IMMUNOTHERAPY OF HEMATOLOGIC MALIGNANCIES

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Disclosures

- WindMIL Therapeutics - Receipt of Intellectual Property Rights/Patent Holder
- Bristol-Myers Squibb, Celgene Corporation - Contracted Research
- I will be discussing non-FDA approved treatments during my presentation.

Unique Attributes of Immune Trials in Hematologic Malignancies

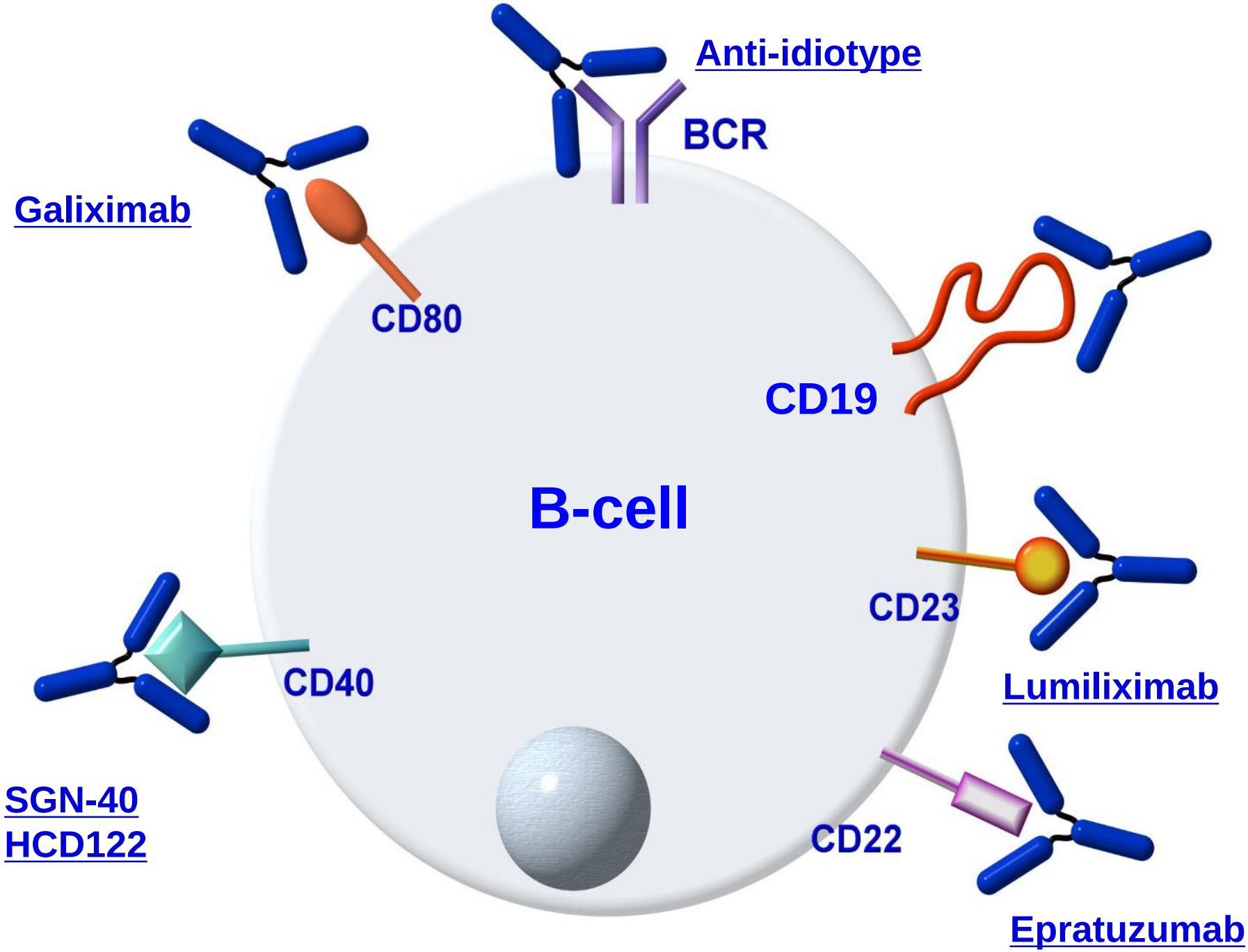
- B cell lymphoid malignancies possess many features of antigen presenting cells –
- Easy access to tumor facilitates serial biopsies

