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Society for Immunotherapy of Cancer

Adoptive Therapy Utilizing TILs

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Amsterdam

My disclosures

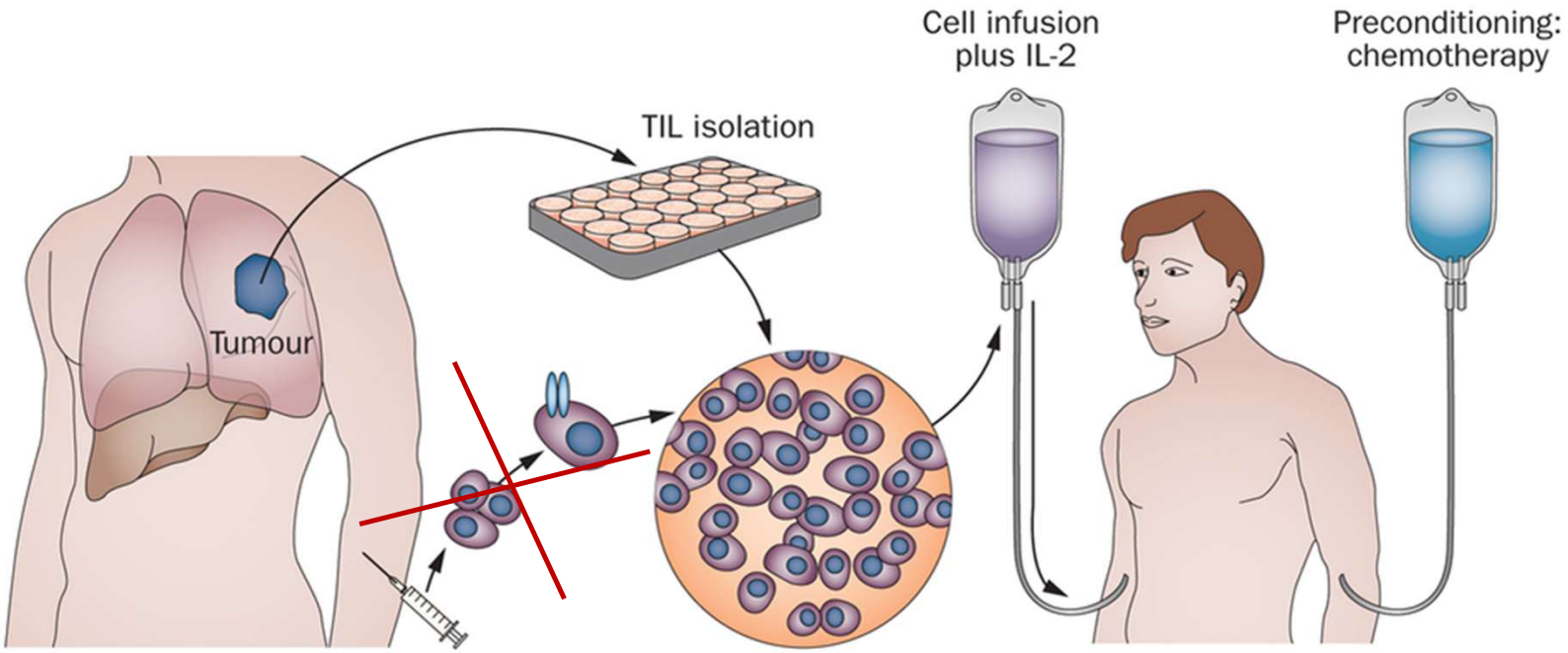
- I have provided consultation, attended advisory boards, and/or provided lectures for: **AIMM, Amgen, BioNTech, BMS, GSK, Ipsen, Merck Serono, Molecular Partners, MSD, Novartis, Pfizer, Roche/Genentech, Sanofi, Seattle Genetics, Third Rock ventures**
- I am on the **SAB** of **AIMM, BioNTech US, Gadeta, Immunocore, T-Knife and Neogene Therapeutics.**
- I have stock options in **Neogene Therapeutics**
- Through my work NKI received grant support from **Amgen**, **BioNTech US, BMS, MSD, Novartis**
- I am Editor-in-Chief of **ESMO IOTECH**

Development of TIL therapy

- Based on preclinical work in the late 80-ies showing that tumors consist not only of tumor cells but also of immune infiltrates by the Rosenberg lab at NCI
- Data showing that in melanoma, T cells residing in the tumor often have anti-melanoma reactivity
- Discovery that tumor antigens, belonging to melanocyte differentiation antigens, cancer/testis antigens and mutated antigens can be recognized by T cells coming from TIL
- Observation that lymphodepletion either by non-myeloablative chemotherapy (NMA), total body irradiation (TBI) or the combination, improved outcome (both in preclinical models and melanoma patients)
- Data showing that the inhibited exhausted T cell state of TIL can be overcome by ex vivo exposure to IL-2
- Discovery that T cells specific for neoantigens appear to be the main drivers of the clinical responses of TIL therapy

Refs

ACT: Treatment with tumor-infiltrating lymphocytes



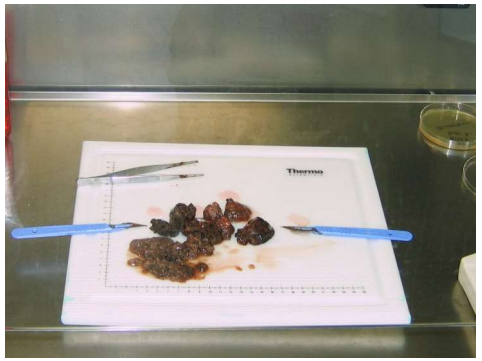
Rosenberg Nat Rev Clin Oncol., 2014

Cancer Regression and Autoimmunity in Patients After Clonal Repopulation with Antitumor Lymphocytes

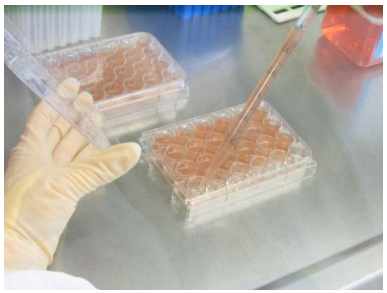
Mark E. Dudley,[1] John R. Wunderlich,[1] Paul F. Robbins,[1] James C. Yang,[1] Patrick Hwu,[1] Douglas J. Schwartzentruber,[1] Suzanne L. Topalian,[1] Richard Sherry,[1] Nicholas P. Restifo,[1] Amy M. Hubicki,[1] Michael R. Robinson,[2] Mark Raffeld,[3] Paul Duray,[3] Claudia A. Seipp,[1] Linda Rogers-Freezer,[1] Kathleen E. Morton,[1] Sharon A. Mavroukakis,[1] Donald E. White,[1] Steven A. Rosenberg[1]*

Dudley et al., Science 2002

Generation of TIL for melanoma patients at the NKI-BTU: tumor preparation



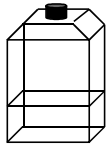


- Isolate tumor mass and mincing of tumor
- Generate single cell suspension by enzymatic digestion of tumor
- Set-up of max 2x24 well plates with tumor digest in 6000 IU/ml IL-2

Van den Berg et al. JiTC 2020

Expansion phase of TIL: start expansion in T175 flasks

Day 0



T175 x 20

TIL expansion : - non-specific stimulation (αCD3)
- 200-fold excess of allogenic irradiated PBMC
- high concentrations of IL-2

Starting number of TIL: $20x10^6$

- logistically challenging
- success rate 90%

Van den Berg et al. JiTC 2020

Harvest and infusion of TIL

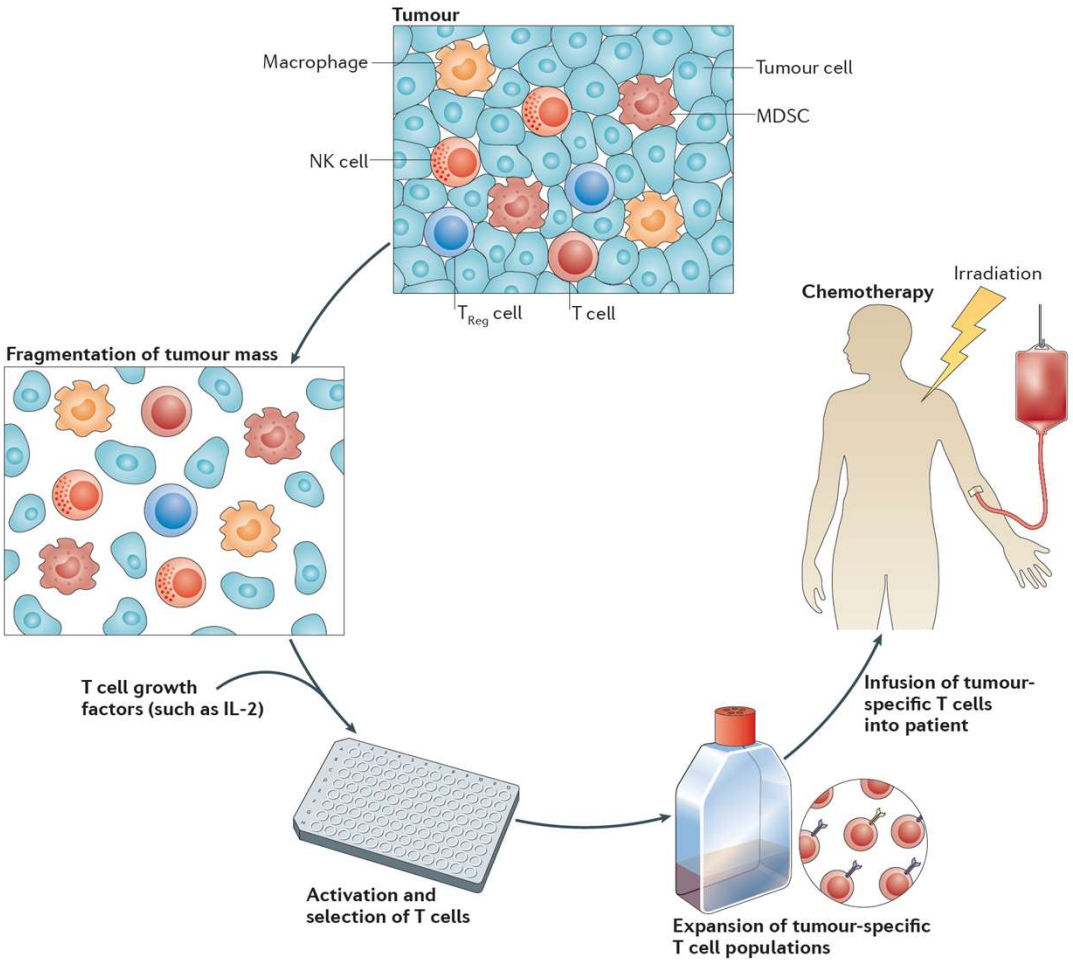
- Washing and preparing 200 ml infusion fluid with TIL

$1.2x10^{11}$ cells

Quality Controls (QC)	Specification
QC(1) Microbiological contamination	negative (day -2 before infusion)
QC(3) Total cell number	$>5x10^9$ TIL and $< 2x10^{11}$
QC(4) Viability	>70% living cells

