Tumor-Infiltrating Lymphocyte Therapy in Lung Cancer: Where We Are and Where We're Going

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2025 Cell Coast Conference

Memorial Sloan Kettering Cancer Center

Disclosures

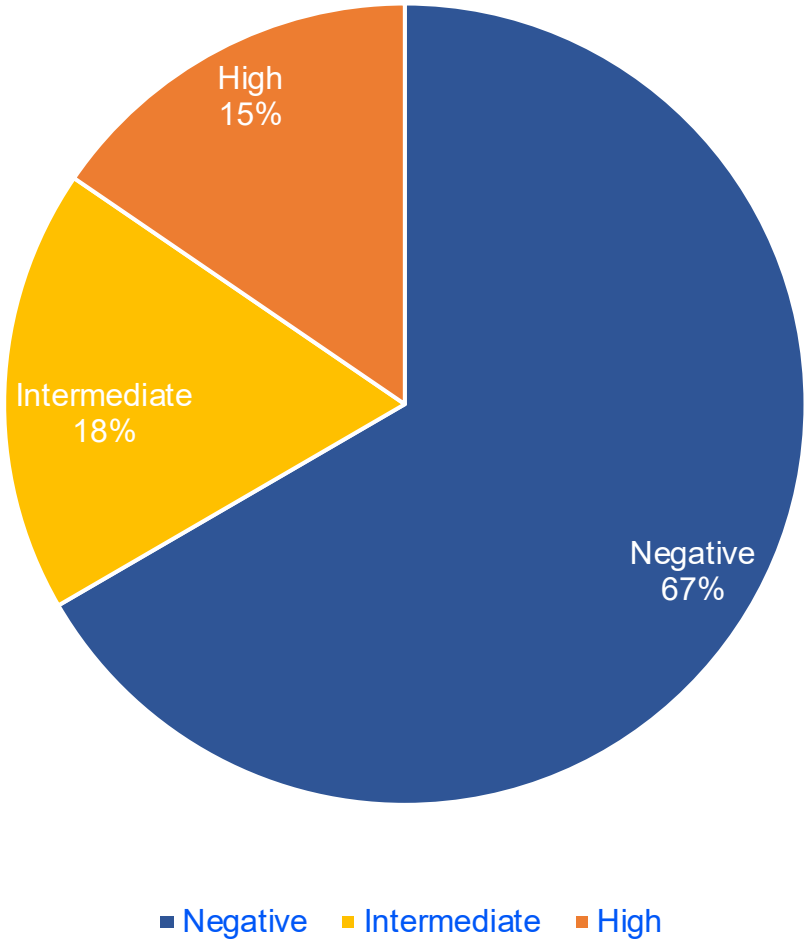
AJS reports consulting/advising role to J&J, Bayer, KSQ therapeutics, BioNtech, BMS, Merck, Astrazeneca, Oxford Biotherapeutics, Roche, Synthekine, cTRL therapeutics, Regeneron, Enara Bio, Perceptive Advisors, Foresight Diagnostics, Oppenheimer and Co, Umoja Biopharma, Legend Biotech, Iovance Biotherapeutics, Obsidian Therapeutics, Prelude Therapeutics, Immunocore, Lyell Immunopharma, Amgen and Heat Biologics. Research funding: GSK (Inst), Obsidian (Inst), Lilly (Inst), PACT pharma (Inst), Iovance Biotherapeutics (Inst), Achilles therapeutics (Inst), Merck (Inst), Synthekine (Inst), BMS (Inst), Harpoon Therapeutics (Inst), AffiniT therapeutics (Inst), Legend Therapeutics (Inst), Synthekine (Inst) and Amgen (Inst).

Outline

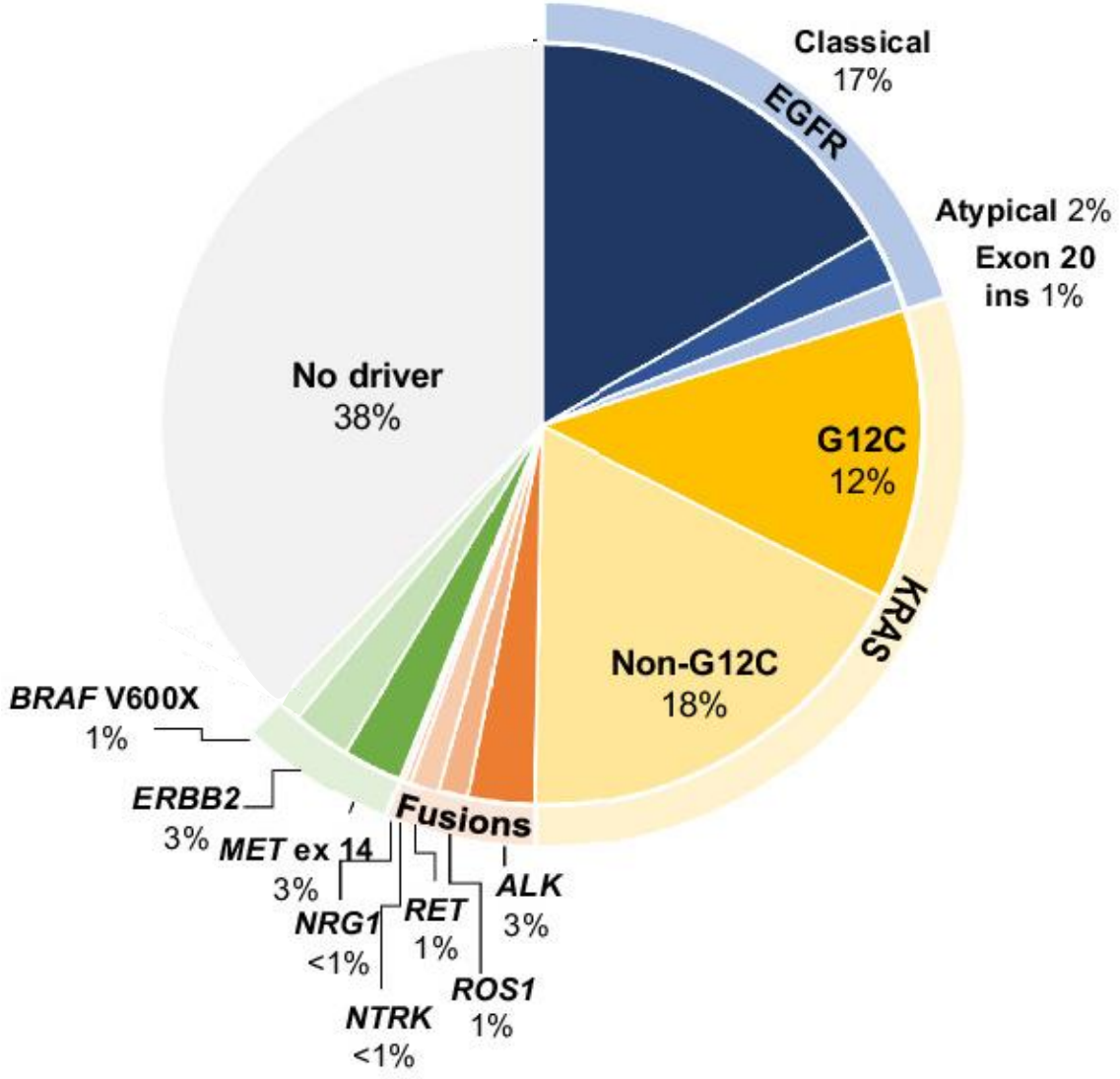
- Evolving Treatment Landscape in Lung Cancer
- Early Clinical Experience with TIL Therapy in Lung Cancer
- The Road Ahead for TIL Therapy in Lung Cancer and Solid Tumors

Lung cancer is a heterogeneous disease

PD-L1 expression (IHC)

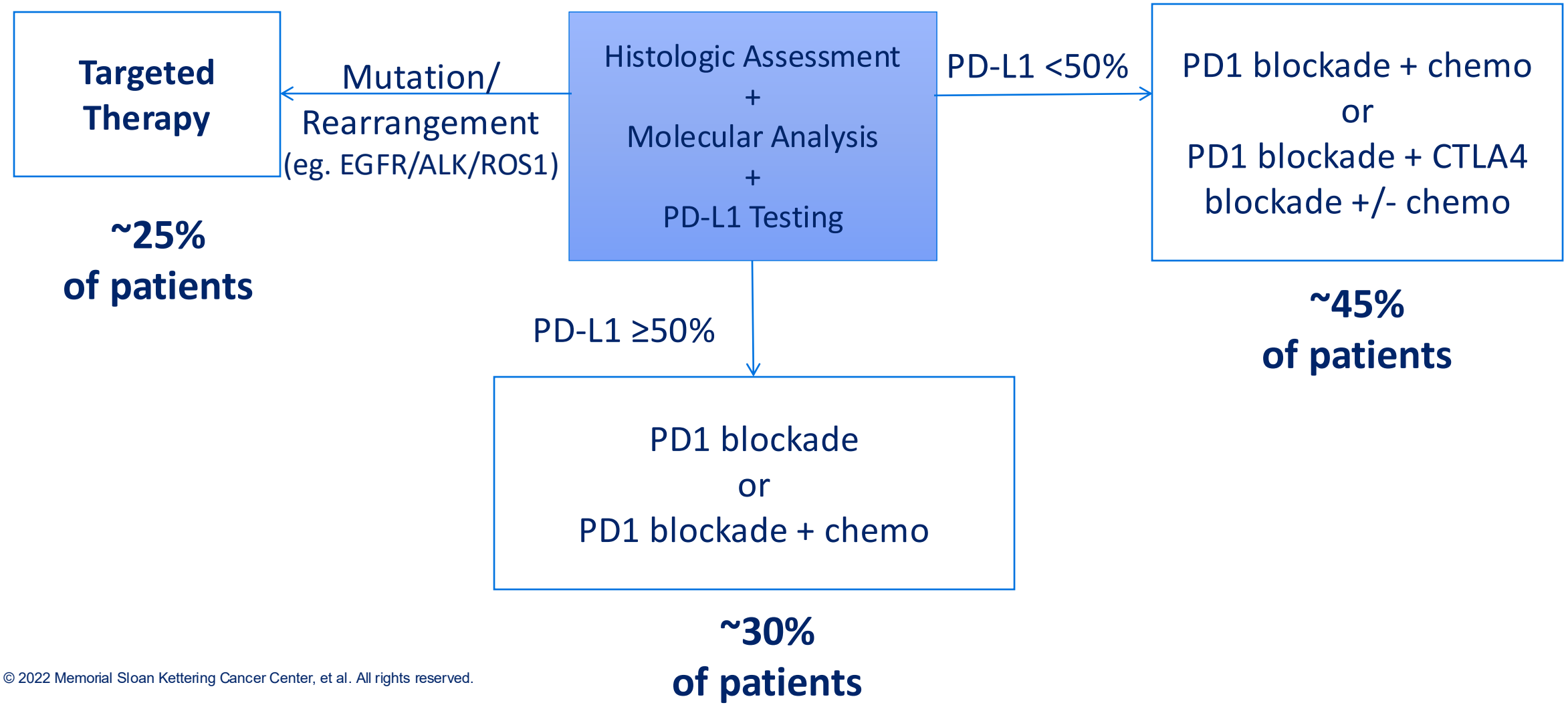


Mutations/fusions (NGS)