LYMPHOMAS

Rituximab: Things That We Know ….
18 years later

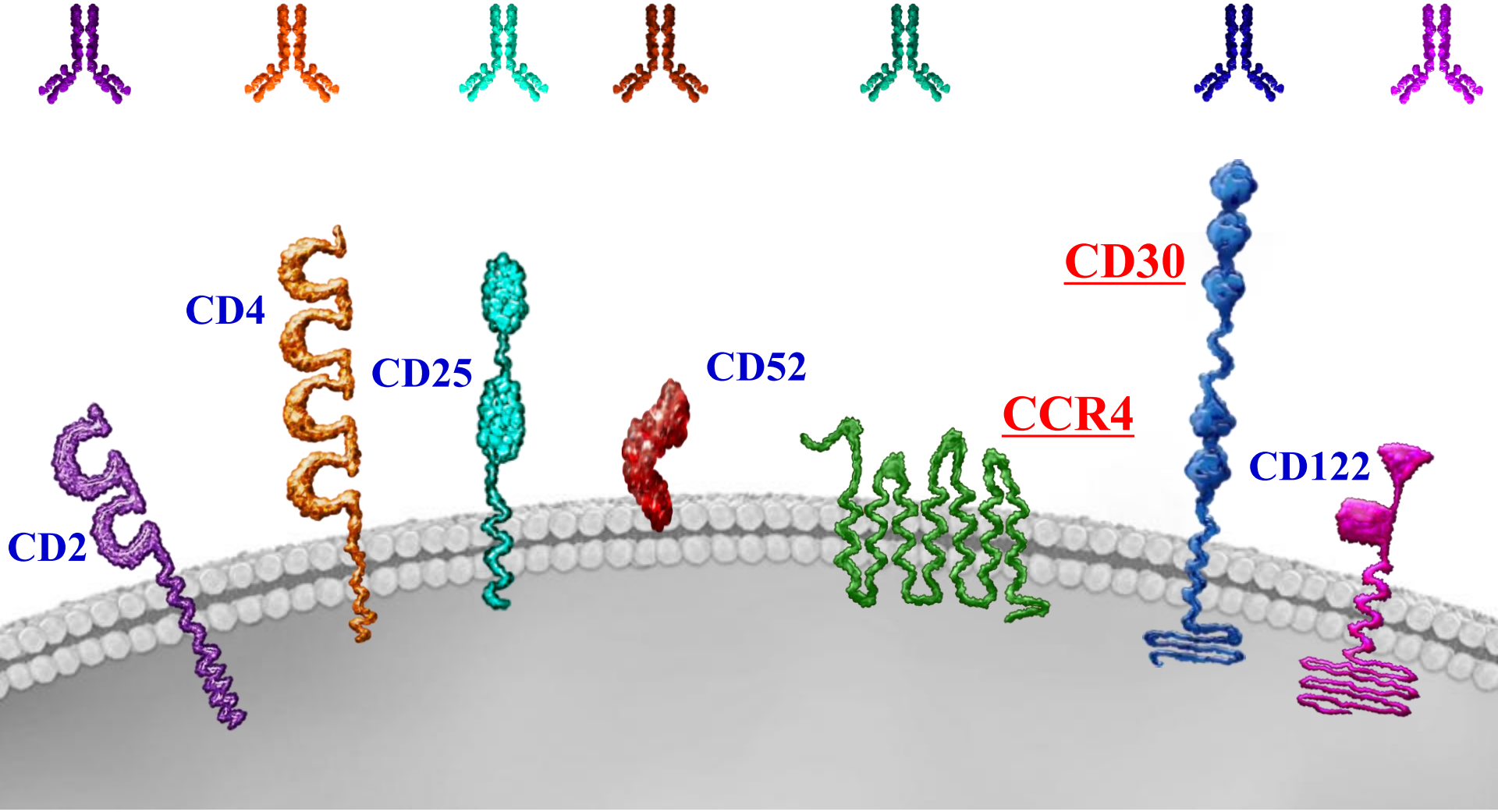
- **Addition of rituximab to chemotherapy:**
  - **Increases ORR, CR, PFS, and OS in DLBCL**
  - **Increases ORR, CR, PFS, OS in Follicular lymphoma**
  - **Increases ORR, CR, PFS in MCL, SLL and other indolent lymphomas**

- **Rituximab maintenance after chemo-R induction:**
  - **Prolongs PFS, FFS, without difference in OS in follicular lymphoma (PRIMA Study)**
  - **Improves OS in elderly patients with MCL *(Kluin-Nelemans et al. NEJM 367:520-31,2012)***

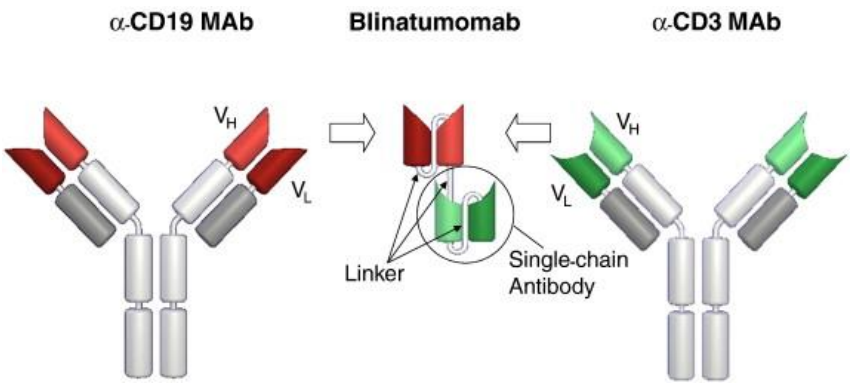

Anti-idiotype
BCR
Galiximab
CD80
CD19
B-cell
CD23
Lumiliximab
CD40
SGN-40
HCD122
CD22
Epratuzumab

Good news for patients with T-cell lymphomas:

Several monoclonal antibodies targeting T-cell lymphomas



BiTE: Blinatumumab



- Combines the F(ab) of an antibody with an anti-CD3 F(ab)
- Lacks the Fc region
- Requires continues infusions
- Shown considerable activity in:
  - follicular NHL
  - DLBCL
  - ALL

