Jointly provided by the Annenberg Center for Health Sciences at Eisenhower, International Myeloma Foundation, and Clinical Care Options, LLC

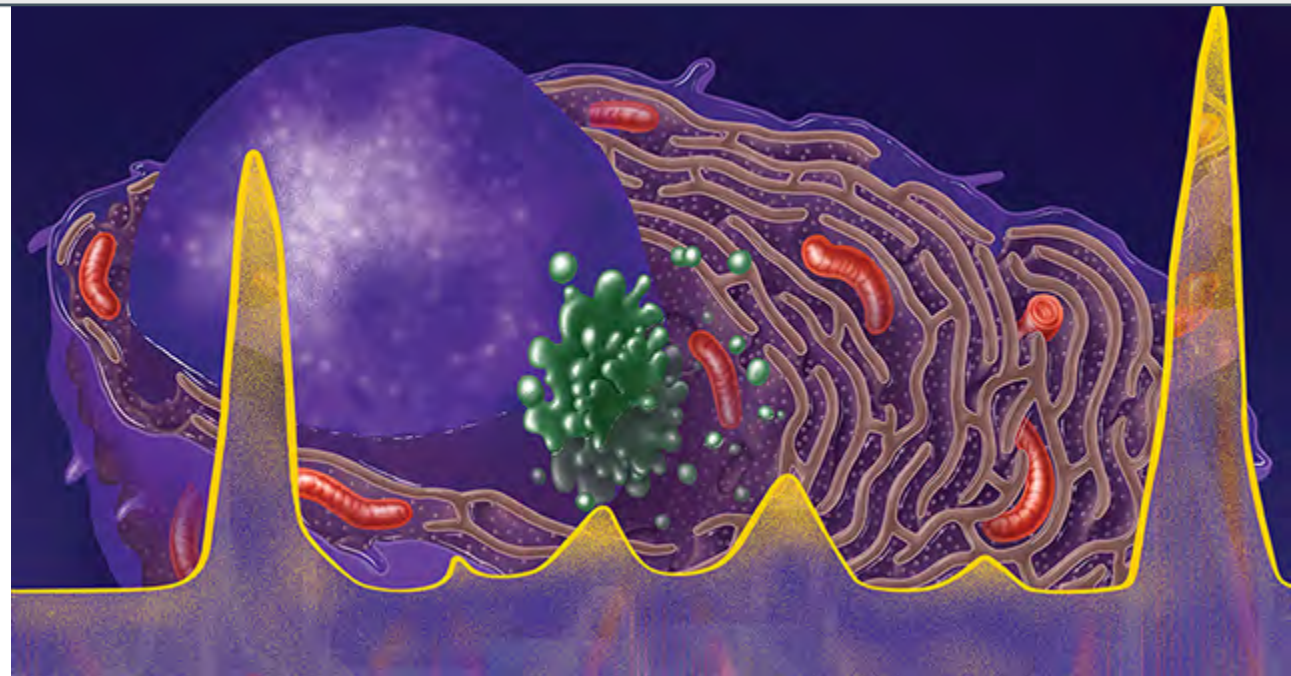
ANNENBERG CENTER FOR HEALTH SCIENCES AT EISENHOWER

INTERNATIONAL MYELOMA FOUNDATION

CCO LIVE

New Strategies for Multiple Myeloma Care: Next Steps for the Future

Friday, November 30, 2018
San Diego, California



Friday Satellite Symposium preceding the 60th ASH Annual Meeting & Exposition.

This activity is supported by educational grants from AbbVie; Amgen; Bristol-Myers Squibb; Celgene Corporation; Janssen Biotech, Inc., administered by Janssen Scientific Affairs, LLC; and Takeda Oncology.

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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.

Program Faculty

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

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

Program Faculty

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Mayo Clinic
Rochester, Minnesota

Shaji Kumar, MD, has disclosed that he has consulted with payment to Mayo Clinic from AbbVie, Amgen, Celgene, Dr. Reddy's Laboratory, Genentech, Janssen, Kite, MedImmune, Merck, Oncopeptides, and Takeda and funds for research support from AbbVie, Amgen, Bristol-Myers Squibb, Celgene, Janssen, Kite, MedImmune, Merck, Novartis, Roche/Genentech, Sanofi, and Takeda.

Program Faculty

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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.

Program 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, MSD, Novartis, Roche, Sanofi, and Takeda.

Symposium Format

Each topic discussion will include the following:

- Case presentation with interactive polling question(s) for the audience
- Presentation by faculty
- Panel discussion with expert recommendations
- Audience question and answer session
- Second audience vote on case question(s)

Agenda

- Risk stratification of plasma cell disorders
- Are we ready for personalized therapy in newly diagnosed MM?
- Considering the recent data on transplantation, consolidation, and maintenance after induction therapy
- Advances in the optimal choice of therapeutic strategies for patients with relapsed/refractory disease
- Proposed 2019 treatment algorithms for MM

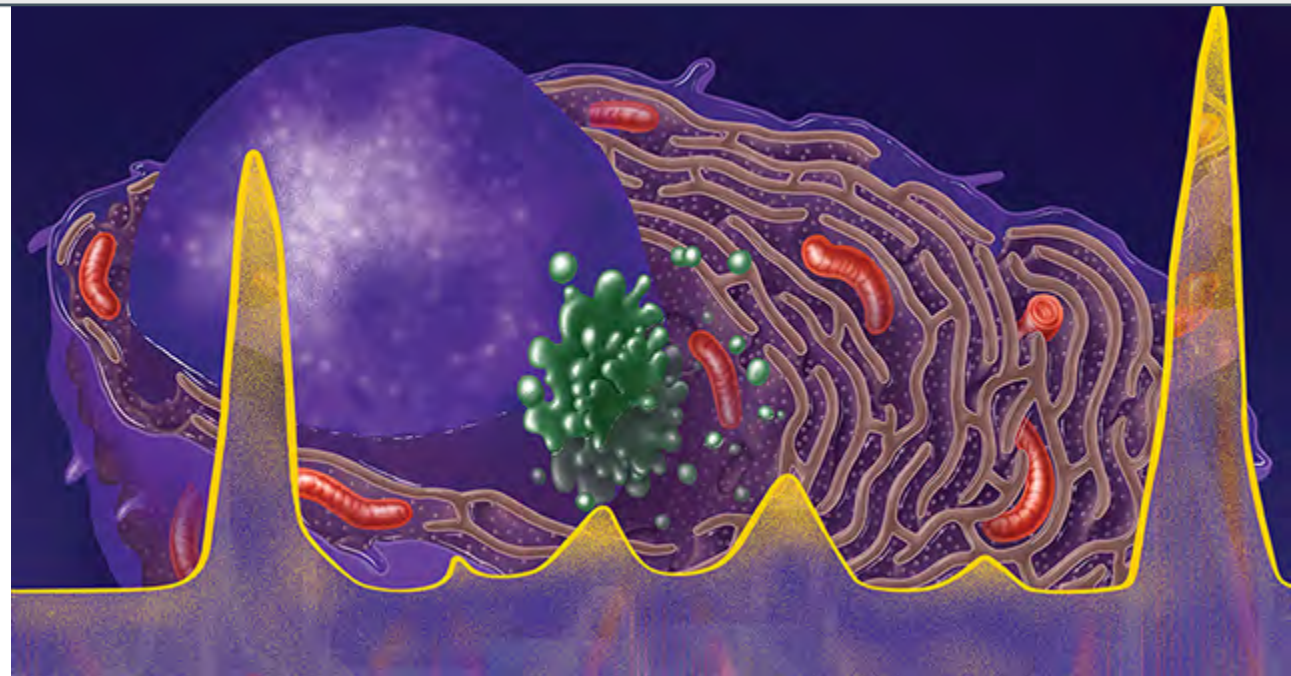
INTERNATIONAL MYELOMA FOUNDATION

IMF LIVE

Risk Stratification of Plasma Cell Disorders

Faculty Presenter:

S. Vincent Rajkumar, MD



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Risk Stratification of Plasma Cell Disorders

S. Vincent Rajkumar
Professor of Medicine
Mayo Clinic

Scottsdale, Arizona

Rochester, Minnesota

Jacksonville, Florida

MAYO CLINIC

Disclosures

No conflicts to disclose

Patient Case Example

- A 54-year-old patient was found to have elevated monoclonal protein during work up for unexplained arthritis of 2 weeks' duration
  - Arthritis has since resolved
  - M spike is 1.9 g/dL, IgG kappa
- Additional workup shows:
  - Serum free kappa is 5.0 mg/dL, serum free lambda is 1.0 mg/dL
  - CBC, calcium, creatinine are normal
- He has no additional symptoms

What would you recommend next for this patient?

Faculty	Recommendation
Brian G.M. Durie, MD	Bone marrow biopsy and bone imaging
Shaji Kumar, MD	Bone marrow biopsy and bone imaging
Philippe Moreau, MD	Bone marrow biopsy and bone imaging
S. Vincent Rajkumar, MD	Bone marrow biopsy and bone imaging
Jesús F. San-Miguel, MD, PhD	Bone marrow biopsy and bone imaging

Patient Case Example, Continued

- The patient undergoes bone marrow biopsy, which shows 8% plasma cells in bone marrow
- Bone imaging is negative
- He is watched annually for 3 years
- He now presents with an increase in M protein to 2.5 g/dL but has no symptoms
  - CBC, calcium, creatinine are normal
  - However, repeat bone marrow biopsy shows 25% plasma cells

Which of the following are NOT consistent with high-risk smoldering myeloma?

Faculty	Recommendation
Brian G.M. Durie, MD	3 focal lesions on MRI measuring 8-10 mm in size
Shaji Kumar, MD	3 focal lesions on MRI measuring 8-10 mm in size
Philippe Moreau, MD	3 focal lesions on MRI measuring 8-10 mm in size
S. Vincent Rajkumar, MD	3 focal lesions on MRI measuring 8-10 mm in size
Jesús F. San-Miguel, MD, PhD	3 focal lesions on MRI measuring 8-10 mm in size

In a newly diagnosed patient with myeloma, which of the following indicates standard-risk disease?

Faculty	Recommendation
Brian G.M. Durie, MD	Trisomy 3, 5, 9, and 15
Shaji Kumar, MD	Trisomy 3, 5, 9, and 15
Philippe Moreau, MD	Trisomy 3, 5, 9, and 15
S. Vincent Rajkumar, MD	Trisomy 3, 5, 9, and 15
Jesús F. San-Miguel, MD, PhD	Trisomy 3, 5, 9, and 15

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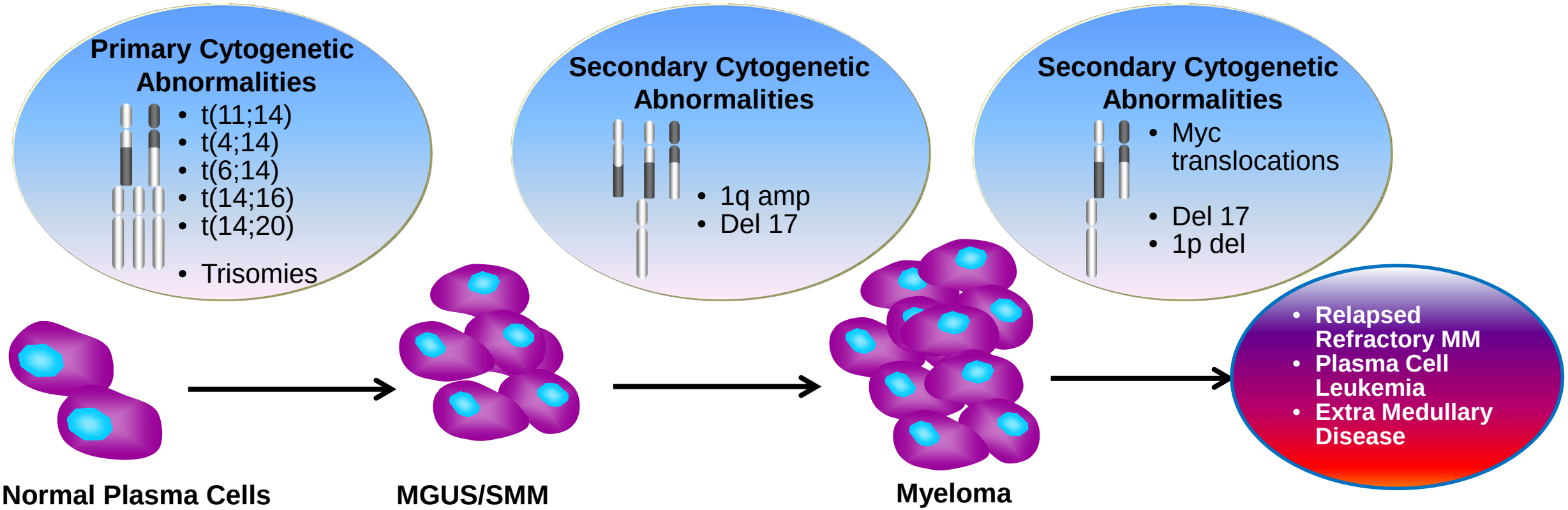
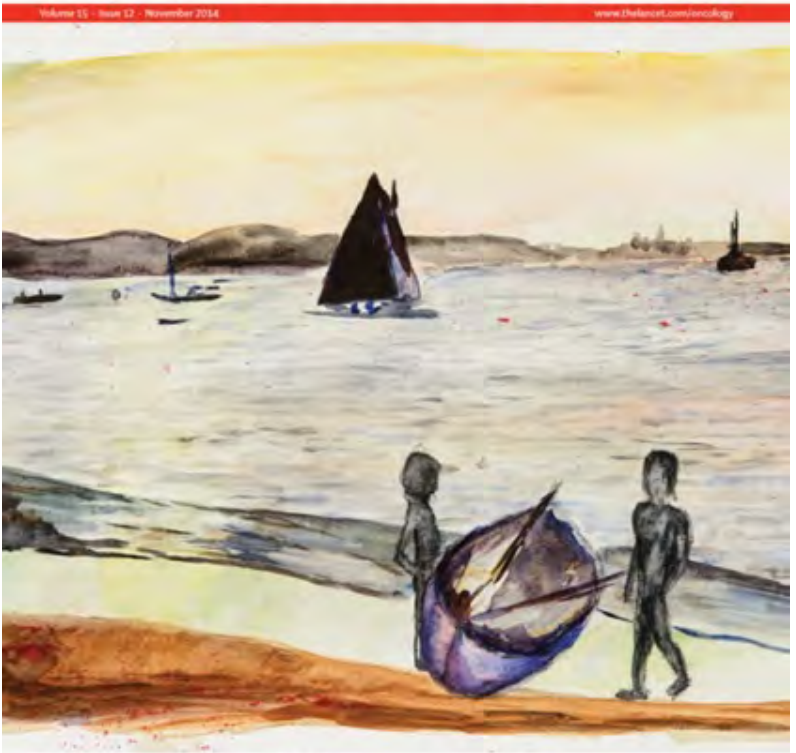
Progression of MGUS to Myeloma



Trisomies/IgH Translocations	Secondary Cytogenetic Abnormalities	Secondary Cytogenetic Abnormalities
Establishment of the clone	Del(17p), Gain(1q)	Occur with progression

Rajan. Blood Cancer J. 2015; 5: e365.

THE LANCET Oncology



Review

International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma

S Vincent Rajkumar, Meletios A Dimopoulos, Antonio Palumbo, Joan Blade, Giampaolo Merlini, María-Victoria Mateos, Shaji Kumar, Jens Hillengass, Efstathios Kastritis, Paul Richardson, Ola Landgren, Bruno Paiva, Angela Dispenzieri, Brendan Weiss, Xavier LeLeu, Sonja Zweegman, Sagar Lonial, Laura Rosinol, Elena Zamagni, Sundar Jagannath, Orhan Sezer, Sigurdur Y Kristinsson, Jo Caers, Saad Z Usmani, Juan José Lahuerta, Hans Erik Johnsen, Meral Beksac, Michele Cavo, Hartmut Goldschmidt, Evangelos Terpos, Robert A Kyle, Kenneth C Anderson, Brian G M Durie, Jesus F San Miguel

This International Myeloma Working Group consensus updates the disease definition of multiple myeloma to include validated biomarkers in addition to existing requirements of attributable CRAB features (hypercalcaemia, renal failure, anaemia, and bone lesions). These changes are based on the identification of biomarkers associated with near inevitable development of CRAB features in patients who would otherwise be regarded as having smouldering multiple myeloma. A delay in application of the label of multiple myeloma and postponement of therapy could be

Lancet Oncol 2014; 15: e538–48

See Online for a podcast interview with S Vincent Rajkumar

Division of Hematology, Mayo

Rajkumar. Lancet Oncol. 2014; 15: PE538.

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Revised IMWG Criteria for Myeloma

- **< 10% BMPC AND**
- **< 3 g/dL M protein**
- **No MDE**

- **10-60% BMPC OR**
- **≥ 3 g/dL M protein**
- **No MDE**

- Clonal plasma cell disorder AND
- 1 or more MDE
  - CRAB
  - ≥ 60% BMPC
  - ≥ 100 FLC ratio
  - > 1 MRI focal lesion

No MDE | ***MDE***

MDE= Myeloma Defining Events
*CRAB= Hyper**c**alcemia, **r**enal failure, **a**nemia, or lytic **b**one lesions attributable to a clonal plasma cell disorder*

Rajkumar. Lancet Oncol. 2014; 15: PE538.

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MGUS

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Classification of MGUS

Type of MGUS	Type of Progression	Risk of Progression
Non IgM MGUS (IgG, IgA)	Myeloma, Plasmacytoma	1% per year
IgM MGUS	Waldenstrom Macroglobulinemia	1.5% per year
LC-MGUS	Light Chain Myeloma	Not known

All can progress to AL amyloidosis

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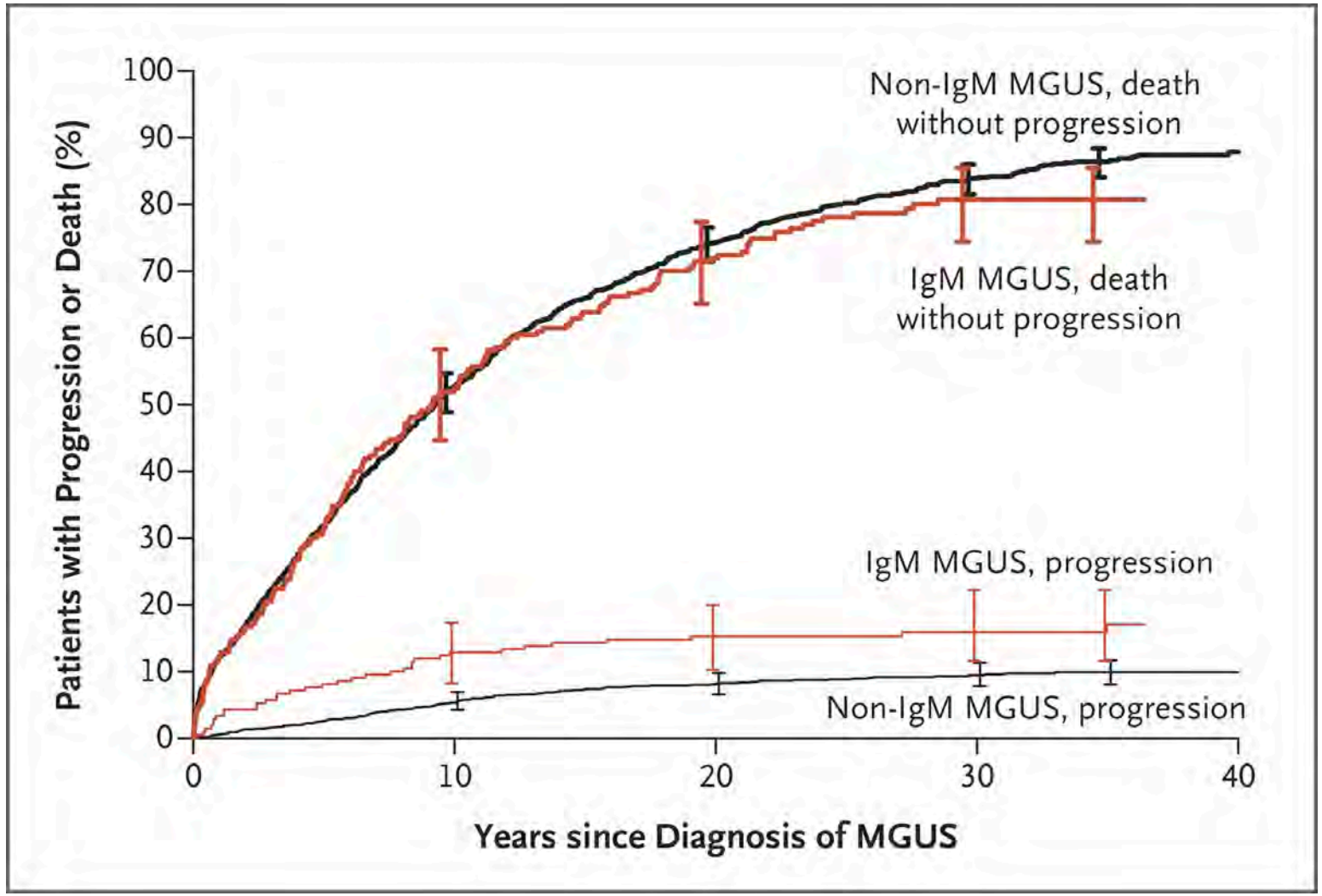
Risk of Progression of MGUS



Kyle. N Engl J Med. 2018;378:241.

The NEW ENGLAND JOURNAL of MEDICINE

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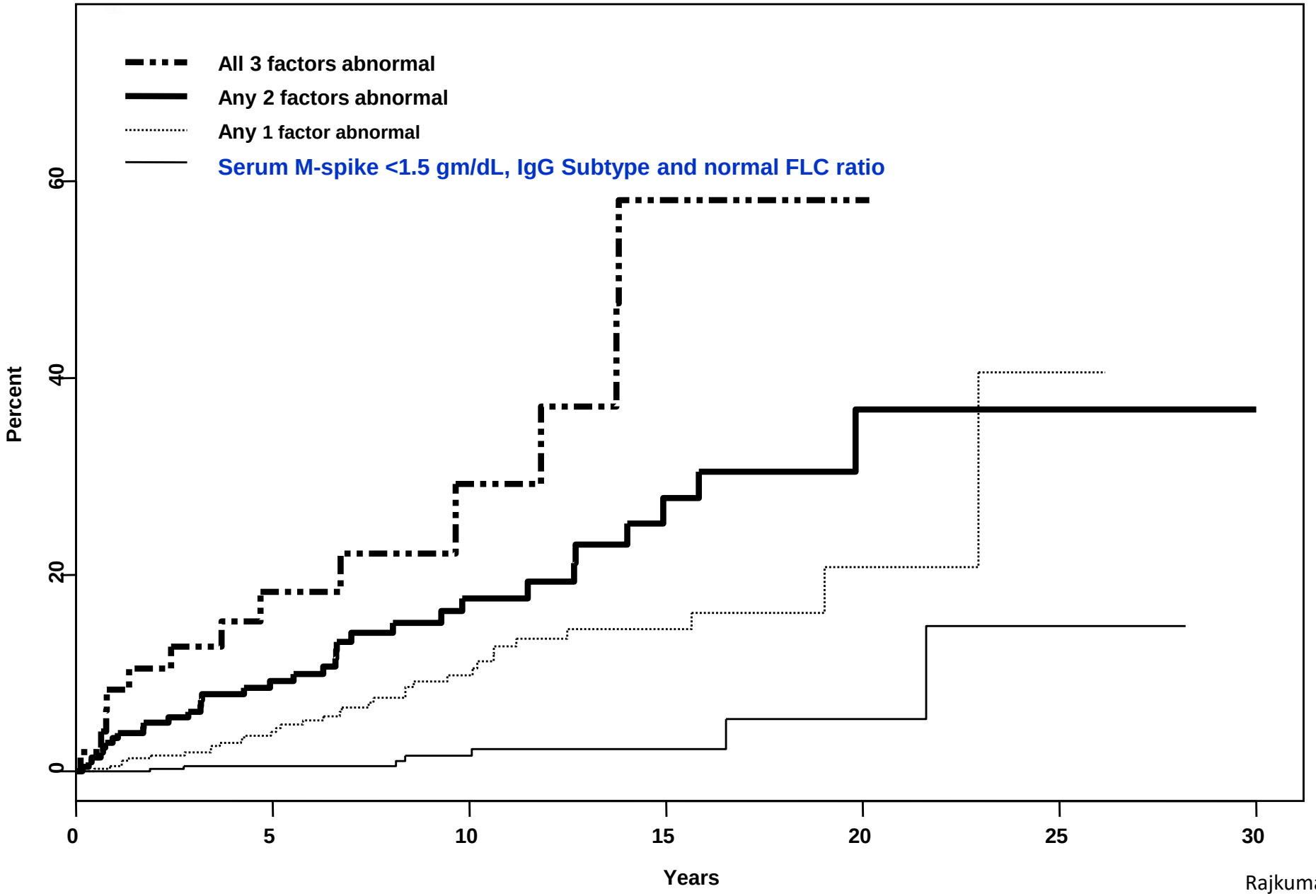
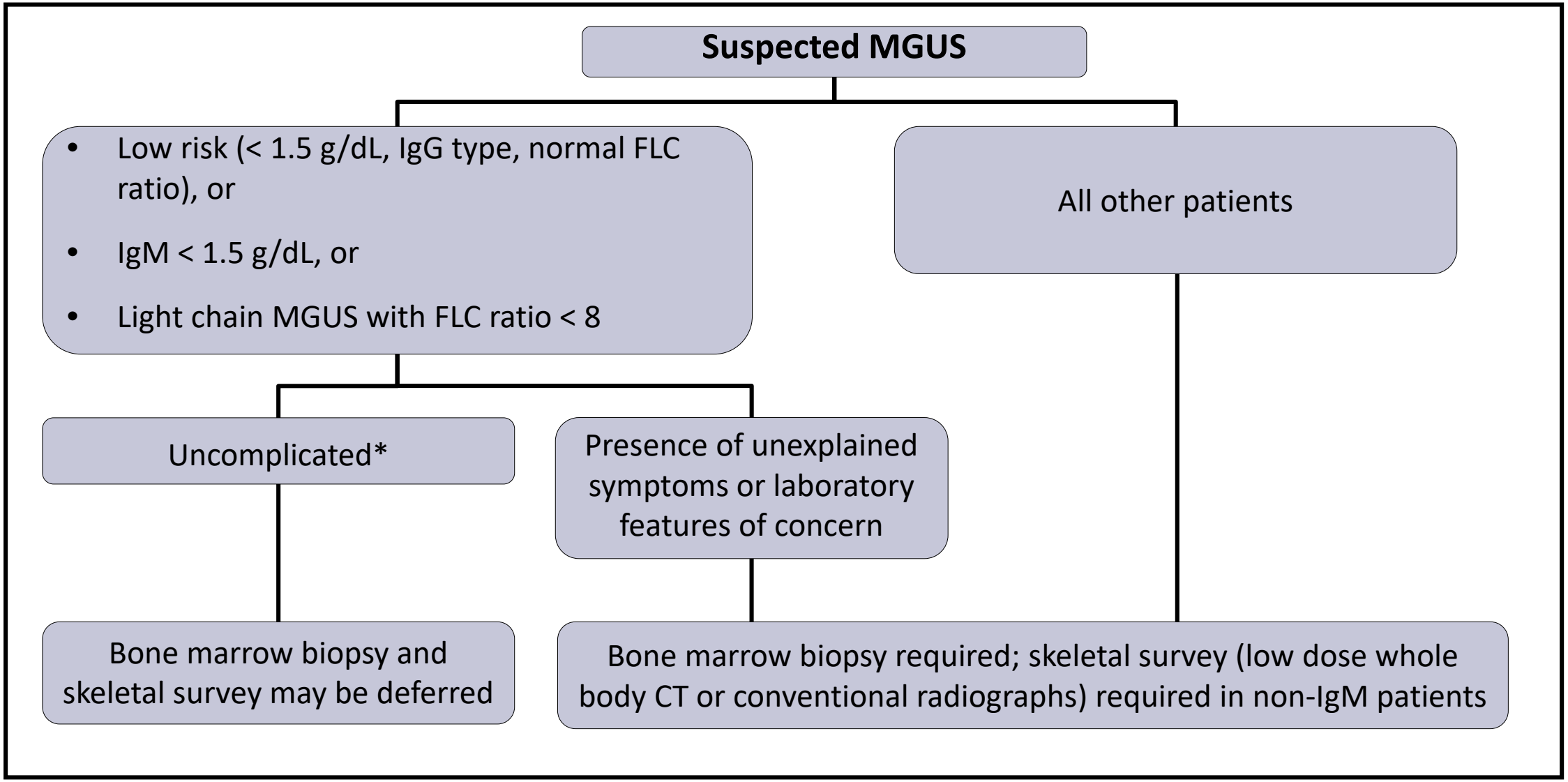
MGUS Risk Stratification: M spike size, M spike type, and FLC ratio



Rajkumar. Blood 2005;106:812.

Workup of Suspected MGUS



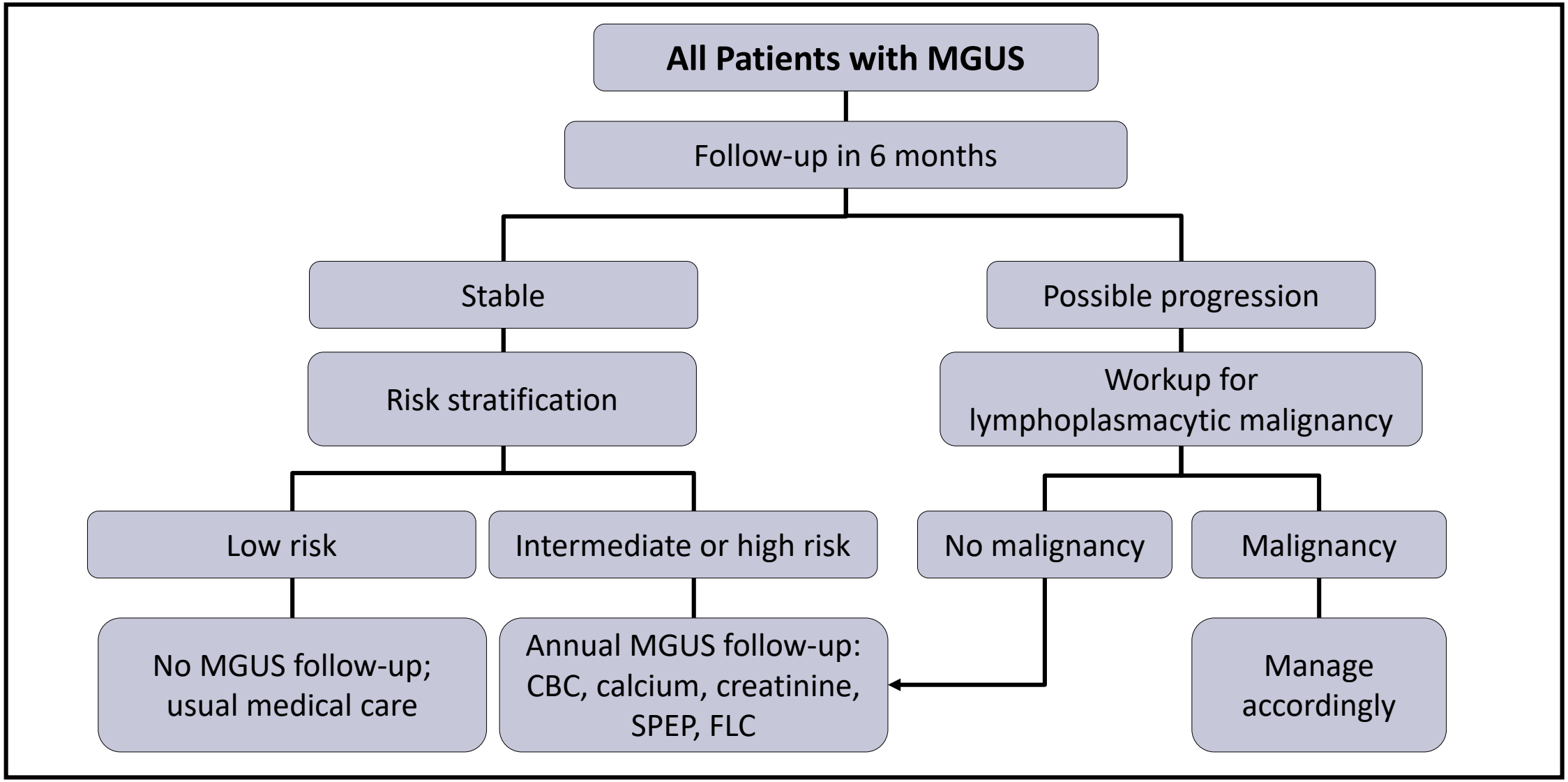
*No unexplained symptoms or laboratory features concerning for serious plasma cell disorder.

©2018 by American Society of Hematology

Ronald S. Go and S. Vincent Rajkumar. Blood 2018;131:163.

blood

Management of MGUS



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Ronald S. Go and S. Vincent Rajkumar. Blood 2018;131:163.

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MEDICAL INTELLIGENCE ARCHIVE

Smoldering Multiple Myeloma

Robert A. Kyle, M.D., and Philip R. Greipp, M.D.

N Engl J Med 1980; 302:1347-1349 | June 12, 1980 | DOI: 10.1056/NEJM198006123022405

Kyle. N Engl J Med. 1980; 302:1347.

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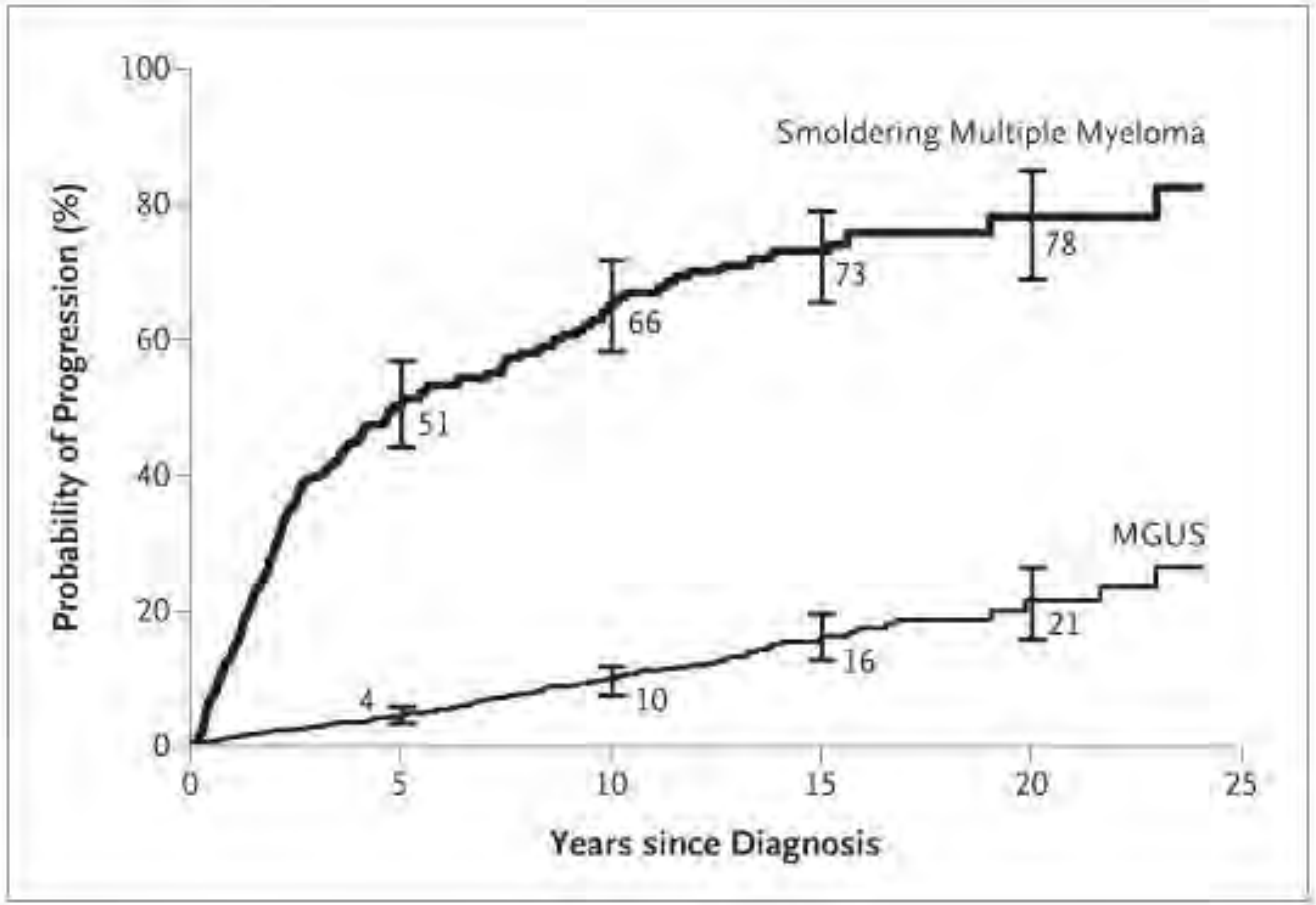
SMM vs MGUS



Kyle. N Engl J Med. 2007;356:2582.

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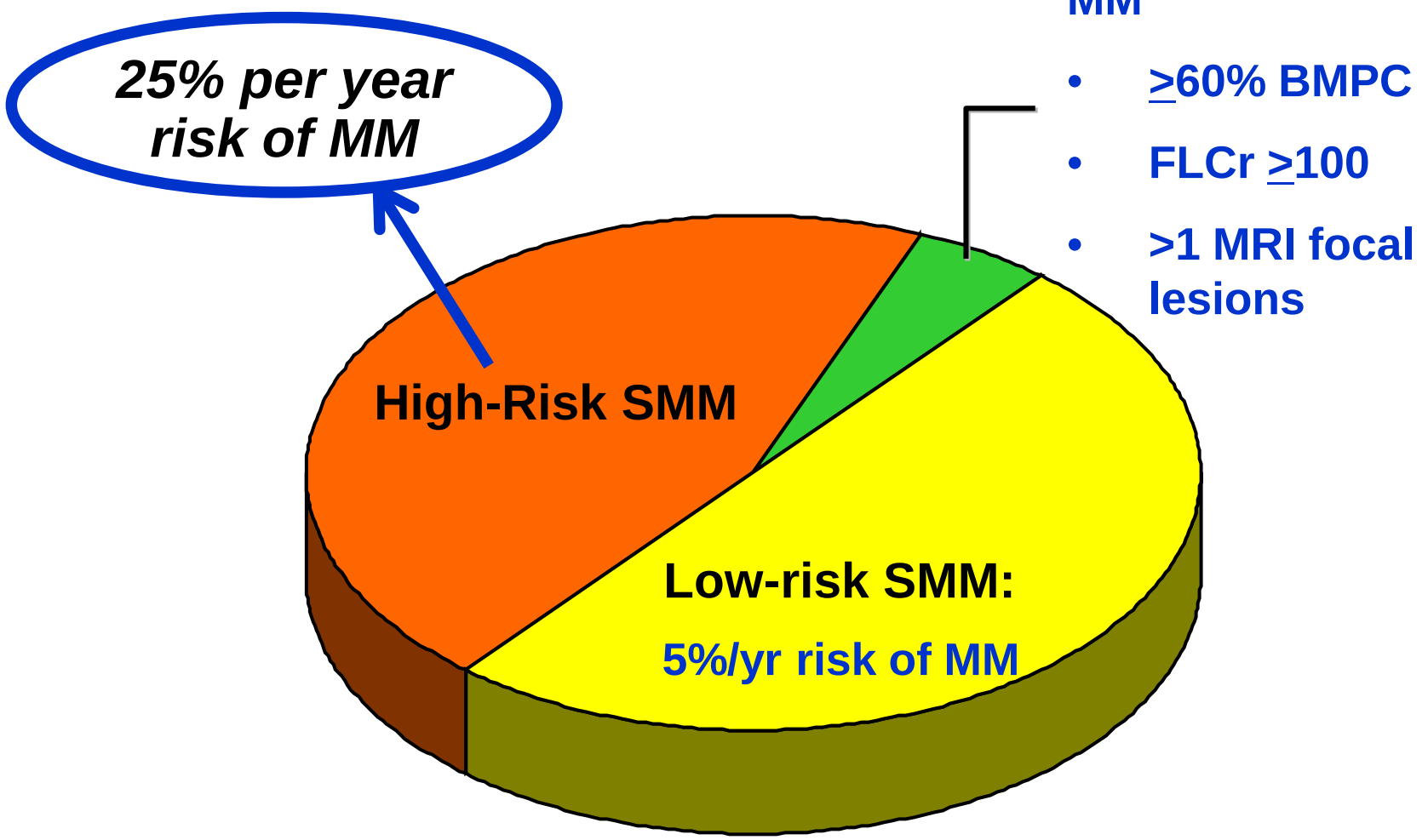
Smoldering Multiple Myeloma



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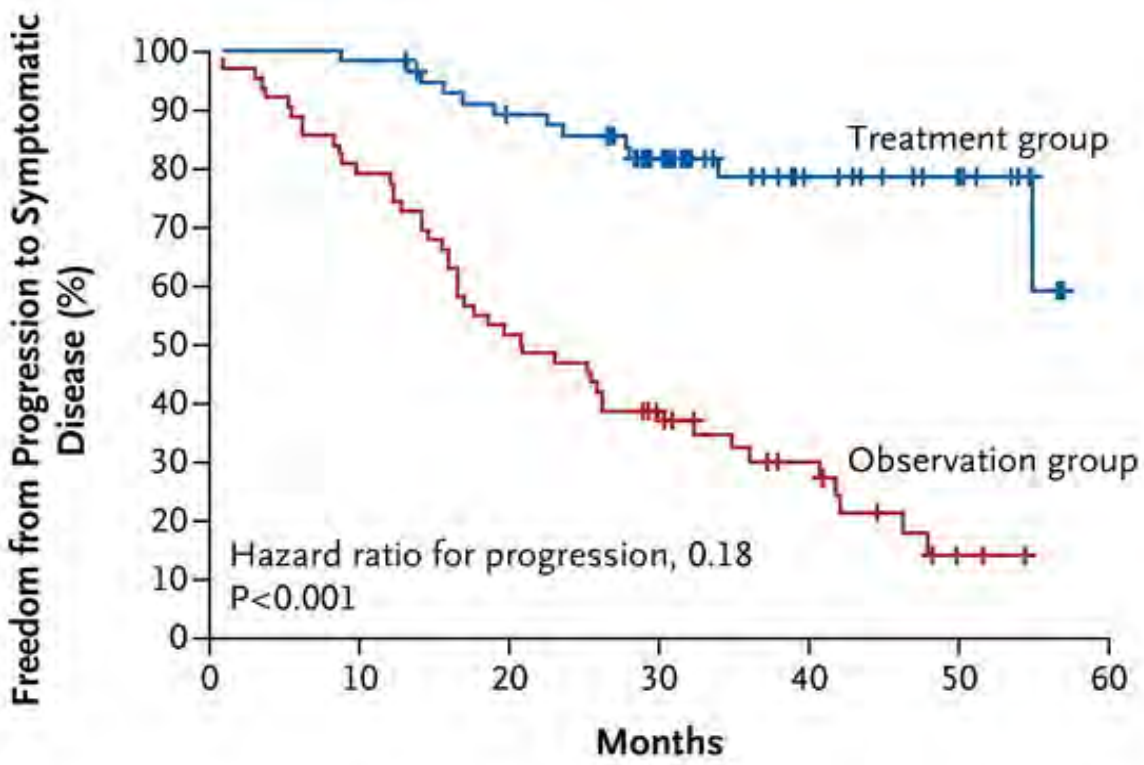
Len/Dex versus Observation in High Risk SMM: TTP



No. at Risk							
Treatment group	57	57	48	38	20	14	0
Observation group	62	49	32	21	11	3	0

Mateos. N Engl J Med 2013;369:438.

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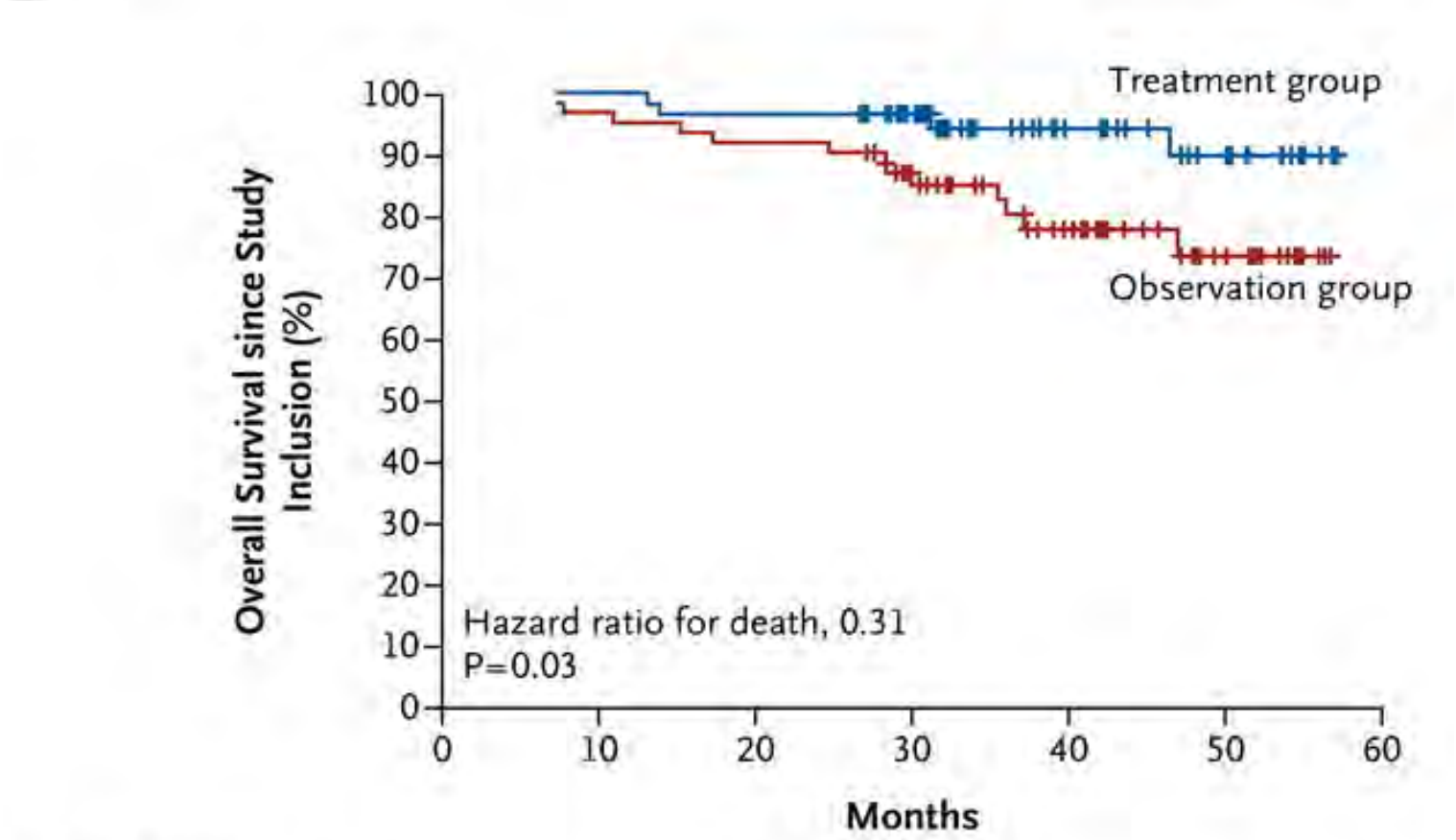
Len/Dex vs Observation in High-Risk SMM: OS



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

Mateos. N Engl J Med 2013;369:438.

The NEW ENGLAND JOURNAL of MEDICINE

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High-Risk SMM: Median TTP ~ 2 Years

≥ 10% PCs plus:

- **SMM with M protein ≥ 3 g/dL**
- **Absence (< 5%) of normal PCs by immunophenotyping plus Immunoparesis**
- **Abnormal FLC ratio 8-100**
- **Del(17p), t(4;14), gain(1q21)**
- **IgA SMM**
- **Evolving pattern**
- **Increased circulating plasma cells**

Rajkumar. Blood. 2015; 125: 3069.

