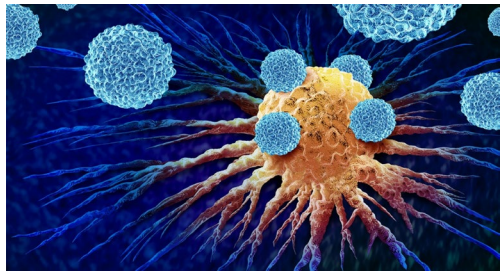
Raising the Bar with Immunotherapy: CAR-T Cells in Non-Small Cell Carcinoma



T cells attacking tumor cell

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October 26, 2024

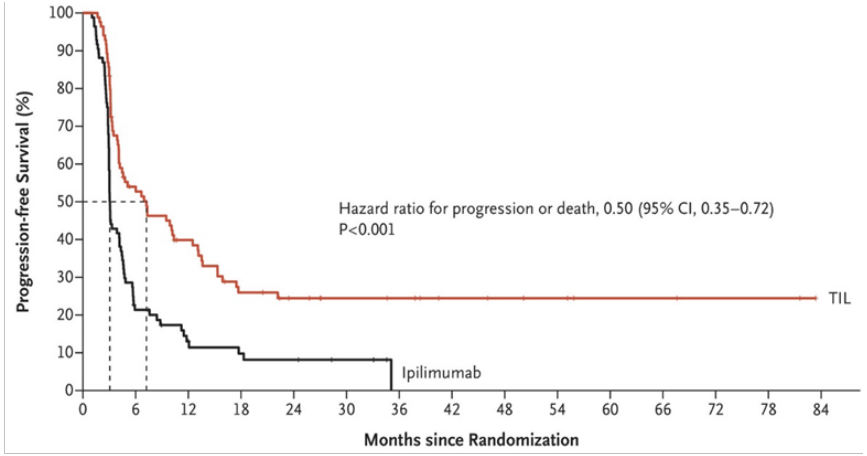
H. Lee Moffitt Cancer Center, Tampa FL USA

Topic Outline

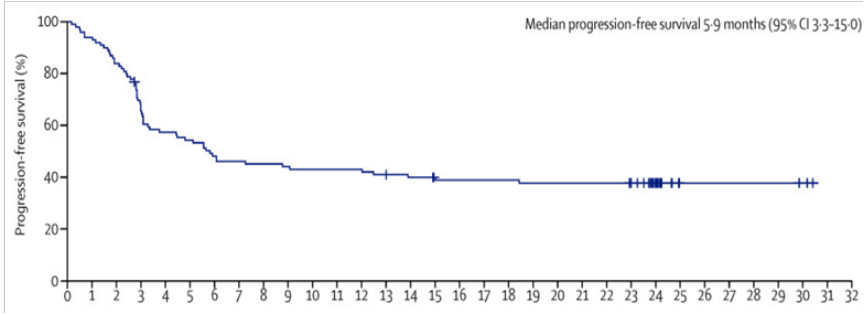
- **Overview of Cell Therapy in NSCLC**
- CAR-T Targets in CLinic
  - GPC-3
  - DLL-3
  - Mesothelin
  - CEA
  - Emerging targets:
    - EGFR
    - ROR-1
    - ALK*
    - HER2
    - ICAM-1
- Lessons Learned
- Take-Home Messages

Adoptive cell therapy may eradicate **drug-tolerant** tumor cells.

TIL *vs.* Ipi.
Melanoma
PFS
***n* = 168**

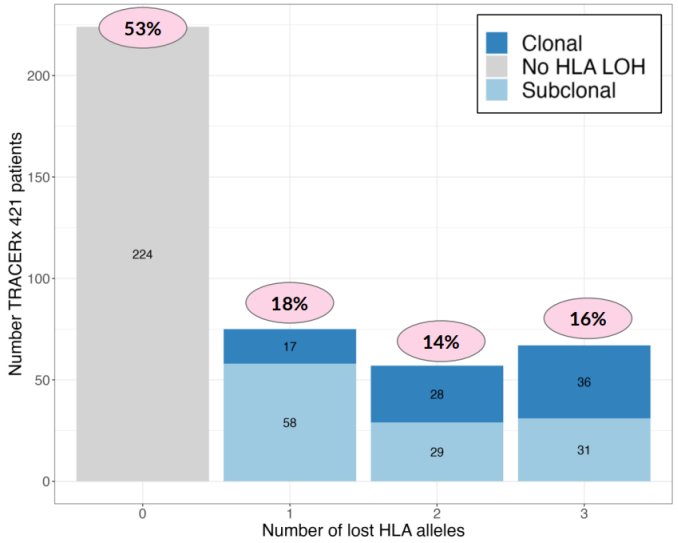


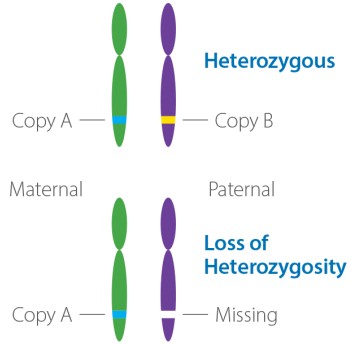
CD19 CAR-T
DLBCL
PFS
***n* = 101**



Rohaan, M. W., Borch, T. H., van den Berg, J. H., *et al* . NEJM, *387*(23), 2022 2113-2125.
Locke, F. L., Ghobadi, A., Jacobson, C. A *et al.* Lancet Onc , *20*(1), 31-42.

Half of lung cancer patients have HLA loss of heterozygosity at **baseline.**



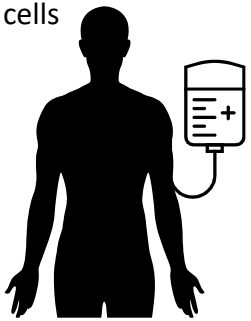


Puttick Jones et al. Cancer Res (2024) 84 (6_Supplement): 1201.
McGranahan, N. et al. (2017). *Cell*, *171*(6), 1259-1271.

CAR T-Cell Therapy: Underlying Principles

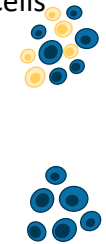
Leukapheresis

Collect patient's white blood cells

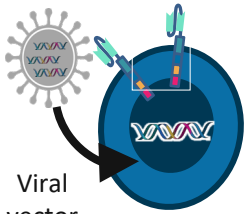


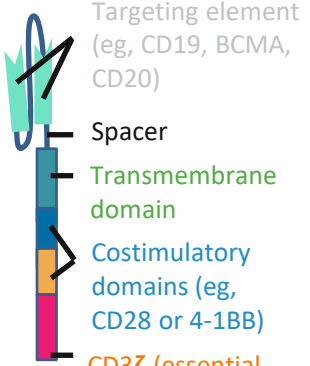
Manufacturing

Isolate and activate T-cells

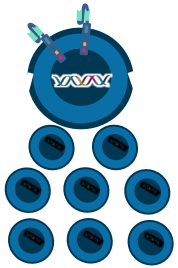


Engineer T-cells with CAR gene





Expand CAR T-cells

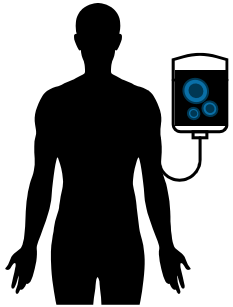


Median manufacturing time: 17-28 days

Patients undergo lymphodepleting therapy

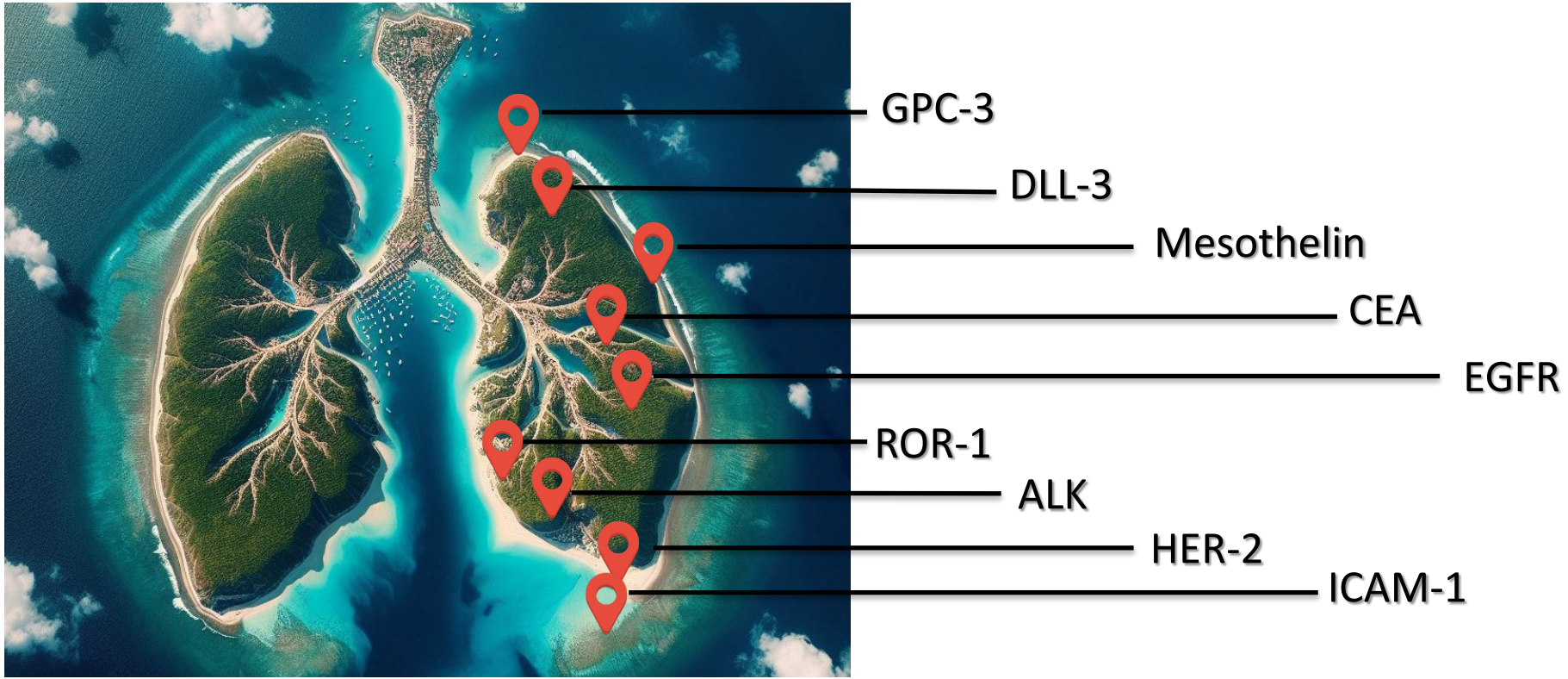
Infusion

Infuse same patient with CAR T-cells

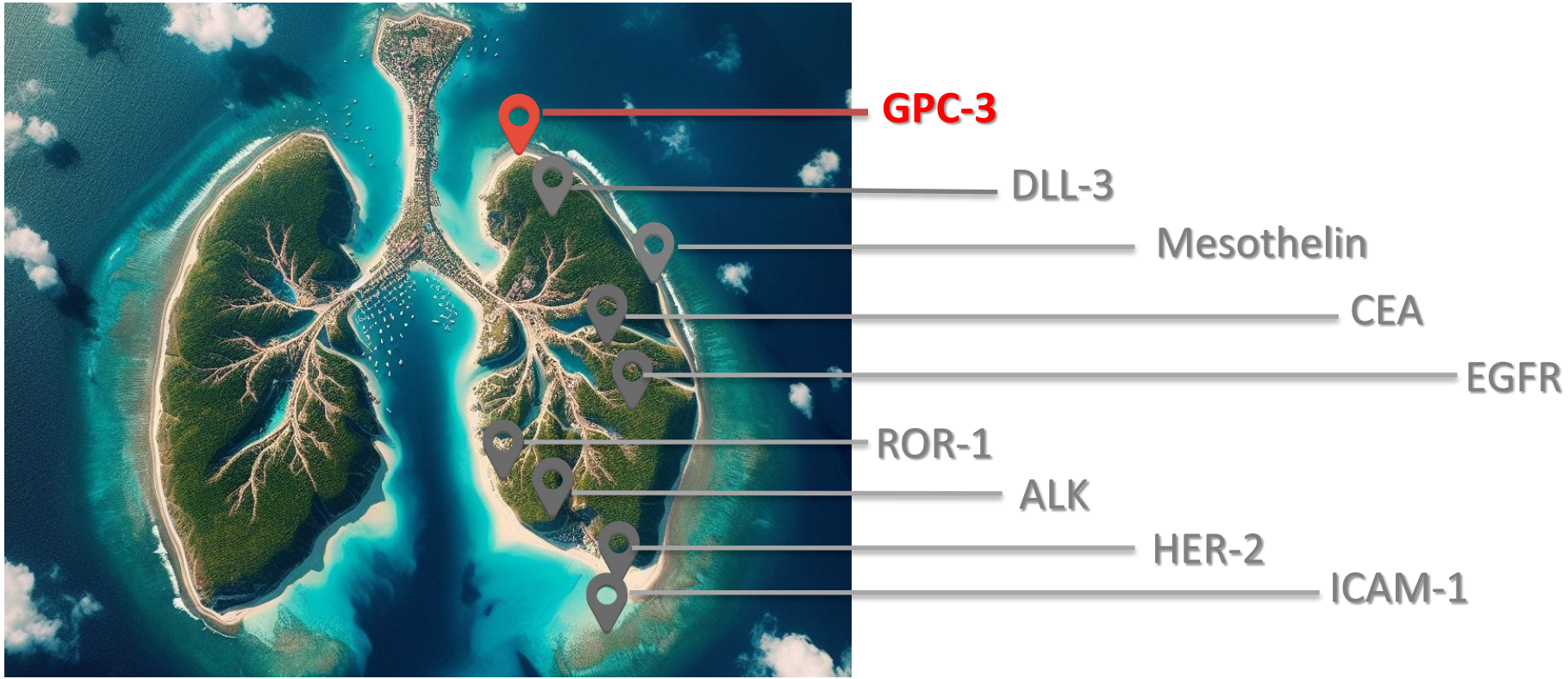


Majors. EHA 2018. Abstr PS1156. Lim. Cell. 2017;168:724. Sadelain. Nat Rev Cancer. 2003;3:35.
Brentjens. Nat Med. 2003;9:279. Park. ASH 2015. Abstr 682. Axicabtagene ciloleucel PI. Tisagenlecleucel PI.

