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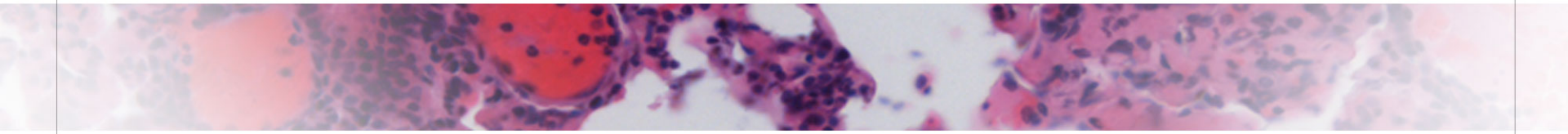

Daratumumab Monotherapy For Patients With Intermediate or High-risk Smoldering Multiple Myeloma (SMM): CENTAURUS, a Randomized, Open-label, Multicenter Phase 2 Study*

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*ClinicalTrials.gov Identifier: NCT02316106

Background: SMM

- Multiple myeloma evolves from a premalignant asymptomatic precursor stage[1,2]
- No uniform accepted definition of high-risk or intermediate-risk SMM[1]

		% Progressing to Symptomatic MM		
Mayo Clinic[3]	**3 Criteria:**	**1/3 Criteria (Low risk)**	**2/3 Criteria (Intermediate risk)**	**3/3 Criteria (High risk)**
	1. M-protein ≥3 g/dL 2. ≥10% clonal bone marrow plasma cells 3. Free light-chain <0.125 or >8	**25%**	**51%**	**76%**
PETHEMA[4]	**2 Criteria:**	**0/2 Criteria (Low risk)**	**1/2 Criteria (Intermediate risk)**	**2/2 Criteria (High risk)**
	1. ≥95% abnormal plasma cells 2. Low uninvolved serum immunoglobulins	**4%**	**46%**	**72%**

1. Rajkumar SV, et al. *Blood*. 2015;125(20):3069-3075.
2. Landgren O, et al. *Blood*. 2009;1139(22):5412-5417.
3. Dispenzieri A, et al. *Blood*. 2008;111(2):785-789.
4. Pérez-Persona E, et al. *Blood*. 2007;110(7):2586-2592.

SMM, smoldering multiple myeloma; MM, multiple myeloma.

