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DARZALEX FASPRO®
(DARATUMUMAB AND HYALURONIDASE-FIHJ)
AS MONOTHERAPY FOR THE TREATMENT OF ADULT PATIENTS WITH HIGH-RISK SMOLDERING MULTIPLE MYELOMA

SPONSOR BRIEFING DOCUMENT

ONCOLOGIC DRUGS ADVISORY COMMITTEE

MEETING DATE: 20 MAY 2025

ADVISORY COMMITTEE BRIEFING MATERIALS AVAILABLE FOR PUBLIC RELEASE

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List of Abbreviations

Abbreviation	Definition
ADR	adverse drug reaction
AE	adverse event
AL	amyloid light chain
ALL	acute lymphoblastic leukemia
AQUILA	Phase 3 Study 3001
ASCT	autologous stem cell transplant
BMPC	bone marrow plasma cell
CCO	clinical cutoff
CENTAURUS	Phase 2 Study 2001
CI	confidence interval
C_{max}	maximum observed serum concentration
COVID-19	Coronavirus Disease 2019
CR	complete response
CRAB	calcium, renal, anemia, bone
C_{trough}	trough concentration
Dara	daratumumab SC
ECG	electrocardiograms
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organization for Research and Treatment of Cancer
EQ-5D-5L	European Quality of Life Five Dimensions Questionnaire
E-R	exposure-response
EU	European Union
FDA	Food and Drug Administration
FLC	free light chain
HR	hazard ratio
HRQoL	health-related quality of life
Ig	immunoglobulin
IMWG	International Myeloma Working Group
IRC	independent review committee
IRR	infusion-related reaction
ITT	intent-to-treat
IV	intravenous(ly)
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MGUS	monoclonal gammopathy of undetermined significance
M protein	monoclonal protein
MRI	magnetic resonance imaging
NCCN	National Comprehensive Cancer Network

List of Abbreviations

NCI	National Cancer Institute
NDMM	newly diagnosed multiple myeloma
ORR	overall response rate
OS	overall survival
PD	progressive disease/disease progression
PET	positron emission tomography
PFS	progression-free survival
PFS2	progression-free survival on first-line treatment for multiple myeloma
PI	protease inhibitor
PK	pharmacokinetic(s)
PPK	population pharmacokinetics
PR	partial response
PRO	patient-reported outcome
PT	preferred term
QLQ	quality of life questionnaire
QW	once every week
rHuPH20	recombinant human hyaluronidase
RRMM	relapsed or refractory multiple myeloma
SAE	serious adverse event
SAP	statistical analysis plan
sARR	systemic administration-related reaction
sBLA	supplemental Biologics License Application
SC	subcutaneous(ly)
sCR	stringent complete response
SD	standard deviation
SLiM-CRAB	clonal bone marrow plasma cells ≥60%, serum (involved/uninvolved) FLC ratio ≥100, >1 focal bone lesions on MRI, calcium elevation, renal insufficiency, anemia, or bone disease due to lytic bone lesion
SMM	smoldering multiple myeloma
SOC	system organ class
Study SMM2001	Study 54767414SMM2001; CENTAURUS
Study SMM3001	Study 54767414SMM3001; AQUILA
US	United States
USPI	United States Prescribing Information
VGPR	very good partial response

1 EXECUTIVE SUMMARY

1.1 Introduction

This briefing document summarizes a positive benefit-risk profile for treatment with daratumumab subcutaneous (SC) compared with active monitoring in participants with high-risk smoldering multiple myeloma (SMM) based on the Phase 3, 54767414SMM3001 (AQUILA) study (hereafter referred to as AQUILA). The data from the study support approval for DARZALEX FASPRO® as monotherapy for the treatment of adult patients with high-risk smoldering multiple myeloma.

Daratumumab SC demonstrated a clinically meaningful and statistically significant improvement in the primary endpoint (progression-free survival [PFS]) and key secondary endpoint of overall response rate (ORR) compared with active monitoring. In addition, health-related quality of life (HRQoL) was similar to active monitoring at baseline and end of study and across individual domains in participants at high risk for developing multiple myeloma. For other key secondary endpoints, progression-free survival on first-line treatment for multiple myeloma (PFS2) showed no apparent detriment with daratumumab SC and overall survival (OS) showed early evidence of a positive trend in favor of treatment with daratumumab SC.

Overall, the safety data from the AQUILA study demonstrated that daratumumab was well tolerated in participants with high-risk of developing multiple myeloma, with clinically manageable side effects and a safety profile that was consistent with the known safety profile of daratumumab.

With no approved treatments for patients with high-risk SMM, daratumumab can provide a proven therapeutic that delays the progression of high-risk SMM to active multiple myeloma. Overall, treatment with daratumumab in patients with high-risk SMM has the potential to fulfill an unmet need for this patient population.

1.2 Background and Unmet Need

1.2.1 Multiple Myeloma

Multiple myeloma is a blood cancer that develops in plasma cells in the bone marrow (BMPCs). Bone marrow plasma cells are terminally differentiated, non-dividing cells that produce antigen-specific immunoglobulins (Ig or monoclonal proteins) comprised of 2 heavy chains and 2 light chains. Malignant plasma cell clones produce excess light chains and high levels of abnormal monoclonal (M) proteins which displace the normal cells in the bone marrow, resulting in conditions such as anemia, thrombocytopenia, cytopenia, and impaired immune function (i.e., immunoparesis). Excess light chains and the buildup of M protein in the blood and urine can damage the kidneys and other organs. Myeloma cells may also activate osteoclasts in the marrow that can cause bone pain, osteolytic lesions, and bone loss.

The most common presenting symptoms of multiple myeloma are fatigue and bone pain. Anemia contributes to fatigue and occurs in approximately 75% of patients with multiple myeloma (Rajkumar 2016). Severe destructive bone disease, a hallmark of multiple myeloma, is a frequent cause of bone pain. Some of the most common clinical signs (observed in 80% of patients) are refractory pain, fracture, vertebral collapse, or spinal cord compression (Mansour 2023). Hypercalcemia, caused by bone lysis, can lead to abdominal pain, constipation, and confusion. Renal dysfunction and infection, particularly pneumonia, are common symptoms of multiple myeloma; infection is due to the immunoparesis associated with the disease state.

1.2.1.1 Diagnostic Criteria for Multiple Myeloma- Biomarkers of End-Organ Damage

The International Myeloma Working Group (IMWG) established the criteria for diagnosis and classification of multiple myeloma, based on the SLiM-CRAB criteria (Table 1).

Table 1: Multiple Myeloma SLiM-CRAB Criteria for Diagnosis

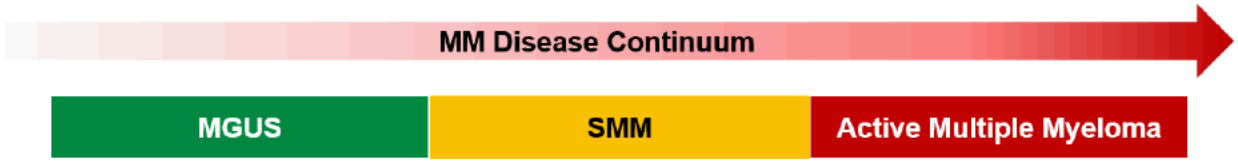
S: bone marrow plasmacytosis of ≥60% **Li**: the presence of an elevated involved serum FLC ratio (≥100 serum light chain [kappa or lambda] involved/uninvolved ratio as high ratios indicate a clonal expansion of plasma cells producing only one type of light chain). **M**: MRI lesions (≥1 focal bone lesion of ≥5 mm in size)
C: calcium elevation due to release of cytokines that cause local osteolytic lesions resulting in extra blood calcium (hypercalcemia; >11.5 mg/dL), **R**: renal insufficiency due to excess M protein and calcium in the blood causing kidney damage (creatinine >2 mg/dL or creatinine clearance <40 mL/min), **A**: anemia due to plasma cells crowding out normal red blood cells in the bone marrow (hemoglobin <10 g/dL or >20 g/L below lower limit of normal), **B**: bone disease (lytic or osteopenia)

Key: FLC= free light chain; MRI=magnetic resonance imaging
IMWG 2003; Rajkumar 2014

1.2.2 Smoldering Multiple Myeloma

Multiple myeloma disease progression can be characterized as a continuum, starting with the precursor condition of monoclonal gammopathy of undetermined significance (MGUS) on one end of the continuum and progressing to active multiple myeloma on the other (Figure 1).

Figure 1: Continuum of Multiple Myeloma



Key: MGUS = monoclonal gammopathy of undetermined significance; MM=multiple myeloma; SMM = smoldering multiple myeloma

Smoldering multiple myeloma is an asymptomatic malignancy and intermediate disease state between MGUS and active multiple myeloma characterized by abnormal monoclonal BMPC proliferation (10% to 60%) and/or abnormally high levels of circulating M proteins (serum ≥3 g/dL or urine ≥500 mg/24 hour), in the absence of myeloma-defining events (SLiM-CRAB; Table 1) (Rajkumar 2014). Smoldering multiple myeloma is typically detected incidentally based on blood and/or urine testing during a routine check-up.

Smoldering multiple myeloma accounts for approximately 15% of myelomas (Rios-Tamayo 2014) and has an estimated US prevalence of 5.0 per 100,000 persons based on the incidence 0.9 per 100,000 (Thorsteinsdottir 2021; Ravindran 2016). Within the SMM patient population, there is a subset of patients whose disease will progress slowly, and a subset who will develop clinical symptoms and end-organ damage within the first 2 years of diagnosis (Rajkumar 2014; Kyle 2010; Rosinol 2003).

Smoldering multiple myeloma is associated with an overall risk of progression to multiple myeloma of 10% per year for the first 5 years after diagnosis (Kyle 2010). Risk-stratification models have been implemented to identify patients at the highest risk of progression to active multiple myeloma. Approximately 40% of patients with SMM were classified as high risk across real-world populations regardless of the risk-stratification model used (Perez-Persona 2007; Dispenzieri 2008; Lakshman 2018; Mateos 2020; de Daniel 2024).

1.2.3 Diagnosis of High-risk Smoldering Multiple Myeloma

Because SMM is a heterogenous disease with varying risks of progression (Section 1.2.2), efforts have been made to better define the characteristics of patients with SMM. Examination of this patient population led to the identification of risk factors associated with a high risk of progression to active myeloma. Accordingly, high-risk SMM is now considered a stage of SMM. Patients with high-risk SMM have an approximately 50% risk of developing multiple myeloma within approximately 2 years of diagnosis (Rajkumar 2015) and these patients are likely to benefit most from treatment to delay development of active myeloma.

At the foundation of characterizing SMM risk is a set of key disease markers based on BMPC infiltration, serum M protein level, and serum free light chain (FLC) ratio (Lakshmam 2018). Risk models used to characterize high-risk SMM continue to be refined in terms of which biomarkers are selected to define the criteria, and the specific ranges used to define the biomarkers (Dispenzieri 2008; Rajkumar 2013; Mateos 2016; Lakshmam 2018; Mateos 2020; Cowan 2023). The risk of progression to multiple myeloma, however, appears to be consistent across the risk models and treating clinicians are informed of the modifications via commonly accepted myeloma guidelines.

For the AQUILA study, high-risk SMM was determined based on a compilation of risk factors identified in several risk models recognized at the time of study development in 2015. High-risk SMM was defined in the AQUILA study as follows:

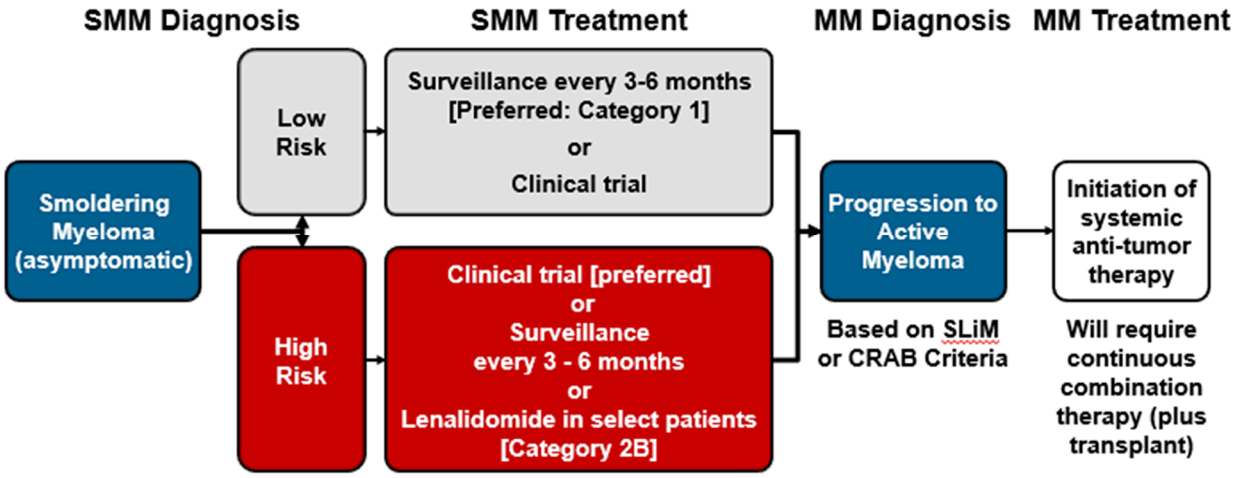
- Clonal BMPCs ≥10%

  AND at least 1 of the following high-risk factors:
  - Serum M protein ≥30 g/L
  - IgA SMM
  - Immunoparesis with reduction of 2 uninvolved Ig isotypes (only IgA, IgM, and IgG were considered in determination for immunoparesis; IgD and IgE were not considered in this assessment)
  - Serum involved: uninvolved FLC ratio ≥8 and <100
  - Clonal BMPCs >50% to <60% with measurable disease

1.2.4 Current Treatment Options for High-risk Smoldering Multiple Myeloma

The overall approach for patients with SMM is to observe without treatment until criteria for active multiple myeloma are met. This approach is termed 'Watch and Wait' and entails hematology check-ups, typically several times a year (McCaughan 2023). For high-risk SMM, current National Comprehensive Cancer Network (NCCN) guidelines recommend entry into clinical studies, observation for patients, and in certain circumstances treatment with lenalidomide (Figure 2).

Figure 2: National Comprehensive Cancer Network Standard of Care for Smoldering Multiple Myeloma



Adapted from NCCN Guidelines Version 1.2025 Multiple Myeloma
Key: CRAB=MM diagnostic criteria based on end-organ damage; MM=multiple myeloma; SLiM=MM diagnostic criteria based on biomarkers; SMM=smoldering multiple myeloma

1.2.5 Unmet Medical Need for Patients with High-risk Smoldering Multiple Myeloma

The psychological burdens of stress, anxiety, and uncertainty regarding future health can impact day-to-day life for patients with no effective treatment options (McCaughan 2023). The 'Watch and Wait' approach of observation can also be described as 'Worry and Wait' for patients who understand that their disease may progress, but for whom there are no approved therapies (Jean-Baptiste 2020).

Although current NCCN guidelines recommend participation in a clinical study for patients with high-risk SMM, this recommendation is often not feasible due to a lack of accessibility to clinical trials, failure to meet eligibility requirements, or the inability of patients to meet the demands of study participation.

Although published Phase 3 studies showed meaningful clinical benefit by delaying progression to active multiple myeloma with lenalidomide/dexamethasone or lenalidomide (Mateos 2013; Mateos 2022; Lonial 2019), lenalidomide is not currently approved for the treatment of patients with high-risk SMM. Lenalidomide is not adopted as the standard of care by the myeloma community for reasons including enrollment of heterogeneous populations, lack of advanced imaging at screening, and high discontinuation rates during clinical studies. In addition, lenalidomide carries a boxed warning in the Unites States Prescribing Information (USPI) for embryofetal toxicity, hematologic toxicity, and venous and arterial thromboembolism (REVLIMID USPI 2023).

Once patients progress to active multiple myeloma, multi-drug (i.e., 3- to 4-drug) treatment regimens, possibly including autologous stem cell transplant (ASCT), are used. Various treatment regimens are utilized as the disease progresses, since there is no cure for multiple myeloma. In addition, many of the regimens carry significant side effects. Therefore, patients and clinicians need an approved treatment for high-risk SMM with a tolerable safety profile that can delay disease progression to active myeloma and the need for continuous multi-drug systemic therapy.

As described in this document, results from the Phase 3 AQUILA study establish that daratumumab monotherapy can provide this proactive therapy and meet this unmet need.

1.3 Product Description

Daratumumab is a human IgG1k monoclonal antibody (mAb) immunotherapy that binds with high affinity to CD38-expressing cells. CD38 is a multifunctional glycoprotein ectoenzyme that is highly expressed on the cell surface of diverse hematologic malignancies including myeloma, lymphomas, and leukemias. Daratumumab induces tumor-cell death through multiple mechanisms of action that include several immune-mediated activities: complement-dependent cytotoxicity, antibody-dependent cell-mediated cytotoxicity, antibody-dependent cellular phagocytosis, and direct cytotoxicity by induction of apoptosis by Fc γ receptor-mediated crosslinking of tumor-bound mAbs (Overdijk 2016).

Daratumumab is administered in combination or as monotherapy for the treatment of newly diagnosed multiple myeloma (NDMM) and all phases of relapsed/refractory multiple myeloma (RRMM). Initially approved in 2015, there is deep experience among clinicians with this therapeutic, and clinicians will be able to effectively manage the side effects of treatment in the high-risk SMM population.

For the treatment of high-risk SMM, daratumumab is formulated with recombinant human hyaluronidase (rHuPH20) for SC injection. Hyaluronidase facilitates absorption of daratumumab by the body. Daratumumab+hyaluronidase for SC injection (referred to as daratumumab or daratumumab SC) was the formulation administered in the Phase 3 study AQUILA at a fixed dose of 1800 mg daratumumab/30,000 units hyaluronidase per 15 mL single dose vial.

For the treatment of high-risk SMM, daratumumab SC is intended as a finite therapy to be administered for 3 years.

1.4 Development Program

1.4.1 Overview of the Daratumumab Development Program

Daratumumab, available as an IV and SC formulation, is a well-established standard of care for the treatment of multiple myeloma and is recommended by the NCCN. Currently, daratumumab is being evaluated in participants across the multiple myeloma disease continuum (i.e., SMM, NDMM, RRMM, and other diseases including amyloid light chain [AL] amyloidosis and pediatric acute lymphoblastic leukemia [ALL]). The IV formulation of daratumumab (DARZALEX) is approved in over 100 countries worldwide for the treatment of multiple myeloma. DARZALEX was initially approved in the US and EU as monotherapy for the treatment of heavily pre-treated patients with RRMM and since that time, several indications have been approved for DARZALEX in combination with background therapies for both RRMM and NDMM.

An SC formulation of daratumumab and hyaluronidase is also approved in over 60 countries worldwide for the treatment of RRMM and NDMM in combination with various background therapies. Since the initial approval of daratumumab, over 500,000 patients have been treated with daratumumab regimens worldwide.

1.4.2 High-Risk Smoldering Multiple Myeloma Development Program

The studies in the clinical development program for daratumumab SC for the treatment of SMM included a Phase 2 study (54767414SMM2001 [CENTAURUS]; hereafter referred to as CENTAURUS) and the Phase 3 AQUILA study.

The proposed indication for daratumumab and hyaluronidase (DARZALEX FASPRO) is as monotherapy for the treatment of adult patients with high-risk smoldering multiple myeloma. The clinical efficacy and safety data presented in this application are from the Phase 3 study, AQUILA.

The Sponsor sought input and agreement from the FDA on the AQUILA protocol design, statistical analysis plan (SAP), and the content and format of the supplemental Biologics License Application (sBLA) submission of daratumumab for high-risk SMM.

1.4.2.1 Phase 3 Study AQUILA

Study AQUILA is a Phase 3, randomized, open-label, 2-arm, multicenter study of daratumumab SC monotherapy versus active monitoring in participants with high-risk SMM. Eligible participants (n=390) were randomized in a 1:1 ratio to either of the following arms:

- Daratumumab: daratumumab SC 1800 mg + rHuPH20 [2000 U/mL] weekly in Cycles 1 and 2, then every 2 weeks in Cycles 3 to 6, then every 4 weeks thereafter for fixed duration of up to 39 cycles or 36 months, whichever occurred first.
- Active Monitoring: no disease-specific treatment given.

Randomization was stratified based on the number of risk factors associated with progression to multiple myeloma as summarized in Table 2.

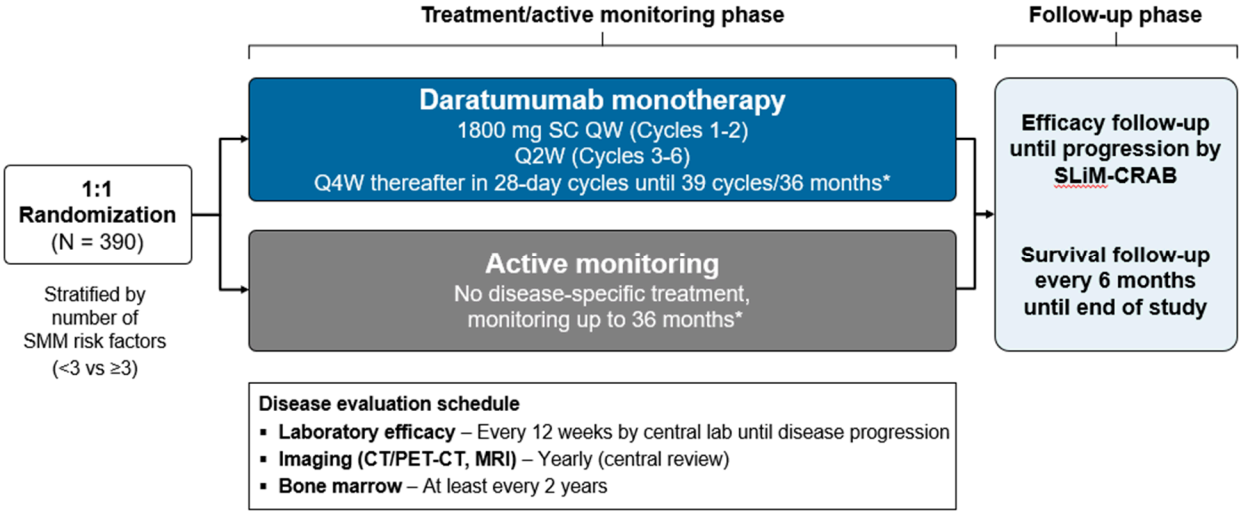
Table 2: Randomization Stratification Factors for Study AQUILA

Stratification	**Criteria**
Number of Risk Factors	**<3 vs ≥3**
Risk Factors	
FLC ratio≥8 (involved:uninvolved)	Yes/No
Serum M protein ≥30 g/L	Yes/No
IgA SMM	Yes/No
Immunoparesis (reduction of 2 uninvolved Ig isotypes)	Yes/No
Bone Marrow Plasma Cells	>50% to <60% vs ≤50%

Key: FLC=free light chain; Ig=immunoglobulin; M protein=monoclonal protein; SMM=smoldering multiple myeloma

Following completion of the treatment/active monitoring phase, participants continue to be followed for progression (per SLiM-CRAB [Table 1]) and for survival until the end of the study, which will occur approximately 8 years after the first participant was randomized (approximately December 2025). The study design is summarized in Figure 3.

Figure 3: Phase 3 AQUILA Study Design



Key: AE=adverse events; CT=computed tomography; MRI=magnetic resonance imaging; QW=once every week; Q2W=one every 2 weeks; Q4W=once every 4 weeks; PET=positron emission tomography; SC subcutaneous; SLiM-CRAB=diagnostic criteria for symptomatic multiple myeloma; SMM=smoldering multiple myeloma
* or confirmed disease progression (whichever occurred first)

Key inclusion criteria for participation in this study were:

- ≥18 years of age
- Diagnosis of SMM (per IMWG criteria) for ≤5 years with measurable disease at the time of randomization, defined as serum M protein ≥10 g/L **or** urine M protein ≥200 mg/24 hours **or** involved serum FLC ≥100 mg/L and abnormal serum FLC ratio
- Clonal BMPCs ≥10%

  AND at least 1 of the following high-risk factors:
  - Serum M protein ≥30 g/L
  - IgA SMM
  - Immunoparesis with reduction of 2 uninvolved Ig isotypes (only IgA, IgM, and IgG were considered in determination for immunoparesis; IgD and IgE were not considered in this assessment)
  - Serum involved: uninvolved FLC ratio ≥8 and <100
  - Clonal BMPCs >50% to <60% with measurable disease
- Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1

Key exclusion criteria were myeloma-defining events:

- Multiple myeloma requiring treatment per SLiM-CRAB criteria
- Primary systemic Ig AL amyloidosis

1.5 Clinical Pharmacology

The clinical pharmacology of daratumumab SC has been well characterized as monotherapy and in combination with a variety of background therapies for participants with multiple myeloma.

Results from the Phase 3 AQUILA study and the population pharmacokinetics (PPK) analyses showed the pharmacokinetics (PK) profile and immunogenicity of daratumumab administered to participants with high-risk SMM were consistent with observations in previous daratumumab SC monotherapy and combination therapy studies in participants with multiple myeloma and support the 1800 mg dose regimen.

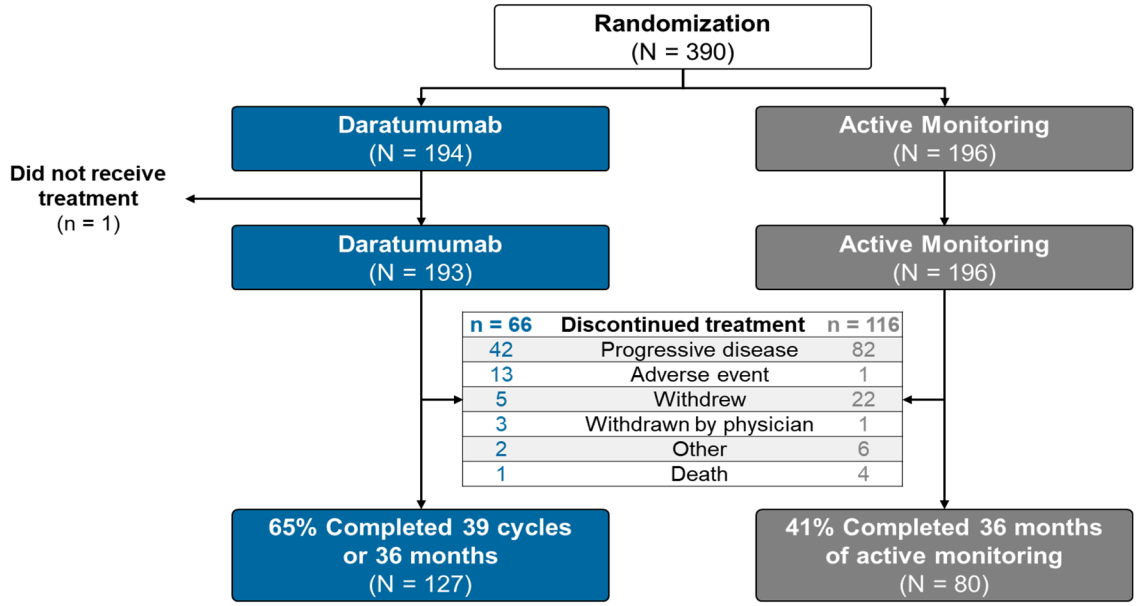
Clinical pharmacology data from AQUILA, including PPK and exposure-response (E-R) analyses with regards to efficacy and safety, support that the administration of daratumumab SC 1800 mg dose regimen provides effective exposure for the treatment of patients with high-risk SMM.

