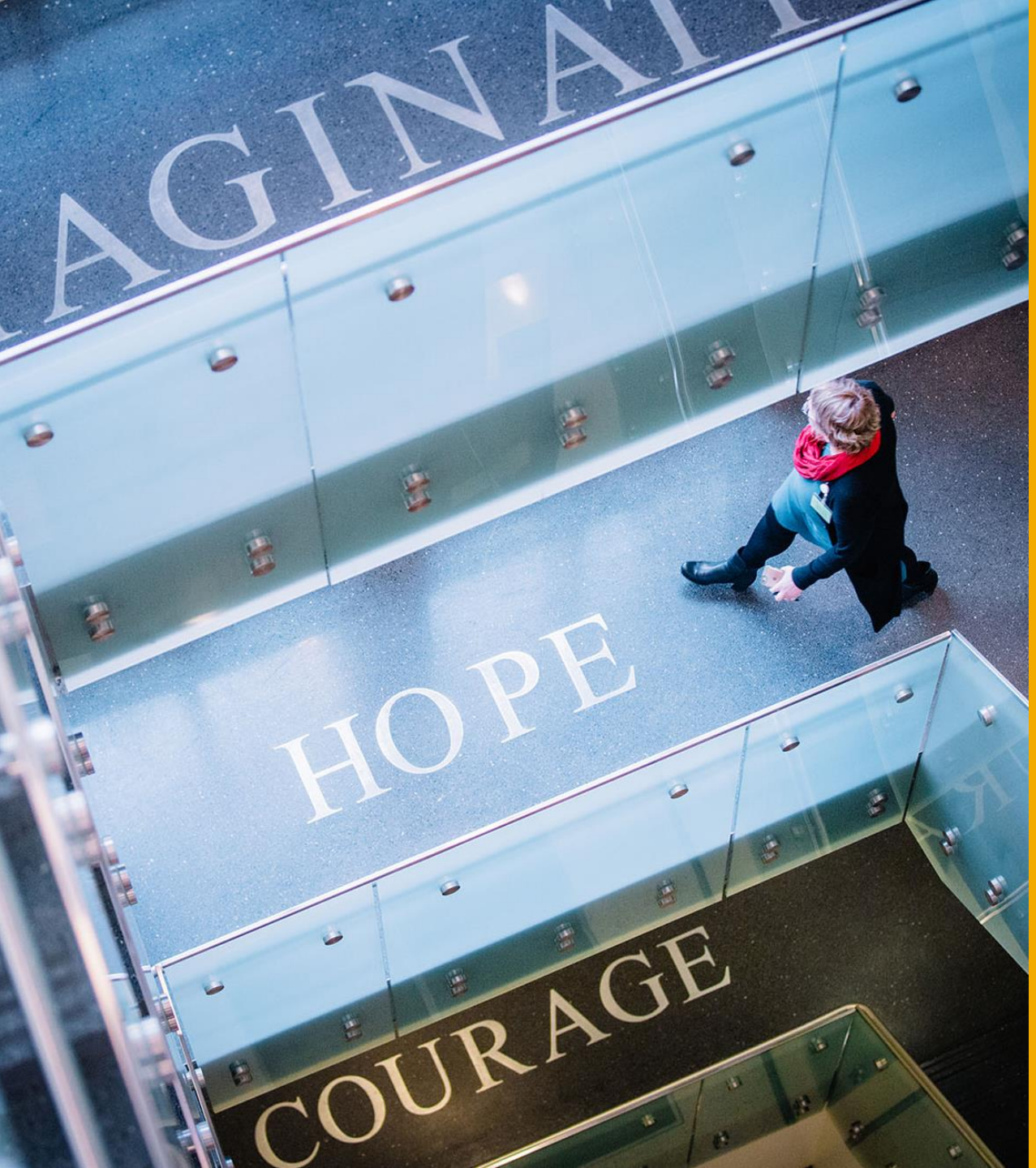

UPDATES IN SMOLDERING MYELOMA

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National Cancer Institute-Designated Comprehensive Cancer Center

NCI
Designated Comprehensive Cancer Center

LET'S START WITH A PATIENT CASE…

44 year old F referred to Hematology for an incidentally found elevated total protein.

Labs notable for: Hgb 12.1 g/dL, Ca 9.2, Cr 0.84

Immunologic studies: SPEP/IFE 3.1 g/dL IgG-lambda paraprotein, Free kappa light chain 6 mg/L, Free lambda light chain 274 mg/L, FLCr 0.02, UPEP/IFE negative

BMBX: 40% kappa restricted clonal plasma cells, FISH positive for +9, +11, +1q

PET-CT: no evidence of FDG-avid osseous lesions

WHAT IS THE NEXT STEP IN MANAGEMENT/TREATMENT OF THIS PATIENT?

