Optimizing Durability of Allogeneic CAR T Therapy in Non-Hodgkin Lymphoma: Update on 1ˢᵗ and 2ⁿᵈ Gen CD19 Programs

June 4, 2021

Forward Looking Statements

This presentation (together with any other statements or information that we may make in connection herewith) contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. All statements contained in this presentation (together with any other statements or information that we may make in connection herewith) that do not relate to matters of historical fact should be considered forward-looking statements, including, without limitation, statements regarding the expected timing of clinical updates and interim updates related to PBCAR0191, the expected timing of clinical updates and interim updates related to PBCAR19B, the expected timing of clinical updates and interim updates related to PBCAR20A, the expected timing of clinical updates and interim updates related to PBCAR269A, clinical studies of our CAR T product candidates and our *in vivo* gene correction program; expected milestones for 2021; and the potential success, efficacy and capabilities of our product candidates. In some cases, you can identify forward-looking statements by terms such as "aim," "anticipate," "believe," "could," "expect," "should," "plan," "intend," "estimate," "target," "mission," "goal," "may," "will," "would," "should," "could," "target," "potential," "project," "predict," "contemplate," "potential," or the negative thereof and similar words and expressions.

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All forward-looking statements speak only as of the date of this presentation, and except as required by applicable law, we have no obligation to update or revise any forward-looking statements contained herein, whether as a result of any new information, future events, changed circumstances or otherwise. This presentation may also contain estimates, projections, and/or other information regarding our industry, our business and the markets for certain of our product candidates, including data regarding the estimated size of those markets, and the incidence and prevalence of certain medical conditions. Unless otherwise expressly stated, we obtained this industry, business, market and other data from reports, research surveys, clinical trials, studies and similar data prepared by market research firms and other third parties, from industry, medical and general publications, and from government data and similar sources. Information that is based on estimates, forecasts, projections, market research, or similar methodologies is inherently subject to uncertainties and actual events or circumstances may differ materially from events and circumstances reflected in this information.

Presentation Agenda

Introduction

-Matt Kane, Chief Executive Officer

PBCAR0191 Updated Interim Results

-Alan List, M.D., Chief Medical Officer

PBCAR19B Stealth Cell Update

-Derek Jantz, Ph.D., Chief Scientific Officer and Co-Founder

Closing and Q&A

Delivering on the Promise of Therapeutic Genome Editing

ARCUS® Genome Editing Platform
built for translation with full freedom to operate

Allogeneic CAR T
platform validated with clinical response and safety data

***In Vivo* Gene Correction**
pipeline seeking to cure genetic and infectious diseases
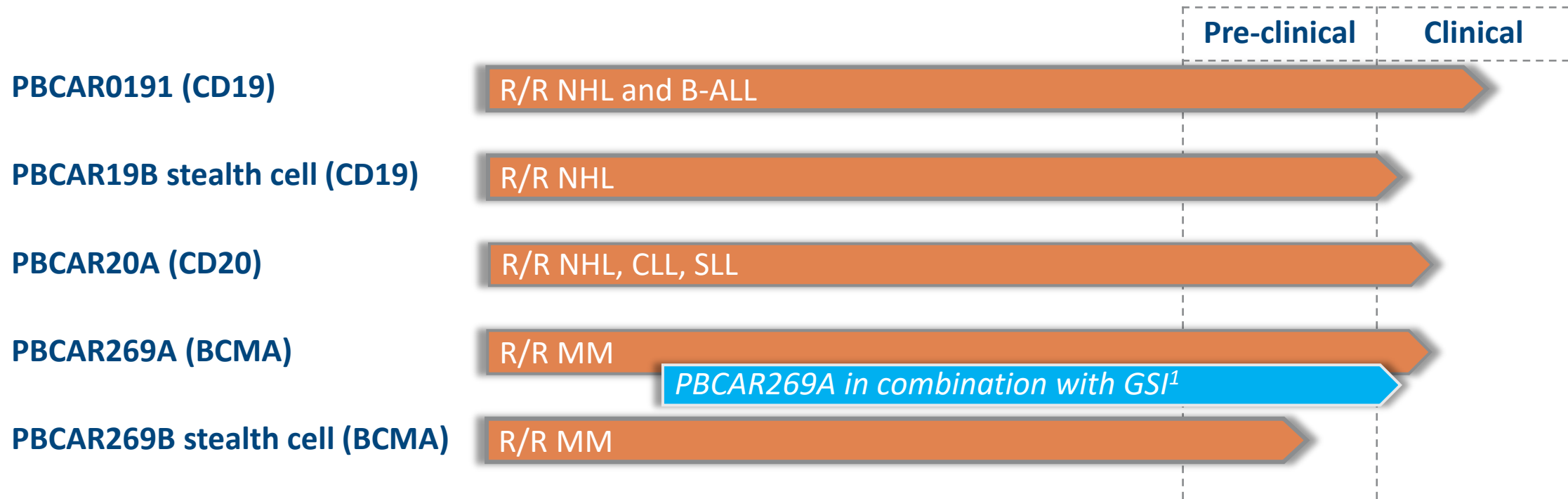
Pioneers in Genome Editing

cGMP Manufacturing
scalable, in-house capabilities
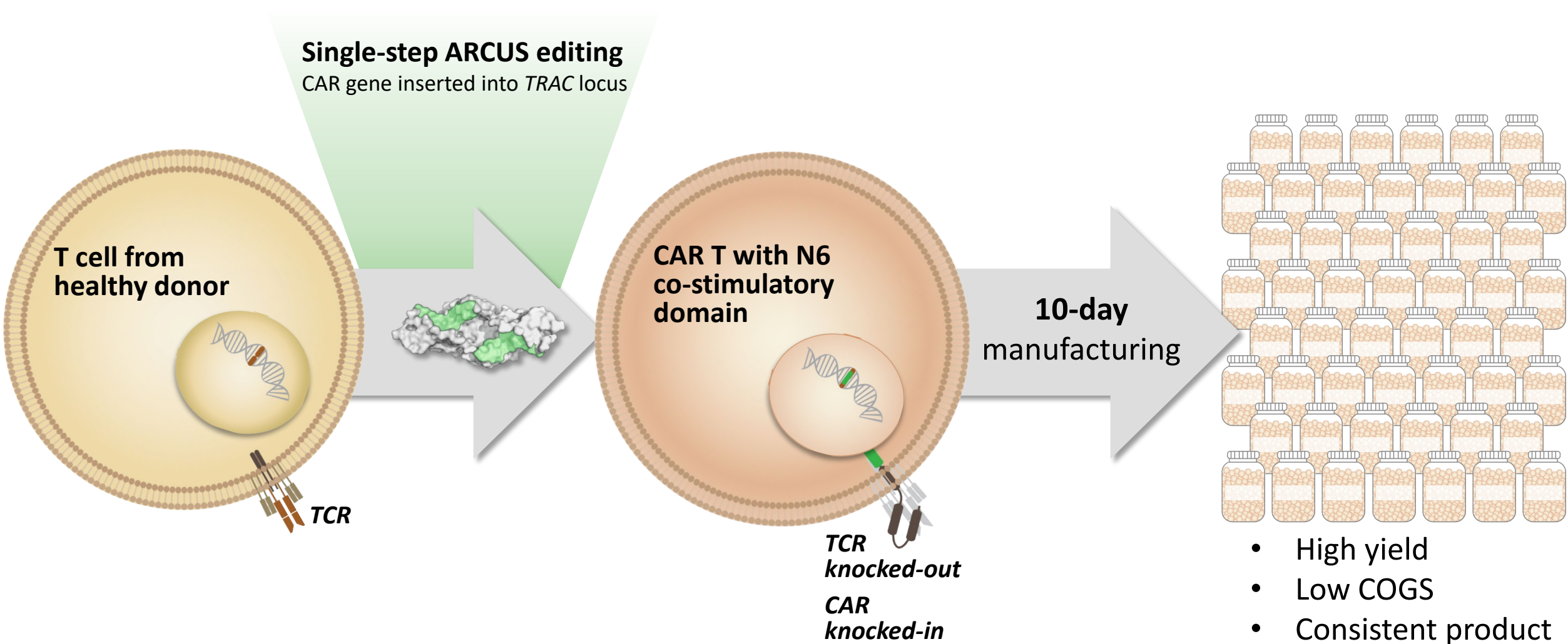
Precision BioSciences Allogeneic CAR T Pipeline

