V SIMPOSIO GETHI | 18/19 noviembre de 2019
Ilustre Colegio Oficial de Médicos de Madrid. Aula Jiménez Díaz. Madrid

Terapia Celular en sarcoma sinovial y otros tumores sólidos

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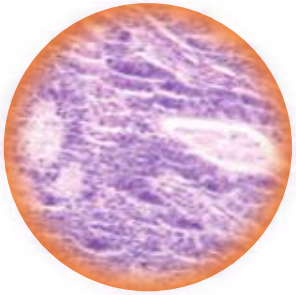
START Madrid-FJD, Early Phase Clinical Trials Unit

University Hospital Fundación Jiménez Díaz

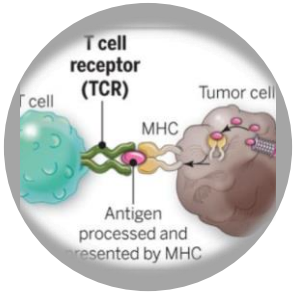
Adoptive cell transfer

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

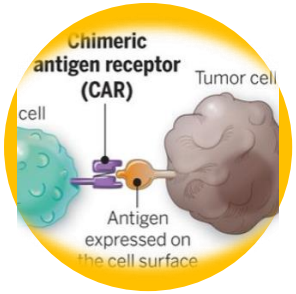


TUMOR INFILTRATING LYMPHOCYTES.

TUMOR



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

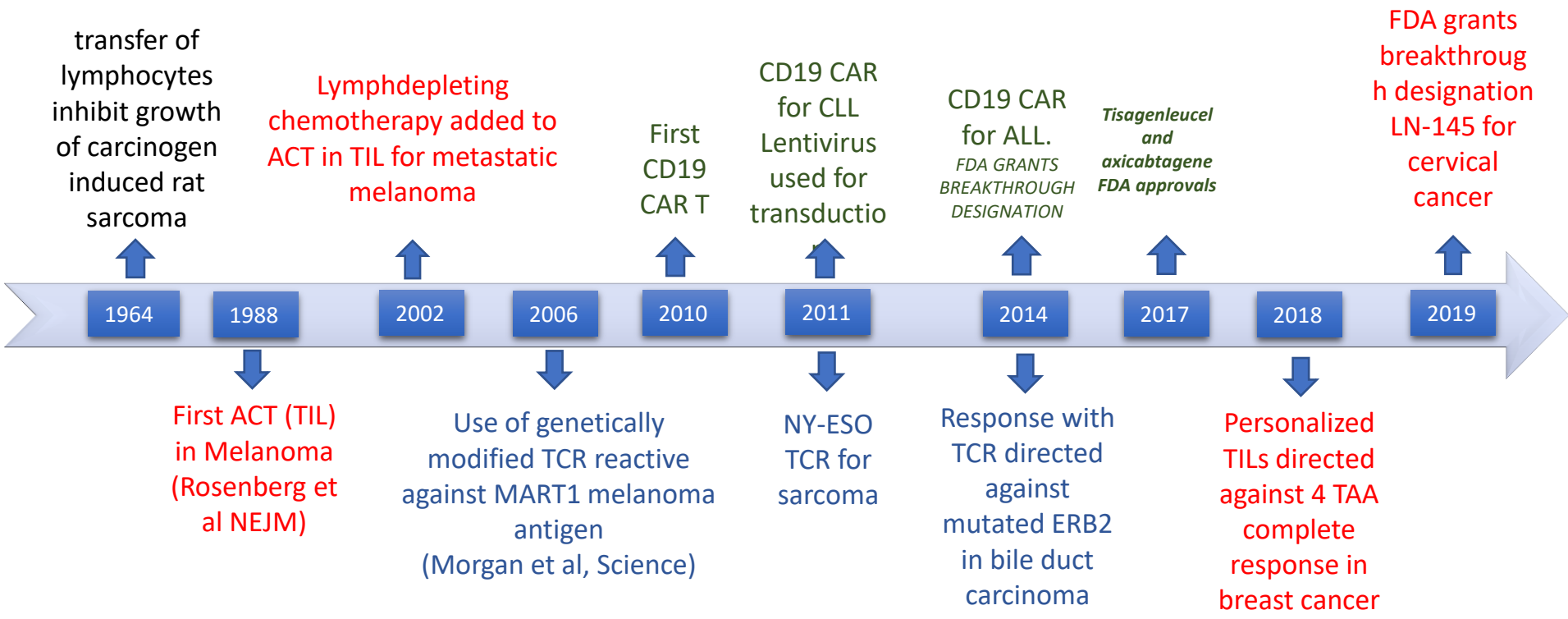


CHIMERIC ANTIGEN RECEPTOR (CAR)

PERIPHERAL BLOOD

Steven A. Rosenberg, and Nicholas P. Restifo Science 2015;348:62-68

ACT for cancer timeline



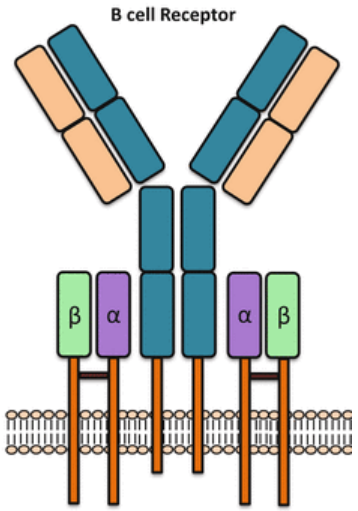
Adapted from Nat Rev Cancer. 2008 Apr; 8 (4) 299-308 and Science 2015, April, 3, vol 348 issue 6230

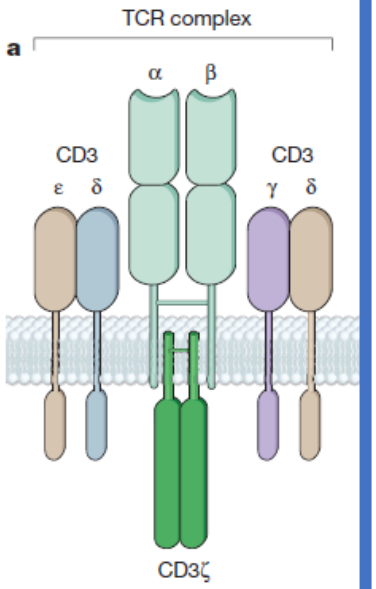
CD-19 targeted CAR T-cell approaches for ALL and NHL

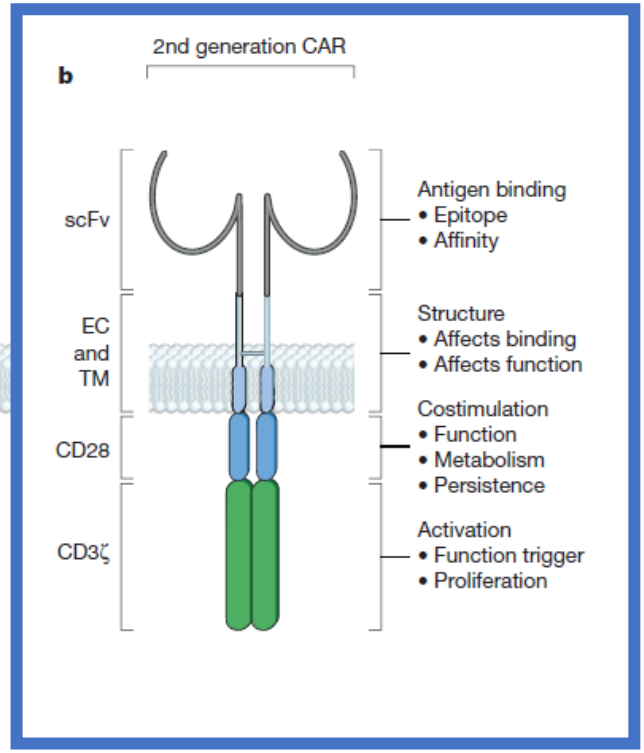
	Author (trial)	Sites	Phase	Costim	T-cell subset	Vector	Time[a]	Enrolled	Treated	Population	LD[b]	CRS[c] (grade 3+)[d]	NT[c] (grade 3+)[d]	Response[e]	Analysis
Pre-B-ALL	Maude (ELIANA)[1]	Multicenter	II	4-1BB	Unselected	Lentivirus	45 d (S)	92	75	Pediatric	95% Flu/CPM	77% (48%)	40% (13%)	81%	Of treated
	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

Jacoby E, Shahani SA, Shah NN. Updates on CAR T-cell therapy in B-cell malignancies. Immunol Rev. 2019;290(1):39–59.

