APPROCCI INTERDISCIPLINARI IN REUMATOLOGIA

5a Edizione

REUMATOLOGIA E MALATTIE NEOPLASTICHE

Torino, 13-14 ottobre 2017

Linee Guida per la gestione delle Gammopatie Monoclonali di significato indeterminato (MGUS)

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Monoclonal gammopathy

Malignant

Plasma cell disease

- Monoclonal gammopathy of undetermined significance
- Multiple myeloma
- Smouldering multiple myeloma
- AL amyloidosis
- Other rarer malignant plasma cell disorders

B-cell (usually IgM) disease

- Lymphoplasmacytic lymphoma/Waldenstrom macroglobulinemia
- Chronic lymphocytic leukemia
- Small lymphocytic lymphoma
- Marginal zone lymphoma
- Other indolent lymphomas (rare)

Benign

Autoimmune/inflammatory disease

- Rheumatoid arthritis, ankylosing spondylitis
- Systemic lupus erythematosis, scleroderma, Sjogren syndrome
- Vasculitis, polymyalgia rheumatica
- Paraprotein-associated neuropathies

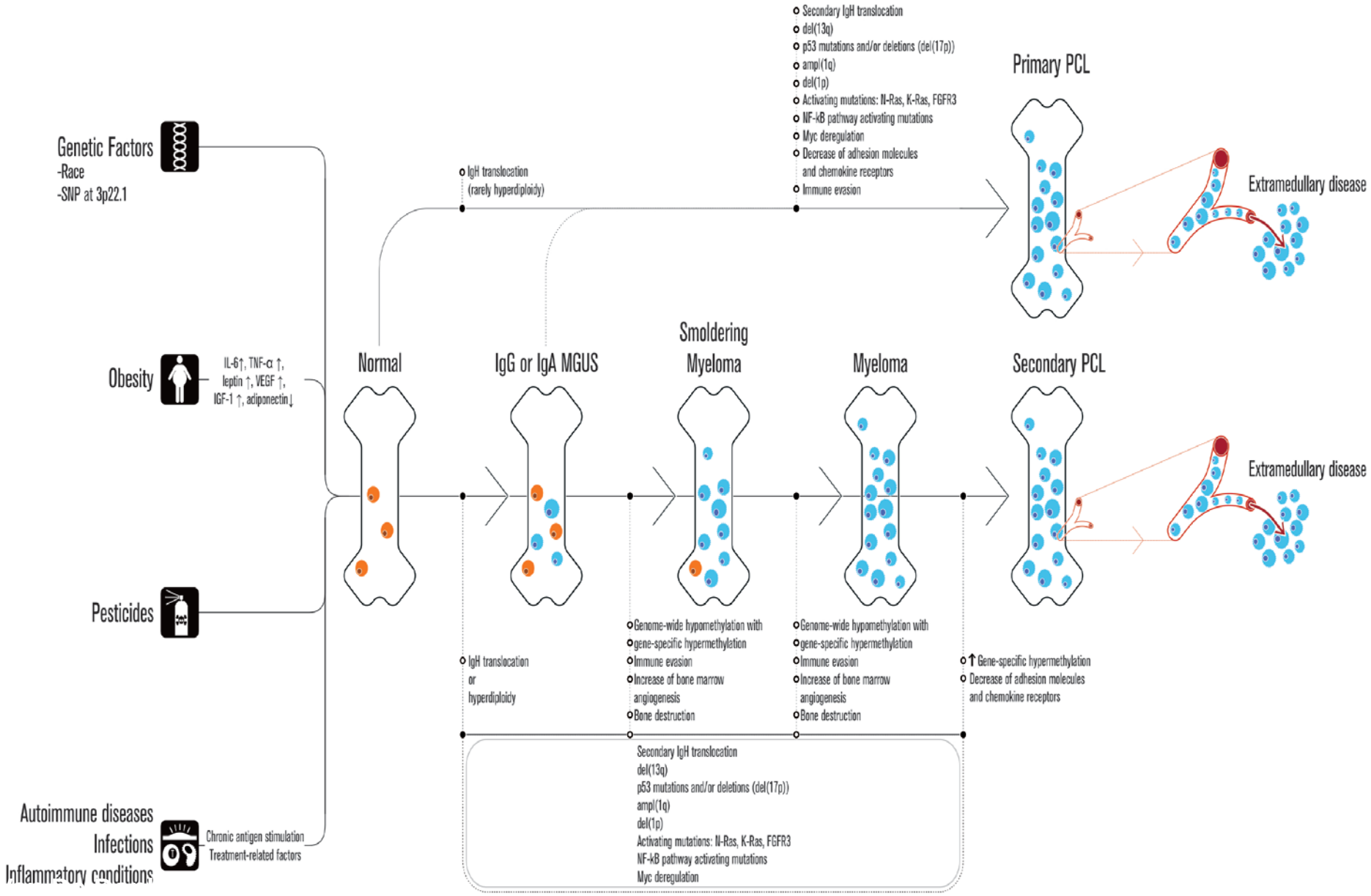
Infectious disease

- Viral infections (EBV, CMV, HIV, HBV, HCV)
- Severe acute infections
- Subacute or chronic infections (osteomyelitis, endocarditis, abscess)

Posttransplant effect

- Response to stem cell or solid organ transplantation

Biology: IgG and IgA MGUS



MGUS: 3 subtypes

Tumor load

Aymptomatic low-risk of progression	Asymptomatic high-risk of progression	Symptomatic
Non-IgM MGUS	SMM	MM
IgM MGUS	SWM	WM
Light-chain MGUS	Idiopathic Bence Jones proteinuria	Light-chain MM

Differential diagnosis of MGUS, SMM and Multiple Myeloma

Feature	MGUS	SMM	MM requiring therapy
Serum M-protein	<3 g/dL and	≥3 g/dL and/or	–
Clonal BMPC infiltration	<10 %	10–60 %	≥10 % or biopsy-proven plasmacytoma
Symptomatology	Absence of MDE*	Absence of MDE*	Presence of MDE*

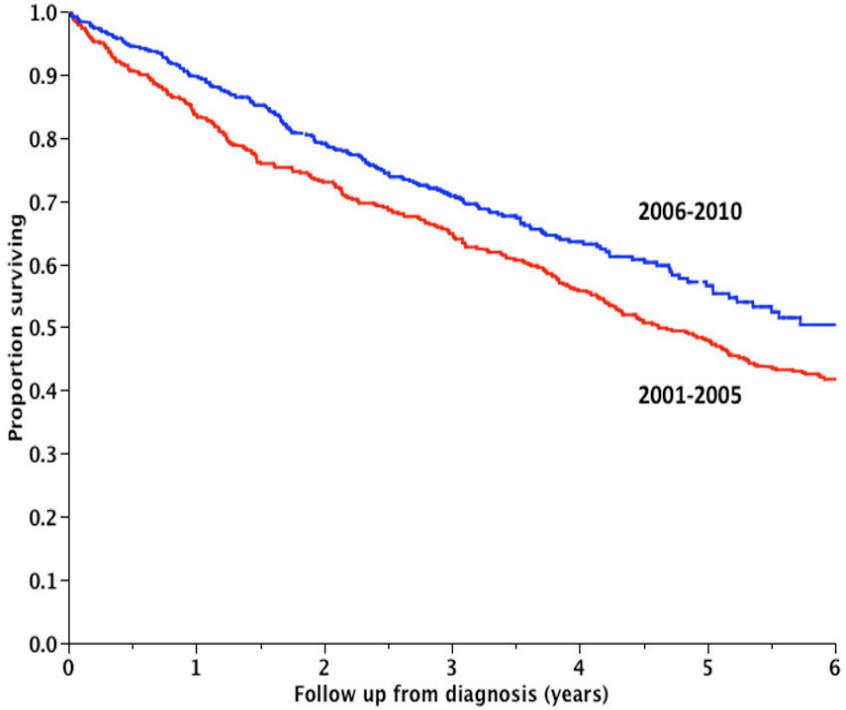
*__MDE includes__ (1) **hypercalcemia**: serum calcium > 0.25 mmol/L (>1 mg/dL) higher than the upper limit of normal or >2.75 mmol/L (>11 mg/dL); (2) **renal insufficiency**: serum creatinine >177 μmol/L (2 mg/dL) or creatinine clearance <40 ml/min; (3) **anemia**: hemoglobin value of >2 g/dL below the lower normal limit, or a hemoglobin value <10 g/dL; (4) **bone lesions**: one or more osteolytic lesion revealed by skeletal radiography, CT, or PET-CT or the presence of any one or more of the following **biomarkers of malignancy: clonal bone marrow plasma cell percentage ≥60 %; involved/uninvolved serum free-light chain ratio ≥100; >1 focal lesions revealed by MRI studies**.