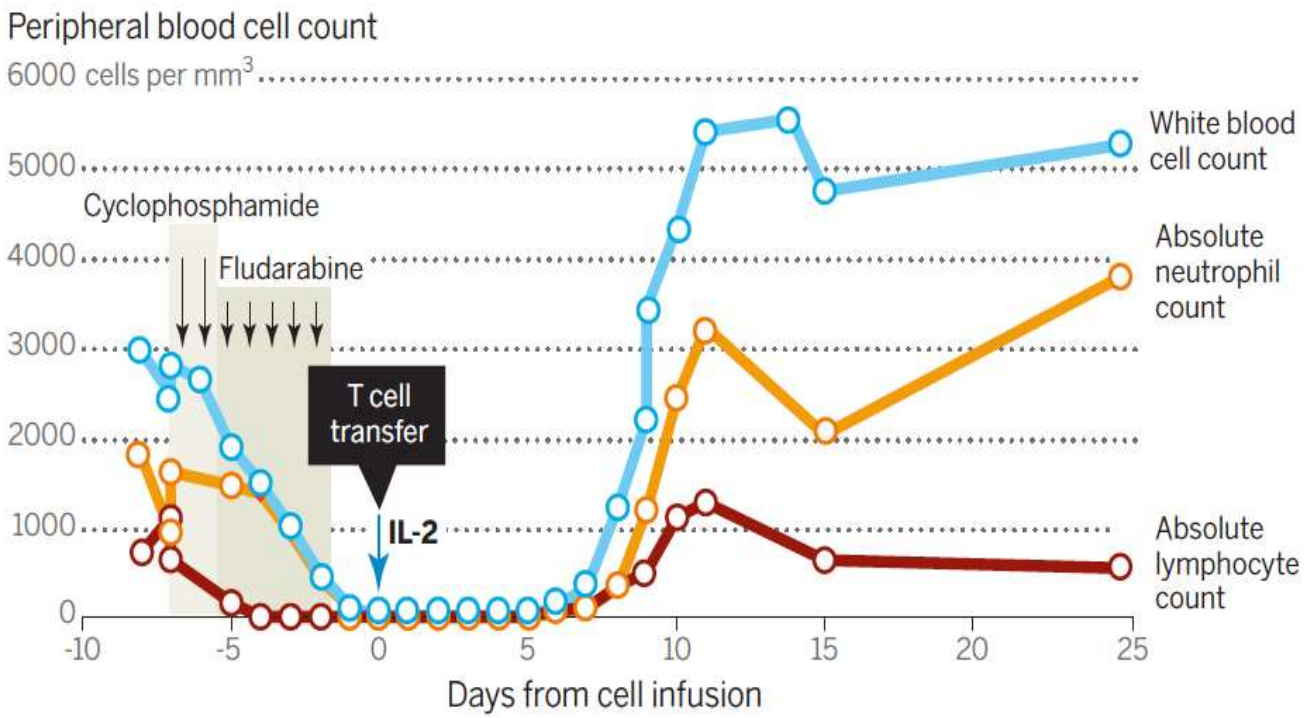
Van den Berg et al. JiTC 2020

Tumor infiltrating lymphocytes: TIL therapy



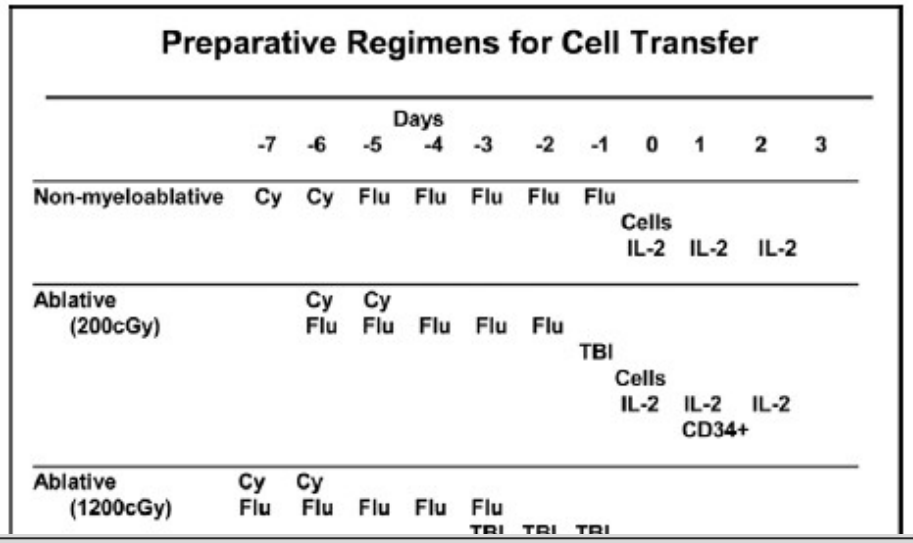
From: Restifo et al., Nat Rev Immunol 2012

Lymphodepletion prior to T cell transfer is followed by immune reconstitution



Rosenberg & Restifo Science 2015

Is increasing lymphodepletion resulting in improved ORR



Cell transfer therapy.[a]

Treatment	Total	PR	CR	OR (%)
No TBI	43	17 (77+, 45+, 34+, 29, 28, 14, 13, 11, 8, 8, 7, 4, 3, 3, 2, 2, 2)	3 (75+, 70+, 60+, 59+)	21 (49%)
200 cGy TBI	25	11 (45+.41+.35+.14 10, 6, 5, 5, 4, 3, 3)	2 (49+, 38+)	13 (52%)
1200 cGy TBI	25	11 (26+, 19+, 19+, 19+, 13, 7, 6, 6, 5, 4, 3)	7 (29+, 19, 25+, 25+, 19+, 19+, 18+)	18 (72%)

52 responding patients: 42 had prior IL-2, 21 had prior IL-2+ chemotherapy.

[a] All patients with metastatic melanoma received a preparative regimen of cyclophosphamide (60 mg/kg/day × 2d) and fludarabine (25 mg/m^2/day × 5d) either with no total body irradiation (TBI) or with 200 or 1200 cGy TBI followed by the administration of autologous TIL plus IL-2 (720,000 IU/kg q 8 h).

Rosenberg and Dudl

VOLUME 34 · NUMBER 20 · JULY 10, 2016

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Randomized, Prospective Evaluation Comparing Intensity of Lymphodepletion Before Adoptive Transfer of Tumor-Infiltrating Lymphocytes for Patients With Metastatic Melanoma

Stephanie L. Goff, Mark E. Dudley, Deborah E. Citrin, Robert P. Somerville, John R. Wunderlich, David N. Danforth, Daniel A. Zlott, James C. Yang, Richard M. Sherry, Udai S. Kammula, Christopher A. Klebanoff, Marybeth S. Hughes, Nicholas P. Restifo, Michelle M. Langhan, Thomas E. Shelton, Lily Lu, Mei Li M. Kwong, Sadia Ilyas, Nicholas D. Klemen, Eden C. Payabyab, Kathleen E. Morton, Mary Ann Toomey, Seth M. Steinberg, Donald E. White, and Steven A. Rosenberg

Goff et al., J Clin Oncol 2016

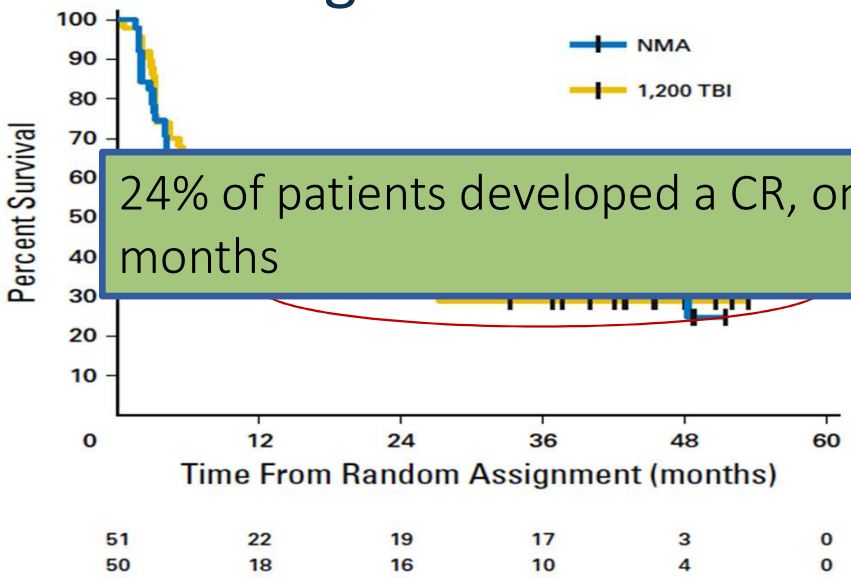
Patient characteristics

Characteristic	Treatment Arm		P
	NMA	1,200 TBI	
Patients	51	50	
Sex			.54
Female	17 (33)	20 (40)	
Male	34 (67)	30 (60)	
Age, years			
Median	45	47	.73
18-30	8 (16)	3 (6)	.19*
31-45	18 (35)	16 (32)	
46-60	22 (43)	29 (58)	
61-65	3 (6)	2 (4)	
HLA			.32
A2	19 (37)	24 (48)	
Non-A2	32 (63)	26 (52)	
Stage†			.63
M1a	3 (6)	6 (12)	
M1b	8 (16)	8 (16)	
M1c	40 (78)	36 (72)	
Prior systemic treatment			.44
None	14 (27)	12 (24)	
1 systemic therapy	22 (43)	19 (38)	
≥ 2 systemic therapies	15 (29)	19 (38)	
Immunotherapy			
High-dose IL-2	17 (33)	12 (24)	.38
Anti–CTLA-4 only	13 (26)	18 (36)	.29
Anti–PD-1 only	1 (2)	2 (4)	.62
Anti–CTLA-4 and anti–PD-1	6‡ (12)	2 (4)	.27
Adjuvant (IFN-α, vaccine, etc)	20 (39)	18 (36)	.84
Chemotherapy			
Dacarbazine or temozolomide	3 (6)	8 (16)	.12
BRAF and/or MEK inhibitor	4 (8)	5 (10)	.74
Other (including biochemotherapy)	5 (10)	5 (10)	1.0
Select baseline value, median (25th to 75th percentile)			
LDH, U/L	182 (152-238)	198 (154-317)	.29
NLR	2.40 (1.46-4.02)	3.02 (1.92-4.61)	.05
Platelets, K/μL	222 (193-313)	242 (197-305)	.62

