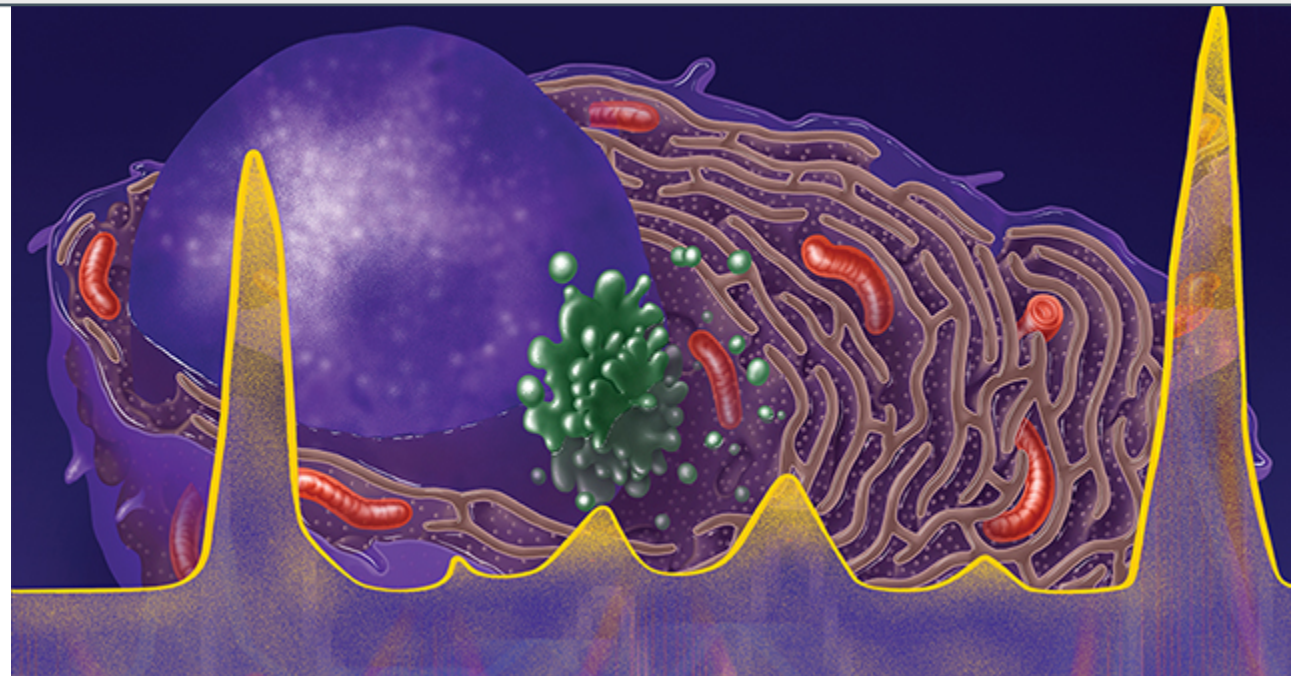
INTERNATIONAL MYELOMA FOUNDATION

CCO LIVE

Are We Ready for Personalized Therapy in Newly Diagnosed MM?

Faculty Presenter:

Brian G.M. Durie, MD



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Faculty Presenter

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.

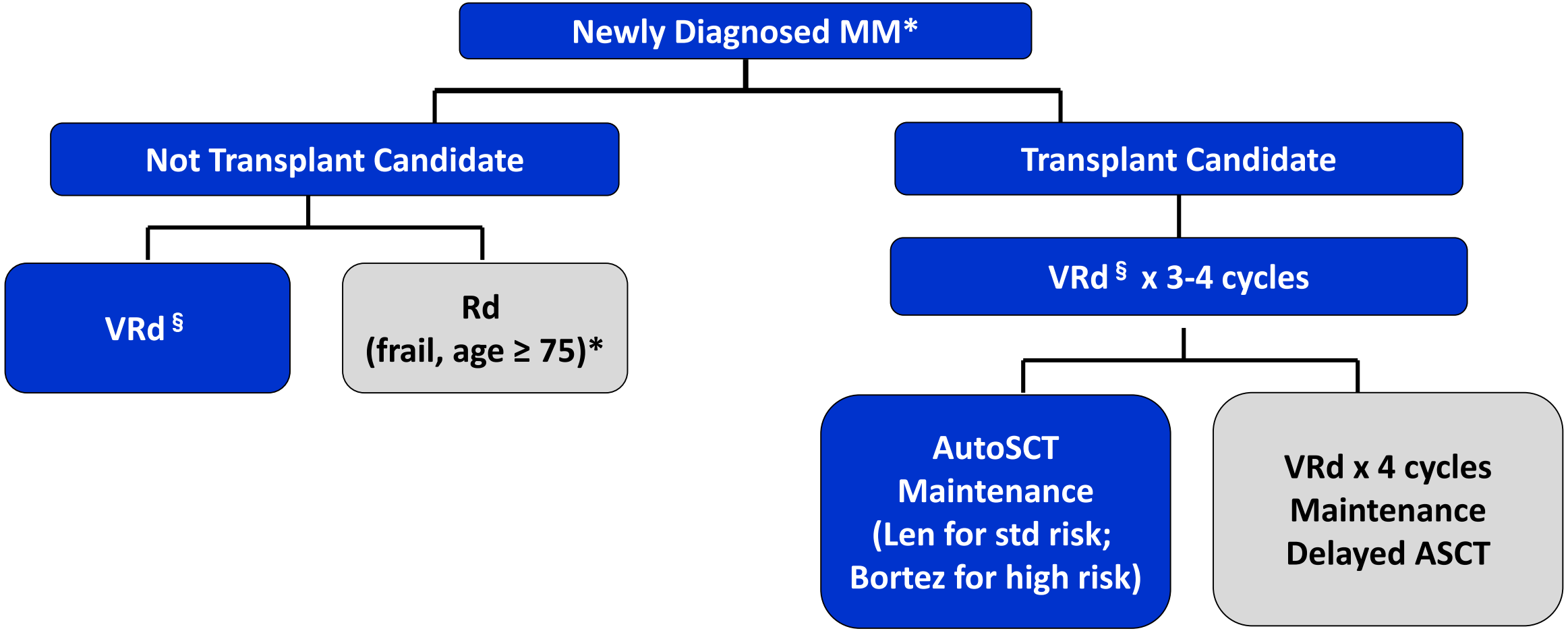
Patient Case Example

- A 55-year-old woman presented with bone pain and a whole-body low-dose CT scan showed multiple lytic lesions
- Additional testing revealed:
  - SPEP plus IFE revealed IgAk of 4.6 g/dL
  - Hemoglobin of 10.4 g/dL; WBC and platelets normal
  - Calcium and creatinine normal
  - Bone marrow shows 41% plasma cells
  - FISH testing shows trisomies of 3, 5, 9 and 15
  - Serum free light chain ratio (sFLC: involved/uninvolved) is 157

What treatment would you recommend for this patient?

Faculty	Recommendation
Brian G.M. Durie, MD	Bortezomib/lenalidomide/dexamethasone (VRd)
Shaji Kumar, MD	Bortezomib/lenalidomide/dexamethasone (VRd)
Philippe Moreau, MD	Bortezomib/lenalidomide/dexamethasone (VRd)
S. Vincent Rajkumar, MD	Bortezomib/lenalidomide/dexamethasone (VRd)
Jesús F. San-Miguel, MD, PhD	Bortezomib/lenalidomide/dexamethasone (VRd)

