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Real-World Outcomes in Smoldering Multiple Myeloma in Europe: First Results From the SPARK Study

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Key Takeaway

In this large, real-world, European dataset, despite active monitoring, more than half of patients with high-risk SMM who progressed to MM had major organ damage, reinforcing the unmet need for early treatment intervention

Conclusions

- Regardless of how high-risk SMM was defined, >50% of MM progressions were CRAB events, and >50% included organ damage, most commonly bone pain, bone fractures, and anemia
- Our results show that active monitoring alone might be insufficient for preventing organ damage in many patients with high-risk SMM
- These findings reinforce the need for enhanced monitoring strategies and improved risk stratification in order to identify patients with SMM who could benefit from early intervention

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Disclosures

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Introduction

- Smoldering multiple myeloma (SMM) is a precursor plasma cell disorder with variable risk of progression to symptomatic multiple myeloma (MM)[1]
- SMM management generally consists of active monitoring, in an attempt to intercept active MM before serious organ damage occurs. Accurate risk stratification is essential to identify patients at highest risk of progression and to address the unmet need for early intervention[1,2]
- However, real-world data on characteristics of European patients with SMM, progression rates, overall survival (OS), organ damage at MM diagnosis, and treatment patterns by risk category remain limited
- The SPARK study aims to provide a comprehensive description of these parameters using different risk models, including the Mayo 20-2-20, the International Myeloma Working Group (IMWG) 2020 scoring system incorporating cytogenetics, and the AQUILA study criteria

Methods

- SPARK is a real-world, retrospective chart review study involving hematology centers across Europe
- Adult patients (≥18 years) diagnosed with SMM between January 2016 and December 2021 were included if they had at least 2 years of follow-up data available, or died within 2 years of diagnosis
- Categorical data were expressed as frequencies and percentages, and continuous data were summarized using median, mean, standard deviation, and range
- Time-to-event outcomes, including time to MM progression, progression-free survival (PFS), and OS, were analyzed using Kaplan-Meier methods
- This first SPARK publication includes all available data collected up to the cut-off date of October 27, 2025
- High-risk SMM per AQUILA study criteria[3] was defined as clonal bone marrow plasma cells (BMPCs) ≥10% and ≥1 of the following:
  - Serum M protein ≥3 g/dL
  - Immunoglobulin A (IgA) SMM
  - Immunoparesis with reduction of 2 uninvolved Ig isotypes
  - Serum involved-to-uninvolved free light chain ratio (FLCr) ≥8 to <100
  - Clonal BMPCs >50% to <60%
- High-risk SMM per Mayo 20-2-20[4] was defined as >1 of the following:
  - BMPCs >20%
  - Serum M protein >2 g/dL
  - Serum involved-to-uninvolved FLCr >20
- High-risk SMM per IMWG 2020 scoring system incorporating cytogenetics[5] was defined as a score of ≥9

Results

Patients

- SPARK included a total of 373 patients with SMM from 27 sites across UK, Germany, Italy, Spain, and France (**Figure 1**)
- Median follow-up was 53.1 months (range, 1–95.4)
- Patient baseline and disease characteristics are shown in **Table 1**

Figure 1: 373 patients were included from 27 sites across 5 countries

- SMM treatment was initiated in 8/373 (2.1%) patients (with high-risk, non–high-risk, and unclassified risk status SMM) with regimens including proteasome inhibitors, immunomodulatory drugs, corticosteroids, and monoclonal antibodies

