How I Treat Multiple Myeloma

Morie Gertz
Professor of Medicine
Mayo Clinic

Scottsdale, Arizona

Rochester, Minnesota

Jacksonville, Florida

Disclosures

- Dr. Gertz reports personal fees from Ionis/Akcea, personal fees from Alnylam, personal fees from Prothena, personal fees from Celgene, personal fees from Janssen, grants and personal fees from Spectrum, personal fees from Annexon, personal fees from Appellis, personal fees from Amgen, personal fees from Medscape, personal fees from Physicians Education Resource, personal fees for Data Safety Monitoring board from Abbvie, personal fees from Research to Practice, speaker fees from Teva, Speaker fees from Johnson and Johnson; Speaker fees from Medscape, Speaker fees DAVA oncology; Advisory Board for Pharmacyclics Advisory Board for Proclara outside the submitted work;
- Royalties from Springer Publishing
- Grant Funding Amyloidosis Foundation; International Waldenstrom Foundation
- NCI SPORE MM SPORE 5P50 CA186781-04

INITIAL THERAPY

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

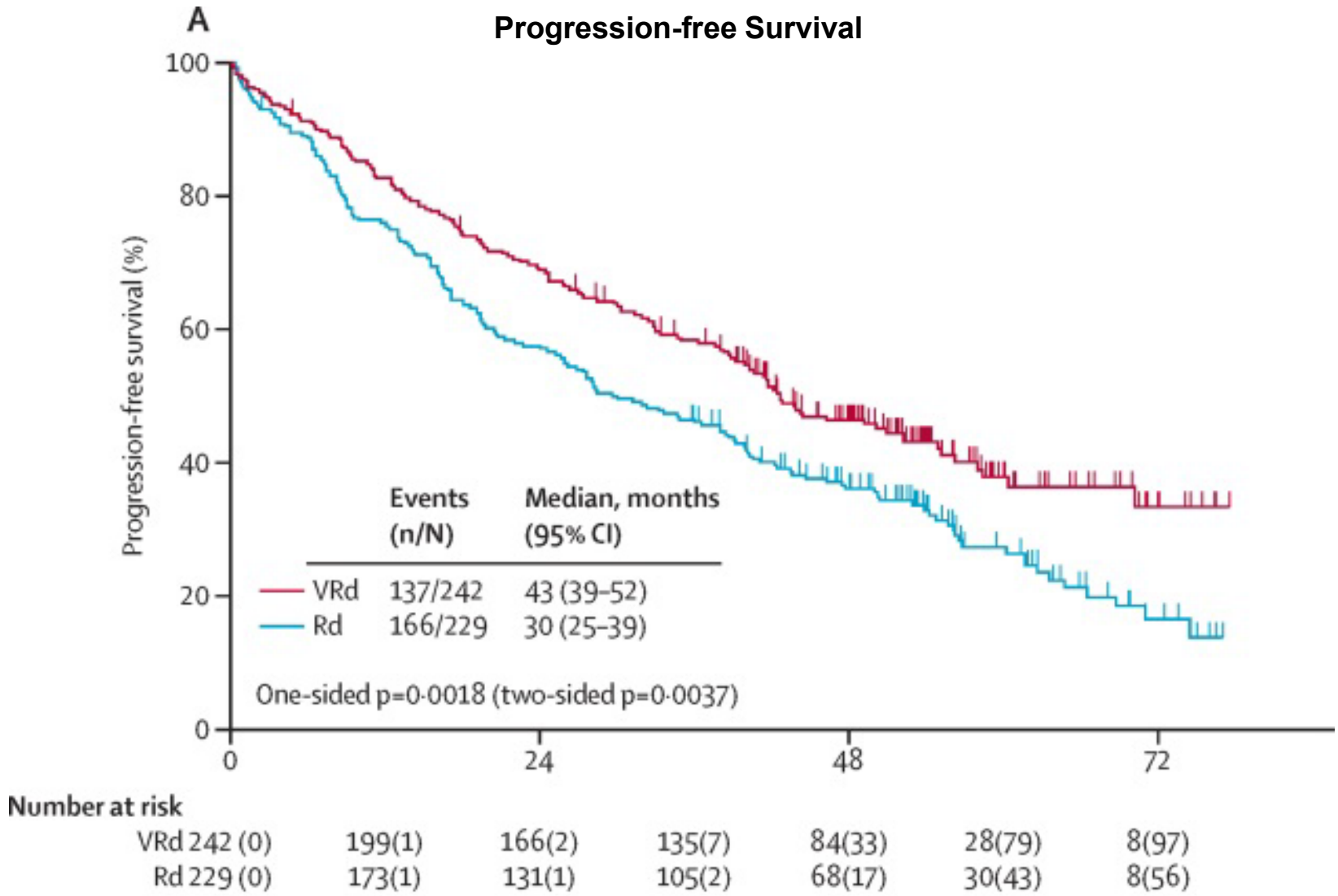
Six 28-day Cycles of Rd

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

S0777 Trial: VRd vs Rd



Durie et al. The Lancet 2017 389, 519-527DOI: (10.1016/S0140-6736(16)31594-X)
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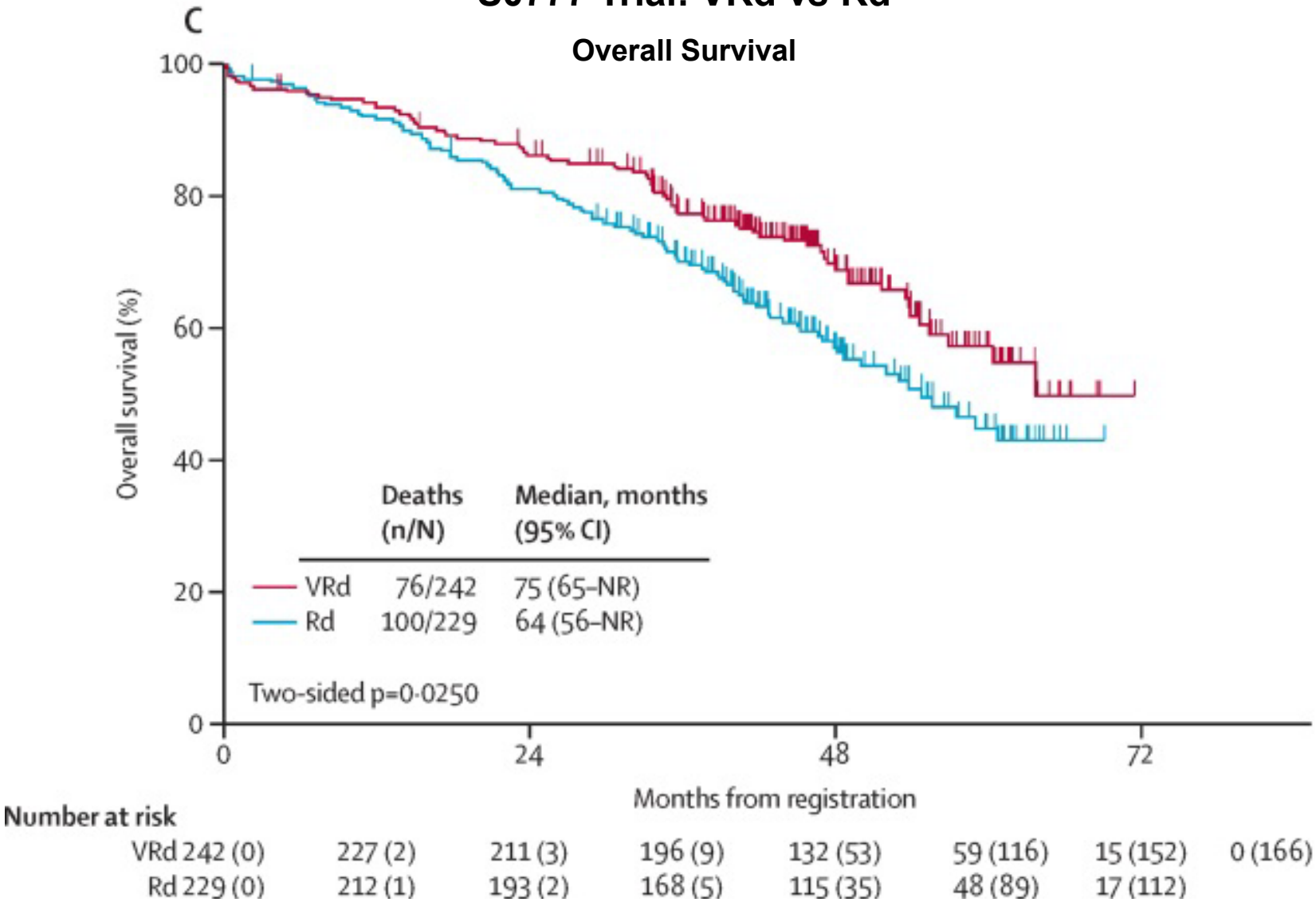
S0777 Trial: VRd vs Rd



