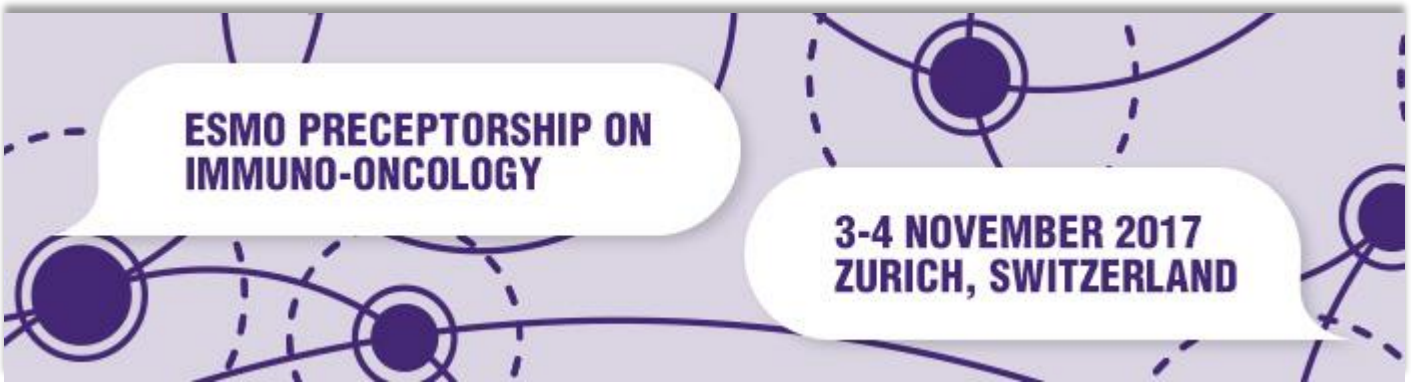
Immunotherapy for Ovarian Cancer



Prof. Lana E. Kandalaft

Director| Centre of Experimental Therapeutics, Deparment of Oncology, UNIL CHUV

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RESEARCH

Is there a role for immunotherapy in Ovarian Cancer?

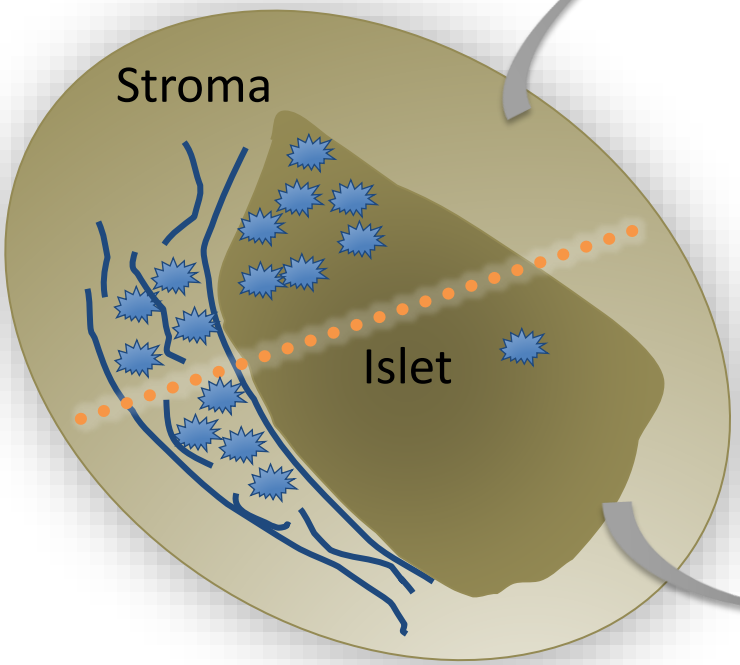
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

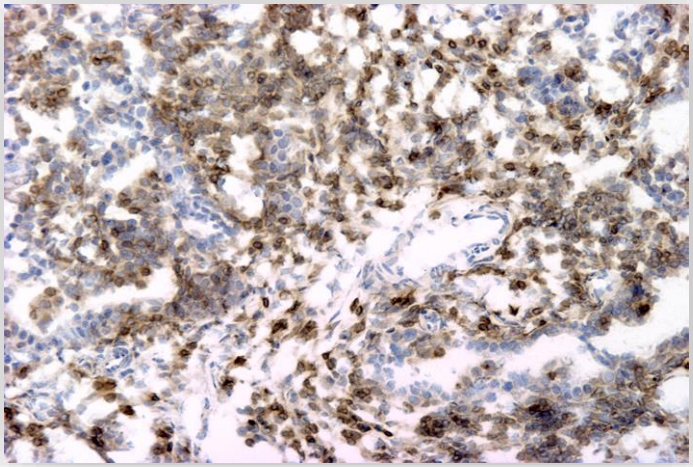
Intratumoral T Cells, Recurrence, and Survival in Epithelial Ovarian Cancer

Lin Zhang, M.D., Jose R. Conejo-Garcia, M.D., Ph.D., Dionyssios Katsaros, M.D., Ph.D., Phyllis A. Gimotty, Ph.D., Marco Massobrio, M.D., Giorgia Regnani, M.D., Antonis Makrigiannakis, M.D., Ph.D., Heidi Gray, M.D., Katia Schlienger, M.D., Ph.D., Michael N. Liebman, Ph.D., Stephen C. Rubin, M.D., and George Coukos, M.D., Ph.D.

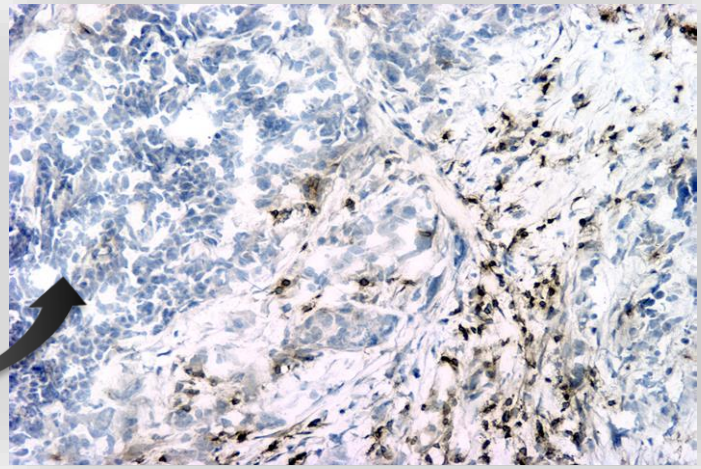
$CD3^+$



TIL Present
55%



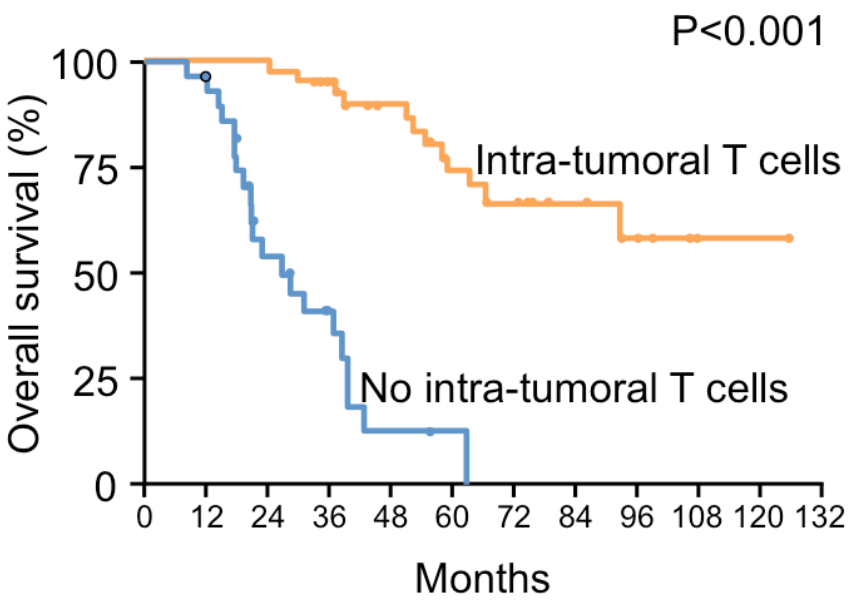
TIL Absent
40%



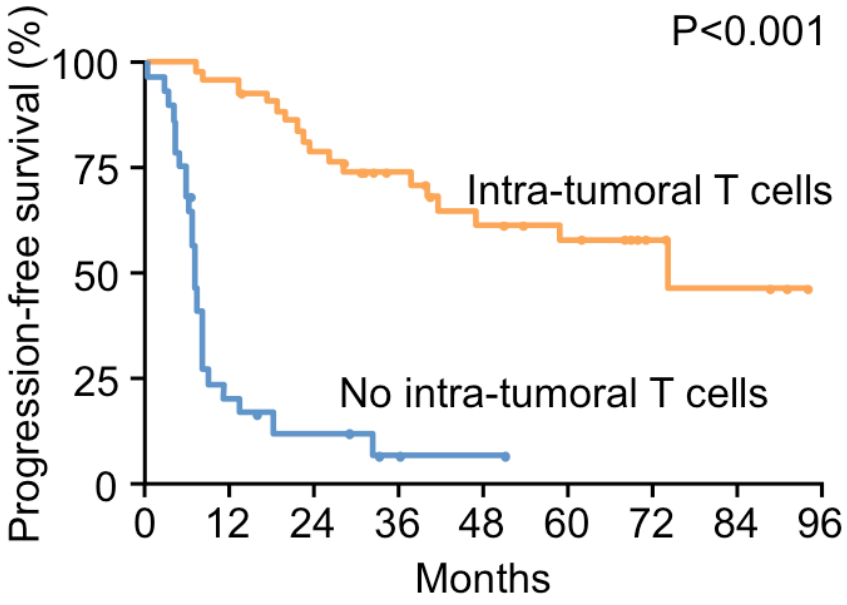
Zhang, et al. *N Engl J Med* 2003

After CR with chemotherapy, only patients with TILs survive or are in remission long-term

At 96–132 months:
>60% alive



At 96 months:
50% in remission



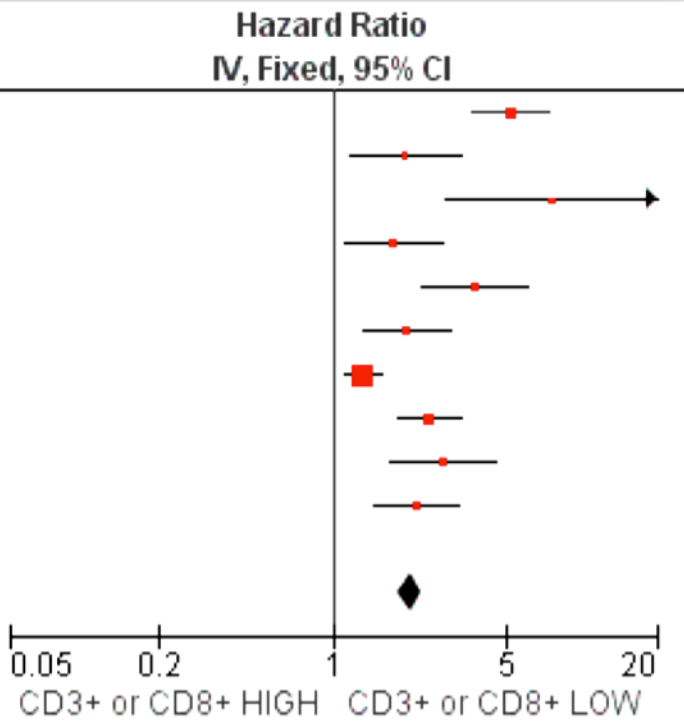
Zhang, et al. *N Engl J Med* 2003

Meta-analysis of intraepithelial TIL impact in ovarian cancer: 10 studies; 1,815 patients

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI	Year
Zhang(2003)	1.65	0.18	9.8%	5.21 [3.66, 7.41]	2003
Sato(2005)	0.67	0.26	4.7%	1.95 [1.17, 3.25]	2005
Hamanishi(2007)	2.03	0.5	1.3%	7.61 [2.86, 20.29]	2007
Han(2008)	0.56	0.23	6.0%	1.75 [1.12, 2.75]	2008
Tomsova(2008)	1.32	0.25	5.1%	3.74 [2.29, 6.11]	2008
Adams(2009)	0.69	0.21	7.2%	1.99 [1.32, 3.01]	2009
Clarke(2009)	0.28	0.09	39.1%	1.32 [1.11, 1.58]	2009
Stumpf(2009)	0.89	0.15	14.1%	2.44 [1.81, 3.27]	2009
Leffers(2009)	1.02	0.25	5.1%	2.77 [1.70, 4.53]	2009
Milne(2009)	0.78	0.2	7.9%	2.18 [1.47, 3.23]	2009
Total (95% CI)			**100.0%**	**2.05 [1.83, 2.28]**	