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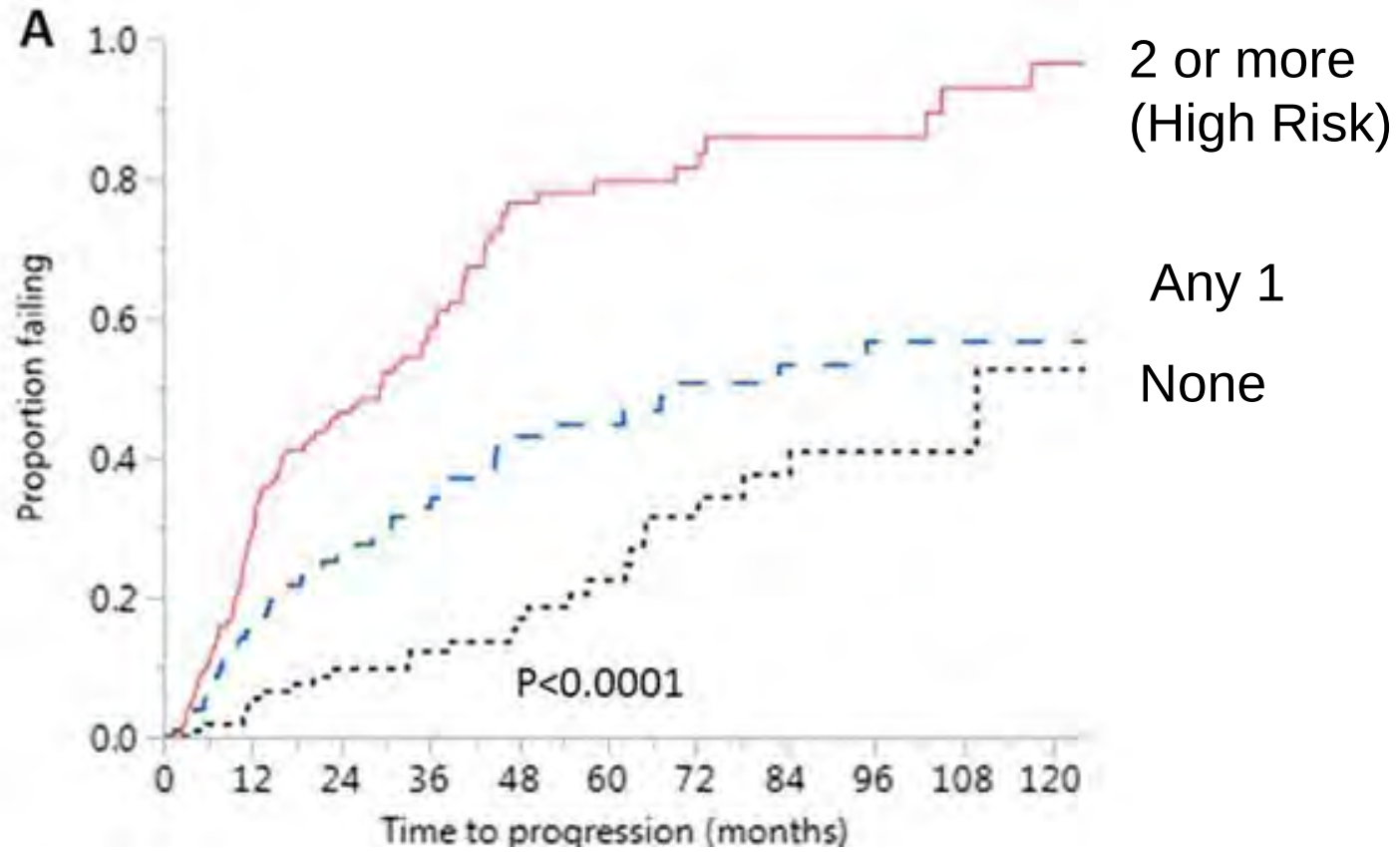
Mayo 20-2-20 Risk Stratification of SMM

BMPC > 20%, M protein > 2 g/dL, and FLC ratio (FLCr) > 20



Lakshman. Blood Cancer J. 2018; 8:59.

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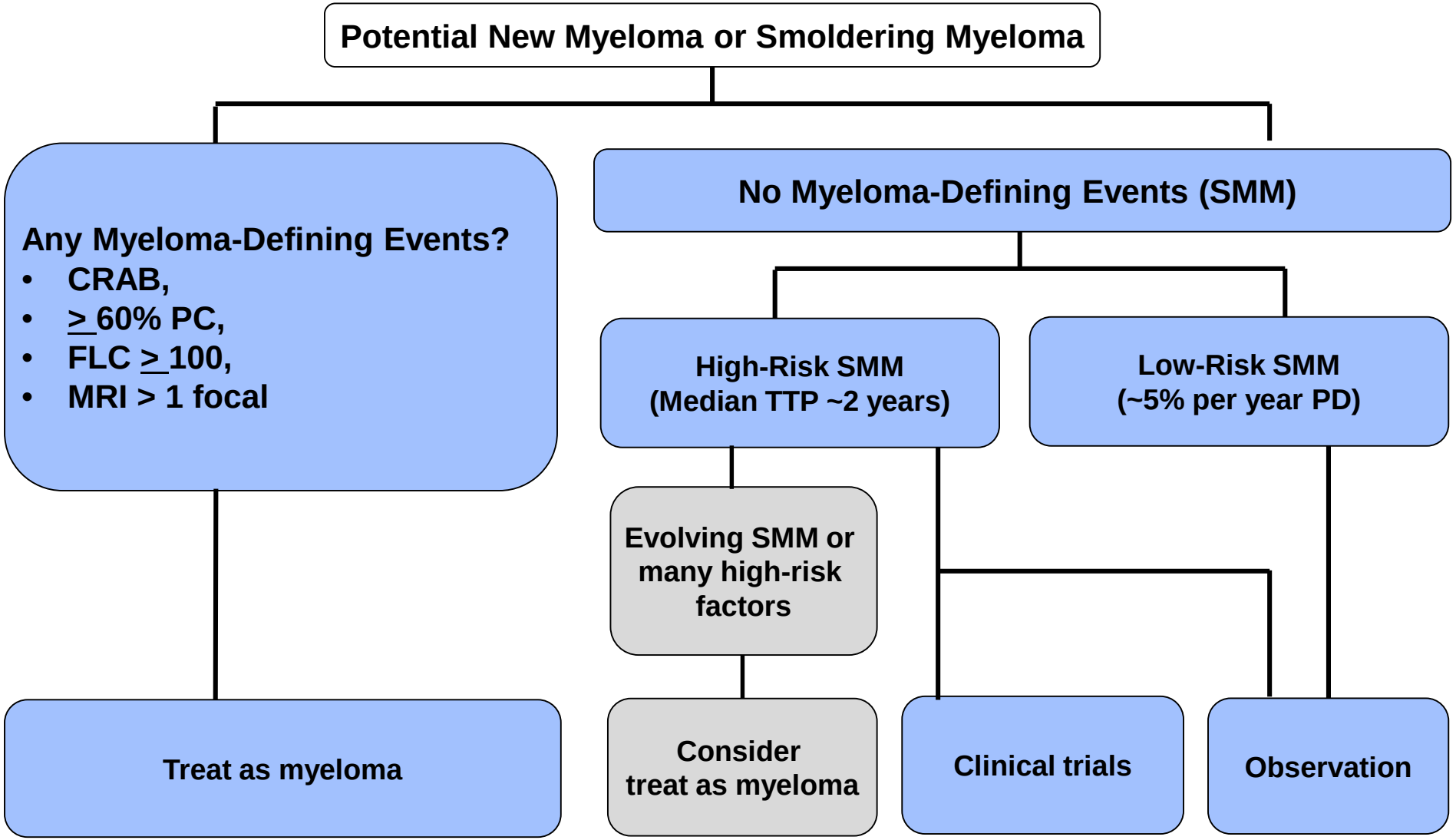
Management of SMM



Rajkumar. Blood. 2015; 125: 3069.

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SMM Trial Strategy

Conceptual/ Regulatory	Strategic: Delay Progression	Strategic: ? Cure
▪ Len v Obs ▪ Rd vs Obs ▪ Dara vs Obs	▪ DRd vs Rd ▪ KRd	▪ CESAR ▪ ASCENT
▪ Necessary trials	▪ Survival benefit with early therapy	▪ ? Cure possible with early therapy

Rajkumar SV © 2018

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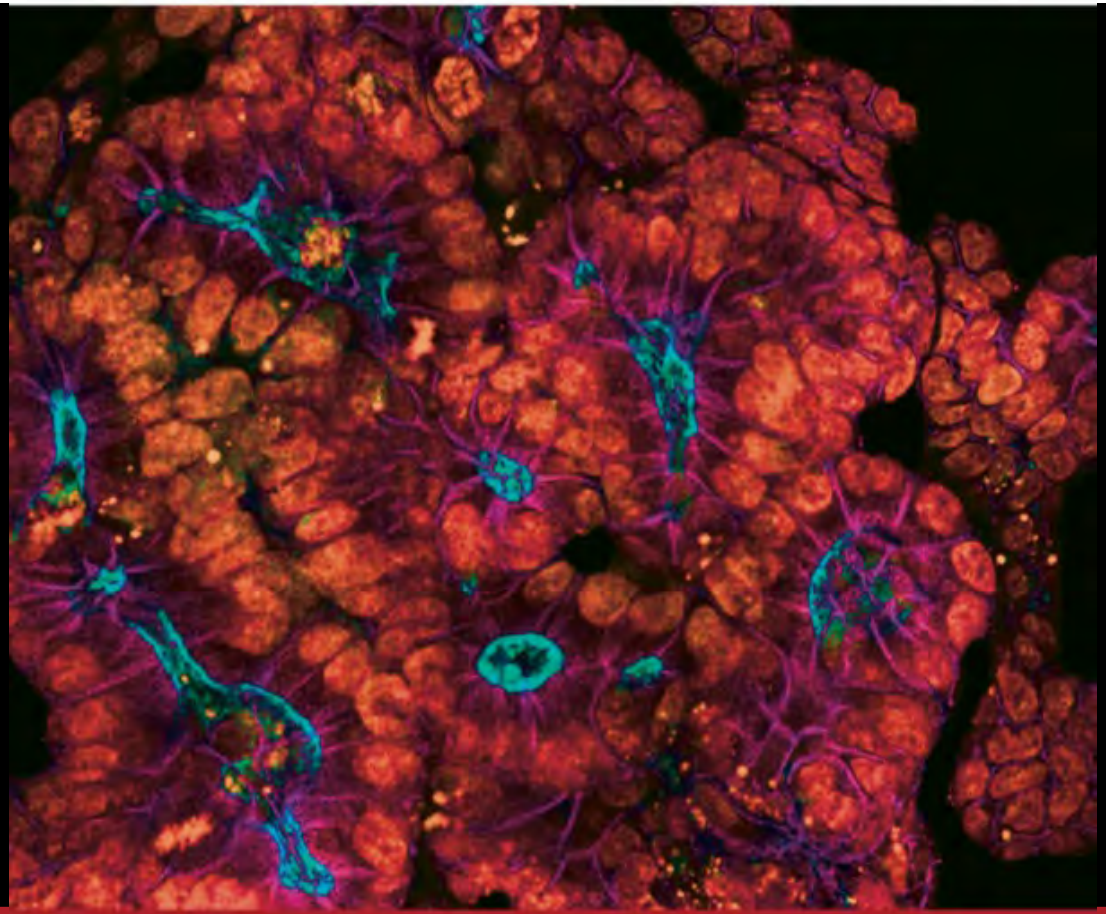
Multiple Myeloma

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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Molecular Classification of Myeloma

Trisomic MM	IgH Translocations	
▪ 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

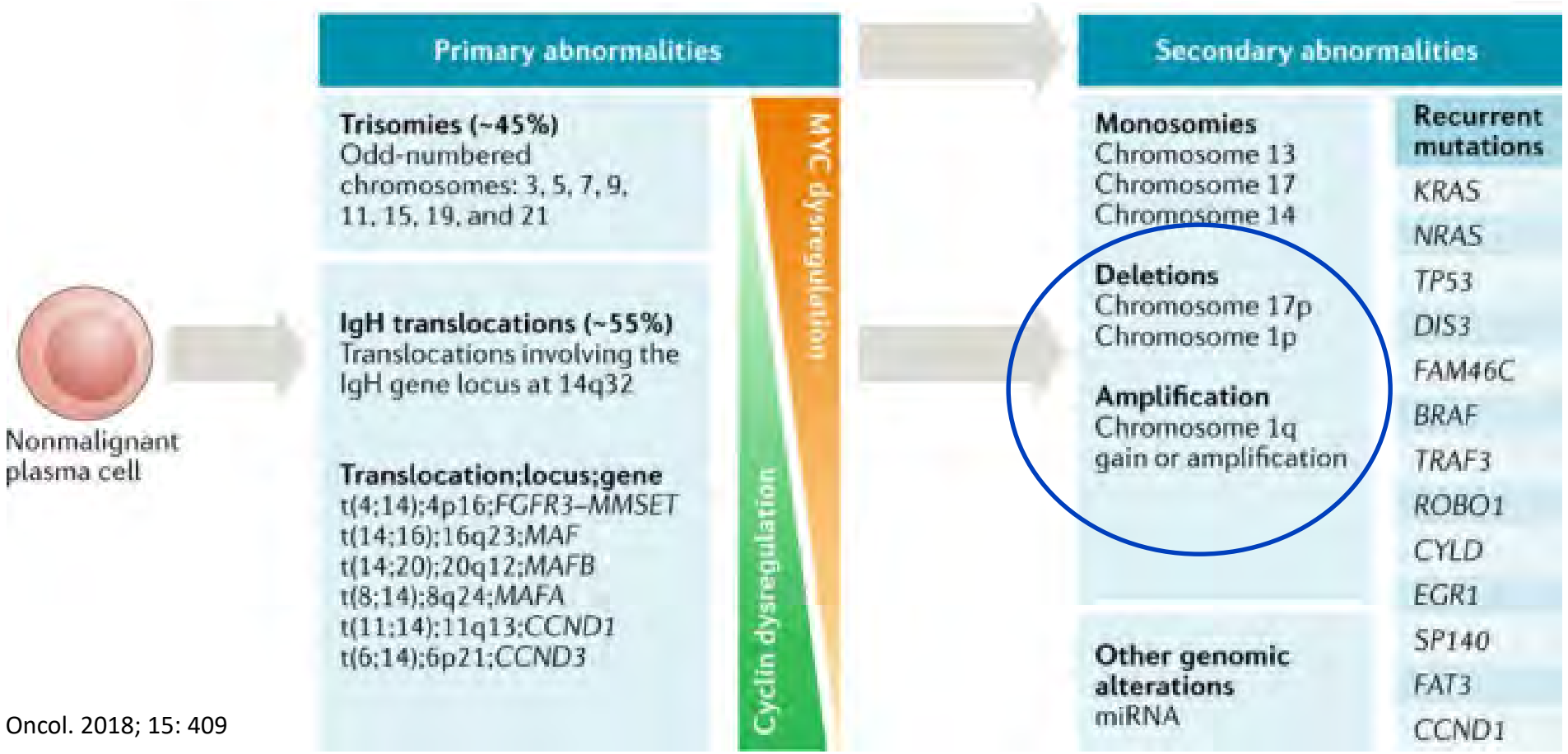
Kumar. Blood. 2012;119:2100.

Rajkumar SV © 2018

MENU nature REVIEWS CLINICAL ONCOLOGY

The multiple myelomas — current concepts in cytogenetic classification and therapy

Shaji K. Kumar & S. Vincent Rajkumar



Kumar. Nature Rev Clin Oncol. 2018; 15: 409

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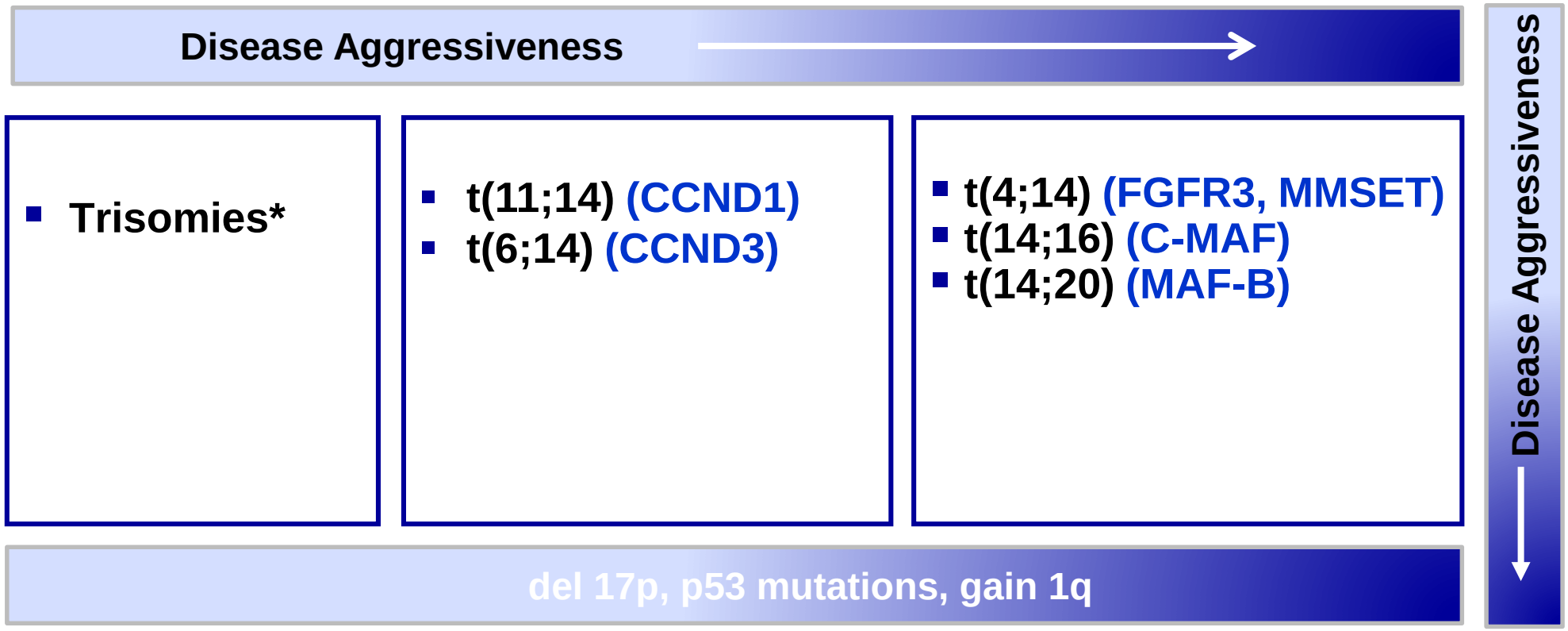
Cytogenetic Risk Stratification of Myeloma



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

Rajkumar SV © 2018

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Revised International Staging System

Stage	Frequency (% of patients)	5-year survival rate (%)
Stage I • Serum albumin >3.5 • Serum beta-2-microglobulin <3.5 • No high risk cytogenetics • Normal LDH	28%	82%
Stage II • Neither stage I or III	62%	62%
Stage III • Serum beta-2-microglobulin >5.5 and • High-risk cytogenetics [t(4;14), t(14;16), or del(17p)] *or* elevated LDH	10%	40%

Palumbo. J Clin Oncol. 2015;33:2863.

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Plasma Cell Leukemia

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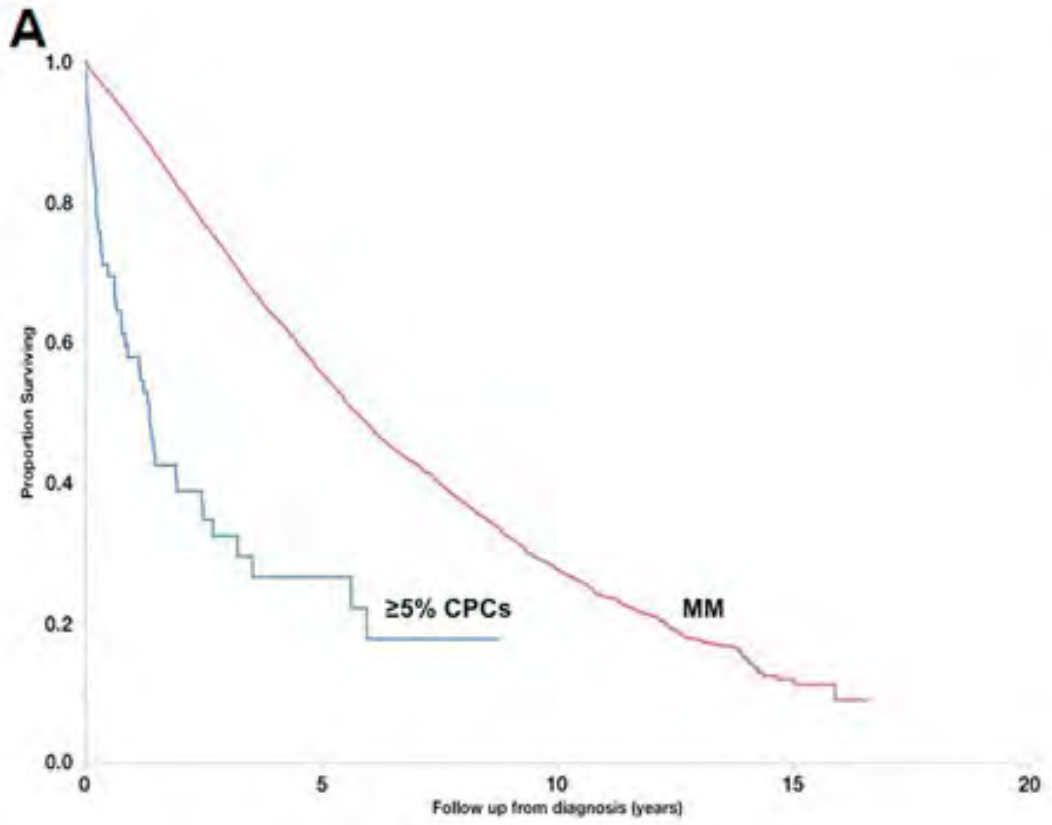
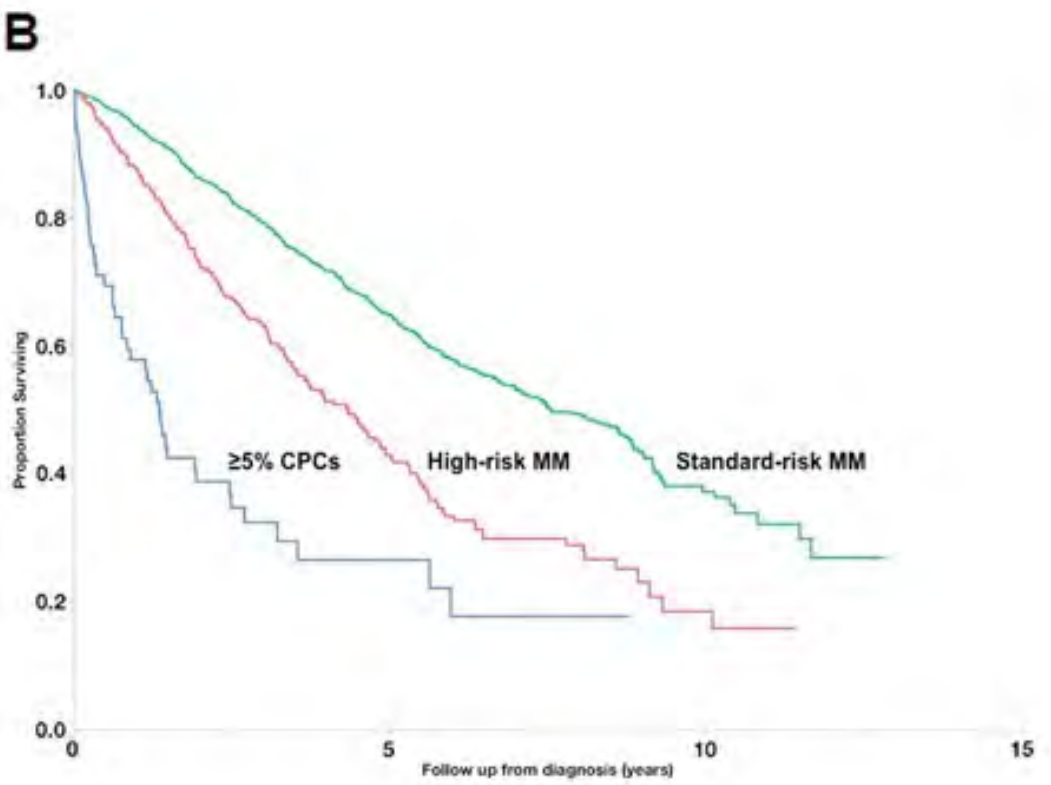
Plasma Cell Leukemia





PCL: ≥ 5% or more PCs on regular WBC differential

Ravi P, et al. Blood Cancer J. 2018; 8: 116.

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Summary

- New diagnostic criteria
- Molecular classification of MM
- Risk stratification systems for MGUS, SMM, MM are different
- New staging system for MM

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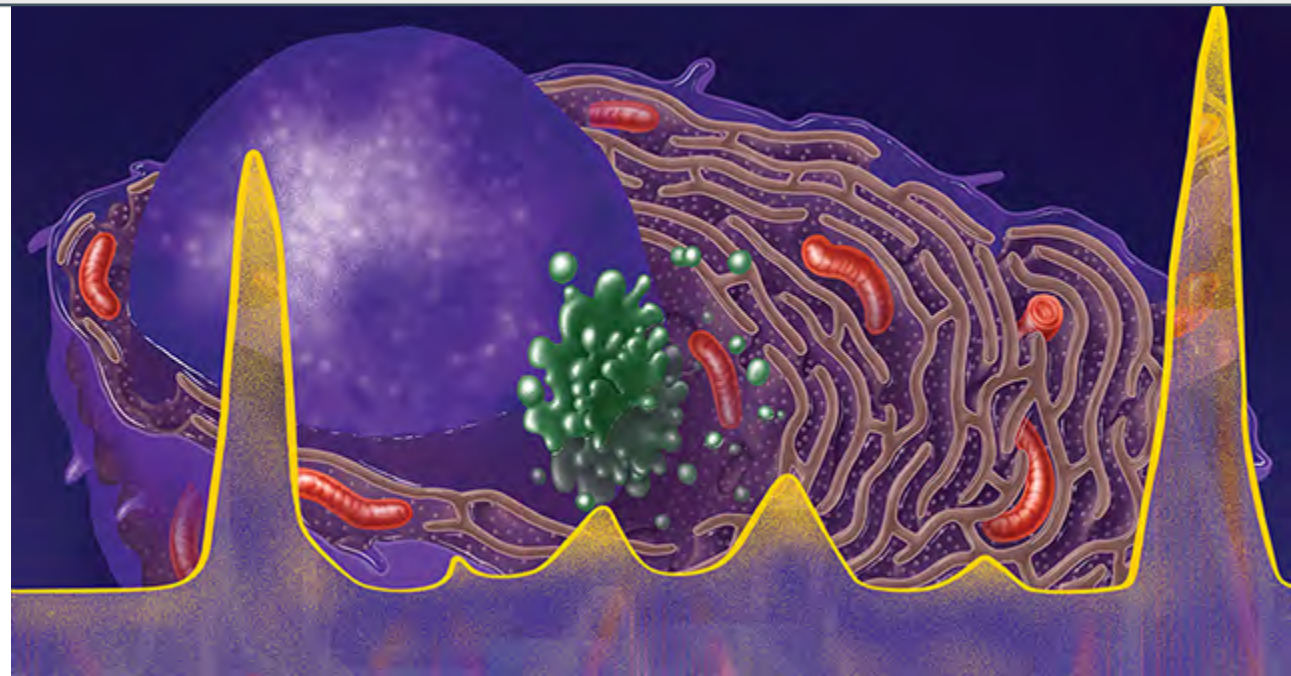
Panel Discussion and Audience Q&A



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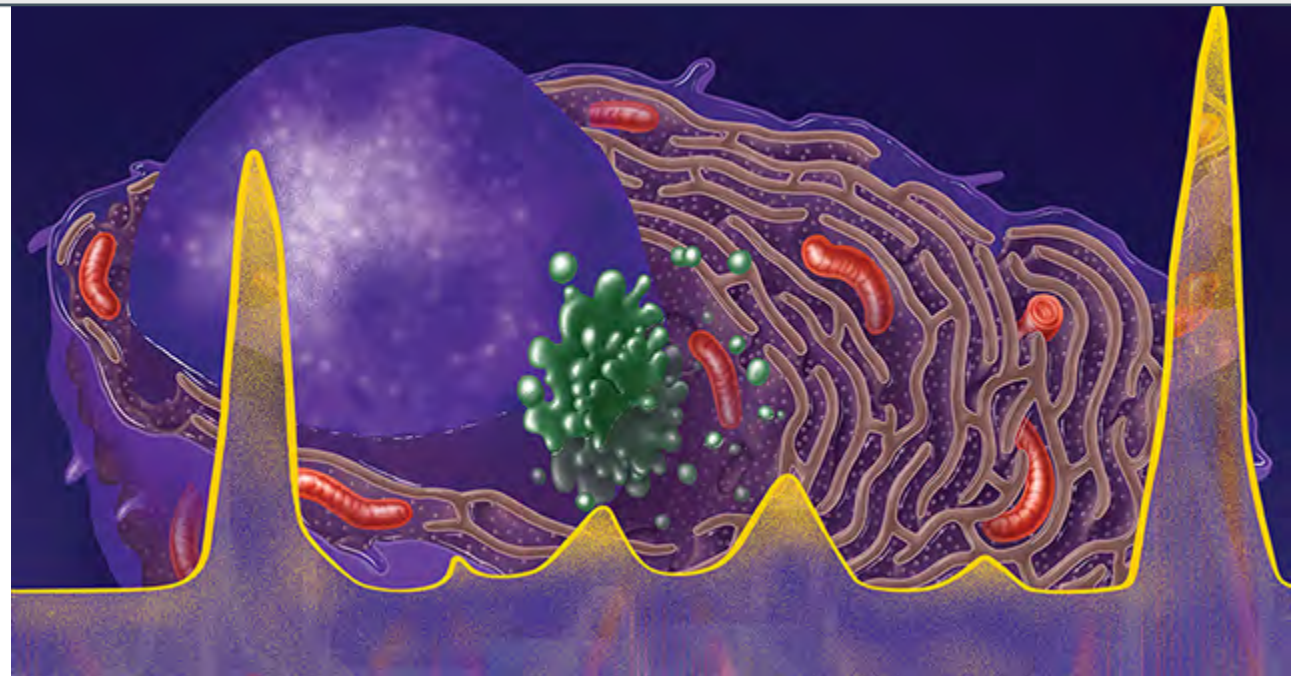
Are We Ready for Personalized Therapy in Newly Diagnosed MM?

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.

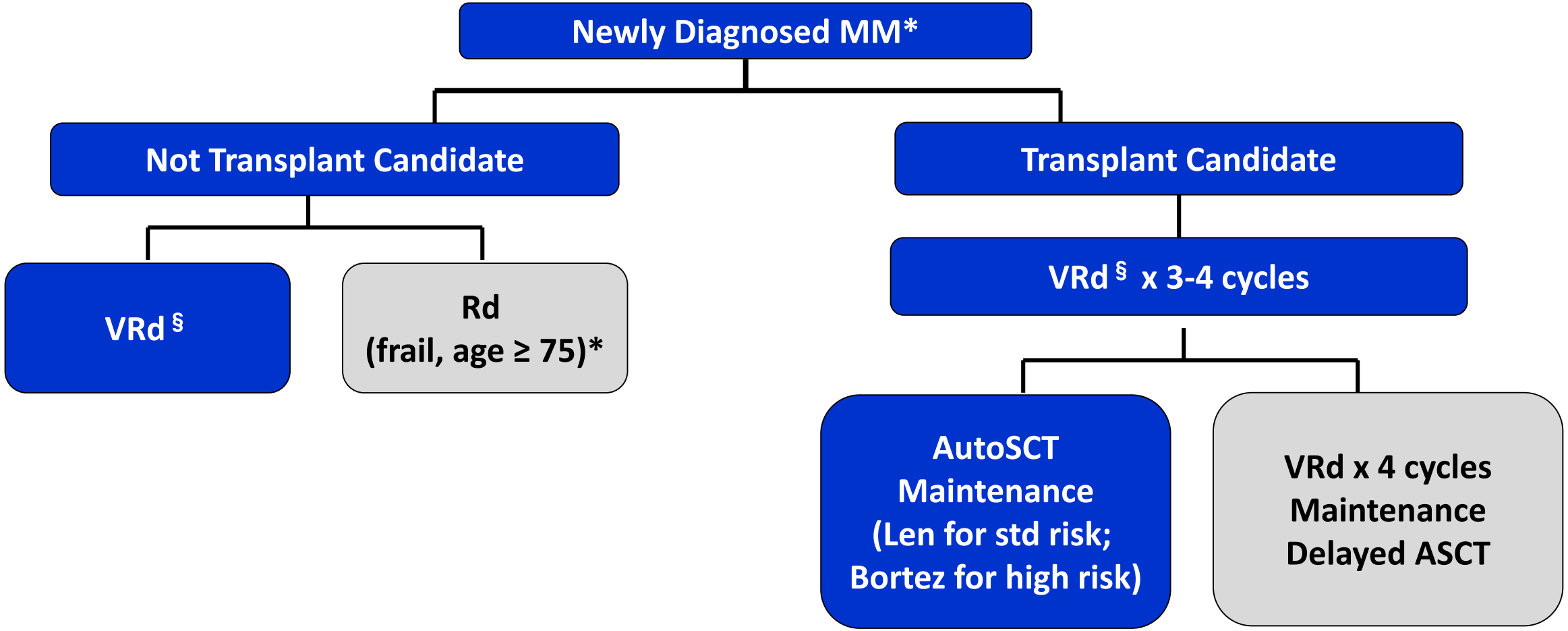
Patient Case Example

- 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

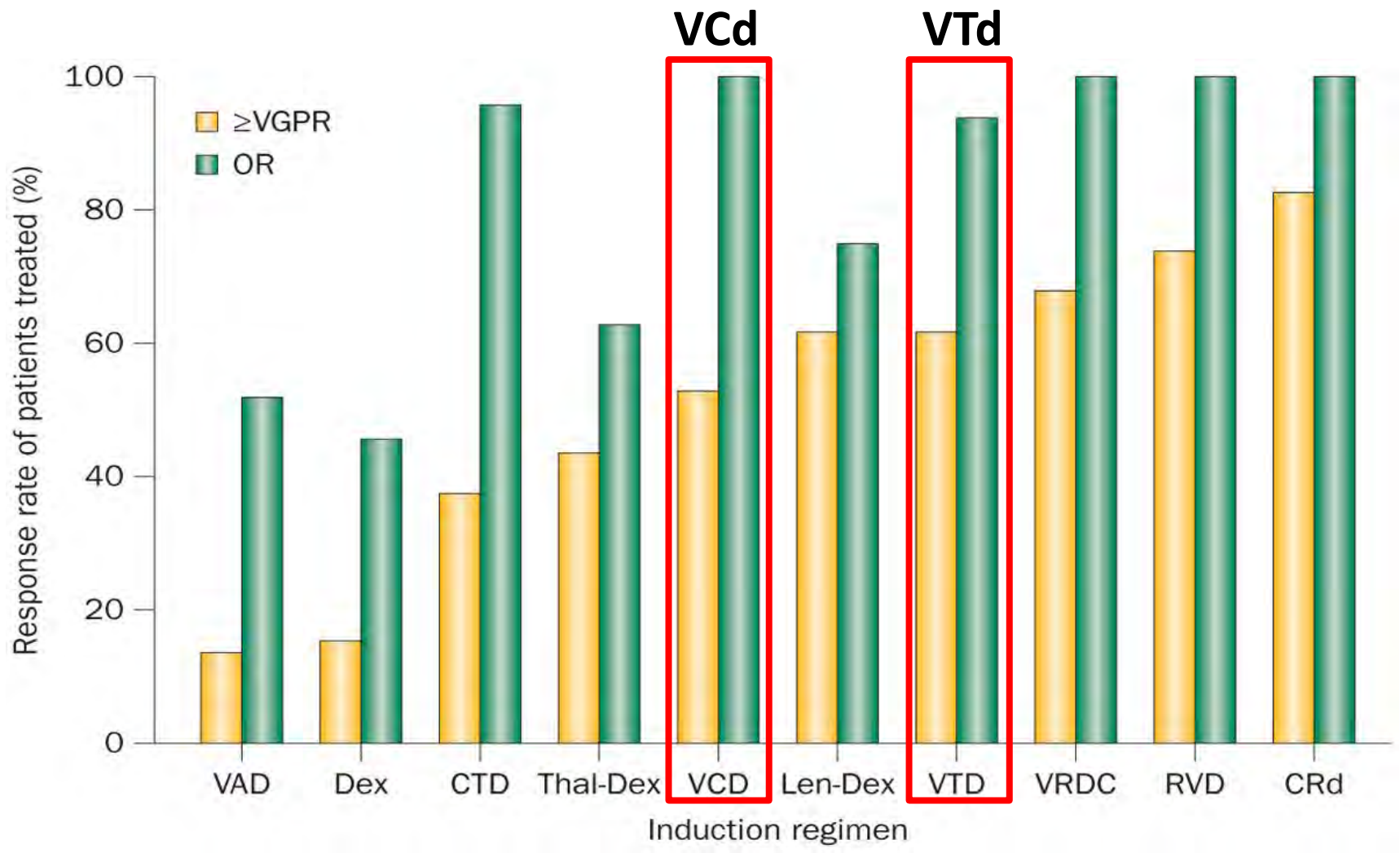


*Based on CALGB 100104, S0777, IFM-DFCI, CTN 0702 HOVON

§ VTd/VCd if VRd not available

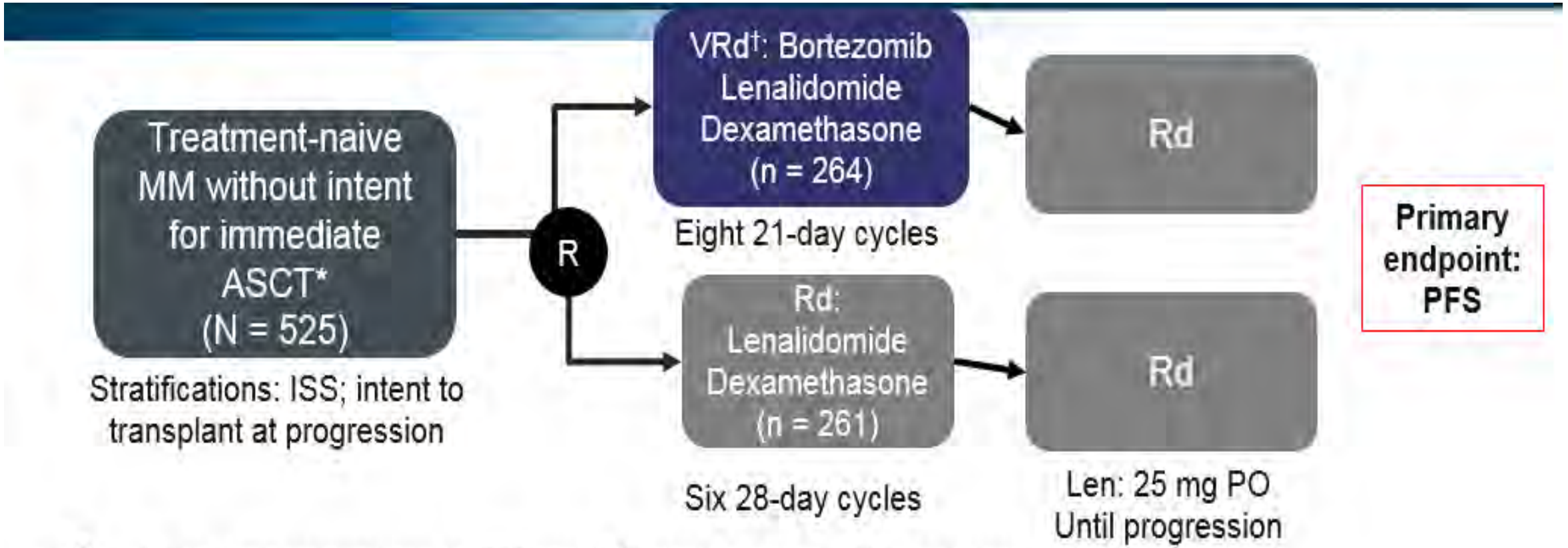
Rajkumar SV. 2016.

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)

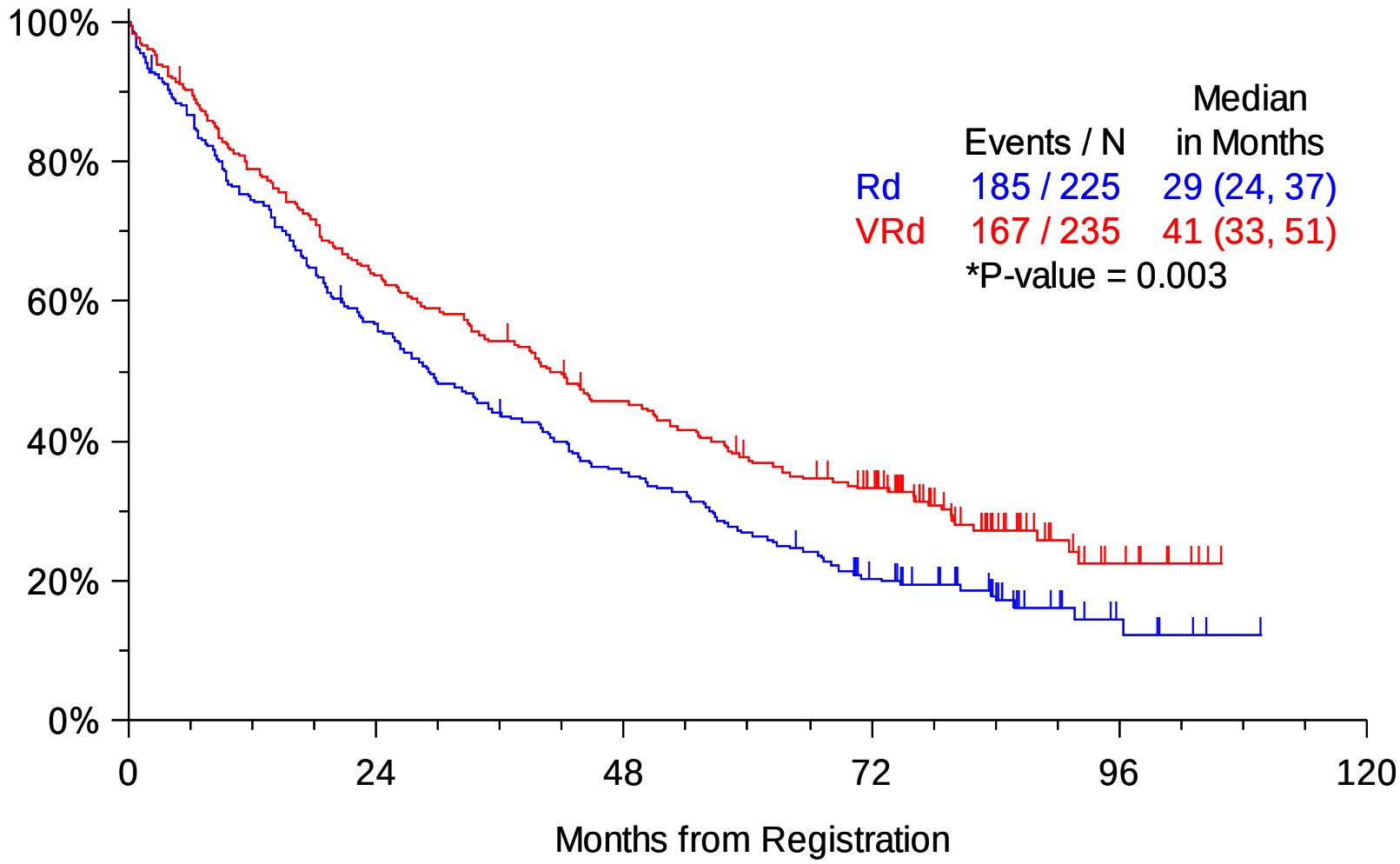
*Both SWOG and IRC stratified Cochran-Mantel-Haenszel analyses indicated improved responses with RVd (odds ratio: 0.528, *P* =.006 [ITT]; odds ratio: 0.38, *P* = .001 [sensitivity analysis])
**Both SWOG and IRC assessments

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

SWOG 0777: Progression-Free Survival

CURRENT ELIGIBILITY (N = 460) – CURRENT DATA

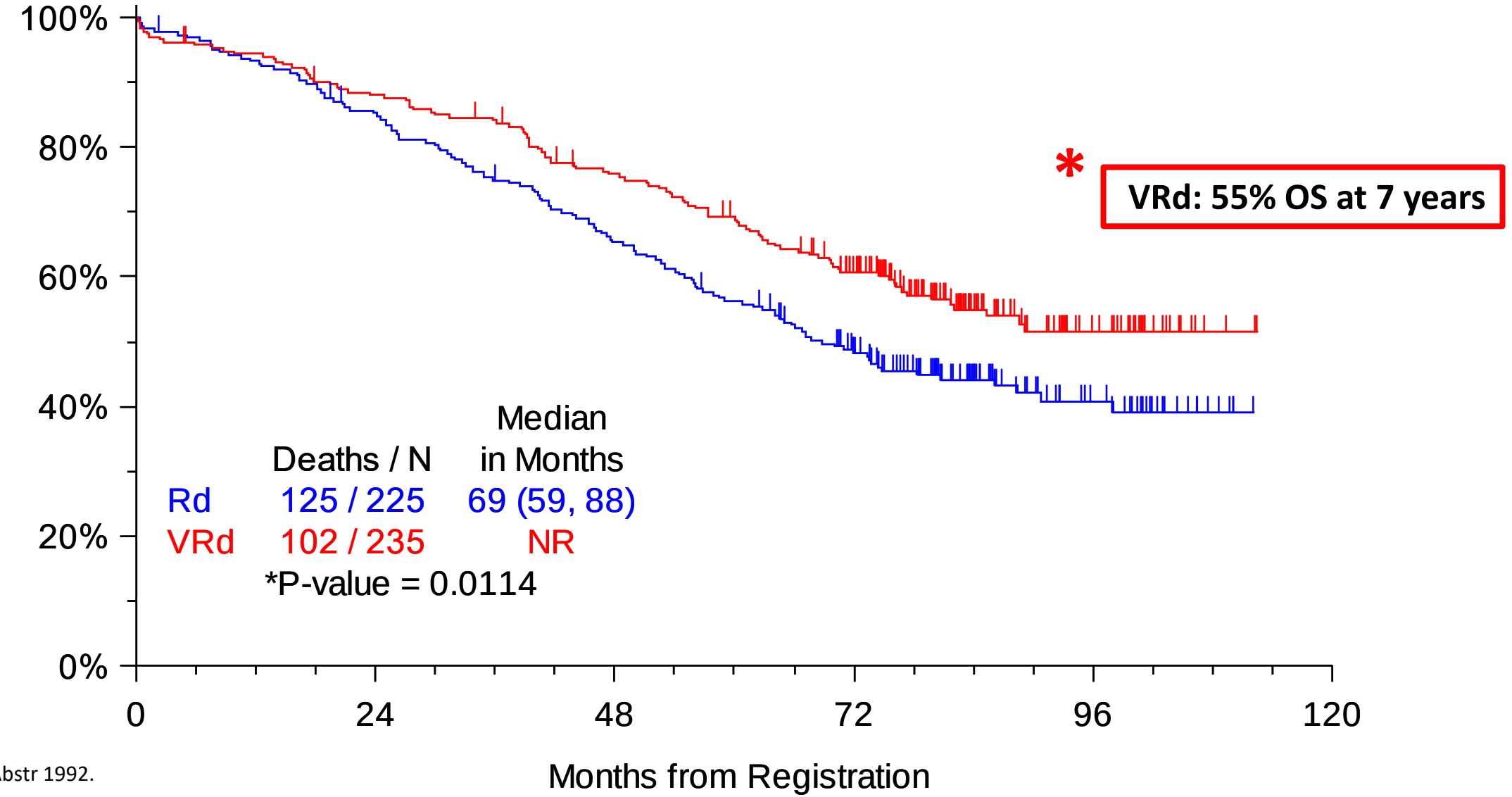
PFS



Durie. ASH 2018. Abstr 1992.

