Cellular Therapies in NSCLC – Is it feasible?

MaTOS – November 18th, 2023

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Cellular Therapies

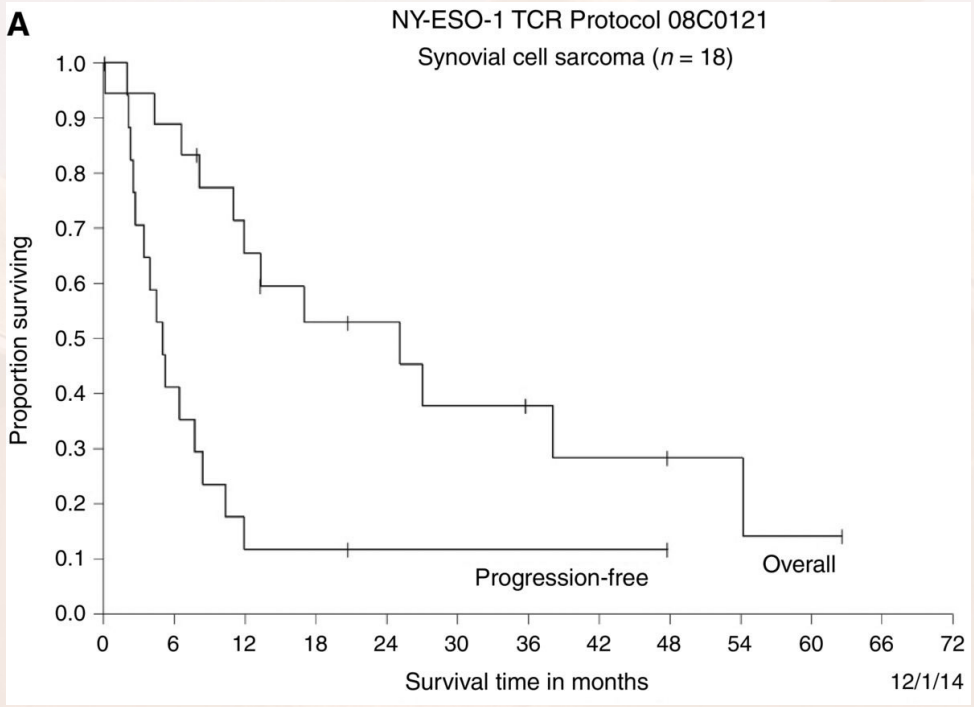
- Encompasses T-cell engaging therapies (TCEs) tumor-infiltrating lymphocytes (TILs), chimeric antigen receptor (CAR) T cell therapies and tumor vaccines.

- Key advantages of leveraging the adaptive immune system:
  - **Inherent cytotoxicity**
  - **Ability to overcome MHC downregulation**
  - **Cellular memory**

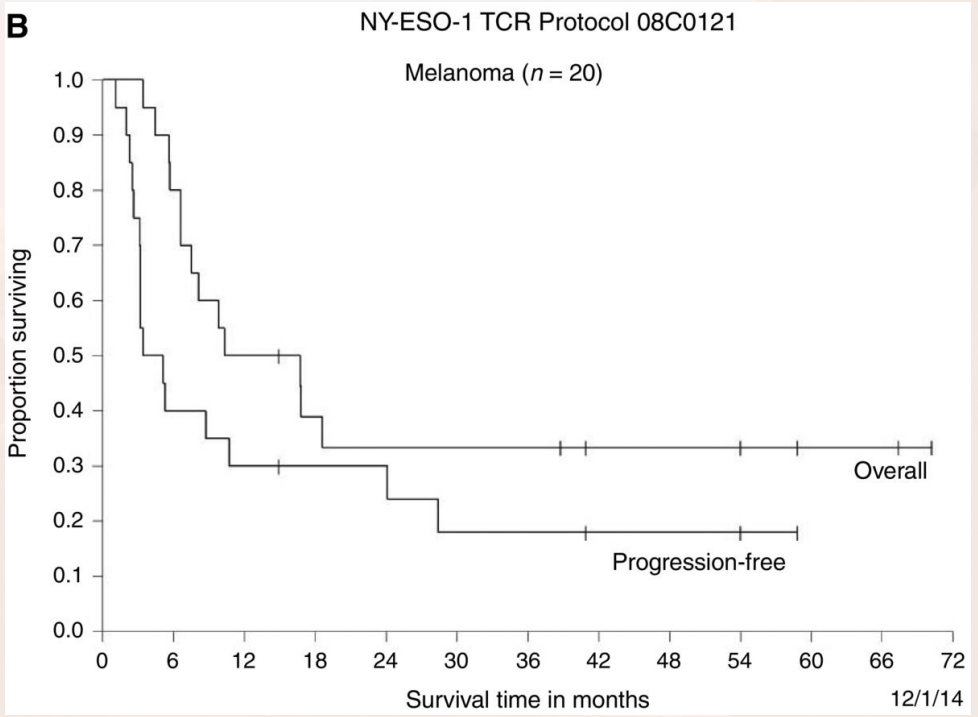
- Successes seen in hematologic malignancies using TCEs (ie blinatumomab) and CAR-T (ie tisagencleucel, axicabtagene ciloleucel and lisocabtagene maraleucel)

