Melanoma TILS

Tumor-Infiltrating Lymphocyte Therapy for Metastatic Melanoma
- Single Institutional Data
- Multicenter Clinical Trial Data

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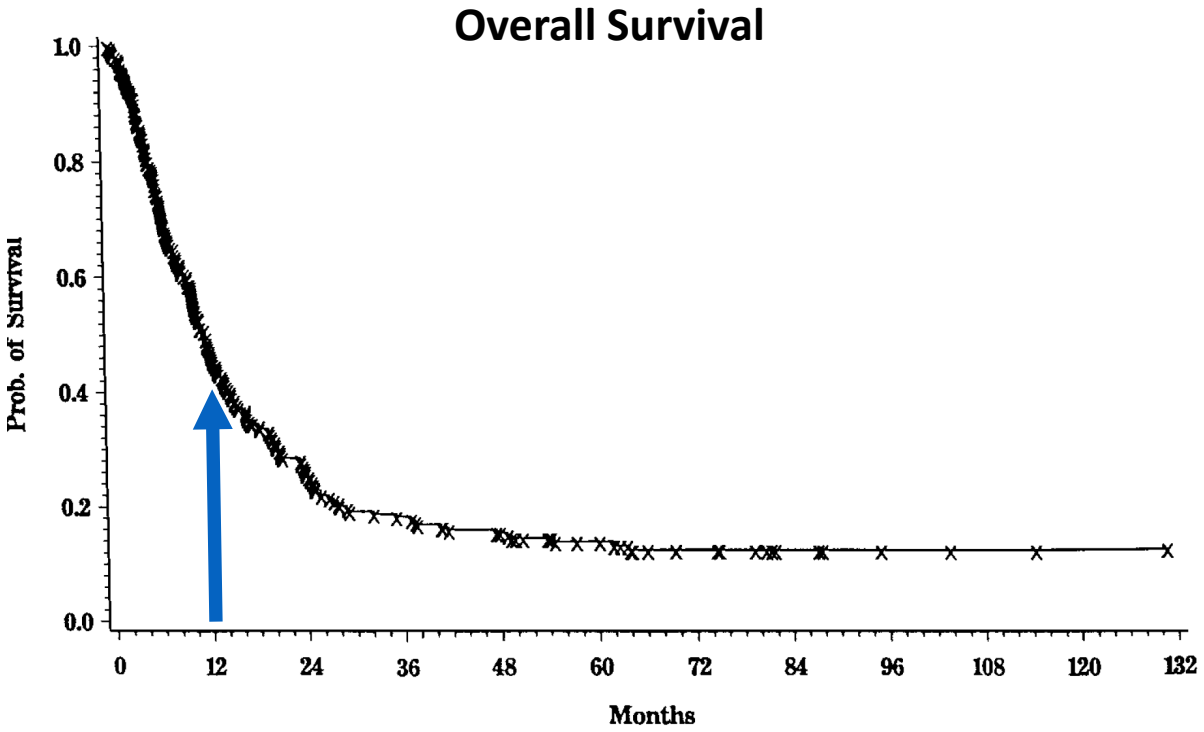
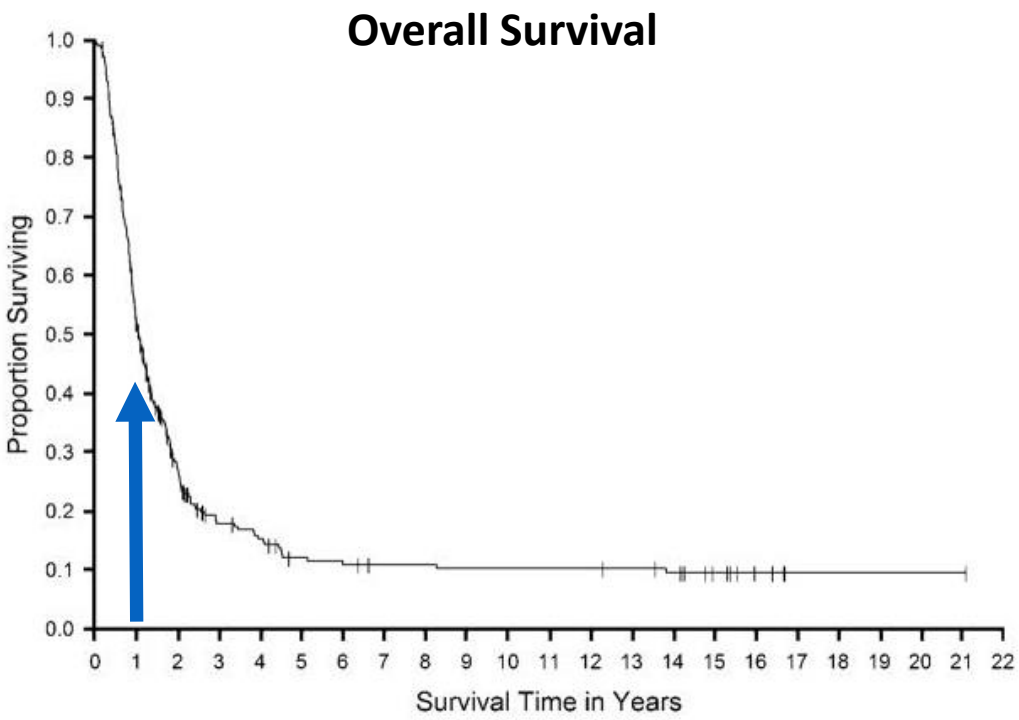
Disclosures

- **Dr. Sarnaik has received ad hoc consulting fees from Blueprint Oncology Concepts, Second City Science, Iovance Biotherapeutics, Guidepoint, and Gerson Lehrman Group.**
- **Dr. Sarnaik is a co-inventor on a patent filed with Provectus Biopharmaceuticals.**
- **Dr. Sarnaik's institution, Moffitt Cancer Center, has licensed intellectual property to Iovance Biotherapeutics of which Dr. Sarnaik is a co-inventor.**
- **Dr. Sarnaik's institution, Moffitt Cancer Center, has received research funding from Iovance Biotherapeutics and Turnstone Biologics.**
- **Dr. Sarnaik will be presenting information regarding treatments that are not FDA approved**

Interleukin-2 immunotherapy achieves durable overall survival in ~10% of patients with metastatic melanoma



