib ▪ Pomalidomide ▪ Panobinostat ▪ Ixazomib ▪ Daratumumab ▪ Elotuzumab ▪ Isatuximab ▪ Selinexor ▪ Belantamab	▪ CAR-Ts ▪ AMG 701 ▪ Venetoclax

Rajkumar SV. 2020

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SUPPORTIVE CARE

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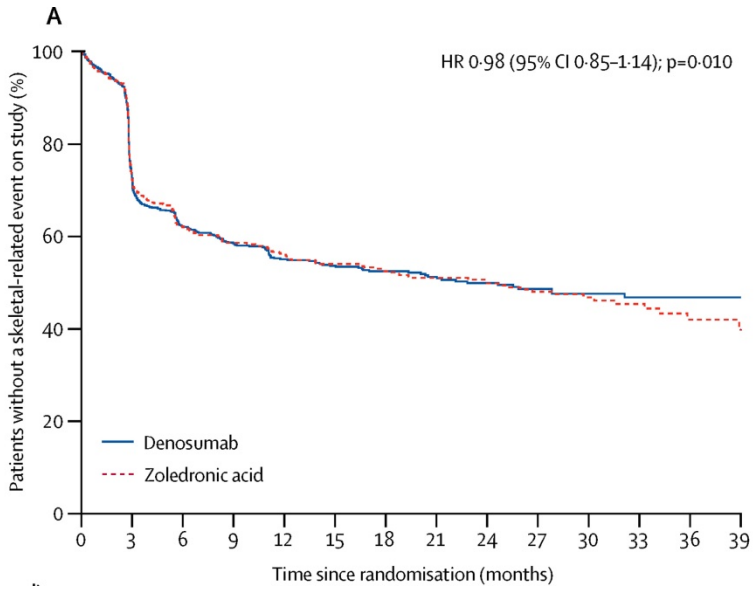
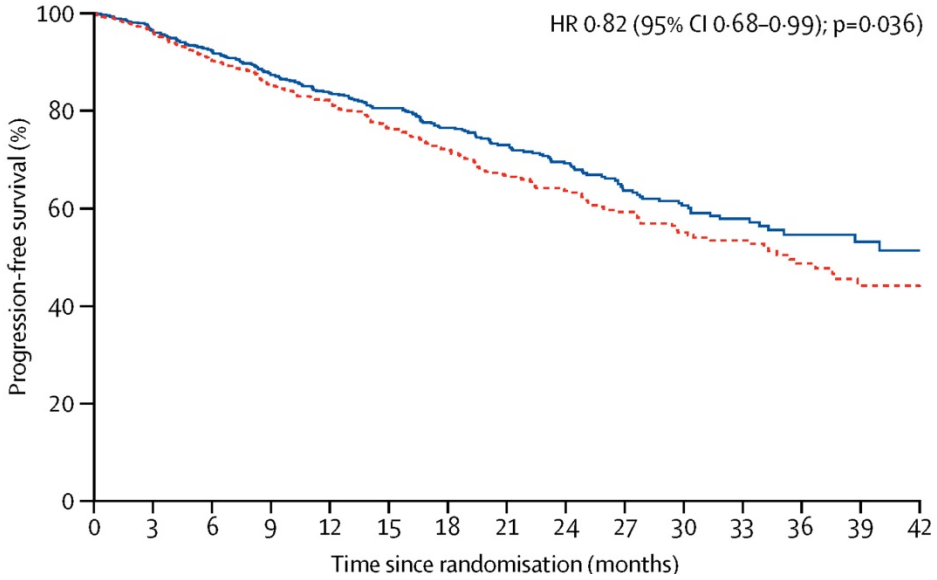
Denosumab vs Zoledronic Acid





