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)

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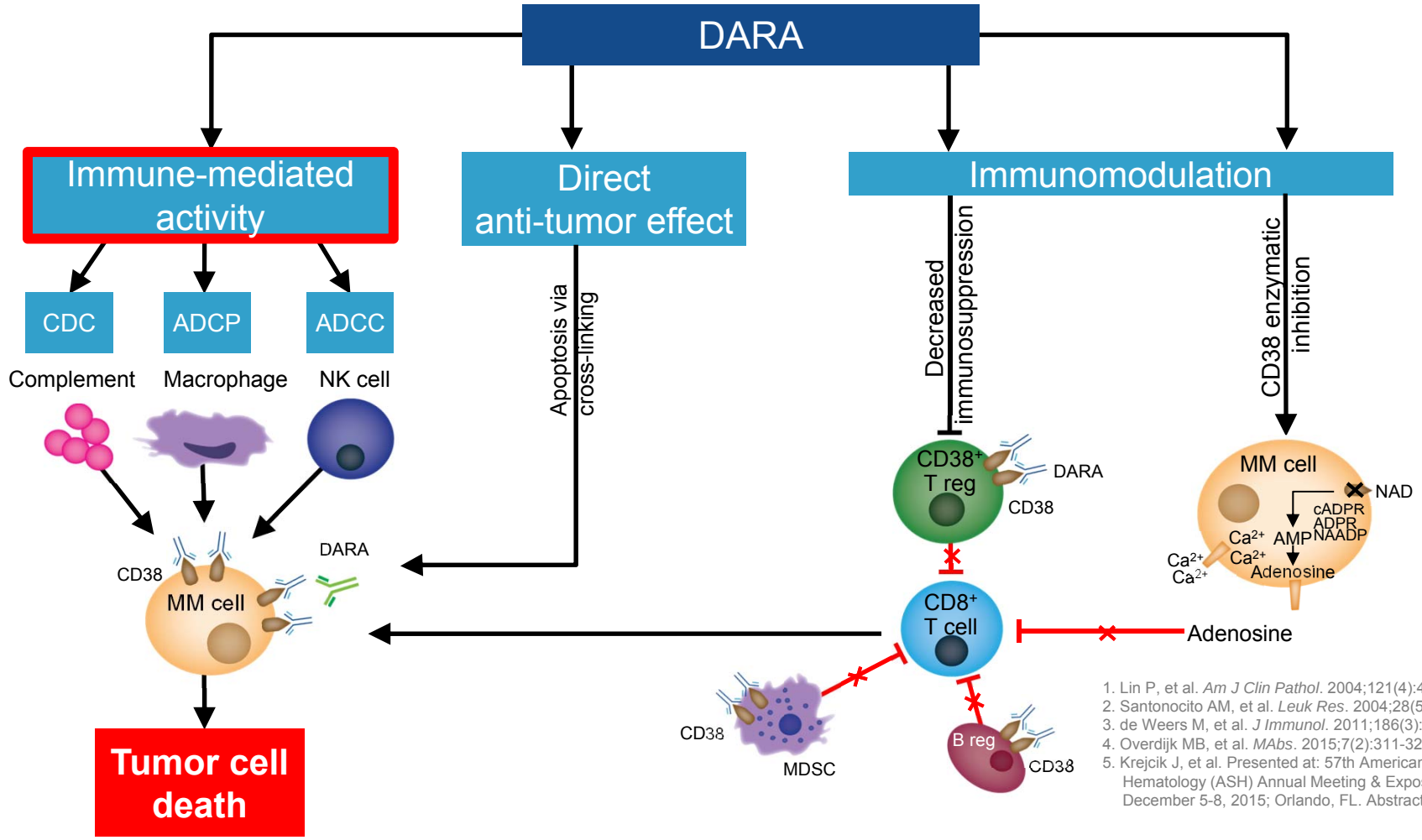
Background

- In DARA monotherapy studies in patients with heavily pretreated/ highly refractory MM, we observed an ORR of 31% and a median OS of 19.9 months[1]
- Based on these data, DARA received FDA approval in this population
  - DARA is the first monoclonal antibody approved for the treatment of myeloma
- In randomized, phase 3 studies, LEN/DEX resulted in an ORR of 61% to 66% and a median PFS of 11 to 14.9 months in patients receiving ≥1 line of previous treatment[2,3]
- Here, we present data from a phase 1/2 study of DARA + LEN/DEX in relapsed or relapsed and refractory patients

1. Usmani S, et al. Presented at: 57th American Society of Hematology (ASH) Annual Meeting & Exposition; December 5-8, 2015; Orlando, FL. Abstract 29.
2. Dimopoulos MA, et al. *Leukemia*. 2009;23(11):2147-2152.
3. Lonial S, et al. *New Engl J Med*. 2015;373(7):621-631.