Anti-PD-1 in Hodgkin's Lymphoma

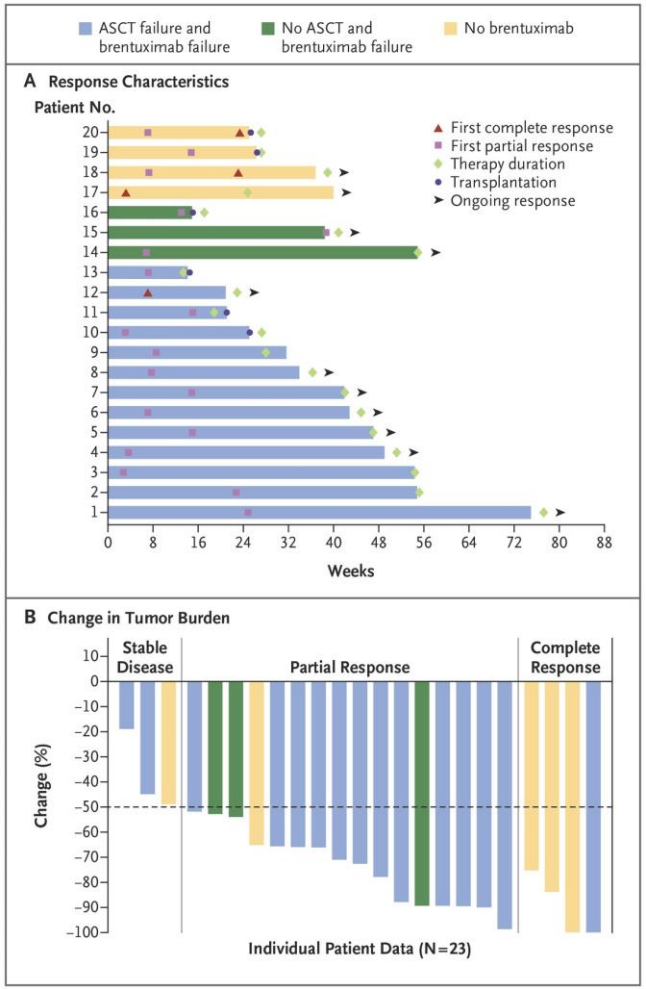


Table 3. Clinical Activity in Nivolumab-Treated Patients.*

Variable	All Patients (N=23)	Failure of Both Stem-Cell Transplantation and Brentuximab (N=15)	No Stem-Cell Transplantation and Failure of Brentuximab (N=3)	No Brentuximab Treatment (N=5)†
Best overall response — no. (%)				
Complete response	4 (17)	1 (7)	0	3 (60)
Partial response	16 (70)	12 (80)	3 (100)	1 (20)
Stable disease	3 (13)	2 (13)	0	1 (20)
Progressive disease	0	0	0	0
Objective response				
No. of patients	20	13	3	4
Percent of patients (95% CI)	87 (66–97)	87 (60–98)	100 (29–100)	80 (28–99)
Progression-free survival at 24 wk — % (95% CI)‡	86 (62–95)	85 (52–96)	NC§	80 (20–97)
Overall survival — wk				
Median	NR	NR	NR	NR
Range at data cutoff¶	21–75	21–75	32–55	30–50

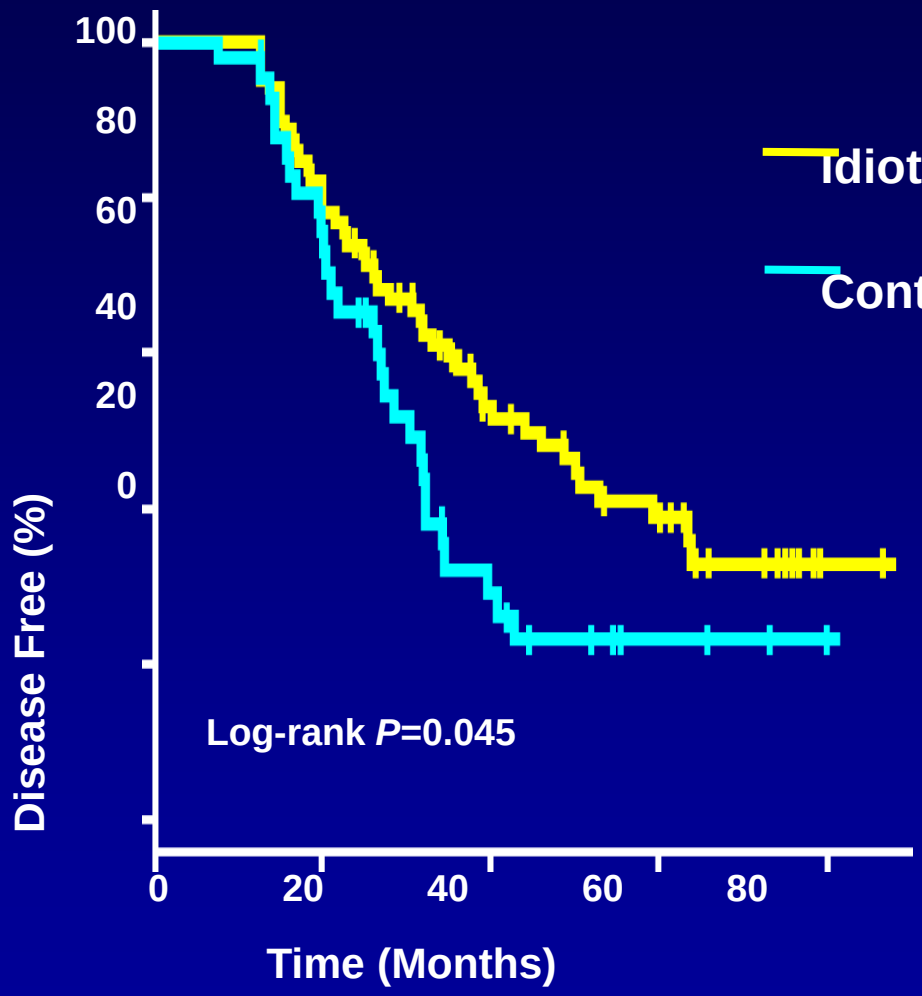
* NC denotes not calculated, and NR not reached.
† In this group, two patients had undergone autologous stem-cell transplantation and three had not.
‡ Point estimates were derived from Kaplan–Meier analyses; 95% confidence intervals were derived from Greenwood's formula.
§ The estimate was not calculated when the percentage of data censoring was above 25%.
¶ Responses were ongoing in 11 patients.

Ansell SM et al. N Engl J Med 2015;372:311-319

Nivolumab in R/R B Cell Malignancies: Efficacy

Types	n	ORR, n (%)	CR, n (%)	PR, n (%)	SD, n (%)
B cell lymphoma	29	8 (28)	2 (7)	6 (21)	14 (48)
DLBCL	11	4 (36)	1 (9)	3 (27)	3 (27)
FL	10	4 (40)	1 (10)	3 (30)	6 (60)
T cell lymphoma	23	4 (17)	0	4 (17)	10 (43)
Mycosis fungoides	13	2 (15)	0	2 (15)	9 (69)
PTCL	5	2 (40)	0	2 (40)	0
Multiple myeloma	27	0	0	0	18 (67)
Primary mediastinal B-cell lymphoma	2	0	0	0	2 (100)

Vaccination with Patient-Specific Tumor-Derived Antigen in First Remission Improves Disease-Free Survival in Follicular Lymphoma

