Open-label, Multicenter, Phase 1b Study of Daratumumab in Combination With Pomalidomide and Dexamethasone in Patients With ≥2 Lines of Prior Therapy and Refractory or Relapsed and Refractory Multiple Myeloma (MM)

Ajai Chari, MD[1]; Sagar Lonial, MD[2]; Attaya Suvannasankha, MD[3]; Joseph W. Fay, MD[4]; Bertrand Arnulf, MD, PhD[5]; Jainulabdeen J. Ifthikharuddin, MD[6]; Xiang Qin, MS[7]; Tara Masterson, MS[7]; Kerri Nottage, MD, MPH[8]; Jordan Schecter, MD[8]; Tahamtan Ahmadi, MD, PhD[7]; Brendan Weiss, MD[9]; Amrita Krishnan, MD[10]; Suzanne Lentzsch, MD, PhD[11]

[1]Tisch Cancer Institute, Mount Sinai School of Medicine, New York, NY, USA; [2]Department of Hematology and Medical Oncology, Winship Cancer Institute, Emory University, Atlanta, GA, USA; [3]Indiana University School of Medicine and Simon Cancer Center, Richard L. Roudebush VAMC, Indianapolis, IN, USA; [4]Baylor Institute for Immunology Research, Dallas, TX, USA; [5]Hôpital Saint Louis, Paris, France; [6]James P. Wilmot Cancer Center, University of Rochester Strong Memorial Hospital, Rochester, NY, USA; [7]Janssen Research & Development, LLC, Spring House, PA, USA; [8]Janssen Research & Development, LLC, Raritan, NJ; [9]Abramson Cancer Center and Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA; [10]City of Hope, Duarte, CA, USA; [11]Columbia University Medical Center, New York, NY, USA.
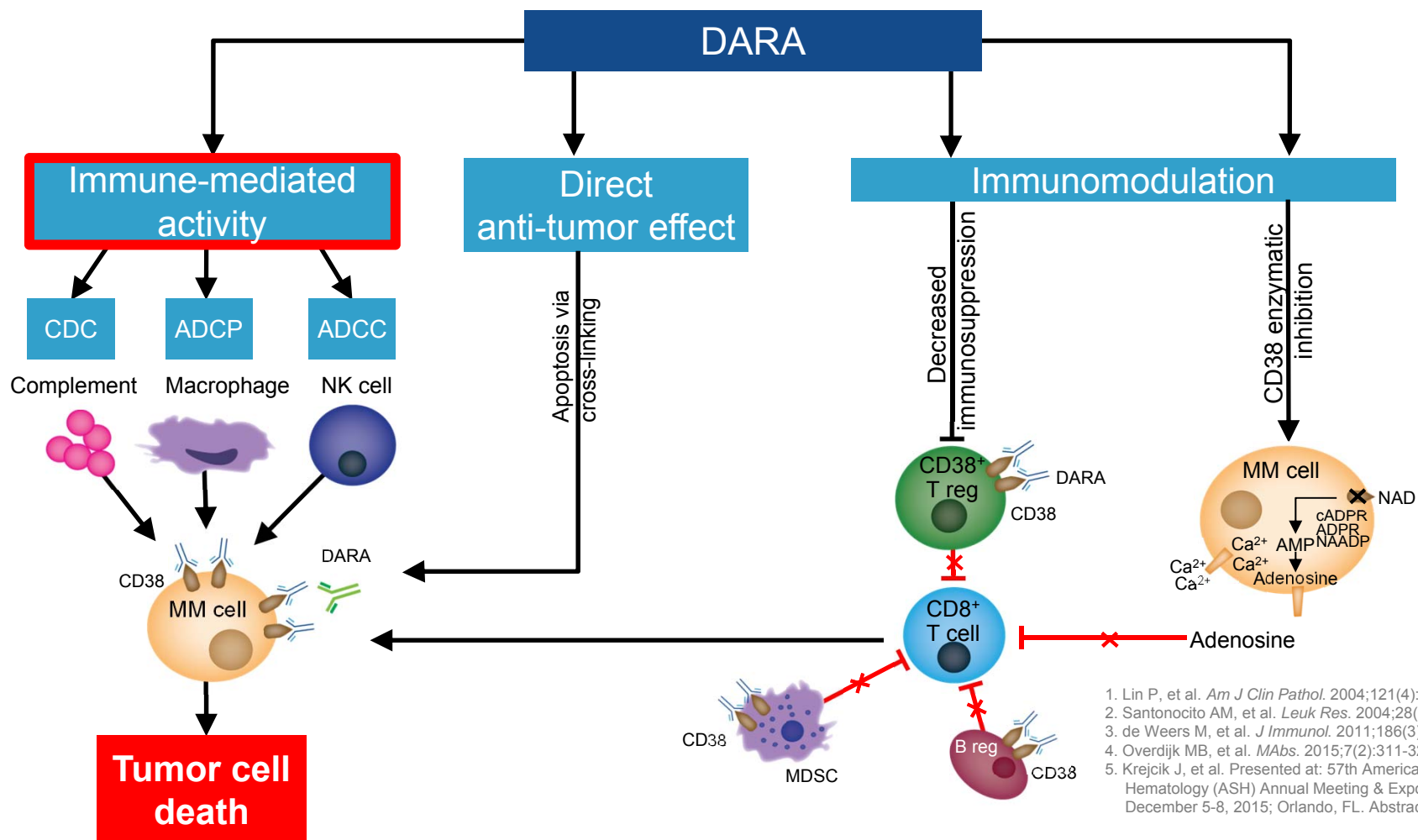
Background