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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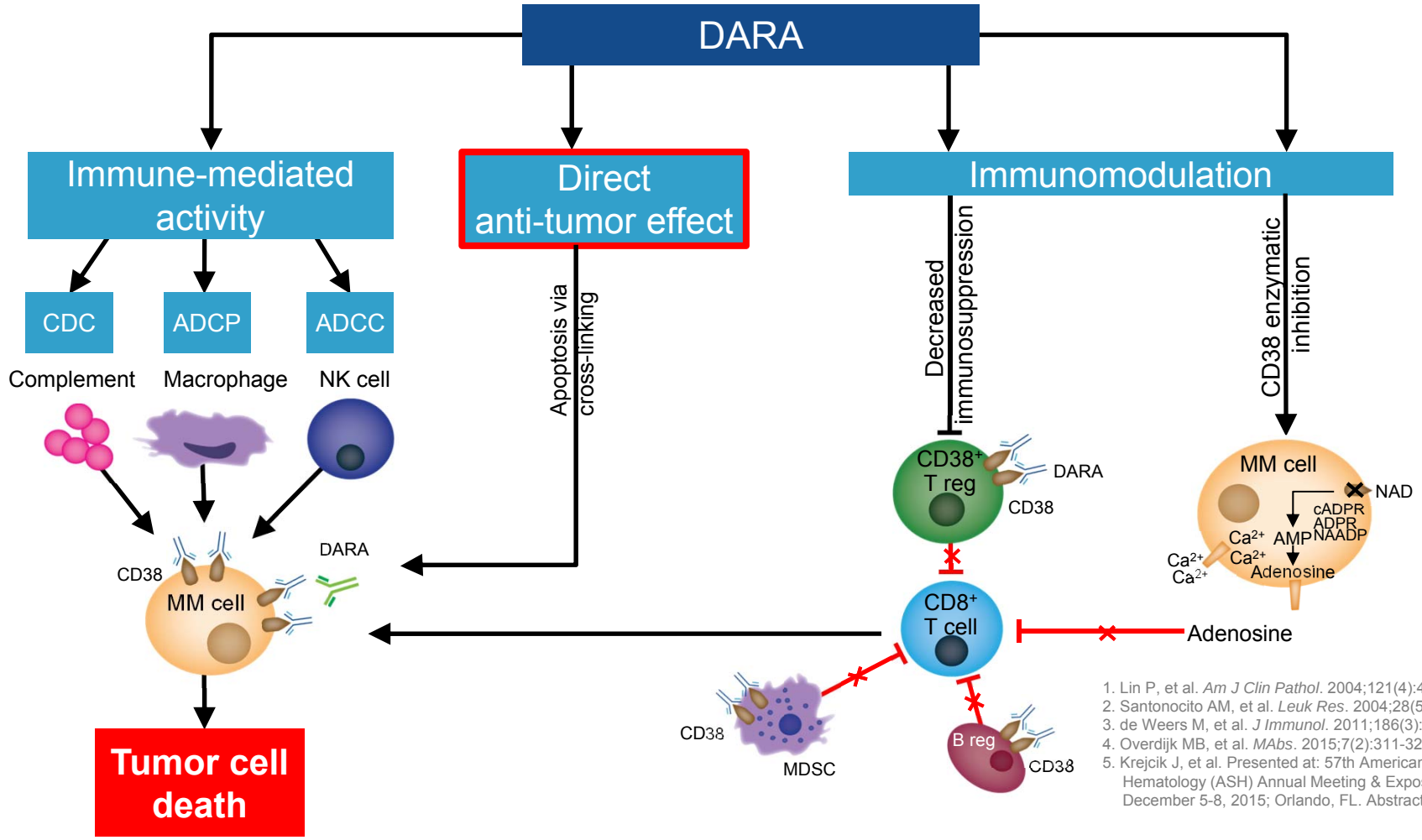

