Update on *A Phase I Study of CD19 CAR-Expressing T Cells in B-Cell NHL and CLL*

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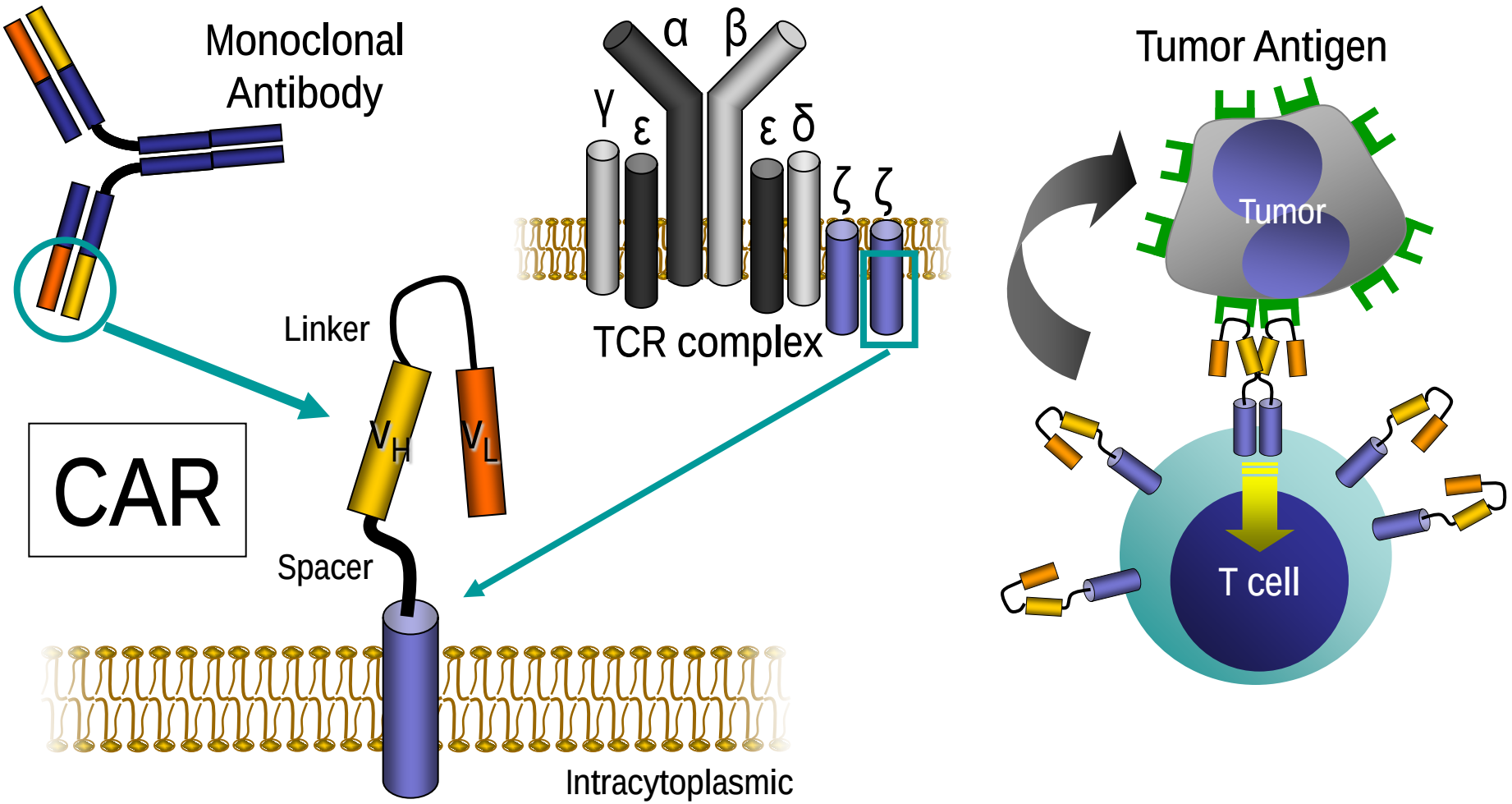
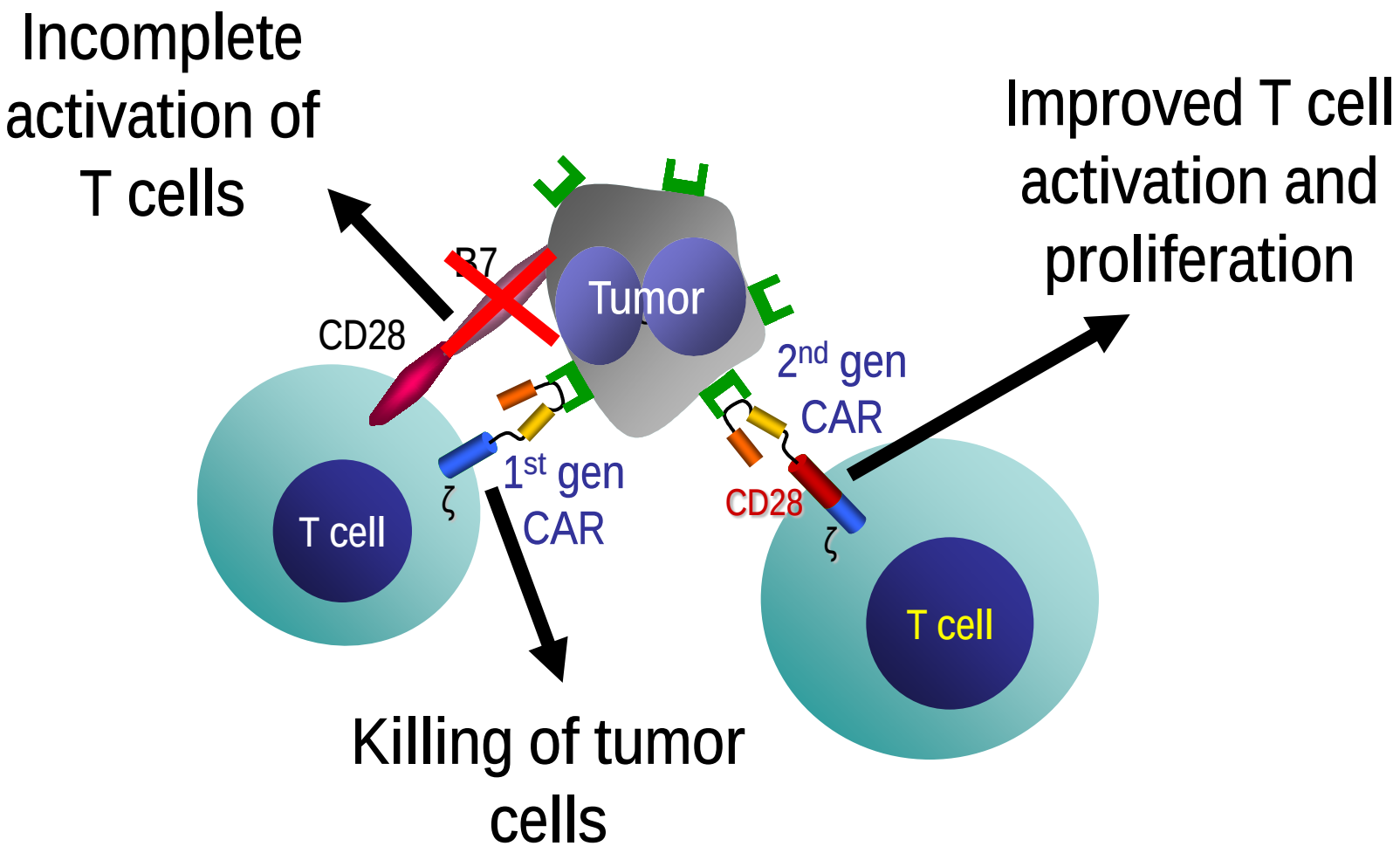
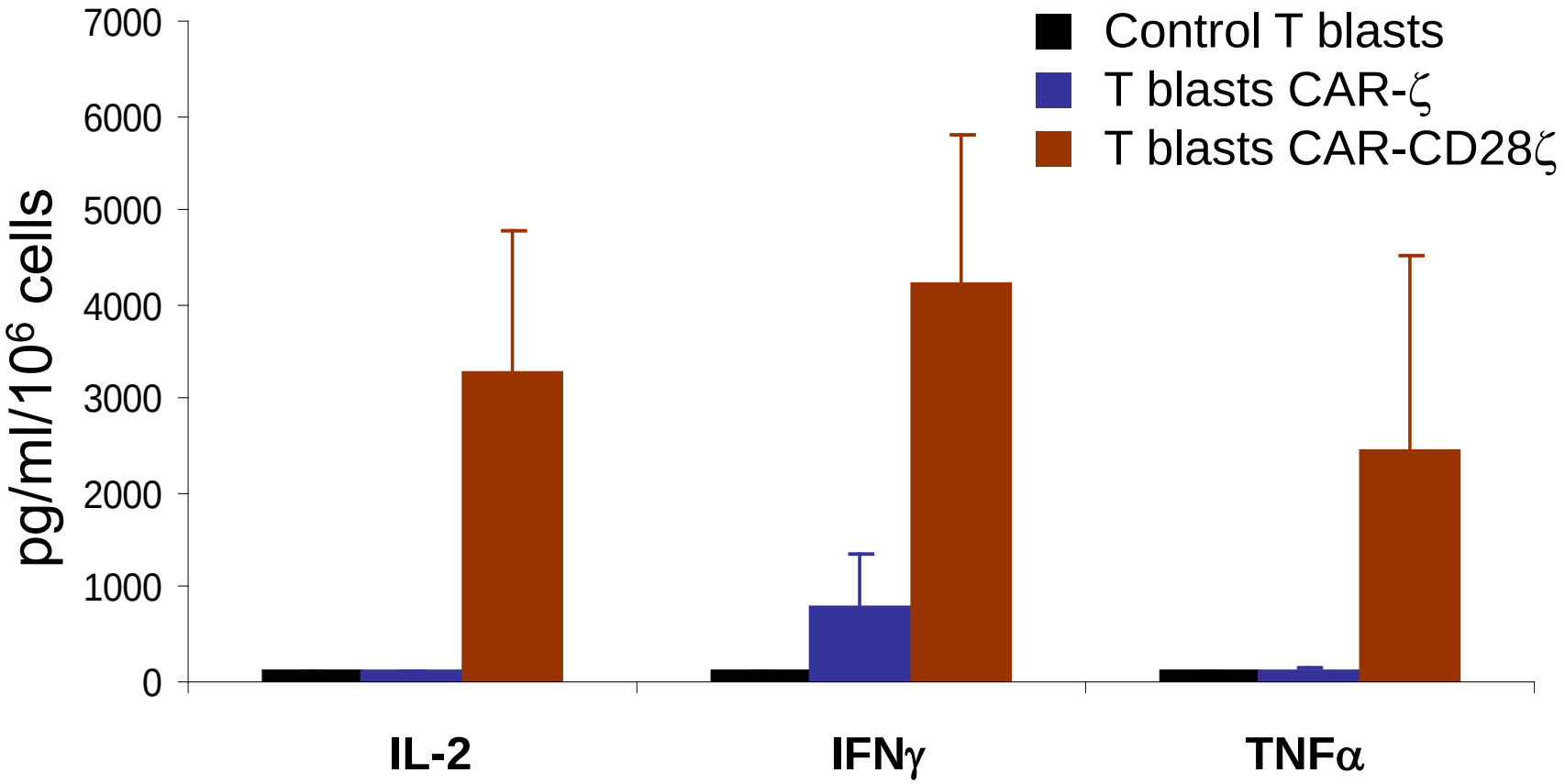
Chimeric Antigen Receptors



