Tumor infiltrating lymphocyte (TIL) therapy: future directions after FDA approval

Cell Coast Conference
October 18th, 2025

Daniel Olson, MD
Assistant Professor of Medicine
The University of Chicago

Disclosures

I will discuss investigational agents in the context of ongoing clinical trials

Consulting fees: Novartis, Iovance, Obsidian, Aadi, BMS, Deciphera, Immunocore Replimune

Associated institutional research funding: Adaptimmune, Inhibrx, Astellas, Immunocore, Bayer, Iovance, Tscan, Immuneering, Numab, Chimeric, CRISPRx

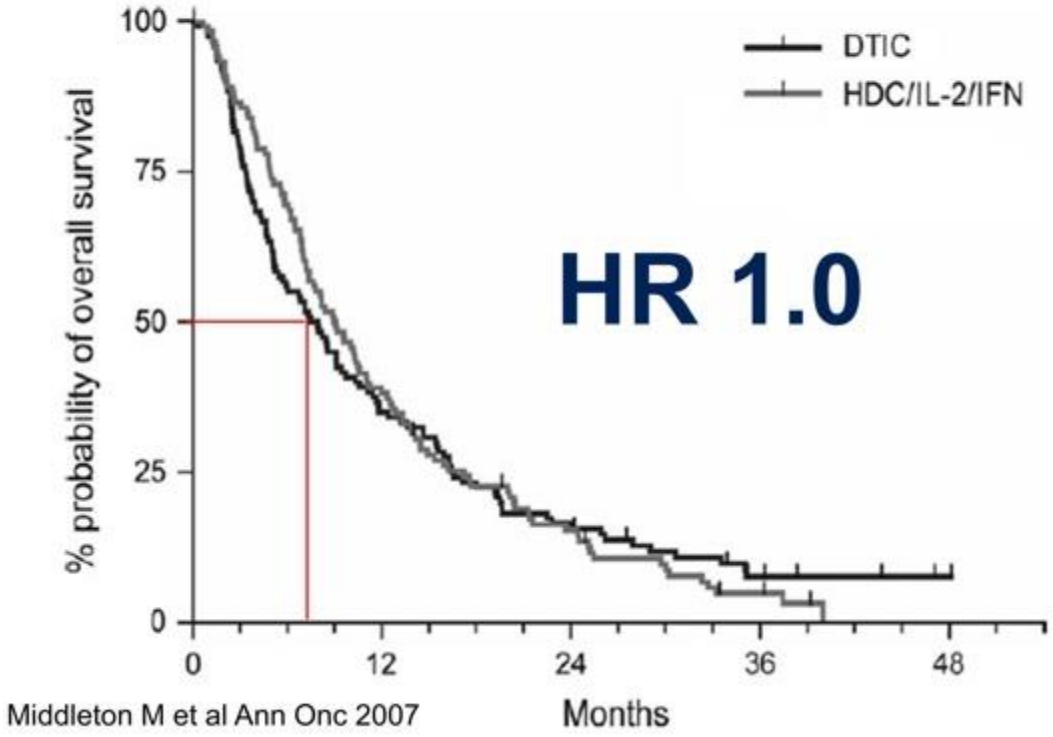
Direct research funding: American Cancer Society

Objectives

1. To discuss data leading to the recent approval of lifileucel and initial observations on the use of lifileucel post FDA approval

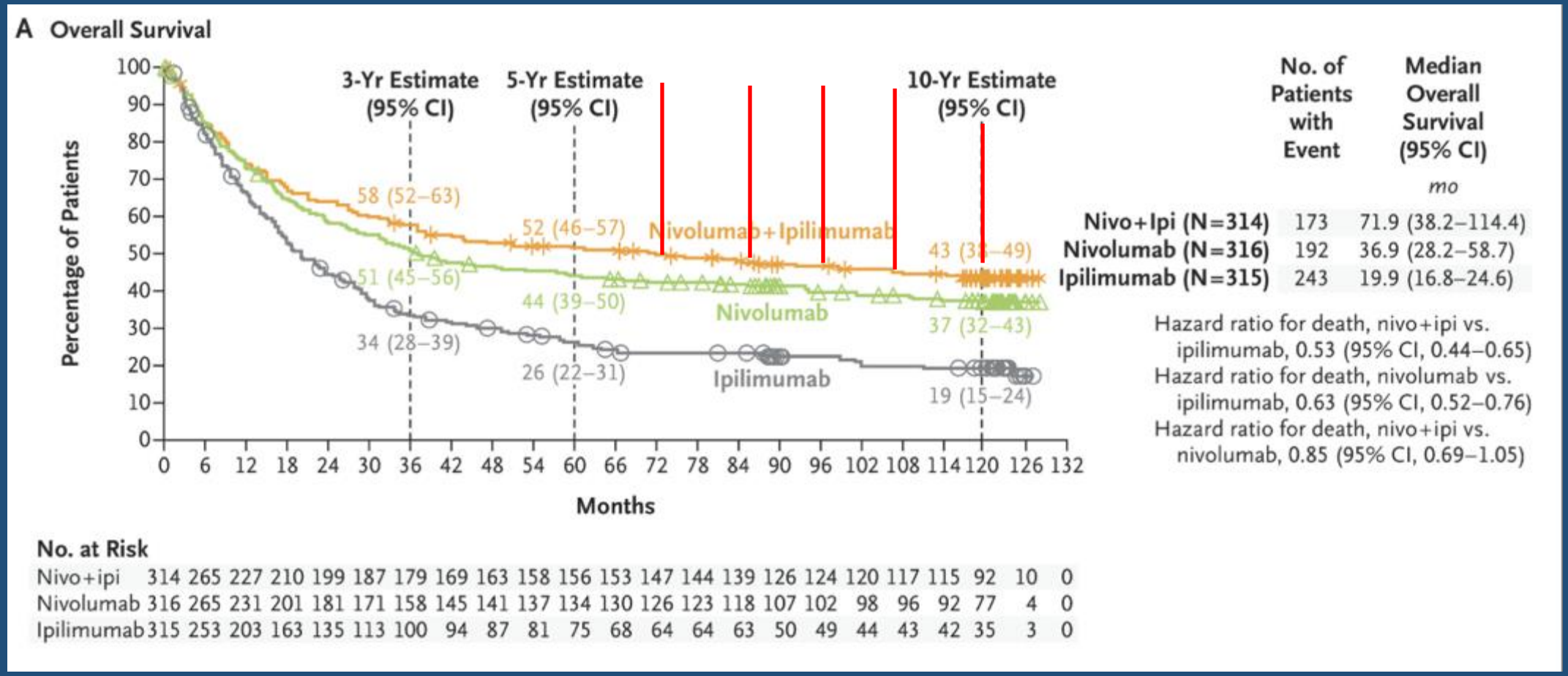
2. To review future directions for TIL across solid tumors