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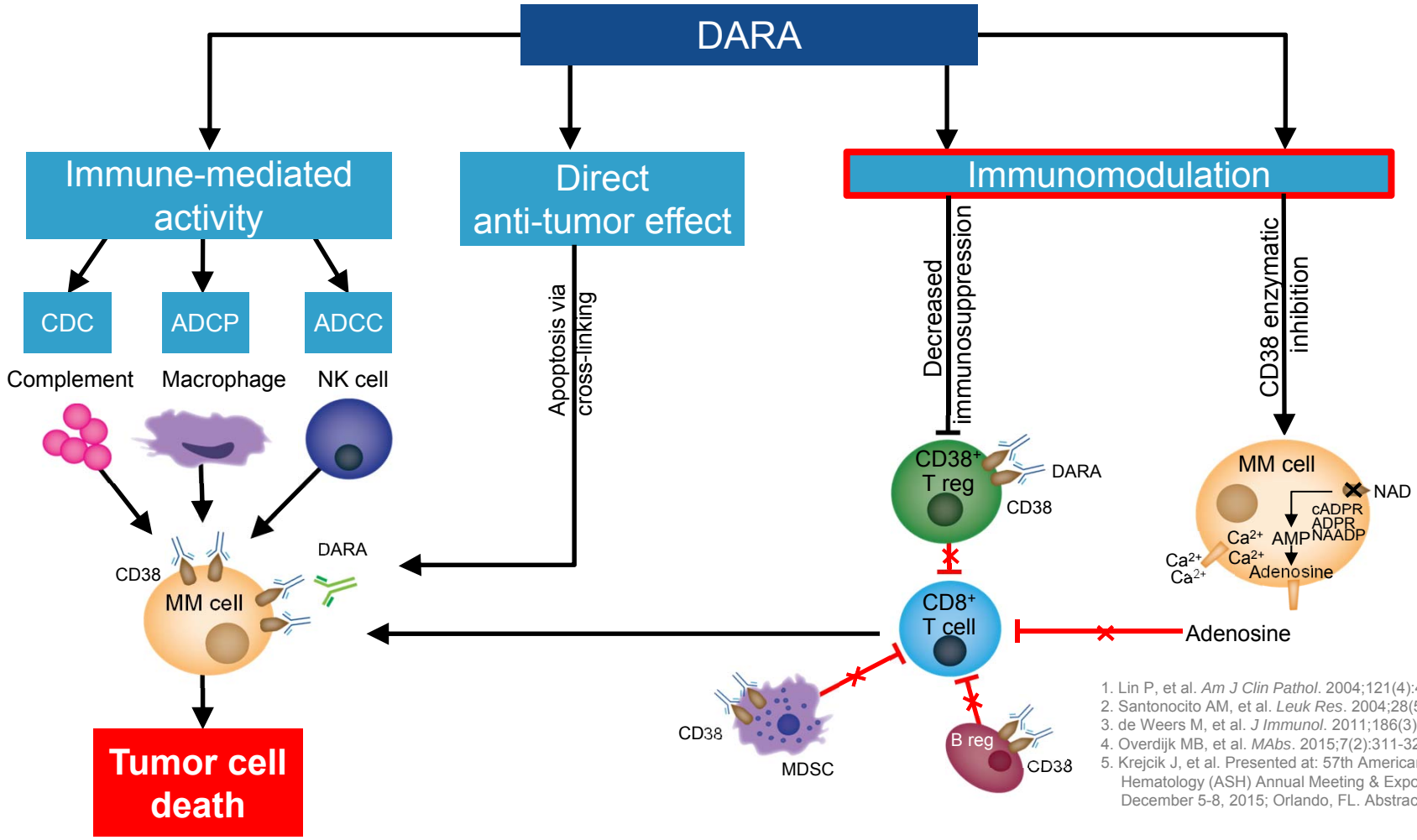

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Phase 2 DARA + LEN/DEX

Key eligibility

- Measurable disease by M-protein
- Patients refractory or intolerant to LEN were excluded

Part 1

- Relapsed MM following 2 to 4 prior lines of therapy

Part 2

- Relapsed MM following ≥1 prior line of therapy (no upper limit)

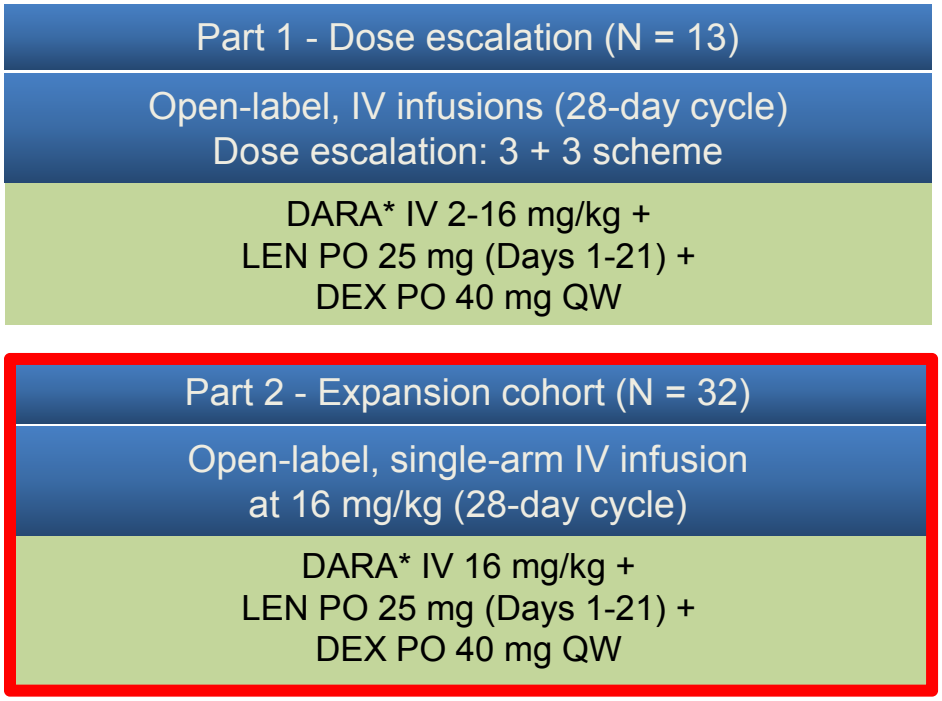
Endpoints

Primary endpoint

- Incidence of adverse events

Key secondary endpoints

- Rate of response
- Pharmacokinetics
- Time to progression
- Duration of response
- Progression-free survival

