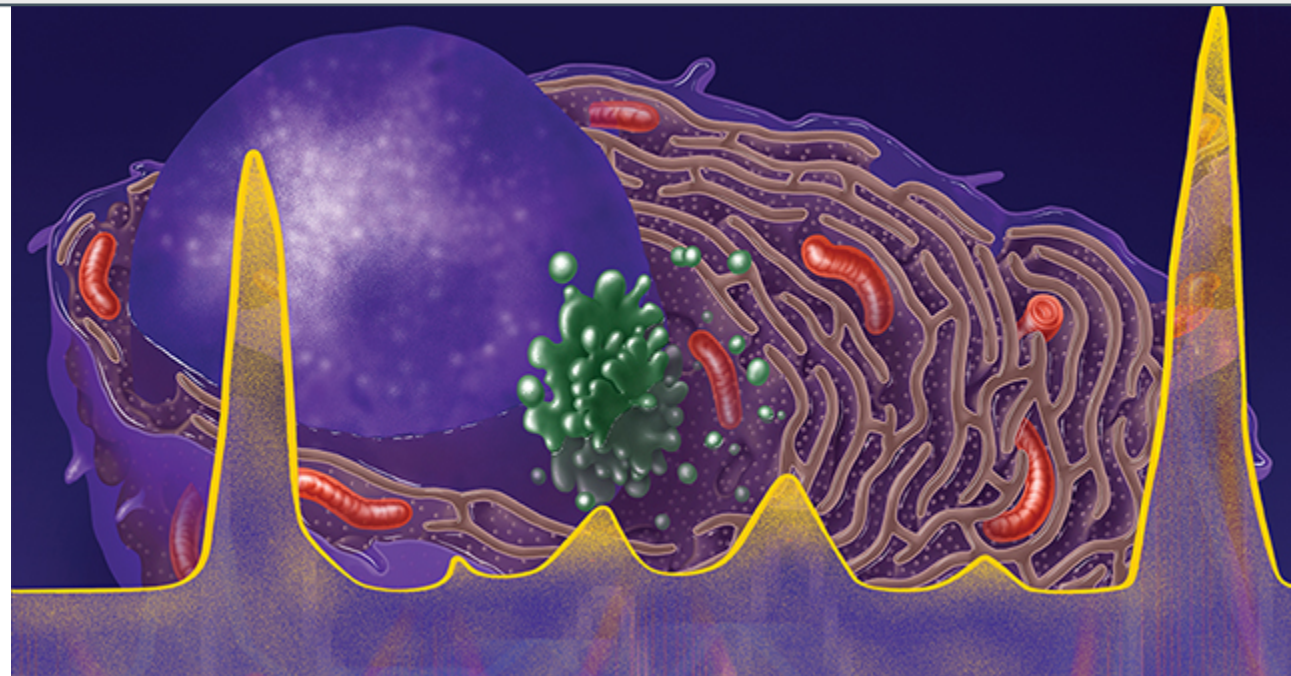
INTERNATIONAL MYELOMA FOUNDATION

CCO LIVE

Risk Stratification of Plasma Cell Disorders

Faculty Presenter:

S. Vincent Rajkumar, MD



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Risk Stratification of Plasma Cell Disorders

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

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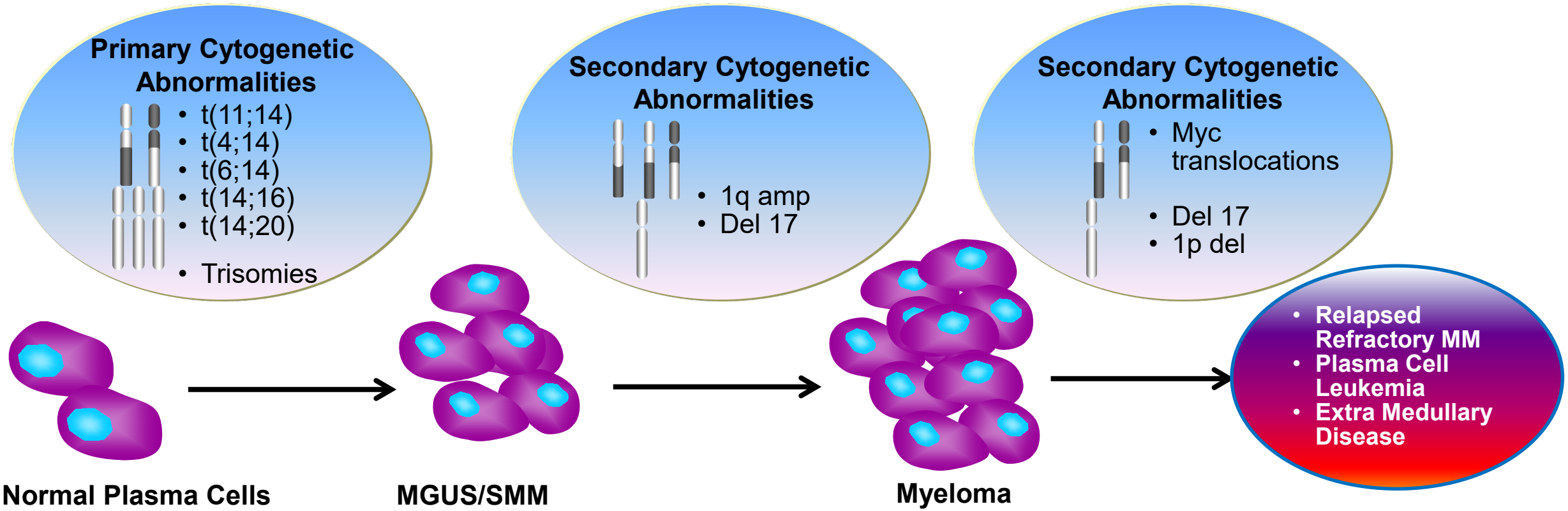
Progression of MGUS to Myeloma



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.