Historical context: dismal melanoma outcomes, pre-2010



Georgina Long, ASCO Annual Meeting 2021

Immune checkpoint inhibitors (ICIs), in combination or sequence, deliver long-term remission in > 50% of patients

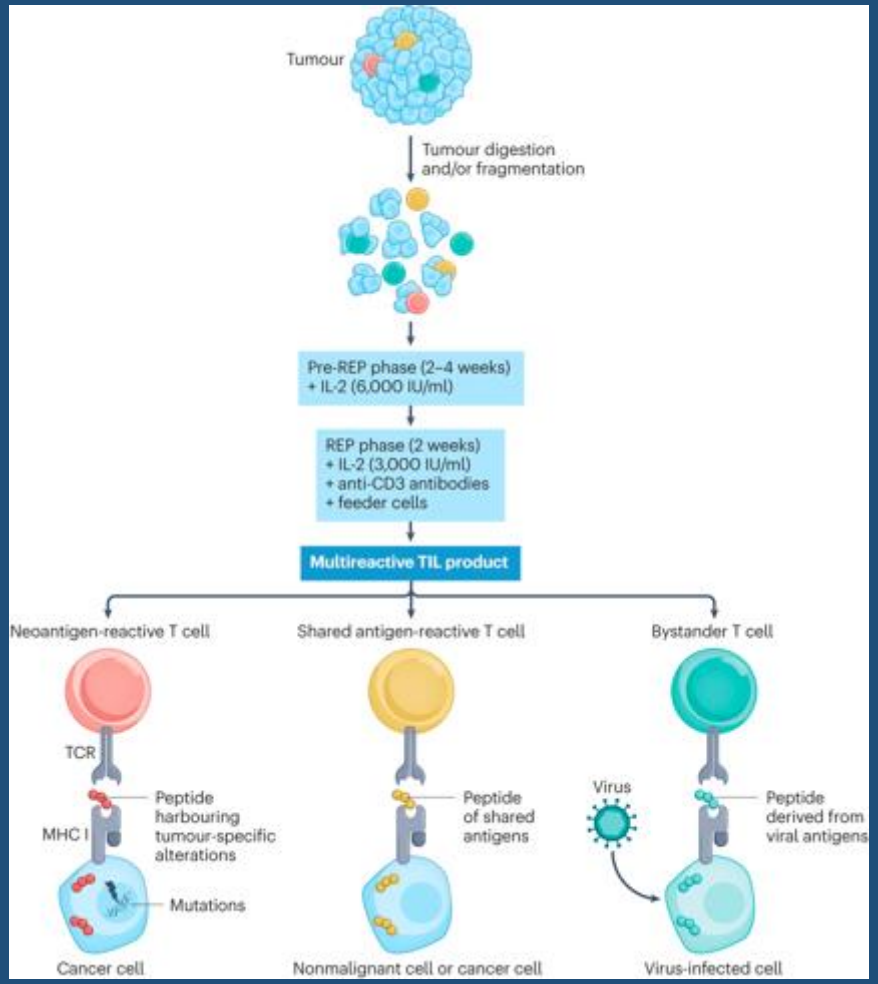


	No. of Patients with Event	Median Overall Survival (95% CI)
		mo
Nivo+Ipi (N=314)	173	71.9 (38.2–114.4)
Nivolumab (N=316)	192	36.9 (28.2–58.7)
Ipilimumab (N=315)	243	19.9 (16.8–24.6)

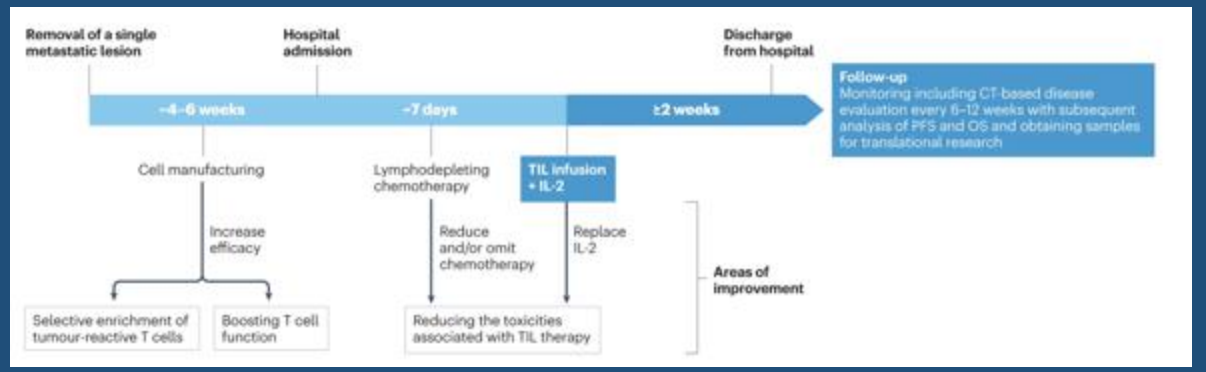
Hazard ratio for death, nivo+ipi vs. ipilimumab, 0.53 (95% CI, 0.44–0.65)
Hazard ratio for death, nivolumab vs. ipilimumab, 0.63 (95% CI, 0.52–0.76)
Hazard ratio for death, nivo+ipi vs. nivolumab, 0.85 (95% CI, 0.69–1.05)

