HOSPITAL UNIVERSITARIO DE SALAMANCA

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Management of Smoldering Myeloma

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Conflict of interest

Honoraria derived from lectures and participation in advisory boards from Janssen, Celgene-BMS, Takeda, Amgen, GSK, Abbvie, Pfizer, Roche, Genentech, Regeneron, Adaptive, Sea-Gen, Blue-bird bio

Management of SMM should be risk-adapted

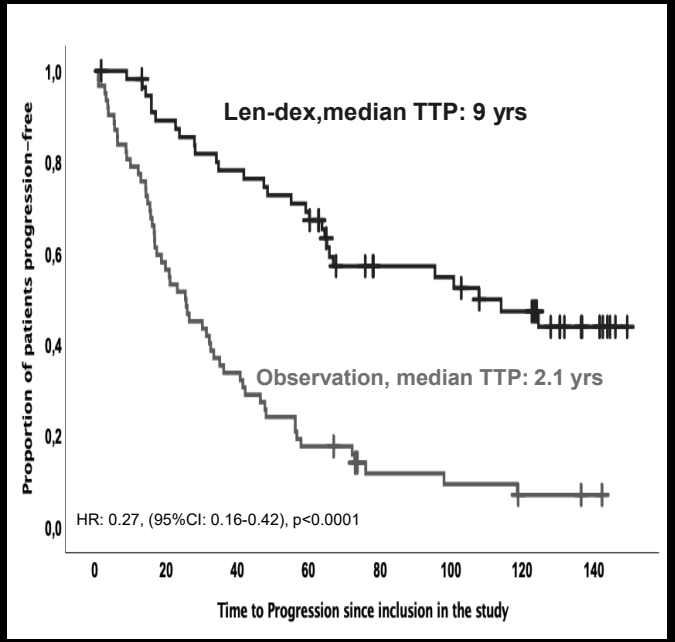
56 y old man Asymptomatic Routine analysis: M-prot IgG-K **1.8 g/dL** PCBM infilt: **12%** sFLC ratio: **9** No MDE	68 y old woman Osteoporosis Routine analysis: M-prot IgA-K: **1,8g/dL** PCBM infilt: **22%** sFLC ratio: **10** No MDE	38 y old woman Asymptomatic Routine analysis: M-prot IgA-K: **3,8 g/dL** PCBM infiltration: **39%** sFLC ratio: **79** No MDE	50 y old man (asymptom) Routine analysis: M-prot IgA-K: **3,5 g/dL** PCBM infiltration: **25%** FISH: **+1q** sFLC ratio: **46** No MDE
Low risk SMM	Intermediate SMM	High risk SMM	High risk SMM
I would not treat. **Management like MGUS pts**	**I would not treat.** **F/u every 4-6 months during the first 2 yrs and annually thereafter with hemogram, creat and calcium plus protein studies** **If 1 FL at MRI: alternating WBMRI with WBLDCT/6m; the rest-> yearly WBMRI***	**I would treat**	**I would treat**

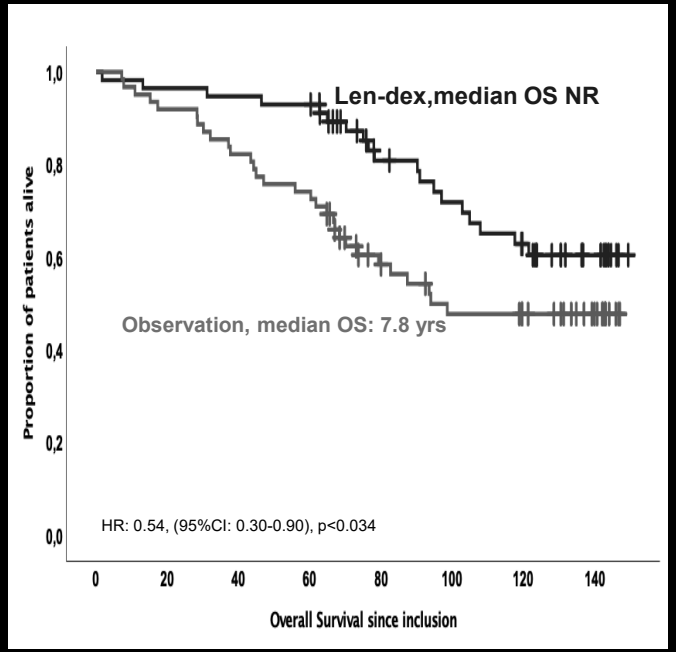
This appraoch is based on the 2/20/20 model but others are feasible and other markers will be incorporated in the future like genomic-ones, CTCs,...

