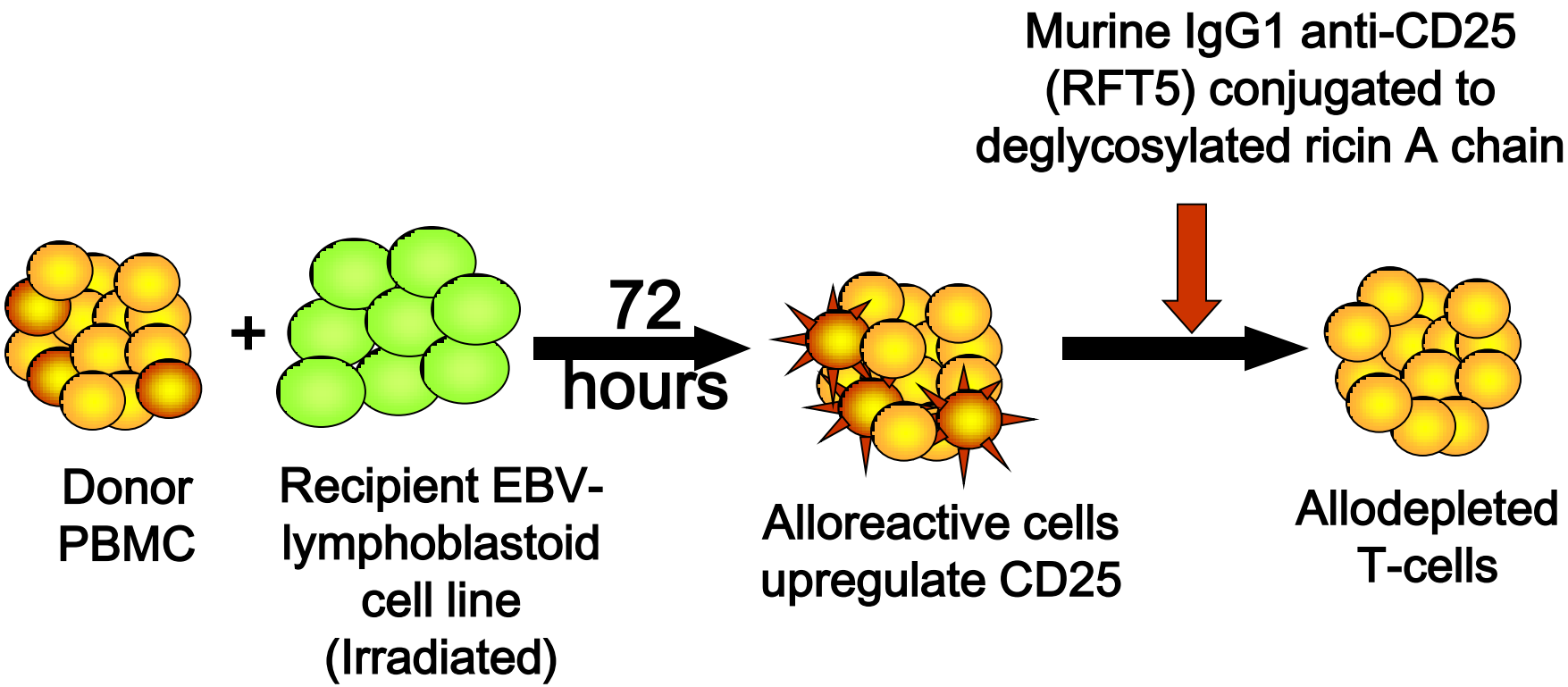
Adoptive Immunotherapy After HLA Haploidentical SCT

- Rigorous T-cell depletion avoids GVHD ***BUT*** lose GVL (relapse) ***AND*** anti-viral immunity
- Addback T-cells responsible for GVL and anti-viral responses, but remove allo-reactive T-cells that cause GVHD.

Selective Depletion Of Alloreactive Cells



Amrolia et al, Blood 2006

Allodepleted T Cell Addback After Haploidentical SCT

- Accelerates T cell recovery and reconstitution of anti-viral immunity
- $10^5 - 10^6$ cells/kg decreases rate of death from virus disease but relapse remains high

Amrolia et al, Blood 2006

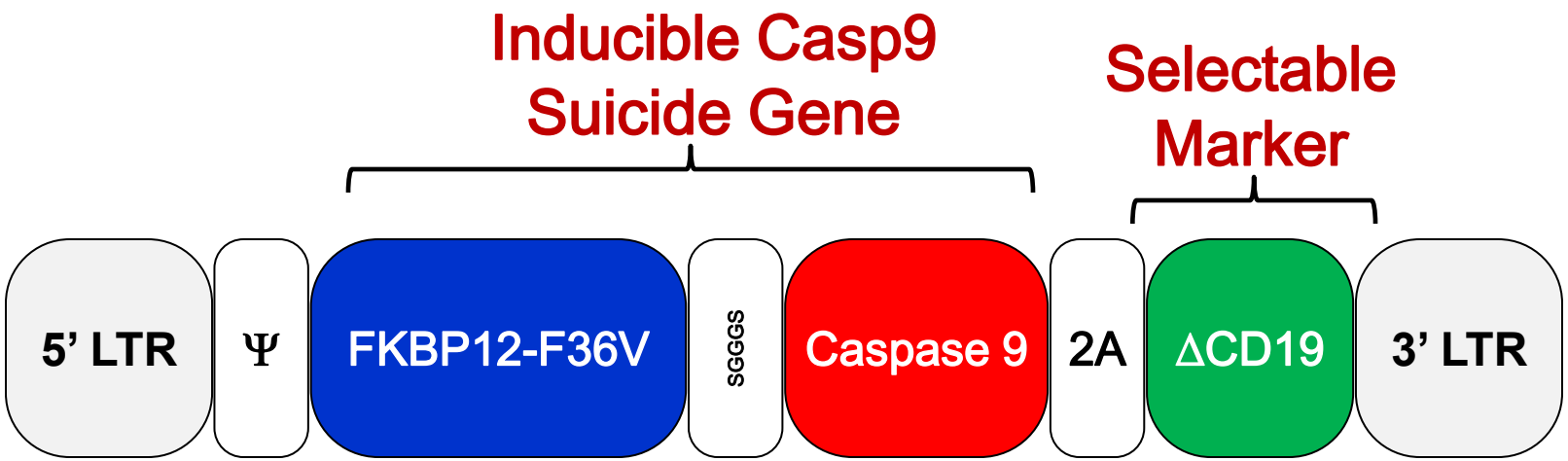
<u>Our Proposed Strategy:</u>

- Increase number of allodepleted T cells we infuse
- Incorporate inducible suicide gene for safety

