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- **ODAC@fda.hhs.gov**

BLA 761145
Daratumumab and hyaluronidase-fihj (Dara SC)
(DARZALEX FASPRO)

Oncologic Drugs Advisory Committee Meeting

FDA Introductory Comments
May 20, 2025

Bindu Kanapuru, MD
Division of Hematologic Malignancies II
Office of Oncologic Diseases

Introduction

Proposed Indication: Dara SC for the treatment of adult patients with ***high-risk smoldering multiple myeloma***

Proposed Dosing Regimen:

1800 mg Dara SC Dosing Schedule

Table 6: Dara SC dosing schedule for monotherapy (4-week cycle)

Weeks	Schedule
Weeks 1 to 8	weekly (total of 8 doses)
Weeks 9 to 24[a]	every two weeks (total of 8 doses)
Week 25 onwards until disease progression or a maximum of 3 years[b]	every four weeks

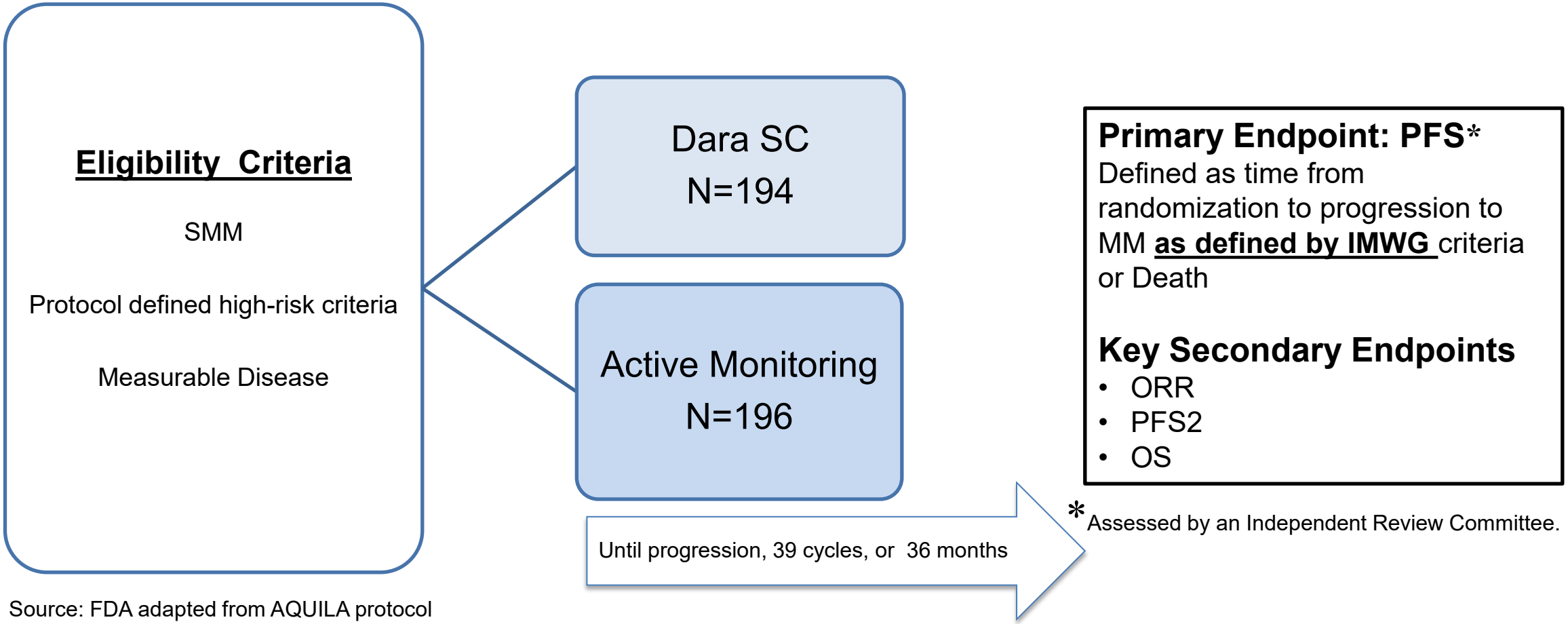
[a] First dose of the every-2-week dosing schedule is given at Week 9
[b] First dose of the every-4-week dosing schedule is given at Week 25

Source: Adapted from proposed USPI

Currently approved for multiple indications for patients with multiple myeloma and patients with newly diagnosed AL amyloidosis

Abbreviations: SC: subcutaneous, USPI: United States Prescribing Information

AQUILA Trial



Source: FDA adapted from AQUILA protocol

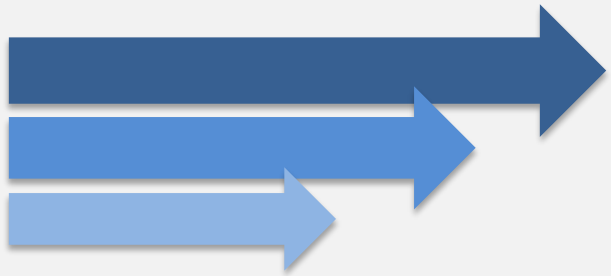
Abbreviations: SC: subcutaneous, SMM: smoldering multiple myeloma, MM: multiple myeloma, IMWG: International Myeloma Working Group, ORR: overall response rate, PFS: progression-free survival, PFS2: progression-free survival 2, OS: overall survival

Smoldering Multiple Myeloma

Precursor condition

Asymptomatic

No end-organ damage



Multiple Myeloma

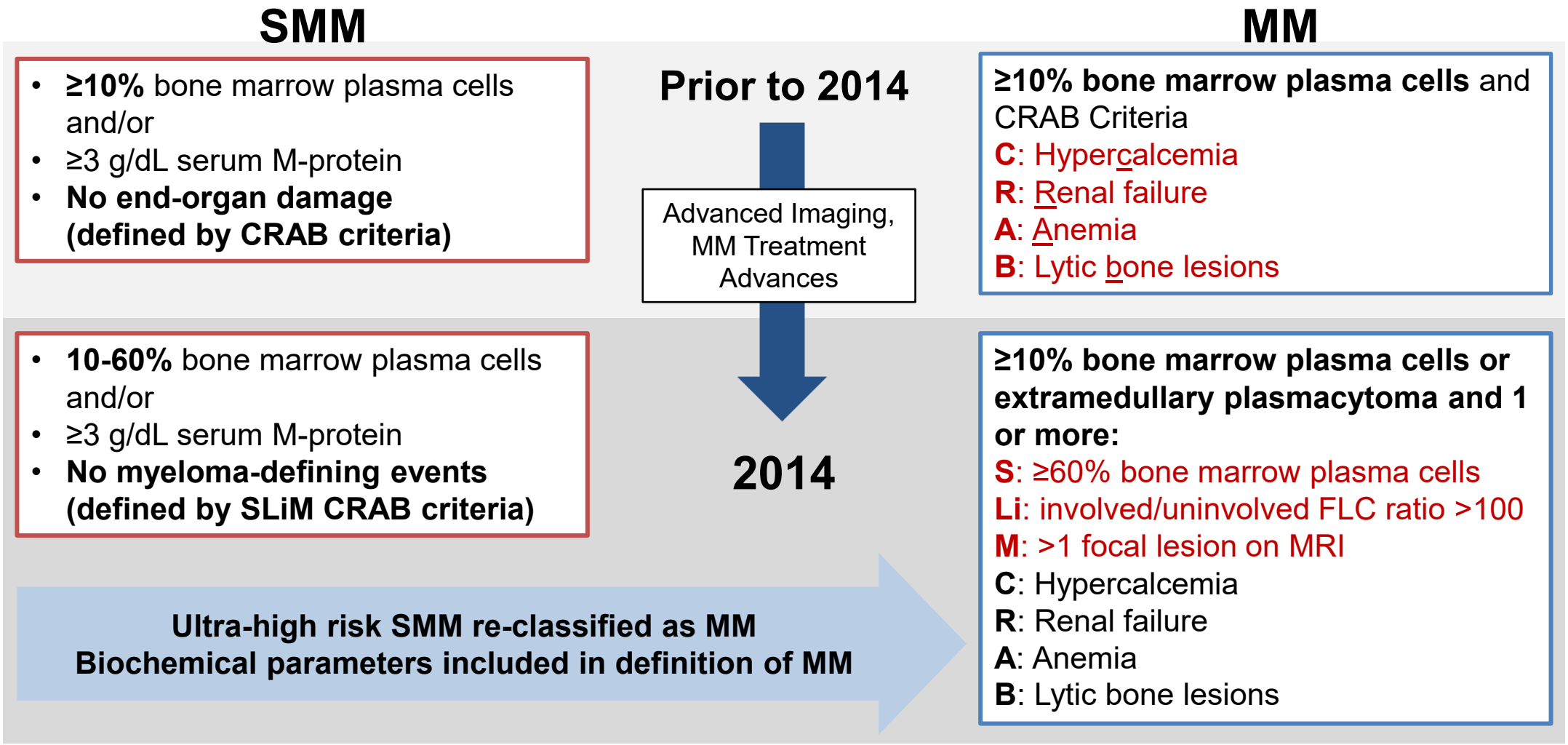
Variable rate of progression

10% per year for the first 5 years → 3% per year for the next 5 years → 1% per year thereafter

Several models have been developed for risk assessment

Kyle RA, Leukemia 2010

Changing Disease Definitions



Rajkumar et al. Lancet Oncol.2014

Abbreviations: SMM: smoldering multiple myeloma, MM: multiple myeloma, M-protein: monoclonal protein, FLC: free light chain, MRI: magnetic resonance imaging

Multiple Models to Predict Risk of Progression

PETHEMA 2007

Definition
- ≥95% aberrant BMPCs by flow cytometry
- Immunoparesis

Risk Level
- 0- Low risk
- 1- Intermediate risk
- 2- High risk

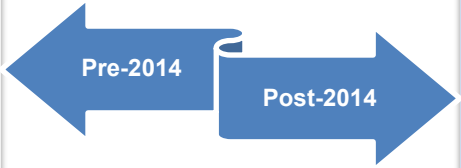
PFS at 5y
- Low risk- 4%
- Intermediate risk- 46%
- High risk- 72%

Mayo 2008

Definition
- BMPCs ≥10%
- M-spike ≥3 g/dL
- sFLC ratio ≤0.125 or ≥8

Risk Level
- 1- Low risk
- 2- Intermediate risk
- 3- High risk

PFS at 5y
- Low risk- 25%
- Intermediate risk- 51%
- High risk- 76%



Mayo 2018*

Definition
- BMPCs >20%
- M-spike >2 g/dL
- sFLC ratio >20

Risk Level
- 0- Low risk
- 1- Intermediate risk
- 2/3- High risk

Progression risk at 5y
- Low risk- 23%
- Intermediate risk- 47%
- High risk- 82%

IMWG 2020

Definition
- BMPCs >20%
- M-spike >2 g/dL
- sFLC ratio >20
- FISH abnormalities

Risk Level
- 0-4 points- Low risk
- 5-8 points- Low/Intermediate risk
- 9-12 points- Intermediate risk
- >12 points- High risk

Progression risk at 5y
- Low risk- 20%
- Low/Intermediate risk- 55%
- Intermediate risk- 70%
- High risk- 85%

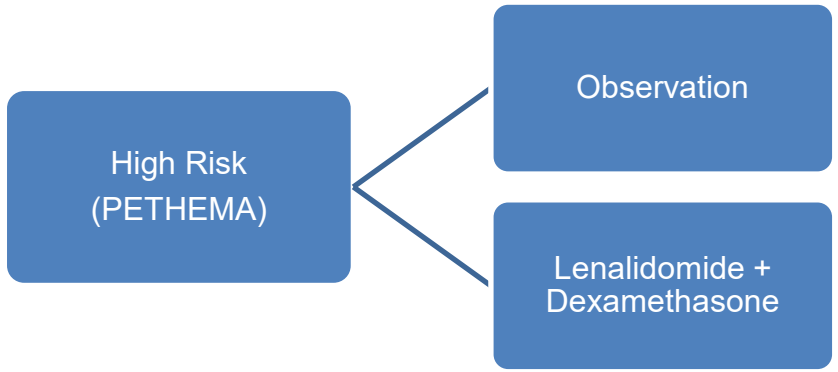
5-year risk of progression is 80-85% for patients at high risk with recent models.

*NCCN Guidelines

Abbreviations: BMPC: bone marrow plasma cells, M-spike: monoclonal spike, sFLC: serum free light chain, PFS: progression-free survival, FISH: fluorescence in situ hybridization

Prior Randomized Trials in SMM

QuiRedex Study



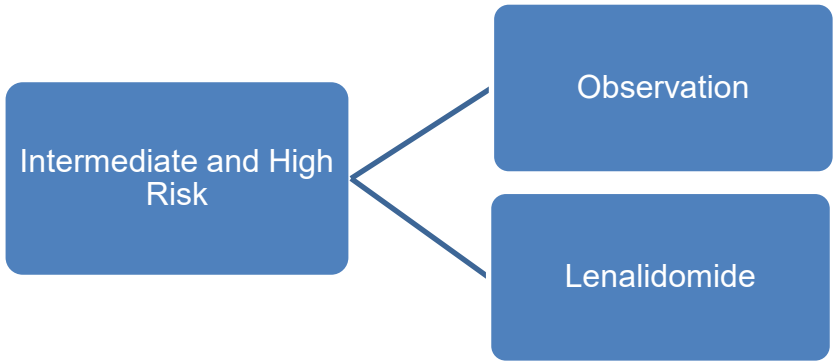
TTP* and OS benefit

Limitations

- Included patients with active myeloma
  - Prior to 2014 update of IMWG criteria
  - No advanced imaging for bone lesions
- Did not isolate the treatment effect of each agent

Mateos MV. et al. NEJM (2013)

ECOG E3A06



PFS* benefit

Limitations

- Heterogeneous population including intermediate and high risk
- PFS pronounced in the Mayo 2018 high-risk
- No OS benefit

Lonial S. et al. J Clin Oncol (2020)

No approved therapies for high-risk SMM

Abbreviations SMM: smoldering multiple myeloma, TTP: time to progression, OS: overall survival, PFS: progression-free survival, IMWG: International Myeloma Working Group

* Primary Endpoint

Current MM Landscape

2014 IMWG Definition

>10% plasma cells or extramedullary plasmacytoma and 1 or more:

S: ≥60% clonal bone marrow plasma cells
Li: involved/uninvolved FLC ratio >100
M: >1 focal lesion on MRI

+

CRAB* Criteria

MM diagnosed prior to end-organ damage
Multiple effective therapies
Improved overall survival

Approved MM Treatments

Newly Diagnosed Transplant Eligible	**D-VTd, D-VRd,** Rd, Td, VMP
Newly Diagnosed Transplant Ineligible	**DRd, D-VMP**, Isa- VRd, Rd, Td, VMP
Relapsed or Refractory	**DRd,** KRd, IRd, ERd, Vd, SVd, **DVd** EPd, IsaPd, **DPd, DKd,** IsaKd, Rd, Kd, Pd, V, **Daratumumab**, Cilta-cel, Ide-cel, Teclistamab, Elranatamab, Talquetamab

* CRAB: Hypercalcemia, renal dysfunction, Anemia, Bone disease

Abbreviations: MM: multiple myeloma, IMWG: International Myeloma Working Group. FLC: free light chain ratio, MRI: magnetic resonance imaging. Proteasome Inhibitors: V: Velcade (bortezomib), K: Kyprolis (carfilzomib), I: ixazomib. immunomodulatory Agents: T: thalidomide, R: Revlimid (lenalidomide), P: pomalidomide. CD38 Monoclonal Antibodies: Isa: isatuximab, D: daratumumab. SLAMF7 Monoclonal Antibody: E: elotuzumab. XPO1 Inhibitor: S: selinexor. Chimeric Antigen Receptor T-cell Therapy: Cilta-cel: ciltacabtagene autoleucel, Ide-cel: idecabtagene vicleucel. Bispecific CD3 T-cell Engagers: teclistamab, elranatamab, talquetamab. Other: MP: melphalan and prednisone, D: dexamethasone.

Issues

- Applicability of AQUILA results to patients with high-risk SMM
- Appropriateness of the endpoints for high-risk SMM population
- Benefit-risk of Dara SC in patients with high-risk SMM

Abbreviation: SMM: smoldering multiple myeloma

Patient Population

- Trial subjects should closely mirror the intended use population

- Results can be applicable to the definable group of patients in routine practice

AQUILA Trial Population

PETHEMA 2007

MAYO 2008

AQUILA Trial Initiated 2017

MAYO 2018

IMWG 2020

Clonal BMPC ≥10% with measurable disease and high-risk defined as at least 1 of the following:

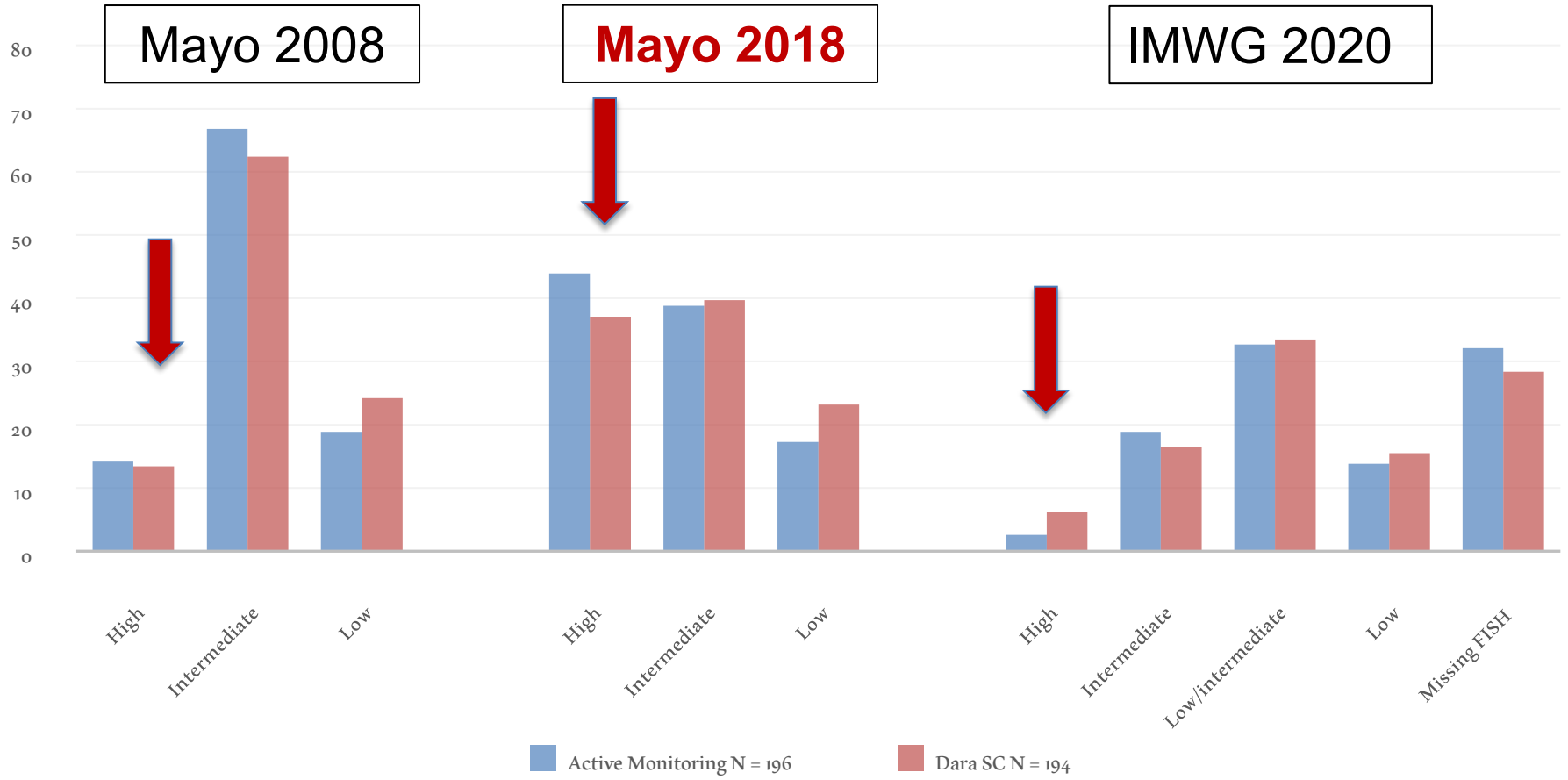
Serum M-protein ≥30 g/L
IgA SMM*
Immunoparesis
50-60% Bone Marrow Plasma Cells with measurable disease*
Serum involved: uninvolved FLC ratio ≥8 and <100

Protocol defined high-risk criteria not aligned with any established models

*Parameters not present in any established risk models

Abbreviations: BMPC: bone marrow plasma cells, M-spike: monoclonal spike, SMM: smoldering multiple myeloma, FLC: free light chain

AQUILA: High Risk SMM Population^



Protocol defined population may not be representative

Source: FDA Analysis

^ PETHEMA Criteria not presented.

