Clinical Efficacy of Daratumumab Monotherapy in Patients With Heavily Pretreated Relapsed or Refractory Multiple Myeloma

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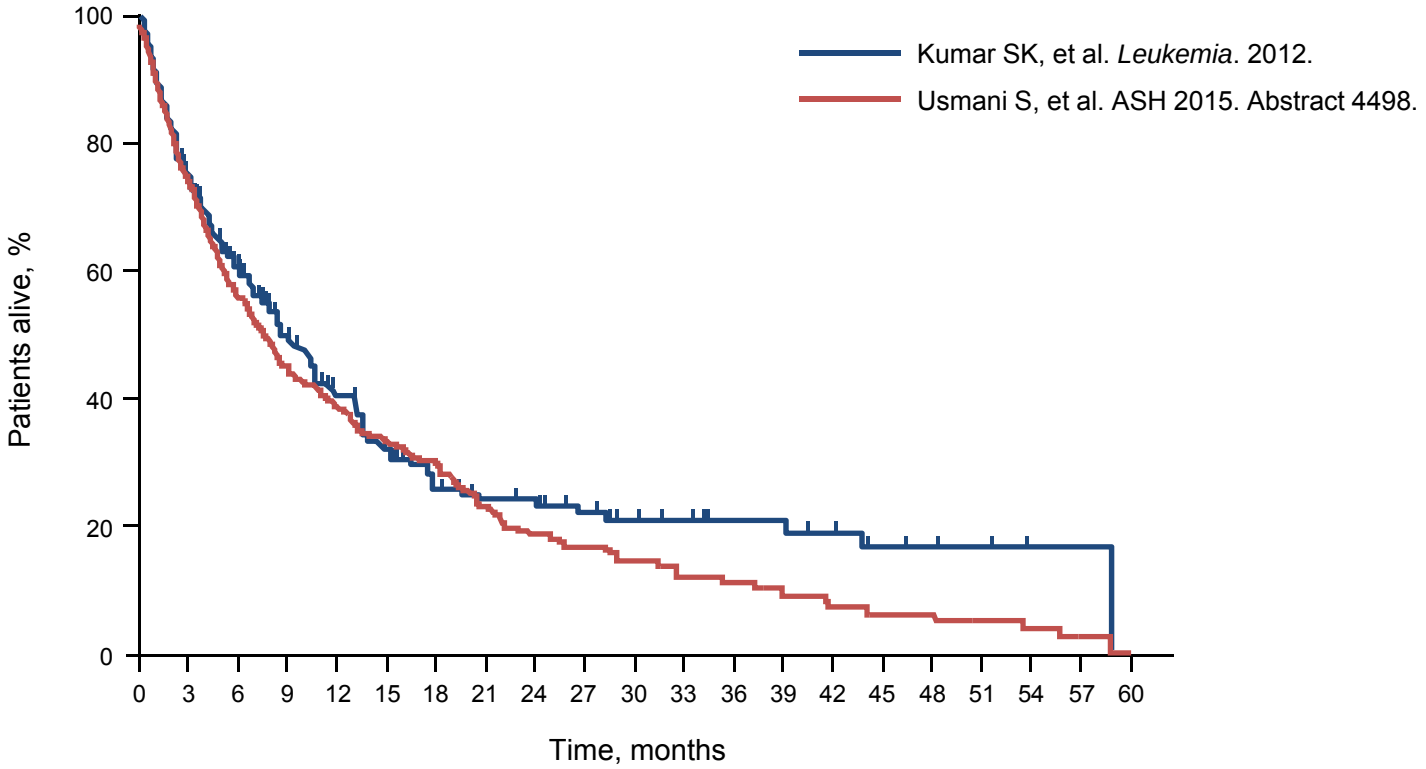
Relapsed and Refractory MM

