Monoclonal gammopathies and multiple myeloma

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MGUS: definition

- **All three criteria must be met:**
  - **Serum monoclonal protein < 3 gm/dl**
  - **Clonal bone marrow plasma cells < 10%**
  - **Absence of end-organ damage (CRAB)**

MGUS: background

- MGUS is present in 3% of the general population≥50 years old, 5.3% ≥ 70 but only 0.3% among those <50 years old
- These premalignant conditions can progress to lymphoproliferative diseases(NHL,CLL,WM), amyloidosis, multiple myeloma or monoclonal immunoglobulin deposition disease(MIDD)
- Rate of progression of IgG & IgA MGUS to multiple myeloma is 1% per year
- Rate of progression of IgM MGUS is 1.5%/yr

Outcome of MGUS

- Cohort of 241 patients with MGUS was followed up to 39 years (median, 13.7 years)
- Twenty-seven percent (n = 64) developed multiple myeloma (44), Waldenstrom's macroglobulinemia (7), primary AL amyloidosis (8), or a lymphoproliferative disorder (5)
- Interval from recognition of MGUS to diagnosis of multiple myeloma or a related disorder ranged from 1 to 32 years (median 10.4 years)

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

MGUS: risk stratification

Risk group	*No. of patients*	*Relative risk*	*Absolute risk of progression at 20 years (%)*	*Absolute risk of progression at 20 years accounting for death as a competing risk (%)*
Low-risk (serum M protein <1.5 gm/dl, IgG subtype, normal FLC ratio (0.26–1.65)	449	1	5	2
Low-intermediate-risk (any 1 factor abnormal)	420	5.4	21	10
High-intermediate-risk (any two factors abnormal)	226	10.1	37	18
High-risk (all three factors abnormal)	53	20.8	58	27

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

Management of low-risk MGUS

SPEP ≤ 1.5 g/dL, IgG isotype, and normal FLC ratio

- **Majority of patients are low risk (50%)**
- **Risk of progression to MM or related malignancy low**
- **Baseline marrow or skeletal survey not routinely indicated if labs are normal**
- **BM required if pt has unexplained anemia, renal insufficiency, hypercalcemia or bone lesions**
- **f/u SPEP in 6 months, if stable follow every 2–3 yrs or when symptoms suggestive of a PC malignancy arise**

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

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

Management of low-risk MGUS

SPEP ≤ 1.5 g/dL, IgG isotype, and normal FLC ratio

- **Lifetime risk of progression in low risk MGUS is 2% !**
- **Probability of finding ≥ 10% plasma cells in these patients is 4.7%**
- **Probability of finding bone lesions is 2.5%**
- **Routine skeletal imaging and bone marrow biopsy in low-risk MGUS has a low yield**

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

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

Management of all other MGUS patients (intermediate and high risk)

- BM aspirate and biopsy at baseline to rule out underlying PC malignancy are recommended
- Conventional cytogenetics and FISH needed
- **Skeletal survey (out of date)** or **low-dose whole body CT, CT/PET or bone marrow MRI**
- CT of chest abdomen and pelvis in IgM MGUS for asymptomatic retroperitoneal lymph nodes
- If testing is normal follow with SPEP and CBC in 6 months and then annually for life

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

Light chain MGUS

- Roughly 80% of patients with multiple myeloma have IgH expression (ie, IgG, IgA, IgM, IgD, and IgE); no IgH is expressed in the remaining 20%
- One estimate is that 0.8% of the population ≥ 50 has light-chain MGUS
- Defined as an abnormal free light-chain ratio with no IgH expression, plus increased concentration of the involved light chain

Dispenzieri. Lancet 2010; 375: 1721–28.

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

Dispenzieri. Lancet 2010; 375: 1721–28.

