Abstract #8019
Daratumumab – a CD38 mAb – for the Treatment of Relapsed /Refractory Multiple Myeloma Patients: Preliminary Efficacy Data from a Multicenter Phase I/II Study

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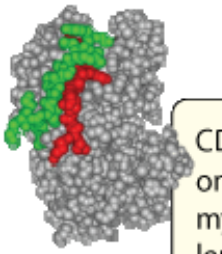
Disclosures

Consultant for Genmab. Member of Advisory Boards for Janssen and Celgene.
Investigator for Genmab, Janssen, Celgene, Bristol Myers Squibb, Novartis, Roche, Nordic Myeloma Study Group, HOVON, German CLL Study Group.
Teacher for Janssen, Celgene, Novartis and Norpharma/ Mundipharma.
Recipient of research grants from Janssen, Celgene, Roche and Novartis.

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

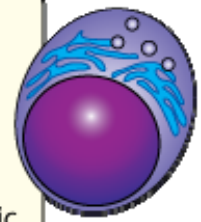
Currently in a Phase I/II clinical trial for multiple myeloma

5

4

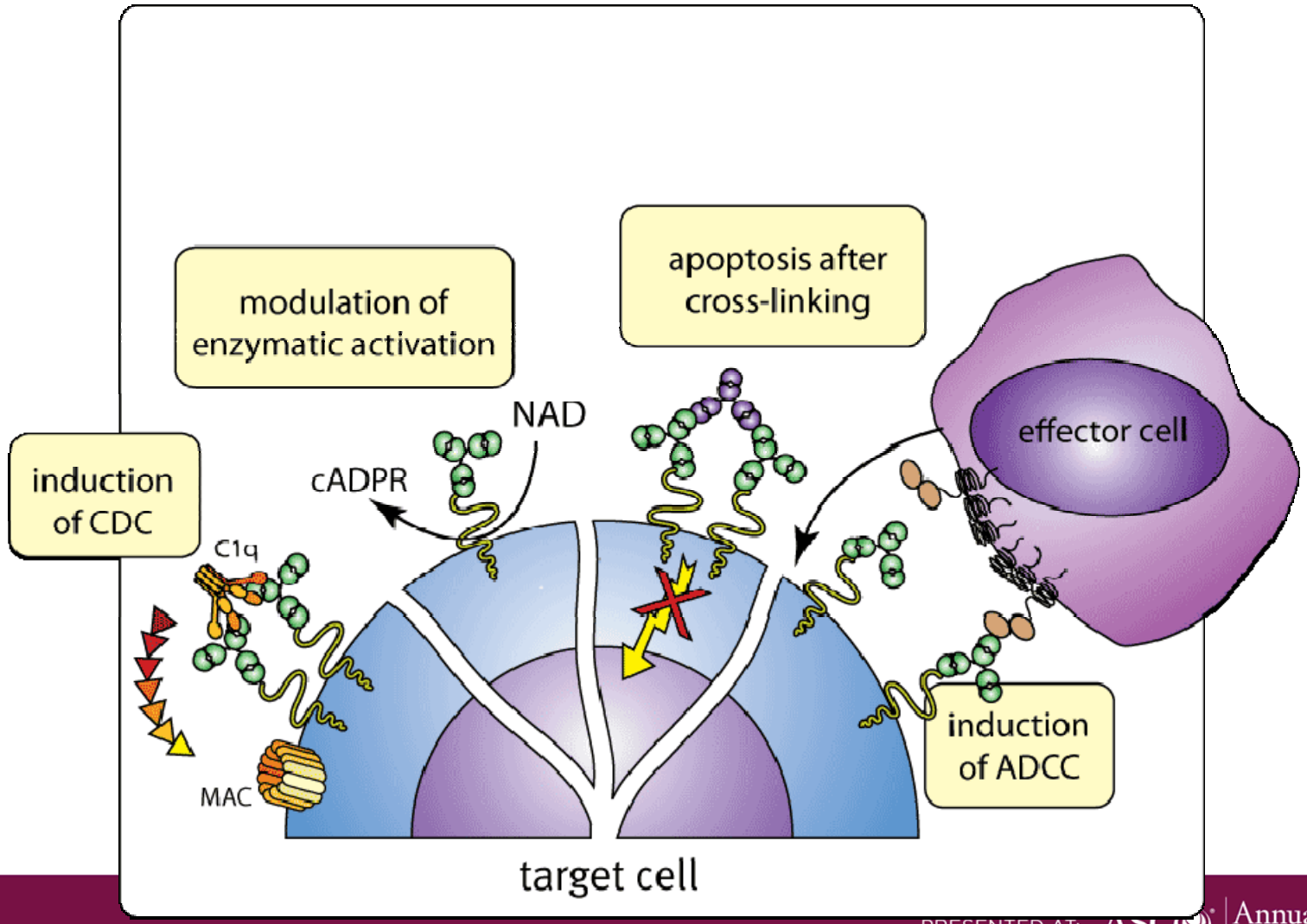
Effectively kills CD38^{+} tumor cells, e.g. in multiple myeloma