A) Active surveillance

B) Induction therapy with Dara-RVD and referral for ASCT

C) Lenalidomide

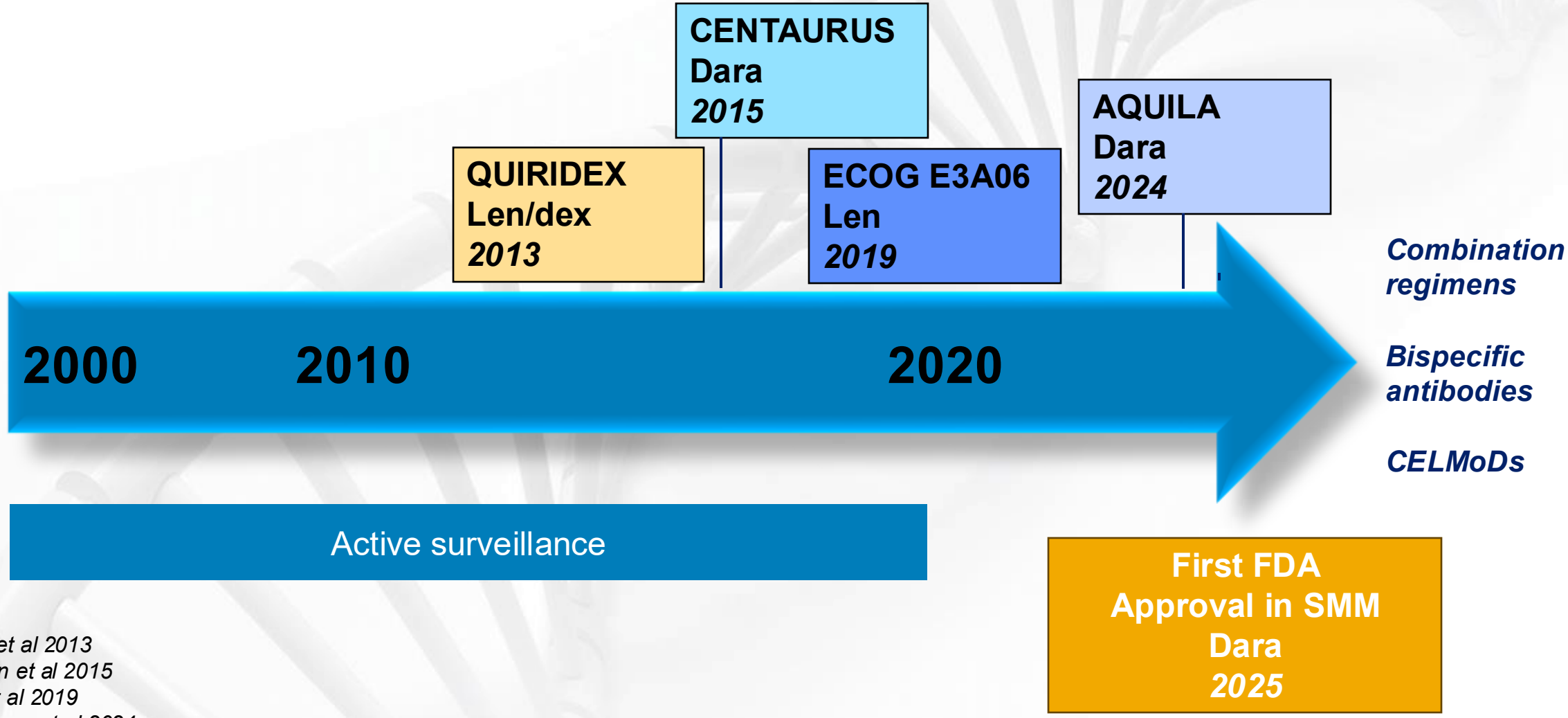
D) Lenalidomide and dexamethasone

E) Clinical trial

F) Daratumumab

G) Bispecific antibody?

ADVANCEMENTS IN SMOLDERING MYELOMA



Mateos et al 2013
Landgren et al 2015
Lonial et al 2019
Dimopolous et al 2024

Revised IMWG Diagnostic Criteria

MGUS

- M-protein < 3 g/dL
- Clonal plasma cells in marrow <10 %
- No SLiM-CRAB criteria

Smoldering Myeloma

- M-protein ≥ 3 g/dL (serum) or ≥ 500 mg/24 hrs (urine) and/or
- Clonal plasma cells in marrow >10 %
- No SLiM-CRAB criteria

Multiple Myeloma

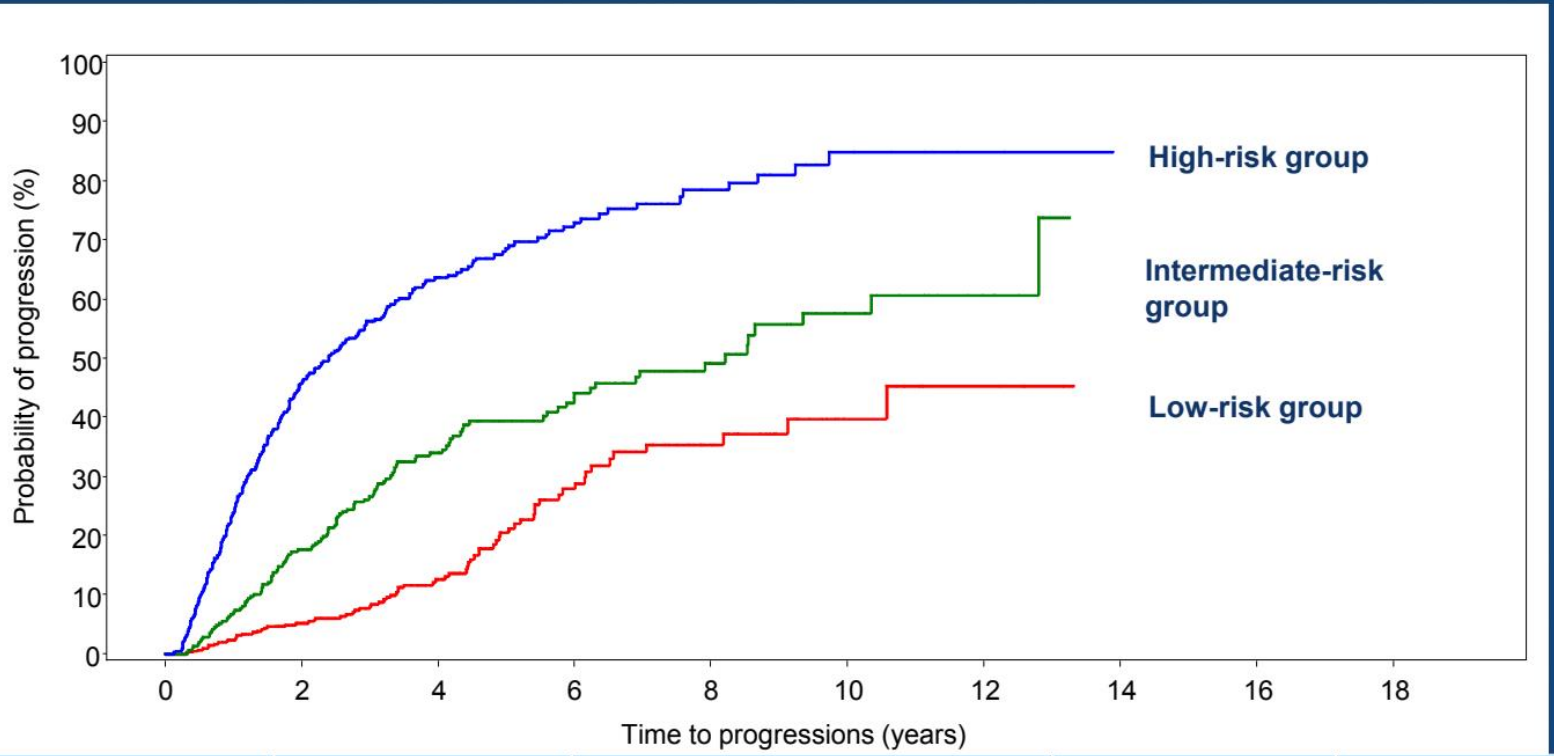
- Clonal plasma cells ≥ 10% or ≥ 1 biopsy-proven plasmacytoma
- SLiM-CRAB criteria

SLiM	CRAB
S Clonal plasma cells in BM ≥ 60% Li Serum FLC ratio ≥ 100 * M > 1 MRI focal lesion ≥ 5 mm Any of these criteria associated with 75-95% risk of progression to symptomatic MM at 2 years	C Calcium elevated (> 11 mg/dL or >1 mg/dL higher than ULN R Renal insufficiency (CrCl <40 mL/min or serum Cr > 2 mg/dL A Anemia (Hgb < 10 g/dL or 2 g/dL <normal) B Bone disease (≥ 1 lytic lesion on skeletal radiography, CT, or PET/CT)

*** Involved FLC ≥ 100 mg/L**

Rajkumar SV, et al. *Lancet Oncology*. 2014; 15(12):e538-e548.

