Fred Hutch Cancer Center

Monoclonal gammopathies: MGUS, Smoldering myeloma and Monoclonal gammopathies of clinical significance

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Land Acknowledgement

Fred Hutch Cancer Center acknowledges the Coast Salish peoples of this land, the land which touches the shared waters of all tribes and bands within the Duwamish, Puyallup, Suquamish, Tulalip and Muckleshoot nations.

1. Understand the lab, imaging and bone marrow evaluation of patients presenting with plasma cell dyscrasias

2. Define and risk stratify MGUS and smoldering myeloma using current IMWG criteria

3. Recognize monoclonal gammopathies of clinical significance

4. Understand the diagnostic evaluation and treatment of AL amyloidosis

5. Understand the diagnostic evaluation and treatment of AL amyloidosis

Plasma cell disorders

- How are plasma cell disorder typically diagnosed?
  - Typically diagnosed during workup for
    - Lab abnormalities: elevated total protein, anemia, elevated creatinine, proteinuria, hypercalcemia
    - Bone pain
    - Neuropathy
    - Osteoporosis
- What do you need for evaluation?
  - Labs:
    - SPEP
    - Serum immunofixation
    - Serum free light chains
    - CBC with diff
    - CMP
    - 24h UPEP/IFE
  - Imaging:
    - Whole body low dose CT scan
    - Whole body MRI
    - PET/CT

Monoclonal gammopathy of undetermined significance (MGUS)

All three criteria must be met:

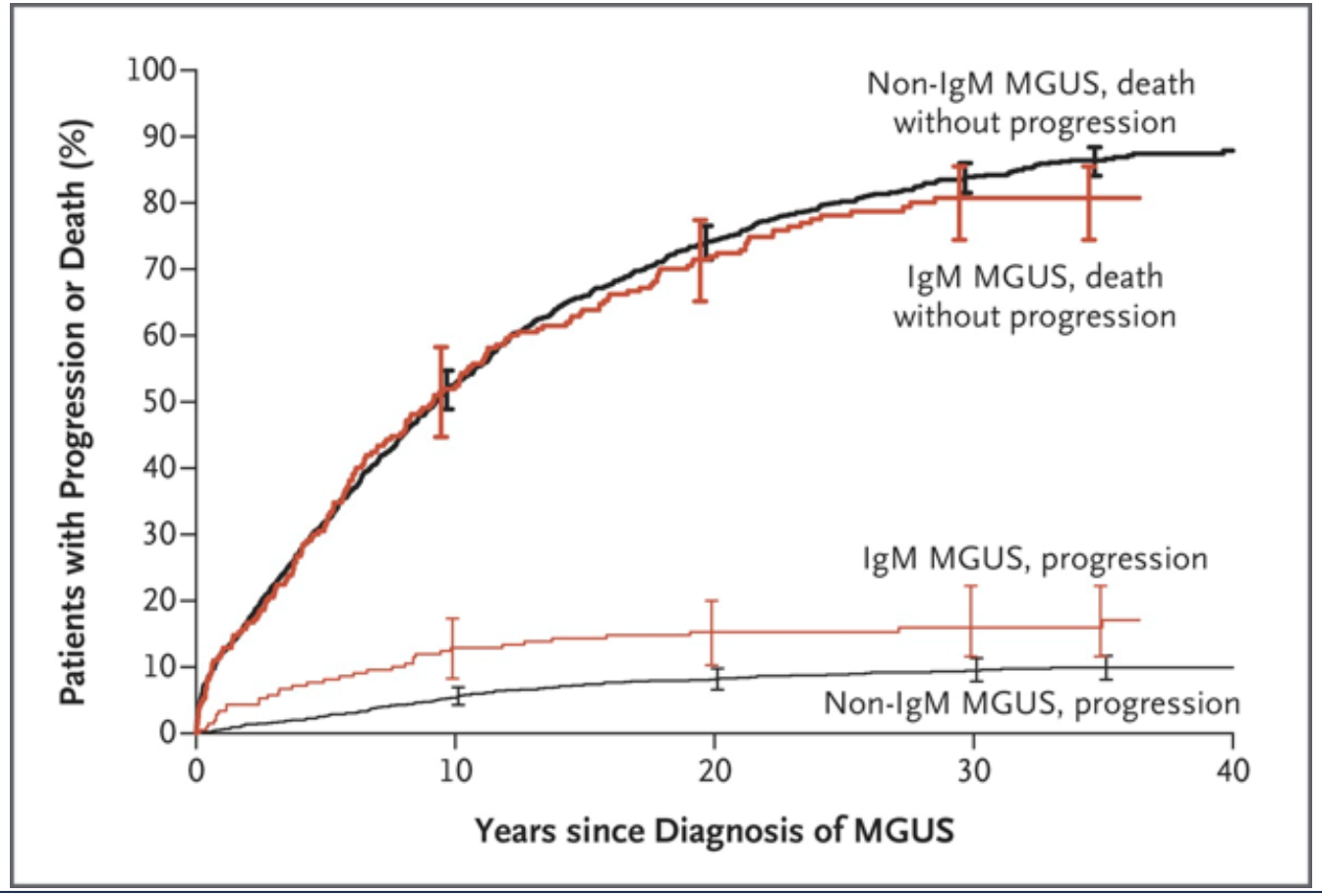
- Serum monoclonal protein < 3 g/dL
- Clonal bone marrow plasma cells < 10%
- Absence of any myeloma defining features (SLiM-CRAB)

MGUS

All three criteria must be met:

- MGUS is present in 3% of the general population ≥50 years old, 5.3% ≥ 70 but only 0.3% among those <50 years old
- A **pre-malignant** condition can progress to:
  - Lymphoproliferative disease (non-Hodgkin lymphoma, CLL, Waldenstrom's)
  - Amyloidosis
  - Multiple myeloma
  - Other (MIDD, POEMS, MGRS)
- Rate of progression of IgG & IgA MGUS to multiple myeloma is **1% per year**
- Rate of progression of IgM MGUS is **1.5%/yr**
- Rate of progression of light chain MGUS is **0.3% per year**

Two major subtypes of MGUS: IgM and non-IgM



<u>34 of 210 patients with IgM MGUS had progression</u>
17 progressed to **NHL**
3 progressed to **AL amyloidosis**
11 progressed to **WM**
3 progressed to **CLL**

<u>107 of 1129 patients with non-IgM MGUS had progression</u>
93 progressed to **MM**
2 progressed to **NHL**
11 progressed to **AL amyloidosis**
1 progressed to **plasmacytoma**

RA Kyle et al. N Engl J Med 2018;378:241-249.