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

Per-protocol Patients population

Median follow-up: 10.8 years

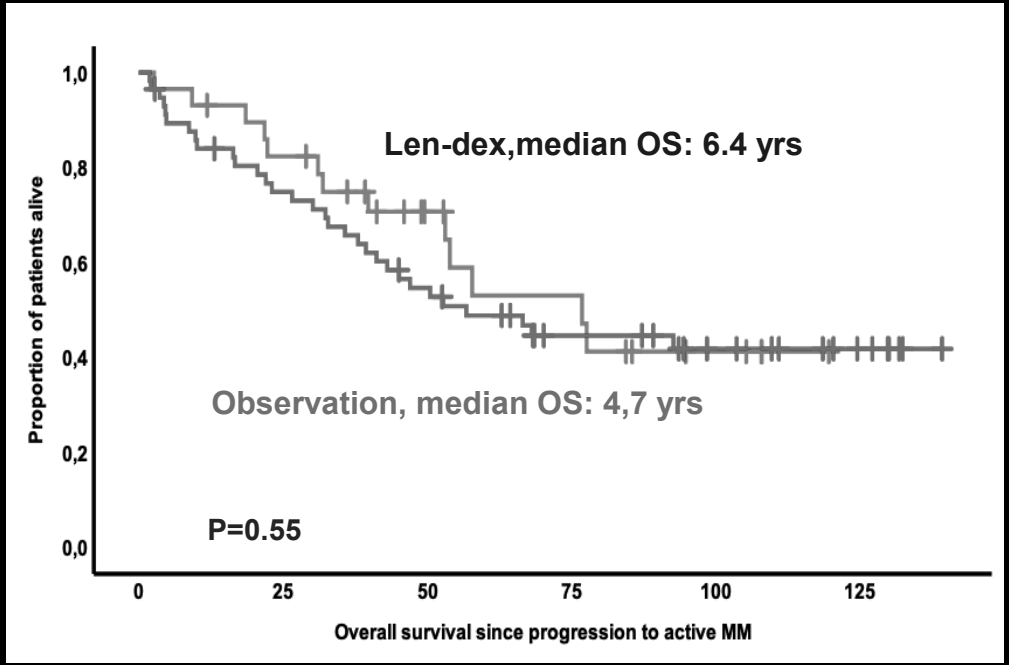




Mateos MV, et al. Manuscript in preparation

Len-dex vs no treatment: OS from progression to active disease (n = 119)