Abbreviations: SMM: smoldering multiple myeloma, IMWG: International Myeloma Working Group, FISH: fluorescence in situ hybridization

Endpoint Considerations

- Primary endpoint
  - Valid and reliable measure of clinically relevant and important treatment effect in the patient population
  - The primary endpoint should provide most clinically relevant and convincing evidence

- Secondary endpoints are supportive
  - Should generally be important in interpretation of trial results

International Council of Harmonization (ICH) E9 Guideline Statistical Principles for Clinical Trials

Endpoint Considerations Multiple Myeloma

OS

- Established clinically meaningful endpoint
- May require large sample size
- Always evaluated for harm

Abbreviations: OS: overall survival

Endpoint Considerations Multiple Myeloma

OS

- Established clinically meaningful endpoint
- May require large sample size
- Always evaluated for harm

PFS

- Assessed earlier than OS
- Requires smaller sample size
- PFS is thought to, or in some instances, predict OS

Abbreviations: OS: overall survival, PFS: progression-free survival

Endpoint Considerations Multiple Myeloma

OS

- Established clinically meaningful endpoint
- May require large sample size
- Always evaluated for harm

PFS

- Assessed earlier than OS
- Requires smaller sample size
- PFS is thought to, or in some instances, predicts OS

PFS2

- Not validated
- Limited due to factors not related to initial therapy
- Variability in subsequent therapy use

Abbreviations: OS: overall survival, PFS: progression-free survival, PFS2: progression-free survival2

Endpoint Considerations Smoldering Multiple Myeloma

OS

- May require longer follow-up and large sample size
- OS clinically meaningful endpoint
- ? Demonstrate OS benefit

PFS

- Clinical relevance of the observed delay in progression to MM
- Impact of PFS improvement on OS unknown

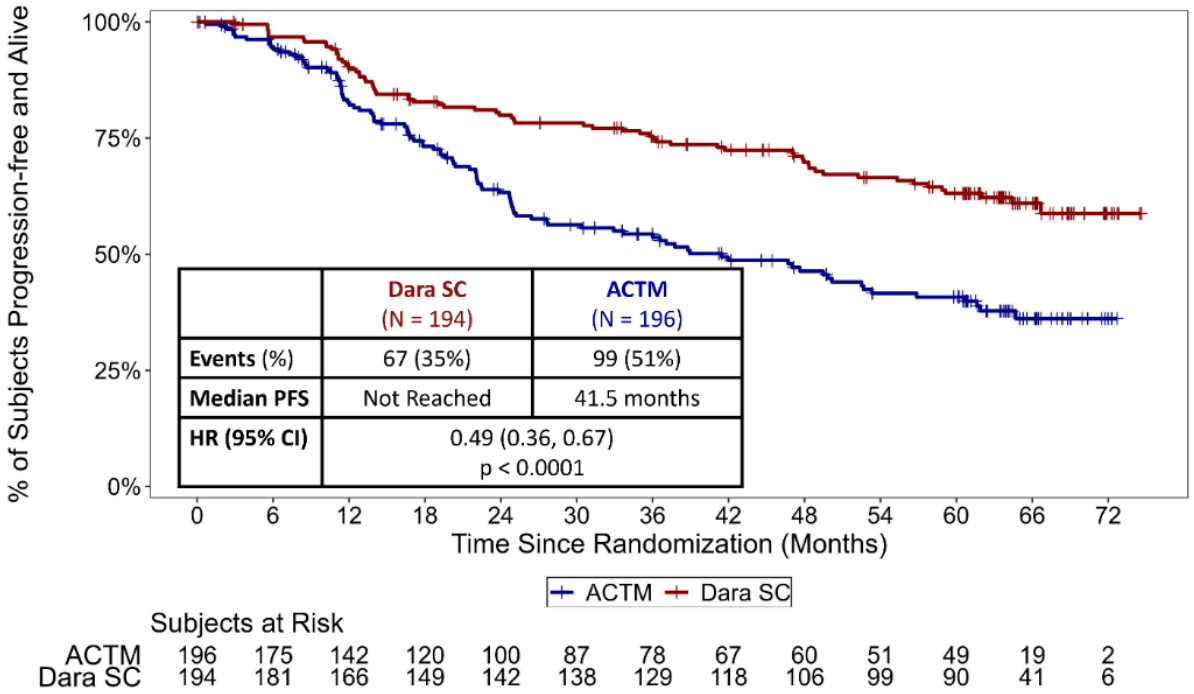
PFS2

- Not validated
- In a precursor setting may help in evaluating impact of treatment sequencing

Abbreviations: OS: overall survival, PFS: progression-free survival, PFS2: progression-free survival2

Clinical Meaningfulness of the PFS Endpoint

PFS



Source: FDA Analysis

≥10% bone marrow plasma cells or extramedullary plasmacytoma and 1 or more:

S: ≥60% bone marrow plasma cells

Li: involved/uninvolved FLC ratio >100

M: >1 focal lesion on MRI

C: Hypercalcemia

R: Renal failure

A: Anemia

B: Lytic bone lesions

PFS endpoint was met

Abbreviations: PFS: progression-free survival, ACTM: active monitoring arm, HR: hazard ratio, CI: confidence interval, FLC: free light chain, MRI: magnetic resonance imaging

Clinical Meaningfulness of PFS Endpoint

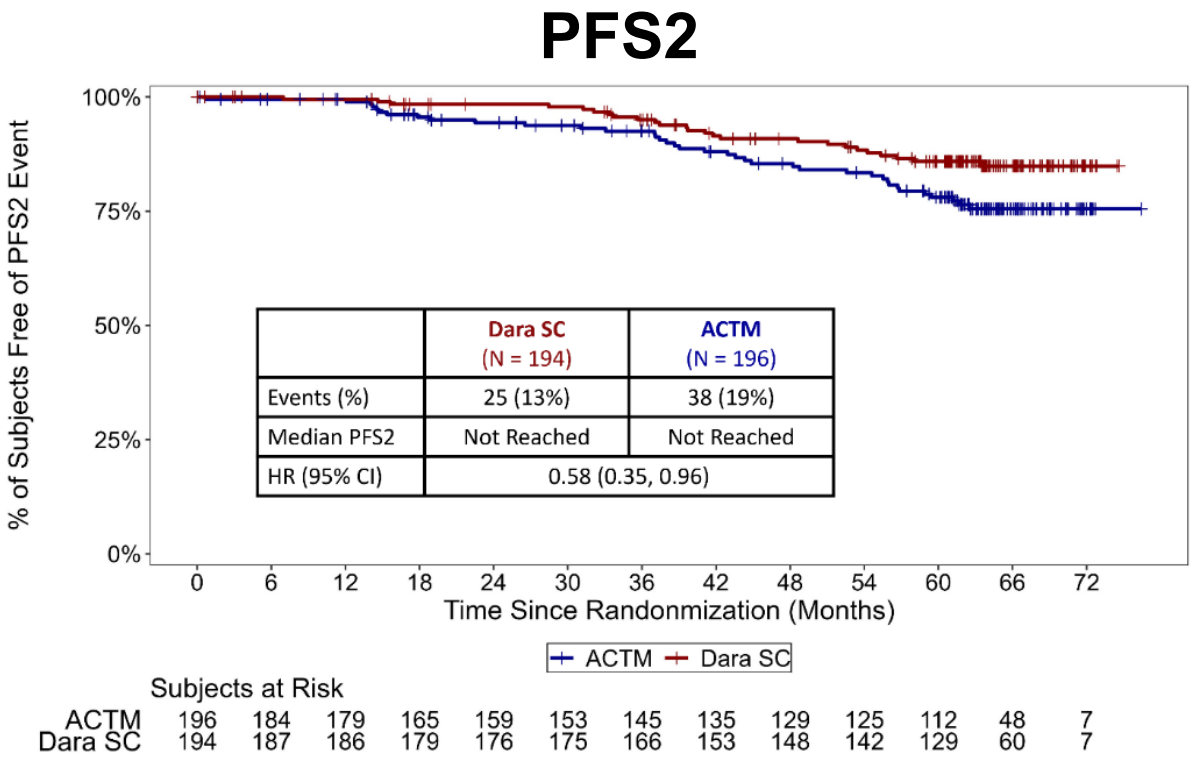
	Daratumumab N = 194 n (%)	Active Monitoring N = 196 n (%)
Subjects with PFS event	67 (35)	99 (51)
Progressive disease (PD)	62 (32)	94 (48)
Reason for PD		
Calcium elevation	0 (0)	2 (1)
Renal insufficiency	0 (0)	0 (0)
Anemia	2 (1)	14 (7)
Bone disease	10 (5)	18 (9)
BM plasma cells	5 (3)	16 (8)
Serum FLC ratio	33 (17)	33 (17)
Focal lesion by MRI	12 (6)	16 (8)
Death	5 (3)	5 (3)

- Low rate of deaths equal between the arms
- Majority of the PFS events were progression in laboratory parameters
- Few PFS events of renal insufficiency and anemia in both arms
- Bone disease was noted predominantly on imaging
- Variability in MM treatment initiation

Source: FDA Analysis

Abbreviations: PFS: progression-free survival, MM: multiple myeloma

AQUILA: PFS2 Endpoint



	Dara SC (N = 194)	ACTM (N = 196)
Events (%)	25 (13%)	38 (19%)
Median PFS2	Not Reached	Not Reached
HR (95% CI)	0.58 (0.35, 0.96)	

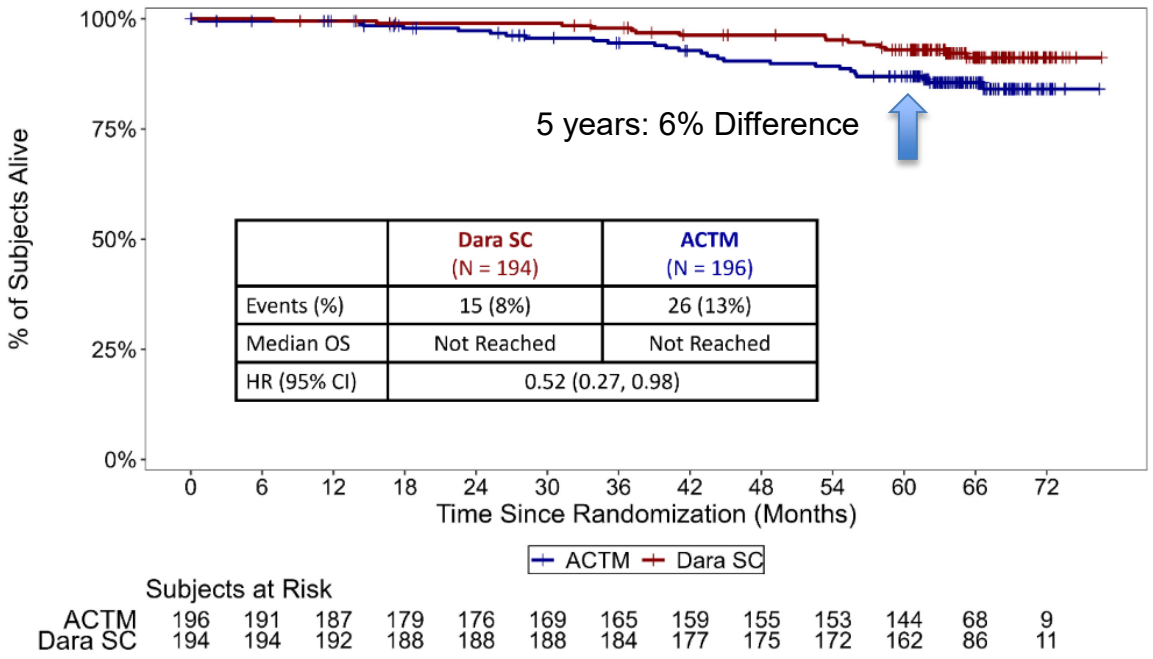
Source: FDA Analysis

- PFS2 results are not significantly different between the two arms
- PFS2 results confounded by receipt of subsequent therapy and type of therapy
  - Approximately 20% did not initiate therapy at MM diagnosis.
  - Low percentage received Daratumumab based therapy at MM diagnosis.
- Uncertainty regarding the sequencing of therapies and benefit of upfront treatment

Abbreviations: PFS2: progression-free survival2, ACTM: active monitoring arm, HR: hazard ratio, CI: confidence interval

AQUILA: Overall Survival

OS



Source: FDA Analysis

- Low OS event rates
- Marginal difference at 5 years
- Lack of sufficient information regarding cause of deaths
- Limitations of the OS results to inform benefit-risk

Abbreviations: OS: overall survival, ACTM: active monitoring arm, HR: hazard ratio, CI: confidence interval

Safety and PROs

- Administration of Dara SC is associated with significant toxicities
  - A higher overall incidence of TEAEs, severe TEAEs (Grade 3 or 4), SAEs and dose modifications
- Rates of infections were 2-fold higher with Dara SC
- Several AEs including musculoskeletal pain, upper respiratory tract infection, fatigue, diarrhea, nasopharyngitis, sleep disorder, rash, and sensory neuropathy were higher in the Dara SC arm compared to the ACTM arm
- PROs were not informative
  - Sparse assessment
  - Measures may not be not appropriate for this population

Abbreviations: TEAEs: treatment emergent adverse events, SAEs: serious adverse events, PROs: patient reported outcomes, ACTM: active monitoring arm

Uncertain Benefit-risk

- Less than half the participants were high-risk based on the current criteria
- Clinical meaningfulness of the observed benefit is unclear
  - Delay in progression to MM but uncertainty in PFS results
  - No appreciable improvement in PFS2
  - Lack of robust OS data
- Impact of SMM treatment on MM treatment and outcomes unclear
- Safety profile may not be favorable for the SMM population
  - High rates of several clinically relevant toxicities

Abbreviations: MM: multiple myeloma, PFS2: progression-free survival2, OS; overall survival, SMM: smoldering multiple myeloma

Evidentiary Criteria for Approval

- Safe and Effective
  - FDA must determine that the drug is safe and effective for use under the conditions prescribed, recommended, or suggested in the proposed labeling

- Benefits must outweigh the risks
  - Demonstration of effectiveness requires substantial evidence that the drug will have the effect it purports or is represented to have
  - Demonstration of safety requires showing that benefits of the drug outweigh its risks

Guidance for Industry: Benefit-Risk Assessment for New Drug and Biological Products
Guidance for Industry: Demonstrating Substantial Evidence of Effectiveness for Human Drugs and Biological Products

Discussion Topics

- Discuss the clinical meaningfulness of the efficacy endpoints assessed in the AQUILA trial

- Discuss the benefit-risk of Dara SC for the intended high-risk SMM population

Abbreviation: SMM: smoldering multiple myeloma

Voting Question

Do the results from the AQUILA trial provide sufficient evidence to support a favorable benefit-risk profile for Dara SC for patients with high-risk SMM?

