Controversies in Cancer Care: Evidence, Interpretation, & Clinical Decision Making

Bringing Cellular Therapy to Melanoma: The City of Hope Experience with Tumor-Infiltrating Lymphocyte (TIL) Therapy

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Disclosures

- Advisor for Iovance Biotherapeutics

This presentation and/or comments will be free of any bias toward or promotion of the above referenced companies or their product(s) and/or other business interests.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

This presentation has been peer-reviewed and no conflicts were noted.

Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:
The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

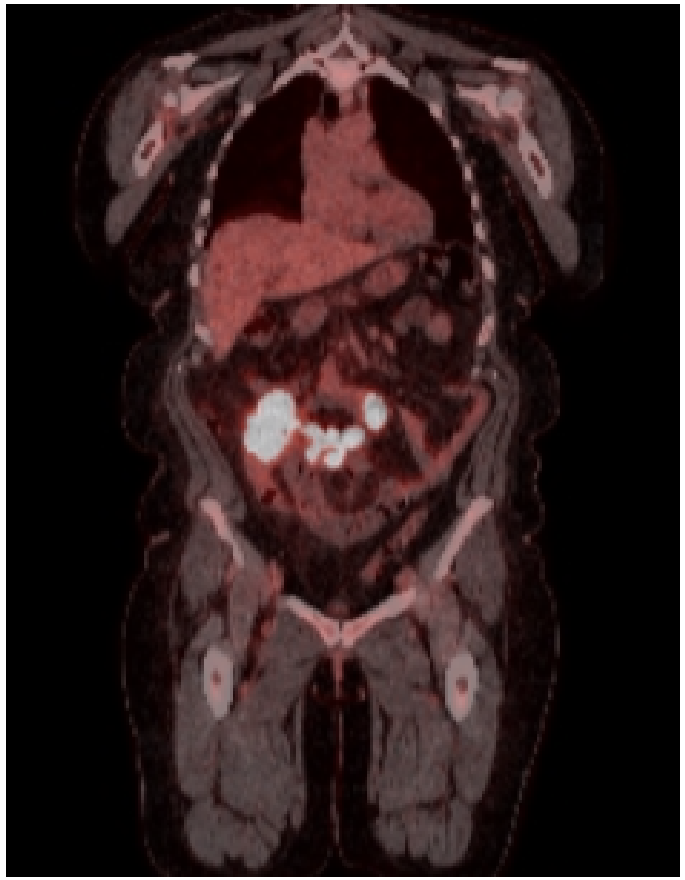
EXEMPTION:
Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

This presentation is dedicated solely to research or other issues that do not contain a direct patient care component.

Patient Example

51-year-old woman with history of BRAF WT Stage IIC (pT4bN0M0) melanoma dx 1/2024 with early metastatic progression on adjuvant Nivolumab and subsequent progression on Ipilimumab/Nivolumab presenting with partial small bowel obstruction.

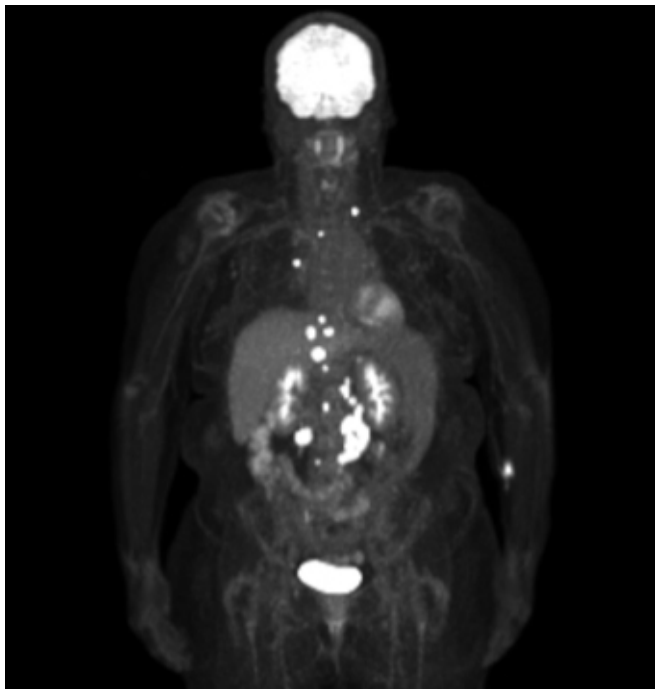
Dilated small bowel with progression of mesenteric and small bowel metastases



- 9/8/2025: Admitted for partial bowel obstruction
- Temporized patient at home on full liquid diet with TIL therapy planning/authorization performed
- 10/9/2025: Tumor TIL Procurement / Palliative Surgery
  - Mesenteric lymph nodes excised for TIL therapy production
  - Small bowel resection with anastomosis (x2) to alleviate obstruction

