First experience with Daratumumab for treatment of relapsed-refractory multiple myeloma

Czech Myeloma Group meeting

Mikulov, April 2014

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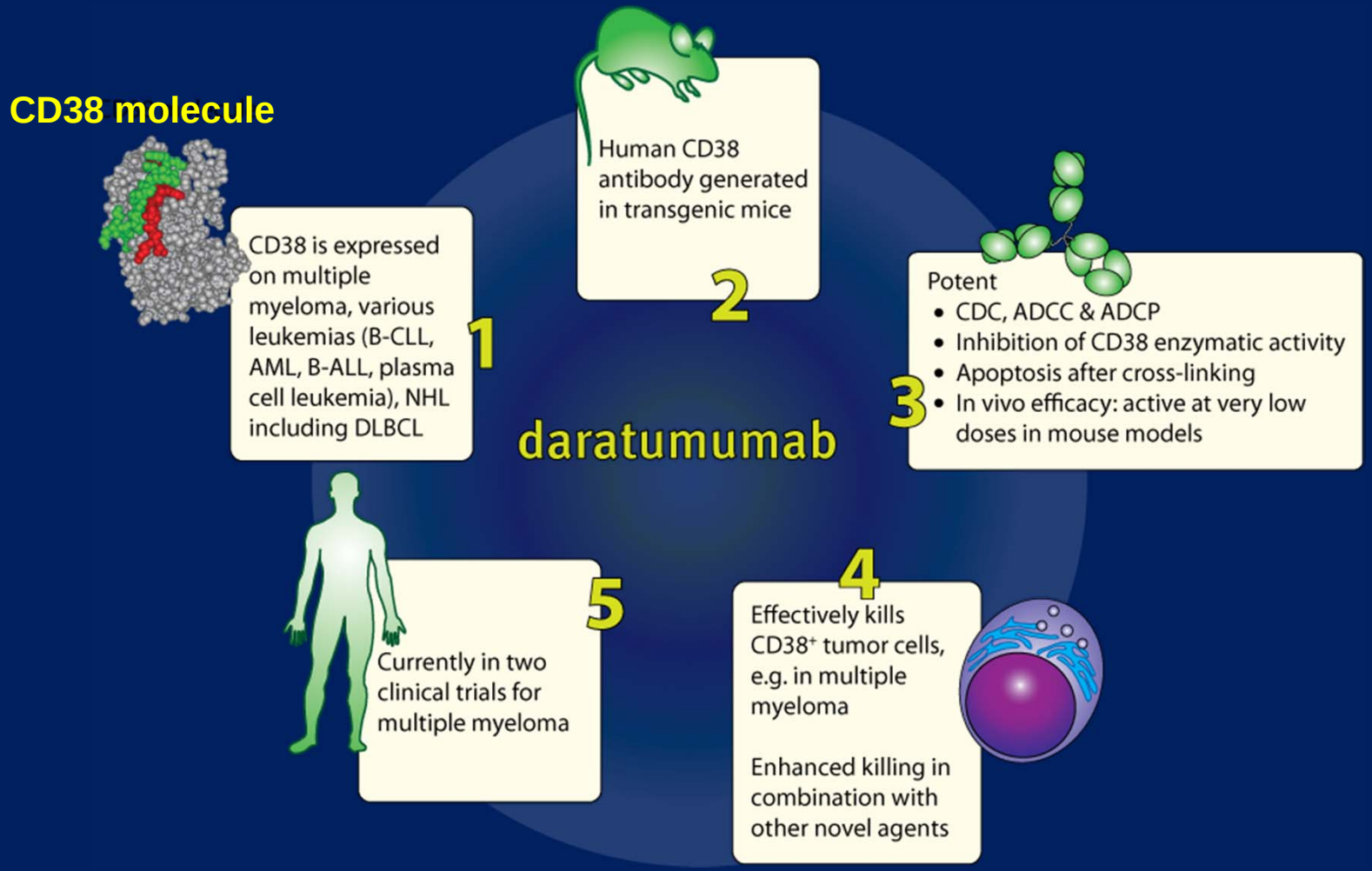
Monoclonal antibodies in MM

Target	mAb	Stage of development
Surface molecules		
CS1	Elotuzumab	Phase 2/3
CD38	Daratumumab (Genmab/Janssen)	Phase 1/2/3
	SAR650984 (Sanofi)	Phase 1/1b
	MOR202 (MorphoSys/Celgene)	Phase 1/2
CD74	Milatuzumab	Phase 1/2
CD40	Dacetuzumab	Phase 1
CD56	Lorvotuzumab mertansine	Phase 1
CD138	BT062	Phase 1
Signaling molecules		
IL-6	Siltuximab	Phase 3
RANKL	Denosumab	Phase 3
B cell activating factor (BAFF)	Tabalumab	Phase 2/3
VEGF	Bevacizumab	Phase 2
DKK1	BHQ880	Phase 2

