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CD19 CAR T “Booster” T-Antigen Presenting Cells (T-APCs)

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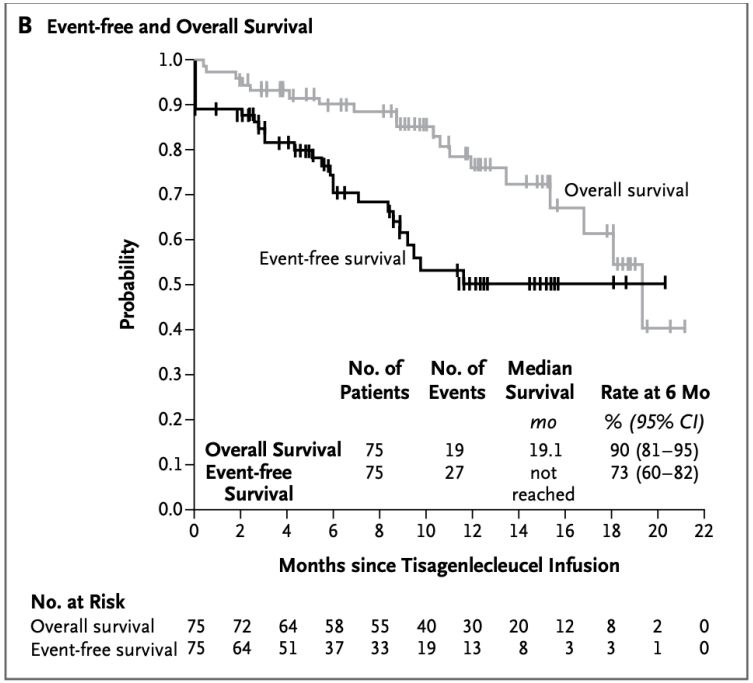
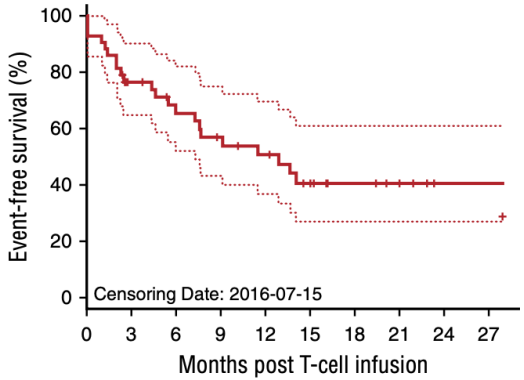
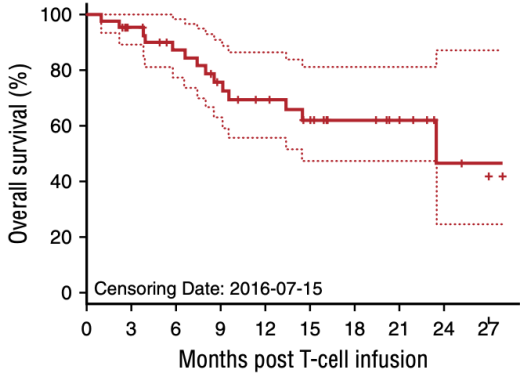
Seattle Children’s Hospital

CD19 targeting CAR T cell therapy in B-ALL: Effectively induces remissions; recurrences still a problem



Maude et al. NEJM 2018





Gardner et al. Blood 2017

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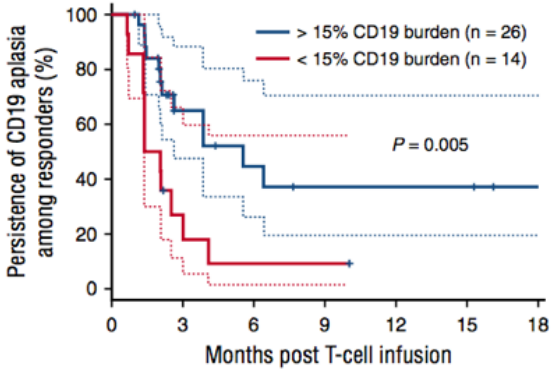
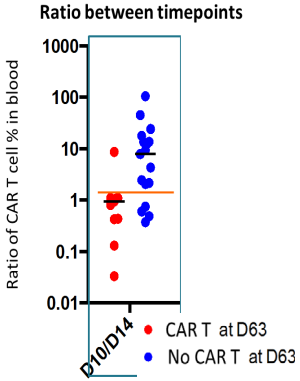
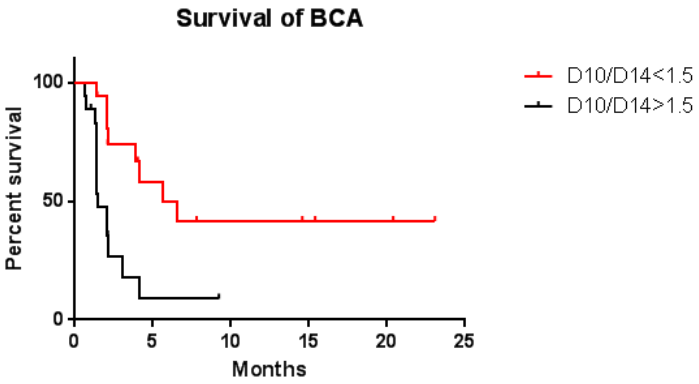
Risk factors for early loss of persistence



