TIL, TCR ou CAR: Qual a melhor opção?

Dr. Gustavo Schvartsman

Oncologista Clínico

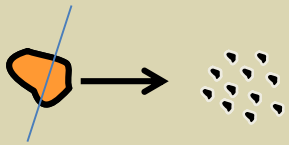
Hospital Israelita Albert Einstein

Terapia Celular Adotiva para Tratamento de Câncer

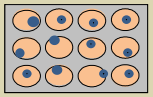
Tumor Infiltrating Lymphocytes (TIL)

Amplification of naturally occurring tumor-specific T cells

Tumor



Mincing of a small part of the tumor



Culture from tumor fragments
Small scale culture (IL-2)
3-5 wks

Initial TIL outgrowth from the tumor
≈ 50-300 X10^6 cells

REP
≈ 10-100 X10^9 cells

Large scale culture
(anti-CD3, IL-2 and feeders)
2 wks

IL-2

TCR- or CAR-modified T cells

Engineering tumor-reactivity in peripheral T cells

Peripheral Blood T cells

PBMCs (apheresis product)

T-cell enrichment and activation

Gene modification TCR or **CAR** transduction

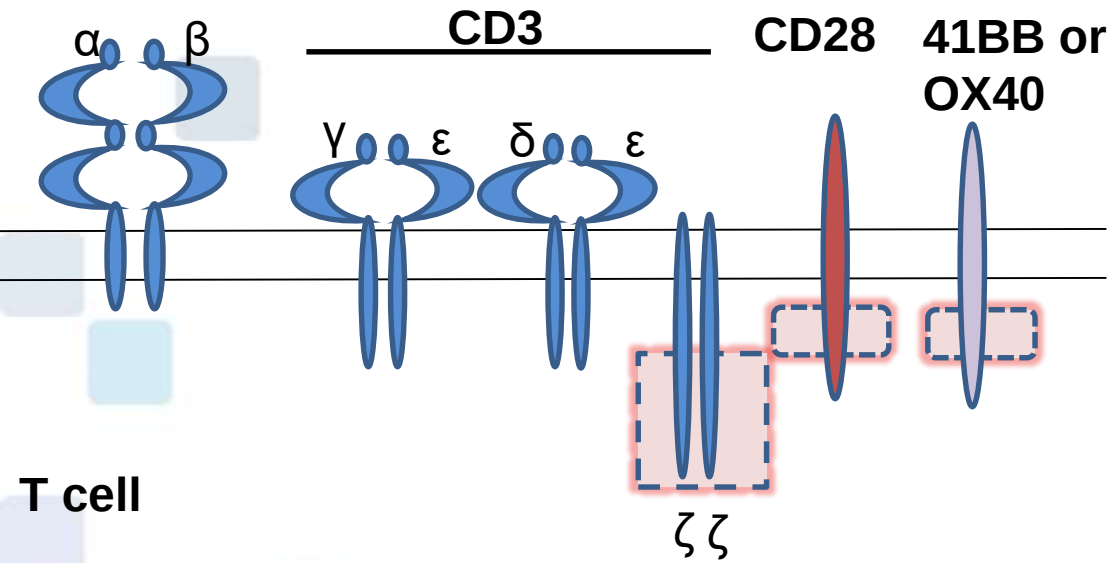
2 wks

Expansion in IL-2 alone or REP-type protocol
≈ 10^6 - 10 X10^9 cells

Adapted from Bernatchez, C., Radvanyi, L. G. & Hwu, P., Semin Oncol 39, 215-226, (2012).

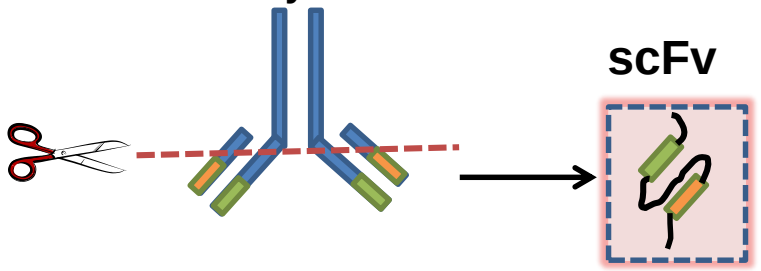
TCR and chimeric antigen receptor (CAR) structures

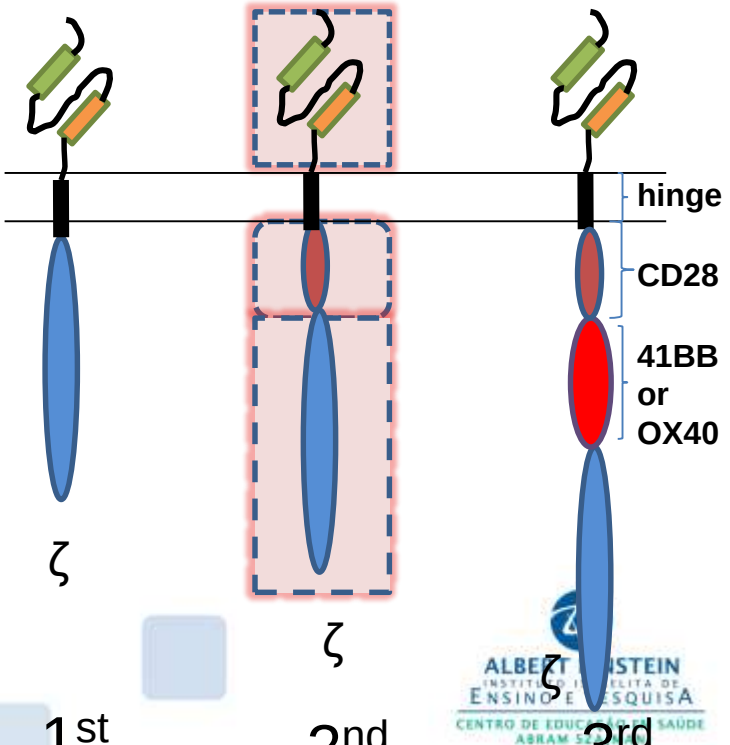
Classical TCR



CAR generations

Tumor antigen specific
Antibody

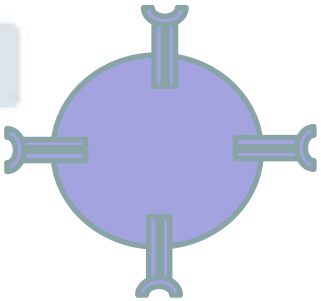




Gao, J., et al., Trends Immunol, 2013. 34(2): p. 90-8.

