

# Immunotherapy for Ovarian Cancer

Lana E. Kandalaft, Pharm.D, Ph.D, MTR

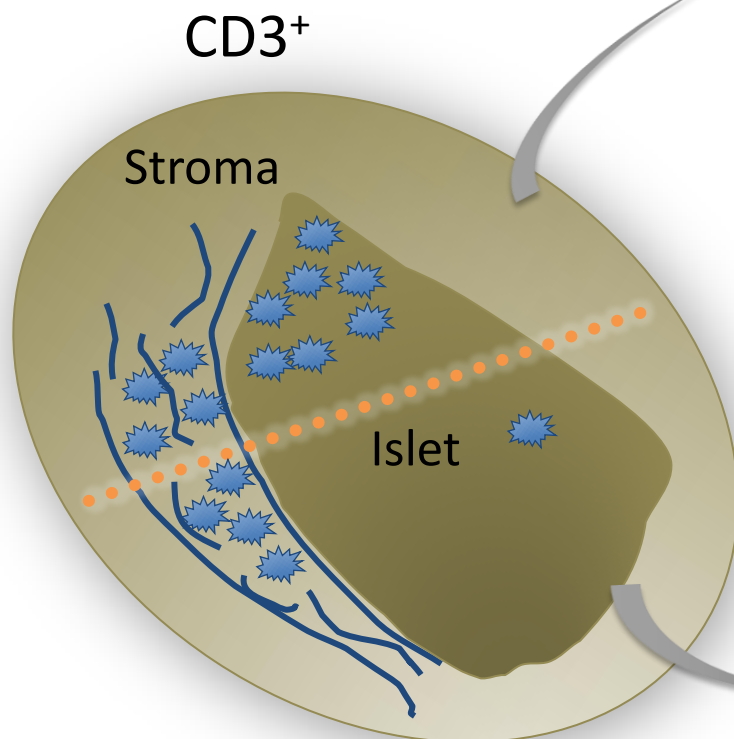
Adjunct Assistant Professor, University of Pennsylvania  
Director , Center of Experimental Therapeutics, LICR, CHUV



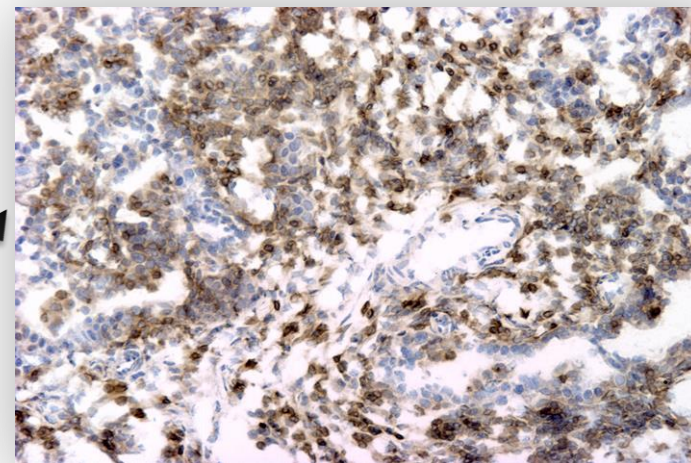
ORIGINAL ARTICLE

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

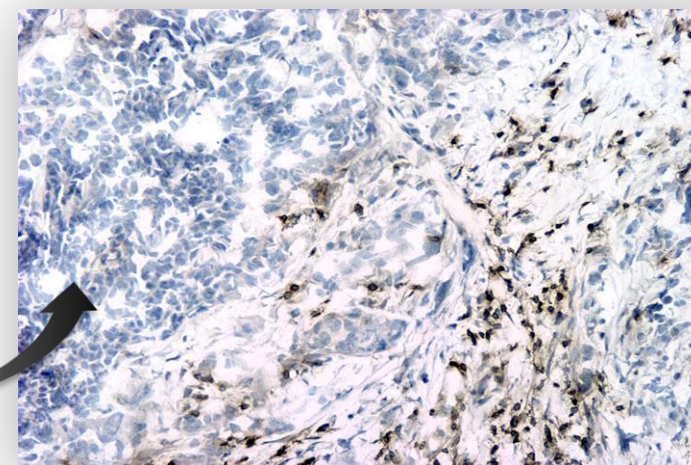
Lin Zhang, M.D., Jose R. Conejo-Garcia, M.D., Ph.D.,  
Dionyssios Katsaros, M.D., Ph.D., Phyllis A. Gimotty, Ph.D.,  
Marco Massobrio, M.D., Giorgia Regnani, M.D.,  
Antonis Makrigiannakis, M.D., Ph.D., Heidi Gray, M.D.,  
Katia Schlienger, M.D., Ph.D., Michael N. Liebman, Ph.D.,  
Stephen C. Rubin,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



