THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

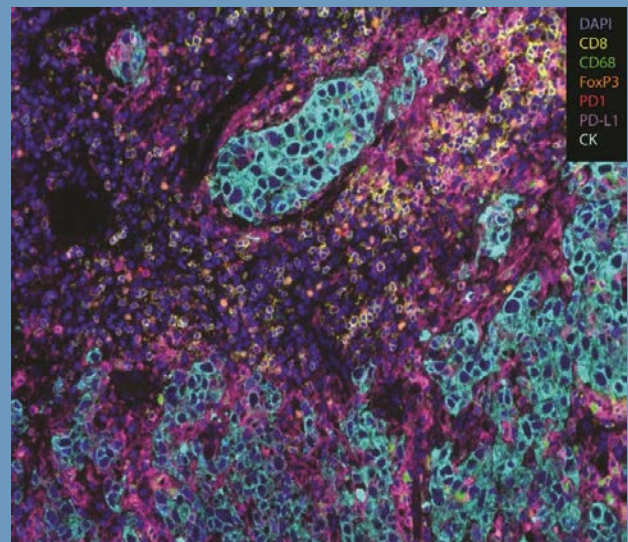
Getting to

Novel Immunotherapy Approaches and Cellular-based Therapies for Gynecologic Oncology Patients

Amir Jazaeri, MD

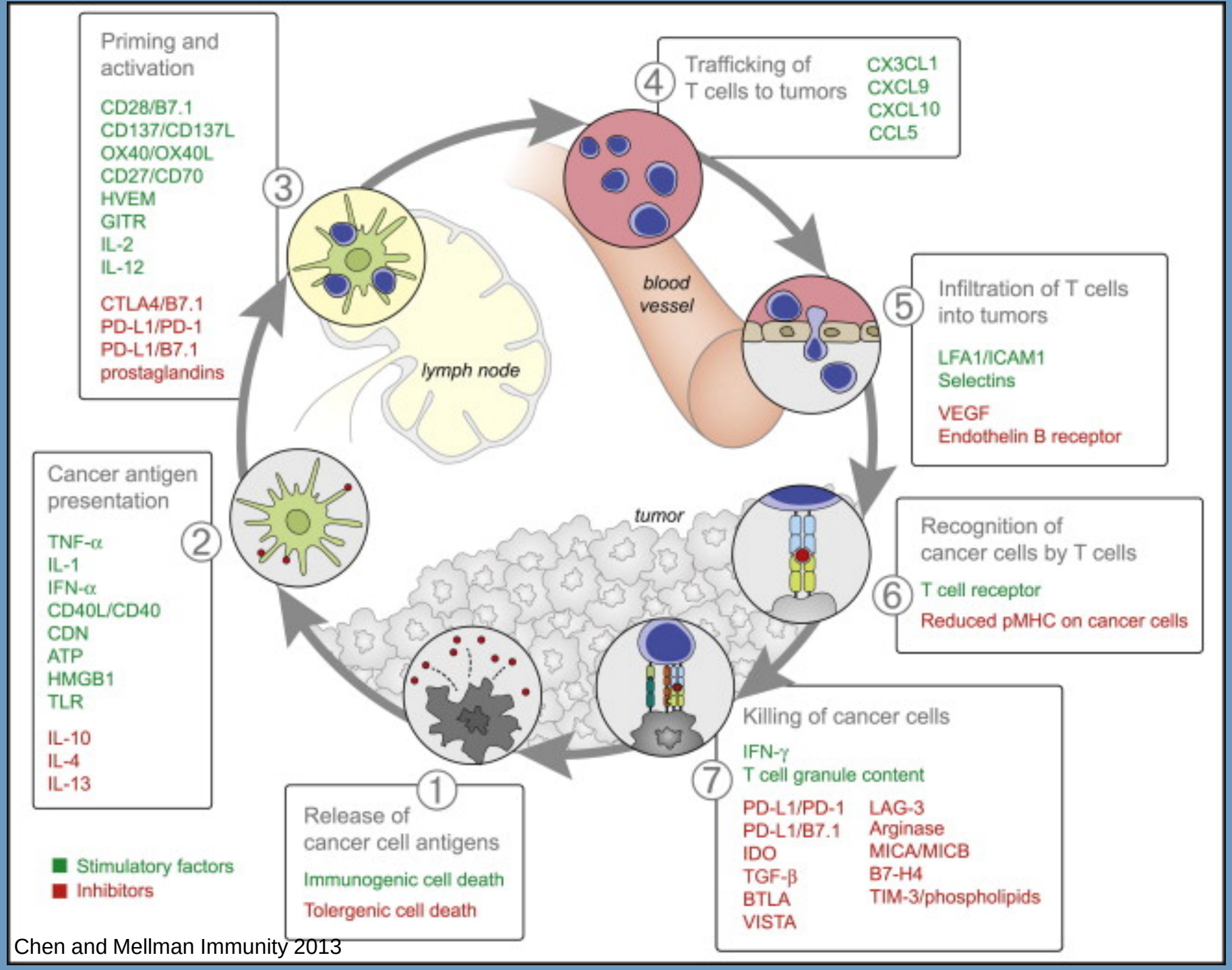
Director, Gynecologic Cancer Immunotherapy Program

MD Anderson Cancer Center, Houston TX



Disclosures

- Research Funding
  - Iovance
  - Pfizer
  - BMS
  - AZ
- Advisory Board
  - Aravive
  - Almac
- DSMB
  - Genentech-Roche