Abbreviation: SMM: smoldering multiple myeloma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ADMINISTRATION

BLA 761145

Daratumumab and hyaluronidase-fihj (Dara SC)
(DARZALEX FASPRO)

Oncologic Drugs Advisory Committee Meeting
May 20, 2025

Payal Aggarwal, DO, MS
Division of Hematologic Malignancies II
Office of Oncologic Diseases

FDA Review Team

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Darzalex Faspro (Dara SC)

- **Proposed Indication**: For the treatment of adult patients with *high-risk smoldering multiple myeloma* as monotherapy

- **Proposed Dosing Regimen**: 1800 mg Dara SC

Weeks	Schedule
Weeks 1 to 8	Weekly (total of 8 doses)
Weeks 9 to 24[a]	Every 2 weeks (total of 8 doses)
Week 25 onwards until disease progression or a maximum of three years[b]	Every 4 weeks

[a] First dose of the every-2-week dosing schedule is given at Week 9
[b] First dose of the every-4-week dosing schedule is given at Week 25
Source: Adapted from current USPI

- FDA approved for newly diagnosed or relapsed or refractory multiple myeloma and newly diagnosed AL amyloidosis

Abbreviations: AL= amyloid light chain, SC= subcutaneous, USPI= United States prescribing information

Presentation Outline

- ❑ Applicability of AQUILA trial results to patients with high-risk Smoldering Multiple Myeloma
- ❑ Endpoints for high-risk SMM in the AQUILA trial
  - Clinical relevance of Progression Free Survival endpoint
  - PFS2 endpoint
  - Overall Survival as an endpoint in SMM
- ❑ Safety findings and patient reported outcomes from the AQUILA trial

Abbreviations: SMM= smoldering multiple myeloma, PFS2= progression-free survival 2

Background: Smoldering Multiple Myeloma

- **Precursor condition**
- **Plasma cell proliferation in the bone marrow without end-organ damage**

Current Definition of SMM:

- Clonal bone marrow plasma cells: 10-60% and/or
- Serum M-protein: ≥3 g/dL and/or
- Urinary M-protein ≥0.5 g/24h

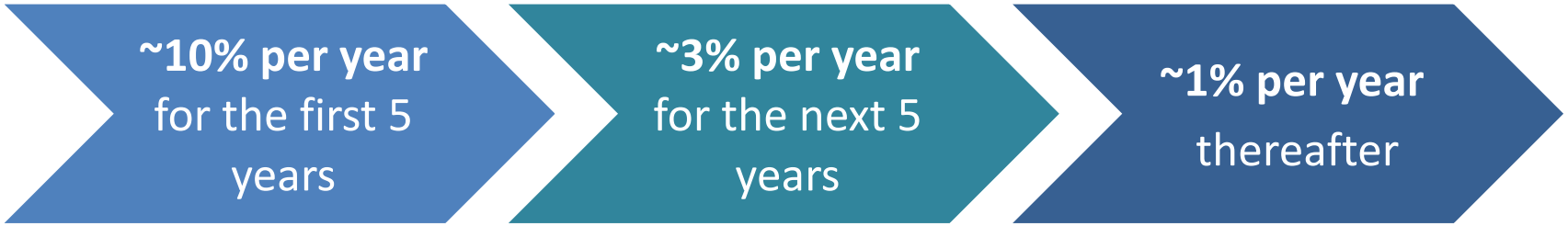
AND

- No evidence of other B-cell proliferative disorder
- No myeloma-related organ or tissue impairment or bone lesion

Abbreviations: M-protein= monoclonal protein, SMM= smoldering multiple myeloma

Source: Rajkumar SV, Blood (2015)

Background: SMM



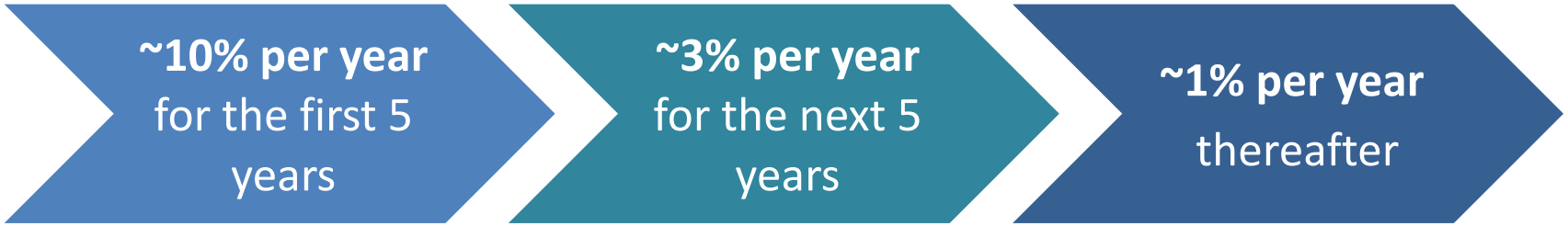
Risk stratification of patients with SMM and 2-year risk of progression

Low Risk	Intermediate Risk	High Risk
4% – 10%	26% – 51%	47% – 73%

Abbreviations: SMM= smoldering multiple myeloma

Source: Kyle RA, Leukemia (2010), Rajkumar SJ, Am J Hematol (2022)

Background: SMM



Risk stratification of patients with SMM and 2-year risk of progression

Low Risk	Intermediate Risk	High Risk
4% – 10%	26% – 51%	47% – 73%

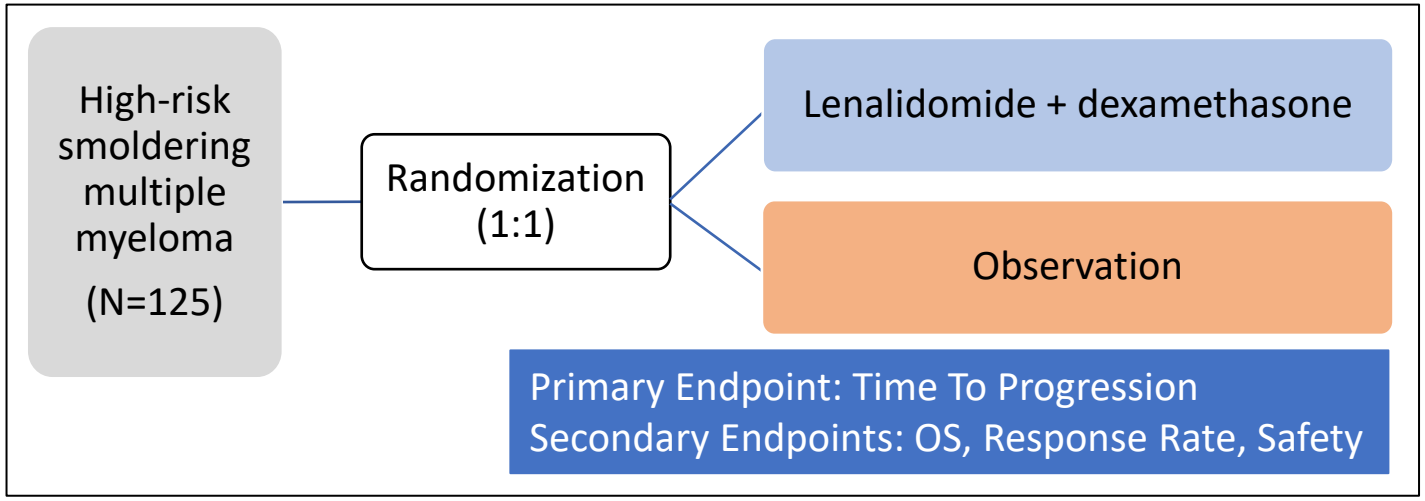
Treatment Landscape

Observation	Observation	Observation, Lenalidomide, Clinical Trials

Abbreviations: SMM= smoldering multiple myeloma

Source: Kyle RA, Leukemia (2010), Rajkumar SJ, Am J Hematol (2022)

Trials in SMM: QuiRedex



Inclusion criteria:

- Patients with SMM and high risk of progression to symptomatic disease

High Risk criteria:

- Bone marrow plasma cell infiltration ≥10% and/or
- Presence of a monoclonal component (IgG ≥3g/dL or IgA ≥2g/dL or Bence-Jones proteinuria >1g/24 h)
- Plus at least 95% phenotypically aberrant plasma cells with immunoparesis (reductions in one or two uninvolved immunoglobulins of >25%)

Abbreviations: TTP= time to progression, OS= overall survival, Ig= immunoglobulin, IMWG= International Myeloma Working Group, SMM= smoldering multiple myeloma

Source: Mateos MV, NEJM, (2013)

Trials in SMM: QuiRedex

High-risk smoldering multiple myeloma (N=125)

Randomization (1:1)

- Lenalidomide + dexamethasone
- Observation

Primary Endpoint: Time To Progression
Secondary Endpoints: OS, Response Rate, Safety

Inclusion criteria:

- Patients with SMM and high risk of progression to symptomatic disease

High Risk criteria:

- Bone marrow plasma cell infiltration ≥10% and/or
- Presence of a monoclonal component (IgG ≥3g/dL or IgA ≥2g/dL or Bence-Jones proteinuria >1g/24 h)
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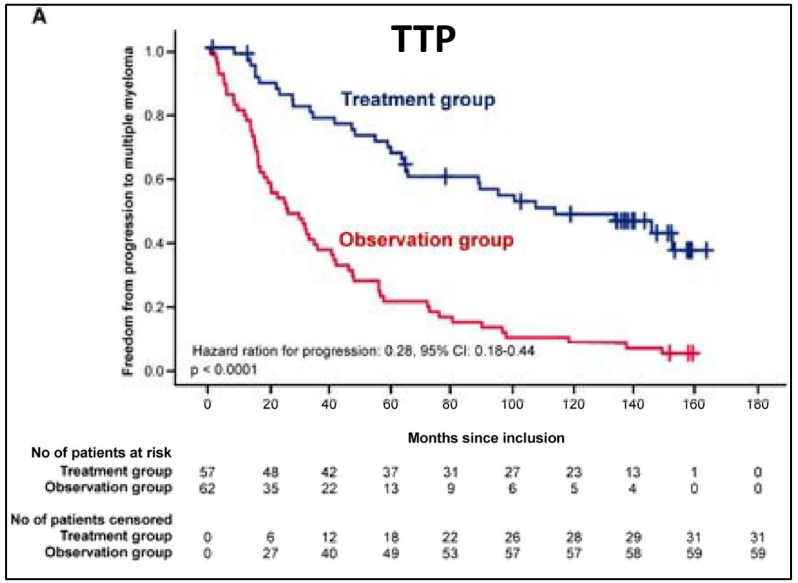
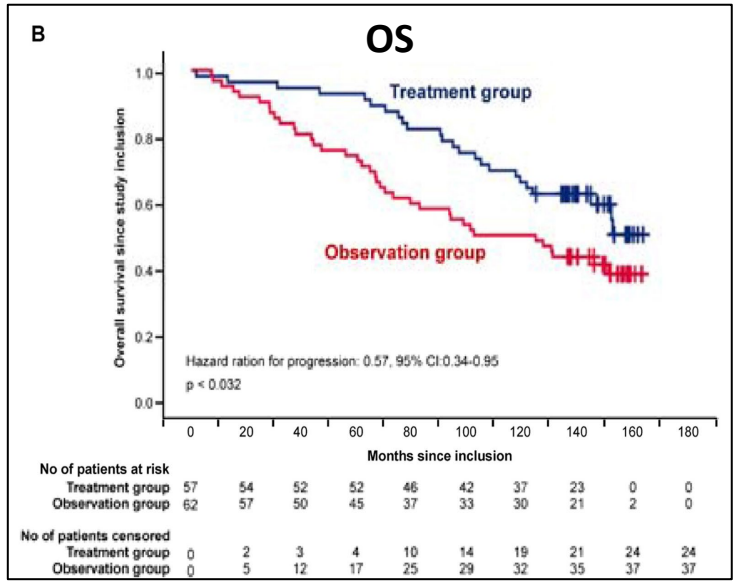




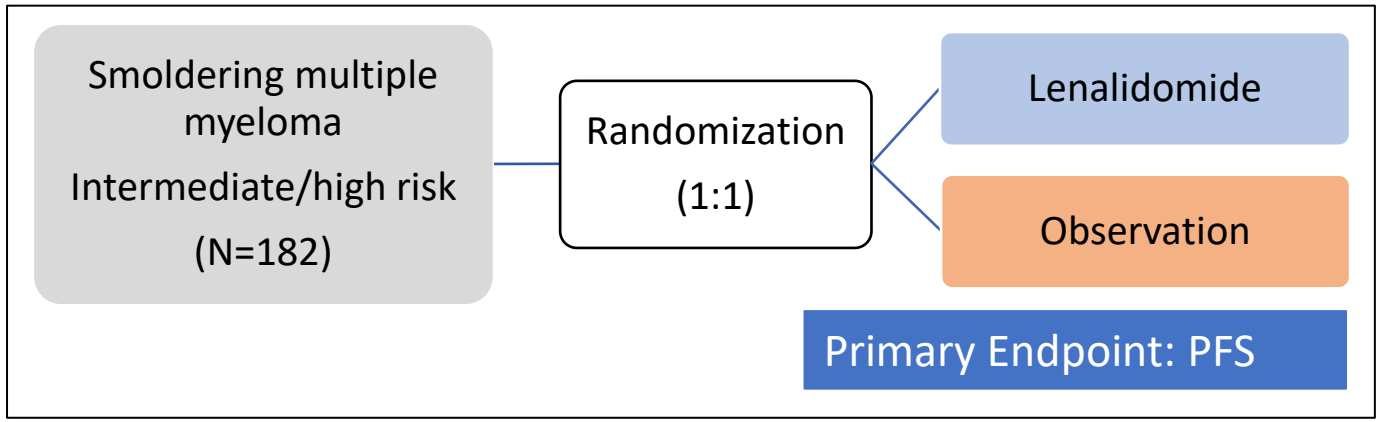
Key Limitations:

- Possible inclusion of patients with active myeloma
  - Prior to 2014 update of IMWG criteria
- Combination regimen does not isolate effect of each agent

Abbreviations: TTP= time to progression, OS= overall survival, Ig= immunoglobulin, IMWG= International Myeloma Working Group, SMM= smoldering multiple myeloma

Source: Mateos MV, NEJM, (2013)

Trials in SMM: ECOG E3A06



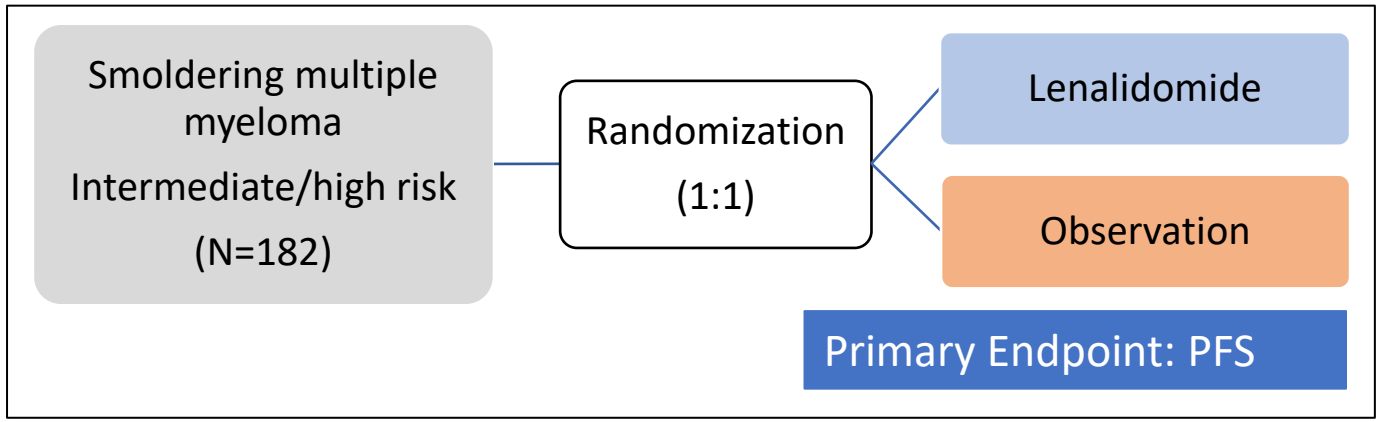
Inclusion criteria:

- Asymptomatic intermediate or high-risk SMM confirmed by both:
  - Bone marrow plasmacytosis ≥10%
  - Abnormal serum FLC ratio (<0.26 or >1.65)

Abbreviations: FLC= free light chains, OS= overall survival, PFS= progression-free survival, SMM= smoldering multiple myeloma

Source: Lonial S, J Clin Oncol (2020)

Trials in SMM: ECOG E3A06



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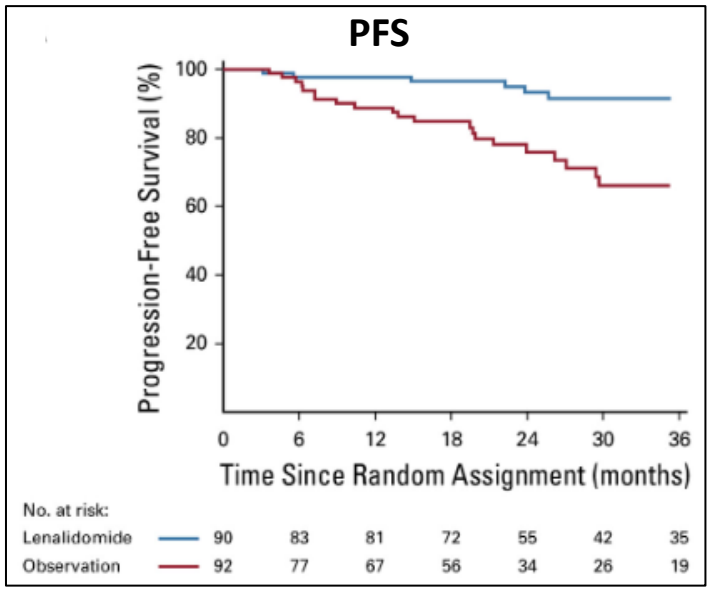
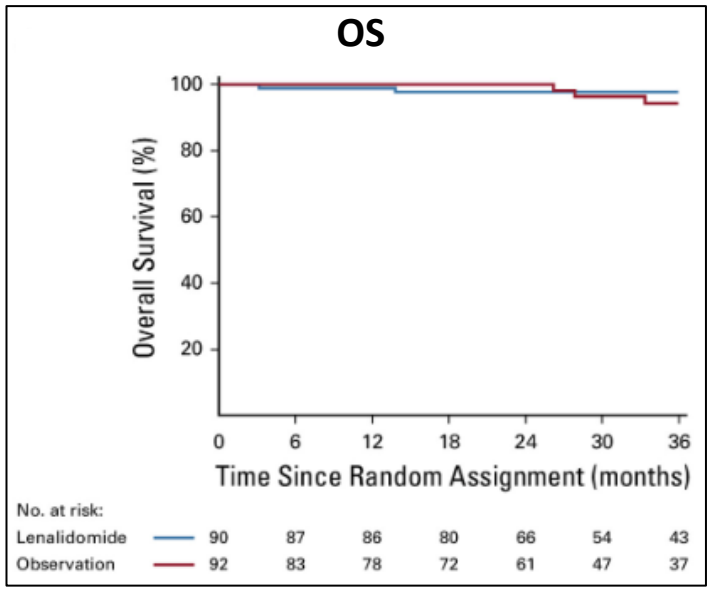




Key Limitations:

- Heterogenous population including intermediate and high risk (by protocol defined criteria)
- PFS endpoint included biochemical progression
- No OS benefit seen

Abbreviations: FLC= free light chains, OS= overall survival, PFS= progression-free survival, SMM= smoldering multiple myeloma