Current Management of SMM

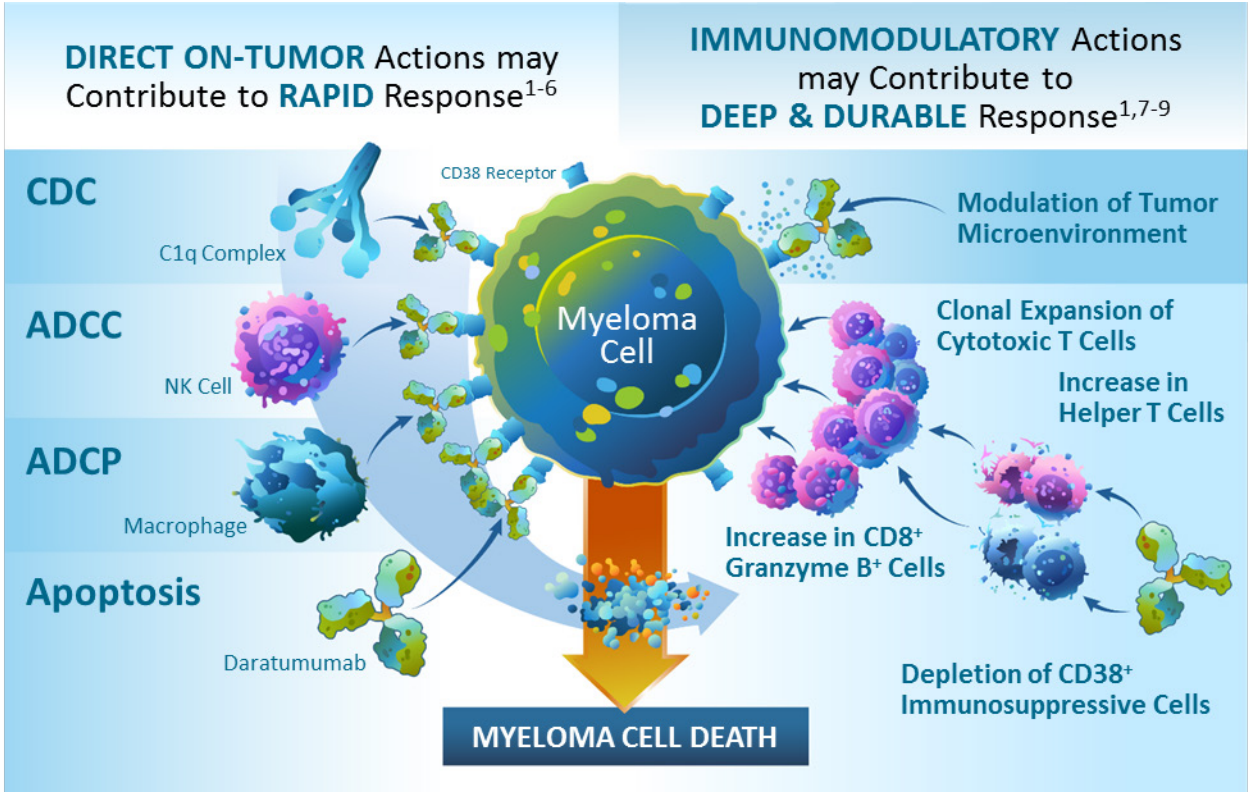
- Current guidelines recommend monitoring SMM patients every 3-6 months for active MM before initiating treatment[1]
- Most high- or intermediate-risk SMM patients **do** progress to MM[2,3]
- Phase 3 study (QuiRedex)[4] in SMM showed a survival benefit with Rd[a] before published **SLiM-CRAB** criteria (≥**S**ixty% marrow PCs, **Li**ght chain ratio ≥100, >1 focal **M**RI lesion + **CRAB**)
- Intercepting high/intermediate-risk SMM may yield clinical benefit

This phase 2 study was designed to inform the phase 3 registration study

1. National Comprehensive Cancer Network. https://www.nccn.org/patients/guidelines/myeloma/files/assets/common/downloads/files/myeloma.pdf. Accessed October 20, 2017.
2. Dispenzieri A, et al. *Blood*. 2008;111(2):785-789.
3. Pérez-Persona E, et al. *Blood*. 2007;110(7):2586-2592.
4. Mateos MV, et al. *New Engl J Med*. 2013;369:438-447.

[a]Rd was lenalidomide 25 mg d1-21 + dexamethasone 20 mg d1-4 & 12-15, followed by maintenance therapy (lenalidomide 10 mg per day on days 1–21 of each 28-day cycle) up to 2 years; MRI, magnetic resonance imaging.

Daratumumab Acts Through Multiple Mechanisms



1. DARZALEX [US PI], Horsham, PA: Janssen Biotech, Inc.; 2017. **2.** Liszewski MK, et al. *Adv Immunol*. 1996;61:201-283. **3.** Debets JM, et al. *J Immunol*. 1988;141(4):1197-1201. **4**. Overdijk MB, et al. *mABs*. 2015;7(2):311-321. **5.** Lokhorst HM, et al. *NEJM*. 2015;373(13):1207-1219. **6.** Plesner T, et al. Oral presentation at: ASH; December 8-11, 2012; Atlanta, GA. **7**. Krejcik J, et al. *Blood*. 2016;128(3):384-394. **8**. Adams H, et al. Poster presented at: ASH; December 3-6, 2016; San Diego, CA. **9**. Chiu C, et al. Poster presented at: ASH; December 3-6, 2016; San Diego, CA.

CDC, complement-dependent cytotoxicity; ADCC, antibody-dependent cell-mediated cytotoxicity; ADCP, antibody-dependent cellular phagocytosis; NK, natural killer.