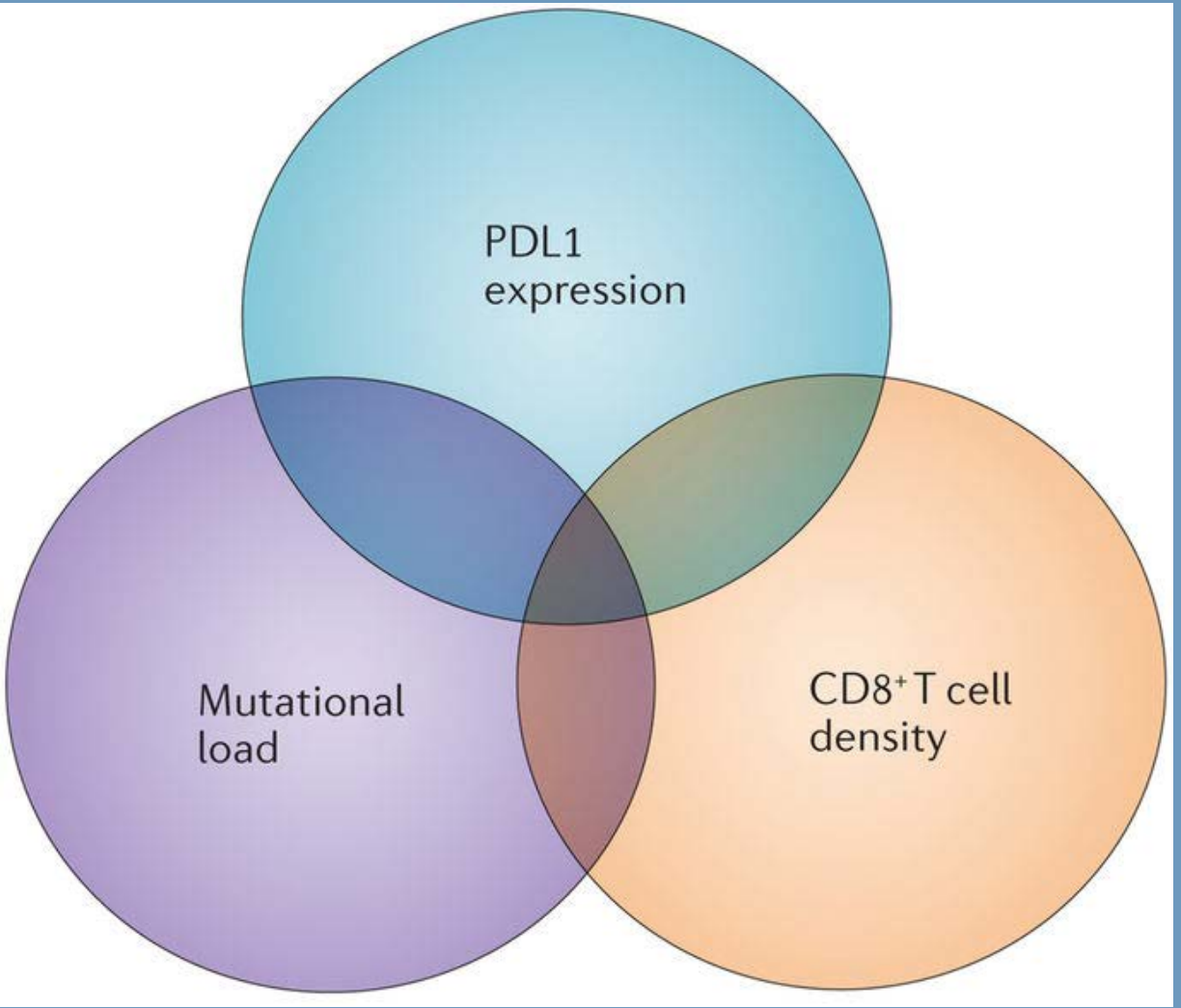


Chen and Mellman Immunity 2013

Approaches for Increasing the Efficacy of Checkpoint Inhibitors

- Increasing tumor cell death and/or DNA damage
  - Chemotherapy, radiotherapy, PARPi
- Combining with other immune-modulating drugs
  - Co-stimulatory (OX40, 4-1BB)
  - Co-inhibitory (TIM3, LAG3)
  - Vaccines, STING agonists, ACT
- Modulating the tumor micro-environment
  - Targeting components of the microenvironment (e.g. macrophages, cancer associated fibroblasts)
  - Targeting the tumor and draining lymph nodes directly
- Importance of on-treatment biopsies

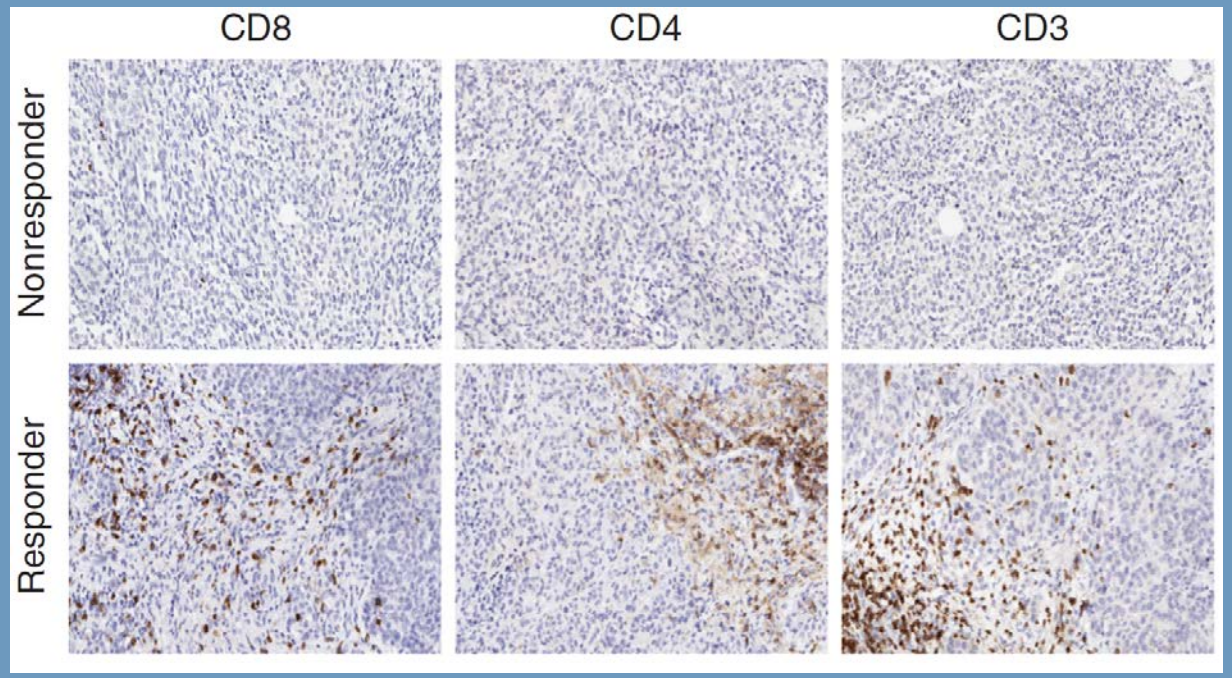
Biomarkers for Response to ICB?



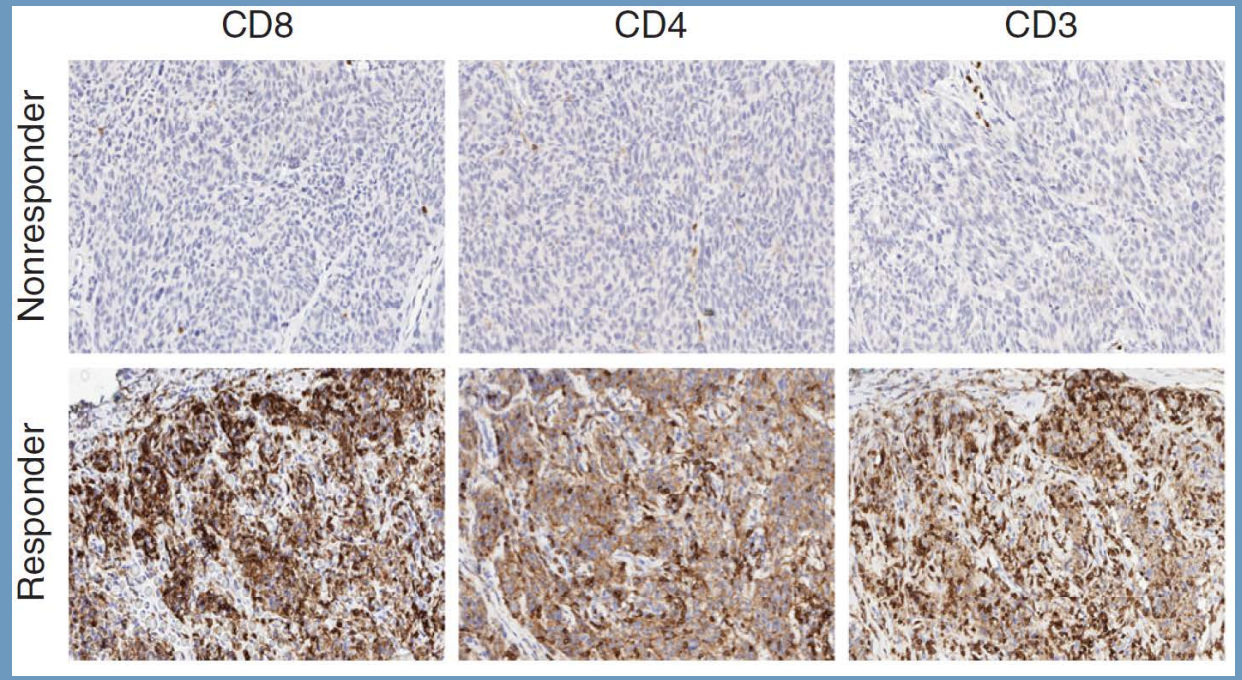
Topalian et al, *Nature Reviews Cancer*, 2016

Biomarkers: When not What?