Raje N et al. Lancet Oncol. Volume 19, Issue 3, March 2018, Pages 370-381

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SMOLDERING MULTIPLE MYELOMA

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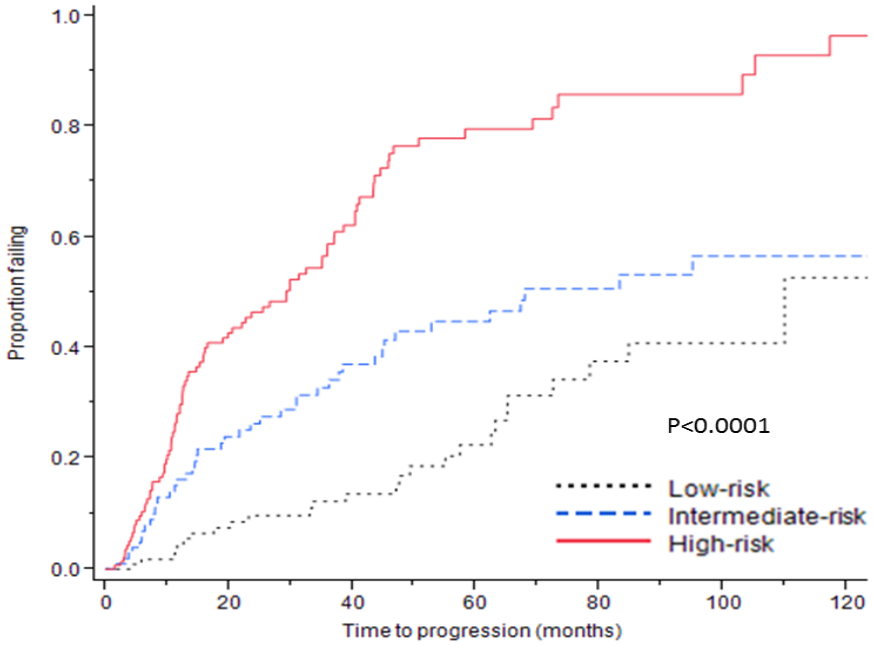
Mayo 2018 Risk Stratification of Smoldering Multiple Myeloma (2-20-20)



Factors

- **M Spike >2g/dL**
- **BMPC >20%**
- **FLC ratio >20**

Stratification

Low-risk: 0
Intermediate-risk: 1
High-risk: >=2

Lakshman et al, BCJ, 2018

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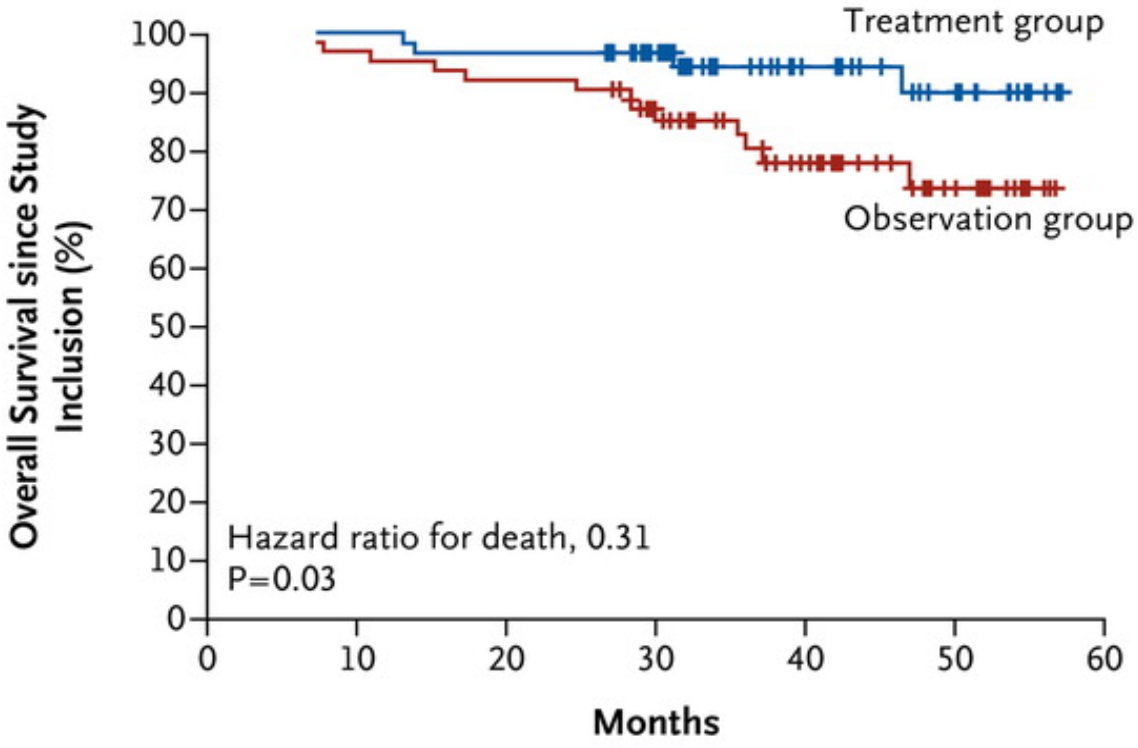
The NEW ENGLAND JOURNAL of MEDICINE

