



# Tumor-Infiltrating Lymphocytes (TIL) em Melanoma

**Dr. Gustavo Schvartsman**

Oncologista Clínico

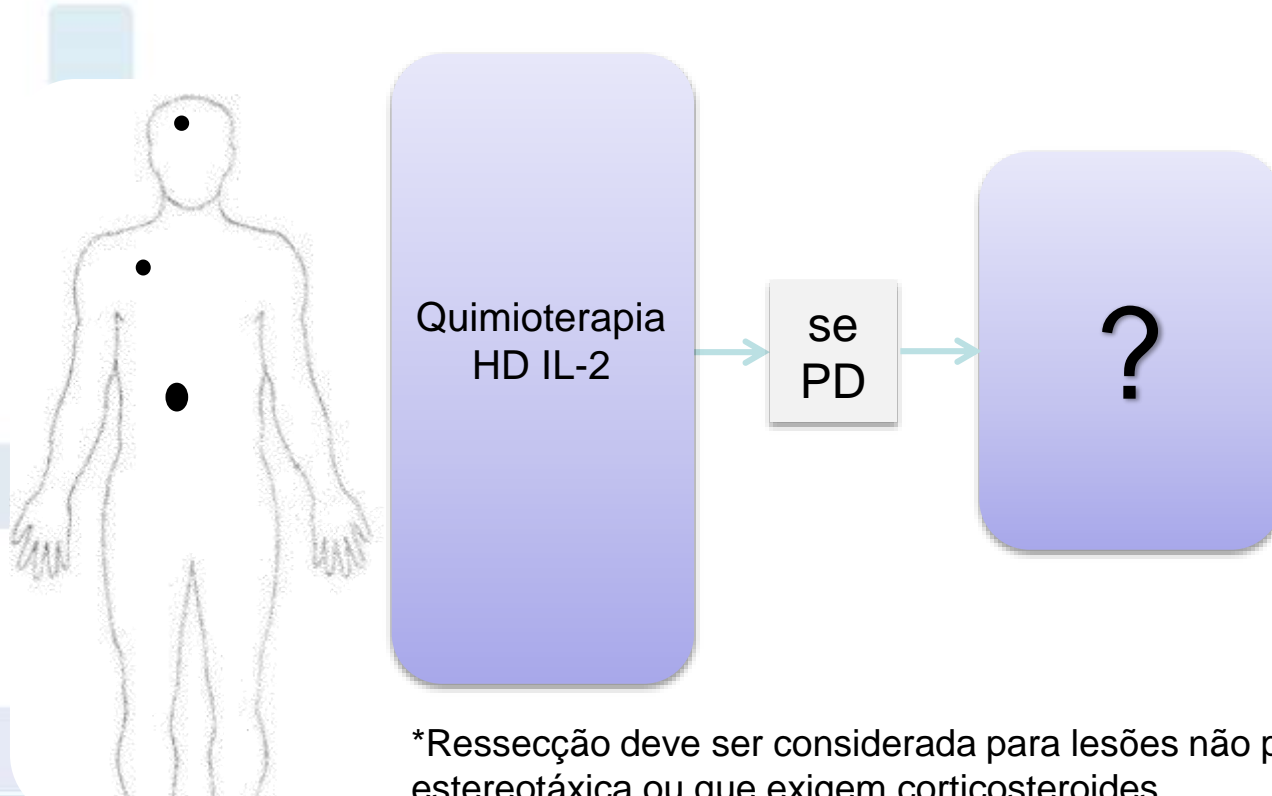
Hospital Israelita Albert Einstein

# Conflitos de Interesse



- Speaker/Consultoria: BMS, Amgen, MSD, Roche, Novartis, Sanofi
- Travel Support: MSD, BMS
- Research Funding: BMS

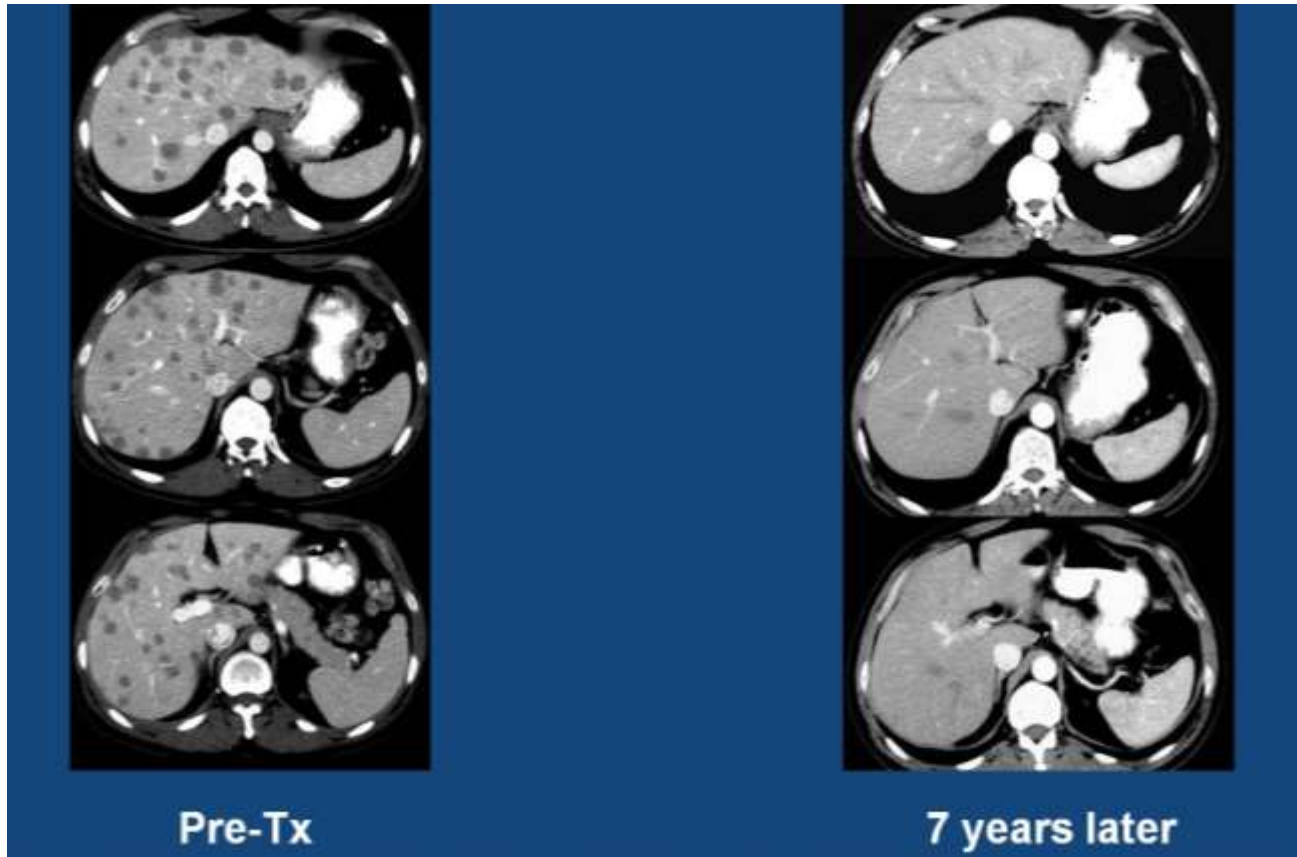
# Algoritmo de Tratamento de melanoma: Até 2012



\*Ressecção deve ser considerada para lesões não passíveis de radiocirurgia estereotáxica ou que exigem corticosteroides

