CD38: A Unique Target In Multiple Myeloma

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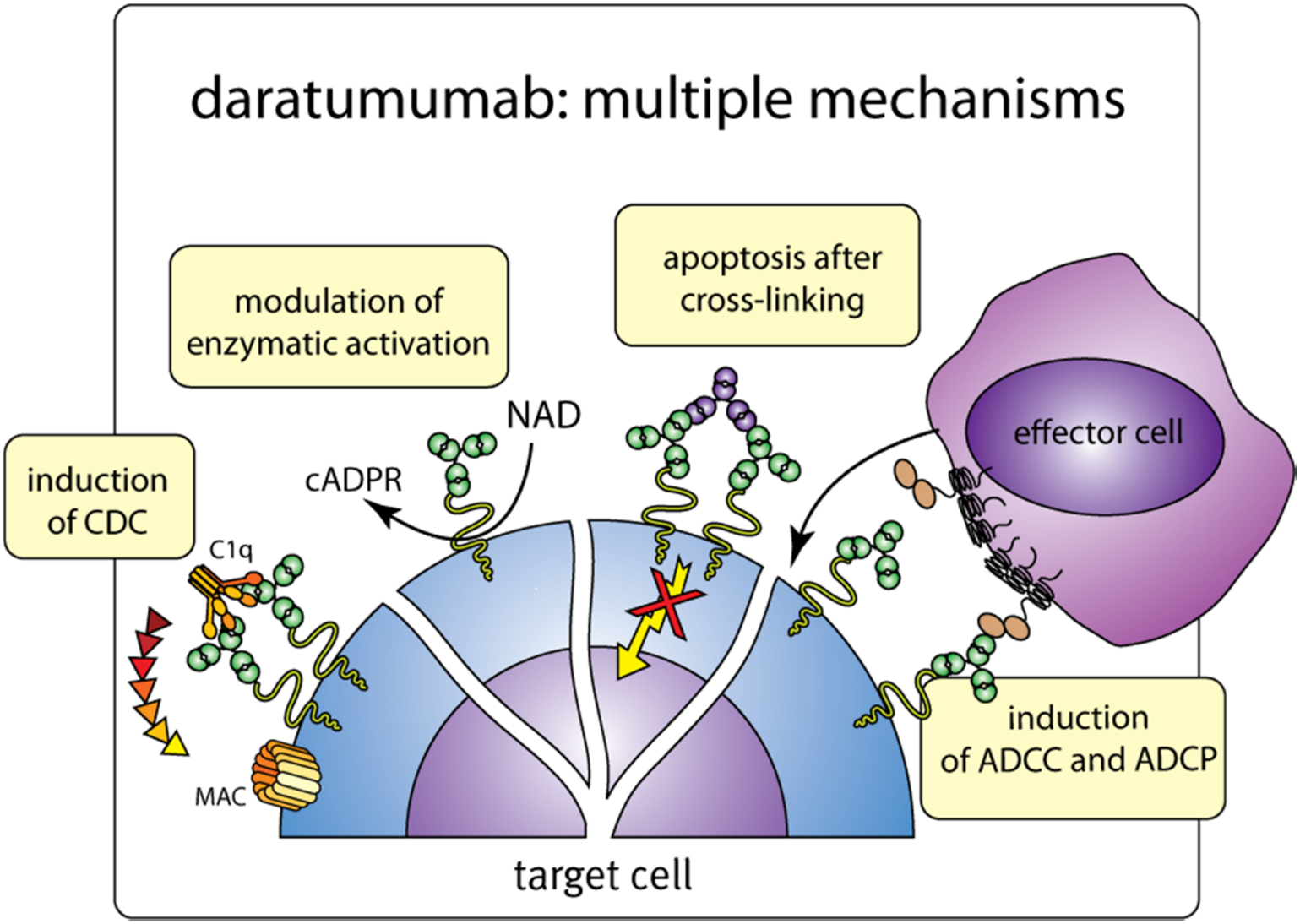
Daratumumab

