

Diagnosis, Prognosis, and Risk Assessment in Multiple Myeloma

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Scottsdale, Arizona



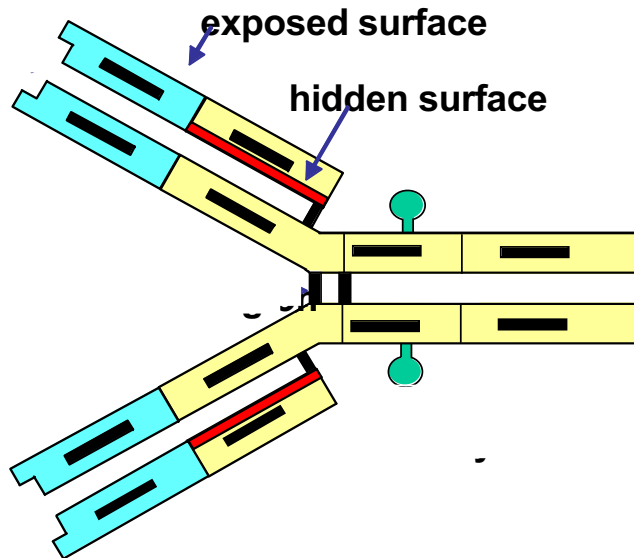
Rochester, Minnesota



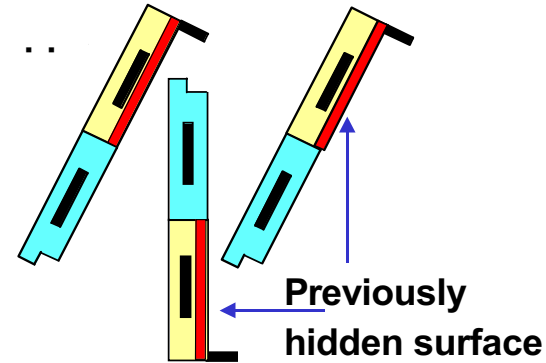
Jacksonville, Florida



Basis of the Free Light Chain Assay



Intact Immunoglobulin



Free Light Chain

Sensitivity 97%; Specificity 100%

Lachmann HJ, et al. Br J Haematol. 2003;122:78-84.

Katzmann JA, et al. Clin Chem. 2002;48:1437-1444

Bradwell, Serum free light chain assay

FLC assay

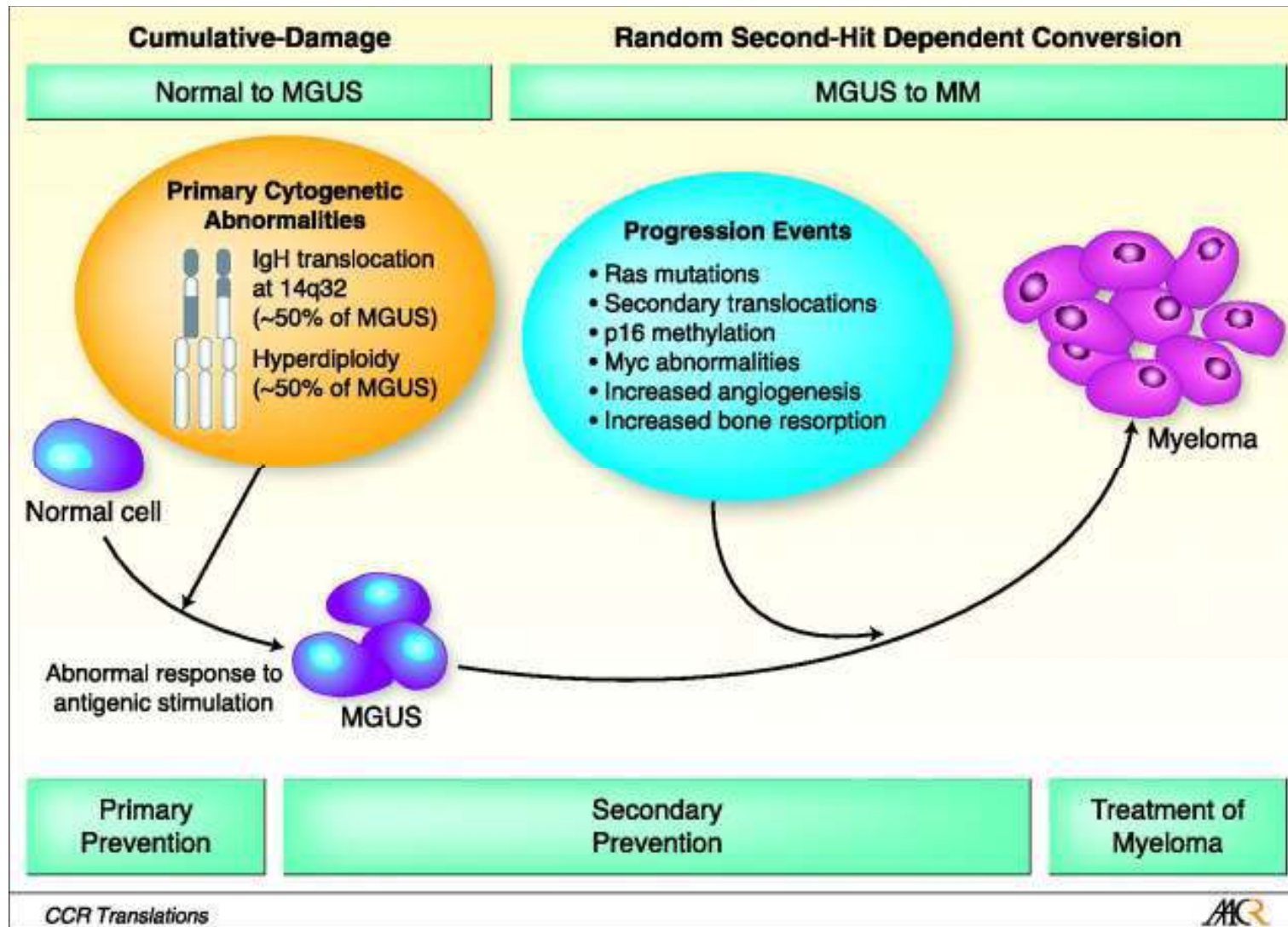
- **Free kappa: 0.33-1.94 mg/dL (3.3-19.4 mg/L)**
- **Free lambda: 0.57-2.63 mg/dL (5.7-26.3 mg/L)**
- **Normal K/L ratio: 0.26-1.65**



Role of the FLC Assay

- **Response assessment in patients who lack measurable disease**
- **Risk stratification of MGUS, SMM, solitary plasmacytoma**
- **Screening for MM instead of the UPEP**

Pathogenesis of MGUS and its progression to myeloma.



Rajkumar SV. Clin Cancer Res. 2009;15:5606-5608.