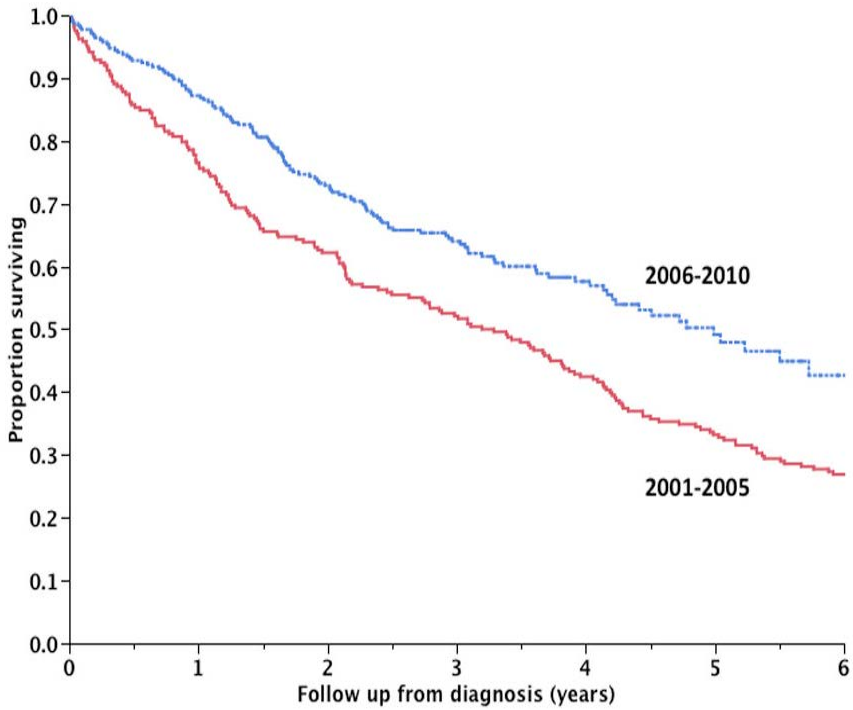
María-Victoria Mateos and Ola Landgren. Cancer Treatment and Research 2016

Introduction of novel agents has improved overall survival in MM

1038 patients diagnosed 2001-2010, median age at dg 66 years
52% >65 years, 19% >75 years of age

OS
Patients 65 years or older

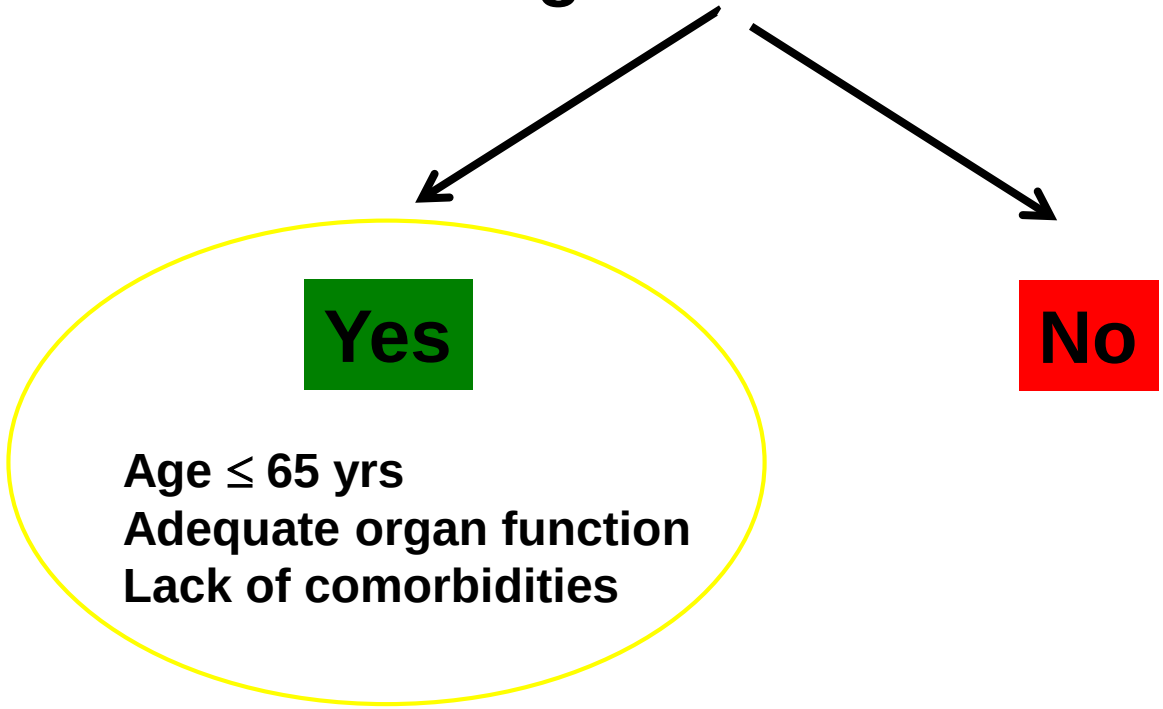




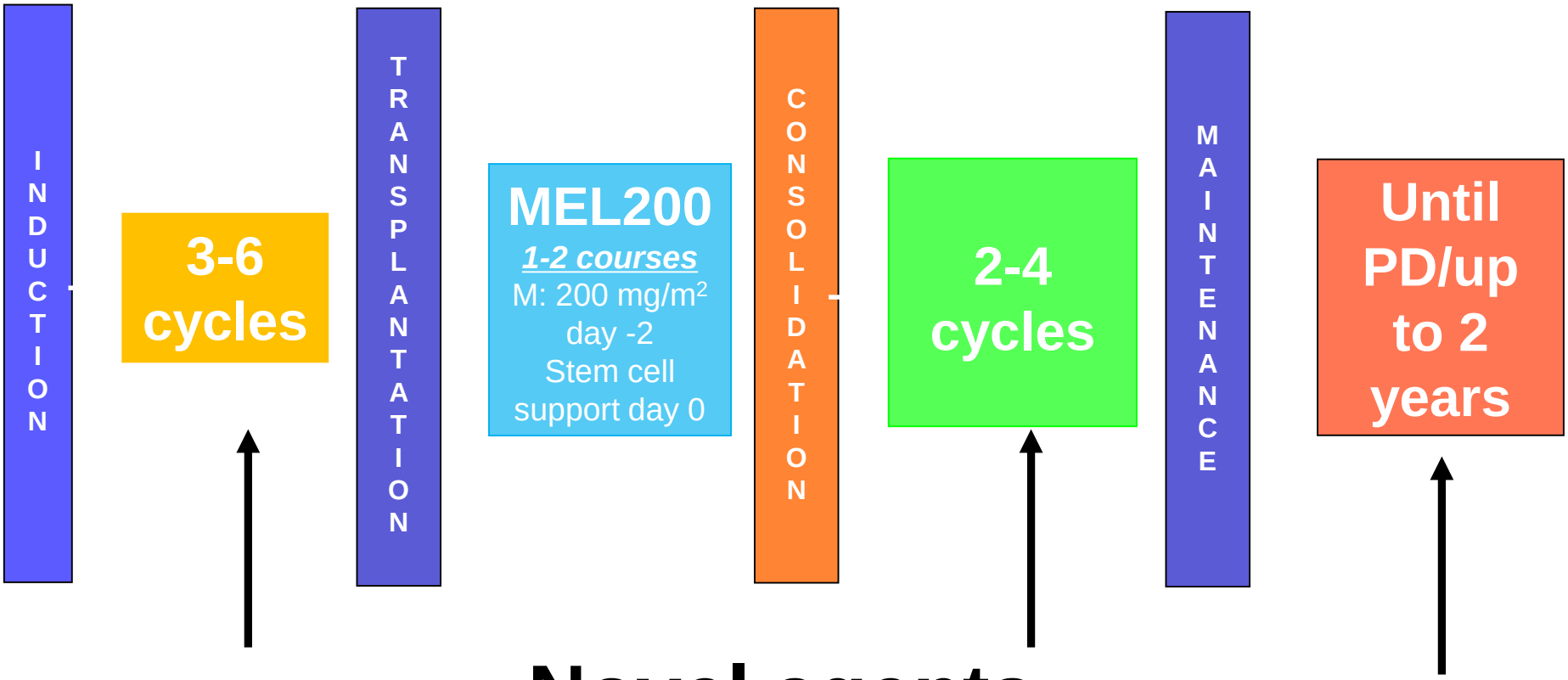
Kumar S H, et al. Leukemia. 2014 May ; 28(5): 1122–1128.

