

Cell therapy in solid tumors

Dr. Victor Moreno

START Madrid-FJD, Early Phase Clinical Trials Unit
University Hospital Fundación Jiménez Díaz



**CDDF 11TH SPRING
CONFERENCE 2020**
THE NETHERLANDS | 10-12 FEBRUARY 2020

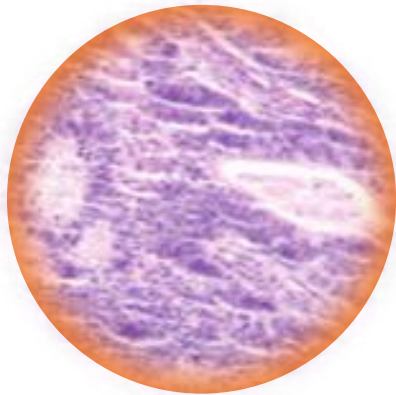
→ WWW.CDDF.ORG

Disclosures

- Advisory: BMS, Janssen, Bayer, Basilea, Pieris.
- Clinical Trials related to the topic:
 - Adaptimmune
 - GSK
 - Iovance

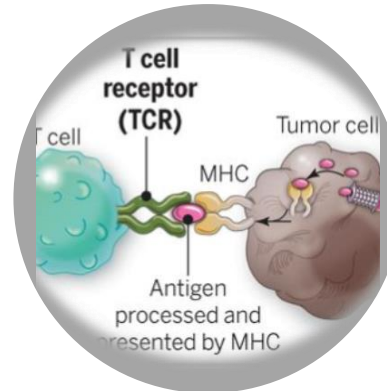
Adoptive cell transfer

personalized cancer immunotherapy that involves the administration of a patient's own autologous immune cells

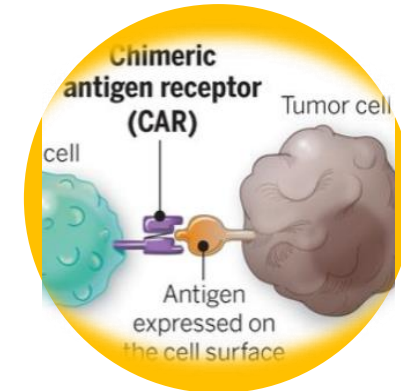


TUMOR INFILTRATING LYMPHOCYTES.

TUMOR



T-CELL RECEPTOR (TCR) DIRECTED
AGAINST A PARTICULAR TARGET
ANTIGEN

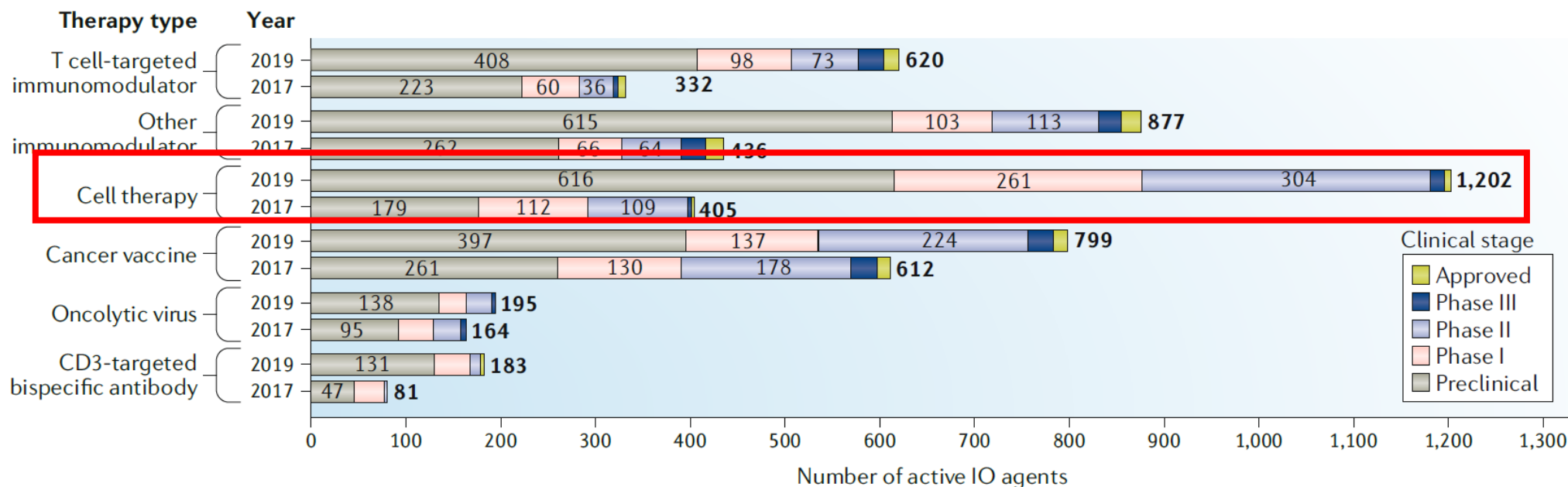


CHIMERIC ANTIGEN RECEPTOR (CAR)

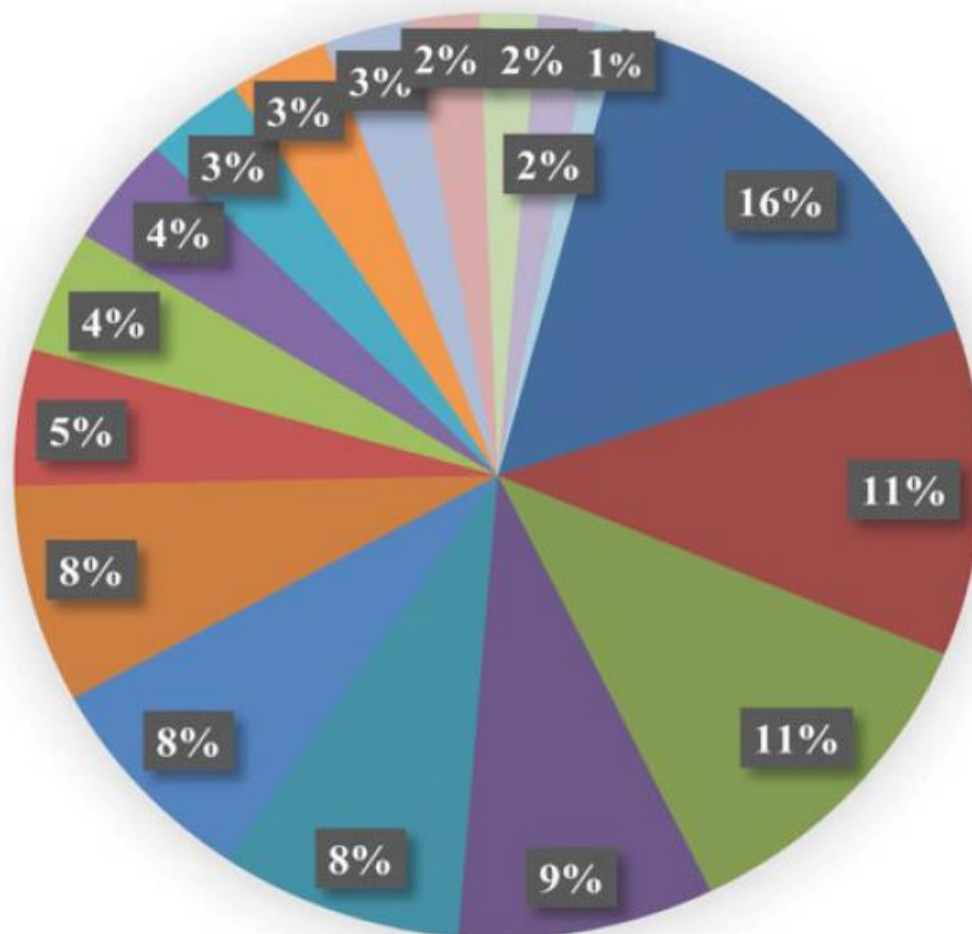
PERIPHERAL BLOOD

Immuno-oncology Drug Development in 2019

Increase from 2017 to 2019 : 300% in Cell therapy



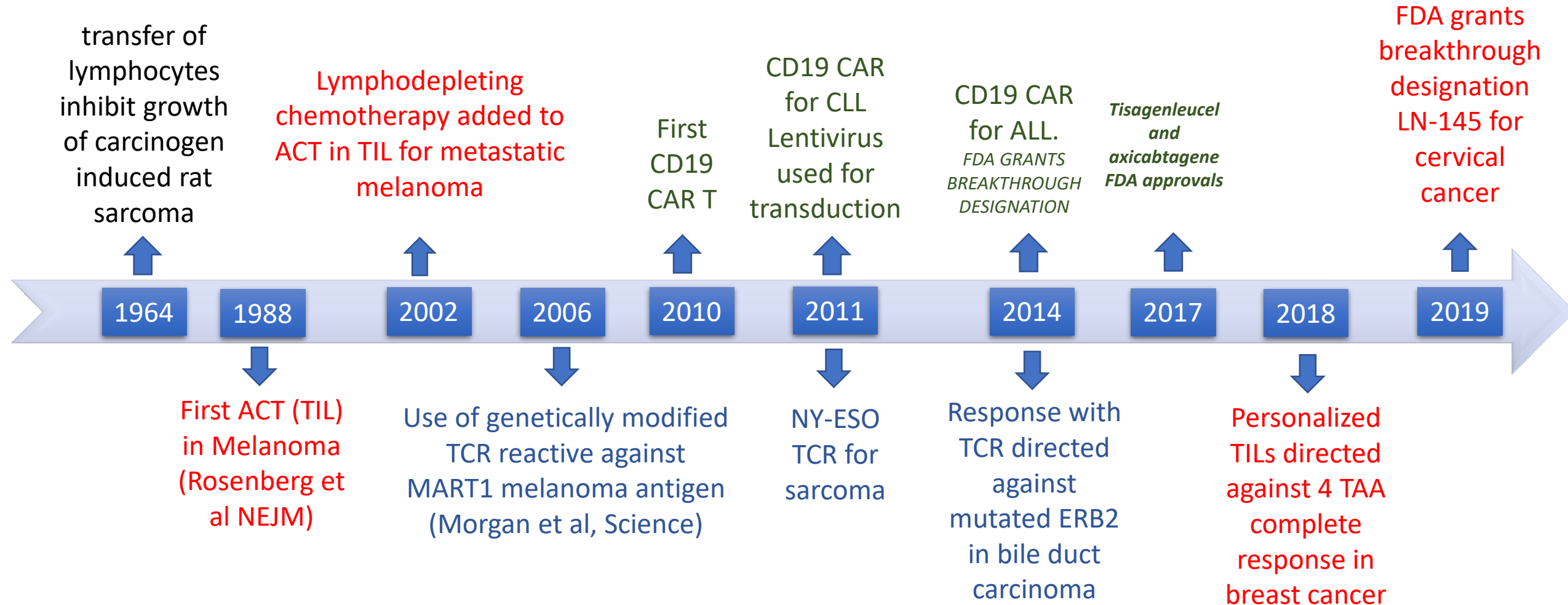
B Condition Type



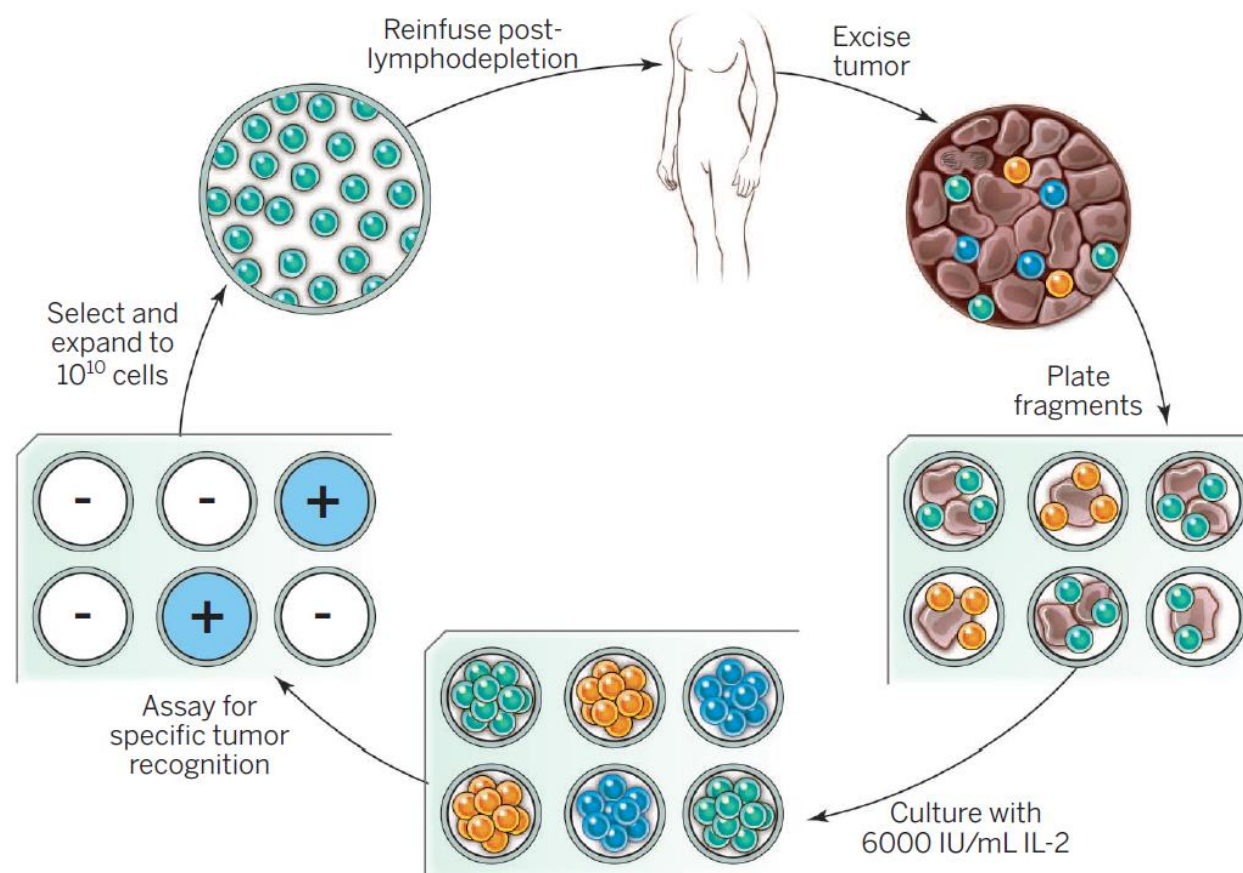
- Melanoma
- Gastrointestinal Cancer
- Leukemia
- Lung Cancer
- Unspecified
- Other
- Sarcoma
- Ovarian, Fallopian Tube, and Peritoneal Cancer
- Neoplasm
- Myeloma
- Bladder Cancer
- Kidney Cancer
- Breast Cancer
- Skin Cancer
- Cervical Cancer
- Mesothelioma
- Brain Cancer