TIL Present  
55%

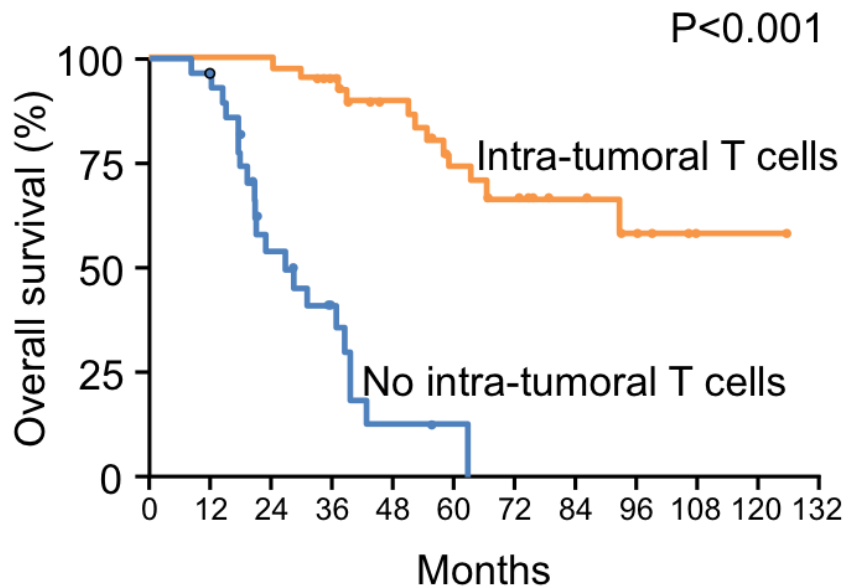


TIL Absent  
40%

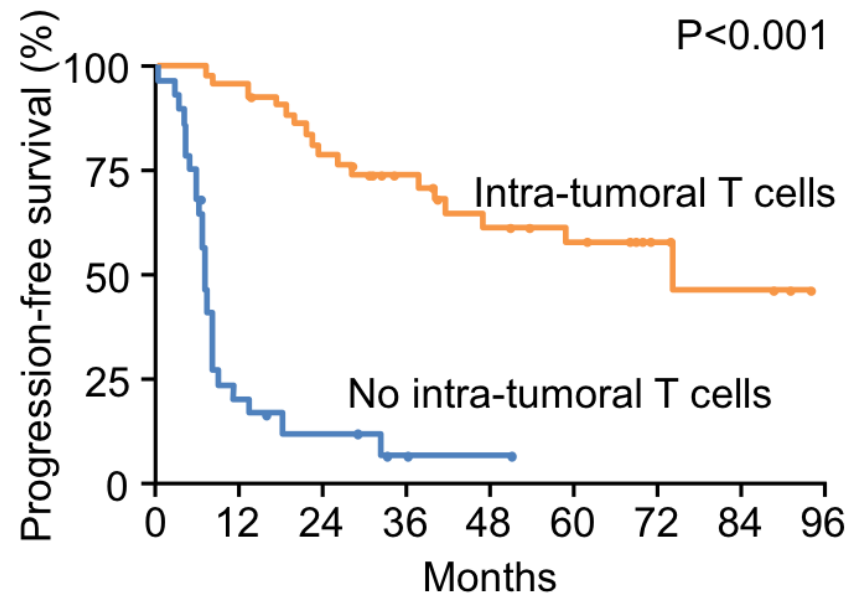


# After CR with chemotherapy, only patients with TILs survive or are in remission