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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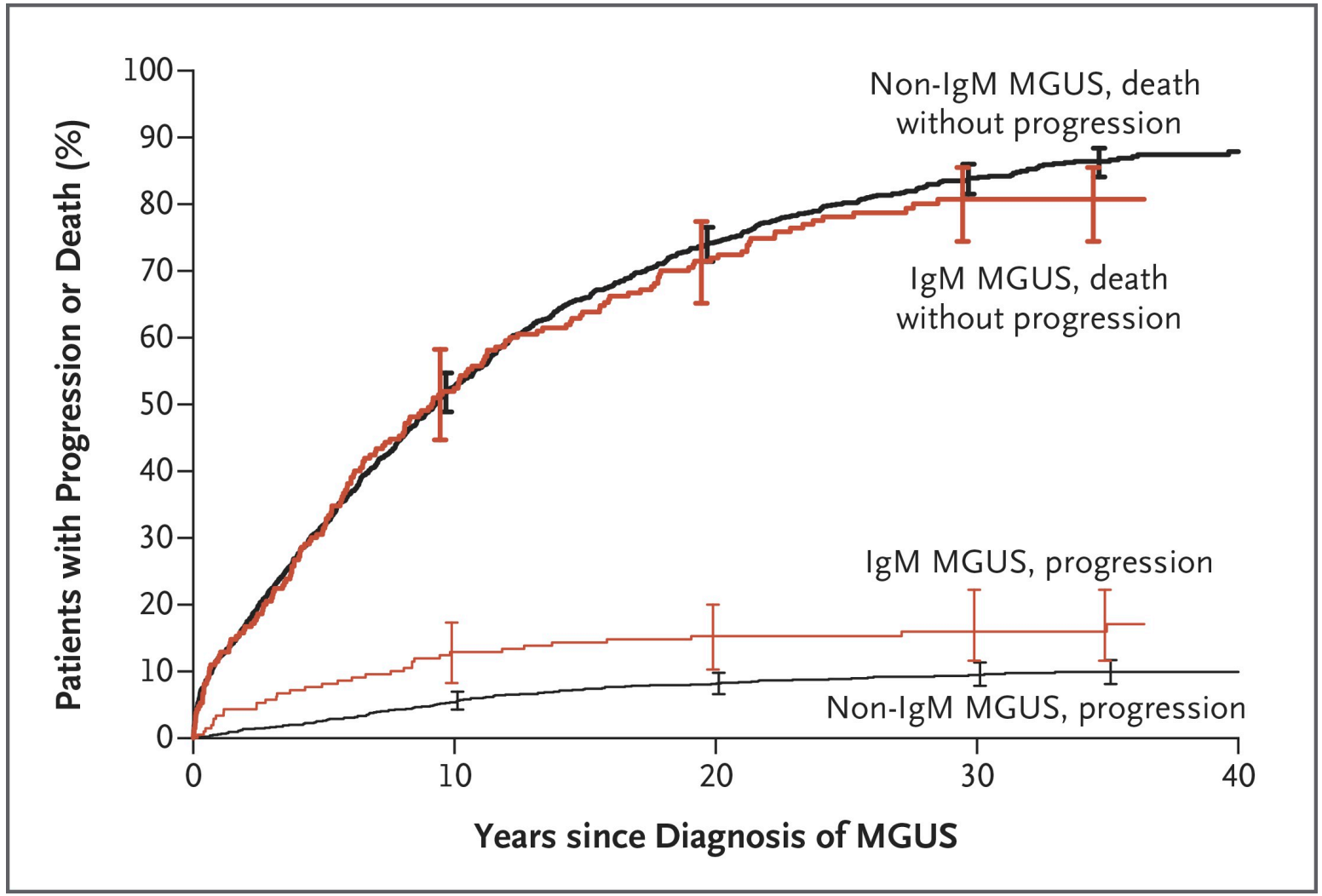
Risk of Progression of MGUS



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

The NEW ENGLAND JOURNAL of MEDICINE

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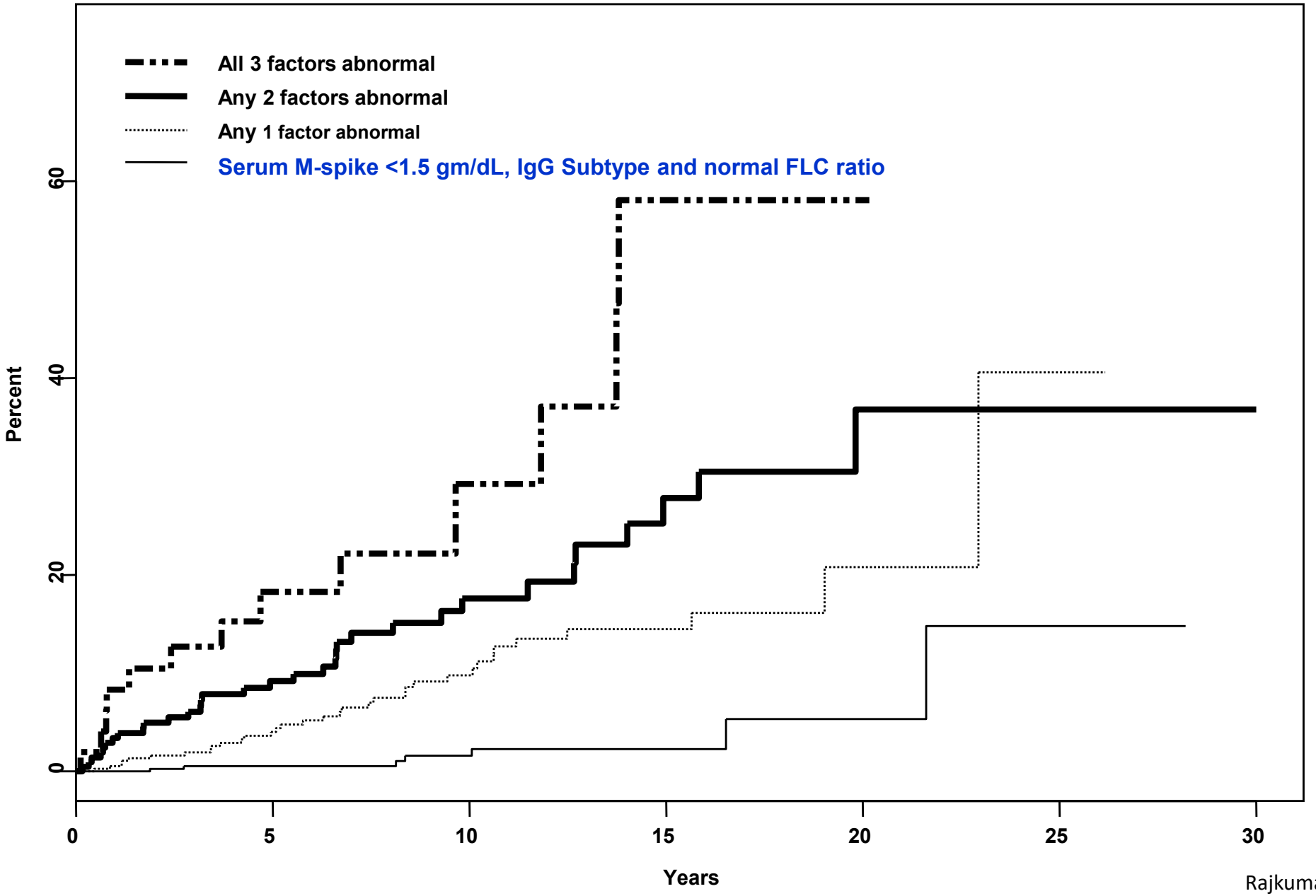
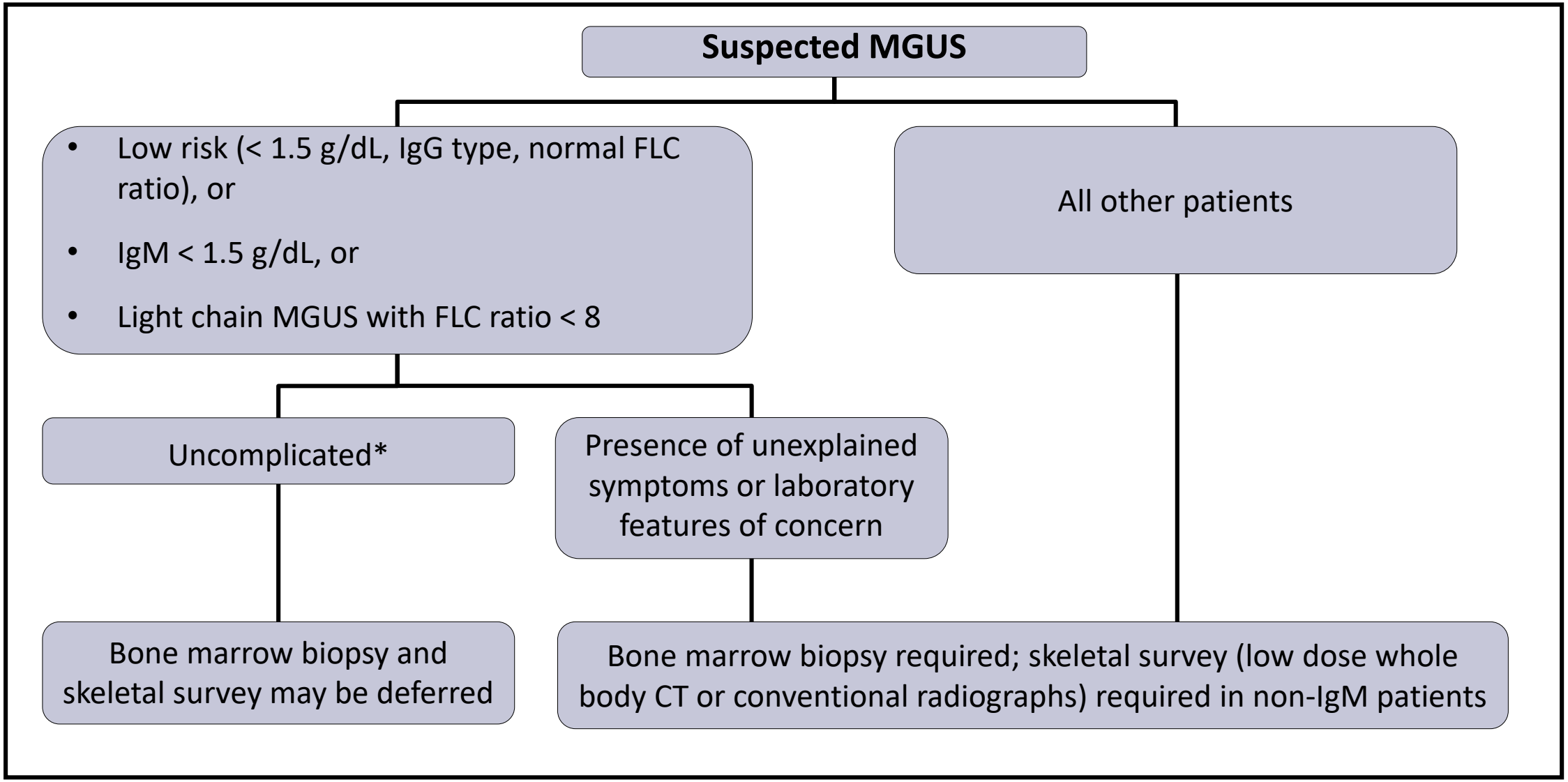
MGUS Risk Stratification: M spike size, M spike type, and FLC ratio