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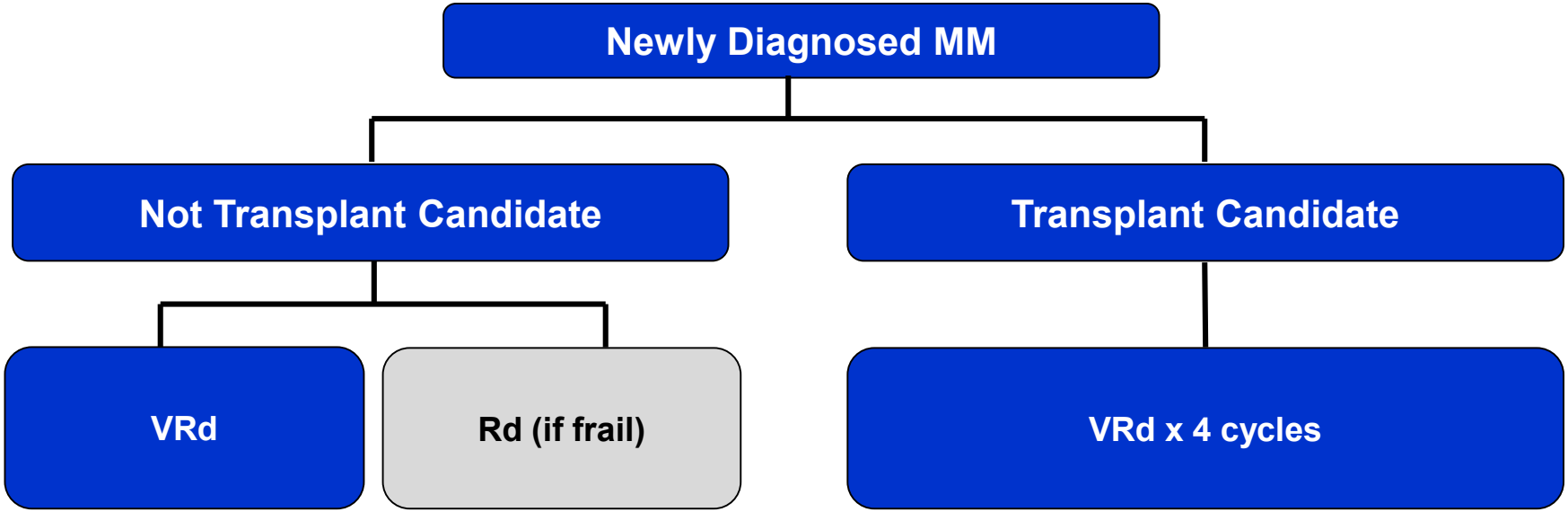
Initial Treatment of Myeloma



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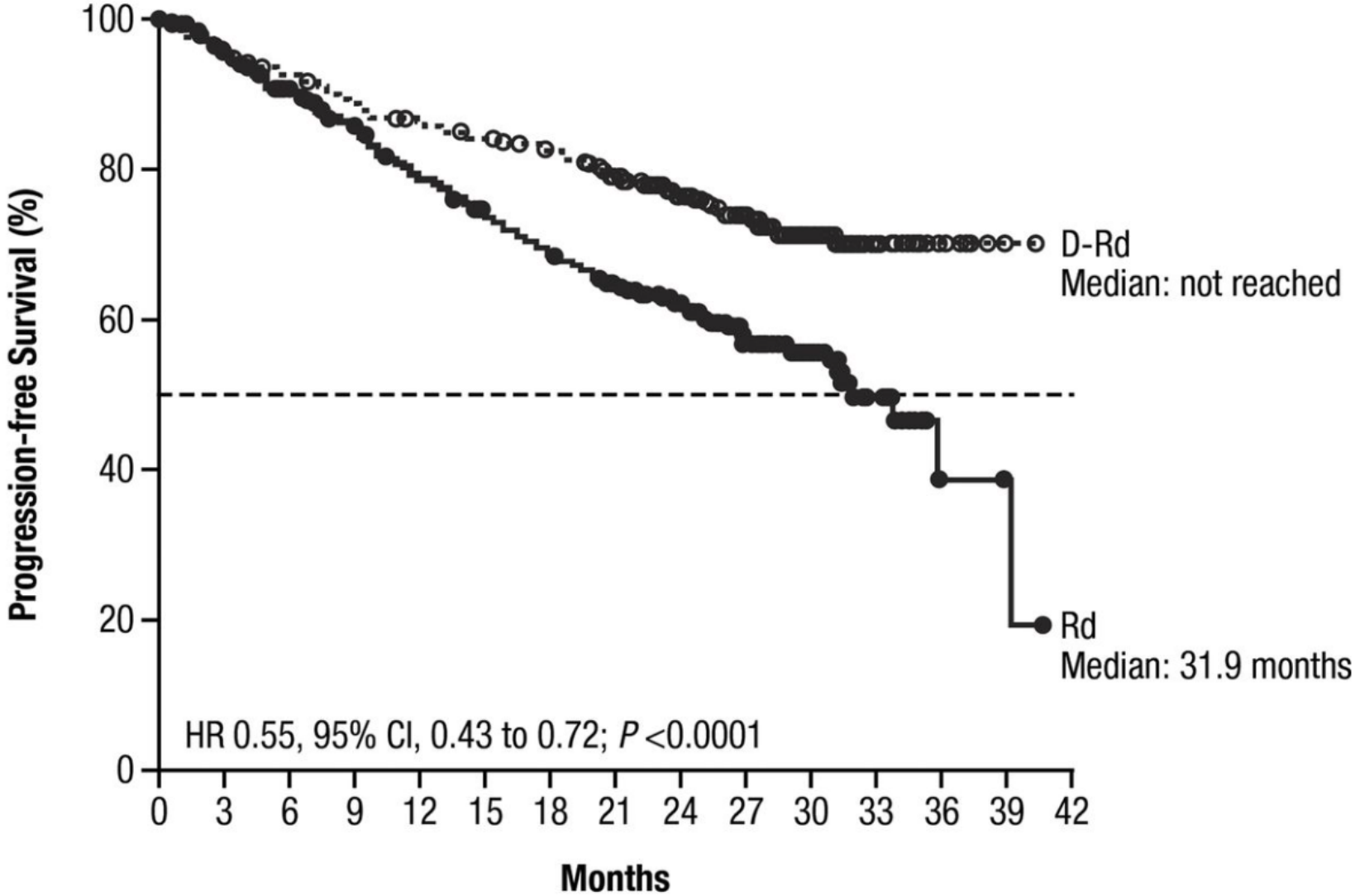
Phase 3 Randomized Study of Daratumumab Plus Lenalidomide and Dexamethasone (D-Rd) Versus Lenalidomide and Dexamethasone (Rd) in Patients with Newly Diagnosed Multiple Myeloma (NDMM) Ineligible for Transplant (MAIA)

