Phase 2 Study of Daratumumab (DARA) in Patients with ≥3 Lines of Prior Therapy or Double Refractory Multiple Myeloma: 54767414MMY2002 (Sirius)*

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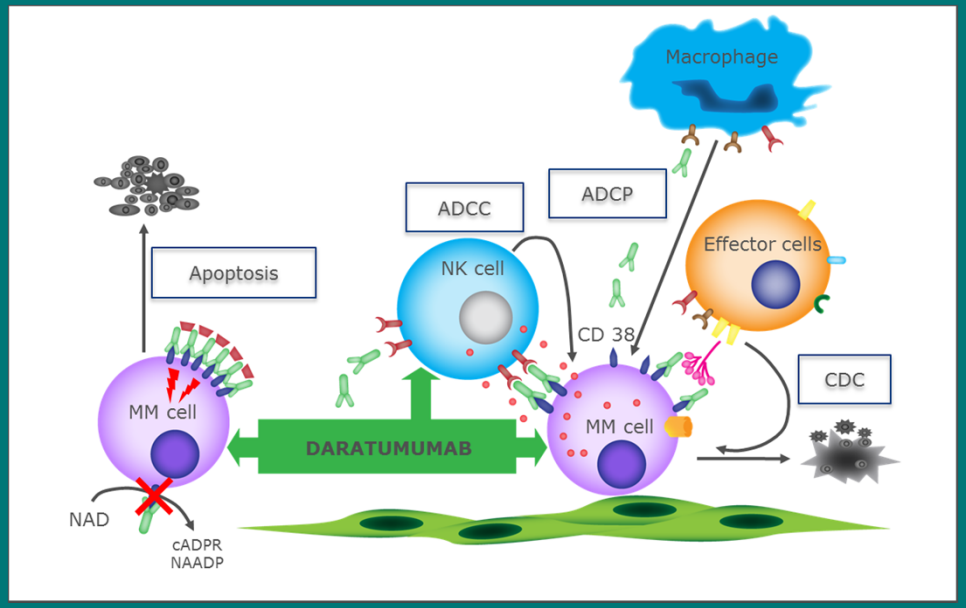
Background

- CD38 is highly and ubiquitously expressed on myeloma cells and at low levels on normal lymphoid and myeloid cells, making it a promising therapeutic target in multiple myeloma (MM)[1,2]
- Daratumumab (DARA) is a human monoclonal antibody (mAb) that binds to CD38-expressing malignant cells, inducing cell death through multiple pathways including CDC,[3] ADCC,[3] ADCP[4] and apoptosis[5]

DARA Mechanism of Action



Adapted from Laubach JP, et al. *Expert Opin Investig Drugs*. 2014;23:445-52.

CDC, complement-dependent cytotoxicity; ADCC, antibody-dependent cell-mediated cytotoxicity; ADCP, antibody-dependent cellular phagocytosis; NK, natural killer cell; NAD, nicotinamide adenine dinucleotide; cADPR, cyclic adenosine diphosphate-ribose; NAADP, nicotinic acid adenine dinucleotide phosphate.

1. Lin P, et al. *Am J Clin Pathol*. 2004;121:482-88.
2. Laubach JP, et al. *Expert Opin Investig Drugs*. 2014;23:445-52.
3. de Weers M, et al. *J Immunol*. 2011;186:1840-48.
4. Overdijk MB, et al. *MAbs*. 2015;7:311-21.
5. Jansen JH, et al. *Blood*.2012; 120. 2974.

GEN501: First in Human Study

- During ASCO 2014, data from a first-in-human, Phase 1/2 study were presented that demonstrated single-agent DARA activity in relapsed/refractory MM patients[1]
  - No maximum tolerated dose was reached (up to 24 mg/kg DARA)
  - Overall response rate (ORR) was 35% in the 16 mg/kg DARA cohort
- FDA Breakthrough Therapy designation in May 2013

Change in Paraprotein From Baseline

1. Lokhorst HM, et al. *J Clin Oncol*. 2014;32(suppl):5s. Abstract 8513.

MMY2002 SIRIUS: Objectives and Eligibility

Primary objective

- Overall response rate of DARA monotherapy in patients with MM who had received ≥3 prior lines of therapy or had disease refractory to both a proteasome inhibitor (PI) and an immunomodulatory drug (IMiD)
- Responses assessed by an independent review committee (IRC)