Daratumumab

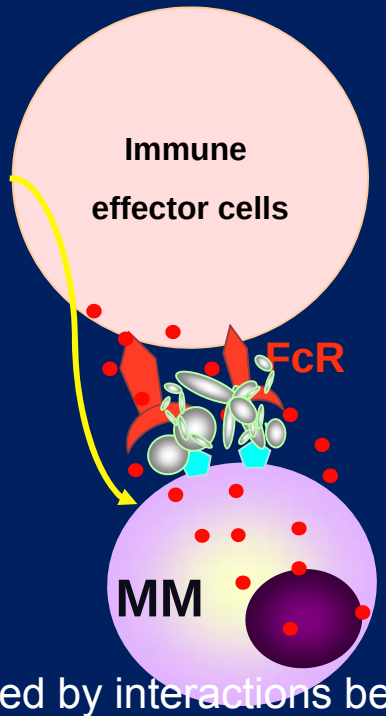
A Human CD38 mAb with Broad-Spectrum Killing Activity



Mechanism of action

Antibody-dependent cellular cytotoxicity (ADCC)

ADCC



- ADCC triggered by interactions between Ab bound to tumor cell and receptors for Ab on immune cells (neutrophils, macrophages, natural killer cells)
- → tumor cells phagocytozed by macrophages or cytolysis by NK cells

Adapted from: Tai & Anderson Bone Marrow Res 2011;2011:924058

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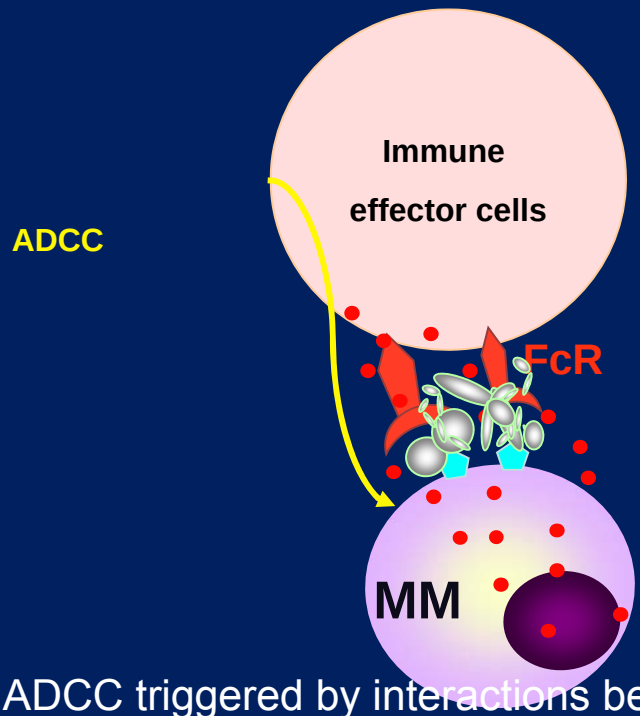

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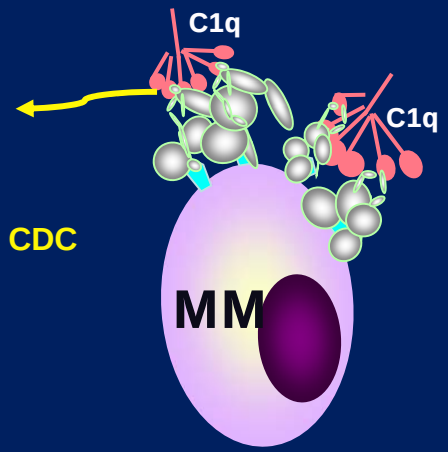
Complement-dependent cytotoxicity (CDC)



- Recruitment of complement factor (C1q) by Ab bound to tumor cell
- → triggers proteolytic cascade: generation of effector molecule, C3b, formation of membrane attack complex
- → killing of target cell by disruption of cell membrane

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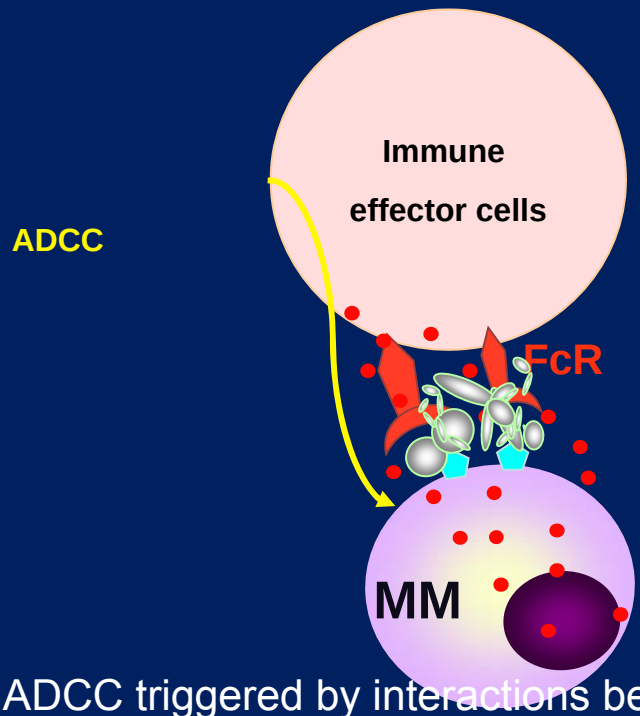