Rajkumar. Blood 2005;106:812.

Workup of Suspected MGUS

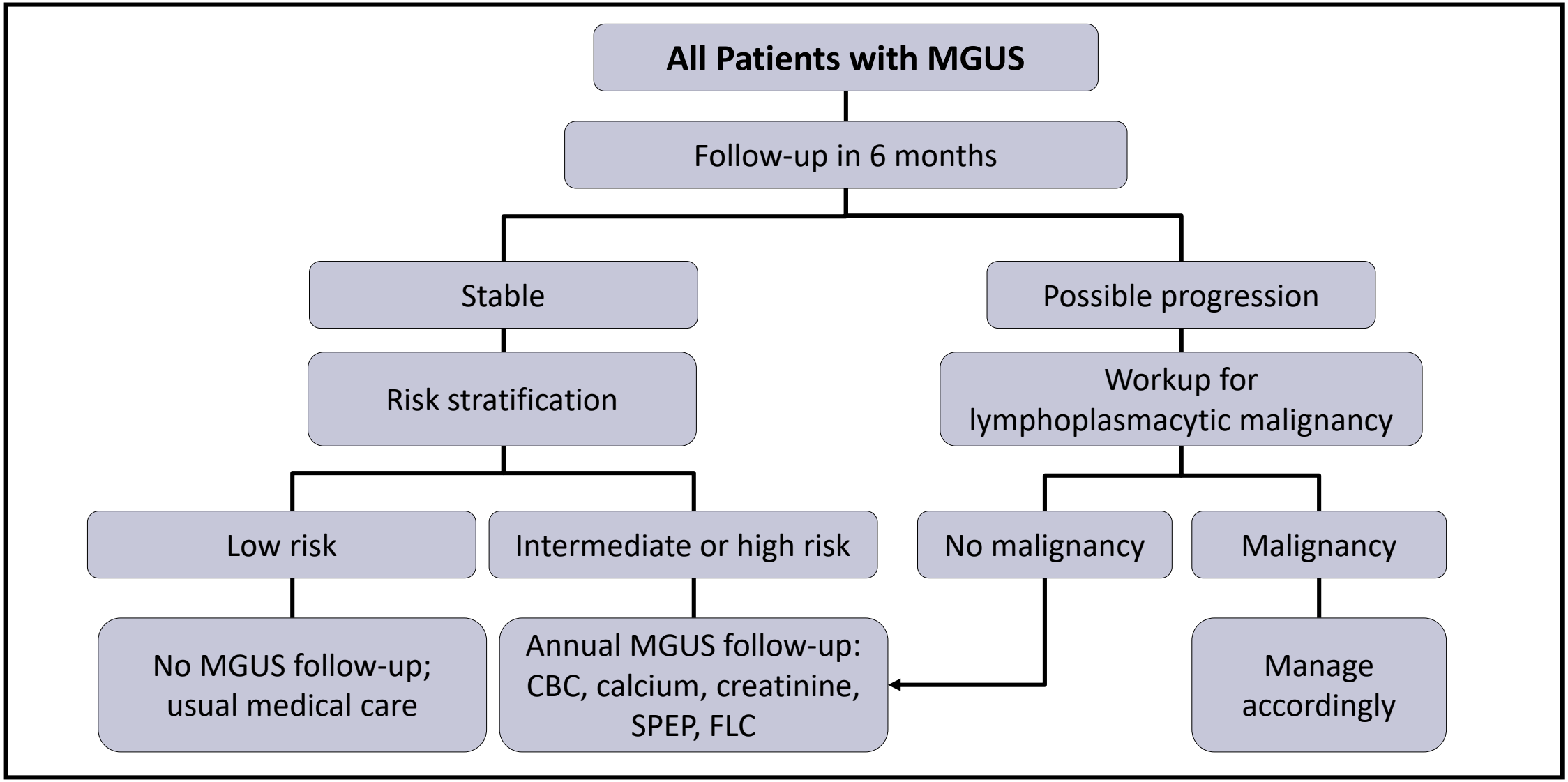


*No unexplained symptoms or laboratory features concerning for serious plasma cell disorder.

