Fred Hutch Cancer Center

Smoldering Myeloma and MGUS

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Land Acknowledgement

Fred Hutchinson 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

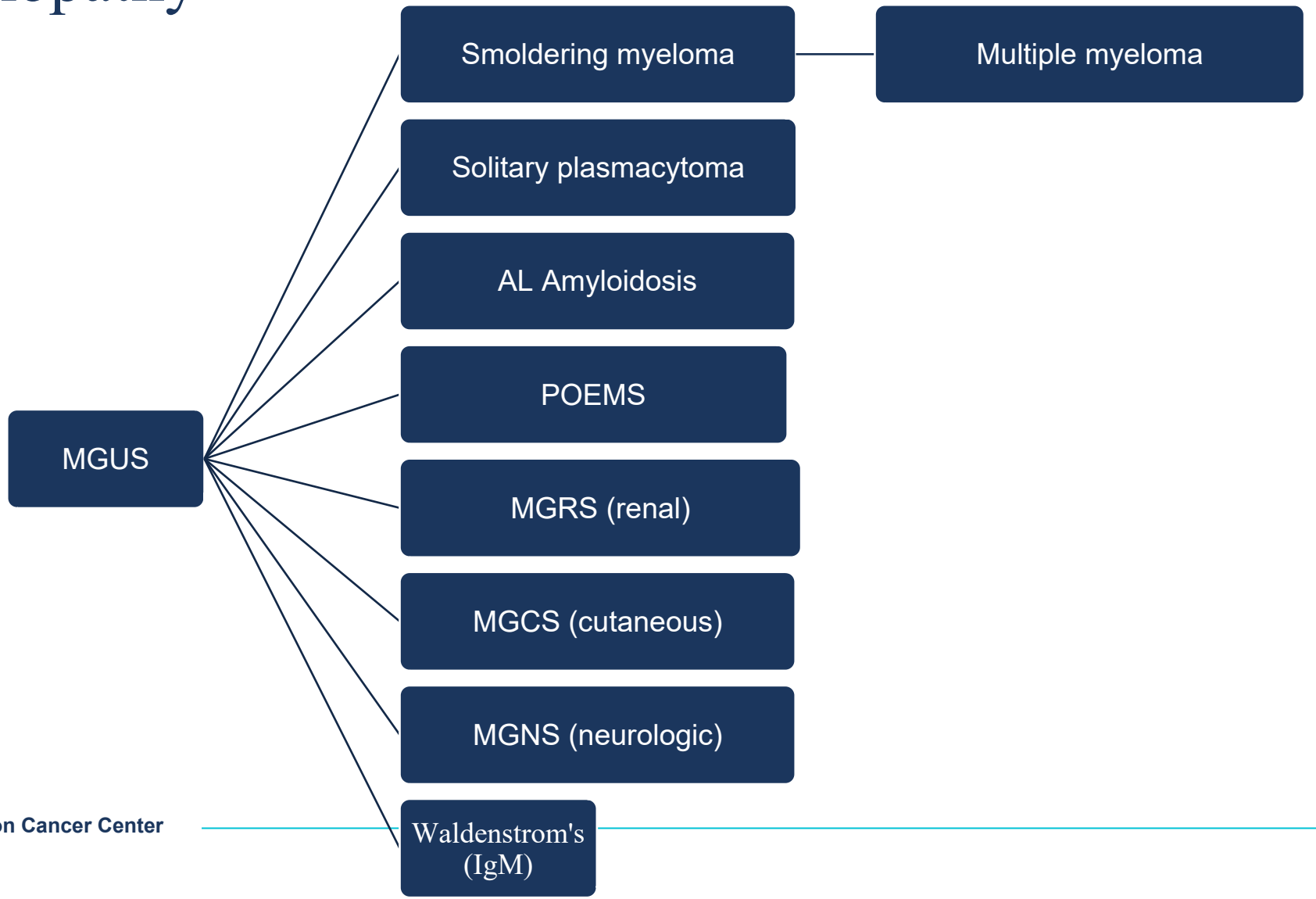
2. Learners will define MGUS and smoldering myeloma using current IMWG criteria

3. Understand current risk stratification schema for MGUS and smoldering myeloma

4. Review treatment options for patients with high risk smolderingmyeloma

5. Recognize monoclonal gammopathies of clinical significance, suchas AL amyloidosis

Spectrum of disorders associated with a monoclonal gammopathy



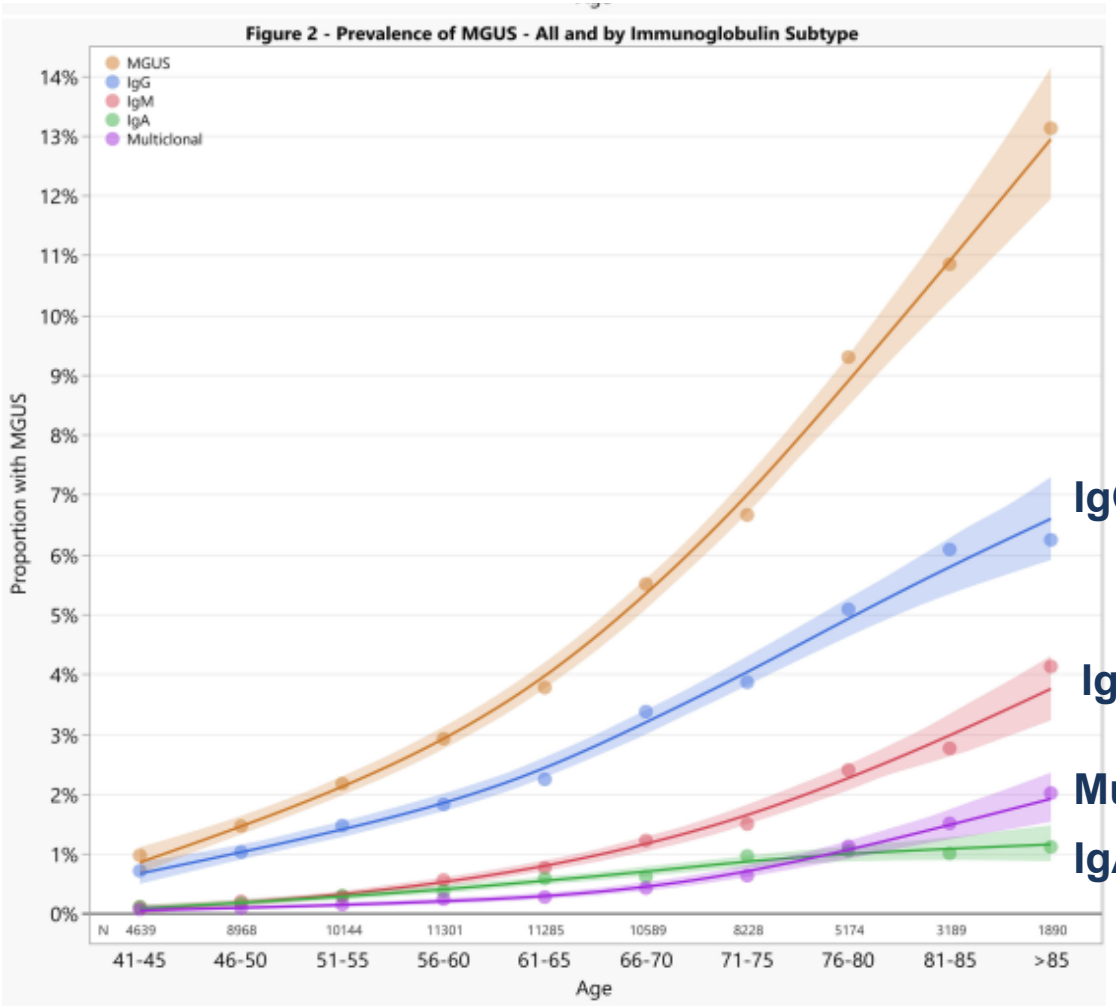
Diagnosis of MGUS, SMM and Multiple myeloma

MGUS	Smoldering myeloma	Multiple myeloma
• **Clonal bone marrow plasma cells <10%** • **No myeloma defining event** --- **Non-IgM MGUS:** • M-spike < 3 g/dL **IgM MGUS:** • IgM M-spike <3 g/dL • No symptoms **Light chain MGUS:** • Abnormal FLC ratio • Increased level of appropriate FLC • Urine M-spike <500 mg/24h	• **IgG or IgA M-spike ≥3 g/dL** • **Clonal plasma cells 10-60%** • **No Myeloma defining event** **Light chains smoldering MM:** • Urine M-spike >500 mg/24h • Clonal plasma cells 10-60% • No Myeloma defining event	• **Clonal bone marrow plasma cells >10% *or* biopsy proven plasmacytoma** **AND** **A myeloma defining event:** • Hypercalcemia • Renal dysfunction • Anemia • Bone lesions • 60% bone marrow plasma cells • Free light chain ratio >100 • 2 or more focal lesions on MRI

Rajkumar SV, Dimopoulos MA, Palumbo A, et al. Lancet Oncol. 2014 Nov;15(12):e538-48..