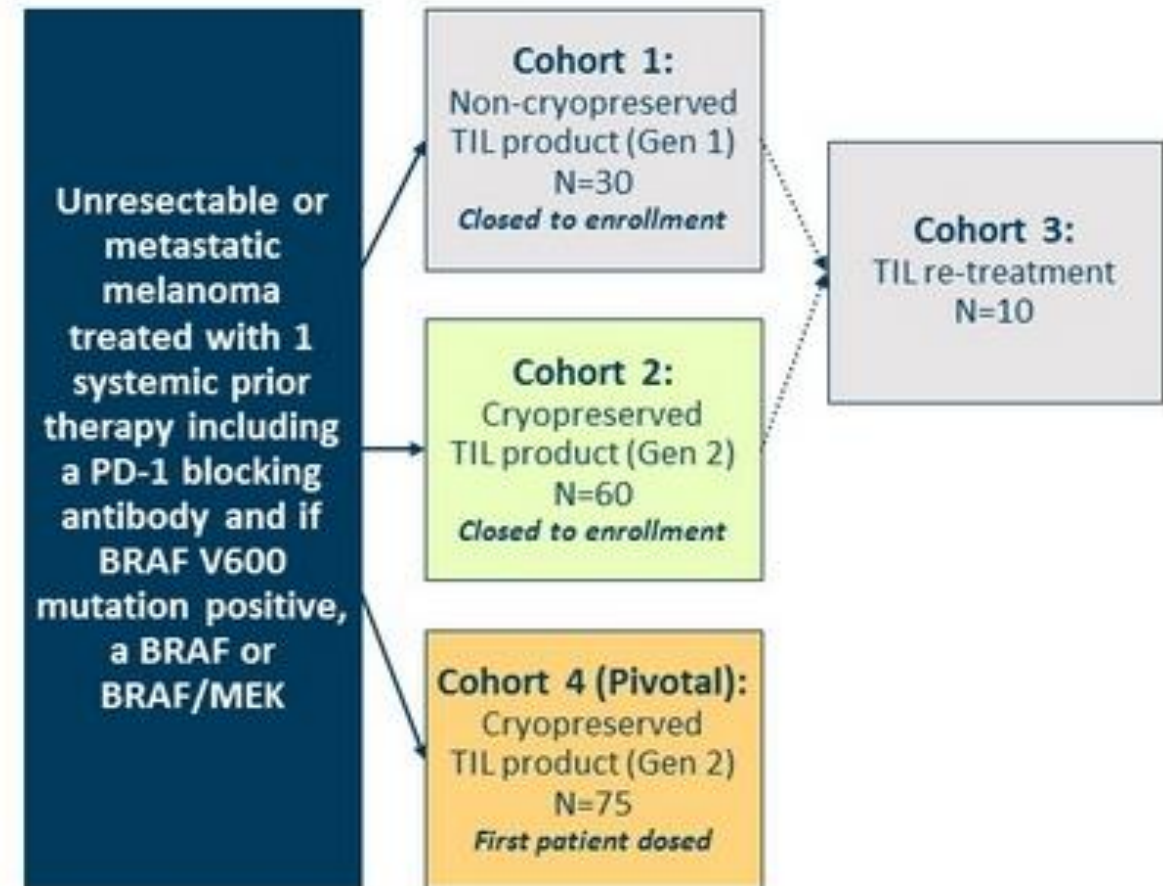
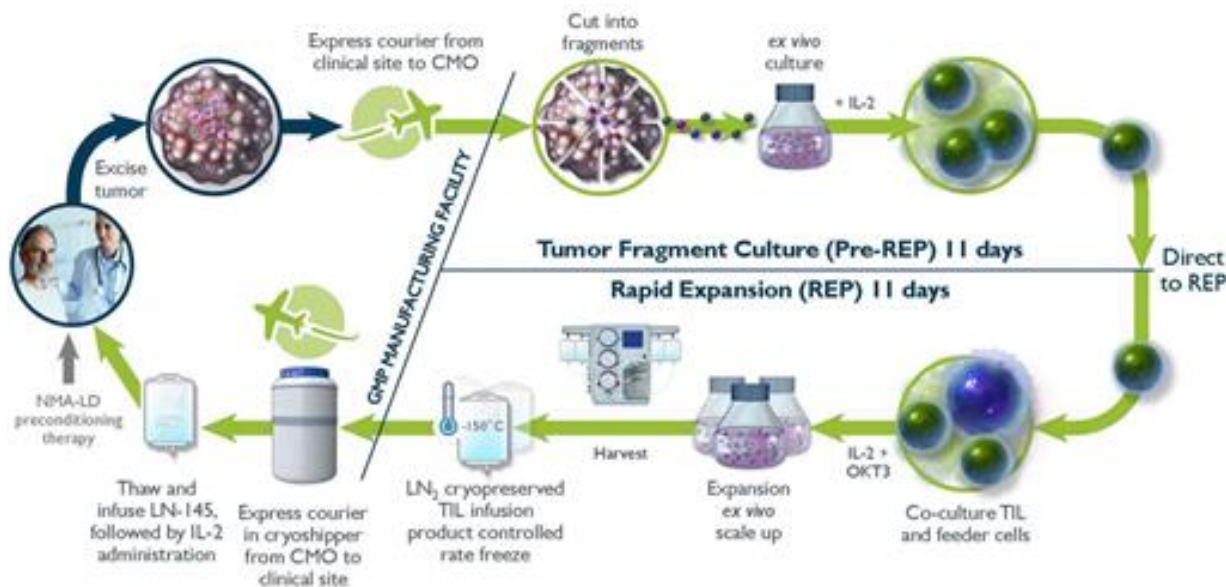


ACT for cancer timeline



TIL





Lifileucel (LN-144) results in melanoma

Table 3. 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 +

ORR BY SUBGROUP PATIENTS, N=66
n (%)

Prior Anti-CTLA-4

Yes (n=53) 20 (38)

No (n=13) 5 (39)

BRAF Mutation Status

Mutated (V600E or V600K), (n=17) 8 (47)

Non-Mutated (n=49) 17 (35)

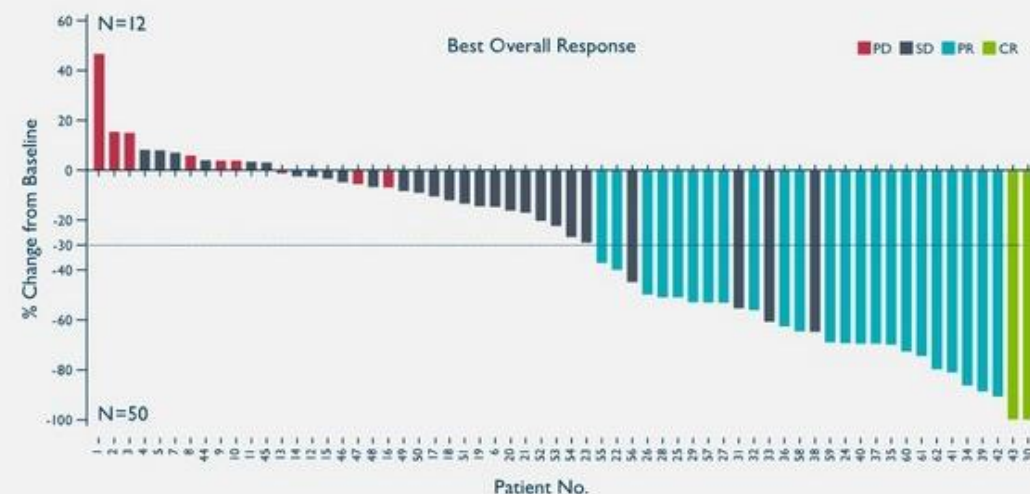
• Cohort 2: Lifileucel Infusion Product and TIL Therapy Characteristics

- Mean number of TIL cells infused: 27.3×10^9
- Median number of IL-2 doses administered was 5.5

- 81% of patients had a reduction in tumor burden
- Mean Time to response 1.9 months (range 1.3-5.6)
- All assessments are by RECIST 1.1
- Responses are deep – nearly all responders are greater than 30%

COHORT 2

Lifileucel best overall response rate⁽¹⁾



(1) Three subjects had no post-TIL disease assessment due to early death; one subject had no post-TIL disease assessment due to new cancer therapy. For subject #30, 100% change from baseline is displayed for the CR visit involved lymph nodes.

Safety & efficacy of adoptive cell transfer using autologous tumor infiltrating lymphocytes (LN-145) for treatment of recurrent, metastatic, or persistent cervical carcinoma

Amir A. Jazaeri¹, Emese Zsiros², Rodabe Navroze Amaria¹, Andrew S. Artz³, Robert P. Edwards⁴, Robert Michael Wenham⁵, Brian M. Slomovitz⁶, Axel Walther⁷, Sajeev Samuel Thomas⁸, Jason Alan Chesney⁹, Robert Morris¹⁰, Koji Matsuo¹¹, Stephanie Gaillard¹², Peter G. Rose¹³, Jesus Garcia Donas¹⁴, Jacqueline Maria Tromp¹⁵, Kelly DiTrapani¹⁶, Huiling Li¹⁶, Maria Fardis¹⁶, Bradley J. Monk¹⁷

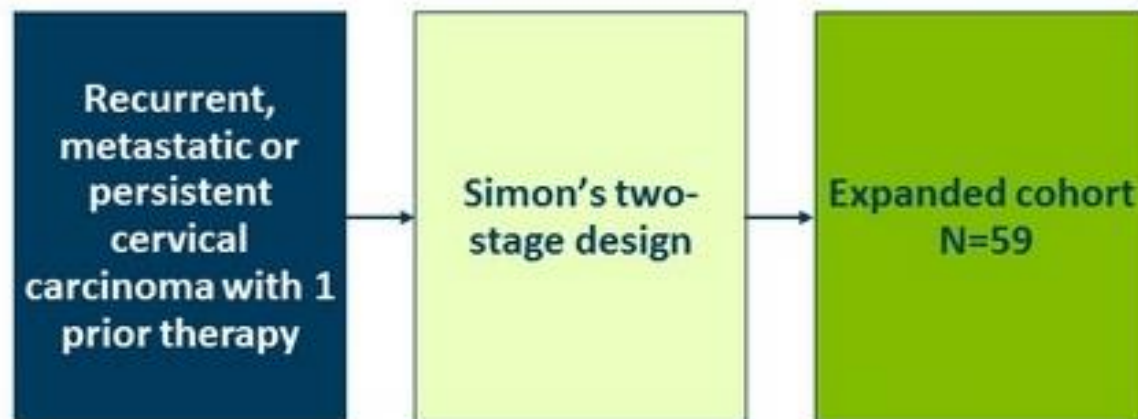
¹The University of Texas - MD Anderson Cancer Center, Houston, TX; ²Roswell Park Comprehensive Cancer Center, Buffalo, NY; ³University of Chicago Comprehensive Cancer Center, Chicago, IL; ⁴Hillman Cancer Institute, University of Pittsburgh Medical Center, Pittsburgh, PA; ⁵Lee Moffitt Cancer Center, Tampa, FL; ⁶Sylvester Comprehensive Cancer Center, University of Miami Miller School of Medicine, Miami, FL; ⁷University Hospitals Bristol, Bristol, United Kingdom; ⁸University of Florida Health Cancer Center at Orlando Health, Orlando, FL; ⁹James Graham Brown Cancer Center, University of Louisville, Louisville, KY; ¹⁰Barbara A. Karmanos Cancer Center, Wayne State University, Detroit, MI; ¹¹Los Angeles County Hospital, University of Southern California, Los Angeles, CA; ¹²Johns Hopkins School of Medicine, Baltimore, MD; ¹³Cleveland Clinic Foundation, Cleveland, OH; ¹⁴Hospital Universitario Madrid Sancharro, Madrid, Spain; ¹⁵Academical Medical Center, Amsterdam, Netherlands; ¹⁶Iovance Biotherapeutics, Inc., San Carlos, CA; ¹⁷University of Arizona Cancer Center at Dignity Health St. Joseph's Hospital and Medical Center, Phoenix, AZ

NCT03108495

Copies of this poster obtained through
Onc's Response (OR) Guide are for
personal use only and may not be
reproduced without permission from
ASCO and the author of this poster



For more information, please contact
kellydtrapani@iovance.com



METHODS

- 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

RESULTS

Table 1. Patient Characteristics

CHARACTERISTIC	N=27, (%)	CHARACTERISTIC		N=27, (%)
Age		ECOG score, n (%)	Screening	Baseline
Median	45	0	19 (70)	9 (33)
Min, Max	30, 68	1	8 (30)	17 (63)
Prior therapies, n (%)		≥2	0	1 (4)
Mean # prior therapies	2.4	Histologic Cell Type, n (%)		
Platinum-Based	27 (100)	Squamous Cell Carcinoma		12 (44)
Taxane	26 (96)	Adenocarcinoma		12 (44)
Anti-VEGF	22 (82)	Adenosquamous Carcinoma		3 (11)
Radiotherapy	20 (74)	Target Lesion Sum of Diameters (mm)		
Anti-PD-1/PD-L1	4 (15)	Mean (SD)		41 (38)
Cancer Status at Screening		Min, Max		10, 165
Metastatic	14 (52)	Number of Target & Non-Target Lesions (at Baseline)		
Recurrent	10 (37)	>3		17 (63)
Persistent	3 (11)	Mean (Min, Max)		4 (1,9)

Safety & efficacy of adoptive cell transfer using autologous tumor infiltrating lymphocytes (LN-145) for treatment of recurrent, metastatic, or persistent cervical carcinoma

Amir A. Jazaeri¹, Emese Zsiros², Rodabe Navroze Amaria¹, Andrew S. Artz³, Robert P. Edwards⁴, Robert Michael Wenhams⁵, Brian M. Slomovitz⁶, Axel Walther⁷, Sajeev Samuel Thomas⁸, Jason Alan Chesney⁹, Robert Morris¹⁰, Koji Matsuo¹¹, Stephanie Gaillard¹², Peter G. Rose¹³, Jesus Garcia Donas¹⁴, Jacqueline Maria Tromp¹⁵, Kelly DiTrapani¹⁶, Huiling Li¹⁶, Maria Fardis¹⁶, Bradley J. Monk¹⁷

