Monoclonal gammopathies: MGUS, Smoldering myeloma and Amyloidosis

Comprehensive Hematology and Oncology Review

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Seattle Cancer Care Alliance

Fred Hutch · Seattle Children's · UW Medicine

Learning objectives

1. Understand the lab, imaging and bone marrow evaluation of patients presenting with plasma cell dyscrasias
2. Define MGUS, smoldering myeloma and multiple 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 smoldering myeloma
5. Understand the workup for a patient with suspected AL amyloidosis
6. Review treatment options for patients with AL amyloidosis

A case

A previously healthy 71 year old man was told he could not donate blood due to mild anemia. A CBC was notable for Hgb 11.9 g/dL (previously 15-16 g/dL) prompting workup demonstrating:

- No iron deficiency, normal B12/folate, normal TSH, no hemolysis
- SPEP: IgG lambda monoclonal protein of 2.3 g/dL
- Serum free light chain ratio of 17.8 (kappa 13.1 mg/dL and lambda 0.73 mg/dL)

What is your next step in evaluation?

Workup of a patient with plasma cell dyscrasia

- History and physical examination
- CBC
- Serum calcium and creatinine
- SPEP and immunofixation
- 24 hour UPEP and immunofixation
- Serum free light chain assay
- Quantitative immunoglobulins (IgG, IgA, IgM)
- Bone marrow aspiration and biopsy
- Cross sectional imaging (Whole body low-dose CT scan, MRI, PET/CT)

IMWG Diagnostic Criteria for MGUS, SMM, MM

MGUS	Smoldering myeloma	Multiple myeloma
Serum M-spike < 3 g/dL and Urine M-spike <500 mg/24h	Serum M-spike ≥3 g/dL or Urine M-spike ≥500 mg/24h	Presence of serum and/or urinary monoclonal protein (except inpatients with non-secretory or hyposecretory MM)
and Clonal bone marrow plasma cells <10%	**or** Clonal bone marrow plasma cells 10-59%	**and** Clonal bone marrow plasma cells ≥10%
and Absence of myeloma defining events, amyloidosis *Also consider MGRS or MGNS	**and** Absence of myeloma defining events or amyloidosis	**and a myeloma defining event:** <u>End organ damage:</u> • Hypercalcemia: serum calcium <u>≥</u>11.5 mg/dl • Renal insufficiency: serum creatinine >2.0 mg/dL or CrCl <40 mL/mi • Anemia: hemoglobin value of >2 g/dL below the lower limit of normal or <10 g/dL • Osteolytic bone lesions <u>Any one of the Biomarkers of Malignancy:</u> • Clonal Bone Marrow Plasma Cells >60% • Involved:Uninvolved SFLC ratio <u>≥</u>100 • >1 focal lesions on MRI studies

MGUS

- MGUS is present in 3% of persons age ≥ 50 years and 5.3% ≥ 70 years
  - but only 0.3% among those <50 years old

- Can progress to lymphoproliferative diseases (CLL, NHL, WM), amyloidosis, multiple myeloma or monoclonal immunoglobulin deposition disease(MIDD)