long-term

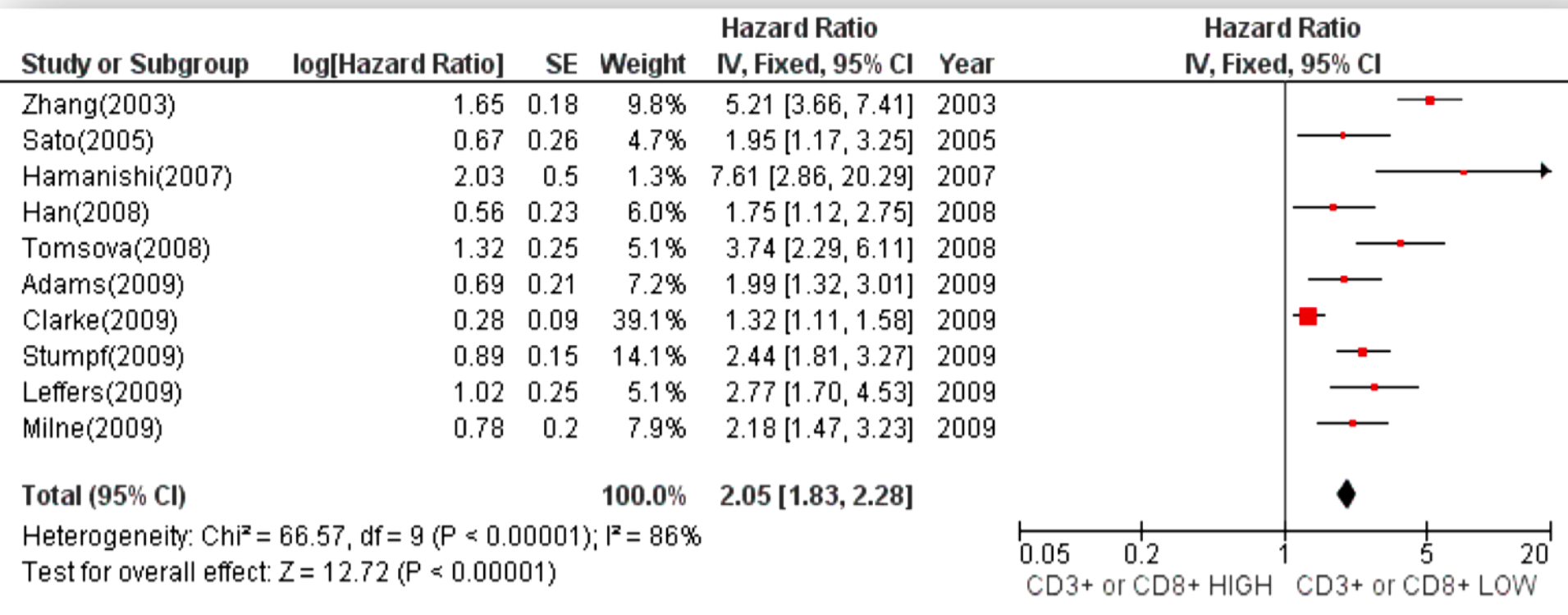
At 96–132 months:  
>60% alive



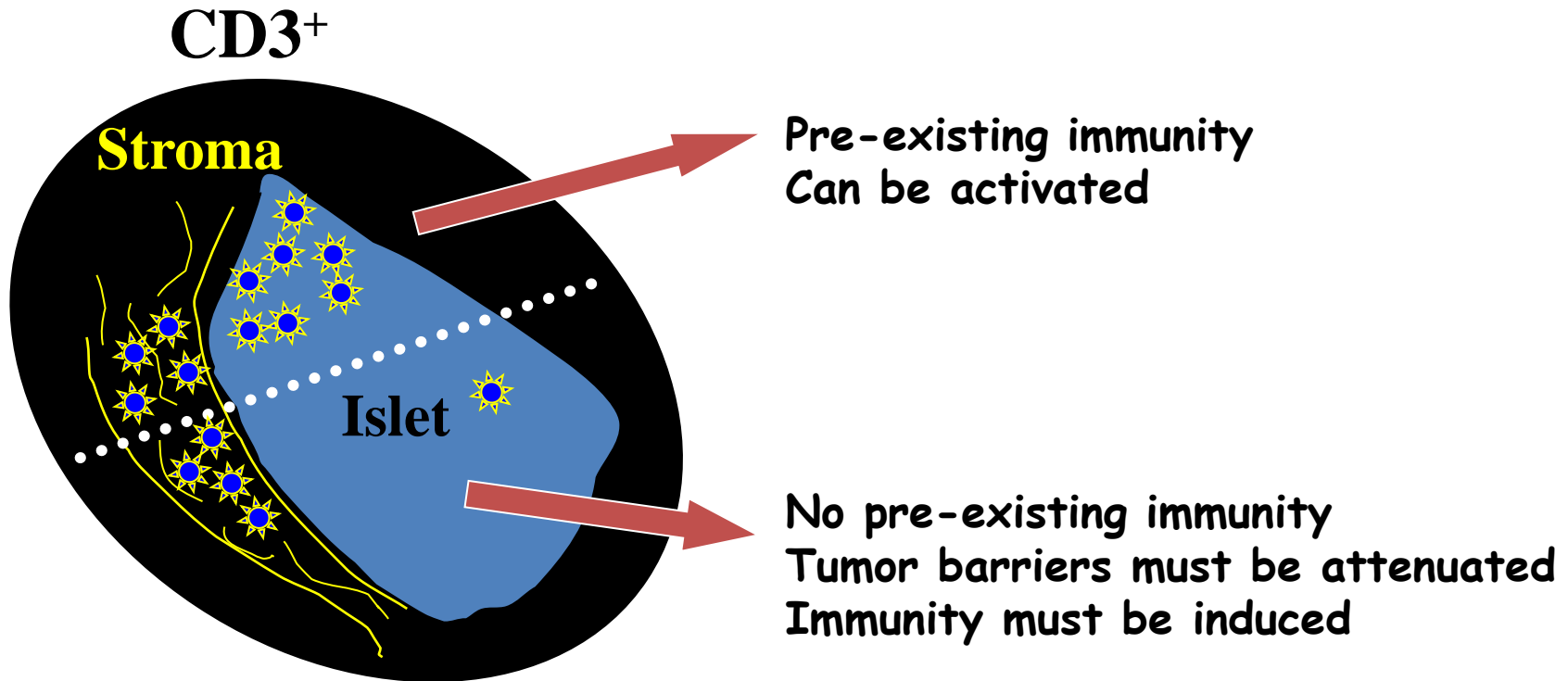
At 96 months:  
50% in remission



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



# Classification of ovarian tumors



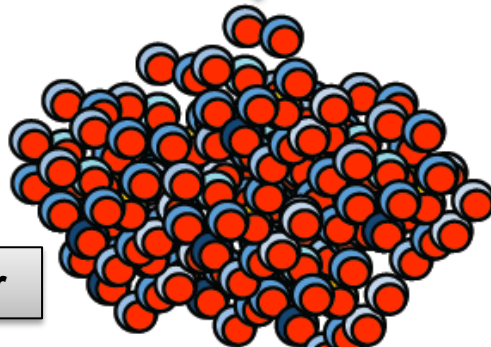
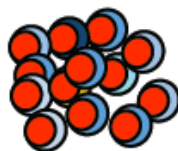
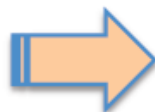
# Cellular Immunotherapy Approaches