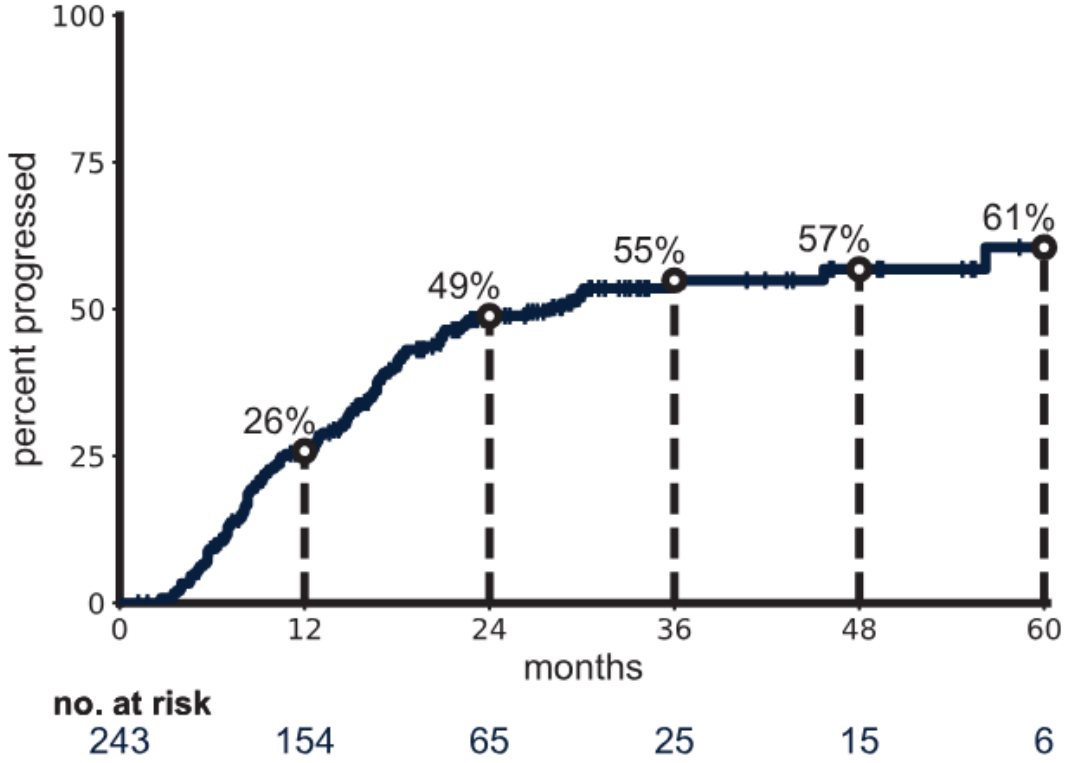
Schoenfeld AJ et al Annals of Oncol 2020; Choudhury NJ et al Clin Canc Res 2024

The Current Approach to First-Line Treatment of Patients with Advanced NSCLC



No actionable driver: Immune checkpoint blockade has significantly improved outcomes but...

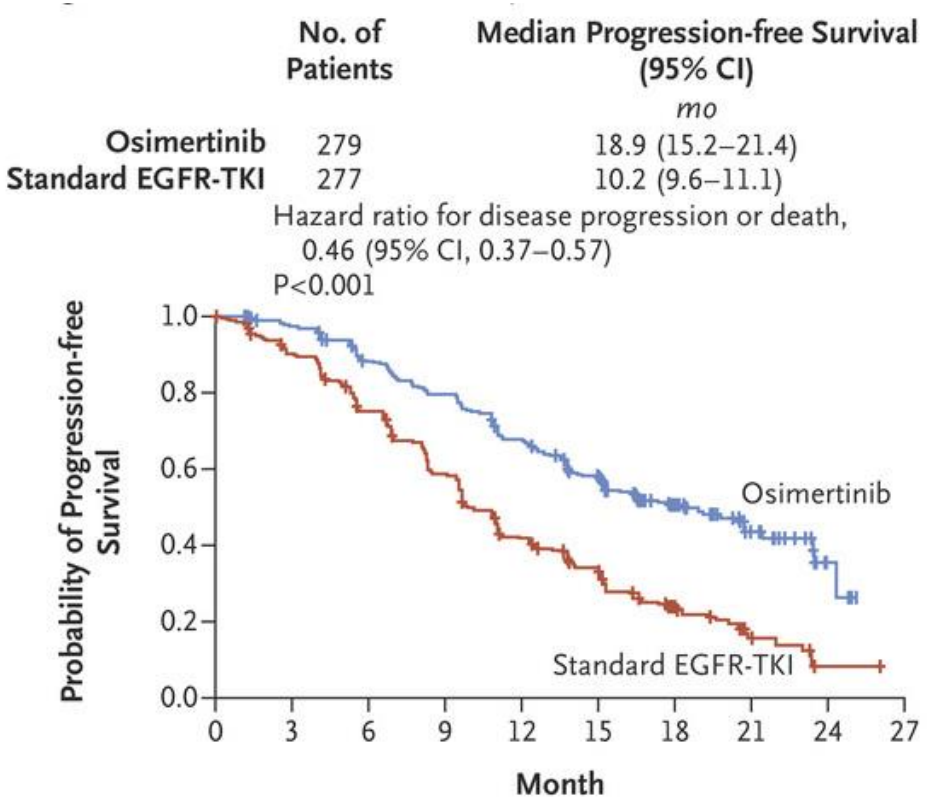
Durable long-term responses are uncommon in lung cancer



Memon D*, Schoenfeld AJ* et al Cancer Cell 2024

Actionable driver: Targeted therapy has significantly improved outcomes but...

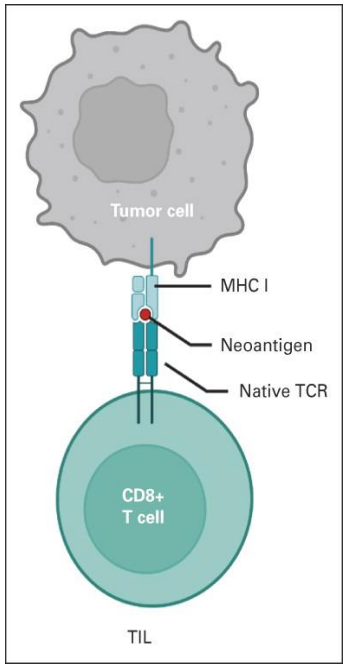
Durable long-term responses are uncommon in lung cancer



Soria JC et al NEJM 2018

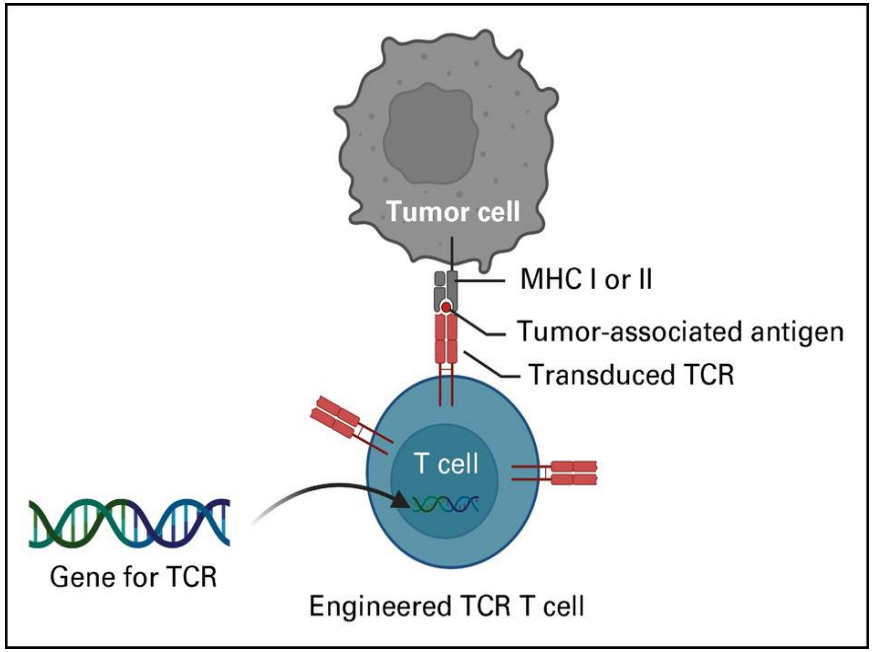
Adoptive T Cell Therapies: TILs, TCRs, and CARs

TILs



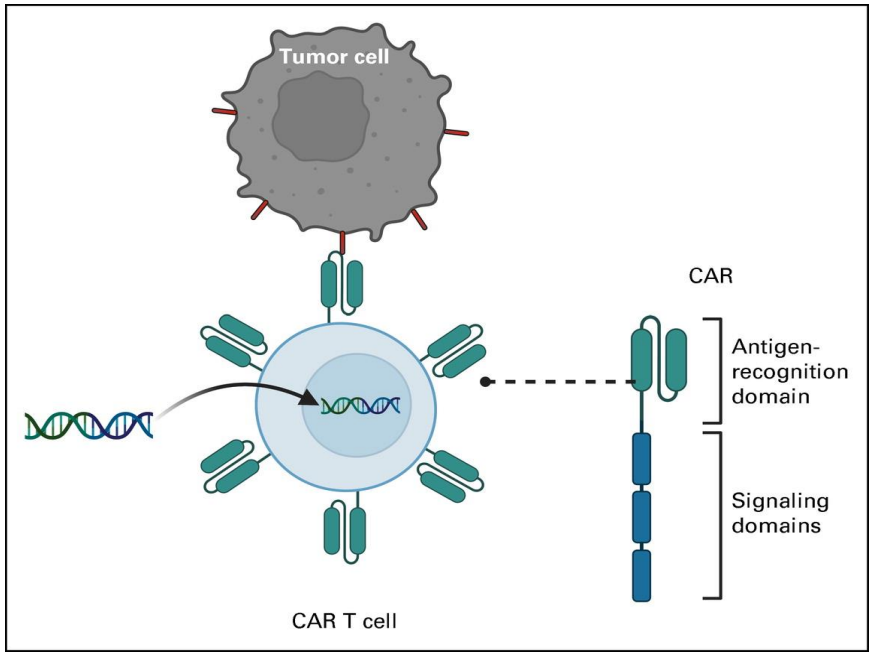
- Native TCR
- No need for antigen selection or HLA matching
- Requires tissue harvesting