✓ PBCAR19B stealth cell clinical trial open for enrollment
✓ Progressed Phase 1/2a studies for PBCAR20A for non-Hodgkin lymphoma (NHL) and B-cell acute lymphoblastic leukemia (B-cell ALL) and PBCAR269A for multiple myeloma (MM) to Dose Level 3
✓ Expect to dose first patient in PBCAR269A in combination with gamma secretase inhibitor (GSI) in 1H/2021
✓ Initiated IND enabling studies for PBCAR269B (anti-BCMA stealth cell)

		Pre-clinical	Clinical
PBCAR0191 (CD19)	R/R NHL and B-ALL		
PBCAR19B stealth cell (CD19)	R/R NHL		
PBCAR20A (CD20)	R/R NHL, CLL, SLL		
PBCAR269A (BCMA)	R/R MM	*PBCAR269A in combination with GSI[1]*	
PBCAR269B stealth cell (BCMA)	R/R MM		

[1] In combination with gamma secretase inhibitor from SpringWorks Therapeutics

Key Features of Precision's Allogeneic CAR T Platform

Single-step ARCUS editing
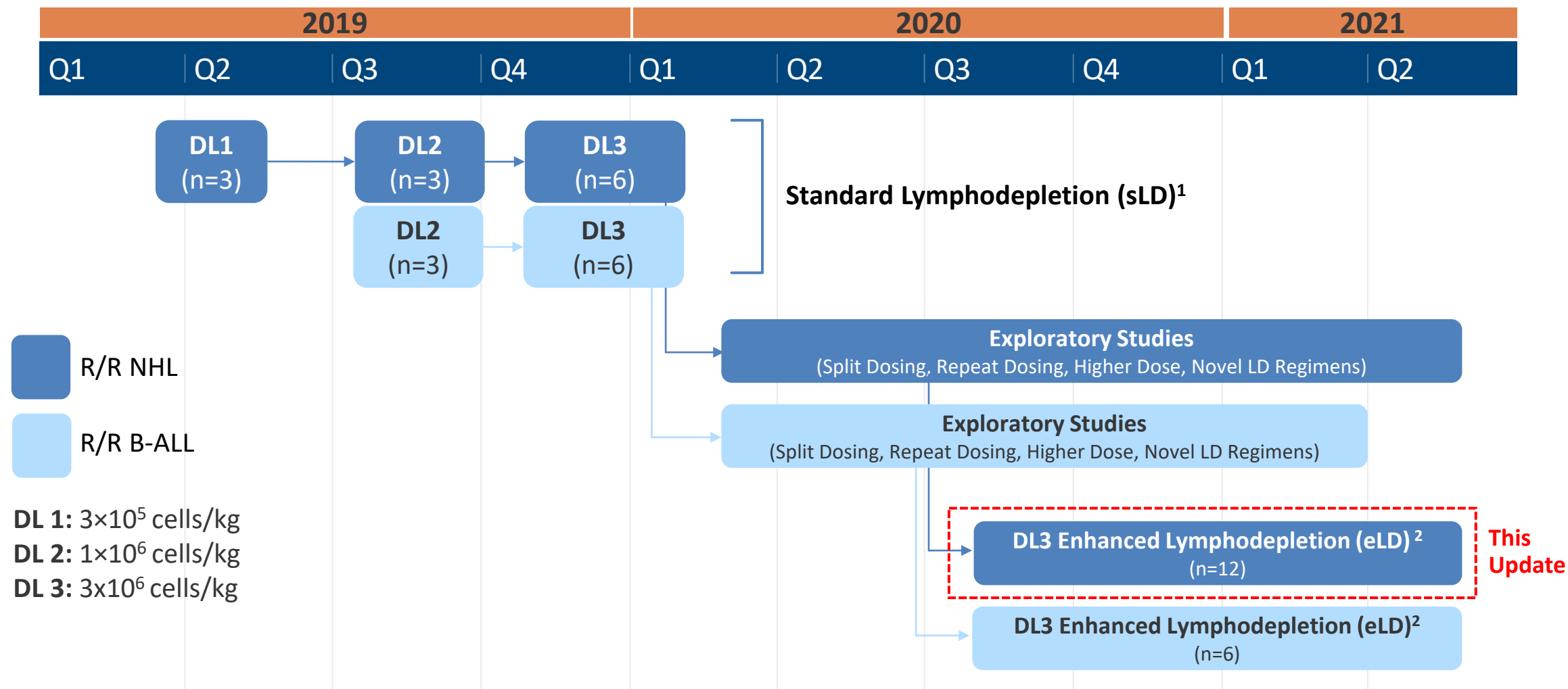CAR gene inserted into *TRAC* locus

T cell from healthy donor

TCR

CAR T with N6 co-stimulatory domain

TCR knocked-out

CAR knocked-in

10-day manufacturing

- High yield
- Low COGS
- Consistent product

PBCAR0191 Updated Interim Results

Alan List, M.D.

Chief Medical Officer, Precision BioSciences

PBCAR0191 Study Overview

	2019				2020				2021	
Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	

DL1 (n=3) → **DL2** (n=3) → **DL3** (n=6)

DL2 (n=3) → **DL3** (n=6)

Standard Lymphodepletion (sLD)[1]

R/R NHL

R/R B-ALL

DL 1: 3×10^5 cells/kg
DL 2: 1×10^6 cells/kg
DL 3: 3×10^6 cells/kg

Exploratory Studies
(Split Dosing, Repeat Dosing, Higher Dose, Novel LD Regimens)

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(Split Dosing, Repeat Dosing, Higher Dose, Novel LD Regimens)

DL3 Enhanced Lymphodepletion (eLD)[2]
(n=12)

This Update

DL3 Enhanced Lymphodepletion (eLD)[2]
(n=6)

[1]Fludarabine 30 mg/m^2/day x 3 days + Cyclophosphamide 500 mg/m^2/day x 3 days
[2]Fludarabine 30 mg/m^2/day x 4 days + Cyclophosphamide 1000 mg/m^2/day x 3 days

Findings from Standard Dose Lymphodepletion

- No dose-limiting toxicity in Dose Levels (DL) 1-3 using standard lymphodepletion

- No Grade 3 or greater immune effector cell-associated neurotoxicity (ICANs) or cytokine release syndrome (CRS)

- No evidence of graft versus host disease (GvHD)

- Dose-dependent increase in CAR T expansion with modest peak and rapid attrition attributed to CAR T cell rejection

- Clear evidence of CAR T activity but limited durability

Enhanced Lymphodepletion in R/R NHL

Screening | **Follow-up** | **Long-Term Follow-Up**

Enhanced LD (eLD):

Fludarabine 30 mg/m²/day x 4 days plus

Cyclophosphamide 1000 mg/m²/day x 3 days

PBCAR0191

DL3: 3×10^6 cells/kg

- **Objectives**
  - Mitigate host immune rejection to improve CAR T cell expansion and persistence
  - Increase frequency and durability of Complete Responses (CRs)
  - Assess safety (e.g., Grade ≥3 CRS or ICANS)
  - Evaluate activity in patients with prior autologous CD19 CAR therapy