1.6 AQUILA Efficacy Findings

A total of 390 participants were randomized in a 1:1 ratio to either the Daratumumab or Active Monitoring arm for up to 39 cycles or 36 months, or disease progression, whichever occurred first. As of the clinical cutoff (CCO) date of 01 May 2024, 127 (65.5%) participants in the Daratumumab arm completed 39 cycles or 36 months of study treatment per protocol compared with 80 (40.8%) participants in the Active Monitoring arm who completed 36 months of active monitoring. A lower percentage of participants in the Daratumumab arm discontinued study treatment (34.2%) compared with those who discontinued active monitoring in the Active Monitoring arm (59.2%). A total of 15.5% and 26.0% of participants discontinued the study in the Daratumumab and Active Monitoring arms, respectively.

Participant treatment disposition is summarized in Figure 4.

Figure 4: Participant Treatment Disposition; Intent-to-treat Analysis Set (AQUILA)



For all participants in the study, the median age was 64.0 years (range 31-86). A total of 48.2% of participants were male and 51.8% of participants were female.

Demographic characteristics were balanced between-treatment arms (Table 3). Participant randomization by region/country/territory was balanced between the treatment arms for the EU, US, and Other.

Table 3: Summary of Key Demographics; Intent-to-treat Analysis Set (AQUILA)

		Daratumumab (N = 194)	Active Monitoring (N = 196)
Age (years)	**Median** (range)	**63.0** (31, 86)	**64.5** (36, 83)
	18 to < 65, %	55%	50%
	65 to < 75, %	35%	38%
	≥ 75 years, %	11%	12%
Sex, %	Female	51%	53%
Race	White	83%	83%
	Black	2%	4%
	Asian	9%	7%
	Other / NR	6%	6%
ECOG PS score, %	0	85%	82%
	1	15%	18%

Key: ECOG=Eastern Cooperative Oncology Group; NR=not reported

Baseline disease characteristics were generally balanced between arms and representative of patients with high-risk SMM (Table 4). Approximately 60% of participants had 2 or more risk factors.

Table 4: Summary of Key Baseline Disease Characteristics; Intent-to-treat Analysis Set (AQUILA)

		Daratumumab (N = 194)	Active Monitoring (N = 196)
Median time from SMM diagnosis to randomization (range)		**0.80 years** (0, 4.7)	**0.67 years** (0, 5.0)
Time from diagnosis < 2 years		77%	76%
Median BMPCs (range)		**20%** (8, 60)	**20%** (10, 55)
Risk Factors for High-Risk SMM			
Serum M Protein ≥ 3 g/L		**18%**	**20%**
Serum Involved: uninvolved FLC Ratio ≥ 8 and < 100		**70%**	**75%**
Immunoparesis with reduction of ≥ 2 uninvolved immunoglobulin isotypes		**60%**	**59%**
IgA SMM		**28%**	**21%**
Clonal BMPCs > 50% to < 60%		**3%**	**2%**
Number of risk factors	**< 3***	**81%**	**82%**
	≥ 3	**19%**	**18%**
Cytogenetic risk profile		**n = 167**	**n = 170**
≥ 1 of del(17p), t(4;14), and/or t(14;16)		**17%**	**13%**

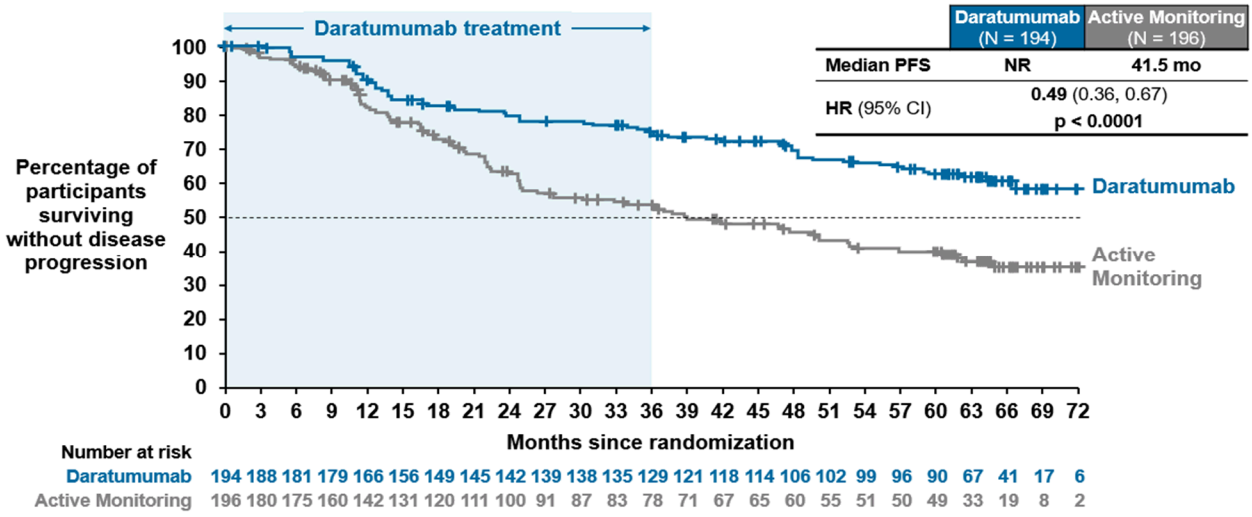
Key: BMPC=bone marrow plasma cell; FLC=free light chain; Ig=immunoglobulin; SMM=smoldering multiple myeloma
*Median number of risk factors was 2.

1.6.1 Progression-free Survival – Primary, Subgroup, and Supplemental Analyses

The primary endpoint in the AQUILA study was PFS as evaluated by an Independent Review Committee (IRC), defined as the time from the date of randomization to the date of documented disease progression to active multiple myeloma (per IMWG diagnostic criteria) or the date of death, whichever occurred first.

Treatment with daratumumab SC resulted in a clinically meaningful and statistically significant improvement in PFS, with a 51% reduction in the risk of progression or death compared with active monitoring (hazard ratio [HR]=0.49; 95% confidence interval [CI]: 0.36, 0.67; 2-sided p<0.0001). Median PFS was not reached in the Daratumumab arm and was 41.5 months (95% CI: 26.4, 53.3) in the Active Monitoring arm (60-month PFS rate: Daratumumab 63.1%; Active Monitoring 40.8%; Figure 5).

Figure 5: Progression-free Survival as Assessed by Independent Review Committee; Intent-to-treat Analysis Set (AQUILA)

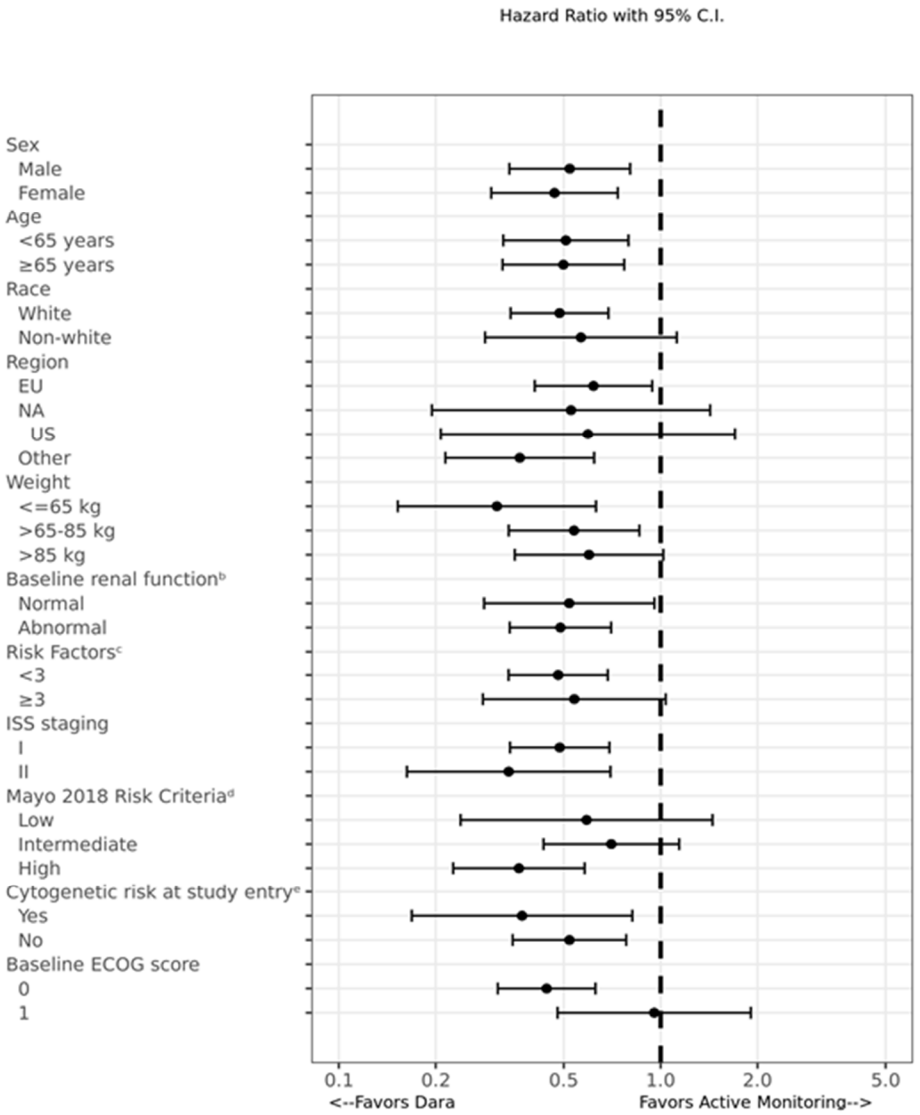


Key: HR=hazard ratio; NR=not reached; NR=not reached; PFS=progression-free survival
Median follow-up was 65.2 months (Daratumumab 65.9 months; Active Monitoring 64.8 months).
A total of 166 PFS events per IRC assessment (Daratumumab 67; Active Monitoring 99) were observed.

Data from 127 (65.5%) participants in the Daratumumab arm and 97 (49.5%) participants in the Active Monitoring arm were censored. The 3 most common reasons for censoring were no PD at the time of the CCO (Daratumumab 77.2%; Active Monitoring 53.6%), starting subsequent antimyeloma therapy prior to disease progression (PD; Daratumumab 12.6%; Active Monitoring 26.8%), and withdrawal of consent to study participation (Daratumumab 7.1%; Active Monitoring 12.4%).

Subgroup analyses showed the PFS benefit per IRC was consistent across the prespecified subgroups of sex, age, race, region, baseline renal function and SMM risk factors and showed improved outcomes for participants in the Daratumumab arm compared with the Active Monitoring arm; however, for subgroups with small sample sizes, the results should be interpreted with caution (Figure 6).

Figure 6: Forest Plot of Subgroup Analyses on Progression-free Survival Based on Independent Review Committee; Intent-to-treat Analysis Set (AQUILA)



	Active Monitoring		Dara		
	EVT/N	Median (95% CI)	EVT/N	Median (95% CI)	Hazard Ratio 95% CI[a]
Sex					
Male	48/93	41.5 (23.8, 53.3)	37/95	NE (57.8, NE)	0.52 (0.34, 0.80)
Female	51/103	38.9 (25, 61.9)	30/99	NE (66.7, NE)	0.47 (0.30, 0.74)
Age					
<65 years	45/98	42 (25, NE)	34/106	NE (66.7, NE)	0.51 (0.32, 0.79)
≥65 years	54/98	38.8 (22, 52.7)	33/88	NE (57.8, NE)	0.50 (0.32, 0.77)
Race					
White	79/162	38.8 (25, 61.6)	53/161	NE (66.7, NE)	0.49 (0.34, 0.69)
Non-white	20/34	47 (24.7, NE)	14/33	NE (47.8, NE)	0.57 (0.28, 1.12)
Region					
EU	50/95	36 (22.2, 64.7)	39/98	NE (55.3, NE)	0.62 (0.41, 0.94)
NA	9/33	NE (18.7, NE)	7/32	NE (NE, NE)	0.53 (0.19, 1.42)
US	7/27	NE (18.7, NE)	7/30	NE (56.6, NE)	0.59 (0.21, 1.70)
Other	40/68	41.5 (25, 53.3)	21/64	NE (NE, NE)	0.36 (0.21, 0.62)
Weight					
<=65 kg	26/46	36 (19.6, 60.6)	11/43	NE (NE, NE)	0.31 (0.15, 0.63)
>65-85 kg	39/84	38.8 (22.5, NE)	33/96	NE (64.4, NE)	0.54 (0.34, 0.86)
>85 kg	34/64	46.7 (24.9, 61.6)	23/55	NE (48.3, NE)	0.60 (0.35, 1.02)
Baseline renal function[b]					
Normal	27/58	50.2 (33.7, NE)	17/54	NE (55.3, NE)	0.52 (0.28, 0.96)
Abnormal	72/138	36 (24.7, 52.7)	50/140	NE (64.4, NE)	0.49 (0.34, 0.70)
Risk Factors[c]					
<3	78/161	47.6 (36, 61.6)	51/157	NE (NE, NE)	0.48 (0.34, 0.69)
≥3	21/35	23.8 (11.9, 26.4)	16/37	66.7 (17.1, NE)	0.54 (0.28, 1.04)
ISS staging					
I	79/155	38.9 (26.4, 61.9)	50/154	NE (NE, NE)	0.49 (0.34, 0.69)
II	19/33	22.1 (11.6, 50.2)	14/33	66.7 (31.2, NE)	0.34 (0.16, 0.70)
Mayo 2018 Risk Criteria[d]					
Low	10/34	NE (61.6, NE)	9/45	NE (NE, NE)	0.59 (0.24, 1.45)
Intermediate	35/76	47.6 (36.6, NE)	31/77	NE (48.9, NE)	0.70 (0.43, 1.14)
High	54/86	22.1 (18.7, 26.4)	27/72	NE (55.3, NE)	0.36 (0.23, 0.58)
Cytogenetic risk at study entry[e]					
Yes	14/22	19.6 (11.2, 46.7)	13/29	66.7 (25, NE)	0.37 (0.17, 0.82)
No	59/118	49.5 (30.4, 61.9)	39/116	NE (59.1, NE)	0.52 (0.35, 0.78)
Baseline ECOG score					
0	80/160	37.7 (25, 56.9)	53/165	NE (NE, NE)	0.44 (0.31, 0.63)
1	19/36	41.5 (22.4, NE)	14/29	48.3 (14, NE)	0.95 (0.48, 1.91)

Key: BMPC=bone marrow plasma clone; CI=confidence interval; ECOG=Eastern Cooperative Oncology Group; EU=European Union; EVT=event; FLC=free light chain; GFR=globular filtration rate; HR=hazard ratio; Ig=immunoglobulin; ISS=International Staging System; NA=North America; NE=not estimable; SMM=smoldering multiple myeloma

[a] Hazard ratio and 95% CI was calculated using the Cox proportional hazards model with treatment as the sole explanatory. A hazard ratio <1 indicates an advantage for daratumumab SC.

[b] Normal: GFR (mL/min/1.73m^2) ≥90

[c] The risk factors were: a. Serum M protein ≥30 g/L; b. IgA SMM; c. Immunoparesis with reduction of 2 uninvolved Ig isotypes (only IgA, IgM, and IgG were considered in determination for immunoparesis, IgD and IgE were not considered in this assessment); d. serum involved: uninvolved FLC ratio ≥8 and <100, or e. clonal BMPCs >50% to <60% with measurable disease.

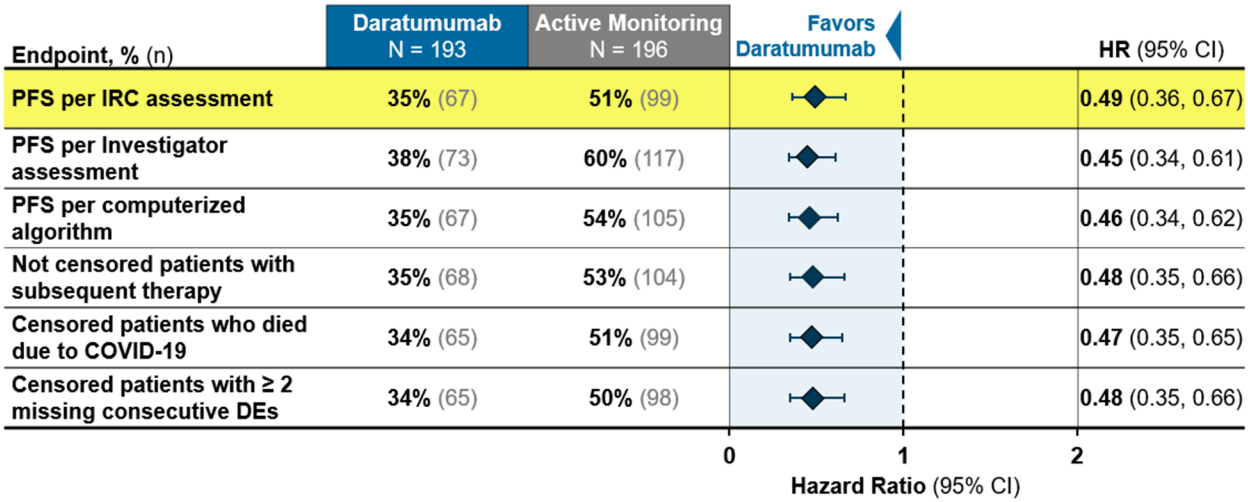
[d] Mayo 2018 risk criteria: Serum M protein >2 g/dL, I/U FLC ratio >20 and BMPC >20%. Participants with presence of 0 factors are considered as low risk, 1 factor are considered as intermediate risk and ≥2 factors are considered as high risk.

[e] Yes: presence of del(17p13), t(4;14), or t(14;16) at baseline; No: tested for these probes but did not have any abnormality.

Note: The subgroups with less than 10 participants in either treatment arm are suppressed in this table.

Consistent results were observed in additional supplemental analyses of PFS, summarized in Figure 7, further supporting the robustness of the primary PFS analysis.

Figure 7: Forest Plot of Sensitivity and Supplementary Analyses on Progression-free Survival; Intent-to-treat Analysis Set (AQUILA)



Key: CI=confidence interval; COVID-19=coronavirus 2019; DE=disease evaluations; IRC=independent review committee; PFS=progression-free survival

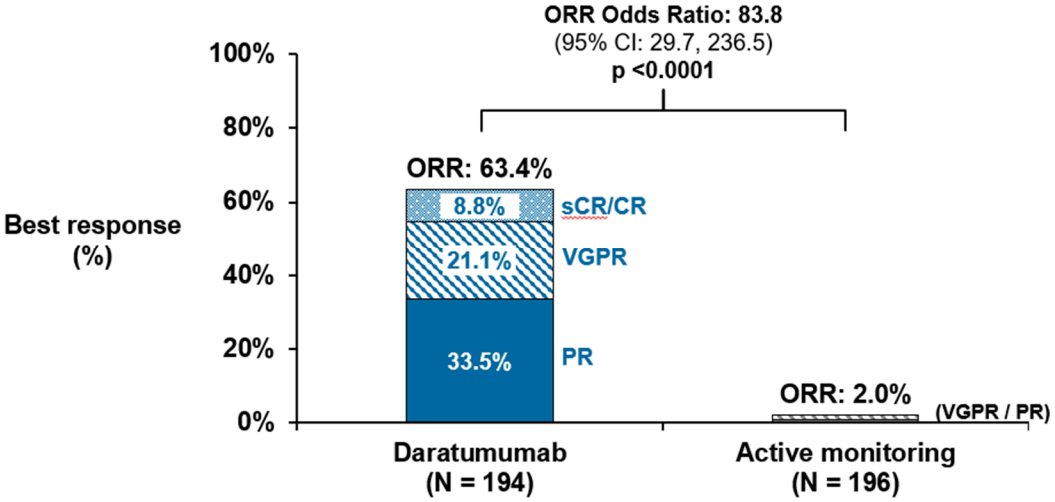
1.6.2 Key Secondary Endpoints

Key secondary endpoints in the AQUILA study included:

- Overall response rate per computerized algorithm, defined as the proportion of participants with a partial response (PR) or better as defined by IMWG response criteria;
- Progression-free survival on first-line treatment for multiple myeloma, defined as the time from the date of randomization to the date of documented PD on the first-line treatment for multiple myeloma or death, whichever occurred first;
- Overall survival, defined as, the time from the date of randomization to the date of death;

Overall response rate was significantly higher in the Daratumumab arm (63.4%) compared with the Active Monitoring arm (2.0%). Best confirmed response is summarized in Figure 8.

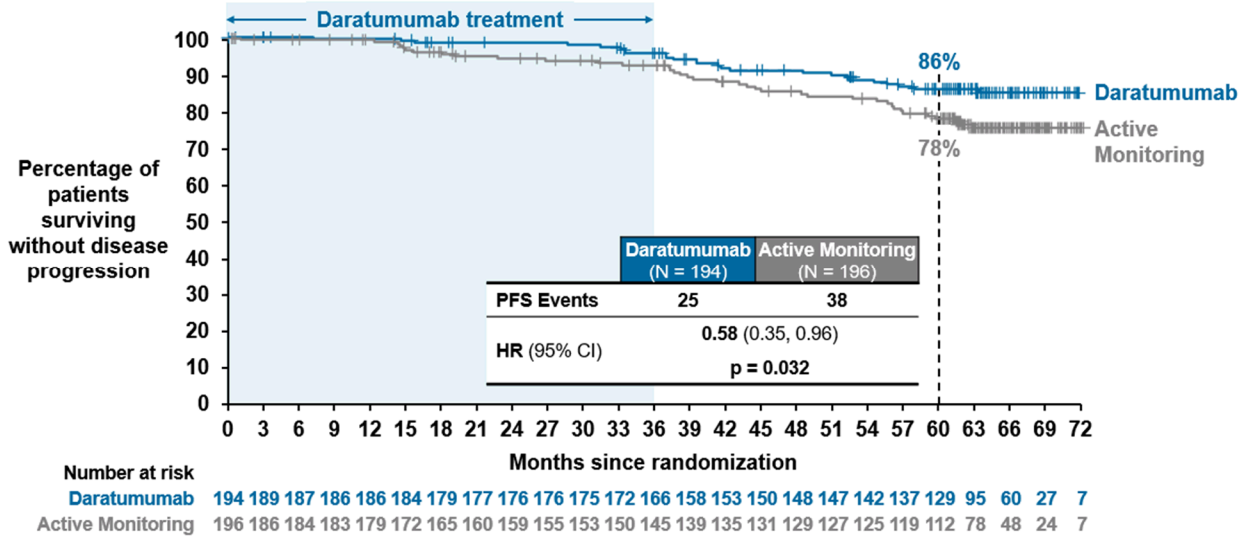
Figure 8: Summary of Overall Best Confirmed Response based on Computerized Algorithm; Intent-to-treat Analysis Set (AQUILA)



Key: CI=confidence interval; CR=complete response; ORR=overall response rate; PR=partial response; sCR=stringent complete response; VGPR=very good partial response

At the time of the CCO, the PFS2 data were not yet mature, and statistical significance of PFS2 was not established at this primary analysis for PFS. However, there was no indication of a detrimental effect on the first-line treatment for active myeloma (Figure 9). The final analysis of PFS2 will be performed at the end of study per protocol.

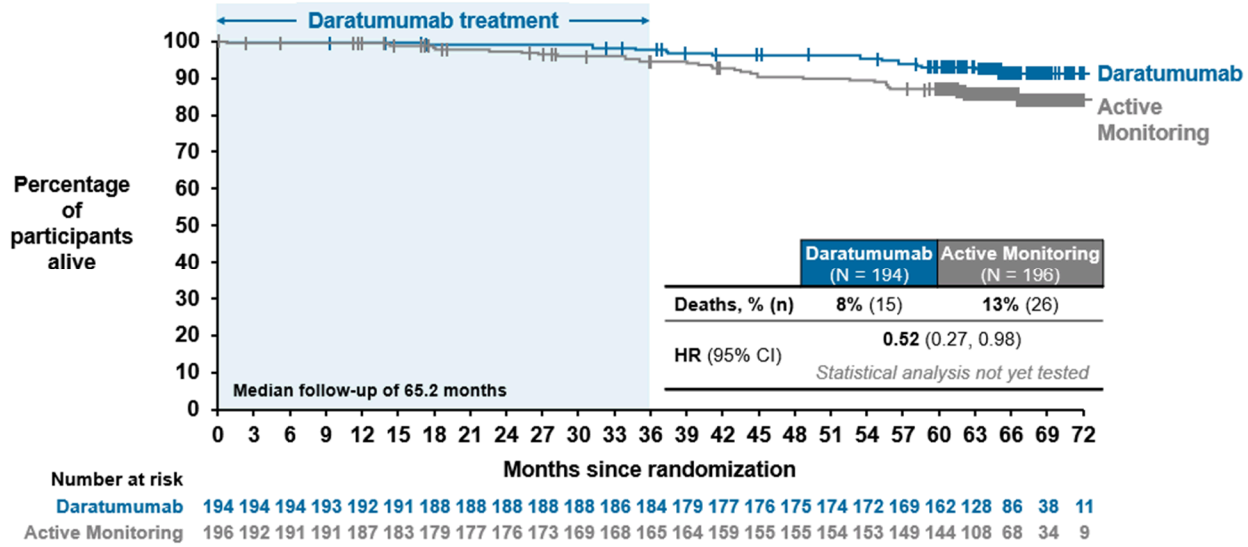
Figure 9: Kaplan-Meier Plot for Progression-free Survival on First-Line Treatment (PFS2) for Multiple Myeloma; Intent-to-treat Analysis Set (AQUILA)



Key: CI=confidence interval; HR=hazard ratio

Overall survival data were not mature at the time of the CCO, with 41 events observed (Daratumumab 15/194 [7.7%]; Active Monitoring 26/196 [13.3%]). Overall survival was not formally tested as it was to be tested only if PFS2 was significant based on the hierarchical testing paradigm used in this study; however, the estimated OS HR (Daratumumab vs Active Monitoring) was 0.52 (95% CI: 0.27, 0.98), indicates early evidence of a positive OS trend in favor of the Daratumumab arm (60-month OS rate: Daratumumab 93.0%; Active Monitoring 86.9%). The study will continue to collect additional survival data. The final OS analysis will be performed at the end of study per protocol. The OS analysis is summarized in Figure 10.

Figure 10: Kaplan-Meier Plot for Overall Survival; Intent-to-treat Analysis Set



Key: CI=confidence interval; HR=hazard ratio

1.6.3 Additional Efficacy Analyses

Additional endpoints in the AQUILA study included:

- Time to biochemical or diagnostic (SLiM-CRAB) progression, defined as the time between the date of randomization and the date of first documented evidence of confirmed biochemical or diagnostic progression, or death (due to any cause, prior to subsequent multiple myeloma therapy), whichever occurs first;
- Time to first-line treatment for multiple myeloma, defined as the time from the date of randomization to the date of the first-line treatment for multiple myeloma;
- Time to response, defined as the time from randomization until onset of first response;
- Change from baseline in global health status and emotional functioning scales of the European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ)-C30, future perspective scale of the EORTC

QLQ-MY20, and utility and visual analog scale of the European Quality of Life Five Dimensions Questionnaire (EQ-5D-5L).