Incomplete activation of 1st generation CAR-directed T cells



CAR-CD28 co-stimulation increases cytokine secretion after antigen exposure

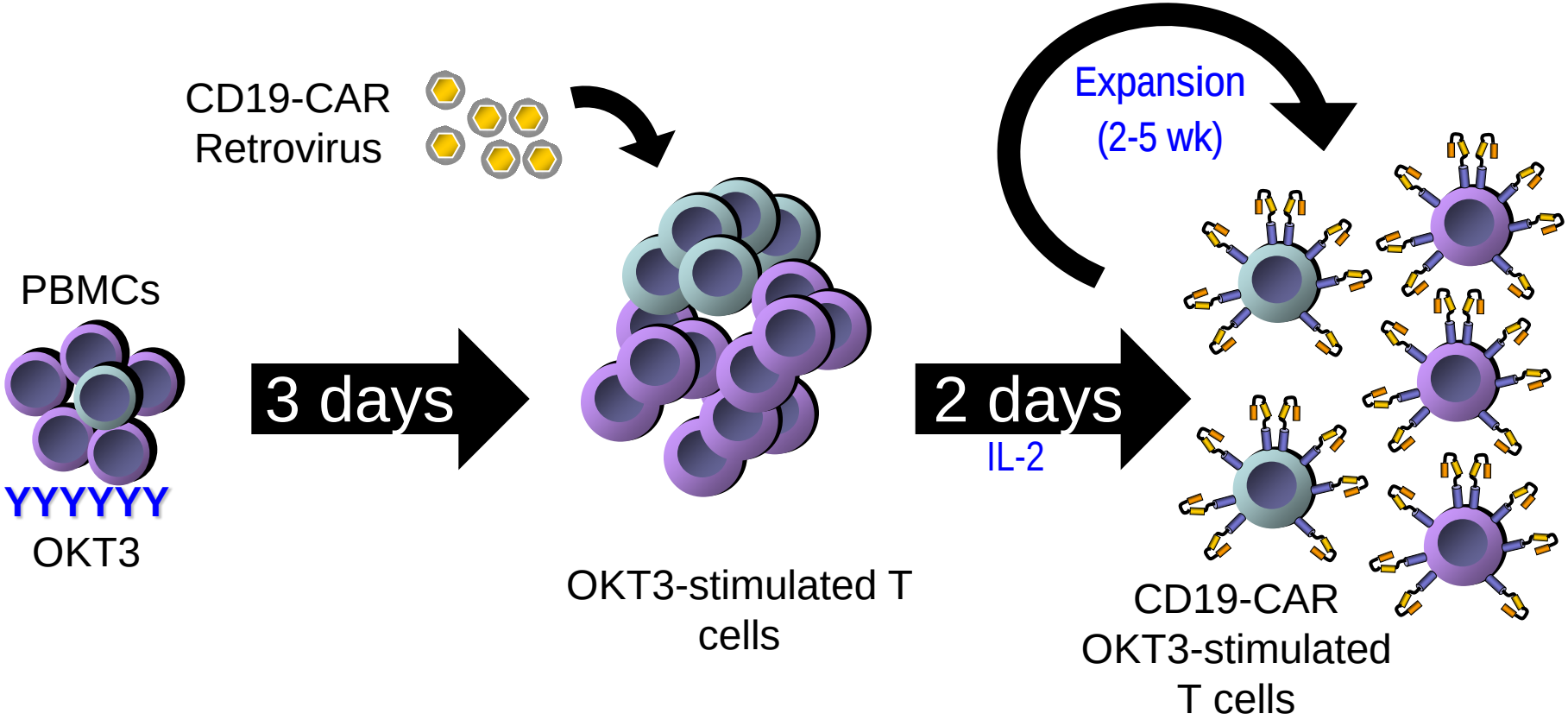


(Vera *et al.*, Blood 2006)

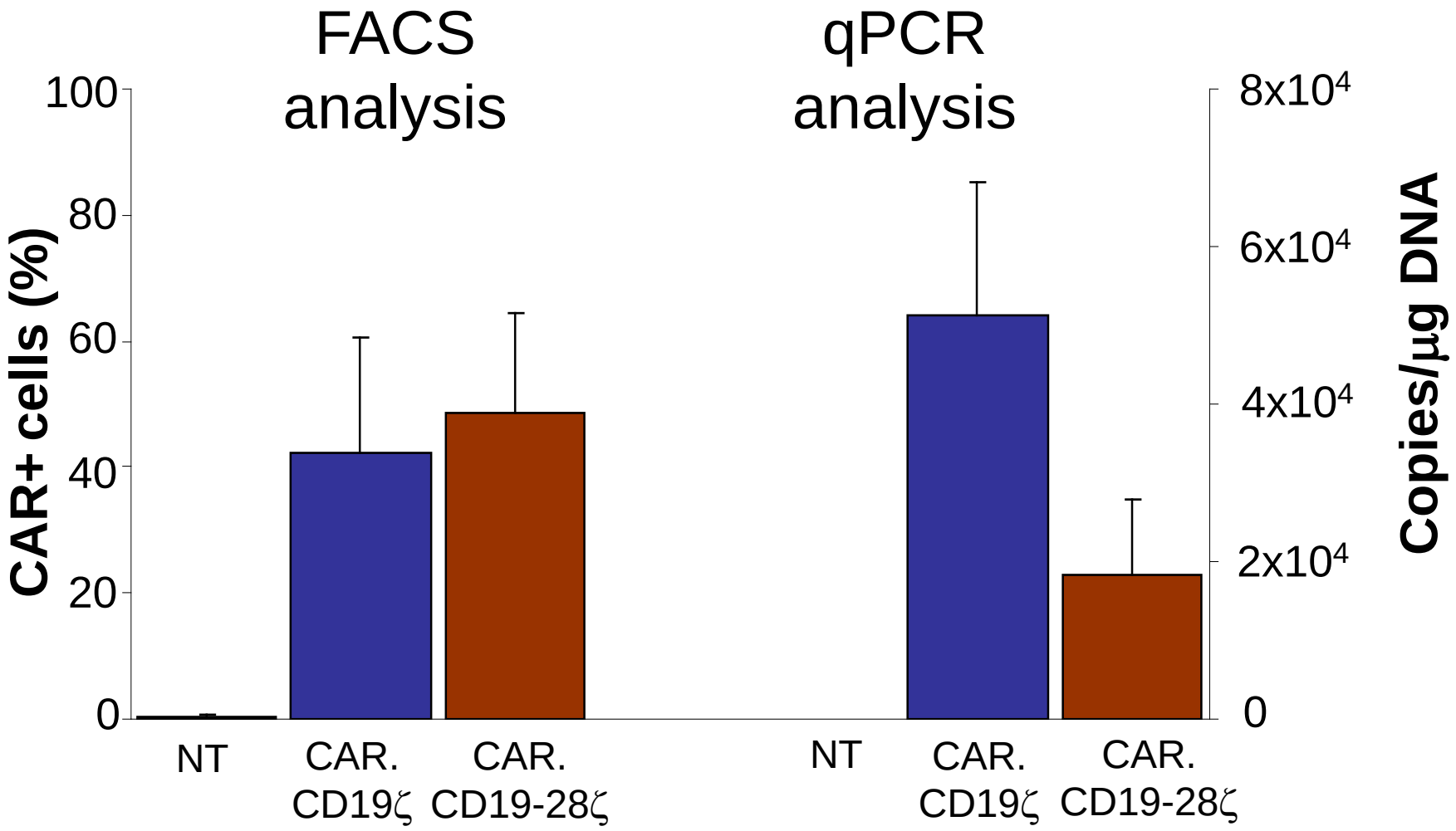
Are CAR-CD28 T cells superior to CAR T cells against CD19?

- Prepare two autologous activated T cell lines expressing **CAR.CD19ζ** or **CAR.CD19-28ζ** for each patient
- Infuse both T cell populations
- Track each T cell population in vivo