- **Eligibility (≥2 prior chemotherapies)**
  - DLBCL including Richter's transformation
  - Primary mediastinal B-cell lymphoma (PMBL)
  - FL including Grade 3B or transformed FL
  - High-grade B-cell lymphoma
  - Small lymphocytic lymphoma (SLL)
  - Mantle cell lymphoma (MCL)

- **Inclusion/exclusion criteria modified** to exclude patients with prolonged cytopenia or serious infection within 30 days prior to enrollment

- **8 additional NHL subjects enrolled in eLD cohort** since December 2020 interim update (total = 12)

Subjects Enrolled with Advanced and Aggressive R/R NHL

- Over 80% of subjects had aggressive lymphomas

- Median and mean of ~7 lines of prior NHL therapy

- 4 subjects (33%) had prior CD19 directed CAR treatment

- Median time from eligibility confirmation to start of treatment (LD) was 1 day

		eLD (n=12)
Age (y) median (min-max)		57 (34-76)
Subtype n (%)	Diffuse Large B-Cell	7 (58%)
	CLL/Richter's Trans.	2 (17%)
	High grade Lymphoma	1 (8%)
	Follicular Lymphoma	2 (17%)
R/R n (%)	Refractory	3 (25%)
	Relapsed	9 (75%)
Stage n (%)	III/IV	9 (75%)
Extranodal disease n (%)		5 (45%)
Median lines of prior therapy n (min,max)		7 (2,15)
Prior CD19 CAR n (%)		4 (33%)
Prior auto-SCT n (%)		6 (50%)
LDH > ULN n (%)		10 (83%)
Ki-67 Median (min-max) (%)		60 (10-90)[1]
SPPD (cm^2) Median (min-max)		27.0 (0-256)

AESI* Profile with eLD vs. Standard Lymphodepletion

Data cutoff of May 21, 2021 for R/R NHL subjects treated at DL3 with Day 28 evaluation (N=18)

Adverse Event Max Grade		sLD (n=6)	eLD (n=12)
CRS *(Cytokine release syndrome)*	Grade 1 or Grade 2	3 (50%)	7 (58%)
	Grade 3 or higher	0	0
ICANS *(Immune effector cell-associated neurotoxicity)*	Grade 1 or Grade 2	2 (33%)	3 (25%)
	Grade 3 or higher	0	1 (8%)
GvHD *(Graft versus host disease)*		0	0
Neutropenia	Grade 3 or higher	0	2 (17%)
	Grade 3+ at Day 28	0	2 (17%)
Infection	Grade 1 or Grade 2	0	1 (8%)
	Grade 3 or higher	0	3 (25%)

Treatment emergent deaths without disease progression: 2 sepsis** (1 deemed possibly related to treatment by investigator, previously disclosed); 1 cardiac arrest after choking incident

*AESI denotes Adverse Events of Special Interest
**One patient received 10 lines and another patient received 15 lines of prior therapy

PBCAR0191 CAR T Cell Expansion in Peripheral Blood
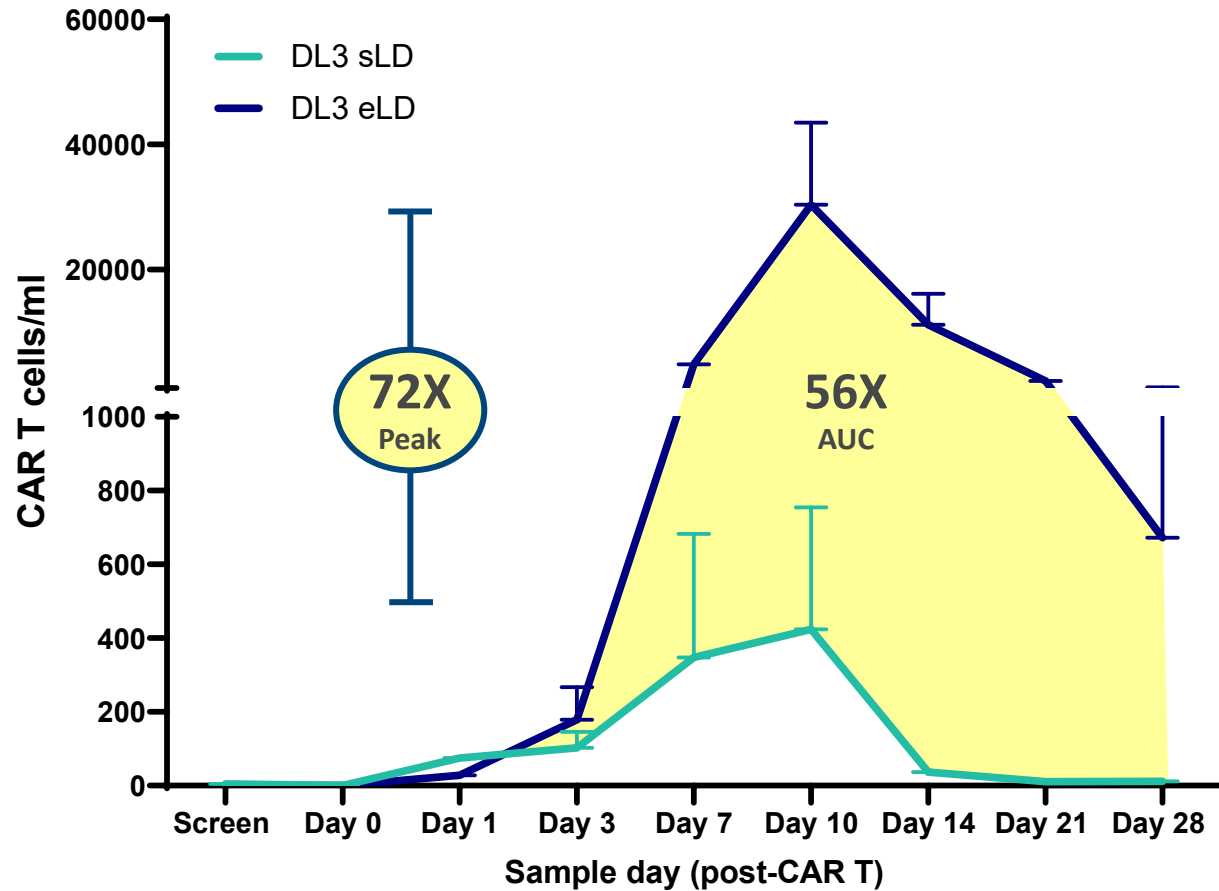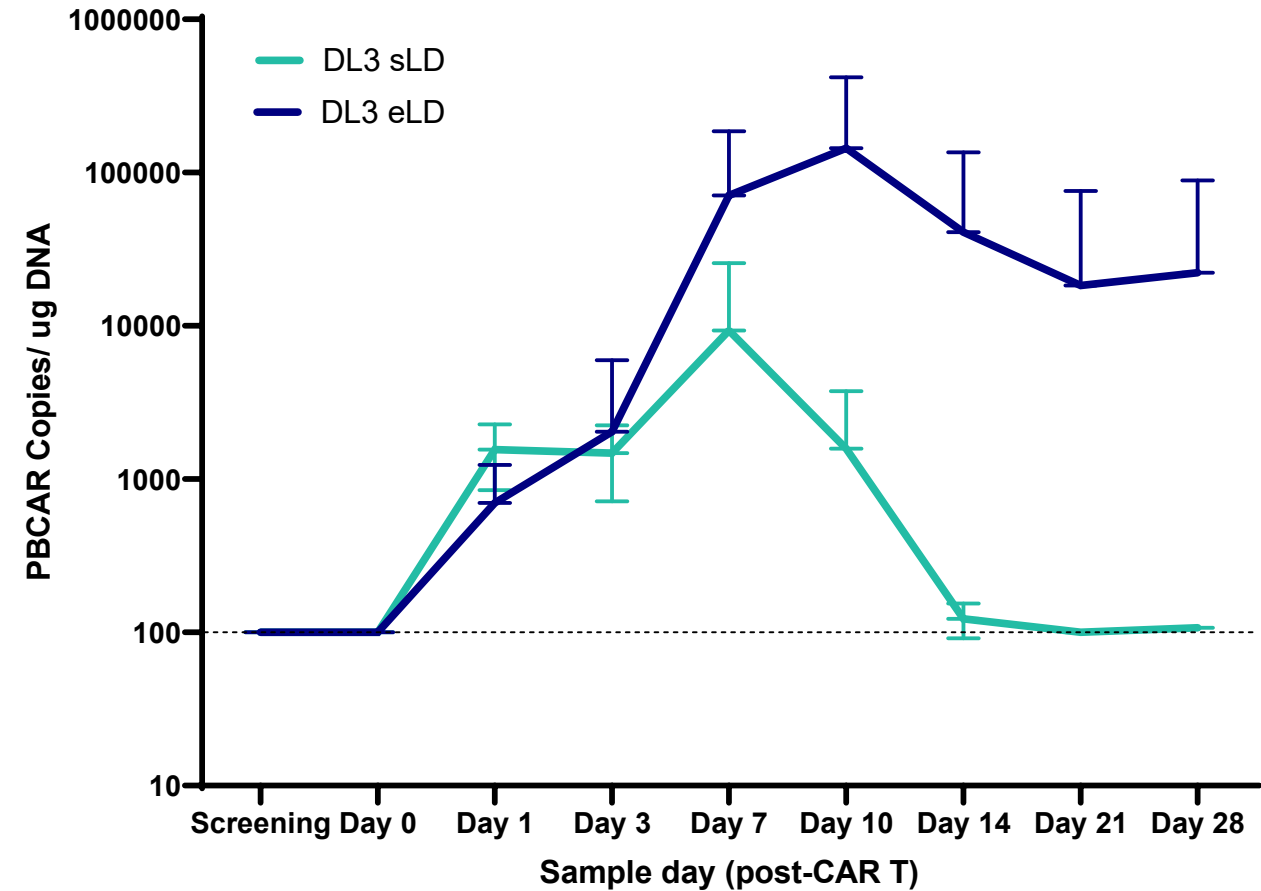
eLD significantly increased peak CAR T cell expansion and persistence