Treatment with daratumumab delayed the time to biochemical or diagnostic (SLiM-CRAB) progression per computerized algorithm. The HR (daratumumab vs active monitoring) was 0.51 (95% CI: 0.40, 0.66), 2-sided nominal p-value <0.0001. Median biochemical or SLiM-CRAB progression was 44.1 months (95% CI: 38.9, 55.2) in the Daratumumab arm and 17.8 months (95% CI: 14.4, 22.0) in the Active Monitoring arm (60-month biochemical or diagnostic PFS rate: Daratumumab 38.8%; Active Monitoring 22.2%).

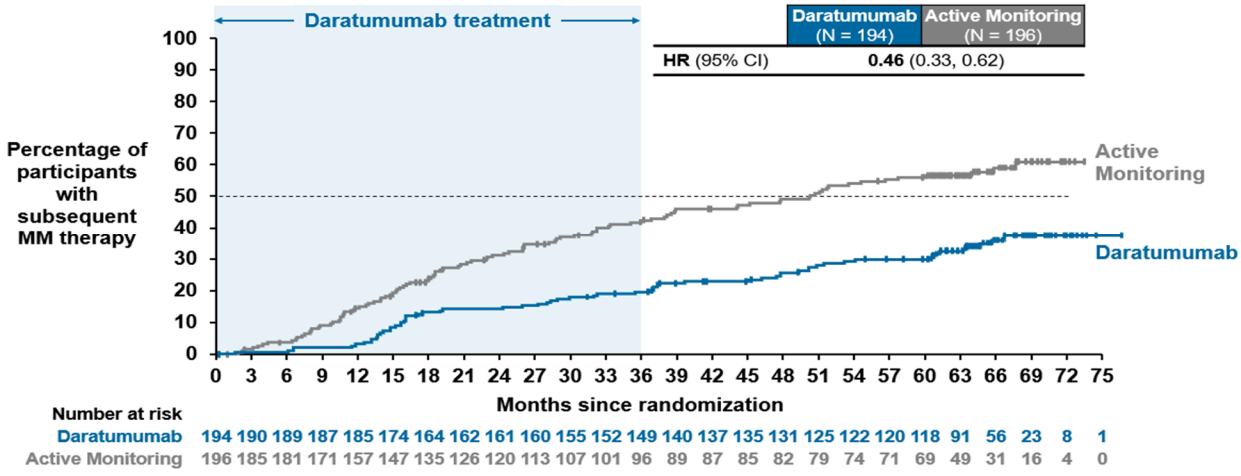
A total of 33.2% of participants in the Daratumumab arm and 53.6% in the Active Monitoring arm started a subsequent antimyeloma therapy (Table 5). Daratumumab delayed the time to first-line treatment for multiple myeloma versus active monitoring, with an HR of 0.46; 95% CI: 0.33, 0.62; 2-sided nominal p<0.0001 (Figure 11).

Table 5: Summary of Subsequent Antimyeloma Therapy by Treatment Regimens Occurring in ≥5% of Participants in Either Treatment Arm; Safety Analysis Set (AQUILA)

	Daratumumab	Active Monitoring
Analysis set: safety	193	196
Total number of participants with first line subsequent therapies	64 (33.2%)	105 (53.6%)
VRd	19 (9.8%)	29 (14.8%)
VCd	6 (3.1%)	14 (7.1%)
VTd	9 (4.7%)	8 (4.1%)
DVRd	4 (2.1%)	10 (5.1%)
DRd	3 (1.6%)	10 (5.1%)

Key: C=cyclophosphamide; d=dexamethasone; D=daratumumab; R=lenalidomide; T=thalidomide; V=bortezomib
Note: Percentages are calculated with the number of participants in each treatment arm as denominator.
Note: Treatment regimens are generated based on the concomitant medicine subsequent therapies.

Figure 11: Kaplan-Meier Plot for Time to First Treatment for Multiple Myeloma; Intent-to-treat Analysis Set (AQUILA)

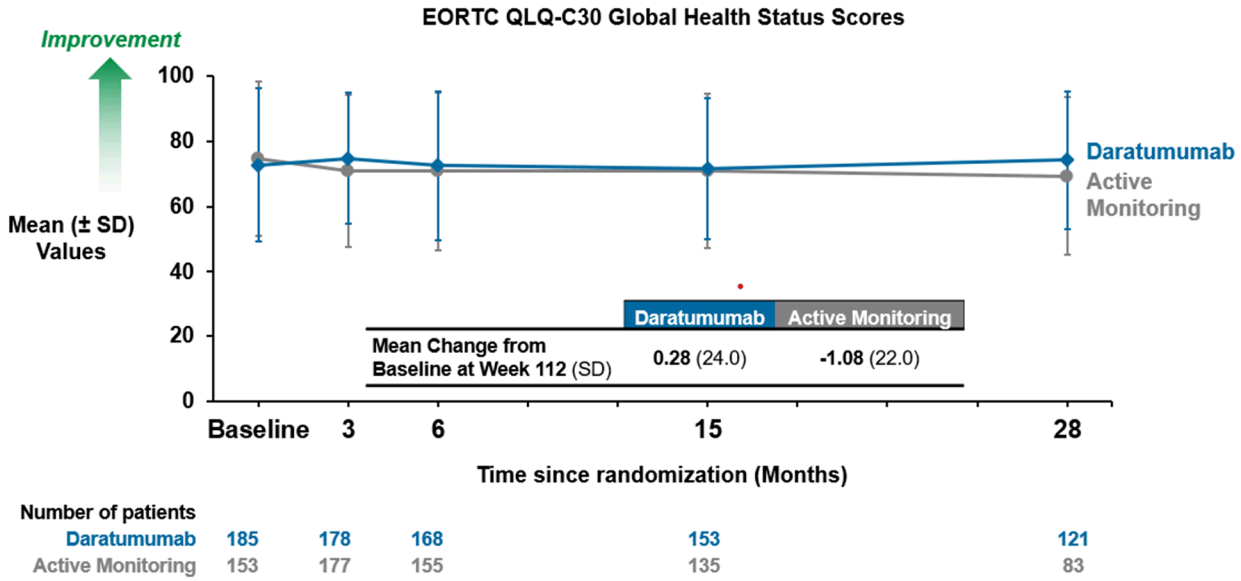


Key: CI=confidence interval; HR=hazard ratio; MM=mulitple myeloma

In responders, the median time to first response (PR or better) (Daratumumab 2.9 months; Active Monitoring 10.5 months) and the median time to very good partial response (VGPR) or better (Daratumumab 8.4 months; Active Monitoring 31.8 months) were substantially shorter in the Daratumumab arm compared with the Active Monitoring arm.

EORTC QLQ-C30, EORTC QLQ-MY20, and EQ-5D-5L demonstrated comparable quality of life (QoL) over time in the Daratumumab and Active Monitoring (Figure 12).

Figure 12: Baseline and Mean Changes Over Time: EORTC QLQ-C30 Global Health Status Scores; Intent-to-treat Analysis Set (AQUILA)



Key: EORTC QLQ-C30=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30; SD=standard deviation

1.6.4 Efficacy Conclusions

In the AQUILA study, daratumumab demonstrated a statistically significant and clinically meaningful improvement in PFS compared with active monitoring in participants with SMM who are at high risk for developing multiple myeloma. The efficacy of daratumumab was demonstrated in the secondary endpoint of ORR and further supported by other endpoints, including time to first multiple myeloma treatment, time to response, and importantly, QoL was comparable in the Daratumumab and Active Monitoring arms. Progression-free survival on first-line treatment for multiple myeloma indicated that the treatment of high-risk SMM with daratumumab had no detrimental treatment effect on the first-line treatment for active myeloma. Although OS data are not mature, data demonstrated early evidence of a positive OS trend in favor of the Daratumumab arm.

Taken together, the efficacy results show that daratumumab can offer patients with high-risk SMM an opportunity to delay disease progression to active multiple myeloma

and to maintain their current lifestyles. Daratumumab is intended as a finite therapy to be administered for 3 years.

1.7 AQUILA Safety Findings

The safety profile of daratumumab administered SC and IV has been extensively evaluated in prior clinical investigations and daratumumab has a well-understood safety profile that clinicians are familiar with monitoring and managing.

1.7.1 Treatment Exposure

A total of 193 participants received daratumumab. The median number of treatment cycles was 38 cycles (range: 1 to 39), median dose intensity was 2,273.7 mg/cycle (range: 1,800.0 to 7,200.0), and median relative dose intensity was 100% (range: 25% to 100%). Exposure to daratumumab SC was generally consistent across the treatment cycles.

The median duration of active monitoring in the Active Monitoring arm was 25.9 months (range 0.1 to 36.0) compared with the median duration of treatment in the Daratumumab arm of 35.0 months (range 0.03 to 36.1), resulting in an approximately 9 months longer adverse event (AE) reporting period for participants treated with daratumumab.

1.7.2 Adverse Events

The AE profile of daratumumab SC in participants with high-risk SMM was consistent with the known safety profile of daratumumab.

The incidence of AEs was as follows:

- The incidence of AEs was higher in the Daratumumab arm compared with the Active Monitoring arm (Daratumumab 96.9%; Active Monitoring 82.7%). The majority of AEs were Grade 1 or 2 in severity.
- The incidence of Grade 3 or 4 AEs was higher in the Daratumumab arm compared with the Active Monitoring arm (Daratumumab 40.4%; Active Monitoring 30.1%).
- The incidence of serious adverse events (SAEs) was higher in the Daratumumab arm compared with the Active Monitoring arm (Daratumumab 29.0%; Active Monitoring 19.4%).
- The incidence of AEs with an outcome of death (Grade 5) was low and balanced in both arms (Daratumumab 1.0%; Active Monitoring 2.0%).
- The rate of AEs leading to discontinuation of daratumumab was 5.7%.

1.7.2.1 Common Adverse Events

The most common AEs of any grade (≥10% of participants in either arm) are summarized in Table 6.

Adverse events that occurred with a frequency of ≥20% of participants in the Daratumumab arm and at a ≥10% higher frequency in the Daratumumab arm compared with the Active Monitoring arm were:

- Fatigue (Daratumumab 34%; Active Monitoring 13%)
- Upper respiratory tract infection (Daratumumab 30%; Active Monitoring 8%)
- Diarrhea (Daratumumab 28%; Active Monitoring 5%)
- Nasopharyngitis (Daratumumab 25%; Active Monitoring 12%)
- Insomnia (Daratumumab 22%; Active Monitoring 3%)

Table 6: Most Common Adverse Events (≥10% of Participants) by Preferred Term; Safety Analysis Set (AQUILA)

	Daratumumab (N = 193)	Active Monitoring (N = 196)
Any AE, %	97%	83%
Fatigue	34%	13%
Upper respiratory tract infection	30%	8%
Arthralgia	27%	18%
Diarrhea	27%	5%
Nasopharyngitis	25%	12%
Back pain	24%	19%
Insomnia	22%	3%
Nausea	19%	5%
Headache	18%	7%
Cough	17%	6%
Pyrexia	17%	3%
Injection site erythema	16%	0
Pain in extremity	15%	8%
Dyspnea	15%	5%
Pneumonia	11%	5%
Hypertension	10%	10%
Myalgia	10%	5%
Edema peripheral	10%	2%

Key: AE=adverse event

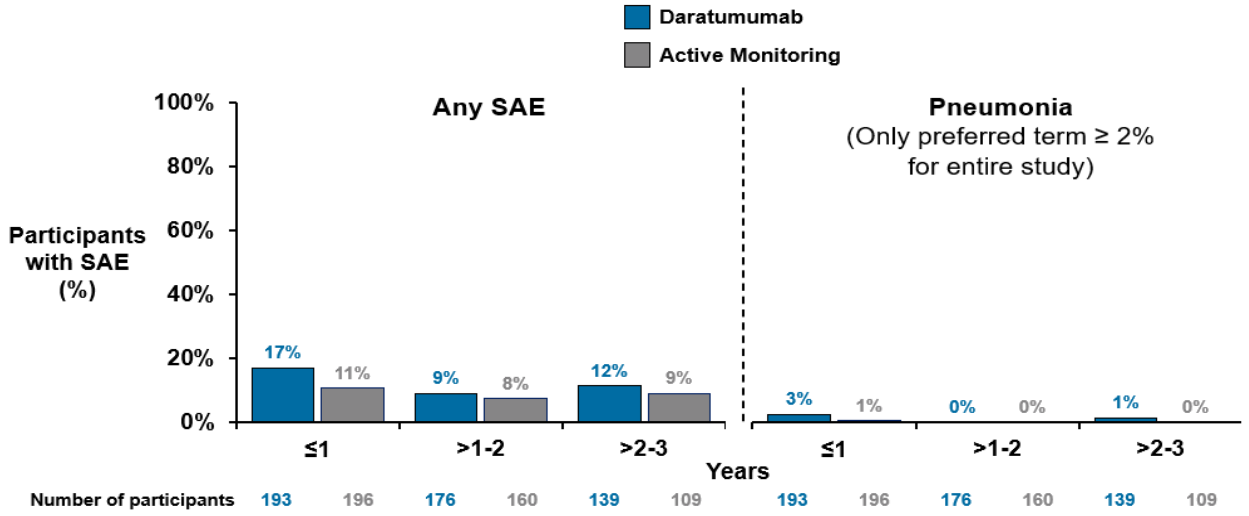
1.7.2.2 Fatal Adverse Events

Adverse events with an outcome of death were reported in 2 (1.0%) participants in the Daratumumab arm and 4 (2.0%) participants in the Active Monitoring arm. Adverse events with an outcome of death in the Daratumumab arm were COVID-19 and COVID-19 pneumonia (1 participant each), both of which occurred in participants.

1.7.2.3 Serious Adverse Events

The only SAE occurring in ≥2% of participants in either arm was Pneumonia (Daratumumab 3.6%; Active Monitoring 0.5%). The highest proportion of participants with SAEs in the Daratumumab arm was observed within the first year of treatment (Figure 13).

Figure 13: Serious Adverse Events Over Time (by Yearly Intervals); Safety Analysis Set (AQUILA)

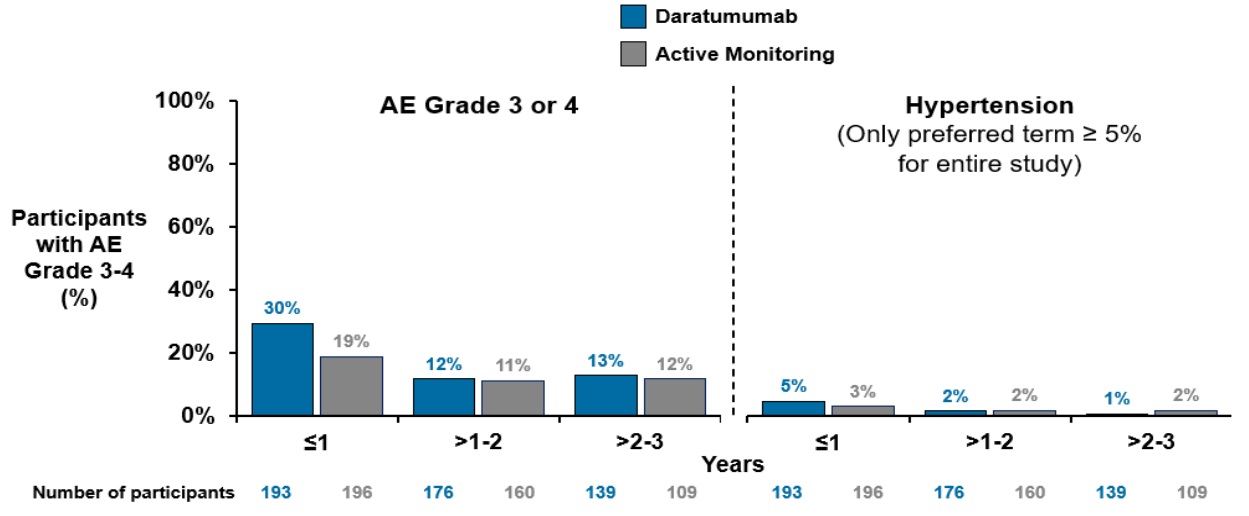


Key: SAE=serious adverse event

1.7.2.4 Grade 3 and Grade 4 Adverse Events

The only Grade 3 or 4 AE that occurred in ≥5% of participants in either arm was Hypertension (Daratumumab 5.7%; Active Monitoring 4.6%). The highest proportion of participants with Grade 3 or 4 AEs in the Daratumumab arm was observed within the first year of treatment. The highest proportion of participants with Grade 3 or 4 AEs in the Daratumumab arm was observed within the first year of treatment. The proportions of participants with Grade 3 or 4 AEs were similar to the Active Monitoring arm after the first 12 months (Figure 14).

Figure 14: Grade 3 or 4 Adverse Events Over Time (by Yearly Intervals); Safety Analysis Set (AQUILA)



Key: AE=adverse event

1.7.2.5 Adverse Events Leading to Discontinuation

Adverse events leading to discontinuation of daratumumab were reported in 11 (5.7%) participants; events reported in ≥2 participants were Fatigue, Anxiety, and Dyspnea (2 [1.0%] each).

Grade 3 or 4 AEs leading to discontinuation of daratumumab were reported in 5 (2.6%) participants.

1.7.2.6 Adverse Events Leading to Dose Modification

Dose modification of daratumumab (increase or decrease) was not permitted per protocol. Dose delay was recommended as the primary method for managing daratumumab-related toxicities.

The incidence of dose delays, cycle delays, or dose skipped due to AEs was 46.6%. The most common (≥5% of participants) AEs leading to dose or cycle delays or skipped doses were Upper respiratory tract infection (14 [7.3%]), Pneumonia (11 [5.7%]), and COVID-19 (10 [5.2%]).

1.7.2.7 Selected Adverse Events of Special Interest

Selected AEs of special interest are described in the daratumumab USPI (DARZALEX FASPRO 2024) and are summarized below.

Systemic administration-related reactions (sARRs, also referred to as infusion-related reactions [IRRs]) were reported in 16.6% of participants receiving daratumumab. Systemic administration-related reactions were most frequently associated with the first administration of daratumumab. No single sARR preferred term (PT) was reported in ≥5% of participants. Grade 3 or 4 sARRs were reported in 2 (1.0%) participants.

Local injection-site reactions were reported in 27.5% of participants. Local injection-site reactions reported in ≥5% of participants were Injection-site erythema (15.5%) and Erythema (5.2%). No Grade 3 or 4 local injection-site reactions were reported.

Overall, the proportion of participants reporting cytopenia (comprising neutropenia, anemia, thrombocytopenia, and lymphopenia group terms) was similar between the Daratumumab and Active Monitoring arms (Daratumumab 11.9%; Active Monitoring 12.2%). Grade 3 or 4 cytopenias were reported in 9 (4.7%) participants in the Daratumumab arm and 6 (3.1%) participants in the Active Monitoring arm.

The overall incidence of Infections and Infestations (SOC) was higher in the Daratumumab arm (79.8%) compared with the Active Monitoring arm (44.9%). The median duration of any grade Infections and Infestations was 14.0 days in both arms and 98% of any grade Infections and Infestations AEs in participants treated with daratumumab were recovered or resolved. Most Infections and Infestations were Grade 1 or 2. The incidence of Grade 3 or 4 Infections and Infestations (SOC) was higher in the Daratumumab arm (16.1%) compared with the Active Monitoring arm (4.6%); however, the median duration of the events was 5.0 days in the Daratumumab arm and 9.0 days in

the Active Monitoring arm. Of the Grade 3 or 4 Infection and infestations AEs, most events had an outcome of recovered or resolved (Daratumumab 35 [94.6%]; Active Monitoring 8 [72.7%]). The incidence of SAEs of Infections and Infestations was higher in the Daratumumab arm (16.6%) compared with the Active Monitoring arm (5.1%). Adverse events of Infections and Infestations that led to discontinuation of daratumumab SC were reported in 2 (1.0%) participants. In the Daratumumab arm, the proportion of participants with AEs of Infections or Infestations SOC decreased over time. A similar pattern was observed with respect to individual AEs of Upper respiratory tract infection, Nasopharyngitis, and Pneumonia.

1.7.3 Safety Conclusions

The safety data for daratumumab SC in the Phase 3 AQUILA study were consistent with the known safety profile of daratumumab. Although more AEs occurred in the Daratumumab arm, daratumumab was well tolerated in participants with high-risk SMM, with clinically manageable side effects, well known to clinicians who are familiar with monitoring and managing daratumumab treatment.

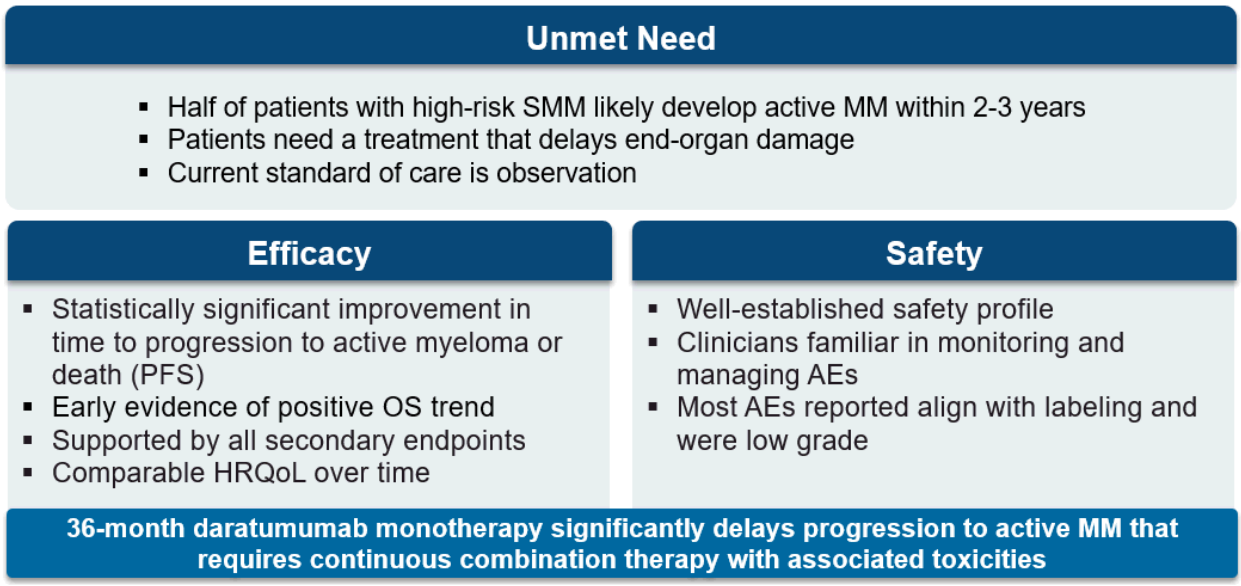
1.8 Benefit-Risk Summary

Daratumumab demonstrated a statistically significant and clinically meaningful improvement in PFS compared with active monitoring in participants with SMM who are at high risk for developing multiple myeloma. The efficacy of daratumumab was demonstrated in the secondary endpoint of ORR and further supported by other endpoints, including HRQoL, which was comparable over time in the Daratumumab and Active Monitoring arms. Although OS data are not mature, data demonstrated early evidence of a positive OS trend in favor of the Daratumumab arm.

Overall, the safety data from the AQUILA study reflected the known safety profile for daratumumab, with key risks of sARRs, local injection-site reactions, and Infections and Infestations. Although more AEs occurred in the Daratumumab arm, daratumumab was well tolerated in participants with high-risk SMM, with clinically manageable side effects, well known to clinicians who are familiar with monitoring and managing daratumumab treatment.

Taken together, the benefit-risk profile is positive for daratumumab (Figure 15).

Figure 15: Daratumumab Benefit-Risk Summary for Patients with High-risk SMM (AQUILA)



Key: AE=adverse event; HRQoL=health-related quality of life; MM=multiple myeloma; OS=overall survival; PFS=progression-free survival; SMM=smoldering multiple myeloma

2 BACKGROUND ON HIGH-RISK SMOLDERING MULTIPLE MYELOMA

Summary

- Smoldering multiple myeloma, an asymptomatic, malignant intermediate disease state of multiple myeloma, is associated with an overall risk of progression to multiple myeloma of 10% per year for the first 5 years after diagnosis.
- Patients with high-risk SMM have an approximately 50% risk of developing multiple myeloma within approximately 2 years of diagnosis.
- Current standard of care for patients with SMM is observation until progression to active myeloma.
- Early treatment intervention in patients with high-risk SMM has shown clinical benefit by delaying or preventing progression to active multiple myeloma and the development of potentially irreversible end-organ damage.
- Because patients with high-risk SMM are asymptomatic and have an active lifestyle, effective therapies with minimal toxicities that do not diminish quality of life are needed.

2.1 Overview of High-risk Smoldering Multiple Myeloma

2.1.1 Smoldering Multiple Myeloma

Multiple myeloma is a blood cancer that develops in BMPCs. Bone marrow plasma cells are terminally differentiated, non-dividing cells that produce antigen-specific Igs (or monoclonal proteins) comprised of 2 heavy chains and 2 light chains. Malignant plasma cell clones produce excess light chains and high levels of abnormal monoclonal (M) proteins which displace the normal cells in the bone marrow, resulting in conditions such as anemia, thrombocytopenia, cytopenia, and impaired immune function (i.e., immunoparesis). Excess light chains and the buildup of M protein in the blood and urine can damage the kidneys and other organs. Myeloma cells may also activate osteoclasts in the marrow that can cause bone pain, osteolytic lesions, and bone loss.

The most common presenting symptoms of multiple myeloma are fatigue and bone pain. Anemia contributes to fatigue and occurs in approximately 75% of patients with multiple myeloma (Rajkumar 2016). Severe destructive bone disease, a hallmark of multiple myeloma, is a frequent cause of bone pain. Some of the most common clinical signs (observed in 80% of patients) are refractory pain, fracture, vertebral collapse, or spinal cord compression (Mansour 2023). Hypercalcemia, caused by bone lysis, can lead to abdominal pain, constipation, and confusion. Renal dysfunction and infection, particularly pneumonia, are common symptoms of multiple myeloma; infection is due to the immunoparesis associated with the disease state.

2.1.1.1 *Diagnostic Criteria for Multiple Myeloma – Biomarkers of End-organ Damage*

The IMWG established the criteria for diagnosis and classification of multiple myeloma, based on the SLiM-CRAB criteria (Table 7).