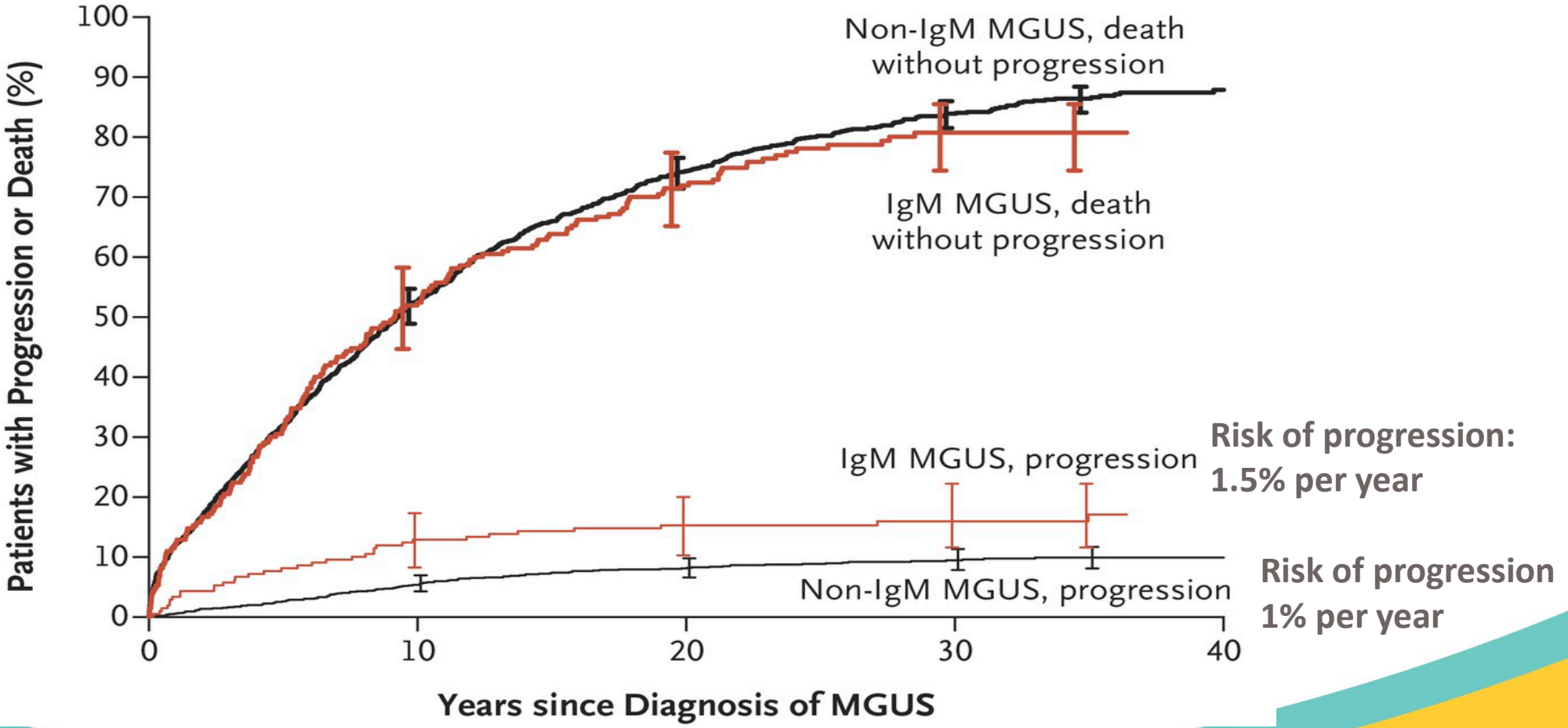
IMWG 2014 diagnostic criteria: MGUS

Plasma cell disorder	Disease Definition	Risk of progression	Primary Progression Events
Non IgM MGUS	1. Serum monoclonal protein <3 g/dL 2. Clonal bone marrow plasma cells <10% 3. Absence of end-organ damage such as hypercalcemia, renal insufficiency, anemia and bone lesions (CRAB) or amyloidosis that can be attributed to the plasma cell disorder	1% per year	Multiple myeloma, solitary plasmacytoma, Ig-related amyloidosis
IgM MGUS	1. Serum IgM monoclonal protein <3 g/dL 2. Bone marrow lymphoplasmacytic infiltration <10% 3. Absence of anemia, constitutional symptoms, hyperviscosity, lymphadenopathy, hepatosplenomegaly or other end-organ damage	1.5% per year	Waldenstrom macroglobulinemia, Ig-related amyloidosis
Light chain MGUS	1. Abnormal FLC ratio 2. Increased level of appropriate involved light chain 3. No IgH expression on IFE 4. Absence of end-organ damage 5. Urinary monoclonal protein <500 mg/24 hours	0.3% per year	Light chain MM, AL amyloidosis *23% of this group have or will develop renal disease

Rajkumar et al. Int'l Myeloma Working Group. Lancet Oncology 2014

Dispenzieri. Lancet 2010; 375: 1721–28.

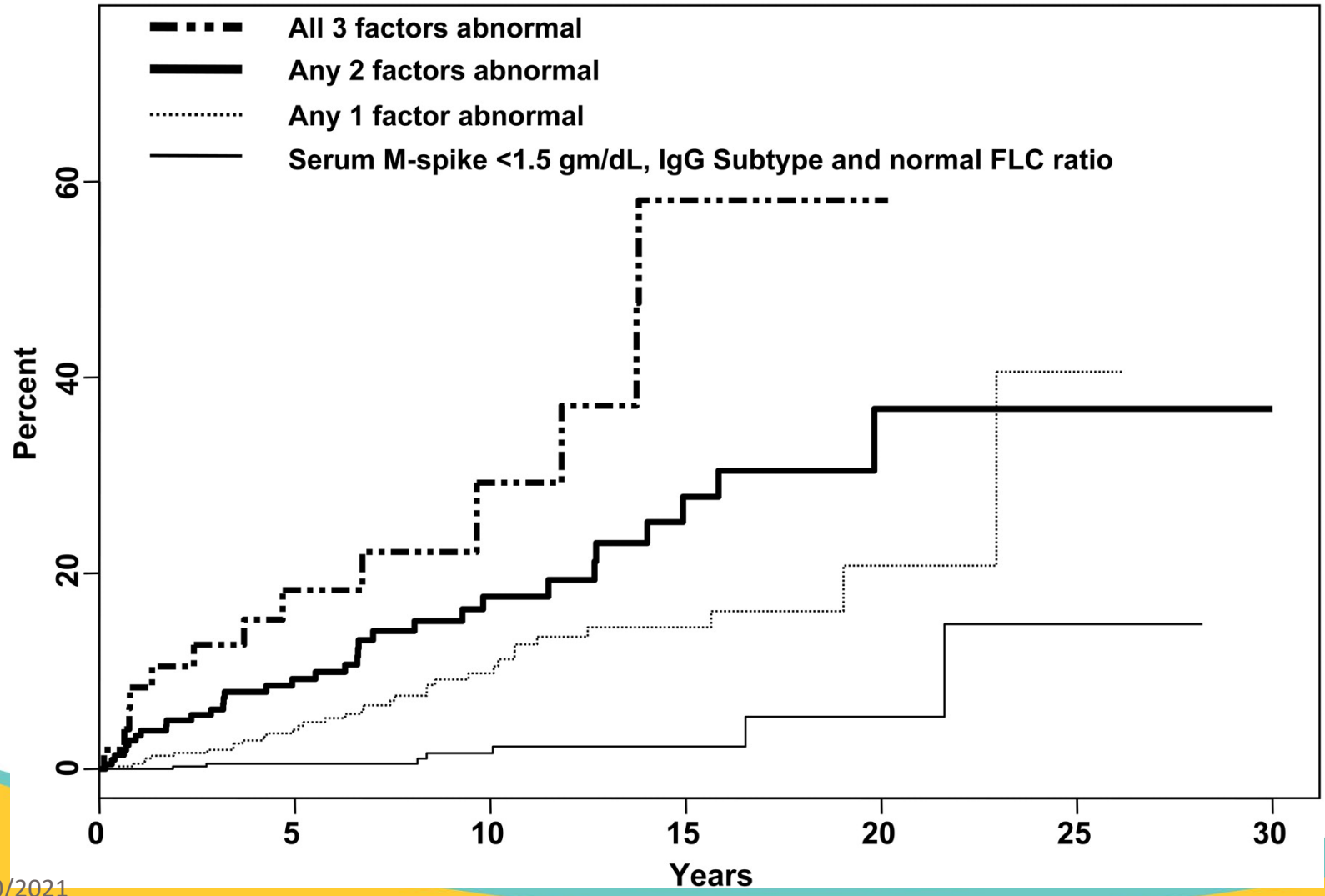
Cumulative incidence of progression of MGUS, with death accounted for as a competing risk



