CAR-T and Other Immunotherapies in Myeloma

Ivan Borrello, M.D.

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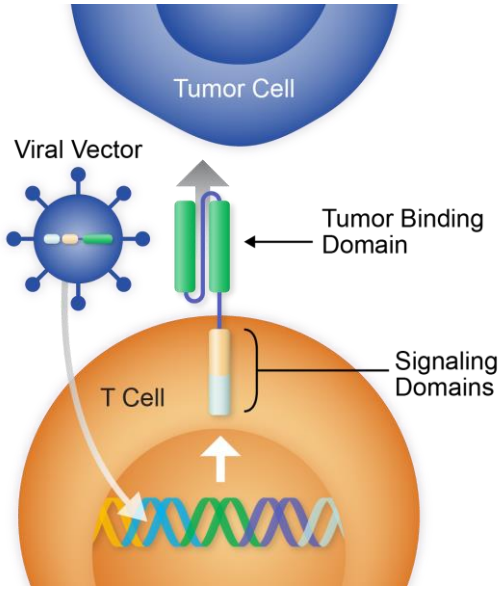
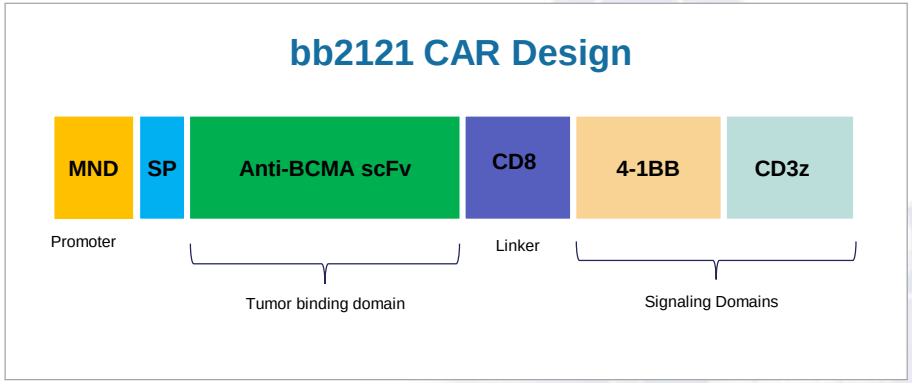
bb2121: BCMA CAR T Cell Design





- Autologous T cells transduced with a lentiviral vector encoding a CAR specific for human BCMA
- Optimal 4-1BB costimulatory signaling domain: associated with less acute toxicity and more durable CAR T cell persistence than CD28 costimulatory domain[1]

1. Ali SI, et al. *Blood*. 2016;128(13):1688-700.

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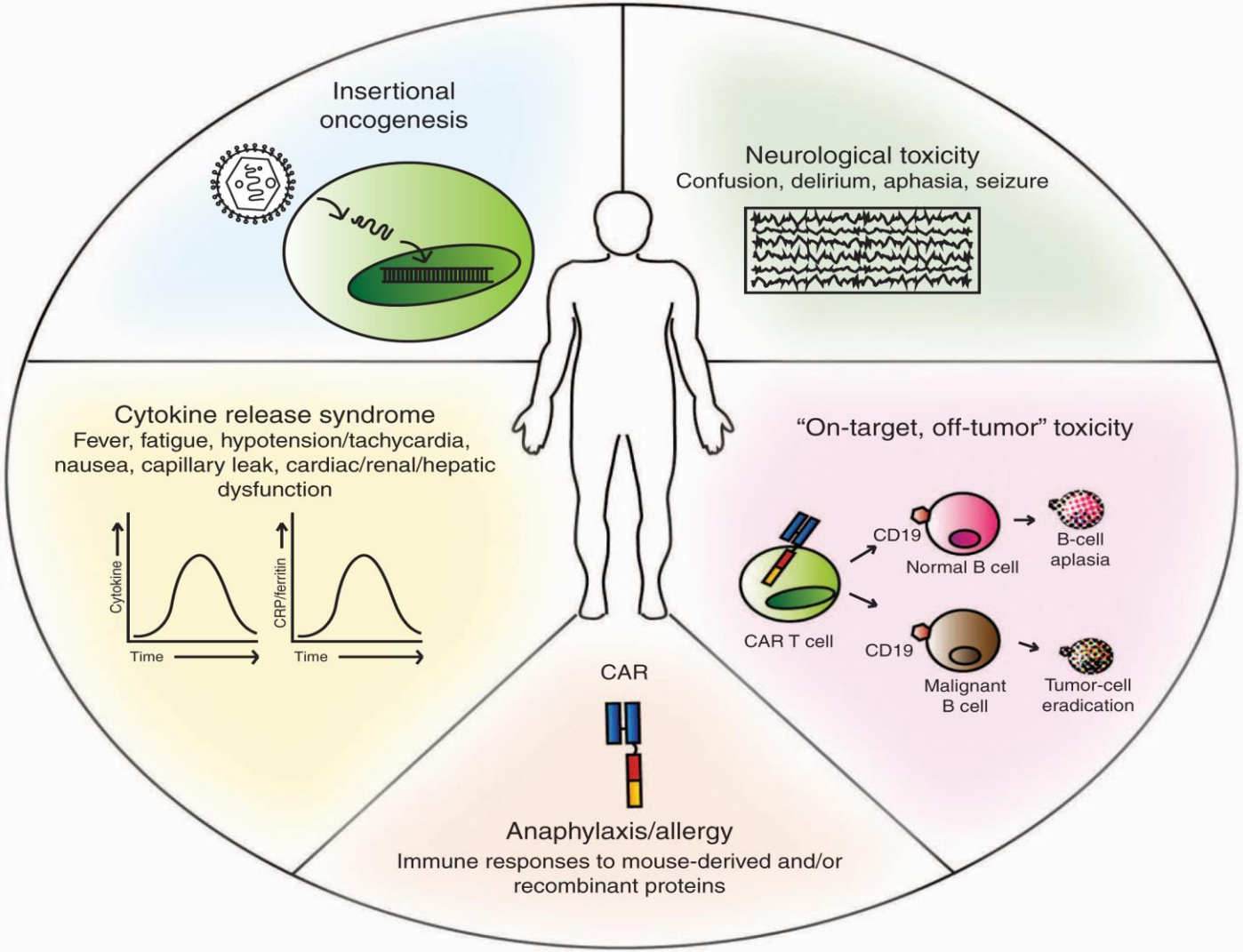
CAR-T Toxicities