Gardner et al. Blood 2017

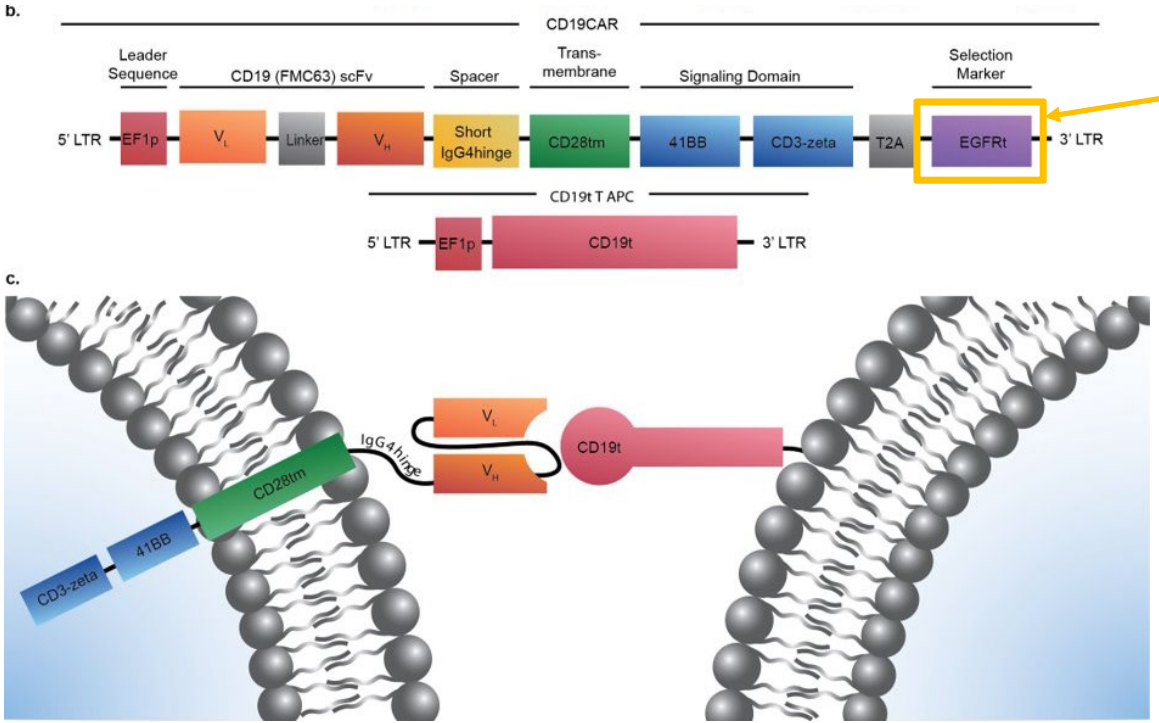




unpublished data

- *Hypothesis:* Episodic antigen stimulation could promote reactivation and expansion of functional CAR T cells, possibly leading to enhanced persistence and durable remissions

CD19 expressing T-APCs: novel approach to overcome low antigen burden



"Tag" for detection of CAR+ cells

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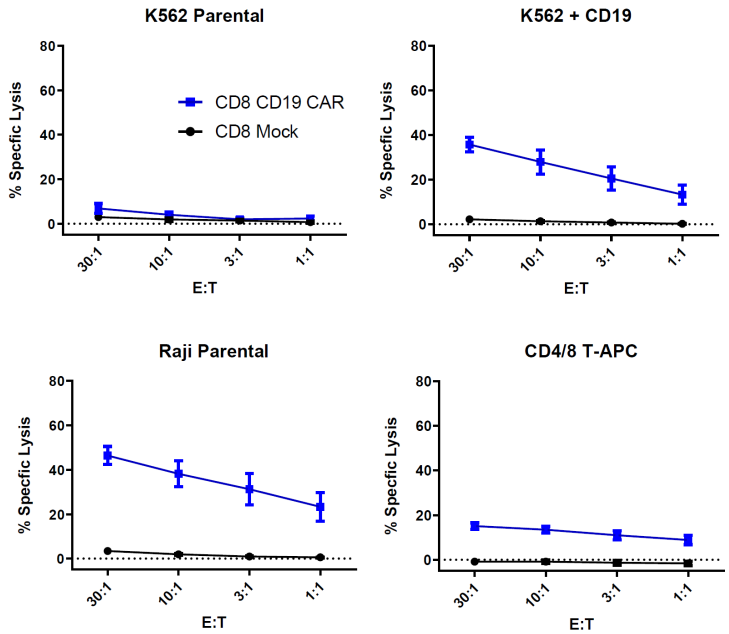
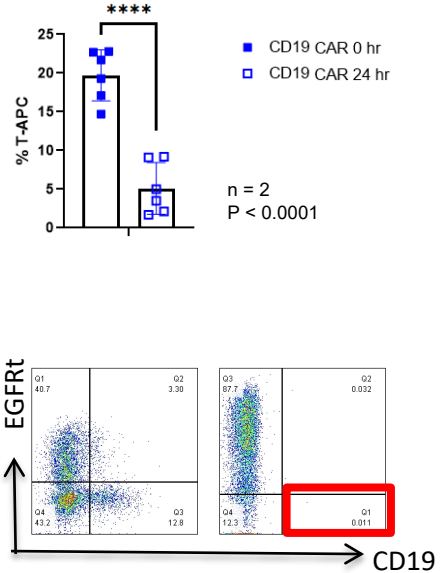
CD19 T-APCs are targeted by CD19 CAR in vitro, inducing cytokine production

