National Institutes of Health (NIH) Safety Symposium

Gene-Modified T cells: Challenges in Clinical Trial Design

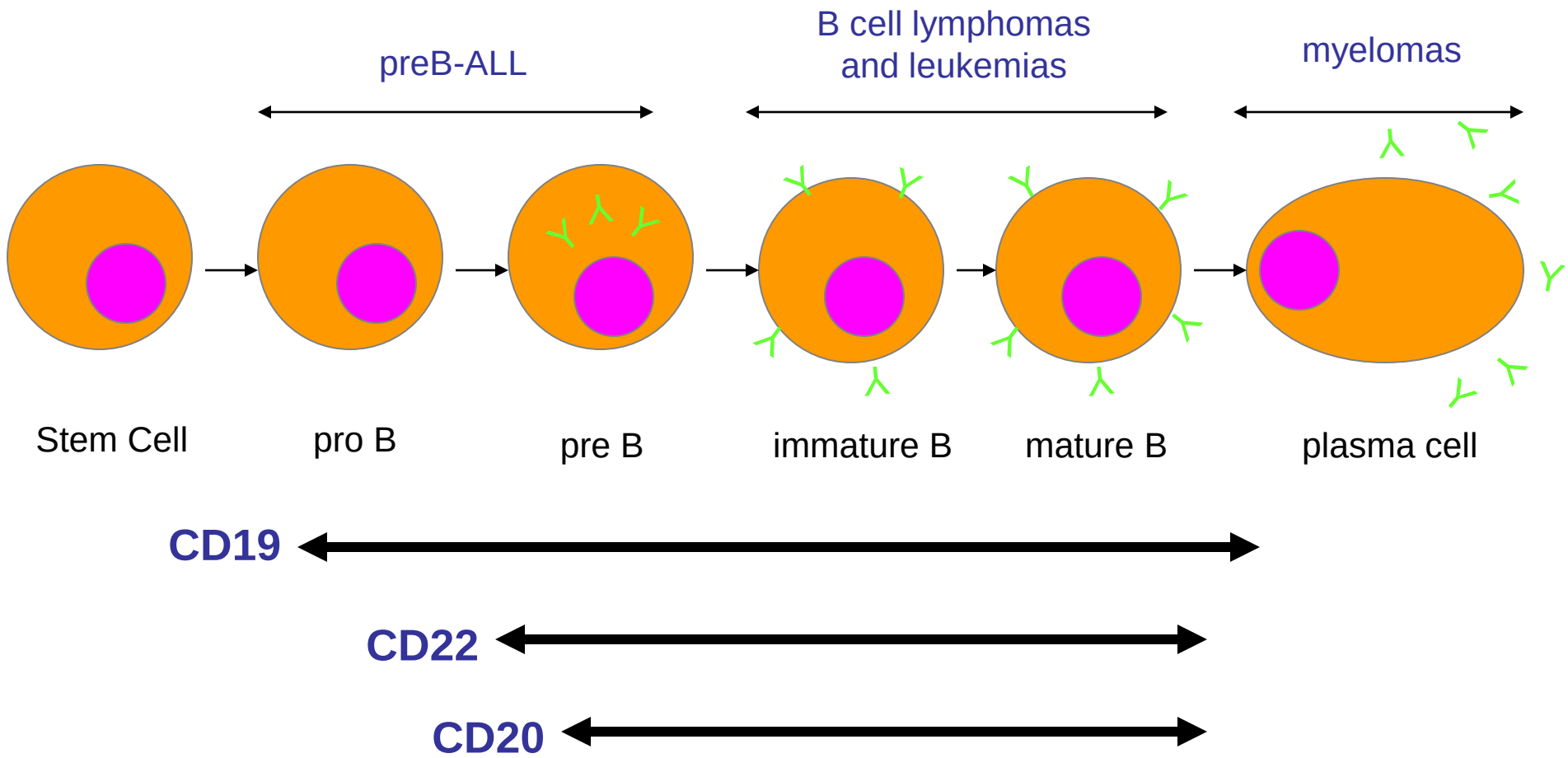
June 15, 2010

Serious Adverse Events in Trials Utilizing Chimeric Antigen Receptors: Lessons for Trial Design

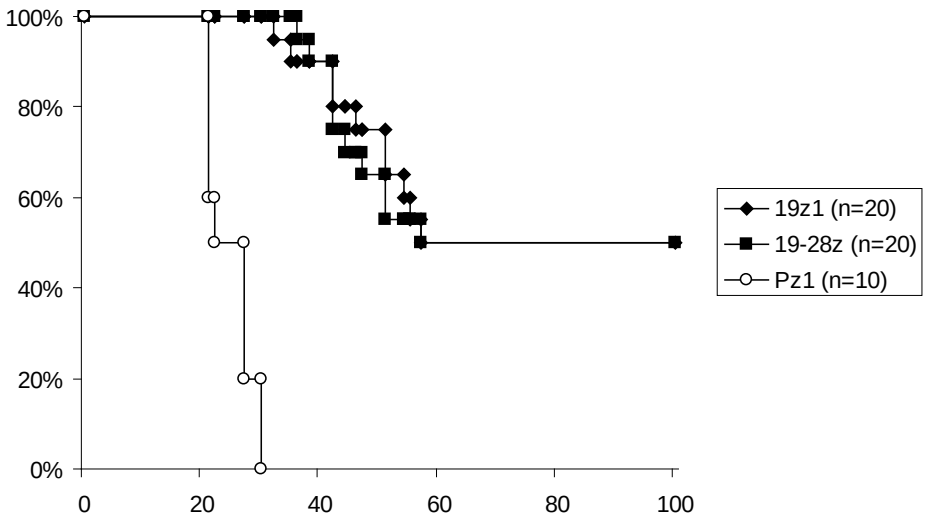
Clinical Trial #06-138

Renier Brentjens MD PhD

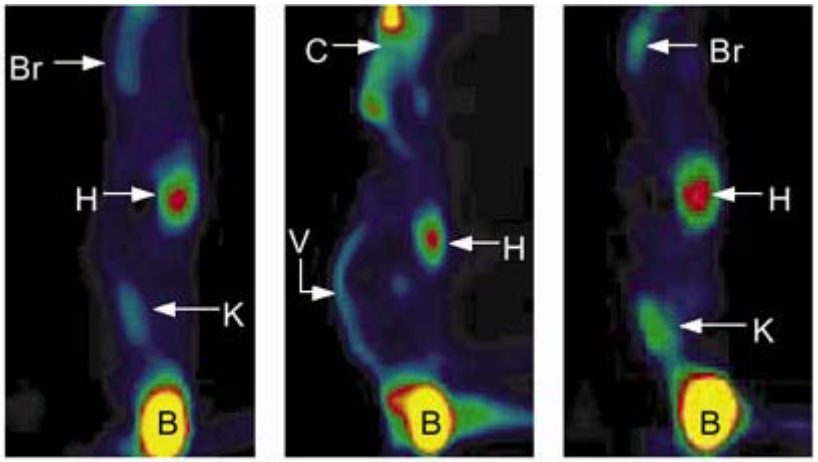
Expression of CD19 and other B cell markers on B lineage cells