Mapping Lung Cancer: Targets for CAR-T



Mapping Lung Cancer: Targets for CAR-T



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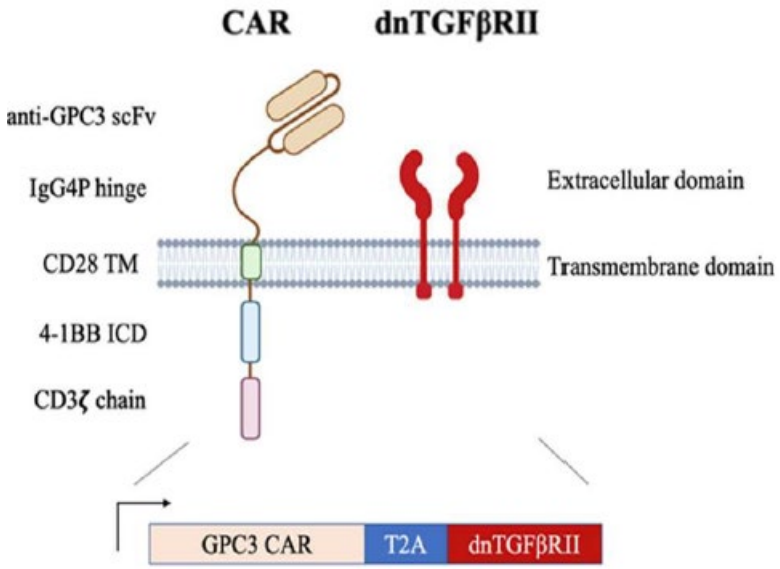
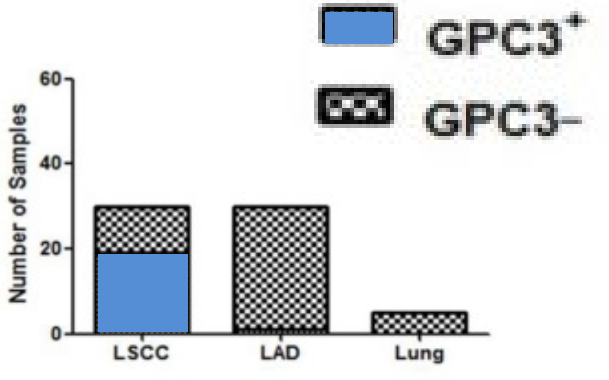
GPC3-specific TGFβRIIDN Armored CAR (C-CAR031) Applies to Squamous Lung Cancer



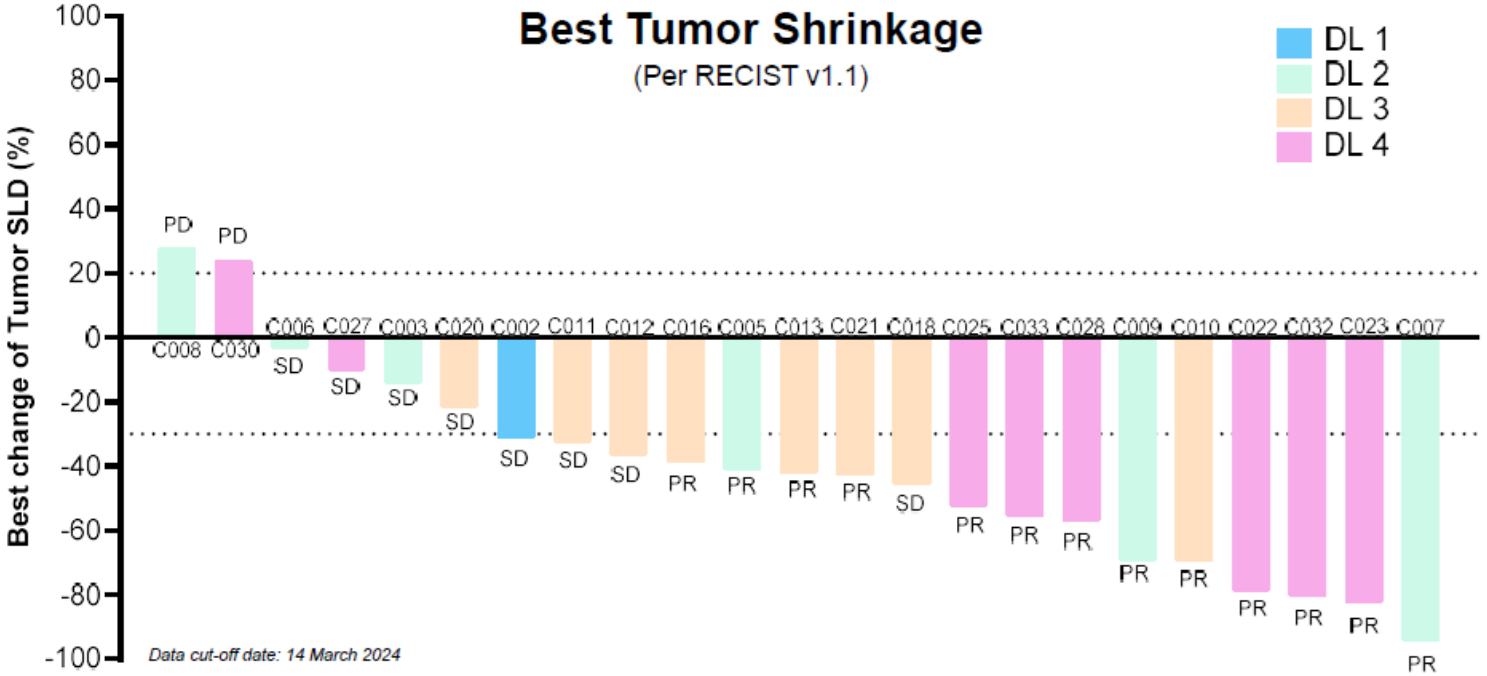


- **63.3% (**19 /30) LUSC[2]
- Virtually absent in normal tissues
- 4x higher in LUSC vs. normal lung[3]

1. Qi Zhang et al *JCO* 42, 4019-4019(2024).
2. Ning, Jing, et al. *BMC pulmonary medicine* 21.1 (2021): 199.
3. 3. Li, Kesang, et al. *Oncotarget* 7.3 (2016): 2496.

GPC3-specific TGFβRIIDN Armored CAR-T

Phase I data in Hepatocellular Cancer



ORR (all confirmed PR)

- **56.5%** overall
- **75.0%** at DL 4

DCR

- **91.3%** overall

Tumor Size Reductions

- **42.2%** median target lesion reductions (range: -28.1% to 94.4%)

1. Qi Zhang et al *JCO* 42, 4019-4019(2024).

PRESENTED BY: Ben Creelan, MD @BenCreelan

GPC3-specific TGFβRIIDN Armored (C-CAR031) Phase I data in Hepatocellular Cancer

Most patients experienced Grade 1/2 CRS

Adverse Events	N=24 n (%)
TRAEs[1]	24 (100)
• Grade 3/4	9 (37.5)
• Grade 5	0
SAE[2]	5 (20.8)
AESI	22 (91.7)
• CRS*	22 (91.7)
• Grade 3	**1 (4.2)**
• ICANS*	0

CRS	DL 1 N=1	DL 2 N=6	DL 3 N=9	DL 4 N=8	Overall N=24
***CRS, n (%)**	1 (100)	5 (83.3)	8 (88.9)	8 (100)	22 (91.7)
• Grade 1/2	1 (100)	5 (83.3)	8 (88.9)	7 (87.5)	21 (87.5)
• Grade 3	0	0	0	**1 (12.5)**	**1 (4.2)**
Median Days to Onset, d (range)	7 (7, 7)	3 (2, 3)	3 (2, 4)	2 (1, 3)	**3 (1, 7)**
Median Days to Resolution, d (range)	4 (4, 4)	6 (4, 8)	3 (2, 6)	5 (3, 8)	**4 (2, 8)**
Treated with					
• Tocilizumab, n (%)	0	4 (66.7)	6 (66.7)	7 (87.5)	17 (70.8)
• Corticosteroids, n (%)	0	2 (33.3)	1 (11.1)	1 (12.5)	4 (16.7)

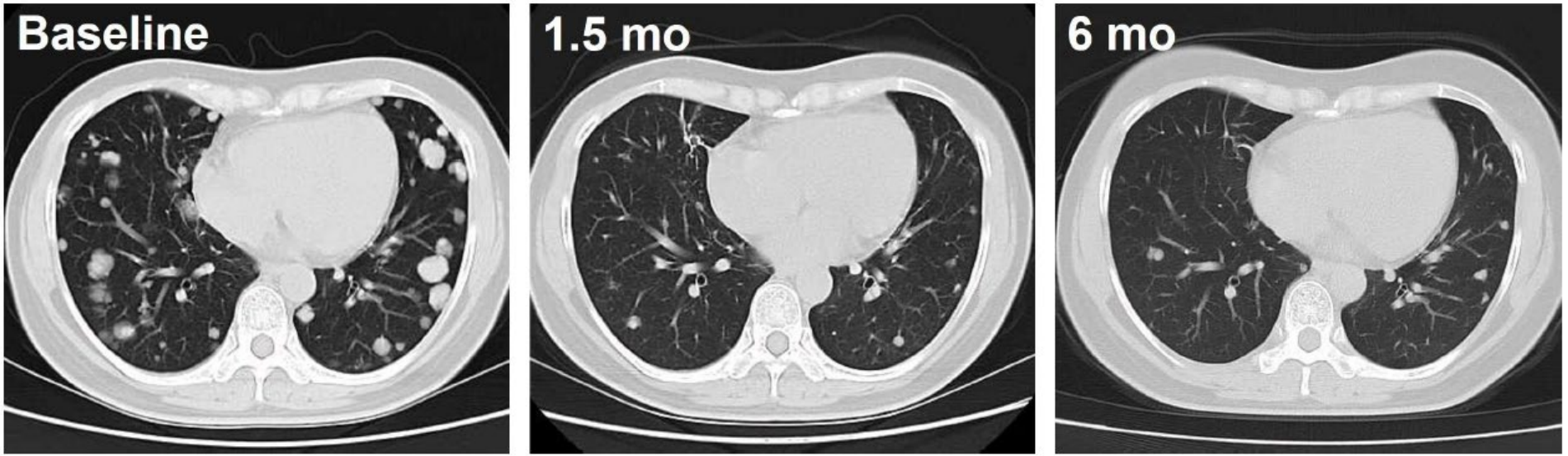
TRAE, treatment-related adverse event; SAE, serious adverse event; AESI, adverse event of special interest; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome

[1]. Defined as C-CAR031 related; [2]. Only 2 cases were C-CAR031 related; *, CRS/ICANS were graded per ASTCT Consensus (2019)

1. Qi Zhang et al *JCO* 42, 4019-4019(2024

GPC3-specific TGFβRIIDN Armored CAR-T
Phase I C-CAR031 data in Hepatocellular Cancer