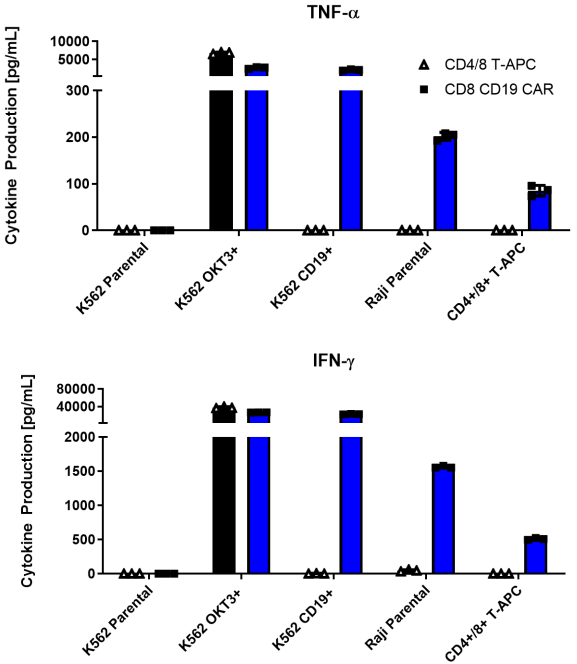
A. Chromium release assay



B. CD19 CAR + T-APC co-culture



C. Cytokine production



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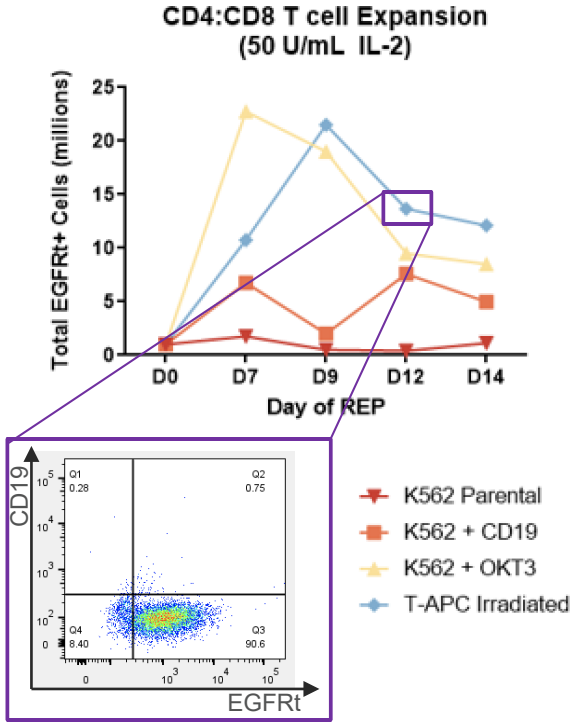
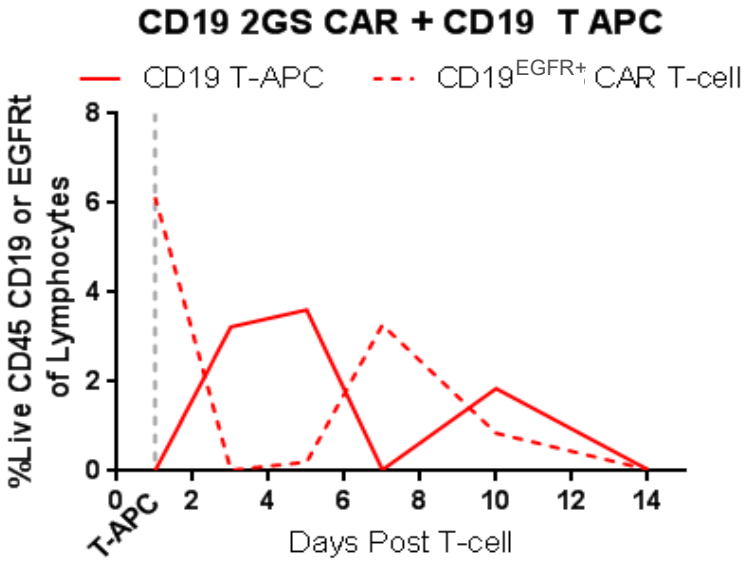
CD19 T-APCs expand CD19 CARs in vitro and in vivo





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PLAT-03: Pilot study of CAR19 + CD19t T-APCs

CD19t T-APC Manufacturing Platform

Cryopreserved CD4/CD8 T cells are thawed and activated with anti-CD3/CD28

↓

Transduce CD4/CD8 cells with CD19t T-APC lentiviral vector

↓

Expand CD4/CD8 T-APC in culture (+rh-IL2)