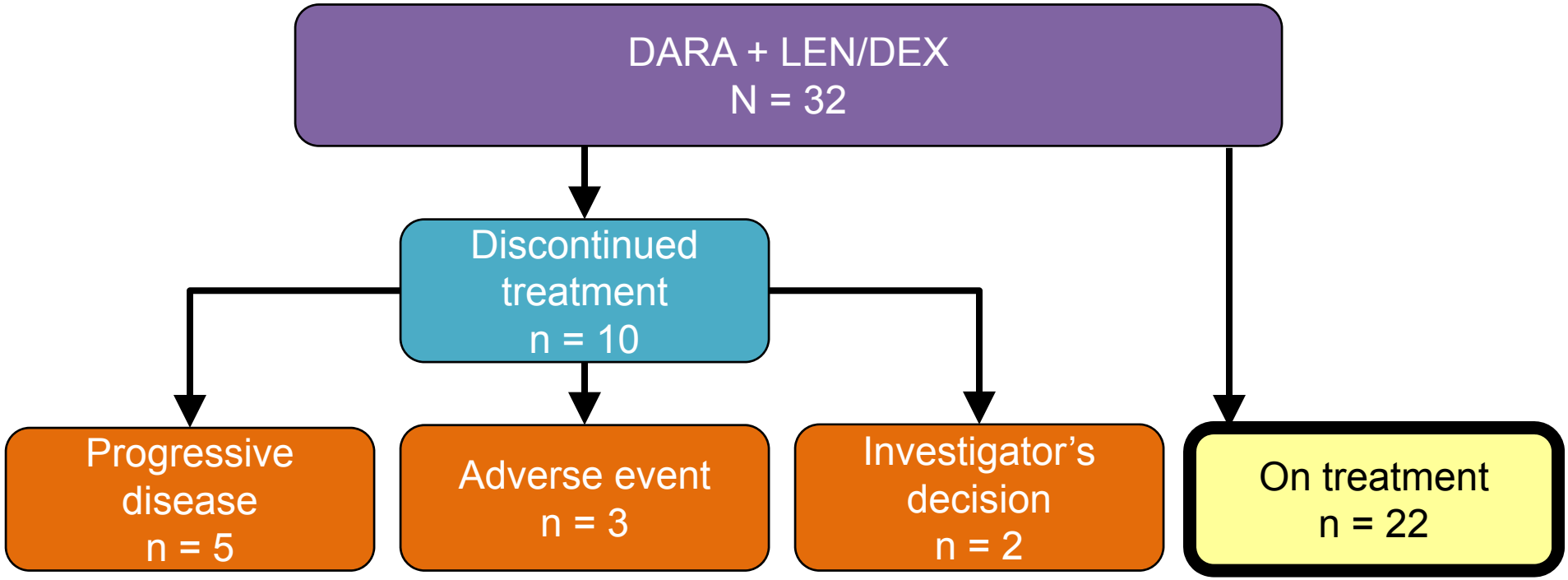


*QW for Months 1-2, Q2W for Months 3-6, and Q4W beyond.

Baseline Characteristics

	N = 32
Median (range) age, y	60 (41-76)
≥65 years of age, n (%)	9 (28)
Female/male sex, %	31/69
ECOG score, n (%)	
0	19 (59)
1	12 (38)
2	1 (3)
Median (range) time since diagnosis, y	3.2 (0.9-12.7)
Median (range) number of lines of prior therapy	2 (1-3)
≥2 prior lines of therapy, n (%)	17 (53)
Refractory to last line of therapy	7 (22)
Prior autologous stem cell transplant, n (%)	25 (78)
Prior PI, n (%)	29 (91)
Bortezomib	28 (88)
Prior IMiD, n (%)	23 (72)
Lenalidomide	11 (34)
Thalidomide	14 (44)
Prior chemotherapy, n (%)	32 (100)
Alkylating agents	29 (91)
Anthracyclines	15 (47)

Patient Disposition



- 3 treatment-related AEs led to discontinuation: 1 case of gastric adenocarcinoma (unrelated to DARA or LEN), 1 case of laryngeal edema (DARA-related) and 1 case of viral pneumonia (DARA- and LEN/DEX-related)
- 3 deaths occurred in Part 2 of the study, 2 due to progressive disease and 1 due to an AE (viral pneumonia)
- 22 of 32 (69%) patients remain on treatment at a median of 15.6 months of follow-up

Adverse Events in >20% of Patients

	N = 32	
Treatment-emergent adverse event, n (%)	**Any grade**	**Grade ≥3**
Any event	32 (100)	28 (88)
Neutropenia	27 (84)	25 (78)
Cough	16 (50)	0
Diarrhea	14 (44)	1 (3)
Muscle spasms	14 (44)	0
Fatigue	11 (34)	0
Pyrexia	10 (31)	0
Thrombocytopenia	10 (31)	4 (13)
Hypertension	9 (28)	3 (9)
Nausea	9 (28)	0
Anemia	8 (25)	4 (13)
Peripheral edema	8 (25)	0
Upper respiratory tract infection	8 (25)	1 (3)
Peripheral sensory neuropathy	7 (22)	0

- 16 (50%) patients had serious AEs, 8 (25%) of which were due to infection
  - Serious AEs occurring in >1 patient included neutropenia (n = 3), and gastroenteritis and pyrexia (n = 2, each)
- 22 (69%) patients received GCSF during the study