A Human CD38 mAb with Broad-Spectrum Killing Activity



CD38 Landscape

Direct in-house Comparison with Competitor Surrogates

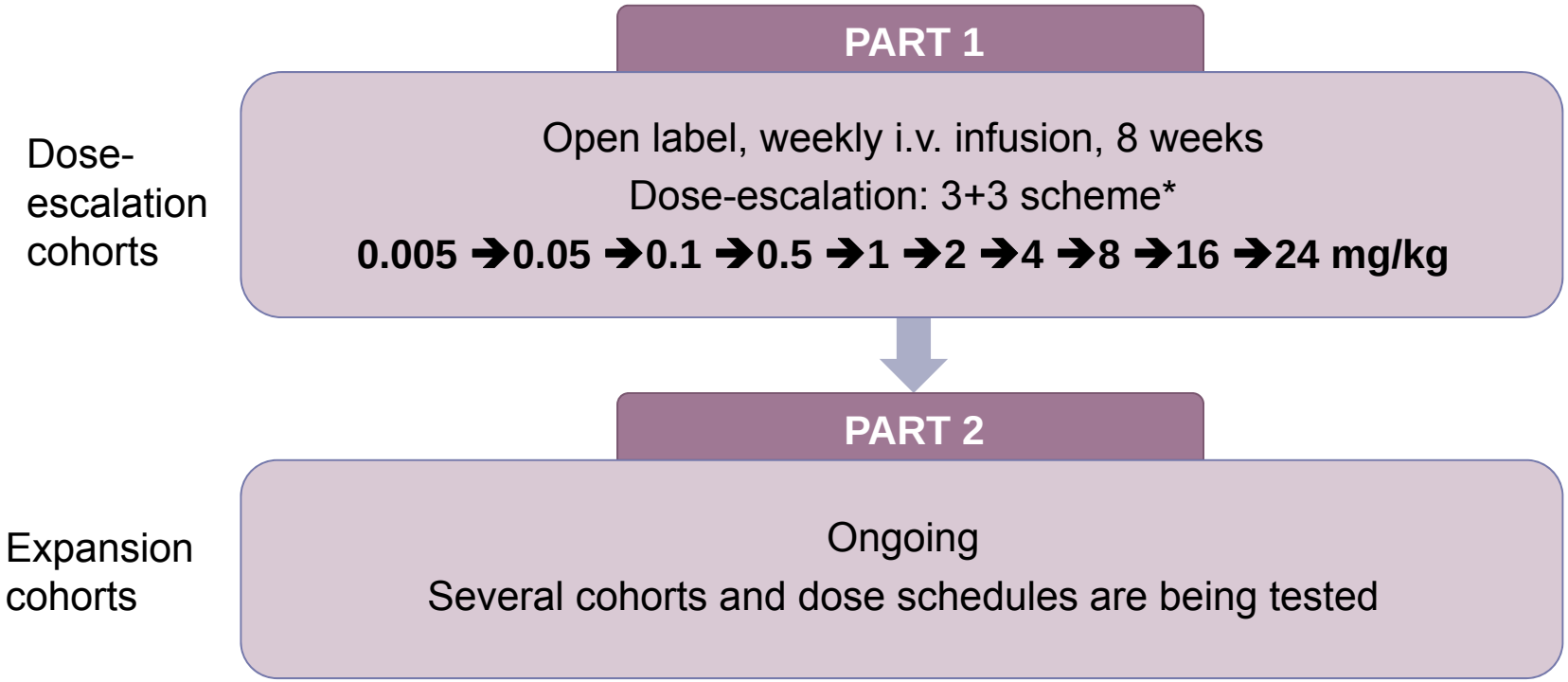
		Daratumumab (Genmab)	MOR202 [1] (MorphoSys)	SAR 650984 [1, 2] (Sanofi-Aventis)
Origin		Human	Human	Humanized
Development phase		Phase II	Phase I/IIa	Phase I
Binding [3]		+++	++	+++
Mechanism of Action	ADCC (max lysis) [3]	++	++	++
	CDC (max lysis) [3]	+++	+	+
	Phagocytosis [3, 4]	+++	++	nd
	Ecto-enzyme function	+	nd	++
	Direct PCD [5, 6]	-	-	++
	PCD after cross-linking [5, 6]	+++	+++	+++

*MOR202 clone MOR03087; [1]:surrogate mAb produced in HEK cells, generated using VH and VL sequences as published in patents WO2012/041800 (MOR03087) and WO2008/047242 A2 (38SB19); [2]:38SB19; [3]:Daudi cells; [4]:based on EC50 data, [5]:Ramos cells [6]: PCD: Programmed cell death, measured by Annexin V positivity and caspase-3 activation. nd = not determined

Daratumumab: GEN501

Phase I/II Study of ***Monotherapy*** in Relapsed or Relapsed and Refractory Multiple Myeloma

Trial Design



* - start with pre-dose at 10% of the full dose, max 10 mg
- three weeks' delay after first full dose
- governed by independent data monitoring committee