19z1+ T cells eradicate systemic Raji tumors in SCID-Beige mice



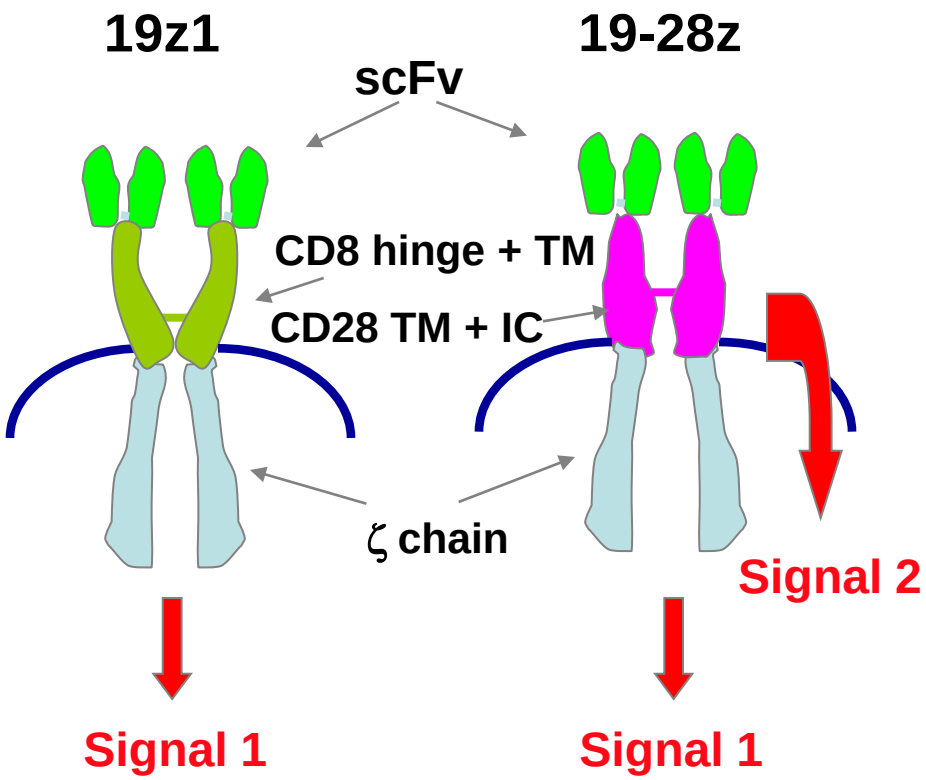
Days since tumor injection

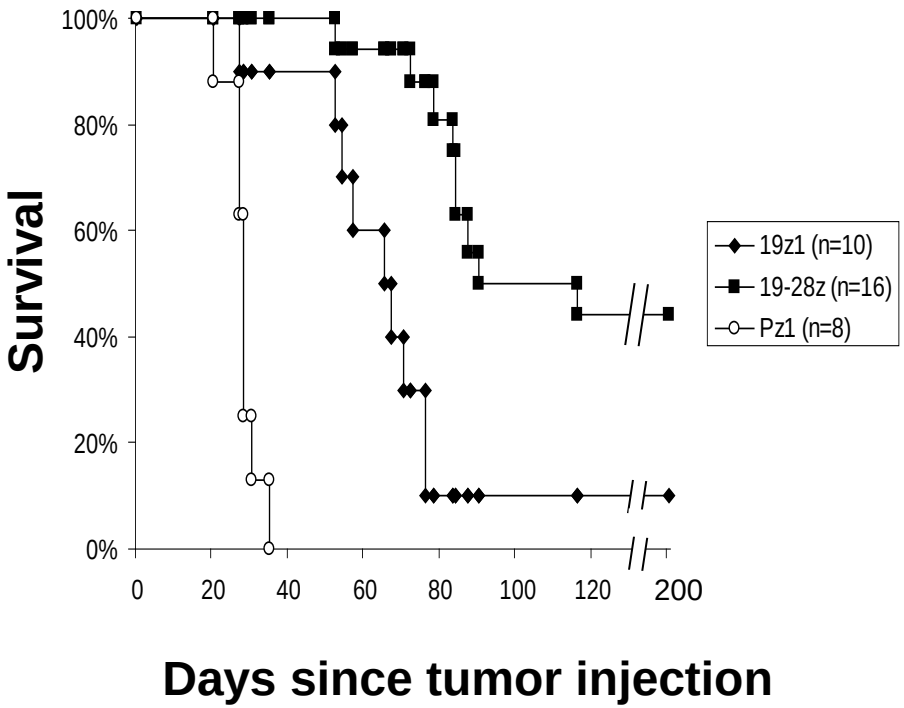


No tumor | Untreated | Treated 4 weeks

Brentjens, *Nat Med*, 2003

CD28/CD3ζ receptors potentiate NALM/6 tumor rejection

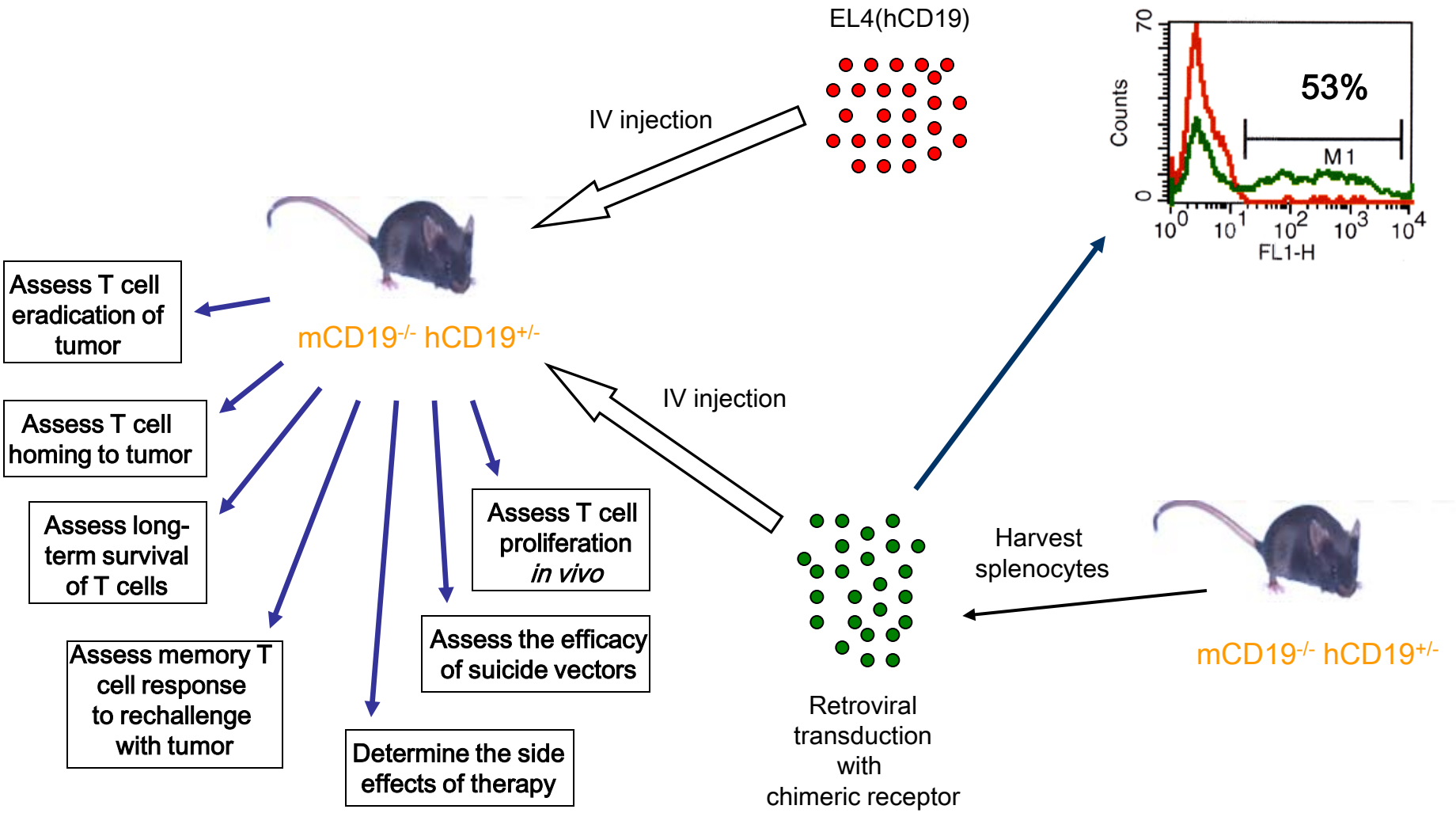




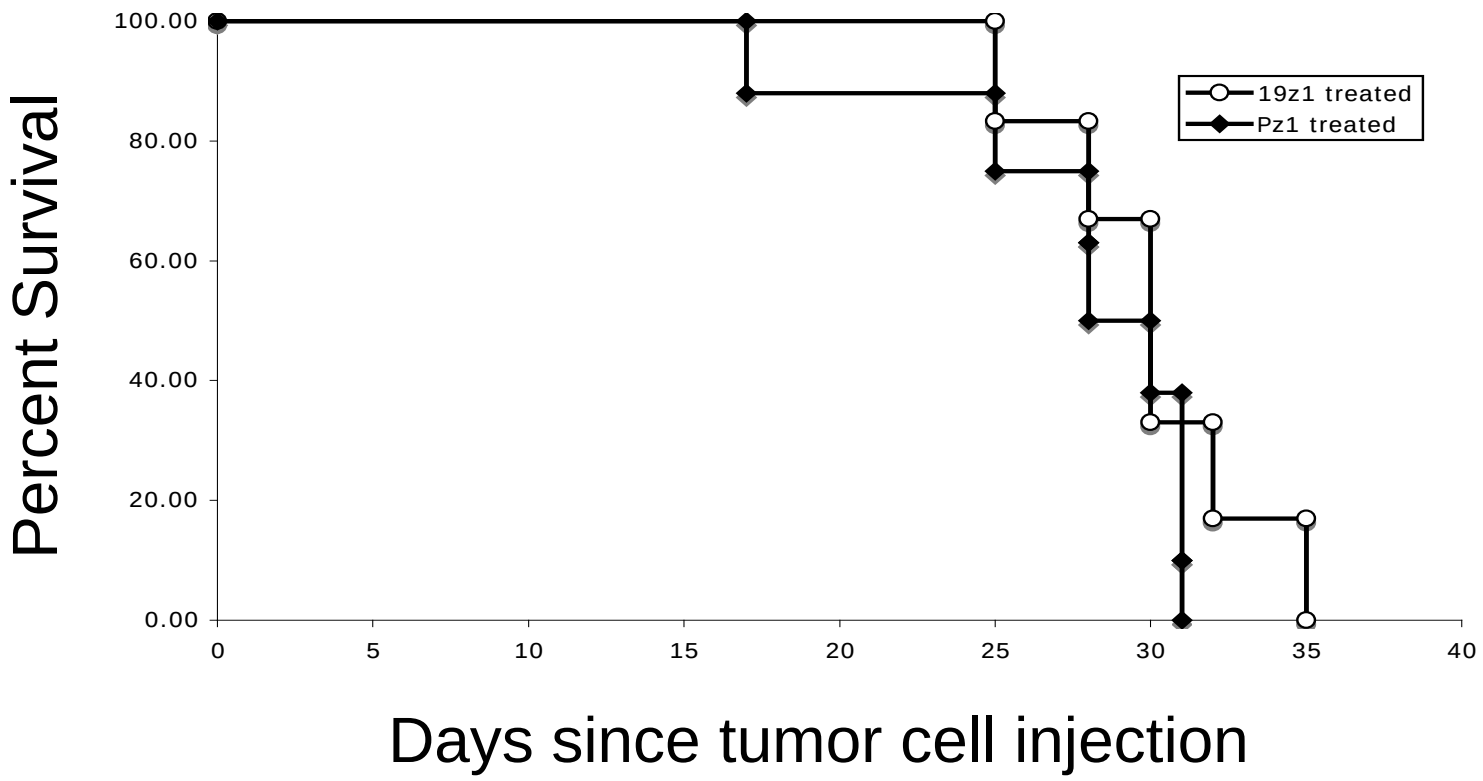
Maher, *Nat Biotechnol*, 2002

Brentjens, *Clin Can Res*, 2007

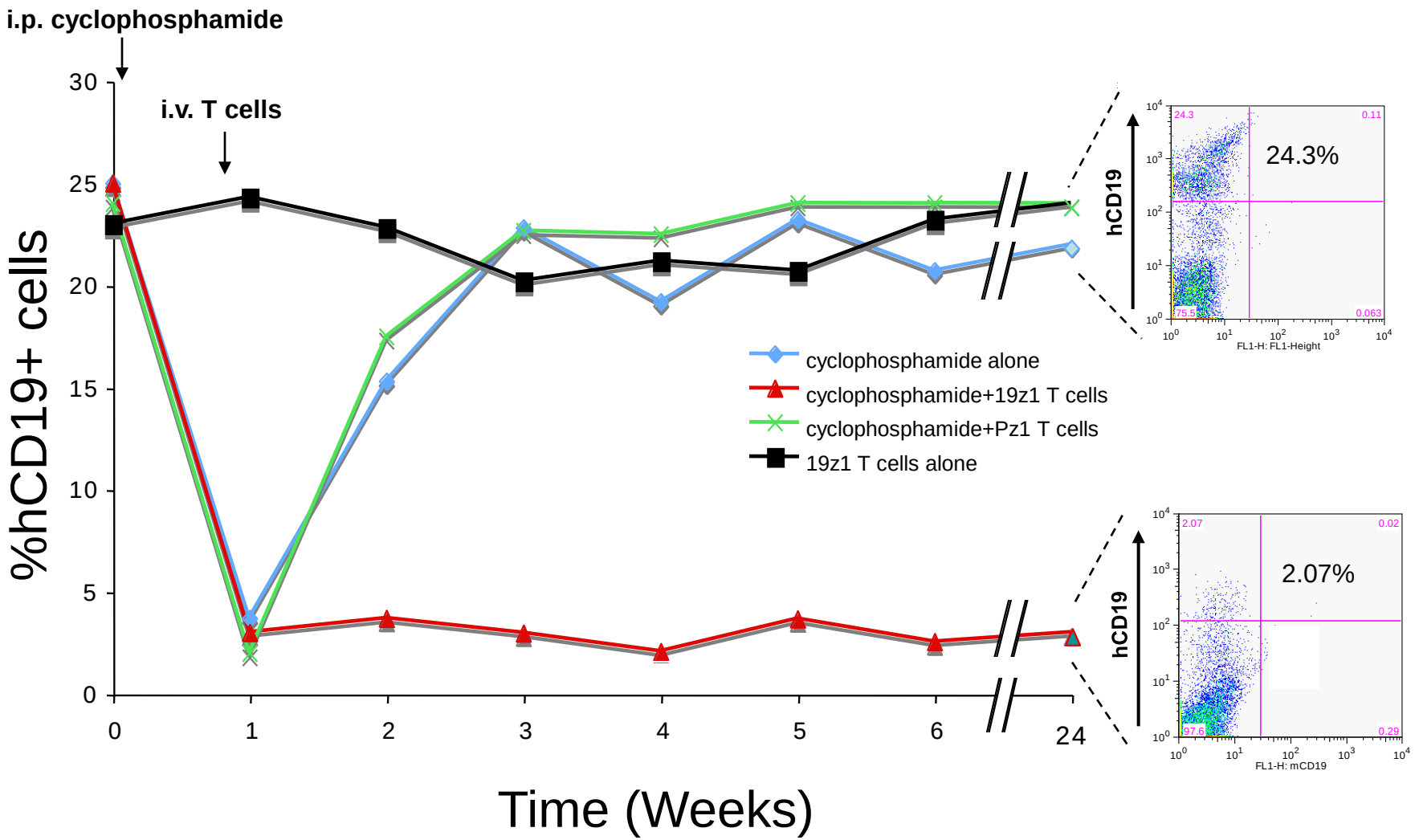
Syngeneic EL4(hCD19) tumor model



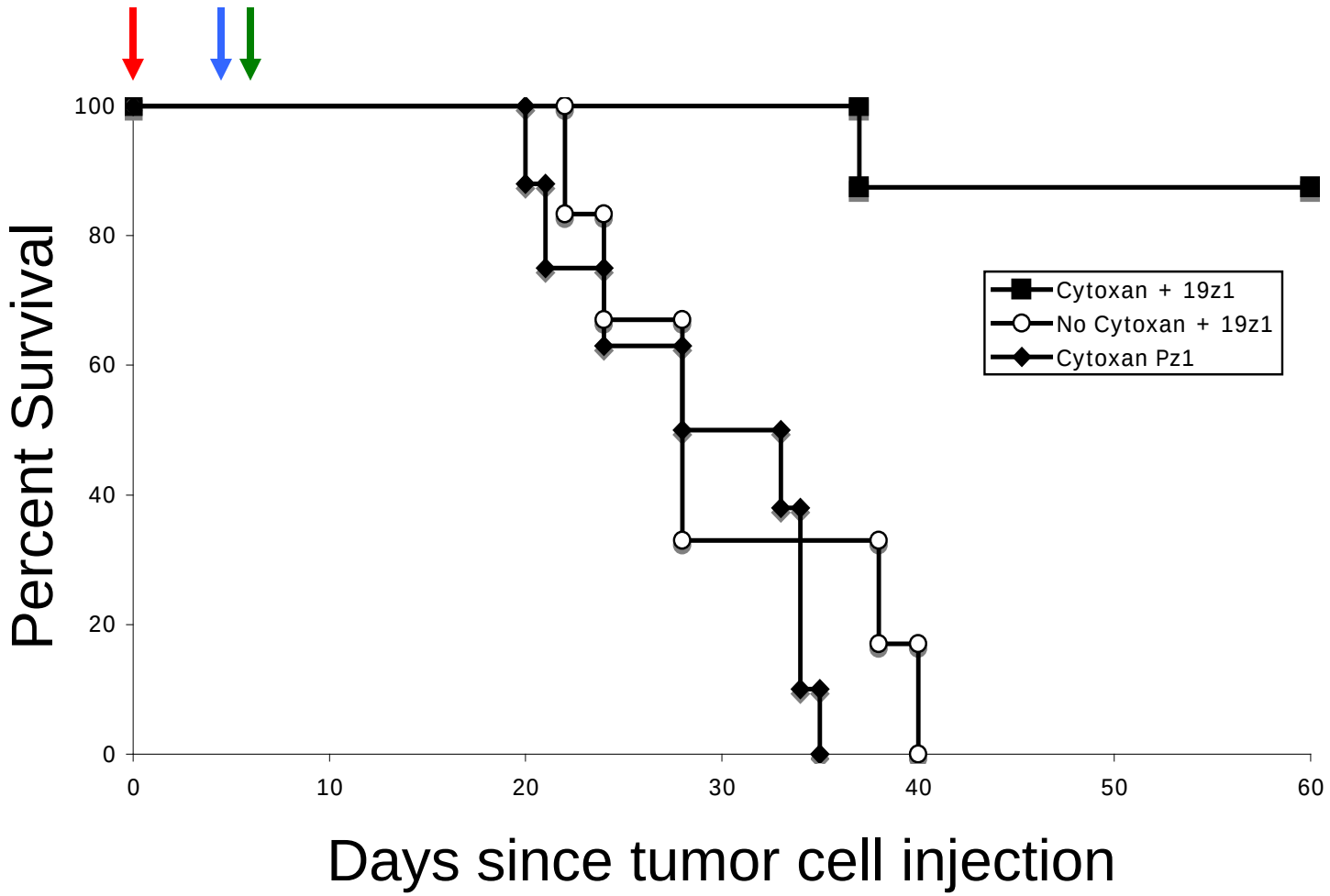
Syngeneic EL4(hCD19) tumor model



Persistent B cell aplasias induced by lymphodepletion and 19z1^{+} T cells



Lymphodepletion enhances anti-tumor efficacy of 19z1^{+} T cells