Table 7: Multiple Myeloma SLiM-CRAB Criteria for Diagnosis

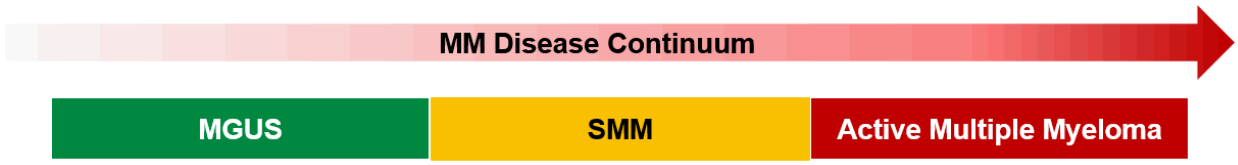
S: bone marrow plasmacytosis of ≥60% **Li**: the presence of an elevated involved serum FLC ratio (≥100 serum light chain [kappa or lambda] involved/uninvolved ratio as high ratios indicate a clonal expansion of plasma cells producing only one type of light chain). **M**: MRI lesions (≥1 focal bone lesion of ≥5 mm in size)
C: calcium elevation due to release of cytokines that cause local osteolytic lesions resulting in extra blood calcium (hypercalcemia; >11.5 mg/dL), **R**: renal insufficiency due to excess M protein and calcium in the blood causing kidney damage (creatinine >2 mg/dL or creatinine clearance <40 mL/min), **A**: anemia due to plasma cells crowding out normal red blood cells in the bone marrow (hemoglobin <10 g/dL or >20 g/L below lower limit of normal), **B**: bone disease (lytic or osteopenia)

Key: FLC= free light chain; MRI=magnetic resonance imaging
IMWG 2003; Rajkumar 2014

2.1.2 *Smoldering Multiple Myeloma*

Multiple myeloma disease progression can be characterized as a continuum, starting with the precursor condition of MGUS on one end of the continuum and progressing to active multiple myeloma on the other (Figure 16). Monoclonal gammopathy of undetermined significance is a premalignant, asymptomatic intermediate characterized by M protein levels <3 g/dL in blood and <10% clonal BMPCs and absence of end-organ damage or amyloidosis. The risk of progression from MGUS to multiple myeloma or related disorder is approximately 1% per year (Kyle 2010). Smoldering multiple myeloma is an asymptomatic, malignant, intermediate disease state characterized by abnormal monoclonal plasma cell proliferation in the bone marrow (10% to 60%) and/or abnormally high levels of circulating M proteins (serum ≥3 g/dL or urine ≥500 mg/24 hour), in the absence of myeloma-defining events (SLiM-CRAB; Table 7) (Rajkumar 2014). Smoldering multiple myeloma is distinguished from MGUS due to a higher risk of progression to multiple myeloma or related disorder; 10% per year for the first 5 years after diagnosis (Kyle 2010). These asymptomatic intermediates in the disease progression of multiple myeloma, including SMM, are typically detected incidentally based on blood and/or urine testing during a routine check-up, as there is no standard screening, thus resulting in many patients not being diagnosed before presenting with active myeloma.

Figure 16: The Continuum of Multiple Myeloma



Key: MGUS=monoclonal gammopathy of undetermined significance; MM=multiple myeloma; SMM=smoldering multiple myeloma

Smoldering multiple myeloma accounts for approximately 15% of myelomas across the continuum (Rios-Tamayo 2014). A national screening program in Iceland found that the prevalence of SMM in the general population aged 40 years and older was 0.5% (Thorsteindottir 2021). However, the prevalence of clinically detectable SMM in the absence of a national screening program in the US can be estimated as 5.0 per 100,000, which is calculated by multiplying the incidence (0.9 per 100,000) and the median OS (5.6 years) identified from a study of the US National Cancer Database (Ravindran 2016). Within the SMM patient population, there is a subset of patients whose disease will progress slowly, and a subset who will develop clinical symptoms and end-organ damage within the first 2 years of diagnosis (Rajkumar 2014; Kyle 2010; Rosinol 2003).

Overall, SMM is associated with a risk of progression to multiple myeloma of 10% per year for the first 5 years after diagnosis (Kyle 2010). Risk-stratification models have been implemented to further categorize the spectrum of SMM to identify patients at the highest risk of progression to active multiple myeloma. Approximately 40% of patients with SMM were classified as high risk across real-world populations regardless of the risk-stratification model used (Perez-Persona 2007; Dispenzieri 2008; Lakshman 2018; Mateos 2020; de Daniel 2024).

2.1.2.1 Diagnosis of High-risk Smoldering Multiple Myeloma

Because SMM is a heterogenous disease with varying risks of progression (Section 2.1.2), efforts have been made to better define the characteristics of patients with SMM. Examination of this patient population led to the identification of risk factors associated with the high risk of progression to active myeloma. Accordingly, high-risk SMM is now considered a stage of SMM. Patients with high-risk SMM have an approximately 50% risk of developing multiple myeloma within approximately 2 years of diagnosis (Rajkumar 2015) and these patients are likely to benefit most from treatment to delay development of active myeloma.

At the foundation of characterizing SMM risk is a set of key disease markers based on BMPC infiltration, serum M protein level, and serum FLC ratio (Lakshmam 2018). Risk models used to characterize high-risk SMM continue to be refined in terms of which biomarkers are selected to define the criteria, and the specific ranges used to define the biomarkers (Dispenzieri 2008; Rajkumar 2013; Mateos 2016; Lakshmam 2018; Mateos 2020; Cowan 2023). The risk of progression to multiple myeloma, however,

appears to be consistent across the risk models and treating clinicians are informed of the modifications via commonly accepted myeloma guidelines.

For the AQUILA study, high-risk SMM was determined based on a compilation of risk factors identified in several risk models recognized at the time of study development in 2015. High-risk SMM was defined in the AQUILA study as follows:

- Clonal BMPCs ≥10%

  AND at least 1 of the following high-risk factors:
  - Serum M protein ≥30 g/L
  - IgA SMM
  - Immunoparesis with reduction of 2 uninvolved Ig isotypes (only IgA, IgM, and IgG were considered in determination for immunoparesis; IgD and IgE were not considered in this assessment)
  - Serum involved: uninvolved FLC ratio ≥8 and <100
  - Clonal BMPCs >50% to <60% with measurable disease

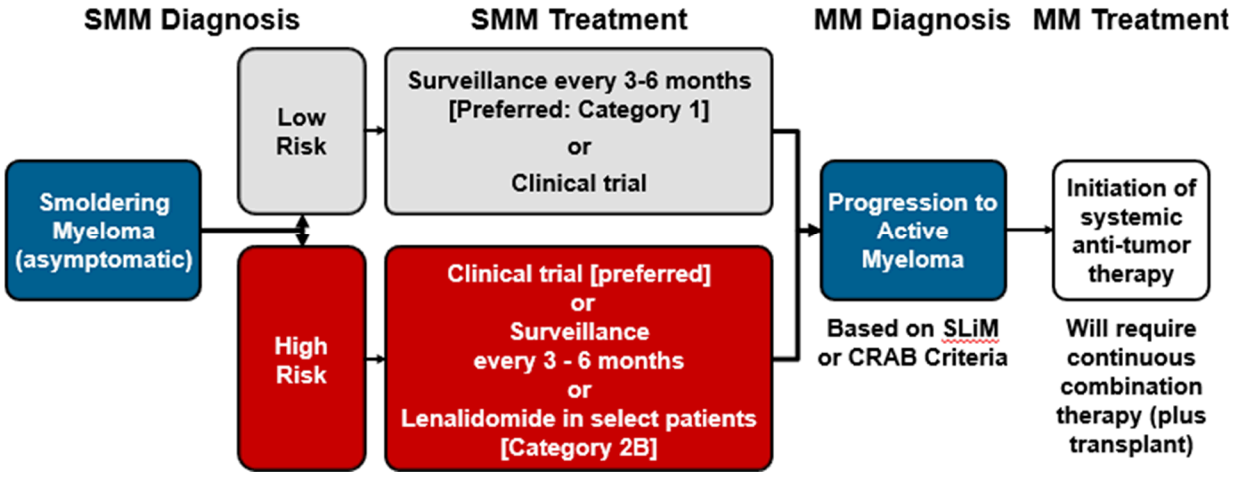
A current risk model for patients with SMM is the Mayo 2018 risk criteria, also referred to as the 2/20/20 criteria (Mateos 2020). Patients with 2 or more of the following risk factors are considered to have high-risk SMM according to this model:

- clonal BMPCs >20%
- serum M protein >20 g/L
- serum involved: uninvolved FLC ratio >20

2.2 Current Treatment Options for High-risk Smoldering Multiple Myeloma

The overall approach for patients with SMM is to observe without treatment until criteria for active multiple myeloma are met. This approach is termed 'Watch and Wait' and entails hematology check-ups, typically several times a year (McCaughan 2023). For high-risk SMM, current NCCN guidelines recommend entry into clinical studies or observation for patients (Figure 17; Multiple Myeloma NCCN Guidelines 2025). In certain circumstances, the NCCN guidelines also recommend treatment with lenalidomide. In an academic setting, approximately 15% of patients with high-risk SMM received lenalidomide monotherapy or lenalidomide with dexamethasone (Abdallah 2024).

Figure 17: National Comprehensive Cancer Network Standard of Care for Smoldering Multiple Myeloma



Adapted from NCCN Guidelines Version 1.2025 Multiple Myeloma
Key: CRAB=MM diagnostic criteria based on end-organ damage; MM=multiple myeloma; SLiM=MM diagnostic criteria based on biomarkers; SMM=smoldering multiple myeloma

2.3 Unmet Medical Need for Patients with High-risk Smoldering Multiple Myeloma

2.3.1 Need for Effective Treatment Options

Although patients with SMM are asymptomatic, the current treatment option of observation is contrary to treatment-delay avoidance policies established for many cancer types and may be incongruent with lay expectations (Levin 2007). The 'Watch and Wait' approach can also be described as 'Worry and Wait' for patients who understand that their disease may progress, but for whom there are no approved therapies (Jean-Baptiste 2020). Following in-depth interviews in patients with chronic blood cancers, McCaughan et al., discovered that difficulties were higher in patients who felt responsible for monitoring their symptoms but struggled to do this, and some were particularly anxious prior to appointments, fearing progression (McCaughan 2023).

Although current NCCN guidelines recommend participation in a clinical study for patients with high-risk SMM, this recommendation is often not feasible due to a lack of accessibility to clinical trials, failure to meet eligibility requirements, or the inability of patients to meet the demands of study participation. The psychological burdens of stress, anxiety, and uncertainty regarding future health can impact day-to-day life for these patients (McCaughan 2023).

Currently, there are no approved treatments for patients with high-risk SMM. Lenalidomide has not been adopted as the standard of care for reasons described in Section 2.3.2.

Once patients progress to active multiple myeloma, multi-drug (i.e., 3- to 4-drug) treatment regimens, possibly including ASCT, are used. Patients are often overwhelmed

with a 3- to 4-drug treatment regimen with a treatment schedule that changes daily. These regimens generally continue until disease progression and carry significant side effects. The disease can be managed for many years in this manner; however, because there is no cure for multiple myeloma, patients are at risk for relapse resulting in periods of observation interspersed with treatment(s), as needed.

Patients with multiple myeloma require regular consultations with their oncology team to ensure early intervention in the event of adverse effects, complications of the disease process, or evidence of relapse (Vrtis 2024). In addition, physical and occupational therapy for fall prevention may be needed due to the high risk of pathological fractures and serious injury if the patient should fall. Safety education and exercise programs to help prevent decline in physical functioning and reduce cancer-related fatigue may also be required (Vrtis 2024). Caregivers are often needed to help manage the overall care and treatment of the patients. Therefore, an early intervention treatment for patients with high-risk SMM that can extend the asymptomatic period and delay the progression to active myeloma is needed.

2.3.2 Potential Benefit for Early Therapeutic Intervention

Multiple early intervention strategies and treatments are being investigated and mounting evidence from clinical trials suggest a benefit for early therapeutic intervention in high-risk SMM patients (Visram 2021). Two published Phase 3 trials, the QuiRedex and ECOG studies, showed meaningful clinical benefit by delaying progression to active multiple myeloma with lenalidomide/dexamethasone or lenalidomide, respectively (Mateos 2013; Mateos 2022; Lonial 2019; Table 8). These treatments, however, were not adopted as the standard of care by the myeloma community for reasons including enrollment of heterogeneous populations, lack of advanced imaging at screening, and high discontinuation rates during clinical studies. In addition, lenalidomide carries a boxed warning in the USPI for embryofetal toxicity, hematologic toxicity, and venous and arterial thromboembolism (REVLIMID USPI 2023).

Table 8: Clinical Benefit Observed with Early Treatment in Patients W ith SMM

Study	N	Response	OS (HR, 95% CI)	3-Year Progression to MM
QuiRedex[1,2] (Rd vs observation)	119	ORR: 90%	0.57 (0.34, 0.95)	77%
ECOG[3] (R vs observation)	182	PR or better: 50%	-	91%

Key: HR=hazard ratio; CI=confidence interval; MM=multiple myeloma; ORR=overall response rate; OS=overall survival; PR=partial response; R=lenalidomide; Rd=lenalidomide + dexamethasone
[1]Mateos 2013
[2]Mateos 2022
[3]Lonial 2019

Taken together, patients with high-risk SMM can benefit from proactive therapy to treat high-risk SMM. The availability of a proven therapeutic with a tolerable safety profile that slows or prevents the progression of high-risk SMM to active multiple myeloma represents an unmet need for this patient population. As described in this document, the AQUILA study now establishes that daratumumab monotherapy can provide this proactive therapy and meet this unmet need.

3 PRODUCT DESCRIPTION AND DEVELOPMENT FOR MULTIPLE MYELOMA

Summary

- Daratumumab is a mAb that binds with high affinity to CD38, a transmembrane glycoprotein expressed on tumor cells and induces tumor-cell death through multiple immune-mediated mechanisms of action.
- Daratumumab+hyaluronidase is formulated for subcutaneous injection at a fixed dose of 1800 mg daratumumab per dose. Subcutaneous administration provides for greater patient convenience with a short injection time of 3 to 5 minutes.
- Daratumumab and daratumumab-containing regimens are considered standard of care for the treatment of multiple myeloma and demonstrates a statistically significant and clinically meaningful reduction in risk of PD or death.
  - Daratumumab is a treatment option recommended by the NCCN.
  - Since the initial approval in 2015, over 500,000 patients have received treatment with daratumumab.
- Regardless of the combination regimen or disease state (newly diagnosed or relapsed/refractory), daratumumab improved the long-term outcome of patients with multiple myeloma through significantly deepened responses and statistically significant and clinically meaningful reductions in risk of disease progression or death.

3.1 Product Overview

Daratumumab is administered in combination or as monotherapy for treatment of NDMM and all phases of RRMM. Initially approved in 2015, there is deep experience among clinicians with this therapeutic. Clinicians are well versed in the safety profile of this product and will be able to effectively manage the side effects of treatment in the high-risk SMM population.

3.1.1 Product Description

Daratumumab is formulated with rHuPH20 for SC injection. Hyaluronidase facilitates absorption of daratumumab by the body. Daratumumab+hyaluronidase for SC injection was the formulation administered in the Phase 3 study AQUILA with a fixed dose of 1800 mg daratumumab/30,000 units hyaluronidase per 15 mL single dose vial. Daratumumab+hyaluronidase is referred to as daratumumab or daratumumab SC throughout this document.

3.1.2 Mechanism of Action of Daratumumab in Multiple Myeloma

Daratumumab is a human mAb that binds with high affinity to CD38, a transmembrane glycoprotein expressed on multiple myeloma cells and induces tumor-cell death through multiple mechanisms of action. These mechanisms of action include several immune-mediated activities, including complement-dependent cytotoxicity, antibody-dependent cell-mediated cytotoxicity, antibody-dependent cellular phagocytosis, and direct cytotoxicity by induction of apoptosis by Fc γ receptor-mediated crosslinking of tumor-bound mAbs (Overdijk 2016).

3.2 Overview of Daratumumab Approvals

Currently, daratumumab is being evaluated in participants across the multiple myeloma disease continuum including SMM, NDMM, RRMM and in other diseases including AL amyloidosis and pediatric ALL. The IV formulation of daratumumab (DARZALEX®) is approved in over 100 countries worldwide for the treatment of multiple myeloma. DARZALEX was initially approved in the US and EU as monotherapy for the treatment of heavily pre-treated patients with RRMM and since that time, various indications have been approved for DARZALEX in combination with background therapies for both RRMM and NDMM.

An SC formulation of daratumumab and hyaluronidase (DARZALEX Faspro®) is approved in over 60 countries worldwide for the treatment of RRMM and NDMM in combination with various background therapies. The SC administration of daratumumab offers greater convenience with a reduced incidence of sARRs/IRRs, decreased administration burden to both patients and healthcare professionals, reduced volume of drug administered, a fixed dose regimen, and reduced in-patient time.

A summary of approved indications with key results is provided in Table 9.

Table 9: Approved Daratumumab Indications with Key Results Based on USPI

Approved Indication	Efficacy Result
In combination with VRd for induction and consolidation in patients with NDMM who are eligible for ASCT[1]	• PFS SC median not reached vs VRd HR [95% CI]: 0.40 [0.29, 0.57]; p<0.0001
In combination with Rd in patients with NDMM who are ineligible for ASCT and in patients with RRMM who have received at least one prior therapy	• PFS IV median not reached vs 31.9 months Rd HR [95% CI]: 0.56 [0.43, 0.73]; p<0.0001 • OS IV Medians not reached HR [95% CI]: 0.68 [0.53, 0.86]; p=0.0013 • PFS IV 45.0 months (95% CI: 34.1, 53.9) vs 17.5 months (95% CI: 13.9, 20.8) Rd HR [95% CI]: 0.37 [0.27, 0.52]; p<0.0001 • OS IV 67.6 months vs 51.8 months Rd

Table 9: Approved Daratumumab Indications with Key Results Based on USPI

Approved Indication	Efficacy Result
	HR [95% CI]: 0.73 [0.58, 0.91]; p=0.0044
In combination with VTd in patients with NDMM who are eligible for ASCT	• sCR SC Day 100 post-transplant IV 28.9% vs 20.3% VTd; p=0.0010 • PFS IV vs VTd medians not reached HR [95% CI]: 0.47 [0.33, 0.67]; p<0.0001
In combination with Vd in patients with MM who have received at least one prior therapy	• PFS IV 16.7 months (95% CI: 13.1, 19.4) vs 7.1 months (95% CI: 6.2, 7.7) Vd HR [95% CI]: 0.39 [0.28, 0.53]; p<0.0001 • OS IV 49.6 months vs 38.5 months Vd HR [95% CI]: 0.74 [0.59, 0.92]; p=0.0075
In combination with Pd in patients with MM who have received at least one prior line of therapy including R and a PI[1]	• PFS SC 12.4 months vs 6.9 months (Pd) HR [95% CI]: 0.63 [0.47, 0.85]; p=0.0018
In combination with Pd in patients with MM who have received at least 2 prior therapies including Rd and a PI[2]	• ORR IV 59.2% [95% CI: 49.1, 68.8]
In combination with Kd in patients with RRMM who have received 1 to 3 prior lines of therapy	• PFS 2QW IV median not reached vs 15.8 months Kd HR [95% CI]: 0.63 [0.46, 0.85] p=0.0014), • ORR 1QW IV 81% [95% CI: 71, 89]
As monotherapy, in patients with MM who have received at least 3 prior lines of therapy including a PI and an immunomodulatory agent or who are double refractory to a PI and an immunomodulatory agent	• ORR IV 29.2% [95% CI: 20.8, 38.9]
In combination with VMP in patients with NDMM who are ineligible for ASCT	• PFS IV 36.4 months [95% CI: 32.1, 45.9] vs 19.3 months [95% CI: 18.0, 20.4] VMP HR [95% CI]: 0.50 [0.38, 0.65] p<0.0001 • OS IV 83 months [95% CI: 72.5, NE] vs 53.6 months [95% CI: 46.3, 60.9] VMP HR [95% CI]: 0.60 [0.46, 0.80] p=0.0003
In combination with VCd in patients with newly diagnosed AL amyloidosis[1]	• MOD-PFS median not reached vs 30.2 months VCd HR [95% CI]: 0.44 [0.31, 0.63] p<0.0001

Key: 1QW=once every week; 2QW=one every 2 weeks; ASCT=autologous stem cell transplant; CI=confidence interval; Dara=daratumumab; HR=hazard ratio; IV=intravenous; Kd=carfilzomib, dexamethasone; MM=multiple myeloma; MOD-PFS=major organ deterioration progression-free survival; NDMM=newly diagnosed multiple myeloma; ORR=overall response rate; OS=overall survival; Pd=pomalidomide, dexamethasone; PFS=progression-free survival; PI=proteosome inhibitor; Rd=lenalidomide, dexamethasone; SC=subcutaneous; RRMM=relapsed/refractory multiple myeloma; sCR=stringent complete response; VMP=bortezomib, melphalan, prednisone; VRd=bortezomib, lenalidomide, and dexamethasone; VTd=bortezomib, thalidomide, and dexamethasone

[1] approved indication is specific to SC formulation only.

[2] approved indication is specific to IV formulation only.

Note: unless noted, approved indications listed apply to both SC and IV formulations.

3.2.1 Daratumumab is Standard of Care Across Guidelines for Multiple Myeloma

Daratumumab is a well-established standard of care for the treatment of multiple myeloma and is recommended by the NCCN. Initially approved in 2015 as monotherapy for the treatment of RRMM, the daratumumab IV formulation is now approved in NDMM and RRMM in combination regimens or as monotherapy. Since the approval of daratumumab in 2015, over 500,000 patients have been treated with daratumumab regimens worldwide and approximately 250,000 patients in the US. Daratumumab SC was initially approved in 2020 and is similarly approved in NDMM and RRMM in combination with background therapies.

Regardless of the combination regimen or disease state, daratumumab significantly deepened responses and resulted in statistically significant and clinically meaningful reductions in risk of PD or death. Across studies, daratumumab improved the long-term outcome of patients with multiple myeloma including OS benefit in frontline (3 studies) and in RRMM (2 studies).

3.2.2 Well-Established Safety Profile

In addition to safety data obtained from over 15 years of daratumumab clinical trials, the AQUILA study continues to demonstrate that treatment with daratumumab has a manageable safety profile that is consistent with the known safety profile of daratumumab monotherapy.

3.3 Proposed Supplemental Smoldering Multiple Myeloma Indication

DARZALEX FASPRO as monotherapy is indicated for the treatment of adult patients with high-risk smoldering multiple myeloma.

4 DARATUMUMAB REGULATORY HISTORY AND CLINICAL DEVELOPMENT FOR THE TREATMENT OF SMOLDERING MULTIPLE MYELOMA

Summary

- The daratumumab clinical development program was designed with input from the FDA.
- The efficacy and safety of daratumumab for the treatment of high-risk SMM is demonstrated by data collected in a pivotal randomized Phase 3 study (AQUILA).

4.1 Regulatory Milestones for Study AQUILA

The Sponsor sought input and agreement from the FDA on the content and format of the planned submission of daratumumab for high-risk SMM. Interactions with the FDA regarding AQUILA are summarized in Table 10.

Table 10: FDA Interactions Regarding AQUILA

Date	Consultation	Topic
12 Jan 2016	Type B End of Phase 2 meeting	Discuss a registration program for the use of daratumumab for the treatment of patients with intermediate and high-risk SMM
09 May 2017	Type B End of Phase 2 meeting	Discussed the design of the Phase 3 study in SMM using daratumumab for SC injection. The FDA did not agree to a comparator arm of lenalidomide + dexamethasone and recommended daratumumab be administered as monotherapy.
08 December 2020	Information Request	FDA provided statistical comments on the draft SAP for AQUILA. The FDA's advice was incorporated into the final SAP.
13 September 2024	Type B pre-BLA meeting	Discuss the topline results of the primary analysis for AQUILA and to obtain agreement regarding the proposed content, format, and planned efficacy and safety analyses for the sBLA

Key: sBLA=supplemental Biologics License Application; SC=subcutaneous; SMM=smoldering multiple myeloma

4.2 Clinical Development Program for Smoldering Multiple Myeloma

The studies included in the clinical development program for daratumumab SC for the treatment of SMM are summarized in Table 11.

The clinical efficacy and safety data that are part of this application are derived from the pivotal Phase 3 study, AQUILA.

Table 11: Summary of Clinical Studies for Daratumumab SC in Smoldering Multiple Myeloma

Study ID (Name) Study Status	Study Design Study Population Primary Objective(s)	Dose Regimen Duration of Treatment	# Treated (by Treatment Arm)
54767414SMM3001 (AQUILA) Ongoing	Phase 3, randomized, open-label, 2-arm, multicenter study Men or women at least 18 years of age with a diagnosis of high-risk SMM per protocol and SMM diagnosis ≤5 years To determine whether treatment with daratumumab administered SC prolongs PFS compared with active monitoring	Daratumumab SC monotherapy: 1800 mg • weekly Cycles 1 and 2 • q2 weeks for Cycles 3 - 6 • q4 weeks until 39 cycles, up to 36 months, or confirmed PD, unacceptable toxicity, or other protocol-specified reasons as outlined, whichever occurred first Active monitoring	Daratumumab: 193 Active Monitoring: 196
54767414SMM2001 (CENTAURUS) Completed	Phase 2, randomized, open-label, 3-arm multicenter study Men or women at least 18 years of age with intermediate or high-risk SMM per protocol and SMM diagnosis <5 years. To evaluate whether daratumumab can effectively decrease M protein as assessed by complete response rate and to determine if daratumumab reduces the progression/ death rate	Daratumumab IV monotherapy: 16 mg/kg • Arm A (long intense) (8-week cycles): once every week in Cycle 1, every other week in Cycles 2 and 3, every 4 weeks in Cycles 4 to 7, and from Cycles 8 to 20 on Day 1 of each cycle • Arm B (intermediate) (8-week cycles): once every week in Cycle 1, and then on Day 1 of each cycle from Cycles 2 to 20 • Arm C (short intense) (8-week cycles): once every week for 1 cycle only	Arm A: 41 Arm B: 41 Arm C: 40

Key: IV=intravenous; M protein=monoclonal protein; PFS=progression-free survival; SC=subcutaneous; SMM=smoldering multiple myeloma

[1] Beginning in protocol amendment 5, participants continuing in the Treatment Extension Phase could switch to daratumumab 1800 mg SC Q8W at the discretion of the investigator.

5 CLINICAL PHARMACOLOGY

Summary

- The clinical pharmacology of daratumumab SC has been well characterized as monotherapy and in combination with a variety of background therapies for participants with multiple myeloma.
- Results from the Phase 3 AQUILA study, and the population PK analyses showed the PK profile and immunogenicity of daratumumab administered to participants with high-risk SMM were consistent with observations in previous daratumumab SC monotherapy and combination therapy studies in participants with multiple myeloma and support the 1800 mg dose regimen.
- Clinical pharmacology data from AQUILA, including PPK and E-R analyses with regards to efficacy and safety, support that the administration of daratumumab SC 1800 mg dose regimen provides effective exposure for the treatment of patients with high-risk SMM.

The clinical pharmacology of daratumumab SC has been well characterized as monotherapy and in combination with a variety of background therapies for participants with multiple myeloma. Based on the results from the AQUILA study and the population PK analyses, the PK profile and the incidence of anti-daratumumab and anti-rHuPH20 antibodies in participants with SMM were consistent with observations in previous daratumumab SC monotherapy and combination therapy studies in participants with multiple myeloma.

5.1 Pharmacokinetics

The PK results from participants with high-risk SMM were consistent with observations following daratumumab SC 1800 mg administration in previous monotherapy and combination studies in multiple myeloma.