Newly Diagnosed Multiple Myeloma

Candidate for autologous stem cell transplantation



Early intensification in trasplant eligible patients

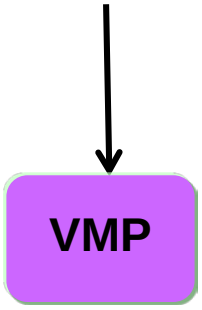


MEL200, melphalan 200 mg/m^2 ; PD, progressive disease

Standards of care for elderly MM patients not eligible for ASCT

Alkylators-based regimens

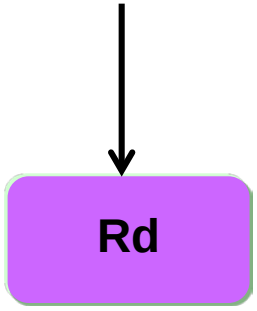
MP



VISTA randomized trial:
Benefit in PFS 8 mo
OS 13mo

Alkylators-free regimens

IMiD's



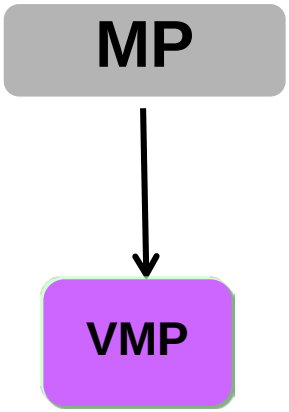
FIRST randomized trial:
Benefit in PFS and OS vs MPT

San Miguel. N Engl J Med 2008;359:906-17
San Miguel . J Clin Oncol. 2013; 31: 448-55

Benboubker L, et al. NEJM 2014; 371: 906-17
Courtesy by Dr Mateos.

Standards of care for elderly MM patients not eligible for ASCT

Alkylators-based regimens

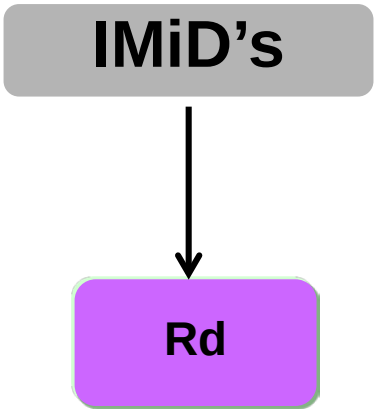


Potential new standards

- VMP-Daratumumab vs VMP
- KCyDex→K (58 patients)
  ORR:95% including sCR 20%
  Good tolerability

San Miguel. N Engl J Med 2008;359:906-17
San Miguel . J Clin Oncol. 2013; 31: 448-55

Alkylators-free regimens



Potential new standards

- Len-dex + Elotuzumab
- Len-dex + Ixazomib
- Len-dex + Daratumumab
- Len-dex + Carfilzomib

Benboubker L, et al. NEJM 2014; 371: 906-17
Courtesy by Dr Mateos.

Treatment options for relapsed refractory MM patients

Transplant Eligible Patients
Bortezomib-based Induction
Autologous Transplant

Transplant Inelegible Patients
VMP
Rd

FIRST RELAPSE

Second Transplant

Lenalidomide-dexamethasone

Daratumumab-Vd; Elotuzumab-Vd; Carfilzomib-dexamethasone

SECOND RELAPSE

Lenalidomide-dexamethasone

Pomalidomide-Dexamethasone*

Daratumumab-Vd; Elotuzumab-Vd, Cd

*at second or subsequent relapse in pts previously treated with both lenalidomide and bortezomib

MGUS

- 1. Prevalence
- 2. Risk of Progression
- 3. Follow-up
- 4. Work-up

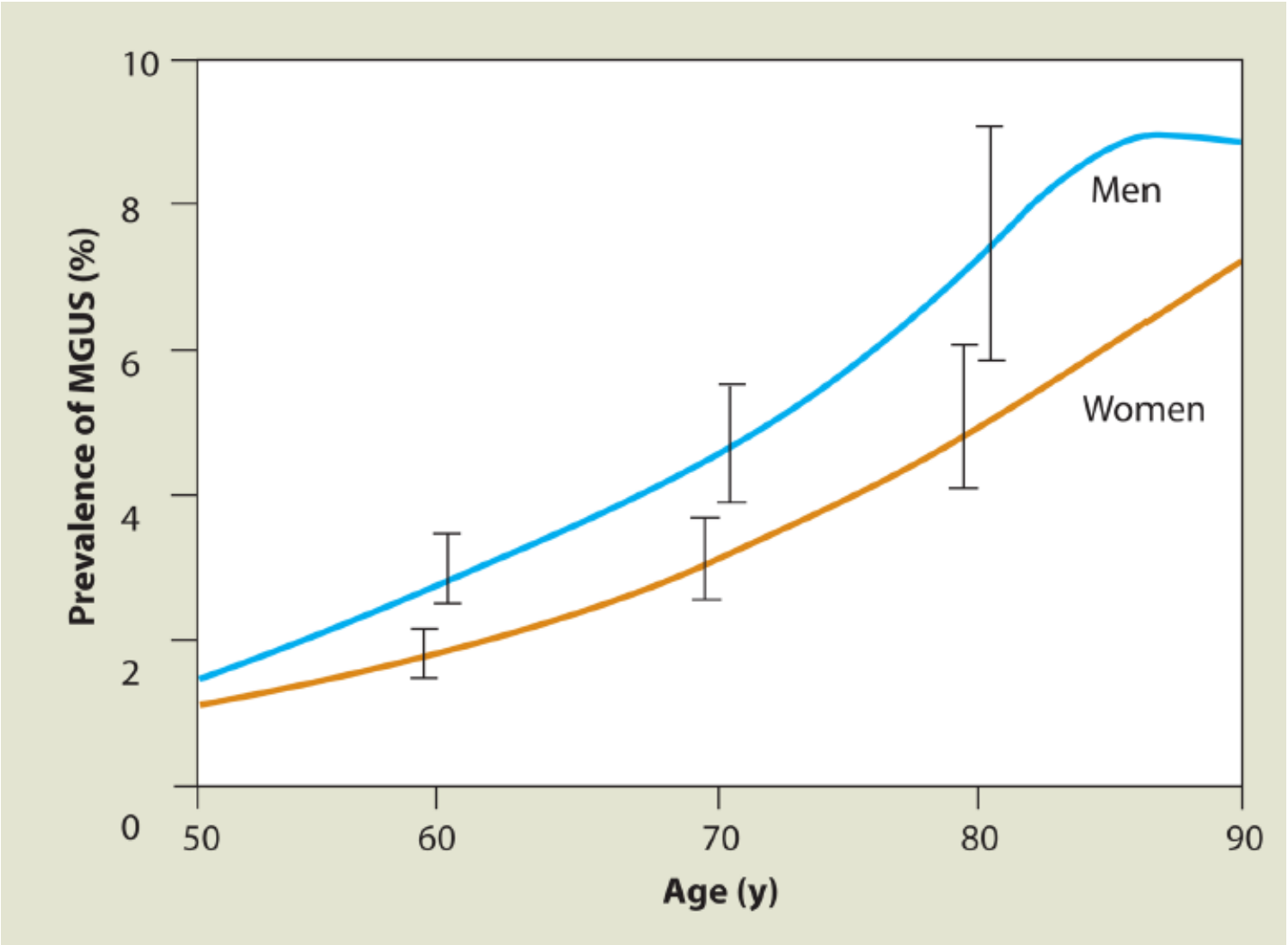
Prevalence of MGUS

Table 1. Prevalence of MGUS in Reported Studies.

Location	Age (yr)	No. of Persons Studied	Prevalence of MGUS (%)	Test Used to Identify Monoclonal Protein	Population Based	Reference
Swedish nursing home	≥70	294	3.1	Paper electrophoresis Immunoelectrophoresis	No	Hallen[6]
Southern Sweden	≥25	6,995	0.9	Paper electrophoresis Immunoelectrophoresis	No	Axelsson et al.[7]
Finistère, France	≥50	17,968	1.7	Cellulose acetate Immunoelectrophoresis	No	Saleun et al.[8]
Ragiora, New Zealand	>21	2,192	0.5	Cellulose acetate	No	Carrell et al.[12]
Northern Minnesota	≥50	1,200	1.2	Cellulose acetate Immunoelectrophoresis	No	Kyle et al.[13]
North Carolina (1 urban and 4 rural counties)	≥70	816	3.6	Agarose gel Immunofixation	No	Cohen et al.[14]
Large city hospital, United States	Not given	73,630	1.2	Agarose gel Immunoelectrophoresis	No (inpatient)	Vladutiu[9]
General hospital, Italy	Not given	102,000	0.7	Cellulose acetate Immunoelectrophoresis	No (inpatient)	Malacrida et al.[10]
Provincial hospital, Italy	11 to >75	35,005	2.9	Cellulose acetate Immunofixation	No (inpatient and outpatient)	Aguzzi et al.[11]
Olmsted County, Minnesota	≥50	21,463	3.2	Agarose gel Immunofixation	Yes	Current study

Kyle RA et al., N Engl J Med 2006;354:1362-9.