Len/Dex versus Observation in High Risk SMM: OS

B



No. at Risk							
Treatment group	57	57	55	48	26	17	0
Observation group	62	60	57	46	27	17	0

Mateos M et al. N Engl J Med 2013;369:438-447.

The NEW ENGLAND JOURNAL of MEDICINE

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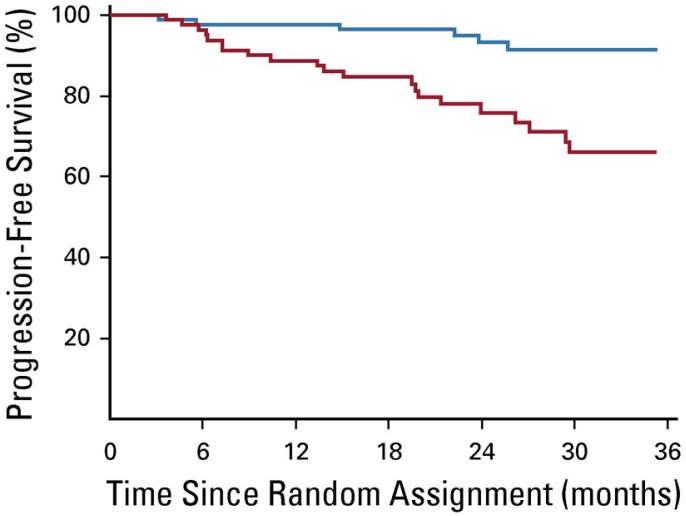
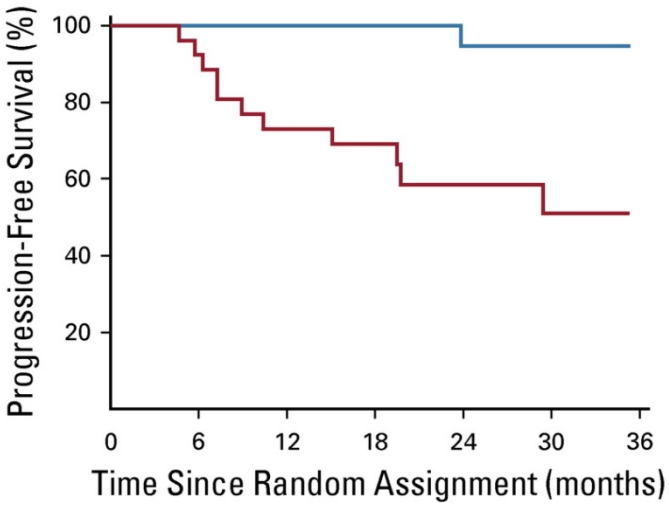
Lenalidomide vs Observation. ECOG E3A06

PFS in all patients



No. at risk:							
Lenalidomide	90	83	81	72	55	42	35
Observation	92	77	67	56	34	26	19

PFS in Mayo 2018 High Risk SMM



No. at risk:							
Lenalidomide	25	25	23	22	18	15	13
Observation	31	24	19	14	8	7	5

Published in: Sagar Lonial; Susanna Jacobus; Rafael Fonseca; Matthias Weiss; Shaji Kumar; Robert Z. Orlowski; Jonathan L. Kaufman; Abdulraheem M. Yacoub; Francis K. Buadi; Timothy O'Brien; Jeffrey V. Matous; Daniel M. Anderson; Robert V. Emmons; Anuj Mahindra; Lynne I. Wagner; Madhav V. Dhodapkar; S. Vincent Rajkumar; *Journal of Clinical Oncology* 2020 381126-1137.
DOI: 10.1200/JCO.19.01740