MGUS: Risk Stratification:
IgG isotype; M-spike <1.5 g/dL, FLC ratio normal

Risk Group	# Risk Factors	Absolute risk of progression at 20 years (%)	Absolute risk for progression at 20 years, accounting for death as a competing risk
Low	0	**5**	2
Low-intermediate	1	**21**	10
High-intermediate	2	**37**	18
High risk	3	**58**	27

Rajkumar. Lancet Oncol .2014;15(12): e538-48.

Management of MGUS

Low risk MGUS (50% of MGUS patients)

- Workup: CBC, CMP
- If normal:
  - Baseline marrow or skeletal survey not indicated
- If anemia, renal insufficiency, hypercalcemia or bone pain/lesions:
  - bone marrow biopsy required
- f/u SPEP in 6 months, if stable follow every 2–3 yrs or when symptoms suggestive of a PC malignancy arise

Intermediate or High risk MGUS

- Bone marrow aspirate and biopsy
- Conventional cytogenetics and FISH
- Imaging:
  - Non-IgM MGUS: low-dose whole body CT
  - IgM MGUS: CT chest abdomen and pelvis (lymph nodes, spleen eval)
- If testing is normal follow with SPEP and CBC in 6 months and then annually for life

Go. Blood. 2018;131(2):163-173.

Rajkumar. Lancet Oncol .2014;15(12): e538-48.

Serum Free Light Chain Ranges in patients with CKD

Free light chain concentration is greatly affected by kidney function

- iStopMM study – Iceland study with 75,422 participants screened with SFLC, SPEP and SIFE
- 6461 with eGFR <60 mL/min/1.73 m2, not receiving renal replacement therapy, and without evidence of monoclonality

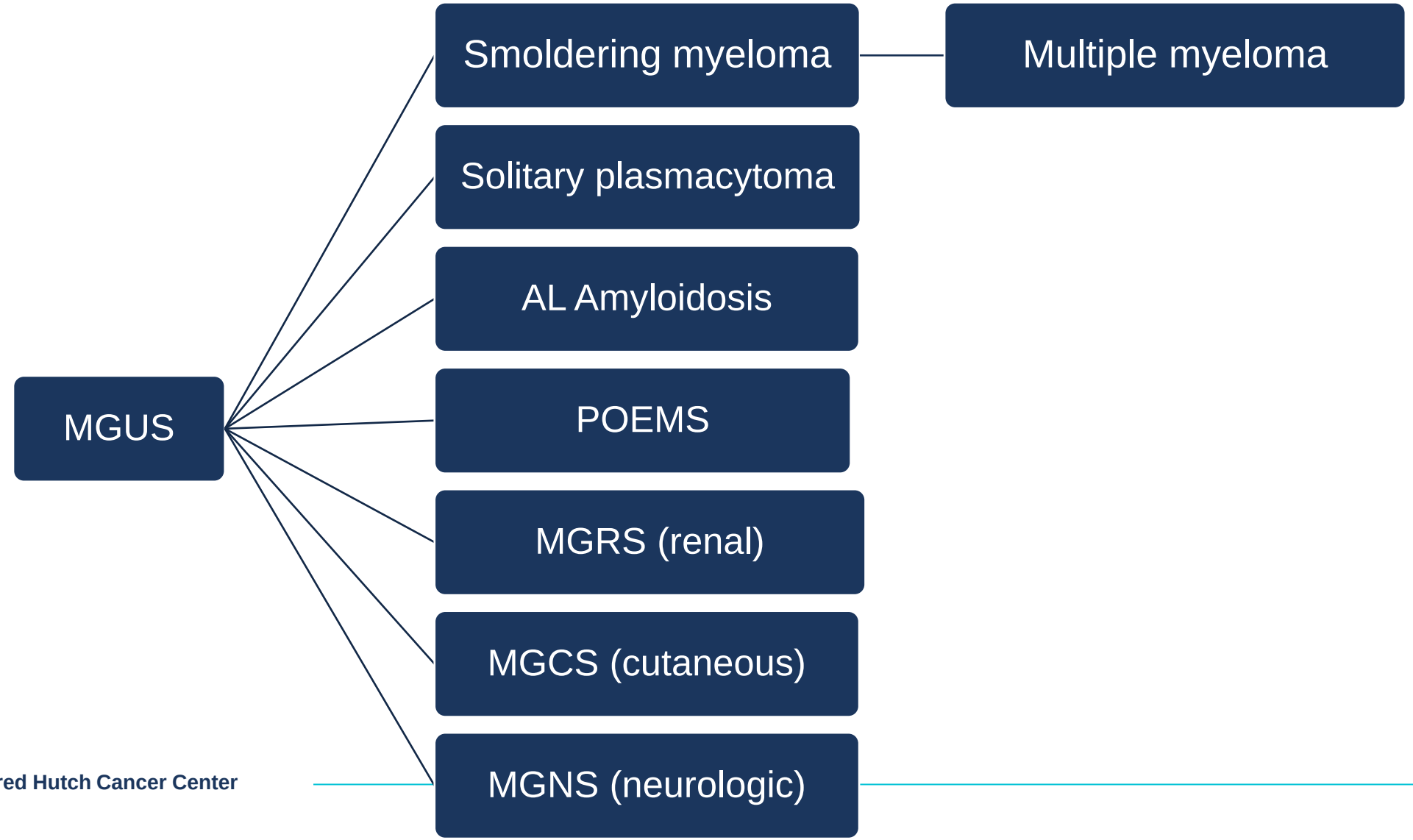
eGFR	Normal light chain
Normal	0.26 – 1.65
45-59	0.46-2.62
30-44	0.48-3.38
<30	0.54-3.3