Prevalence of MGUS according to age



Kyle NEJM 2006

MGUS

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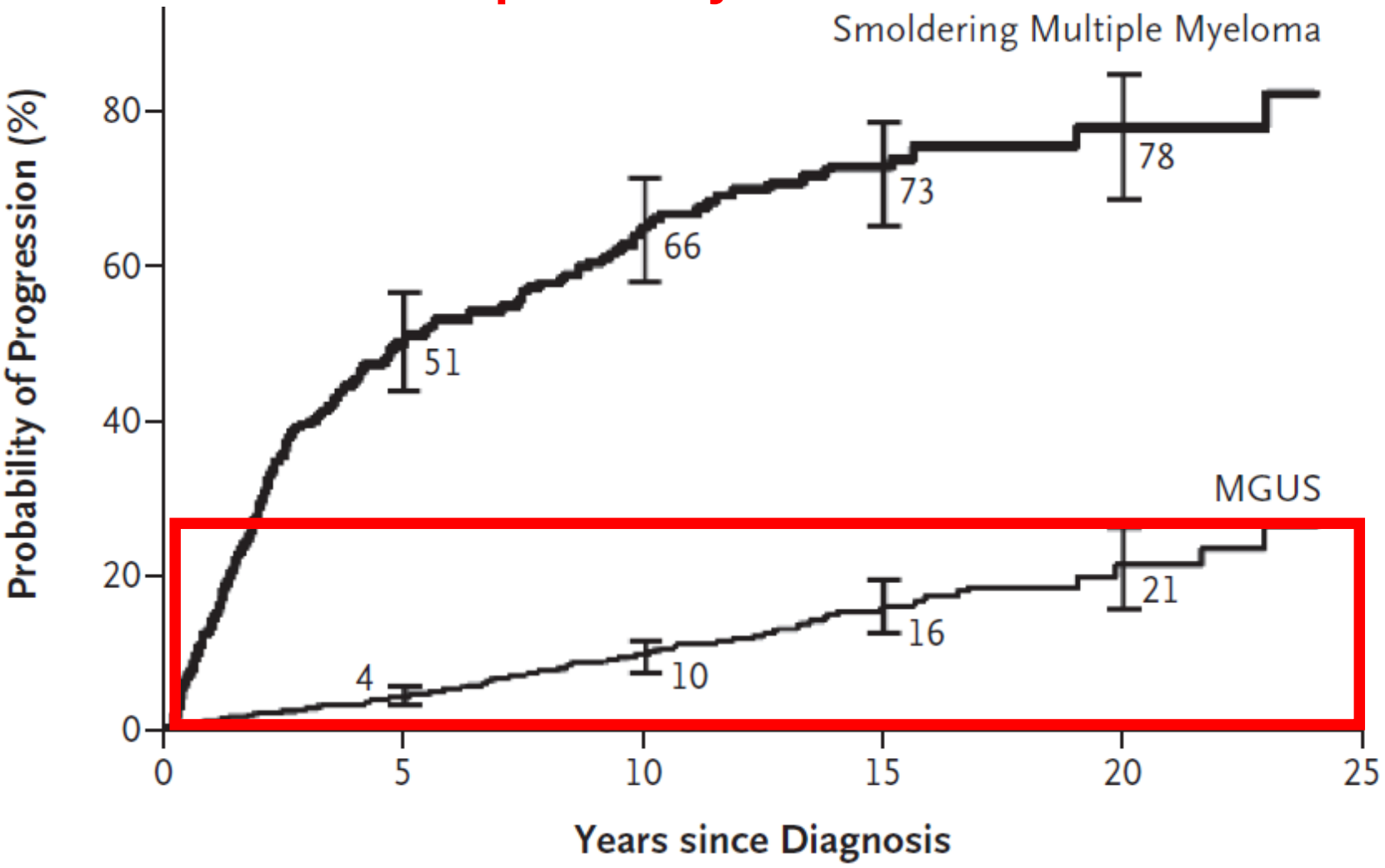
Multiple myeloma is consistently preceded by MGUS

Years prior to MM diagnosis	M-protein,* n/N (%; 95% CI)	Abnormal FLC ratio,‡ n/N (%; 95% CI)	MGUS,§ n/N (%; 95% CI)
2	25/27 (93; 76–99)	23/27 (85; 66–96)	27/27 (**100;** 87–100)
3	54/58 (93; 83–98)	46/58 (79; 67–89)	57/58 (**98**; 91–100)
4	45/48 (94; 83–99)	29/46 (63; 48–77)	47/48 (**98**; 89–100)
5	34/37 (92; 78–98)	25/37 (68; 50–82)	35/37 (**95**; 82–99)
6	25/25 (100; 86–100)	19/25 (76; 55–91)	25/25 (**100**; 86–100)
7	14/15 (93; 68–100)	11/15 (73; 45–92)	14/15 (**93**; 68–100)
> 8	13/17 (77; 50–93)	8/17 (47; 23–72)	14/17 (**82**; 57–96)

Based on all MM patients with available serum obtained ≥ 2 years prior to MM diagnosis (n = 71).
*Detectable by electrophoresis, immunofixation, or both. ‡Normal reference range: 0.26–1.65.
§Defined as having evidence of an M-protein, an abnormal FLC-ratio, or both.

Landgren O, et al. Blood. 2009;113:5412-7.

Probability of progression of MGUS to: MM, IgM lymphoma, primary amyloidosis, LPL, CLL or plasmacytoma



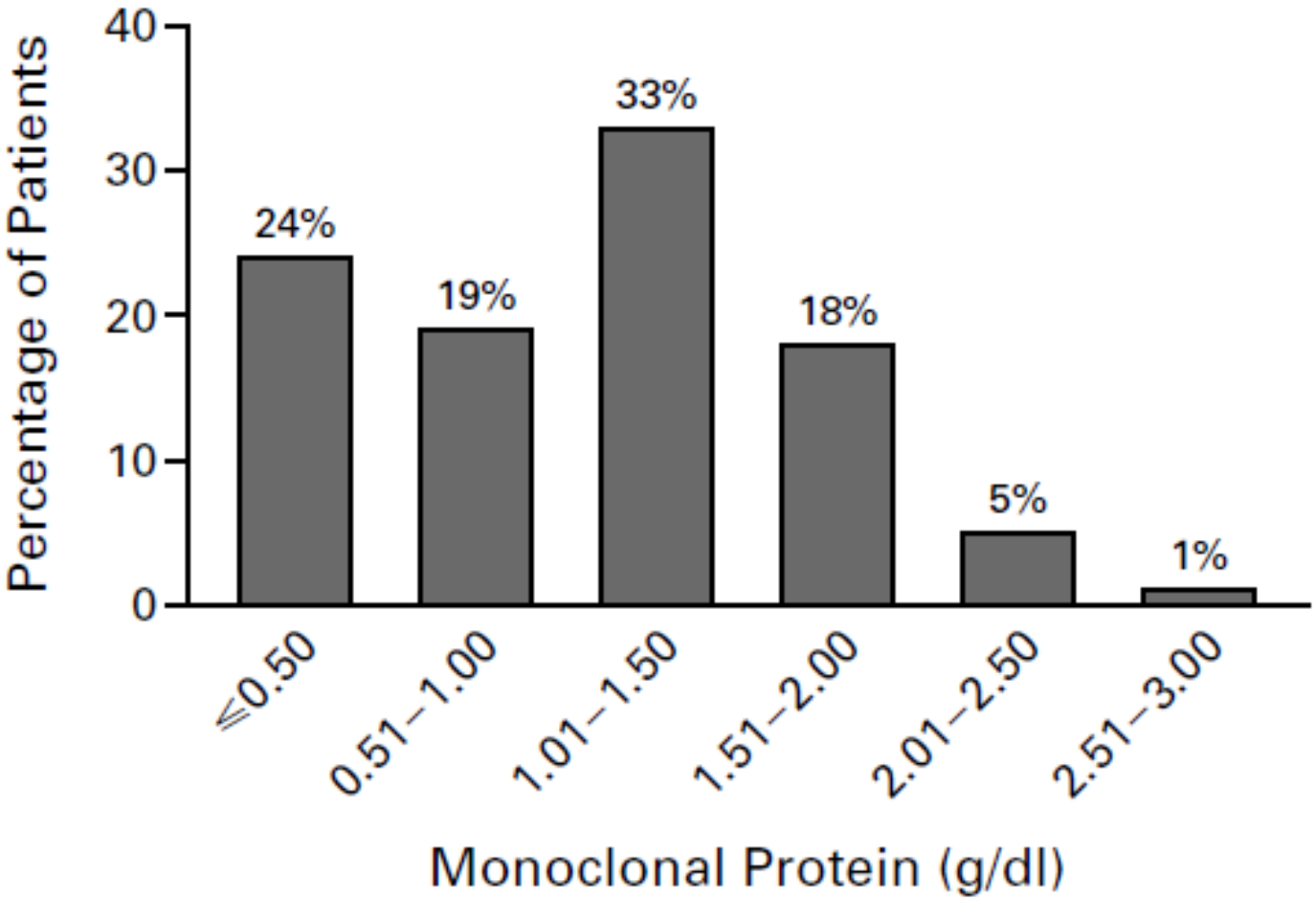
Probability of progression of MGUS 1% per year

Kyle NEJM 2007

- **The risk of transformation is life-long and MGUS individuals should be monitored throughout their lives**