CENTAURUS: Eligibility Criteria

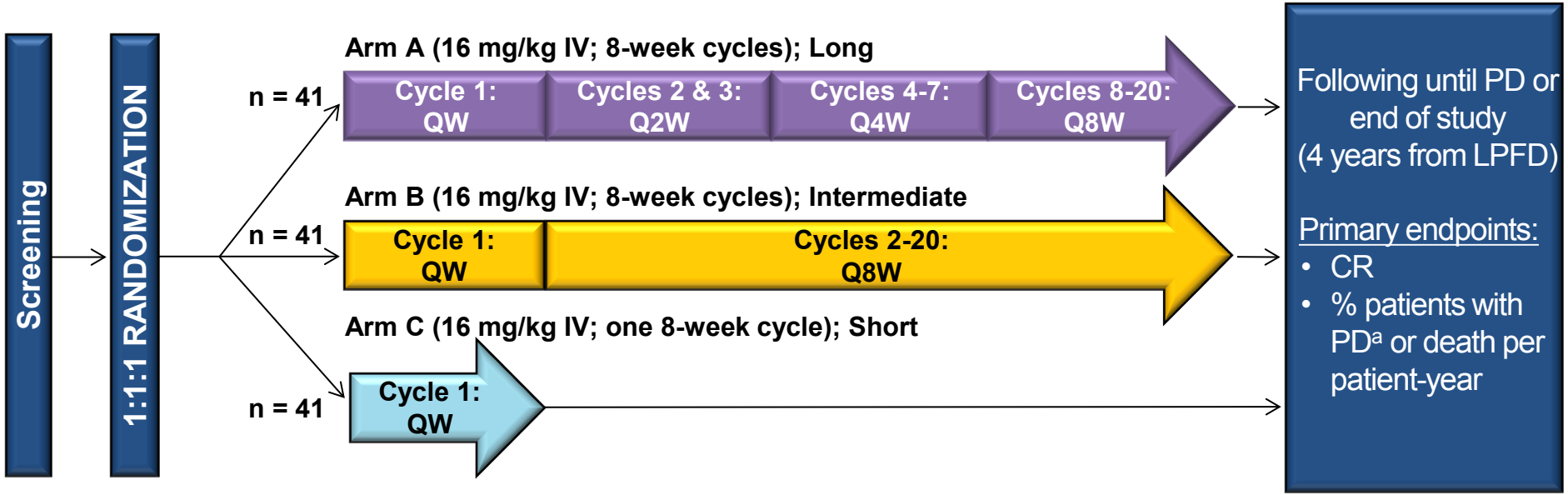
- Key inclusion criteria
  - Diagnosis of SMM <5 years
  - Bone marrow plasma cells ≥10% to <60% and ≥1 of the following:
    - Serum M-protein ≥3 g/dL (IgA ≥2 g/dL)
    - Urine M-protein >500 mg/24 hours
    - Abnormal free light chain ratio (<0.126 or >8) and serum M-protein <3 g/dL but ≥1 g/dL
    - Absolute involved serum free light chain ≥100 mg/L with an abnormal free light chain ratio (<0.126 or >8, but not ≤0.01 or ≥100)
- Key exclusion criteria
  - Presence of ≥1 SLiM-CRAB myeloma-defining event[a] (as defined in the 2014 IMWG criteria[1])
  - Clinically relevant organ dysfunction
  - Primary systemic AL amyloidosis

[a]Defined as ≥60% bone marrow plasma cells, free light chain involved/uninvolved ratio ≥100, >1 focal bone lesions on MRI, calcium elevation, renal insufficiency by creatinine clearance, anemia, or bone disease due to lytic bone lesions.

IMWG, International Myeloma Working Group; AL amyloidosis, light-chain amyloidosis.

1. Rajkumar SV, et al. *Lancet Oncol.* 2014;15:e538-e548.

CENTAURUS: Study Design



[a]As defined by 2014 IMWG criteria for SMM.

