Highlights from IMW 2019

Tommaso Caravita di Toritto
UOSD Ematologia ASL Roma 1

MM smoldering
Filosofie e paradigmi di terapia

Conflitti di interesse

Advisory Board: Amgen, BMS, Celgene, Janssen-Cilag, Takeda.

Consulenza: BMS

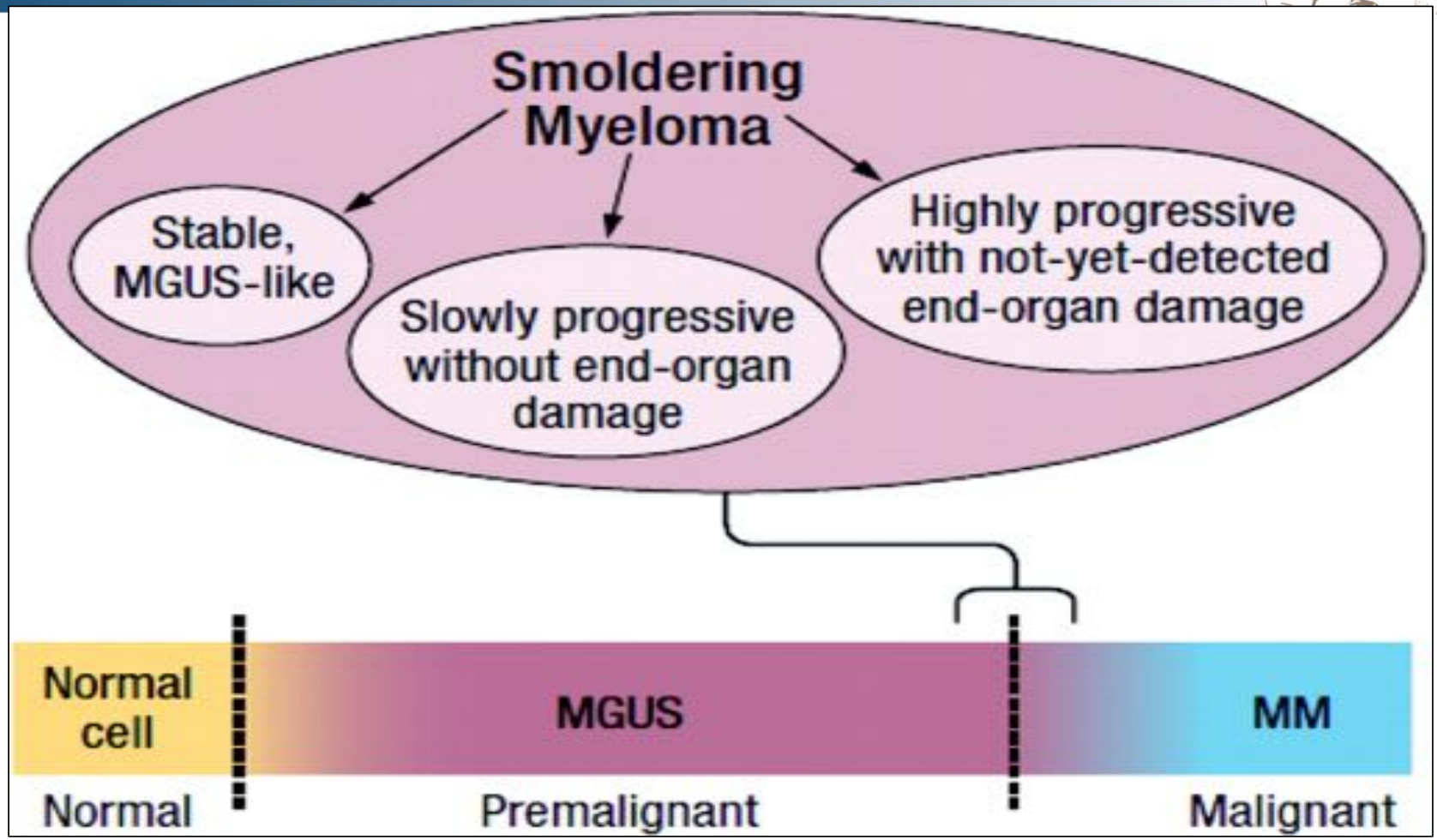
Fondi di ricerca: Celgene

Moderatore/relatore a congressi: Amgen, BMS, Celgene, Janssen-Cilag

PI in trials clinici: Amgen, BMS, Celgene, Janssen-Cilag,

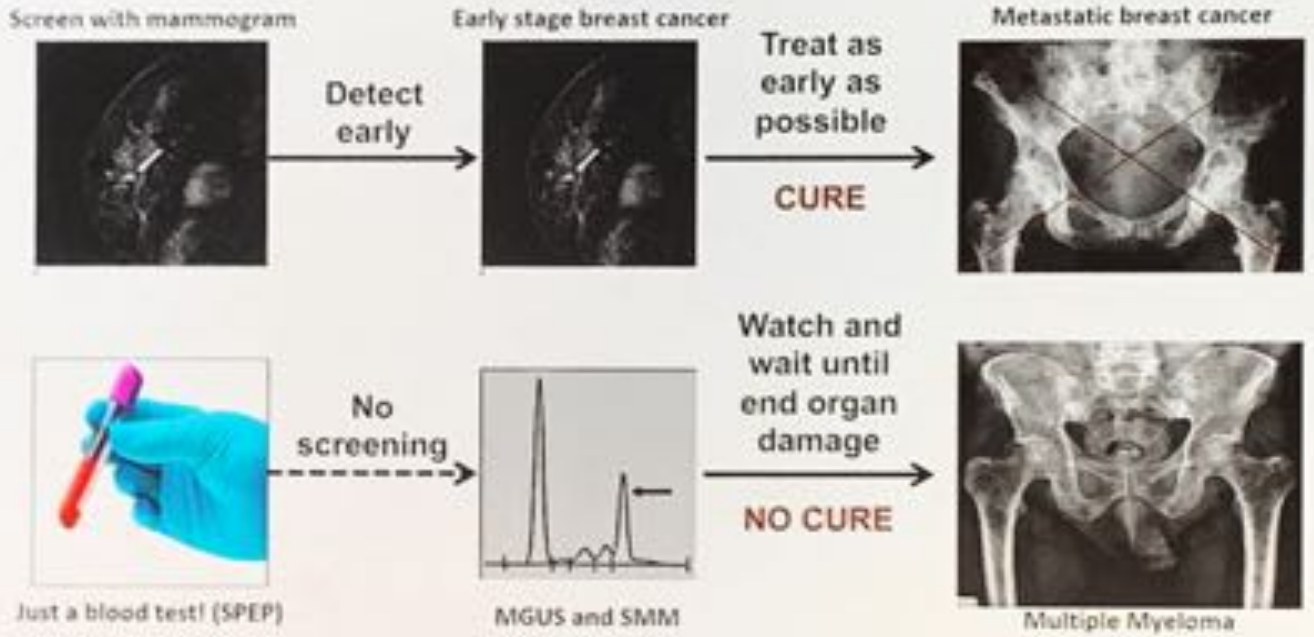
Spese per partecipazione a congressi: Amgen, BMS, Celgene, Janssen-Cilag