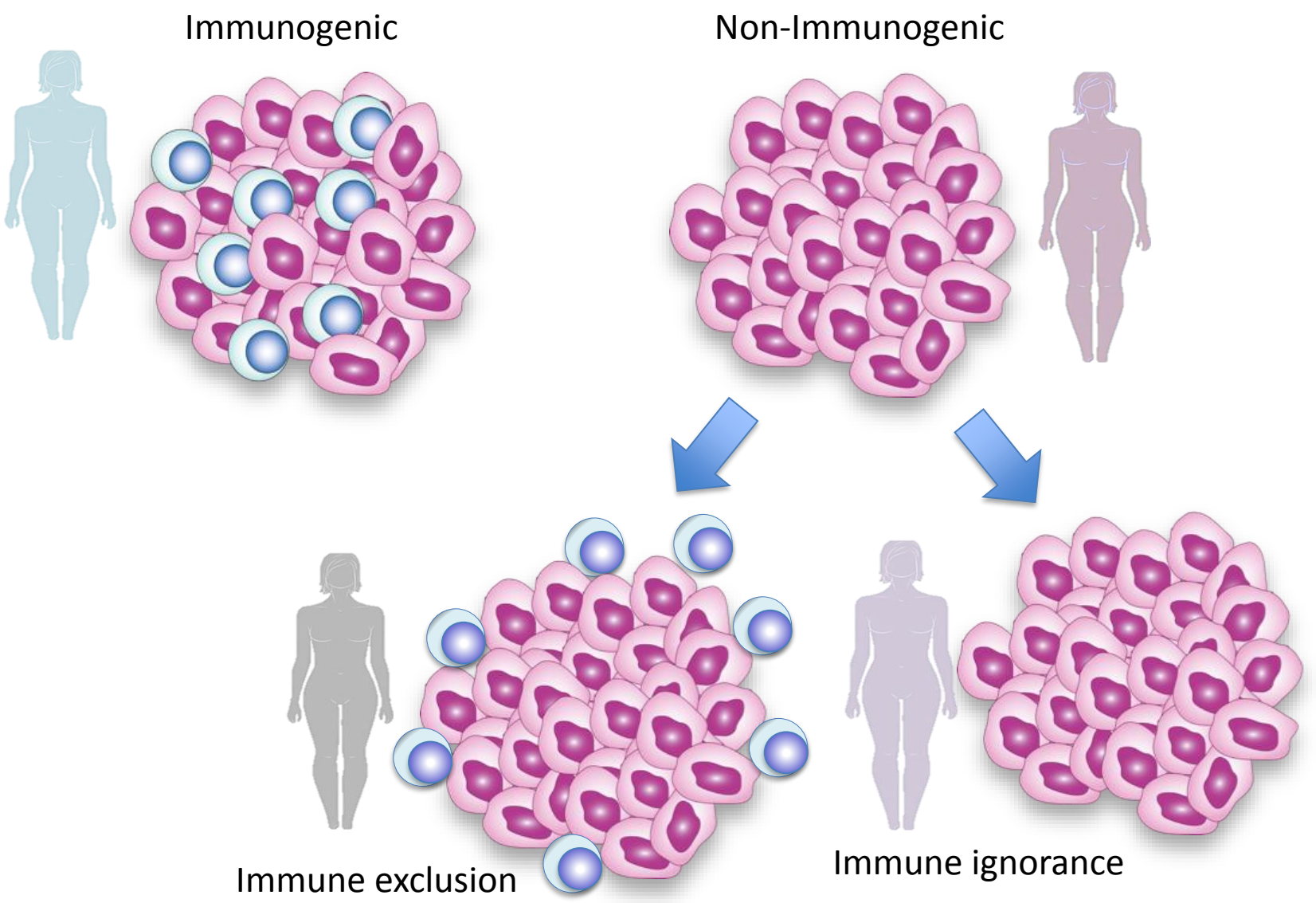
Heterogeneity: $Chi^2 = 66.57$, $df = 9$ ($P < 0.00001$); $I^2 = 86\%$

Test for overall effect: $Z = 12.72$ ($P < 0.00001$)

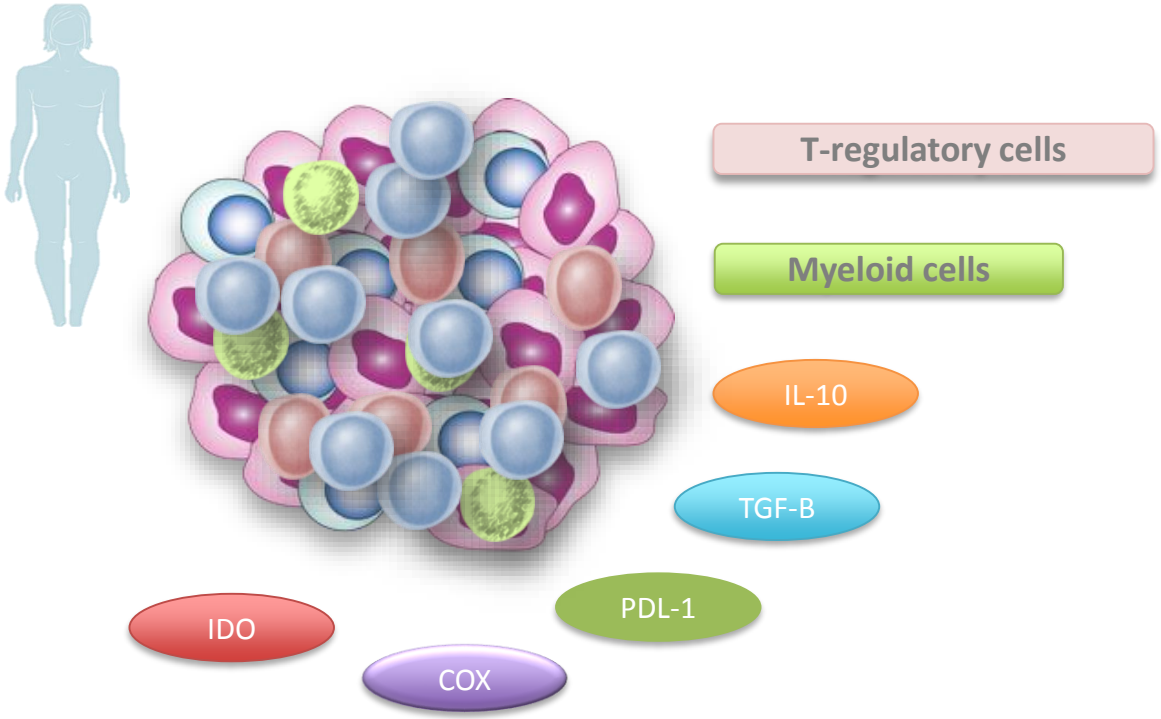


Hwang et al, *Gynecol Oncol* 2011

Two (or three) immunophenotypes of ovarian cancer



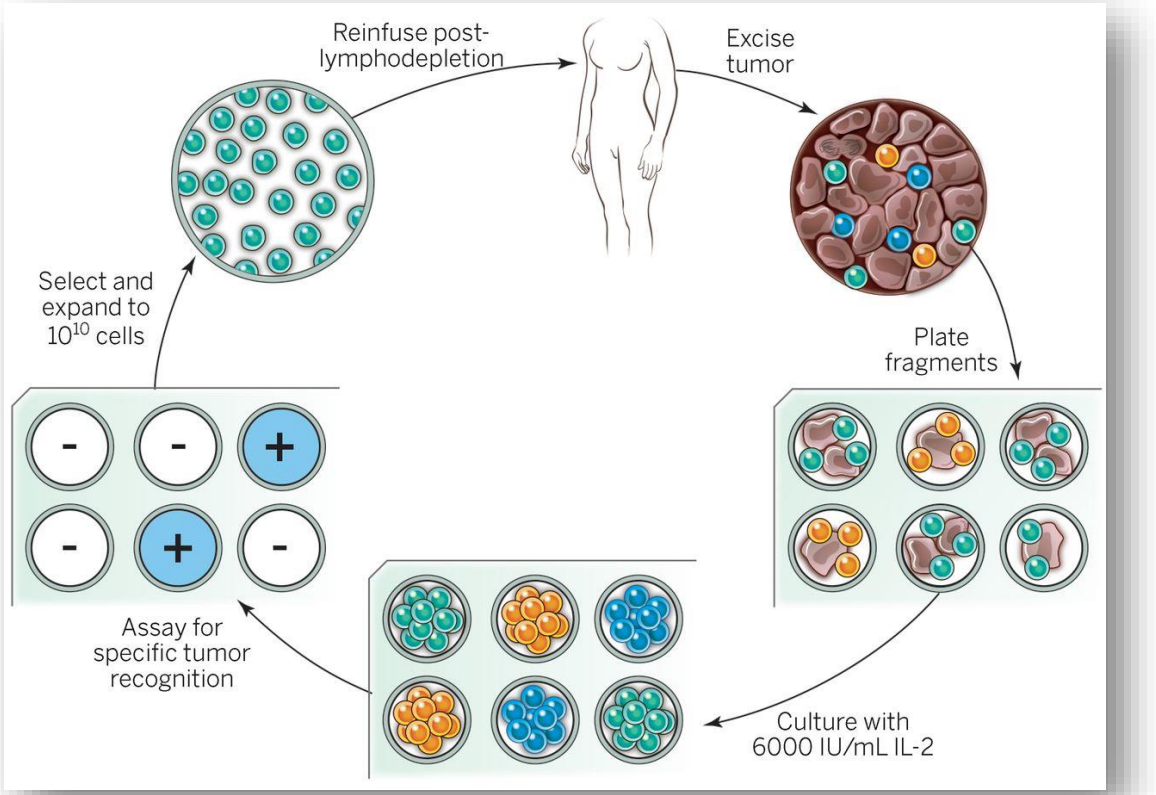
What do we know about the “immunogenic subtype”?



Pharmacological Intervention

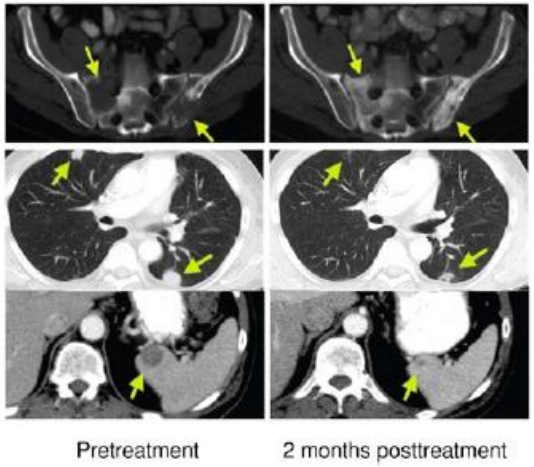
Checkpoint Inhibitors
Cyclophosphamide
IDO inhibitor
Aspirin

Natural “completely personal” TILs
The generation of anti-tumour T cells used for adoptive cell therapy



Rosenberg & Restifo Science 03 Apr 2015:

TILS are powerful: Compelling Results in Late Stage Disease

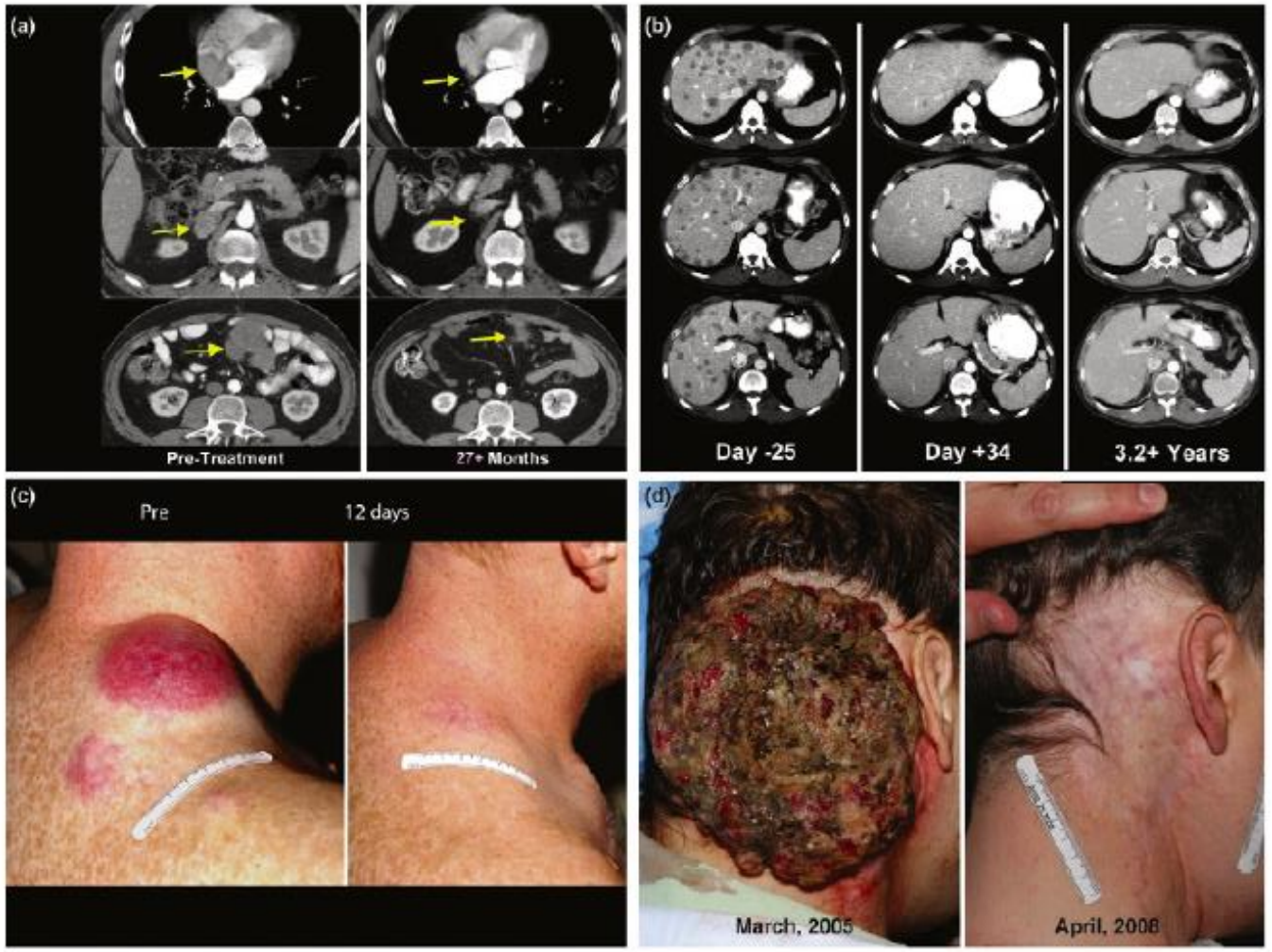


Pretreatment 2 months posttreatment

Day –9 Day +11 Day +76

Clinical Cancer Research December 15, 2010 16: 6122

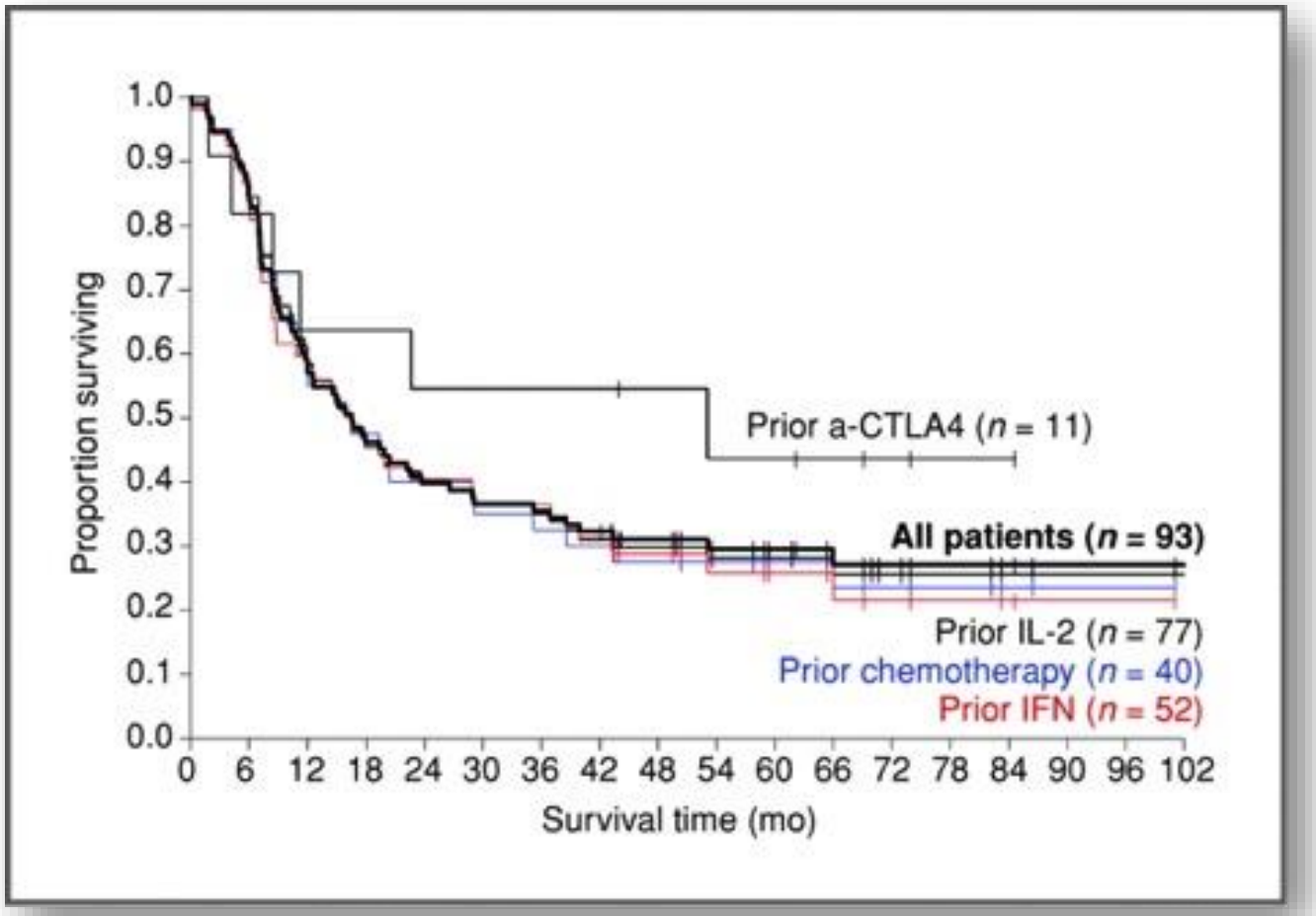
TILs: Regressions in Late-Stage Disease



Current Opinion in Immunology 2009, 21:233–240

Current Opinion in Immunology 2009, 21:233–240

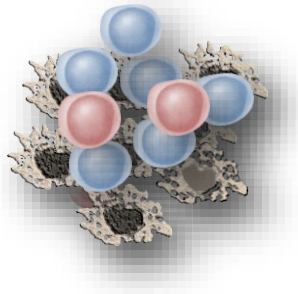
TILs: Durable Responses in Advanced Melanoma



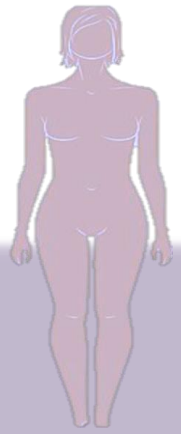
19 of 20 complete responders are ongoing to >10 years

Rosenberg S A et al. *Clin Cancer Res* 2011

TILs in Ovarian Cancer



- TILs recognize Tumors
- TILs are anitgen specific
- TILs are activated
- TILs are polyfunctional



- TIL Therapy for Metastatic Ovarian Cancer, NCT02482090
Inge Marie Svane, Herlev Hospital

- TIL And Low-Dose Interleukin-2 Therapy in Patients With Platinum Resistant High Grade Serous Ovarian, Fallopian Tube, or Primary Peritoneal Cancer, NCT01883297
University Health Network, Toronto

Challenges of TIL Therapy

- Patients have to undergo surgery- Tissue needs to be stored PROPERLY
- T cells are functionally ‘exhausted’
- TILs are of unknown antigen specificity
- Need for IL-2 and lymphodepletion (toxic)

Overcoming the Challenges

Cancer Therapy: Clinical

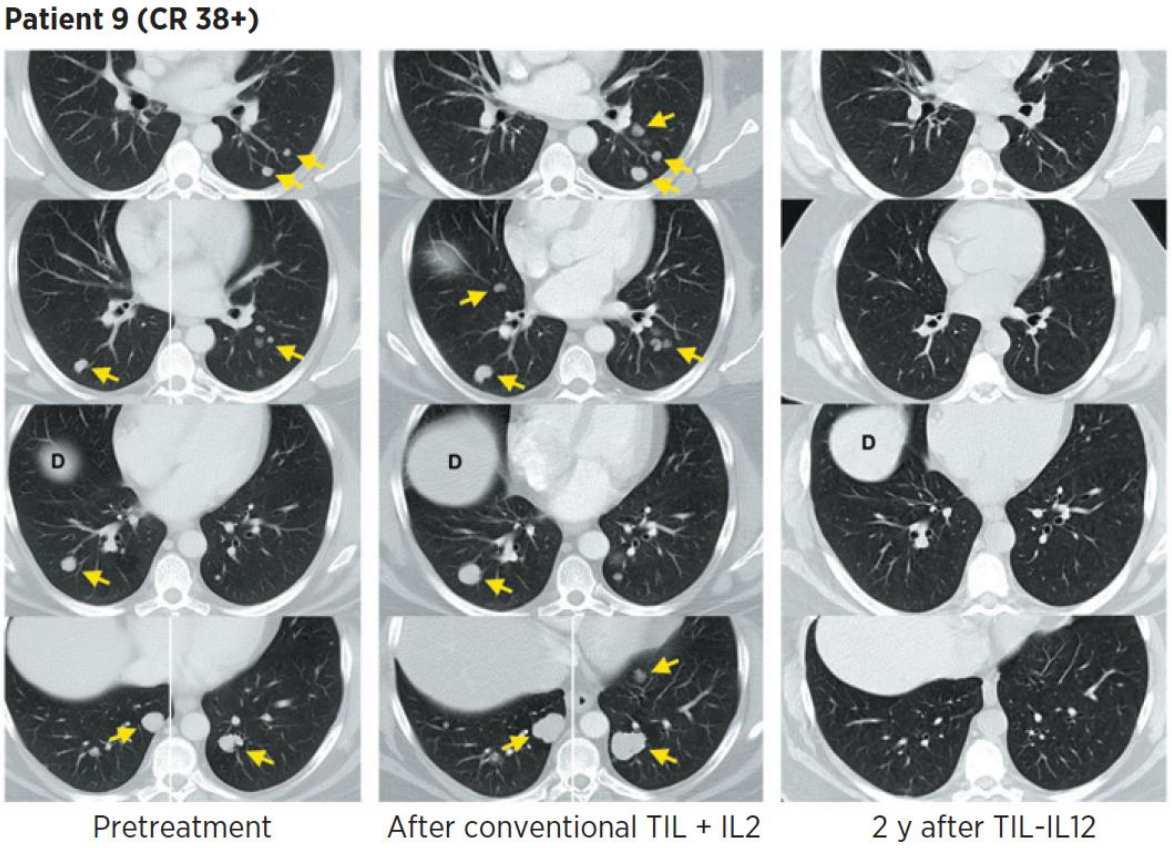
Clinical Cancer Research

Tumor-Infiltrating Lymphocytes Genetically Engineered with an Inducible Gene Encoding Interleukin-12 for the Immunotherapy of Metastatic Melanoma

Patient had previously been treated with **30 billion conventional nontransduced TILs**, plus 7 doses of IL2 (720,000 IU/kg) and tumors progressed.

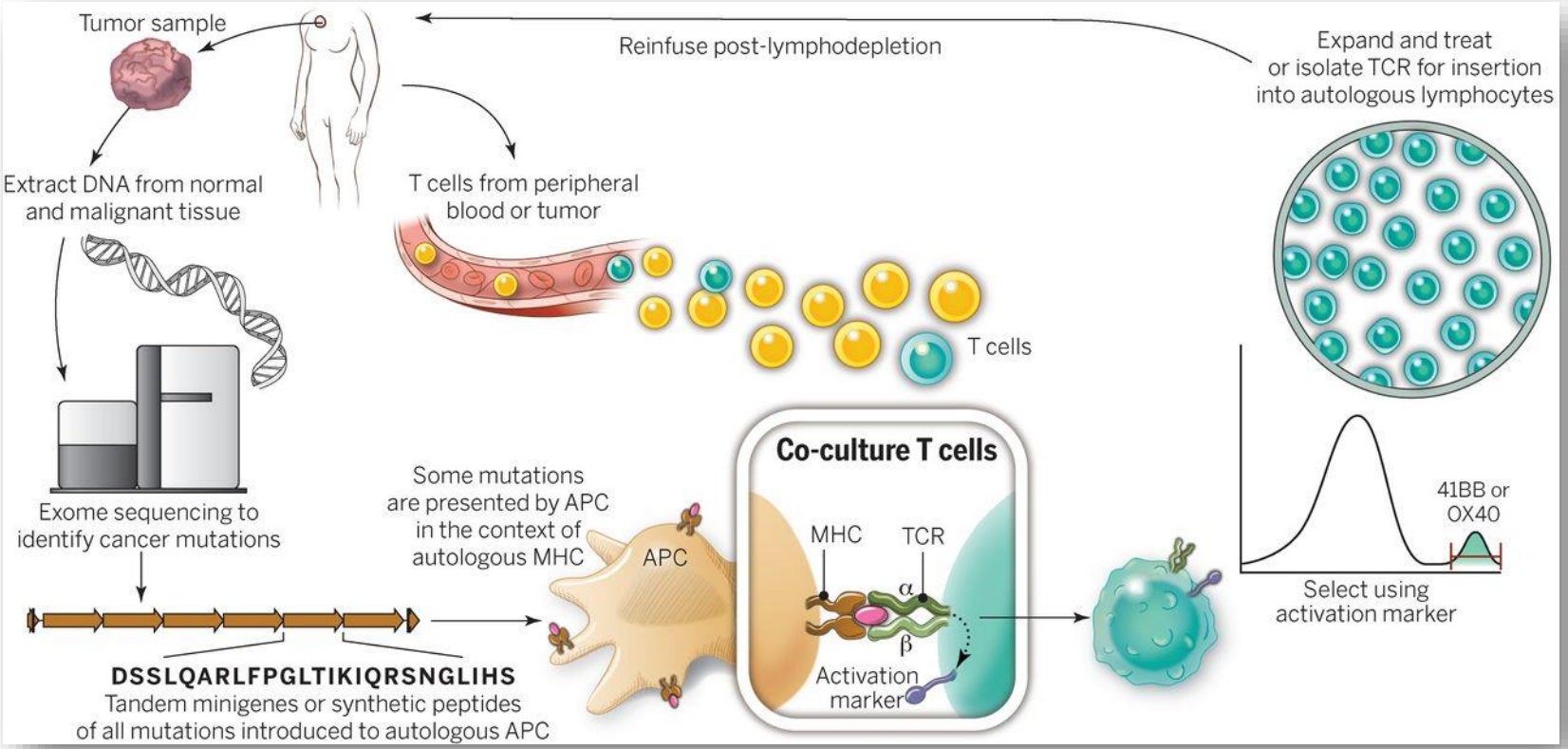
Using TILs expanded from the same original culture, the patient was retreated with a culture of **3 × 100 million NFAT.IL12 gene–modified TILs**

and has an ongoing **complete regression at 38 months** of disease metastatic to lung and lymph nodes



Overcoming the Challenges

A “blueprint” for the treatment of patients with T cells recognizing tumor-specific mutations.



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

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Science

AAAS

Cancer Immunotherapy Based on Mutation-Specific CD4+ T Cells in a Patient with Epithelial Cancer

Eric Tran,[1] Simon Turcotte,[1]* Alena Gros,[1] Paul F. Robbins,[1] Yong-Chen Lu,[1] Mark E. Dudley,[1]† John R. Wunderlich,[1] Robert P. Somerville,[1] Katherine Hogan,[1] Christian S. Hinrichs,[1] Maria R. Parkhurst,[1] James C. Yang,[1] Steven A. Rosenberg[1]‡

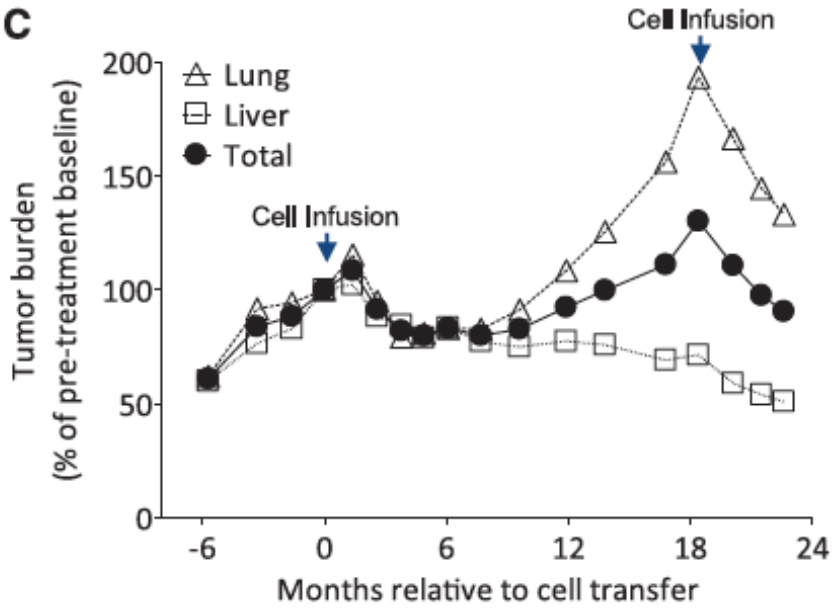
Patient with ***metastatic cholangiocarcinoma***

Identified a ***T cell*** contained (CD4+ T helper 1 (TH1) cells) recognizing a ***mutation in erbb2*** interacting protein (ERBB2IP) expressed by the cancer.

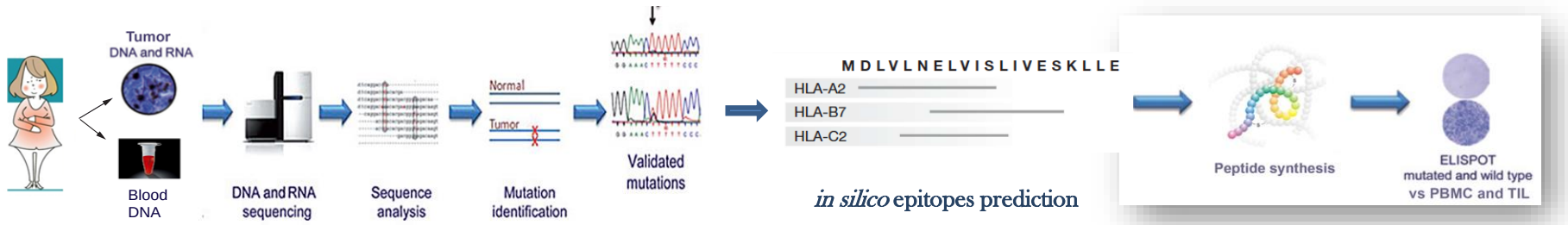
ACT of TIL containing about 25% of the mutation-specific T-cells

the patient achieved a decrease in target lesions with prolonged stabilization of disease.