- **Which are the tools we can use to monitor the risk of MGUS transformation?**

Monoclonal Component



Kyle RA et al. *N Engl J Med*. 2002

Monoclonal Component

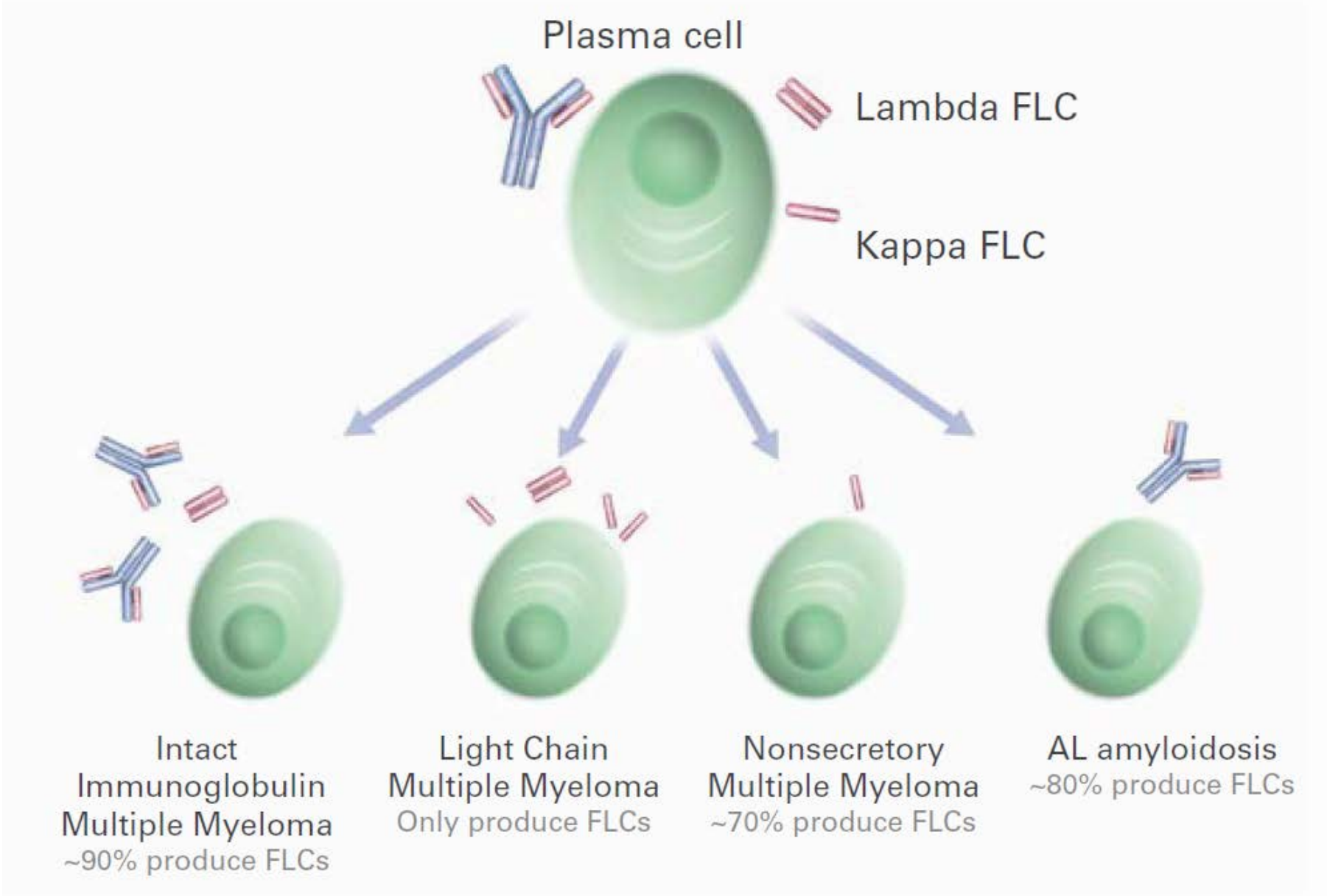
Risk of progression at 20 years:

Initial M protein levels:

≤500 mg/dL	→	14%;
500-1,500 mg/dL	→	25%;
1,500-2,000 mg/dL	→	41%;
2,000-2,500 mg/dL	→	49%
2,500-3,000 mg/dL	→	64%

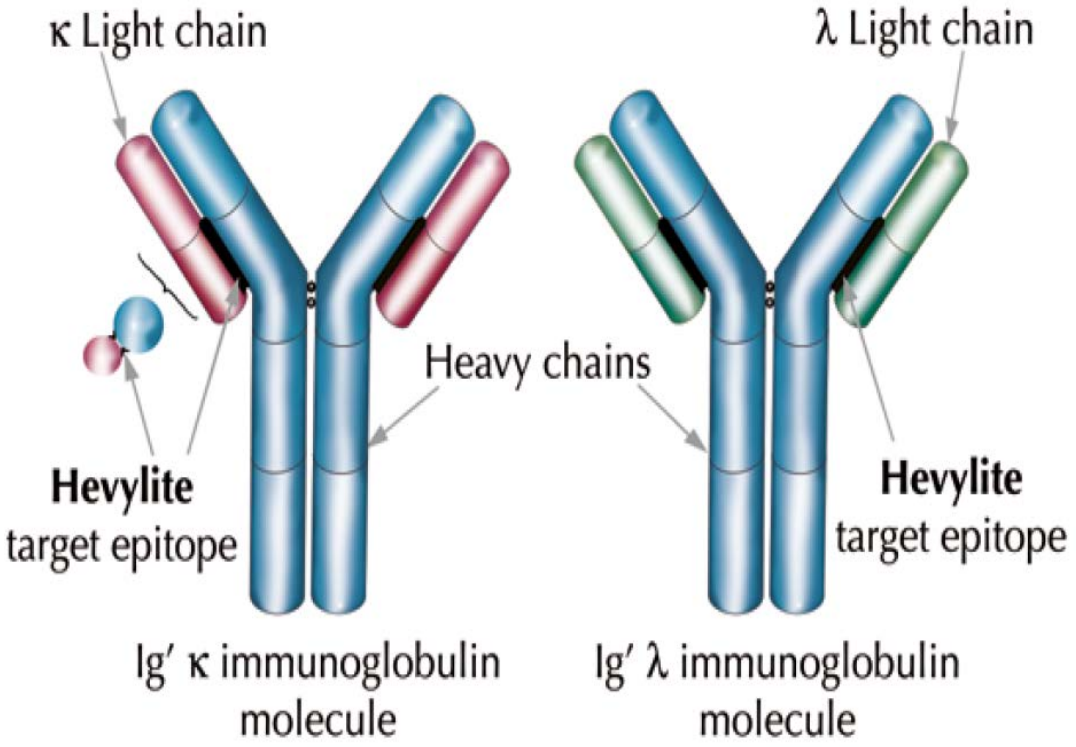
Kyle RA et al. *N Engl J Med*. 2002

Serum Free Light Chain (FLC)



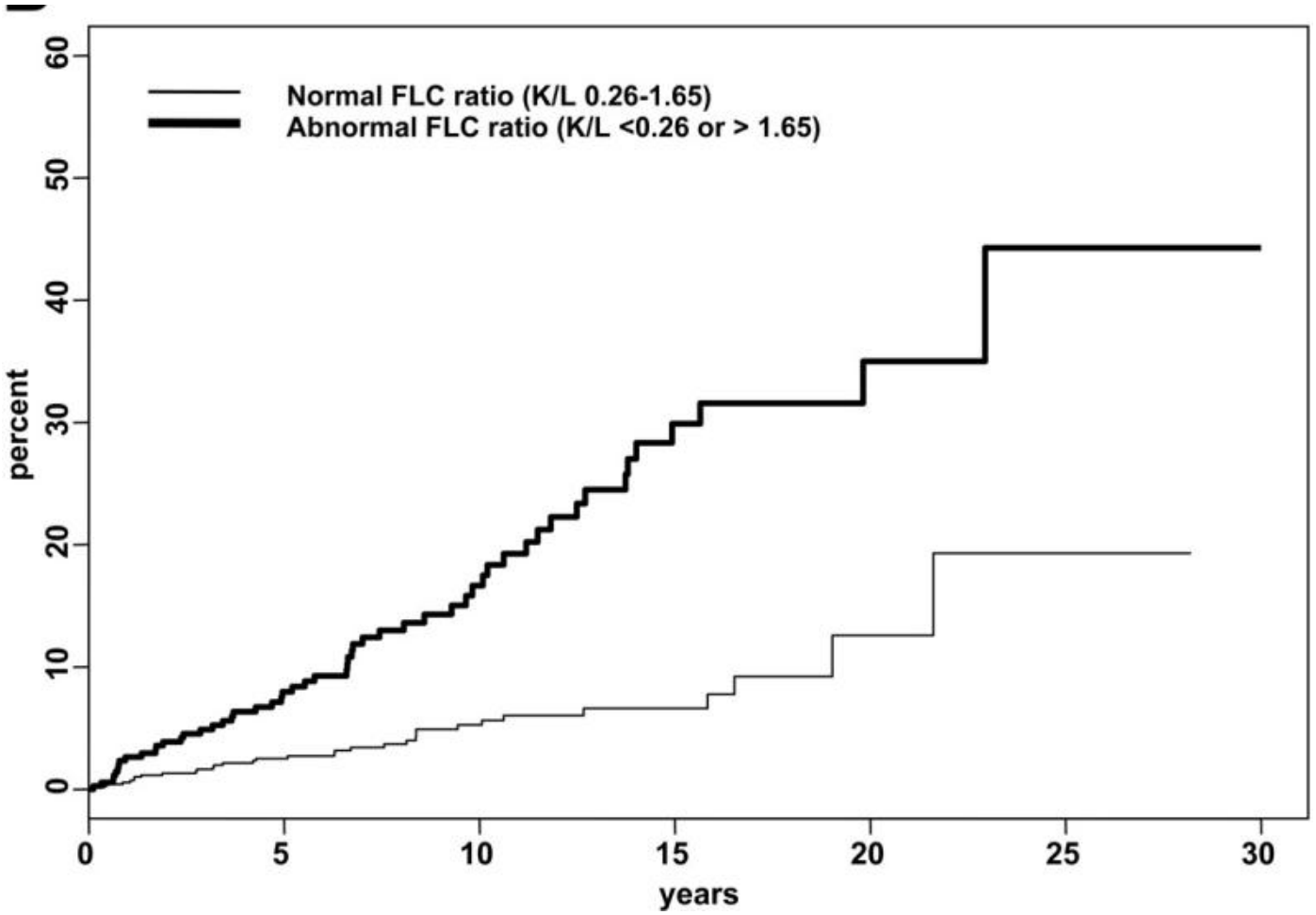
Serum Free Light Chain (FLC)