Generation of CD19-CAR OKT3-stimulated T cells

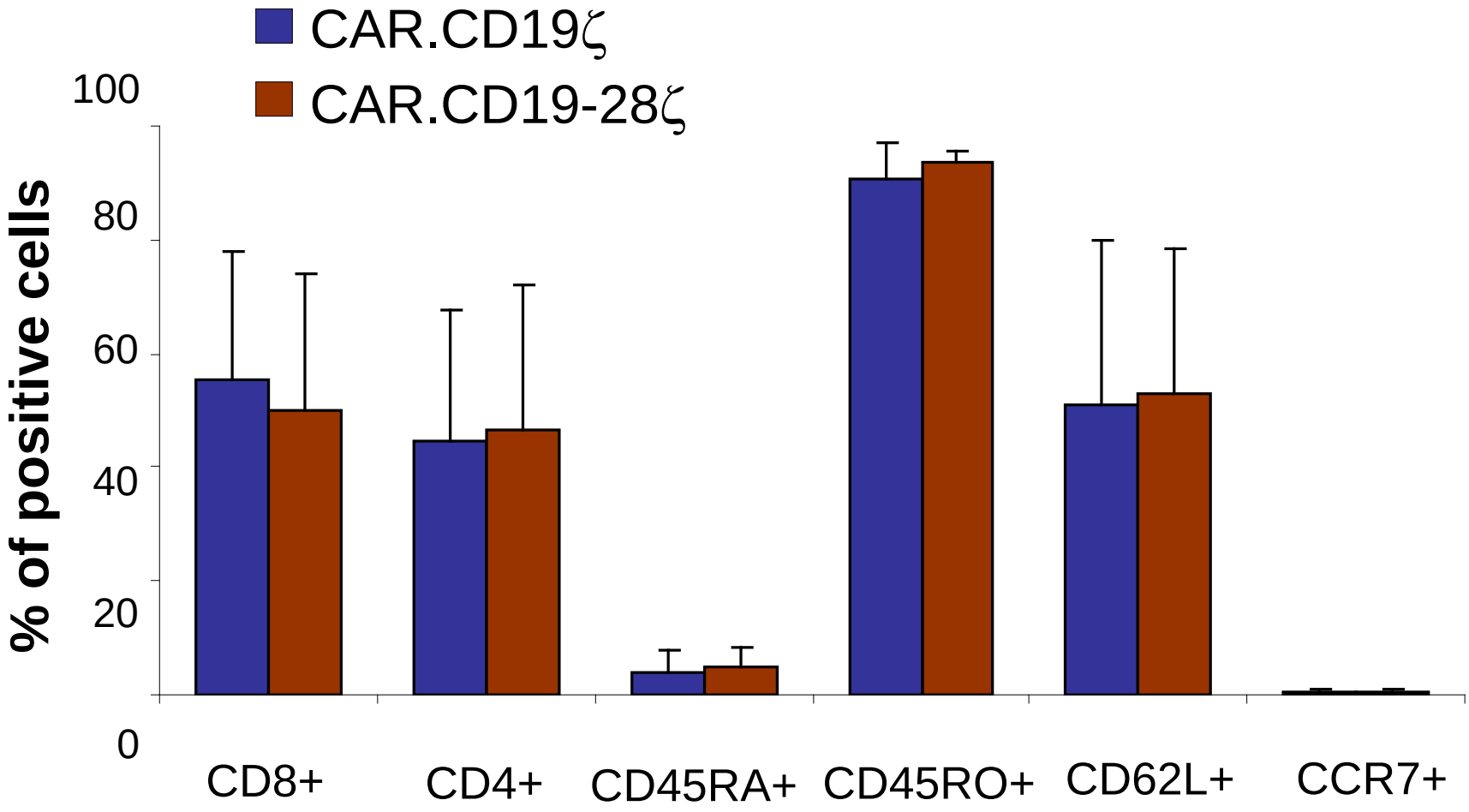


Transduction of CAR.CD19 and CD19-28 T cells is comparable



n=6

CAR.CD19 and CD19-28 T cells have similar immunophenotypes



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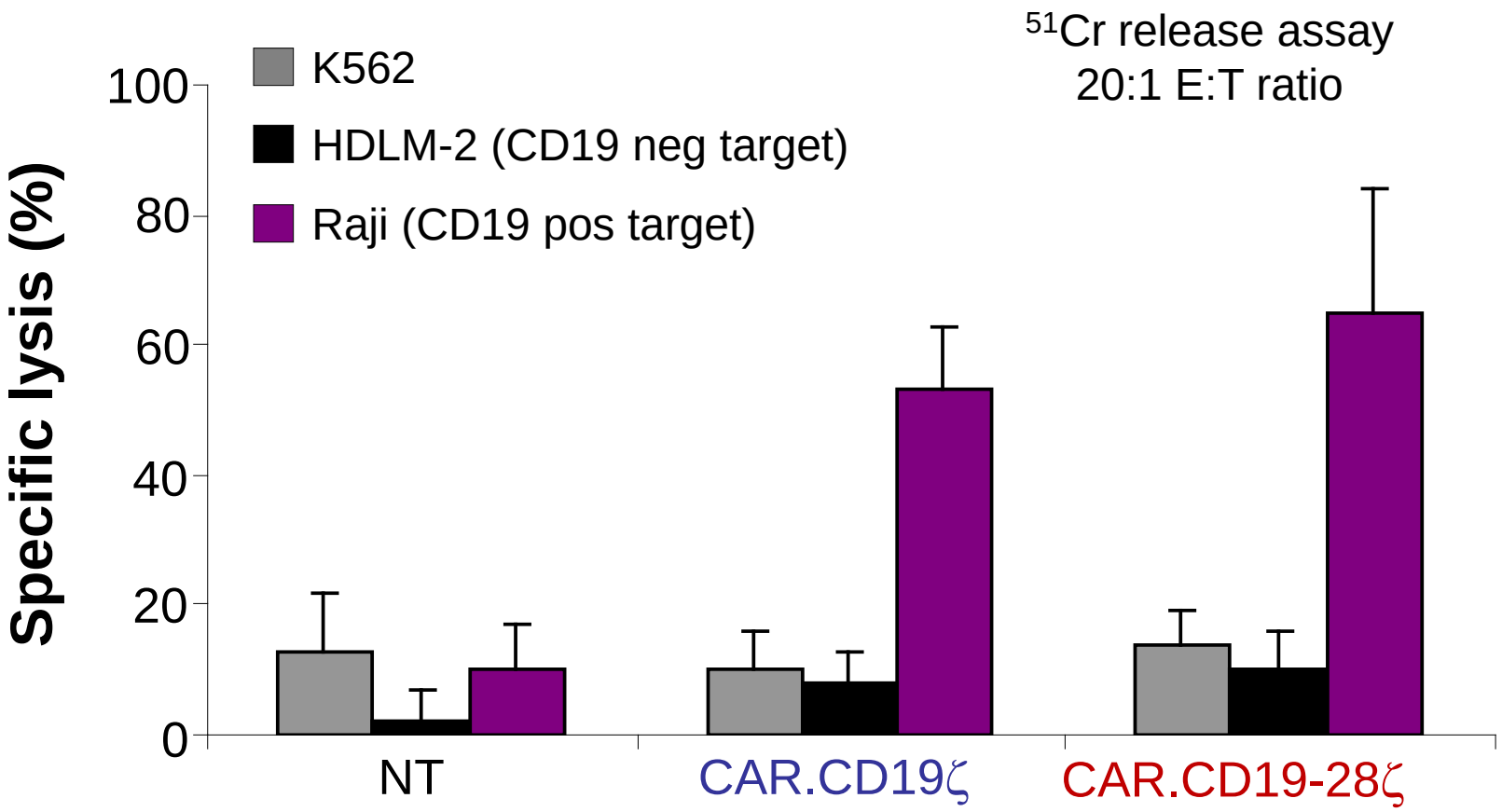
In vitro killing by CAR.CD19 and CAR.CD19-28 T cells is similar