TCR Therapy in NY-ESO1 Expressing Tumors

- Autologous PMBCs were retrovirally transduced with an NY-ESO1 reactive T cell receptor (TCR)
- NY-ESO-1 is expressed in 70-80% of synovial sarcomas and 25% of melanomas



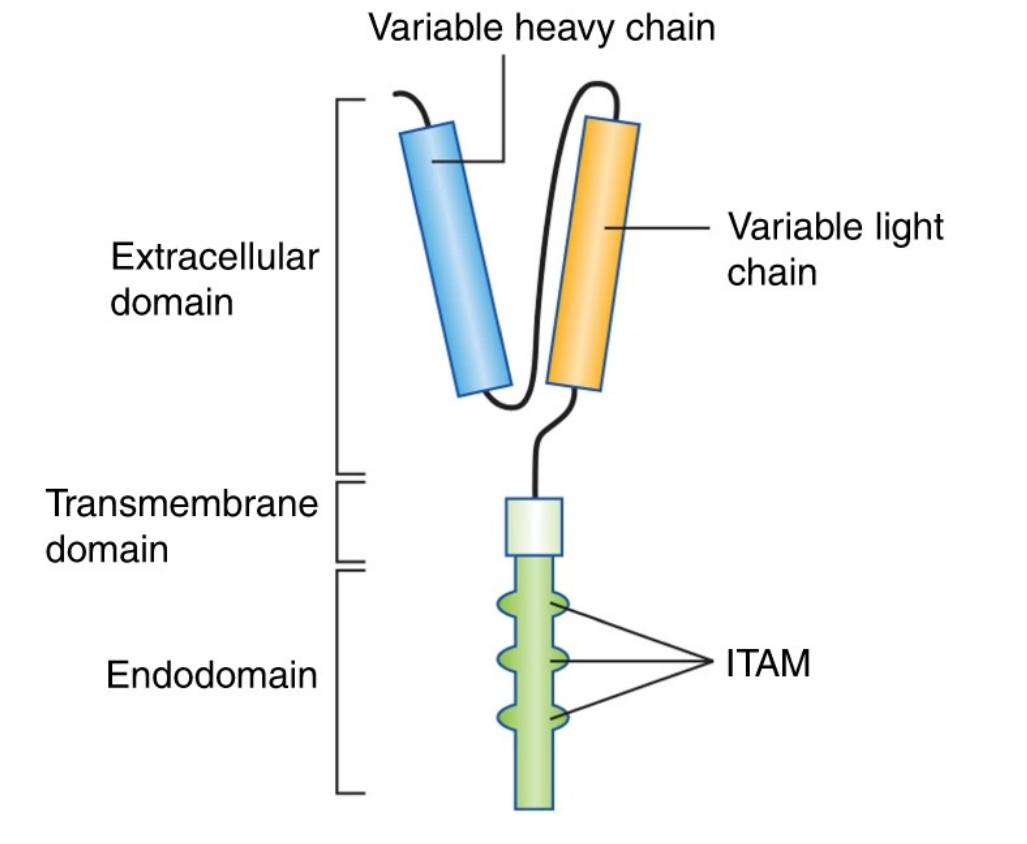
ORR 61% (11/18) in sarcoma patients
3-yr OS: 38% and 5-yr OS: 14%



ORR 55% (11/20) in melanoma patients
3-yr OS: 33% and 5-yr OS: 33%

Robbins et al., CCR 2015.