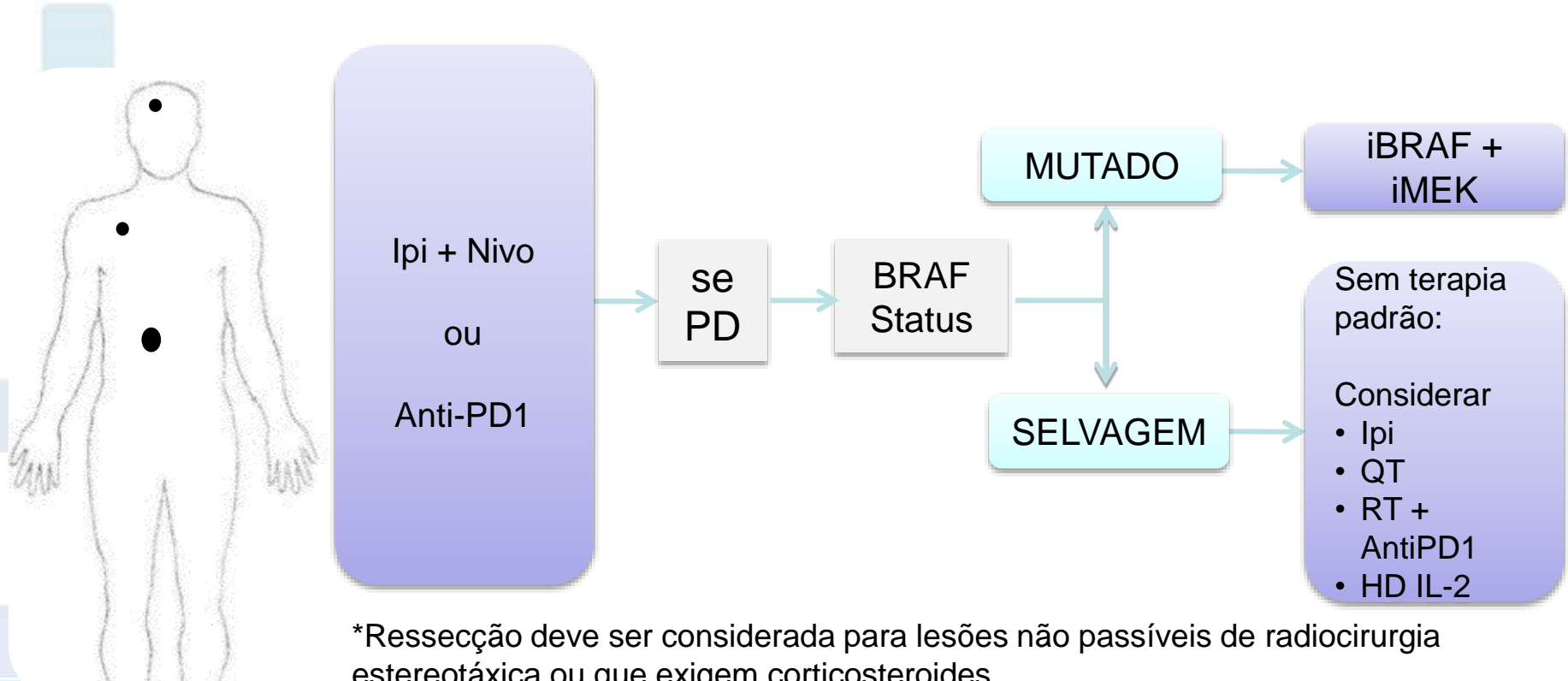
\*\*Ipi+antiPD1 representa também um sólida opção, se disponível

# Algoritmo de Tratamento de melanoma: Até 2012



- Presented by Stephanie Goff, ASCO Annual Meeting 2018

# Algoritmo de Tratamento de melanoma: A partir de 2018



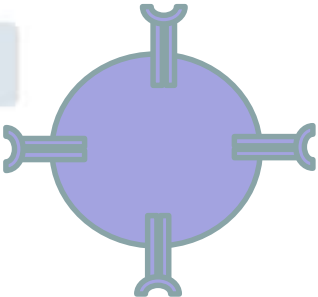
\*Ressecção deve ser considerada para lesões não passíveis de radiocirurgia estereotáxica ou que exigem corticosteroides

\*\*Ipi+antiPD1 representa também um sólida opção, se disponível

# Adoptive T-cell therapy to treat cancer

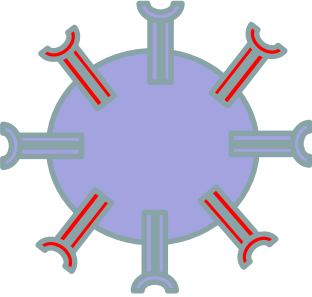


Endogenous T cell



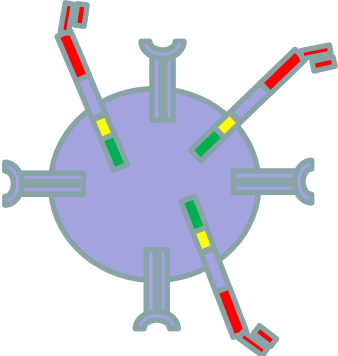
Endogenous TCR

TCR-transduced T cell



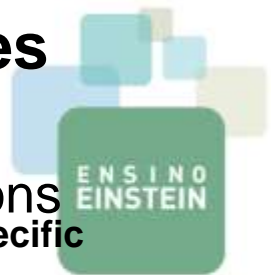
Transduced TCR

CAR T cell

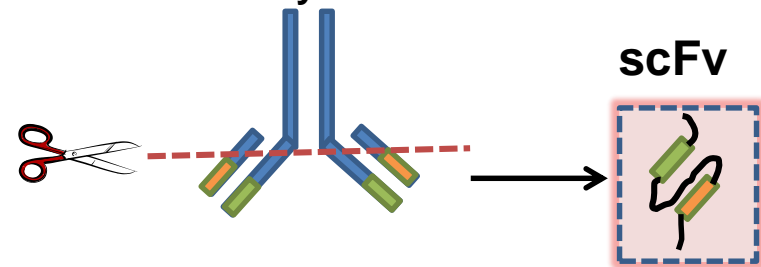


CAR

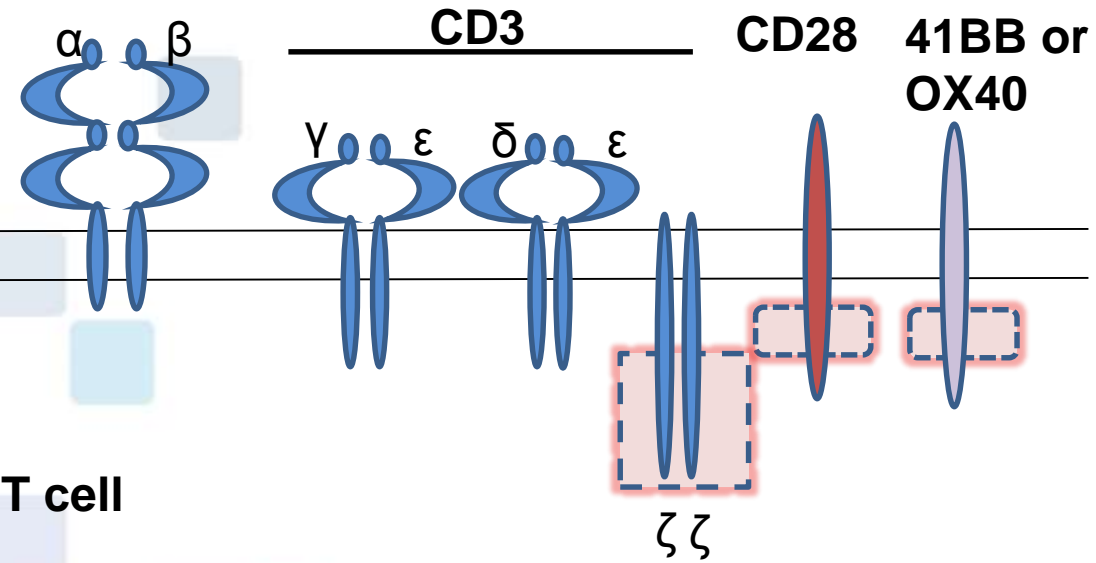
# TCR and chimeric antigen receptor (CAR) structures