- Daratumumab (DARA) was recently approved by the FDA on November 16, 2015

- Combined analysis of Phase 2 (GEN501/SIRIUS) monotherapy studies in heavily pretreated/highly refractory MM[1]
  - 86% refractory to PI and IMiD
  - ORR = 31%
  - Median OS of 19.9 months (95% CI, 15.1-NE)

1. Usmani S, et al. Presented at: 57th American Society of Hematology (ASH) Annual Meeting & Exposition; December 5-8, 2015; Orlando, FL. Abstract 29.
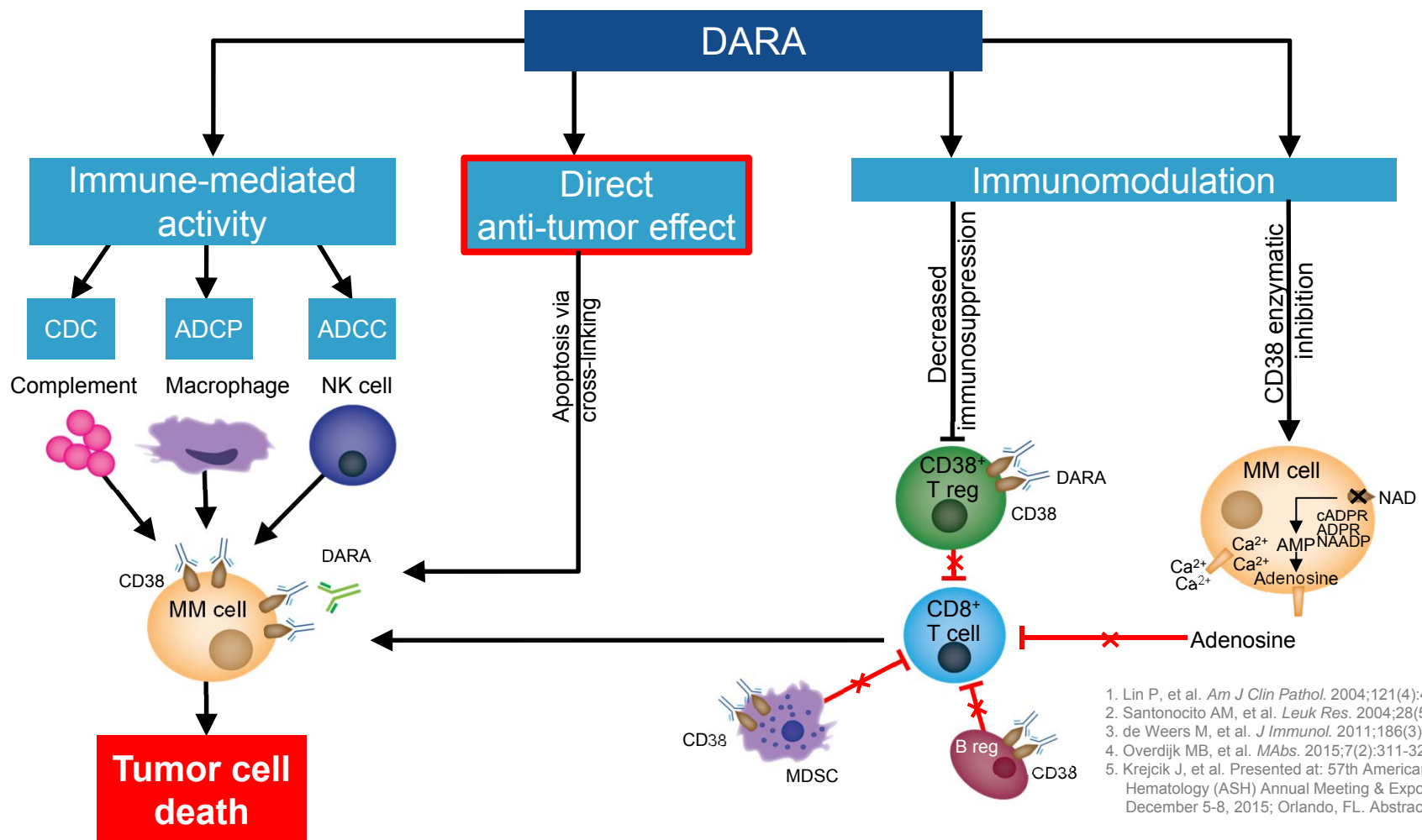
DARA: Mechanisms of Action

- 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.

