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

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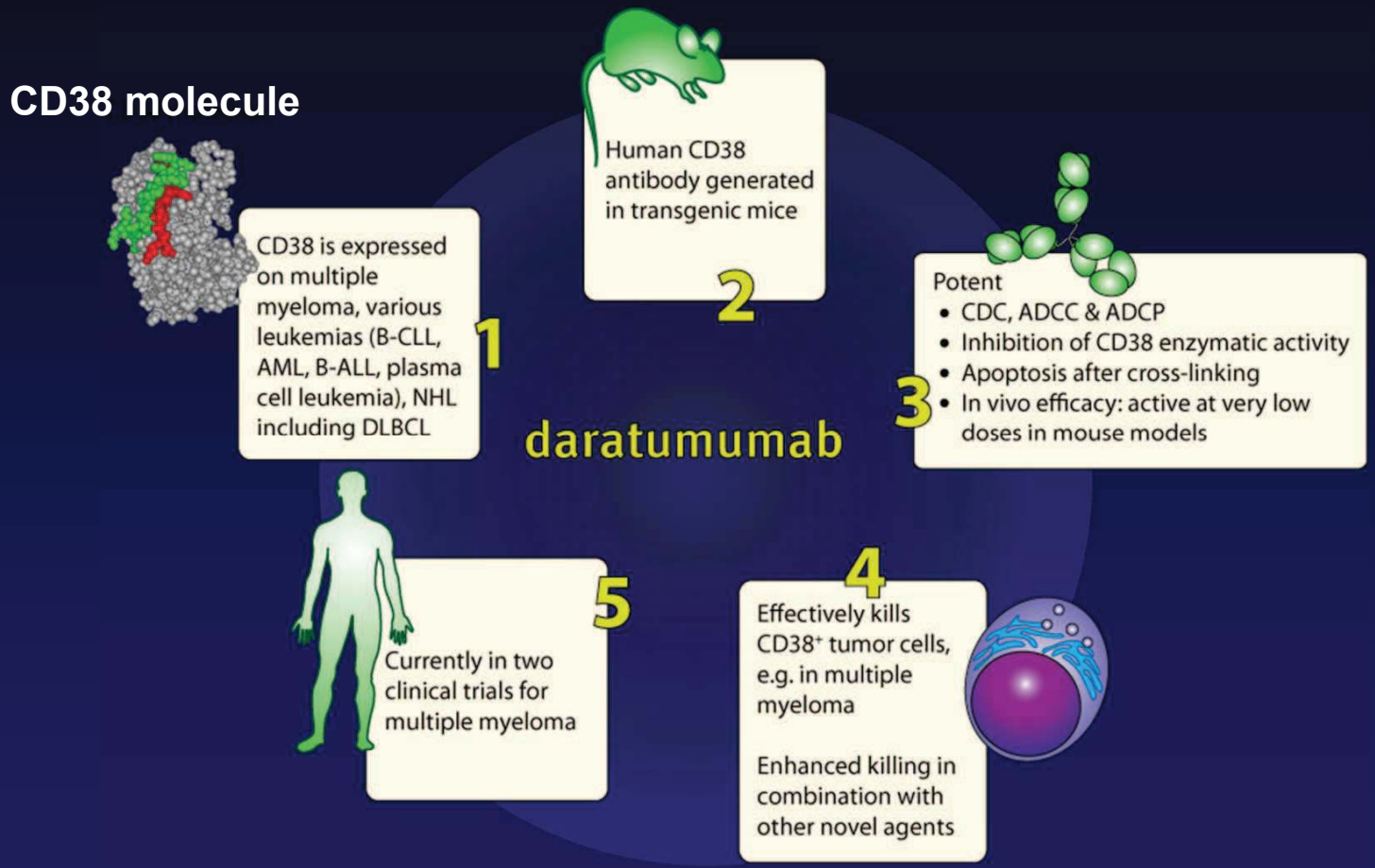
Daratumumab
A Human CD38 mAb with Broad-Spectrum Killing Activity



