Smoldering multiple myeloma

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Disclosures and Conflicts of Interest

- No disclosures
- No conflicts of interest

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Learning Objectives

- Provide overview of smoldering multiple myeloma
- Discuss biology and risk stratification
- Discuss treatment options and monitoring

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Case 1

- A 62 y/o black male with HTn, type 2 DM, h/o localized prostate cancer treated with radiation in 2017 noted to have worsening anemia (Hgb 12g/dl, baseline ~14), and increasing serum creatinine (1.6mg/dl, previously 1-1.2)
- Anemia work up negative except for mildly reduced serum iron saturation of 15%
- SPEP showed a monoclonal protein of 1.9g/dl; immunofixation showed IgA kappa
- Serum free kappa was 48, serum free lambda 1, ratio 48
- Serum calcium was normal
- Patient had increasing low back pain, with no recent trauma; back pain had started >10 years back

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Case 1

- A bone marrow biopsy was done after nearly 6 months after his initial SPEP, delayed due to COVID 19
- He had a hypocellular (~25%) marrow with 20-25% kappa restricted clonal plasma cells
- Cytogenetics showed normal male karyotype; plasma cell FISH showed 1q duplication
- Skeletal survey was normal
- A skull-mid thigh PET CT was negative for lytic or hypermetabolic lesions
- A diagnosis of smoldering multiple myeloma made

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Case 1

- He had MRI spine 8 weeks later
- It showed 2 small enchancing lesions:

-A 1cm lesion in the pedicle of T3

-A 8mm enhancing lesion at T12

- Diagnosis – now changed to multiple myeloma
- Patient refused treatment as he ‘feels well’
- Still being monitored

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Case 2

- 52 y/o white female, with hypertension, CKD, hyperlipidemia, chronic body aches, had work up for worsening CKD (Cr had increased from 1.3..>1.6 in ~ 6 months)
- Hemoglobin had decreased from 13..>12.5..>11 g/dl over a period of 18 months, had mild microcytosis
- SPEP showed M spike 1.9g/dl, IgG lambda on immunofixation; serum free light chains elevated, ratio lambda: kappa 33

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Case 2

- Skeletal survey negative
- PET CT not approved by insurance
- Non-contrast CT thoracic spine showed ‘mottled appearance’ of L1 vertebral body; no lesions on cervical spine
- 2 months later Cr had increased to 1.9, Hgb was 10.7
- BM biopsy showed a normocellular marrow with 35% lambda restricted plasma cells
- She had 17p deletion on FISH

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Case 2

- She was started on chemotherapy with lenalidomide, bortezomib, dexamethasone (RVd), completed 5 cycles
- Developed severe neuropathy
- Repeat BM biopsy,after 5 cycles showed 4% plasma cells
- Chemotherapy now on hold

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Myeloma: Statistics

-14th most common malignancy

-2nd most common hematologic malignancy

- more common in men and in African-Americans and in patients with MGUS

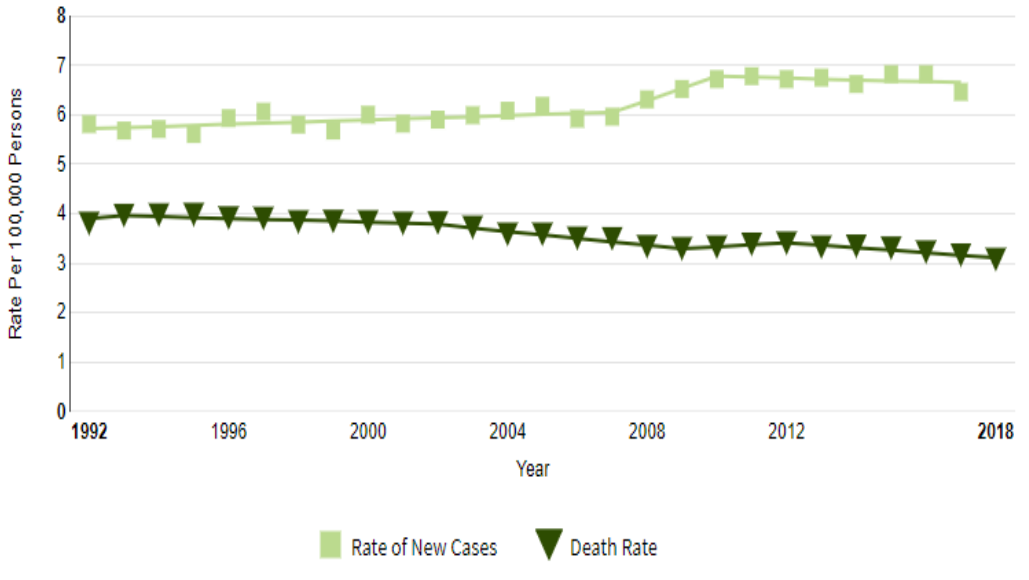
Source: SEER

At a Glance

Estimated New Cases in 2020	32,270
% of All New Cancer Cases	1.8%

Estimated Deaths in 2020	12,830
% of All Cancer Deaths	2.1%

5-Year Relative Survival
53.9%
2010–2016



New cases come from SEER 13. Deaths come from U.S. Mortality.
All Races, Both Sexes. Rates are Age-Adjusted.