Suicide Genes

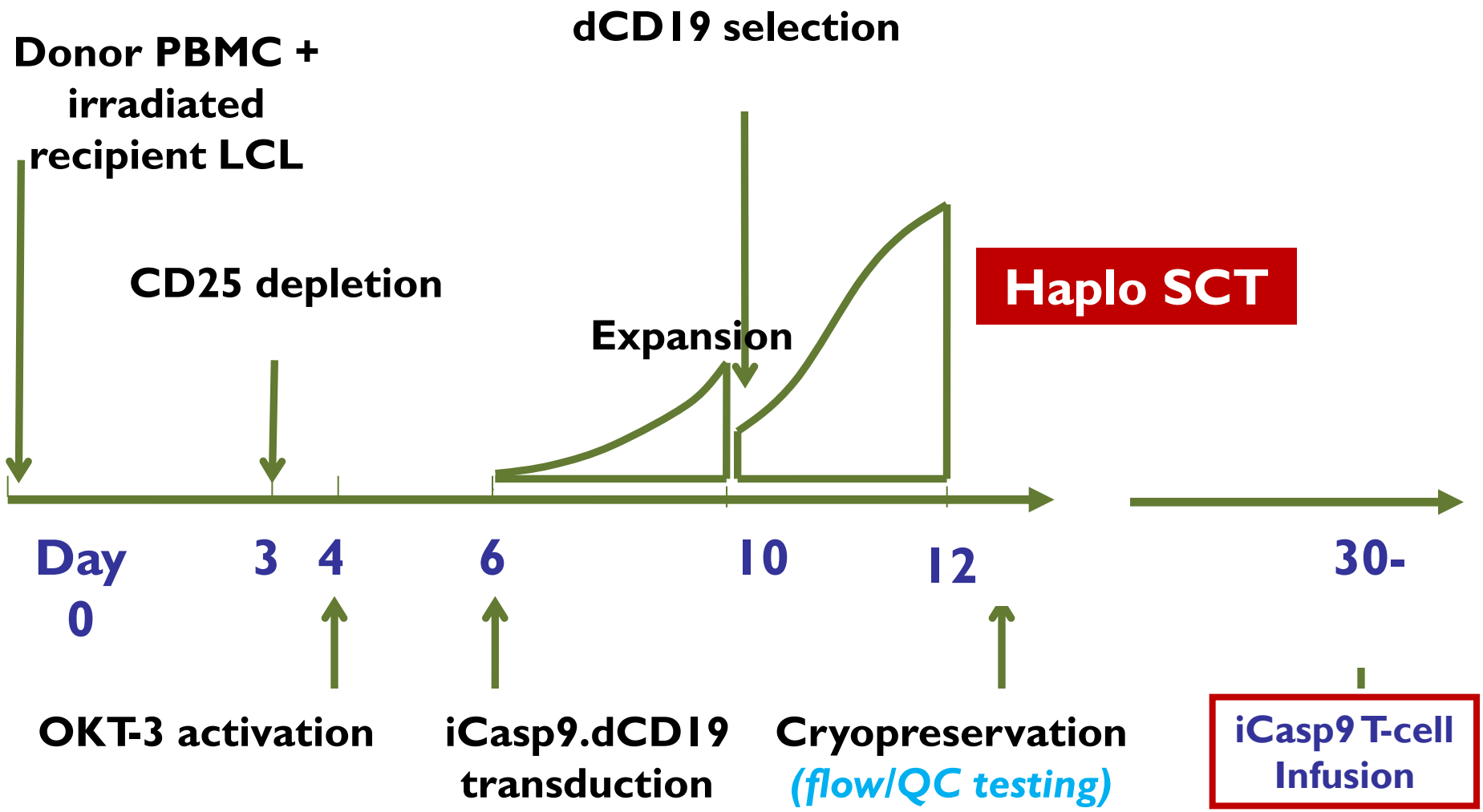
	HSVtk	iCasp9
Source	Foreign →Immunogenic	Human derived → less immunogenic
Activating drug	Ganciclovir. Widely used to treat CMV.	Non therapeutic small molecule
Mechanism	Dividing Cells (DNA synthesis)	All cells by apoptotic pathway. Rapid killing.