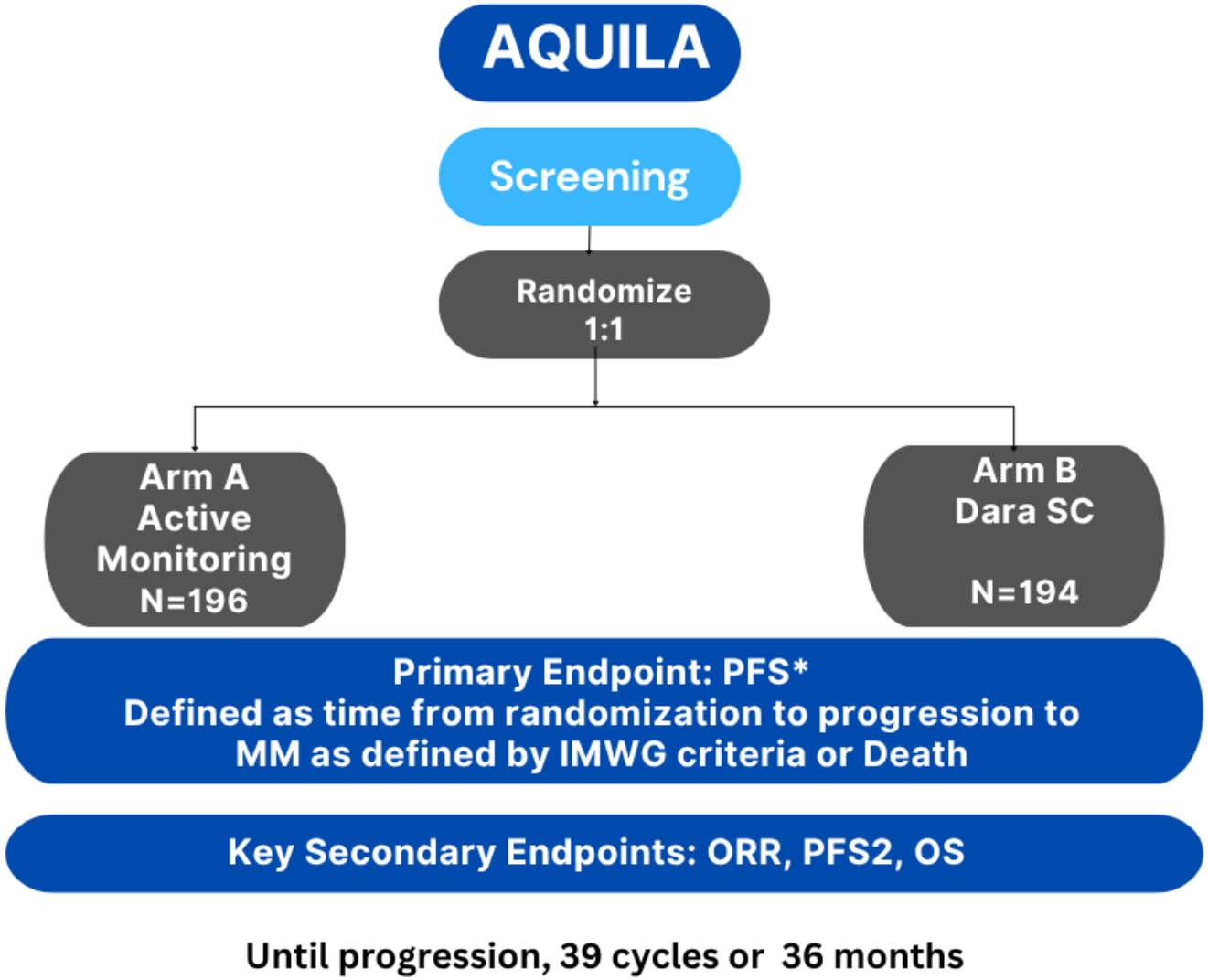
Source: Lonial S, J Clin Oncol (2020)

Presentation Outline

- ❑ Applicability of AQUILA trial results to patients with high-risk Smoldering Multiple Myeloma
- ❑ Endpoints for high-risk SMM in the AQUILA trial
  - Clinical relevance of Progression Free Survival endpoint
  - PFS2 endpoint
  - Overall Survival as an endpoint in SMM
- ❑ Safety findings and patient reported outcomes from the AQUILA trial

Abbreviations: PFS2= progression-free survival 2, SMM= smoldering multiple myeloma,

SMM3001 (AQUILA): Pivotal Phase 3 Study



*Assessed by an Independent Review Committee

Abbreviations: IMWG= International Myeloma Working Group, MM= multiple myeloma, ORR= overall response rate, OS= overall survival, PD= progressive disease, PFS= progression-free survival, PFS2= progression-free survival 2, SC= subcutaneous

Source: FDA Adapted Image

AQUILA: Demographics

	Dara SC N=194	ACTM N=196
Median Age (range), years	63 (31, 86)	64.5 (36, 83)
Age Group, years (%)		
18 to <65	55	50
65 to <75	35	38
≥75	11	12
Sex (%)		
Female	51	53
Male	49	47
Race (%)		
White	83	83
Black/African American	2	4
Asian	9	7
American Indian	0	2
Native Hawaiian	0	1

	Dara SC N=194	ACTM N=196
Ethnicity (%)		
Hispanic or Latino	7	5
Not Hispanic or Latino	87	90
Not Reported	6	6
Geographic Region (%)		
USA	15	14
Israel	14	14
United Kingdom	9	9
Japan	8	7
Spain	5	7
Australia	3	5

Abbreviations: ACTM= active monitoring

Source: FDA Analysis

High-Risk Models for SMM

PETHEMA 2007

Definition
- ≥95% aberrant BMPCs by flow cytometry
- Immunoparesis (reduction of >1 uninvolved heavy chain)

Risk Level
- 0- Low risk
- 1- Intermediate risk
- 2- High risk

PFS at 5y
- Low risk- 4%
- Intermediate risk- 46%
- High risk- 72%

Mayo 2008

Definition
- BMPCs ≥10%
- M-protein ≥3 g/dL
- sFLC ratio ≤0.125 or ≥8

Risk Level
- 1- Low risk
- 2- Intermediate risk
- 3- High risk

PFS at 5y
- Low risk- 25%
- Intermediate risk- 51%
- High risk- 76%

Pre-2014

Post-2014

Mayo 2018*

Definition
- BMPCs >20%
- M-protein >2 g/dL
- sFLC ratio >20

Risk Level
- 0- Low risk
- 1- Intermediate risk
- 2/3- High risk

Progression risk at 5y
- Low risk- 23%
- Intermediate risk- 47%
- High risk- 82%

IMWG 2020

Definition
- BMPCs >20%
- M-protein >2 g/dL
- sFLC ratio >20
- FISH abnormalities

Risk Level
- 0-4 points- Low risk
- 5-8 points- Low/Intermediate risk
- 9-12 points- Intermediate risk
- >12 points- High risk

Progression risk at 5y
- Low risk- 20%
- Low/Intermediate risk- 55%
- Intermediate risk- 70%
- High risk- 85%

Risk varies from 4 to 25% for low-risk to 72 to 85% for patients at high-risk of progression

*National Comprehensive Cancer Network (NCCN Guidelines)

Abbreviations: BMPCs= bone marrow plasma cells, FISH= fluorescence in situ hybridization, M-protein= monoclonal protein, PFS= progression-free survival, sFLC= serum free light chains

AQUILA: Protocol-Defined High-Risk Criteria

PETHEMA 2007

Definition
- ≥95% aberrant BMPCs by flow cytometry
- Immunoparesis (reduction of >1 uninvolved heavy chain)

Risk Level
- 0- Low risk
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IMWG 2020

Definition
- BMPCs >20%
- M-protein >2 g/dL
- sFLC ratio >20
- FISH abnormalities

Risk Level
- 0-4 points- Low risk
- 5-8 points- Low/Intermediate risk
- 9-12 points- Intermediate risk
- >12 points- High risk

Progression risk at 5y
- Low risk- 20%
- Low/Intermediate risk- 55%
- Intermediate risk- 70%
- High risk- 85%

AQUILA Protocol

Diagnosis of SMM per IMWG criteria, Clonal BMPC ≥10% and

at least 1 of the following high-risk factors

a) **Serum M-protein ≥30 g/L**
b) **IgA SMM**
c) **Immunoparesis with reduction of 2 uninvolved immunoglobulin isotypes**
d) **Serum involved-uninvolved FLC ratio ≥8 and <100 OR**
e) **Clonal BMPCs >50% to <60% with measurable disease**

AQUILA protocol used criteria from various SMM high-risk models and additional criteria to define patients with high-risk MM

*NCCN Guidelines

Abbreviations: BMPCs= bone marrow plasma cells, FISH= fluorescence in situ hybridization, M-protein= monoclonal protein, PFS= progression-free survival, sFLC= serum free light chains

AQUILA: High-Risk Criteria

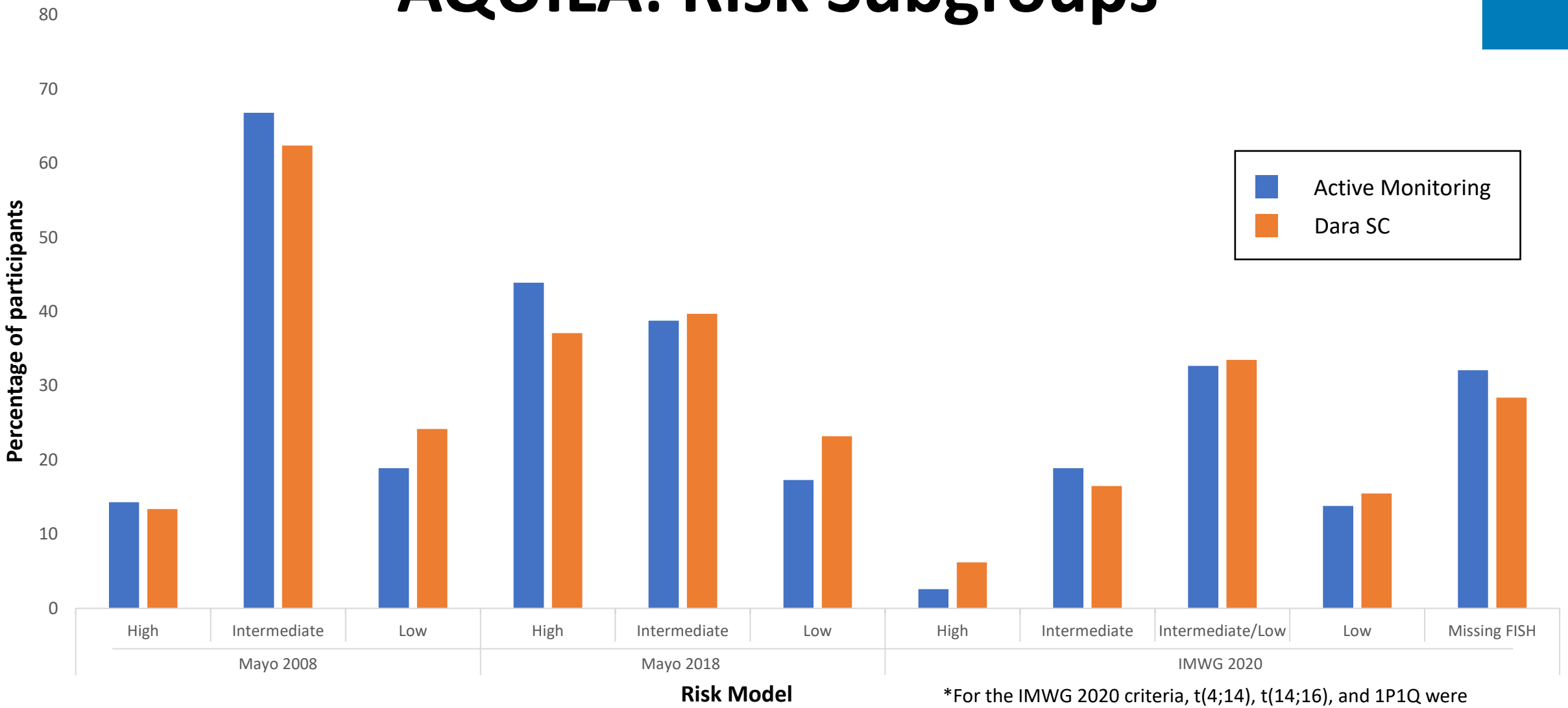
High Risk Criteria§ (Protocol-defined)	Dara SC N=194	ACTM N=196
Serum M-protein ≥30g/L (%)	18	20
Involved:Uninvolved serum FLC ratio ≥8 and <100 (%)	70	75
Clonal BMPC >50% to <60% (%)	3	2
IgA SMM (%)	28	21
Immunoparesis with reduction of 2 uninvolved immunoglobulin isotypes (%)	60	59
Number of Risk Factors (%)		
0	3	0
1	37	41
2	41	41
3	18	16
4	2	2
Number of High-Risk Criteria (%)		
≤2	81	82
>2	19	18

Majority of participants met the serum FLC and immunoparesis criteria

Abbreviations: ACTM= active monitoring, BMPC= bone marrow plasma cell, FLC= free light chains, M-protein= monoclonal protein, SC= subcutaneous, SMM= smoldering multiple myeloma. § Participants may meet one or more risk criteria

Source: FDA Analysis

AQUILA: Risk Subgroups



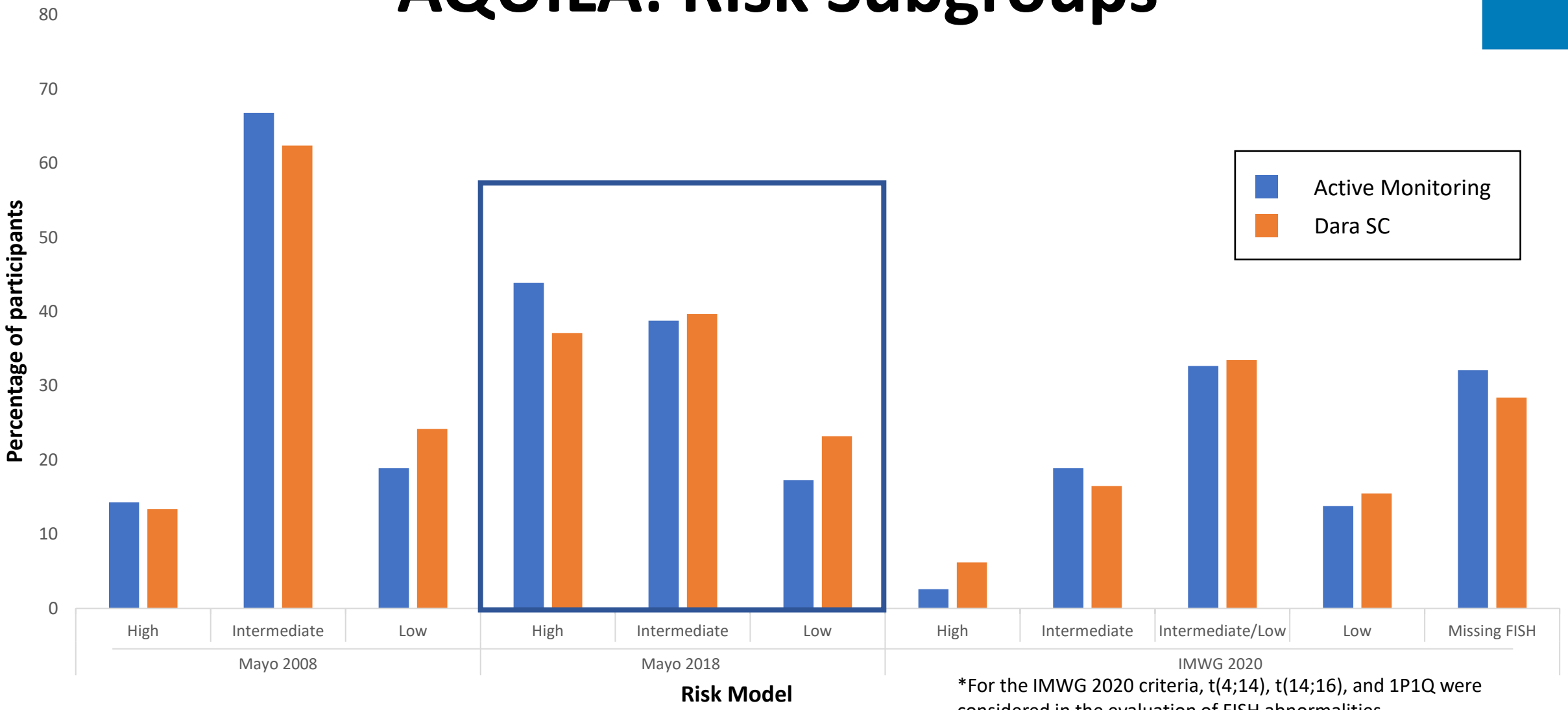
*For the IMWG 2020 criteria, t(4;14), t(14;16), and 1P1Q were considered in the evaluation of FISH abnormalities.

Various risk groups of participants were enrolled on the AQUILA trial

Abbreviations: FISH= fluorescence in situ hybridization, IMWG= International Myeloma Working Group, SC= subcutaneous

Source: FDA Analysis

AQUILA: Risk Subgroups



*For the IMWG 2020 criteria, t(4;14), t(14;16), and 1P1Q were considered in the evaluation of FISH abnormalities.