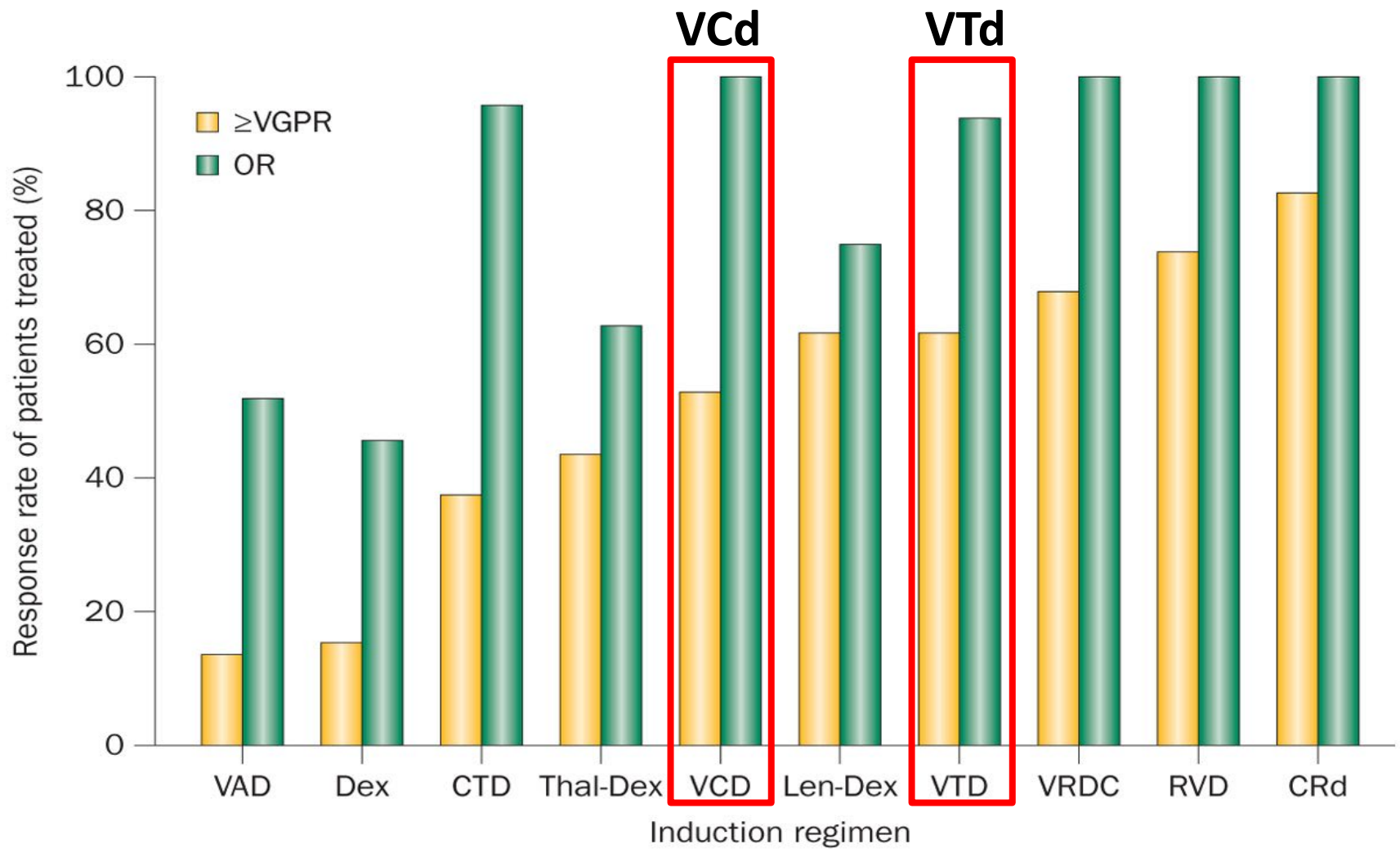
Frontline Treatment of Myeloma



*Based on CALGB 100104, S0777, IFM-DFCI, CTN 0702 HOVON
§ VTd/VCd if VRd not available

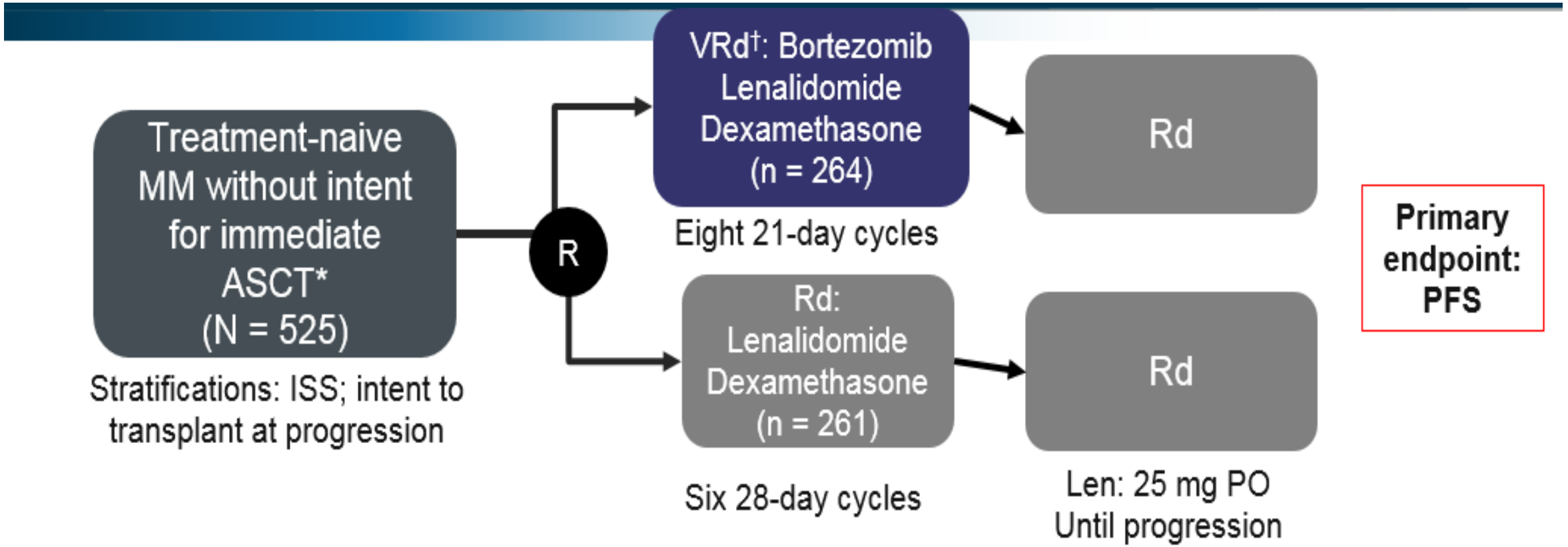
Rajkumar SV. 2016.

Induction Regimens for Patients Eligible for ASCT



Mailankody. Nat Rev Clin Oncol. 2015;12:286..

SWOG 0777 Trial



- *All patients received aspirin (325 mg/d). †Patients received HSV prophylaxis.
- ‡High-risk cytogenetics included: t(4;14), t(14;16), or del(17p); preliminary data from 316 patients.

Durie. Lancet. 2017;389:519. Durie. ASH 2018. Abstr 1992.

SWOG 0777 Trial

Updated Response Results*

	VRd (n = 215)	Rd (n = 207)
Complete response (CR)	24.2% (52)	12.1% (25)
Very good partial response (VGPR)	50.7% (109)	41.1% (85)
VGPR or better	**74.9%**	**53.2%**
Partial response (PR)	15.3% (33)	25.6% (53)
Overall Response Rate (ORR)	**90.2% (194)**	**78.8% (163)**
Stable disease (SD)	7.0% (15)	16.4% (34)
PD or death	2.8% (6)	4.8% (10)

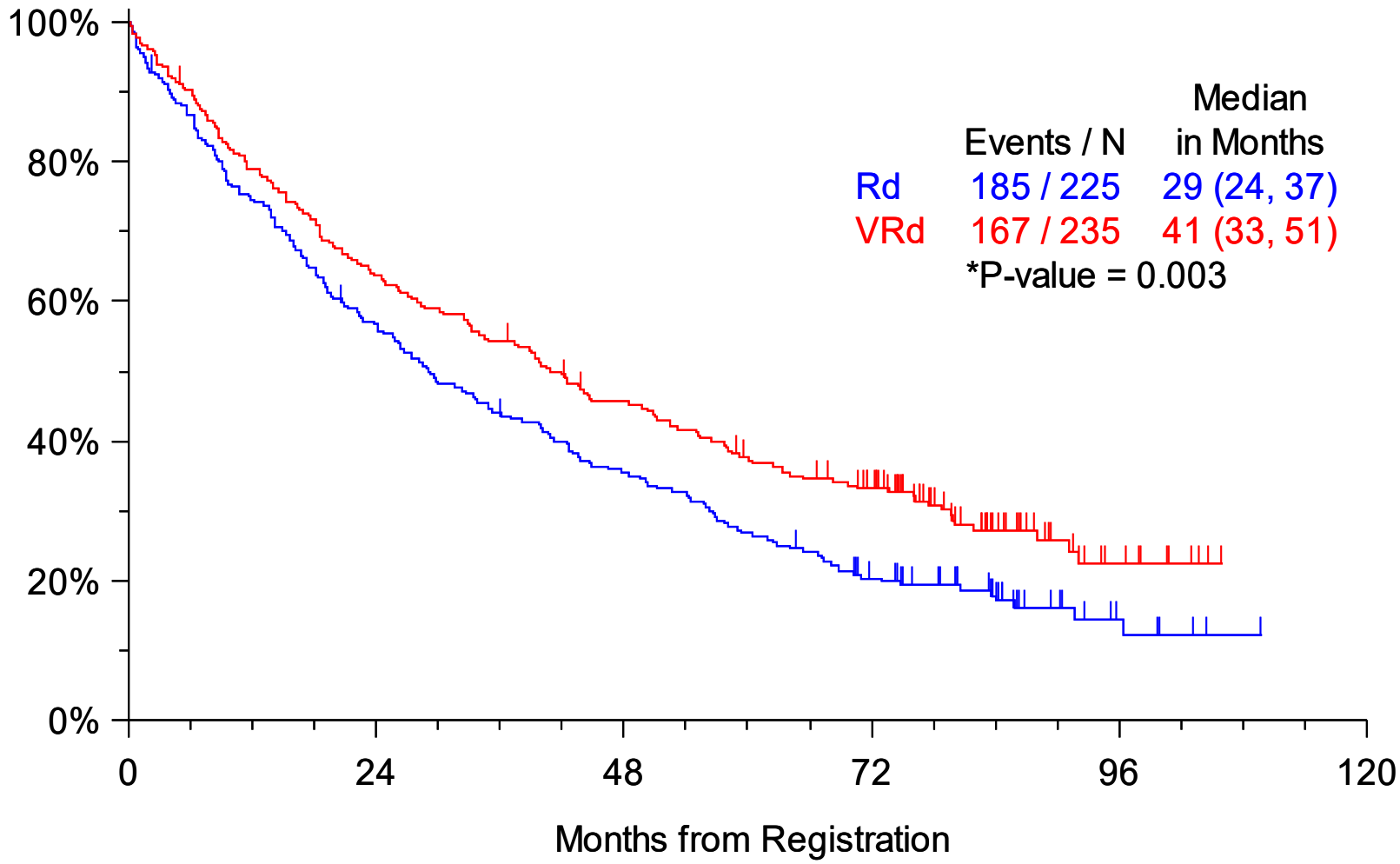
*Both SWOG and IRC stratified Cochran-Mantel-Haenszel analyses indicated improved responses with RVd (odds ratio: 0.528, *P* =.006 [ITT]; odds ratio: 0.38, *P* = .001 [sensitivity analysis])
**Both SWOG and IRC assessments

Durie. Lancet. 2017;389:519. Durie. ASH 2018. Abstr 1992.