Secondary objectives

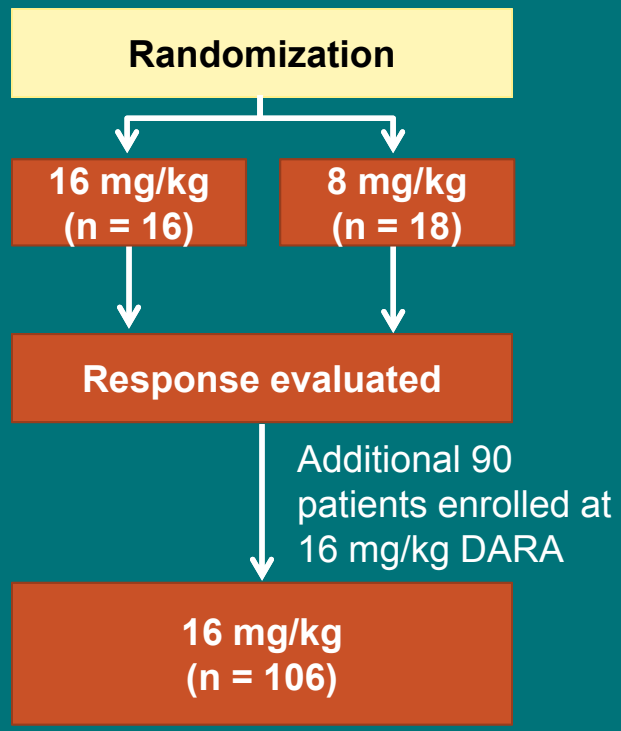
- Progression-free survival (PFS), overall survival (OS), duration of and time to response, and clinical benefit rate (ORR + minimal response [MR])
- Safety

Eligibility

- Documented MM with disease progression on the most recent treatment regimen
- Received ≥3 prior lines of therapy including a PI and an IMiD, or refractory to their most recent PI and IMiD irrespective of number of prior lines of therapy
- Eastern Cooperative Oncology Group (ECOG) performance status of ≤2
- Absolute neutrophil count >1 x 10^9/L
- Hemoglobin >7.5 g/dL
- Platelet count ≥50 x 10^9/L
- Creatinine clearance >20 mL/min/1.73 m^2

Study Design

- Open-label, international, multicenter study of Simon-2-stage design
- Initially, patients randomized 1:1 to receive DARA
  - 8 mg/kg every 4 weeks (Q4W) or
  - 16 mg/kg every week (QW) for 8 weeks, every 2 weeks (Q2W) for 16 weeks, then Q4W thereafter
- 16 mg/kg DARA was established as the recommended dose for further study
- Results are reported for all patients who were treated with 16 mg/kg DARA (n = 106)



Patient Disposition

- Patients were enrolled between October 2013 and May 2014
- Data cutoff January 9th 2015
- Of 106 patients treated with 16 mg/kg DARA, 16 (15%) patients remained on study at data cutoff
- Discontinuations predominantly due to disease progression
  - 82 (77%) due to progressive disease
  - 3 (3%) withdrew consent due to symptoms related to disease progression
  - 5 (5%) due to adverse events (not related to DARA)
    - General physical health deterioration (n = 2)
    - H1N1 influenza (n =1)
    - Hypercalcemia (n =1)
    - Spinal cord compression (n =1)

Baseline Characteristics

Demographics (n = 106)			
Median (range) age, y	63.5 (31–84)	Renal function (CrCl), n (%)	
Age ≥75 y, n (%)	12 (11)	≥60 mL/min	60 (57)
		<60 mL/min	46 (43)
ISS staging, n (%)		ECOG score	
I	26 (25)	0	29 (27)
II	40 (38)	1	69 (65)
III	40 (38)	2	8 (8)
Median (range) time since diagnosis, y	4.8 (1-24)	High risk cytogenetics, n (%)	20 (19)
Prior therapies (n = 106)			
Median (range) number of prior therapies	5 (2–14)	>3 lines of prior therapy, n (%)	87 (82)
Prior chemotherapy, n (%)	106 (100)	Prior IMiD, n (%)	106 (100)
Alkylating agents	106 (100)	LEN	105 (99)
Anthracyclines	55 (52)	POM	67 (63)
		THAL	47 (44)
Prior ASCT, n (%)	85 (80)	Prior PI, n (%)	106 (100)
		BORT	105 (99)
		CARF	53 (50)

CrCl, creatinine clearance; ISS, International Staging System; LEN, lenalidomide; POM, pomalidomide; THAL, thalidomide; ASCT, autologous stem cell transplantation; BORT, bortezomib; CARF, carfilzomib.