Late breaking ASH abstract 2018

- Patients ineligible for high-dose chemotherapy with autologous stem cell transplantation due to age ≥65 years or comorbidities
- median (range) age was 73 (45-90) years with 44% of patients ≥75 years,
- 45% reduction in the risk of progression or death in patients treated with D-Rd
- complete response (CR) or better rate of 47.6% in the D-Rd arm compared with 24.7% in the Rd arm

Figure: Progression-free survival for patients with NDMM ineligible for transplant treated with D-Rd or Rd in MAIA



No. at risk

Rd	369	332	307	280	254	236	219	200	149	94	50	18	3	2	0
D-Rd	368	347	335	320	309	300	290	271	203	145	86	35	11	1	0

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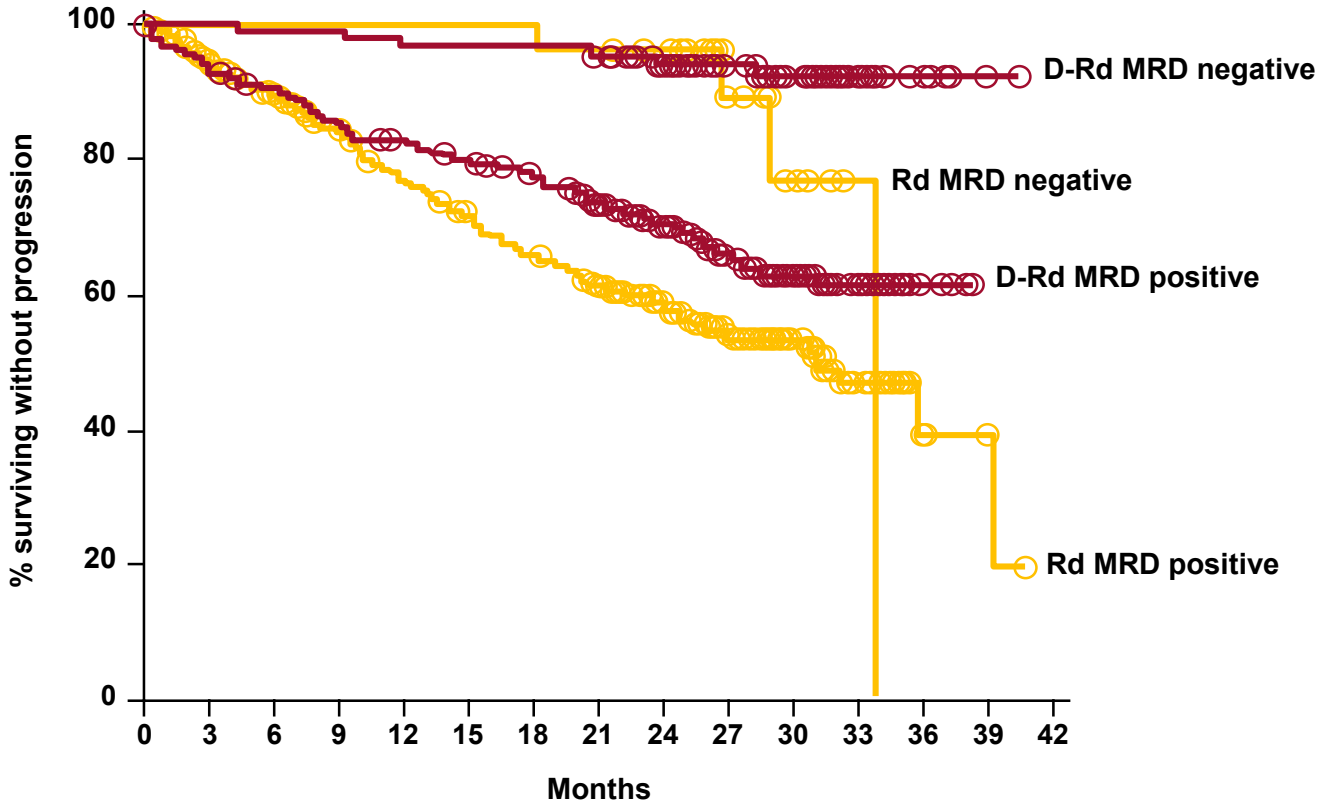
Efficacy: PFS by MRD Status



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

- >3-fold higher MRD negativity achieved with D-Rd
- Lower risk of progression or death with MRD negativity

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Conclusions

- D-Rd significantly reduced the risk of progression or death by 44% in patients with transplant-ineligible NDMM
- D-Rd induced significantly deeper responses, including >3-fold higher MRD-negative rate
- No new safety signals were observed using D-Rd in NDMM

These results support D-Rd as a new standard of care for patients with transplant-ineligible NDMM

IFM 2009 : Study Design.