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

The NEW ENGLAND JOURNAL of MEDICINE

Mayo Clinic Model for risk progression from MGUS to MM: FLC ratio, M-spike, Isotype of M-protein



3 risk factors: 58%

2 risk factors: 37%

1 risk factor: 21%

0 risk factors: 5%

Rajkumar S V et al. Blood 2005;106:812-817

Current clinical recommendations for MGUS

"Low-risk MGUS" (<1.5g/dL, IgG isotype, normal FLC ratio, asymptomatic):

- Baseline bone marrow biopsy and skeletal imaging not routinely indicated
- Serum electrophoresis repeated in 6 months, and, if stable, follow either every 2-3 years, or if symptoms arise

"Intermediate-/high-risk MGUS" (≥1.5g/dL, non-IgG isotype, abnormal FLC ratio):

- Baseline bone marrow biopsy
- Skeletal imaging (whole body low dose CT scan, PET/CT, whole body MRI)
- CT chest, abdomen, pelvis for IgM MGUS
- Serum electrophoresis and CBC repeated in 6 months and then annually for life

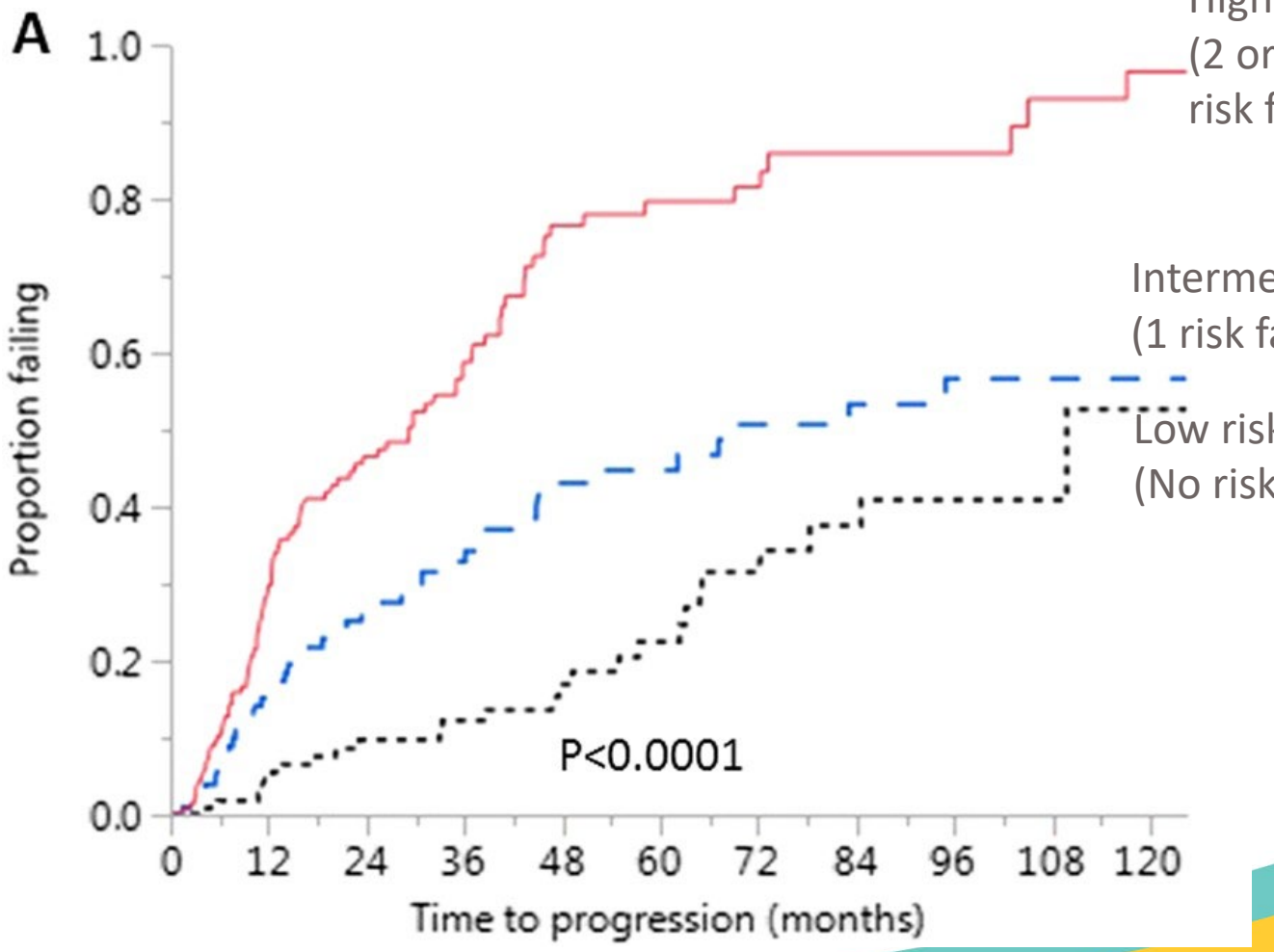
Kyle et al. IMWG Consensus Perspectives. *Leukemia 2010*

IMWG Diagnostic Criteria for Smoldering Myeloma

Smoldering myeloma
Serum M-spike ≥3 g/dL or Urine M-spike ≥500 mg/24h
or Clonal bone marrow plasma cells 10-59%
and Absence of myeloma defining events or amyloidosis

Risk stratification of smoldering myeloma using the Mayo 20/2/20 criteria

- BMPC >20%
- M-spike > 2 g/dL
- SFLC ratio > 20



Lakshman, A., Rajkumar, S.V., Buadi, F.K. *et al. Blood Cancer Journal* **8,** 59 (2018).