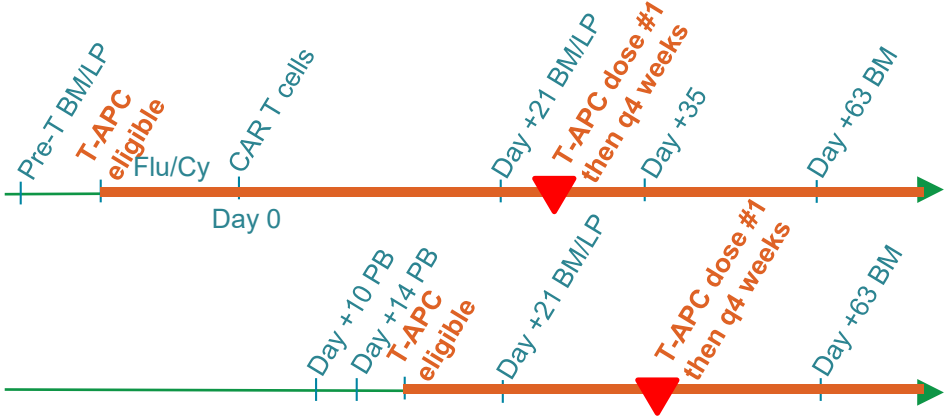
10-day culture

↓

Cryopreserved CD4/CD8 T-APC

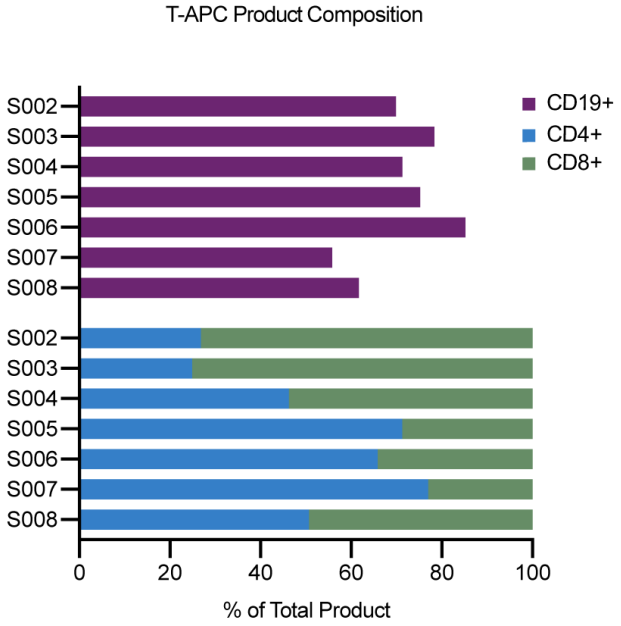
Cohort A:
low antigen burden

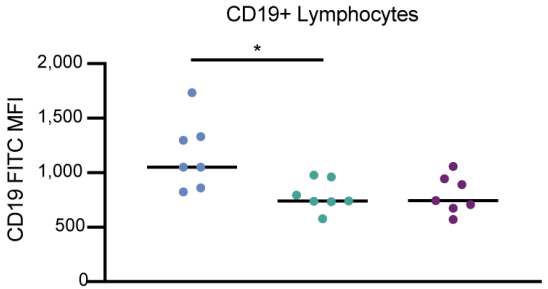
Cohort B:
rapid contraction

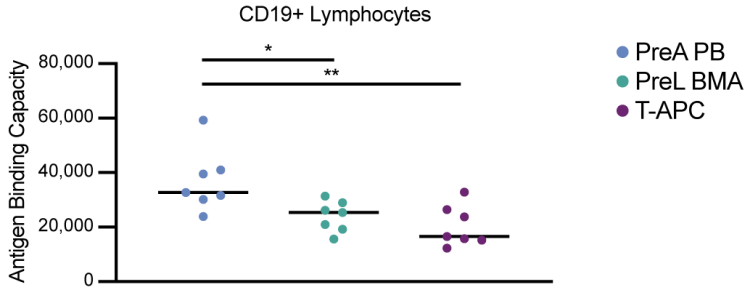


- SCRI-CAR19:
  - $1x10^6$ CAR+ cells/kg
- T-APC dose:
  - ≥ 25kg: $5x10^8$ flat
  - <25kg: $10x10^6$/kg
- Design:
  - Up to **6 doses** T-APCs q4weeks
  - Must demonstrate BCA prior to each dose

Characterization of clinical T-APC products: CD19 expression







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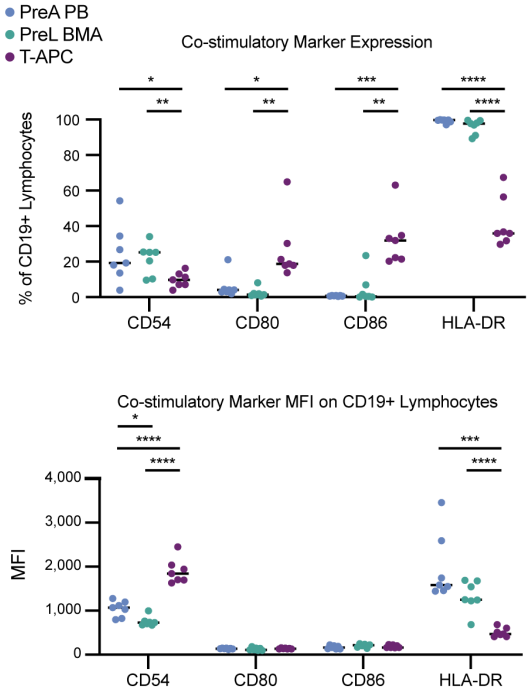
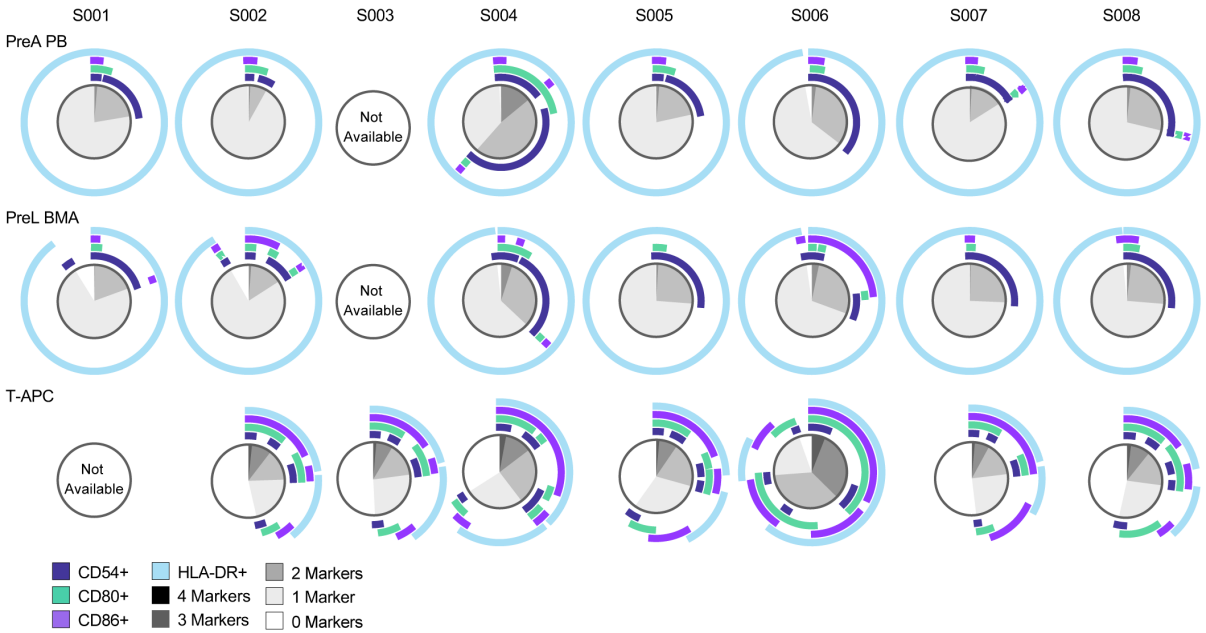
Characterization of clinical T-APC products: co-stimulatory markers