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

blood

Management of MGUS



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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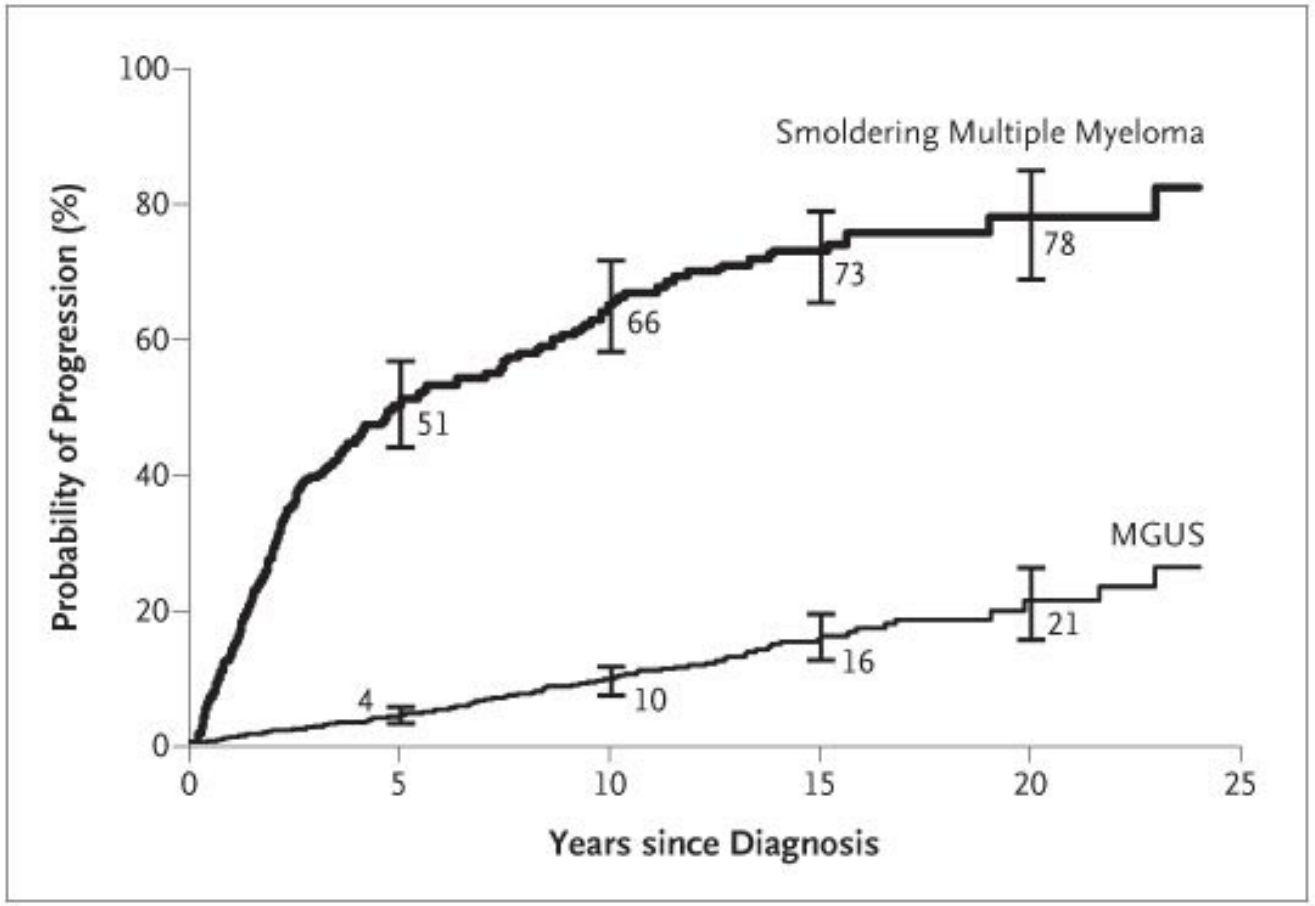
SMM vs MGUS



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

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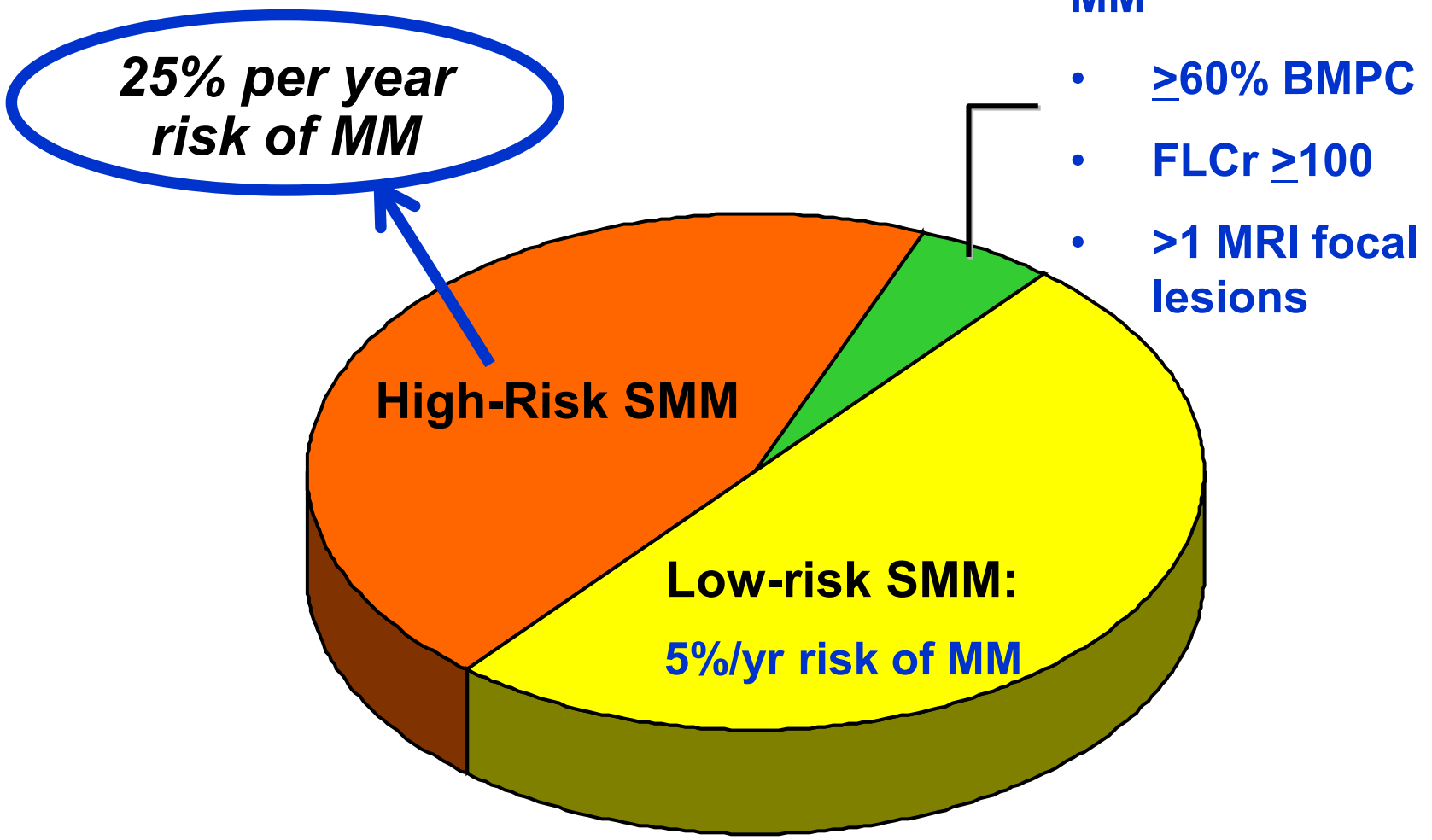
Smoldering Multiple Myeloma