Daratumumab: GEN501

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

Objectives

Primary

- Establishment of the safety profile of *daratumumab*

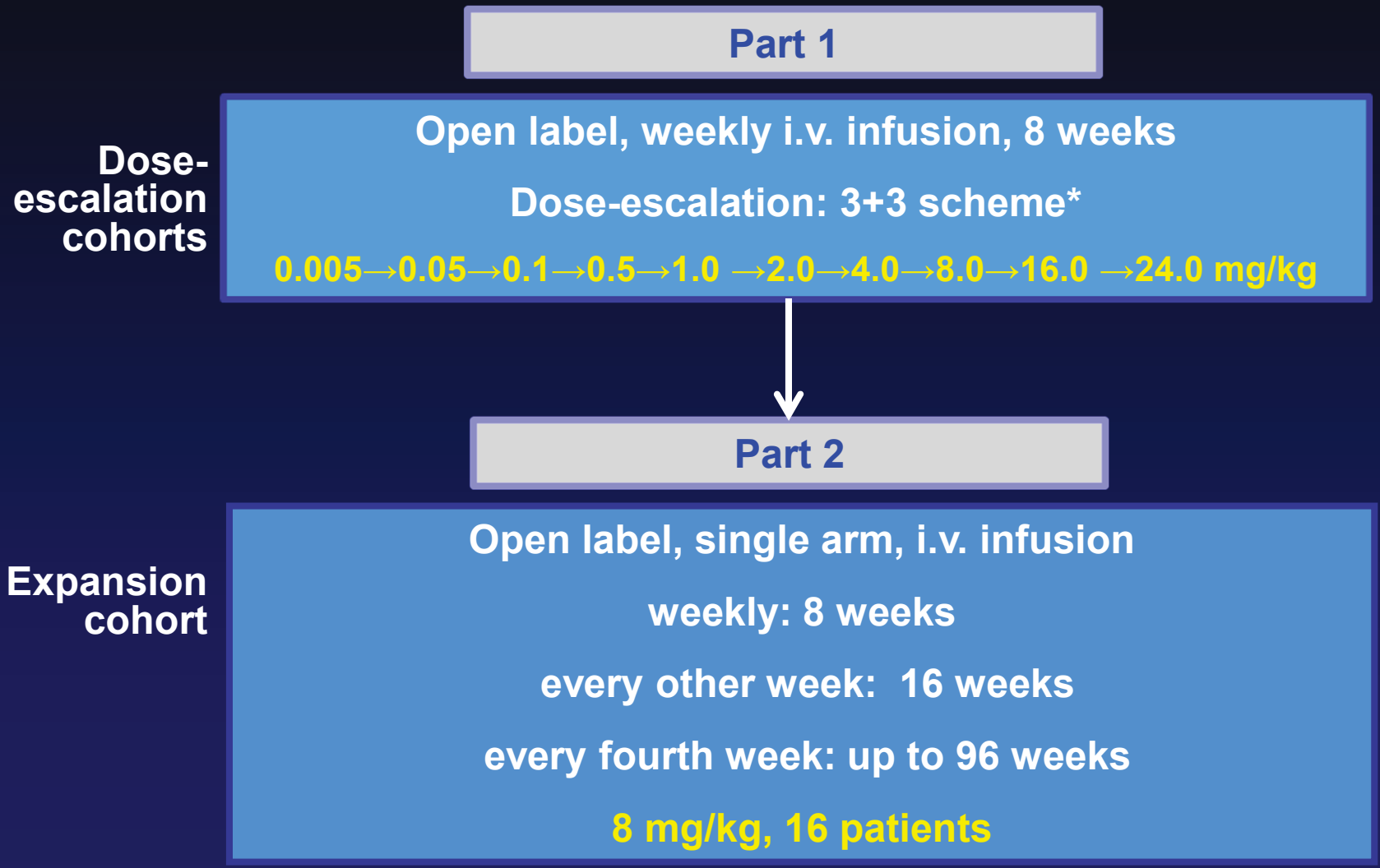
Secondary

- 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*

Daratumumab
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 of 0-2
- Patients having a life expectancy > 3 months