The clinical dilemma of smoldering myeloma

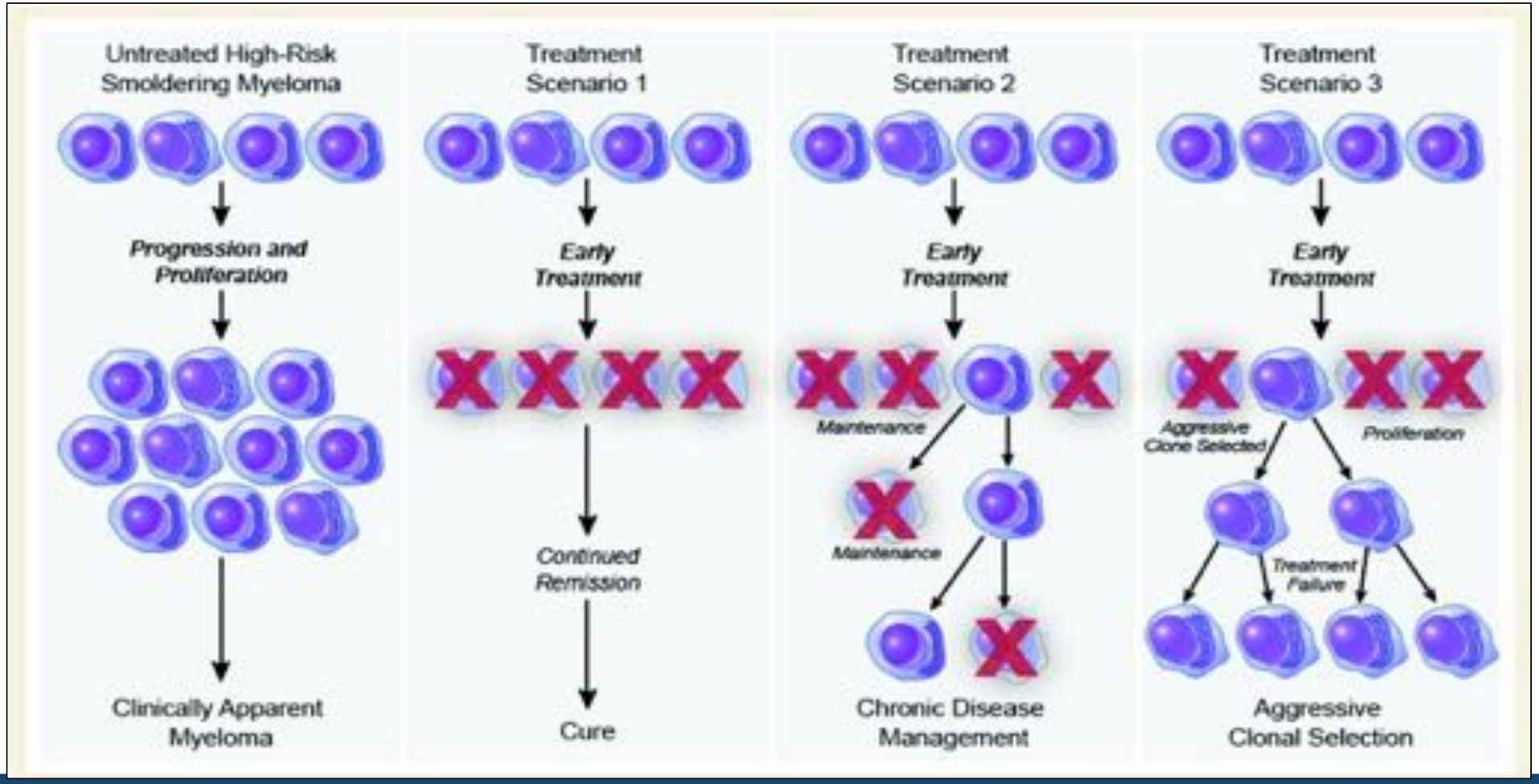


Landgren, O. Hematology 2010;2010:295-302
Landgren, O. Clin Cancer Res. 2011;17:1243-52

Can intervention prevent progression in MM?



Theoretically possible scenarios resulting from early treatment of SMM



Landgren, O. Hematology 2010;2010:295-302
Landgren, O. Clin Cancer Res. 2011;17:1243-52

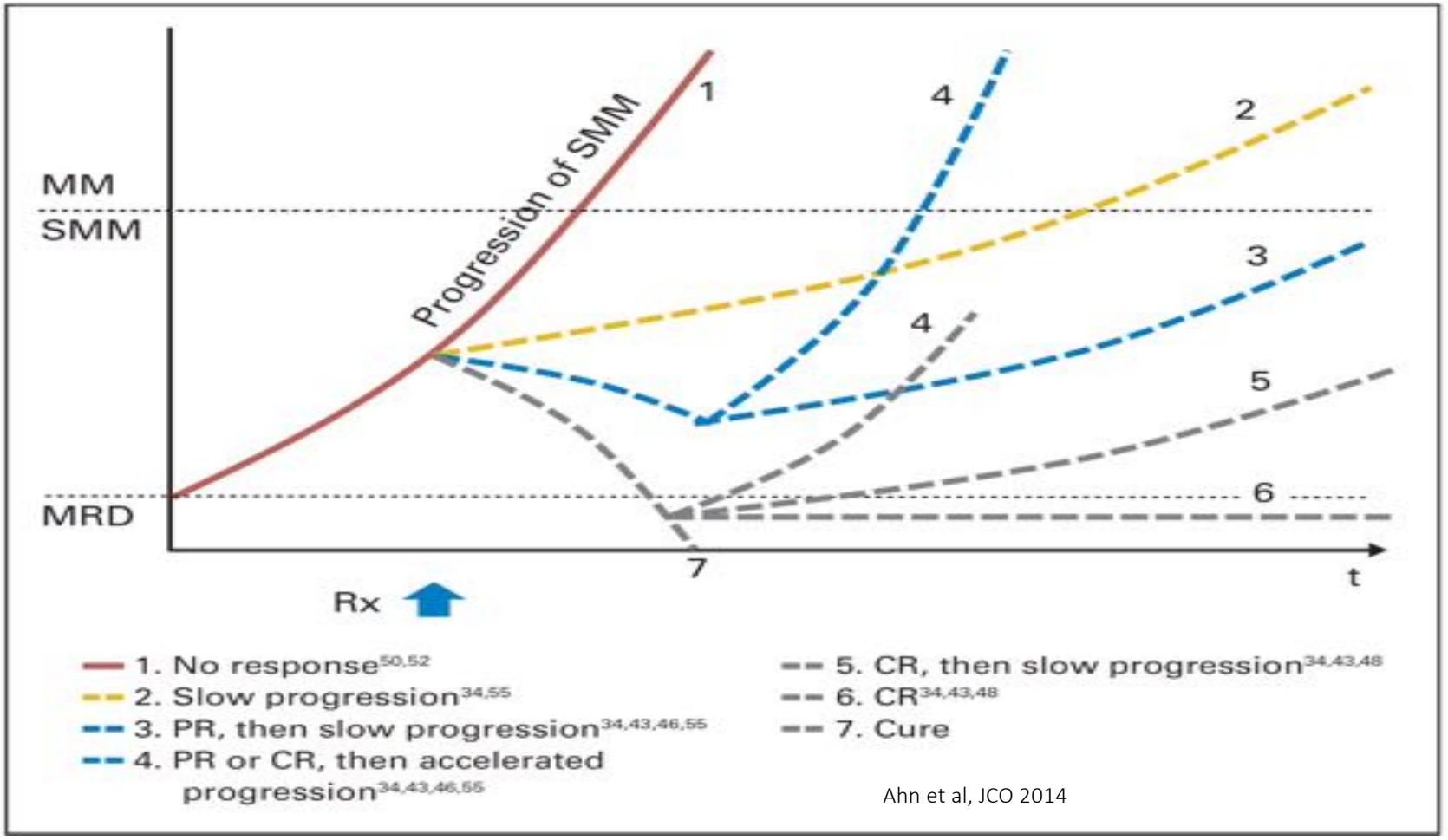
New concepts in preventing SMM progression