Progression by risk group (n=1151 pts)



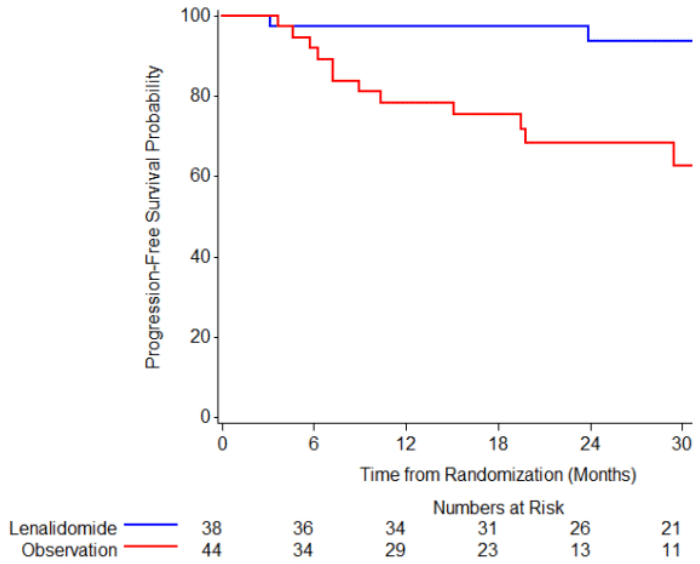
Characteristics included in the model

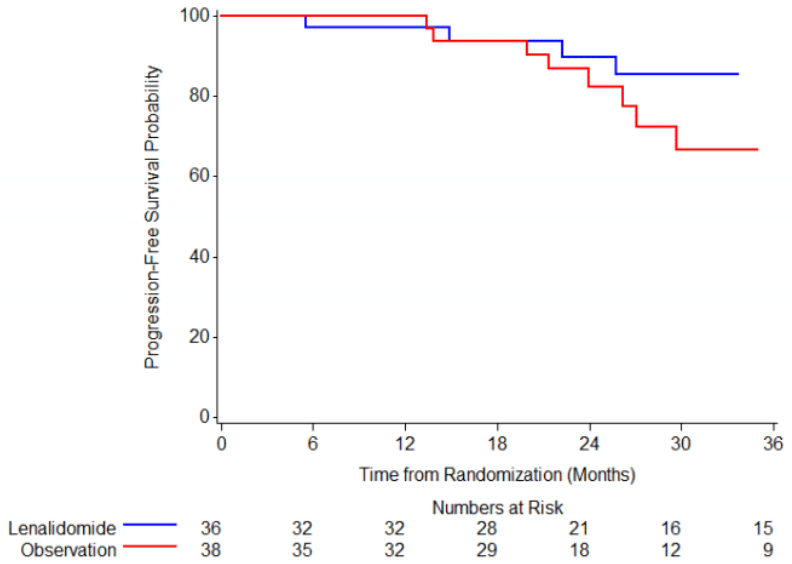
Serum M Spike: >2g/dL
FLC Ratio: >20
BMPC: >20%

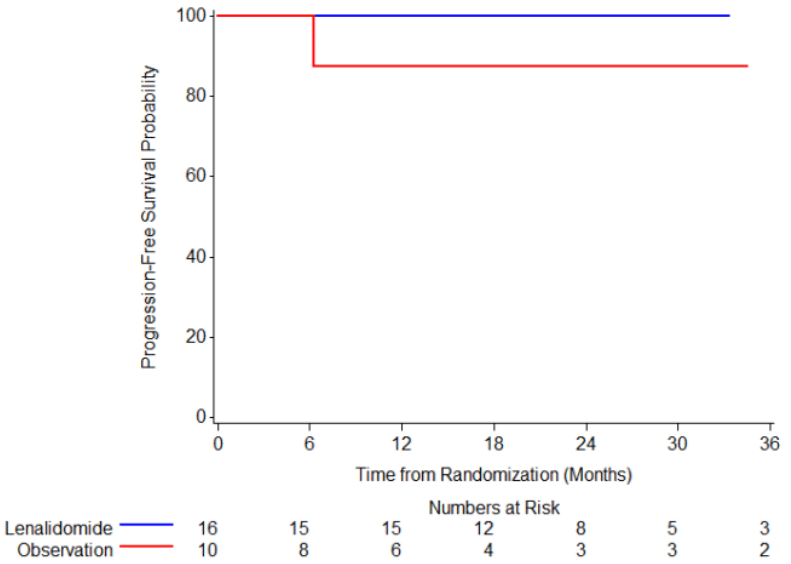
Risk Stratification Groups	Number of risk factors	Hazard Ratio (95% CI) Versus Low-risk group	Risk of Progression at 2 years	Number of patients
Low-risk group	0	Reference	5%	424 (37%)
Intermediate-risk group	1	2.25 (1.68 to 3.01)	17%	312 (27%)
High-risk group	2-3	5.63 (4.34 to 7.29)	46%	415 (36%)

ANNUAL MEETING
permission required for reuse.

ECOG E3A06: Phase 3 PFS by Mayo 2018 Risk Criteria







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High Risk

Intermediate Risk

Low Risk

ECOG-ACRIN cancer research group
Reshaping the future of patient care

Lonial et al ASCO 2019

STUDY DESIGN

**Currently enrolling at Emory

Safety Run-in

Eligibility:
High-risk SMM diagnosed within 5 years
Age ≥ 18 yrs

1.3 mg

1.6 mg

- No DLTs at 1.6 mg dose
- Given recurrent issue with G3/4 neutropenia, decided to continue at 1.3 mg dose

Randomized Phase

Eligibility:
Intermediate- and High-risk SMM diagnosed within 5 years
Age ≥ 18 yrs