κ FLC
λ FLC
FLC ratio 0.26-1.65



Increase of monoclonal light chain derives from an excessive production of κ or λ chain by a clone of cells of the B-lymphocyte lineage

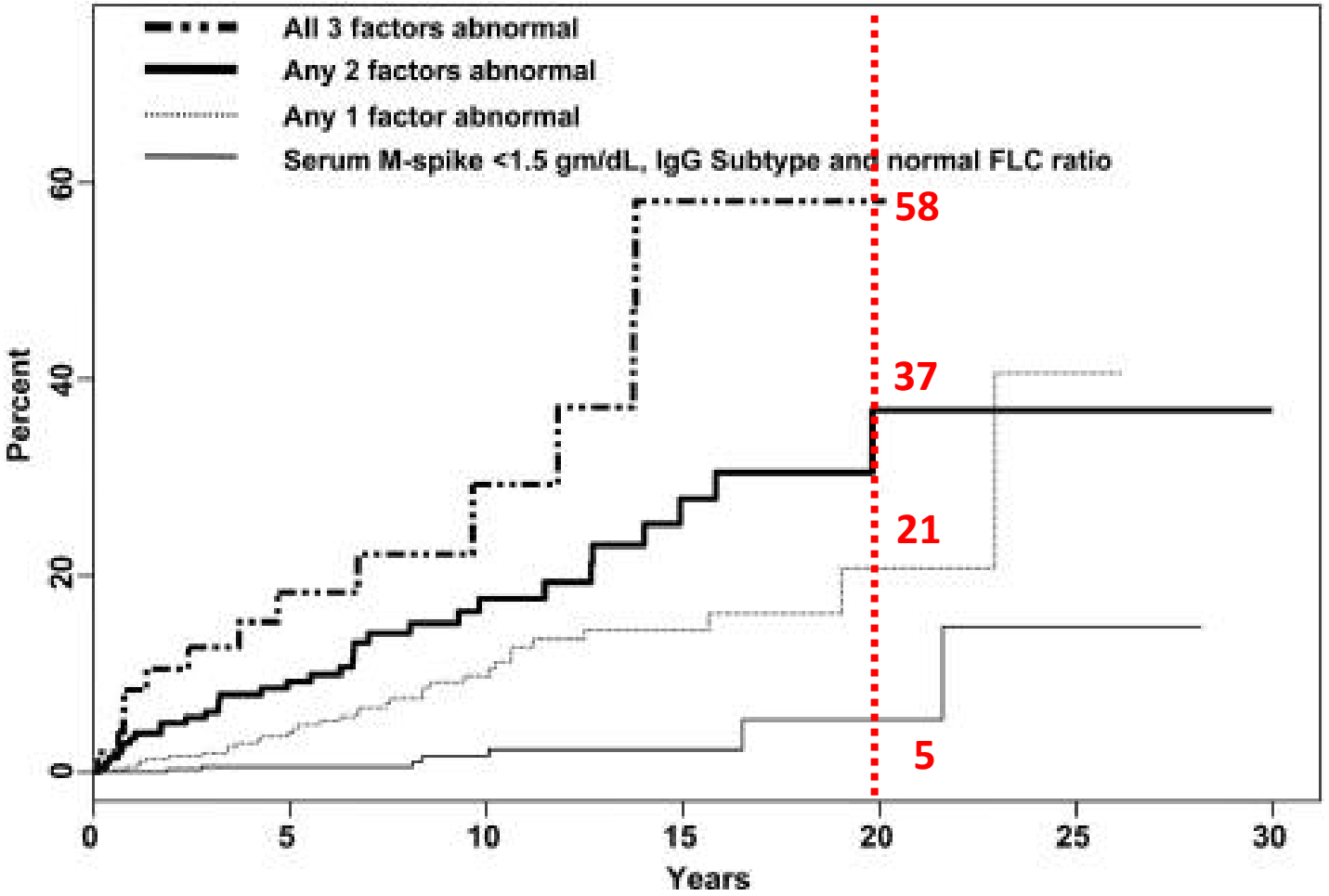
Serum FLC ratio is an independent risk factor for progression in MGUS



Rajkumar V et al., *Blood*. 2005; 106(3): 812–81

Predictive factors: combinations

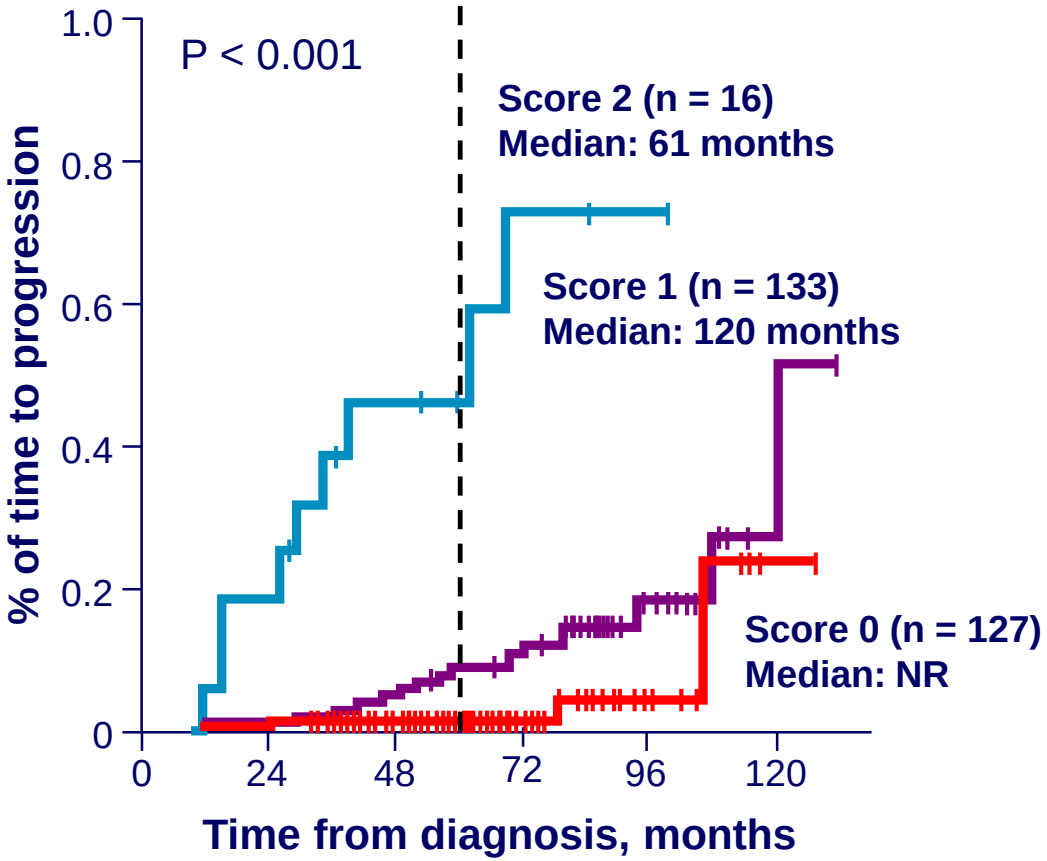
1) M-protein <1.5 g/dL;
2) IgG (non-IgA/IgM)
3) normal FLC



Rajkumar V et al., *Blood*. 2005; 106(3): 812–81

Predictive factors: combinations

Used flow cytometry of bone marrow to quantify the ratio of abnormal neoplastic plasma cells to normal cells.
aPC/BMPC ratio > 95% is associated with a higher risk of progression (p < 0.001)



Risk factors

- •aPC/BMPC ratio > 95%
- •DNA aneuploidy

Score 2 – aPC/BMPC ratio > 95% + aneuploid

Score 1 – aPC/BMPC ratio > 95% or aneuploid

Score 0 – no risk factors

aPC = aberrant plasma cell;
BMPC = bone marrow plasma cell.