Response to PBCAR0191 in R/R NHL eLD Subjects

	All eLD Subjects (n=12)	CD19-CAR Naïve (n=8)	Prior Auto CAR (n=4*)
Overall Response Rate (ORR), n (%)	9 (75%)	6 (75%)	3 (75%)
Complete Response (CR), n (%)	6 (50%)	4 (50%)	2 (50%)

DL3 sLD at Day ≥ 28: ORR 3/6 (50%), CR 2/6 (33%).

Response Duration for PBCAR0191 with eLD in R/R NHL
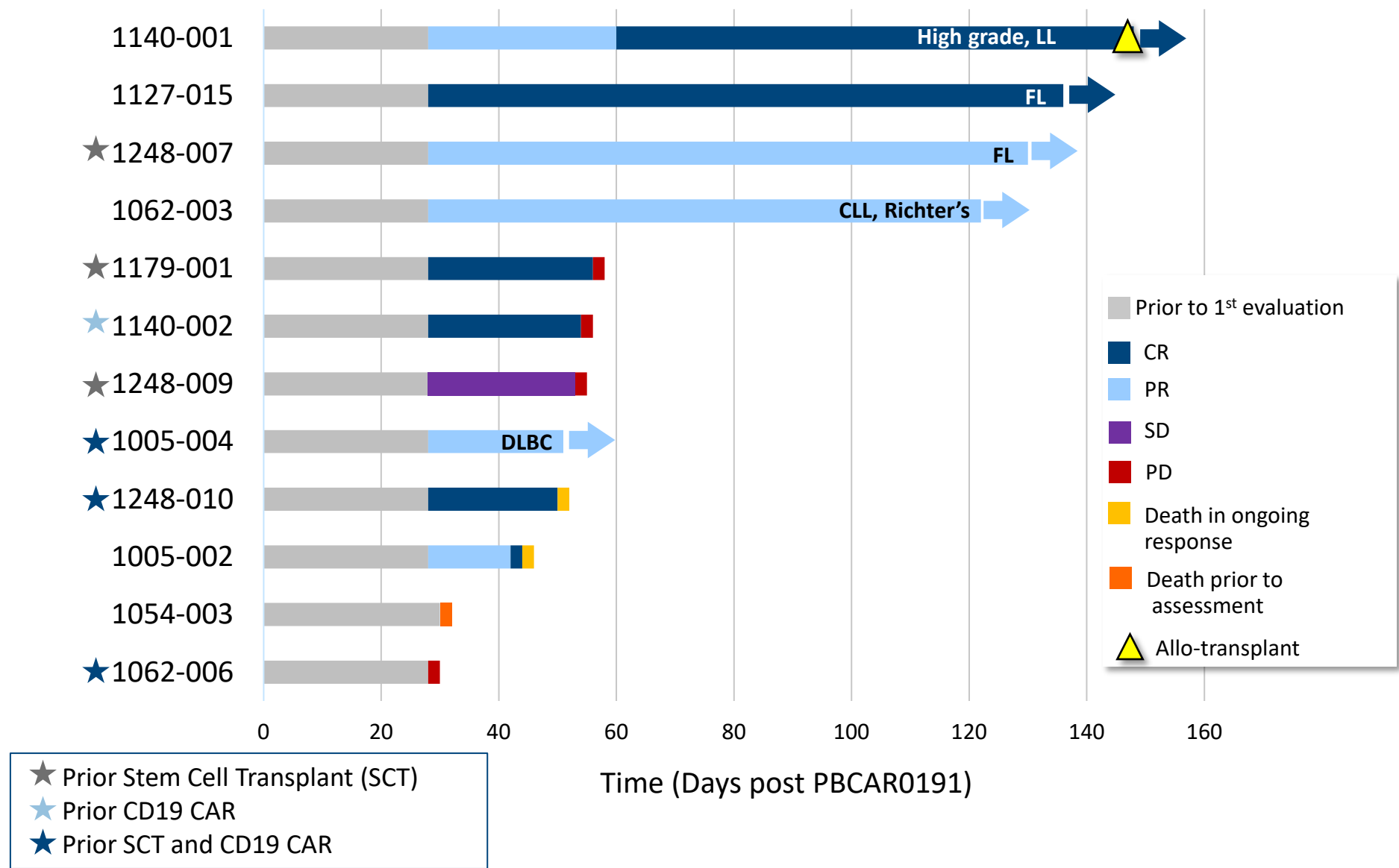
- Five subjects with ongoing response, including 3/9 evaluable subjects with DLBC/High Grade NHL

- Four subjects with response duration >4 months

- Among six subjects with prior SCT, ORR 66%: 2 CR, 2 PR

Time (Days post PBCAR0191)

★ Prior Stem Cell Transplant (SCT)
★ Prior CD19 CAR
★ Prior SCT and CD19 CAR

15

PBCAR0191 eLD Conclusions

- Enhanced LD mitigates PBCAR0191 rejection to markedly increase peak cell expansion (~72x) and AUC (~56x) compared to sLD

- Similar frequency of ICANS and CRS compared to sLD, while myelosuppression increased; no evidence of GvHD

- A single dose of PBCAR0191 cells is highly active, yielding ORR and CR rates of 75% and 50%, respectively, in both CD19-CAR naïve subjects as well as those previously treated with CD19-directed CAR therapy

- Five of nine responders (56%) remain progression-free, including 4 for > 4 months

- Median interval from confirmation of eligibility to start of LD was 1 day, reinforcing the advantage of off-the-shelf, allogeneic cellular therapy for high-risk patients

- A total of 15 patients are currently enrolled with continuing follow-up of response duration with the goal of 1 out of 3 patients achieving durable responses greater than 6 months

PBCAR19B Stealth Cell

Derek Jantz, Ph.D.