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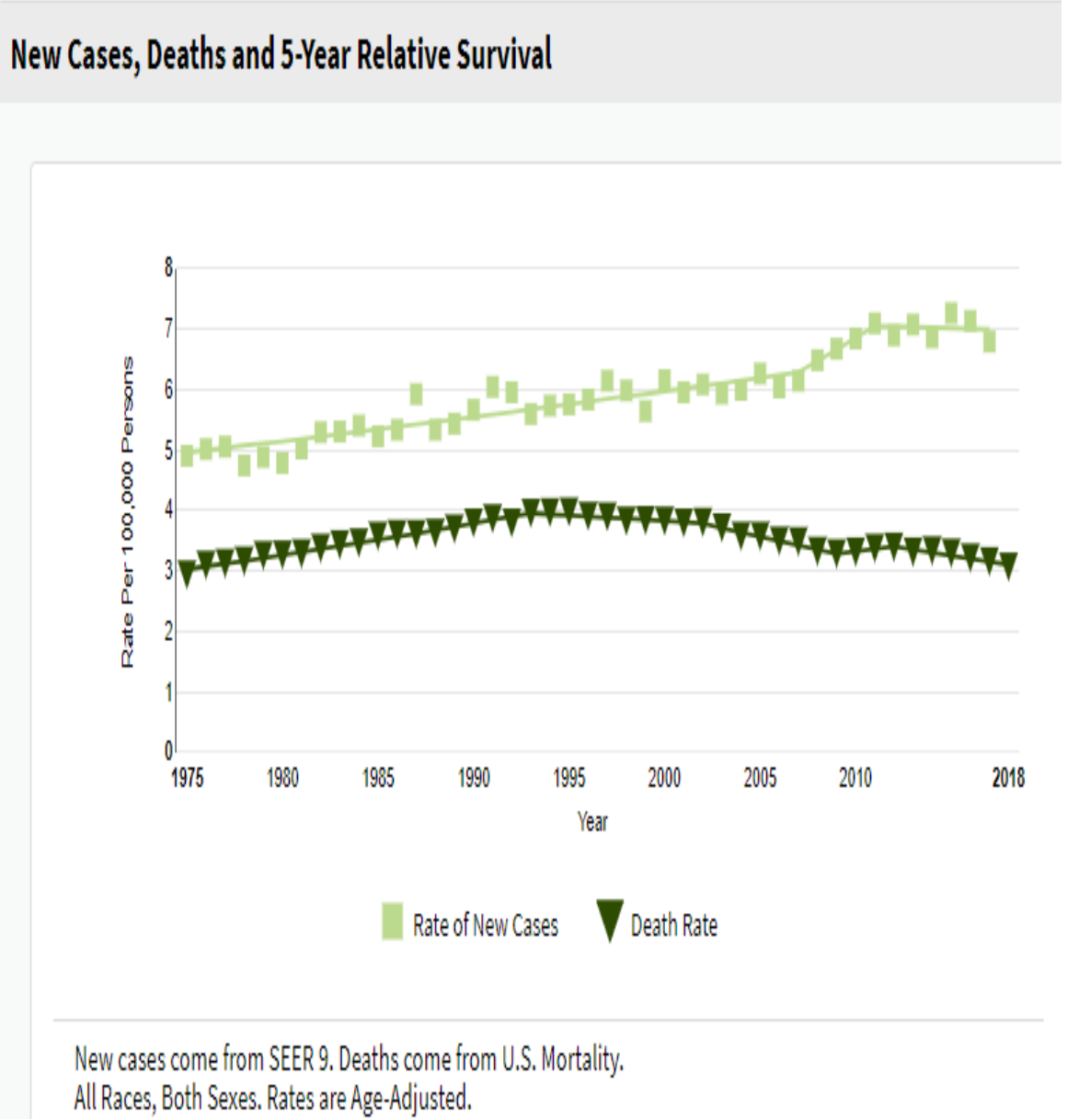
Age-adjusted rates for new myeloma cases have remained stable 2008 – 2017.

Age-adjusted death rates have not changed significantly over 2009 – 2018.

Source: SEER



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What defines active multiple myeloma in 2022 ?

Revised IMWG 2014 diagnostic criteria:

- In addition to the classic CRAB features, three myeloma defining events (MDEs) are used.
- The presence of **at least one of these markers** is considered sufficient for a diagnosis of multiple myeloma, **regardless** of the presence or absence of symptoms **or** CRAB features.
- Each of these markers has been shown in two or more independent studies to be associated with an approximately 80% or higher risk of developing myeloma-related organ damage within two years.

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

2014 IMWG criteria for multiple myeloma

- Clonal bone marrow plasma cells >10%

OR

- biopsy-proven bony or extramedullary plasmacytoma

AND

- any **one or more** of the following CRAB features and myeloma-defining events:

- Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically:

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CRAB criteria

- **H**ypercalcemia: serum calcium >0.25 mmol/L (>1mg/dL) higher than the upper limit of normal or >2.75 mmol/L (>11mg/dL)
- **R**enal insufficiency: creatinine clearance < 40 mL per minute or serum creatinine >177mol/L (>2mg/dL)
- **A**nemia: hemoglobin of >2 g/dL below the lowest limit of normal, or a hemoglobin value <10 g/dL
- **B**one lesions: one or more osteolytic lesion on skeletal radiography, CT, or PET/CT.
- If bone marrow has <10% clonal plasma cells, more than one bone lesion is required to distinguish from solitary plasmacytoma with minimal marrow involvement

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Myeloma defining events

Presence of any **ONE** of these:

- 60% or greater **clonal** plasma cells on bone marrow examination (typically on core biopsy)
- Serum involved / uninvolved free light chain ratio of 100 or more, provided the absolute level of the **involved light chain** is at least 100 mg/L
- Two or more focal lesions on MRI (of bone or bone marrow) that is at least 5mm or greater in size.

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Defining smoldering multiple myeloma (SMM)

- Serum monoclonal protein (IgG or IgA) ≥ 30g/L (3g/dl)

OR

- urinary monoclonal protein ≥ 500mg per 24h

AND/OR

- clonal bone marrow plasma cells 10-60%
- Absence of myeloma-defining events or amyloidosis

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Smoldering multiple myeloma

- Definition of SMM pretty straight forward
- However, in practice, diagnosing SMM marked by numerous confounders!

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What is the diagnosis?