Amyloidosis

blood
2006 108: 2520-2530
Prepublished online Jun 22, 2006;
doi:10.1182/blood-2006-03-001164

Dangerous small B-cell clones

Giampaolo Merlini and Marvin J. Stone

- **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**

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

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

Definition of smoldering:
To burn slowly but with no flame

Smoldering multiple myeloma (SMM)

- Multiple myeloma is defined as smoldering (asymptomatic) or active (symptomatic)
- Criteria for smoldering multiple myeloma are as follows:
- M-protein in serum: IgG ≥3 g/dL, IgA >1 g/dL *or*
- Bence-Jones protein >1 g/24h *and/or*
- Bone marrow clonal plasma cells ≥10%.
- **Absence of CRAB criteria** including myeloma defining events

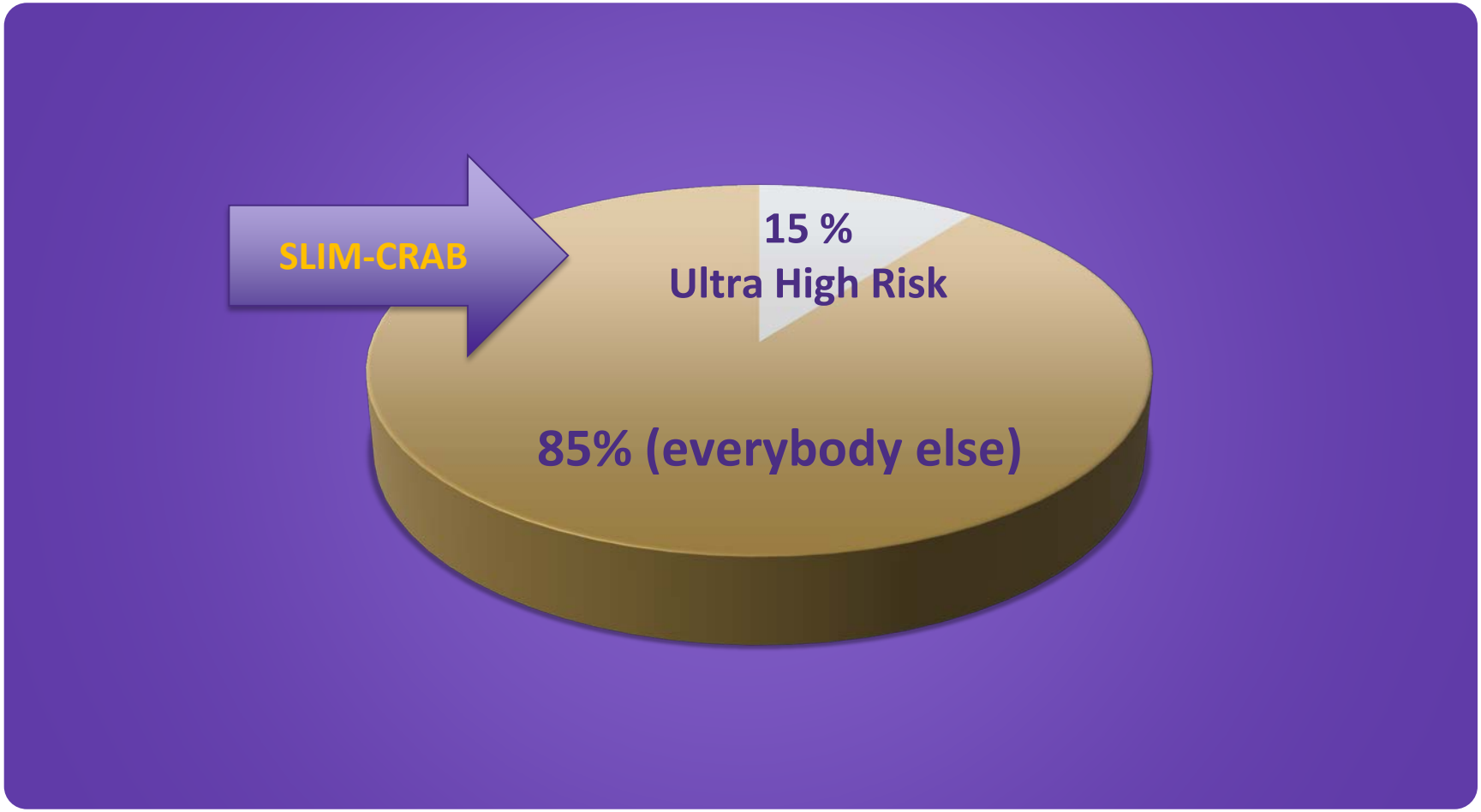
Rajkumar. Lancet Oncol.2014;15(12): e538-48.