Additive/synergistic effects with novel agents



Daratumumab

A human CD38 mAb with broad-spectrum killing activity

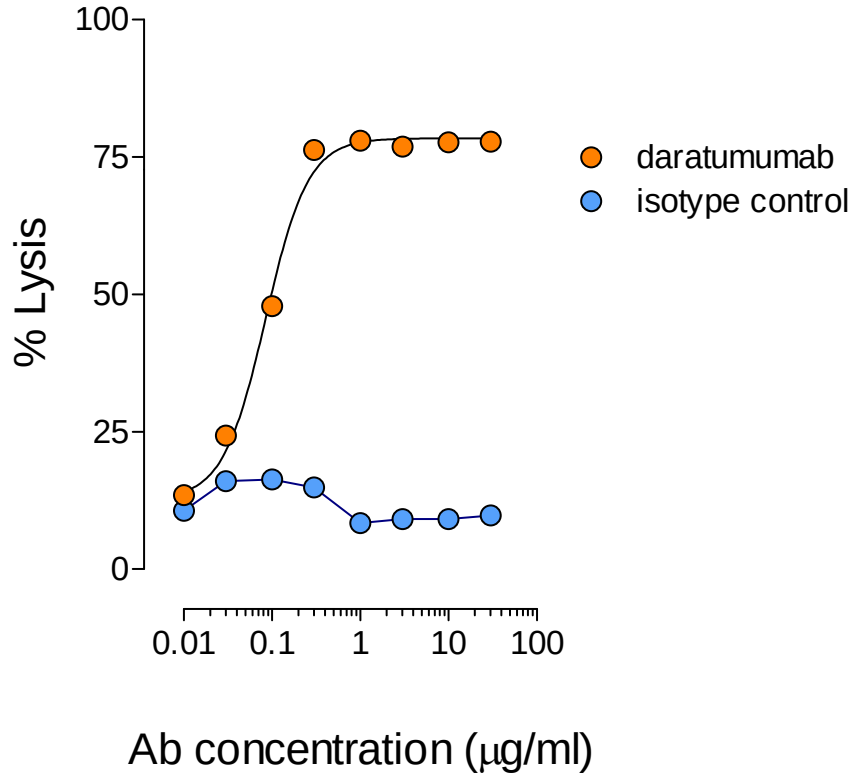


Daratumumab

Induces Potent CDC of patient MM tumor cells

Patient	Clinical status	Lysis (%)
1	relapse	+++
2	relapse	-
3	relapse	+++
4	untreated	+++
5	relapse	+++
6	relapse	++
7	relapse	+
8	untreated	+++
9	relapse	+
10	relapse	++
11	relapse	-
12	relapse	++
13	relapse	+++

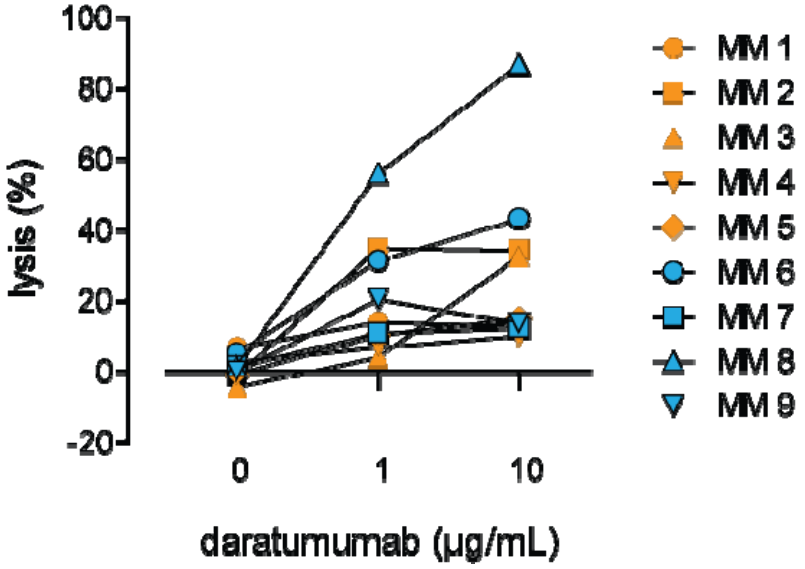
Representative example of DARA-induced lysis