Patient Example

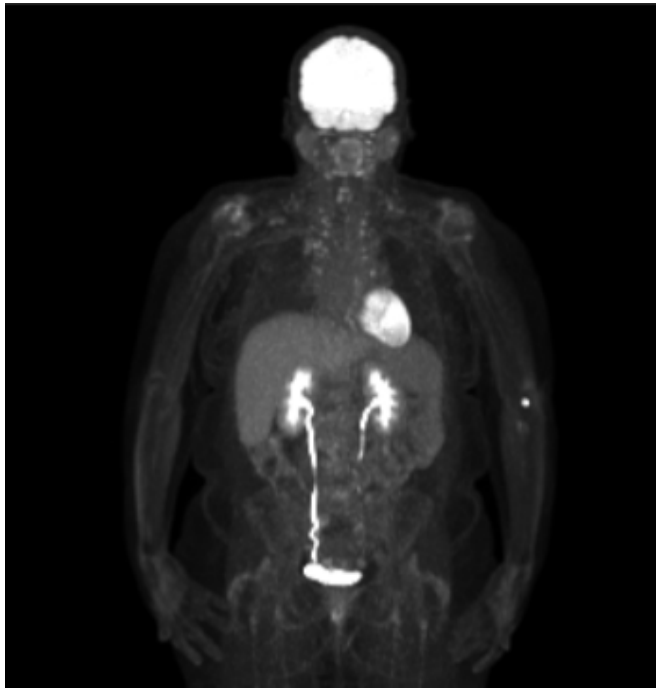
51-year-old woman with history of BRAF WT Stage IIC (pT4bN0M0) melanoma with progression on ICI who underwent TIL adoptive cell therapy