C023 (at DL 4) showed deep response in lung metastases starting from 1.5 mo

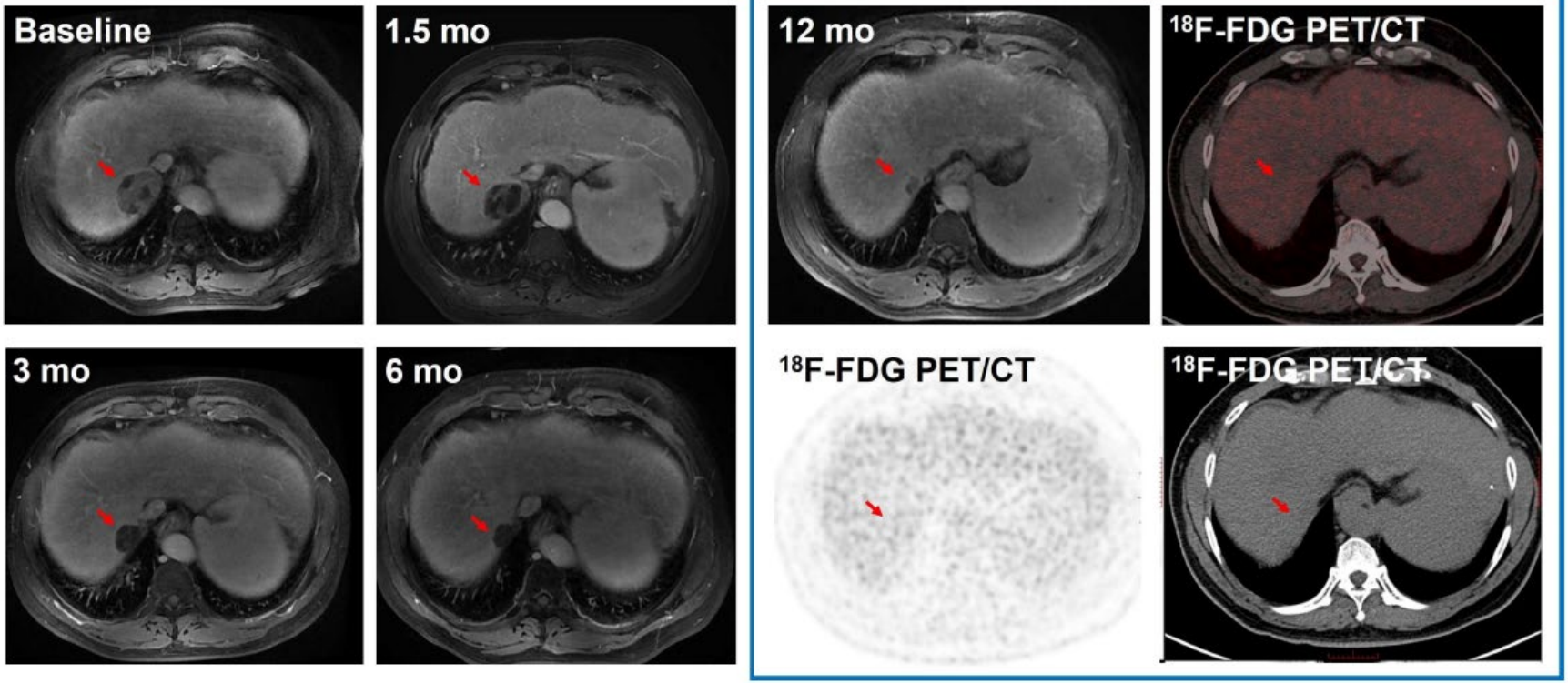


1. Qi Zhang et al *JCO* 42, 4019-4019(2024).

GPC3-specific TGFβRIIDN Armored CAR-T

Phase I C-CAR031 data in Hepatocellular Cancer

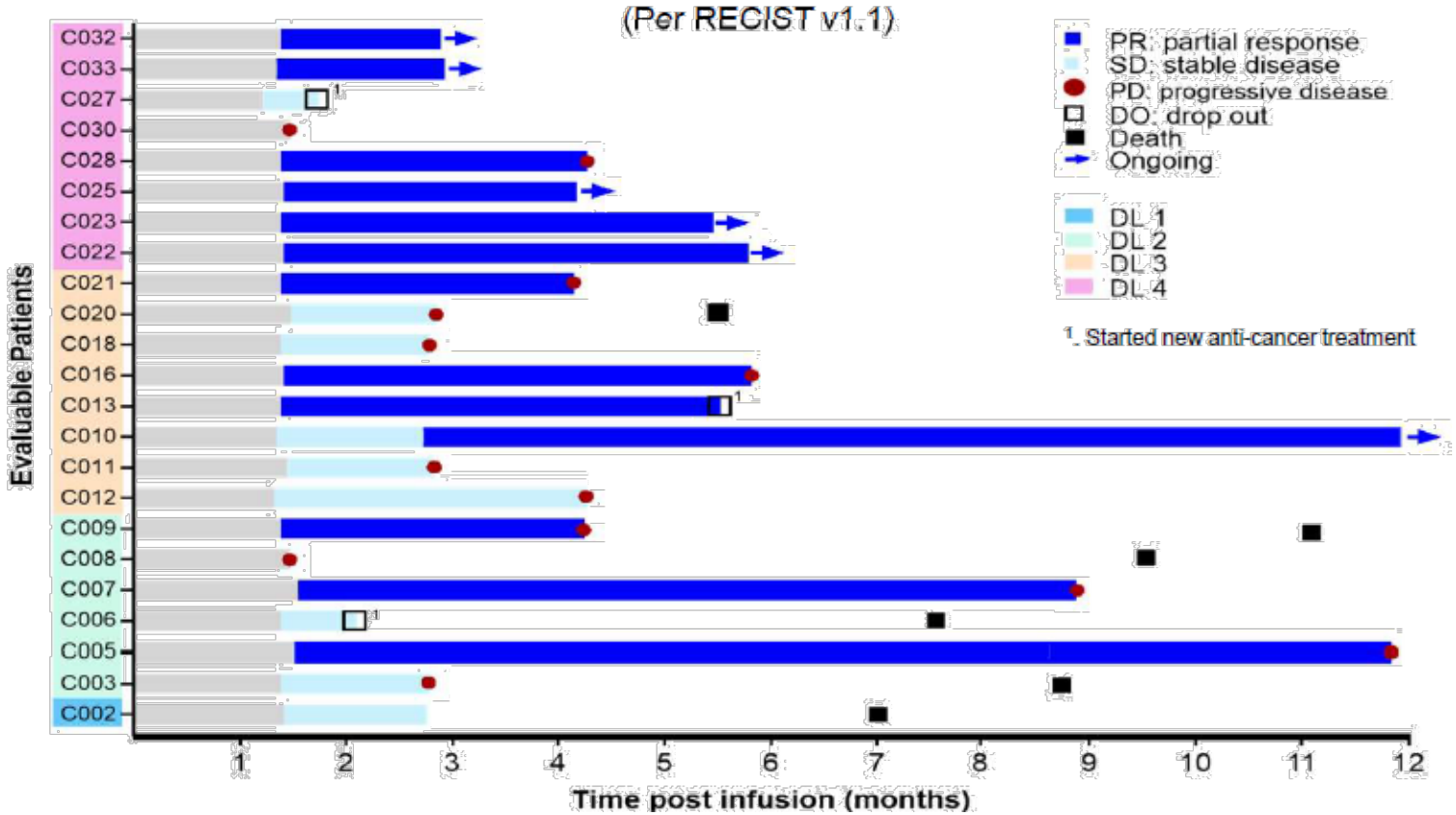
C010 (at DL 3) showed durable response up to 12 mo and potentially beyond



Data cut-off date: 14 March 2024

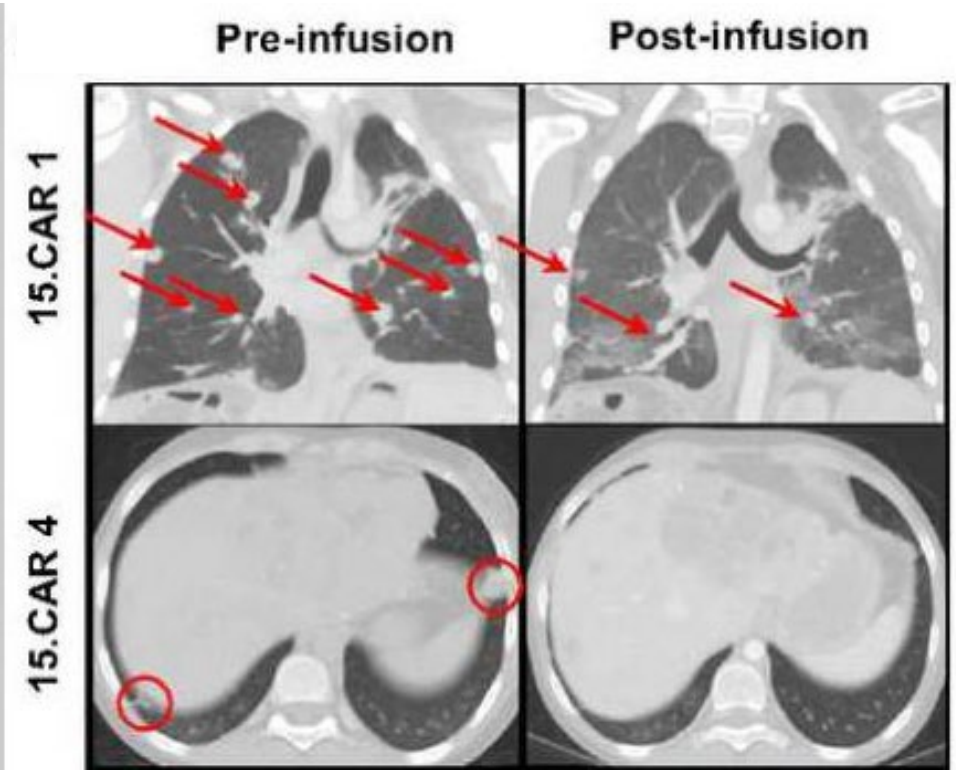
1. Qi Zhang et al *JCO* 42, 4019-4019(2024).

GPC3-specific TGFβRIIDN Armored CAR-T Phase I C-CAR031 data in Hepatocellular Cancer



1. Qi Zhang et al *JCO* 42, 4019-4019(2024).

GPC3-specific CAR-T in GPC3+ Solid Tumors
Includes IL-15 Co-expression (15.CAR)



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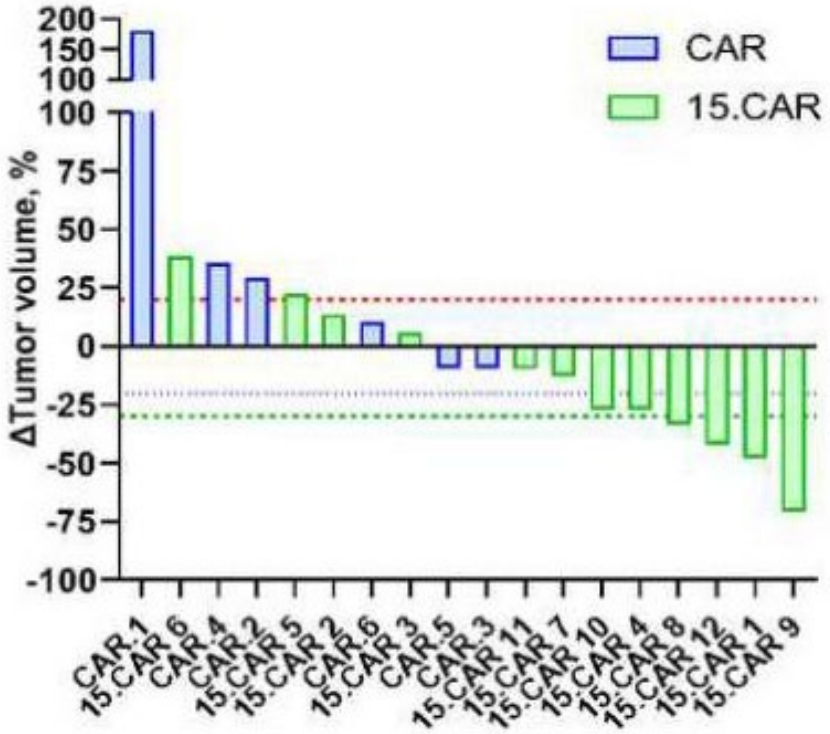
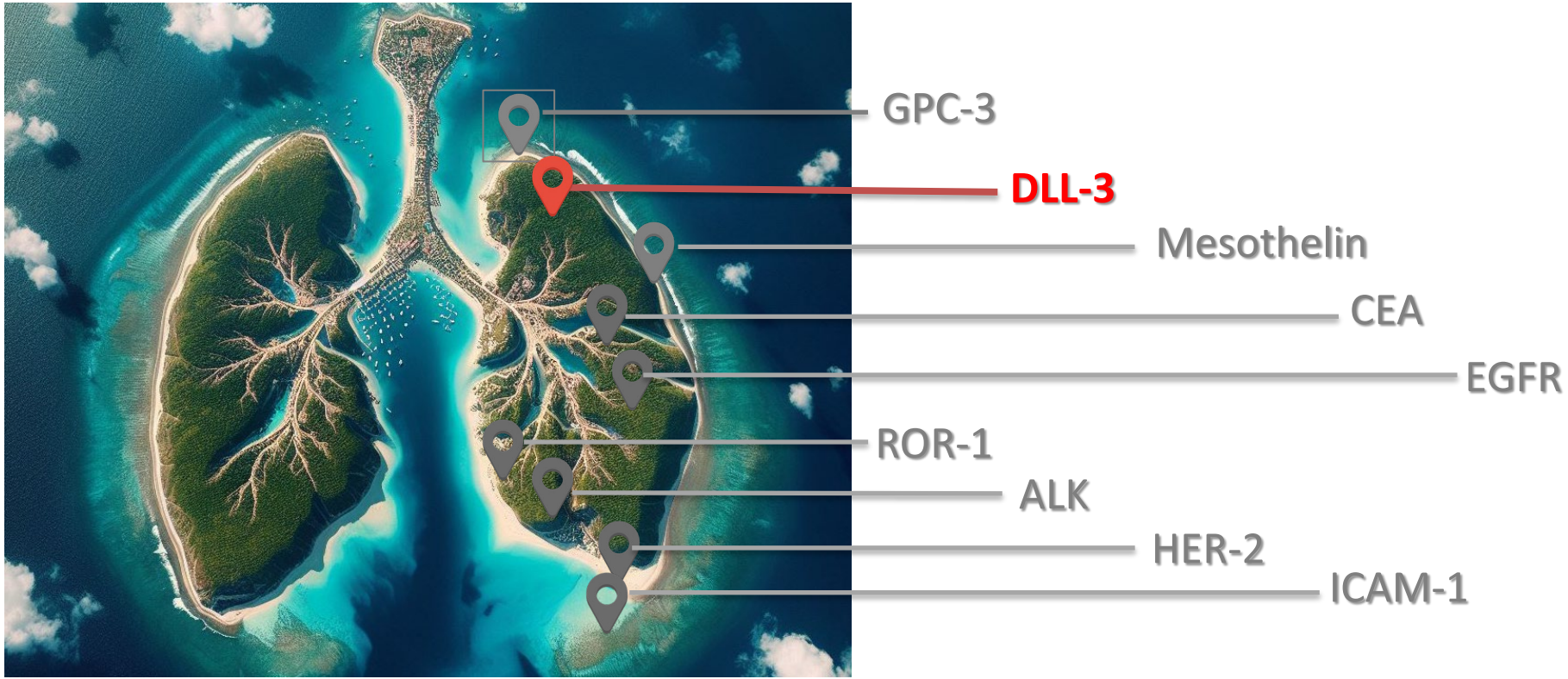


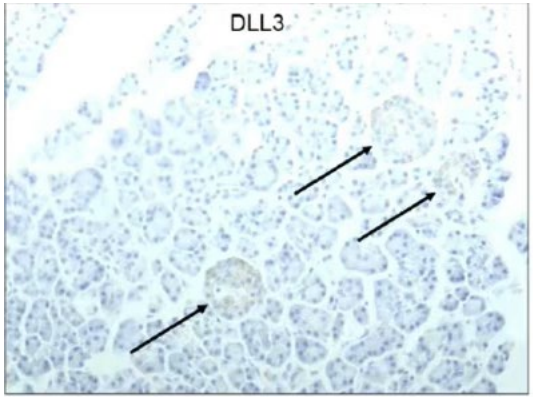
Steffin D. Ghatwai N, *et al.* Preprint. 2024 Apr 3 PMID: 38645165

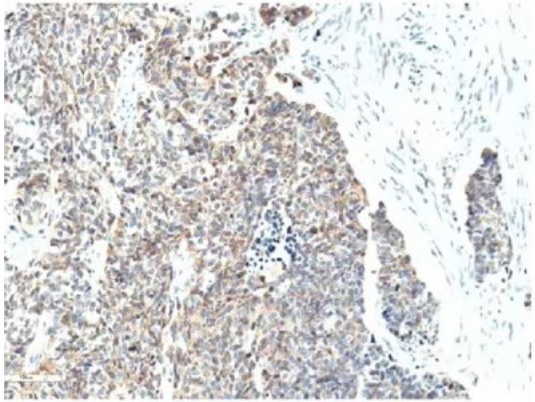
Mapping Lung Cancer: Targets for CAR-T



PRESENTED BY: Ben Creelan, MD @BenCreelan

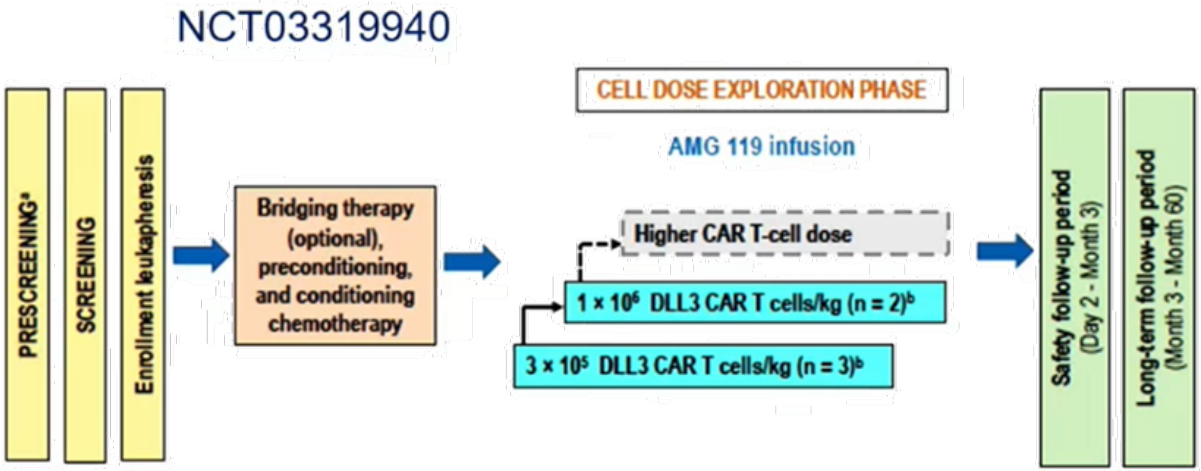
Delta-Like Ligand 3 (DLL3)

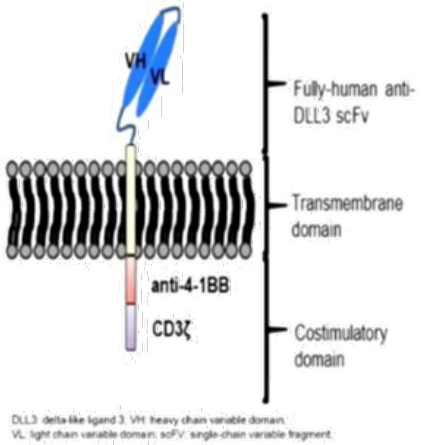




- Minimal expression (pituitary, ovary) normal cells
- Aberrantly expressed 85% LCNEC, SCLC
- Heterogenous expression