Definitions

MGUS

- **<3 g M spike AND
<10% PC**

SMM (AMM)

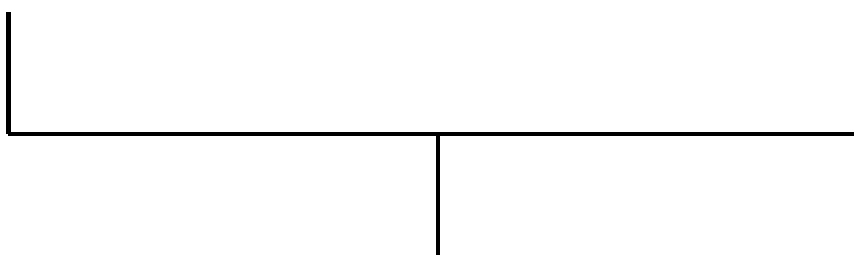
- **≥3 g M spike OR
≥10% PC**

MM

- **≥10% PC
• M spike +**

AND

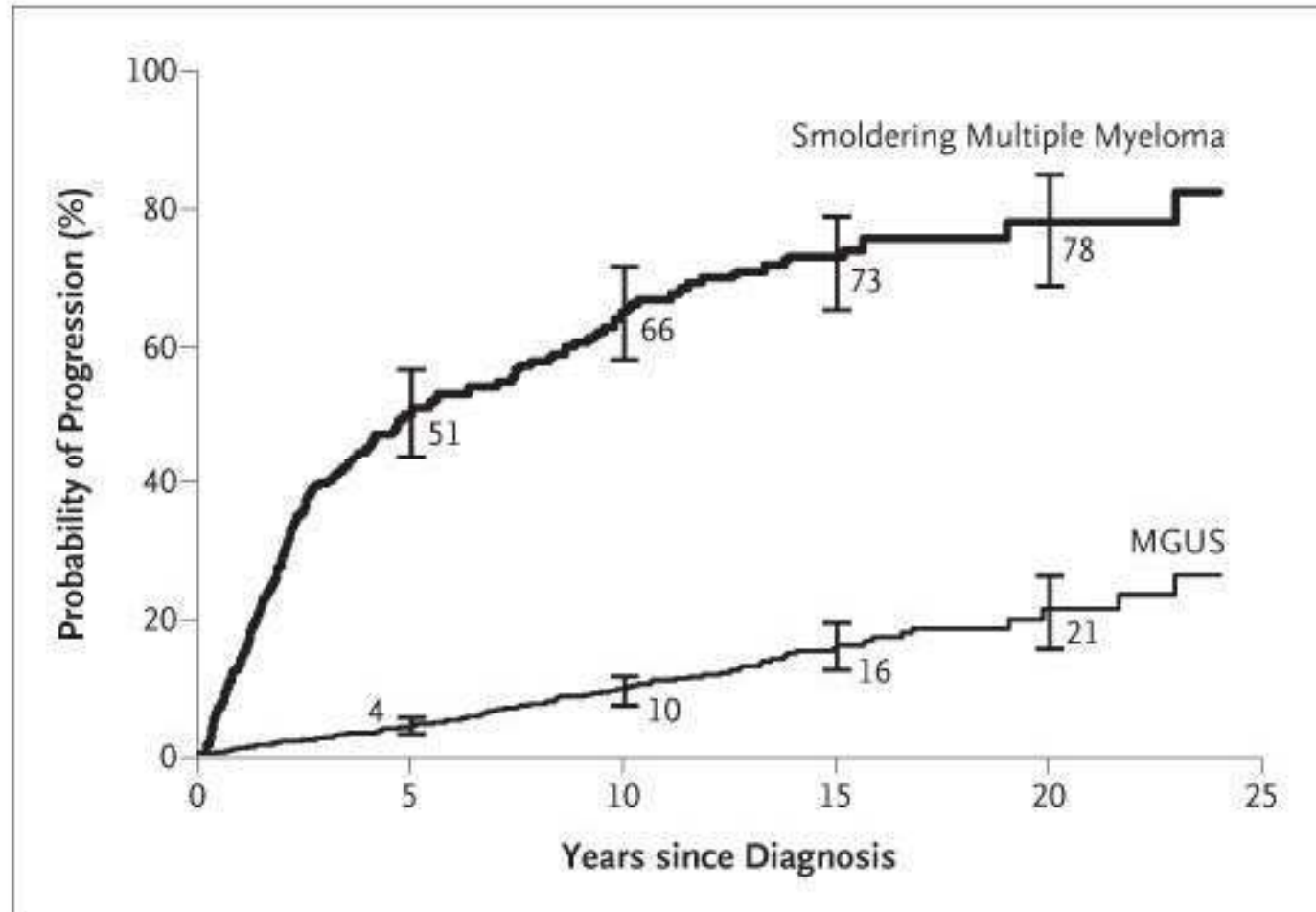
AND



**No anemia, bone lesions
Normal calcium and
kidney function**

**Anemia, bone lesions,
high calcium or
abnormal
kidney function felt
related to PCPD**

Probability of Progression to Active Multiple Myeloma or Primary Amyloidosis in Patients with Smoldering Multiple Myeloma or Monoclonal Gammopathy of Undetermined Significance (MGUS)