4 Rules to really cure MM by early therapeutic intervention

1. Therapy that is applied only to patients who are truly going to progress in their lifetime
2. Agents that truly eradicate the early clones (progenitor cell) of MM
3. Re-normalize the immune microenvironment
4. Are non-toxic and not for a long duration ("surgical" approach)

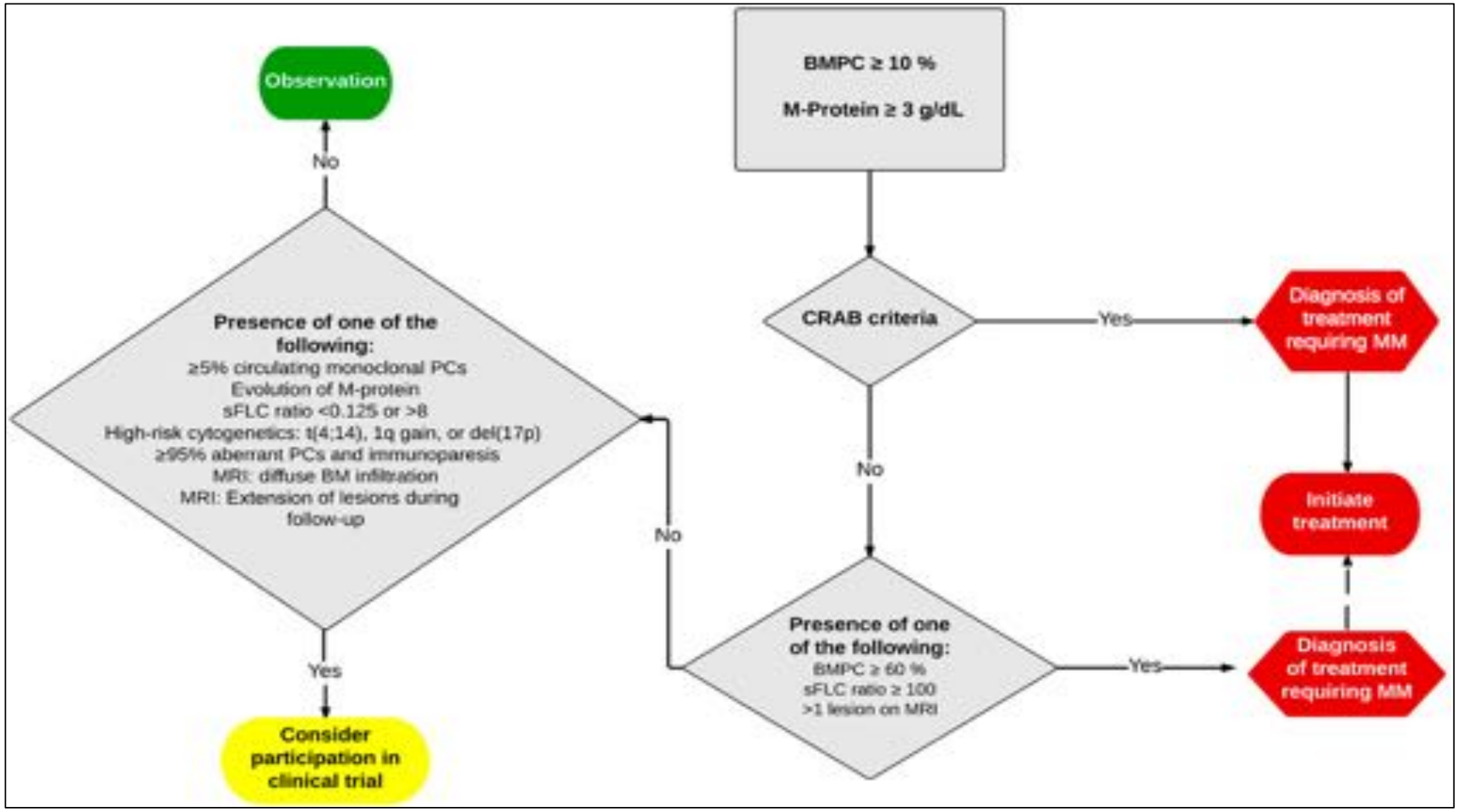
Ghobrial I, IMW 2019

Trajectories of treatment in SMM

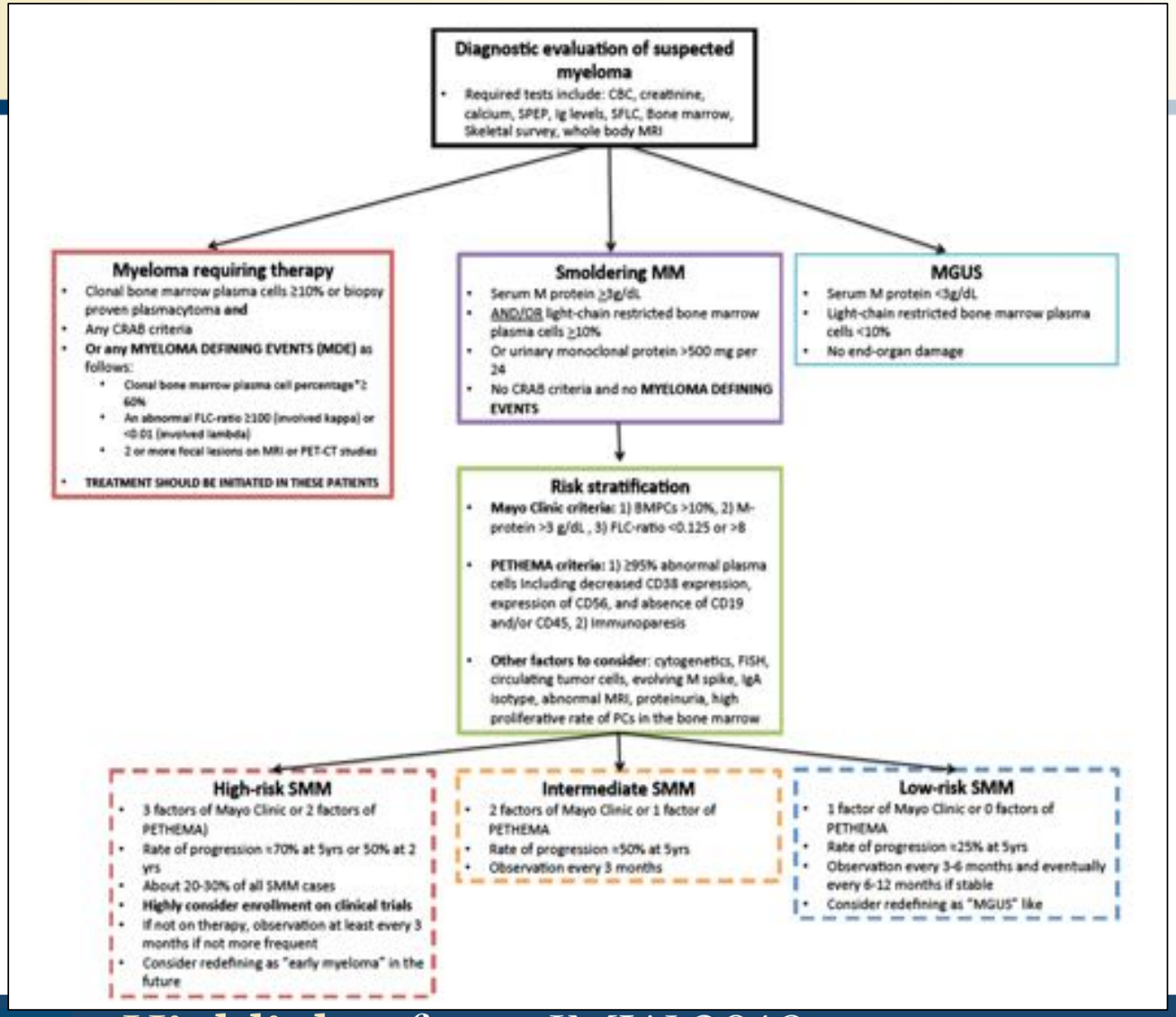


Ahn et al, JCO 2014

Proposed algorithm for the management of SMM/MM in 2015



CAERS J, et al The Oncologist 2016



Proposed guidelines of follow-up and management of SMM

Ghobrial IM and Landgreen O., Blood 2015

Mateos MV, IMW 2019

How to treat HR SMM?

- Numerous clinical trials (51 in clinicaltrials.gov) with several drugs are currently ongoing
- To prevent the myeloma development:

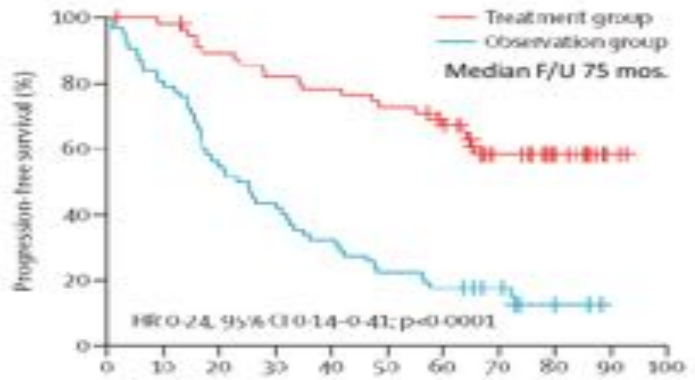
  -Len-dex or Len alone, Elo-Rd, Daratumumab, KRd, Ixa –Rd, pembrolizumab, nivolumab-Rd, Isatuximab, etc.
- To cure the disease before myeloma development:

  - CESAR trial

  -ASCENT trial

Delay Clonal Evolution (RD) or Eradicate the Clone (KRD)

PFS



Response	Overall[a] Patients With NDMM (n = 45)	Patients With SMM (n = 12)
Best Response, No. (%)		
CR or sCR	25 (56)	12 (100)
nCR	3 (7)	0
VGPR	12 (27)	0
PR	4 (9)	0
SD	1 (2)	0

- CR 14% after induction
- Median PFS NR after Vs. 23 mos. for control arm
- Improved OS (HR 0.43) in favor of treatment arm
- Median age 65 years (36-89)

- SMM Median age 58 years (48-65)

- Triplet therapy
- Incorporating ASCT
- Addition of monoclonal antibodies

Mateos et al. Lancet Oncol. 2016; 17:1127

Korde et al. JAMA Oncol. 2015; 1:746

Results from clinical trials exploring early treatment in HR-SMM

Clinical trial	Phase	Treatment	Follow-up, median (range), mo	Results	Safety profile (grade ≥3 AE)
QuiRedex (NCT00480363)[77]	3	Rd vs observation. Induction: 9 × 28-d cycles R 25 mg/d on d 1-21 + Dex 20 mg/d on d 1-4, 12-15. Maintenance: 2 y 28-d cycles with R 10 mg/d on d 1-21.	73 (66-84)	n = 119. Median TTP: NR (95% CI, 47 mo to NR) vs 23 mo (95% CI, 16-31 mo); HR, 0.34 (95% CI, 0.14-0.41); $P < .0001$). Median OS: NR in both arms (HR, 0.43; 95% CI, 0.21-0.92; $P = .02$.	Infection (8%; 1 death), asthenia (6%), neutropenia (5%), and skin rash (3%)
NCT01188837[71]	2/3	R vs observation. R alone at 25 mg d 1-21 every 28 d.	17	Preliminary ASH 2013 meeting; n = 44; PR, 33%, SD, 58%	Neutropenia and fatigue (25%)
