Abstract #1143

DARATUMUMAB, A CD38 MONOCLONAL ANTIBODY IN PATIENTS WITH MULTIPLE MYELOMA - PRELIMINARY EFFICACY AND PHARMACOKINETICS DATA FROM A DOSE-ESCALATION PHASE I/II STUDY

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My disclosures

- Genmab: Research support, advisory board
- Celgene: Research support, speaker's fee
- Janssen-Cilag: Speaker's fee
- Mundipharma: Advisory Board

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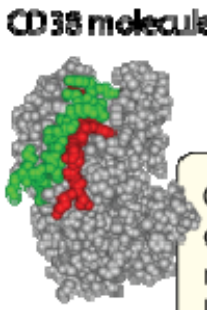
Daratumumab



CD38 is expressed on multiple myeloma, various leukemias (B-CLL, AML, B-ALL, plasma cell leukemia), NHL including DLBCL

1

Human CD38 antibody generated in transgenic mice

2

daratumumab

Potent

- ADCC & CDC
- Inhibition of CD38 enzyme activity
- Apoptosis after cross-linking
- In vivo efficacy: active at very low doses in mouse models

3

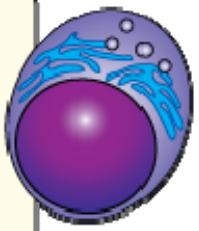
Currently in a Phase I/II clinical trial for multiple myeloma

5

4

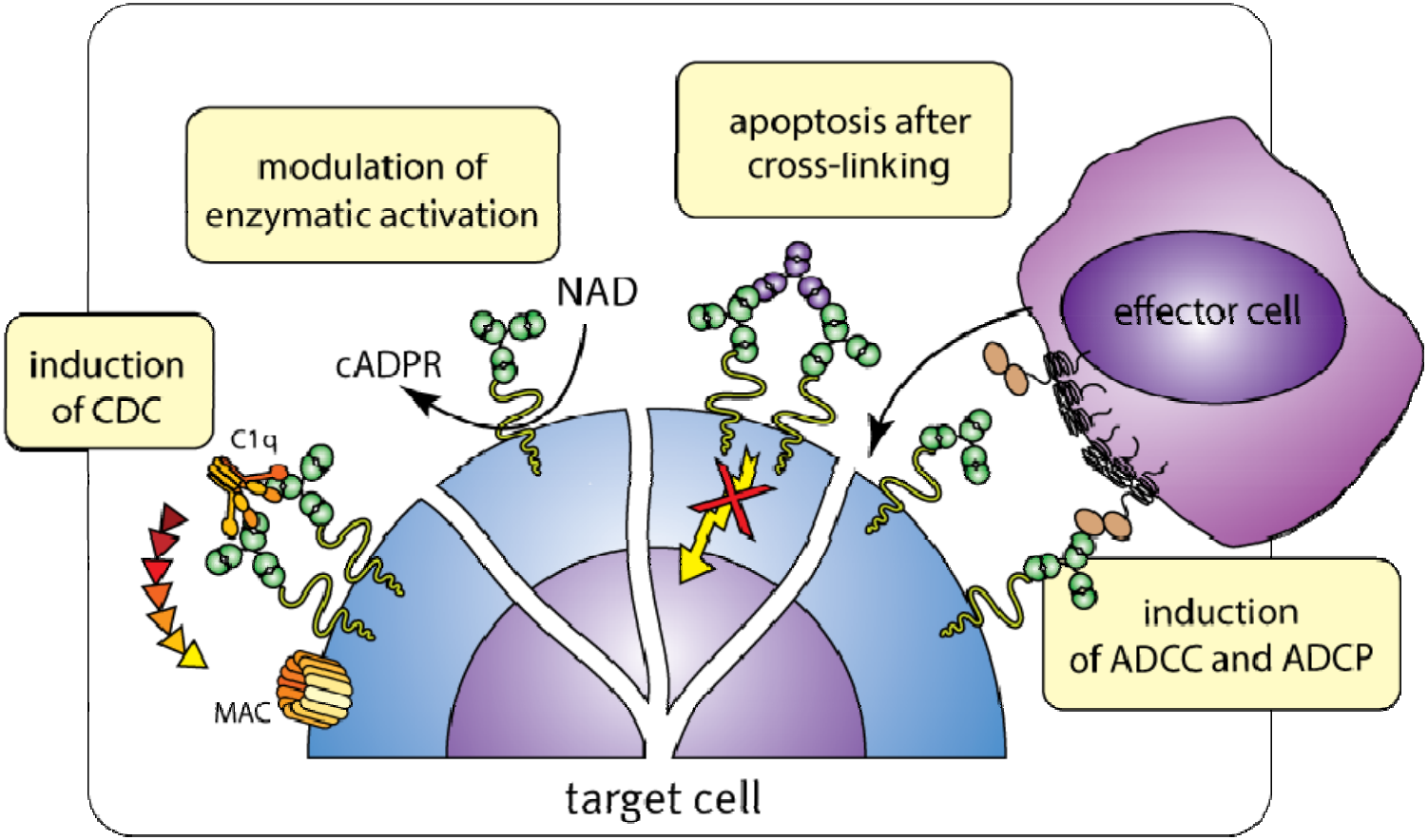
Effectively kills CD38$^+$ tumor cells, e.g. in multiple myeloma