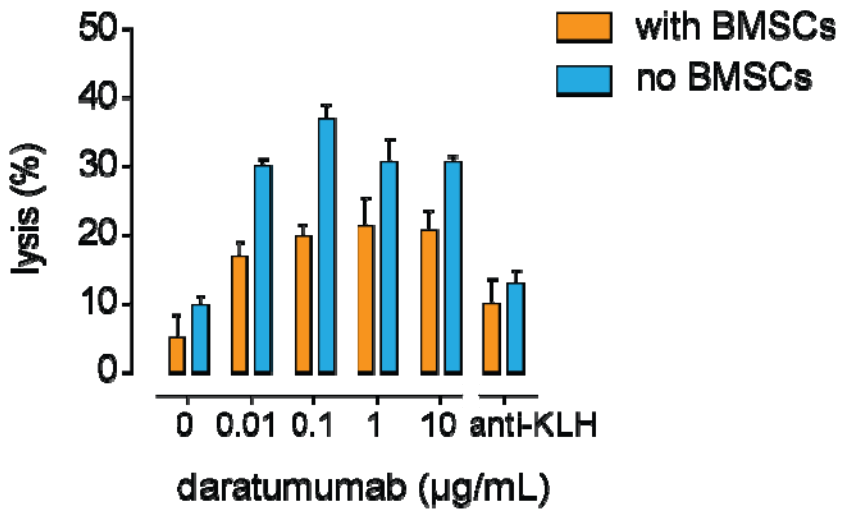
De Weers et al, J Immunol 186, 1840-1848 (2011)

Daratumumab

ADCC Induced in the Presence or Absence of BMSCs



Primary MM cells (9 patients)



Dexamethasone-resistant cell line (MM1R)

De Weers et al, J Immunol, 2011, 186, 1840.

Daratumumab: GEN501 - Phase I/II Study of Monotherapy in Relapsed and Relapsed, Refractory MM; *Objectives*