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]
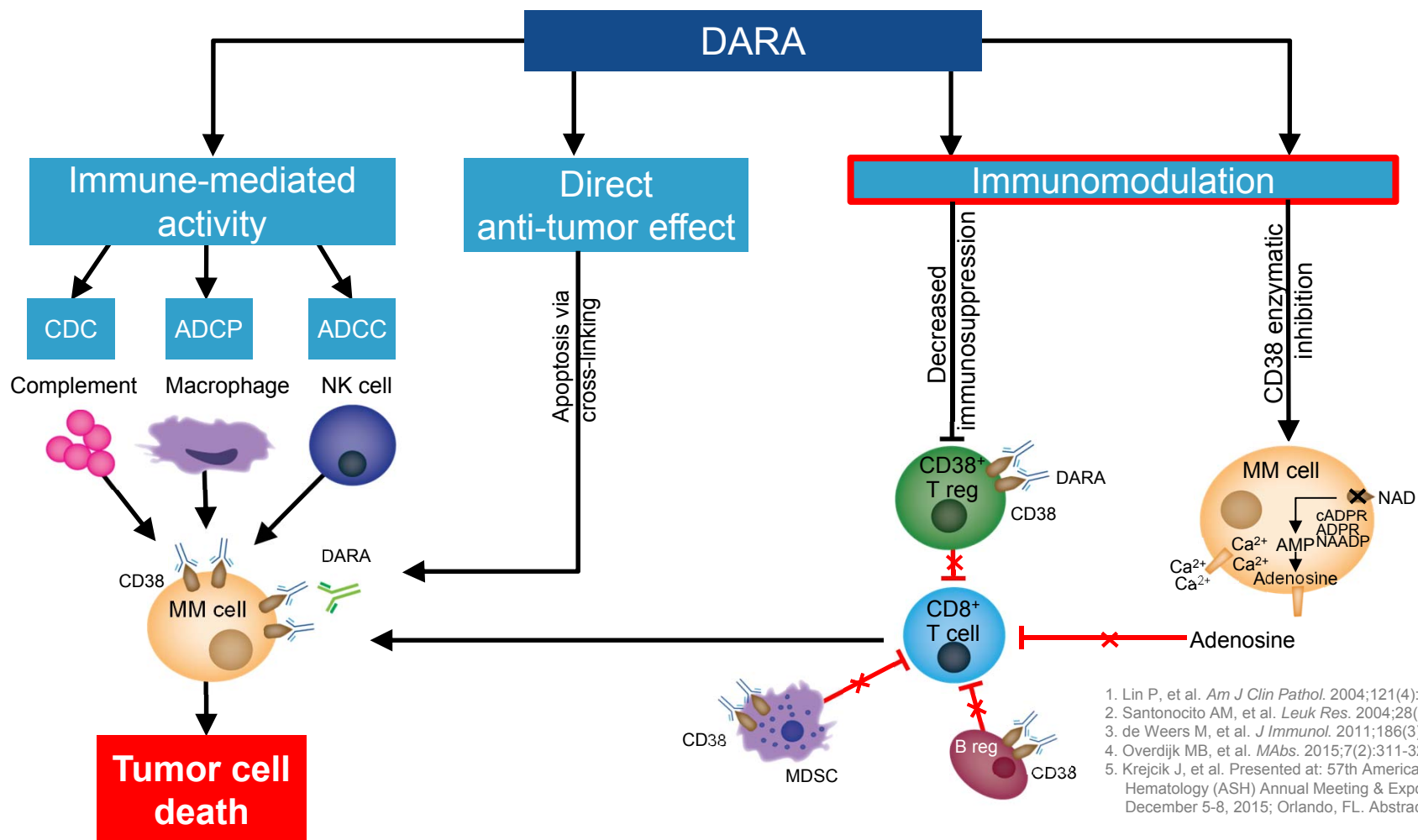
DARA

Immune-mediated activity

Direct anti-tumor effect

Immunomodulation

CDC — Complement

ADCP — Macrophage

ADCC — NK cell

Apoptosis via cross-linking

Decreased immunosuppression

CD38 enzymatic inhibition

DARA

CD38

MM cell

Tumor cell death

CD38+ T reg

DARA

CD38

CD8+ T cell

Adenosine

CD38

MDSC

B reg

CD38

MM cell

NAD

cADPR ADPR NAADP

Ca2+ Ca2+ Ca2+

AMP

Adenosine

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.