Recommended evaluation for a patient with SMM

- **Advanced imaging** for all patients with SMM
  - MRI of the spine and pelvis (preferably whole body)
  - Whole body PET-CT Scan

High risk SMM	Follow-up and re-test every 2-3 months
Intermediate risk SMM	Re-test at 3 months from diagnosis, then every 4 months
Low risk SMM	Re-test at 3 months from diagnosis, then every 6 months for 5 years, and then annually

Repeat bone marrow biopsy and imaging if there are signs of progression

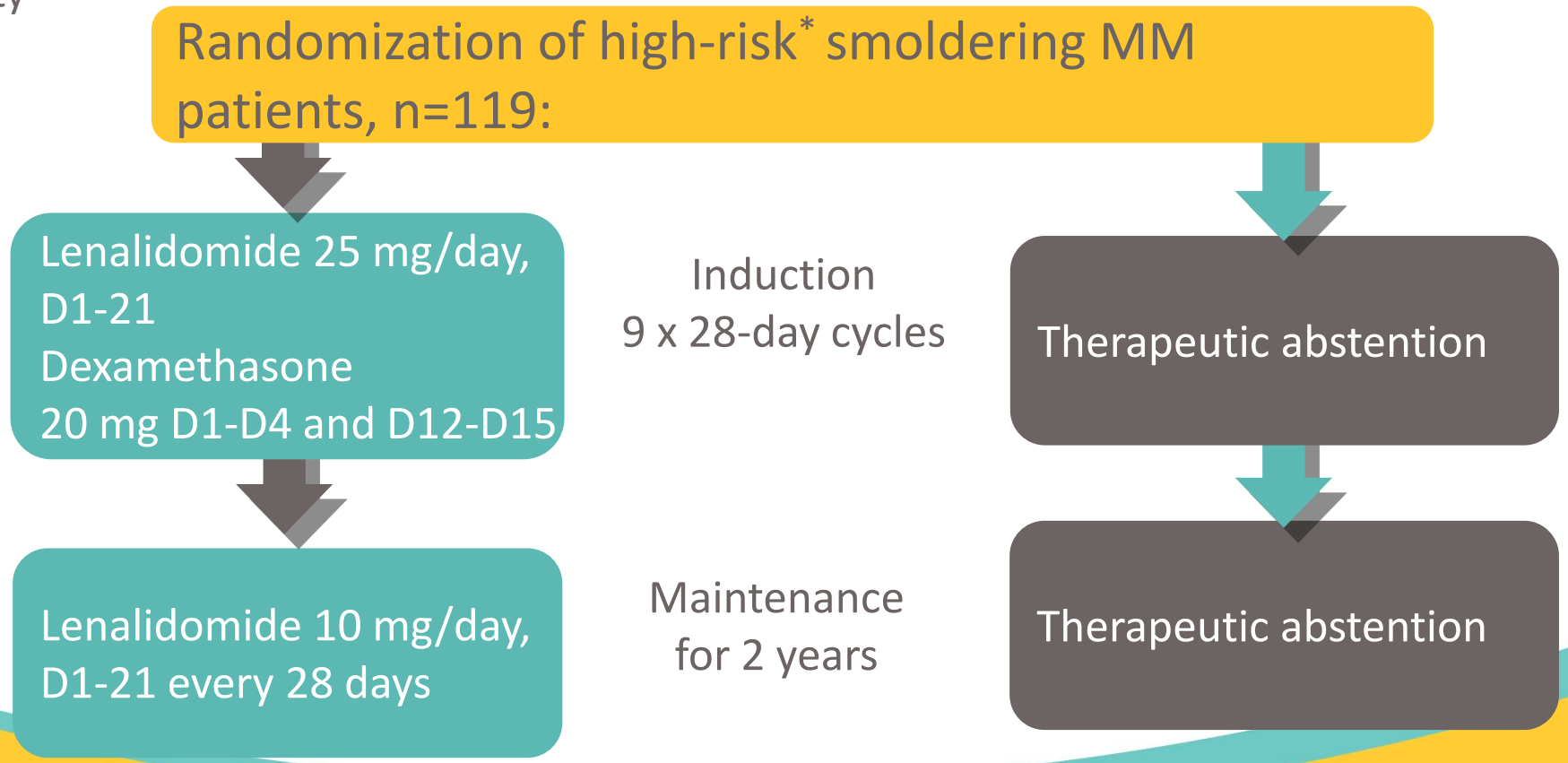
Lakshman, A., Rajkumar, S.V., Buadi, F.K. *et al. Blood Cancer Journal* **8,** 59 (2018).

Should we treat smoldering myeloma?

Phase 3 Queridex trial: Rd-R vs. observation for high risk SMM

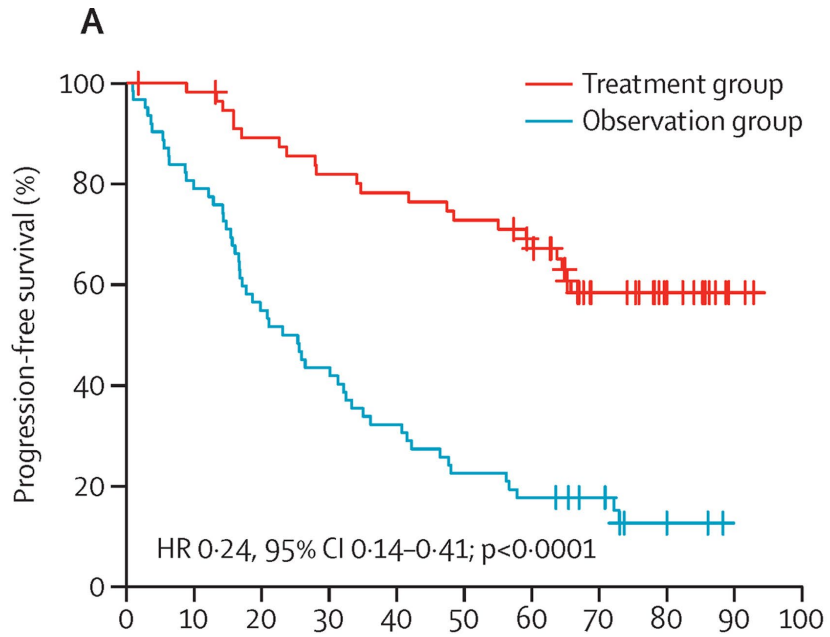
Primary endpoint: time to progression to symptomatic MM

