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TIL for PD-1 Refractory Melanoma

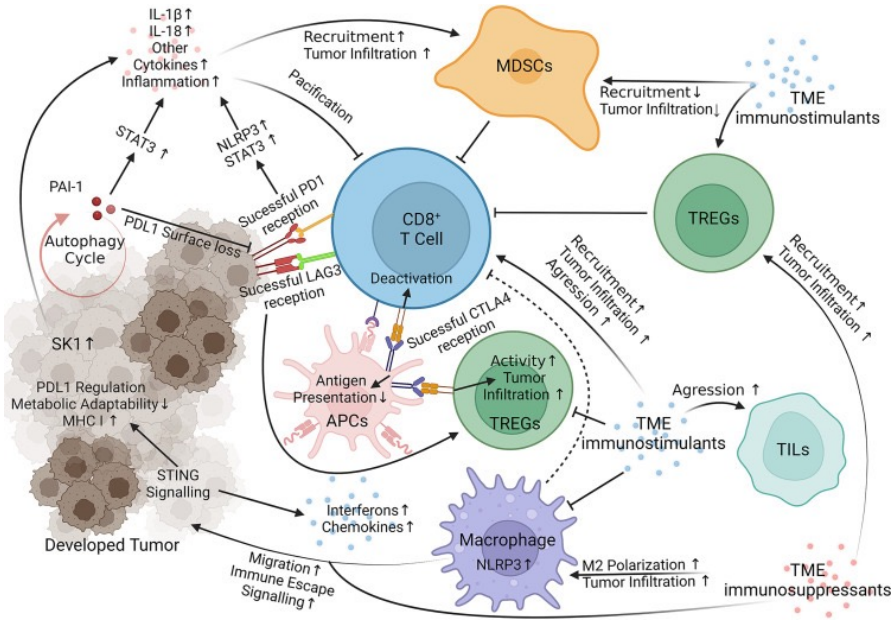
Melinda L. Yushak, MD MPH
Winship Cancer Institute

TIL for PD-1 Refractory Melanoma

- Background
- TIL procedure
- Efficacy
- Practical considerations

Overall survival in melanoma

- 49% overall survival at 6.5 years with ipilimumab and nivolumab
- 34% overall survival at 5 years with dabrafenib and trametinib
- Despite improvements in overall survival many patients develop refractory disease



Front Oncol. 2022; 12: 880876.

