T cell immunotherapies for metastatic solid cancer

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Disclosures

- Research grants:
  - Iovance Biotherapeutics, Turnstone Biologics, Alethia Bio, BMS
- Scientific advisory:
  - Turnstone Biologics
- PI of clinical studies sponsored by :
  - GSK, Iovance Biotherapeutics, Turstone Biologics, Triumvira Immunologics
- I will be discussing FDA approved and non-FDA approved indications during my presentation.

Pre-Test Question 1

For metastatic solid cancer, what type of T cell immunotherapy has generally been associated with the highest and most durable responses?

A. CAR (chimeric antigen receptor) -engineered T cells
B. TCR (T-cell receptor) -engineered T cells
C. TIL (Tumor infiltrating T lymphocytes)
D. TAC (T cell antigen coupler) –engineered T cells

Pre-Test Question 2

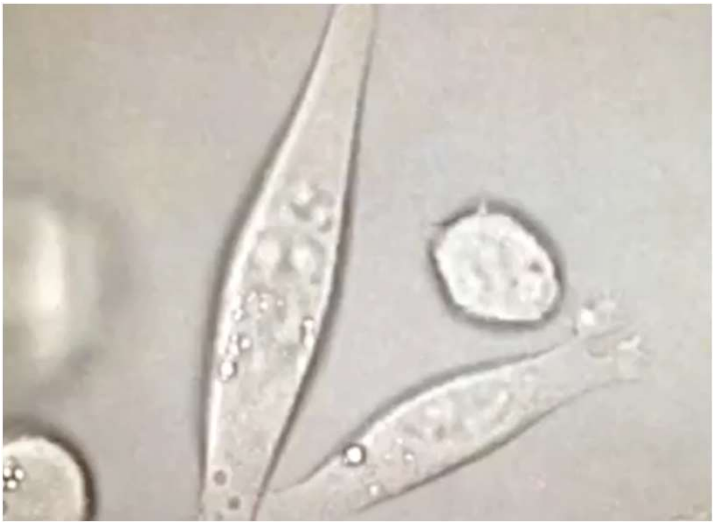
Among the following severe complications, which one is more frequently seen with TIL (Tumor infiltrating T lymphocytes) immunotherapy?

A. Cytokine-release syndrome
B. Bacteremia and infections
C. Auto-immune toxicities
D. Ventilation support for hypoxia

Presentation outline

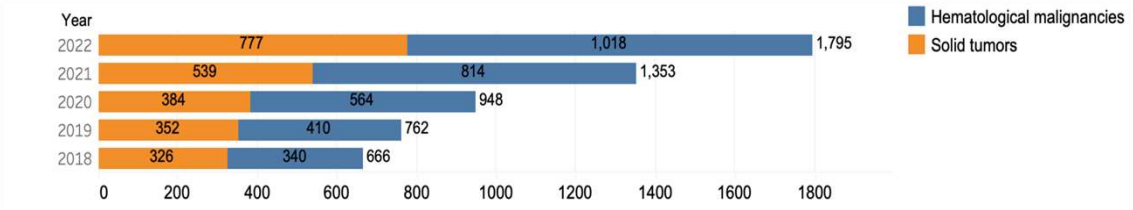
1. General introduction to T cell immunotherapy
2. Overview of TIL (tumor-infiltrating T lymphocyte) immunotherapy
3. Overview of gene-engineered (CAR and TCR) immunotherapy
4. Take home messages

T cell immunotherapy: transfusion of autologous T cells capable of recognizing and destroying cancer cells



Walter and Eliza Hall Institute, 23-May-2016
https://www.eurekalert.org/pub_releases/2016-05/waeh-ht052016.php

Exponential increase in the number of T cell therapy trials worldwide in both solid and heme malignancies



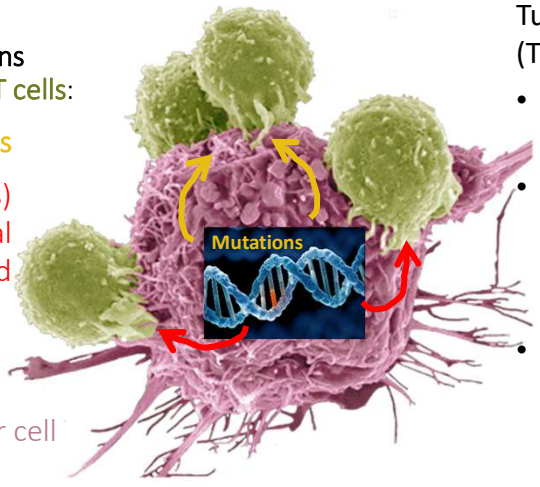
Worldwide market estimated to reach 15.4 billions USD by 2028

Saez-Ibañez, A. R. *et al.* Landscape of cancer cell therapies: trends and real-world data. *Nat Rev Drug Discov* 2022;**21**:631–632

Multiple cancer antigens can be recognized by T cells:

Neoantigens

Germline (Cancer testis)
Viral / retroviral
Normal overexpressed

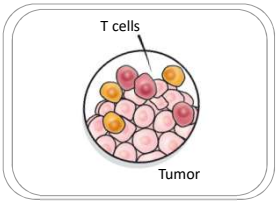


Features of naturally occurring Tumor-infiltrating T lymphocytes (TIL):