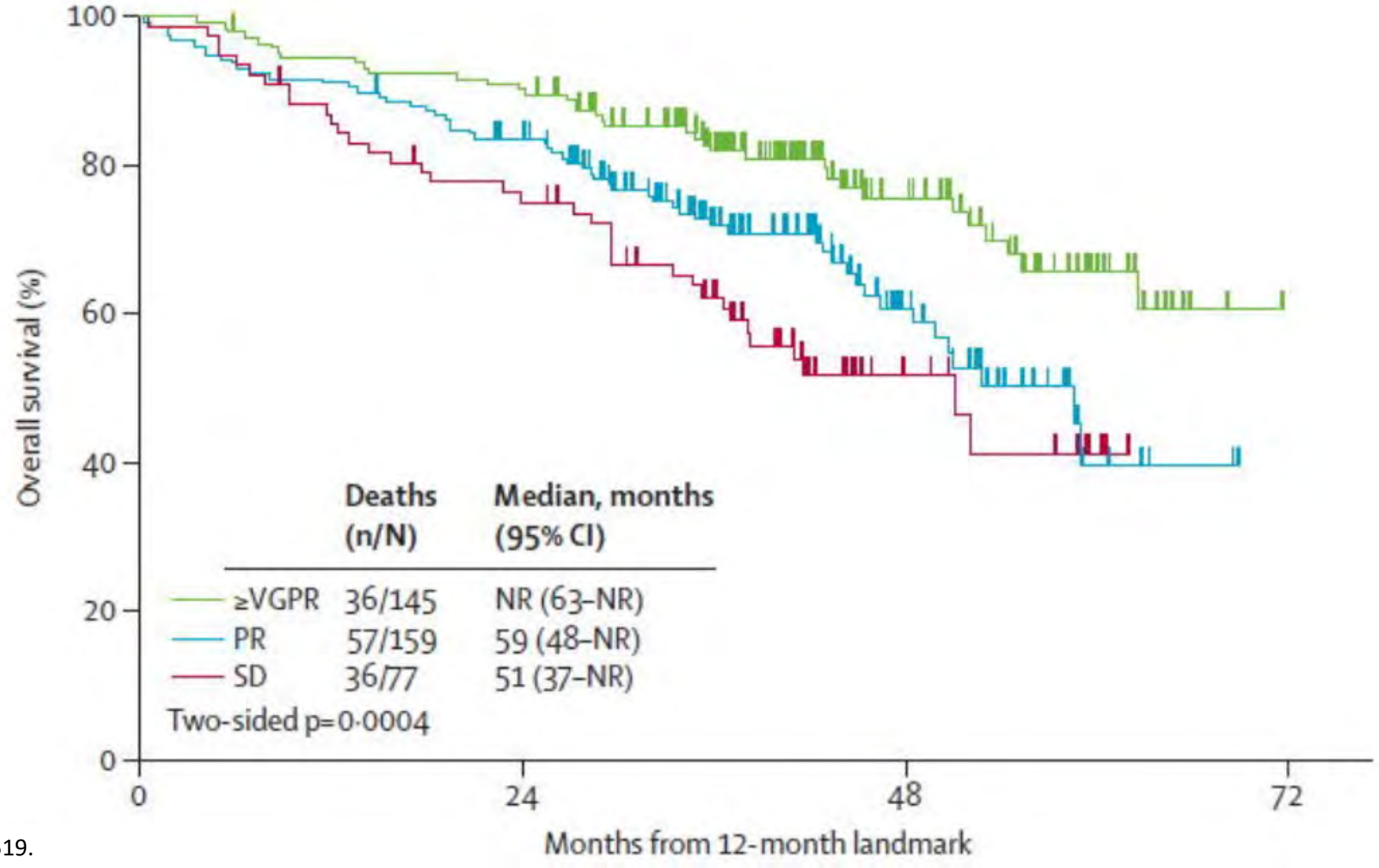
SWOG 0777: Overall Survival

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

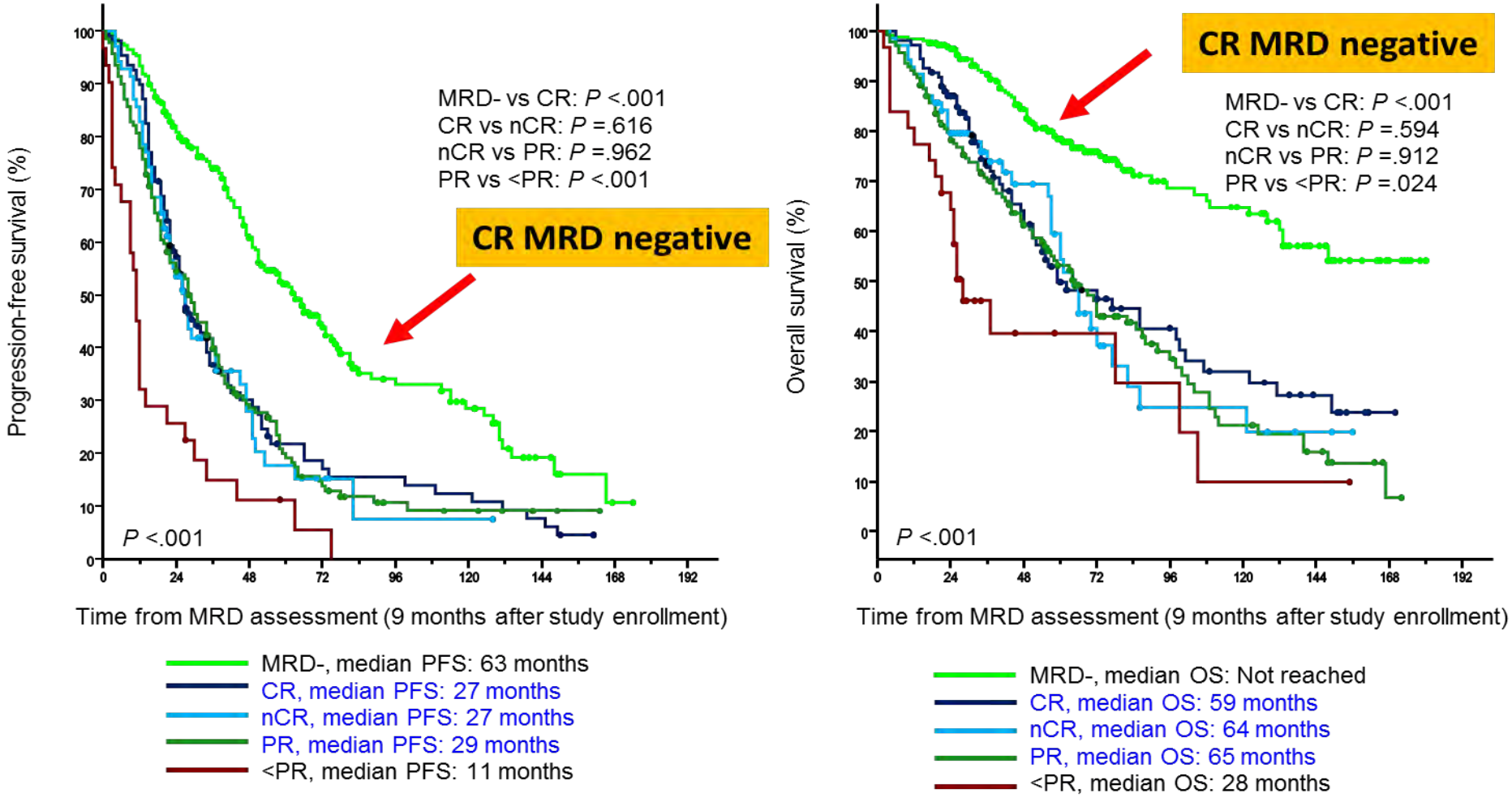
INTERNATIONAL MYELOMA FOUNDATION

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**

INTERNATIONAL MYELOMA FOUNDATION

Patient Case Example

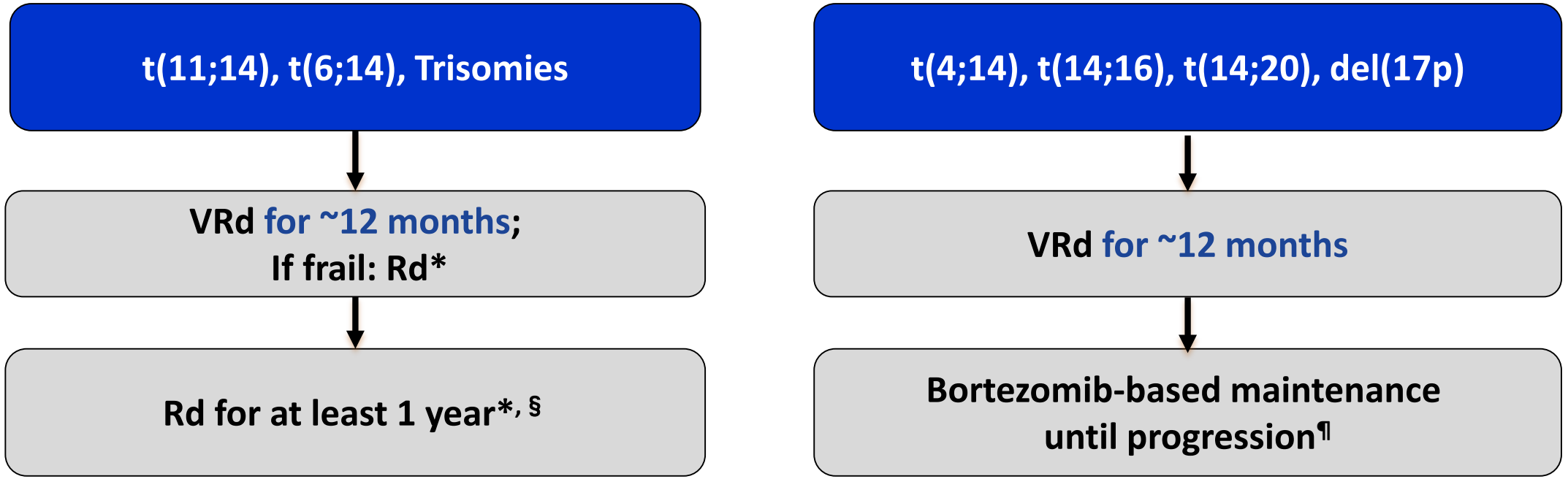
- A **76-year-old woman** presented with bone pain and a whole-body low-dose CT scan showed multiple lytic lesions
- Additional testing revealed:
  - SPEP plus IFE revealed IgAk: 4.6 g/dL
  - Hemoglobin: 10.4 g/dL; WBC and platelets normal
  - Calcium and creatinine normal
  - Bone marrow shows 41% plasma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



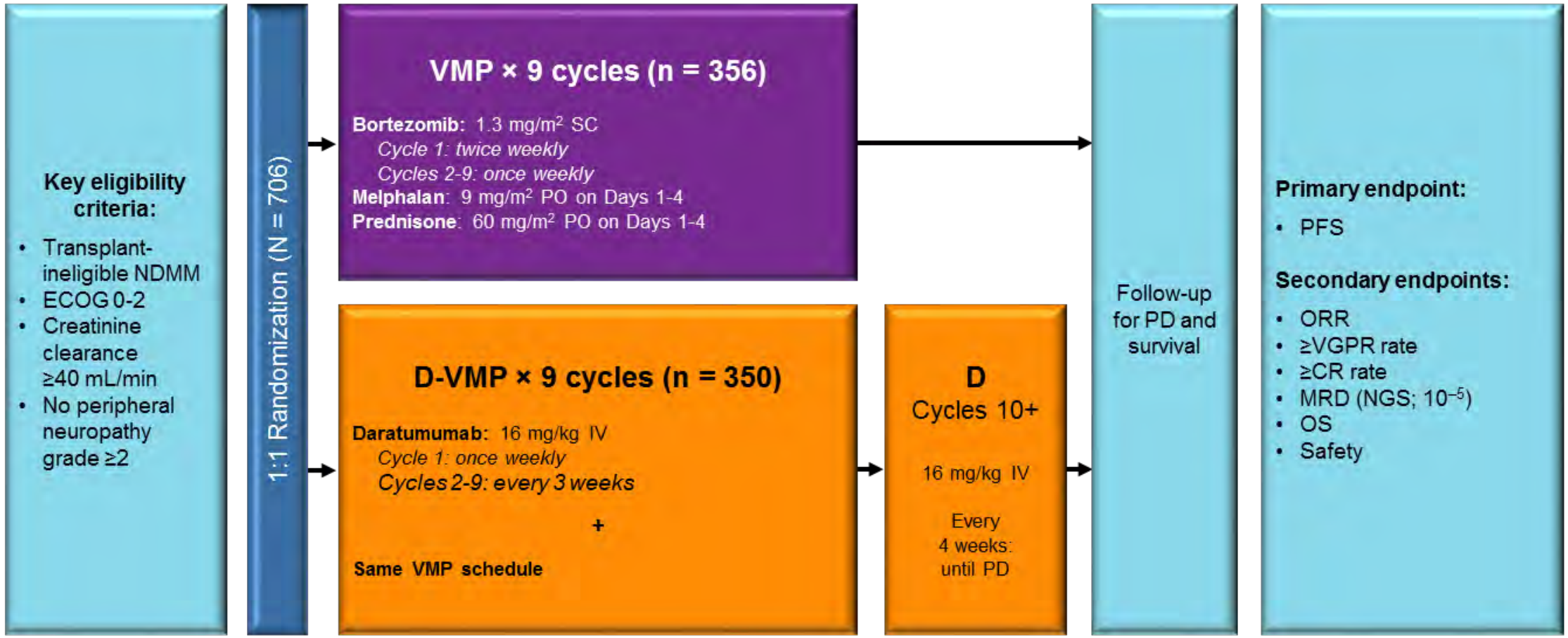
*In patients treated initially with Rd, continuing treatment until progression is an options for patients responding well with low toxicities

§ 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



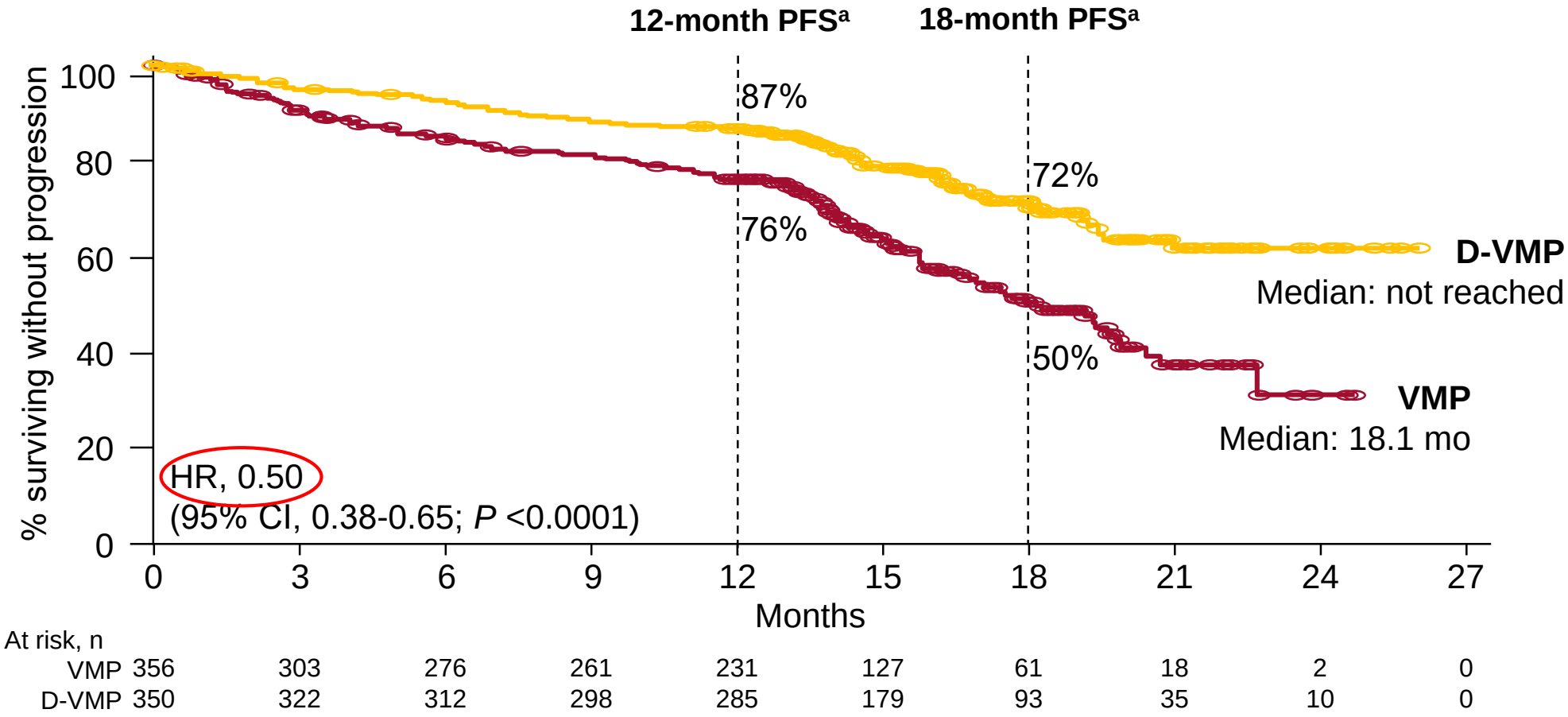
Stratification factors
- ISS (I vs II vs III)
- Region (EU vs other)
- Age (<75 vs ≥75 years)

- 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

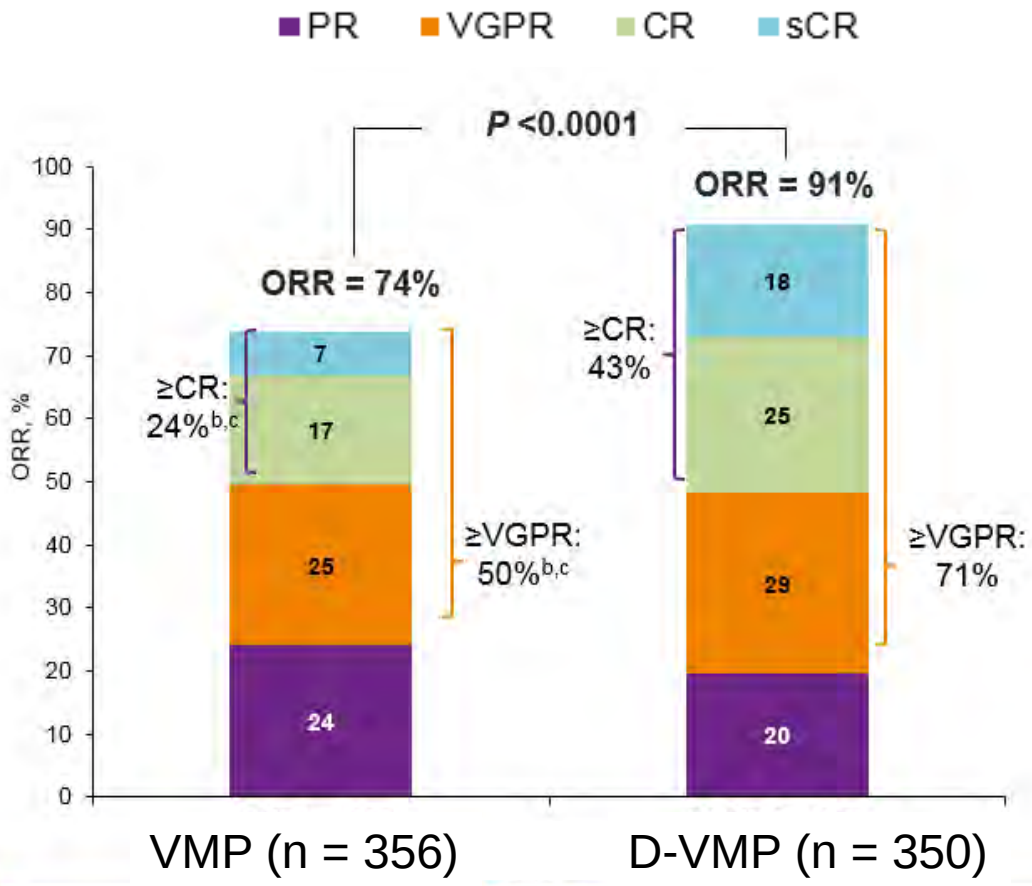


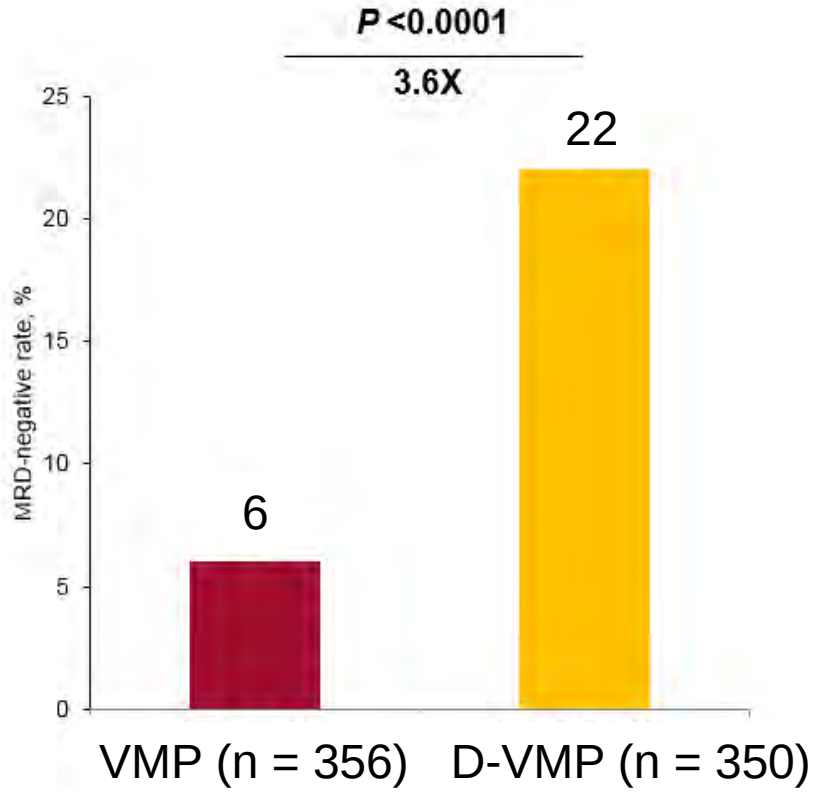
- **Median follow-up: 16.5 months (range: 0.1-28.1)**
- **Consistent PFS treatment benefit across subgroups**

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)



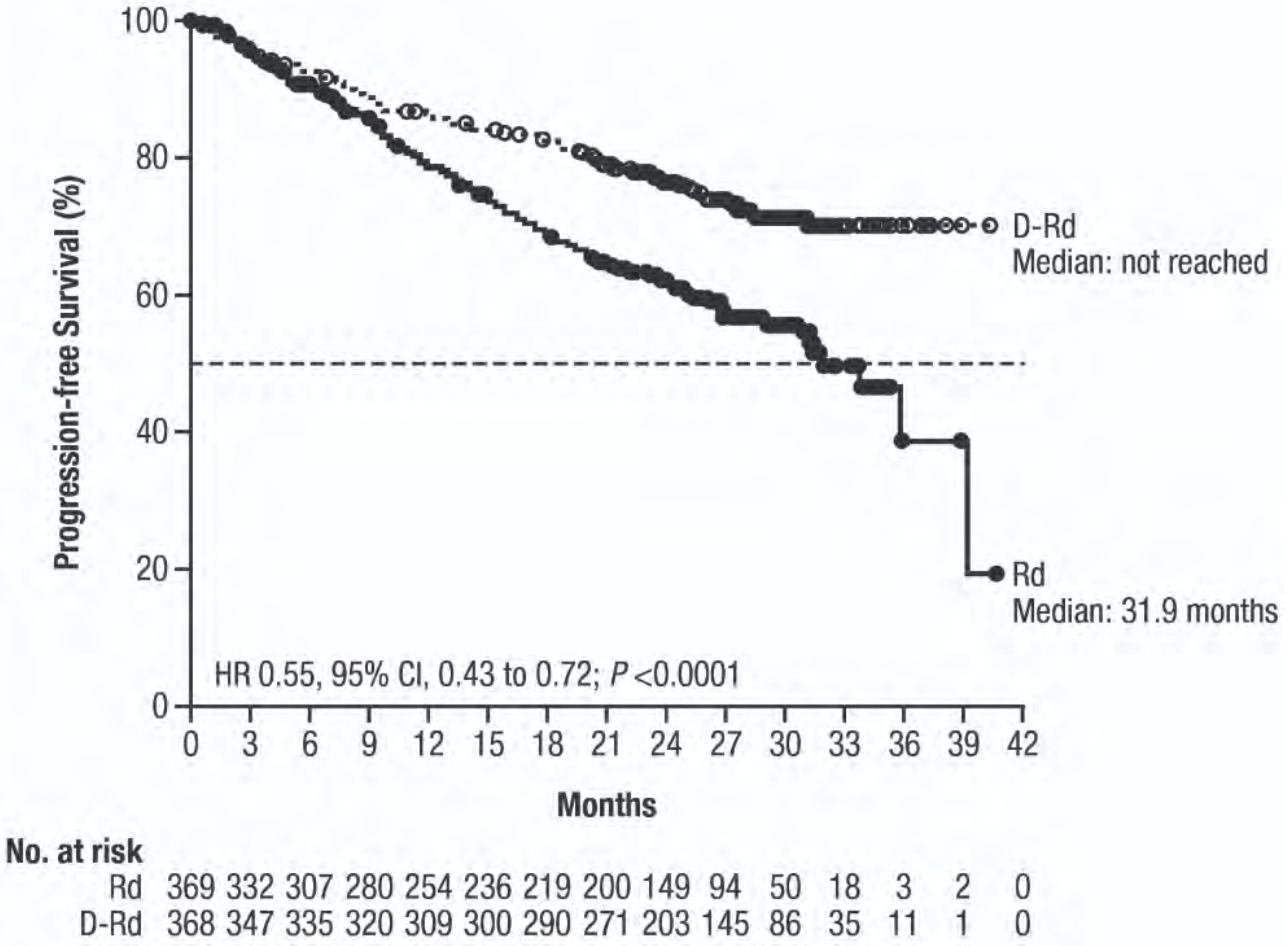


Significantly higher ORR, ≥VGPR, and ≥CR with D-VMP
>3-fold higher MRD-negativity rate with D-VMP

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.

Patient Case Example

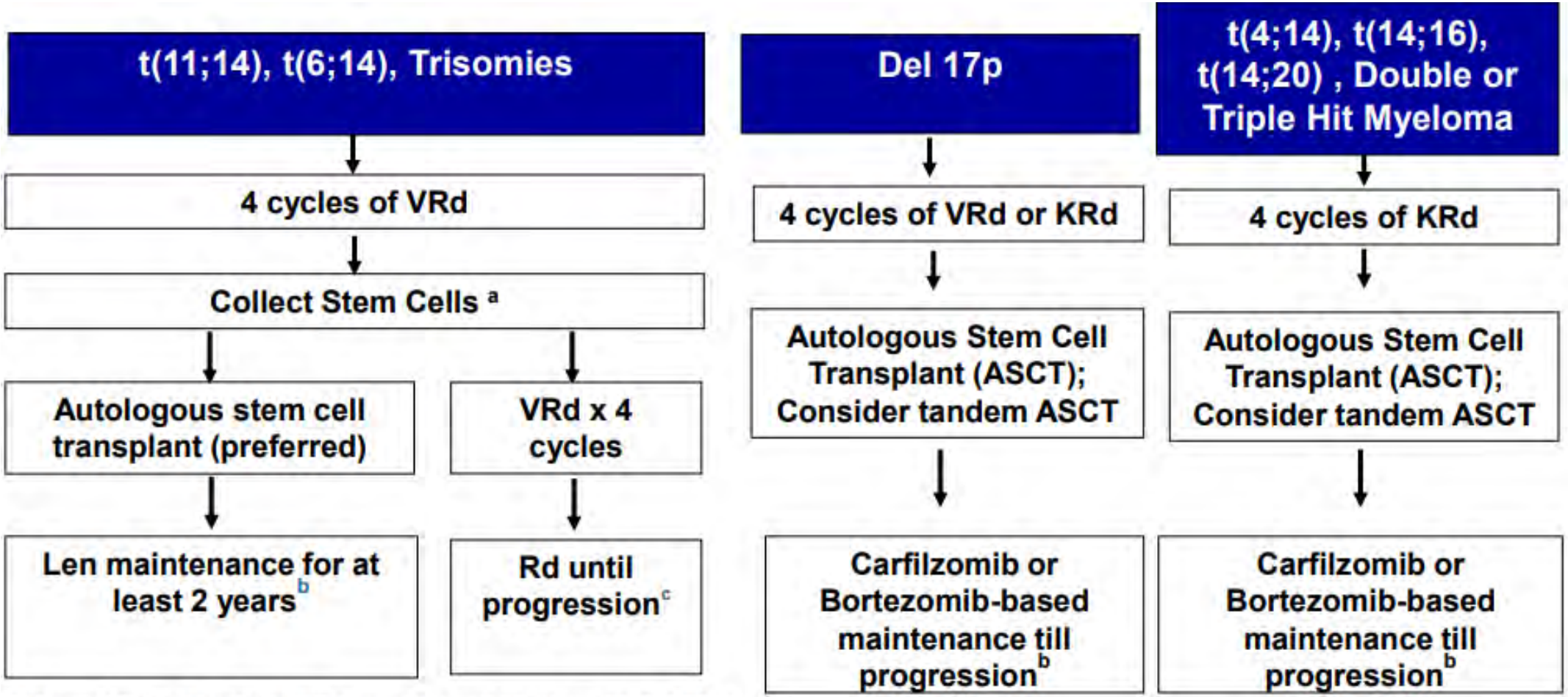
- A 55-year-old woman presented with bone pain and a whole-body low-dose CT scan showed multiple lytic lesions
- Additional testing revealed:
  - SPEP plus IFE revealed IgAk: 4.6 g/dL
  - Hemoglobin: 10.4 g/dL; WBC and platelets normal
  - Calcium and creatinine normal
  - Bone marrow shows 41% plasma cells
  - **FISH testing 1q+, 17p- and t(14;16)**
  - 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	Carfilzomib/lenalidomide/dexamethasone (KRd)
Shaji Kumar, MD	Carfilzomib/lenalidomide/dexamethasone (KRd)
Philippe Moreau, MD	Bortezomib/lenalidomide/dexamethasone (VRd)
S. Vincent Rajkumar, MD	Carfilzomib/lenalidomide/dexamethasone (KRd)
Jesús F. San-Miguel, MD, PhD	Carfilzomib/lenalidomide/dexamethasone (KRd)

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]**

INTERNATIONAL MYELOMA FOUNDATION

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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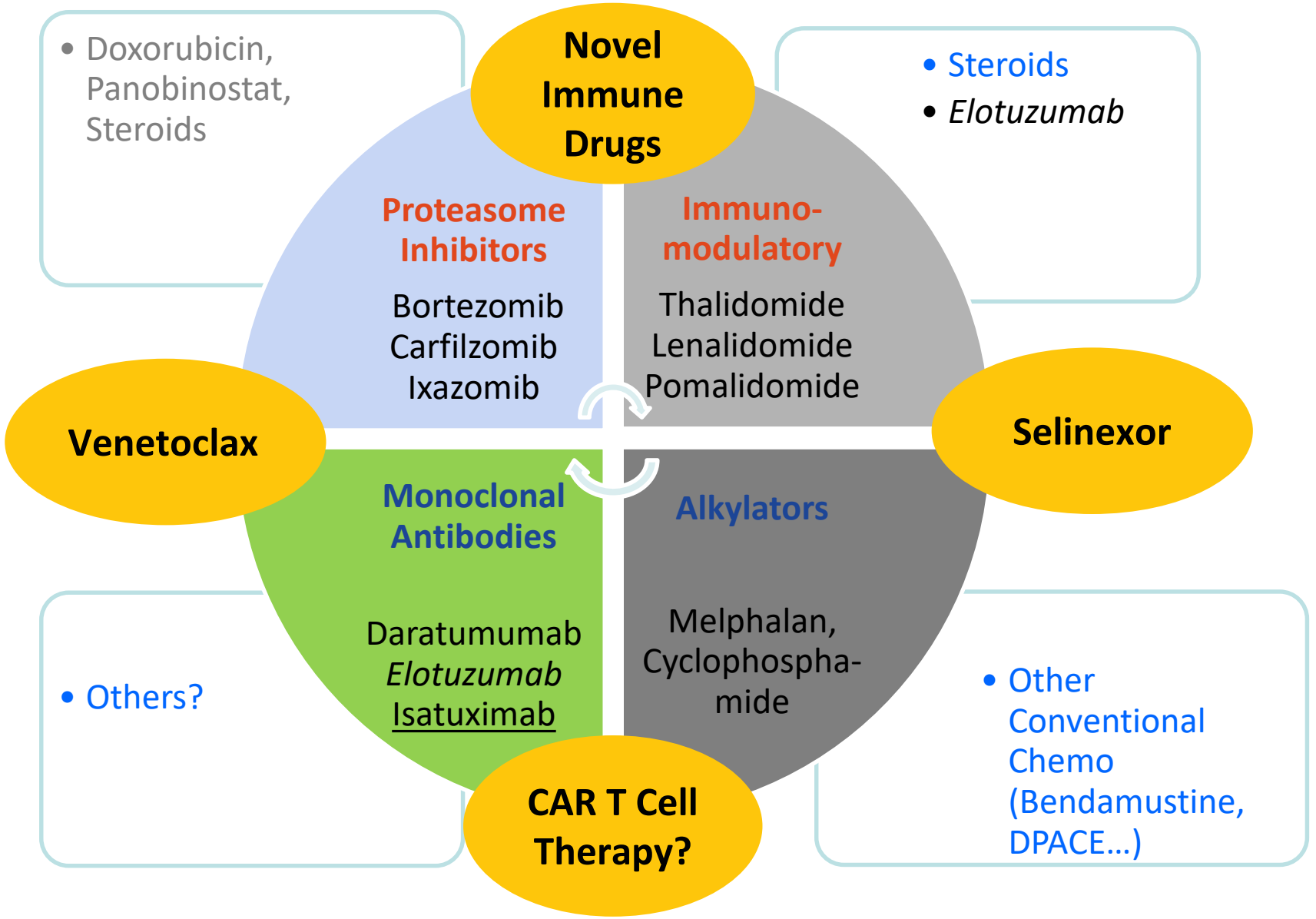
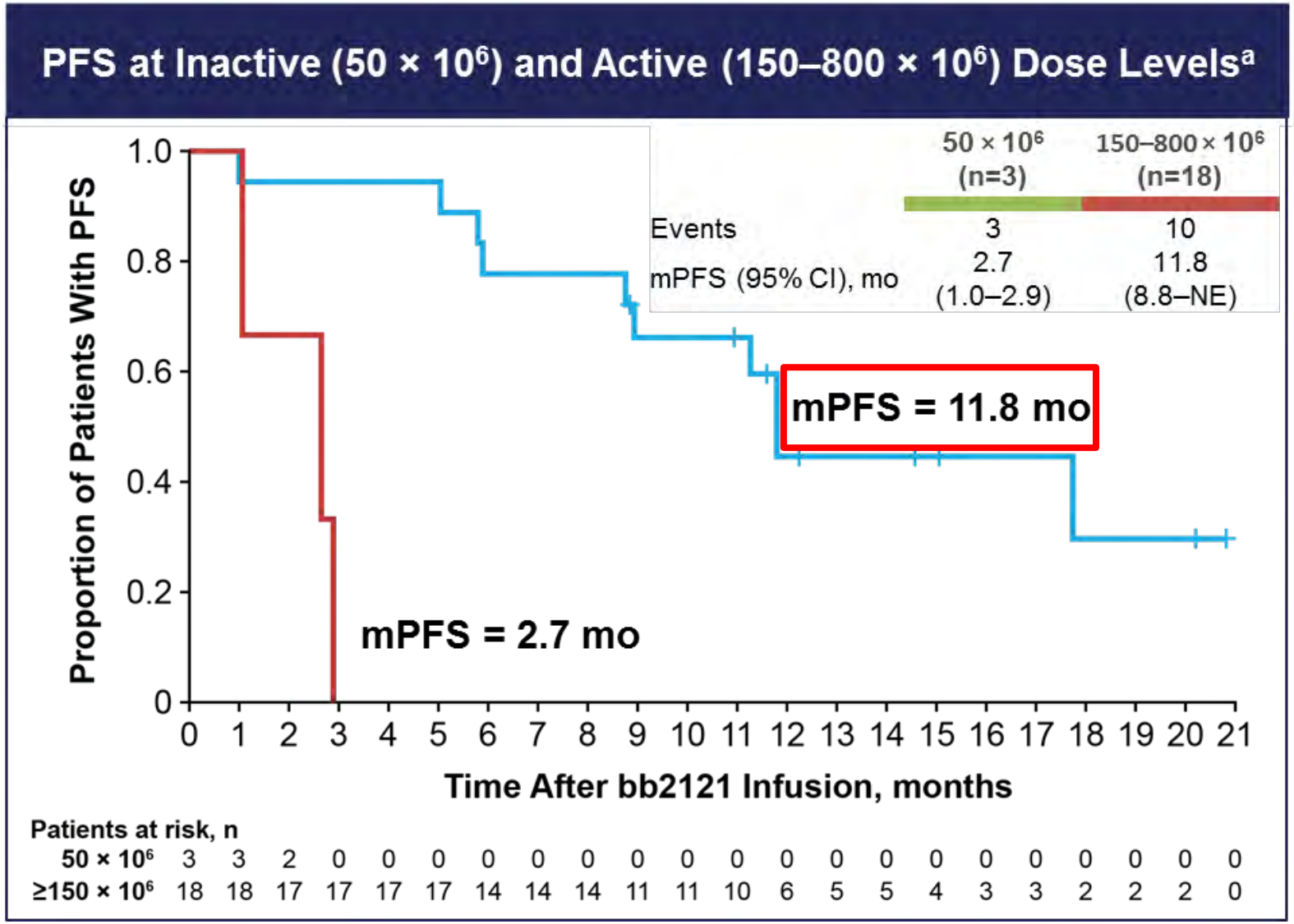
Pillars of Myeloma Therapy



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.

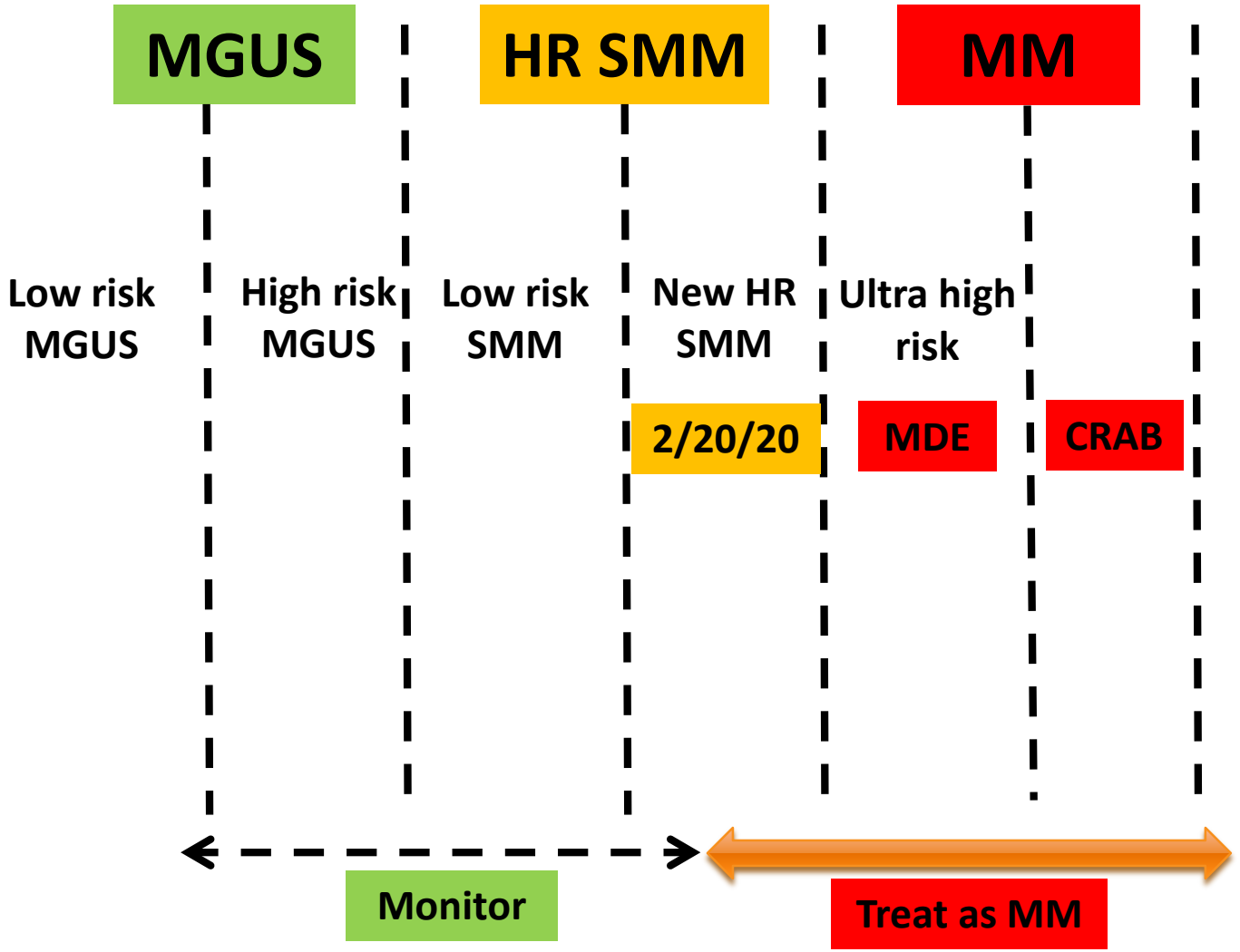
Can CAR T Therapy Be Introduced Early?

- **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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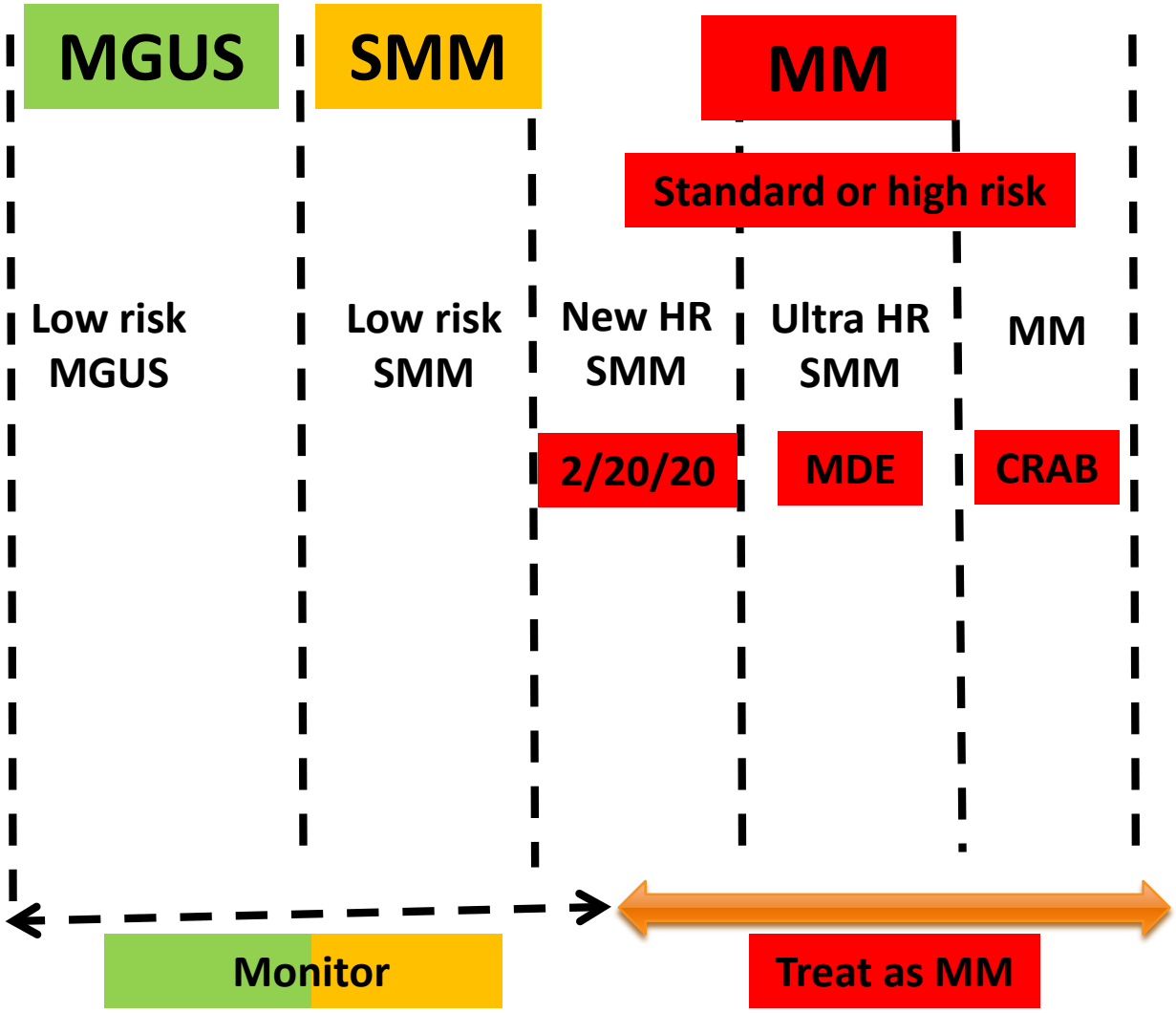
Future of Myeloma Therapy in 2019 and Beyond

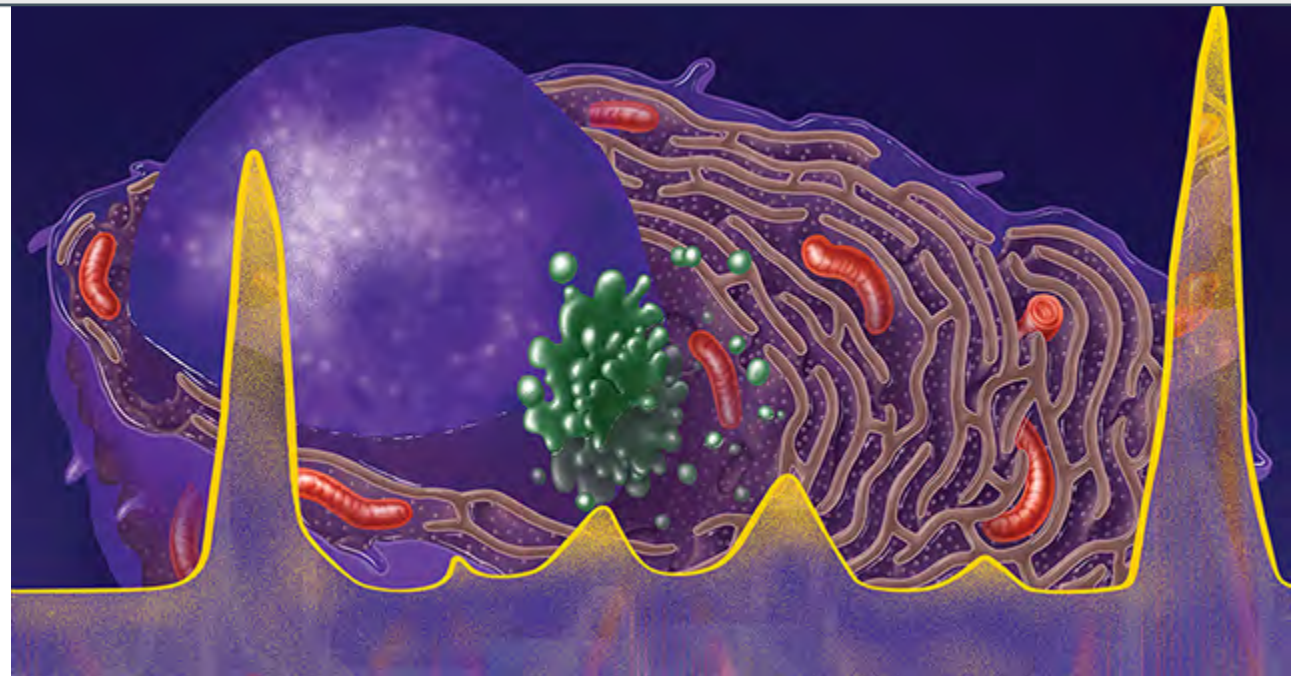


INTERNATIONAL MYELOMA FOUNDATION

INTERNATIONAL MYELOMA FOUNDATION

LIVE

Panel Discussion and Audience Q&A



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INTERNATIONAL MYELOMA FOUNDATION

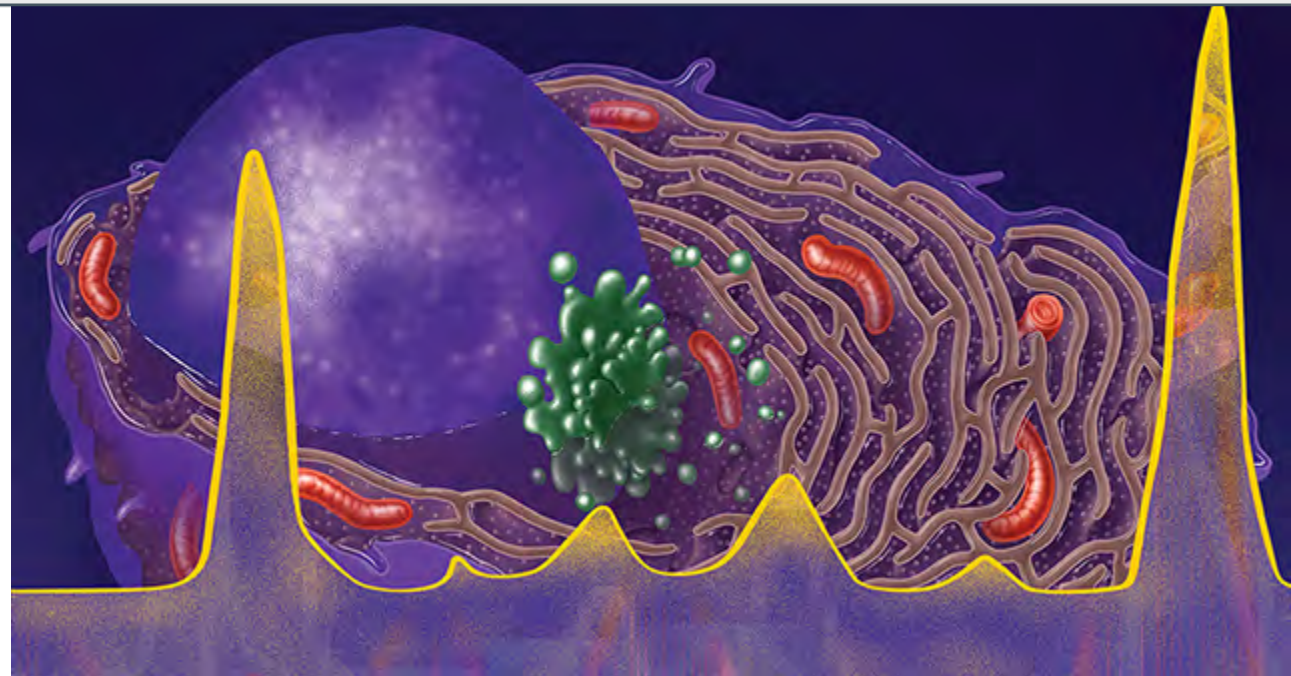
CCO LIVE

Considering the Recent Data on Transplantation, Consolidation, and Maintenance After Induction

Faculty Presenters:

Shaji Kumar, MD

Philippe Moreau, MD



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Program Faculty

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

Shaji Kumar, MD, has disclosed that he has consulted with payment to Mayo Clinic from AbbVie, Amgen, Celgene, Dr. Reddy's Laboratory, Genentech, Janssen, Kite, MedImmune, Merck, Oncopeptides, and Takeda and funds for research support from AbbVie, Amgen, Bristol-Myers Squibb, Celgene, Janssen, Kite, MedImmune, Merck, Novartis, Roche-Genentech, Sanofi, and Takeda.