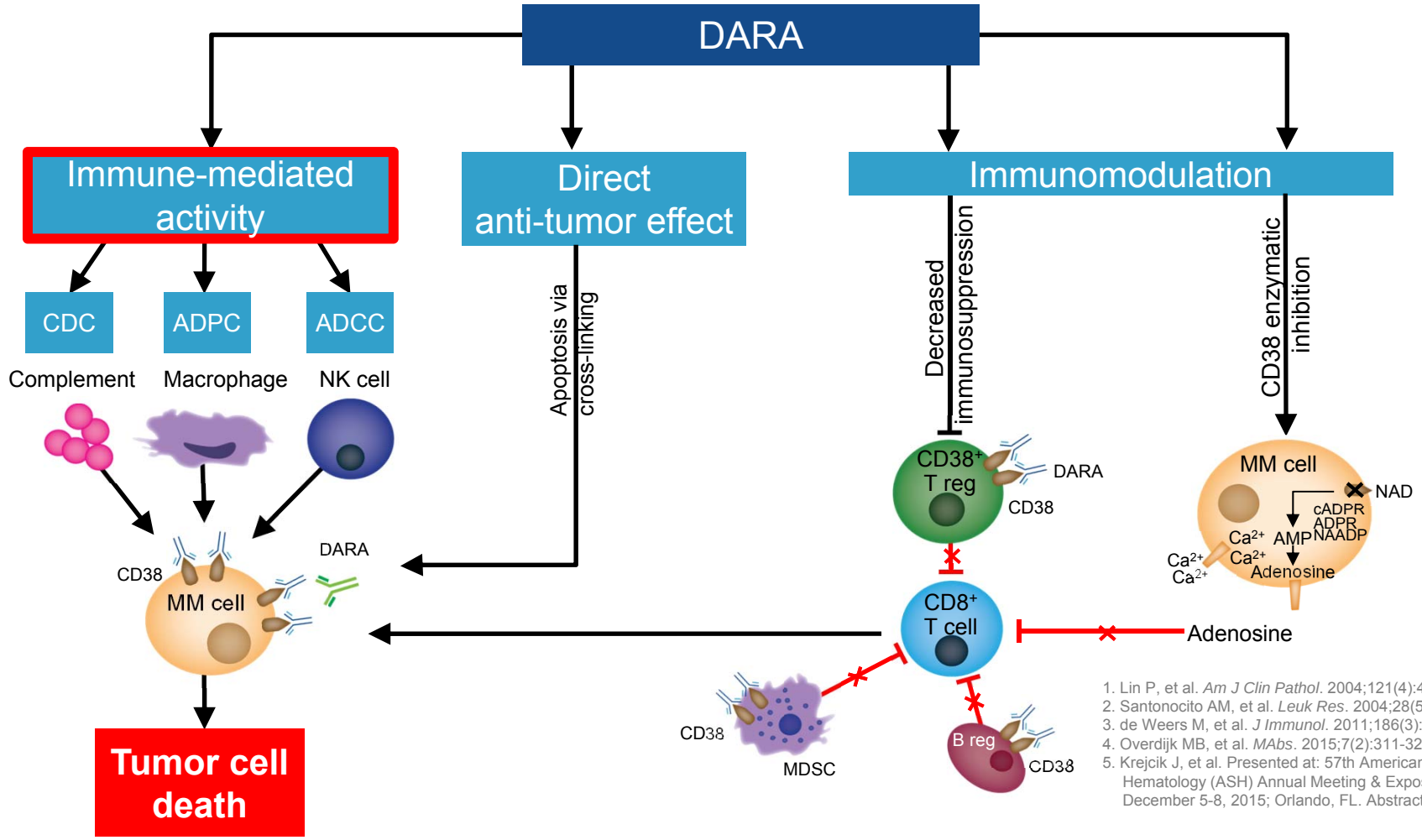
- Despite the introduction of IMiDs and PIs, most patients relapse and outcomes are poor in relapsed or refractory patients[1]
  - Median OS of 9 months in patients refractory to bortezomib and at least 1 IMiD[1]
  - Median OS of 8 months in patients with relapsed or refractory MM who were double refractory or had relapsed after ≥3 prior lines of therapy, including pomalidomide and carfilzomib[2]



1. Kumar SK, et al. *Leukemia*. 2012;26(1):149-157.
2. Usmani S, et al. Presented at: 57th American Society of Hematology (ASH) Annual Meeting & Exposition; December 5-8, 2015; Orlando, FL. Abstract 4498.

DARA: Mechanisms of Action

- CD38 is highly and ubiquitously expressed on myeloma cells[1,2]
- DARA is a human IgG1 monoclonal antibody that binds CD38-expressing cells
- DARA binding to CD38 induces tumor cell death through direct and indirect mechanisms[3-5]



1. Lin P, et al. *Am J Clin Pathol*. 2004;121(4):482-488.
2. Santonocito AM, et al. *Leuk Res*. 2004;28(5):469-477.
3. de Weers M, et al. *J Immunol*. 2011;186(3):1840-1848.
4. Overdijk MB, et al. *MAbs*. 2015;7(2):311-321.
5. Krejcik J, et al. Presented at: 57th American Society of Hematology (ASH) Annual Meeting & Exposition; December 5-8, 2015; Orlando, FL. Abstract 3037.

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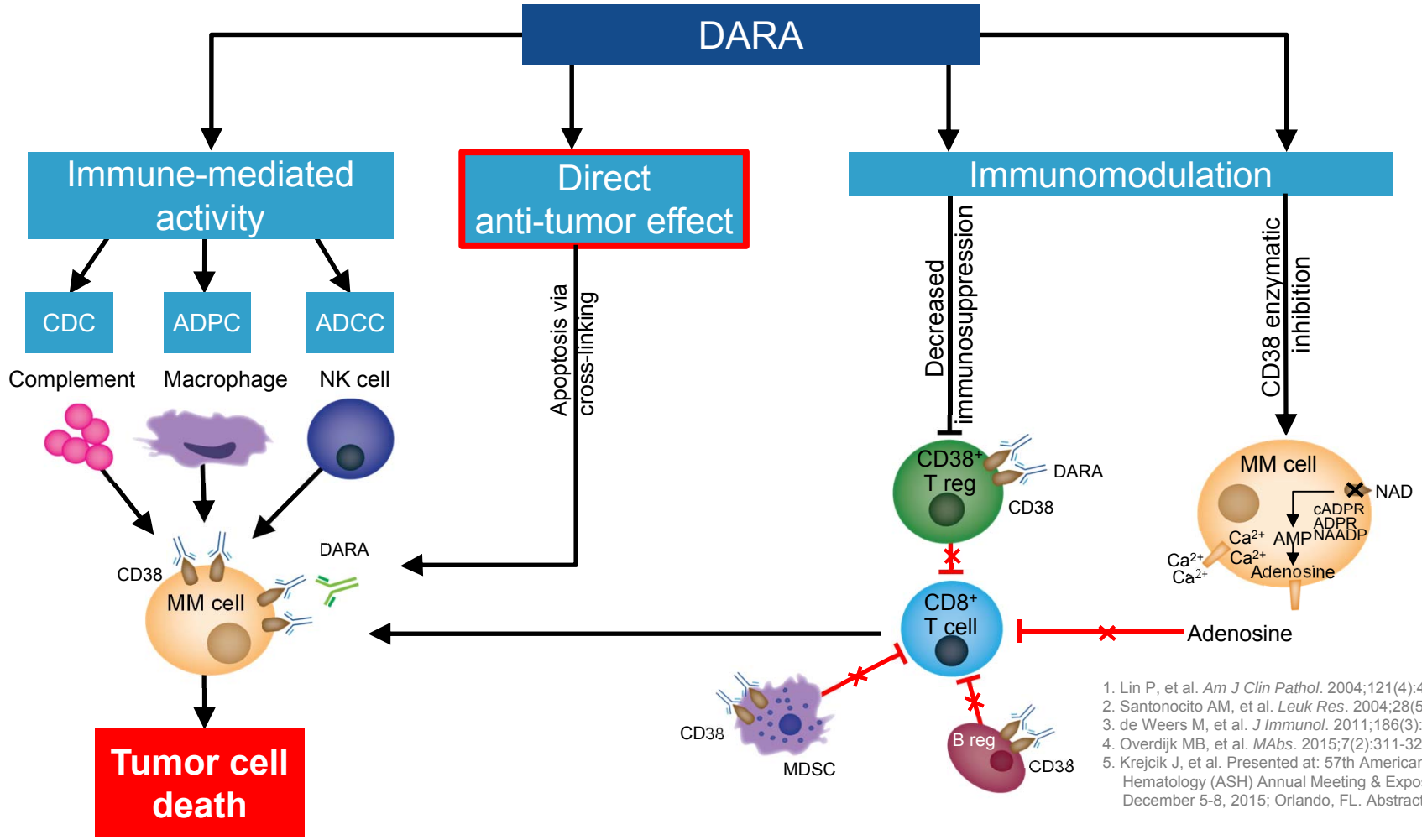