Enhanced killing in combination with novel agents



Daratumumab

A human CD38 mAb with broad-spectrum killing activity



Daratumumab: GEN501

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

Objectives

Primary

- Establishment of the safety profile of *daratumumab*

Secondary

- To establish the pharmacokinetic profile of *daratumumab*
- Evaluation of the efficacy of *daratumumab* according to International Myeloma Workshop Consensus Panel 1, Blood 2011;117:4691-5
- Evaluation of the immunogenicity of *daratumumab*

Inclusion Criteria

Main inclusion criteria

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

Patient Characteristics

Cohort	Number of patients	Age[1]	Number of treatments[1]	Len[2]	Thal[2]	Bor[2]	Dex/Pred[1]	Chemo[2,3]	ASCT[2]
≤1 mg/kg	17	63 (42-76)	5 (2-8)	15	12	17	15/7	17	11
2 mg/kg	3	64 (60-71)	8 (6-10)	3	3	3	3/3	3	3
4 mg/kg	3	64 (62-66)	6 (3-6)	3	1	3	3/1	3	2
8 mg/kg	3	60 (56-68)	11 (5-12)	3	2	3	3/2	3	3
16 mg/kg	3	55 (54-59)	7 (4-8)	2	2	3	3 1	3	3

1: Data are in median (range)

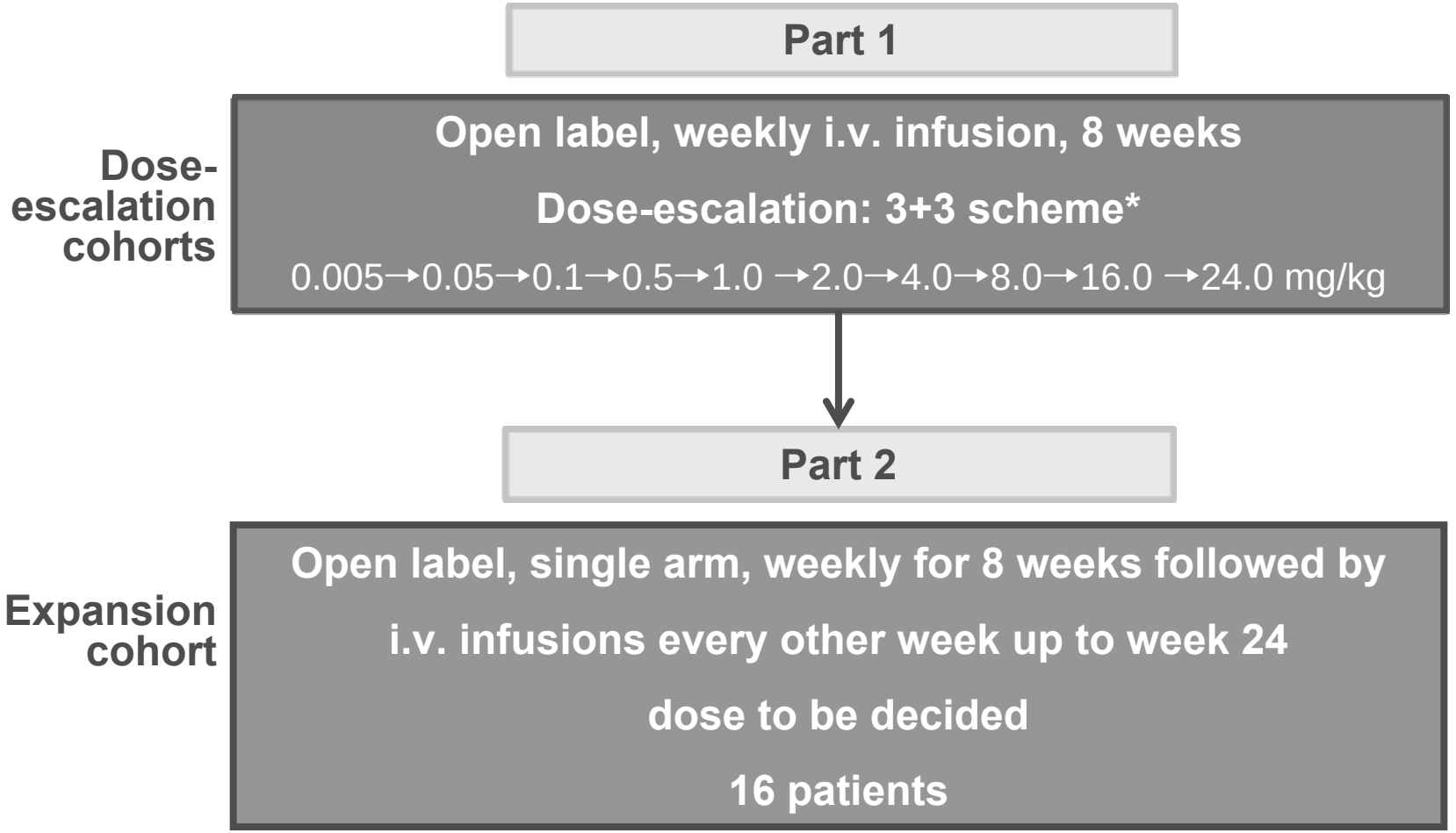
2: Number of patients exposed to the drug/treatment