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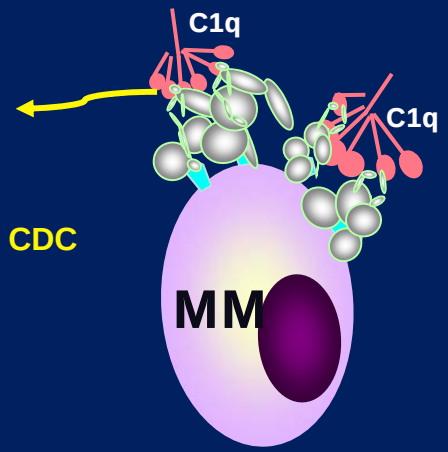

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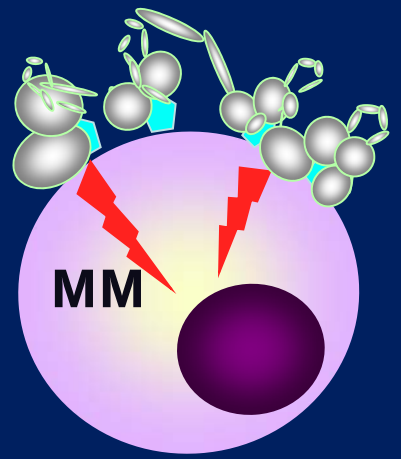
Apoptosis/growth arrest via targeting signaling pathways



- Direct induction of apoptosis or growth arrest upon binding of Ab on tumor cells

Adapted from: Tai & Anderson Bone Marrow Res 2011;2011:924058

GEN 501: Main Inclusion Criteria

- Patients with advanced Multiple Myeloma requiring systemic therapy
- Patients with relapsed or relapsed and refractory disease with at least 2 prior lines of therapy and without further established treatment options
- Patients with ECOG performance status 0-2
- Patients having a life expectancy >3 months

GEN 501: 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)	▪	88% / 71%	100%	88% / 41%	100%	65% / 12%
2 mg/kg	3	64 (60-71)	8 (6-10)	▪	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

