



Cell therapy

John B. Haanen MD PhD

ICOS6, April 2019, Vienna

My disclosures

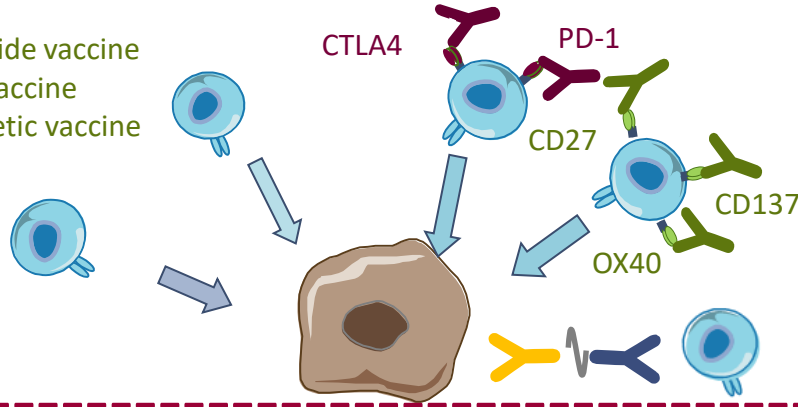
- I have provided consultation, attended advisory boards, and/or provided lectures for: **Amgen, AZ/Medimmune, Bayer, BMS, GSK, Ipsen, Merck Serono, MSD, Novartis, Pfizer, Roche/Genentech, Sanofi, Seattle Genetics** for which NKI received honoraria
- I am on the **SAB** of **AIMM, Celsius Therapeutics, Immunocore and Neon Therapeutics**. Financial compensation goes to NKI
- Through my work NKI received grant support from **Bayer, BMS, MSD, Novartis, Neon Therapeutics, Pfizer**
- I am member of **ESMO, ASCO, AACR**
- I am member of **ESMO W40** committee, **ESMO Press** committee, **ESMO Educational** Committee
- I am scientific (co-)chair of **ESMO IO congress 2019, MAP 2019, and ESMO congress 2020**
- I am member of the scientific committee of **ECIC 2019 and ICOS6 2019**
- I am faculty chair of **ESMO Immunotherapy of Cancer**
- I am Editor-in-Chief of **ESMO IOTECH**
- I am member of the advisory board of “**Stichting Melanoom**”
- I am on the board of the **Dutch Melanoma Treatment Registry (DMTR)**

Overview Immunotherapy

Active Immunotherapy

Peptide vaccine
DC vaccine
Genetic vaccine

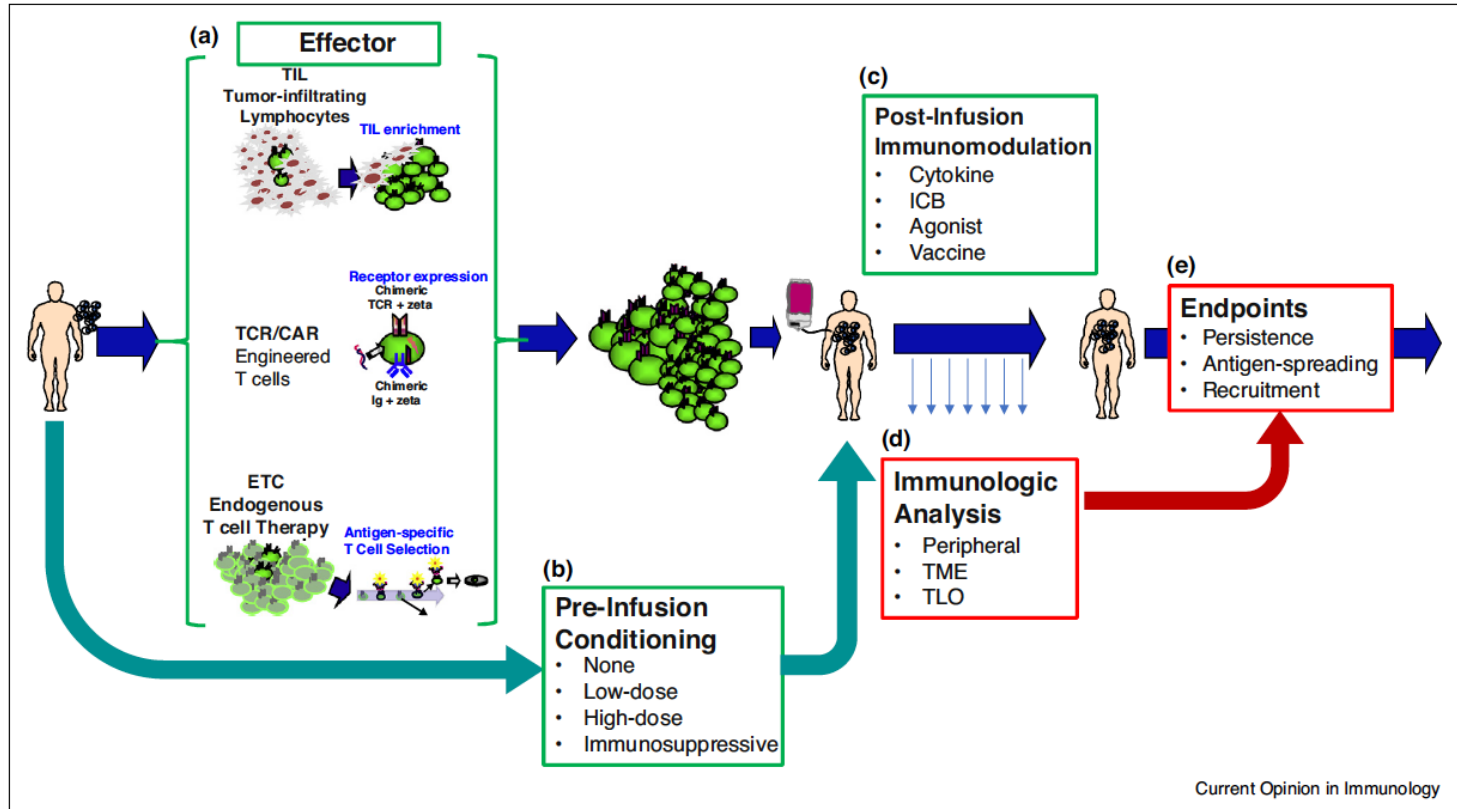
IL-2
IFN
IL-15
IL-21



T cell checkpoint
blocking and
stimulating
antibodies

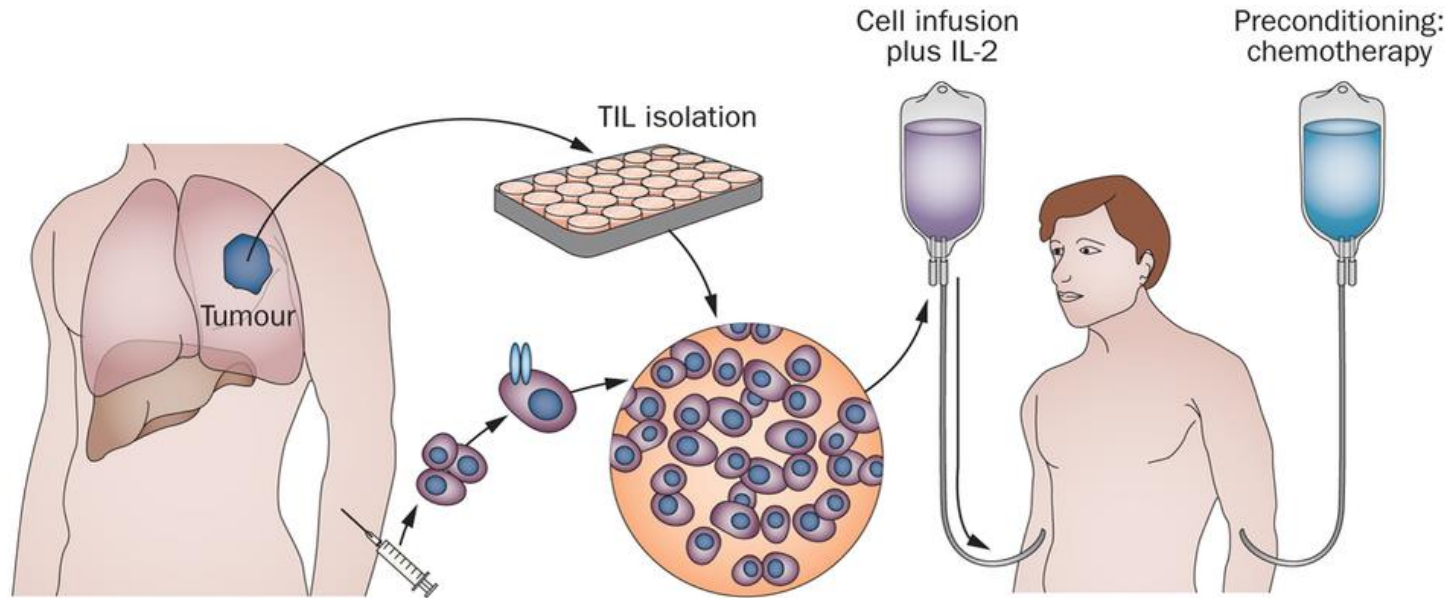
Bi-specific
antibodies

Adoptive cell therapy platforms



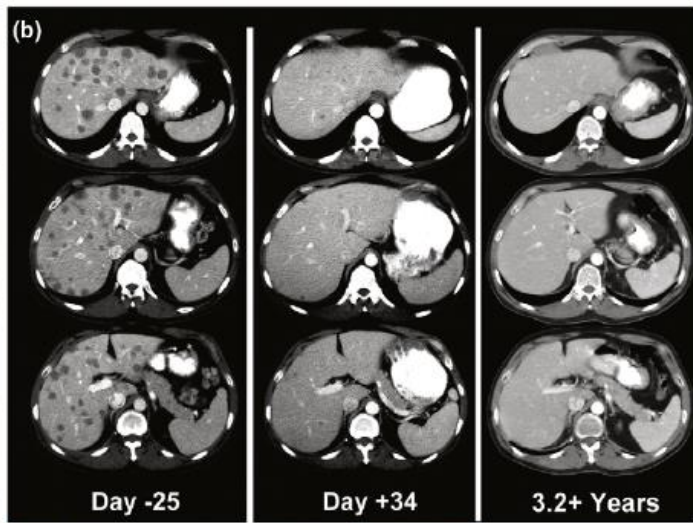
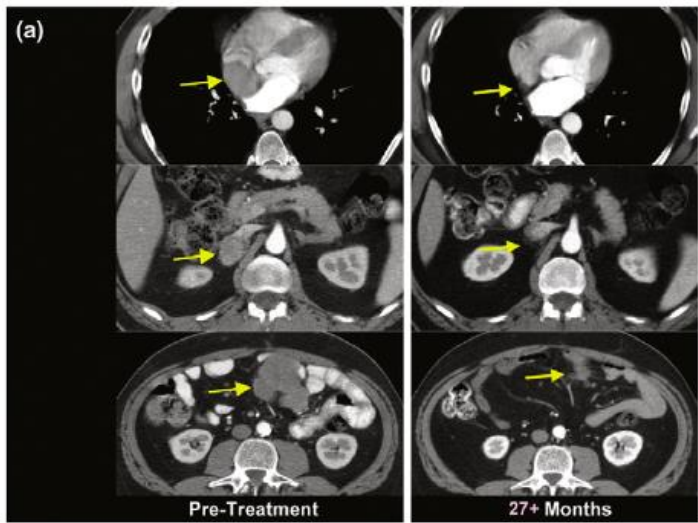
Current Opinion in Immunology

Treatment with tumor-infiltrating lymphocytes

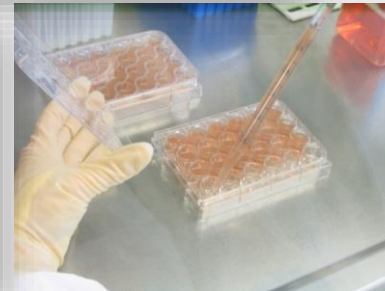


Cancer Regression and Autoimmunity in Patients After Clonal Repopulation with Antitumor Lymphocytes

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*}



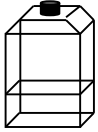
Generation of TIL for melanoma patients at the NKI-BTU: tumor preparation



- 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

Expansion phase of TIL: start expansion in T175 flasks

Day 0



T175 x 20



TIL expansion : - non-specific stimulation (α CD3)
- 200-fold excess of allogenic irradiated PBMC
- high concentrations of IL-2

