Monoclonal Antibodies in The Treatment of Multiple Myeloma

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Disclosure

- Honorarium:
  - Celgene
  - Millennium Takeda
  - Merck
  - Onyx

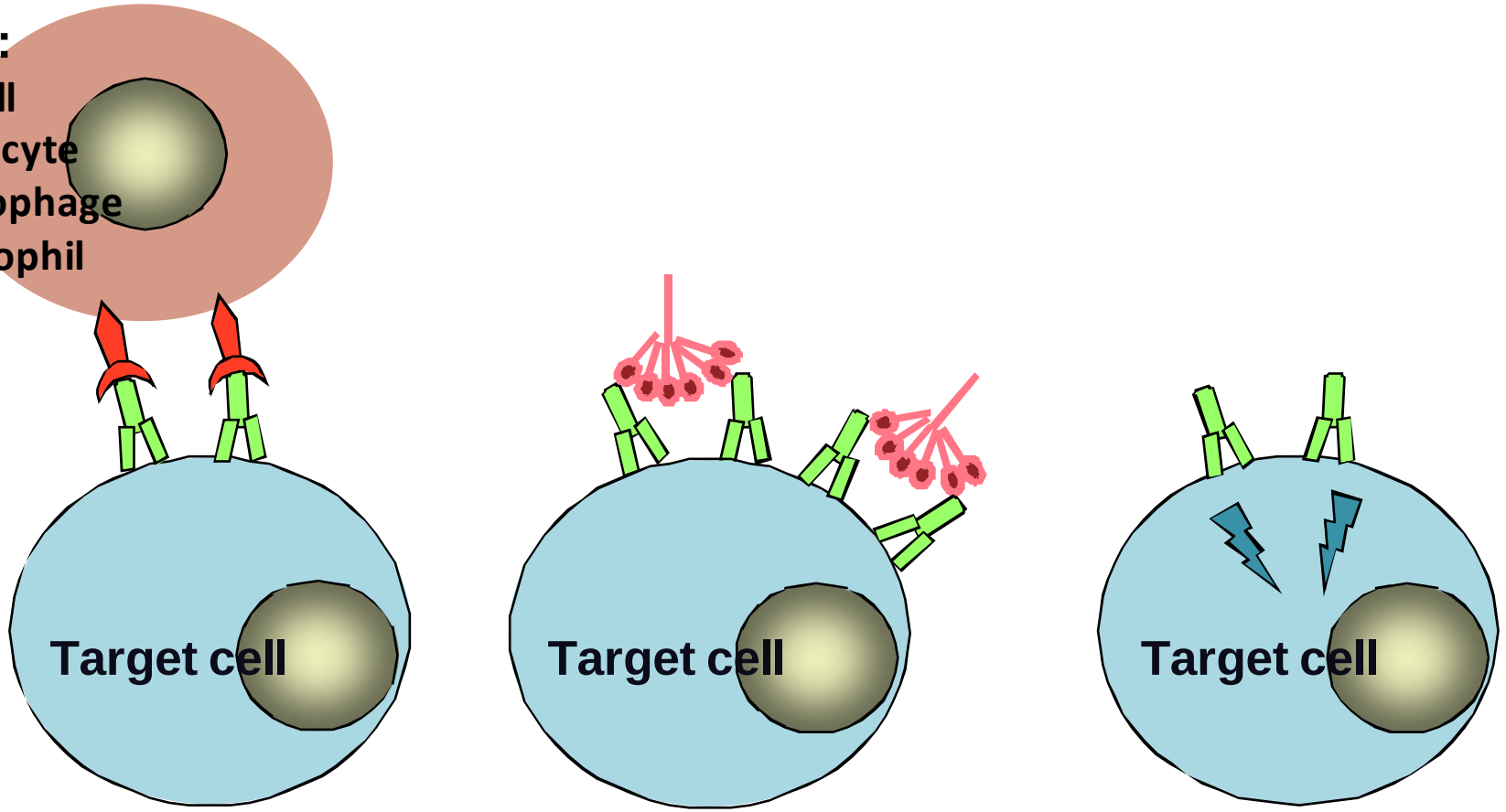
Milestones in the development of MCAB for therapy

- 1975 - George Kohler and Cesar Milstein develop Hybridoma technology - The *Nobel Prize* in Physiology or Medicine 1984
- 1982 - The first report of successful use of a MCAB to treat lymphoma (patient specific anti-idiotype antibody therapy)
- 1986 – First MCAB, muromonab-CD3 (OKT3) approved by FDA
- 1997 – First MCAB to treat cancer (rituximab) approved