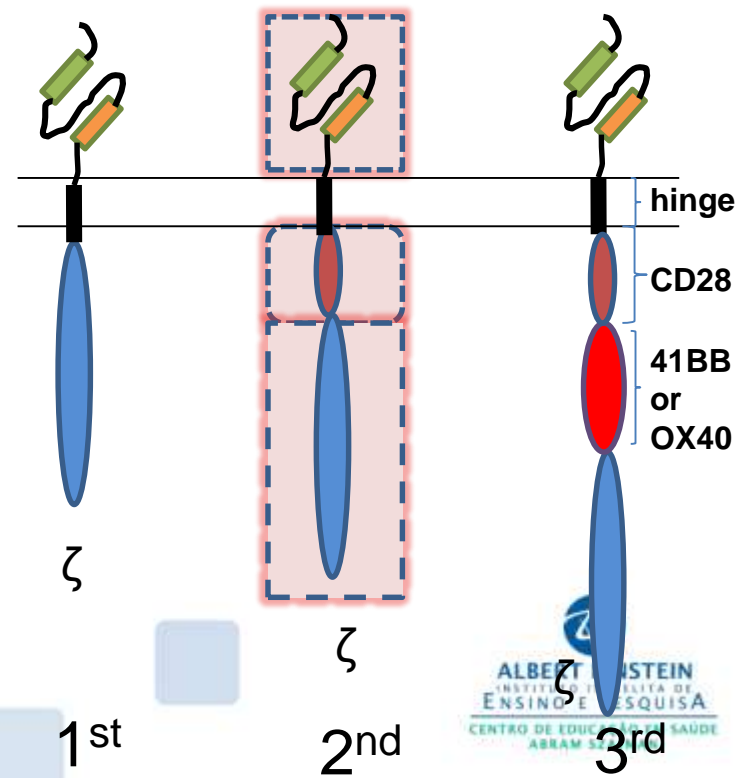
**CAR generations**  
Tumor antigen specific  
Antibody



## Classical TCR



T cell



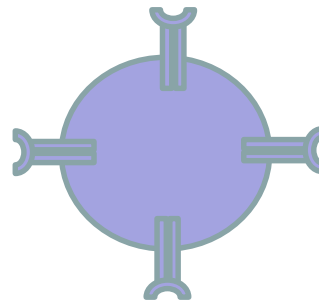
1<sup>st</sup>

2<sup>nd</sup>

3<sup>rd</sup>

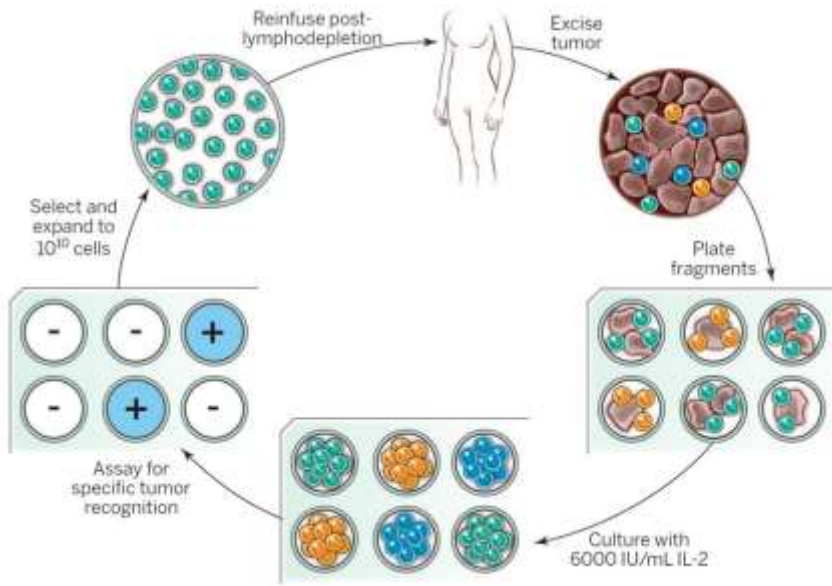


# TERAPIA COM TIL





# Tumor Infiltrating Lymphocytes

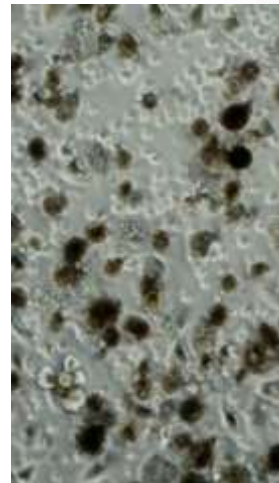


*Rosenberg, S. Science, 2015*

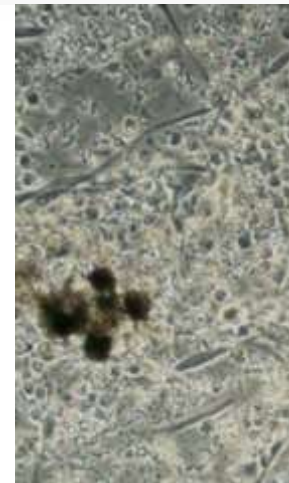
## Personalized Immunotherapy



**Steven A. Rosenberg**  
National Cancer Institute, NIH



Fresh digest



One week










Two weeks

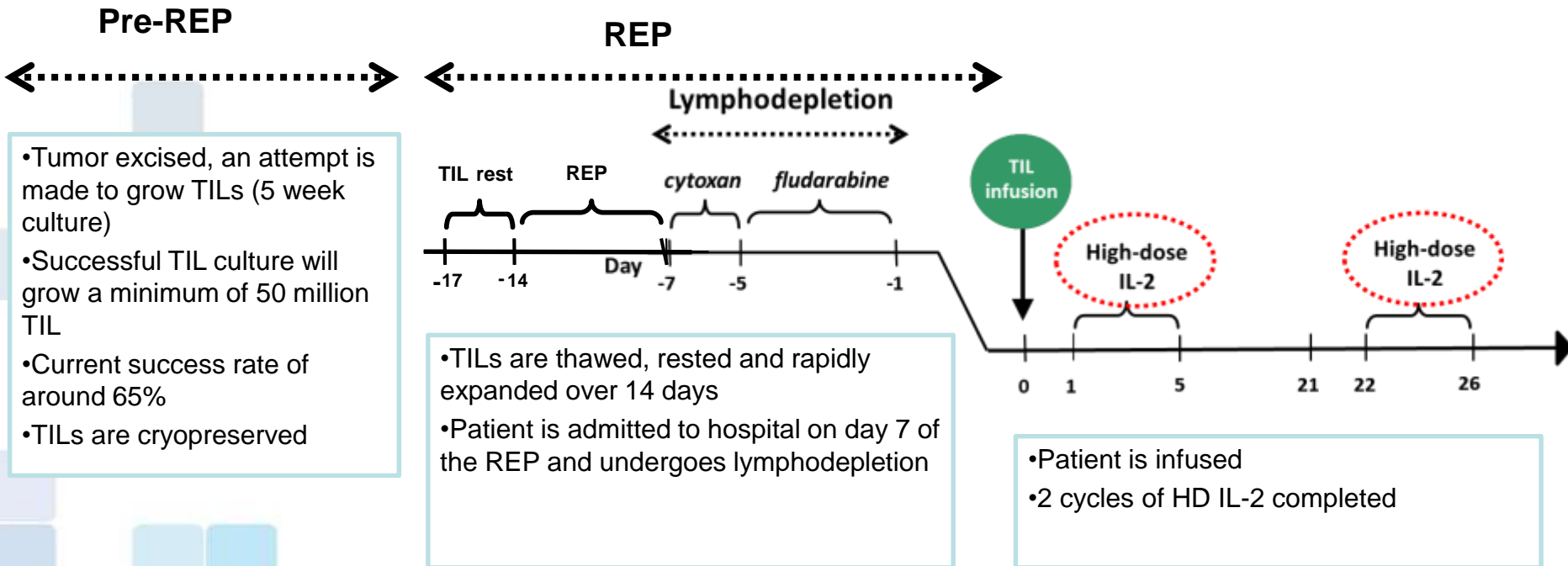
*Rosenberg, S. 1985*

# Tumor Infiltrating Lymphocytes

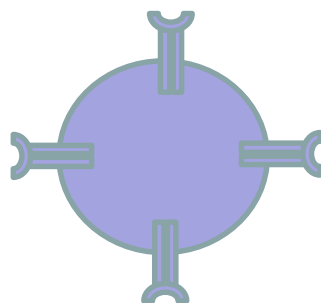


-  Utiliza células T endógenas encontradas em tumores sólidos, no contexto do paciente
-  Se beneficia de um microambiente tumoral rico em TILs
-  Seleção tímica – menos células auto-reativas
-  Múltiplos antígenos
-  TILs tendem a expressar altos níveis de checkpoints, como PD-L1 (inibição em conjunto?)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