CASPALLO: Inducible Caspase 9 (iCasp9).2A.dCD19 Transgene Construct

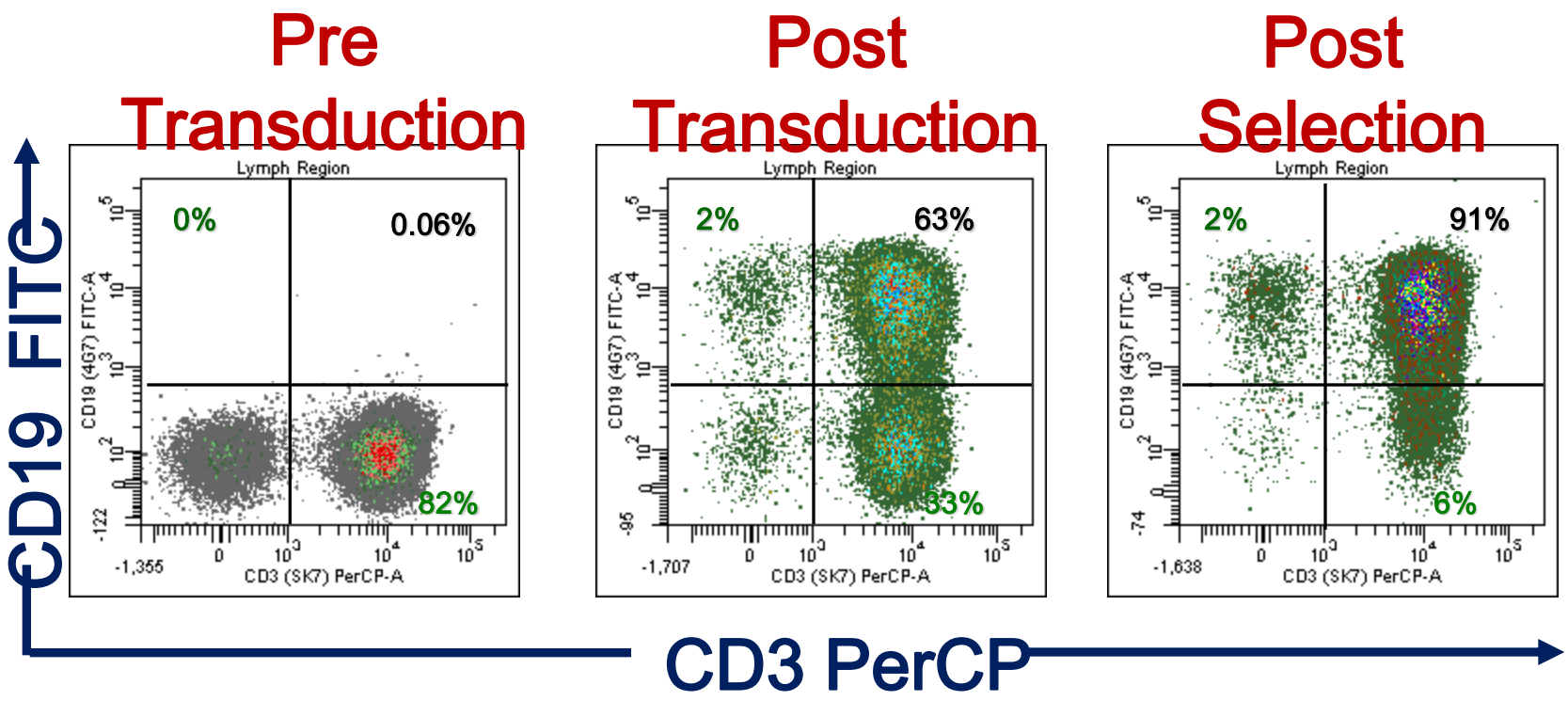


Tey SK *et al. Biol Blood Marrow Transplant 13* (2007)

Protocol Overview



CASPALLO: Genetic Modification Of Allodepleted T Cells



CASPALLO: Study objectives

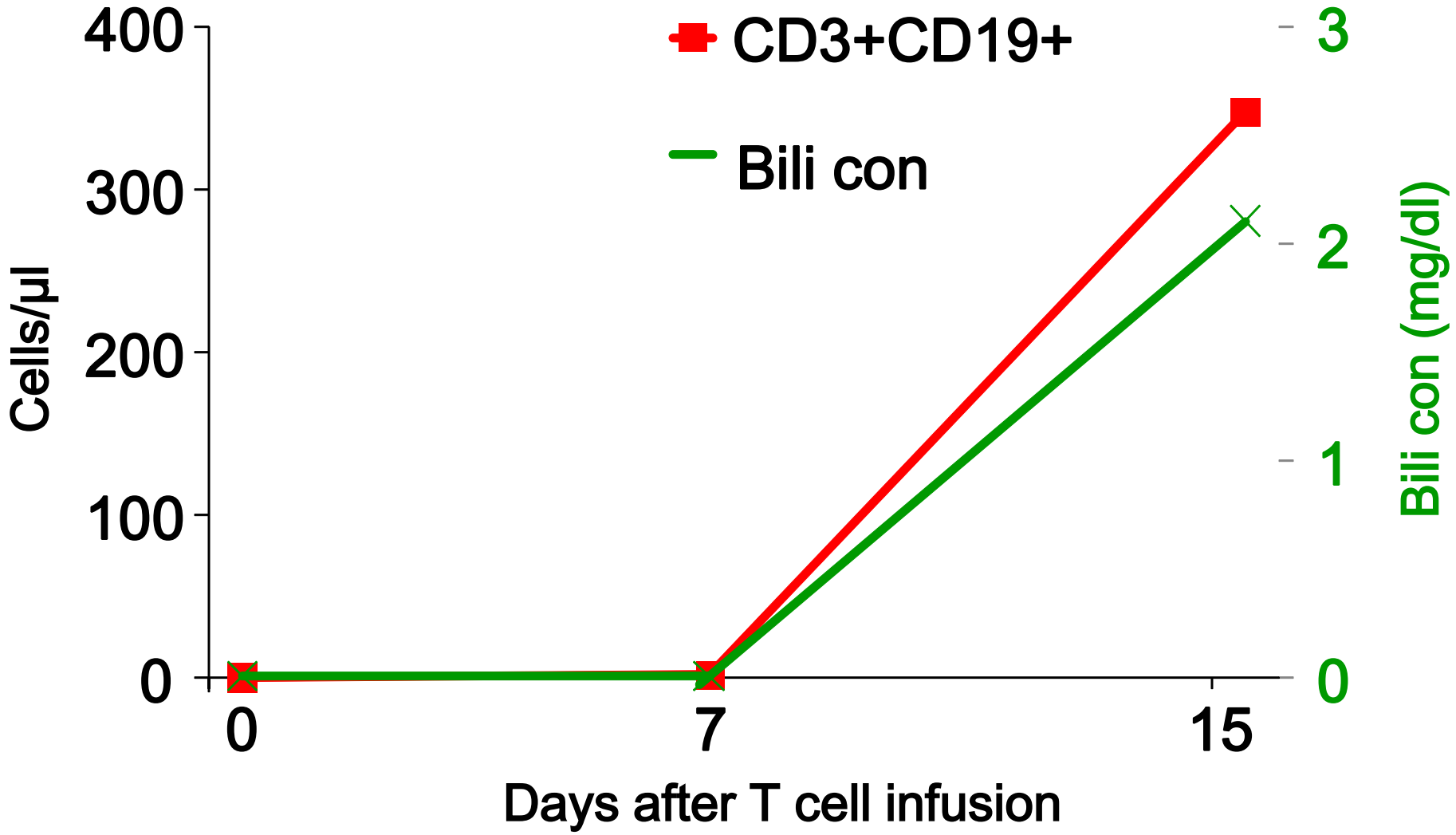
PRIMARY

- Highest dose of allodepleted donor T cells with grade III-IV acute GvHD rate ≤ 25%
- Biological and clinical effects of administration of AP1903