Diagnosis of MGUS, SMM and Multiple myeloma

- 6% of all referral to hematology are for MGUS
- Incidence of MGUS is about **5% of the population above age 50**
  - Incidence increases with age



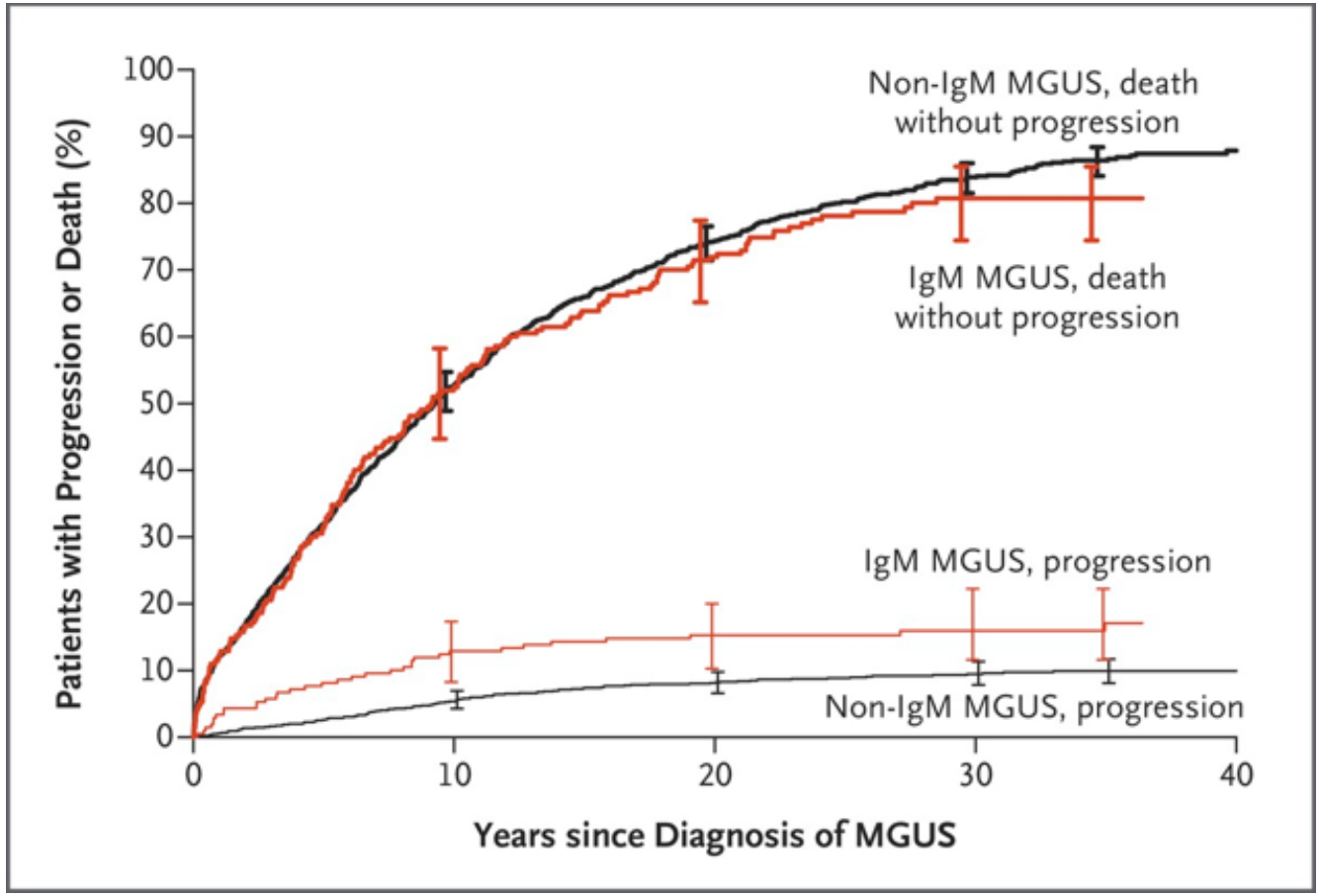
Pallavi G, Dyba J, Hay AE, et al. *Blood* 2023; 142 (Supplement 1): 908.

Love TJ, Rognvaldsson S, Thorsteindottir S, et al. *Blood* 2022; 140 (Supplement 1): 256–258

What are the risk factors for developing a monoclonal gammopathy?

- Age
- Obesity (BMI >30)
- 9/11 first responders
- Black race
- Autoimmune disease (?)
- Radiation exposure
- Agent orange
- Asbestos paint, fertilizers
- Gaucher disease

Two major subtypes of MGUS: IgM and non-IgM



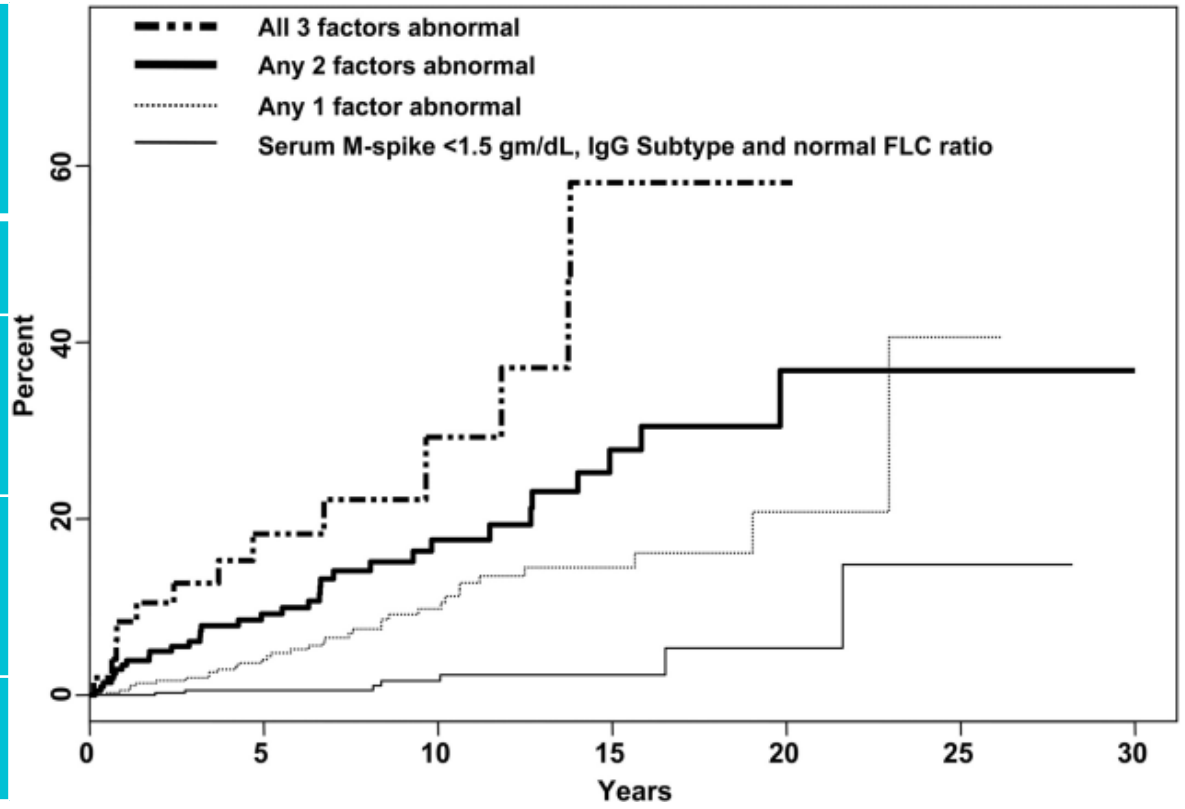
<u>34 of 210 patients with IgM MGUS had progression</u>
17 progressed to **NHL**
3 progressed to **AL amyloidosis**
11 progressed to **WM**
3 progressed to **CLL**

<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.