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.

Rationale for DARA + POM-D

- In a randomized, Phase 3 study, pomalidomide plus low-dose dexamethasone (POM-D) in patients relapsed from or refractory to previous treatment with bortezomib or lenalidomide[1] resulted in the following:
  - ORR = 31%
  - Median PFS of 4.0 months
  - Median OS of 12.7 months

- Pomalidomide increases CD38 expression in a time and dose-dependent fashion in multiple myeloma cells[2]

1. San Miguel J, et al. *Lancet Oncol.* 2013;14(11)1055-1066.
2. Boxhammer R, et al. Presented at 51st American Society of Clinical Oncology (ASCO) Annual Meeting; May 29 -June 2, 2015; Chicago, IL. Abstract 8588.

MMY1001: DARA + POM-D Arm

Eligibility criteria

- Refractory to last line of therapy
- ≥2 prior lines of therapy, including 2 consecutive cycles of lenalidomide and bortezomib
- Pomalidomide naïve
- ECOG score ≤2
- Absolute neutrophil count ≥1.0×10^9/L, and platelet count ≥75×10^9/L for patients with <50% plasma cells (>50×10^9/L, otherwise)
- Calculated creatinine clearance ≥45 mL/min/1.73 m^2

**Open-label, multicenter, six-arm, Phase 1b study
(28-day cycles)**

DARA* IV 16 mg/kg +
Pomalidomide 4 mg (Days 1-21) +
Dexamethasone 40 mg QW

*QW for Cycles 1-2, Q2W for Cycles 3-6, and Q4W beyond.

Treat 6 patients with DARA + POM-D

↓

If ≤1 patient has DLTs

↓

Enroll 6 additional patients

↓

Expand up to 88 patients

Baseline Characteristics

	DARA + POM-D N = 98
Median (range) age, y	64.5 (35-86)

Age category, n (%)
    18 to 69 years
    ≥70 years
	
	70 (71)
	28 (29)

Female/male, %	44/56

Race, n (%)
    White
    Black or African American
    Not reported
	
	71 (72)
	14 (14)
	13 (13)

Baseline ECOG score, n (%)
    0
    1
    2
	
	27 (28)
	60 (61)
	11 (11)

Prior Therapy Status

- Patients were heavily pretreated and highly refractory per inclusion criteria

	DARA + POM-D N = 98
Median (range) time since MM diagnosis, y	5.2 (0.4-16.0)
	N = 97
Median (range) number of prior lines of therapy	4.0 (2-13)
Prior	
Autologous stem cell transplant	73 (75)
PI	97 (100)
Carfilzomib	31 (32)
Bortezomib	96 (98)
IMiD	97 (100)
	N = 98
Refractory to	
PI	74 (76)
Bortezomib	65 (66)
Carfilzomib	29 (30)
Lenalidomide	87 (89)
PI and IMiD	66 (67)