Long TE, et al. Blood Cancer Journal. 2022. 12:133

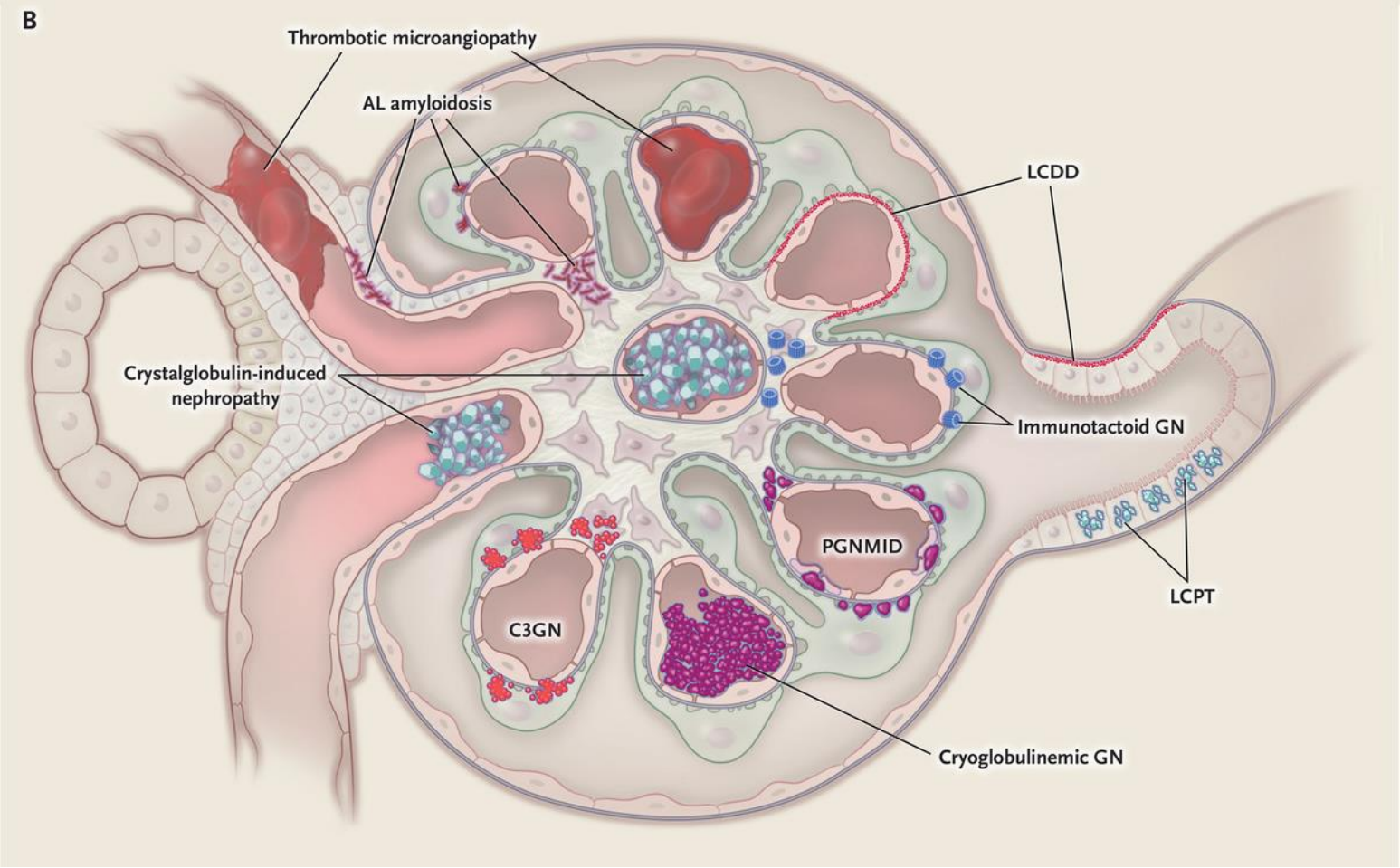
Light Chain MGUS

- Risk of progression to MM in light-chain MGUS is 0·3% per 100 person-years as compared to 0.5 % in patients with IGH expression
- 23% of this group have or will develop **renal disease**
- Periodic monitoring of renal function is prudent
- Can progress to light chain myeloma and/or AL(light chain) amyloidosis

Development of other disorders



Monoclonal Gammopathy of Renal Significance



Diagnosis requires kidney biopsy

Suspect if proteinuria or rapidly rising Creatinine or hypertension

Bone marrow biopsy frequently with <10% PC

Treatment is similar to that of MM

N Leung et al. N Engl J Med 2021;384:1931-1941.

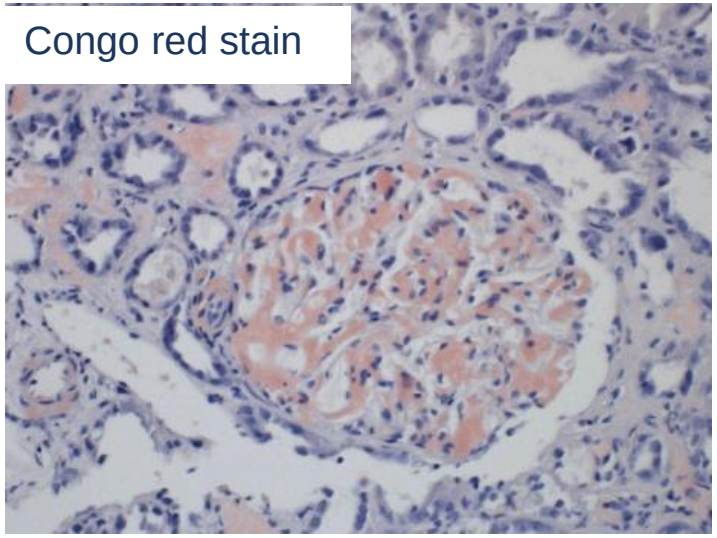
MGUS: Takeaways

- MGUS is a **precursor condition**
  - IgM vs. non-IgM
- Risk stratification: M-spike, free light chain ratio and IgG vs. non-IgG
- Renal function can impact serum free light chain
- Think about the **“small but dangerous clone”** scenarios – may have <10% bone marrow plasma cells, but could be AL amyloidosis, POEMS, MGRS, solitary plasmacytoma with minimal marrow involvement
- **Monitor for progression to a plasma cell disorder that requires treatment**

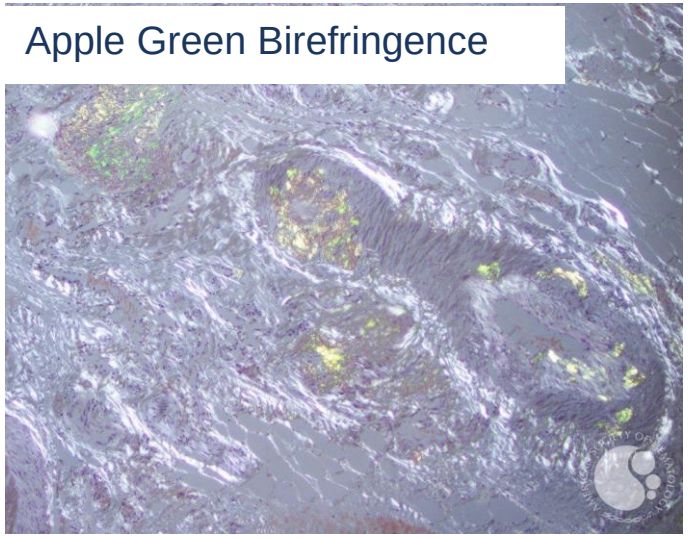
AL Amyloidosis

- Protein misfolding disorder causing insoluble amyloid fibrils
- Functional and structural organ damage
- **Plasma cell clone generally modest in size (median = 7% BMPC)**
- **Lambda light chains >> kappa (lambda/kappa 4:1)**