(Chimaeric) Antigen Receptors

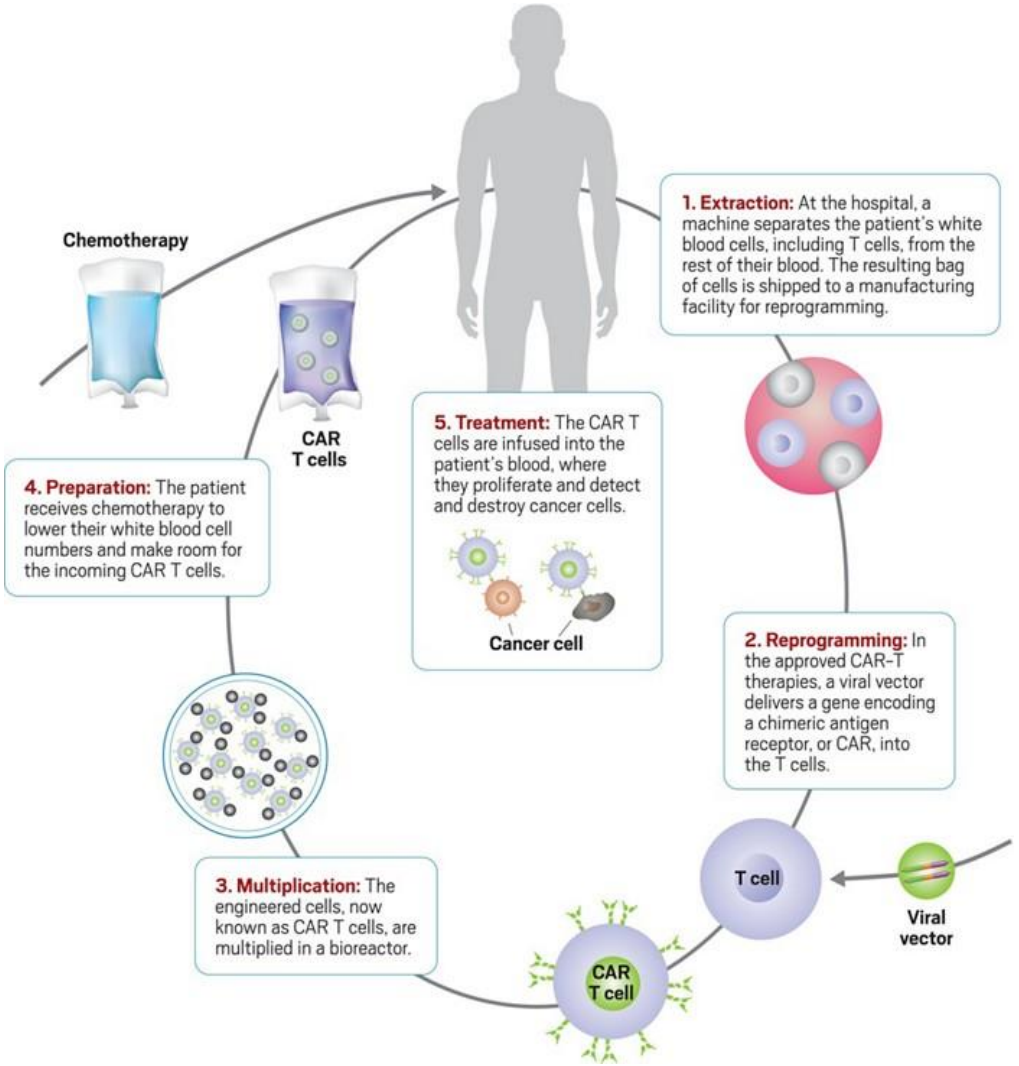




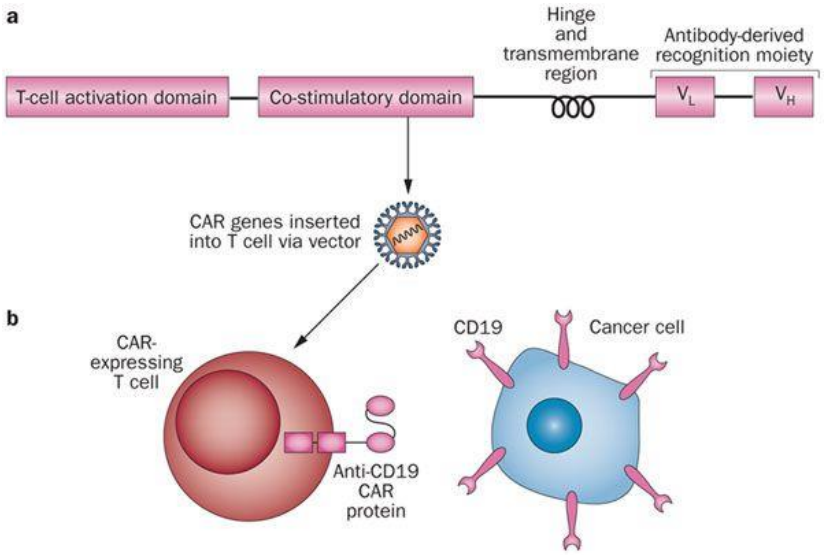


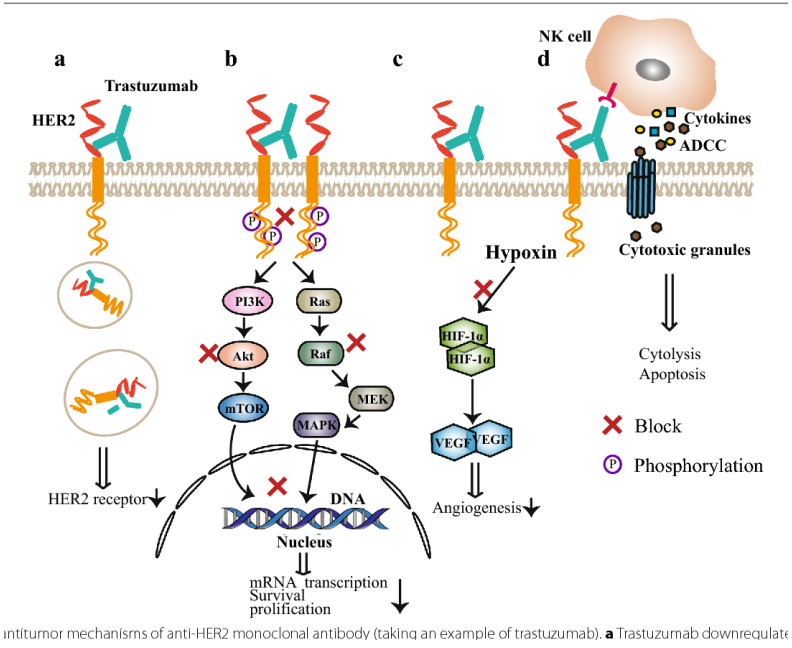
Sadelain, Nature 2017

CART treatment process



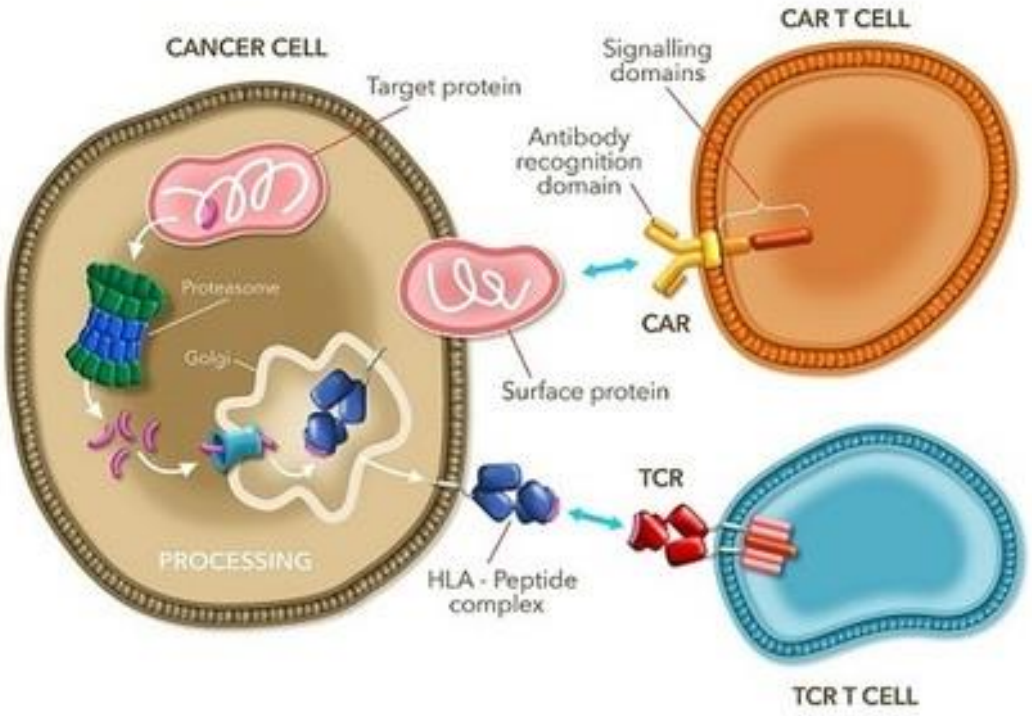
Liquid vs. Solid tumor





intitumor mechanisms of anti-HER2 monoclonal antibody (taking an example of trastuzumab). **a** Trastuzumab downregulate

Modified TCR



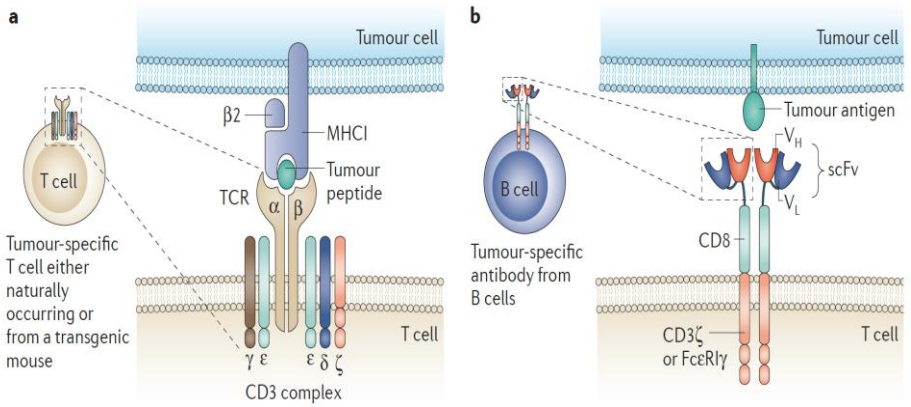
Modified TCR vs. CAR

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 APC required)

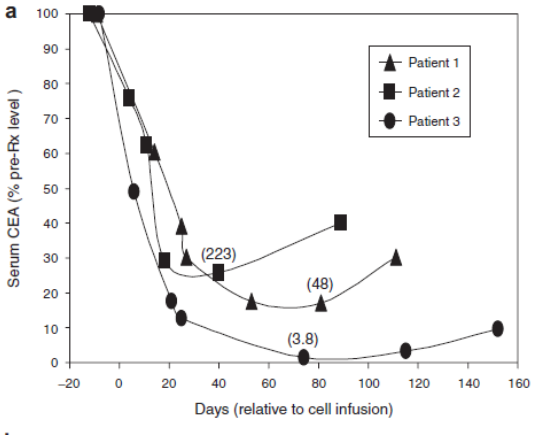
Cons

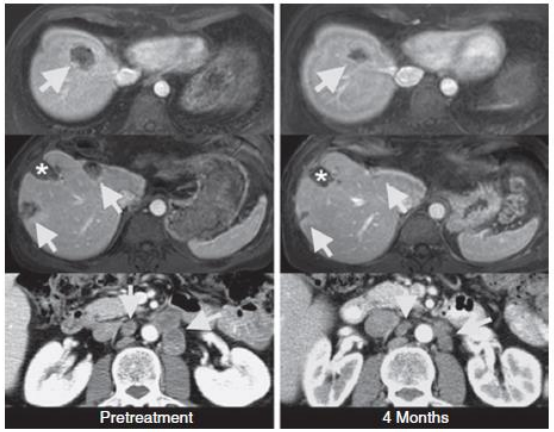
- Difficult to find surface protein specific of cancer cell only.
- Potentially blocked by soluble antigen