Starting number of TIL: 20×10^6

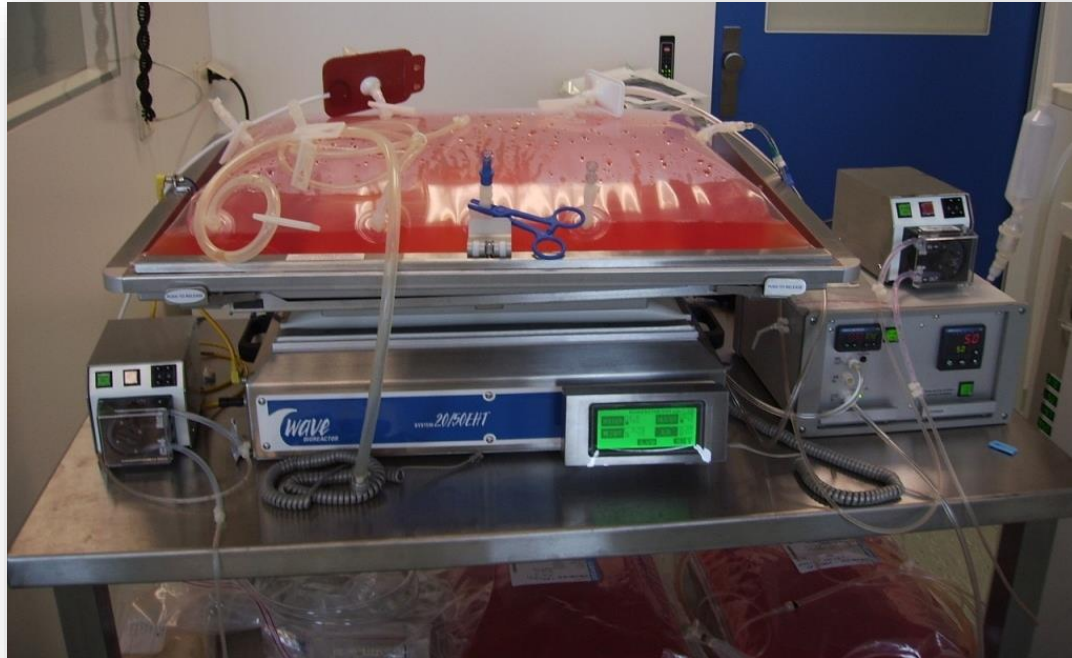


- logistically challenging

- success rate 90%

Expansion phase of TIL: transfer to the WAVE Bioreactor (d6)

- Culture in closed system (up to 10L)
- Automated heating, rocking and O₂/CO₂ inflation
- Possibility for perfusion to increase cell density to $\sim 10 \times 10^6$ cells/ml



Harvest and infusion of TIL

- Washing and preparing 200 ml infusion fluid with TIL

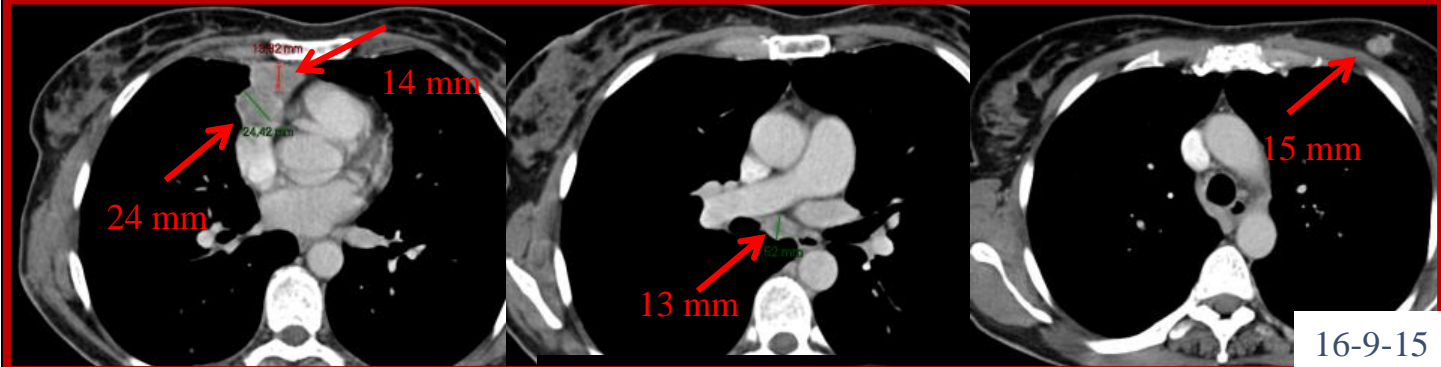
1.2×10^{11} cells



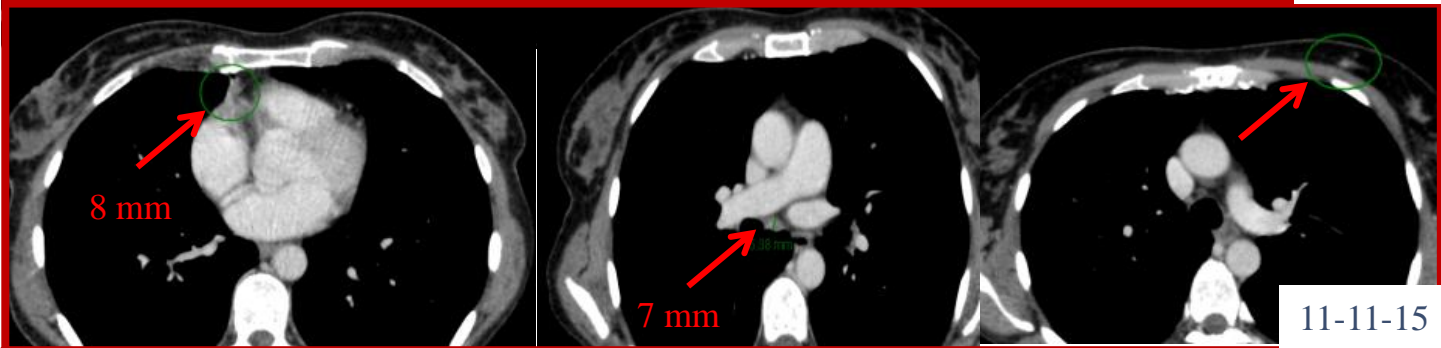
Quality Controls (QC)	Specification
QC(1) Microbiological contamination	negative (day -2 before infusion)
QC(3) Total cell number	$>5 \times 10^9$ TIL and $< 2 \times 10^{11}$
QC(4) Viability	$>70\%$ living cells

TIL Trial - NCT02278887

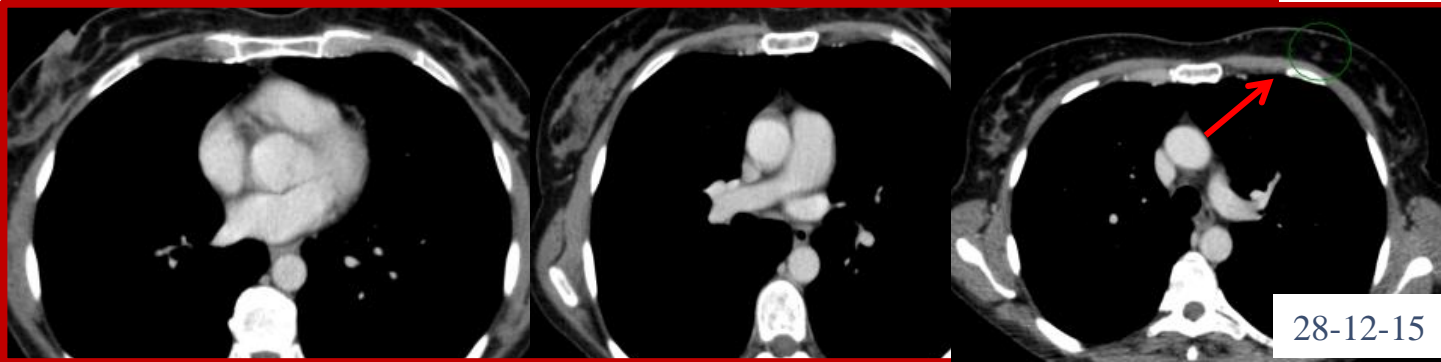
- International, multicenter, open-label, randomized controlled phase III study
- NKI + Herlev Hospital, Denmark
- *CHUV, Lausanne, Val d'Hebron, Barcelona, DKFZ, Heidelberg will be opened*
- Patients with irresectable stage IIIc/IV melanoma
 - 168 patients need to be randomized. Currently 80 patients have been included
 - 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 health insurance (temporarily)



16-9-15



11-11-15



28-12-15

Is increasing lymphodepletion resulting in improved ORR

		Days										
		-7	-6	-5	-4	-3	-2	-1	0	1	2	3
Non-myeloablative		Cy	Cy	Flu	Flu	Flu	Flu	Flu		Cells		
										IL-2	IL-2	IL-2
Ablative (200cGy)			Cy	Cy	Flu	Flu	Flu			TBI		
			Flu	Flu	Flu	Flu	Flu			Cells		
										IL-2	IL-2	IL-2
											CD34+	
Ablative (1200cGy)		Cy	Cy	Flu	Flu	Flu	Flu			TBI		
		Flu	Flu	Flu	Flu	Flu	Flu			Cells		
										IL-2	IL-2	IL-2
											CD34+	

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/m²/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).

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

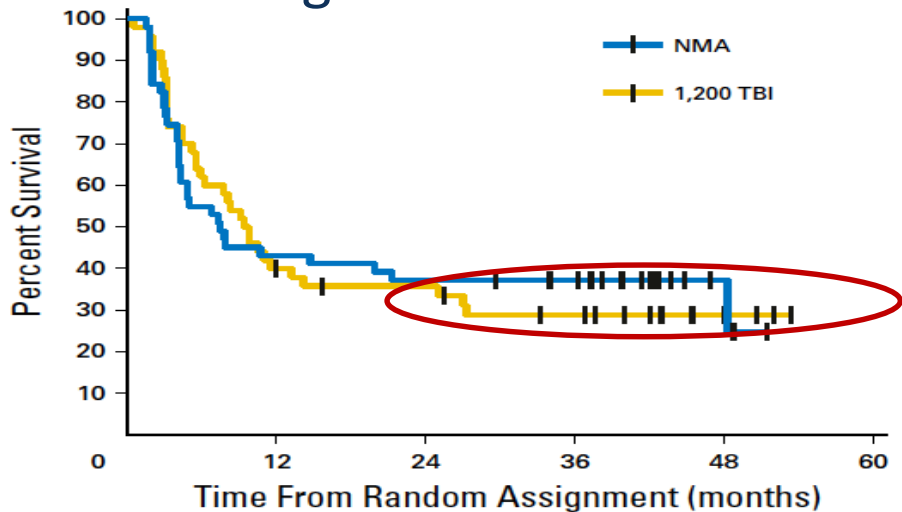
Stephanie L. Goff, Mark E. Dudley, Deborah E. Citrin, Robert P. Somerville, John R. Wunderlich, David N. Danforth, Daniel A. Zlott, James C. Yang, Richard M. Sherry, Udai S. Kammula, Christopher A. Klebanoff, Marybeth S. Hughes, Nicholas P. Restifo, Michelle M. Langan, Thomas E. Shelton, Lily Lu, Mei 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

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

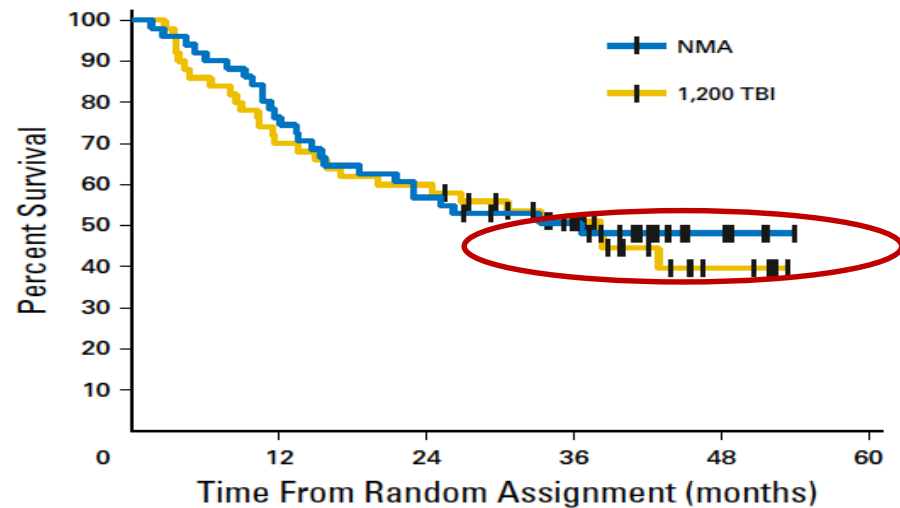
Survival of patients receiving TIL treatment