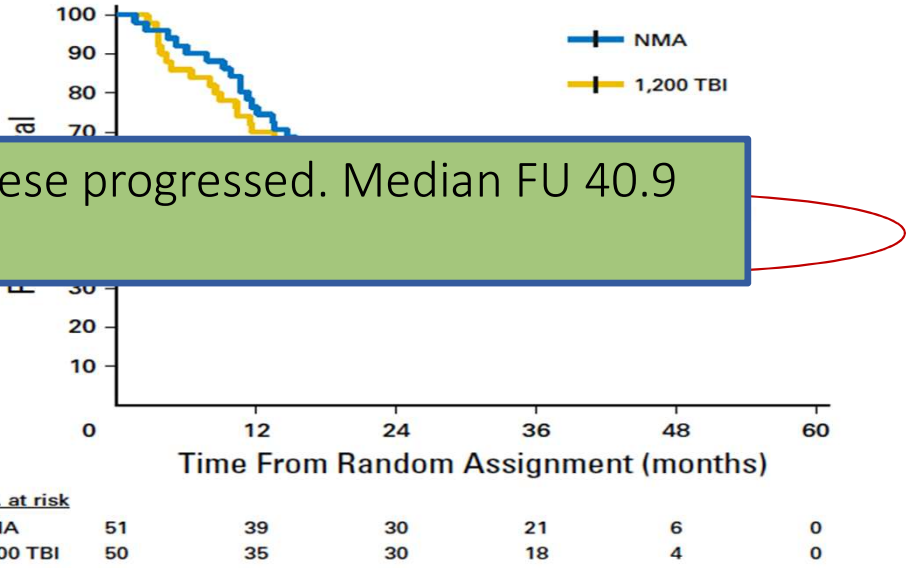
Goff et al., J Clin Oncol 2016

Survival of patients receiving TIL treatment

Progression Free Survival



Overall Survival



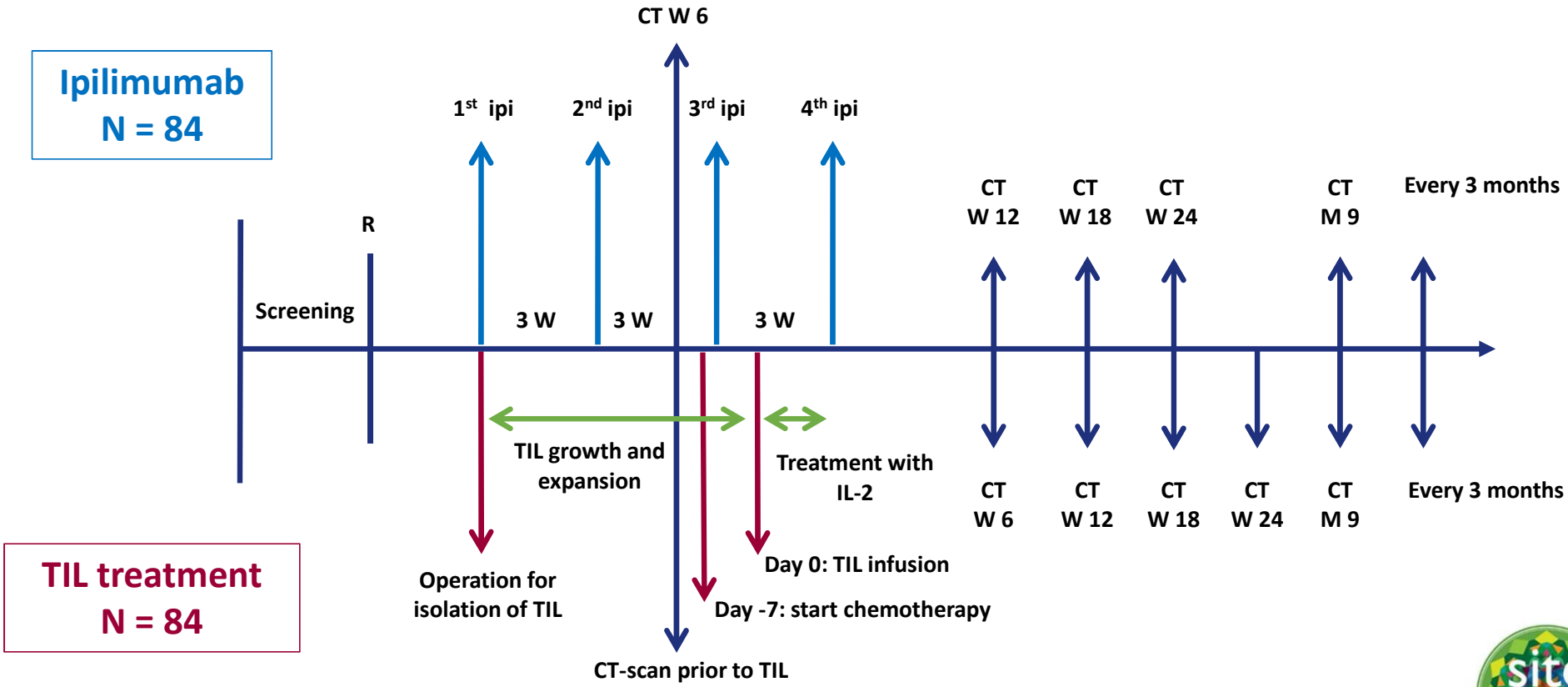
24% of patients developed a CR, only 1 of these progressed. Median FU 40.9 months

Goff et al., J Clin Oncol 2016

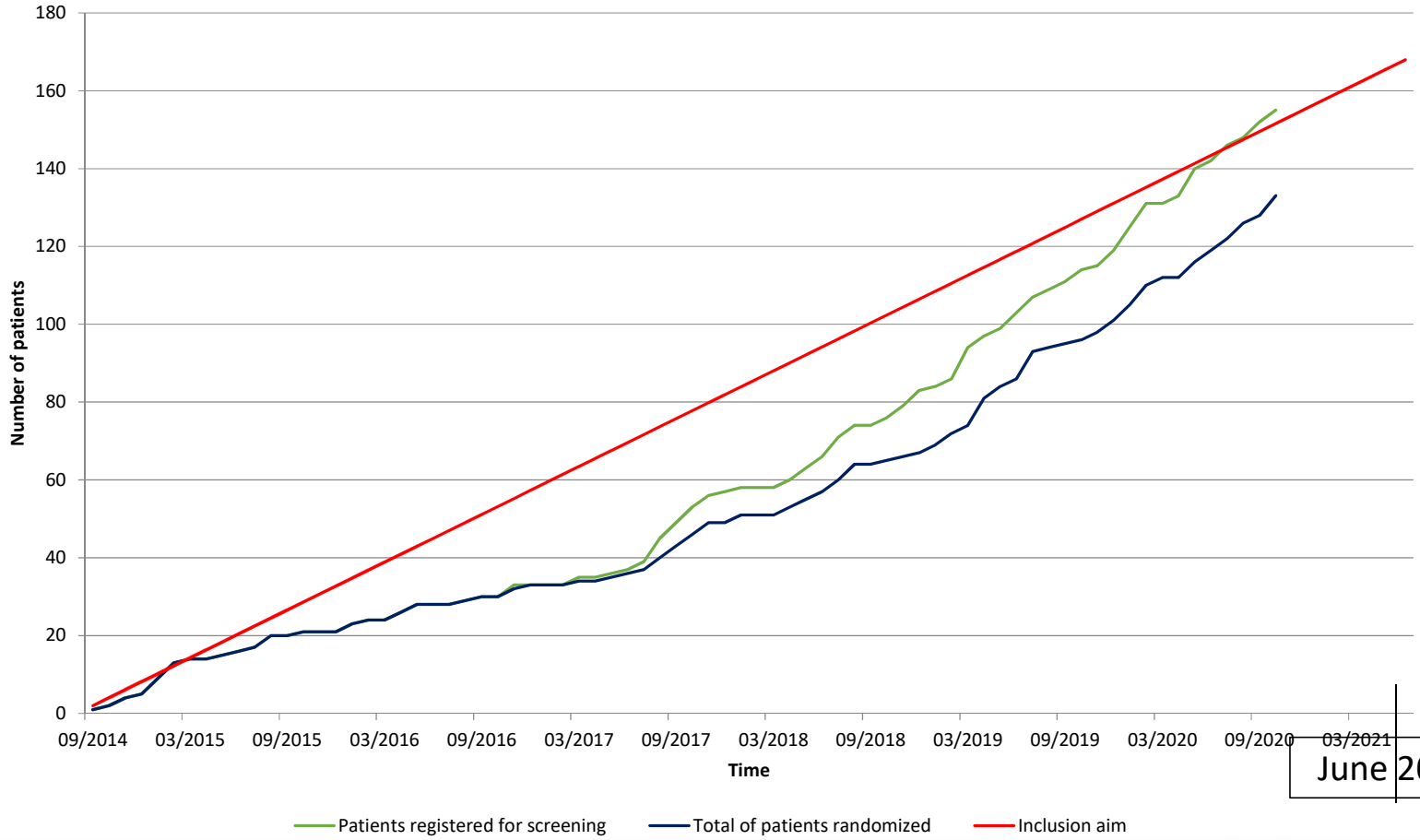
TIL Trial - NCT02278887

- International, multicenter, open-label, randomized controlled phase III study
- NKI + Herlev Hospital, Denmark
- *DKFZ, Heidelberg will be opened*
- Patients with irresectable stage IIIc/IV melanoma
  - 168 patients need to be randomized.
  - 1:1 randomization
  - Ipilimumab vs. CTx + TIL + HD IL-2
  - Endpoint: 50% improvement in PFS rate at 6 months
- TIL treatment is fully reimbursed from Dutch and Danish health insurance (temporarily)

Study Design



Current accrual TIL trial *(dd. 16-10-2020)*



168 inclusion aim

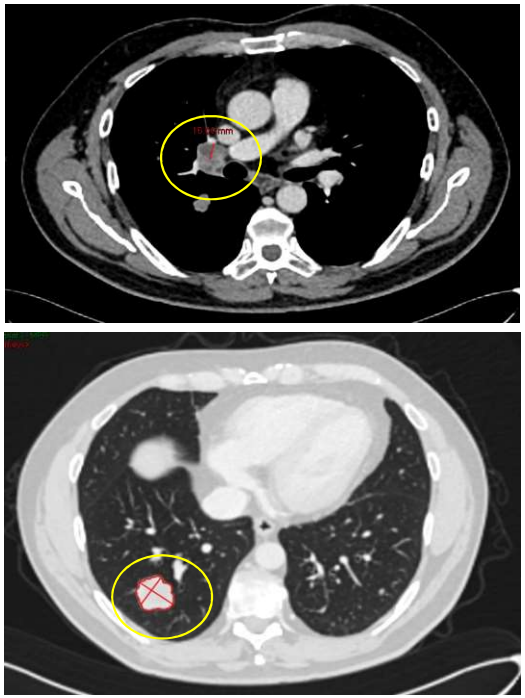
155 screened

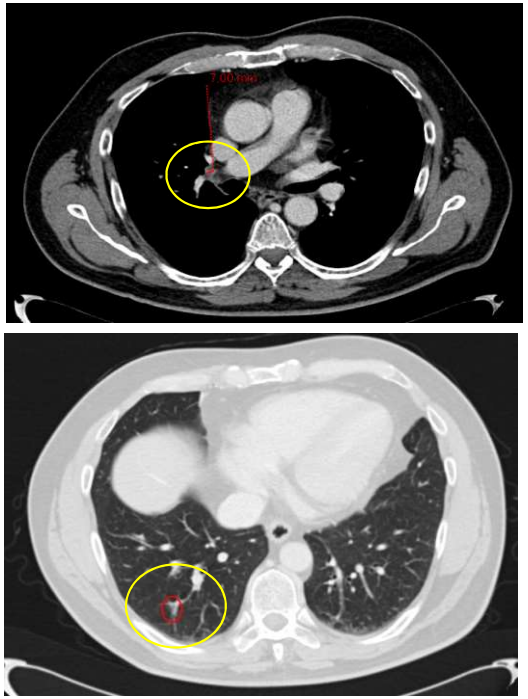
133 randomized for treatment

Preliminary Responses

- M, 55yr, stage IV melanoma
- Progression upon prior anti-PD1 treatment (7 months pembrolizumab)