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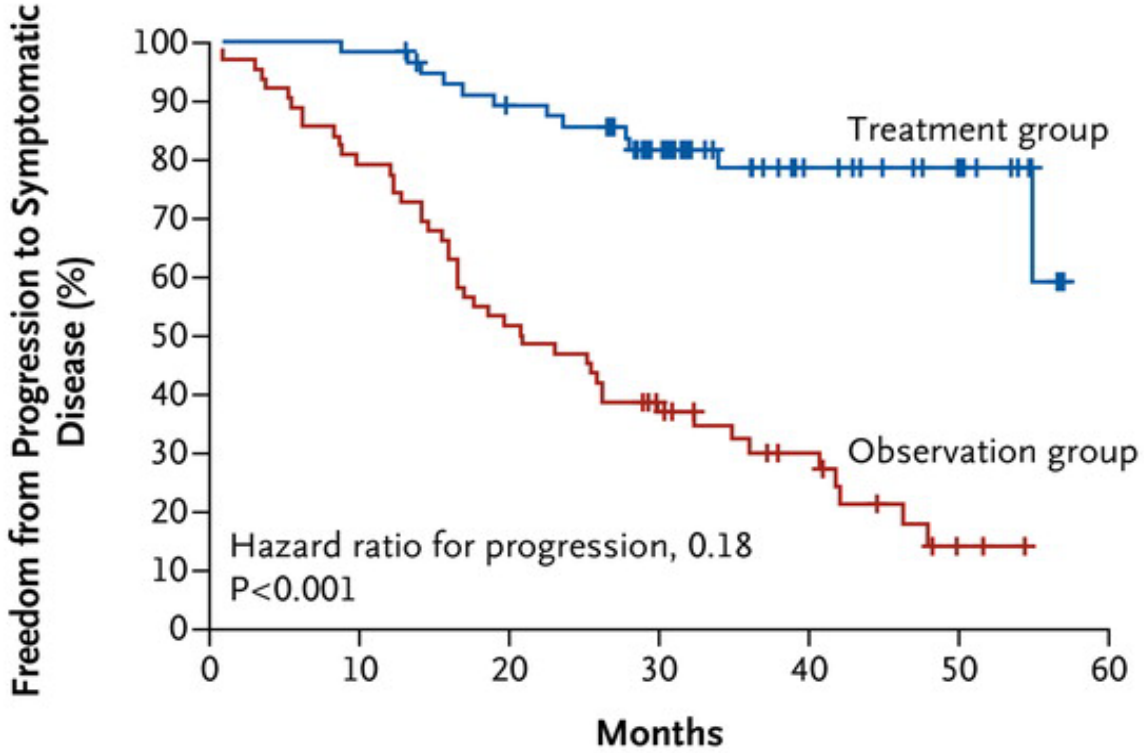
Len/Dex versus Observation in High Risk SMM: TTP



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.

The NEW ENGLAND JOURNAL of MEDICINE

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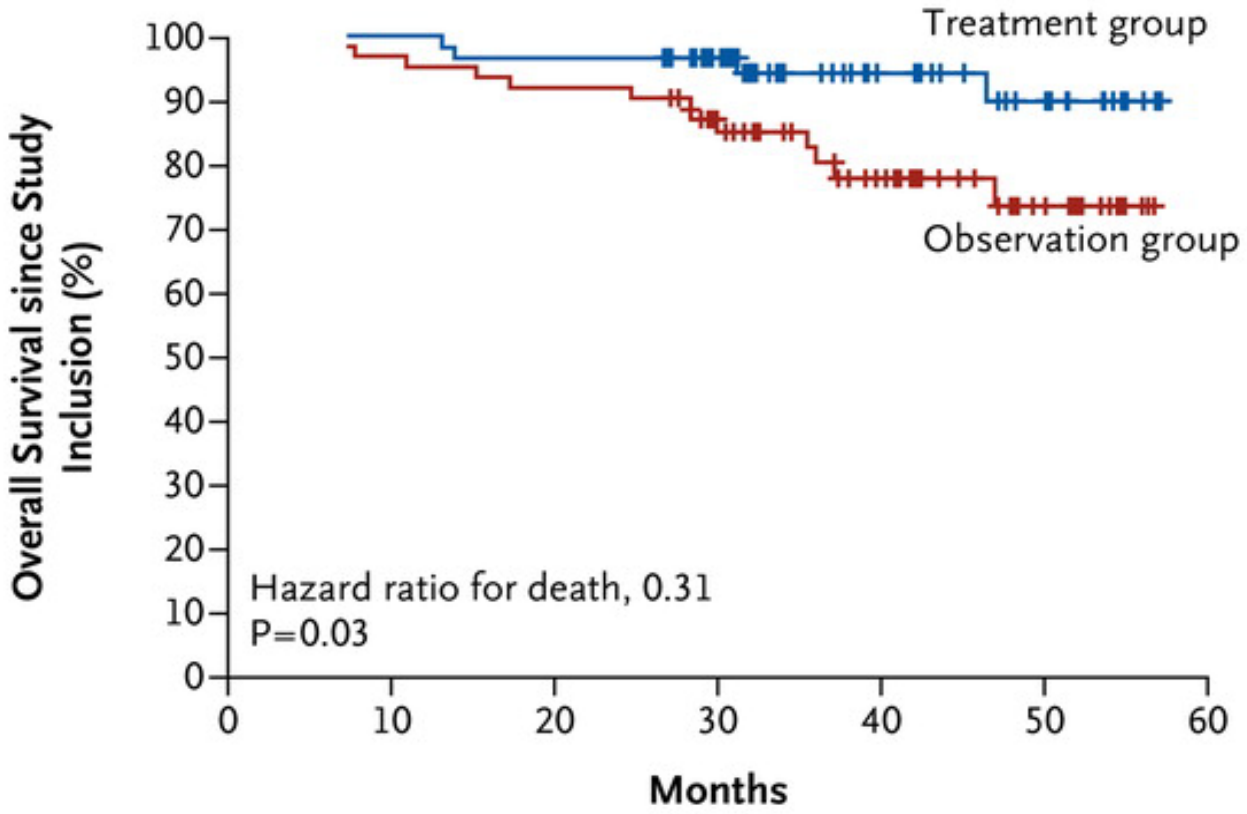
Len/Dex vs Observation in High-Risk SMM: OS



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.