- CR rate: proportion of subjects who achieve CR in each arm
  - First assessed 6 months after last patient randomized
- PD/death rate: ratio of subjects with an event (PD or death) to the total follow-up for all patients
  - Assessed 12 months after last patient randomized
  - **Disease progression to MM assessed according to IMWG guidelines[1]**
- Pre-infusion medication: methylprednisolone 60-100 mg, diphenhydramine 25-50 mg, acetaminophen 650-1,000 mg, montelukast 10 mg (optional)

IV, intravenous; QW, once weekly; Q2W, every 2 weeks; Q4W, every 4 weeks; Q8W, every 8 weeks; PD, progressive disease; LPFD, last patient, first dose; CR, complete response.

1. Rajkumar SV, et al. *Lancet Oncol.* 2014;15:e538-e548.

CENTAURUS: Baseline Demographics

	Arm A Long (n = 41)	Arm B Intermediate (n = 41)	Arm C Short (n = 41)
Median (range) age, years	65 (34-79)	62 (31-81)	59 (39-78)
Female, n (%)	24 (59)	24 (59)	20 (49)
Race, n (%)			
White	35 (85)	37 (90)	35 (85)
Black or African American	2 (5)	1 (2)	2 (5)
Asian	2 (5)	1 (2)	1 (2)
Other	2 (5)	2 (5)	3 (7)
ECOG score, n (%)			
0	32 (78)	34 (83)	35 (85)
1	9 (22)	7 (17)	6 (15)

Baseline demographics are balanced across arms

ECOG, Eastern Cooperative Oncology Group.

CENTAURUS: Baseline Disease Characteristics

	Arm A Long (n = 41)	Arm B Intermediate (n = 41)	Arm C Short (n = 41)
Risk factors at screening,[a] n (%)			
<2	8 (20)	8 (20)	7 (17)
≥2	33 (81)	33 (81)	34 (83)
Type of myeloma, n (%)			
IgG	33 (81)	30 (73)	27 (66)
IgA	6 (15)	7 (17)	9 (22)
Others	2 (5)	4 (10)	5 (12)
% plasma cells in bone marrow, n (%)			
≥10 to <20%	18 (44)	17 (42)	21 (51)
≥20 to <40%	15 (37)	17 (42)	13 (32)
≥40 to <60%	8 (20)	7 (17)	7 (17)
Median (range) time from SMM diagnosis to randomization, months	6.47 (0.4-46.2)	5.52 (0.7-46.7)	7.43 (1.0-56.0)

Baseline disease characteristics are balanced across arms

[a]Risk factors include abnormal free light chain ratio (<0.126 or >8), serum M-protein ≥3 g/dL, IgA subtype, urine M-protein >500 mg/24 hrs, and immunoparesis (at least 1 uninvolved immunoglobulin [IgG, IgA, IgM] decreased more than 25% below the lower limit of normal).

CENTAURUS: Patient Disposition

- Prespecified primary analysis: 12 months after randomization of the last patient
- Median follow up: 15.8 (range: 0-23.9) months