IMWG consensus for 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 (%)	% of patients (iStopMM cohort)
Low	0	**5**	43%
Low-intermediate	1	**21**	40%
High-intermediate	2	**37**	16%
High risk	3	**58**	0.3%



Rajkumar SV, Kyle RA, Therneau TM, et al. Blood. 2005 Aug 1;106(3):812-7. Figure 3.
Love TJ, Rognvaldsson S, Thorsteindottir S, et al. *Blood* 2022; 140 (Supplement 1): 256–258

IMWG Consensus Guidelines: **Management of Low risk MGUS**

- Majority of patients are low risk (43-50%)
- Risk of progression to MM or malignancy is low

- Workup:
  - CBC, Creatinine, Calcium, assess for symtoms
  - If abnormal: evaluate with bone marrow biopsy and skeletal imaging
  - If normal: Bone marrow examination and imaging is not routinely indicated if above normal

- Monitoring:
  - Re-evaluate with clinic visit and CBC, Creatinine, Calcium, SPEP, light chains in 6 months
    - If stable: monitor every 2-3 years or when symptoms suggestive of plasma cell malignancy arise

Kyle RA, Durie BG, Rajkumar SV, et al. Leukemia. 2010 Jun;24(6):1121-7.

IMWG Consensus Guidelines:
Management of Intermediate or High risk MGUS

- **Workup:**
  - Bone marrow biopsy and aspiration
  - Labs: CBC with diff, creatinine, calcium
  - Imaging
    - Skeletal Imaging (if non-IgM)
    - CT abdomen (if IgM)
  - Evaluate for signs or symptoms suggestive of AL amyloidosis

- **Monitoring:**
  - SPEP, free light chains, CBC and chemistry panel in 6 months, and then annually for life
  - Evaluate sooner if there are any changes to their clinical condition

- **Treatment:** not indicated outside of clinical trial

Kyle RA, Durie BG, Rajkumar SV, et al. Leukemia. 2010 Jun;24(6):1121-7.

Light chain MGUS

- Light chain MGUS
- Risk for progression to MM is 0.3% per 100 person-years
  - Compared to 0.5% in patients with a heavy chain
- 23% of this group will have **renal disease**
  - Must monitor renal function
- Can progress to **light chain myeloma** and/or **AL amyloidosis**

- Special consideration in CKD:
  - Free light chain concentration is affected by kidney function

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

MGUS: takeaways

- MGUS is a precursor condition
- IgM vs. non-IgM vs. Light chain
- Risk stratification: M-spike, free light chain ratio and IgG vs. non-IgG
- Renal function can impact serum free light chain
- Monitor for progression to a plasma cell disorder that requires treatment
  - “small but dangerous clone” scenarios: AL amyloidosis, POEMS, MGRS, MGCS, MGTS

Real world tools to help guide risk

- https://istopmm.com/riskmodel
- myelomarisk.com

Diagnosis of MGUS, SMM and Multiple myeloma

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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 SV, Dimopoulos MA, Palumbo A, et al. Lancet Oncol. 2014 Nov;15(12):e538-48..

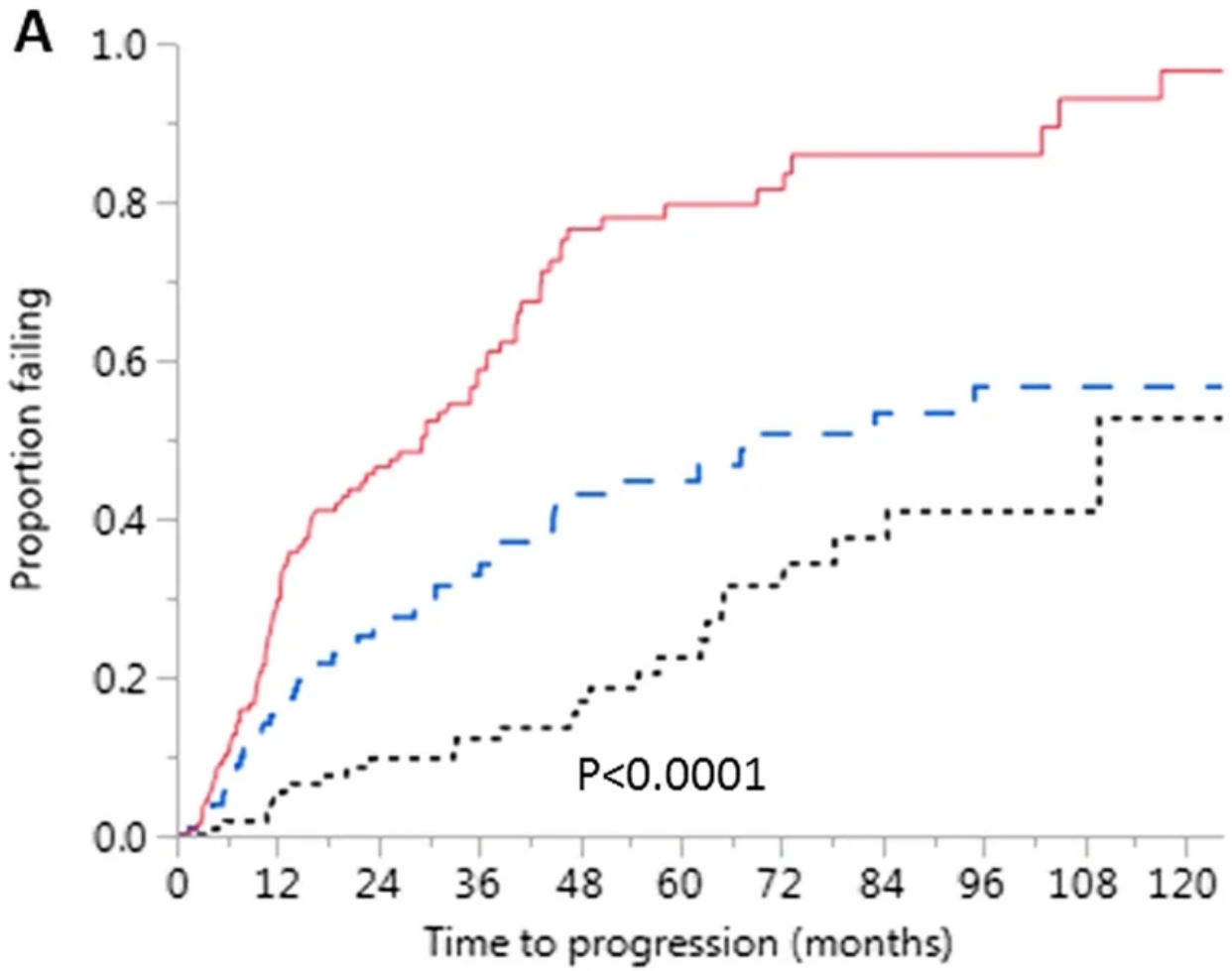
How do I risk stratify my patient with SMM?

- Mayo "20/2/20" Criteria
  - BM plasma cell % > **20**%
  - M-protein > **2** g/dL
  - FLC ratio > **20**