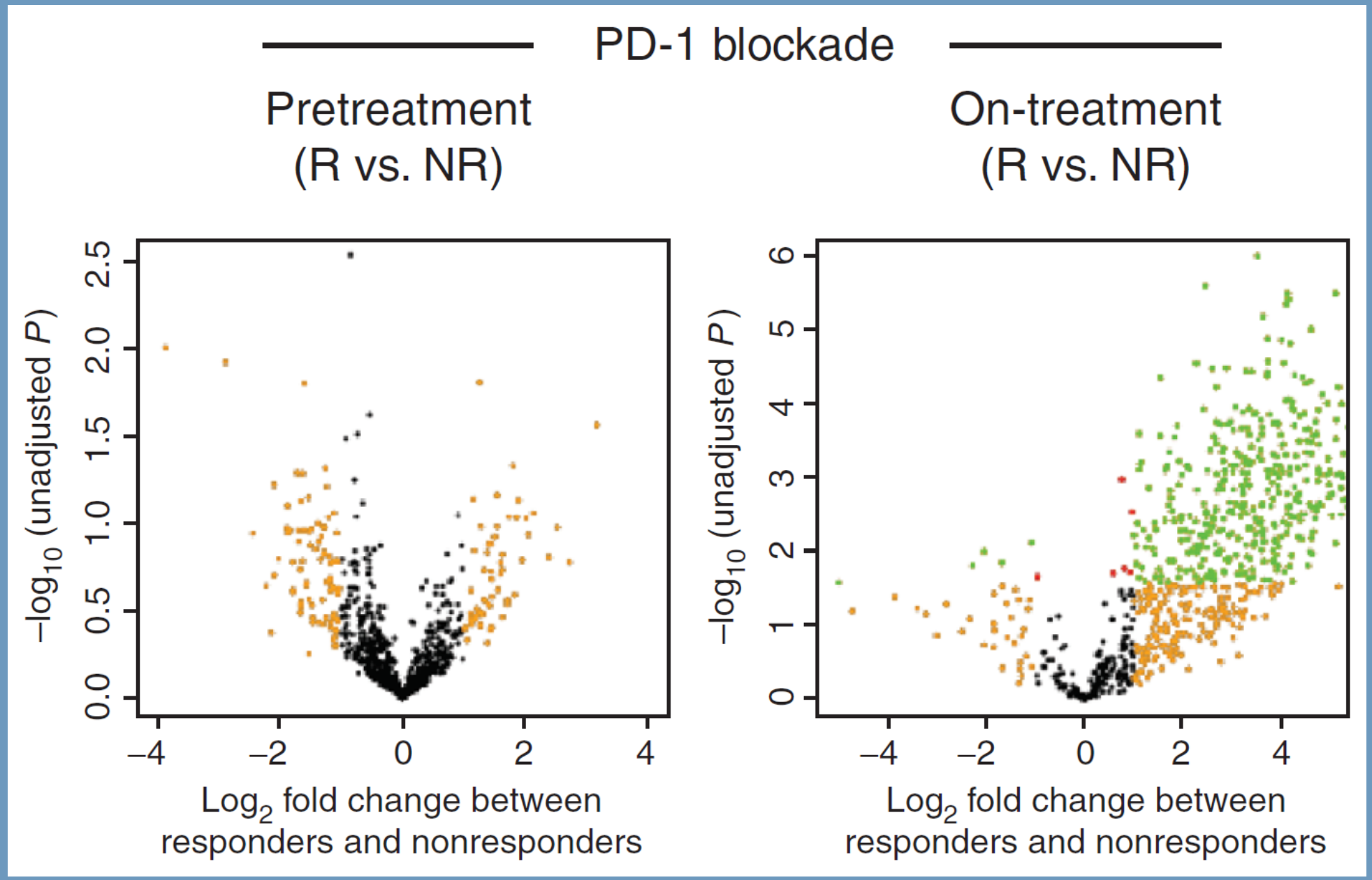
Pre-Treatment



Early On-Treatment

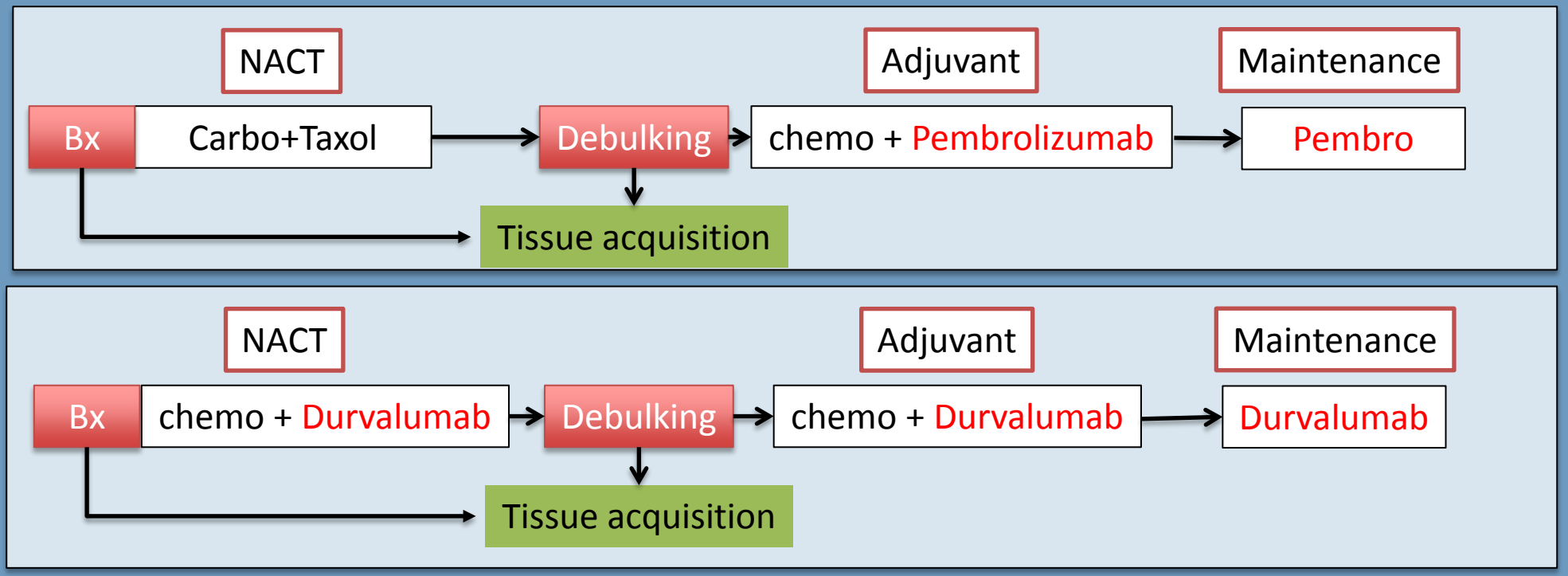


Chen..Wargo, Cancer Discovery, 2016

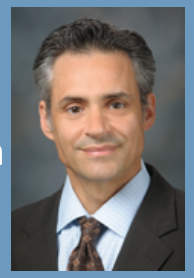


Chen..Wargo, Cancer Discovery, 2016

Checkpoint Inhibitors in Patients Treated with Neoadjuvant Chemotherapy