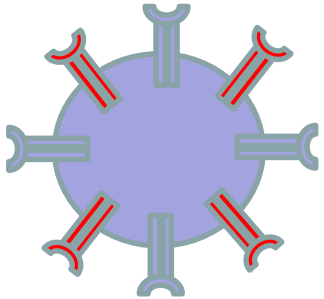
Adoptive T-cell therapy to treat cancer

Endogenous T cell



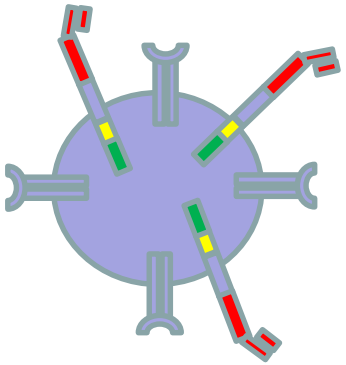
Endogenous TCR

TCR-transduced T cell



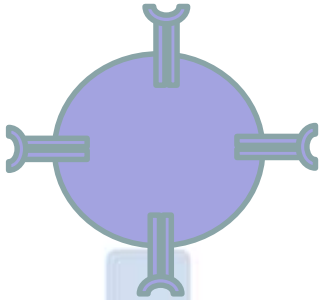
Transduced TCR

CAR T cell

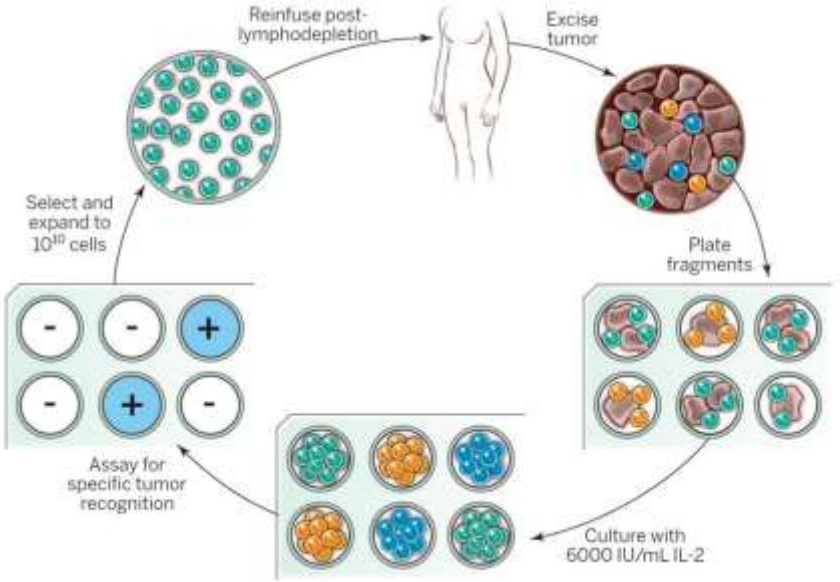


CAR

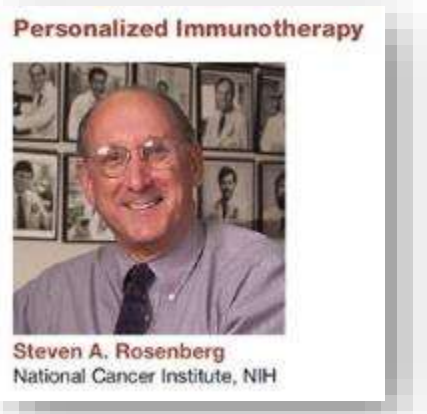
TERAPIA COM TIL

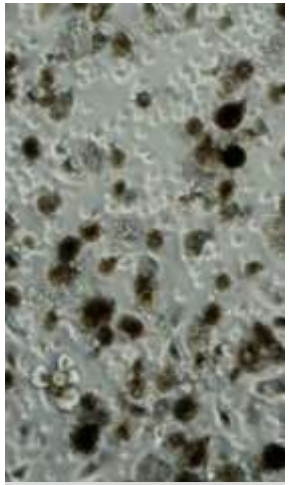


Tumor Infiltrating Lymphocytes

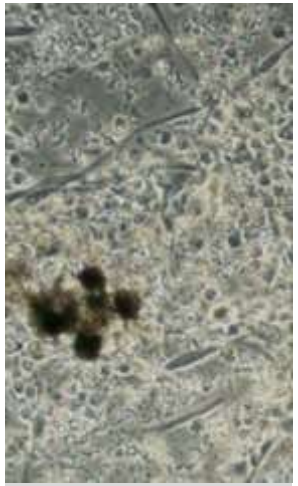


Rosenberg, S. Science, 2015





Fresh digest



One week

Two weeks

Rosenberg, S. 1985

Tumor Infiltrating Lymphocytes

- ✅ Utiliza células T endógenas encontradas em tumores sólidos, no contexto do paciente
- ✅ Se beneficia de um microambiente tumoral rico em TILs
- ✅ Seleção tímica – menos células auto-reativas
- ✅ Múltiplos antígenos
- ❌ TILs tendem a expressar altos níveis de checkpoints, como PD-L1 (inibição em conjunto?)
- ❌ Tratamento autólogo apenas
- ❌ 5-7 semanas de confecção