1

Tumor

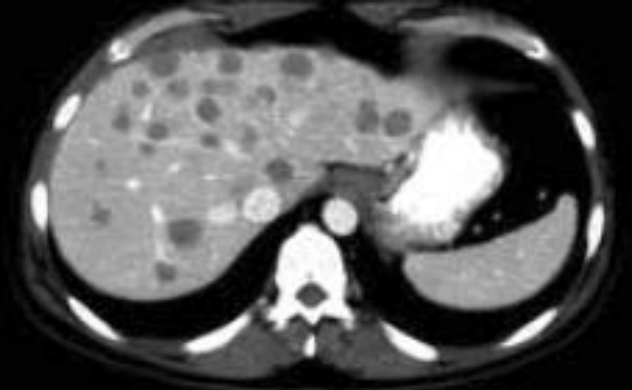


Extract,  
activate and  
expand

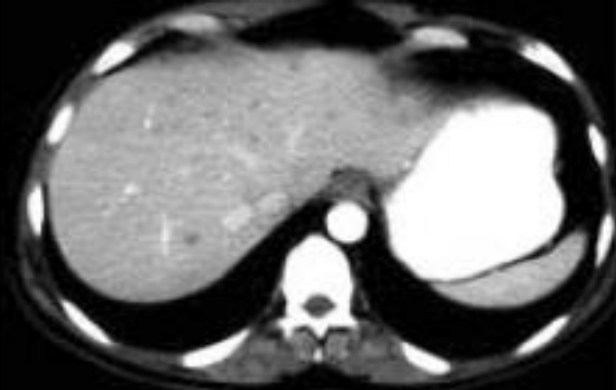


Administer

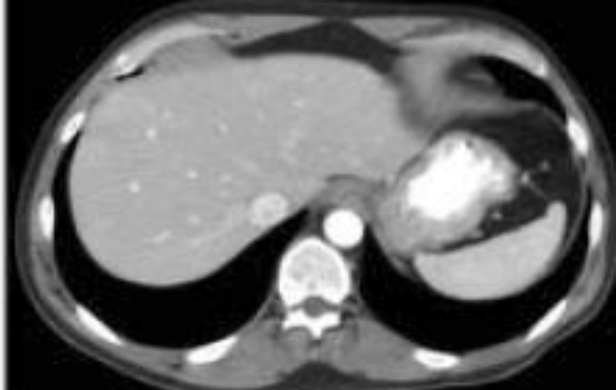




**Day -25**



**Day +34**



**3.2+ Years**

**Pre-Treatment**



**30+ Months**



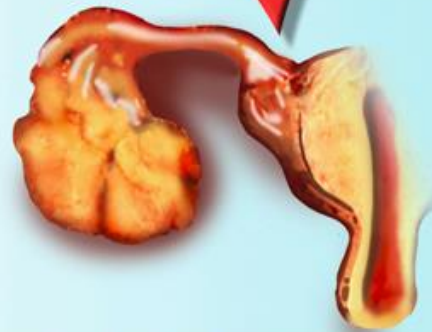


# Trial 3

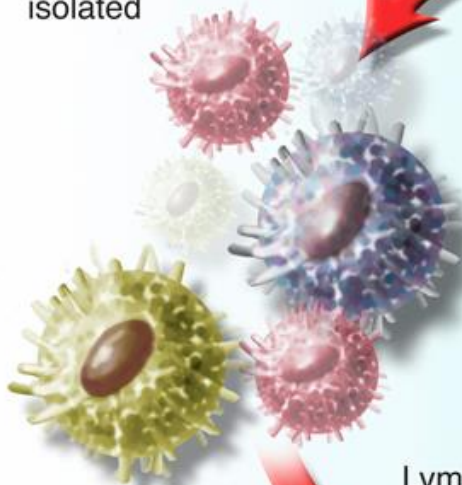
## Extract and Expand TILs



Debulking surgery  
performed

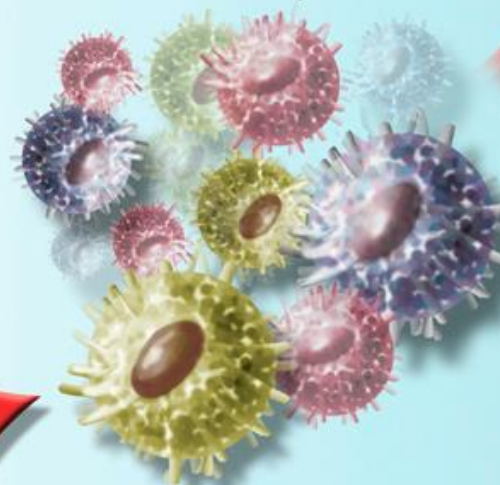


Lymphocytes  
isolated