CAR Structure



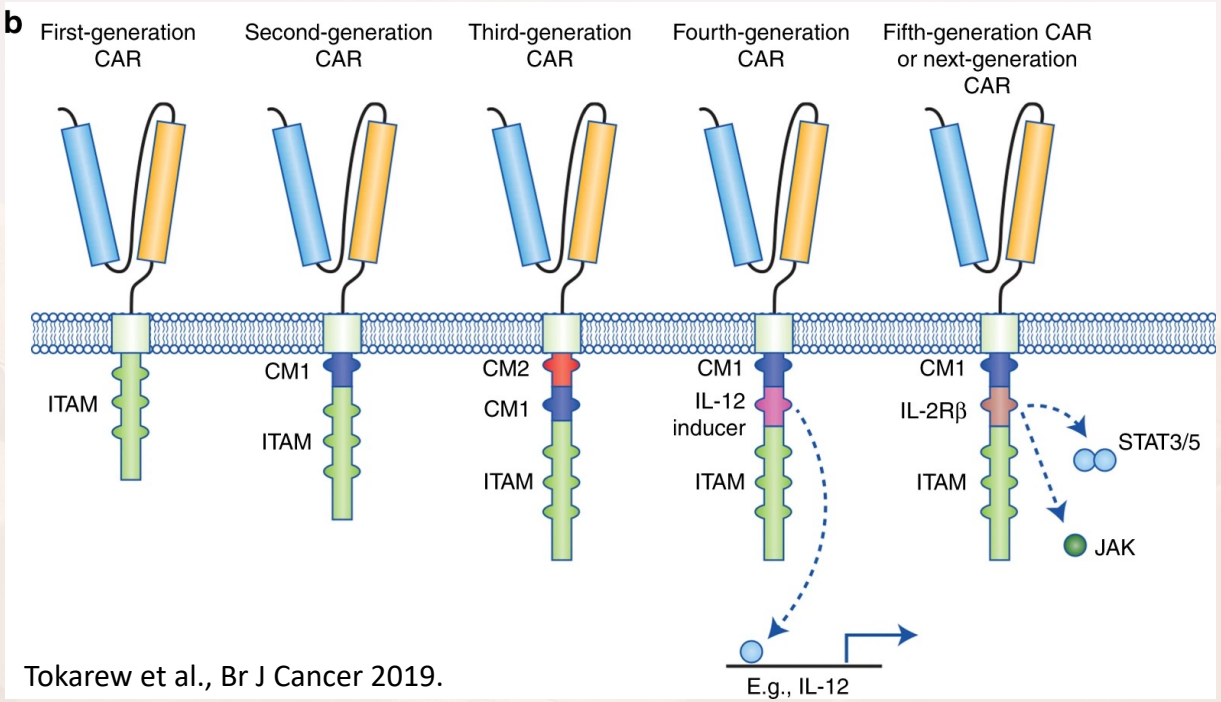
Tokarew et al., Br J Cancer 2019.

1. Single chain variable domain (**scFV**) for **antigen recognition**

2. Transmembrane domain

3. Intracellular **T cell co-receptor CD3ζ** – most important for **signal transduction** and **activation**. (ITAM: immunoreceptor tyrosine-based activation motifs)

Overcoming Challenges in Solid Tumors



Tokarew et al., Br J Cancer 2019.

- Improving **T cell recruitment** to tumors
  - Engineering expression of chemokine receptors (CCR2, CCR4, CCR7, CXCR2, CXCR3, CXCR4) onto CARs
- Enhancing **T cell survival and activation**
  - Addition of co-stimulatory molecules such as CD23, 41BB , IL2
- Overcoming the **immunosuppressive TME**
  - Chimeric switch receptors – immunomodulatory fusion proteins
  - Extracellular ligand binding domain is fused with a co-stimulatory pathway – PD1-CD28 CSR

On-Target, Off-Tumor Toxicities

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2022: NCI-Based CD19 CAR T

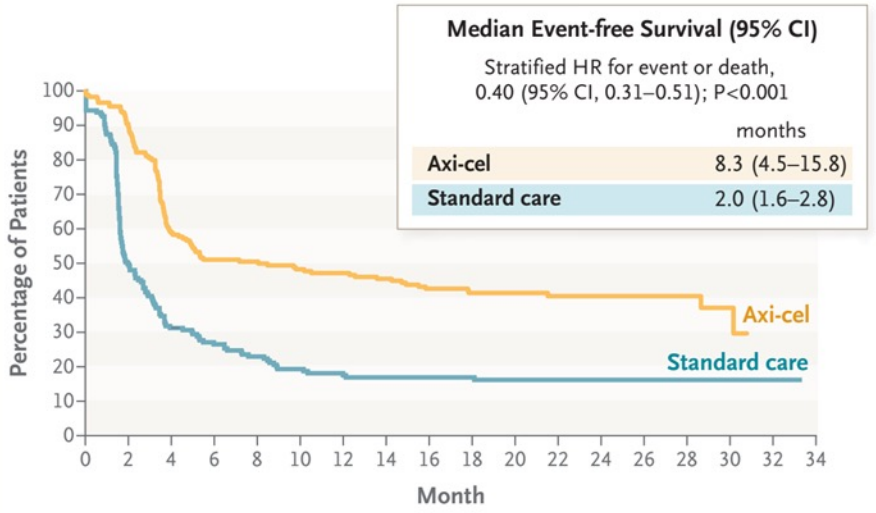
The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

