Highlights from IMW 2021

1-2 febbraio 2022
Bologna
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Smoldering Multiple Myeloma: osservazione vs trattamento

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Prevalence of Smoldering Multiple Myeloma: Results from the Iceland Screens, Treats, or Prevents Multiple Myeloma (iStopMM) Study

- The iStopMM study (Iceland Screens Treats or Prevents Multiple Myeloma) is a nationwide screening study for MM precursors where all residents in Iceland over 40 years of age and older were invited to participate.
- Of the 148,704 individuals over 40 years of age in Iceland, 75,422 (51%) were screened for M-protein and abnormal free light chain ratio.
- A total of 180 patients were diagnosed with SMM
- According to the proposed 2/20/20 risk stratification model for SMM, 116 (64%) patients were low-risk, 47 (26%) intermediate-risk, and 17 (10%) high-risk.
- The prevalence of SMM in the total population was estimated to be **0.53% in individuals 40 years of age or older.** In men and women, the prevalence of SMM was 0.70% and 0.37%, respectively, and it increased with age in both sexes

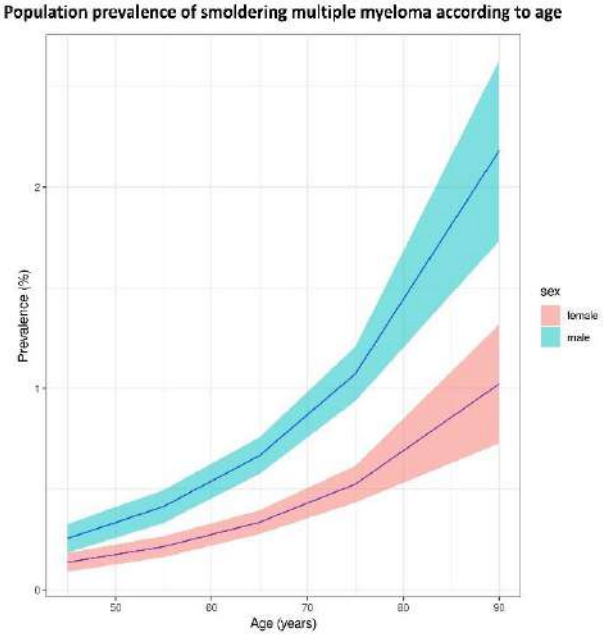
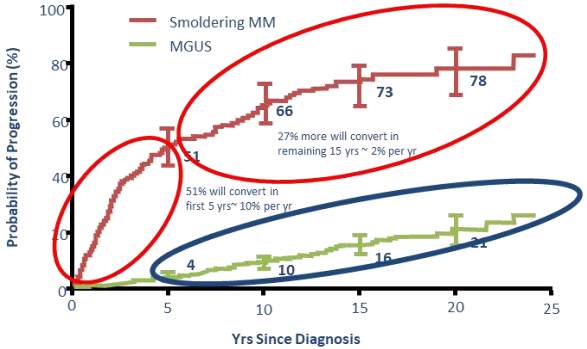


Figure: Estimated prevalence of smoldering multiple myeloma in men and women according to age with 95% confidence intervals.

Thorsteinsdottir S., et al. ASH Meeting 2021, abs. 151

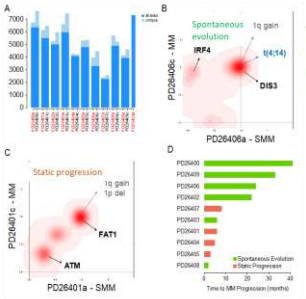
Multiple myeloma spectrum diseases



Kyle RA, et al. N Engl J Med. 2007;356:2582-2590. Greipp PR, et al. J Clin Oncol. 2005;23:3412-3420.

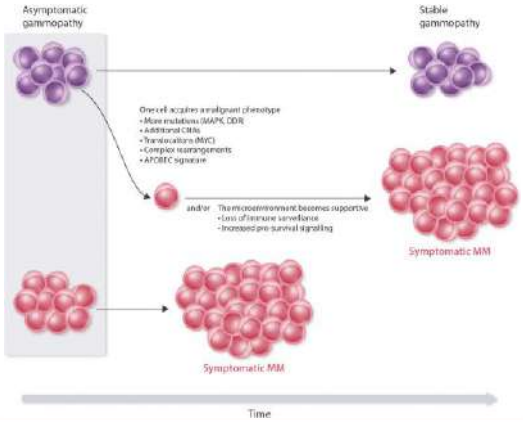
Two genomic routes of evolution from SMM to MM

These cases are
- «de facto» MM already?
- dependent on the microenvironment?



These cases need an evolutionary shift to become myeloma

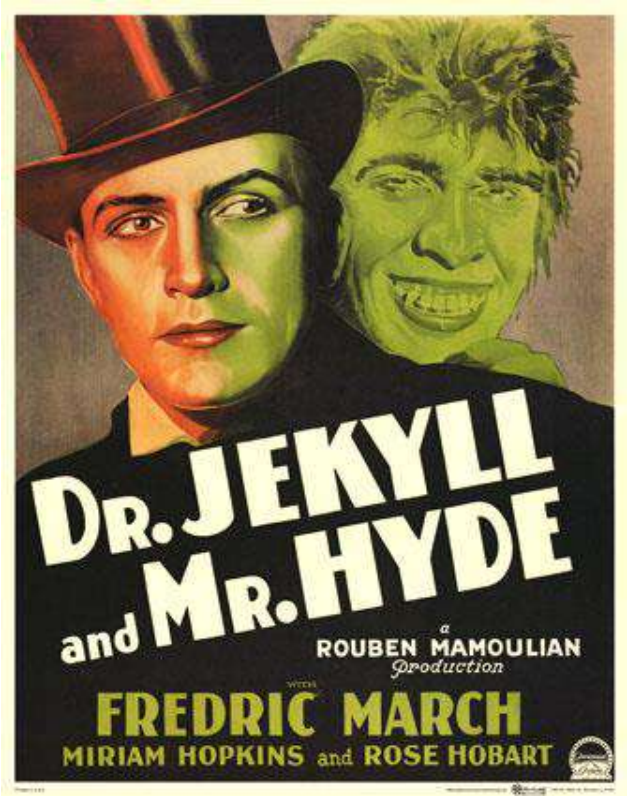
Bolli et al, Nat Comms 2018



Da Via' et al, Hemasphere 2020

Smoldering (but how much «smoldering»?) myeloma: a paradigm for early treatment?

From a bioloigcal point of view, SMM is an heterogeneous disease: it may present characteristics that are similar to those of MGUS, with a true indolent and asymptomatic clinical outcome, or are, instead, more similar to those observed in patients with overt, symptomatic myeloma, with a significantly higher probability of progression.



Robert Louis Stevenson

Table 2. Most recent prognostic models for smoldering multiple myeloma.

Model	Risk factors	Risk Group	2-year PD rate (%)	Median TTP (months)
SWOG 2014[67]	MC >3 g/dL, sFLC >25 mg/dL, GEP-70 >0.26	Low (0 factors), n=60	3.4	
		Intermediate (1 factor), n=39	21.9	
		High (≥2 factors), n=18	66.7	
Mayo 2018[68]	sFLCr >20, MC >2 g/dL, BMPC >20%	Low (0 factors), n=143	9.7	109.8
		Intermediate (1 factor), n=121	26.3	67.8
		High (≥2 factors), n=153	47.4	29.2
IMWG 2020[69]	MC >2 g/dL, sFLCr >20, BMPC >20%	Low (0 factors), n=522	6	
		Intermediate (1 factor), n=445	18	
		High (≥2 factors, n=396	44	
	+ high risk cytogenetics: [t(4;14), t(14;16), +1q, del(13q)]	Low (0 factors/score 0-4) *, n=241	6/3.8	
		Low-intermediate (1 factor/score 5-8), n=264	22/26.2	
		Intermediate (2 factors/score 9-12), n=233	45.5/51.1	
		High (3-4 factors/score >12), n=51	63.1/72.5	
CMG 2020[70]	Immunoparesis (at least one uninvolved immunoglobulin below reference levels), sFLCr >30, MC ≥2.3 g/dL	Low (0 factors), n=48/26 **	8.5 / 5.3 **	
		Intermediate (1 factor), n=44/34	20.9 / 7.5	
		High (2 factors), n=32/41	41.9 / 44.8	
		Very high (3 factors), n=15/12	78.7 / 81.3	
Dana Farber 2020[71]	DNA repair pathway gene alterations [mutations in *TP53* and *ATM*, del(17p)], MAPK pathway gene mutations (*KRAS*, *NRAS*), *MYC* aberrations (translocations or copy-number variations).	0 factors, n=58	86.4	
		At least 1 factor, n=24	14.4	

PD: progressive disease; TTP: time to progression; SWOG; Southwest Oncology Group;.MC: monoclonal component; sFLC: serum free light chains; sFLCr: serum free light chain ratio; BMPC: bone marrow plasma cells; GEP-70: University of Arkansas Medical Sciences 70-gene expression profile signature; CMG: Czech Myeloma Group. *sFCLr score: <10: 0; 10-25: 2; >25-40: 3; >40: 5. MC score: 0-1.5 g/dL: 0; >1.5-3 g/dL: 3; >3 g/dL: 4. BMPC score: 0-15%: 0; >15-20%: 2; >20-30%: 3; >30-40%: 5; >40%: 6. ** Validation cohort.