Progression Free Survival



Time (months)	0	12	24	36	48	60
NMA	51	22	19	17	3	0
1,200 TBI	50	18	16	10	4	0

Overall Survival

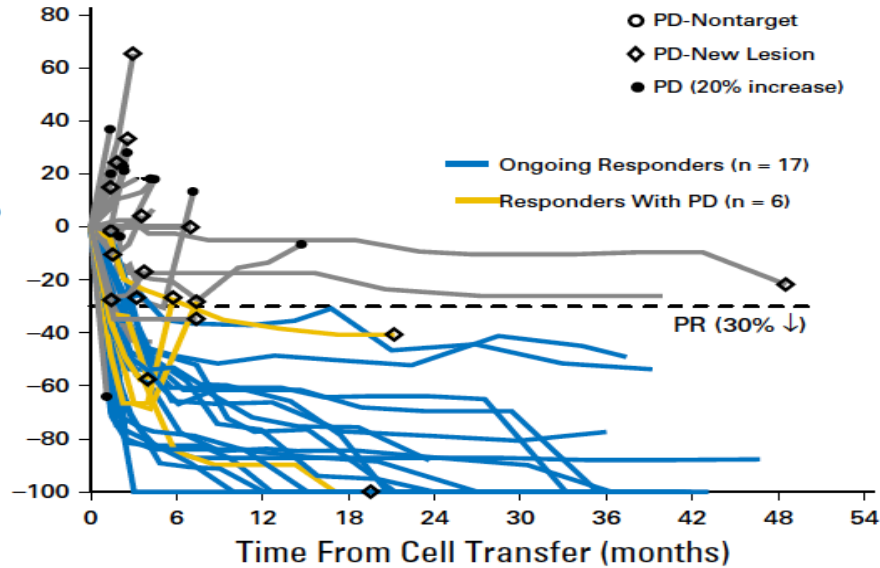


No. at risk

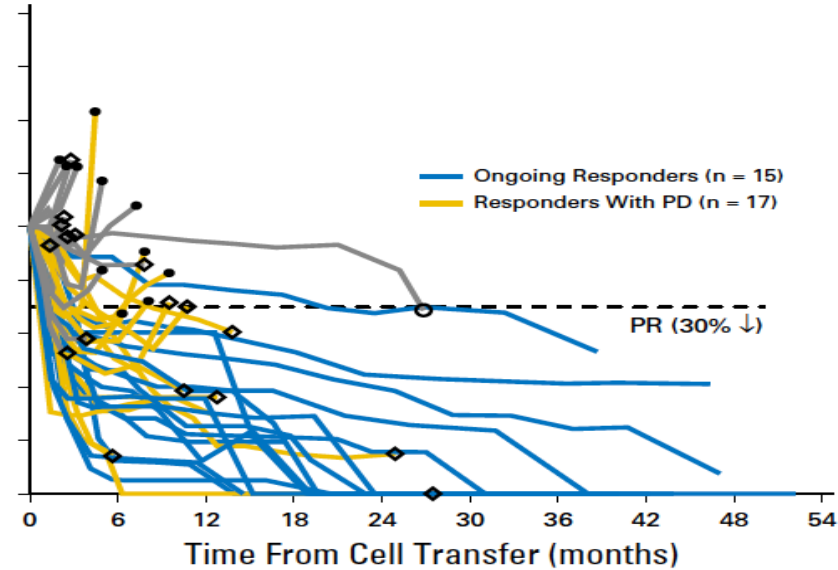
Time (months)	0	12	24	36	48	60
NMA	51	39	30	21	6	0
1,200 TBI	50	35	30	18	4	0

Response to TIL treatment

NMA TIL



NMA + 1200cGy TIL






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

ORIGINAL RESEARCH



Adoptive cell therapy with tumor-infiltrating lymphocytes in patients with metastatic ovarian cancer: a pilot study

Magnus Pedersen^{a,b}, Marie Christine Wulff Westergaard^a, Katy Milne^c, Morten Nielsen ^{a,b}, Troels Holz Borch ^{a,b}, Lars Grønlund Poulsen^d, Helle Westergren Hendel^e, Mia Kennedy^c, Gillian Briggs^c, Stacey Ledoux^c, Trine Jakobi Nøttrup^f, Pernille Andersen^g, Thomas Hasselager^h, Özcan Met ^{a,b}, Brad H. Nelson^{c,i}, Marco Donia^{a,b}, and Inge Marie Svane^{a,b}

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

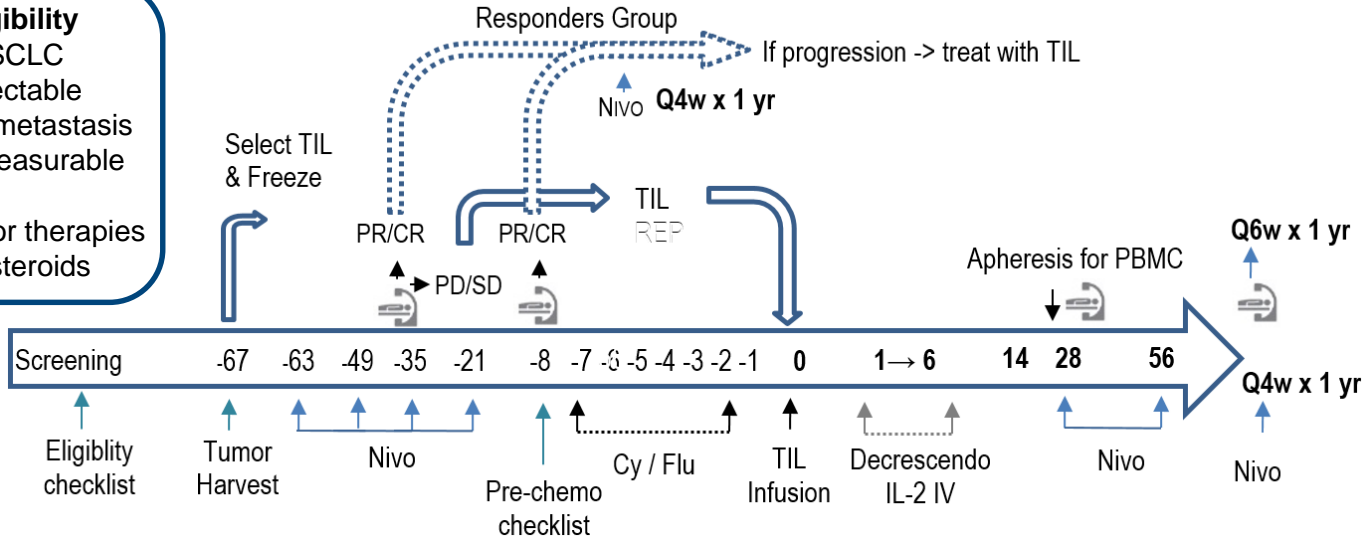
Presenting Author(s): Ben C Creelan

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

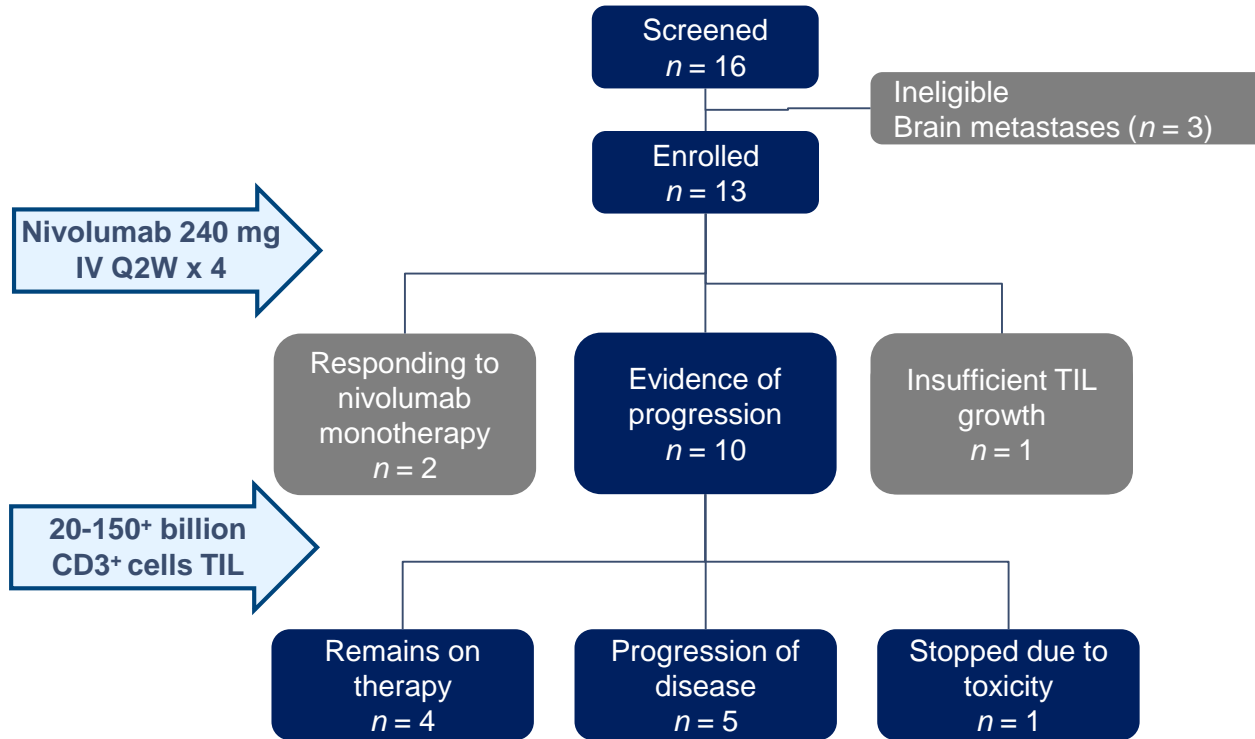
NSCLC TIL Study Design

Key Eligibility

- Stage 4 NSCLC
- Safety resectable confirmed metastasis
- RECIST measurable disease
- Up to 5 prior therapies
- No corticosteroids



Disposition of Patients [CONSORT diagram]



Study Endpoints

- **Primary:** Safety/tolerability
- **Other:** Preliminary efficacy, PK, PD, Tumor proteomics, whole exome sequencing, transcriptomics
- Serial PBMC phenotyping and TCR chain sequencing

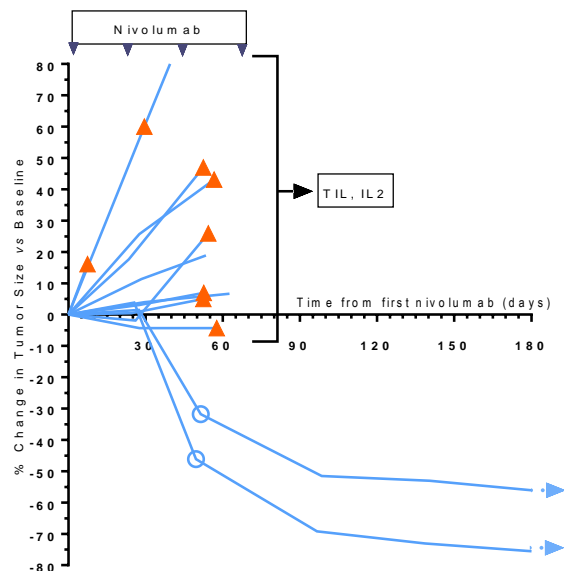
Updated results in this ongoing study are presented (median follow-up range, 0.2+ to 35+ weeks)

Evidence of progression: Formal PD, Non-target enlargement, Increase in tumor markers

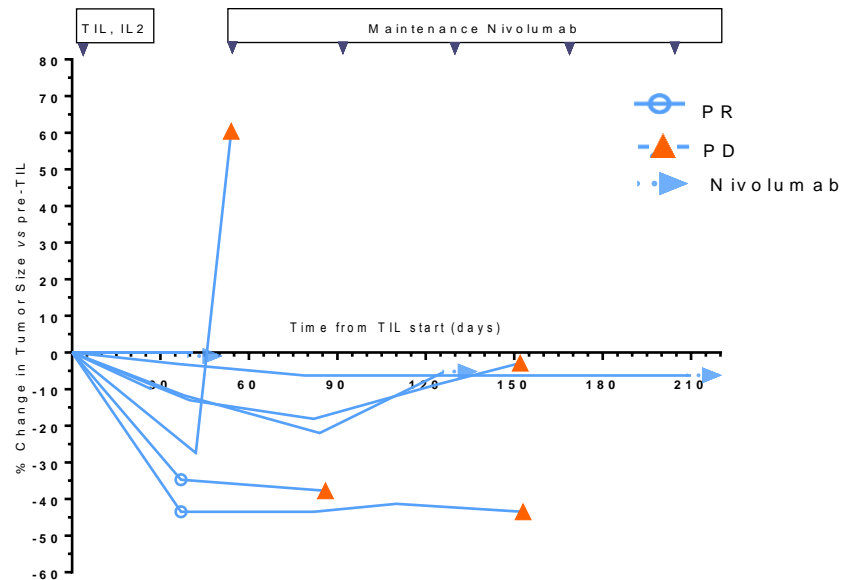
CONSORT; Consolidated Standards of Reporting Trials. IV, intravenous; ORR, objective response rate; PD, pharmacodynamics; Q2W, every 2 weeks;. Seven patients were response evaluable with measurable disease and CT scans at Day 28 evaluation.