# 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

Mayo 20/2/20 Risk Stratification



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

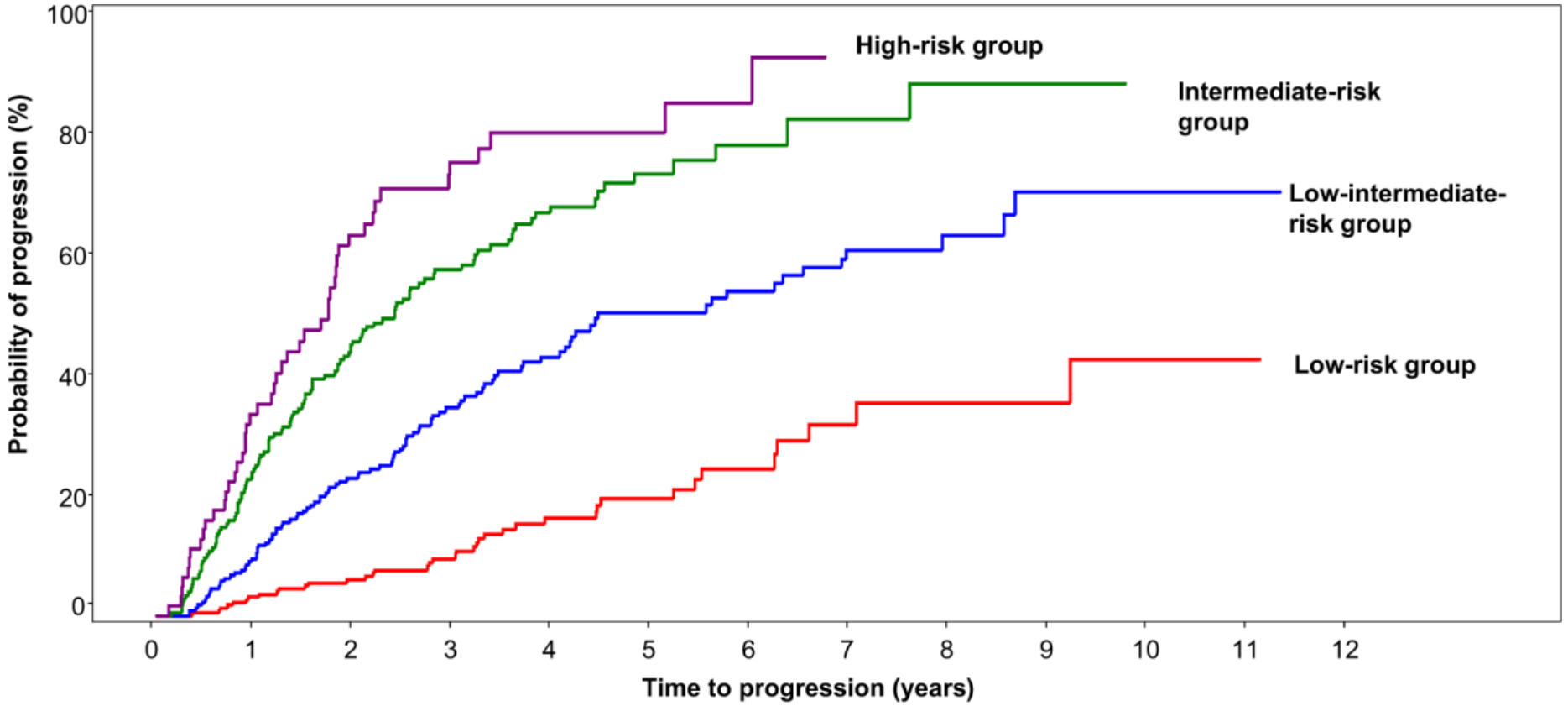
Intermediate Risk (1 risk factor):
median TTP = **67.8 months**

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

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

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:

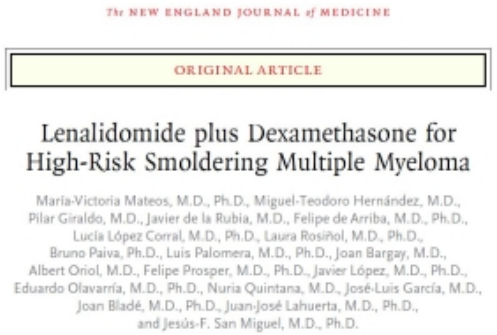
- **Observation** or clinical trial
- Clinic visit and laboratories
  - SPEP/IFE, Free light chains, CBC, CMP every 3 months --> q4-6 months
  - Follow-up imaging consider annually (or sooner if focal lesion on MRI

High risk SMM:

- Consider treatment
  - Lenalidomide
  - Daratumumab

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

QuiReDex: lenalidomide for high risk 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.

High risk SMM patients (n=119)

Lenalidomide + Dexamethasone

Induction
9 x 28-day cycles

Therapeutic abstention

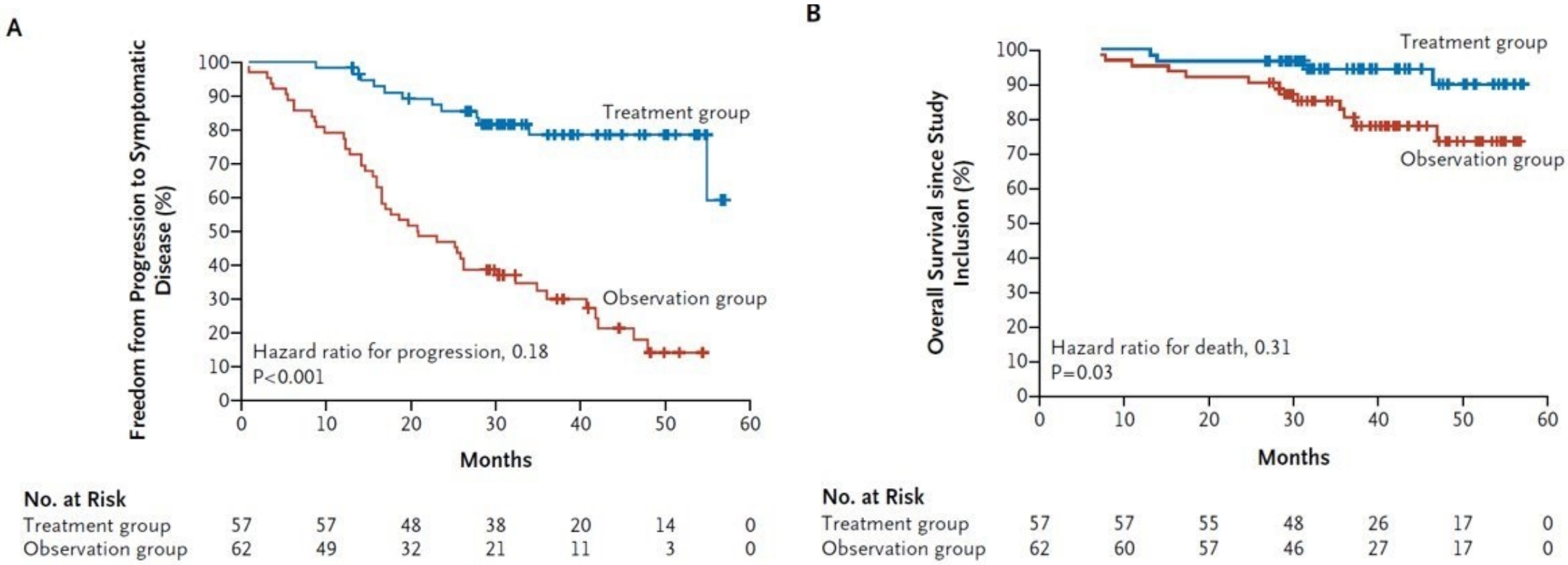
**Maintenance until progression

Lenalidomide maintenance

Therapeutic abstention

Mateos MV, Hernández MT, Giraldo P, et al. N Engl J Med. 2013 Aug 1;369(5):438-47.

Spanish QuiReDex study: Rd improved PFS and OS



Mateos MV, Hernández MT, Giraldo P, et al. N Engl J Med. 2013 Aug 1;369(5):438-47.

Spanish QuiReDex study: Limitations

- 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 MV, Hernández MT, Giraldo P, et al. N Engl J Med. 2013 Aug 1;369(5):438-47.

US study: E3A06: A Randomized Trial of Lenalidomide Versus Observation in Smoldering Multiple Myeloma

- Patients with intermediate or high risk SMM
  - Definition of 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

- Randomizes to Lenalidomide (single agent) versus observation

- 182 pts randomly assigned. Median follow-up is 35 months.