Musto et al, Haematologica 2021

Blood Cancer Journal

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ARTICLE OPEN

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Assessing the prognostic utility of smoldering multiple myeloma risk stratification scores applied serially post diagnosis

Alissa Visram[1,2], S. Vincent Rajkumar[1], Prashant Kapoor[1], Angela Dispenzieri[1], Martha Q. Lacy[1], Morie A. Gertz[1], Francis K. Buadi[1], Suzanne R. Hayman[1], David Dingli[1], Taxiarchis Kourelis[1], Wilson Gonsalves[1], Rahma Warsame[1], Eli Muchtar[1], Nelson Leung[3], Linda B. Baughn[4,5], Robert A. Kyle[1] and Shaji Kumar[1]

The Mayo-2018 smoldering multiple myeloma (SMM) risk score is used routinely in the clinical setting but has only been validated at diagnosis. In SMM patients, the progression risk decreases over time. However, the utility of applying risk stratification models after diagnosis is unknown. We retrospectively studied 704 SMM patients and applied the Mayo 2018 and IMWG-2020 risk stratification models at annual landmark timepoints up to 5 years post diagnosis. The Mayo-2018 and IMWG-2020 models reliably stratified patients based on progression risk when applied post diagnosis. The respective 2-year progression risk in Mayo-2018 high risk patients versus IMWG-2020 intermediate-high risk patients was 51% versus 62% at the 1-year landmark and 47% versus 45% at the 4-year landmark. We showed that patients categorized at Mayo-2018 high-risk at follow-up had a similar risk of progression if the baseline risk assessment was low-intermediate versus high-risk (HR 1.04, 95% CI 0.46–2.36, $p = 0.931$ at 5-year landmark). Patients migrating to a higher risk category during follow up had a higher progression risk compared to patients with stable/decreased risk categorization. Our findings support the use of these risk scores post-diagnosis and suggest that patients evolving to a high-risk category may benefit from early intervention therapeutic approaches.

Blood Cancer Journal (2021)11:186 ; https://doi.org/10.1038/s41408-021-00569-2

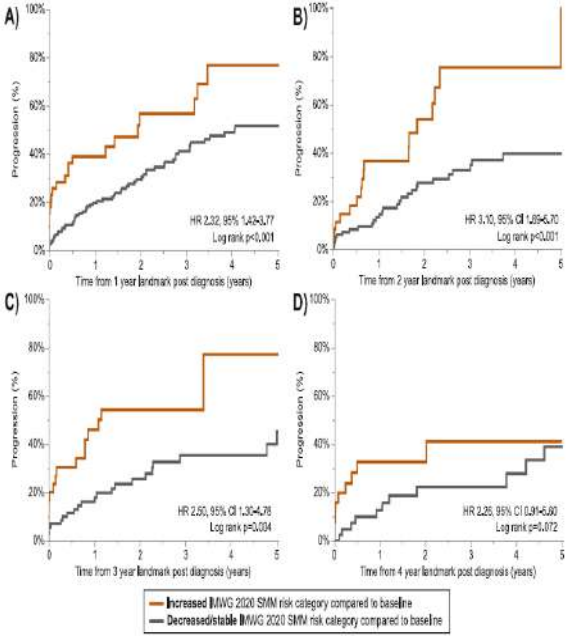

Fig. 5 The time to progression, stratified by migration of SMM IMWG 2020 risk category during follow up. Patients were grouped based on whether the IMWG 2020 category at follow up was increased or stable/decreased compared to baseline. The stage migration of SMM patients without progression at 1 year (**A**), 2 years (**B**), 3 years (**C**), and 4 years (**D**) post SMM diagnosis is shown. The percentage of patients evolving to a higher risk category was 20% at the 1-year landmark, 26% at the 2-year landmark, 30% at the 3-year landmark, and 36% at the 5-year landmark.

HEMATOLOGIC MALIGNANCIES

The Role of Early Intervention in High-Risk Smoldering Myeloma

Nisha S. Joseph, MD[1]; Madhav V. Dhodapkar, MBBS[1]; and Sagar Lonial, MD, FACP[1]

overview

Smoldering multiple myeloma (SMM) is a precursor disease state that precedes the development of symptomatic myeloma. As we have learned more about the disease biology of SMM and risk factors for progression, updated risk stratification models, such as the Mayo 2018 model, or 20/2/20, have been developed. More accurate risk stratification and the development of effective and well-tolerated therapeutic agents have led to the investigation of early treatment of select patients with high-risk SMM with the aim of delaying time to progression to multiple myeloma. Ongoing debate surrounds which subset of patients with SMM to target, as well as the best treatment approach: preventative versus curative. Phase III data from the Spanish Myeloma Group/PETHEMA as well as the Eastern Cooperative Oncology Group (ECOG) E3A06 trial have shown the efficacy of lenalidomide with and without dexamethasone in high-risk SMM in delaying progression to symptomatic disease. Conversely, there exists an alternate strategy attempting to cure the disease prior to progression utilizing more intensive regimens similar to what is used for patients with newly diagnosed myeloma. However, our understanding of the disease biology of SMM and the role of immune regulation in preventing malignant transformation provides a strong rationale for an interventional strategy. Here, we review the definition of SMM, the current models for risk stratification, and the current data available supporting the early treatment of patients with high-risk SMM.

HEMATOLOGIC MALIGNANCIES

Treatment of Smoldering Multiple Myeloma: Expectant Observation Should Still Be the Standard

Rafael Fonseca, MD[1] and Miguel Gonzalez-Velez, MD[1]

overview

Recent clinical trials have addressed the notion of early treatment of smoldering multiple myeloma (SMM). The results evidence improvement in progression-free survival and, in one study, overall survival. Although the treatment of SMM can be considered under specific circumstances, we propose here that careful interpretation of the clinical trials and the patient-specific data are needed before recommending therapy. In particular, many questions remain regarding the best regimen to be used as well as how to adapt based on the underlying disease biology. Hematologists should have a very thorough understanding of models designed to predict the progression from SMM to multiple myeloma, because their correct interpretation is paramount to establish proper care. Although there is no doubt that treatment should be started before overt end-organ damage, we do not believe that the current data support the widespread treatment of all SMM.

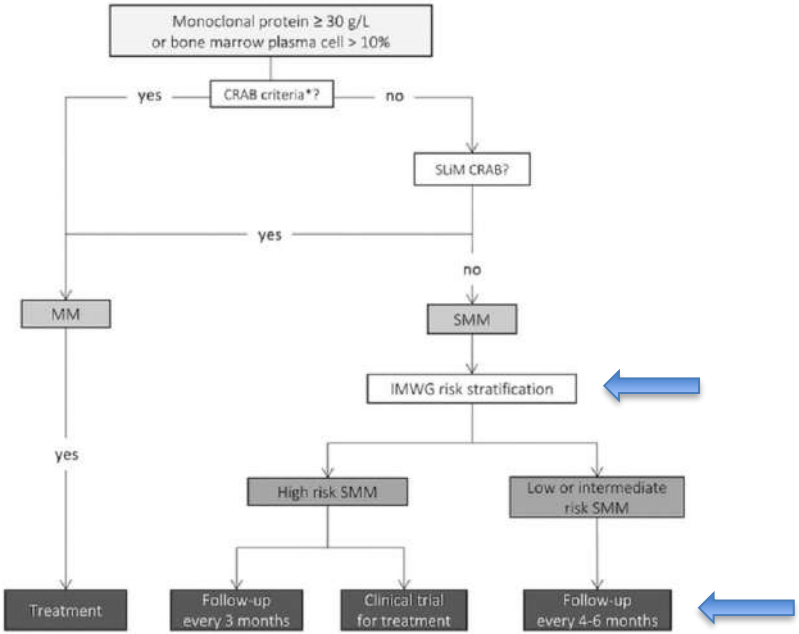

Figure 1. Algorithm for diagnosis and identification and management of high-risk SMM. MM: multiple myeloma; SMM: smoldering multiple myeloma; CRAB: calcemia; renal failure; anemia; bone lesions. M-protein: monoclonal protein; SLiM-CRAB: serum free light chain ratio ≥ 20 g/L; bone marrow plasma cell.

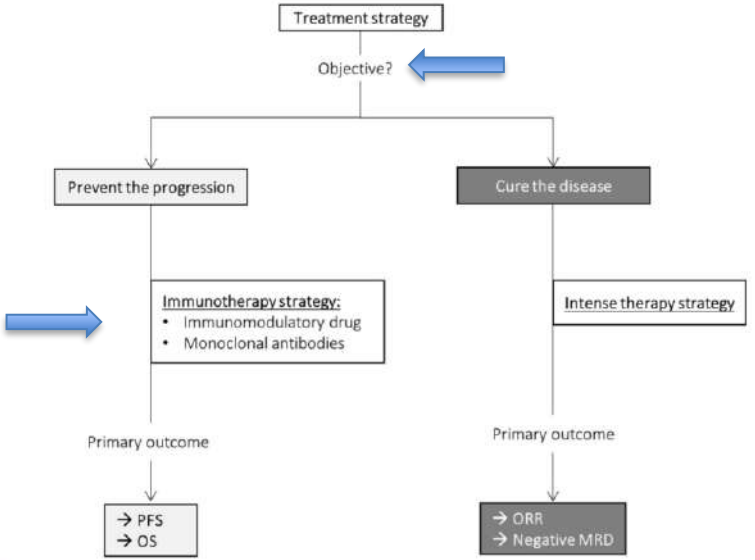

Figure 2. Therapeutic approaches for SMM in the context of clinical trial. PFS: progression-free survival; OS: overall survival; OR; overall response rate; MRD: minimal residual disease

Nsiala et al, Leuk Lymphoma 2021

Table 1. Summary of selected phase 2 and 3 studies within reported outcome data within the past decade