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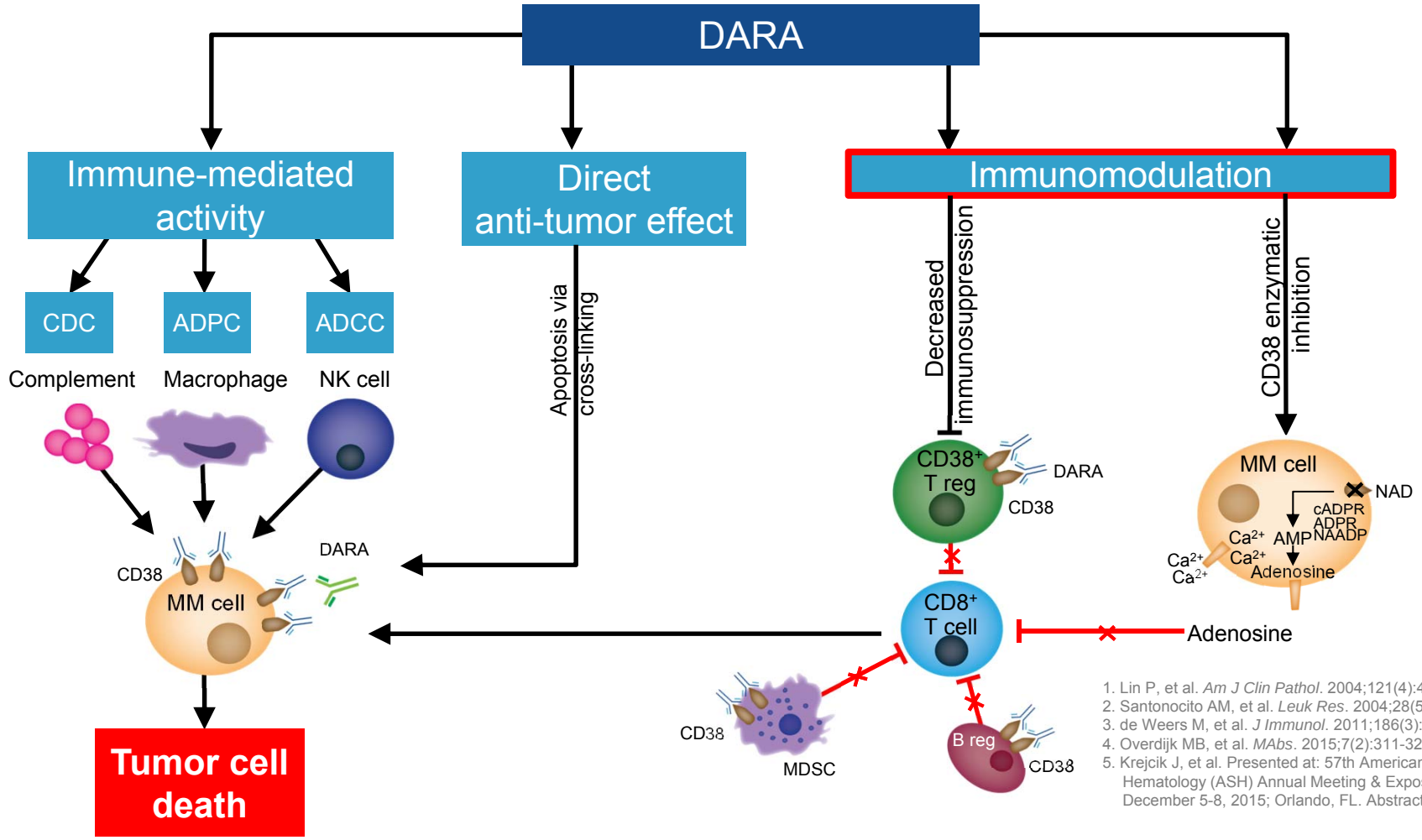