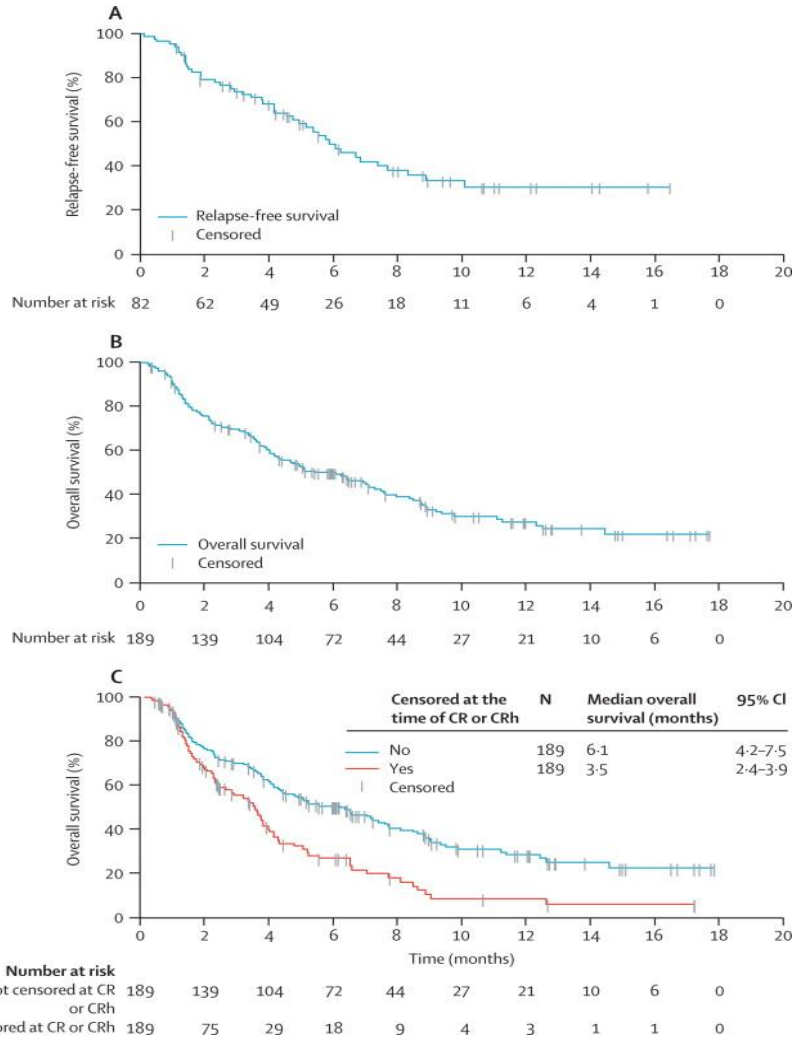


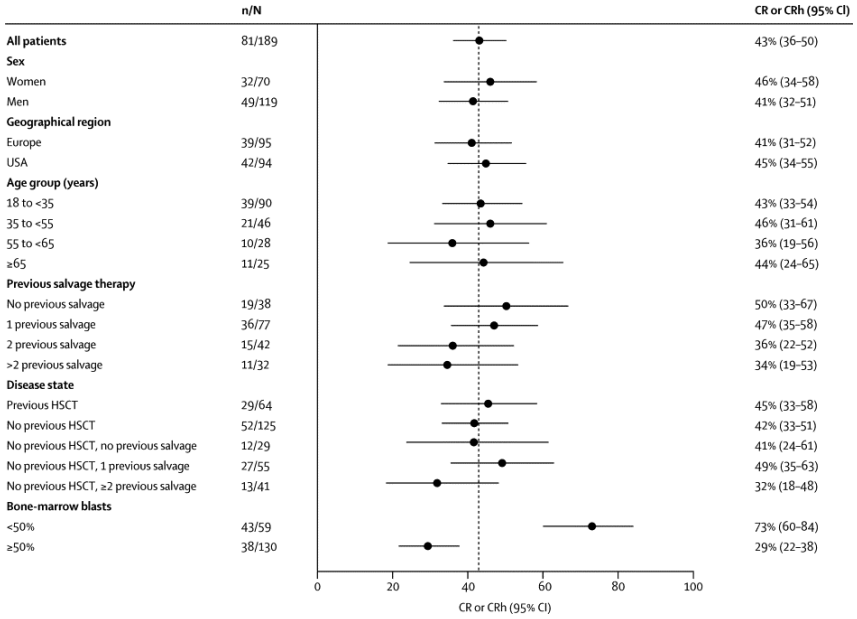
	Median DFS
Idiotype vaccine	44.2 mos
Control vaccine	30.6 mos