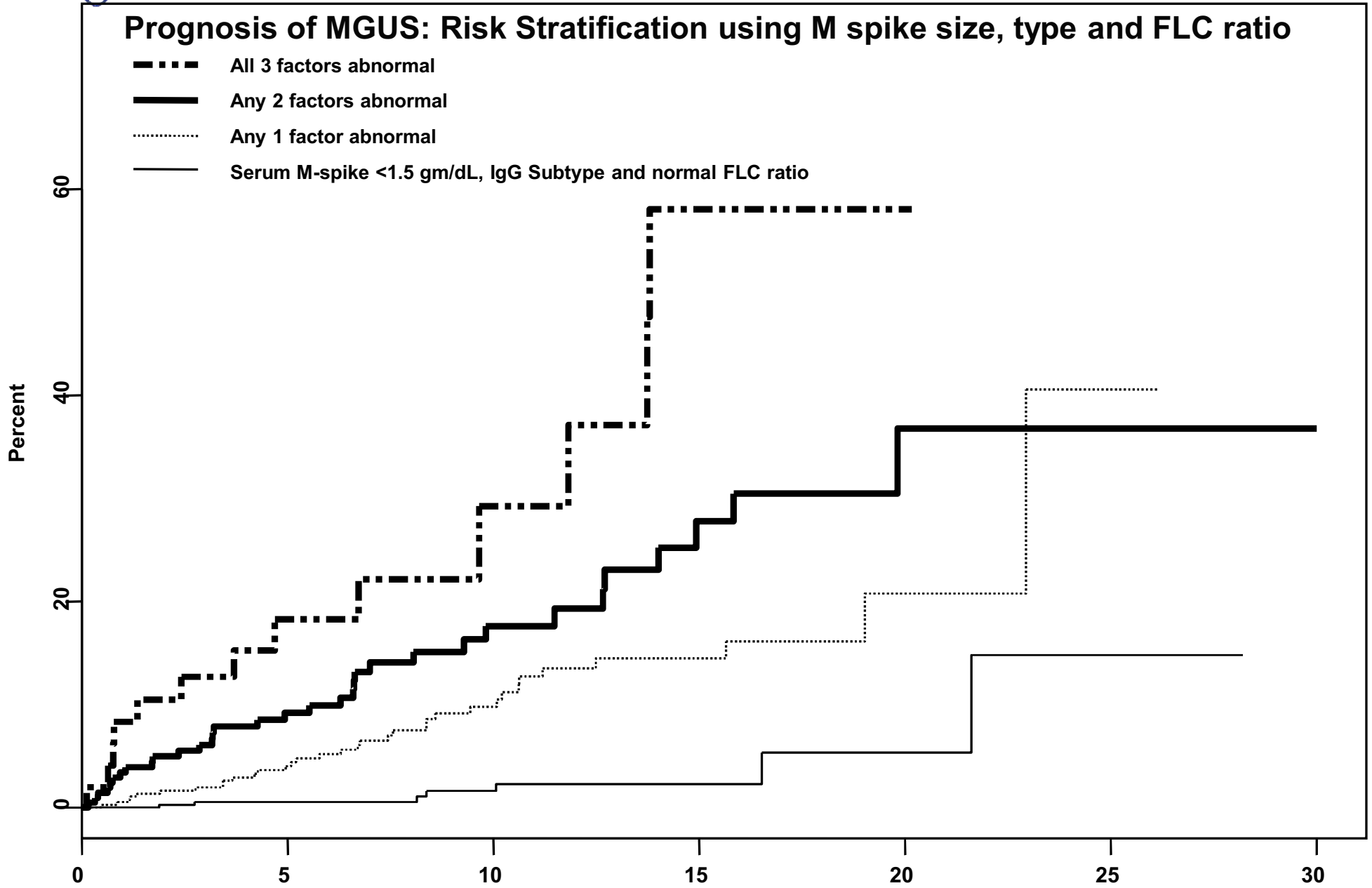
Kyle R, et al. *N Engl J Med.* 2007;356:2582-2590
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Prognosis of MGUS: Risk Stratification using M spike size, type and FLC ratio

- All 3 factors abnormal
- Any 2 factors abnormal
- Any 1 factor abnormal
- Serum M-spike <1.5 gm/dL, IgG Subtype and normal FLC ratio



This research was originally published in Blood.

© The American Society of Hematology.

Years

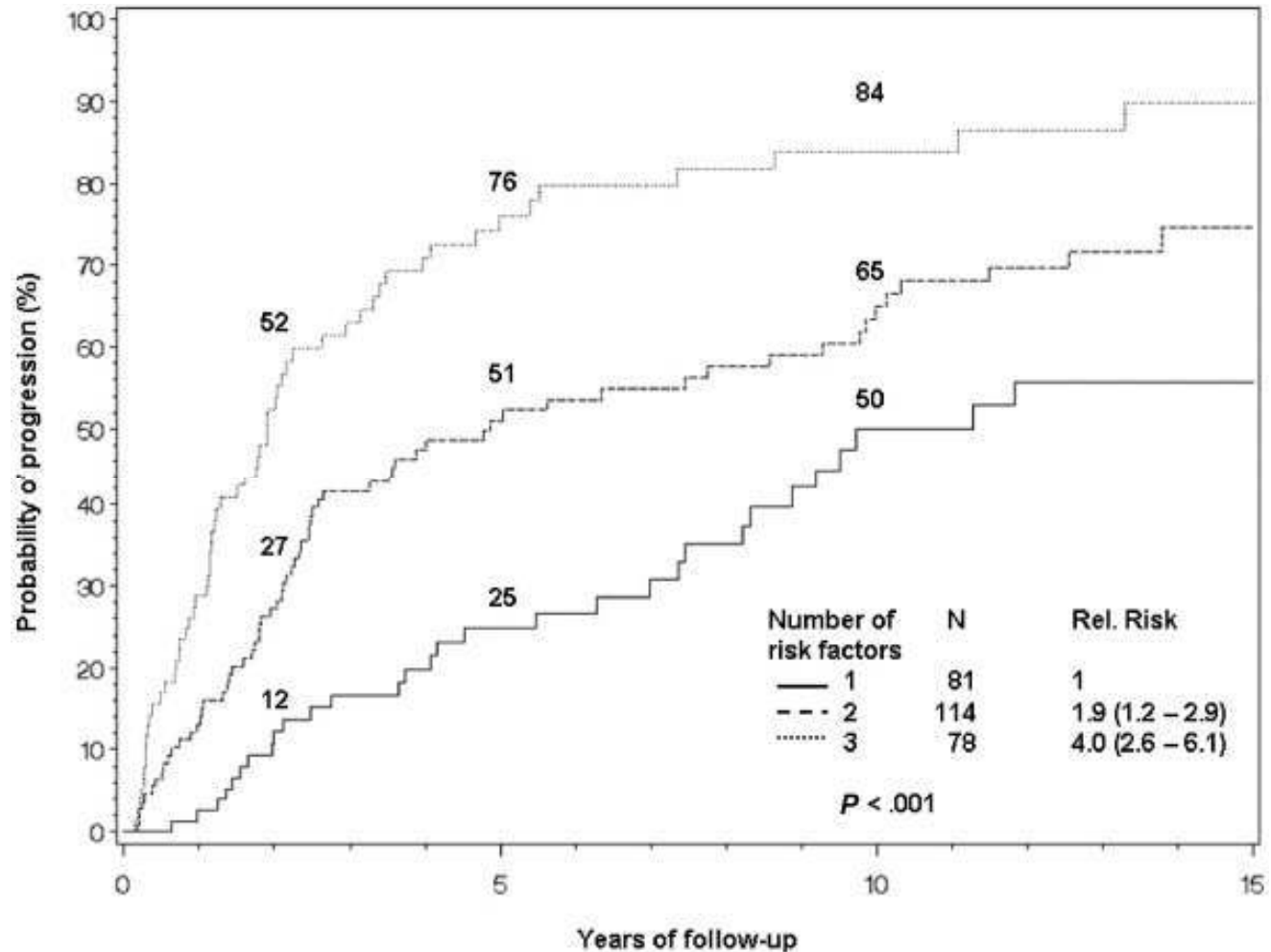
Rajkumar SV, et al. Blood. 2005;106:812-817.