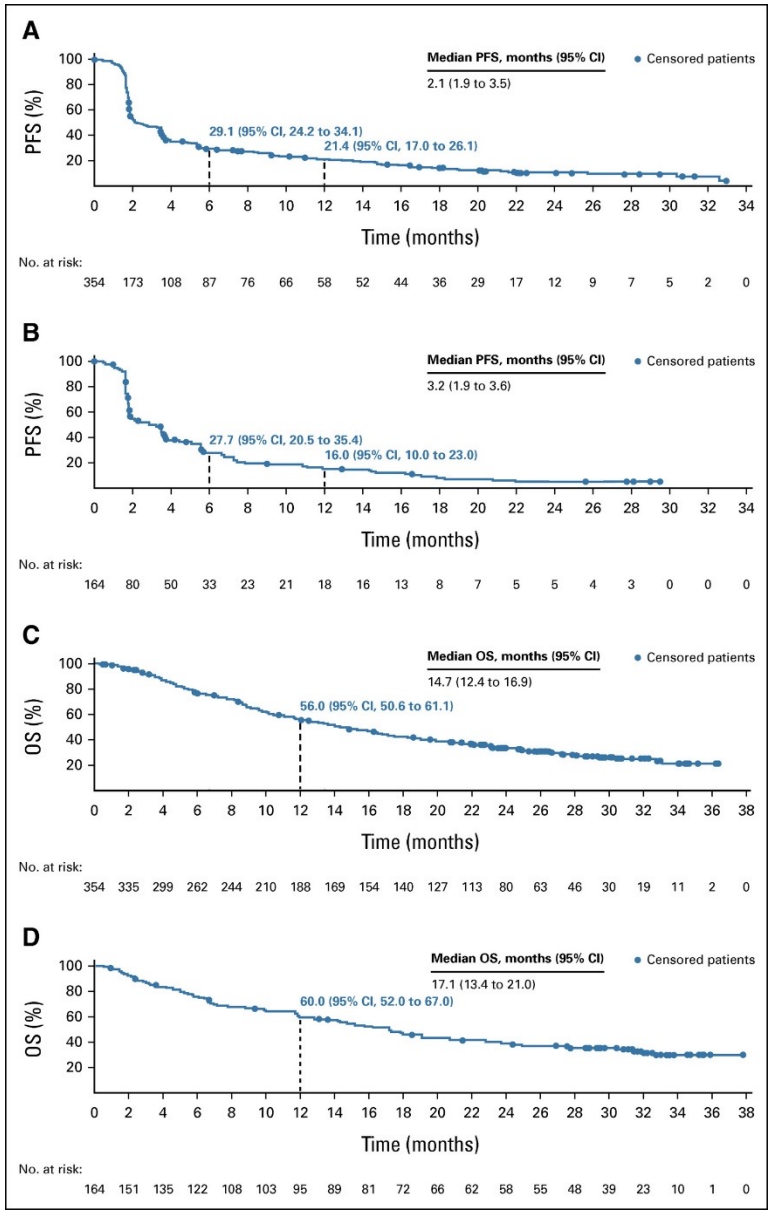
Clinical Scenario

47 year old male with metastatic melanoma has multiple lung lesions. He was initially treated with ipilimumab and nivolumab. He now has progression. He is BRAF WT. ECOG PS is 0. What would you treat him with?

1. nivolumab and relatlimab
2. clinical trial
3. TIL
4. carboplatin and paclitaxel

Options after progression

- RELATIVITY-0200
  Nivolumab and relatlimab
- Patients had progressed on PD-1 or PD-1/CTLA-4
- Objective response rate 12%
- PFS at 6 months was 20 percent



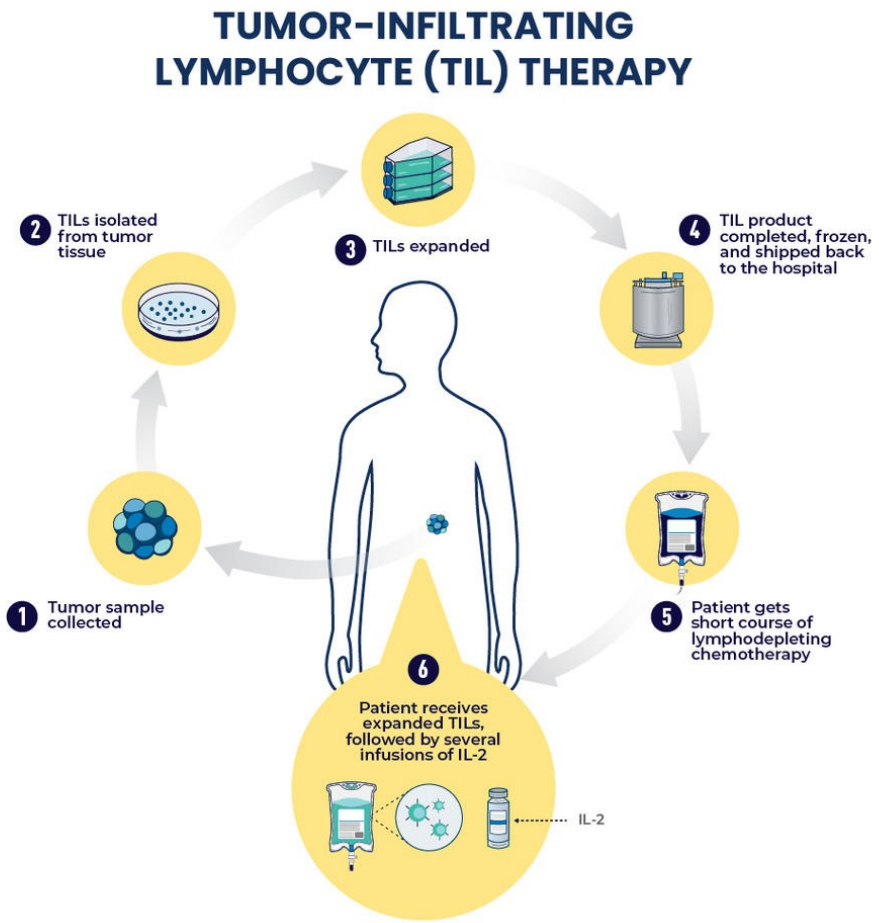
J Clin Oncol. 2023 May 20;41(15):2724-2735.