Secondary endpoints: response rates, duration of response, progression-free survival, overall survival, and safety and tolerability



Mateos MV, et al. The Lancet Oncology. 2016. 17(8):1127-1136.

Phase 3 Queridex trial: Improved PFS with Rd-R vs. observation for high risk SMM



Number at risk											
Treatment group	57	55	49	45	43	40	35	20	11	1	..
Observation group	62	49	33	26	19	14	11	7	2	0	..
Number censored											
Treatment group	0	1	6	10	12	15	17	22	22	22	..
Observation group	0	13	28	35	42	48	51	51	53	53	..

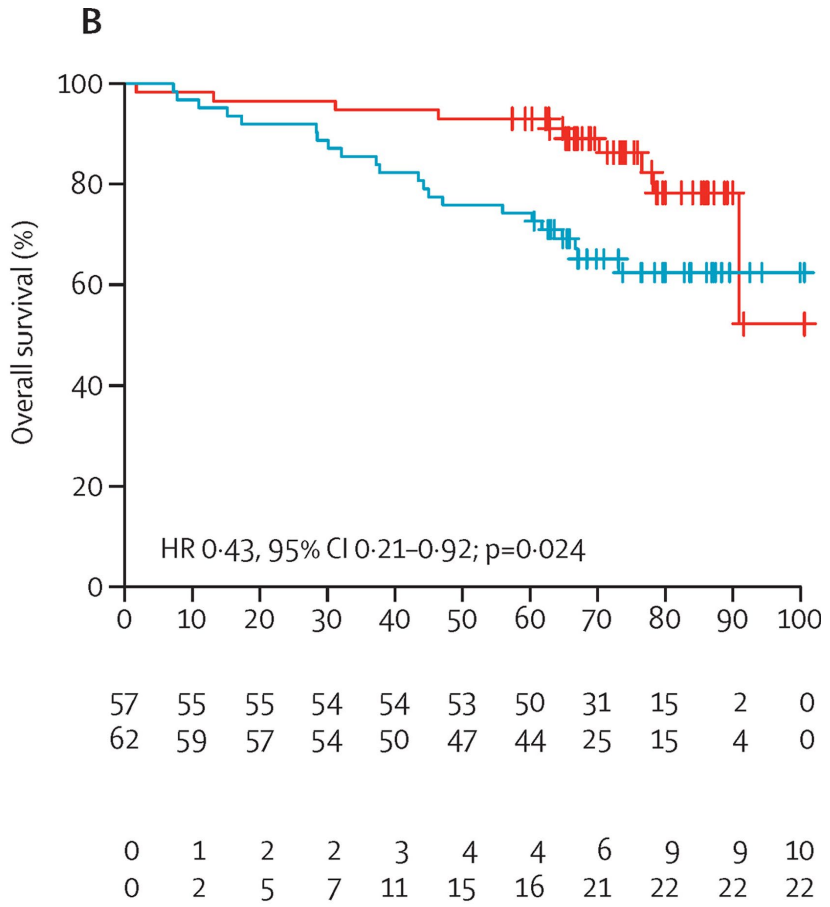
Median follow-up 75 months:

Median time to disease progression:

NR for treatment group
23 months for observation group

Mateos MV, et al. The Lancet Oncology. 2016. 17(8):1127-1136.

Phase 3 Queridex trial: Improved OS with Rd-R vs. observation for high risk SMM



At median follow-up of 75 months:

82% of those on treatment arm were alive
64% of those on placebo arm were alive

Mateos MV, et al. The Lancet Oncology. 2016. 17(8):1127-1136.

Takeaways from the Queridex Trial

- First study to demonstrate benefit in treating smoldering myeloma
  - High-risk SMM population was targeted rather than all SMM patients

- Was not widely adopted due to concerns about trial design
  - Modern imaging (PET/CT or MRI) was not used at randomization
  - Multiparametric flow cytometry criteria used to define high-risk SMM not readily available outside of the centers that conducted the trial

- Given ongoing OS and PFS benefit, current recommendations are to treat high risk SMM with a lenalidomide-based regimen.

E3A06: Lenalidomide vs. observation for SMM

Intermediate or high risk SMM within 5 years, BMPC >10% abnormal FLC ratio, no lytic lesions by skeletal survey, no baseline bone lesions or plasmacytoma by MRI

Lenalidomide 25 mg PO daily, on days 1-21 of 28 days until PD or toxicity

(n=90)

Observation

(n=92)

Lonial, et al. *Journal of Clinical Oncology* 37, no. 15_suppl (May 20, 2019) 8001-8001.

ECOG E3A06

- Overall response rate 50% for treated pts, no responses in the observation arm.
- 3-year PFS rate was 91% in the lenalidomide arm vs. 66% in the observation arm

- Early intervention with lenalidomide in smoldering multiple myeloma significantly delays progression to symptomatic multiple myeloma and the development of end-organ damage
- Current NCCN guidelines recommend treatment of high risk SMM with a lenalidomide-based regimen

Lonial, et al. *Journal of Clinical Oncology* 37, no. 15_suppl (May 20, 2019) 8001-8001.