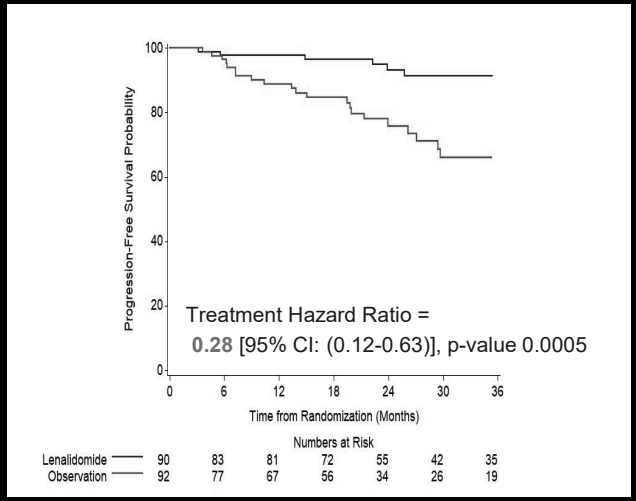
Median follow-up: 10.8years

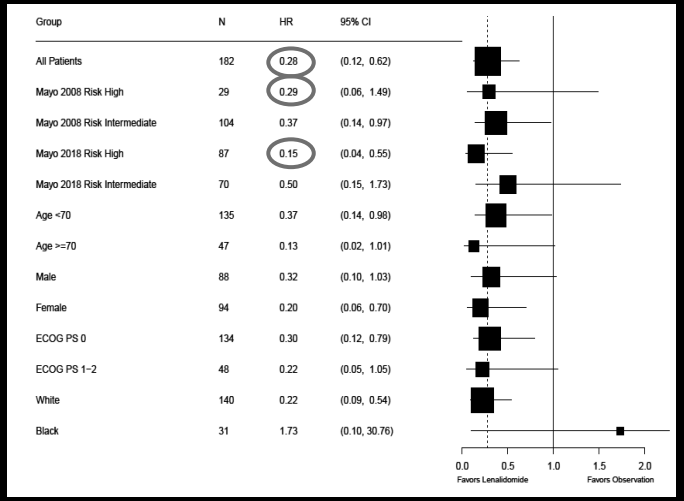


Early treatment does not induce more resistant relapses

Mateos MV, Manuscript in preparartion

E3A06: Len vs Observation in patients with asymptomatic Smoldering Multiple Myeloma (n=182)





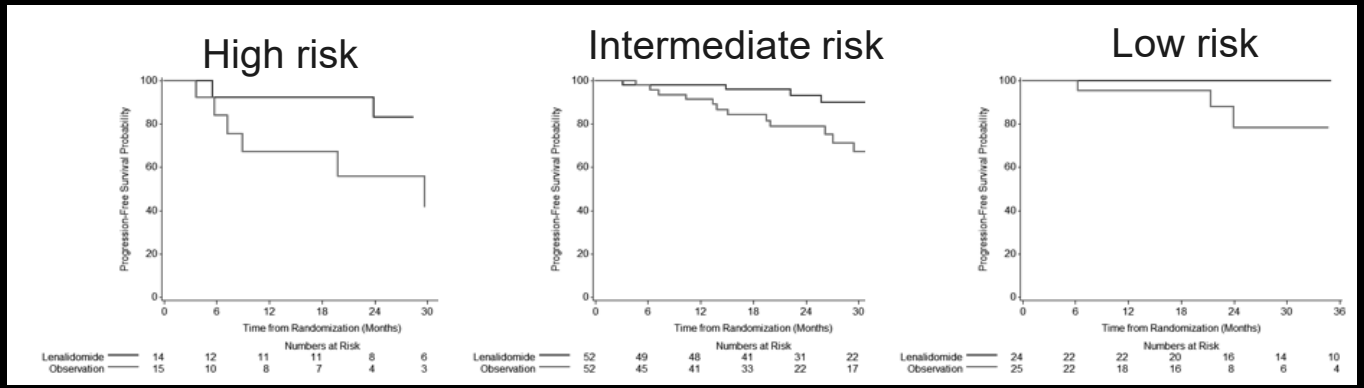
Criteria: PCBM ≥ 10% and sFLC ratio >8 or <0.125

Mayo2008: PCBM ≥ 10% + MC ≥ 3g/dl
Mayo2018: 2/20/20

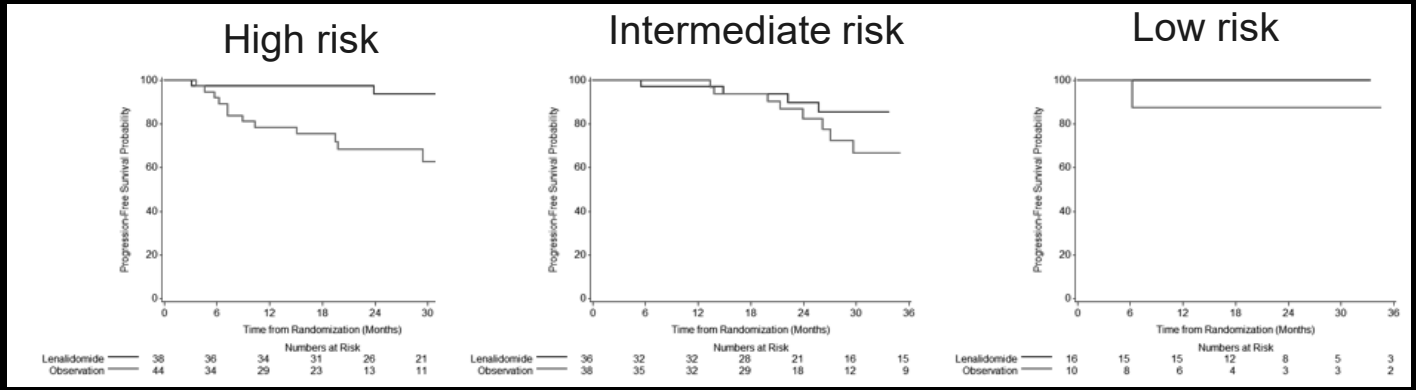
Early treatment with R significantly prevented the progression to MM especially in the high risk subgroup