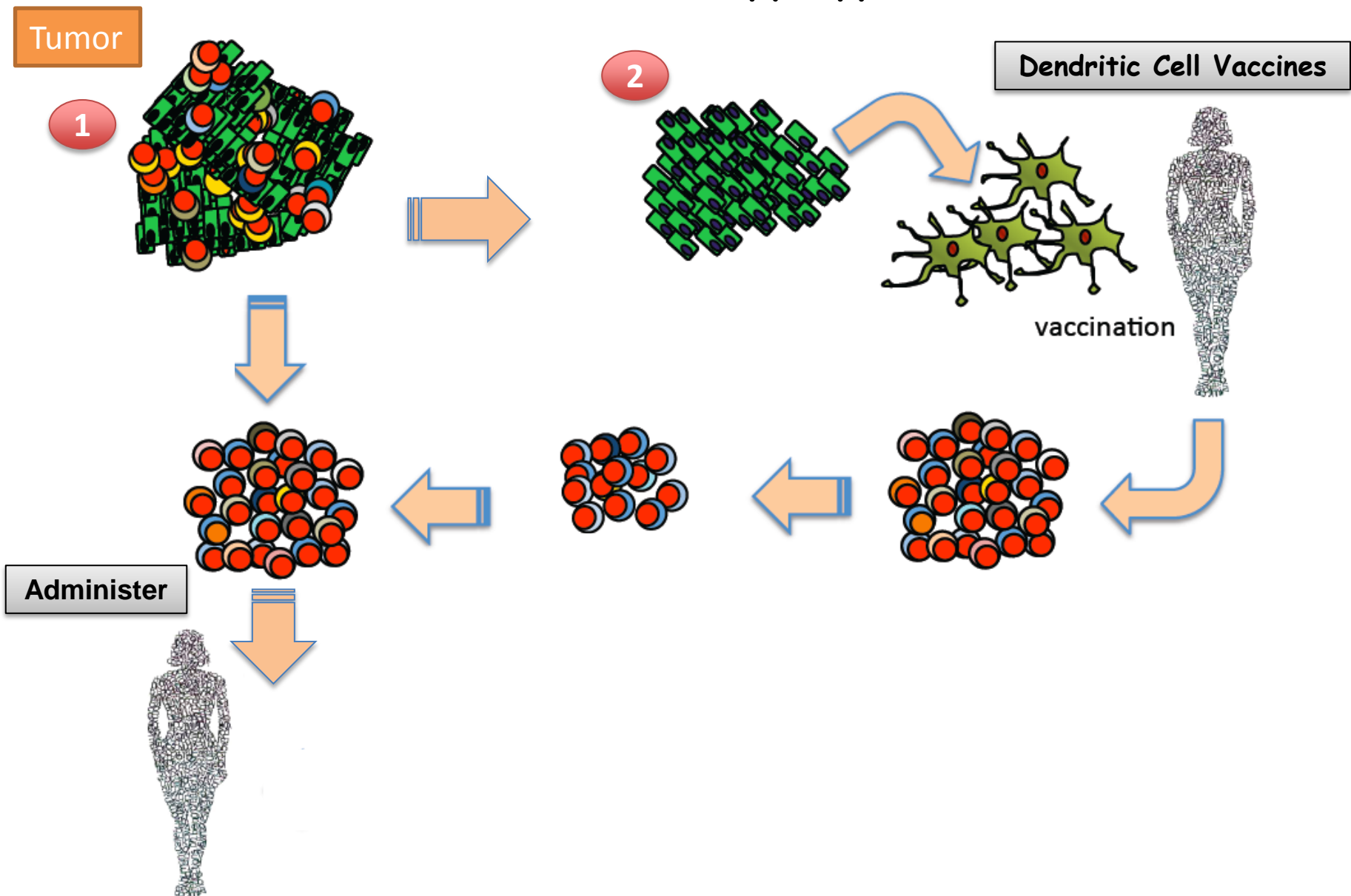


Lymphocytes  
expanded

Tumor infiltrating lymphocytes  
administered into the patient



# Cellular Immunotherapy Approaches



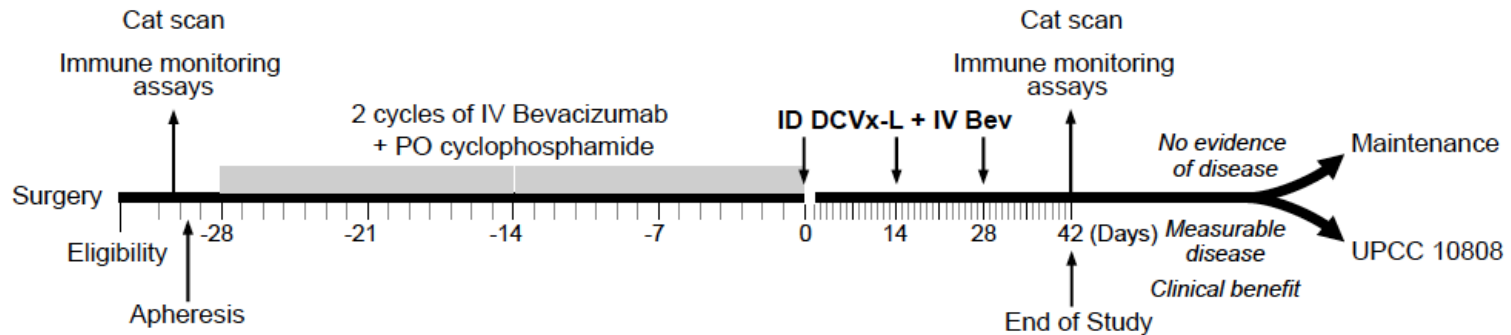
# Whole Tumor Vaccines

## ADVANTAGES

- 1) Target multiple antigens at the same time
- 1) Bypass the limitations of molecularly defined Ag (eg NYESO-1 30%).
- 2) Patients are vaccinated against their own tumor-associated antigens
- 4) Meta-analysis (Neller et al 2008) (3444 patients in 173 trials were examined) Patients with Objective Response:
  - (8.1%): Whole tumor or tumor extracts as antigens
  - (3.6%): Molecularly defined antigens were used
- 5) TCGA DATA: Average of **60 private**, non-synonymous mutations per tumor (Integrated genomic analyses of ovarian carcinoma, *Nature* 2011)

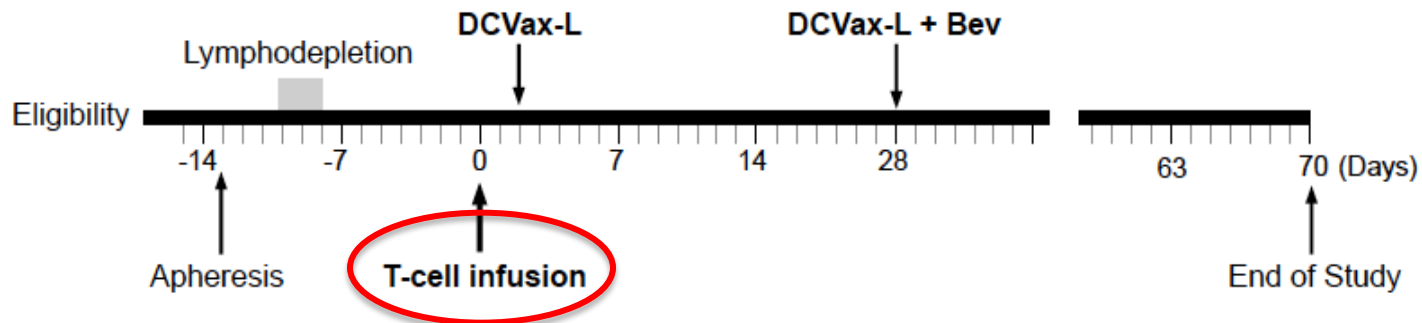
# Phase I Clinical Trial Of Autologous Dendritic Cell Vaccine Loaded With Autologous Tumor Cell Lysate For Recurrent Ovarian or Primary Peritoneal Cancer