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

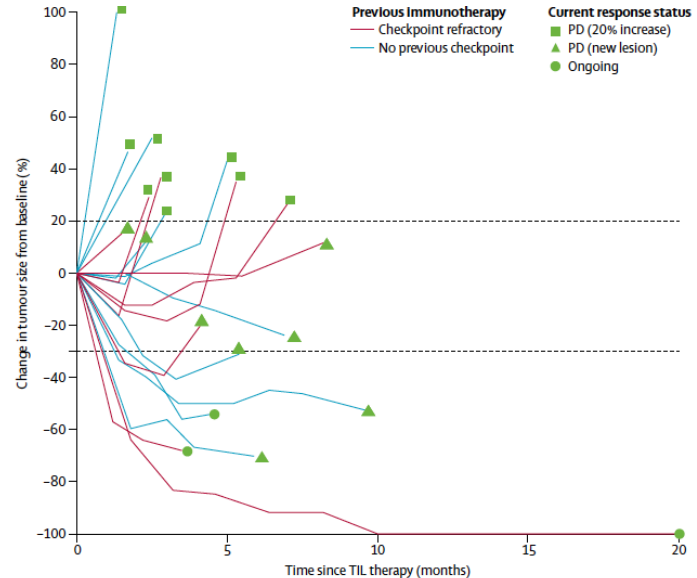
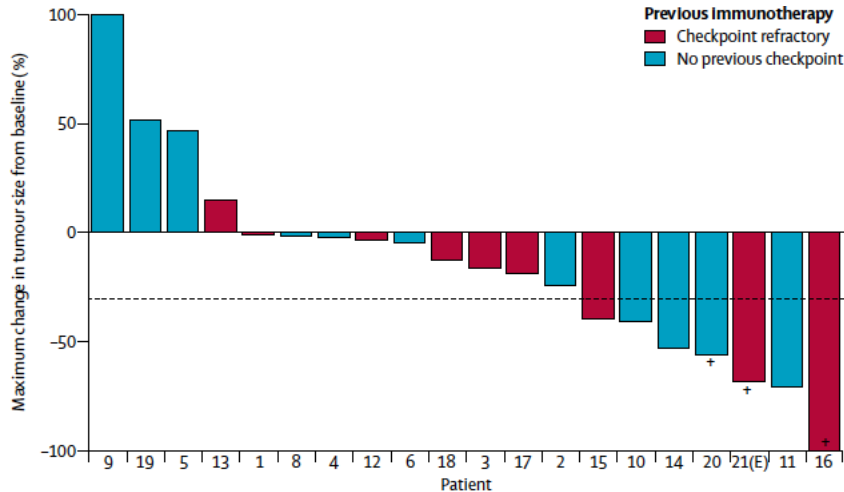
PR, unconfirmed or confirmed partial response; PD, progressive disease; TIL, tumor infiltrating lymphocytes. For "%Change in Tumor Size vs. pre-TIL", the Day -8 CT scan serves as baseline for further comparison. For Pre-TIL, nivolumab is given every 2 weeks; for Post-TIL, maintenance nivolumab is given every 4 weeks starting approximately at Day +29;

Seven patients were response evaluable with measurable disease and CT scans at Day 28 evaluation. Final sample-set still accruing (goal $n = 14$).



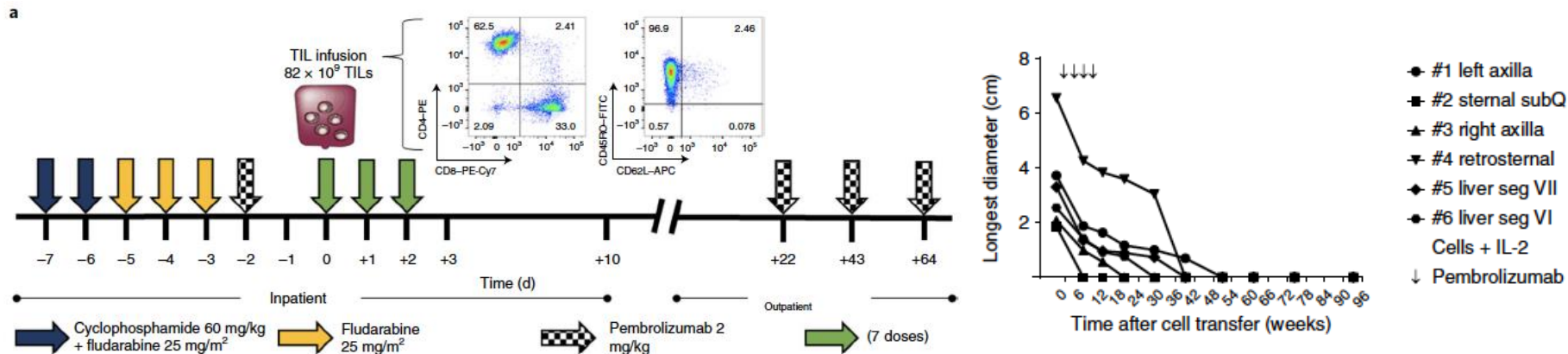
Treatment of metastatic uveal melanoma with adoptive transfer of tumour-infiltrating lymphocytes: a single-centre, two-stage, single-arm, phase 2 study

Smita S Chandran, Robert PT 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, MaryAnn Toomey, Steven A Rosenberg, Udai S Kammula



Immune recognition of somatic mutations leading to complete durable regression in metastatic breast cancer

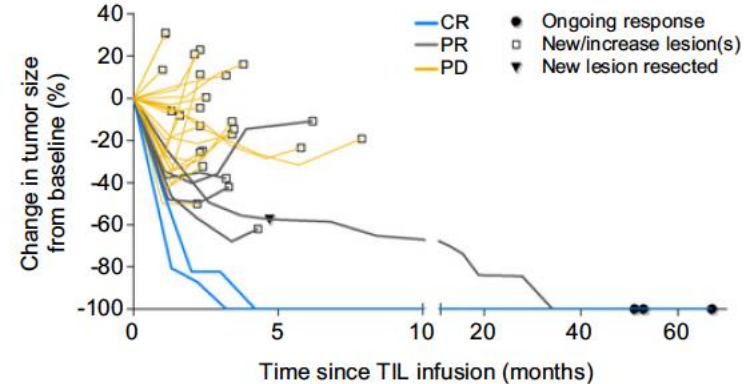
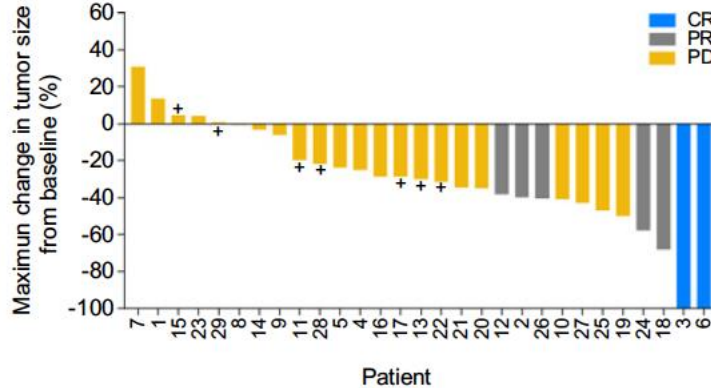
Nikolaos Zacharakis¹, Harshini Chinnasamy¹, Mary Black¹, Hui Xu¹, Yong-Chen Lu¹, Zhili Zheng¹, Anna Pasetto¹, Michelle Langhan¹, Thomas Shelton¹, Todd Prickett¹, Jared Gartner¹, Li Jia¹, Katarzyna Trebska-McGowan², Robert P. Somerville¹, Paul F. Robbins¹, Steven A. Rosenberg^{1*}, Stephanie L. Goff¹ and Steven A. Feldman¹



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



Sanja Stevanović¹, Sarah R. Helman¹, John R. Wunderlich², Michelle M. Langan², Stacey L. Doran¹, Mei Li M. Kwong², Robert P.T. Somerville², Christopher A. Klebanoff², Udai S. Kammula², Richard M. Sherry², James C. Yang², Steven A. Rosenberg², and Christian S. Hinrichs¹



A microscopic image showing several bright green, spiky spherical cells (likely TILs) interacting with a larger, textured blue cell. The background is a soft-focus green and blue.

TIL (Tumor Infiltrating Lymphocytes) technology is an ideal cancer therapy targeting heterogeneous solid tumors.

EXPLORE

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](https://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 →](#)

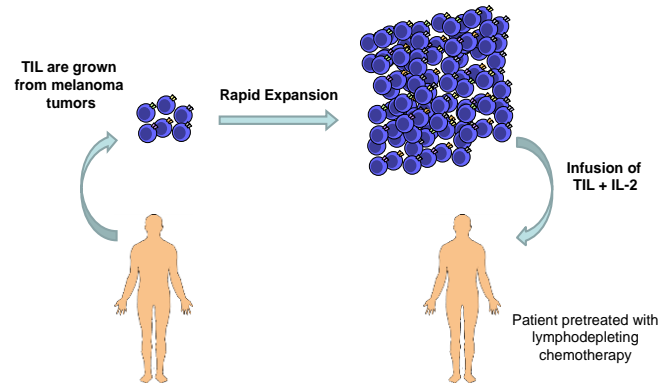
IOV-LUN-201: NON-SMALL CELL LUNG CANCER (NSCLC)

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 →](#)

Value of mobilizing endogenous tumor-specific T cell responses

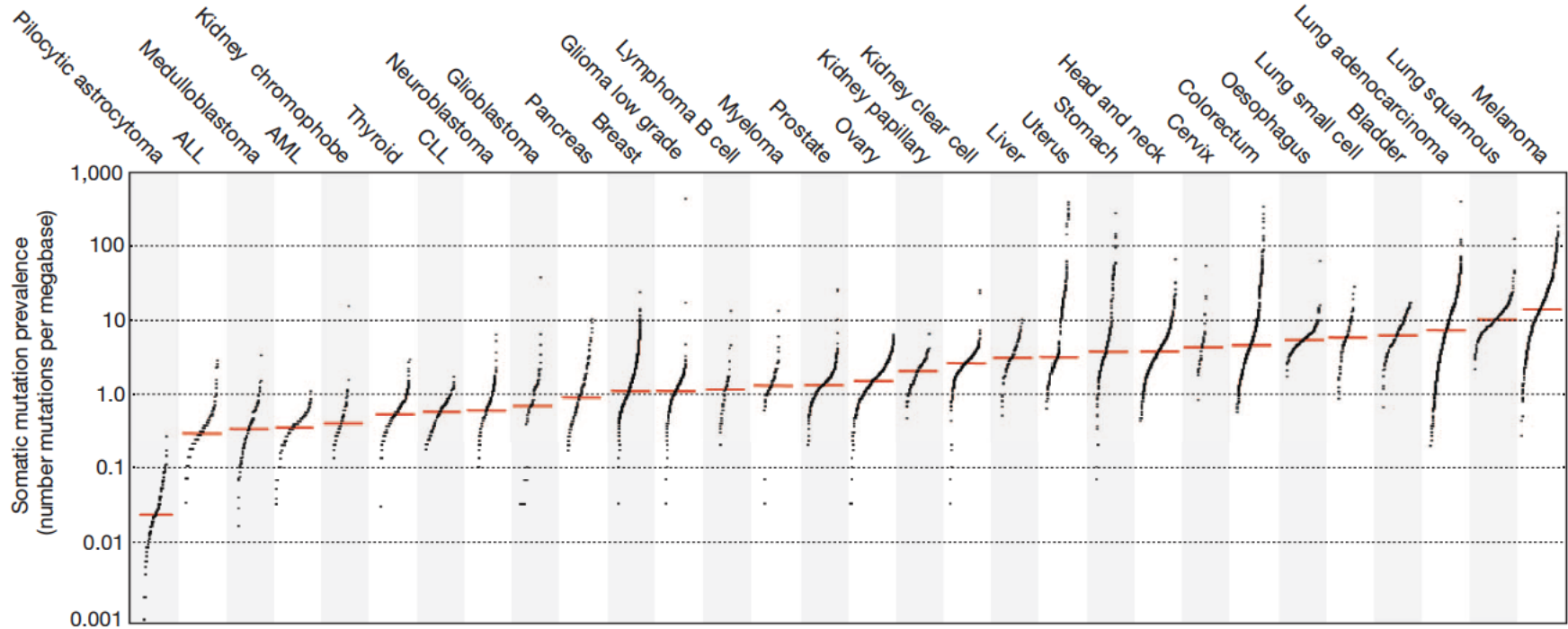
TIL therapy



Black box:

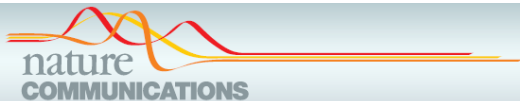
On bulk level anti-tumor reactivity
How much does the infusion product resemble the original TIL composition?
Which tumor antigens are recognized?