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

E3A06: Len vs Observation benefit the most to high-risk SMM patients



Mayo 2008 model: PCBM ≥ 10%, MC ≥ 3g/dL and sFLC ratio >8 or <0.125



IMWG 2019 model: 2/20/20

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

Management of Smoldering MM

- These two trials support the early treatment in high-risk SMM patients

- Numerous clinical trials (76 in clinicaltrials.gov) with several drugs are currently ongoing in this group of patients

- To prevent the Myeloma development: Most consolidated strategy
  - Len vs observation, Elo-Rd, Daratumumab, KRd, Ixazomib-Rd, pembrolizumab, nivolumab-Rd, isatuximab,…
- To cure the disease before Myeloma development:
  - CESAR trial
  - ASCENT trial

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

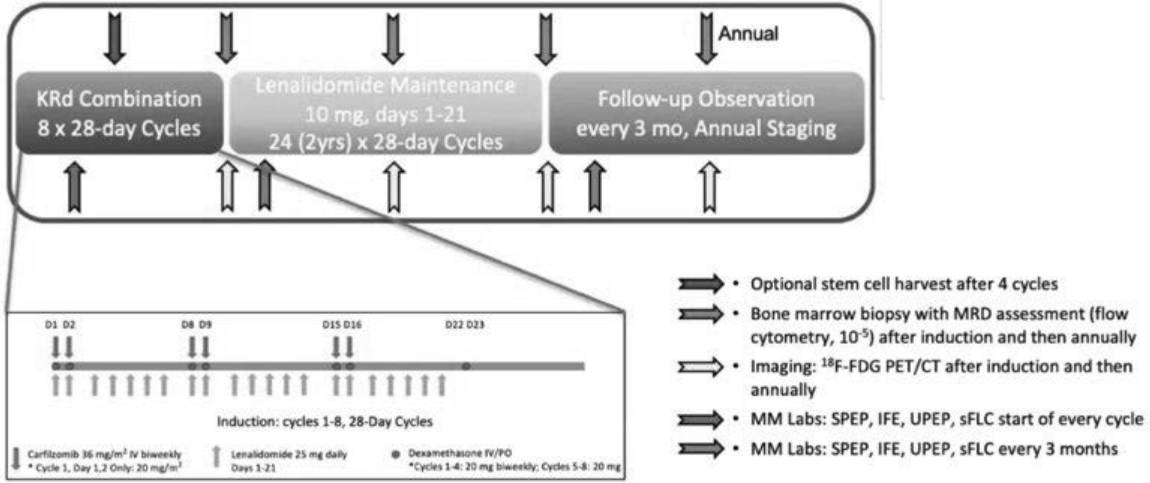
Elo Rd/ Ixa Rd/ K Rd

	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**
- **New endpoints necessary in this population**

Ghobrial I, et al. ASH 2018: abstract 154
Ghobrial I et al. ASH 2018: abstract 804
Landgren O et al. JAMA 2017