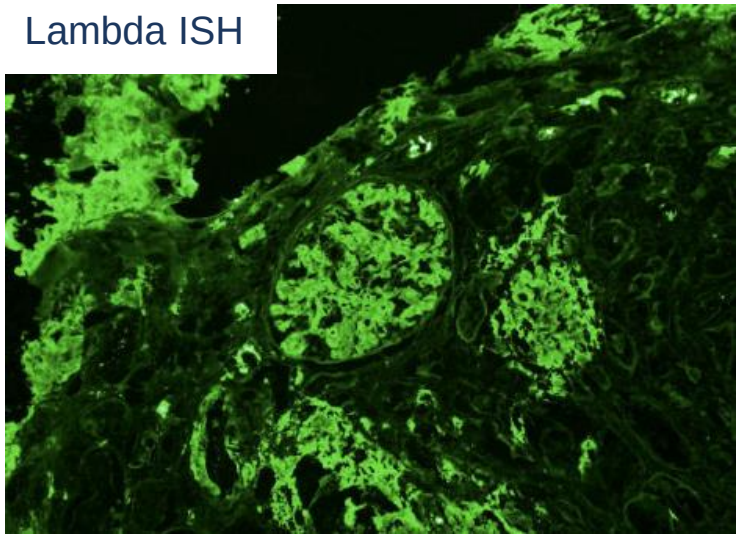
Congo red stain



Apple Green Birefringence



Lambda ISH



https://imagebank.hematology.org/image/62419/amyloid-deposition-in-the-blood-vessel-show-apple-green-birefringence-under-polarized-light?type=upload

Diagnosis depends on an alert clinician

- Non-diabetic nephrotic syndrome
- Heart failure (HF) with *preserved ejection fraction* (HFpEF)
- Peripheral neuropathy
- Unexplained hepatomegaly
- Increased alkaline phosphatase
- Autonomic neuropathy with weight loss
- Unexplained fatigue
- Edema
- Unintentional weight loss

Step #1: Type the Amyloid (LC MS/MS)

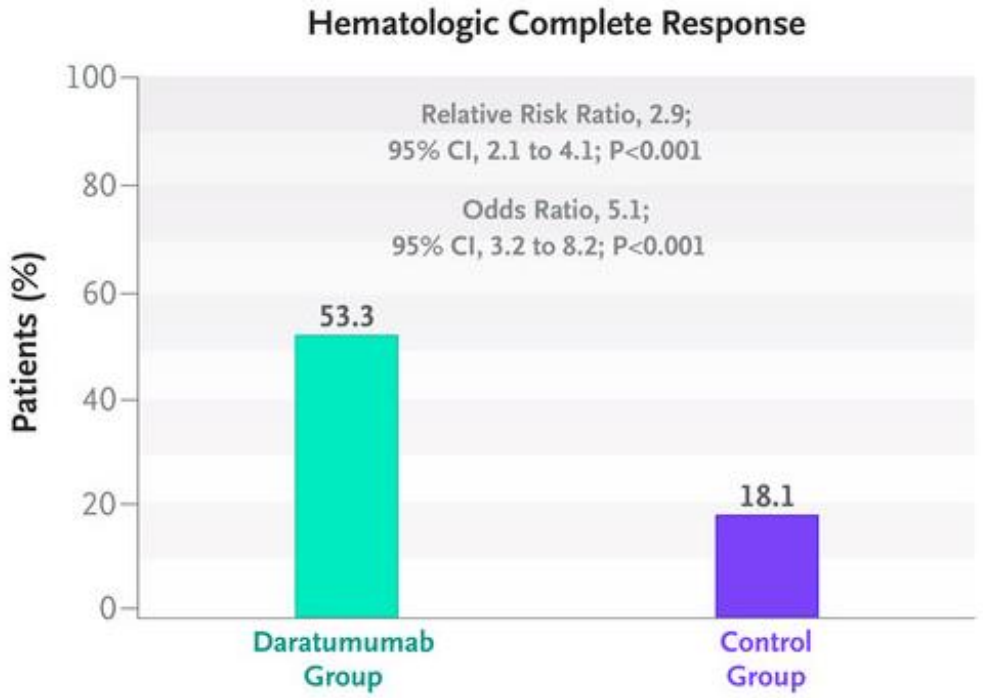
There is a differential diagnosis that must be considered when diagnosing amyloidosis (Congo red deposits found in tissue)

- Light chain (AL) amyloidosis
- Inherited (ATTR)
- Reactive systemic [AA] amyloidosis
- Wild-type transthyretin amyloidosis ATTRwt; or senile systemic amyloidosis
- β2-microglobulin [β2M] dialysis-related amyloidosis
- Others

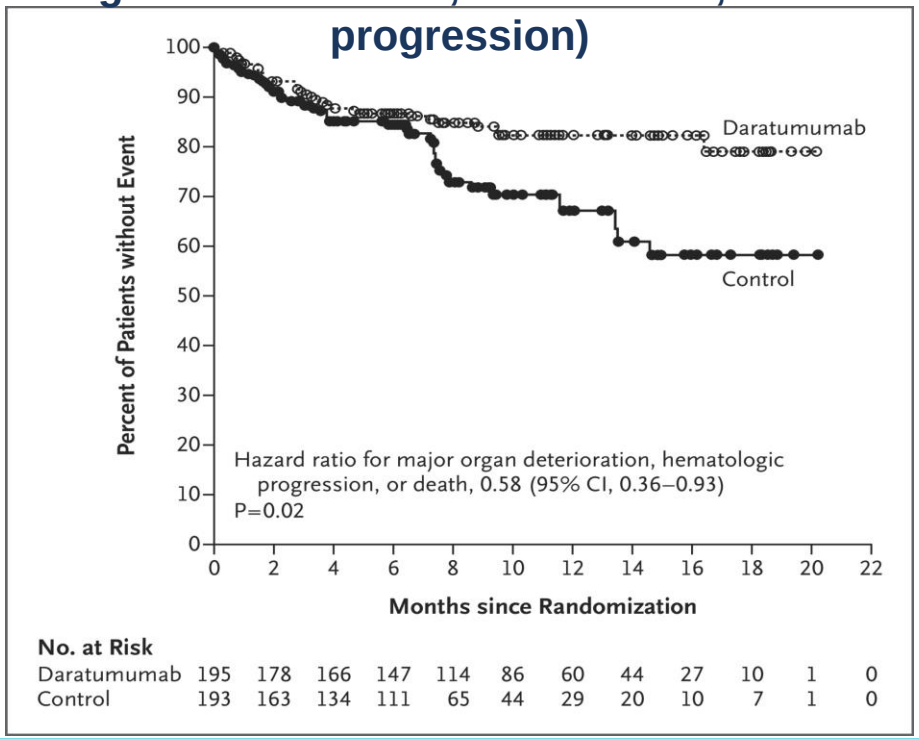
Treatment of AL amyloidosis: Phase III ANDROMEDA trial