# Preparo e Tratamento com TILs

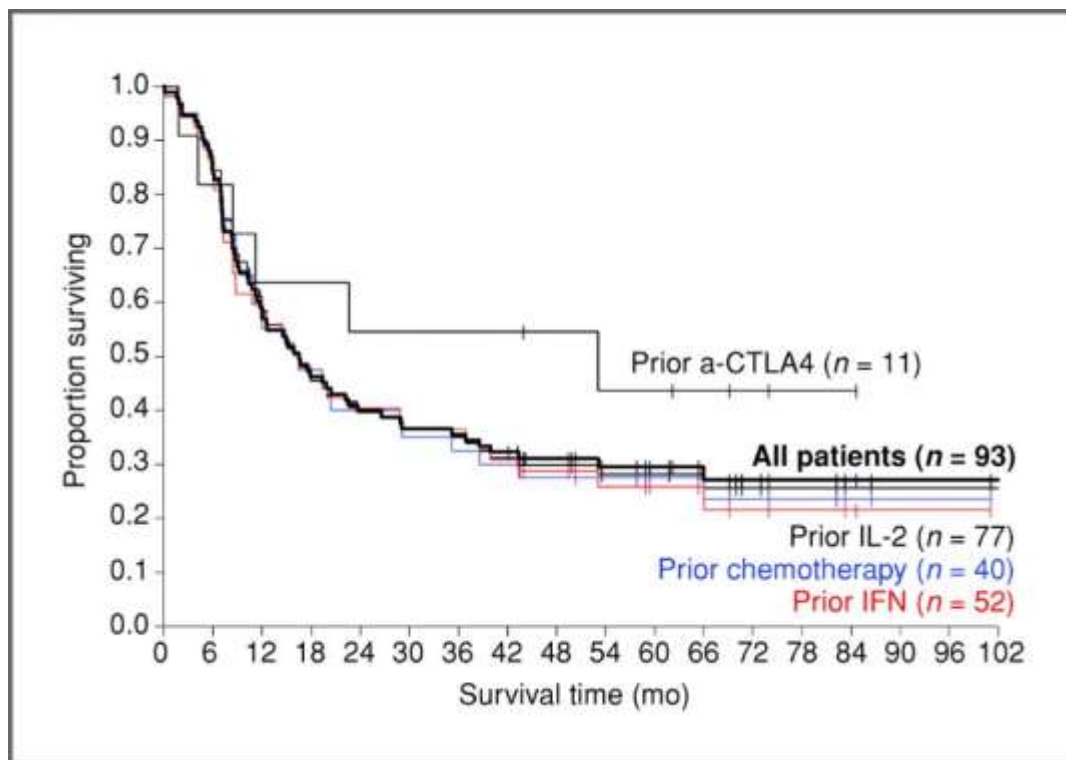


# TERAPIA COM TIL



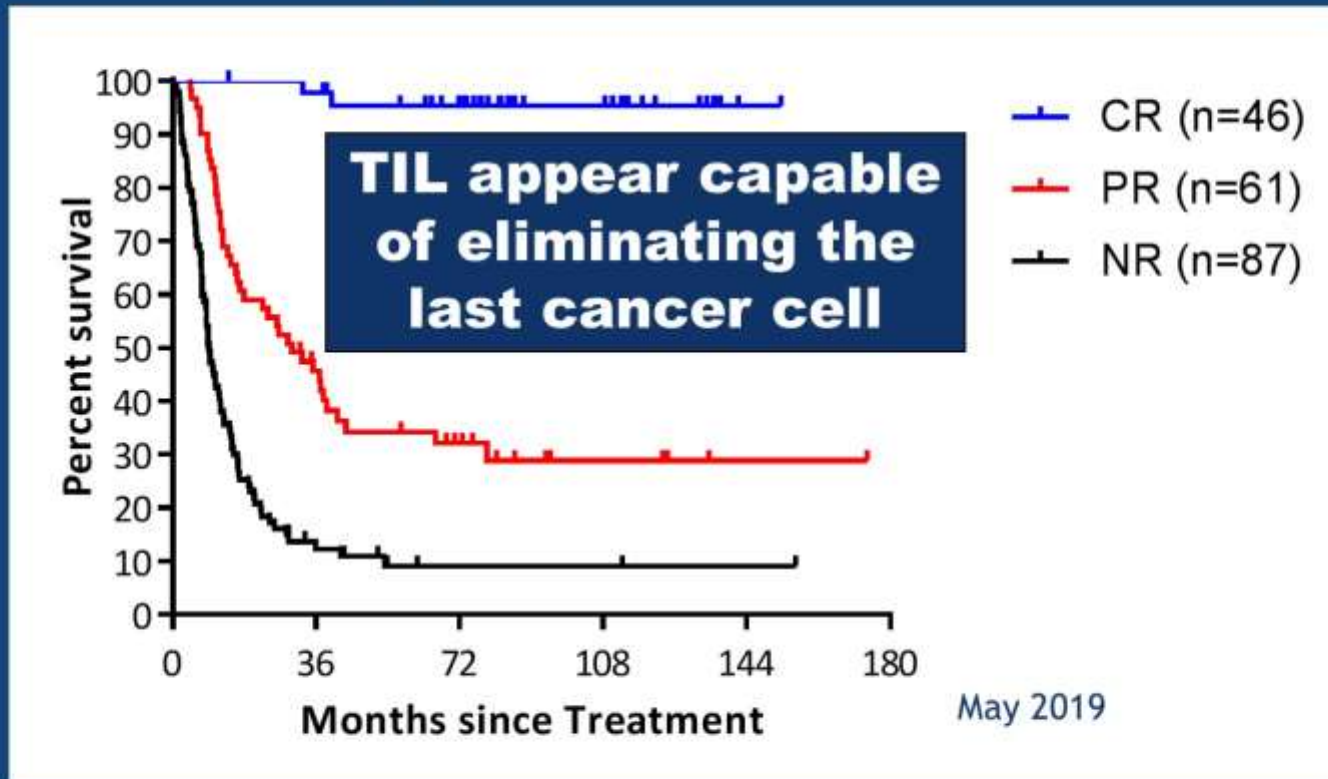
## RESULTADOS CLÍNICOS

# Resposta a TILs em melanoma metastático



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

# Melanoma-specific survival after ACT-TIL



NATIONAL  
CANCER  
INSTITUTE

PRESENTED AT:

2019 ASCO  
ANNUAL MEETING

#ASCO19

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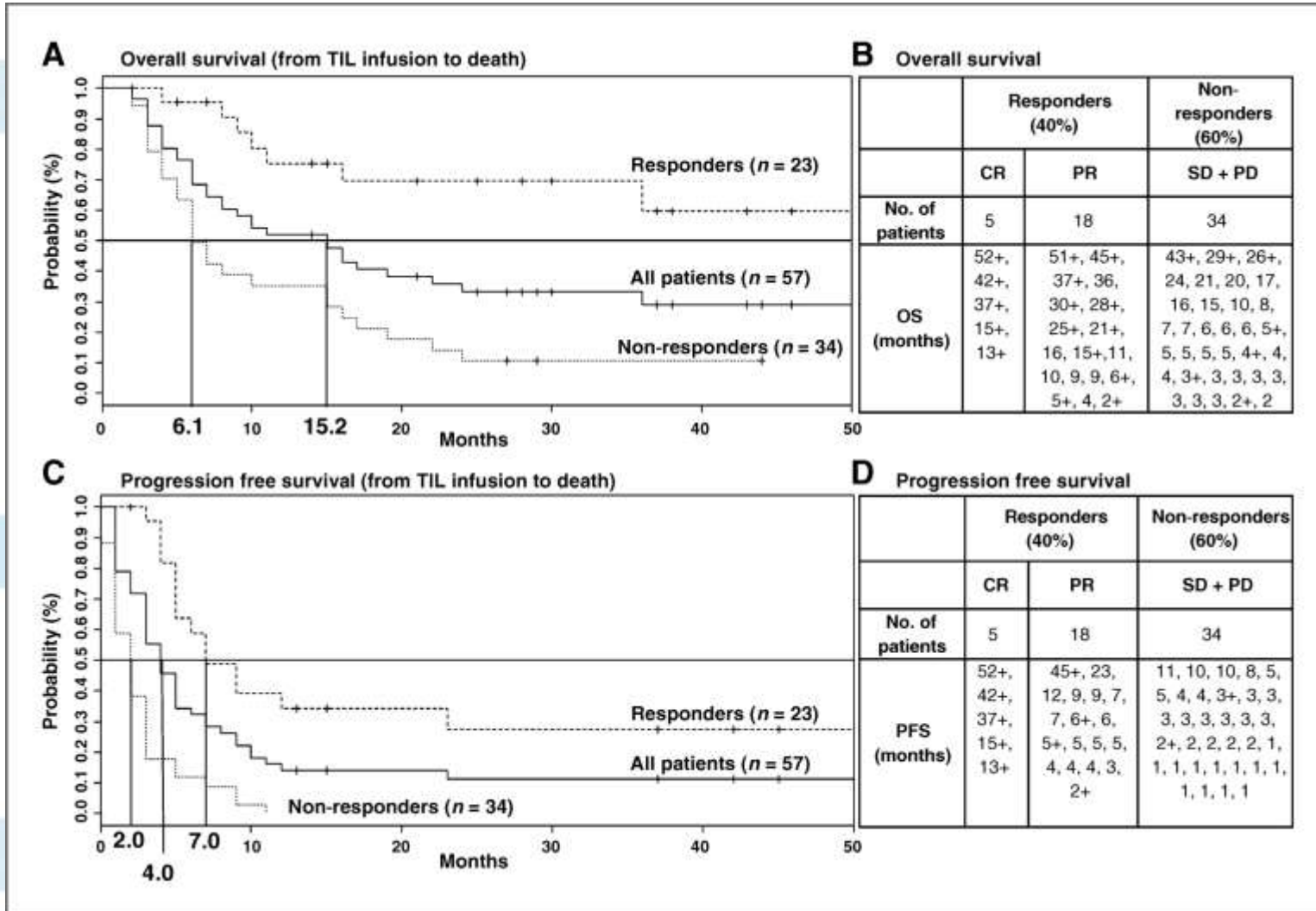
PRESENTED BY: Stephanie L. Goff, MD, FACS