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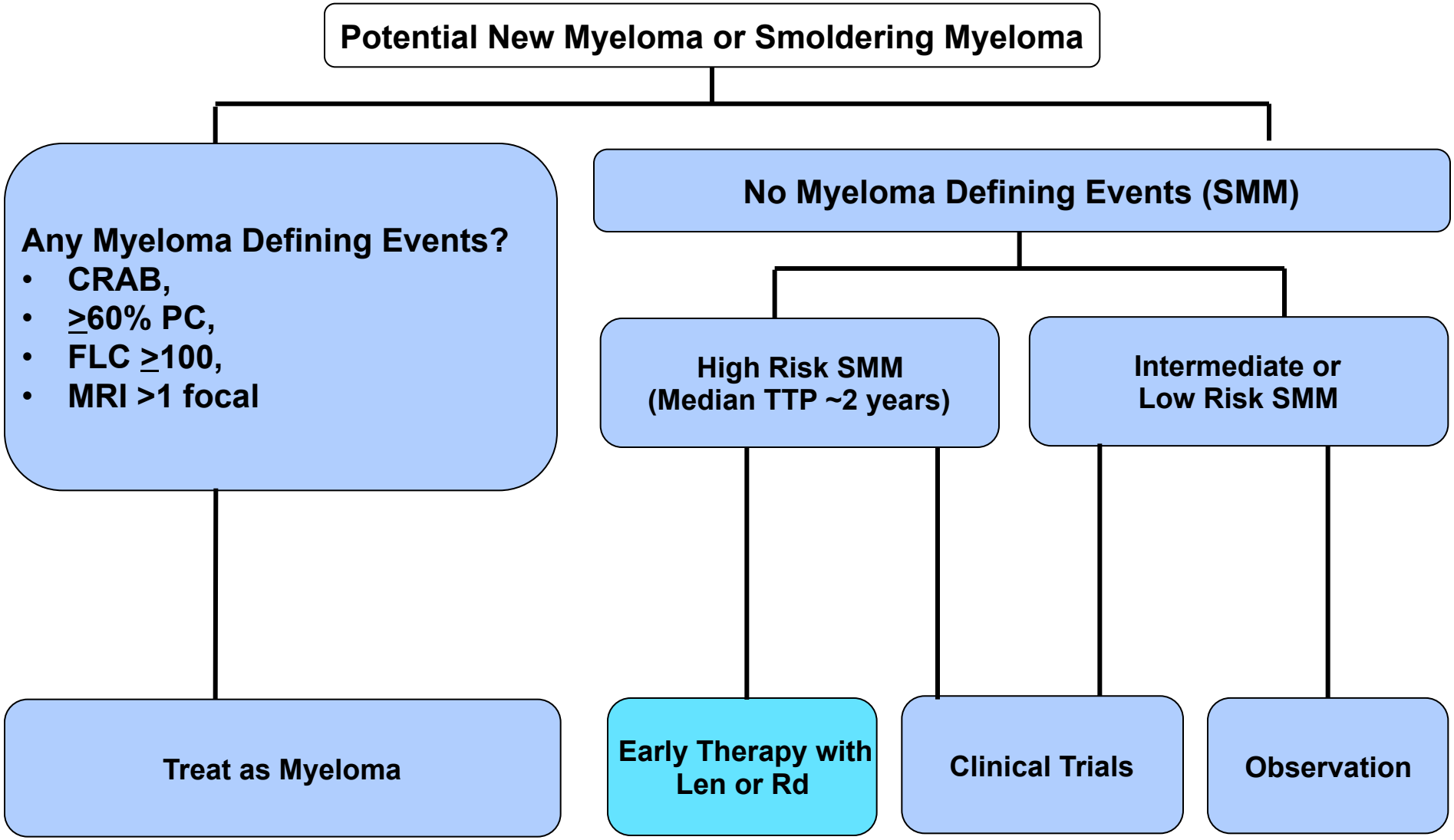
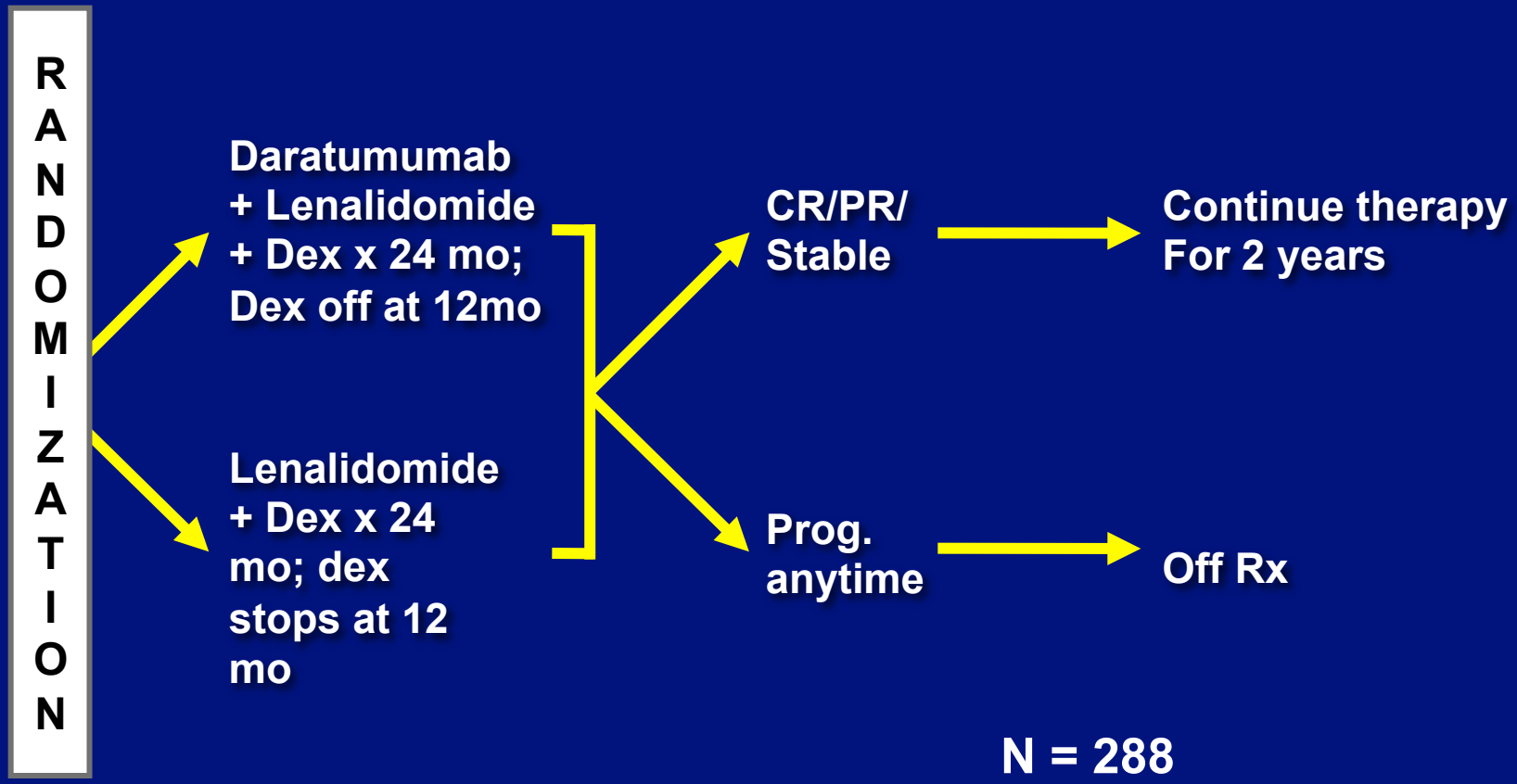


Smoldering MM

EAA173: Phase III –Daratumumab to Enhance Therapeutic Effectiveness of Revlimid in Smoldering Myeloma (DETER-SMM)(PI: NC)



N = 288

PI: Natalie Callander
(Activated May 30, 2019)