Axicabtagene Ciloleucel as Second-Line Therapy for Large B-Cell Lymphoma

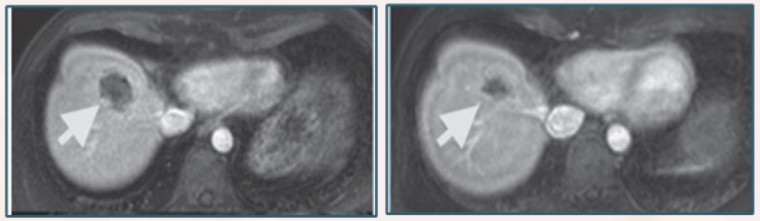
Efficacy: Global Randomized Phase 3 Trial

Event-free Survival

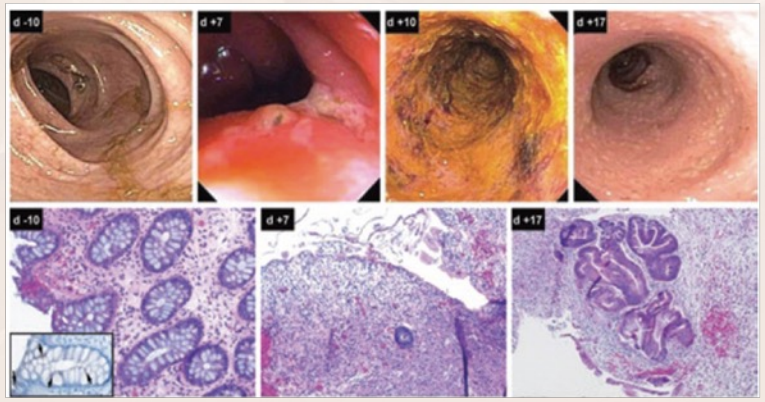


2011: NCI CEA HLA-A*02 TCR-T

Efficacy: Reduction in Tumor Size

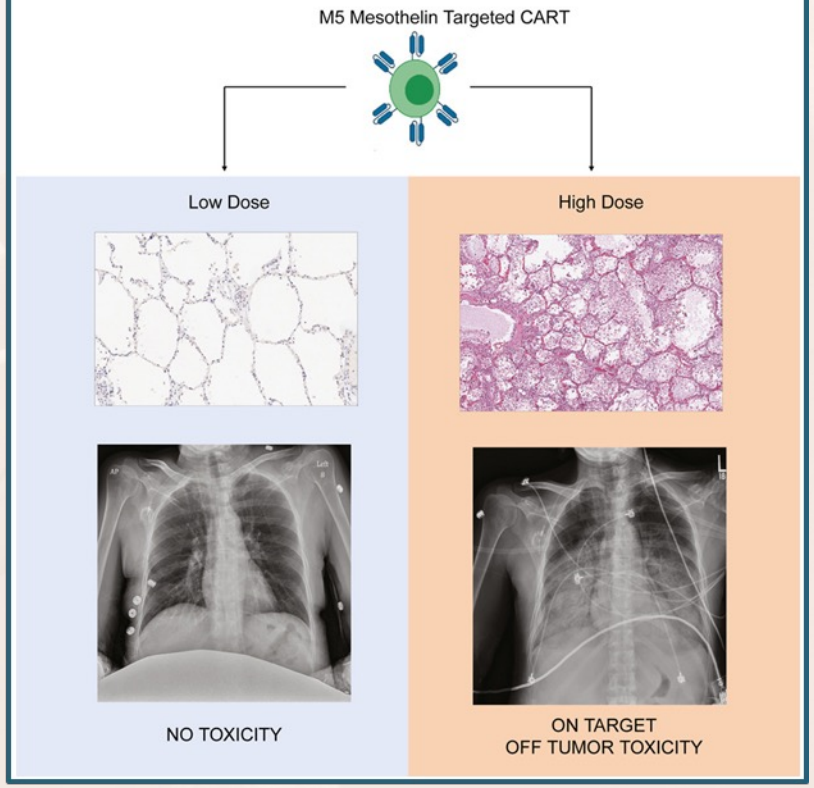


Toxicity: Grade 3 Diarrhea and Colitis



2021: Penn M5 MSLN CAR T-Cell

Toxicity: Grade 4 CRS and Grade 5 Pulmonary Failure



Axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; CEA, carcinoembryonic antigen 5; CI, confidence interval; CRS, cytokine release syndrome; HLA, human leukocyte antigen; HR, hazard ratio; MSLN, mesothelin; NCI, National Cancer Institute; TCR-T, T-cell receptor T-cell.