Trial name/date	Study design	Criteria for defining SMM patient inclusion	Intervention (I) and control (C) arms	Median follow-up	Key outcomes
QUIREDEX Mateos et al (2013, updated 2016)[59,60]	Phase 3 Randomized, open label	SMM (diagnosed <5 years) and either: • BM PC ≥10% and M-protein (IgG ≥3 g/dL, IgA ≥2 g/dL, Bence-Jones proteinuria >1 g/24h) • BM PC ≥10% or M-protein (defined as above), with ≥95% aberrant PC and immunoparesis (≥1 uninvolved immunoglobulin >25% below LLN)	• I: Lenalidomide and dexamethasone (n=57)—Lenalidomide 25 mg×21/28 days for 9 cycles, then 10 mg×21/28 days for a 2-year total duration. Dexamethasonase 20mg days 1–4 and days 12–15 of first 9 cycles and days 1–4 at biochemical progression. • C: Observation (n=62)	75 months*	Primary outcome—TTP (progression defined as end-organ damage) • Median TTP (I vs C): NR vs 23 months (HR, 0.24; 95% CI, 0.14–0.41) Secondary outcome—OS • Median OS (I vs C): NR in both groups (HR, 0.43; 95% CI, 0.21–0.92)
ECOG-ACRIN E3A06 Lonial et al (2019)[19]	Phase 2/3 Randomized, open label	SMM (diagnosed <5 years) with ≥10% PCs and abnormal sFLC ratio (<0.26 or >1.65)	• I: Lenalidomide (n=90)—25 mg (days 1–21 of 28 days), until progression or toxicity • C: Observation (n=92)	35 months	Primary outcome—PFS (progression defined as biochemical progression in addition to end-organ damage): • 3-year PFS (I vs C)—91% vs 66%, (HR, 0.28; 95% CI, 0.12–0.65) Additional outcomes (I vs C): • PFS in high-risk SMM subgroup (n=56)—HR, 0.09 (95% CI, 0.02–0.44) • OS—HR, 0.46 (95% CI, 0.08–2.53)
CENTAURUS Landgren et al (2020)[61]	Phase 2 Randomized, open label	SMM (diagnosed <5 years) with absence of SLiM or CRAB criteria and 1 of: • Serum M-protein ≥ 3 g/dL • iFLC/uFLC >8 if serum M-protein 1–3 g/dL • Urine M-protein >500 mg/24 h • Serum iFLC ≥100 mg/dL (if iFLC/uFLC between 8 and 99)	3 arms based on daratumumab 16-mg/kg IV dosing schedule: • Intense (n=41)—Q1W×8, Q2W×8, Q4W×8, Q8W×8 • Intermediate (n=41)—Q1W×8, Q8W×19 • Short (n=41)—Q1W×8	25.8 months (prespecified primary analysis)	Co-Primary endpoint—≥ Complete response rate: • Intense arm—4.9% • Intermediate arm—9.8% • Short arm—0% Co-Primary endpoint—Progression† (progression defined as biochemical or end-organ damage) or death rate per patient year: • Intense arm—4.9% • Intermediate arm—9.8% • Short arm—0%

*Median follow-up for surviving patients.[60]

†Progression was defined based on the IMWG 2014 diagnostic criteria for MM, as well as the IMWG FLC progression criteria (a ≥25% increase from nadir in the difference between involved and uninvolved FLC with absolute increase >10 mg/dL).

C, control arm; CRAB, C-hyperCalcemia, R-Renal impairment, A-Anemia, B-Bone lesions related to multiple myeloma; iFLC, involved FLC; I, intervention arm; IV, intravenous; LLN, lower limit of normal; NR, not reached; sFLCr, serum FLC ratio; uFLC, uninvolved FLC.

Visram et al, ASH 2021 Education Book

Highlights from IMW 2021

1-2 Febbraio 2022
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Lenalidomide plus dexamethasone versus observation in patients with high-risk smouldering multiple myeloma (QuiRedex): long-term follow-up of a randomised, controlled, phase 3 trial

María-Victoria Mateos, Miguel-Teodoro Hernández, Pilar Giraldo, Javier de la Rubia, Felipe de Arriba, Lucía López Corral, Laura Rosiñol, Bruno Paiva, Luis Palomera, Joan Bargay, Albert Oriol, Felipe Prosper, Javier López, José-María Arguiñano, Nuria Quintana, José-Luis García, Joan Bladé, Juan-José Lahuerta, Jesús-F San Miguel

Summary

Background The standard of care for smouldering multiple myeloma is observation. We did the QuiRedex study to compare early treatment with lenalidomide plus dexamethasone with observation in patients with high-risk smouldering multiple myeloma. Here we report the long-term follow-up results of the trial.

Methods We did this open-label, randomised, controlled phase 3 study at 19 centres in Spain and three centres in Portugal. Patients aged 18 years or older with high-risk smouldering multiple myeloma were randomly assigned (1:1), via a computerised random number generator, to receive either early treatment with lenalidomide plus dexamethasone or observation, with dynamic balancing to maintain treatment balance within the two groups. Randomisation was stratified by time from diagnosis of smouldering multiple myeloma to study enrolment (≤6 months *vs* >6 months). Patients in the treatment group received nine 4-week induction cycles (lenalidomide 25 mg per day on days 1–21, plus dexamethasone 20 mg per day on days 1–4 and days 12–15), followed by maintenance therapy (lenalidomide 10 mg per day on days 1–21 of each 28-day cycle) up to 2 years. Group allocation was not masked from study investigators or patients. The primary endpoint was time from randomisation to progression to symptomatic myeloma. The primary analysis was based on the per-protocol population, restricted to patients who fulfilled the protocol in terms of eligibility. Safety assessments were based on the intention-to-treat population. This trial is registered with ClinicalTrials.gov, number NCT00480363.

Findings Between Nov 8, 2007, and June 9, 2010, 125 patients were enrolled and underwent randomisation. 119 patients comprised the per-protocol population and were randomly assigned to receive either lenalidomide plus dexamethasone (n=57) or observation (n=62). The cutoff date for this update was June 30, 2015. Median follow-up for surviving patients was 75 months (IQR 67–85). Lenalidomide plus dexamethasone continued to provide a benefit on time to progression compared with observation (median time to progression not reached [95% CI 47 months–not reached] *vs* 23 months [16–31]; hazard ratio [HR] 0·24 [95% CI 0·14–0·41]; p<0·0001). Progression to multiple myeloma occurred in 53 (86%) of 62 patients in the observation group compared with 22 (39%) of 57 patients in the treatment group. At data cutoff, ten (18%) patients had died in the treatment group and 22 (36%) patients had died in the observation group; median overall survival from the time of study entry had not been reached in either group (95% CI 65 months–not reached *vs* 53 months–not reached; HR 0·43 [95% CI 0·21–0·92], p=0·024). Survival in patients who had received subsequent treatments at the time of progression to active disease did not differ between groups (HR 1·34 [95% CI 0·54–3·30]; p=0·50). The most frequently reported grade 3 adverse events in patients given lenalidomide plus dexamethasone were infection (four [6%]), asthenia (four [6%]), neutropenia (three [5%]), and skin rash (two [3%]); these events all occurred during induction therapy. No grade 4 adverse events occurred, but one (2%) patient in the lenalidomide plus dexamethasone group died from a respiratory infection during induction therapy. The frequency of second primary malignancies was higher in patients in the treatment group than in those in the observation group (six [10%] of 62 patients *vs* one [2%] of 63 patients), but the cumulative risk of development did not differ significantly between the groups (p=0·070).

Interpretation This study is, to our knowledge, the first randomised trial in which early treatment has been assessed in selected patients with high-risk smouldering multiple myeloma. Positive results from ongoing trials would support the use of early treatment for patients with high-risk disease in the near future.

Median follow-up surviving patients 75 months

Lancet Oncol 2016; 17: 1127–36

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See Comment page 1030

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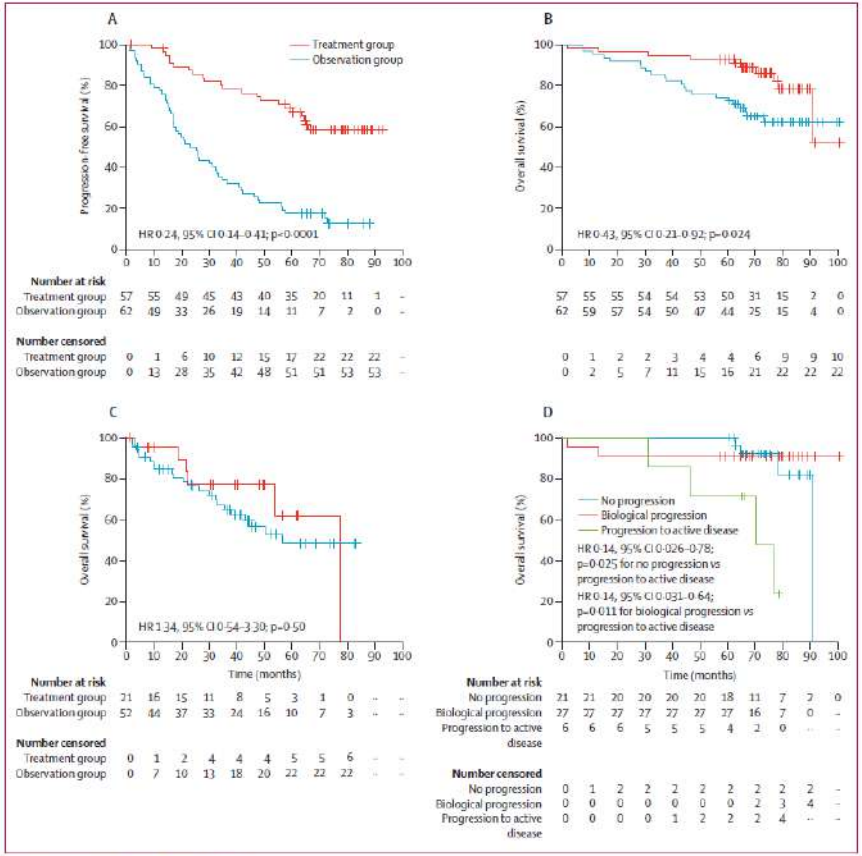


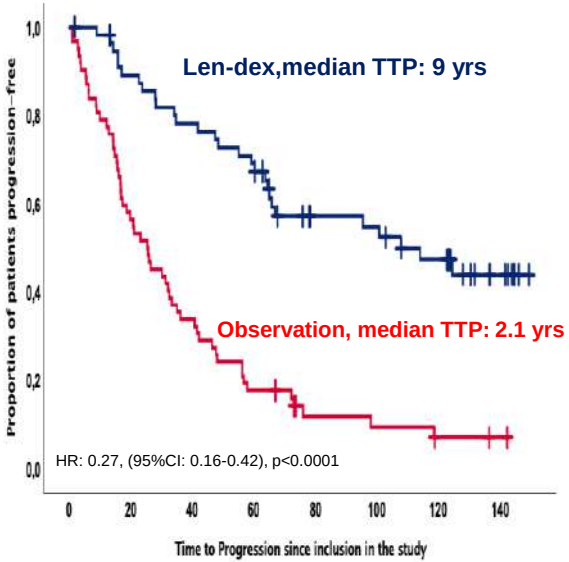
Figure 2: **Progression-free and overall survival**
(A) Time to progression to myeloma. (B) Overall survival from the point of enrolment into the trial. (C) Overall survival from the point of progression to myeloma. (D) Overall survival from the point of inclusion in the trial according to type of progression versus no progression. Vertical lines indicate censored patients. HR=hazard ratio.