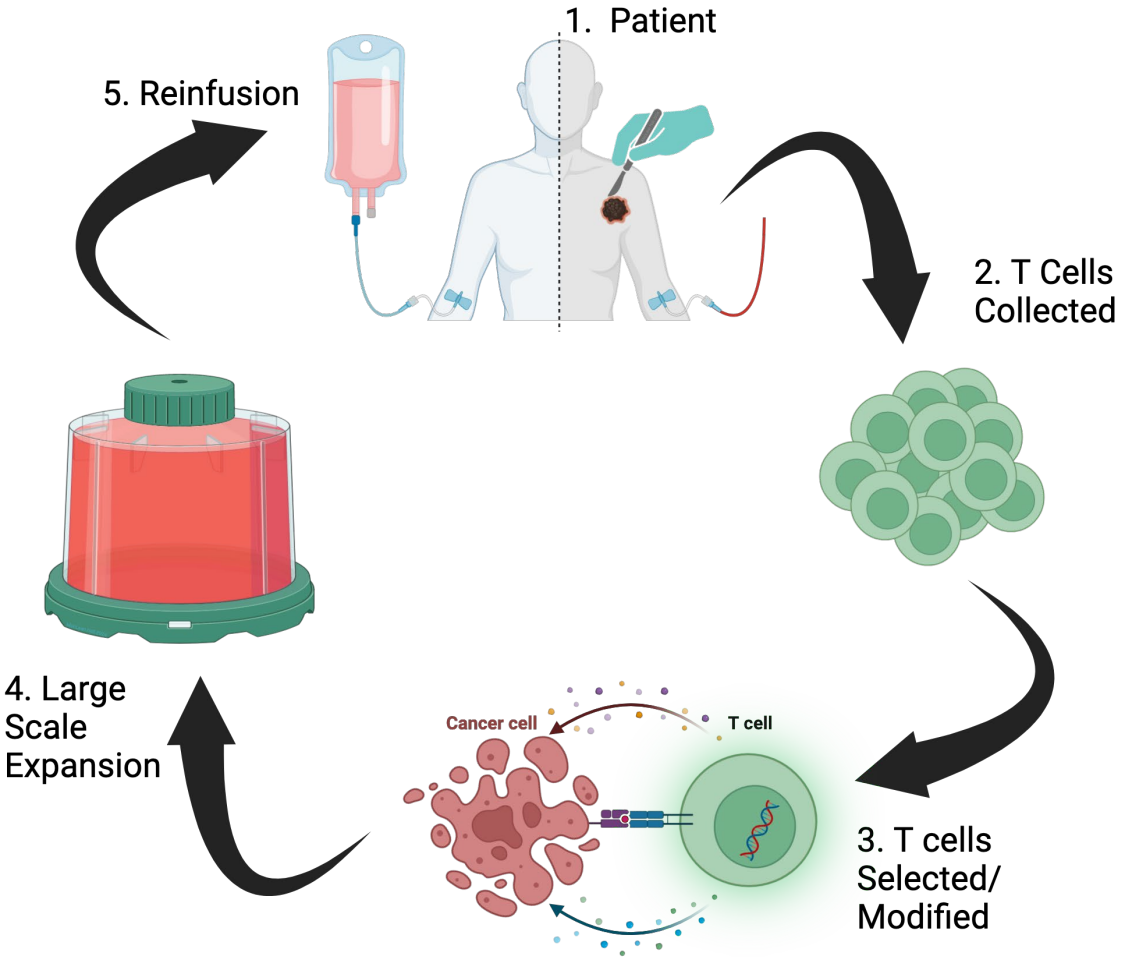
Atkins MB, et al. J Clin Oncol. 1999;17:2105-16.



Smith FO, et al. Clin Cancer Res. 2008;14:5610-8.

But cytokine-based immunotherapy like Interleukin-2 is associated with considerable toxicity and disease progression is still common

Treatment Schema for Adoptive Cell Therapy with TIL



- **Requires chemotherapy before TIL**
- **Requires Interleukin-2 (IL-2) after TIL**
- **Manufacturing can take 6 to 8+ weeks**
  - **Complex**
  - **Relatively High Side Effects**
  - **Expensive**
- **Treatment originated at the National Cancer Institute and was subsequently implemented at elite cancer centers**

TIL therapy requires lymphodepleting chemotherapy and an abbreviated course of IV bolus interleukin-2.

Sarnaik AA, Hwu P, Mulé JJ, Pilon-Thomas S. *Cancer Cell.* 2024;42:1315-8.

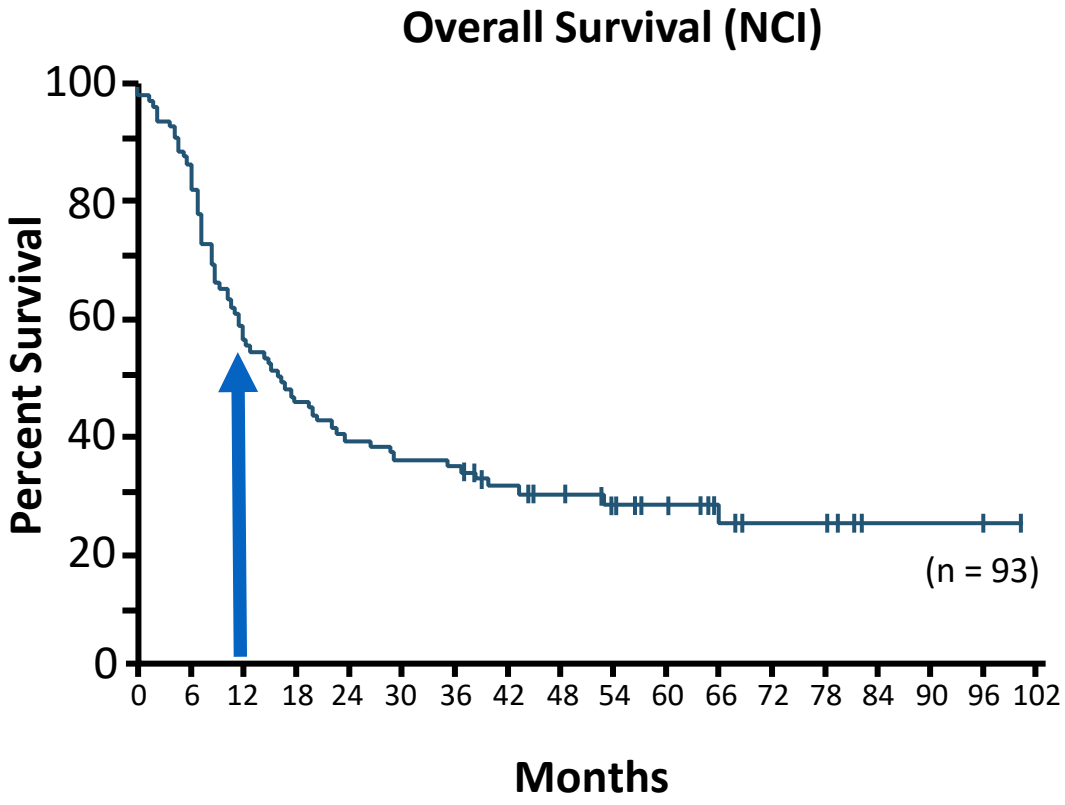
Typical Criteria for Patient Selection for TIL