Preparo e Tratamento com TILs

Pre-REP

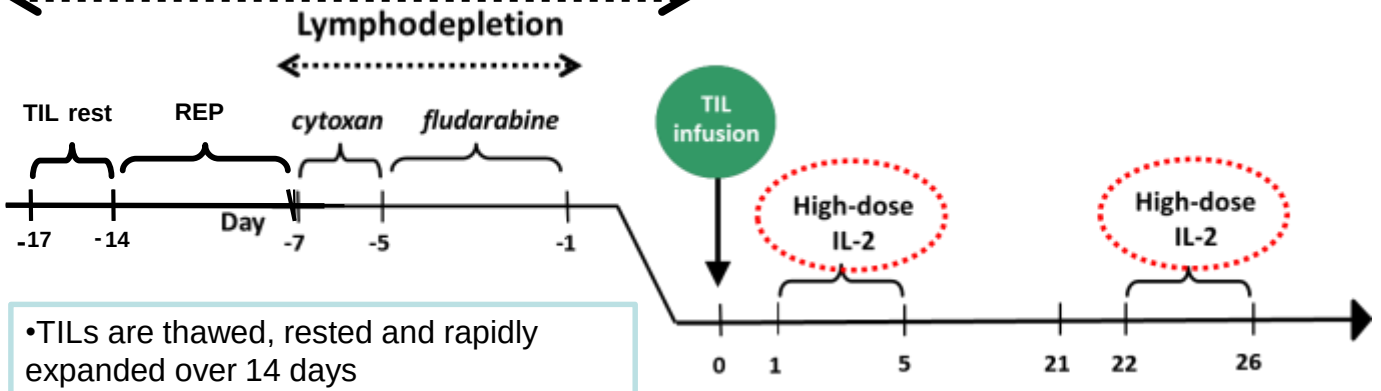
•Tumor excised, an attempt is made to grow TILs (5 week culture)

•Successful TIL culture will grow a minimum of 50 million TIL

•Current success rate of around 65%

•TILs are cryopreserved

REP



•TILs are thawed, rested and rapidly expanded over 14 days

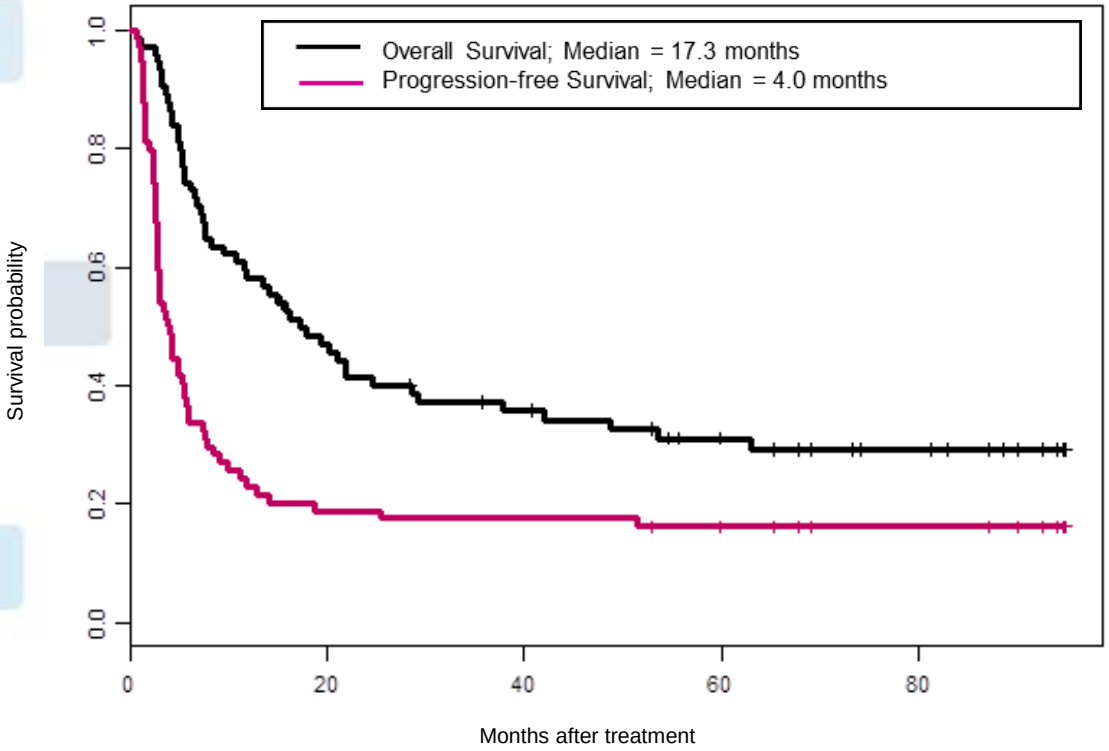
•Patient is admitted to hospital on day 7 of the REP and undergoes lymphodepletion