Patient Disposition
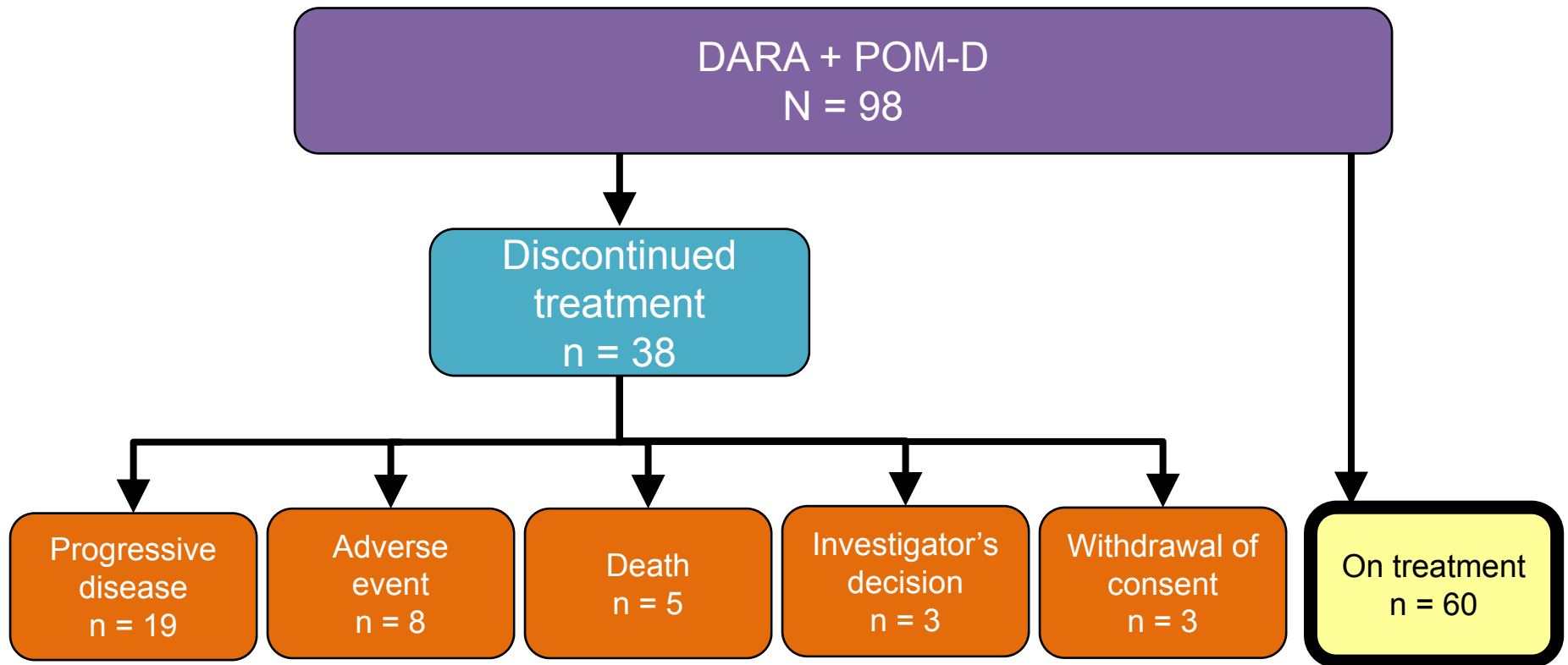
Common (>20% of Patients) AEs

	N = 98	
	Any grade	**Grade ≥3**
Any grade	97	91
Neutropenia	63	60
Anemia	42	25
Fatigue	41	8
Thrombocytopenia	34	15
Leukopenia	32	20
Cough	31	0
Diarrhea	30	1
Dyspnea	28	6
Nausea	25	0
Constipation	22	0

- Rates of grade ≥3 AEs were similar to those observed with POM-D alone
- Serious AEs occurred in 42% of patients
- 17 (17%) deaths occurred
- 45 (46%) patients required GCSF and 24 (25%) required blood transfusions during treatment
  - No blood transfusion–related AEs were reported
- No new safety signals were identified with DARA + POM-D

Infusion-related Reactions in >3 Patients

Infusion-related reaction, n (%)	N = 98	
	Any grade	Grade 3
Any event	52 (53)	6 (6)
Chills	14 (14)	0
Cough	11 (11)	0
Dyspnea	11 (11)	0
Nasal congestion	7 (7)	0
Throat irritation	7 (7)	0
Nausea	7 (7)	0
Chest discomfort	6 (6)	0
Pyrexia	6 (6)	0

- IRRs were predominantly grade ≤2
  - 6 (6%) patients had grade 3 IRRs
  - Only 2 patients discontinued due to an IRR
- 53%, 1%, and 0% of patients had IRRs during the first, second, and subsequent infusions, respectively
- IRRs were managed with premedication and reduced infusion rates