	Serum Cr	Cr cl (estimated)	Hgb	Serum calcium	Co-morbidities
Pt # 1 30% plasma cells in BM	1.8mg/dl	35	11 g/dl	normal	DM, HTn, PCKD
Pt # 2 45% plasma cells in BM	1.2mg/dl	55	10.8 g/dl	11.5 mg/dl, elevated	Parathyroid adenoma, hemorrhoids
Pt # 3 8- 10% plasma cells in marrow, solitary plasma cytoma of bone	1.4mg/dl	42	10.5 g/dl	normal	none

SMM prevalence

- Prevalence of SMM is not well-defined due to the difficulty in acquiring epidemiological data stemming from lack of population-based disease registries, paucity of epidemiologic studies resulting from the lack of International Classification of Diseases (ICD) codes differentiating SMM from active MM.
- ~8–20% of patients carrying a diagnosis of MM actually have SMM.
- Based on these studies, the incidence of SMM can be estimated at 0.4–0.9 cases per 100,000 persons [

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Imaging in smoldering myeloma

VERY IMPORTANT

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How useful is whole body imaging in making diagnosis?

- What is the prognostic significance of the presence /absence, as well as the number, of focal lesions(FLs) for progression to symptomatic MM ?
- WB-MRI was performed in 149 patients with asymptomatic MM
- FLs were present in 28% of patients

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Hillengass J, Fechtner K et al. J Clin Oncol 28:1606-1610, 2010

How useful is whole body imaging in making diagnosis?

- 23 patients (15.4%) had > one focal lesion, and would currently be classified as having active myeloma
- Nine patients (6%) had **extra-axial lesions only**, which would have been missed by axial MRI alone.
- In this study, the presence per se of FLs and a > one FL were the strongest adverse prognostic factors for progression into sMM ($p < .001$) in multivariate analysis.

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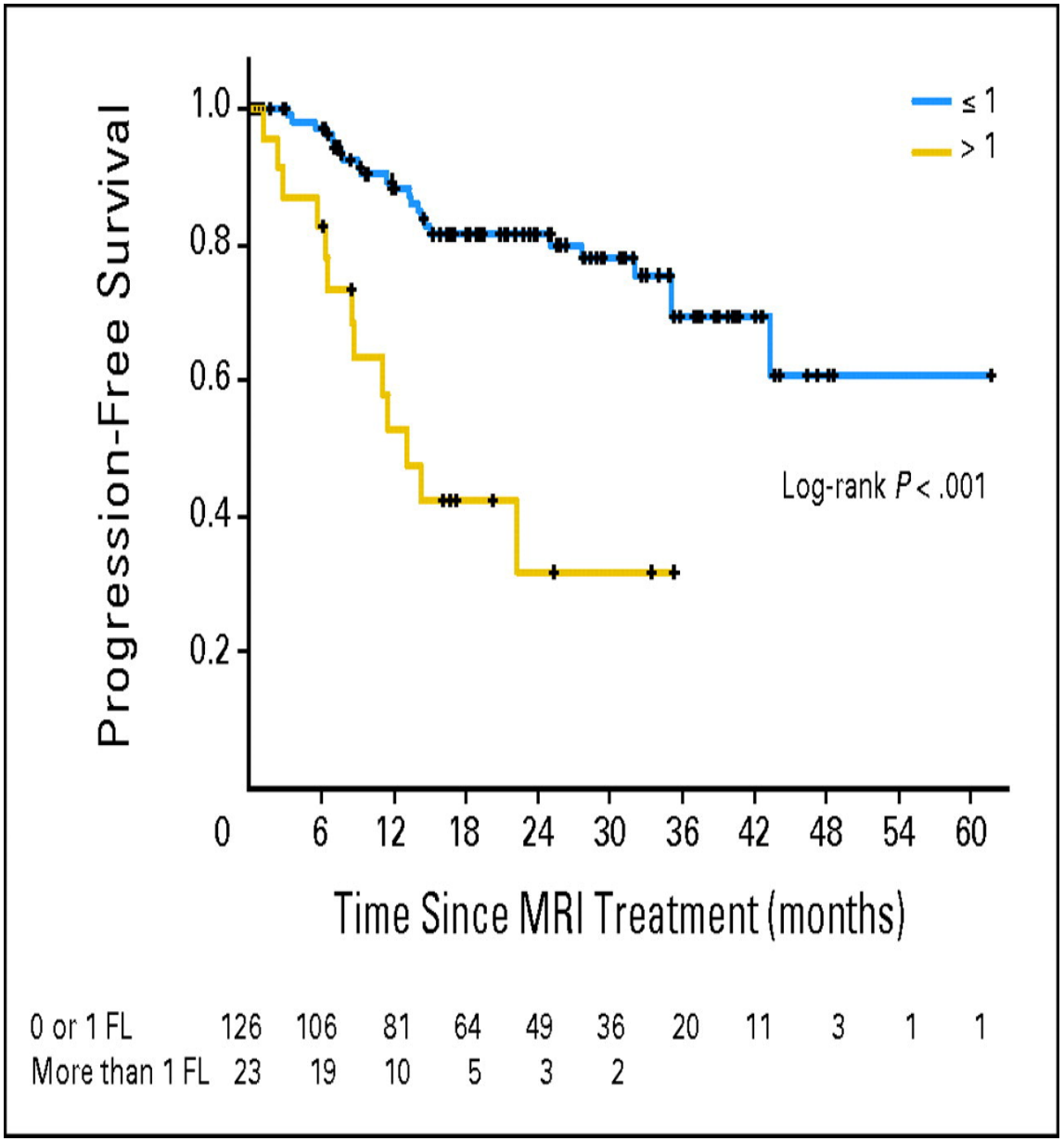
Kaplan-Meier plots for progression into symptomatic myeloma of patients who had no or one focal lesion (FL) compared with patients who had greater than one FL. The median time to progression was not reached (last event at 43 months) for the patient group with no or one FL and 13 months for the patient group with greater than one FL, respectively. MRI, magnetic resonance imaging.