Risk stratification based on bone marrow plasmacytosis, serum M protein, and serum immunoglobulin FLC ratio

blood

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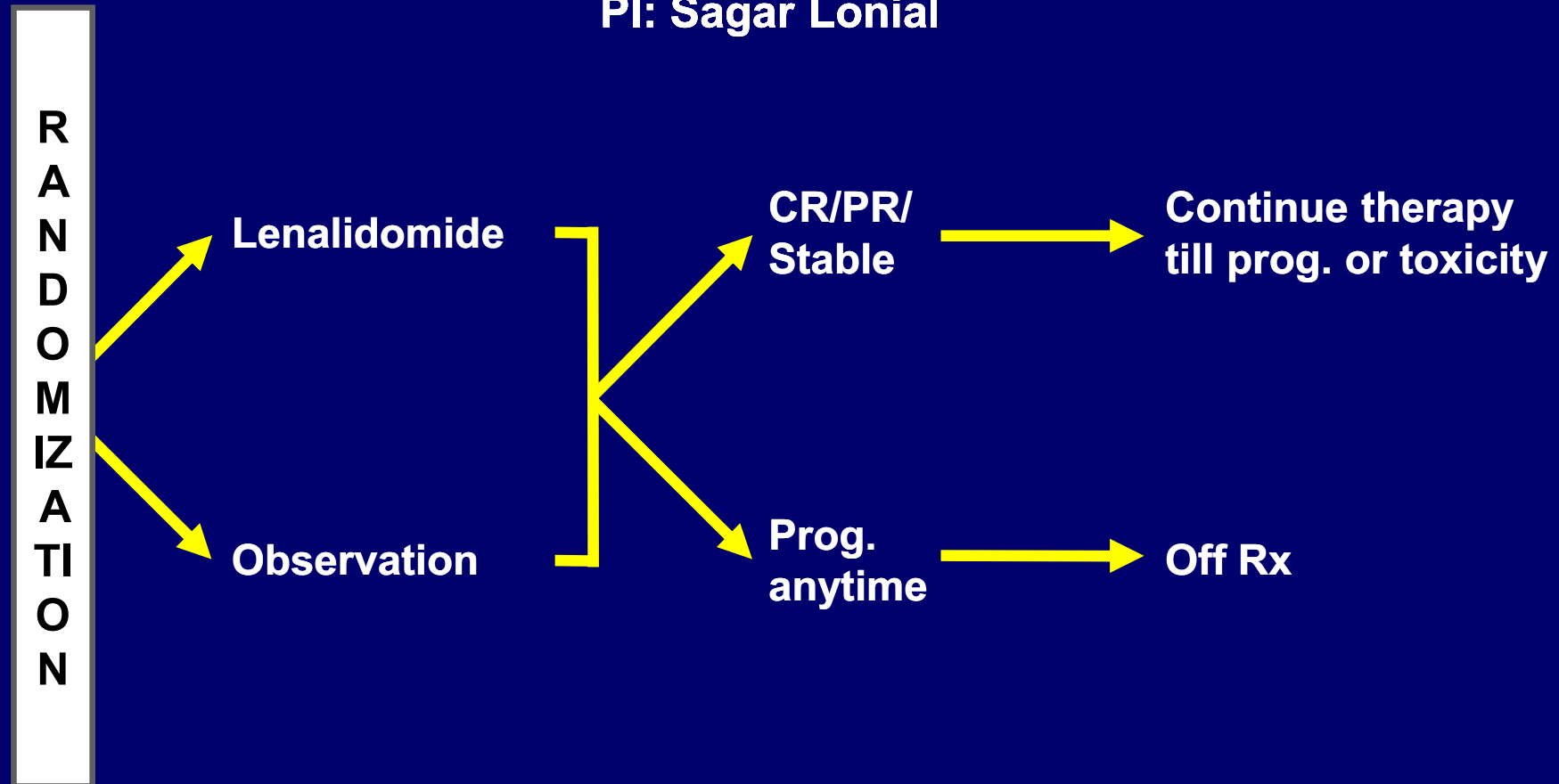
Dispenzieri A, et al. Blood. 2008;111:785-789.

Initial Therapy of MM

E3A06: Phase III – High-Risk Smoldering Myeloma*

Lenalidomide vs. observation

PI: Sagar Lonial



ClinicalTrials.gov. NCT01169337.

* Concept approved by CTEP

eastern cooperative oncology group

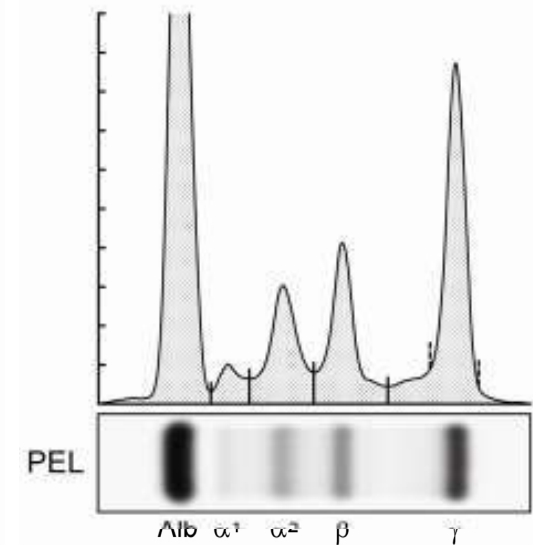
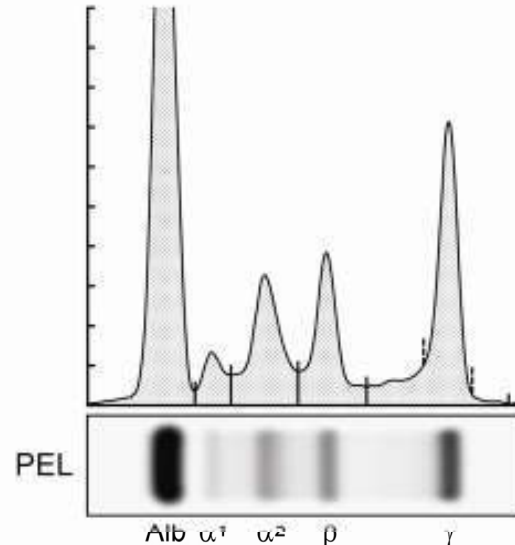
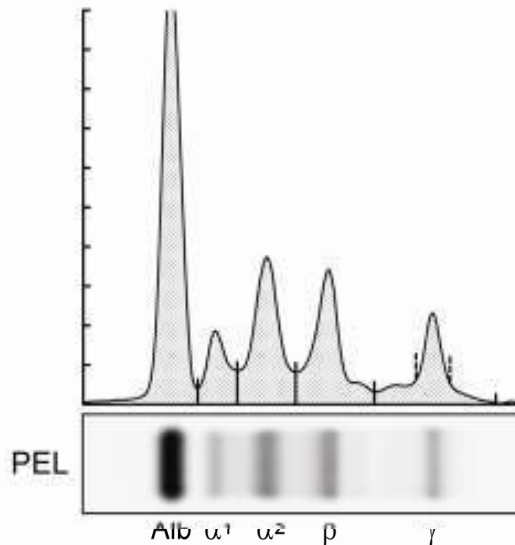