Wolchok *et al*. *N Engl J Med*. 2024

TILs: decades-old concept advanced to clinic by improved manufacturing and new investment

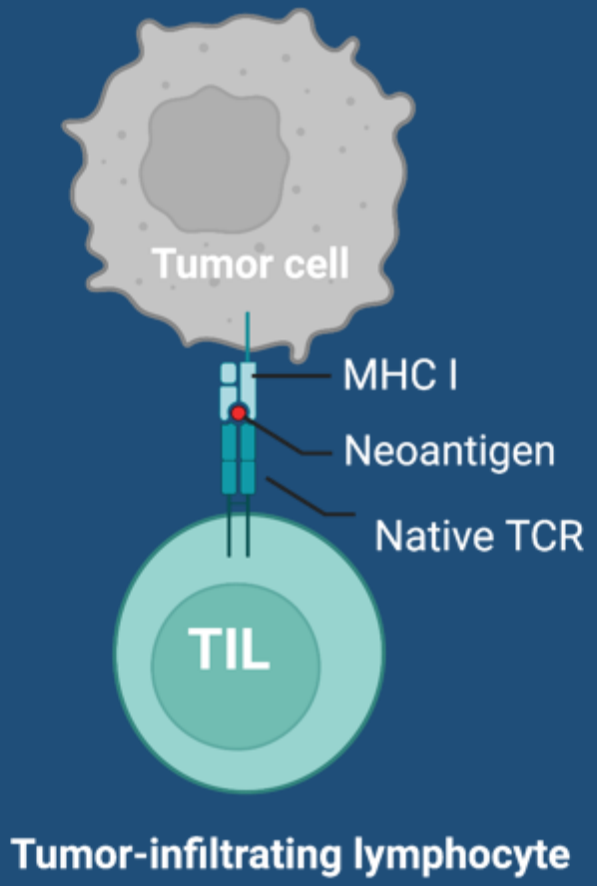


- NCI → academic labs → industry
- Requires non-myeloablative, lympho-depleting chemotherapy (NMA-LD)
- Timeline surgery → treatment is now 35 days
- Patients require IL-2 for in vivo TIL activation



Klobuch et al. Nature Reviews Clinical Oncology. 2024

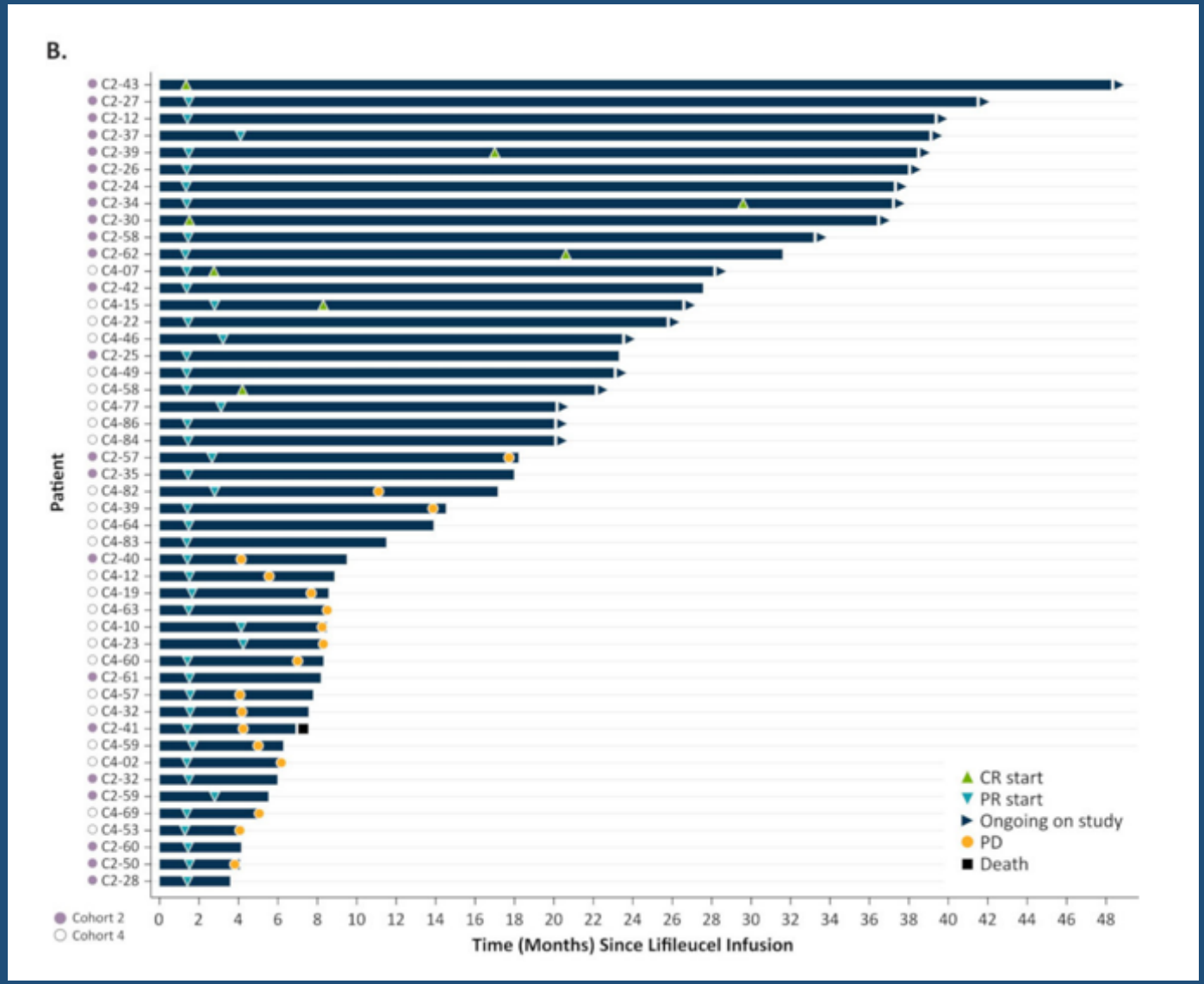
TIL therapy hinges on the unique recognition of patient-specific antigens by native T cells