1. Locke F, et al. *N Engl J Med*. 2022;386(7):640-654; 2. Parkhurst M, et al. *Mol Ther*. 2011;19(3):620-626; Haas AR, et al. *Mol Ther*. 2023;31(8):2309-2325.

Slide reproduced with permission – Simeone et al., SITC 2023

Candidate Antigens

Candidate Antigens	Solid Tumors	Clinical Trials
EGFR vIII	NSCLC, CRC, gallbladder, glioblastoma	Minimal efficacy NCT02209376 NCT01454596
Mesothelin	NSCLC, mesothelioma, ovarian cancer, PDAC, CRC, gastric tumors, TNBC	Poor persistence in the TME NCT01355965 NCT02159716
HER2	Breast, NSCLC, PDAC, gastric, gallbladder	Toxicity and poor persistence NCT01109095
CEA	CRC, PDAC, gastric, NSCLC	Toxicity NCT01373047
PSMA	Prostate cancer	NCT04053062 NCT04227275 NCT04249947 NCT04429451
B7H3	Ovarian, PDAC, lung, neuroblastoma	NCT04185038 NCT04077866

DLL3 T Cell Engager Therapies in SCLC

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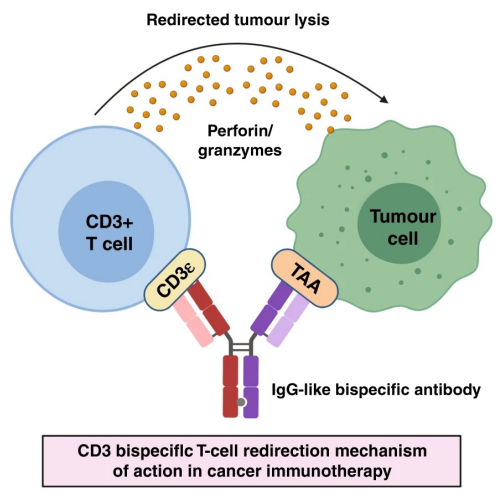
- DLL3 is an antigen that is expressed in >80% of SCLC but **rarely expressed in normal cells – represents an excellent target** for BiTEs.

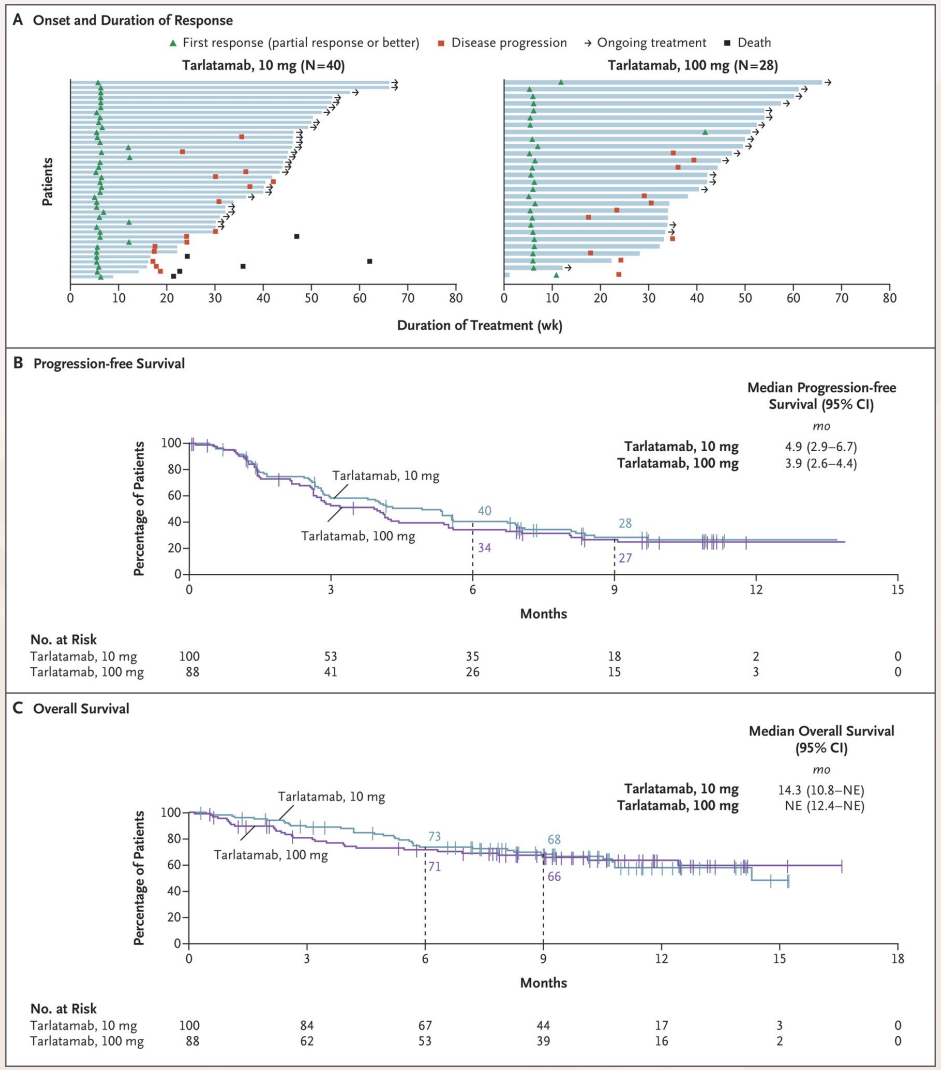
- **Cellular therapies** that **redirect T cells** towards **tumor antigens**.