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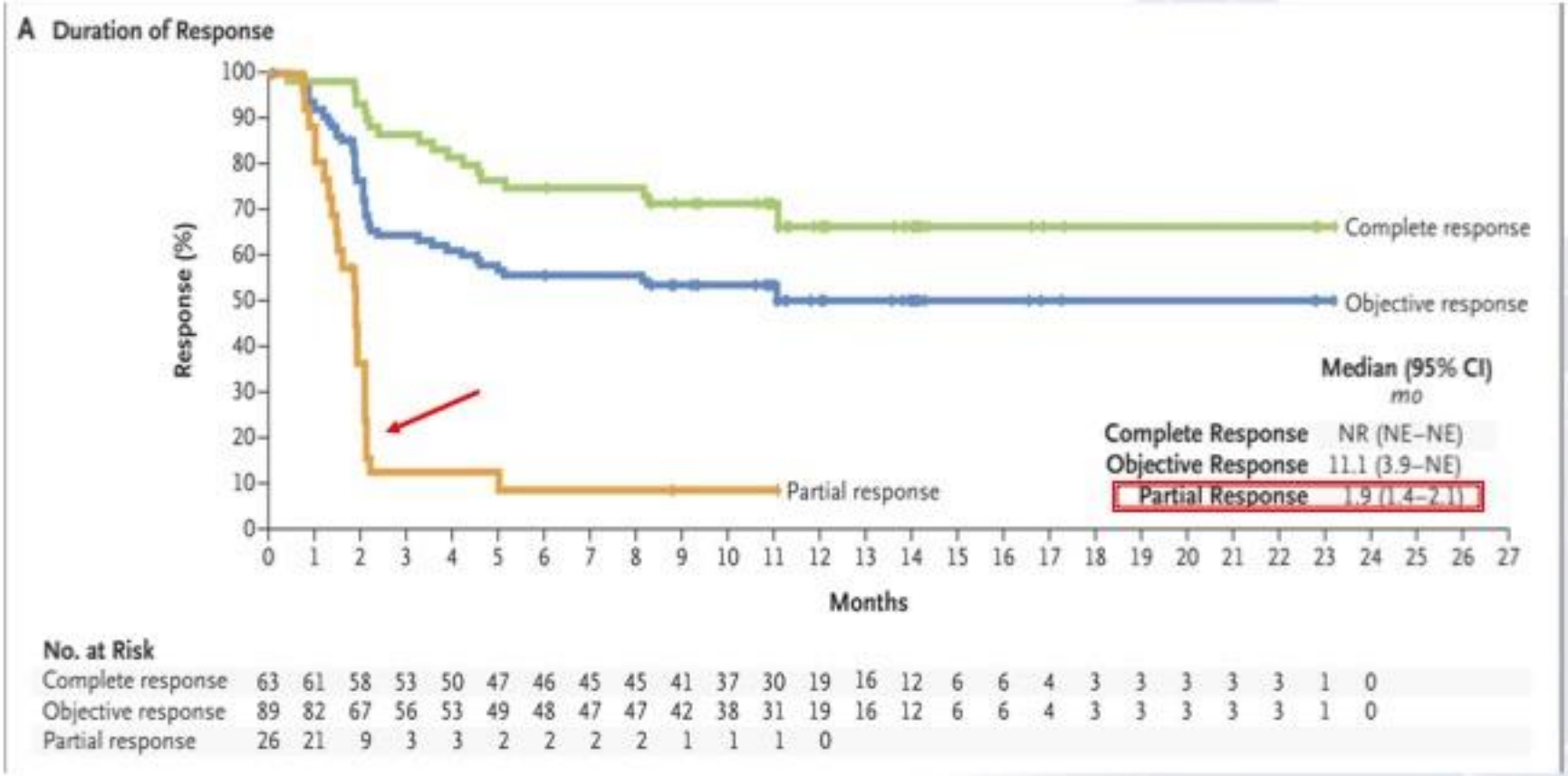
Clinical Efficacy of CAR-T Therapy in Patients Not Achieving a CR



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Treatment History

Parameter	Escalation (N=21)	Expansion (N=22)
Median (min, max) prior regimens	7 (3, 14)	8 (3, 23)
Prior autologous SCT, n (%)	21 (100)	19 (86)
0	0	3 (14)
1	15 (71)	14 (64)
>1	6 (29)	5 (23)

	Escalation (N=21)		Expansion (N=22)	
Parameter	**Exposed**	**Refractory**	**Exposed**	**Refractory**
Prior therapies, n (%)				
Bortezomib	21 (100)	14 (67)	22 (100)	16 (73)
Carfilzomib	19 (91)	12 (57)	21 (96)	14 (64)
Lenalidomide	21 (100)	19 (91)	22 (100)	18 (82)
Pomalidomide	19 (91)	15 (71)	22 (100)	21 (96)
Daratumumab	15 (71)	10 (48)	22 (100)	19 (86)
Cumulative exposure, n (%)				
Bort/Len	21 (100)	14 (67)	22 (100)	14 (64)
Bort/Len/Car/Pom/Dara	15 (71)	6 (29)	21 (96)	7 (32)

Data cutoff: March 29, 2018. SCT, stem cell transplant.

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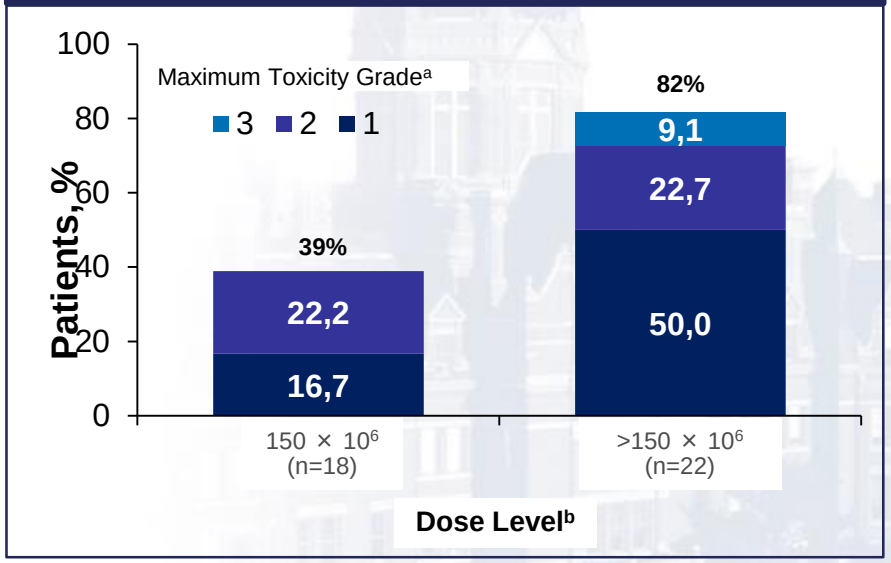
Cytokine Release Syndrome

Cytokine Release Syndrome Parameters

Parameter	Dosed Patients (N=43)
Patients with a CRS event, n (%)	27 (63)
Maximum CRS grade[a]	
None	16 (37)
1	16 (37)
2	9 (21)
3	2 (5)
4	0
Median (min, max) time to onset, d	2 (1, 25)
Median (min, max) duration, d	6 (1, 32)
Tocilizumab use, n (%)	9 (21)
Corticosteroid use, n (%)	4 (9)

Cytokine Release Syndrome By Dose Level



Data cutoff: March 29, 2018. [a]CRS uniformly graded according to Lee DW, et al. *Blood.* 2014;124(2):188-195. [b]3 patients were treated at the 50 x 10^6 dose level for a total of 43 patients.

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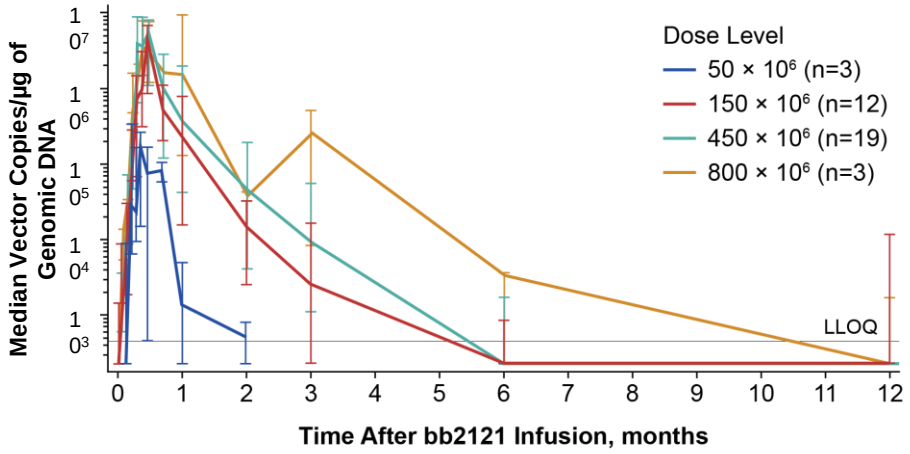
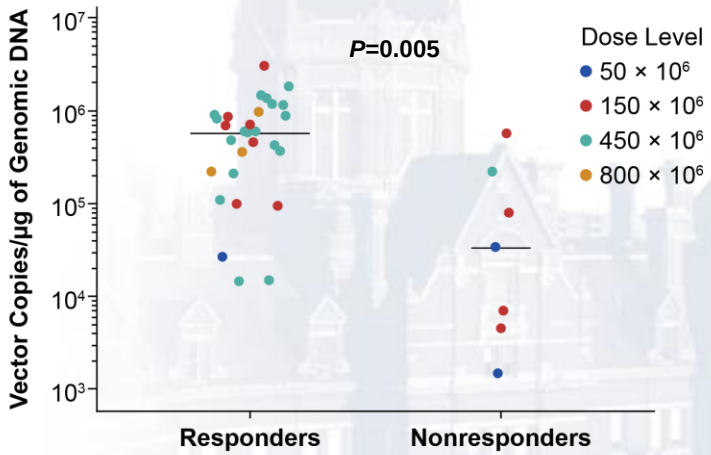
bb2121 CAR+ T Cell Expansion