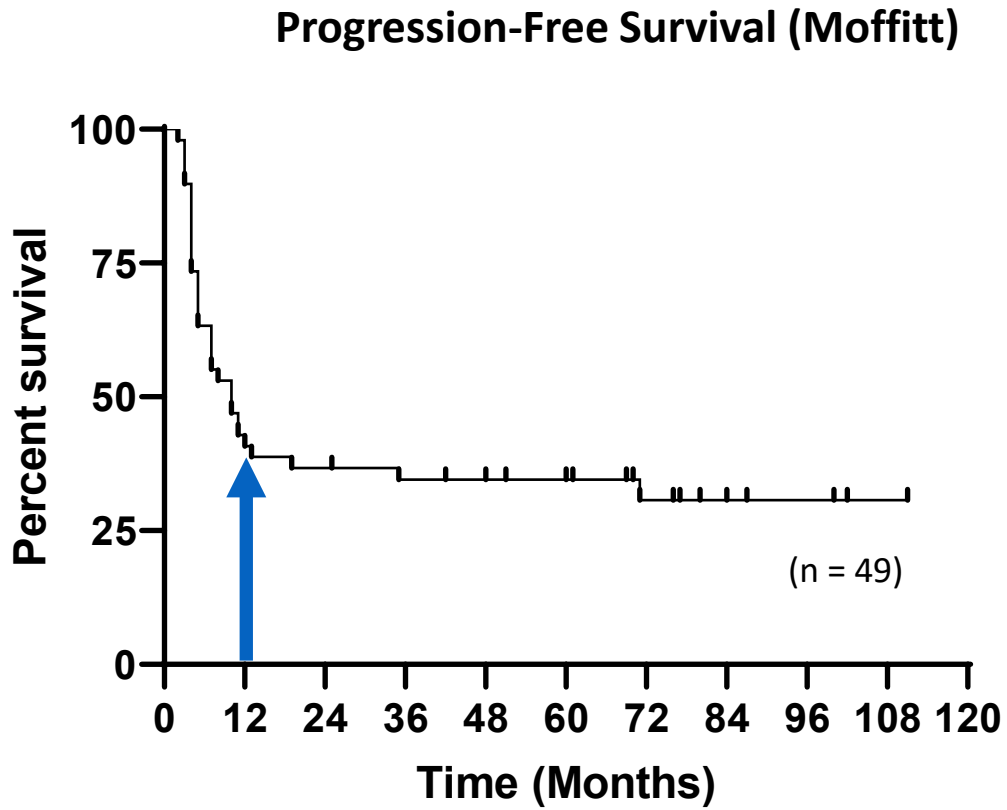
- Age <75 years*
- Acceptable performance status
  - To tolerate side effects of lymphodepletion and intravenous bolus IL-2
  - Cardiopulmonary status evaluation required cardiac (heart) stress test and pulmonary (lung) function testing
- Lack of active CNS metastasis – due to risk of bleeding from low platelets due to the chemotherapy
- Tumor amenable to surgical resection with acceptable side effects

Some patient selection parameters are important to consider for TIL therapy.

Pilon-Thomas S, et al. *J Immunother.* 2012;35:615-620.

Long-Term Outcomes of Melanoma Patients Treated With TIL at the National Cancer Institute and Moffitt



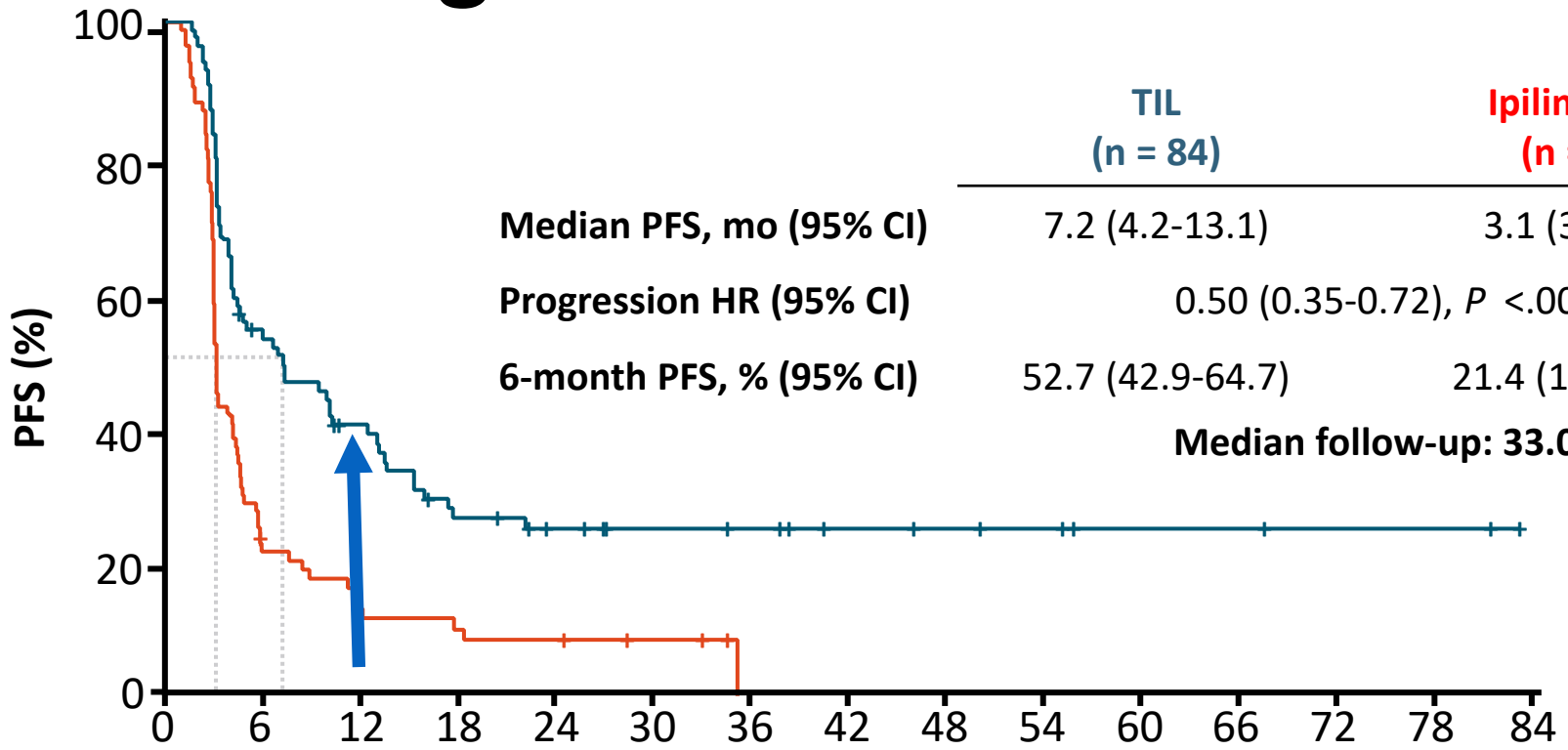


Rosenberg SA, et al. *Clin Cancer Res*. 2011;17:4550-4557.

