Dominant-negative TGFBR2-armored DLL3-targeted CAR-T Cells Maintain TGF-β Resistance, With Early Signals of T-cell Exhaustion Modulation After Expansion in Patients With Small-cell Lung Carcinoma

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Conflict of Interest Statement

- The Presenter, Paul Schwarzenberger, is an employee of Legend Biotech USA Inc.
- This study was funded by Legend Biotech USA Inc. and Novartis AG.

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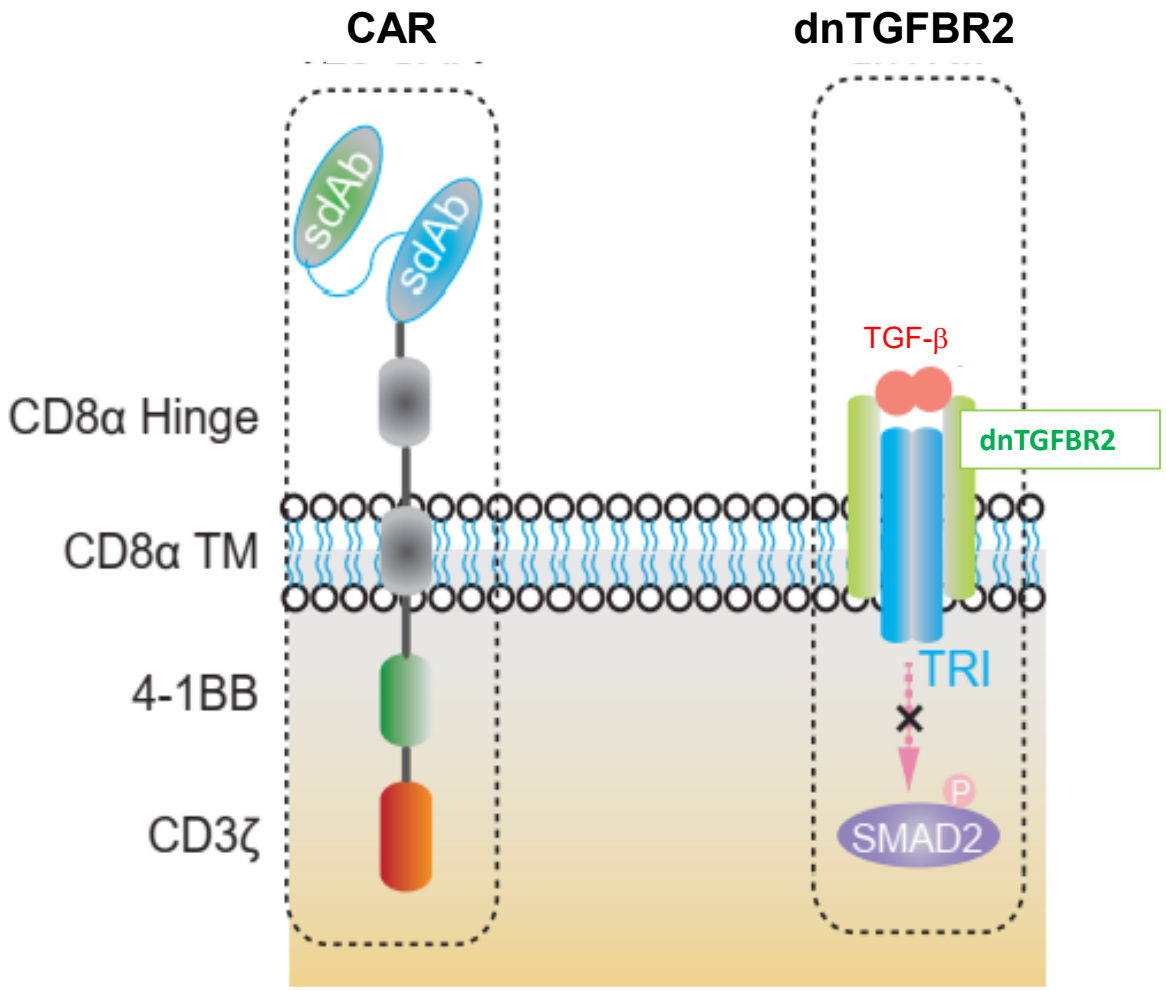
LEGEND BIOTECH