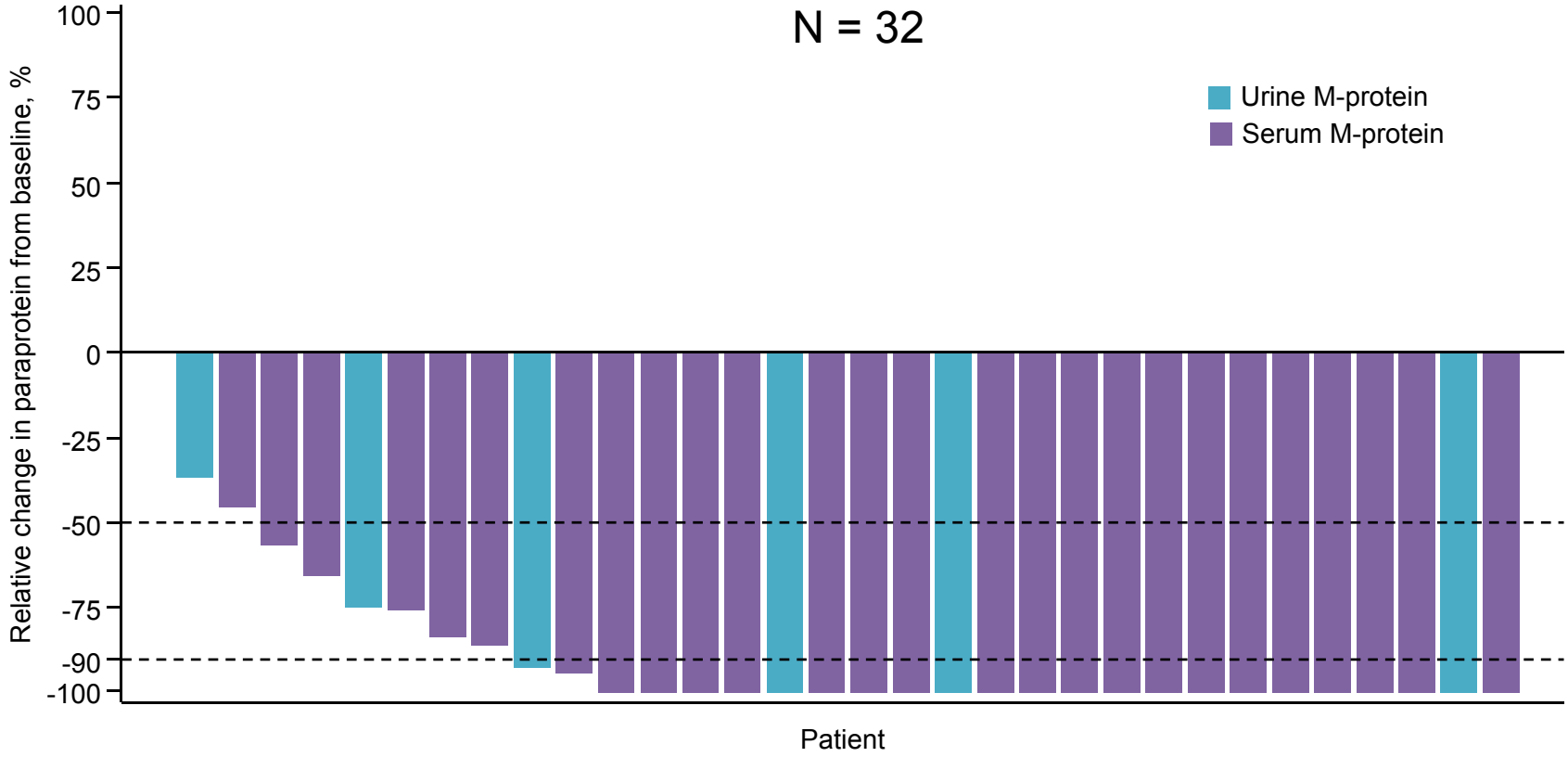
Infusion-related Reactions in >2 Patients

	N = 32	
Infusion-related reaction, n (%)	**Any grade**	**Grade 3**
Any event	18 (56)	2 (6)
Cough	8 (25)	0
Allergic rhinitis	3 (9)	0
Nausea	3 (9)	0
Vomiting	3 (9)	0
Dyspnea	2 (6)	0
Nasal congestion	2 (6)	0