Primary

- Establishment of the safety profile of *daratumumab*

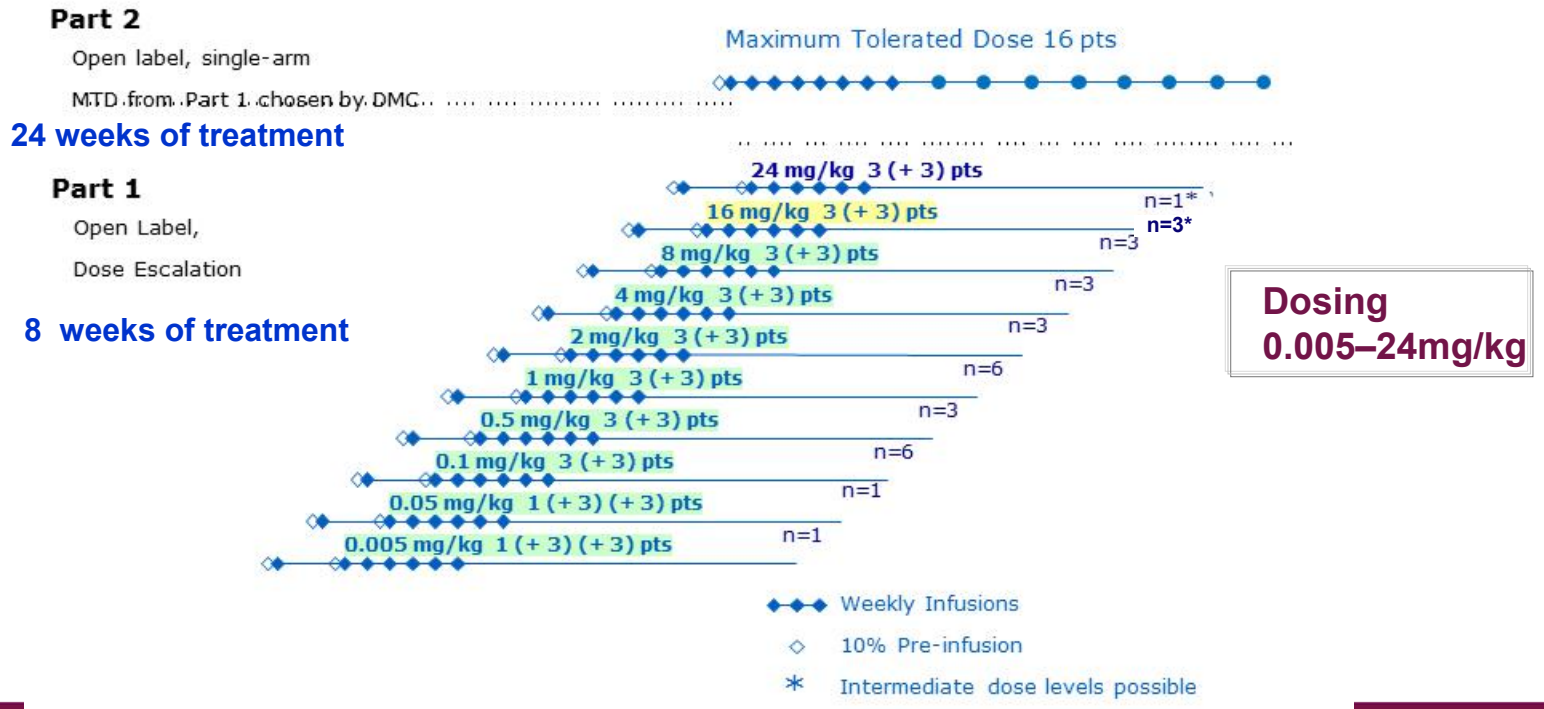
Secondary

- 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

GEN501 - Ongoing Study in MM; *Study Design*

- **GEN501 First In Human, daratumumab monotherapy in relapsed or relapsed, refractory MM, phase I/II**
  - **Part 1: ongoing: determine MTD, safety**
  - **Part 2: cohort expansion at MTD or dose chosen by IDMC/sponsor, for safety & efficacy**



Patient Characteristics (Part 1; N=29)

* median

- Patients [pts] with advanced Multiple Myeloma
- Relapsed or relapsed and refractory disease with at least 2 prior *lines of therapy* and without further established treatment options
- All IMiD, Bortezomib exposed.
- 76 % of pts had received a SCT before entering study incl 1 allo

Cohort/ pt number	Age (yrs)	Number of prior lines of treatment
≤1 mg/kg (n=17)	**63***	**5***
2mg/kg	**64***	**8***
Pt 018	60	6
Pt 019	64	10
Pt 020	71	8
4 mg/kg	**64***	**6***
Pt no 21	64	6
Pt no 22	62	6
Pt no 23	66	3
8 mg/kg	**60***	**11***
Pt no 26	68	11
Pt no 27	60	12
Pt no 28	56	5
16mg/kg	**55***	**7***
Pt no 29	59	4
Pt no 30	55	7
Pt no 31	54	8

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 AE's :

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

Other AEs:

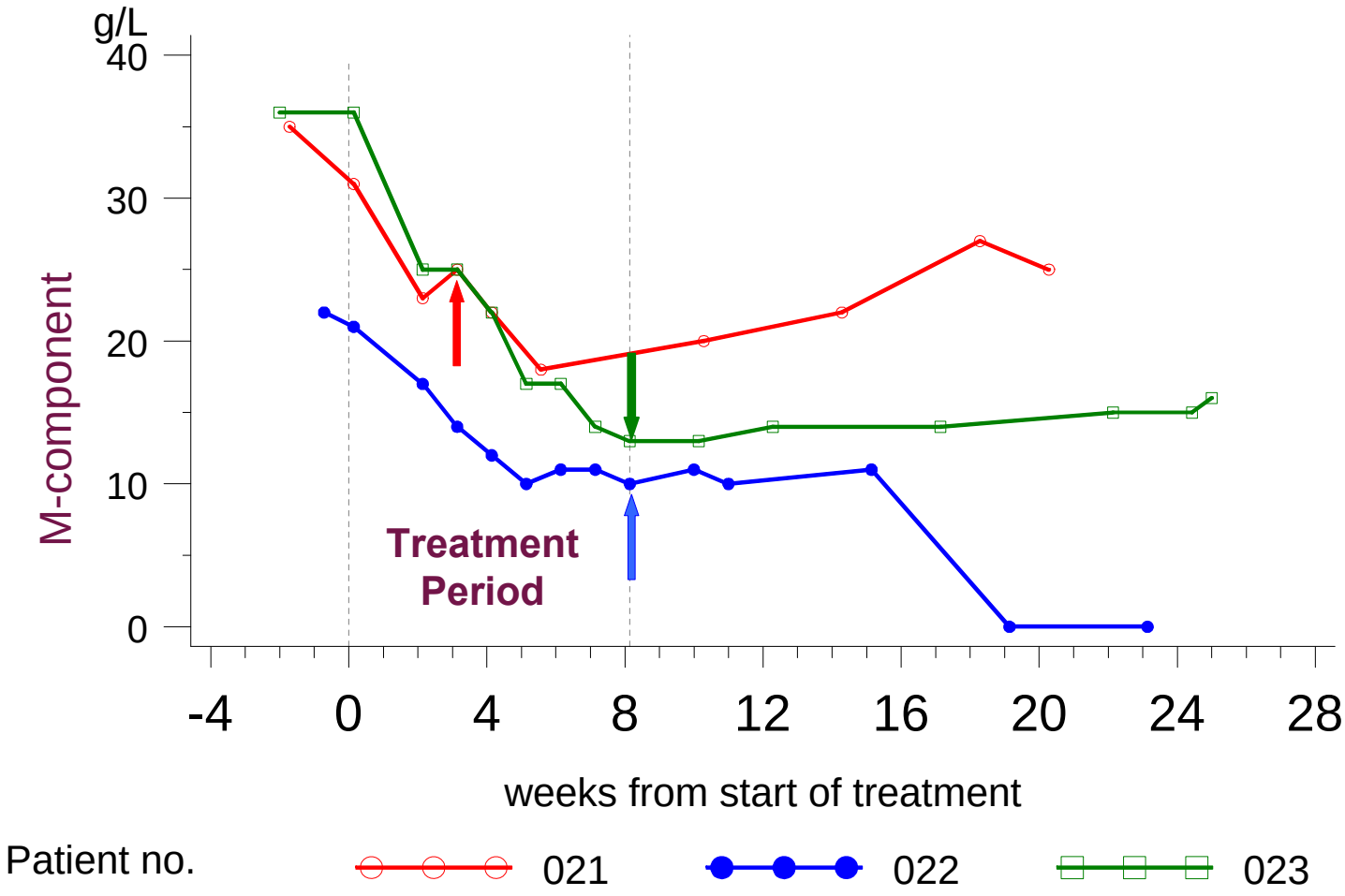
- diarrhea (10%)
- pneumonia (7%)
- vomiting (7%)