NCT02279394[72]	2	Elotuzumab + Rd. Elotuzumab 10 mg/kg IV d 1, 8, 15, and 22. Cycles 1 and 2, 10 mg/kg IV d 1 and 15; cycles 3-6, lenalidomide 25 mg d 1-21; cycles 1-24, Dex 40 mg oral d 1, 8, 15, and 22; cycles 1 and 2, 40 mg oral d 1, 8, and 15 in cycles 3-6.	—	n = 31. ORR: 84%; CR: 7%; VGPR: 38%; PR: 42%; clinical benefit rate: 100%.	Hypophosphatemia (30%), neutropenia (14%), infection (12%), anemia (2%), pulmonary embolism (2%), rash (4%), and diarrhea (2%)
NCT01441973[35]	2	Elotuzumab. Cohort 20 mg/kg IV: cycle 1, d 1 and 8; monthly thereafter; cohort 10 mg/kg: cycles 1 and 2 weekly; every 2 wk thereafter.	28	n = 31. ORR (90% CI) 10%; 2-y PFS: 69% (52-81%).	7 (47%) in the 20 mg/kg cohort and 6 (38%) in 10 mg/kg cohort; no grade 3 infusion reactions
NCT01484275[34]	2	Siltuximab vs placebo.15 mg/kg siltuximab or placebo 1-h IV infusion every 4 wk until disease progression to MM.	29.2	n = 86. 1-y PFS: 84.5% (95% CI, 68.6-92.8) vs 74.4% (95% CI, 57.3-85.5).	Infections and renal and urinary disorders (1 patient in the siltuximab group and 3 patients in the placebo group); 7 patients died (3 in the siltuximab group [pneumonia (n = 1)] and unknown (n = 2))
CENTAURUS (NCT02316106)[33]	2	Daratumumab. 16 mg/kg IV in 8-wk cycles. Long: every wk in cycle 1, every other wk in cycles 2 and 3, every 4 wk in cycles 4-7, and every 8 wk up to cycle 20. Intermediate: every wk in cycle 1 and every 8 wk up to cycle 20. Short: every wk for 1 cycle.	15.8 (0.0-23.8)	n = 41 in each arm; ORR: 56%/54%/39%; 12-mo PFS, 95%/89%/81%	Infection (<5% in all arms)
NCT01573480[73]	2	Carfilzomib + Rd. Eight 28-d cycles of carfilzomib 20/36 mg/m^2 on d 1, 2, 8, 9, 15, and 16; lenalidomide 25 mg on d 1-21; and Dex 20/10 mg (cycles 1-4/5-8) on days 1, 2, 8, 9, 15, 16, 22, and 23 + 2-y R maintenance.	15.9	n = 12; CR, 100%; MRD (flow), 92%	Skin (33%), neutropenia (17%), anemia (17%), infection (8%), and cardiac (8%)
CESAR (NCT02415413)[74]	2	Induction: KRd × 6 cycles (carfilzomib IV 20/36 mg/m^2 d 1, 2, 8, 9, 15, and 16/lenalidomide 25 mg d 1-21/Dex 40 mg d 1, 8, 15, and 22). ASCT: consolidation, KRd × 2 cycles; maintenance, Rd × 2 cycles.	17 (5-36)	n = 90; efficacy after ASCT (+100); ORR, 100%; ≥CR, 63%; VGPR, 23%; MRD-ve rate (flow), 55%	Neutropenia (8%), thrombocytopenia (11%), infections (18%), and skin rash (9%)
ASCENT (NCT03290209)	2	Induction: 6 cycles, KRd + daratumumab. Consolidation: 6 cycles, KRd + daratumumab vs ASCT maintenance: 12 cycles, R + daratumumab	—	Ongoing	Not yet available