Sarnaik AA, et al. unpublished data.

While the long-term clinical results are impressive, it was unclear where TIL fits in the era of PD-1 blockade for metastatic melanoma.

Phase II Trial Randomizing TIL vs Ipilimumab Progression-Free Survival



	TIL (n = 84)	Ipilimumab (n = 84)
Median PFS, mo (95% CI)	7.2 (4.2-13.1)	3.1 (3.0-4.3)
Progression HR (95% CI)	0.50 (0.35-0.72), *P* <.001	
6-month PFS, % (95% CI)	52.7 (42.9-64.7)	21.4 (14.2-32.2)

Median follow-up: 33.0 mo.

Patients at risk, n

TIL	84	41	29	18	14	11	10	7	6	5	3	3	2	2	0
Ipilimumab	84	17	8	6	5	3	0	0	0	0	0	0	0	0	0

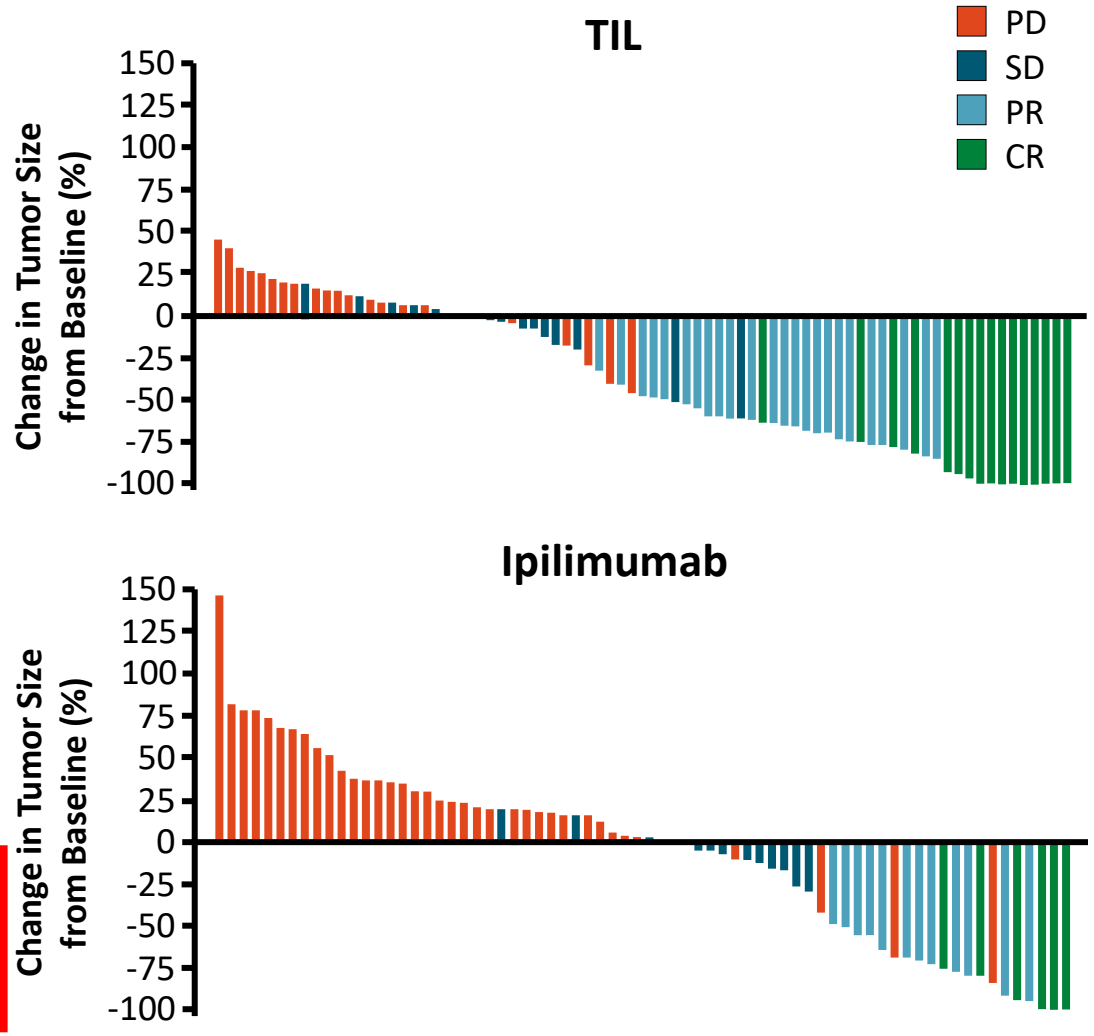
This trial demonstrated TIL has improved PFS over ipilimumab.

Rohaan et al. N Engl J Med. 2022;387:2113-25.

Phase II Trial Randomizing TIL vs Ipilimumab Best Responses

Response	TIL (n = 84)	Ipilimumab (n = 84)
Best overall response, n (%)		
▪ CR	17 (20)	6 (7)
▪ PR	24 (29)	12 (14)
▪ SD	16 (19)	15 (18)
▪ PD	24 (29)	40 (48)
▪ NE	3 (4)	11 (13)
ORR, n (%)	41 (49)	18 (21)

Patients on this trial had a median of 1 prior line of therapy (PD-1 antibody).