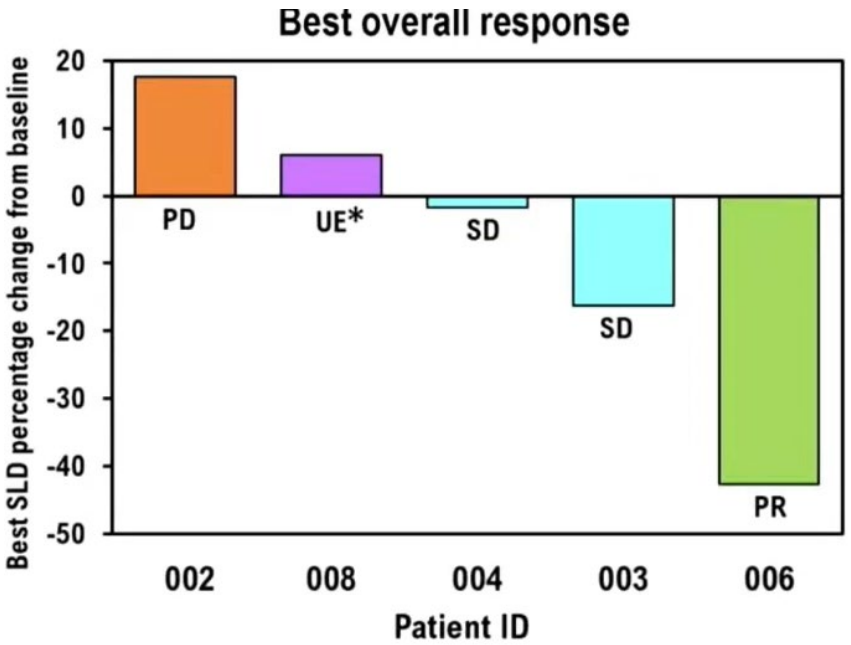
AMG119 CAR-T for SCLC: Ph1 Trial Design





Byers, L *et al*. SITC 2022

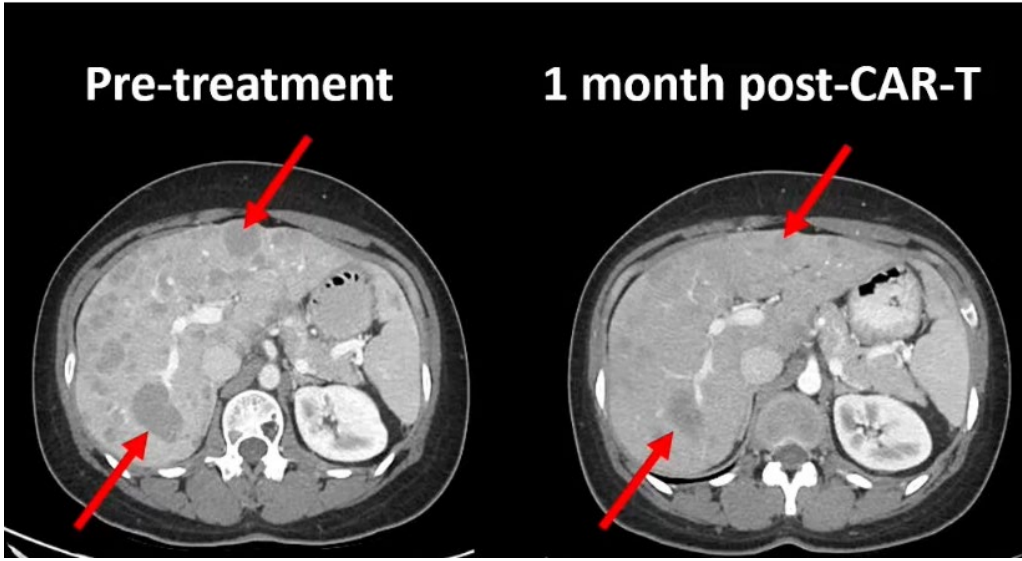
CAR T cell therapy for DLL3 is **safe** and **active** in neuroendocrine lung cancer.



- AMG119: *n* = 5 treated R/R ED-SCLC
- No DLTs or G4 TEAEs
- Benefit correlated w/ DLL3 expression
- CAR persistence >86 days post-infusion

Byers, L *et al.* SITC 2022

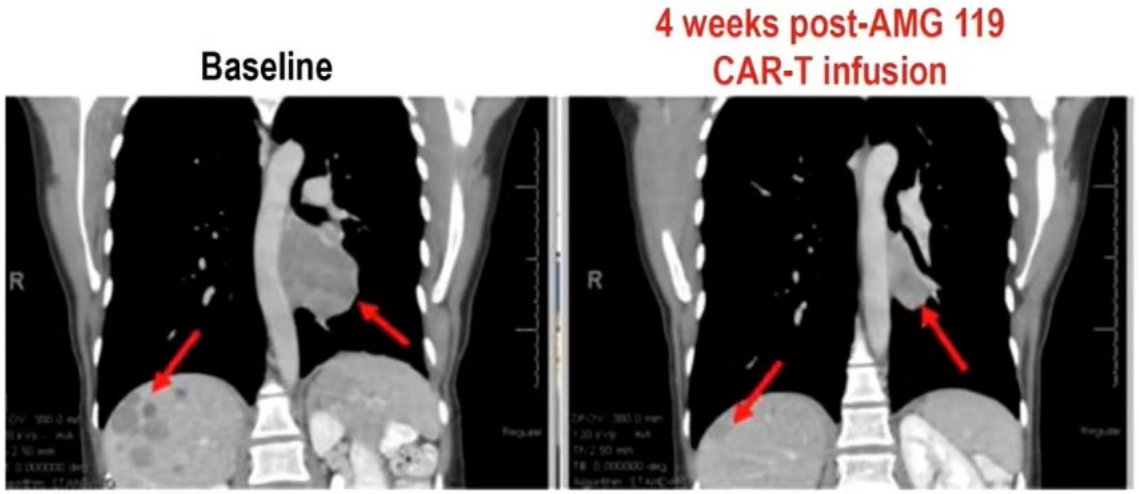
Example of **minor response** to DLL3 CAR_T AMG119



- Treated at lowest dose level ($3x10^5$ cells/kg)
- Two prior lines of chemotherapy
- 16% decrease in target lesions
- PFS 6.7 mo, OS 15.4 mo

Byers, L *et al.* SITC 2022

2nd Example of **partial response** to AMG119, DLL3 CAR-T

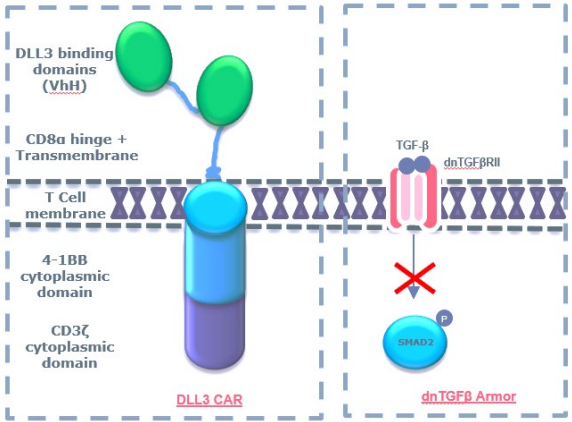


- Treated at 2nd lowest dose level (1x10^6 cells/kg)
- 43% decrease in target lesions by RECIST
- PFS 6 mo, OS 19 mo

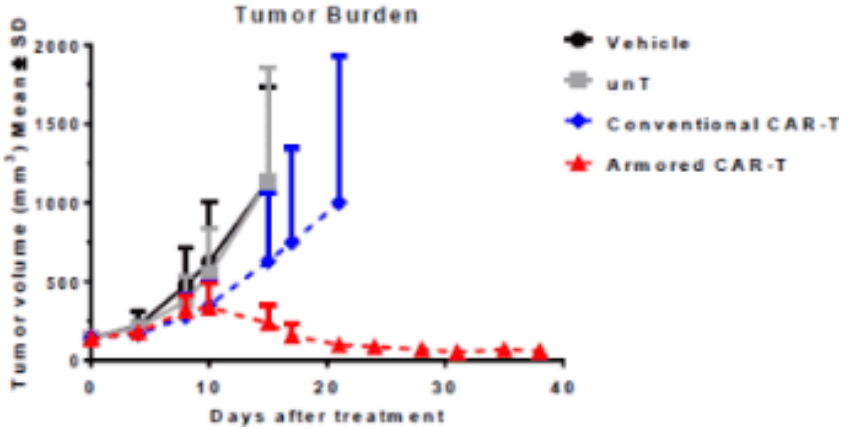
Byers, L *et al.* SITC 2022

LB2102: CAR-T V_HH targeting DLL3

Can an armored CAR do even better for SCLC?



- Tandem binders w/ high affinity and specificity
- TGFB for TME to promote infiltration
- Well-tolerated *in vivo* in s.c and pulmonary xenograft
- Accruing 1st pts Q4 2023



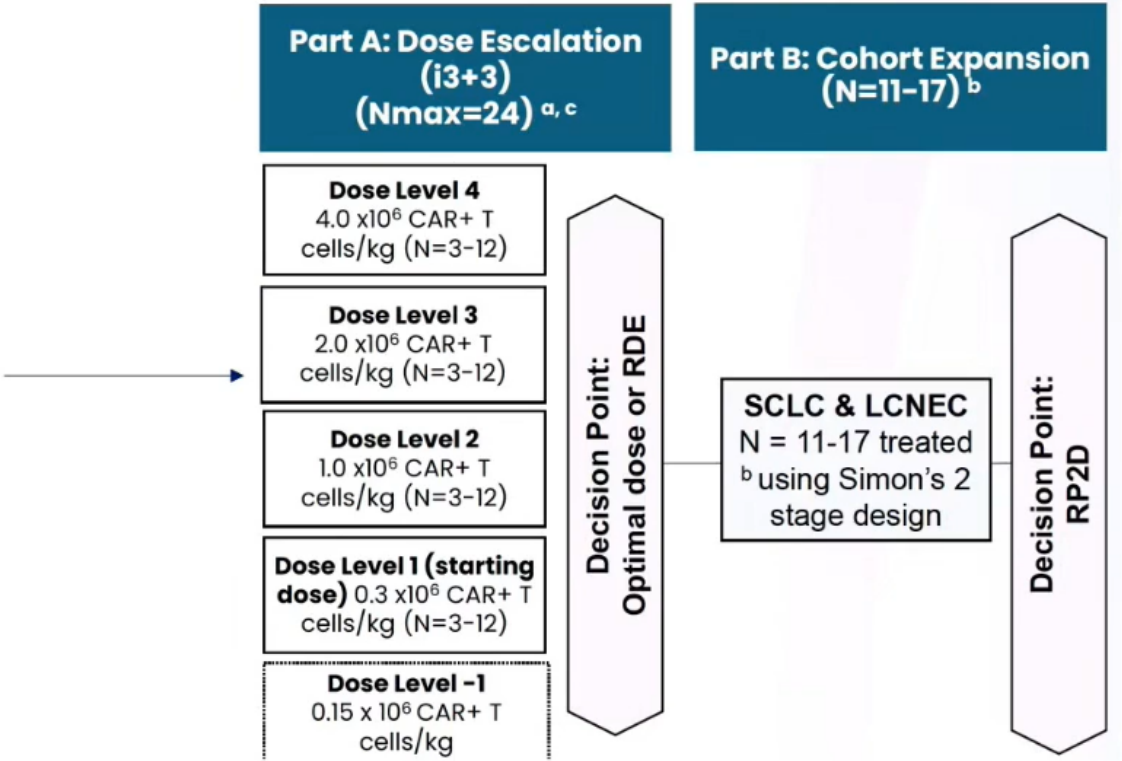
Sands, J. *et al.* SITC 2023

LB2102: CAR-T V_HH targeting DLL3

Can a CAR do even better than a BiTE for SCLC?

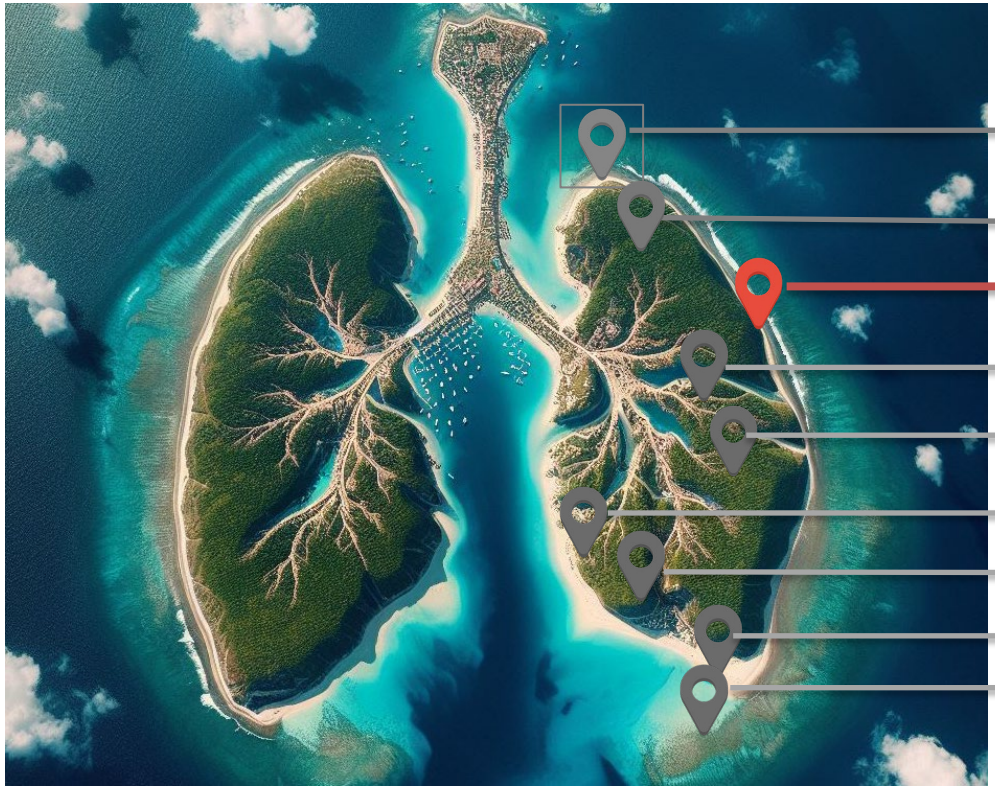
Patient population:

- Extensive stage small cell or large cell lung cancer
- Received at least 1 prior line of therapy
- No active CNS disease
- No prior DLL3 therapy