LB2102: DLL3-targeting CAR-T Cells



LB2102 CAR-T Cell Design

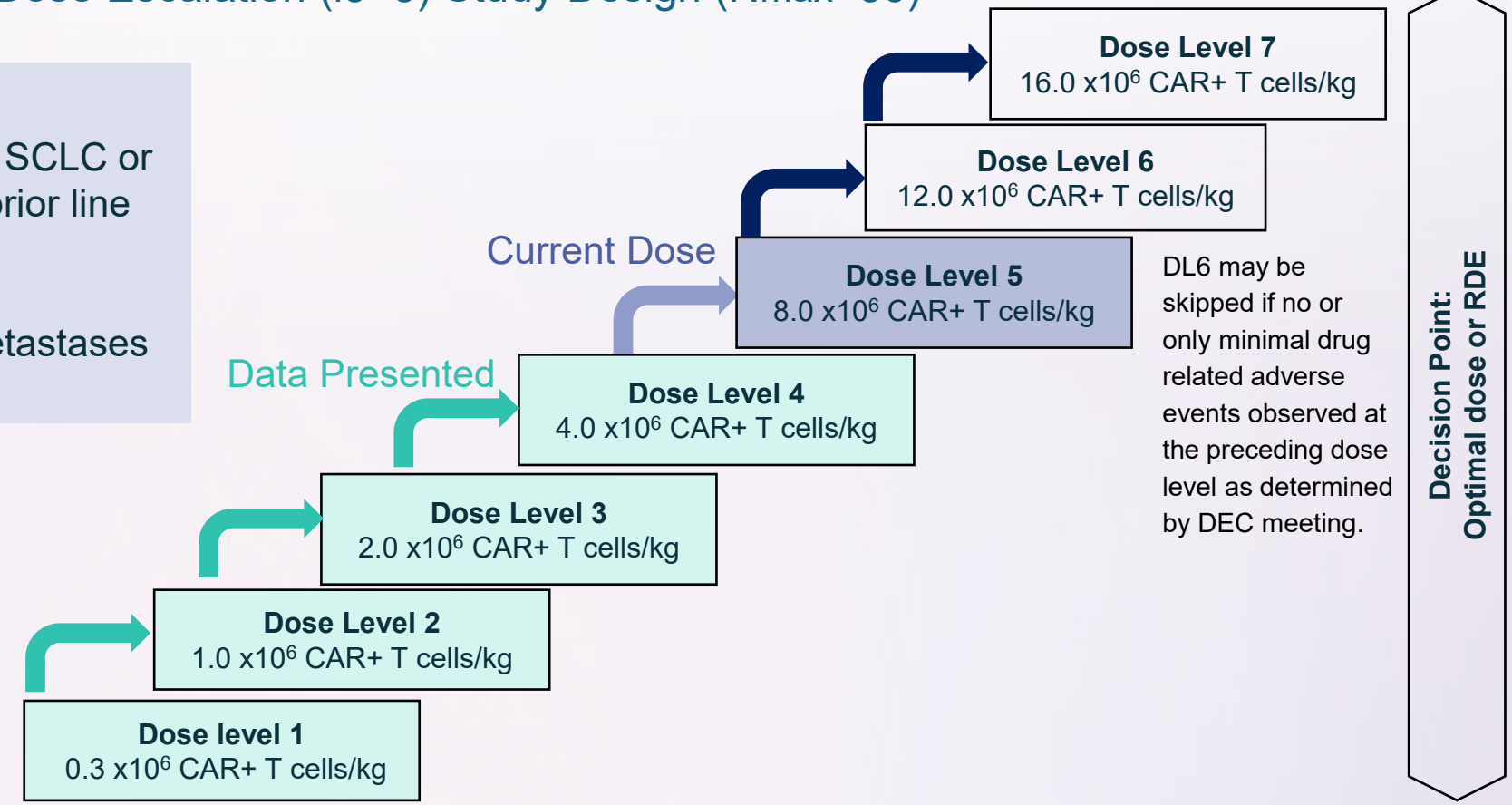
- **Chimeric Antigen Receptor (CAR):** Dual single-domain antibodies (sdAb) with high-affinity binding for DLL3
- No cross-reactivity with DLL1, DLL4, or other membrane proteins
- **Dominant Negative TGF-beta Receptor 2 (dnTGFBR2):** Non-signaling receptor that blocks TGF-β–mediated SMAD signaling
- Increases proliferation and reduces exhaustion

First-in-human phase 1 dose-escalation and cohort expansion study in patients with extensive-stage SCLC or LNEC

Part A: Dose Escalation (i3+3) Study Design (Nmax=36)

Target Population:

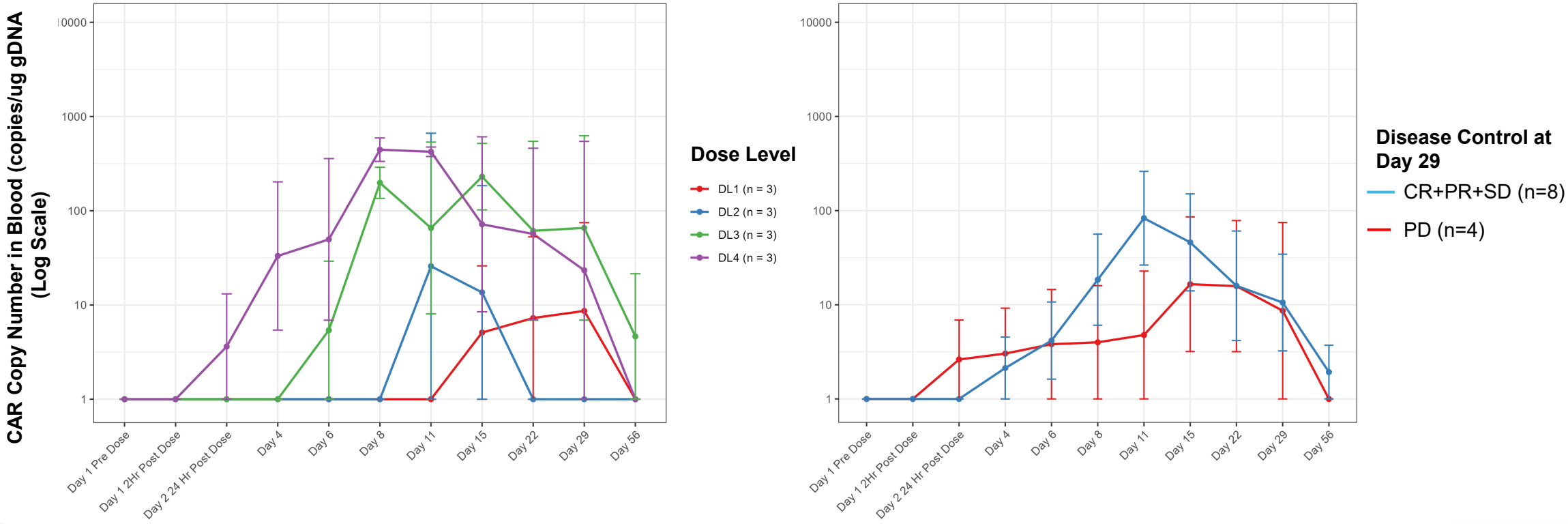
- Adult patients with relapsed/refractory SCLC or LCNEC that progressed following ≥1 prior line of standard treatment
- ECOG ≤1
- No untreated or symptomatic brain metastases (n=12)



This study is currently ongoing, at Dose Level 5 (8 x10⁶ CAR+ T cells/kg)

- No dose-limiting toxicities (DLTs), delayed hypersensitivity reactions, or neurotoxicity have been observed
- Preliminary data suggest dose-dependent pharmacokinetics (PK) and early signs of clinical activity
- **Detailed results of safety and efficacy to presented at ASCO Annual Meeting 2025 (Abstract no. 506978)**

CAR Transgene Copy Number Related to Dose Level and Disease Control at Day 29



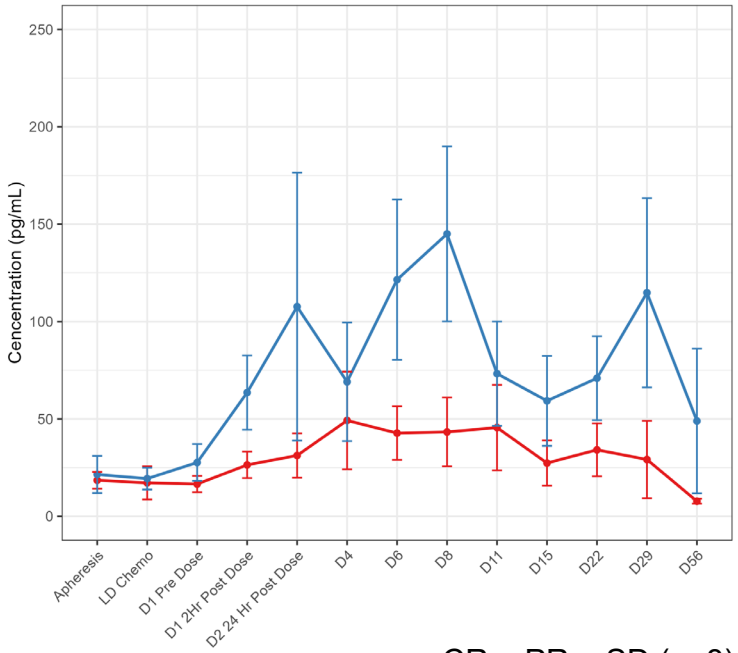
Patients with disease control (CR+PR+SD) had higher peak CAR-T cell expansion, measured by peripheral CAR+ transgene copy numbers