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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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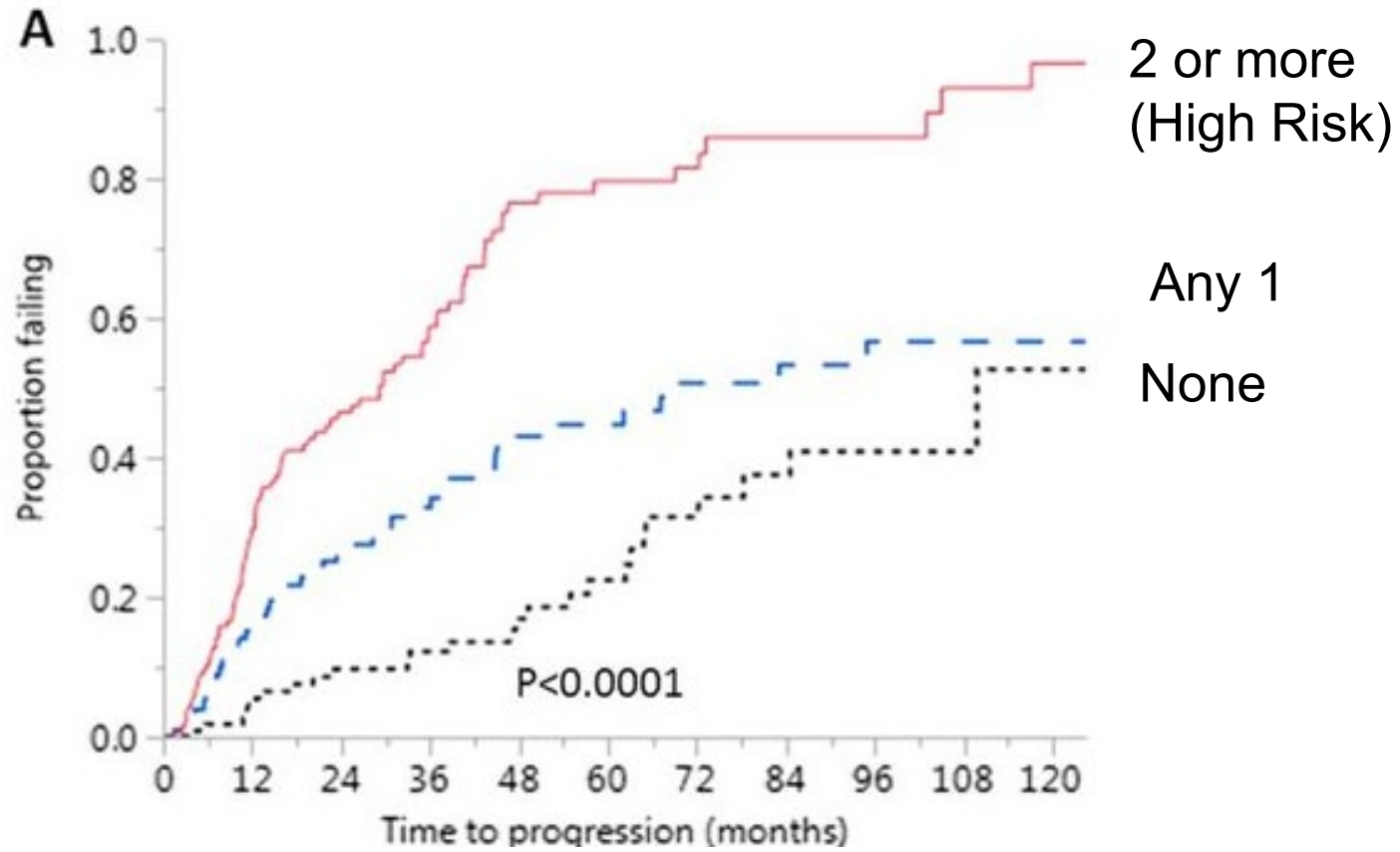
Mayo 20-2-20 Risk Stratification of SMM

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



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

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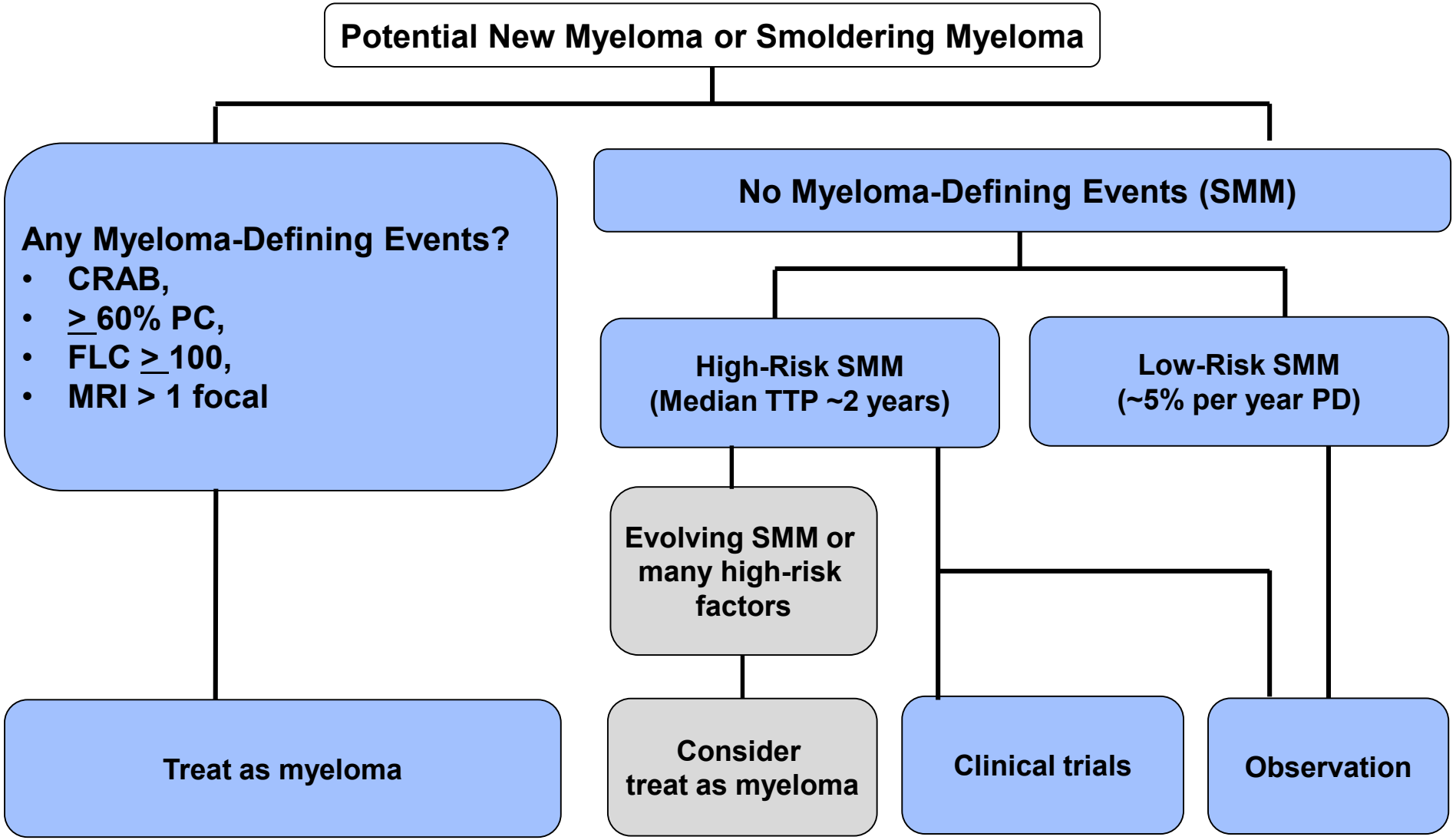
Management of SMM