GEN 501: Phase 1/2 study of single-agent daratumumab in rel/ref MM

Part 1 completed: 32 pts

Dose-escalation cohorts

Open label, weekly i.v. infusion, 8 weeks

Dose-escalation: 3+3 scheme*

0.005→0.05→0.1→0.5→1.0 →2.0→4.0→8.0→16.0 →24.0 mg/kg

***: - 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

Part 2 ongoing: 80 pts

Expansion cohort and extended treatment period for close to 2 years

Open label, single arm, 8 and 16 mg/kg

8 weekly infusions followed by

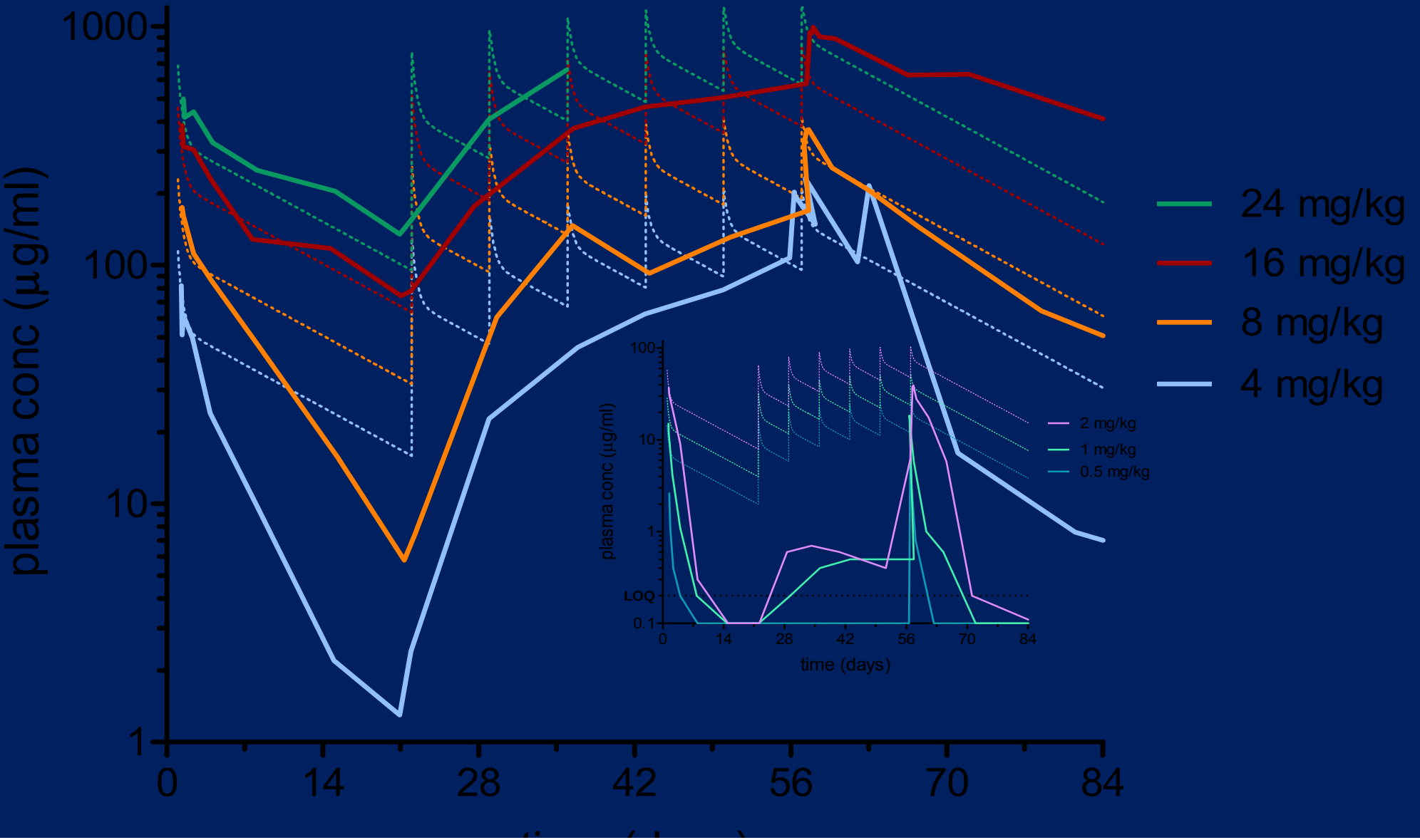
8 biweekly infusions followed by up to

72 monthly infusions

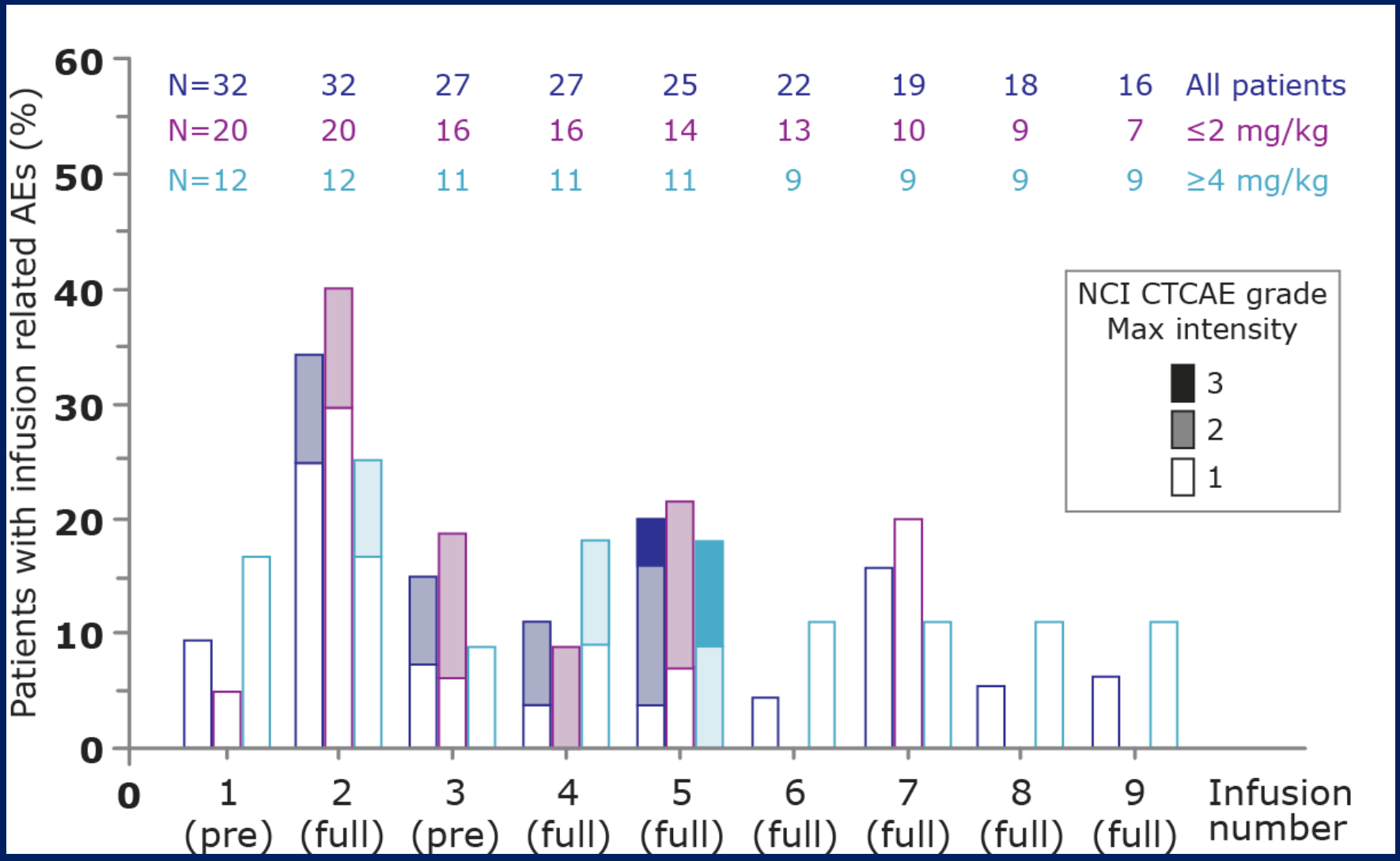
Different combinations of premedications, predose infusions, infusion volumes, and infusion rates (3 – 4 hours)