CR, complete response; DL, dose level; PD, progressive disease; PR, partial response; SD, stable disease

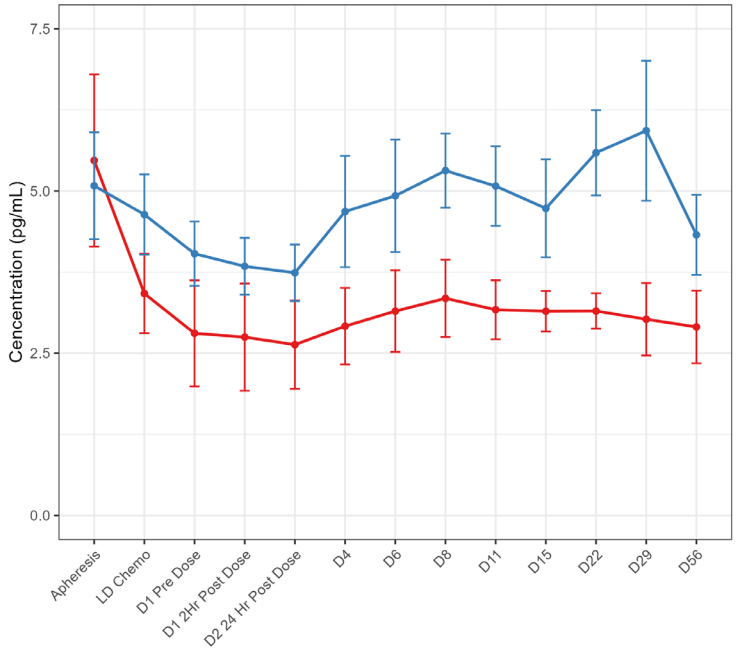
Notes: Disease control at Day 29 is defined as patients with CR, PR, or SD at D29. PK data from 1 patients at Day 29 and 2 patient at Day 56 are pending. The analysis presented is exploratory in nature and intended for research purposes only.

Cytotoxic T-cell Cytokines are Elevated in Patients With Disease Control

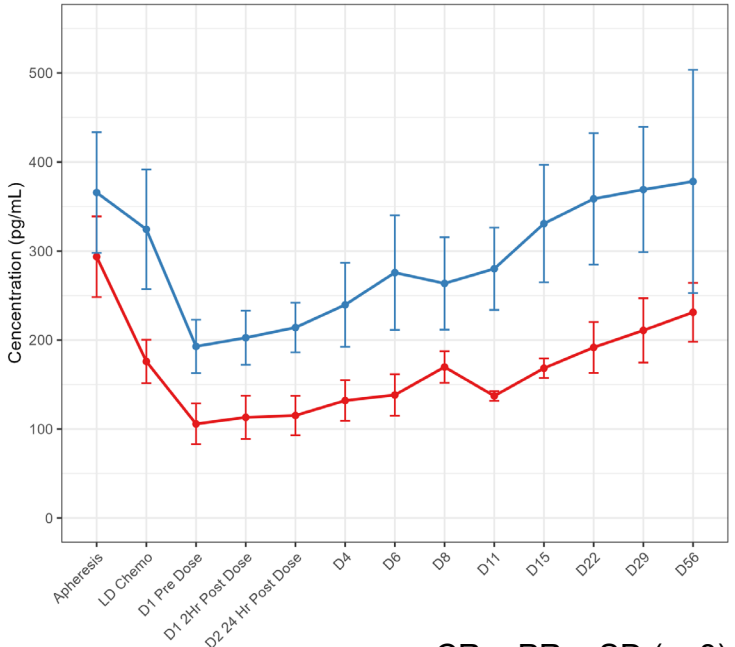
IFN-γ



TNF-α



IL-12/IL23p40



Disease Control at Day 29:

CR + PR + SD (n=8)
PD (n=4)

CR + PR + SD (n=8)
PD (n=4)