- However **NO APPROVED MCAB** for Multiple Myeloma

Mechanisms of MAB Mediated Cytotoxicity

Effector cells:
NK cell
monocyte
macrophage
neutrophil



Antibody-dependent Cellular cytotoxicity (ADCC)

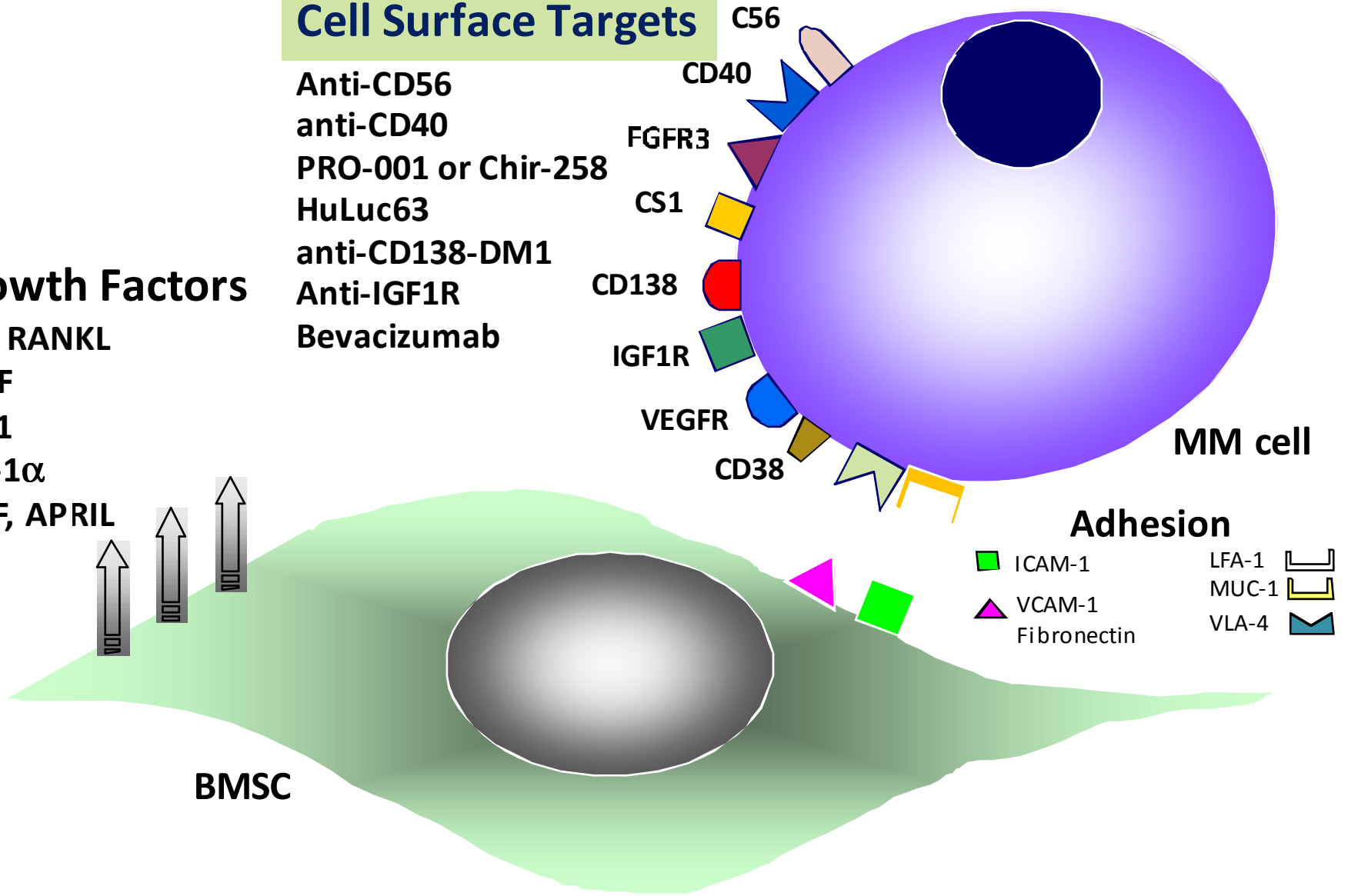
Complement-dependent Cytotoxicity (CDC)