In the AQUILA study, mean [SD] maximum C_{max} was observed on Cycle 3 Day 4 (789 [271] µg/mL) following weekly doses of daratumumab SC for 8 weeks, which was a 5.72-fold increase compared with the C_{max} at Cycle 1 Day 4 (138 [57.9] µg/mL). Mean (SD) maximum C_{trough} (654 [243] µg/mL) was observed at Cycle 3 Day 1 predose at the end of weekly dosing of daratumumab SC. Overall, mean C_{trough} in participants with high-risk SMM in the studied cycles were in a similar range as observations in participants with multiple myeloma following the same daratumumab SC dose regimen.

5.2 Population Pharmacokinetics and Exposure-response Analysis

The observed concentration-time data of daratumumab after IV and SC administration were well described by a 2-compartment population PK model with first-order absorption, and parallel linear and nonlinear elimination pathways.

Overall, none of the investigated factors (i.e., age, sex, race, body weight, albumin concentration, renal and hepatic function, and ECOG performance status) had clinically meaningful effects on daratumumab PK.

Exposure-response (E-R) analysis indicated that individual variation in daratumumab exposure at 1800 mg SC is not expected to introduce clinically relevant differences in PFS in participants with high-risk SMM.

The E-R relationship for safety showed no apparent increase in AE rate with increasing daratumumab exposure for sARRs, thrombocytopenia, anemia, neutropenia, lymphopenia, or infections, indicating an acceptable safety profile across the concentration range, which is consistent with the known E-R relationship for safety of daratumumab SC monotherapy.

5.3. Immunogenicity

To date, a low incidence (<1%) of antibodies to daratumumab was reported in monotherapy and combination clinical studies of daratumumab SC and IV in participants with SMM and multiple myeloma. A relatively low incidence of antibodies to rHuPH20 (<10%) was reported in monotherapy and combination clinical studies of daratumumab SC in participants with SMM and multiple myeloma to date. No clinically meaningful differences in the PK, efficacy, and safety profiles of daratumumab SC were observed in high-risk SMM participants who tested positive for anti-daratumumab and/or anti-rHuPH20 antibodies.

5.3 Pharmacodynamics

No new pharmacodynamics data or PK/pharmacodynamics analyses were conducted in the AQUILA study.

5.4 Dose Justification

- The monotherapy daratumumab SC dose regimen for the treatment of participants with SMM (1800 mg once every week [QW] for Cycles 1-2, Q2W for Cycles 3-6, and Q4W for Cycles 7+) is identical to the approved daratumumab SC dose regimens in patients with multiple myeloma. The 1800 mg daratumumab SC dose has a well-established efficacy and safety profile in multiple myeloma monotherapy and combination therapies.

- The dose for the AQUILA study was selected based on the totality of safety, efficacy, PK/ pharmacodynamics data in patients with multiple myeloma and SMM. Daratumumab SC dose (1800 mg regimen) demonstrated acceptable safety with manageable side effects and clinical efficacy. In addition, the selected dose regimen quickly achieves and maintains effective daratumumab concentrations throughout the treatment period to endure efficacy.
- Data from Phase 2 study in participants with SMM (CENTAURUS) demonstrated that daratumumab 16 mg/kg IV has single-agent activity in intermediate- and high-risk SMM. The long and intense treatment arm, which is largely aligned with the approved dose (except the Q8W in CENTAURUS is replaced with Q4W in AQUILA), demonstrated better efficacy and comparable safety to the other 2 less intense treatment arms explored.
- The 1800 mg daratumumab SC regimen was demonstrated to be noninferior to the 16 mg/kg IV regimen based on co-primary endpoints of PK and ORR.
- Altogether, the recommended dose regimen of daratumumab SC dose regimen provides a balanced benefit–risk profile in SMM patient population.

6 CLINICAL EFFICACY

Summary

- Daratumumab demonstrated statistically significant and clinically meaningful improvement in PFS compared with active monitoring in participants at high risk for developing multiple myeloma. Significant results were also observed for daratumumab in the key secondary endpoint of ORR compared with active monitoring.
- The efficacy of daratumumab was further supported by all other secondary endpoints.
- Comparable HRQoL over time was observed between the Daratumumab and Active Monitoring arms.
- Though OS data are not mature, data indicate early evidence of a positive OS trend in favor of the Daratumumab arm.
- Daratumumab offers patients with high-risk SMM an opportunity to delay disease progression to active multiple myeloma and to extend their current lifestyles.

6.1 Overall Study Design

AQUILA is a Phase 3, randomized, open-label, 2-arm, multicenter study of active monitoring and daratumumab SC monotherapy in participants with high-risk SMM. Eligible participants were randomized to 1 of 2 treatment arms:

- Daratumumab SC: daratumumab 1800 mg + rHuPH20 [2000 U/mL] weekly in Cycles 1 and 2, then every 2 weeks in Cycles 3 to 6, then every 4 weeks thereafter for fixed duration of up to 39 cycles or 36 months or disease progression, whichever occurred first.
- Active Monitoring: no disease-specific treatment given.

Randomization was stratified based on the number of risk factors associated with progression to multiple myeloma (Table 12).

Table 12: Randomization Stratification Factors for Study AQUILA

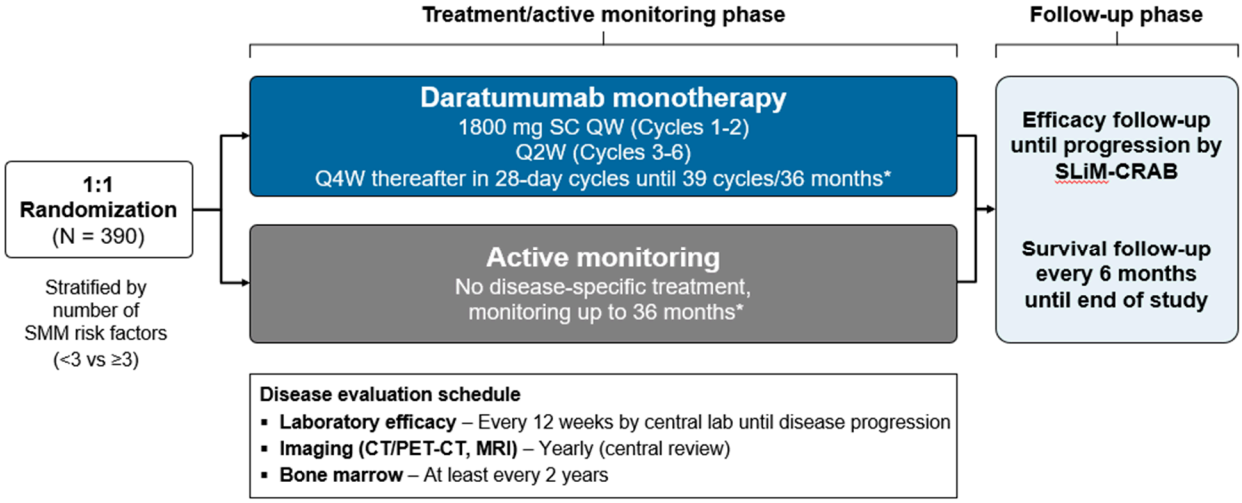
Stratification	Criteria
Number of Risk Factors	**<3 vs ≥3**
Risk Factors	
FLC ratio≥8 (involved:uninvolved)	Yes/No
Serum M protein ≥30 g/L	Yes/No
IgA SMM	Yes/No
Immunoparesis (reduction of 2 uninvolved Ig isotypes)	Yes/No
Bone Marrow Plasma Cells	>50% to <60% vs ≤50%

Key: FLC=free light chain; Ig=immunoglobulin; SMM=smoldering multiple myeloma

A total of 390 participants were randomized in a 1:1 ratio to either the Daratumumab or Active Monitoring arms for up to 39 cycles or 36 months, or disease progression, whichever occurred first. Following completion of the treatment/active monitoring phase, participants continue to be followed every 3 months for progression (per SLiM-CRAB criteria) and for survival until the end of the study (Figure 18).

This primary analysis was completed with a CCO date of 01 May 2024. The end of the study will occur approximately 8 years after the first participant was randomized (approximately December 2025).

Figure 18: Phase 3 AQUILA Study Design



Key: AE=adverse events; CT=computed tomography; MRI=magnetic resonance imaging; PET=positron emission tomography; QW=once every week; Q2W=one every 2 weeks; Q4W=once every 4 weeks; SC=subcutaneous; SLiM-CRAB=diagnostic criteria for active multiple myeloma; SMM=smoldering multiple myeloma
* or confirmed disease progression (whichever occurred first)

6.2 Selection of Participant Population

Key inclusion criteria for participation in this study were:

- ≥18 years of age
- Diagnosis of SMM (per IMWG criteria) for ≤5 years with measurable disease at randomization, defined as serum M protein ≥10 g/L or urine M protein ≥200 mg/24 hours or involved serum FLC ≥100 mg/L and abnormal serum FLC ratio
- Clonal BMPCs ≥10%

  AND at least 1 of the following high-risk factors:
  - Serum M protein ≥30 g/L
  - IgA SMM
  - Immunoparesis with reduction of 2 uninvolved Ig isotypes (only IgA, IgM, and IgG should be considered in determination for immunoparesis; IgD and IgE were not considered in this assessment)
  - Serum involved: uninvolved FLC ratio ≥8 and <100
  - Clonal BMPCs >50% to <60% with measurable disease
- ECOG performance status score of 0 or 1

Key exclusion criteria were myeloma-defining events:

- Multiple myeloma requiring treatment per SLiM-CRAB criteria
- Primary systemic AL (Ig light chain) amyloidosis

6.3 Endpoints

The results of the primary analysis for PFS, as of the CCO date of 01 May 2024, are presented. The final analysis of PFS2 and OS will be performed at the end of study per protocol.

6.3.1 Primary

PFS, defined as the time from the date of randomization to the date of documented disease progression to multiple myeloma, as evaluated by an IRC was defined as the time from the date of randomization to the date of documented progression to multiple myeloma according to the IMWG diagnostic criteria for multiple myeloma or the date of death, whichever occurs first.

6.3.2 Key Secondary

To demonstrate additional clinical benefit, the following key secondary endpoints were evaluated:

- ORR per computerized algorithm, defined as the proportion of participants with a PR or better as defined by the IMWG response criteria;
- PFS2, defined as the time from the date of randomization to the date of documented PD on the first-line treatment for multiple myeloma or death, whichever occurred first;
- OS, defined as, the time from the date of randomization to the date of death.

6.3.3 Other Secondary Endpoints

Other secondary endpoints included:

- Time to biochemical or diagnostic (SLiM-CRAB) progression, defined as the time between the date of randomization and the date of first documented evidence of confirmed biochemical or diagnostic progression, or death (due to any cause, prior to subsequent multiple myeloma therapy), whichever occurs first;
- Time to first treatment for multiple myeloma, defined as the time from the date of randomization to the date of the first-line treatment for multiple myeloma;
- Time to response, defined as the time from randomization until onset of first response;
- Change from baseline in global health status and emotional functioning scales of the EORTC quality of life questionnaire QLQ-C30, future perspective scale of the EORTC QLQ-MY20, and utility and visual analog scale EQ-5D-5L.

6.4 Statistical Methodology

There was no imputation planned for missing efficacy endpoint values.

6.4.1 Analysis of Primary Endpoint: Progression-Free Survival

Analysis of PFS was performed on the intent-to-treat (ITT) analysis set. The Kaplan-Meier method was used to estimate the distribution of overall PFS for each treatment arm. The median PFS with 95% CI is provided. The Kaplan-Meier curve for PFS was plotted by treatment arm.

The PFS distributions between the 2 treatment arms were compared using the stratified log-rank test. The p-value from a stratified log-rank test was reported. The treatment effect (HR) and its 2-sided 95% CI was estimated using a stratified Cox regression model with treatment as the sole explanatory variable. The stratification factor used in the analyses was the number of risk factors associated with progression to multiple myeloma (<3 vs ≥3).

A total of 165 PFS events would provide a power of 85% to detect a reduction of 37.5% in the risk of either progression or death (HR [Daratumumab vs. Active Monitoring] of 0.625) with a log-rank test, assuming a 2-sided significance level of 5%. A 24-month accrual period and an additional 24-month follow-up were assumed.

All hypotheses testing were conducted at a 2-sided level of significance of 0.05. When required, 95% CIs were constructed.

The primary hypothesis was tested at the 0.05 significance level. The following secondary endpoints ordered below were sequentially tested, each with an overall 2-sided alpha of 0.05, by utilizing a hierarchical testing approach as proposed by Tang and Geller (Tang 1999) that strongly controls Type I error rate:

- ORR
- PFS2
- OS

If the null hypothesis for any of the endpoints failed to be rejected at the primary analysis time point, then any of the subsequent endpoint(s) listed above would not be tested until the next analysis timepoint, if applicable. If the null hypothesis for an endpoint was rejected at an analysis time point, it would remain rejected and would not be re-tested at the next analysis time point, if any. The significance level for each of the above secondary endpoints was to be determined by the alpha-spending function specific to the endpoint. The ORR would only be tested at the primary analysis time point with a 2-sided level of significance of 0.05. For PFS2, and OS, alpha spending at the primary analysis time point and the final analysis point were to be determined by a linear alpha-spending function based on the observed number of the events at the time, i.e., the cumulative alpha to be spent would be the total alpha (0.05) multiplied by the proportion of the observed number of the events out of the total expected number of the events.

A sensitivity analysis of PFS, in which disease progression to multiple myeloma according to the IMWG 2014 diagnostic criteria for multiple myeloma, based on investigator assessment and the validated computer algorithm, was performed in a similar manner as described above.

Determination of dates of PFS event and dates for censoring is summarized in Table 13.

Table 13: Progression-Free Survival Event and Censoring Methods

Situation	Date of Progression or Censoring	Outcome
No post-baseline disease assessment	Randomization	Censored
Disease progression prior to start of anti-cancer therapy for multiple myeloma	Earliest date that indicates disease progression	PFS event
Death prior to start of anti-cancer therapy for multiple myeloma in the absence of disease progression	Date of death	PFS event
Other, such as: • Withdrawal of consent to study participation • Lost to follow-up • Start of subsequent anti-cancer therapy prior to disease progression or death	Date of last disease assessment on or prior to withdrawal of consent to study participation, lost to follow-up, or start of subsequent anti-cancer therapy	Censored
Alive without PD before CCO	Date of last disease assessment before the CCO	Censored

Key: CCO=clinical cutoff; PD=disease progression; PFS=progression-free survival
Note: Participants who were already diagnosed with multiple myeloma per baseline central imaging review will be censored at randomization.

The primary estimand, the main clinical quantity of interest to be estimated in the study, is defined by the following 4 components:

- Population: participants with high-risk SMM;
- Variable: PFS;
- Intercurrent events: 1) start of subsequent anti-myeloma treatment prior to disease progression or death, 2) treatment discontinuation, 3) study discontinuation;
- Population-level summary: HR between the 2 treatment arms.

The strategies to account for the intercurrent events are,

- Participants were censored at the last disease assessment prior to start of subsequent therapy (while on treatment strategy),
- Treatment discontinuation was ignored (treatment policy strategy),
- Participants were censored at the last disease assessment prior to study discontinuation (hypothetical strategy).

6.4.2 Analysis of Key Secondary Endpoints

The analysis of ORR was performed on the ITT analysis set. Two-sided 95% Clopper-Pearson exact CI are presented by treatment arm.

Stratified Cochran–Mantel–Haenszel test was used to test treatment difference in the proportion of participants who achieved an overall response stratified by the stratification factor.

The analysis of PFS2 and OS were similar to the analysis of primary endpoint PFS described above. If year or month was missing for PFS2, no imputation was applied. If

year and month of progression date on subsequent antimyeloma therapy were available and day was missing, the day was imputed as 15, except:

1. If the Month & Year of Date of progression was the same as the Month & Year of the start date of first-line treatment, then the day was imputed as the day of the start date of first-line treatment.
2. If the Month & Year of Date of progression was the same as the Month & Year of start date of second line, then the day was imputed as minimum (15, [start day of the second line]).

The study continues to collect additional data for PFS2 and OS; the prespecified hierarchical test of PFS2 and OS will be completed at the final analysis, which will occur approximately 8 years after the first participant was randomized (approximately December 2025).

6.5 Study AQUILA Efficacy Results

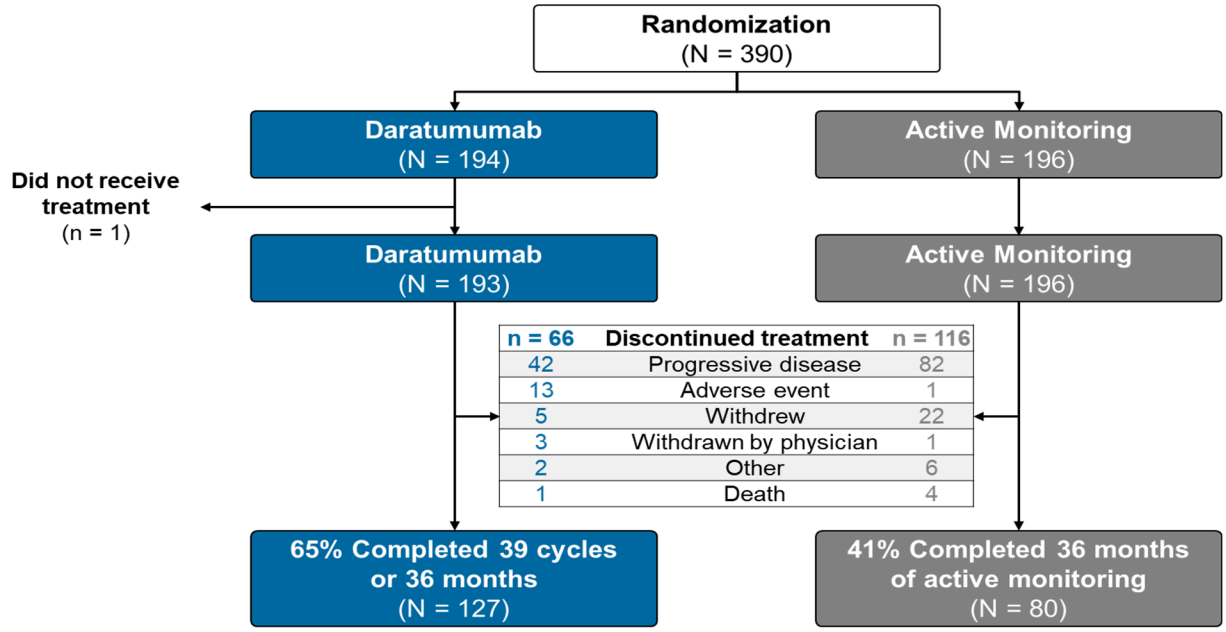
6.5.1 Participants Demographics and Disposition

A total of 194 participants and 196 participants were randomized in the Daratumumab and Active Monitoring arms, respectively.

As of the CCO (01 May 2024), 127 (65.5%) participants in the Daratumumab arm completed 39 cycles or 36 months of study treatment per protocol compared with 80 (40.8%) participants in the Active Monitoring arm who completed 36 months of active monitoring (Figure 19). The median duration of treatment was approximately 9 months longer in the Daratumumab arm compared with the Active Monitoring arm. A lower percentage of participants in the Daratumumab arm (34.2%) discontinued study treatment compared with those in the Active Monitoring arm who discontinued active monitoring (59.2%). The most common reasons for discontinuing study treatment/active monitoring (>10% of participants in either arm) were PD (Daratumumab 21.8%; Active Monitoring 41.8%) and participant refused further treatment/active monitoring (Daratumumab 2.6%; Active Monitoring 11.2%). A total of 6.7% of participants in the Daratumumab arm discontinued study treatment due to AEs.

A total of 15.5% and 26.0% of participants discontinued the study in the Daratumumab and Active Monitoring arms, respectively. The most common reasons for study discontinuation (>10% of participants in either arm) were death (Daratumumab 7.7%; Active Monitoring 13.3%) and withdrawal by participant (Daratumumab 6.2%; Active Monitoring 11.7%). Participant treatment disposition is summarized in Figure 19.

Figure 19: Participant Treatment Disposition; Intent-to-treat Analysis Set (AQUILA)



For all participants in the study, the median age was 64.0 years (range 31-86). A total of 48.2% of participants were male and 51.8% of participants were female.

Demographic characteristics were balanced between-treatment arms (Table 14). Participant randomization by region/country/territory was balanced between the treatment arms for the EU, US, and Other. Countries that randomized ≥10% of participants were the US (14.6%) and Israel (14.4%).

Table 14: Summary of Demographics; Intent-to-treat Analysis Set (AQUILA)

Parameter	Daratumumab (N=194)	Active Monitoring (N=196)
Age (years)		
N	194	196
Mean (SD)	61.9 (11.17)	63.0 (10.76)
Median	63.0	64.5
Range	(31; 86)	(36; 83)
18-<65	106 (54.6%)	98 (50.0%)
65-<75	67 (34.5%)	74 (37.8%)
>=75	21 (10.8%)	24 (12.2%)
Sex, n (%)		
N	194	196
Male	95 (49.0%)	93 (47.4%)
Female	99 (51.0%)	103 (52.6%)
Region, n (%)		
North America	32 (16.5%)	33 (16.8%)
United States	30 (15.5%)	27 (13.8%)
EU[a]	98 (50.5%)	95 (48.5%)
Other[b]	64 (33.0%)	68 (34.7%)
Race, n (%)		
N	194	196
White	161 (83.0%)	162 (82.7%)
Black or African American	4 (2.1%)	7 (3.6%)
Asian	18 (9.3%)	13 (6.6%)
American Indian or Alaska Native	0	3 (1.5%)
Native Hawaiian or Other Pacific Islander	0	2 (1.0%)
Multiple	1 (0.5%)	0
Not Reported	10 (5.2%)	9 (4.6%)
Ethnicity, n (%)		
N	194	196
Hispanic or Latino	14 (7.2%)	9 (4.6%)
Not Hispanic or Latino	169 (87.1%)	176 (89.8%)
Not Reported	11 (5.7%)	11 (5.6%)
Weight (kg)		
N	194	194
Mean (SD)	78.00 (16.045)	79.64 (18.326)
Median	78.00	78.25
Range	(46.2; 159.0)	(41.4; 152.9)
≤65	43 (22.2%)	46 (23.7%)
>65-≤85	96 (49.5%)	84 (43.3%)
>85	55 (28.4%)	64 (33.0%)

Table 14: Summary of Demographics; Intent-to-treat Analysis Set (AQUILA)

Parameter	Daratumumab (N=194)	Active Monitoring (N=196)
Baseline ECOG score, n (%)		
N	194	196
0	165 (85.1%)	160 (81.6%)
1	29 (14.9%)	36 (18.4%)
>1	0	0

Key: ECOG=Eastern Cooperative Oncology Group; EU=European Union; SD=standard deviation
[a] EU includes: Belgium, Czech Republic, Denmark, France, Germany, Greece, Hungary, Italy, Netherlands, Norway, Poland, Spain, Sweden, Turkey, United Kingdom
[b] 'Other' includes Argentina, Australia, Brazil, Israel, Italy, Japan, Russian Federation
Note: Percentages are calculated with the number of participants in each arm with available data as the denominators.

Baseline disease characteristics were generally balanced between arms and representative of patients with high-risk SMM (Table 15). Approximately 60% of participants randomized had 2 or more risk factors.

Table 15: Summary of Baseline Disease Characteristics; Intent-to-treat Analysis Set (AQUILA)

Parameter	Daratumumab (N=194)	Active Monitoring (N=196)
Type of myeloma by immunofixation or serum FLC assay, n (%)		
N	194	196
IgG	127 (65.5%)	138 (70.4%)
IgA	55 (28.4%)	42 (21.4%)
IgM	1 (0.5%)	0
IgD	0	2 (1.0%)
IgE	0	0
Light chain	9 (4.6%)	9 (4.6%)
Kappa	6 (3.1%)	7 (3.6%)
Lambda	3 (1.5%)	2 (1.0%)
Biclonal	1 (0.5%)	5 (2.6%)
Serum FLC only[a]	1 (0.5%)	0
Not detected	0	0
Focal lesions		
N	194	196
No	172 (88.7%)	179 (91.3%)
Yes	22 (11.3%)	17 (8.7%)
Serum M protein (g/dL)		
N	194	196
<1	29 (14.9%)	36 (18.4%)
>=1 to <=2	84 (43.3%)	73 (37.2%)

Table 15: Summary of Baseline Disease Characteristics; Intent-to-treat Analysis Set (AQUILA)

Parameter	Daratumumab (N=194)	Active Monitoring (N=196)
>2 to <3	47 (24.2%)	47 (24.0%)
>=3	34 (17.5%)	40 (20.4%)
Plasma cell (%), bone marrow aspirate/biopsy[b]		
N	194	196
Mean (SD)	21.78 (11.416)	24.21 (11.630)
Median	20.00	20.00
Range	(8.0; 59.5)	(10.0; 55.0)
<10	1 (0.5%)	0
>=10 to <=20	124 (63.9%)	102 (52.0%)
>20 to <40	50 (25.8%)	66 (33.7%)
>=40	19 (9.8%)	28 (14.3%)
Serum free light chain (involved/uninvolved) ratio		
N	194	196
Mean (SD)	28.19 (29.898)	25.59 (25.320)
Median	16.78	15.86
Range	(0.5; 160.6)	(0.4; 97.6)
<8	54 (27.8%)	49 (25.0%)
>=8 to <=20	53 (27.3%)	63 (32.1%)
>20	87 (44.8%)	84 (42.9%)
AQUILA risk factors		
Serum M protein ≥30 g/L	34 (17.5%)	40 (20.4%)
IgA SMM	55 (28.4%)	42 (21.4%)
Immunoparesis with reduction of at least 2 uninvolved Ig isotypes	116 (59.8%)	116 (59.2%)
Serum involved: uninvolved FLC ratio ≥8 and <100	135 (69.6%)	147 (75.0%)
Clonal BMPCs >50% to <60% with measurable disease	6 (3.1%)	4 (2.0%)
Number of risk factors met per participant		
N	194	196
Mean (SD)	1.8 (0.82)	1.8 (0.77)
Median	2.0	2.0
Range	(0; 4)	(1; 4)
<3	157 (80.9%)	161 (82.1%)
≥3	37 (19.1%)	35 (17.9%)

Table 15: Summary of Baseline Disease Characteristics; Intent-to-treat Analysis Set (AQUILA)

Parameter	Daratumumab (N=194)	Active Monitoring (N=196)
Time from initial diagnosis date of SMM to randomization (years)		
N	194	196
Mean (SD)	1.23 (1.170)	1.26 (1.301)
Median	0.80	0.67
Range	(0.0; 4.7)	(0.0; 5.0)
<=1 year	108 (55.7%)	114 (58.2%)
>1 year	86 (44.3%)	82 (41.8%)
Risk-associated molecular subtypes		
Number of participants with evaluable cytogenetic results (n, %)[c]	167 (86.1%)	170 (86.7%)
Number of participants with at least one of the following subtypes (n, %)[d]	29 (17.4%)	22 (12.9%)
del(17p13) (n/m, %)[e]	3/166 (1.8%)	8/166 (4.8%)
t(4;14) (n/m, %)[e]	19/151 (12.6%)	11/157 (7.0%)
t(14;16) (n/m, %)[e]	7/146 (4.8%)	3/145 (2.1%)
Mayo 2018 Risk Criteria[h]:		
N	194	196
Low	45 (23.2%)	34 (17.3%)
Intermediate	77 (39.7%)	76 (38.8%)
High	72 (37.1%)	86 (43.9%)

Key: AST= aspartate aminotransferase; BMPC=bone marrow plasma clone; FISH=fluorescent in situ hybridization; FLC=free light chain; GFR=glomerular filtration rate; Ig=immunoglobulin; ISS = International staging system; ITT=intent-to-treat; NCI=National Cancer Institute; NE= Not Evaluable; SD=standard deviation; SPEP=serum protein electrophoresis; ULN=upper limit of normal; UPEP=urine protein electrophoresis

a Not detected by immunofixation, serum free light chain only.
b The highest plasma cell (%) from bone marrow aspirate or biopsy.
c The evaluable participants are the participants with evaluable results with probes del(17p13), t(14, 16), and t(4,14). The denominator for the % is the ITT participants in the treatment arm. Cytogenetic abnormalities were based on FISH.
d The denominator for the % is the number of the participants with evaluable cytogenetic results in the treatment arm.
e n is the number of the participants with the specific subtype. m is the number of participants with evaluable cytogenetic result for the specific probe in the treatment arm.
f Normal: GFR (mL/min/1.73m2) ≥90.
g Hepatic impairment status is classified into 4 levels per NCI Organ Dysfunction: normal (total bilirubin ≤ULN and AST ≤ULN); mild (total bilirubin ≤ULN and AST > ULN) or (ULN < total bilirubin ≤1.5xULN); moderate (1.5xULN < total bilirubin ≤3xULN); and severe (total bilirubin >3xULN). Impaired includes mild, moderate, and severe.
h Mayo 2018 risk criteria: 1) Serum M protein >2 g/dL, 2) I/U FLC ratio >20, 3) BMPC >20%. Participants with presence of 0 factors are considered as low risk, 1 factor are considered as intermediate risk, ≥2 factors are considered as high risk.