Sands, J. *et al.* SITC 2023

Mapping Lung Cancer: Targets for CAR-T



GPC-3

DLL-3

Mesothelin

CEA

EGFR

ROR-1

ALK

HER-2

ICAM-1

Presented by: Ben Creelan, MD

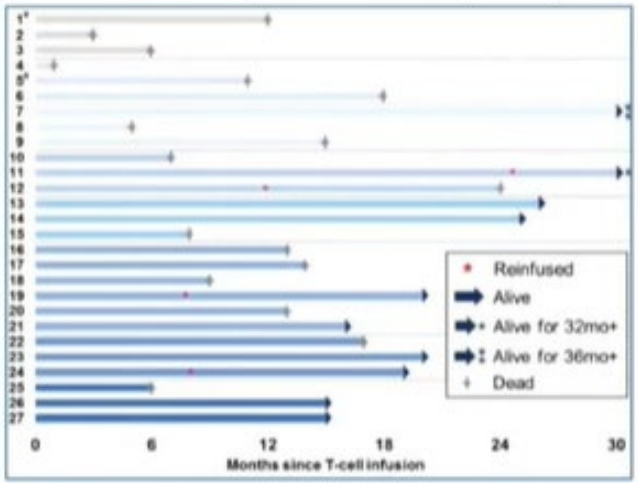
@BenCreelan

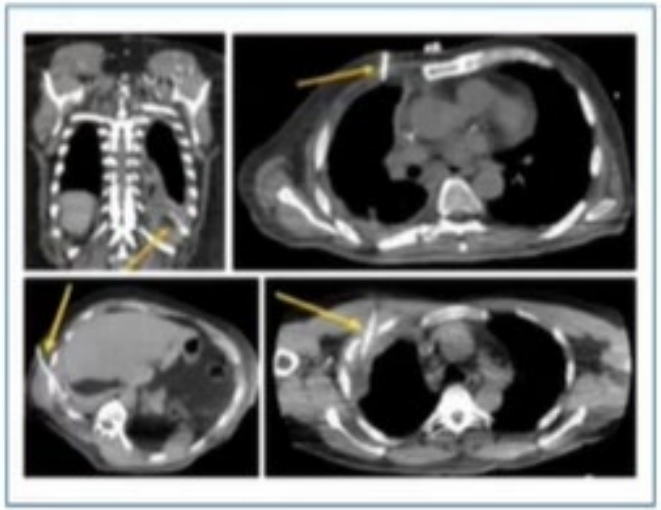
Regional Infusion of anti-Mesothelin CAR-T
Delivers Cells Directly to Ideal Organ

Regional administration -

- avoids pulmonary sequestration
- facilitates immediate dose expansion

Intrapleural administration of CAR T cells in a phase I trial (N=27)

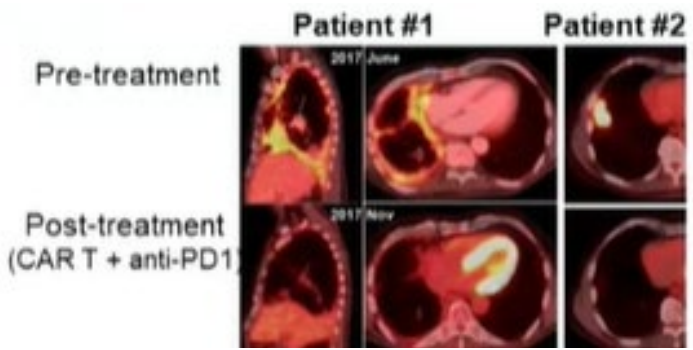




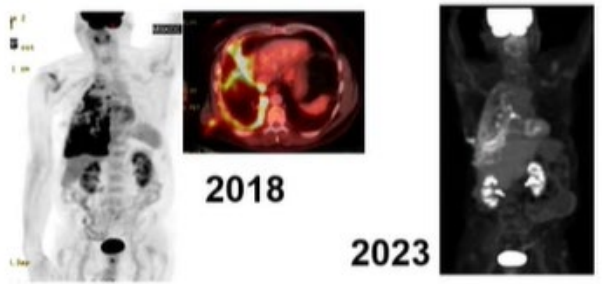
1. Ghosn M., Adusumilli PS, *et al.* Lung Cancer 2022
2. Adusumilli PS., Sadelain M. Cancer Discovery 2021

Anti-Mesothelin Pleural CAR-T Cells Phase I/II with PD1 Antibody

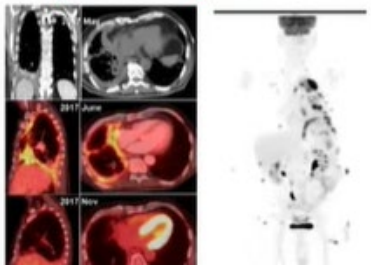
- MPM patients treated with 1 dose CAR-T plus ≥3 doses ICI
- Addition of anti-PD1 well-tolerated
- Complete metabolic response in 2 pts
- Prior lines of therapy 1 (62%), ≥2 (38%)
- Responses regardless of PD-L1 status



➢ 5-year survivor
(unresectable, s/p chemo, SUV>10)

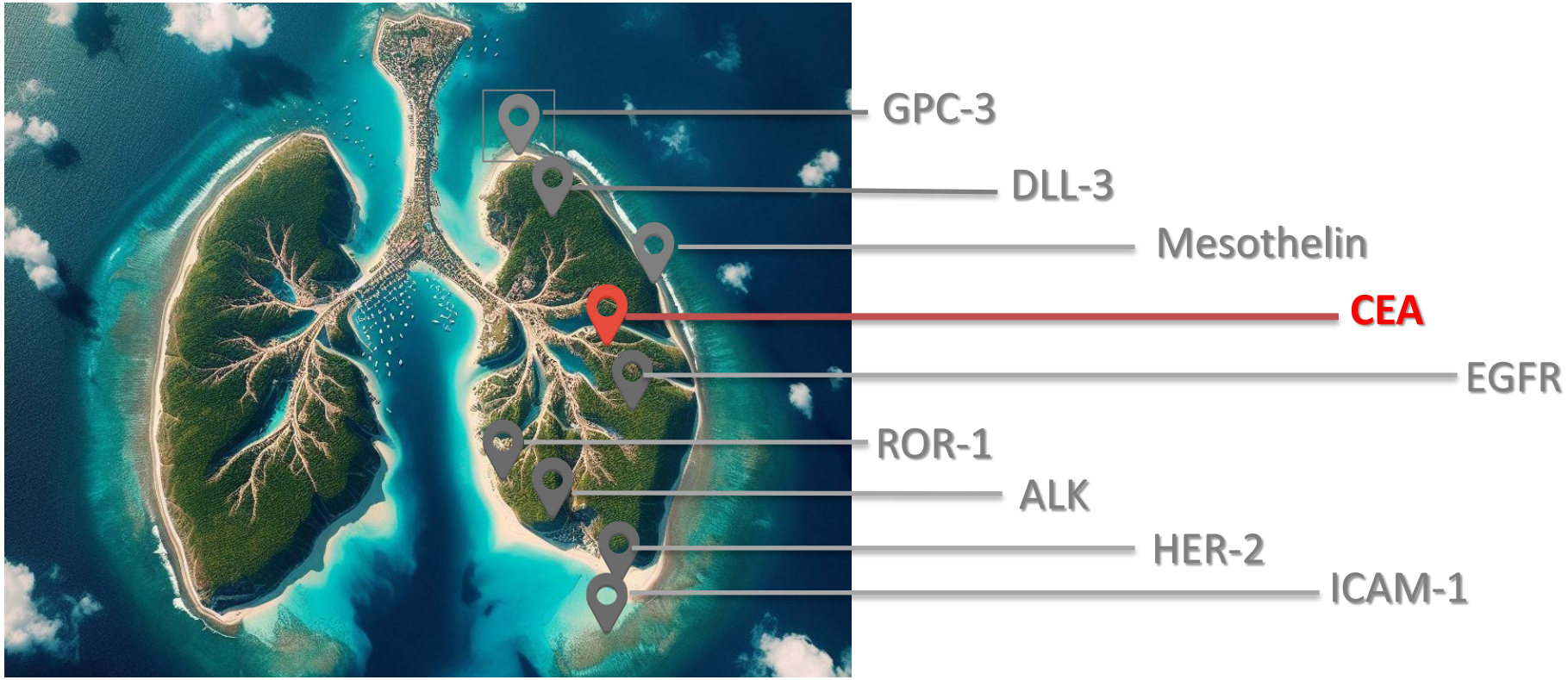


➢ Multiple 3-4 yr. survivors



1. Ghosn M., Adusumilli PS, *et al.* Lung Cancer 2022
2. Adusumilli PS., Sadelain M. et al. Cancer Discovery 2021
3. Adusumili PS., et al. iw-CAR-T Congress 2024

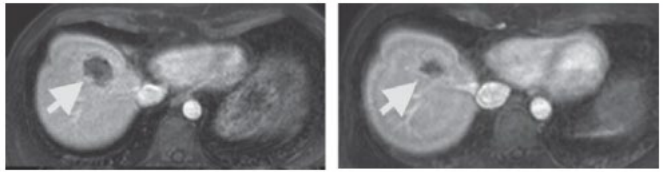
Mapping Lung Cancer: Targets for CAR-T



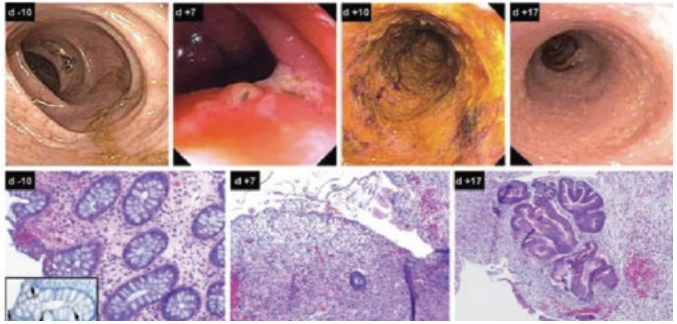
Classic Targets for Transgenic Therapy:
Mixed results over past decade

2011: NCI CEA HLA-A2 TCR T Cells

Efficacy: reduction in tumor size

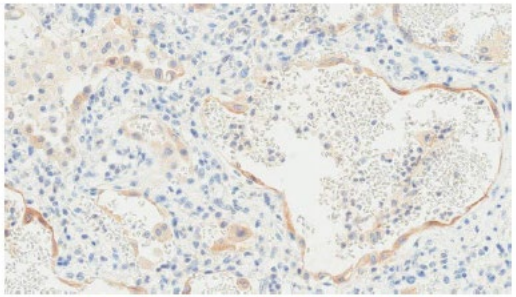


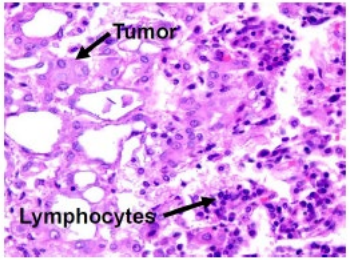
Toxicity: Grade 3 diarrhea and colitis



2021: Penn M5 MSLN CAR T

Toxicity: Grade 4 CRS and Grade 5 pulmonary failure

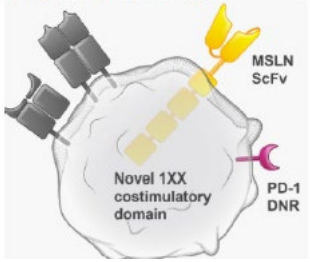




2022: MSKCC MSLN CAR T

Toxicity: Grade 5 SAE

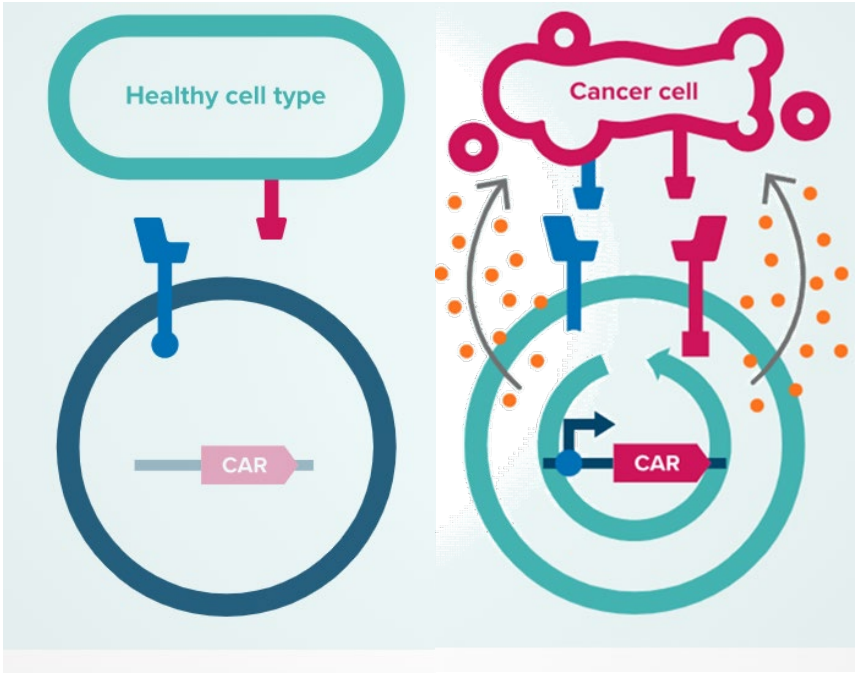
- scFv that binds MSLN above cancer threshold
- 1XX costimulatory domain and PD-1 Dominant Negative Receptor (DNR)
- ATA3271: off-the-shelf, allogeneic EBV mesothelin CAR T

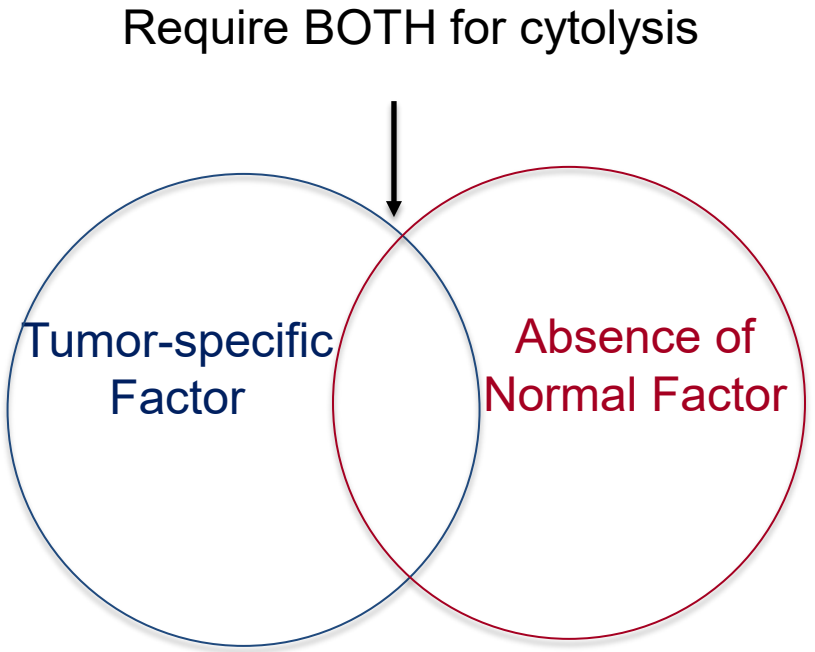


Parkhurst et al Mol Ther. 2011 Mar;19(3):620-6
Tanyi JL et al. Cellicon 2021 May 6th, 2021
BusinessWire, Feb 18, 2022 Atara Biotherapeutics Provides Update on ATA2271