Singh et al., BJC 2021.

- TCEs a **cytolytic synapse** that **bypasses the need for MHC-I** antigen presentation allowing for **MHC-independent** cell kill.

Tarlatamab in relapsed SCLC



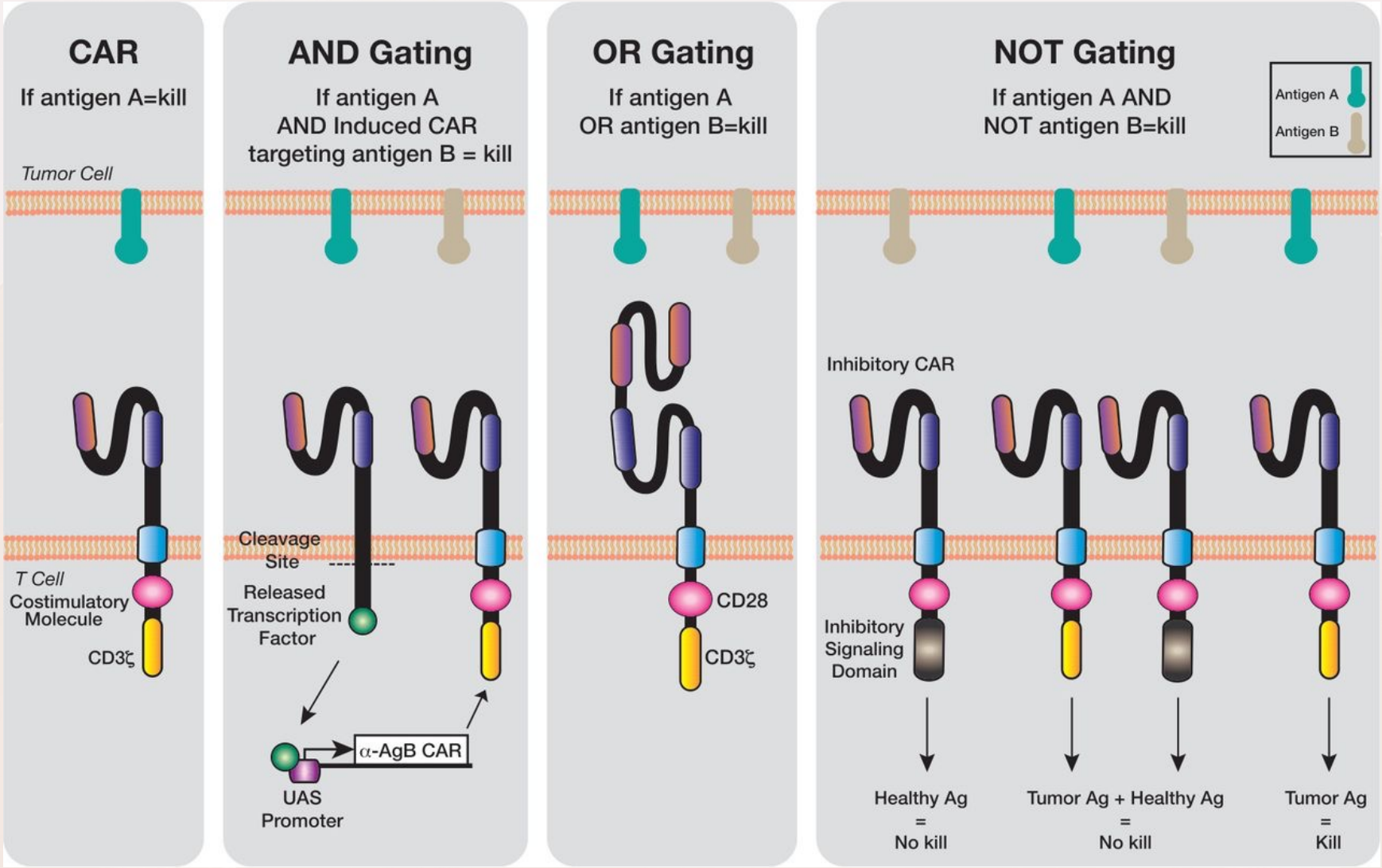
Ahn et al., NEJM 2023.