¹The University of Texas - MD Anderson Cancer Center, Houston, TX; ²Roswell Park Comprehensive Cancer Center, Buffalo, NY; ³University of Chicago Comprehensive Cancer Center, Chicago, IL; ⁴Hillman Cancer Institute, University of Pittsburgh Medical Center, Pittsburgh, PA; ⁵Lee Moffitt Cancer Center, Tampa, FL; ⁶Sylvester Comprehensive Cancer Center, University of Miami Miller School of Medicine, Miami, FL; ⁷University Hospitals Bristol, Bristol, United Kingdom; ⁸University of Florida Health Cancer Center at Orlando Health, Orlando, FL; ⁹James Graham Brown Cancer Center, University of Louisville, Louisville, KY; ¹⁰Barbara A. Karmanos Cancer Center, Wayne State University, Detroit, MI; ¹¹Los Angeles County Hospital, University of Southern California, Los Angeles, CA; ¹²Johns Hopkins School of Medicine, Baltimore, MD; ¹³Cleveland Clinic Foundation, Cleveland, OH; ¹⁴Hospital Universitario Madrid Sancharro, Madrid, Spain; ¹⁵Academical Medical Center, Amsterdam, Netherlands; ¹⁶Iovance Biotherapeutics, Inc., San Carlos, CA; ¹⁷University of Arizona Cancer Center at Dignity Health St. Joseph's Hospital and Medical Center, Phoenix, AZ

NCT03108495

Copies of this poster obtained through
Onc's Response (OR) Guide are for
personal use only and may not be
reproduced without permission from
ASCO and the author of this poster



For more information, please contact
kellyditrapani@iovance.com

Figure 1. Efficacy of adoptive cell transfer using autologous tumor infiltrating lymphocytes (LN-145) for treatment of recurrent, metastatic, or persistent cervical carcinoma

Efficacy

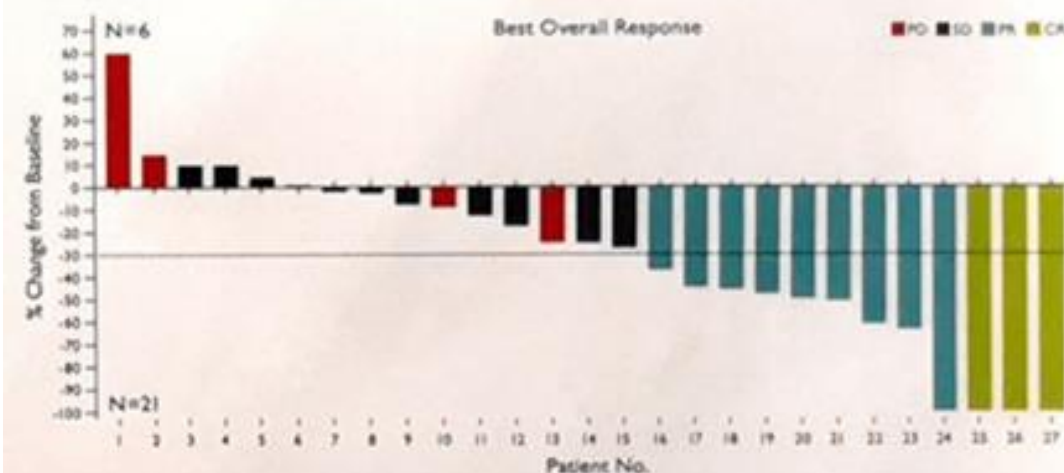
RESPONSE (RECIST v1.1)

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

© Iovance Biotherapeutics, Inc. 2019

Figure 4. Efficacy: Best Overall Response



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

FDA Grants Novel TIL Therapy Breakthrough Therapy Designation for Advanced Cervical Cancer

Lisa Astor

Published Online: 2:55 PM, Fri May 24, 2019



5



9



8



4



<< [Back to all news](#)

The FDA has granted a breakthrough therapy designation to novel tumor-infiltrating lymphocyte therapy LN-145 for the treatment of patients with recurrent, metastatic, or persistent cervical cancer who have progressed on or after chemotherapy.¹



"We are very excited that the FDA has granted LN-145 in advanced cervical cancer Breakthrough Therapy designation. Cervical cancer patients who have progressed on or after chemotherapy have limited treatment options. We hope to bring LN-145 to these patients as quickly as possible," Maria Fardis, PhD, MBA, president and CEO of Iovance, said in a statement. "The designation allows us to expedite our development program through more frequent interactions with the FDA and provides eligibility for rolling review and priority review."

The designation was granted as a result of preliminary data from the ongoing phase II innovaTIL-04 trial (NCT03108495). The open-label, multicenter trial is investigating the adoptive cell therapy with autologous tumor-infiltrating lymphocyte infusion followed by interleukin-2 for the treatment of patients with recurrent, metastatic, or persistent cervical cancer. A tumor sample is resected from each patient in the trial and All patients receive a preparative non-

	Regimen	Trial	Indication	N	Partner	Phase 1	Phase 2	Pivotal
Company sponsored studies	Lifileucel	C-144-01	Melanoma	178	—			
	LN-145	C-145-04	Cervical cancer	~138	—			
	LN-145/ LN-145-S1	C-145-03	Head & neck cancer	55	—			
	<u>Lifileucel</u> + pembrolizumab LN-145 + pembrolizumab LN-145 + pembrolizumab LN-145	IOV-COM-202	Melanoma Head & neck Non-small cell lung Non-small cell lung	48	—			
	IOV-2001	IOV-CLL-01	Chronic lymphocytic leukemia	~70	—			

CD-19 targeted CAR T-cell approaches for ALL and NHL

	Author (trial)	Sites	Phase	Costim	T-cell subset	Vector	Time ^a	Enrolled	Treated	Population	LD ^b	CRS ^c (grade 3+) ^d	NT ^c (grade 3+) ^d	Response ^e	Analysis
Pre-B-ALL	Maude (ELIANA) ¹	Multicenter	II	4-1BB	Unselected	Lentivirus	45 d (S)	92	75	Pediatric	95% Flu/CPM	77% (48%)	40% (13%)	81%	Of treated
	Lee ⁵	NCI	I	CD28	Unselected	γ -Retrovirus	7-11 d (M)	21	21	Pediatric	Flu/CPM or other	76% (29%)	29% (5%)	70%	Intent to treat
	Gardner ⁸²	SCRI	I/II	4-1BB	CD4 and CD8	Lentivirus	15 d (M), 53 d (S)	45	43	Pediatric	Prefer Flu/CPM	93% (23%)	49% (21%)	89%	Intent to treat
	Hay ⁸⁴	FHCRC	I/II	4-1BB	CD4 and TcmCD8	Lentivirus	19 d (M)	61	53	Adult	CPM +/- Flu	75% (19%)	(23%)	85%	Of treated
	Park ³	MSKCC	I	CD28	Unselected	γ -Retrovirus	Unknown	83	53	Adult	CPM +/- Flu	85% (26%)	(42%)	83%	Of treated
	Jacoby ⁸⁶	Israel	Ib/II	CD28	Unselected	γ -Retrovirus	9-10 d (M)	21	20	Pediatric	Flu/CPM	80% (20%)	55% (30%)	90%	Of treated
NHL	Schuster (Juliet) ⁹⁷	Multicenter	II	4-1BB	Unspecified	Lentivirus	54 d (S)	165	111	Adult, DLBCL	73% Flu/CPM	58% (22%)	21% (12%)	3 mo: RR 52%, CR 40%	Of treated
	Neelapu ² (Zuma)	Multicenter	I/II	CD28	Unspecified	γ -Retrovirus	17 days (S)	111	101	Adult, NHL	Flu/CPM	93% (13%)	64% (28%)	6 mo: RR 82%, CR 54%	Modified intent to treat
	Abramson ⁹⁸ (Transcend)	Multicenter	I	4-1BB	CD4 and CD8	Lentivirus	Unknown	39	14	Adult, NHL	Flu/CPM	21% (0%)	(14%)	1 mo: RR 82%, CR73%	Of treated

Genetically redirected T cells for solid tumors

Target	Cancer	Receptor	N patients	Responses	Ref
ERBB2	Colorectal	CAR: CD28-CD137-CD3 ζ	1 (deceased resp distress lung ERBB2 expression)		Morgan, R. A. <i>Mol. Ther.</i> 2010
CEA	Colorectal and breast	CAR: CD3 ζ	7	0	Ma, Q.. 2002.
α FR	Ovarian	CAR: FcR γ	12	0	Kershaw, M. H. <i>et al. Clin. Cancer Res</i> 2006
CD171	Neuroblastoma	CAR: CD3 ζ	6	1	ParK, JR. <i>Mol Ther.</i> 2007
CAIX	Renal	CAR: CD3 ζ	11	0 (+hepatotoxicity)	Lamers CH. <i>Mol Ther.</i> 2013
GD2	Neuroblastoma	CAR: CD3 ζ	19	3 (CR)	Louis, C. U. <i>et al. Blood</i> 2011

Regional delivery of mesothelin-targeted CAR T cells for pleural cancers: safety and preliminary efficacy in combination with anti-PD-1 agent

2019 ASCO Annual Meeting, Chicago



Memorial Sloan Kettering
Cancer Center™

Prasad S. Adusumilli, Marjorie G Zauderer, Valerie W Rusch, Roisin E O'Cearbhaill, Amy Zhu, Daniel Ngai, Erin McGee, Navin Chintala, John Messinger, Waseem Cheema, Elizabeth F Halton, Claudia R Diamonte, John Pineda, Alain Vincent, Shanu Modi, Steve Solomon, David R Jones, Renier J Brentjens, Isabelle C Riviere, Michel W Sadelain



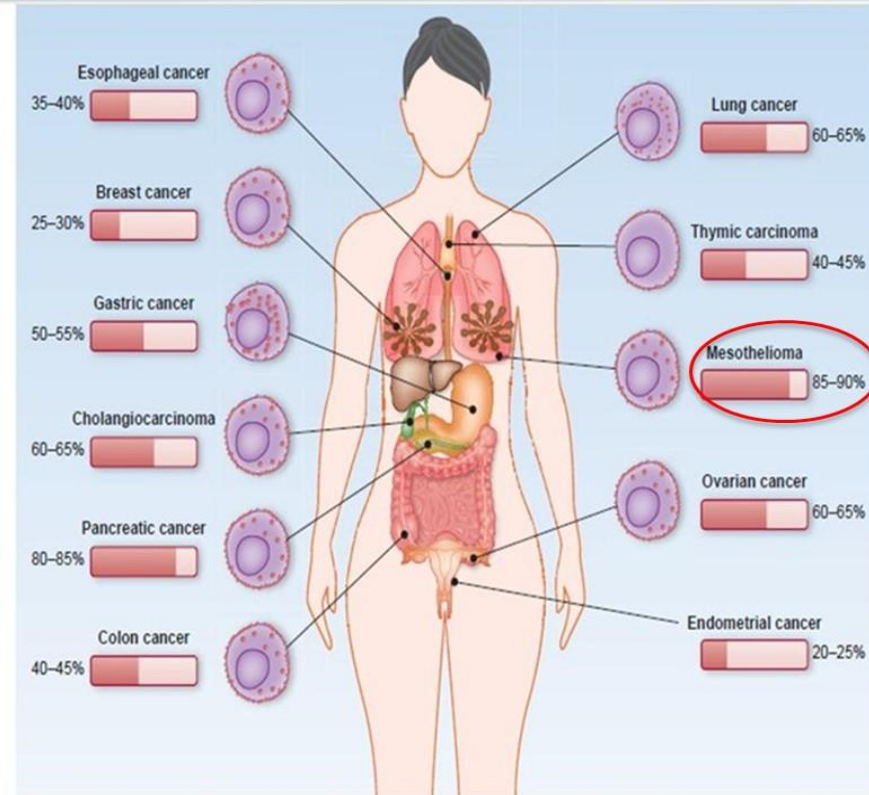
Presented By Prasad Adusumilli at 2019 ASCO Annual Meeting

Mesothelin is a target antigen for solid tumors

- Cell-surface antigen
- Expressed in majority of solid tumors

Annual incidence
371,977

Annual prevalence
2,119,926



Morello A, Adusumilli PS. *Cancer Discov* 2016

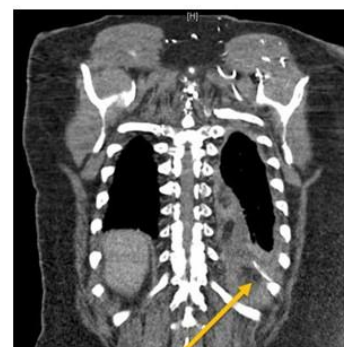
Single dose of CAR T cells administered intrapleurally

Cohort	PT #	Age/ Sex	Diagnosis	Histology	Stage	CAR T Line of Therapy	Route of Administration
1 3e5/kg (no cyclo)	1	59F	Lung Cancer	Adeno Ca	IV	4	Pleural catheter
	2	69M	Mesothelioma	Epithelioid	IV	6	Pleural catheter
	3	66F	Mesothelioma	Epithelioid	IV	5	Pleural catheter
2 3e5/kg	4	56M	Mesothelioma	Epithelioid	IV	6	Pleural catheter
	5	70F	Breast Cancer	Intraductal Ca	IV	9	IR
3 1e6/kg	6	72M	Mesothelioma	Biphasic	IIIA	2	IR
	7	70M	Mesothelioma	Epithelioid	IIIA	2	Pleural catheter
	8	73M	Mesothelioma	Epithelioid	IIIB	6	Pleural catheter
4 3e6/kg	9	66M	Mesothelioma	Epithelioid	IV	4	IR
	10	70M	Mesothelioma	Epithelioid	IIIB	2	Pleural catheter
	11	74M	Mesothelioma	Epithelioid	IIIB	2	Pleural catheter
5 6e6/kg	12*	66M	Mesothelioma	Epithelioid	IIIB	2 / 5	Pleural catheter
	13	76M	Mesothelioma	Epithelioid	IIIA	2	IR
	14	69M	Mesothelioma	Epithelioid	IIIA	2	IR
6 1e7/kg	15	71M	Mesothelioma	Epithelioid	IIIB	2	Pleural catheter
	16	77F	Mesothelioma	Epithelioid	IV	7	IR
	17	71M	Mesothelioma	Biphasic	IIIA	2	IR
7 3e7/kg	18	53M	Mesothelioma	Epithelioid	IIIB	3	IR
	19	64M	Mesothelioma	Epithelioid	IIIB	3	IR
	20	70M	Mesothelioma	Epithelioid	IIIA	3	Pleural catheter
8 6e7/kg	21	61F	Mesothelioma	Epithelioid	IIIB	2	IR
	22	73M	Mesothelioma	Epithelioid	IIIB	2	IR
	23	71F	Mesothelioma	Epithelioid	IV	2	IR
8 6e7/kg	24	70M	Mesothelioma	Epithelioid	IV	5	IR
	25	55M	Mesothelioma	Epithelioid	IV	14	IR
	26	61M	Mesothelioma	Epithelioid	IV	3	IR
	27	77M	Mesothelioma	Epithelioid	II	2	IR