KRd x 8 cycles followed by R maintenance x 2 yrs in HR SMM patients



Key eligibility criteria for HR SMM definition

Classic Mayo model

Pethema model

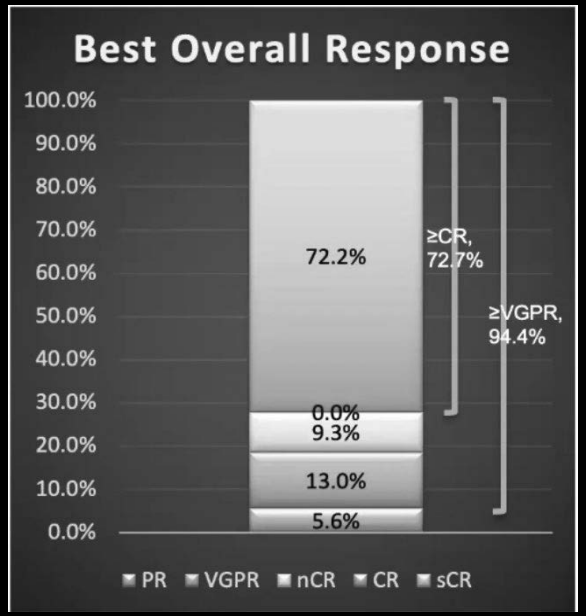
≥10% PCBM infiltration plus anyone or more of the following features: >3g/dl MC, IgA, immunoparesia, high risk CA, circulating tumor cells, PET_CT positive,….

- Primary objective: Determine MRD negative CR rate
- Key secondary objectives: PFS (clinical and biochemical), ORR, DOR, duration of MRD negativity (MFC, sensitivity 10^{-5}) and safety

- 54 patients were included
- Median patient age 59 years
- 37% had disease with high-risk cytogenetic features

Kazanddjian et al. ASH 2020: 548

KRd x 8 cycles followed by R maintenance x 2 yrs in HR SMM patients (f/u of 28 mo)



Sustained MRD negativity

MRD Negativity (flow 10^{-5})	N=50 (95% CI)
MRDneg CR Rate, n	35 (70.2%: 55.4–82.1%)
MRDneg CR Duration	
Median, months	66.8 mo (39.5–not estimable)
2-year Sustained	79.8% (57.7–91.2%)
5-year Sustained	53.2% (27.7–73.3%)
7-year Sustained	39.9% (17.1–62.0%)
MRDneg ≥VGPR Rate, n	38 (76.0%: 61.8–86.9%)
MRDneg ≥VGPR Duration	
Median, months	66.8 mo (39.5–not estimable)
2-year Sustained	77.5% (56.0–89.4%)
5-year Sustained	51.6% (27.0–71.6%)
7-year Sustained	39.9% (16.7–62.5%)

Progression to symptomatic MM and survival

Progression-Free Survival N=54	Progression to MM (clinical PFS)
Events, n	2
Median, months	Not Reached
8-year Milestone (95% CI)	91.0% (67.1–97.8%)

Progression-Free Survival N=54	Biochemical Progression (biochemical PFS)	Overall Survival
Events, n	4	0
Median, months	Not Reached	Not Reached
8-year Milestone (95% CI)	80.2% (54.1–92.4%)	100%

Kazanddjian et al. ASH 2020: 548

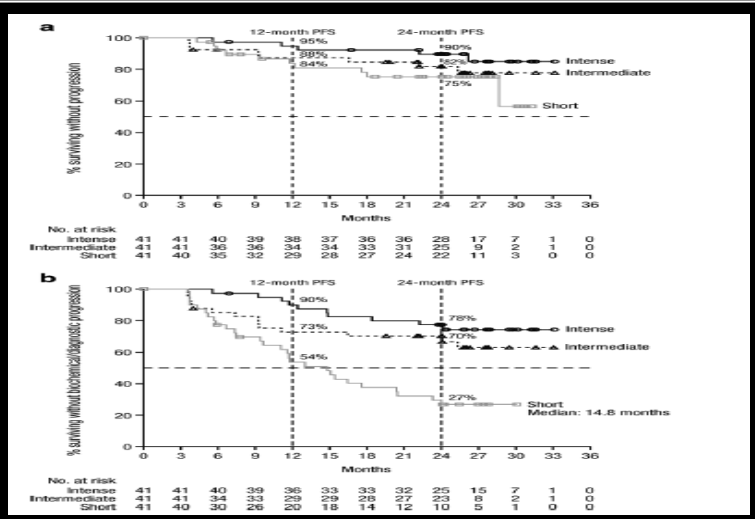
Lenalidomide as backbone for the treatment of intermediate-high risk SMM patients

	Phase	n	ORR/CR/MRD-ve	PFS/OS
Elo-Rd	2	50	84%/6%/NE	100%/1 death
Ixa-Rd	2	48	94%/31%/18%	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				
Isatuximab monotherapy	2	24	63%/-/5% (CRpts)	At 14m: 90%
Dara monotherapy intense/interm/short	2	41/41/41	CR: 4.9%/9.8%/0%	At 24m: 90%/82%/75%