Daratumumab: GEN501
Patient Characteristics

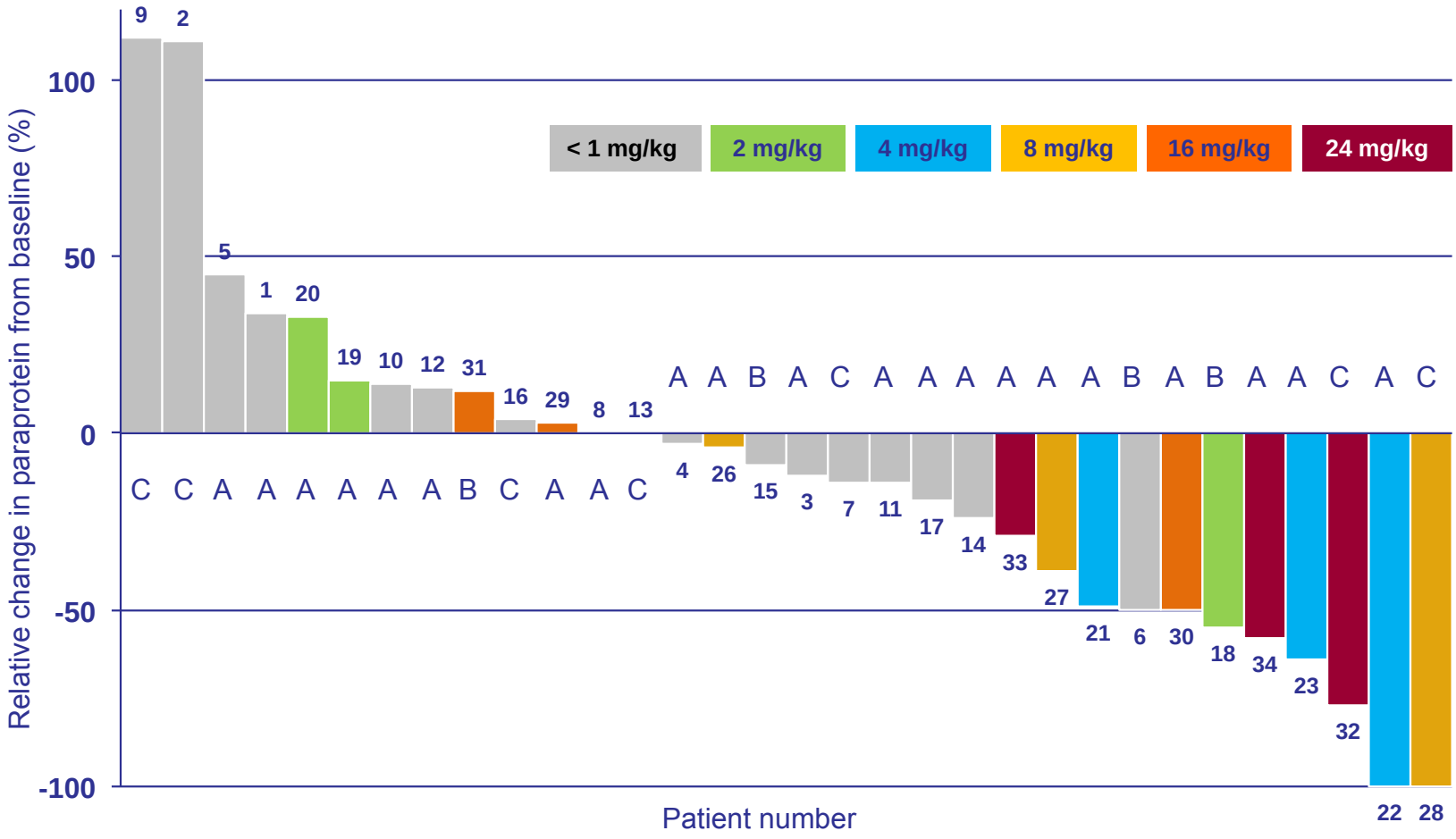
Part 1: N=32

Cohort	No subject	Age[a]	No of prior treatment	Refractory to Len and Bort	Len/Thal[b]	Bort[b]	Dex/Steroid other[b]	Chemo[b,c]	Auto/Allo[b]
≤ 1 mg/kg	17	63 (42-76)	5 (2-8)	[e]	88% / 71%	100%	88% / 41%	100%	65% / 12%
2 mg/kg	3	64 (60-71)	8 (6-10)	[e]	100% / 100%	100%	100% / 100%	100%	100% / 0%
4 mg/kg	3	64 (62-66)	3[d] (3-8)	67%[f]	100% / 33%	100%	100% / 33%	100%	67% / 33%
8 mg/kg	3	60 (56-68)	8[d] (6-12)	100%[f]	100% / 67%	100%	100% / 67%	100%	100% / 33%
16 mg/kg	3	55 (54-59)	4[d] (4-5)	67%[f]	100% / 67%	100%	100% / 33%	100%	100% / 67%
24 mg/kg	3	58 (50-69)	6[d] (4-6)	67%[f]	100% / 67%	100%	100% / 33%	100%	67% / 0%
PART 1 4-24 mg/kg	**12**	**59 (50-69)**	**5.5 (3-12)**	**75%**	**100% / 58%**	**100%**	**100% / 42%**	**100%**	**83% / 33%**

Allo: allogeneic stem cell transplantation, Auto: autologous stem cell transplantation, Bort: bortezomib, Chemo: chemotherapy, Len: lenalidomide, No: number, Thal: thalidomide
a: median (range), b: number of patients exposed to the drug, c: vincristine, doxorubicin, cyclophosphamide, melphalan and others, d: revised after additional data collection, e: data not collected, f: data collected retrospectively

Daratumumab: GEN501 Response (Part 1)

