

# **Dosing Strategies: Goals and Options**

September 10, 2013  
Bethesda MD

Renier Brentjens MD PhD  
Memorial Sloan Kettering Cancer  
Center

# Dosing Strategies: Goals and Options

---

- Starting doses: Is there a usual range?
- Single versus Split: Rationale and improved safety
- Dose escalation: Single subject versus 3 subject cohorts?

# Dosing T cells: Treatment Doses

---

- **NCI (CD19-28z CAR)**
  - Low grade B cell malignancies:  $3 \times 10^6$  -  $3 \times 10^7$  CAR T cells/kg (single infusion, dose escalation)
    - Kochenderfer et al Blood 2010, 2012
- **UPenn (CD19-4-1BBz CAR)**
  - CLL:  $1.45 \times 10^{5*}$  -  $1.6 \times 10^7$  CAR T cells/kg (split infusion, no dose escalation)
    - Kalos et al STM 2011
  - ALL:  $1.4 \times 10^6$  and  $1.2 \times 10^7$  CAR T cells/kg (split infusion, ? no dose escalation)
    - Grupp et al NEJM 2013
- **MSKCC (CD19-28z CAR)**
  - CLL:  $4 \times 10^6$  -  $3 \times 10^7$  CAR T cells/kg (split infusion, dose de-escalation)
    - Brentjens et al Blood 2011
  - ALL:  $1.5 - 3 \times 10^6$  CAR T cells/kg (split infusion, aborted dose escalation)
    - Brentjens et al STM 2013
- **BCM (CD19z and CD19-28z CAR)**
  - B cell lymphoma:  $2 \times 10^7$  -  $2 \times 10^8$  CAR T cells/m<sup>2</sup> (multiple infusion, dose escalation)
    - Savalido et al JCI 2011
- **FHCR (CD20-28-4-1BBz CAR)**
  - Low grade B cell lymphomas:  $4.4 \times 10^9$  CAR T cells/m<sup>2</sup> (multiple infusion)
    - Till et al Blood 2012

# Treatment Doses: Conclusions

---

- Generally all total treatment doses fall within a similar range of roughly  $3 \times 10^6$  -  $3 \times 10^7$  CAR T cells/kg in currently published clinical trial results
- Outlier(s) with very low T cell infusion numbers have been reported ( $1.45 \times 10^5$  CAR T cells/kg)
- There does not appear to be a correlation at this time based on the published literature between dose and clinical outcome
- Multiple variables need to be considered: disease treated, CAR design, conditioning chemotherapy, and gene transfer technology.
- It remains possible that under optimal conditions, optimal T cell generation protocols, optimal phenotype of infused CAR T cells, equally effective clinical outcomes may be achieved with significantly lower T cell doses.
- Lower T cell dosing, with equal efficacy may markedly alter the fiscal feasibility of this technology moving forward.
- To date there is no reliable data to suggest a correlation between T cell dose and observed toxicity.

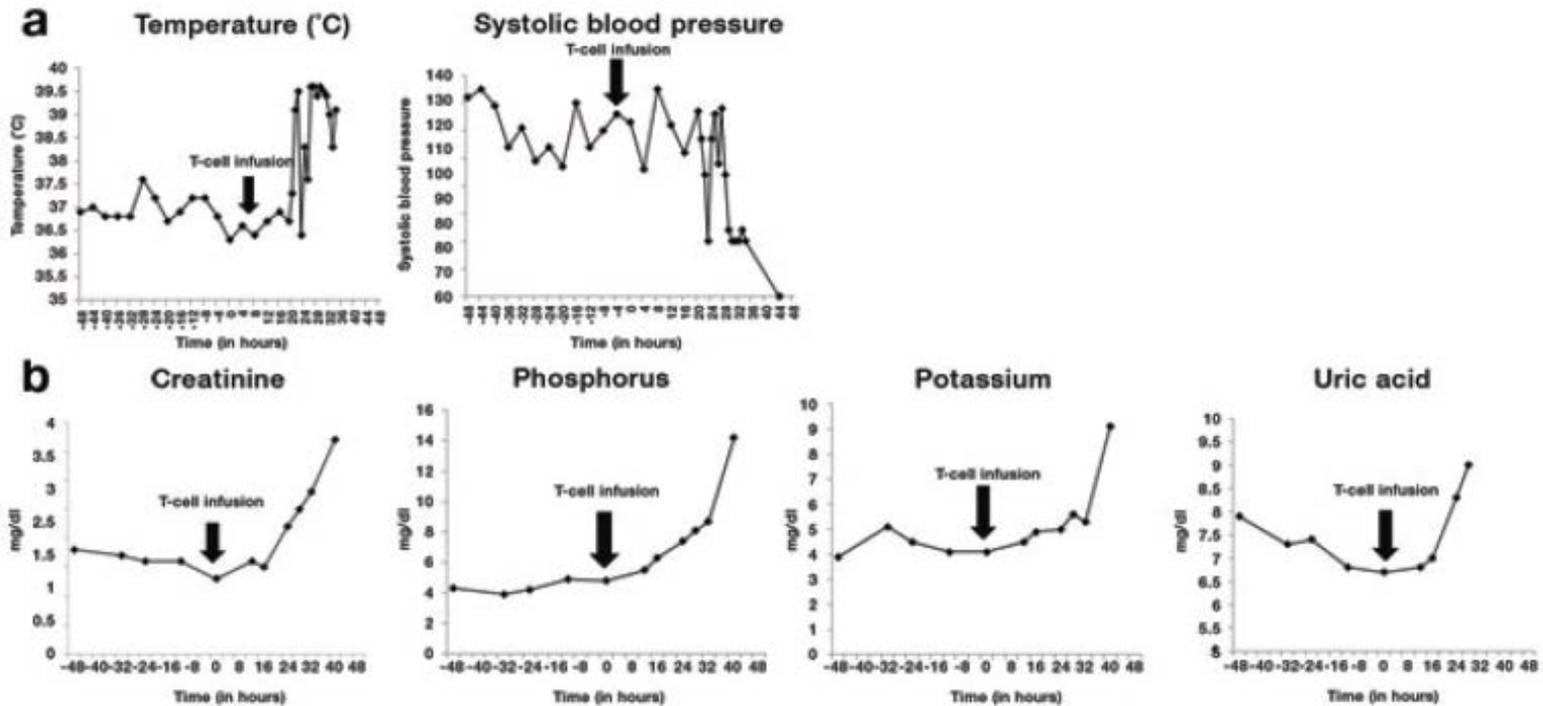
# Single versus Split T cell Dosing: Patient 4 IRB #06-138