Maximum Change in Paraprotein From Baseline: DARA + POM-D

N = 75

Legend: Urine M-protein, Serum M-protein, Free light chain
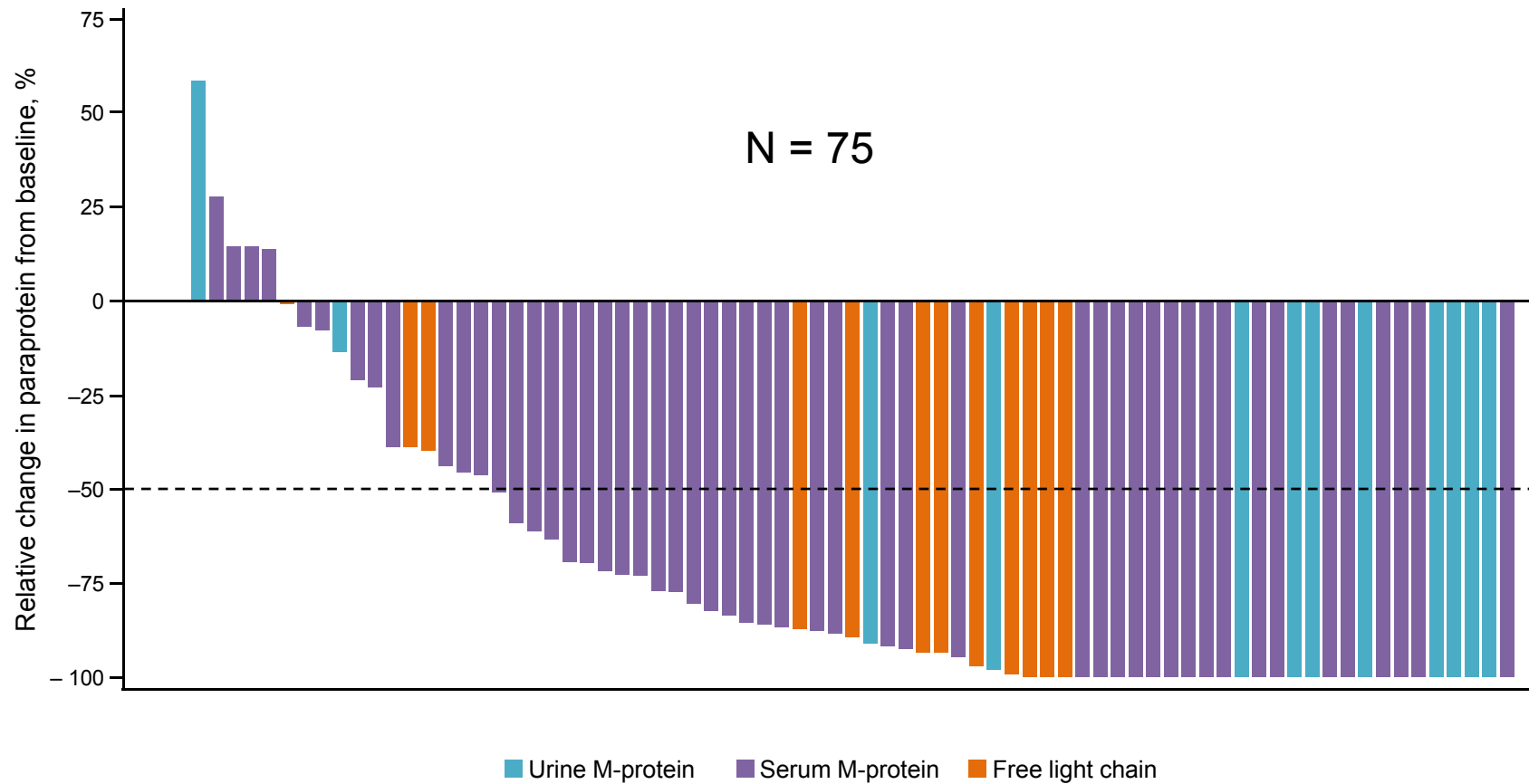
Overall Response Rate:
DARA + POM-D

	DARA + POM-D (N = 75)	
	n (%)	95% CI
Overall response rate (sCR+CR+VGPR+PR)	**53 (71)**	**59.0-80.6**
Best response		
sCR	4 (5)	1.5-13.1
CR	3 (4)	0.8-11.2
VGPR	25 (33)	22.9-45.2
PR	21 (28)	18.2-39.6
MR	2 (3)	0.3-9.3
SD	17 (23)	13.8-33.8
PD	3 (4)	0.8-11.2
VGPR or better (sCR+CR+VGPR)	32 (43)	31.3-54.6
CR or better (sCR+CR)	7 (9)	3.8-18.3

Legend: ■ PR □ VGPR ■ CR ■ sCR

ORR = 71%

- 9% CR or better
  - sCR: 5%
  - CR: 4%
- 43% VGPR or better
  - VGPR: 33%
- PR: 28%

ORR, % (y-axis: 0 to 80)