SWOG 0777: Progression-Free Survival

CURRENT ELIGIBILITY (N = 460) – CURRENT DATA

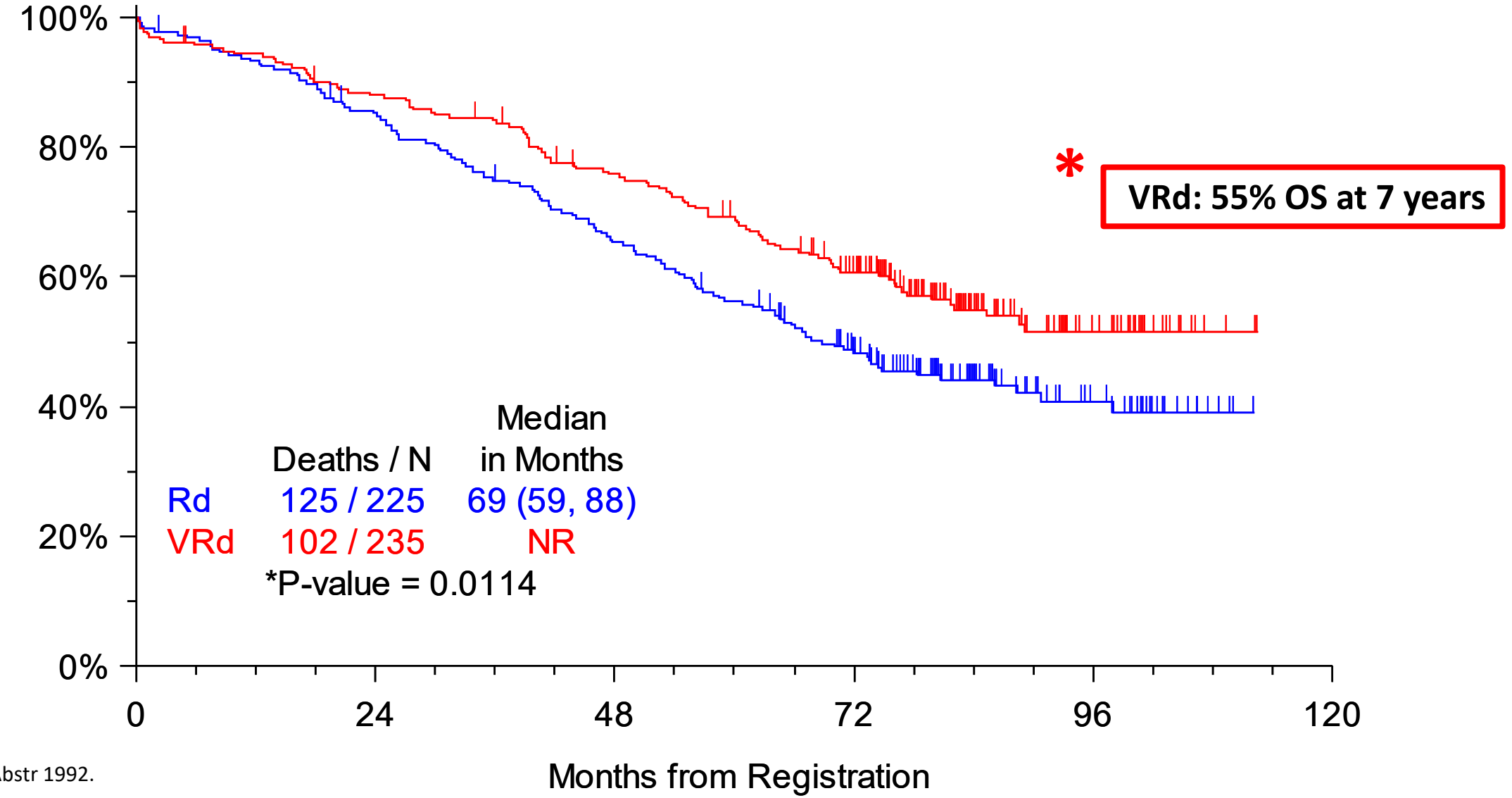
PFS



Durie. ASH 2018. Abstr 1992.

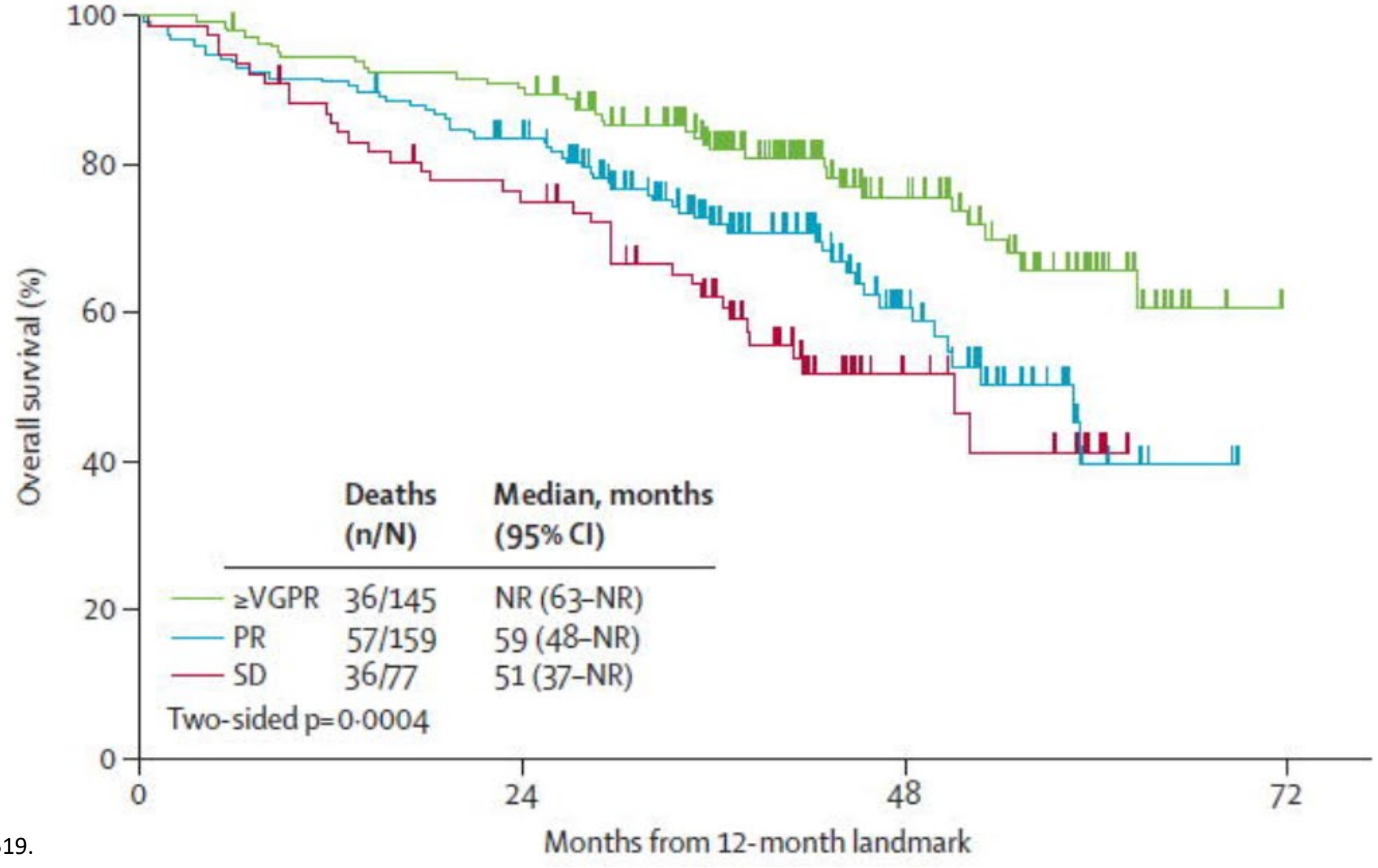
SWOG 0777: Overall Survival

CURRENT ELIGIBILITY (N = 460) – CURRENT DATA



Durie. ASH 2018. Abstr 1992.

SWOG 0777: OS Landmarked at 12 Months (N = 357)



Durie. Lancet. 2017;389:519.