Chief Scientific Officer, Co-Founder, Precision BioSciences

Strategies to Overcome CAR T Cell Rejection

1. **Deepen *in vivo* immune suppression**

   - *e.g.* Enhanced Lymphodepletion

2. **Engineer CAR T cells to avoid immune detection**

   - *e.g.* Stealth cell technology

Knocking-Out β2m May Prevent Rejection by T Cells

Beta-2-microglobulin (β2m) is a component of MHC class I (MHC I). β2m can be knocked-out using gene editing to eliminate the expression of MHC I on the surface of allogeneic CAR T cells.
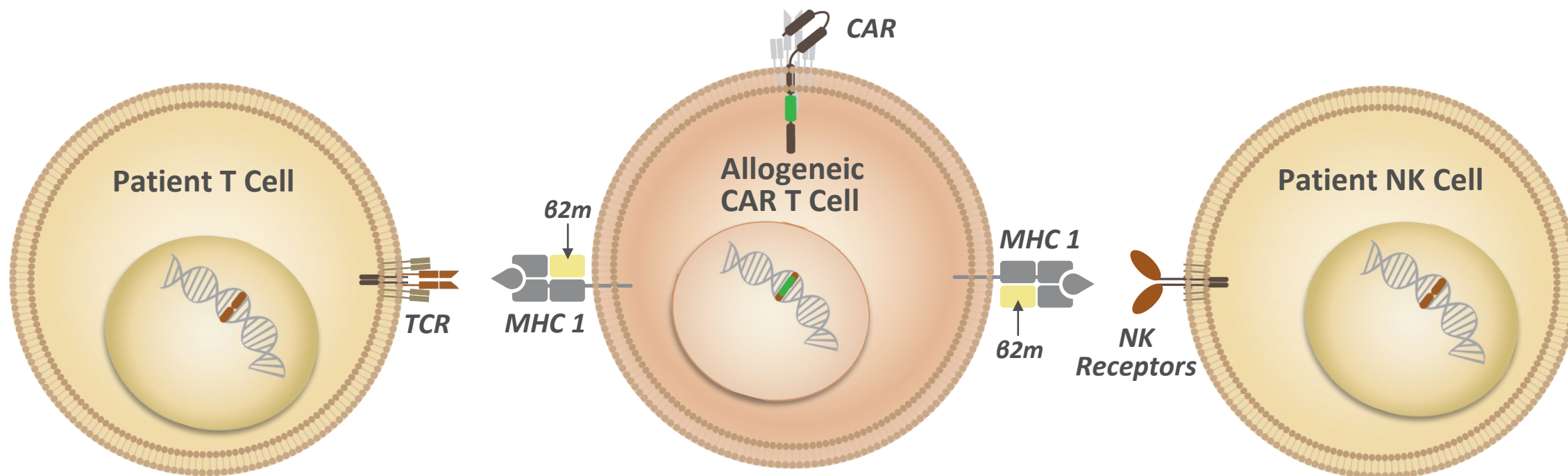
MHC I expression on CAR T cells **promotes rejection by T cells** via interactions with the TCR

MHC I expression on CAR T cells **prevents rejection by NK cells** via interactions with the NK receptors

Knocking-Out β2m May Induce Rejection by NK Cells

In mixed-lymphocyte reactions, β2m-knockout CAR T cells are resistant to rejection by T cells but are efficiently rejected by NK cells.

Rejection by T cells
(n=4 mismatched donors)

Standard CAR T
β2m-knockout CAR T

% Killing of CAR T

T Cell : CAR T Ratio
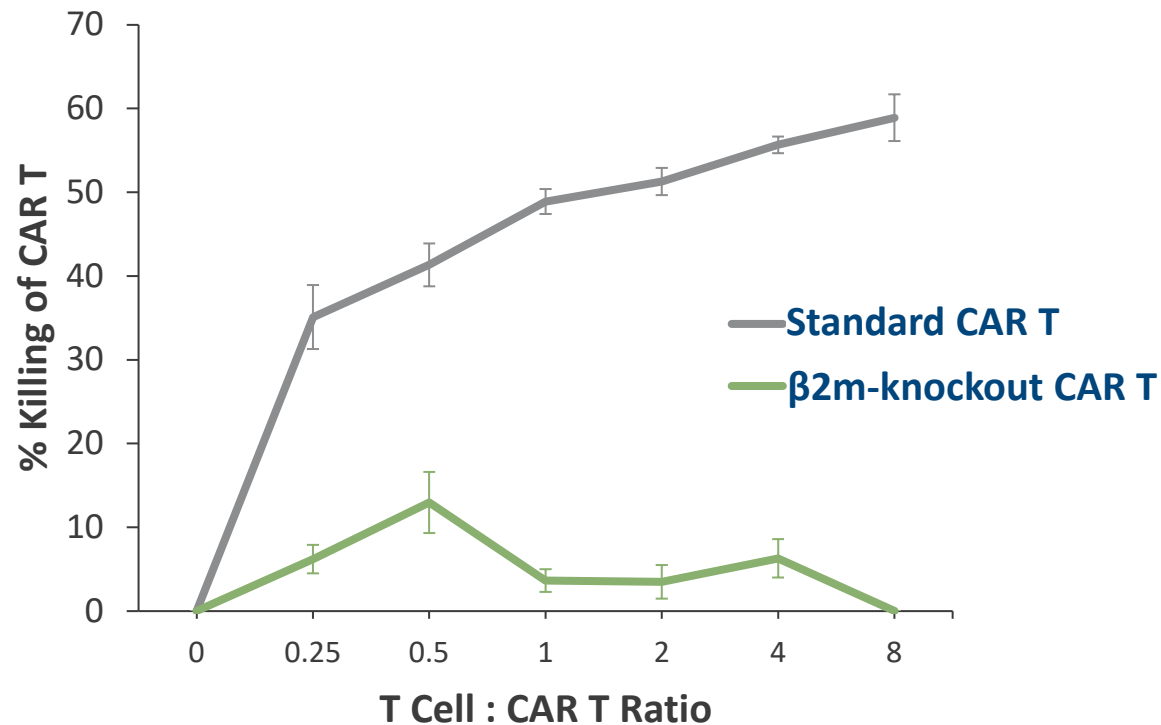
Rejection by NK cells
(n=3 mismatched donors)

Standard CAR T
β2m-knockout CAR T

% Killing of CAR T

NK : CAR T Ratio
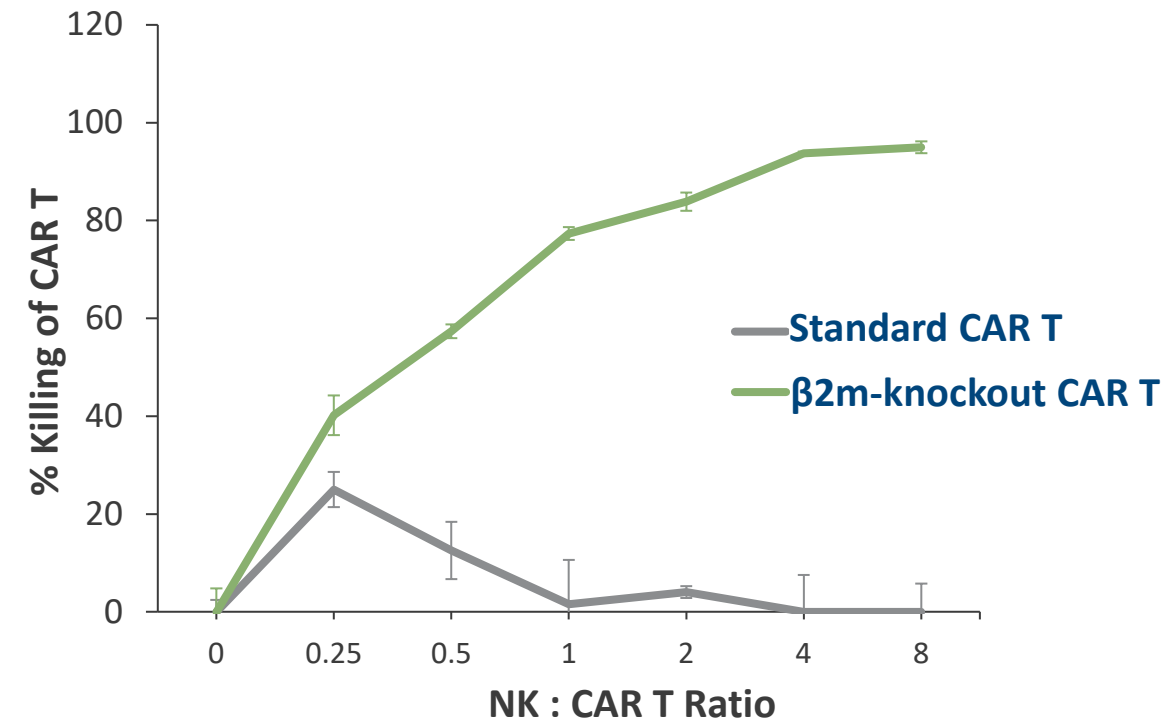
NK Cells Recover Quickly Following Lymphodepletion