Perez-Persona E, et al. Blood. 2007;110:2586-92.

MGUS

- 1. Prevalence
- 2. Risk of Progression
- 3. Follow-up
- 4. Work-up

Follow-up

MGUS
M-protein <30 g/l
BM PC <10%
No end-organ damage

Risk of progression: 1%/year

Risk factors
-non-IgG subtype
-M-protein ≥15 g/l
-Abnormal FLC ratio

→ Low-risk (no risk factors):
Follow-up at 6 months, and if stable every 1-2 years
or
No further follow-up but additional investigations only in case of symptoms suggestive of progression

→ Non low risk (≥1 risk factor):
Follow-up at 6 months, and annually thereafter

Van De Donk et al., *Int. Jnl. Lab. Hem*. 2016, 38 (Suppl. 1), 110–122

Follow-up

Dependent on risk and life expectancy

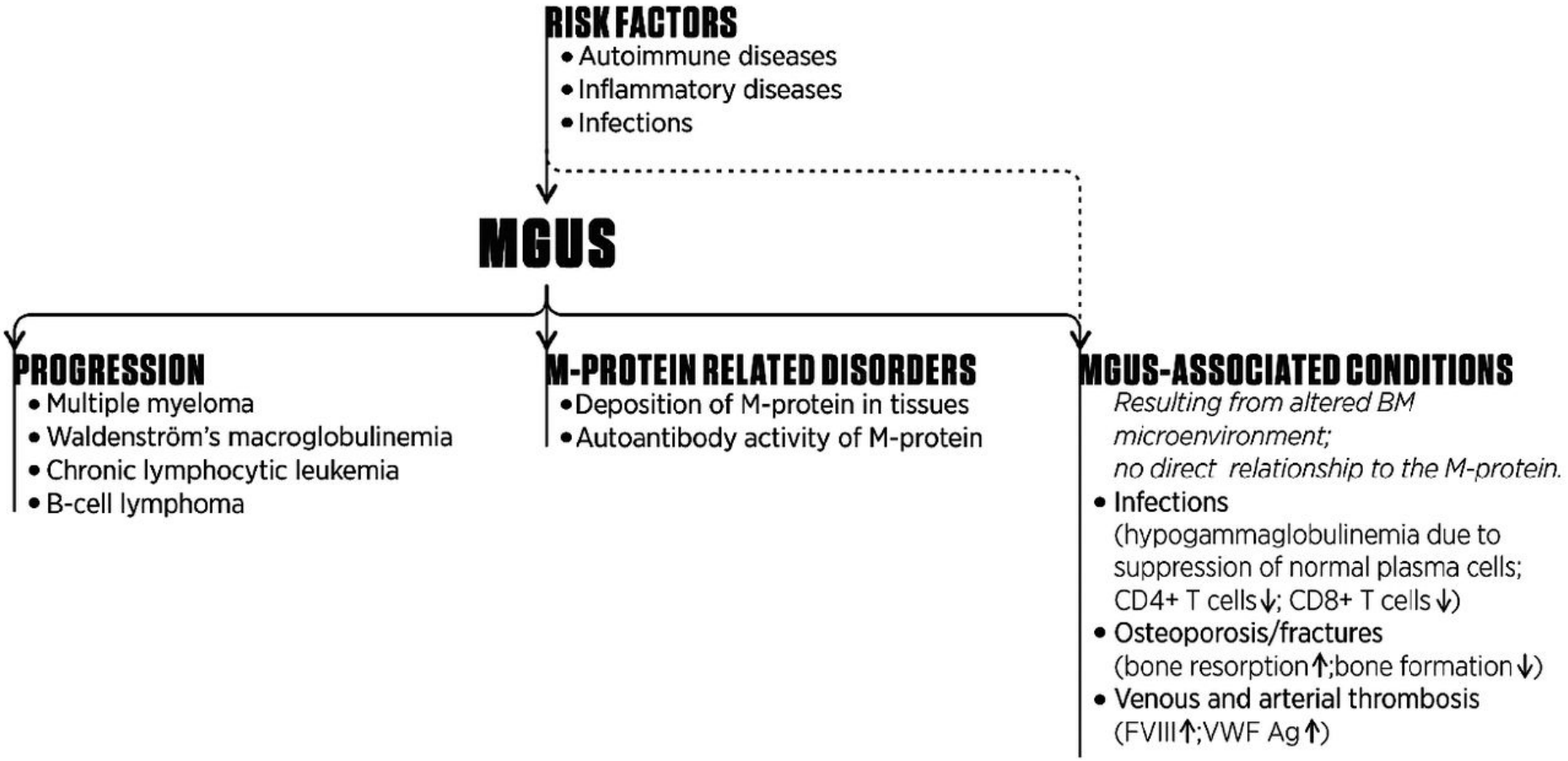
Table 4. Follow up according to risk of progression and life expectancy.

	Low-risk* MGUS and life expectancy ≥5 years	Non-low-risk* MGUS and life expectancy ≥5 years	Light-chain MGUS and life expectancy ≥5 years	MGUS and life expectancy <5 years
Follow up	At 6 months, and if stable every 1-2 years or no further follow up but additional investigations only in case of symptoms suggestive of progression	At 6 months, and annually thereafter	At 6 months, and annually thereafter	No further follow up but additional investigations only in case of symptoms suggestive of progression

*Criteria are partly based on International Myeloma Working Group (IMWG) criteria with some modifications[100] *Risk of progression is predicted by using the Mayo Clinic risk stratification model[17]. Low risk is defined by IgG isotype, M-protein <15 g/L, and normal FLC ratio. Cumulative probability of progression at 20 years for patients with low-risk, low intermediate risk (one risk factor present), high-intermediate risk (two risk factors present), and high-risk MGUS (three risk factors present) is 5%, 21%, 37%, and 58%, respectively.[17] Follow up should include careful history, physical examination (emphasis on symptoms and signs that may suggest progression to MM, WM, AL amyloidosis, or M-protein related disorders), and laboratory studies (quantification of M-protein, complete blood count, creatinine, and calcium). In case of an abnormal free light-chain ratio with elevation of the involved light-chain, NT-pro-BNP and urinary albumin should also be monitored during follow up to detect organ damage caused by light chains. In case a patient with evolving MGUS, develops a M-protein ≥ 30 g/L and fulfils the SMM criteria, then follow up should be like in SMM (every 3-4 months). Further investigations are indicated if during follow up new symptoms or signs develop that are suggestive of underlying MM, WM, or AL amyloidosis, or if a patient has abnormal laboratory results. Patients should be instructed to contact their physician if there is any change in their clinical condition.*

Kyle Leukemia 2010 1121; van de Donk Haematologica 2014

Associations between MGUS and other disorders



haematologica
the hematology journal

van de Donk N W et al. *Haematologica* 2014;99:984-996

Signs or symptoms of systemic amyloidosis

- Heart failure; myocardial wall thickening on echocardiography with normal or low limb lead voltages on ECG; late gadolinium enhancement, ECV, pre-contrast T1 on MRI
- Nephrotic syndrome
- Fatigue, weight loss
- Peripheral (ascending, symmetric, small fibers / axonal) neuropathy in non-diabetic patients
- Autonomic neuropathy (postural hypotension, "resolution" of pre-existing hypertension, erectile / bladder / bowel dysfunction)
- Hepatomegaly with normal imaging
- Purpura, macroglossia, carpal tunnel syndrome, claudication of the jaw, articular deposits

Positive biomarker-based screening in patients at risk (MGUS with abnormal FLC ratio)

- Elevated NT-proBNP in the absence of other causes
- Albuminuria

Tissue biopsy

- **Abdominal fat aspirate**, and if negative
- **Salivary gland biopsy**, or
- **Organ biopsy** (beware of hemorrhagic risk, transjugular approach preferred for liver biopsy)

Identification of the plasma cell clone by serum and urine immunofixation electrophoresis and FLC measurement
Bone marrow studies including iFISH of plasma cells and skeletal survey

Unequivocal identification of amyloid type

- **Tissue typing** by mass spectrometry, immuno-electron microscopy, or immunohistochemistry
- **Gene sequencing** when clinical presentation requires to rule out hereditary amyloidosis, for example transthyretin amyloidosis in subjects with isolated or combined heart and peripheral nervous system involvement, apolipoprotein AI in subjects with mild liver, renal or cardiac involvement, fibrinogen amyloidosis in patients with isolated renal involvement
- **Cardiac scintigraphy with** ^{99m}Tc-DPD or PYP can differentiate AL (mild or no uptake) from transthyretin amyloidosis (strong uptake)