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

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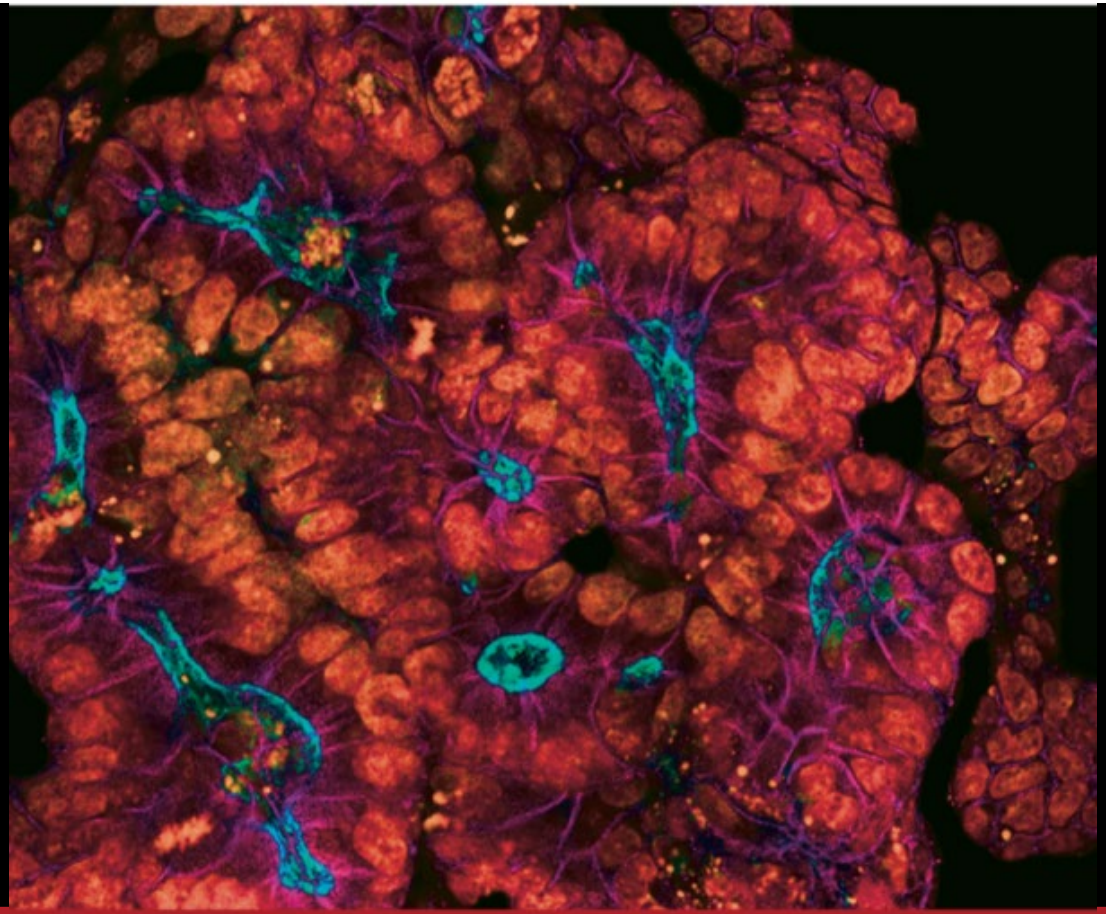
Multiple Myeloma

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)

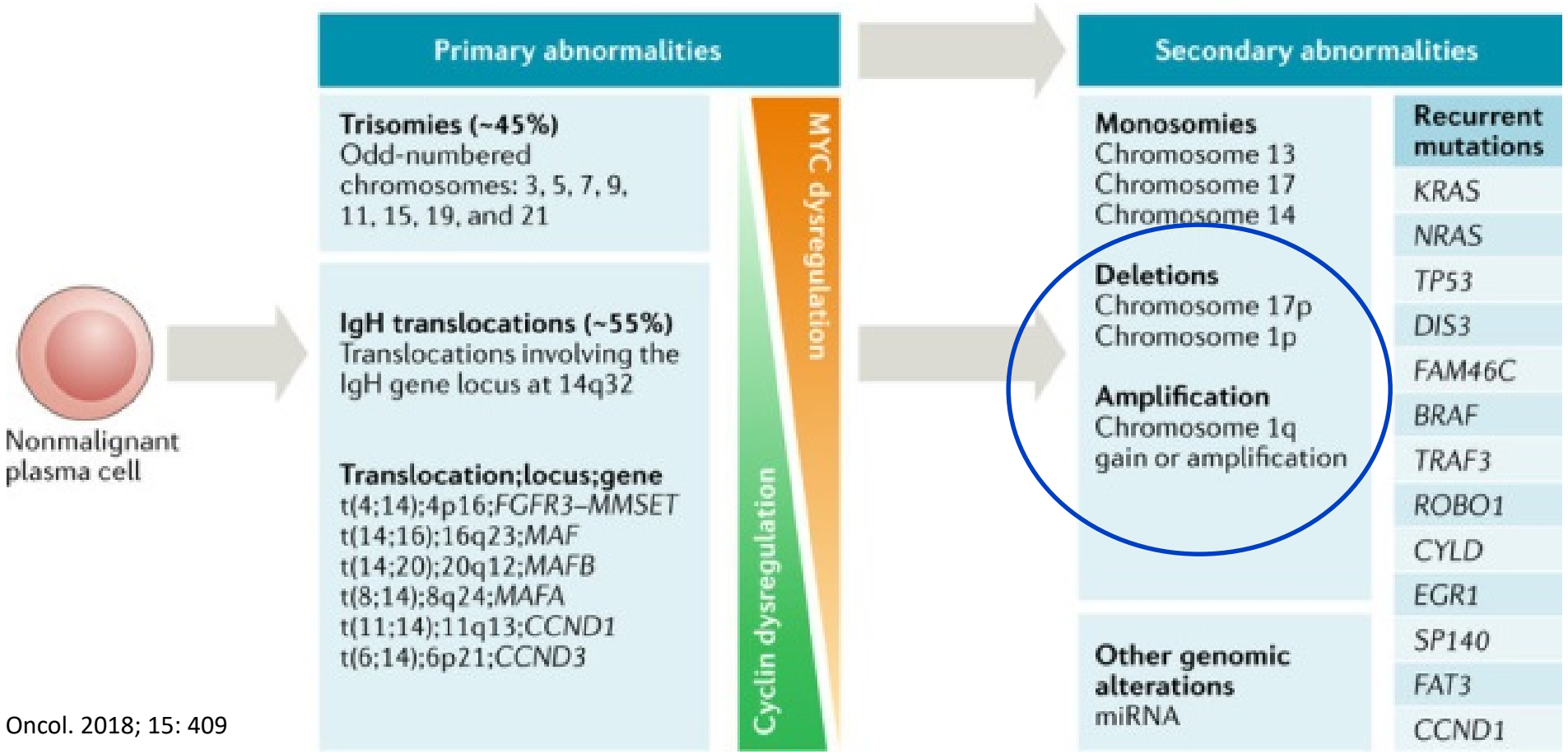
*~10% have both trisomies and IgH translocations

Kumar. Blood. 2012;119:2100.