A Clinical Trial in Patients with Chronic Lymphocytic Leukemia (CLL)

IRB #06-138
A Phase I Trial for the Treatment of Purine Analog-Refractory Chronic Lymphocytic Leukemia using Autologous T cells Genetically Targeted to the B cell Specific Antigen CD19

IRB #06-138

- **Enrollment Criteria:**
  Patients with purine analog-refractory CLL disease

- **Protocol Design:**
  - A 3 step design:
    - Step I: low dose modified T cells alone (3×10^7 modified T cells/kg)
    - Step II: combination with dose escalating lympho-depleting cyclophosphamide chemotherapy (1.5 gm/m^2 and 3.0 gm/m^2)
    - Step III: escalating T cell dose at established cyclophopshamide MTD from Step II (1×10^8 and 3×10^8 modified T cells/kg)

Chronic Lymphocytic Leukemia (CLL)

- A cancer of mature B lymphocytes
- The most common adult leukemia
- Median age of diagnosis is 70 years
- More common in men than women (relative risk 2.8)
- 8,000 new cases diagnosed annually in the US
- An indolent disease with a median survival of 5 years
- Up front treatment generally involves combination chemotherapy including a nucleoside analogue (fludarabine/pentostatin)
- Currently CLL is treatable but not curable.
- Indications for therapy include:
  - Bone marrow failure (anemia, thrombocytopenia)
  - Bulky lymphadenopathy
  - Transformed disease
  - Autoimmune complications of disease (AIHA and ITP)
- Patients with nucleoside analogue refractory disease have a median survival of 8 months.
- Patients with CLL are significantly immune suppressed.
- Infection is the leading cause of death in patients with CLL.