Newly diagnosed AL amyloidosis

- CyBorD x 6
- CyBorD-dara x 6 → Dara (24 cycles)



Event free survival
(End stage cardiac failure, renal failure, hematologic progression)



Kastritis E et al. N Engl J Med 2021;385:46-58

ANDROMEDA Trial: CyBorD+daratumumab is associated with deeper and faster responses compared to CyBorD alone

Response	Dara-CyBorD	CyBorD	P Value
Hematologic CR	**53%**	18%	<0.001
≥Hematologic VGPR	**78.5%**	49%	
Hematologic PR	13%	27.5%	
No Heme Response	4%	19.7%	
Cardiac response	**41.5%**	22.2%	
Renal response	**53%**	23.9%	

Kastritis E et al. N Engl J Med 2021;385:46-58

Treatment of AL amyloidosis

Goal is normalization of light chains

How can we achieve this?

- CyBorD-Dara alone
- Autologous stem cell transplant
  - Fit, CrCl ≥ 30, SBP >90, ECOG PS <2, NYHA class I or II, normal troponin
- Pomalidomide
- Venetoclax - if t(11;14)
- Bortezomib
- Melphalan

Gertz MA. Leukemia. 2012 Feb;26(2):191-8.

AL amyloidosis: Takeaways

- Confirm the diagnosis with **typing of the amyloid protein (with LC MS/MS)**
- Treatment of systemic AL amyloidosis
  - Induction therapy with **CyBorD+daratumumab**
    - ANDROMEDA trial: CyBorD + daratumumab x 6 cycles, followed by daratumumab for total 2 years
  - Transplant?
- Monitor for relapse or recurrent disease

Kastritis E et al. N Engl J Med 2021;385:46-58

Smoldering Myeloma

- Serum M-spike ≥3 g/dL
- Urine M-spike ≥ 500 mg/24 hours
- Clonal bone marrow plasma cells 10-59%

AND

- Absence of Myeloma Defining Events (SLiM-CRAB)
- Sensitive imaging techniques: PET/CT, whole body MRI

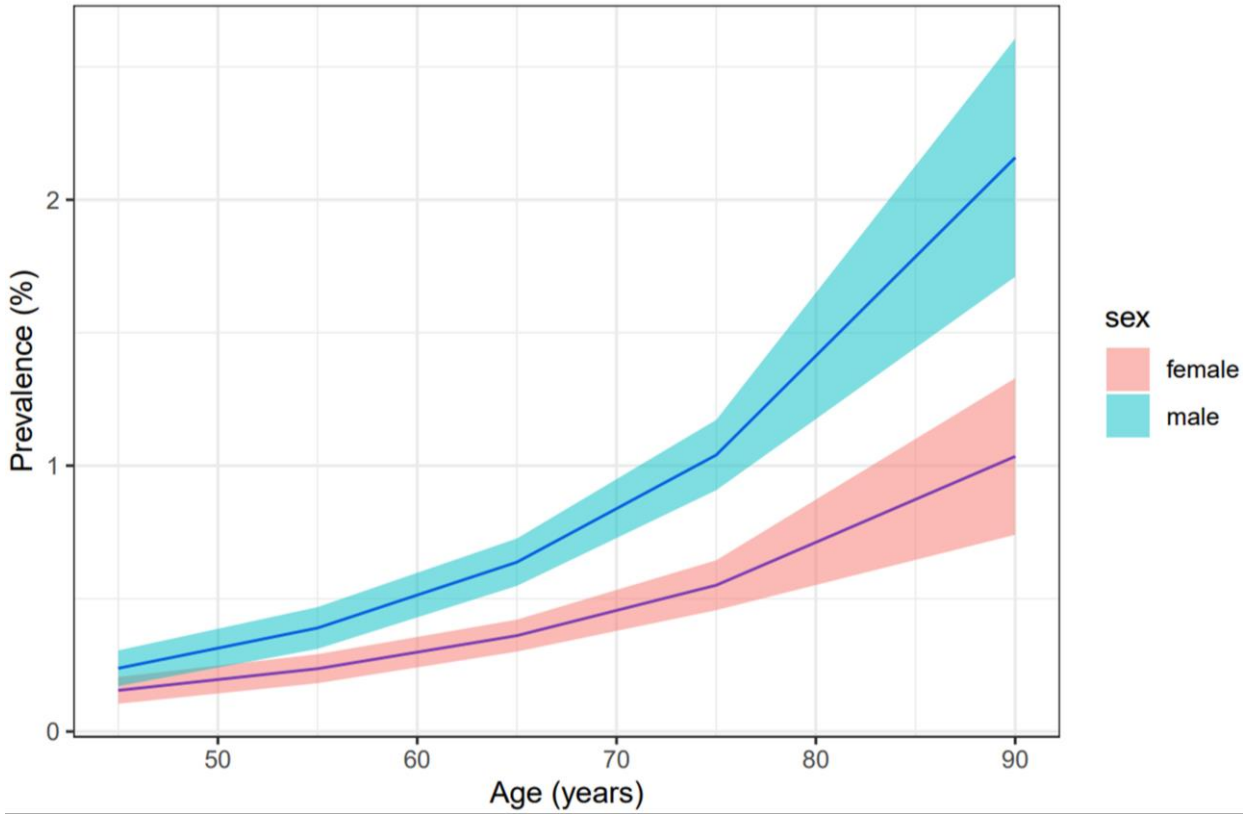
Rajkumar V. Lancet Oncol.2014;15(12): e538-48.

Smoldering myeloma is more prevalent in men

Icelandic iStopMM population-based study

- >75,000 asymptomatic adults over age 40
- 0.5% of the population had SMM

- Higher prevalence of SMM in males
- Prevalence increased with age
  - Median age = 70



Sigrun Thorsteinsdottir,Sigurdur Yngvi Kristinsson, The consultant's guide to smoldering multiple myeloma, Hematology Am Soc Hematol Educ Program, 2022, Figure 1.