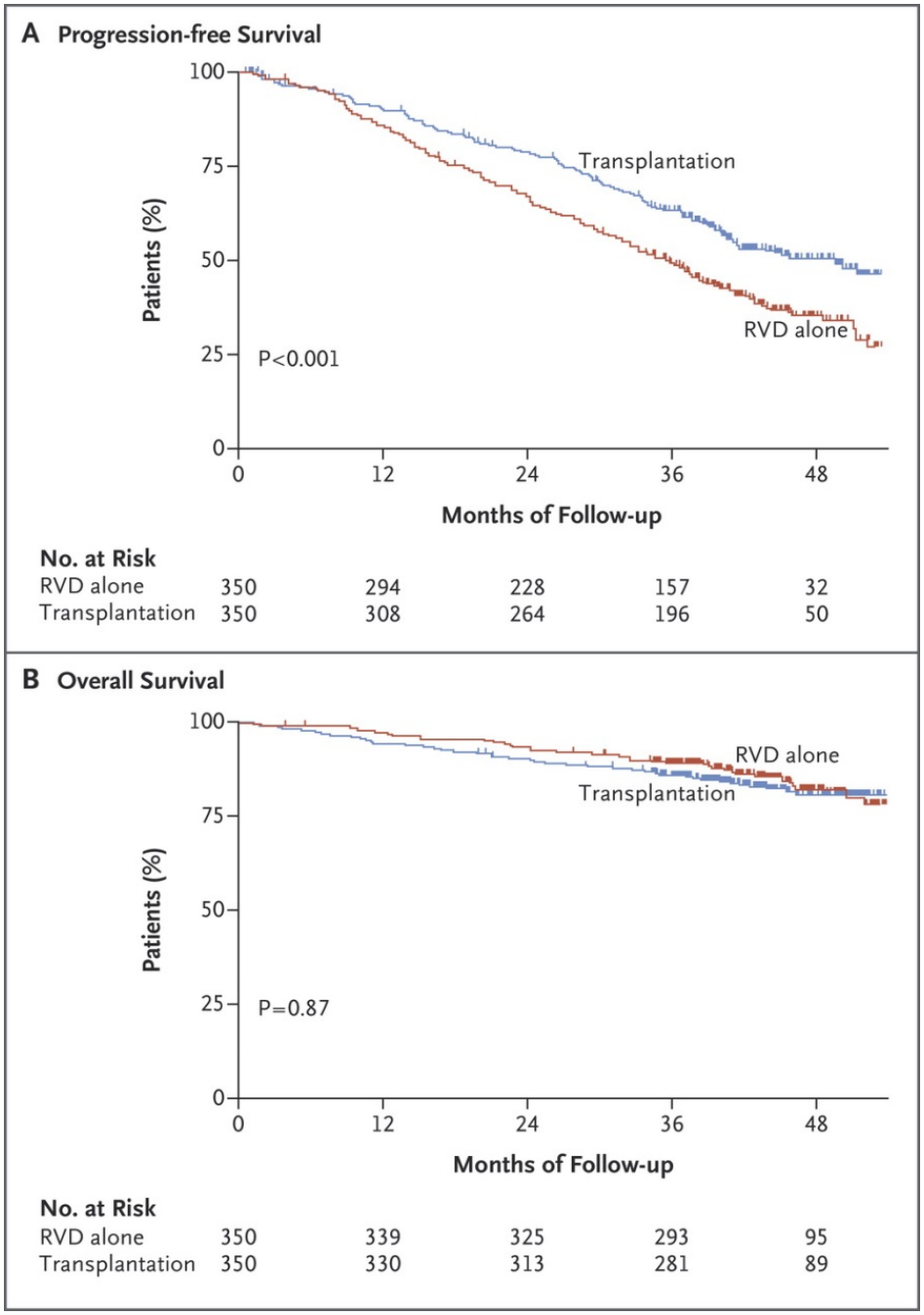
Registration

RVD 1

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

Randomization (stratified on ISS and FISH)

Arm A	Arm B
RVD 2 and 3	RVD 2 and 3
PBSC Collection	PBSC Collection
RVD 4 to 8	ASCT HDM 200mg/m2
Lenalidomide Maintenance 12 months (10-15 mg/d)	RVD 4 and 5
ASCT at relapse HDM 200mg/m2	Lenalidomide Maintenance 12 months (10-15 mg/d)



Progression-free Survival and Overall Survival with ASCT in Myeloma

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

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MAINTENANCE THERAPY

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3. Lenalidomide Maintenance Meta-analysis

PFS and OS

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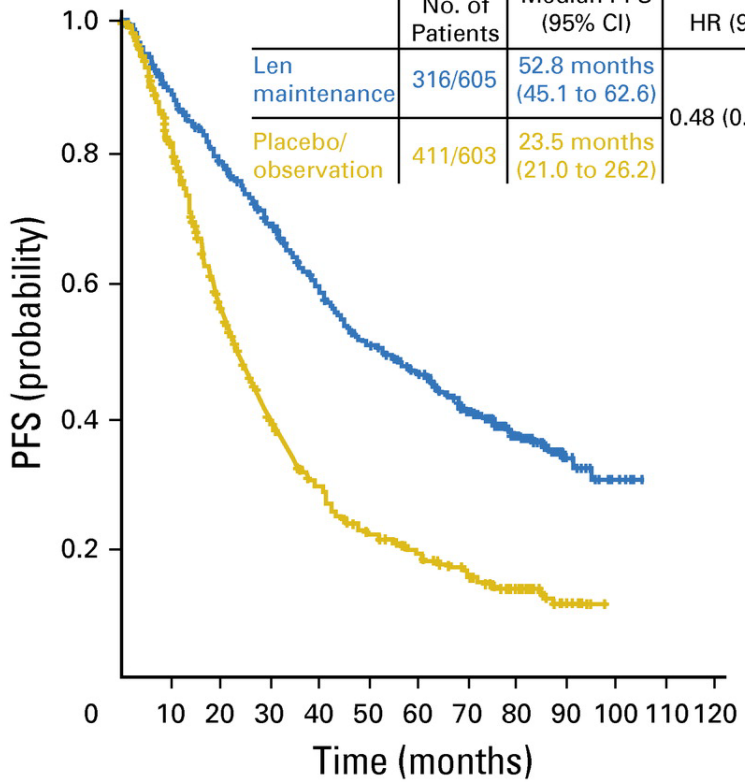

	No. of Events/ No. of Patients	Median PFS (95% CI)	HR (95% CI)
Len maintenance	316/605	52.8 months (45.1 to 62.6)	0.48 (0.41 to 0.55)
Placebo/ observation	411/603	23.5 months (21.0 to 26.2)	

No. at risk:												
Len maintenance	605	499	428	353	293	244	191	131	83	28	5	0
Placebo/ observation	603	419	275	179	125	90	71	52	30	9	0	

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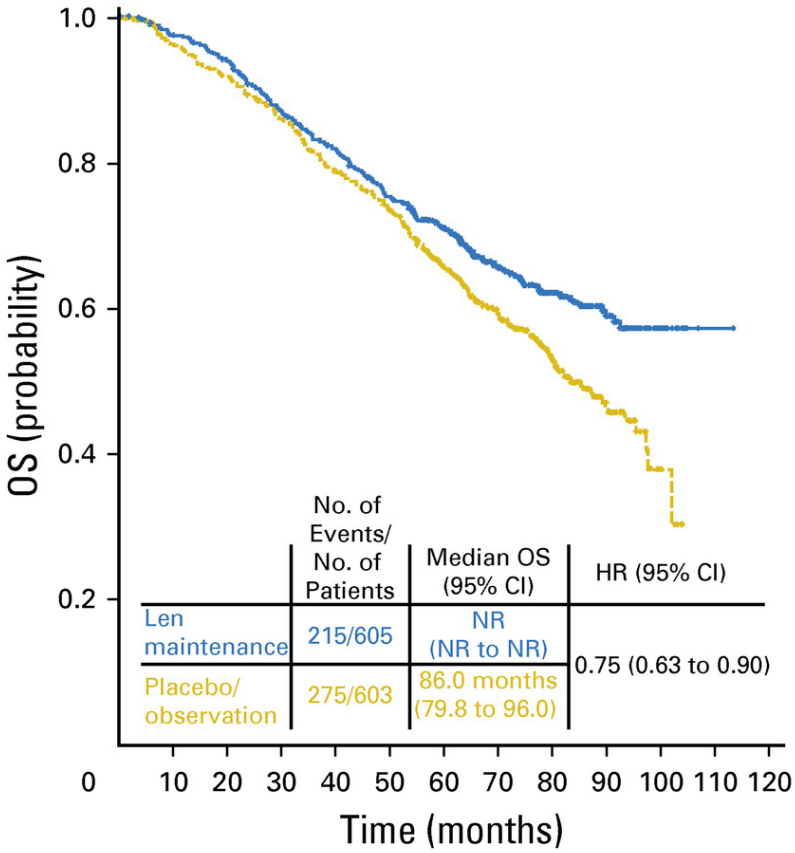

	No. of Events/ No. of Patients	Median OS (95% CI)	HR (95% CI)
Len maintenance	215/605	NR (NR to NR)	0.75 (0.63 to 0.90)
Placebo/ observation	275/603	86.0 months (79.8 to 96.0)	

No. at risk:												
Len maintenance	605	577	555	508	473	431	385	282	200	95	20	1	0
Placebo/ observation	603	569	542	505	459	425	351	270	174	71	10	0	

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

Trial	Regimen	*n*	Median PFS (months)	*P* value for PFS	3-year overall survival rate (%)*	Median overall survival (months)	*P* value for overall survival	Second cancers (%)‡	Reported *P* value for second cancer incidence
McCarthy *et al.* (2012)[1]	Placebo Lenalidomide maintenance	229 231	27 46	<0.001	80 88	NR NR	0.03§	2.6 7.7	0.008
Attal *et al.* (2012)[2]	Placebo Lenalidomide maintenance	307 307	23 41	<0.001	84 80	NR NR	0.70	3.0 7.5	0.002
Palumbo *et al.* (2012)[3]	MP MPR MPR plus lenalidomide maintenance	154 153 152	13 14 31	<0.001	66 62 70	NR NR 45	NS	3 7 7	NR