TCR T cells



- New TCR transduced into autologous T cells
- Enables targeting intracellular peptides presented on HLA molecules
- HLA restricted

CAR T cells

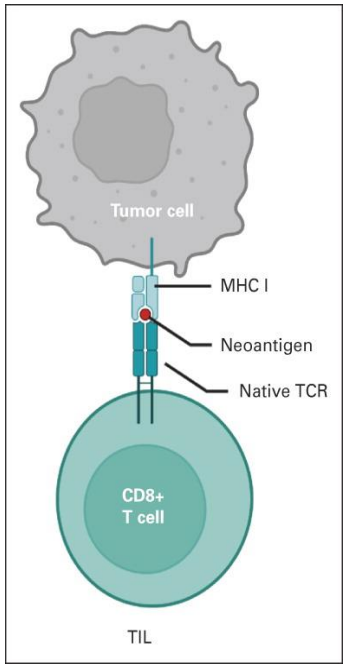


- Antibody derived recognition domain transduced into autologous T cells
- Independent of TCR & HLA restriction
- Only targets cell surface antigens

Adapted from Olsen DJ and Odunsi K *JCO* 2023

Adoptive T Cell Therapies: TILs, TCRs, and CARs

TILs



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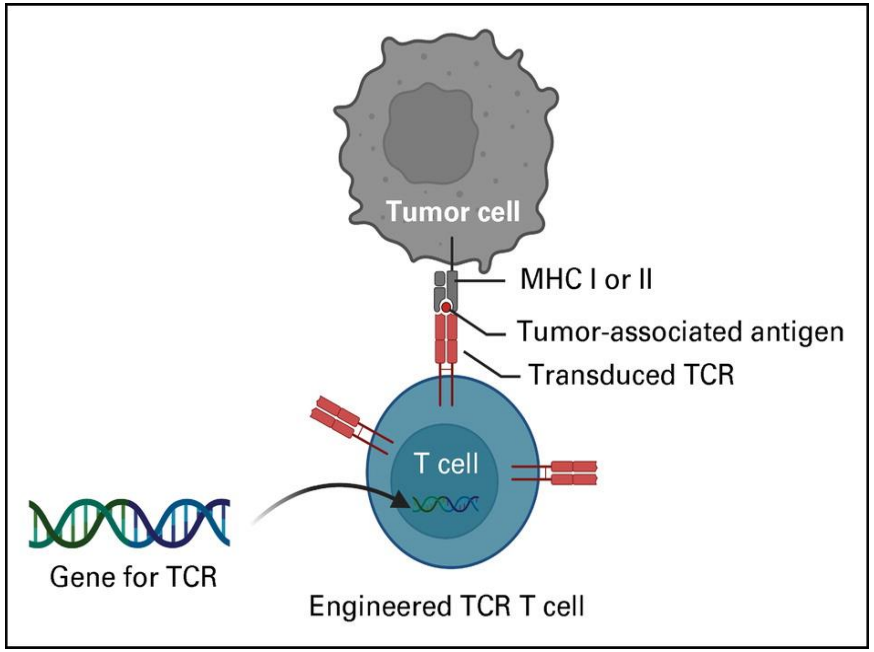
TCR T cells



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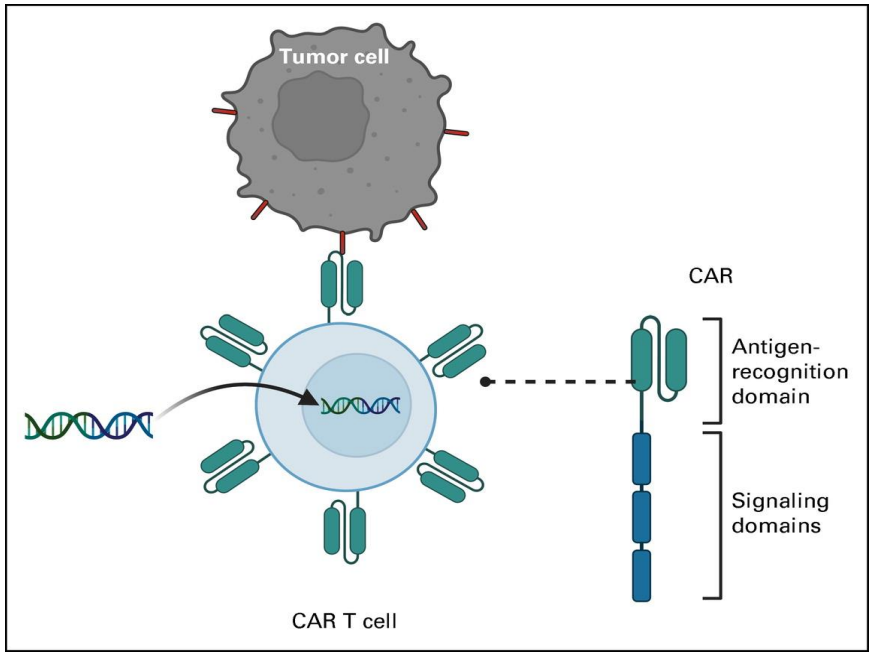

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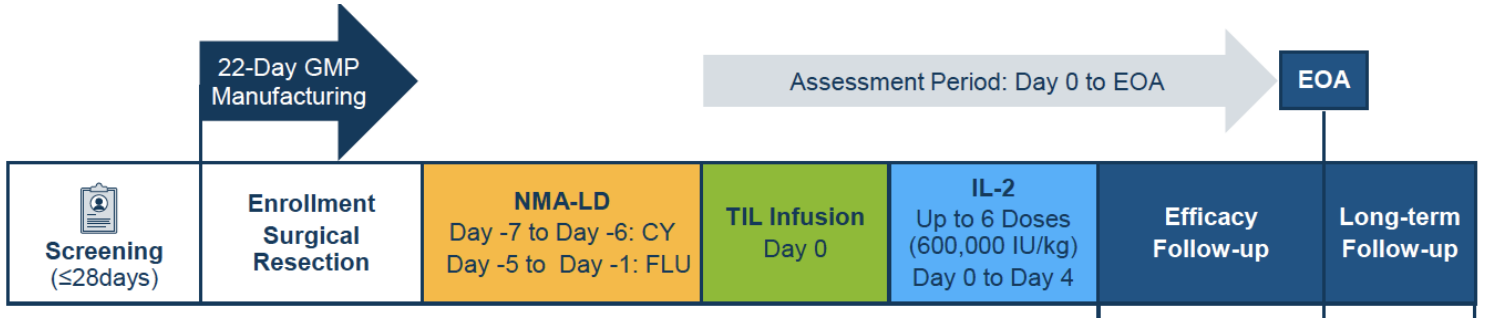
Adapted from Olsen DJ and Odunsi K *JCO* 2023

Lifileucel (TIL) Monotherapy in PD-1–Refractory Lung Cancer: Results from a Phase 2 Multicenter Study

IOV-COM202 Cohort 3B (NCT03645928)

- Stage IV non-small cell lung cancer
- Progression on last line of therapy
- 1 resectable lesion (>1.5cm) and at least 1 recist measurable lesion
- Resection/treatment after PD on last line of therapy