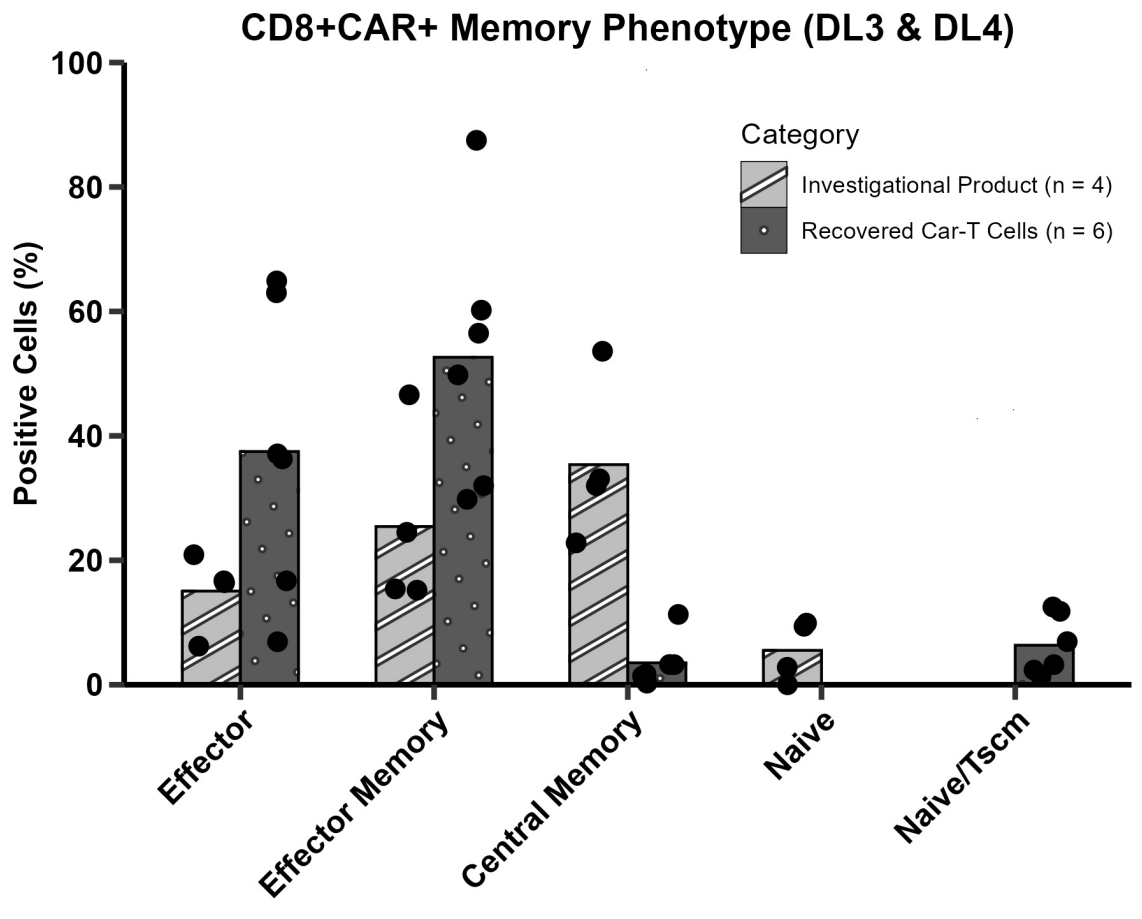
CR + PR + SD (n=8)
PD (n=3)