Mateos MV and Gonzales-Calle V, Blood Advances 2019

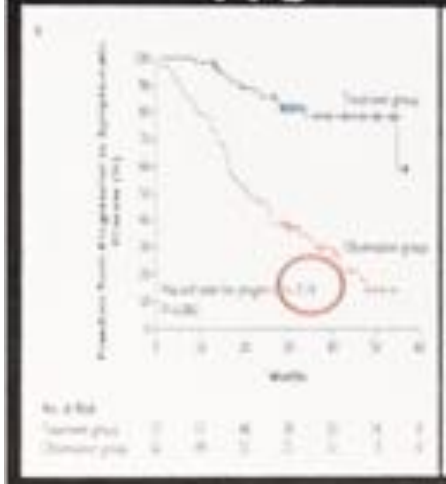
QuiRedex:

Len-dex vs no treatment: TTP to active disease (n = 119)

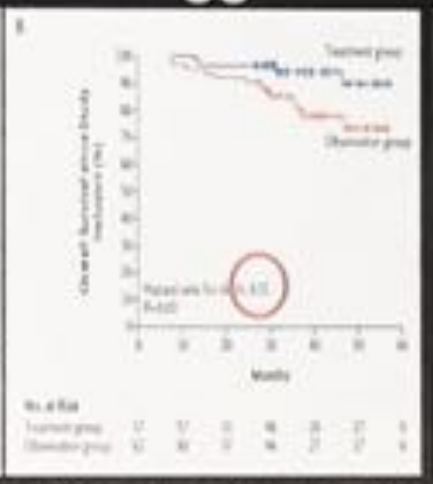
Per-protocol Patients population

Median follow-up: 40 m

PFS

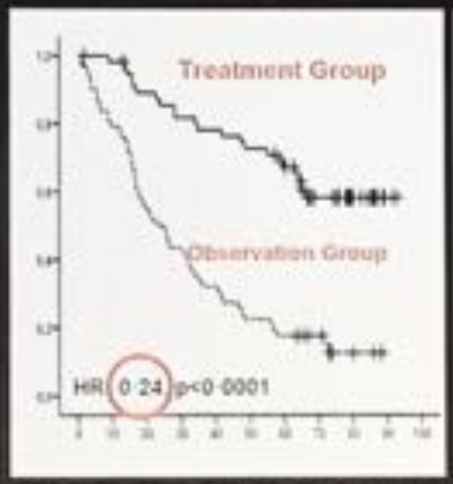


OS

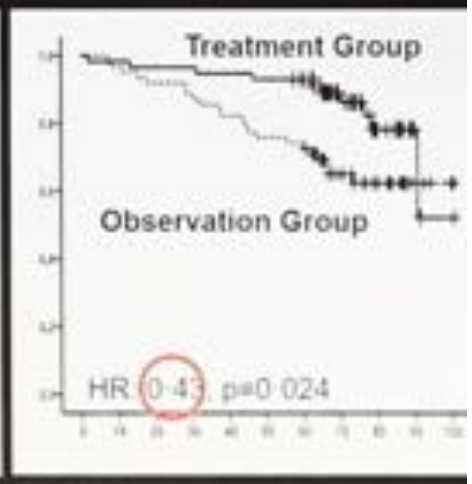


Median follow-up: 75 m

PFS



OS

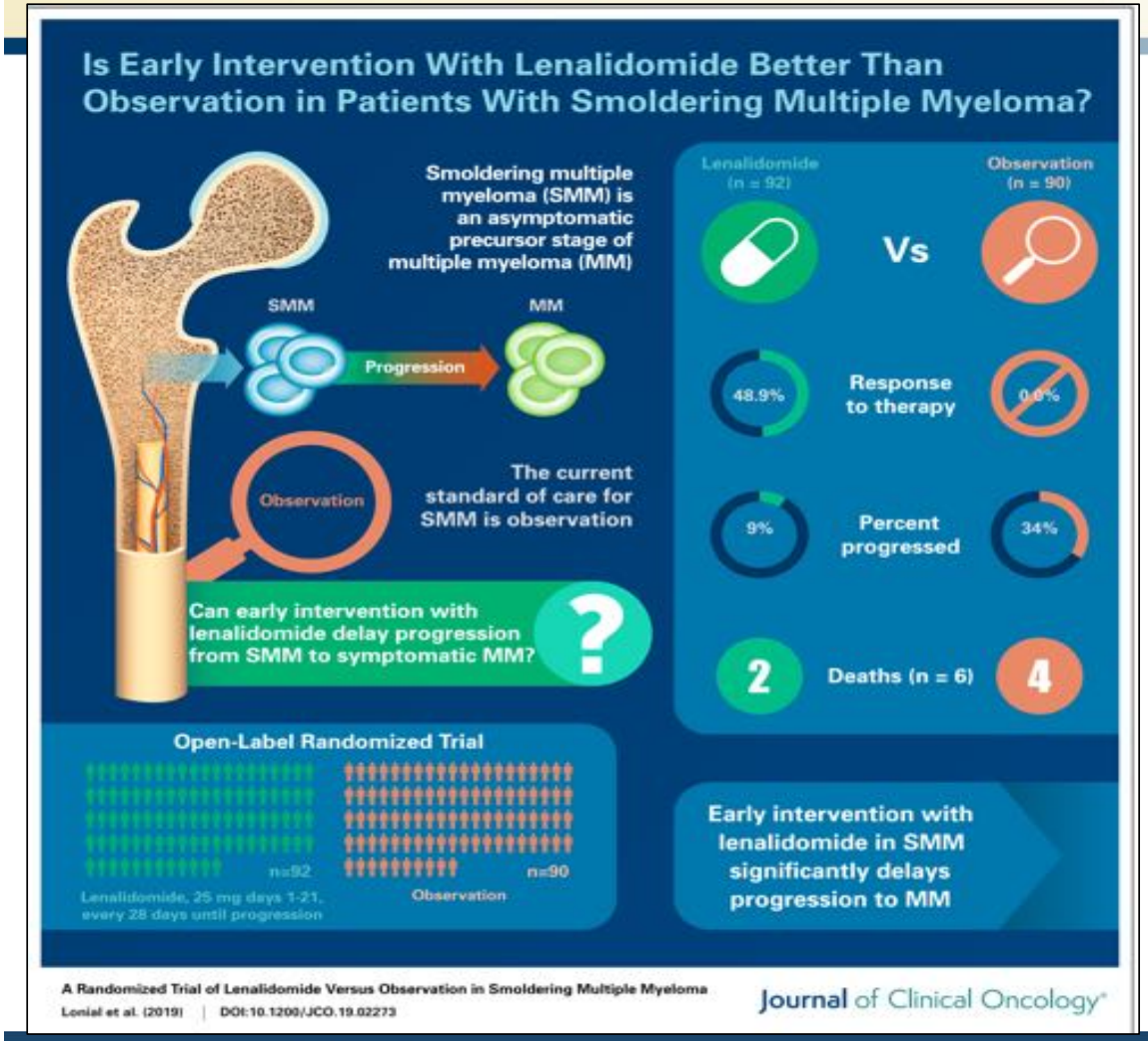


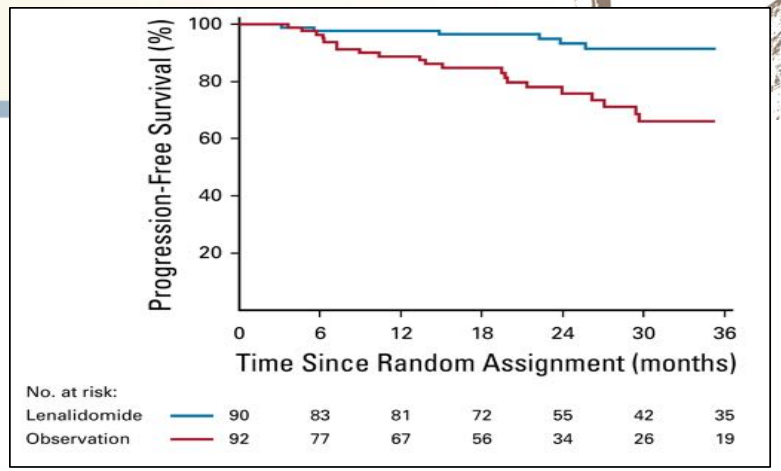
Early treatment did not induce more resistant relapses

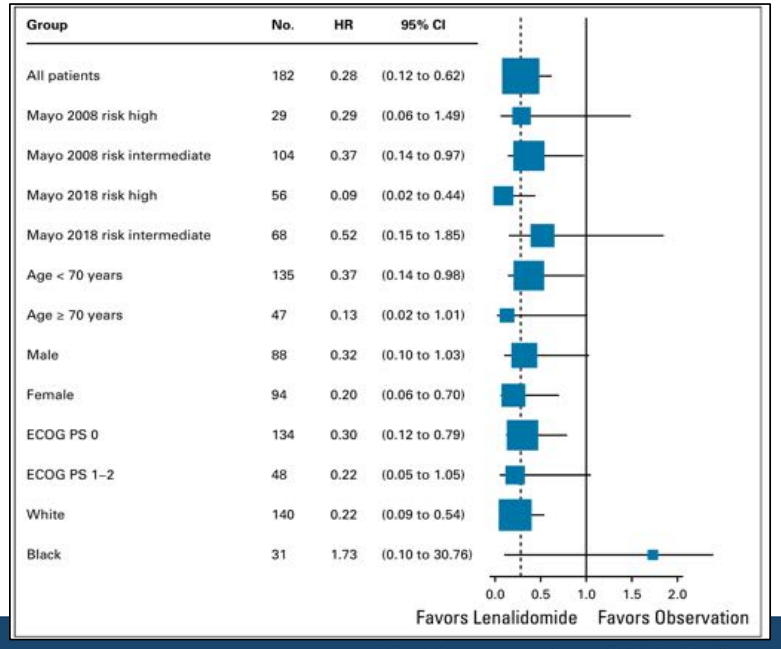
High-risk was defined according to the Mayo 2008 and/or Spanish models with a high concordance

Mateos MV, et al. NEJM 2013

Mateos MV, et al. Lancet Oncology 2016


Is Early Intervention With Lenalidomide Better Than Observation in Patients With Smoldering Multiple Myeloma?
Smoldering multiple myeloma (SMM) is an asymptomatic precursor stage of multiple myeloma (MM)
SMM
MM
Progression
Observation
The current standard of care for SMM is observation
Can early intervention with lenalidomide delay progression from SMM to symptomatic MM?
Lenalidomide (n = 92)
Observation (n = 90)
Vs
48.9%
Response to therapy
0.0%
9%
Percent progressed
34%
2
Deaths (n = 6)
4
Open-Label Randomized Trial
n=92
n=90
Lenalidomide, 25 mg days 1-21, every 28 days until progression
Observation
Early intervention with lenalidomide in SMM significantly delays progression to MM
A Randomized Trial of Lenalidomide Versus Observation in Smoldering Multiple Myeloma
Lonial et al. (2019) | DOI:10.1200/JCO.19.02273
Journal of Clinical Oncology


Progression-Free Survival (%)
100
80
60
40
20
0
6
12
18
24
30
36
Time Since Random Assignment (months)
No. at risk:
Lenalidomide 90 83 81 72 55 42 35
Observation 92 77 67 56 34 26 19