Table 1 Cyclophosphamide and T-cell doses in IRB protocol no. 06-138

Step	Cyclophosphamide	CAR + T-cell dose	No. of enrolled subjects
1	0	$1.2-3.0 \times 10^7/\text{kg}$	3
2	1.5 g/m <sup>2</sup>	$1.2-3.0 \times 10^7/\text{kg}$	1
	3.0 g/m <sup>2</sup>	$1.2-3.0 \times 10^7/\text{kg}$	0
3	MTD	$0.4-1.0 \times 10^8/\text{kg}$	0
-1	1.5 g/m <sup>2</sup>	$4.0-10 \times 10^6/\text{kg}$	2

CAR, chimeric antigen receptor; MTD, maximum-tolerated dose.

# Single versus Split Dosing: Rationale



# Cytokine Profiles of IRB # 06-138 patient 4 during therapy

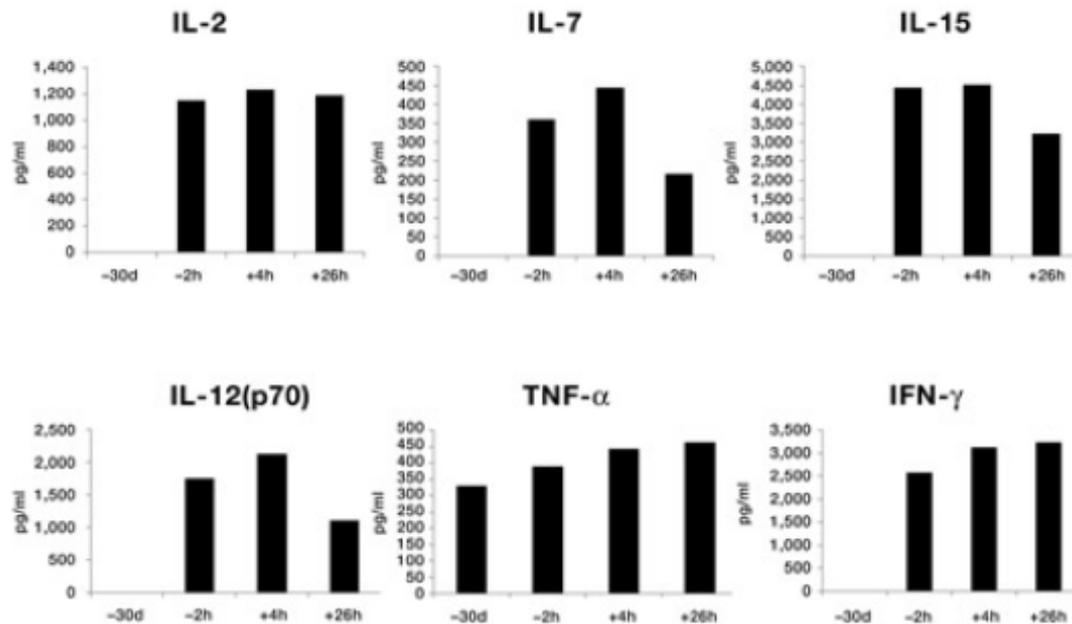


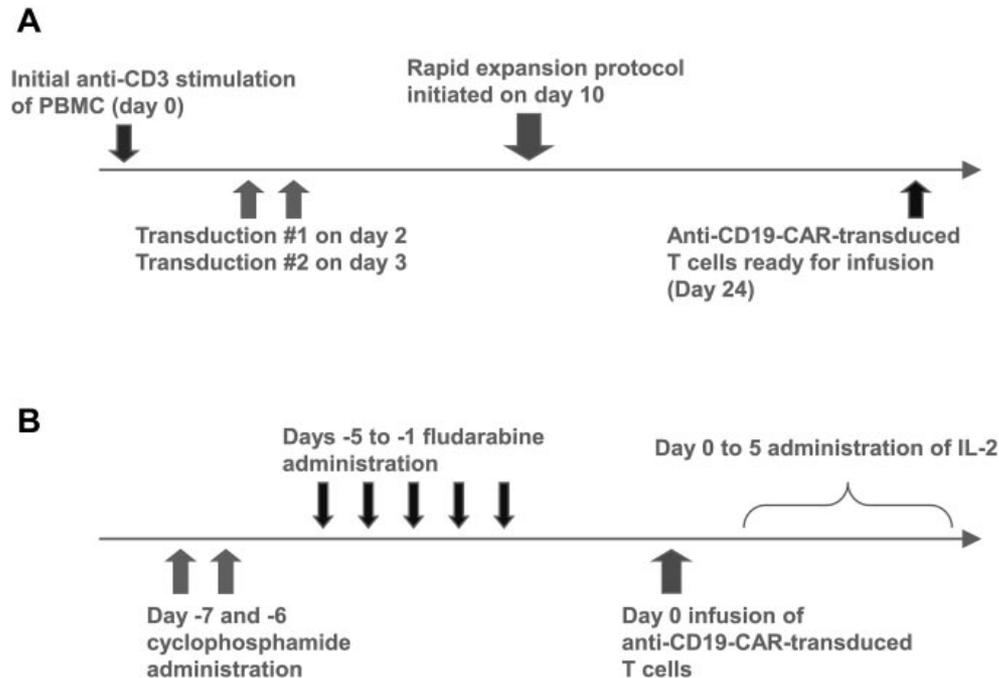
Figure 2 Serum cytokine concentrations measured in subject 4. Serum samples were obtained 30 days before cyclophosphamide (–30 d), 2 hours before T-cell infusion (–2 h), and 4 and 26 hours after T-cell infusion (+4 h, +26 h, respectively). The –2-h sample is therefore post-cyclophosphamide but pre-T-cell infusion. Pretreatment tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) serum values were 200, 50, and 59 ng/ml in subjects 1, 2, and 3, respectively. IFN- $\gamma$ , interferon- $\gamma$ ; IL, interleukin.