Hillengass J, Fechtner K et al. J Clin Oncol 28:1606-1610, 2010



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Diagnostic imaging : pitfalls

- Just hypermetabolic PET avid bone lesions INSUFFICIENT to make diagnosis; need to have **one or more lytic lesion**
- Often PET is delayed or denied by insurance
- WB MRI or WB low dose CT are equally appropriate
- Especially important in hospitalized patients needing urgent staging and treatment

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Smoldering myeloma risk of progression

- ~30% of patients with SMM progress in the first 2 years, 20% in the next 3 years, and a further 20% in the following 5 years vs. a fixed risk of ~1% per year in MGUS
- ~30% of patients with SMM do not progress after 10 years,
- The progression risk decreases to about 1% per year, similar to MGUS, for these patients

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Kyle RA, Remstein ED, Therneau TM, Dispenzieri A, Kurtin PJ, Hodnefield JM, et al. Clinical course and prognosis of smoldering (asymptomatic) multiple myeloma. N Engl J Med. 2007;356:2582–90.

Primary cytogenetic abnormalities in plasma cell neoplasm

Abnormality	Gene(s)/chromosomes affected	Frequency (%)		Implications in SMM	
		In MGUS	In MM	Progression risk	Median TTP
Hyperdiploidy: Trisomy(ies) without IgH abnormality	Trisomy of odd-numbered chromosomes (but not chromosomes 1, 13, 21)	50	55	Intermediate	3 years
IgH-translocations					
• t(11;14)	*CCND1*	12	19	Standard	5 years
• t(4;14)	*FGFR-3* and *MMSET*	9	13	High	2 years
• t(14;16)	*C-MAF*	3	4	Standard	5 years
• t(14;20)	*MAFB*	3	1	Standard	5 years
• t(6;14)	*CCND3*	0	1	Standard	5 years
IgH translocations with trisomy(ies)			15	Standard	5 years
Isolated monosomy 14			4.5	Standard	5 years
Other cytogenetic abnormalities in absence of (1) IgH translocations, (2) trisomy(ies), or (3) monosomy 14			5.5		
Normal	NA		3	Low	7–10 years

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Primary cytogenetic abnormalities in plasma cell neoplasm. Ho et al. *Leukemia* ,volume 34, pages 3111–3125 (2020)

Genetic landscape of plasma cell neoplasms

- Trisomies and/or 14q32 IgH chromosomal translocations are the main myeloma initiating events

- Identified in nearly 100% of precursor MM cells that underlie the transformation of normal plasma cells to MGUS
- CNAs and/or IGH translocations represent secondary cytogenetic abnormalities that contribute to progression from MGUS/SMM to MM

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Abnormality	Gene(s) affected	Frequency (%)	
		In MGUS	In MM
Gains			
• 1q	*CKS1B* and *ANP32E*	25	50
• 12p	*LTBR*		
• 17q	*NIK*		
Deletions			
• 1p	*CDKN2C, FAF1, and FAM46C*	6	40
• 6q			33
• 8p			25
• 11q	*BIRC2* and *BIRC3*	7	7
• 13	*RB1* and *DIS3*	30	70
• 14q	*TRAF3*		38
• 16q	*CYLD* and *WWOX*		35
• 17p	*TP53*	1	12
Translocations			
• t(8;14)	*MYC*	3–4	20
• t(4;14)	*FGFR-3* and *MMSET*		
• t(14;16)	*C-MAF*		
• t(14;20)	*MAFB*		
• Other non-IGH translocations			
Oncogenic pathways			
• MAPK activation	*NRAS*	36	33
	KRAS	<1	33
	BRAF	27	19
• MYC dysregulation	*MYC*	<1	67
• Constitutive NFKB activation	*TRAF6, CYLD*	<1	20

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Secondary cytogenetic abnormalities occuring later in plasma cell neoplasm.
Ho et al. *Leukemia*_volume 34, pages 3111–3125 (2020)

SMM risk stratification

Updated Spanish study (with cytogenetics) ($n = 952$)[1]			2018 updated Mayo Clinic Criteria ($n = 417$)[2]			
Risk factors	**No of risk factors (risk group)**	**Risk of progression at 2 years**	**Risk factors**	**No of risk factors (risk group)**	**Risk of progression**	
					at 2 years	**at 5 years**
1. Serum M-protein >2 g/dL 2. Serum FLC >20 3. BMPCs >20% 4. High-risk cytogenetics [t(4;14), t(14;16), 1q gain, or del 13q]	**0 (low)**	7$	**1. Serum FLC >20 2. BMPCs >20% 3. High-risk cytogenetics [del17p, t(4;14), or hyperdiploidy]**	**0 (low)**	5$	05$
	1 (low-intermediate)	10$		**1 (intermediate)**	21$	48$
	2 (intermediate)	26$		**2 (high)**	58$	0/ / $
	≥3 (high)	48$				

1. Miguel JS, Mateos M-V, Gonzalez V, Dimopoulos MA, Kastritis E, Hajek R, et al. Updated risk stratification model for smoldering multiple myeloma (SMM) incorporating the revised IMWG diagnostic criteria. J Clin Oncol. 2019;37:8000.
2. Lakshman A, Rajkumar SV, Buadi FK, Binder M, Gertz MA, Lacy MQ, et al. Risk stratification of smoldering multiple myeloma incorporating revised IMWG diagnostic criteria. Blood Cancer J. 2018;8:59.