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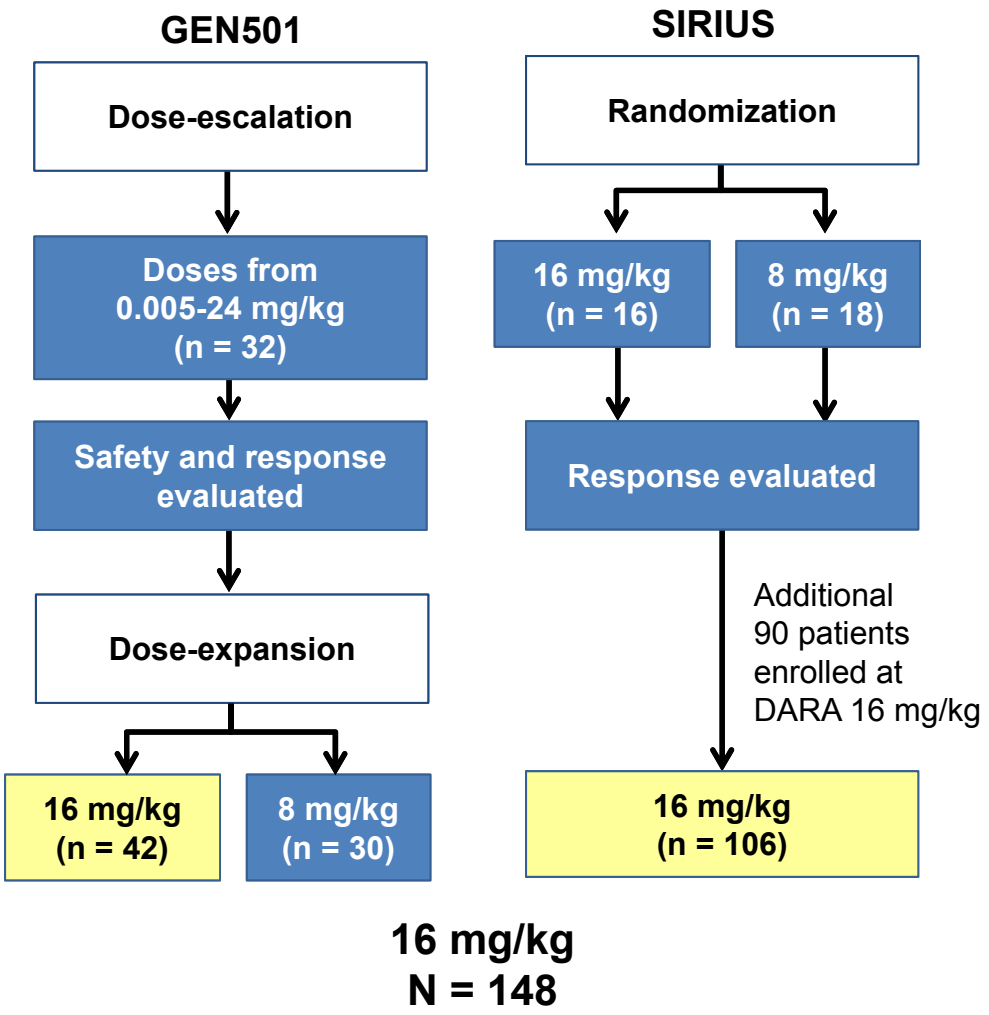
DARA Monotherapy Studies

- ≥18 years of age, ECOG status ≤2[1,2]
- GEN501[1]
  - Open-label, multicenter, phase 1/2, dose-escalation and dose-expansion study
  - Relapsed from or refractory to ≥2 prior lines of therapy including PIs and IMiDs
- SIRIUS[2]
  - Open-label, multicenter, phase 2 study
  - Patients had received ≥3 prior lines of therapy, including a PI and an IMiD, or were double refractory to a PI and an IMID
- DARA was approved by the FDA on November 16, 2015, based on these studies



1. Lokhorst HM, et al. *N Engl J Med*. 2015;373(13):1207-1219.
2. Lonial S, et al. *Lancet*. 2015. In press.

Baseline Characteristics

		16 mg/kg	
	GEN501, Part 2 n = 42	SIRIUS n = 106	Combined N = 148
Median (range) age, y ≥65 years of age, n (%)	64.0 (44-76) 20 (48)	63.5 (31-84) 48 (45)	64 (31-84) 68 (46)
Female/male sex, %	36/64	51/49	53/47
ECOG score, n (%) 0 1 2	 12 (29) 28 (67) 2 (5)	 29 (27) 69 (65) 8 (8)	 41 (28) 97 (66) 10 (7)
Median (range) time since diagnosis, y	5.8 (0.8-23.7)	4.8 (1.1-23.8)	5.1 (0.8-23.8)
Median (range) number of prior lines >3 prior lines, n (%)	4 (2-12) 26 (62)	5 (2-14) 87 (82)	5 (2-14) 113 (76)
Prior ASCT, n (%)	31 (74)	85 (80)	116 (78)
Prior PI, n (%) Bortezomib Carfilzomib	42 (100) 42 (100) 8 (19)	106 (100) 105 (99) 53 (50)	148 (100) 147 (99) 61 (41)
Prior IMiD, n (%) Lenalidomide Pomalidomide Thalidomide	40 (95) 40 (95) 15 (36) 19 (45)	106 (100) 105 (99) 67 (63) 47 (44)	146 (99) 145 (98) 82 (55) 66 (45)