# Resposta a TILs em melanoma metastático

Sheba Medical Center

N=57

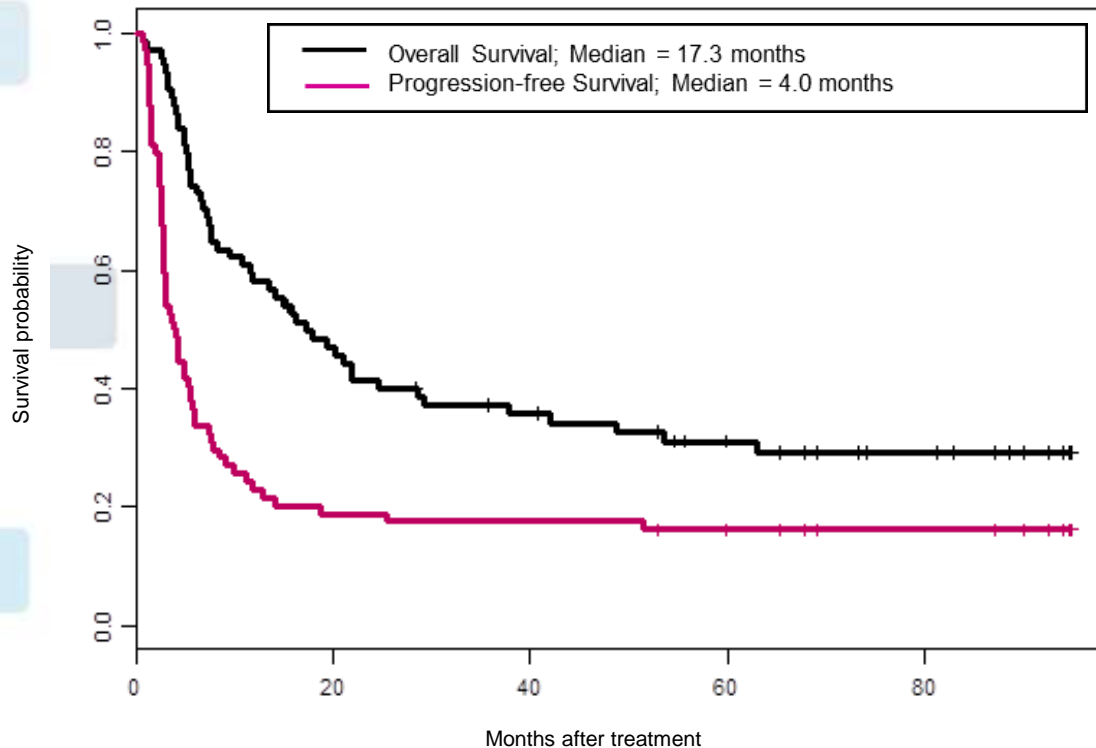


# Resposta a TILs em melanoma metastático



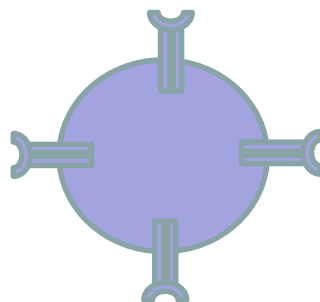
## MDACC

N=74





# TERAPIA COM TIL

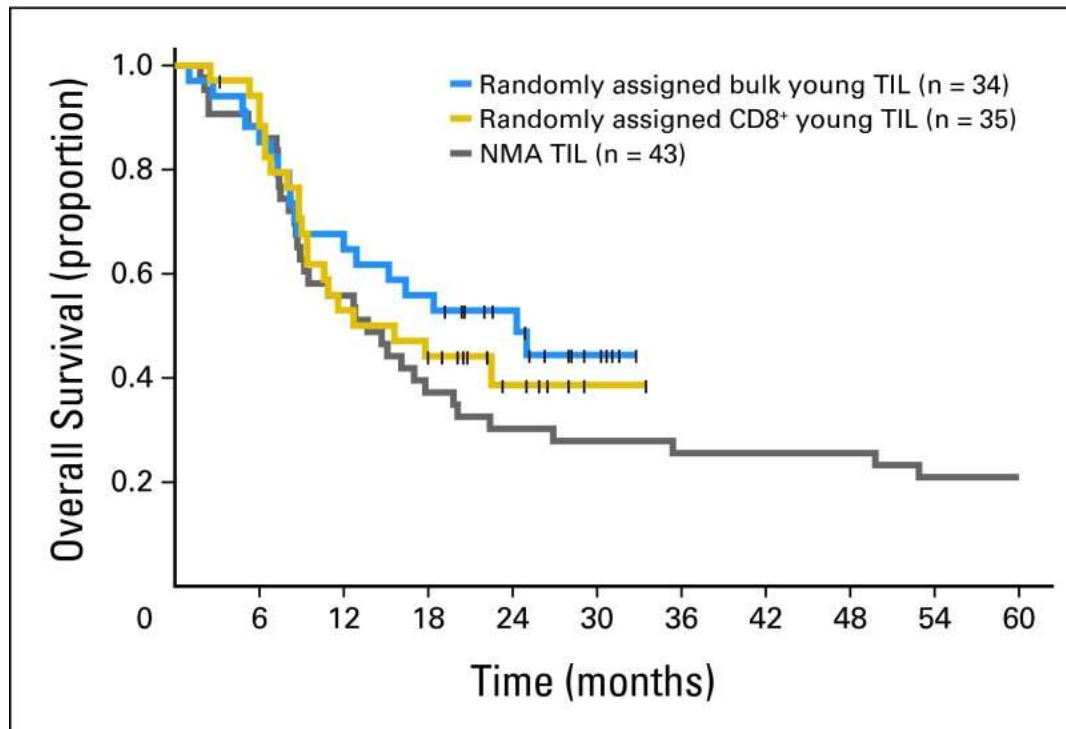


## COMO MELHORAR?

# Resposta a TILs em melanoma metastático



Selecionar por células CD8+?