*** Reduced with subsequent premeds**

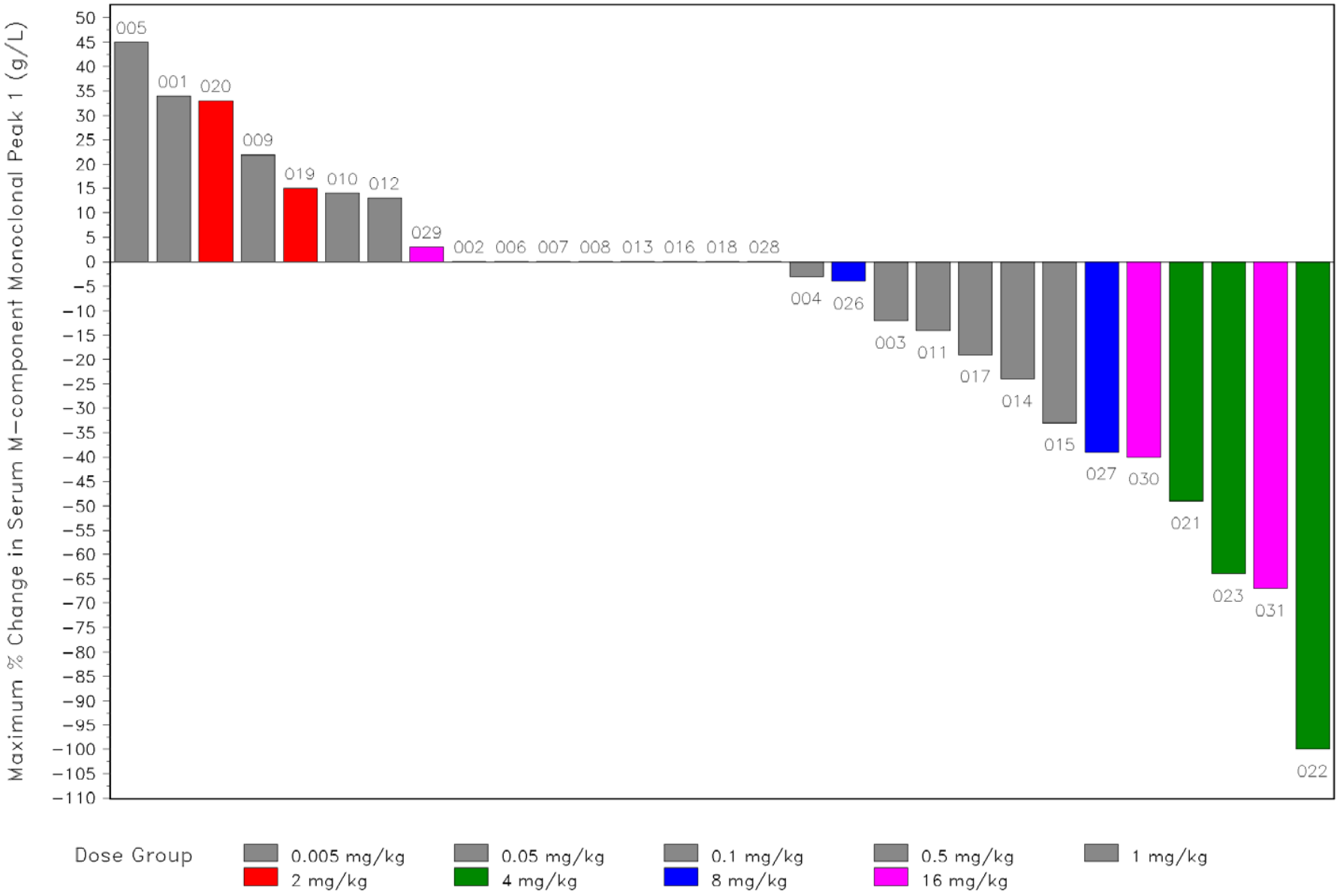
Daratumumab: Related Serious Adverse Events [SAEs]

- Five SAEs assessed as related to daratumumab:
  - One pt: anemia grade 3 (DLT) and thrombocytopenia grade 4
  - One pt: AST grade 3 (DLT)
  - One pt: bronchospasm grade 3
  - One pt: cytokine release syndrome grade 2
- 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

Serum M-Component Results in Patients Treated with Daratumumab 4mg/kg (n=3)



Maximal Reduction of Serum M-Component (Part 1)



Daratumumab: Max Reduction of M-Component/FLC and BM Plasma Cells (Part 1)

Cohort	n/N	Max reduction in M-component		Max reduction of plasma cells in BM smear		Responses according to IMWG Uniform Criiteria[4]
		Serum	Urine	Reduction %	Normalization of PC in BM	
≤0.5 mg/kg	6/11	12% 3%[5] * 0% 0% 14%	22% * 50% 100% * 25%	18% [1] - - 75% NA	NO [1] - - YES NA	**SD** **SD** **MR** **SD** **SD** **SD**
1 mg/kg	3/6	24% 33%[5] 19%	1% 9% *	[1] 94% [1]	[1] YES [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%	YES YES YES	**MR** **PR** **PR**
8 mg/kg	3/3	4% 39% 100%[2]	* * *	- 93% [1]	- YES [1]	**SD** **MR** **PR**
16 mg/kg	2/3	50% *	* 33%[3]	100% [3]	YES [3]	**PR** **SD[3]**

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

Conclusions/Future Directions

- Daratumumab has shown a favorable safety profile as monotherapy in relapsed and relapsed/refractory MM patients
- MTD has not yet been established/reached
- In 18 of 29 heavily pretreated MM patients receiving 8 weeks of daratumumab as monotherapy in doses up to 16mg/kg, a marked reduction in M-component has been observed, corresponding to preliminary responses of:
  - 7 pts achieving PR
  - 4 pts achieving MR
  - 7 pts achieving SD
- Biochemical responses were accompanied by clearance of myeloma cells from the bone marrow
- Dose escalation is ongoing and will be followed by a 24 week study (Part 2) to evaluate long-term safety and efficacy
- Continuous therapy studies and combination strategies planned (e.g. with bortezomib plus dex; lenalidomide plus dex)

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