Smoldering Multiple Myeloma

- By definition, SMM is an asymptomatic condition
- Clinical course of SMM reported by Kyle in retrospective study of 276 patients between 1970 and 1995
- Risk of progression to symptomatic myeloma (CRAB) was 10% per year for the first 5 years
- After 5 years, the risk of progression decreased to 3% per year for the next 5 years and 1% per year thereafter

Kyle. N Engl J Med 2007;356:2582-90.

SMM: 2014



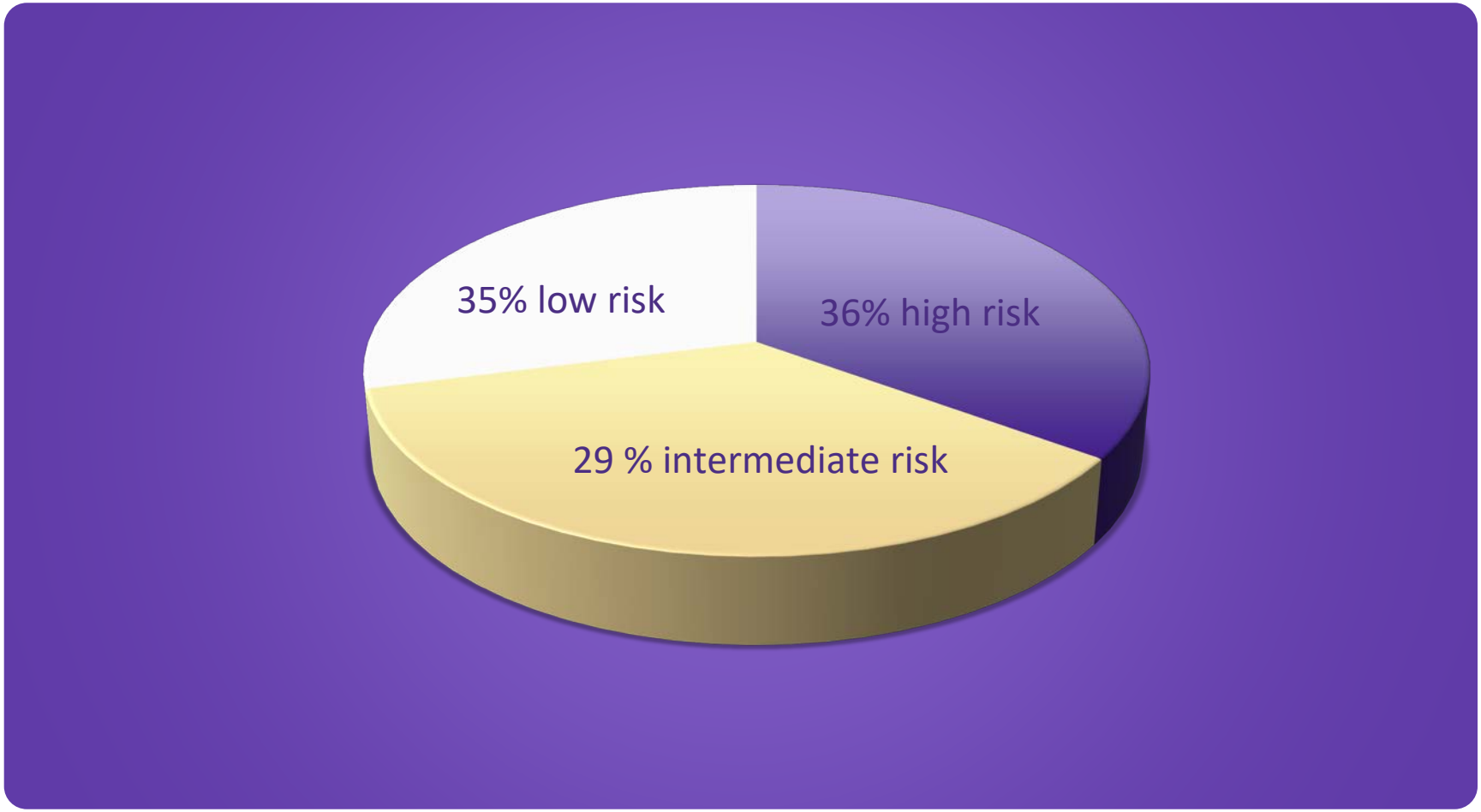
Rajkumar, Lancet Oncol. 15, e538–e548 (2014).