The patient was retreated with a >95% pure population of mutation-reactive T cells



Naturally-occurring neo-epitope specific CD8+ T cells ARE detected in Ovarian Cancer Patients



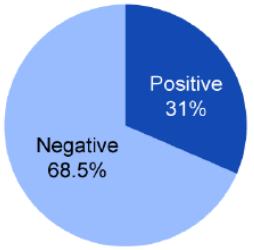
19 Patients

1300 non-synonymous somatic mutations

Average of 69 somatic substitutions/patient

776 (9mer or 10mer) peptide neoepitopes were predicted to bind w/ high affinity to HLA-1

Patients with spontaneous neo-epitope-specific CD8 T-cell responses (n=19)

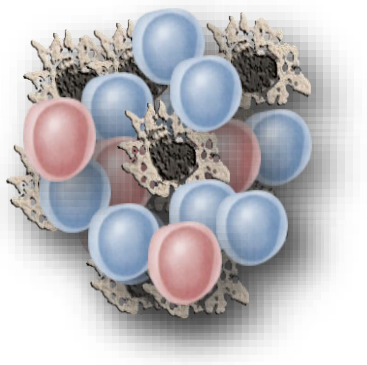


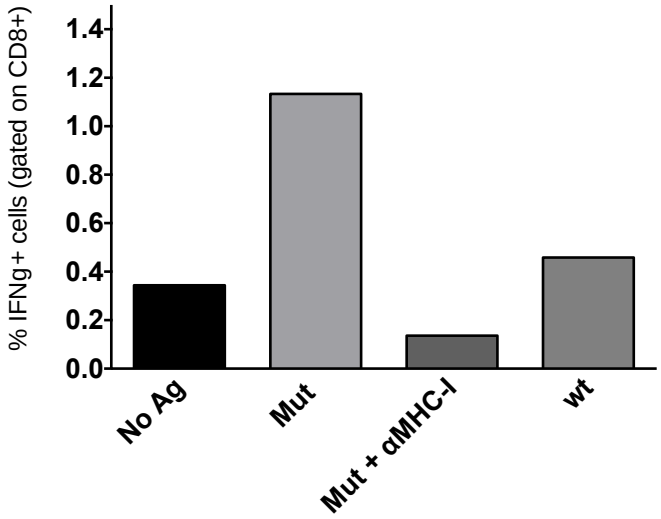
one-third (6/19)

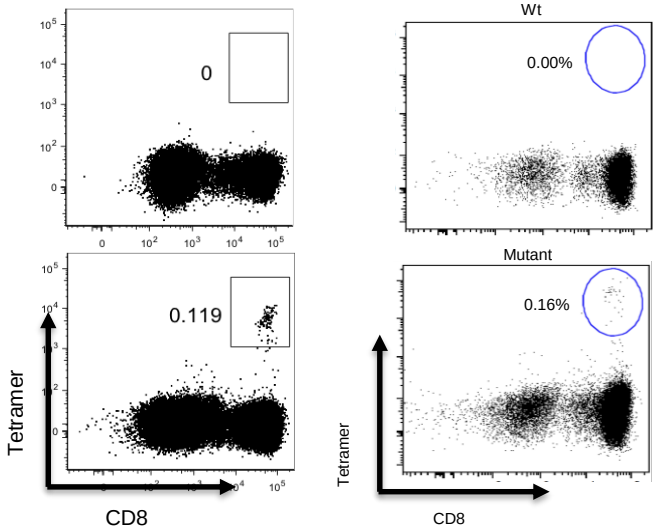
Sara Bobisse
Alex Harari
George Coukos

Ovarian TILs recognize tumor neo-epitopes

patient	somatic mutations	HLA-I	targeted mutations	peptides
1758	26	HLA-A23:01	9	11
		HLA-A29:01	1	1
		HLA-B39:06	0	0
		HLA-B44:03	2	2
		HLA-C04:01	1	1
		HLA-C07:02	1	1
		total	10	16







Annalisa Roberti
Brian Stevenson
Christian Iseli
Sara Bobisse
Alex Harari
George Coukos

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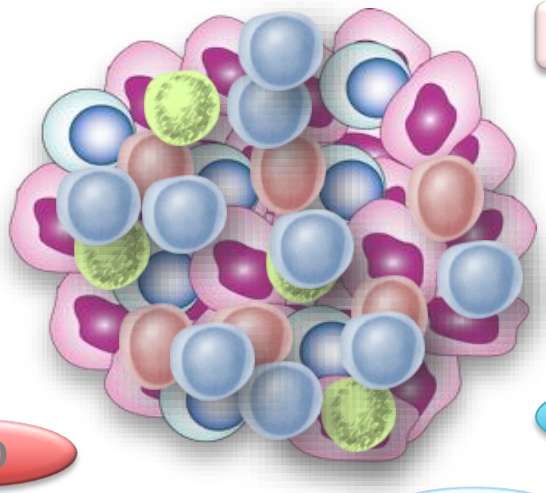
What about Drugs?



T-regulatory cells

Myeloid cells

IL-10

TGF-B

IDO

PDL-1

COX

PD-1/PDL-1 Antibodies

PDL-1+ve Tumors are more likely to respond

Cyclophosphamide/ Other Treg depleting agent (Ontak)

Myelosupressive Chemotherapy

Antibody –IL-10

Antibody TGF-beta (Genzyme)

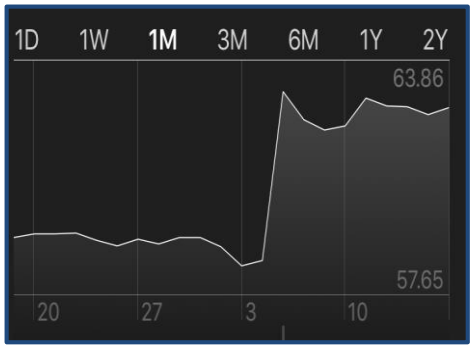
Aspirin/Celebrex

IDO Inhibitor (Incyte/Genentech/BMS)

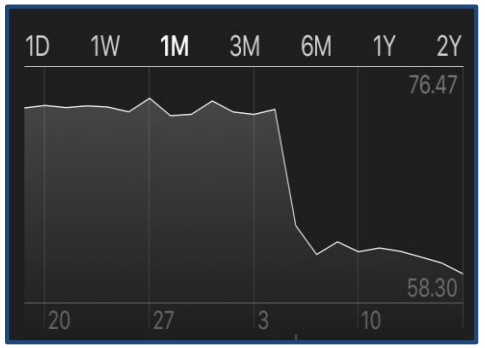
Lessons From Non Small Cell Lung Cancer

June 16, 2016	August 5, 2016
Merck's Pembrolizumab **demonstrates superior PFS** and OS to Chemotherapy in Front line NSCLC patients whose tumors expressed high levels of PD-L1	BMS's Nivolumab **failed to demonstrate superior PFS** to Chemotherapy in Front line NSCLC patients whose tumors expressed high levels of PD-L1

Market Reaction to Merck



Market Reaction to BMS



PD-L1 expression on at least 50% of tumor cells

PD-L1 expression on at least 5% or greater

Adapted -Courtesy of Priti Hedge

Summary of the PD-1/PDL-1 Clinical Trials to date

Table 4. Clinical Trials Targeting the PD-1 Pathway in Ovarian Cancer.

Drug	Target	Population	No. of Cases	PD-L1 Status	ORR	DCR	CR	PR	SD	Reference
Nivolumab	PD-1	Relapsed platinum^{R} ovarian cancer	18	Any	17%	44%	2	1	5	(Hamanishi et al., 2014)
Pembrolizumab	PD-1	Advanced ovarian cancer	26	PD-L1+	11.5%	34.6%	1	2	6	(Varga et al., 2015)
Avelumab	PD-L1	Platinum^{R} or chemotherapy^{R} ovarian cancer	75	Any	10.7%	54.7%	0	8	33	(Disis et al., 2015)
BMS-936559	PD-L1	Advanced ovarian cancer	17	any	1	23.5%	0	1	3	(Brahmer et al., 2012)

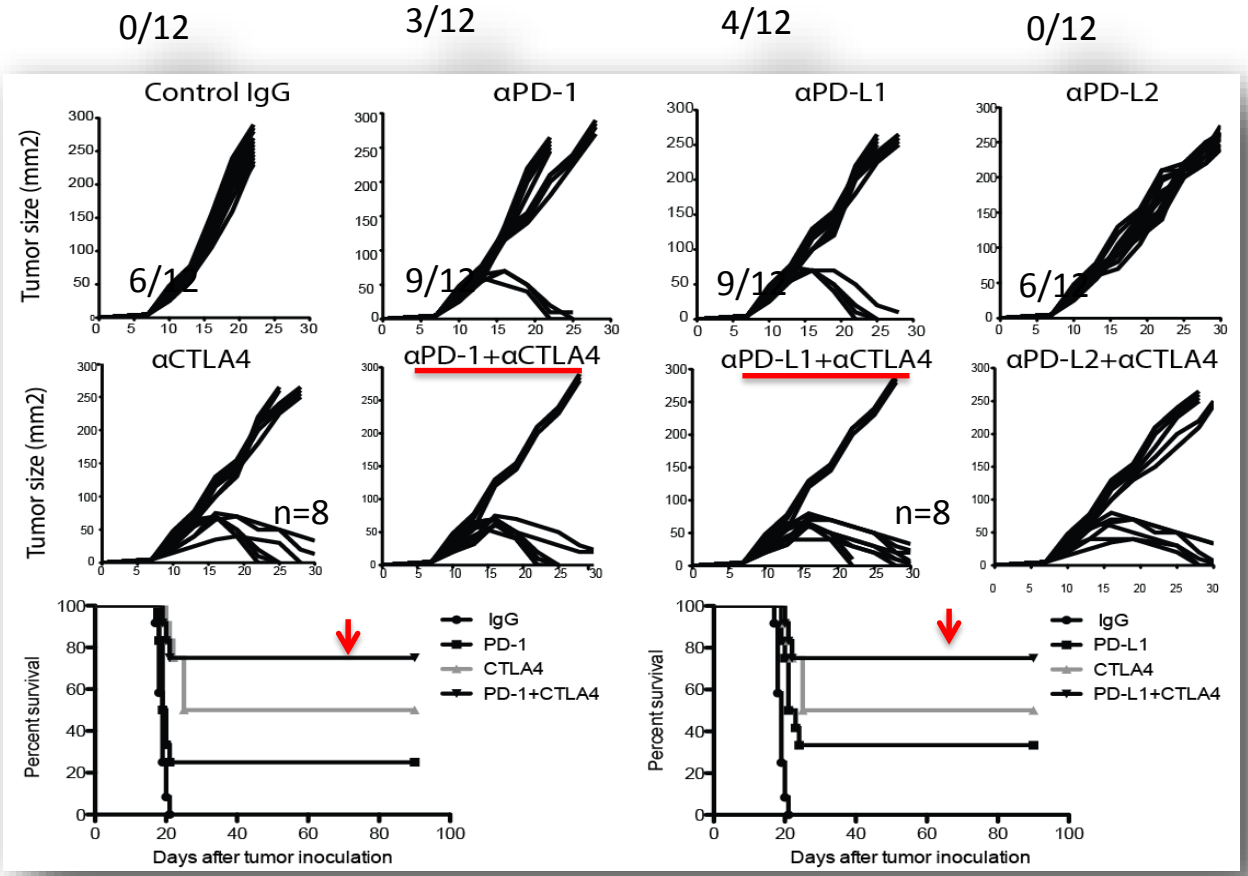
Abbreviations: PD-1, programmed death-1; PD-L1, programmed death ligand 1; platinum^{R}, platinum-resistant; chemotherapy^{R}, chemotherapy resistant; ORR, objective response rate; DCR, disease control rate; CR, complete response; PR, partial response; SD, stable disease.

Emerging immunotherapies in ovarian cancer. Ojalvo LS, Nichols PE, Jelovac D, Emens LA. Discov Med. 2015 Sep;20(109):97-109.