Baseline Refractory Status

Refractory to, n (%)	n = 106
Last prior therapy	103 (97)
PI and IMiD	101 (95)
BORT	95 (90)
CARF	51 (48)
LEN	93 (88)
POM	67 (63)
Alkylating agent	82 (77)
BORT+LEN	87 (82)
BORT+LEN+CARF	42 (40)
BORT+LEN+POM	57 (54)
BORT+LEN+CARF+POM	33 (31)
BORT+LEN+CARF+POM+THAL	12 (11)

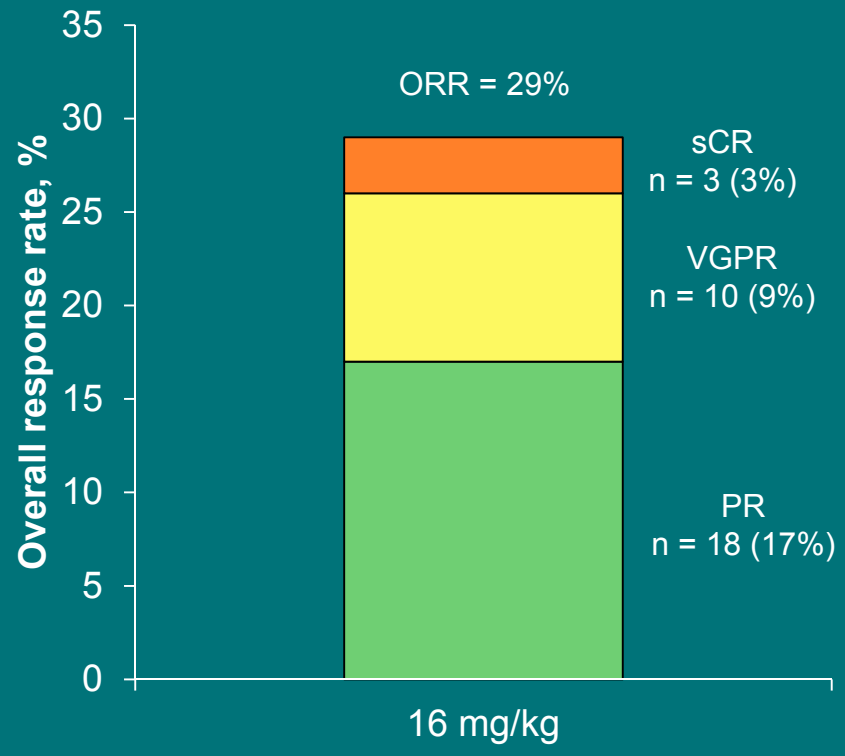
- Patients were heavily pretreated, and most patients were refractory to multiple lines of PI and IMiD treatment
  - 97% were refractory to their last line of therapy
  - 77% were refractory to alkylating agents
  - 95% were double refractory
  - 66% were refractory to 3 of 4 therapies (BORT, LEN, CARF, and POM)
  - 63% were refractory to POM
  - 48% were refractory to CARF