Assessment of organ involvement and staging

- **Heart:** echocardiography (with assessment of strain or MCF), NT-proBNP, troponins, ECG, Holter ECG, MRI
- **Kidney:** 24 hour urinary protein loss, eGFR
- **Liver:** liver function tests, liver imaging (CT, US scan, MRI)

Palladini G et al., *Blood*. 2016 Apr 6. [Epub ahead of print]

MGUS

- 1. Prevalence
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WORK-UP FOR NEWLY DIAGNOSED MGUS

- Medical history and physical examination
- Hemogram
- Biochemical studies, including of creatinine and calcium levels; Beta2-microglobulin, LDH and albumin
- Protein studies
  - –Total serum protein and serum electrophoresis (serum M-protein)
  - –24-h urine sample protein electrophoresis (urine M-protein)
  - –Serum and urine immunofixation
- Serum free light-chain measurement (sFLC ratio)
- Bone marrow aspirate ± biopsy: infiltration by clonal plasma cells, flow cytometry and fluorescence in situ hybridization analysis*
- Skeletal survey, CT, or PET-CT*
- MRI of thoracic and lumbar spine and pelvis; ideally, whole-body MRI (only for SMM)

FLC free light chain; CT computed tomography; PET-CT 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT; MRI magnetic resonance imaging.

***These assessments can be deferred in patient with low-risk MGUS (IgG type, monoclonal protein <1.5 g/dL, normal free light-chain ratio)**

- proBNP or NT-proBNP
- albuminuria
- In selected cases LDH, uric acid, Ab anti MAG

María-Victoria Mateos and Ola Landgren. Cancer Treatment and Research 2016

MGUS: Follow-up

Basso Rischio

- **Primo controllo a 6 mesi**
- **Se esami stazionari controllo ogni 12 mesi**
  (emocromo, creatinina, proteine totali, quadro proteico elettroforetico, calcemia, catene leggere libere, proteinuria sulle urine delle 24 ore, proteinuria di Bence Jones su urine delle 24 ore)

Altre categorie di Rischio

- **Controlli ogni 6 mesi**
- **Esami emocromo, creatinina, proteine totali, quadro proteico elettroforetico, calcemia, catene leggere libere, proteinuria sulle urine delle 24 ore, proteinuria di Bence Jones su urine delle 24 ore**

MGUS: treatment

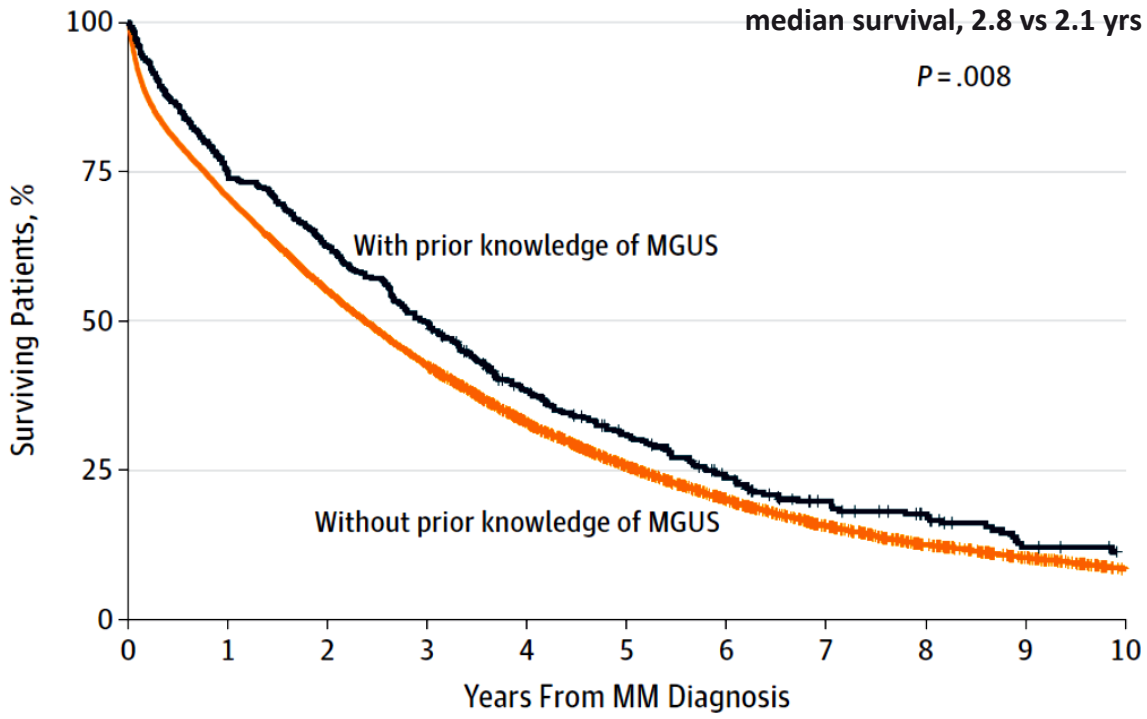
Patients should always be told to obtain medical evaluation promptly if clinical symptom occour

The standard of care is not to treat unless Multiple Myeloma or other plasma cell disorder is developed.

Conclusions

The role of diagnosis and clinical follow-up of MGUS on survival in MM

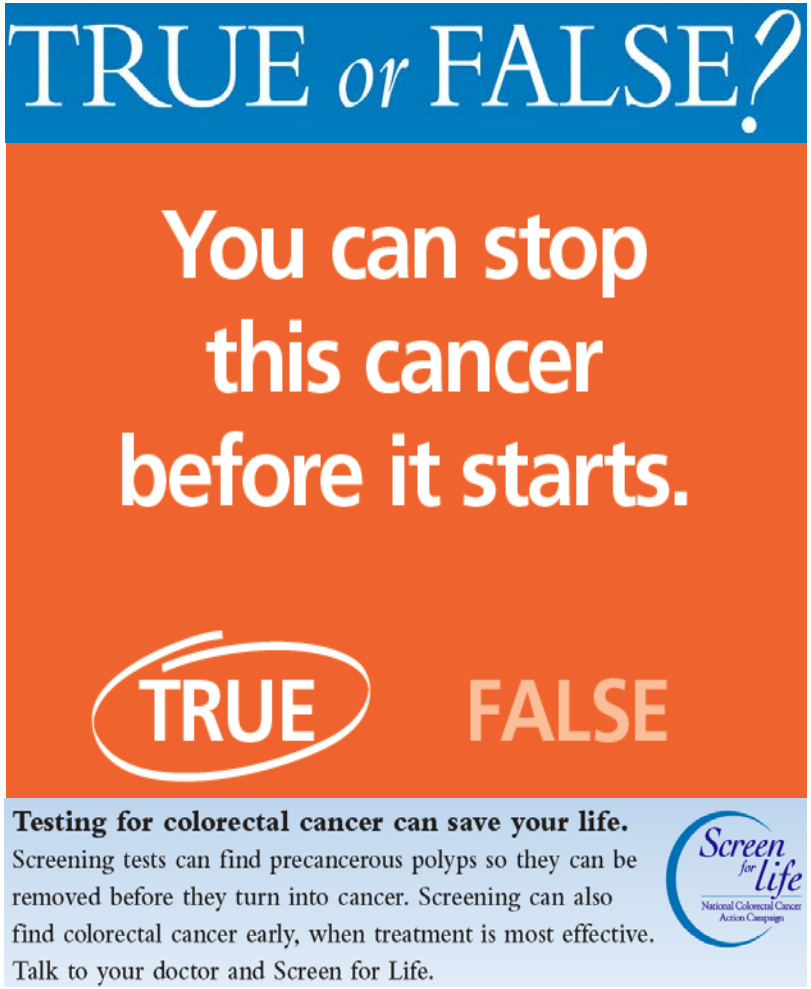
Figure. Survival Among MM Patients With and Without Prior Knowledge of MGUS



Patients with and without prior knowledge of MGUS, No.											
Without prior knowledge	14 404	10 190	7930	6117	4552	3397	2541	1903	1440	1127	854
With prior knowledge	394	295	246	196	136	103	71	48	36	20	15

Sigurdardottir EE et al., *JAMA Oncol*. 2015;1(2):168-174.

Treatment concept of early intervention



In the treatment of other malignancies (breast, colon or prostate cancer), the early intervention is not only appropriate, but also essential for successful treatment and cure.

Curr Opin Oncol. 2014 Nov;26(6):670-6

Acknowledgments

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Dr. Giusy Cetani
Dr. Mattia D'Agostino
Dr. Marco Salvini

Dr. Paola Omedé &
Laboratory Staff

Dr. Benedetto Bruno &
Transplant Unit

Nurses

Data Managing Staff

Dr. Gianni Ciccone and CPO