IRB 06-138 Patient Characteristics

Patient	Age	M/F	Rai Stage	Bulky Dz	WBC count	Prior Chemo
1	51	M	IV	Y	200.1K/mcL	FCR, PCR
2	72	M	IV	Y	4.2K/mcL	F, R, PCR, PCRM
3	73	F	III	Y	124.9K/mcL	PCR, PCRM
4	69	M	IV	Y	187.1K/mcL	PCR, PCRM
5	68	M	III	Y	76.3K/mcL	PCR
6	67	M	IV	Y	106.6K/mcL	RCVP, PCR
7	62	M	IV	Y	5.0K/mcL	CR, PCR, PCRM

IRB 06-138 Patient T cell infusions

Patient	Modified T cell dose	Total T cell dose	Gene Transfer	CD8+
1	2.55 x 10E9	11.1 x 10E9	23%	5%
2	1.16 x 10E9	3.7 x 10E9	31%	5%
3	1.11 x 10E9	2.1 x 10E9	53%	8%
4	3.2 x 10E9	4.6 x 10E9	70%	1%
5	4.0 x 10E8	1.2 x 10E9	32%	12%
6	4.0 x 10E8	1.0 x 10E9	39%	7%
7	7.6 x 10E8	3.0 x 10E9	25%	27%

IRB 06-138 Patient Adverse Events

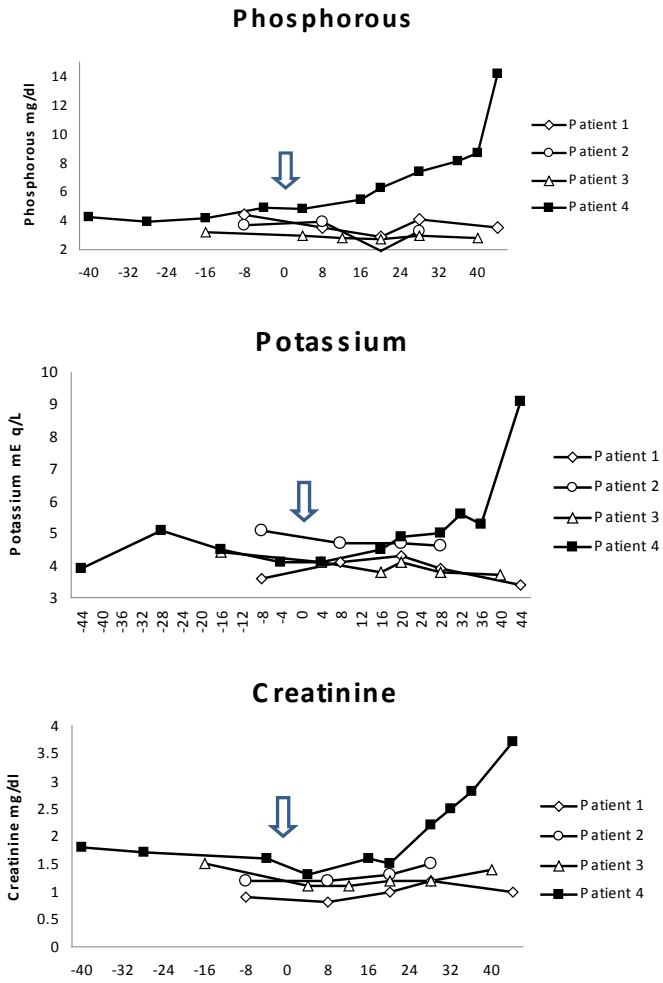
Patient	Adverse event	Grade	Related
1	Febrile Neutropenia	3	Probable
	Rigors/Chills	2	Probable
2	Fever	2	Probable
	Rigors/Chills	2	Probable
	Chest Pain	2	Probable
3	Fever	1	Probable
	Rigors/Chills	1	Probable
4	Dyspnea	1	Possible
	Rigors/Chills	1	Probable
	Fever	2	Probable
	Hypotension	5	Possible
	Renal Failure	5	Possible
5	Hyponatremia	1	Possible
	Rigors/Chills	1	Probable
	Fever	2	Probable
6	Hypotension	2	Possible
	Fever	1	Probable
	Febrile Neutropenia	3	Possible
7	Febrile Neutropenia	3	Probable

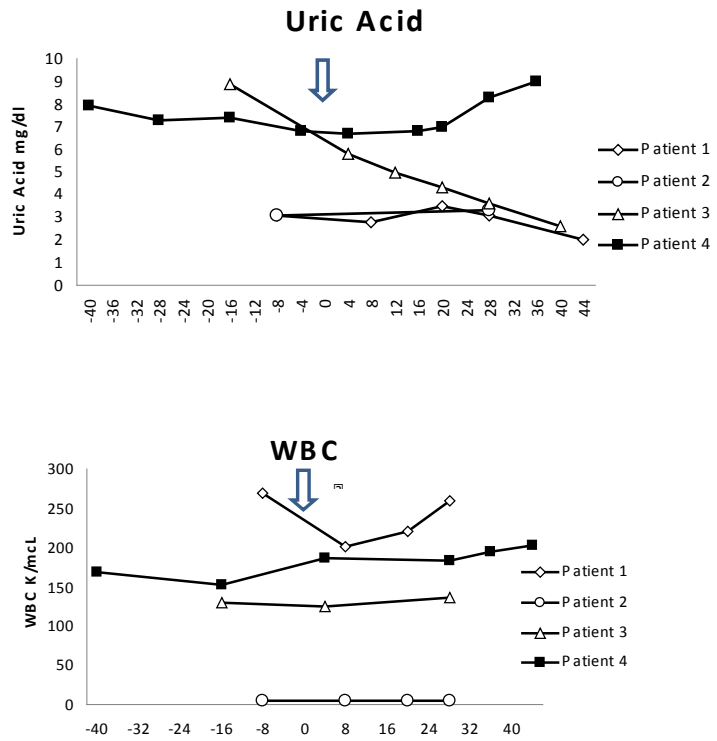
SAE Case Report Patient #4

- First patient to receive prior cyclophosphamide chemotherapy (1.5gm/m^2)
- Patient developed fevers at 6 hours following T cell infusion
- By 24 hours following T cell infusion, patient creatinine levels had increased from 1.3 gm/dl to 2.2 gm/dl
- Patient was hypoxic and required intubation and expired at on hospitalization day 4
- Extensive post-mortem analysis failed to implicate the infused modified T cells as the source of this SAE.
- Post mortem analysis demonstrated presence of modified T cells to sites of tumor involvement.
- Based on available data, most likely cause of this SAE was sepsis from an antecedent sub-acute infection.
- In light of the temporal relation of this event to modified T cell infusion, the protocol was modified to optimize safety.