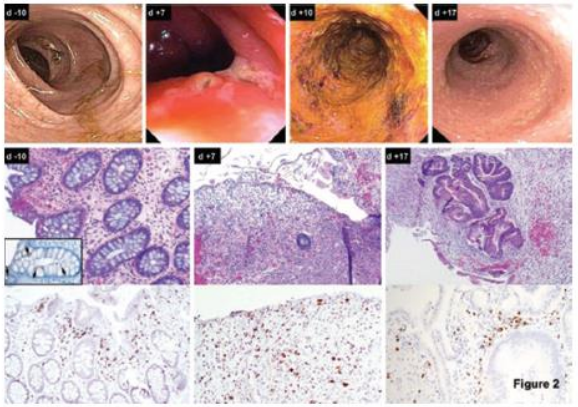
Kershaw, Nat Rev Cancer, 2013

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)





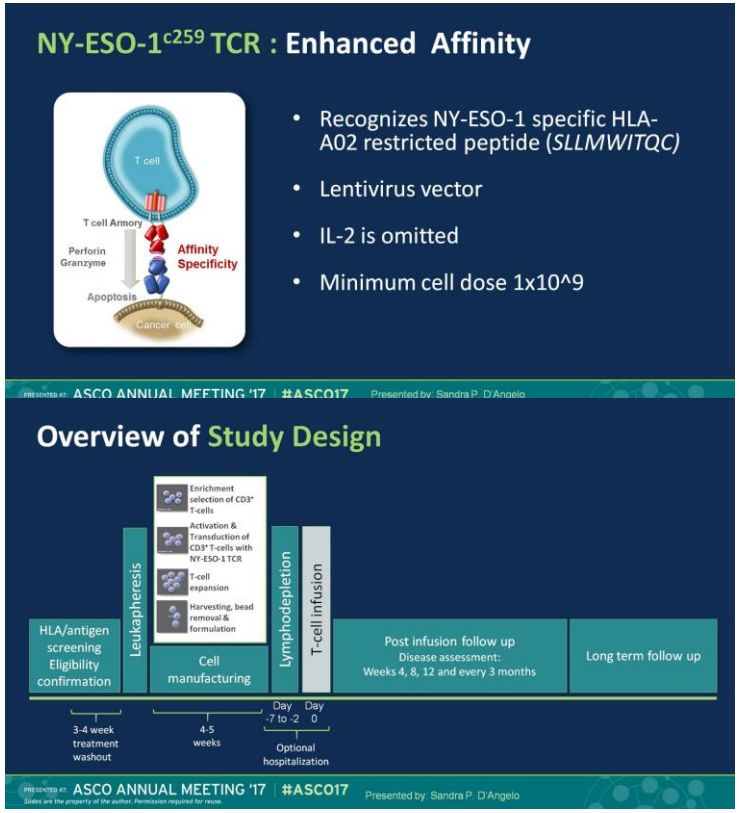


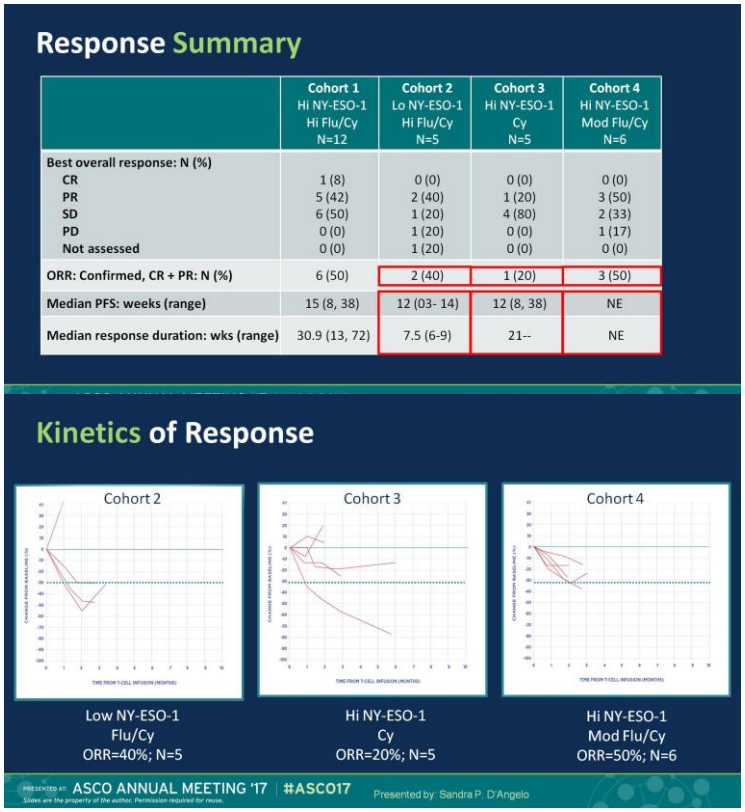
Parkhurst MR, Yang JC, Langan RC, Dudley ME, Nathan DAN, Feldman SA, et al. T cells targeting carcinoembryonic antigen can mediate regression of metastatic colorectal cancer but induce severe transient colitis. Mol Ther. 2011;19(3):620–6.

Genetically redirected T cells for solid tumors

Target	Cancer	Receptor	N patients	Responses	Ref
ERBB2	Colorectal	CAR: CD28-CD137-CD3ζ	1 (deceased resp distress lung ERBB2 expression)		Morgan, R. A. *Mol. Ther.* 2010
CEA	Colorectal	TCR	3 (3 severe colitis)	1	Parkhurst MR, . *Mol Ther* 2011
MAGE A3	Myeloma and melanoma	TCR	2 (deceased) TTN cross reactivity in heart		Linette, G. P. *et al*. *Blood* 2013
CEA	Colorectal and breast	CAR: CD3ζ	7	0	Ma, Q.. 2002.
αFR	Ovarian	CAR: FcRγ	12	0	Kershaw, M. H. *et al. Clin. Cancer Res* 2006
CD171	Neuroblastoma	CAR: CD3ζ	6	1	ParK, JR. *Mol Ther*. 2007
CAIX	Renal	CAR: CD3ζ	11	0 (+hepatotoxicity)	Lamers CH. *Mol Ther*. 2013
GD2	Neuroblastoma	CAR: CD3ζ	19	3 (CR)	Louis, C. U. *et al*. *Blood* 2011

NY-ESO in Synovial Sarcoma

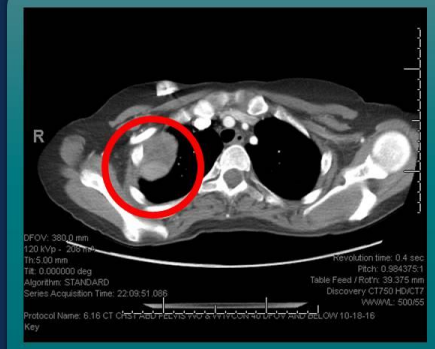




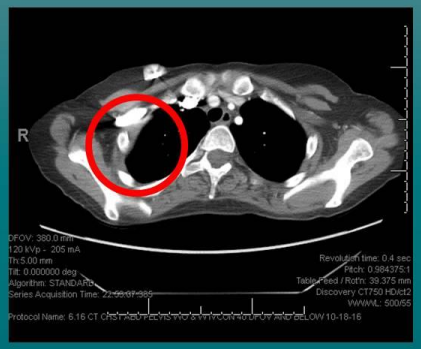
	Cohort 1 Hi NY-ESO-1 Hi Flu/Cy N=12	Cohort 2 Lo NY-ESO-1 Hi Flu/Cy N=5	Cohort 3 Hi NY-ESO-1 Cy N=5	Cohort 4 Hi NY-ESO-1 Mod Flu/Cy N=6
Best overall response: N (%)				
CR	1 (8)	0 (0)	0 (0)	0 (0)
PR	5 (42)	2 (40)	1 (20)	3 (50)
SD	6 (50)	1 (20)	4 (80)	2 (33)
PD	0 (0)	1 (20)	0 (0)	1 (17)
Not assessed	0 (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