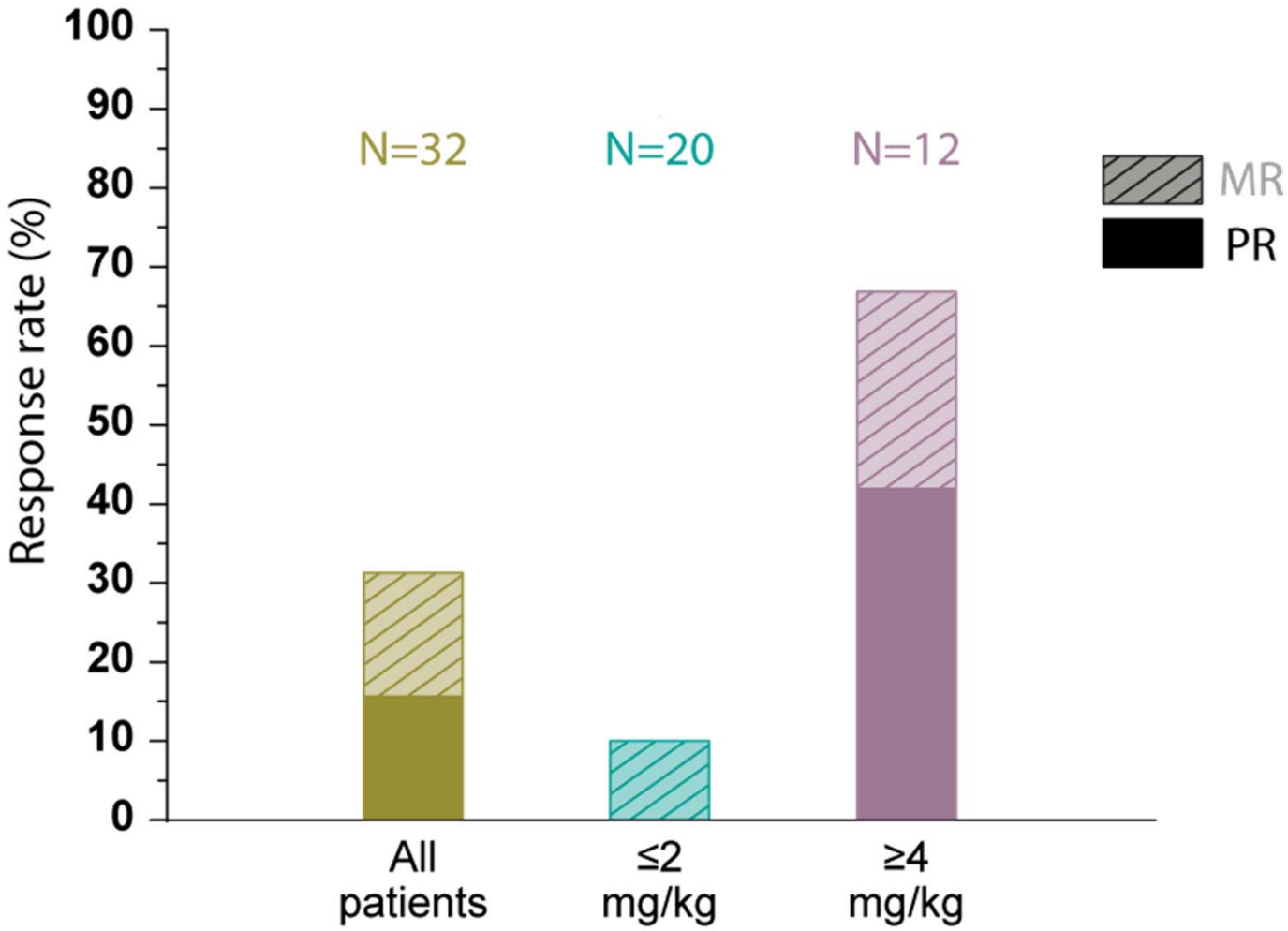
Best Change in Response Paraprotein



A: serum M-component, B: urine M-component, C: Free Light Chains (FLC)

Daratumumab: GEN501 (Part 1)

Clinical benefit according to IMWG



Daratumumab: GEN501 ≥4mg/kg (Part 1)

Max. Reduction of M-Component/FLC/BM PCs and by IMWG Criteria

Cohort (mg/kg)	N	Max. reduction in M-component (%)		Max. reduction in difference between involved and uninvolved FLC (%)	Max. reduction in plasma cells in bone marrow biopsy (%) [Baseline value (%)]	Response according to IMWG[a]
		Serum	Urine			
4	3	49	*	*	80 [12.5]	MR
		100	87	96	89 [23]	PR
		64	*	*	97 [19]	PR
8	3	4	*	*	-29 [14]	SD
		39	*	*	93 [7.5]	MR
		*	*	*	-	NE
16	3	-3	*	-12	-	PD
		50	*	88	100 [31.5]	PR
		*	-12	55	100 [2]	SD
24	3	*	*	80[b]	51 [18.5]	PR
		29	*	*	17 [3.0]	MR
		68[b]	93	94	91 [17.0]	PR