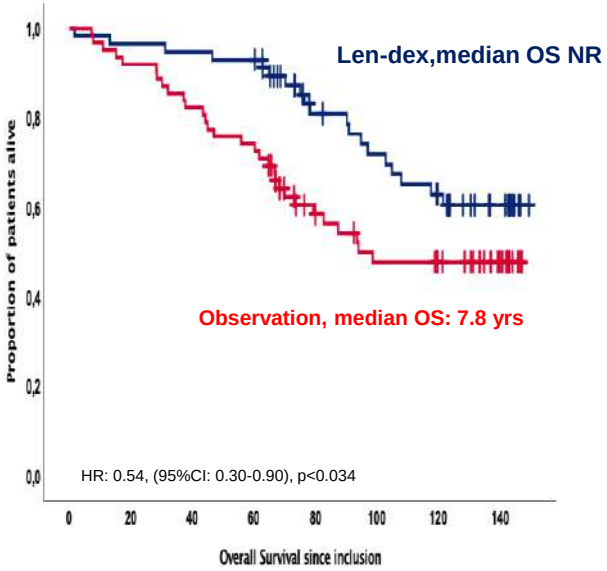
QuiRedex:

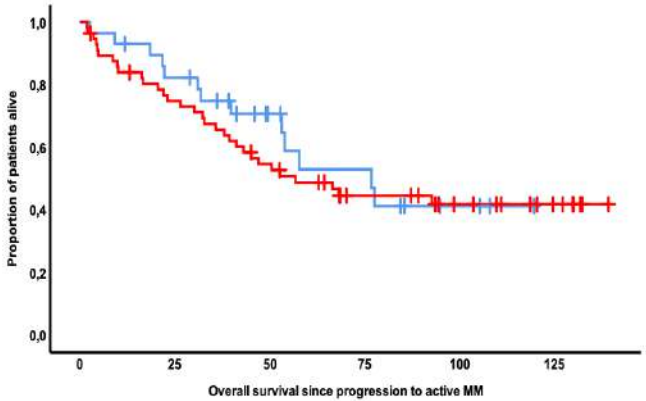
Len-dex vs no treatment: TTP to active disease (n = 119)

Per-protocol Patients population

Median follow-up: 10.8 years







Early treatment does not induce more resistant relapses

46% reduction in the risk of death and 73% in that of progression for the early treatment vs not treatment.

Mateos MV, et al. EHA 2020

Randomized Trial of Lenalidomide Versus Observation in Smoldering Multiple Myeloma

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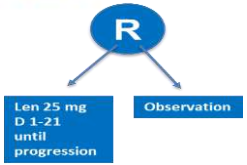


PURPOSE Observation is the current standard of care for smoldering multiple myeloma. We hypothesized that early intervention with lenalidomide could delay progression to symptomatic multiple myeloma.

METHODS We conducted a randomized trial that assessed the efficacy of single-agent lenalidomide compared with observation in patients with intermediate- or high-risk smoldering multiple myeloma. Lenalidomide was administered orally at a dose of 25 mg on days 1 to 21 of a 28-day cycle. The primary end point was progression-free survival, with disease progression requiring the development of end-organ damage attributable to multiple myeloma and biochemical progression.

RESULTS One hundred eighty-two patients were randomly assigned—92 patients to the lenalidomide arm and 90 to the observation arm. Median follow-up is 35 months. Response to therapy was observed in 50% (95% CI, 39% to 61%) of patients in the lenalidomide arm, with no responses in the observation arm. Progression-free survival was 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 progression-free survival was 98%, 93%, and 91% for the lenalidomide arm versus 89%, 76%, and 66% for the observation arm, respectively. Only six deaths have been reported, two in the lenalidomide arm versus four in the observation arm (hazard ratio for death, 0.46; 95% CI, 0.08 to 2.53). Grade 3 or 4 nonhematologic adverse events occurred in 25 patients (28%) on lenalidomide.

CONCLUSION Early intervention with lenalidomide in smoldering multiple myeloma significantly delays progression to symptomatic multiple myeloma and the development of end-organ damage.

J Clin Oncol 38:1126-1137. © 2019 by American Society of Clinical Oncology

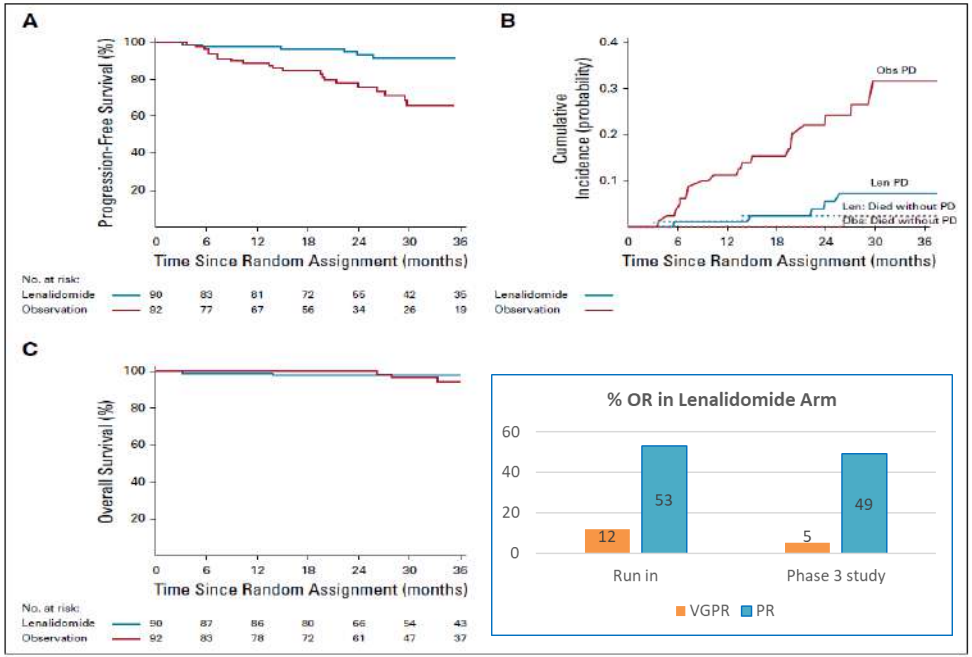


FIG 2. Time to event estimates by treatment arm in phase III: (A) progression-free survival, (B) cumulative incidence of progression, and (C) overall survival in patients with smoldering multiple myeloma. Len, lenalidomide; Obs, observation.

Median follow-up 35 months

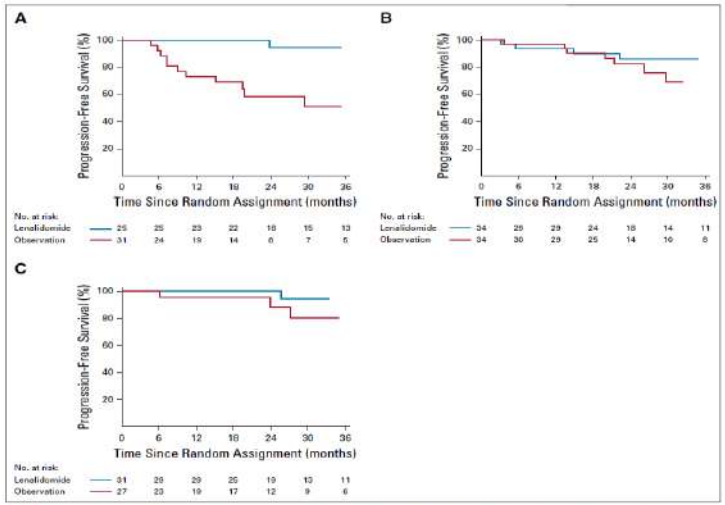
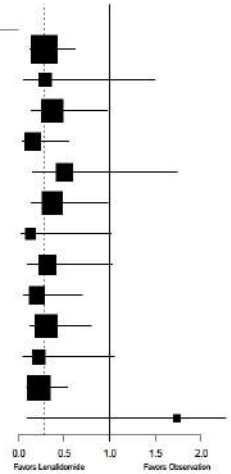
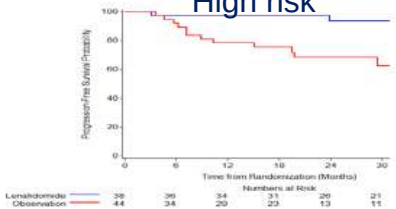


FIG 5. Kaplan-Meier estimates of progression-free survival by treatment arm within Mayo 2018 risk subgroup: (A) high risk, (B) intermediate risk, and (C) low risk.