•Patient is infused

•2 cycles of HD IL-2 completed

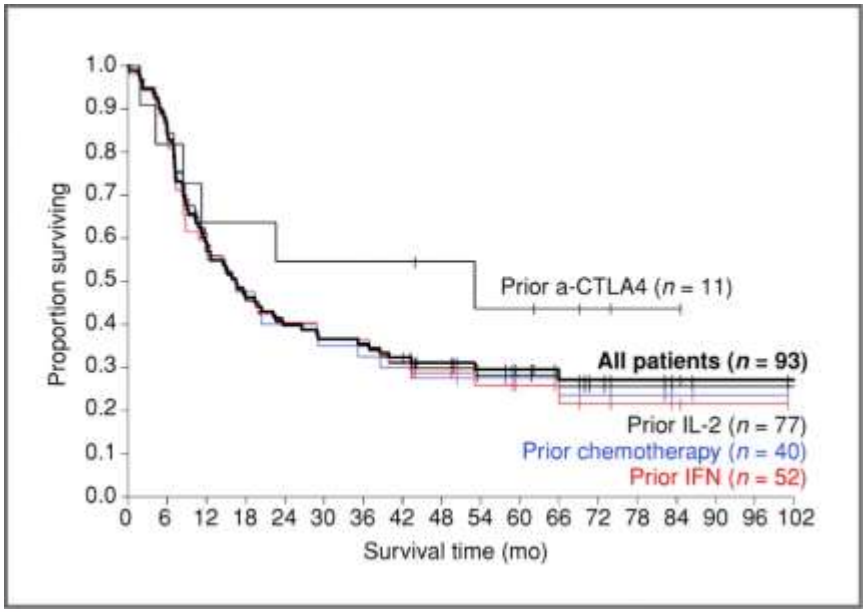
Resposta a TILs em melanoma metastático

MDACC
N=74



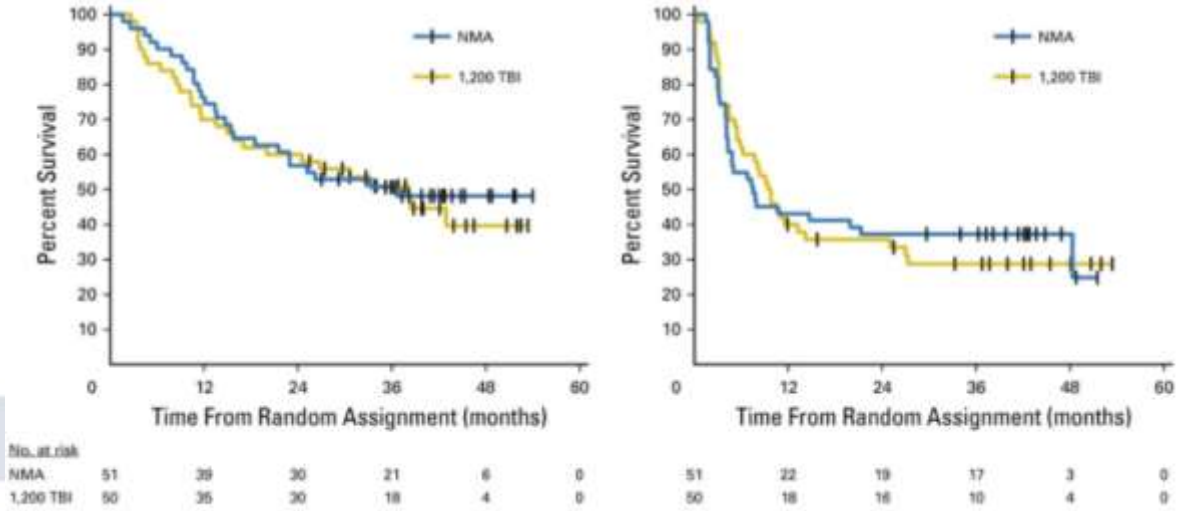
TIL therapy produces durable clinical responses in late stage melanoma patients