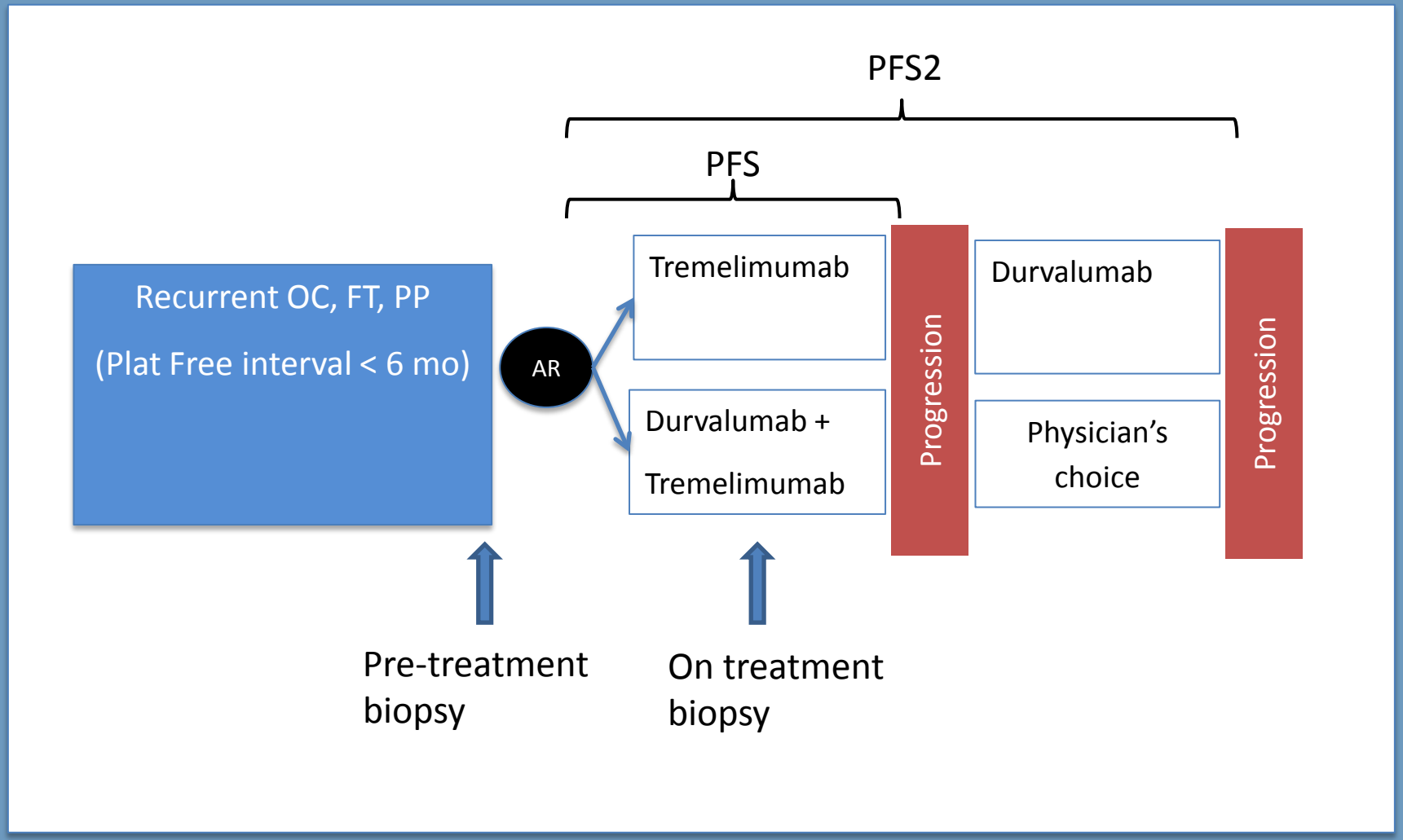


PI: Rob Coleman



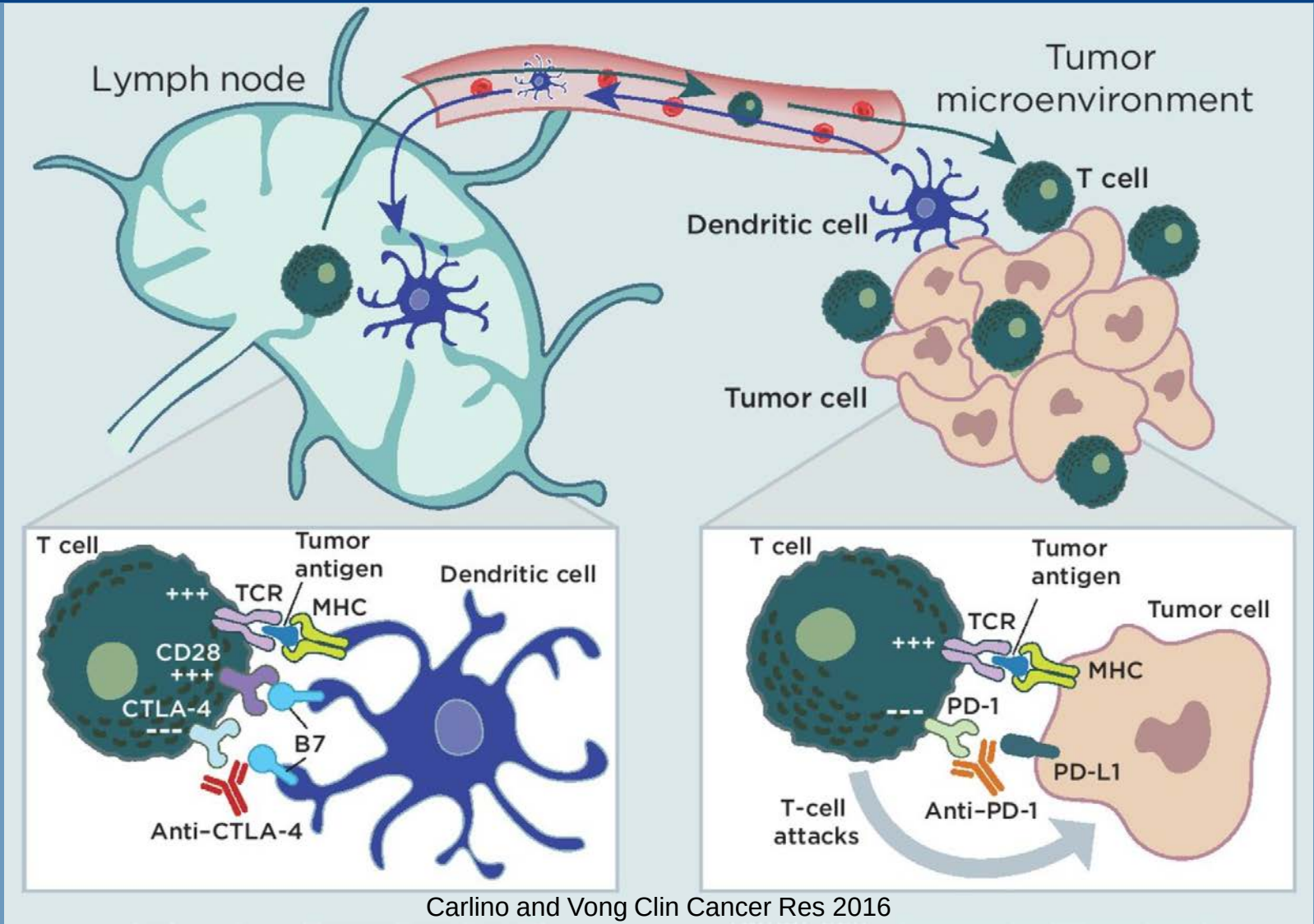
PI: Shannon Westin

Combination versus Sequential Checkpoint Inhibitors in Patients with Platinum Resistant Ovarian Cancer

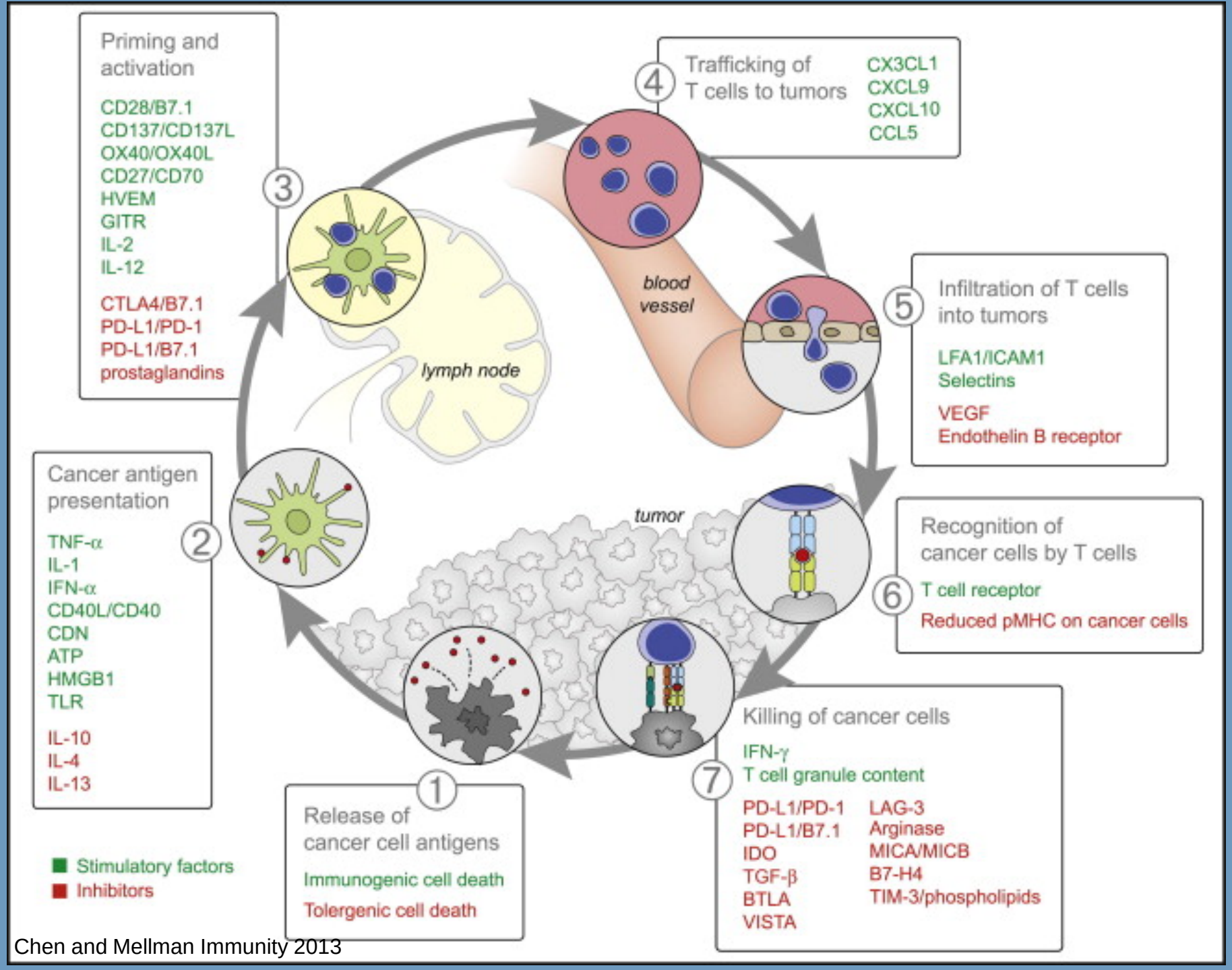


PI: Amir Jazaeri

Can Efficacy be Improved by Route of Administration?