* no measurable disease/normal at Baseline

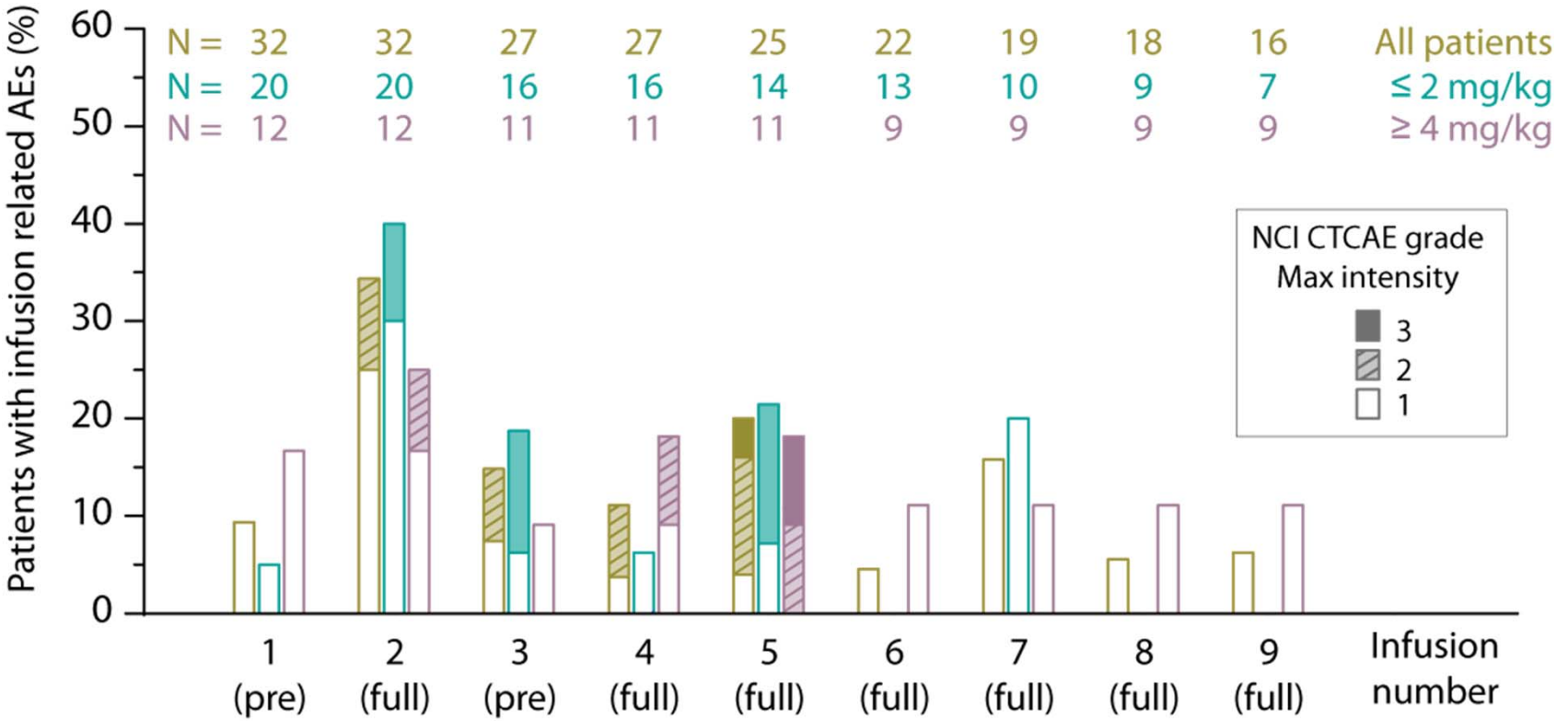
\- data not available

[a] Evaluation based on max. reduction in M-component or FLC

[b] Follow up still ongoing at time of data cut-off

Daratumumab: GEN501

Infusion Related Adverse Events



Daratumumab: GEN501

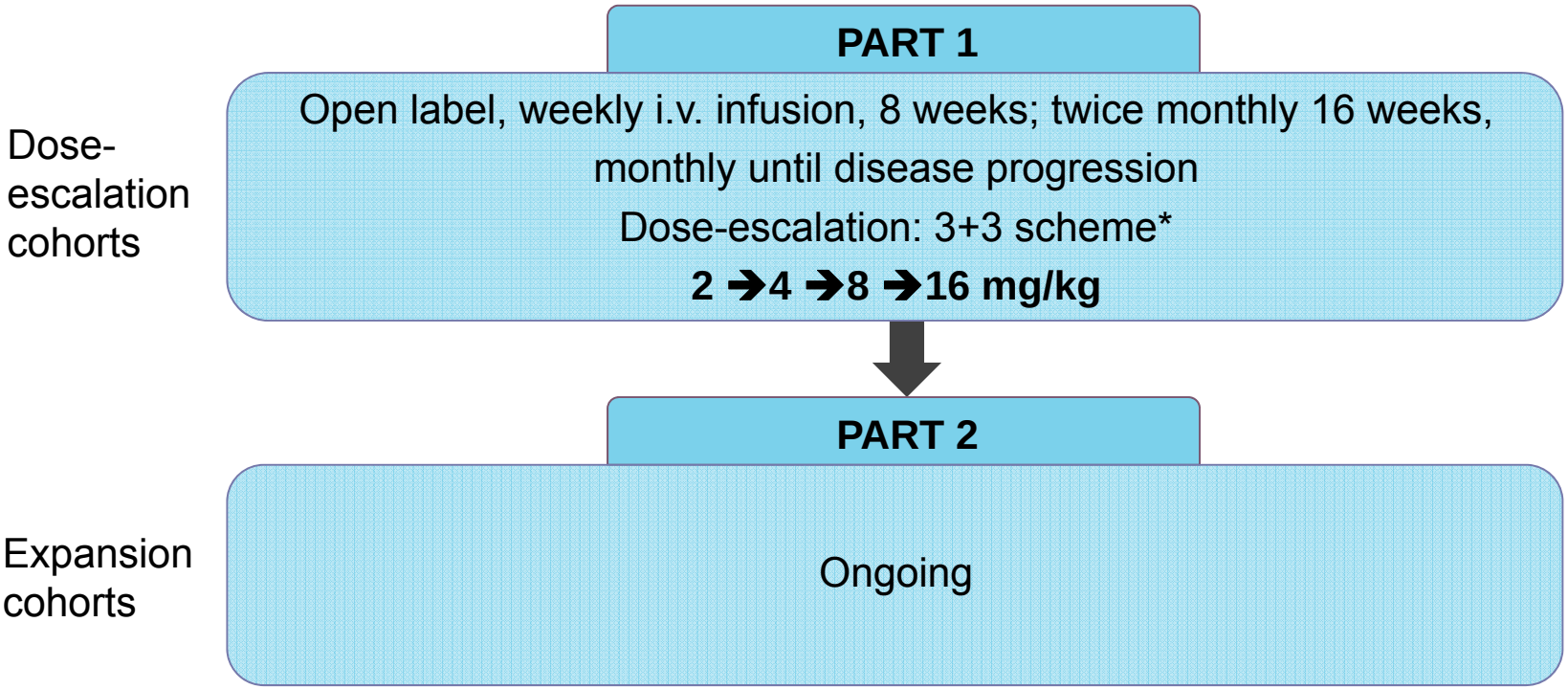
SAEs Assessed Related to Daratumumab

Event	PART 1 N=32
Bronchospasm	1 patient: grade 2 (2 mg/kg) (2 days later grade 3) 1 patient: grade 2 (24 mg/kg)
Anemia	1 patient: grade 3 (0.1 mg/kg) (DLT)
Thrombocytopenia	1 patient: grade 4 (0.1 mg/kg)
ASAT > 5.2 times upper limit of normal	1 patient: grade 2 + grade 3 (1 mg/kg) (DLT)
Cytokine release syndrome	1 patient: grade 2 (0.1 mg/kg)

Daratumumab: GEN503

Combination with Lenalidomide and Dexamethasone in Relapsed or Refractory Multiple Myeloma