Resposta a TILs em melanoma metastático



Steven A. Rosenberg et al. Clin Cancer Res 2011;17:4550-4557

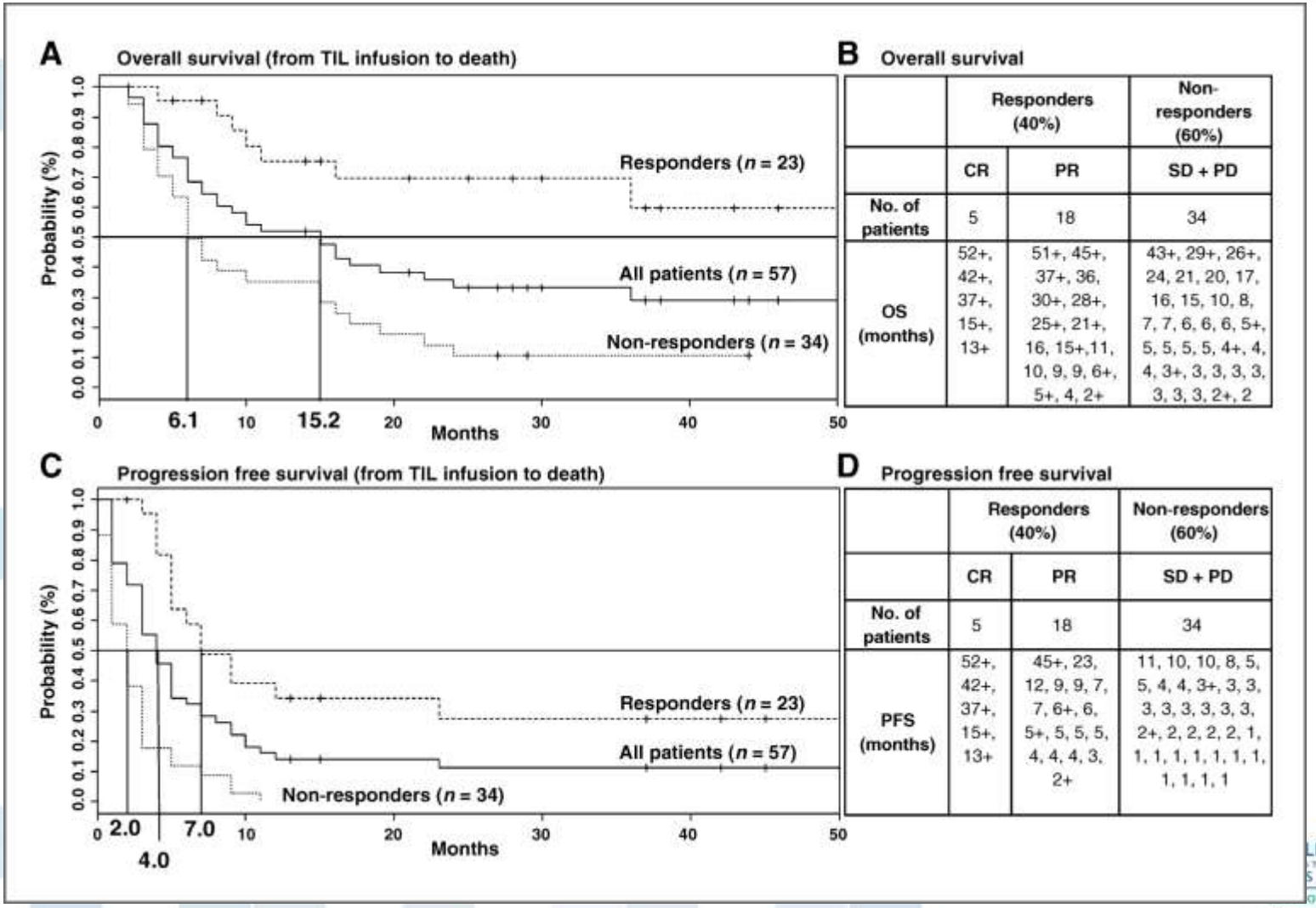
NCI
N=101



Adapted from Stephanie L. Goff et al; *JCO* **2016,** 34, 2389-2397.

Resposta a TILs em melanoma metastático

Sheba Medical Center
N=57



B Overall survival

	Responders (40%)		Non-responders (60%)
	CR	PR	SD + PD
No. of patients	5	18	34
OS (months)	52+, 42+, 37+, 15+, 13+	51+, 45+, 37+, 36, 30+, 28+, 25+, 21+, 16, 15+,11, 10, 9, 9, 6+, 5+, 4, 2+	43+, 29+, 26+, 24, 21, 20, 17, 16, 15, 10, 8, 7, 7, 6, 6, 6, 5+, 5, 5, 5, 5, 4+, 4, 4, 3+, 3, 3, 3, 3, 3, 3, 2+, 2

D Progression free survival

	Responders (40%)		Non-responders (60%)
	CR	PR	SD + PD
No. of patients	5	18	34
PFS (months)	52+, 42+, 37+, 15+, 13+	45+, 23, 12, 9, 9, 7, 7, 6+, 6, 5+, 5, 5, 5, 4, 4, 4, 3, 2+	11, 10, 10, 8, 5, 5, 4, 4, 3+, 3, 3, 3, 3, 3, 3, 3, 3, 2+, 2, 2, 2, 2, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1

Michal J. Besser et al. Clin Cancer Res 2013;19:4792-4800

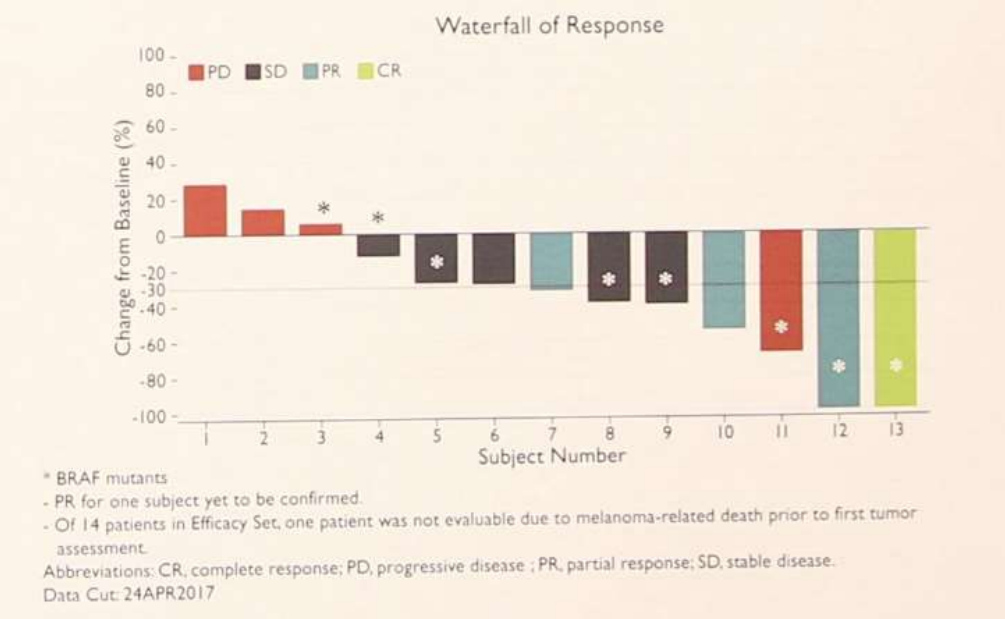
Resposta a TILs em melanoma metastático

Laboratório central para protocolo multicêntrico:

- Moffitt; Yale; James Graham; Earle Chiles
- Pacientes refratários a anti-PD1

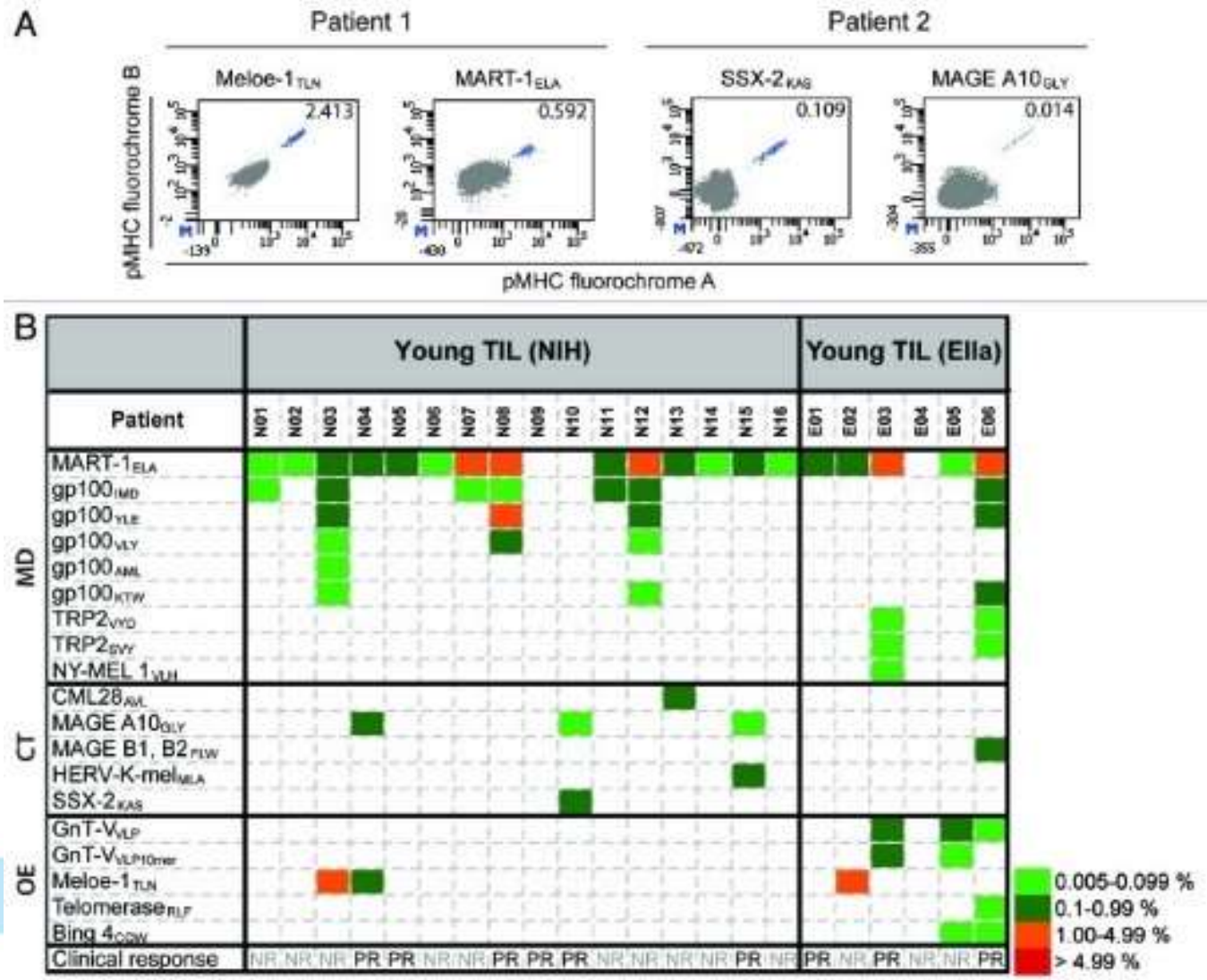
Table 3. Efficacy

RESPONSE	PATIENTS, N=14 n (%)
Objective Response Rate	4 (29%)
Disease Control Rate	9 (64%)
Complete Response	1 (7%)
Partial Response	3 (21%)
Stable Disease	5 (36%)
Progressive Disease	4 (29%)
Non-Evaluable*	1 (7%)



Sarnaik et al. ASCO Annual Meeting, 2017

Antígenos reconhecidos por TILs

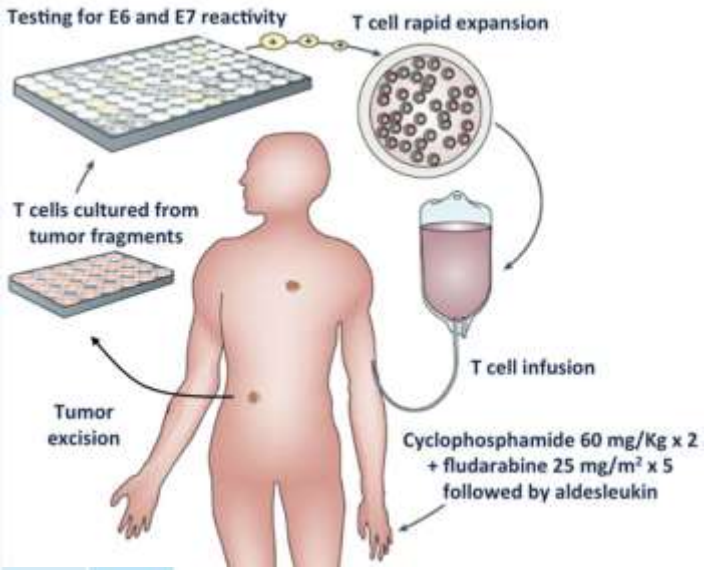


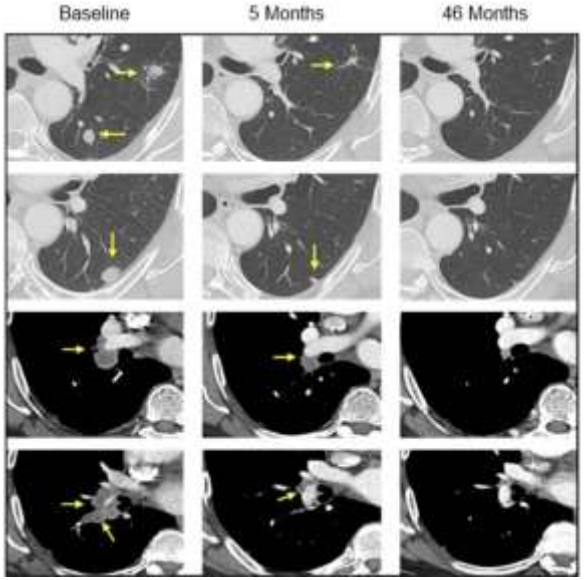
Kvistborg P, Shu CJ, Heemskerk B, et al. TIL therapy broadens the tumor-reactive CD8(+) T cell compartment in melanoma patients. Oncoimmunology. 2012;1(4):409-418.