37% had ≥ 3 lines of therapy

Cyclophosphamide preconditioning in cohorts 2-8

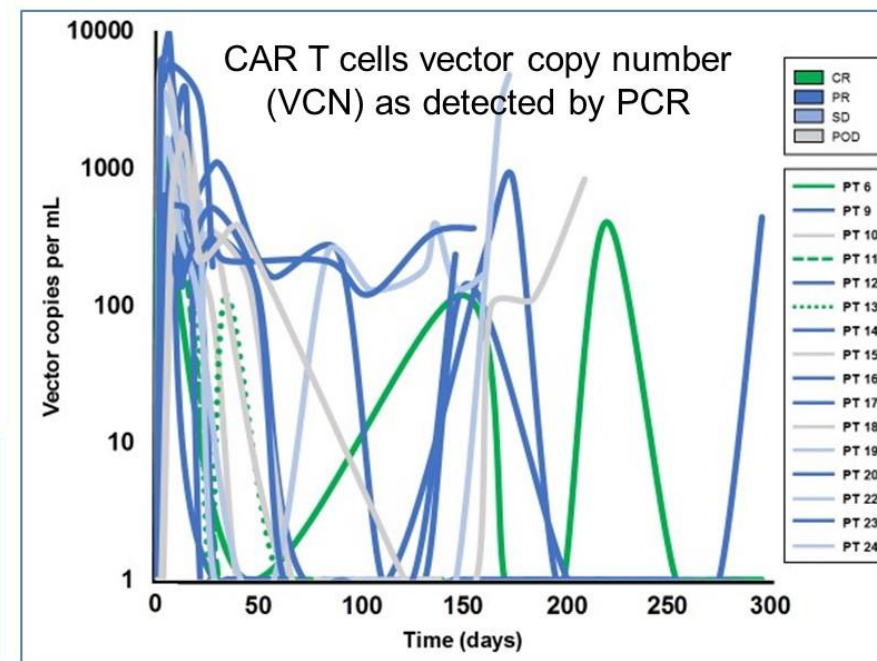
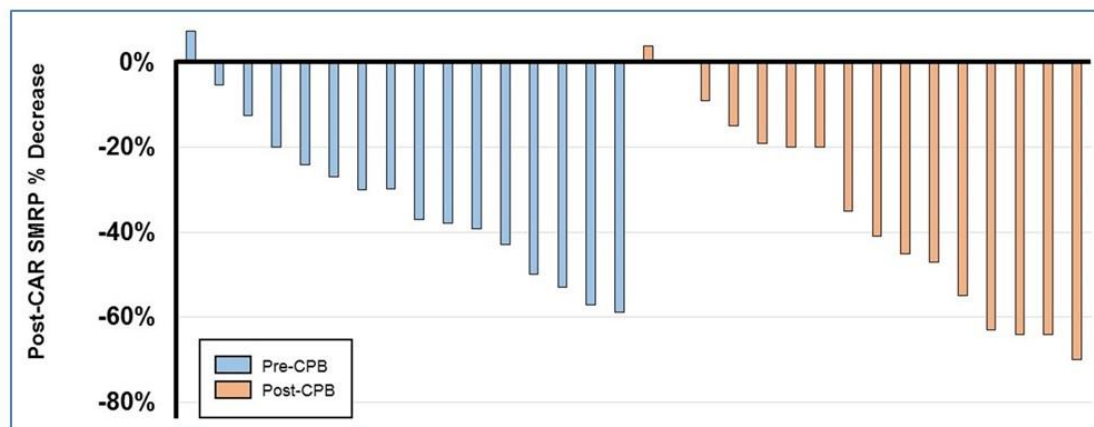
IR - intervention radiology



* Patient #12 re-infused at week 51

CAR T-cell persistence in peripheral blood

- CAR T-cells detected in peripheral blood from day 2 to 42 weeks (as well as in pleural fluid)
- Reduction in serum SMRP (soluble mesothelin related peptide) values observed as shown below



CR – Complete response
PR – Partial response
SD – Stable disease
POD – Progression of disease

Mesothelin-targeted CAR T-cell therapy

Intrapleural CAR T cells + systemic anti-PD1 antibody administration are well tolerated

On-target, off-tumor toxicity monitoring

Monitored by	Method
Clinical	Pleuritis, Pericarditis, Peritonitis
Laboratory	Serum Troponin level
Cardiac	EKG, Echocardiogram
Imaging	CXR, CT, PET
Pathology	Biopsy



No evidence of CAR T-cell related AEs
>Grade 2 (CTCAE V.4)

- No neurotoxicity
- No cytokine release syndrome (CRS)
- No on-target, off-tumor toxicity

Adverse event	Grade	# of patients
Fever and chills	1	6
CRS	1	3
Malaise	1	1
Non-cardiac chest discomfort	1	1
Pain	1	1
Fever	2	1
CRS	2	1
Confusion	2	1
Febrile neutropenia (related to cyclophosphamide)	3	1

Following anti-PD1 agent administration -

- 2 patients developed SOB (grades 2 & 3)
- One patient Rx with IL-6 blockade (two doses) and steroids, currently off oxygen
- One patient treated with short term steroids (3 doses), back on anti-PD1 agent

Anti-PD-1 agent administration following CAR T-cell therapy

Cohort	PT #	Age/ Sex	Diagnosis	Histology	Stage	CAR T Line of Therapy	Route of Administration	PDL1 Status (%)	CPB started (week)	Best Response (Inr interpretation)
1 3e5/kg (no cyclo)	1	59F	Lung Cancer	Adeno Ca	IV	4	Pleural catheter	-	-	POD
	2	69M	Mesothelioma	Epithelioid	IV	6	Pleural catheter	0	9	POD
	3	66F	Mesothelioma	Epithelioid	IV	5	Pleural catheter	0	-	POD
2 3e5/kg	4	56M	Mesothelioma	Epithelioid	IV	6	Pleural catheter	0	-	POD
	5	70F	Breast Cancer	Intraductal Ca	IV	9	IR	0	5	POD
	6	72M	Mesothelioma	Biphasic	IIIA	2	IR	1%	6	CR
3 1e6/kg	7	70M	Mesothelioma	Epithelioid	IIIA	2	Pleural catheter	30%	-	SD
	8	73M	Mesothelioma	Epithelioid	IIIB	6	Pleural catheter	0	-	POD
	9	66M	Mesothelioma	Epithelioid	IV	4	IR	-	17	PR
4 3e6/kg	10	70M	Mesothelioma	Epithelioid	IIIB	2	Pleural catheter	0	6	POD
	11	74M	Mesothelioma	Epithelioid	IIIB	2	Pleural catheter	10%	6	CR
	12*	66M	Mesothelioma	Epithelioid	IIIB	2 / 5	Pleural catheter	0	5 / 9	PR
5 6e6/kg	13	76M	Mesothelioma	Epithelioid	IIIA	2	IR	0	6	CR
	14	69M	Mesothelioma	Epithelioid	IIIA	2	IR	0	7	PR
	15	71M	Mesothelioma	Epithelioid	IIIB	2	Pleural catheter	5%	8	POD
6 1e7/kg	16	77F	Mesothelioma	Epithelioid	IV	7	IR	80%	6	PR
	17	71M	Mesothelioma	Biphasic	IIIA	2	IR	0	6	PR
	18	53M	Mesothelioma	Epithelioid	IIIB	3	IR	0	6	POD
	19	64M	Mesothelioma	Epithelioid	IIIB	3	IR	0	6	SD
	20	70M	Mesothelioma	Epithelioid	IIIA	3	Pleural catheter	0	6	PR
	21	61F	Mesothelioma	Epithelioid	IIIB	2	IR	0	5	PR
7 3e7/kg	22	73M	Mesothelioma	Epithelioid	IIIB	2	IR	0	5	SD
	23	71F	Mesothelioma	Epithelioid	IV	2	IR	0	8	PR
	24	70M	Mesothelioma	Epithelioid	IV	5	IR	0	6	POD
8 6e7/kg	25	55M	Mesothelioma	Epithelioid	IV	14	IR	0	5	POD
	26	61M	Mesothelioma	Epithelioid	IV	3	IR	0	4	SD
	27	77M	Mesothelioma	Epithelioid	II	2	IR	5%	6	SD

CR – Complete response
PR – Partial response
SD – Stable disease
POD – Progression of disease

3 CR (11%)
8 PR (30%)
5 SD (18%)
11 PD (40%)

41% ORR

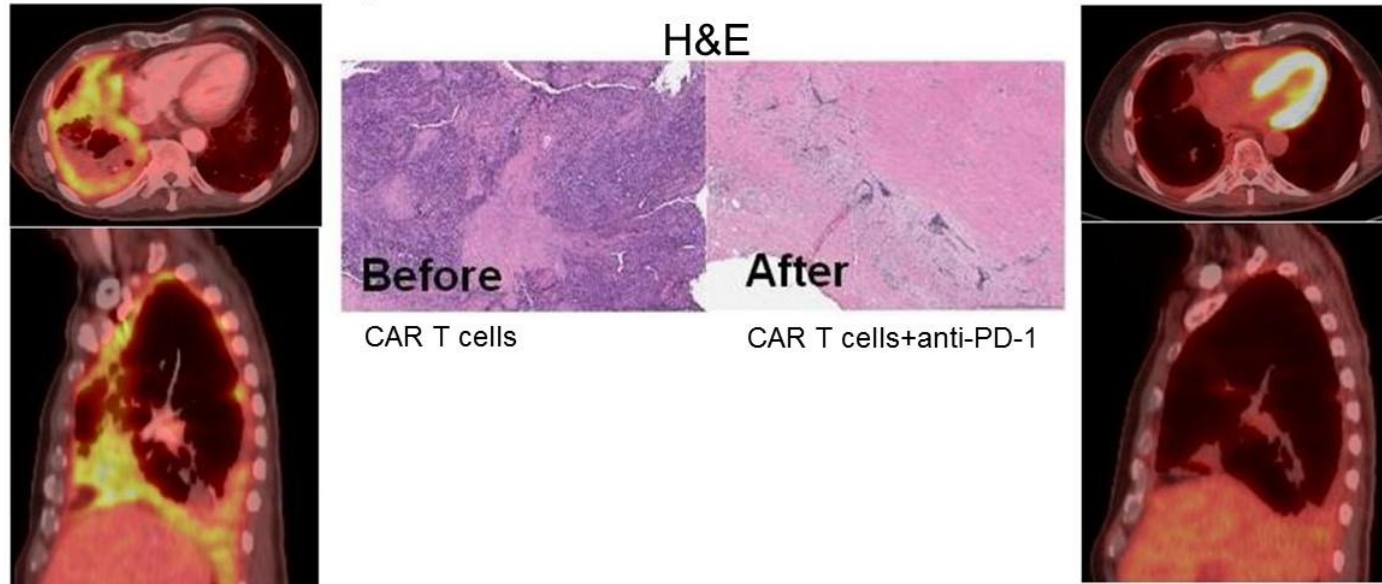
* Patient #12 re-infused at week 51

MSLN CAR T-cells + anti PD-1 agent

Complete response in patient #6 (16 months)

73 yr old h/o served in a battle ship diagnosed with **BIPHASIC** mesothelioma

- April 2017 – Unresectable disease following chemotherapy
- May 2017 – 3e5 CAR T cells/kg following Cyclophosphamide administered
- July 2017 – Pembrolizumab started (**PD-L1 <1%, low mutational burden**)
- Nov 2017 – Complete metabolic response, Serum SMRP normal
- Feb 2018 – CAR T cells detected at 32 weeks in blood and tissue
- No additional therapies for 16 months