Median (Q1, Q3) Vector Copies in CD3-Enriched Peripheral Blood by Dose Cohorts



Patients with a post-baseline vector copy value were included. One patient was dosed at 205 × 10^6 CAR+ T cells instead of the planned 450 × 10^6 and was included in the 450 × 10^6 dose group.

Peak bb2121 Vector Copies in Responders vs Nonresponders



Patients with ≥2 months of response data and 1 month of vector copy data (N=36).
P value based on a 2-sided Wilcoxon rank sum test.

	Month 1	Month 3	Month 6	Month 12
At risk, n	32	26	16	10
With detectable vector, n (%)	31 (97)	22 (85)	7 (44)	2 (20)

Data cutoff: March 29, 2018. C_{max}, maximum serum concentration; LLOQ, lower limit of quantitation.

- Comparable C_{max} in active dose cohorts (≥150 × 10^6 CAR+ T cells)
- Durable bb2121 persistence (≥6 months) in 44%
- Higher peak expansion in patients with response

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Tumor Response: Deep MRD-negative responses observed

Response	50×10^6	150×10^6	450×10^6	800×10^6	Total
MRD-evaluable responders	0	4	11	1	16
MRD-neg[a]	0	4 (100)	11 (100)	1 (100)	16 (100)

Data cutoff: March 29, 2018. [a]Of 16 MRD-negative responses: 4 at 10^{-6}, 11 at 10^{-5}, 1 at 10^{-4} sensitivity by Adaptive next-generation sequencing assay.

- All responding patients evaluated for MRD were MRD negative at 1 or more time points
- 2 nonresponders evaluated for MRD were MRD positive at month 1

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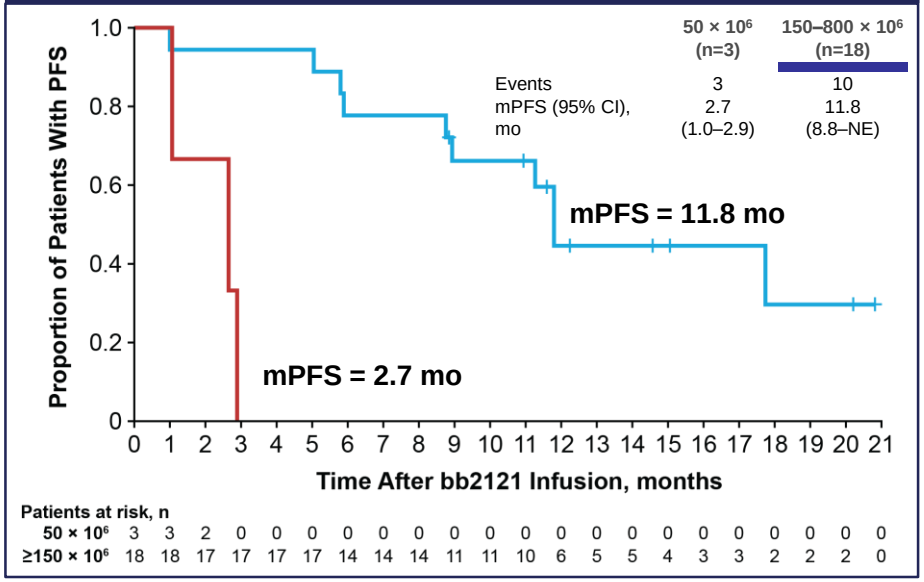
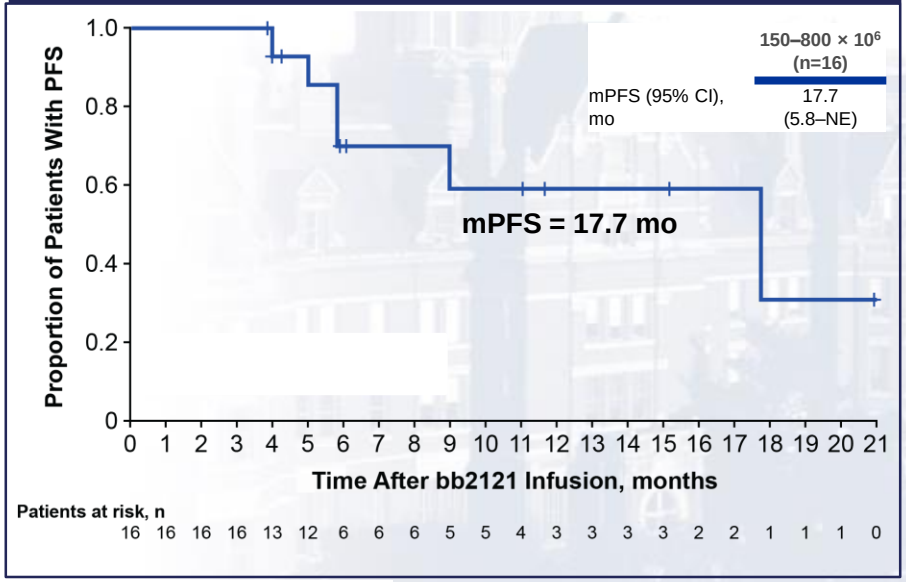
Progression-Free Survival

- mPFS of 11.8 months at active doses (≥150 × 10^6 CAR+ T cells) in 18 subjects in dose escalation phase
- mPFS of 17.7 months in 16 responding subjects who are MRD-negative

PFS at Inactive (50 × 10^6) and Active (150–800 × 10^6) Dose Levels[a]



PFS in MRD-Negative Patients[a]



Data cutoff: March 29, 2018. Median and 95% CI from Kaplan-Meier estimate. NE, not estimable. [a]PFS in dose escalation cohort.

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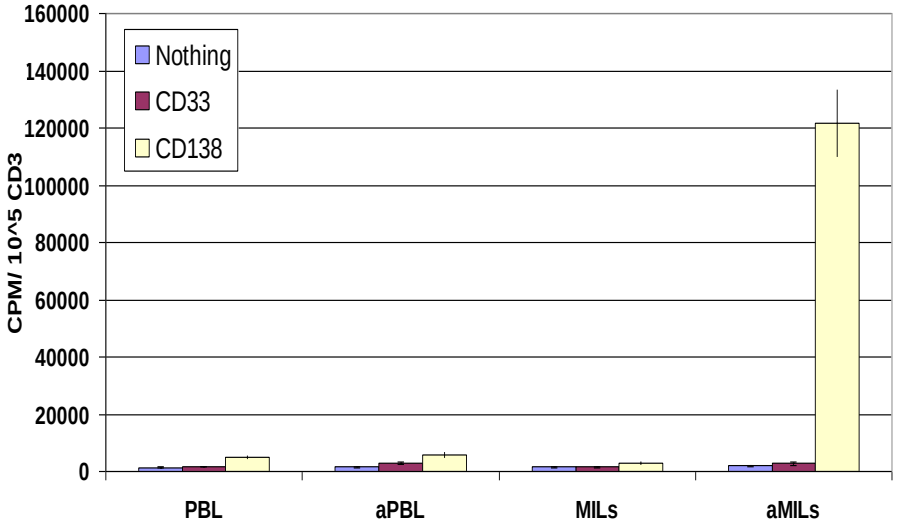
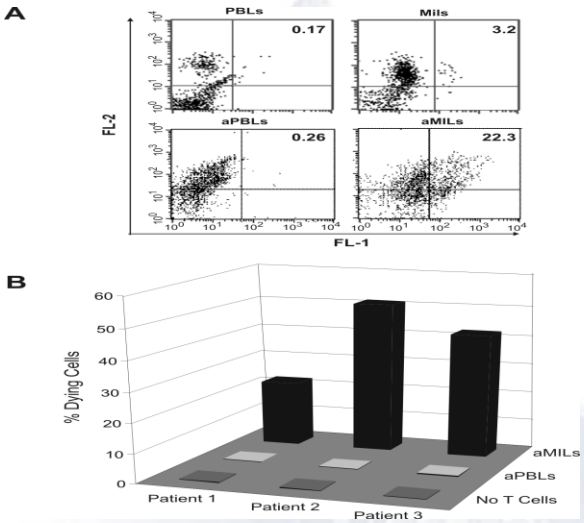
Marrow Infiltrating Lymphocytes