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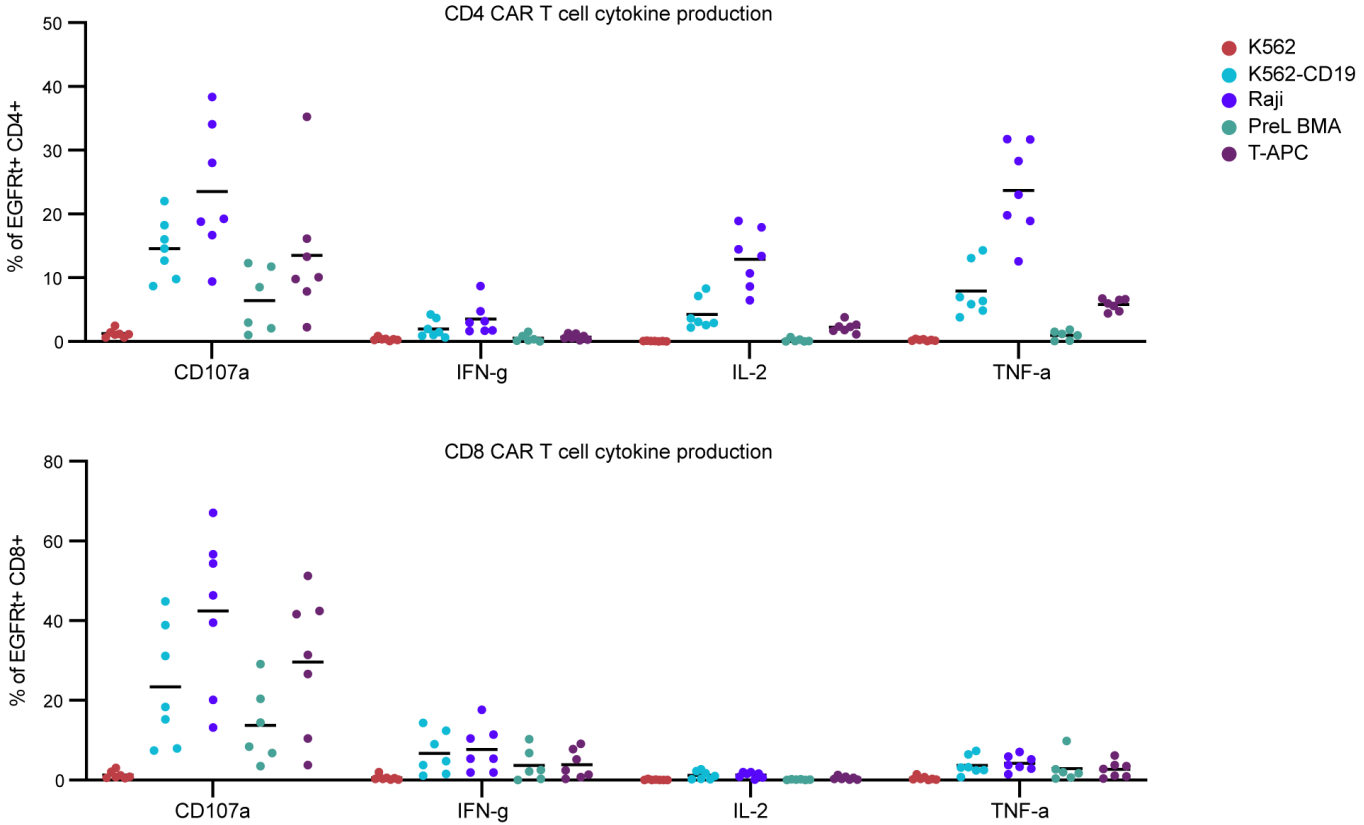
CD19 CAR T cell cytokine production induced by various CD19 targets, including CD19 T-APC products