Prevalence of somatic DNA mutations across human cancer types



Alexandrov et al., Nature 2013

TMB as Biomarkers for Response to TIL






ARTICLE

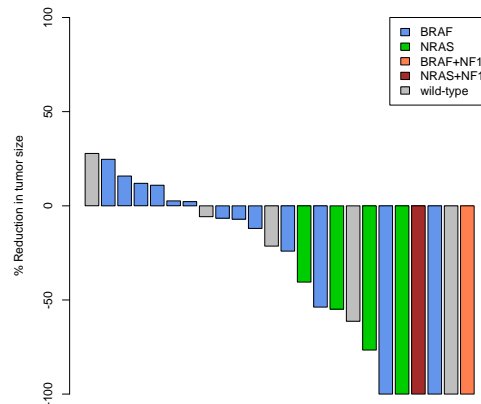
DOI: 10.1038/s41467-017-01460-0

OPEN

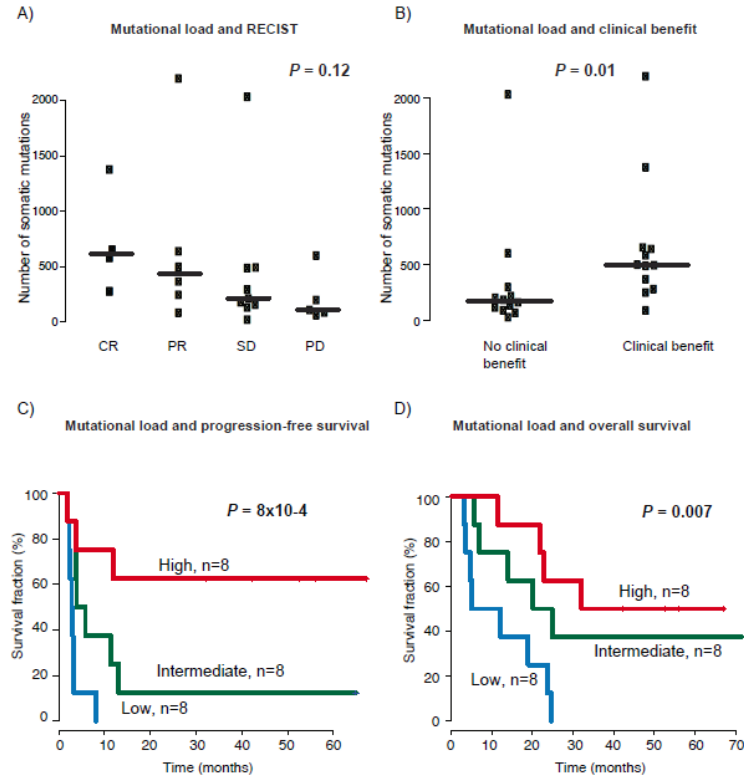
Mutational and putative neoantigen load predict clinical benefit of adoptive T cell therapy in melanoma

Martin Lauss¹, Marco Donia^{2,3}, Katja Harbst¹, Rikke Andersen^{2,3}, Shamik Mitra¹, Frida Rosengren¹, Maryem Salim¹, Johan Vallon-Christersson ¹, Therese Törngren¹, Anders Kvist ¹, Markus Ringnér ⁴, Inge Marie Svane^{2,3} & Göran Jönsson¹

Melanoma key driver mutations are not associated to clinical response

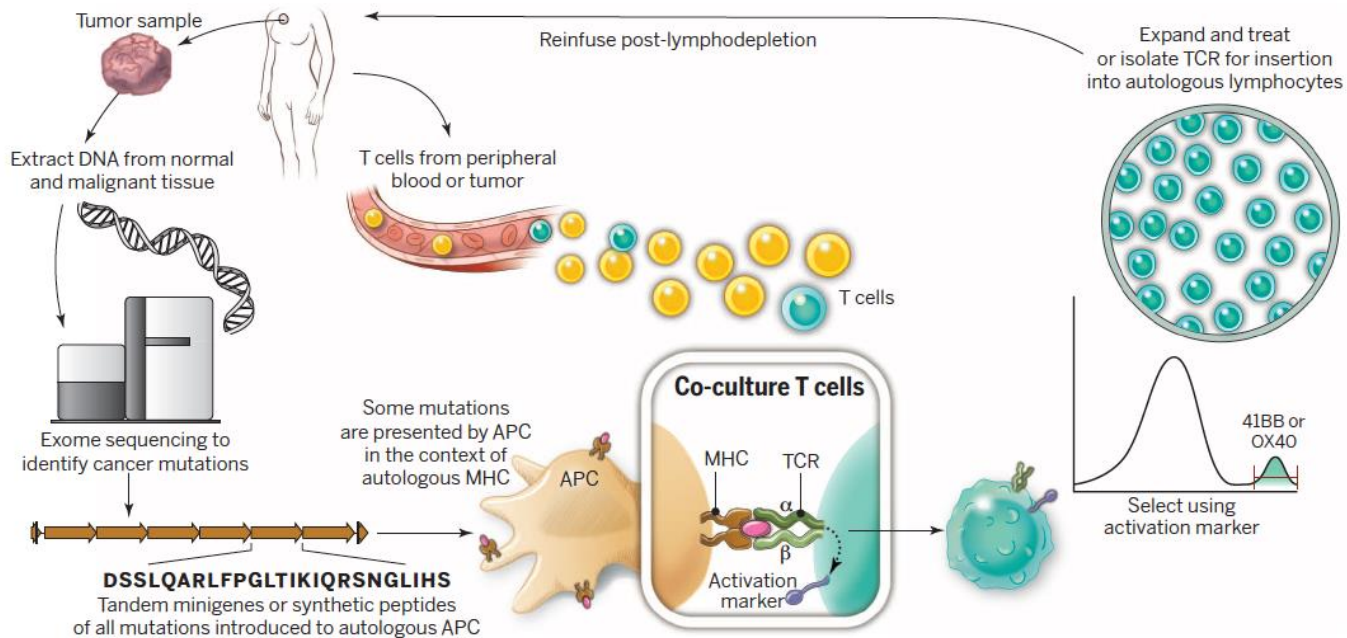


TMB as Biomarkers for Response to TIL

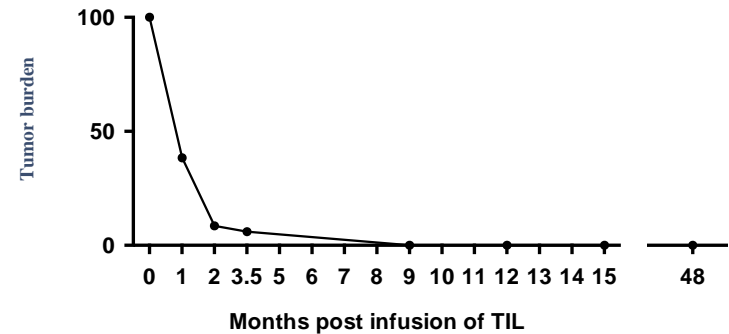
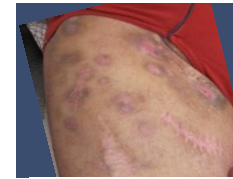
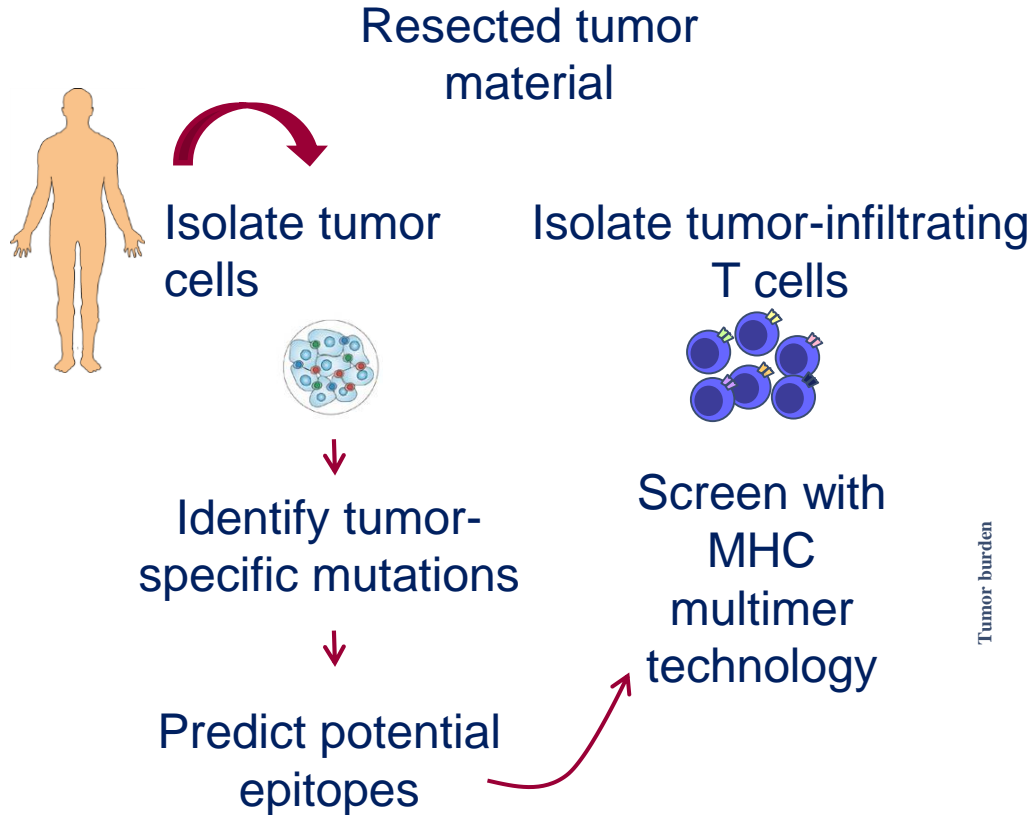


Mining exomic sequencing data to identify mutated antigens recognized by adoptively transferred tumor-reactive T cells

Paul F Robbins¹, Yong-Chen Lu¹, Mona El-Gamil¹, Yong F Li¹, Colin Gross¹, Jared Gartner², Jimmy C Lin³, Jamie K Teer^{4,5}, Paul Cliften³, Eric Tycksen³, Yarden Samuels^{2,5} & Steven A Rosenberg¹

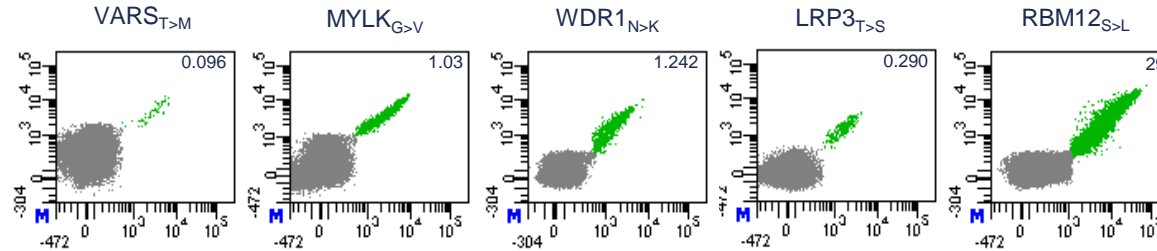


Patient NKI-003: complete response upon TIL therapy



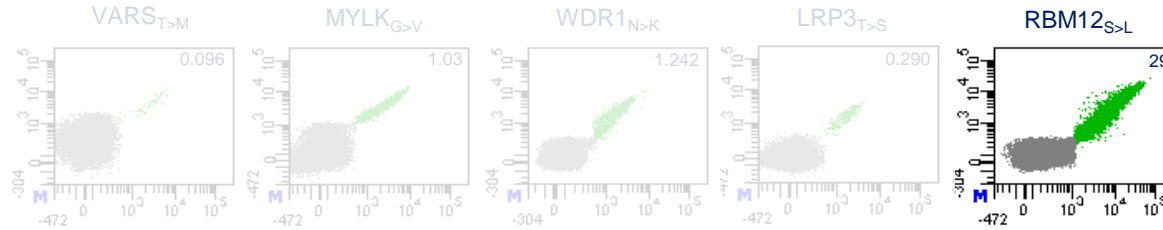
Patient NKI-003: complete response upon TIL therapy