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

US study: E3A06: A Randomized Trial of Lenalidomide Versus Observation in Smoldering Multiple Myeloma

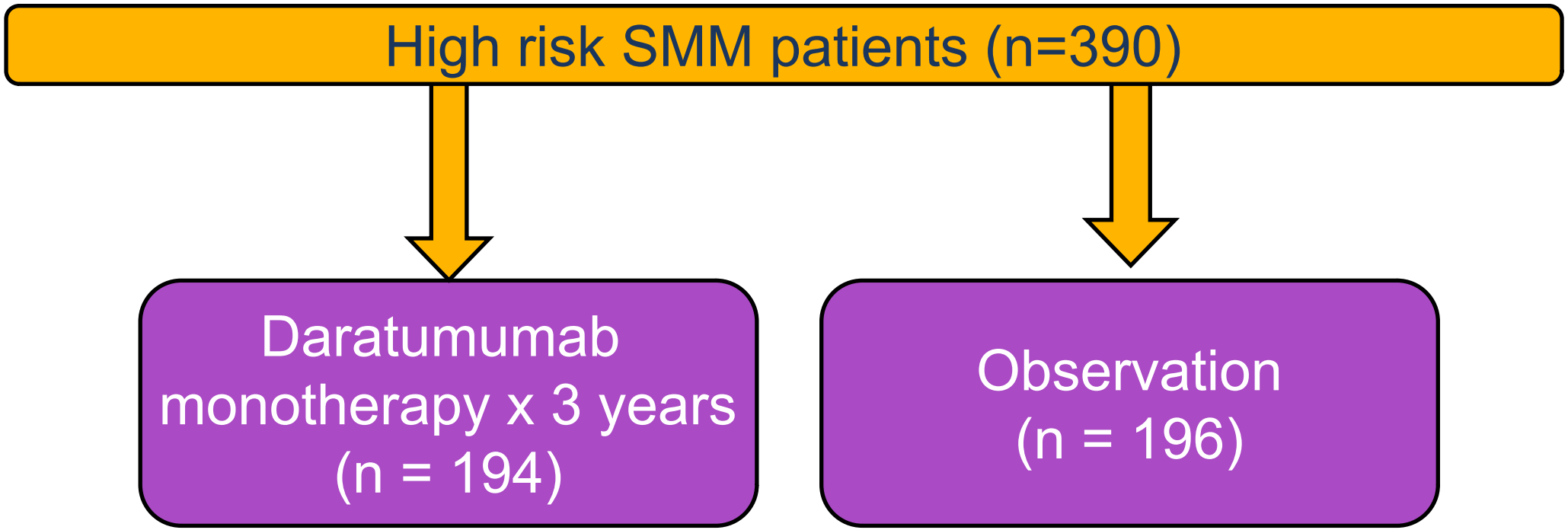
- **Overall response rate 50%** (95% CI, 39% to 61%) treated patients
- No responses in the observation arm

- **PFS significantly longer with lenalidomide compared with observation** (hazard ratio, 0.28; 95% CI, 0.12 to 0.62; P = .002)

- 1, 2, and 3 year PFS was 98%, 93%, and 91% for the lenalidomide arm versus 89%, 76%, and 66% for the observation arm

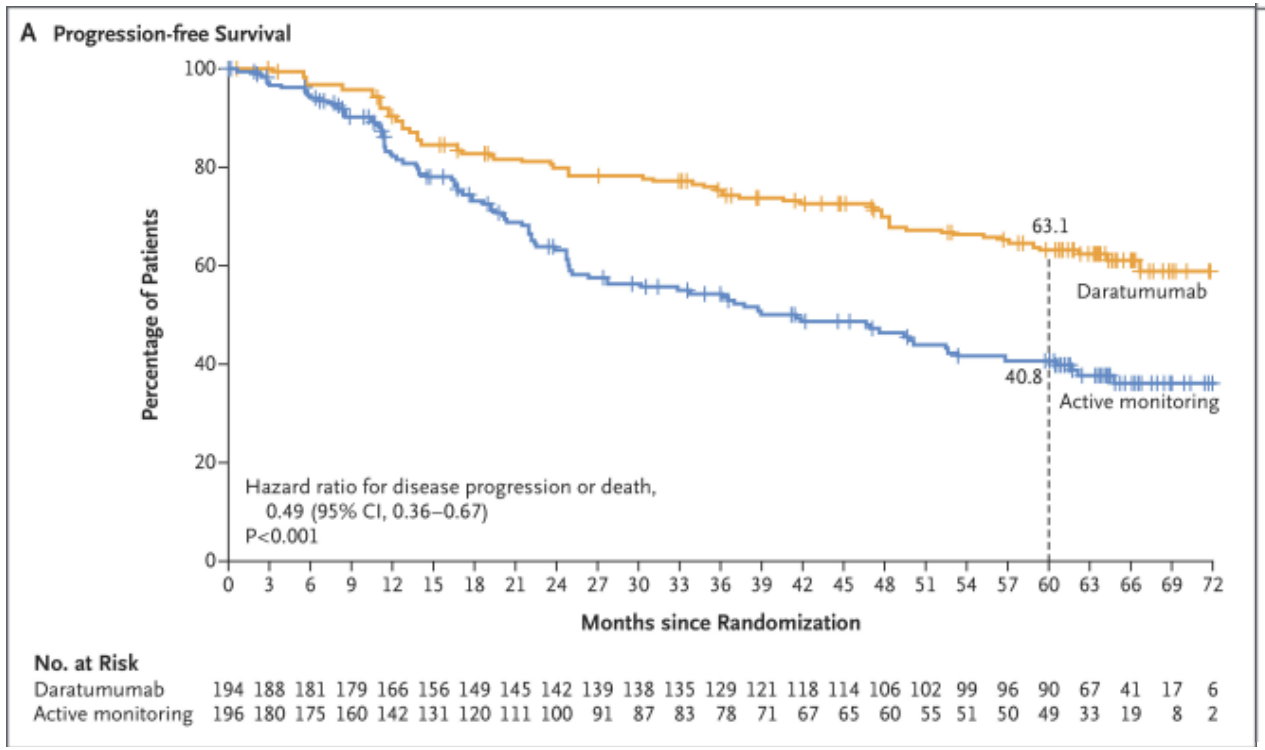
Lonial, J Clin Oncol. 2019. 38:1126-1137.

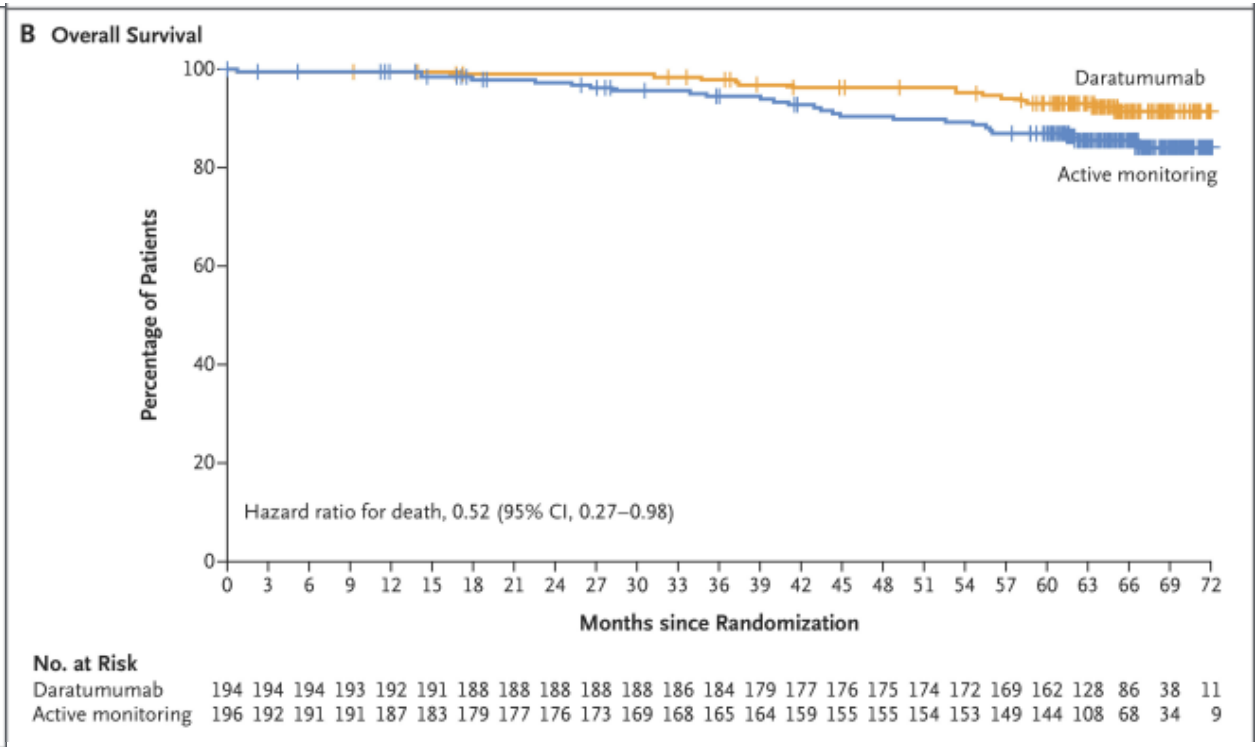
AQUILA trial: Daratumumab versus observation for high risk smoldering myeloma



Dimopoulos MA, Voorhees PM, Schjesvold F, et al. Daratumumab or Active Monitoring for High-Risk Smoldering Multiple Myeloma. N Engl J Med. 2025 May 8;392(18):1777-1788.