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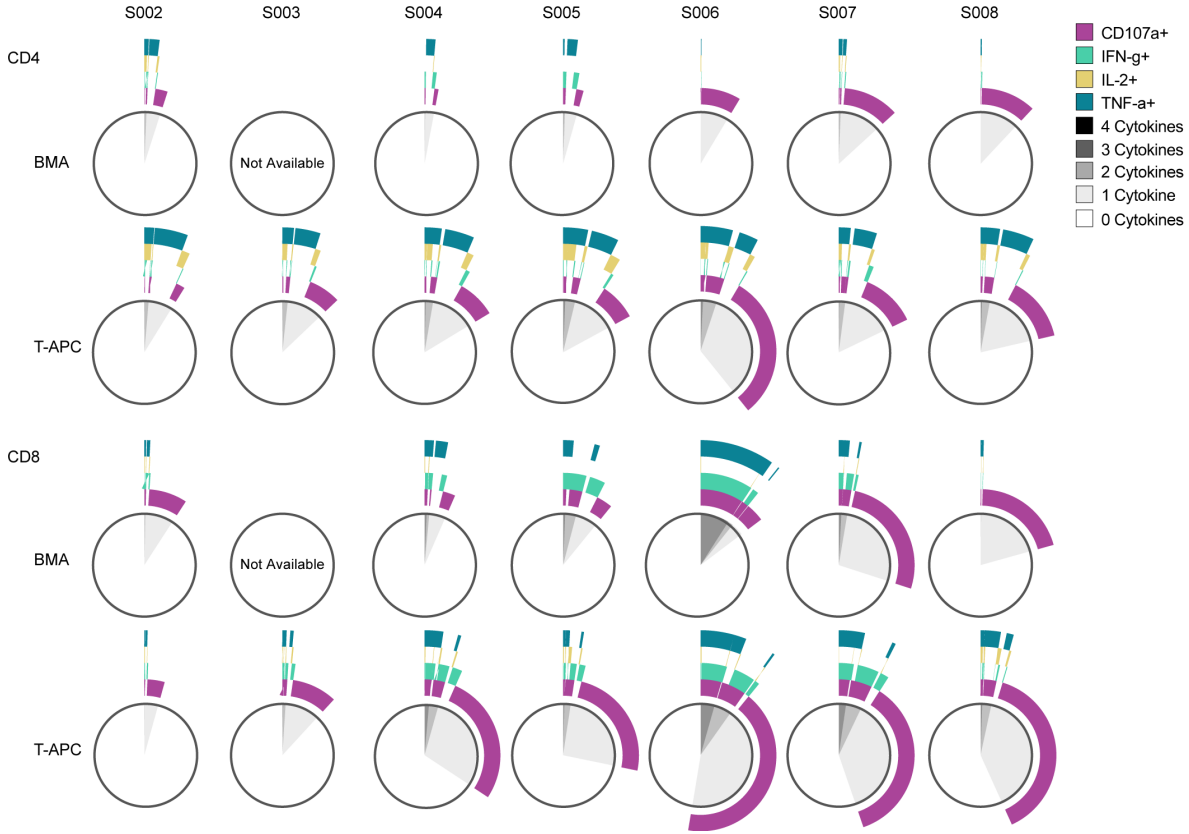
CD19 CAR T cell cytokine production induced by autologous bone marrow and CD19 T-APC products



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Clinical experience: T-APCs successfully manufactured and well tolerated without CRS or neurotoxicity

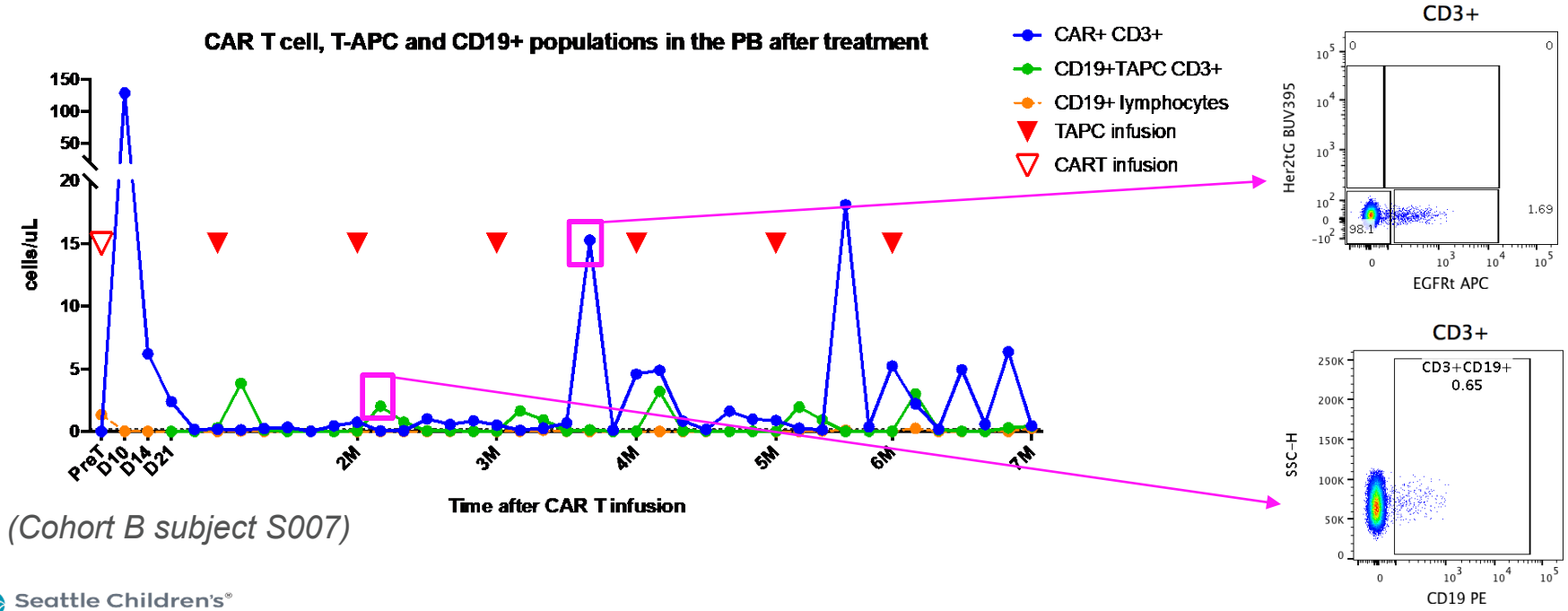
Cohort Details		T-APC manufacture		# subjects treated with T-APCs	Toxicity events (of those followed until D28 after final T-APC dose)
Cohort	Assigned	Product generated	Mean # doses made		
A	10	10/10	5.0	**9/10**	0/9
B	9	**8/9**		8/8	**1/6**