Carlino and Vong Clin Cancer Res 2016

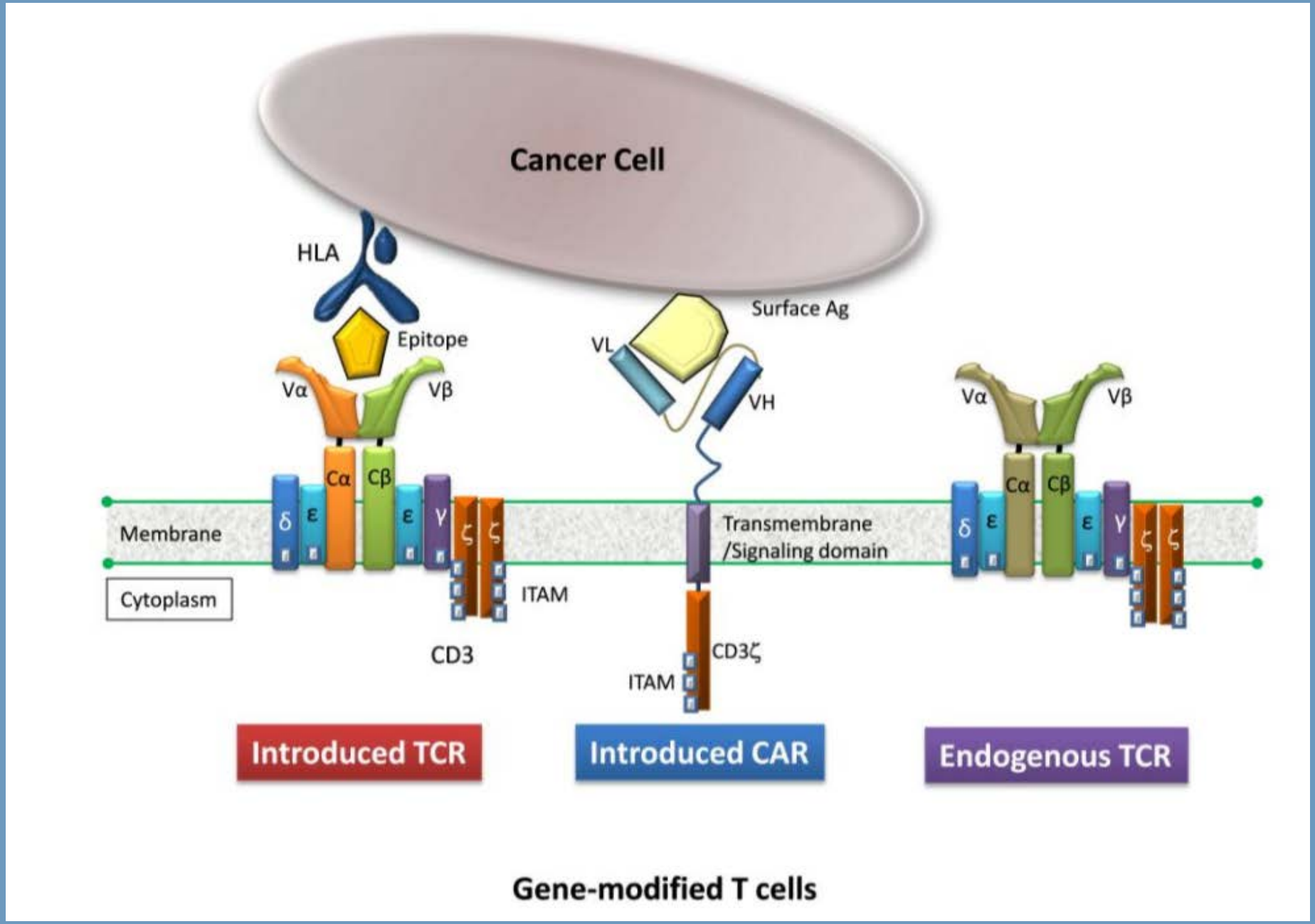


Chen and Mellman Immunity 2013

Adoptive Cell Therapies

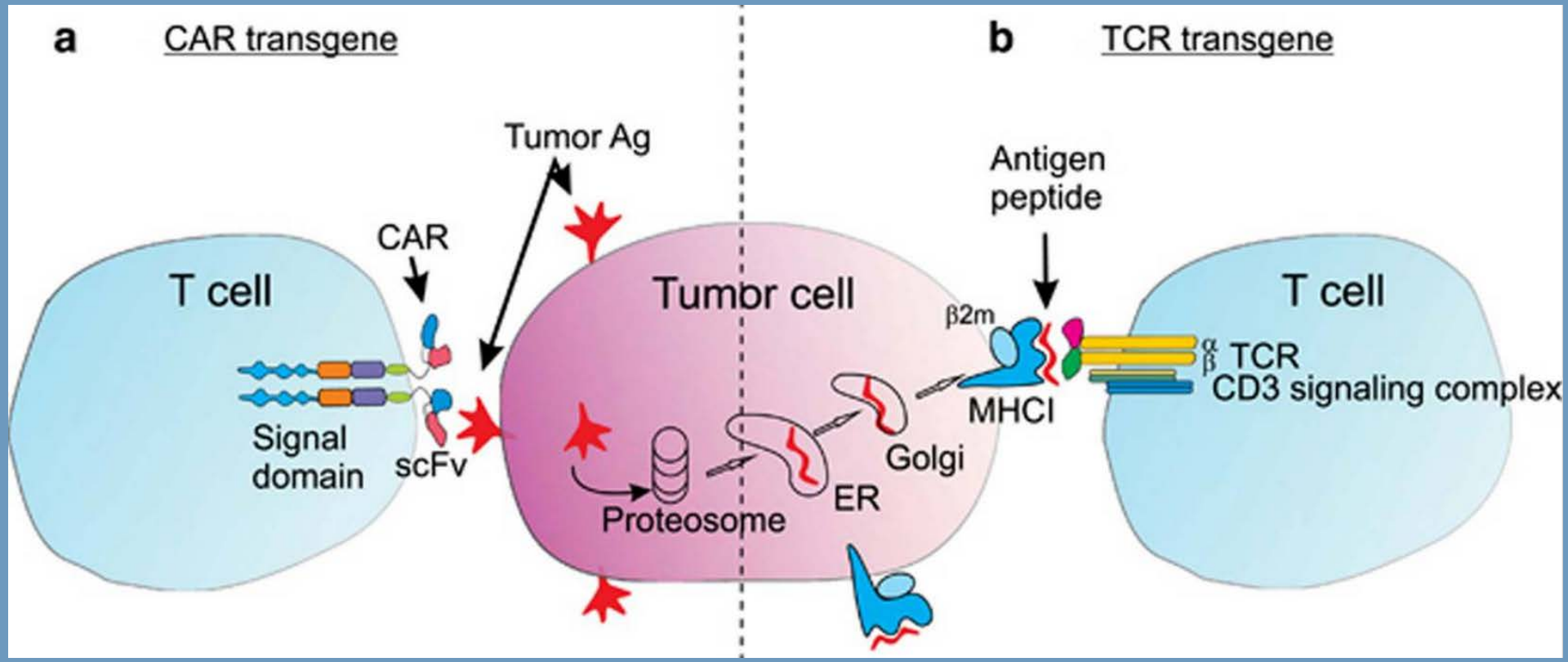
- Treatments in which T cells are collected from a patient and grown and/or modified in the laboratory
- Goal is to increases the number of T cells that are able to kill cancer cells
- T cells are given back to the patient to help the immune system fight disease.