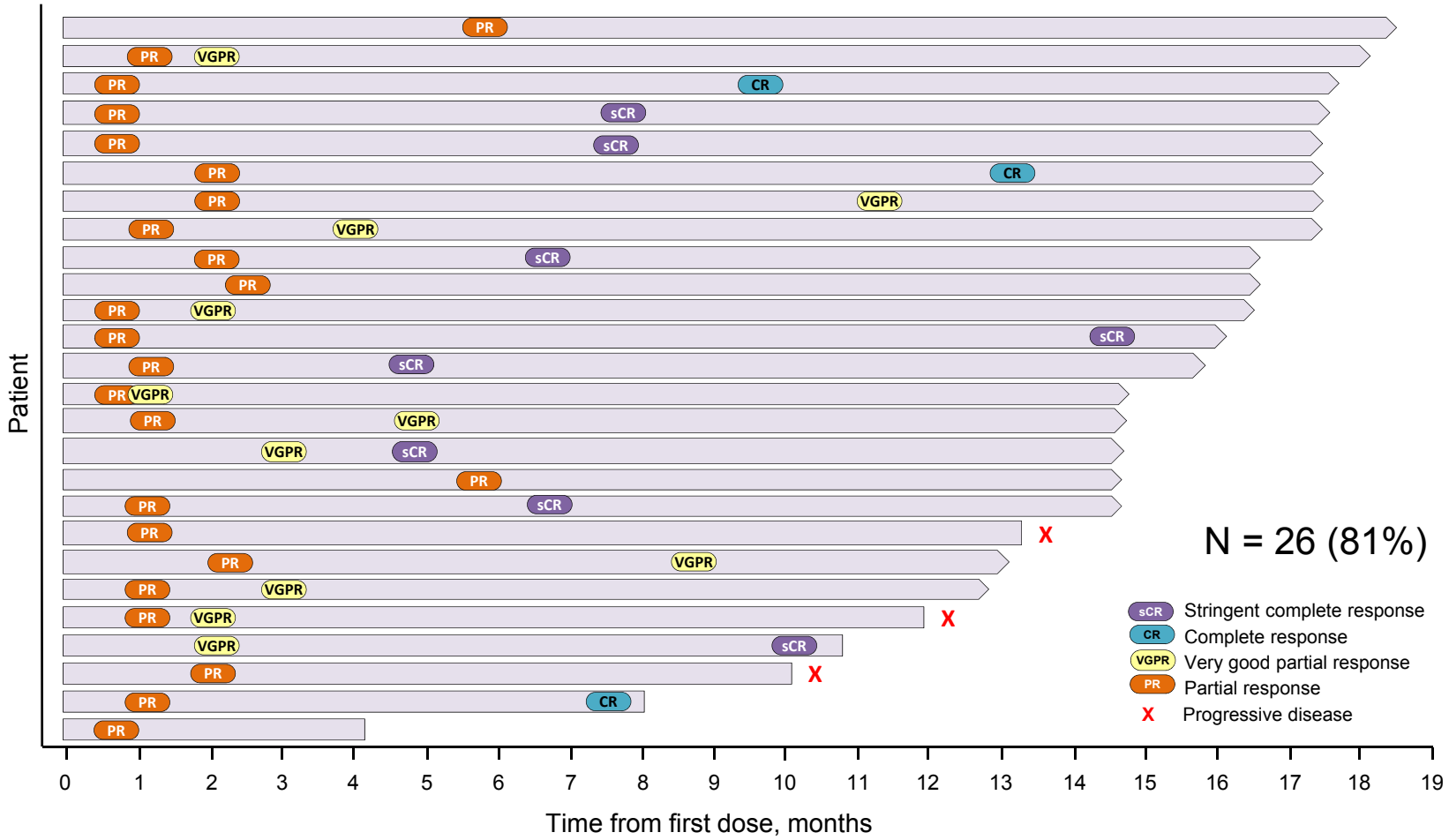
- Type and rate of IRRs were similar to those reported in studies of DARA monotherapy
- The majority of IRRs were grade ≤2
- All patients who experienced IRRs (n = 18) had an IRR during the first infusion
  - 3 patients had IRRs in the second or subsequent infusions
- 2 patients had grade 3 IRRs; 1 patient had laryngeal edema and the other had hypertension
- No grade 4 IRRs were reported

Change in Paraprotein From Baseline:

DARA + LEN/DEX



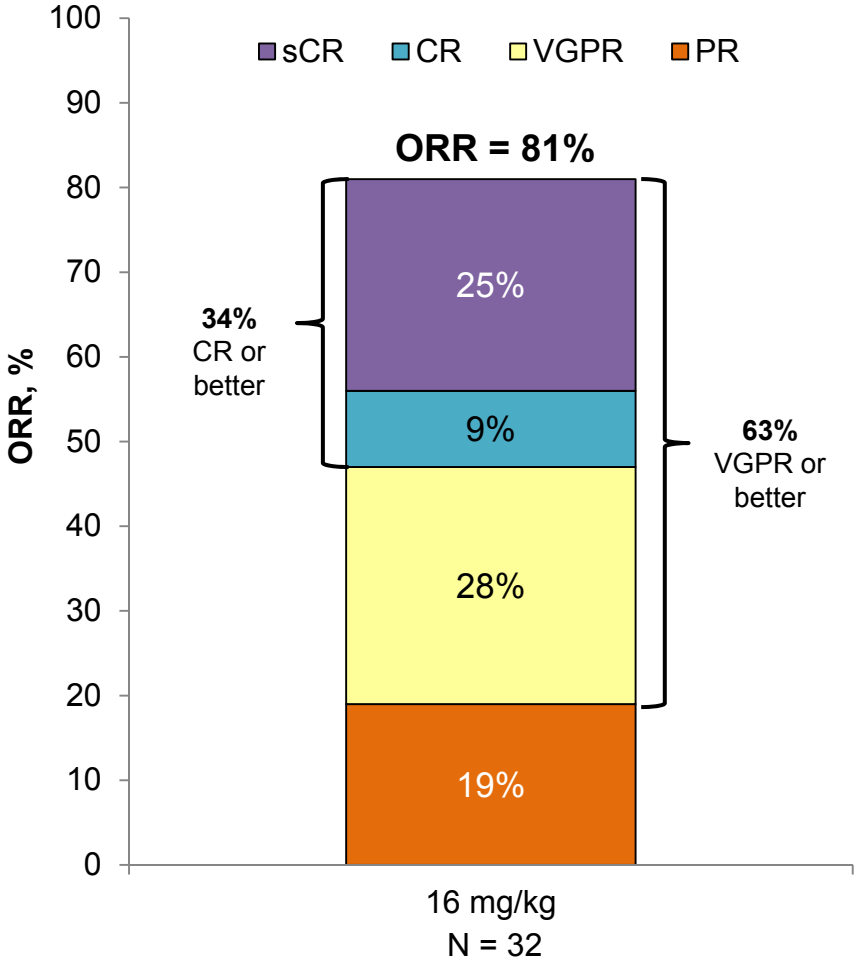
Depth and Duration of Response (≥PR):
DARA + LEN/DEX