Work up of Myeloma

- M protein
 - SPEP: 82%
 - SIFE: 93%→ FLC or UPEP/UIFE: 97-98%
- Lytic bone lesions (67%) → PET-CT or MRI
- $\geq 10\%$ clonal PCs in BM (96%)
- Anemia (73%)
- Hypercalcemia ≥ 11 (13%)
- Renal failure, serum creatinine ≥ 2.0 (19%) → Calculated Creat. Clearance



Monoclonal Protein



Bone Marrow/ M Protein

<10% plasma cells
AND <3 gm/dL M protein

≥10% plasma cells **OR** ≥3 gm/dL M protein

≥10% plasma cells

Clinical Picture

Asymptomatic
No end-organ damage*

Asymptomatic
No end-organ damage

Symptomatic
End-organ damage present

Therapy

Observation only

Observation only

Therapy required

*Hypercalcemia, anemia, renal failure or lytic bone lesions attributable to plasma cell disorder

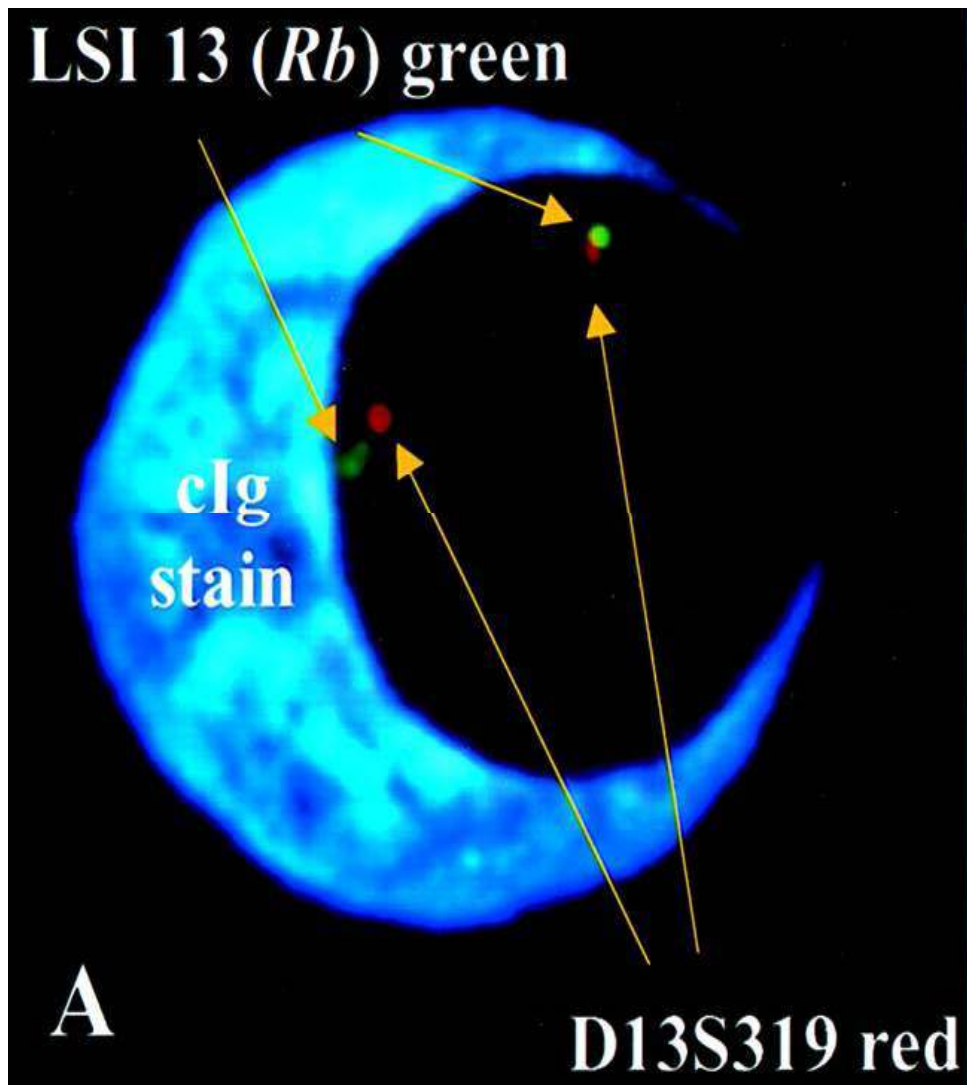
Durie-Salmon Staging System

| Stage | Criteria | Myeloma cell mass (x 10 ¹² cells/m ²) |
|-------|---|--|
| I | Hemoglobin >10 g/dL Serum ca ≤12 mg/dL Normal or solitary plasmacytoma IgG <5 g/dL; IgA <3 g/dL Bence Jones protein <4 g/24 | <0.6 (low) |
| II | Not fitting stage I or II | 0.6–12 (intermediate) |
| III | Hemoglobin <8.5 g/dL Serum ca >12 mg/dL Multiple lytic bone lesions IgG >7 g/dL; IgA <5 g/dL Bence Jones protein >12 g/24 | >1.2 (high) |
| | Subclassification | |
| | A | |
| | B | |