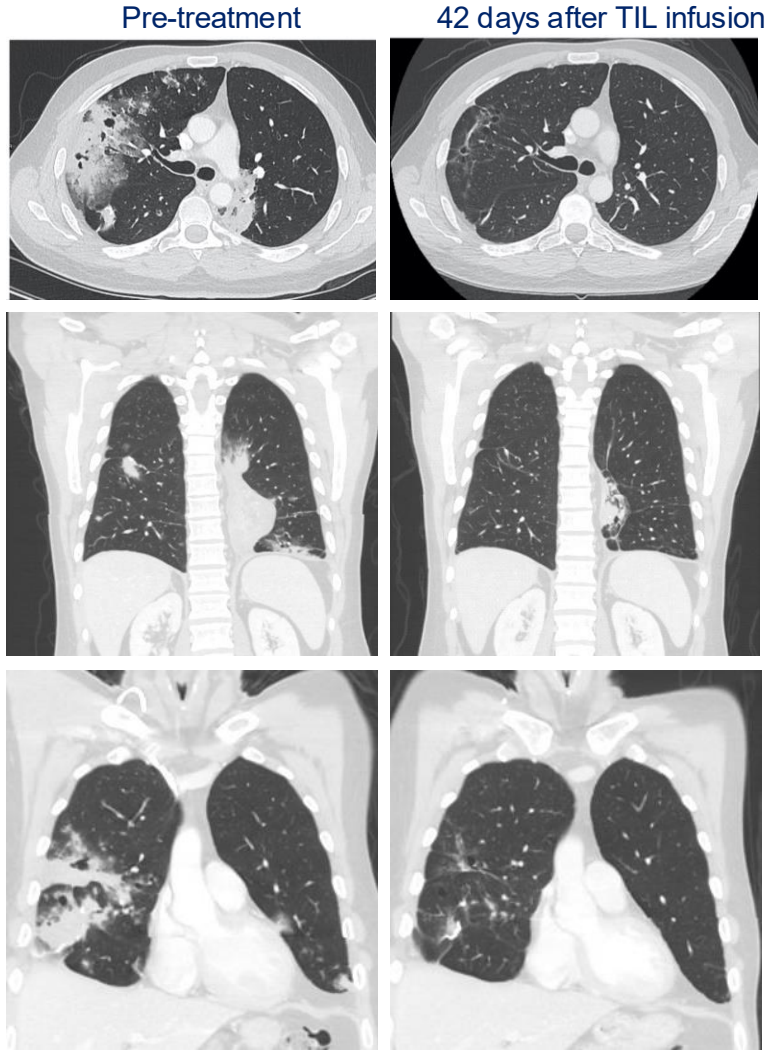
Endpoints

- Primary endpoints: Safety and ORR

Schoenfeld AJ et al. Cancer Discov 2024

Representative Patient Case

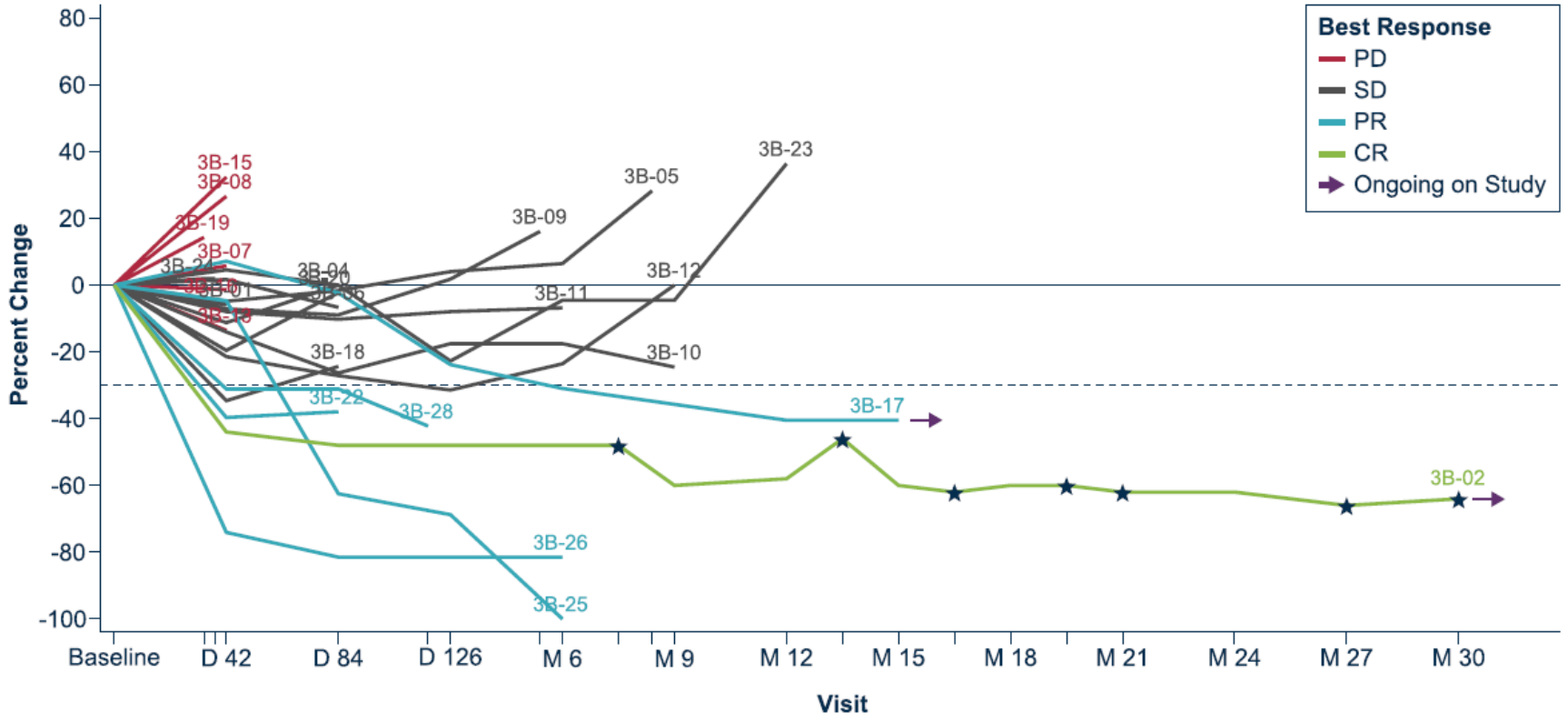
- 41-year-old man with stage IV **mucinous lung adenocarcinoma**
- Tumor mutational burden (TMB): **3.3 mut/Mb; PD-L1 expression: 0%**
- Prior progression on **three lines of therapy,** including carboplatin, paclitaxel, and pembrolizumab
- Achieved an **81% partial response (PR)** by RECIST v1.1 at 12 weeks after TIL infusion



Schoenfeld AJ et al. Cancer Discov 2024

Lifileucel monotherapy in heavily pre-treated patients with PD-(L)1 resistant lung cancer

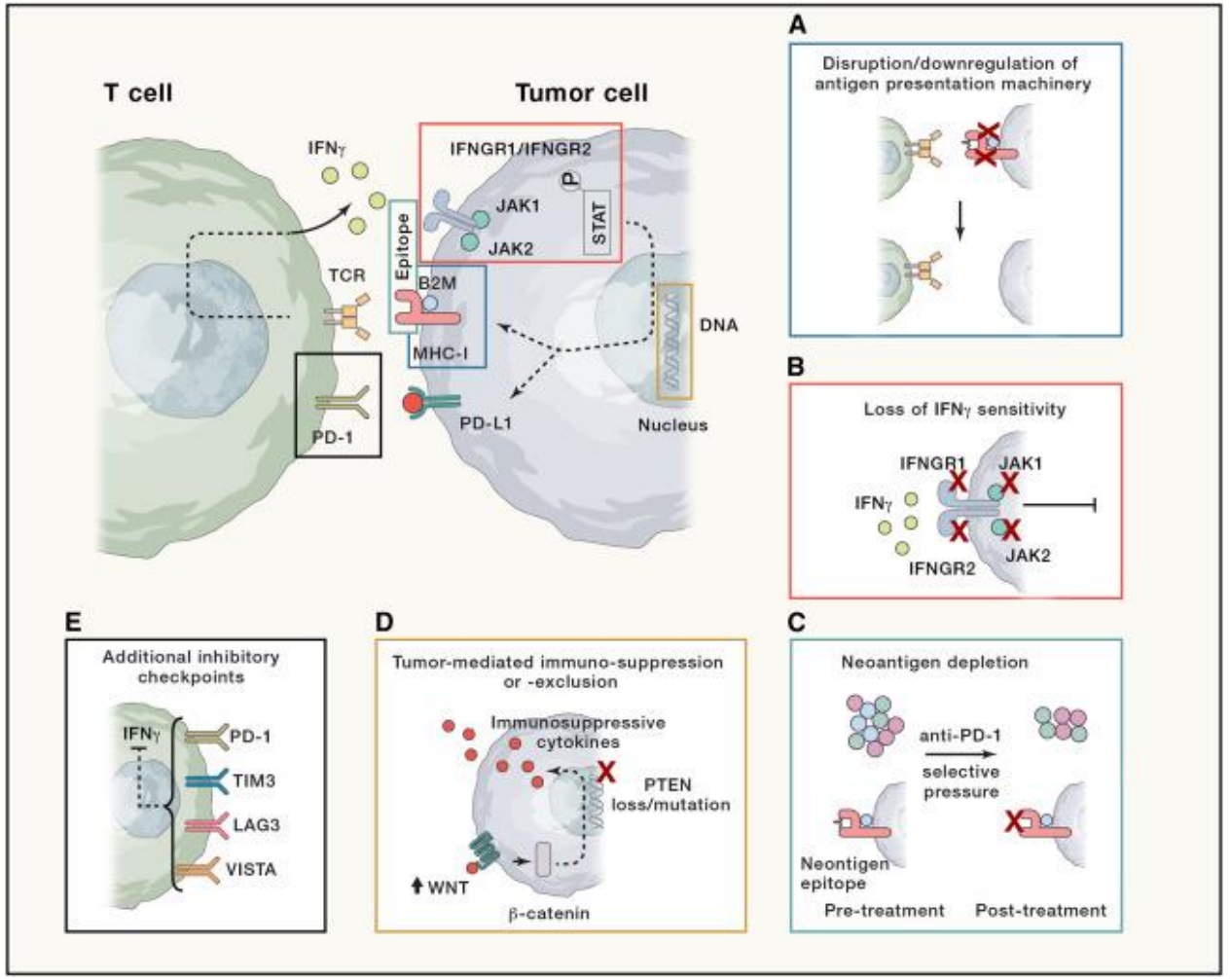
- ORR: 21% (6/28)
- Response were observed in profiles typically resistant to immunotherapy including:
  - PD-L1 negative tumors
  - Low tumor mutational burden
  - STK11-mutant disease



Schoenfeld AJ et al. Cancer Discov 2024

Is earlier TIL treatment better?

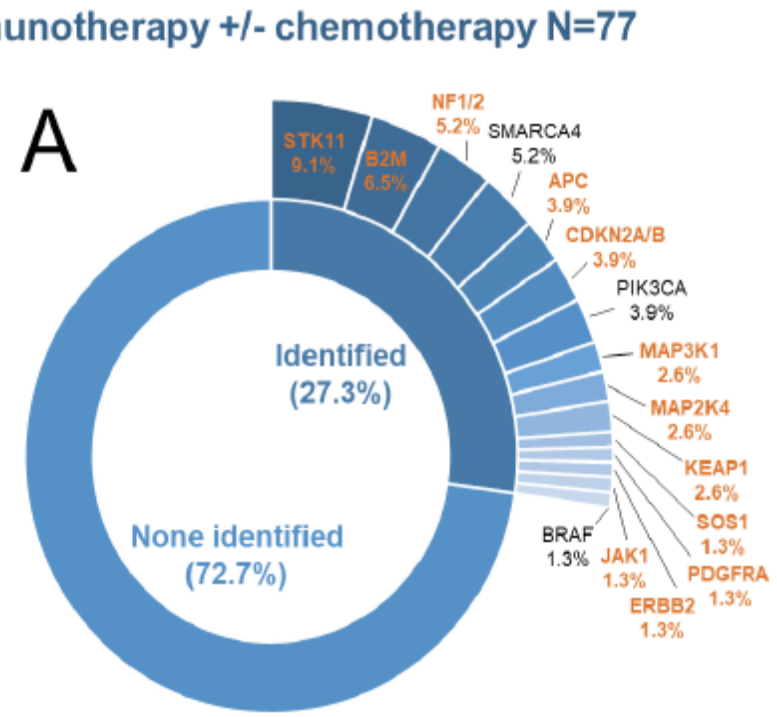
Acquired resistance mechanisms to PD-(L)1 blockade could reduce TIL efficacy

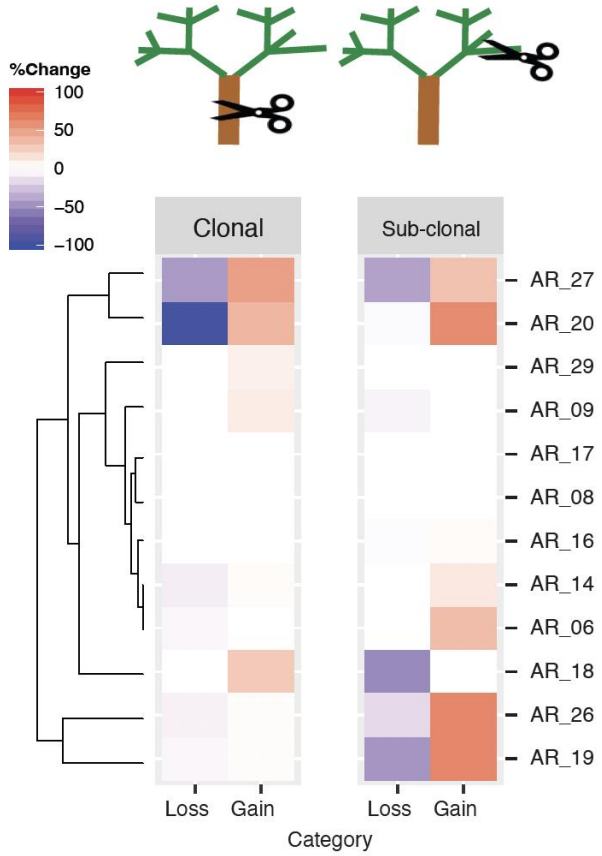


Schoenfeld AJ and Hellmann MD, Cancer Cell 2020

Acquired resistance mechanisms to PD-(L)1 blockade could reduce TIL efficacy

- Acquired loss of function B2M mutations in 7%
- Disruption/downregulation of antigen presentation and HLA expression
- Neoantigen depletion in a subset of patients with acquired resistance