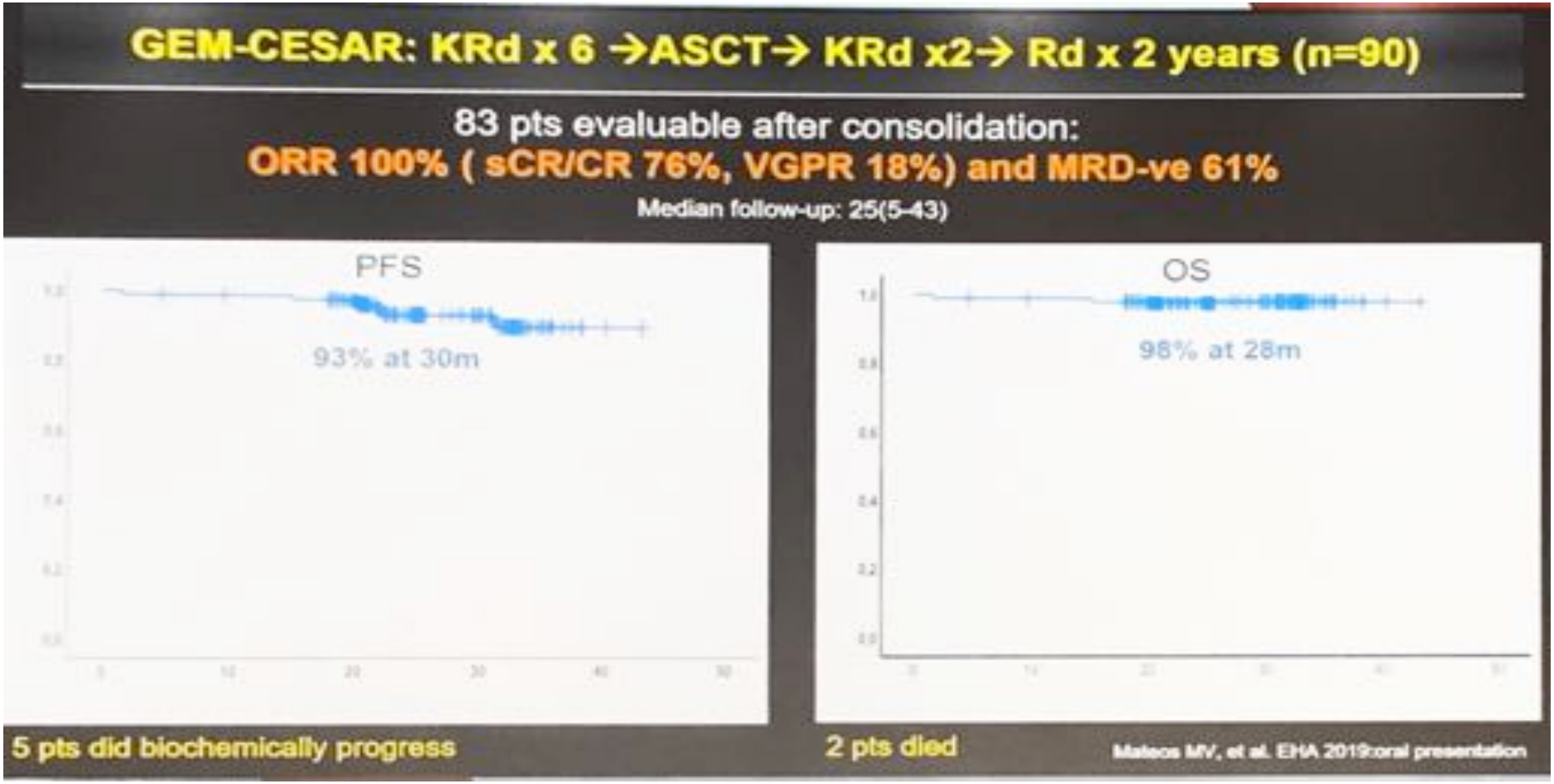

Group No. HR 95% CI
All patients 182 0.28 (0.12 to 0.62)
Mayo 2008 risk high 29 0.29 (0.06 to 1.49)
Mayo 2008 risk intermediate 104 0.37 (0.14 to 0.97)
Mayo 2018 risk high 56 0.09 (0.02 to 0.44)
Mayo 2018 risk intermediate 68 0.52 (0.15 to 1.85)
Age < 70 years 135 0.37 (0.14 to 0.98)
Age ≥ 70 years 47 0.13 (0.02 to 1.01)
Male 88 0.32 (0.10 to 1.03)
Female 94 0.20 (0.06 to 0.70)
ECOG PS 0 134 0.30 (0.12 to 0.79)
ECOG PS 1–2 48 0.22 (0.05 to 1.05)
White 140 0.22 (0.09 to 0.54)
Black 31 1.73 (0.10 to 30.76)
0.0
0.5
1.0
1.5
2.0
Favors Lenalidomide
Favors Observation

Lenalidomide as backbone for the treatment of intermediate-high risk SMM patients

	Phase	n	ORR/CR/MRD-ve	PFS/OS
Elo-Rd	2	50	84%/6%/NE	100%/1 death
Ixa-Rd	2	26	89%/19%/12%	100%/-
KRd	2	12	100%/100%	-
Efficacy of Rd plus something else seems to be superior in SMM than MM Small series of patients Randomized trials are ongoing/planned				
Dara monotherapy Long/interm/short	2	41/41/41	-	At 12m: 95%/88%/781%

Ghobrial I, et al. ASH 2018; abstract 154
Ghobrial I et al. ASH 2018; abstract 804
Landgren O et al. JAMA 2017
Hofmeister C, et al. Presented at ASH 2017 (Abstract 510)