Trial Design



* governed by independent data monitoring committee

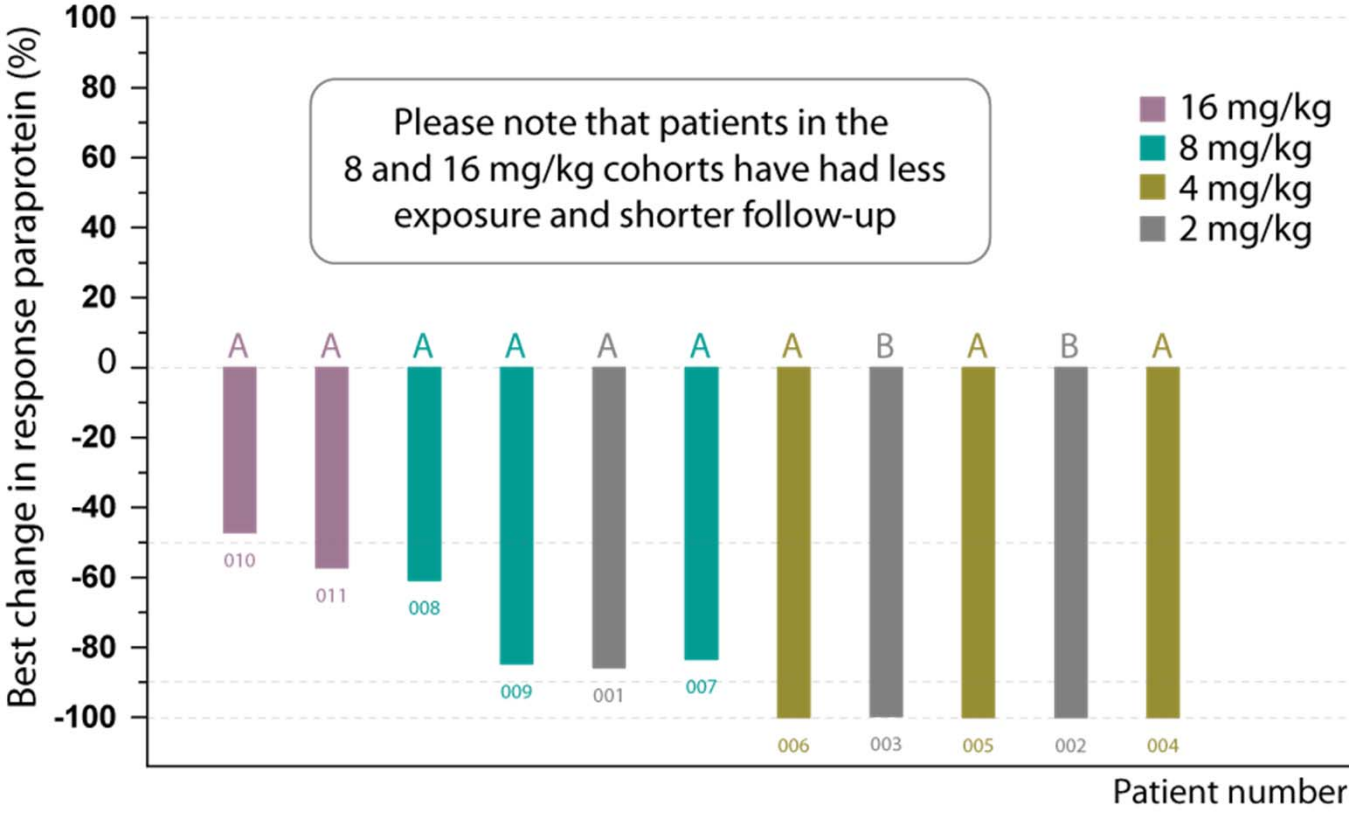
Daratumumab: GEN503

Baseline Characteristics and Demography

Characteristics	2 mg/kg (N=3)	4 mg/kg (N=3)	8 mg/kg (N=4)	16 mg/kg (N=2)	Total (N=12)
Gender, n					
Male/female	3/0	2/1	4/0	1/1	10/2
Age, years					
Median (range)	69 (48-71)	62 (61-65)	56 (49-69)	66 (56-76)	62 (48-76)
Prior lines of therapy					
Median (range)	4 (4-4)	3 (2-4)	4 (3-4)	3 (2-4)	4 (2-4)
LEN, refractory, n					
Refractory	0	1	1	0	2
Non refractory	1	1	1	0	3
LEN naïve	0	0	1	2	3
Not evaluable	2	1	1	0	4
Years since MM diagnosis					
Median (range)	4.0 (2.2-7.6)	2.1 (1.9-5.1)	3.2 (0.9-5.1)	5.5 (1.1-10.0)	3.2 (0.9-10.0)
Body weight, kg					
Median (range)	96 (84-97)	74 (72-83)	88 (79-105)	76 (72-79)	82 (72-105)
ECOG					
0	2	1	1	2	6
1	1	2	3	0	6
2	0	0	0	0	0

Daratumumab: GEN503

Best Change in Response Paraprotein



The best change in response paraprotein evaluated according to IMWG 2011.

A: serum M-protein, B: urine-M-protein

Daratumumab: GEN503

Efficacy

	2 mg/kg (N=3)	4 mg/kg (N=3)	8 mg/kg (N=4)	16 mg/kg (N=2)	Total (N=12)
Number of infusions					
Median (range)	21 (14-23)	18 (18-20)	12.5 (1-15)	5 (5-5)	14.5 (1-23)
Response	(N=3)	(N=3)	(N=3)	(N=2)	(N=11)
CR	1	2	0	0	3
VGPR	1	1	0	0	2
PR	1	0	2	0	3
MR	0	0	1	1	2
SD	0	0	0	1	1
PD	0	0	0	0	0

Time to response	Pt no 1/2/3	Pt no 4/5/6	Pt no 7/8/9	Pt no 10/11	Total (n=8) Median (range)
≥ PR, weeks	4.1 / 2.1 / 4.1	4.3 / 2.0 / 2.1	4.0 / NA / 4.3	NA / NA	4.1 (2.0-4.3)

Daratumumab: GEN503
Safety

- No DLTs were reported at any dose level
- Four SAEs were reported; all assessed as unrelated to daratumumab
- Most frequent AEs reported in >2 patients; shown in table below

% of patients	2 mg/kg (N=3)	4 mg/kg (N=3)	8 mg/kg (N=4)	16 mg/kg (N=2)	Total (N=12)
Neutropenia	100	33	25	0	42
Diarrhoea	33	100	25	0	42
Constipation	100	33	0	0	33
Nausea	33	67	25	0	33
Fatique	100	0	25	0	33
Bone pain	33	33	25	0	25
Muscle spasms	33	67	0	0	25
Anaemia	33	67	0	0	25
Insomnia	0	67	25	0	25
Pyrexia	33	33	25	0	25

Daratumumab
Summary (1/2)