Presented By Crystal Mackall at 2017 ASCO Annual Meeting

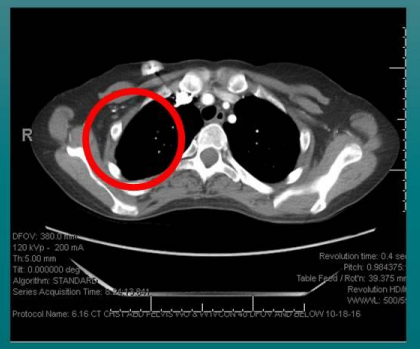
Tumor Responses



Baseline



Week 4

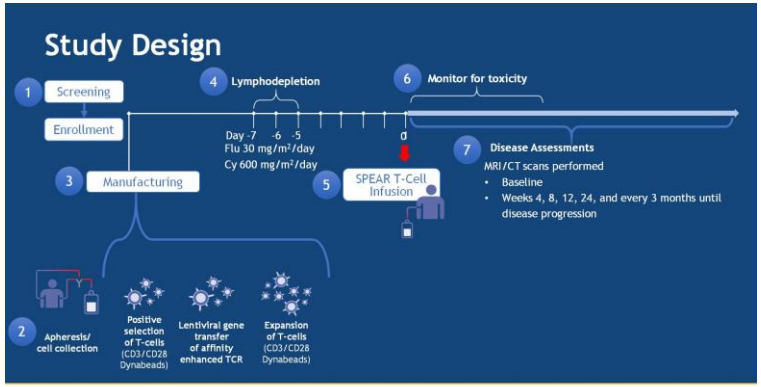


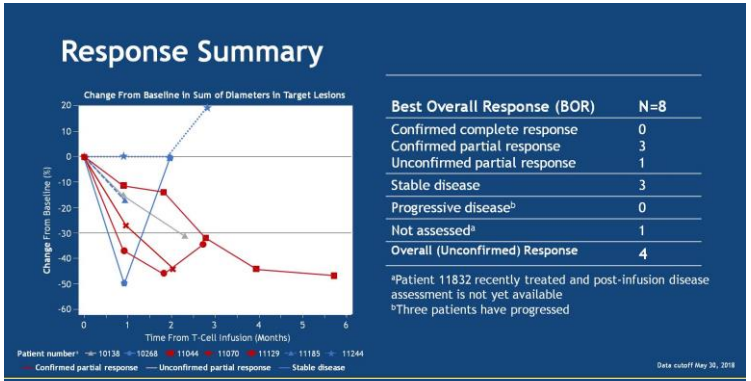
Week 8

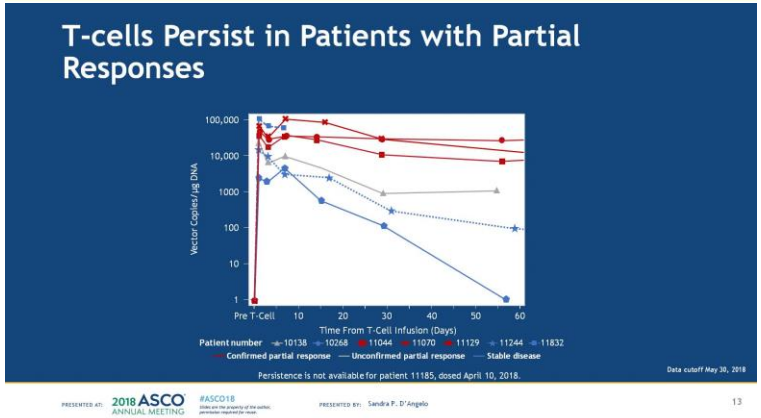
- 34 year old woman patient from cohort 4
- Prior therapies include doxorubicin and ifosfamide, pazopanib, gemcitabine and 7 surgical resections

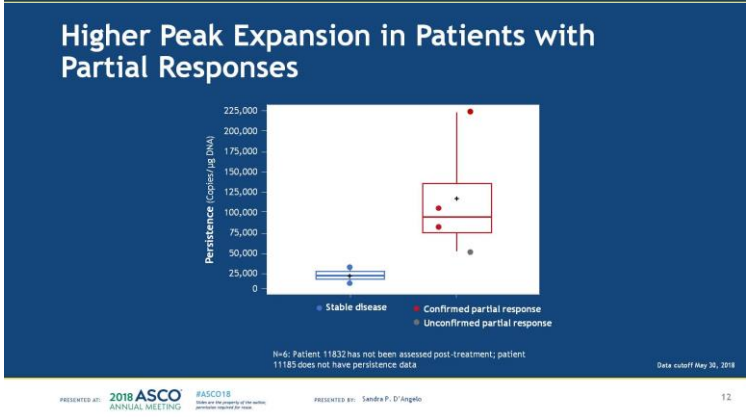
Presented By Crystal Mackall at 2017 ASCO Annual Meeting

NY-ESO in liposarcoma









Presented By Sandra D''Angelo at 2018 ASCO Annual Meeting

ADP-A2M4 (MAGE-A4) Synovial Sarcoma

PATIENT CHARACTERISTICS

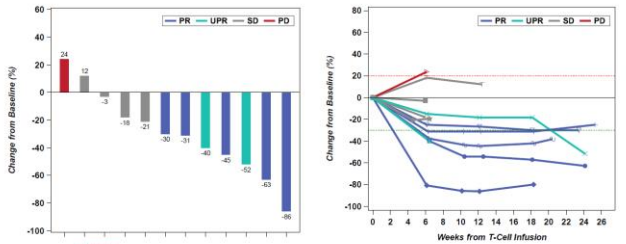
N=13*		
Sex	Male: 8	Female: 5
Age	Median: 53	Range: 31 - 76 *Two patients >70*
Race	White: 11	Asian: 2
ECOG status	ECOG 0 = 7	ECOG 1 = 6
Prior lines of systemic therapies	Median: 2	Range: 1 - 5
Cell dose x 10^9	Median: 9.7	Range: 3.41 - 9.98

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

Data cut off 3-Sep-19

ADP-A2M4 SPEAR T-CELLS INDUCE CLINICAL RESPONSES

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



ORR: 58%
7/12

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 failur	1 (7.7%)
Anal abscess	1 (7.7%)

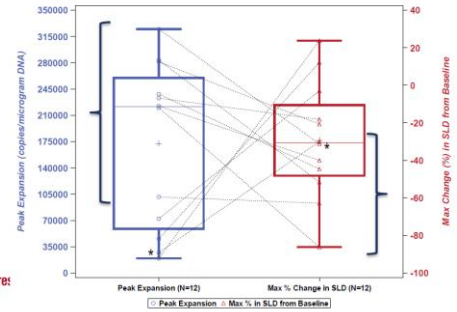
Preferred Term	Grade ≥3 N (%)
Aplastic anemia	1 (7.7%)
Arrhythmia	1 (7.7%)
Decreased appetite	1 (7.7%)
Endocarditis staphylococcal	1 (7.7%)
Hypermagnesemia	1 (7.7%)
Hypocalcemia	1 (7.7%)
Hypotension	1 (7.7%)
Influenza like illness	1 (7.7%)
Pancytopenia	1 (7.7%)
Pleural effusion	1 (7.7%)
Sciatica	1 (7.7%)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

Data cut off 3-Sep-19

TRANSDUCED T-CELLS PEAK EXPANSION

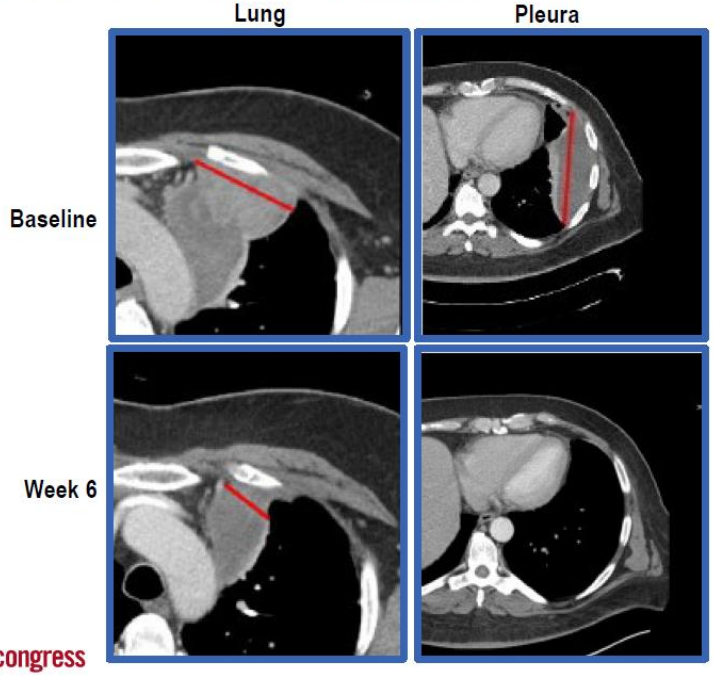
Higher peak expansion associated with decrease in tumor size from baseline



Data cut off 3-Sep-19

Presented by Brian A. Van Tine at ESMO 2019 in Barcelona, Spain

SIGNIFICANT TUMOR REDUCTION



86% decrease in RECIST 1.1 and significant symptom improvement

- 53-year-old male
- Longstanding history of synovial sarcoma
  - Treated with surgery, radiotherapy, and multiple chemotherapy regimens
- High MAGE-A4 expression in tumor
  - Baseline SLD* 24 cm
- 9.87 x 10^9 SPEAR T-cells
- Did well post-infusion
  - Grade 1 CRS and cytopenias
- Baseline scans:
  - Extensive disease in the lung and pleura-based tumor masses
- Week 6 scans:
  - One large pleura-based lesion disappeared and others reduced via RECIST 1.1 criteria

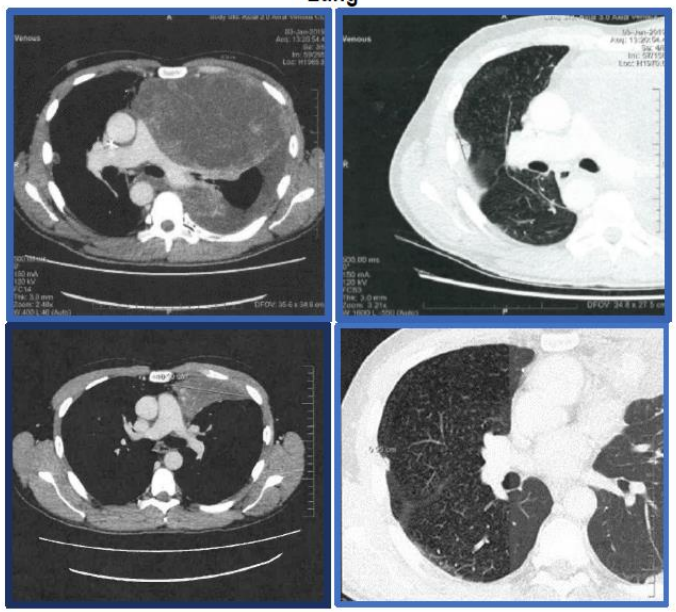
*Sum of the Longest Diameter of the target lesions

REDUCTION IN BULKY TUMOR

Lung

Baseline

Week 12



44% decrease by RECIST 1.1 and shortness of breath resolved

- 42-year-old male
- Diagnosed age 25
  - Recently developed metastatic disease
- Moderate MAGE-A4 expression
  - Baseline SLD 20 cm
- 9.95 x 10^9 SPEAR T-cells
- Did well post-infusion
  - Grade 2 CRS and cytopenias
- At baseline
  - Shortness of breath due to accumulation of fluid in pleural space
  - Tumor (left lung) displacing major blood vessels and compressing right lung
- Week 12 scans:
  - Tumor decreased and non-target lesion disappeared
  - Patient lung expanded; shortness of breath resolved