Plesner et al. ASH 2012 (Abstract 73), oral presentation; Plesner et al. IMW 2013 (Abstract P-130), poster presentation

GEN 501: Plasma concentration



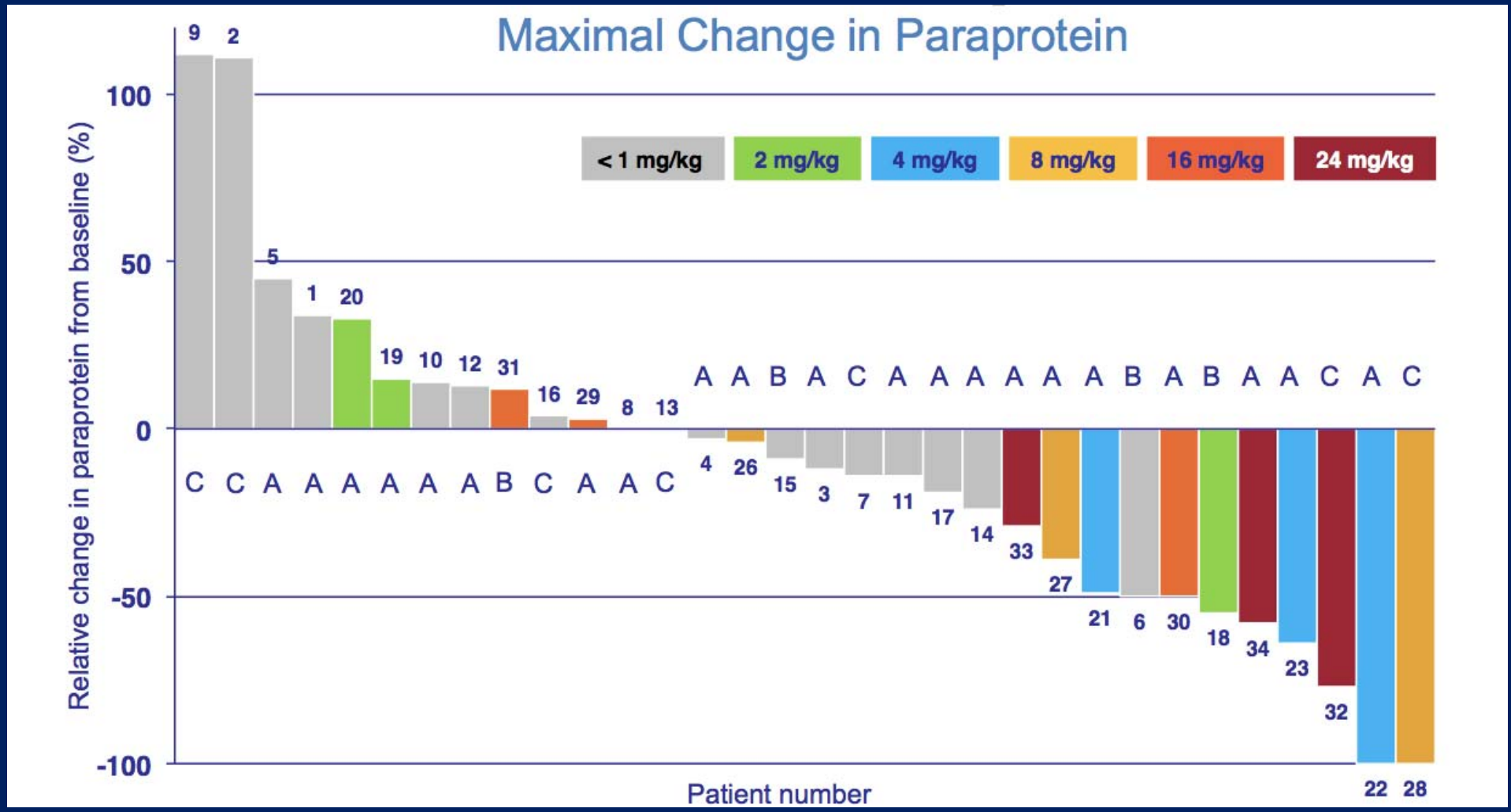
GEN 501: Safety Findings



GEN 501: SAEs Assesed Related to Daratumumab

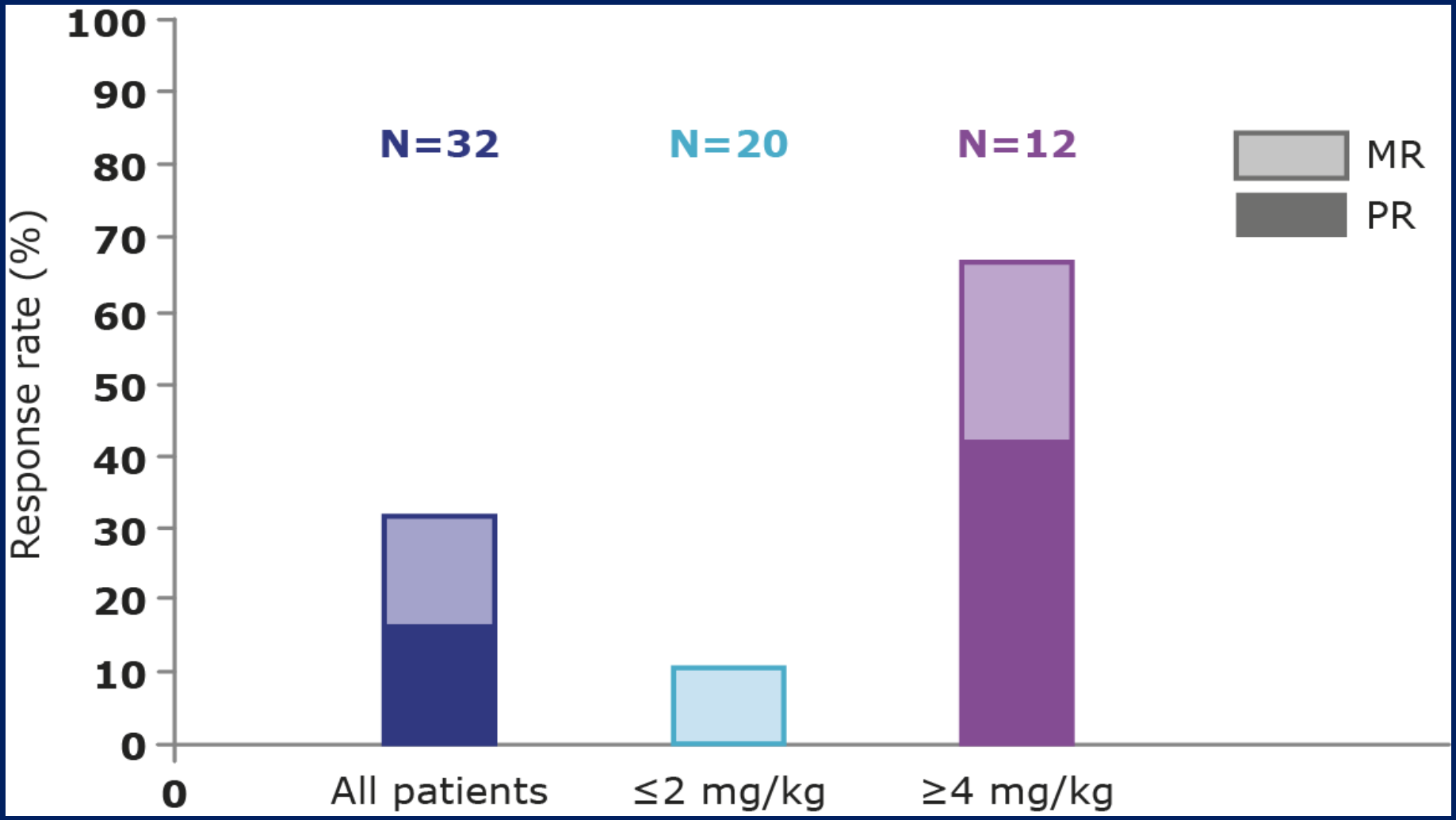
Event	PART 1 N=32
Bronchospasm	1 patient: grade 2 (2 mg/kg) (2 days later grade 3) 1 patient: grade 2 (24 mg/kg)
Anemia	1 patient: grade 3 (0.1 mg/kg) (DLT)
Thrombocytopenia	1 patient: grade 4 (0.1 mg/kg)
ASAT > 5.2 times upper limit of normal	1 patient: grade 2 + grade 3 (1.0 mg/kg) (DLT)
Cytokine release syndrome	1 patient: grade 2 (0.1 mg/kg)