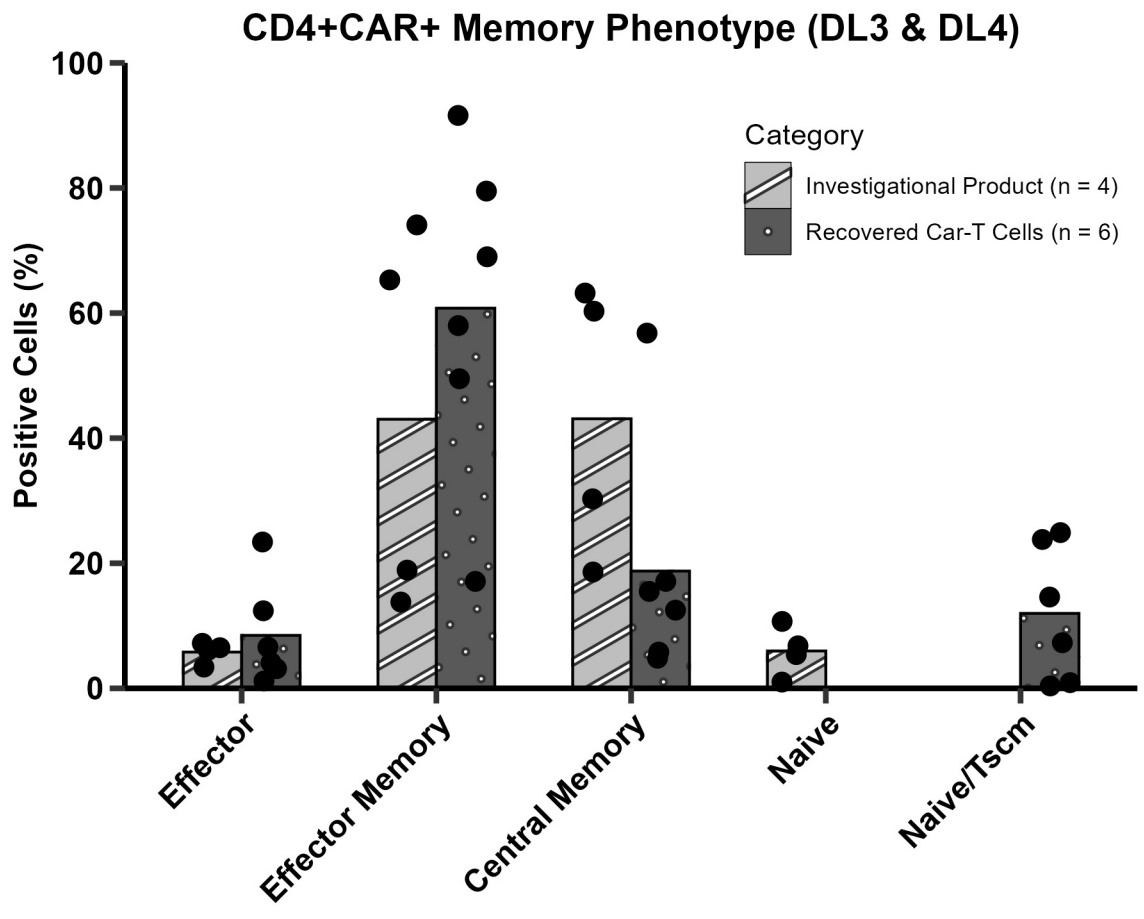
Serum from patients with disease control had **increased concentrations** of IFN-γ, TNF-α, and IL-12/IL-23p40 compared with serum from non-responders, indicating a **stronger immune activation profile** associated with clinical response

CR, complete response; DL, dose level; PD, progressive disease; PR, partial response; SD, stable disease

Notes: Disease control at Day 29 is defined as patients with CR, PR, or SD based on available data at the time of analysis. The analysis presented is exploratory in nature and intended for research purposes only.

LB2102 Cells Shift From Central Memory (Investigational Product) to Effector Memory T cells in Patients (Recovered CAR-T Cells)