Apoptosis/growth arrest via intracellular signaling pathways

Targets for MCAB Therapy in MM

Cell Surface Targets

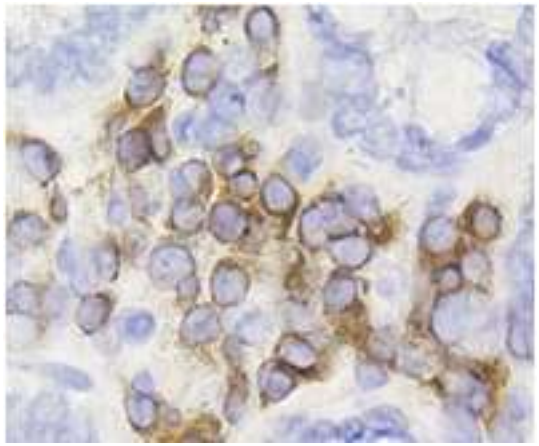
Anti-CD56
anti-CD40
PRO-001 or Chir-258
HuLuc63
anti-CD138-DM1
Anti-IGF1R
Bevacizumab



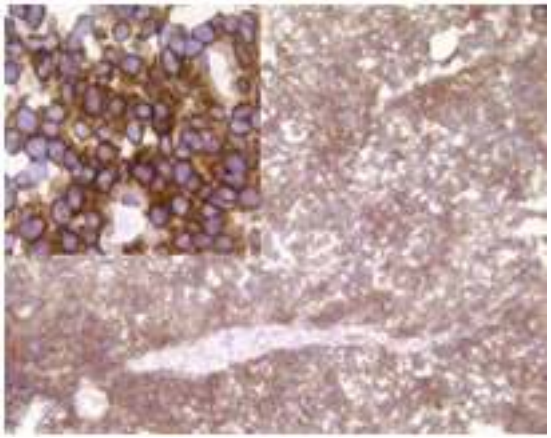
Target	Antibody	Company	Type
CS1	**Elotuzumab**	**Abbot/BMS**	**Humanized**
IL-6	**Siltuximab**	**Orthobiotec**	**Chimeric**
CD138	**BT062**	**Biotest**	**Chimeric; conjugated to Maytansinoid**
Anti-KIR	**IPH2101**	**Innate Pharma**	**Fully Human**
CD40	SGN-40, HCD122 Dacetuzumab, Lucatumumab	Seattle Genetics Novartis	Humanized Fully Human
CD56	IMGN901, Lorvotuzumab Meransine	ImmunoGen	Humanized; conjugated to Maytansinoid
CD74	Immu-110	Immunomedics	Humanized; conjugated to Doxorubicin
IGF1-R	CP751,871	Pfizer	Fully Human
RANKL	Denosumab	Amgen	Fully Human
DKK-1	BHQ880	Novartis	Fully Human
FGFR3	PRO-001	Prochon Biotech Genetech	Humanized

CS1 in Multiple Myeloma

- **Universal gene expression in multiple myeloma**
- **Confirmed CS1 protein expression by flow cytometry and IHC with anti-CS1 antibodies**
- **Normal tissue staining shows exclusive expression only in tissue plasma cells**