Brentjens *Mol Ther* 2010

Clinical course Pts 1-3 vs 4





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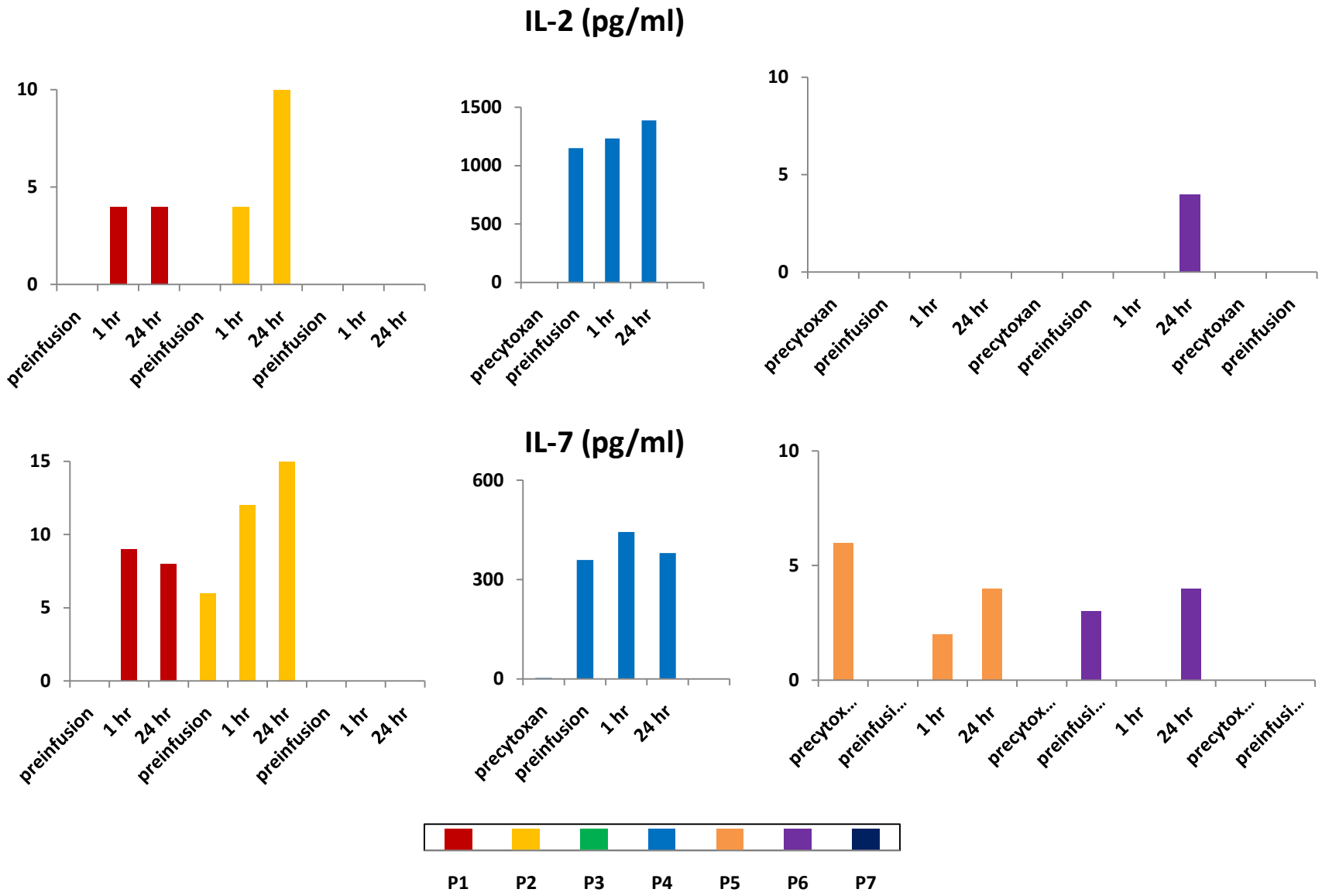
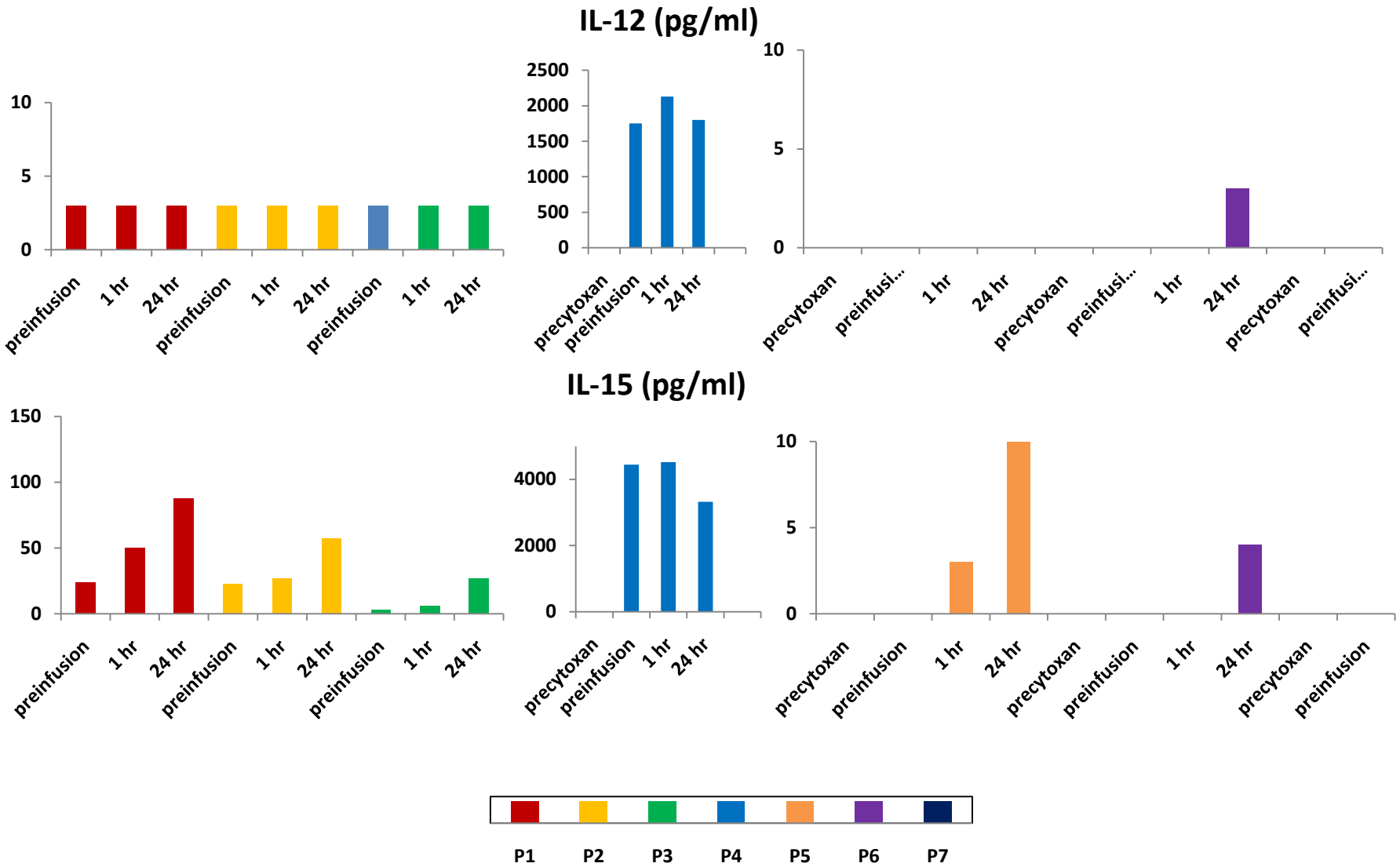
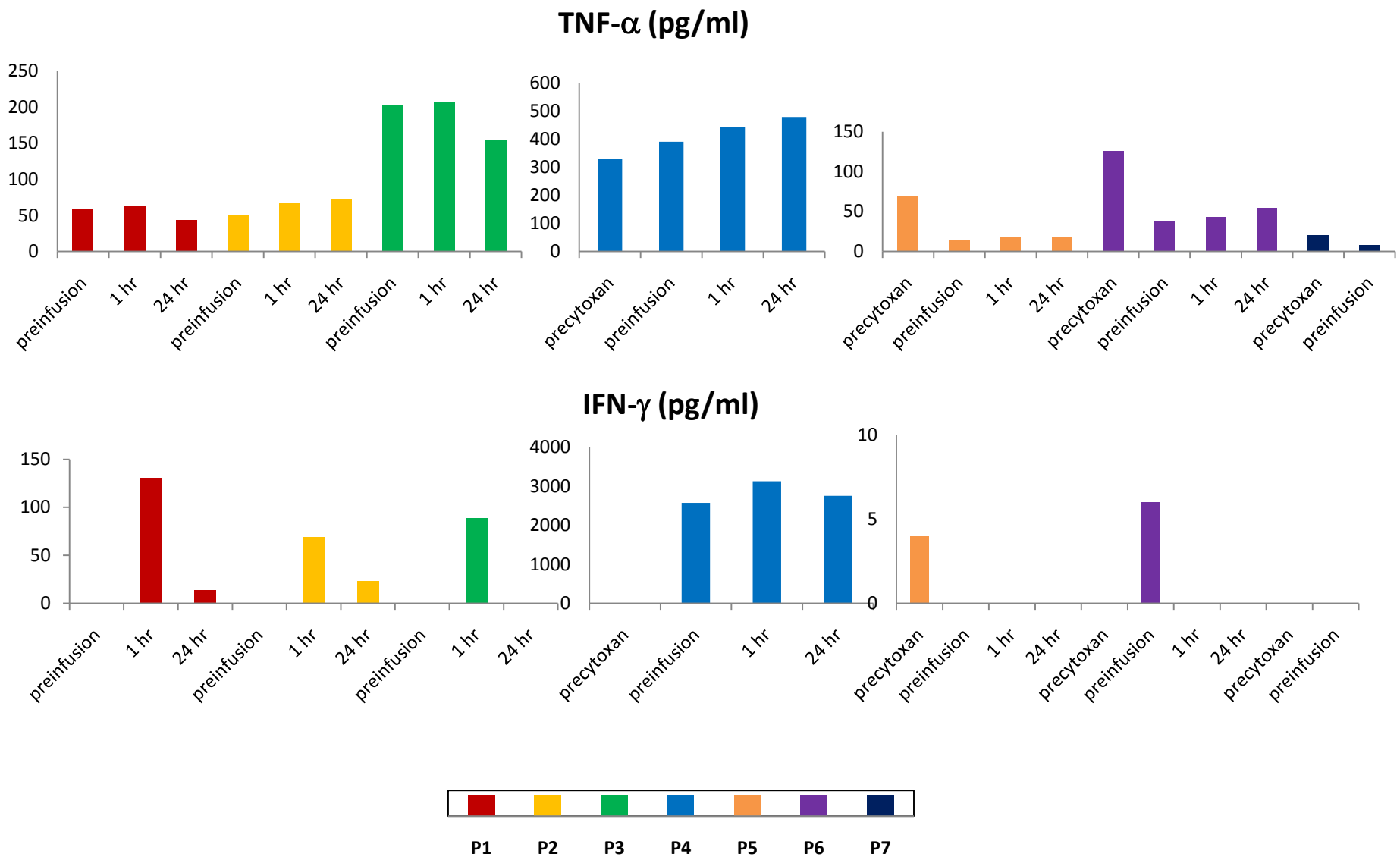
IRB 06-138 Patient Cytokine Profiles