Rajkumar SV. Nat Rev Clin Oncol 2012

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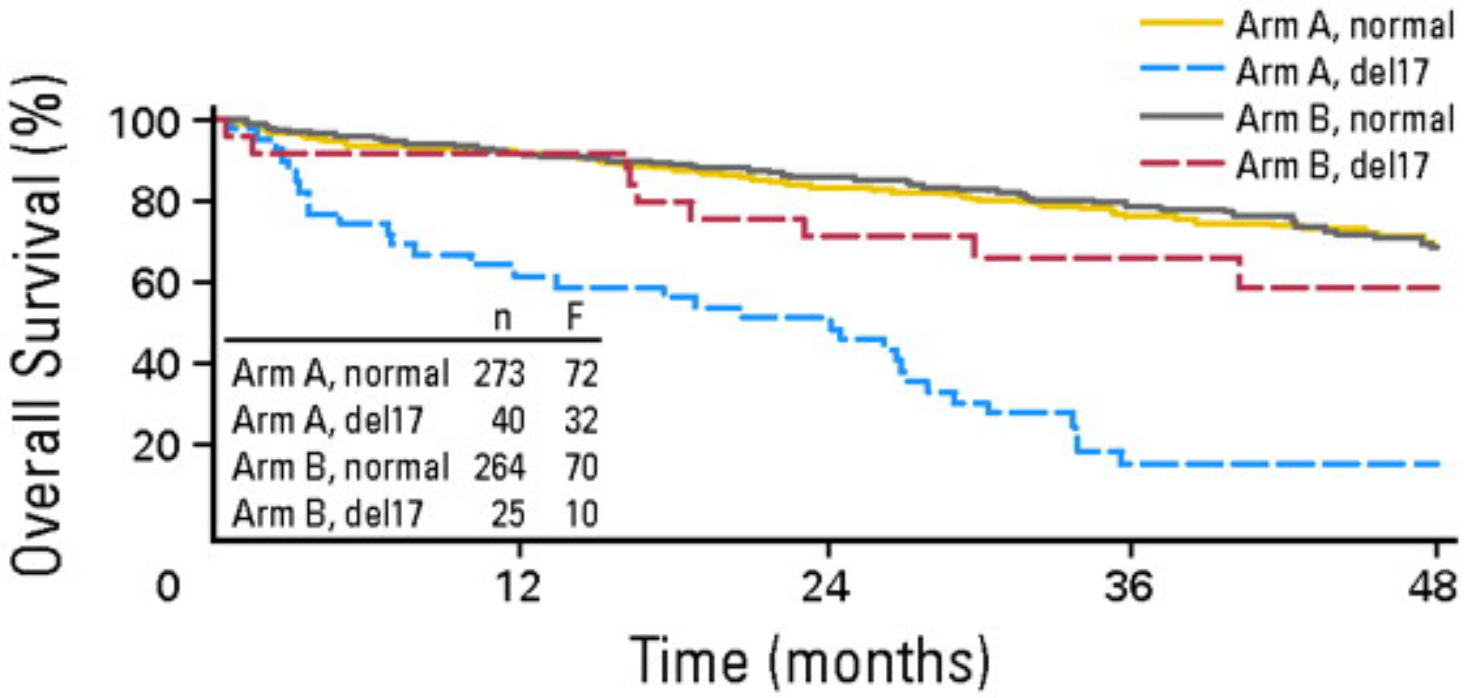
PAD vs VAD: OS according to del(17p)



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

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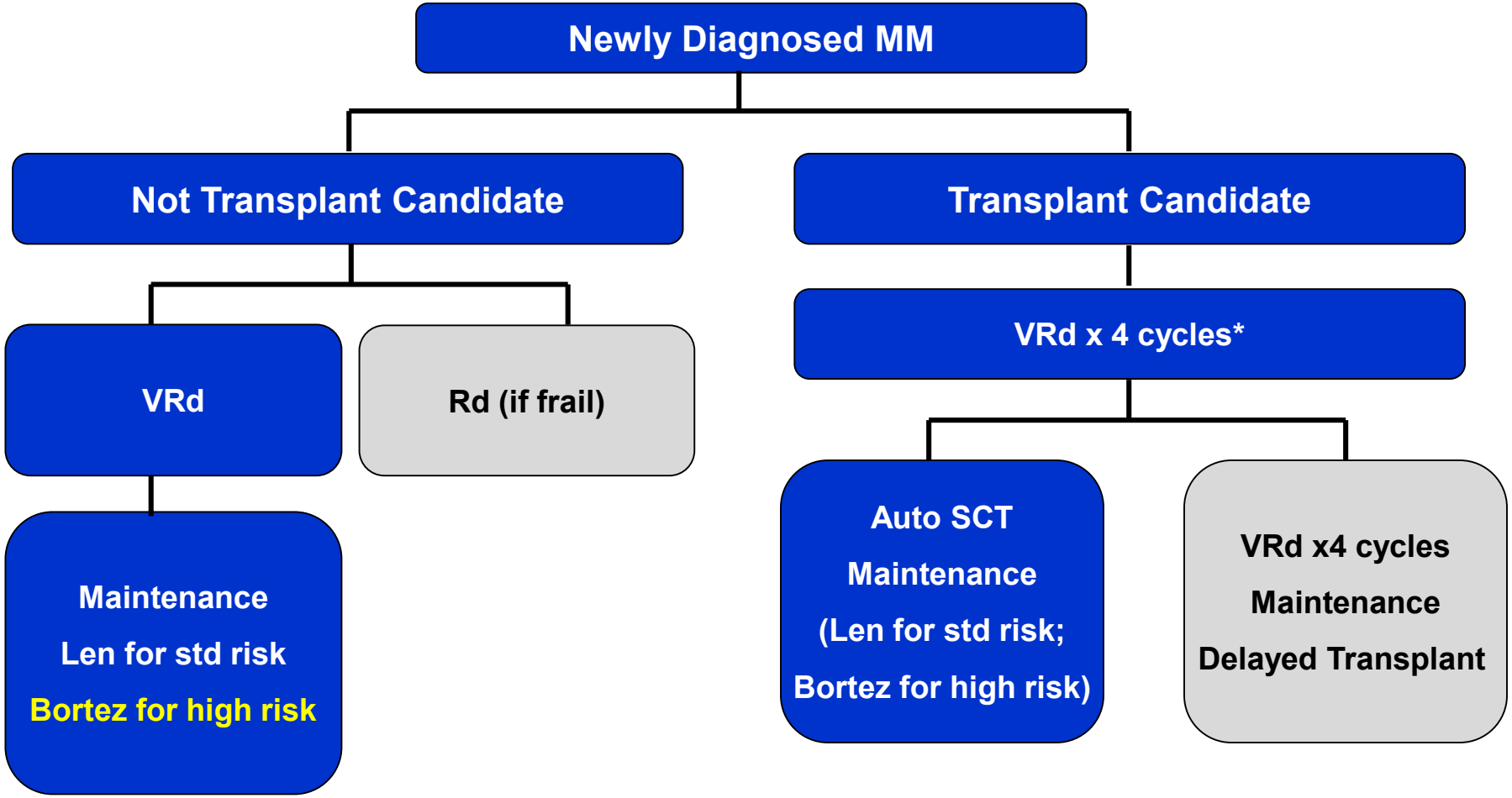
Initial Treatment of Myeloma



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Molecular Classification of Myeloma

Disease Aggressiveness →

- Trisomies*

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

- t(4;14) (FGFR3, MMSET)
- t(14;16) (C-MAF)
- t(14;20) (MAF-B)