Baseline Refractory Status

Refractory to, n (%)	GEN501, Part 2 n = 42	16 mg/kg SIRIUS n = 106	Combined N = 148
Last line of therapy	32 (76)	103 (97)	135 (91)
Both PI and IMiD PI only IMiD only	27 (64) 3 (7) 4 (10)	101 (95) 3 (3) 1 (1)	128 (86) 6 (4) 5 (3)
PI + IMiD + alkylating agent	21 (50)	79 (75)	100 (68)
Bortezomib	30 (71)	95 (90)	125 (84)
Carfilzomib	**7 (17)**	**51 (48)**	**58 (39)**
Lenalidomide	31 (74)	93 (88)	124 (84)
Pomalidomide	**15 (36)**	**67 (63)**	**82 (55)**
Thalidomide	12 (29)	29 (27)	41 (28)
Alkylating agent only	25 (60)	82 (77)	107 (72)

Patient Disposition

	16 mg/kg		
	GEN501, Part 2 n = 42	SIRIUS n = 106	Combined N = 148
Discontinued from treatment, n (%)	31 (74)	96 (91)	127 (86)
Progressive disease	26 (62)	88 (83)	114 (77)
Adverse event	1 (2)	5 (5)	6 (4)
Physician decision	4 (10)	0	4 (3)
Withdrawal of consent	0	3 (3)	3 (2)

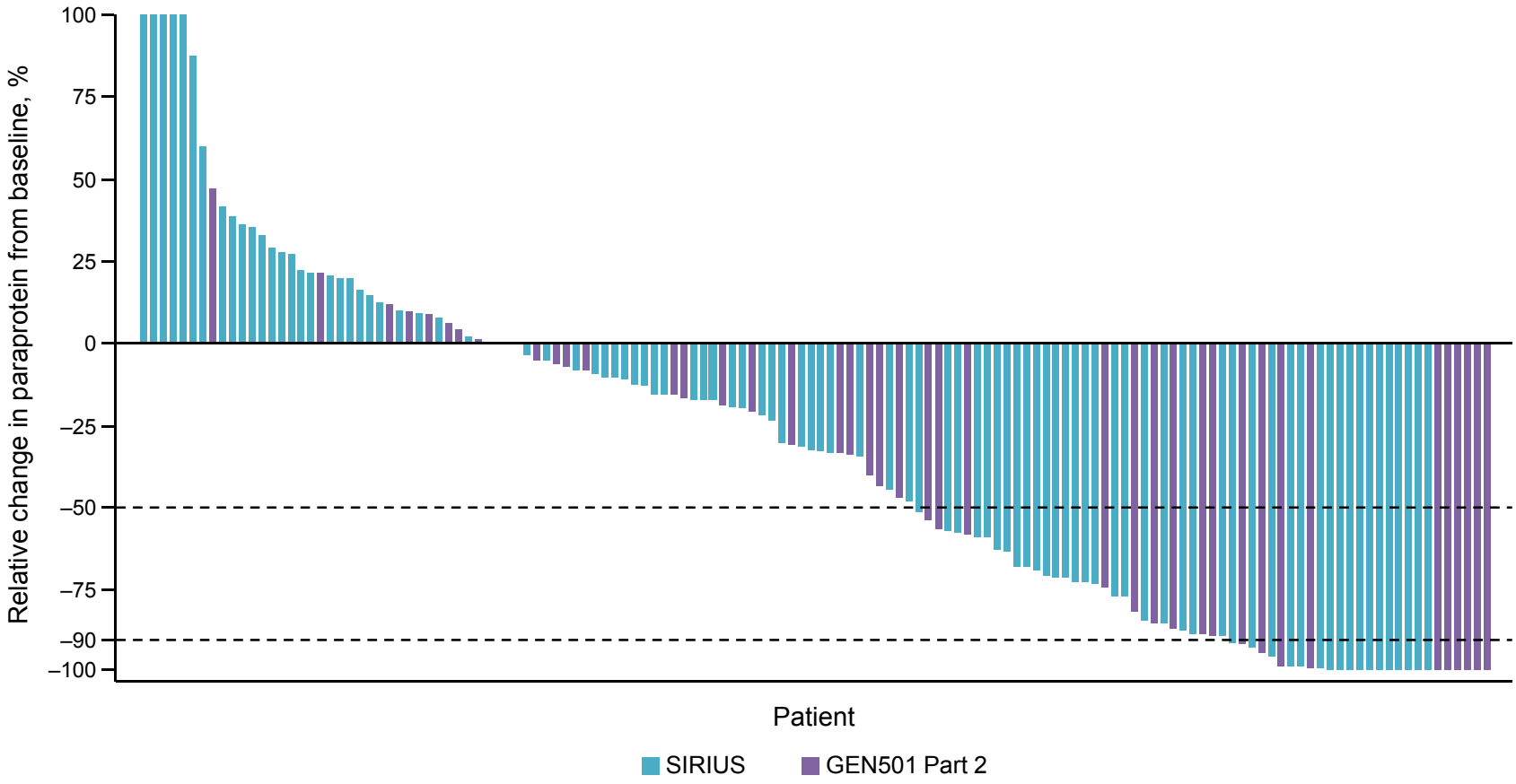
- In the combined dataset
  - Median (range) duration of treatment = 3.4 (0-20) months
  - Median (range) number of infusions = 12 (1-33)
- Death within 30 days of the last dose of treatment = 14
  - 11 (7%) progressive disease
  - 3 (2%) adverse events

Summary of Clinical Safety

Treatment-emergent adverse event, n (%)	Any grade N = 148	Grade ≥3 N = 148
Fatigue	61 (41)	3 (2)
Nausea	42 (28)	0
Anemia	41 (28)	26 (18)
Back pain	36 (24)	3 (2)
Cough	33 (22)	0
Neutropenia	30 (20)	15 (10)
Thrombocytopenia	30 (20)	21 (14)
Upper respiratory tract infection	30 (20)	1 (<1)