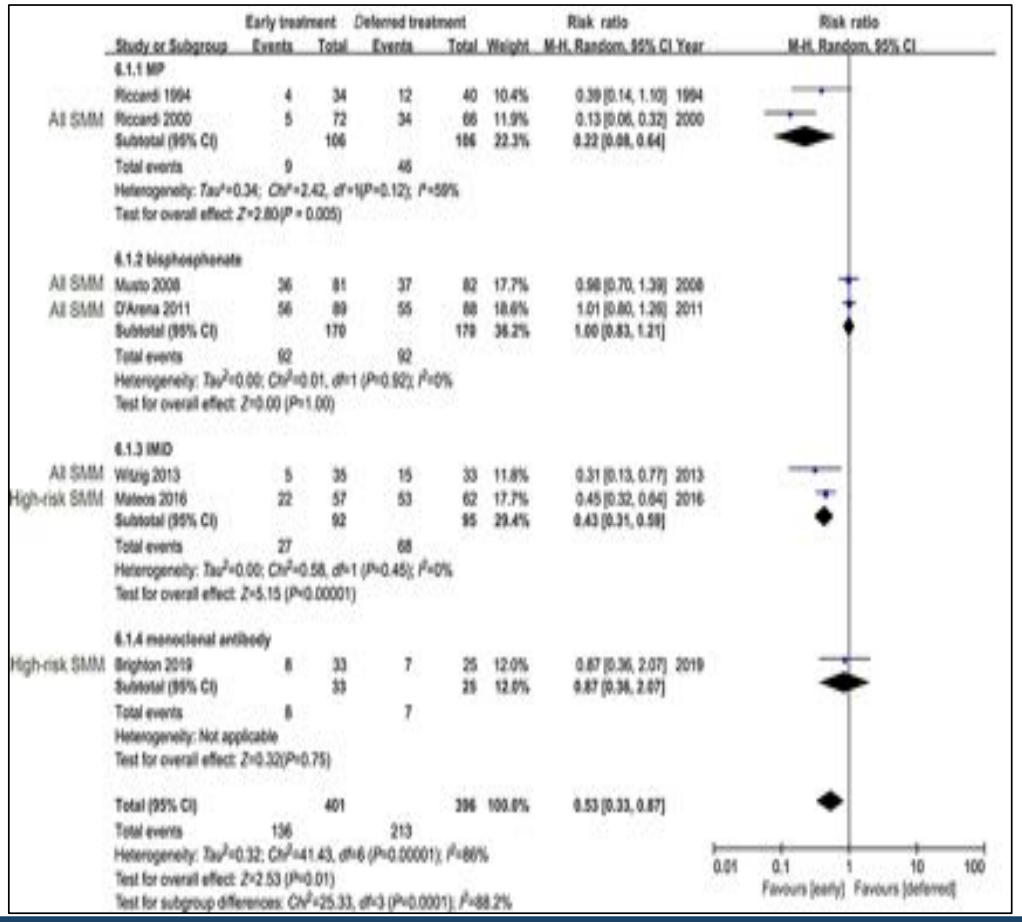
Mateos MV, IMW 2019



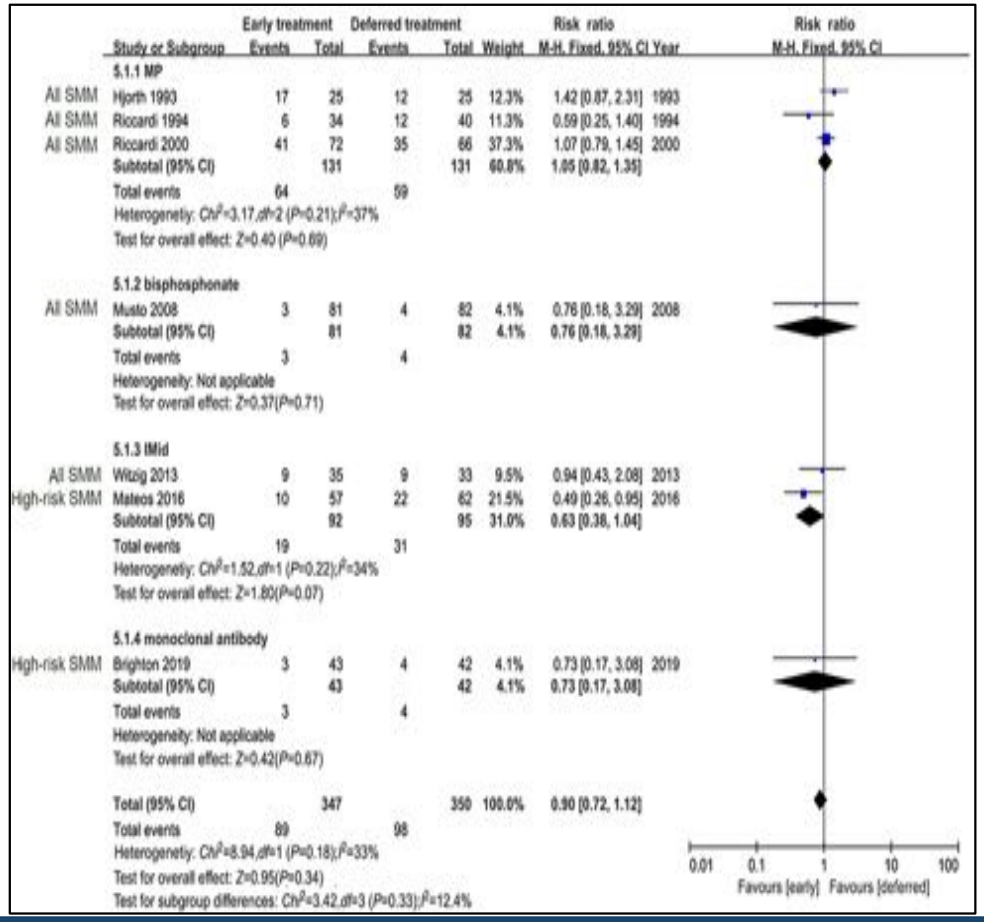
Mateos MV, IMW 2019

Early or deferred treatment of smoldering multiple myeloma: a meta-analysis on randomized controlled studies

Progression in overall SMM patients



Mortality in overall SMM patients



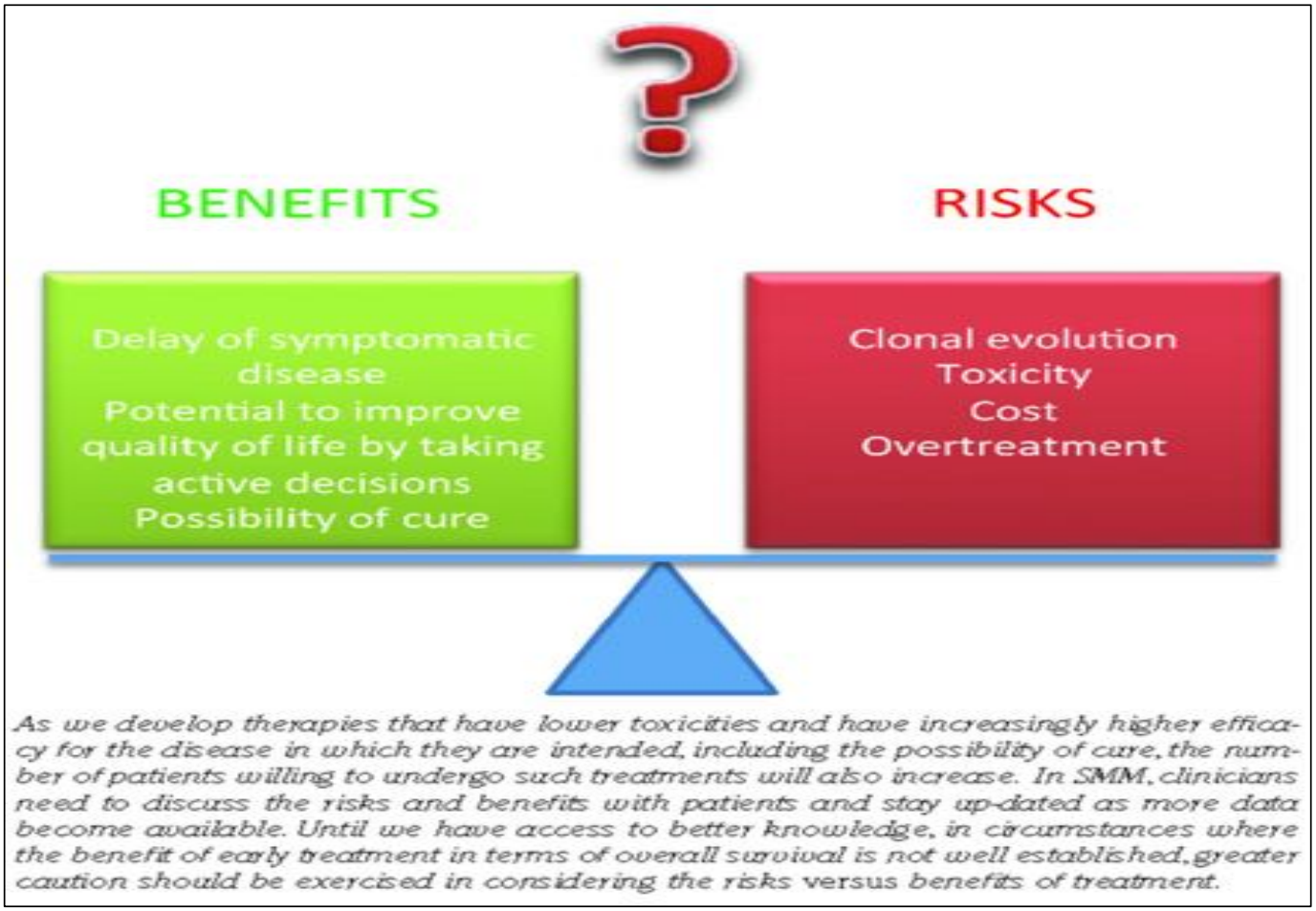
Zhao et al., Cancer Manag. Res. 2019

Ongoing Clinical Trials for High-Risk Smoldering Myeloma

Conceptual/ Regulatory	Strategic: Delay Progression	Strategic: ? Cure
Len v Obs Rd vs Obs Dara vs Obs	DRd vs Rd KRd	CESAR ASCENT
Necessary trials	Survival benefit with early therapy	? Cure possible with early therapy

Slide credit: clinicaloptions.com

The fine balance in the benefit to risk ratio of treatment in patients with smoldering multiple myeloma



As we develop therapies that have lower toxicities and have increasingly higher efficacy for the disease in which they are intended, including the possibility of cure, the number of patients willing to undergo such treatments will also increase. In SMM, clinicians need to discuss the risks and benefits with patients and stay up-dated as more data become available. Until we have access to better knowledge, in circumstances where the benefit of early treatment in terms of overall survival is not well established, greater caution should be exercised in considering the risks versus benefits of treatment.

Manasanch E. et al. Haematologica 2014

Conclusions

- SMM is not a unique biological entity but rather a step in the continuum of clonal evolution and progression of tumor plasma cells.
- Selective treatment pressure on myeloma clone justify early treatment with an aggressive curative intent.
- For current clinical practice, HRSMM should be considered for clinical trials.
- Spanish and ECOG trials support the treatment with Rd/R to prevent the myeloma development to SMM patients with a 50% progression risk at 2 ys.
- Future treatment trials in HRSMM can set MRD negativity as primary end point to demonstrate the depth of response achieved with a study drug and prospectively explore the duration of MRD-ve status as a secondary end point to assess the impact of treatment in preventing clonal evolution.

GRAZIE PER L'ATTENZIONE