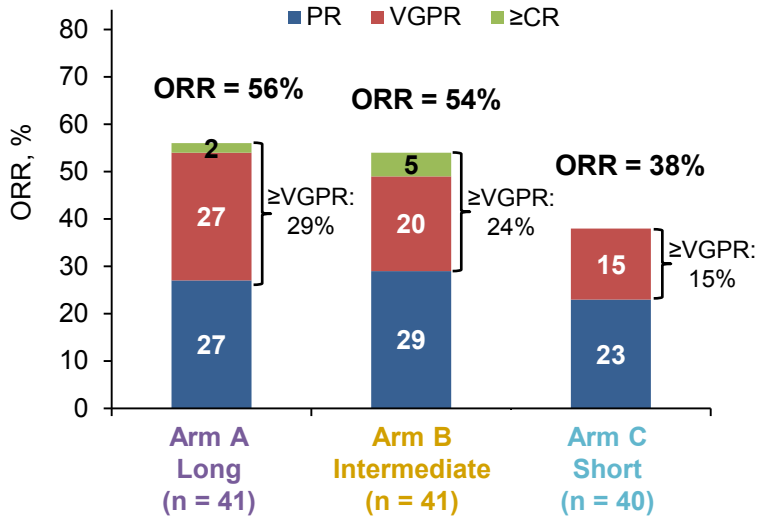
	Arm A Long (n = 41)	Arm B Intermediate (n = 41)	Arm C Short (n = 41)
Median (range) duration of treatment, months	14.9 (1.0-22.1)	14.8 (1.9-22.1)	1.6 (0-1.9)
Discontinued treatment, n (%)	5 (12)	4 (10)	2 (5)
Adverse event[a]	2 (5)	1 (2)	2 (5)
Progressive disease	2 (5)	2 (5)	0 (0)
Refusal of further treatment	0 (0)	1 (2)	0 (0)
Withdrawal of consent	1 (2)	0 (0)	0 (0)

[a]Adverse events included pneumonia, thrombocytopenia, balance disorder, unstable angina, and hypomania (n = 1 each).

Low rates of discontinuation

CENTAURUS: Efficacy

ORR



Co-primary endpoint of CR (>15%) was not met

PD/Death Rate[a]

	Arm A Long (n = 41)	Arm B Intermediate (n = 41)	Arm C Short (n = 41)
P value[b]	<0.0001	<0.0001	0.0213

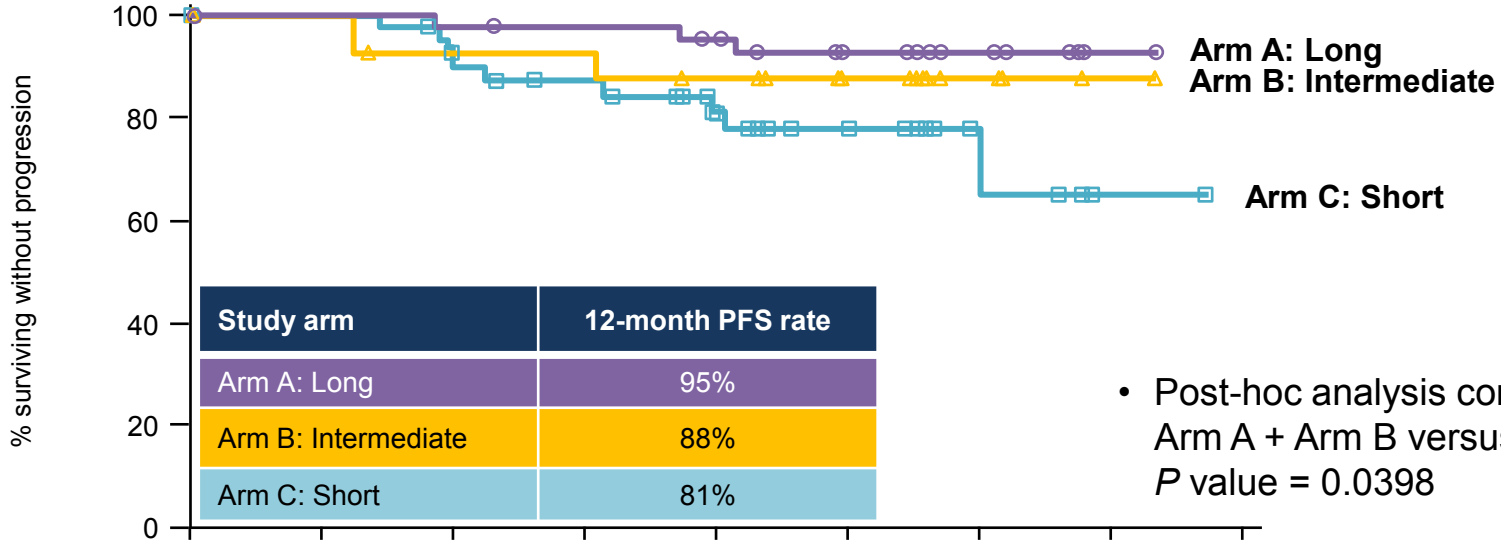
[a]PD/death rate is the ratio of the patients who progressed or died divided by the total PFS for all patients.
[b]*P* value for testing the null hypothesis that the PD/death rate ≥0.346/patient-year (corresponding to median PFS ≥24 months).