Less than half of trial participants would be categorized as high-risk by the Mayo 2018 model

Abbreviations: FISH= fluorescence in situ hybridization, IMWG= International Myeloma Working Group, SC= subcutaneous

Source: FDA Analysis

Summary: Trial Population

- Applicability of AQUILA trial results to patients with high-risk Smoldering Multiple Myeloma
  - Protocol-defined definition of high-risk SMM did not completely align with the available high-risk models
  - AQUILA trial participants have varying risk of progression to MM
  - Less than half of the trial participants would have met high-risk criteria using the Mayo 2018 risk model

Abbreviations: MM= multiple myeloma, SMM= smoldering multiple myeloma

Presentation Outline

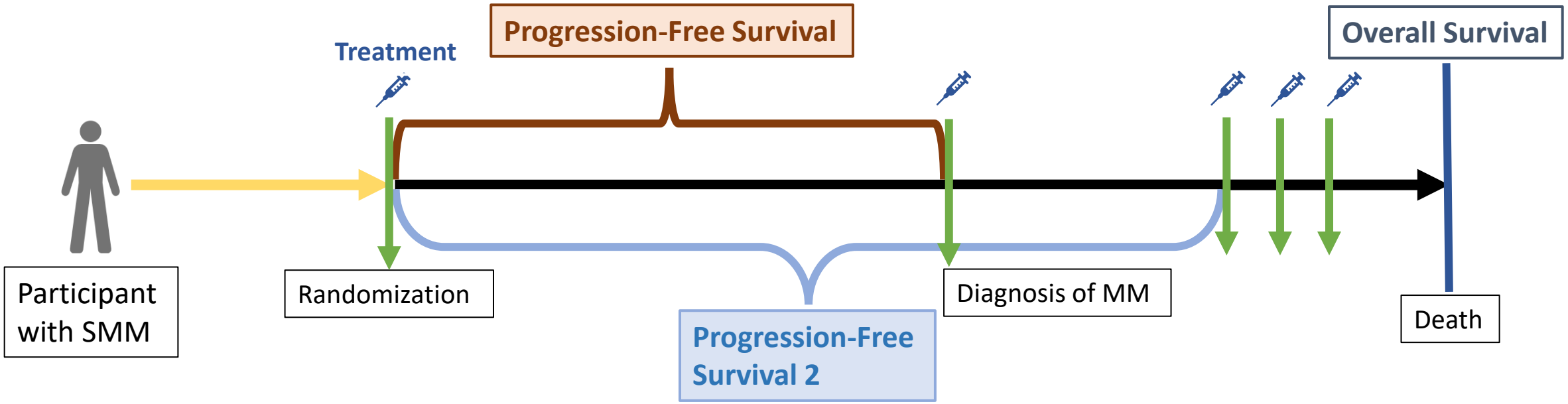
- Applicability of AQUILA trial results to patients with high-risk Smoldering Multiple Myeloma
- Endpoints for high-risk SMM in the AQUILA trial
  - Clinical relevance of Progression-Free Survival endpoint
  - PFS2 endpoint
  - Overall Survival as an endpoint in SMM
- Safety findings and patient reported outcomes from the AQUILA trial

Abbreviations: PFS2= progression-free survival 2, SMM= smoldering multiple myeloma

Endpoints Used in Oncology

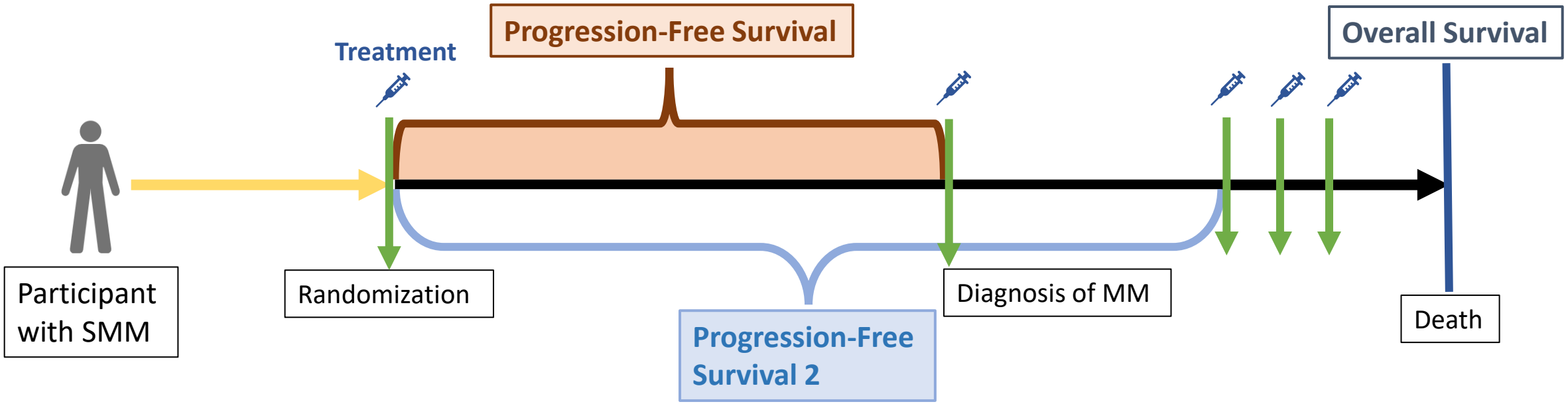
Overall Survival (OS)	Progression-Free Survival (PFS)
• Measures safety and efficacy • Easily and precisely measured • Meaningful to patients	• Usually requires smaller sample size • Assessed earlier than survival
• May require long follow-up and/or large sample size for some diseases • Affected by crossover or subsequent therapy	• May be subject to assessment bias • May be defined differently across trials • **Does not always correlate with overall survival**
• **Always considered in regulatory decisions**	• **Primary endpoint for most trials supporting traditional approval in hematologic malignancies including Multiple Myeloma**

Endpoints for SMM: AQUILA



Abbreviations: MM= multiple myeloma, SMM= smoldering multiple myeloma

Endpoints for SMM: AQUILA



- SMM is a precursor condition and there are no therapies currently approved
- Uncertainties of early treatment prior to the development of Multiple Myeloma

Abbreviations: MM= multiple myeloma, SMM= smoldering multiple myeloma

Disease Criteria Overview

Smoldering Multiple Myeloma

Prior to 2014
- ≥10% bone marrow plasma cells
- ≥3 g/dL serum M-protein
- No end-organ damage

2014 IMWG Update
- 10-60% clonal bone marrow plasma cells and/or ≥3 g/dL serum M-protein
- No MM-defining events

***Updates resulted in some patients with SMM now being classified as having MM**

Multiple Myeloma

Prior to 2014
>10% bone marrow plasma cells and any
"CRAB" Criteria
C: Hypercalcemia
R: Renal failure
A: Anemia
B: Lytic bone lesions

2014 IMWG Update
>10% bone marrow plasma cells and any one
CRAB or SLiM biomarkers
S: ≥60% clonal BMPC
Li: involved/uninvolved FLC ratio >100
M: >1 focal lesion on MRI

Abbreviations: FLC= free light chains, M-protein= monoclonal protein, MM= multiple myeloma, SMM= smoldering multiple myeloma

Source: Lakshman A, Blood Cancer J (2018)

Disease Criteria Overview

Smoldering Multiple Myeloma

Prior to 2014
- ≥10% bone marrow plasma cells
- ≥3 g/dL serum M-protein
- No end-organ damage

2014 IMWG Update
- 10-60% clonal bone marrow plasma cells and/or ≥3 g/dL serum M-protein
- No MM-defining events

***Updates resulted in some patients with SMM now being classified as having MM**

Asymptomatic
CRAB criteria absent
No FDA approved therapies

Multiple Myeloma

Prior to 2014
>10% bone marrow plasma cells and any
"CRAB" Criteria
C: Hypercalcemia
R: Renal failure
A: Anemia
B: Lytic bone lesions

2014 IMWG Update
>10% bone marrow plasma cells and any one
CRAB or SLiM biomarkers
S: ≥60% clonal BMPC
Li: involved/uninvolved FLC ratio >100
M: >1 focal lesion on MRI

May be symptomatic
CRAB or SLiM criteria present
Triplet or quadruplet regimens

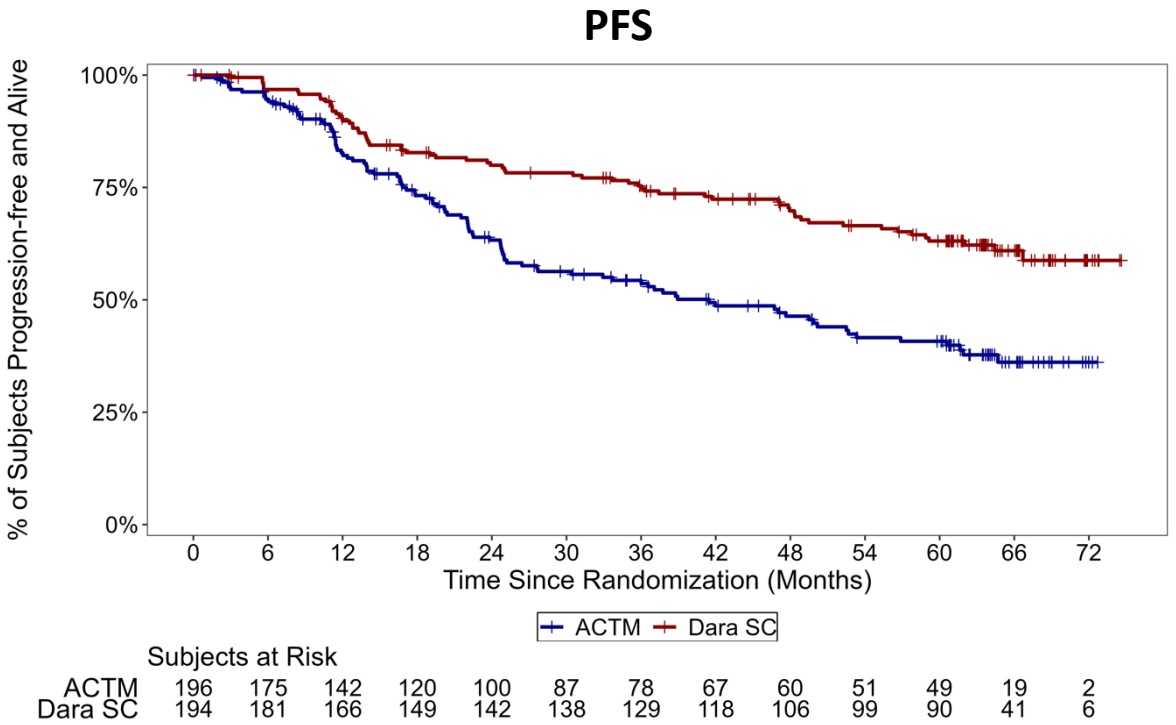
Abbreviations: FLC= free light chains, M-protein= monoclonal protein, MM= multiple myeloma, SMM= smoldering multiple myeloma

Source: Lakshman A, Blood Cancer J (2018)

AQUILA: PFS Primary Endpoint

	Dara SC N=194	ACTM N=196
Number of Events (%)	**67 (35)**	**99 (51)**
Number Censored (%)	**127 (65)**	**97 (49)**
Kaplan-Meier estimate (months)		
Median (95% CI)	**NE (66.7, NE)**	**41.5 (26.4, 53.3)**
Hazard Ratio (95% CI)	**0.49 (0.36, 0.67)**	
P-value (2-sided)	**<0.0001**	

Cut-off date 01 May 2024; median follow-up 65.2 months. P-value crossed the prespecified stopping boundary of 0.05 (2-sided).

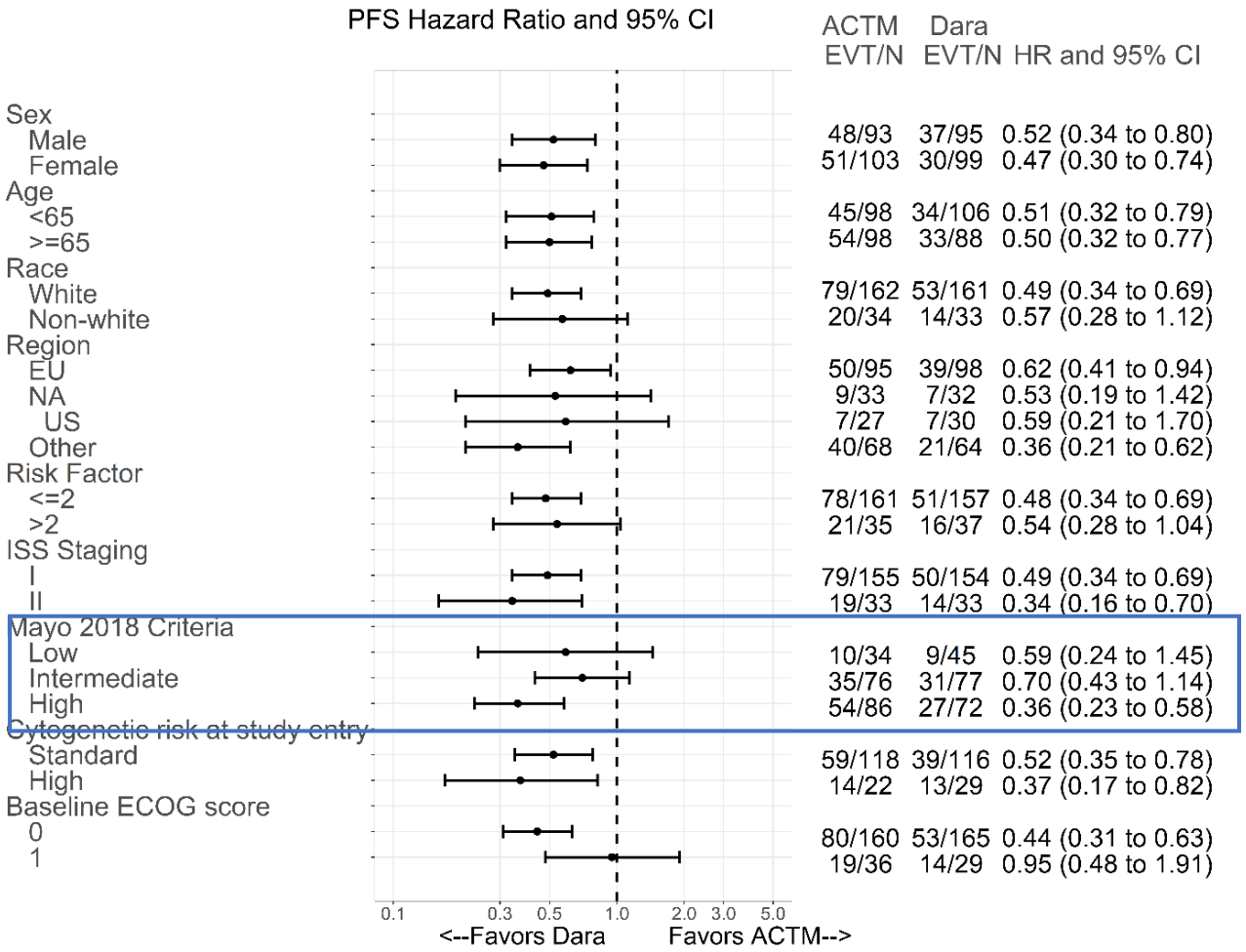


Primary Endpoint of PFS – progression to SLiM CRAB criteria or death – was met

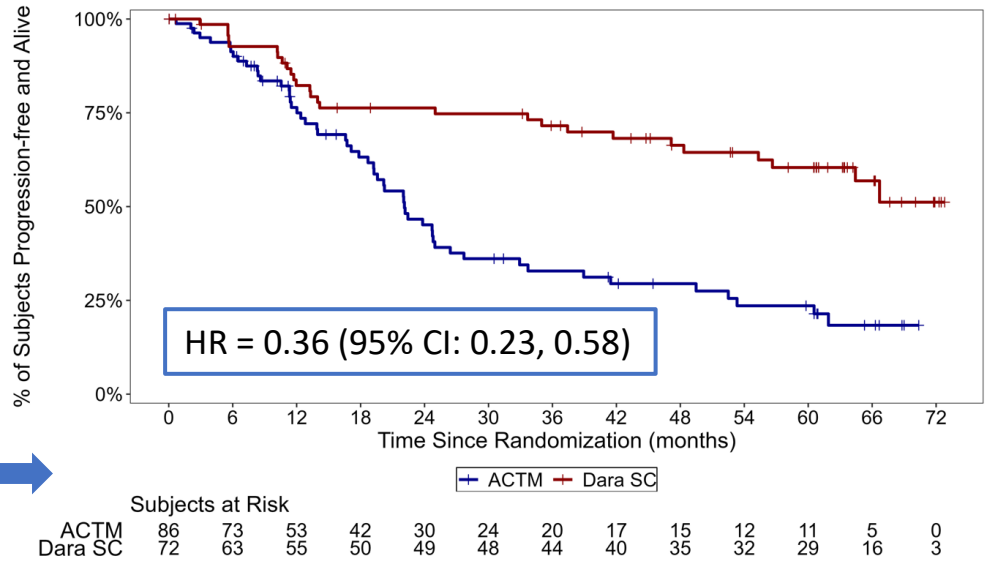
Abbreviations: ACTM= active monitoring, CI= confidence interval, CRAB= C: hypercalcemia, R: renal failure, A: anemia, B: bone lesions, PFS= progression-free survival, NE= not estimable, SC= subcutaneous, SLiM= S: ≥60% clonal BMPC, Li: involved/uninvolved FLC ratio >100, M: >1 focal lesion on MRI

Source: FDA Analysis

AQUILA: PFS Subgroup Analysis



High-Risk by Mayo 2018 Criteria (PFS)



For cytogenetic risk at study entry, subjects are considered not evaluable if: a) they have missing results for all FISH abnormalities considered, or b) they have no abnormal test results and missing results for other abnormalities.

PFS benefit pronounced in Mayo 2018 high-risk group

Abbreviations: ACTM= active monitoring, CI= confidence interval, EU= European Union, EVT= event, ISS= International Staging System, NA= North America, NE= not estimable, PFS=progression-free survival

Source: FDA Analysis

AQUILA: PFS Primary Endpoint

PFS events per IRC	Dara SC N=194 n (%)	ACTM N=196 n (%)
Subjects with progression-free survival event	67 (35)	99 (51)
Subjects with progressive disease	62 (32)	94 (48)
Reason for progressive disease		
Calcium elevation	0 (0)	2 (1)
Renal insufficiency	0 (0)	0 (0)
Anemia	2 (1)	14 (7)
Bone disease	10 (5)	18 (9)
Clonal BM plasma cells	5 (3)	16 (8)
Serum FLC	33 (17)	33 (17)
Focal lesion by MRI	12 (6)	16 (8)
Subjects died without progressive disease	5 (3)	5 (3)

A subject may show PD based on more than one criterion, and the reason listed does not represent the first progression event

PFS definition included death, but rates of death events were low

Abbreviations: ACTM= active monitoring, BM= bone marrow, IRC= independent review committee, FLC= free light chains, MRI= magnetic resonance imaging, PD= progressive disease, PFS= progression-free survival, SC= subcutaneous

Source: FDA Analysis

AQUILA: PFS Primary Endpoint

PFS events per IRC	Dara SC N=194 n (%)	ACTM N=196 n (%)
Subjects with progression-free survival event	67 (35)	99 (51)
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Reason for progressive disease		
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Subjects died without progressive disease	5 (3)	5 (3)

A subject may show PD based on more than one criterion, and the reason listed does not represent the first progression event

Majority of AQUILA participants were diagnosed with MM based on the SLiM criteria

Abbreviations: ACTM= active monitoring, BM= bone marrow, IRC= independent review committee, FLC= free light chains, MRI= magnetic resonance imaging, PD=progressive disease, PFS= progression-free survival, SLiM=S=≥60% clonal BMPCs Li: involved/uninvolved FLC ratio >100 M: >1 focal lesion on MRI

Source: FDA Analysis

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Focal lesion by MRI	12 (6)	16 (8)
Subjects died without progressive disease	5 (3)	5 (3)

A subject may show PD based on more than one criterion, and the reason listed does not represent the first progression event

Very few progression events of hypercalcemia and no events of renal end organ damage

Abbreviations: ACTM= active monitoring, BM= bone marrow, IRC= independent review committee, FLC= free light chains, MRI= magnetic resonance imaging, PD= progressive disease, PFS= progression-free survival, SC= subcutaneous

Source: FDA Analysis

AQUILA: PFS Primary Endpoint

PFS events per IRC	Dara SC N=194 n (%)	ACTM N=196 n (%)
Subjects with progression-free survival event	67 (35)	99 (51)
Subjects with progressive disease	62 (32)	94 (48)
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Focal lesion by MRI	12 (6)	16 (8)
Subjects died without progressive disease	5 (3)	5 (3)