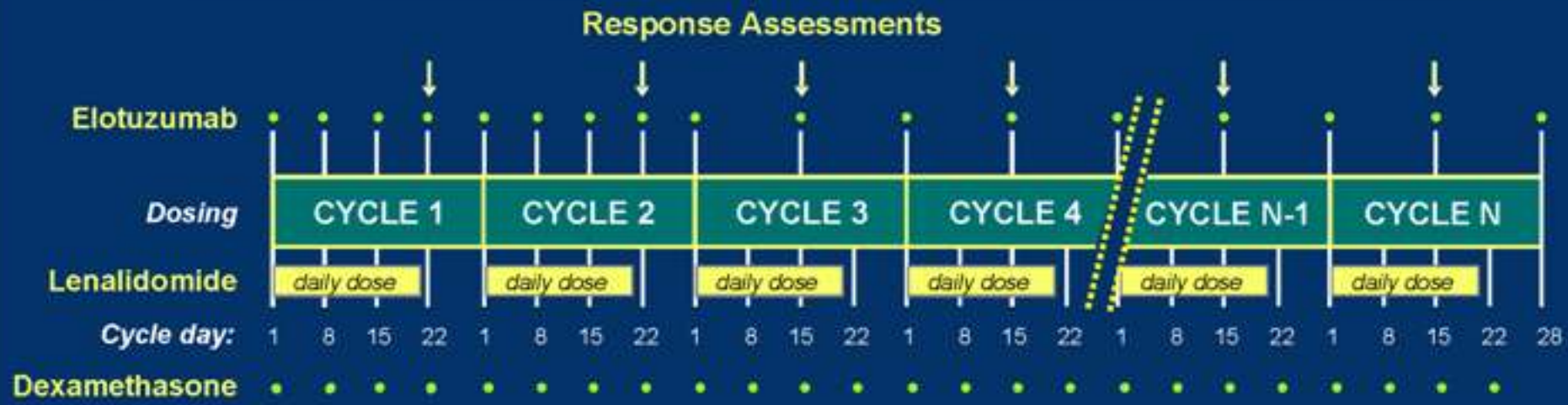
Plasma cells in normal gut



Multiple myeloma cells in a plasmacytoma

Staining was performed with HuLuc63 humanized anti-CS1 monoclonal antibody

Randomized Phase 2 Study Schema



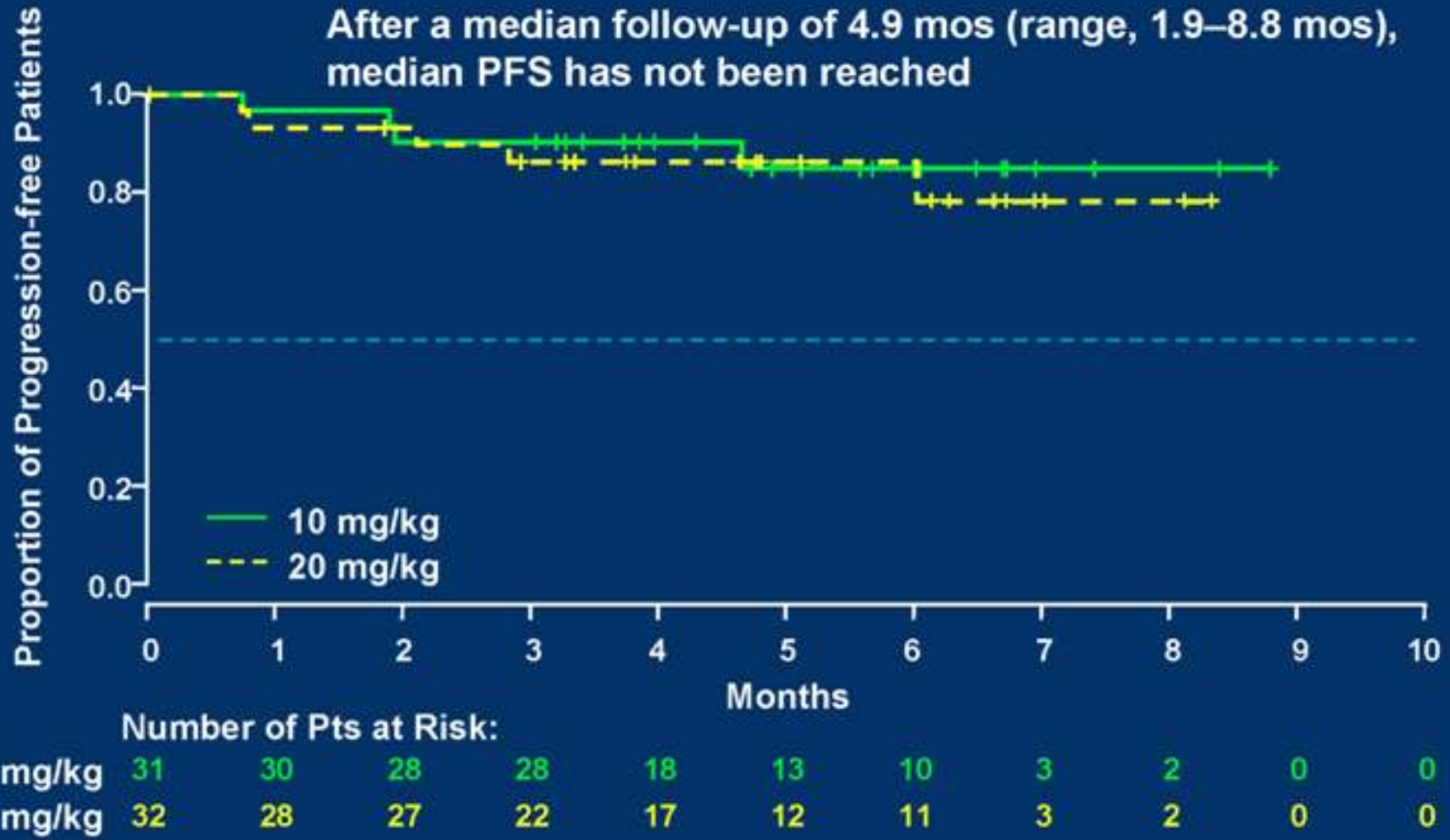
- Pts randomized to receive elotuzumab 10 or 20 mg/kg IV, in combination with lenalidomide 25 mg PO and low-dose dexamethasone 40 mg PO wkly (28-day cycles)
- Treatment continued until PD or unacceptable toxicity
- Premedication regimen (30–60 mins prior to elotuzumab infusion)
  - Methylprednisone 50 mg IV
  - Diphenhydramine 25–50 mg PO or IV (or equivalent)
  - Ranitidine 50 mg IV (or equivalent)
  - Acetaminophen 650–1000 mg PO