AQUILA trial: improved PFS and OS with daratumumab





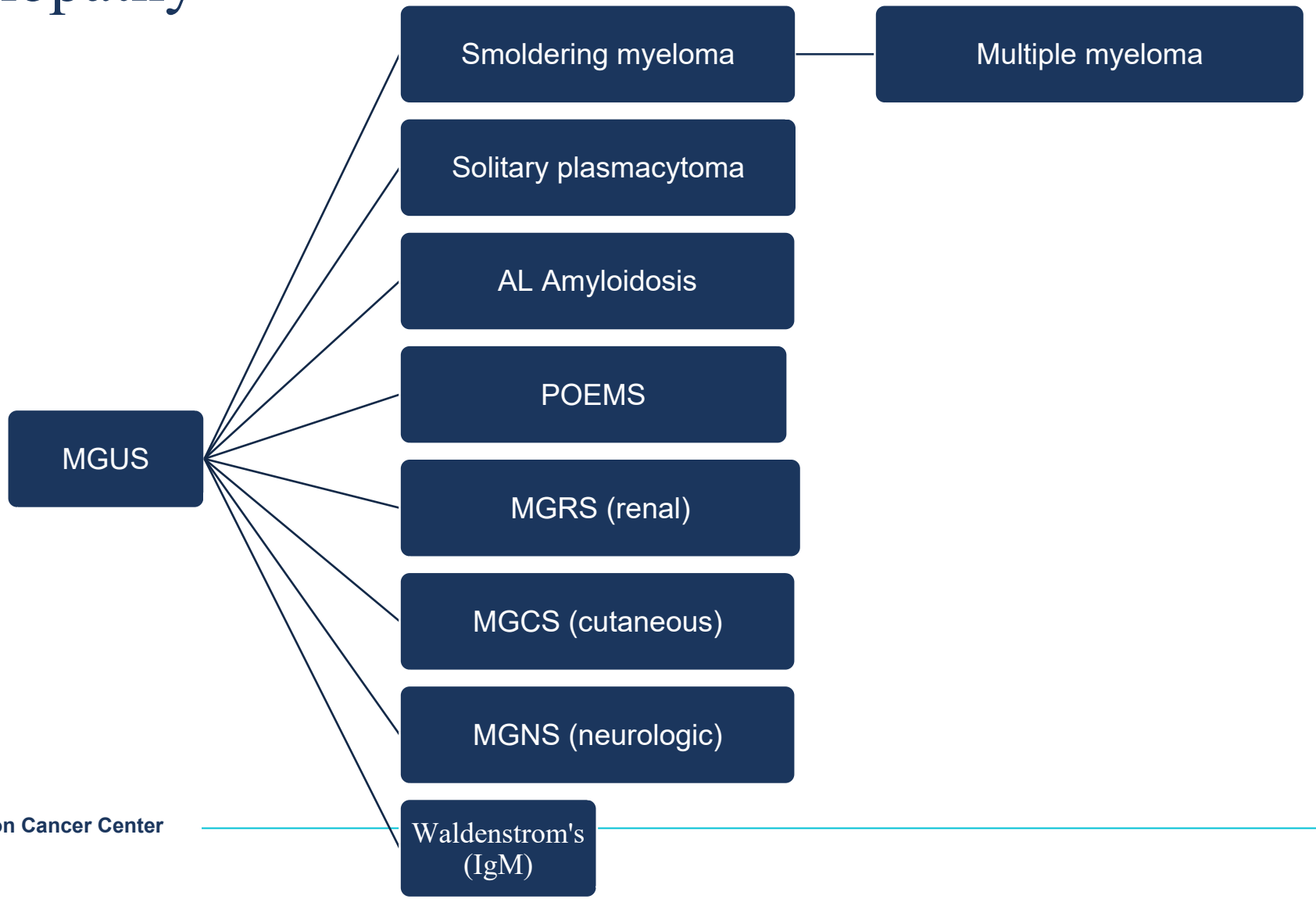
Dimopoulos MA, Voorhees PM, Schjesvold F, et al. Daratumumab or Active Monitoring for High-Risk Smoldering Multiple Myeloma. N Engl J Med. 2025 May 8;392(18):1777-1788.

Smoldering myeloma: takeaways

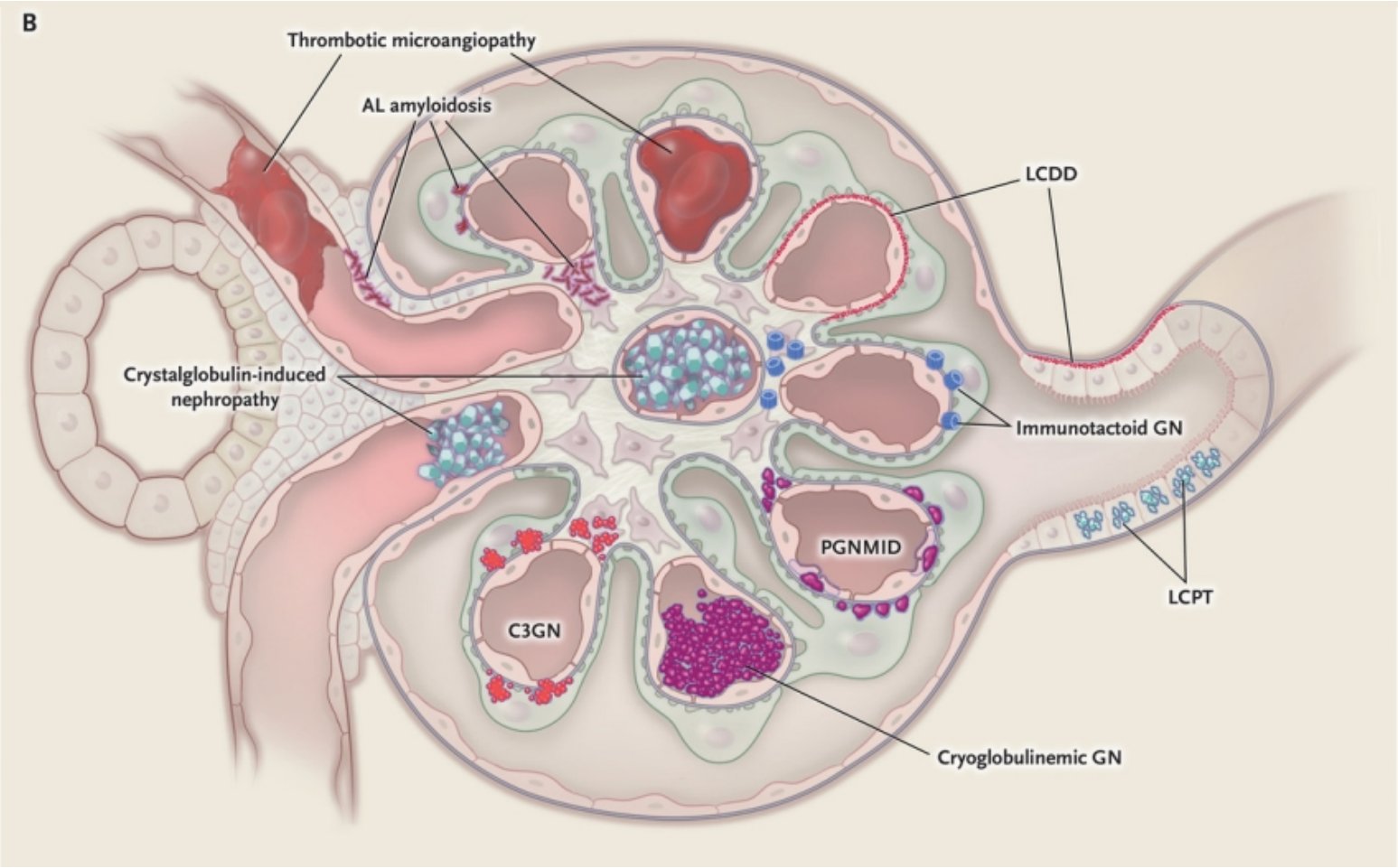
- Recommend **observation** for **low or intermediate risk** smoldering myeloma

- Consider treatment in patients with **high risk smoldering myeloma**
  - Lenalidomide +/- dexamethasone
  - Daratumumab
  - Clinical trials