Pre-TIL Therapy Baseline PET/CT

→ New hepatic, nodal and osseous metastases

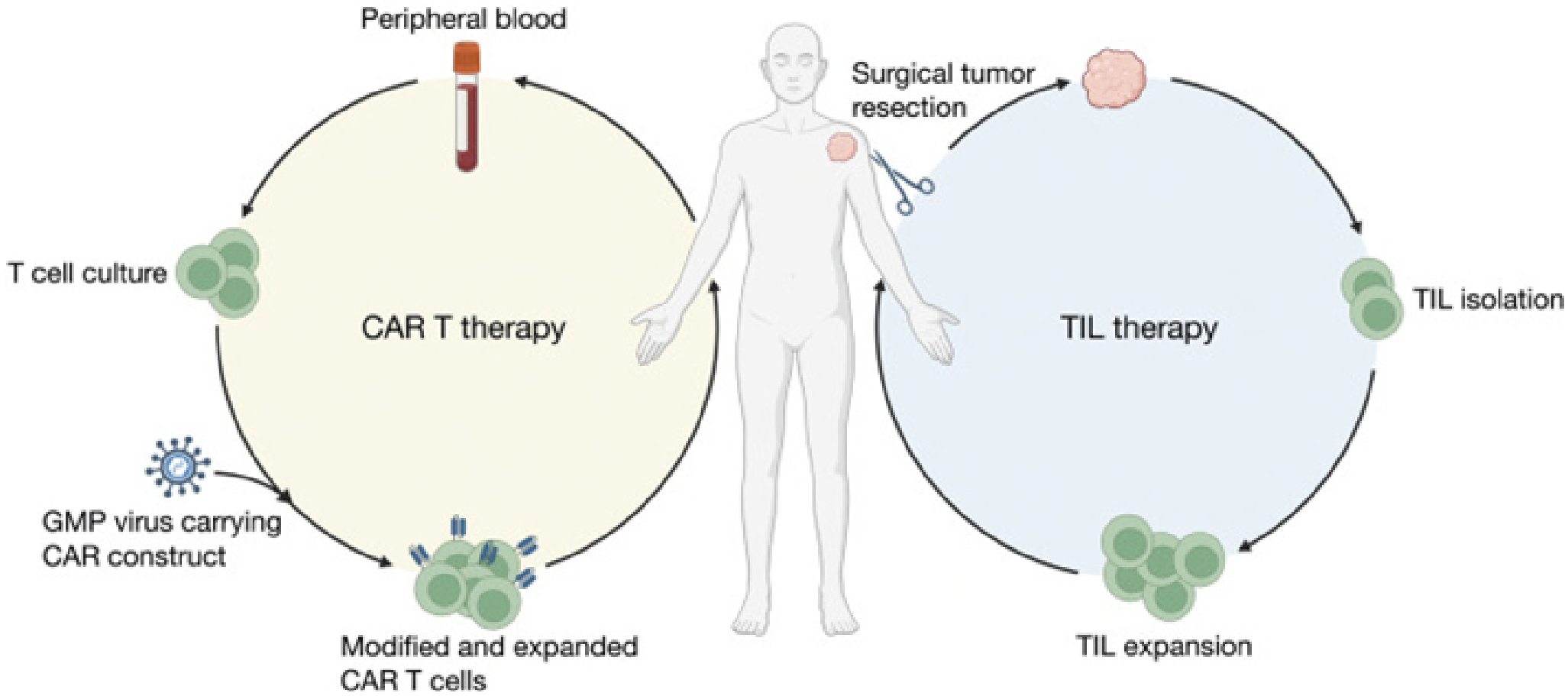
11/25/2025: TIL therapy infusion



3-month Follow-up PET/CT

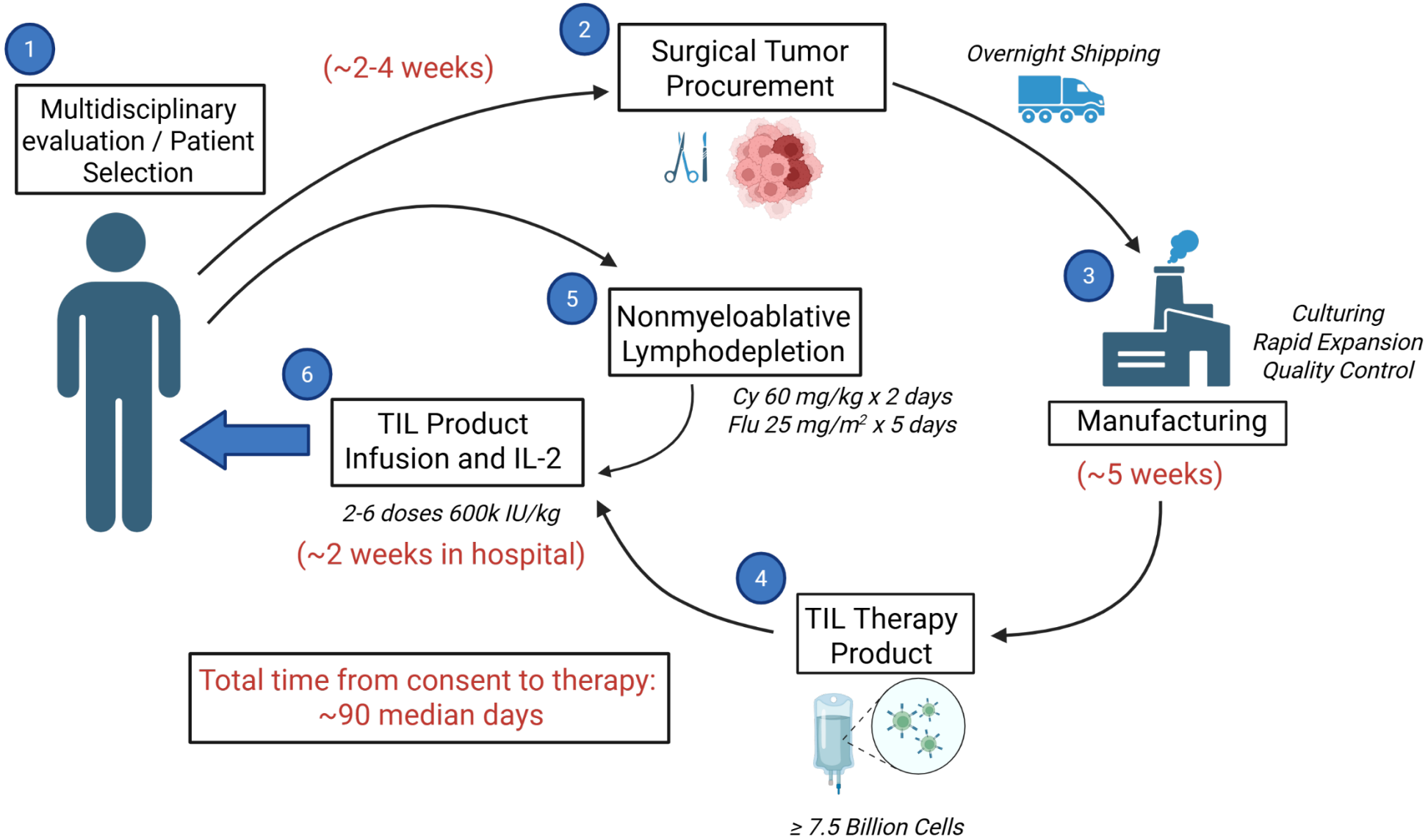
→ Complete response!
→ Remains NED now ~10 months out

Tumor infiltrating lymphocyte (TIL) therapy is an immune cellular therapy utilizing TILs from surgically removed tumors



Singh. Immune Netw. 2024.