SMM risk stratification: Mayo model

- Based on the updated 2018 Mayo Clinic Criteria, low-risk SMM is associated with 0 risk factors and has a 6 and 16% risk of progression at 2 and 5 years;
- Intermediate-risk SMM is associated with 1 risk factor and has a 32 and 59% risk of progression at 2 and 5 years
- High-risk SMM is associated with ≥2 risk factors and has a 69 and 100% risk of progression at 2 and 5 years

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Lakshman A, Rajkumar SV, Buadi FK, Binder M, Gertz MA, Lacy MQ, et al. Risk stratification of smoldering multiple myeloma incorporating revised IMWG diagnostic criteria. Blood Cancer J. 2018;8:59.

SMM risk stratification: Spanish model

- In the updated Spanish model, patients with low-risk SMM (0 risk factors) had a 5% risk of progression at 2 years
- Those with intermediate-risk SMM (1 risk factor) had a 17% risk of progression at 2 years;
- Patients with high-risk SMM (≥2 risk factors) had a 46% risk of progression at 2 years

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Miguel JS, Mateos M-V, Gonzalez V, Dimopoulos MA, Kastritis E, Hajek R, et al. Updated risk stratification model for smoldering multiple myeloma (SMM) incorporating the revised IMWG diagnostic criteria. J Clin Oncol. 2019;37:8000.

Current management of SMM

- Still wait and watch
- No role for routine chemotherapy

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Initial versus deferred melphalan-prednisone therapy for asymptomatic multiple myeloma stage I--a randomized study. Myeloma Group of Western Sweden

- 50 patients with asymptomatic multiple myeloma stage I were included in a prospective randomized multi-center study comparing melphalan-prednisone (MP) therapy started at the time of diagnosis with deferred therapy where MP was started at the time of disease progression.
- 25 patients were randomized to each group.
- The median time from diagnosis to start of therapy in the group with deferred therapy was 12 months.
- The reasons for starting therapy were increasing M-protein in 8 cases, symptomatic bone disease in 9 and anemia in 5. In 2 cases, disease progression was complicated by vertebral fractures necessitating radiotherapy.
- Two patients in the group in which MP was started at the time of diagnosis developed acute leukemia.
- No differences in response rate, response duration or survival were observed between the treatment group.

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Eur J Hemtaol. 1993 Feb;50(2):95-102.

Melphalan-prednisone in asymptomatic MM

- Between January 1987 and March 1993, 145 consecutive previously untreated patients with stage I MM were randomized between treatment with M-P (administered for 4 days every 6 weeks) just after diagnosis and treatment only at disease progression.
- Survival was not influenced by M-P treatment either administered just after diagnosis or at disease progression (64 vs 71 months respectively).
- Disease progression occurred within a year in about 50% of patients who were initially untreated.
- Response rate was similar in both groups, but duration of response was shorter in patients who were treated at disease progression (48 vs 79 months, P = 0.044).
- No benefit in treating asymptomatic pts

Br J Cancer 2000 Apr;82(7):1254-60.

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Lenalidomide in high risk SMM

- patients with asymptomatic high-risk SMM were treated with dexamethasone and lenalidomide or received no treatment until disease progression
- High-risk SMM was defined by having (1) ≥10% BM plasma cell and (2) a monoclonal component (serum IgG ≥3 g/dL, serum IgA ≥2 g/dL, or urinary Bence Jones protein >1 g per 24 h) or only one of the two criteria plus ≥95% phenotypically abnormal BM plasma cells with reductions of one or more uninvolved immunoglobulins of ≥25%.
- High-risk SMM patients were treated with induction therapy of Rd (9 cycles), followed by maintenance therapy with lenalidomide for 2 years or until disease progression.
- Median TTP was not reached in the treatment group and was 21 months in the control group that did not receive any therapy.
- Symptomatic disease developed in 76% (47/62) of patients in the observation group, compared to only 23% (13/57) in the treatment group.

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Mateos MV HM, Salvador C, de la Rubia J, de Arriba F, López-Corral L, et al. Over Ten Years Of F/U For Phase 3 Trial In Smoldering Myeloma At High Risk Of Progression To Myeloma: Sustained Ttp And Os Benefit With Rd Versus No Treatment. 25th EHA Congress. Virtual: European Hematology Association; 2020

Lenalidomide in high risk SMM

- During the induction phase of treatment, 79% (45/57) achieved a PR or better, including 7% with a stringent CR (sCR), 7% with a CR, and 11% with a very good PR (VGPR).
- Patients on maintenance therapy had a mean follow-up time of 26 months (range 4–40).
- 24 patients developed biologic progression of disease during this time, and low-dose dexamethasone was added to the maintenance therapy of 18 of these patients.
- Of the patients on maintenance therapy, 3 had a PR, 11 patients had SD, and symptomatic myeloma developed in 4 patients.
- The ORR in the treatment group was 90%.
- In the treatment group, 3-year and 5-year survival was 98% and 94%, respectively, compared to 80 and 78% in the control group.
- Toxicity was moderate.
- Grade 1 and 2 infections were the most common non-hematological adverse effect, and 5-year cumulative risk of a second primary tumor was not significantly different between the treatment and control groups.

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Lenalidomide in high risk SMM

- The 10-year follow-up data showed that Rd use in SMM had a sustained survival benefit in prolonging OS (median OS not reached in treatment arm vs. 7.8 years in the control arm) as well as delaying progression to symptomatic MM.
- At median follow-up of 10.8 years, progression to MM occurred in 49% of patients in the treatment arm vs. 90% of patients in the control arm
- Median TTP was 9.0 vs. 2.1 years in the treatment vs. control arm
- In patients who progressed to active MM, the early use of dexamethasone and lenalidomide in SMM was not associated with resistance to standard of care therapy at the time of progression.
- Patients who received dexamethasone and lenalidomide prior to progression had better, albeit statistically insignificant, median OS compared to patients who did not (6.4 vs. 4.7 years in the treatment vs. control arm)

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Len dex in high risk SMM:promising, but..