IRB 06-138 Patient Cytokine Profiles



IRB 06-138 Patient Cytokine Profiles



Amended IRB #06-138

- **T cell dose:**

  As per the protocol guidelines, the next cohort of patients would be treated at the -1 planned T cell dose (1×10^7 CAR^+ T cells/kg)

- **Modified infusion schedule:**
  - Split T cell infusion over 2 days
    - Day 2: Patients receive 1/3 of the planned T cell dose.
    - Day 3: Assess for persistent fevers or hypotension. AM labs obtained to assess for evidence of tumor lysis or renal failure.
    - Infusion of remaining 2/3 of T cell dose if patient is stable without evidence of adverse reaction.

IRB 06-138 Patient Responses

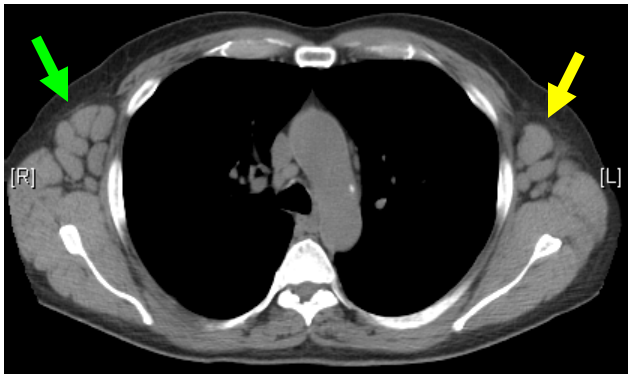
Patient	
1	Transient decreased transfusion requirements Transient subjective decrease in LNs
2	Transient subjective decrease in LNs
3	No response
4	Not evaluable, patient died soon after modified T cell infusion
5	Marked reduction in peripheral lymphadenopathy, stable BM disease
6	Progressive disease at 1 month, patient expired at 3 months post-Tx
7	Patient treated 1 month ago, not yet evaluable