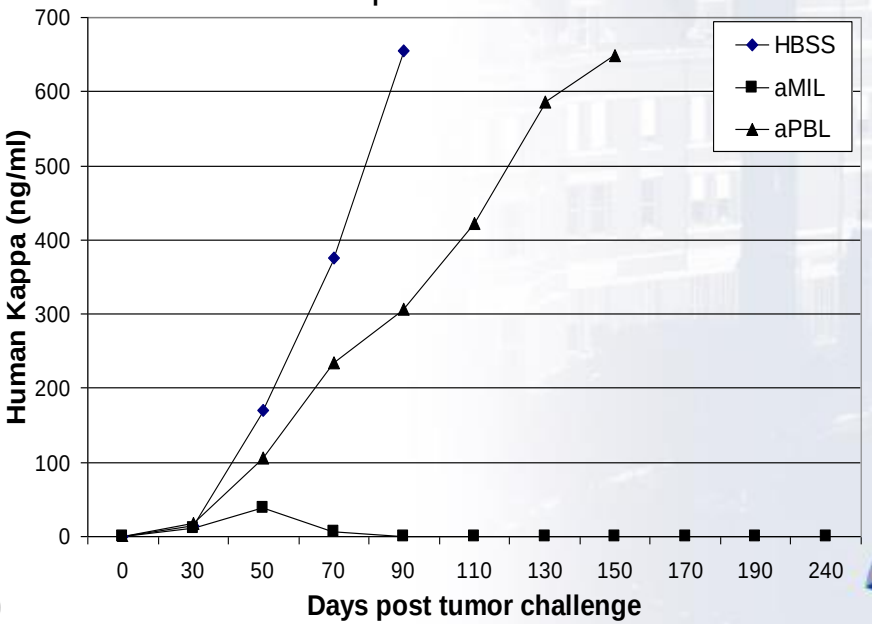
MILs Exhibit Significant Anti-Myeloma Specificity



aMILs Effectively Kill Myeloma Cells



MILs eradicate pre-established disease



Noonan et al Ca Res 2005; 65(5)

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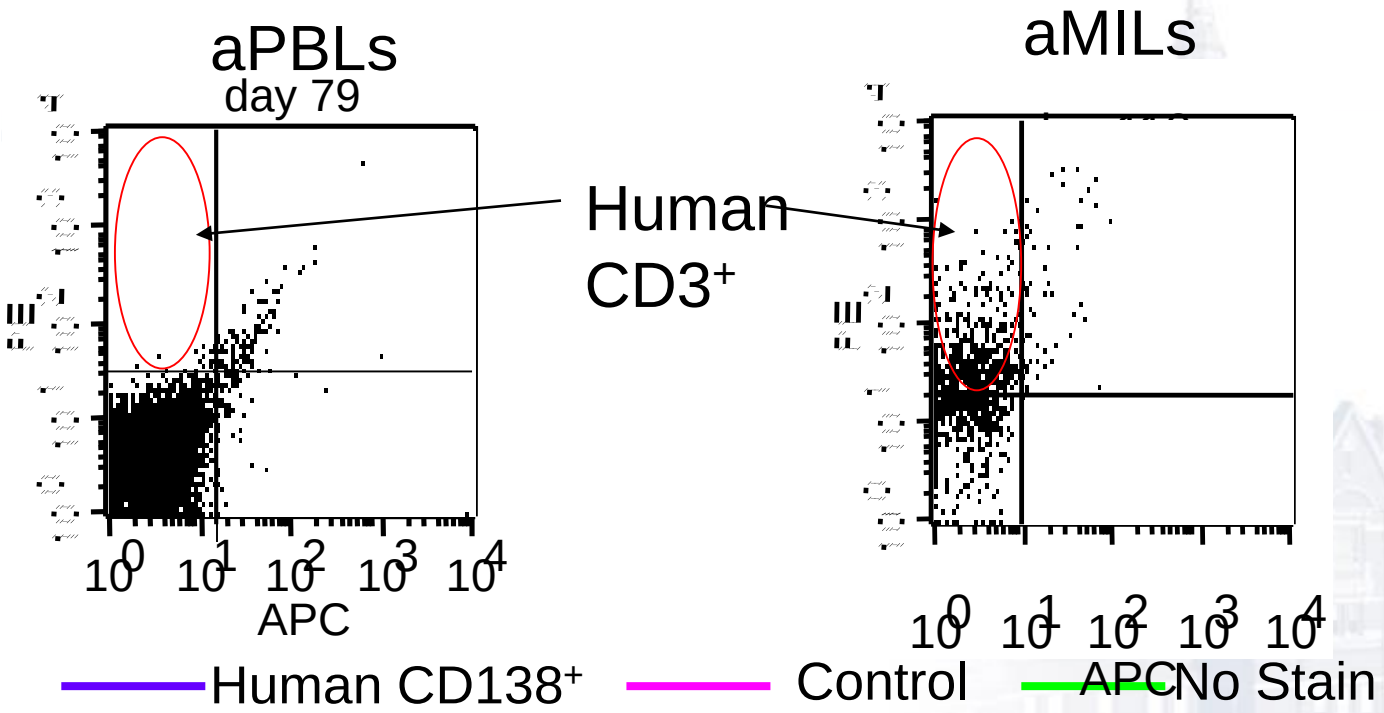
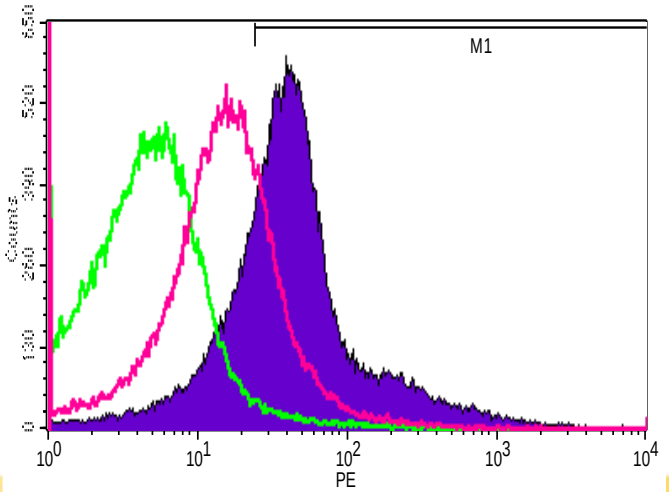
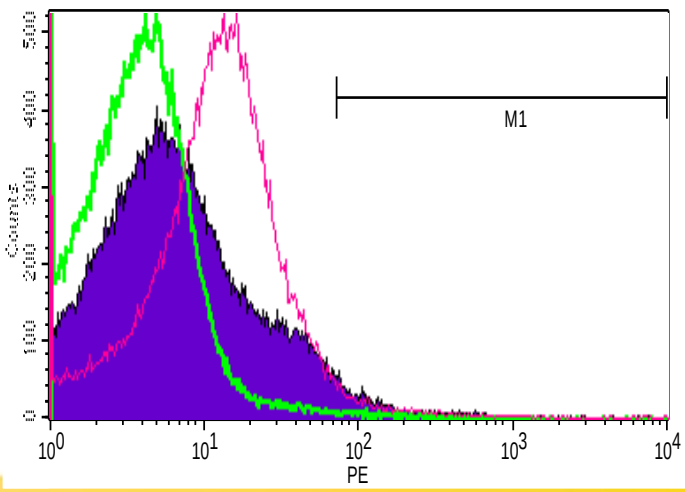
MILs Persist in the Bone Marrow and Eradicate Myeloma