Pre TIL



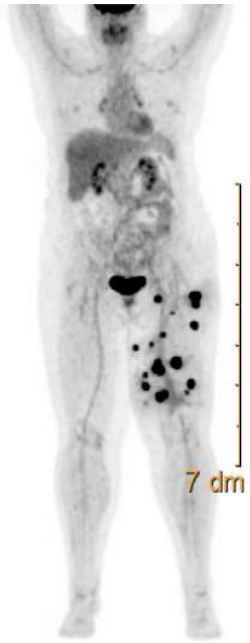


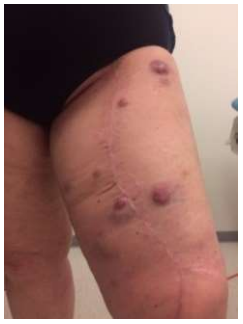
Radiologic near complete response 9 months after TIL

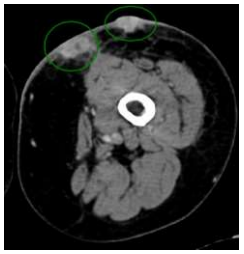
Preliminary Responses

- Irresectable stage IIIc melanoma
- Progression upon prior anti-PD1 treatment

Pre TIL

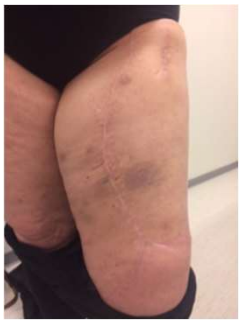


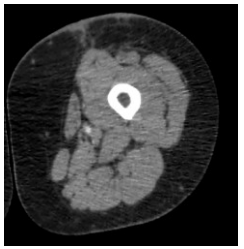


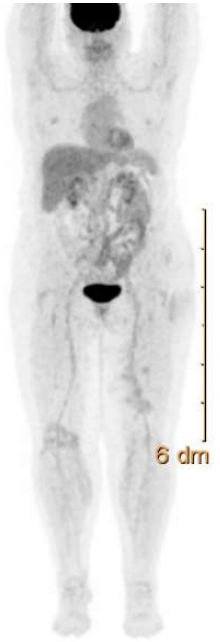


Ongoing CR > 18 months

20 weeks post TIL







Rohaan et al. unpublished

Rohaan et al. unpublished

ADVANCING IMMUNO-ONCOLOGY

IOVANCE Biotherapeutics is focused on the development and commercialization of autologous cellular immunotherapies optimizing personalized, tumor-directed Tumor Infiltrating Lymphocytes (TIL)

Current Clinical Trials

PHYSICIANS: To learn more about the trial on **ClinicalTrials.gov**, including eligibility criteria, locations and contacts.

C-144-01: METASTATIC MELANOMA

A Phase 2, Multicenter Study to Assess the Efficacy and Safety of Autologous Tumor Infiltrating Lymphocytes (LN-144) for Treatment of Patients with Metastatic Melanoma.

VIEW →

C-145-03: SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK (HNSCC)

A Phase 2, Multicenter Study to Assess the Safety and Efficacy of Autologous Tumor Infiltrating Lymphocytes (LN-145) for Treatment of Patients with Squamous Cell Carcinoma of the Head and Neck.

VIEW →

C-145-04: CERVICAL CARCINOMA

A Phase 2, Multicenter study to Assess the Safety and Efficacy of Autologous Tumor Infiltrating Lymphocytes (LN-145) for Treatment of Patients with Cervical Carcinoma.

VIEW →

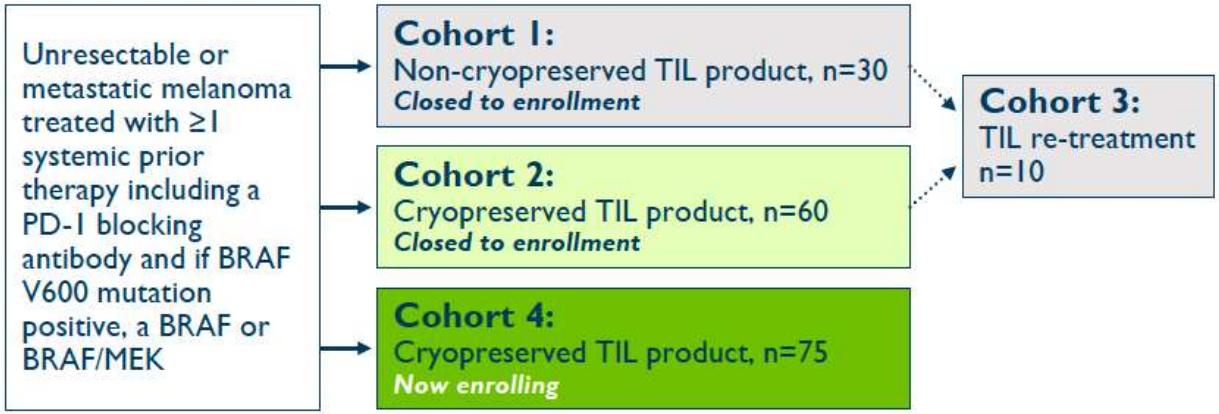
IOV-LUN-201: NON-SMALL CELL LUNG CANCER (NSCLC)

A Phase 2 Study to Assess the Efficacy and Safety of Autologous Tumor Infiltrating Lymphocytes (LN-145) Alone and in Combination with Anti-PD-L1 Durvalumab (MEDI4736) in Patients with Locally Advanced or Metastatic Non-Small Cell Lung Cancer (NSCLC).

VIEW →

innovaTIL-01 Study Design

Phase 2, multicenter study to assess the efficacy and safety of autologous Tumor Infiltrating Lymphocytes (LN-144) for treatment of patients with metastatic melanoma (NCT02360579)



Poster #2518 presented at ASCO 2019 by Amod Sarnaik

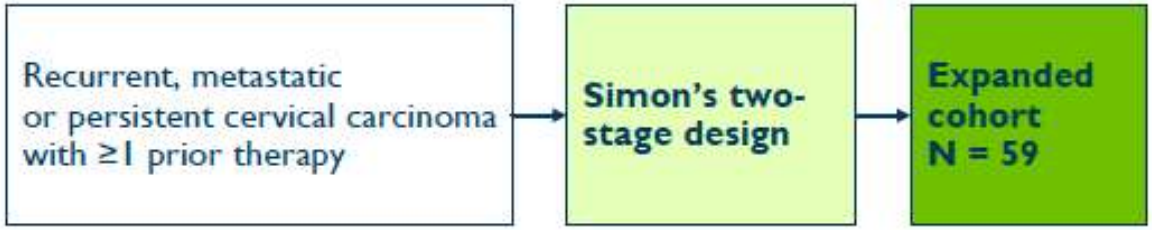
Efficacy

RESPONSE (RECIST v1.1)	PATIENTS, N=66 n (%)
Objective Response Rate (ORR)	**25 (38%)**
Complete Response (CR)	2 (3%)
Partial Response (PR)	23 (35%)
Stable Disease (SD)	28 (42%)
Progressive Disease (PD)	9 (14%)
Non-Evaluable	4 (6%)
Disease Control Rate (DCR)	53 (80%)
Median Duration of Response (DOR)	**Not Reached**
Min, Max	1.4+, 19.8 +

Poster #2518 presented at ASCO 2019 by Amod Sarnaik

innovaTIL-04 Study Design

Phase 2, multicenter study to evaluate the efficacy and safety of autologous Tumor Infiltrating Lymphocytes (LN-145) in patients with recurrent, metastatic or persistent cervical carcinoma (NCT03108495)



Poster #2538 presented at ASCO 2019 by Amir A. Jazaeri

- Data extract as of 14 May 2019
- Safety & Efficacy Sets: 27 patients who underwent resection for the purpose of TIL generation and received LN-145 infusion

Efficacy

RESPONSE (RECIST v1.1)	PATIENTS, N=27 n (%)
Objective Response Rate (ORR)	**12 (44.4%)**
Complete Response (CR)	3 (11.1%)
Partial Response (PR)	9 (33.3%)
Stable Disease (SD)	11 (40.7%)
Progressive Disease (PD)	4 (14.8%)
Non-Evaluable	0
Disease Control Rate (DCR)	23 (85.2%)
Median Duration of Response (DOR)	**Not Reached**
Min, Max (range)	2.6+ to 9.2+ months

Poster #2538 presented at ASCO 2019 by Amir A. Jazaeri

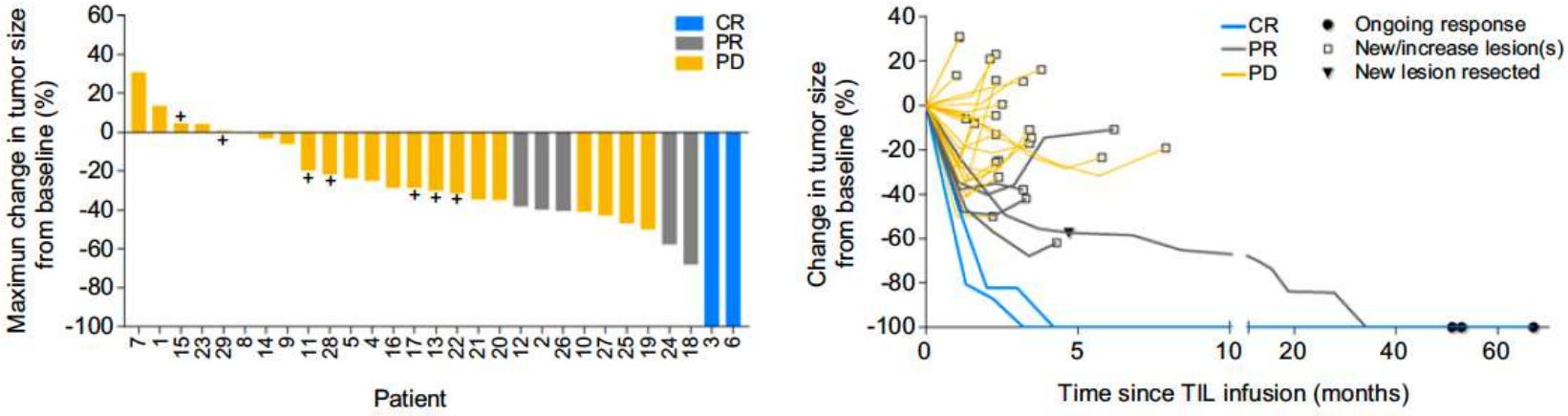
- 78% of patients had a reduction in tumor burden
- Median follow up is 7.4 months
- Mean number of TIL cells infused: 28 x 10^9
- Median number of IL-2 doses administered was 6.0

Poster #2538 presented at ASCO 2019 by Amir A. Jazaeri

Clinical Cancer Research

A Phase II Study of Tumor-infiltrating Lymphocyte Therapy for Human Papillomavirus–associated Epithelial Cancers