TIL	Circulating tumor-specific T cells	Engineered Receptors (CAR/TCR)



Fujiwara Pharmaceuticals 2014

CAR vs Transgenic TCR



Kershaw et al., Clin Trans Immunology 2014

Transferred Receptor: TCR / CAR

Target Antigen/ Cancer

Antigen	CAR or TCR	Cancer
MART-1, gp100	TCR	Melanoma
HPV E6	TCR	Cervical, Anal, Vaginal
NY-ESO-1	TCR	Sarcoma, Myeloma, (Breast, Lung)
MAGE-A3	TCR	Any cancer MAGE-A3+
P53	TCR	Any cancer overexpresses p53
CD19	CAR	Lymphoma
EGFRvIII	CAR	Glioblastoma, Breast, Lung
Kappa Light Chain	CAR	CLL, B cell NHL
Her2Neu	CAR	Osteosarcoma, Breast
CD30	CAR	Lymphoma (NHL and HD)
GD2	CAR	EBV-specific CTL targeting GBM

CAR T-cell Therapy for Ovarian Cancer

Koneru et al. Journal of Translational Medicine (2015) 13:102
DOI 10.1186/s12967-015-0460-x

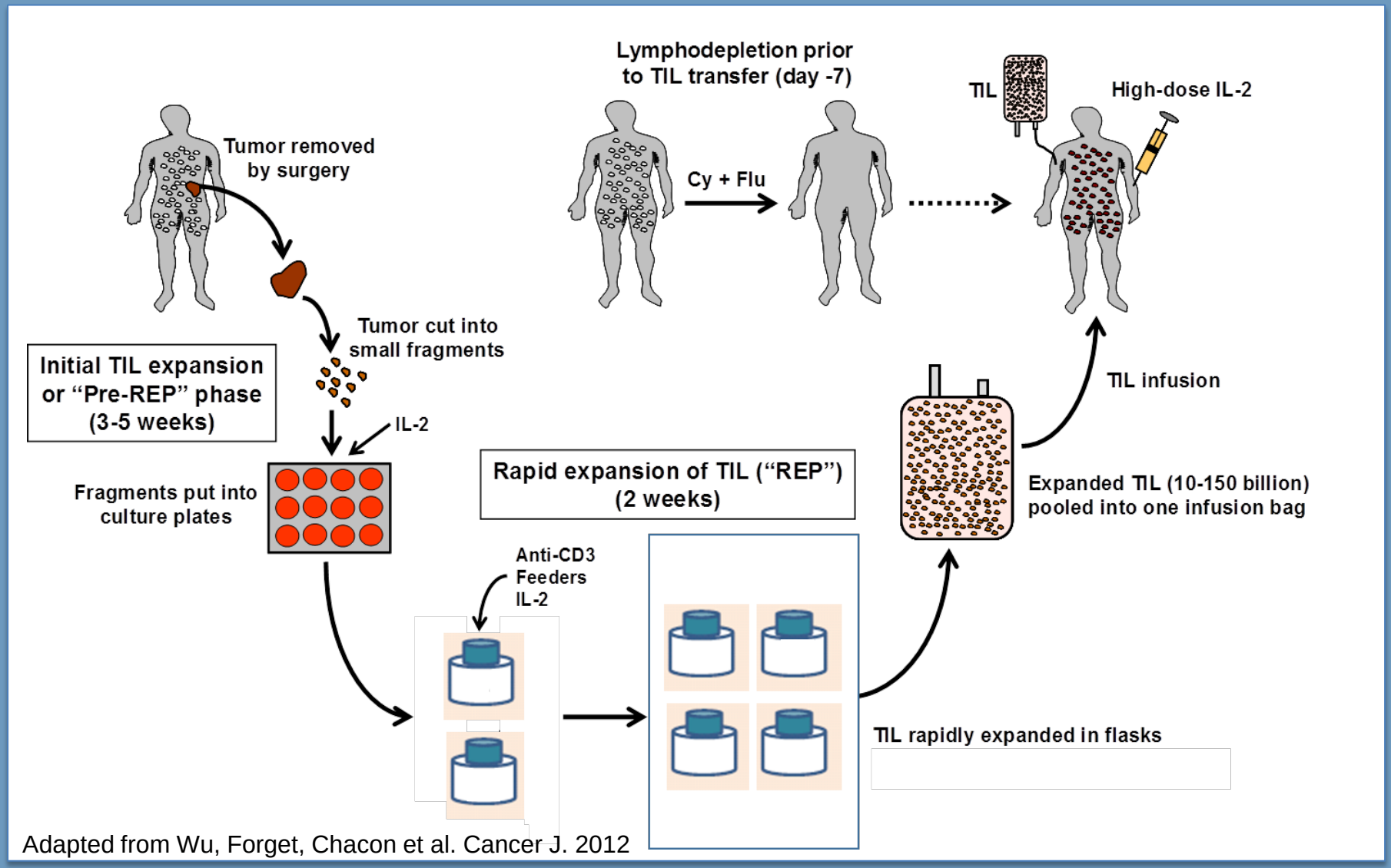
JOURNAL OF TRANSLATIONAL MEDICINE

PROTOCOL Open Access

A phase I clinical trial of adoptive T cell therapy using IL-12 secreting MUC-16^{ecto} directed chimeric antigen receptors for recurrent ovarian cancer

Mythili Koneru[1,2], Roisin O'Cearbhaill[1,2], Swati Pendharkar[1], David R Spriggs[1,2] and Renier J Brentjens[1,2*]

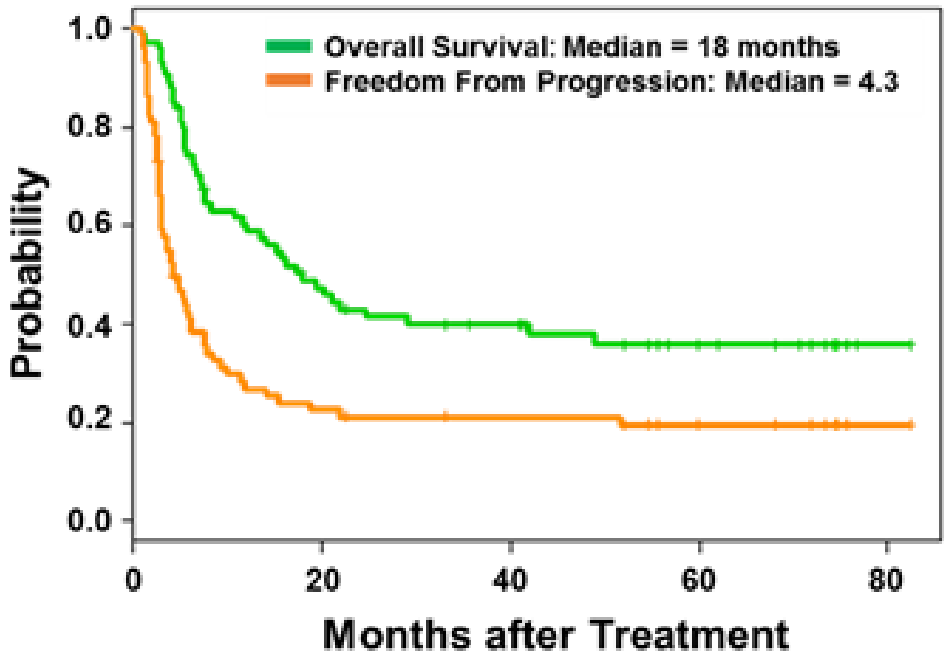
Adoptive Cell Therapy: TIL



Adapted from Wu, Forget, Chacon et al. Cancer J. 2012

TIL outcomes in melanoma

43% clinical response rate
Including 6 CR



Adapted from Wu, Forget, Chacon et al. Cancer J. 2012

TIL outcomes in Cervical Cancer

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Complete Regression of Metastatic Cervical Cancer After Treatment With Human Papillomavirus–Targeted Tumor-Infiltrating T Cells

Sanja Stevanović, Lindsey M. Draper, Michelle M. Langhan, Tracy E. Campbell, Mei Li Kwong, John R. Wunderlich, Mark E. Dudley, James C. Yang, Richard M. Sherry, Udai S. Kammula, Nicholas P. Restifo, Steven A. Rosenberg, and Christian S. Hinrichs