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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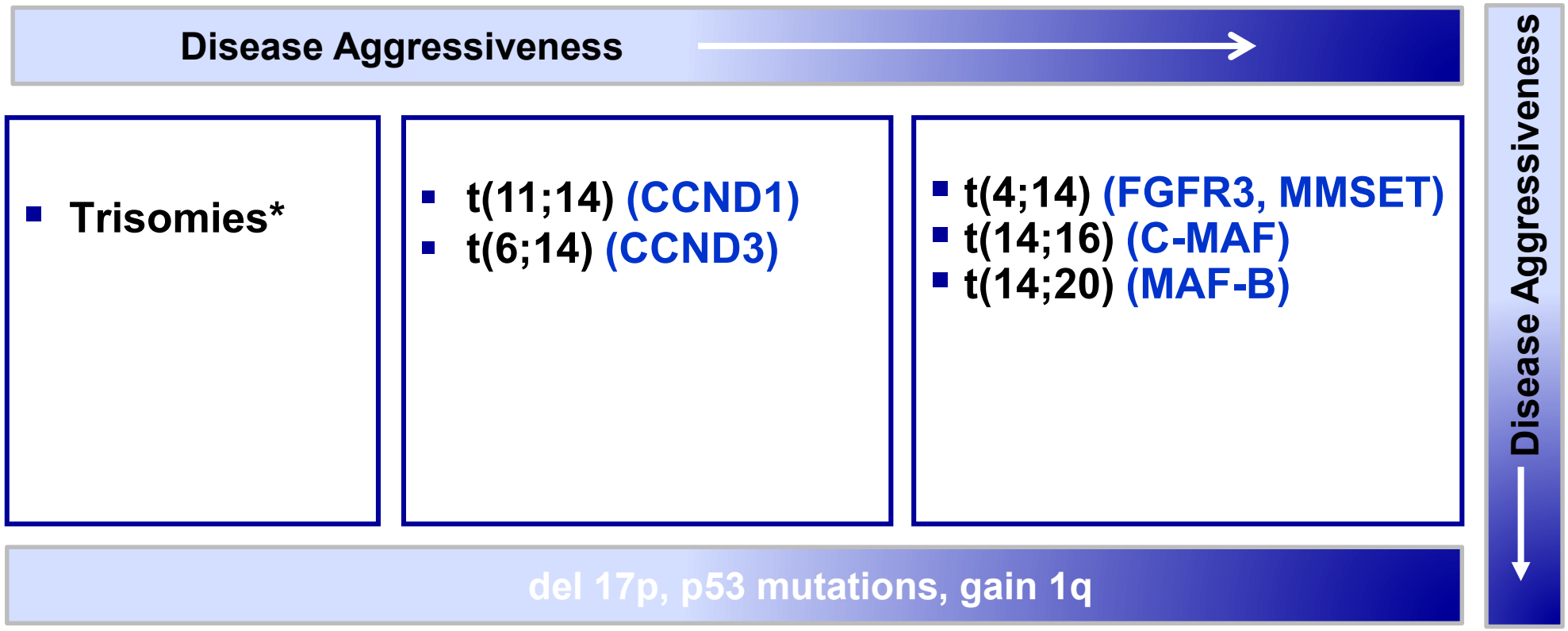
Cytogenetic Risk Stratification of Myeloma



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

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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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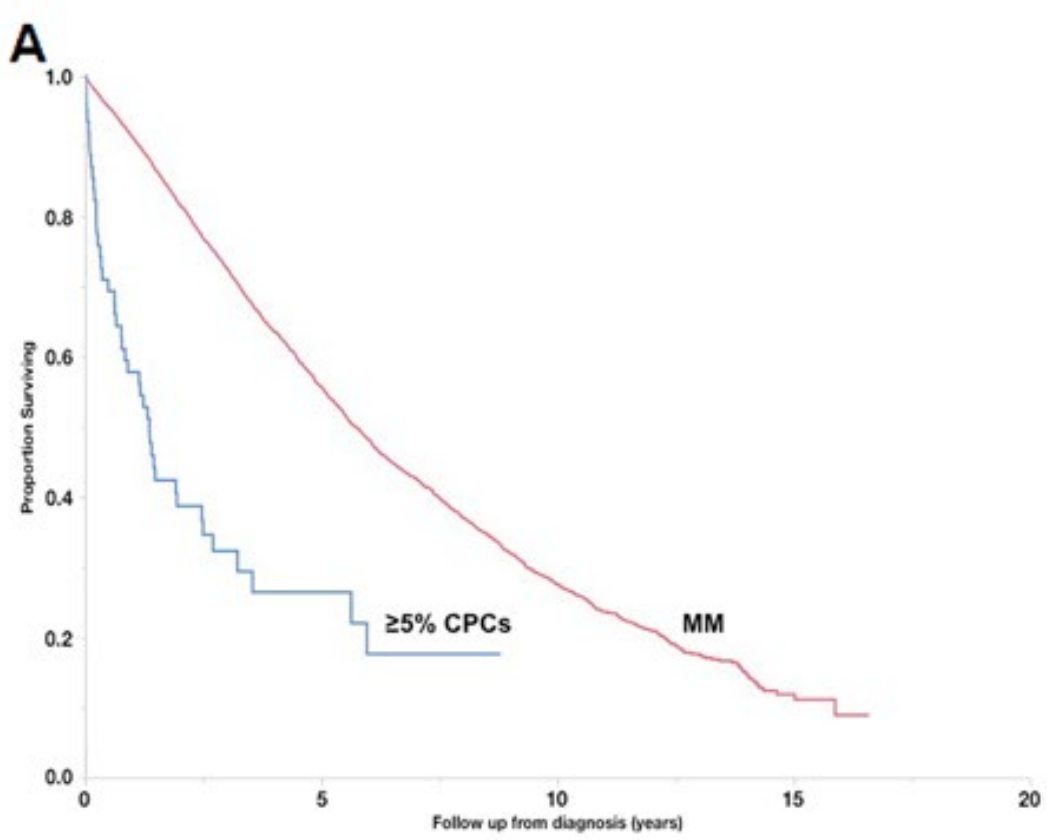
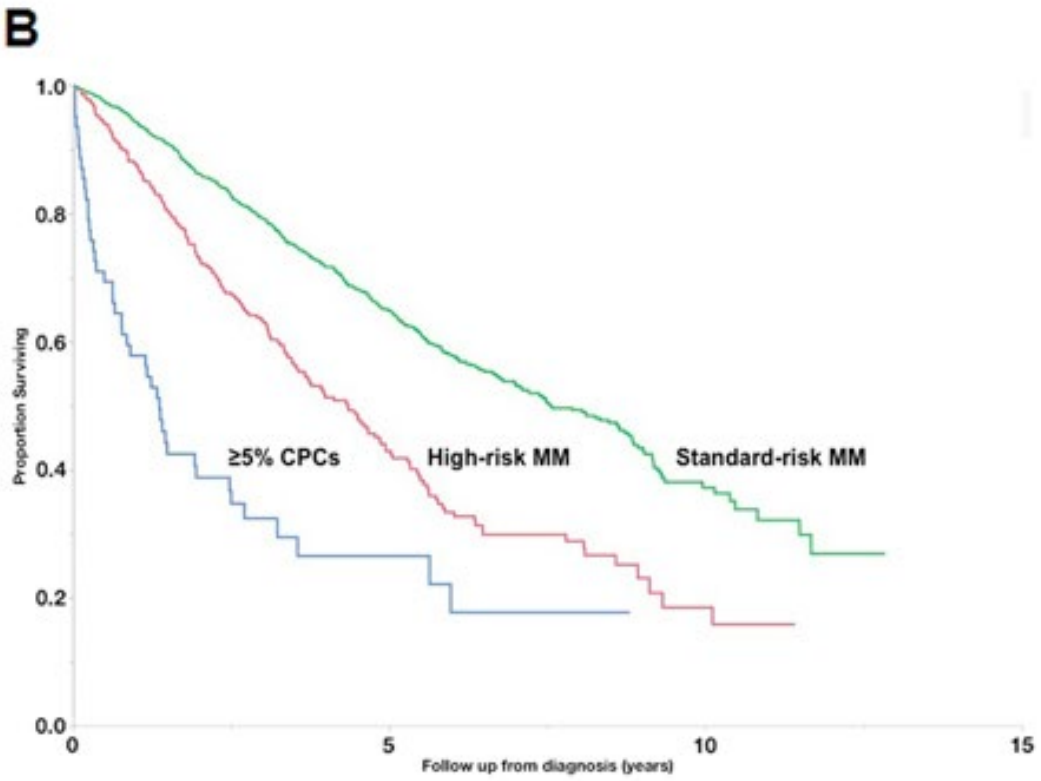
Plasma Cell Leukemia





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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Downloadable slides from this symposium (IMF link below)

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

clinicaloptions.com/MyelomaTool

clinicaloptions.com/oncology/topics/Multiple-Myeloma

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