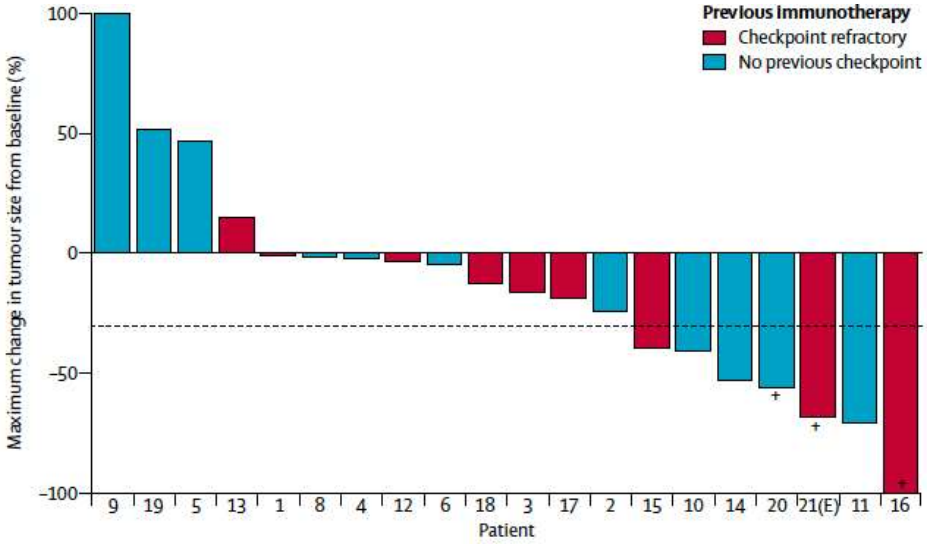
Sanja Stevanović[1], Sarah R. Helman[1], John R. Wunderlich[2], Michelle M. Langhan[2], Stacey L. Doran[1], Mei Li M. Kwong[2], Robert P.T. Somerville[2], Christopher A. Klebanoff[2], Udai S. Kammula[2], Richard M. Sherry[2], James C. Yang[2], Steven A. Rosenberg[2], and Christian S. Hinrichs[1]

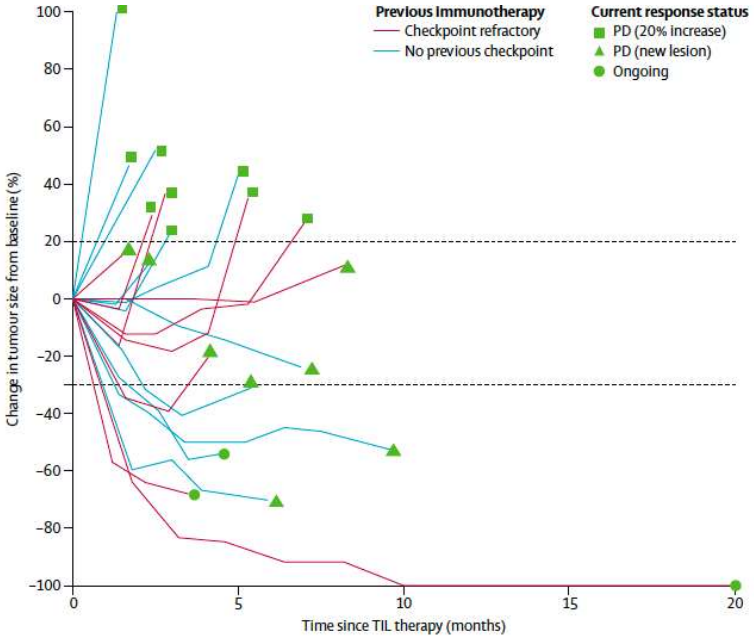


Stevanovic et al. Clin Cancer Res 2019

Treatment of metastatic uveal melanoma with adoptive transfer of tumour-infiltrating lymphocytes: a single-centre, two-stage, single-arm, phase 2 study

Smita S Chandran, Robert P T Somerville, James C Yang, Richard M Sherry, Christopher A Klebanoff, Stephanie L Goff, John R Wunderlich, David N Danforth, Daniel Zlott, Biman C Paria, Arvind C Sabesan, Abhishek K Srivastava, Liqiang Xi, Trinh H Pham, Mark Raffeld, Donald E White, Mary Ann Toomey, Steven A Rosenberg, Udai S Kammula





Chandran et al., Lancet Oncol 2017

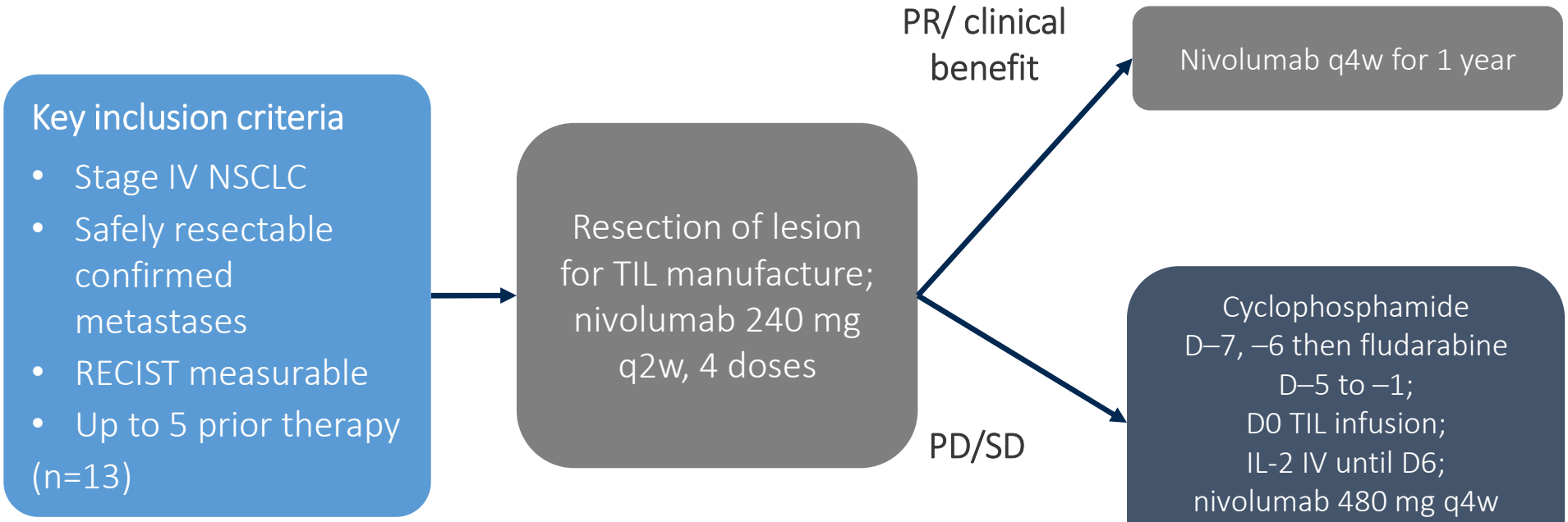
Safety and Clinical Activity of Adoptive Cell Transfer Using Tumor Infiltrating Lymphocytes (TIL) Combined with Nivolumab in Metastatic Non-small Cell Lung Cancer

Presenting Author(s): Ben C Creelan

Author(s): Jamie K Teer, Eric M Toloza, John E Mullinax, Ana M Landin, Jhanelle E Gray, Tawee T Tanvetyanon, Matthew C Taddeo, David R Noyes, Linda L Kelley, Bin Fang, John M Koomen, Amod A Sarnaik, Sungjune Kim, Eric B Haura, Scott J Antonia

Presented by S Antonia at AACR 2019; Courtesy of S Peters

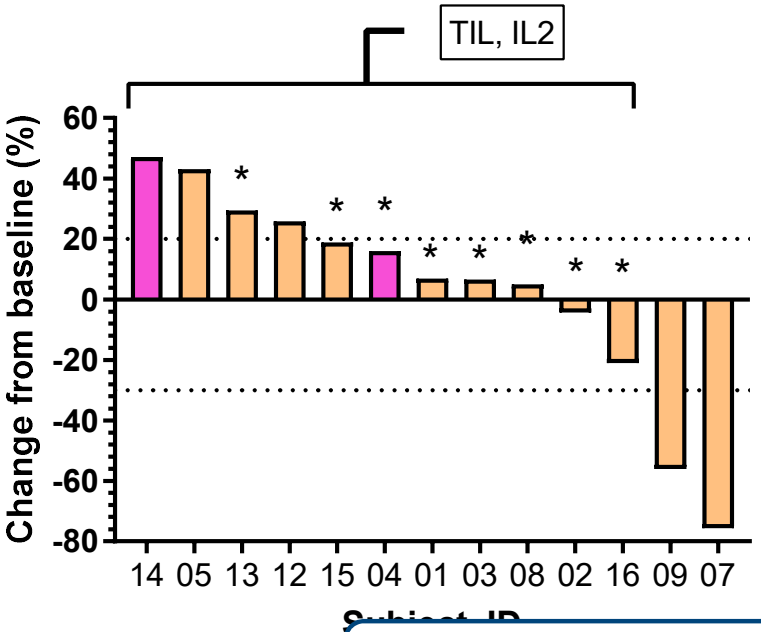
Trial Schema



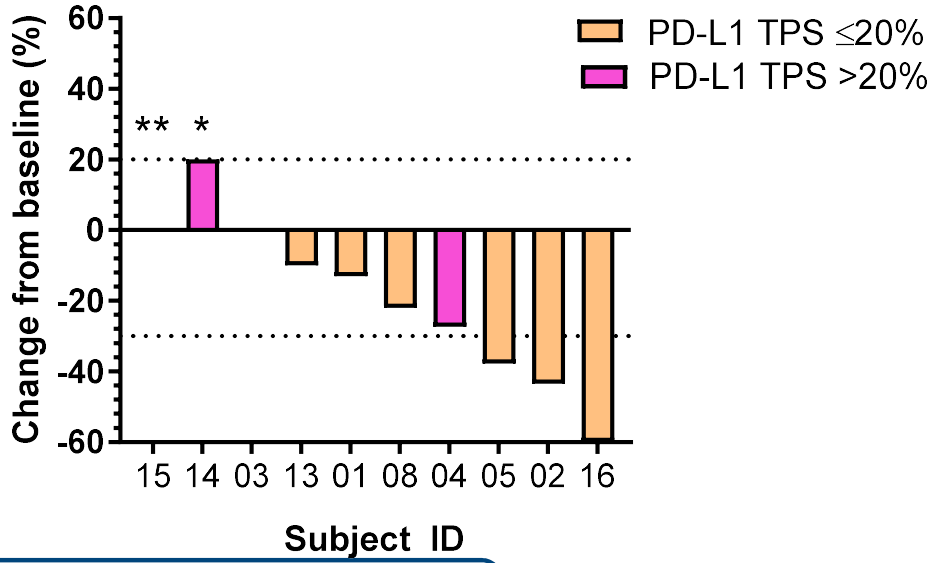
Presented by S Antonia at AACR 2019; Courtesy of S Peters