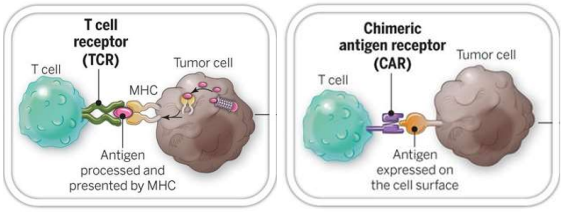
- Polyclonal, multifunctional, great proliferative potential
- Can **recognize multiple neoantigens** (cancer-exclusive, patient-specific), and other antigens
- Underwent thymic selection, thus **low affinity to self-antigens**

Major types of T cell immunotherapies

A. Tumor infiltrating T lymphocytes (TIL)



B. Antigen-receptor engineered T cells



Figures adapted from Rosenberg & Restifo ***Science*** 2015

Major types of T cell immunotherapies

A. Tumor infiltrating T lymphocytes (TIL)

B. Antigen-receptor engineered T cells

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A New Approach to the Adoptive Immunotherapy of Cancer with Tumor-Infiltrating Lymphocytes

Steven A. Rosenberg, Paul Spiess, Rene Lafreniere

Science 1986;233:1318

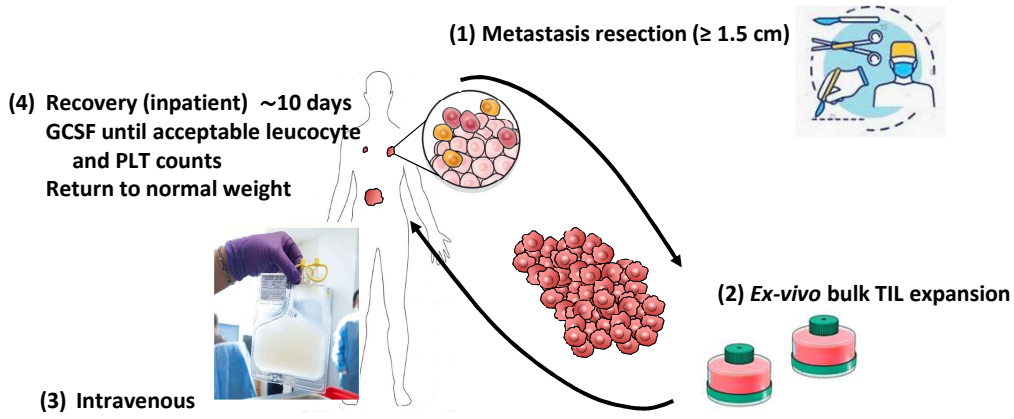
Treatment			No. of mice		Median survival time (days)
Cy	IL-2	TIL	Total	Cured	
0	0	0	6	0	17
0	0	+	5	0	18
0	+	0	6	0	18
0	+	+	5	0	17
+	0	0	5	0	28
+	+	0	6	0	28
+	0	+	6	0	38*
+	+	+	6	6	>100*
+	+	LAK†	5	0	29

Three key components for efficacy:

1. Lymphodepletion
2. T cells (TIL)
3. IL-2

- C57BL/6 mice bearing MC38 syngeneic colon cancer metastatic to the lungs induced by IV injection of tumor cells (0.5e6)
- 12e6 TIL injected 12 or 14 days after tumor induction
- † 100e6 Peripheral blood T cells expanded with IL-2, called LAK cells

Classic TIL immunotherapy



TIL for metastatic melanoma – main studies

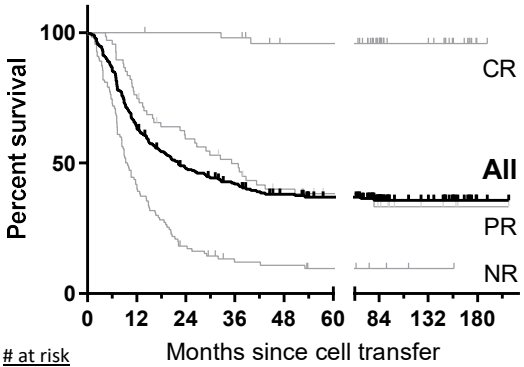
Ref	Institution / Company	Design N	Objective response rate (PR + CR)	Complete response (CR)
Seitter et al. 2021	NCI - SB	Prosp. cohort 226	116 (51%)	49 (22%)
Rohaan et al. NEJM 2022	Netherlands Cancer Institute and Herlev, Denmark	RCT 84 vs 84 (ipi)	41 (48.8%)	17 (20%)
2022 SITC and product label	Iovance Biotherapeutics (Study C-144-01)	Prosp. cohorts 153	48 (31.4%)	8 (5.2%)

Historical cohort with ≥ 9 years median f/up

Dec 2023 - countries approval for post-PD-1

Feb 2024 - FDA approval (lifileucel) for post-PD-1 blocking antibody and post-BRAF inhibitor with/without MEK inhibitor if $BRAF^{V600E}$