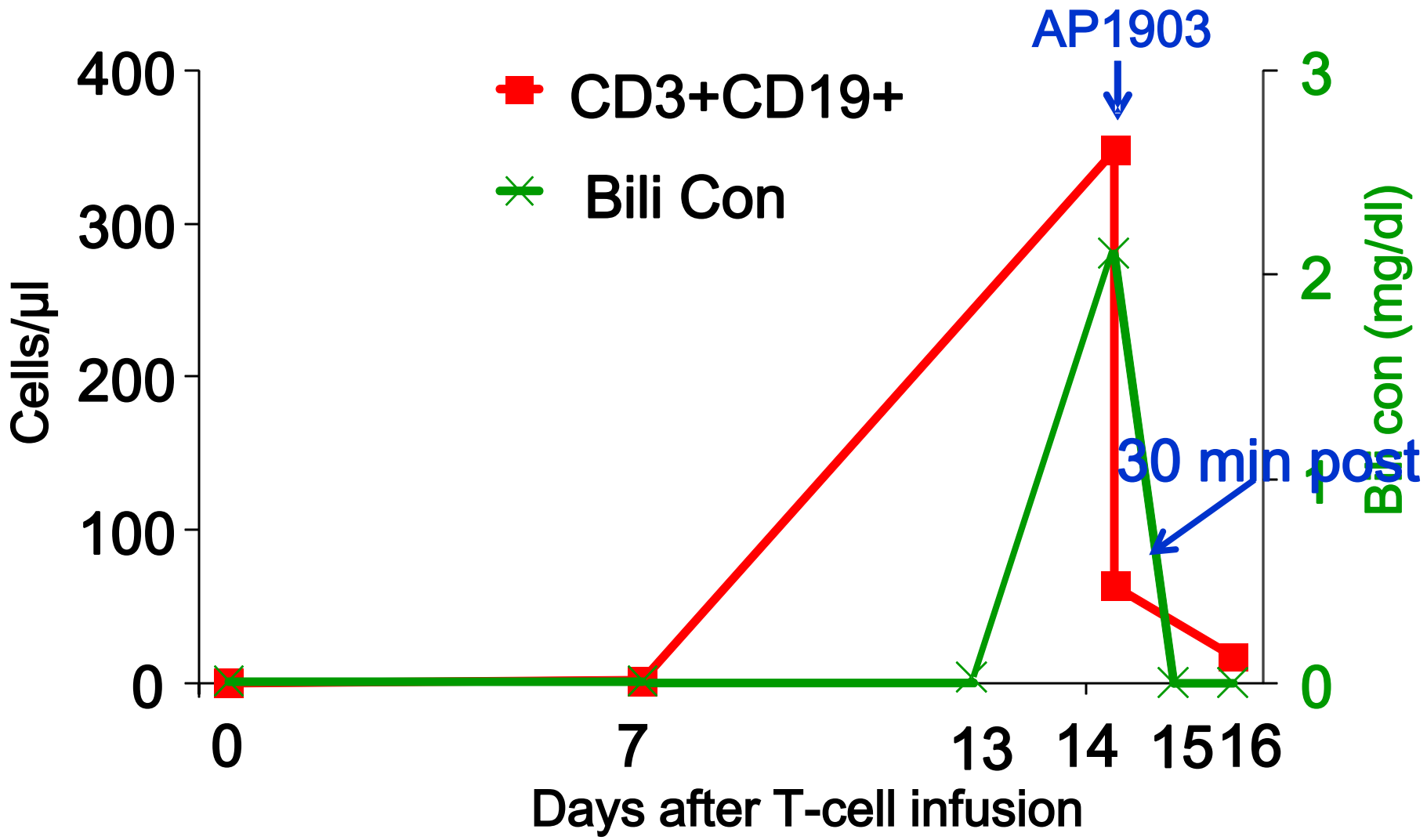
CASPALLO -Patients on Study

- 10 patients received allodepleted T cells
  - 3 at 1 x 10^6 cells/kg
  - 2 at 3 x 10^6 cells/kg
  - 5 at 1 x 10^7 cells/kg
- 4 developed Grade 1 GVHD and received the dimerizer

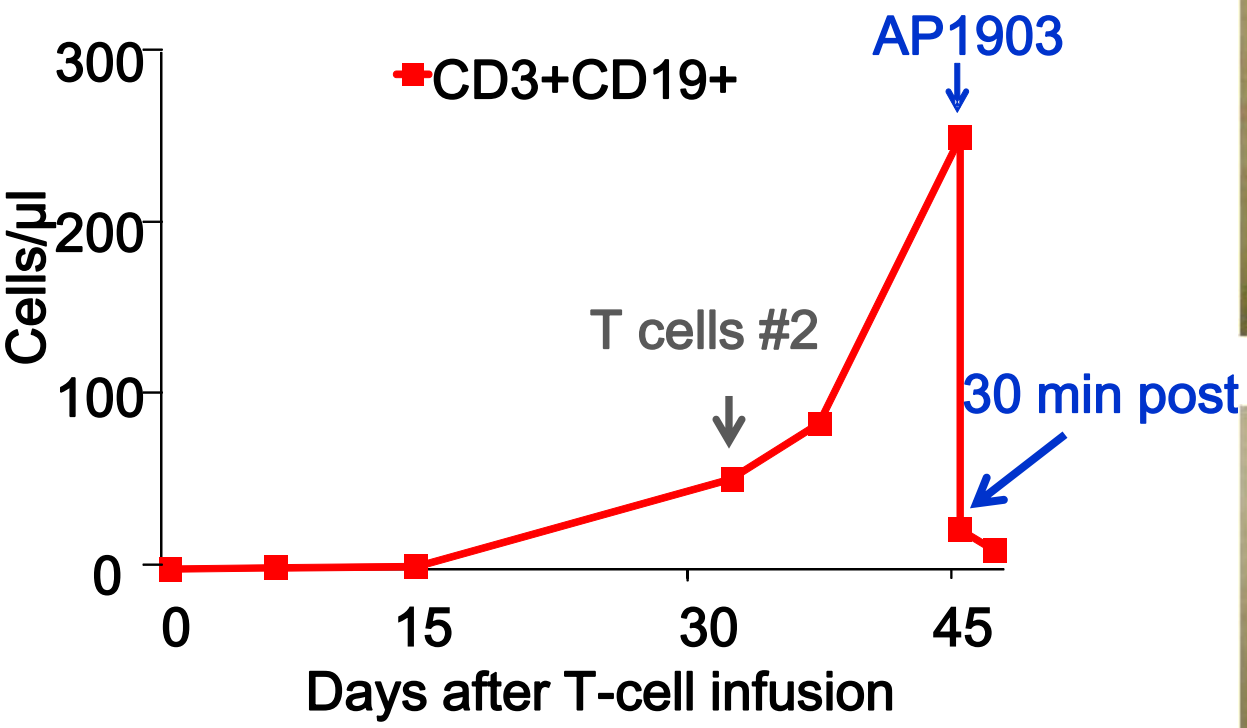
Acute Liver GVHD After Icasp9 T Cell Expansion (Pt 1)