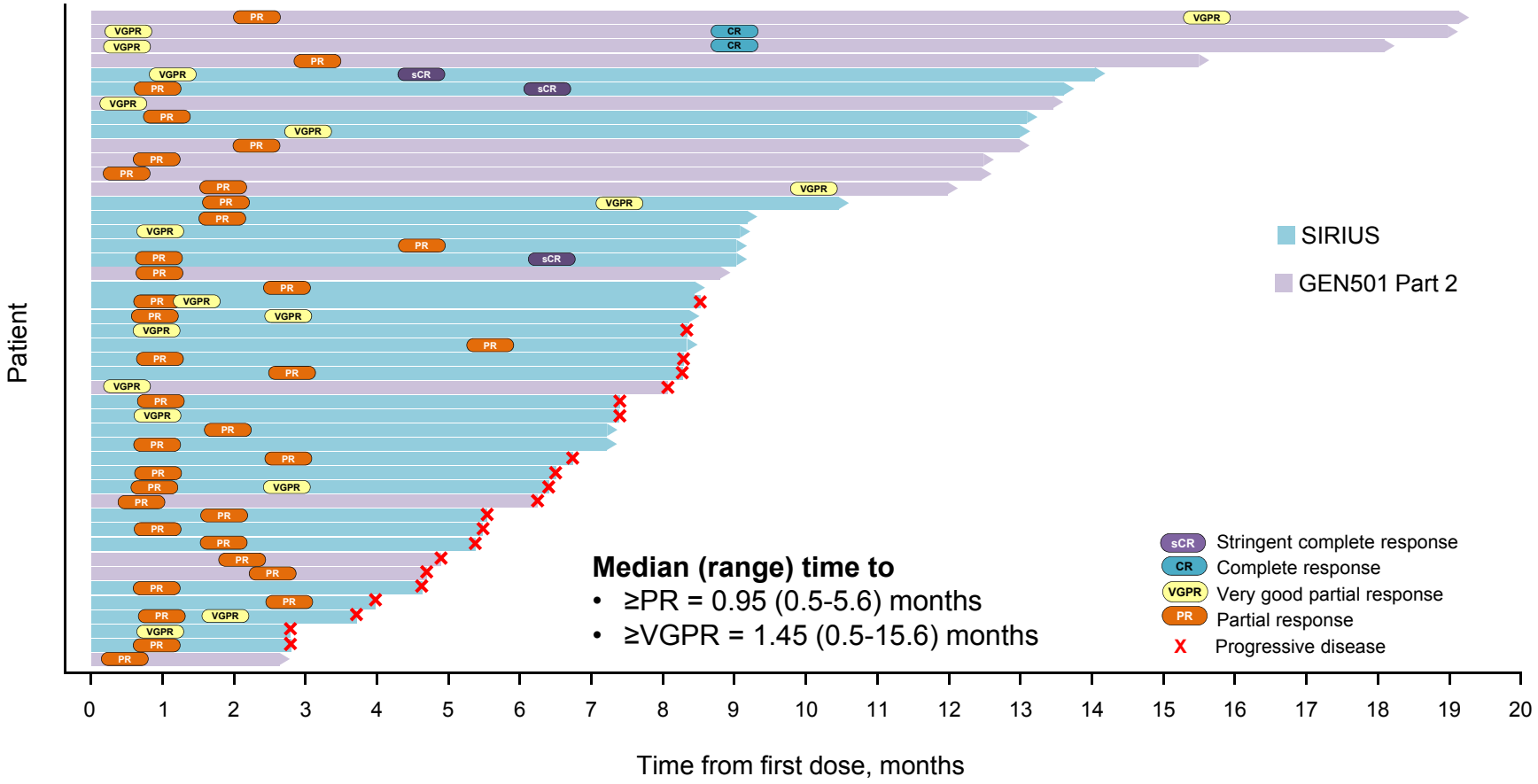
- AEs were consistent with the individual GEN501 and SIRIUS studies; no new safety signals were identified
- 48% of patients had infusion-related reactions
  - 46%, 4%, and 3% occurred during the first, second, and subsequent infusions, respectively