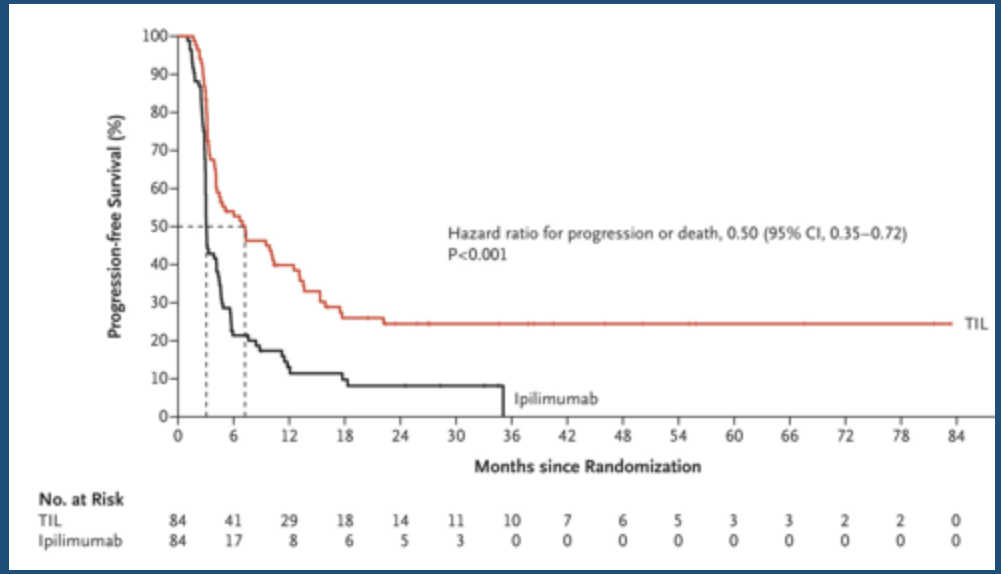


- HLA-matching is inherent in autologous cells
- Antigen targeting is agnostic and multi-targeted
  - Occurs across MHC I and MHC II molecules
  - T-cell clones predominantly target *personal* neoantigens
  - rare shared antigens in responders (MAGE, gp100)
- Native TCRs among TILs have low likelihood for off tumor targeting
- Favorable responses among T cell-inflamed tumors

Tran, Rosenberg et al. Nature Immunology 2017

TILs in melanoma is effective after PD-1 Ab and can offer long-term remission in some





Sarnaik et al. JCO 2021
Rohaan et al. NEJM 2022

U Chicago TIL Experience

- **49 procurement surgeries**
- **36 patients successfully infused**
  - 9 patients progressed after surgery and could not receive TIL
  - 2 patient had no viable tumor and were then NED after bridging therapy
  - 1 surgical complication leading to deferral to subsequent TIL therapy
  - 1 patient had delayed response to bridging therapy and did not need TIL infusion
- **12 out-of-spec patients**
  - 6 made it to infusion, 2 who had successful in-spec repeat procurement
- **Age range**: 34-84y/o
- **Unconfirmed ORR = 58% (18/31)**
- **Confirmed ORR = 38% (11/29)**

U Chicago TIL Experience

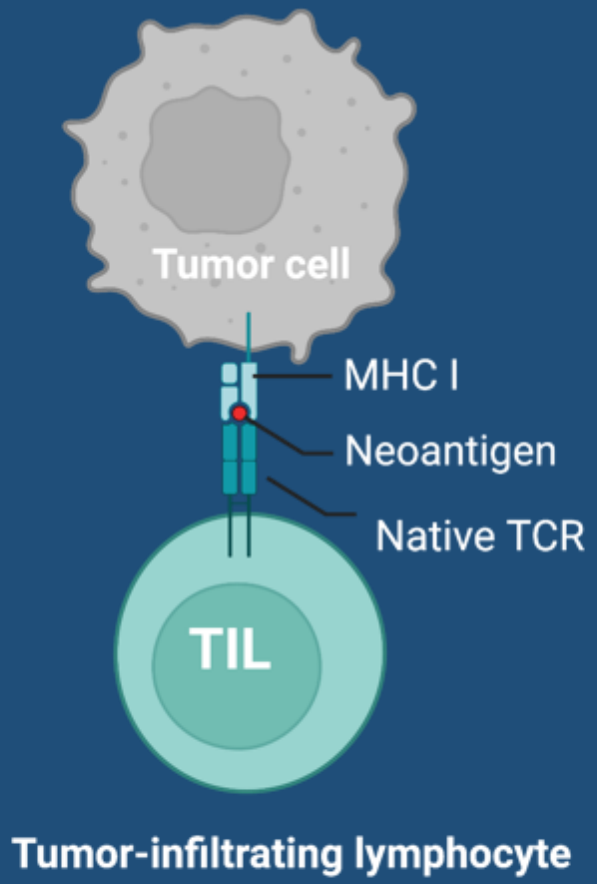
- **Treatment related mortality**
  - No on-treatment deaths
  - One possibly treatment-related death (sepsis > 30 days post infusion)
- **Notable toxicities**
  - One case of marrow failure attributed to prior ICI therapy
  - One CNS hemorrhage during LD chemo requiring emergent surgery
  - One syndrome of tinnitus/uveitis/vitiligo patient (known direct TIL toxicity)
- **Take aways**
  - TIL works similarly well in a real-world population
  - Out-of-spec rates improve over time with improved tumor selection
  - Room for improvement in terms of efficacy and safety