PD—1/CTLA-4 dual blockade are beneficial in vivo

ID8 model
Immunocompetent B6 mice

a dual blockage of PD-1 and CTLA-4 resulted in the reversal of CD8+ T-cell dysfunction and led to tumor rejection in two thirds of the mice



Duraiswamy et al Cancer Res 2014

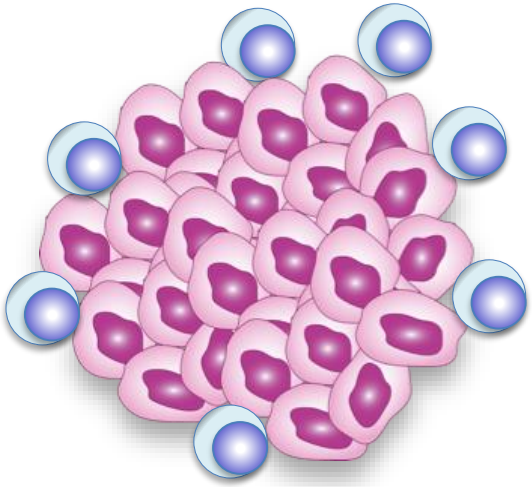
Immune check-point inhibitors trials in OC

Table 4 Ongoing studies of immune checkpoint inhibitors in ovarian cancer

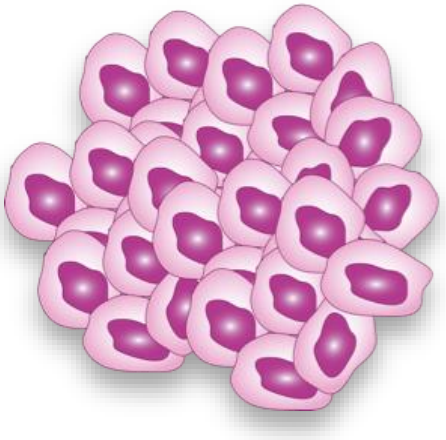
Phase	Trial number	Trial	Disease status	Immunotherapy agent(s)	Concurrent therapy
3	NCT02580058	A Study Of Avelumab Alone Or In Combination With Pegylated Liposomal Doxorubicin Versus Pegylated Liposomal Doxorubicin Alone In Patients With Platinum Resistant/Refractory Ovarian Cancer (JAVELIN Ovarian 200)	recurrent platinum resistant	Avelumab	Liposomal Doxorubicin
3	NCT02718417	Avelumab in Previously Untreated Patients With Epithelial Ovarian Cancer (JAVELIN OVARIAN 100)	primary	Avelumab	Carboplatin Paclitaxel
3	ENGOT-ov29-GCIG	A randomized, double-blinded, phase III study of atezolizumab versus placebo in patients with late relapse of epithelial ovarian, fallopian tube, or peritoneal cancer treated by platinum-based chemotherapy and bevacizumab	recurrent platinum sensitive	Atezolizumab	Carb
2	NCT02440425	Dose Dense Paclitaxel With Pembrolizumab (MK-3475) in Platinum Resistant Ovarian Cancer	recurrent platinum resistant		
2	NCT02498600	Nivolumab With or Without Ipilimumab in Treating Patients With Persistent or Recurrent Epithelial Ovarian, Primary Peritoneal, or Fallopian Tube Cancer	recurr		
2	NCT02520154	Pembrolizumab in Combination With Chemoth in Frontline Ovarian Cancer		mab	Carboplatin Paclitaxel
2	NCT02659384	Anti-programmed Cell Death-1 Li Antibody Atezolizumab, Bev Acetylsalicylic Acid in R Ovarian Cancer		Atezolizumab	Bevacizumab Acetylsalicylic Acid
2	NCT02674061	Efficacy an (MK-3	ecurrent platinum sensitive/resistant	Pembrolizumab	
2	NCT027	ate EDI4736 latinum	recurrent platinum resistant	Durvalumab	TPIV200/huFR-1 (anti-folate receptor vaccine)
		umab/Carboplatin/Taxol in ry Cancer	suboptimally cytoreduced primary	Pembrolizumab	Carboplatin Paclitaxel
		se 1/2 Study of Motolimod (VTX-2337) and MEDI4736 in Subjects With Recurrent, Platinum-Resistant Ovarian Cancer for Whom Pegylated Liposomal Doxorubicin (PLD) is Indicated	recurrent platinum resistant	Durvalumab	Motolimod Pegylated Liposomal Doxorubicin
1/2	NCT02484404	Phase 1 and 2 Study of MEDI4736 in Combination With Olaparib or Cediranib for Advanced Solid Tumors and Recurrent Ovarian Cancer	recurrent platinum sensitive/resistant	Durvalumab	Olaparib or Cediranib
1/2	NCT02485990	Study of Tremelimumab Alone or Combined With Olaparib for Patients With Persistent EOC (Epithelial Ovarian, Fallopian Tube or Primary Peritoneal Carcinoma)	recurrent or persistent	Tremelimumab	Olaparib
1/2	NCT02571725	PARP-inhibition and CTLA-4 Blockade in BRCA-deficient Ovarian Cancer	BRCA-deficient recurrent platinum sensitive/resistant	Tremelimumab	Olaparib
1/2	NCT02657889	Study of Niraparib in Combination With Pembrolizumab (MK-3475) in Patients With Triple-negative Breast Cancer or Ovarian Cancer (KEYNOTE-162)	recurrent platinum resistant	Pembrolizumab	Niraparib
1/2	NCT02726997	Matched Paired Pharmacodynamics and Feasibility Study of Durvalumab in Combination With Chemotherapy in Frontline Ovarian Cancer	primary	Durvalumab	Carboplatin Paclitaxel
1	NCT02737787	A Study of WT1 Vaccine and Nivolumab For Recurrent Ovarian Cancer	≥2nd remission	Nivolumab	WT1 vaccine
0	NCT02728830	A Study of Pembrolizumab on the Tumoral Immunoprofile of Gynecologic Cancers	primary	Pembrolizumab	

AN EXCITING TIME!

What do we know about the Immunology of “non Immunogenic” Tumors?

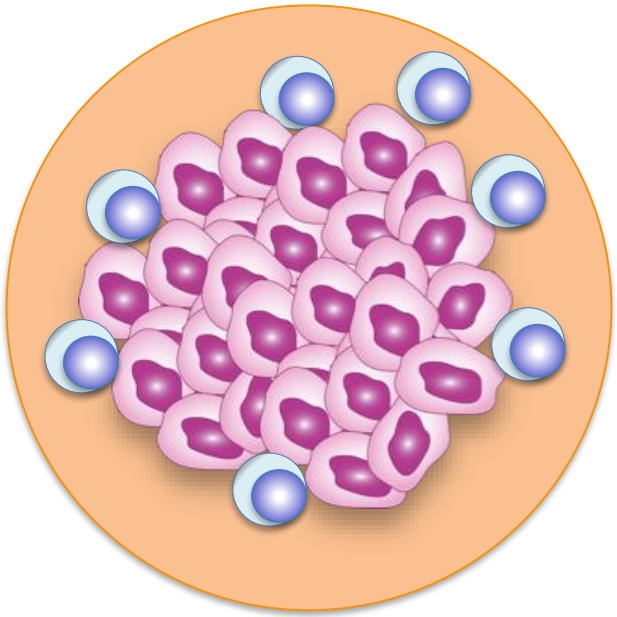


Immune exclusion



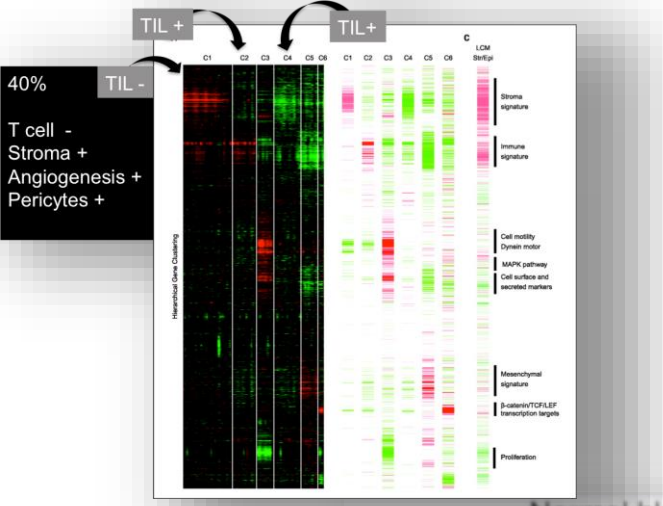
Immune ignorance

The Immune Excluded Tumor

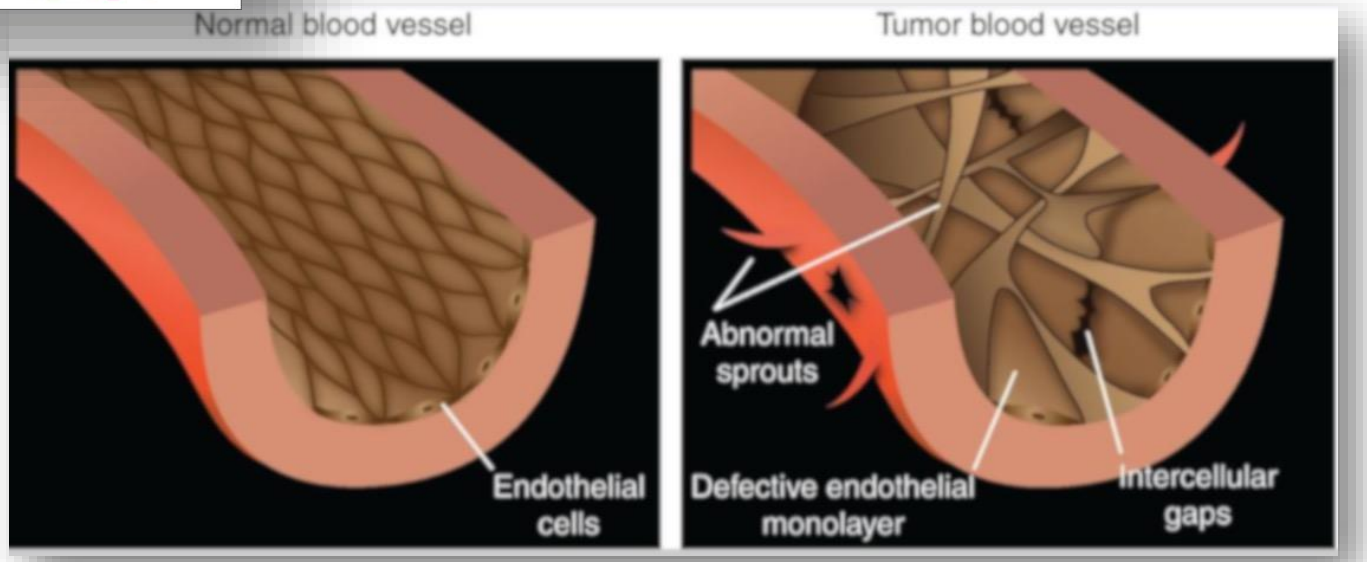


“A Homing Defect”

Angiogenesis
Extracellular Matrix
Chemokines
Protease processing
B cells



Why is there a negative correlation?



Abnormalities in tumor endothelial cells (TEC)

High VEGF-A secreted by the tumor → morpholgical changes of TEC

Low adhesion molecules → lymphocytes cannot pentetrate

Dudley, 2012.

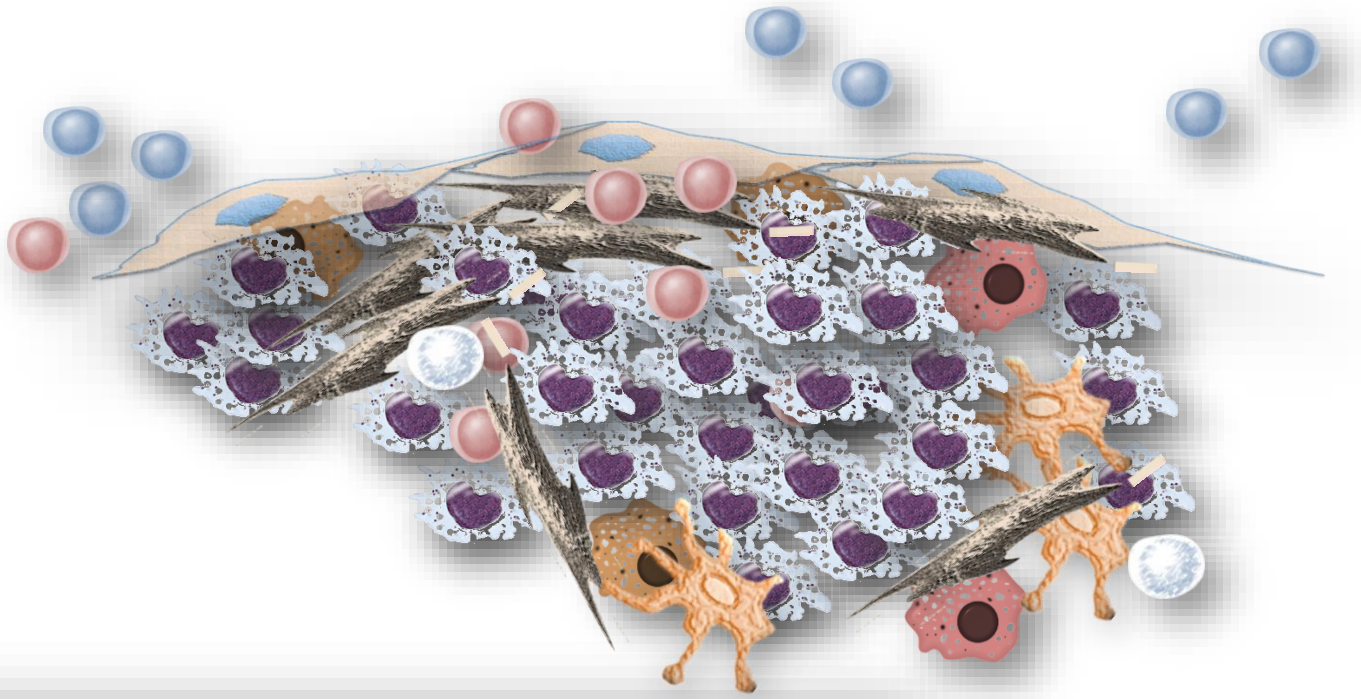
The Endothelial Tumor Barrier Hypothesis
Many More Players

PGED2

Fas L

VEGF

ETBR



Endothelin B receptor mediates the endothelial barrier to T cell homing to tumors and disables immune therapy

Ronald J Buckanovich[1,2,7,8], Andrea Facciabene[1,8], Sarah Kim[1], Fabian Benencia[1,3], Dimitra Sasaroli[1,4], Klara Balint[1], Dionysios Katsaros[6], Anne O'Brien-Jenkins[1], Phyllis A Gimotty[1,5] & George Coukos[1,3]

nature medicine

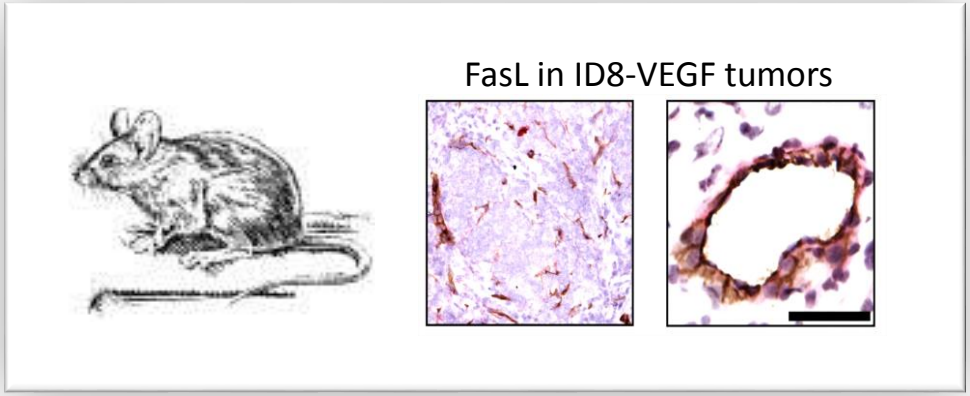
Tumor endothelium FasL establishes a selective immune barrier promoting tolerance in tumors

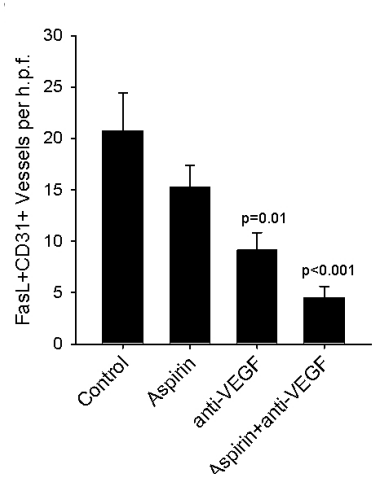
Gregory T Motz[1], Stephen P Santoro[1], Li-Ping Wang[2], Tom Garrabrant[1], Ricardo R Lastra[2], Ian S Hagemann[2], Priti Lal[2], Michael D Feldman[2], Fabian Benencia[1] & George Coukos[1,3]