Schuster et al. J. Clin Oncol. 29 (20): 2787-94, 2011

LEUKEMIA

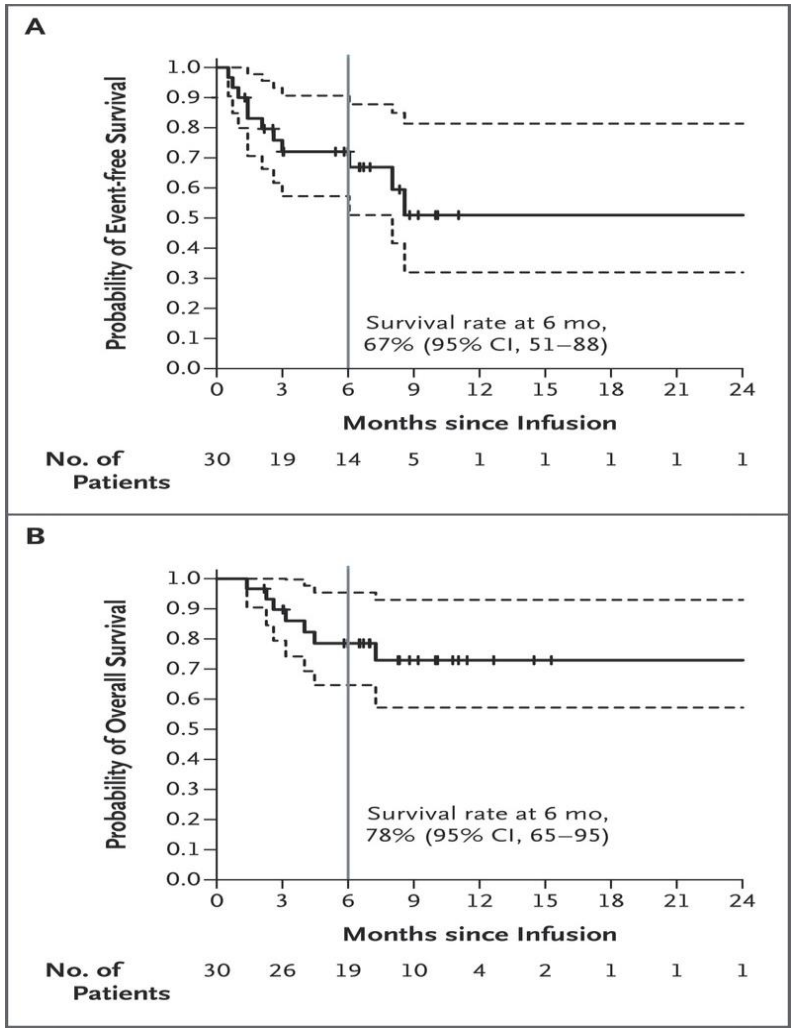
Blinatumumab in ALL





CD-19 CAR-T in ALL

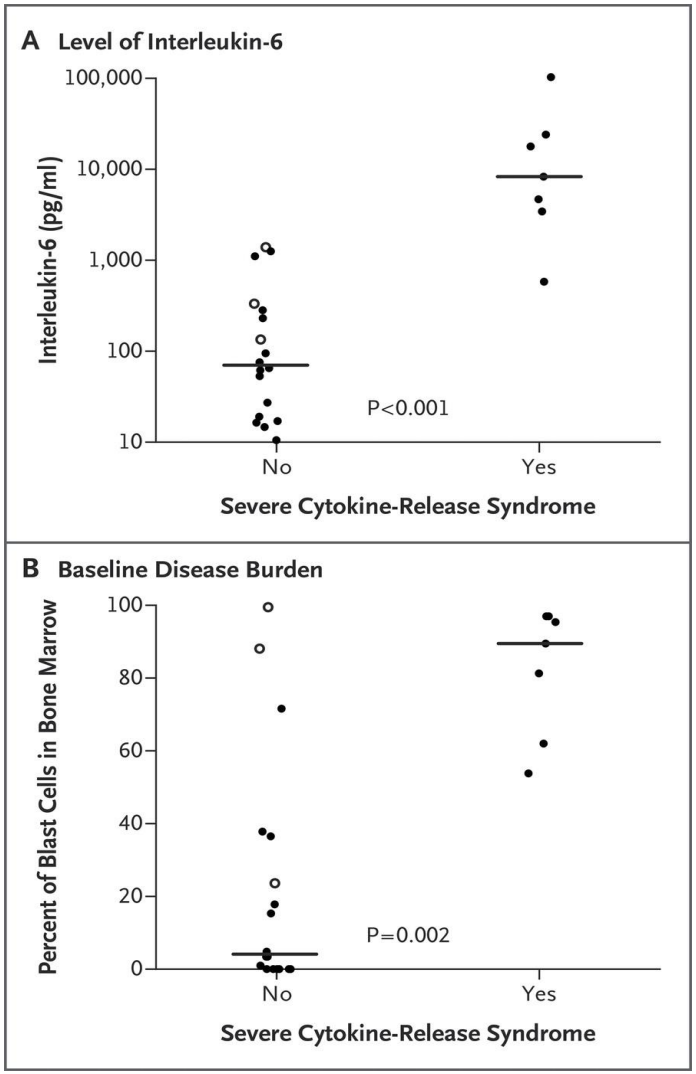
Probability of Event-free and Overall Survival at 6 Months.



Maude SL et al. N Engl J Med 2014;371:1507-1517.

CD-19 CAR-T in ALL

Correlates of the Cytokine-Release Syndrome.



Antigen-specific Approaches in ALL

Technology:	CART	ADC	BiTE
Example	CART-19	Inotuzumab (anti-CD22 + toxin)	Blinatumumab (anti-CD3/CD19)
Dosing	One infusion	Every 3 weeks	Continuous 28 days
Complete Response	90%	19%	66%
Survival	78% 6 mos OS	5-6 months median	9 mos median
Major toxicity	Cytokine release	Hepatotoxicity	Cytokine release
Antigen loss relapse?	Yes	No	Yes
Challenges	Complex manufacturing, individualized	Lower response rates	Burdensome infusion