Current state of the art in classification of risk for progression in SMM [20/2/20 criteria]

- Stratified 421 pts into three groups: low risk (no risk factors; *n* = 143(35%); intermediate risk (one of three risk factors; *n* = 121 (29%); and high risk (≥2 of the three risk factors; *n* = 153(36%)
- Median TTP for low-, intermediate-, and high-risk groups were 110, 68, and 29 months,($p < 0.0001$)
- **CONCLUSION: BMPC% > 20%, M-protein > 2 g/dL, and FLCr > 20 at diagnosis can be used to risk stratify patients with SMM**

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

New classification of SMM 2020



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

Other proposed risk factors for progression in SMM

Clonal BMPCs ≥10% and any one or more of the following:
Serum M protein ≥30g/L
IgA SMM
Immunoparesis with reduction of 2 uninvolved immunoglobulin isotypes
Serum involved/uninvolved FLC ratio ≥8 (but <100)
Progressive increase in M protein level (evolving type of SMM; increase in serum M protein by ≥25% on 2 successive evaluations within a 6-month period)
Clonal BMPCs 50%-60%
Abnormal PC immunophenotype (≥95% of BMPCs are clonal) and reduction of ≥1 uninvolved immunoglobulin isotypes
t(4;14) or del(17p) or 1q gain
Increased circulating PCs
MRI with diffuse abnormalities or 1 focal lesion
PET-CT with focal lesion with increased uptake without underlying osteolytic bone destruction