Spectrum of disorders associated with a monoclonal gammopathy



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

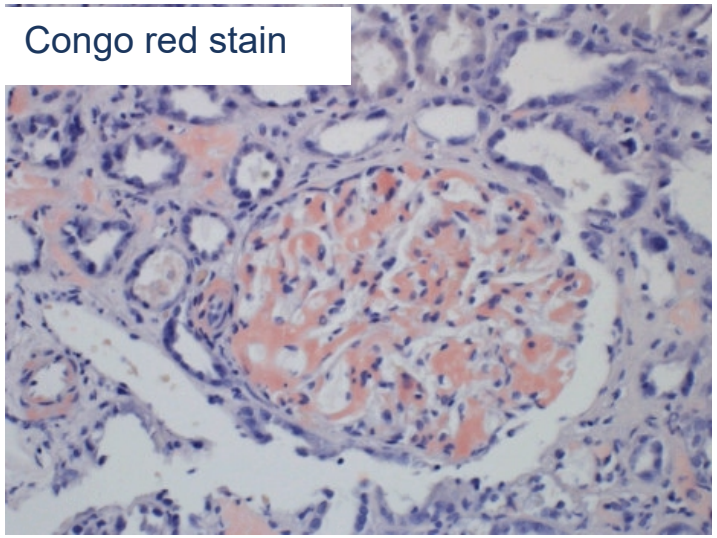
Treatment is similar to that of MM

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

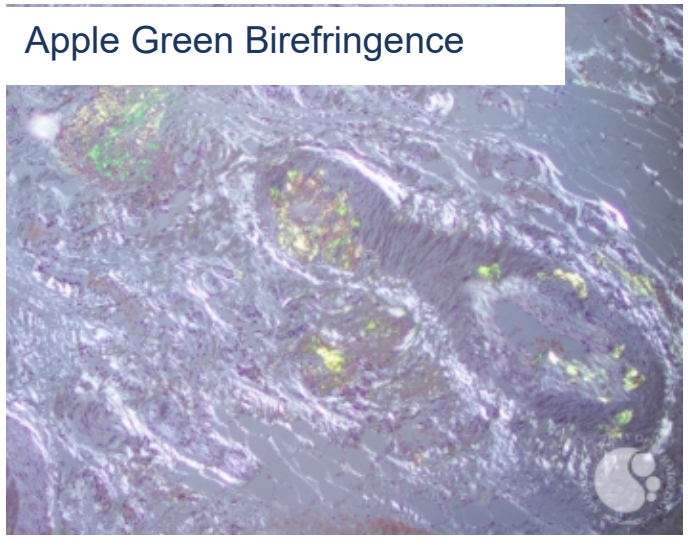
AL amyloidosis

- 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)

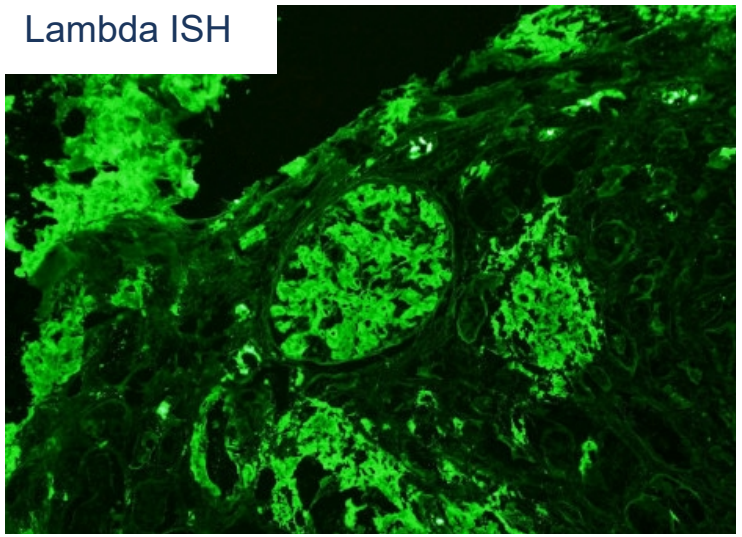
Congo red stain



Apple Green Birefringence



Lambda ISH

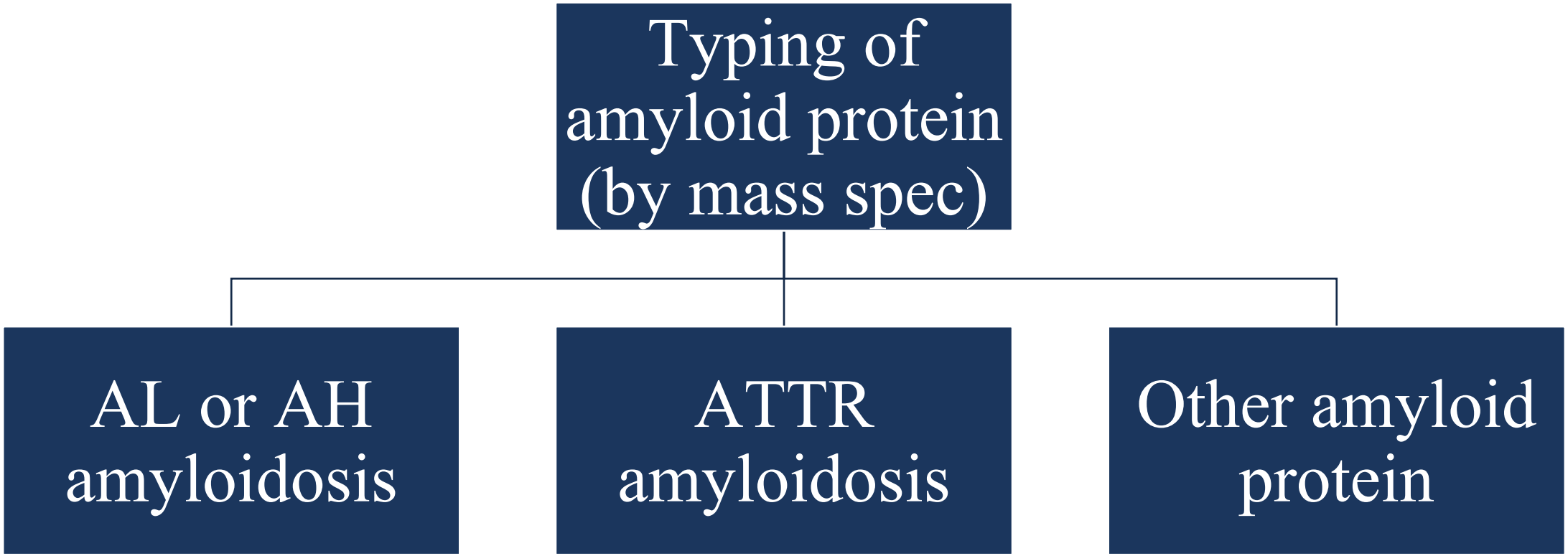


https://imagebank.hematology.org/image/62419/amyloid-deposition-in-the-blood-vessel-show-apple-green-birefringence-under-polarized-light?type=upload