BiTES vs CAR T

	BiTEs	**CAR T cells**
Effector cell	Endogenous T cells	Engineered T cells
MHC Dependency	**MHC Independent**	**MHC Independent**
TCR Dependency	Independent of endogenous co-stimulatory signaling	Independent of endogenous TCR and co-stimulatory signaling
Toxicity	CRS, ICANS	CRS, ICANS
Cell trafficking	Passive – redistribution of endogenous T cells	Active trafficking of CAR T cells to malignant tissues with in vivo expansion after encounter with tumor antigen
Immune escape	Loss of target antigen, upregulation of immune checkpoints	Loss of target antigen
Long term efficacy	Repeated treatments needed	**Engraftment of CAR T can provide ongoing responses**
Availability	**Off the shelf**	Individual

Goebeler et al., Nat Rev Clin Oncol 2020.

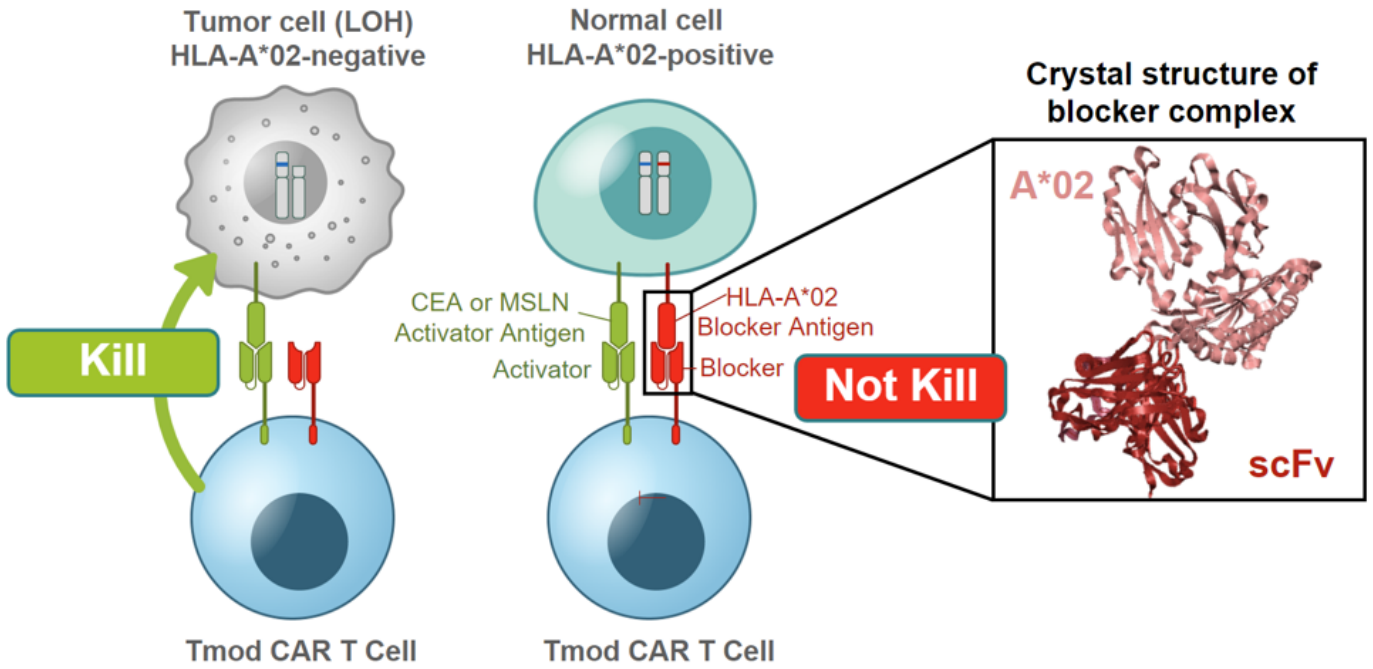
Logic Gates



Abbott et al., JITC 2021.

Logic Gates

Tmod is a Novel Logic-Gated CAR T-Cell Therapy That Discriminates Tumor From Normal Cells Designed to Mitigate On-Target, Off-Tumor Toxicity[1,2]



LIR-1-based HLA-A*02:01 blocker is peptide-independent and recognizes diverse A*02 alleles

CAR, chimeric antigen receptor; CEA, carcinoembryonic antigen 5; HLA, human leukocyte antigen; LIR, leukocyte immunoglobulin-like receptor; LOH, loss of heterozygosity; MSLN, mesothelin; scFv, single-chain variable fragment.