Resposta a TILs em outros tumores sólidos

Clinical response to TIL therapy reported for:

- Metastatic HPV^{+} cervical cancer (5/18 patients, 2 CRs)
- Metastatic HPV+ HNSCC (1/5)
- Metastatic uveal melanoma (7/21, 1CR)





Stevanovic S, et al. Treatment of metastatic human papillomavirus-associated epithelial cancers with adoptive transfer of tumor-infiltrating T cells. ASCO Annual Meeting, 2018

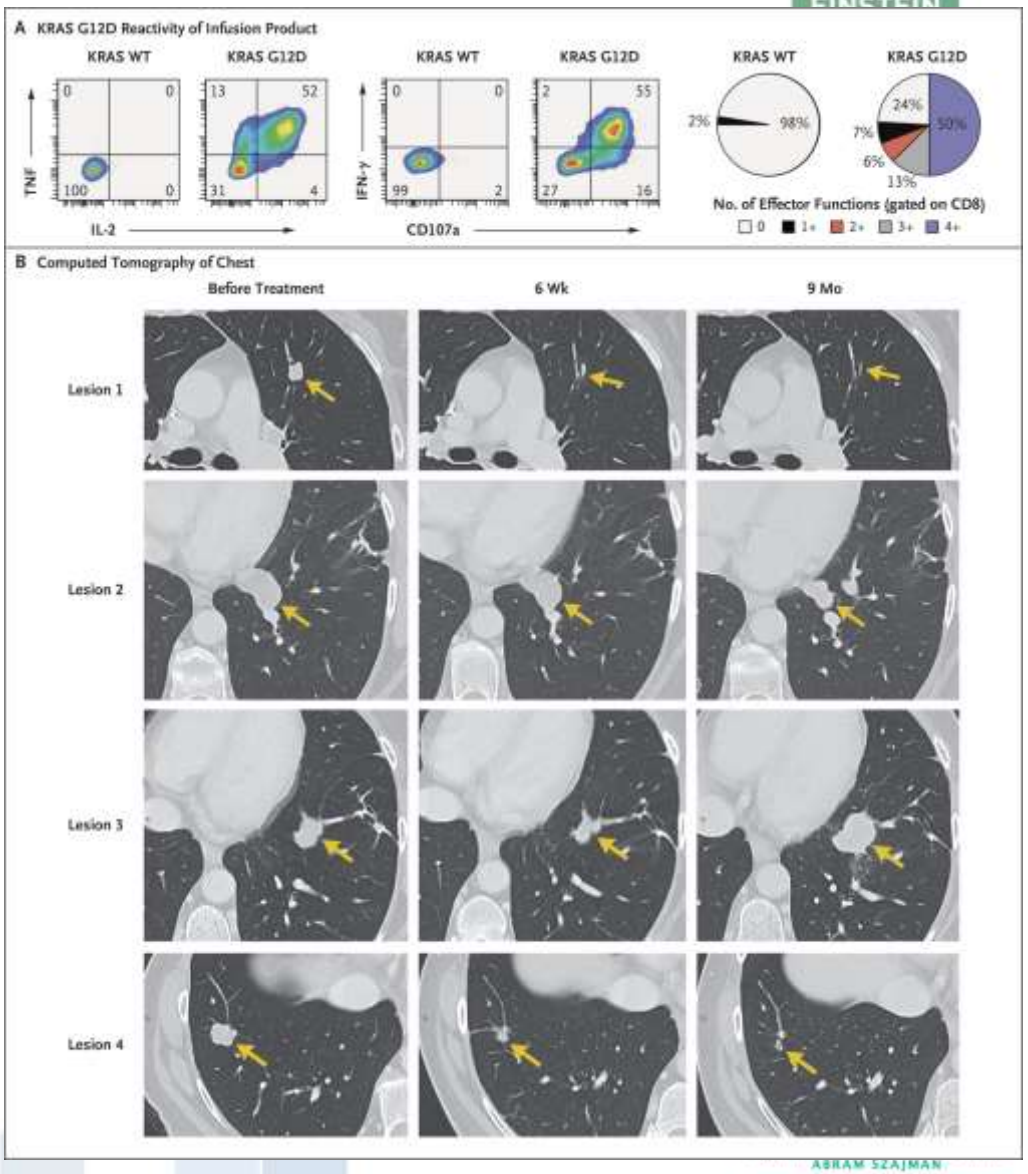
Chandran SS, Somerville RPT, Yang JC, et al. Treatment of metastatic uveal melanoma with adoptive transfer of tumour-infiltrating lymphocytes: a single-centre, two-stage, single-arm, phase 2 study. Lancet Oncol. 2017;18(6):792-802

Antígenos reconhecidos por TILs

Mutation targeted; KRAS G12D
HLA restricting the response; HLA-C*08:02 allele

TIL reactive to a mutation that is shared between patients lead to clinical benefit