R

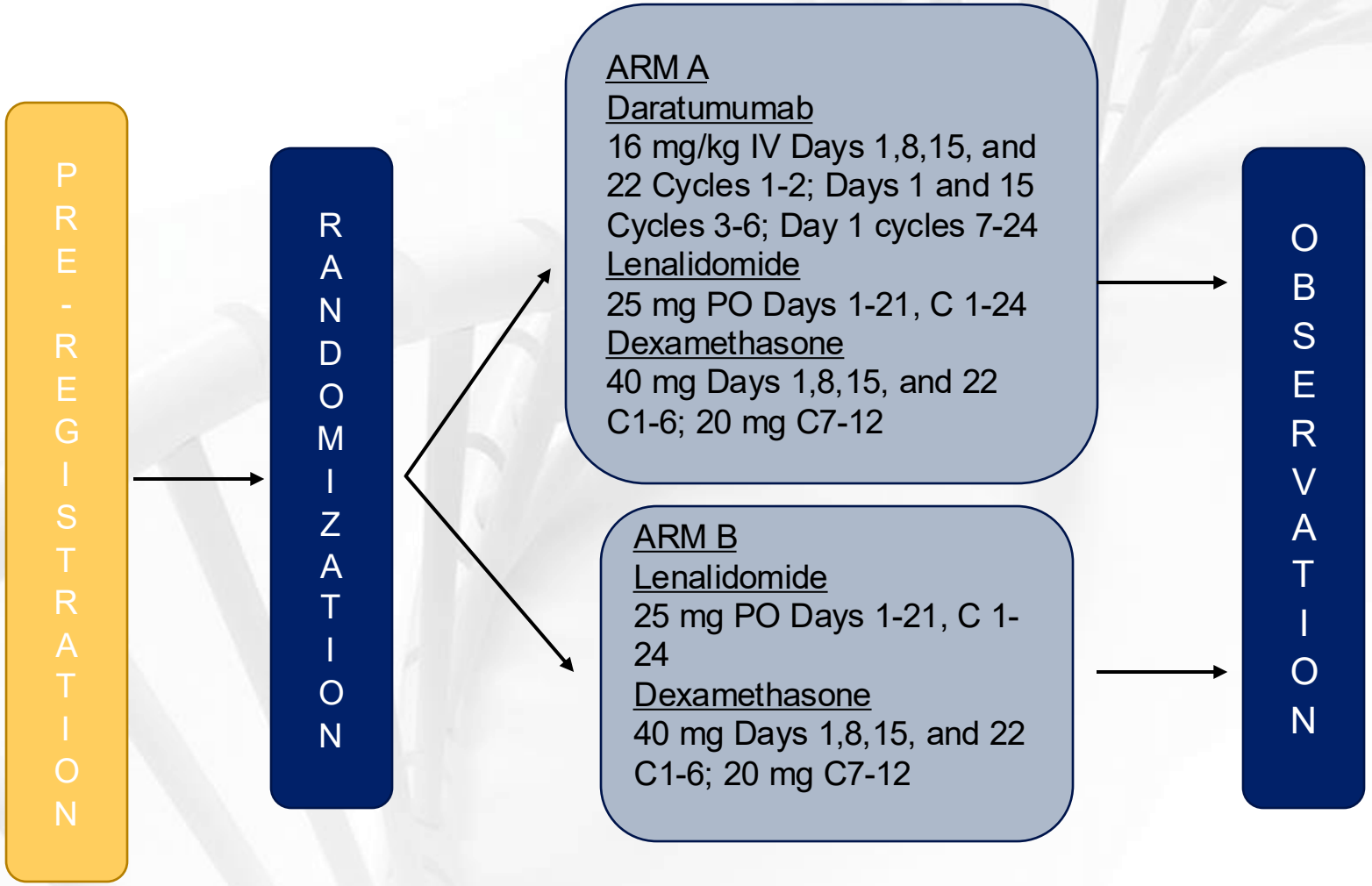
- Iberdomide 1.3 mg on days 1-21 every 28 days
- Iberdomide 1.3 mg with dex 20 mg weekly x 4 cycles

2 yrs

Continue on follow up on observation

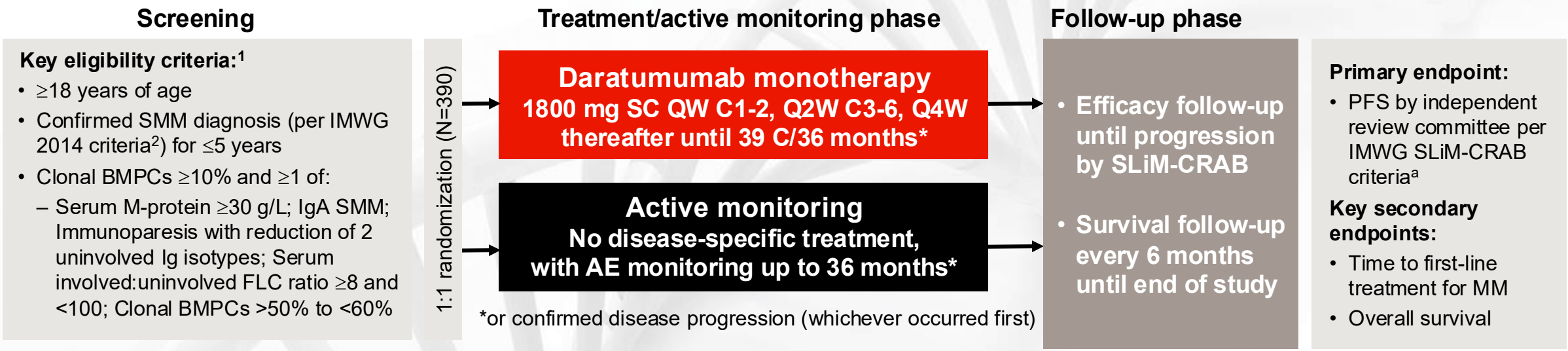
DETER-SMM

**Currently enrolling at Emory



** Peripheral blood stem cells for future transplants should be collected between cycles 4-6 of therapy though not required

AQUILA: STUDY DESIGN AND RISK STRATIFICATION METHODS



- For this *post hoc* analysis, outcomes were assessed by:

IMWG 2020 validated risk stratification:
BMPC >20%, M spike >2 g/dL, serum l/U FLC ratio >20

0 factors=low risk; 1 factor=intermediate risk; ≥2 factors=high risk

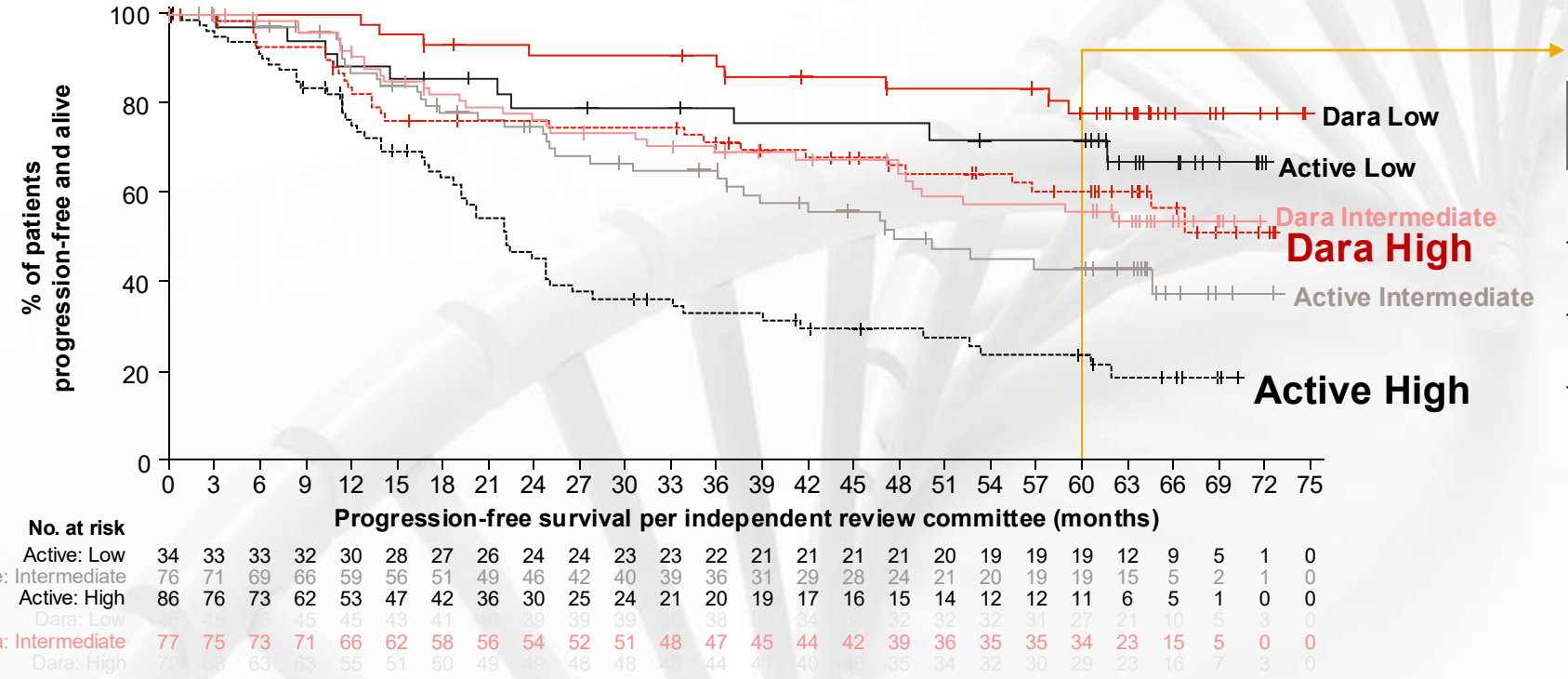
IMWG scoring system:
Points given based on values of serum FLC ratio, M spike g/dL, percentage of BMPCs, and FISH abnormalities