Note: Values at screening visit will be taken into considerations in the derivation of the type of measurable disease if either SPEP or UPEP at baseline does not meet measurable disease definition.
Note: Percentages are calculated with the number of participants in each arm with available data as denominator.

6.5.2 Primary Efficacy Analysis – Progression-Free Survival

Median follow-up was 65.2 months (Daratumumab 65.9 months; Active Monitoring 64.8 months). A total of 166 PFS events per IRC assessment (Daratumumab 67; Active Monitoring 99) were observed. Treatment with daratumumab SC resulted in a clinically meaningful and statistically significant improvement in PFS, with a 51% reduction in the risk of progression or death compared with Active Monitoring (HR=0.49; 95% CI: 0.36, 0.67; 2-sided p<0.0001). Median PFS was not reached in the Daratumumab arm and was 41.5 months (95% CI: 26.4, 53.3) in the Active Monitoring arm (60-month PFS rate: Daratumumab 63.1%; Active Monitoring 40.8%; Table 16; Figure 20).

Table 16: Summary of Progression-free Survival as Assessed by Independent Review Committee; Intent-to-treat Analysis Set (AQUILA)

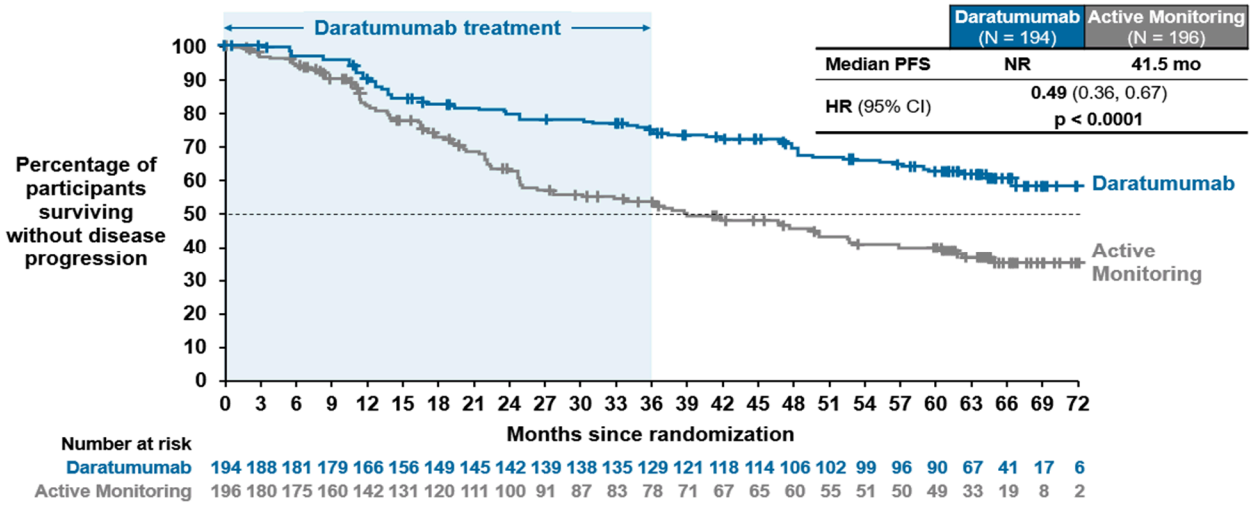
Parameter	Daratumumab (N=194)	Active Monitoring (N=196)
Progression-free survival (PFS)		
Number of events (%)	67 (34.5%)	99 (50.5%)
Number of censored (%)	127 (65.5%)	97 (49.5%)
Kaplan-Meier estimate (months)		
Median (95% CI)	NE (66.69, NE)	41.46 (26.41, 53.32)
P-value[a]	<0.0001	
Hazard ratio (95% CI)[b]	0.49 (0.36, 0.67)	
12-month PFS rate % (95% CI)	89.8 (84.5, 93.4)	82.7 (76.3, 87.5)
24-month PFS rate % (95% CI)	79.9 (73.4, 85.0)	63.3 (55.5, 70.0)
36-month PFS rate % (95% CI)	75.4 (68.4, 81.0)	54.3 (46.4, 61.6)
48-month PFS rate % (95% CI)	69.8 (62.4, 76.0)	46.4 (38.4, 53.9)
60-month PFS rate % (95% CI)	63.1 (55.3, 69.9)	40.8 (32.9, 48.5)

Key: BMPC=bone marrow plasma clone; CI=confidence interval; FLC=free light chain; Ig=immunoglobulin; NE=not estimable; PFS=progression-free survival; SC=subcutaneous; SMM=smoldering multiple myeloma

a p-value is based on the log-rank test stratified by the stratification factor (number of risk factors associated with progression to multiple myeloma [<3 vs ≥3]). The risk factors were: a. serum M protein ≥30 g/L; b. IgA SMM; c. immunoparesis with reduction of 2 uninvolved Ig isotypes (only IgA, IgM, and IgG were considered in determination for immunoparesis, IgD and IgE were not considered in this assessment); d. serum involved: uninvolved FLC ratio ≥8 and <100, or clonal BMPCs >50% to <60% with measurable disease.

b Hazard ratio and 95% CI was calculated using the Cox proportional hazards model with treatment as the sole explanatory variable and stratified by the stratification factor. A hazard ratio <1 indicates an advantage for daratumumab SC.

Figure 20: Progression-free Survival as Assessed by Independent Review Committee; Intent-to-treat Analysis Set (AQUILA)



Key: CI=confidence interval; HR=hazard ratio; NR=not reached; PFS=progression-free survival

Table 17 summarizes the reasons for PD and censoring of PFS. There was a reduction in the proportion of participants experiencing PFS events in the Daratumumab arm (34.5% vs 50.5%). The 3 most common reasons for progression to multiple myeloma were serum FLC (Daratumumab 53.2%; Active Monitoring 35.1%), detection of focal lesion by MRI (Daratumumab 19.4%; Active Monitoring 17.0%), and development of bone disease (Daratumumab 16.1%; Active Monitoring 19.1%).

Data from 127 (65.5%) participants in the Daratumumab arm and 97 (49.5%) participants in the Active Monitoring arm were censored. The 3 most common reasons for censoring were no PD at the time of CCO (Daratumumab 77.2%; Active Monitoring 53.6%), starting subsequent antimyeloma therapy prior to PD (Daratumumab 12.6%; Active Monitoring 26.8%), and withdrawal of consent to study participation (Daratumumab 7.1%; Active Monitoring 12.4%).

Table 17: Summary of Reasons for Progressive Disease and Censoring of Progression-free Survival Based on Independent Review Committee; Intent-to-treat Analysis Set (AQUILA)

	Daratumumab (N=194)	Active Monitoring (N=196)
Participants with progression-free survival event	**67 (34.5%)**	**99 (50.5%)**
Participants with progressive disease[a,b]	62 (92.5%)	94 (94.9%)
Reason for progressive disease[c] - SLiM Criteria		
Serum FLC	33 (53.2%)	33 (35.1%)
Focal lesion by MRI	12 (19.4%)	16 (17.0%)
Clonal BM plasma cells	5 (8.1%)	16 (17.0%)
Reason for progressive disease[c] - CRAB Criteria		
Bone disease	10 (16.1%)	18 (19.1%)
Anemia	2 (3.2%)	14 (14.9%)
Calcium elevation	0	2 (2.1%)
Renal insufficiency	0	0
Participants died without progressive disease[b]	5 (7.5%)	5 (5.1%)
Participants censored	**127 (65.5%)**	**97 (49.5%)**
Reason for censoring[d]		
Clinical cutoff	98 (77.2%)	52 (53.6%)
Received subsequent anti-cancer therapy	16 (12.6%)	26 (26.8%)
Withdrawal of consent to study participation	9 (7.1%)	12 (12.4%)
Lost to follow-up	1 (0.8%)	1 (1.0%)
No post-baseline disease assessment	0	3 (3.1%)
Other[e]	3 (2.4%)	3 (3.1%)

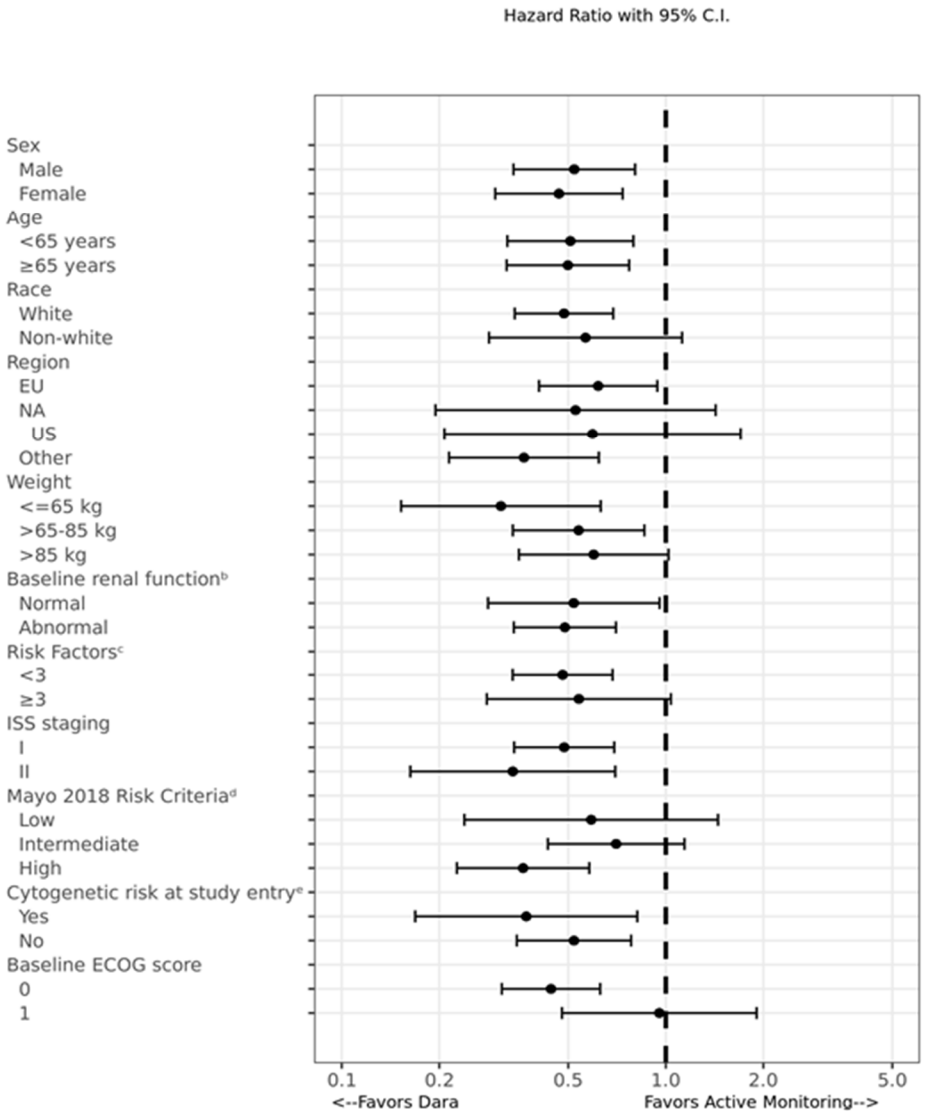
Key: BM=bone marrow; FLC=free light chain; PD=progressive disease; MRI=magnetic resonance imaging; SLiM-CRAB=diagnostic criteria for symptomatic multiple myeloma

a A participant may show PD based on more than one criterion.
b Percentages are based on number of participants with PFS event in each treatment arm.
c Percentages are based on number of participants with progressive disease in each treatment arm.
d Percentages are based on number of participants censored in each treatment arm.
e Includes participants who were already diagnosed with multiple myeloma per baseline central imaging review and were censored at randomization.

6.5.2.1 Subgroup Analyses of Progression-Free Survival

The PFS benefit per IRC assessment was consistent across the prespecified subgroups of sex, age, race, region, baseline renal function, and SMM risk factors and showed improved outcomes for participants in the Daratumumab arm compared with the Active Monitoring arm; however, for subgroups with small sample sizes, the results should be interpreted with caution (Figure 21).

Figure 21: Forest Plot of Key Subgroup Analyses for Progression-free Survival Based on Independent Review Committee; Intent-to-treat Analysis Set (AQUILA)



	Active Monitoring		Dara		
	EVT/N	Median (95% CI)	EVT/N	Median (95% CI)	Hazard Ratio 95% CI[a]
Sex					
Male	48/93	41.5 (23.8, 53.3)	37/95	NE (57.8, NE)	0.52 (0.34, 0.80)
Female	51/103	38.9 (25, 61.9)	30/99	NE (66.7, NE)	0.47 (0.30, 0.74)
Age					
<65 years	45/98	42 (25, NE)	34/106	NE (66.7, NE)	0.51 (0.32, 0.79)
≥65 years	54/98	38.8 (22, 52.7)	33/88	NE (57.8, NE)	0.50 (0.32, 0.77)
Race					
White	79/162	38.8 (25, 61.6)	53/161	NE (66.7, NE)	0.49 (0.34, 0.69)
Non-white	20/34	47 (24.7, NE)	14/33	NE (47.8, NE)	0.57 (0.28, 1.12)
Region					
EU	50/95	36 (22.2, 64.7)	39/98	NE (55.3, NE)	0.62 (0.41, 0.94)
NA	9/33	NE (18.7, NE)	7/32	NE (NE, NE)	0.53 (0.19, 1.42)
US	7/27	NE (18.7, NE)	7/30	NE (56.6, NE)	0.59 (0.21, 1.70)
Other	40/68	41.5 (25, 53.3)	21/64	NE (NE, NE)	0.36 (0.21, 0.62)
Weight					
<=65 kg	26/46	36 (19.6, 60.6)	11/43	NE (NE, NE)	0.31 (0.15, 0.63)
>65-85 kg	39/84	38.8 (22.5, NE)	33/96	NE (64.4, NE)	0.54 (0.34, 0.86)
>85 kg	34/64	46.7 (24.9, 61.6)	23/55	NE (48.3, NE)	0.60 (0.35, 1.02)
Baseline renal function[b]					
Normal	27/58	50.2 (33.7, NE)	17/54	NE (55.3, NE)	0.52 (0.28, 0.96)
Abnormal	72/138	36 (24.7, 52.7)	50/140	NE (64.4, NE)	0.49 (0.34, 0.70)
Risk Factors[c]					
<3	78/161	47.6 (36, 61.6)	51/157	NE (NE, NE)	0.48 (0.34, 0.69)
≥3	21/35	23.8 (11.9, 26.4)	16/37	66.7 (17.1, NE)	0.54 (0.28, 1.04)
ISS staging					
I	79/155	38.9 (26.4, 61.9)	50/154	NE (NE, NE)	0.49 (0.34, 0.69)
II	19/33	22.1 (11.6, 50.2)	14/33	66.7 (31.2, NE)	0.34 (0.16, 0.70)
Mayo 2018 Risk Criteria[d]					
Low	10/34	NE (61.6, NE)	9/45	NE (NE, NE)	0.59 (0.24, 1.45)
Intermediate	35/76	47.6 (36.6, NE)	31/77	NE (48.9, NE)	0.70 (0.43, 1.14)
High	54/86	22.1 (18.7, 26.4)	27/72	NE (55.3, NE)	0.36 (0.23, 0.58)
Cytogenetic risk at study entry[e]					
Yes	14/22	19.6 (11.2, 46.7)	13/29	66.7 (25, NE)	0.37 (0.17, 0.82)
No	59/118	49.5 (30.4, 61.9)	39/116	NE (59.1, NE)	0.52 (0.35, 0.78)
Baseline ECOG score					
0	80/160	37.7 (25, 56.9)	53/165	NE (NE, NE)	0.44 (0.31, 0.63)
1	19/36	41.5 (22.4, NE)	14/29	48.3 (14, NE)	0.95 (0.48, 1.91)

Key: BMPC=bone marrow plasma clone; CI=confidence interval; ECOG= Eastern Cooperative Oncology Group; EU=European Union; EVT=event; FLC=free light chain; GFR=globular filtration rate; HR=hazard ratio; Ig=immunoglobulin; ISS=International Staging System; NA=North America; Overall response=sCR, CR, VGPR, or PR; SMM=smoldering multiple myeloma; US=United States

a Hazard ratio and 95% CI was calculated using the Cox proportional hazards model with treatment as the sole explanatory. A hazard ratio <1 indicates an advantage for daratumumab SC.

b Normal: GFR (mL/min/1.73m^2) ≥90

c The risk factors were: a. Serum M protein ≥30 g/L; b. IgA SMM; c. Immunoparesis with reduction of 2 uninvolved Ig isotypes (only IgA, IgM, and IgG were considered in determination for immunoparesis, IgD and IgE were not considered in this assessment); d. serum involved: uninvolved FLC ratio ≥8 and <100, or e. clonal BMPCs >50% to <60% with measurable disease.

d Mayo 2018 risk criteria: Serum M protein >2 g/dL, I/U FLC ratio >20 and BMPC >20%. Participants with presence of 0 factors are considered as low risk, 1 factor are considered as intermediate risk and ≥2 factors are considered as high risk.

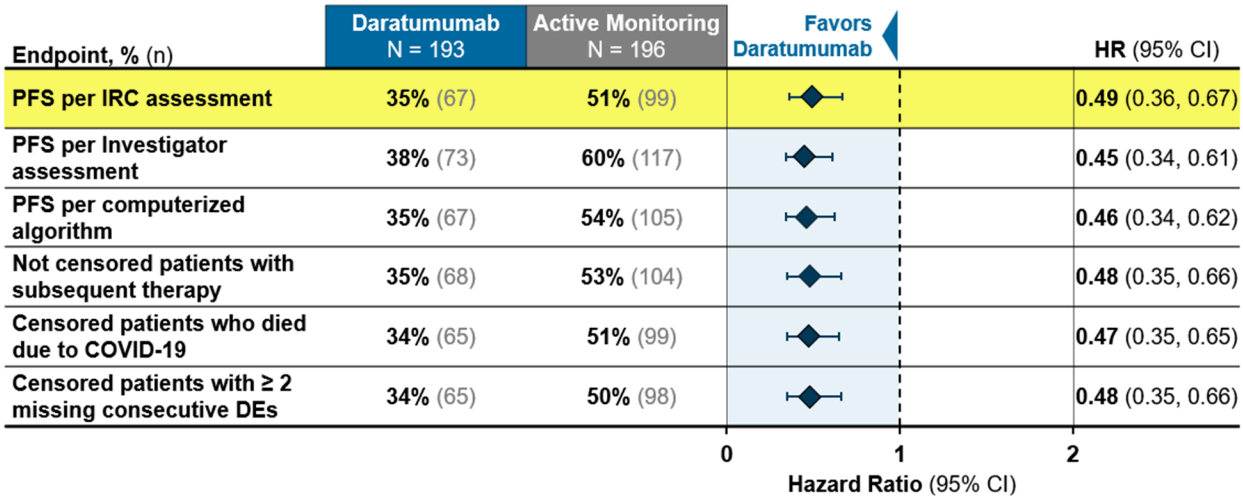
e Yes: presence of del(17p13), t(4;14), or t(14;16) at baseline; No: tested for these probes but did not have any abnormality.

Note: The subgroups with less than 10 participants in either treatment arm are suppressed in this table.

6.5.2.2 *Additional Analysis for Progression-Free Survival*

Consistent results were observed in additional preplanned analyses of PFS per IRC assessment, summarized in Figure 22, to further support the robustness of the PFS result. Analyses include PFS per investigator assessment, PFS per computerized algorithm, no censoring for start of subsequent therapy (based on IRC), censoring for death due to COVID-19 (based on IRC), and censoring for participants who missed 2 or more consecutive disease evaluations prior to the PFS event date (based on IRC).

Figure 22: Forest Plot of Sensitivity and Supplementary Analyses on Progression-free Survival; Intent-to-treat Analysis Set (AQUILA)



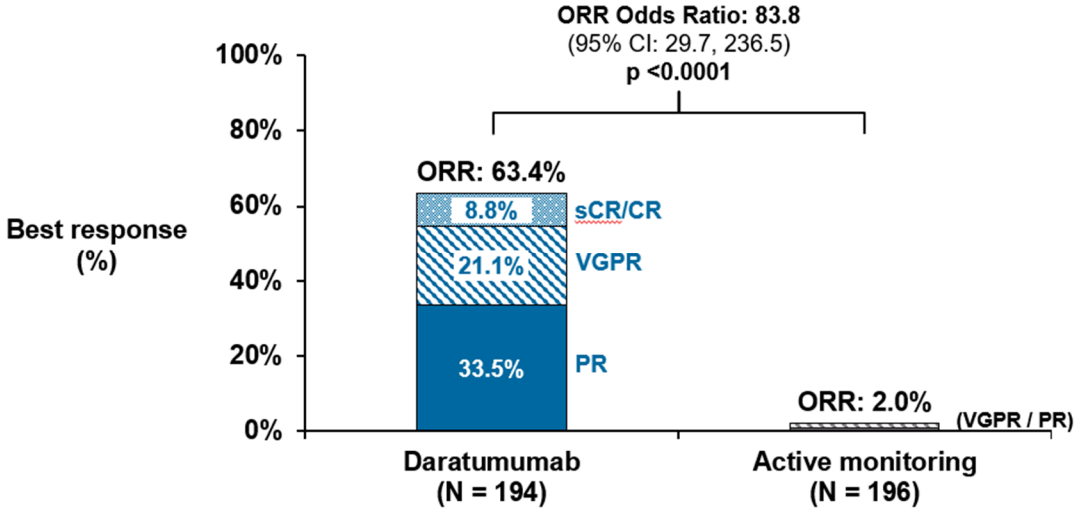
Key: CI=confidence interval; COVID-19=coronavirus disease 2019; DE=disease evaluations; HR=hazard ratio; IRC=independent review committee; PFS=progression-free survival

6.5.3 *Key Secondary Efficacy Analyses*

6.5.3.1 *Overall Response Rate*

Overall response rate was significantly higher in the Daratumumab arm (63.4%) compared with the Active Monitoring arm (2.0%). The odds ratio (Daratumumab vs Active Monitoring) was 83.8 (95% CI: 29.7, 236.54), with a 2-sided p<0.0001 crossing the prespecified Type I error rate of 0.05. Best overall response between-treatment arms is summarized in Figure 23.

Figure 23: Summary of Overall Best Confirmed Response based on Computerized Algorithm (AQUILA)

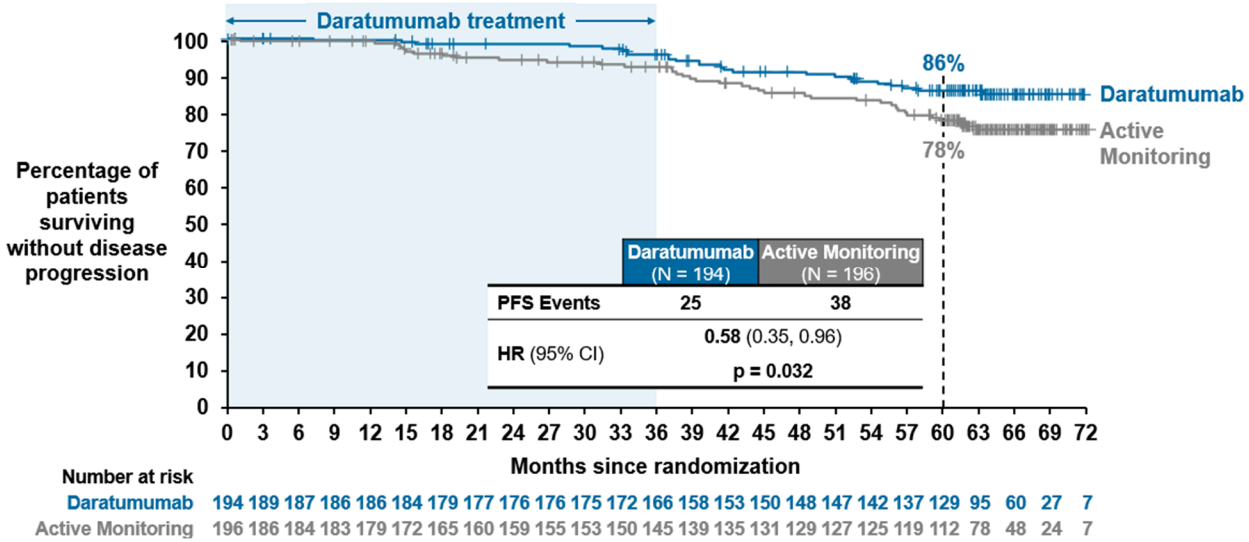


Key: CI=confidence interval; CR=complete response; ORR=overall response rate; PR=partial response; sCR=stringent complete response; VGPR=very good partial response

6.5.3.2 Progression-Free Survival 2

At the time of the CCO, the PFS2 data were not yet mature, with 63 PFS2 events observed (Daratumumab 25/194 [12.9%]; Active Monitoring 38/196 [19.4%]). The HR (Daratumumab vs Active Monitoring) was 0.58 (95% CI: 0.35, 0.96) with a 2-sided p=0.0318, which did not cross the prespecified stopping boundary of 0.0235 (Figure 24). Although the statistical significance of PFS2 was not established at this primary analysis, there was no apparent detriment in PFS2 for the Daratumumab arm (i.e., daratumumab in asymptomatic SMM participants did not result in a detriment to response during frontline treatment for active myeloma). Median PFS2 was not reached in either arm (60-month PFS2 rate: Daratumumab 85.9%; Active Monitoring 78.0%). The final analysis of PFS2 will be performed at the end of study per protocol.