3: vincristine, doxorubicin, cyclophosphamide, melphalan and others

Results are based on data before database lock

Daratumumab

Trial Design



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

Adverse Events (AEs) Reported in >1 Patient Across all Cohorts, all Grades (CTC 4.0)

AEs primarily related to Infusion: *

- pyrexia (31%)
- cough (21%)
- hypo/hypertension (7%/14%)
- nausea (14%)
- dizziness (10%)
- influenza-like illness (10%)
- rash (10%)
- arthralgia (7%)
- flushing (7%)
- chest pain (7%)
- fatigue (7%)
- headache (7%)
- tachycardia (7%)
- hypersensitivity (7%)
- cytokine release syndrome (7%)

Other Treatment Emergent Laboratory AEs:

- monocytopenia (21%)
- lymphopenia (21%)
- free hemoglobin (17%)
- anemia (17%)
- hemolysis (14%)
- thrombocytopenia (7%)

Other AEs:

- diarrhea (10%)
- pneumonia (7%)
- vomiting (7%)

Daratumumab

Related Serious Adverse Events (SAEs)

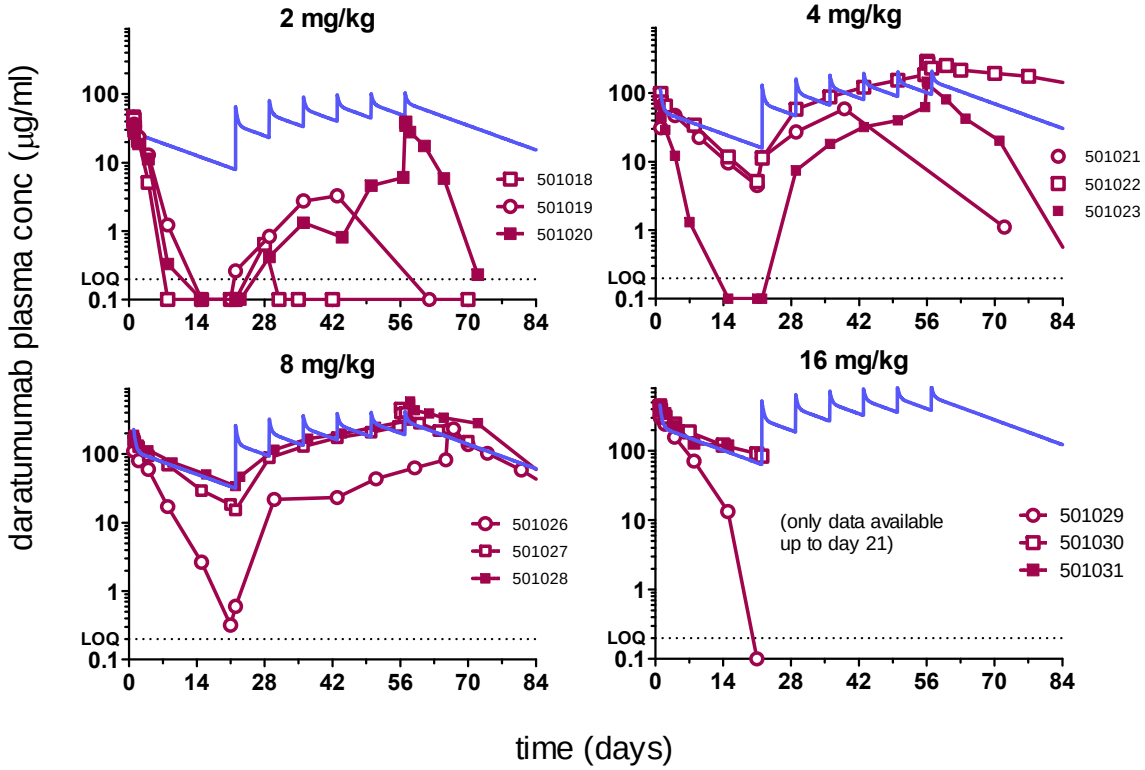
- Five SAEs assessed as related to daratumumab:
  - One pt: anemia grade 3 (DLT) and thrombocytopenia grade 4 (0.1 mg/kg)
  - One pt: AST grade 3 (DLT) (1 mg/kg)
  - One pt: bronchospasm grade 3 (2 mg/kg)
  - One pt: cytokine release syndrome grade 2 (0.1 mg/kg)
- In total, 2 DLT events reported; 3 more patients were enrolled in the 0.1 mg/kg and 1.0 mg/kg cohorts
- All patients recovered after relevant treatment
- No serious infusion-related AEs reported after implementation of relevant pre-medication and dilution of trial drug
- No major changes in platelet count or hemoglobin observed over time