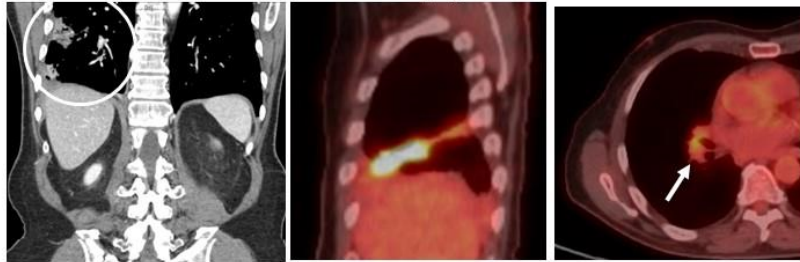


Mesothelin-targeted CAR T-cell therapy

MSLN CAR T-cells + anti PD-1 agent

Complete response in patient #13 – 14 months and ongoing

Post chemotherapy - Pre CAR T-cells



Partial response with
CAR T cells alone

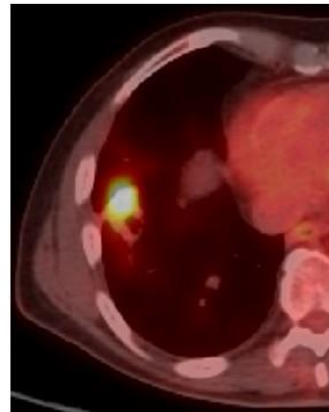
Post CAR T-cells



CAR T-cells
administered in
interventional
radiology

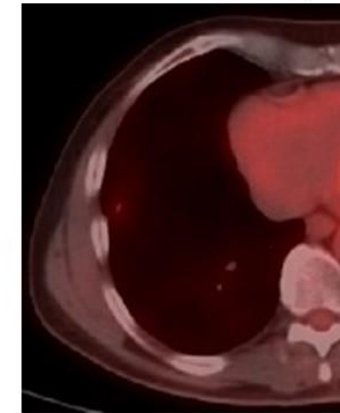


April



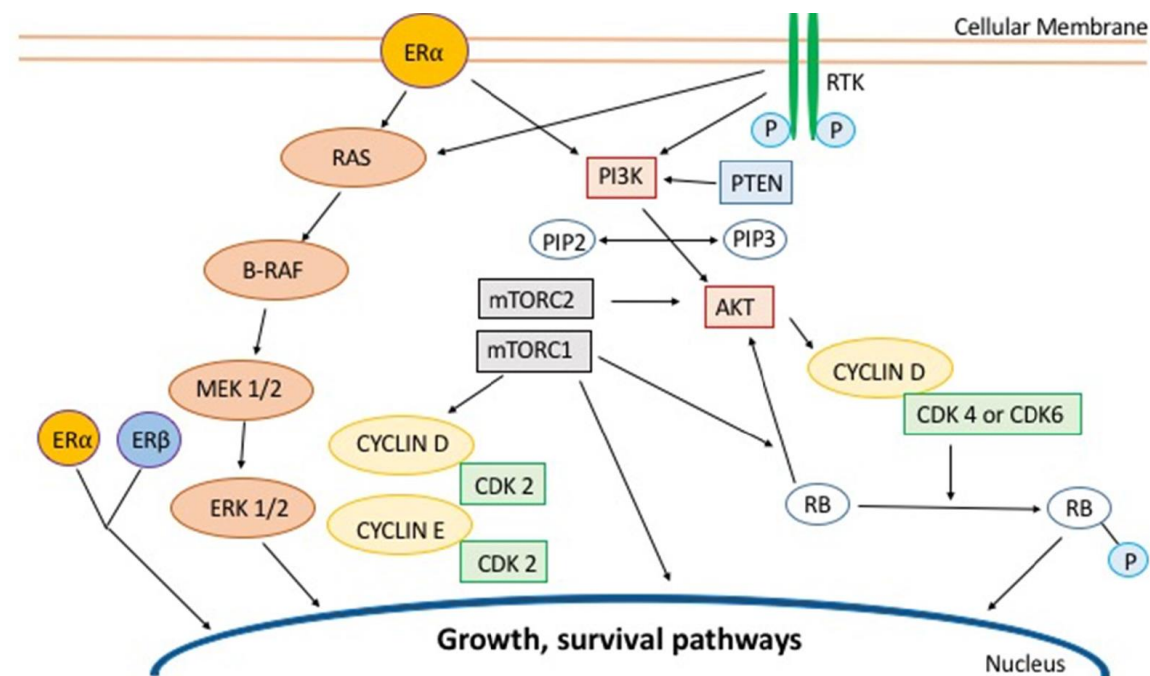
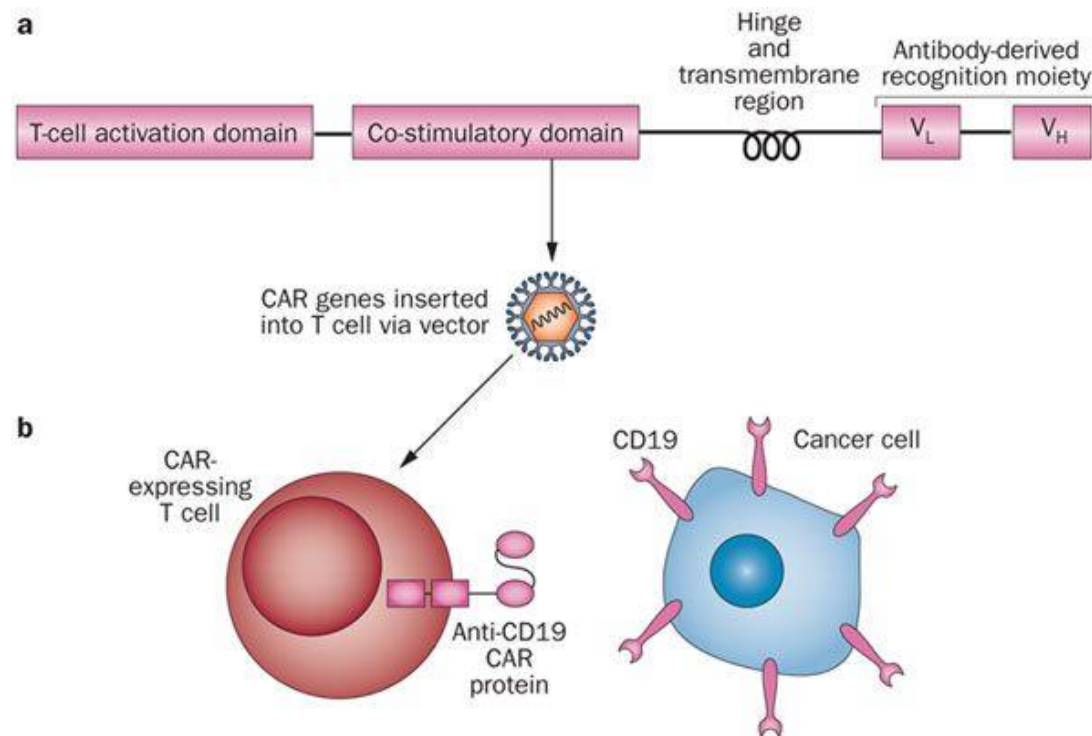
May

Addition of anti-
PD-1 antibody

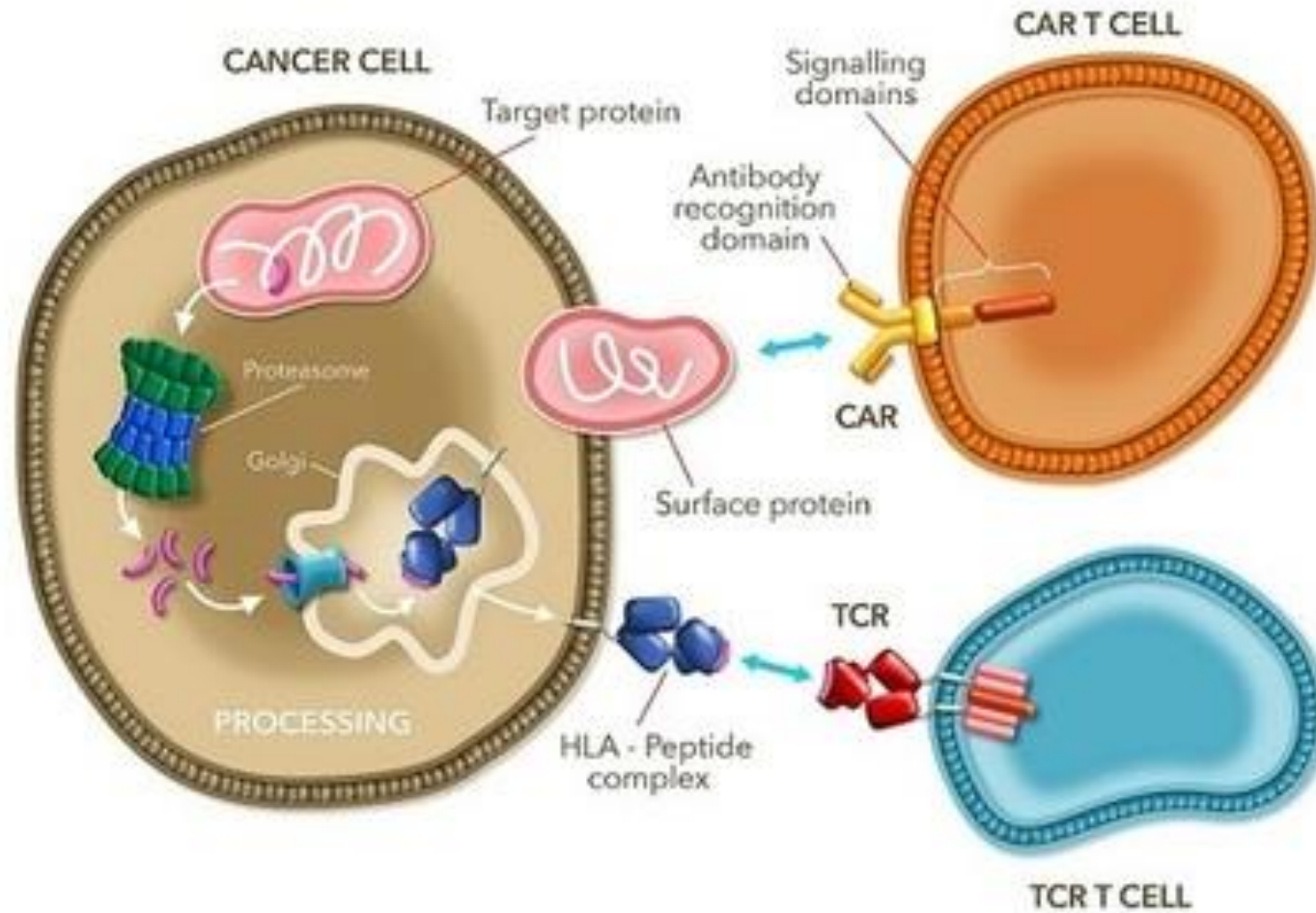


Nov

Liquid vs. Solid tumors



Modified TCR



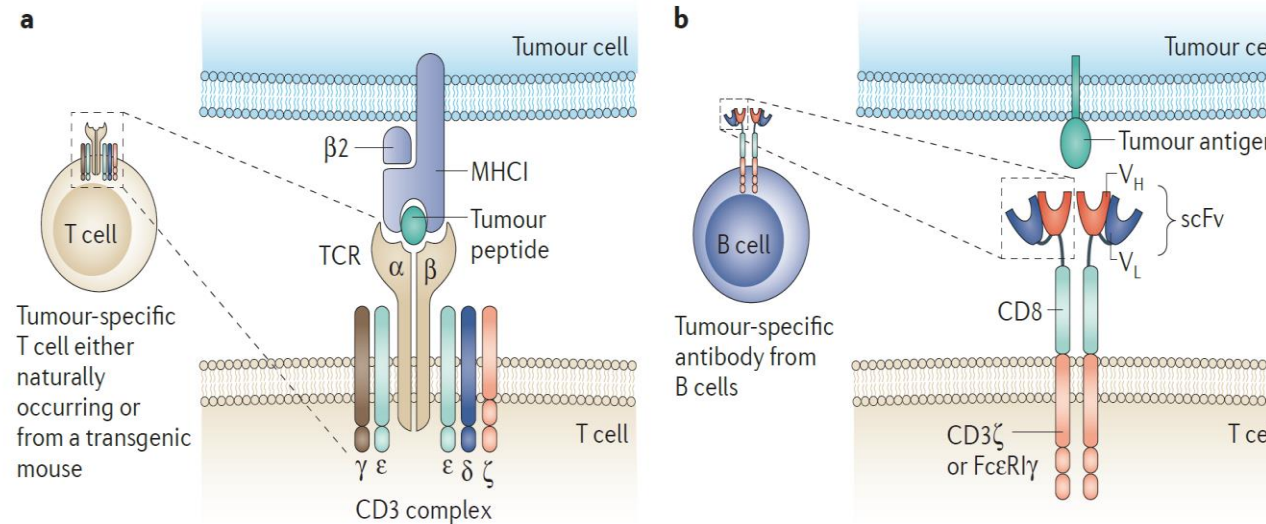
Modified TCR vs. CAR

Pros

- Intracellular proteins.
- Identification of mutant proteins specific of cancer cells.

Cons

- HLA selection.
- Resistance mechanisms antigen presentation



Pros

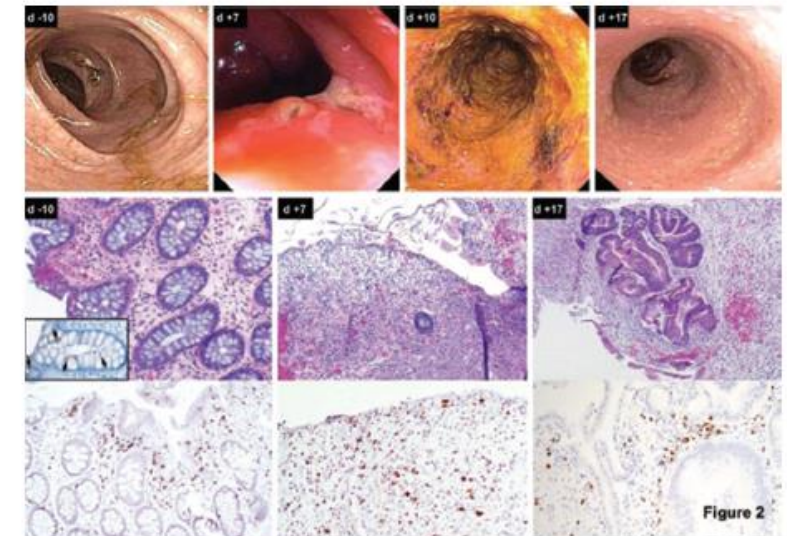
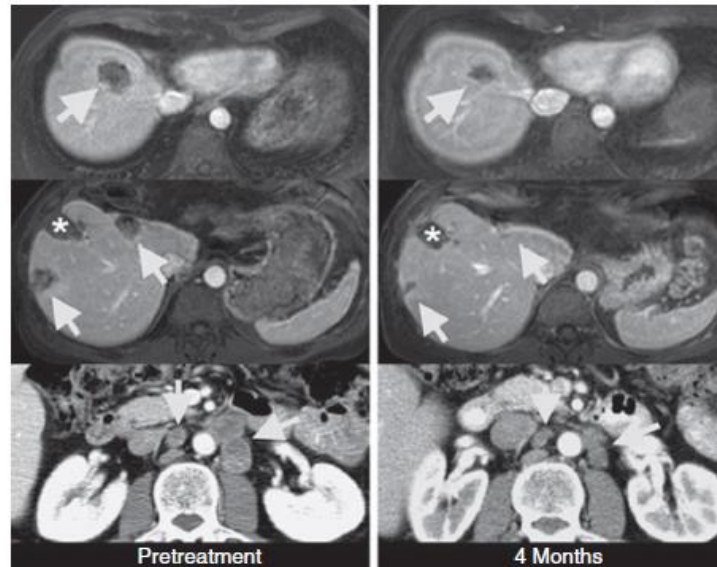
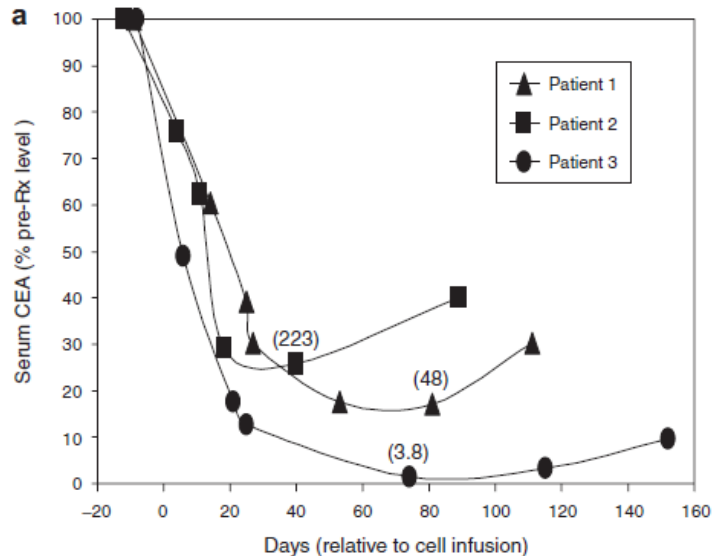
- No HLA selection
- Direct activation of T lymphocyte from tumor cell (no AP required)

Cons

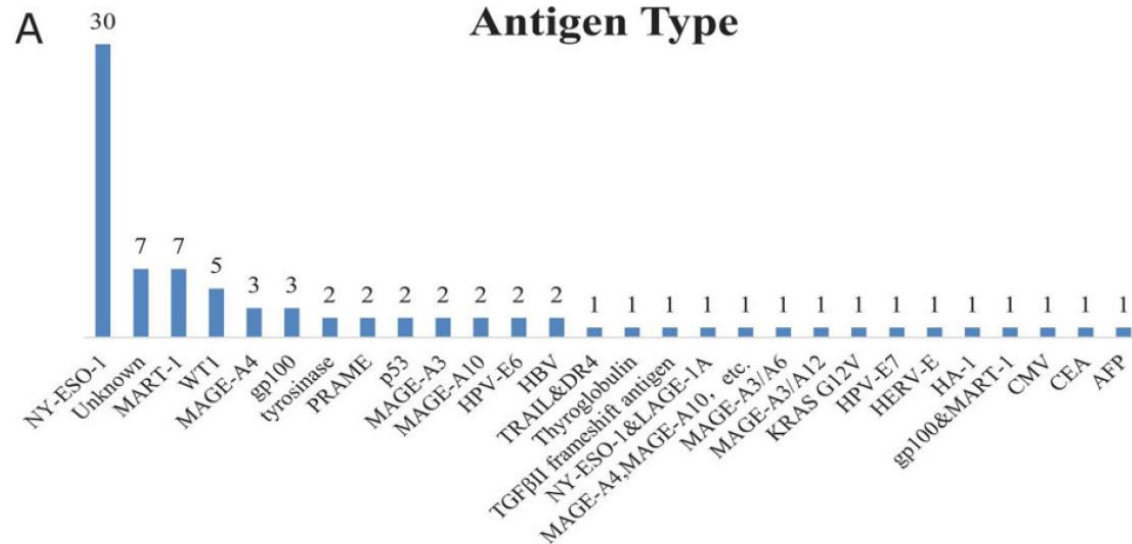
- Difficult to find surface protein specific of cancer cell only.
- Potentially blocked by soluble antigen