An analysis of patient samples from PBCAR0191 Dose Level 3 reveals that **patient NK cells return to baseline levels within two weeks post-lymphodepletion.**
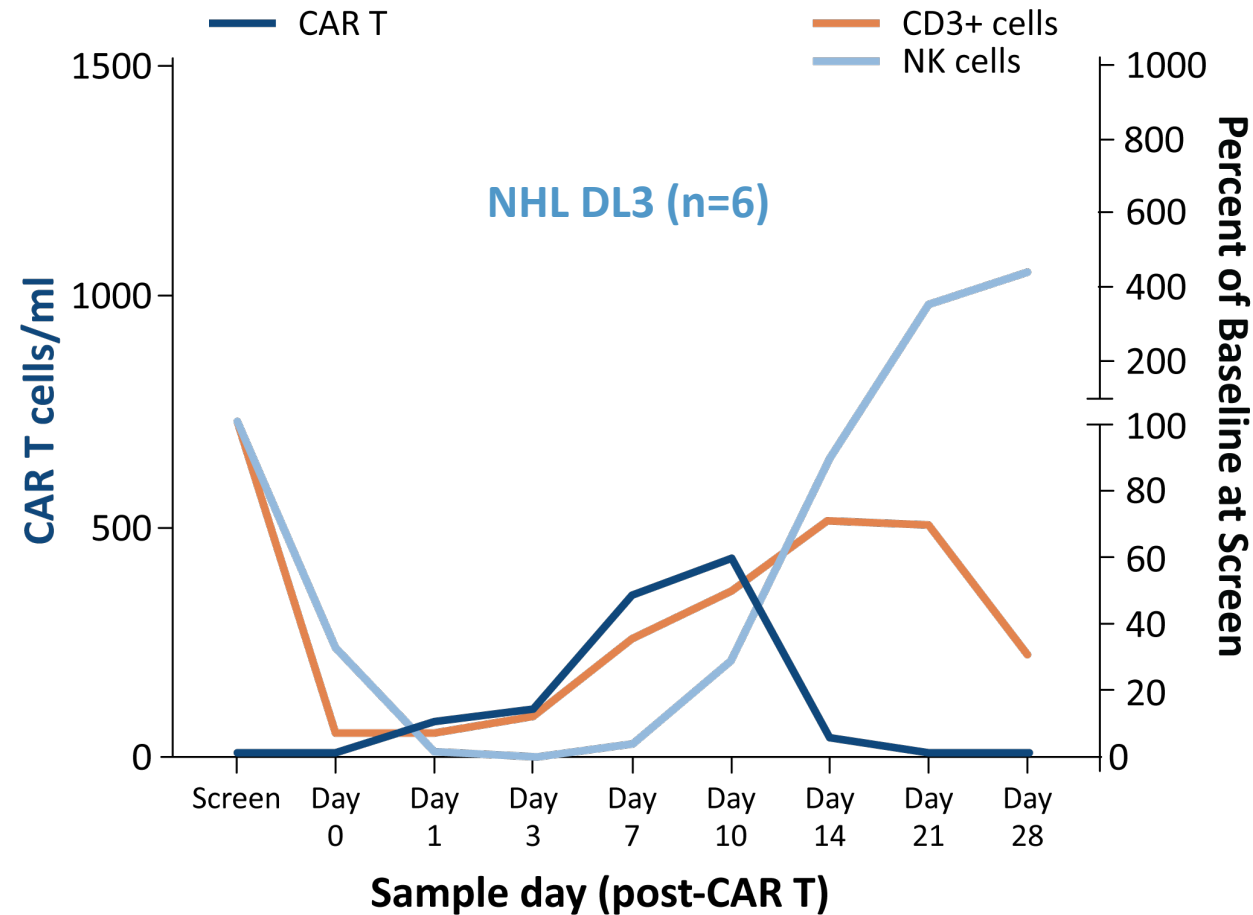
Alternative Strategy: β2m Knock-*down* with RNAi

In mixed-lymphocyte reactions, suppressing expression of β2m by ~80-90% using an shRNA confers significant protection against T cells without inducing a strong NK response.