- Median (range) time to first response = 1.0 (0.5-5.6) month
- Median (range) time to best response = 5.1 (0.5-14.4) months
- Median duration of response not reached
- 91% were disease progression-free at 12 months

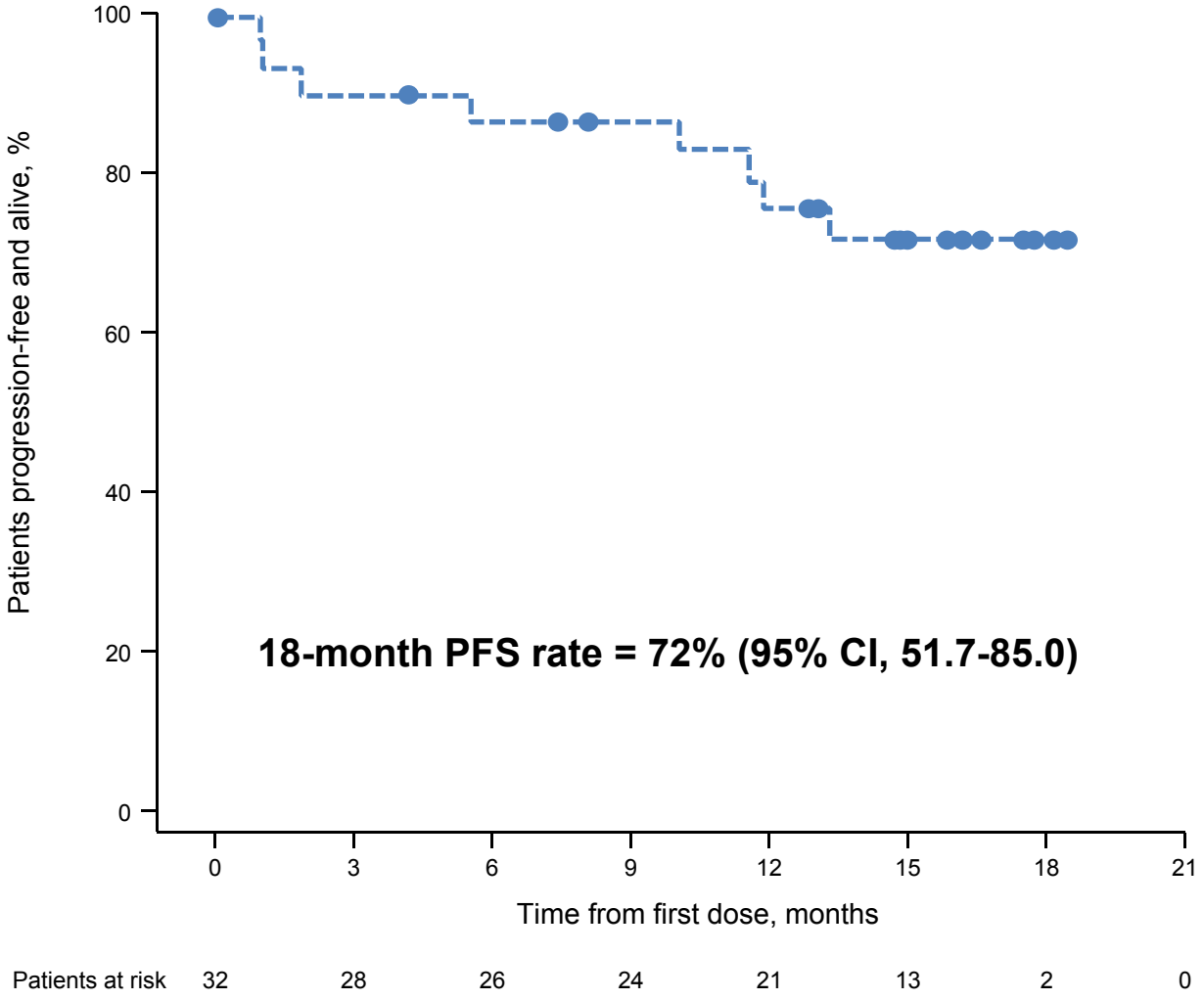
Overall Response Rate:
DARA + LEN/DEX

	N = 32	
	n (%)	**95% CI**
Overall response rate (sCR+CR+VGPR+PR)	**26 (81)**	**63.6-92.8**
Best response		
sCR	8 (25)	11.5-43.4
CR	3 (9)	2.0-25.0
VGPR	9 (28)	13.7-46.7
PR	6 (19)	7.2-36.4
VGPR or better (sCR+CR+VGPR)	20 (63)	43.7-78.9
CR or better (sCR+CR)	11 (34)	18.6-53.2