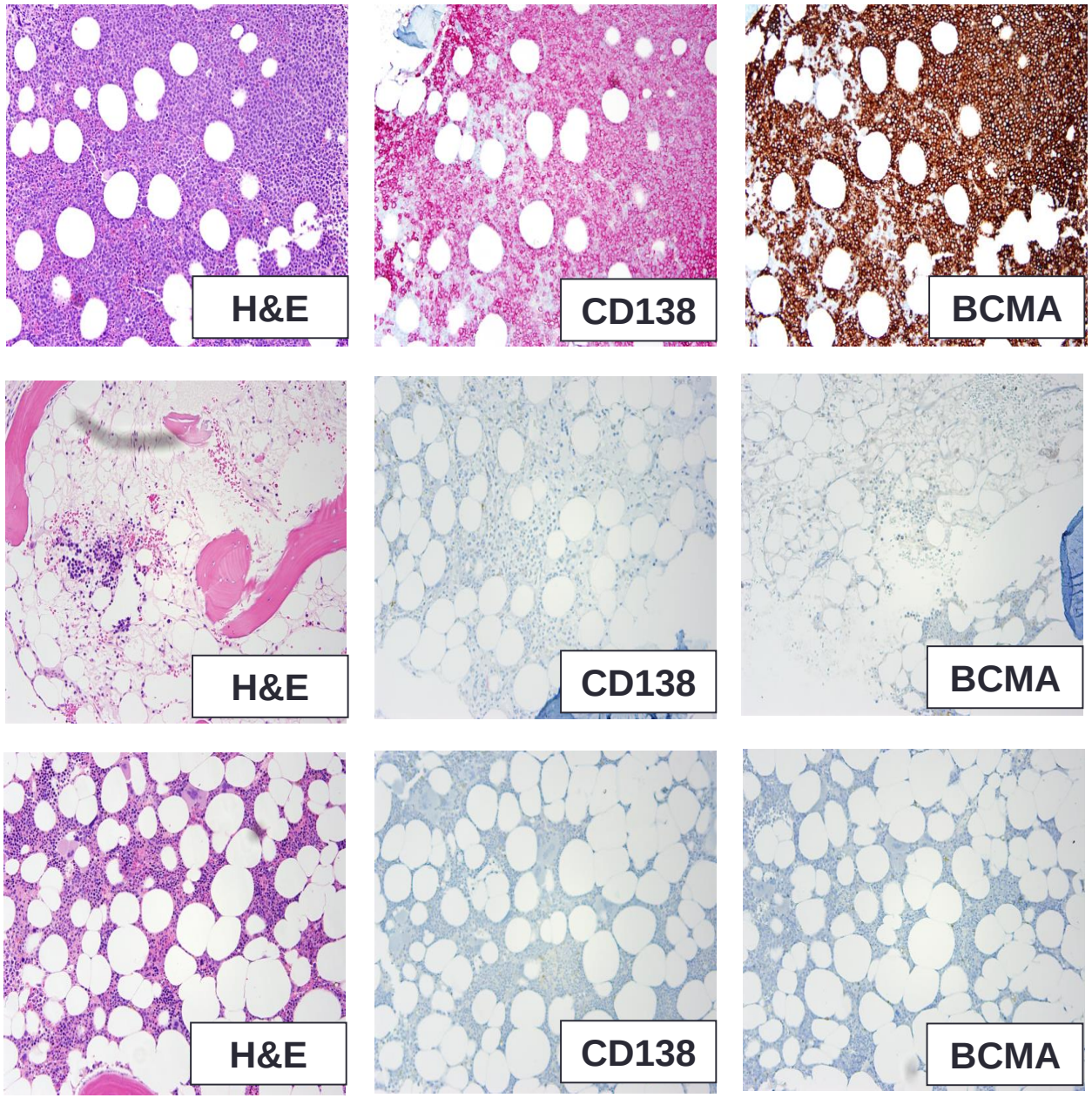
Gill Immunol Rev Dec 2014

MYELOMA

Myeloma CARs

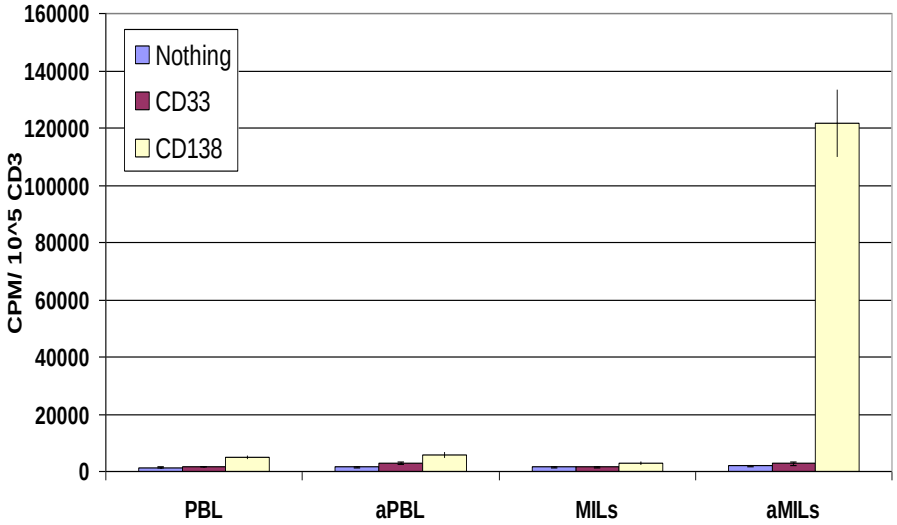
Antigen	CAR	Site	Pro's	Con's
CD38	4-1BB	Utrecht	Daratumumab	Expressed on monocytes, B cells, T cells
Kappa light chain	CD28	Baylor		Often secreted or downregulated on mature PC
CD138	4-1BB	China		Expressed on epithelial cells Shed in advanced disease
BCMA	CD28	NIH	Minimal expression on normal tissue Antibodies found in DLI responders	
SLAMF7	CD28	OSU	Elotuzumab	Expressed on NK, T cells, monocytes, DCs
CD19		U Penn		Expressed on MM stem cell

CAR-BCMA Effectively Eradicates Disease

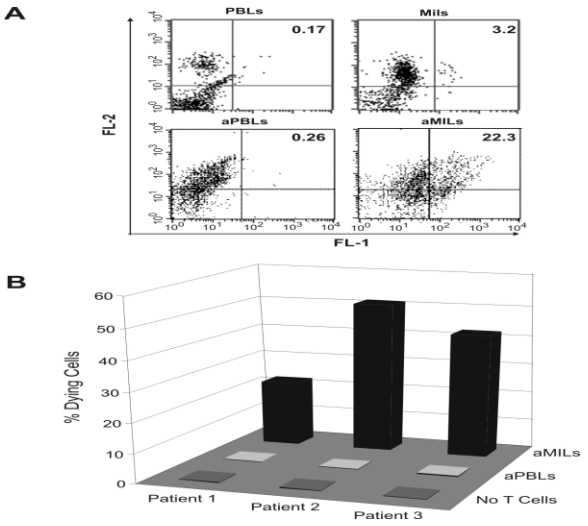


Marrow Infiltrating Lymphocytes

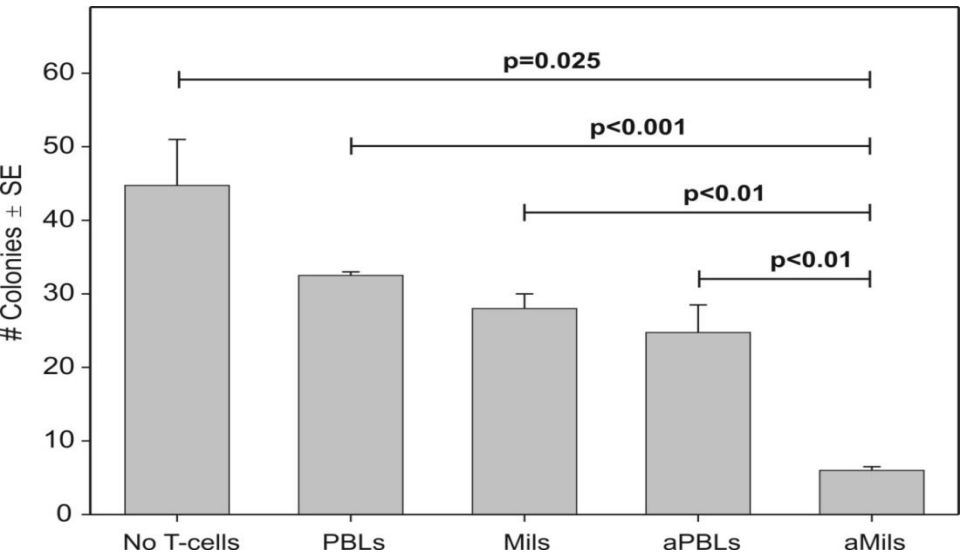
MILs Exhibit Significant Anti-Myeloma Specificity