Multivariate COX Proportional Hazards Model

VRd Irrespective of Age

			PFS		OS	
	Variable	n/N (%)	HR (95% CI)	P-value	HR (95% CI)	P-value
Multivariate	RVd arm	235/460 (51%)	0.77 (0.62, 0.95)	0.013	0.75 (0.58, 0.98)	0.033
	ISS Stage III	155/460 (34%)	1.34 (1.01, 1.77)	0.041	1.98 (1.38, 2.86)	<.001
	ISS Stage II	179/460 (39%)	1.12 (0.86, 1.47)	0.398	1.36 (0.95, 1.97)	0.096
	Intent to Transplant	315/460 (68%)	0.95 (0.74, 1.23)	0.714	0.73 (0.54, 0.99)	0.043
	Age >= 65 yr	197/460 (43%)	1.27 (1.00, 1.61)	0.048	1.63 (1.21, 2.19)	0.001

HR- Hazard Ratio, 95% CI- 95% Confidence Interval, P-value from Score Chi-Square Test in Cox Regression

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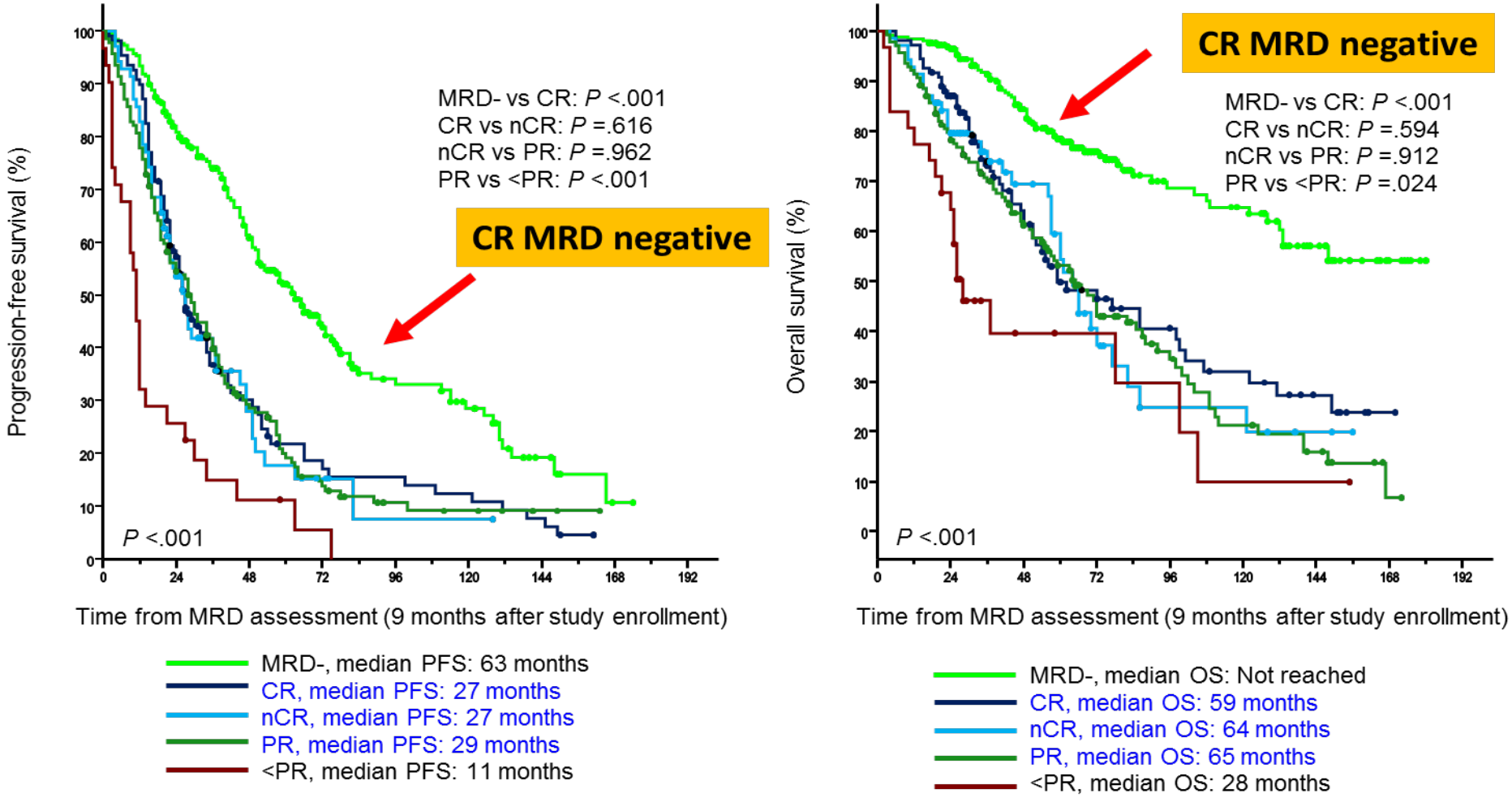
In 2018/2019:

Achievement of MRD undetected status at 10^{-6} is the goal of therapy.

Concept to Influence Decisions

True value of CR comes from the MRD status



Lahuerta. J Clin Oncol. 2017;35:2900.

MAJOR GOAL OF I²TEAMM SUBMISSIONS

MRD approved by FDA and EMA as surrogate endpoint for myeloma

Trials included:

- IFM 2009
- EMN/Hovon
- MM05 [Heidelberg]
- STAMINA
- MRC
- Clarion
- CASTOR/POLLUX
- C16010
- IXA maintenance: C16019

MAYO CLINIC

→ **FDA meeting December 11th, 2018**

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Patient Case Example

- A **76-year-old woman** presented with bone pain and a whole-body low-dose CT scan showed multiple lytic lesions
- Additional testing revealed:
  - SPEP plus IFE revealed IgAk: 4.6 g/dL
  - Hemoglobin: 10.4 g/dL; WBC and platelets normal
  - Calcium and creatinine normal
  - Bone marrow shows 41% plasma cells
  - FISH testing shows trisomies of 3, 5, 9 and 15
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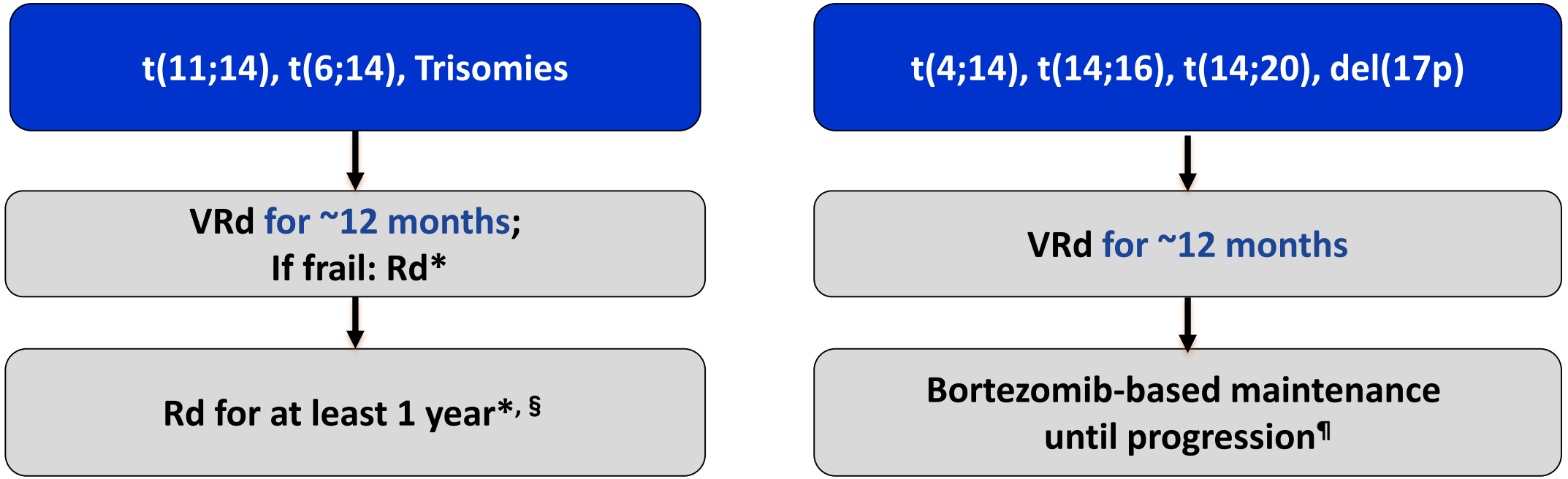
What treatment would you recommend for this patient?

Faculty	Recommendation
Brian G.M. Durie, MD	Bortezomib/lenalidomide/dexamethasone (VRd), full dose or “lite”
Shaji Kumar, MD	Bortezomib/lenalidomide/dexamethasone (VRd), full dose or “lite”
Philippe Moreau, MD	Bortezomib/lenalidomide/dexamethasone (VRd), full dose or “lite”
S. Vincent Rajkumar, MD	Bortezomib/lenalidomide/dexamethasone (VRd), full dose or “lite”
Jesús F. San-Miguel, MD, PhD	Daratumumab/lenalidomide/dexamethasone