- Median age in the control group (69) was > treatment group (63 y).
- Patients who developed biologic progression of disease during the maintenance were treated off-protocol with len-dex, complicating analysis
- The study did not use contemporary imaging techniques to define MM versus SMM

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Randomized Trial of Lenalidomide Versus Observation in Smoldering Multiple Myeloma

- An open-label, phase III clinical trial (E3A06) was conducted to assess the efficacy of single-agent oral lenalidomide (len) for SMM
- Intermediate or high risk SMM patients included
- 50% of patients receiving len therapy had a PR or better (44/88; 40 PR, 4 VGPR) and median time to response was 5 months.
- There were no responses seen in the control group (no treatment).
- PFS was significantly higher in the len group (HR 0.28, $p = 0.002$).
- 1-, 2-, and 3-year PFS in the treatment group was 98%, 93%, and 91%, vs. 89%, 76%, and 66% in the control group, respectively.
- Cumulative incidence of progression after 3 years in the len group was 7.6% compared to 31.6% in the control group.
- There were also fewer deaths in the len group (2 patients) compared to the control group (4 patients), but this was not statistically significant (HR for death 0.46, 95% CI 0.08–2.53).

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Lonial et al.J Clin Oncol. 2020 Apr 10;38(11):1126-1137

Randomized Trial of Lenalidomide Versus Observation in Smoldering Multiple Myeloma

- Subgroup analysis was conducted based on risk group (high, intermediate, and low) as determined by the 2008 and 2018 Mayo Clinic criteria
- In all subgroups, PFS in the len group was favorable to the control group,
- The difference was most pronounced in high-risk SMM patients as determined by the 2018 Mayo Clinic Criteria.
- This trial included a phase II run-in period to assess the safety of oral len therapy.

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Randomized Trial of Lenalidomide Versus Observation in Smoldering Multiple Myeloma

- During the phase II run-in, 45% (20/44) of patients experienced a grade 3 or 4 adverse event.
- One death due to pulmonary embolism was reported in this study which was considered to be related to len therapy.
- During the phase III trial, similar rates of adverse events were seen in the len group.
- The study shows len treatment in patients with SMM significantly delays progression to symptomatic MM compared to the current “watch-and-wait” strategy.

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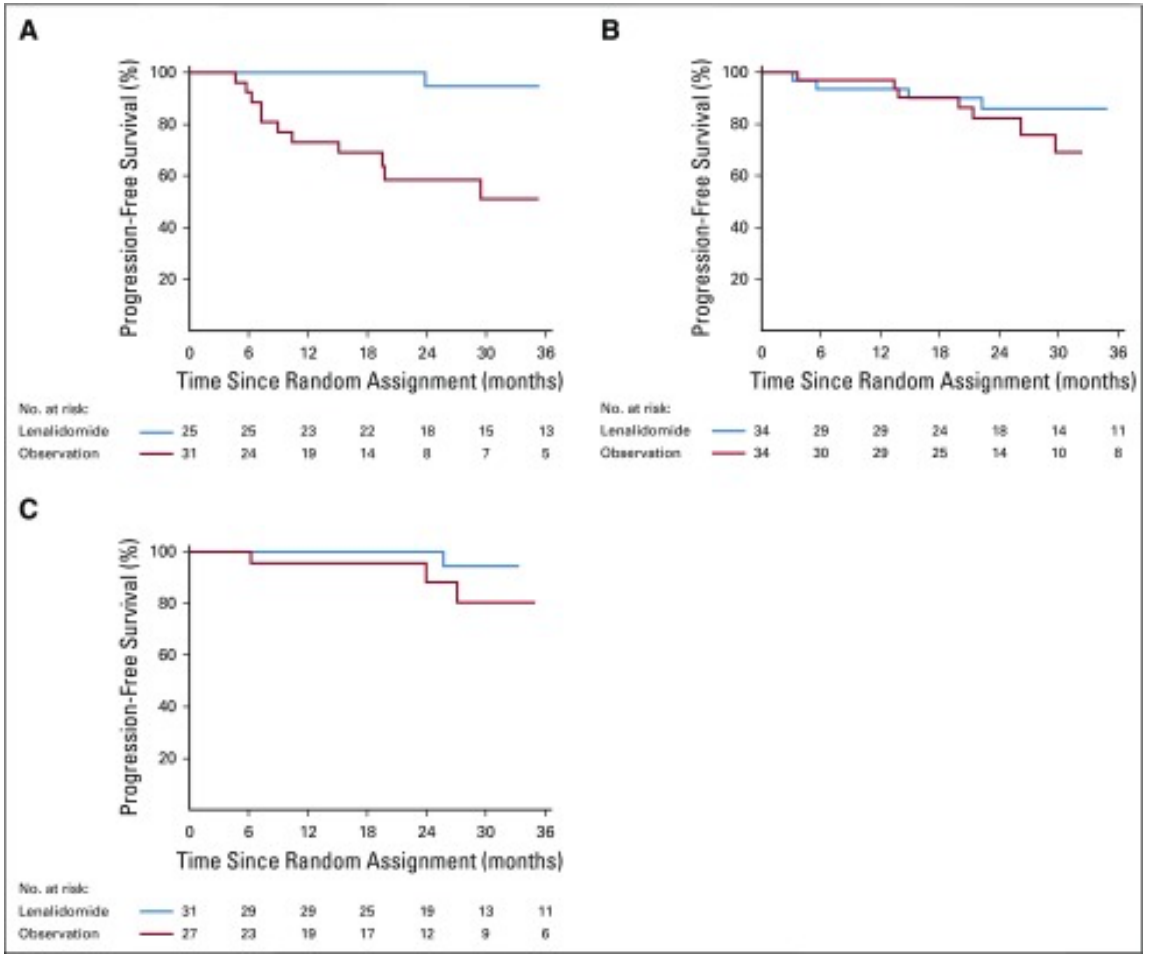
Kaplan-Meier estimates of progression-free survival by treatment arm within Mayo 2018 risk subgroup: (A) high risk, (B) intermediate risk, and (C) low risk.