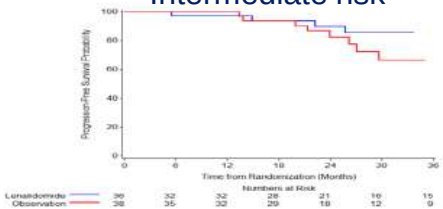
Group	N	HR	95% CI
All Patients	182	0.28	(0.12, 0.62)
Mayo 2008 Risk High	29	0.29	(0.06, 1.49)
Mayo 2008 Risk Intermediate	104	0.37	(0.14, 0.97)
Mayo 2018 Risk High	87	0.15	(0.04, 0.55)
Mayo 2018 Risk Intermediate	70	0.50	(0.15, 1.73)
Age <70	135	0.37	(0.14, 0.98)
Age >=70	47	0.13	(0.02, 1.01)
Male	88	0.32	(0.10, 1.03)
Female	94	0.20	(0.06, 0.70)
ECOG PS 0	134	0.30	(0.12, 0.79)
ECOG PS 1–2	48	0.22	(0.05, 1.05)
White	140	0.22	(0.09, 0.54)
Black	31	1.73	(0.10, 30.76)



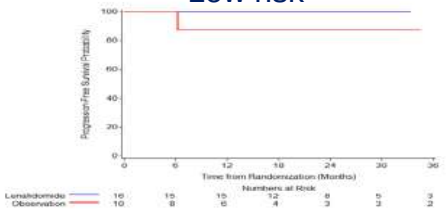
High risk



Intermediate risk



Low risk



IMWG 2019 model: 2/20/20

Both these studies raised some concerns and have not changed the current "no treatment" paradigm, due to several limitations:

- Their sample size was limited, with less than 100 patients in each arm.
- The Spanish study was conducted between 2007 and 2013, when some new MM drugs were not available, while bone involvement was assessed by a low-sensitivity technique like plan radiograph.
- In the US trial, the high discontinuation rate voluntarily or because of adverse effects in the experimental treatment; the fact that the group achieving the most significant benefit with lenalidomide in terms of PFS included only 25 patients could be a concern.
- Both studies started before the 2014 update criteria had been settled, therefore, a proportion of the patients enrolled were likely to be reclassified as having active disease.
- Clinical results of the studies were not presented to the regulatory agencies for the drug authorization in the market.

Highlights from IMW 2021

1-2 Febbraio 2022
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ARTICLE

Multiple myeloma gammopathies

Daratumumab monotherapy for patients with intermediate-risk or high-risk smoldering multiple myeloma: a randomized, open-label, multicenter, phase 2 study (CENTAURUS)

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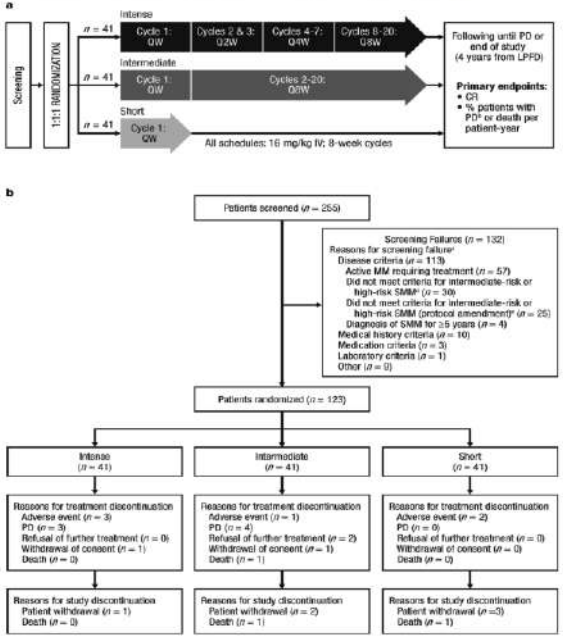
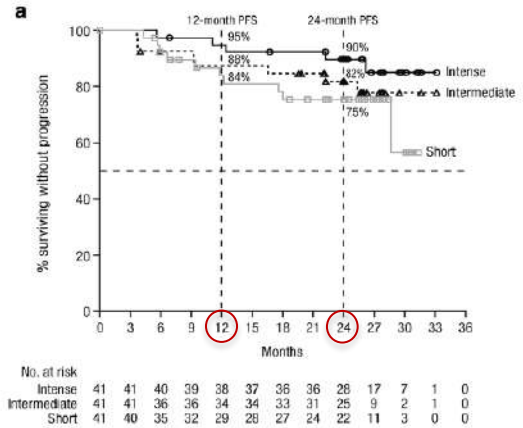
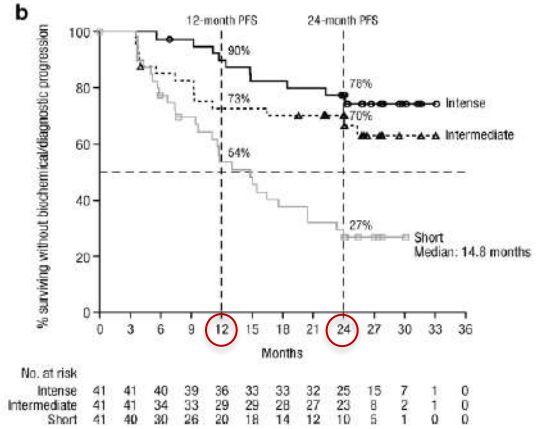
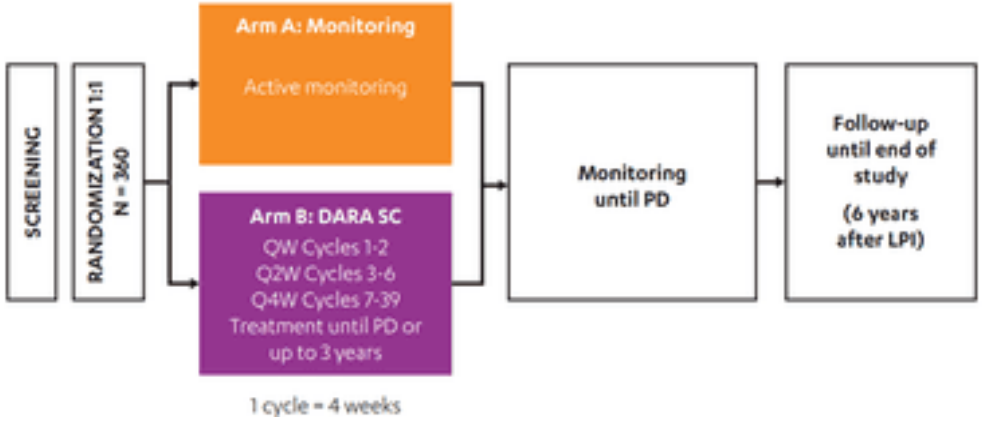






	Intense ($n = 41$)	Intermediate ($n = 41$)	Short ($n = 41$)
ORR summary, n[b]	41	41	40[c]
ORR, n (%)	23 (56.1)	22 (53.7)	15 (37.5)
90% CI	42.1–69.4	39.8–67.1	24.7–51.7
CR (sCR + CR) rate	2 (4.9)	4 (9.8)	0
P value[d]	0.9569	0.7567	
90% CI[e]	(0.9–14.6)	(3.4–21.0)	
sCR	2 (4.9)	3 (7.3)	0
CR	0	1 (2.4)	0
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
P value[i,j]	<0.0001	<0.0001	<0.0001
80% CI[j]	(0.0251–0.0923)	(0.0583–0.1548)	(0.0893–0.2110)
Biochemical PFS, n	41	41	41
Patients who progressed or died, n (%)	7 (17.1)	13 (31.7)	25 (61.0)
Median PFS, months (90% CI)	NR (NE–NE)	NR (NE–NE)	15.1 (11.6–23.3)
12-month PFS rate, % (90% CI)	94.9 (84.5–98.4)	77.7 (64.6–86.5)	58.0 (43.6–69.9)
24-month PFS rate, % (90% CI)	84.3 (71.6–91.7)	70.2 (56.5–80.3)	31.5 (19.2–44.6)

AQUILA trial: Study Design



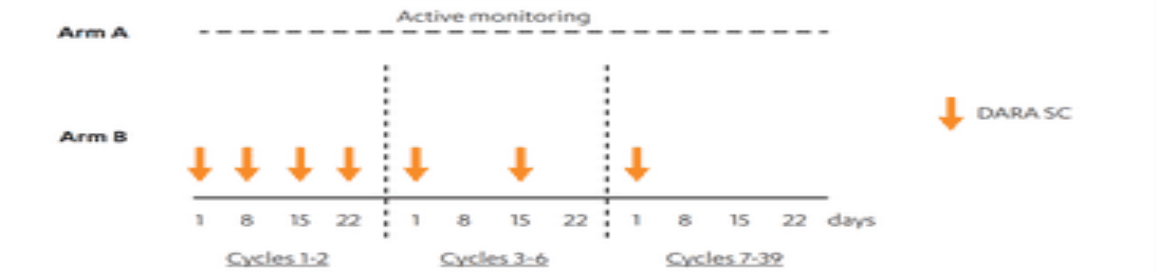


Table 2. Active or planned phase 2 and 3 studies for intermediate- and high-risk SMM