Change in Paraprotein From Baseline



- 40 of 46 responders are still alive at a median follow-up of 14.8 months

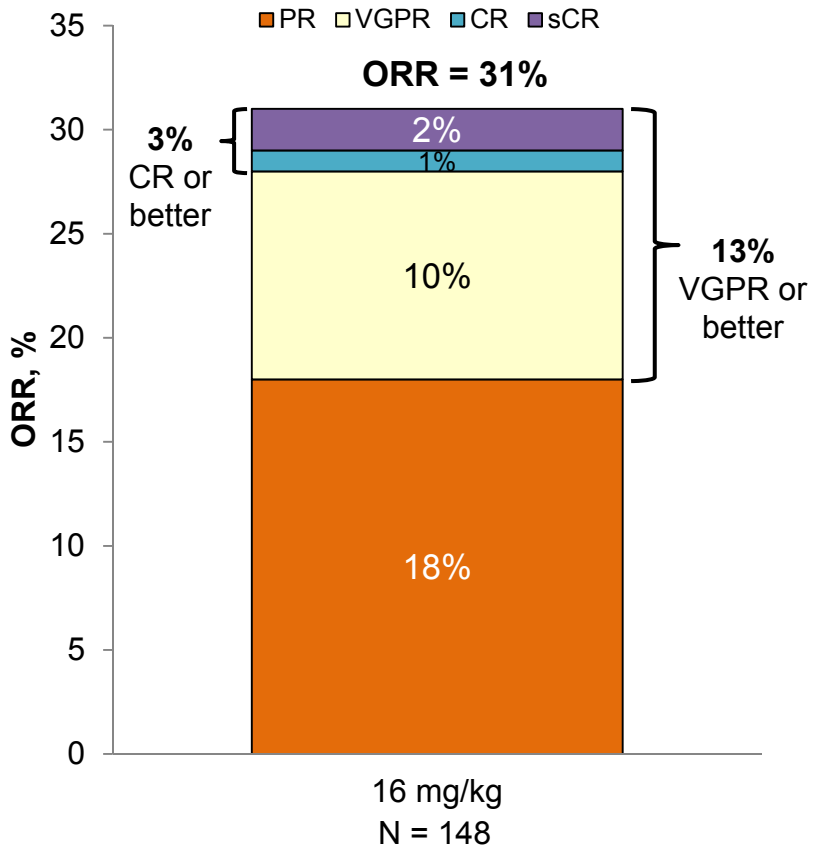
Depth and Duration of Response



- In many patients, responses deepened with continued DARA treatment
- Median duration of response = 7.6 (95% CI, 5.6-NE) months
- At a median follow-up of 14.8 months, 50% (95% CI, 33.6-63.9) of responders were progression-free at 12 months

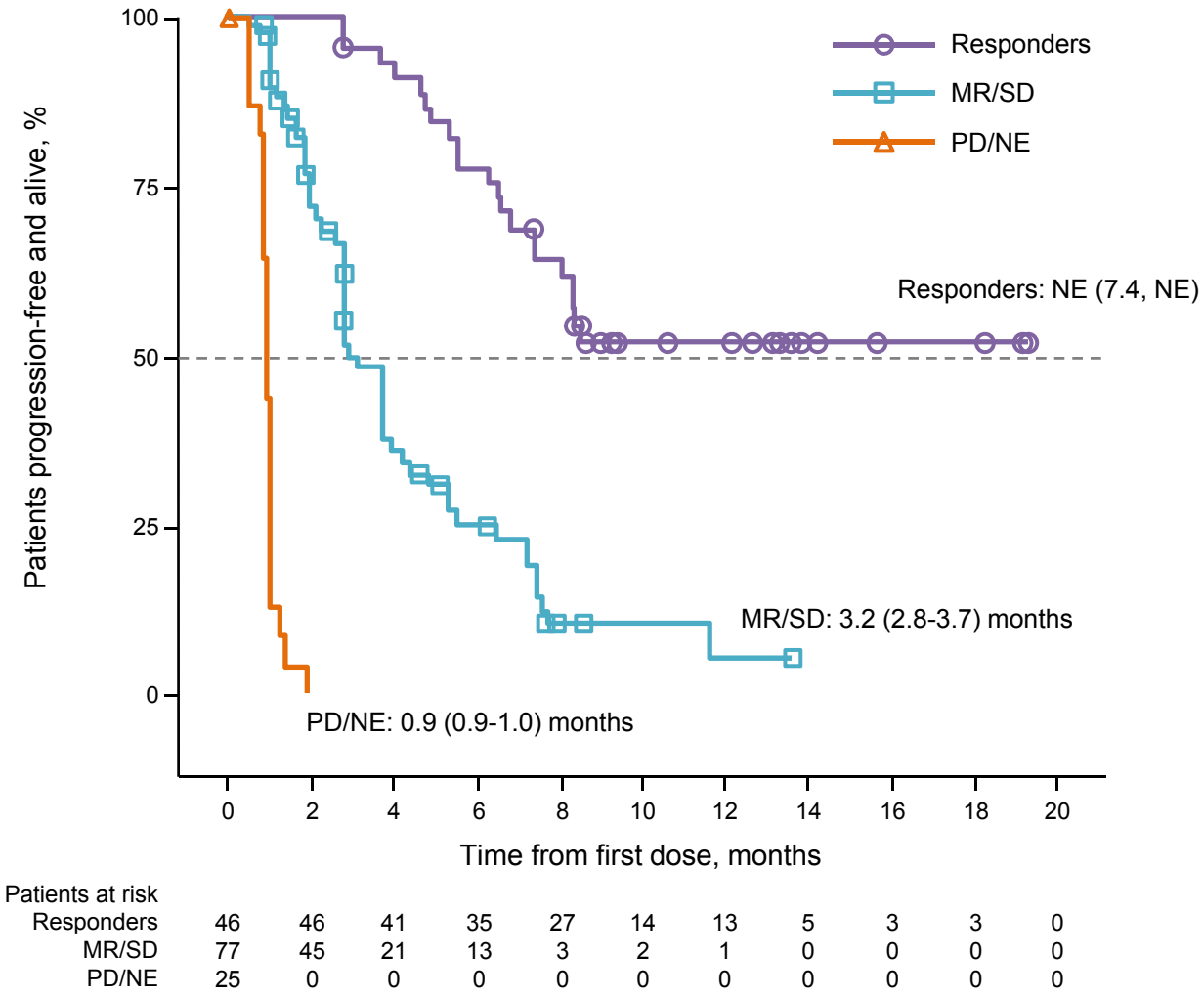
Efficacy in Combined Analysis

	16 mg/kg (N = 148)	
	n (%)	**95% CI**
Overall response rate (sCR+CR+VGPR+PR)	**46 (31)**	**23.7-39.2**
Best response		
sCR	3 (2)	0.4-5.8
CR	2 (1)	0.2-4.8
VGPR	14 (10)	5.3-15.4
PR	27 (18)	12.4-25.4
MR	9 (6)	2.8-11.2
SD	68 (46)	37.7-54.3
PD	18 (12)	7.4-18.5
NE	7 (5)	1.9-9.5
VGPR or better (sCR+CR+VGPR)	19 (13)	7.9-19.3
CR or better (sCR+CR)	5 (3)	1.1-7.7