Clinical need

- Patients who are BRAF WT and progressed after ipilimumab and nivolumab

- Patients who are BRAF mutated and progressed after ipilimumab and nivolumab and BRAF/MEK inhibitors

Tumor Infiltrating Lymphocyte (TIL) therapy



https://www.cancer.gov/news-events/cancer-currents-blog/2024/fda-amtagvi-til-therapy-melanoma

Lifileucel

- Commercial autologous TIL product
- FDA approved in February 2024
- Phase III trial of 168 patients randomly assigned to receive TIL versus ipilimumab

Lifileucel- Phase III eligibility

- Stage IIIC unresectable or stage IV metastatic melanoma
- Progression on at least one prior line of therapy (excluding ipilimumab)
  - 24% adjuvant anti PD-1
  - 62% first line anti PD-1
- 1 or more resectable lesions collectively 2 to 3 cm in size
- Serum LDH ≤ 2 times the upper limit of normal

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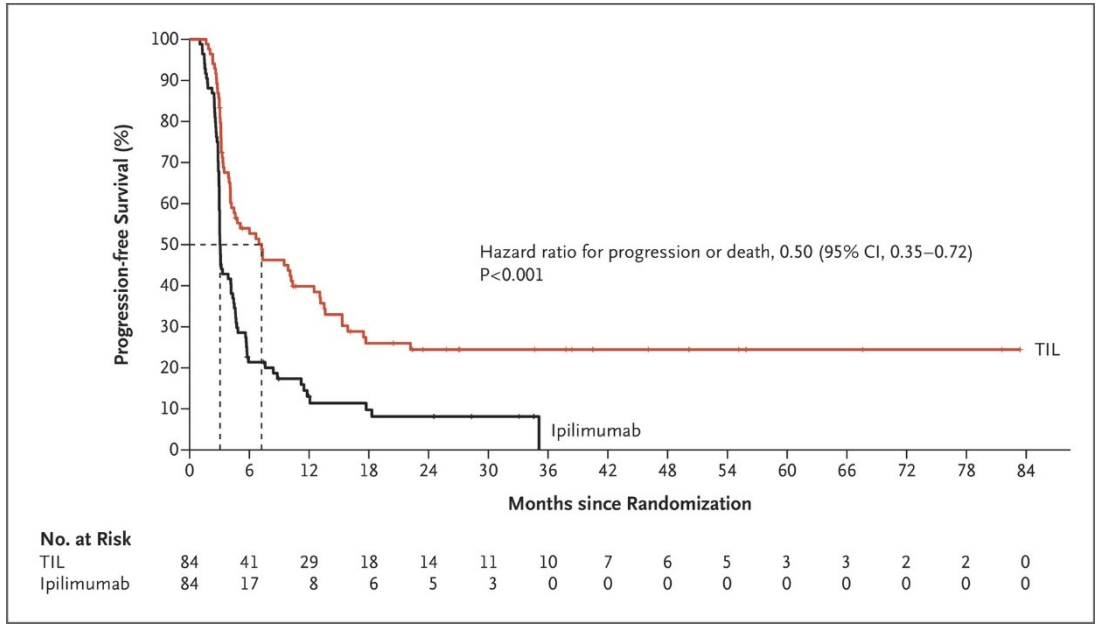
Lifileucel

- Nonmyeloablative lymphodepleting regimen with cyclophosphamide (60 mg/kg) for 2 days then fludarabine (25 mg/m^2) for 5 days
- One dose of lifileucel (5 x 10^9- 2 x 10^{11} TILs)
- IL-2 (600,000 IU/kg) every 8 hours for up to 15 doses

Tumor Infiltrating Lymphocyte Therapy (TIL)

- PFS 7.2 vs. 3.1 months
- OS 25.8 vs. 18.9 months
  - (HR for death 0.83; 95% CI 0.54-1.27)