Efficacy
Best Confirmed Response (IMWG Criteria) [N=63]

	Elotuzumab 10 mg/kg	Elotuzumab 20 mg/kg	Total
Pts, n	31	32	63
≥ PR, n (%)	28 (90)	23 (72)	51 (81)
Stringent CR, n (%)	1 (3)	1 (3)	2 (3)
CR, n (%)	2 (7)	1 (3)	3 (5)
VGPR, n (%)	10 (32)	8 (25)	18 (29)
PR, n (%)	15 (48)	13 (41)	28 (44)
SD, n (%)	3 (10)	7 (22)	10 (16)
PD, n (%)	0 (0)	0 (0)	0 (0)
Not evaluable, n (%)	0 (0)	2 (6)	2 (3)

CR, complete response; IMWG, International Myeloma Working Group; PD, progressive disease; PR, partial response; SD, stable disease; VGPR, very good partial response.

Progression-free Survival



Number of Pts at Risk:

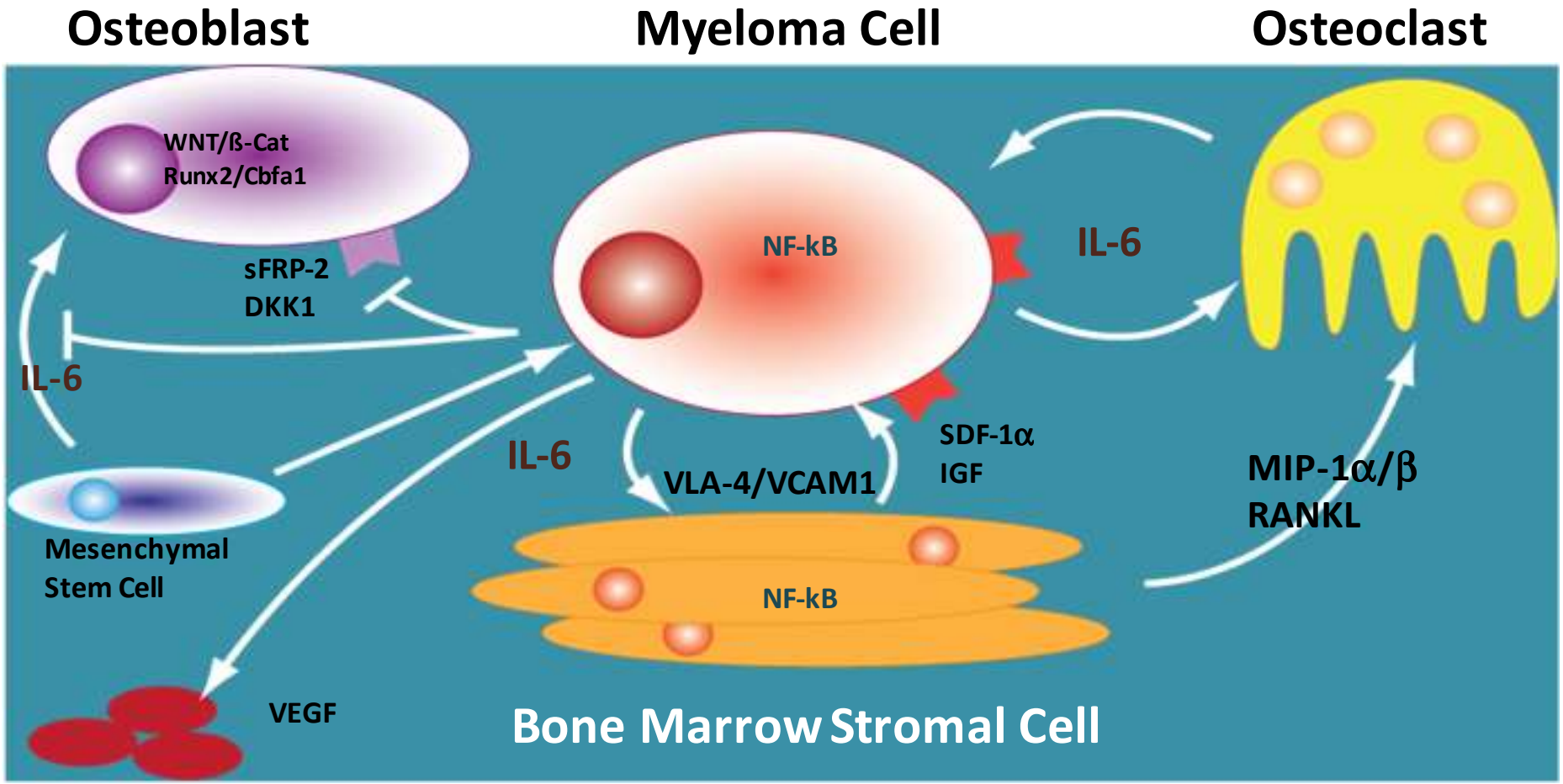
10 mg/kg	31	30	28	28	18	13	10	3	2	0	0
20 mg/kg	32	28	27	22	17	12	11	3	2	0	0