Dual Antigen Logic Gate for Tumor Specificity

Either Yes/Yes or Yes/No Signals to Avoid Off-Tumor Toxicity

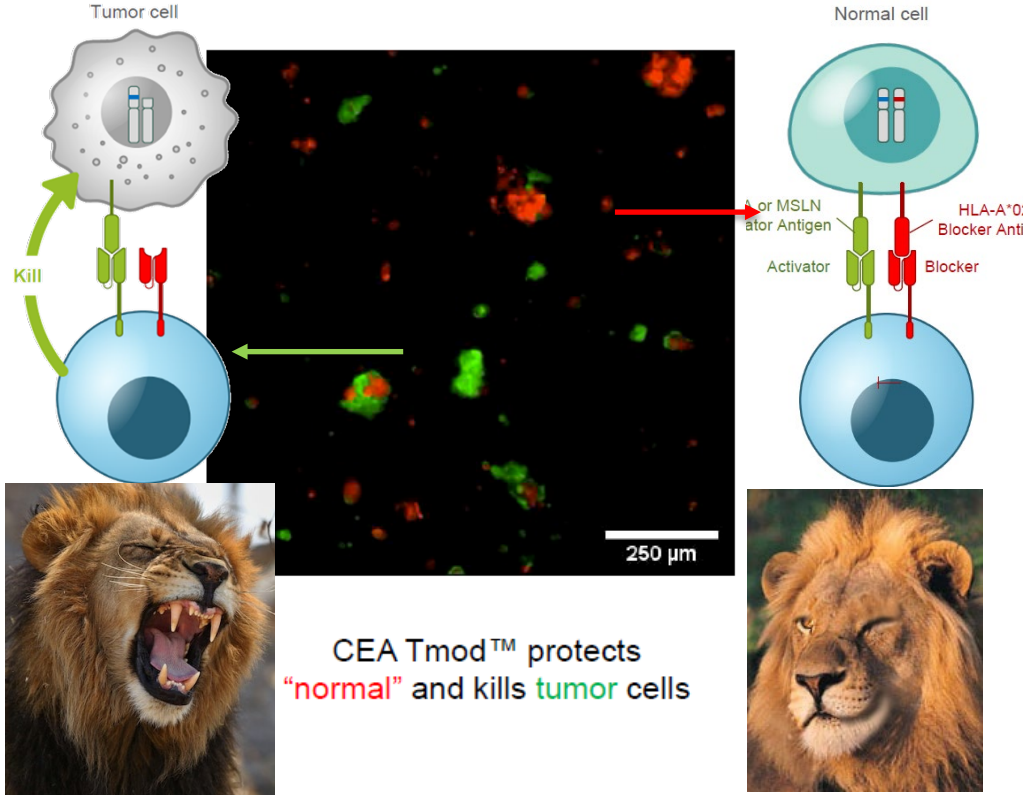




Buroughs AC et al. Cancer Res (2023) 83 (7_Supplement): 4088.

CAR-T targeting CEA and HLA-LOH in Solid Tumors

Gated to turn-on near tumor cells



CEA Tmod™ protects
"normal" and kills tumor cells

- Targets clonal loss of heterozygosity (LOH) in HLA
- 33% in certain cancers
- First blocker HLA-A*02 30-50% prevalence

Hamburger et al, Mol Immuno 2020

"Normal" = CEA(+)HLA-A*02(+) H508 colorectal cancer cell line (endogenous)
Tumor = CEA(+)HLA-A*02(-) H508 cell line (A*02 KO) E:T = 3:1; Tumor:Normal = 1:1
https://www.a2bio.com/our-pipeline/

CAR-T targeting CEA in Solid Tumors
Gated to turn-on near Tumor

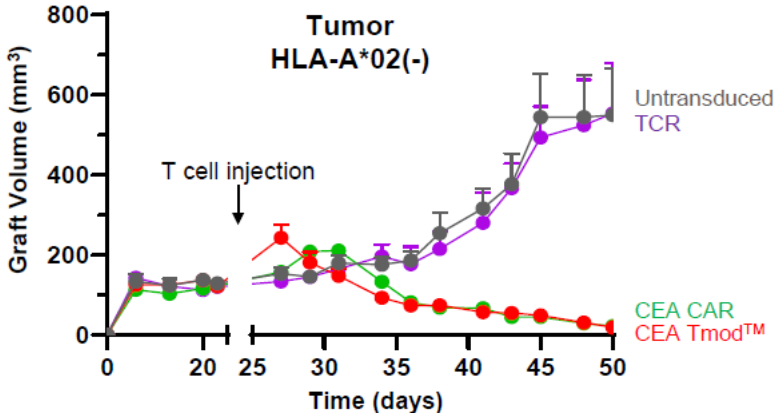
Xenograft Dual Flank Injection

Tumor
CEA(+)
HLA-A*02(-)

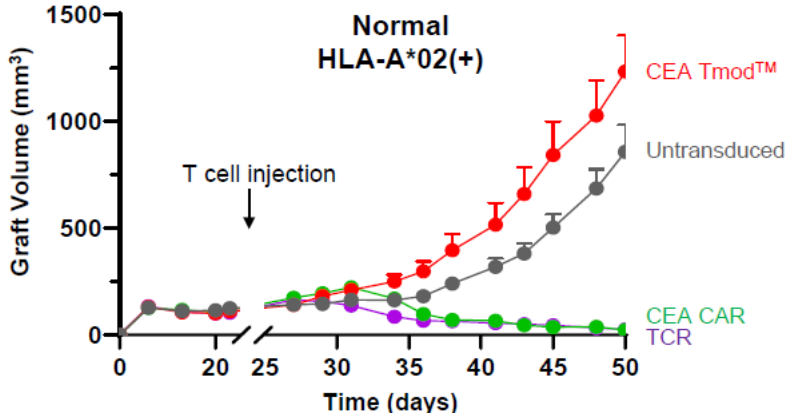
Normal
CEA(+)
HLA-A*02(+)

- N = 5 mice/group
- Xenograft = H508 colon cancer cell line
- Dose = 2E7 T cells/mouse (tail vein injection)
- TCR is HLA-A*02 restricted

CEA Tmod™ cells kill tumor equivalent to CAR-Ts

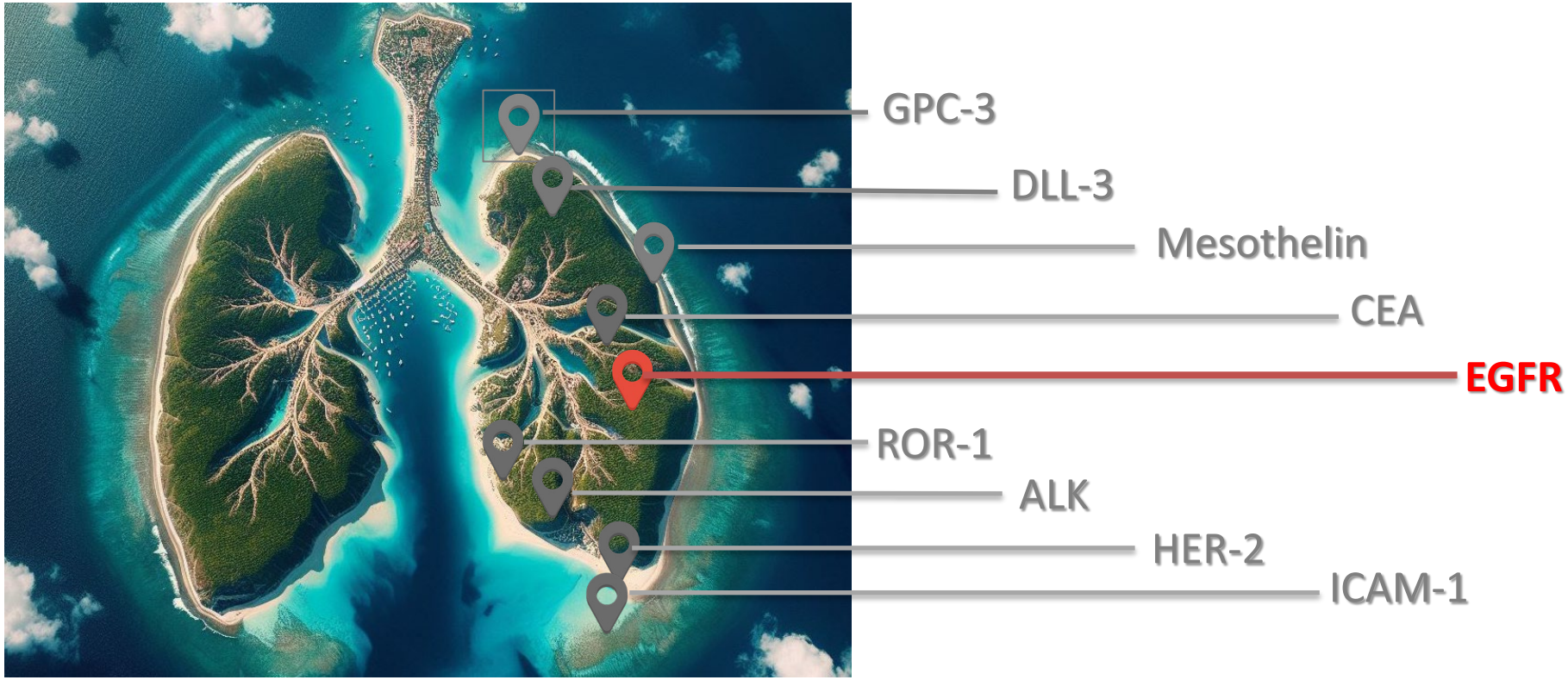


TCR-Ts kill normal equivalent to CAR-Ts



Sandberg et al. *Sci Trans Med* 2022.

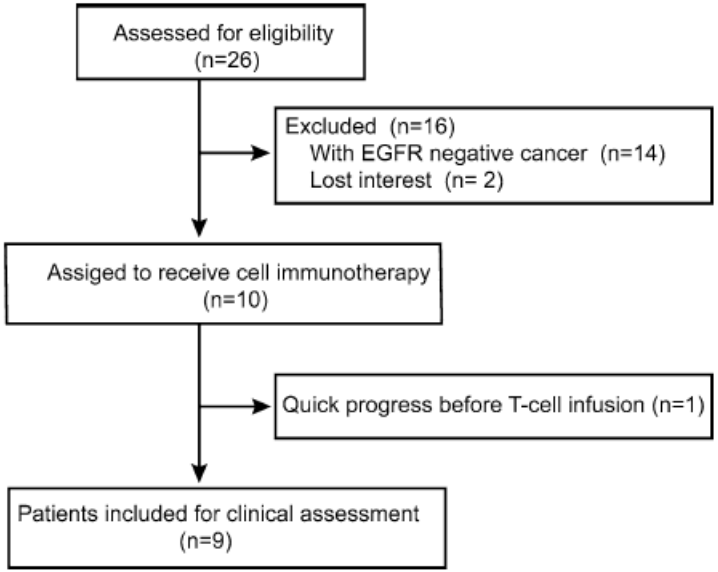
Mapping Lung Cancer: Targets for CAR-T



PRESENTED BY: Ben Creelan, MD @BenCreelan

Transposase-generated α-EGFR CAR-T

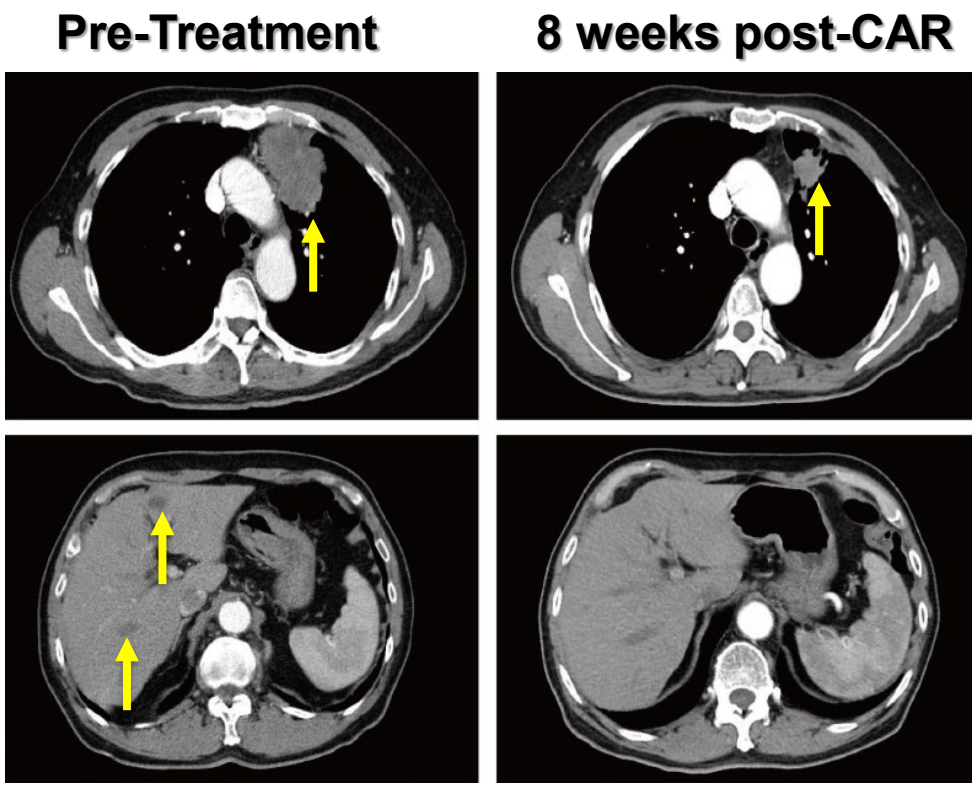
Tolerable adverse effects



Adverse event	No. of Patients ($N=9$)			
	Grade 1	Grade 2	Grade 3	Grade 4
Fever	2	4	1	0
Chill	2	0	0	0
Muscle weakness	2	0	0	0
Nausea/vomiting	1	0	0	0
Skin rash	1	0	0	0