Daratumumab
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
Patient Characteristics

Cohort	No. of subjects	Age[a]	No. of treatments[a]	Len[b]	Thal[b]	Bor[b]	Dex/ Pred[b]	Chemo[b,c]	ASCT[b]
≤1 mg/kg	17	63 (42-76)	5 (2-8)	88%	71%	100%	88%/41%	100%	65%
2 mg/kg	3	64 (60-71)	8 (6-10)	100%	100%	100%	100%/100%	100%	100%
4 mg/kg	3	64 (62-66)	6 (3-6)	100%	33%	100%	100%/33%	100%	67%
8 mg/kg	3	60 (56-68)	11 (5-12)	100%	67%	100%	100%/67%	100%	100%
16 mg/kg	3	55 (54-59)	7 (4-8)	67%	67%	100%	100%/33%	100%	100%
24 mg/kg	3	58 (50-69)	5 (4-6)	100%	67%	100%	100%/33%	100%	67%

ASCT=autologous stem cell transplant; Bor=bortezomib; Chemo=chemotherapy; Dex=dexamethasone; Len=lenalidomide; No.=number; Pred=prednisolone; Thal=thalidomide.
Note: These results are based on data before database lock.
a Median (range).
b Number of subjects exposed to the drug/treatment.
c Vincristine, doxorubicin, cyclophosphamide, melphalan, and others.