Conclusion for Elotuzumab Therapy in MM

- Elotuzumab + lenalidomide and dexamethasone is well tolerated
- High response rate that is durable
- Phase III trial is ongoing:

  Lenalidomide-Dexamethasone +/- Elotuzumab

Role of IL6 in Myeloma Bone Marrow Micro Environment



Bernard Klein

Phase II Study of Siltuximab in Relapsed/Refractory Multiple Myeloma

- **Relapsed myeloma after Bortezomib (100%), IMiDs 87% and Transplant 59%**
- **Siltuximab 6 mg/kg IV every 2 weeks + Dexamethasone**
- **Treatment Responses (N = 44 evaluable patients)**
- **Duration of therapy = 3.0 months (range 0.5 to 24.3 months)**

Best Response*	Number of Patients	Duration of Response (median)
CR	0	
PR	9	5.5 months (2.8 – 19.8)
MR	4	3.2 months (1.6 – 6.4)
SD	23	
PD	8	

20% (CR + PR)

PR+MR 30%

*EMBT criteria, 44 patients evaluable for response

Voorhees, et al. *J Clin Oncol* 2009; 27. Abstract 8527.

Study T-05

Phase II Study of Siltuximab and Bortezomib in Relapsed/Refractory Multiple Myeloma

- **Patient Disposition (Part 1 – Safety Group): N = 21 patients**
- **Bortezomib naive**

Response	Number of Patients
CR	3
VGPR*	3
PR	6
SD	6
PD	3

29%

ORR 57%

*VGPR = Very Good Partial Response (>90% reduction in serum M-spike)

- Median time to progression = 8.7 months (1.2 – 22.4+)

Study T-06

Phase II Study of Siltuximab and Bortezomib in Relapsed/Refractory Multiple Myeloma

- **Conclusions**
- **Preliminary efficacy encouraging in Part 1 results**
  - **57% response (CR + VGPR + PR)**
  - **29% response (CR + VGPR)**
- **No unexpected toxicity**
- **Part 2 of the study completed enrollment and is ongoing**