Waterfall Plot: Best Overall Change in Target Lesions

Pre-TIL



Post-TIL

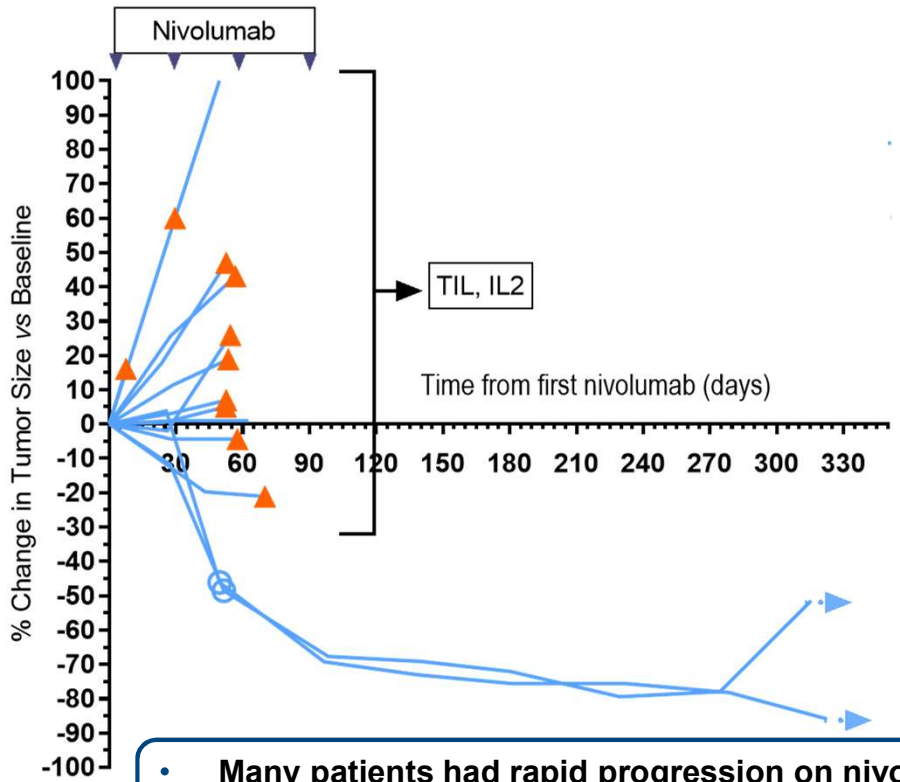


Most patients had rapid progression on nivolumab, then some tumor decrease after Cy/Flu/TIL/IL2

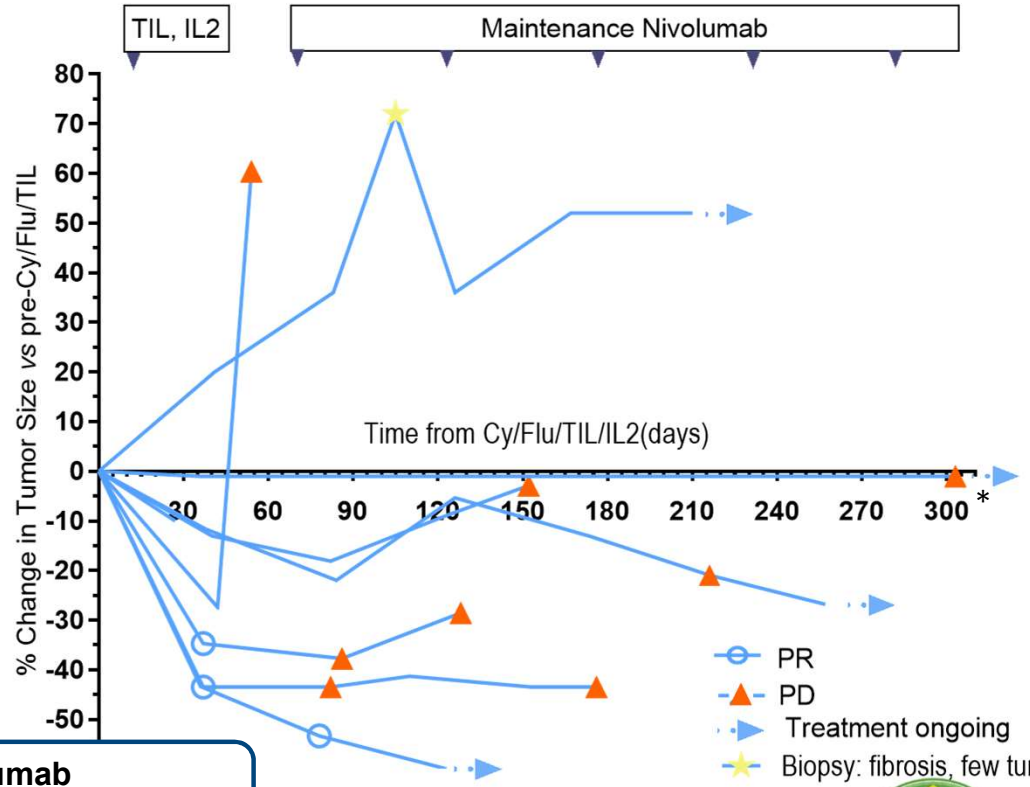
Presented by S Antonia at AACR 2019; Courtesy of S Peters

Depth and Duration of Response

Pre-TIL

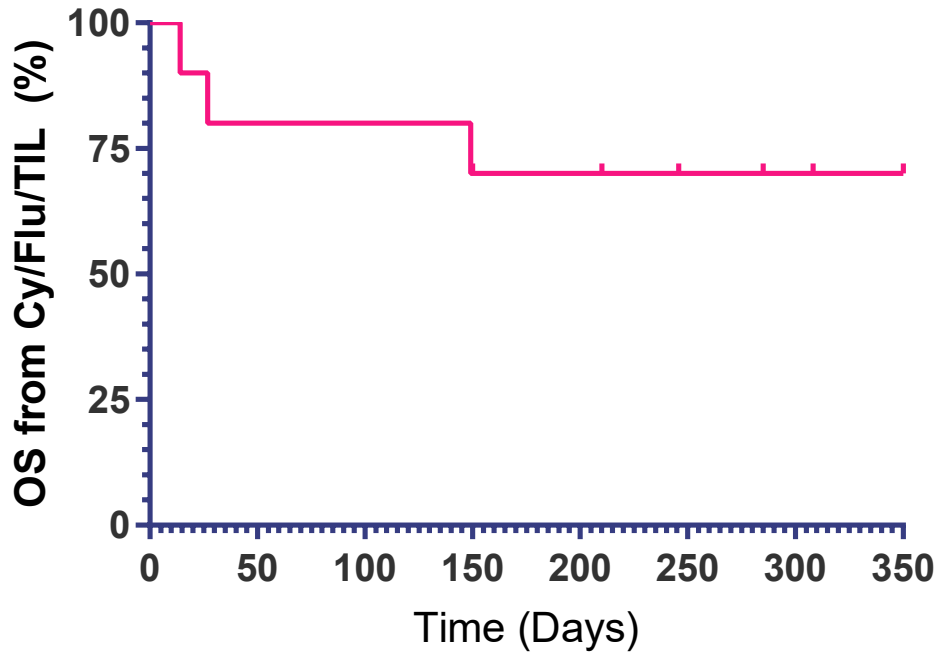


Post-TIL



- **Many patients had rapid progression on nivolumab**
- **Decreases in tumor size were observed after Cy/Flu+TIL+IL2**

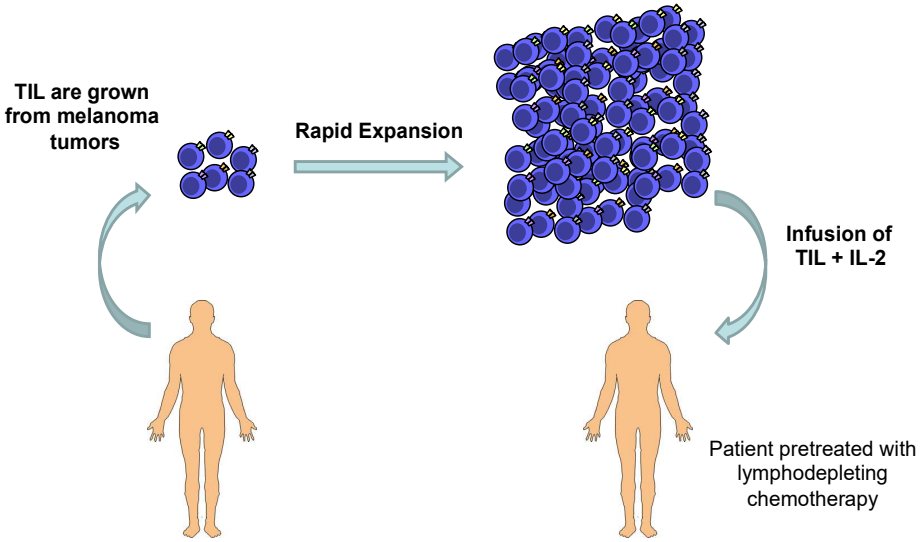
Overall Survival after Cy/Flu/TIL/IL2



Presented by S Antonia at AACR 2019; Courtesy of S Peters

Value of mobilizing endogenous tumor-specific T cell responses

TIL therapy



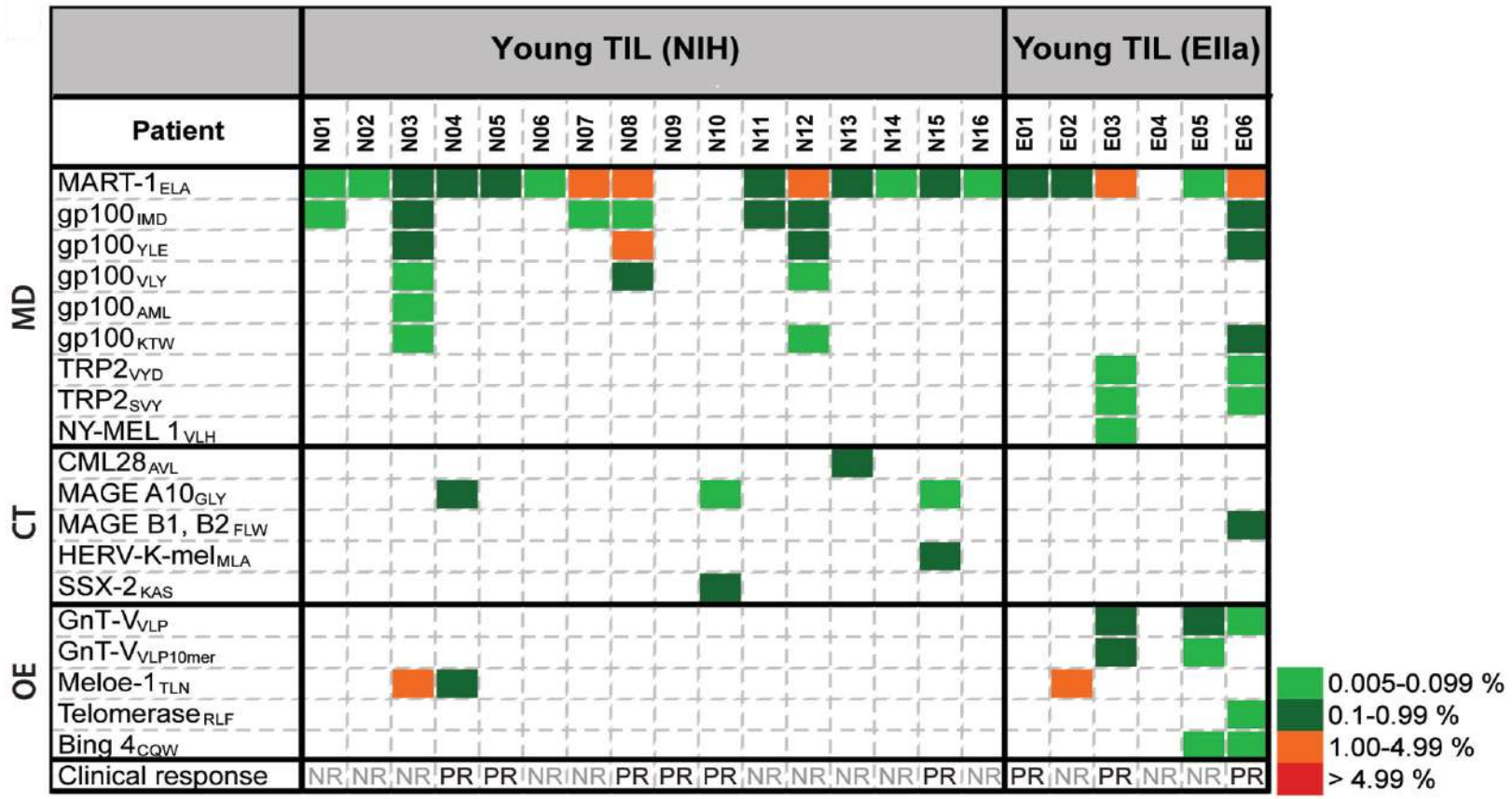
Black box: On bulk level anti-tumor reactivity, but how much does the infusion product resemble the original TIL composition?
Which tumor antigens are recognized?