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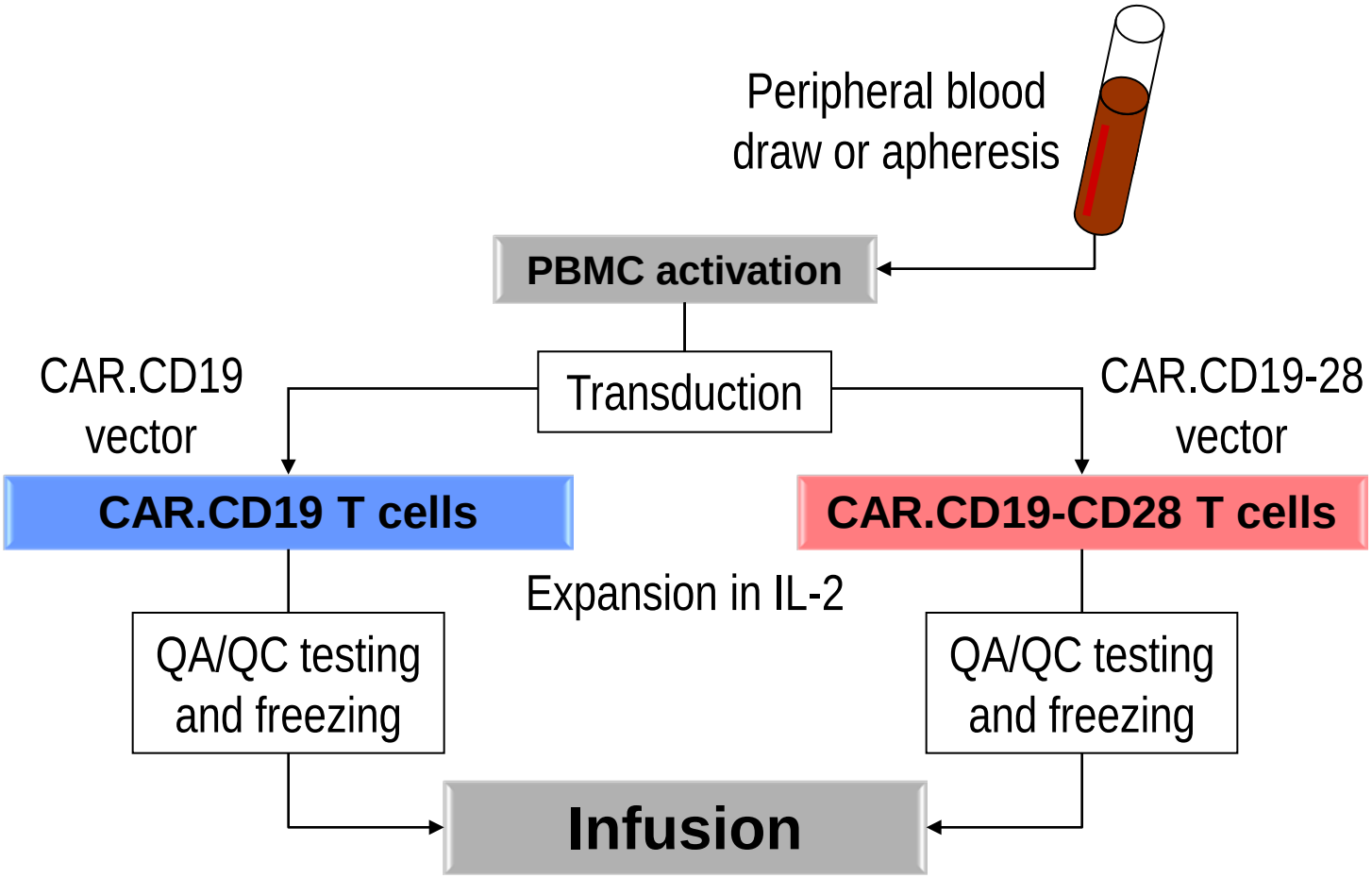
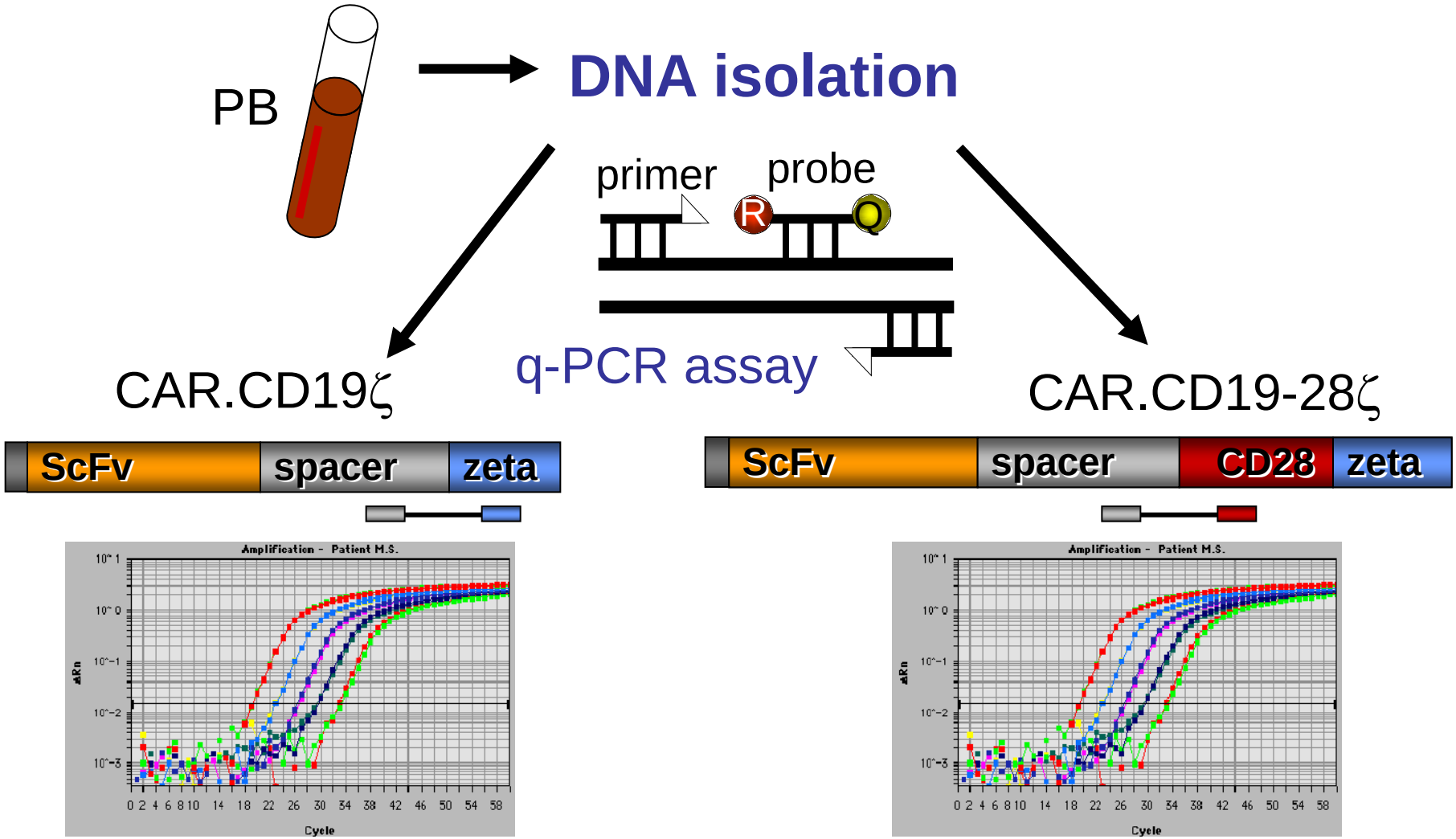
Are CAR-CD28 T cells superior to CAR T cells against CD19? (CRETI-NH)