How do I risk stratify my patient with SMM?

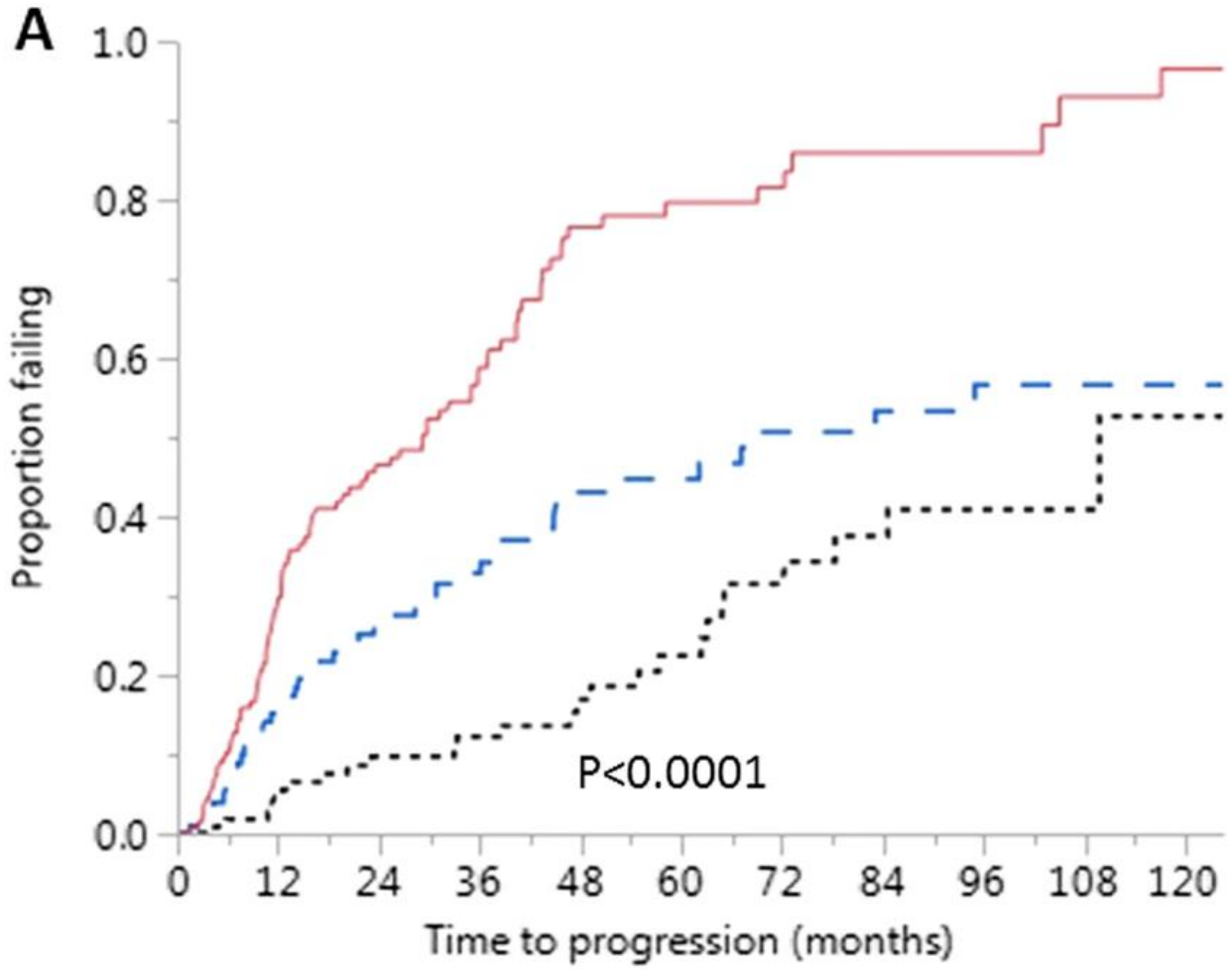
- MAYO 20/2/20 Criteria can be used to risk stratify patients with SMM
  - BMPC% > 20%
  - M-protein > 2 g/dL
  - FLCr > 20 at diagnosis

# of risk Factors	Risk Category	Median TTP to MM	N (total = 421)
0	Low Risk	110 months	143 (35%)
1	Intermediate risk	68 months	121 (29%)
2-3	High risk	29 months	153 (36%)

Lakshman. Blood Cancer J. 2018 Jun; 8(6): 59

- BMPC% > 20%
- M-protein > 2 g/dL
- FLC ratio > 20

MAYO 20/2/20 Risk Stratification



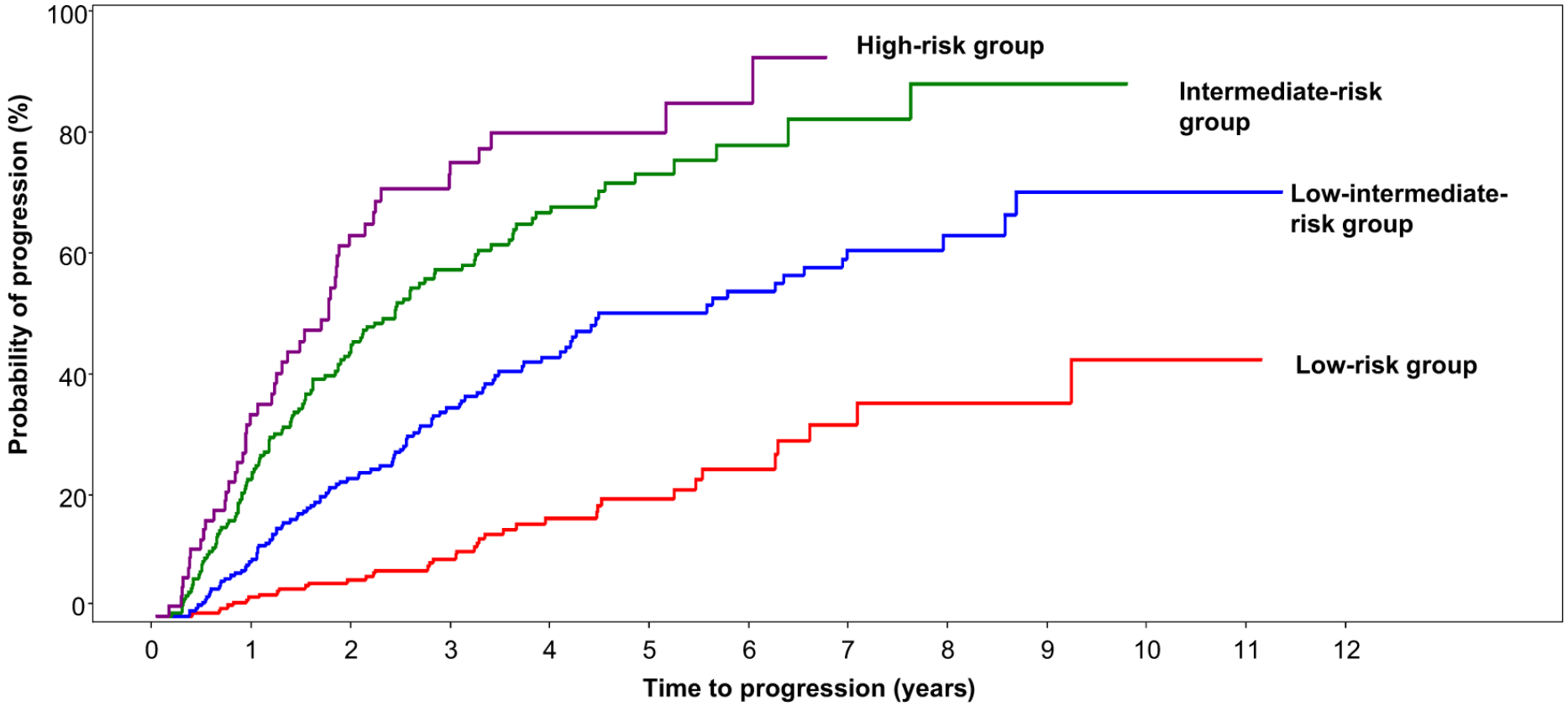
High Risk (2-3 risk factors):
median TTP = **29.2 months**