Many studies ongoing in SMM

Phase 3 DETER-SMM: DaraRd vs Rd

Phase 2 KRd vs Rd

Phase 2 ASCENT: DaraKRd vs Rd

Phase 3 AQUILA: Dara SQ vs observation

Phase 2: Isatuximab

Phase 1b: PVX 410 vaccine

Others

Back to the 71 year old man

SPEP: IgG lambda monoclonal protein of 2.3 g/dL
Serum free light chain ratio of 17.8 (kappa 13.1 mg/dL and lambda 0.73 mg/dL)

Bone marrow biopsy: 20-30% kappa light chain restricted bone marrow plasma cells

Cytogenetics: 46,XY[20]
FISH: negative for +7, +9, +15, 13q-, 17p-, gain of 1q21, t(11;14), t(4;14), t(14;16)
Hgb: 11.6 g/dL (normal: 12.8 – 17.7)
CMP: normal
IgG 3463 (high), IgA 21 (low), IgM 18 (low)
PET/CT: negative

What is his risk for progression to MM?
How do you manage this patient?

Question 1

What is his risk for progression to multiple myeloma?

A. Low risk – no further follow-up is needed
B. Low risk – repeat labs in 3 months and then every 6 months
C. Intermediate risk – repeat labs in 3 months and then every 4 months thereafter
D. High risk – consider treatment with lenalidomide now

Question 1

What is his risk for progression to multiple myeloma?

A. Low risk – no further follow-up is needed
B. Low risk – repeat labs in 3 months and then every 6 months
C. Intermediate risk – repeat labs in 3 months and then every 4 months thereafter
D. High risk – consider treatment with lenalidomide now

A 77 year old woman

Has had gradual exercise intolerance with fatigue and dyspnea over the past 9 months

Cardiology and pulmonary workup unremarkable

Developed frequent UTI's and UA's with persistent proteinuria

Urine spot protein/creatinine: 3.68

Examination is unremarkable other than orthostatic vital signs showing:

Supine: 120/74 mmHg Heart Rate: 66 bpm

Standing: 103/70 mmHg Heart Rate: 85 bpm

Pertinent lab data

CBC unremarkable other than platelet count of 453,000/microL

BMP: unremarkable, sCr 0.75 mg/dL

Urine spot Prot/creatinine ratio: **4.28**

PT 12.8 sec

SPEP/IFE: **M-protein of 0.8 g/dL, IgG lambda**

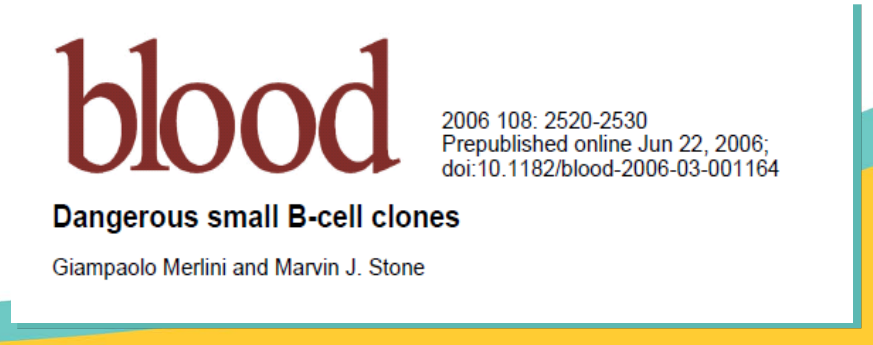
SFLC: kappa 14.7 mg/L, **lambda 314.7 mg/L**, kappa/lambda ratio: 0.05

24h UPEP: urine M-spike 86.5 mg/24h, free lambda bence jones

What is your next step in evaluation?

AL Amyloidosis

- Protein misfolding disorder
- Soluble proteins aggregate as extracellular insoluble amyloid fibrils, causing functional and structural organ damage
- Plasma cell clone generally modest in size
    - median percentage of plasma cells in marrow = 7%
- **Lambda light chains** >> kappa (lambda/kappa 4:1)
- Molecular basis for tissue localization to heart, kidney, liver, or other organs is not understood



“Delayed diagnosis remains a major obstacle to initiating effective therapy prior to the development of end-stage organ failure”

Gertz M. American Journal of Hematology, Volume: 95, Issue: 7, Pages: 848-860

Diagnosis depends on an alert hematologist

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

Diagnosis of AL amyloidosis: Clinical suspicion + Tissue biopsy

All of the following:

- Presence of **amyloid-related systemic syndrome**
  - Kidney, Heart, Liver, Nerve, GI tract, Lung, Soft tissue
- Positive amyloid staining by **Congo Red** or **EM**
- Clear evidence that amyloid is immunoglobulin related by **subtyping** the amyloid deposits
- Evidence of a **monoclonal plasma cell proliferative disorder**
  - Serum or Urine M-protein
  - Abnormal free light chain ratio
  - Clonal plasma cells in the bone marrow

Rajkumar SV, Dimopoulos MA, Palumbo A, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. Lancet Oncol 2014; 15:e538.

YOU GOTTA TYPE THE AMYLOID!