- 1 toxicity event: grade 3 infusion reaction
- No evidence of cytokine release syndrome (CRS) or neurotoxicity
- 2 Cohort B subjects still receiving T-APCs

unpublished data

T-APCs trigger subsequent expansion(s) of CAR T cells

- CAR T cells (blue) are re-expanded in peripheral blood after T-APC doses (▼)
- T-APCs (green) are transiently detected



(Cohort B subject S007)

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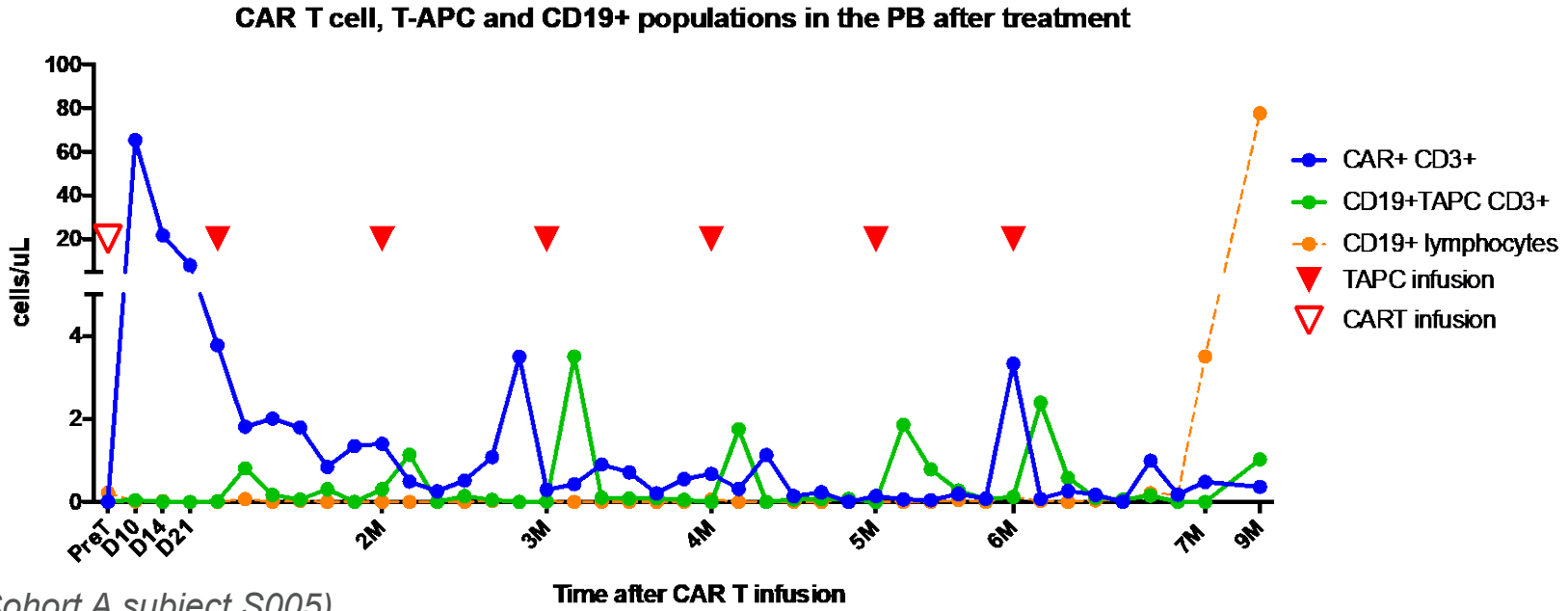
Loss of B cell aplasia, 2 months after completing T-APCs

- CD19+ B cells are shown in orange



(Cohort A subject S005)