What’s next after induction?

The US Perspective

Patient Case Example

- A 53-year-old woman with no other health problems was diagnosed with myeloma when she presented with back pain and increasing fatigue

Lab Test	Result
Hemoglobin	10.8 g/dL
Serum Ca^{2+}	Normal
Serum creatinine	Normal
Serum LDH	Normal
Serum $\beta_2$microglobulin	2.8 mg/dL
Serum albumin	4.1 g/dL

- Serum protein electrophoresis: IgGK monoclonal protein of 3.2 g/dL
- 24-hour urine protein electrophoresis: 210 mg monoclonal protein, kappa light chain

Patient Case Example

- Whole-body low-dose CT showed multiple lytic lesions
- Bone marrow biopsy showed 40% plasma cell involvement, FISH showed no abnormality
- She was started on treatment with a combination of bortezomib, lenalidomide, and dexamethasone
- At the completion of 4 cycles of therapy:
  - Repeat bone marrow biopsy shows no MRD
  - Serum and urine immunofixation were both negative

What would you do next for this patient?

Faculty	Recommendation
Brian G.M. Durie, MD	ASCT followed by RVD consolidation and lenalidomide maintenance
Shaji Kumar, MD	ASCT followed by lenalidomide maintenance
Philippe Moreau, MD	ASCT followed by RVD consolidation and lenalidomide maintenance
S. Vincent Rajkumar, MD	ASCT followed by lenalidomide maintenance
Jesús F. San-Miguel, MD, PhD	ASCT followed by RVD consolidation and lenalidomide maintenance

Patient Case Example

- A 53-year-old woman with no other health problems was diagnosed with myeloma when she presented with back pain and increasing fatigue

Lab Test	Result
Hemoglobin	10.8 g/dL
Serum Ca^{2+}	Normal
Serum creatinine	Normal
Serum LDH	**Above ULN**
Serum $\beta_2$microglobulin	**7.1 mg/dL**
Serum albumin	4.1 g/dL

- Serum protein electrophoresis: IgGK monoclonal protein of 3.2 g/dL
- 24-hour urine protein electrophoresis: 210 mg monoclonal protein, kappa light chain

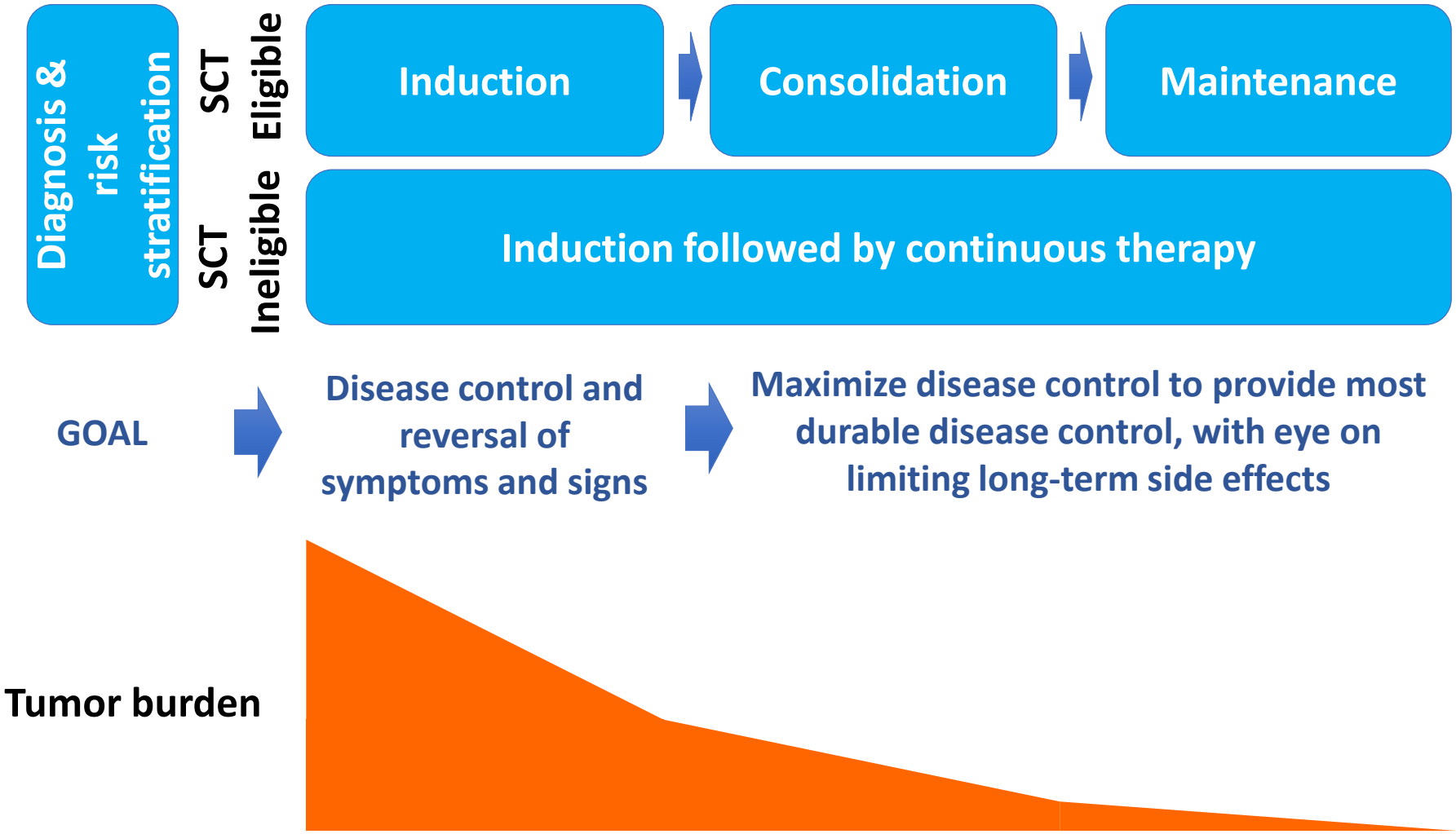
Patient Case Example

- Whole-body low-dose CT showed multiple lytic lesions
- Bone marrow biopsy showed 40% plasma cell involvement, **FISH showed 17p deletion in > 50% of tumor cells**
- She was started on treatment with a combination of bortezomib, lenalidomide and dexamethasone
- At the completion of 4 cycles of therapy:
  - Repeat bone marrow biopsy shows no MRD
  - Serum and urine immunofixation were both negative

Now, what would you do next for this patient?

Faculty	Recommendation
Brian G.M. Durie, MD	ASCT followed by RVD consolidation and PI-based maintenance
Shaji Kumar, MD	ASCT followed by PI-based maintenance
Philippe Moreau, MD	Tandem ASCT followed by RVD consolidation and PI-based maintenance
S. Vincent Rajkumar, MD	ASCT followed by PI-based maintenance
Jesús F. San-Miguel, MD, PhD	Tandem ASCT followed by RVD consolidation and lenalidomide maintenance

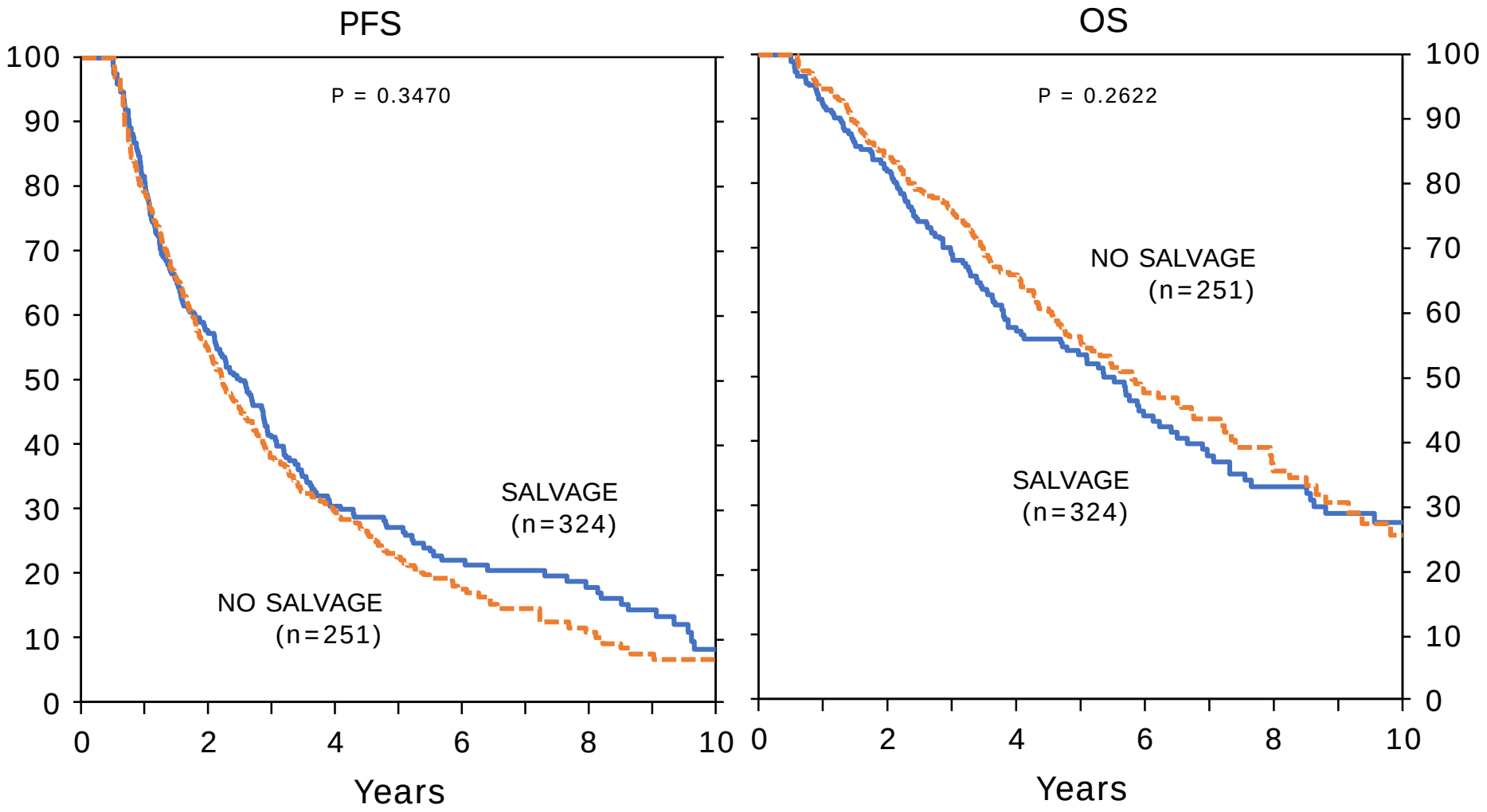
Myeloma Treatment Paradigm



Consolidation and Maintenance

- Stem cell transplantation (SCT): one or two?
- Post-transplantation consolidation?
- Post-transplantation maintenance?

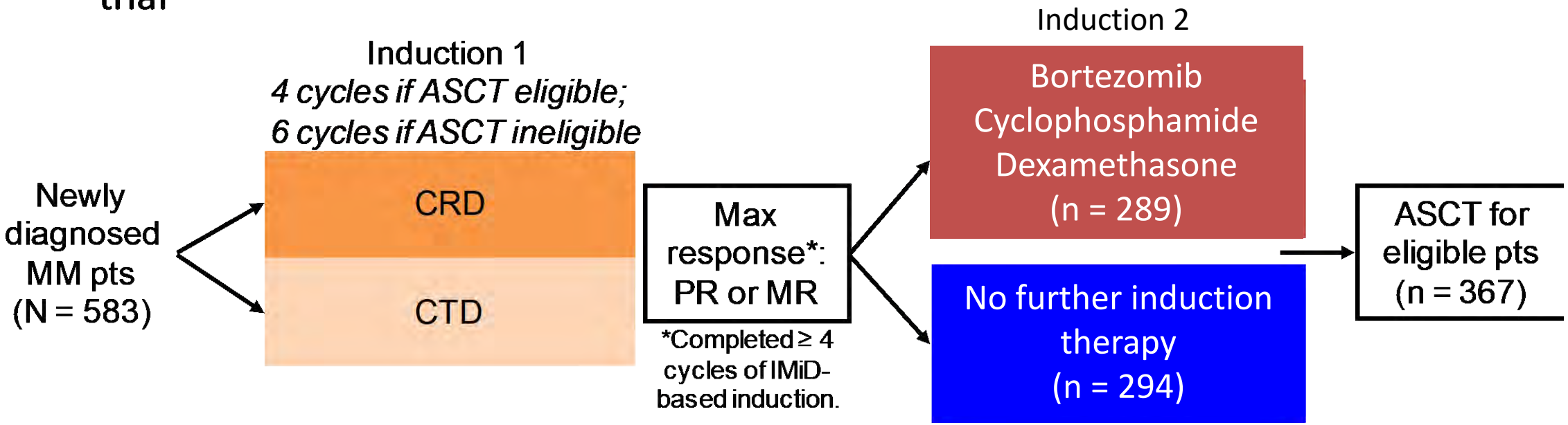
When Do You Stop Induction Therapy?



Vij R, Biol Blood Marrow Transplant. 2014.

Ideal Duration of Induction Prior to SCT?

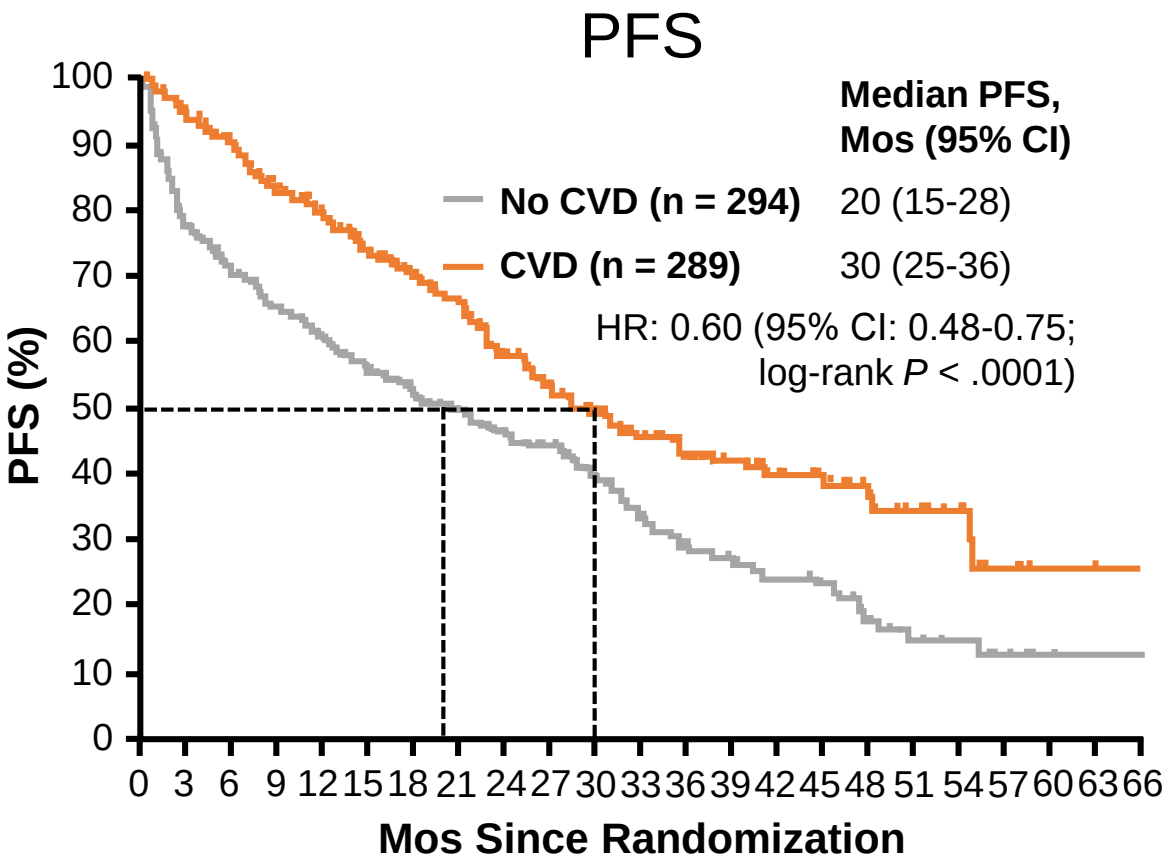
- UK-based multicenter, open-label, parallel group, randomized controlled phase III trial

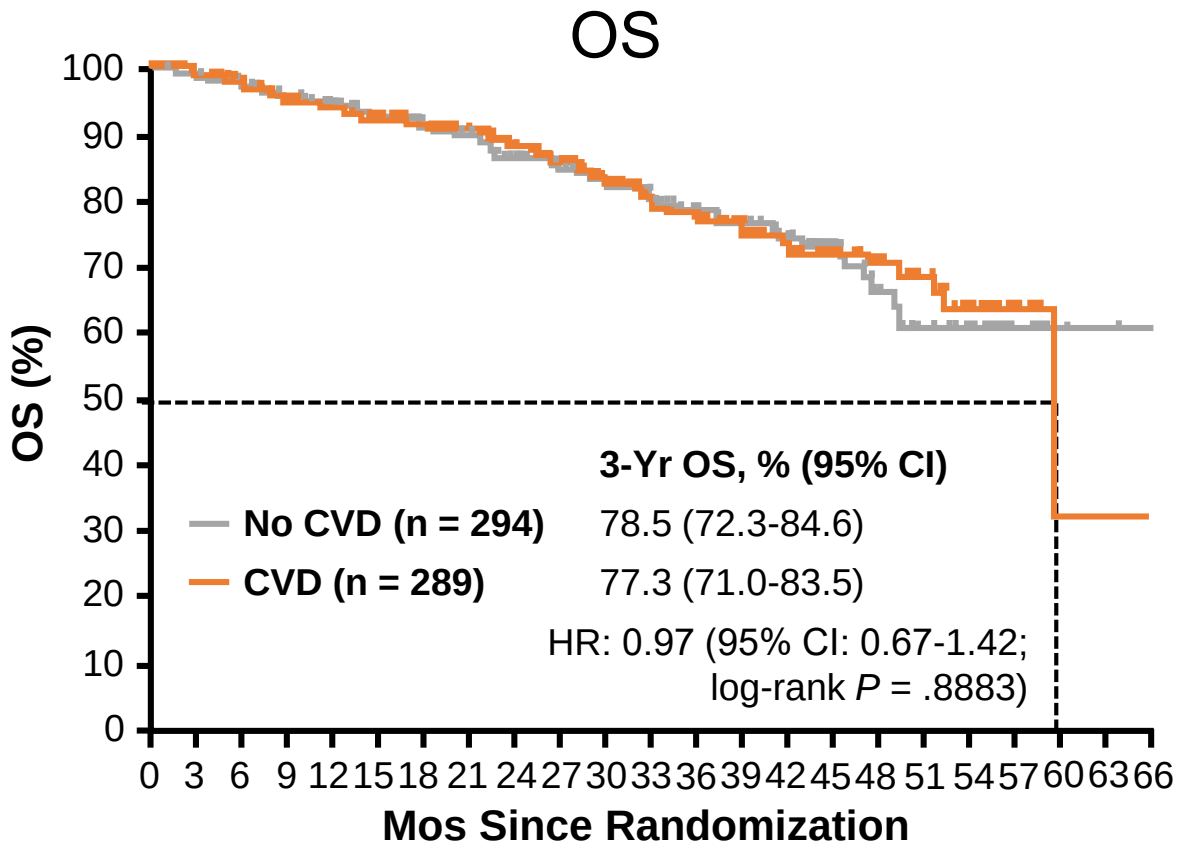


- Primary endpoints: PFS, OS
- Secondary endpoints: Improved response vs baseline, PI effect in high-risk pt group

Jackson. ASH 2016. Abstr 244.

Myeloma XI: Results

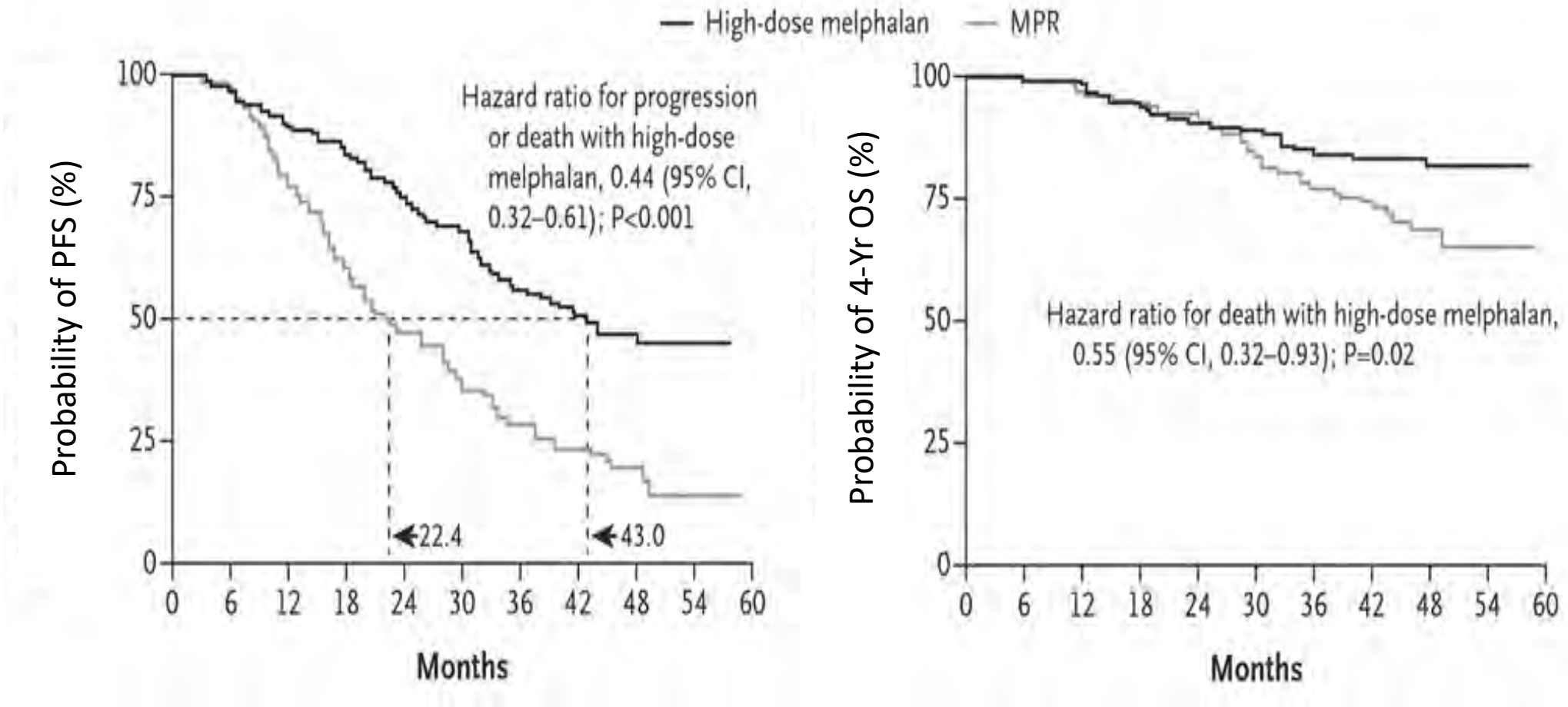




Recommendation: 4-6 cycles of induction and then transplant

Jackson. ASH 2016. Abstr 244.

Do We Still Need ASCT with Novel Drugs?



Palumbo. N Engl J Med 2014;371:895.

Do We Still Need ASCT? IFM 2009

Registration

RVD 1
Lenalidomide + Bortezomib + Dexamethasone

Randomization (stratified on ISS and FISH)

Arm A	Arm B
RVD 2 and 3	RVD 2 and 3
PBSC Collection (cyclophosphamide and G-CSF)	PBSC Collection (cyclophosphamide and G-CSF)
RVD 4 to 8	ASCT HDM 200 mg/m^2
Lenalidomide Maintenance 12 months (10-15 mg/day)	RVD 4 and 5
	Lenalidomide Maintenance 12 months (10-15 mg/day)

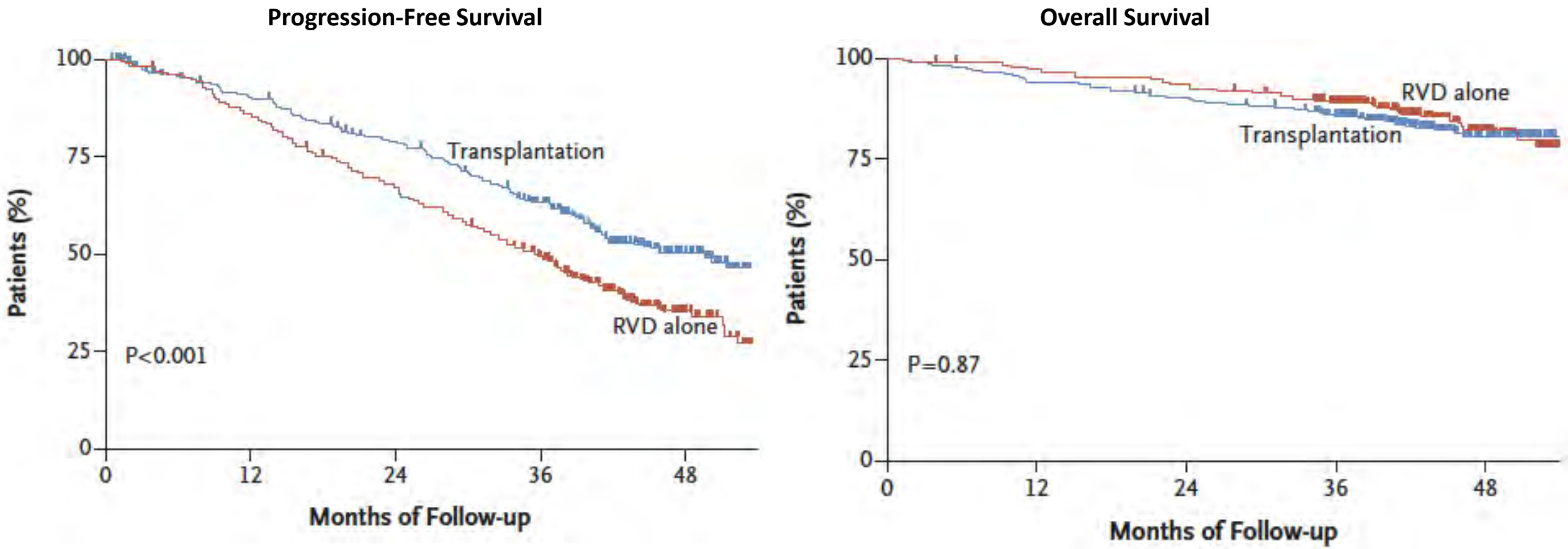
Attal. NEJM. 2017;376:1311.

Deeper Responses With SCT

Outcome	RVD-Alone Group (N = 350)	Transplantation Group (N = 350)
Best response during the study , n (%)		
Complete response	169 (48)	205 (59)
Very good partial response	101 (29)	102 (29)
Partial response	70 (20)	37 (11)
Stable disease	10 (3)	6 (2)
Complete response, n (%)	169 (48)	205 (59)
Complete response or very good partial response, n (%)	270 (77)	307 (88)
Minimal residual disease not detected during study, n/ total n with complete or very good partial response (%)	171/265 (65)	220/278 (79)

Attal. NEJM. 2017;376:1311.

Better PFS; Comparable OS



Recommendation: upfront SCT recommended, but a delayed approach is acceptable

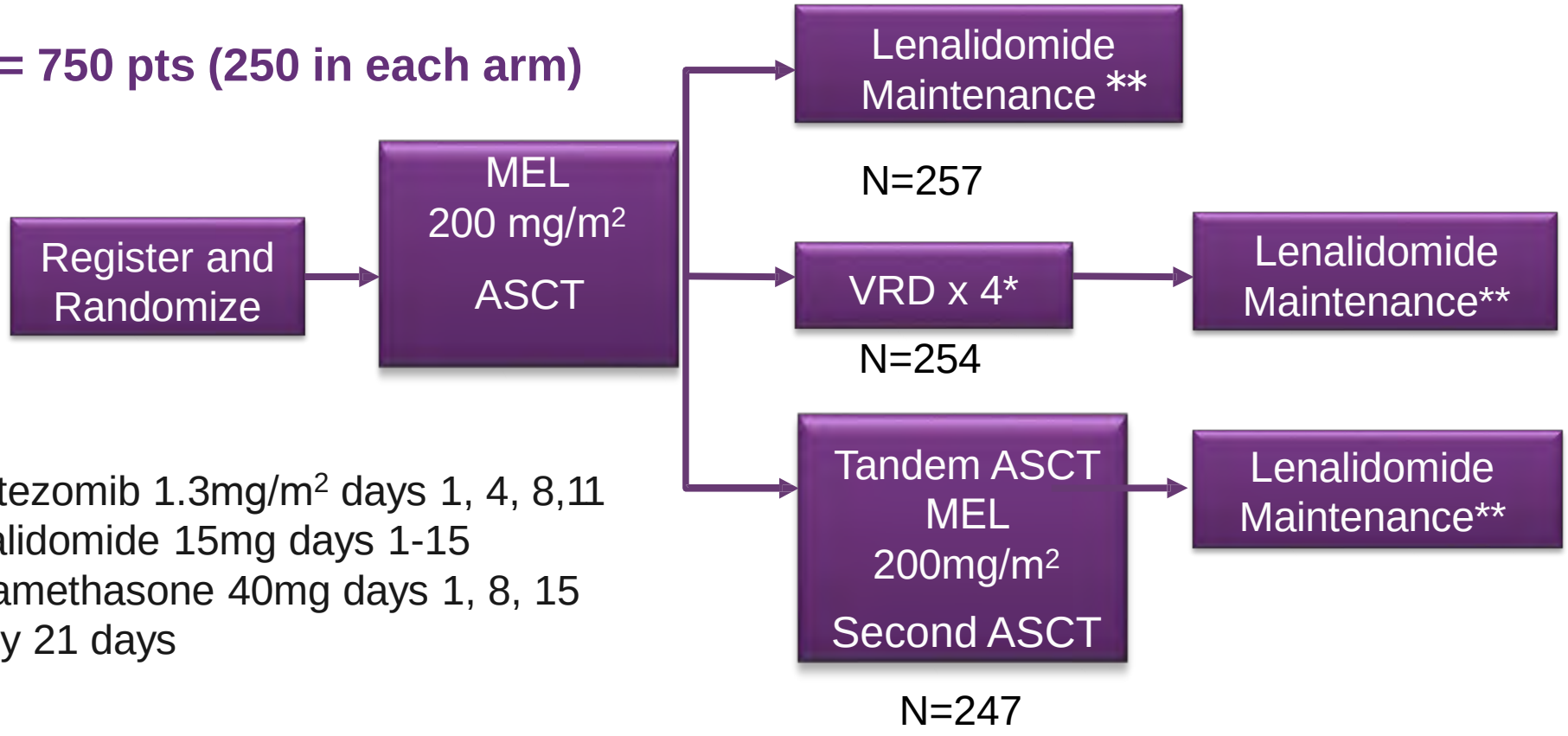
Attal. NEJM. 2017;376:1311.

What Should Be Done Post ASCT?

- Consolidation with tandem ASCT?
- Non-transplant consolidation?
- Maintenance?

STaMINA Trial: BMT CTN 0702

N = 750 pts (250 in each arm)

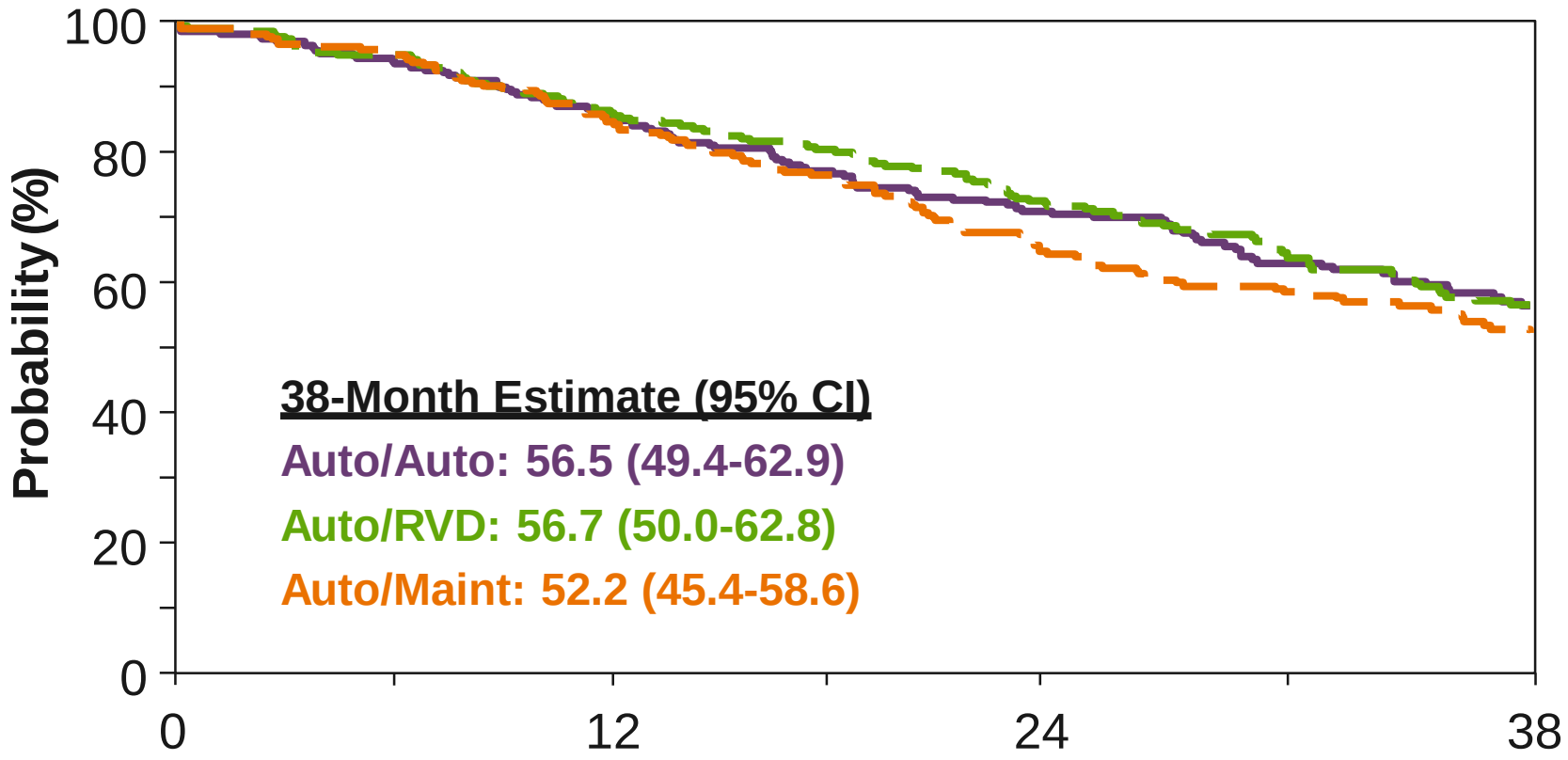


*Bortezomib 1.3mg/m^2 days 1, 4, 8,11
Lenalidomide 15mg days 1-15
Dexamethasone 40mg days 1, 8, 15
Every 21 days

**Lenalidomide x 3 years :
10 mg/d for 3 cycles , then 15 mg/d
Amendment in 2014 changed: lenalidomide maintenance until disease progression after report of CALGB 100104.

Stadtmauer. ASH 2016. Abstr LBA-1.

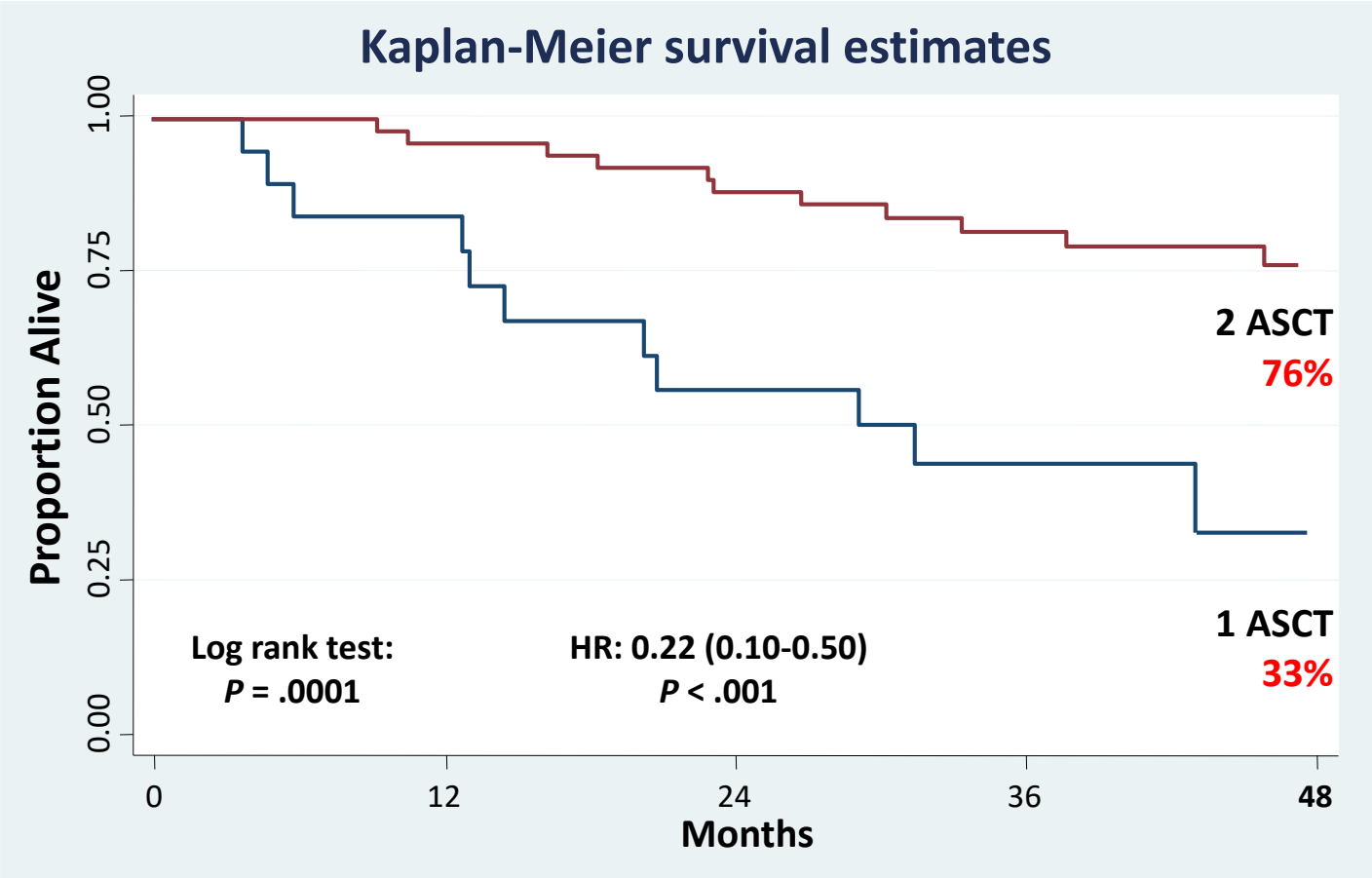
STaMINA Trial: Primary Endpoint—PFS



Recommendation: with VRd induction, no role for additional VRd consolidation

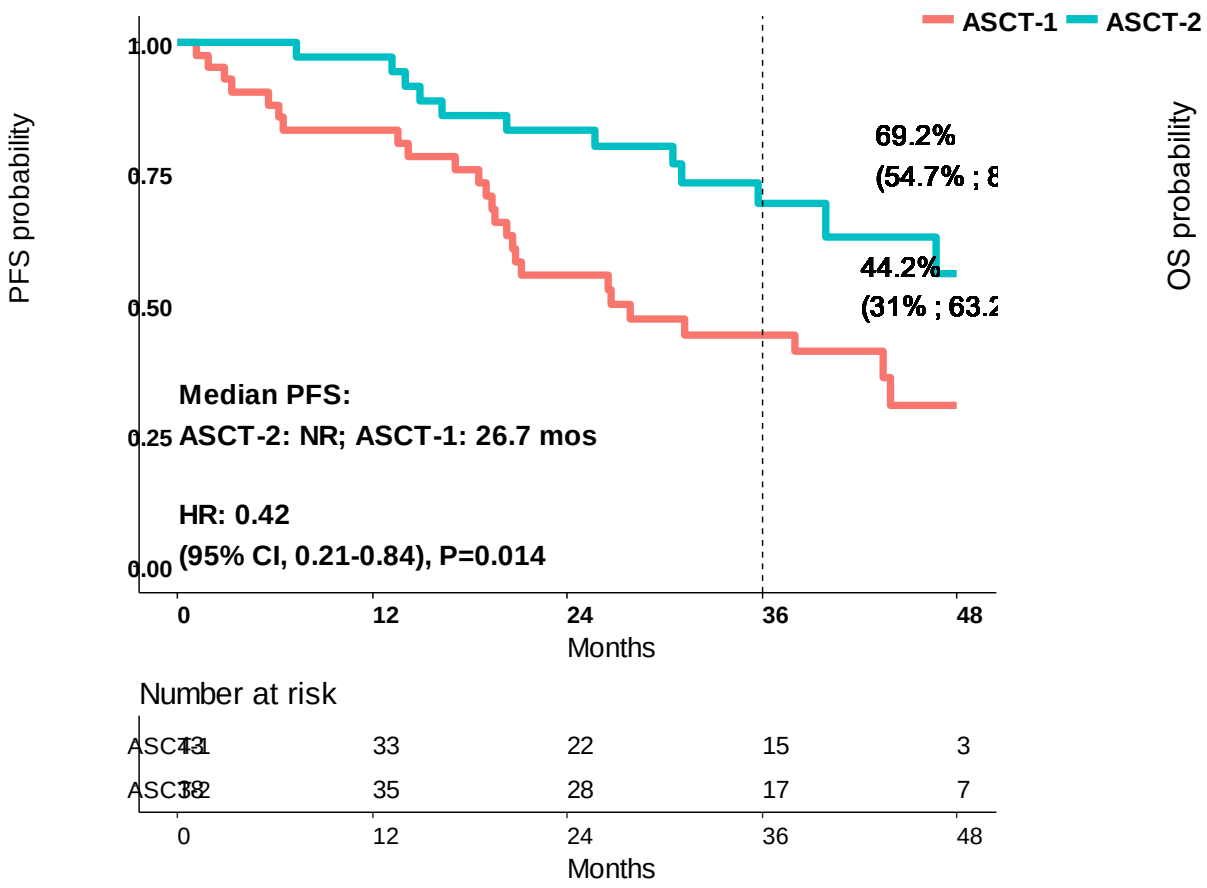
Stadtmauer. ASH 2016. Abstr LBA-1.

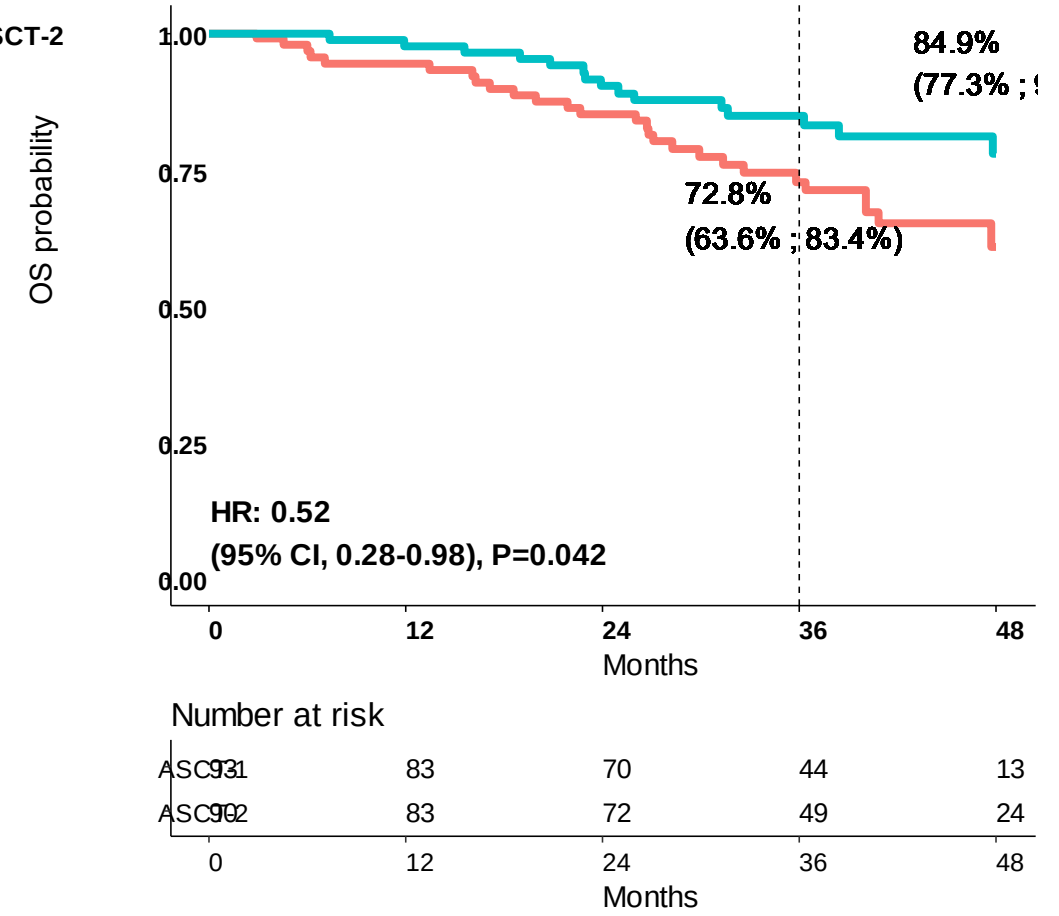
Tandem ASCT: del(17p) ± t(4;14)



Cavo. ASH 2013. Abstr 767.