Intermediate Risk (1 risk factor):
median TTP = **67.8 months**

Low Risk (0 risk factor):
median TTP = **109.8 months**

Lakshman A, et al. Blood Cancer Journal. 2018. 8:59.

IMWG incorporates 20/2/20 + cytogenetics



- BMPC% > 20%
- M-protein > 2 g/dL
- FLC ratio > 20
- t(4;14), t(14;16),+1q, del13q

Mateos MV, et al. *Blood Cancer Journal* **volume 10**, Article number: 102 (2020)

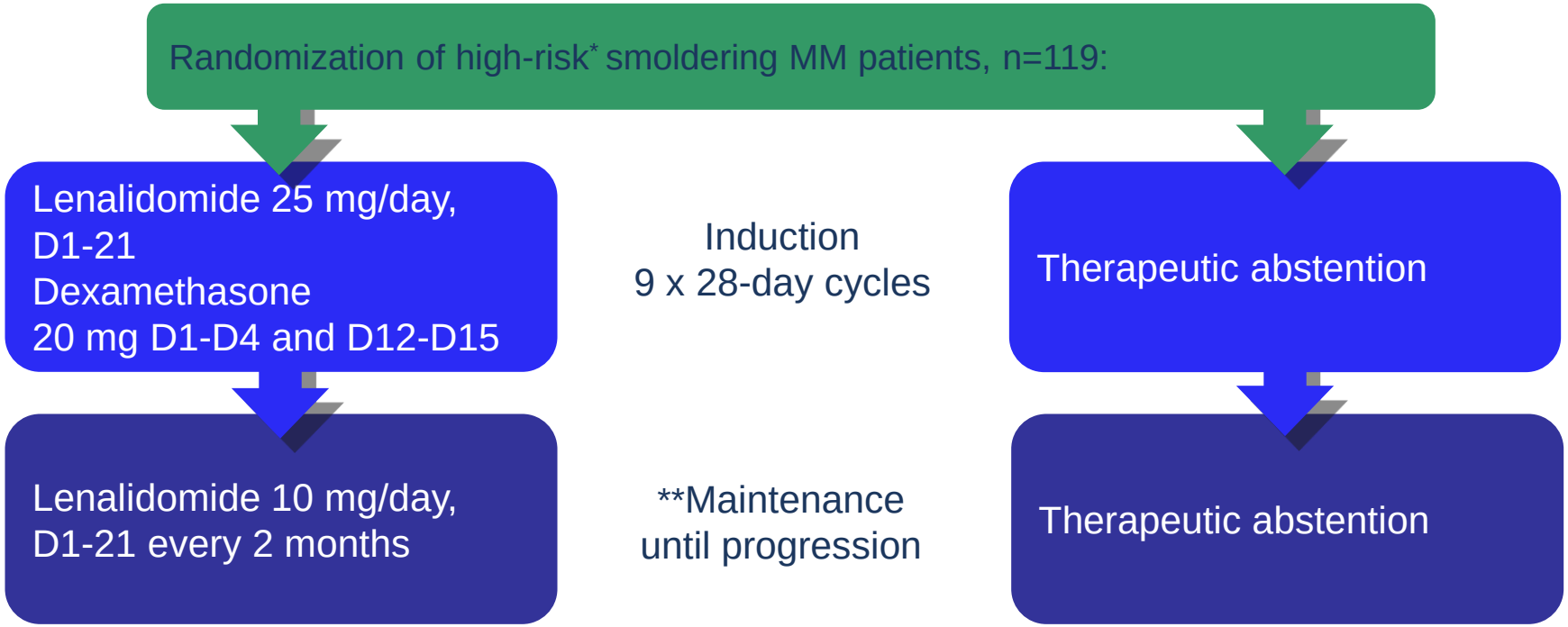
How do I manage patients with smoldering myeloma?

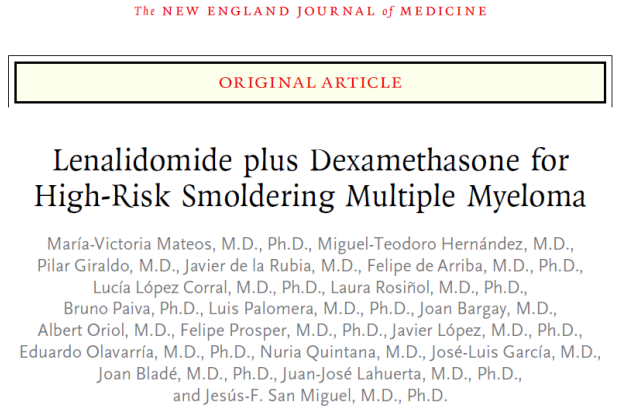
- **Low or Intermediate risk SMM:**
  - No role for therapy
  - Clinic visit and laboratories (SPEP/IFE, UPEP/IFE, Free light chains, CBC, CMP) every 3 months, could increase interval if stable to every 4-6 months
  - Follow-up imaging consider annually (or sooner if focal lesion on MRI