Pharmacokinetics

Red: observed daratumumab concentrations as measured by ELISA

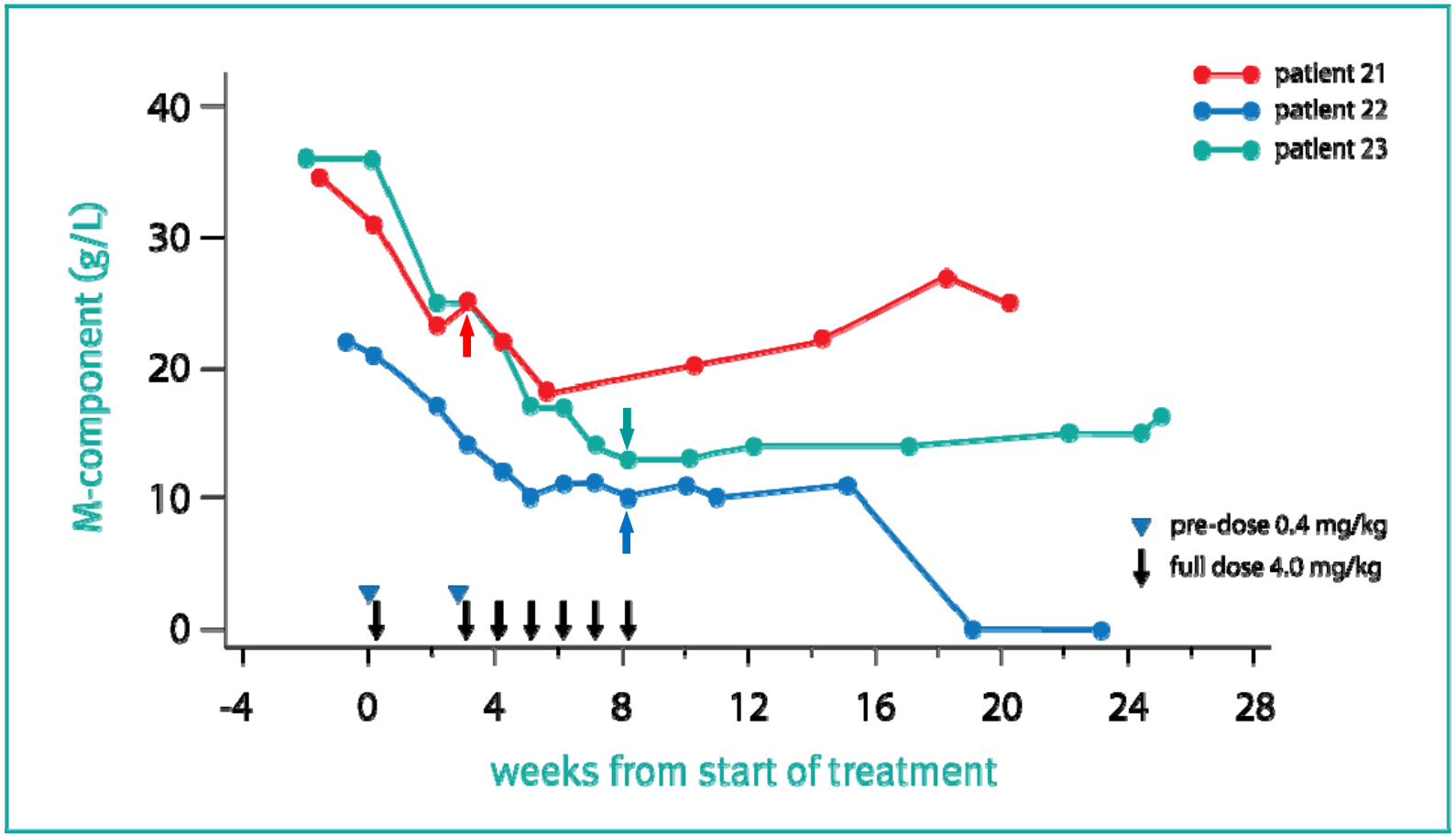
(day 21 – 56: trough levels only, no peak levels)

Blue : concentrations predicted using a 2-comp PK model with Vcen = 40 ml/kg and elimination half life = 21 days.



- Plasma peak levels after first full dose: as expected for IgG
- Rapid clearance at low dose: indicates target-mediated clearance
- High inter-patient variability suggests effect of tumor load on PK
- ⩽ 1 mg/kg: pre-dose trough levels far below prediction
- ⩾ 4 mg/kg: sustained trough levels > 10 µg/ml indicate that impact target-mediated clearance becomes negligible at higher doses