Zhang Y, Zhang Z, Ding Y,et eta l. J. Ca Res Clin Onc

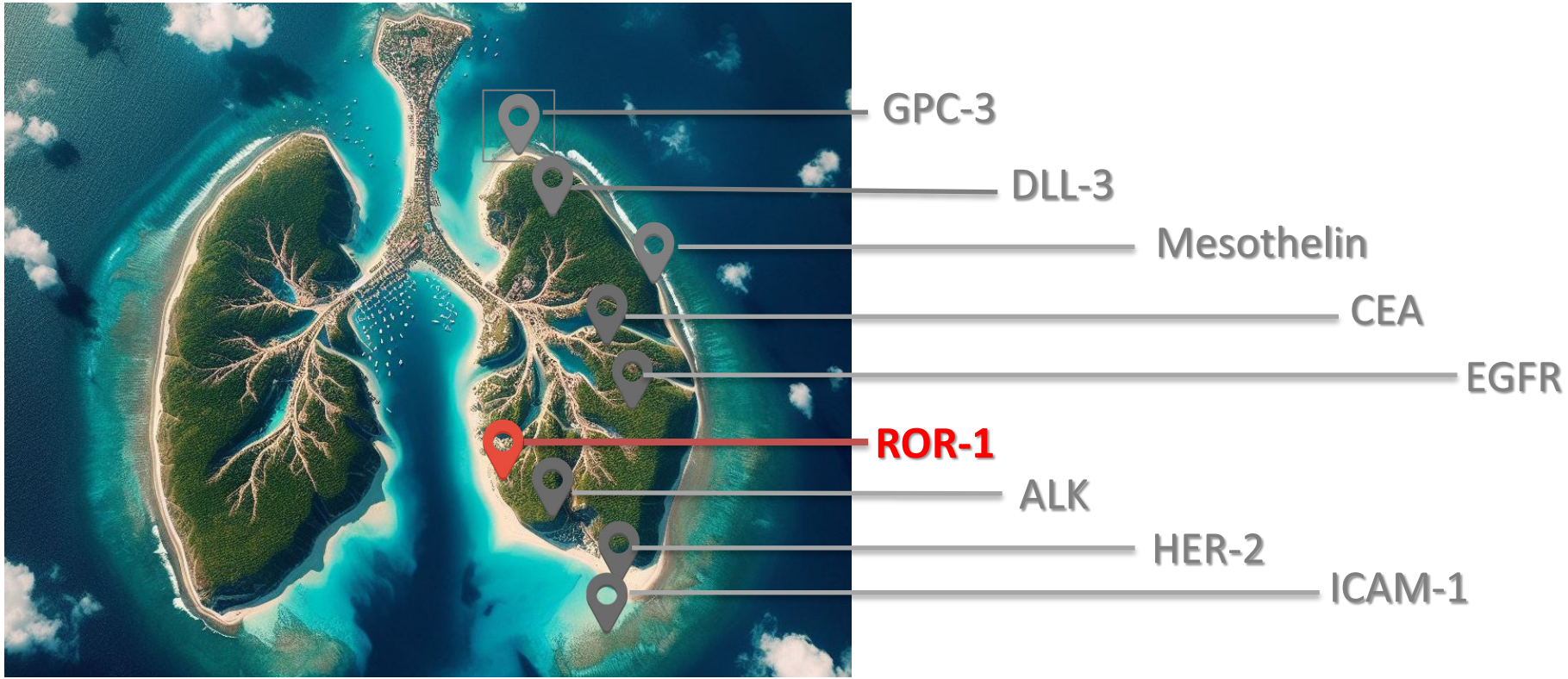
Example of **partial response** to α-EGFR CAR-T



- Stage 4 Squamous lung cancer
- Treated at low dose level ($3x10^6$ cells/kg)
- PR lasted for 13 months, 78% CRS, no co-stim

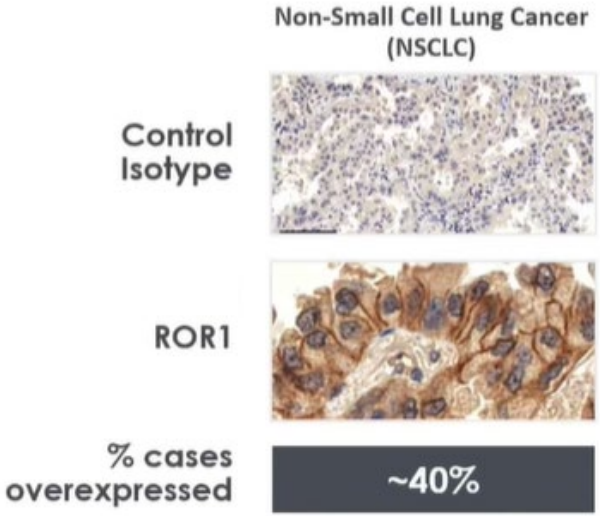
Zhang Y, Zhang Z, Ding Y,et eta l. J. Ca Res Clin Onc

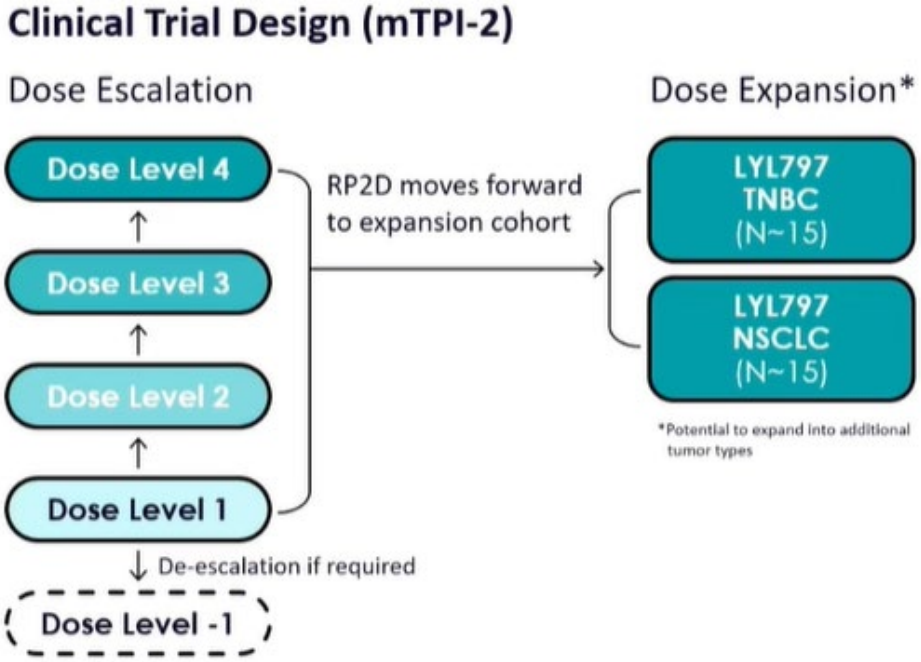
Mapping Lung Cancer: Targets for CAR-T



ROR-1 targeting CAR-T (LYL797) for ROR-1+ NSCLC

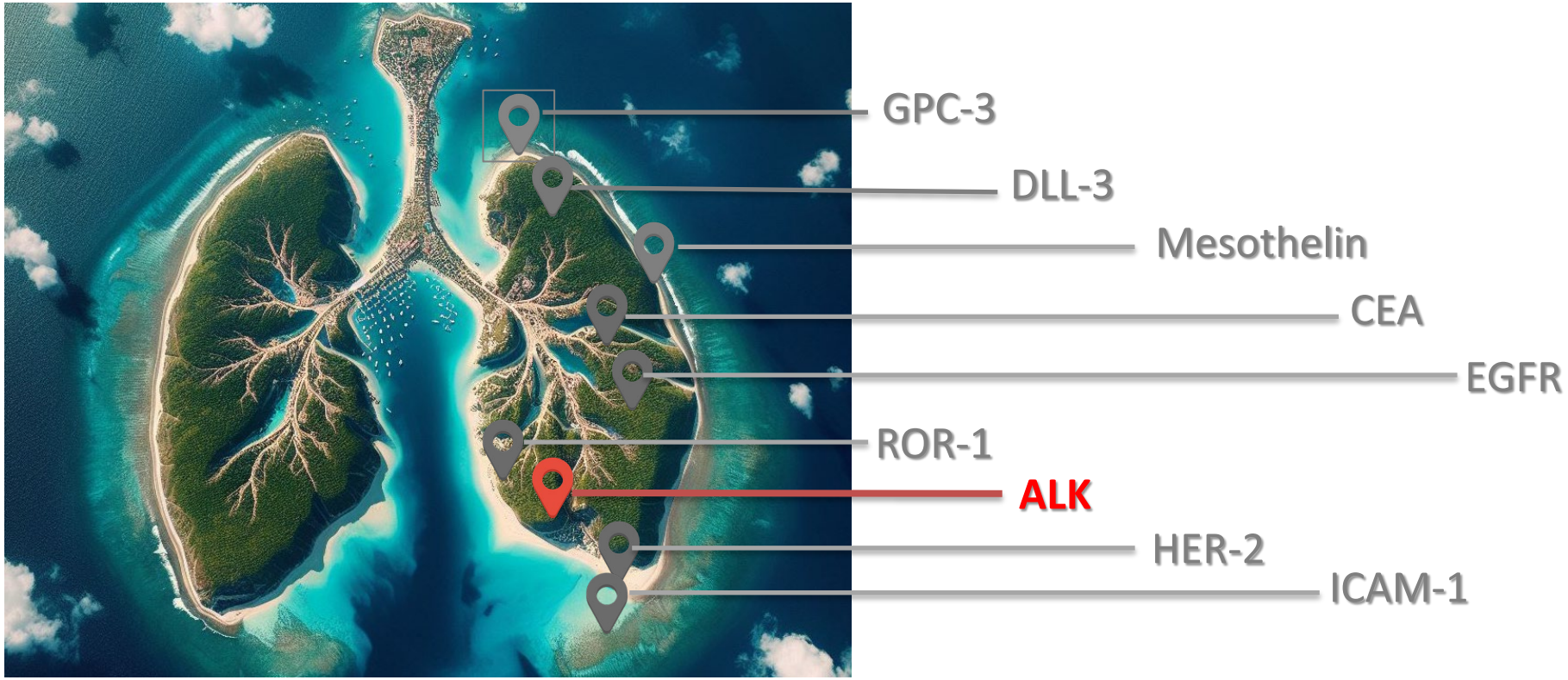
Includes c-Jun overexpression, cytokine signaling to overcome exhaustion





Balakrishan CCR 2017
Spigel et al. SITC 2023 NCT05274451

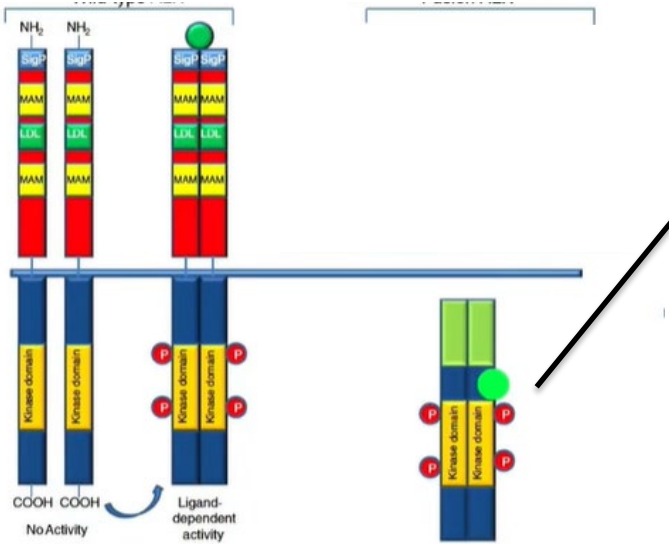
Mapping Lung Cancer: Targets for CAR-T

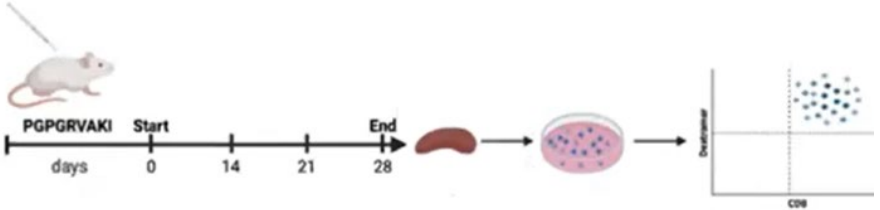


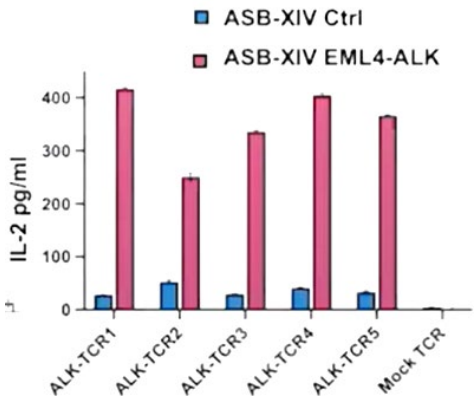
How to target aberrant ALK fusion with live T cells?
CAR-T if aberrant ALK, TCR if EML4-ALK fusion

Wild-type ALK
Membranous
90% Neuroblastoma

ALK Fusion
Cytoplasmic
4% NSCLC



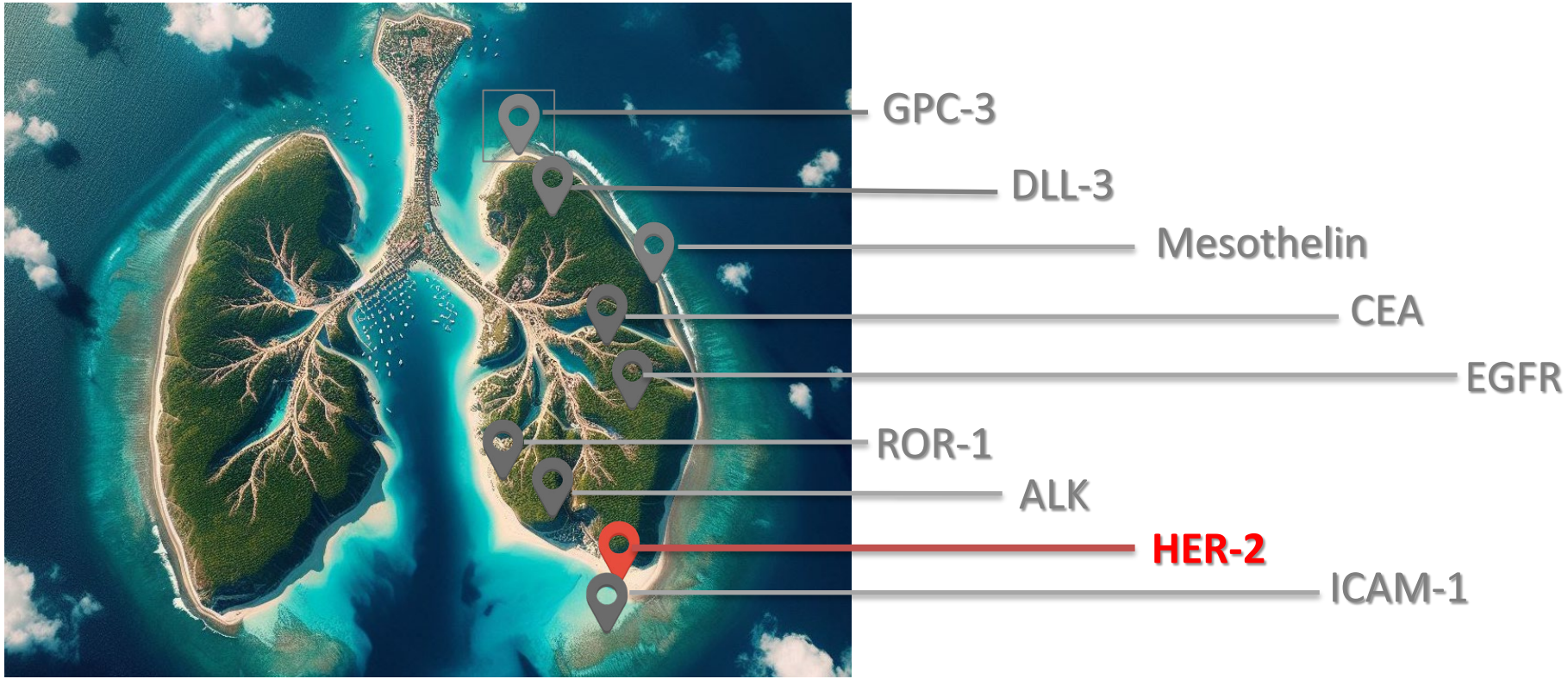




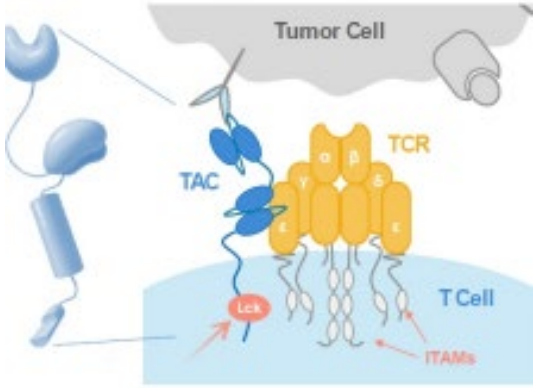
Morales La Madrid et al. Targ Onc 2012

Mecca, Carmen, et al. *Cancer Research* 84.6 Sup 2024: 21.