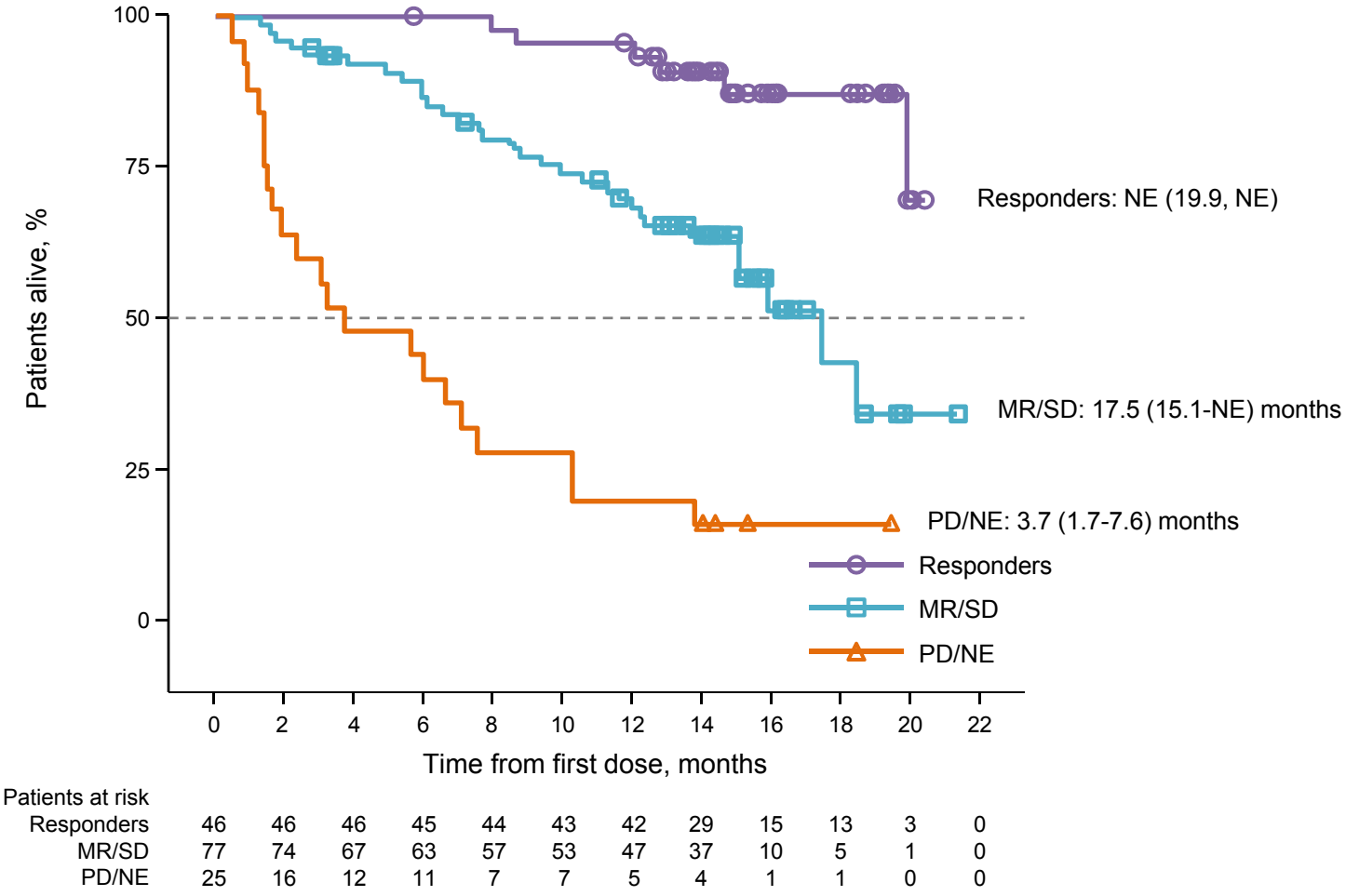


- ORR = 31%
- ORR was consistent in subgroups including age, number of prior lines of therapy, refractory status, or renal function

Progression-free Survival



Overall Survival



- For the combined analysis, median OS = 19.9 (95% CI, 15.1-NE) months
- 1-year overall survival rate = 69% (95% CI, 60.4-75.6)

Conclusions

- As a single agent, DARA induced rapid, deep, and durable responses in a heavily pretreated/highly refractory population
- Remarkable depth of response observed in patients refractory to newer agents, including pomalidomide and carfilzomib
- DARA conferred an OS benefit even in patients who achieved stable disease or minimal response
- Updated analysis of the combined dataset of GEN501 and SIRIUS did not identify any new safety signals
- DARA has immune-mediated and immunomodulatory mechanisms that may be contributing to a survival benefit

Selected DARA Presentations

- **Sunday, Dec. 6 from 6:00-8:00 PM: Jakub Krejcik, MD, et al. Poster 3037**
  - Immunomodulatory Effects and Adaptive Immune Response to Daratumumab in Multiple Myeloma
- **Monday, Dec. 7 at 7:30 AM: Torben Plesner, MD, et al. Oral 507**
  - Daratumumab in Combination With Lenalidomide and Dexamethasone in Patients With Relapsed or Relapsed and Refractory Multiple Myeloma: Updated Results of a Phase 1/2 Study (GEN503)
- **Monday, Dec. 7 at 7:45 AM: Ajai Chari, MD, et al. Oral 508**
  - Open-label, Multicenter, Phase 1b Study of Daratumumab in Combination With Pomalidomide and Dexamethasone in Patients With ≥2 Lines of Prior Therapy and Relapsed or Relapsed and Refractory Multiple Myeloma (MM)

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