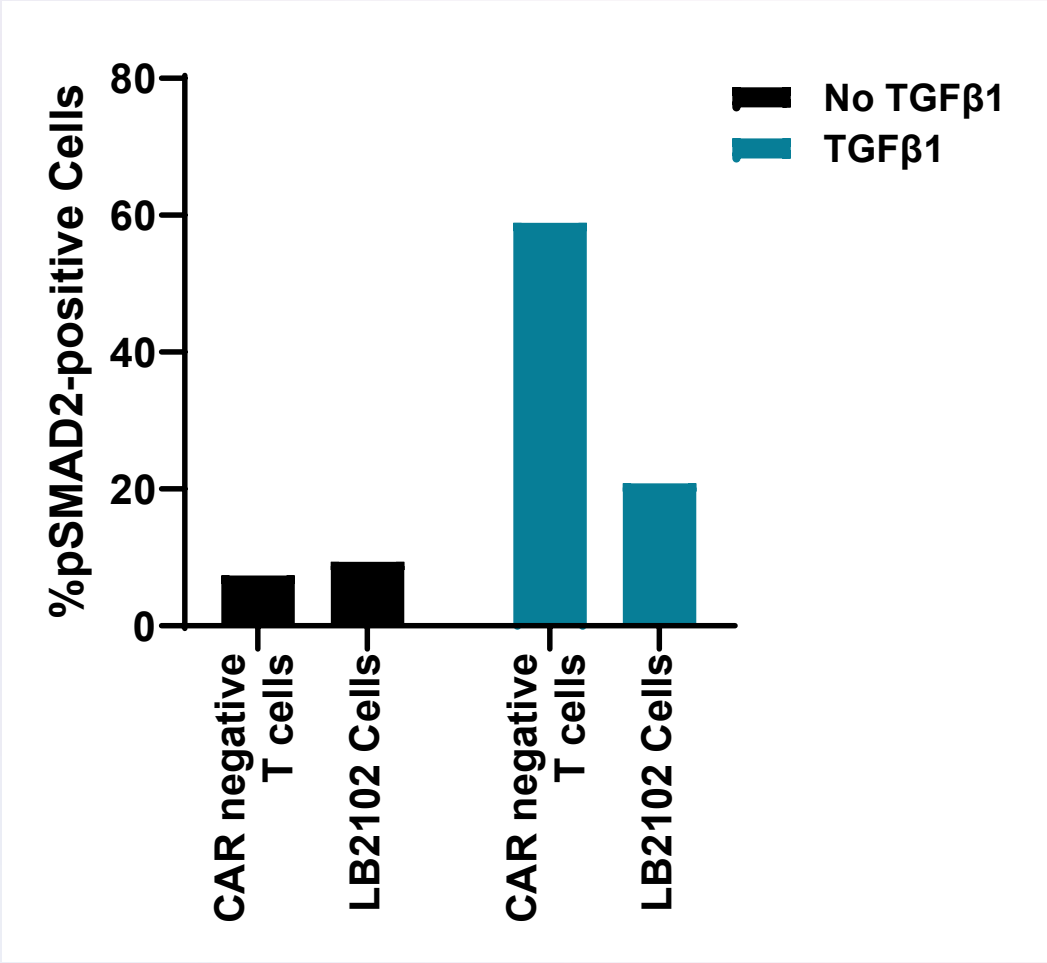


Among CD8+ T cells, the proportion of **effector and effector memory cells** approximately **doubled** in recovered CAR-T cells compared to the investigational product, whereas central memory cells nearly disappeared

Among CD4+ T cells, **central memory cells decreased ≥50%** in recovered CAR-T cells compared to the investigational product whereas changes in effector memory cells proportions were modest

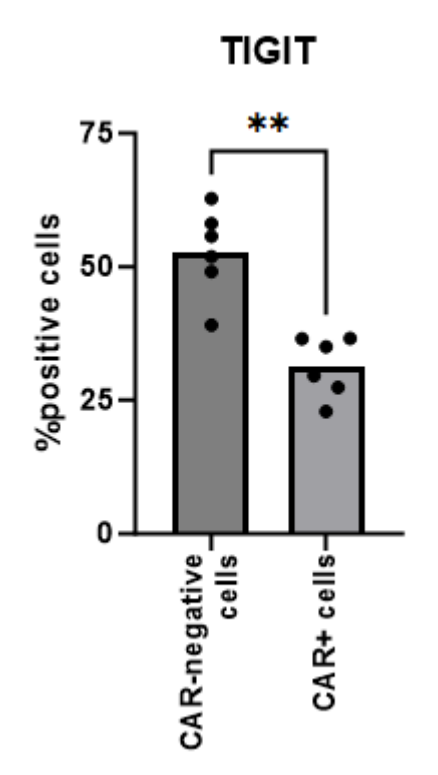
Clinical Validation: TGF-β1 Signaling in LB2102 CAR+ T Cells Remains Inhibited Following Expansion in Patients

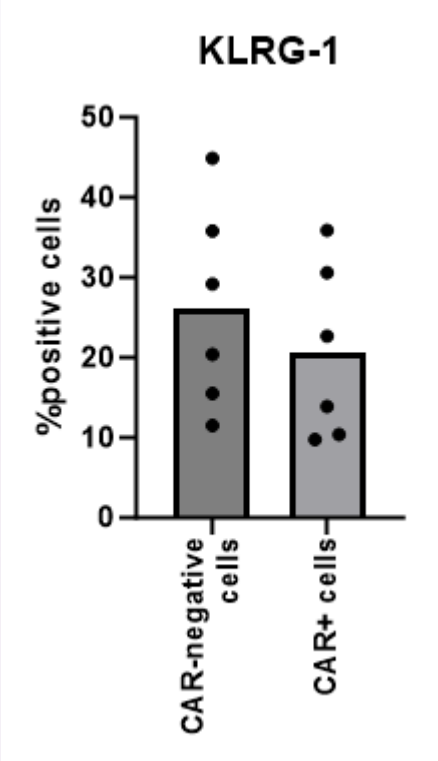
Inhibition of SMAD2 Phosphorylation in CAR-T Cells vs CAR-negative T Cells Recovered From Patients