0–4 points=low risk; 5–8 points=low-intermediate risk; 9–12 points=intermediate; >12 points=high risk

Age:
<65 years
65 to <75 years
≥75 years

AQUILA: IMWG 2020 SUBGROUPS: PFS

5 year PFS for overall population: 63.1% vs 40.8% (HR 0.49)



60-month PFS rates, %:

IMWG 2020 Risk group	Daratumumab	Active monitoring
Low	78.2	71.6
Intermediate	56.2	42.9
High	60.4	23.6

PFS active monitoring vs daratumumab monotherapy, high-risk group:
62.8% vs 37.5% events
HR 0.36 (95% CI: 0.23, 0.58)

Daratumumab monotherapy showed a PFS benefit vs active monitoring across IMWG 2020 risk subgroups, with the largest benefit observed in the high-risk subgroup

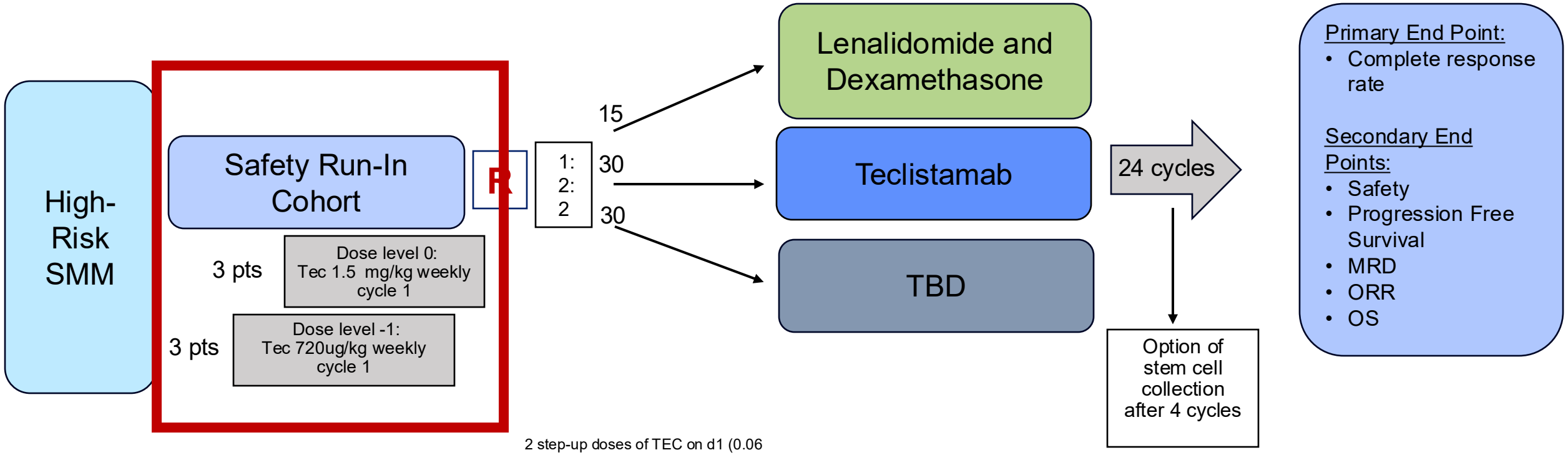
IMWG 2020 (aka Mayo 2018 or 20-2-20) risk stratification: BMPC >20%, monoclonal spike >2 g/dL, serum l/U FLC ratio >20.
0 factors=low risk; 1 factor=intermediate risk; ≥2 factors=high risk

AQUILA: AGE SUBGROUPS: SAFETY SUMMARY

n (%)	Daratumumab			Active monitoring		
	<65 yrs n=105	65 to <75 yrs n=67	≥75 yrs n=21	<65 yrs n=98	65 to <75 yrs n=74	≥75 yrs n=24
Any TEAE	101 (96.2)	66 (98.5)	20 (95.2)	81 (82.7)	60 (81.1)	21 (87.5)
Infections and infestations SOC, any grade	86 (81.9)	57 (85.1)	11 (52.4)	49 (50.0)	29 (39.2)	10 (41.7)
Infections and infestations SOC, grade ≥3	10 (9.5)	18 (26.9)	3 (14.3)	3 (3.1)	3 (4.1)	3 (12.5)
Any serious TEAE	26 (24.8)	24 (35.8)	6 (28.6)	12 (12.2)	14 (18.9)	12 (50.0)
Serious TEAEs occurring in ≥5% of any group:						
Pneumonia	1 (1.0)	6 (9.0)	0	0	1 (1.4)	0
TEAE leading to discontinuation	2 (1.9)	6 (9.0)	3 (14.3)	-	-	-
TEAE leading to dose modification[a]	35 (33.3)	44 (65.7)	11 (52.4)	-	-	-

The rates of TEAEs and serious TEAEs in the daratumumab group were similar across age groups