CAR T Vector with anti-β2m shRNA
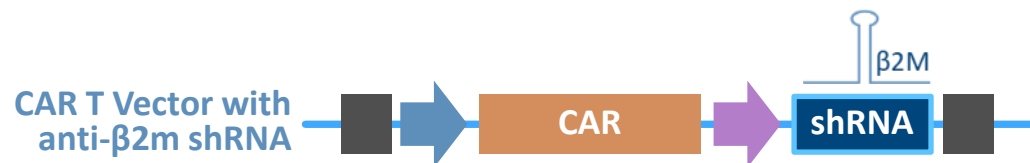
Rejection by T cells
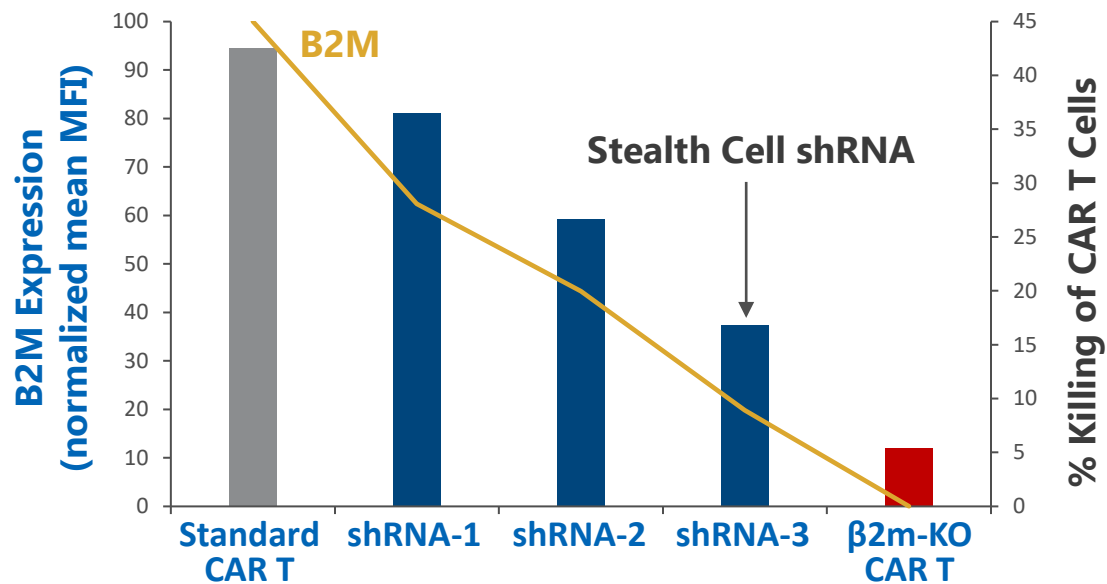
Rejection by NK cells
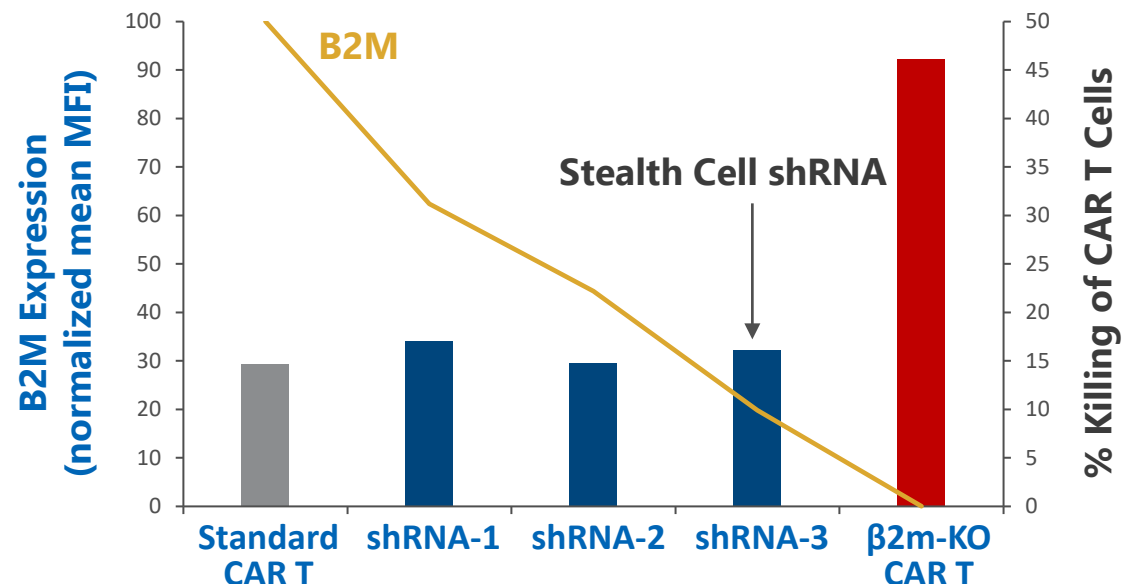
Highly-Activated NK Cells Can Kill CAR Ts With β2m Knocked-Down

NK cells obtained from certain donors and activated using more potent protocols killed β2m knock-down CAR T cells in mixed-lymphocyte reactions despite the presence of ~10-20% normal MHC I on the cell surface.
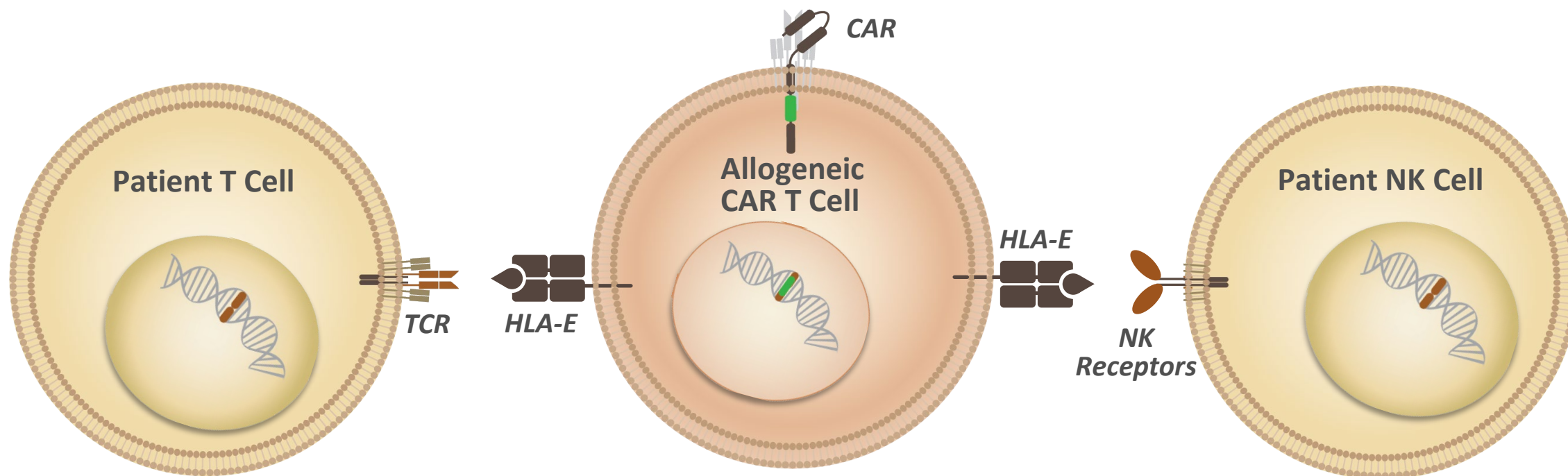
Rejection by NK cells
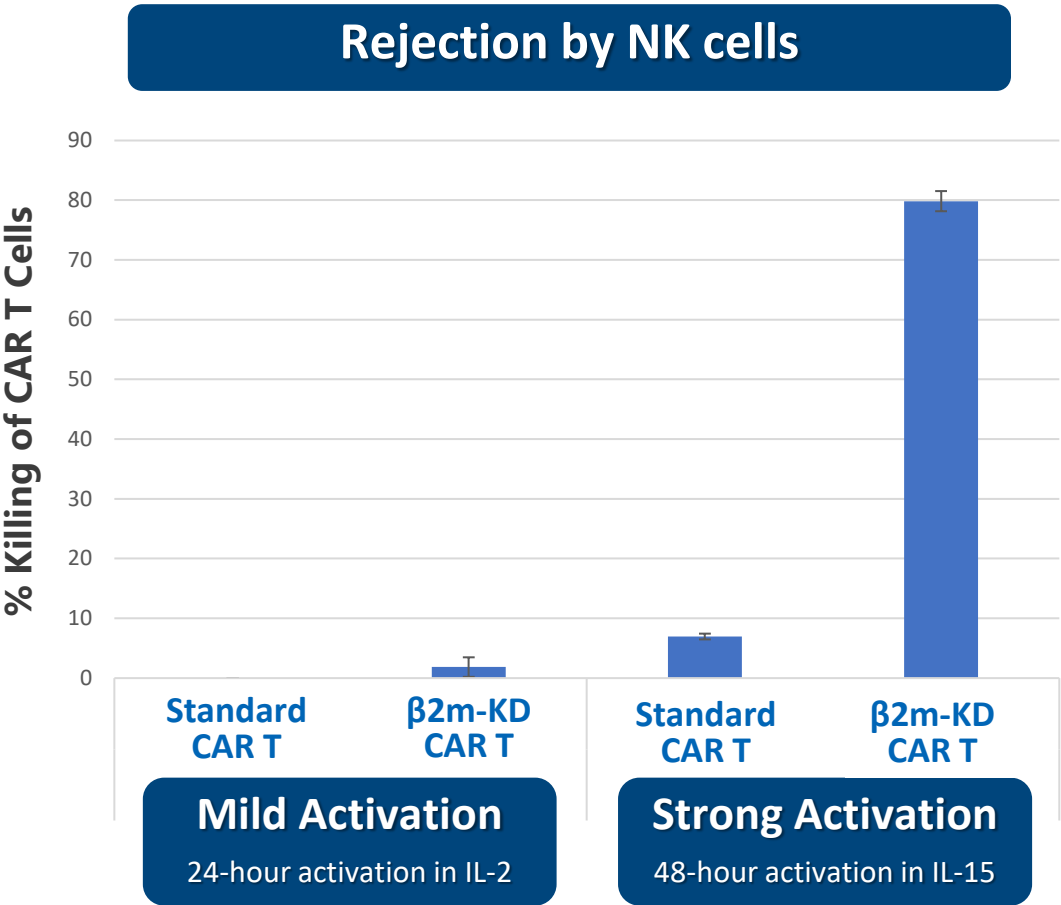
Standard PBCAR0191 CAR T cells or β2m knock-down (KD) CAR T cells were incubated in a 1:1 ratio with NK cells from an unmatched donor. NK cells were activated with either a mild protocol (24 hours in the presence of IL-2) or a potent protocol (48 hours in the presence of IL-15). NK cells activated using the potent protocol were able to mediate cytolysis of the β2M-KD CAR T cells to a much greater extent than the standard CAR T cells.