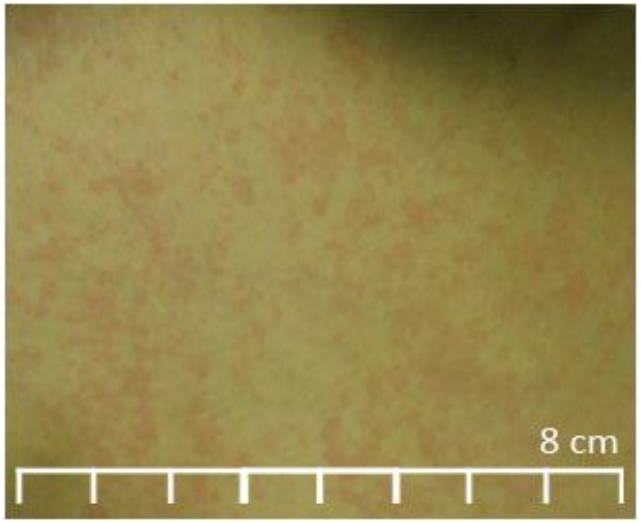
Prompt Resolution Of liver GvHD After A Single Dose of AP1903 (Patient 1)



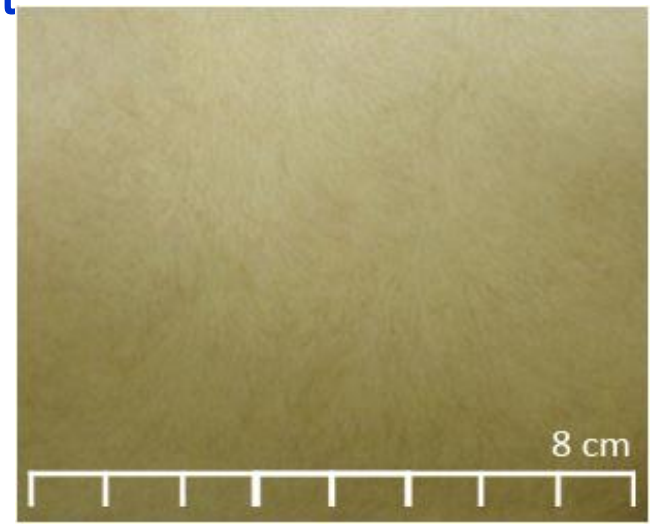
Prompt Resolution Of Skin GVHD After A Single Dose Of AP1903 (Patient 2)