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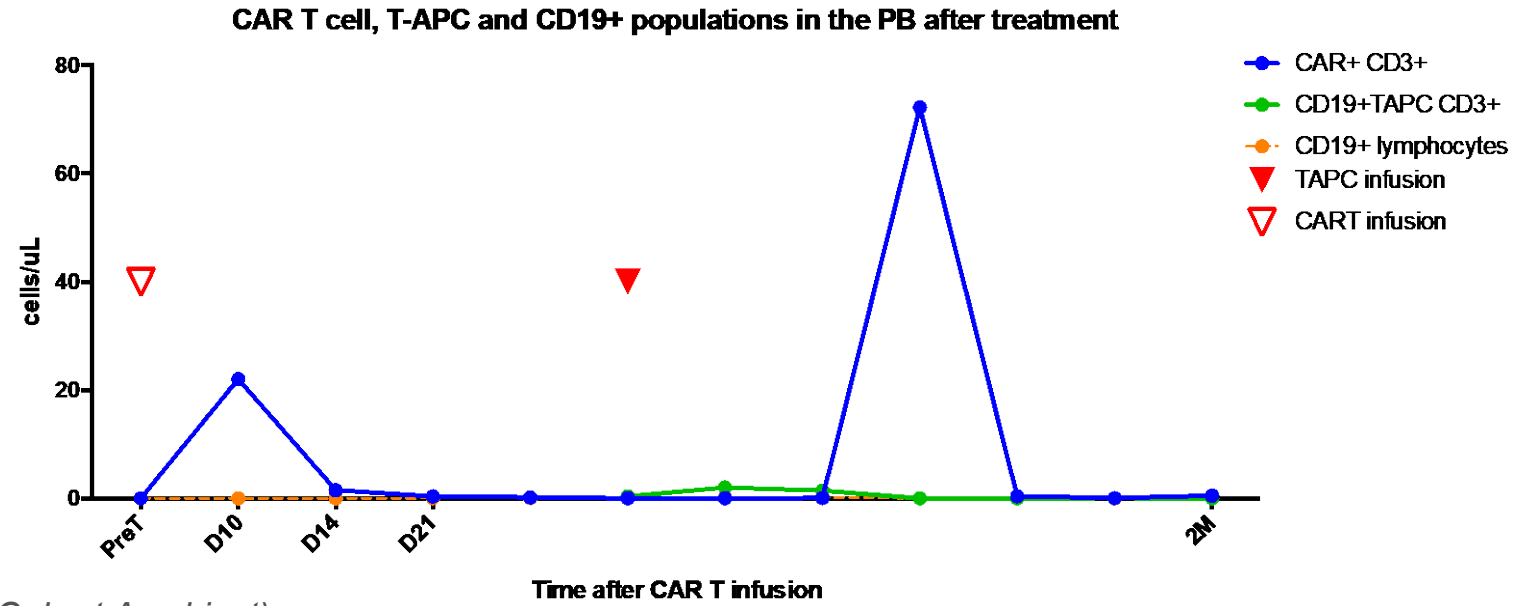
3/15 treated demonstrated higher CAR+ engraftment following T-APCs than after the initial CAR infusion

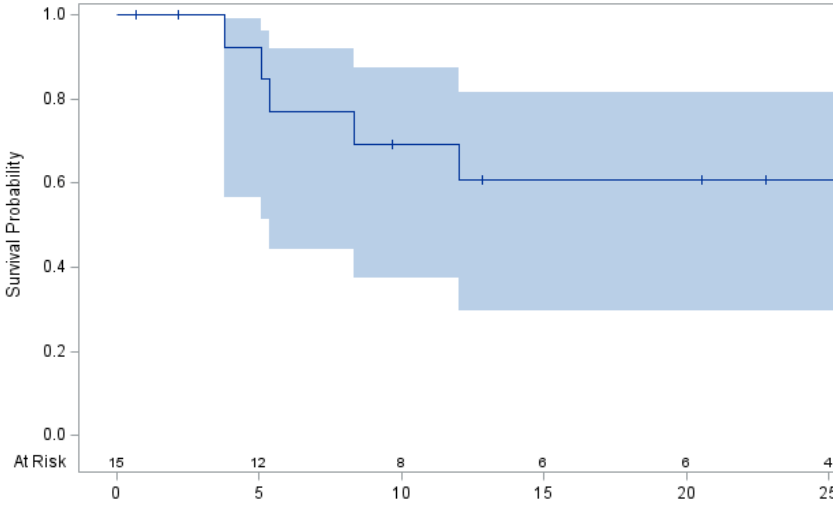


(Cohort A subject)

LFS and BCA to date for PLAT-03 subjects (n = 15)

Leukemia-Free Survival: PLAT-03 Cohort A/B

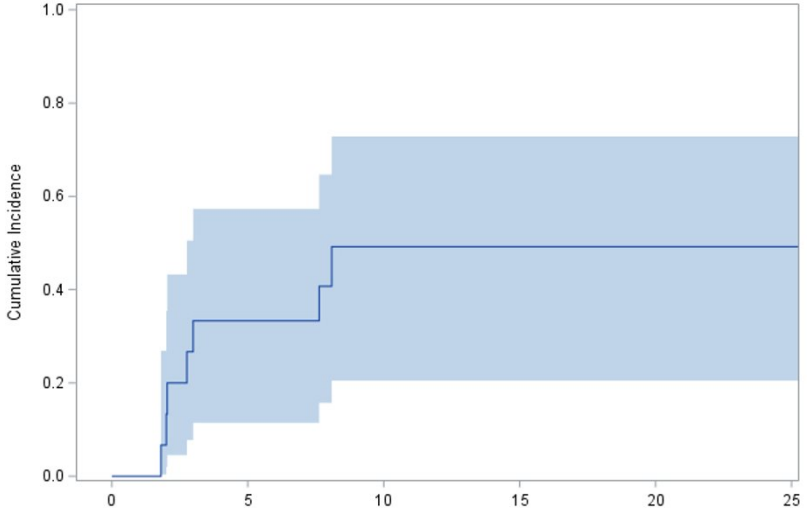
with number of subjects at risk and 95% confidence limits



Months since achieving MRD-CR*

Loss of BCA: PLAT-03 Cohort A/B

with 95% confidence limits



Months since CAR T infusion

*if subject was in MRD-CR at CAR T infusion, t_0=CAR T infusion date

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Conclusions and Next steps for T-APCs

- CD19t T-APCs are successfully manufactured from stored apheresis products and have been well tolerated to date without significant associated toxicity
- CD19t T-APCs can induce episodic re-expansion of CD19 CAR T cells in patients
- Longer follow up may elicit a signal whether CD19t T-APCs enhance persistence and lead to more durable remissions in B-ALL; a randomized trial is the next step
- With future T-APC dosing, we aim to establish a platform to prospectively interrogate the phenotype of CAR T cells during these secondary

Acknowledgements

PLAT-Study Committees
Rebecca Gardner
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Our patients and families