Table 1: Baseline and disease characteristics

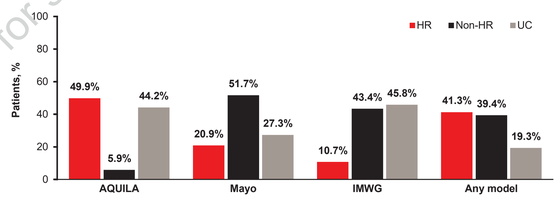
Variable	AQUILA			Mayo			IMWG			Any model[a]			Total
	HR (n=186)	Non-HR (n=22)	UC (n=165)	HR (n=78)	Non-HR (n=193)	UC (n=102)	HR (n=40)	Non-HR (n=162)	UC (n=171)	HR (n=154)	Non-HR (n=147)	UC (n=72)	N=373
Age (years)													
Median	67.5	69.0	68.0	69.0	66.0	68.5	65.0	67.5	69.0	69.0	65.0	68.0	68.0
Range	33–92	44–86	37–89	41–92	33–88	37–89	41–92	33–87	37–89	38–92	33–88	37–89	33–92
Sex, %													
Female	44.1	45.5	49.1	37.2	48.2	50.0	27.5	48.1	49.1	44.8	45.6	51.4	46.4
Male	55.9	54.5	50.9	62.8	51.8	50.0	72.5	51.9	50.9	55.2	54.4	48.6	53.6
Total M protein (g/dL)	n=172	n=19	n=107	n=72	n=168	n=58	n=38	n=144	n=116	n=133	n=125	n=40	n=298
Median	1.9	1.7	1.8	2.6	1.4	2.3	2.8	1.4	2.2	2.2	1.4	2.2	1.8
Range	0.0–10.4	0.2–4.3	0.0–4.1	0.0–7.4	0.0–10.4	0.3–4.9	0.0–7.4	0.0–10.4	0.2–4.9	0.0–7.4	0.0–10.4	1.0–4.1	0.0–10.4
Involved-to-uninvolved FLCr	n=147	n=20	n=55	n=61	n=148	n=13	n=37	n=144	n=41	n=99	n=115	n=8	n=222
Median	15.0	3.5	3.1	25.0	4.4	10.6	25.0	4.2	19.1	15.0	4.2	16.8	8.0
Range	0.02–124.0	0.9–9.9	0.02–187.1	1.3–124.0	0.02–187.1	0.02–44.0	1.2–124.0	0.02–94.3	0.02–187.1	0.02–124.0	0.02–187.1	1.1–44.0	0.02–187.1
BMPC (%)	n=171	n=21	n=130	n=69	n=180	n=73	n=35	n=154	n=133	n=139	n=135	n=48	n=322
Median	19.0	15.0	15.0	27.0	15.0	16.0	30.0	14.0	18.0	18.0	15.0	20.0	16.0
Range	3.0–54.0	3.0–45.0	6.0–40.0	3.0–54.0	3.0–50.0	6.2–35.0	3.0–54.0	3.0–41.0	6.2–50.0	3.0–54.0	3.0–50.0	6.2–35.0	3.0–54.0

[a]A patient was classified as having high-risk SMM if they were identified as having high-risk SMM by Mayo, IMWG, or physician assessment.
HR, high-risk SMM; UC, unclassified risk status SMM.

Risk classification

- Distribution of patients with high-risk, non–high-risk, and unclassified risk status SMM by different risk criteria is presented in **Figure 2**

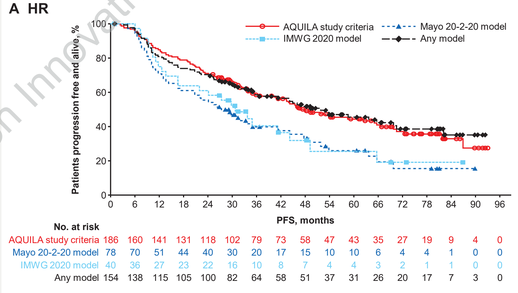
Figure 2: SPARK analysis population by SMM risk group



Outcomes

- Of the 373 patients, 166 (44.5%) had a PFS event (**Figure 3**)
  - 139 (37.3%) patients progressed to MM
  - 27 (7.2%) patients died
- There were 56 deaths in total (**Figure 4**)
  - The median OS was not reached (NR); the 25th percentile survival time was 81.7 months (95% CI, 58.6–NR)

Figure 3: PFS by SMM risk group

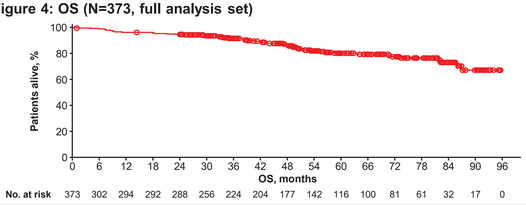


- Median PFS was 58.4 months (95% CI, 46.2–70.0)
  - For patients with high-risk SMM, the median PFS was similar between the AQUILA and Any-model criteria, as well as between the Mayo and the IMWG criteria (**Table 2**)
  - For patients with non–high-risk SMM, the median PFS was longer than that of patients with high-risk SMM in all 4 risk models (**Table 2**)
  - For patients with unclassified risk status SMM, the median PFS was similar in all 4 risk models