Figure 24: Kaplan-Meier Plot for Progression-free Survival on First-Line Treatment (PFS2) for Multiple Myeloma; Intent-to-treat Analysis Set (AQUILA)

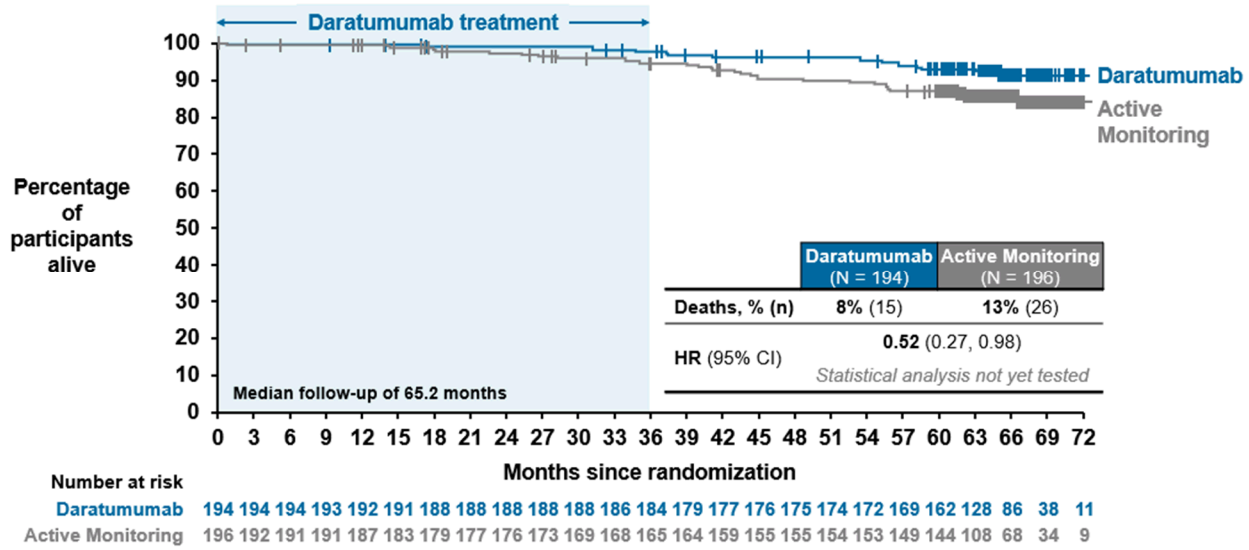


Key: CI=confidence interval; HR=hazard ratio; PFS=progression-free survival

6.5.3.3 Overall Survival

Median follow-up was 65.2 months (Daratumumab 65.9 months; Active Monitoring 64.8 months). Overall survival data were not mature, with 41 events observed (Daratumumab 15/194 [7.7%]; Active Monitoring 26/196 [13.3%]). Overall survival was not formally tested as it was to be tested only if PFS2 was significant based on the hierarchical testing paradigm used in this study. The estimated OS HR (Daratumumab vs Active Monitoring) was 0.52 (95% CI: 0.27, 0.98), indicating early evidence of a positive OS trend in favor of the Daratumumab arm. Median OS was not reached in either arm (60-month OS rate: Daratumumab 93.0%; Active Monitoring 86.9%). The study will continue to collect additional survival data. The final OS analysis will be performed at the end of study per protocol, which will occur approximately 8 years after randomization of the first participant (approximately December 2025). The OS analysis is summarized in Figure 25.

Figure 25: Kaplan-Meier Plot for Overall Survival; Intent-to-treat Analysis Set



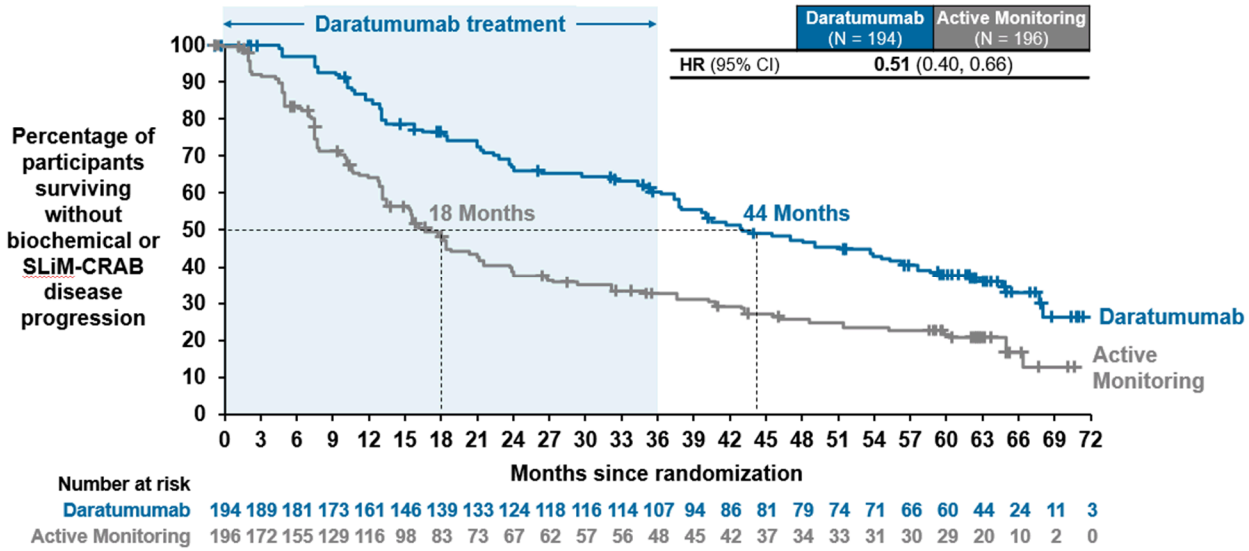
Key: CI=confidence interval; HR=hazard ratio

6.5.4 Additional Efficacy Analyses

6.5.4.1 Time to Biochemical or Diagnostic (SLiM-CRAB) Progression per Computerized Algorithm Analyses

A total of 255 events (Daratumumab 116; Active Monitoring 139) were observed for biochemical or SLiM-CRAB progression. The HR (Daratumumab vs Active Monitoring) was 0.51 (95% CI: 0.40, 0.66); 2-sided nominal p<0.0001. Median biochemical or SLiM-CRAB progression was 44.1 months (95% CI: 38.9, 55.2) in the Daratumumab arm and 17.8 months (95% CI: 14.4, 22.0) in the Active Monitoring arm (60-month PFS rate: Daratumumab 38.8%; Active Monitoring 22.2%; Figure 26). Biochemical progression is a primary reason for progression in the active myeloma treatment phase, thus an analysis was performed to evaluate the timing of progression based on blood biomarkers versus SLiM-CRAB criteria which is required to diagnose and initiate treatment for active myeloma.

Figure 26: Time to Biochemical or SLiM-CRAB Progression; Intent-to-treat Analysis Set (AQUILA)



Key: CI=confidence interval; HR=hazard ratio; SLiM-CRAB=diagnostic criteria for symptomatic multiple myeloma

6.5.4.2 Time to First Treatment for Multiple Myeloma

A total of 33.2% of participants in the Daratumumab arm and 53.6% in the Active Monitoring arm started a first subsequent antimyeloma (Table 18). Daratumumab delayed the time to first-line treatment for multiple myeloma versus active monitoring, with an HR of 0.46; 95% CI: 0.33, 0.62; 2-sided nominal p<0.0001 (Figure 27).

Table 18: Summary of Subsequent Antimyeloma Therapies by Treatment Regimens; Safety Analysis Set (AQUILA)

	Daratumumab	Active Monitoring
Analysis set: safety	193	196
Total number of participants with first line subsequent therapies	64 (33.2%)	105 (53.6%)
VRd	19 (9.8%)	29 (14.8%)
VCd	6 (3.1%)	14 (7.1%)
VTd	9 (4.7%)	8 (4.1%)
DVRd	4 (2.1%)	10 (5.1%)
DRd	3 (1.6%)	10 (5.1%)
Rd	5 (2.6%)	7 (3.6%)
DVMP	1 (0.5%)	5 (2.6%)
KRd	3 (1.6%)	3 (1.5%)
DVTd	2 (1.0%)	2 (1.0%)
Isa+VRd	1 (0.5%)	3 (1.5%)
Vd	2 (1.0%)	1 (0.5%)
Daratumumab[a]	2 (1.0%)	0
IRd	0	2 (1.0%)
R[b]	1 (0.5%)	1 (0.5%)
RCd	1 (0.5%)	1 (0.5%)
VMP	1 (0.5%)	1 (0.5%)
D+VTCd	0	1 (0.5%)
Dara+Iber+d	1 (0.5%)	0
DKRd	1 (0.5%)	0
DVd	0	1 (0.5%)
Elo+KRd	0	1 (0.5%)
Isa[b]	0	1 (0.5%)
KCd	0	1 (0.5%)
Venetoclax+VTd	0	1 (0.5%)
VTCd	1 (0.5%)	0
Other subsequent therapies[c]	1 (0.5%)	2 (1.0%)
CD38-Ab containing regimens[d]	16 (8.3%)	35 (17.9%)

Key: Ab=antibody; C=cyclophosphamide; d=dexamethasone; D=daratumumab; Elo=elotuzumab; Iber=iberdomide; I=ixazomib; K=carfilzomib; M=melphalan; P=prednisone; R=lenalidomide; T=thalidomide; V=bortezomib

[a] Two participants in the Daratumumab group who continued to receive Daratumumab.

[b] Participants who initiated treatment before disease progression to multiple myeloma.

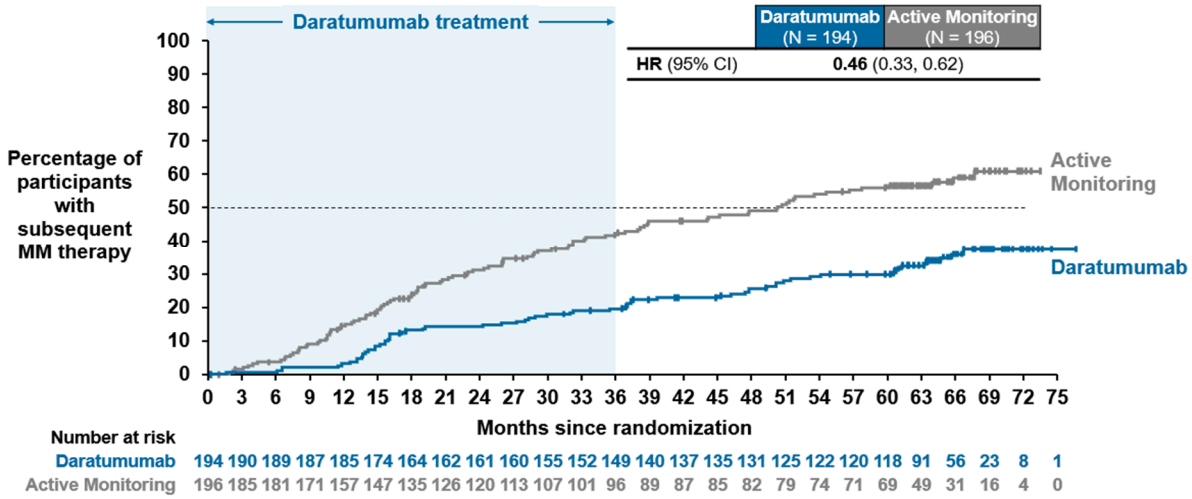
[c] Includes subsequent therapy regimens that cannot be classified within the list of therapies.

[d] All regimens with CD38 Abs, including regimens within other subsequent therapies

Note: Percentages are calculated with the number of participants in each treatment arm as denominator.

Note: Treatment regimens are generated based on the concomitant medicine subsequent therapies.

Figure 27: Kaplan-Meier Plot for Time to First Treatment for Multiple Myeloma; Intent-to-treat Analysis Set (AQUILA)



Key: CI=confidence interval; HR=hazard ratio; MM=multiple myeloma

6.5.4.3 Time to Response

In responders, the median time to first response (PR or better) (Daratumumab 2.9 months; Active Monitoring 10.5 months) and the median time to VGPR or better (Daratumumab 8.4 months; Active Monitoring 31.8 months) were substantially shorter in the Daratumumab arm compared with the Active Monitoring arm. Median time to CR or better was 13.9 months in the Daratumumab arm.

6.5.4.4 Patient-Reported Outcomes (HRQoL)

Concepts included in the EORTC QLQ-C30 and the EORTC QLQ-MY20 provide good coverage of the experiences reported by patients with SMM, supporting the use of these patient-reported outcomes (PRO) instruments in the AQUILA study (Jean-Baptiste 2020). Standard meaningful change threshold for the EORTC QLQ-C30 and supplementary modules is defined as a 10-point change, with a range from 5 points (a little) to 20 points (very much) (Fayers 2001).

EORTC QLQ-C30, EORTC QLQ-MY20, and EQ-5D-5L demonstrated comparable QoL over time in the Daratumumab and Active Monitoring arms (Figure 28; Table 19).

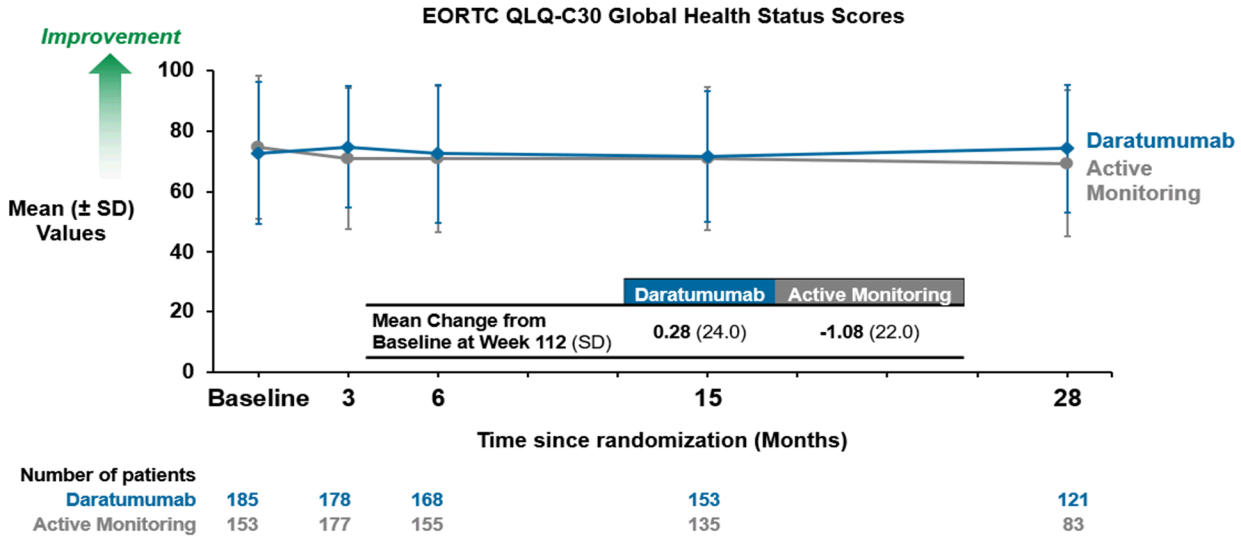
Compliance rates for PRO assessments were calculated as the ratio of observed to expected rates and exclude participants who experienced PD or death. At baseline, PRO compliance was numerically higher for the Daratumumab arm (95%-96%) compared with the Active Monitoring arm (79%-80%). Compliance rates were similar between-treatment arms at subsequent visits, with overall compliance exceeding 80% at the majority of time points up to Month 28.

Baseline PRO was collected on Cycle 1 Day 1 visit. However, participants in the Active Monitoring arm were not required to visit the site except for the completion of the PRO questionnaires which resulted in missing data. After this was observed, the protocol was

amended to require participants in the Active Monitoring arm to complete the baseline questionnaire during screening. A high rate of missing data was noted after Month 28, largely due to the COVID-19 pandemic.

To assess the impact of missing data, a sensitivity analysis was conducted utilizing a pattern mixture model for data imputation. The results of this analysis were found to be consistent with those obtained without imputation, with PRO assessments demonstrating comparable QoL over time in the Daratumumab and Active Monitoring arms.

Figure 28: Baseline and Mean Changes Over Time: EORTC QLQ-C30 Global Health Status Scores; Intent-to-treat Analysis Set (AQUILA)



Key: SD=standard deviation

Table 19: Summary of Patient-Reported Outcomes: Baseline Value and Mean Change from Baseline; Intent-to-treat Analysis Set (AQUILA)

	Daratumumab		Active Monitoring	
	Baseline Mean Value (SD)	Mean Change from Baseline to Week 112 (SD)	Baseline Mean Value (SD)	Mean Change from Baseline to Week 112 (SD)
Symptom Scales*				
Pain	19.80 (25.0)	-1.96 (20.7)	15.91 (26.3)	0.53 (24.1)
Fatigue	21.45 (21.4)	-1.40 (18.7)	20.72 (21.0)	1.41 (27.0)
Disease Symptoms	15.97 (16.5)	0.51 (16.2)	15.83 (20.1)	0 (18.3)
Functioning Scales*				
Cognitive	86.94 (18.2)	2.3 (16.3)	88.02 (19.4)	0 (19.6)
Emotional	82.28 (18.6)	3.87 (16.4)	84.51 (18.8)	0.85 (21.6)
Physical	88.28 (14.8)	-1.37 (12.6)	89.25 (16.2)	-3.12 (14.1)
Role	89.61 (18.1)	-0.42 (17.3)	89.03 (21.1)	-5.29 (21.6)
Social	90.18 (16.8)	1.57 (17.6)	91.61 (20.6)	1.34 (22.2)
Future Perspective	61.89 (24.9)	11.77 (28.6)	62.87 (26.0)	10.04 (30.9)

* Scores range from 0-100 with higher scores representing better health-related quality of life and better functioning (global health status and functional scales) or more/worse symptoms (symptom scales and single items) with a clinically meaningful change defined as 10 points.

6.6 Ongoing Evaluation of Participants

AQUILA included a Follow-up Phase, which began once a participant completed 39 cycles or 36 months (whichever occurred first) of active monitoring or daratumumab treatment.

- If participants discontinued treatment or active monitoring before PD, disease evaluations continued every 12 weeks until study completion or confirmed PD, after which follow-up occurred every 6 months.
- If participants did not progress to multiple myeloma, then no other treatment for SMM or multiple myeloma was allowed during the study.
- Follow-up for first-line multiple myeloma treatment (including the response to first-line multiple myeloma treatment) and second primary malignancies occurred every 6 months as part of the post-PD follow-up.
- Survival was followed until the end of the study and at a frequency of every 12 weeks until PD, then every 6 months until the end of the study.

6.7 Efficacy Conclusions

The primary efficacy data for daratumumab in the proposed indication are derived from the pivotal Phase 3 AQUILA study.

In the Phase 3 AQUILA study, treatment with daratumumab resulted in a clinically meaningful and statistically significant improvement in PFS, with a 51% reduction in the risk of progression or death compared with active monitoring (HR=0.49; 95% CI: 0.36, 0.67; 2-sided $p<0.0001$). The PFS benefit per IRC assessment was consistent across the prespecified subgroups of sex, age, race, region, baseline renal function, and SMM risk factors. Consistent results were observed in all prespecified sensitivity and supplementary analyses, supporting the robustness of the PFS result.

The efficacy of daratumumab was demonstrated in the secondary endpoint of ORR and further supported by other endpoints, including PFS2 which indicated that the treatment of high-risk SMM with daratumumab had no detrimental treatment effect on the first-line treatment for active myeloma. While the survival data remain immature and median survival has not yet been reached, treatment with daratumumab demonstrated early evidence of a positive trend in OS, with a 48% reduction in the risk of death compared with Active Monitoring (HR=0.52; 95% CI: 0.27, 0.98). In addition, PRO assessments demonstrated comparable QoL over time in the Daratumumab and Active Monitoring arms.

These data demonstrate anti-tumor benefit across markers of disease progression that support a durable benefit compared with active monitoring that would be likely to predict a meaningful clinical benefit in morbidity and mortality.

7 CLINICAL SAFETY

Summary

- Daratumumab has been administered to over 500,000 patients, leading to a well-established safety profile.
- The safety profile of daratumumab SC in participants with SMM is consistent with the known safety profile of daratumumab.
- In the AQUILA study, the majority of AEs were Grade 1 or 2 in severity in the Daratumumab arm.
- Daratumumab was well tolerated in participants with high-risk SMM, with clinically manageable side effects, well known to clinicians who are familiar with monitoring and managing daratumumab treatment.

7.1 Safety Profile of Daratumumab in Multiple Myeloma

The safety of daratumumab administered SC and IV has been evaluated in prior clinical investigations. Daratumumab has a well-understood safety profile that is consistent between the 2 formulations, with a lower risk of sARRs with SC administration (DARZALEX FASPRO USPI 2024).

Systemic administration-related reactions, including severe or life-threatening reactions, can occur with daratumumab. Fatal reactions have been reported. Systemic administration-related reactions are managed with premedications (histamine-1 receptor agonists, acetaminophen, corticosteroids, and leukotriene inhibitors), monitoring (especially after the first and second injections), interruption of daratumumab administration, and timely treatment of signs and symptoms of the reactions.

Primary evidence of safety in participants with high-risk SMM with the recommended posology comes from the AQUILA study. The safety profile of daratumumab SC in participants with SMM is consistent with the known safety profile of daratumumab.

7.2 Study AQUILA Safety Results

In the AQUILA study, safety was assessed by AEs, physical examinations, electrocardiograms (ECGs), SC injection-site evaluations, clinical laboratory test results (hematology and chemistry), and ECOG performance status. Any clinically relevant changes occurring during the study were recorded on the Adverse Event section of the electronic case report form.

The safety summary provided in this document describes the AE reporting; all other safety evaluations showed no clinically meaningful findings.

7.2.1 Treatment Exposure

A total of 193 participants received daratumumab. The median number of treatment cycles was 38 cycles (range: 1 to 39), median dose intensity was 2,273.7 mg/cycle (range: 1,800.0 to 7,200.0), and median relative dose intensity was 100% (range: 25% to 100%). Exposure to daratumumab SC was generally consistent across the treatment cycles.

The median duration of active monitoring in the Active Monitoring arm was 25.9 months (range 0.1 to 36.0) compared with the median duration of treatment in the Daratumumab arm of 35.0 months (range 0.03 to 36.1), resulting in an approximately 9 months longer AE reporting period for participants treated with daratumumab.

7.2.2 Adverse Events

7.2.2.1 Overview of Adverse Events

The AE profile of daratumumab SC in participants with high-risk SMM was consistent with the known safety profile of daratumumab.

The incidence of AEs was as follows (Table 20):

- The incidence of AEs was higher in the Daratumumab arm compared with the Active Monitoring arm (Daratumumab 96.9%; Active Monitoring 82.7%). The majority of AEs were Grade 1 or 2 in severity.
- The incidence of Grade 3 or 4 AEs was higher in the Daratumumab arm compared with the Active Monitoring arm (Daratumumab 40.4%; Active Monitoring 30.1%).
- The incidence of SAEs was higher in the Daratumumab arm compared with the Active Monitoring arm (Daratumumab 29.0%; Active Monitoring 19.4%).
- The incidence of AEs with an outcome of death (Grade 5) was low and balanced in both arms (Daratumumab 1.0%; Active Monitoring 2.0%).
- The rate of AEs leading to discontinuation of daratumumab was 5.7%.

Table 20: Overview of Adverse Events; Safety Analysis Set (AQUILA)

Parameter	Daratumumab (N=193)	Active Monitoring (N=196)
Analysis set: safety	193	196
Any AE	**187 (96.9%)**	**162 (82.7%)**
At least one related	138 (71.5%)	-
Maximum toxicity grade	-	-
Grade 1	17 (8.8%)	32 (16.3%)
Grade 2	92 (47.7%)	70 (35.7%)
Grade 3	67 (34.7%)	51 (26.0%)
Grade 4	9 (4.7%)	5 (2.6%)
Grade 5	2 (1.0%)	4 (2.0%)
Any serious AE	**56 (29.0%)**	**38 (19.4%)**
At least one related	15 (7.8%)	
AEs leading to discontinuation of daratumumab	**11 (5.7%)**	**-**
At least one related to daratumumab	6 (3.1%)	-
AEs leading to dose modification[a]	**90 (46.6%)**	**-**
At least one related	36 (18.7%)	-
AE with outcome of death	**2 (1.0%)**	**4 (2.0%)**
At least one related	2 (1.0%)	-
Death due to COVID-19	2 (1.0%)	0
AE of COVID-19	**17 (8.8%)**	**10 (5.1%)**
Serious AE of COVID-19	5 (2.6%)	1 (0.5%)

[a] Dose modification includes dose delay within cycle, cycle delay and dose skipped.
Note: Percentages are calculated with the number of participants in each arm as denominators.
Note: For Daratumumab treatment arm, AEs with onset date and time on or after that of the first dose through 30 days after the last study drug administration are considered AEs. For Active Monitoring arm, AEs with onset on or after the randomization are considered AEs through 3 years on study and up to 30 days thereafter.
Note: Adverse events are reported using MedDRA version 26.1.

7.2.2.2 Common Adverse Events

The most common AEs (≥10% of participants in either arm) are presented in Table 21 and are known adverse drug reactions (ADRs) for daratumumab. Adverse events that occurred with a frequency of ≥20% of participants in the Daratumumab arm and at a ≥10% higher frequency in the Daratumumab arm compared with the Active Monitoring arm were:

- Fatigue (Daratumumab 34.2%; Active Monitoring 13.3%)
- Upper respiratory tract infection (Daratumumab 30.1%; Active Monitoring 7.7%)
- Diarrhea (Daratumumab 27.5%; Active Monitoring 5.1%)
- Nasopharyngitis (Daratumumab 25.4%; Active Monitoring 11.7%)
- Insomnia (Daratumumab 22.3%; Active Monitoring 2.6%)

Table 21: Most Common Adverse Events (≥10% of Participants) by Preferred Term; Safety Analysis Set (AQUILA)

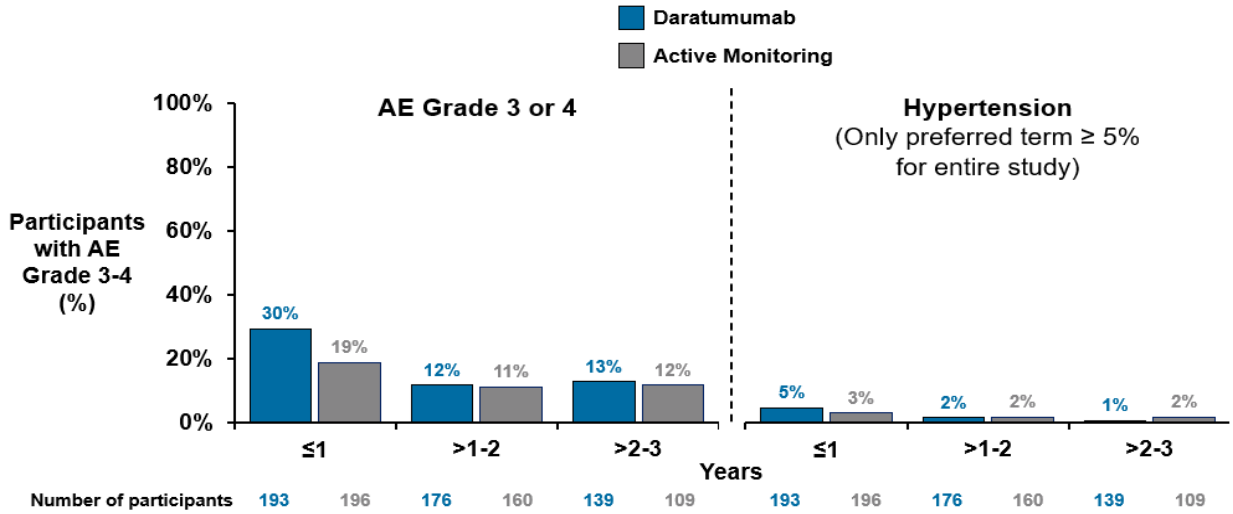
	Daratumumab (N = 193)	Active Monitoring (N = 196)
Any AE, %	97%	83%
Fatigue	34%	13%
Upper respiratory tract infection	30%	8%
Arthralgia	27%	18%
Diarrhea	27%	5%
Nasopharyngitis	25%	12%
Back pain	24%	19%
Insomnia	22%	3%
Nausea	19%	5%
Headache	18%	7%
Cough	17%	6%
Pyrexia	17%	3%
Injection site erythema	16%	0
Pain in extremity	15%	8%
Dyspnea	15%	5%
Pneumonia	11%	5%
Hypertension	10%	10%
Myalgia	10%	5%
Edema peripheral	10%	2%

Key: AE= adverse event

7.2.2.3 Grade 3 or 4 Adverse Events

The only Grade 3 or 4 AE that occurred in ≥5% of participants in either arm was Hypertension (Daratumumab 5.7%; Active Monitoring 4.6%). The highest proportion of participants with Grade 3 or 4 AEs in the Daratumumab arm was observed within the first year of treatment. The proportions of participants with Grade 3 or 4 AEs were similar to the Active Monitoring arm after the first 12 months (Figure 29).