HLA-E is a "Decoy" to Prevent Killing by NK Cells

HLA-E is an invariant form of MHC that is conserved between individuals and presents as "self" to T cells and NKs.

HLA-E expression on CAR T cells **will not promote rejection by T cells** via interactions with the TCR
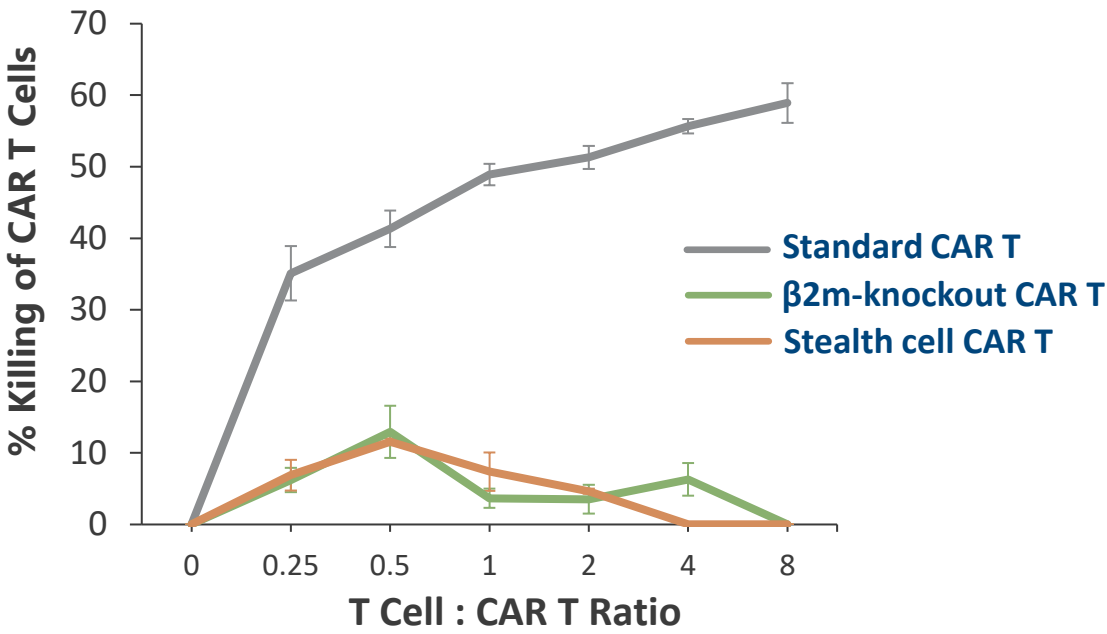
HLA-E expression on CAR T cells **prevents rejection by NK cells** via interactions with the NK receptors

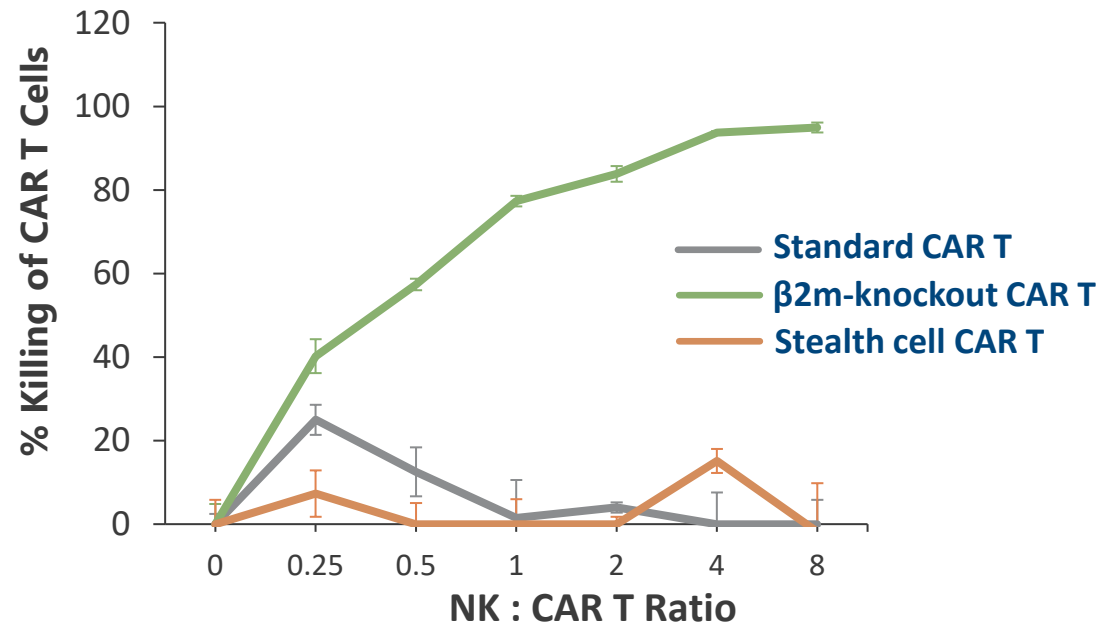# PBCAR19B Incorporates an anti-β2m shRNA and an HLA-E Transgene

In mixed-lymphocyte reactions, stealth cell CAR Ts are highly-resistant to rejection by T cells and NK cells.

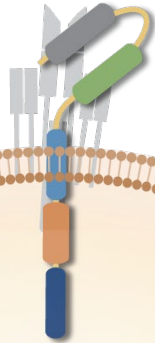# PBCAR19B is an Anti-CD19 CAR T Built on the Stealth Cell Platform

PBCAR19B is open for enrollment

Phase 1 study of patients with R/R NHL will evaluate the safety and clinical activity of PBCAR19B at increasing flat dose levels (2.7×10^8 - 8.1×10^8 CAR T cells)

PBCAR19B DL 1 is comparable to PBCAR0191 DL 3

1 **Anti-CD19 CAR**
TCR is knocked-out to prevent GvHD

2 **Anti-beta-2 microglobulin (β2m) shRNA**
Reduces MHC I expression to prevent rejection by T cells

PBCAR19B

3 **HLA-E transgene**
Prevents rejection by NK cells

Multiple Paths to Realize the Potential of Allogeneic CAR T

- **PBCAR0191** highly active following eLD yielding ORR of 75% and CR of 50% at Day ≥28
  - Acceptable safety profile
  - Enrolling more patients and monitoring for durability

- **PBCAR19B** engineered to evade rejection by NK and T cells
  - Potential to build on promising PBCAR0191 clinical data, reduce need for prolonged immunosuppression
  - Clinical study open for enrollment

- **PBCAR0191** and **PBCAR19B** data will be evaluated to determine the best path for overcoming rejection prior to making pivotal trial decision

- Three strategies to target BCMA
  - **PBCAR269A** interim data in 2021
  - **Combination with a Gamma Secretase Inhibitor** initiating in 1H/2021
  - **PBCAR269B** (anti-BCMA stealth cell) Plan to file IND early 2022

- **PBCAR20A** interim update expected by the end of 2021

Precision plans to showcase our in vivo gene editing pipeline at a Summer 2021 event