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

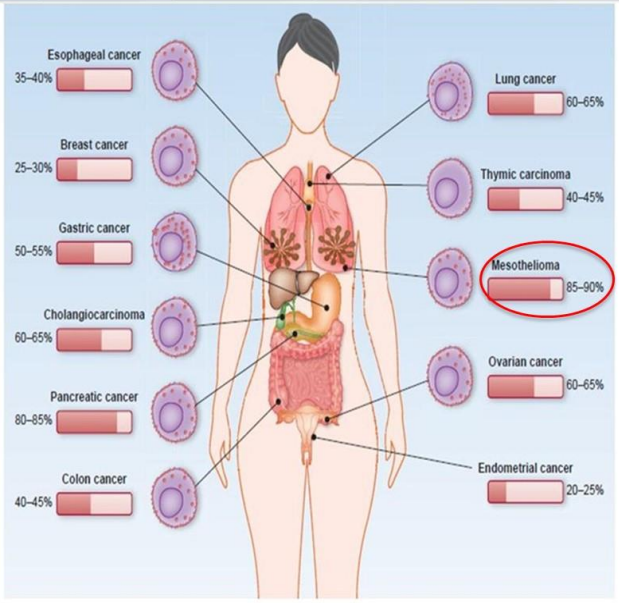
Presented By Prasad Adusumilli at 2019 ASCO Annual Meeting

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

Mesothelin-targeted CAR T-cell therapy

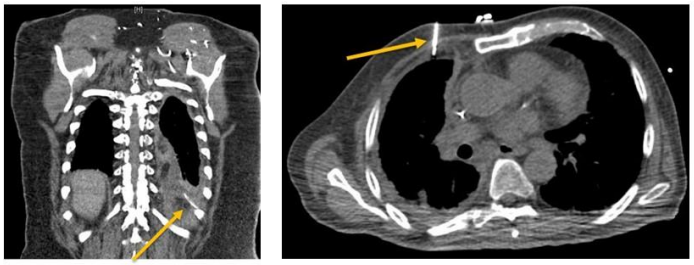
Single dose of CAR T cells administered intrapleurally

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
	6	72M	Mesothelioma	Biphasic	IIIA	2	IR
3 1e6/kg	7	70M	Mesothelioma	Epithelioid	IIIA	2	Pleural catheter
	8	73M	Mesothelioma	Epithelioid	IIIB	6	Pleural catheter
	9	66M	Mesothelioma	Epithelioid	IV	4	IR
4 3e6/kg	10	70M	Mesothelioma	Epithelioid	IIIB	2	Pleural catheter
	11	74M	Mesothelioma	Epithelioid	IIIB	2	Pleural catheter
	12*	66M	Mesothelioma	Epithelioid	IIIB	2 / 5	Pleural catheter
5 6e6/kg	13	76M	Mesothelioma	Epithelioid	IIIA	2	IR
	14	69M	Mesothelioma	Epithelioid	IIIA	2	IR
	15	71M	Mesothelioma	Epithelioid	IIIB	2	Pleural catheter
6 1e7/kg	16	77F	Mesothelioma	Epithelioid	IV	7	IR
	17	71M	Mesothelioma	Biphasic	IIIA	2	IR
	18	53M	Mesothelioma	Epithelioid	IIIB	3	IR
	19	64M	Mesothelioma	Epithelioid	IIIB	3	IR
	20	70M	Mesothelioma	Epithelioid	IIIA	3	Pleural catheter
	21	61F	Mesothelioma	Epithelioid	IIIB	2	IR
7 3e7/kg	22	73M	Mesothelioma	Epithelioid	IIIB	2	IR
	23	71F	Mesothelioma	Epithelioid	IV	2	IR
	24	70M	Mesothelioma	Epithelioid	IV	5	IR
8 6e7/kg	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

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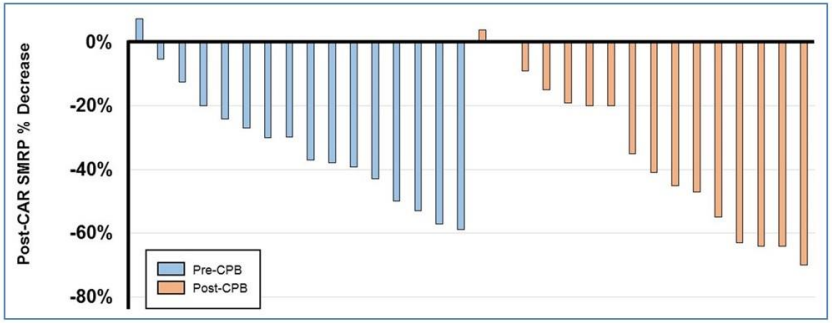
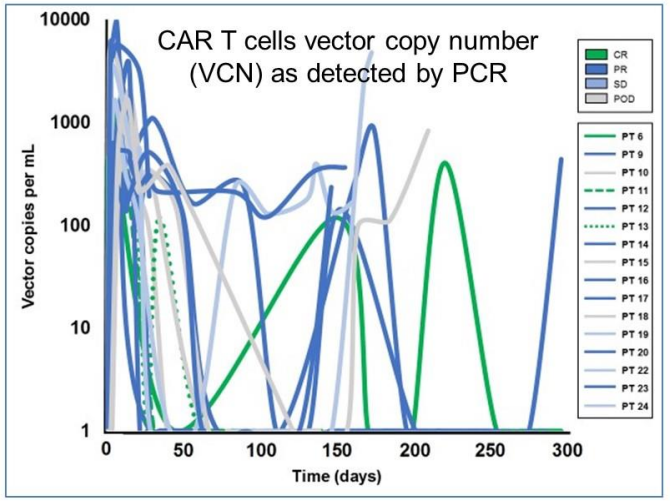
CAR T-cell persistence in peripheral blood

- 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

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

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

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 (Inv 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%)

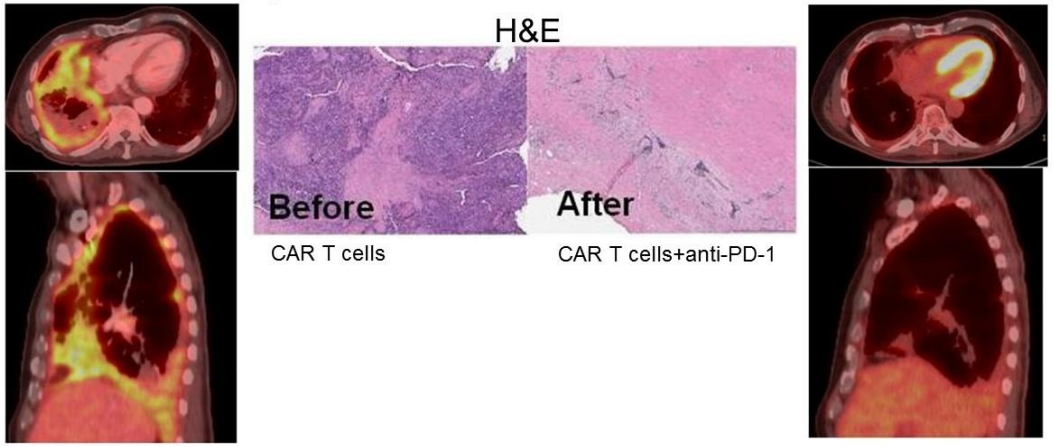
41% ORR

* 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

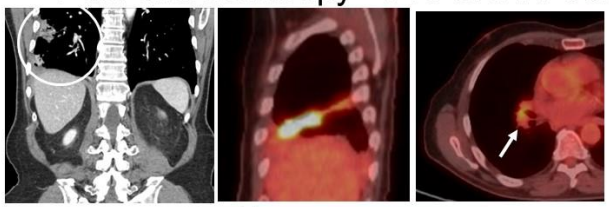
- April 2017 – Unresectable disease following chemotherapy
- May 2017 – 3e5 CAR T cells/kg following Cyclophosphamide administered
- July 2017 – Pembrolizumab started (PD-L1 <1%, low mutational burden)
- Nov 2017 – Complete metabolic response, Serum SMRP normal
- Feb 2018 – CAR T cells detected at 32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

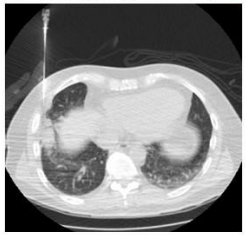


Mesothelin-targeted CAR T-cell therapy

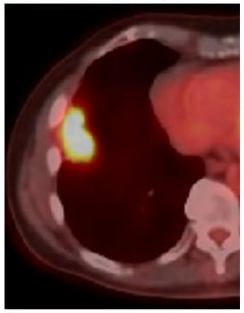
MSLN CAR T-cells + anti PD-1 agent
Complete response in patient #13 – 14 months and ongoing

Post chemotherapy - Pre CAR T-cells





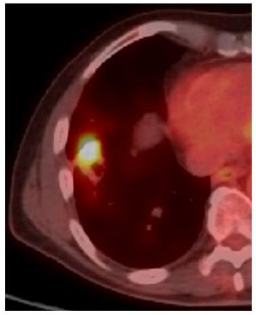
CAR T-cells administered in interventional radiology



April

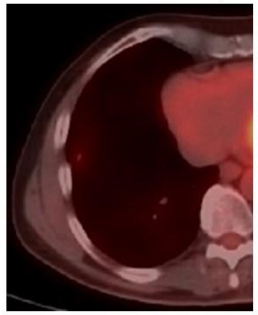
Partial response with CAR T cells alone

Post CAR T-cells



May

Addition of anti-PD-1 antibody



Nov

Presented By Prasad Adusumilli at 2019 ASCO Annual Meeting

162 ASCO ANNUAL MEETING | MAY 31– JUNE 4, 2019 | CHICAGO, IL, USA

Safety and efficacy of cryopreserved autologous tumor infiltrating lymphocyte therapy (LN-144, lifileucel) in advanced metastatic melanoma patients who progressed on multiple prior therapies including anti-PD-1

Amod Sarnaik[1], Nikhil I. Khushalani[1], Jason Alan Chesney[2], Harriet M. Kluger[3], Brendan D. Curti[4], Karl D. Lewis[5], Sajeve Samuel Thomas[6], Eric D. Whitman[7], Omid Hamid[8], Jose Lutzky[9], Anna C. Pavlick[10], Jeffrey S. Weber[10], James M.G. Larkin[11], Debora Barton[12], Kelly DiTrapani[12], Renee Wu[12], Maria Fardis[12], John M. Kirkwood[13]