Study (clinicaltrials.gov identifier)	Phase	Estimated enrollment	Recruitment status	Estimated study completion date	Interventions	Primary end point	Preliminary efficacy data reported
NCT04270409	Phase 3 Randomized	300	Recruiting	2033	• Intervention arm: Isatuximab + Rd • Control arm: Rd	PFS	—
DETER-SMM NCT03937635	Phase 3 Randomized	288	Recruiting	2028	• Intervention arm: DRD • Control arm: Rd • Both arms treated for up to 24 cycles (in the absence of disease progression or unacceptable toxicity)	OS and FACT-G score (quality-of-life measure)	—
AQUILA NCT03301220	Phase 3 Randomized	390	Active, not recruiting	2025	• Intervention: subcutaneous daratumumab • Control: observation	PFS	—
NCT03850522	Phase 2a Single arm	20	Recruiting	2021	• PD-L1 peptide vaccination subcutaneously every 2 weeks (total 26-week treatment duration)	ORR (≥PR)	—
NCT03839459	Phase 2 Single arm	20	Recruiting	2024	• Subcutaneous Denosumab every 4 weeks	Reduction in SMM risk category	—
ASCENT NCT03289299	Phase 2 Single arm	83	Recruiting	2026	• D-KRD×6 cycles (induction) • D-KRD×6 cycles (consolidation) • DR×12 cycles (maintenance)	Stringent CR at any point during treatment	(Only safety data reported to date)
HO147SMM NCT03673826	Phase 2 Randomized	120	Recruiting	2025	• Intervention arm: KRD×9 cycles → R alone (up to 24 cycles) • Control arm: Rd×9 cycles → R alone (up to 24 cycles)	PFS	—
NCT04775550	Phase 2 Single arm	30	Not yet recruiting	2026	• D-VRD×up to 24 cycles (in absence of disease progression or toxicity)	2-y MRD−rate	—
NCT04776395	Phase 2	68	Not yet recruiting	2023	• Arm A: Iberdomide + dexamethasone×4 cycles (induction) → Iberdomide alone until disease progression or unacceptable toxicity • Arm B: Iberdomide alone until disease progression or unacceptable toxicity	ORR (≥PR)	—
E-PRISM NCT02279394[122]	Phase 2 Single arm	51	Active, not recruiting	2023	• Elotuzumab + Rd×8 cycles (induction) → Elotuzumab + R×cycles 9–24 (maintenance)	PFS	• Median follow-up not reported (n=50) • PFS data NR • ORR 84%, CR 6%
NCT02916771[43]	Phase 2 Single arm	55	Active, not recruiting	2024	• Ixazomib + Rd×9 cycles (induction) → Ixazomib + R cycles 10–24 (maintenance)	PFS	• Median 8 cycles completed (n=26) • No progression to date • ORR 89%, CR 19%
NCT02960555[44]	Phase 2 Single arm	61	Active, not recruiting	2022	• Intervention: Isatuximab IV×up to 30 cycles (in absence of disease progression or toxicity)	ORR (≥PR)	• Median 11.5 cycles completed (n=24) • ORR 62.5%
GEM-CESAR NCT02415413[45,46]	Phase 2 Single arm	90	Active, not recruiting	2027	• KRD×6 cycles (induction) → melphalan conditioning and ASCT (intensification) → KRD×2 cycles (consolidation) → Rd×2 years (maintenance)	MRD−NGF (next generation flow) postinduction and ASCT	• Median follow-up 32 months (n=90) • MRD−: 30% postinduction, 52% post-ASCT, 57% postconsolidation • MRD− and ≥CR: 23% postinduction, 44% post-ASCT, 55% postconsolidation
NCT01572480[47]	Phase 1/2 Single arm	52	Active, not recruiting	2025	• Phase 1: KRD×8 cycles (induction) → R alone for 12 cycles (maintenance) • Phase 2: KRD×8 cycles (induction) → R alone for up to 24 cycles (maintenance)	MRD−CR (NGF, $\leq 10^{-5}$ sensitivity)	• Median follow-up 27.3 months (n=52) • MRD−CR: 70.2 months

ASCT, autologous stem cell transplant; D-KRD, daratumumab, carfilzomib, lenalidomide, and dexamethasone; DRD, daratumumab, lenalidomide, and dexamethasone; D-VRD, daratumumab, lenalidomide, dexamethasone; FACT-G, functional assessment of cancer therapy-general; IV, intravenous; ORR, overall response rate; NGF, next generation flow; PR, partial response.

Visram et al, ASH 2021 Education Book

Highlights from IMW 2021

1-2 Febbraio 2022
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JAMA Oncology | Original Investigation

Carfilzomib, Lenalidomide, and Dexamethasone Followed by Lenalidomide Maintenance for Prevention of Symptomatic Multiple Myeloma in Patients With High-risk Smoldering Myeloma

A Phase 2 Nonrandomized Controlled Trial

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IMPORTANCE High-risk smoldering myeloma has a 5-year risk of progression to symptomatic multiple myeloma of approximately 75%. Treatment with lenalidomide decreases the risk of progression; however, novel triplet regimens are superior, and earlier disease may be more treatment sensitive.

OBJECTIVE To evaluate the use of carfilzomib, lenalidomide, and dexamethasone (KRd) with lenalidomide maintenance therapy as early intervention in high-risk smoldering myeloma and to determine the rates of minimal residual disease (MRD)–negative complete response (CR).

DESIGN, SETTING, AND PARTICIPANTS In this single-arm, single-center, phase 2 nonrandomized controlled trial, responses were evaluated at every cycle during KRd treatment and every 3 cycles subsequently. Bone marrow biopsies and imaging were performed by cycle 8 and then annually. The study enrolled patients from May 29, 2012, to July 23, 2020, at the National Institutes of Health Clinical Center, a highly specialized tertiary cancer center. Patient key eligibility criteria included a diagnosis of high-risk smoldering myeloma based on the Mayo Clinic, Spanish, and/or Rajkumar, Mateos, and Landgren criteria.

INTERVENTIONS Patients received eight 4-week cycles of intravenous carfilzomib 36 mg/m^2 (first 2 doses, 20 mg/m^2), dexamethasone (20 mg, cycles 1-4; 10 mg, cycles 5-8 twice weekly), and lenalidomide 25 mg (days 1-21) followed by twenty-four 28-day cycles of maintenance lenalidomide 10 mg (days 1-21). Stem cell harvest and storage were optional.

MAIN OUTCOMES AND MEASURES The primary outcome was the MRD-negative CR rate. Key secondary outcomes included duration of MRD-negative CR and progression to multiple myeloma.

RESULTS A total of 54 patients (median age, 59 years [range, 40-79 years]; 30 men [55.6%]; and 2 Asian [3.7%], 15 Black [27.8%], 1 Hispanic [1.9%], and 36 White [66.7%] patients) were enrolled, with a median potential follow-up time of 31.9 months (range, 6.7-102.9 months). The MRD-negative CR rate was 70.4% (95% CI, 56.4%-82.0%), with a median sustained duration of 5.5 years (95% CI, 3.7 years to not estimable). The 8-year probability of being free from progression to multiple myeloma was 91.2% (95% CI, 67.4%-97.9%), and no deaths occurred. Nonhematologic grade 3 adverse events occurred in 21 patients (38.9%) and included thromboembolism, rash, and lung infection, with no grade 4 events.

CONCLUSIONS AND RELEVANCE Results of this phase 2 nonrandomized controlled trial suggest that treatment of high-risk smoldering myeloma with novel triplet regimens, such as KRd and lenalidomide maintenance therapy, may alter the natural history of smoldering myeloma by significantly delaying development of end-organ disease. Randomized clinical trials are needed to confirm this favorable benefit-to-risk profile.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT01572480

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Supplemental content

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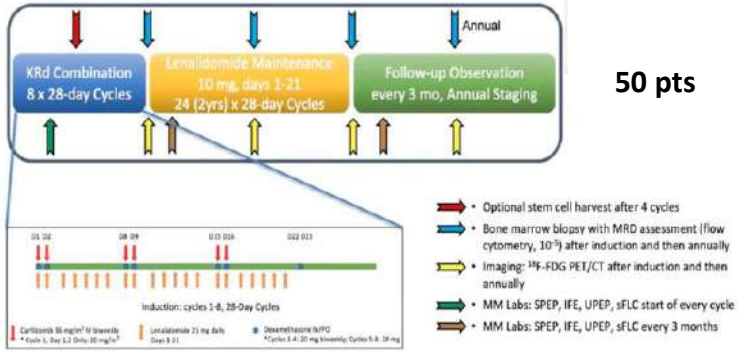
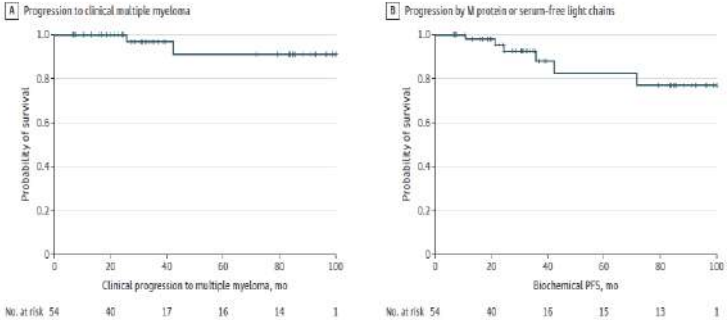


50 pts

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%)

Figure 2. Kaplan-Meier Estimates for Progression to Clinical Multiple Myeloma (Clinical Progression-Free Survival [PFS]) and Progression by M Protein or Serum-Free Light Chains (Biochemical PFS)

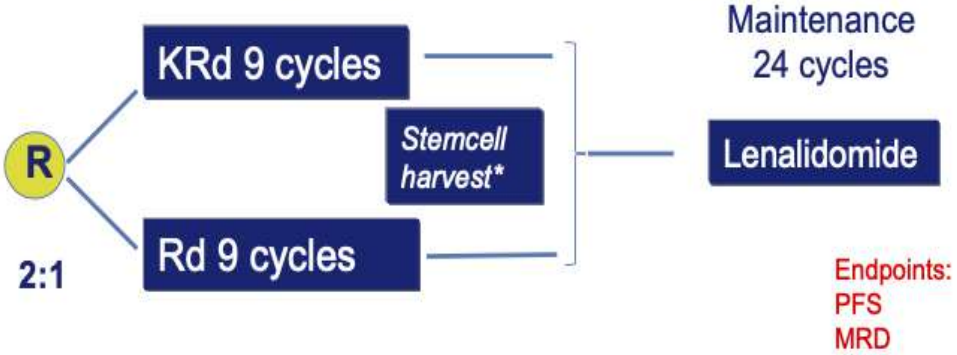


A, For the clinical PFS outcome (development of multiple myeloma), the median was not reached, with 2 events reported. B. For the biochemical PFS outcome, the median was not reached, with 6 events reported. The plus sign (+) denotes censoring of patients.