GEN 501: Response to treatment

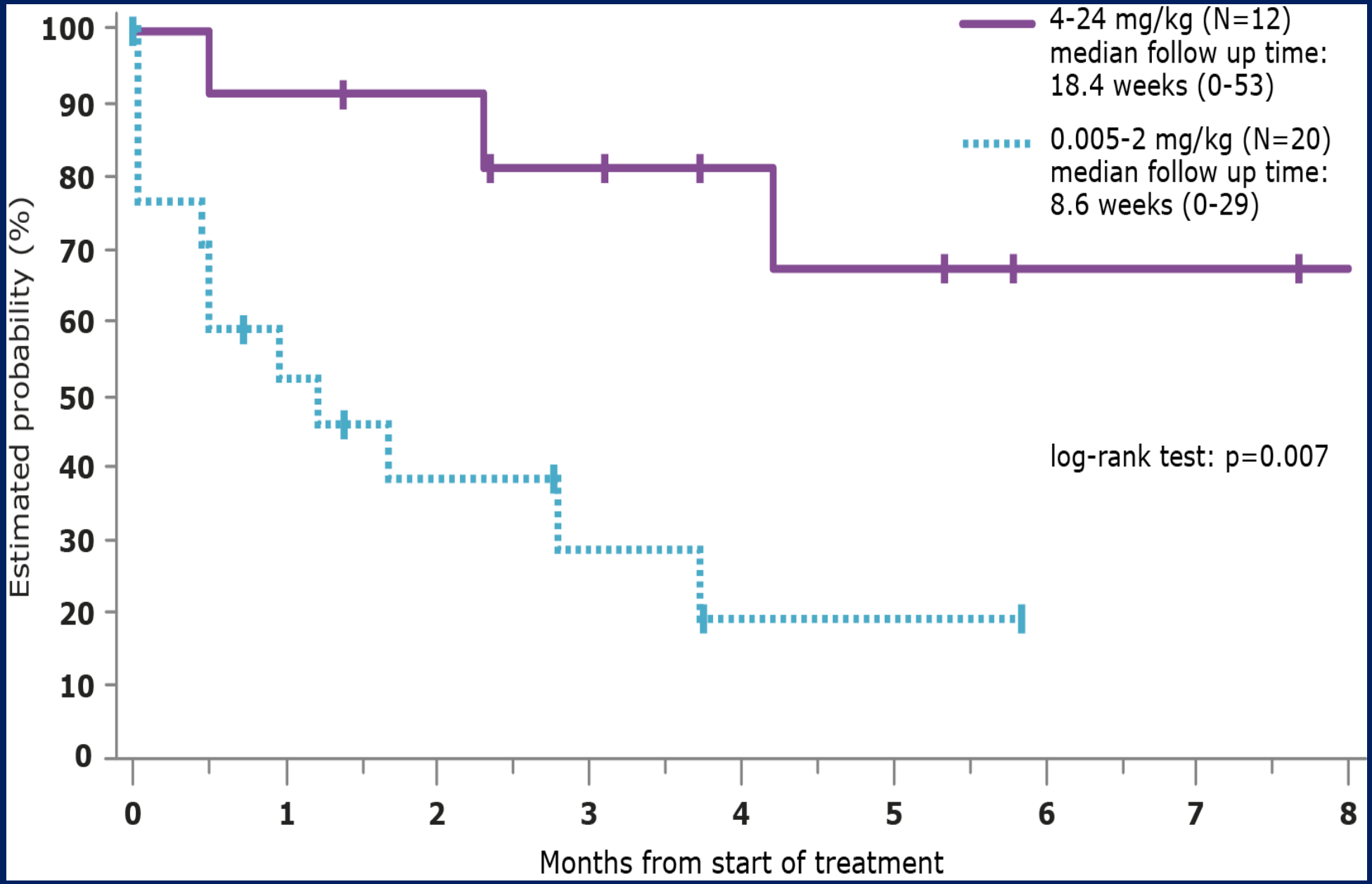


A: serum M-component, B: urine M-component, C: Free Light Chains (FLC)

GEN 501: Response according to IMWG



GEN 501: Progression-Free Survival



GEN503: Phase 1/2 study of daratumumab + len/dex in relapsed or refractory MM

Pts with rel/ref MM (part 1: 2-4, part 2: 1-3 prior l.o.t).