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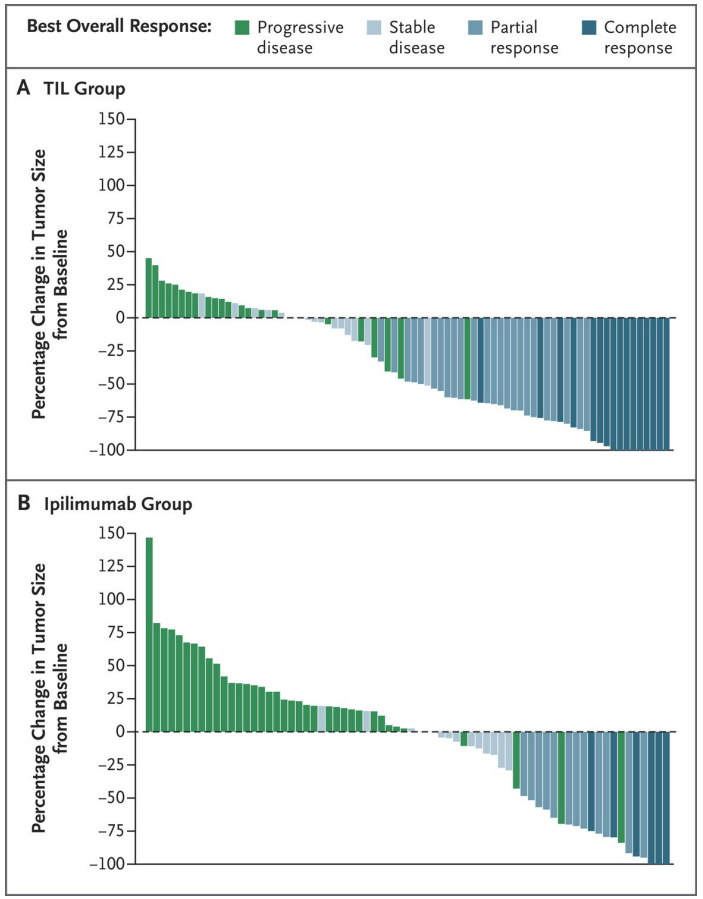
Outcomes

- ORR 49 vs. 21 percent
  - CR 20 vs. 7 percent
  - PR 29 vs. 14 percent



Adverse Events

- Grade ≥ 3 adverse events occurred in 100 versus 57 percent
  - All patients receiving TIL had grade ≥ 3 neutropenia
  - Median duration of 7 days
- 30% patients had capillary leak after TIL
- 10% of patients required ICU care after TIL
- 1 patient receiving TIL died, but death was felt to not be related

Table 3. Most Common Treatment-Related Adverse Events.*

Adverse Event	TIL Group (N = 80)				Ipilimumab Group (N = 82)	
	Chemotherapy		TILs and Interleukin-2		Ipilimumab	
	Any Grade	≥Grade 3	Any Grade	≥Grade 3	Any Grade	≥Grade 3
	number of patients (percent)					
Neutrophil count decreased	80 (100)	80 (100)	—	—	—	—
Platelet count decreased	73 (91)	71 (89)	—	—	—	—
Anemia	73 (91)	16 (20)	—	—	—	—
Nausea	69 (86)	2 (2)	41 (51)	0	30 (37)	2 (2)
Febrile neutropenia	69 (86)	69 (86)	59 (74)	59 (74)	—	—
White-cell count decreased	57 (71)	57 (71)	—	—	—	—
Fatigue	49 (61)	4 (5)	54 (68)	7 (9)	37 (45)	1 (1)
Hypophosphatemia	49 (61)	20 (25)	57 (71)	48 (60)	—	—
Alopecia†	37 (46)	0	—	—	—	—
Diarrhea	36 (45)	2 (2)	36 (45)	2 (2)	37 (45)	12 (15)
Hypocalcemia	36 (45)	1 (1)	29 (36)	0	—	—
Hypoalbuminemia	27 (34)	0	31 (39)	0	—	—
Vomiting	26 (32)	2 (2)	15 (19)	0	11 (13)	1 (1)
Headache	20 (25)	0	19 (24)	0	22 (27)	1 (1)
Hypokalemia	20 (25)	2 (2)	12 (15)	0	—	—
Elevated AST level	18 (22)	4 (5)	26 (32)	8 (10)	18 (22)	7 (9)
Rash	18 (22)	2 (2)	37 (46)	9 (11)	28 (34)	4 (5)
Weight gain	17 (21)	0	28 (35)	0	—	—
Elevated ALT level	14 (18)	7 (9)	25 (31)	8 (10)	22 (27)	8 (10)
Elevated alkaline phosphatase level	14 (18)	3 (4)	17 (21)	3 (4)	12 (15)	4 (5)
Anorexia	13 (16)	1 (1)	—	—	14 (17)	1 (1)
Dizziness	12 (15)	0	—	—	—	—
Increased γ-glutamyltransferase level	11 (14)	6 (8)	12 (15)	6 (8)	—	—
Fever	11 (14)	1 (1)	74 (92)	36 (45)	11 (13)	2 (2)
Dysgeusia	11 (14)	0	—	—	—	—
Hypomagnesemia	11 (14)	0	—	—	—	—
Dyspnea	10 (12)	2 (2)	63 (79)	15 (19)	—	—
Constipation	9 (11)	0	—	—	—	—
Edema limbs	8 (10)	0	23 (29)	0	—	—
Chills	—	—	67 (84)	6 (8)	—	—
Pruritus	—	—	—	—	34 (41)	0
Sinus tachycardia	—	—	40 (50)	1 (1)	—	—
Colitis	—	—	—	—	20 (24)	16 (20)
Abdominal pain	—	—	—	—	19 (23)	1 (1)
Hypotension	—	—	33 (41)	6 (8)	—	—
Malaise	—	—	—	—	13 (16)	0
Creatine kinase level increased	—	—	29 (36)	9 (11)	—	—
Dry mouth	—	—	—	—	9 (11)	0
Pulmonary edema	—	—	26 (32)	1 (1)	—	—
Capillary leak syndrome	—	—	24 (30)	1 (1)	—	—
Hypoxia	—	—	19 (24)	5 (6)	—	—
Hypertension	—	—	15 (19)	11 (14)	—	—
Myalgia	—	—	12 (15)	1 (1)	—	—
Blurred vision	—	—	9 (11)	0	—	—
Skin hypopigmentation	—	—	9 (11)	0	—	—