Erasmus MC Kanker Instituut

EMN015/ HOVON147

Collaboration with MSKCC, O. Landgren



Carfilzomib 36 mg/m2

* If eligible for subsequent HDM/ASCT in the future, stemcell harvest after 4th cycle

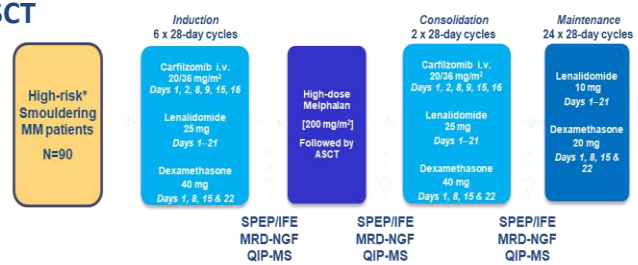
Target number of patients: 120

Expected accrual period: 2 years

Follow-up every 3 months until 5 years after randomization or death, whatever comes first

GEM-CESAR trial
KRd + AuSCT

Multicenter, open-label, phase II trial



**High-risk was defined according to the Mayo and/or Spanish models*

- Patients with any one or more of the biomarkers predicting imminent risk of progression to MM were allowed to be included but…
- New imaging assessments were mandatory at screening and if bone disease was detected by CT or PET-CT, patients were excluded

After induction	After ASCT	After consolidation	After maintenance x 2 yrs
VGPR	sCR/MRD+ve	sCR/MRD-ve	MRD-ve and sustained for at least 1 year (March. 2021)

CT, tomography-computed tomography; IFE, immunofixation electrophoresis; MRD, minimal residual disease; NGF, next-generation flow cytometry; PET-CT, positron emission tomography-computed tomography; QIP-MS, quantitative immunoprecipitation mass spectrometry; SPEP, serum protein electrophoresis

Mateos. ASH 2019. Puig. ASH 2020

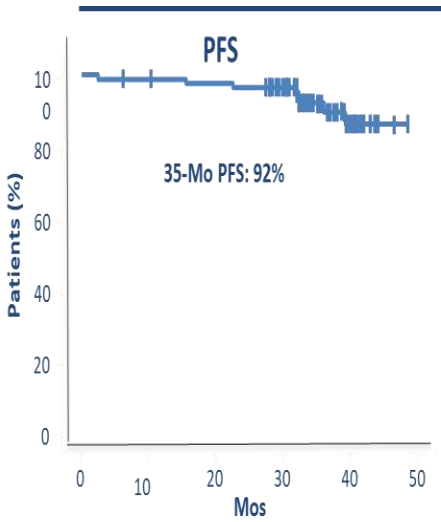
GEM-CESAR: Outcomes

77 patients completed induction, HDT-ASCT, consolidation, and 1 yr of maintenance

Response, %	Induction (KRd x 6) (n = 77)	HDT-ASCT (n = 77)	Consolidation (KRd x 2) (n = 77)	Maintenance (Rd x 1 Yr) (n = 77)
≥ CR	43	63	75	81
VGPR	43	24	18	13
PR	13	13	7	5
Progressive disease	--	--	--	1*
MRD negative	33	49	65	62

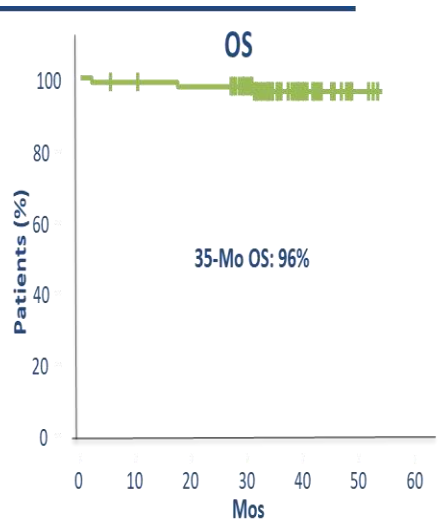
*Biological progressive disease at end of maintenance, MRD positive.

HDT-ASCT, high-dose therapy with autologous stem cell transplantation; KRd, carfilzomib/lenalidomide/dexamethasone; MRD, measurable residual disease.



Median follow-up: 35.2 (5.4-53.2)

6 patients progressed (biological PD, n = 5), 4 patients with PD were at ultrahigh risk



Median follow-up: 35.2 (5.4-53.2)

3 patients died; only , 1 death was consideredtreatment- related

Mateos. ASH 2019. Abstr 781.

ASCENT Trial: Study Design KRdD

- The ASCENT trial was designed to examine if an intense but limited duration therapy can provide significant elimination of tumor burden and potentially lead to long term responses in SMM[1,2]

N = ~ 83
Key inclusion criteria:
- High-risk SMM
- Age 18–80 years

Induction
6 x 28-day cycles

KRdD
Carfilzomib 56 mg/m² IV: days 1, 8, 15
Lenalidomide 25 mg PO: days 1–21
Daratumumab 16 mg/kg IV: days 1, 8, 15, 22 of cycles 1–2; days 1, 15 of cycles 3–6
Dexamethasone 40 mg PO: days 1, 8, 15, 22 of cycles 1–6

Consolidation
6 x 28-day cycles

KRdD
Carfilzomib 56 mg/m² IV: days 1, 8, 15
Lenalidomide 25 mg PO: days 1–21
Daratumumab 16 mg/kg IV: day 1 of cycles 7–12
Dexamethasone 20 mg PO: days 1, 8, 15, 22 of cycles 7–12

Maintenance
12 x 28-day cycles

RD
Lenalidomide 10 mg PO: days 1–21
Daratumumab 16 mg/kg IV: day 1 of odd cycles for cycles 13–24

Primary endpoint: sCR rate*
Secondary endpoints: MRD negativity,† OS, PFS, adverse events

ASCENT Trial: Initial Analysis of Safety

- 46 patients have been accrued to the trial as of July 14, 2020
- Reason for going off treatment was patient preference

Patient Demographics	N = 46
Age in years, median (range)	63 (47–76)
Male, n (%)	32 (70%)

Study Phase	Patients that have completed phase
Maintenance	2%
Consolidation	50%
Induction	80%
Currently in induction phase	**15%**

- At least one patient needed a dose modification for each drug

Drug	Patients requiring dose modification, %	Relative median dose intensity, %
Carfilzomib	17	85
Daratumumab	2	92
Lenalidomide	13	80
Dexamethasone	7	98

- A grade 3 or higher AE was seen in 52% of patients
  - The two most common grade ≥ 3 AEs were neutropenia (9%) and hypertension (9%)
- No treatment-related deaths occurred

Initial safety analysis has been as expected for this regimen in myeloma and further analysis is pending completed accrual

AE, adverse event; KRdD, carfilzomib, lenalidomide, dexamethasone, daratumumab; RD, lenalidomide, daratumumab; SMM, smoldering multiple myeloma.

Kumar S, et al. ASH 2020; Abstract 2285.

ITHACA, a Randomized Multicenter Phase 3 Study of Isatuximab in Combination With Lenalidomide and Dexamethasone in High-Risk Smoldering Multiple Myeloma: Safety Run-In Preliminary Results

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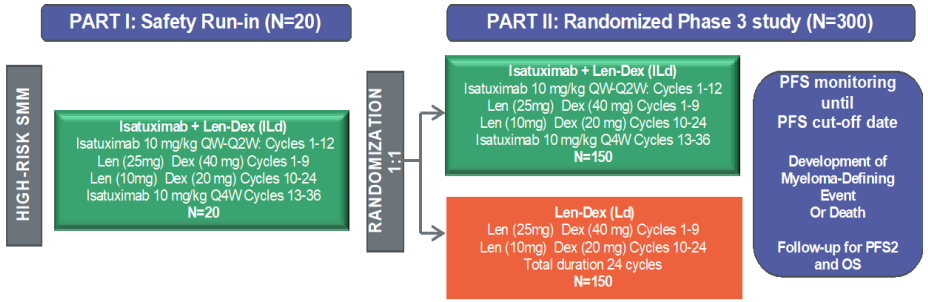

Stratification on:

- 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

RESULTS

Patients and treatment

- As of May 26, 2021, 23 patients had received Isa 10 mg/kg once weekly then every 2 weeks (QW–Q2W) in combination with Rd (**Table 1**)
- Two (8.7%) patients met the Mayo clinical model criteria, 13 (56.5%) patients the PETHEMA model criteria, and 8 (34.8%) patients both models' criteria for HR-SMM
- At the time of database extraction, 21 patients were still on study; no patient discontinued for a treatment-emergent adverse event (TEAE), 1 patient discontinued due to disease progression (Cycle 6), and 1 patient for poor compliance to protocol (after 4 cycles)
- 6 patients underwent stem cell mobilization before the cut-off date; median CD34+ cell mobilization was 5.6 x 10^6 cells/kg

Table 1. Patient demographic and baseline characteristics

	Isa-Rd (N=23)
Median age, years (range)	63 (28–85)
65–75 years, n (%)	7 (30.4)
>75 years, n (%)	3 (13.0)
Female, n (%)	8 (34.8)
Male, n (%)	15 (65.2)
ECOG PS, n (%)	
0	20 (87.0)
1	3 (13.0)
Median time from initial SMM diagnosis, years (range)	1.14 (0.1–5.2)
SMM subtype at initial diagnosis, n (%)	
IgG	15 (65.2)
IgA	7 (30.4)
K light chain only	1 (4.3)
HR-SMM definition, n (%)	
Model 1 only	2 (8.7)
Model 2 only	13 (56.5)
Model 1 and 2	8 (34.8)
Cytogenetic abnormalities, n (%)	
del(17p)	2 (8.7)
gain(1q21)	9 (39.1)
t(4;14)	5 (21.7)
t(14;16)	1 (4.3)
MYC (8q24)	0
Patients with focal lesion at baseline, n (%)	0
Median serum M-protein, g/L (range)	20.0 (0–50)
Median involved/uninvolved sFLC ratio (range)	15.04 (1.9–72.5)
Median BMPC at study entry, % (range)	17.0 (0–34)

BMPC, bone marrow plasma cell; d, dexamethasone; ECOG, Eastern Cooperative Oncology Group; HR-SMM, high-risk smoldering multiple myeloma; Ig, immunoglobulin; Isa, isatuximab; K, kappa; PS, performance status; R, lenalidomide; sFLC, serum free light chain; SMM, smoldering multiple myeloma