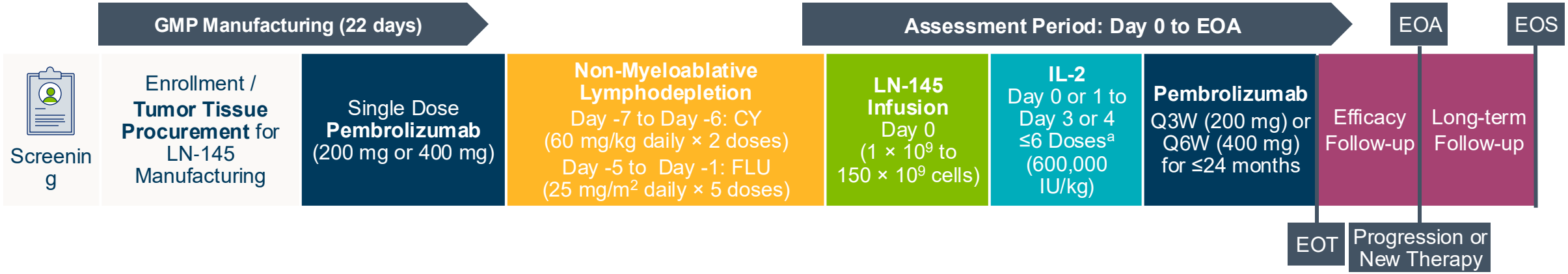




Ricciuti B, Lamberti G, et al J Clin Oncol, 2024; Memon D*, Schoenfeld AJ* et al Cancer Cell 2024

Lifileucel + Pembrolizumab in PD-(L)1 Blockade–Naïve Metastatic NSCLC

Treatment Schema
IOV-COM202 Cohort 3A
(NCT03645928)



1. Schoenfeld A, et al. *J Immunother Cancer* 2021;9(Suppl 2):A458. 2. Creelan BC, et al. *Nat Med* 2021;27(8):1410–1418.
[a]Every 8–12 hours (3–24 hours after completion of LN-145 infusion).
CY, cyclophosphamide; EOA, end of assessment; EOS, end of study; EOT, end of treatment; FLU, fludarabine; GMP, Good Manufacturing Practice; ICI, immune checkpoint inhibitor; IL-2, interleukin-2; IU, international units; mNSCLC, metastatic non-small cell lung cancer; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand-1; TIL, tumor-infiltrating lymphocyte.

Majority of Patients with EGFR Wild-Type Lung Cancer Responded to Lifileucel

Response Outcomes by *EGFR* Mutation Status

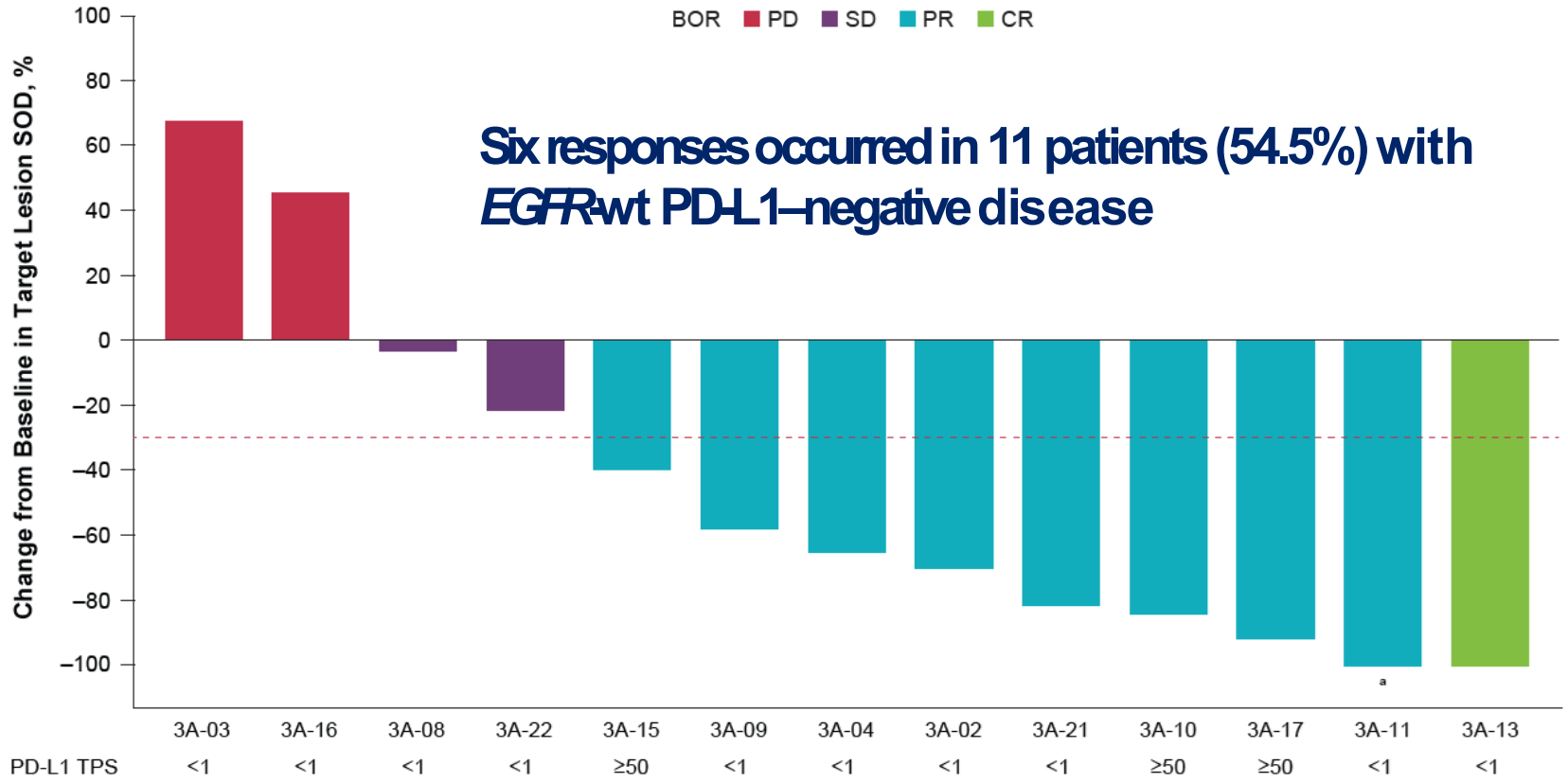
Response Parameter	*EGFR* wt (n=14)	*EGFR* Mutated Post-TKI (n=8)
ORR, n (%)	9 (64.3)	1 (12.5)
DCR, n (%)	11 (78.6)	7 (87.5)
BOR, n (%)		
CR	1 (7.1)	1 (12.5)
PR	8 (57.1)	0
SD	2 (14.3)	6 (75.0)
PD	2 (14.3)	0
NE	1 (7.1)	1 (12.5)
Median DOR (95% CI), months	NR (3.7, NR)	13.7 (NR–NR)

- At a median follow-up of 25.6 months, the ORR in the *EGFR*-wt subgroup was 64.3% (95% CI: 35.1–87.2)
  - Median duration of response was not reached in the *EGFR*-wt subgroup (95% CI: 3.7 months–NR)
- One of the 8 patients with *EGFR*-mutated post-TKI disease had a complete response

BOR, best overall response; CI, confidence interval; CR, complete response; DCR, disease control rate; DOR, duration of response; *EGFR*, endothelial growth factor receptor gene; *EGFR*-wt, endothelial growth factor receptor gene wild-type; NE, not evaluable; NR, not reached; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease; TKI, tyrosine kinase inhibitor.

Lifileucel Elicits Responses even in PD-L1–Negative Disease

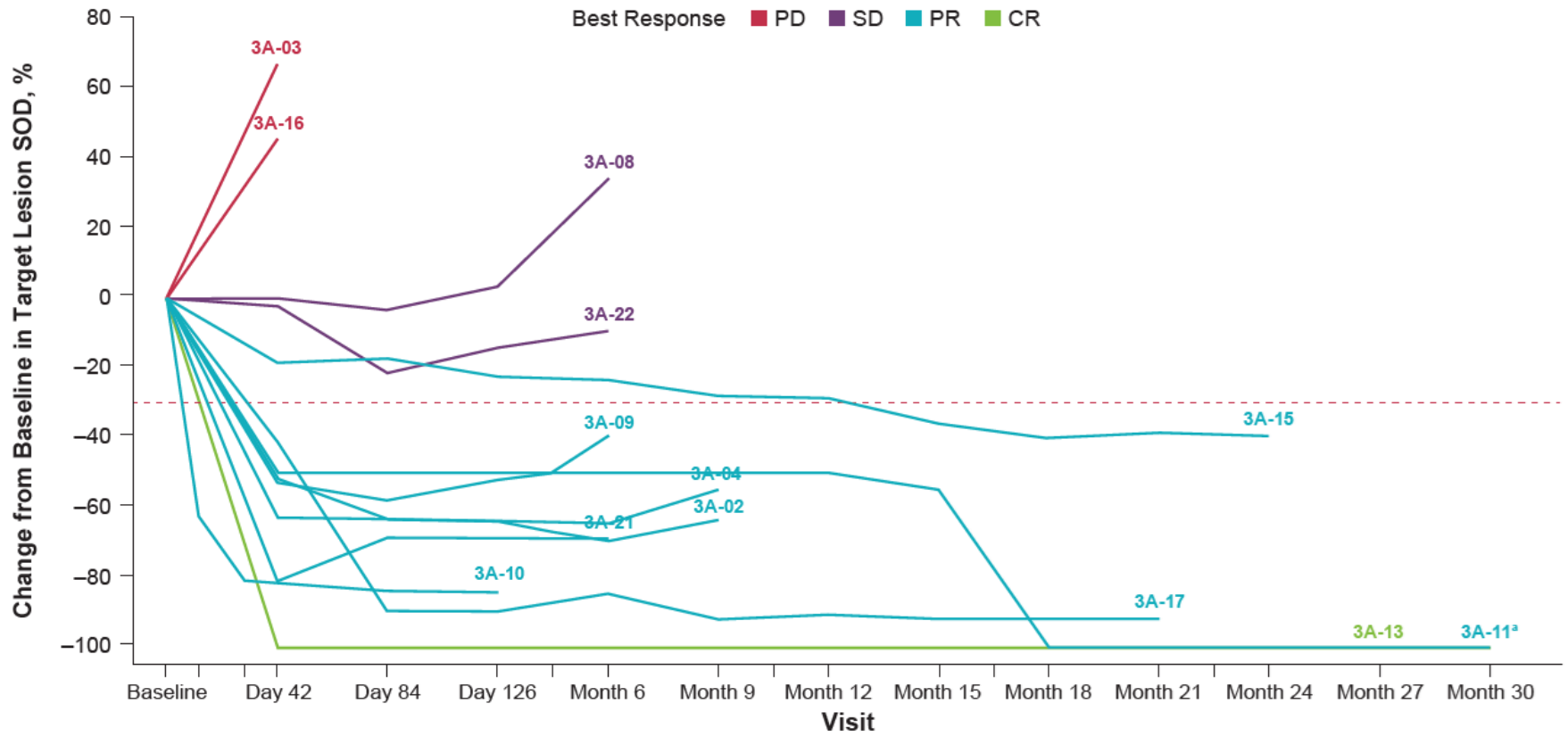
Best Percentage Change from Baseline in Target Lesion SOD in the *EGFR*-wt Subgroup