EMN02: Single vs Tandem: High Risk Genetics

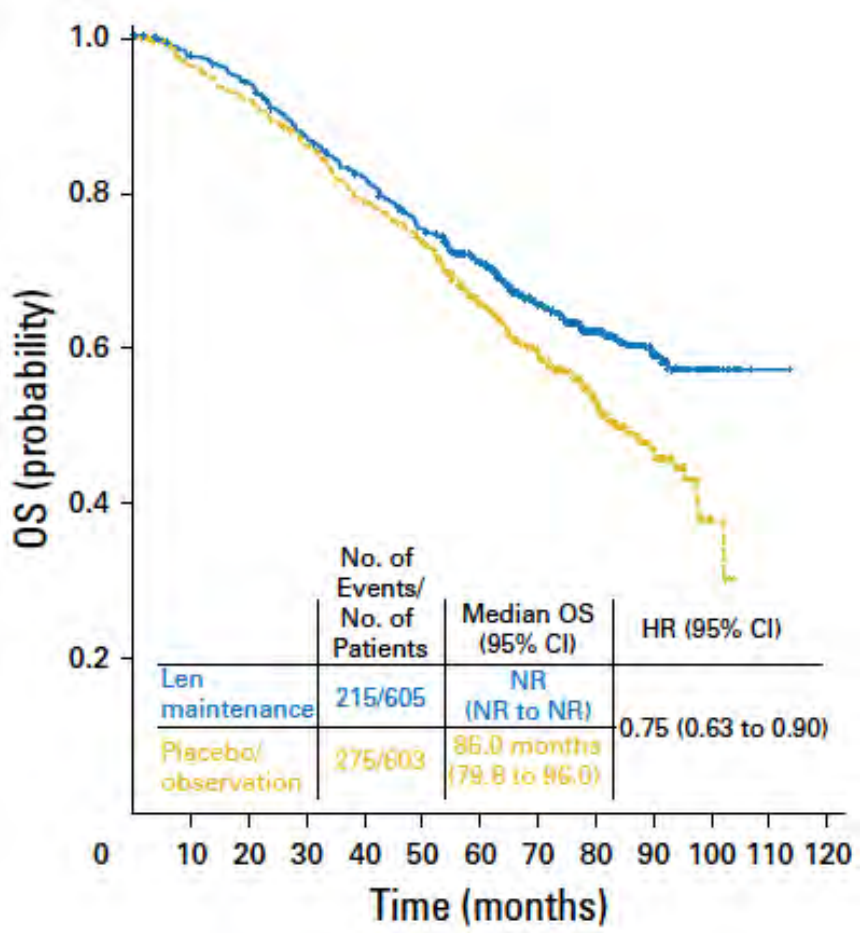


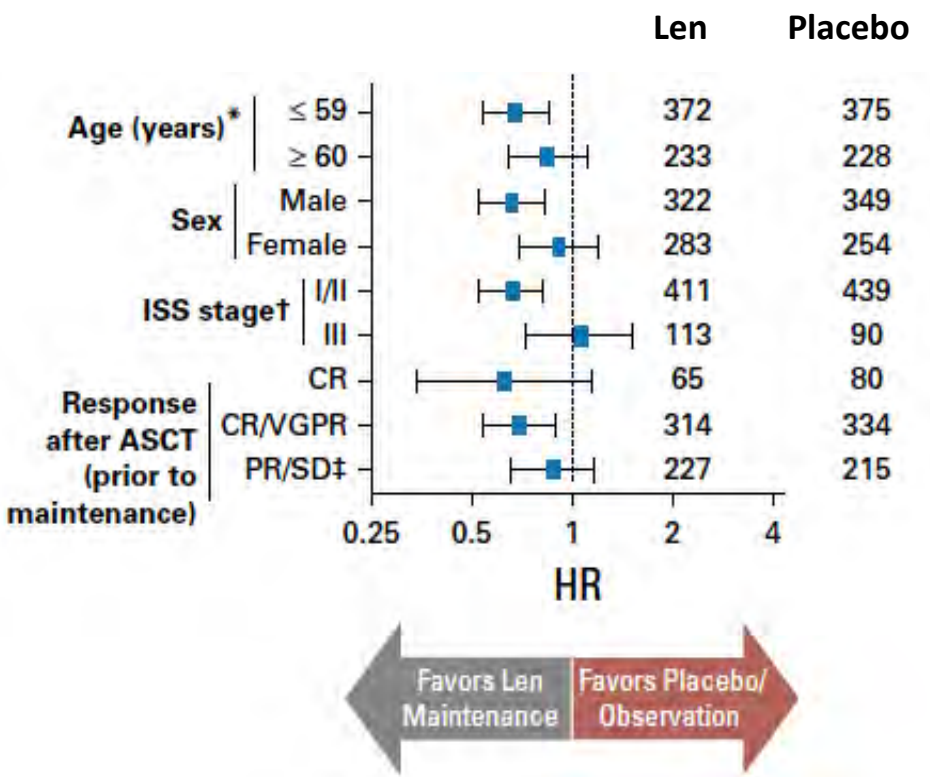


Recommendation: in high-risk patients, a discussion regarding tandem SCT is warranted

Cavo. ASH 2017. Abstr 401.

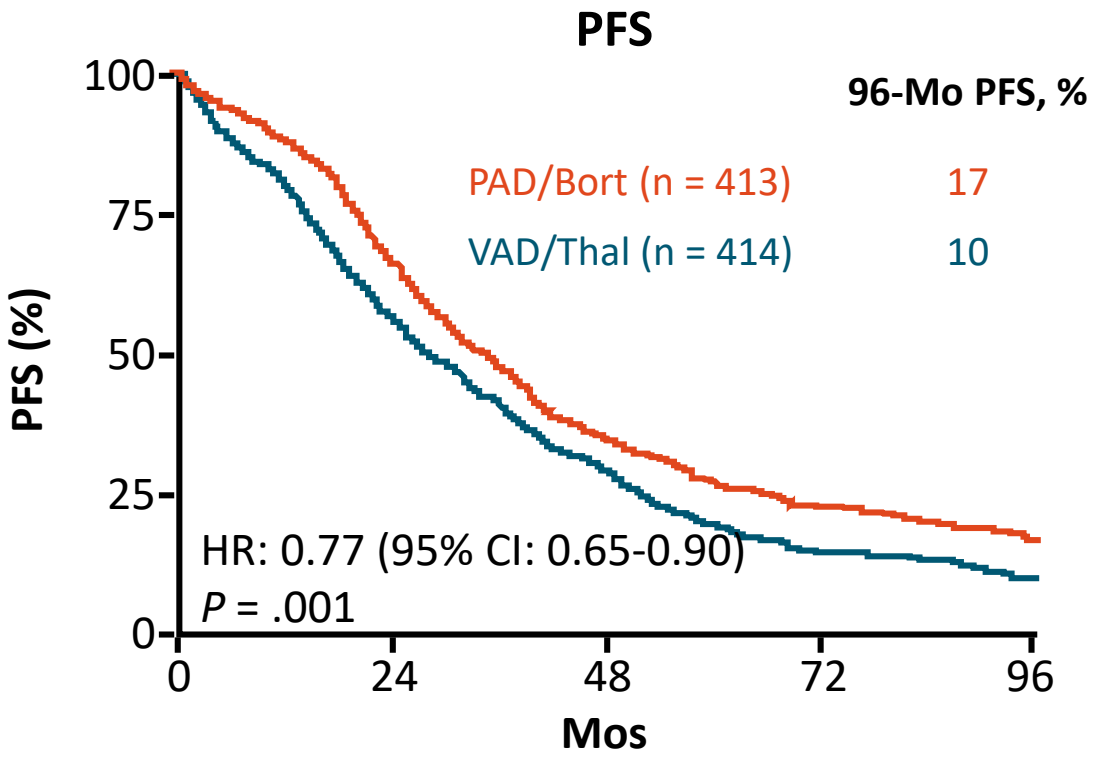
Lenalidomide Maintenance

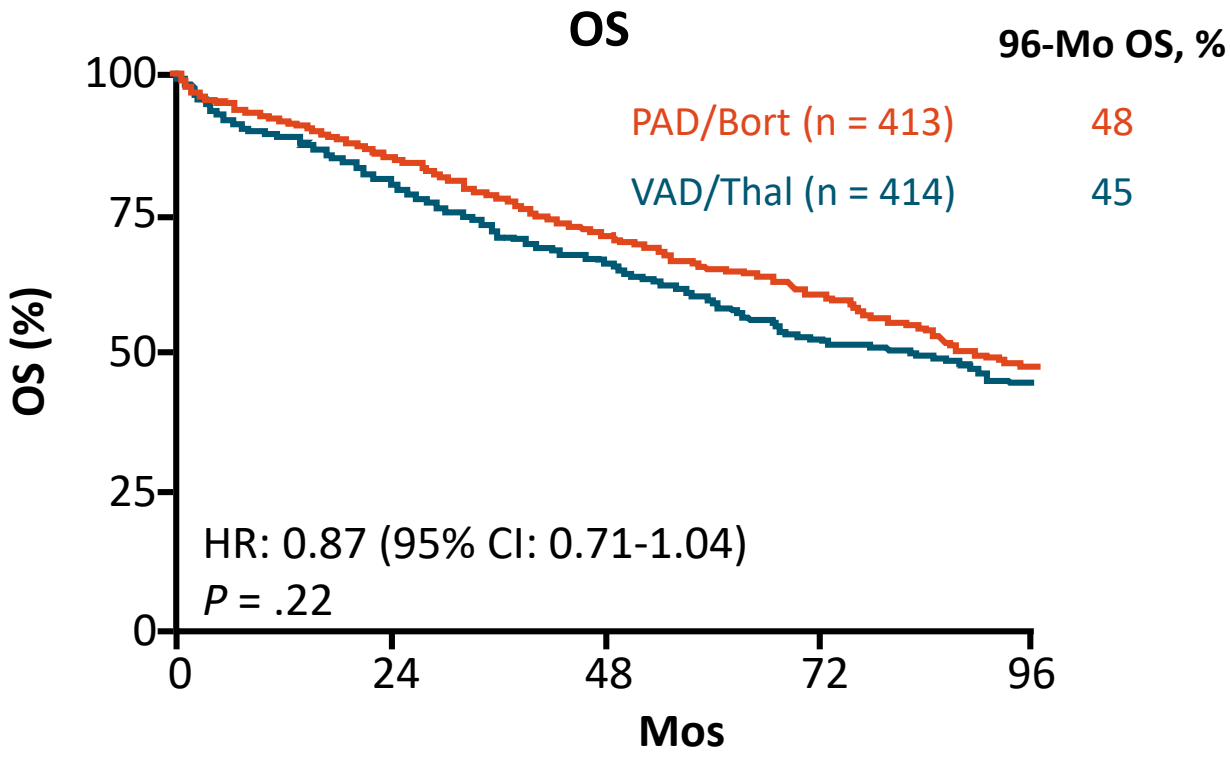




McCarthy. JCO. 2017;35:3279.

Phase III HOVON-65/GMMG-HD4 Trial: Bortezomib Maintenance



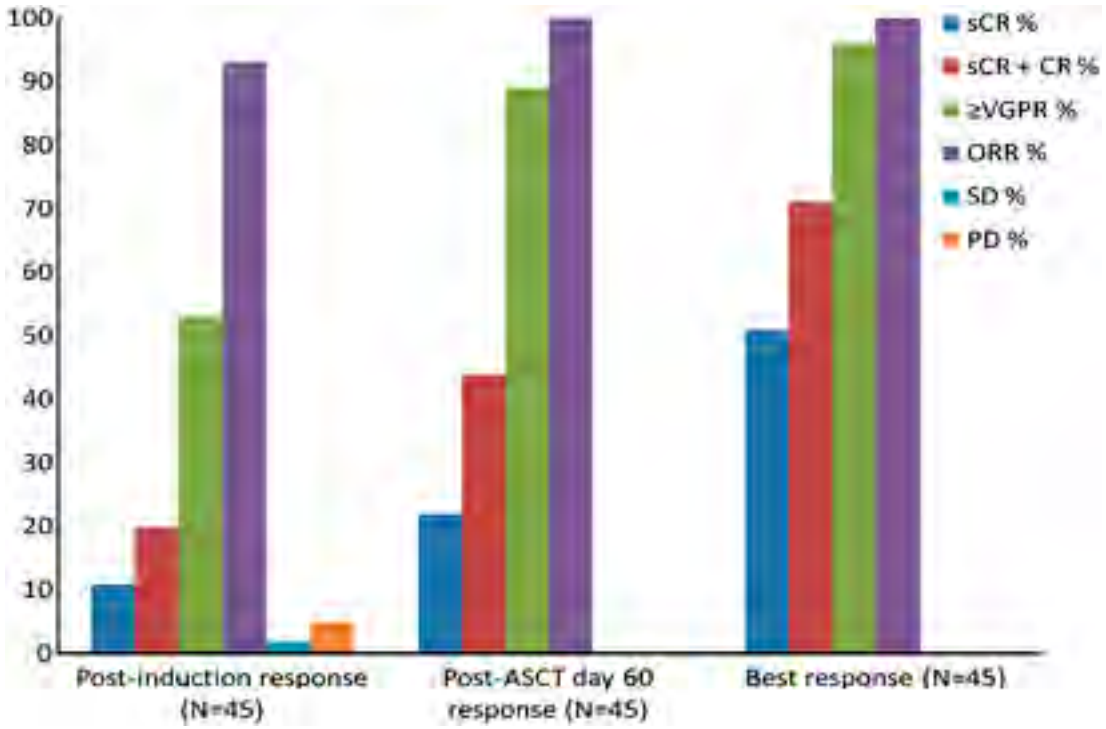


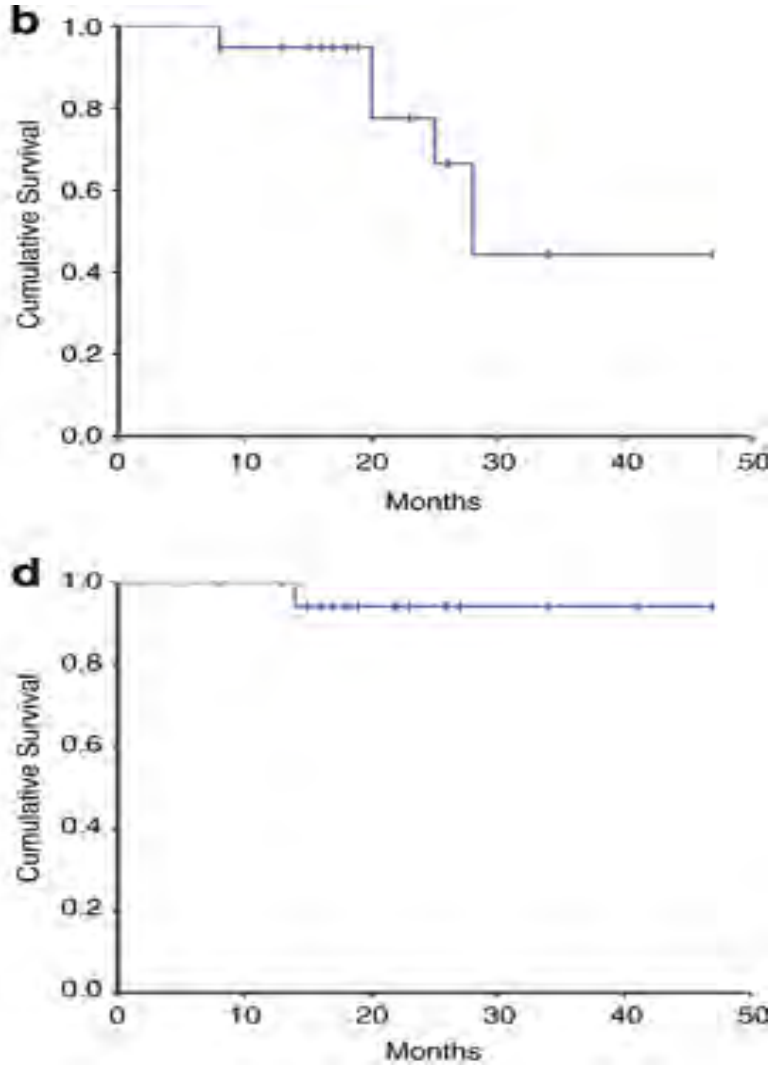
Recommendation: Lenalidomide maintenance should be considered for standard risk and bortezomib maintenance for high risk

Outcome, %	PAD/Bort	VAD/Thal
CR/nCR	50	35
≥ VGPR	75	56
ORR	91	83

Goldschmidt. Leukemia. 2018;32:383.

Different strategy for HR? VRD Maintenance





Nooka. Leukemia. 2014;28:690.

Take Home Points

- In transplant-eligible patients: upfront transplant after 4-6 cycles of induction regardless of the depth of response is standard
  - Delayed SCT at first relapse is acceptable
- If VRd induction is used, additional consolidation with VRd is not recommended
- Tandem transplant is not standard approach
  - In high-risk MM, possibility of benefit should be discussed
- Lenalidomide maintenance recommended for all standard-risk MM and bortezomib based maintenance for high risk
  - del17p: VRd maintenance could be considered

MAYO CLINIC

Thank you

kumar.shaji@mayo.edu

What's Next After Induction in Patients Eligible for ASCT ?

The European Perspective

Pr Philippe Moreau

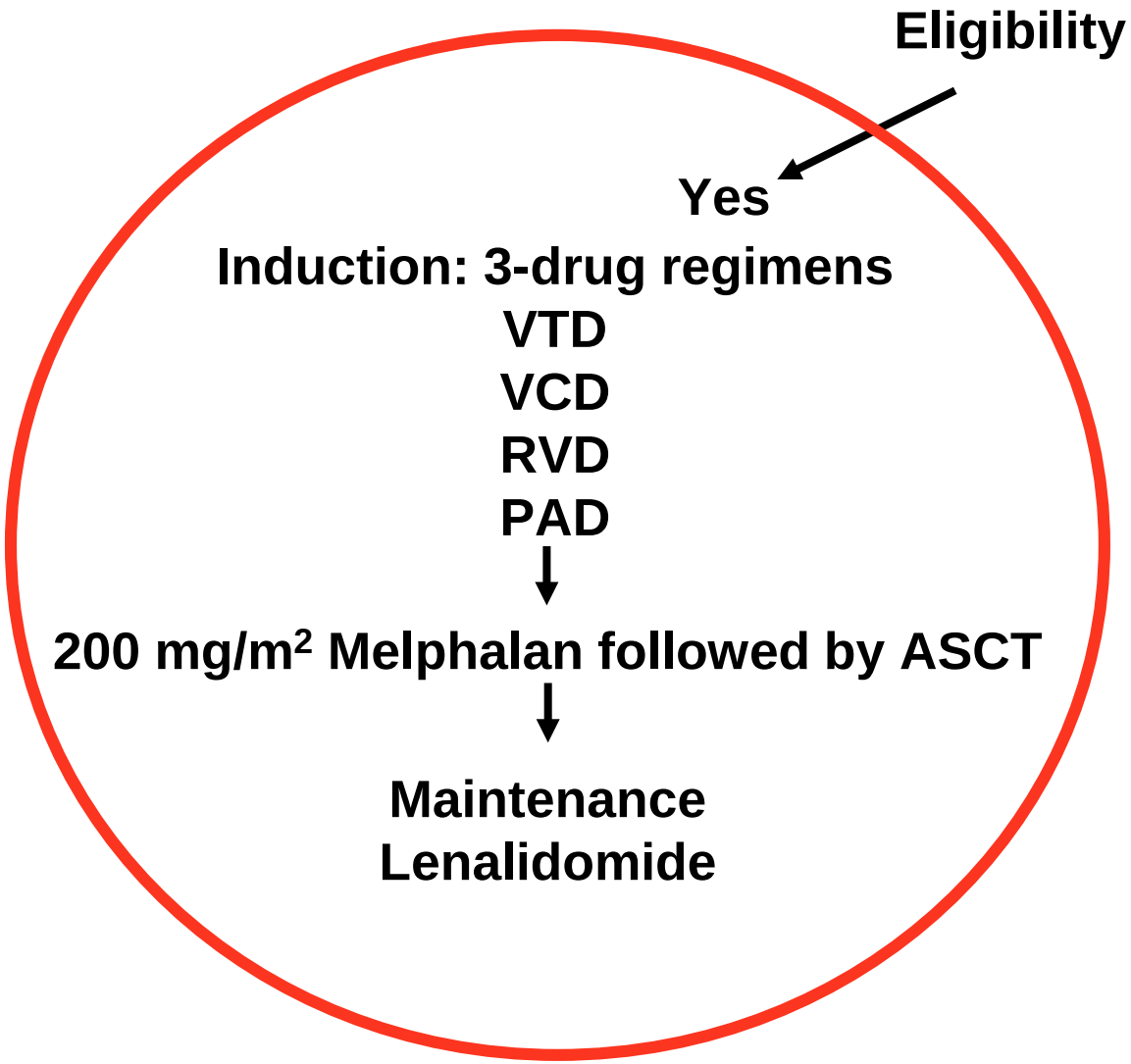
University Hospital, Nantes, France

CENTRE HOSPITALIER
UNIVERSITAIRE DE NANTES

Program 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.



FRONTLINE THERAPY
ESMO guidelines
Moreau et al, Ann Oncol 2017

No Consolidation!

Single ASCT!

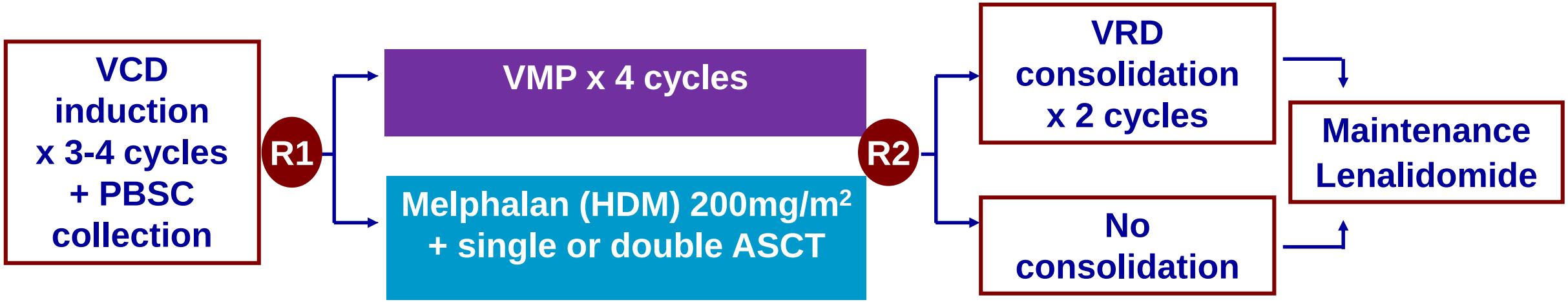
No Delayed ASCT!

≤ 65 Years or
Fit Patients ≤ 70 Years in Good Clinical Condition

In the context of novel-agent based therapy, frontline ASCT is the standard of care !

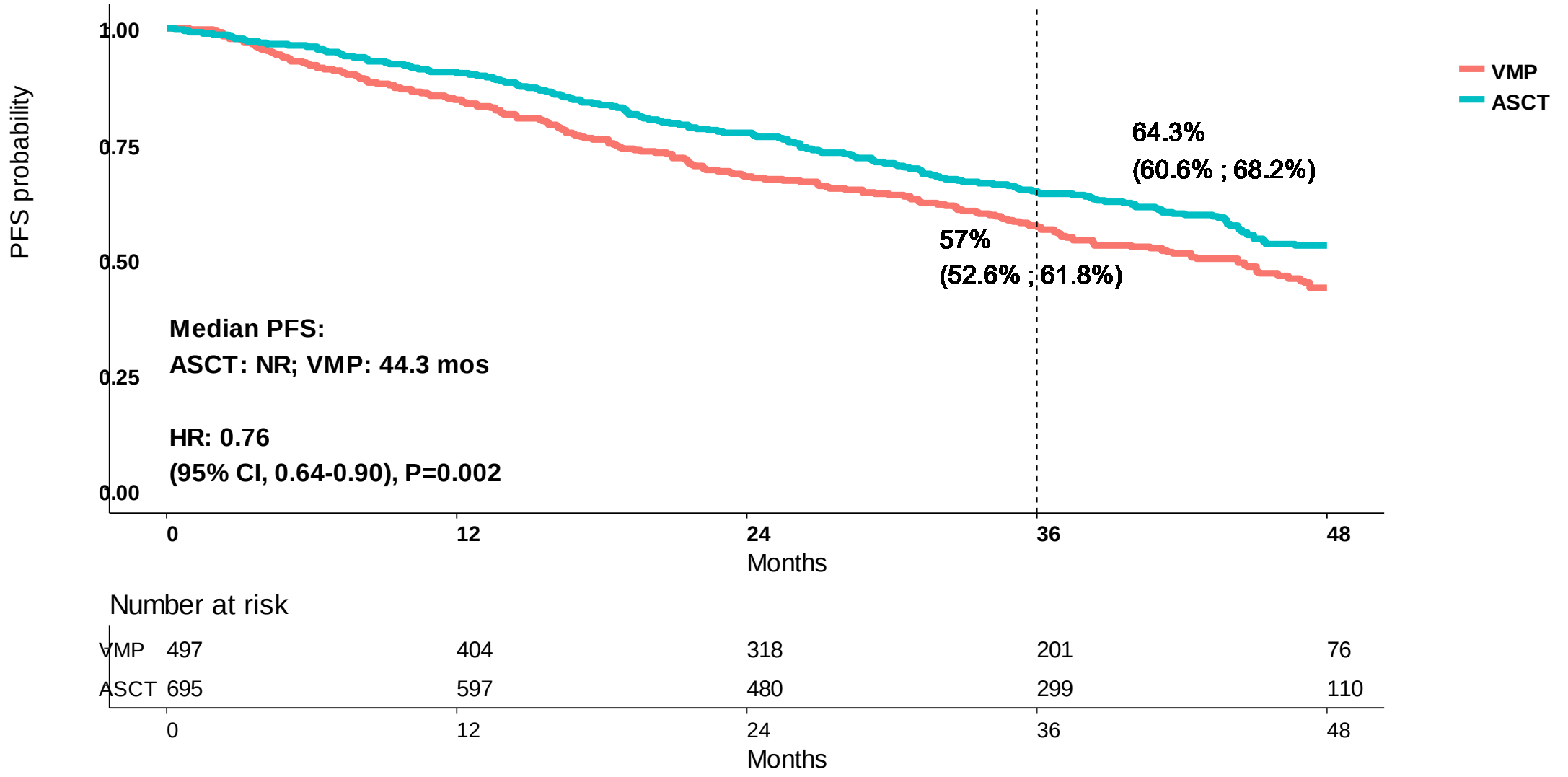
IFM 2009
EMN02

EMN02/HO95 MM Trial: Study Design



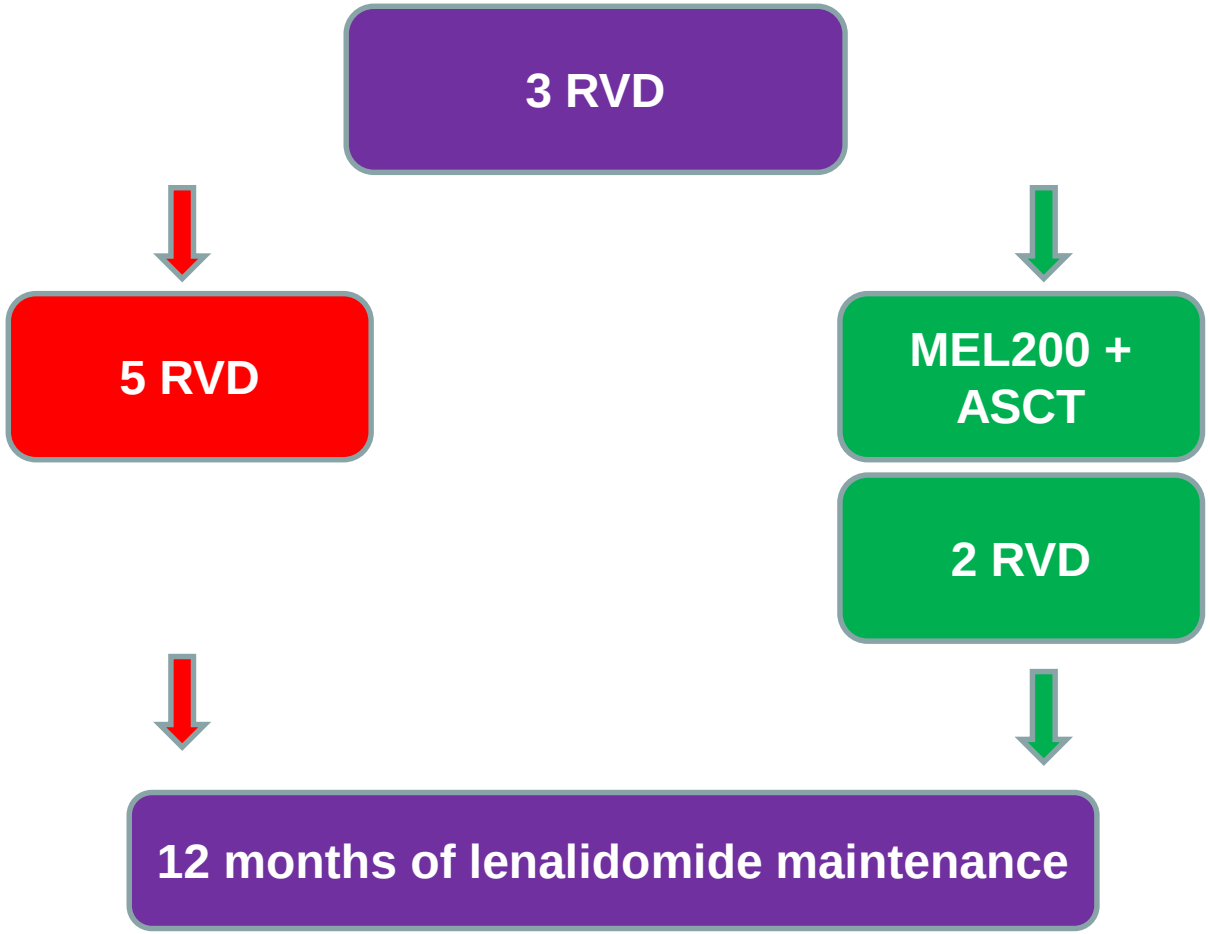
Cavo. ASH 2017. Abstr 401.

PFS by randomization (VMP *vs* ASCT)

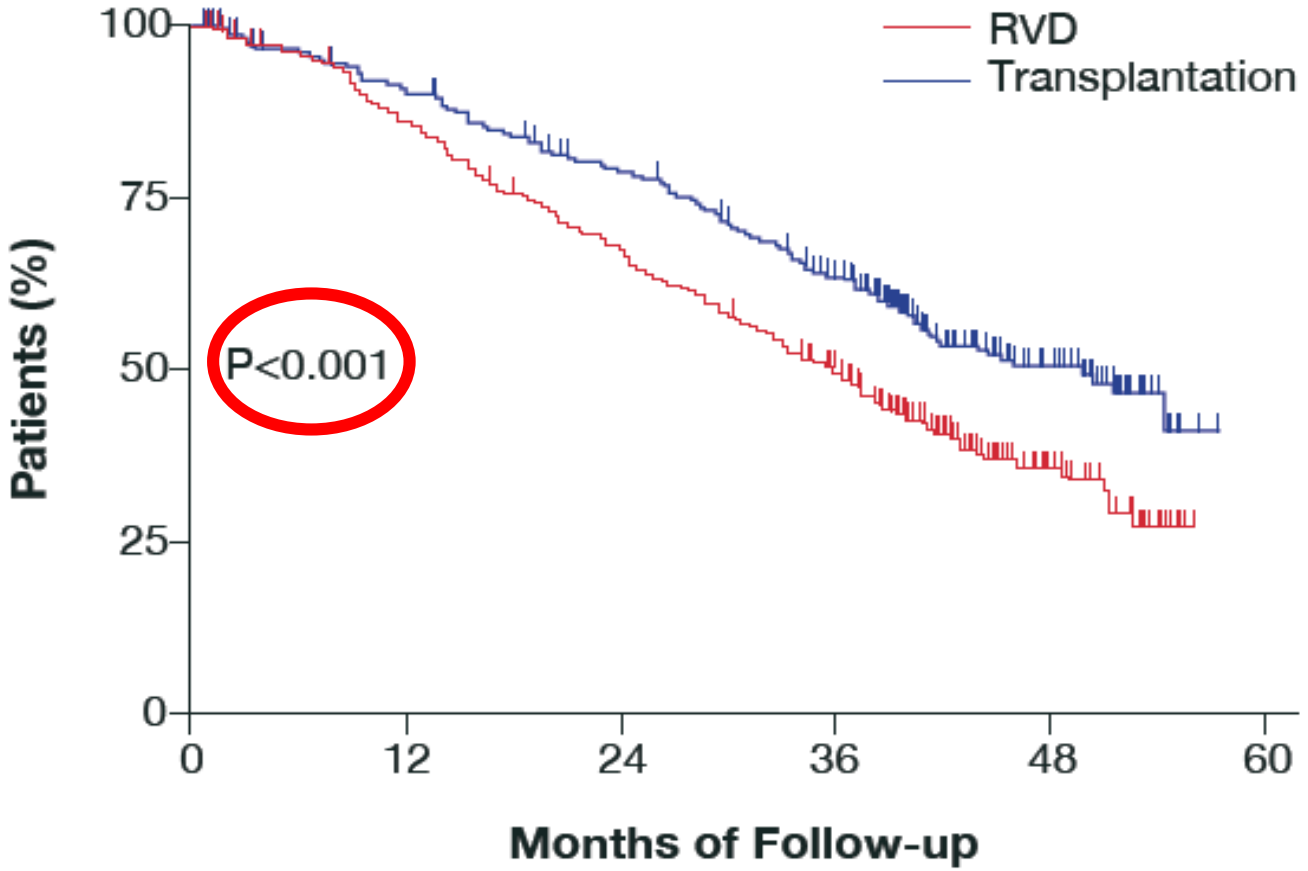


Cavo. ASH 2017. Abstr 401.

IFM DFCI 2009 Trial
700 patients < 66y,
Newly diagnosed symptomatic MM



Attal. NEJM. 2017;376:1311.



No. at Risk						
RVD	350	294	228	157	32	0
Transplantation	350	308	264	196	50	0

PROGRESSION-FREE SURVIVAL

Attal. NEJM. 2017;376:1311.

IFM 2009: PFS, Prognostic Factors

	Multivariate Analysis aHR	*P* Value
Treatment arm (B/A)	0.80	0.02
ISS II vs I III vs I	1.33 1.45	0.02 0.01
FISH (high risk/standard)	2.22	< 0.001
CR	0.58	< 0.001
MRD (FCM)	0.39	< 0.001

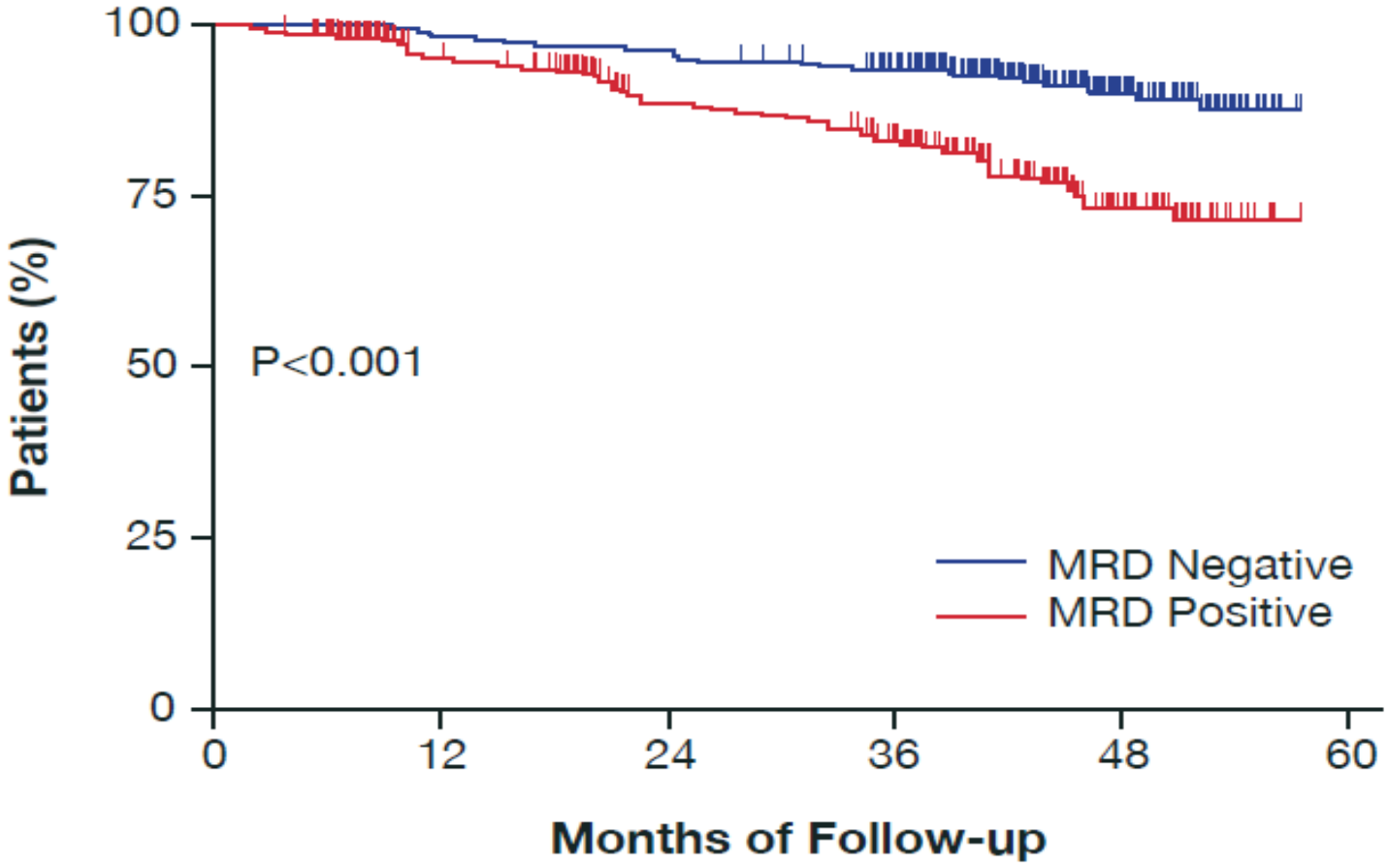
Attal. NEJM. 2017;376:1311.

IFM 2009: Best Response.

	RVD group N=350	Transplant group N=350	p-value
CR	48%	59%	
VGPR	29%	29%	0.004
PR	20%	11%	
<PR	3%	2%	
At least VGPR	77%	88%	<0.001
MRD neg by FCM , n (%)	171/265 (65%)	220/278 (80%)	<0.001

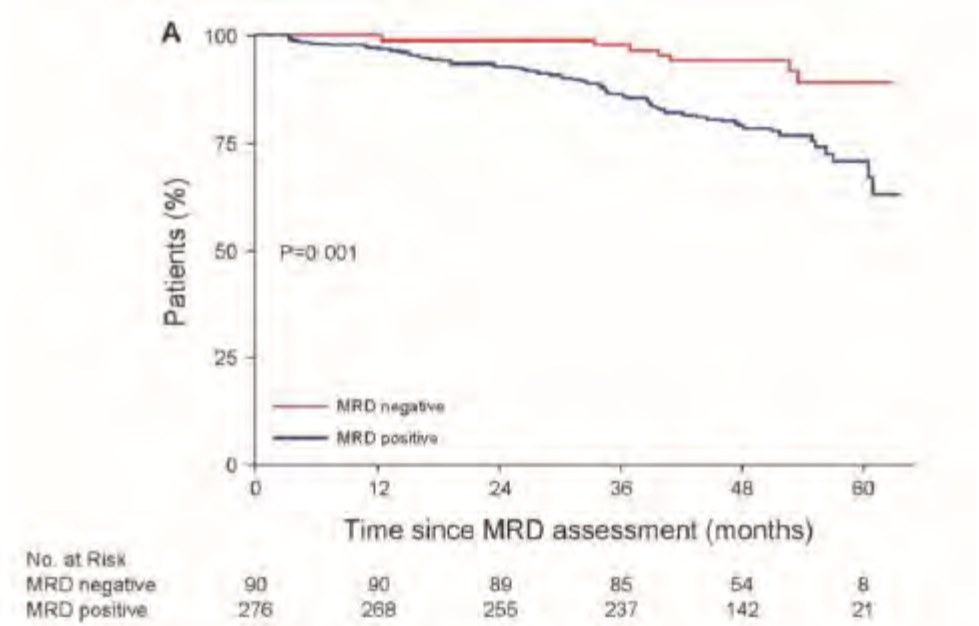
IFM/DFCI 2009: OS According to MRD (FCM) (9/2015)

S2B

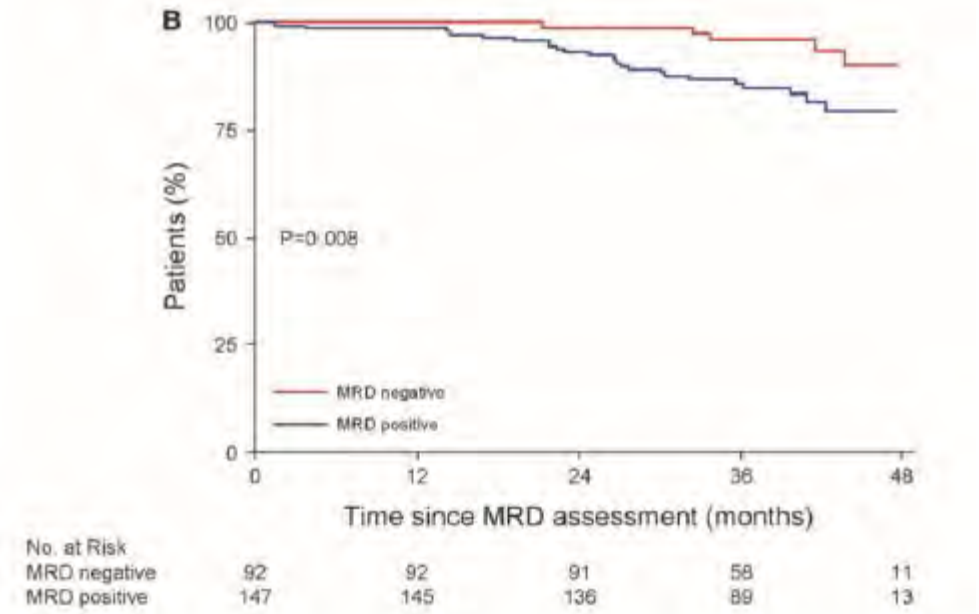


No. at Risk

MRD Negative	0	311	379	347	119	0
MRD Positive	700	358	259	227	65	0



Overall survival
at the start of maintenance
NGS, 10^{-6}



Overall survival
after 12 months of maintenance
NGS, 10^{-6}

Perrot. Blood. 2018;[Epub].

Role of Induction

- Fast control of the disease

- Achieve high response rates (MRD neg?)

- Minimal toxicity

- Allow adequate stem cell harvest

VTD and VCD are widely used in Europe

VRD in US, less toxic, as effective : future in Europe following approval of Len ?

→ easily up to 6 cycles

blood
2012 120: 1589-1596
Prepublished online July 12, 2012;
doi:10.1182/blood-2012-02-408922

Superiority of bortezomib, thalidomide, and dexamethasone (VTD) as induction pretransplantation therapy in multiple myeloma: a randomized phase 3 PETHEMA/GEM study

Laura Rosiñol, Albert Oriol, Ana Isabel Teruel, Dolores Hernández, Javier López-Jiménez, Javier de la Rubia, Miquel Granell, Joan Besalduch, Luis Palomera, Yolanda González, Mª Asunción Etxebeste, Joaquín Díaz-Mediavilla, Miguel T. Hernández, Felipe de Arriba, Norma C. Gutiérrez, Mª Luisa Martín-Ramos, Mª Teresa Cibeira, Mª Victoria Mateos, Joaquín Martínez, Adrián Alegre, Juan José Lahuerta, Jesús San Miguel and Joan Bladé

Table 2. Response rate to induction therapy according to treatment arm

6 cycles of VTD

	QT + V, n = 129	TD, n = 127	VTD, n = 130
CR, %	21*	12*	35*
VGPR, %	15	15	25
PR, %	39	33	25
SD, %	12	12	6
PD, %	12†	23	7‡
Early deaths, %	1	1	2

60%

*VTD vs QT + V, *P* = .01; VTD vs TD, *P* = .0001. †QT + V vs TD, *P* = .02. ‡VTD vs TD, *P* = .0004.

Median number of CD34+ cells : 3.8×10^6/kg

Rosiñol. Blood. 2012;120:1589.

Pethema/GEM Phase 3 Study: VRD-GEM Induction 6 Cycles (N=455 Patients)

Response, n (%)	Overall 455 (100%)
Complete response (CR + sCR)	**176 (39)**
VGPR	**133 (29)**
MRD negative, NGF, 3 x 10^{-6}, n = 320	**35%**
PR	77 (17)
Stable disease	30 (6)
Progressive disease	30 (6)
Non-evaluable	12 (3)
Early death	7 (1.5)
Overall response rate	**386 (85)**

68%

Median number of CD34+ cells (3 cycles) : 4.66x10^6/kg

Rosiñol. ASH 2017. Abstr 130.

Abstract 3245; Poster
Dec. 2, 6:00 PM
Rosinol et al

Toxicity

	VTD, n = 130 Grade 3-4 %	VRD, n= 455 Grade 3-4 %
Neutropenia	10	11
Thrombocytopenia	8	6
Peripheral neuropathy		
Grade 2	46	13
Grade 3	12	1
Grade 4	2	0
Discontinuation during induction		
Toxicity	7	2
Disease progression	7	6
Death	2	1.5

Rosiñol. Blood. 2012;120:1589. Rosiñol. ASH 2017. Abstr 130.

Kinetics of Response According to MRD, NGF/Euroflow (n=320), 10^{-6}

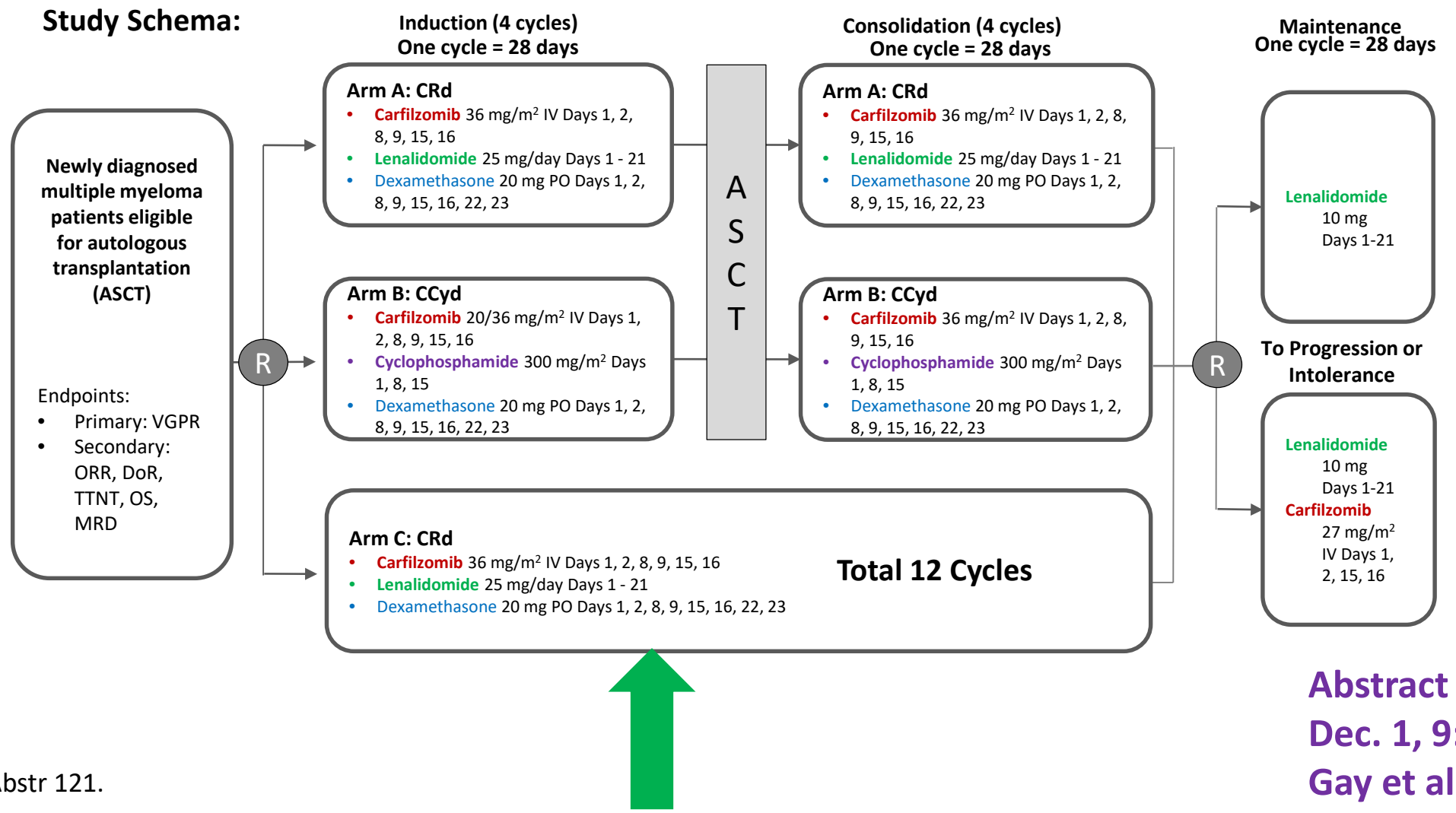
	Induction (VRDx6)	HDT/ASCT	Consolidation (VRDx2)
MRD negative	35%	54%	58%
MRD positive	65%	46%	42%

Paiva. ASH 2017. Abstr 905.

How to improve ?