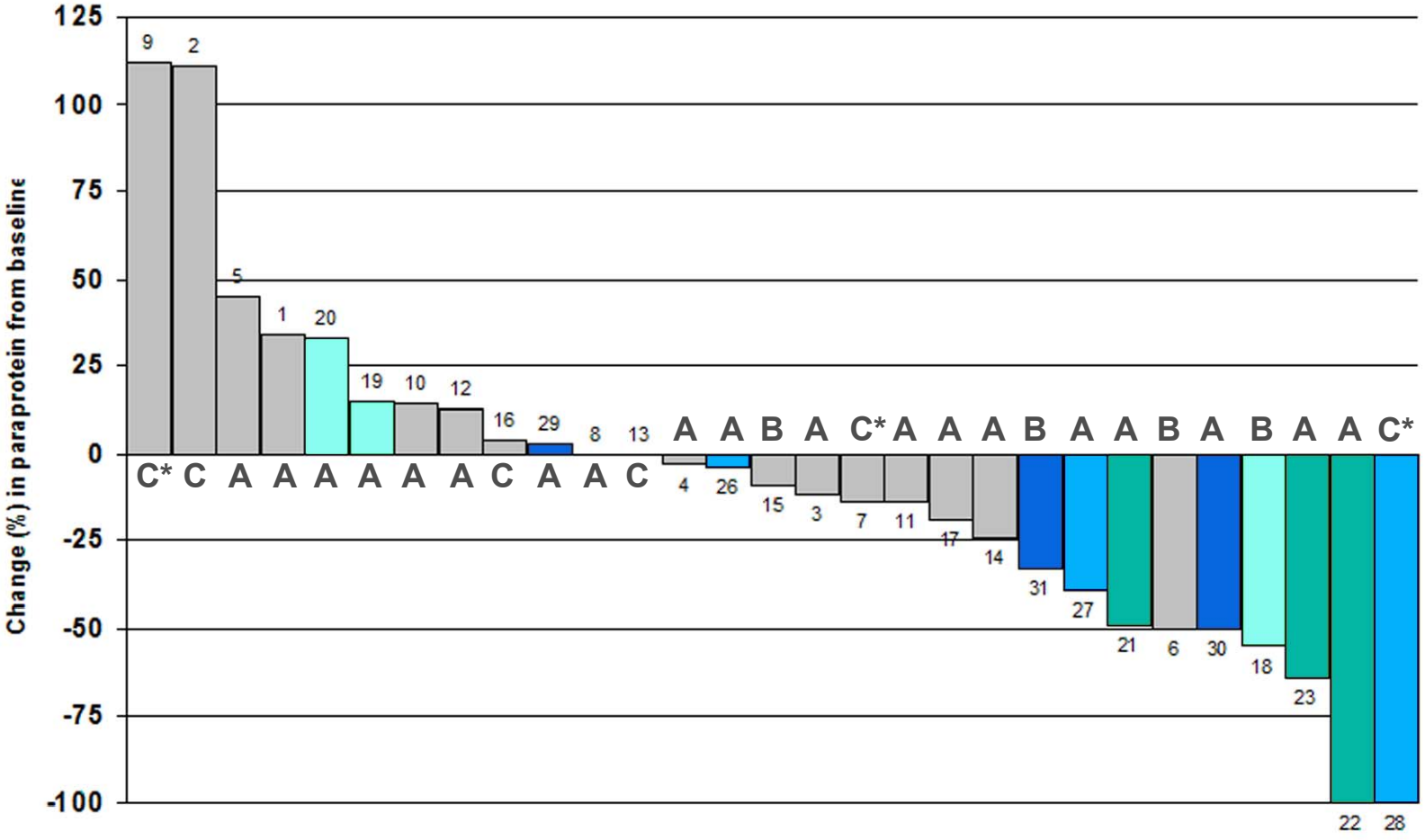
M-Component in Patients Treated with Daratumumab 4 mg/kg



: Indicates last dose

Maximal Change in Paraprotein