Frontline Treatment of Myeloma

Non-Transplant Candidate: Off-Study



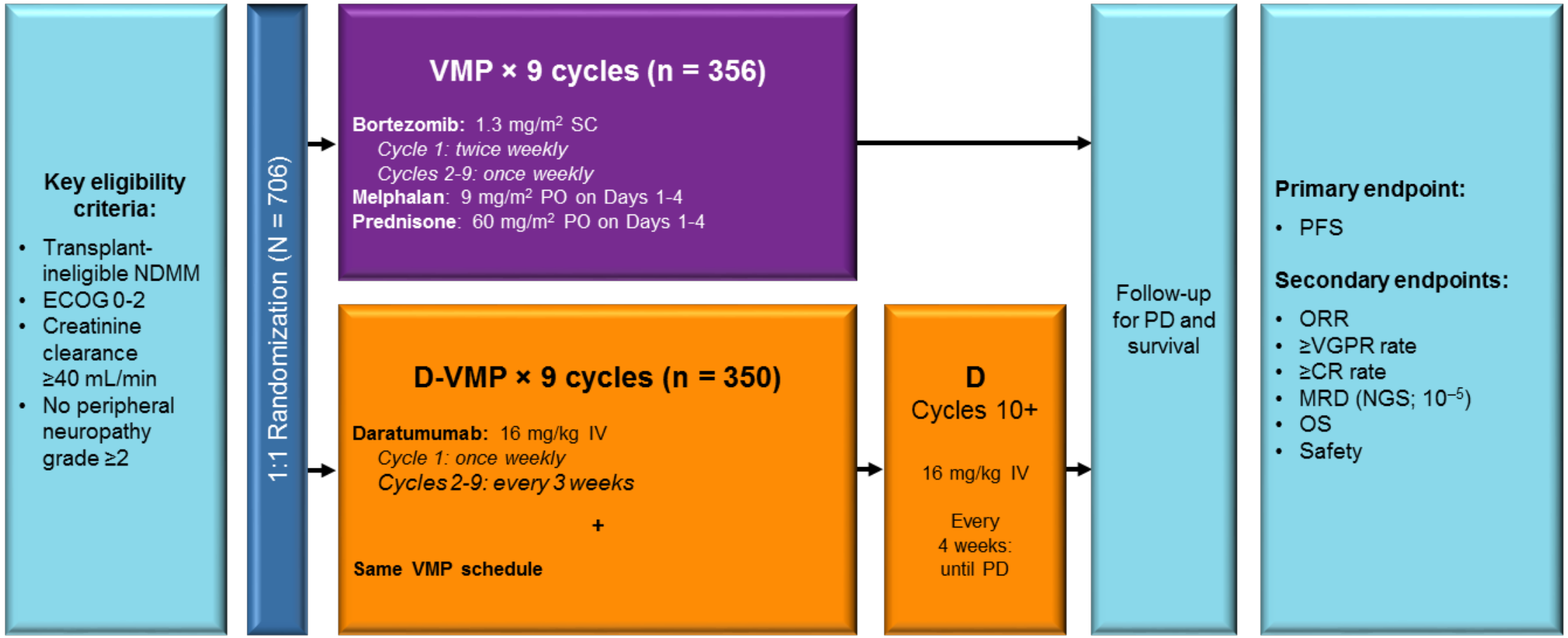
*In patients treated initially with Rd, continuing treatment until progression is an options for patients responding well with low toxicities

§ Dex is usually discontinued after first year

¶Duration based on tolerance; consider risks and benefits for treatment beyond 3 years

Dispenzieri. Mayo Clin Proc. 2007;82:323; Kumar. Mayo Clin Proc. 2009;84:1095. Mikhael. Mayo Clin Proc. 2013;88:360. v14 ///last reviewed May 2018

ALCYONE Study Design



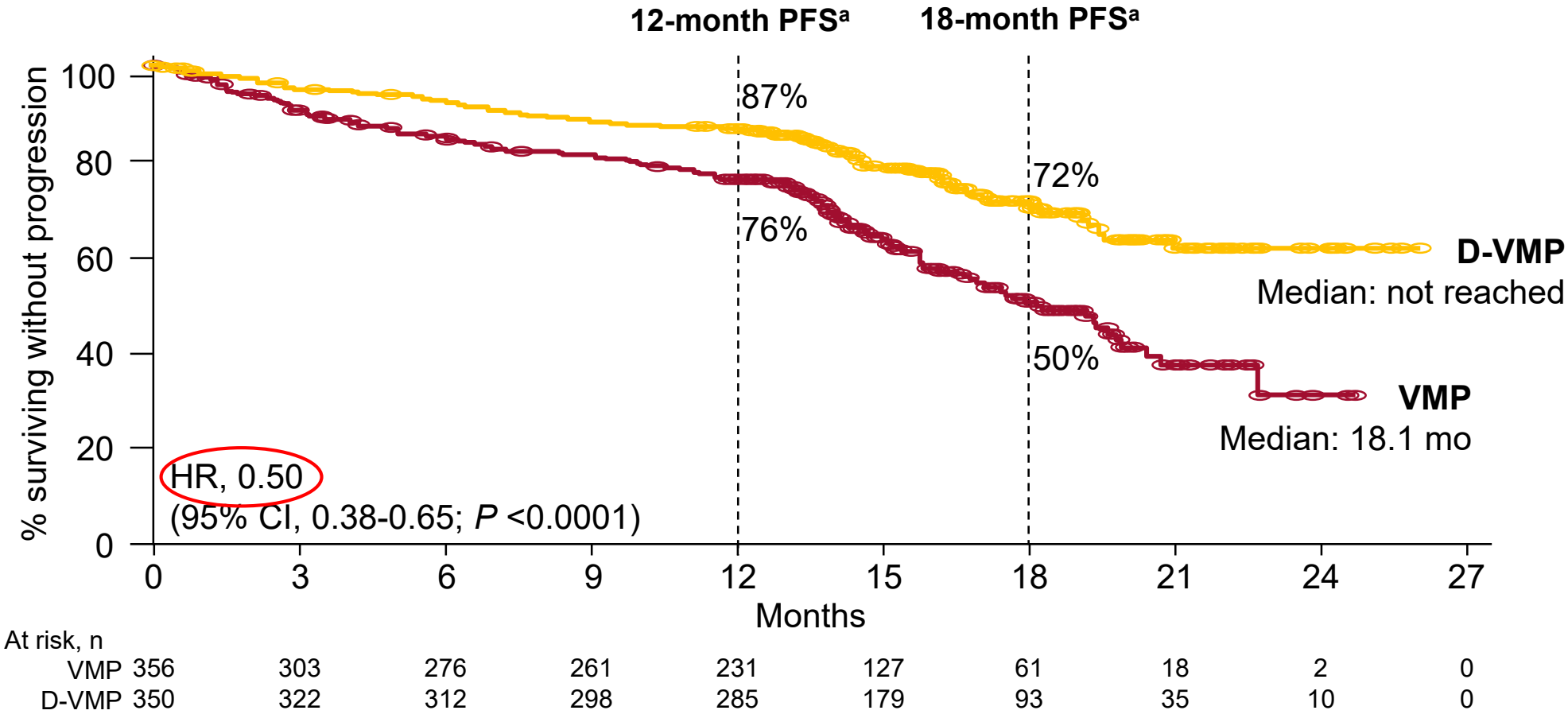
Stratification factors
- ISS (I vs II vs III)
- Region (EU vs other)
- Age (<75 vs ≥75 years)

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

Statistical analyses
- 360 PFS events: 85% power for 8-month PFS improvement
- Interim analysis: ~216 PFS events

Mateos. NEJM. 2018; 378:518.