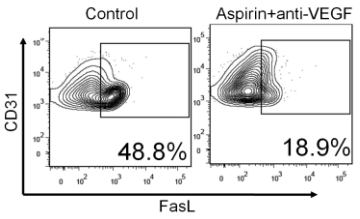
nature medicine

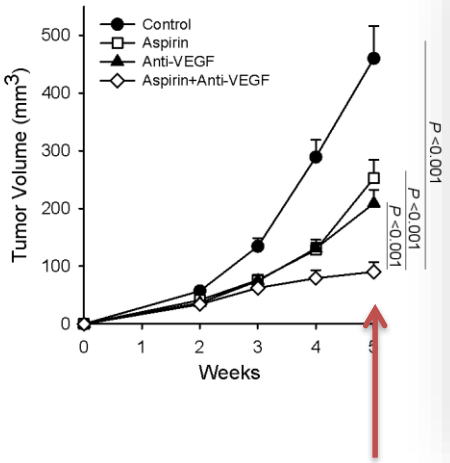
R. Buckanovich
A. Facciabene
G. Motz
G. Coukos

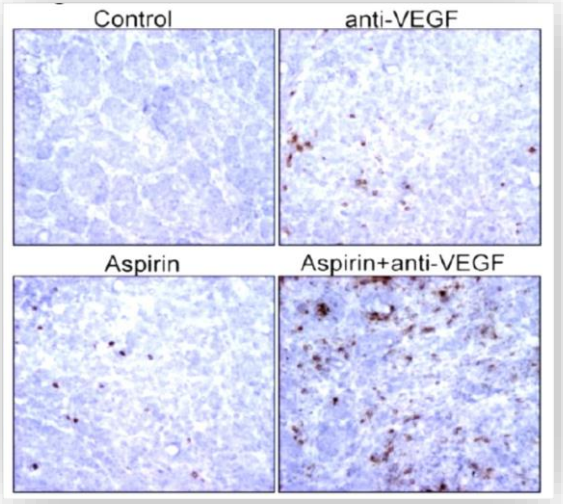
VEGF and PGE2 blockade reduce endothelial FasL & allow TIL accumulation











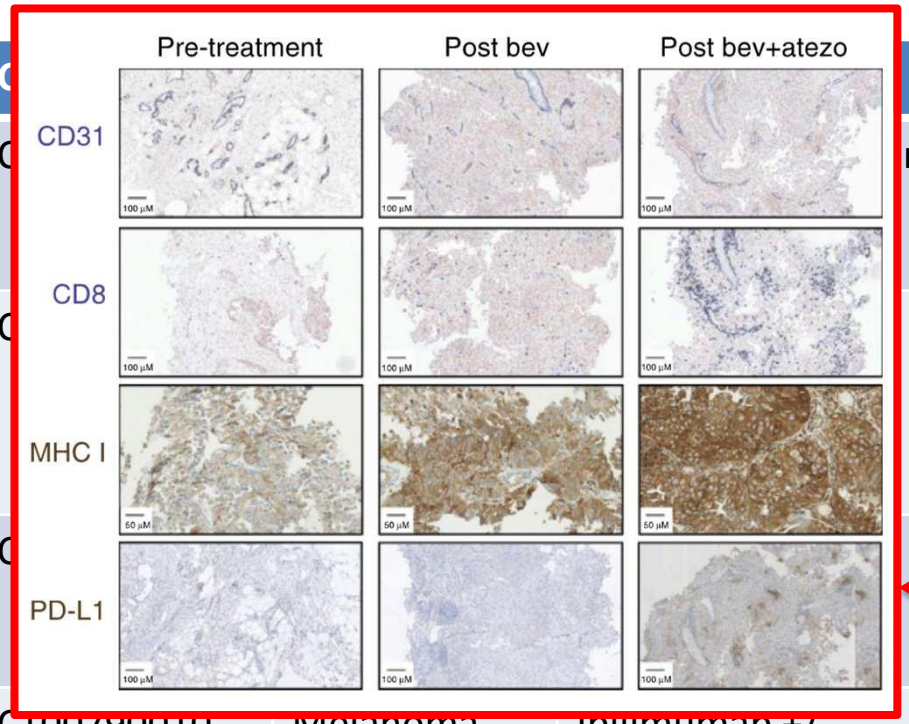
George Coukos

Greg Motz

Anti-VEGF therapy and immune checkpoint inhibitors

NCT Reference	Condition	Treatment	Early results
NCT01472081	RCC	Nivolumab + Sunitinib	Encouraging anti-tumor activity, frequent AEs [Amin, J Clinical Oncology, 32:5s, 2014]
NCT01984242	RCC	Atezolizumab + Bevacizumab or Sunitinib	Bevacizumab arm: good anti-tumor response in PDL1+ patients Sunitinib arm: recruiting [Dermott, J Clin Oncol 35, 2017]
NCT01633970	Advanced Solid Cancer	Atezolizumab + Bevacizumab +/- Chemotherapy	Increased intratumoral CD8+ T cells in the Bevacizumab + atezolizumab arm [Sznol, J Clin Oncol 33, 2015]
NCT00790010	Melanoma Patients	Ipilimumab +/- Bevacizumab	Increased T cell infiltration in presence of Bevacizumab [Hodi, Cancer Immun Research, 2014]
NCT02348008	RCC	Pembrolizumab + Bevacizumab	Acceptable safety profile [Dudek, J Clin Oncol 34, 2016]
NCT02366143	NSCLC	Atezolizumab + Bevacizumab + SOC	Not yet reported, outcome include TIL evaluation [Papadimitrakopoulou, J Clinic Oncol 34, 2016]

Clinical studies with anti-VEGF therapy and immune checkpoint inhibitors



NC			Early results
NC		nib	Encouraging anti-tumor activity, frequent AEs [Amin, J Clinical Oncology, 32:5s, 2014]
NC			Bevacizumab arm: good anti-tumor response in PDL1+ patients Sunitinib arm: recruiting [Dermott, J Clin Oncol 35, 2017]
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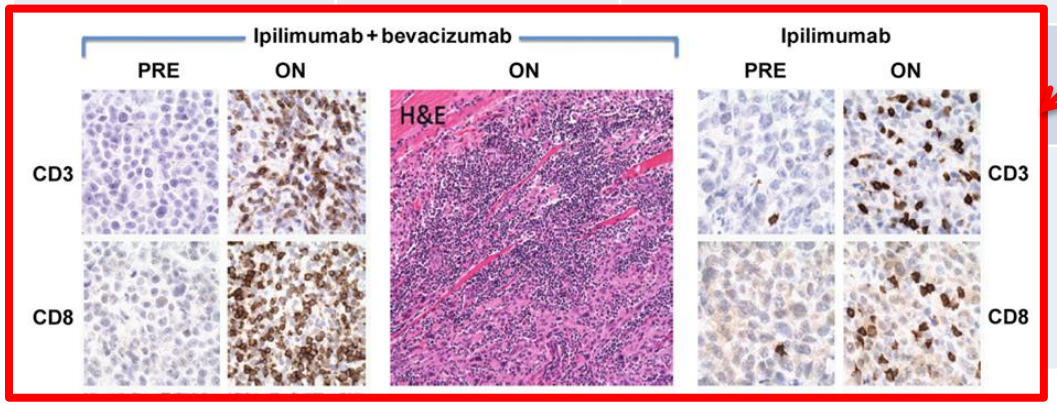


Blockade of VEGF-A and PD-1 and PGEDE2

Anti-programmed Cell Death-1 Ligand 1 (aPDL-1) Antibody Atezolizumab, Bevacizumab and Acetylsalicylic Acid in Recurrent Platinum Resistant Ovarian Cancer

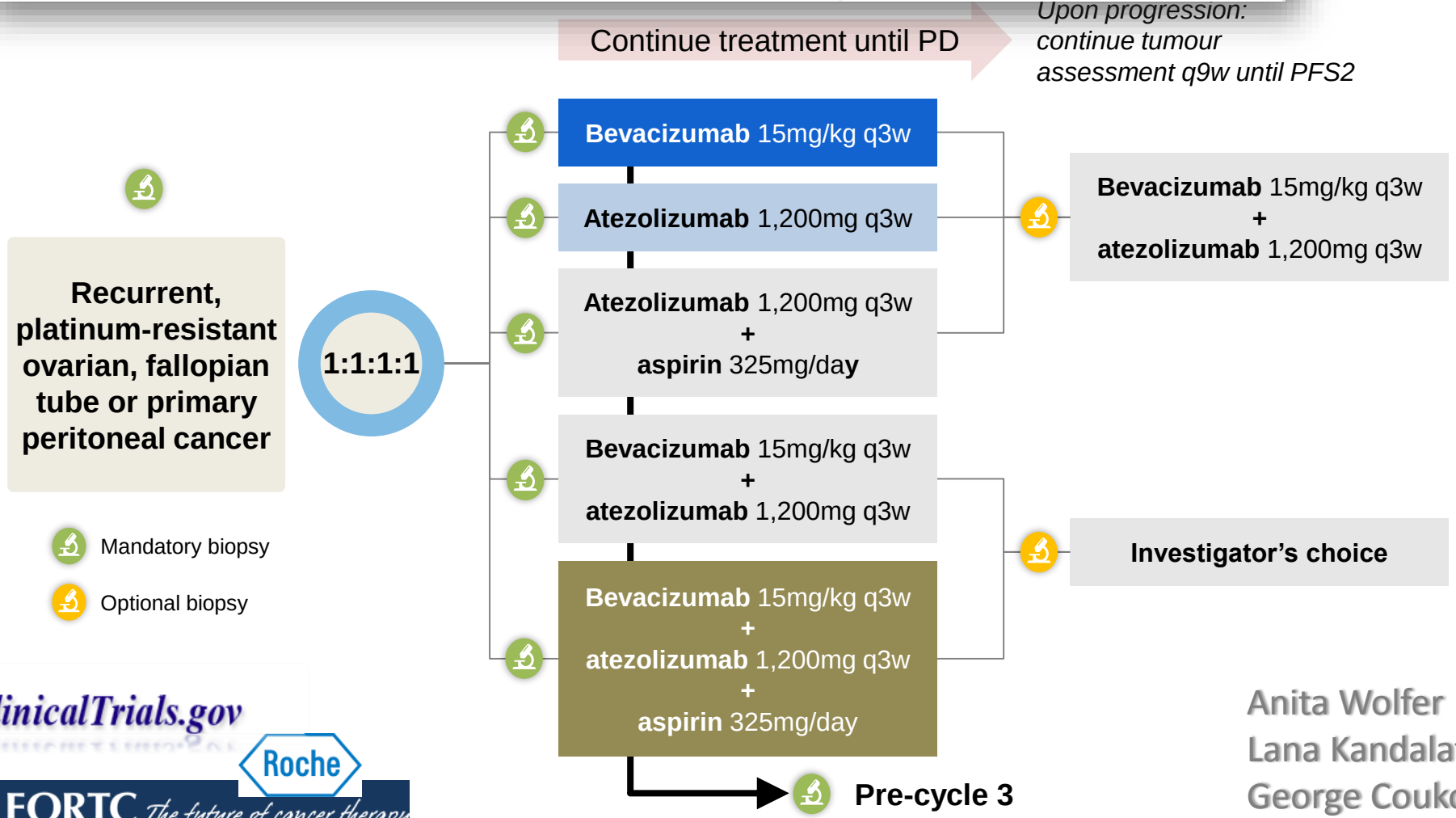
This study is currently recruiting participants. (see Contacts and Locations)

Verified December 2016 by European Organisation for Research and Treatment of Cancer - EORTC

Sponsor:
European Organisation for Research and Treatment of Cancer - EORTC

ClinicalTrials.gov Identifier:
NCT02659384

First received: January 14, 2016
Last updated: December 23, 2016
Last verified: December 2016



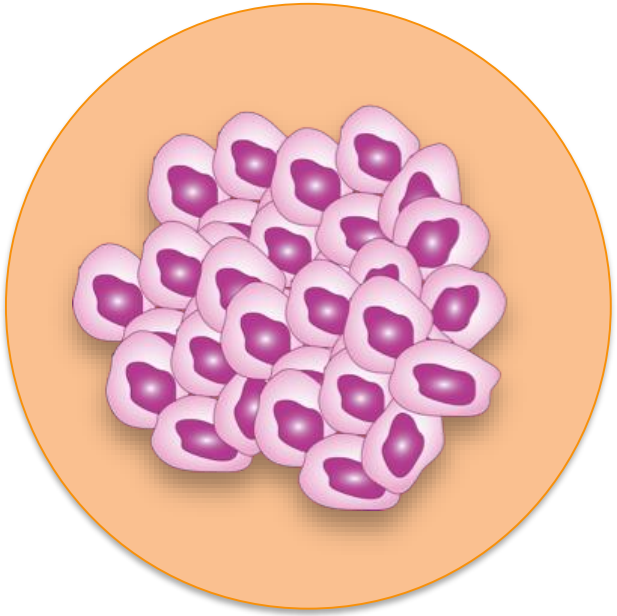
ClinicalTrials.gov

Roche

EORTC The future of cancer therapy

Anita Wolfer
Lana Kandalaft
George Coukos

The Immune Ignored Phenotype

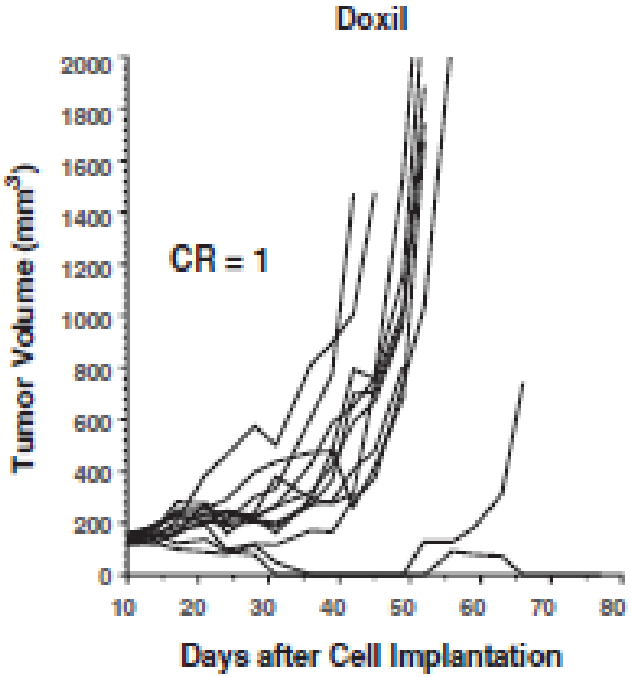


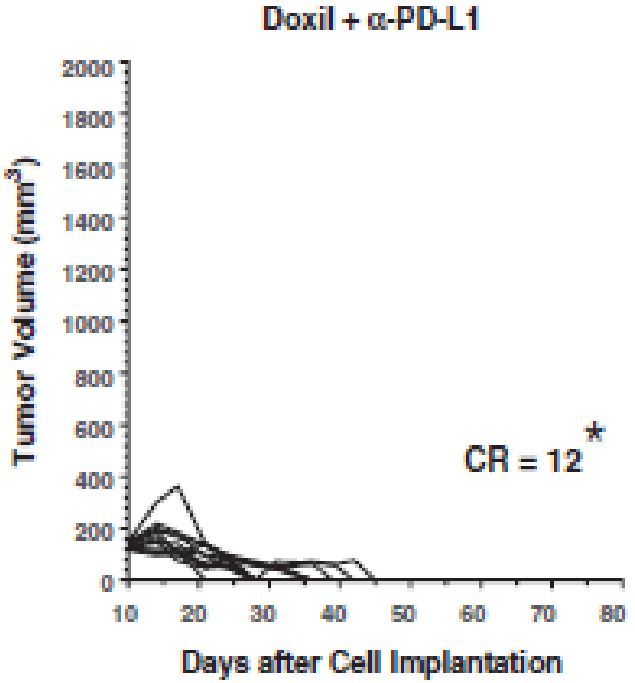
“A T Cell Priming Defect”