Future …

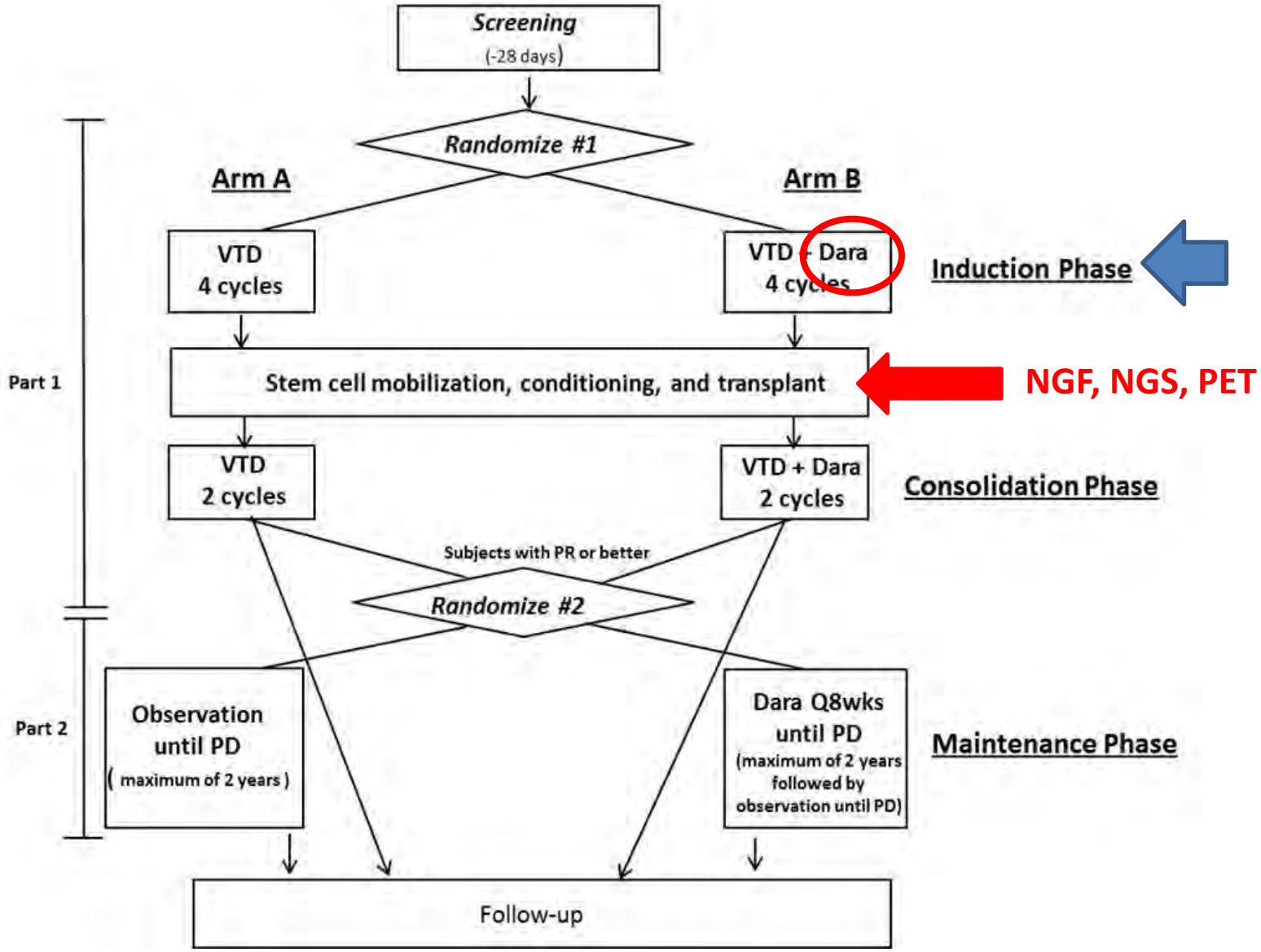
Forte: KRd Study Design (Gimema)



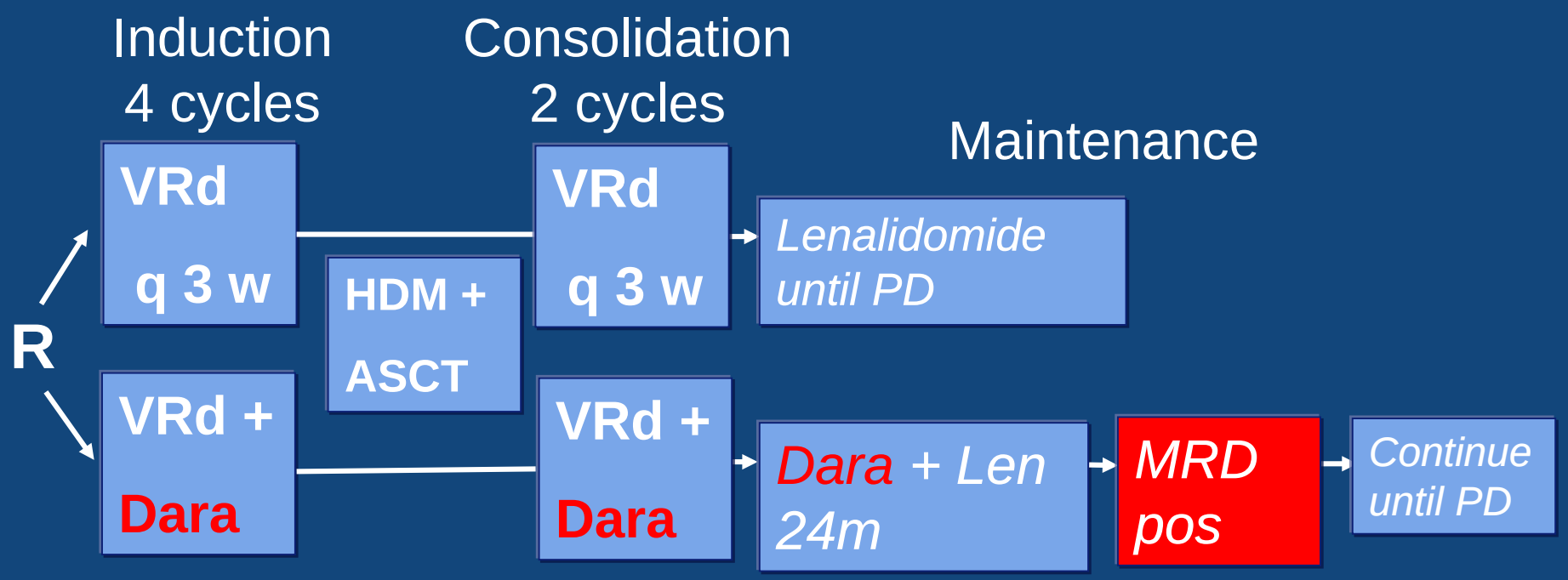
Abstract 121; Oral
Dec. 1, 9:30 AM
Gay et al

Gay. ASH 2018. Abstr 121.

CASSIOPEIA – 1080 Patients – ASCO 2019



Daratumumab-VRd Trial in Transplant-Eligible NDMM
EMN017/HOVON158/MMY3014 Registration Trial



Primary endpoint: PFS
Secondary endpoint: MRD 10^{-5} by NGS after consolidation

Perseus, PI, P.Sonneveld

Role of Consolidation

- Short duration after ASCT

- Increased the depth of response (MRD neg)

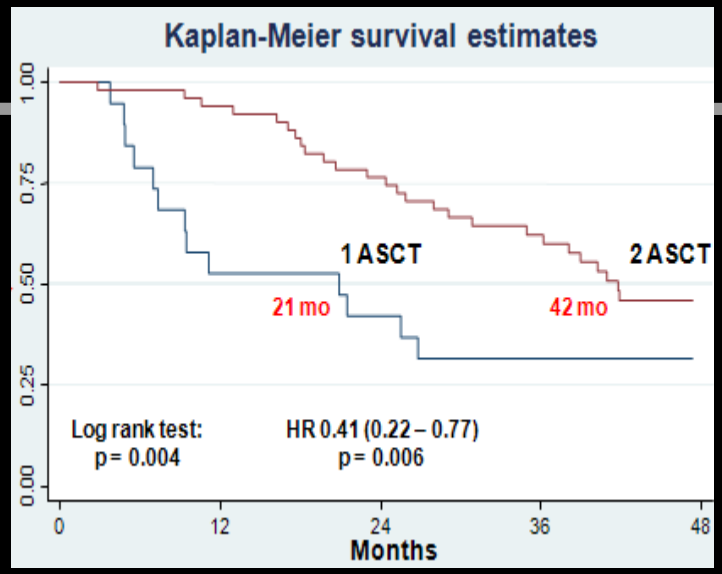
- Reduced toxicity allowing maintenance

Tools and Issues

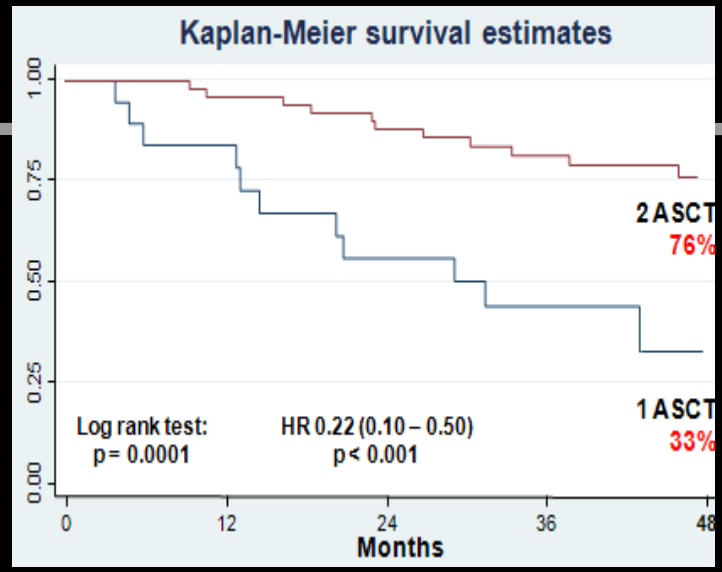
- Novel-agent based
- Second (tandem) ASCT

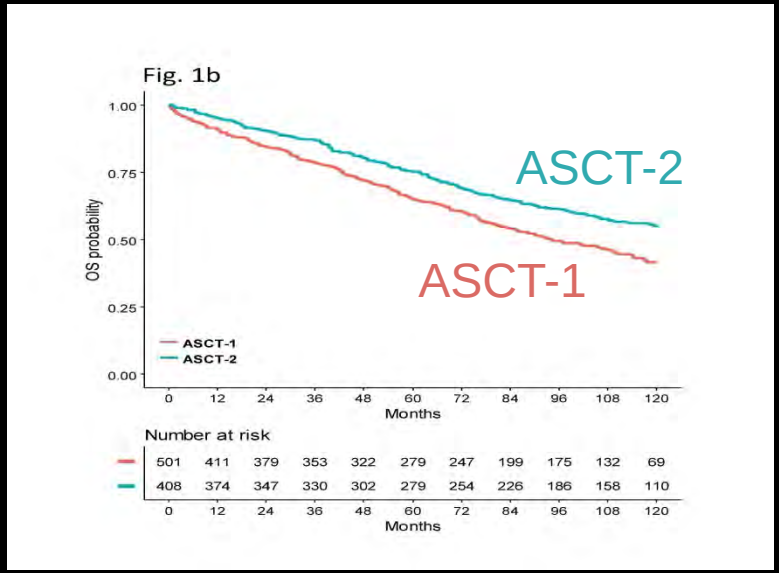
- Necessary?
- Best one?
- Optimal duration?

Double vs Single ASCT After Bortezomib-Based Induction



Cavo et al. ASH 2013
Abstract 767.

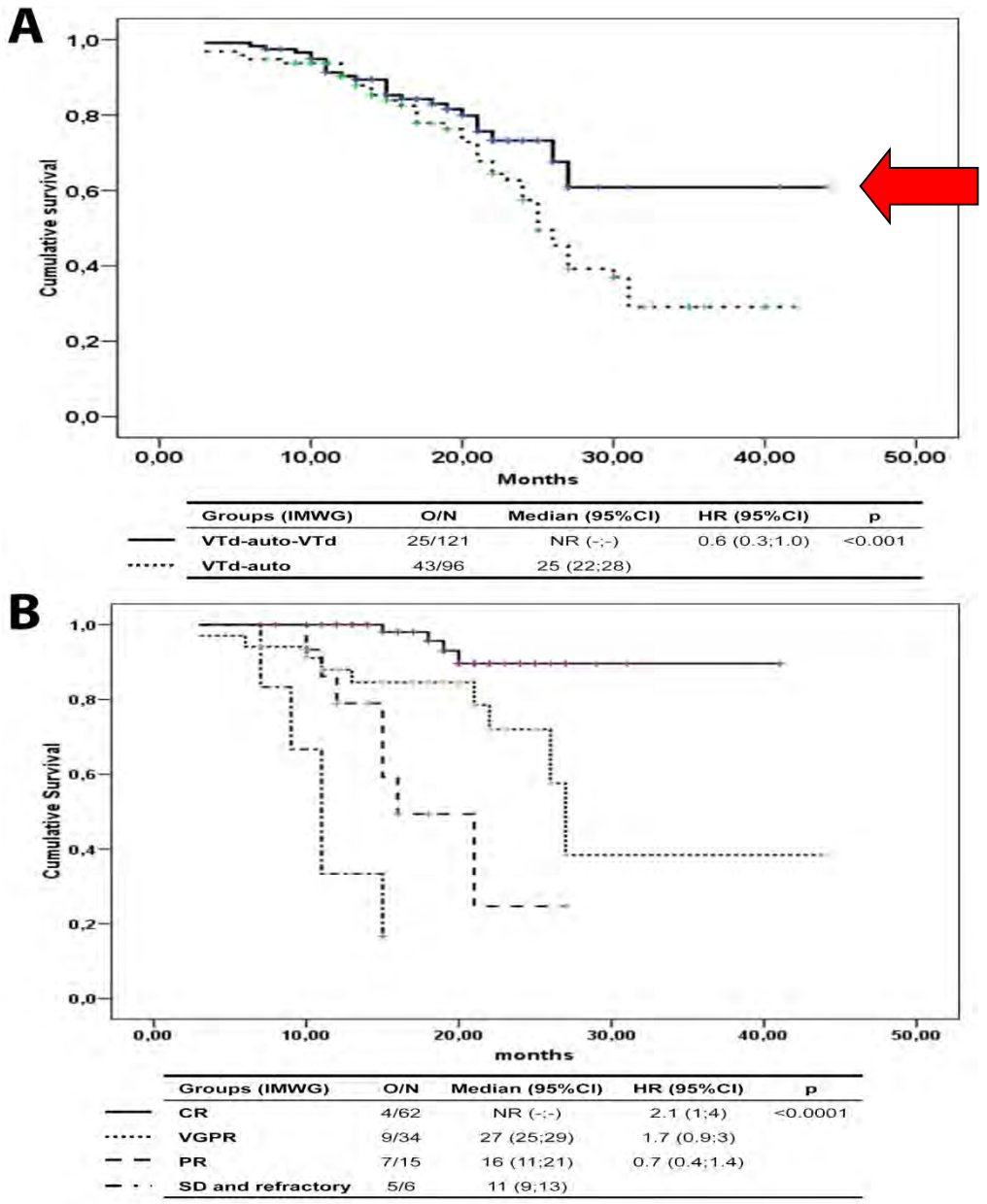




Cavo et al. ASH 2018
Abstract 124
Saturday, December 1, 2018: 9:30 AM

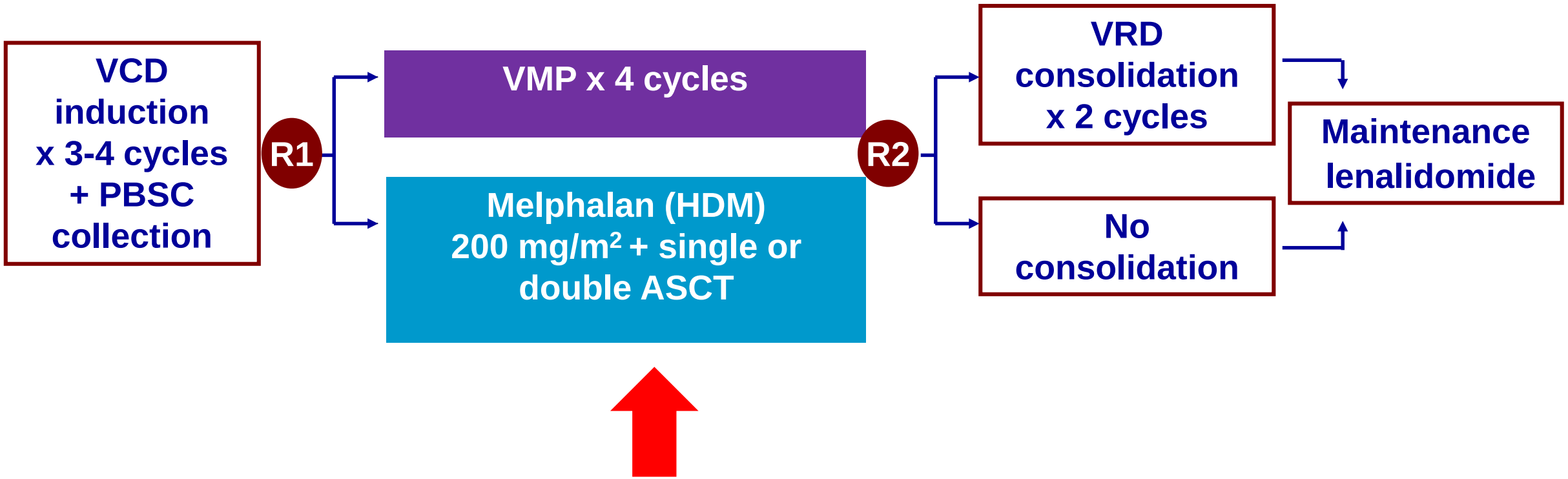
Retrospective trial
217 patients

VTD – auto
vs
VTD – auto - VTD



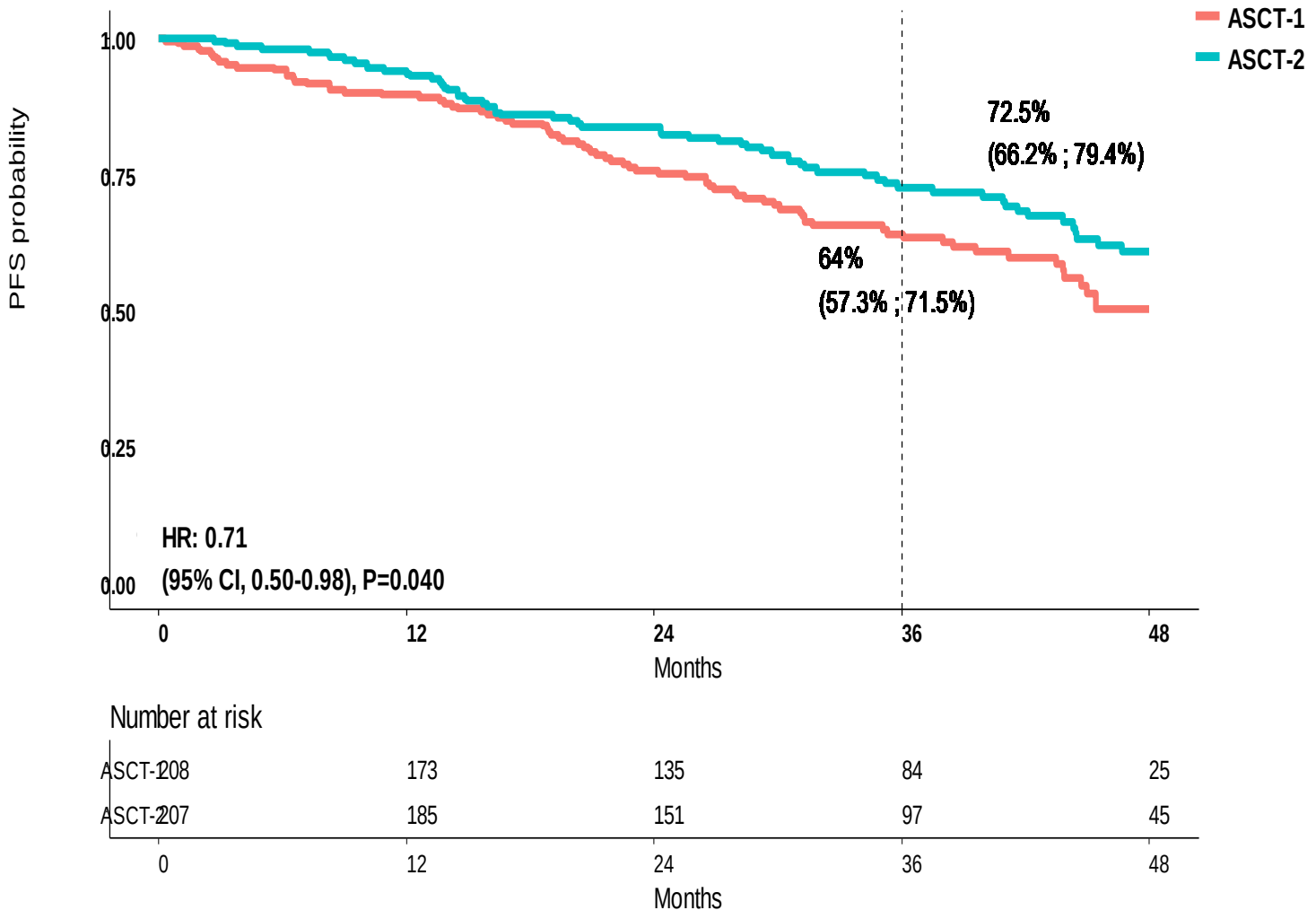
Leleu X, Moreau P. Leukemia 2013;27:2242.

EMN02/HO95 MM Trial: Study Design



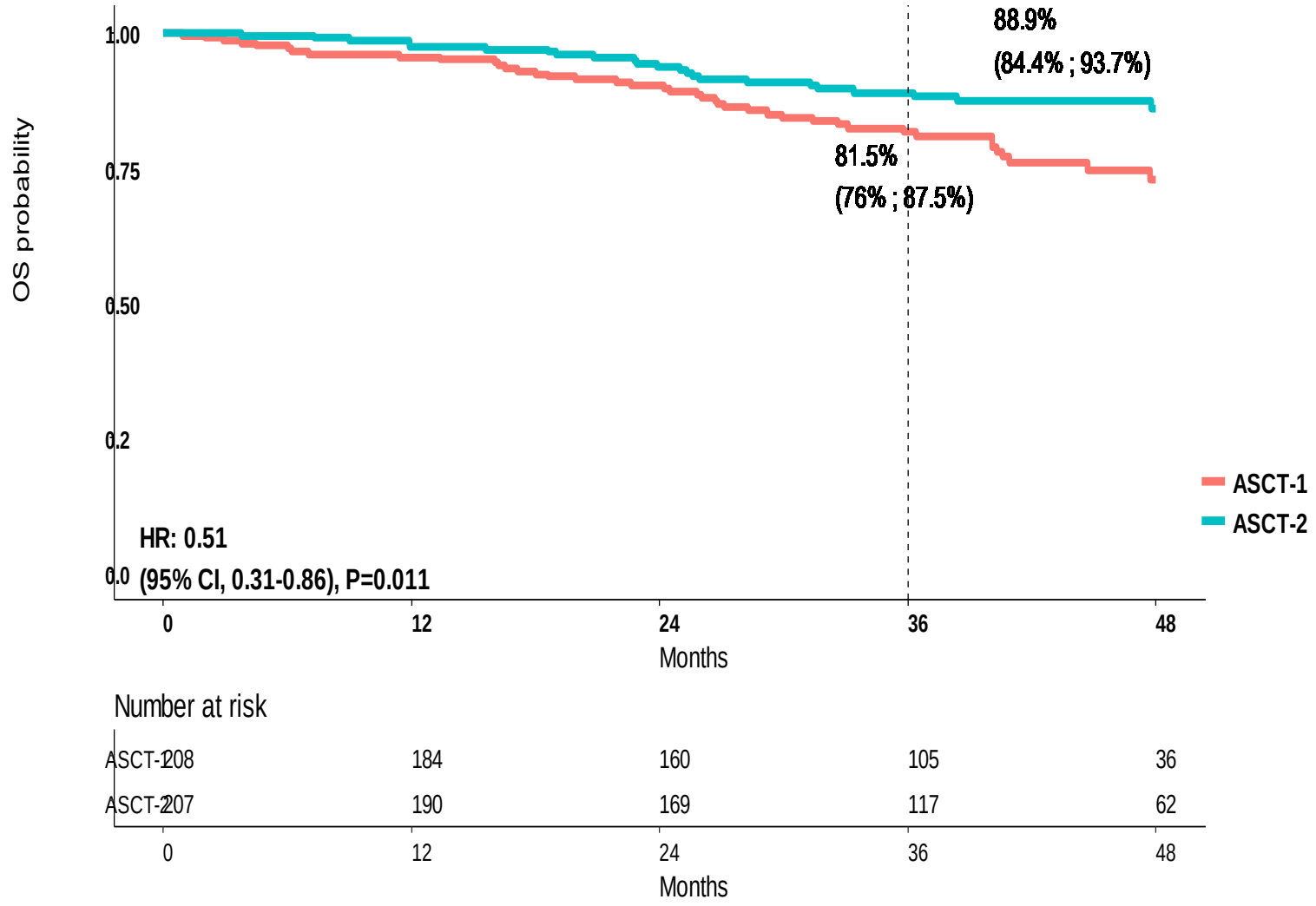
Cavo. ASH 2017. Abstr 401.

PFS by Randomization (ASCT-1 *vs* ASCT-2)



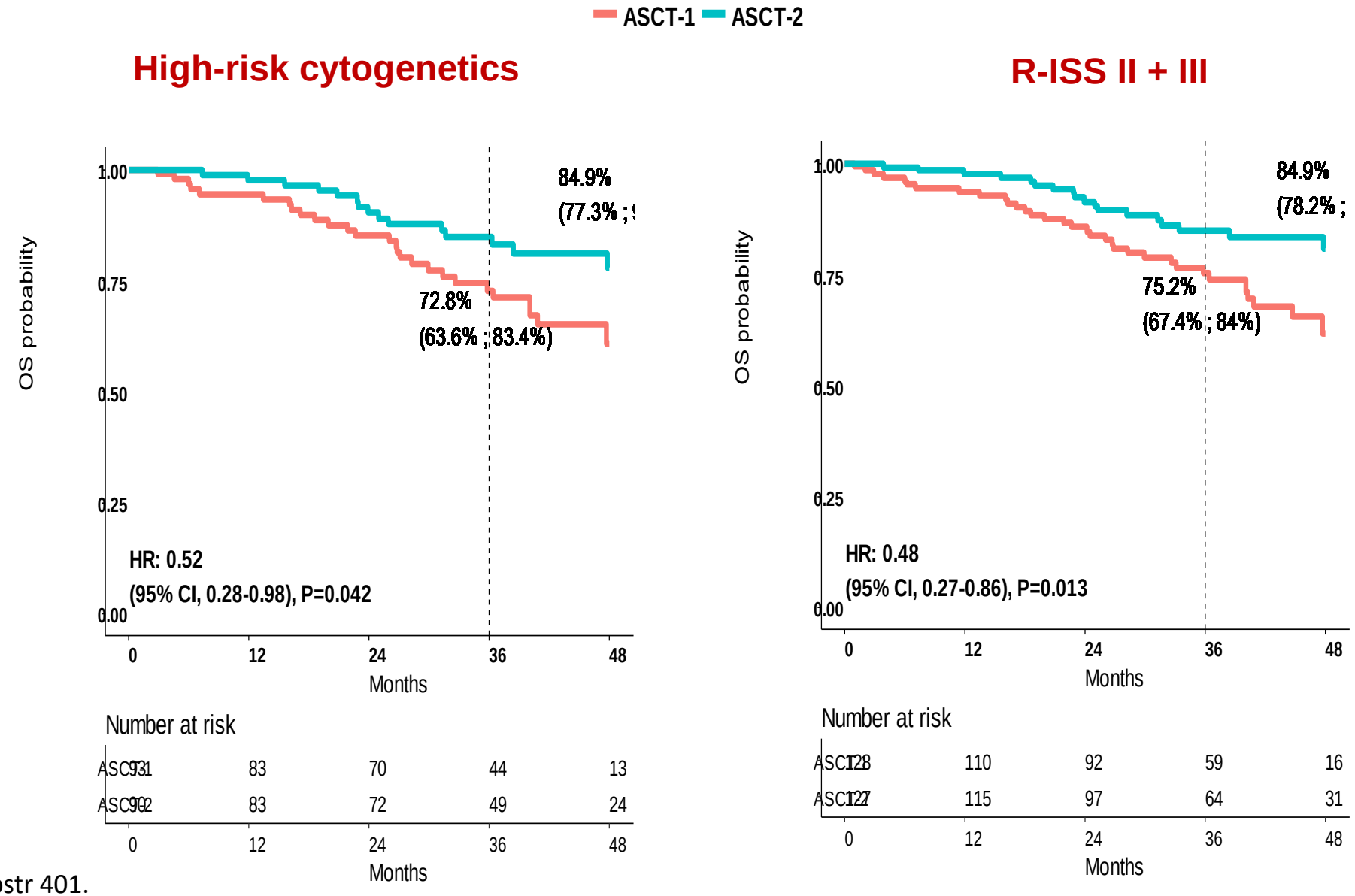
Cavo. ASH 2017. Abstr 401.

OS by Randomization (ASCT-1 *vs* ASCT-2)



Cavo. ASH 2017. Abstr 401.

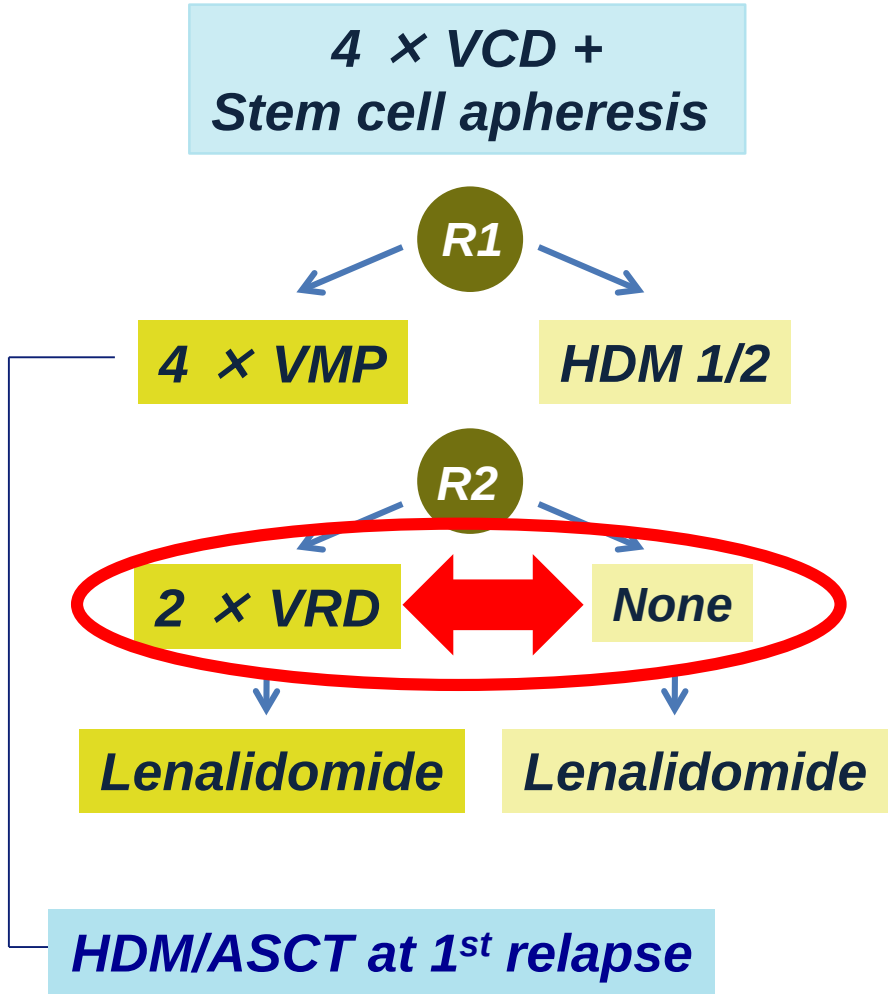
OS by Randomization in High-Risk Subgroups



Cavo. ASH 2017. Abstr 401.

Sonneveld et al. ASH 2016. Abstr 242.

Design of EMN02 Trial



Registration
Induction

Early or late ASCT, once or twice

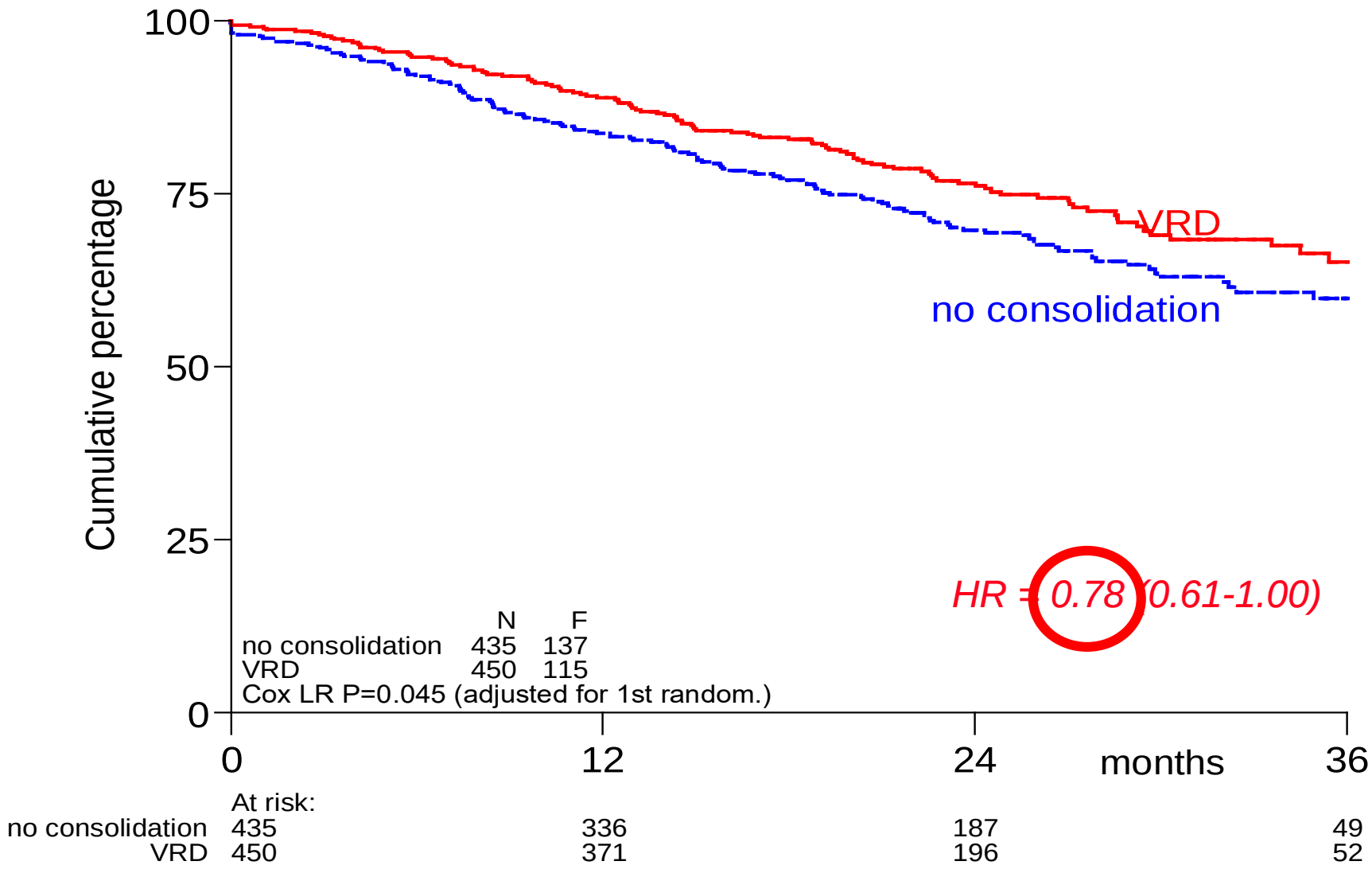
MRD

Consolidation

Maintenance until relapse

https://clinicaltrials.gov/ct2/show/NCT01208766 [Accessed March 2015]

Progression-Free Survival



EMN02 / HO95 MM

Sonneveld. ASH 2016. Abstr 242.

Kinetics of Response According to MRD, NGF/Euroflow (n=320), 10^{-6}

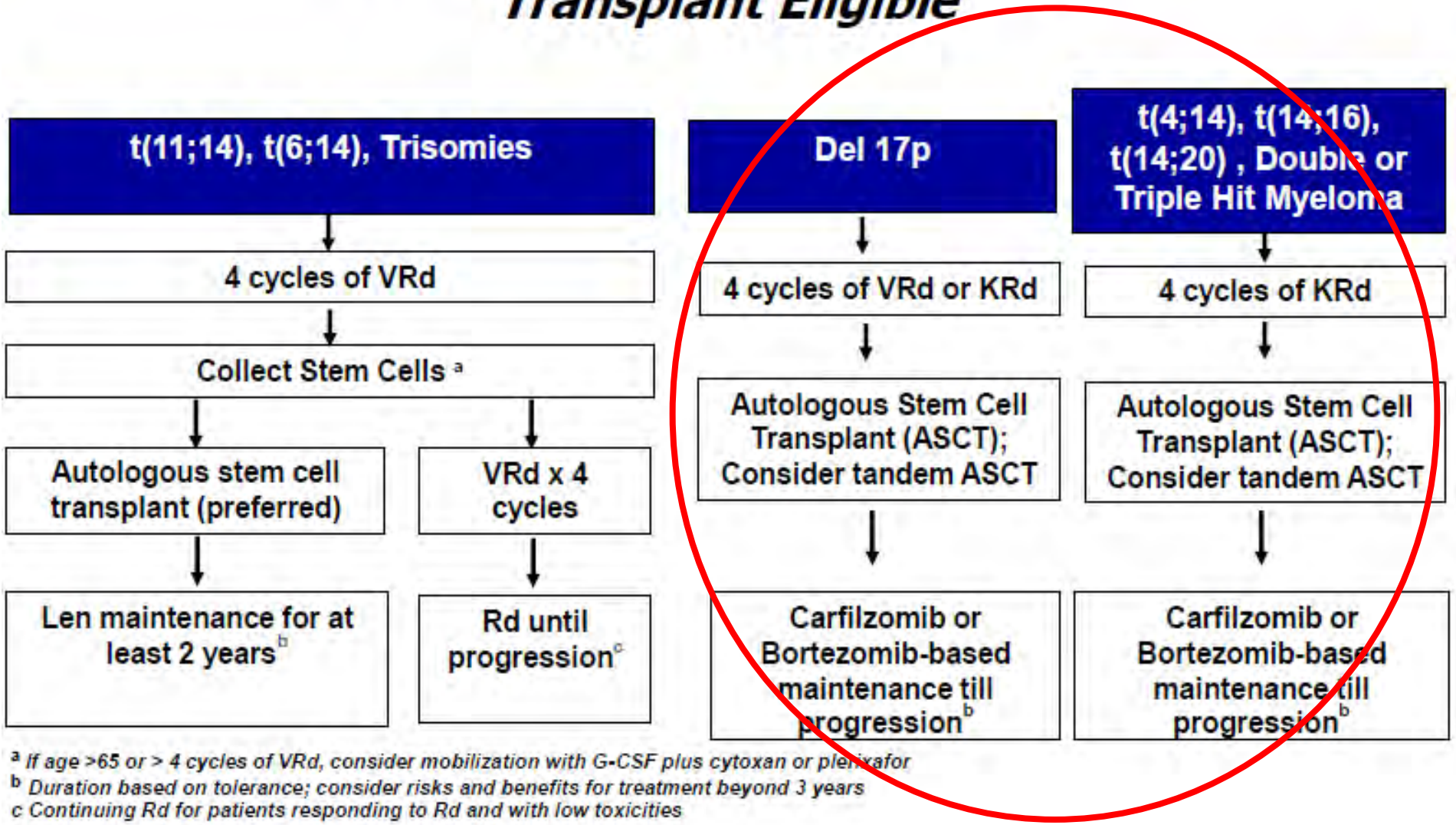
	Induction (VRDx6)	HDT/ASCT	Consolidation (VRDx2)
MRD negative	35%	54%	58%
MRD positive	65%	46%	42%

Paiva. ASH 2017. Abstr 905.

MAYO CLINIC

mSMART – Off-Study

Transplant Eligible



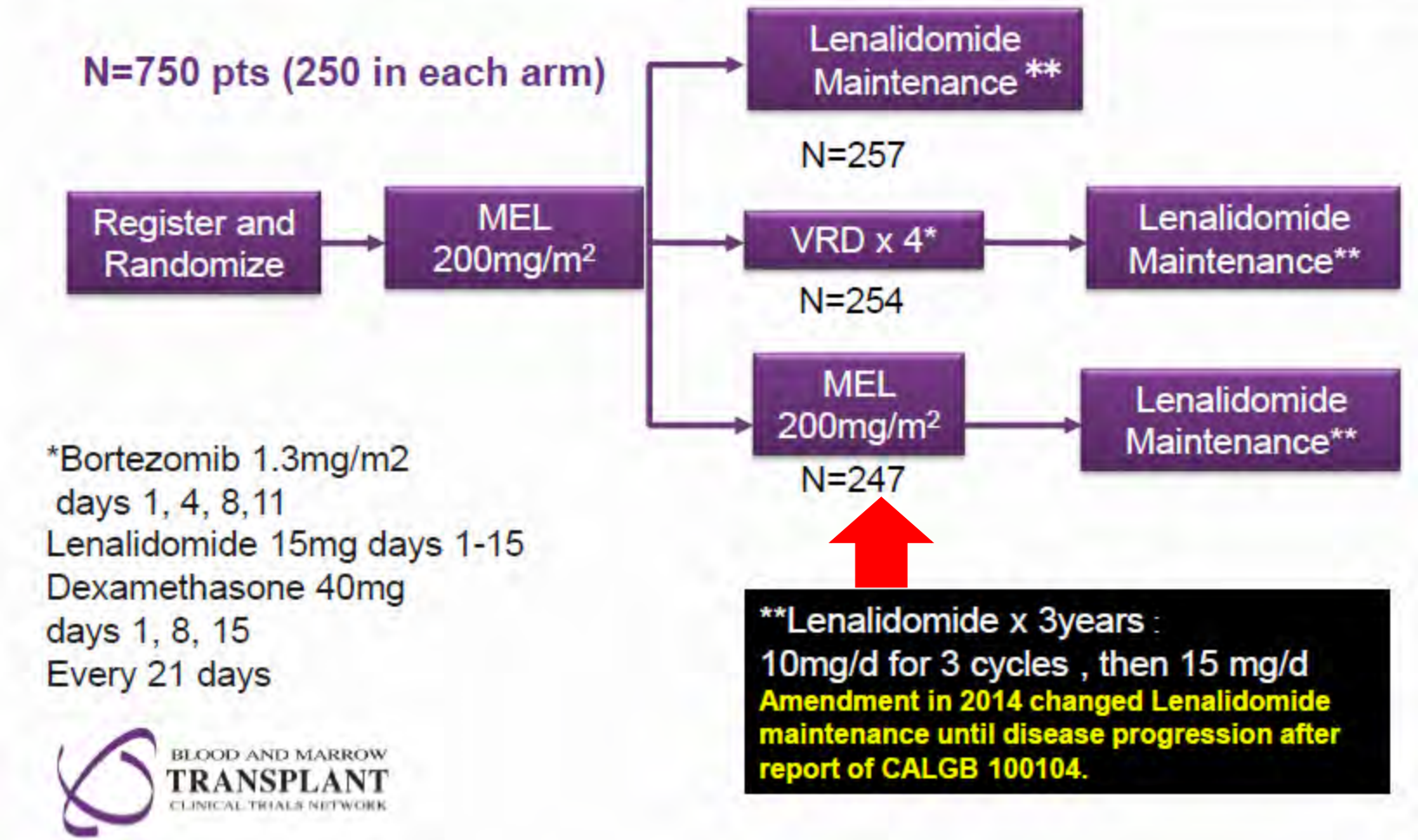
[a] *If age >65 or > 4 cycles of VRd, consider mobilization with G-CSF plus cytoxan or plerixafor*

[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. 2007;82:323; Kumar. Mayo Clin Proc. 2009;84:1095; Mikhael. Mayo Clin Proc. 2013;88:360.

BMT CTN 0702 Stem Cell Transplantation for Multiple Myeloma Incorporating Novel Agents: SCHEMA



Stadtmauer. ASH 2016. Abstr LBA-1.

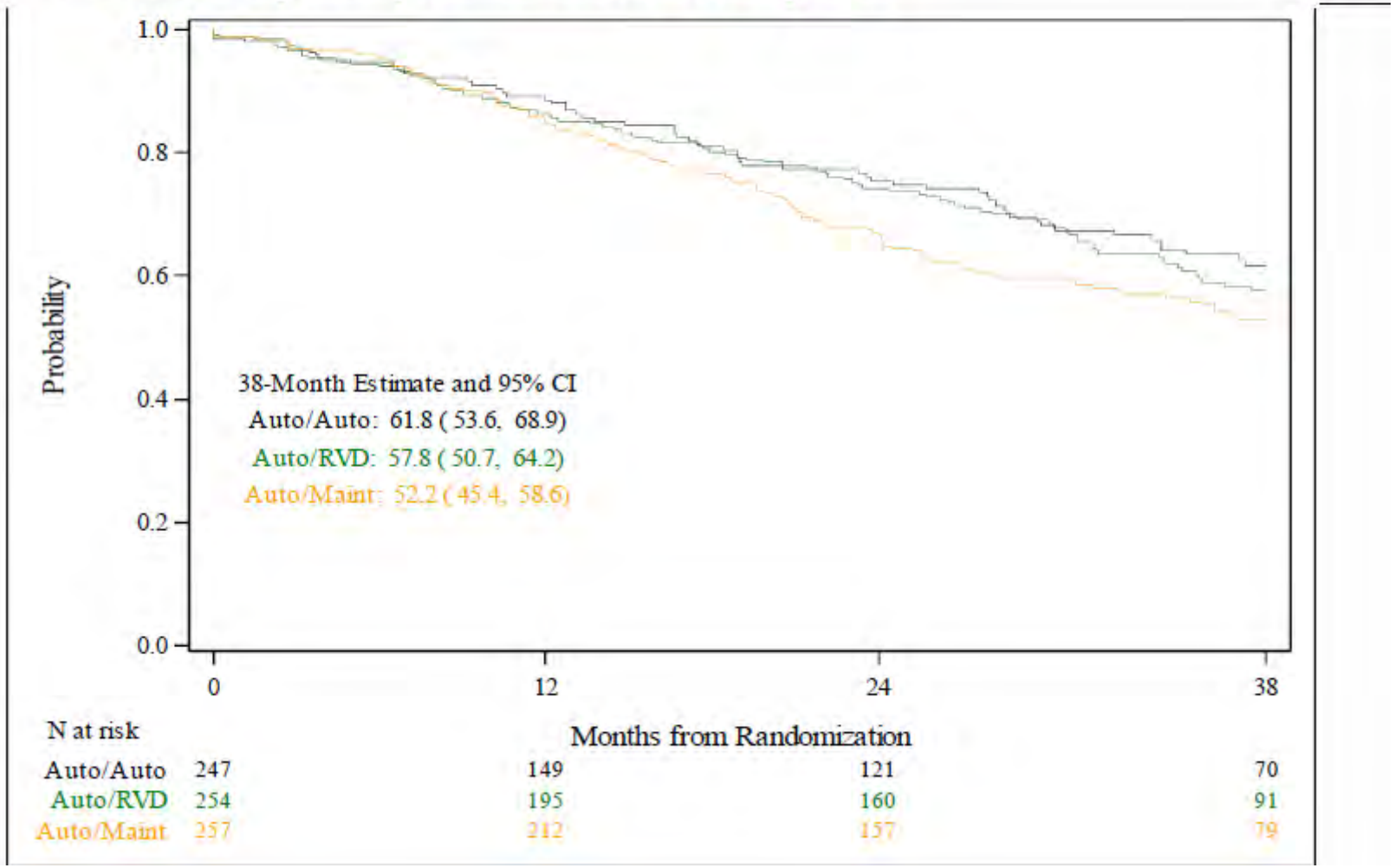
Compliance with each intervention

	Auto/Auto (N=247)		Auto/RVD (N=254)		Auto/Maint (N=257)	
	N	%	N	%	N	%
Received 2nd Intervention						
No	79	32.0	30	11.8	-	-
Yes	168	68.0	224	88.2	-	-
Started maintenance						
No	41	16.6	43	16.9	14	5.4
Yes	206	83.4	211	83.1	243	94.6

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Stadtmauer. ASH 2016. Abstr LBA-1.

Progression-Free Survival – as treated/per protocol Analysis



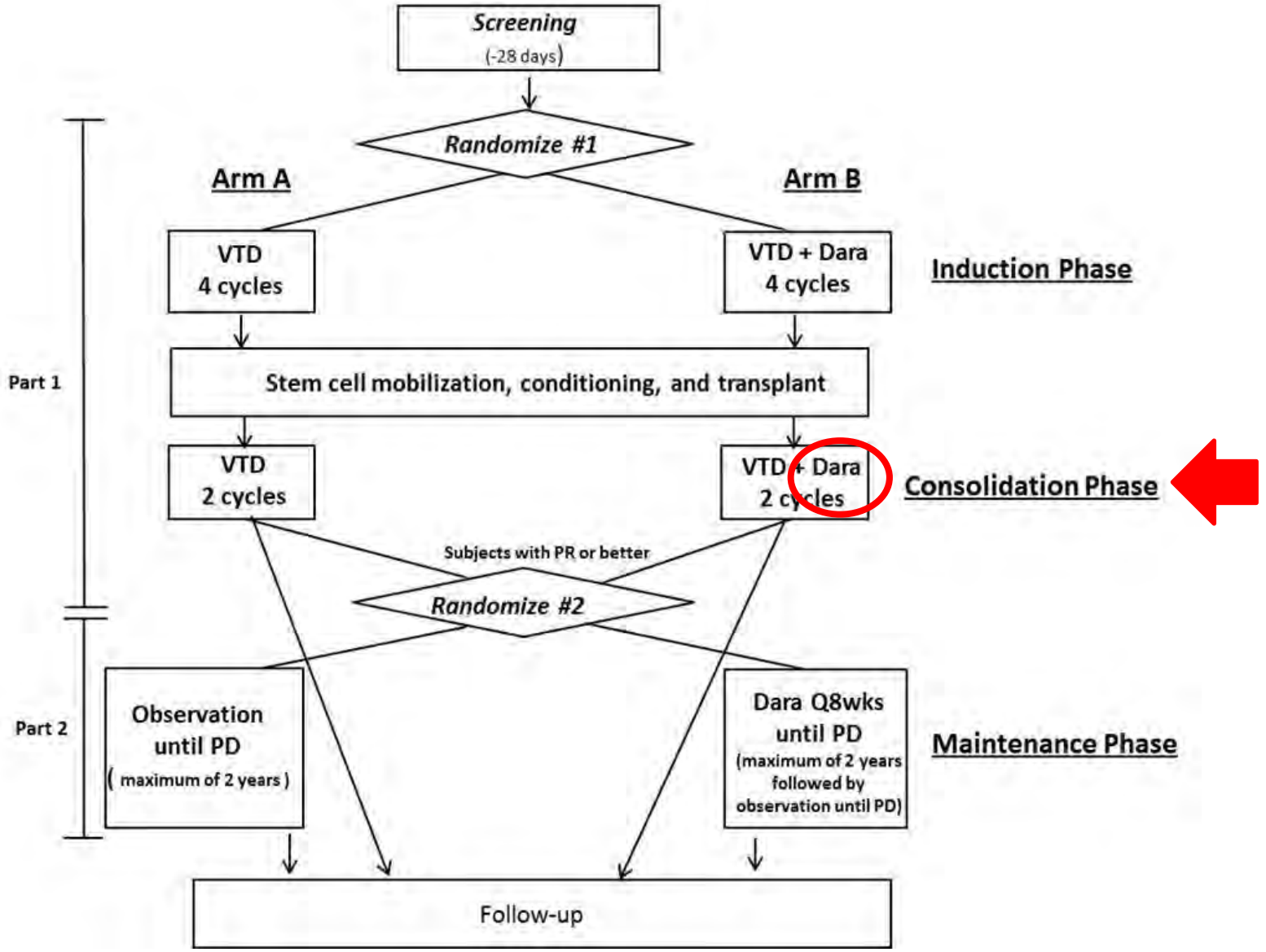
Stadtmauer. ASH 2016. Abstr LBA-1.