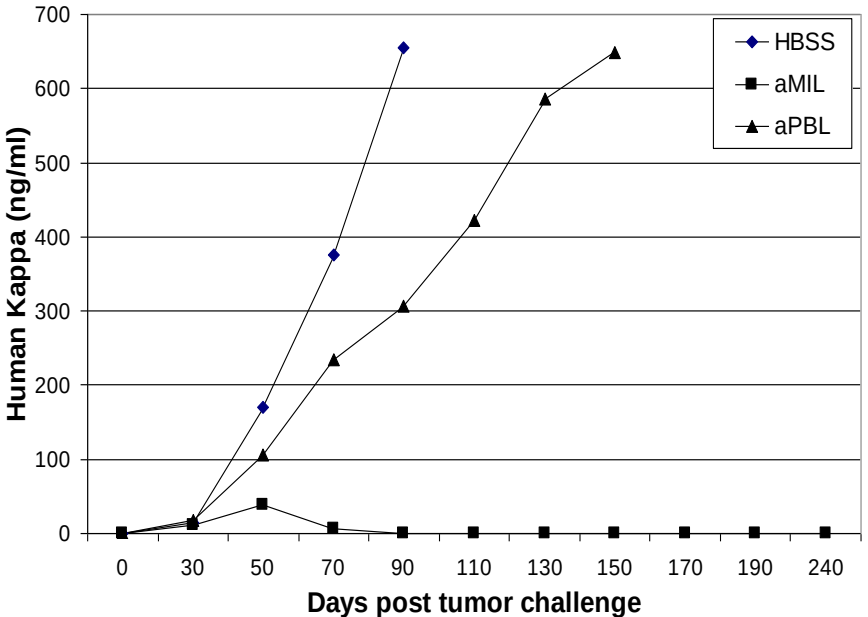
aMILs Effectively Kill Myeloma Cells



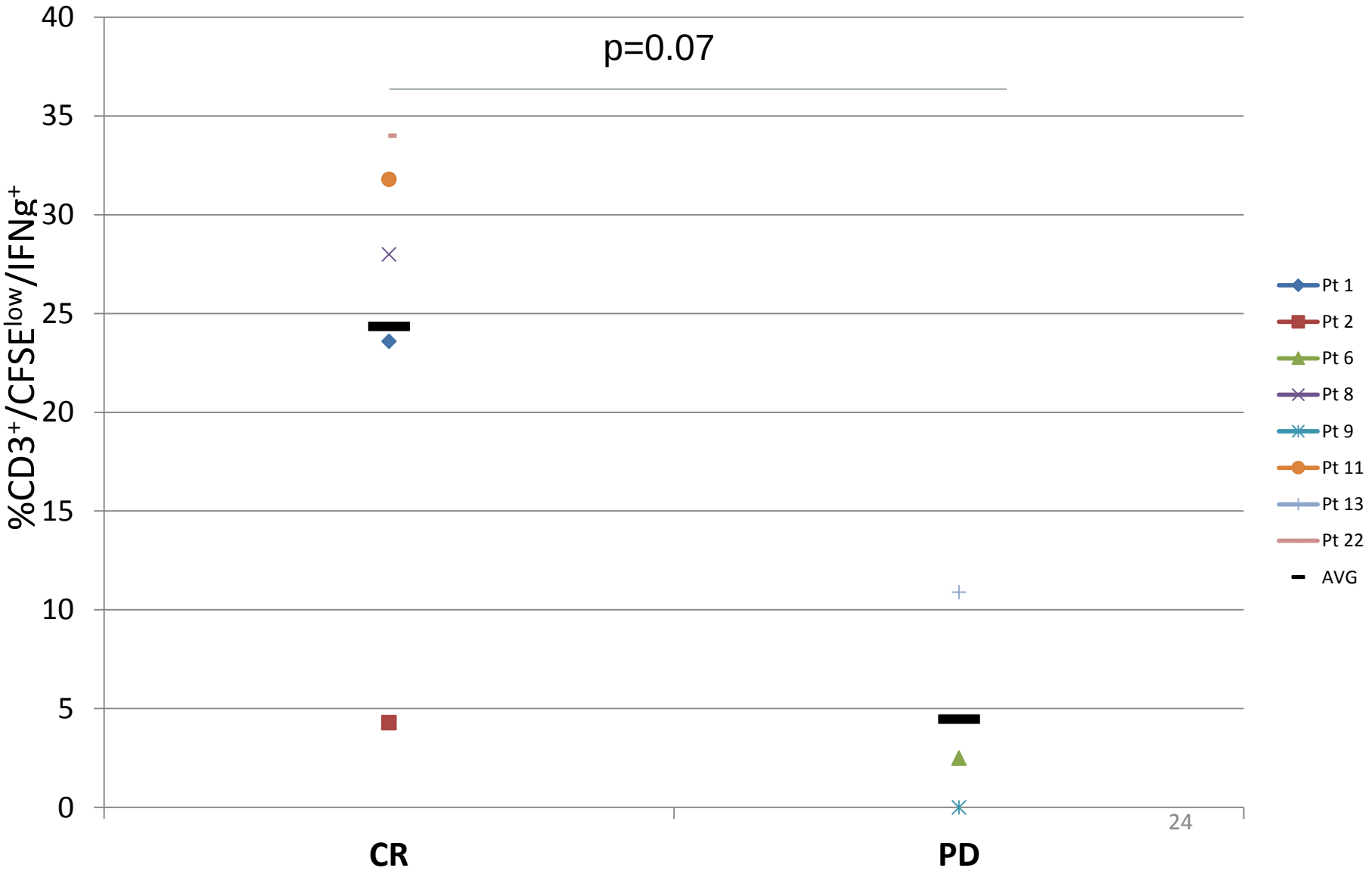
aMILs Impair Outgrowth of Myeloma stem Cells