AL amyloidosis- clues to diagnosis

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

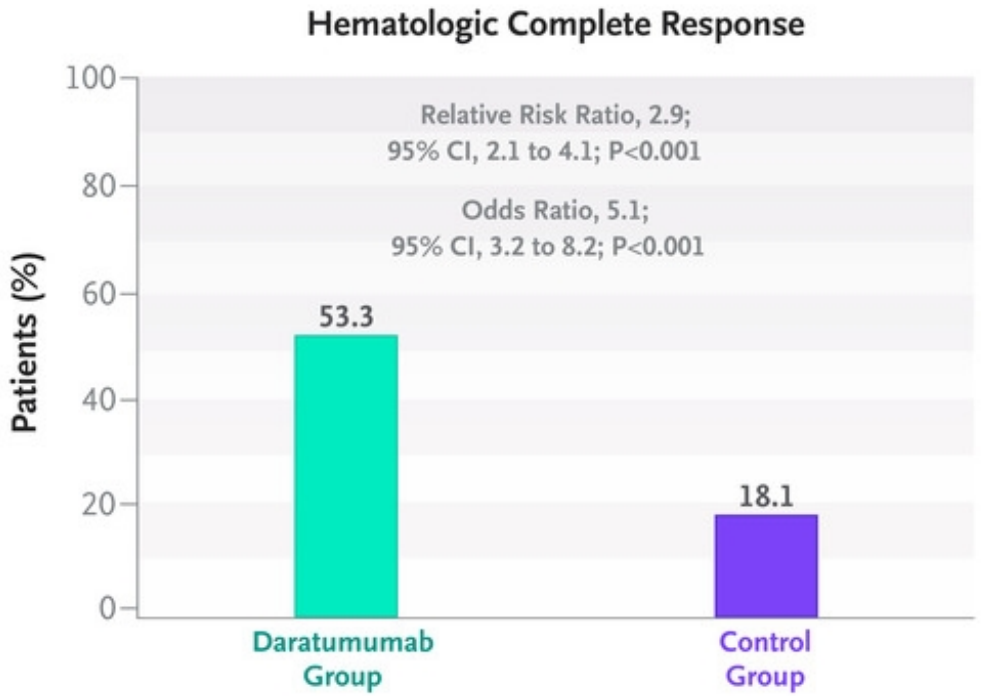
AL amyloidosis



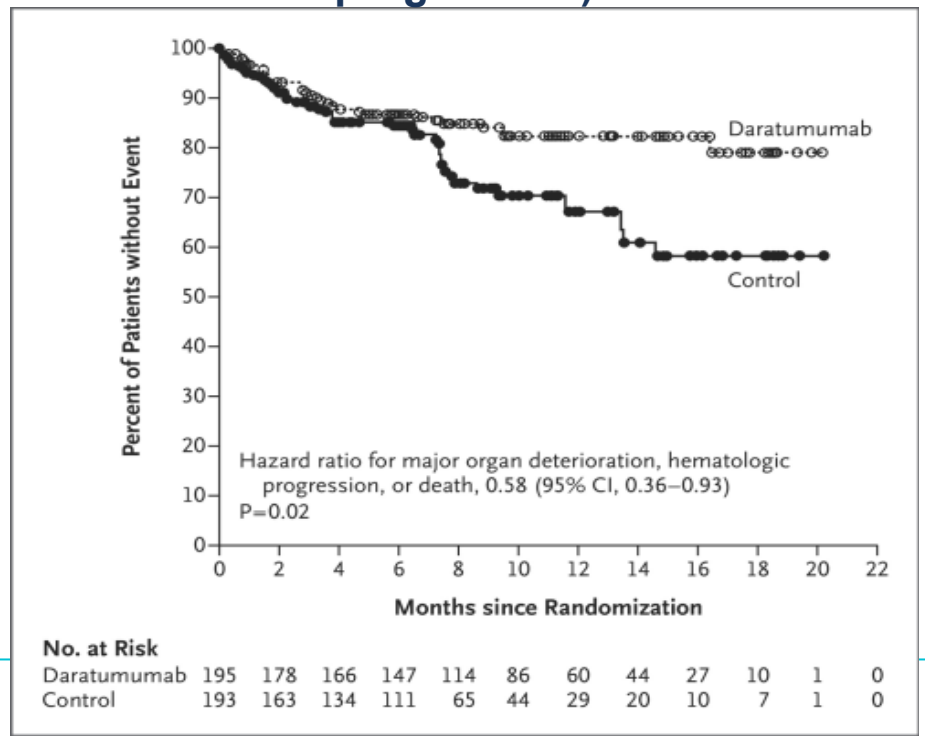
Treatment of AL amyloidosis: ANDROMEDA

Newly diagnosed AL amyloidosis

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

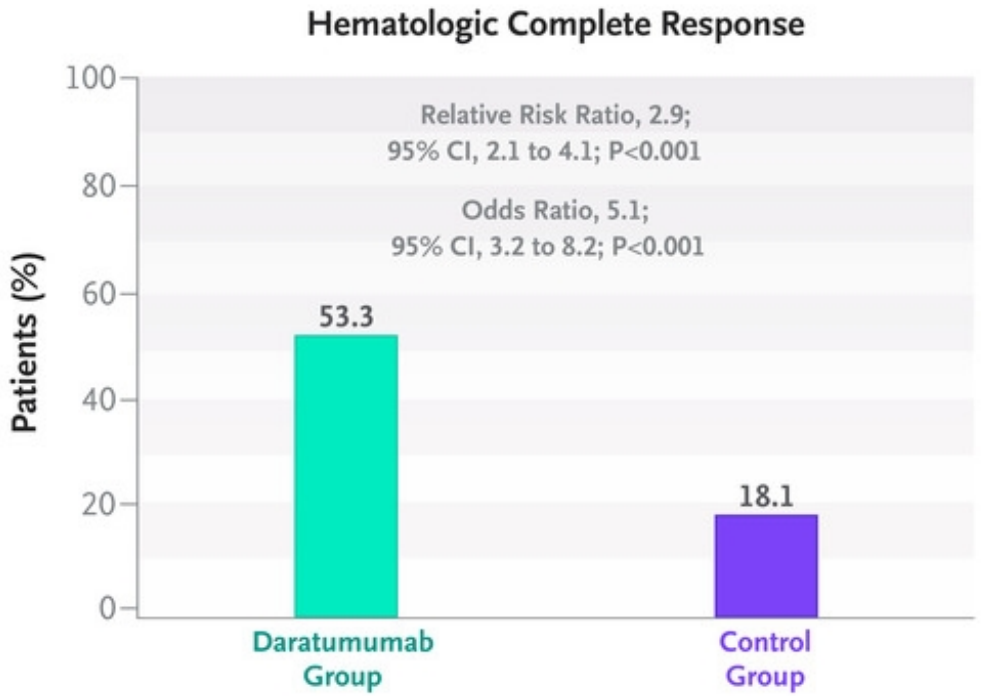


Event free survival
(End stage cardiac failure, renal failure, hematologic progression)



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

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



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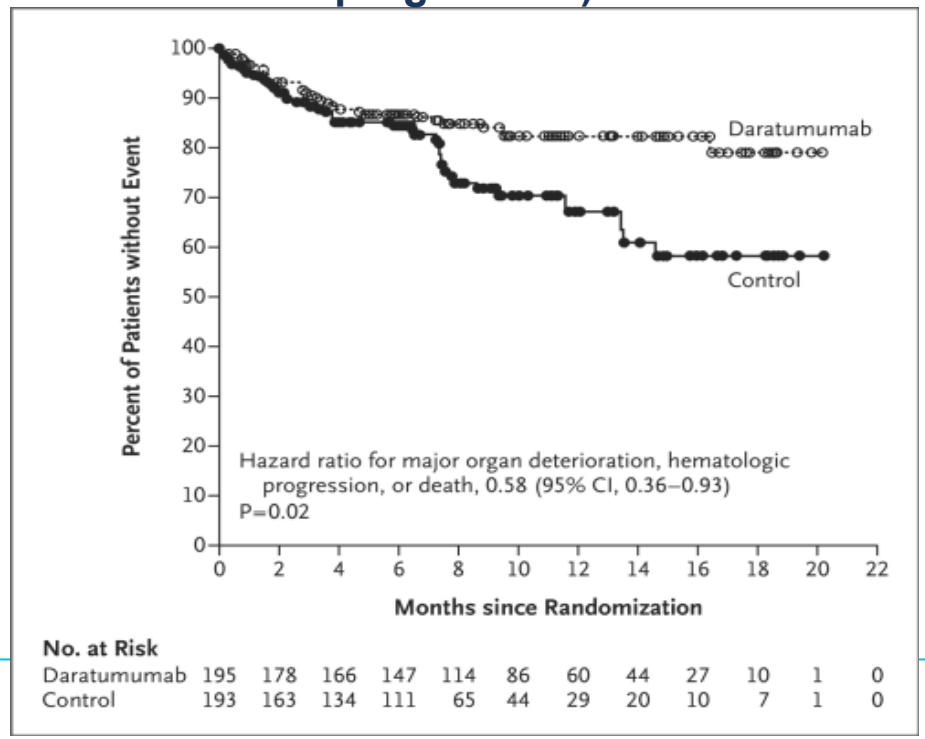

Kastritis E et al. N Engl J Med 2021;385:46-58

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**
  - Autologous stem cell transplant
    - Fit, CrCl ≥ 30, SBP >90, ECOG PS <2, NYHA class I or II, normaltroponin
  - Pomalidomide
  - Venetoclax - if t(11;14)
  - Bortezomib
  - Melphalan
  - Bispecifics? CAR T-cell?

AL amyloidosis: takeaways

- Confirm the diagnosis with typing of the amyloid protein

- Treatment of systemic AL amyloidosis
  - CyBorD + daratumumab x 6 cycles, followed by daratumumab for total 2 years
- Transplant?
- Monitor for relapse or recurrent disease

Fred Hutch Cancer Center

Thank you

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