TIL infusion product

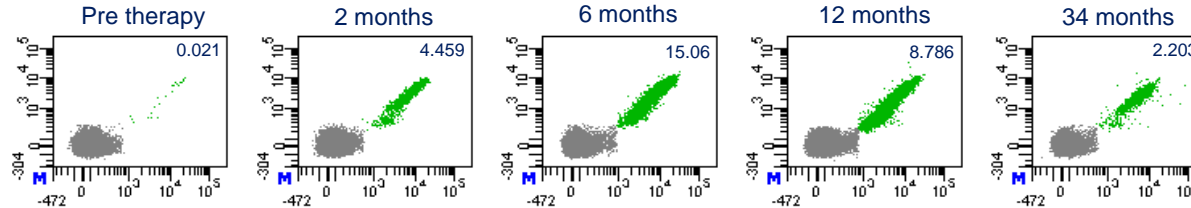


Patient NKI-003: complete response upon TIL therapy

TIL infusion product

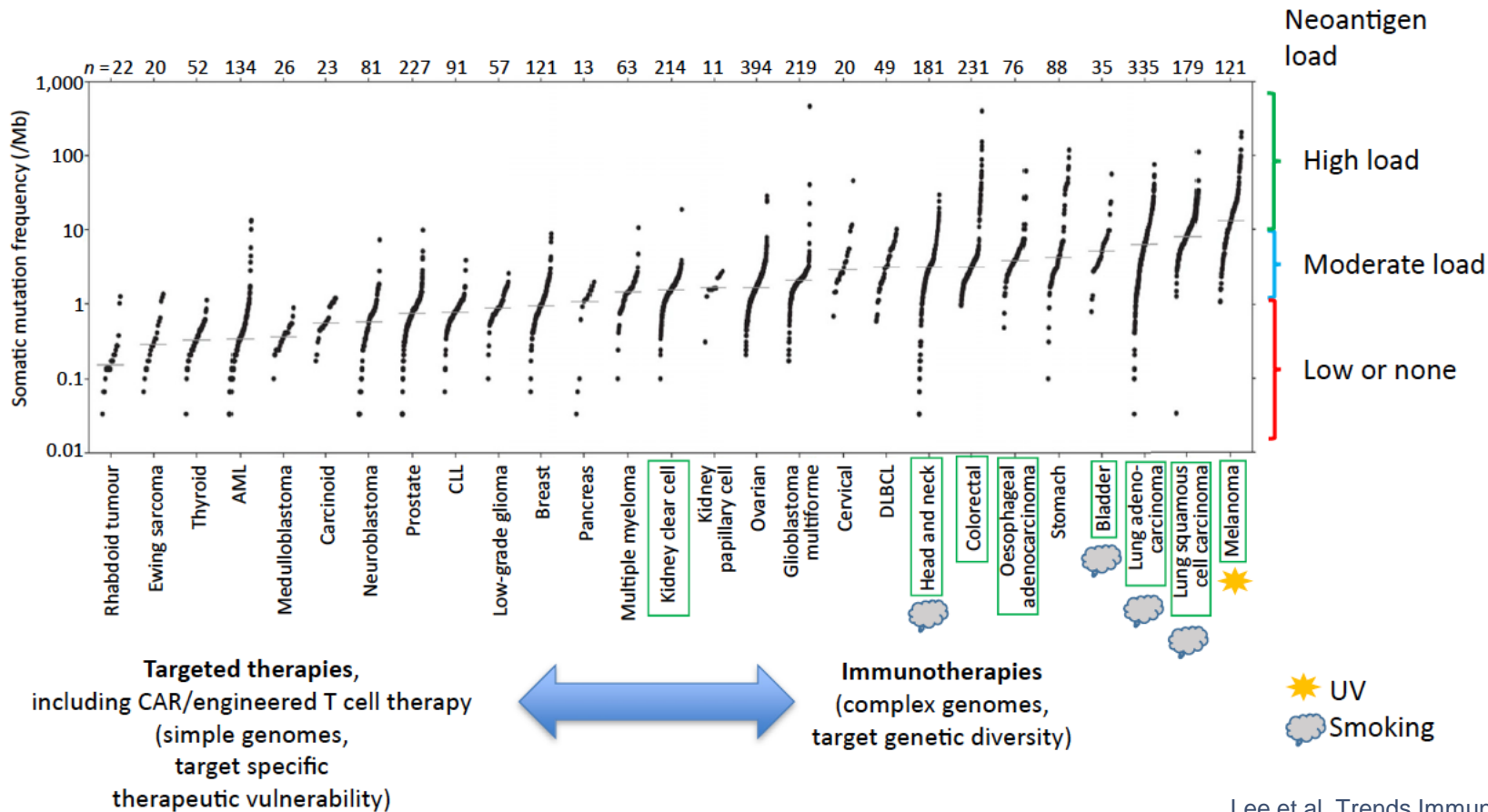


Peripheral blood

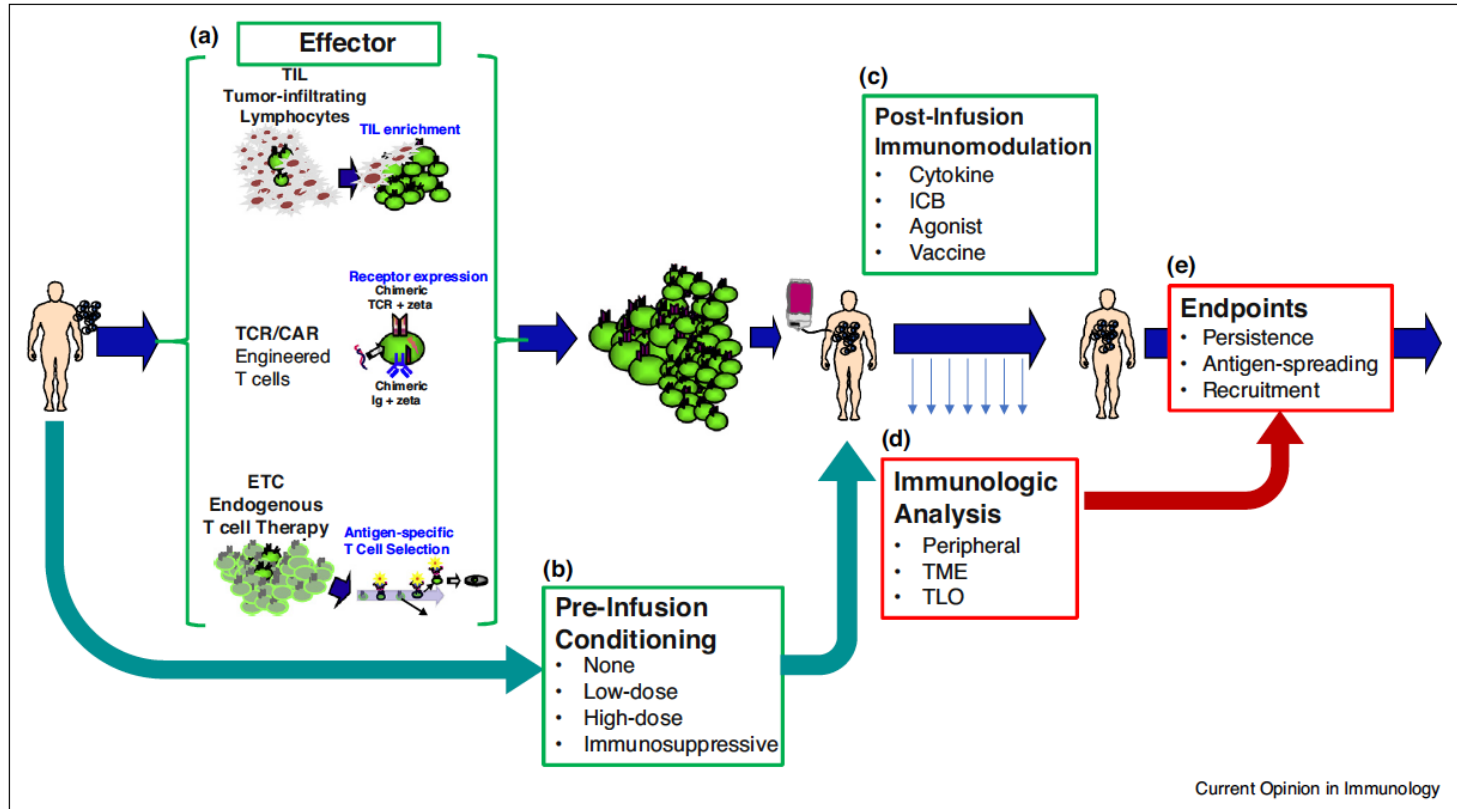


>450 fold increase in neo-antigen specific T cell reactivity upon TIL therapy

Knowledge about the importance of neoantigens in IO has sparked research in neoantigen directed clinical approaches

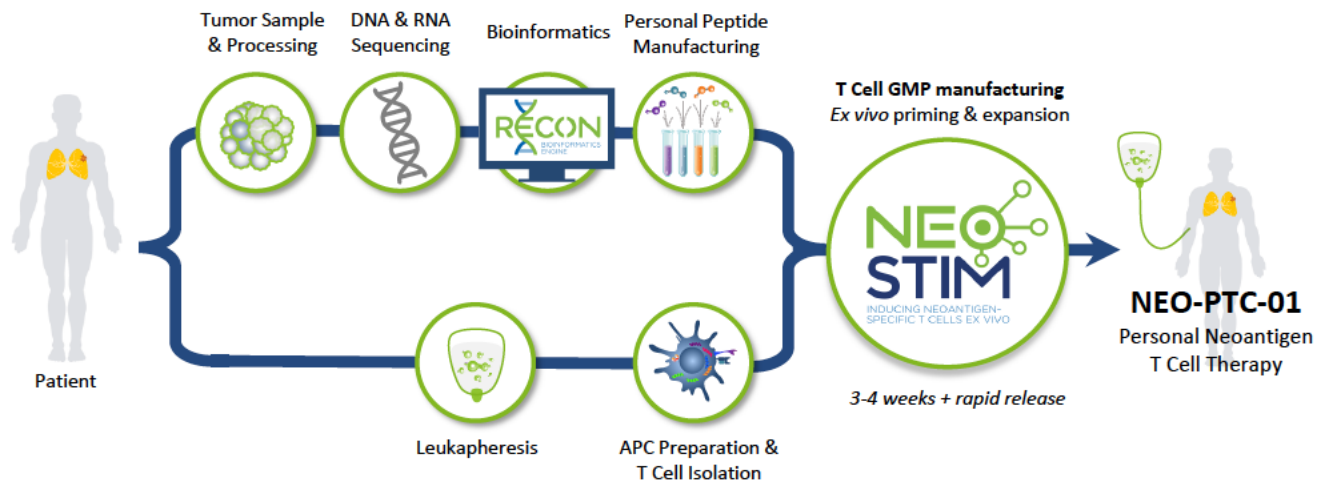


Adoptive cell therapy platforms



NEO-PTC-01 Personal Neoantigen T Cell Therapy

A personal T cell therapy consisting of multiple enriched T cell populations against high-priority neoantigens unique to each patient

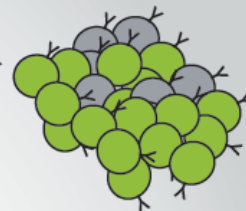


Objective

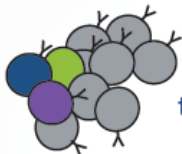
1. Expand out pre-existing memory responses