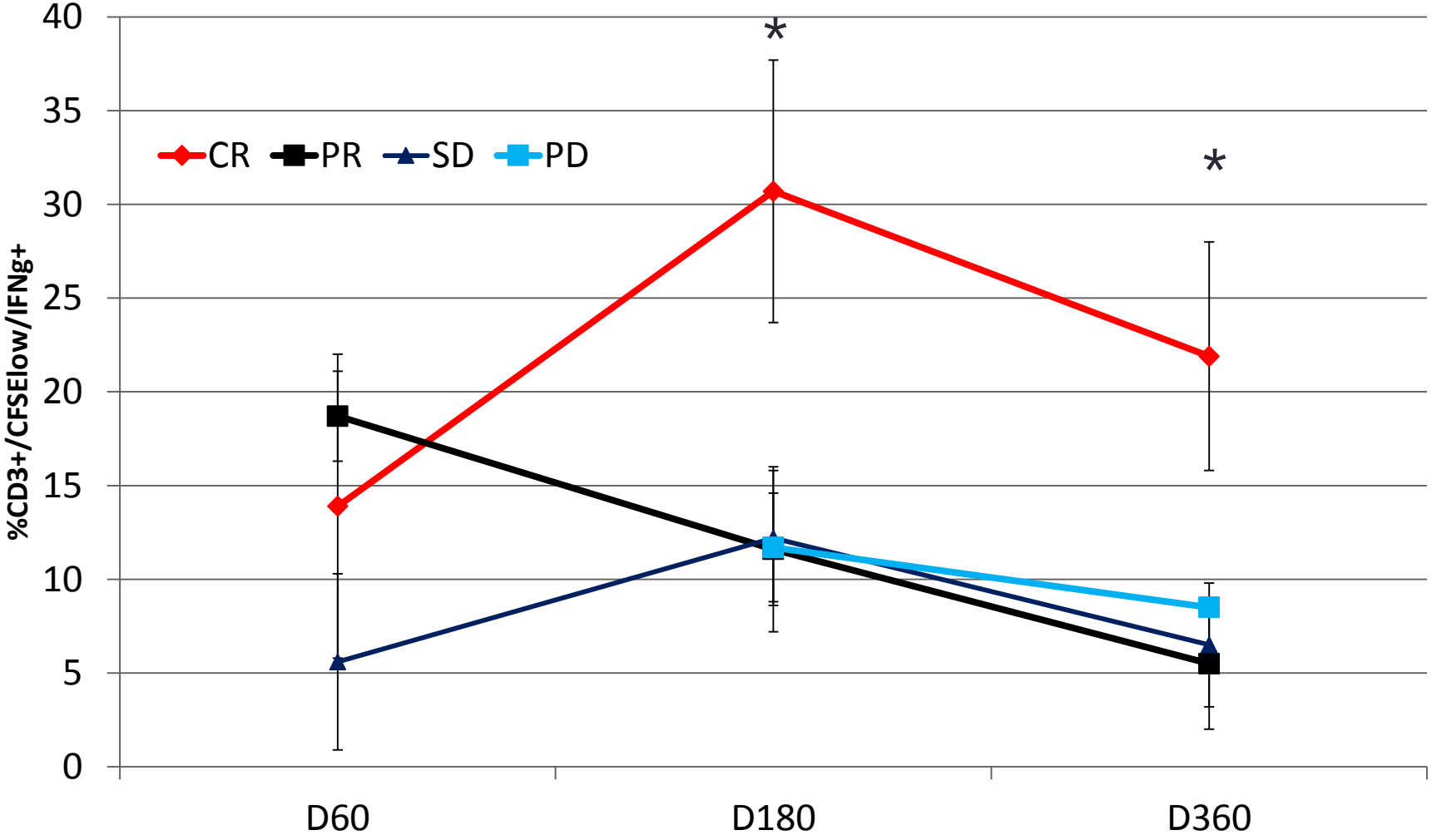
MILs eradicate pre-established disease



Tumor Specificity of aMILs Product



Correlation of Anti-tumor Immunity and Clinical Outcomes



*p<0.001

Pembrolizumab + Lenalidomide: Prior Therapies

	Pembro + Len + Dex N = 50
Prior therapies, median (range)	4 (1-5)
≥3 Lines of therapy, n (%)	36 (**72**)
Prior therapies, n, (%) Lenalidomide Bortezomib Pomalidomide Carfilzomib	 48 (**96**) 48 (**96**) 13 (**26**) 11 (**22**)
Prior ASCT, n (%)	43 (**86**)

	Pembro + Len + Dex N = 50
Refractory to lenalidomide, n (%)*	38 (**76**)
Double refractory	15 (30)
Triple refractory	6 (12)
Quadruple refractory	4 (8)
Refractory to bortezomib, n (%)	32 (64)
Refractory, last line, n (%)	40 (**80**)
Refractory to lenalidomide as last line, n (%)	10 (20)

50%

*Double refractory = Len/Bort
Triple refractory = Len/Bort/Pom or Len/Bort/Carf
Quadruple refractory = Len/Bort/Pom/Carf
Data cutoff date: September 22, 2015

Pembrolizumab + Lenalidomide: Response Rates

N (%)	Total N = 17	Len Refractory* N = 9
Overall Response Rate	13 (**76**)	5 (**56**)
Very Good Partial Response	4 (**24**)	2 (**22**)
Partial Response	9 (**53**)	3 (**33**)
Disease Control Rate†	15 (**88**)	7 (**78**)
Stable Disease	3 (**18**)	3 (**33**)
Progressive Disease	1 (**6**)	1 (**11**)

*3 patients double refractory and 1 triple refractory (Len/Bor +Pom)
†Disease Control Rate = CR +VGPR + PR + SD >12 weeks.
Data cutoff date: September 22, 2015

Patient Characteristics

	Vaccinated (n=15)	Observation (n=15)
Age	66 (45-81)	65.7 (40-83)
FISH high risk	0%	0%
ISS III	2 (16%)	2 (16%)
Pre-enrollment IFE neg	0 (0%)	7 (46%)
Prior Therapies	1.8 (1-4)	1.8 (1-3)
Prior ASCT	5 (33%)	4 (26%)

GVAX Significantly Prolongs PFS in Patients in a nCR