Long-term results from TIL (single treatment) for metastatic melanoma at NCI

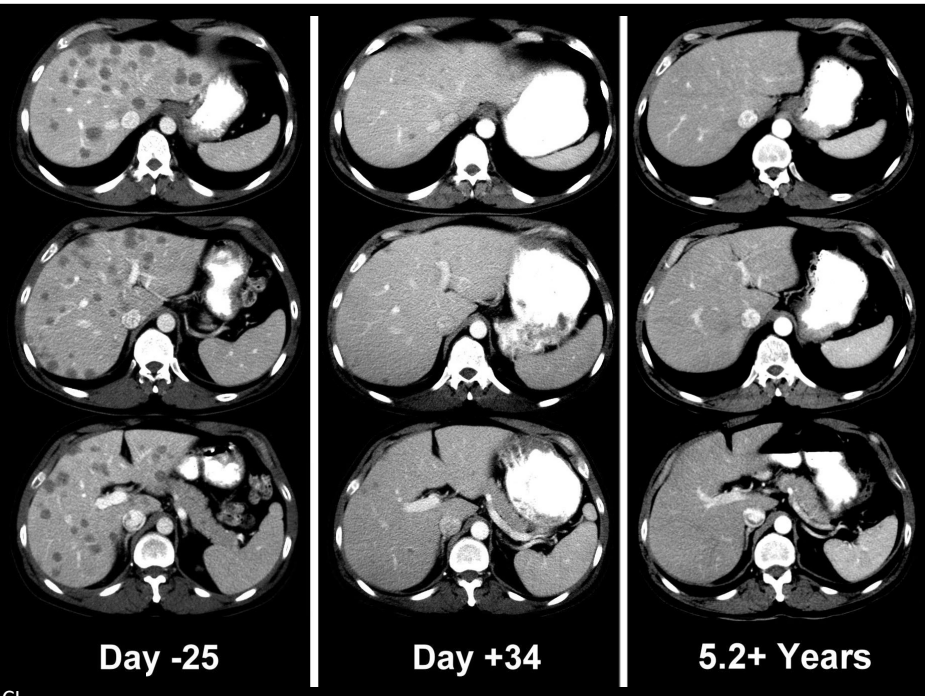


# at risk								
All:	226	146	105	88	74	65	43	21
Complete Response:	49	49	48	47	42	42	30	16
Partial Response:	67	51	38	31	23	18	10	4
No Response:	110	46	19	10	9	5	3	1

- Objective Response Rate
  51% (116/226)
- Complete Response Rate
  22% (49/226)
  96% alive 10 years after TIL
- Median Survival (all)
  22.2 months (95% CI 16.2-32.4)
  Plateau at 5 year = ~ 40%

Seitter et al, 2021 - slide provided by S. Goff, NCI

Example of complete response to TIL, melanoma metastatic to the liver



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- Funded by national grant RCT that binded Holland and Denmark to reimbursement if trial positive
- Point of care manufacturing (hospital & bood service provider Sanquin)
- 87% of patients after anti-PD-1 antibody
- 40.9e9 median TIL infused, fresh product

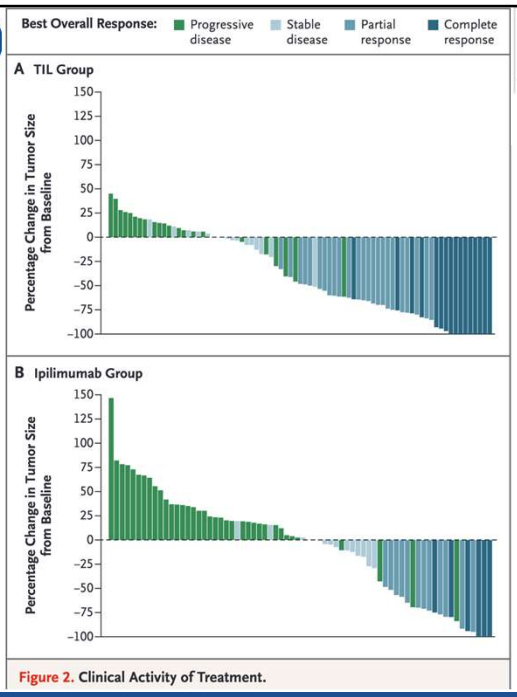


Figure 2. Clinical Activity of Treatment.

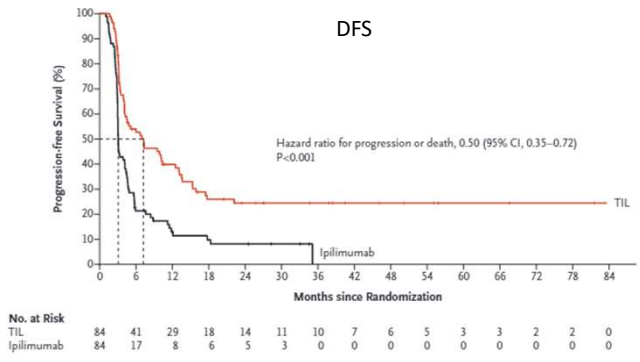
The NEW ENGLAND JOURNAL of MEDICINE

Tumor-Infiltrating Lymphocyte Therapy or Ipilimumab in Advanced Melanoma

The NEW ENGLAND JOURNAL of MEDICINE

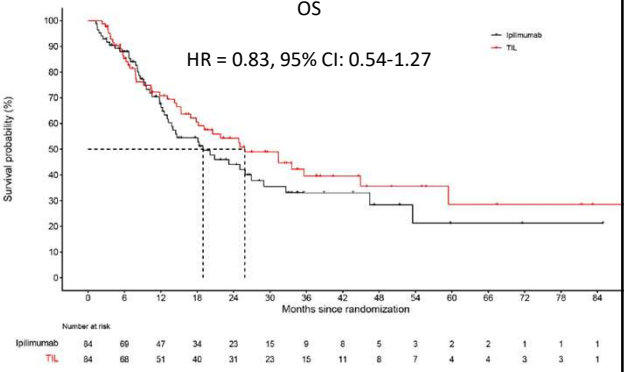
Tumor-Infiltrating Lymphocyte Therapy or Ipilimumab in Advanced Melanoma