Induce Immunogenicity

Radiation
Vaccines
Chemotherapy
CAR-T cells
Oncolytic Viruses
T cell-directed bispecific antibodies

Complete Remission Rates are increased when PDL-1 is combined with PLD (doxil)





Rios-Doria J et a. Neoplasia 2015

JAVELIN 200 phase III study:
Avelumab in Platinum Resistant/Refractory Ovarian Cancer

PI: E Pujade-Lauraine

Enrollment Criteria

- Progression ≤ 6 mo or no response to most recent platinum-based therapy
- No more than 3 prior therapies for platinum-sensitive disease, and no prior therapies for platinum-resistant disease
- Measurable disease
- ECOG PS 0 or 1
- Available tissue at baseline

RANDOMIZATION

1:1:1

Avelumab

PLD + Avelumab

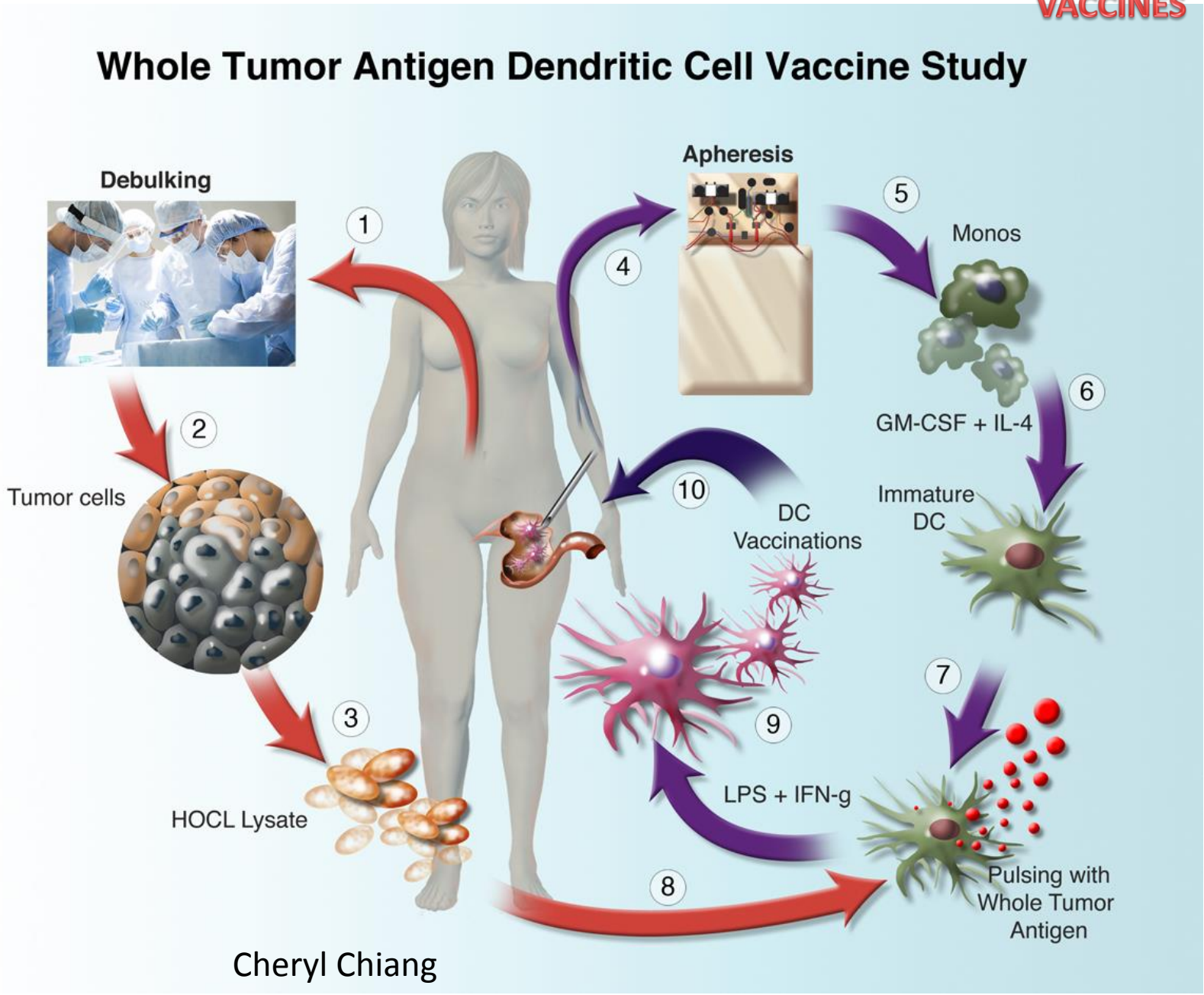
PLD

pegylated liposomal doxorubicin

n = ~550
(282 events)

Stratification: Platinum refractory vs resistant, #prior therapies, bulky disease.

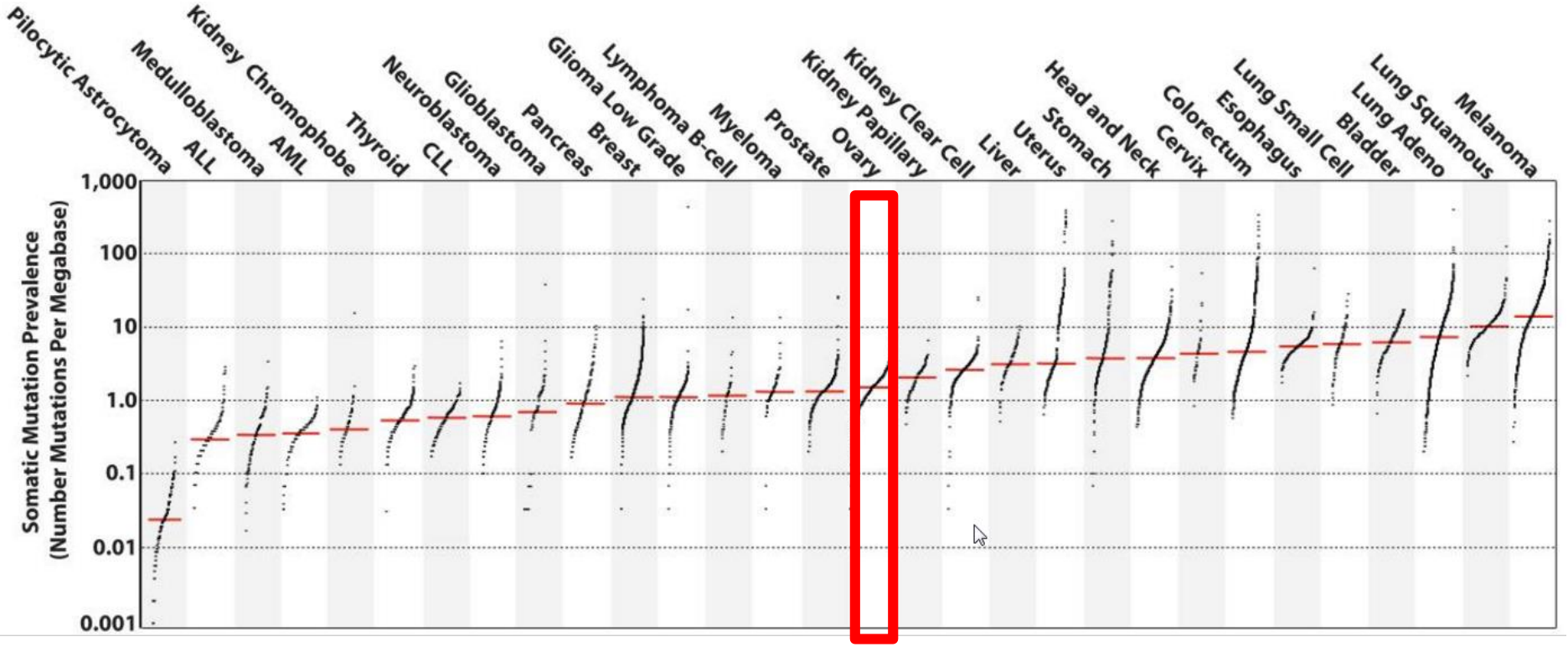
co-Primary Endpoints:	OS,PFS
Secondary Endpoints:	ORR, Duration of response, PROs, Safety



Kandalaft et al, JTM 2013

What About the Mutational Load of Ovarian Cancer?

The prevalence of somatic mutations across human cancer types



Indications with higher mutational load have a higher frequency of neoantigens

High neoantigen load is associated with better outcome

Neoantigen based vaccines are feasible in tumors with high mutational load

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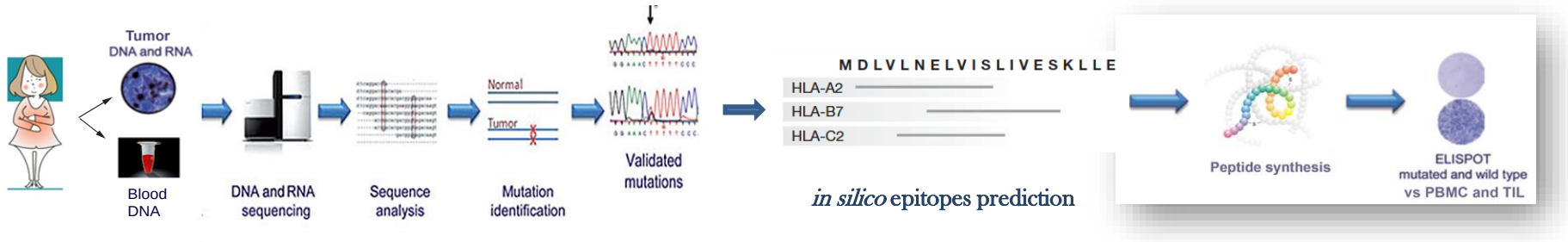
LUDWIG CANCER RESEARCH

Alexandrov *et al.*, Nature (2013)

Naturally-occurring neo-epitope specific CD8+ T cells ARE detected in Ovarian Cancer Patients



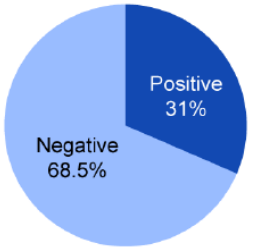
19 Patients

1300 non-synonymous somatic mutations

Average of 69 somatic substitutions/patient

776 peptide neoepitopes were predicted to bind w/ high affinity to HLA-1

Patients with spontaneous neo-epitope-specific CD8 T-cell responses (n=19)



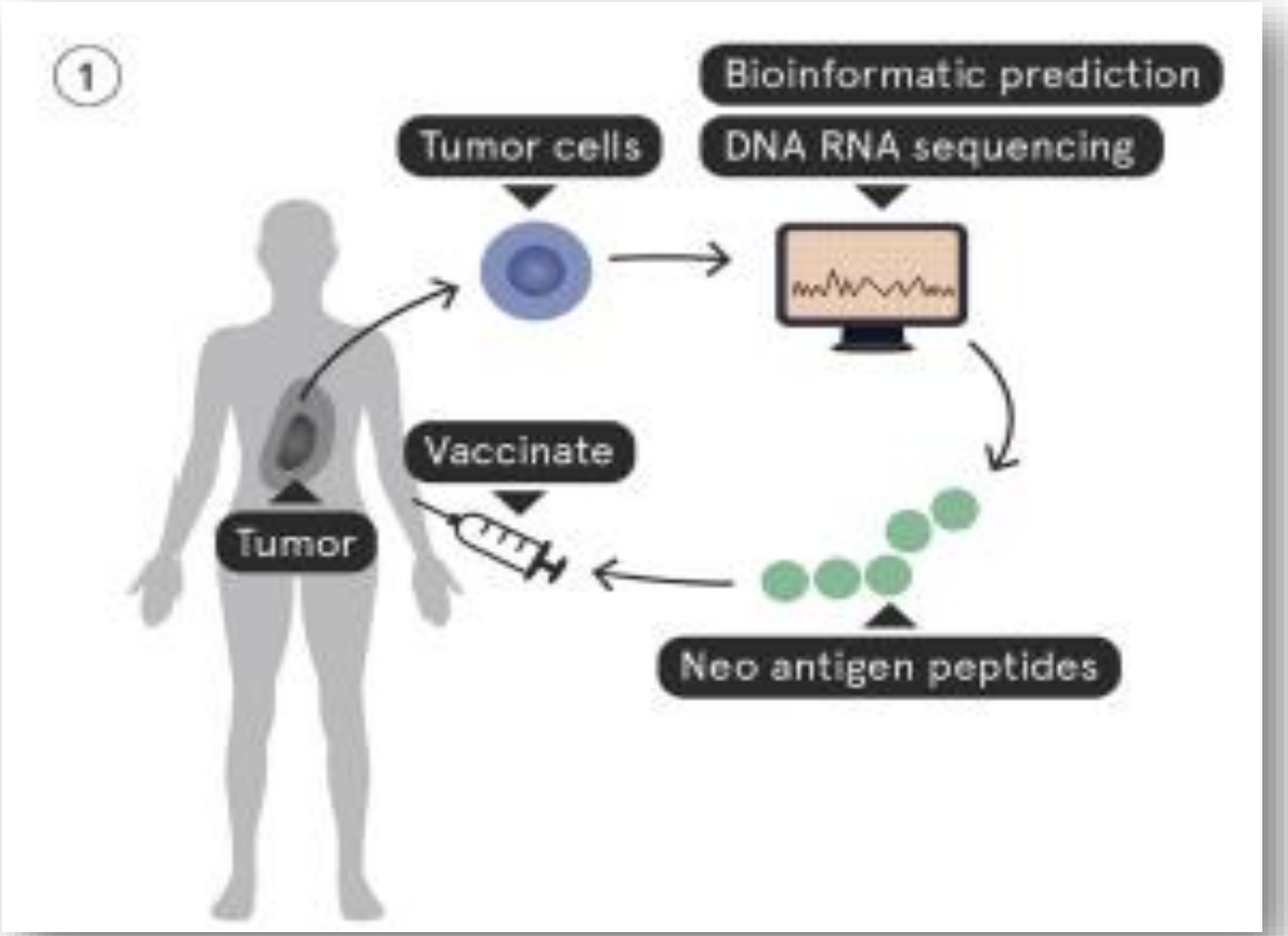
one-third (6/19)