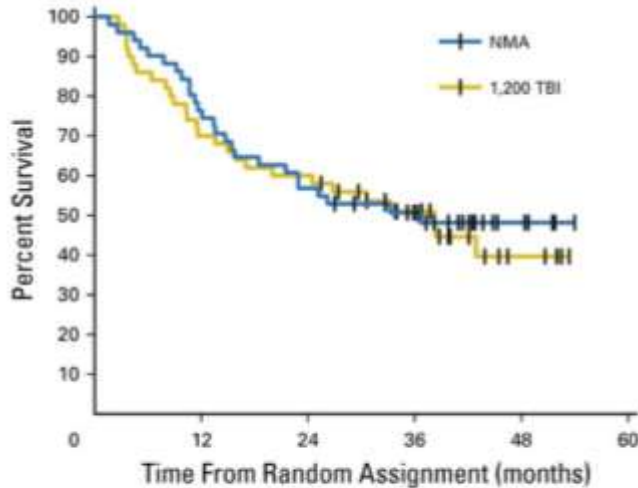


Dudley et al. J Clin Oncol, 2013

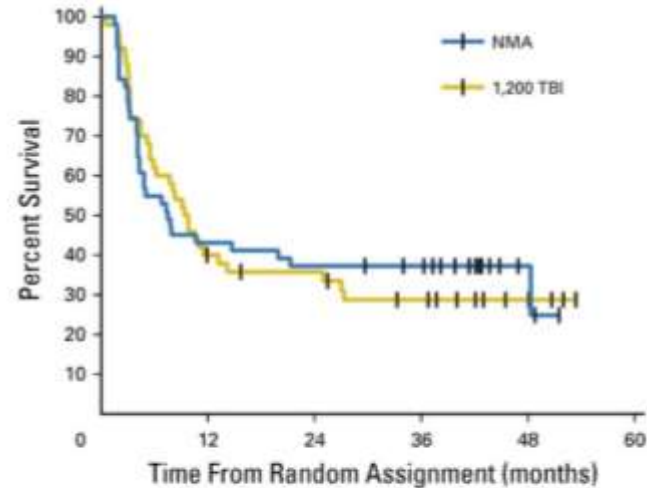
# Resposta a TILs em melanoma metastático



Intensificar linfodepleção?



No. at risk	0	12	24	36	48	60
NMA	51	39	30	21	6	0
1,200 TBI	50	35	30	18	4	0

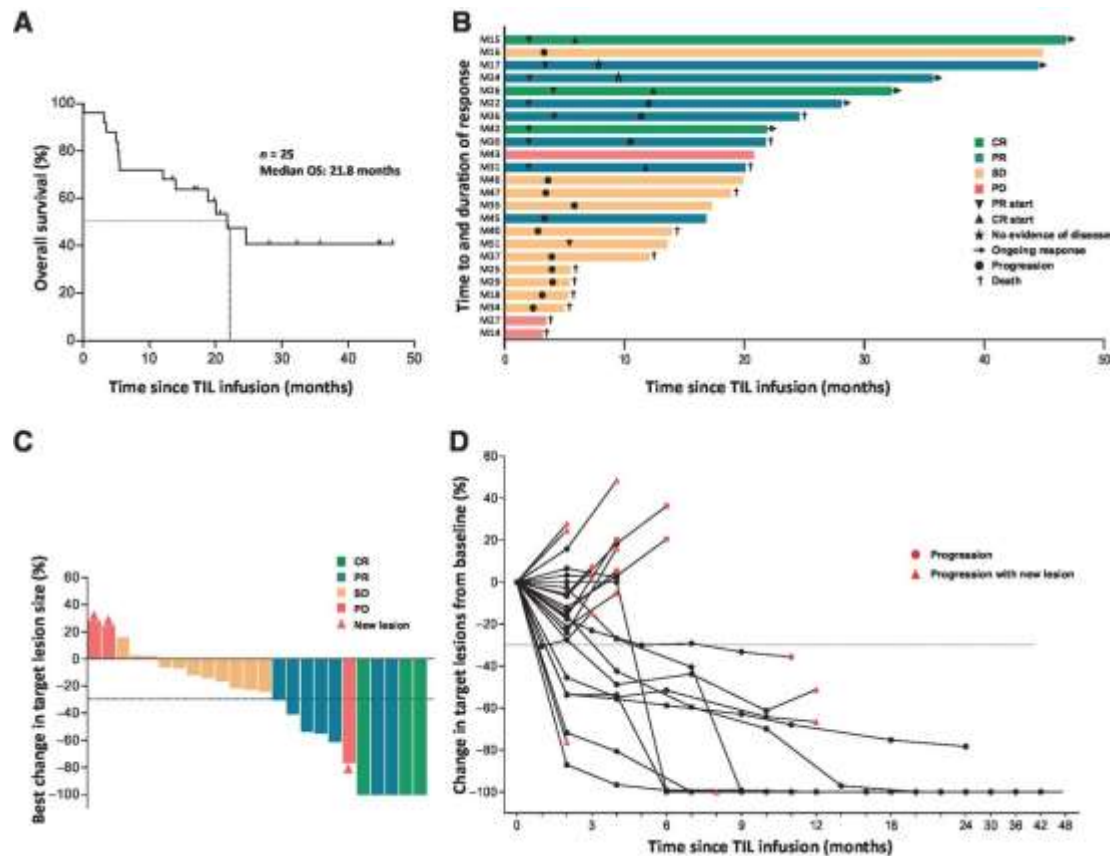


No. at risk	0	12	24	36	48	60
NMA	51	22	19	17	3	0
1,200 TBI	50	18	16	10	4	0

**NCI**  
N=101

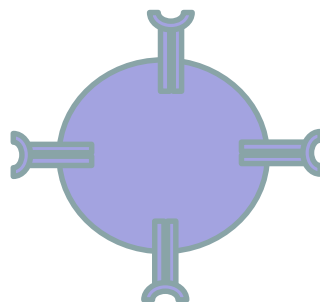
# Resposta a TILs em melanoma metastático

Atenuar a dose de IL-2?



Andersen et al. Clin Cancer Res, 2016

# TERAPIA COM TIL



## PÓS ANTI-PD-1

# Resposta a TILs em melanoma metastático

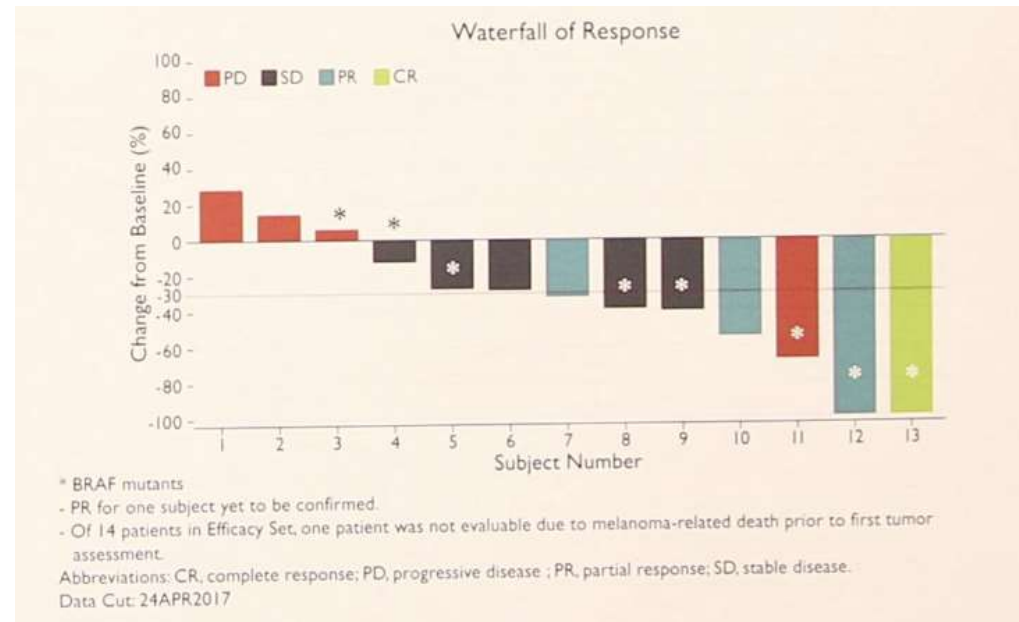


Laboratório central para protocolo multicêntrico:

- 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

# Estudos com TILs + anti-PD-1 em melanoma metastático

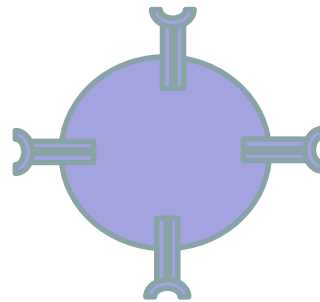


**A Prospective Randomized and Phase 2 Trial for Metastatic Melanoma Using Adoptive Cell Therapy With Tumor Infiltrating Lymphocytes Plus IL-2 Either Alone or Following the Administration of Pembrolizumab**