Treatment plan

- Single infusion
- Three dose levels
- Modified continual reassessment escalation
  - Dose level 1: 2×10^7 cells/m^2 of each product
  - Dose level 2: 1×10^8 cells/m^2 of each product
  - Dose level 3: 2×10^8 cells/m^2 of each product
- Additional infusions allowed if benefit

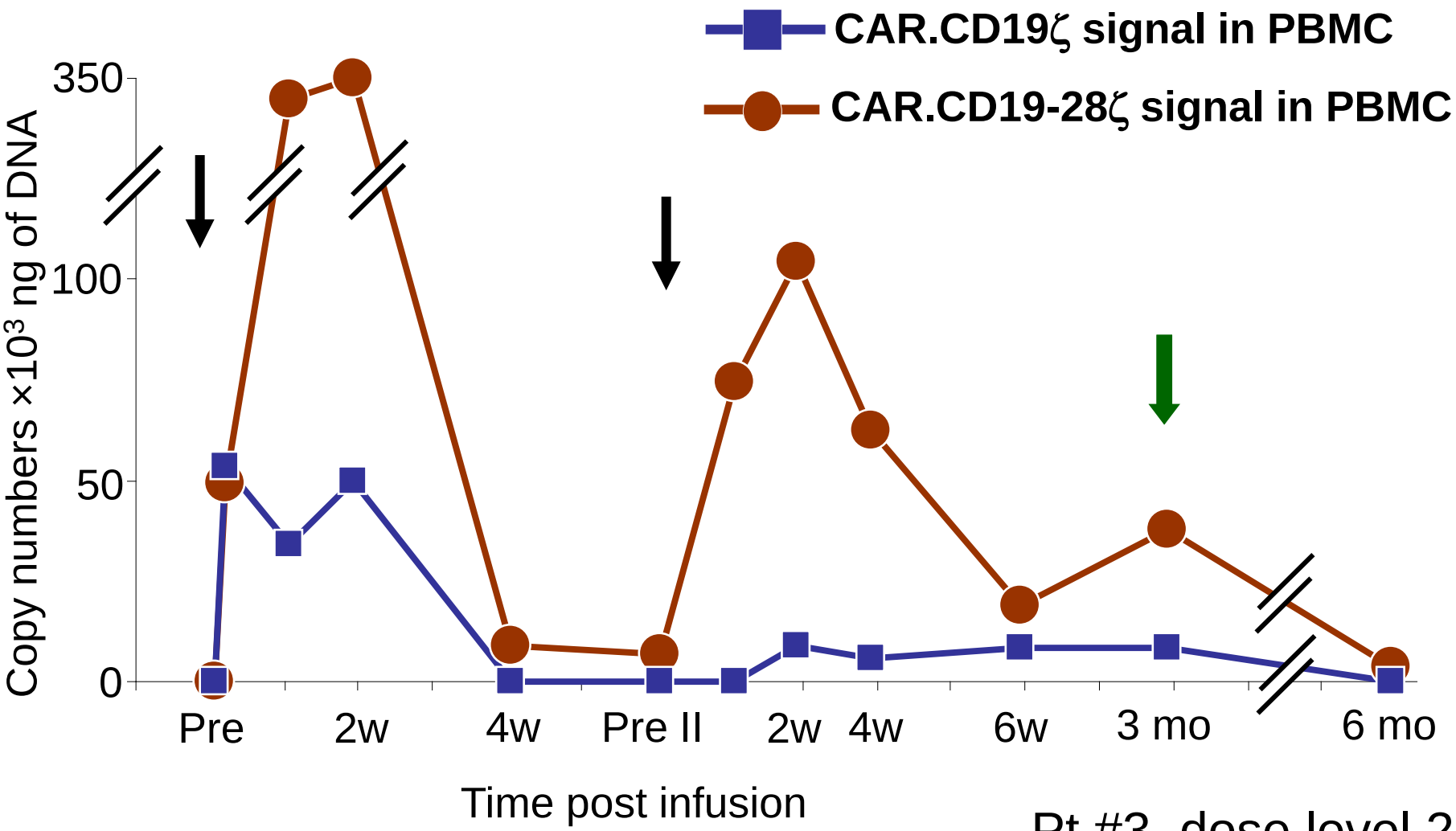
Monitoring expansion and persistence of each product



Patient details

Age	Diagnosis	Previous therapy	Disease status
M/53	B-CLL	FCR, FC	Cervical, axillary, RP, inguinal LAD
M/56	FL→ DLBCL	R-CHOP×8, XRT, FCR×6, R-ICE×2, CDDP/Ara-C, TTR×2	Cervical LAD
M/46	DLBCL	R-CHOP×6, R-ESHAP×4, R-ICE×2, R-IGEV, TTR, R, HyperCVAD×2	Retroperitoneal (RP) lymphadenopathy (LAD)
M/57	DLBCL	R-CHOP×4,R-ESHAP×2, R-BEAM/ASCT, XRT	Cervical, RP LAD
F/59	FL→ DBLCL	R-CHOP×8, R-ESHAP×3, R-BEAM/ASCT, XRT, R	Muscle and skin
M/49	DLBCL CNS & systemic	MTX×4, ESHAP, temozol., R-ICE×6, R-HyperCVAD×2, R-BEAM/ASCT, XRT×2	Brain & RP LAD

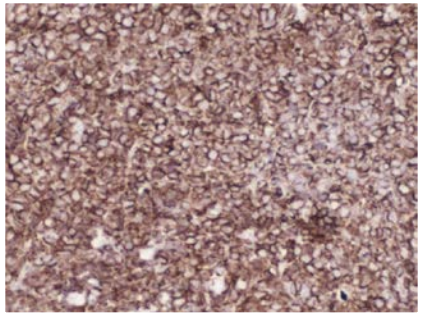
CAR.CD19-28 T cells have greater in vivo expansion and persistence