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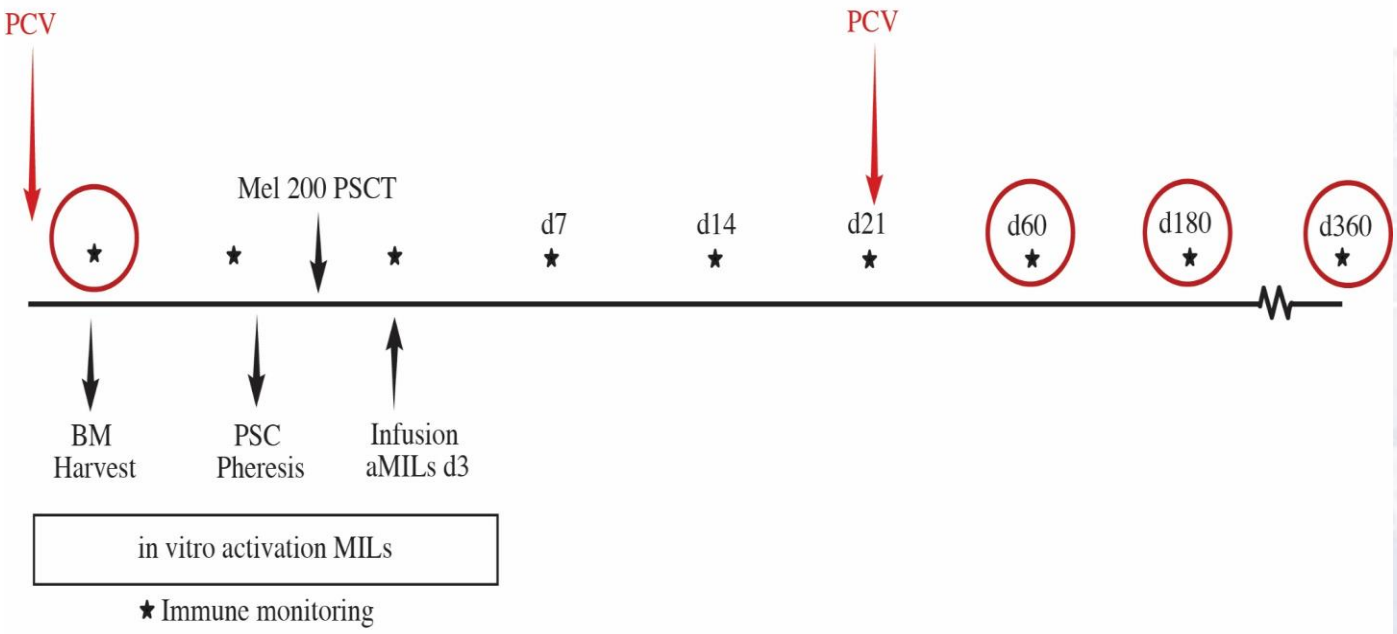
First MILs Clinical Trial

Figure 1: Study Schema



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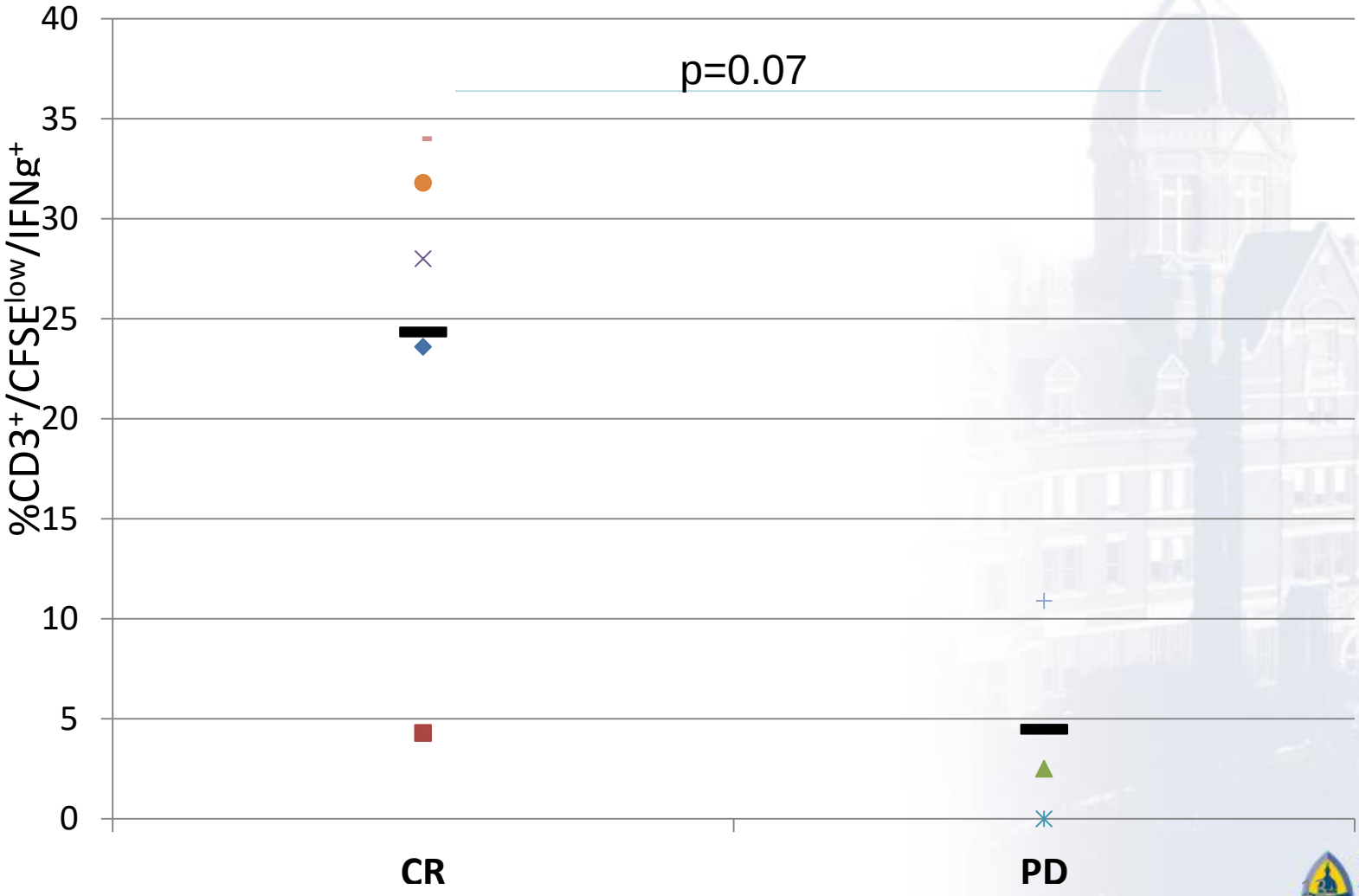
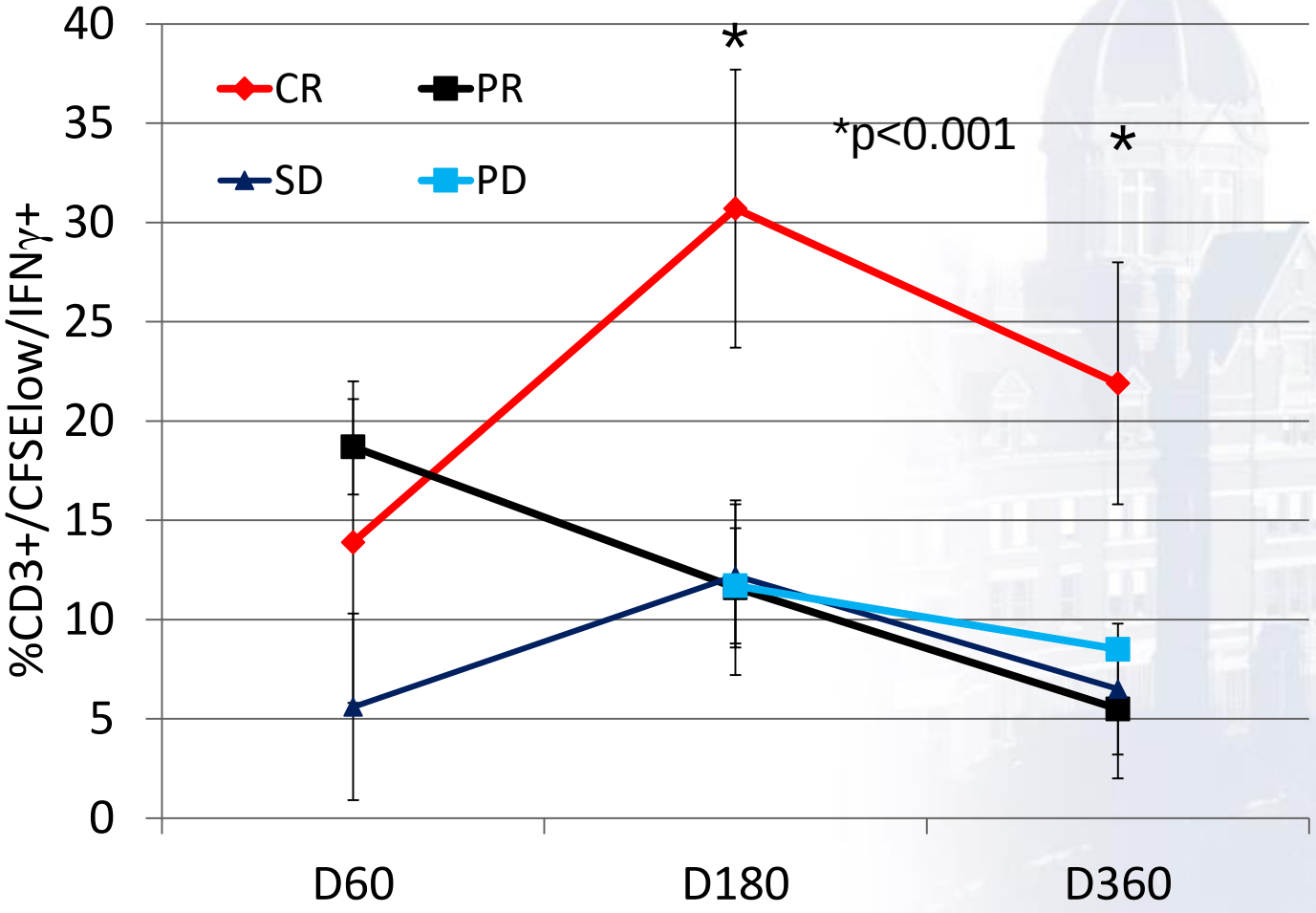
Tumor Specificity of aMILs Product