Increase cell numbers for pre-existing responses



2. Induce T-cell responses from the naïve repertoire



Broaden the T-cell repertoire that can potentially target the tumor

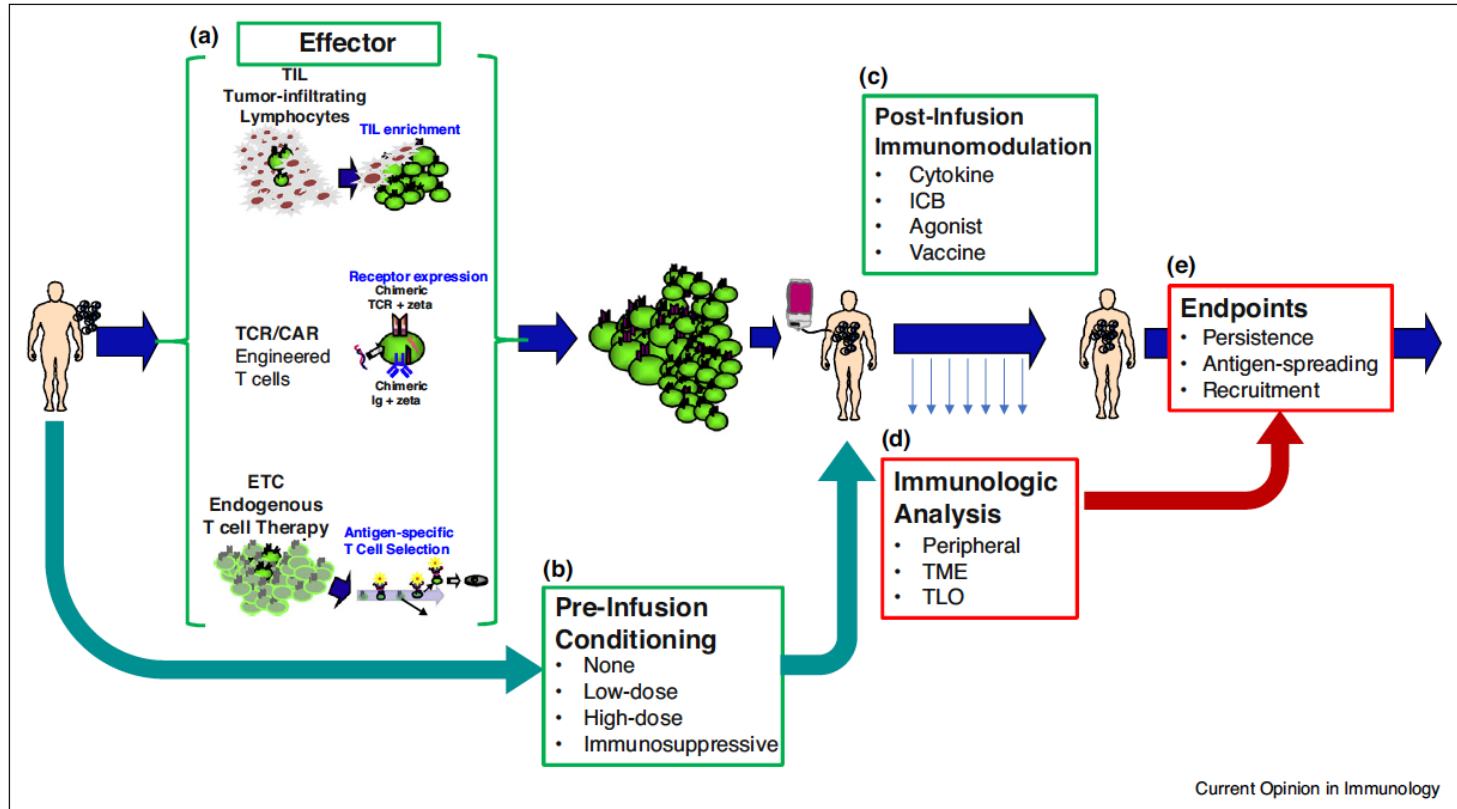


3. Generate a T-cell product with clinical efficacy

Steer towards favorable phenotype and function



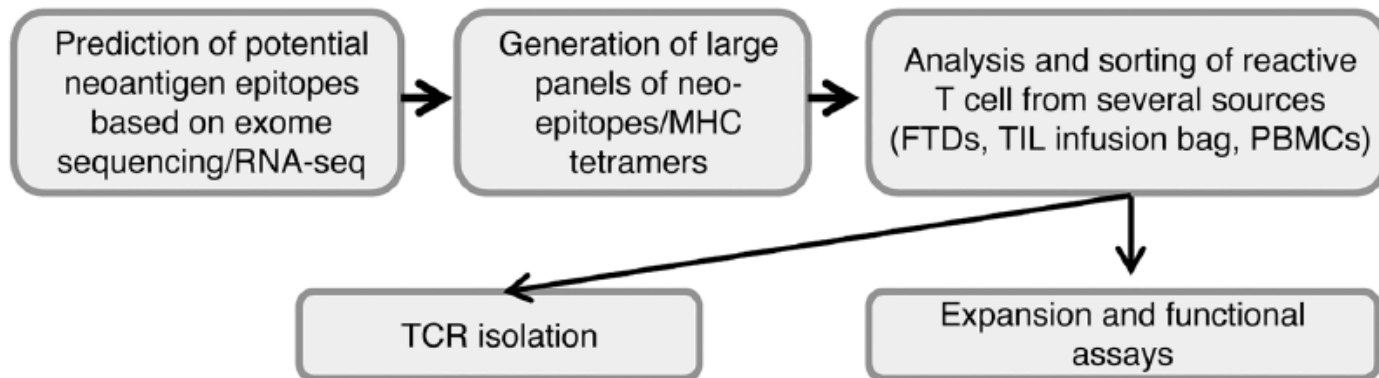
Adoptive cell therapy platforms



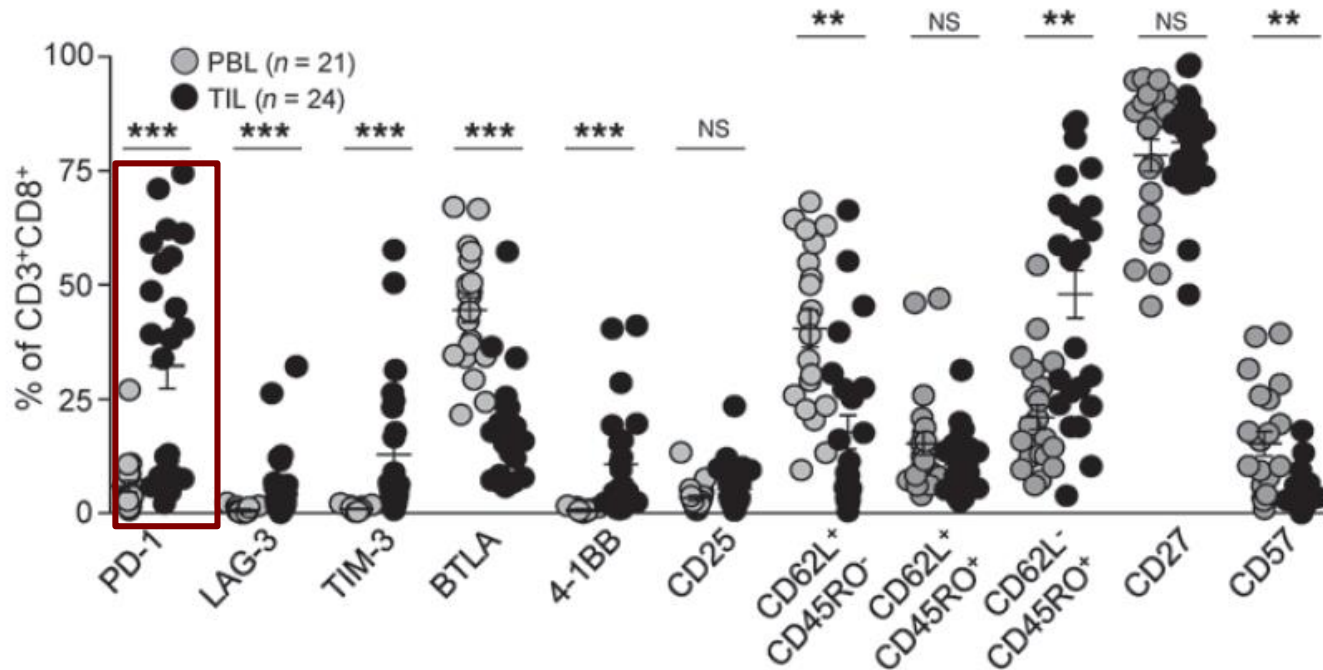
Isolation of neoantigen-specific T cells from tumor and peripheral lymphocytes

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PD-1 identifies patient-specific tumor-reactive TIL



Immunogenicity of somatic mutations in human gastrointestinal cancers

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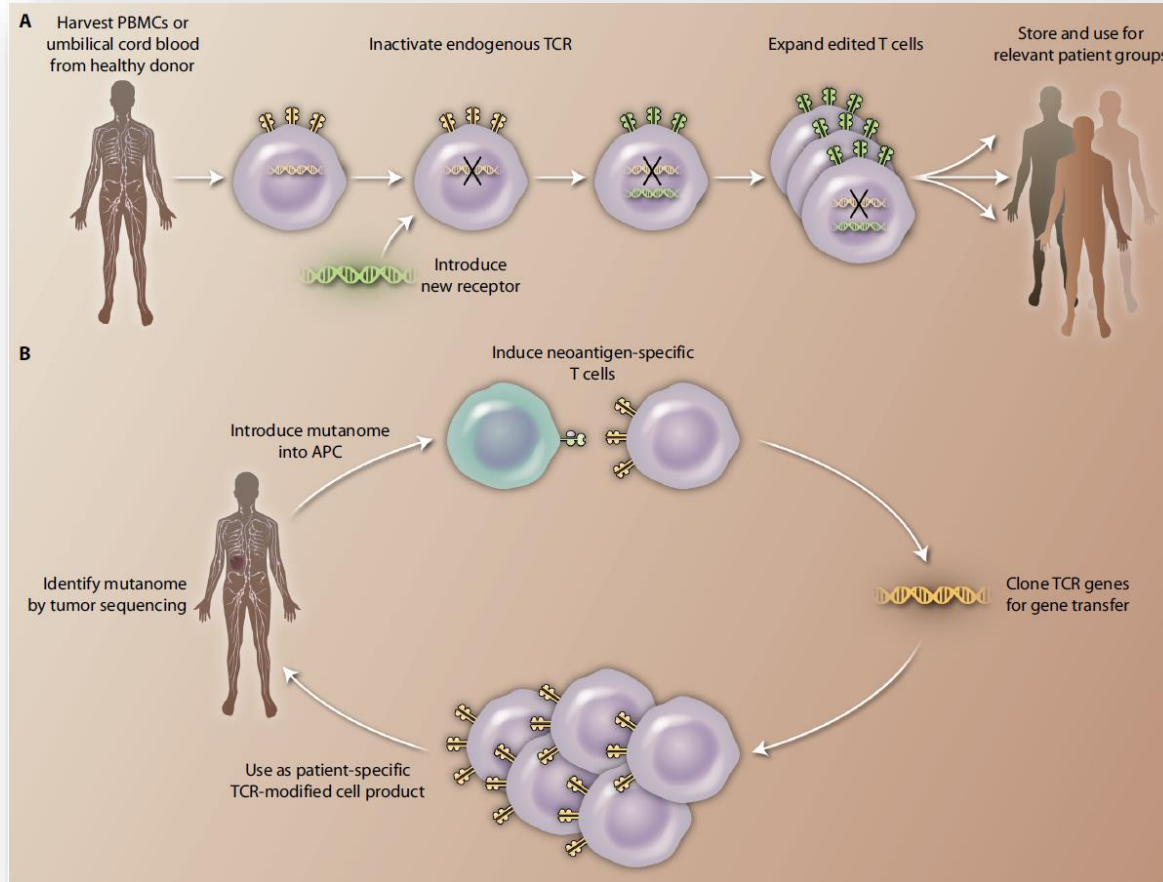
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Mutation-specific TIL in GI cancers harboring a low mutational load

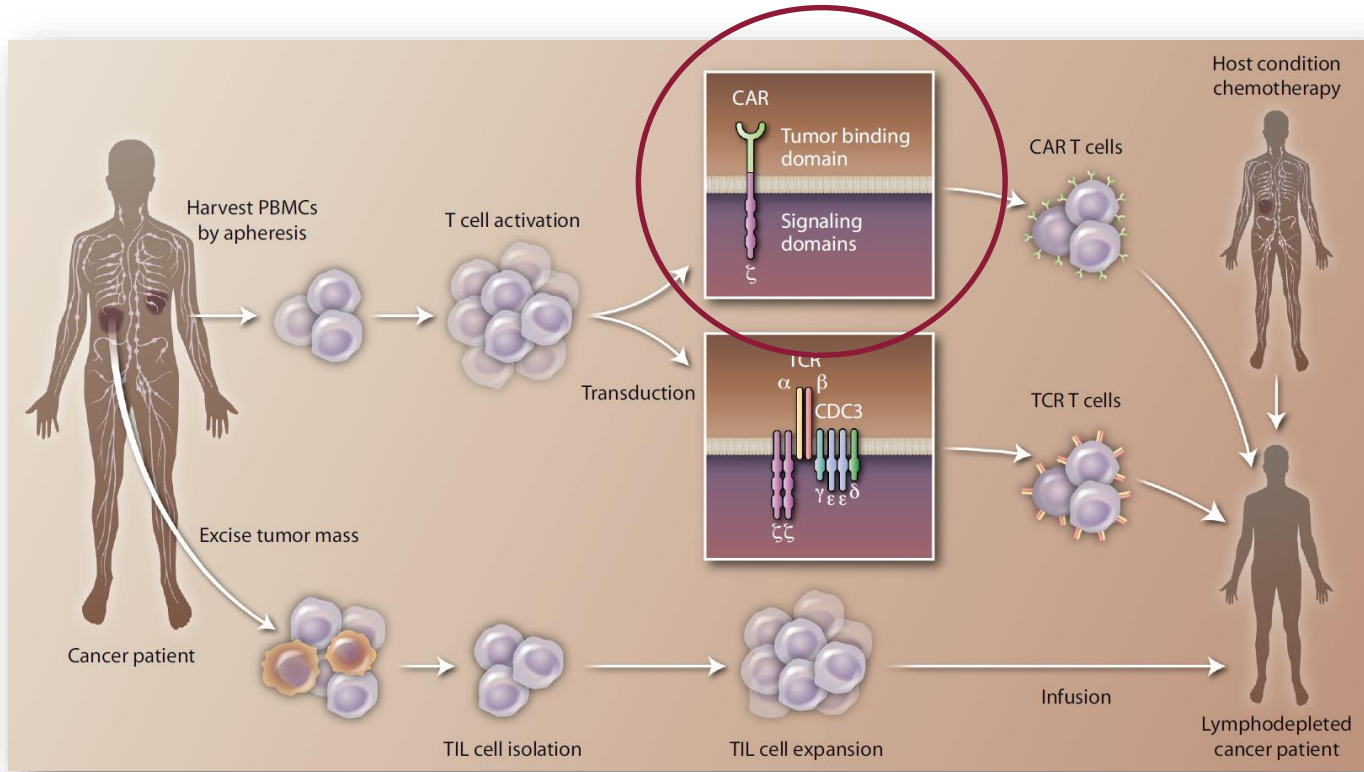
Table 1. Mutation-reactive T cells in metastatic GI cancers. NE, not evaluated.