A: serum M-component ➡ B: urine M-component ➡ C: FLC



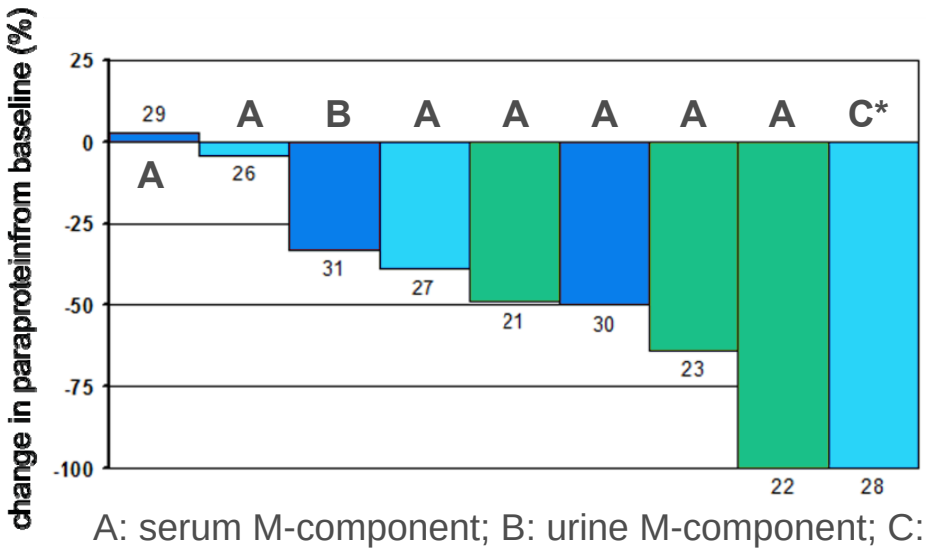
- Data at baseline below limits for measurable disease