Objectives

1. To discuss data leading to the recent approval of lifileucel and initial observations on the use of lifileucel post FDA approval

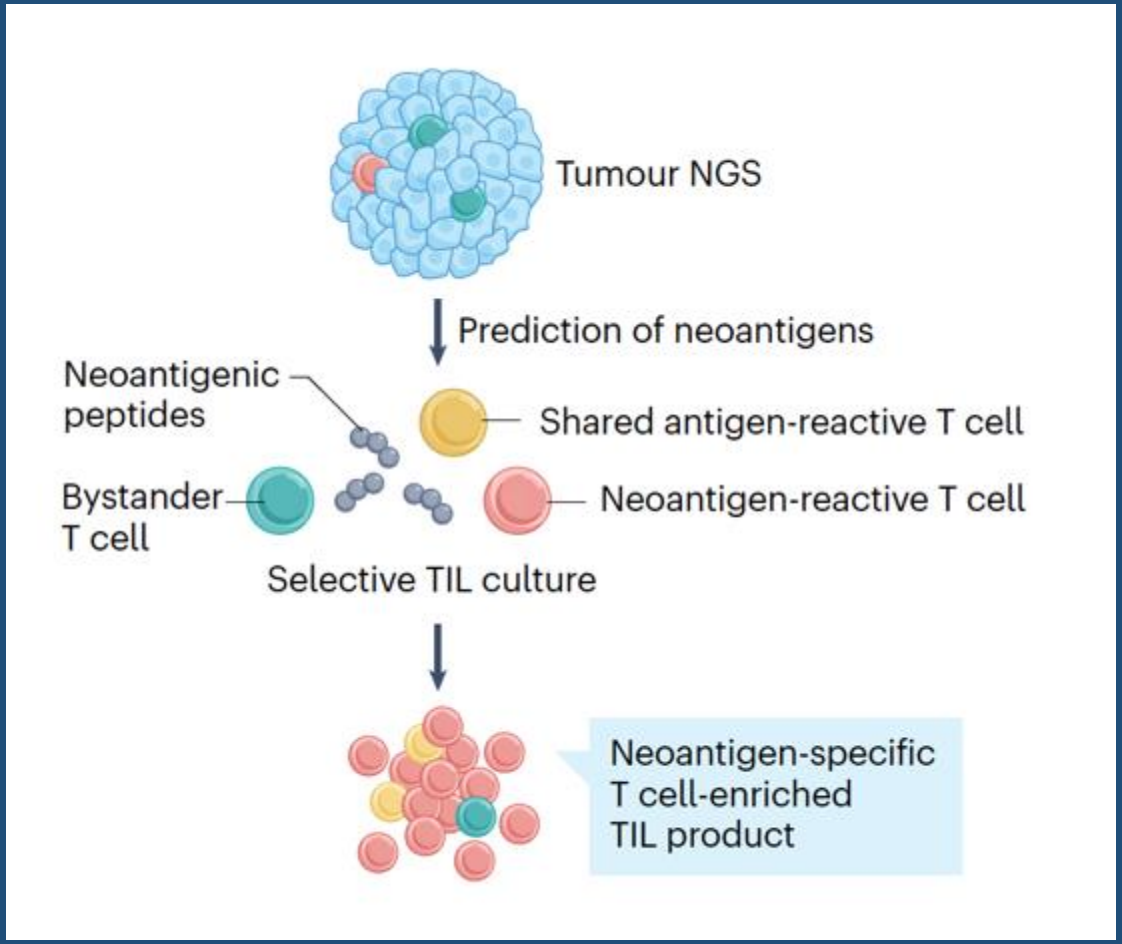
2. **To review future directions for TIL across solid tumors**

Strategies to improve TIL therapies



- Selecting TILs by antigen specificity
- Selecting TILs by phenotype to boost function
- Direct engineering of TILs to alter function
- Improving cytokine partners for TIL

Neoantigen-specific TIL selection allows for refinement of tumor-reactive and persistent TIL populations



Advantages

- expansion of low-frequency TILs
- elimination of bystander cells

Disadvantage

- manufacturing timeline and cost

Early activity in breast cancer and cholangiocarcinoma with TIL selection

Trials ongoing: uveal melanoma, colon and breast cancers

Tran E, Robbins P, Rosenberg S. Nature Immunology 2017
Klobuch et al. Nature Reviews Clinical Oncology. 2024

Neoantigen-specific TIL faces challenges in scalability of approach


BIOTECH

Turnstone ends last remaining clinical program due to costs, plots more layoffs

By **James Waldron** · Feb 4, 2025 10:30am


BIOTECH

Achilles drops cell therapy program, braces for layoffs after missing 'commercial viability' goals