Table 2: Median PFS

	AQUILA	Mayo	IMWG	Any model
HR, median (95% CI), months	47.7 (40.5–65.7)	27.4 (17.1–41.2)	30.8 (16.7–44.2)	51.8 (36.7–40.6)
Non-HR, median (95% CI), months	NR	36.7 (28.6–45.5)	33.8 (23.6–43.4)	65.0 (49.5–NR)

Figure 4: OS (N=373, full analysis set)

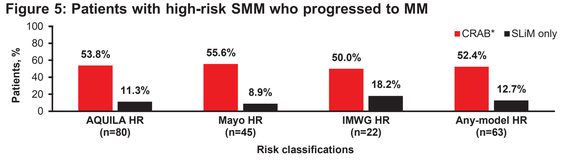


- Of the 139 patients who progressed to MM (**Table 3**, **Figure 5**):
  - 80 (57.6%) met the SLiM-CRAB (sixty percent clonal plasma cells, light-chain ratio, magnetic resonance imaging [MRI] focal lesions, calcium elevation, renal impairment, anemia, and bone lesions) criteria
  - 14 (10.1%) had organ damage (but no CRAB or SLiM)
  - 45 (32.4%) had unknown type of progression (missing data/under queries)

Table 3: MM progression and reasons (CRAB or SLiM)

	AQUILA HR (n=186)	Mayo HR (n=78)	IMWG HR (n=40)	Any-model HR (n=154)	Total (N=373)
Progression to MM, n	80	45	22	63	139
CRAB or SLiM in patients who progressed to MM, n (%)	52 (65.0)	29 (64.4)	15 (68.2)	41 (65.1)	80 (57.6)
CRAB only, n	33	18	6	26	53
SLiM only, n	9	4	4	8	15
Both CRAB and SLiM, n	10	7	5	7	12
Organ damage (but no CRAB/SLiM), n (%)	10 (12.5)	4 (8.9)	2 (9)	6 (9.5)	14 (10.1)
Missing data/under queries, n (%)	18 (22.5)	12 (26.7)	5 (22.7)	16 (25.4)	45 (32.4)

Figure 5: Patients with high-risk SMM who progressed to MM



*Included patients with CRAB only and patients with both CRAB and SLiM.

- The most common manifestations :
  - CRAB: bone lesions and anemia
  - SLiM: involved-to-uninvolved serum FLCr and focal lesion on MRI
- The distribution pattern was similar for patients with high-risk SMM in AQUILA, Mayo, IMWG, and Any-model criteria (**Table 4**)

Table 4: Incidence of organ damage in patients who progressed to MM

Variable	AQUILA			Mayo			IMWG			Any model			Total
	HR (n=186)	Non-HR (n=22)	UC (n=165)	HR (n=78)	Non-HR (n=193)	UC (n=102)	HR (n=40)	Non-HR (n=162)	UC (n=171)	HR (n=154)	Non-HR (n=147)	UC (n=72)	N=373
Progressed to MM, n	80	4	55	45	55	39	22	47	70	63	47	29	139
Progressed to MM and had organ damage at the time of MM, n (%)	46 (57.5)	0	25 (45.5)	26| (57.8)	25 (45.5)	20 (51.3)	11 (50.0)	23 (48.9)	37 (52.9)	38 (60.3)	21 (44.7)	12 (41.4)	71 (51.1)
Type of organ damage, %													
Bone pain	30.4		36.0	26.9	40.0	30.0	27.3	43.5	27.0	31.6	38.1	25.0	32.4
Bone fracture	23.9		36.0	19.2	28.0	40.0	18.2	26.1	32.4	15.8	28.6	66.7	28.2
Renal failure	6.5		0	3.8	4.0	5.0	0	4.3	5.4	7.9	0	0	4.2
Hypercalcemia	6.5		0	3.8	0	10.0	0	0	8.1	5.3	0	8.3	4.2
Anemia symptom	39.1		40.0	50.0	28.0	40.0	54.5	26.1	43.2	47.4	23.8	41.7	39.4
Other	30.4		20.0	23.1	32.0	25.0	27.3	26.1	27.0	26.3	33.3	16.7	26.8

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Multiple Myeloma

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