DFS



OS

HR = 0.83, 95% CI: 0.54-1.27



Median PFS 7.2 months in the TIL arm (95% CI: 4.2– 13.1)
vs 3.1 months in ipi arm (95% CI: 3.0-4.3)

Unplanned (interim) analysis (median follow-up 33 months)
median OS in the TIL arm was 25.8 months (95% CI: 18.2-not reached)
vs in the ipilimumab arm 18.9 months (95% CI: 13.8-32.6)

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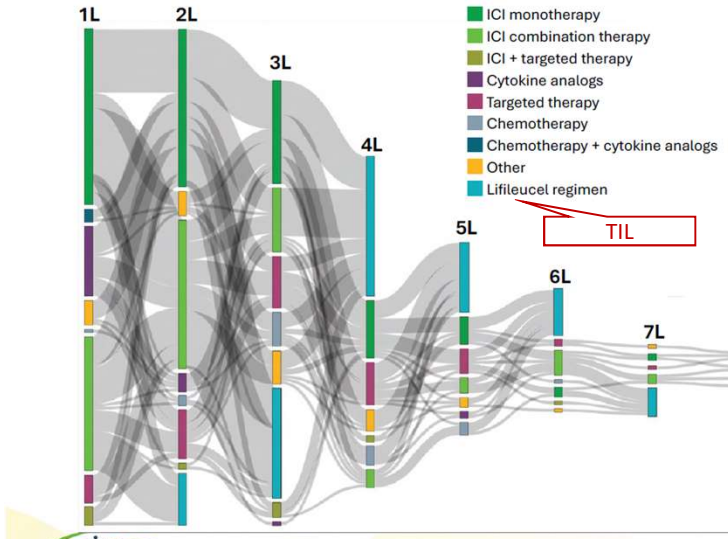
Patient Treatment Patterns



- Patients were heavily pretreated
  - 17 (11.1%) received only 1 line of prior therapy
  - 125 (81.7%) received anti–CTLA-4
  - 82 (53.6%) received anti–PD-1 + anti–CTLA-4 combination
  - Median of 2 lines (range, 1-7) of ICI-containing therapy
  - 113 (73.9%) were retreated with ICI-containing therapy prior to receiving lifileucel

Median number of TIL administered: 21.1e9
Cryopreserved cell product, thawed at bedside

The R package networkD3 was used to generate the Sankey plot.
ICI, immune checkpoint inhibitors; L, line of therapy.

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Slide adapted by Turcotte S, with comments in red

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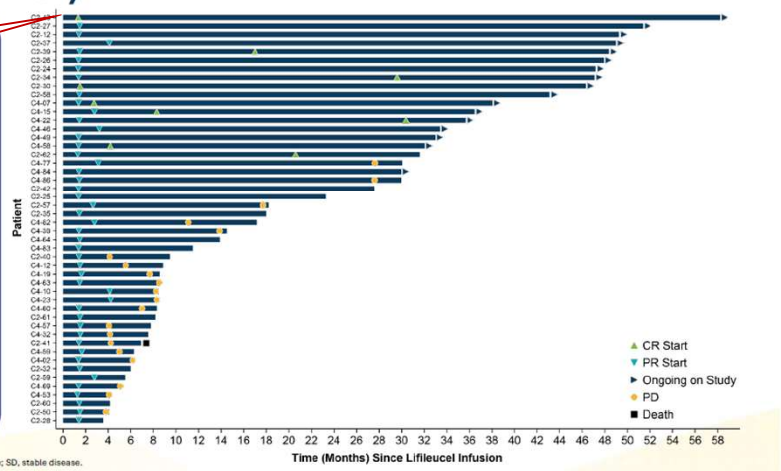
Time to Response, Duration of Response, and Time on Efficacy Assessment for Confirmed Responders (PR or Better)

Response usually seen on first scans

In this study, PR can:
- convert to CR in ~ 19%
- convert to progressive disease in 42%



CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

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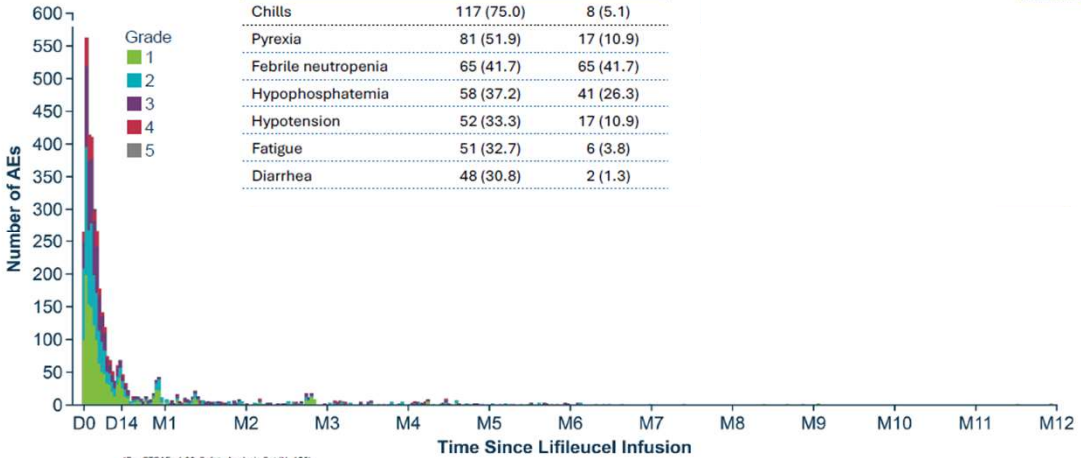
Safety