T Cells Targeting Carcinoembryonic Antigen Can Mediate Regression of Metastatic Colorectal Cancer but Induce Severe Transient Colitis

- Murine T cell receptor (TCR) against human carcinoembryonic antigen (CEA)



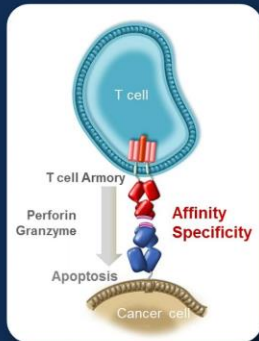
Current approach public antigens (non mutated)



Type of antigens	Antigen characteristics	Example of human tumor antigens
Cancer-germline	Expressed only by tumor cells and adult reproductive tissues	MAGE, BAGE, GAGE, NY-ESO-1
Differentiation	Expressed by tumors and a limited range of normal tissues	Tyrosinase, Melan-A, gp100, CEA, MART-1
Overexpressed	Expressed by both normal and tumor cells, but much highly expressed in tumor cells	HER2, WT1, MUC1, ppCT
Viral	Expressed only by tumor cells as a result of viral infection	HPV, HBV, EBV, HTLV

NY-ESO in Synovial Sarcoma

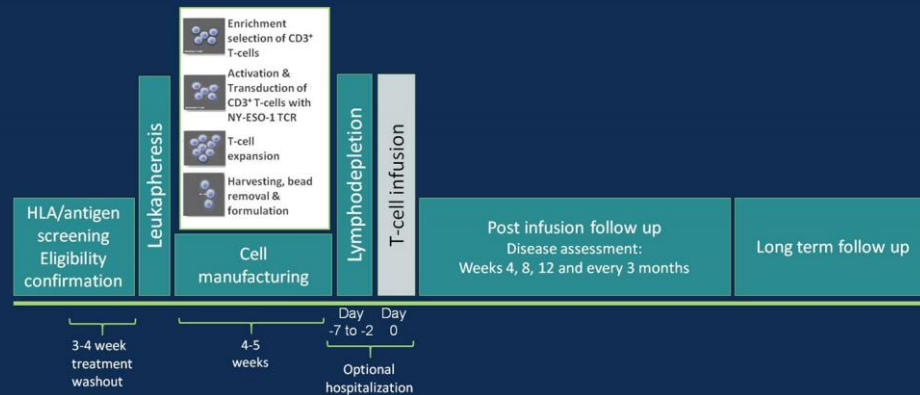
NY-ESO-1^{c259} TCR : Enhanced Affinity



- Recognizes NY-ESO-1 specific HLA-A02 restricted peptide (*SLLMWITQC*)
- Lentivirus vector
- IL-2 is omitted
- Minimum cell dose 1×10^9

PRESENTED AT: ASCO ANNUAL MEETING '17 #ASCO17 Presented by: Sandra P. D'Angelo

Overview of Study Design

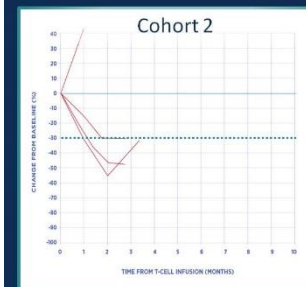


PRESENTED AT: ASCO ANNUAL MEETING '17 #ASCO17 Presented by: Sandra P. D'Angelo
Slides are the property of the author. Permission required for reuse.

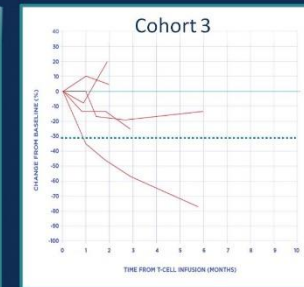
Response Summary

	Cohort 1 Hi NY-ESO-1 Hi Flu/Cy N=12	Cohort 2 Lo NY-ESO-1 Hi Flu/Cy N=5	Cohort 3 Hi NY-ESO-1 Cy N=5	Cohort 4 Hi NY-ESO-1 Mod Flu/Cy N=6
Best overall response: N (%)				
CR	1 (8)	0 (0)	0 (0)	0 (0)
PR	5 (42)	2 (40)	1 (20)	3 (50)
SD	6 (50)	1 (20)	4 (80)	2 (33)
PD	0 (0)	1 (20)	0 (0)	1 (17)
Not assessed	0 (0)	1 (20)	0 (0)	0 (0)
ORR: Confirmed, CR + PR: N (%)	6 (50)	2 (40)	1 (20)	3 (50)
Median PFS: weeks (range)	15 (8, 38)	12 (03- 14)	12 (8, 38)	NE
Median response duration: wks (range)	30.9 (13, 72)	7.5 (6-9)	21--	NE

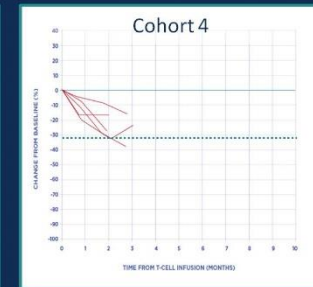
Kinetics of Response



Low NY-ESO-1
Flu/Cy
ORR=40%; N=5



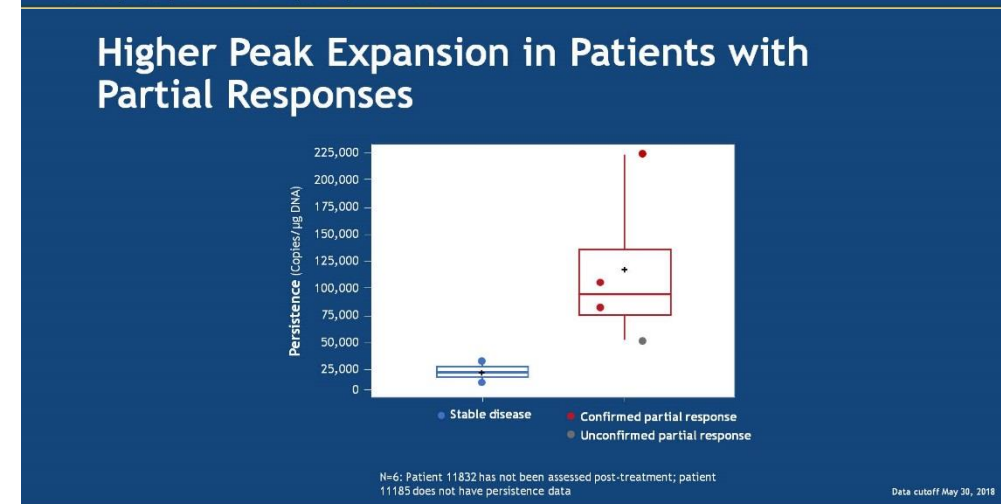
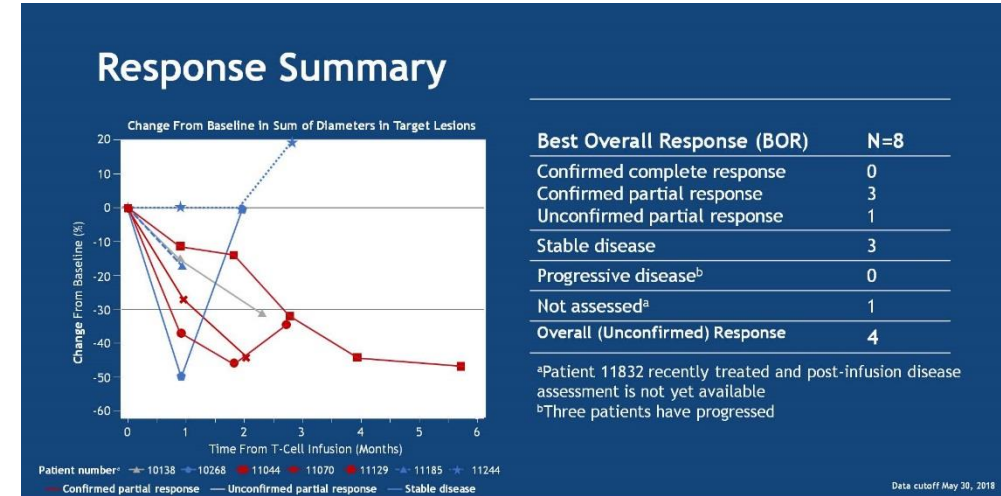
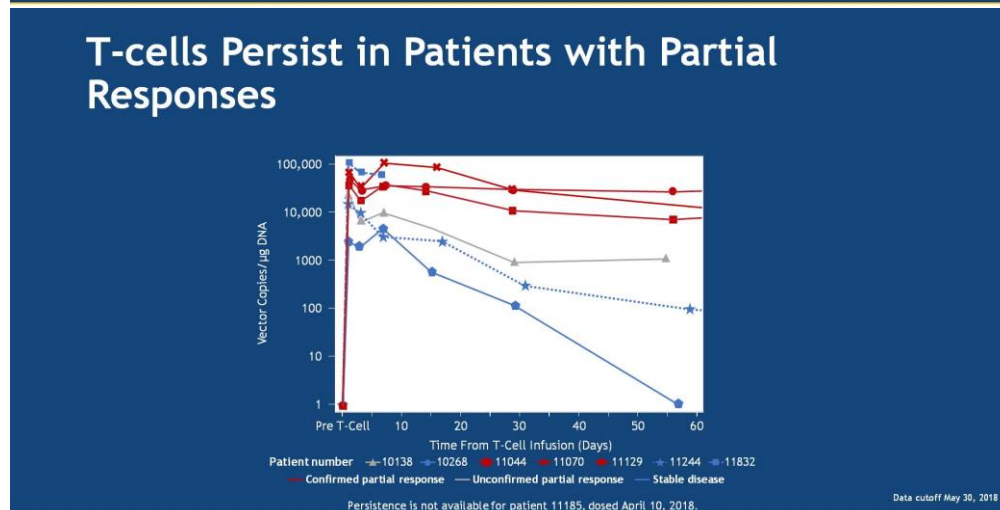
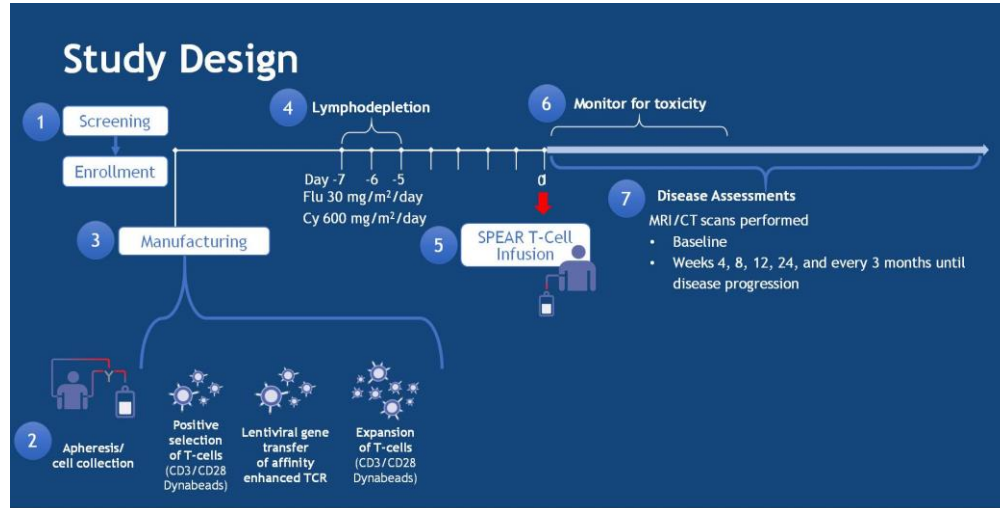
Hi NY-ESO-1
Cy
ORR=20%; N=5



Hi NY-ESO-1
Mod Flu/Cy
ORR=50%; N=6

PRESENTED AT: ASCO ANNUAL MEETING '17 #ASCO17 Presented by: Sandra P. D'Angelo
Slides are the property of the author. Permission required for reuse.

NY-ESO in liposarcoma



ADP-A2M4 (MAGE-A4) Synovial Sarcoma

PATIENT CHARACTERISTICS

N=13*		
Sex	Male: 8	Female: 5
Age	Median: 53	Range: 31 - 76 Two patients >70
Race	White: 11	Asian: 2
ECOG status	ECOG 0 = 7	ECOG 1 = 6
Prior lines of systemic therapies	Median: 2	Range: 1 - 5
Cell dose x 10 ⁹	Median: 9.7	Range: 3.41 - 9.98

*13th treated patient did not have post-baseline assessment at time of data cut off.