*~10% have both trisomies and IgH translocations

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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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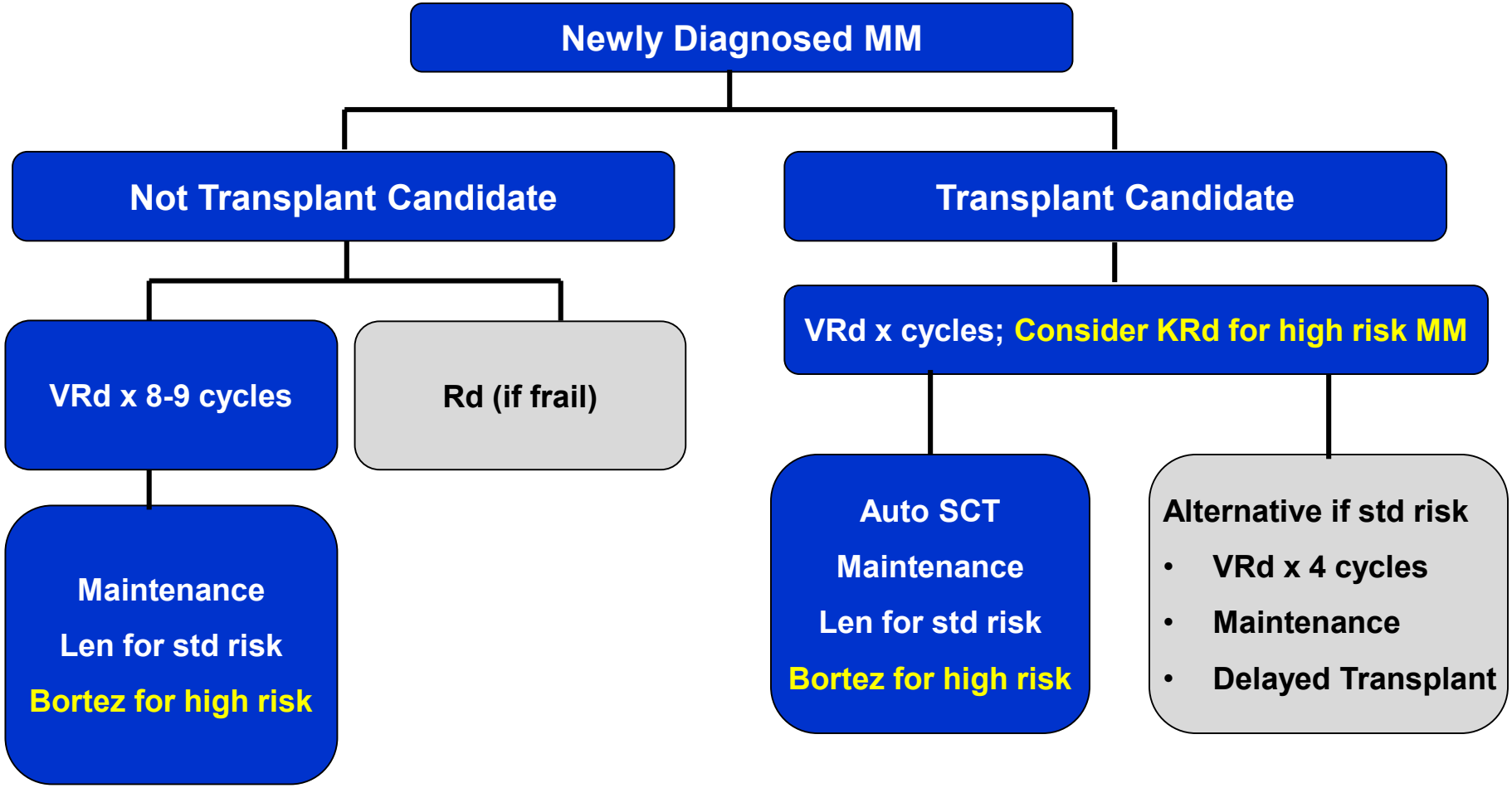
Initial Treatment of Myeloma



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Myeloma with special circumstances

- Plasma cell leukemia (PCL)
- Extensive extramedullary disease (EMD)
- Acute renal failure due to cast nephropathy

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Acute renal failure: Cast Nephropathy

Biopsy proven, or
Presumptive (ARF with FLC ≥ 150 mg/dL

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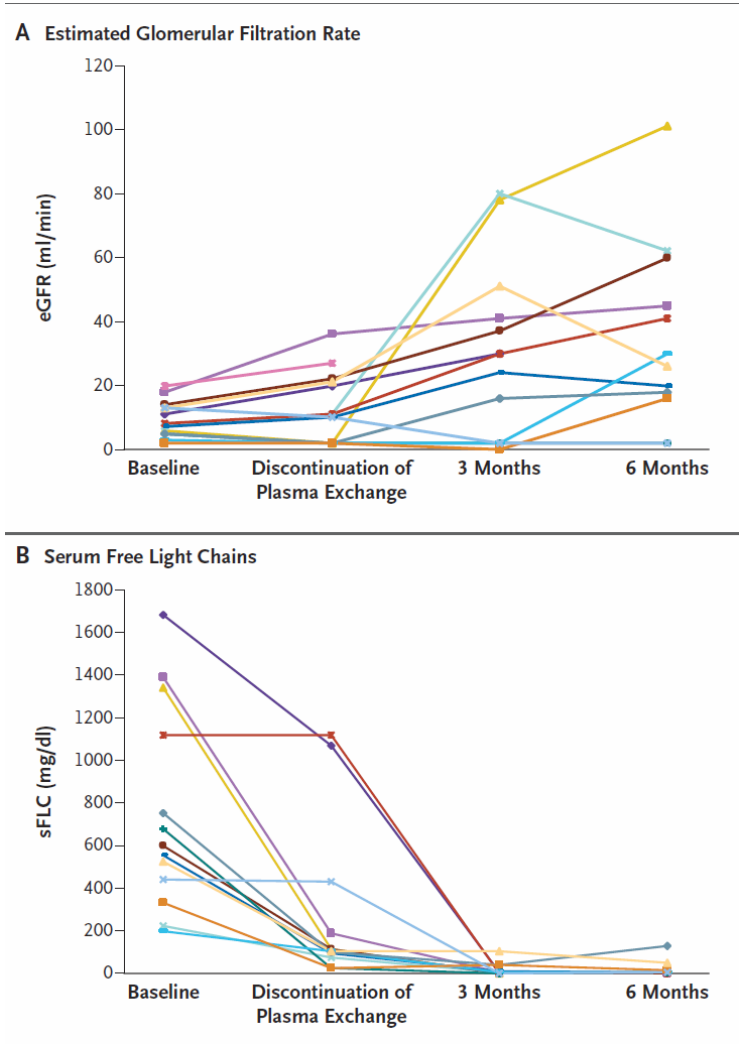
- **VCD or VTD instead of VRD**
- **Plasma exchange and**
- **If needed hemodialysis**



Burnette, N Engl J Med 2011

RELAPSED MYELOMA

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Active Drugs in Multiple Myeloma

Old Drugs

- Alkylators
- Steroids
- Interferon
- Anthracyclines

Older Drugs (2003-2007)

- Bortezomib
- Thalidomide
- Lenalidomide

Recently Approved Drugs (2013-2015)

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

Rajkumar SV. 2017

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Carfilzomib Rd vs Rd (PFS): Aspire Trial