Efficacy: PFS

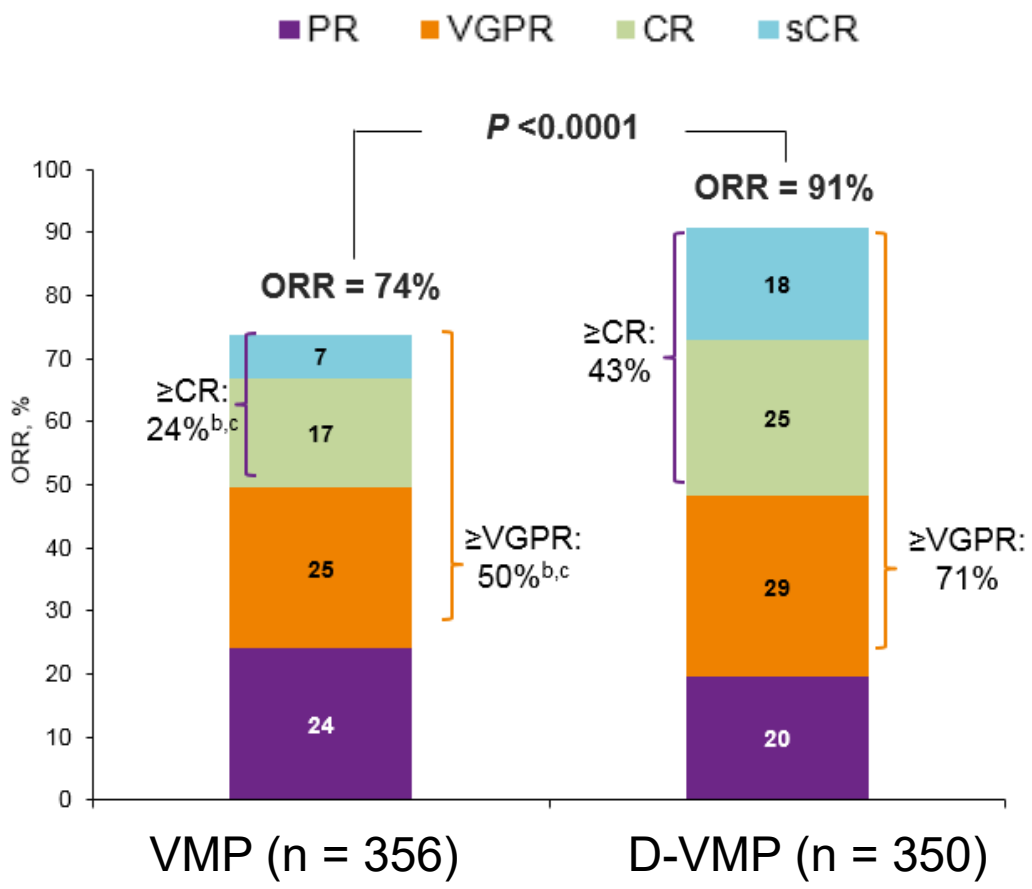


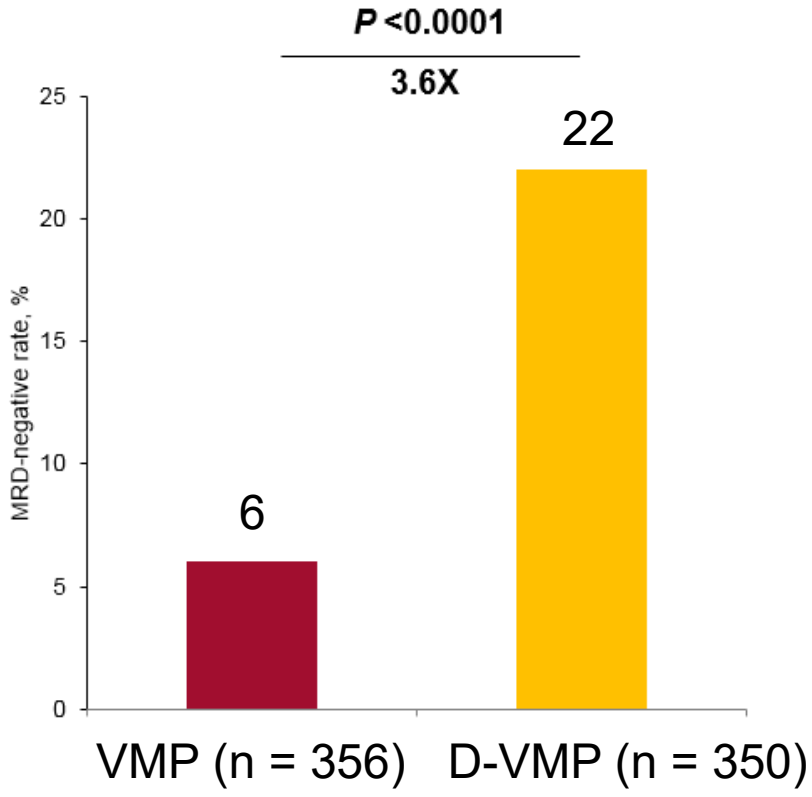
- **Median follow-up: 16.5 months (range: 0.1-28.1)**
- **Consistent PFS treatment benefit across subgroups**

50% reduction in the risk of progression or death in patients receiving D-VMP

Mateos. NEJM. 2018; 378:518.

Efficacy: ORR and MRD (NGS; 10^{-5} Threshold)



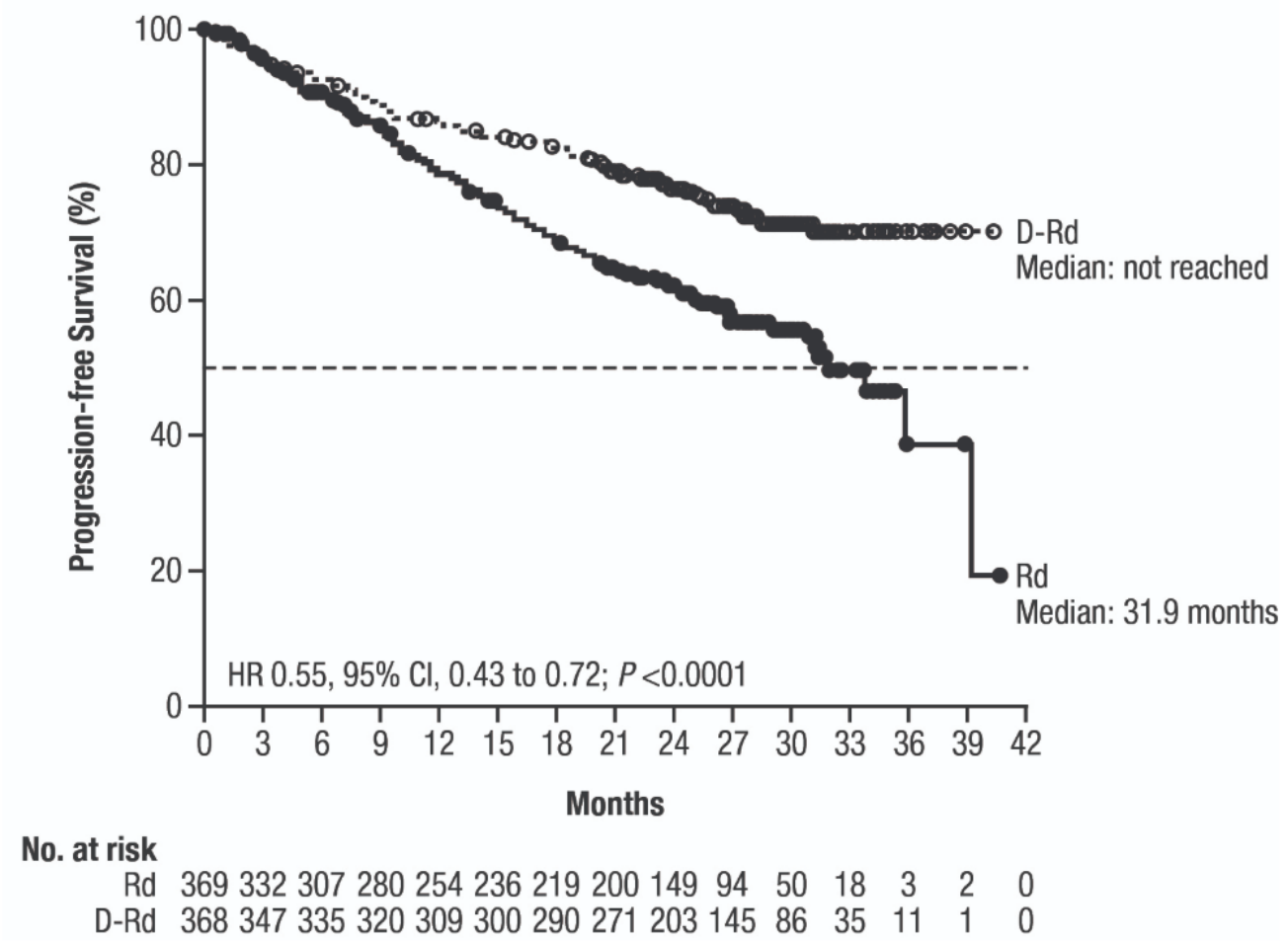


Significantly higher ORR, ≥VGPR, and ≥CR with D-VMP
>3-fold higher MRD-negativity rate with D-VMP

Mateos. NEJM. 2018; 378:518.

Updates at ASH 2018

- **LBA-2 Phase 3 dara/len/dex (dara Rd) versus len/dex (Rd)**
  - ➢ **NDMM not eligible for transplant**



Facon. ASH 2018. Abstract LBA-2.

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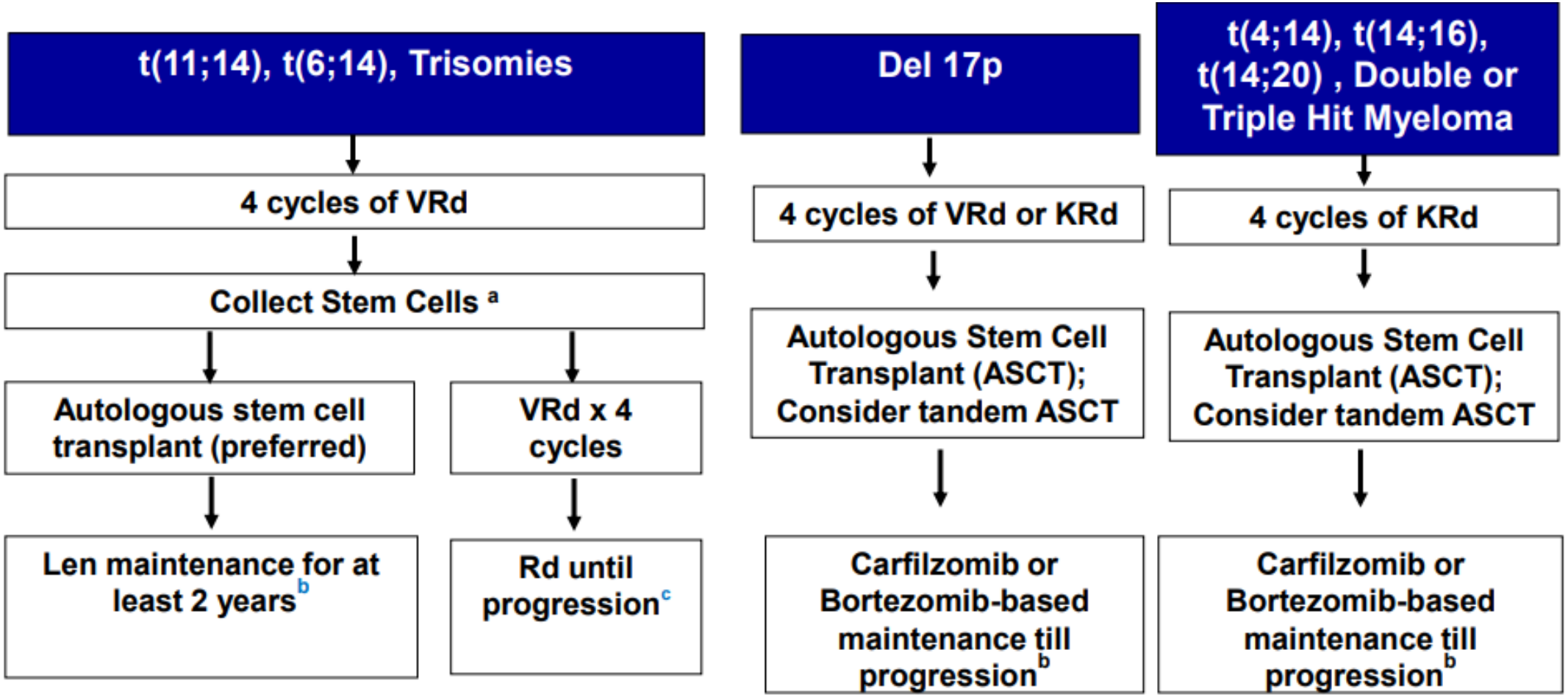
Initial Treatment of Myeloma