BARCELONA 2019 ESMO congress

Data cut off 3-Sep-19

SAFETY: ADVERSE EVENTS ≥ GRADE 3

Preferred Term	Grade ≥3 N (%)
Leukopenia	12 (92.3%)
Lymphopenia	12 (92.3%)
Neutropenia	10 (76.9%)
Anemia	5 (38.5%)
Thrombocytopenia	5 (38.5%)
Hypophosphatemia	5 (38.5%)
Rash	3 (23.1%)
Febrile neutropenia	3 (23.1%)
CRS	2 (15.4%)
Hyponatremia	2 (15.4%)
Acute kidney injury	1 (7.7%)
Acute left ventricular failure	1 (7.7%)
Anal abscess	1 (7.7%)

Preferred Term	Grade ≥3 N (%)
Aplastic anemia	1 (7.7%)
Arrhythmia	1 (7.7%)
Decreased appetite	1 (7.7%)
Endocarditis staphylococcal	1 (7.7%)
Hypermagnesemia	1 (7.7%)
Hypocalcemia	1 (7.7%)
Hypotension	1 (7.7%)
Influenza like illness	1 (7.7%)
Pancytopenia	1 (7.7%)
Pleural effusion	1 (7.7%)
Sciatica	1 (7.7%)
Sepsis	1 (7.7%)
Troponin increased	1 (7.7%)

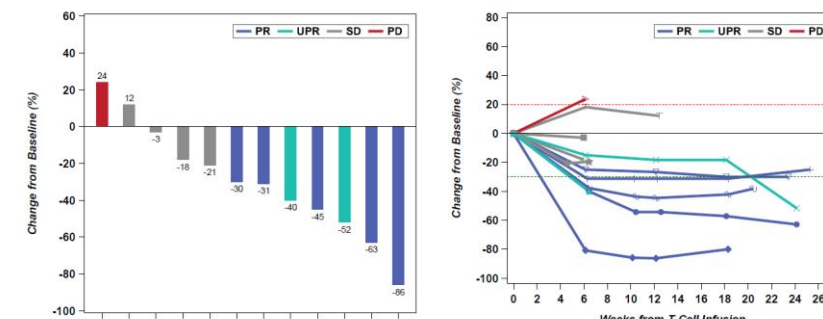
Most AEs were typical for this treatment and patient population
Any Grade CRS is common in synovial sarcoma patients treated with ADP-A2M4

BARCELONA 2019 ESMO congress

Data cut off 3-Sep-19
CDDF
Cancer Drug Development Forum

ADP-A2M4 SPEAR T-CELLS INDUCE CLINICAL RESPONSES

Best overall response in 12 patients* with post-baseline assessments



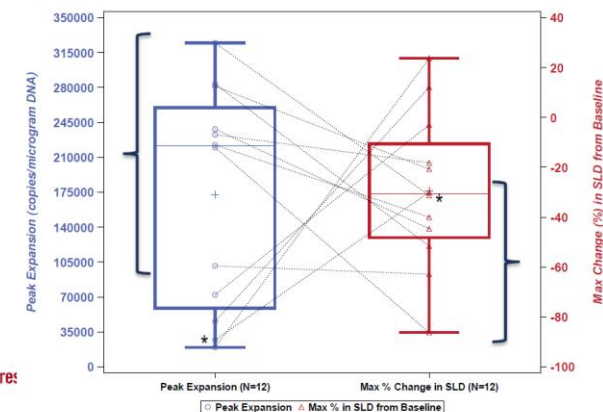
ORR: 58%
7/12

BARCELONA 2019 ESMO congress

*13th treated patient did not have post-baseline assessment at time of data cut off.

TRANSDUCE T-CELLS PEAK EXPANSION

Higher peak expansion associated with decrease in tumor size from baseline



Data cut off 3-Sep-19

Adaptimmune Announces that SPEAR T-cell Platform Delivers Initial Responses in Four Solid Tumor Indications

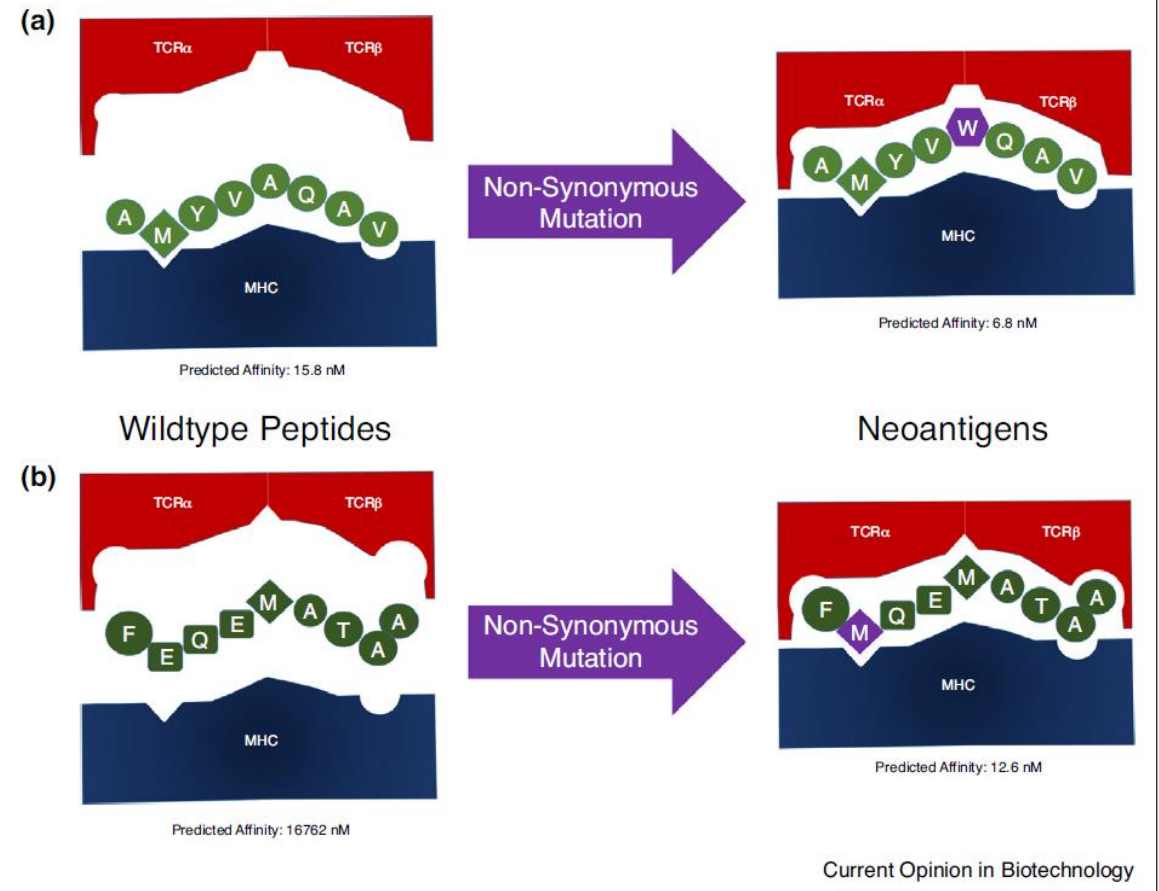
January 13, 2020

Best overall responses:

- A confirmed PR (decrease of 100% in target lesions) in a patient with hepatocellular carcinoma (liver cancer) – the first patient treated in the third cohort of the Phase 1 ADP-A2AFP trial
- A confirmed PR (decrease of 42% in target lesions) in a patient with metastatic rectal mucosal melanoma – the first patient treated in the low-dose radiation sub-study of the Phase 1 ADP-A2M4 trial
- An unconfirmed PR (decrease of 42% in target lesions) in a patient with metastatic gastro-esophageal junction cancer – the first patient treated in the first cohort of the next-generation SURPASS trial
- An unconfirmed PR (decrease of 36% in target lesions) in a patient with head and neck cancer treated in the expansion phase of the Phase 1 ADP A2M4 trial

Private neoantigens

- Neoantigen: somatic mutation creates a peptide epitope that is expressed, processed, presented by one of the patient's MHC molecules, and recognized by a subset within the patient's T cell repertoire.
- Stochastic: each mutation increases the odds of neoantigen formation

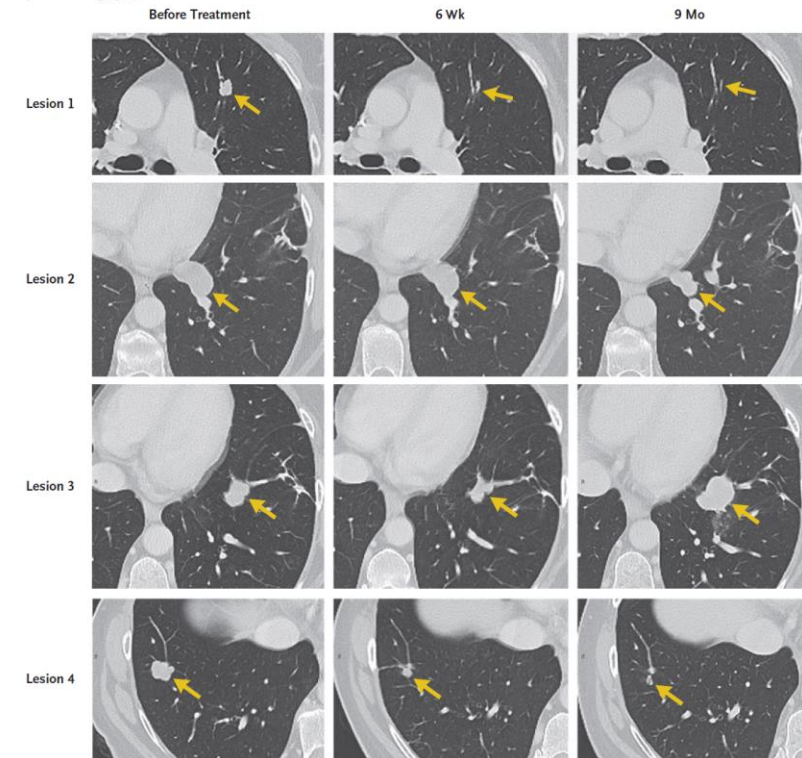


BRIEF REPORT

T-Cell Transfer Therapy Targeting Mutant KRAS in Cancer

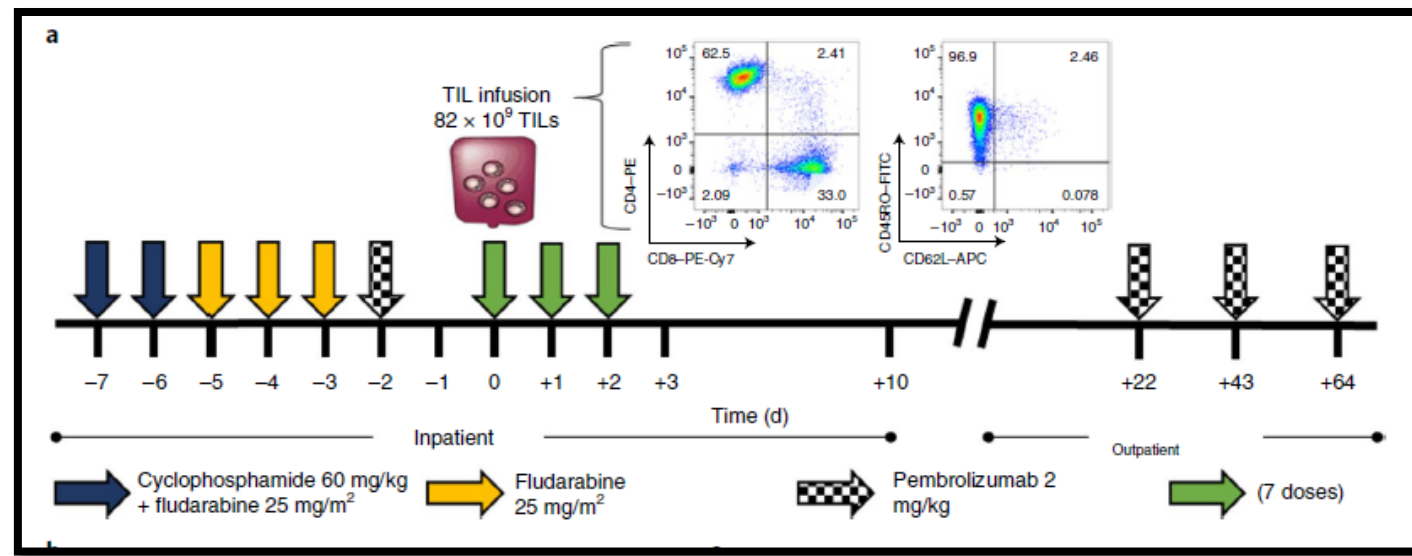
- HLA-C*08:02–restricted tumor-infiltrating lymphocytes that were composed of four different T-cell clonotypes that specifically targeted KRAS G12D.
- Objective regression of all seven lung metastases
- one of these lesions had progressed on evaluation 9 months after therapy. The lesion was resected and found to have lost the chromosome 6 haplotype encoding the HLA-C*08:02 class I major histocompatibility complex (MHC) molecule.

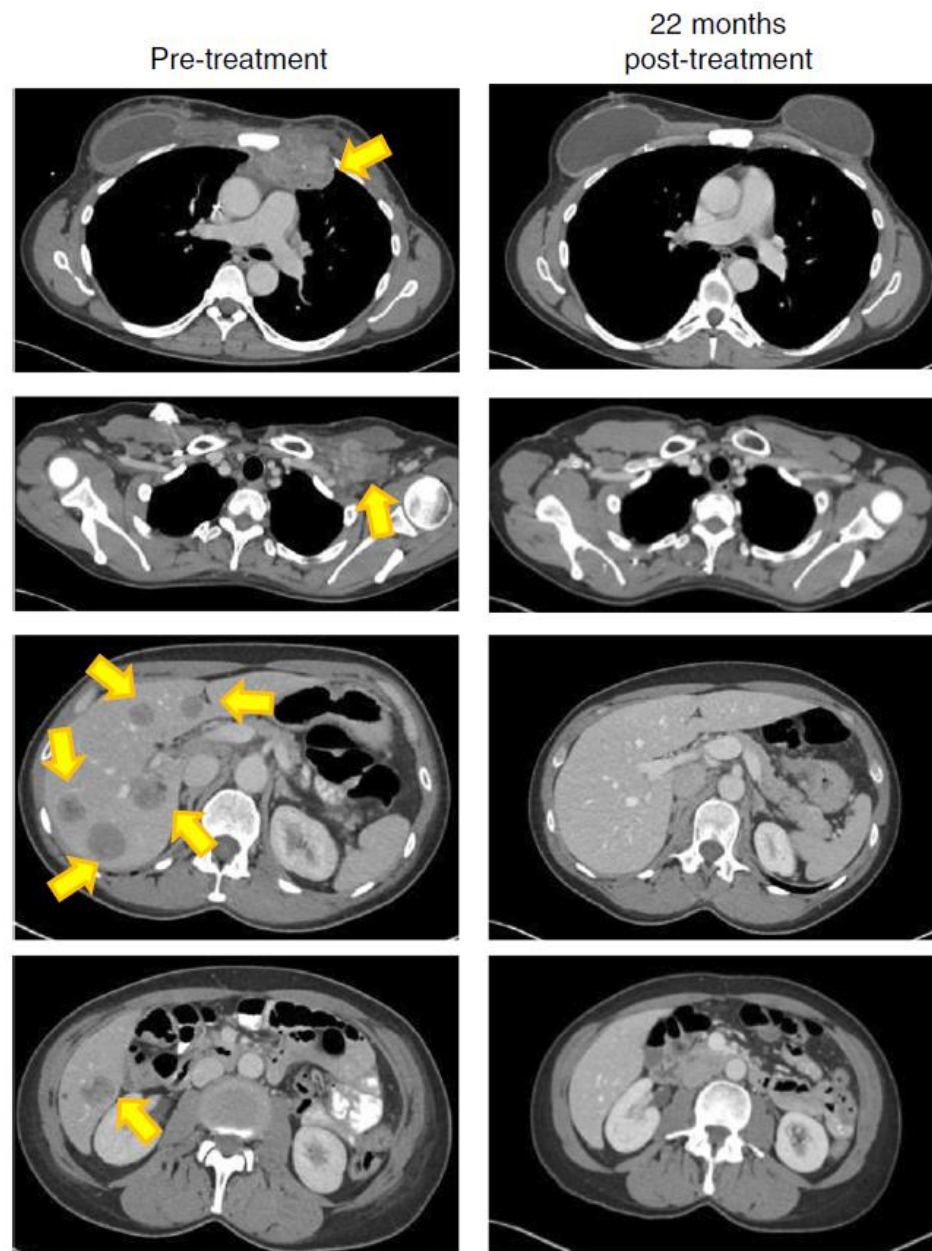
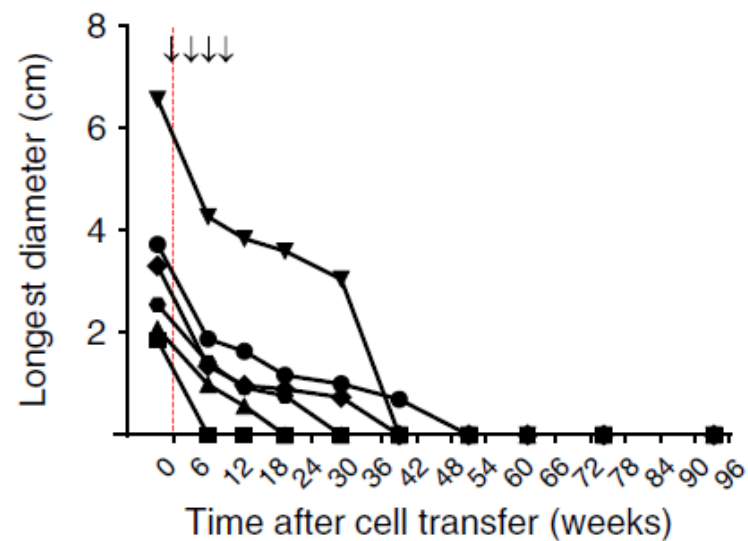
B Computed Tomography of Chest