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

*** Amyloid tissue subtyping with mass spectrometry**

Mayo 2012 Staging System: cardiac involvement is prognostic

NT-proBNP ≥1800 pg/mL

Serum TnT ≥0.025 ng/mL

dFLC ≥18 mg/dL

Score	Stage	Median OS (months)
0	I	94.1
1	II	40.3
2	III	14
3	IV	5.8

Kumar S, et al. JCO 2012;30:989-995

Cardiac evaluation in a patient with AL amyloidosis

Strain echocardiography	Cardiac MRI	99m-Tc-Pyrophosphate Scan

Differentiate AL amyloidosis vs other causes of increased LVH
 	
• GLS < -17% was a strong predictor of poor outcome
• Baseline global longitudinal strain (GLS) < -10.2%
  • Associated with poor survival
  • Superior to both BNP and Troponin in predicting survival
• GLS can improve with therapy
	Late gad enhancement in the myocardium
	
	• Diagnostic tool for amyloidosis
	• Prognostic value
	• More sensitive than echocardiogram
	• Does not differentiate between AL or ATTR amyloidosis
		Helps differentiate between ATTR and AL amyloidosis
		
		• Pyrophosphate preferentially binds to the ATTR amyloid fibrils
		• High sensitivity (97%) and High Specificity (100%) for ATTR

Bhutani D, Lentzsch S. Pharmacol Ther. 2020 Oct;214:107612

Treatment of AL amyloidosis

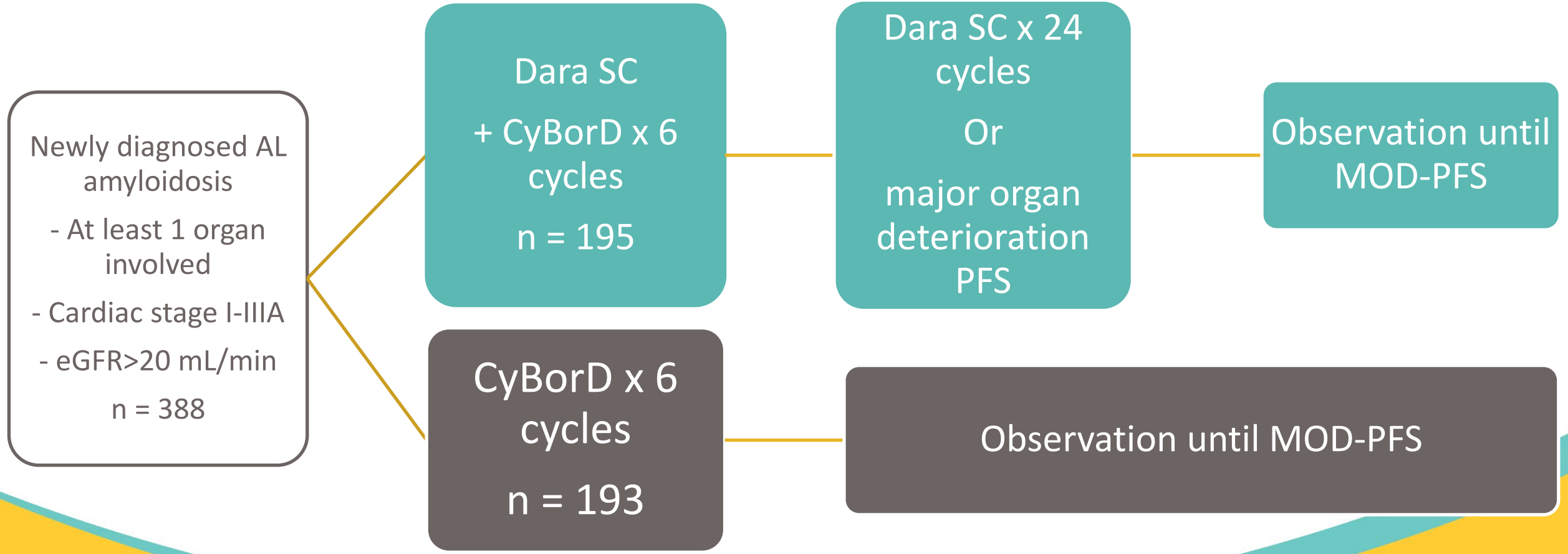
Goals of therapy: prevent deposition of amyloid in other organs and prevent progressive organ failure

Treatment is guided by transplant eligibility:

- “Physiologic” Age <= 70 years
- Performance Score <= 2
- Systolic BP > 90 mmHg (and caution when SBP < 100 mg Hg)
- TnT < 0.06 ng/mL (or hs-TnT < 75 ng/mL)
- CrCl >= 30 mL/min, Serum creatinine <1.7 mg/dL
- NYHA Class I/II