(Noonan et al. STM 2015; 7:288)

Tumor-specific Response in the BM Correlates with Clinical Outcomes



(Noonan et al. STM 2015; 7:288)

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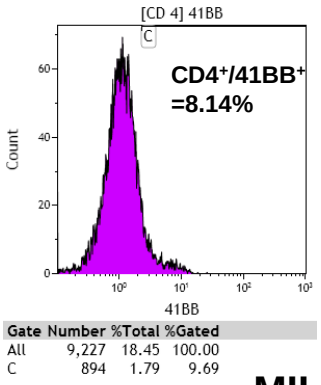
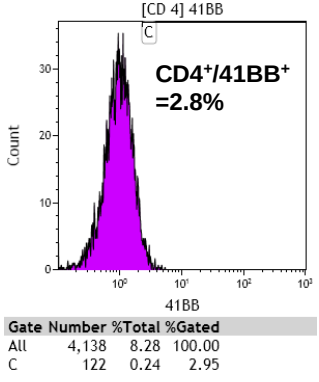
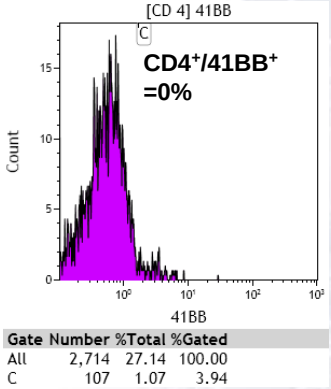
41BB Expression with Expansion

PBL

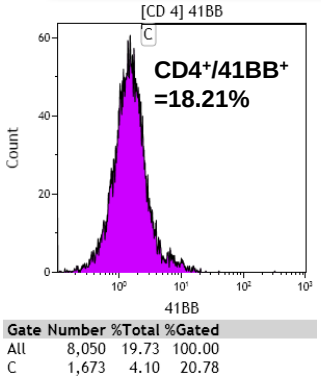
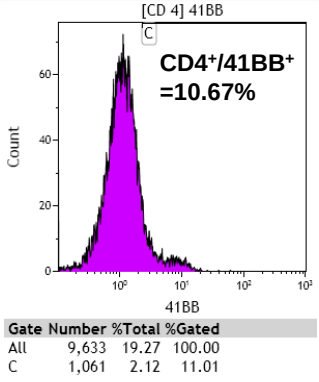
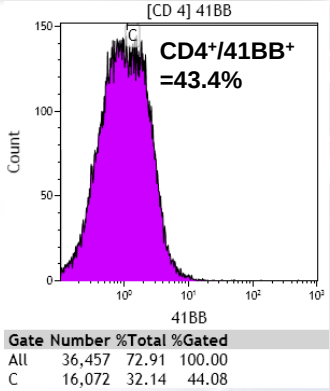
	Pre-Activation	Normoxia	Hypoxia
CD4+			