* Included are the most common treatment-related adverse events of any grade and those of grade 3 or higher, as defined according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03, that occurred in at least 10% of the patients who received chemotherapy and TILs or at least one dose of ipilimumab (the safety analysis population). Dashes indicate that the adverse events did not occur in at least 10% of the patients. All the patients had more than one adverse event. ALT denotes alanine aminotransferase, and AST aspartate aminotransferase.

† Transient alopecia totalis occurred in all patients in the TIL group after chemotherapy. However, this event was not systematically reported in medical records and thus cannot be reported.

Quality of life

Table 4. Health-Related Quality-of-Life Scores at 6 Months.

Variable	Mean Score		Difference (95% CI)*
	TIL Group	Ipilimumab Group	
Scores on the EORTC QLQ-C15 PAL quality-of-life and functioning scales†			
Global quality of life	77.4	69.6	7.7 (5.1 to 10.4)
Physical functioning	82.0	79.1	2.9 (1.4 to 4.5)
Emotional functioning	85.4	75.7	9.7 (7.5 to 11.9)
Scores on the EORTC QLQ-C15 PAL symptom scales‡			
Fatigue	25.9	33.8	−7.9 (−11.2 to −4.6)
Nausea and vomiting	7.5	5.9	1.6 (0.7 to 2.5)
Pain	14.3	20.7	−6.4 (−9.3 to −3.5)
Dyspnea	10.0	12.4	−2.4 (−5.0 to 0.1)
Insomnia	23.6	28.1	−4.5 (−7.2 to −1.9)
Appetite loss	12.4	13.5	−1.1 (−2.9 to 0.7)
Constipation	6.7	7.1	−0.4 (−1.3 to 0.5)

* The widths of the confidence intervals have not been adjusted for multiplicity and cannot be used in place of a hypothesis test.
† Scores on the European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire Core 15 palliative care (EORTC QLQ-C15 PAL) global quality-of-life and functioning scales range from 0 to 100, with higher scores indicating better functioning.
‡ Scores on the EORTC QLQ-C15 PAL symptom scales range from 0 to 100, with higher scores indicating higher levels of symptom burden.

Longer term data with TIL

- In heavily pretreated patients OS at 4 years was 47 percent in responders
- Median DOR was not reached

Annals of Oncology (2023) 20 (suppl_1): 100589-100589. 10.1016/iotech/iotech100589

Practical considerations with TIL

- Many patients who have been pretreated may not have a good PS
  - ECOG performance status of 0 or 1
  - No major cardiac or pulmonary issues
- Must have sufficient tumor volume that can be resected

Practical considerations with TIL

- Time to make the product
- What is the best bridging therapy?
- Cost and insurance authorization
- Must live or stay within clinic area for 30 days after treatment

Conclusion

- TIL should be considered in patients that are PD-1 and BRAF (if mutated) inhibitor refractory who have an excellent performance status

- Patient selection is important in helping patients receive timely treatment