Highlights from IMW 2021

1-2 Febbraio 2022
Bologna
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Safety

- The median number of cycles started by patients was 9 (range 4–11) and the median duration of exposure was 36 (range 16–45) weeks
- Seven (30.4%) patients developed 8 Grade ≥3 non-hematologic TEAEs (**Table 2**), including COVID-19 pneumonia (n=2), insomnia (n=2), papular rash (n=1), muscle spasms (n=1), retinal detachment (n=1), and hyperglycemia (n=1)
- Serious TEAEs, reported in 5 (21.7%) patients, were COVID-19 pneumonia (n=2, Grade ≥3), and pneumonia, musculoskeletal chest pain, and pyrexia (n=1 each, Grade <3)
- None of the patients experienced a Grade 5 TEAE
- There were no treatment discontinuations due to a TEAE

Table 3. Most common TEAEs (in >10% of patients)

	Isa-Rd (N=23)	
TEAE, n (%)	All grades	Grade ≥3
Insomnia	9 (39.1)	2 (8.7)
Constipation	5 (21.7)	0
Peripheral edema	5 (21.7)	0
Headache	4 (17.4)	0
Muscle spasms	4 (17.4)	1 (4.3)
Accidental overdose[a]	3 (13.0)	0
Arthralgia	3 (13.0)	0
Asthenia	3 (13.0)	0
Diarrhea	3 (13.0)	0
Maculo-papular rash	3 (13.0)	0
Upper respiratory tract infection	3 (13.0)	0

[a]Dexamethasone overdose
d, dexamethasone; Isa, isatuximab; R, lenalidomide; TEAE, treatment-emergent adverse event

The most common TEAEs were generally Grade 1–2 and included insomnia (39.1%), constipation (21.7%), peripheral edema (21.7%), headache (17.4%), and muscle spasms (17.4%). Other TEAEs reported in >10% of patients are listed in **Table 3**

Infusion reactions (Grade 2) occurred in 2 (8.7%) patients (first infusion day/Cycle 1)

Table 2. Safety summary

n (%)	Isa-Rd (N=23)
Any TEAE	23 (100)
Any Grade ≥3 TEAE	7 (30.4)
Any Grade 5 TEAE	0
Any serious TEAE	5 (21.7)
Any TEAE leading to definitive treatment discontinuation	0

d, dexamethasone; Isa, isatuximab; R, lenalidomide; TEAE, treatment-emergent adverse event

Table 4. Hematologic laboratory abnormalities

	Isa-Rd (N=23)				
n (%)	All grades	Grade 1	Grade 2	Grade 3	Grade 4
Anemia	16 (69.6)	9 (39.1)	7 (30.4)	0	0
Neutropenia[a]	19 (82.6)	4 (17.4)	10 (43.5)	5 (21.7)	0
Thrombocytopenia	14 (60.9)	11 (47.8)	3 (13.0)	0	0

[a]Patients did not receive G-CSF support
d, dexamethasone; G-CSF, granulocyte colony-stimulating factor; Isa, isatuximab; R, lenalidomide

By laboratory results, no Grade 3–4 anemia or thrombocytopenia was observed; Grade 3 neutropenia was reported in 5 (21.7%) patients, with no Grade 4 (**Table 4**)

Table 5. Best overall response by investigator assessment

	Isa-Rd (N=23)
Best overall response, n (%)	
Stringent complete response (sCR)	1 (4.3)
Complete response (CR)	3 (13.0)
Very good partial response (VGPR)	5 (21.7)
Partial response	11 (47.8)
Minimal response	1 (4.3)
Stable disease	1 (4.3)
Progressive disease	0
Not evaluable/not assessed	1 (4.3)
Overall response rate	20 (87.0)
sCR/CR rate	4 (17.4)
≥VGPR rate	9 (39.1)

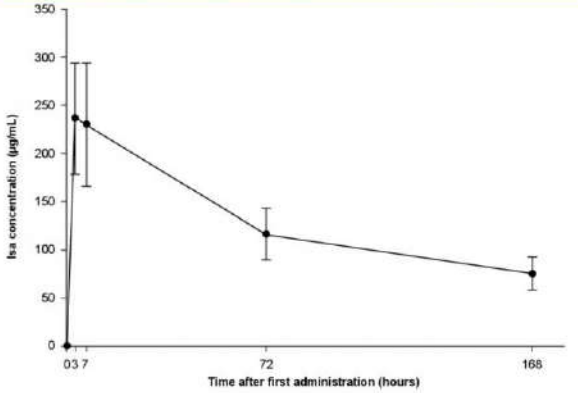
[a]Data cut-off date: May 26, 2021
d, dexamethasone; Isa, isatuximab; R, lenalidomide

At the cut-off date, the confirmed ORR was 87.0% (20/23 patients) and the ≥VGPR rate was 39.1% (9/23 patients) (**Table 5**)

In addition, 3 patients had an unconfirmed VGPR

Isa PK and CD38 receptor occupancy

Figure 2. Mean (SD) concentration of Isa 10 mg/kg in combination with Rd (n=22)



d, dexamethasone; Isa, isatuximab; R, lenalidomide; SD, standard deviation

- Mean [CV%] $AUC_{tau,ss}$ (22500 µg.h/mL [28]) and C_{max} (242 µg/mL [26]) after the first administration were in accordance with other MM studies (data on file; NCT03194867, NCT03275285)
- Mean CD38 receptor occupancy in BMPCs at Day 1/Cycle 2 was 77.6% (range 70.7–83.7; n=12)

CONCLUSIONS

- The addition of Isa 10 mg/kg QW–Q2W to Rd was associated with a favorable safety profile in patients with HR-SMM, which compares well with Rd literature data in the same patient population[2]
- There were no TEAEs leading to definitive treatment discontinuation
- Isa exposure and CD38 receptor occupancy results after intravenous infusion at 10 mg/kg in patients with HR-SMM were in accordance with those observed in other MM studies, reaching target saturation in BMPCs
- Isa in combination with Rd has shown encouraging preliminary efficacy (17.4% sCR/CR and 39.1% ≥VGPR rates) in patients with HR-SMM
- These results confirm the recommended dose of Isa in combination with Rd for patients enrolled in the randomized Part II of the Phase 3 ITHACA study, which will further evaluate efficacy and safety of Isa-Rd in HR-SMM

Single-cell RNA-sequencing identifies immune biomarkers of response to immunotherapy in patients with high-risk Smoldering Myeloma

- Sequential single-cell RNA-sequencing on CD138- immune cells from 40 BM and PB samples of 14 patients enrolled in a Phase II trial with Elo-RD in patients with high-risk SMM (E-PRISM).
- Higher baseline abundance of mature B-cells, Th17 cells and Granzyme K (GZMK)+ T-cells (not normal-like immune composition) were associated with significantly longer PFS (p=0.031) (baseline immune reactivity may help to identify patients who will benefit the most from early treatment).
- The expansion of tissue-resident NK cells and exhausted GZMK+ CD8+ T-cells at C9D1 of treatment, as well as higher gene expression signature marked by amphiregulin (*AREG*), was also associated with significantly shorter PFS (p=0.039) (these immune biomarkers may also help to monitor response to immunotherapy, not be fully explained by residual tumor burden alone).
- Patients whose immune profile normalized at the end of therapy (EOT) (Post-therapy Immune Normalization, PIN), potentially signifying the resolution of the immune challenge, had significantly longer biochemical PFS (p=0.04) (assessment of PIN at EOT may improve stratification of patients with minimal residual disease).
- Biomarker status could be assessed in both BM and PB, making minimally invasive immune profiling
- **Next generation clinical assays that assess both tumor biology and immune state, to accurately predict, with common clinical biomarkers, patients who may benefit from early treatment, monitor response and improve clinical outcomes.**

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2021 European Myeloma Network review and consensus statement on smoldering multiple myeloma: how to distinguish (and manage) Dr. Jekyll and Mr. Hyde

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Who are the patients with SMM that might benefit by an early treatment?

- Regarding patients with lower risk SMM, diagnosed according to current criteria, only active observation is recommended.
- About high-risk SMM early treatment, there is no consensus yet.
- Two prospective randomized trials have shown significant benefits with lenalidomide +/- dexamethasone in these patients, but they were not registration studies and they were not presented to regulatory agencies.
- However, it should be considered that (for) patients presenting with the coexistence of multiple risk factors, particularly evolving MC/BMPC or significant hemoglobin decrease, high FLC ratio and/or high-risk cytogenetics….. physicians may consider to start early treatment, with the intention to either delay progression or even achieve cure.
- It will be the individual physician's responsibility to seek active risk/benefit discussion with their patients, also considering that HRQoL (as well as OS) is an essential outcome parameter.
- The decision of treatment will also depend on national healthcare system whether such unlicensed treatment approach falls within the legal framework.
- The Panel agreed that therapy in these selected, very high-risk SMM patients, should be similar to that offered to patients with active myeloma, and that treatment should be performed in a controlled setting, such as clinical trial.

What should be done in the close future to further improve the management of SMM?

- i) To identify new predictive biomarkers (clinical, molecular/genomics, immunological, microenvironment, imaging) for further refining risk prediction and selecting SMM patients who may do well with observation ("Dr. Jekyll") and those who require more stringent monitoring in order to establish the most appropriate moment to start treatment ("Mr. Hyde" ones).

ii) To assess the necessary balance between reduced risk of progression (and of consequent MM complications) with early treatment vs short- and long-term possible adverse effects, specifically deteriorating HRQoL, SPM and induction of refractory disease, elucidating, in particular, whether an early treatment may select resistant clones or, the opposite, if delaying therapy may favor a more resistant disease for future therapies.

iii) To determine which intensity and type of treatment is preferable in selected high-risk SMM, i.e. short term, intensive approaches with "curative" intent vs prolonged immunological control of the disease ...., according to a "preventive" strategy. Both these approaches should have the primary objective of improving OS, without negatively affecting HRQoL.

EMN Consensus Statement on Smouldering Myeloma, Haematologica 2021