TIL Therapy Process Overview

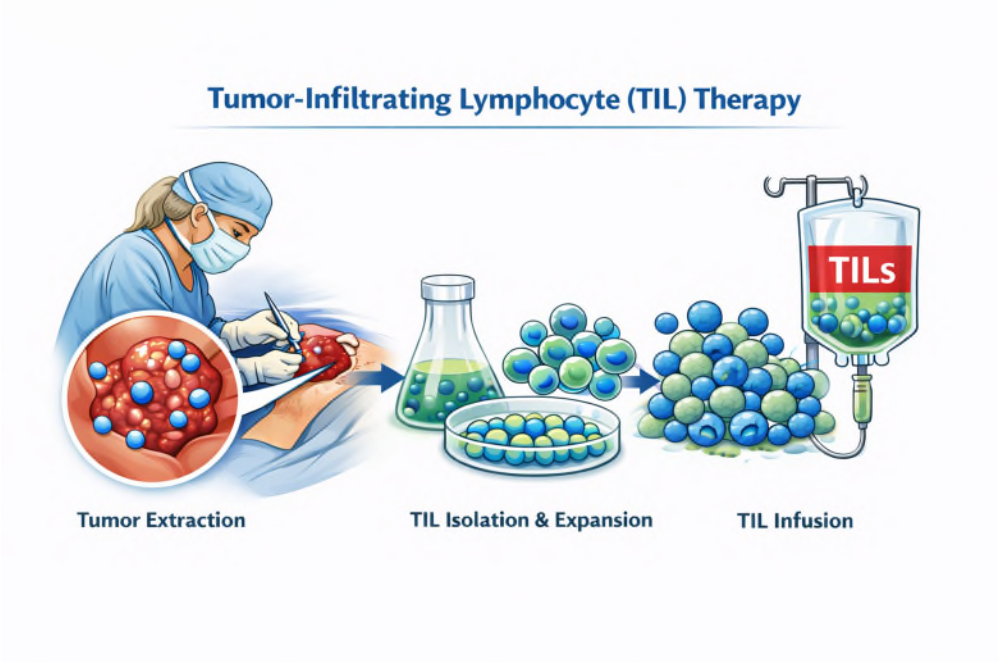


Eligibility Criteria for Commercial TIL Therapy

- Metastatic or unresectable advanced melanoma (uveal excluded)
- Age ≥ 18 years
- Progressed on immune checkpoint inhibitors (PD-1 containing)
- Exposed* to BRAF/MEK inhibitors if BRAF V600E/K mutation present
- Good performance status/organ reserve to tolerate lymphodepletion and high-dose IL-2
- No active or untreated brain metastases
- Cannot be on chronic high-dose systemic steroids (greater than 10 mg of prednisone equivalent)
- Social Support

Surgical Considerations

- ~1.5 – 4.0 cm of tumor
- Avoid sites at risk for bacterial contamination (i.e. GI/GU, nasopharyngeal, ulcerated skin)
- Most sites can be used for TIL harvest
  - Lymph nodes, subcutaneous nodules, lung, liver, adrenal gland, spleen
  - Option to combine tumors
- Avoid radiated tumors (and oncolytic virus injected)
- Minimize morbidity– goal to get patient to therapy!
  - Robotic/MIS when feasible
  - LN/subcutaneous > intrathoracic/abdominal
- Potential for palliation



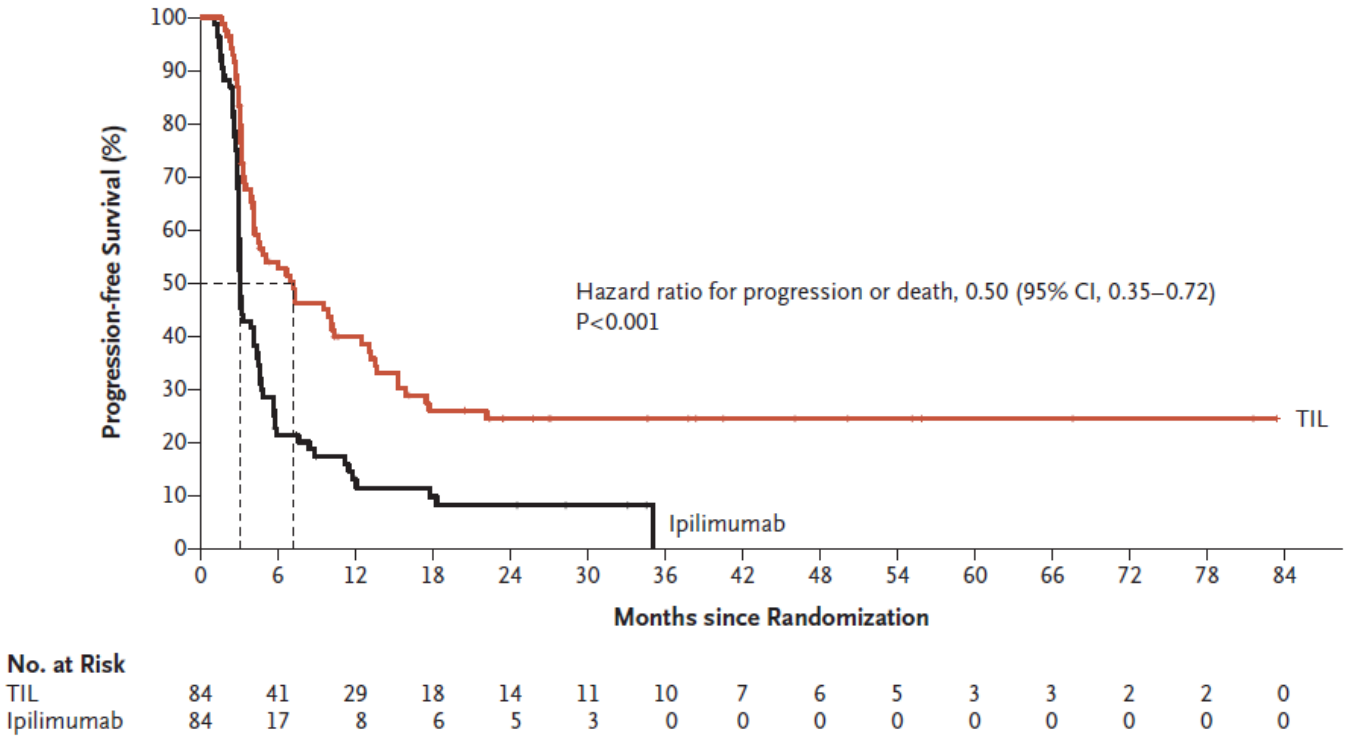
Phase III trial – Improved PFS with TIL therapy versus Ipilimumab in Advanced Melanoma