16 mg/kg

N = 75
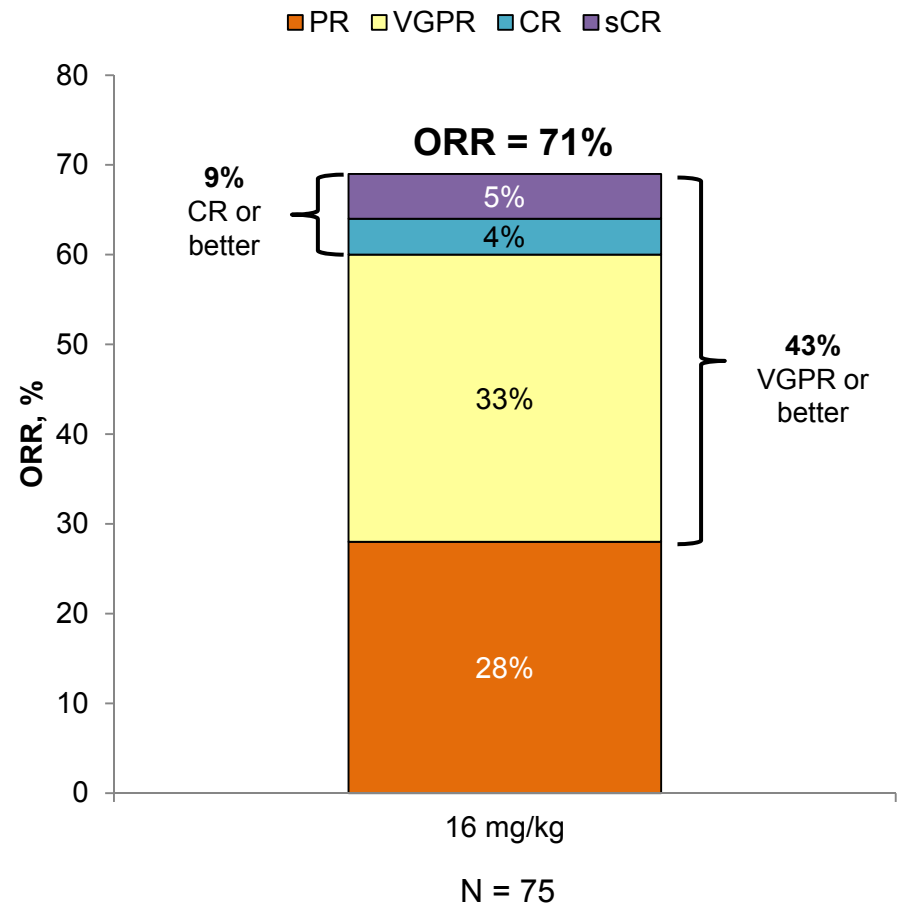
- ORR = 71%
- ORR in double-refractory patients = 67%
- Clinical benefit rate (ORR + minimal response) = 73%

14

Depth and Duration of Response:
DARA + POM-D
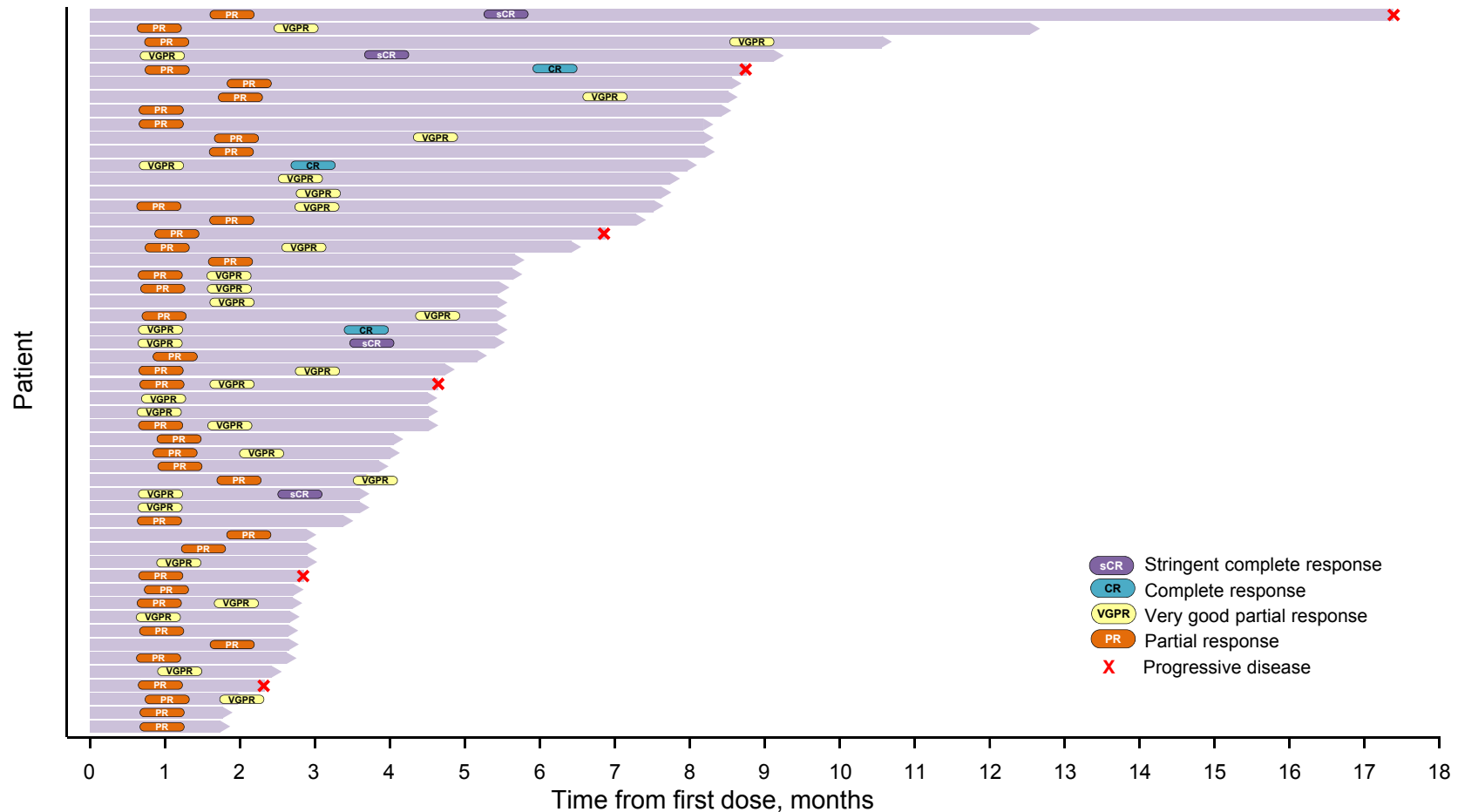
- Median time to first response was 1.2 months
- At a median follow-up time of 4.2 months
  - Median time to best response was 2.8 months; responses are deepening over time
  - 47 of 53 (89%) responders had not progressed