Ghobrial I, et al. ASH 2018: abstract 154
Bustoros M et al. ASH 2019: abstract 804
Landgren O et al. JAMA 2017
Landgren O et al. Leukemia 2020
Manansanch E ASH 2019

Dara monotherapy in SMM patients: phase 2 Centaurus study

	Intense ($n=41$)	Intermediate ($n=41$)	Short ($n=41$)
ORR summary, n[b]	41	41	40[c]
ORR, n (%)	23 (56.1)	22 (53.7)	15 (37.5)
90% CI	42.1–69.4	39.8–67.1	24.7–51.7
CR (sCR + CR) rate	2 (4.9)	4 (9.8)	0
P value[d]	0.9569	0.7567	
90% CI[e]	(0.9–14.6)	(3.4–21.0)	
sCR	2 (4.9)	3 (7.3)	0
CR	0	1 (2.4)	0
VGPR	10 (24.4)	6 (14.6)	7 (17.5)
PR	11 (26.8)	12 (29.3)	8 (20.0)
SD	18 (43.9)	19 (46.3)	25 (62.5)
PD/death rate summary, n[f]	41	41	41
Patients who progressed or died, n (%)	5 (12.2)	8 (19.5)	10 (24.4)
Progressed[g]	5 (12.2)	7 (17.1)	10 (24.4)
Died	0	1 (2.4)	1 (2.4)
Total duration of PFS, patient-years	85.2	75.1	66.6
PD/death rate[h]	0.059	0.107	0.150



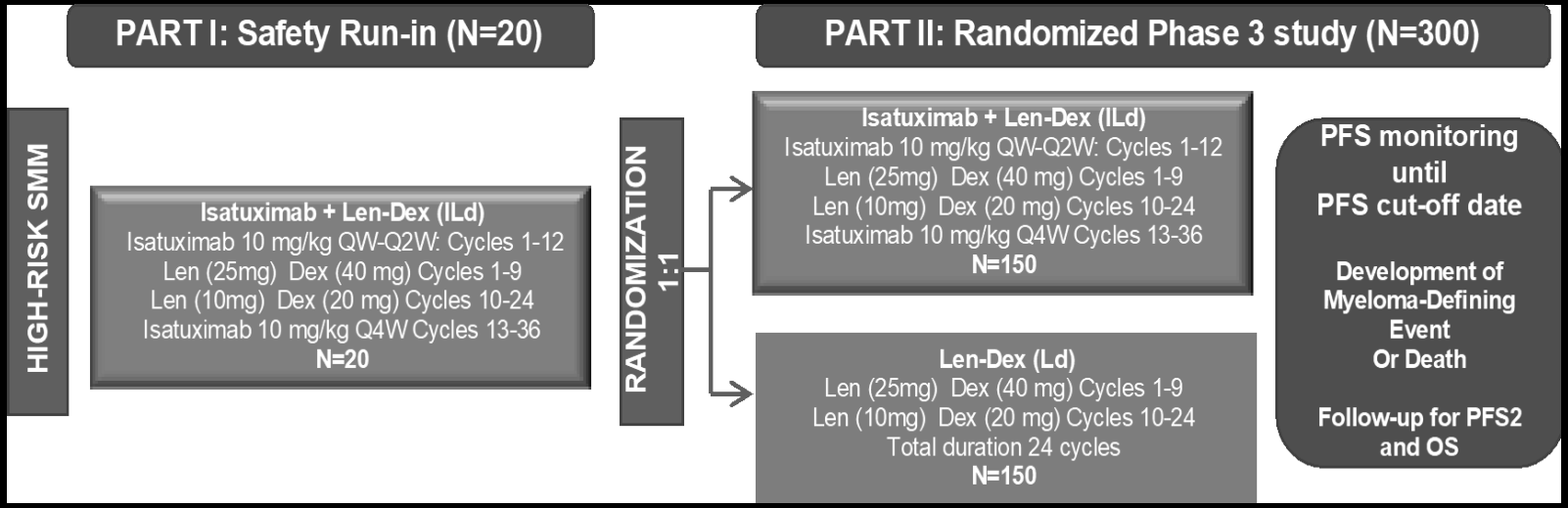
CR rate is not different

Dara monotherapy in the intense scheme delays both PD and BPD

Dara monotherapy in SMM patients: phase 3 Aquila study ongoing

Landgren O et al. Leukemia 2020

Rd plus/minus Isatuximab in HR-SMM patients: phase 3 Ithaca study



Stratification on:

- **Age (≤ 65 vs > 65)**
- **BMPC (<20% vs ≥20%)**
- **Serum involved/uninvolved FLC ratio (≤ 20 vs >20 but ≤100)**

Inclusion criteria:

- **IMWG model 2/20/20**
- **Presence of ≥10% BMPC and at least one of the following: serum M-protein ≥3g/dL, i/uFLC ratio ≥8, ≥95% of BMPCs phenotypically aberrant plus immunoparesis, evolving pattern**

Rd plus/minus daratumumab in HR-SMM patients: phase 3 trial (ECOG)

Patients with high-risk smouldering MM

(N = 288)

24 x 28-day cycles

Lenalidomide 25 mg/day on Days 1-21 +

Dexamethasone 40 mg/day weekly

Daratumumab SC conventional schedule

Lenalidomide 25 mg/day on Days 1-21 +

Dexamethasone 40 mg/day weekly

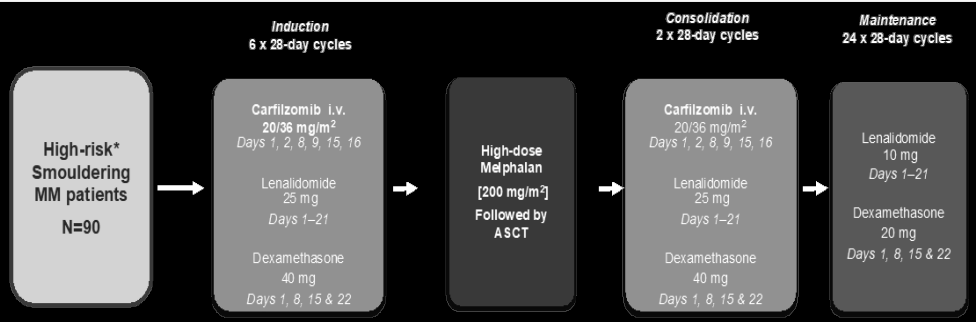
Primary endpoint

- **Overall Survival**
- **Functional Assessment of Cancer-therapy General score**

Inclusion criteria:

- **Presence of ≥10% and less than 60% BMPC and at least one of the following: serum M-protein ≥3g/dL, i/uFLC ratio ≥8, or high risk CA**

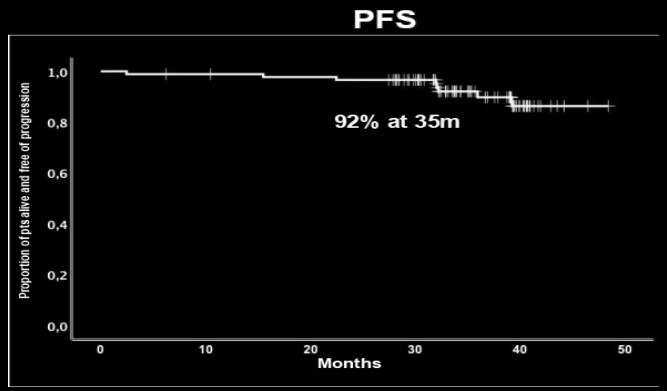
GEM-CESAR:
Primary objective: Sustained MRD –ve rate

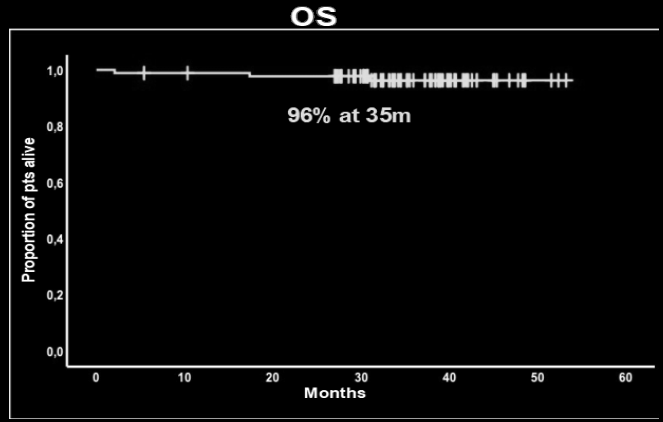


	Induction (KRdx6) N = 90	HDT/ASCT N = 90	Consolidation (KRdx2) N = 90
≥CR	41%	65%	72%
MRD-negative	40%	63%	68%