Transplant Candidate: Off-Study



a If age >65 or > 4 cycles of VRd, consider mobilization with G-CSF plus cytoxan or plerixafor
b Duration based on tolerance; consider risks and benefits for treatment beyond 3 years
c Continuing Rd for patients responding to Rd and with low toxicities

Dispenzieri. Mayo Clin Proc. 2007;82:323; Kumar. Mayo Clin Proc. 2009;84:1095; Mikhael. Mayo Clin Proc. 2013;88:360. v14 ///last reviewed May 2018

Controversies in 2018/2019

Triplets:

- KRd/KCd/KTd
- Dara-Rd or Vd or Cyd or Td
- IxaRd/IxaCyD/IxaTd (also combos with elotuzumab or pomalidomide if feasible)

Four-drug combos:

- Dara Rd + K or Ixa triplets
- Globally, Dara + VRd/VTd/VCd or VMP

Only 6/225 (3%) Relapses With VRd + ASCT (Spanish)

Patient	359	454	502	635	751	767
Diagnosis						
ISS	III	III	I	III	I	I
FISH	1q+(59%)	del17p(22%)	1q+(50%) & 1p-(61%)	1q+(85%) & 1p-(89%)	NE	-
Bone-related plasmacytomas	+	+	+	+	NE	+
Relapse						
M-protein	-	-	+	-	-	+
BMPCs (%)	4	3	46	1	58	4
Clonal PCs (%)	0	0	100	0	100	0
Bone-related plasmacytomas	+	+	+	+	NE	+

NE: not evaluated

Note: "Double hit" myeloma

- **Double loss/mutation of p53 [17p-]**
- **≥ 4 copies Iq21 [CKS1B]**

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Subclonal Mutational Patterns for 1q+

Single-cell exomes in an index case of amp1q21 multiple myeloma reveal more diverse mutanomes than the whole population

- RAS genes most frequently "co-mutated"
  - NRAS 19%
  - KRAS 16%
- 21 variant subclones
- 5 driver genes
  - ANK 3: ANKRIN membrane protein
  - AXIN 1: Wnt/βcatenin signaling
  - BRCA2: DNA repair
  - MAP4K3: cell signaling/c Jun
  - Tripio: stat3 interacting

Increasing subclonal heterogeneity strongly supports early intervention

Bryant. Blood. 2018;132:232.

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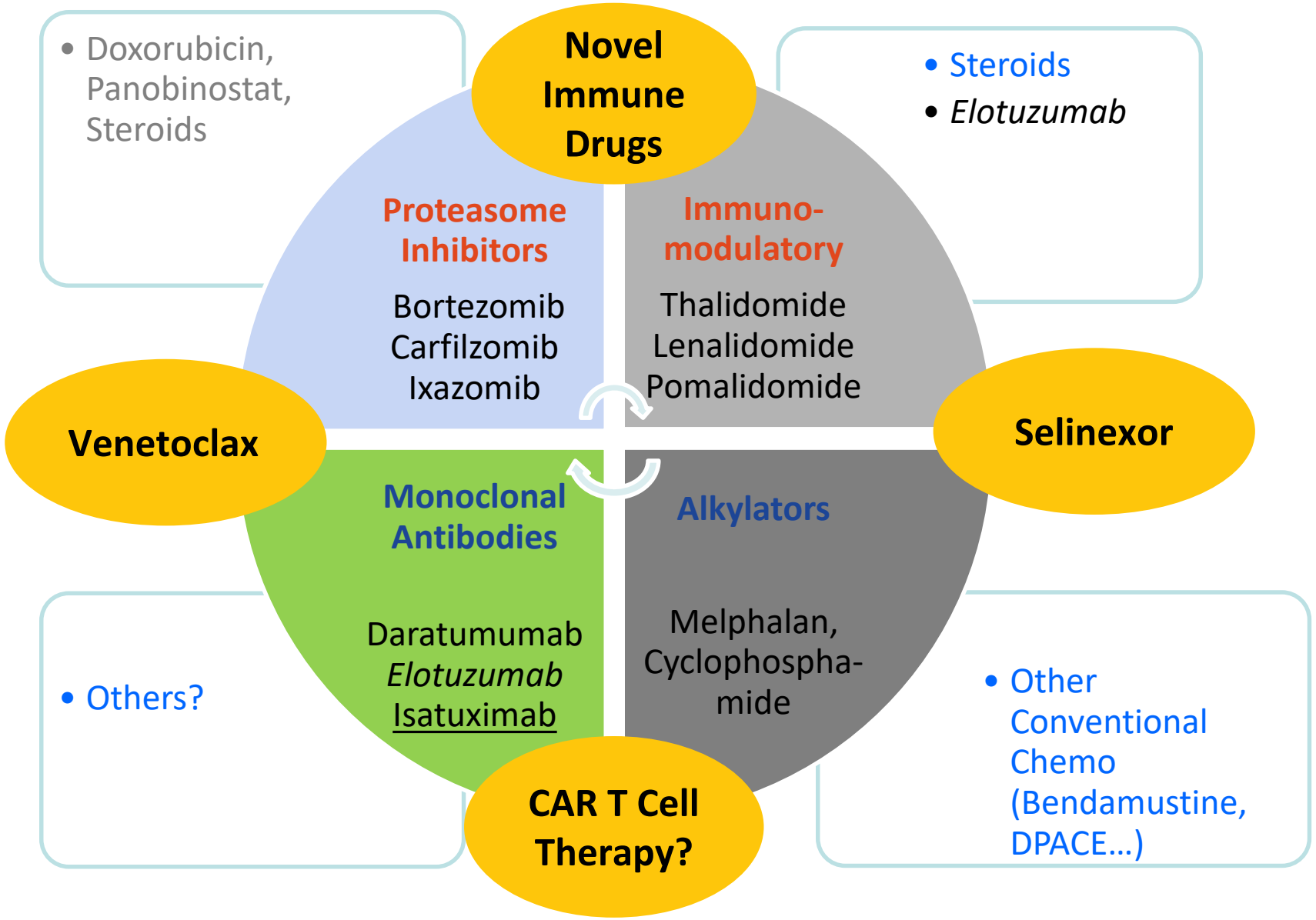
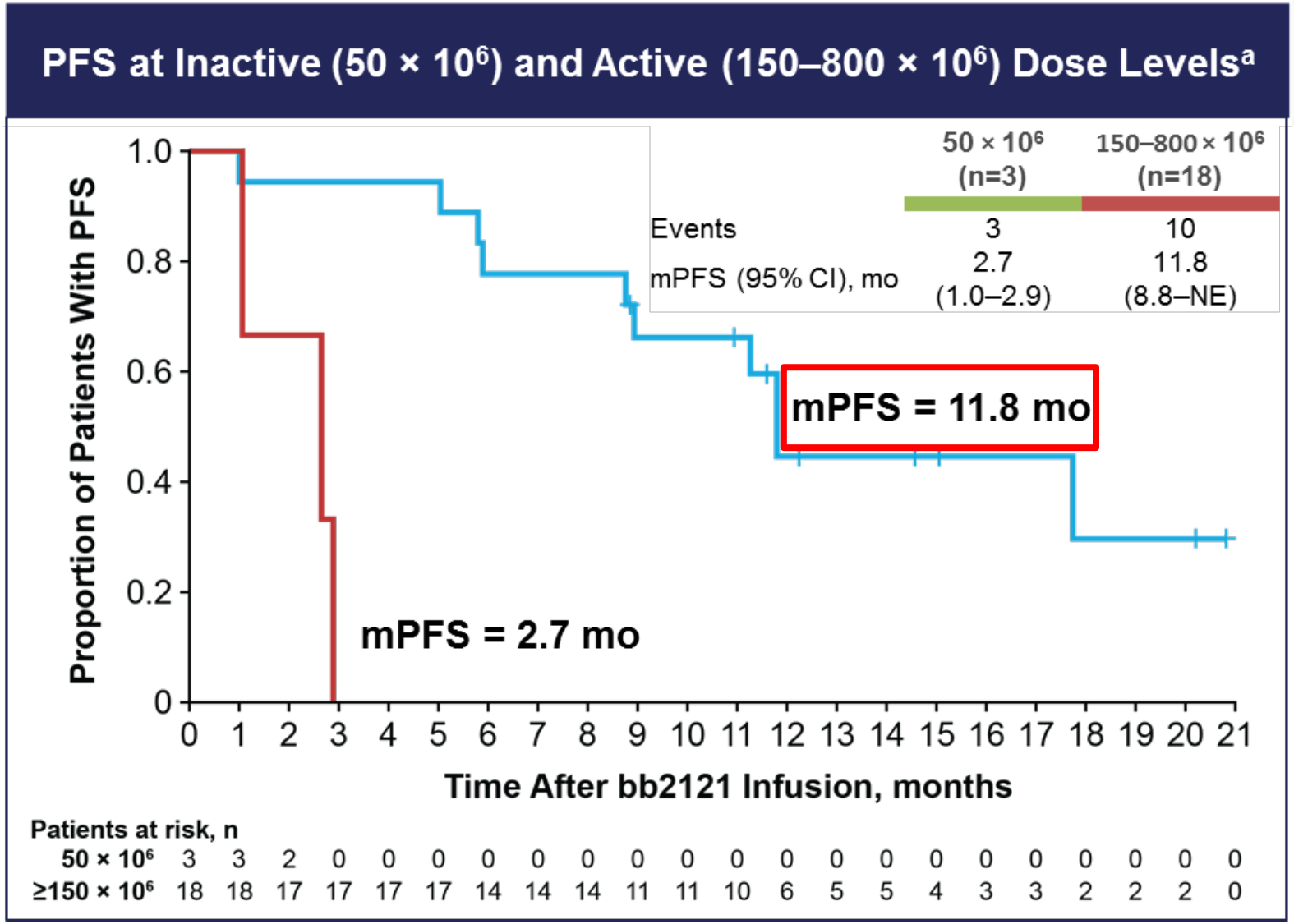
Pillars of Myeloma Therapy



New Agents in Frontline Setting

- Daratumumab (or isatuximab): Add to create 4-drug combo?
- Venetoclax (or Mcl-1 inhibitions): Add if t(11;14) present?
- CAR T or BiTEs: Consider adding early in high risk and/or with suboptimal response?