Non-Hematologic TEAEs in ≥30% of Patients*†

Preferred Term, n (%)	Any Grade	Grade 3/4
Chills	117 (75.0)	8 (5.1)
Pyrexia	81 (51.9)	17 (10.9)
Febrile neutropenia	65 (41.7)	65 (41.7)
Hypophosphatemia	58 (37.2)	41 (26.3)
Hypotension	52 (33.3)	17 (10.9)
Fatigue	51 (32.7)	6 (3.8)
Diarrhea	48 (30.8)	2 (1.3)



*Per CTCAE v4.03; Safety Analysis Set (N=156).
†Grade 5 TEAEs included pneumonia (n=1), acute respiratory failure (n=1), arrhythmia (n=1), and intra-abdominal hemorrhage (n=1).
All occurrences of AEs were counted if a patient experienced a new onset of the same AE at different timepoints. If multiple records were reported on the electronic case report form because of toxicity grade decrease of the same AE that had not resolved, then the event was counted once with the highest grade reported.
15 events were reported after Month 12 (Grade 1, n=7; Grade 2, n=6; Grade 3, n=1; Grade 5, n=1).
AE, adverse event; D, day; IL-2, interleukin 2; M, month; NMA-LD, nonmyeloablative lymphodepletion; TEAE, treatment-emergent adverse event.

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TIL relevant toxicities

Relevant Grade ≥3 toxicity for TIL immunotherapy in melanoma studies

Treatment-emergent adverse event - n (%)	Dudley 2010 *N*=33	Dudley 2013 *N*=69	Goff 2016 *n*=51	Rohaan 2023 n = 80	Lifileucel label n = 156
Hematological					
Febrile neutropenia	17(51.5)	28 (40.6)	25 (49.0)	59 (74.0)	73 (46.8)
Infectious complications					
Catheter related infection	-	3 (4.3)	-	1 (1.3%)	-
Bacteremia / sepsis	8 (24.2)	14 (20.3)	13 (25.5)	-	-
All infections				4 (5.0)	23 (14.7%)
Renal					
Renal failure	-	-	1 (2.0)	1 (1.3%)	-
Respiratory					
Dyspnea requiering ventilatory support	-	3 (4.3)	-	5 (6.0)	13 (8.3)
Death	1 (3.0)	-	-	1 (1.3)	12/160 (7.5)

Melanoma-specific autoimmune toxic effects (low grade) – from Rohaan et al. 2023 :

- skin hypopigmentation 9/80 (11%)
- uveitis 6/80 (8%) / vision loss in 1
- hearing impairment 3/80 (4%)

} Usually low grade and resolve with corticosteroid drops

Surgeon's role in TIL immunotherapy

PRE surgery → **Surgery**: tumor procurement for TIL manufacturing → **POST surgery**

1. Take part in the multidisciplinary oncology team: *does TIL make sense for given patient?*
2. Review patient fitness and potential source of sepsis
3. Review imaging to determine whether a **non necrotic, non cystic** ≥ 1.5 cm metastasis can be resected with minimally invasive technique (lung, pleural nodule, nodes, liver, adrenal)
4. Plan for pre-op visit/consent/book surgery – outpatient & day-surgery prefered

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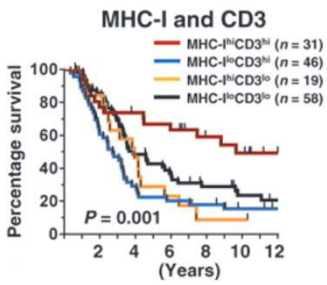
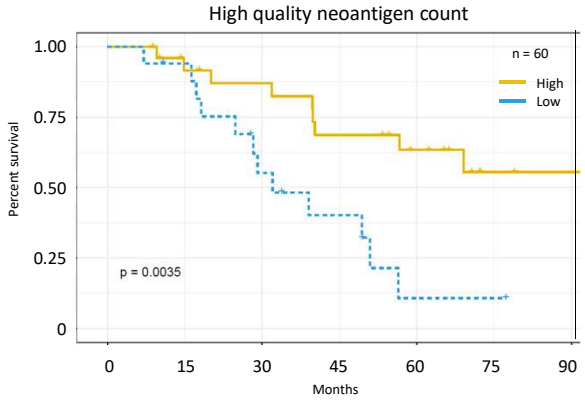
And for non-melanoma cancers?

The spontaneous, adaptive immune T-cell response to most solid cancer is likely associated with better disease control and outcome

Example in colorectal liver metastasis resected with curative intent





Gigoux M – Turcotte Lab, unpublished

- Turcotte S et al. *Tumor MHC Class I Expression Improves the Prognostic Value of T-cell Density in Resected Colorectal Liver Metastases.* ***Cancer Immunol Research*** 2014;2(6):530–7.
- Messaoudi N, Henault D, … Turcotte S. *Prognostic implications of adaptive immune features in MMR-proficient colorectal liver metastases classified by histopathological growth patterns.* ***Brit J Cancer*** 2022;126(9):1329–38.
- Henault D, … Turcotte S. *Homogeneity in immune features between colorectal liver metastases better identifies patients with good prognosis compared to pathological response to preoperative chemotherapy.* ***OncoImmunology*** 2023;12(1):2253642.