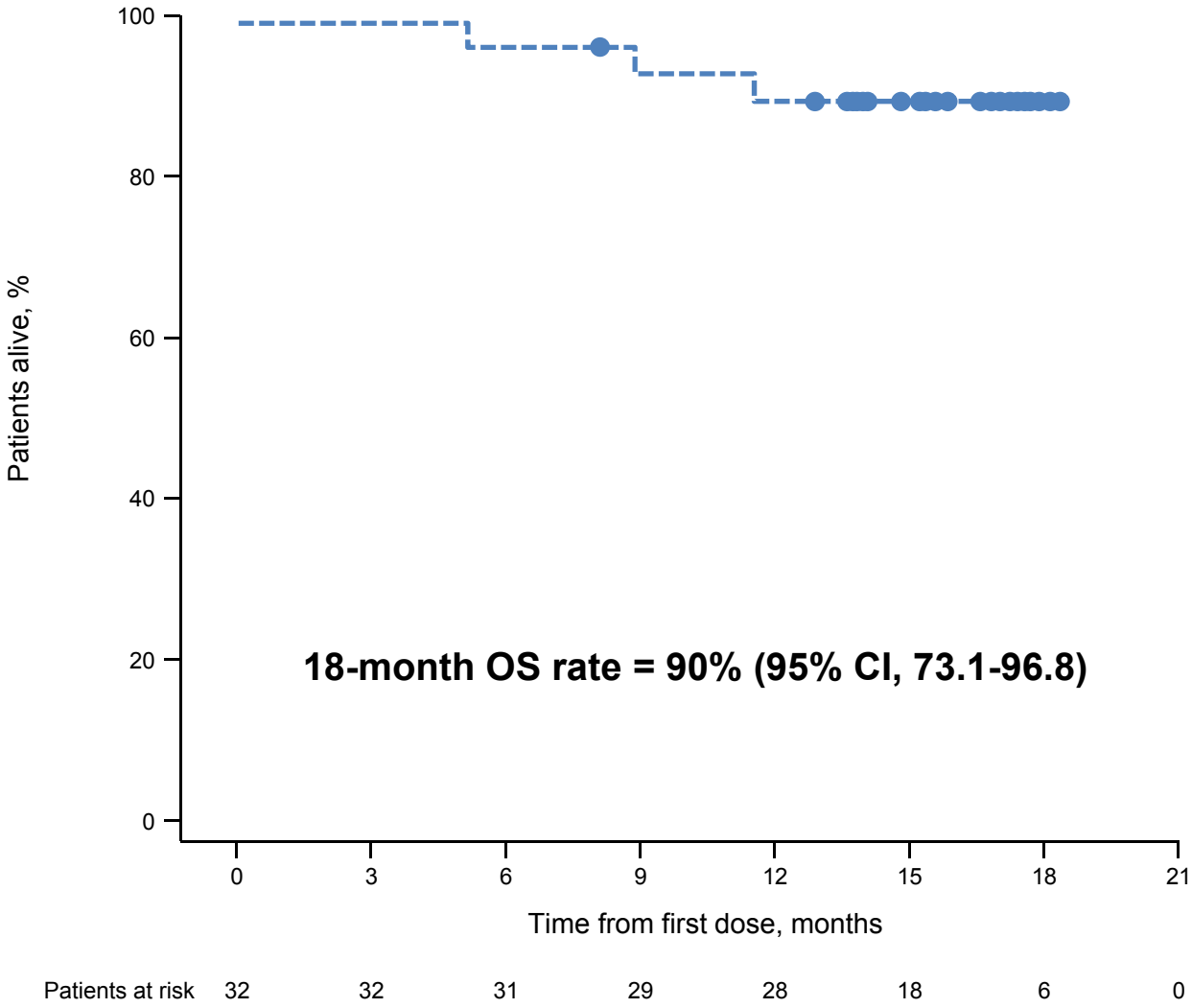
- ORR = 81%
- Clinical benefit rate (ORR + minimal response) = 88%

Progression-free Survival:
DARA + LEN/DEX



Overall Survival:

DARA + LEN/DEX



Conclusions

- DARA + LEN/DEX induced rapid, deep, and durable responses
  - At a median follow-up time of 15.6 months, ORR was 81% including 28% VGPR and 34% CR/sCR
  - Median time to first response was 1 month
  - PFS rate of 72% at 18 months
  - OS rate of 90% at 18 months
- DARA can be safely combined with LEN/DEX with no additional safety signals
- Randomized phase 3 studies of DARA are ongoing:
  - DARA + LEN/DEX in relapsed/refractory patients (POLLUX)*
  - DARA + LEN/DEX in newly diagnosed patients (MAIA)†

*ClinicalTrials.gov Identifier: NCT02076009
†ClinicalTrials.gov Identifier: NCT02252172

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