Change in Paraprotein From Baseline

The majority of patients had reductions in paraprotein from baseline

- 40 patients (38%) had reductions >50%
- 17 patients (16%) had reductions >90%

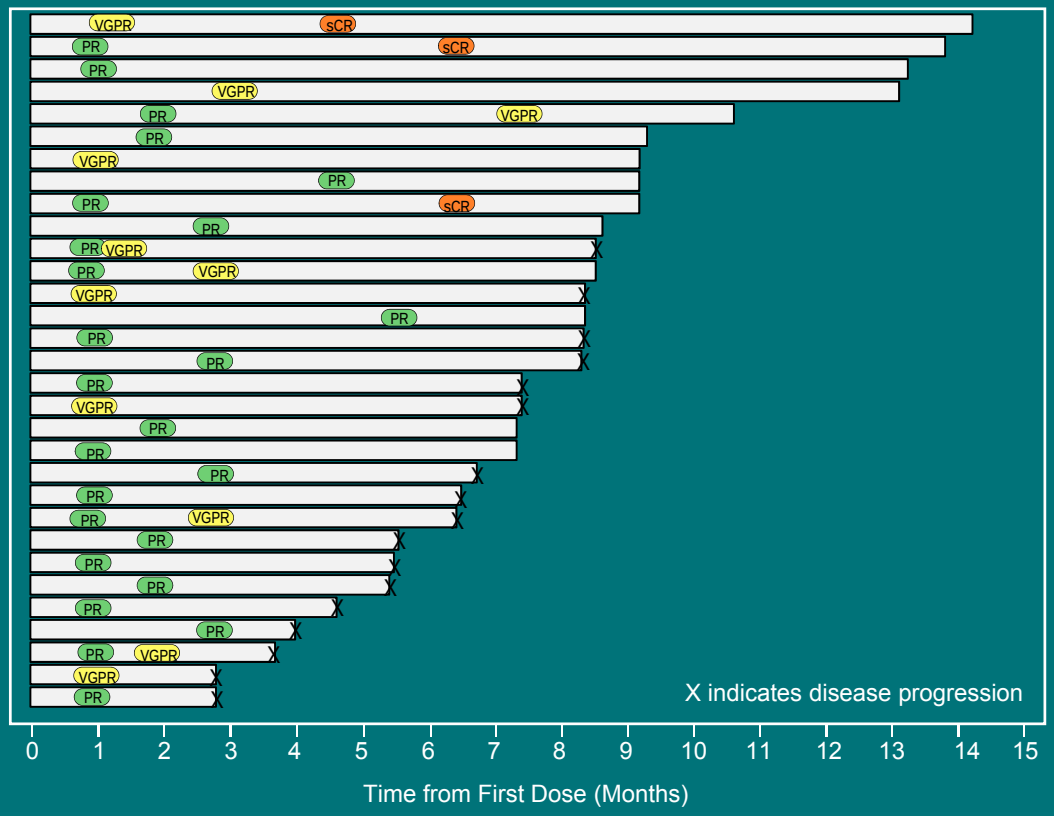
Overall Response Rate



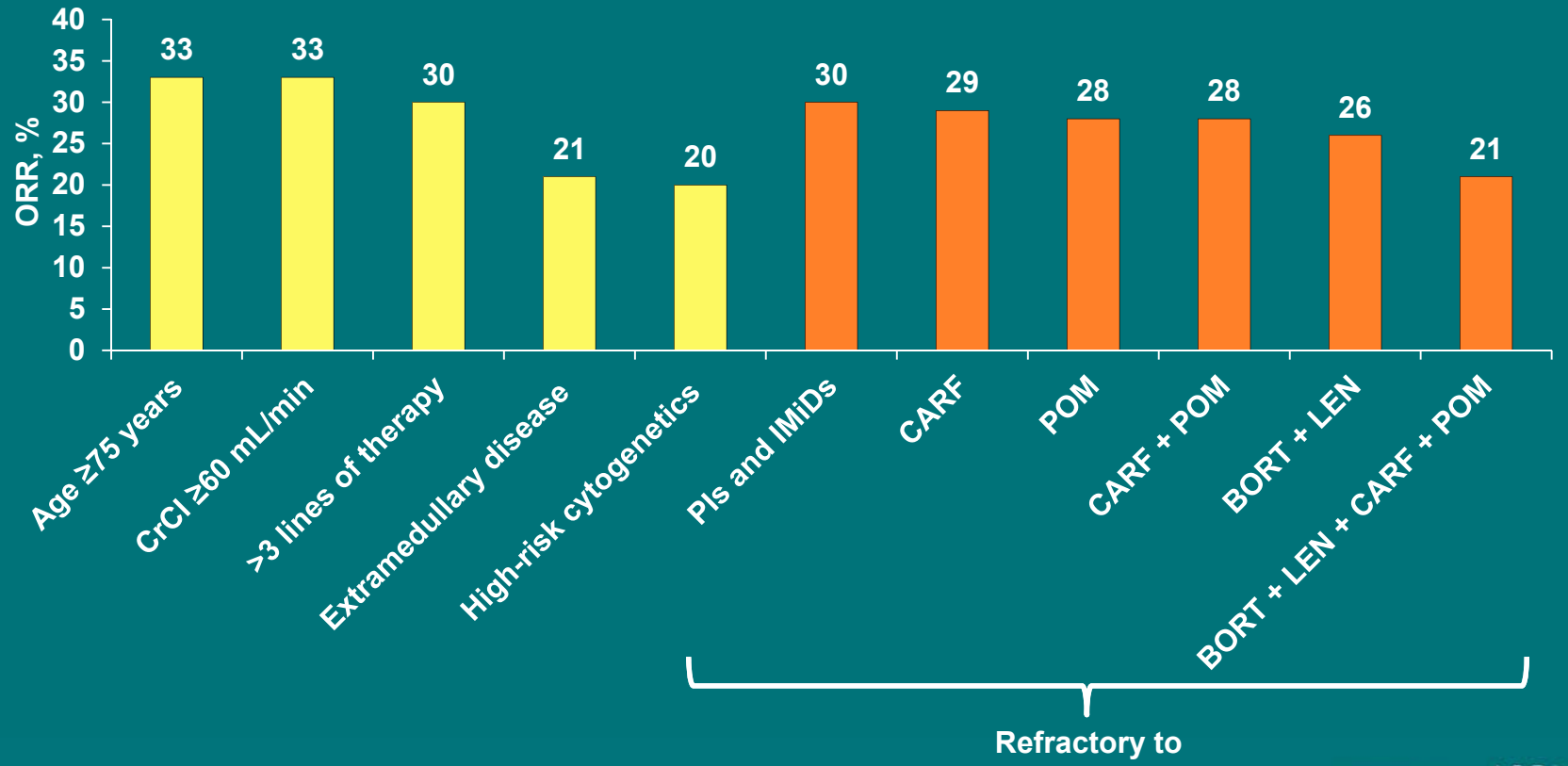
- **ORR was 29% (95% CI, 21–39) in patients receiving 16 mg/kg DARA**
- Stringent complete response (sCR) in 3% of patients (95% CI, 0.6–8.0)
- VGPR or better achieved in 12% (95% CI, 7–20) of patients
- Clinical benefit rate (ORR + MR) was 34% (95% CI, 25–44)