RESEARCH PAPER

OncoImmunology 1:4, 409–418; July 2012; © 2012 Landes Bioscience

TIL therapy broadens the tumor-reactive CD8+ T cell compartment in melanoma patients

Pia Kvistborg,[1,†] Chengyi Jenny Shu,[1,†] Bianca Heemskerk,[1] Manuel Fankhauser,[1] Charlotte Albæk Thrue,[2] Mireille Toebes,[1] Nienke van Rooij,[1] Carsten Linnemann,[1] Marit M. van Buuren,[1] Jos H.M. Urbanus,[1] Joost B. Beltman,[3] Per thor Straten,[2] Yong F. Li,[4] Paul F. Robbins,[4] Michal J. Besser,[5,6] Jacob Schachter,[5] Gemma G. Kenter,[7] Mark E. Dudley,[4] Steven A. Rosenberg,[4] John B.A.G. Haanen,[1] Sine Reker Hadrup[2] and Ton N.M. Schumacher[1,*]



Kvistborg et al., Oncoimmunol 2012

TMB as Biomarkers for Response to TIL

nature COMMUNICATIONS

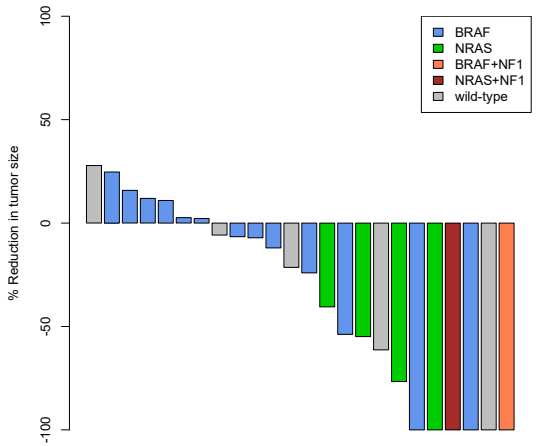
ARTICLE

DOI: 10.1038/s41467-017-01460-0 OPEN

Mutational and putative neoantigen load predict clinical benefit of adoptive T cell therapy in melanoma

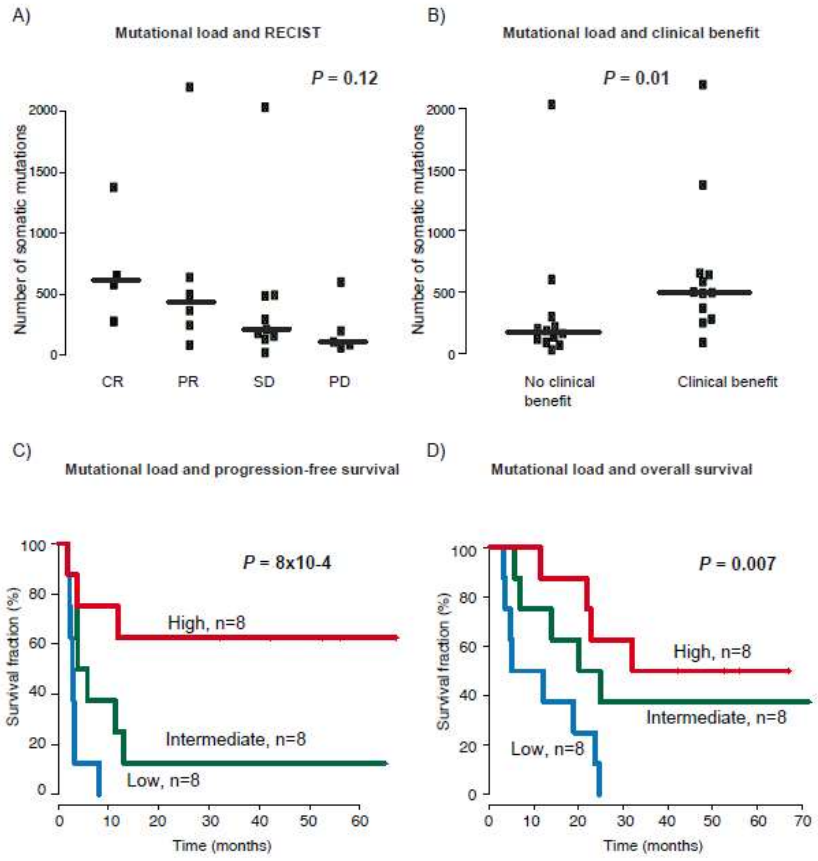
Martin Lauss[1], Marco Donia[2,3], Katja Harbst[1], Rikke Andersen[2,3], Shamik Mitra[1], Frida Rosengren[1], Maryem Salim[1], Johan Vallon-Christersson[1], Therese Törngren[1], Anders Kvist[1], Markus Ringnér[4], Inge Marie Svane[2,3] & Göran Jönsson[1]

Melanoma key driver mutations
are not associated to clinical response



Lauss et al. Nat Comm 2017

TMB as Biomarkers for Response to TIL



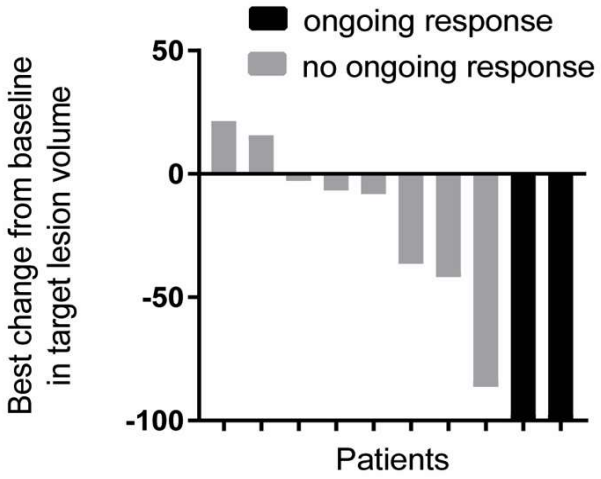
Lauss et al. Nat Comm 2017

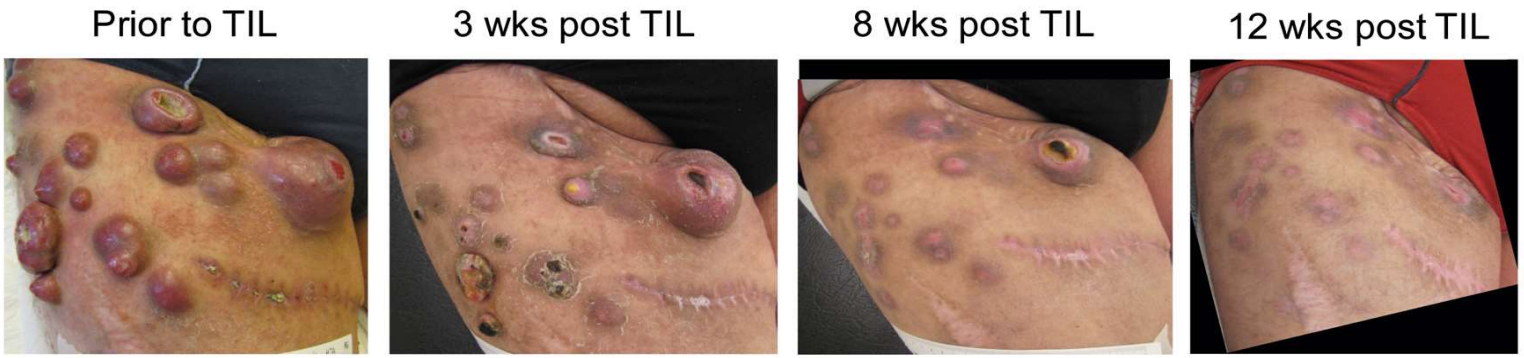
Patient baseline characteristics of phase Ib feasibility trial in metastatic melanoma

Patient nr	Gender	Age	Prior treatments	Metastatic sites	Location for tumor resection	Performance status
1	M	67	DTIC, ipilimumab	lung, adrenal, subcutaneous	subcutaneous	0
2	M	68	DTIC, DC vaccination, ipilimumab	lung, LN, spleen, subcutaneous	LN	0
3	M	46	vemurafenib, ipilimumab	LN, subcutaneous	subcutaneous	0
4	F	44	DTIC, vemurafenib, ipilimumab	LN, subcutaneous, soft tissue	subcutaneous	0
5	F	40	DTIC, ipilimumab	lung, subcutaneous, soft tissue	subcutaneous	0
6	F	43	temozolamide, IFN-α, DC vaccination, ipilimumab, vemurafenib	LN, long, subcutaneous	axillary LN	0
7	M	52	DTIC, ipilimumab	LN, lung, subcutaneous	LN	0
8	M	40	peptide vaccination, ipilimumab	LN, small intestine	Large intestine mesoduodenum	0
9	F	60	vemurafenib, DTIC, ipilimumab	LN, subcutaneous	LN	1
10	M	55	DC vaccination, ipilimumab	LN, subcutaneous, liver, lung	jejunum	1

Van den Berg et al. JiTC 2020

Objective responses observed in the N10TIL trial





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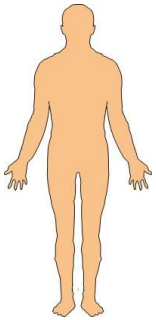
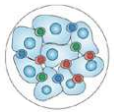
Patient NKI-003: complete response upon TIL therapy