IMMUNOPRISM STUDY DESIGN



Teclistamab Dosing Schedule

2 step-up doses of TEC on d1 (0.06 mg/kg) and d3 (0.3mg/kg) for cycle 1

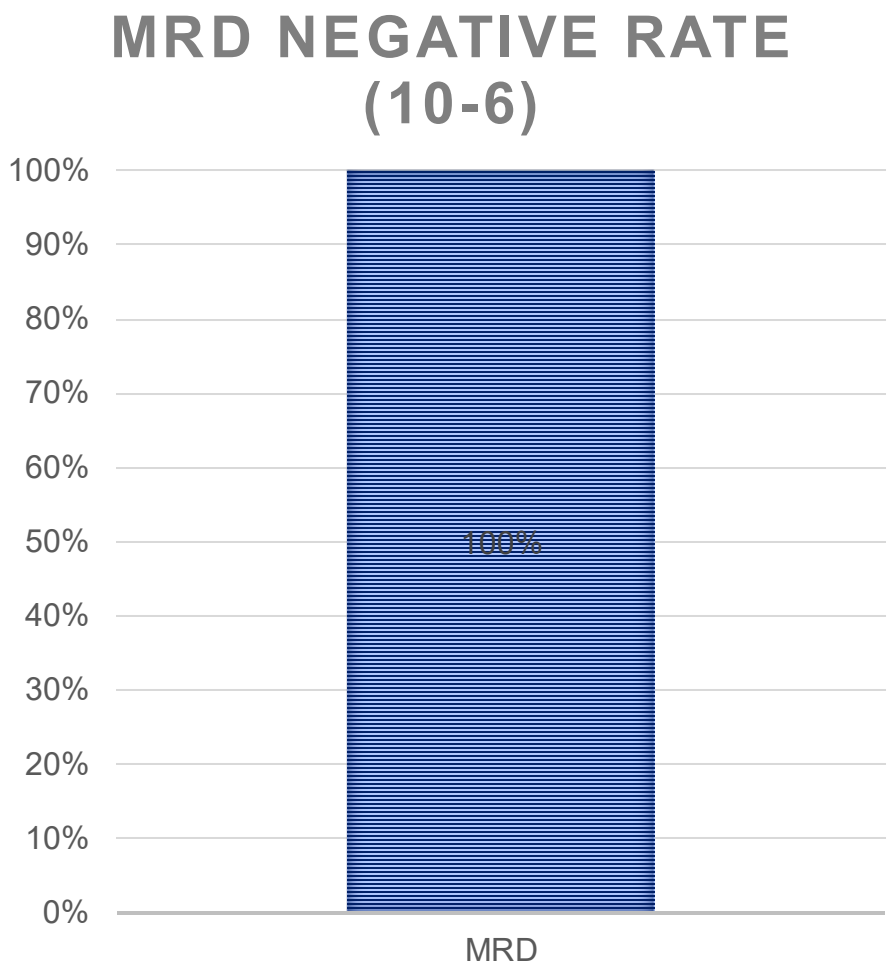
Screening	C1	C2	C3	C4	C5	C6	C7 +

C1-2:* ***TEC 1.5mg/kg QW***

C3-6: ***TEC 3mg/kg Q2W***

C7-24: ***3mg/kg Q4W***

MINIMAL RESIDUAL DISEASE (NEXT GENERATION SEQUENCING) IN TECLISTAMAB ARM N = 12



- **MRD-negativity rate at 10^{-5} is 100%**
- **MRD-negativity rate at 10^{-6} is 100%*** including 2 patients with VGPR-MRD negative disease.
- Average time to MRD-ve was **4.25 cycles**

**1 patient with 0-1 cells/mill (detected below LOD)*

SAFETY: INFECTIONS IN TECLISTAMAB ARM, N=12

Infections (Grade 2 or Greater)	N=12	
	Grade 2	Grade 3
Salmonella	0	1
Sinusitis	2	1
Upper respiratory infections		0
COVID-19	1	0
Adenovirus	1	0
Nonspecific	1	0

Other Notable Toxicities	N=12	
	Grade 2	Grade 3
Uveitis	1	0
Pancreatitis	0	1

- Uveitis resolved with supportive care and patient remains on therapy.
- Pancreatitis was attributed to sulfamethoxazole and trimethoprim and resolved after removal of agent.

All patients with hypogammaglobulinemia treated with TEC are receiving **IVIG;** with mean IgG level of 418mg/dL prior to IVIG initiation, 64% of patients have achieved normalization of IgG within two IVIG doses.

EMN34 ERASMM PHASE 2 STUDY DESIGN

Key inclusion criteria

- **Smoldering MM**
  ≥10% BMPC and/or M-spike >3 g/dL,
  absence of SLiM/CRAB criteria

- **At least 2 high-risk 2/20/20 criteria**:
  BMPC>20%, M-spike >2 g/dL, FLC ratio >20

Objectives

- **Primary objective**: CR rate (after 6 cycles)

- **Key secondary endpoint**: safety

- **Secondary Objectives:** ORR, MRD, PFS, time to SLiM/CRAB, PFS2, OS

Elranatamab single agent SQ (28-day cycle) – Fixed duration (2 years)

C1D1 = 12 mg; C1D4 = 32 mg; C1D8 and further doses = 76 mg

Cyrille Touzeau

MM, multiple myeloma; BMPC, bone marrow clonal plasma cells; M, monoclonal; SliM, clonal bone marrow plasma cell percentage ≥60% (BMPC ≥60), involved:uninvolved serum-free light chain ratio ≥100, and ≥1 focal lesion of ≥5 mm on MRI (SLiM: sixty, light chain, MRI); MRI, magnetic resonance imaging; CRAB, hypercalcemia (C), renal impairment (R), anemia (A), and bone lesions (B); FLC, free light chain; CR, complete response ;ORR, overall response rate; MRD, minimal residual disease; PFS, progression-free survival; PFS2, progression-free survival 2; OS, overall survival; SQ, subcutaneous; D, day; C, cycle.

EMN34 ERASMM - SAFETY

Most common hematologic AEs ≥10% of total, n (%)	N=50	
	Any grade	Grade 3–4
Neutropenia	22 (44)	20 (40)

5 (10%) patients discontinued therapy due to AE:

- Guillain-Barré syndrome: n=1 (AE recovered, patient in sCR)
- Hypertransaminasemia: n=1 (AE recovered, patient in PR)
- Infections: n=2 (patients respectively in VGPR and sCR)
- Peripheral neuropathy : n=1 (patients in VGPR)

Most common non-hematologic AEs[a] ≥10% of total, n (%)	N=50	
	Any grade	Grade 3
CRS	35 (70)	2 (4)
Infections	27 (54)	7 (14)
Skin rash	19 (38)	0
Fatigue	16 (32)	1 (2)
Diarrhea	13 (26)	1 (2)
Peripheral neuropathy	8 (16)	0
Injection site reaction	7 (14)	0
Weight loss	5 (10)	0

No new safety signals observed with elranatamab monotherapy in HR-SMM patients compared to RRMM patients

Low incidence of grade 3 non-hematologic adverse events

Data cut-off: April 13, 2026

AEs, adverse events; CRS, cytokine release syndrome; sCR, stringent complete response; PR, partial response; VGPR, very good partial response; RRMM, relapsed/refractory multiple myeloma.