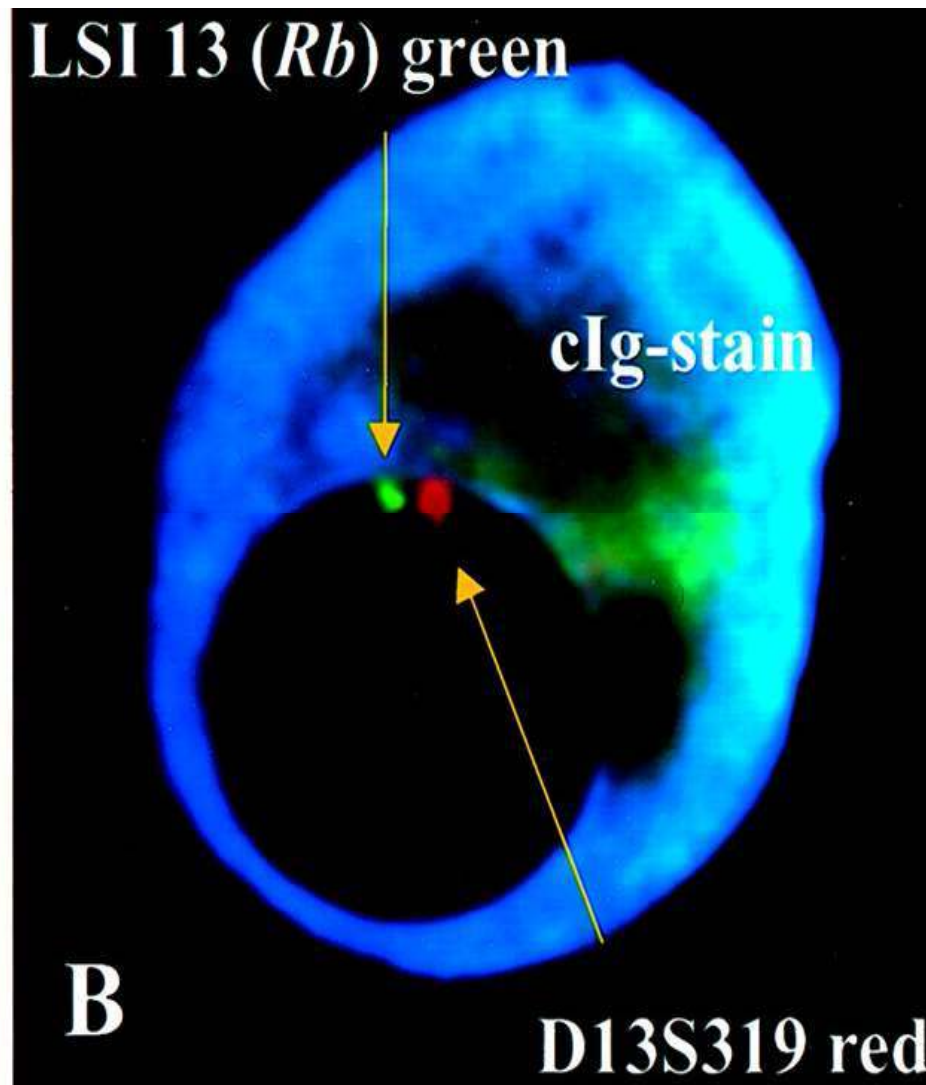
International Staging System for Myeloma

| Stage | Survival in Months |
|---|--------------------|
| Stage I $\beta 2M < 3.5$ and albumin ≥ 3.5 | 62 |
| Stage II Not meeting criteria for Stage I or III | 44 |
| Stage III $\beta 2M \geq 5.5$ | 29 |

Deletion 13



Normal

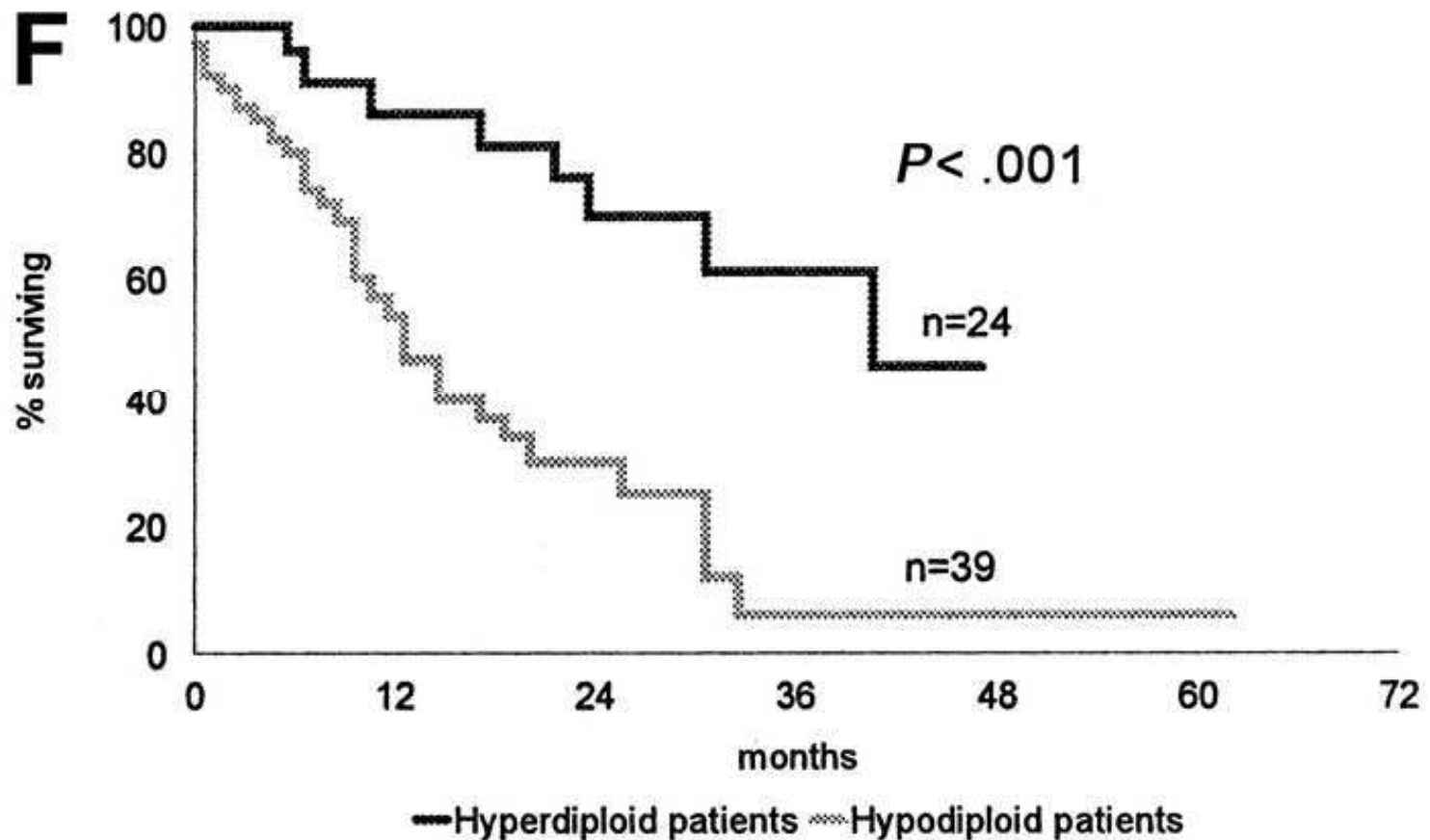


Deletion 13

Impact of Del 13 and Hypodiploidy in TT1 Trial

- Median OS (from start of protocol therapy)
 - No CA: 83 months
 - Other CA: 68 months
 - CA13/HYPO: 32 months
- } $P = .004$