Sara Bobisse
Alex Harari
George Coukos

CONFIDENTIAL

Kandalaft et al, submitted

A Personalized NeoAntigen Specific Vaccine Could be Feasible in Ovarian Cancer

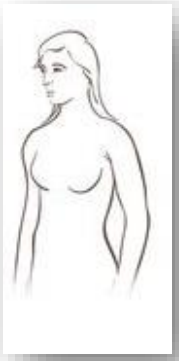


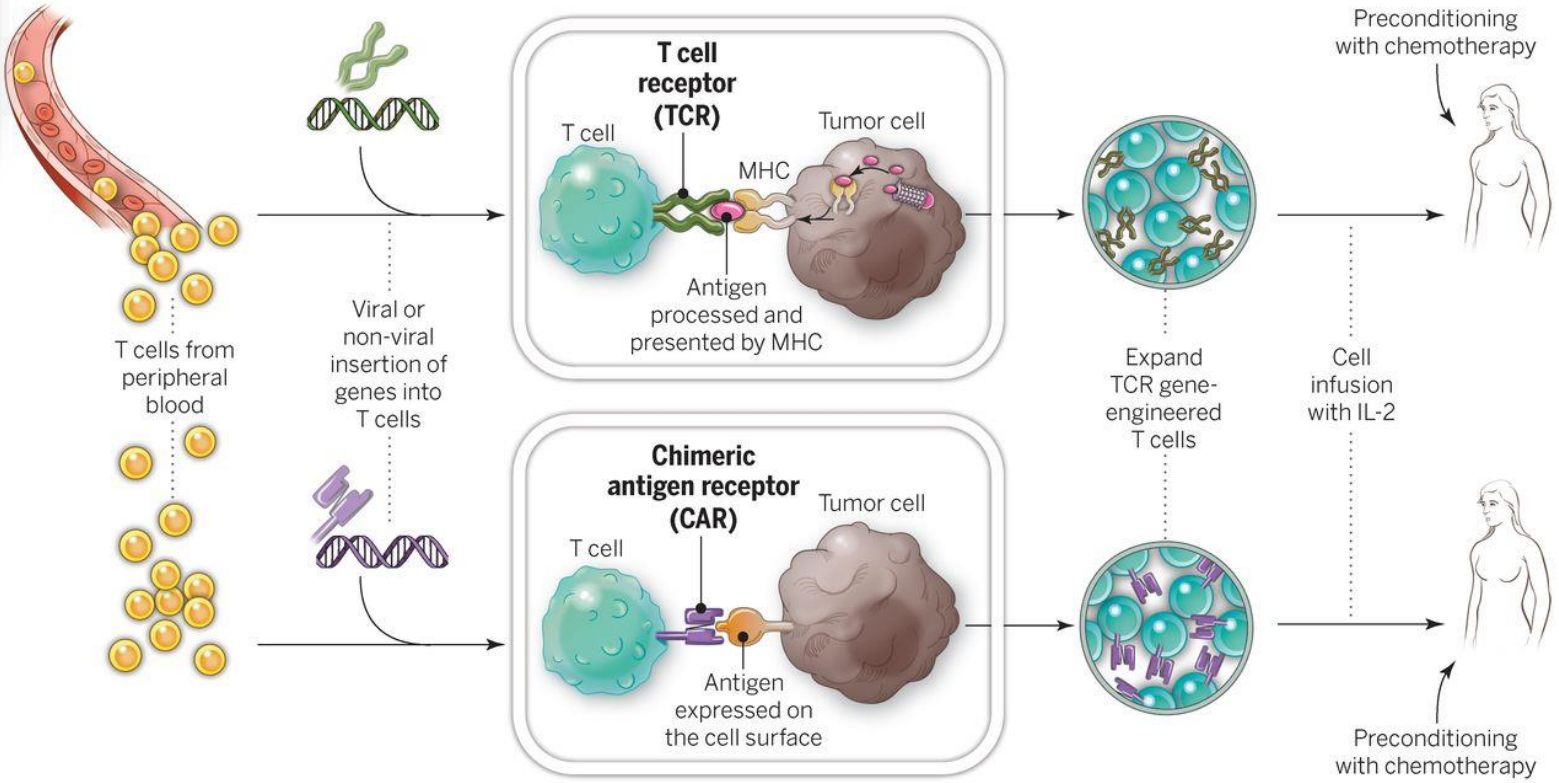
Personalized approaches to active immunotherapy in cancer
Eran Ophir, Sara Bobisse, George Coukos, Alexandre Harari, ***Lana E. Kandalaft***

Biochimica et Biophysica Acta (BBA)- August 2015

CAR/TCR T CELL THERAPY

Adoptive T cell Therapy with Genetically Engineered Peripheral Blood Lymphocytes.





Science AAAS

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LUDWIG CANCER RESEARCH

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

The CD19 CAR T Cell Success Story for relapsed ALL and CLL

Emily Whitehead

- Complete remission and long-term responses in up to 90% of acute lymphoblastic leukemia (ALL) patients (both adult and pediatric)
- And in > 50% of chronic lymphocytic leukemia (CLL) patients.

- On target side effects include B cell aplasia and cytokine release syndrome.

Maud et al, NEJM 2015 & Blood 2015

CHUV

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LUDWIG CANCER RESEARCH

Anti-mesothelin chimeric antigen receptor T cells in patients with Ovarian Cancer

Janos L. Tanyi (Univ. of Pennsylvania)

- **6 recurrent serous ovarian cancer** patients were treated with autologous lentiviral vector transduced T cells expressing a second generation chimeric antigen receptor (CAR) construct targeting mesothelin.

- **100% of the manufacturing** and administration were successful
- **No** Acute **AEs** and no **CRS**
- Anti-tumor efficacy is suggested by all **6 SD** from 6 treated patients on Day 28
- CART-meso cells **trafficked** to several tumor sites

ASCO Annual '16 Meeting

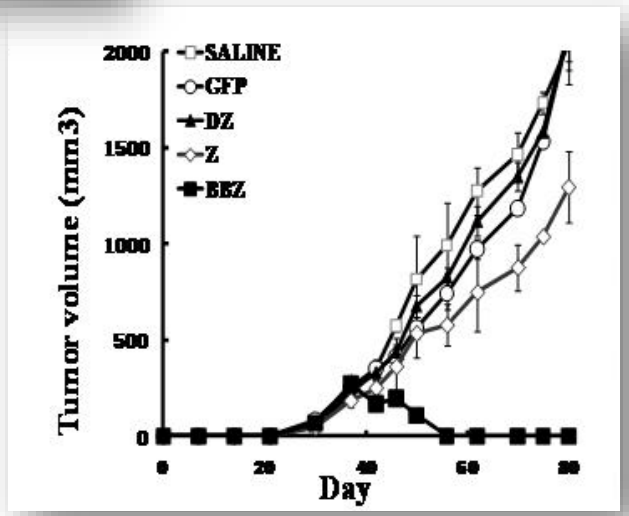
Kandalaft et al. Journal of Translational Medicine 2012, 10:157
http://www.translational-medicine.com/content/10/1/157

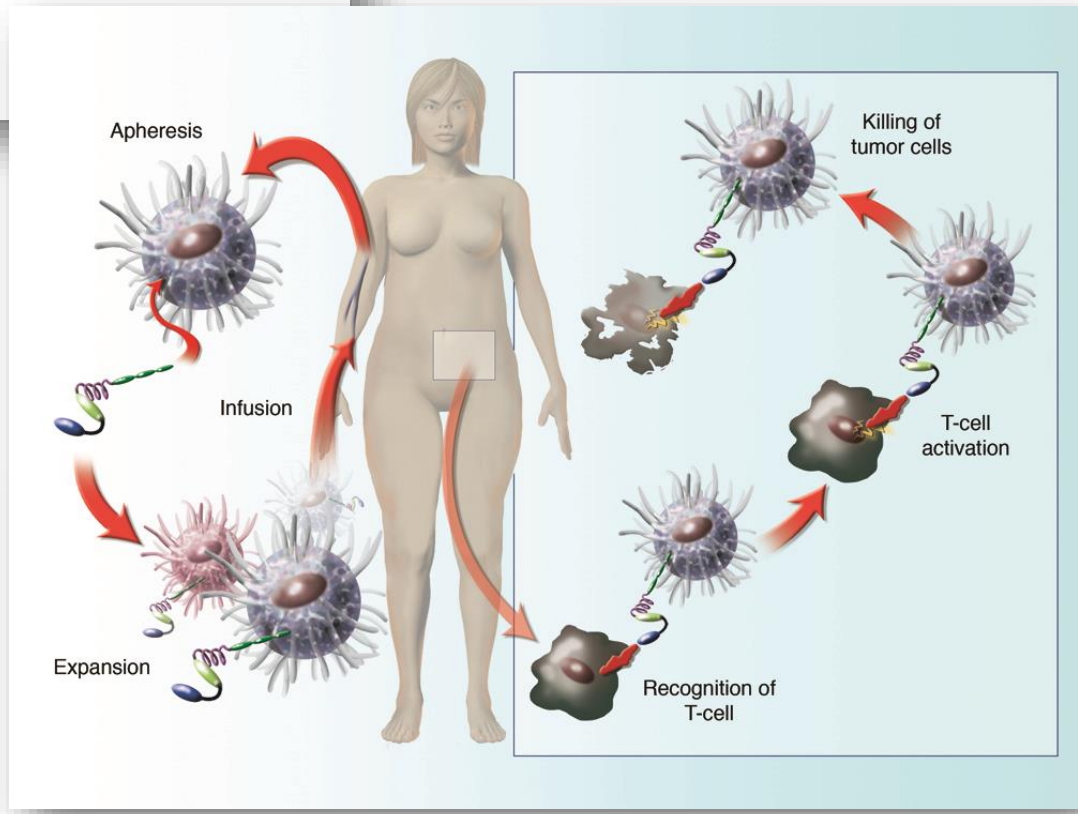
JOURNAL OF TRANSLATIONAL MEDICINE

RESEARCH Open Access

A phase I clinical trial of adoptive transfer of folate receptor-alpha redirected autologous T cells for recurrent ovarian cancer

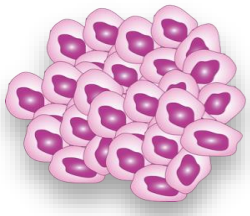
Lana E Kandalaft*, Daniel J Powell Jr and George Coukos





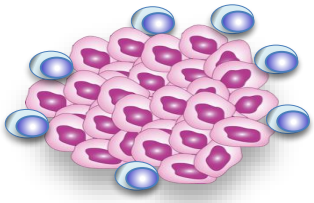
Three Phenotypes of Ovarian Cancer represent Three different limiting steps in the Cancer Immunity Cycle

Immune Ignored

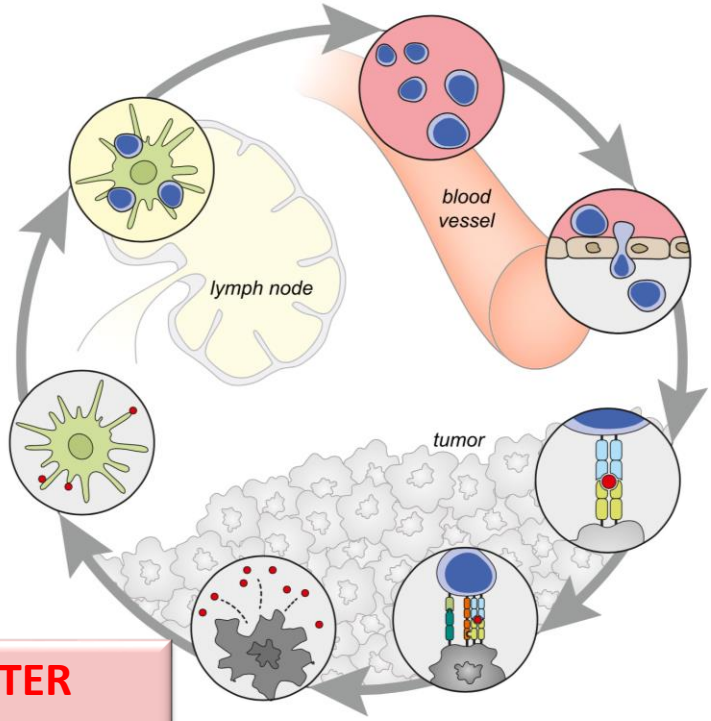


Induce Immunogenicity

Immune excluded

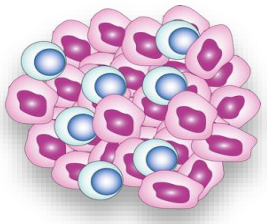


Disrupt the barrier



COMBINATIONS

Immunogenic



DEVELOPMENT OF A BETTER IMMUNOSCORE

CRYOPRESERVE TUMOR

Activate T cells
✕ Immunosupressive mechanisms

Adapted from Chen & Mellman, Immunity, 2013

George Coukos

Janos Tanyi
Dan Powell
Cheryl Chiang
Rosemarie Mick
Drew Torigian
Harvey Nisenbaum

Alex Harari
Sara Bobisse
Eran Ophir
Raphael Genolet
Annalisa Roberti
Brian Stevenson
Christian Iseli

Carl June
Bruce Levine

Anita Wolfer
Silvia Martin Lluesma

Our Patients

THANK YOU