[1]H. Lee Moffitt Cancer Center, Tampa, FL; [2]James Graham Brown Cancer Center, University of Louisville, Louisville, KY; [3]Yale School of Medicine, New Haven, CT; [4]Earle A. Chiles Research Institute at Robert W. Franz Cancer Center, Providence Cancer Institute, Portland, OR; [5]University of Colorado Comprehensive Cancer Center, Aurora, CO; [6]University of Florida Health Cancer Center at Orlando Health, Orlando, FL; [7]Atlantic Health System Cancer Care, Morristown, NJ; [8]The Angeles Clinic and Research Institute, Los Angeles, CA; [9]Mount Sinai Comprehensive Cancer Center, Miami, FL; [10]Laura and Isaac Perlmutter Cancer Center, NYU Langone Medical Center, New York, NY; [11]Royal Marsden NHS Foundation Trust, London, United Kingdom; [12]Iovance Biotherapeutics, Inc., San Carlos, CA; [13]Melanoma Program, UPMC Hillman Cancer Center, University of Pittsburgh, Pittsburgh, PA

NCT02360579

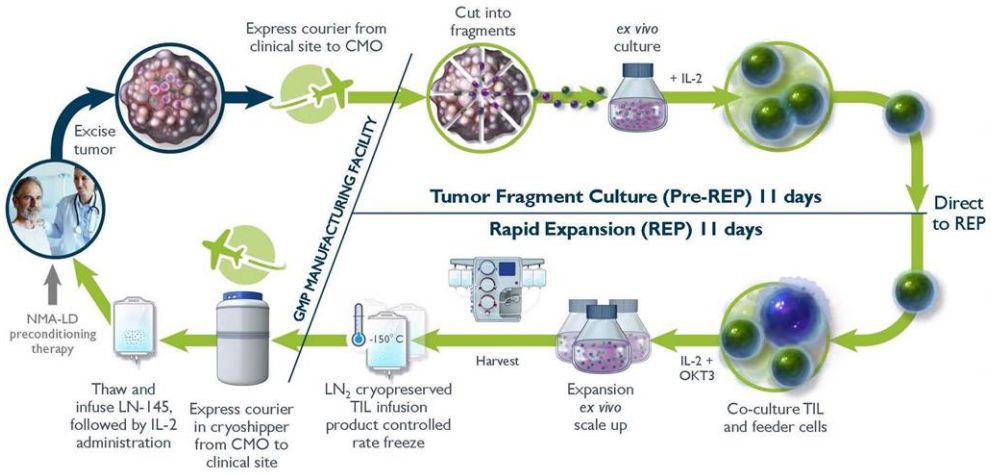
For more information, please contact kellyditrapani@iovance.com

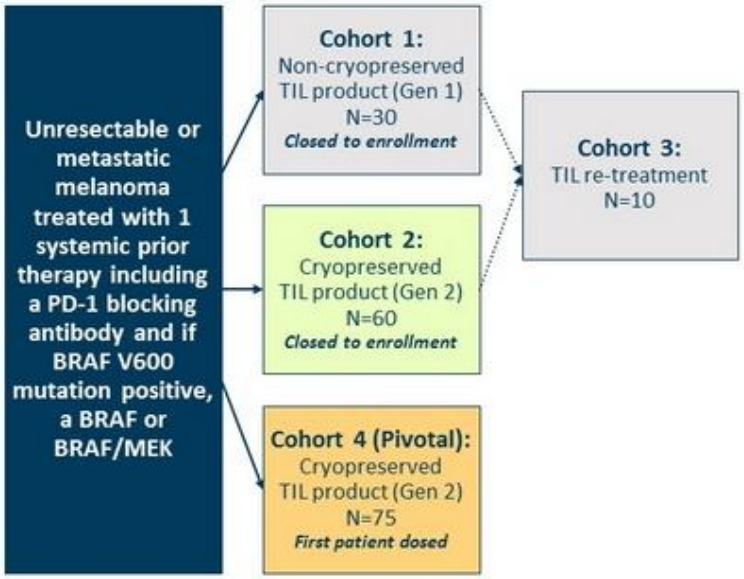
BACKGROUND

- Treatment options are limited for patients with advanced melanoma who have progressed on checkpoint inhibitors and targeted therapies
- Adoptive cell therapy (ACT) utilizing tumor-infiltrating lymphocytes (TIL) leverages and enhances the body's natural defense against cancer
- TIL has demonstrated antitumor efficacy:
  - Durable long-term responses in heavily pretreated patients[1]

- **innovaTIL-01** (NCT02360579) is an ongoing Phase 2 multicenter study:
  - Investigational agent: autologous TIL (lifileucel; LN-144)
  - Patient population: unresectable metastatic melanoma who have progressed on checkpoint inhibitors and BRAF/MEK inhibitors (if BRAF mutated)
  - Manufacturing conditions: central manufacturing of cryopreserved TIL, 22 day duration

[1]Rosenberg, S.A., et al. Durable Complete Responses in Heavily Pretreated Patients with Metastatic Melanoma Using TCell Transfer Immunotherapy. *Clinical Cancer Research*. 2011. 17(13). 4550-4557.





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Adverse events LN-144

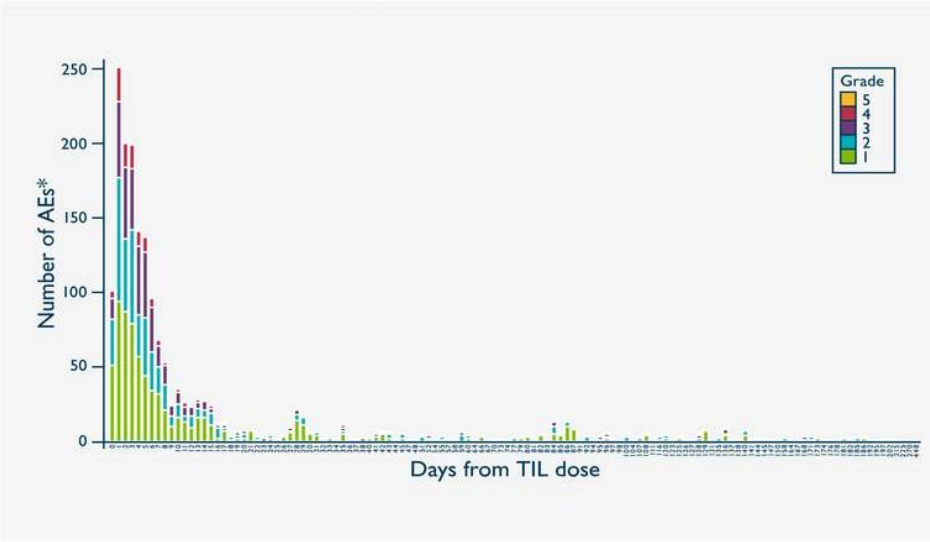
COHORT 2

Frequency of AEs over time is reflective of potential benefit of one time treatment with lifileucel

Lifileucel Treatment-Emergent Adverse Events (≥ 30%)

	Cohort 2, N=66		
PREFERRED TERM	Any Grade, n (%)	Grade 3/4, n (%)	Grade 5, n (%)
Number of patients reporting at least one Treatment-Emergent AE**	65 (98.5)	63 (95.5)	2 (3.0)
Thrombocytopenia	59 (89.4)	53 (80.3)	0
Chills	52 (78.8)	4 (6.1)	0
Anemia	44 (66.7)	36 (54.5)	0
Pyrexia	39 (59.1)	11 (16.7)	0
Febrile neutropenia	36 (54.5)	35 (53.0)	0
Neutropenia	36 (54.5)	25 (37.9)	0
Hypophosphatemia	29 (43.9)	22 (33.3)	0
Fatigue	27 (40.9)	1 (1.5)	0
Leukopenia	27 (40.9)	22 (33.3)	0
Hypotension	23 (34.8)	7 (10.6)	0
Tachycardia	22 (33.3)	1 (1.5)	0
Lymphopenia	21 (31.8)	19 (28.8)	0

Adverse Events Over Time



**Treatment-Emergent Adverse Events refer to all AEs starting on or after the first dose date of TIL up to 30 days. Patients with multiple events for a given preferred term are counted only once using the maximum grade under each preferred term. Safety terms which describe the same medical condition were combined.
*The number of AEs is cumulative and represent the total number of patients dosed

Iovance Biotherapeutics. Presented at ASCO 2019 by A Sarnaik et al.

LN-144 results in melanoma

Table 3. Efficacy

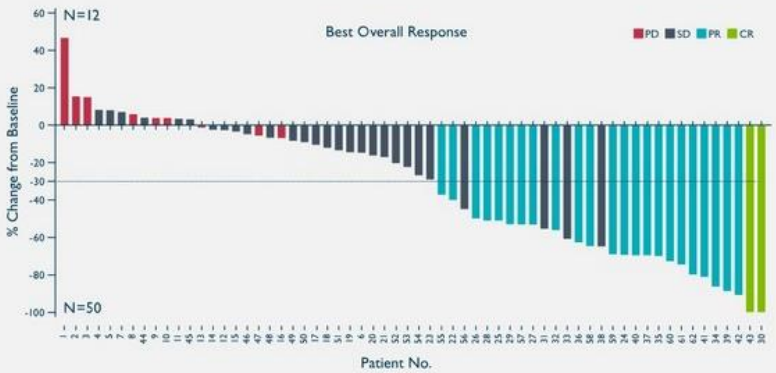
RESPONSE (RECIST v1.1)	PATIENTS, N=66 n (%)
Objective Response Rate (ORR)	**25 (38%)**
Complete Response (CR)	2 (3%)
Partial Response (PR)	23 (35%)
Stable Disease (SD)	28 (42%)
Progressive Disease (PD)	9 (14%)
Non-Evaluable	4 (6%)
Disease Control Rate (DCR)	53 (80%)
Median Duration of Response (DOR)	**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

COHORT 2

- 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%

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.