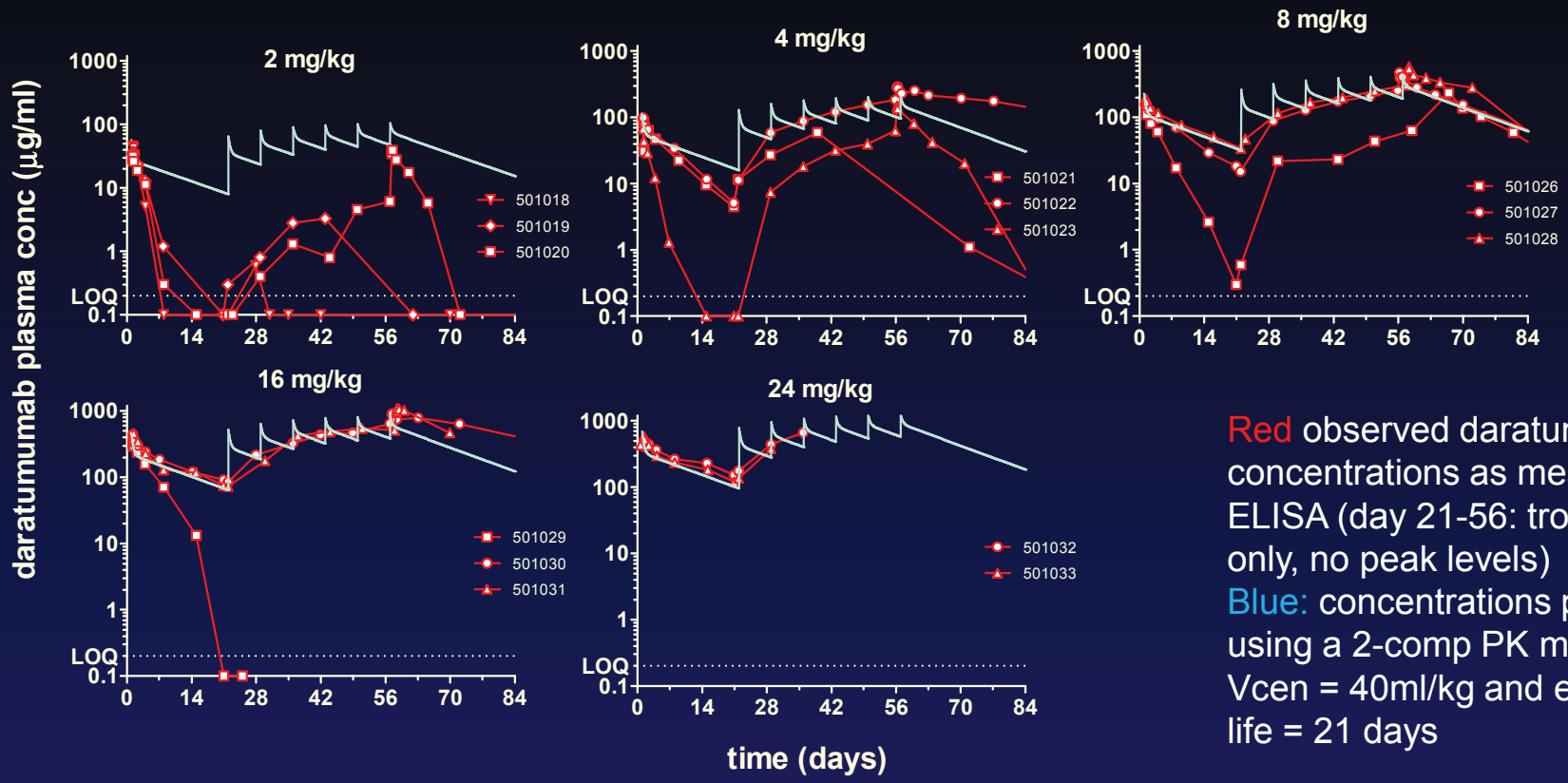
Daratumumab
Safety Findings

- Infusion-related reactions were observed during the initial infusions:
  - 9% during the pre-dose infusion
  - 26% during the first full infusion with a gradual decrease in frequency during the subsequent infusions
  - No dose relationship
  - Two events grade 3, the remaining grade 1-2
  - Onset of events within 3 to 4 hours of infusion
  - Five late reactions:
    - 2 events of bronchospasm, 1 event each of headache, dyspnoea and fever
    - Patients with bronchospasm had a medical history of chronic bronchitis and asthma
- No major changes in platelet count or hemoglobin were observed over time
- A dose-dependent decrease in NK cells as measured in the peripheral blood was observed, with full recovery after treatment

Daratumumab
Safety Findings

- Six SAEs were assessed as related to daratumumab:
  - One patient: anemia grade 3 (DLT) and thrombocytopenia grade 4 (0.1 mg/kg)
  - One patient: AST grade 3 (DLT) (1 mg/kg)
  - One patient: cytokine release syndrome grade 2 (0.1 mg/kg)
  - One patient: bronchospasm grade 3 (2 mg/kg)
  - One patient: bronchospasm grade 2 (24 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