Resected tumor material



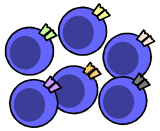
Isolate tumor cells



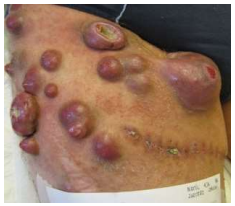
Identify tumor-specific mutations

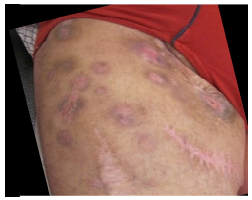
Predict potential epitopes

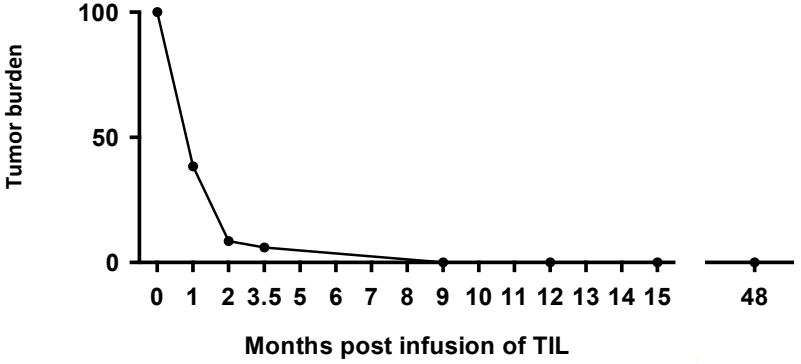
Isolate tumor-infiltrating T cells



Screen with MHC multimer technology







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Neoantigen-specific responses observed in 3 responding patients

	Gene mutation	WT peptide	Mutant peptide	Frequency (% multimer$^+$CD8$^+$ T cells of total CD8$^+$ T cells)	Restriction element
Patient 3	RBM12 $_{S>L}$	SPHEAGFCV	LPHEAGFCV	29.00	HLA-B*51:01
	VARS $_{T>M}$	EVADEATGAL	EVADEAMGAL	0.096	HLA-A*25:01
	MYLK $_{G>V}$	EVFPEDTGTY	EVFPEDTVTY	1.90	HLA-A*25:01
	LRP3 $_{T>S}$	LTAARPSQTVL	LTAARPSQSVL	0.039	HLA-A*25:01
	WDR1 $_{N>K}$	DSFAGKGHTN	DSFAGKGHTK	0.500	HLA-A*68:01
Patient 4	TTC37 $_{A>V}$	YLDGKAVDY	YLDGKVVDY	1.14	HLA-A*01:01
	ENTPD4 $_{P>L}$	ATDTNNPNVNY	ATDTNNLNVNY	3.35	HLA-A*01:01
	MAB21L1 $_{V>M}$	LRIRDRYVV	LRIRDRYVM	0.007	HLA-B*08:01
Patient 8	RAD51AP1-002 $_{S>F}$	KVKSPVEKK	KVKFPVEKK	0.195	HLA-A*03:01

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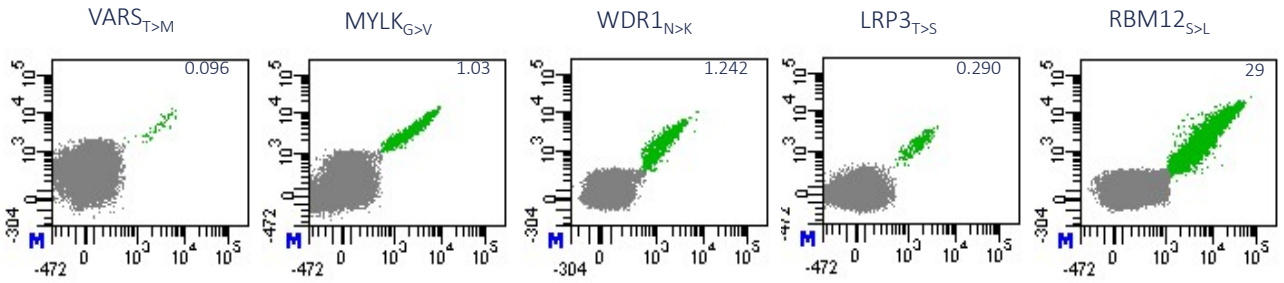
Patient NKI-003: complete response upon TIL therapy

TIL infusion product



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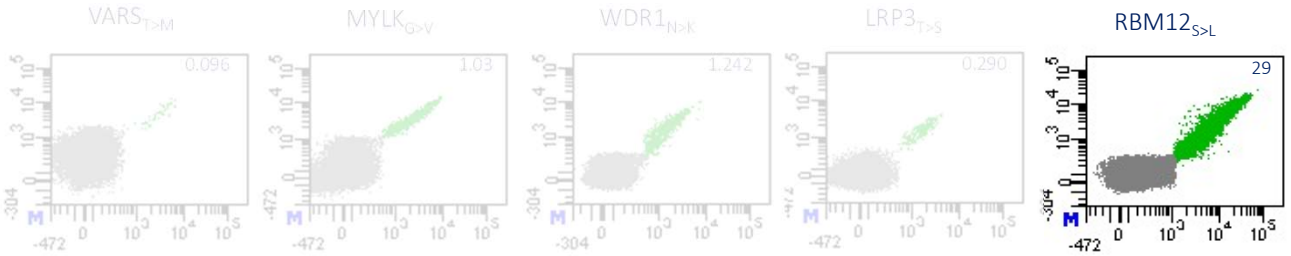
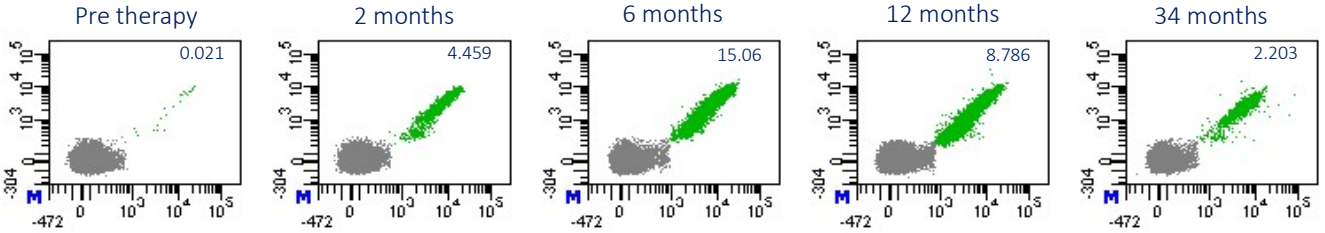
Patient NKI-003: complete response upon TIL therapy

TIL infusion product



Peripheral blood



>450 fold increase in neo-antigen specific T cell reactivity upon TIL therapy

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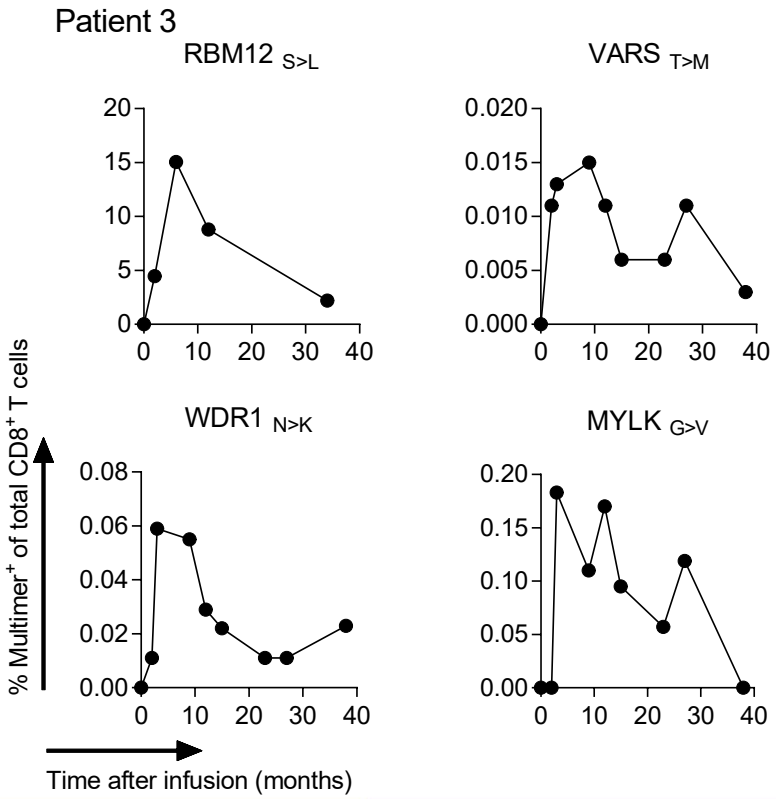
Kinetics of neoantigen-specific T cell responses following TIL infusion



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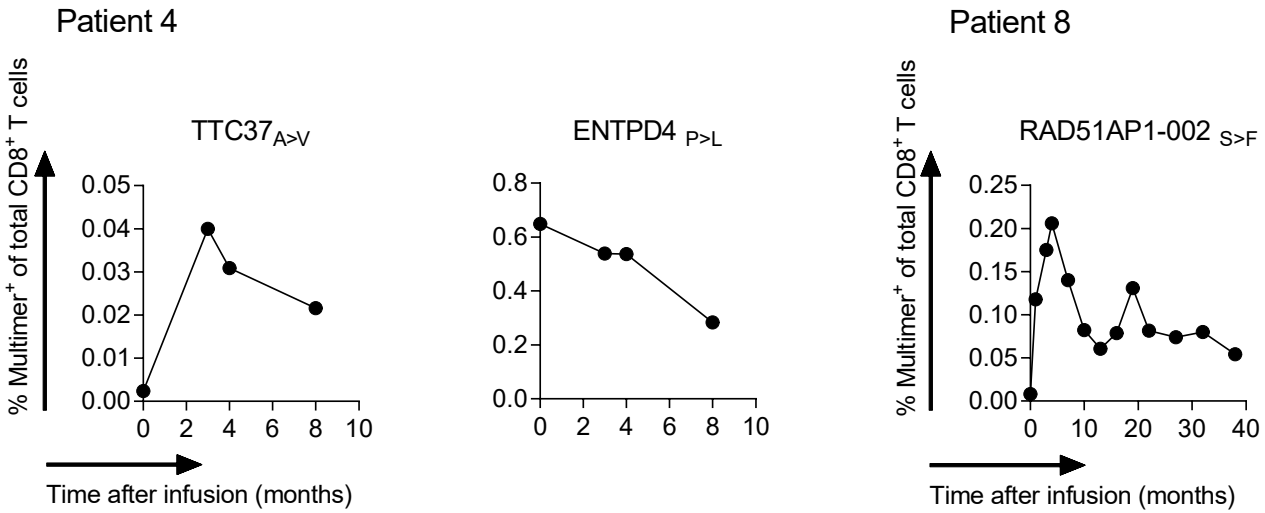
Kinetics of neoantigen-specific T cell responses following TIL infusion



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TIL therapy: summary

- Active treatment strategy in metastatic melanoma, even after anti-PD-1 failure
  - Data coming from many phase II single center trials
  - Awaiting data from multicenter phase II (Iovance) trial
  - Awaiting data from RCT phase III academically run trial

- TIL treatment now feasible for other cancers than only melanoma (NSCLC, Cervical cancer, HNSCC, uveal melanoma and more)

- Neoantigen-specific T cells appear more important for the anti-tumor effect than shared tumor antigen-specific T cells

- ACT with selected TIL may increase the efficacy.

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