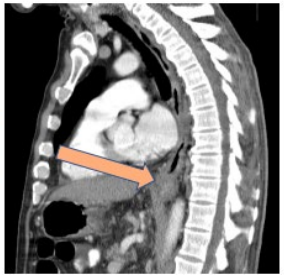
Mapping Lung Cancer: Targets for CAR-T



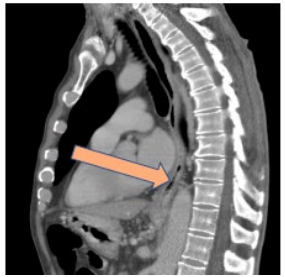
Targeting HER2 using T cell Antigen Couplers
A Lower Toxicity Alternative to CAR-T?



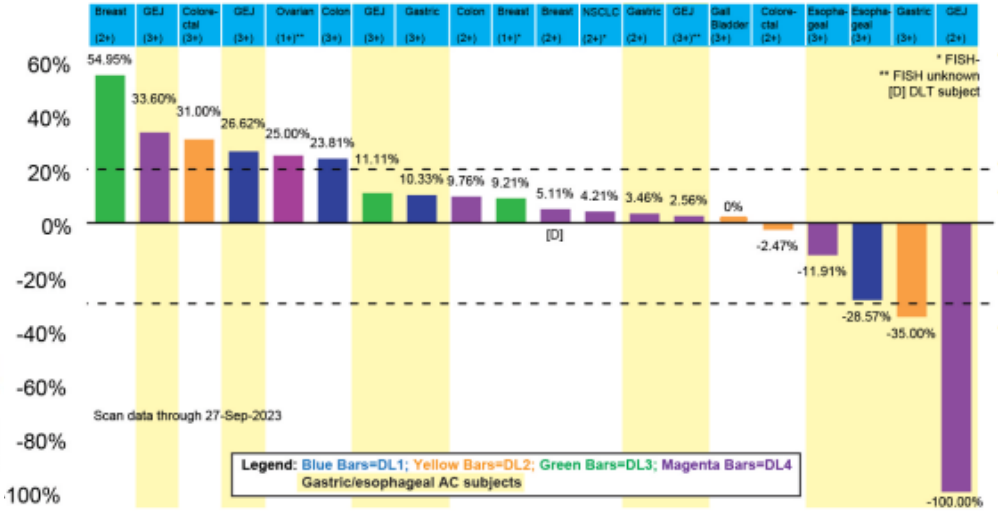
RECIST 1.1 Tumor Response Assessments (Measurable Disease)		
Baseline	Day 29	% change
30 mm	0 mm	-100%



Baseline
Day 0
(3.00 cm)

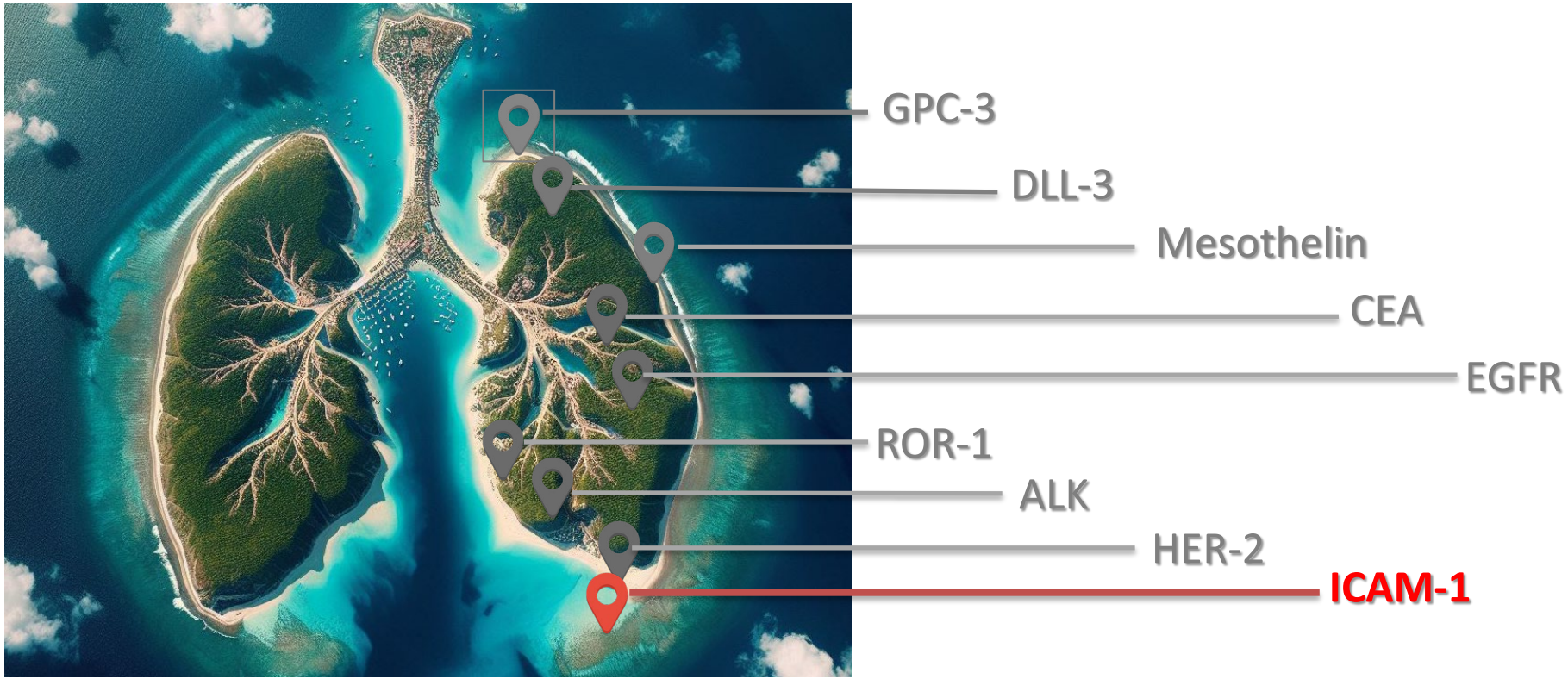


Day 29
(0 cm)



9/10 Pts had CRS
Olson D Dumbrava E et al. SITC (2023) 83

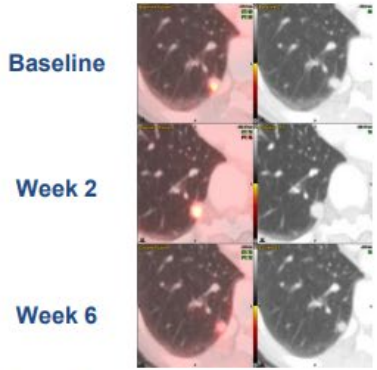
Mapping Lung Cancer: Targets for CAR-T



PRESENTED BY: Ben Creelan, MD @BenCreelan

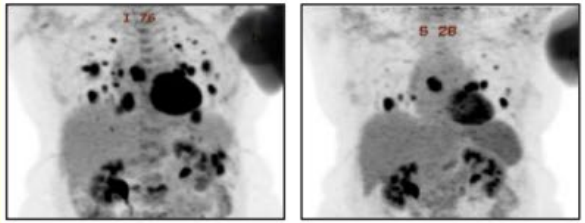
CAR-T Targeting ICAM-1 in Thyroid Cancer
Potential to Treat ICAM-1+ Lung Cancers Too?

Deep Tumor Regression at Low Dose



Confirmed partial response at month three at 100M cell dose

Tumor Shrinkage Observed in Metastatic Lesions



Tumor shrinkage in distant lung lesions

No DLT at High Dose

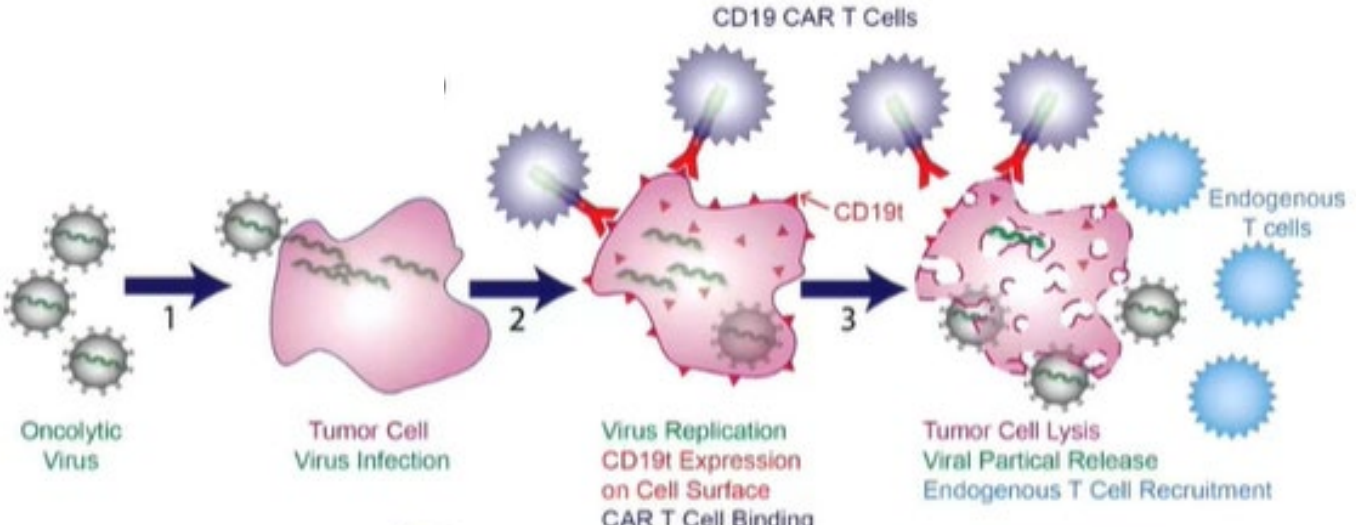
No DLT at 500M cell dose

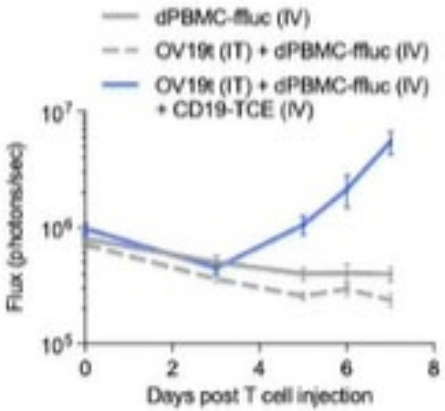
- ORR 33%, DCR 67%.
- ICAM1 expressed in ~33% NSCLC

Srour SA et al. J Clin Oncol 42, 2024 (suppl 16; abstr 6112)

Off-the-shelf Cell Therapy Using Oncolytic Virus for All Solid Tumors

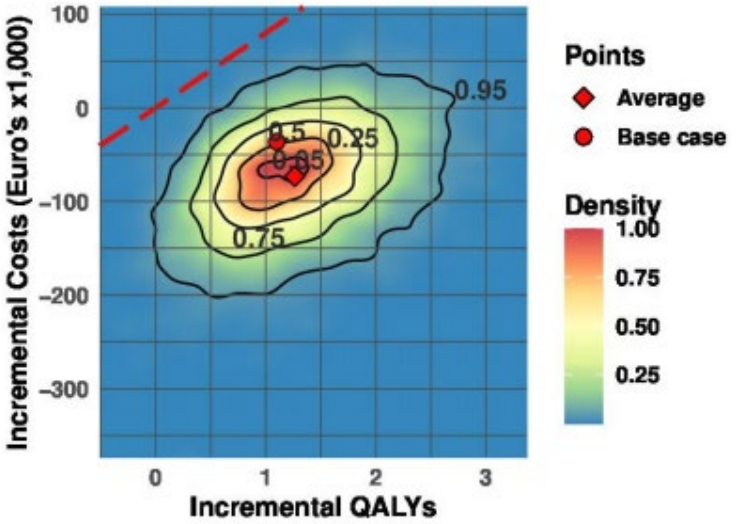
Forces tumor to express truncated CD19





1. Park, Priceman *et al.* Sci. Trans. Med. 2020
2. NCT06063317 onCARlytics (CF33-CD19) With Blinatumomab in Solid Tumors (OASIS)

Cell therapy can be more **cost-effective** than frequent infusions.



- Probabilistic sensitivity analysis
- Compares TIL vs ipilimumab for stage IIIC/IV melanoma in Danish/Dutch economy

QALY: quality adjusted life-years

J Immunother Cancer 2024; 12(3): e008372.

Goals: Industry vs. Patients

Not Every FDA Approval is a Victory for Patients

Industry Goal:

- *Lowest* possible bar
- *Continuous* therapy
- Medians >> Plateau
- Risk Adverse

Patient Goal:

- Potential for long remission
- *One-time* treatment
- Plateau >> Median
- Risk-motivated (some)

CAR-T in Non-small Cell Lung Cancer: Key Takeaways

- GPC3 CARs show astonishing efficacy in HCC, may translate to SqNSCLC
- DLL3 CAR-T can induce cancer regression in neuroendocrine lung ca
- Classical antigens (mesothelin, CEA) revisited using **multi-pronged gating**
- Development of HLA-restricted TCRs for ALK pMHC underway
- So Far, Lymphodepletion and Armoring (TGFβ, IL-15) Essential
- T cell:Antigen Coupler Cells have less toxicity than CARs, transient effect

THANK YOU