Consolidation

- Necessary?
- Best one?
- Optimal duration?

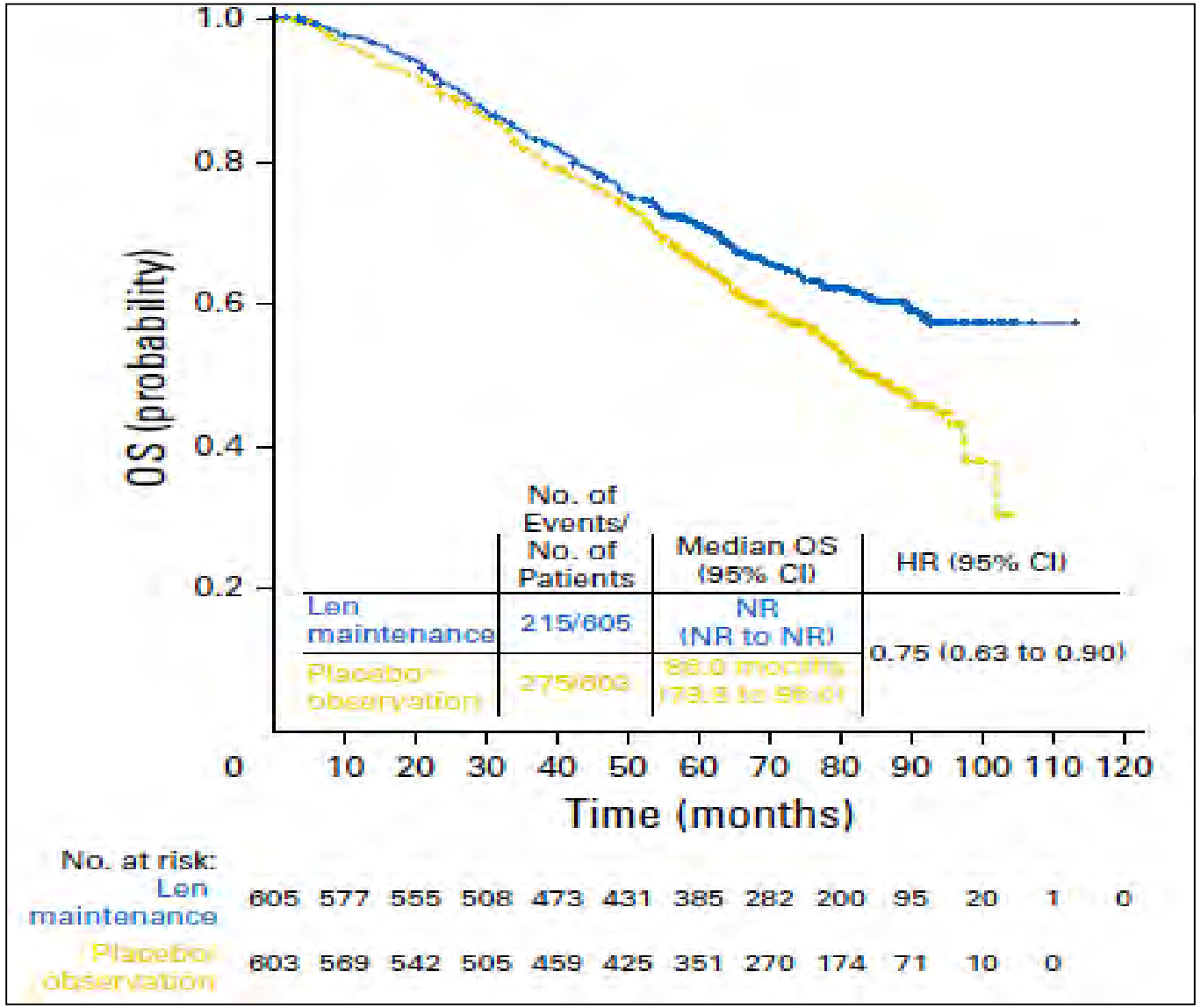
Tandem ASCT in high risk

CASSIOPEIA – 1080 Patients – ASCO 2019

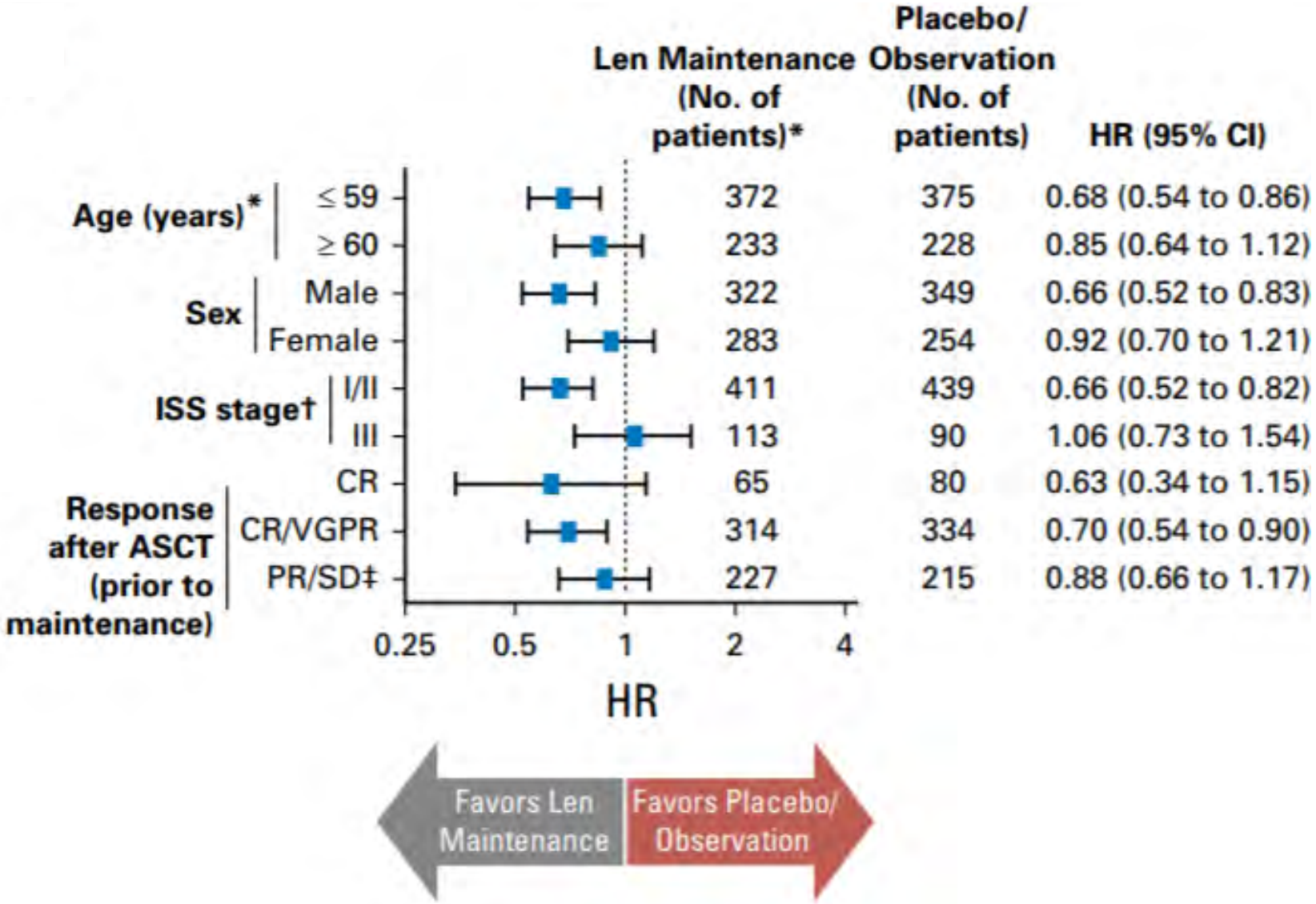


Sustained responses following ASCT are needed:

Impact of maintenance



McCarthy. J Clin Oncol. 2017;35:3279.

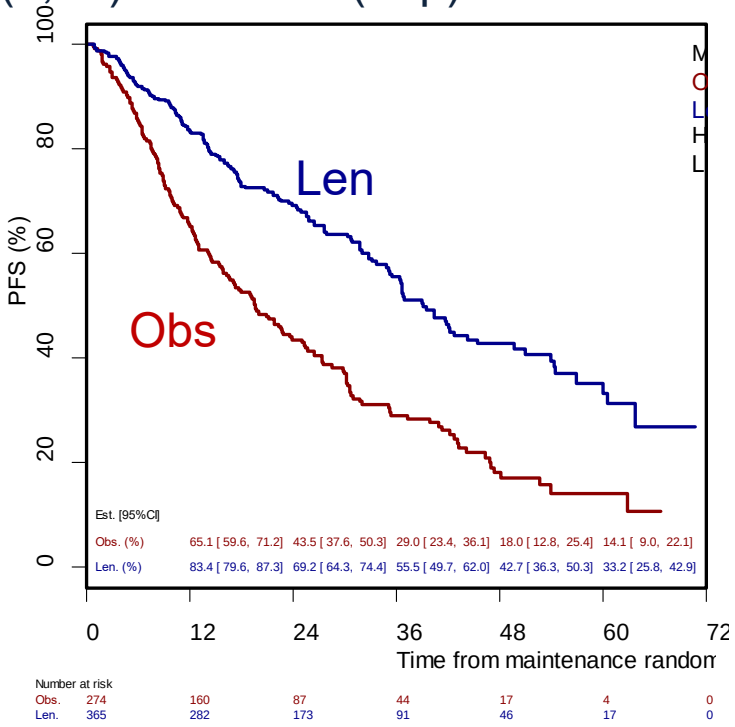


McCarthy. J Clin Oncol. 2017;35:3279.

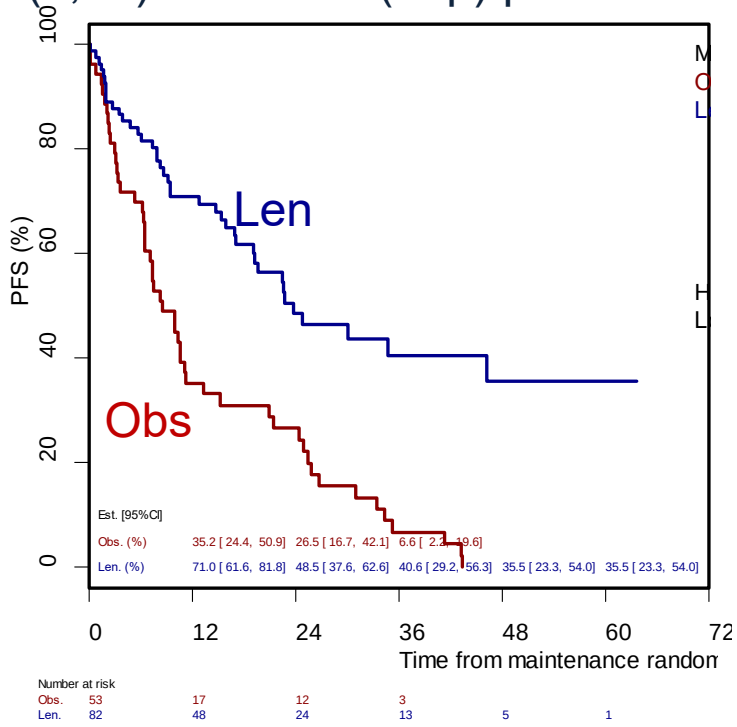
Cytogenetic risk groups

Lenalidomide improved PFS regardless of cytogenetic risk

t(4;14) and/or del(17p) absent: HR 0.50



t(4;14) and/or del(17p) present: HR 0.36

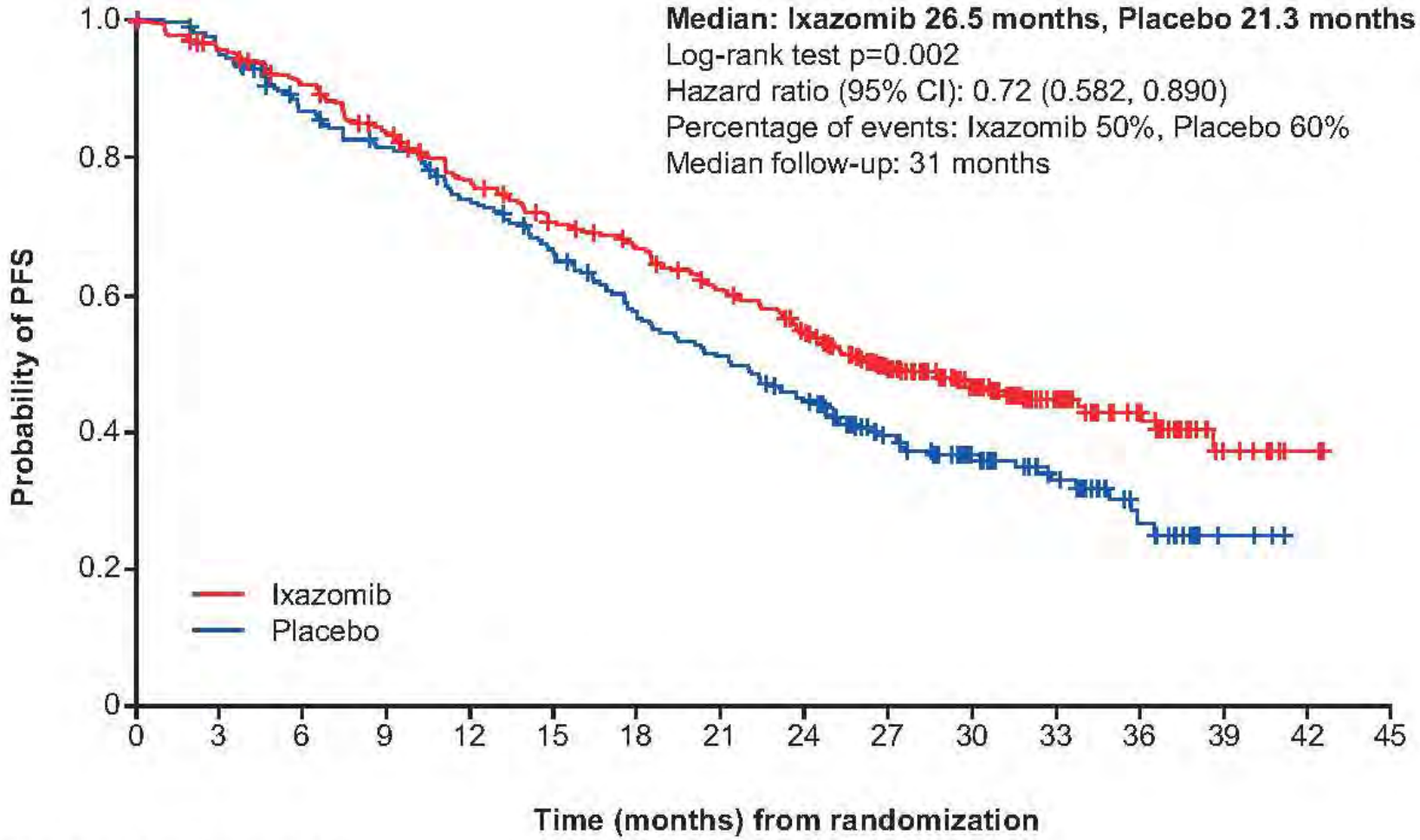


Jackson. ASH 2017. Abstr 436.

TOURMALINE MM-3

- Ixazomib vs placebo, phase 3
- In patients responding to ASCT
- Randomization 3:2
- 656 patients
- D1,8,15 in 28-day cycles
- Primary endpoint: PFS

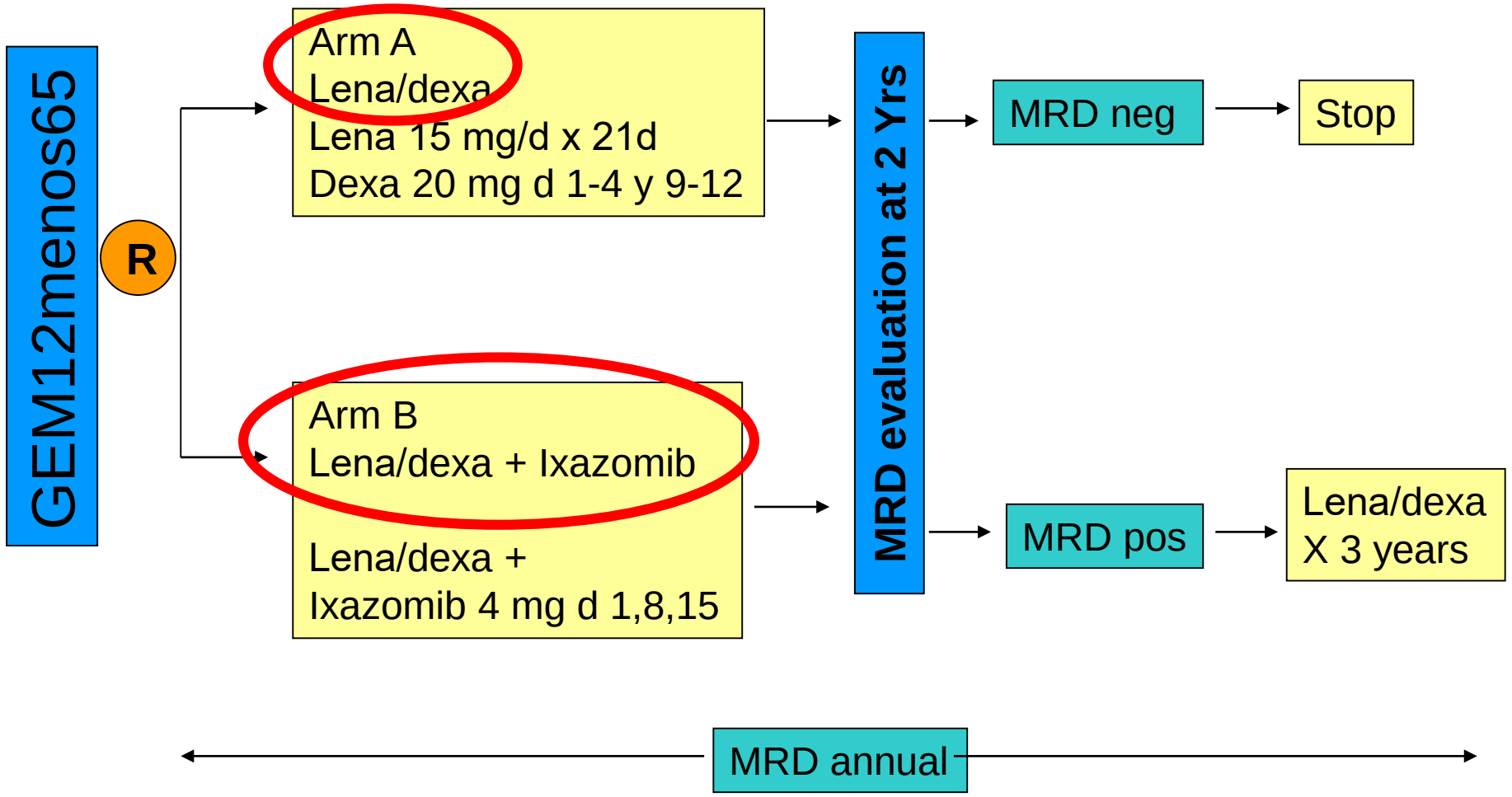
Dimopoulos. ASH 2018. Abstr 301; NCT02181413



Dimopoulos et al. ASH 2018; oral abstract 301. Sunday, December 2, 2018: 7:30 AM

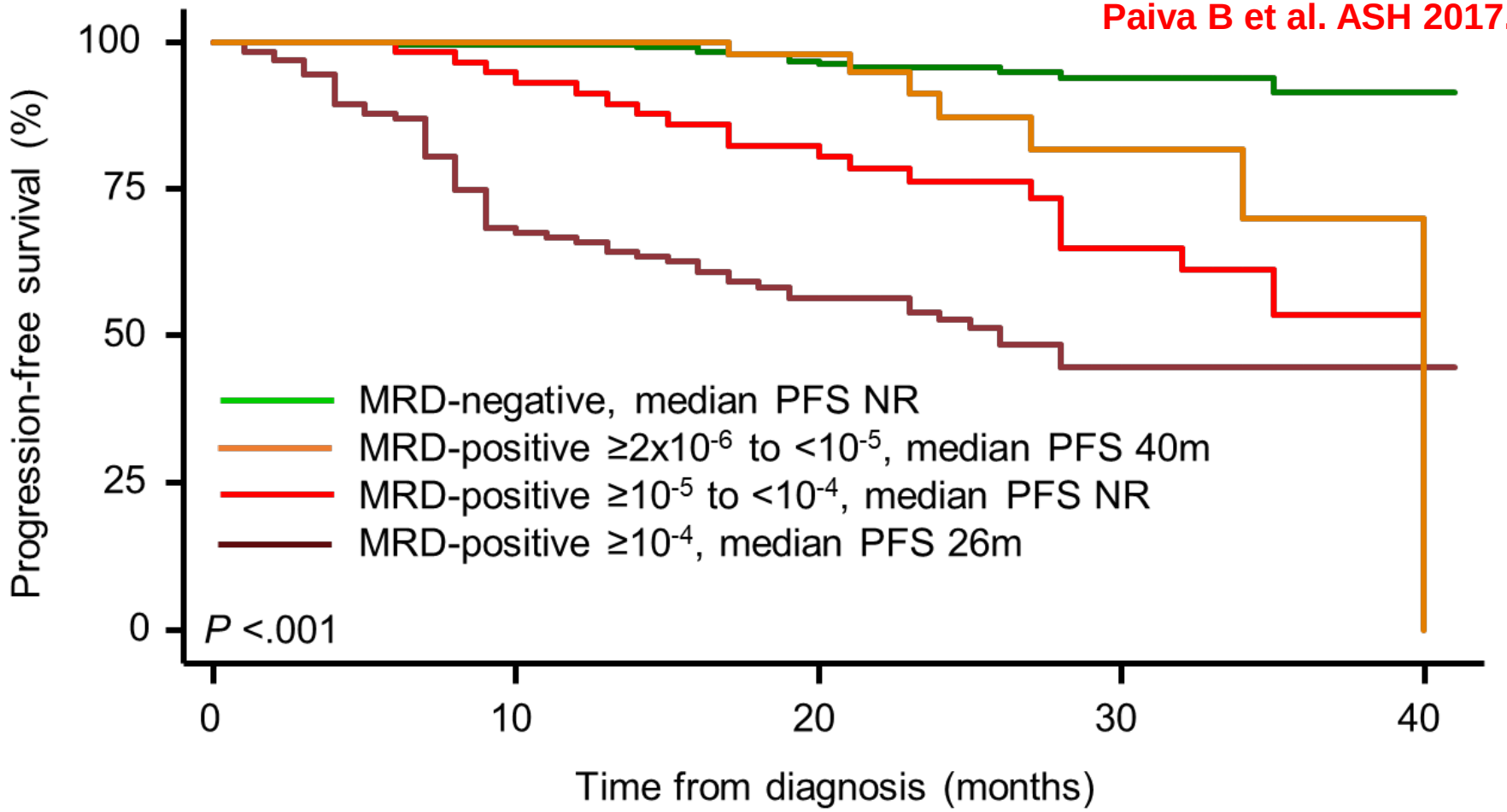
GEM14

Second trial as continuation of the previous one



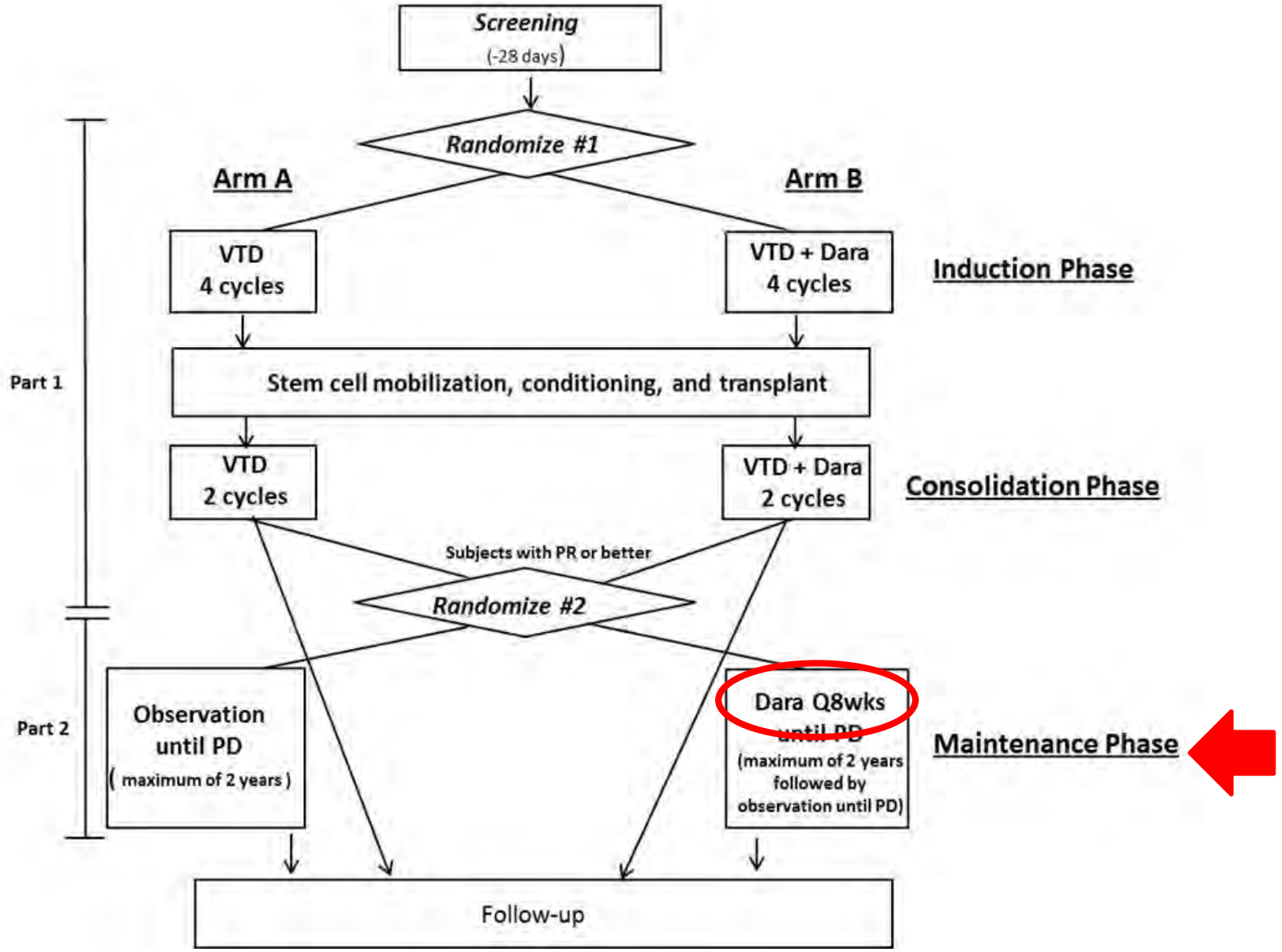
NCT02253316.

Paiva B et al. ASH 2017. Abstr 905.



Number at risk					
MRD-neg	225	224	177	86	4
MRD ≥2x10^{-6} to <10^{-5}	49	49	36	10	1
MRD ≥10^{-5} to <10^{-4}	57	54	43	20	1
MRD ≥10^{-4}	127	84	57	20	2

CASSIOPEIA – 1080 Patients – ASCO 2019



Conclusions: European Perspectives

- **Frontline ASCT: standard of care**

- **VTD / VRD: best induction regimens prior to ASCT**

- **Optimal consolidation has to be defined (tandem in high risk)**

- **Consider the global strategy: induction/ ASCT / consolidation / maintenance**

INTERNATIONAL MYELOMA FOUNDATION

LIVE

Panel Discussion and Audience Q&A

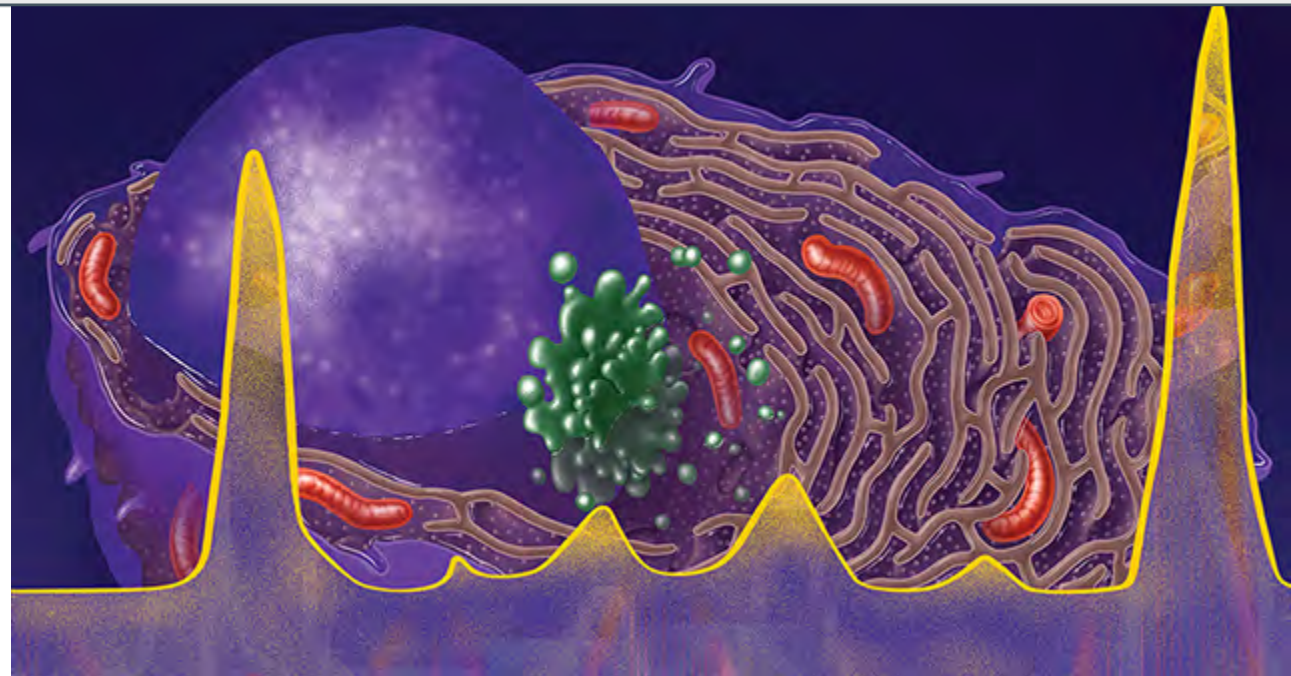


Image: Copyright©2018 DNA Illustrations. All Rights Reserved

Patient Case Example, Repeat

- A 53-year-old woman with no other health problems was diagnosed with myeloma when she presented with back pain and increasing fatigue

Lab Test	Result
Hemoglobin	10.8 g/dL
Serum Ca^{2+}	Normal
Serum creatinine	Normal
Serum LDH	**Above ULN**
Serum $\beta_2$microglobulin	**7.1 mg/dL**
Serum albumin	4.1 g/dL

- Serum protein electrophoresis: IgGK monoclonal protein of 3.2 g/dL
- 24 hour urine protein electrophoresis: 210 mg monoclonal protein, kappa light chain

Patient Case Example, Continued

- Whole-body low-dose CT showed multiple lytic lesions
- Bone marrow biopsy showed 40% plasma cell involvement, **FISH showed 17p deletion in > 50% of tumor cells**
- She was started on treatment with a combination of bortezomib, lenalidomide, and dexamethasone
- At the completion of 4 cycles of therapy:
  - Repeat bone marrow biopsy shows no MRD
  - Serum and urine immunofixation were both negative

Now, what would you do next for this patient?

1. ASCT followed by RVD consolidation and lenalidomide maintenance
2. ASCT followed by RVD consolidation and PI-based maintenance
3. ASCT followed by lenalidomide maintenance
4. ASCT followed by PI-based maintenance
5. Tandem ASCT followed by RVD consolidation and lenalidomide maintenance
6. Tandem ASCT followed by RVD consolidation and PI-based maintenance
7. Uncertain

INTERNATIONAL MYELOMA FOUNDATION

CCO LIVE

Advances in the Optimal Choice of Therapeutic Strategies for Patients With R/R Myeloma

Faculty Presenters:

Jesús F. San-Miguel, MD, PhD

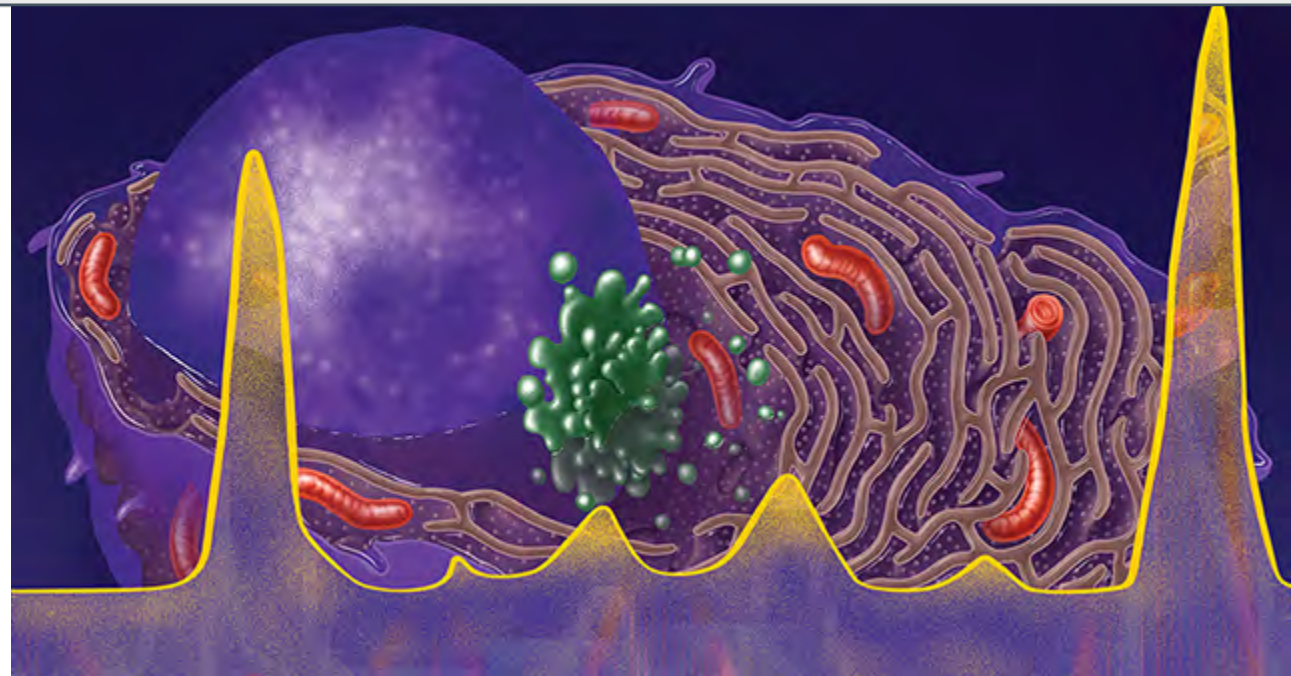


Image: Copyright©2018 DNA Illustrations. All Rights Reserved

Program 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, MSD, Novartis, Roche, Sanofi, and Takeda.

Therapeutic Strategies at Relapse in Multiple Myeloma

Jesus San-Miguel

Universidad Navarra

Patient Case Example

- A 66-year-old woman was diagnosed with IgG lambda **R-ISS stage II** myeloma
  - BM showed 60% PC with **1q gain plus t(4;14)**
  - MC: 43 g/L; **Hb: 10.3 g/dL**, creatinine: 1.2 mg/dL; calcium: 9.2 mg/dL
  - She had extensive **bony disease**
- She was treated **VTD + ASCT + lenalidomide for 2 years** and achieved **sCR**
- **After 4 years,** she relapsed

How would you treat this patient?

Faculty	Recommendation
Brian G.M. Durie, MD	Daratumumab/bortezomib/dexamethasone
Shaji Kumar, MD	Daratumumab/lenalidomide/dexamethasone
Philippe Moreau, MD	Daratumumab/lenalidomide/dexamethasone
S. Vincent Rajkumar, MD	Daratumumab/lenalidomide/dexamethasone
Jesús F. San-Miguel, MD, PhD	Rescue treatment followed by second ASCT

66-Year-Old Man Relapsing After VTD + ASCT + Len x 2-Yrs: How to Make the RIGHT CHOICE?

Decisions based on the **duration of the previous response**

Late relapse (> 3-4 years post ASCT)

- ***Aggressive relapse:*** **Reinduction (VRD/KRD +/- Dara) + 2nd ASCT**
- ***Biochemical relapse*****: Repeat the initial approach or same as above**

Early relapse (< 1 year post ASCT)

"Overcome drug resistance"

Combination of non cross-resistant agents

VRD (KRD)-PACE + Dara → RIC-Allo/CAR-T

Intermediate relapse (1-3 years post ASCT)

"Prolong survival until curative treatments are developed"

Sequential novel agent combinations: Dara + PomDex.....KRD...

Patient Case Example, Continued

- A 66-year-old woman was diagnosed with IgG lambda R-ISS stage II MM
  - BM showed **1q gain plus t(4;14)** with extensive **bony disease**
  - She was treated VTD + ASCT + lenalidomide for 2 years and achieved sCR
  - After 4 years, she relapsed
- She refused 2nd ASCT (70 years, with hypertension) and was treated with **VCD x 8 cycles** and **achieved CR**
- **She relapsed 10 months later**

How would you treat this patient?

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

Lenalidomide-Based Regimens: Efficacy

Efficacy	POLLUX (n=569) DaraRd vs Rd [1-3]	ASPIRE (n=792) KRd vs Rd [4,5]	ELOQUENT-2 (n=646) ERd vs Rd [6]	TOURMALINE-MM1 (n=722) IRd vs Rd [7]
PFS HR (▲m)	**0.44** (▲ 27) **44.5** vs 17.5 m	**0.67**(▲ 8.7 m) **26.3** vs 17.6 m	**0.71** (▲ 4.5 m) **19.4** vs 14.9 m	**0.74**(▲ 5.9 m) **20.6** vs 14.7 m
ORR, %	93	87	79	78
≥ CR, %	**51**	**32**	**5**	**14**
OS HR (95% CI)	**0.63**	**0.79** (▲ 8 m) 48 vs 40 m	**0.78** (▲ 4.1 m) 43.7 vs 39.6 m	**NE**
High Risk: m (HR)	**22.6** (0.64)	**23** (0.70)	**19** (0.60)	**21** (0.54)

This table is provided for ease of viewing information from multiple trials with different patient populations. Direct comparison across trials is not intended and should not be inferred.
DOR, duration of response; NE, not evaluated.

1. Bahlis NJ, et al. ASH 2018; abstract 1996. 2. Dimopoulos M, et al. Poster presented at EHA 2017; abstract P334.
3. Usmani SZ, et al. Oral presentation at ASH 2016; abstract 1151. 4. Siegel DS, et al. Poster presented at EHA 2017; abstract P333.
5. Stewart AK, et al. N Engl J Med. 2015;372:142-52. 6. Lonial S, et al. NEJM 2015,373:621-31; Oral presentation at ASCO 2017; abstract 8028.
7. Moreau P, et al. N Engl J Med. 2016;374:1621-34. 8. Dimopoulos MA, et al. N Engl J Med. 2016;375:1319-31.
9. Dimopoulos MA, et al. Br J Haematol. 2017;178:896-905.

Patient Case Example

- A 66-year-old woman was diagnosed with IgG lambda R-ISS stage II MM
  - BM showed **1q gain plus t(4;14)** with extensive **bony disease**
  - She was treated VTD + ASCT + lenalidomide for 2 years and achieved sCR
  - After 4 years, she relapsed
- She refused 2nd ASCT (70 years, with hypertension) and was treated with VCD x 8 cycles and achieved CR
- She relapsed 10 months later
- She began tx with **lenalidomide/dexamethasone** until progression
  - On cycle 5, she was already in VGPR and maintained her response for 15 months before relapse

How would you treat this patient?

Faculty	Recommendation
Brian G.M. Durie, MD	Elotuzumab/pomalidomide/dexamethasone
Shaji Kumar, MD	Daratumumab/bortezomib/dexamethasone
Philippe Moreau, MD	Daratumumab/bortezomib/dexamethasone
S. Vincent Rajkumar, MD	Daratumumab/bortezomib/dexamethasone
Jesús F. San-Miguel, MD, PhD	Daratumumab/bortezomib/dexamethasone

70-Yr-Old Woman 1st Relapse Following Continuous Lenalidomide-Dex

Proteasome Inhibitors-Based Regimens: Efficacy

Efficacy	ENDEAVOR (n=929) **Kd vs Vd** [3]	CASTOR (n=499) **DaraVd vs Vd** [1-2]	OPTIMISMM (n=559) **PVd vs Vd** [4]	PANORAMA-1 (n=768) **PanoVd vs Vd** [5]
PFS HR	**0.53** (▲ 9.3 m) **18.7** vs 9.4 m	**0.32** (▲ 9.6 m) **16.7** vs 7.1 m	**0.61** (▲ 4.1 m) * **11.2** vs 7.1 m	**0.63** (▲ 4 m) * **12** vs 8 m
ORR, %	77	85	82.2	60.7
≥ CR, %	**13**	**30**	**15.7**	**27.6**
OS HR (95% CI)	**0.79** (▲ 7.6 m) **47.6 vs 40 m**	--	--	--
Len Refract	24% (8.6m)	18% (9.3m)	71% (9.5m)	<10%
High Risk: m (HR)	**8.8** (0.73)	**11.2** (0.45)	**8.4** (0.56)	NA

1. Palumbo et al. NEJM 2016. 2. Spencer A et al. ASH 2017. Poster presentation. Abstract 3145 ; 3. Dimopoulos MA et al, Lancet Oncology 2016; 4. Richardson P, et al. ASCO 2018 5. San Miguel et al . Lancet Oncology 2014

Patient Case Example

- A 66-year-old woman was diagnosed with IgG lambda R-ISS stage II MM
  - BM showed **1q gain plus t(4;14)** with extensive **bony disease**
  - She was treated VTD + ASCT + lenalidomide for 2 years and achieved sCR but relapsed after 4 years
- She refused 2nd ASCT (70 years, with hypertension) and was treated with VCD x 8 cycles and achieved CR
  - She relapsed 10 months later
- She began tx with lenalidomide/dexamethasone until progression
  - She achieved VGPR but relapsed 15 months later
- **She received Dara-Vd and achieved PR on C2 but progressed with extramedullary disease on C8**

How would you treat this patient now?

Faculty	Recommendation
Brian G.M. Durie, MD	Carfilzomib/pomalidomide/dexamethasone
Shaji Kumar, MD	Elotuzumab/pomalidomide/dexamethasone
Philippe Moreau, MD	Clinical trial with BCMA CAR T-cell therapy
S. Vincent Rajkumar, MD	Carfilzomib/pomalidomide/dexamethasone
Jesús F. San-Miguel, MD, PhD	Elotuzumab/pomalidomide/dexamethasone

Treatment at 3rd/subsequent relapses

Poma – Dexa[1] *(backbone)*
ORR: 31%; PFS 4 m; OS: 13.1 m

PCyDex (ORR 65%; PFS 9.5m)[2]
EloPom Dex (ORR:53%, PFS 10.2m)[3]

Daratumumab[5]
ORR: 31%; PFS 4m; OS 20.1 m

DaraCfzDex *

DaraPomDex (ORR 60%, PFS 8.8m)
IxaPomDex (ORR 55%)[4]

CfzPomDex **n=(60) EMN011**[7]
- **ORR: 87% (31%CR)**
- **PFS: 18m**

*DaraCfzDex **n=85 (60% Len Ref)**[6]
- **ORR: 86% (81%)**
- **PFS: 71% at 12m (14.1m)**

[1]San-Miguel et al Lancet Oncology 2013;14(11):1055-66; [2]*Baz et al. Blood. 2016;127(21):2561-2568;* [3]Dimopoulos NEJM2018, 379:1811-22. [4] ***Voorhees PM, ASH 2015 Abst 375;*** [5]**Usmani S, et al. Blood 2016; 6 Lonial ASH 2017 1869; 7 Sonneveld ASH 2018, (Abstr 801)**

Elotuzumab-Poma-Dexa vs Poma-Dex in RRMM: Phase 2 Randomized ELOQUENT-3 Trial – Efficacy (N = 117)

KEY INCLUSION

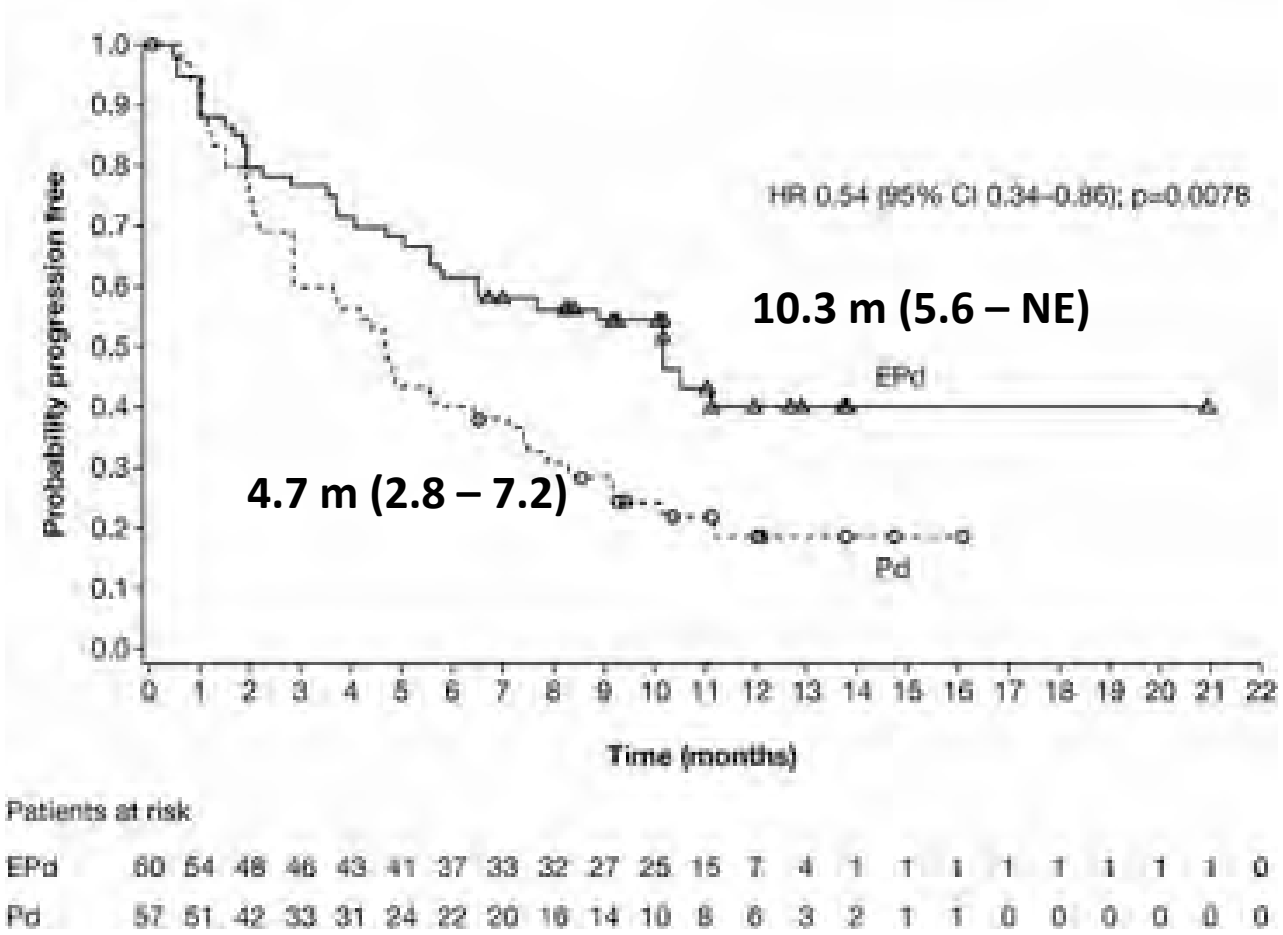
- ≥ 2 prior regimens
- Prior IMID and PI treatment
- Refractory to last line
- Refractory to Len and a PI

POM:4 mg days 1-21 ; 40 mg (20 of >75y) weekly

ELO: 10 mg/kg/w C1&C2; >C3: 20mg/kg/ 4 w

- **Median number of prior lines: 3 (2 – 8)**
- Prior exposure to: BORT (100%), CFZ (21%), LEN (99%)
- Refractory to: PI 80%, LEN 87%, double refractory (70%)

EPd vs Pd: ORR 53% vs 26% **VGPR: 20% vs 9%**



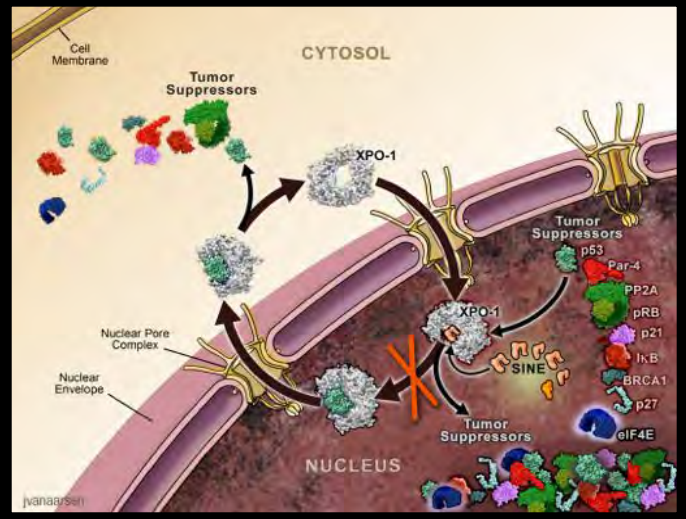
Safety Epd vs Pd : Grade 3-4 neutropenia: 13% vs 27% // Anemia: 10% vs 20% // Infections any grade: 65% vs 65%.