1. Hamburger A, et al. *Mol Immunol*. 2020;128:298-310. 2. Mock J-Y, et al. *Mol Ther Oncolytics*. 2022;27:157-166.

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Logic Gates

CEA Tmod CAR T Cell (A2B530) IND-Enabling In Vivo Study Demonstrates Potency Comparable to NCI Benchmark CEA TCR

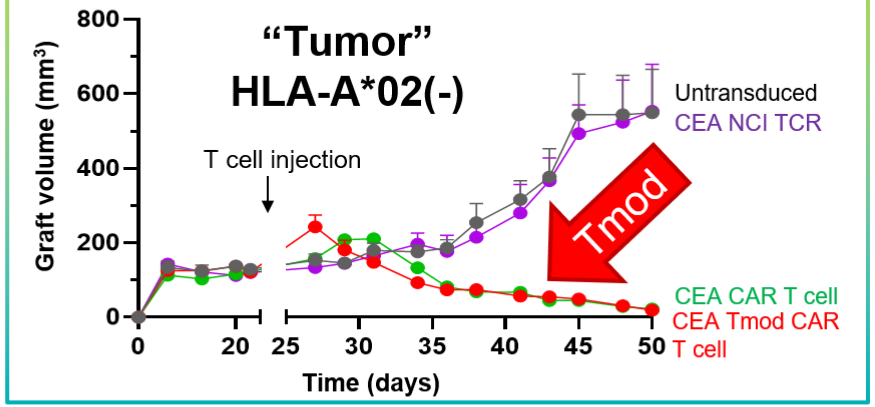
H508 colon cancer xenograft dual flank injection (2 x10^7 cells, n= 5 mice per group)

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

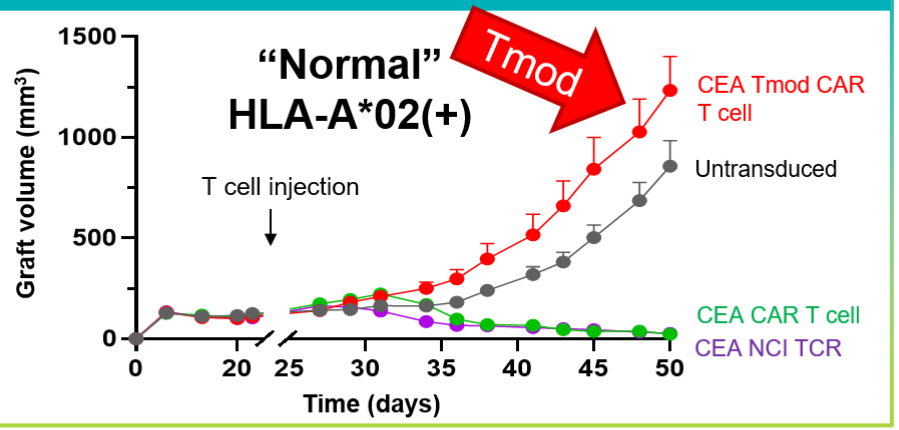
Normal
CEA(+)
HLA-A*02(+)

TCR is HLA-A*02 restricted

CEA Tmod CAR T Cells (With the Blocker) Kill Tumor Equivalent to CAR T Cells Alone (Without the Blocker)

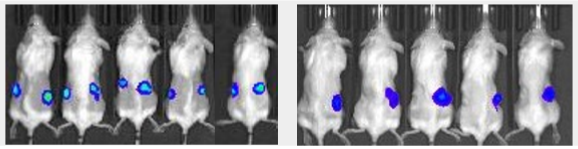


CEA TCRs Kill Normal Equivalent to CAR T Cells



CEA Tmod CAR T cell cohort

Day 0 (pre–T-cell injection)



Day 14 (post–T-cell injection)

CAR, chimeric antigen receptor; CEA, carcinoembryonic antigen 5; HLA, human leukocyte antigen; IND, investigational new drug; NCI, National Cancer Institute; TCR, T-cell receptor.
Sandberg ML, et al. *Sci Transl Med.* 2022;14(634): eabm0306.

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Summary

- Cellular therapies are attractive treatment strategies because of **T-cell mediated cytotoxicity**, **memory** and their ability to **overcome barriers in antigen presentation**.

- Major barriers for cellular therapies in solid tumors:
  - **T cell trafficking**
  - **T cell activation**
  - **On target, off tumor toxicities**

- **Novel designs** to overcome these barriers for both BiTEs and CAR-T with some **impressive results seen in SCLC**.

- Cellular therapies are **feasible in solid tumors** and we will be seeing more of them in the future.