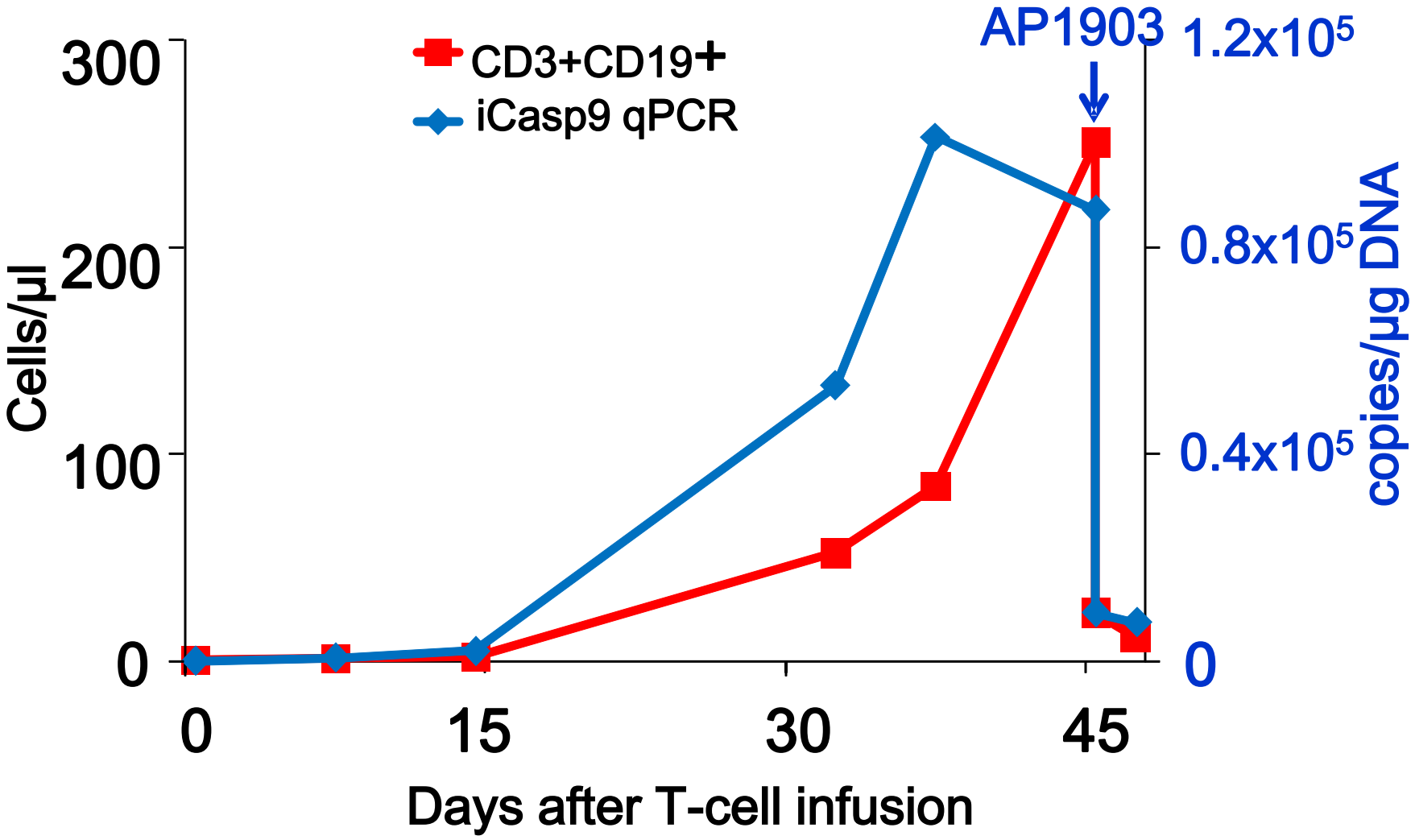
Pre AP1903



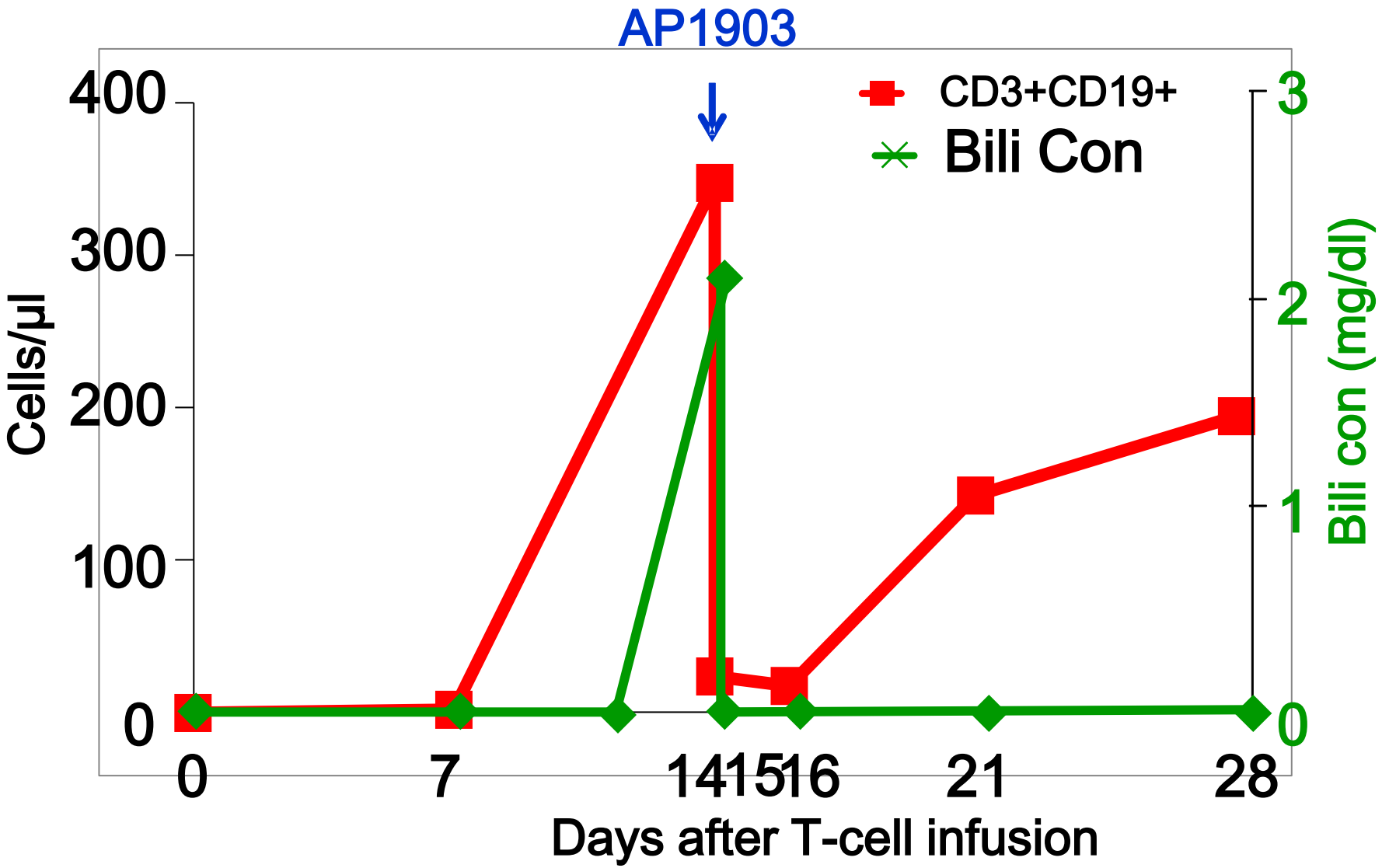
24 hrs Post AP1903



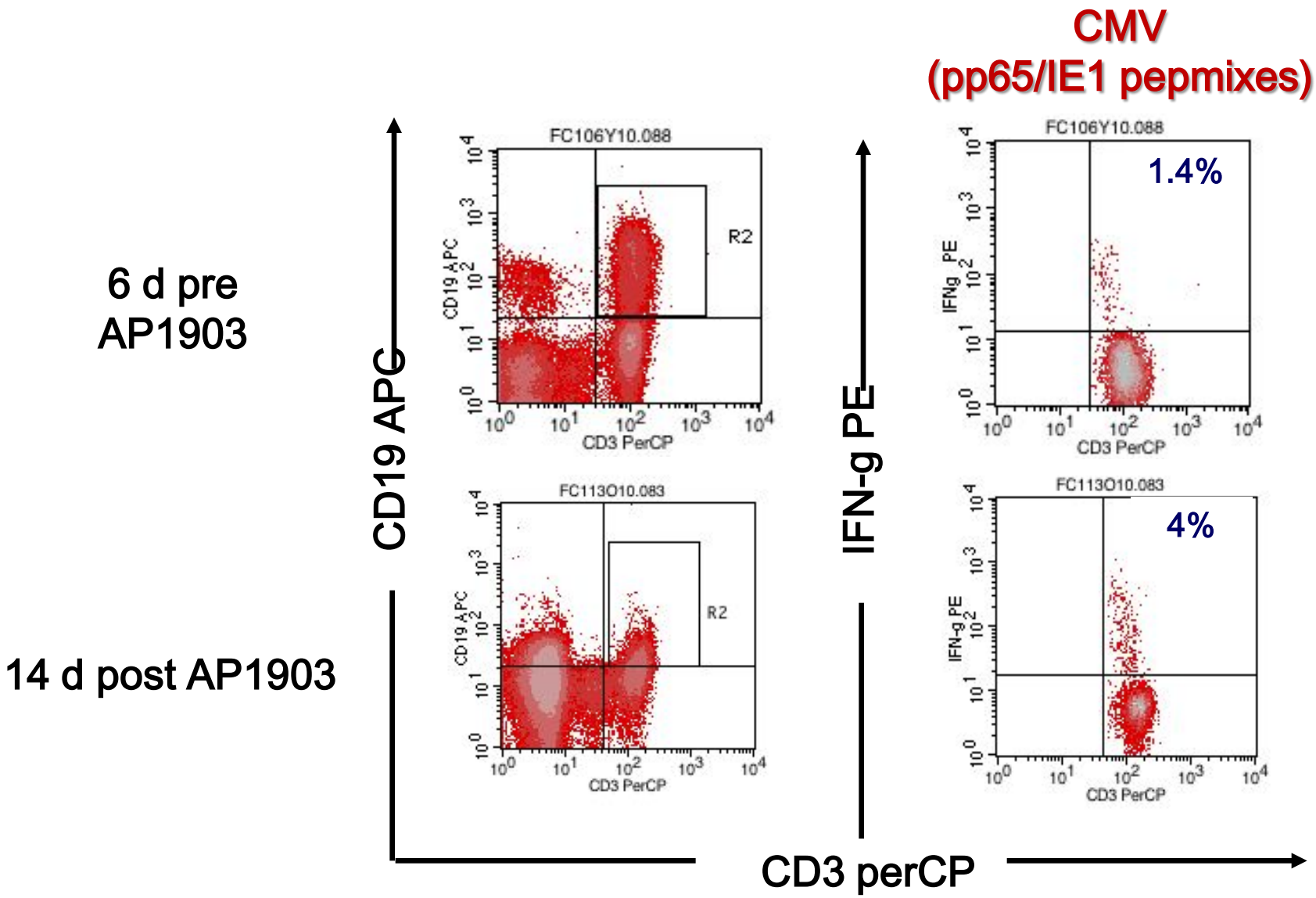
iCasp9 Transgene qPCR Also Falls After Dimerizer (patient 2)