EMN34 ERASMM – INFECTIONS

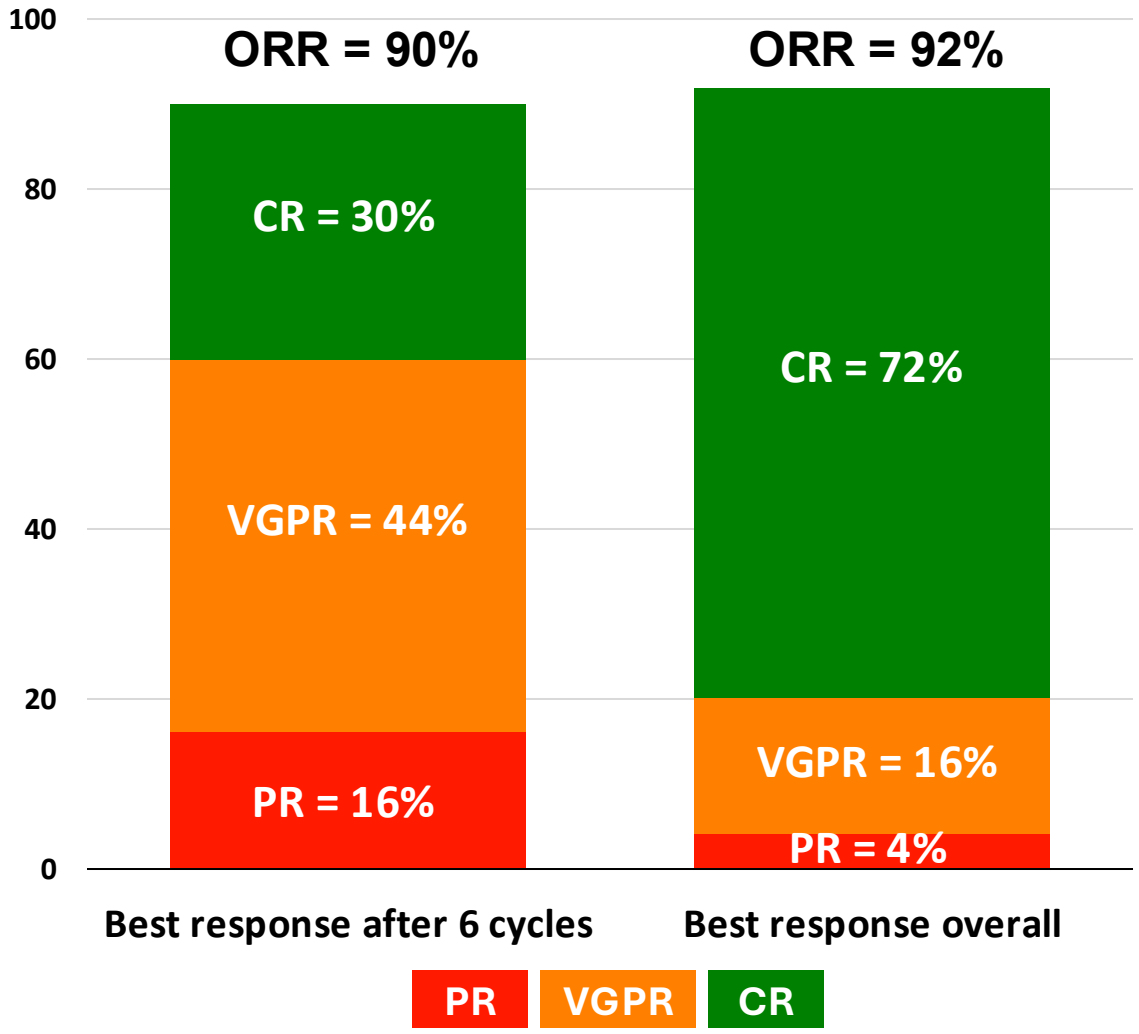
	Any grade n (%)	Grade 3 n (%)
Infections	27 (54)	7 (14)
Most common infections (>5%)		
ENT infection	12 (24)	1 (2)
Respiratory tract infection	10 (20)	3 (6)
COVID-19	4 (8)	2 (4)

- No grade 4 or grade 5 infections
- 43 (86%) patients received prophylactic Ig replacement (SC/IV)
- 10 (20%) patients had IgG levels never lower than 400 mg/dL

The rate of infections with elranatamab in HR-SMM compared favorably with elranatamab in RRMM, including lower rates of grade 3 infections, and no grade ≥4 events

ENT, ear nose and throat; COVID-19, coronavirus disease 2019; CMV, cytomegalovirus; IV, intravenously; SC, subcutaneous; IG, immunoglobulin; IgG, immunoglobulin G; HR, high risk; SMM, smoldering multiple myeloma; RRMM, relapse refractory multiple myeloma.

EMN34 ERASMM – RESPONSE RATES AND MRD



- **After 6 cycles :**

  ORR: 90%
  CR rate*: 30%

- **With a median follow-up of 14 months:**

  ORR: 92%
  CR rate*: 72%

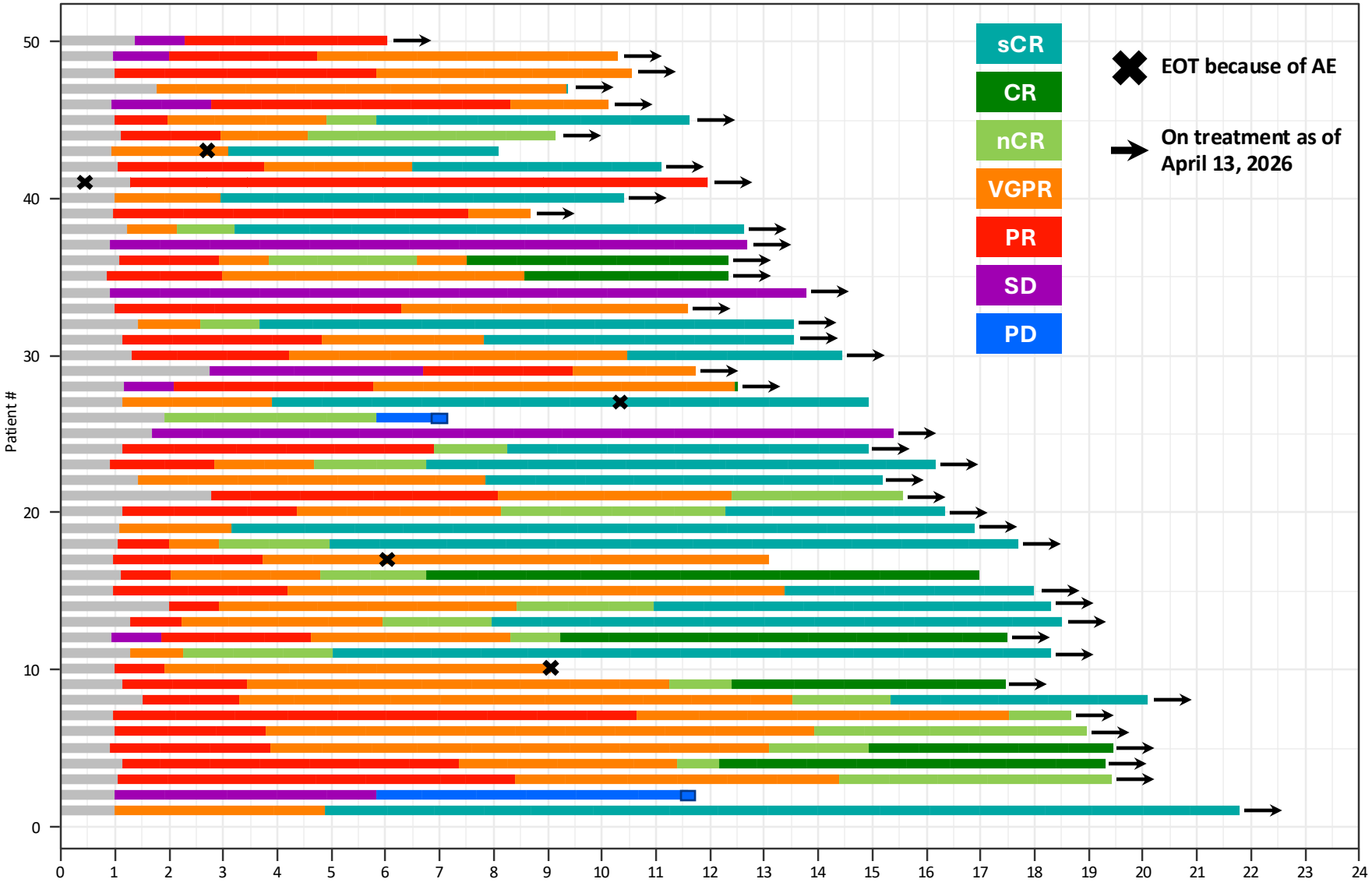
- **MRD (NGS, available in 29 patients**):**

  undetectable MRD (10^{-6}): 90%

**Includes nCR, CR, and sCR.*
***MRD was performed in patients with suspected CR*
Sample collection up to Nov 2025 in the present analysis.