Lonial et al.J Clin Oncol. 2020 Apr 10;38(11):1126-1137

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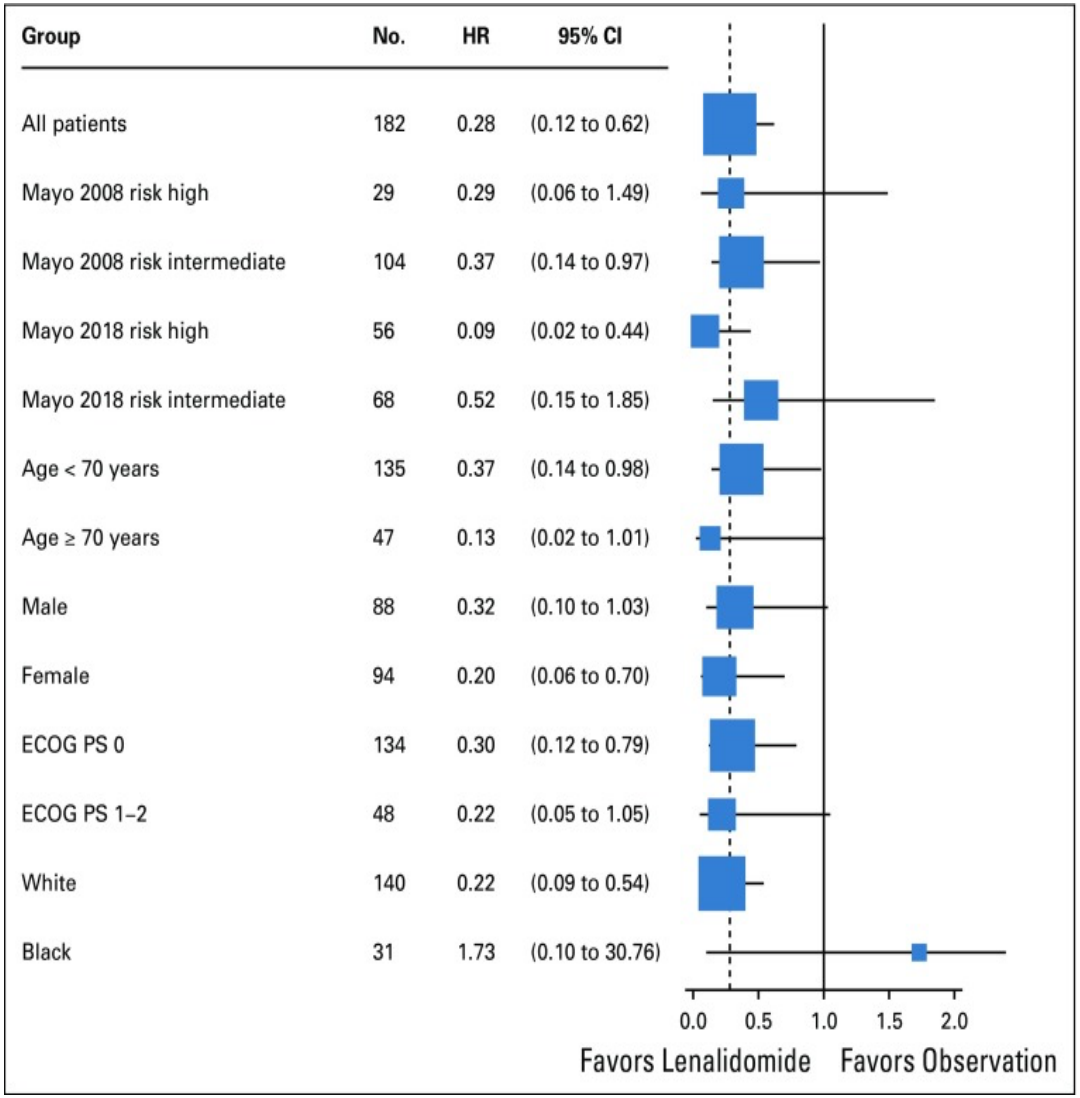
Treatment hazard ratio (HR) for progression-free survival in subgroups in phase III.

ECOG PS, Eastern Cooperative Oncology Group performance status.



Lonial et al.J Clin Oncol. 020 Apr 10;38(11):1126-1137

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PI based trial in SMM

- Patients with NDMM or high-risk SMM were enrolled
- After 2 cycles of KRd, all 12 patients with high-risk SMM achieved at least a PR, with 6/12 (50%) patients achieving a VGPR.
- 11 of the 12 patients completed 8 cycles of KRd, after which all 11 patients achieved at least a VGPR with 6/11 (55%) stringent CRs, 2/11 (18%) CRs, and 3/11 (27%) near CRs.
- The median time to CR or stringent CR was 6 cycles (range 6–20).
- Of the patients who achieved a best overall response of near CR, 11/12 (92%) of patients were minimal residual disease (MRD) negative as determined by multiparametric flow cytometry.