# Split dosing: Rationale (?)

---

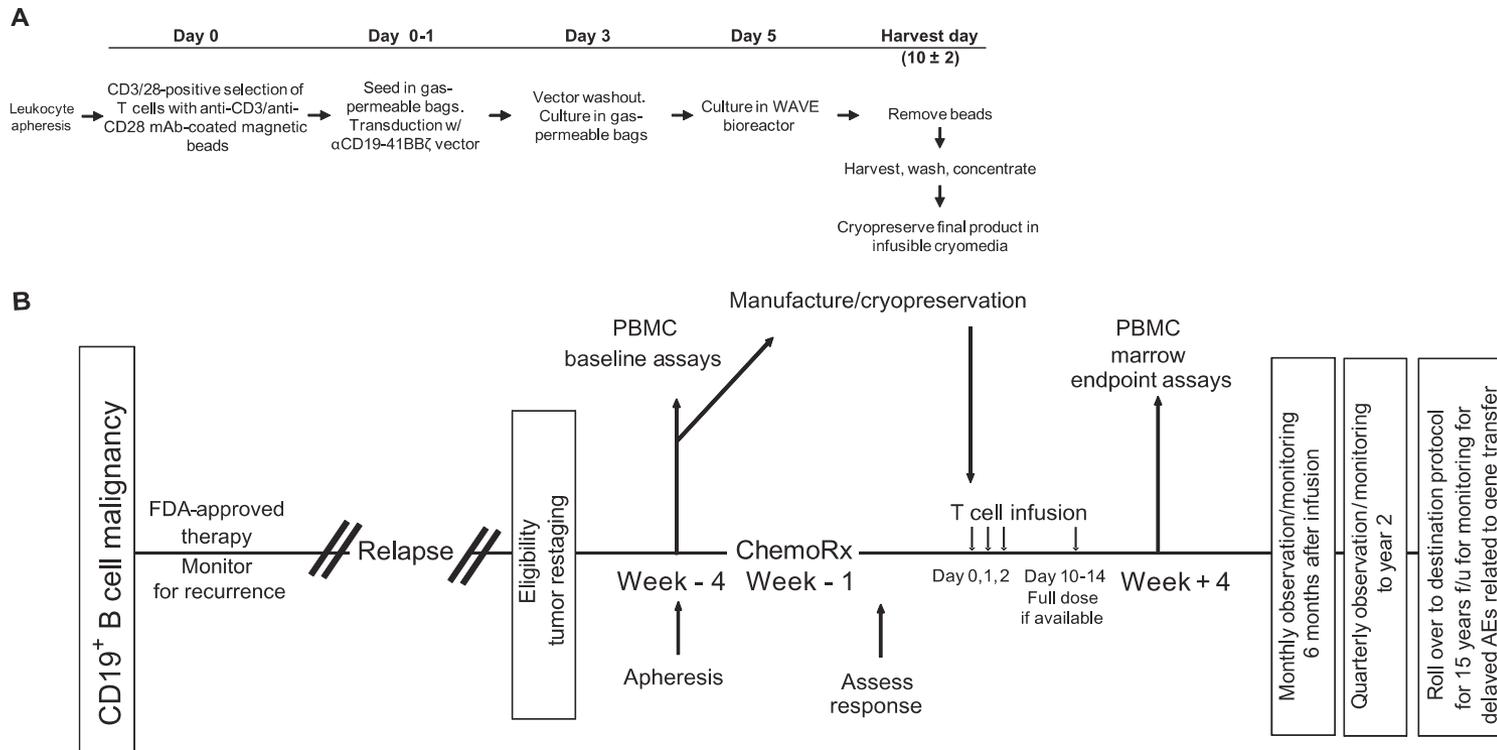
- Toxicity of Patient 4 treated on protocol 06-138 prompted amended clinical trial design to enhance safety of CAR T cell infusions with split dose infusions
- Detailed cytokine analyses of toxicity in this patient suggests prior infectious process as the source of toxicity
- To enhance safety, despite the fact that there is NO data to suggest CAR T cell toxicity in this setting, we proposed to split dose infusion of CAR T cells to enhance the safety of this therapy
- To date all data presented on this death on study is related to a prior sub-acute infectious process with NO data to suggest that this outcome was related to infusion of CD19-targeted CAR T cells

# Schema of NCI Clinical Trials



**Figure 1. Anti-CD19-CAR-transduced T-cell production and clinical treatment protocols.** (A) PBMCs were stimulated with the anti-CD3 mAb OKT3 on day 0. The cells were transduced with gammaretroviruses encoding the anti-CD19 CAR on days 2 and 3. On day 10, a rapid expansion protocol was started, and the cells were ready for infusion on day 24. (B) Patients received 60 mg/kg cyclophosphamide chemotherapy daily for 2 days. Next, patients received 25 mg/m<sup>2</sup> fludarabine chemotherapy daily for 5 days. One day later, the patients received a single infusion of anti-CD19-CAR-transduced T cells. Starting on the same day as the T-cell infusion, the patients received IV IL-2 every 8 hours.

# UPenn CD19 CART T cell therapy of CLL



# Split Dosing: Other Centers

---

- MSKCC
  - Split dosing days 2 and 3 post conditioning chemotherapy (33% then 67% of T cell dose)