One patient in EGFR-wt PD-L1–negative group who did not have post-dose tumor response assessment was not included in the plot. [a]A response of PR for this patient was based on a target lesion reduction of 100% with the persistence of nontarget lesions. BOR, best overall response; CR, complete response; *EGFR*-wt, endothelial growth factor receptor gene wild-type; PD, progressive disease; PD-L1, programmed death-ligand 1; PR, partial response; SD, stable disease; SOD, sum of diameters; TPS, tumor proportion score.

Tumor Responses Were Durable

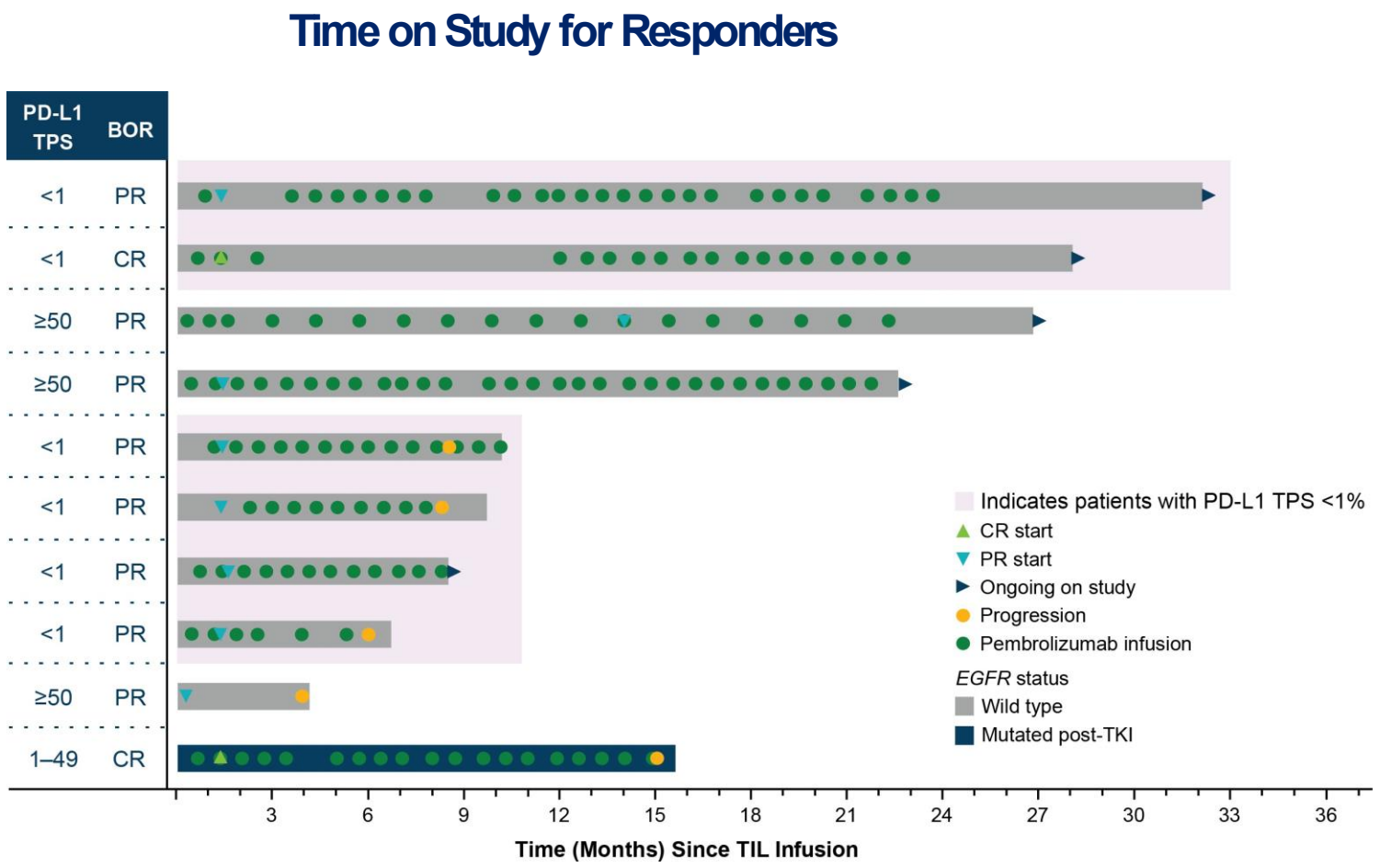
Percentage Change from Baseline in Target Lesion SOD Over Time in the *EGFR*-wt Subgroup



[a]A response of PR for this patient was based on a target lesion reduction of 100% with the persistence of nontarget lesions.
CR, complete response; *EGFR*-wt, endothelial growth factor receptor gene wild-type; PD, progressive disease; PR, partial response; SD, stable disease; SOD, sum of diameters.

Responses in PD-L1–Negative Tumors Were Durable

- Five patients had ongoing responses at last follow-up, including three patients with PD-L1–negative tumors
- Four of these patients maintained responses beyond 20 months from the start of TIL infusion

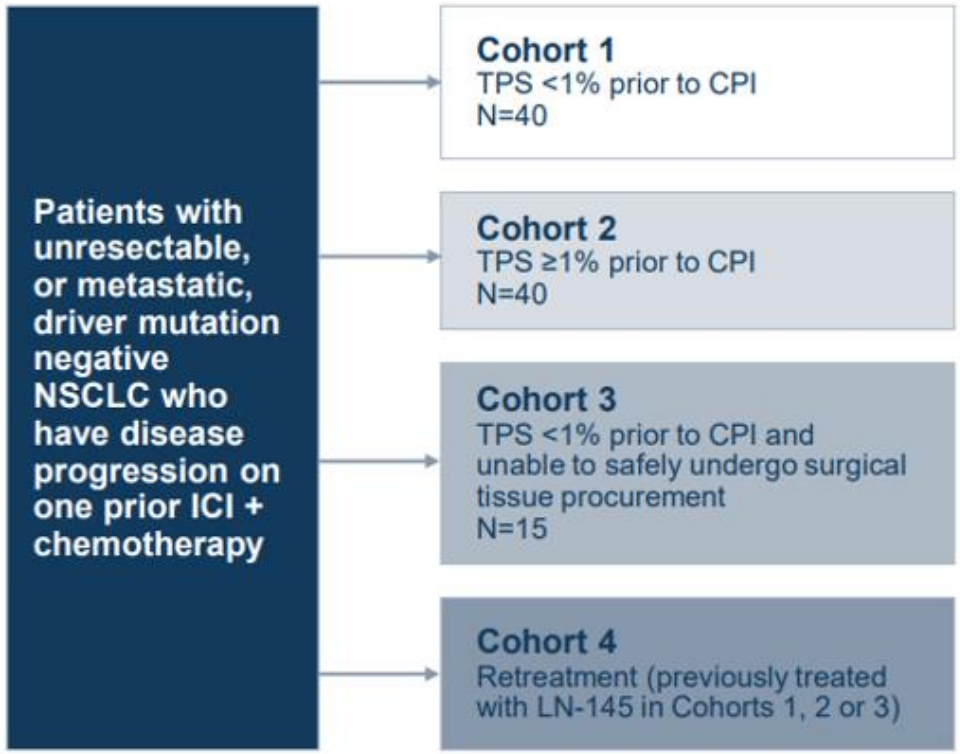


Pink boxes denote patients with PD-L1–negative disease. BOR, best overall response; CR, complete response; *EGFR*, endothelial growth factor receptor gene; *EGFR*-wt, endothelial growth factor receptor gene wild-type; PD, progressive disease; PD-L1, programmed death-ligand 1; PR, partial response; SOD, sum of diameters; TIL, tumor-infiltrating lymphocyte; TKI, tyrosine kinase inhibitor; TPS, tumor proportion score.

Is TIL Ready to Become the Next Second-Line Therapy for Stage IV NSCLC?

Pivotal Phase 2 Trial of TIL monotherapy after front-line chemoimmunotherapy

IOV-LUN-202 of TIL (LN-145)



Endpoints

- Primary: ORR by IRC
- Secondary: Safety

Preliminary Clinical Results for IOV-LUN-202 Cohorts 1 and 2

All Patients Progressed On or After Anti-PD-1 Therapy and Chemotherapy

	Cohort 1 + 2 (n=23)[2]
Objective Response Rate, n (%)[1]	6 (26.1)
(95% CI)	(10.2, 48.4)
Best overall response, n (%)	
CR	1 (4.3)
PR	5 (21.7)
SD	13 (56.5)
PD	2 (8.7)
NE	2 (8.7)

TEAEs were consistent with the underlying disease and known AE profiles of NMA-LD and IL-2