Selected promising results with classic TIL in non-melanoma

Indication	First author	Pub year	Institution / Company	N	OR (%)	CR (%)	2y OS (%)
Cervical Late stage	Stevanović	2015	NCI-SB	18	5 28%	2 11%	-
Cervival Late stage	Jazaeri	2019	Iovance	27	12 44%	3 11%	-
NSCLC 2nd line after progression xPD-1	Creelan	2021	Moffitt Cancer Center	16	3/13 23%	1/13 4%	38%
NSCLC After 2 prior lines	Schoenfeld	2021 SITC	Iovance	28	6 21%	1 3.6%	-
				89 *Total*	***29%*** *Means*	***9%*** *Means*	

Next gen TIL in active development

Table 1 | Selected TIL candidates in and approaching the clinic

Candidate	Sponsor	Properties	Lead indication	Trial status
Lifileucel/LN-144	Iovance	TIL	Melanoma	BLA
TILs	NKI	TIL	Melanoma	MAA planned
LN-145	Iovance	TIL	NSCLC, HNSCC	II
ATL001	Achilles	Neoantigen-reactive TILs	Melanoma, NSCLC	I/II
NEXTGEN-TIL	VHIO	Neoantigen-reactive TILs	Solid tumours	I
TIDAL-01	Turnstone	Neoantigen-reactive TILs	Breast, CRC, uveal melanoma	I
BNT221	BioNTech	Neoantigen-reactive T cells from peripheral blood	Melanoma	I
LN-145-S1	Iovance	PD1-selected TIL	Melanoma, HNSCC	II
IOV-4001	Iovance	PD1-inactivated engineered TIL	Melanoma, NSCLC	I/II
KSQ-001EX eTIL	KSQ	SOCS1-inactivated engineered TIL	Solid cancers	I to start
KSQ-004EX eTIL	KSQ	Regnase-1/SOCS1 dual-inactivated engineered TIL	Solid cancers	Preclinical
CISH-inactivated TILs	Intima	CISH-inactivated neoantigen-reactive engineered TILs	Solid cancers	I/II
ITIL-306	InstilBio	Anti-folate receptor alpha CoStAR-boosted engineered TIL	Ovarian, NSCLC and RCC	I
OBX-115	Obsidian	IL15-boosted engineered TIL (IL2 free)	Melanoma	I
iTCR	NCI	TIL-derived TCRs engineered into peripheral T cells	Metastatic cancer	II
LYL-845	Lyell	Epigenetically reprogrammed TILs	Melanoma, NSCLC, CRC	I
AGX-148 plus PH-762	AgonOx/ Phio	CD8-positive TILs plus PD-1 silencing siRNA	Solid tumours	I

BLA, Biologics License Application; CoStAR, costimulatory antigen receptor; CRC, colorectal cancer; HNSCC, head and neck squamous cell carcinomas; MAA, marketing authorisation application; NCI, National Cancer Institute; NKI, Netherlands Cancer Institute; NSCLC, non-small cell lung cancer; RCC, renal cell *cancer*; TCR, T-cell receptor; TIL, tumour-infiltrating lymphocyte; VHIO, Vall d'Hebron Institute of Oncology.

Mullard A. Tumour-infiltrating lymphocyte cancer therapy nears FDA finish line. **Nat Rev Drug Discov 2024**;23(1):3–7.

A case of neoantigen-selected TIL for metastatic cholangiocarcinoma

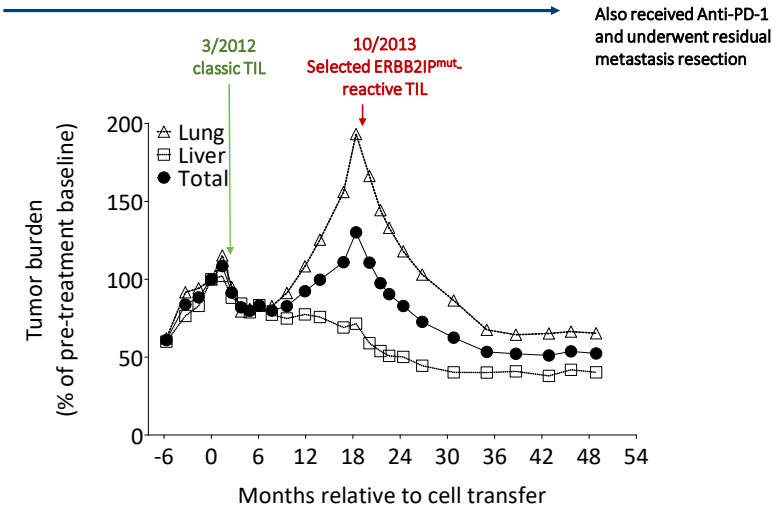
45 y.o. female with metastatic cholangiocarcinoma

12/2009 Right hepatectomy for cholangiocarcinoma

4/2010 Multiple lung and liver metastases

Received cisplatin and gemcitabine: PD

5/2011 Taxotere chemotherapy: PD in lung and liver



Tran E, Turcotte S, et al, ***Science*** 2014

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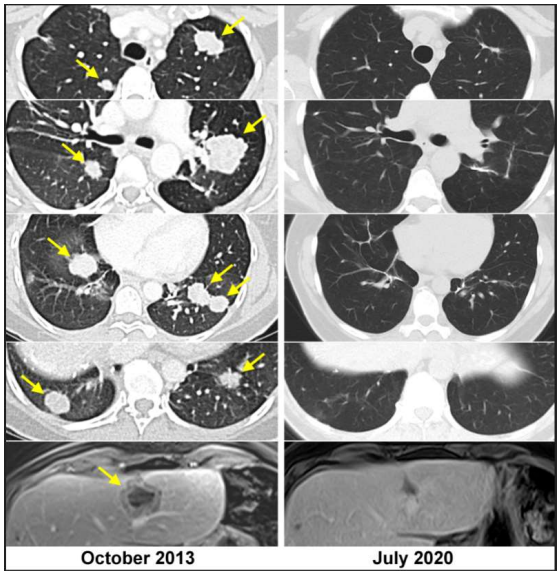