Co-primary endpoint of median PFS ≥24 months was met

Single-agent daratumumab shows activity in SMM

ORR, overall response rate; PR, partial response; VGPR, very good partial response; PFS, progression-free survival.

CENTAURUS: PFS (Based on SLiM-CRAB)

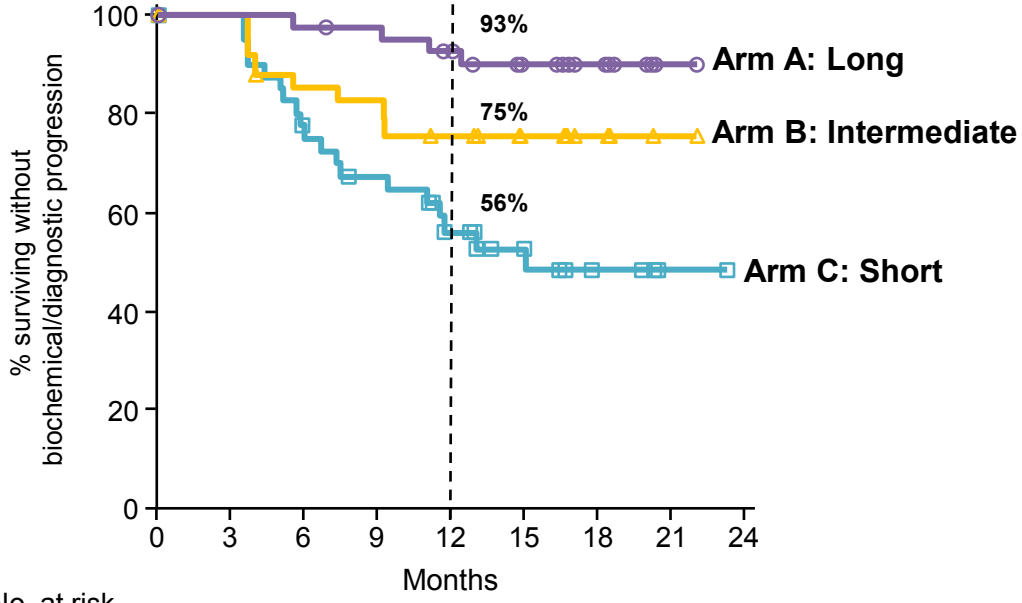


Study arm	12-month PFS rate
Arm A: Long	95%
Arm B: Intermediate	88%
Arm C: Short	81%

- Post-hoc analysis comparing Arm A + Arm B versus Arm C: *P* value = 0.0398

Fewer patients progressed on long and intermediate arms

CENTAURUS: PFS (Biochemical or Diagnostic)



No. at risk									
Long	41	41	40	39	36	21	12	1	0
Intermediate	41	41	34	33	28	16	7	1	0
Short	41	40	30	25	18	13	5	1	0

- Biochemical/diagnostic PFS is defined as the earlier of time to biochemical or diagnostic progression or death
  - Biochemical progression: measurable disease increase from nadir by ≥25% in 2 subsequent assessments per IMWG[1]
  - Diagnostic progression: SLiM-CRAB criteria
- Post-hoc analysis comparing Arm A + Arm B versus Arm C: *P* value = 0.0002