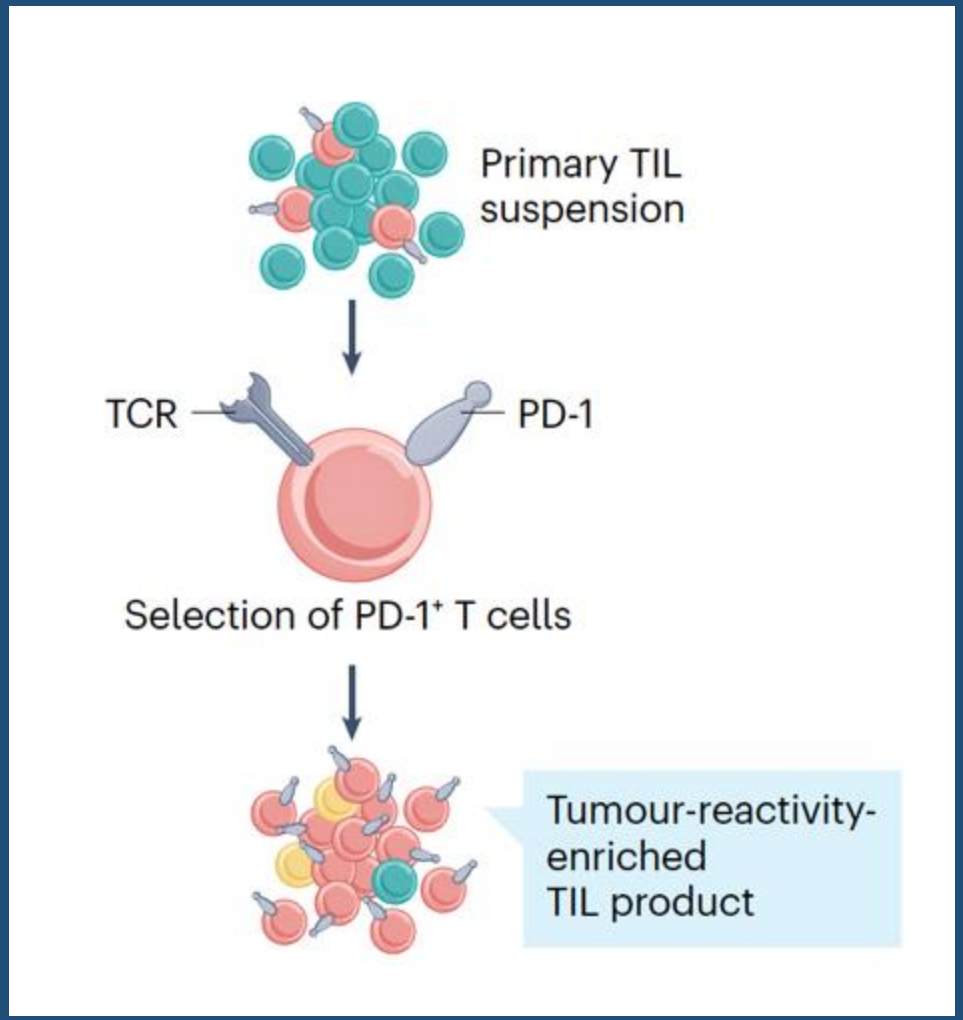
By **Nick Paul Taylor** · Sep 19, 2024 9:24am


Article | Published: 01 April 2025

Neoantigen-specific tumor-infiltrating lymphocytes in gastrointestinal cancers: a phase 2 trial

Frank J. Lowery, Stephanie L. Goff, Billel Gasmi, Maria R. Parkhurst, Nivedita M. Ratnam, Hyunmi K. Halas, Thomas E. Shelton, Michelle M. Langhan, Aarushi Bhasin, Aaron J. Dinerman, Victoria Dulemba, Ian S. Goldlust, Alexandra M. Gustafson, Abraham A. Hakim, Kyle J. Hitscherich, Lisa M. Kenney, Lior Levy, Juliette G. Rault-Wang, Alakesh Bera, Satyajit Ray, Courtney D. Seavey, Chuong D. Hoang, Jonathan M. Hernandez, Jared J. Gartner, ... Steven A. Rosenberg + Show authors

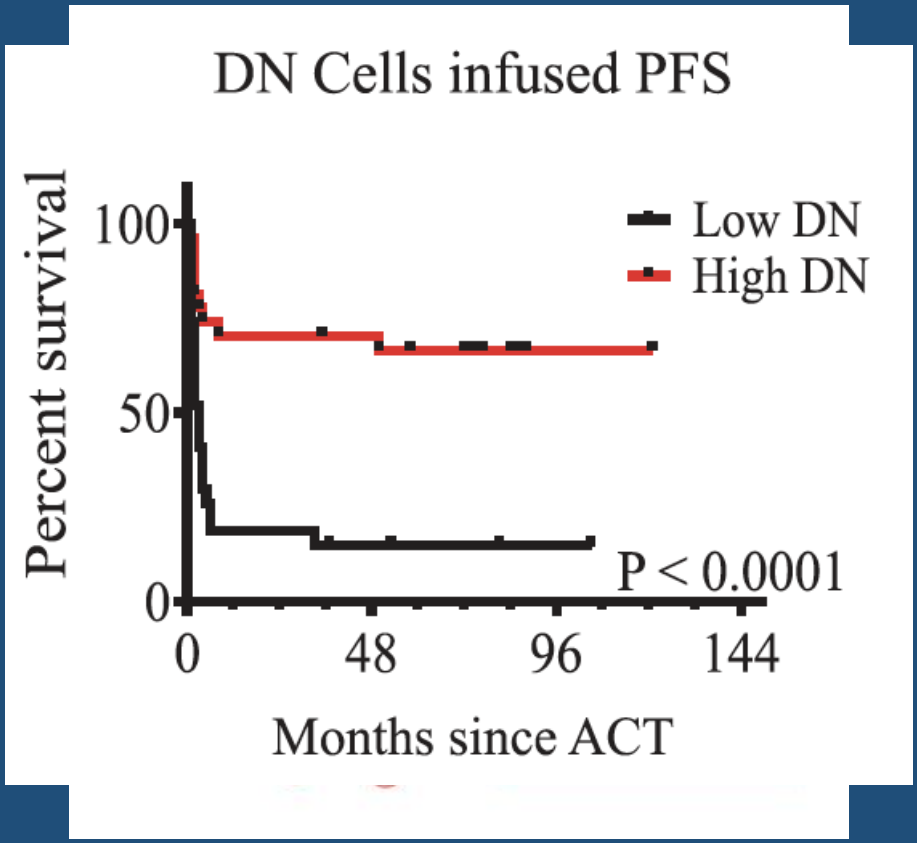
Future Solution: TIL selection by phenotype