Stevanovic JCO 2015

TIL outcomes in melanoma

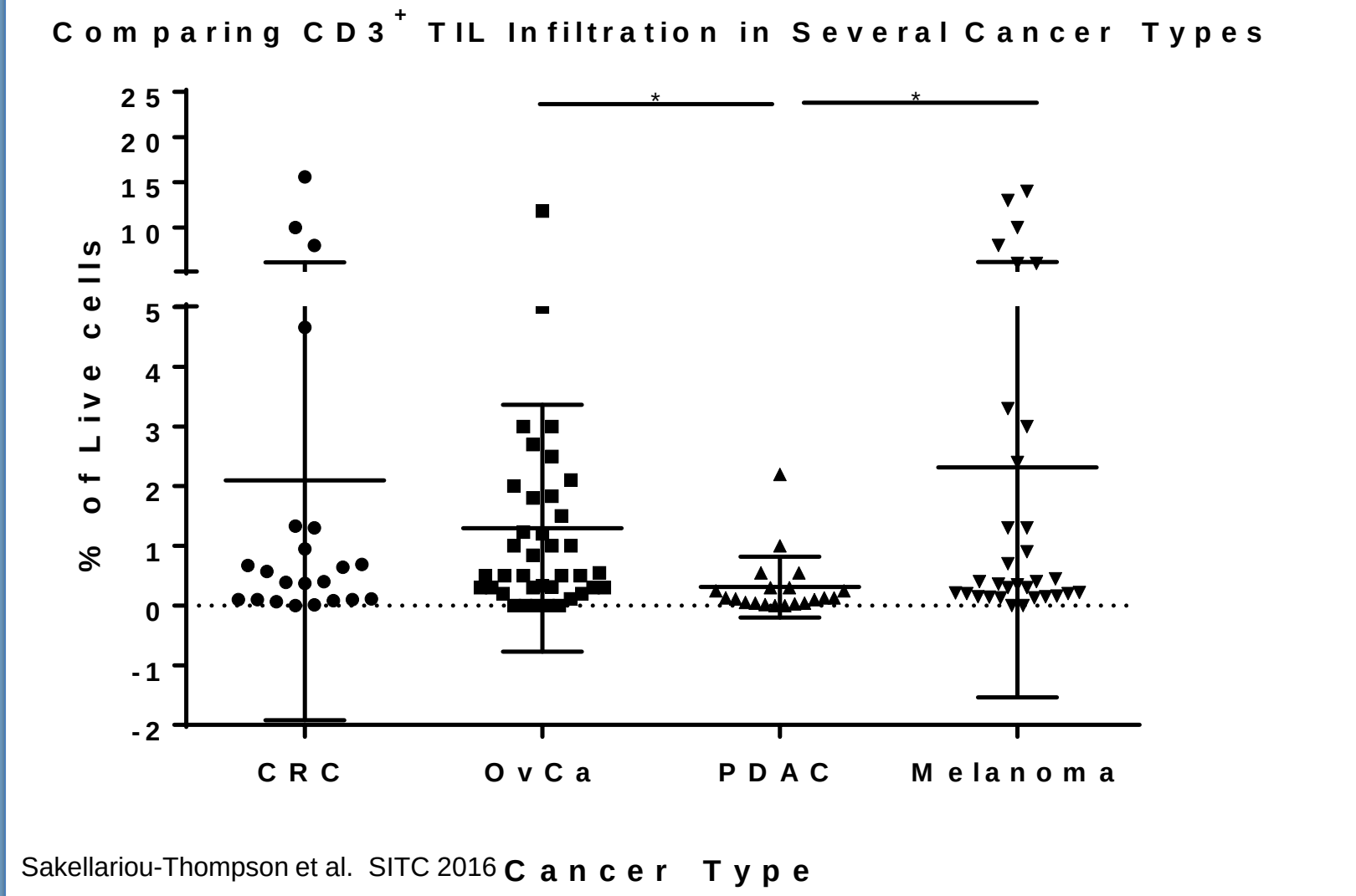
Table 1. Characteristics of Patients and Administered T Cells

Patient	Age (years)	Histology	HPV Type	Sites of Disease	Prior RT	Prior Systemic Treatment	Cells ($\times 10^9$)	Within CD3+ (%)		No. of IL-2 Doses	Response	
								CD4+	CD8+		Type	Duration or TTP (months)
1	30	ASC	18	Iliac lymph nodes, lung, lung hilum, retroperitoneum, vaginal cuff	Yes	Cisplatin	101.4	29	72	7	PD	1
2	53	SCC	18	Bone, liver, lung, lung hilum, mediastinum, pelvis	Yes	Cisplatin, carboplatin, paclitaxel, topotecan, ixabepilone dimethane sulfonate	126.0	10	94	3	PR	3
3	36	SCC	16	Iliac lymph nodes, lung hilum, mediastinum, retroperitoneum	Yes	Cisplatin, vincristine, bleomycin, gemcitabine, paclitaxel, topotecan	152.0	21	83	2	CR	22+
4	55	SCC	16	Axilla, breast, liver, omentum, pleura, soft tissue	Yes	Cisplatin, carboplatin, paclitaxel, fluorouracil, irinotecan, dovitinib, pemetrexed	80.1	23	76	7	PD	2
5	44	SCC	18	Brain, mediastinum, supraclavicular nodes	Yes	Cisplatin	90.0	66	29	5	PD	2
6	36	AC	18	Abdominal wall, liver, paracolic, pelvis, retroperitoneum	Yes	Cisplatin	74.7	61	35	8	CR	15+
7	59	AC	18	Abdominal wall, lung	Yes	Cisplatin, paclitaxel, carboplatin, bevacizumab	33.4	36	58	8	PD	1
8	31	ASC	18	Pelvis, perihepatic mass	No	Cisplatin, paclitaxel	46.1	64	29	9	PD	2
9	37	AC	18	Axilla, bone, lung, mediastinum, pelvis, retroperitoneum	Yes	Cisplatin, carboplatin, paclitaxel, ipilimumab	70.2	33	59	1	PD	1

Abbrevations: AC, adenocarcinoma; ASC, adenosquamous cell carcinoma; CR, complete response; HPV, human papillomavirus; IL-2, interleukin-2; PD, progressive disease; PR, partial response; RT, radiotherapy; SCC, squamous cell carcinoma; TTP, time to progression.