Residual iCasp9 T Cells Re-expand After AP1903 Without GVHD (pt 1)



Virus-specific T Cells Are Retained After AP1903 Infusion (Pt 2)



Allodepleted T cells With Suicide Gene

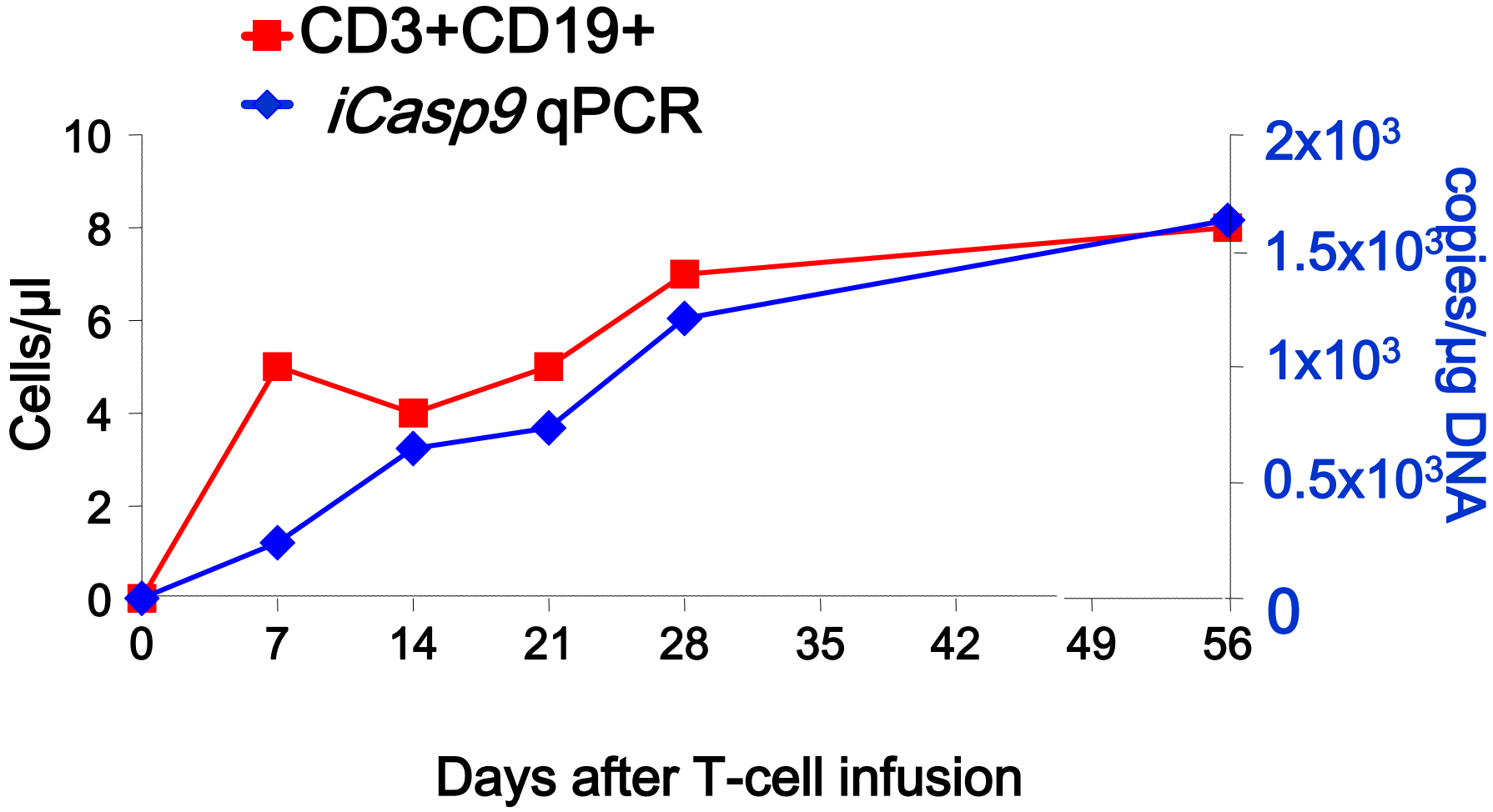
- iCasp9 expressing allodepleted T cells can persist and expand in vivo
- Treatment with single dose AP1903 **rapidly ablated** (>90%) alloreactive iCasp9 T cells with resolution of aGVHD in all 4 patients treated