PFS With BCMA (bb2121) CAR T



Raje. ASCO 2018. Abstr 8007.

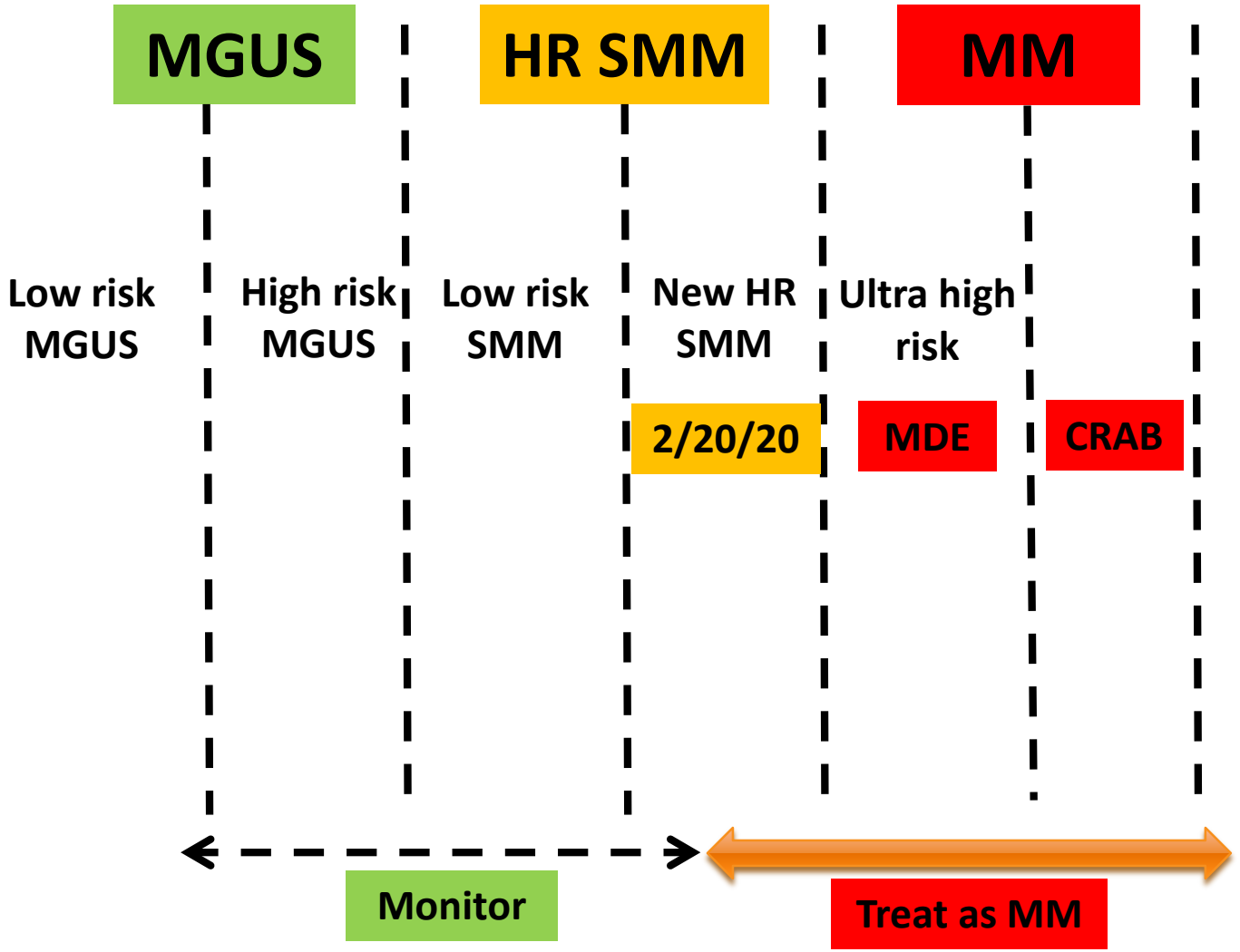
Can CAR T Therapy Be Introduced Early?

- **Can consider harvesting T-cells early!**
- **Potential of great efficiency BUT concerns about both short term and long-term toxicities.**

Need New Response Criteria to Encompass Very Rapid Responses

- MRD assessment at 1, 3, 6 and 12 months
- Consider adding mass spec for M-component monitoring
- Define “sustained response” as endpoint

The Future of Myeloma Therapy



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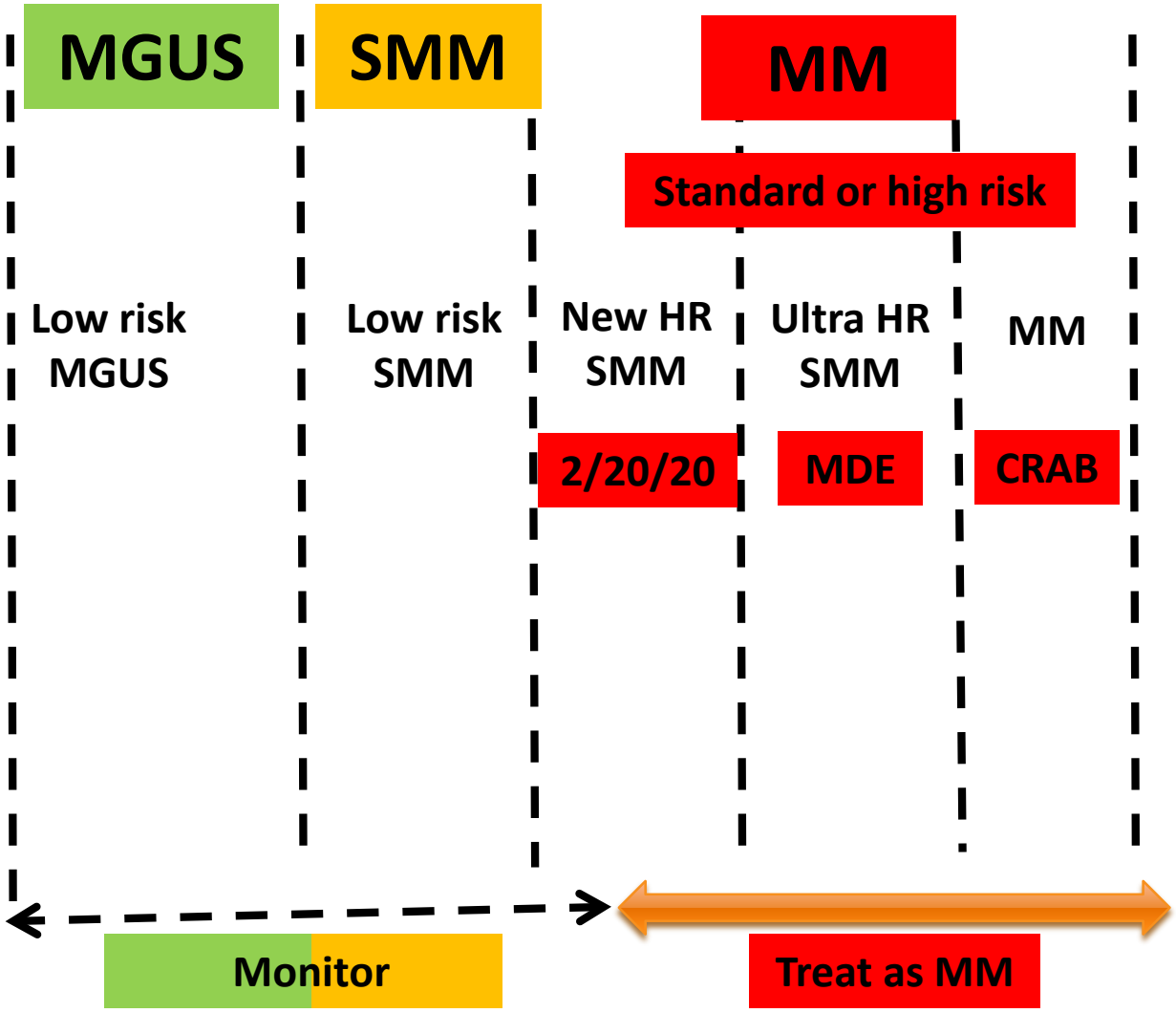
Future of Myeloma Therapy in 2019 and Beyond



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Go Online for More Educational Programs on Myeloma!

On-demand Webcast of this symposium, including expert faculty commentary (IMF link below)

Downloadable slides from this symposium (IMF link below)

Interactive Decision Support Tool for myeloma, with personalized expert recommendations for your patients with myeloma

Online programs on caring for your patients with myeloma

myeloma.org/videos/new-strategies-multiple-myeloma-care-next-steps-future

clinicaloptions.com/MyelomaTool

clinicaloptions.com/oncology/topics/Multiple-Myeloma

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