Korde et al. JAMA Oncol.2015 Sep;1(6):746-54

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High intensity treatment approach for SMM

- Focus of early treatment of SMM has been to delay progression to MM, avoid MM-related complications, and minimize treatment-related side effects.
- GEM-CESAR study enrolled 90 high-risk SMM patients (defined as BMPCs ≥10% and serum M-protein ≥3d/dL, or 95% of aberrant PCs within the total PCs BM compartment)
- Treatment was with 6 induction cycles of KRd (*n* = 90; ≥CR: 42%); followed by intensification with melphalan and ASCT (HDT-ASCT) (*n* = 83; ≥CR: 64%), consolidation with 2 cycles of KRd (*n* = 83; ≥CR: 72%), and maintenance with lenalidomide and dexamethasone for up to 2 years.
- MRD negativity was observed in 31%, 56%, and 63% of patients after induction, HDT-ASCT, and consolidation, respectively .
- After 1 year of maintenance therapy (*n* = 40), 85% of patients were ≥CR, 10% VGPR, 5% PR, and the MRD-negative rate was 68%

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Mateos M-V, Martinez-Lopez J, Rodriguez Otero P, Gonzalez-Calle V, Gonzalez MS, Oriol A, et al. Curative Strategy (GEM-CESAR) for High-Risk Smoldering Myeloma (SMM): Carfilzomib, Lenalidomide and Dexamethasone (KRd) As Induction Followed By HDT-ASCT, Consolidation with Krd and Maintenance with Rd. Blood 2019;134(Supplement_1):781

High intensity treatment approach for SMM

- The OS rate was 98% (at 28 months follow-up) and the PFS rate was 93% (at 30 months follow-up)
- PFS rate at 30 months in the GEM-CESAR study (treating to cure, high intesnity approach) was similar to the 2- and 3-year PFS rate (93% and 91%, respectively) in the E3A06 study (low intesnity, len only, treating to delay progression).

Mateos M-V, Martinez-Lopez J, Rodriguez Otero P, Gonzalez-Calle V, Gonzalez MS, Oriol A, et al. Curative Strategy (GEM-CESAR) for High-Risk Smoldering Myeloma (SMM): Carfilzomib, Lenalidomide and Dexamethasone (KRd) As Induction Followed By HDT-ASCT, Consolidation with Krd and Maintenance with Rd. Blood 2019;134(Supplement_1):781

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SMM: to treat or not

- Is there potential for clonal selection in high-risk patients with low intensity therapy?
- Risk of 2nd malignancies with longer follow up?
- Longer follow-up including analysis of duration of response to second line treatment in patients evolving to MM will determine whether low-intensity approaches will select for highly virulent clones
- Newer treatment approaches and combinations might address this issue

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National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2023
Multiple Myeloma

NCCN Guidelines Index
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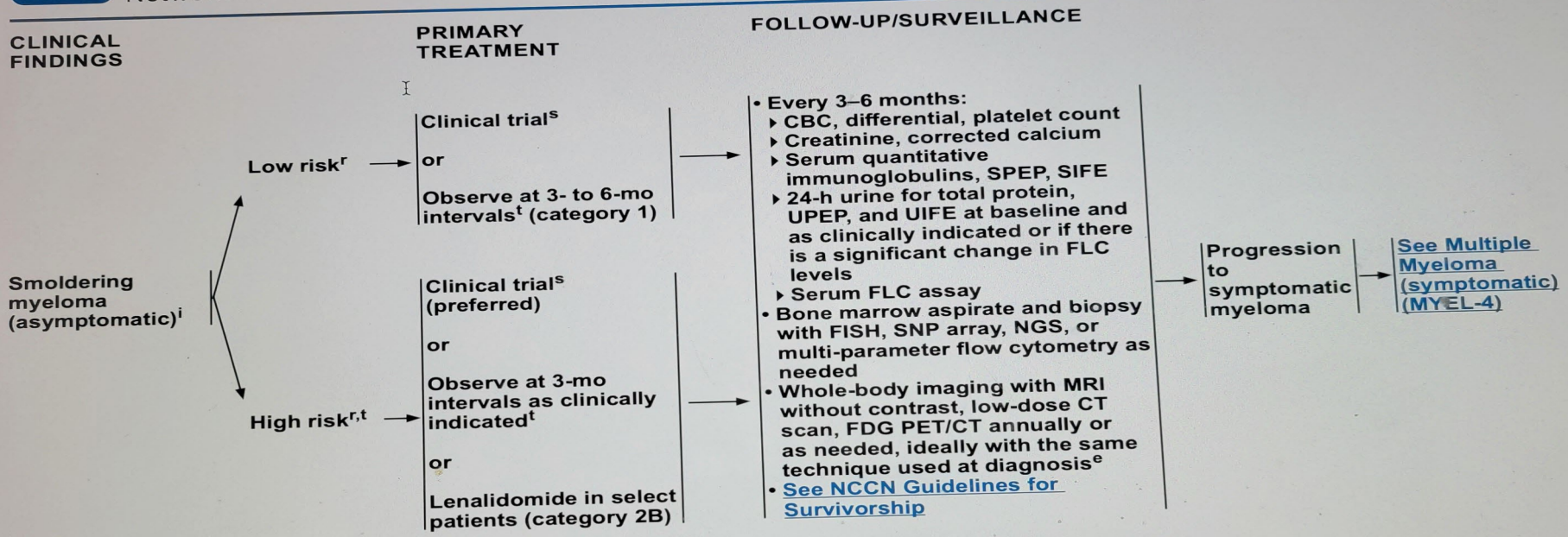
Discussion



[e] See Principles of Imaging (MYEL-B).
[i] See Definitions of Smoldering and Multiple Myeloma (MYEL-C).
[r] Bone marrow plasma cells (BMPCs) >20%, M-protein >2 g/dL, and serum FLC ratio (FLCr) >20 are variables used to risk stratify patients at diagnosis. Patients with two or more of these risk factors are considered to have high risk of progression to MM. Lakshman A, et al. Blood Cancer J 2018;8:59.
[s] The NCCN Panel strongly recommends enrolling eligible patients with smoldering myeloma in clinical trials.
[t] Patients with rising parameters are considered high risk and should be closely monitored.

What is next?

- There are at least 80 trials on clinicaltrials.gov currently listed for SMM
- Various combinations, including anti-CD 38, IMId, PI, elotuzumab are being used , in singly, or in combination

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