**TIL and Anti-PD1 in Metastatic Melanoma (ACTME)**

**Combined Therapy of Nivolumab and Adoptive T Cell Therapy in Metastatic Melanoma Patients (Nivo-TIL)**

# TERAPIA COM TIL



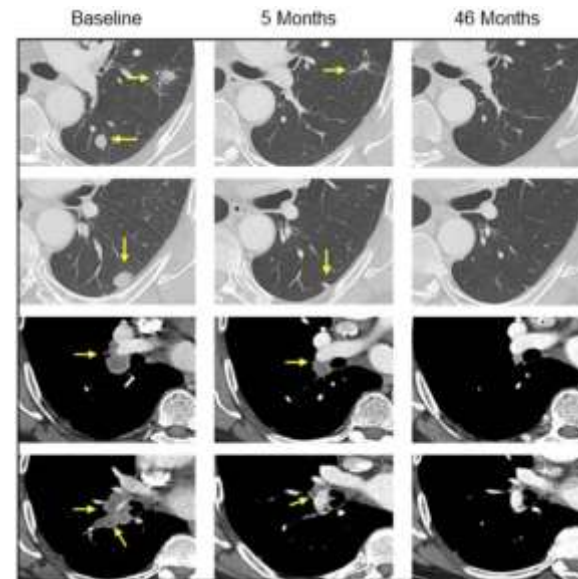
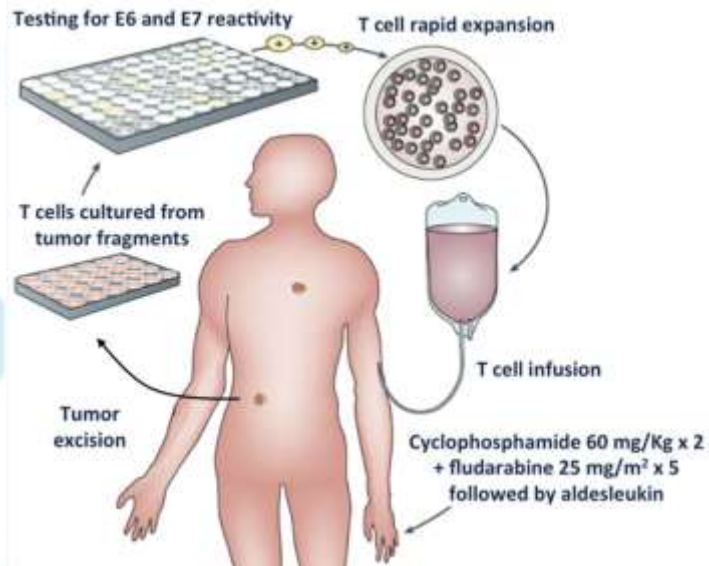
- OUTROS TUMORES
- TIL SELECIONADAS



# 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)



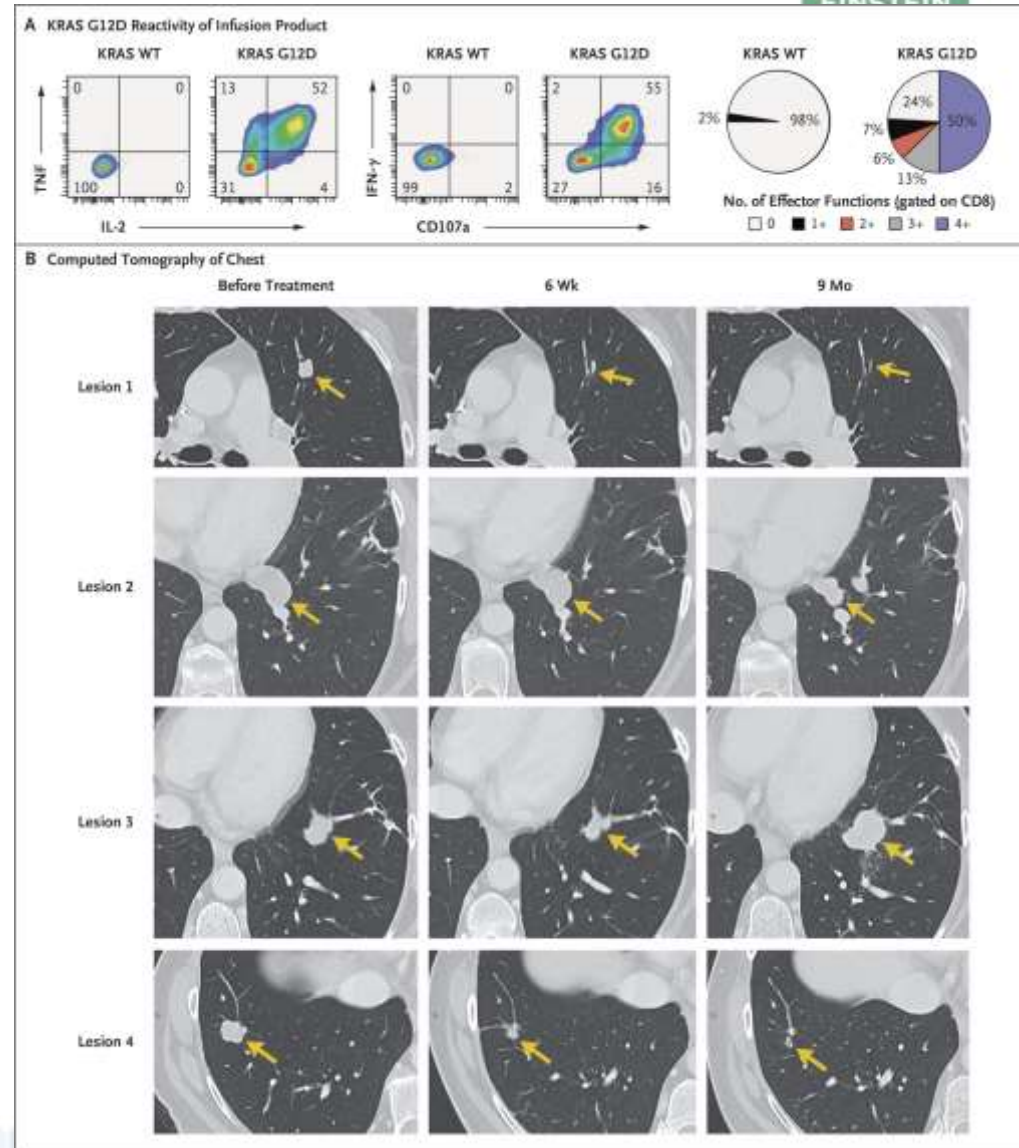
Stevanovic S, et al. Treatment of metastatic human papillomavirus-associated epithelial cancers with adoptive transfer of tumor-infiltrating T cells. ASCO Annual Meeting, 2018

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



## Adoptive Transfer of KRAS G12D-Specific TIL

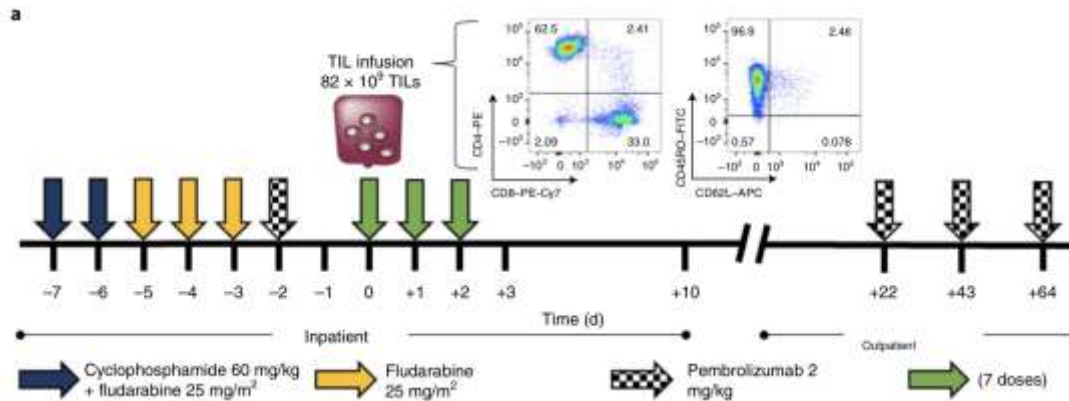
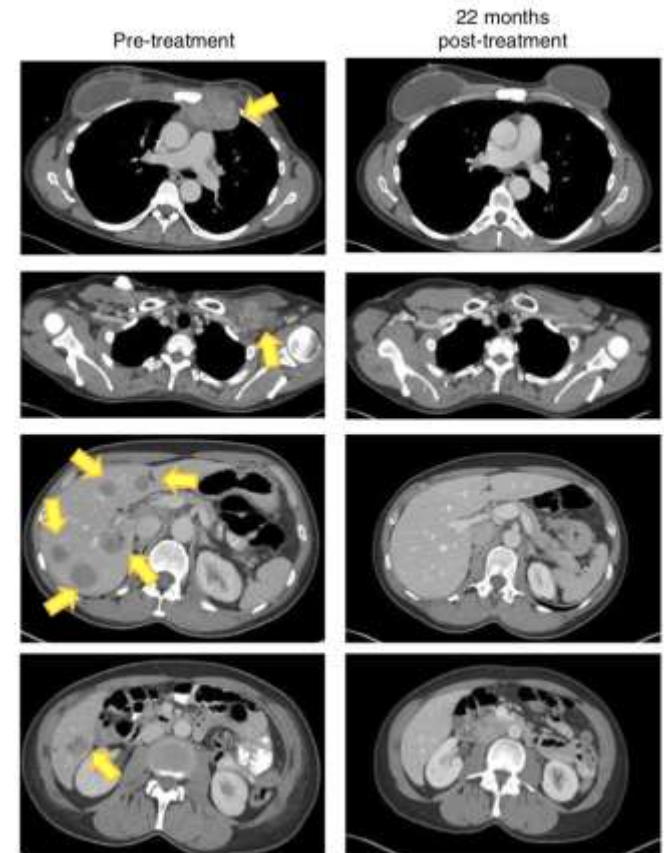