Must be eligible for Len/dex

Part 1: 3 + 3 dose-escalation design

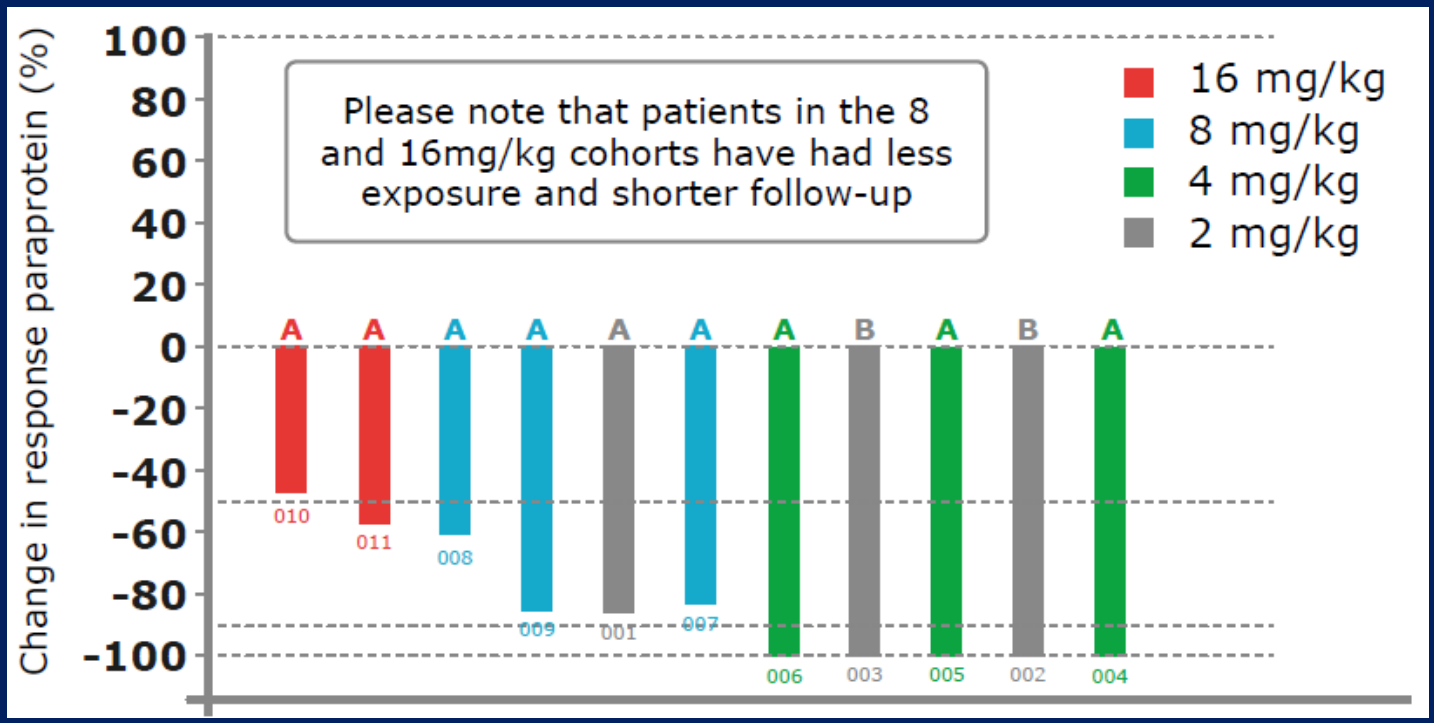
- DARA: 2, 4, 8 or 16 mg/kg weekly for 8 weeks, twice a month for 16 weeks, then once a month until disease progression, unmanageable toxicity or up to maximum 24 months

  Dose level of DARA maintained as assigned per cohort
- LEN administered according to label (25 mg on 21/28 days)
- DEX 40 mg weekly (on days of DARA infusion split into 20/20 mg iv/oral)

Plesner et al. ASH 2013 (Abstract 1987), poster presentation

GEN503: Phase 1 part of daratumumab + len/dex in relapsed or refractory MM

- All patients have a marked decrease in paraprotein



- CR 3, VGPR 2, PR 3, MR 2, SD 1
- Most frequent AEs reported in >2 patients: neutropenia, GI, musculoskeletal disorders
  - Mostly related to len + dex

Plesner et al. ASH 2013 (Abstract 1987), poster presentation

mAbs in combination with Len/dex

	Daratumumab + Len/Dex	Elotuzumab + Len/Dex
Target	CD38	CS1
Single-agent activity	Yes	Limited
Study details	Phase 1/2 dose escalation & expansion	Phase 2
Patients	n=13 with rel/ref MM	n=73 with rel/ref MM
Results	3 CR, 2 VGPR, 3 PR, 2 MR, 1 SD	• 10 mg/kg (Phase 3 dose): ORR 92%, PFS not reached • 20 mg/kg: ORR 76%, PFS 18.6 months
Planned/ ongoing studies	Phase 1/2/3 •Single agent •+ Len/dex •Other combinations	Phase 2/3 •+ Len/Dex •+ Vel/Dex •+ VRD

Plesner et al. ASH 2013 (Abstract 1987), poster presentation

Richardson et al. et al. IMW 2013 (Abstract P-214), poster presentation

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THANK YOU FOR YOUR ATTENTION.

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