MRD, minimal residual disease; ORR, overall response rate; CR, complete response; VGPR, very good partial response; PR, partial response; NGS, next-generation sequencing; nCR, near complete response; sCR, stringent complete response.

EMN34 ERASMM – RESPONSE RATES AND MRD



Median follow-up: 14 months

All patients are alive

Progression-free survival is 96%

- No progression to active myeloma

- 2 patients had biochemical progression

Treatment ongoing in 86% of patients

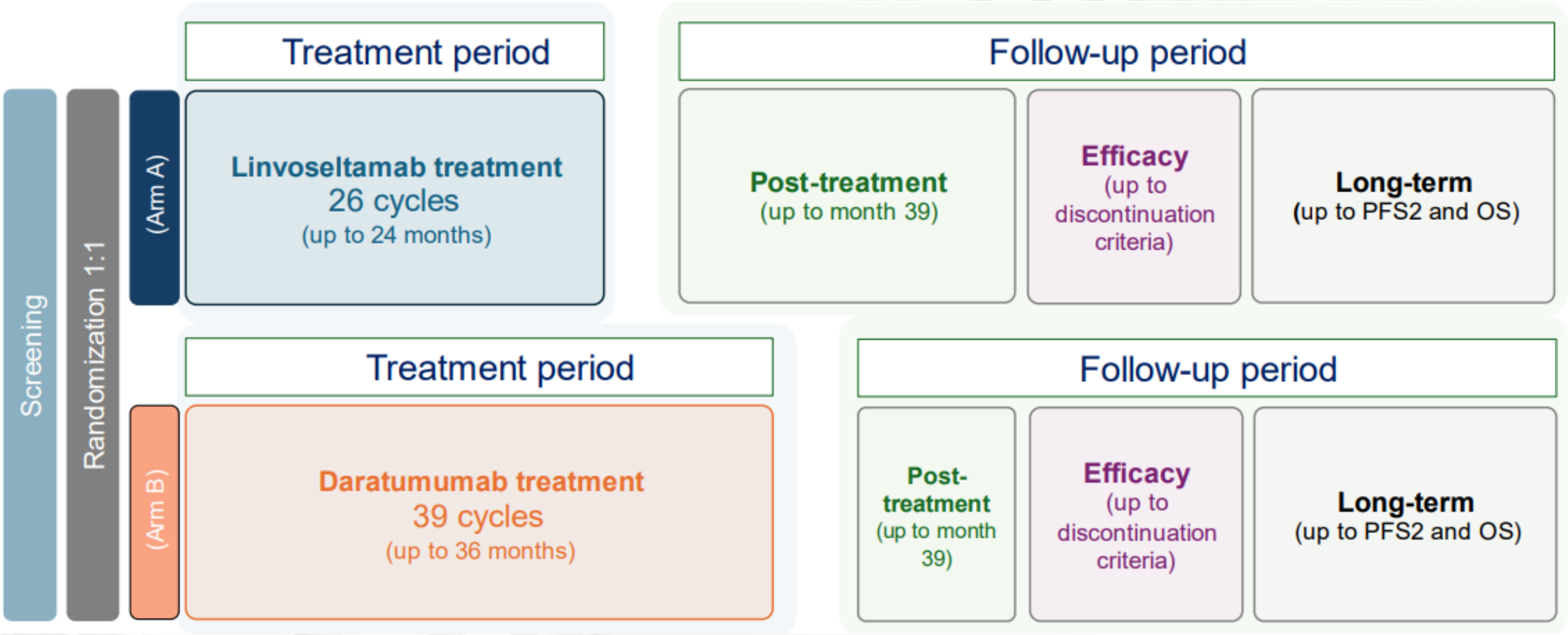
- 5 patients had treatment discontinuation due to AE, all still responders

Cyrille Touzeau

MRD, minimal residual disease; EOT, end of treatment; sCR, stringent complete response; CR, complete response; nCR, near complete response; VGPR, very good partial response; PR, partial response; SD, stable disease; PD, progressive disease; AE, adverse event.

LINKER-SMM2

**Currently enrolling at Emory



SMMART-1: STUDY DESIGN

Multicenter Study: 3 total sites (TBD)

Plan to open in regional sites at MSK

Phase 1

RRMM
≥2 prior LOTs
Prior anti-CD38 allowed
(≥6mos past exposure)
N=2-18 patients

→ **Isatuximab + Etentamig**
ISA 1400 mg SC D8, 15, 22 for C1
D1 and 15 for C2+
Etentamig
Dose level -1: 20 mg
Dose level 1: 40 mg
Dose level 2: 60 mg

Phase 1 primary endpoint:

RP2D ISA + ABBV-383

Phase 2

HRSMM
IMWG 20-2-20 criteria
N=20 pts each cohort

Cycles 1-8	Maintenance
Isatuximab + Etentamig ISA 1400 mg SC D8, 15, 22 for C1, D1 and 15 for C2-8 Etentamig @ RP2D	→ Isatuximab 1400 SC + Etentamig x 12 months (every 8 weeks)
Etentamig monotherapy ABBV-383 60 mg IV every 4 weeks *This cohort will start enrollment before the phase 1 and 2 combination cohort	→ Etentamig x 12 months (every 8 weeks)

Phase 2 primary endpoint: ≥CR rate

Key secondary endpoints: rates of MRD negativity, ORR, DoR, PFS, OS, safety

Response assessment including MRD testing


2019
2020
2021
2022
2023
2024
2025
2026
2.25
Para Concentration gm/dL
6/25/2019 10:04
2.2
2.1
2
1.9
1.8
1.7
1.6
1.5
1.4
1.3
1.2
1.1
1
0.9
0.8
0.7

SUMMARY

- Mayo 2018 or 20-2-20 criteria is used for risk stratification of SMM patients
- Results of the phase 3 AQUILA study led to first FDA approved treatment for SMM but optimal therapy for HRSMM is still debatable
- Ongoing clinical trial investigation regarding other approaches including BsAb in SMM
- Treatment should be considered for HR-SMM
  - Low and intermediate → observation or clinical trial
  - High risk → Pace of progression is an important caveat