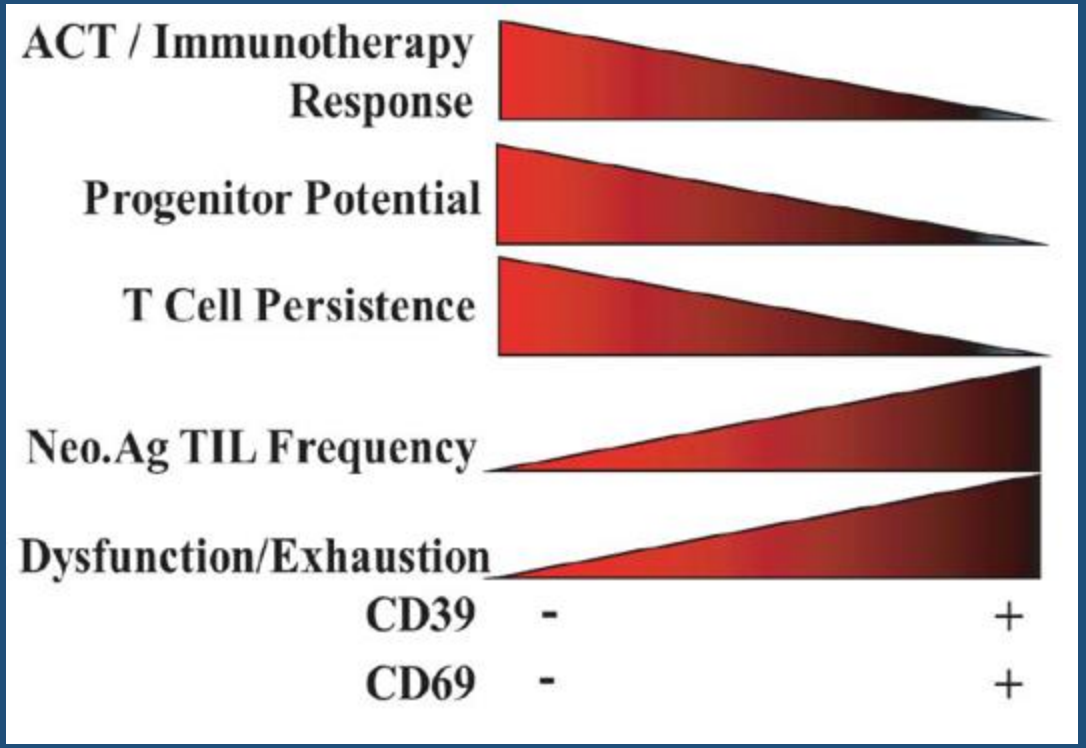


- TILs sorted by surface markers and phenotype rather than antigen recognition
  - e.g. PD-1, 4-1BB
- Markers known to enrich for tumor-reactive TILs or proliferative capacity
- Sorting by surface markers may improve scalability while improving efficacy of TIL

Klobuch et al. Nature Reviews Clinical Oncology. 2024

TIL selection by T-cell *phenotype* may improve activity of TILs, even without antigen identification

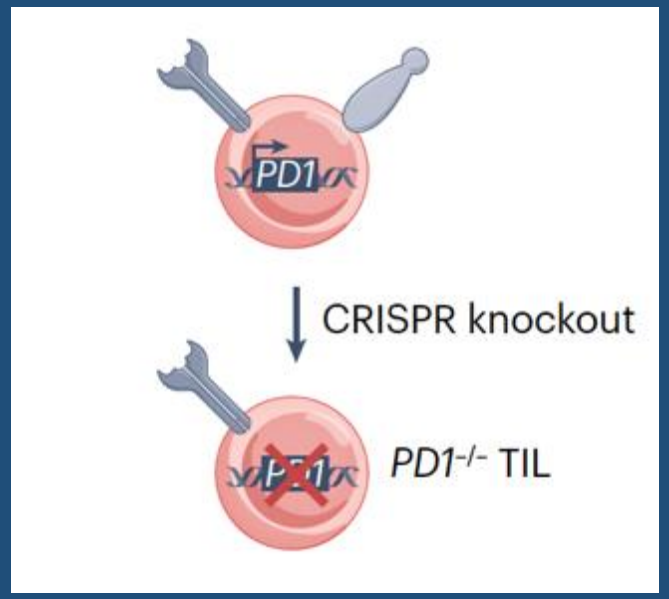


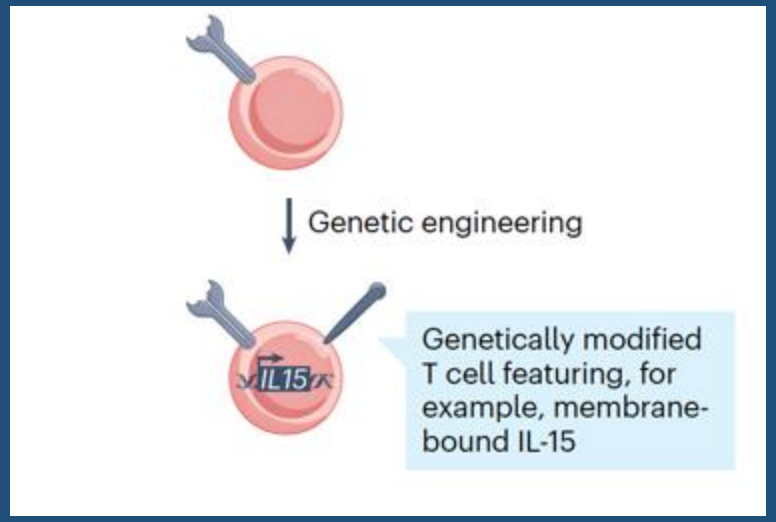


DN = double negative for CD39–CD69–

Krishna et al. *Science 2020*

Engineering of TILs during manufacturing may improve persistence and activity





1. “Armoring” of TILs again known resistance mechanisms (PD-1 knockout, dnTGF-B receptor)