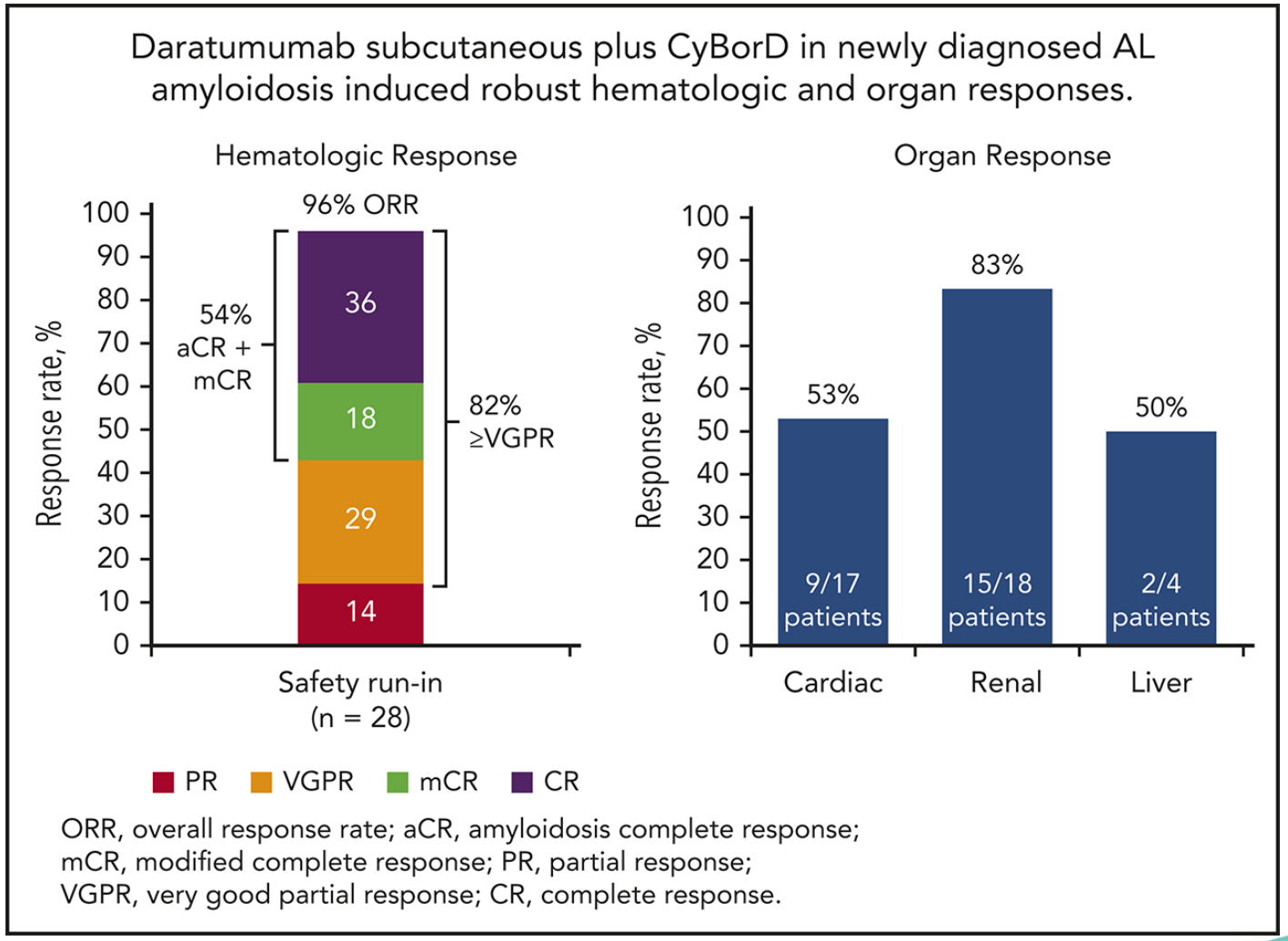
*Only about 20% of patients with amyloidosis are eligible

ANDROMEDA trial



Kastritis E, Palladini G, Minnema MC, et al. Subcutaneous daratumumab + cyclophosphamide, bortezomib, and dexamethasone (CyBorD) in patients with newly diagnosed light chain (AL) amyloidosis: primary results from the phase 3 ANDROMEDA study. Oral abstract #LB2604. 25th European Hematology Association Annual Congress; June 13, 2020; Virtual.

ANDROMEDA: safety run-in results



Palladini G, Kastritis E, Maurer MS, Zonder J, et al. Blood. 2020 Jul 2;136(1):71-80.

ANDROMEDA: deeper and faster responses with Dara

- Median follow-up was 11.4 months
- Median duration of treatment was 9.6 months for Dara-CyBorD, 5.3 months for CyBorD
- CR rate was 53% for Dara-CyBorD vs. 18% for CyBorD
- 6-month cardiac response rate was 42% vs. 22% ($p = 0.0029$)
- 6-month renal response rate was 54% vs. 27% ($p < 0.0001$)
- Among responders, median time to ≥VGPR/CR was 17/60 days vs. 28/85 days

***FDA Approval of daratumumab-hyaluronidase as part of dara-CyBorD regimen for newly diagnosed AL amyloidosis.**

Kastritis E, Palladini G, Minnema MC, et al. Subcutaneous daratumumab + cyclophosphamide, bortezomib, and dexamethasone (CyBorD) in patients with newly diagnosed light chain (AL) amyloidosis: primary results from the phase 3 ANDROMEDA study. Oral abstract #LB2604. 25th European Hematology Association Annual Congress; June 13, 2020; Virtual.

Back to our patient

Completed baseline workup

- Whole body low-dose CT scan shows no bone lesions
- Bone marrow biopsy with congo red staining is positive for amyloid deposition
- TTE with strain assessment shows preserved LVEF but with abnormal strain pattern, GLS -16%
- TnT is normal but NT-ProBNP is 435 pg/mL

She began therapy with CyBorD+dara, not a candidate for transplant

What is Monoclonal Gammopathy of Renal Significance?

International Kidney & Monoclonal Gammopathy Research Group

Any B cell or plasma cell clonal lymphoproliferation with:

- One or more kidney lesions that are related to the produced monoclonal immunoglobulin
- The underlying B cell or plasma cell clone does not cause tumor complications or meet any current hematologic criteria for specific therapy (i.e. MM, WM, CLL, MZL, etc.)

Leung N, Bridoux F, Batuman V. et al. Nature Reviews Nephrology. 2019;15:45-59

Workup of a patient with suspected MGRS

International Kidney & Monoclonal Gammopathy Research Group

- **Requires a kidney biopsy**
  - For patients with monoclonal gammopathy and unexplained kidney disease
  - For patients with known risk factors for CKD but atypical clinical course
  - For patients with kidney disease and monoclonal gammopathy aged <50 years
- SPEP/IFE, UPEP/IFE (can be negative 13-40% of the time)
- Serum free light chains (always positive)
- Metabolic testing: Bicarb, Chloride, Phosphate, Uric Acid, Glucose levels
- Bone marrow aspiration and biopsy, with cytogenetic analysis
- Bone imaging (to evaluate for MM)

Leung N, Bridoux F, Batuman V. et al. Nature Reviews Nephrology. 2019;15:45-59

Summary

- MM is consistently preceded by precursor disease state
- Risk stratification in smoldering myeloma identifies patients at high risk for progression and provides opportunities for early intervention
- Liberal use of sensitive imaging techniques
- Diagnosis of MM can be made before end-organ damage occurs, per new IMWG guidelines
- High-risk SMM patients looks promising and these patients should be considered for clinical trials
  - Outside trials, observation is still the standard
- Consider diagnoses other than myeloma in patients with M-proteins