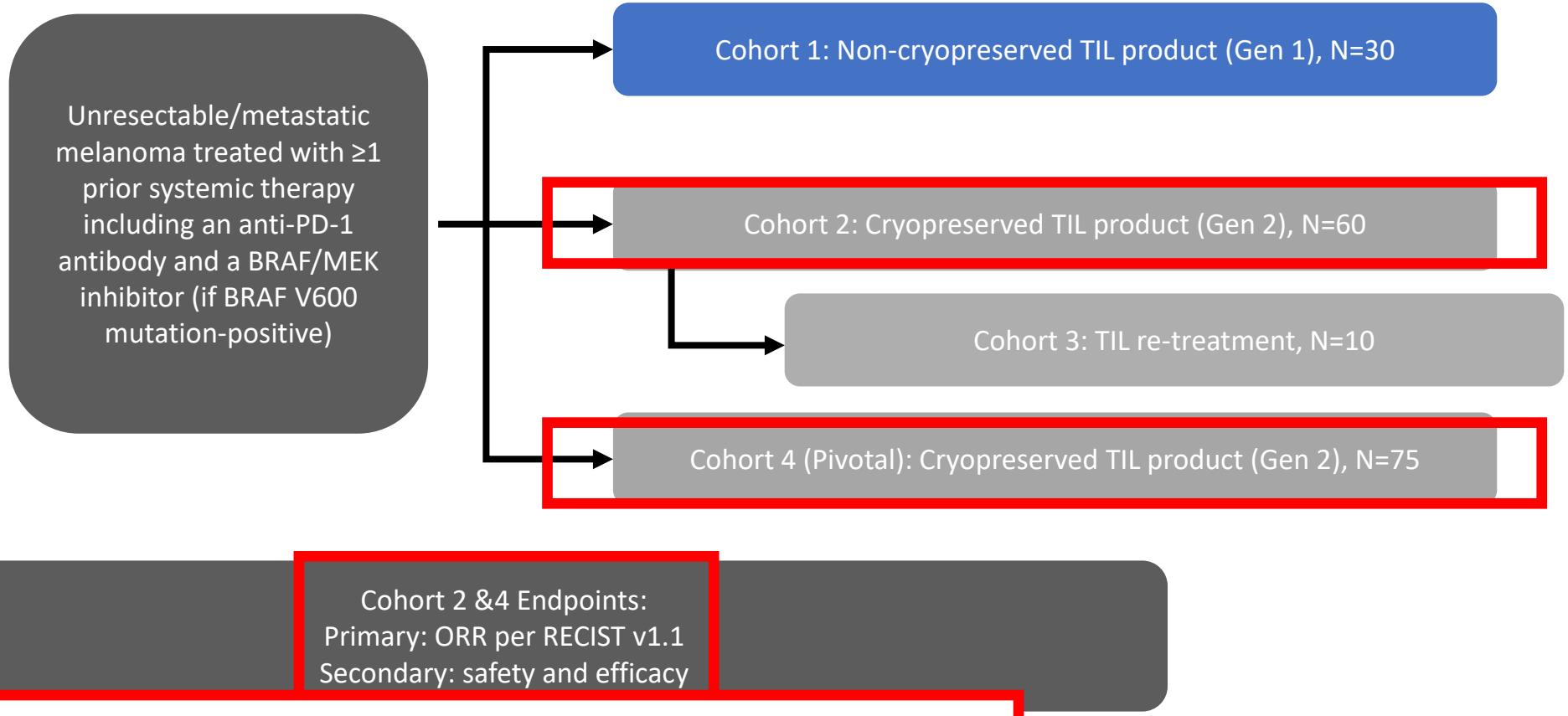
Rohaan et al. N Engl J Med. 2022;387:2113-25.

Multicenter Single-Arm Phase 2 TIL Clinical Trial

- To assess efficacy and safety of autologous TIL (lifileucel) in metastatic melanoma

Key Patient Factors:

- **Median sum of target diameters = 9.8cm**
- **≥ 3 anatomic sites 76%**
- **Liver/brain mets 47%**
- **Elevated LDH 54%**
- **Median 3 lines of prior rx**



The trial enrolled heavily pre-treated patients with relatively high disease burden.

et al., ASCO Virtual 2020. Abstract 10006.

Phase 2 TIL Trial Study Procedures

1 → 2 → 3 → 4 → 5 → 6

Screening

Surgical Resection

Surgically resected lesion is shipped to a Central GMP facility for a 22-day process that generates a cryopreserved TIL infusion product.

TIL were generated from **skin, lymph nodes, liver, lung, peritoneal, musculo-skeletal, breast, and other organs.**

NMA-LD

Patient undergoes nonmyeloablative lymphodepletion: Cyclophosphamide followed by fludarabine.

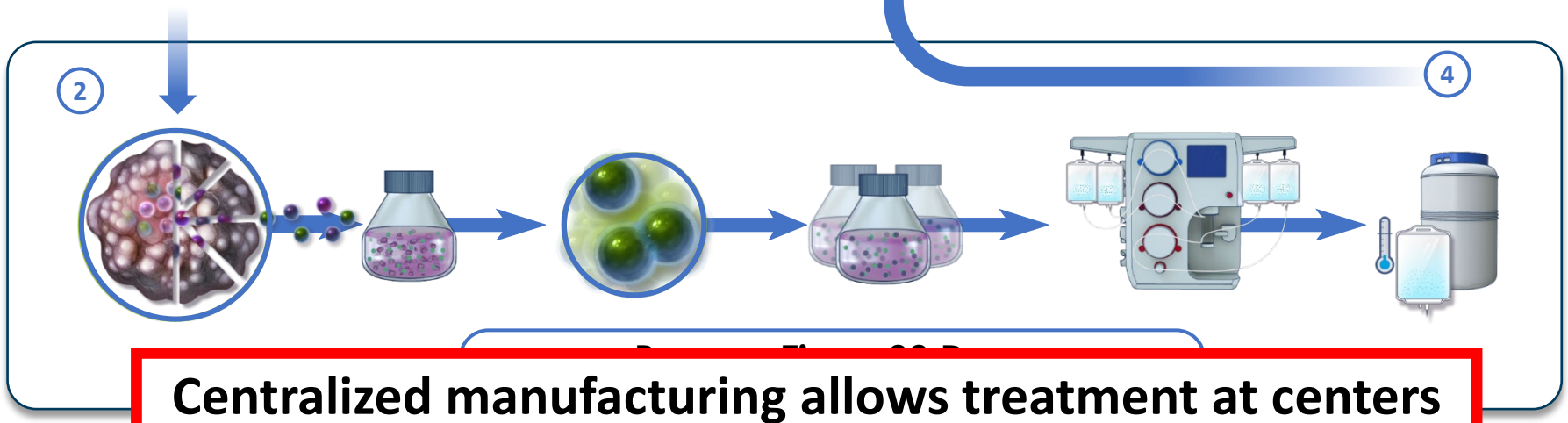
TIL Infusion

Patient receives a one time treatment of expanded and activated lifileucel TIL product infusion.

IL-2 Infusions

Following TIL, patients complete a short course of up to 6 doses of interleukin-2 (IL-2) infusions.