Depth and Duration of Response

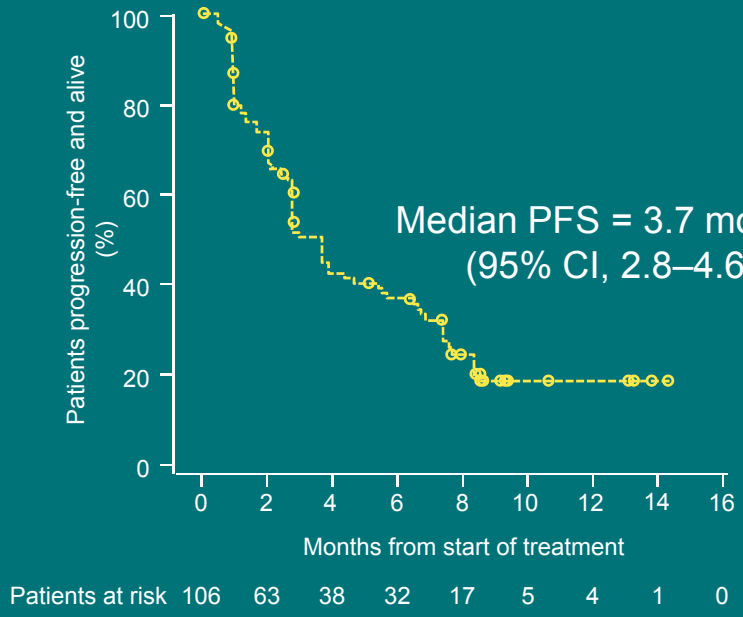
- Median follow-up of 9.3 months
- Median time to response among responders was 1 month
- Median duration of response was 7.4 months (95% CI, 5.5–not estimable [NE])
- Initial responses deepened with continued DARA treatment in many patients

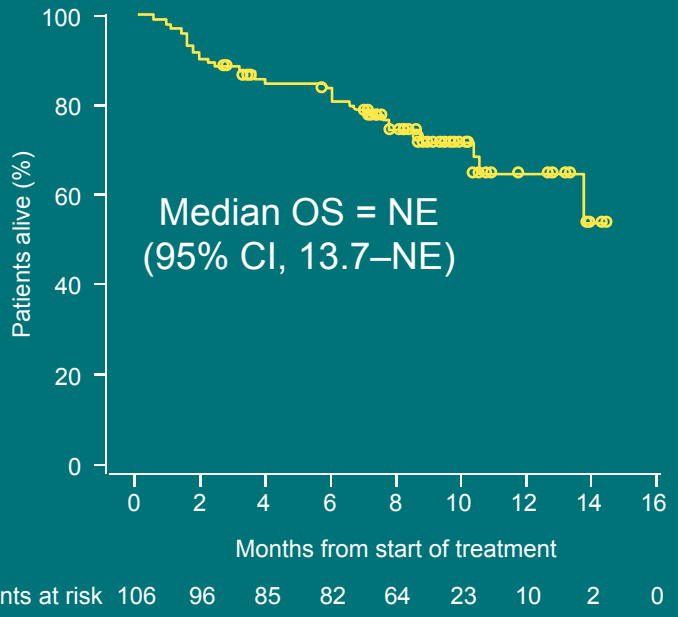


ORR by Subgroup



Progression-free and Overall Survival





- 29 of 31 responders are still alive
- The 1-year survival rate was 65% (95% CI, 51.2–75.5)