Patient 5

- 68 year old male with RAI stage II disease
- Previously treated with PCR
- Treated at the -1 dose level
- Tolerated therapy well
- Initially exhibited stable/progressive disease by CT
- At 3 months, by PE, decreasing lymphadenopathy was noted
- CT scans demonstrated marked reduction of tumor bulk, with stable disease in the BM
- PET with decreased FDG avidity in cervical LNs
- Response was sustained for 9 months, most recent (5/10) scans demonstrate mildly progressive disease

Patient 5: decreased LNs in axilla

6.22.09



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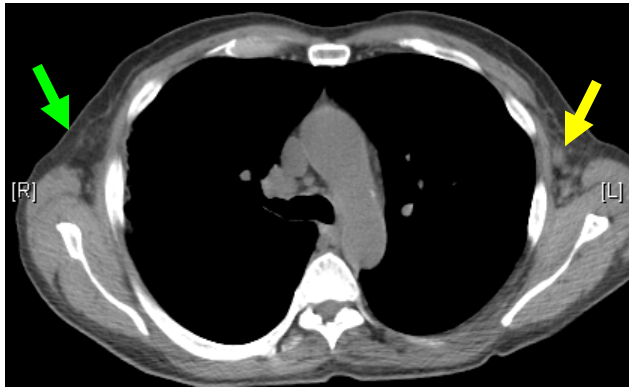

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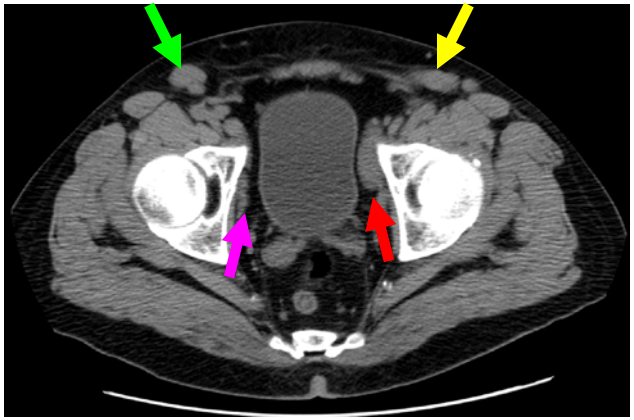
Patient 5: decreased LNs in pelvis



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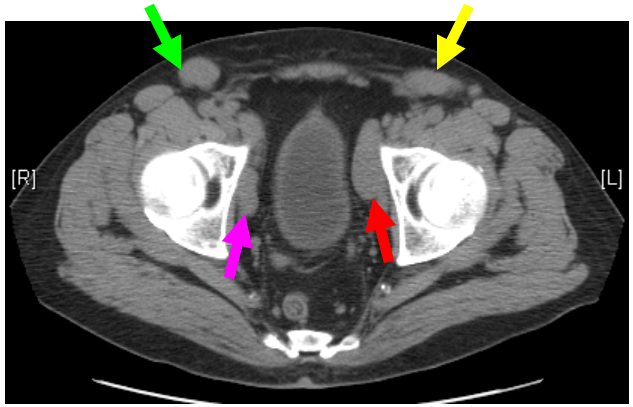

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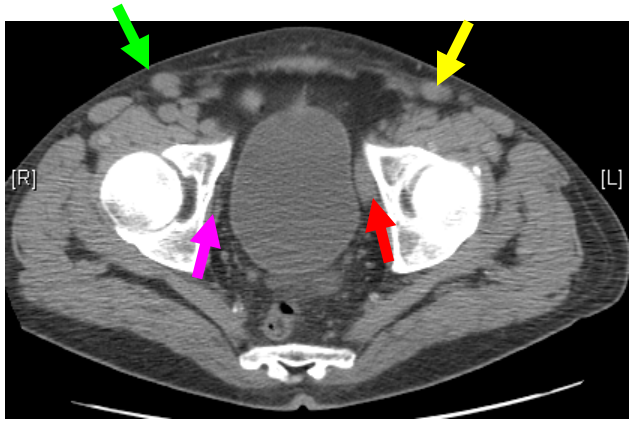

11.27.09

A Clinical Trial in Patients with Acute B cell Lymphoblastic Leukemia (B-ALL)

IRB #09-114
A Phase I trial of precursor B cell Acute Lymphomblastic Leukemia (B-ALL) treated with autologous T cells genetically targeted to the B cell specific antigen CD19.

ALL Patient 1

- 64 year old male with preB cell ALL
- Achieved remission upon initial ALL-2 induction therapy.
- Enrolled on protocol prior to consolidation #3 chemotherapy
- At time of T cell collection was found to have relapsed disease by BM analysis.
- Received re-induction chemotherapy with prednisone, vincristine and asparaginase and achieved a second remission.
- Treated with modified T cells at dose level 1 (3×10^6 modified T cells/kg) following high dose cyclophosphamide chemotherapy.
- Patient tolerated therapy well.
- No “cytokine storm” noted
- Patient has an HLA compatible sibling and is currently planned to undergo allo-BMT

Conclusions

- Infusion of genetically modified, CD19-targeted T cells was well tolerated with no severe adverse events in 6 of 7 patients treated on protocol #06-138, and in 1 of 1 patients treated on protocol #09-114.
- Based on currently available data of patients treated on protocol #06-138, advanced age or bulky disease should not be considered exclusion criteria for enrollment on this study.
- Patient #4, when compared to the other 6 patients treated on 06-138, had a markedly aberrant, and unique, cytokine profile prior to modified T cell infusion.
- Based on cytokine profiles obtained from 3 patients enrolled on clinical trial #06-138 following the SAE reported on patient #4, the aberrant cytokine profile seen in patient #4 was unlikely due to a cyclophosphamide-mediated “cytokine storm.”
- Further, based on cytokine profiles, especially IFNγ and TNFα, the patient exhibited no evidence of an infused T cell mediated “cytokine storm.”
- Based on an extensive post-mortem analysis, patient #4 most likely died of septic shock secondary to a sub-acute infection potentially exacerbated by subsequent cyclophosphamide lymphodepleting chemotherapy.

Lessons learned from patients treated on protocol #06-138: Recommendations to enhance safety in CAR-modified T cell clinical trials.

- Prior to lymphodepleting chemotherapy and modified T cell infusion, all patients should be screened for potential sub-acute infections including a detailed review of systems, an extensive physical examination, and a screening chest X-ray.
- Cytokine profiling, prior to lymphodepleting cyclophosphamide chemotherapy and subsequent infusion of targeted T cells is recommended to enhance safety in clinical trials using genetically modified T cells.
- Most patients treated on protocol #06-138 developed transient fevers following modified T cell infusion, and 2 of 7 patients had associated hypotension. For this reason, inclusion criteria should include parameters based on an ECHO and EKG to assess cardiac function, % oxygen saturation to assess pulmonary function, and a creatinine level to assess renal function.
- Safety from potential unforeseen toxicities related to modified T cells may be further enhanced through split infusion of the planned modified T cell dose over several days. This recommendation should be applied to all clinical trials using CAR-modified T cells.

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