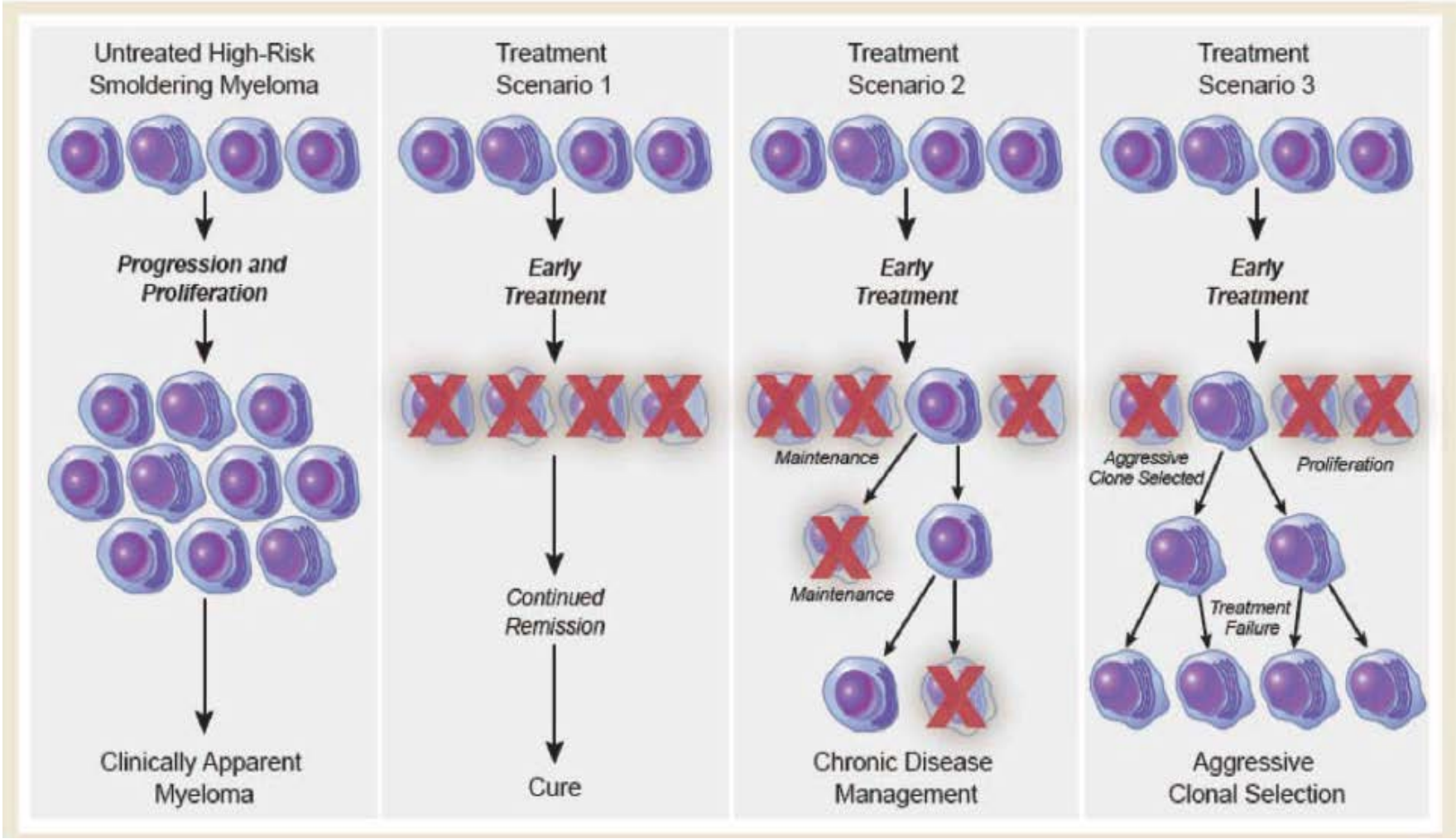
Rajkumar. Lancet Oncol .2014;15(12): e538-48.

High risk SMM 2020

- The Lakshman criteria have gained a high level of acceptance
- Still no pathological or molecular feature that distinguishes SMM patients who have only clonal premalignant PCs from those who have clonal malignant myeloma cells
- Outside of a trial ….**treatment is still not indicated**
- Watch and worry
- For higher risk patients regular reassessment and annual imaging