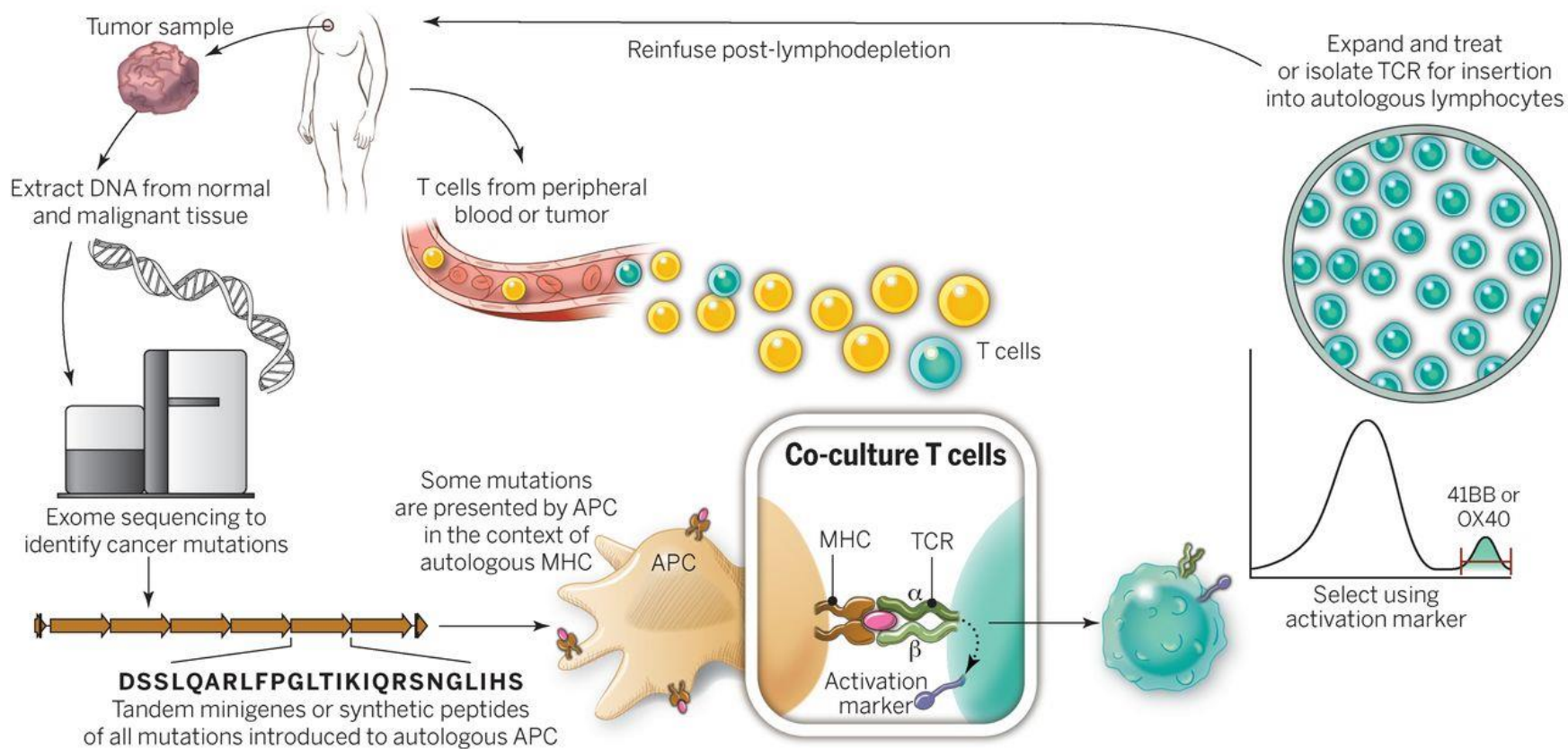
Immune recognition of somatic mutations leading to complete durable regression in metastatic breast cancer

- One patient with metastatic breast cancer.
- Tumor-infiltrating lymphocytes (TILs) reactive against mutant versions of four proteins—SLC3A2, KIAA0368, CADPS2 and CTSB





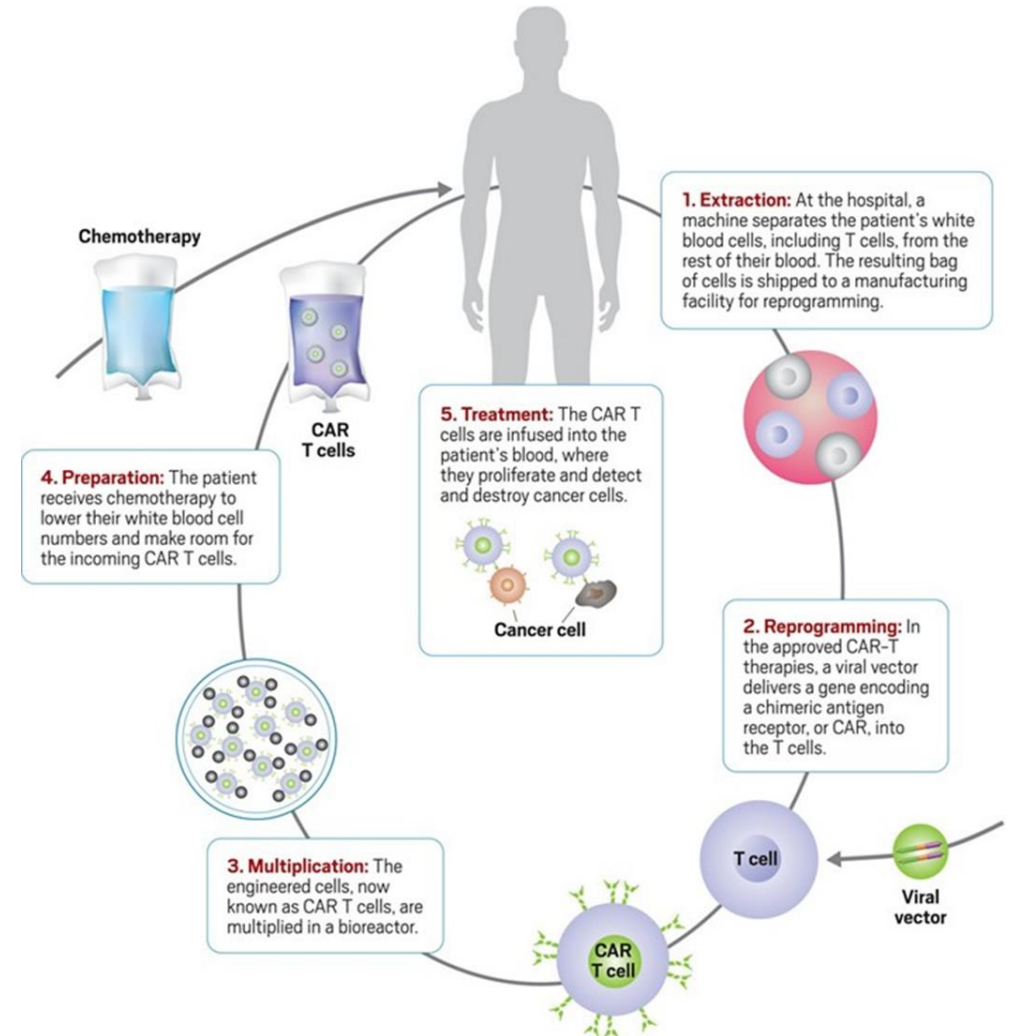
Treatment of patients with T cells recognizing tumor-specific mutations



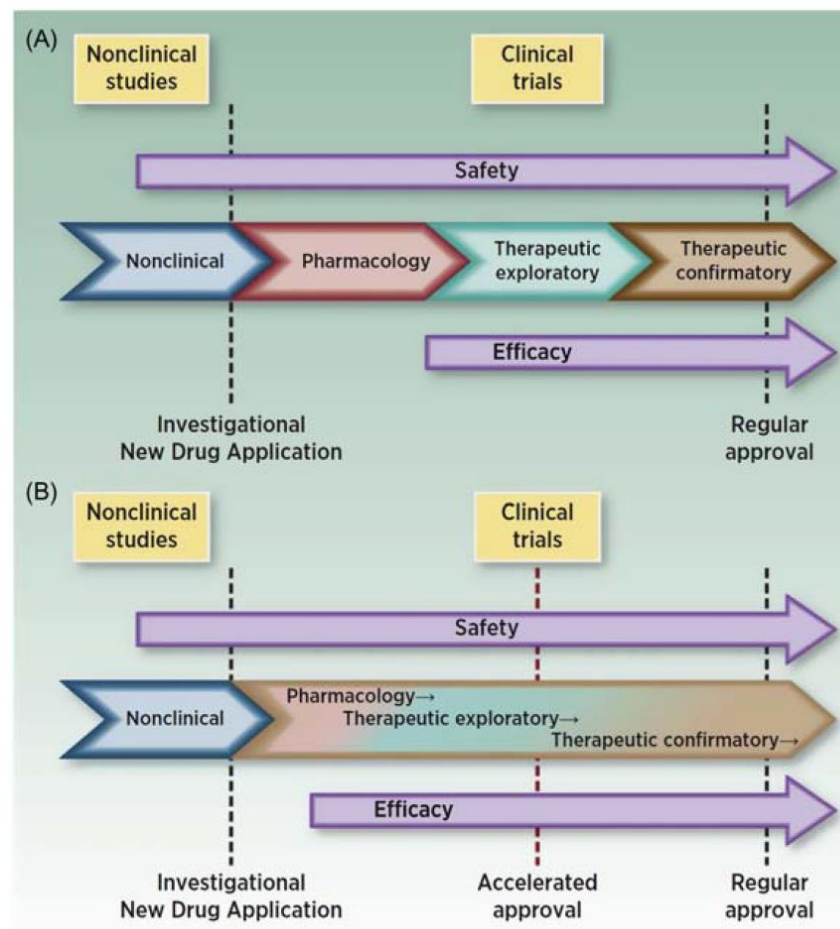
Developing ACT clinical trials



Vs.

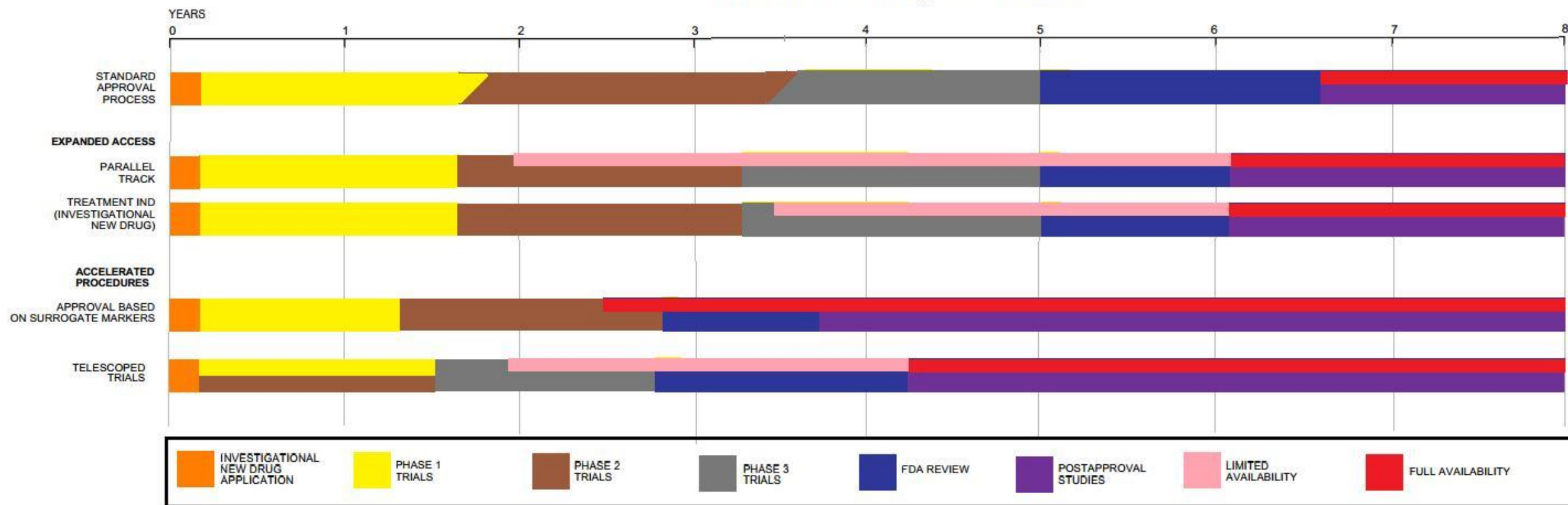


Evolving drug development paradigm



Timeline

Timeline for Drug Evaluation



Conclusion

**Adoptive cell therapy (ACT)
is no longer a promise to
treat solid tumors**

- TIL: Melanoma and cervical cancer
- TCR: Synovial sarcoma and responses in other solid tumors
- CART: mesothelioma

**However there are still
some critical points**

- Ideal target identification
- Logistics (time from identification to infusion)
- Clinical trial design



victor.moreno@startmadrid.com



@vicmorenogarcia



**CDDF 11TH SPRING
CONFERENCE 2020**

THE NETHERLANDS | 10-12 FEBRUARY 2020

→ WWW.CDDF.ORG