Safety was consistent with prior reports of ELO and POM

Dimopoulos MA et al. NEJM 2018, 379:1811-22

XPO1-Inhibitor Selinexor in RRMM. Summary of Phase I data

First-in-class, oral Selective Inhibitor of Nuclear Export (SINE) that inhibits XPO1 and activates tumor suppressor proteins & reduces oncoproteins



- Cancer cells (and MM) overexpress XPO1, causing increased export of tumor suppressors and growth regulatory proteins from the nucleus
- Selinexor inhibit XPO1 mediated nuclear-cytoplasmic transport by transiently binding to XPO1 cargo binding site.
- Accumulation of Tumor suppressors in the nucleus amplifies the natural apoptotic function in cancer cells with damaged DNA.

Tai et al. Leukemia 2014

PHASE I OF SELINEXOR PLUS/MINUS DEX IN RRMM→

- **Single agent** (oral:3-45 mg twice/ w)…. **17% MR,** *Chen et al. ASH 2014*

  Main AEs: Anorexia, nausea/vomiting, fatigue, thrombocytopenia.

- **+Dex** (n=122) (STORM)…….**26% ORR** (Pent a-Refrct) PFS: 3,7m *Vogl et al. JCO 2018; Chari ASH 2018 (Abs 598)*

  AEs: nausea 73%, vomiting 49%, anorexia 49%, thrombocytopenia 73% /59% gr 3-4)

- **+ Bortz/dex** (n=42)……. 63% (**43%** in Btz Rfct) (PFS: 9 (6,1)m)*Bahlis NJ, Blood 2018, (PH III BOSTON trial ongoing)*

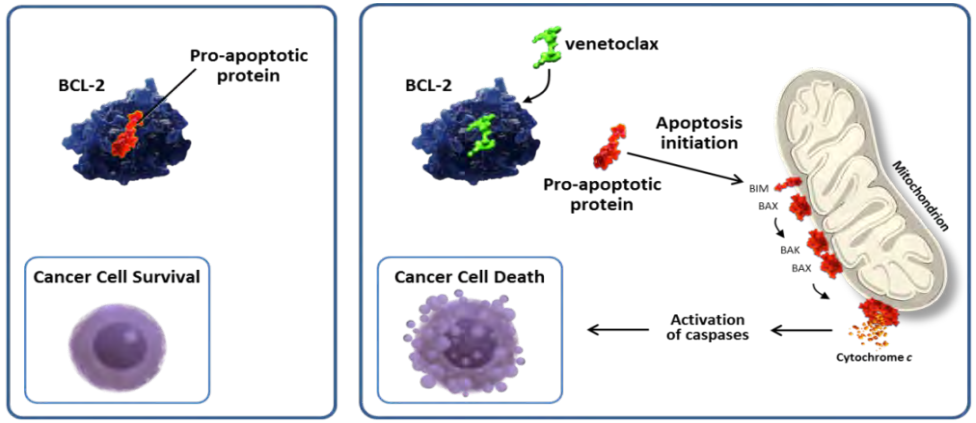
  AEs: anorexia 33%, nausea 67%, Thrombocytopenia 17%

- **+ Pom/dex** (n=24)……. 65% % in Pom Naive/Len R (**29%** in Pom/Len Rft). *Chen et al, ASH 2017)*

- **+ Dara/dex** (n=25)……. **74%** % in double Rft. *Gasparetto et al, ASH 2018, Abs 599)*

Venetoclax (bcl-2 inhibitor) in RRMM. Summary of Ph1 data

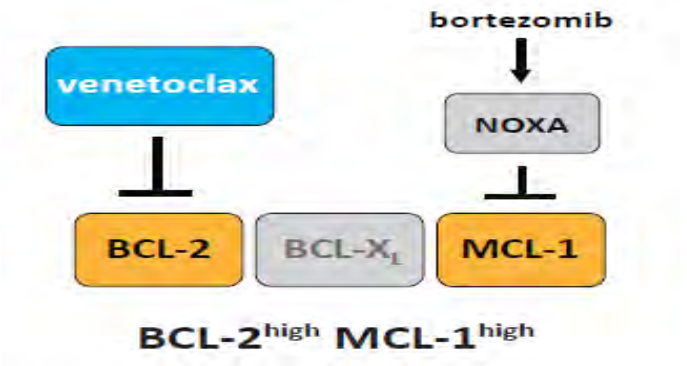
- Venetoclax is a selective, orally available small molecule BCL-2 inhibitor[1], induces cell death in multiple myeloma (MM) cell lines and primary samples, particularly those positive for the translocation t(11;14), which correlates with higher ratios of *BCL2* to *MCL1* and *BCL2* to *BCL2L1* (BCL-X_L) mRNA[1],



BCL-2 overexpression allows cancer cells to evade apoptosis by sequestering pro-apoptotic proteins.[1-3]

Venetoclax binds selectively to BCL-2, freeing pro-apoptotic proteins that initiate programmed cell death (apoptosis).[4-6]

1. Leverson JD, et al. *Sci Transl Med* 2015; 7:279ra40. 2. Czabotar, et al. *Nature Reviews* 2014;15:49-63. 3. Plati J, Bucur O, Khosravi-Far R. *Integr Biol (Camb)* 2011;3:279–296.
4. Certo M, et al. *Cancer Cell*. 2006;9(5):351-65. 5. Souers AJ, et al. *Nat Med*. 2013;19(2):202-8. 6. Del Gaizo Moore V et al. *J Clin Invest*. 2007;117(1):112-21.



1. Roberts AW et al. *NEJM* 2015
2. Punnoose E et al. *Mol Cancer Ther* 2016

- **Monotherapy** (n=66) (61% double Ref) ..... **ORR 21% (40% in t(11;14) DOR: 9.7m**

  G 3-4 AEs: thrombocytopenia (26%) & neutropenia (21%)

- **+Btz/Dex** (n=66) ..... **ORR 67% (90% in BTz sensitive & 94% in BCL2 high)**

  G3-4 AEs: Thrombocytopenia (29%), anemia (15%), neutropenia (14%),

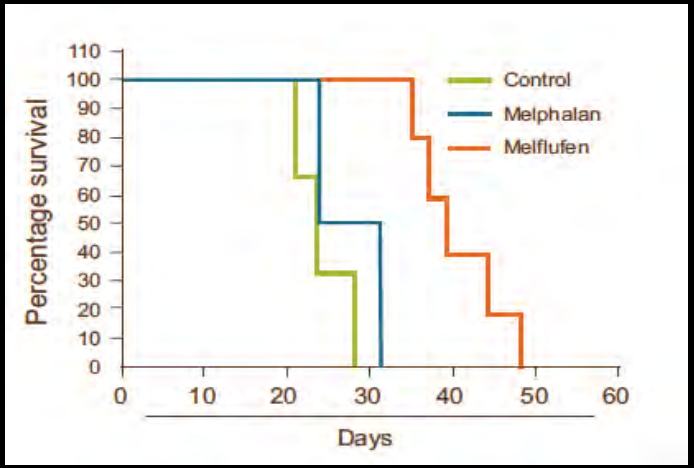
- **+Cfz/Dex** (n=42) (33% double Ref).....**ORR 78% (PFS: 5,7m. The VGPR in t(11,14): 88%)**

Kumar, et al. Blood 2017; 130: 2401-09, Moreau P, et al. Blood 2017 130:2392-4 ; Costa et al ASH 2018, Abst 303

Melflufen

- Melflufen is a highly lipophilic alkylator, belonging to the **novel class of Peptidase Enhanced Compounds**, consisting of melphalan + 4-fluoro-L-phenylalanine.
- **Intracellular amino-peptidases** that are overexpressed in most malignant cells, will rapidly **cleave melflufen releasing the hydrophilic, active metabolite melphalan**.
- In vitro, equimolar treatment of tumor cells with melphalan and melflufen, results in a 20-50 fold higher intracellular concentration.

Melflufen 40 mg iv every 28 days + Dex 40 mg weekly



Chauhan Clin Cancer Res 2013 & Wickström Invest New Drugs 2008

Phase II O-12-M1 trial

RRMM pts ≥ 2 lines and refr. to last line.

n = 45; 4 (2-14) lines; 64% double refr.; 53% Alkylator refr.

ORR 31% ..... 5 VGPR & 9 PR 36% in Alkylator refr.
PFS: 5,7m ; OS: 20M

G3/4 AEs: Thromboc. (58%), Neutrop(51%), Anemia: 42%

Blood 2017, 130: 3150

Phase II Horizon trial

RRMM pts ≥ 2 lines and 89% double Ref
n = 62 6 (3-11) lines; Alkylator refr. 58%;Pom & Dara Refr: 56%

ORR 32% ..... PFS: 5,7M; OS: 20,7M

G3/4 rel. TEAEs: Thromboc. (45%), Neutropenia (39%), Anemia: 21%

Richardson P. ASH 2018 (Abst 600)

Four Major Targets for Cancer Immunotherapy

Direct targeting of surface tumor antigens:

Monoclonal antibodies

Overcoming inhibitory immune suppression:

Immunomodulators: IMiDs, checkpoint inhibitors

Boosting immune effectors:

Adoptive cell therapy

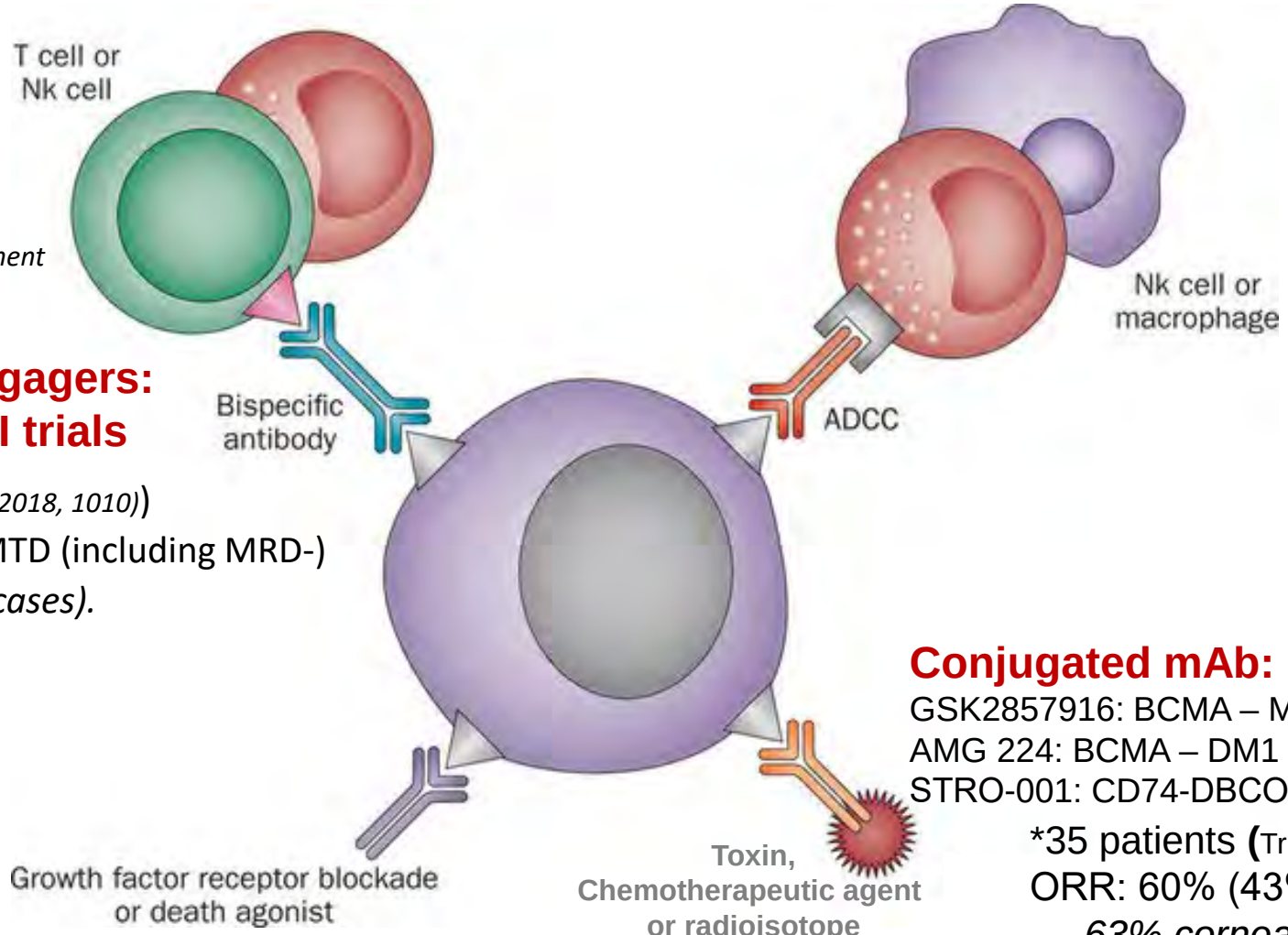
Activating tumor specific immunity:

Vaccines

IMiD, immunomodulatory drugs.

Monoclonal Antibodies: Futures Perspectives

To overcome the limitations of an immunosuppressive tumor microenvironment by linking CTLs with the tumor cell.



Bispecific T-cell engagers: BCMA–CD3 Phase I trials

- AMG 420: 35 pts: *(Topp et al ASH 2018, 1010)*)
  28% ORR (6CR). 83% ORR at MTD (including MRD-)
  SAE: 49% (infections); CRS (3 cases).

Conjugated mAb:

GSK2857916: BCMA – MMAF*
AMG 224: BCMA – DM1
STRO-001: CD74-DBCO

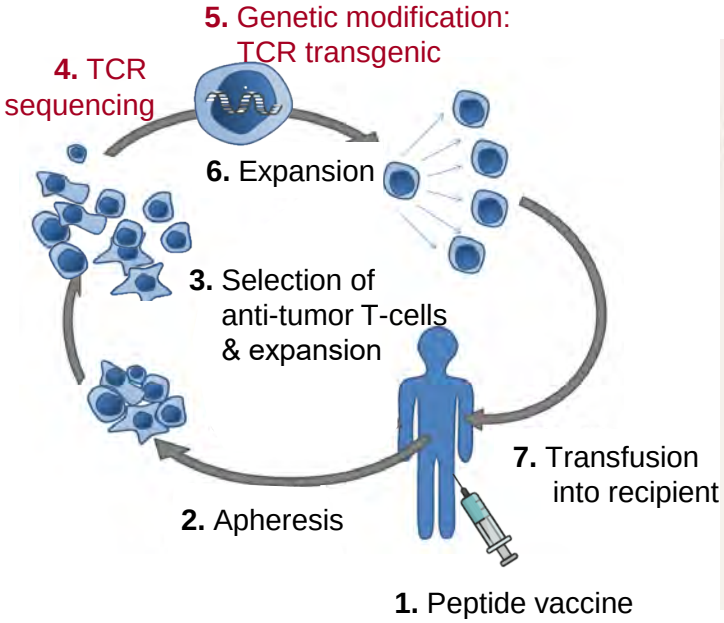
*35 patients (Trudel S, *et al. Blood* 2017;130:741)
ORR: 60% (43% previous dara) PFS: 7.9m
63% corneal events most G1-2

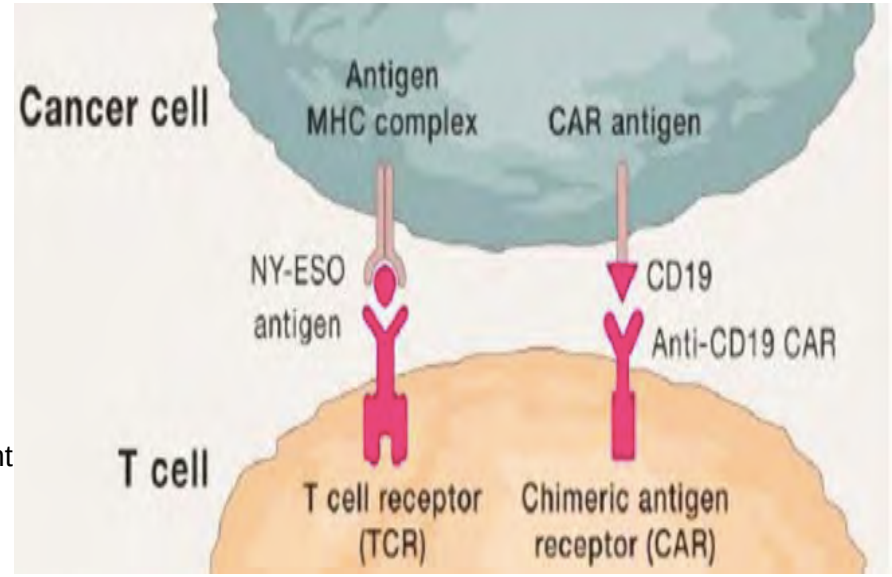
*

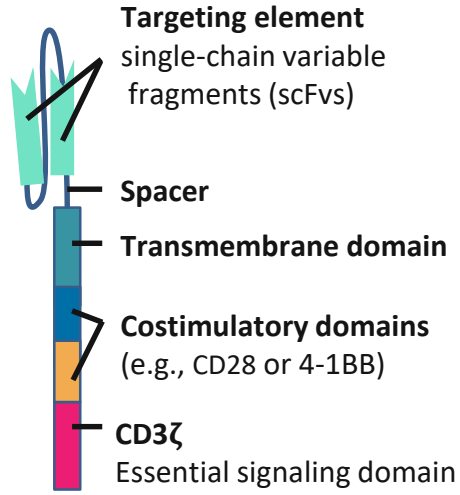
Mackall CL, *et al. Nat Rev Clin Oncol* 2014;11:693-703.

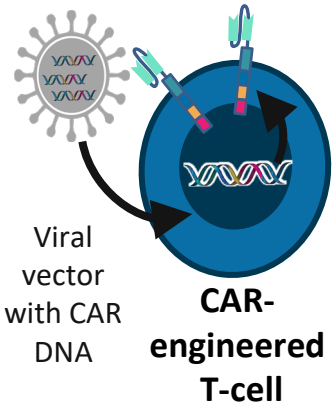
MMAF, monomethyl auristatin F; DM1, maytansinoid N(2')- deacetyl-N(2')-(3-mercapto-1-oxopropyl)-maytansine.

Adoptive Cell Therapy: Genetically Modified T-Cell Therapy









This construct is then transfected or transduced into patients' autologous T-cells

TCR engineered T-cells	CAR T-cells
HLA - restricted	Antigen recognition is independent of MHC molecule
Potential recognition of intracellular antigens	Only extracellular proteins can be recognized (like mAb)
TCR-mediated activation	Possibility to insert other genes

HLA, human leukocyte antigen; mAb, monoclonal antibody; MHC, major histocompatibility complex; TCR, T-cell receptor., Chimeric antigen receptor (CAR) T-cells
Lim WA & June CH. *Cell* 2017;168:724–40.

BCMA CAR T-Cells in MM

Trial site	ScFv	Co-s domain	Gene transfer	Conditioning therapy	T-cell dose CAR+ T-cells/kg
NCI	11D5-3	CD28	Y- retroviral	Cy 300 mg/m^2 x3 + Flu 30 mg/m^2 x3	0.3–9.0 x 10^6
Bluebird Celgene	NR, murine	4-1BB	Lentiviral	Cy 300 mg/m^2 x3 + Flu 30 mg/m^2 x3	50, 150, 450 and 800 x 10^6
University of Pennsylvania	NR, human	4-1BB	Lentiviral	None or Cy 1.5 g/m^2	10–50 x 10^6 or 100–500 x 10^6
Nanjing Legend Biotech	NR	NR	Lentiviral	Cy 300 mg/m^2 x3	1.5–7.0 × 10^6
Memorial Sloan Kettering Cancer Center	NR, human	4-1BB	Y- retroviral	Cy 3000 mg/m^2 or Cy 300 mg/m^2 x 3 + Flu 30 mg/m^2 x3	1x10^6 150, 450 and 800 x 10^6

This slide is provided for ease of viewing information from multiple trials. Direct comparison between trials is not intended and should not be inferred.
ScFv, single-chain fragment variable.

BCMA CAR T-cell Therapies for MM

	Anti-BCMA CAR[1] NCT02215967	Bb2121[2] NCT02658929	CART-BCMA[3] NCT02546167	LCAR-B38M[4] NCT03090659
Group/company	***NIH***	***Bluebird/Celgene***	***University of Pennsylvania/ Novartis***	***Nanjing Legend Biotech***
Patients	**16** patients at 9x10^6/kg dose level	22 (>150 x 10^6 cells)	**21** (**3 cohorts**): 9 (10-500 x 10^6, No Cyt) 5 (10–50 x 10^6 , Cyt) 7 (5 (100–500 x 10^6 , Cyt)	**57**
BCMA expression required?	Yes	Yes; ≥ 50% BCMA expression	No	Yes
Median prior lines of therapy	7	7	7 (3–11)	3
Reported efficacy	ORR 14/16 (**81%**) 11/14 (**79%**) MRD- EFS: **7.2 months**	**86.4%** ≥VGPR (**50%** sCR/CR) **PFS: 11.8 months**	#1**: 67%** (1 sCR, 1VGPR) #2: (**40%**) 1 PR, 1 MR both PD #3: (**83%**) 1 CR, 3 PR, 1 MR	ORR: **88%** **CR: 74%** **MRD-: 93% of CR** **PFS:15m**
Safety data	CRS all grades:100%, 37%G3-4	CRS all grades: 63% 2 events of CRS grade ≥3 resolved within 24 hours	CRS: 17 pts (grade 3: 32%) Neurotoxicity: 3 (2 grade 4) 1 death – PD candidaemia	Transient CRS (5,7% G3) No neurotoxicity

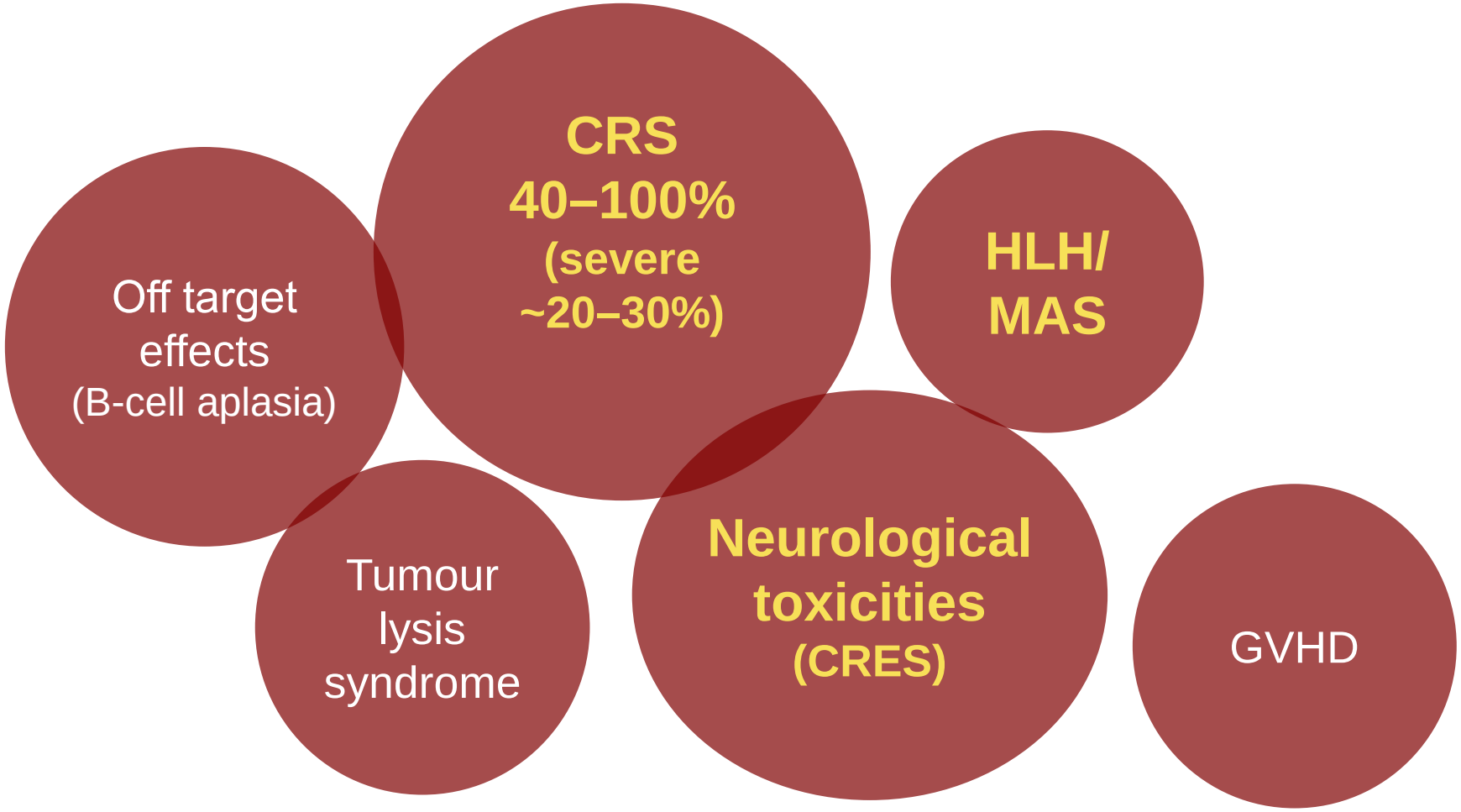
This slide is provided for ease of vie
BCMA, B-cell maturation antigen; C
partial response

1. Ali A, *et al.* Presented at ASH 2015. Abstract LBA 1; 2. Raje NS, *et al. JCO*. 2018;36:(suppl; abstr 8007); 3. Cohen AD, *et al. Blood* 2017;130:505.; 4. Zhang W, *et al.* Presented at EHA 2017. Abstract S103.

Abstracts ASH 2018: 488, 955-7, 959, 960, 1009, 1011-14

Safety Concerns Regarding CAR T-Cell Therapy

CRS is the most common toxicity triggered by the activation of T-cells and bystander immune cells → release of cytokines and chemokines: IFN-γ, soluble IL-2R, IL-6, etc



CRS, cytokine release syndrome, (Tocilizumab & Corticosteroids) CRES, CAR T-cell-related encephalopathy syndrome, GVHD, graft-versus-host disease, HLH, haemophagocytic lymphohistiocytosis, MAS, macrophage activation syndrome.

Improvements of CAR T-Cell Therapies

Limitation	Potential Improvements
Immunological rejection & safety	• **Humanised** CARs to reduce immunogenicity • **Allogeneic CAR T:** Gene editing (CRISPR/Cas9) of normal donor T-cells to remove naive TCR (to avoid GVHD) and transfection with a CAR with post-conditioning vaccination to improve memory • **Safety marker gene** to extinguish the CAR-T activity.
Immune system limitations	• Rational **combination strategies** : Checkpoint inhibitors, IMiDs, BTK inhibitors
Efficacy & antigen escape	• **Bi-specific CAR** (e.g. CD19, CD123, BCMA, SLAMF7) • Use of **specific T-cell subpopulations** (from naive to **central memory** and to terminal effector T-cells) • **APRIL** as the natural BCMA/TACI ligand instead of the Ab (anti-BCMA) • **Antibody-Coupled T-Cell Receptor (ACTR):** engages antibody to direct T-cell attack against many different Ags • **Armored CAR** (*2nd gene that generate a cytokine: i.e. IL12)*

AICD, activation-induced cell death, ScFv, single-chain fragment variable, TRAC, T-cell receptor α constant.

Brudno JN & Kochenderfer JN. *Nat Rev Clin Oncol* 2018;15:31–46.

Conclusions

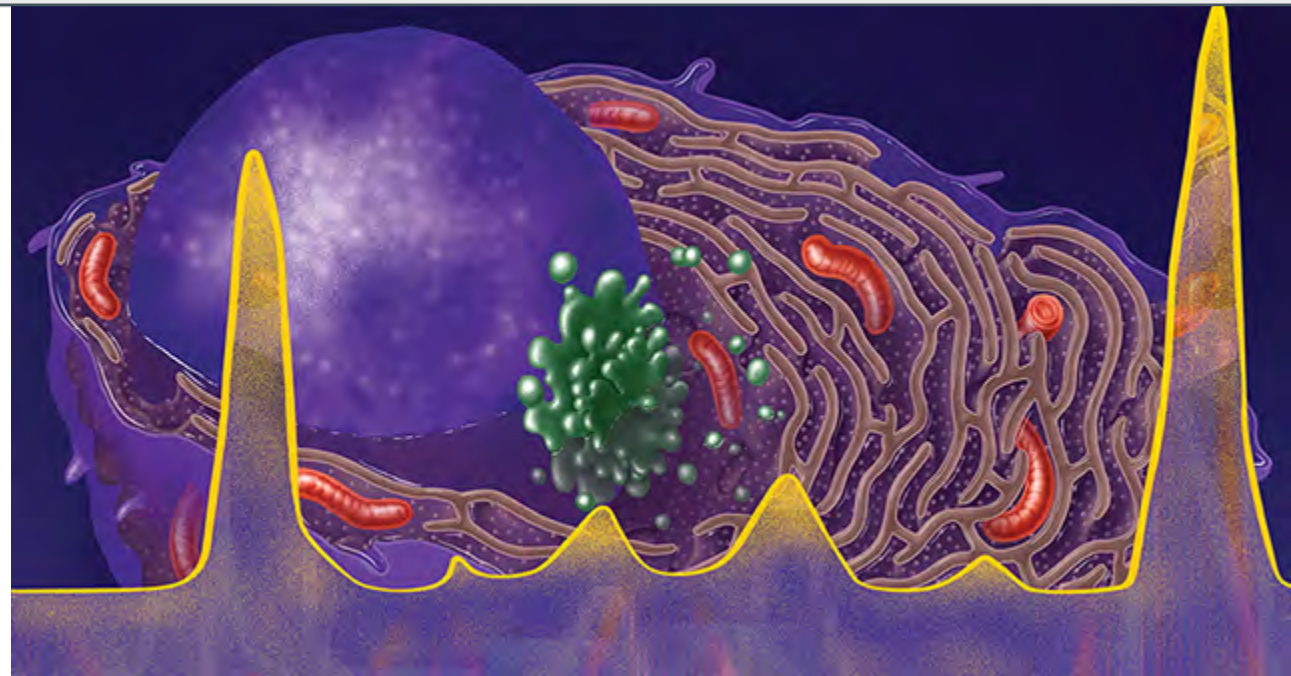
- The discovery and development of new therapies addressing a variety of therapeutic targets is already changing the natural history of MM
- The understanding of the mechanisms of progression and immune-surveillance escape as well as the manipulation of autologous immune cells and gene editing are opening new frontiers in the treatment of advanced or difficult-to-treat MM
- The combination of different class of drugs with complementary immunological strategies and earlier in the natural history of the disease may offer the future possibility of long-term control or even disease eradication in some subsets of patients


FOR CHRISTMAS I WANT A DRAGON!
BE REALISTIC
OK I WANT my paper to be accepted without revisions
WHAT COLOR DO YOU WANT YOUR DRAGON
RED

INTERNATIONAL MYELOMA FOUNDATION

LIVE

Panel Discussion and Audience Q&A



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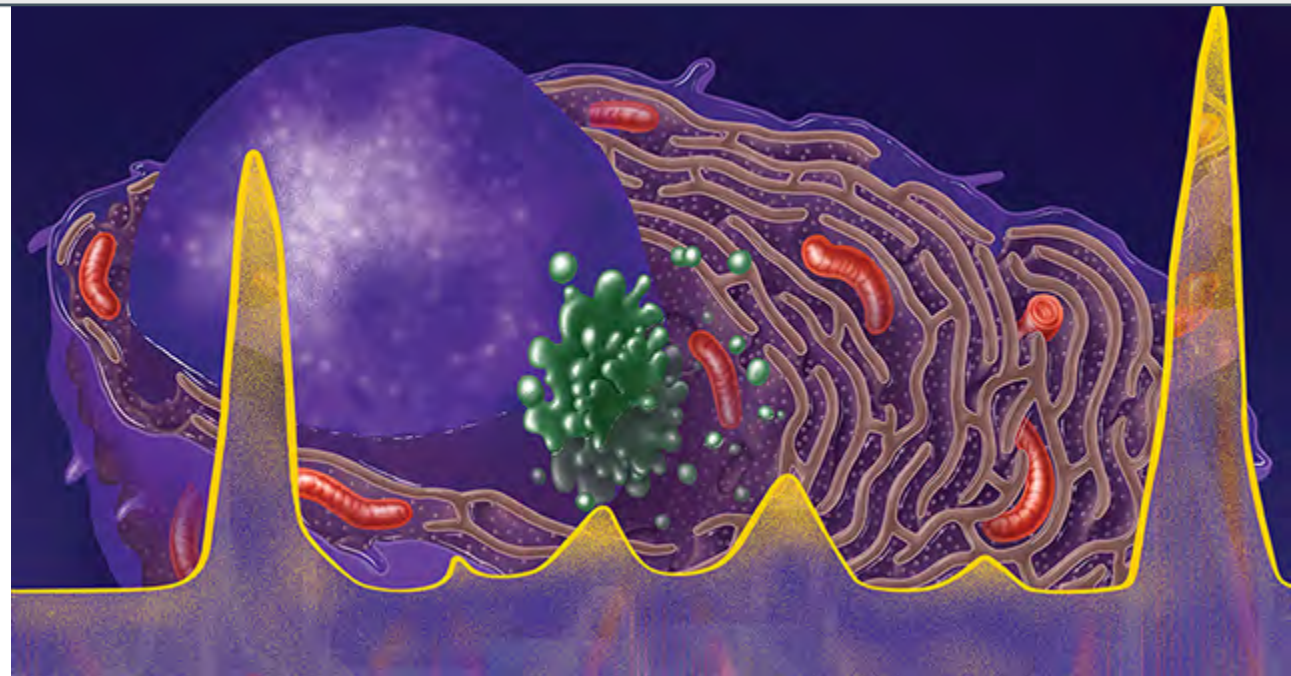
INTERNATIONAL MYELOMA FOUNDATION

IMF LIVE

Proposed 2019 Treatment Algorithm for MM



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Myeloma: 2019 Algorithms

S. Vincent Rajkumar
Professor of Medicine
Mayo Clinic

Scottsdale, Arizona

Rochester, Minnesota

Jacksonville, Florida

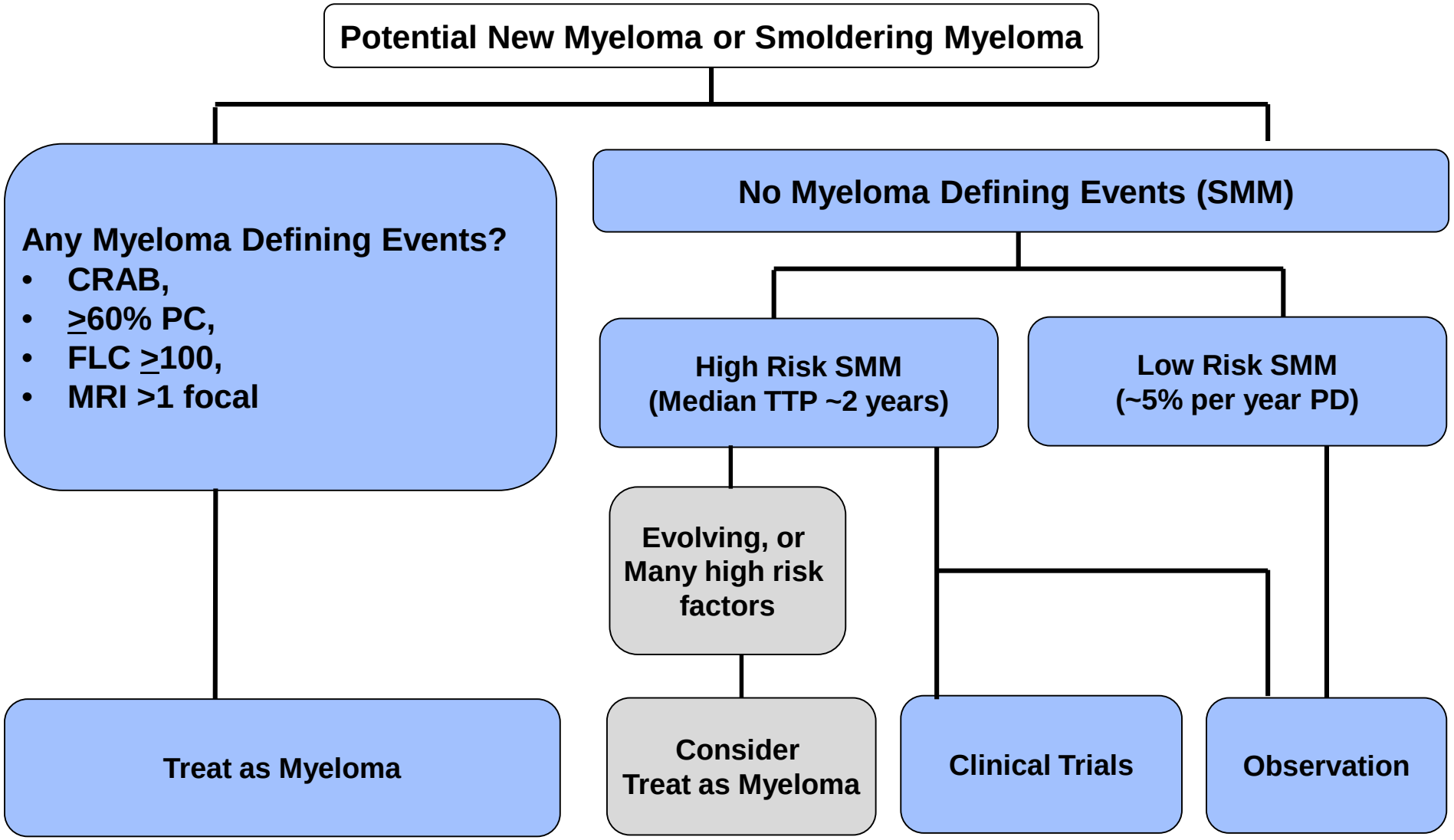
MAYO CLINIC

2019 Algorithms

- **Clinical Trials preferred**
- **Only commercially available options**
- **Assumes all drugs available**

MAYO CLINIC

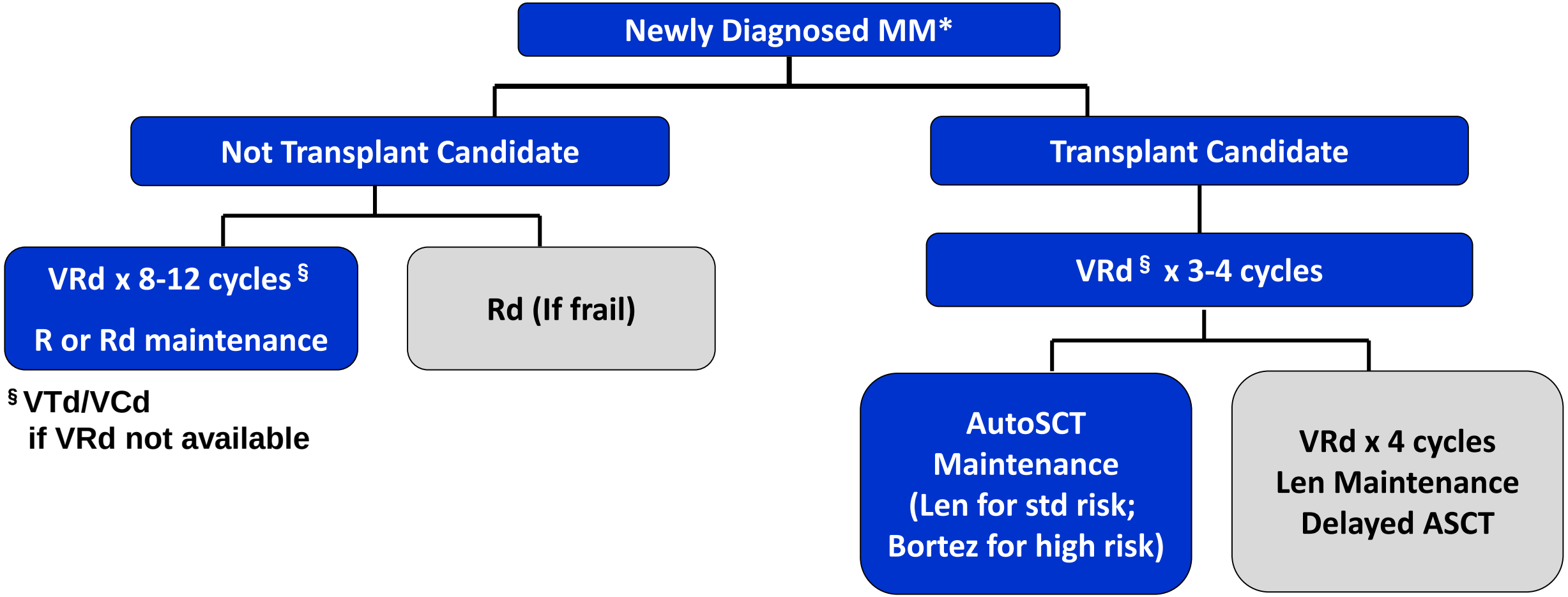
When Should Treatment Be Initiated?



Rajkumar SV, Landgren O, Mateos MV. Blood 2015

MAYO CLINIC

Myeloma: Frontline Treatment



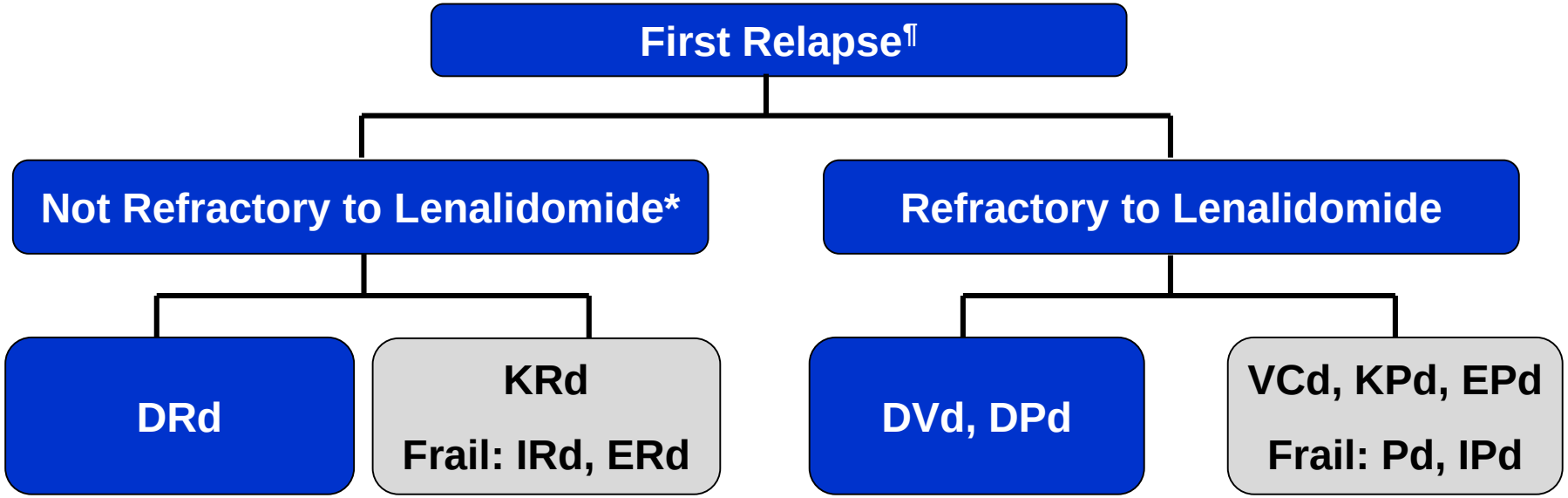
§ VTd/VCd
if VRd not available

*Based on CALGB 100104, S0777, IFM-DFCI, CTN 0702 HOVON

Rajkumar SV. 2019.

MAYO CLINIC

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

MAYO CLINIC

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 regimens
- Melphalan
- Venetoclax (t11;14)
- Bendamustine-based regimens
- Adding Panobinostat
- Quadruplet regimens

Rajkumar SV. 2019.

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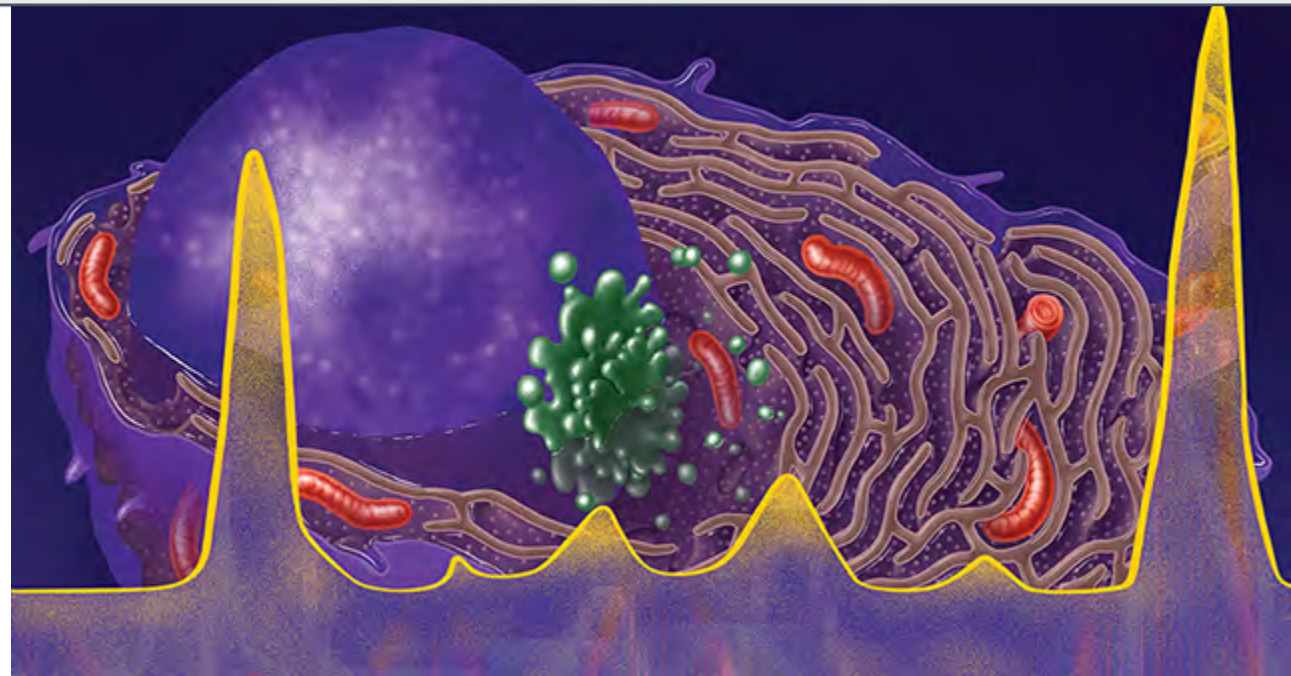
IMF LIVE

Final Thoughts and Audience Questions



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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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