Phase III Trial: MPV +/- Siltuximab

Rossi, et al., *Blood* 2008:112. Abstract 867

BT062: MCAB-drug Conjugate Maytansinoid linked to CD138

Targeted Antibody Payload (TAP) Technology

Chimeric antibody conjugate is stable and inactive in blood plasma

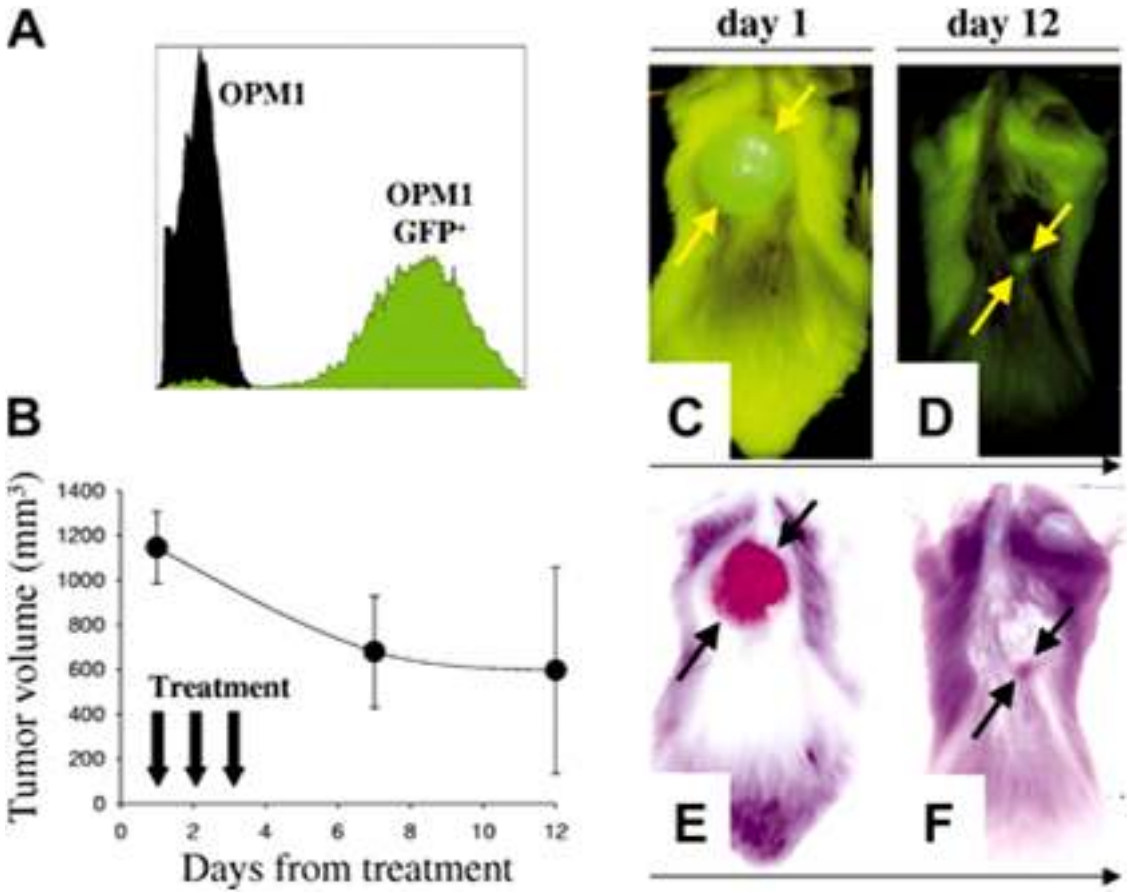
Binding to CD138 expressing cells and internalization of BT-062 into the target cell

Processing and release of active DM4 inside the target cell killing of dividing target cells

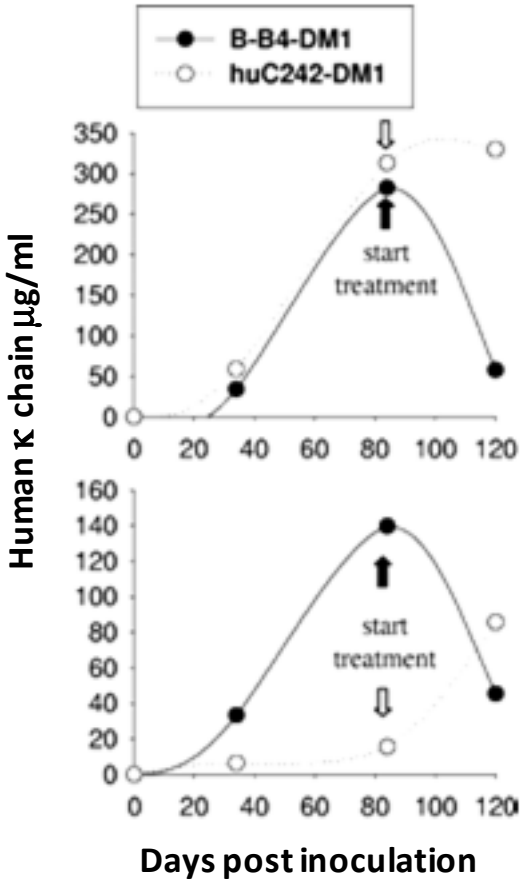
Jagannath et al. ASH Abs#3010, 2010

BT062: MCAB-drug Conjugate Maytansinoid linked to CD138

Xenograft model



SCID-hu model



Tassone et al Blood 2004;104:3688

BT062: Phase I Results

Number of patients	Total	Percentage	Objective response rate	Clinical benefit rate
treated with BT-062	32			
Number of pts. evaluable for response*	27	100%		
- disease progression after < 9 weeks	13	48%		
- stable disease for ≥ 9 weeks**	11	41%		52%
- minor response	2	7%	11%	
- partial response	1	4%		