- CD38 represents a unique target and holds promise as a new treatment option for multiple myeloma
- Daratumumab is a human CD38 mAb with broad-spectrum killing activity
  - ***CDC***, ADCC, apoptosis, phagocytosis, modulation ecto-enzyme activity
- Daratumumab has shown favorable safety profile as monotherapy and in combination with lenalidomide and dexamethasone in multiple myeloma patients
- MTD not reached in mono & combination (Len/Dex) therapy
- In monotherapy study GEN501 part 1, 15 of 32 (47%) heavily pre-treated evaluable multiple myeloma patients, showed a reduction in paraprotein
- In 10 of these 32 patients (31%), this reduction qualified as a clinical benefit:
  - 5 patients achieving PR (16%)
  - 5 patients achieving MR (16%)
- 8 of 12 patients (67%) at doses 4 mg/kg and above achieved a clinical benefit:
  - 5 patients achieving PR (42%)
  - 3 patients achieving MR (25%)
- Biochemical response was accompanied by clearance myeloma cells from bone marrow

Daratumumab
Summary (2/2)

- Daratumumab in combination with lenalidomide and dexamethasone in relapsed or refractory multiple myeloma patients lead to a reduction in M-protein in 8 of 11 patients (73%)
  - 3 CR (27%)
  - 2 VGPR (18%)
  - 3 PR (27%)
  - 2 MR (18%)

Outlook

- These results warrant further development of daratumumab as monotherapy as well as in combination with other multiple myeloma treatment modalities
- Preclinical data suggest activity of daratumumab combinations with lenalidomide and bortezomib even in patients refractory to lenalidomide and bortezomib (Nijhof et al., ASH 2013)

- Given CD38 is expressed in other hematological diseases than multiple myeloma, these might be addressable with daratumumab as well
- Daratumumab shows anti-tumor activity In mouse models of MCL, FL and CLL (Matas-Céspedes et al., ASH 2013)

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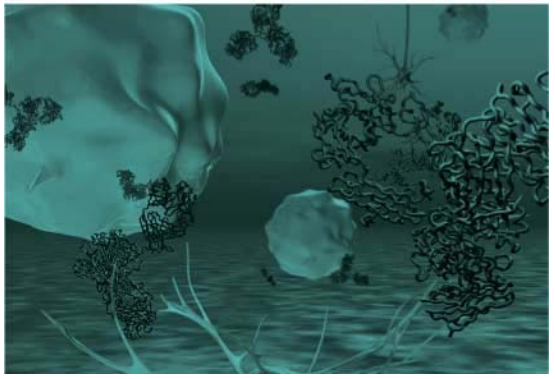

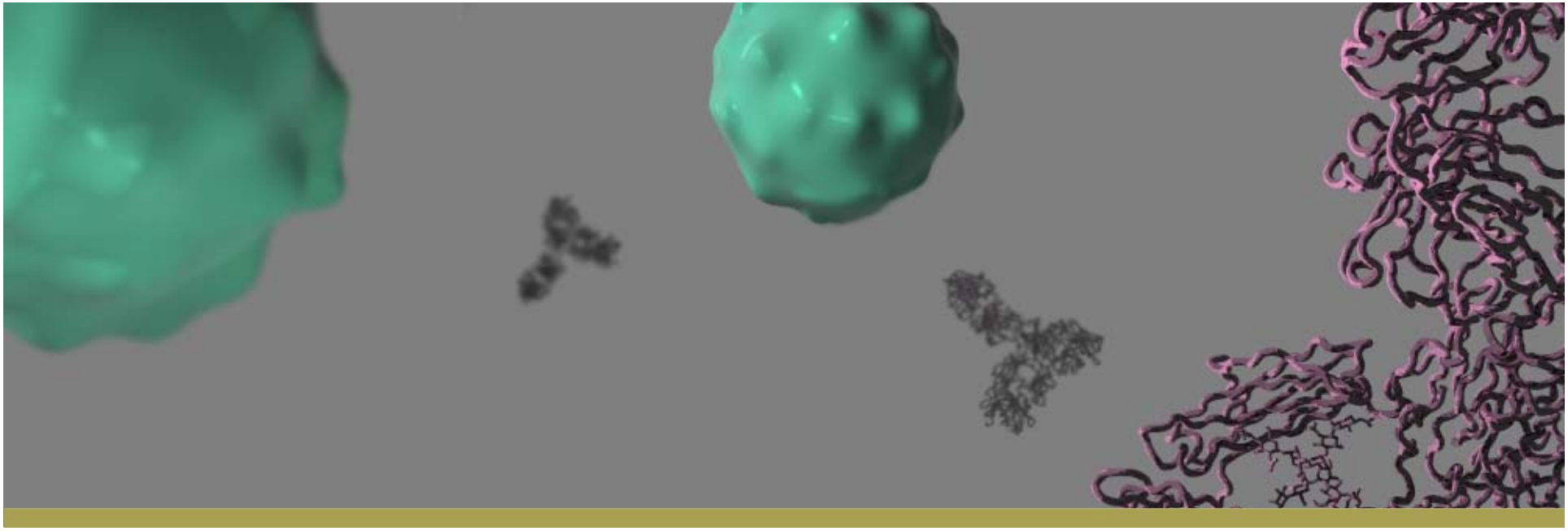

Thank You!