- BCM
  - Single infusion, second infusion possible with SD or disease response
- FHCRC
  - Split dose infusion (2-5 days apart, with dose escalation)

# Conclusions regarding T cell split infusion protocol

---

- There is no data, to date, to support enhanced safety with split dose T cell infusions.
- Safety concerns which prompted split dose T cell infusions upon refection do not appear to be based on toxicities associated with CAR T cell infusions (MSKCC experience).
- Overall, multiple dosing needs to be considered in the context of disease response versus toxicities associated with a single T cell infusion.

# Dose escalation: Single subject versus 3 subject cohorts?

---

- None of the cited protocols include dose escalation of T cells dose within a single patient.
- Most protocols to date, with limited numbers of published patient outcomes, lend very little data with regard to dose escalation making subjective conclusions regarding any dose escalation (single subject versus 3 subject cohorts) difficult to evaluate at this time.

# An additional but more relevant question to address: Multiple CAR T cell infusions

---

- Several current protocols stipulate additional CAR T cell infusions after the initial treatment (UPenn and BCM)
- At MSKCC, we are investigating additional T cell infusions in ALL patients ineligible for Allo-BMT or those who have relapsed after initial CAR T cell therapy
- It remains to be seen what if any role additional “consolidation” CAR T cell infusions may have in the setting of relapsed disease, transplant ineligible patients, or in the setting of limited CAR T cell persistence.