Gate	Number	%Total	%Gated
All	9,227	18.45	100.00
C	894	1.79	9.69

Gate	Number	%Total	%Gated
All	4,138	8.28	100.00
C	122	0.24	2.95

Gate	Number	%Total	%Gated
All	2,714	27.14	100.00
C	107	1.07	3.94

MIL

CD4+			

Gate	Number	%Total	%Gated
All	8,050	19.73	100.00
C	1,673	4.10	20.78

Gate	Number	%Total	%Gated
All	9,633	19.27	100.00
C	1,061	2.12	11.01

Gate	Number	%Total	%Gated
All	36,457	72.91	100.00
C	16,072	32.14	44.08

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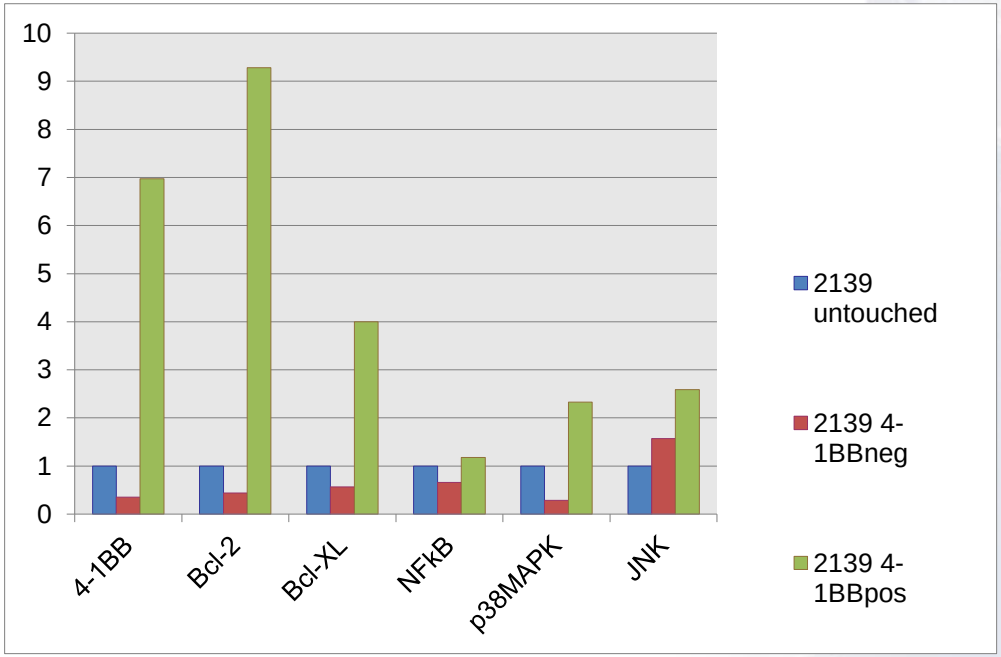
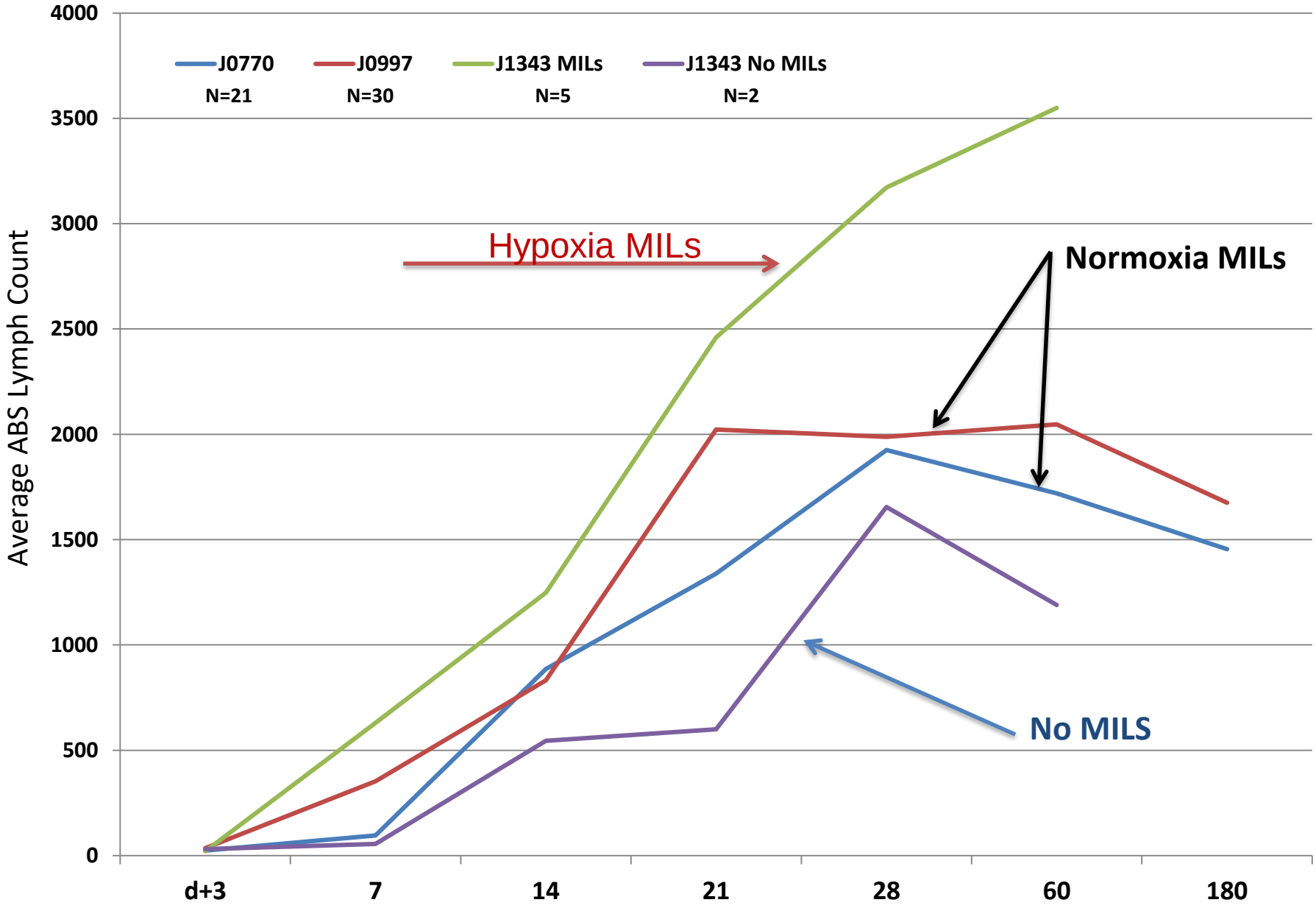
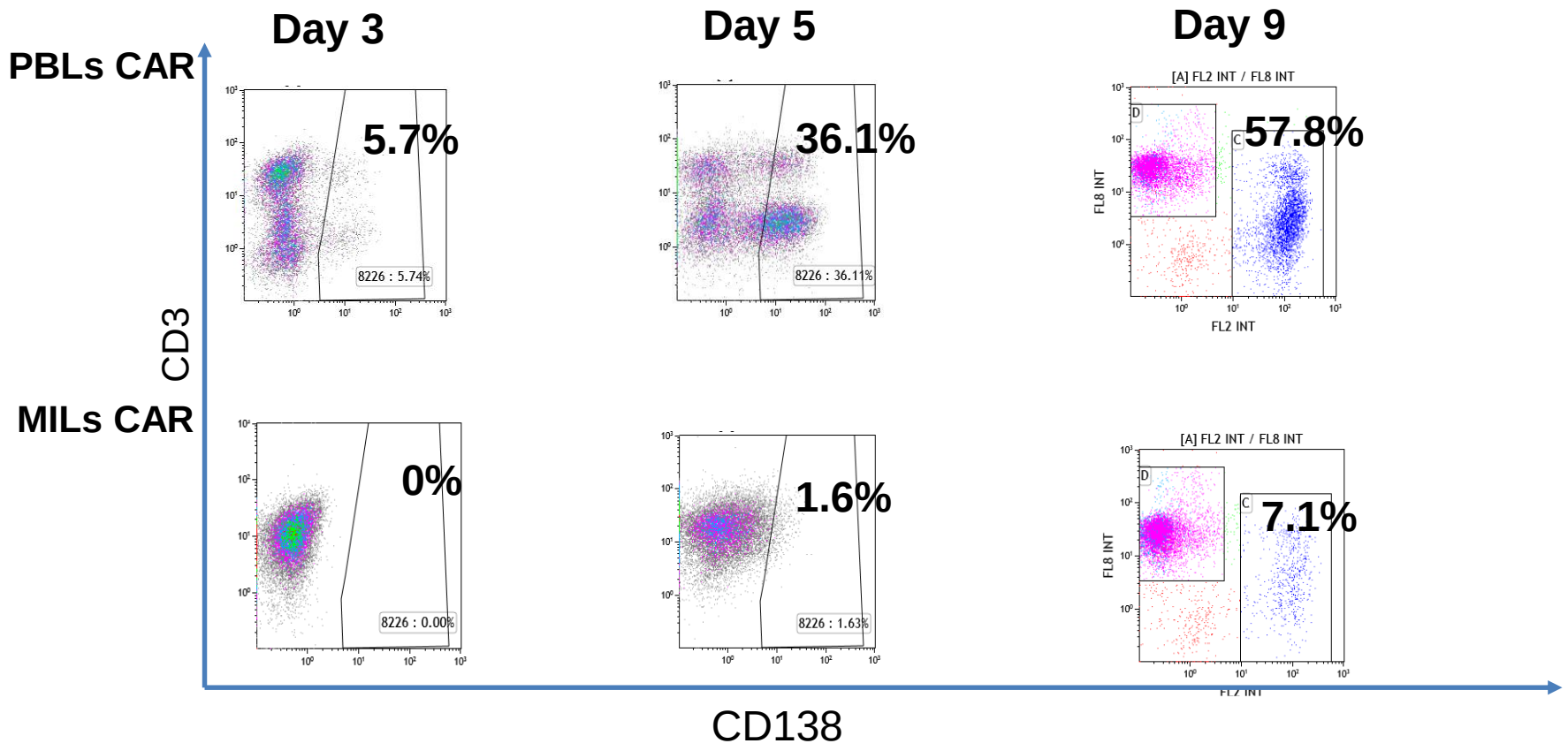
Hypoxia Enhances Function in 4-1BB+ T cell Subset