Patient ID	Age/sex	Tumor type	Number of mutations †	Number of mutations assessed ‡	Number of TIL cultures assessed	Number TIL cultures with mutation reactivity §	Mutated protein recognized	Amino acid change	T cell type	Frequency of mutation-reactive TCR in tumor (%)
3737*	45/F	Bile duct	26	25	5	5	ERBB2IP	E805G E805G	CD4 CD4	0.009 0.375
3812	44/M	Bile duct	48	179	5	0	—	—	—	—
3942	46/F	Rectal	155	144	6	2 4 3	NUP98 KARS GPD2	A359D D356H E426K	CD8 CD8 CD4	0.67 0.020 0.037
3948	48/M	Esophageal	84	211	5	2 2 2	PLEC XPO7 AKAP2	E1179K P274S Q418K	CD4 CD4 CD4	NE NE NE
3971	49/M	Colon	118	118	23	11	CASP8	F67V	CD8	1.25
3978	46/F	Bile duct	39	38	9	1	ITGB4	S1002I	CD4	NE
3995	50/M	Colon	58	154	19	2 15 2	TUBGCP2 RNF213 KRAS	P293L N1702S G12D	CD8 CD8 CD8	0.023 0.60 0.055
4007	52/M	Colon	134	264	23	4 5	SKIV2L H3F3B	R653H R653H A48T	CD8 CD8 CD8	0.090 0.014 1.19
4032	46/M	Colon	101	222	24	12 1 7	API5 RNF10 PHLPP1	R243Q R243Q E572K G566E	CD8 CD8 CD8 CD8	0.083 0.059 0.030 0.081
4069	57/M	Pancreatic	10	97	15	1	ZFYVE27	R6H	CD8	0.088

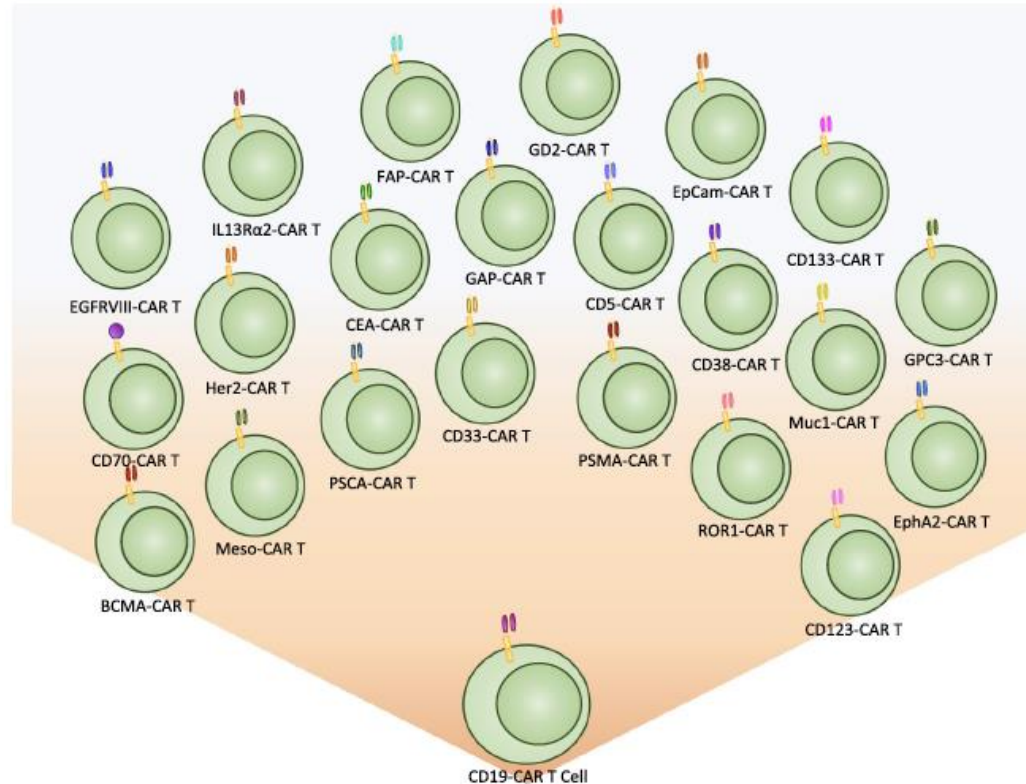
From universal to highly personalized gene-modified ACT



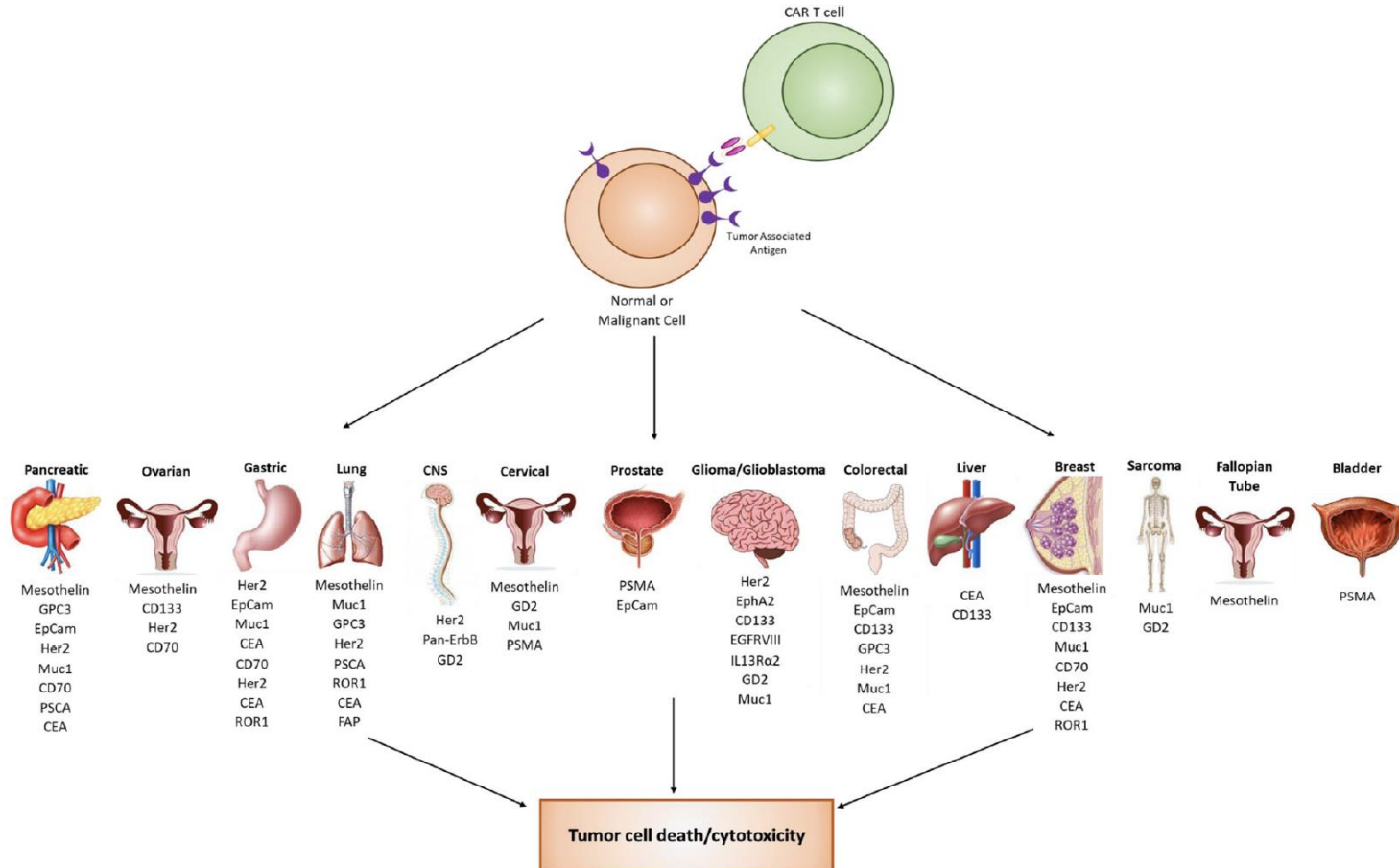
Adoptive cell therapy platforms



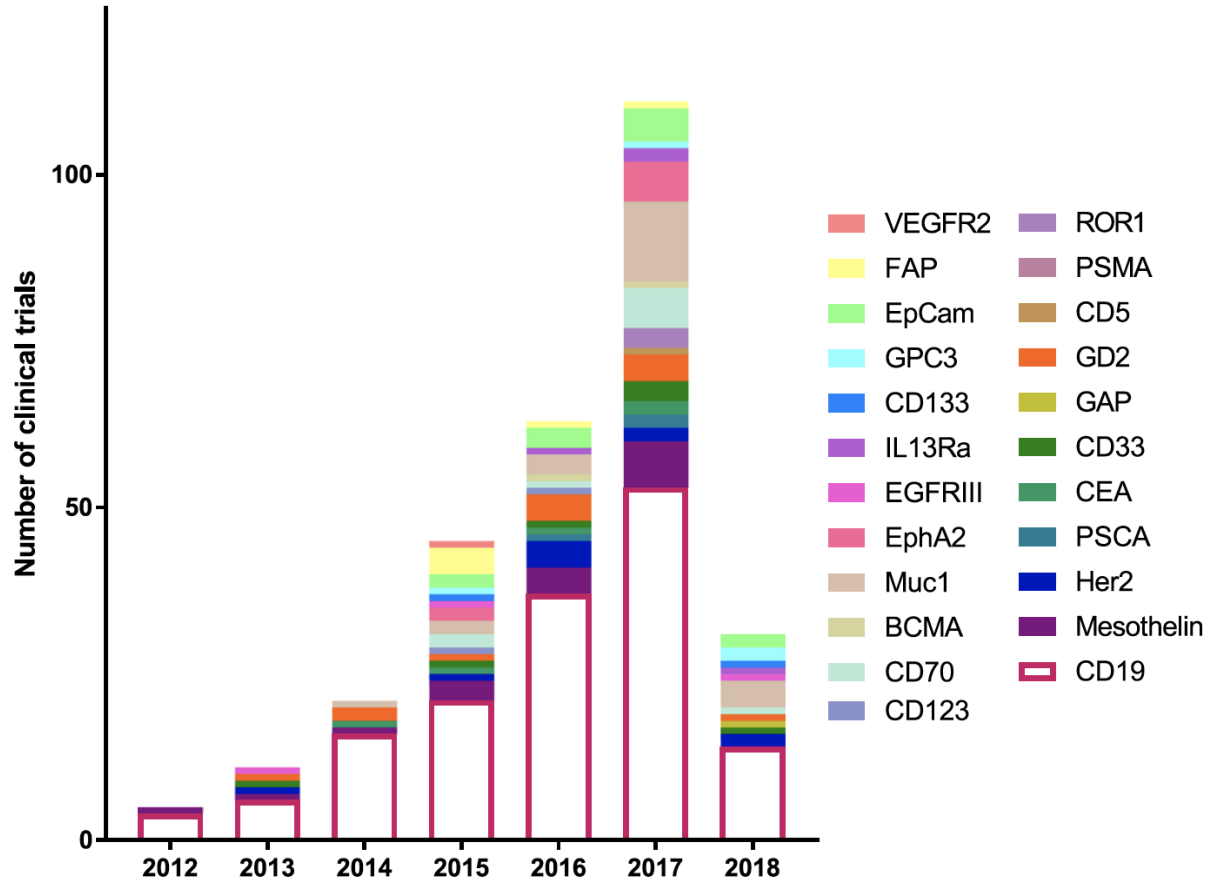
CAR-T currently in clinical trials



Growing list of targets for solid cancers



Exponential growth of CAR-T trials up to May 2018



Conclusions

- Cell therapy for solid cancer is coming of age
 - New developments in:
 - TIL therapy (expansion beyond melanoma)
 - Induction/expansion of blood-derived T cells (focus on neoantigens)
 - Use of gene modified T cells
 - CAR-T
 - TCR-T (focus on neoantigens)
 - Novel developments in gene modification
 - Transposon/transposase-based
 - CRISPR/Cas9-based

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Thank you for your attention!

Questions?