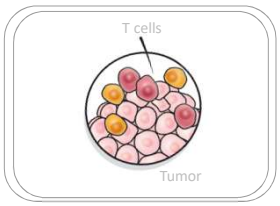
Image provided by Steven Rosenberg oct 2023

Oct. 2023
Cholangiocarcinoma-free

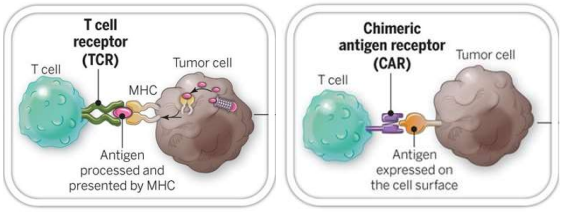
A Clinical Trial Saved My Life. Diagnosed with stage IV cholangiocarcinoma, I enrolled in a study investigating tumor-infiltrating lymphocyte therapy. That was 10 years ago.
By MELINDA BACHINI, AS TOLD TO JO CAVALLO, April 25, 2020
https://ascopost.com/issues/april-25-2020/a-clinical-trial-saved-my-life/

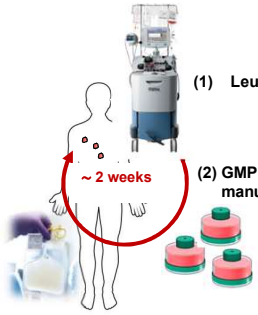
Major types of T cell immunotherapies

A. Tumor infiltrating T lymphocytes (TIL)



B. Antigen-receptor engineered T cells





(1) Leukapheresis

(2) GMP cell manufacturing

(3) **Lymphodepletion** (non myelo-ablative)
(4) **T cell infusion**
(5) **Inpatient recovery**

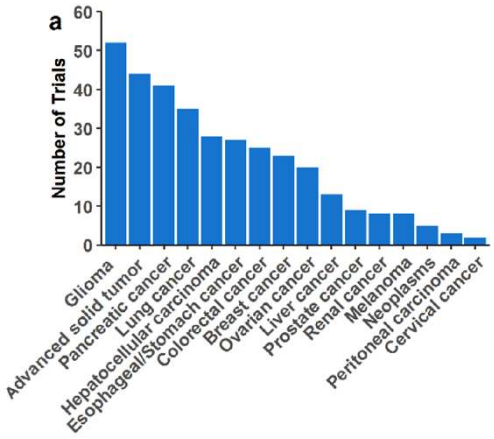
Generally no IL-2, but may be associated with immune checkpoint inhibitors

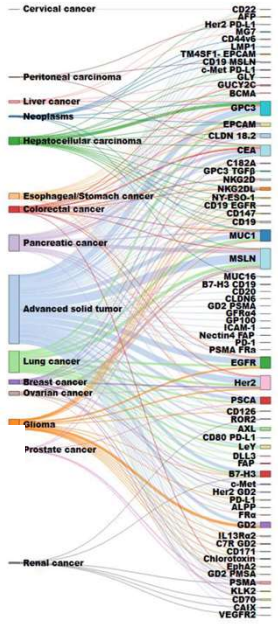
Figures adapted from Rosenberg & Restifo ***Science*** 2015

TCR engineered T cells – representative published trials

Antigen	Indication	First author	Pub year	Institution / Company	Patients (treated)	ORR	CR	median PFS (months)	Immune ≥ Grade 3 Toxicity
Shared, self antigens									
MART-1	Melanoma	Morgan/Johnson	2006/2009	NCI -SB	20	30%	0%	-	Skin, eye, ear
GP100	Melanoma	Johnson	2009	NCI -SB	16	19%	6.3%	-	Skin, eye, ear
CEA	Colorectal	Parkhurst	2010	NCI -SB	3	33%	0%	-	Severe enteritis
Cancer germline antigens									
NY-ESO-1	Melanoma	Robbins	2015	NCI -SB	20	55%	20%	4.5	None
	Synovial cell sarcoma	Robbins	2015	NCI -SB	18	61%	5.5%	6.0	None
		D'Angelo	2017	MSKCC/NCI	12	50%	8.3%	-	CRS 16.7%
		Ramachandran	2019	Adaptimune	42	36%	2.3%	-	None
MAGE-A3 (CD8+)	Various	Morgan	2013	NCI -SB	9	56%	0%	-	Brain (2 deaths, 3 grade 3-4)
	Melanoma, myeloma	Linette	2013	U Pennsylvania	2	-	-	-	Cardiac fatal tox
MAGE-A3 (CD4+)	Various	Lu	2017	NCI -SB	17	23.5%	5.8%	-	None
MAGE-A4	Ovarian late stage	Hong	2022 ESMO	Adaptimune	44	28%	2.2%	3.0 (DOR)	CRS 14%
Viral antigens									
HPV16-E6	HPV-associated cancers	Doran	2019	NCI	12	17%	0%	-	None
HPV16-E7	HPV-associated cancers	Nagarsheth	2021	NCI	12	50%	0%	-	None
Neoantigens from driver mutations									
KRAS	Pancreatic	Leidner	2021	Providence	2	50%	0%		None
					229 *Total*	*49%*	*3%* *Mean*		