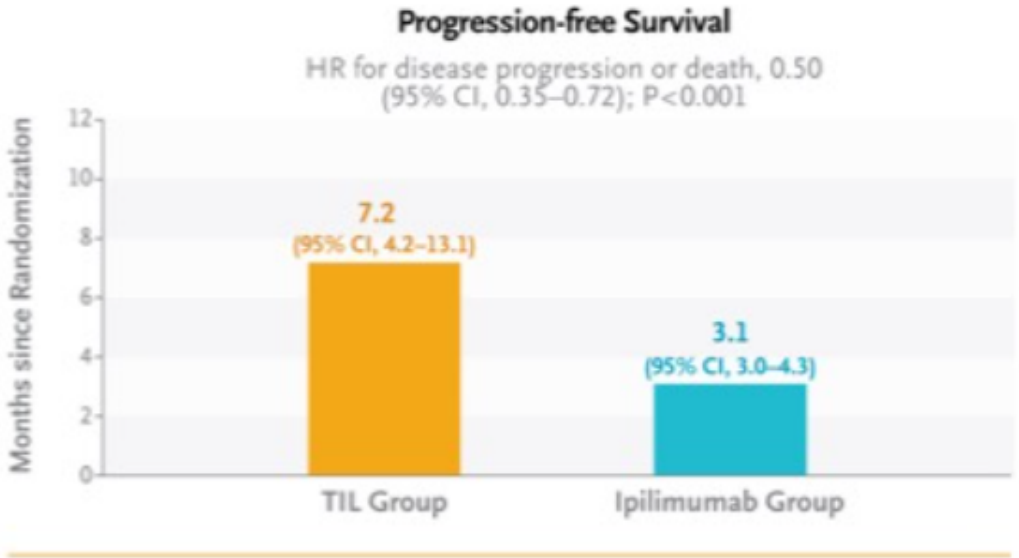
- Phase 3, multicenter RCT
- Metastatic or unresectable IIIC advanced melanoma patients **refractory to anti-PD-1** were assigned to TIL therapy or ipilimumab
- Primary endpoint = PFS
- TRAE ≥ 3 occurred in all TIL patients (mostly cytopenia) and 57% of ipilimumab group

	TIL Group (n=84)	Ipilimumab Group (n=84)
Best Response, % (95% CI)		
Complete response	20 (12–30)	7 (3–15)
Partial response	29 (19–40)	14 (8–24)
Stable disease	19 (11–29)	18 (10–28)
Progressive disease	29 (19–40)	48 (37–59)
ORR (CR or PR), % (95% CI)	49 (38–60)	21 (13–32)
DCR (CR, PR, or SD), % (95% CI)	68 (57–78)	39 (29–51)

Rohaan et al. NEJM. 2022.

Phase III trial – Improved PFS with TIL therapy versus Ipilimumab in Advanced Melanoma