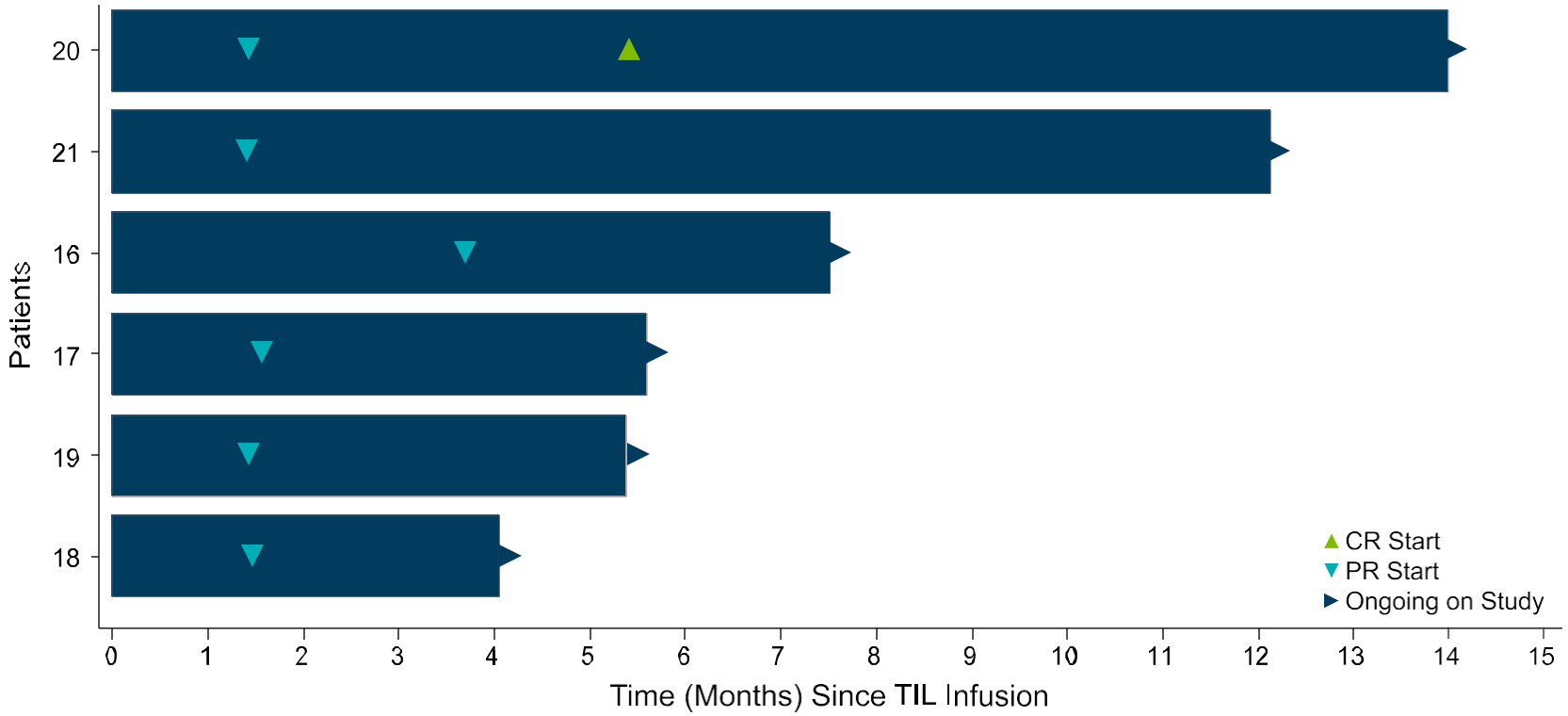
ORR= 26.1% by RECIST 1.1
DCR= 82.6%
Regardless of PD-L1 Status

1. Data cut: July 6, 2023. Responses were assessed by investigator.
2. Patients who have progressed on or after chemotherapy and anti-PD-1 therapy for advanced (unresectable or metastatic) NSCLC without EGFR, ROS or ALK genomic mutations and had received at least one line of an FDA-approved targeted therapy if indicated by other actionable tumor mutations.

Abbreviations: AE, adverse event; CI, confidence interval; CR, complete response; ICI, immune checkpoint inhibitor; NE, not evaluable; NMA-LD, non-myeloablative lymphodepletion; NSCLC, non-small-cell lung cancer; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease; TEAE, treatment-emergent AE.

Preliminary Clinical Results for IOV-LUN-202 Cohorts 1 and 2

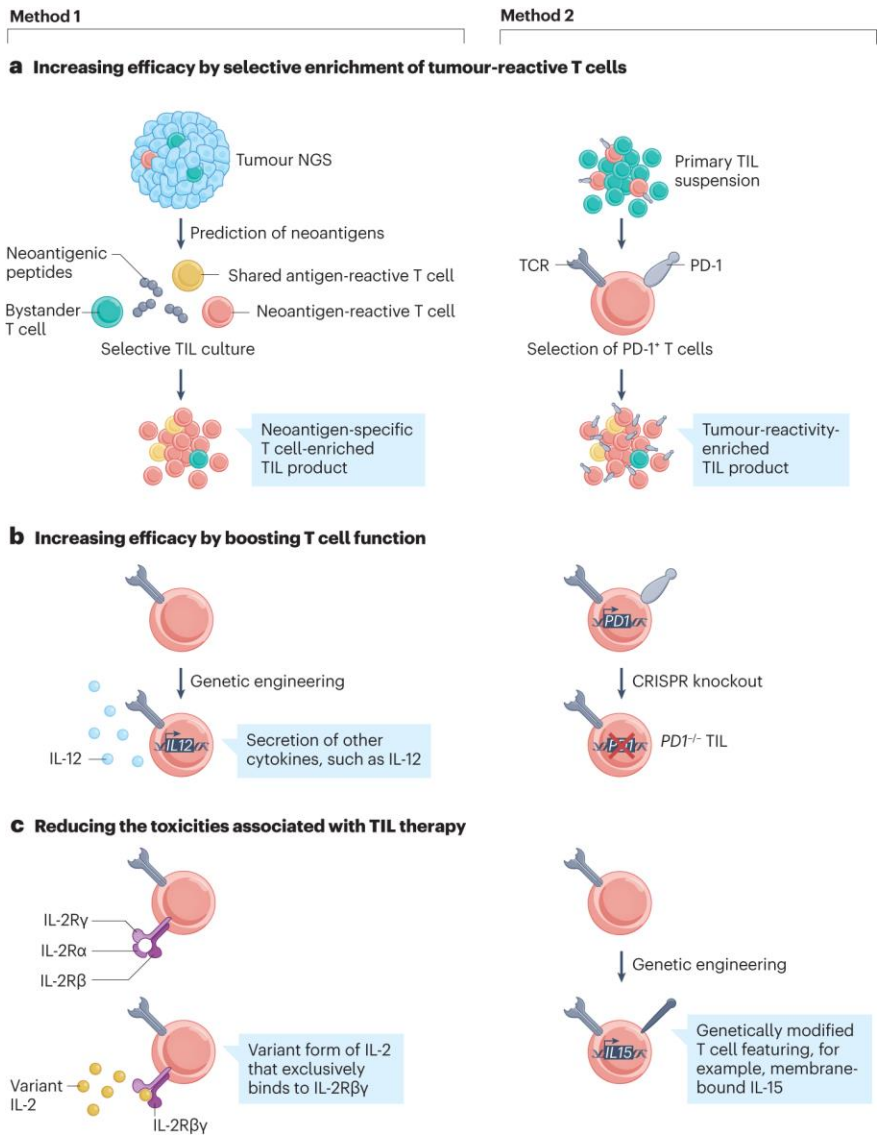
All Responses were ongoing at time of data cut



Data cut: July 6, 2023.
A bar is presented for each patient starting from date of LN-145 infusion up to date of new anti-cancer therapy, end of assessment, death, or data cutoff date, whichever occurs earlier.
Abbreviations: CR, complete response; DOR, duration of response; NSCLC, non-small-cell lung cancer; PR, partial response.

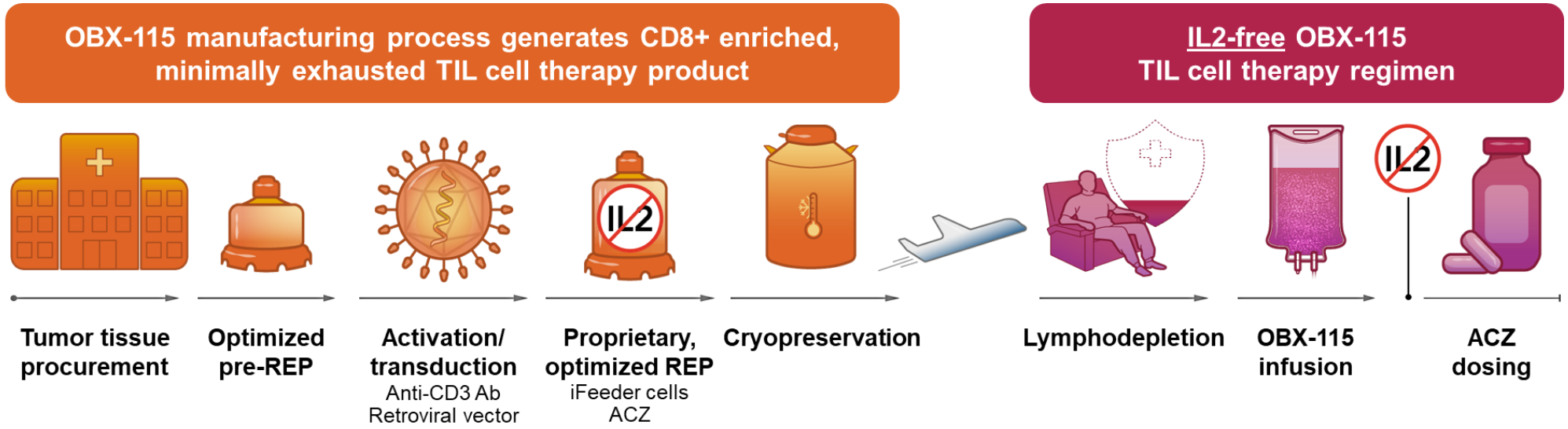
Beyond First-Generation: What's Next for TIL in NSCLC?

Next-generation TIL therapies



Klobuch S et al Nat Rev Clin Oncol 2024

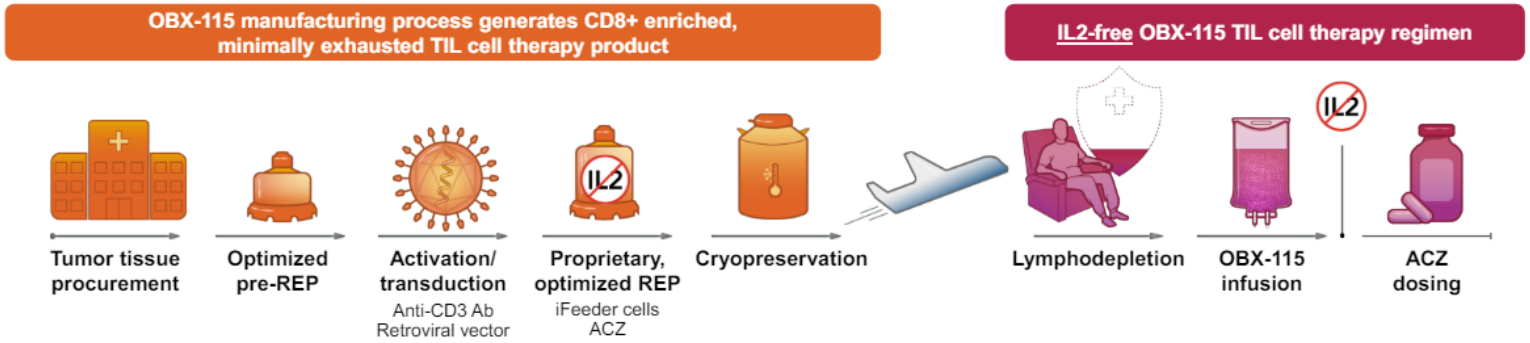
Can Engineering TIL with Membrane-Bound IL-15 Enhance Activity While Minimizing Toxicity?