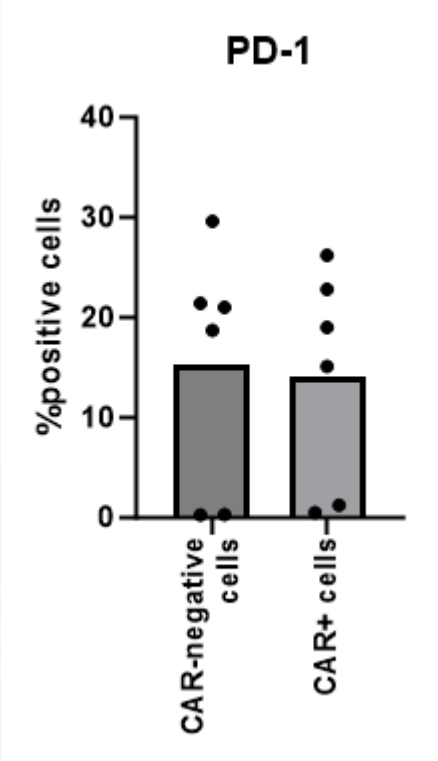


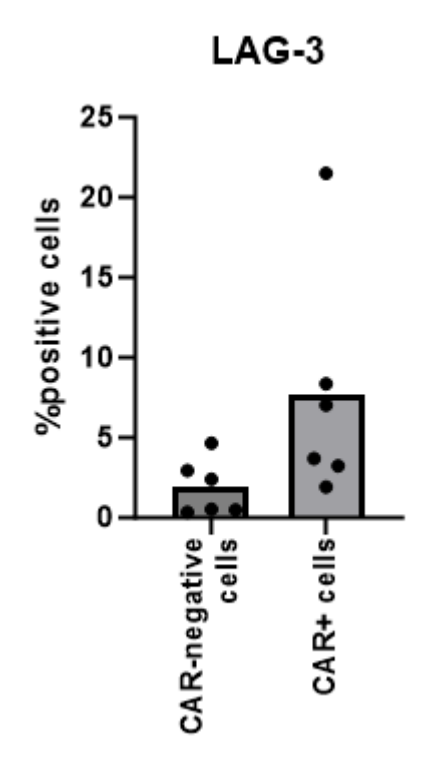
- Baseline percentage of cells positive for phosphorylated SMAD (pSMAD2) were low in both cell populations (left columns)
- Ex vivo incubation with TGF-β1 (blue) induced SMAD phosphorylation in CAR-negative T cells but not in LB2102 (CAR-T+ cells)
- **dnTGFBR2 blocks TGF-β signaling in CAR-T Cells**

Expression of Exhaustion Markers at Peak Expansion (Dose Levels 3 and 4)









Dots indicate individual patients; **Bars** present mean values for each group (n=6)

** p=.005 (paired t-test)

- CAR-T cells (expressing dnTGFBR2) express significantly lower levels of TIGIT than CAR-negative T cells, but higher levels of LAG-3
- Expression levels of PD-1 and KLRG1 vary among patients
- Further studies are needed to evaluate the effects of the dnTGFBR2 construct on TGF-β-mediated T-cell exhaustion in patients

Conclusions

Key Findings:

- dnTGFBR2 inhibits TGF-β signaling in CAR-T cells and retains functionality in patients
- Compared with the investigational product, LB2102 cells recovered from patients express markers of effector and effector memory T cells (more than 2-fold higher levels), at the expense of the central memory population, indicating antigen exposure
- Two patients treated at DL 3 (1 off-protocol, 1 with brain metastasis) do not show any evidence of disease > 6 months after infusion of LB2102
- No high-grade cytokine-release syndrome or immune effector cell-associated neurotoxicity syndrome events were observed; **LB2102 appeared to be well tolerated, with no DLTs noted to date**

CAR-T cell expansion and response:

- A trend toward dose-dependent expansion was observed, with preliminary data suggesting that higher peripheral peak levels of LB2102 may be associated with improved disease control

Cytokine profiles:

- T-cell effector cytokines (IFN-γ, TNF, IL-12/IL-23p40) were elevated at the time of CAR-T expansion in patients with improved disease control vs patients with no disease control, suggesting an association between cytokine profiles during LB2102 expansion and response

Exhaustion markers:

- CAR-T cells express lower levels of TIGIT and higher levels of LAG-3, with minimal changes in PD-1 and KLRG-1, showing a temporal snapshot of immune exhaustion, compared with CAR-negative T cells

Future Directions

- Larger and longer studies are needed to increase our understanding of the temporal dynamics of CAR T cells, and markers of exhaustion, in patients
- Although the complex biology of this system and inter-patient variations limitations do not permit a unifying hypothesis, the combined data suggest in vivo function of armored CAR-T cells (LB2102), with a strong signal for activity and potential clinical benefit

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