Results are before database lock

≤1 mg/kg	2 mg/kg	4 mg/kg	8 mg/kg	16 mg/kg

Correlation between Exposure and Decline in Paraprotein

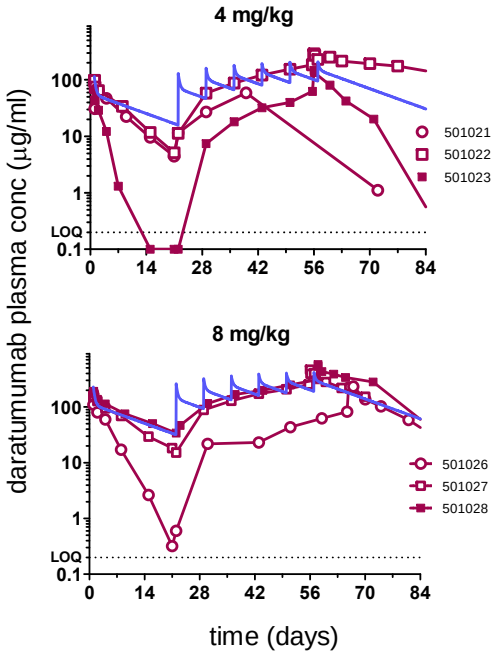
- At doses 4 mg/kg, daratumumab trough levels were consistent 10 µg/ml and observed PK values approximately estimated PK values
- In 9 patients dosed with daratumumab 4 mg/kg, 6 clinical responses were observed - 4 PR and 2 MR



A: serum M-component; B: urine M-component; C: FLC

* Data at baseline below limits for measurable disease

Results are before database lock



4 mg/kg | 8 mg/kg | 16 mg/kg

Daratumumab

Max Reduction of M-Component/FLC and BM Plasma Cells

Cohort	n/N	Max reduction in M-component		Max reduction of plasma cells in BM smear	Responses according to Rajkumar[3]
		Serum %	Urine %	Reduction %	
≤0.5 mg/kg	6/11	12 3[4] * 0 0 14	22 * 50 100 * 25	18 [1] - - 75 NA	SD SD MR SD SD SD
1 mg/kg	3/6	24 33[4] 19	1 9 *	[1] 94 [1]	SD MR SD
2 mg/kg	1/3	67[2]	55	-	PR
4 mg/kg	3/3	49 100 64	* 87 *	80 89 97	MR PR PR
8 mg/kg	3/3	4 39 100[2]	* * *	- 93 [1]	SD MR PR
16 mg/kg	2/3	50[4] *	* 33	100 [1]	PR SD

*: Not measurable at baseline
-: Not available; NA: not applicable
[1]: Normal at baseline
[2]: FLC only measurable
[3]: Evaluation based on maximal reduction in M-component or FLC according to consensus of uniform reporting of clinical trials (Rajkumar. Blood 2011;117:4691-5)
[4] Based on only one measurement (no consecutive measurements); SD: stable disease; MR: minimal response; PR: partial response

Conclusion 1/2

- Daratumumab has shown a favorable safety profile as monotherapy in relapsed and relapsed - refractory Multiple Myeloma patients
- MTD has not yet been established/reached
- In 18 of 29 heavily pretreated Multiple Myeloma patients receiving 8 weeks of daratumumab as monotherapy in doses up to 16mg/kg, a marked reduction in paraprotein has been observed, corresponding to preliminary responses of:
    - 5 patients achieving PR
    - 4 patients achieving MR
    - 9 patients achieving SD

Conclusion 2/2

- Biochemical response was accompanied by clearance of myeloma cells from the bone marrow
- At higher dose levels, observed plasma concentrations are close to those predicted
- Dose escalation is ongoing and will be followed by a 24 week study to evaluate long-term safety and efficacy

Future Directions

Continuous therapy studies and combination strategies planned:

- GEN503 trial: Daratumumab in combination with lenalidomide and low-dose dexamethasone

  and

- GEN504 trial: Daratumumab in combination with bortezomib and low-dose dexamethasone

Acknowledgments

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- Karolinska Institutet, Sweden
- Copenhagen University Hospital, Denmark
- University Medical Center Utrecht, Netherlands
- Vejle Hospital, Denmark
- Dana-Farber Cancer Institute, USA

Back-up Slides

Total Number of Patients who Received other Treatments

	Len	Thal	IMiD	Bor	Dex/ Pred	Chemo	ASCT
Number of patients out of the 29 patients enrolled (%)	26 (90)	20 (69)	29 (100)	29 (100)	27/14 (93/48)	29 (100)	22 (76)