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182 ASCO ANNUAL MEETING | MAY 31 – JUNE 4, 2019 | CHICAGO, IL, USA

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

Amir A. Jazaeri[1], Emese Zsiros[2], Rodabe Navroze Amaria[3], Andrew S. Artz[3], Robert P. Edwards[4], Robert Michael Wenham[5], Brian M. Slomovitz[6], Axel Walther[7], Sajeve Samuel Thomas[8], Jason Alan Chesney[9], Robert Morris[10], Koji Matsuo[11], Stephanie Gaillard[12], Peter G. Rose[13], Jesus Garcia Donas[14], Jacqueline Maria Tromp[15], Kelly DiTrapani[16], Huiling Li[16], Maria Fardis[16], Bradley J. Monk[17]

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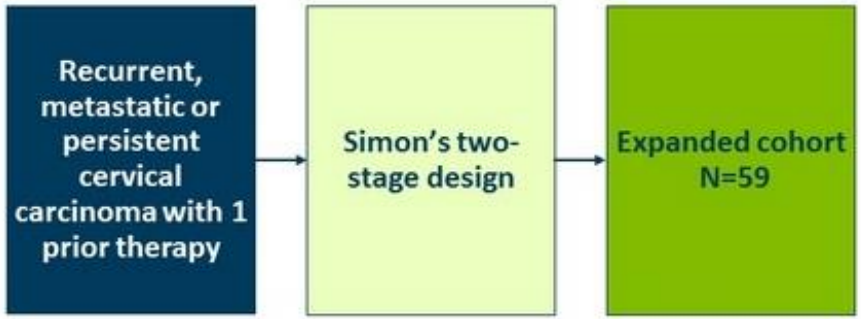
NCT03108495

For more information, please contact kellyditrapani@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, (%)
Age	
Median	45
Min, Max	30, 68
Prior therapies, n (%)	
Mean # prior therapies	2.4
Platinum-Based	27 (100)
Taxane	26 (96)
Anti-VEGF	22 (82)
Radiotherapy	20 (74)
Anti-PD-1/PD-L-1	4 (15)
Cancer Status at Screening	
Metastatic	14 (52)
Recurrent	10 (37)
Persistent	3 (11)

CHARACTERISTIC		N=27, (%)
ECOG score, n (%)	**Screening**	**Baseline**
0	19 (70)	9 (33)
1	8 (30)	17 (63)
≥2	0	1 (4)
Histologic Cell Type, n (%)		
Squamous Cell Carcinoma		12 (44)
Adenocarcinoma		12 (44)
Adenosquamous Carcinoma		3 (11)
Target Lesion Sum of Diameters (mm)		
Mean (SD)		61 (38)
Min, Max		10, 165
Number of Target & Non-Target Lesions (at Baseline)		
>3		17 (63)
Mean (Min, Max)		4 (1, 9)

Iovance Biotherapeutics. Presented at ASCO 2019 by A Jazzaeri et al.

182 ASCO ANNUAL MEETING | MAY 31 – JUNE 4, 2019 | CHICAGO, IL, USA

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

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NCT03108495

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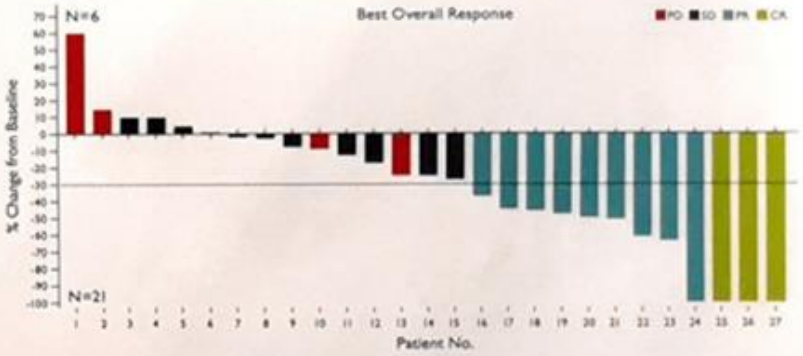
Figure 1. Efficacy of adoptive cell transfer using autologous tumor infiltrating lymphocytes (LN-145) for treatment of recurrent, metastatic, or persistent cervical carcinoma

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

Figure 4. Efficacy: Best Overall Response

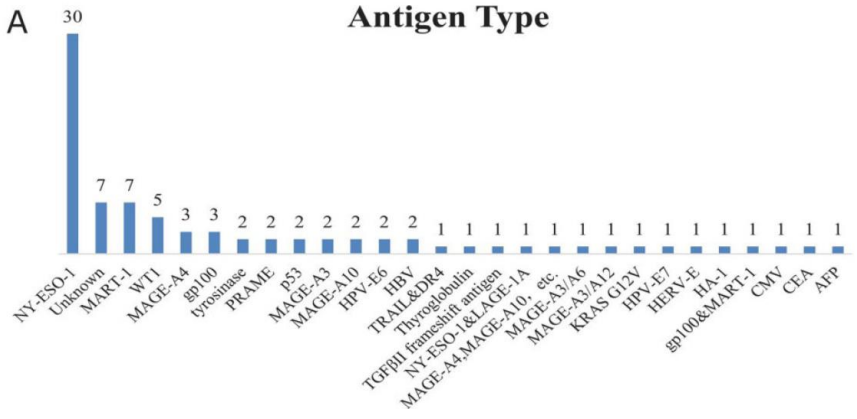


- 78% of patients had a reduction in tumor burden
- Median follow up is 7.4 months
- Mean number of TIL cells infused: 28 x 10^9
- Median number of IL-2 doses administered was 6.0

Iovance Biotherapeutics. Presented at ASCO 2019 by A Jazzaeri et al.

Current approach public antigens (non mutated)

- Limited potential
- On-target off tumor reactivity



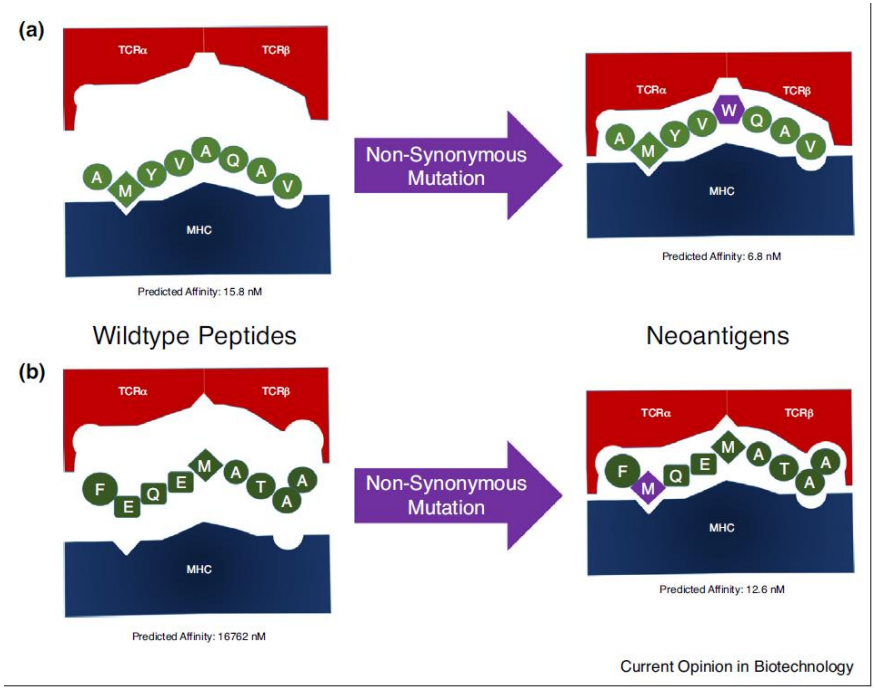
Zhang 2019

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

Durgeau A, 2018

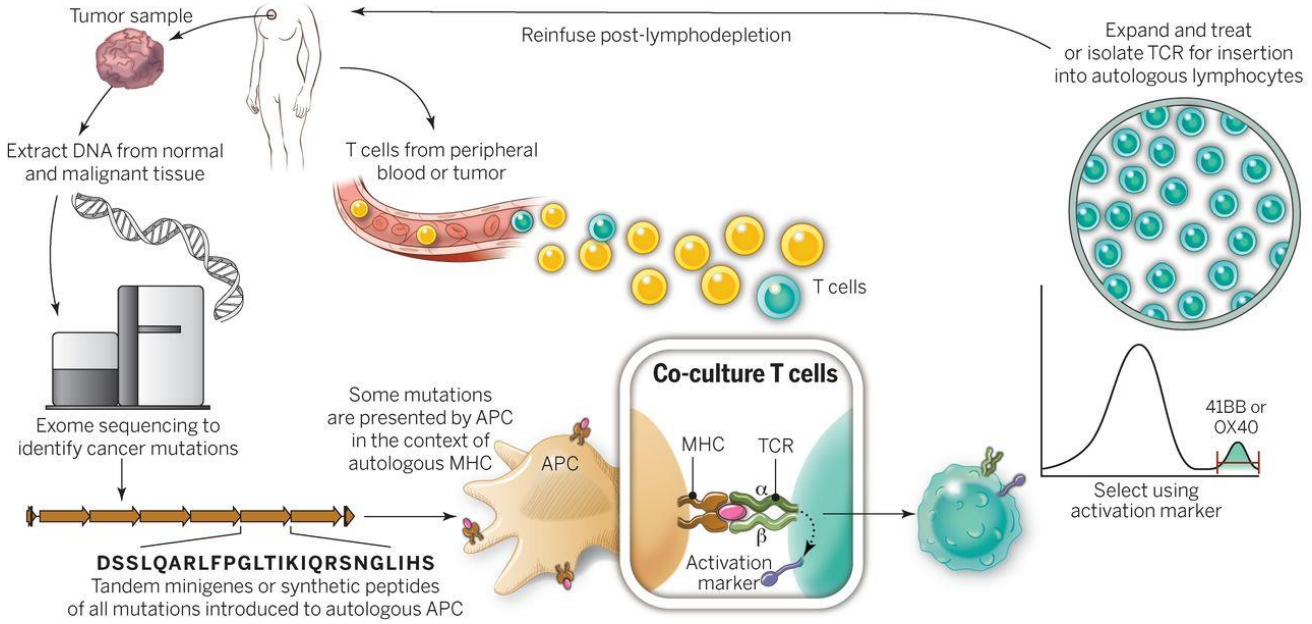
Private neoantigens

- 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



Bethune et al, 2017

Treatment of patients with T cells recognizing tumor-specific mutations



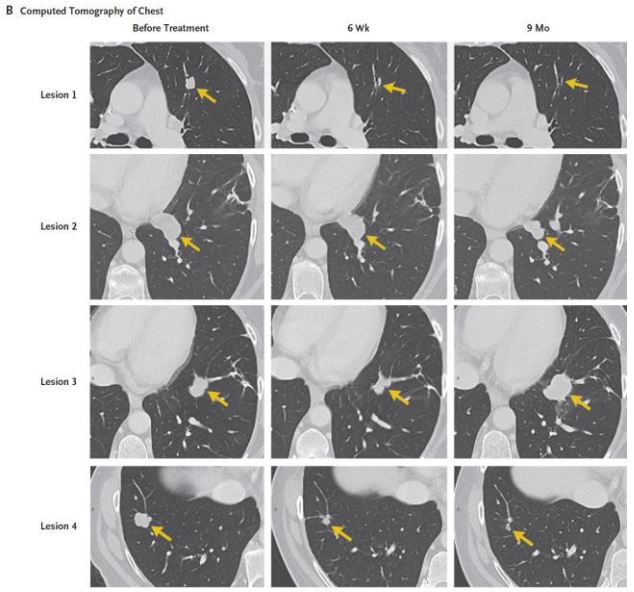
Steven A. Rosenberg, and Nicholas P. Restifo Science 2015;348:62-68