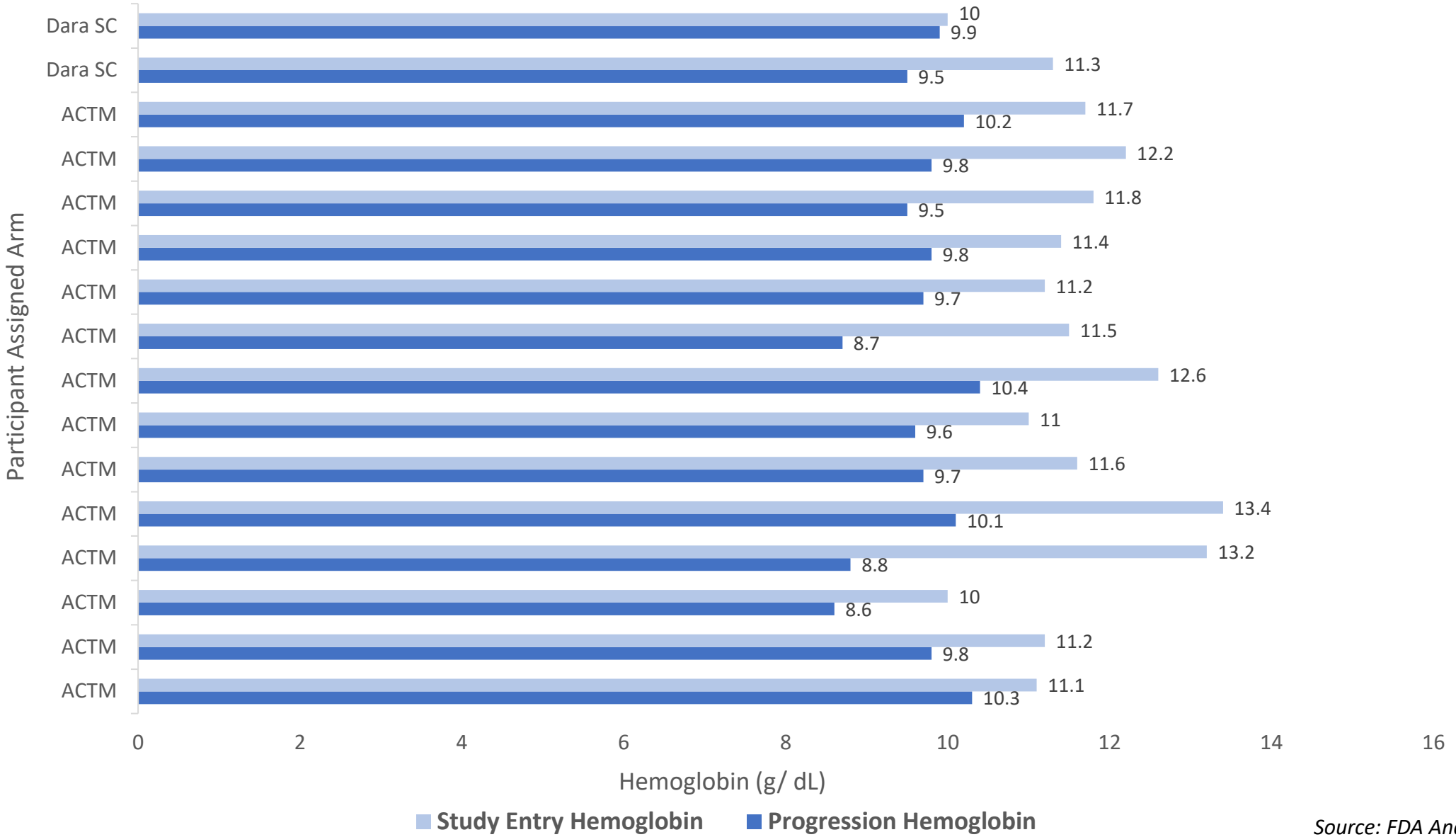
A subject may show PD based on more than one criterion, and the reason listed does not represent the first progression event

Results of workup regarding alternative etiologies of anemia not available

Abbreviations: ACTM= active monitoring, BM= bone marrow, IRC=independent review committee, FLC= free light chains, MRI= magnetic resonance imaging, PD= progressive disease, PFS= progression-free survival, SC= subcutaneous

Source: FDA Analysis

Anemia Events



Source: FDA Analysis

Abbreviations: ACTM= active monitoring, SC= subcutaneous

AQUILA: PFS Primary Endpoint

PFS events per IRC	Dara SC N=194 n (%)	ACTM N=196 n (%)
Subjects with progression-free survival event	67 (35)	99 (51)
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Serum FLC	33 (17)	33 (17)
Focal lesion by MRI	12 (6)	16 (8)
Subjects died without progressive disease	5 (3)	5 (3)

A subject may show PD based on more than one criterion, and the reason listed does not represent the first progression event

Of participants with bone disease, 3 had symptoms

Abbreviations: ACTM= active monitoring, BM= bone marrow, IRC= independent review committee, FLC= free light chains, PD= progressive disease, PFS= progression-free Survival, SC= subcutaneous

Source: FDA Analysis

MM Diagnosis: Therapy

	Dara SC N=194 n (%)	ACTM N=196 n (%)	Overall N=390 n (%)
Participants with PD§ by IRC †	62 (32)	94 (48)	156 (40)
Initiated MM therapy §§	48 (77)	75 (80)	123 (79)
No MM therapy § §	14 (23)	19 (20)	33 (21)

§PD as defined on the AQUILA trial is a MM diagnosis.
† Percentages were based on the participants in the ITT analysis set as denominator.
§§ Percentages were based on participants with PD by IRC as denominator.

Reason for not receiving MM therapy	n (%)*
Controlled disease or no progression^	19 (58)
Primary Investigator or Patient Decision	7 (21)
Consent withdrawn	6 (18)
PD close to CCO	1 (3)

* Percentages were based on the participants who received no MM therapy ^Controlled disease or no progression are based on participants listed as no progression per local labs or imaging and controlled disease

Abbreviations: ACTM= active monitoring, CCO= clinical cut off date, IRC= independent review committee, ITT = Intent-to-Treat, MM= multiple myeloma, PD= progressive disease, SC= subcutaneous

Source: FDA Analysis

MM Diagnosis: Time to Therapy for MM

	Dara SC	ACTM	Overall
Participants with PD* by IRC, n	62	94	156
Initiation of therapy for MM diagnosis, n (%)§	48 (77)	75 (80)	123 (79)
Time from PD by IRC to initiation of therapy for MM, months			
Median (min, max)	2.8 (0.1, 49.4)	1.9 (0.1, 39.6)	2.4 (0.1, 49.4)
25th percentile (Q1)	1.7	1.2	1.2
75th percentile (Q3)	5.8	5.1	5.7

Quantiles were calculated using linear interpolation using R software.
*PD as defined on the AQUILA trial is a MM diagnosis.
§ Percentages were based on the number of participants with PD by IRC as denominator.

Abbreviations: ACTM= active monitoring, IRC= independent review committee, MM= multiple myeloma, PD=progressive disease, Q= quartile, SC= subcutaneous

Source: FDA Analysis

PFS and Initiation of MM Therapy

- About 20% of patients diagnosed with MM did not initiate treatment
- Variable time to MM therapy initiation
- These raise additional uncertainties regarding the clinical meaningfulness of the PFS endpoint

Abbreviations: MM= multiple myeloma, PFS= progression-free survival

Summary: PFS Endpoint

- While the AQUILA trial met the primary endpoint of PFS as defined:
  - Primarily due to delaying diagnosis of MM
  - Majority of the events were SLiM criteria
  - Few events of symptomatic CRAB criteria or death
  - Approximately 20% of participants did not initiate MM therapy
- Clinical meaningfulness of the observed improvement in PFS is unclear

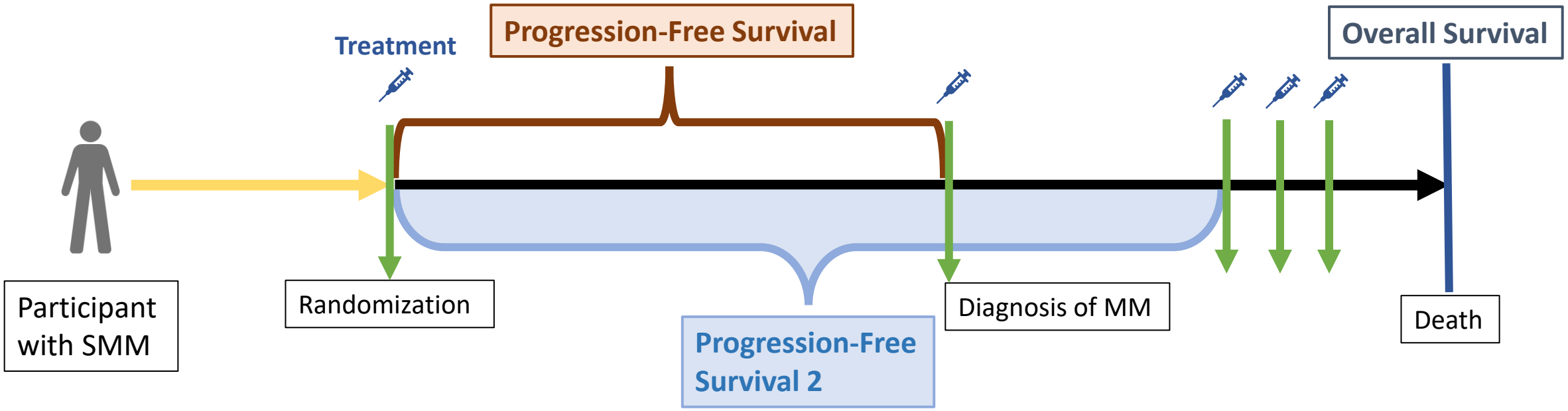
Abbreviations: CRAB= C: hypercalcemia, R: renal failure, A: anemia, B: bone lesions, PFS= progression-free survival, MM=multiple myeloma, SLiM= S: ≥60% clonal BMPC, Li: involved/uninvolved FLC ratio >100, M: >1 focal lesion on MRI

Presentation Outline

- Applicability of AQUILA trial results to patients with high-risk Smoldering Multiple Myeloma
- Endpoints for high-risk SMM in the AQUILA trial
  - Clinical relevance of Progression-Free Survival endpoint
  - PFS2 endpoint
  - Overall Survival as an endpoint in SMM
- Safety findings and patient reported outcomes from the AQUILA trial

Abbreviations: PFS2= progression-free survival 2, SMM= smoldering multiple myeloma

Endpoints for SMM: AQUILA

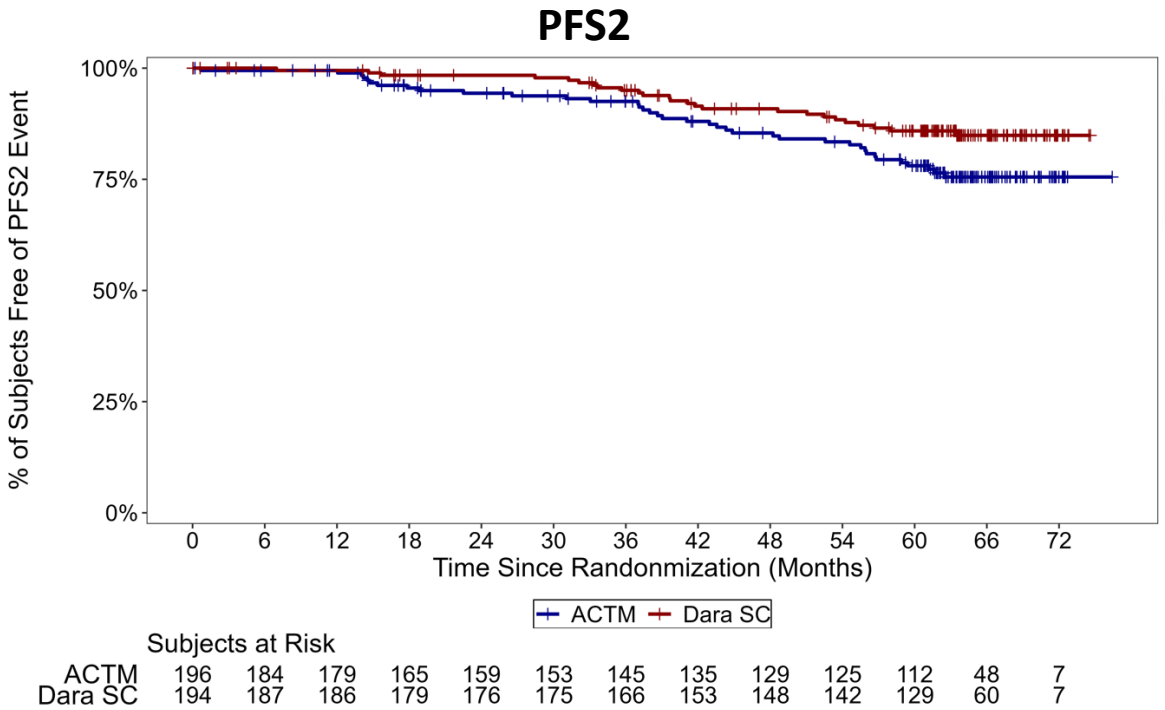


- PFS2 has not supported approval of therapies for patients with cancer in the United States
- PFS2 can be confounded by factors not related to initial therapy
- In precursor conditions, PFS2 may provide assessment of therapy received in the precursor state

Abbreviations: MM= multiple myeloma, PFS= progression-free survival, PFS2 = progression free survival 2

AQUILA: PFS2 Endpoint

	Dara SC N=194	ACTM N=196
Number of Events (%)	**25 (13)**	**38 (19)**
Number Censored (%)	**169 (87)**	**158 (81)**
Kaplan-Meier estimate (months)		
Median (95% CI)	**NE (NE, NE)**	**NE (NE, NE)**
P-value (2-sided)	**0.0318**	
Hazard Ratio (95% CI)	**0.58 (0.35, 0.96)**	
12-month PFS2 rate % (95% CI)	99.5 (96.3, 99.9)	99.5 (96.3, 99.9)
24-month PFS2 rate % (95% CI)	98.4 (95.1, 99.5)	94.4 (89.8, 96.9)
36-month PFS2 rate % (95% CI)	95.0 (90.6, 97.4)	92.5 (87.4, 95.6)
48-month PFS2 rate % (95% CI)	90.9 (85.5, 94.3)	85.4 (79.0, 90.0)
60-month PFS2 rate % (95% CI)	85.9 (79.7, 90.3)	78.0 (70.7, 83.7)



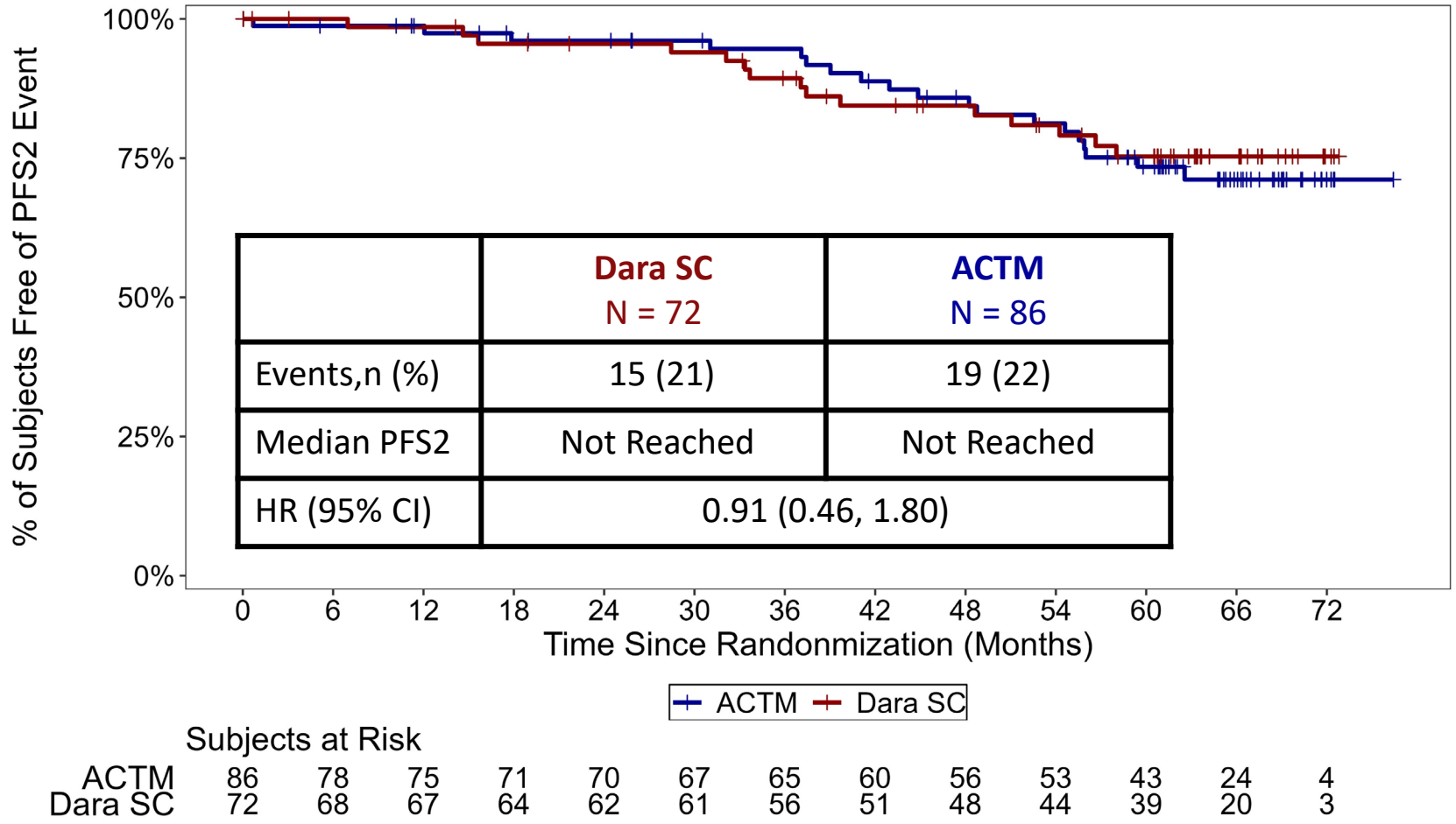
Cut-off date 01 May 2024; median follow-up 65.2 months.
P-value did not cross the pre-specified stopping boundary of 0.0235 (2-sided).

Median PFS2 was not reached in either arm

Abbreviations: ACTM= active monitoring, CI= confidence interval, NE= not estimable, PFS2= progression-free survival 2, SC= subcutaneous

Source: FDA Analysis

AQUILA: PFS2 in Mayo 2018 High-Risk Group



	Dara SC N = 72	ACTM N = 86
Events,n (%)	15 (21)	19 (22)
Median PFS2	Not Reached	Not Reached
HR (95% CI)	0.91 (0.46, 1.80)	

PFS2 results in the Mayo 2018 high-risk group did not show a notable difference between the two arms

Abbreviations: ACTM= active monitoring, CI= confidence interval, HR= hazard ratio, PFS2= progression-free survival 2, SC= subcutaneous

Source: FDA Analysis

AQUILA: PFS2 Endpoint

	Dara SC N=194 n (%)	ACTM N=196 n (%)
Participants with PD* by IRC †	62 (32)	94 (48)
Initiated MM therapy §	48 (77)	75 (80)
No MM therapy §	14 (23)	19 (20)

* PD as defined on the AQUILA trial is a MM diagnosis.
† Percentages were based on the participants in the ITT analysis set as denominator.
§ Percentages were based on participants with PD by IRC as denominator.