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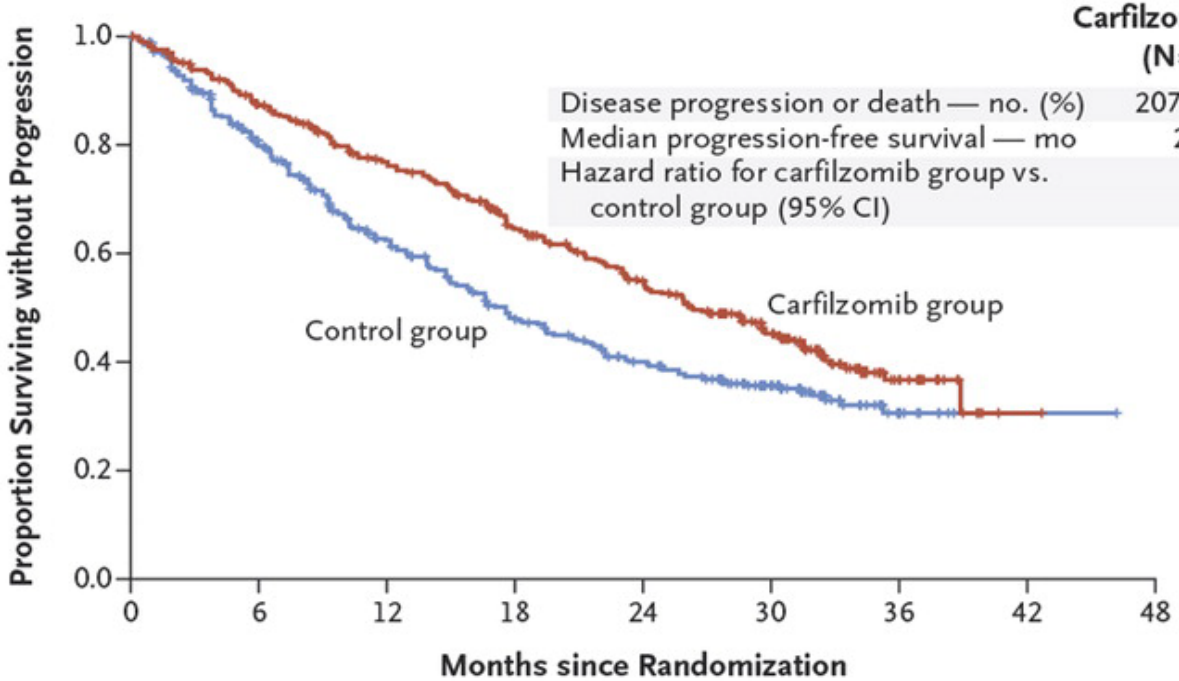

	Carfilzomib Group (N=396)	Control Group (N=396)
Disease progression or death — no. (%)	207 (52.3)	224 (56.6)
Median progression-free survival — mo	26.3	17.6
Hazard ratio for carfilzomib group vs. control group (95% CI)	0.69 (0.57–0.83)	

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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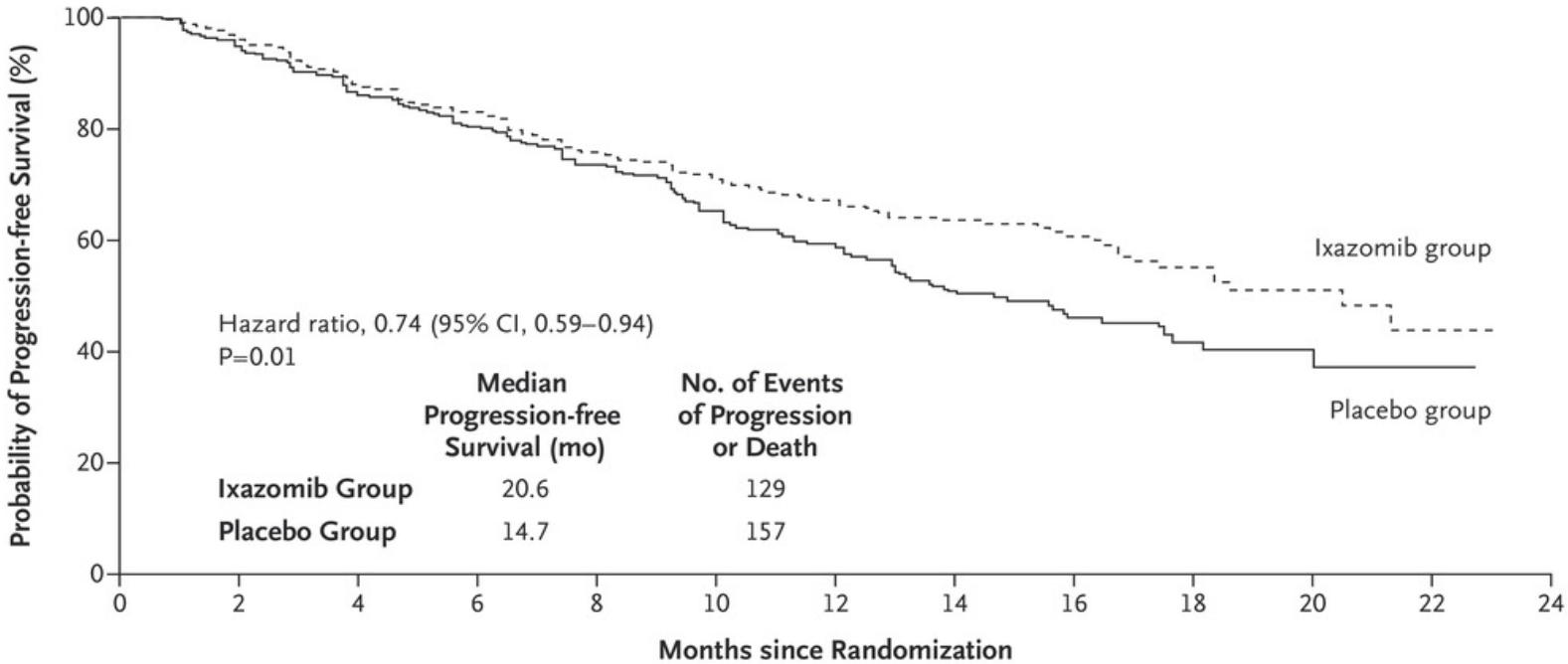
Ixazomib-Rd vs Rd (PFS): Tourmaline Trial