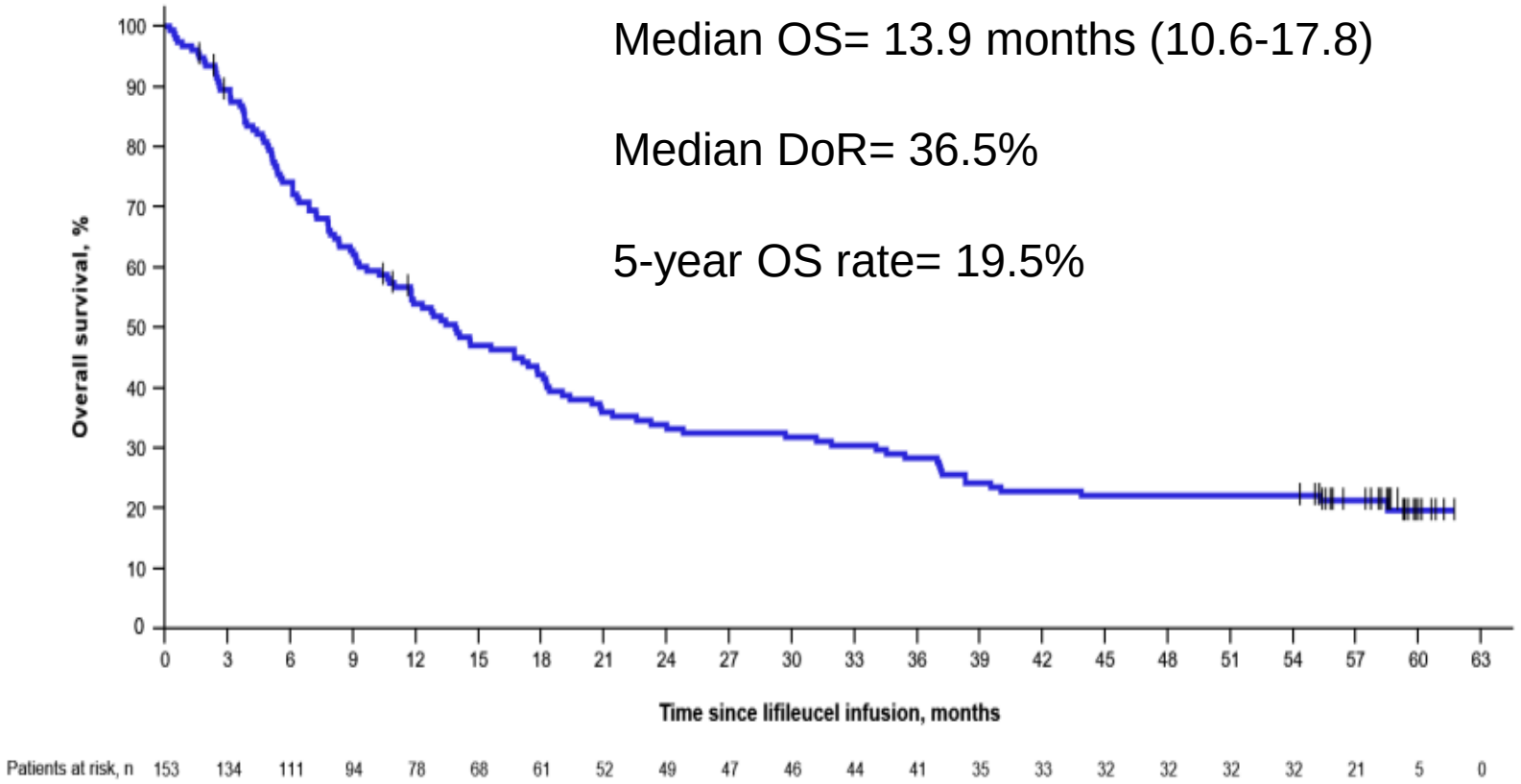


→ Median PFS >2x as long in TIL versus ipilimumab group

Rohaan et al. NEJM. 2022.

Phase II C-144-01 led to FDA approval of Lifileucel in 2024

- Prospective phase 2 study
- Metastatic or unresectable advanced melanoma (n=153) treated with ≥1 prior systemic therapy (PD-1 ± BRAF/MEKi if BRAF V600 mut)
- **Median 3 lines prior therapy (81.7% anti-PD-1/CTLA-4) and high disease burden**
- ORR= 31.4% (CR= 5.9%)



Median OS= 13.9 months (10.6-17.8)