Daratumumab
Pharmacokinetics



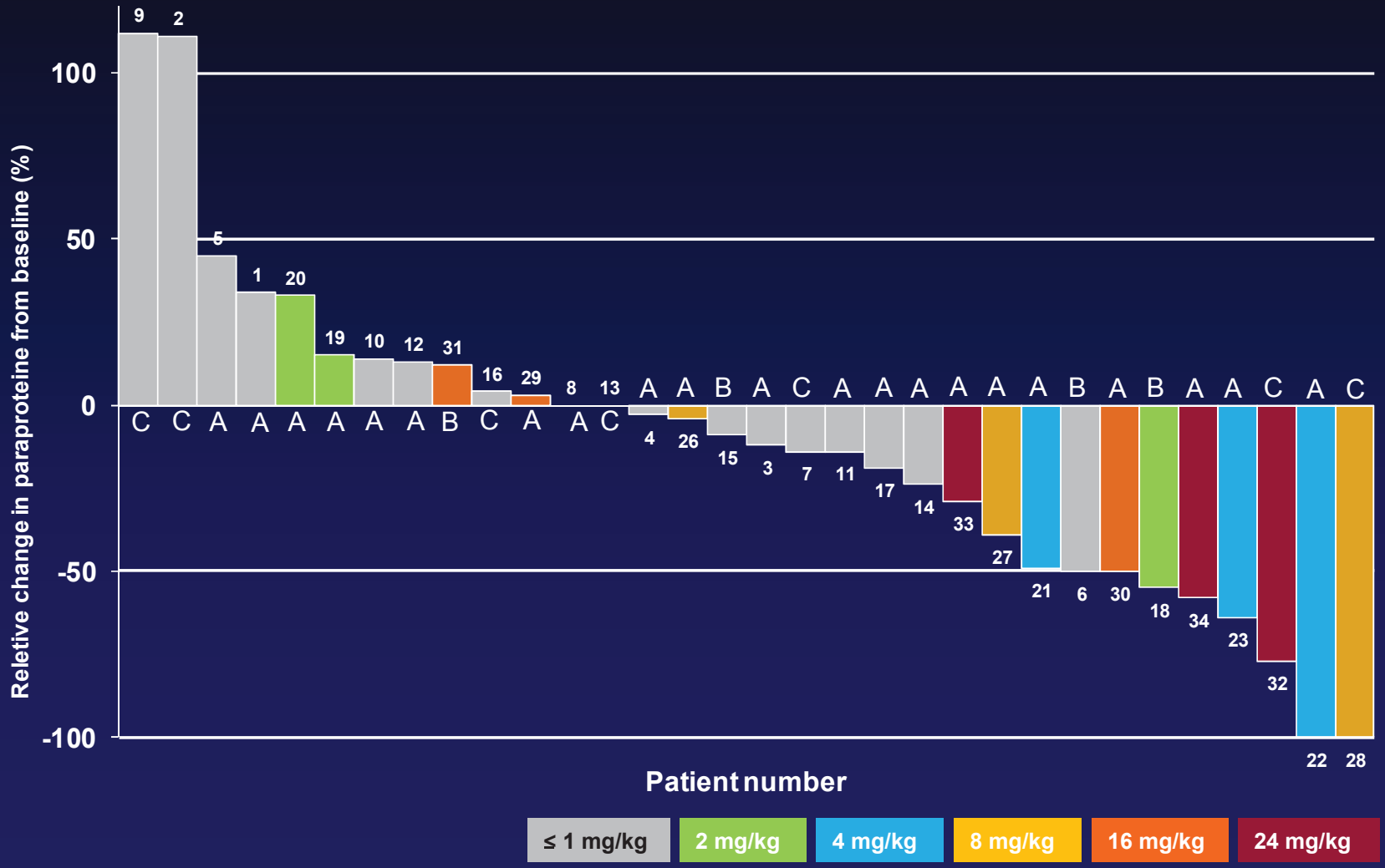
Red observed daratumumab concentrations as measured by ELISA (day 21-56: trough levels only, no peak levels)
Blue: concentrations predicted using a 2-comp PK model with Vcen = 40ml/kg and elimination half life = 21 days

- 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
- 2 mg/kg: pre-dose trough levels far below prediction
- 4 mg/kg and upwards: sustained trough levels > 10 µg/ml indicate that the impact of target-mediated clearance becomes negligible at higher doses

Daratumumab Response

Maximal Change in Paraprotein

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



Daratumumab Response

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 BM smear (%) [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]	MR
		*	-12	55	100 [2]	SD
24	3	*	*	80[b]	51 [18.5]	PR
		29[b]	*	*	17 [3.0]	MR
		58[b]	89	93	[c]	PR

Notes:

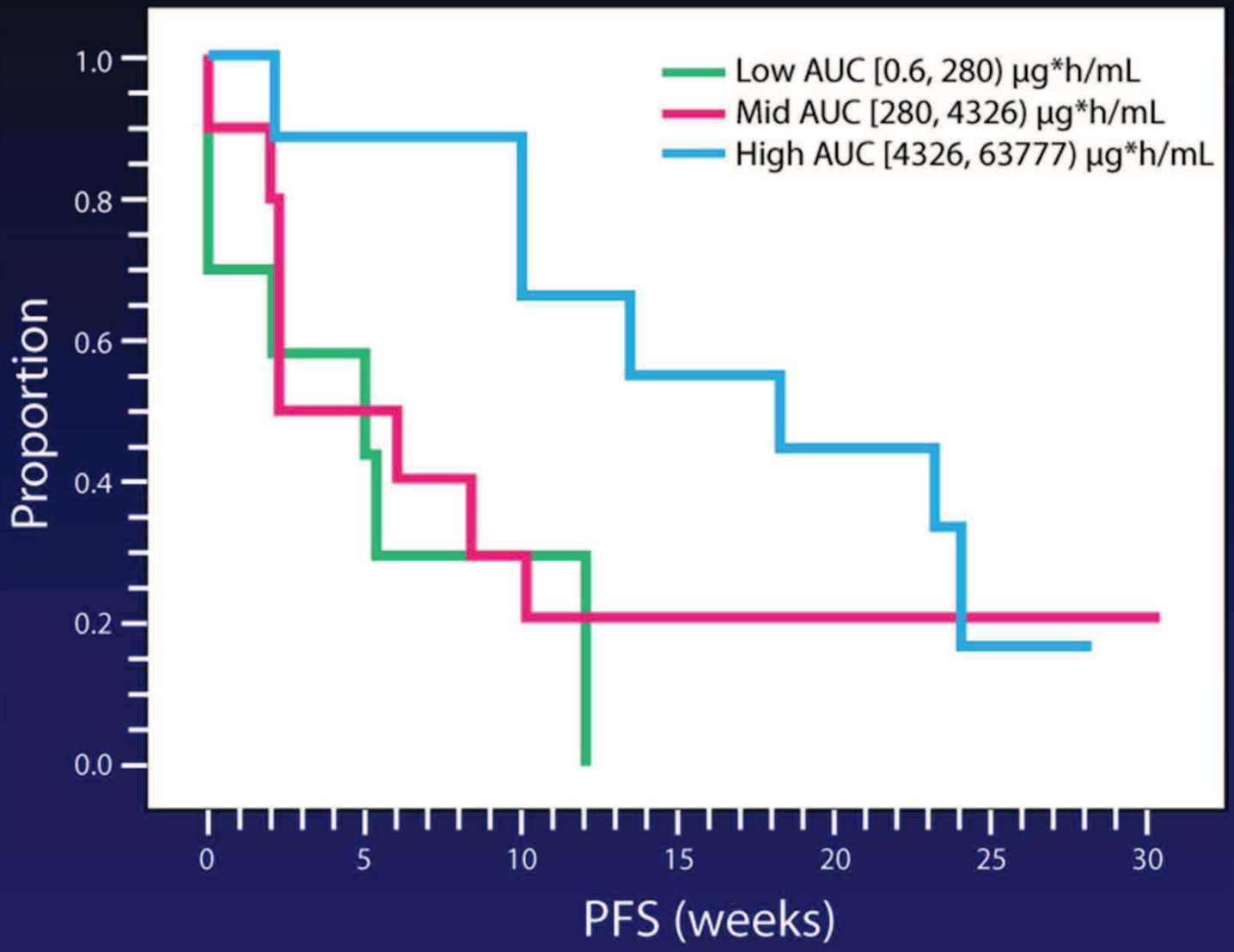
* no measurable disease/normal at Baseline; —=data not available.

a Evaluation based on maximal reduction in M-component or FLC, according to the consensus on uniform reporting of clinical trials

b Follow-up still ongoing.

c Data not yet available.

Daratumumab
Progression free survival vs. Exposure



Daratumumab
Conclusion 1/2

- Daratumumab has shown a favorable safety profile as monotherapy in relapsed or relapsed and refractory Multiple Myeloma patients

- In 15 of 32 (47%) heavily pre-treated evaluable Multiple Myeloma patients receiving 8 weeks of daratumumab as monotherapy in doses up to 24mg/kg, a reduction in paraprotein has been observed, corresponding to preliminary responses of:

  – 4 patients achieving PR (13%)
  – 6 patients achieving MR (19%)
  – 5 patients achieving SD (16%)

- At doses 4mg/kg and above, 8 of the 12 patients had at least MR (66%)

Daratumumab
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
- MTD has not been reached
- Increased daratumumab exposure correlated with longer progression free survival
- Future directions: Extended exposure up to 24 months in MM patients with 8 mg/kg daratumumab as monotherapy and combination studies

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