A Progression-free Survival in the Intention-to-Treat Population



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

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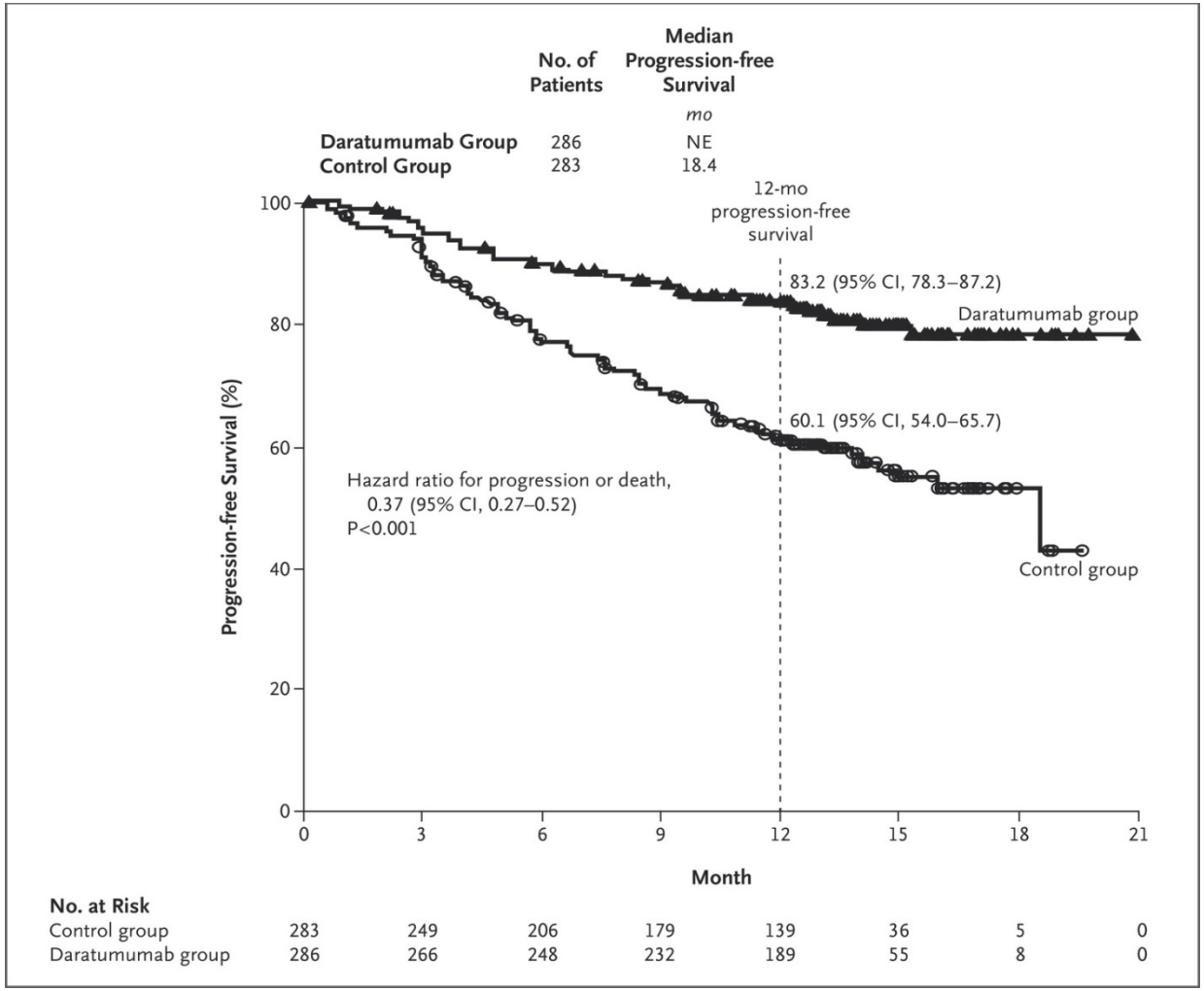
Daratumumab Rd vs Rd (PFS): POLLUX Trial



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

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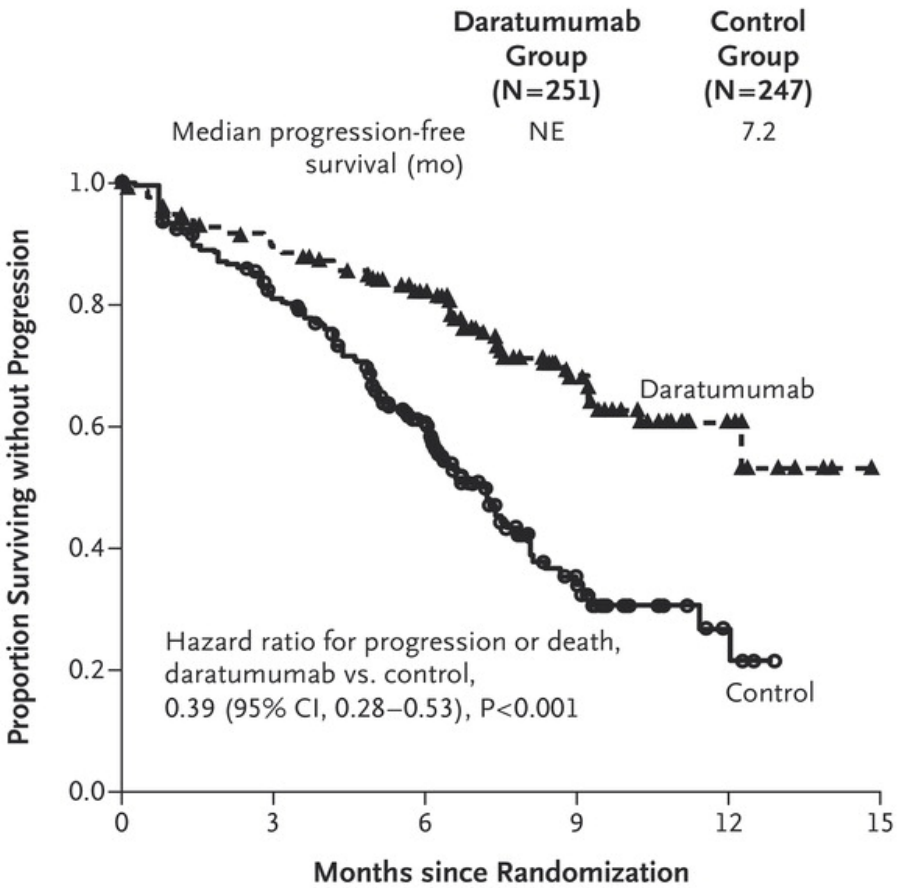
Daratumumab-Vd versus Vel (PFS): CASTOR Trial



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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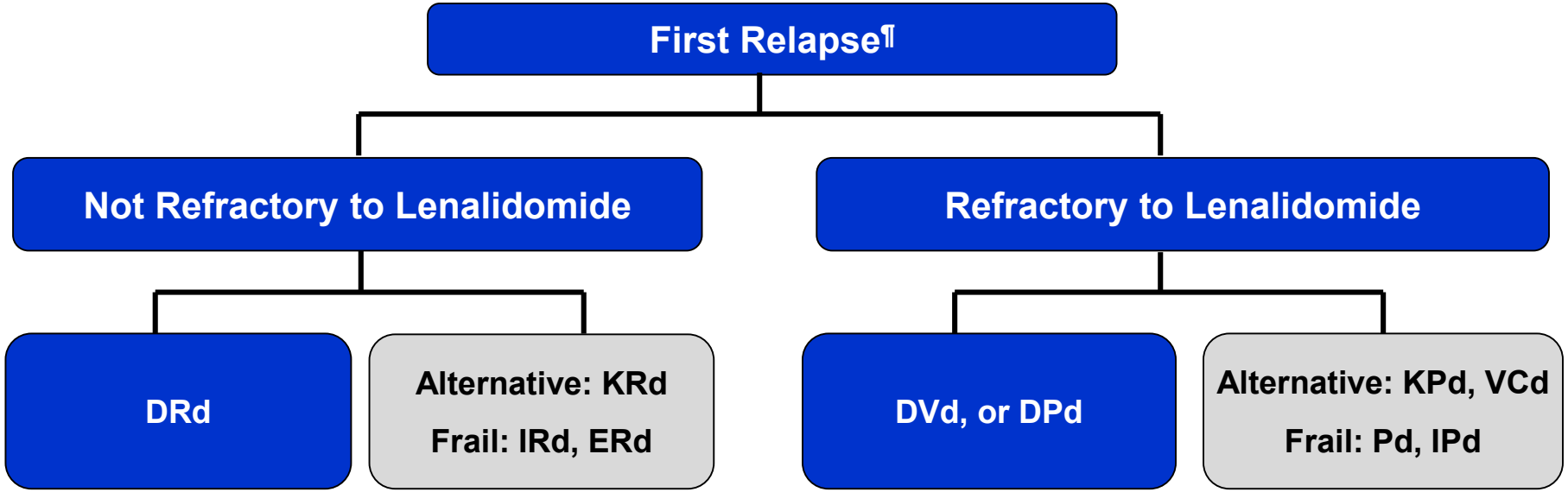
Myeloma: First Relapse



¶ Consider salvage auto transplant in eligible patients

Rajkumar SV. 2018

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

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Second or higher relapse

Consider other First Relapse Options

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- Any first relapse options that have not been tried

Additional Options

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- IV melphalan
- Bendamustine
- VDT-PACE like regimens
- Venetoclax (t11;14)
- Adding Panobinostat
- Quadruplet regimens

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