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

Possible scenarios resulting from early treatment of smoldering myeloma



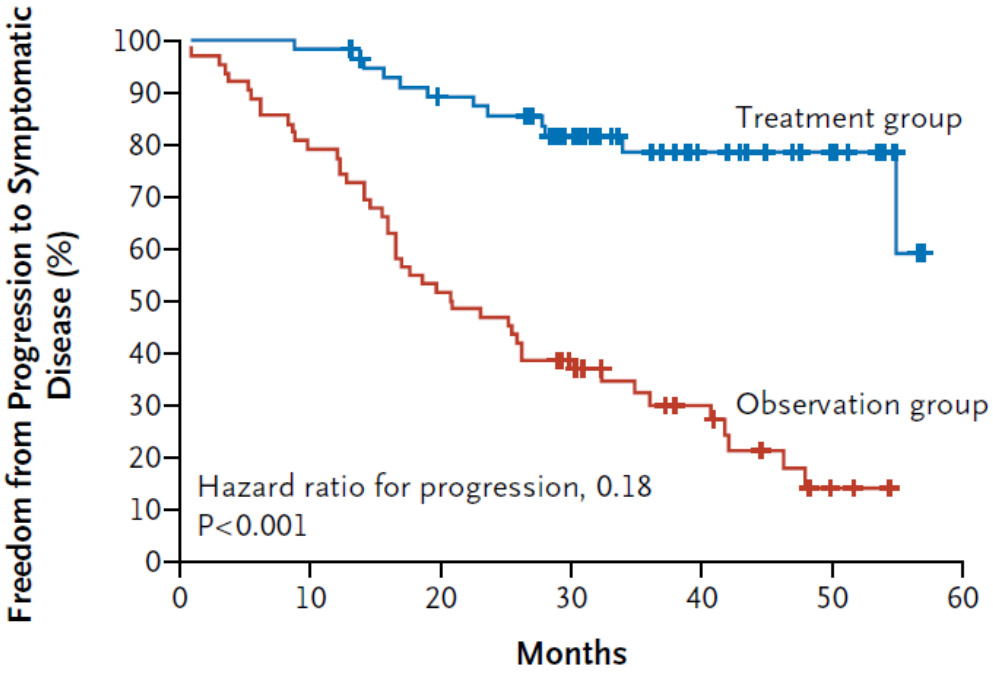
Landgren ASH 2017

1st Positive Treatment Study of SMM

- **QuiRedex**
- Randomized, open-label, phase 3 trial,119 pts
- Len/dex for 9 cycles followed by maintenance len(10mg) X 2years versus observation
- At median follow-up 40 months, median time to progression not reached vs. 21 months; HR 0.18
- 3-year OS (94% vs. 80%);HR for death, [0.31]
- Long term f/u published in 2016

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

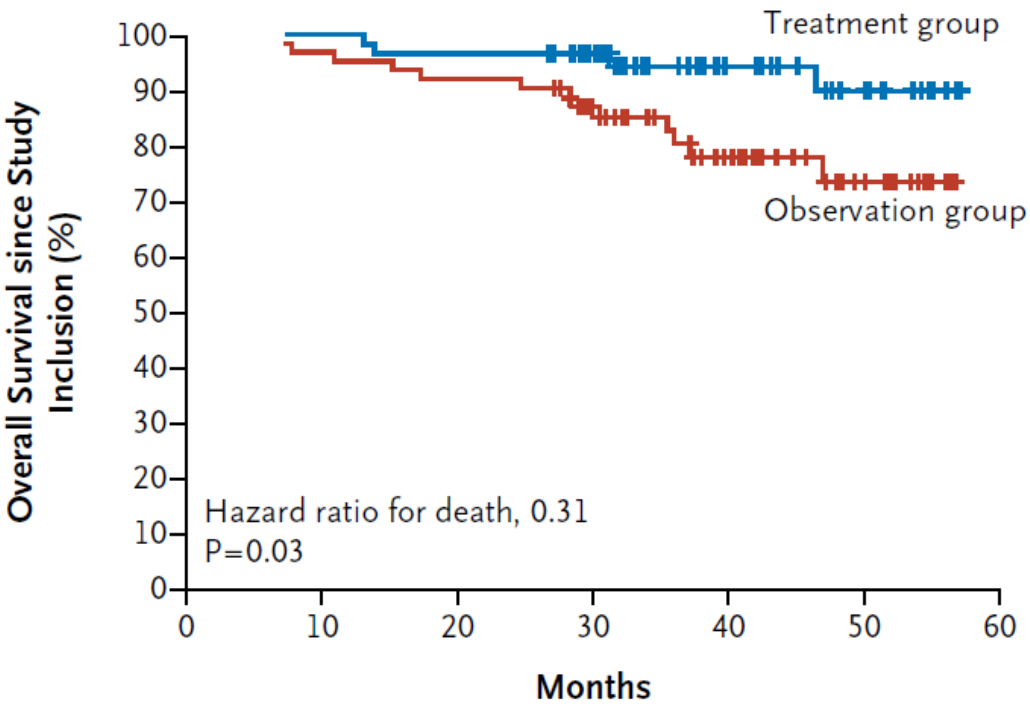
Modern Treatment Studies in High Risk SMM: (QuiRedex)



No. at Risk							
Treatment group	57	57	48	38	20	14	0
Observation group	62	49	32	21	11	3	0

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

Modern Treatment Studies in High Risk SMM: (QuiRedex)



No. at Risk							
Treatment group	57	57	55	48	26	17	0
Observation group	62	60	57	46	27	17	0

But the QuiRedex study was not accepted as the standard of care

- A combination regimen (len + dex) used and therefore the added value of lenalidomide could not be clearly isolated
- Modern imaging not used at randomization (no CT/PET or MRI) leading to concerns regarding possible enrollment of patients with symptomatic MM
- Multiparametric flow cytometry criteria used to define high-risk SMM not readily available outside of the centers that conducted the trial, which limited the generalizability of results.
- 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 .