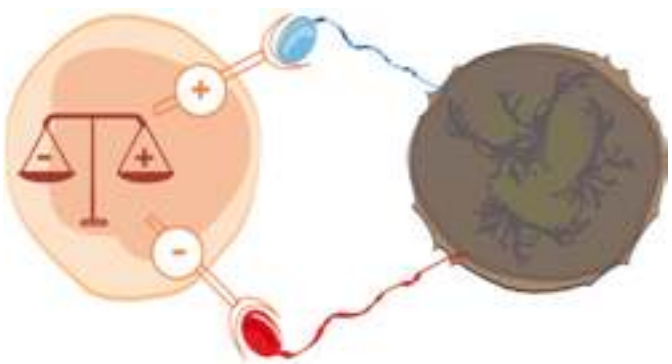
* Patients who received only 1 treatment (3 DLTs; 1 withdrawal, 1 not eligible for further treatment) were defined as not evaluable for response

** 4th treatment was only allowed if stable disease was confirmed by M-Protein or sFLC data

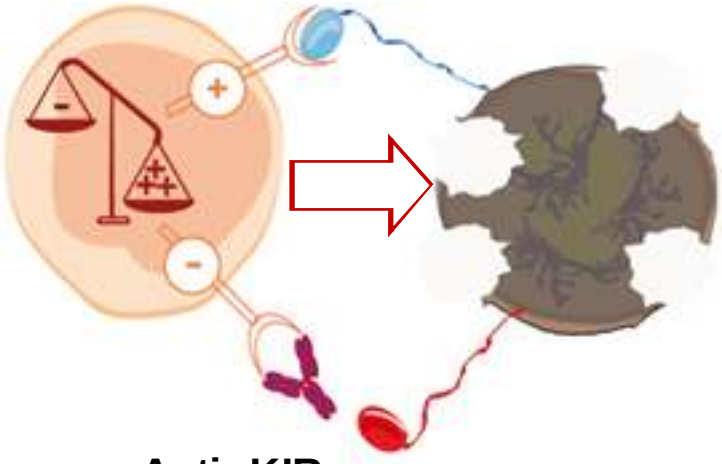
- BT-061 iv once every 3 weeks; dose range 10 to 200 mg/msq
- A few adverse events have also been observed involving skin and/or mucosa (tissues of epithelial origin with CD138 expressing cells),
- All patients had relapsed after bortezomib and Lenalidomide/Thalidomide
- About 50% of the patients achieve clinical benefit

Jagannath et al. ASH Abs#3010, 2010

Principle of anti-KIR: release inhibition of NK cells



NK cell Tumor cell



Anti- KIR

No lysis **Lysis**

NK cell activation is controlled by balanced activation and inhibitory signals
Recognition by NK cells of activating antigens is absolutely required for their activation
Such activating antigens are electively expressed by tumor (or infected) cells and not by healthy cells
KIR blockade promotes NK mediated cytotoxicity against tumor

IPH 2101 Phase II Trial

- Two doses leading to intermittent or sustained KIR
  - 2 doses leading to intermittent or sustained KIR occupancy
    - Smoldering Multiple Myeloma **203 Kirmono** n =30 (4 treated)
      - PI: N Munshi DFCI, Boston
    - Maintenance after any first line therapy **201 Remykir** n=28 (24 treated)
      - PI: M Attal Purpan's Hosp, Toulouse
      - Randomization between the 2 doses
  - A combination of IPH 2101 + lenalidomide
    - Upfront treatment of MM: first relapse **202 Kirimid** n= 12+19
      - PI: D Benson OSU, OH
      - 2 sequential phases beginning by a dose escalation
- To assess the impact of these function on NK cell phenotype and function

Conclusion for MCAB Therapy in MM

- Several promising MCAB are in advanced clinical testing in myeloma
- However single agent antitumor activity of these agents appears to be modest
- One of the challenges for application of MCAB in myeloma may relate to underlying immunoparesis
- Combination approaches with immunomodulatory drugs as in case of elotuzumab appears promising