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

T-Cell Transfer Therapy Targeting Mutant KRAS in Cancer

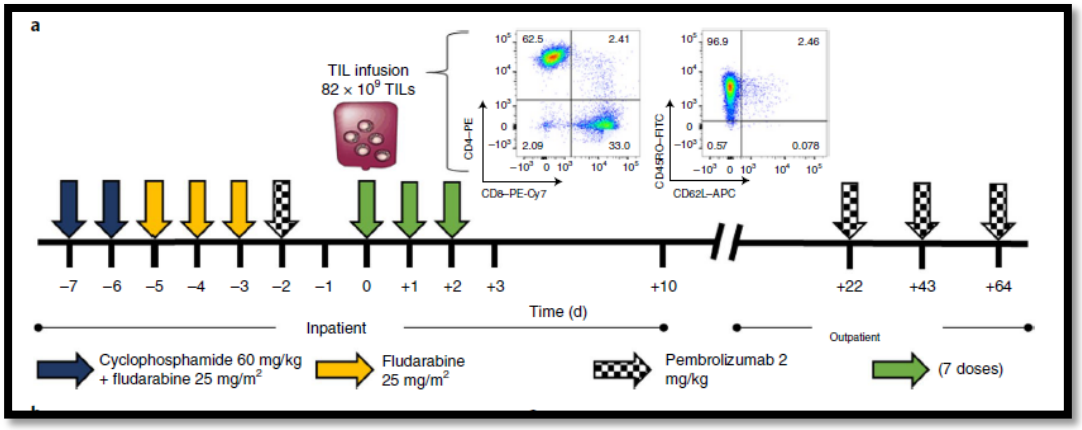
- HLA-C*08:02–restricted tumor-infiltrating lymphocytes that were composed of four different T-cell clonotypes that specifically targeted KRAS G12D.
- Objective regression of all seven lung metastases
- one of these lesions had progressed on evaluation 9 months after therapy. The lesion was resected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



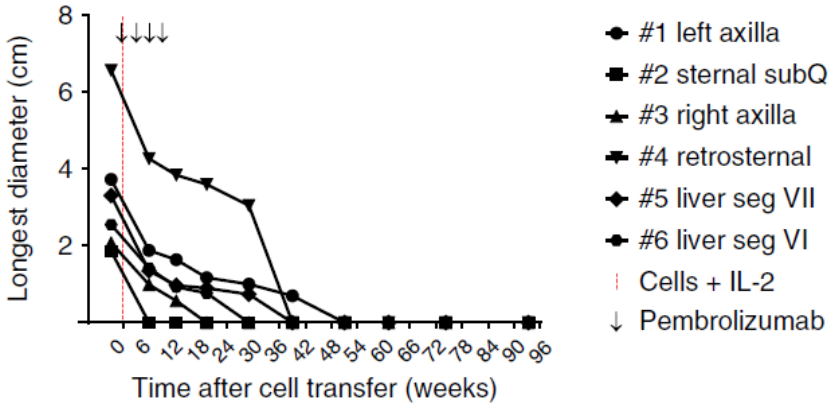
Tran E, Robbins PF, Lu YC, Prickett TD, Gartner JJ, Jia L, et al. T-cell transfer therapy targeting mutant KRAS in cancer. N Engl J Med. 2016;375(23):2255–62.

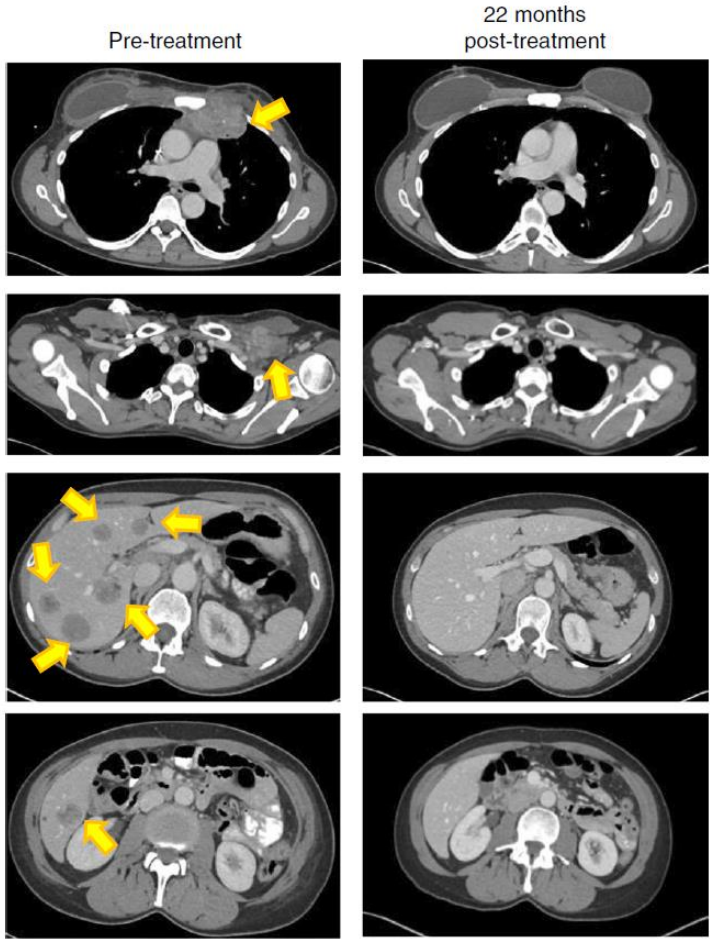
Immune recognition of somatic mutations leading to complete durable regression in metastatic breast cancer

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



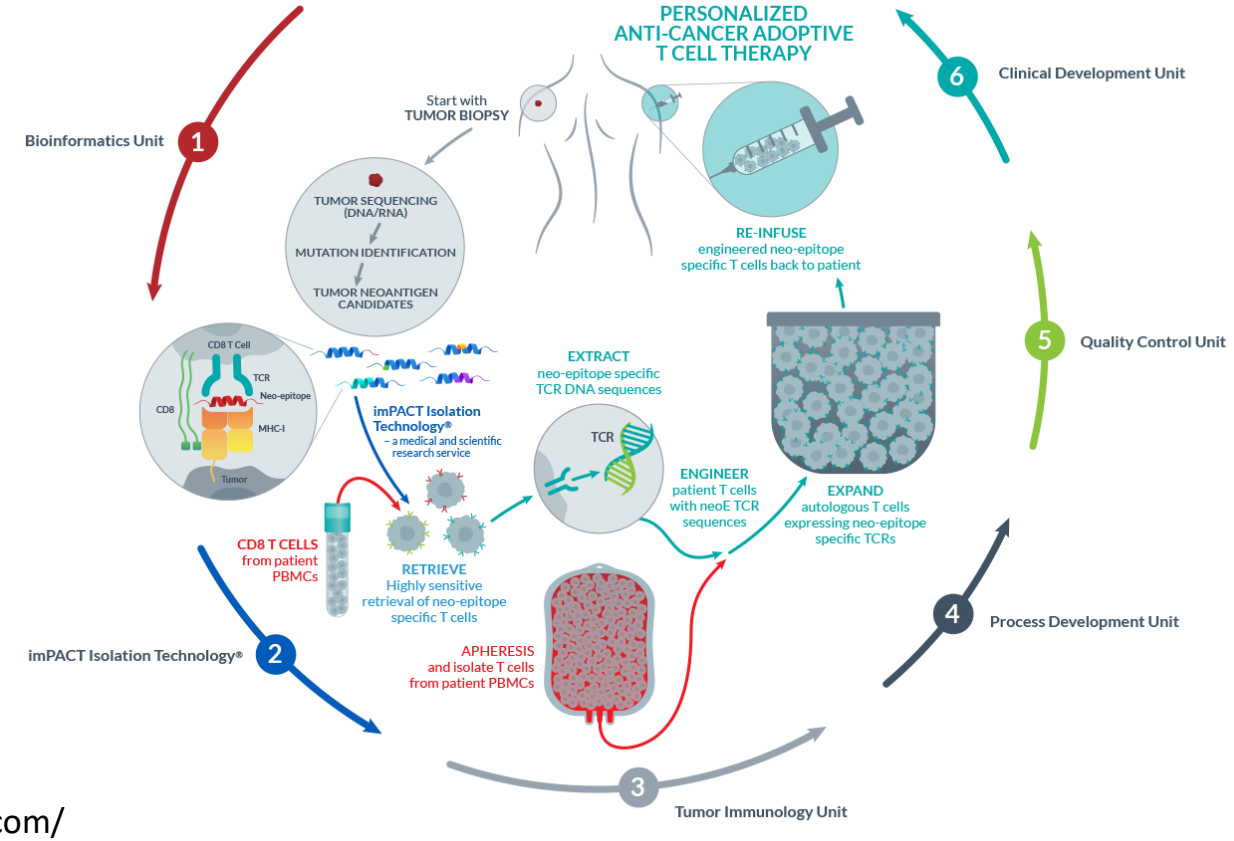
Zacharakis N, Chinnasamy H, Black M, Xu H, Lu YC, Zheng Z, et al. Immune recognition of somatic mutations leading to complete durable regression in metastatic breast cancer. Nat Med. 2018;24(6):724–30.





Zacharakis N et al. Immune recognition of somatic mutations leading to complete durable regression in metastatic breast cancer. Nat Med

Personalized neoantigen targeted T cells



https://pactpharma.com/

Conclusion

- Adoptive cell therapy (ACT) is no longer a promise to treat solid tumors.
  - Tumor Infiltrating Lymphocytes: Melanoma and cervical cancer.
  - TCR: Synovial sarcoma.
  - CART: mesothelioma

- However there are still some critical points:
  - Ideal target identification
  - Resistance mechanisms

Thank you

START MADRID
"The cure starts here."

Hospital Universitario Fundación Jiménez Díaz
Grupo quirónsalud

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