ECOG 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

Lonial, J Clin Oncol 38:1126-1137.

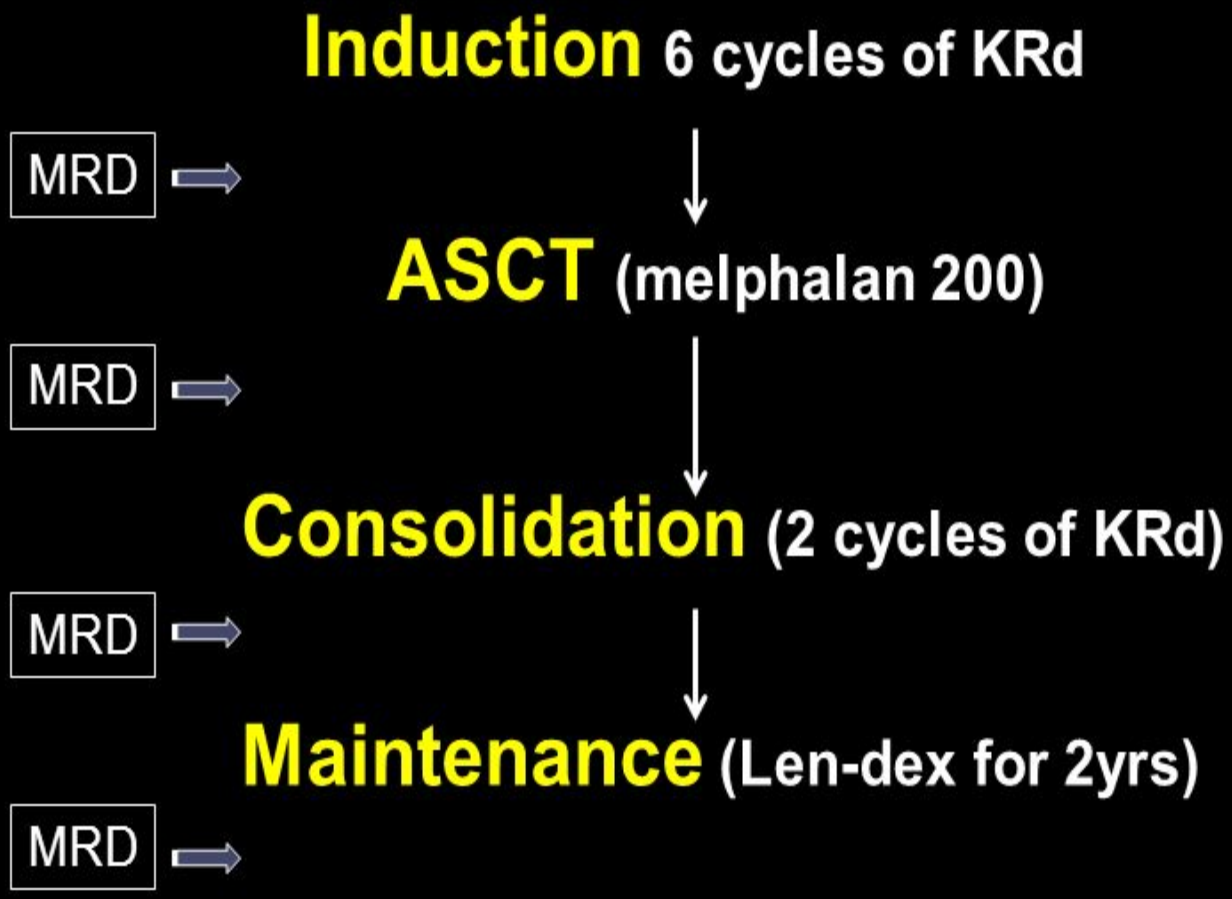
ECOG E3A06

- Overall response rate 50% (95% CI, 39% to 61%) treated pts, 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)
- One, 2, and 3 year PFS was 98%, 93%, and 91% for the lenalidomide arm versus 89%, 76%, and 66% for the observation arm