Treatment-emergent AEs >20%

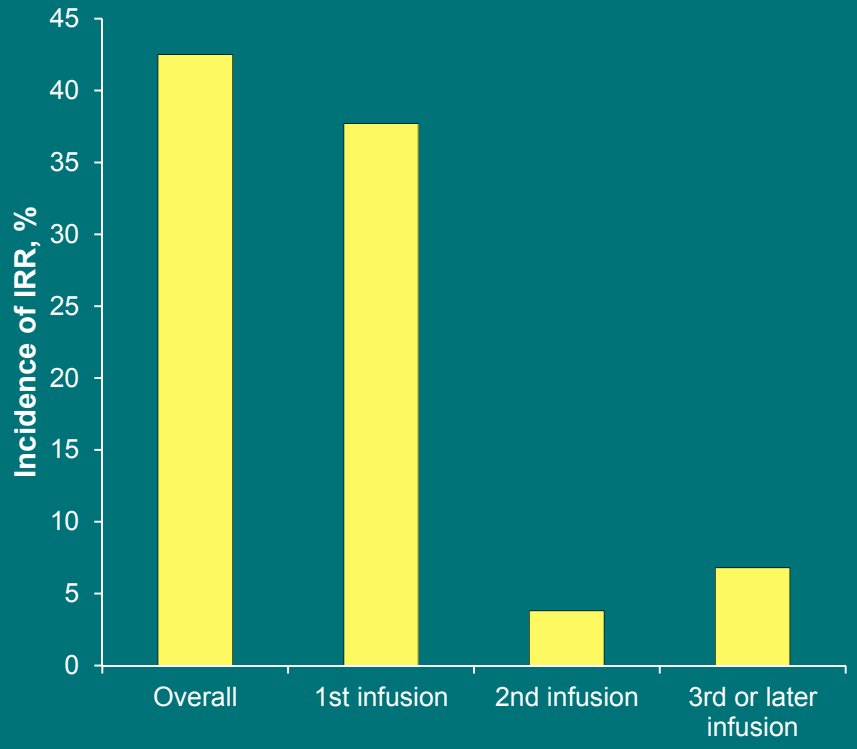
Term	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)
Fatigue	42 (40)	3 (3)	-
Anemia	35 (33)	25 (24)	-
Nausea	31 (29)	-	-
Thrombocytopenia	27 (26)	18 (17)	8 (8)
Neutropenia	24 (23)	12 (11)	3 (3)
Back pain	23 (22)	3 (3)	-
Cough	22 (21)	-	-

- Grade 3 or higher anemia and thrombocytopenia occurred more frequently in nonresponders (32% and 24%, respectively) than responders (3% and 7%, respectively)
- Grade 3 or higher neutropenia rates were similar in nonresponders (12%) and responders (13%)

- Serious treatment-emergent AEs (TEAEs) in 32 (30%) patients and 24 (23%) had Grade 3/4 serious TEAEs
- No discontinuations due to DARA-related AEs
- No febrile neutropenia reported
- Few required additional supportive care
  - Red blood cell transfusion (38%)
  - Platelet transfusion (13%)
  - Granulocyte colony stimulating factor (8%)

Infusion-related Reactions (IRRs)

- Occurred in 43% of patients
- Predominantly Grade 1 or 2
  - Grade 3: 5%; no Grade 4
- >90% of IRRs occurred during the first infusion
- 7% of patients had an IRR at >1 infusion
- Most common IRRs included nasal congestion (12%); throat irritation (7%); cough, dyspnea, chills, and vomiting (6% each)
- No patients discontinued treatment due to IRRs



Conclusions

- DARA is a fully human mAb with remarkable **single-agent** activity in heavily pretreated and refractory MM patients who exhausted other therapeutic options
- Efficacy was consistent across all subgroups
- Responses were rapid, durable, and deepened over time
  - 3 sCRs
  - 10 VGPR
  - Depth of response may translate to prolonged OS
- DARA was well tolerated
  - No patients discontinued treatment due to AEs related to DARA
- IRRs predominantly occurred during the first infusion, were usually Grade 1 or 2, and were manageable
- DARA represents a new standard of care in this setting

Acknowledgments

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