Abbreviations: ACTM= active monitoring, IRC= independent review committee, ITT= Intent to Treat, MM= multiple myeloma, PD= progressive disease

Source: FDA Analysis

AQUILA: PFS2 Endpoint

	Dara SC N=194 n (%)	ACTM N=196 n (%)
Participants with PD* by IRC †	62 (32)	94 (48)
Initiated MM therapy §	48 (77)	75 (80)
No MM therapy §	14 (23)	19 (20)
Daratumumab-containing first line therapy §	9 (15)	23 (24)

*PD as defined on the AQUILA trial is a MM diagnosis.
† Percentages were based on the participants in the ITT analysis set as denominator.
§ Percentages were based on participants with PD by IRC as denominator.

Impact of treatment for SMM on response to anti-CD38 therapy at MM diagnosis is unclear

Daratumumab-containing regimens^	Non-daratumumab-containing regimens^	
Daratumumab	Lenalidomide	KCd
DRd	Isatuximab	VMP
DVd	Rd	**Isa-VRd**
D-Iber-d	Vd	Elo-KRd
D-VMP	VRd	Ven-VTd
D-VRd	VCd	VTCd
D-KRd	VTd	VRd, Isa-Kd, transplant
D-VTd	KRd	VRTd + melphalan, transplant
D-VTCd	IRd	
VMP-DRd	RCd	

^Bolded therapies are FDA approved for newly diagnosed MM
Abbreviations: D=daratumumab, R=lenalidomide, d=dexamethasone, V=bortezomib, Iber=iberdomide, M=melphalan, K=carfilzomib, T=thalidomide, C=cyclophosphamide, I=ixazomib, Isa=isatuximab, Elo=elotuzumab, Ven=venetoclax

Abbreviations: ACTM= active monitoring, IRC= independent review committee, ITT= Intent to Treat, MM= multiple myeloma, PD= progressive disease, SMM= smoldering multiple myeloma

Source: FDA Analysis

Summary: PFS2 Endpoint

- The AQUILA trial PFS2 results were not substantially different between the arms
- Many participants in the AQUILA trial did not receive therapies or regimens considered standard of care for patients with newly diagnosed MM
- Impact of treatment of high-risk SMM on outcomes after first-line treatment of MM is unclear

Abbreviations: MM= multiple myeloma, PFS2= progression-free survival 2, SMM= smoldering multiple myeloma

Presentation Outline

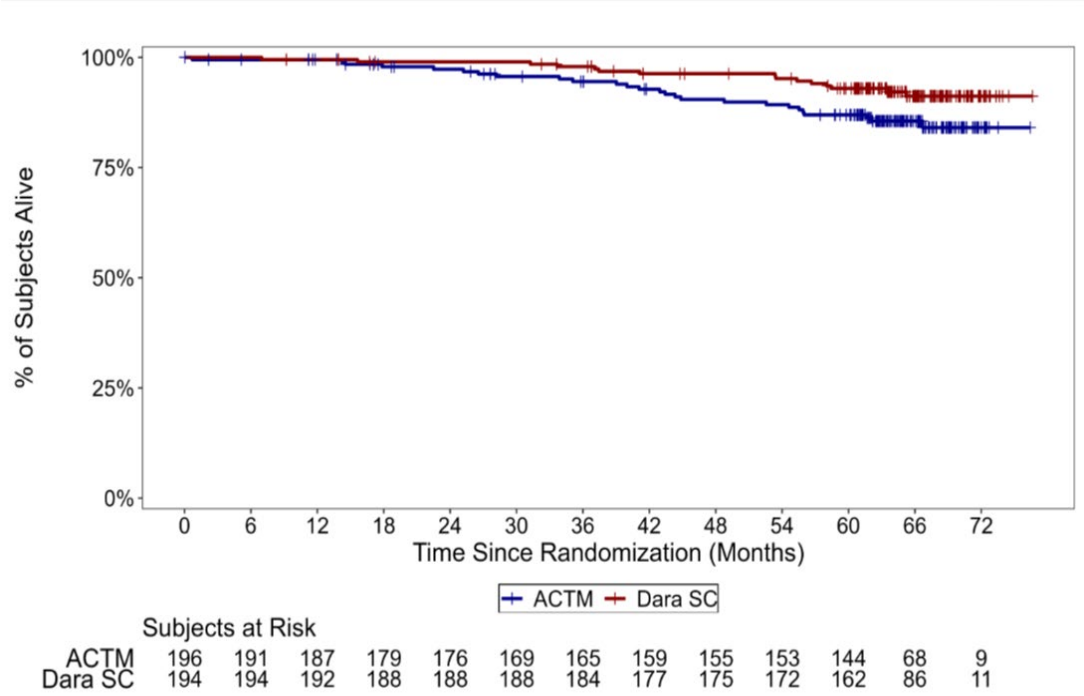
- Applicability of AQUILA trial results to patients with high-risk Smoldering Multiple Myeloma
- Endpoints for high-risk SMM in the AQUILA trial
  - Clinical relevance of Progression-Free Survival endpoint
  - PFS2 endpoint
  - Overall Survival as an endpoint in SMM
- Safety findings and patient reported outcomes from the AQUILA trial

Abbreviations: PFS2= progression-free survival 2, SMM= smoldering multiple myeloma

AQUILA: OS Endpoint

	Dara SC N=194	ACTM N=196
Number of Events (%)	**15 (8)**	**26 (13)**
Number of Censored (%)	**179 (92)**	**170 (87)**
Kaplan-Meier estimate (months)		
Median (95% CI)	**NE (NE, NE)**	**NE (NE, NE)**
Hazard Ratio (95% CI)	**0.52 (0.27, 0.98)**	
12-month survival rate % (95% CI)	99.5 (96.4, 99.9)	99.5 (96.4, 99.9)
24-month survival rate % (95% CI)	99.0 (95.9, 99.7)	97.3 (93.7, 98.9)
36-month survival rate % (95% CI)	97.9 (94.5, 99.2)	94.5 (90.0, 97.0)
48-month survival rate % (95% CI)	96.3 (92.4, 98.2)	90.4 (85.1, 93.9)
60-month survival rate % (95% CI)	**93.0 (88.2, 95.8)**	**86.9 (81.0, 91.1)**

According to the hierarchical testing order, OS was not formally tested because PFS2 did not cross the prespecified stopping boundary.



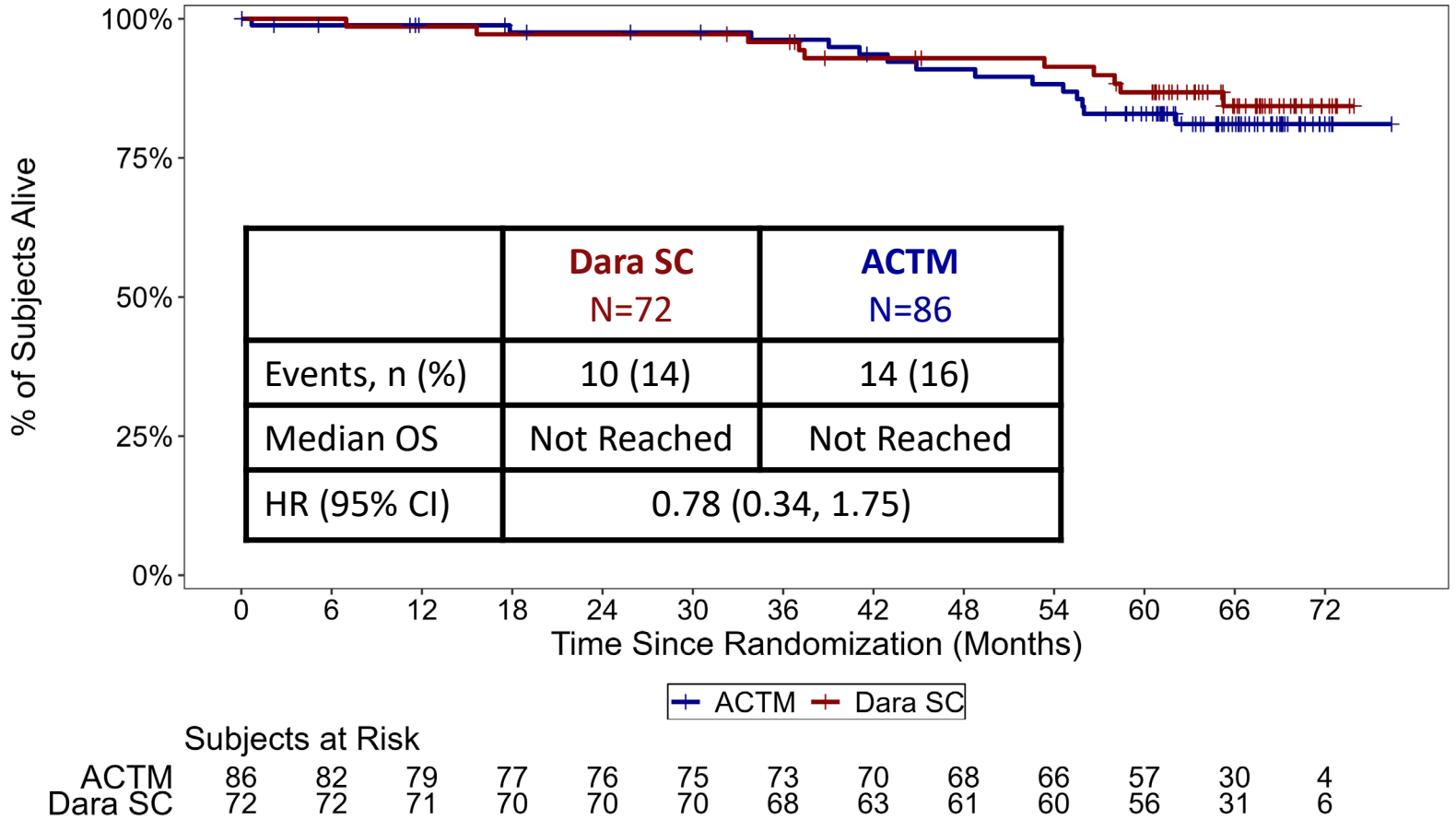
Cut-off Date 01 May 2024; median follow-up 65.2 months

OS results were immature, and at 5-year landmark time, the difference in OS rates was 6%

Abbreviations: ACTM= active monitoring, CI= confidence interval, NE= non-estimable, OS= overall survival, PFS2= progression-free survival 2, SC= subcutaneous

Source: FDA Analysis

AQUILA OS Results: Mayo 2018 High-Risk



	Dara SC N=72	ACTM N=86
Events, n (%)	10 (14)	14 (16)
Median OS	Not Reached	Not Reached
HR (95% CI)	0.78 (0.34, 1.75)	

Limited number of OS events

Abbreviations: ACTM= active monitoring, CI= confidence interval, HR= hazard ratio, KM= Kaplan-Meier, OS= overall survival, SC=subcutaneous

Source: FDA Analysis

Therapy at MM Diagnosis and OS

- Treatment of precursor disease must consider impacts on later treatment
- Daratumumab based triplet or quadruplet regimens are the current standard of care for patients with NDMM
- Not all participants received Daratumumab based regimens at MM diagnosis
- Clinical benefit of treatment in the precursor stage vs. at the time of MM diagnosis is unclear

Abbreviations: OS= overall survival, MM= multiple myeloma, NDMM= newly diagnosed multiple myeloma, SMM= smoldering multiple myeloma

AQUILA: Deaths

	Dara SC N=194	ACTM N=196
Deaths, n (%)	15 (8)	26 (13)
Adverse Event	2 (1)	4 (2)
Progressive Disease	3 (2)	9 (5)
Other	10 (5)	13 (7)
Death within 30 days*, n	0	2
Death between 30-60 days*, n	3	0
AE, n (%)	2 (1)	4 (2)
Other, n (%)	1 (0.5)	0
Death following subsequent therapy, n (%)	9 (5)	20 (10)
PD	3 (2)	9 (5)
Other	6 (3)	11 (6)

* From end of study treatment

Limited information on cause of deaths following subsequent therapy

Abbreviations: ACTM= active monitoring, AE= adverse event, PD= progressive disease, SC= subcutaneous

Source: FDA Analysis

Feasibility of OS as an Endpoint

- OS is a clinically meaningful endpoint
- Based on true HR assumed in the AQUILA trial, sample size would be infeasible
- **Required sample size if the trial were powered to show an OS benefit:**

Hazard Ratio	# of OS events	Sample size
0.80 (AQUILA)	686	2487
0.60	131	529

Abbreviations: HR= hazard ratio, OS= overall survival

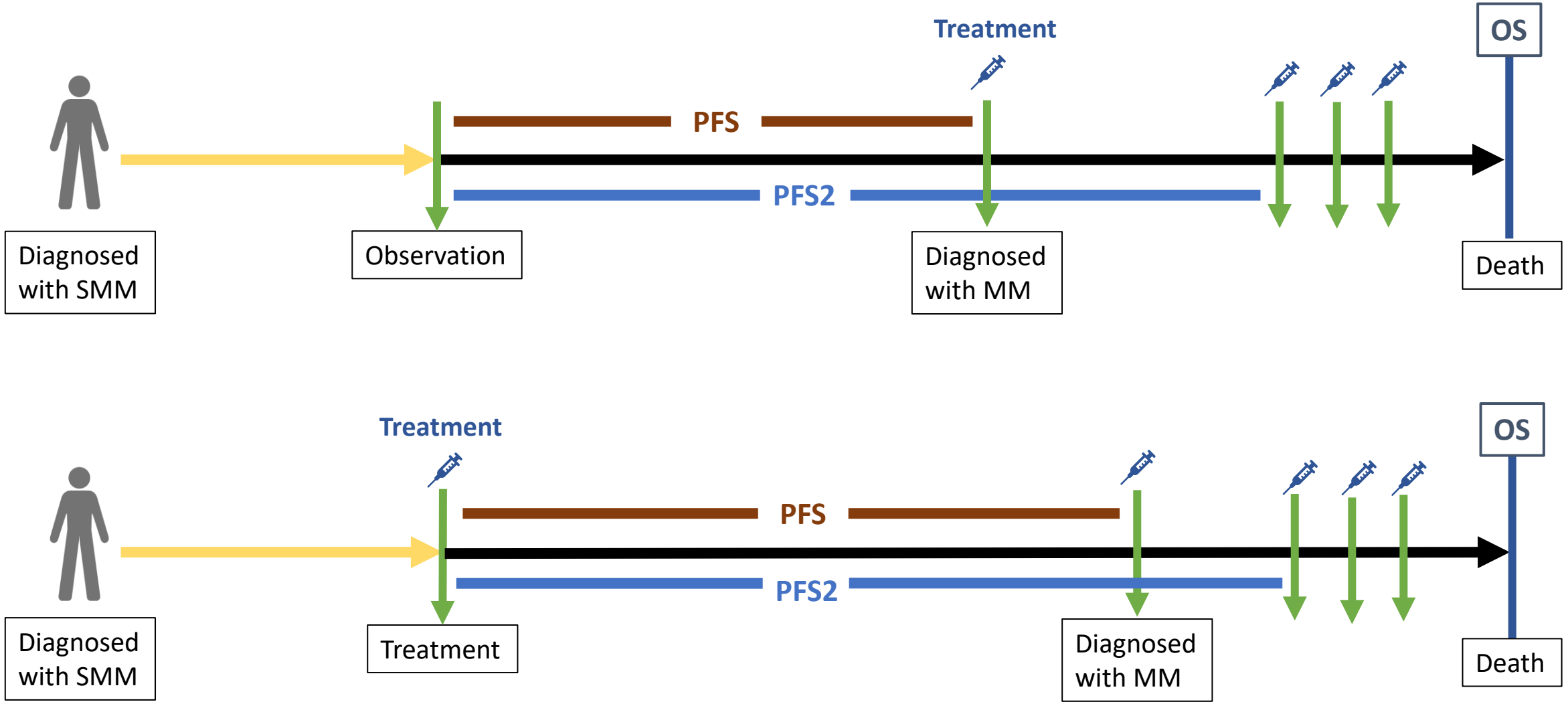
Source: FDA Analysis

Summary: OS Endpoint

- The AQUILA trial was not designed to show a significant improvement in OS
- OS results are immature
  - Fewer than anticipated events for OS at the time of PFS analysis
- Majority of deaths occurred in the “other” category and following receipt of subsequent therapy

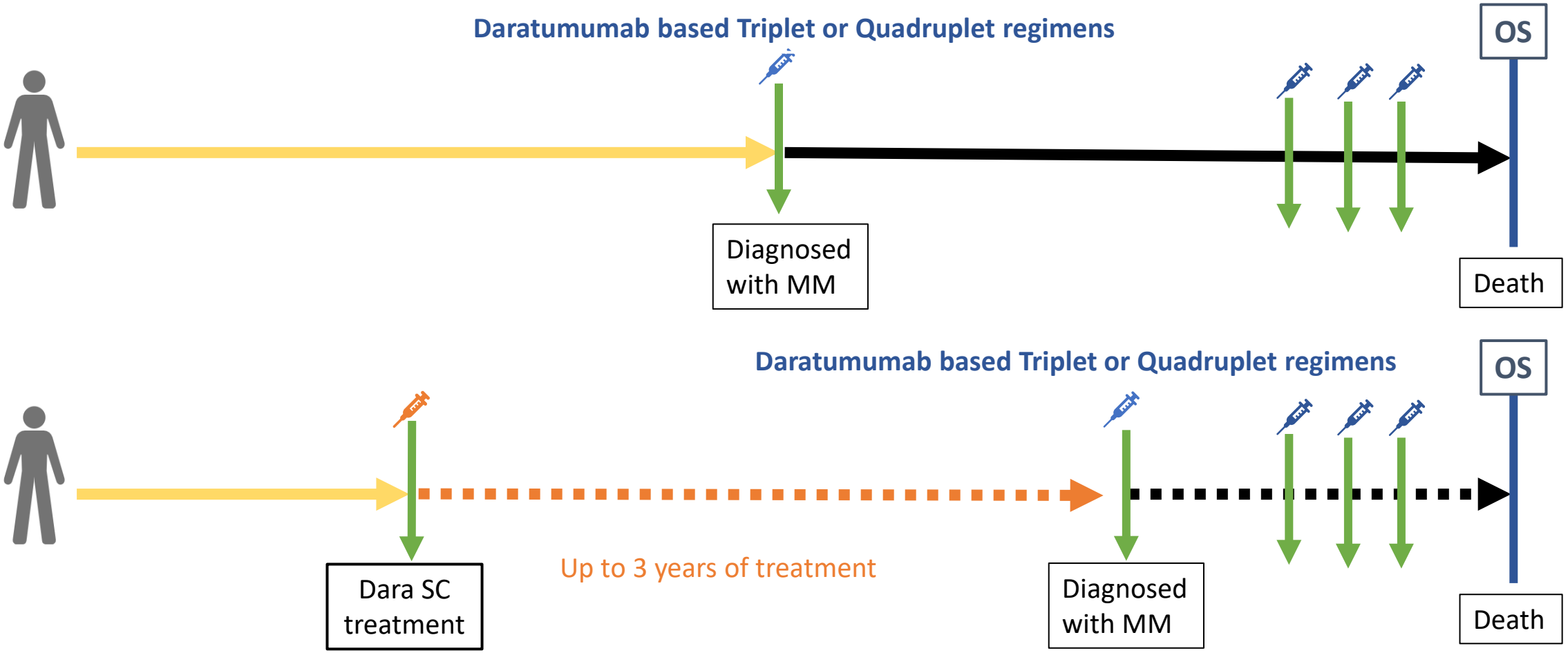
Abbreviations: PFS= progression-free survival, OS= overall survival