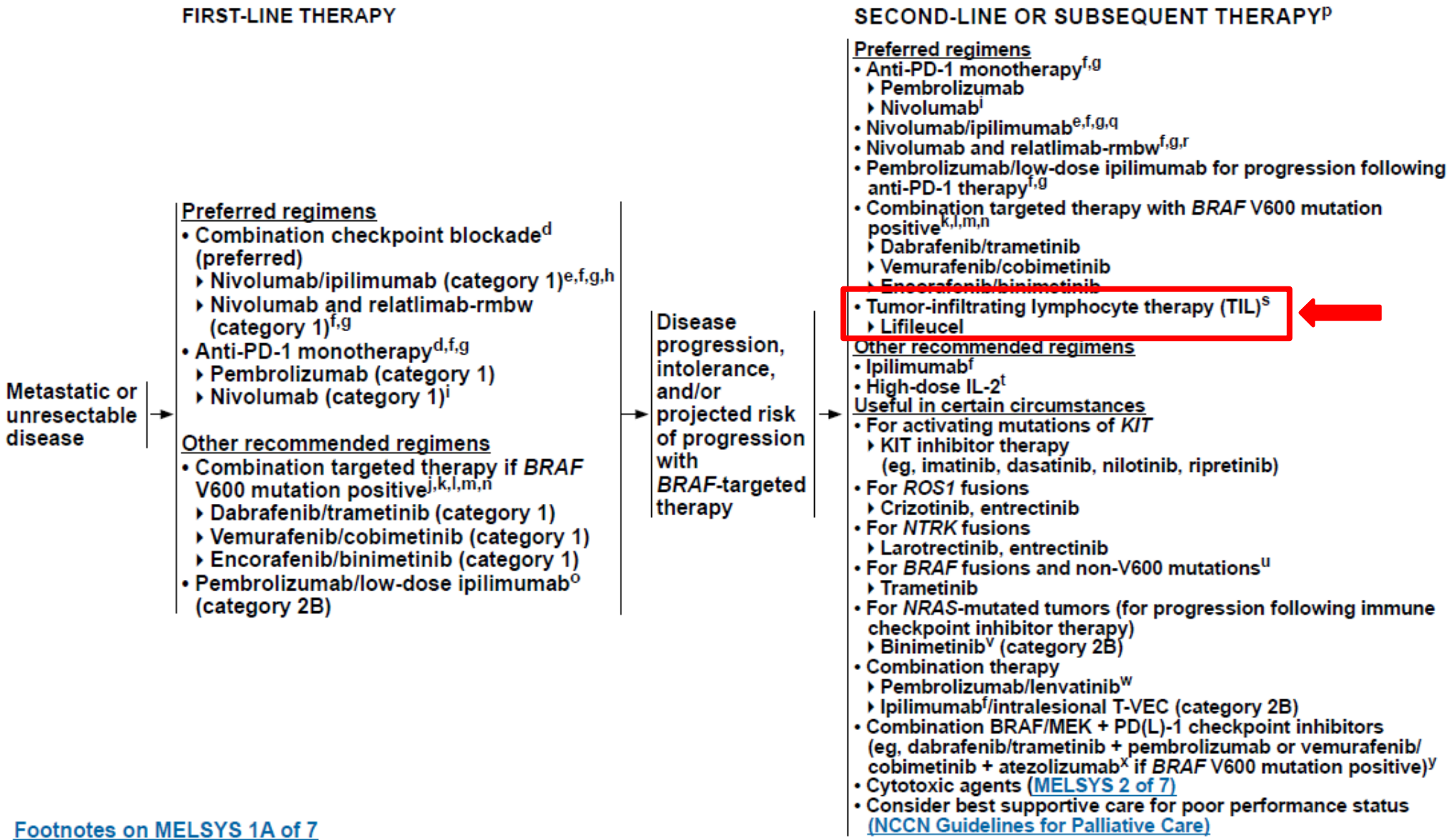
Median DoR= 36.5%

5-year OS rate= 19.5%

→ TIL therapy can lead to <u>durable</u> responses in high-risk, refractory patients!

Chesney J et al. J Immunother Cancer. 2022; Medina T el, J Clin Oncol. 2025

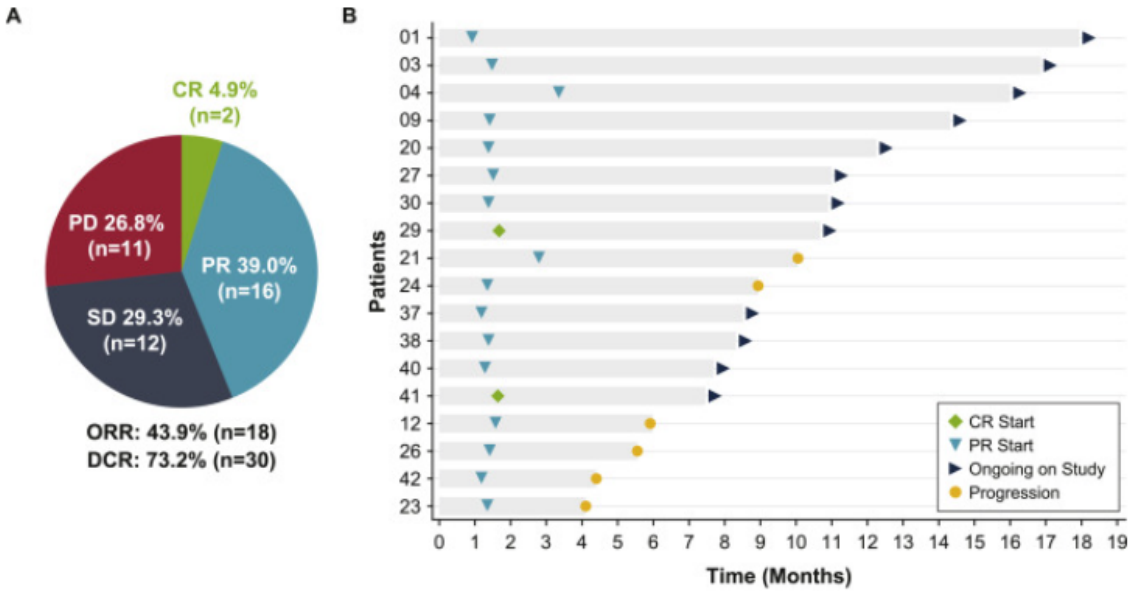
NCCN Guidelines v.2.2025



Footnotes on MELSYS 1A of 7

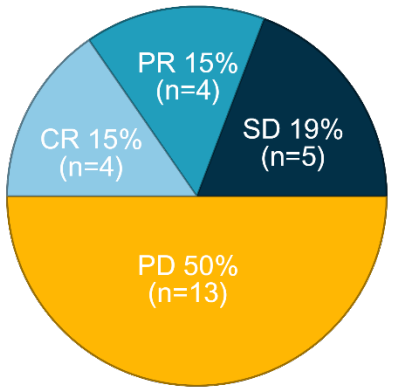
Real World TIL Therapy Outcomes

- Retrospective study of 41 advanced melanoma patients from 4 US centers receiving commercial TIL therapy. Median 5.7 mo
- Median 3 prior therapies
- High disease burden (brain 29%, liver 32%)
- ORR 44% (CR 4.9%)
- PFS 4.4 months (median follow-up 5.7 months)



Karapetyan L et al, ASTCT, 2026

- City of Hope (Duarte) Experience
- 26 patients with evaluable imaging ≥ 12 weeks post-infusion or earlier detected progression
- Mean 2 prior therapies
- Brain mets 27%, liver mets 42%
- ORR 31% **(CR 15%)**
- PFS 4.14 months (median follow-up 10.2 months)