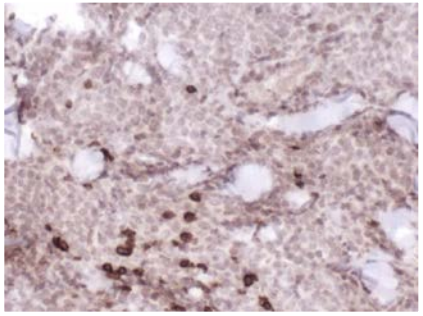
Pt #3, dose level 2

CAR.CD19-28 T cells can be detected in tumor biopsy

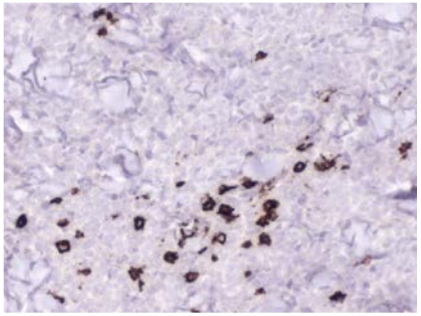
CD20



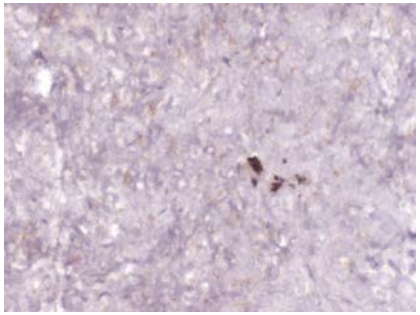
CD3

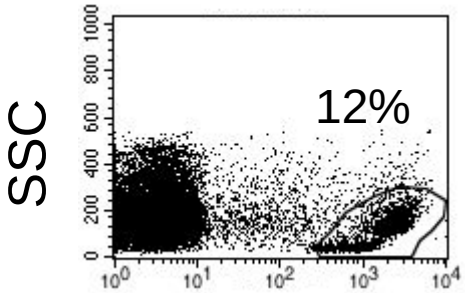


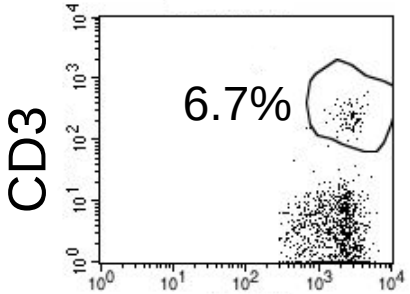
CD8

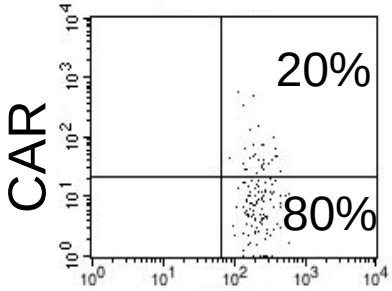


CD4



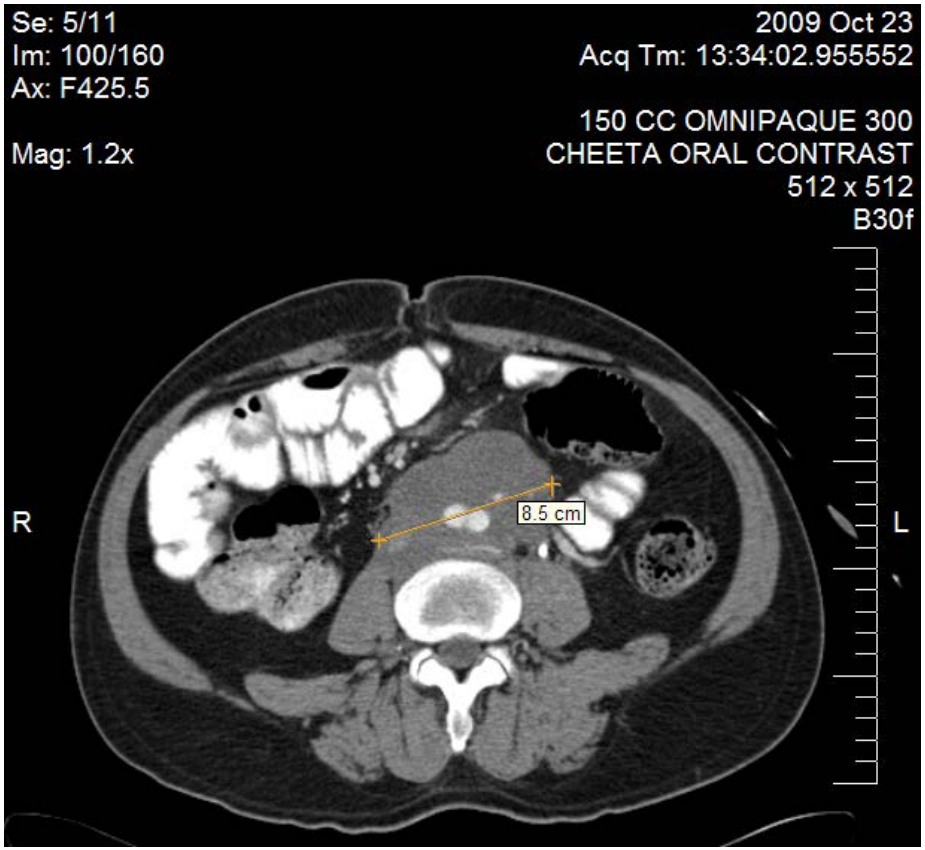




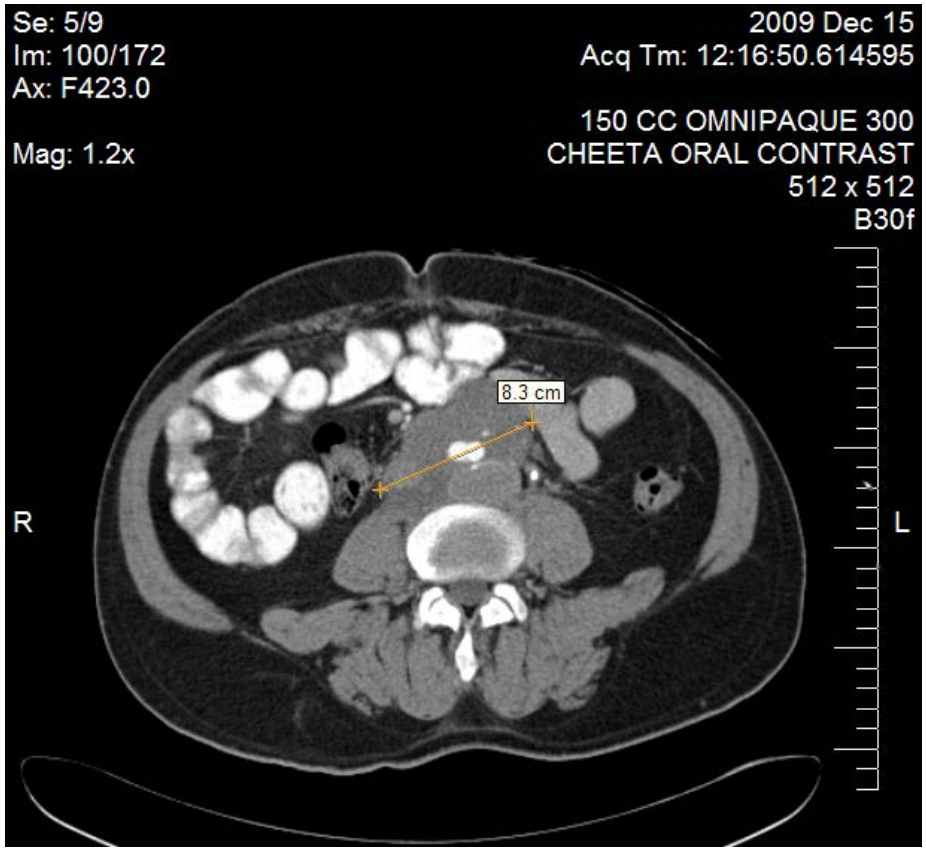


Pt #5, dose level 3

Anti-tumor activity: stable disease



Pre-infusion CT scan



Six-week post-infusion CT scan

Pt #3, dose level 2

Anti-tumor activity: clinical outcome

Pt	Cell dose	Disease at infusion	Clinical response
#1	I: $2\times10^7/m^2$ II: $2\times10^7/m^2$	Cervical, axillary, retroperitoneal, inguinal lymphadenopthy	SD 10 mo post I PD 6 mo post II
#2	I: $2\times10^7/m^2$	Cervical lymphadenopathy	PD 5 wks post I
#3	I: $1\times10^8/m^2$ II: $5\times10^7/m^2$	Retroperitoneal lymphadenopathy	SD 3 mo post I PD 4 wks post II
#4	I: $1\times10^8/m^2$	Cervical, retroperitoneal lymphadenopathy	PD 6 wks post I
#5	I: $2\times10^8/m^2$ II: $2\times10^8/m^2$	Muscle and skin	PD 6 wks post I
#6	I: $2\times10^8/m^2$	Brain & retroperitoneal lymphadenopathy	PD 2 wks post I