Endpoints in SMM



Abbreviations: MM= multiple myeloma, OS= Overall Survival, PFS= progression-free survival, PFS2= progression-free survival 2, SMM= smoldering multiple myeloma

MM Treatment Paradigm



Abbreviations: MM= multiple myeloma, OS= overall survival, SC= subcutaneous, SMM= smoldering multiple myeloma

Presentation Outline

- Applicability of AQUILA trial results to patients with high-risk Smoldering Multiple Myeloma
- Endpoints for high-risk SMM in the AQUILA trial
  - Clinical relevance of Progression Free Survival endpoint
  - PFS2 endpoint
  - Overall Survival as an endpoint in SMM
- ❑ Safety findings and patient reported outcomes from the AQUILA trial

Abbreviations: PFS2= progression-free survival 2, SMM= smoldering multiple myeloma

AQUILA: Safety Overview

	Dara SC N=193	ACTM N=196
Exposure		
Median Duration (range), months	35 (0.03, 36.1)	NA
TEAE Category, %		
Any TEAE	97	84
Grade 3 or 4 TEAE	40	30
Grade 5 TEAE	1	2
Serious AE	29	19
TEAE leading to discontinuation	6	0
TEAE leading to dose modification	47	0

More participants on the Dara SC arm experienced TEAEs and TEAEs leading to dose modification

Abbreviations: ACTM= active monitoring, AE= adverse event, NA= not applicable, SC= subcutaneous, TEAE= treatment-emergent adverse event

Source: FDA Analysis

AQUILA: Adverse Events of Special Interest

	Dara SC N=193		ACTM N=196	
	All Grades (%)	Grade 3-5 (%)	All Grades (%)	Grade 3-5 (%)
Systemic Administration Reactions	17	1	NA	NA
Injection Site Reactions	28	0	NA	NA
Infections and Infestations (SOC)	80	17	45	5
Anemia*	42	0	43	2
Neutropenia*	34	5	29	4
Thrombocytopenia*	19	0.5	9	0.5

* Based on laboratory dataset

More patients on the Dara SC arm experienced infections

Abbreviations: ACTM= active monitoring, SOC= system organ class, NA= not applicable, SC= subcutaneous

Source: FDA Analysis

AQUILA: TEAEs (≥20% in Either Arm)

	Dara SC N=193		ACTM N=196	
	All Grades (%)	**Grade 3-5 (%)**	**All Grades (%)**	**Grade 3-5 (%)**
Any TEAE*	**97**	**40**	**83**	**31**
Musculoskeletal pain	59	1	42	3
URI	52	0.5	17	0
Fatigue	42	3	21	0.5
Diarrhea	28	2	5	0.5
Nasopharyngitis	25	0	12	0
Rash	24	0.5	5	0.5
Sleep Disorder	24	0.5	5	0
Sensory Neuropathy	20	0	8	0

*Each term includes related grouped terms

More participants on the Dara SC arm experienced TEAEs

Abbreviations: ACTM= active monitoring, SC= subcutaneous, TEAE= treatment-emergent adverse event, URI= upper respiratory tract infection

Source: FDA Analysis

AQUILA: PRO Endpoints

- Collected using the EORTC-QLQ-C30 and EORTC-MY-20 at baseline, week 12, week 24, week 60 and week 112
- FDA could not make meaningful conclusions from this data for the following reasons:
  - Infrequent PRO assessment is inadequate to demonstrate tolerability.
  - The PRO measures used in AQUILA may be inappropriate to assess symptoms and function. SMM is an asymptomatic precursor condition and progression was driven by biochemical events.
  - The trial was not designed to detect differences between arms.
- Similar PRO scores are not evidence of tolerability or equivalence

Abbreviations: PRO= patient-reported outcomes, EORTC= European Organization for Research and Treatment of Cancer, QLQ= Quality of life Questionnaire, SMM= smoldering multiple myeloma

Summary: Safety and PROs

- Safety findings and PROS of the AQUILA trial
  - Overall rates of TEAEs higher in the Dara SC arm
    - Grade 3-4 TEAEs
    - Serious TEAEs
    - TEAEs leading to treatment discontinuation and modification
  - Higher rates of most common TEAEs in the Dara SC arm
  - Several limitations to the patient reported outcomes data

Abbreviations: PROs= patient reported outcomes, SC= subcutaneous, TEAEs= treatment-emergent adverse events

Uncertain Benefit-Risk of Dara SC

- Less than half of the participants enrolled on the AQUILA trial would be high-risk based on current criteria
- Uncertainty regarding clinical meaningfulness of the PFS results
- No meaningful impact on delaying initiation of second line MM therapy (PFS2)
- Lack of robust OS data
- Higher rates of toxicities, dose modification and discontinuation on the Dara SC arm

Abbreviations: MM= multiple myeloma, OS=overall survival, PFS2= progression-free survival 2, SC= subcutaneous

Discussion Topics

- Discuss the clinical meaningfulness of the efficacy endpoints assessed in the AQUILA Trial
- Discuss the benefit-risk of Dara SC for the intended high-risk SMM population

Abbreviation: SC= subcutaneous, SMM= smoldering multiple myeloma

Voting Question

Do the results from the AQUILA trial provide sufficient evidence to support a favorable benefit-risk profile for Dara SC for patients with high-risk smoldering multiple myeloma?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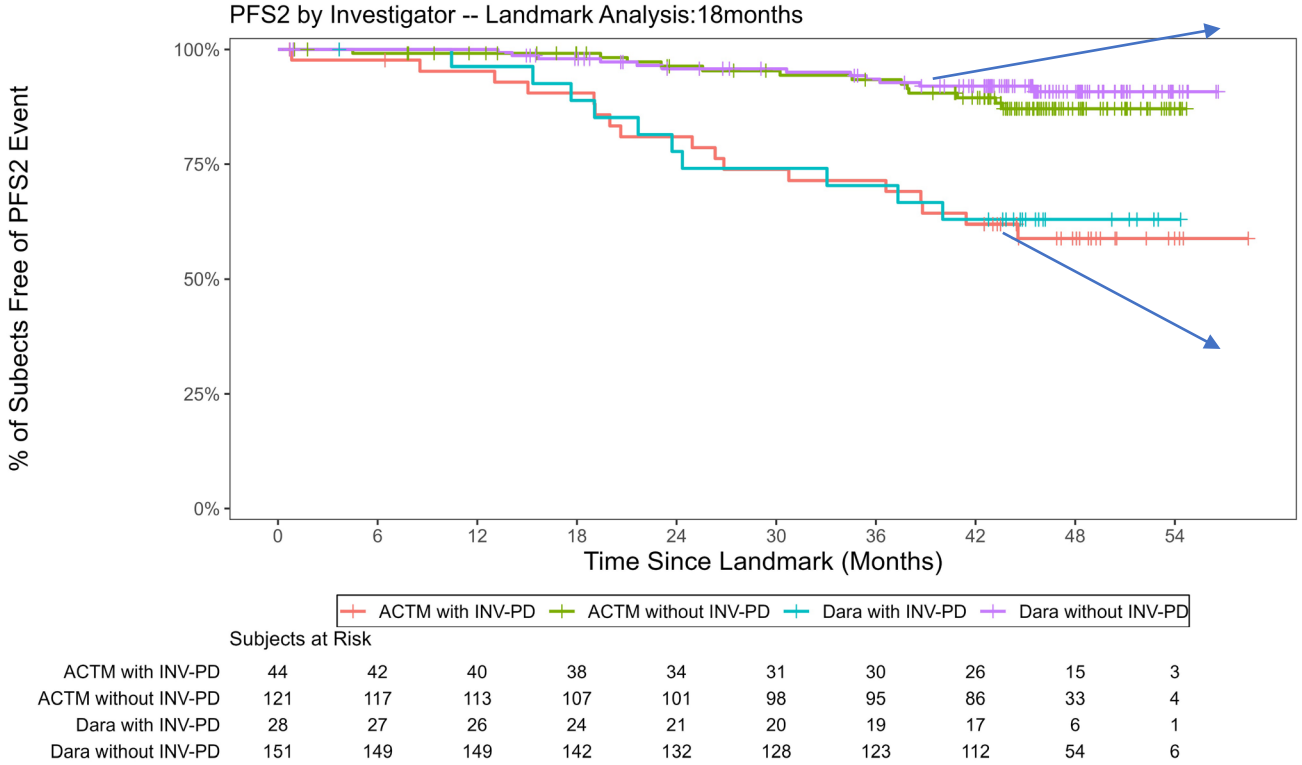
BACKUP SLIDES DISPLAYED

PFS2 Exploratory Analysis: PD status

Conditional Landmark Analysis: 18 months



Landmark	Without PD per INV prior to Landmark		
	Dara SC EVT/N	ACTM EVT/N	HR (95% CI)
Month 18	12/151	13/121	0.71 (0.32,1.56)
Month 24	11/143	6/103	1.31 (0.48,3.54)

Landmark	With PD per INV prior to Landmark		
	Dara SC EVT/N	ACTM EVT/N	HR (95% CI)
Month 18	10/28	17/44	0.91 (0.42,1.99)
Month 24	11/33	22/56	0.83 (0.40,1.72)

PD per investigator as a time varying covariate: HR (95% CI) for Dara SC vs ACTM =0.92 (0.55, 1.55)

Source: FDA analysis.

Abbreviations: ACTM= Active Monitoring, CI= Confidence Interval, Dara SC= daratumumab subcutaneous, EVT= event, HR= hazard ratio, INV= investigator, PD = progressive disease, PFS2= progression-free survival on first-line treatment for multiple myeloma

OS Sensitivity and Supplementary Analyses

	Hazard Ratio (95% CI)
Primary analysis: Treatment Policy strategy	**0.52 (0.27, 0.98)**
Inverse-Probability-of-Censoring Weighting Method†	0.69 (0.23, 2.01)
Two-Stage Model †	0.77 (0.26, 2.29)
Native Censoring at the start of any subsequent therapy in both arms	0.67 (0.21, 2.10)

† Adjusting for any subsequent therapy in both arms

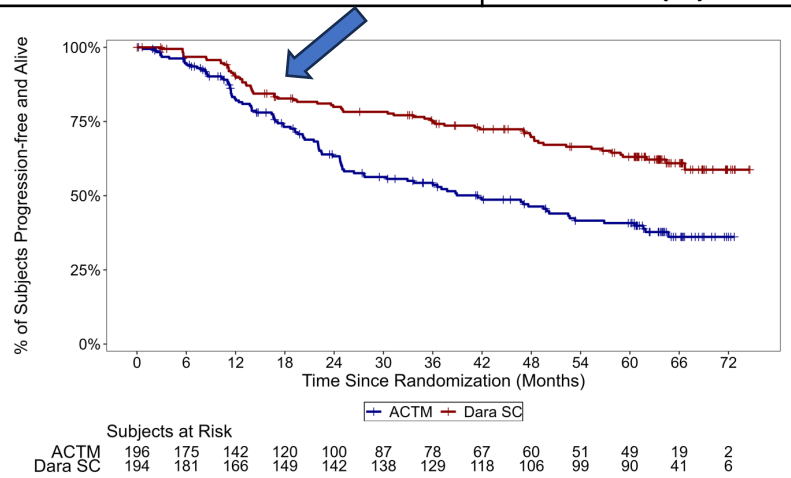
Causal inference methods based on strong and unverifiable assumptions
Naïve censoring non-informative censoring assumption might not be satisfied

Source: FDA analysis.
Abbreviations: ACTM= Active Monitoring, CI= confidence interval, Dara SC= daratumumab subcutaneous, OS= overall survival

PFS : Late Separation of Kaplan Meier Curves

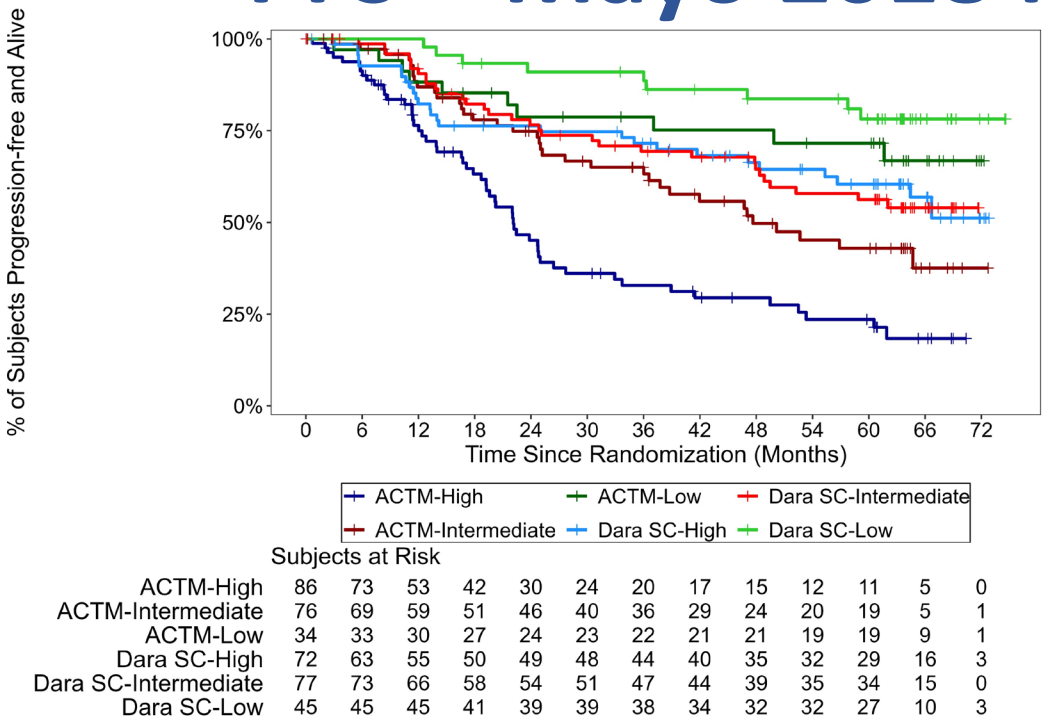
- **Censored before 12 months from randomization**

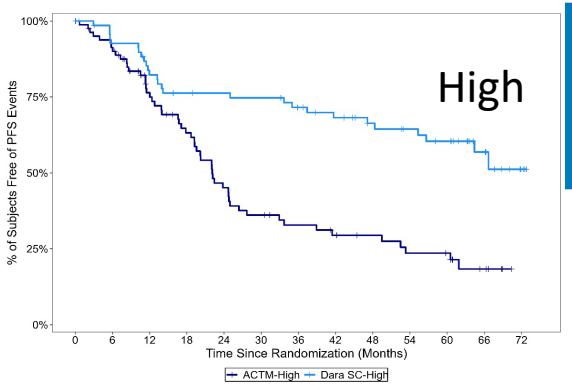
	Dara SC N = 194 n (%)	ACTM N = 196 n (%)	Overall N = 390 n (%)
Censored before 12 months	9 (5)	23 (12)	32 (8)
Received subsequent antimyeloma therapy	5 (3)	13 (7)	18 (5)
Clinical Cutoff	1 (0.5)	1 (0.5)	2 (0.5)
No post-baseline disease assessment	0 (0)	3 (1)	3 (1)
Withdrawal of consent to study participation	0 (0)	3 (2)	3 (1)
Other	3 (2)	3 (2)	6 (2)

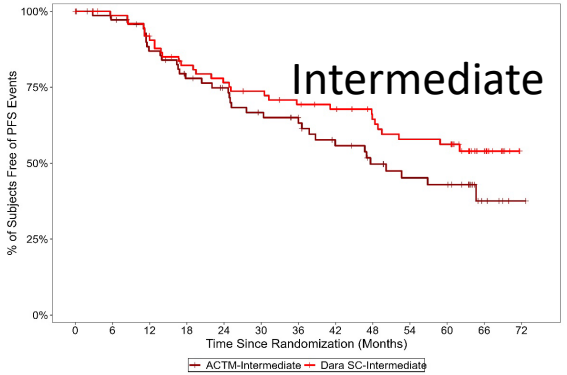


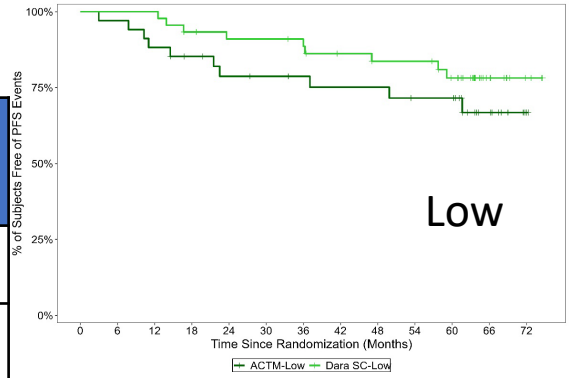
Source: FDA analysis. PFS per IRC assessment.
Abbreviations: ACTM= active monitoring. Dara SC= daratumumab subcutaneous, PFS = progression-free survival

PFS – Mayo 2018 Model









	Dara SC		ACTM		Hazard Ratio (95% CI)
	EVT/N (%)	Median, mos	EVT /N (%)	Median, mos	
Low	9/45 (20%)	NE (NE, NE)	10/34 (29%)	NE (61.6, NE)	0.59 (0.24, 1.45)
Intermediate	31/77 (40%)	NE (48.9, NE)	35/76 (46%)	47.6 (36.6, NE)	0.70 (0.43, 1.14)
High	27/72 (38%)	NE (55.3, NE)	54/86 (63%)	22.1 (18.7, 26.4)	0.36 (0.23, 0.58)

Source: FDA analysis.

Abbreviations: ACTM= active monitoring, CI= confidence interval, Dara SC= daratumumab subcutaneous, EVT= number of events, NE= not estimable; mos = months, PFS = progression-free survival