E3A06 conclusions

- Early intervention with lenalidomide in smoldering multiple myeloma significantly delays progression to symptomatic multiple myeloma and the development of end-organ damage
- But …treatment of smoldering multiple myeloma is still not SOC

Curative Estrategia Smoldering Alto Riesgo (CESAR trial) (n:90)



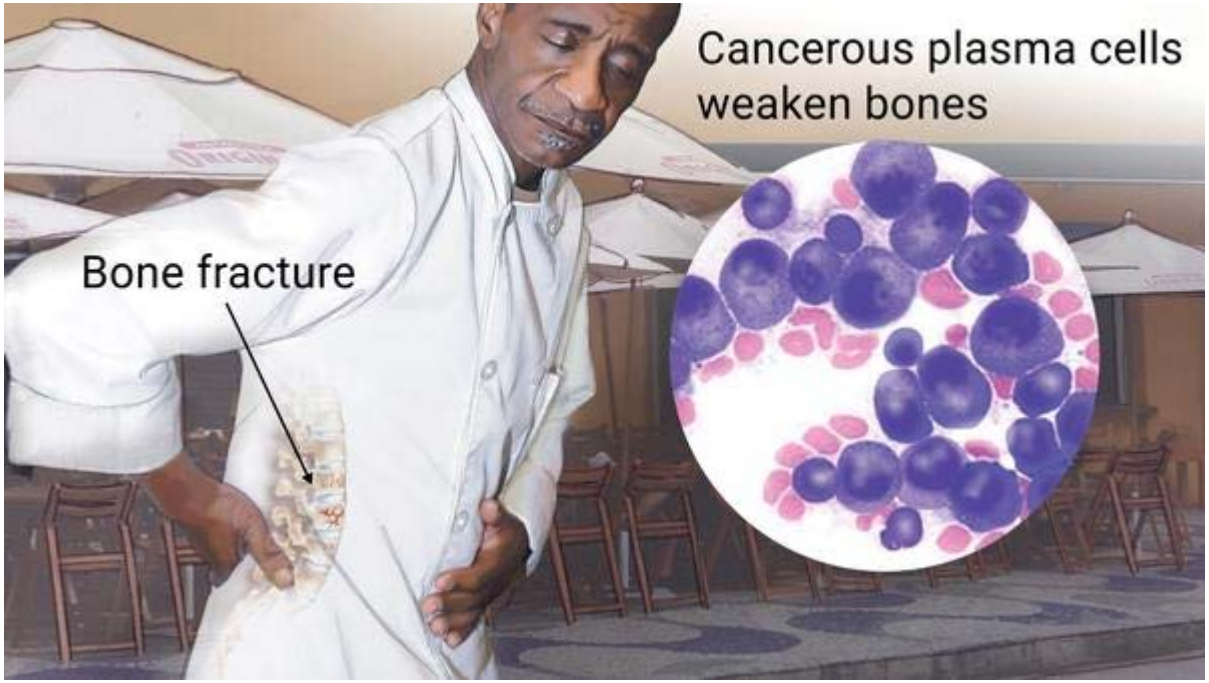
Primary objective: To evaluate the proportion of patients in sustained immunophenotypic response at 5 years

Hypothesis: At least 50% of patients will achieve the objective

20 centers

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


Cancerous plasma cells
weaken bones
Bone fracture

Diagnosis of MM

Clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma* and any one or more of the following myeloma defining events:

CRAB

Hypercalcemia: >1 mg/dL higher than the upper limit of normal or >11 mg/dL

Renal insufficiency: CrCl <40 mL/min or serum creatinine > 2 mg/dL

Anemia: Hgb >2.0 g/L below the lower limit of normal, or <10 g/L

Bone lesions: one or more **osteolytic lesions** on skeletal radiography, CT, or PET-CT

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 lesion on MRI studies

(each focal lesion must be 5 mm or more in size)