During maintenance, 7 pts experienced biological progression
The MRD-ve sustained at 1 year after maintenance was 67%

Median follow-up: 35,2 (5.4-53.2)

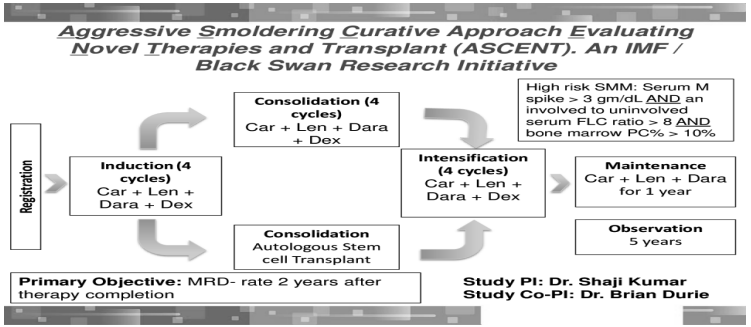




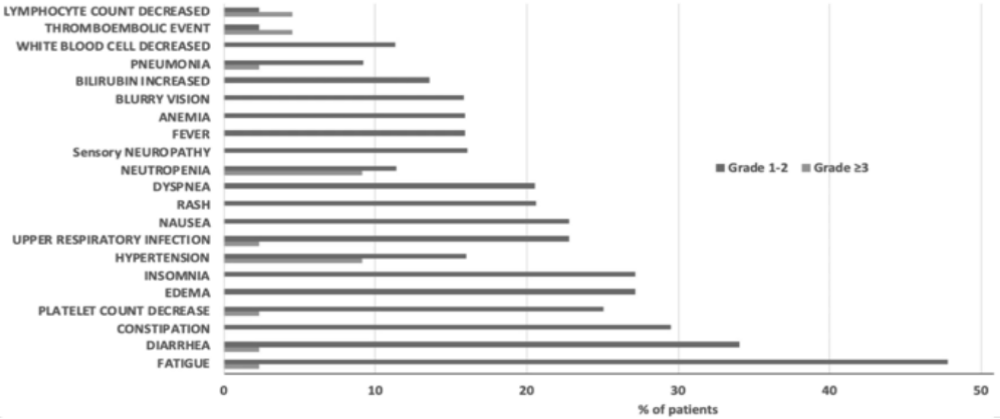
Mateos MV et al. ASH 2019

Aggressive Smoldering Curative Approach Evaluating Novel Therapies and Transplant (ASCENT)

- Primary endpoint: Rate of confirmed sCR
- Secondary objectives: Safety, PFS, OS, MRD negativity



Toxicity profile



Results to date:

- 54 patients accrued
- Median patient age 63 years
- 6% have completed maintenance, 56% consolidation, 80% induction and 17% in induction phase

- ≥1 patient needed a dose modification
- ≥ grade 3 AE seen in 43% of patients

Quadruplet regimen KRd-D is well tolerated in high-risk SMM

AE, adverse event; CR, complete response; KRd-D, carfilzomib, lenalidomide, dexamethasone, daratumumab; MRD, minimal residual disease; OS, overall survival; PFS, progression-free survival; sCR, stringent complete response.

Kumar et al., ASH 2020: Abstract 2285 (poster presentation)

Management of SMM

Management should be risk-adapted and high-risk SMM benefit from early treatment

- **It is possible to identify the high risk subgroup of SMM patients**
- **The oncologic perspective supports the early treatment**
- **The biology of the disease is different,…..**
- **There are phase 3 trials showing a significant benefit for the role of early treatment**

As the treatment for MM patients is rapidly evolving, new approaches will be investigated also in this population

We cannot forget the early treatment will delay or avoid the development of Myeloma-defining events