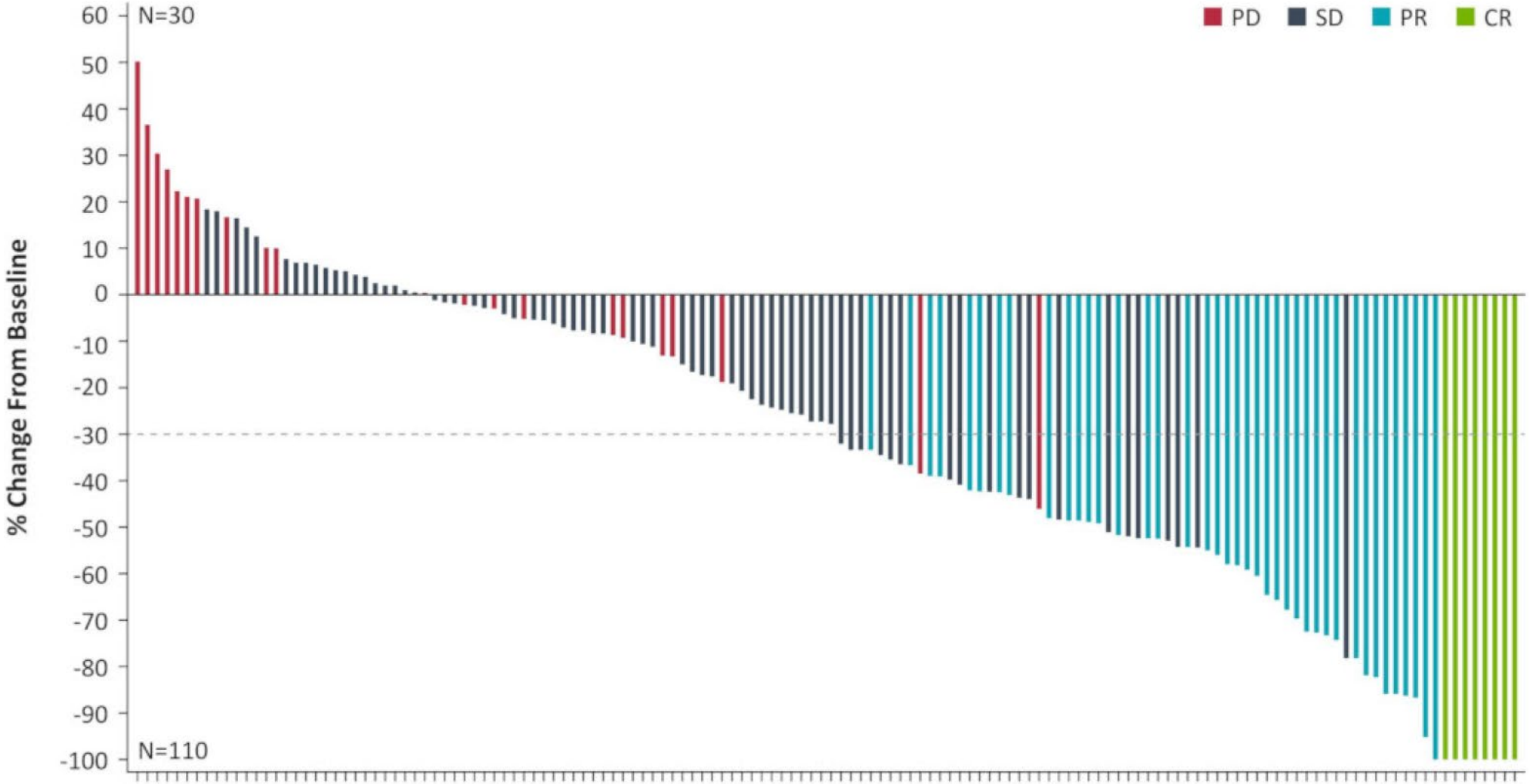
Recovery/Discharge



Centralized manufacturing allows treatment at centers without an onsite manufacturing facility.

SCO Virtual 2020. Abstract 10006.

Best Overall Response Multicenter Trial with Centralized Manufacturing in PD-1 Treatment Refractory Metastatic Melanoma



79% of evaluable patients had tumor burden reduction.

A, et al., *J Clin Oncol*. 2021;39:2656-66.
***mmunother Cancer.* 2022;10:e005755.**

Efficacy in PD-1 Treatment-Refractory Metastatic Melanoma (i.e. lack of benefit to nivolumab or pembrolizumab)

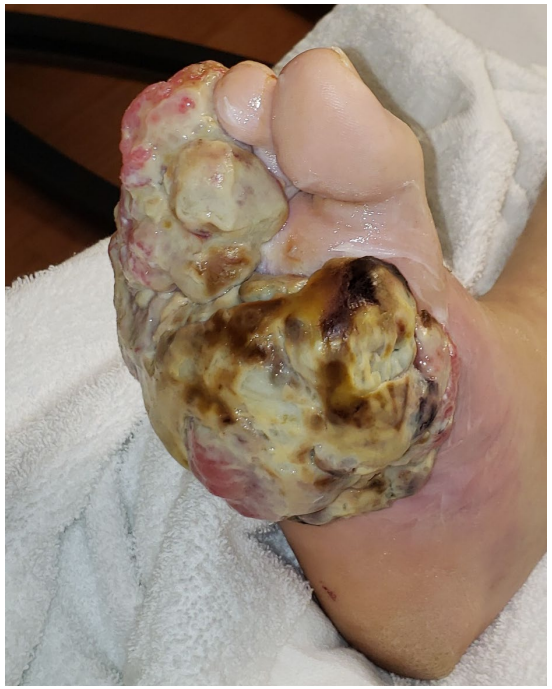
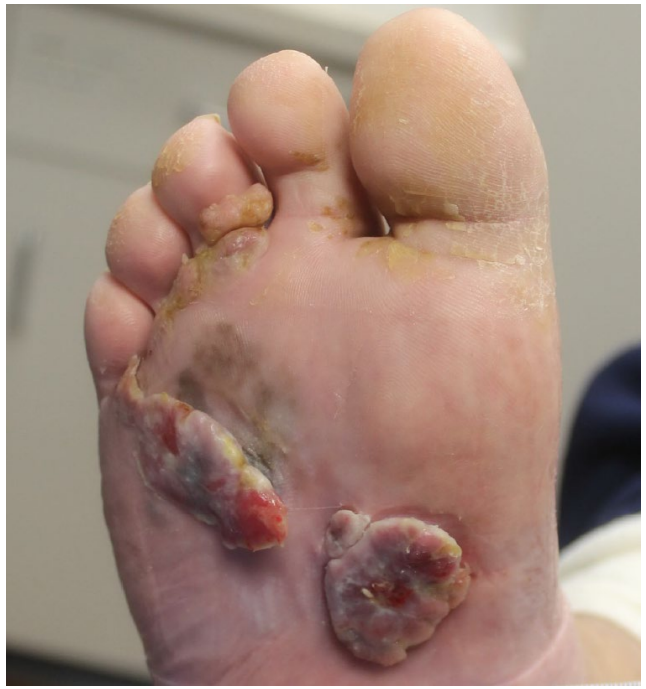
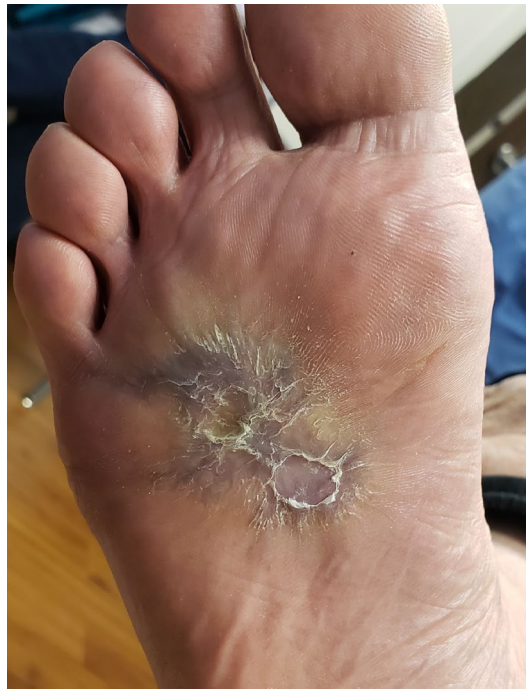
Response (RECIST V.1.1)	(N=153)
ORR, n (%)	48 (31.4)
(95% CI)	(24.1 to 39.4)
Best overall response, n (%)	
CR	8 (5.2)
PR	40 (26.1)
SD	71 (46.4)
Non-CR/non-PD	1 (0.7)
PD	27 (17.6)
Non-evaluable	6 (3.9)
Median DOR, months (range)	NR (1.4+ to 45.0+)
Median study follow-up, months	27.6