Fate Of Infused T Cells

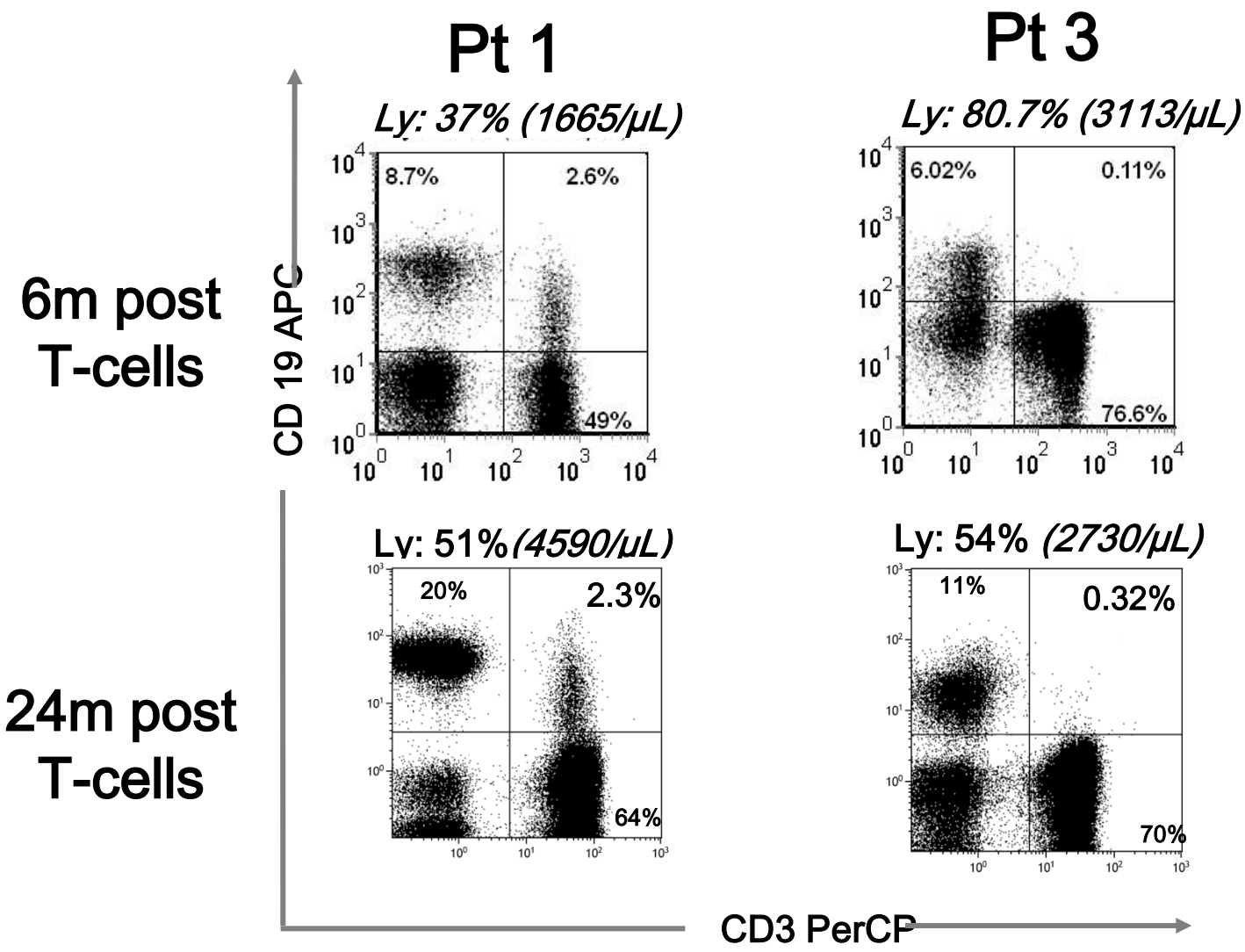
Do transduced T cells persist long term in the absence of GvHD?

Will their TCR V-beta repertoire usage be polyclonal?

Pt 3 T-cell engraftment w/o GvHD

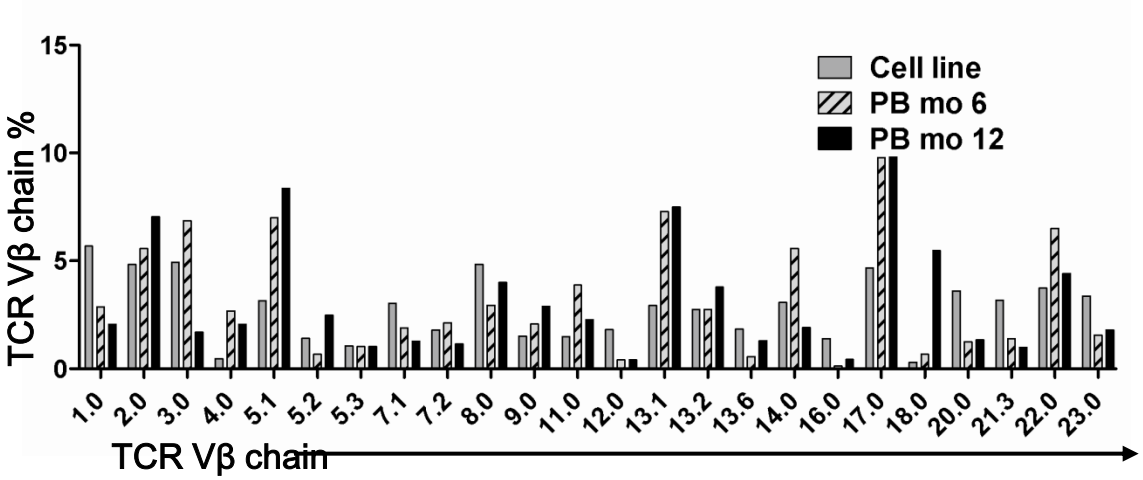


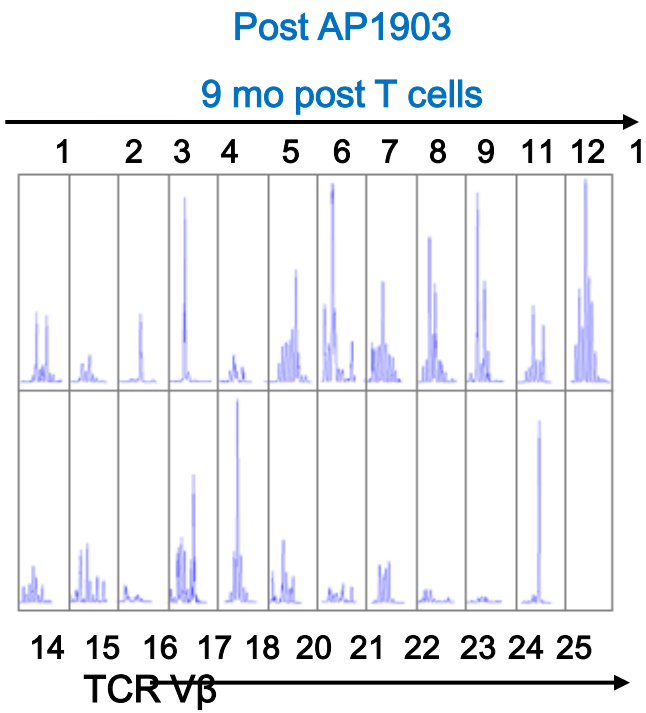
Infused T cells persist in PB >24 months after infusion



$CD3^+CD19^+$ T cells have a polyclonal V-ß repertoire (P1, as P2-9)

$CD3^+CD19^+$ population





CASPALLO -Patient Outcome

- 10 patients received allodepleted T cells
- 3 relapsed and died of their primary hematologic malignancy
- 7 alive 5-29 months post T cells

Conclusions

- iCasp9 expressing allodepleted T cells can expand in vivo
- Treatment with single dose AP1903 rapidly ablates (>90%) iCasp9 T cells with resolution of acute GVHD
- After AP1903 treatment residual iCasp9 T cells re-expanded in the absence of further GvHD
- Residual iCasp9 T cells polyclonal TCR V-β repertoire
- Anti-viral activity retained after AP1903 treatment for aGvHD

Future Directions

- Administration of iCaspase9 donor T cells after haplo-SCT without in vitro allodepletion (DOTTI trial)
- Incorporation of iCasp9 in constructs for first-in-man studies with 3rd generation CARs
- MSC protocols in lung cancer

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