PD: progressive disease, SD: stable disease

Summary – CD28 domain

- Adoptive transfer of CAR.CD19^{+} T cells is safe
- CAR.CD19-28+ T cells expand better and persist longer in vivo
- Clinical responses in patients with DLBCL are limited
  - 2 transient stable diseases
  - 1 of 6 patients with PD is in CR at 2 years

(Savoldo, Ramos *et al.*, J Clin Invest 2011)

Improving persistence further

- Activation of homeostatic expansion mechanisms
  - Lymphodepletion prior to adoptive infusion
- Provision of growth factors
  - IL-2
- Blocking negative feedback pathways
  - CTLA-4 antibody

CAR.CD19-CD28 T cells: Lymphodepletion and IL-2

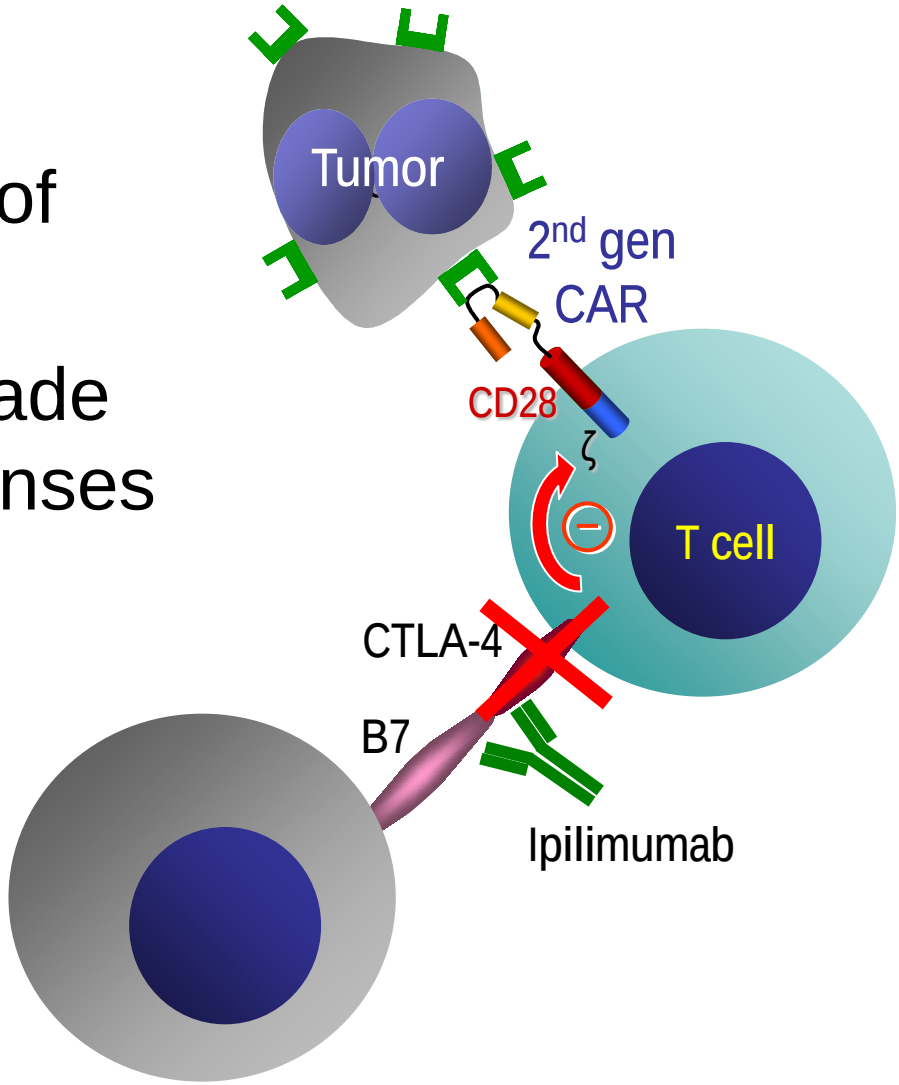
Pt	Dx (Rx)	Status at infusion/Rx	Clinical response
#7 58/M	MCL (hCVAD, ASCT)	CR/day +55 post-ASCT	Continuous complete response 12 mo+
#8 56/M	SLL/CLL (FR, RIT)	Generalized LAD, lymphocytosis/day +4 post-CTX	Stable disease at 6 wks
#9* 84/F	MCL (hCVAD, RB, bortez., XRT)	Cervical LAD/ day +4 post-CTX	Progression at 6 weeks
#10* 65/M	MCL (hCVAD, ASCT)	CR/day +14 post-ASCT	Continuous complete response 6 mo+

*Single patient protocol

- Comparable expansion and persistence, no toxicities

Cytotoxic T-lymphocyte-associated antigen 4

- Homologous to CD28
- Competes with binding of CD80 and CD86
- Triggers inhibitory cascade terminating T-cell responses
- Ipilimumab:
  - mAb that blocks CTLA-4 inhibitory effect
  - Recently approved to treat metastatic melanoma



Experience with ipilimumab

- Pivotal trial used 3 mg/kg q3wk × 4
- Many grade 3-5 autoimmune side effects (~15% patients) (Hodi et al., NEJM 2010)
- Dose ranging phase II study
  - 0.3, 3 and 10 mg/kg q3wk × 4
  - Response rate increased w/ dose (0, 4, 11%)
  - Side effects increased w/ dose (1, 8, 24%)

(Wolchok et al., Lancet Oncol 2010)

Treatment proposed in current amendment

- Use CTLA-4 Ab to increase persistence and expansion of CAR-T cells
- To reduce the risk of toxicity, we will use 25% (0.75 mg/kg) of approved dose × 1
  - Above 0.3 but still below 3
- Administration will coincide with follow-up clinic visit at 2 weeks (peak expansion)

Acknowledgements

Malcolm Brenner
Cliona Rooney
Helen Heslop

Barbara Savoldo
Gianpietro Dotti
Catherine Bollard
George Carrum
Rammurti Kamble
Martha Mims
Michael Keating

Clinical Research
Vicky Torrano
Bambi Grilley
Alicia Brown
Florence Noel

Statistical analysis
Hao Liu

GMP Laboratory
Adrian Gee
Oumar Diouf
Zhang Huimin
Joyce Ku
Weili Liu
Pallavi Mahopatra

Enli Liu
Debbie Lyon
Zhuyong Mei

Funding: Lymphoma SPORE, Leukemia and Lymphoma SCOR, CLL Global Research Foundation, ASCO Career Development Award