Figure 29: Grade 3 or 4 Adverse Events Over Time (Yearly Intervals); Safety Analysis Set (AQUILA)



Key: AE=adverse event

7.2.2.4 Adverse Events Leading to Discontinuation of Study Treatment

Adverse events leading to discontinuation of daratumumab were reported in 11 (5.7%) participants, and those reported in ≥2 participants were Fatigue, Anxiety, and Dyspnea (2 [1.0%] each). Grade 3 or 4 AEs leading to discontinuation of daratumumab were reported in 5 (2.6%) participants (Table 22).

Table 22: Adverse Events Leading to Discontinuation in ≥2% of Participants by Preferred Terms; Safety Analysis Set (AQUILA)

	Daratumumab (N = 193)	
	Any Grade	Grade 3 or 4
Participants with treatment discontinuation due to AEs, % (n)	**6%** (11)	**3%** (5)
Fatigue	**1%** (2)	**0.5%** (1)
Anxiety	**1%** (2)	**0.5%** (1)
Dyspnea	**1%** (2)	**0.5%** (1)

Key: AE=adverse event

7.2.2.5 Adverse Events Leading to Dose Modification

Dose modification of daratumumab SC (increase or decrease) was not permitted per protocol. Dose delay was recommended as the primary method for managing daratumumab-related toxicities.

The incidence of dose delays, cycle delays, or dose skipped due to AEs was 46.6%. Adverse events leading to dose delays, cycle delays, or dose skipped in ≥5% of participants were Upper respiratory tract infection (14 [7.3%]), Pneumonia (11 [5.7%]), and COVID-19 (10 [5.2%]) (Table 23).

Table 23: Adverse Events Leading to Dose Delays, Cycle Delays, or Dose Skips; Safety Analysis Set (AQUILA)

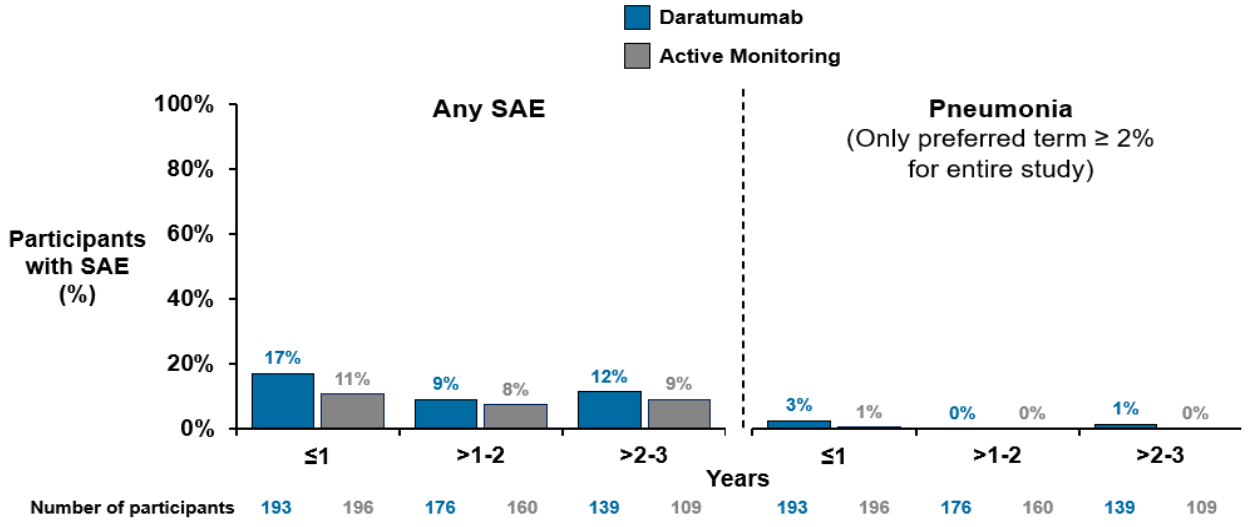
	Daratumumab (N = 193)
AEs leading to dose modification, %	47%
Cycle delays	38%
Dose skips	18%
Dose delay within cycle	4%
By preferred term (≥ 5%)	
Upper respiratory tract infection	7%
Pneumonia	6%
COVID-19	5%

Key: AE = adverse event; COVID-19=coronavirus disease 2019
Note: Percentages in the total column were calculated with the number of participants in the Daratumumab arm as denominator. Percentages in the cycle categories were calculated with the number of participants in each category as the denominator.

7.2.3 Serious Adverse Events

The only SAE occurring in ≥2% of participants in either arm was Pneumonia (daratumumab 3.6%; Active Monitoring 0.5%). The highest proportion of participants with SAEs in the Daratumumab arm was observed within the first year of treatment (Figure 30).

Figure 30: Serious Adverse Events Over Time (Yearly Intervals); Safety Analysis (AQUILA)



Key: SAE = serious adverse event

7.2.4 Deaths

Overall Summary of Deaths

At the time of the CCO, 15 (7.8%) participants in the Daratumumab arm and 26 (13.3%) participants in the Active Monitoring arm died. The primary causes of death were Other (Daratumumab 10 [5.2%]; Active Monitoring 13 [6.6%]), PD (Daratumumab 3 [1.6%]; Active Monitoring 9 [4.6%]), and AEs (Daratumumab 2 [1.0%]; Active Monitoring 4 [2.0%]; Table 24). The causes of death indicated as Other were reported as such because the event occurred outside the AE reporting window. No participants in the Daratumumab arm died within 30 days of the last dose of daratumumab SC or within 60 days of the first dose of daratumumab SC.

Deaths after Starting Subsequent Antimyeloma Therapy

A total of 22 participants (Daratumumab 8 [4.1%]; Active Monitoring 14 [7.1%]) died after IRC confirmed PD and after starting subsequent antimyeloma therapy. Seven participants (Daratumumab 1 [0.5%]; Active Monitoring 6 [3.1%]) died after PD per investigator assessment only (not confirmed by IRC) and after starting subsequent antimyeloma therapy. Ten participants (Daratumumab 5 [2.6%]; Active Monitoring 5 [2.6%]) died prior to IRC confirmed PD and prior to starting subsequent antimyeloma therapy.

Fatal Adverse Events

Adverse events with an outcome of death were reported in 2 (1.0%) participants in the Daratumumab arm and 4 (2.0%) participants in the Active Monitoring arm (Table 24). Adverse events with an outcome of death in the Daratumumab arm were COVID-19 and COVID-19 pneumonia (1 participant each).

Table 24: Summary of Death and Cause of Death; Safety Analysis Set (AQUILA)

	Daratumumab (N = 193)	Active Monitoring (N = 196)
Deaths during study, % (n)	**8%** (15)	**13%** (26)
Progressive disease	**2%** (3)	**5%** (9)
Adverse event	**1%** (2)	**2%** (4)
COVID-19	**1%** (2)	**0**
Other*	**5%** (10)	**7%** (13)

Key: COVID-19=coronavirus 2019
*From signing of informed consent form until 30 days after last daratumumab dose or 36 months from the start of active monitoring or until start of next therapy, whichever was earlier.

7.2.5 Selected Adverse Events of Special Interest

7.2.5.1 Systemic Administration-related Reactions and Infusion-Related Reactions

Both sARRs and IRRs were defined as systemic reactions related to daratumumab administration. These terms are interchangeable.

Systemic administration-related reactions, applicable to the Daratumumab arm, were reported in 16.6% of participants. No sARRS was reported in ≥5% of participants. Grade 3 or 4 sARRs were reported in 2 (1.0%) participants. Twenty-nine (15.0%) participants reported sARRs with the first administration of daratumumab, 4 (2.1%) participants with the second administration, and 5 (2.6%) participants with subsequent administrations.

7.2.5.2 Local injection-site reactions

Local injection-site reactions are applicable to the Daratumumab arm only. Local injection-site reactions were reported in 27.5% of participants. Local injection-site reactions reported in ≥5% of participants were Injection-site erythema (15.5%) and Erythema (5.2%). No Grade 3 or 4 local injection-site reactions were reported.

7.2.5.3 Cytopenia

Any grade cytopenia (comprising neutropenia, anemia, thrombocytopenia, and lymphopenia group terms) was reported in 11.9% of participants in the Daratumumab arm and 12.2% of participants in the Active Monitoring arm. Grade 3 or 4 cytopenia events were reported in 9 (4.7%) participants in the Daratumumab arm and 6 (3.1%) participants in the Active Monitoring arm (Table 25).

Table 25: Cytopenia by Preferred Term and Grade 3 or 4; Safety Analysis Set (AQUILA)

	Daratumumab		Active Monitoring	
	Any Grade	**Grade 3 or 4**	**Any Grade**	**Grade 3 or 4**
Analysis set: safety	193		196	
Total number of participants with Cytopenia	**23 (11.9%)**	**9 (4.7%)**	**24 (12.2%)**	**6 (3.1%)**
Neutropenia[a]	13 (6.7%)	8 (4.1%)	5 (2.6%)	4 (2.0%)
Neutropenia	13 (6.7%)	8 (4.1%)	5 (2.6%)	4 (2.0%)
Febrile neutropenia	0	0	1 (0.5%)	1 (0.5%)
Anemia[a]	9 (4.7%)	0	19 (9.7%)	2 (1.0%)
Anemia	9 (4.7%)	0	19 (9.7%)	2 (1.0%)
Thrombocytopenia[a]	4 (2.1%)	1 (0.5%)	3 (1.5%)	0
Thrombocytopenia	4 (2.1%)	1 (0.5%)	3 (1.5%)	0
Lymphopenia[a]	3 (1.6%)	2 (1.0%)	1 (0.5%)	0
Lymphopenia	3 (1.6%)	2 (1.0%)	1 (0.5%)	0

Key: AE=adverse event; MedDRA=Medical Dictionary for Regulatory Activities
[a] Preferred term grouping.
Note: Percentages are calculated with the number of participants in each arm as denominators.
Note: For Daratumumab treatment arm, AEs with onset date and time on or after that of the first dose through 30 days after the last study drug administration are considered AEs. For Active Monitoring arm, AEs with onset on or after the randomization are considered AEs through 3 years on study and up to 30 days thereafter.
Note: Adverse events are reported using MedDRA version 26.1

7.2.5.4 Infections and Infestations

The overall incidence of Infections and Infestations (SOC) was higher in the Daratumumab arm (79.8%) compared with the Active Monitoring arm (44.9%). The median duration of any grade Infections and Infestations was 14.0 days in both arms and 98% of any grade Infections and Infestations AEs in participants treated with daratumumab were recovered or resolved (Table 26). The most common Infections and Infestations of any grad (≥10% of participants in either arm) were Upper respiratory tract infection (Daratumumab 30.1%; Active Monitoring 7.7%), Nasopharyngitis (Daratumumab 25.4%; Active Monitoring 11.7%), and Pneumonia (Daratumumab 11.4%; Active Monitoring 5.1%). Most Infections and Infestations were Grade 1 or 2 in both arms.

The incidence of Grade 3 or 4 Infections and Infestations (SOC) was higher in the Daratumumab arm (16.1%) compared with the Active Monitoring arm (4.6%); however, the median duration of the events was 5.0 days in the Daratumumab arm and 9.0 days in the Active Monitoring arm. Of the Grade 3 or 4 Infection and infestations AEs, most events had an outcome of recovered or resolved (Daratumumab 35 [94.6%]; Active Monitoring 8 [72.7%]) (Table 26).

Table 26: Duration and Outcomes of Infection and Infestations (SOC); Safety Analysis Set (AQUILA)

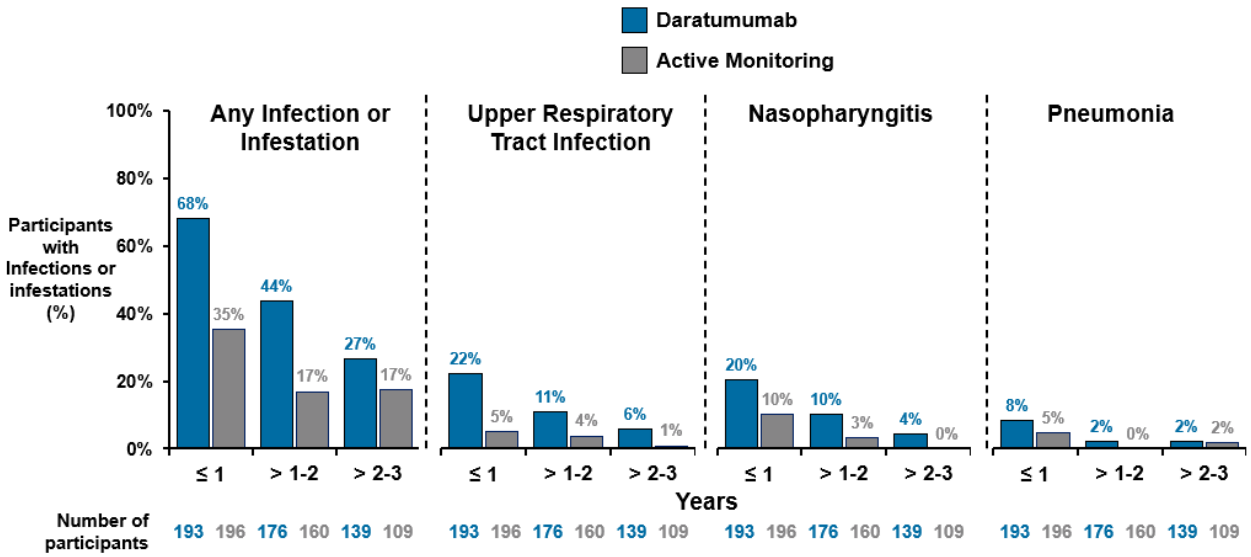
	Daratumumab (N = 193)		Active Monitoring (N = 196)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
Participants with infections or infestations, %	**80%**	**16%**	**45%**	**5%**
Recovered or resolved	**98%**	**95%**	**96%**	**73%**
Duration of infections				
Median, days (Q1, Q3)	**14** (7, 28)	**5** (4, 15)	**14** (8, 31)	**9** (6, 12)

The incidence of SAEs of Infections and Infestations was higher in the Daratumumab arm (16.6%) compared with the Active Monitoring arm (5.1%).

Infections and Infestations (SOC) that led to discontinuation of daratumumab SC were reported in 2 (1.0%) participants.

In the Daratumumab arm, the proportion of participants with AEs of Infections or Infestations SOC decreased over time (Figure 31). A similar pattern was observed with respect to individual AEs of Upper respiratory tract infection, Nasopharyngitis, and Pneumonia.

Figure 31: Infections and Infestations Over Time (Yearly Intervals); Safety Analysis Set (AQUILA)



7.2.5.5 Age Subgroup Analysis of Adverse Events

Age (<65 years, 65 to <75 years, ≥75 years)

- No increased safety concerns were observed in the ≥75 years subgroup in the Daratumumab arm.
- A lower percentage of participants in the <65 years and ≥75 years subgroups compared with the 65 to <75 years subgroup in the Daratumumab arm experienced SAEs (<65 years 24.8%; 65 to <75 years 35.8%; ≥75 years 28.6%). A lower percentage of participants in the <65 years subgroup compared with the 65 to <75 years and ≥75 years subgroups in the Daratumumab arm experienced AEs leading to discontinuation (<65 years 1.9%; 65 to <75 years 9.0%; ≥75 years 14.3%) and AEs leading to dose modification (<65 years 33.3%; 65 to <75 years 65.7%; ≥75 years 52.4%).
- No Grade 5 AEs were reported in the ≥75 years subgroup in the Daratumumab arm.

7.2.6 New Adverse Drug Reactions

Two new ADRs were identified in the AQUILA study: Myalgia and Pain in extremity. Per FDA request, these PTs are grouped under the term musculoskeletal pain, which was already a known ADR of daratumumab.

7.2.6.1 Myalgia

The incidence of Myalgia was higher in the Daratumumab arm compared with the Active Monitoring arm (Daratumumab 10.4%; Active Monitoring 4.6%). Considering other known musculoskeletal ADRs of daratumumab (e.g., Arthralgia, Muscle spasms, Musculoskeletal chest pain) and based on the imbalance in the incidence, Myalgia was assessed as a new ADR for daratumumab. One participant in the Daratumumab arm reported Grade 3 Myalgia; the event was assessed as not related to daratumumab and resolved without dose modification of daratumumab. No Grade 4, serious, or fatal events of Myalgia were reported in either arm. Myalgia led to dose modification of daratumumab for 1 participant and discontinuation of daratumumab for 1 participant.

7.2.6.2 Pain in Extremity

The incidence of Pain in extremity was higher in the Daratumumab arm compared with the Active Monitoring arm (Daratumumab 14.5%; Active Monitoring 7.7%). Considering other known musculoskeletal ADRs of daratumumab (e.g., Arthralgia, Muscle spasms, Musculoskeletal chest pain) and based on the imbalance in the incidence, Pain in extremity was assessed as a new ADR for daratumumab. One participant in the Daratumumab arm reported Grade 3 Pain in extremity; the event was assessed as not related to daratumumab and resolved without dose modification of daratumumab. No Grade 4, serious, or fatal events of Pain in extremity were reported in either arm. Pain in extremity did not lead to dose modification or discontinuation.

7.3 Daratumumab Pharmacovigilance

A cumulative review of the postmarketing spontaneous cases through 31 July 2024 revealed that based on the most commonly reported events, serious events, and fatal events, the postmarketing experience of daratumumab remained generally consistent with that observed in previous cumulative reviews, the known safety profile of daratumumab, and the clinical experience of the patient population under treatment.

7.4 Safety Conclusions

The safety data for daratumumab SC observed in the Phase 3 AQUILA study were consistent with the known safety profile of daratumumab. Although more AEs occurred in the Daratumumab arm, daratumumab was well tolerated in participants with high-risk SMM, with side effects in which clinicians are familiar with monitoring and managing. The new ADRs identified in the AQUILA study are not considered important risks and do not impact the benefit-risk profile of daratumumab.

8 BENEFIT-RISK

8.1 Benefits

The key benefits associated with daratumumab SC treatment in the target patient population are clinically meaningful and statistically significant improvement in the primary endpoint (PFS) and the key secondary endpoint of ORR compared with active monitoring:

- Treatment with daratumumab SC resulted in a 51% reduction in the risk of PD or death compared with Active Monitoring (HR=0.49; 95% CI: 0.36, 0.67; 2-sided p<0.0001). Median PFS was not reached in the Daratumumab arm and was 41.5 months (95% CI: 26.4, 53.3) in the Active Monitoring arm (60-month PFS rate: Daratumumab 63.1%; Active Monitoring 40.8%).
- ORR per computerized algorithm was significantly higher in the Daratumumab arm (63.4%) compared with the Active Monitoring arm (2.0%) (odds ratio [Daratumumab vs Active Monitoring] 83.8; 95% CI: 29.69, 236.54; 2-sided p-value <0.0001).

Consistent results were observed in all prespecified PFS sensitivity and supplementary analyses, supporting the robustness of the primary analysis PFS result.

At the time of the CCO, the PFS2 data were not yet mature, and statistical significance of PFS2 and OS was not established at this primary analysis for PFS. However, there was no indication of a detrimental effect on the first-line treatment of active myeloma. The OS data demonstrated early evidence of a positive trend in favor of the Daratumumab arm. The final analysis of PFS2 and OS will be performed at the end of study per protocol.

8.2 Risks

The safety data for daratumumab SC in the Phase 3 study AQUILA were consistent with the known safety profile of daratumumab.

Systemic administration-related reactions, Local injection-site reactions, and Infections and Infestations were considered as key risks associated with daratumumab SC treatment in the target population. In the AQUILA study:

- Systemic administration-related reactions, applicable to the Daratumumab arm, were reported in 16.6% of participants. Grade 3 or 4 sARRs were reported in 2 (1.0%) participants. Twenty-nine (15.0%) participants reported sARRs with the first administration of daratumumab.
- Local injection-site reactions, applicable to the daratumumab arm, were reported in 27.5% of participants. No Grade 3 or 4 Local injection-site reactions were reported.
- The overall incidence of AEs in the Infections and infestations SOC was higher in the Daratumumab arm (79.8%) compared with the Active Monitoring arm (44.9%), with the majority of infections being Grade 1 and 2. The median duration of any

grade Infections and Infestations was the same (14 days) in both arms. The incidence of Grade 3 or 4 Infections and Infestations was higher in the Daratumumab arm (16.1%) compared with the Active Monitoring arm (4.6%). However, the median duration of Grade 3 or 4 Infections and Infestations was 5.0 days (range 4.0 to 15.0) in the Daratumumab arm (compared with 9.0 days (range 6.0 to 12.0) in the Active Monitoring arm, and the outcome was recovered or resolved in the majority of cases (Daratumumab 94.6%; Active Monitoring 72.7%).

Adverse events (any grade) leading to discontinuation of daratumumab were reported in 11 (5.7%) participants, with 5 (2.6%) participants experiencing Grade 3 or 4 events.

A review of safety data in the AQUILA study identified new ADR terms of Myalgia and Pain in extremity. The new ADRs identified are not considered important risks and do not impact the benefit-risk profile of daratumumab.

Overall, these data demonstrate that daratumumab was well tolerated in participants with high-risk SMM, with clinically manageable side effects.

8.3 Benefit-Risk Conclusion

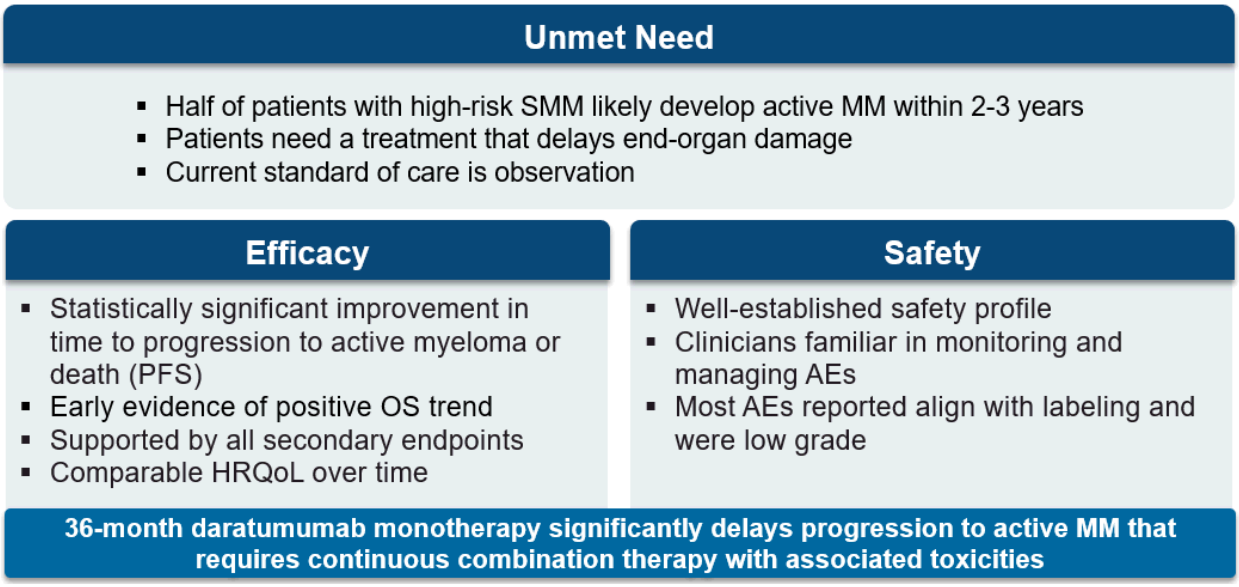
There are currently no approved treatment options for patients with high-risk SMM. The overall approach is to observe without treatment until criteria for active multiple myeloma are met. Patients with high-risk SMM have an approximately 50% risk of developing multiple myeloma within approximately 2 years of diagnosis (Rajkumar 2015). Once patients progress to active multiple myeloma, multi-drug (i.e., 3- to 4-drug) treatment regimens, possibly including ASCT, are used. These treatment regimens are continuous until disease progression at which point subsequent treatment regimens may be required since there is no cure for multiple myeloma. The availability of a proven therapeutic with a tolerable safety profile that delays the progression of high-risk SMM to active multiple myeloma represents an unmet need for this patient population.

Daratumumab demonstrated a statistically significant and clinically meaningful improvement in PFS compared with active monitoring in participants with SMM who are at high risk for developing multiple myeloma. The efficacy of daratumumab was demonstrated in the secondary endpoint of ORR and further supported by other endpoints, including HRQoL, which was comparable over time in the Daratumumab and Active Monitoring arms. Although OS data are not mature, data demonstrated early evidence of a positive OS trend in favor of the Daratumumab arm.

Overall, the safety data from the AQUILA study reflected the known safety profile for daratumumab, with key risks of sARRs, Local injection-site reactions, and Infections and Infestations. Although more AEs occurred in the Daratumumab arm, daratumumab was well tolerated in participants with high-risk SMM, with clinically manageable side effects, well known to clinicians who are familiar with monitoring and managing daratumumab treatment.

The totality of the data, summarized in Figure 32, demonstrate a positive benefit-risk profile for daratumumab SC compared with active monitoring in participants with high-risk SMM, a population with a large unmet medical need.

Figure 32: Daratumumab Benefit-Risk Summary for Patients with High-risk SMM (Study AQUILA)



Key: AE=adverse event; HRQoL=health-related quality of life; MM=multiple myeloma; OS=overall survival; PFS=progression-free survival; SMM=smoldering multiple myeloma

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