Objective response in 153 treated patients was 31.4%.

- **189 patients were enrolled; 25 did not receive TIL (18 for progression/choice)**
- **1 product out of specification**
- **Responses were durable – median duration of response not reached with over two years of median followup**
- **Manufacturing success rate was 95.8%**
- **Response was seen regardless of age, location of tumor resected, BRAF mutational or PD-L1 tumor status.**

Sarnaik AA, et al., *J Clin Oncol*. 2021;39:2656-66.
sney J, et al. *J Immunother Cancer.* 2022;10:e005755.

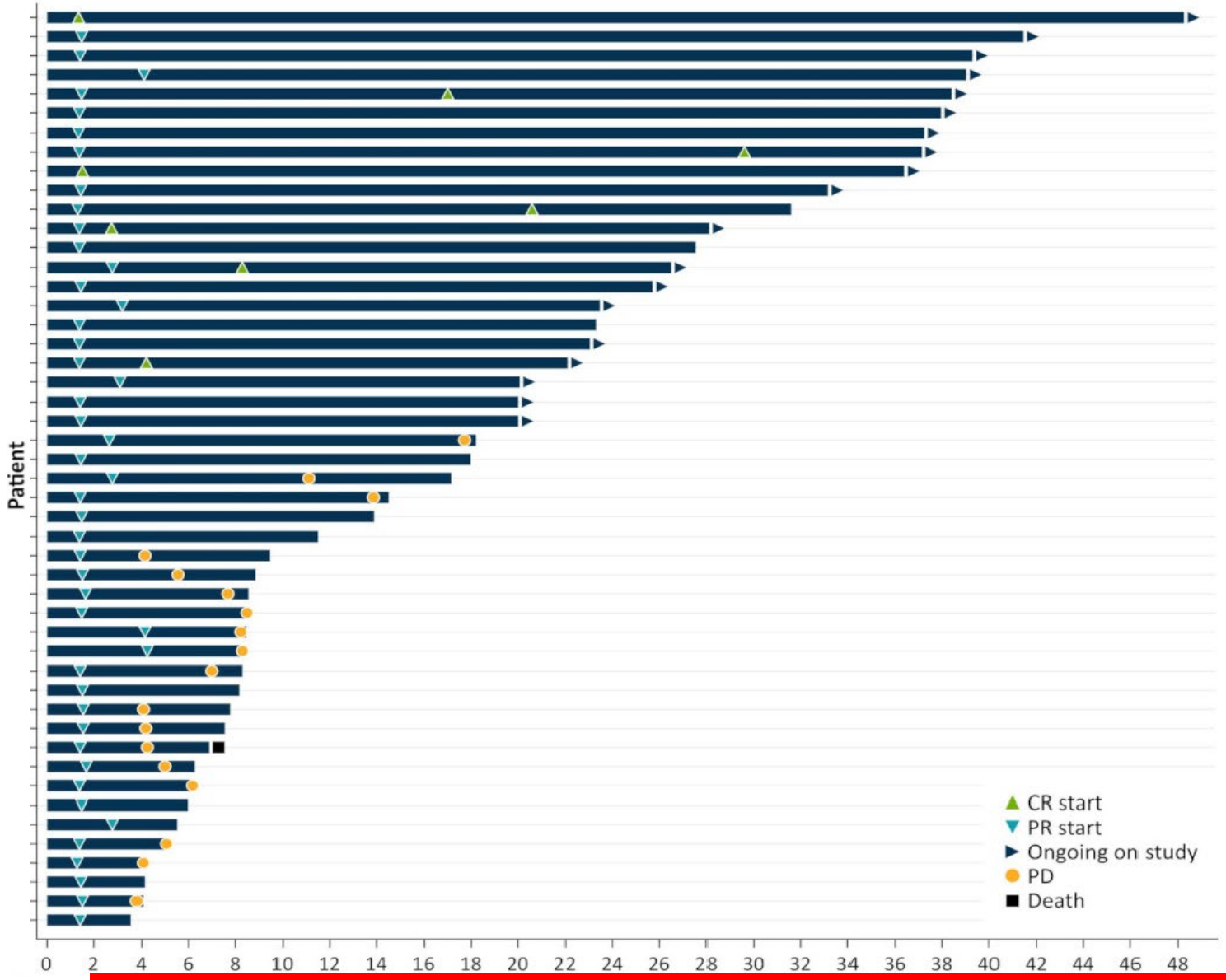
Clinical Response of Bulky Tumor to TIL Therapy – Amputation Averted

PRE	POST	POST 2
		
Baseline	**3 Months Post**	**3 years Post**

TIL harvested from one site can mediate regression of bulky tumors at another site.

Adapted from Dossett L, et al. Mullholland and Greenfield's Surgery: Scientific Principles & Practices, 7th ed.