Supports the long dosing schedule for the phase 3 study

1. Rajkumar SV, et al. *Lancet Oncol.* 2014;15:e538-e548.

CENTAURUS: Safety

	Arm A Long (n = 41)	Arm B Intermediate (n = 41)	Arm C Short (n = 40)
Median (range) duration of treatment, months	14.9 (1.0-22.1)	14.8 (1.9-22.1)	1.6 (0-1.9)
Grade 3/4 TEAE, n (%)	15 (37)	4 (10)	6 (15)
Most common (>25%) any-grade TEAE, n (%)			
Fatigue	16 (39)	25 (61)	9 (23)
Cough	14 (34)	13 (32)	11 (28)
Upper respiratory tract infection	11 (27)	11 (27)	4 (10)
Insomnia	11 (27)	13 (32)	5 (13)
Headache	11 (27)	8 (20)	13 (33)
Most common (>1 pt) grade 3/4 TEAE, n (%)			
Hypertension	2 (5)	1 (2)	1 (3)
Hyperglycemia	1 (2)	2 (5)	0 (0)
Serious adverse events, n (%)	10 (24)	1 (2)	4 (10)
Within the first 8 weeks	5 (12)	0 (0)	4 (10)
Discontinued treatment due to TEAE, n (%)	2 (5)	1 (2)	2 (5)
Related to daratumumab	1 (2)[a]	0 (0)	1 (3)[b]
Any-grade IRR rate, n (%)	23 (56)	17 (42)	22 (55)

- Hematologic TEAE rate was <10% across all arms
- Rates of grade 3/4 infection were ≤5% across all arms
- 1 death due to disease progression in Arm C
- 3 SPMs (Arm A: breast cancer, melanoma; Arm B: melanoma)

Findings are consistent with other single-agent daratumumab studies

IRR, infusion-related reaction; TEAE, treatment-emergent adverse event; SPM, secondary primary malignancy.
[a]Thrombocytopenia; [b]Unstable angina.

Conclusions

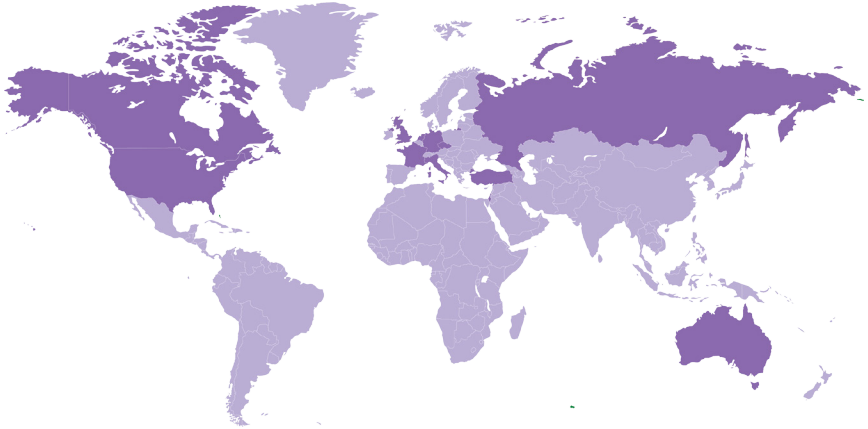
- Daratumumab has single-agent activity in intermediate- and high-risk SMM
- Daratumumab monotherapy has a favorable safety profile in intermediate- and high-risk SMM
- Efficacy and safety data support Arm A (long) dosing compared to Arm B (intermediate) and Arm C (short)

Findings are the basis for the ongoing AQUILA phase 3 study with single-agent daratumumab in SMM

Acknowledgments

CENTAURUS

11 countries



- Patients who participated in these studies
- Staff members at the study sites
- Data and safety monitoring committee
- Staff members involved in data collection and analyses (Pamela Clemens and Kirsten Lantz)