15

Progression-free Survival at 6 Months:
DARA + POM-D
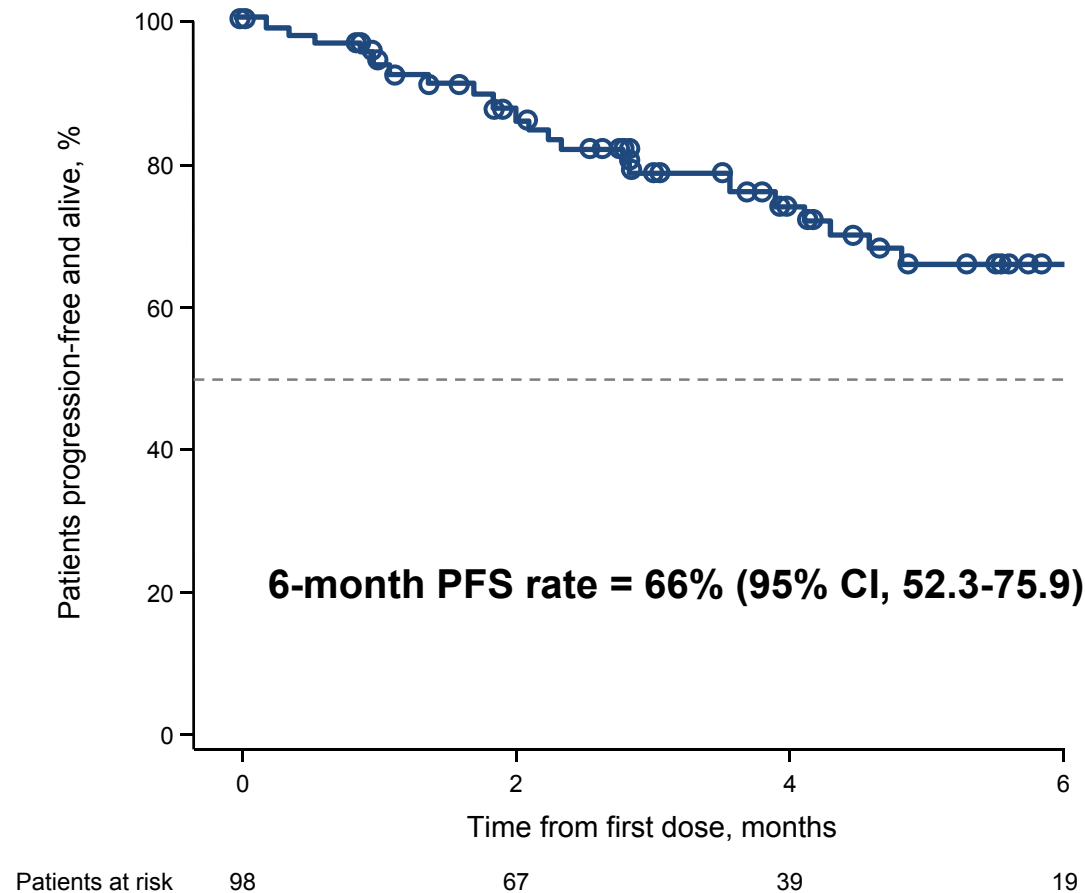
- Median follow-up of 4.2 months

Conclusions

- DARA (16 mg/kg) + POM-D induced rapid, deep, and durable responses in a heavily pretreated patient population
  - Median of 4 prior lines of therapy
  - 67% of patients were double refractory to a PI and an IMiD
- ORR was 71% including 43% ≥VGPR and 5% sCR
- PFS rate at 6 months was 66%
- No additional safety signals observed
- DARA can be safely combined with POM-D
- These data support the conduct of a Phase 3 study evaluating this novel combination

Acknowledgments