Schoenfeld AJ et al ASCO 2024

Can Engineering TIL with Membrane-Bound IL-15 Enhance Activity While Minimizing Toxicity?

Phase 1/2 Study is open for accrual in lung cancer (NCT06060613)



✓ Lower lymphodepletion

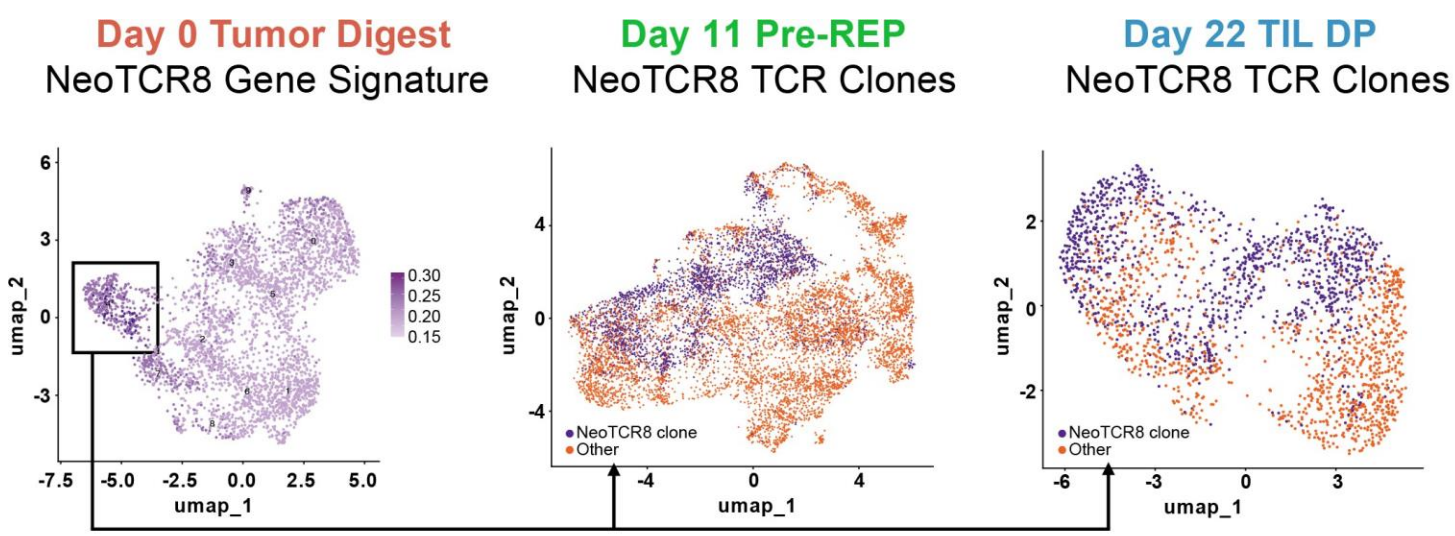
✓ No IL2

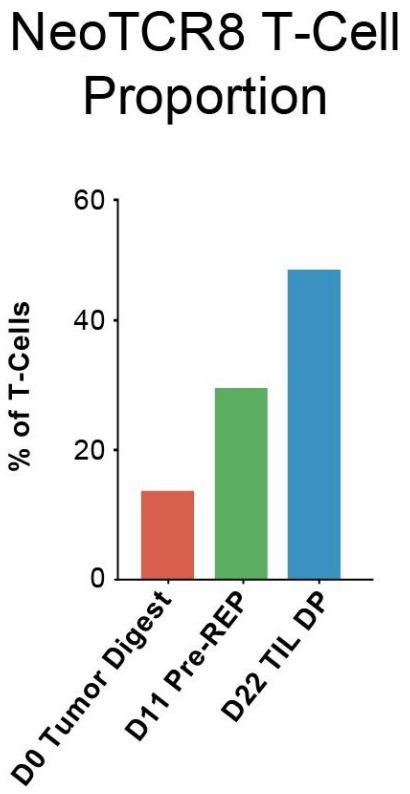
✓ Biopsy to generate TIL

Schoenfeld AJ., ASCO 2024

Identifying Biomarkers to Predict and Monitor Response to TIL Therapy

Tracking Tumor-reactive T cells from tumor to product and beyond

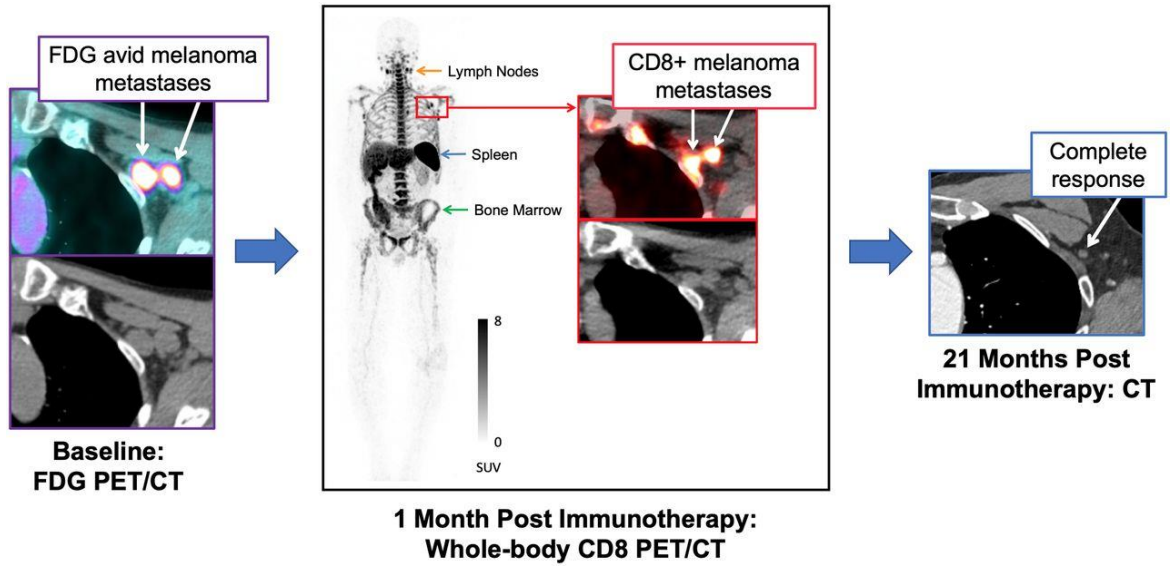




Data are from 1 patient with a durable complete response. D, day; DP, drug product; REP, rapid expansion process; TCR, T-cell receptor; TIL, tumor-infiltrating lymphocyte; UMAP, Uniform Manifold Approximation and Projection.
Lowery FJ, et al. *Science*. 2022;375:877-84.

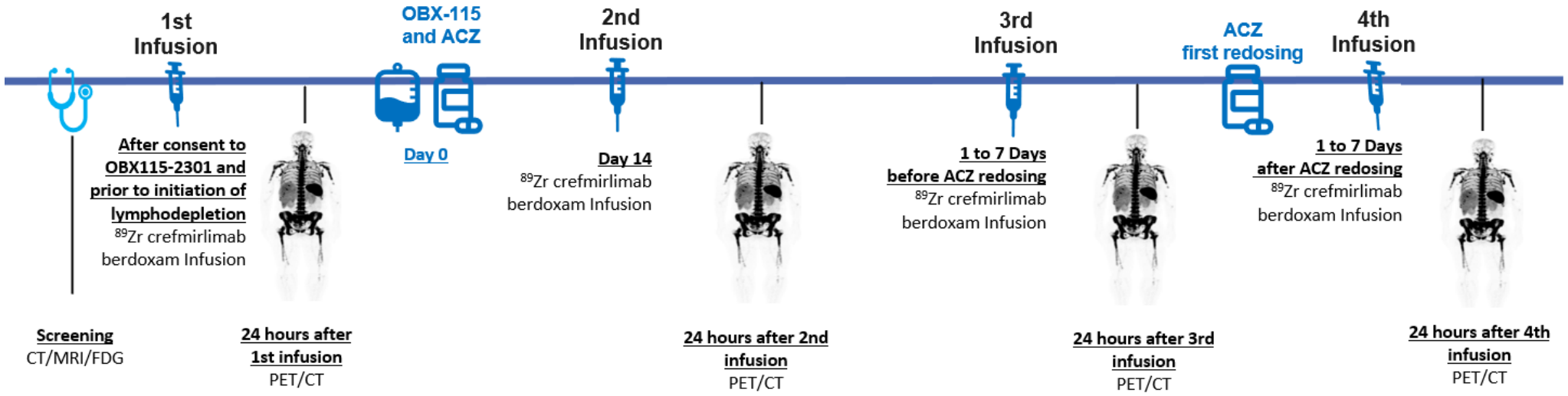
Tracking Engineered TILs *In Vivo*: A CD8 PET Imaging Pilot

- Zirconium-89 crefmirlimab berdoxam is a novel CD8 PET tracer composed of an ~80 kDa minibody (crefmirlimab) with high affinity for the CD8 glycoprotein (EC_{50} = 0.4 nM)
- The minibody is conjugated with deferoxamine (Df; berdoxam) and radiolabeled with ^{89}Zr to enable visualization of $CD8^+$ T-cell trafficking
- The tracer has been well tolerated with established dosing and kinetics from prior phase 1 studies in patients treated with immunotherapy



Farwell et al, JNM 2022

Tracking Engineered TILs *In Vivo*: A CD8 PET Imaging Pilot



- **OBX-115 is a predominantly CD8$^+$ T-cell product (>95%),** with anti-tumor effects likely mediated by CD8$^+$ activation
- **CD8-targeted PET/CT imaging will quantify CD8$^+$ influx** into tumor tissues in patients on the clinical protocol
- **Visualizing CD8$^+$ dynamics** may elucidate mechanism of action and provide a radiographic biomarker of treatment response

Summary

- TIL therapy in lung cancer is feasible and shows early signals of clinical activity
- Preliminary data suggest earlier use may enhance efficacy
- Next-generation engineered TIL products aim to further increase activity and reduce toxicity
- Improved biomarkers of response and resistance are essential for future development

Thank You!

MSKCC

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TIL cell therapy working group:
Omid Hamid, MD
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- **Kay F. Stafford Initiative in Lung Cancer Immunotherapy**

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NIH National Institutes of Health

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Questions?

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