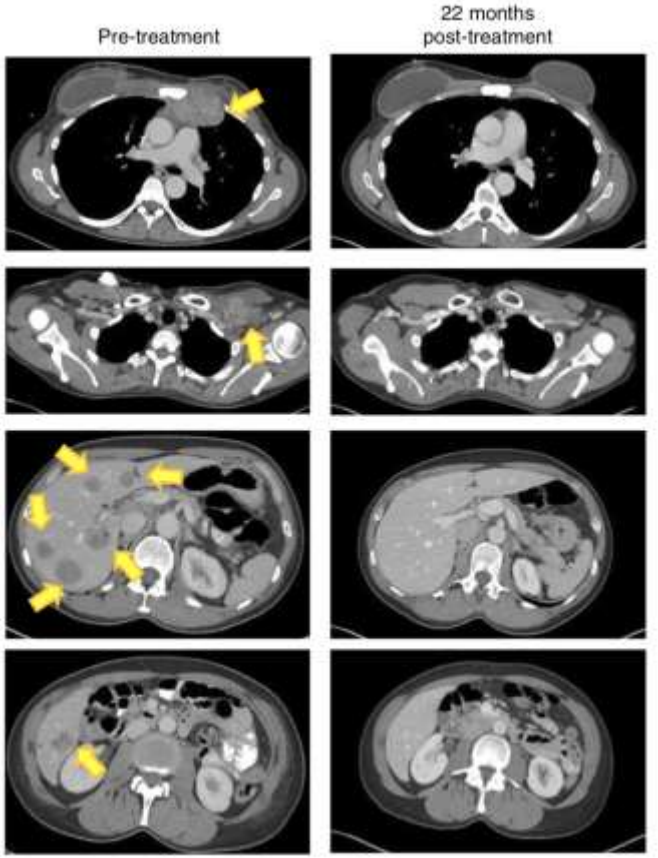
Adoptive Transfer of KRAS G12D–Specific TIL

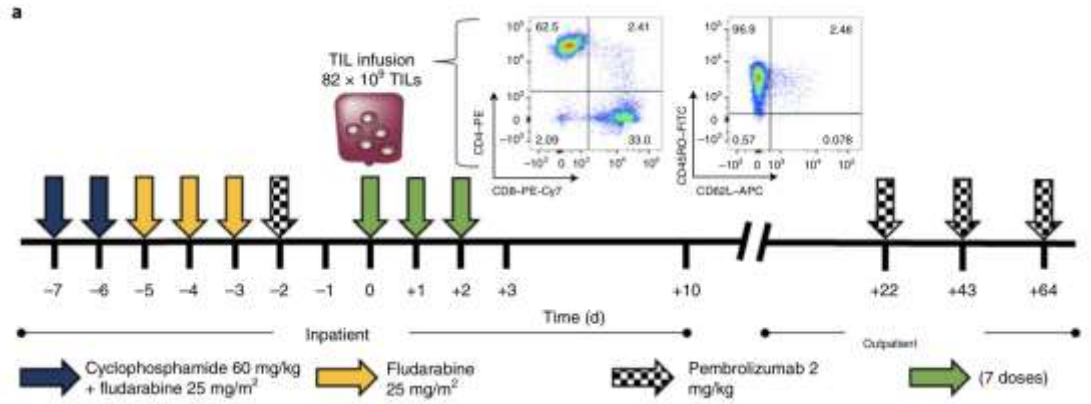


Tran E et al. N Engl J Med 2016;375:2255-2262

Antígenos reconhecidos por TILs

- Mulher, 48a, Ca de mama HR+, HER2-
- Quimiorefratária
- Recebeu TILs autólogas contra mutações:
  - **SLC3A2**
  - **KIAA0368**
  - **CADPS2**
  - **CTSB**
- + Pembrolizumab





Zacharakis et al. Nature Med, 2018

Mecanismos de resistência às terapias celulares

Maximal impact on therapies targeting only one antigen such as **TCR-transduced** T cells and **CAR-T** cells	**Tumor Heterogeneity** Is the antigen targeted expressed by every tumor cell? **Antigen loss** Example; CD19 CAR-T: Characterization of CD19 status at the time of relapse showed that 1 patient had a CD19+ recurrence and 15 patients had CD19− (3 with concomitant CD19+ blasts); 6 patients had unknown CD19 status.
Impacts all types of T-cell therapies	**HLA downregulation** Any loss or downmodulation of the antigen processing and presentation machinery will lead to a deficient recognition by T cells Example; Specific loss of HLA-C*08:02 allele after infusion of KRAS G12D specific, HLA-C*08:02-restricted TIL **Upregulation of immunosuppressive factors such as PD-L1**

TIL, TCR ou CAR-T: Qual a melhor opção?

	TIL	TCR-transduced T cell	CAR-T
Tissue required	tumor	blood	blood
Manufacturing time	4-7 weeks	2 weeks	10 days
Number of tumor antigens targeted	multiple	1	1
Targets selected tumor antigens	No	Yes	Yes
Antigen receptor affinity	moderate	selected to be high	ultra high
Targetable antigens	cell surface and intracellular	cell surface and intracellular	cell surface only
Number of cells infused	up to $150x10^{9}$ - very high	Moderate	Low
Demonstrated effectiveness in solid tumors	Yes	Yes	No
T-cell infusion related deaths	No	Yes	Yes

TIL, TCR ou CAR-T: Qual a melhor opção?

- Para Linfomas/Leucemias CD19+: CAR T
- Para mieloma múltiplo: BCMA CAR-T cells

- Para melanoma: TIL

- Para os demais; the jury is still out. Evidências de segurança e eficácia de TILs em diversos tumores sólidos, mas poucos pacientes. TCR em situações restritas (NY-ESO-1)

Take home message

- Terapia celular pode levar à respostas profundas e duradouras em população refratária a tratamentos convencionais
- Comercialização é viável
- Melhor compreensão de antígenos e mecanismos de resistência são necessários