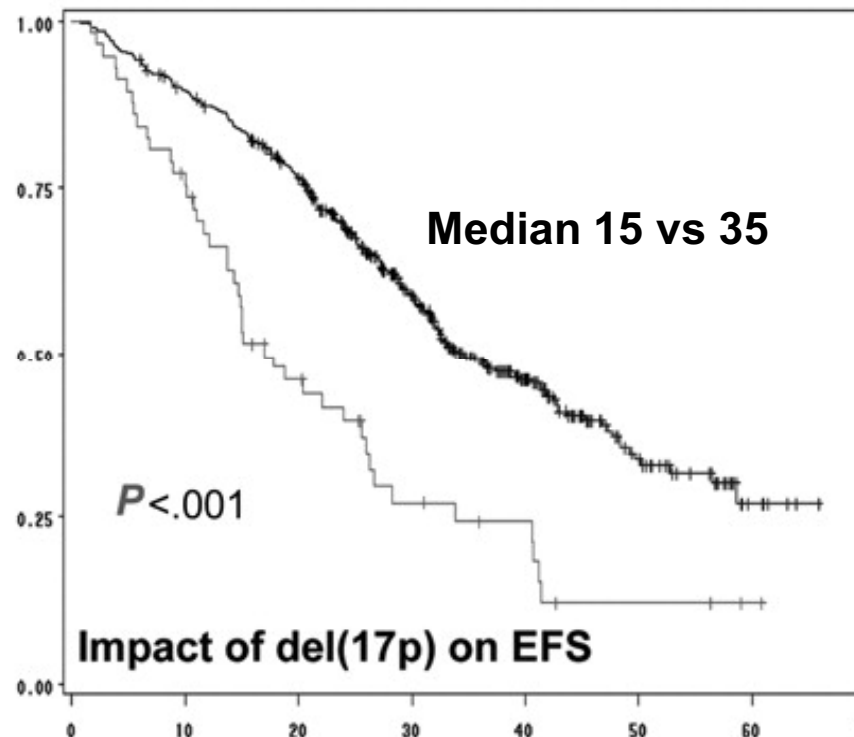
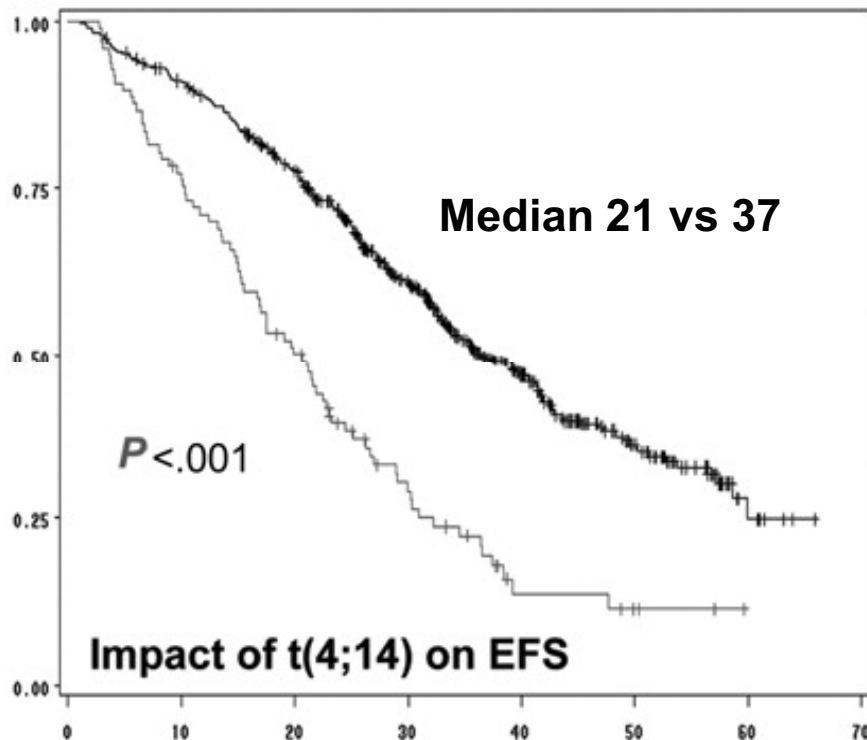
Impact of Hypodiploidy in patients with Del 13



Impact of genomic aberrations* on EFS in IFM 99 Trials

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N=1064



*Significant on multivariate

~15% of pts

(~85% had FISH del 13)

~10% of pts

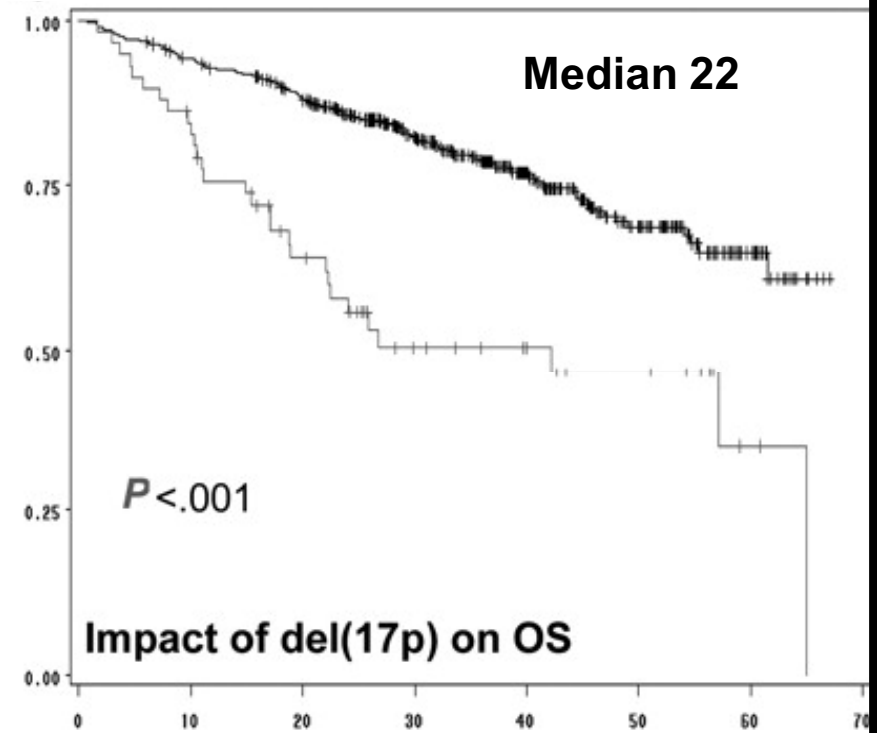
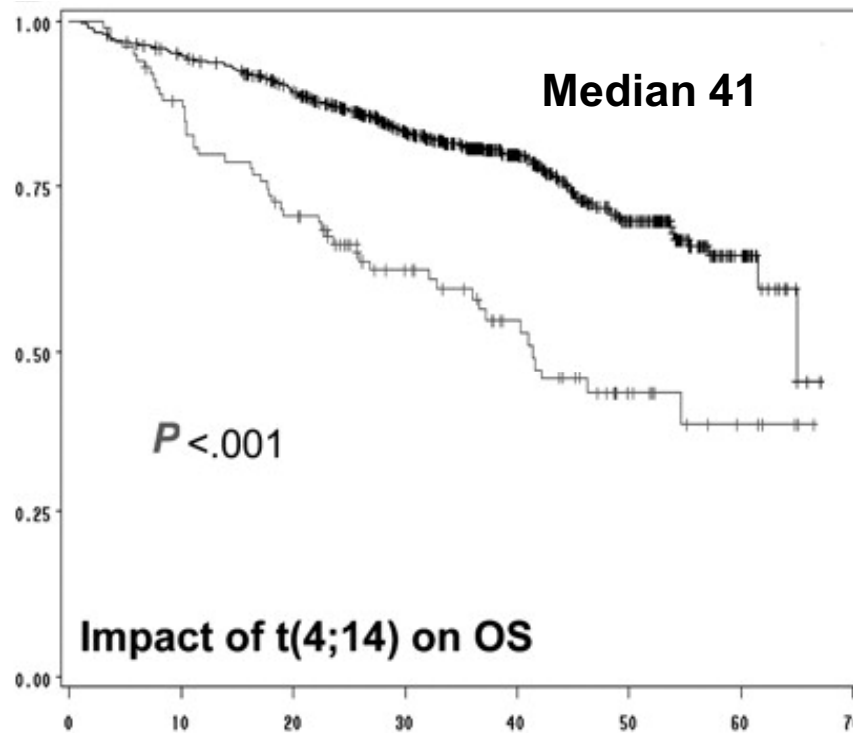
(~80% had FISH del 13)