ORR 31% (n=8)

DCR 50% (n=13)

Median DoR not reached

6/8 (75%) of responders have ongoing response

Mahuron K et al, ASCO abstract, 2026

Advantages, Challenges, and Opportunities

Advantages

- Single-time infusion!
- High-rate of response for treatment refractory, advanced melanoma
- **Potential for durability with long-term remission!**
- Responders may not need any subsequent therapies

Advantages, Challenges, and Opportunities

Challenges

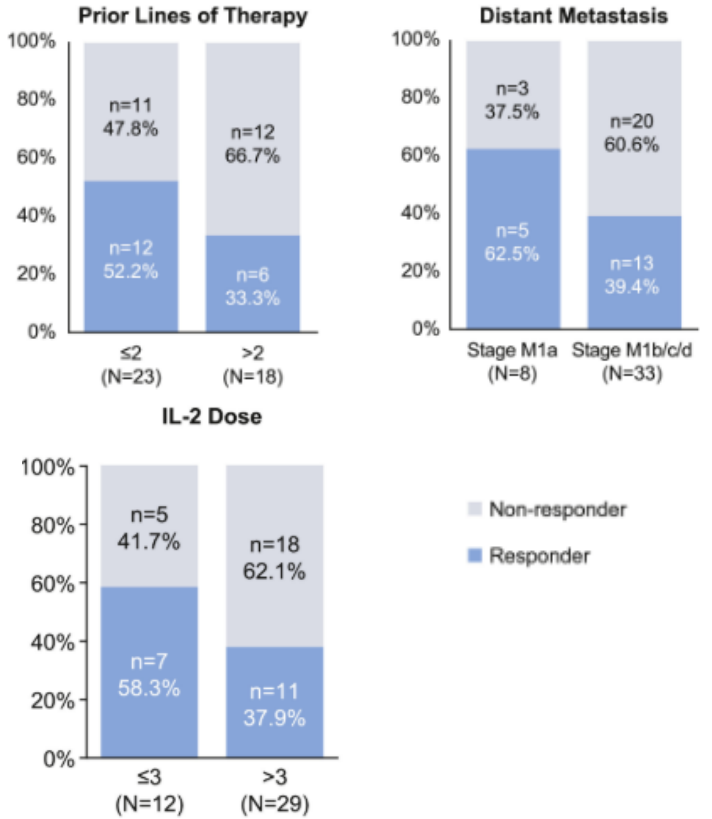
- **Toxicity**
  - TRAEs are common (cytopenias in ~100%) but mostly resolve within 2-4 weeks of infusion
  - Other TRAEs include infection, flu-like symptoms, cardiopulmonary issues, capillary leak syndrome, neurological effects, re-admission, death
  - TRAEs can persistent long-term (Haugh, 2026 ASCO proceedings)
  - May limit patients that can receive TIL therapy
- **Logistic Considerations**
  - Multi-step and multi-disciplinary workflow
  - Limited ATCs
  - Average time from referral to infusion is 3-6 months in real-world settings
  - Many referred patients (up to 50%
  - ~20% of surgeries result in out-of-specification products
  - Many referred patients (up to 50%!) will not ultimately receive therapy
    - *Disease progression*
    - Out-of-specification products (~20% of surgeries)

Haugh ASCO 2026, Desai 2026

Advantages, Challenges, and Opportunities

Opportunities

- Moving therapy *earlier* in patients' disease course for better outcomes
  - Lower tumor burden and previous lines of therapy associated with higher response!
  - Earlier referrals to TIL therapy ATCs
- Patient-tailored lymphodepletion regimens and IL-2 dosing to mitigate toxicities!
  - Consideration of reduced-dose lymphodepletion: age ≥70 years, recently treated brain metastases, renal insufficiency, bowel metastases, high-risk for bleeding
  - Two doses of IL-2 may be sufficient
- Encouraging responses for ICI-refractory melanoma subtypes mucosal and acral lentiginous melanoma



Karapetyan L et al, 2026; McClelland et al 2025; Kluger et al 2025

Future of TIL Therapy

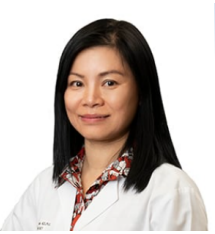
- Genetically modified TILs for improved efficacy and safety
  - Membrane-bound IL-15 (OBX-115)
  - Membrane-tethered IL-12
  - PD-1 Knockout
- Selective TIL expansion (neoantigen)
- **Expansion to other solid tumors type!**
  - NSCLC, Cervical Cancer, HNSCC, TNBC, GI (CRC, cholangiocarcinoma, pancreatic)

Thank you – truly a multidisciplinary effort!

- **Medical Oncology**

- **Surgeons**
  - Surgical Oncology
  - Thoracic
  - OHNS

- **Immune Effector Cell (IEC) Team**
  - Hematologists/Cellular Therapists
  - APPS
  - Nurse Coordinators
  - Pharmacists



- **Pathology**
  - Dermatopathology
  - Pathologists' Assistant

- **Radiation Oncology**

THANK YOU TO OUR PATIENTS

Questions?
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