- **High risk SMM:**
  - Consider treatment

Mateos MV, et al. *Blood Cancer Journal* **volume 10**, Article number: 102 (2020)

Spanish QuiReDex study: first positive treatment study of SMM




The NEW ENGLAND JOURNAL of MEDICINE

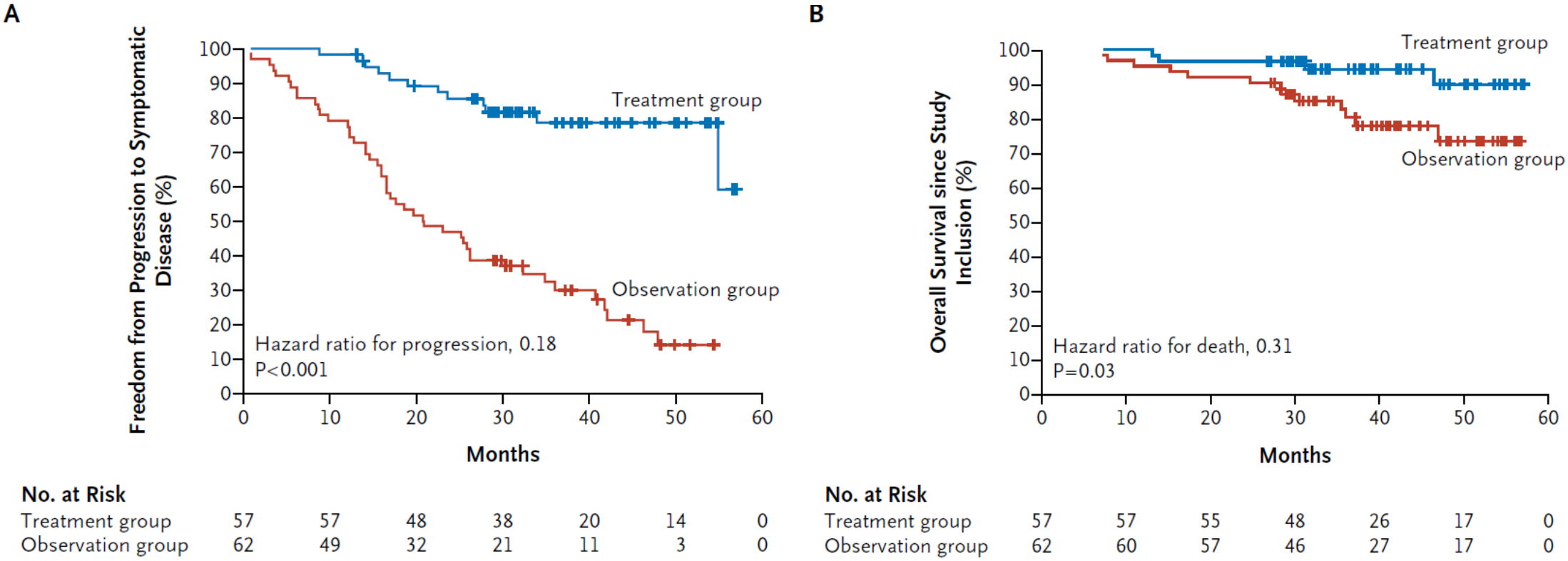
ORIGINAL ARTICLE

Lenalidomide plus Dexamethasone for High-Risk Smoldering Multiple Myeloma

María-Victoria Mateos, M.D., Ph.D., Miguel-Teodoro Hernández, M.D., Pilar Giraldo, M.D., Javier de la Rubia, M.D., Felipe de Arriba, M.D., Ph.D., Lucía López Corral, M.D., Ph.D., Laura Rosiñol, M.D., Ph.D., Bruno Paiva, Ph.D., Luis Palomera, M.D., Ph.D., Joan Bargay, M.D., Albert Oriol, M.D., Felipe Prosper, M.D., Ph.D., Javier López, M.D., Ph.D., Eduardo Olavarría, M.D., Ph.D., Nuria Quintana, M.D., José-Luis García, M.D., Joan Bladé, M.D., Ph.D., Juan-José Lahuerta, M.D., Ph.D., and Jesús-F. San Miguel, M.D., Ph.D.

Mateos N Engl J Med 2013;369:438-47 .

Spanish QuiReDex study: Rd improved PFS and OS



Mateos N Engl J Med 2013;369:438-47 .

Limitations to this study

- Modern imaging (PET/CT or MRI) not used at randomization
- Multiparametric flow cytometry criteria used to define high-risk SMM – not standard technique for plasma cell disorders
- Only 11% of patients in the observation arm who experienced disease progression were treated with lenalidomide (reflecting its limited availability at the time) which likely accounted for differences in OS

Mateos N Engl J Med 2013;369:438-47 .

US study: E3A06

A Randomized Trial of Lenalidomide Versus Observation in Smoldering Multiple Myeloma

- Single-agent lenalidomide vs observation in intermediate- or high-risk SMM
  - Lenalidomide 25 mg on days 1 to 21 of a 28-day cycle
- 182 pts randomly assigned. Median follow-up is 35 months.
- Definition intermediate or high risk- dx within 60 months and abnormal serum free light chain (FLC) ratio (<0.26 or >1.65) by serum FLC assay

➢ **Overall response rate 50%** (95% CI, 39% to 61%) treated pts, no responses in the observation arm.

  ➢ One, 2, and 3 year PFS was 98%, 93%, and 91% for the lenalidomide arm versus 89%, 76%, and 66% for the observation arm

Lonial, J Clin Oncol. 2019. 38:1126-1137.

Ongoing studies in High Risk Smoldering myeloma

AQUILA study	Daratumumab (subcutaneous) versus Observation
DETER-SMM trial	Lenalidomide + dexamethasone +/- Daratumumab
CAR-PRISM	Using cilta-cel (CAR T-cell therapy) in high risk SMM
IMMUNO-PRISM	Bispecific antibodies in high risk SMM

Smoldering Myeloma: Takeaways

- Recommend treatment in patients with high risk smoldering myeloma
  - Rd or single agent lenalidomide
  - Clinical trials

- Recommend observation for low and intermediate risk smoldering myeloma

- FHCC Myeloma Service
  - Andrew Cowan
  - Rahul Banerjee
  - Kara Cicero
  - Danai Dima
  - Andrew Portuguese
  - Evangeline Marasigan
  - Shruthi Pelluri
  - Bonnie Joy
  - Kim Aregood

- Our patients and their families
- Clinical trial participants
- Our community partners

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Thank you