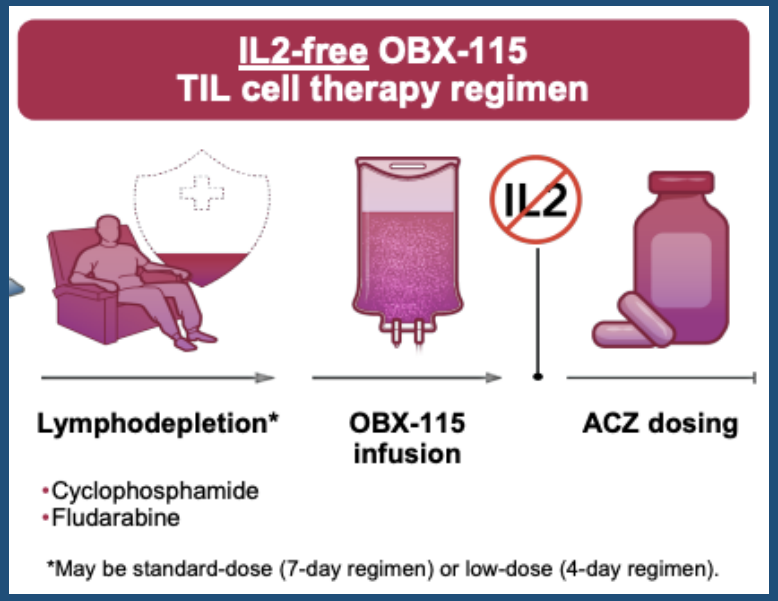
2. Improving metabolic fitness of TILs ex vivo (PI3K–AKT inhibition)

3. Engineered cytokine production

Klobuch et al. Nature Reviews Clinical Oncology. 2024

Engineered TILs in Advanced Melanoma – OBX-115

- mbIL-15 engineered into TIL
- mbIL-15 is regulatable by acetazolamide
- Tumor procured by core needle biopsy
- Promising early results



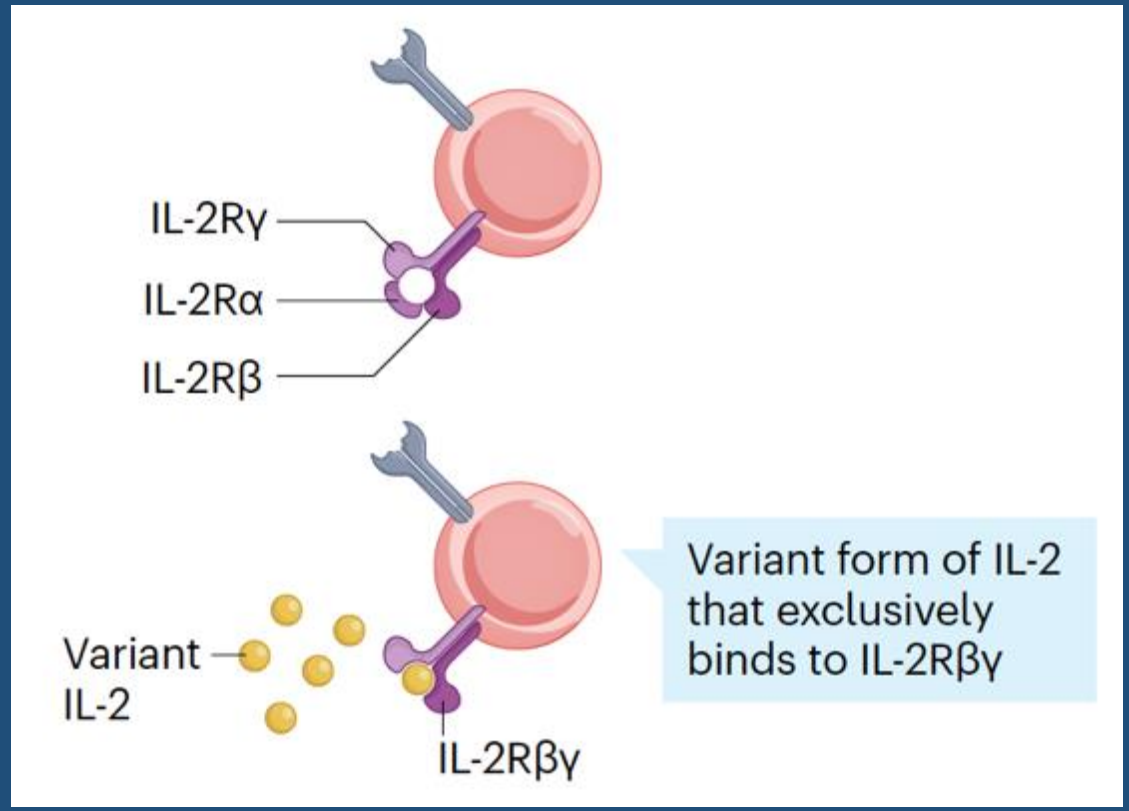
	All Patients DL1, DL2, DL3 (N=11)	DL3 / RP2D (N=6)
Objective response rate, n (%)	**4 (36)**	**4 (67)**
Complete response	**1 (9)**	**1 (17)**
Partial response	3 (27)	3 (50)
Stable disease ≥12 weeks	5 (46)	2 (33)
Progressive disease	2 (18)	0
Disease control rate,* n (%)	9 (82)	6 (100)
Duration of response, months (median [95% CI])	**NR (2.6-NR)**	**NR (2.6-NR)**

Dose Level 3 / RP2D
- ORR 67%
- 1 confirmed CR
- DCR 100%

Dose Level 3 / RP2D is being explored further in **Phase 2**

Shoushtari et al. AACR Annual Meeting 2025
Chesney et al. ASCO Annual Meeting 2025

Improving safety of TILs: IL-2 substitution



Engineering cytokines to eliminate IL-2

IL-2 can be substituted for IL-2 therapies more targeted at IL-2Rβγ

IL-2 is key concern requiring in-patient administration

Protocols in place for use of core needle biopsies for TIL procurement to de-escalate morbidity

Klobuch et al. Nature Reviews Clinical Oncology. 2024

Take home messages

Lifileucel activity is firmly established in PD-1 Ab refractory melanoma

TIL selection offers the promise of increased TIL activity and indications, but logistical complexity limits scalability

Novel strategies to TIL manufacturing – phenotype selection, cytokine engineering – all hold promise for improving TIL across solid tumors, with more favorable manufacturing

Thank you!