Impact of genomic aberrations on OS in IFM 99 Trials

blood

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N=1064



*Significant on multivariate

GEP-based Risk Stratification

- 24-month estimated OS
 - Low GEP risk: 90%
 - High GEP risk: 66%

} $P < .0001$

- 24-month estimated EFS
 - Low GEP risk: 88%
 - High GEP risk: 57%

} $P < .0001$

Myeloma Risk-Stratification v2.0

High-Risk

- FISH
 - Del 17p
 - t(14;16)
 - t(14;20)
- GEP-defined high-risk

Intermediate-Risk

- FISH
 - t(4;14)
- Cytogenetic Deletion 13 or hypodiploidy

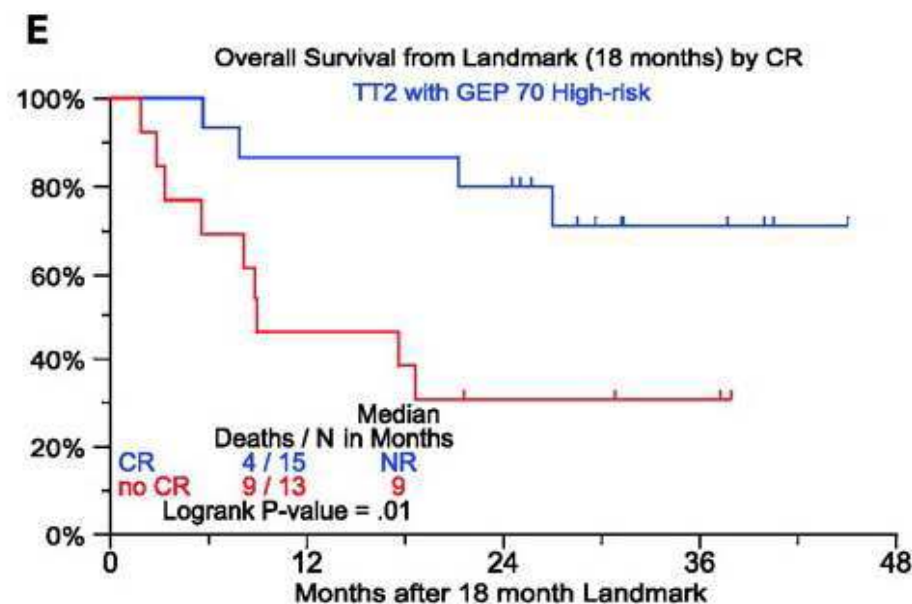
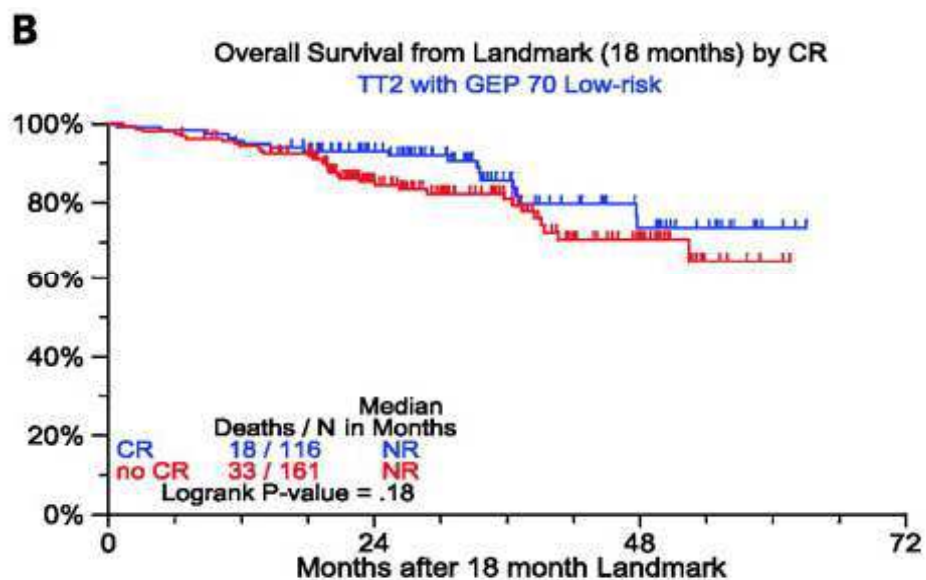
Standard-Risk

- All others including:
- Hyperdiploid
 - t(11;14)
 - t(6;14)

CR is critical in patients with high-risk myeloma

Low-Risk MM (87%)

High-Risk MM (13%)



Haessler J, et al. Clin Cancer Res. 2007;13:7073-7079.

Myeloma Risk-Stratification v2.0

High-Risk Experimental Therapy

- FISH
 - Del 17p
 - t(14;16)
 - t(14;20)
- GEP defined high-risk

Intermediate-Risk Bortezomib-based Therapy

- FISH
 - t(4;14)
- Cytogenetic Deletion 13 or hypodiploidy

Standard-Risk Control approach

- All others including:
- Hyperdiploid
 - t(11;14)
 - t(6;14)