**Mutation targeted; KRAS G12D  
HLA restricting the response;  
HLA-C\*08:02 allele**

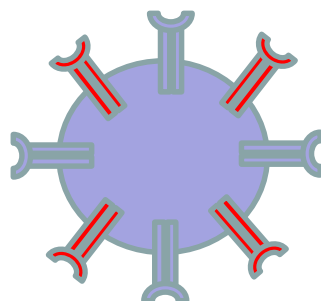
**TIL reactive to a mutation that  
is shared between patients  
lead to clinical benefit**

# Antígenos reconhecidos por TILs

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



# TERAPIA COM TCR ENGENDRADO

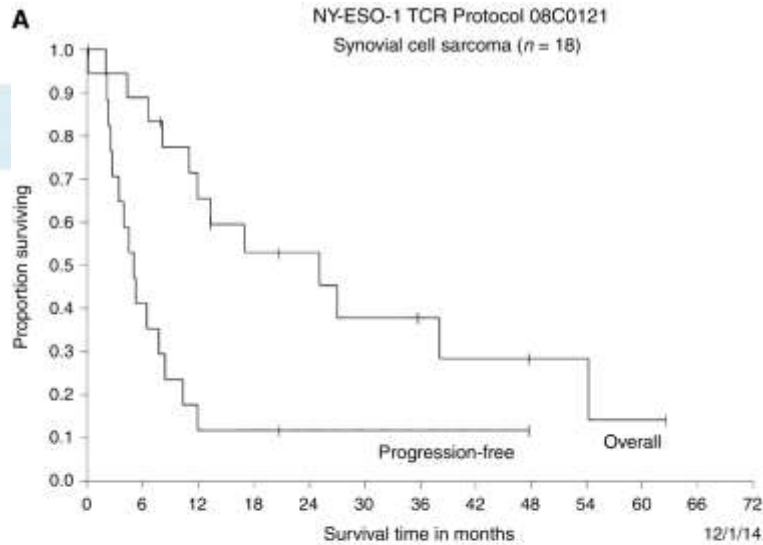


**NY-ESO-1**

# TCR-transduced T cells: NY-ESO-1

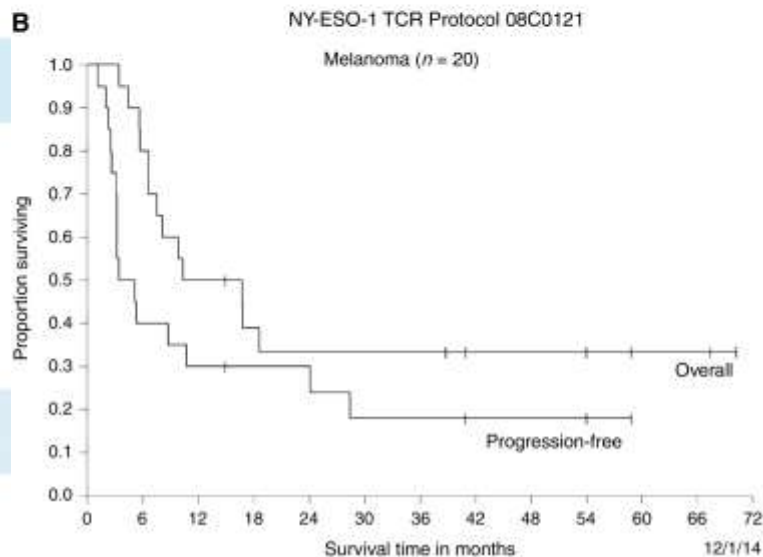


## Kaplan–Meier curve of overall survival and progression-free survival.



objective clinical responses were observed in:

- 11/18 patients with NY-ESO-1+ synovial cell sarcomas (61%)
- 11 of 20 patients with NY-ESO-1+ melanomas (55%)



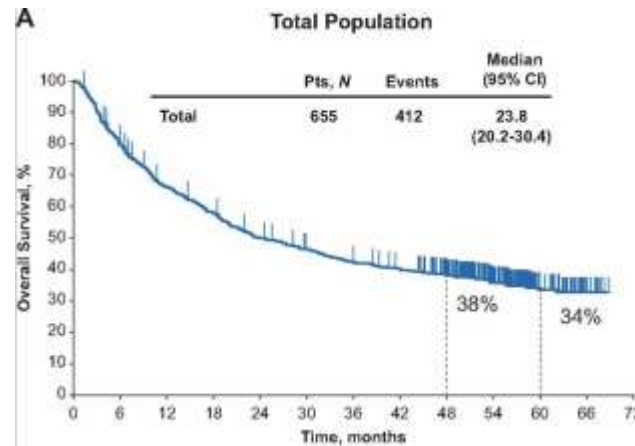


# Conclusões



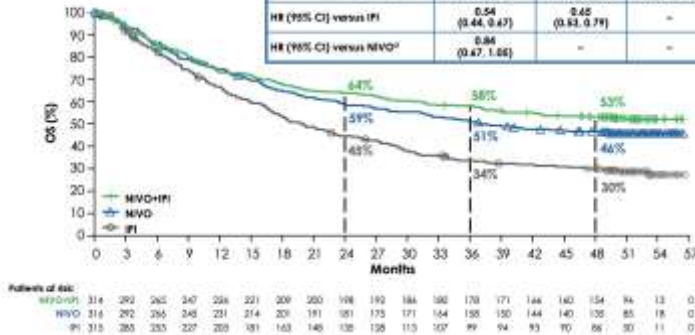
- Terapia de resgate efetiva mesmo após falha de tratamentos anteriores
- Tratamento de primeira linha?

CheckMate-067  
ESMO 2018  
Overall Survival

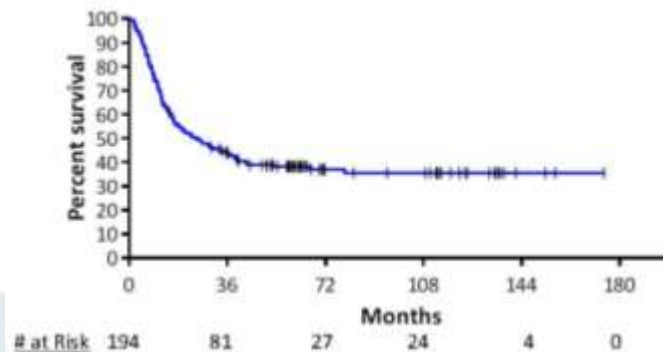


KN-001  
Ann Oncol, 2019

	NIVO+IFI (n=314)	NIVO (n=314)	IFI (n=314)
Median OS, mo [95% CI]	19.9 (18.2, NR)	24.9 (23.3, NR)	19.7 (14.9, 24.4)
HR (95% CI) versus IFI	0.54 (0.44, 0.67)	0.62 (0.53, 0.71)	-
HR (95% CI) versus NIVO <sup>2</sup>	0.84 (0.47, 1.66)	-	-



Overall Survival (TIL)



Rosenberg, 2017  
(unpublished)

# Conclusões



- 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