In vivo MILs Expansion

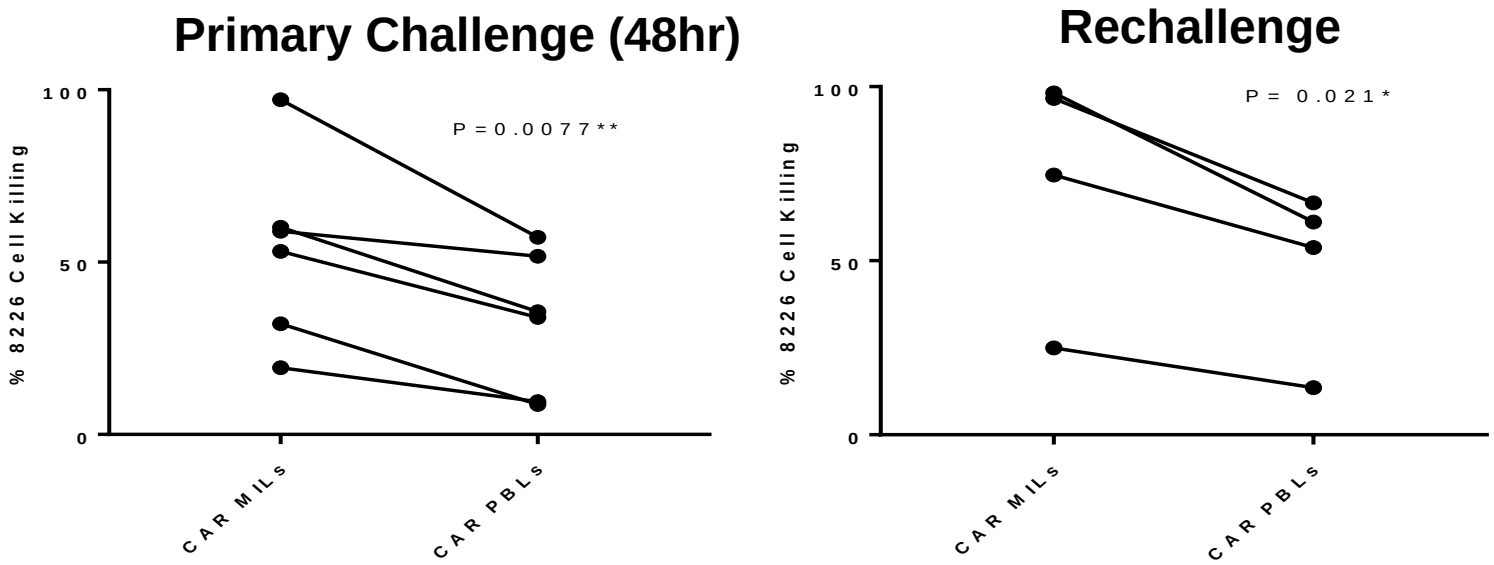


Superior Killing by MIL-CARs Compared to PBL-CARs



N.B: 8226 cells was added on days 3 or 7 days after the primary 8226 challenge

MIL CARs: More Data Showing Superior Killing via the CAR in MIL CARs vs. PBL CARs

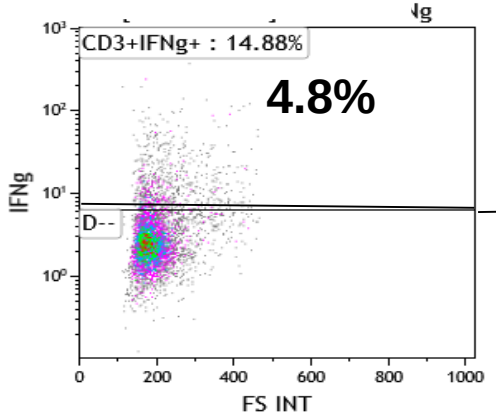


CART:Target ratio = 1:10

MIL CARs: Preserve the Endogenous TCR-mediated Killing

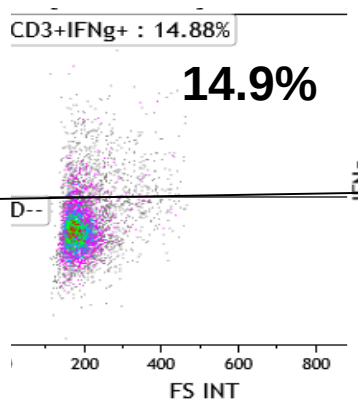
Tumor Specificity Assay Testing ability of Native TCR to Recognize Tumor Ag:

NT MILs



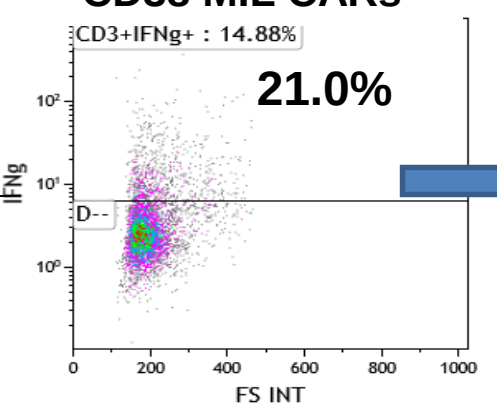
Gate	%Total	%Gated
All	20.19	100.00
CD3+IFNg+	3.00	14.88
D--	17.18	85.12
D+-	0.00	0.00
D++	0.00	0.00

CD38 MIL CARs



Gate	%Total	%Gated
All	20.19	100.00
CD3+IFNg+	3.00	14.88
D--	17.18	85.12
D+-	0.00	0.00
D++	0.00	0.00

CD38 Stimulated CD38 MIL CARs



Gate	%Total	%Gated
All	20.19	100.00
CD3+IFNg+	3.00	14.88
D--	17.18	85.12
D+-	0.00	0.00
D++	0.00	0.00

Native TCR in MIL CARS works even after the CAR has fired

Conclusions

- Tumor specificity of MILs correlates with clinical outcomes
- Memory phenotype, broad antigenic specificity are properties unique to MILs and not found on PBLs
- T cell persistence correlates with responses
- Hypoxia augments T cell function of MILs through
  - upregulation of 4-1BB
  - increase in anti-apoptotic proteins and survival cytokines
  - Enhance ex vivo and in vivo expansion
- The absence of a PFS plateau with BCMA CARs limits the long-term efficacy of this approach in MM
- MILs appear to show better anti-tumor activity as a source of CAR-modified T cells than PBLs

Acknowledgements

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Commonwealth Foundation