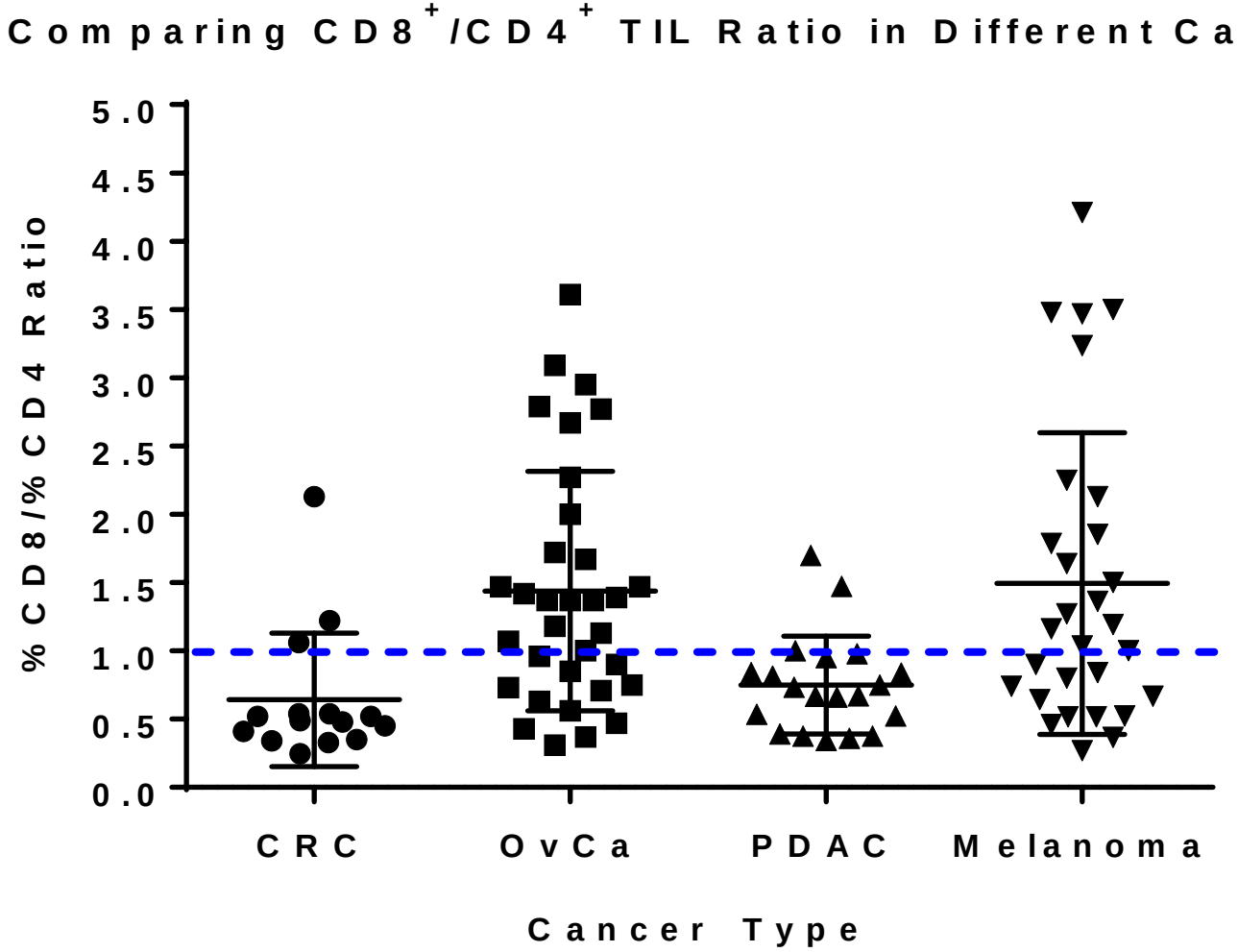
Stevanovic JCO 2015

OvCa has similar CD3+ infiltration to Melanoma



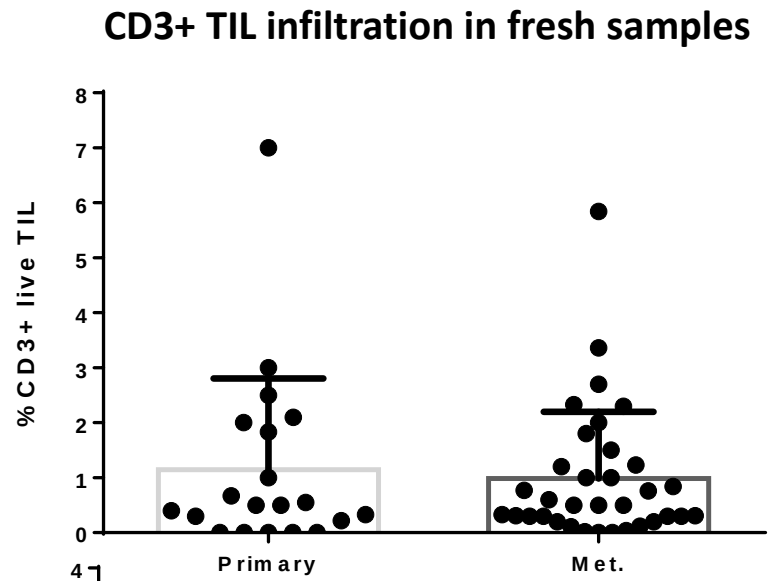
Sakellariou-Thompson et al. SITC 2016

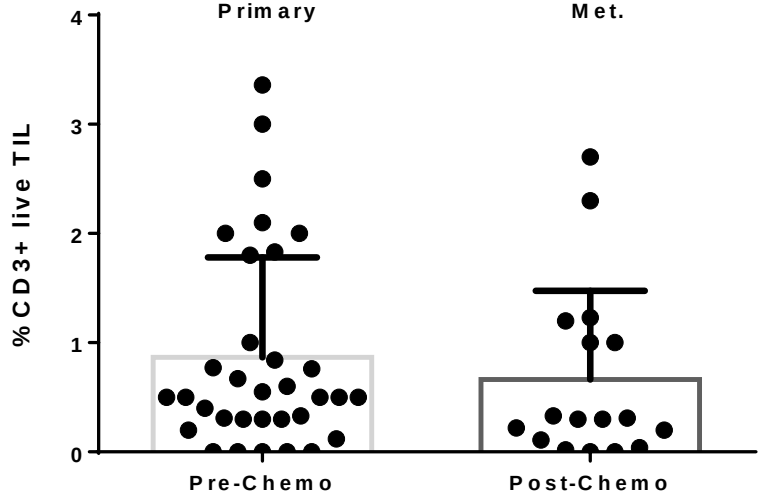
OvCa has similar CD8+ TIL infiltration to Melanoma

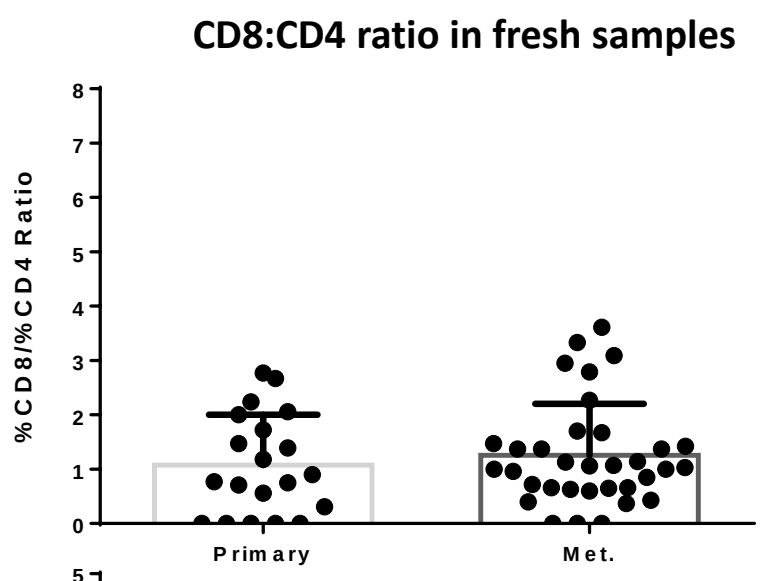


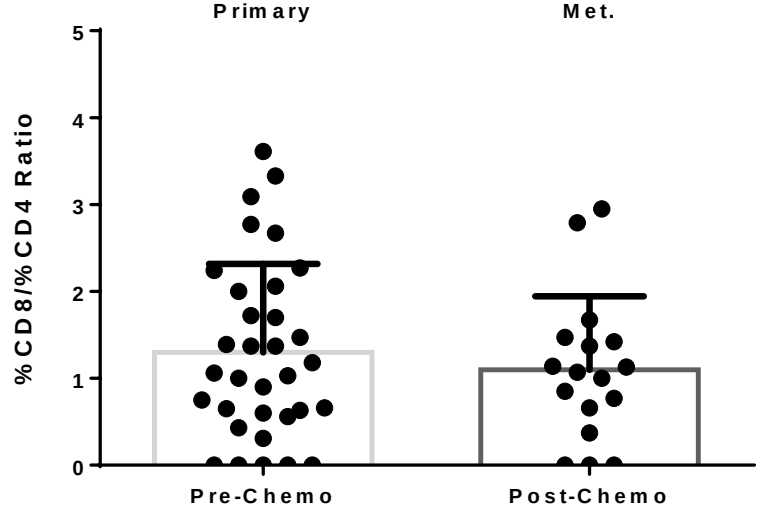
Sakellariou-Thompson et al. SITC 2016

T cell infiltration and CD8/CD4 ratio in primary vs metastasis or pre/post chemotherapy









Donastas Sakellariou-Thompson

Upcoming Adoptive Cell Therapy Trials at MDACC

- 2017-0505 (NCT03108495) A Phase 2, Multicenter Study to Evaluate the Efficacy and Safety Using Autologous Tumor Infiltrating Lymphocytes (LN-145) in Patients with Recurrent, Metastatic, or Persistent Cervical Carcinoma

- 2017-0672 (NCT03449108) Clinical study to assess efficacy and safety of LN-145 (Manufactured by Iovance) Across Multiple Tumor Types
  - PR ovarian cancer, bone sarcomas, and pancreatic cancer

- 2017-0671 Clinical Study to Assess Efficacy and Safety of MDA-TIL (Manufactured at MDACC) Across Multiple Tumor Types
  - PR ovarian cancer, bone sarcomas, poorly differentiated sarcomas, TBD

- 2016-0400 (NCT03318900) Phase I/Ib Study of Adoptive Cellular Therapy Using Autologous IL-21-Primed CD8+ Tumor Antigen-Specific T Cells in Combination With Utomilumab (PF-05082566) in Patients With Platinum Resistant Ovarian Cancer

nature medicine

LETTERS

https://doi.org/10.1038/s41591-018-0040-8

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

Nikolaos Zacharakis[1], Harshini Chinnasamy[1], Mary Black[1], Hui Xu[1], Yong-Chen Lu[1], Zhili Zheng[1], Anna Pasetto[1], Michelle Langhan[1], Thomas Shelton[1], Todd Prickett[1], Jared Gartner[1], Li Jia[1], Katarzyna Trebska-McGowan[2], Robert P. Somerville[1], Paul F. Robbins[1], Steven A. Rosenberg[1]*, Stephanie L. Goff[1] and Steven A. Feldman[1]

Future of Immunotherapy for Gynecologic Cancers

- The goal of rational combination immuno-oncology requires understanding cancer-specific immuno-inhibitory mechanisms at work
- Significant impact will require innovative clinical trial designs and translational science (e.g. looking for dynamic changes using on-treatment biopsies).
- Partner with and industry, scientific societies, and regulatory agencies to focus on the unique win-win opportunities presented by gynecologic cancers to advance the field and improve outcomes for our patients.

Thank you