Time and Duration of Response for Evaluable Patients (PR or Better)

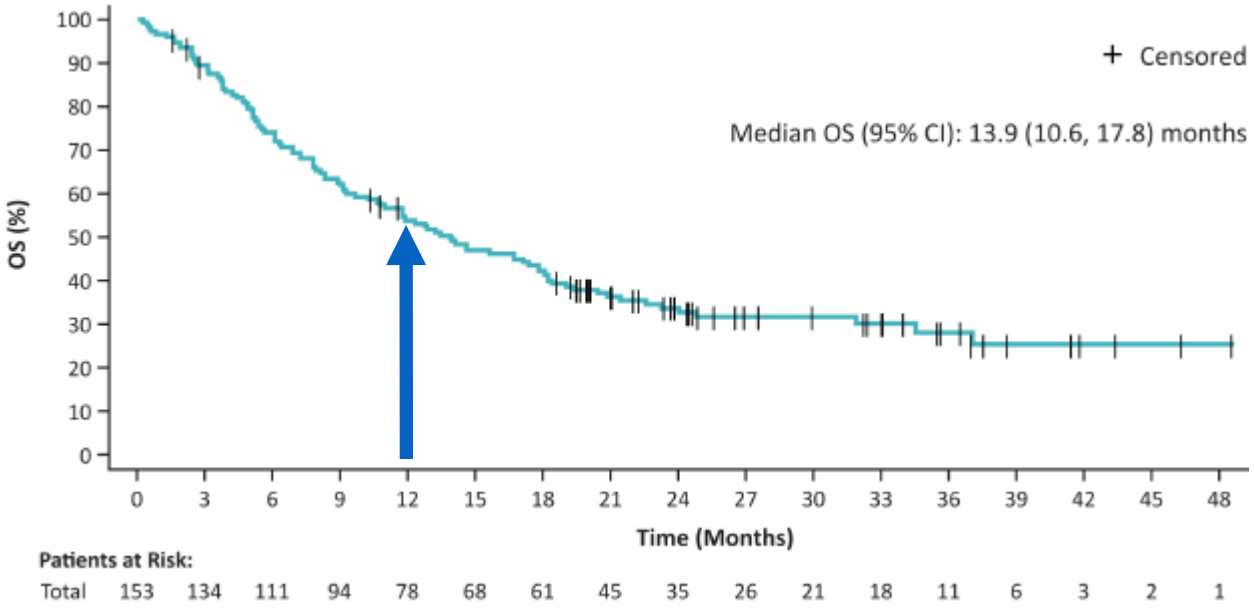


Median time to response was 1.5 months; ECOG performance status, elevated LDH, and sum of target lesion diameters all independently correlated with response (p=0.008).

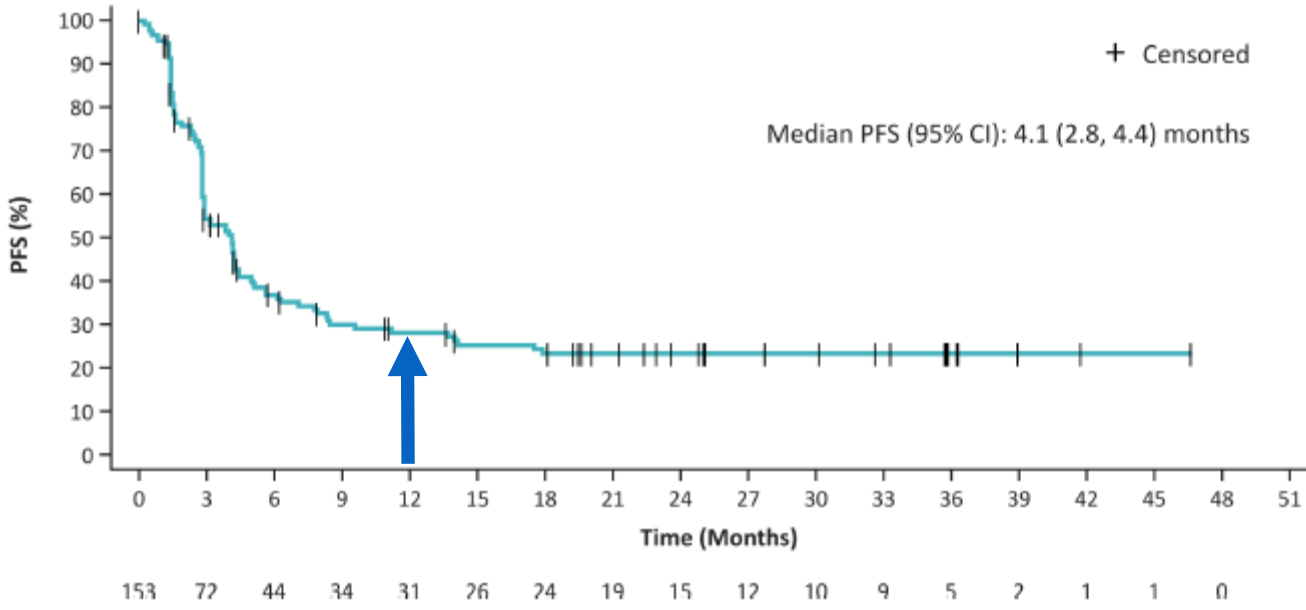
1;39:2656-66.
2;10:e005755.

Survival After TIL for PD-1 Treatment-Refractory Metastatic Melanoma

Overall Survival



Progression-Free Survival



Disease primarily refractory to prior PD-1 antibody had similar outcomes after TIL compared to disease that previously responded to PD-1 antibody.

Sarnaik AA, et al., *J Clin Oncol*. 2021;39:2656-66.
Chesney J, et al. *J Immunother Cancer.* 2022;10:e005755.

Common Toxicities of TIL Therapy

- **Short-term toxicities (related to Chemotherapy, TIL and/or IL-2)**
  - Fever/systemic inflammatory response/capillary leak syndrome
  - Rigors
  - Cardiopulmonary insufficiency (heart failure, lung failure)
  - Renal failure, other organ failure
- **Fortunately, these acute side effects are temporary and generally reversible**

- **Long-term Toxicities (related to chemotherapy or on target/off tumor effect)**
  - Fatigue †
  - Neuropathy (nerve swelling/pain) †
  - bone marrow failure†
  - Hearing loss/disequilibrium ǂ
  - Vitiligo (loss of skin pigmentation) ǂ
  - Uveitis (eye swelling) ǂ

† Chemotherapy-related

ǂ TIL-related

There are very few new treatment-related adverse events after 3 months.
Deaths due to treatment - cytopenias/bone marrow failure

Sarnaik AA, et al., *J Clin Oncol*. 2021;39:2656-66.
Chesney J, et al. *J Immunother Cancer.* 2022;10:e005755.

Modification of TIL / TIL selection – Clinical Trials are Underway

Efficacy of TIL therapy can theoretically be enhanced by:

- **Selection of neoantigen-specific TIL - NCT05628883**
- **Genetic modifications of TIL by gene targeting PD-1 in TIL - NCT05361174**
- **Genetic modifications of TIL by inserting an inducible, membrane-bound IL-15 gene that eliminates the need for IL-2 - NCT06060613**

https://www.clinicaltrials.gov

Conclusions

- **TIL therapy is feasible and effective in salvaging patients after disease progression on multiple prior line(s) of immune checkpoint blockade for metastatic melanoma and is FDA-approved.**

- **Toxicity is relatively high but for the most part is temporary and with very few new adverse events 3 months after treatment.**

- **Means to boosting patient responses may include genetic modifications and/or selection of TIL or improvement in patient selection.**

Thank You for Your Attention!

Acknowledgements

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***** Patients and patient family members**