CAR engineered T cells – multiple surface protein targets pursued





Barros LRC et al. Systematic Review of Available CAR-T Cell Trials around the World. Cancers 2022;14, 2667

CAR engineered T cells – representative published trials

Antigen	Indication	First author	Pub year	Institution / Company	Patients (treated)	ORR	CR	median PFS (months)	Toxicity
HER-2	Breast	Morgan	2010	NCI -SB	1	-	-	-	Cardiac, CRS (death)
	Sarcomas	Ahmed	2015	Frankfurt, Germany	19	0	0	-	No significant cardiac tox
	Glioblastoma	Ahmed	2017	Frankfurt, Germany	17	1	0	-	
	Biliary and pancreatic	Feng	2018	Beijing	11	1	0	4.8	
Mesothelin	Malignant pleural disease (lung, berast, mesothelioma)	Adusumilli	2021	MSKCC	27	10.5% (2/19)	2 PET CR	-	
	Pancreatic	Beatty	2018	U Pennsylvania	6	0	0	best 5.4	no CRS
	mesothelioma, ovarian, pancreatic	Haas	2019	U Pennsylvania	15	0	0	2.1	no on-target tox (pleuritis, pericarditis, or peritonitis)
PSMA + dominant-neg TGF-B receptor	Prostate	Narayan	2022	U Pennsylvania	13	0*	0	-	38% CRS > grade 2
GD2	H3K27M-mutated diffuse midline gliomas	Majzner	2022	Stanford	4	3/4 « radiol resp »	0	-	On-target neurotox
CLDN18.2	Mainly gastric	Changsong	2022	Peking University Cancer Hospital	37	48.6%	0%	3.7	95% CRS all < grade 3, Jaundice 22%
CLDN6 +mRNA vaccine	Testicular (n=13) and various	Mackensen	2022 ESMO	U of Erlangen, Germany	22	33%	4.8%	-	45% CRS (grade 3 or less)

Take home messages

1. TIL is the first effector T cell immunotherapy to enter standard of care for metastatic solid cancer
   - Melanoma refractory to first line immunotherapy & BRAF+/- MEK inhibitors
   - Other indications likely to respond to 1st gen TIL: NSCLC and cervical cancer
2. Surgeons have pioneered TIL immunotherapy and play a critical role to enable patient access to this therapy
   - Identify appropriate patients amenable to metastasectomy with low morbidity
   - Appropriate tumor procurement => key for TIL manufacturing
   - Multiple research opportunities for developing next-gen TIL
3. TCR/CAR-engineered T cells likely to become standard of care for niche indications (e.g. NY-ESO TCR for synovial sarcoma)

Post-Test Question 1

For metastatic solid cancer, what type of T cell immunotherapy has generally been associated with the highest and most durable responses?

A. CAR (chimeric antigen receptor) -engineered T cells
B. TCR (T-cell receptor) -engineered T cells
C. TIL (Tumor infiltrating T lymphocytes)
D. TAC (T cell antigen coupler) –engineered T cells

Post-Test Question 2

Among the following severe complications, which one is more frequently seen with TIL (Tumor infiltrating T lymphocytes) immunotherapy?

A. Cytokine-release syndrome
B. Bacteremia and infections
C. Auto-immune toxicities
D. Ventilation support for hypoxia

Thank you

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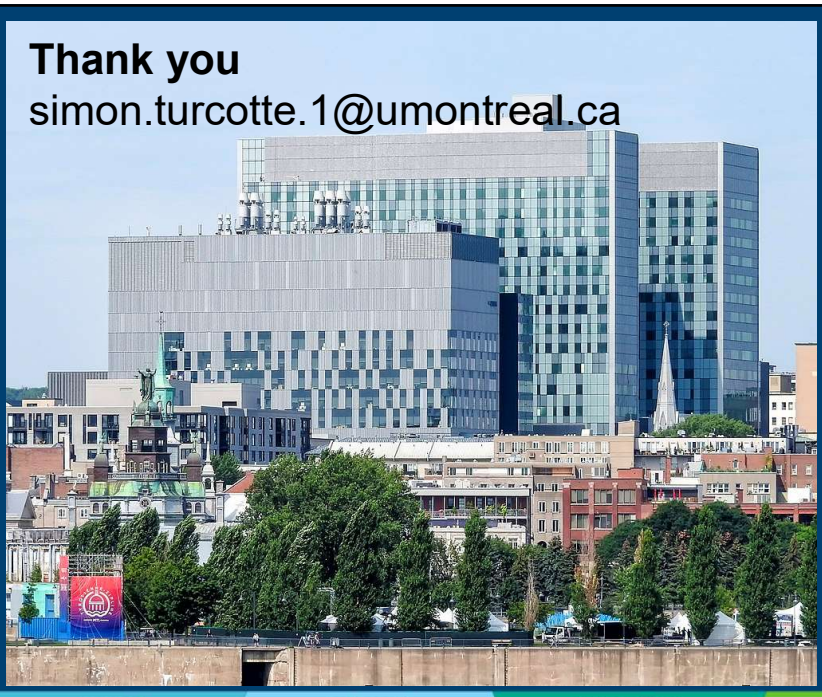

CHUM

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