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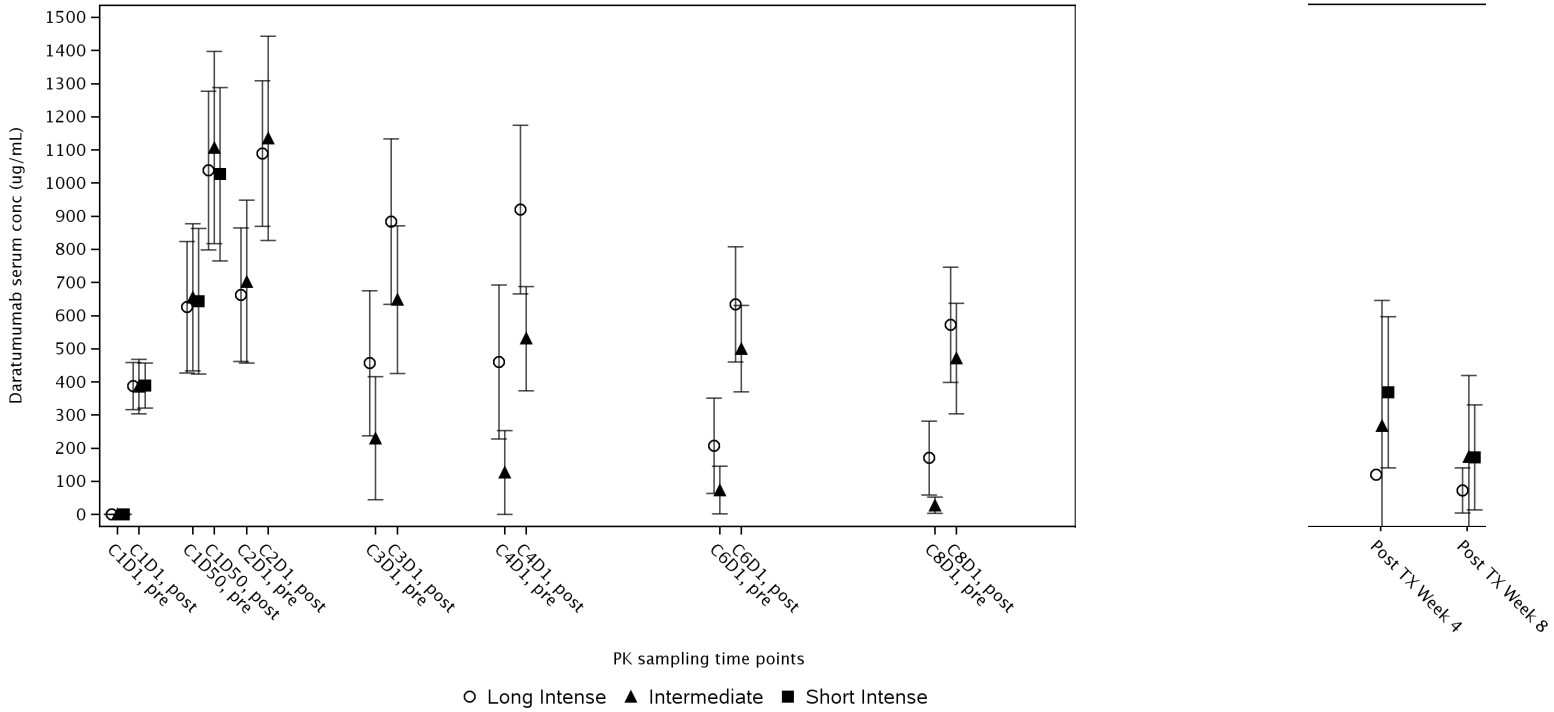
Backup

Mean Serum Peak and Trough Concentrations



Error bars are mean ± standard deviation.
Note: Predose samples with a time of collection after the start of infusion will be excluded from summary statistics. Postdose samples with a time of collection more than 20 minutes before the end of infusion or before the start of infusion will be excluded from summary statistics.
C1D50 = Cycle 1 Day 50, the 8th weekly daratumumab administration.

Progression Events

- >1 focal lesion on MRI studies (n = 4)
- Lytic bone disease (n = 1)
- Involved/uninvolved serum free light chain ratio ≥100 (n = 12)
- Total PD events (n = 17)
- Note: no fractures related to MM lytic lesions were reported