## A. UPCC 11807



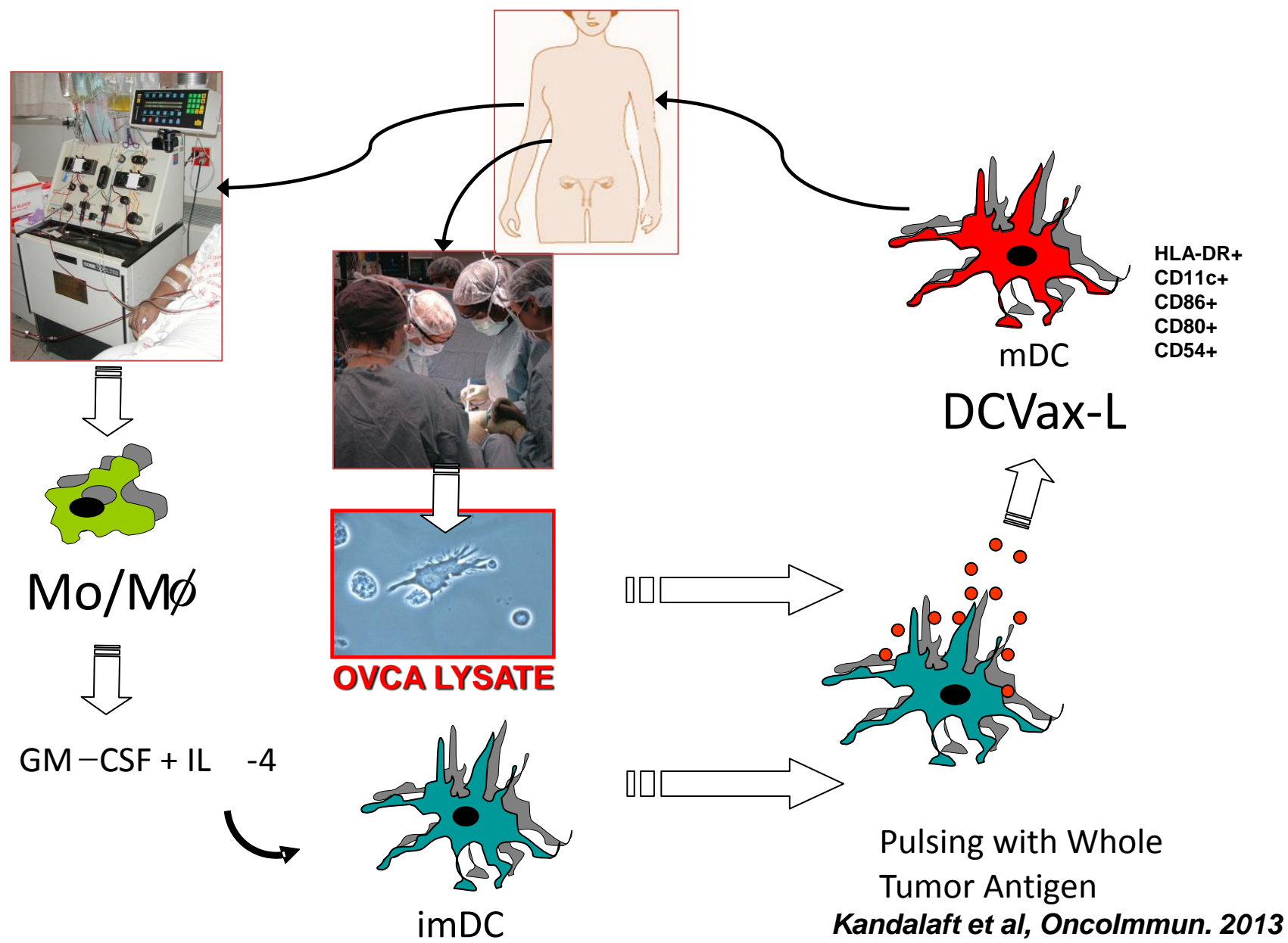
## Adoptive Transfer of Vaccine-Primed CD3/CD28-Costimulated Autologous T-cells Combined with Vaccine Boost

## B. UPCC 10808



Lymphodepletion: intravenous cyclophosphamide (Cy, 300 mg/m<sup>2</sup>/day) and fludarabine (Flu, 30 mg/m<sup>2</sup>/day) for 3 days

UPCC-11807:Study Schema





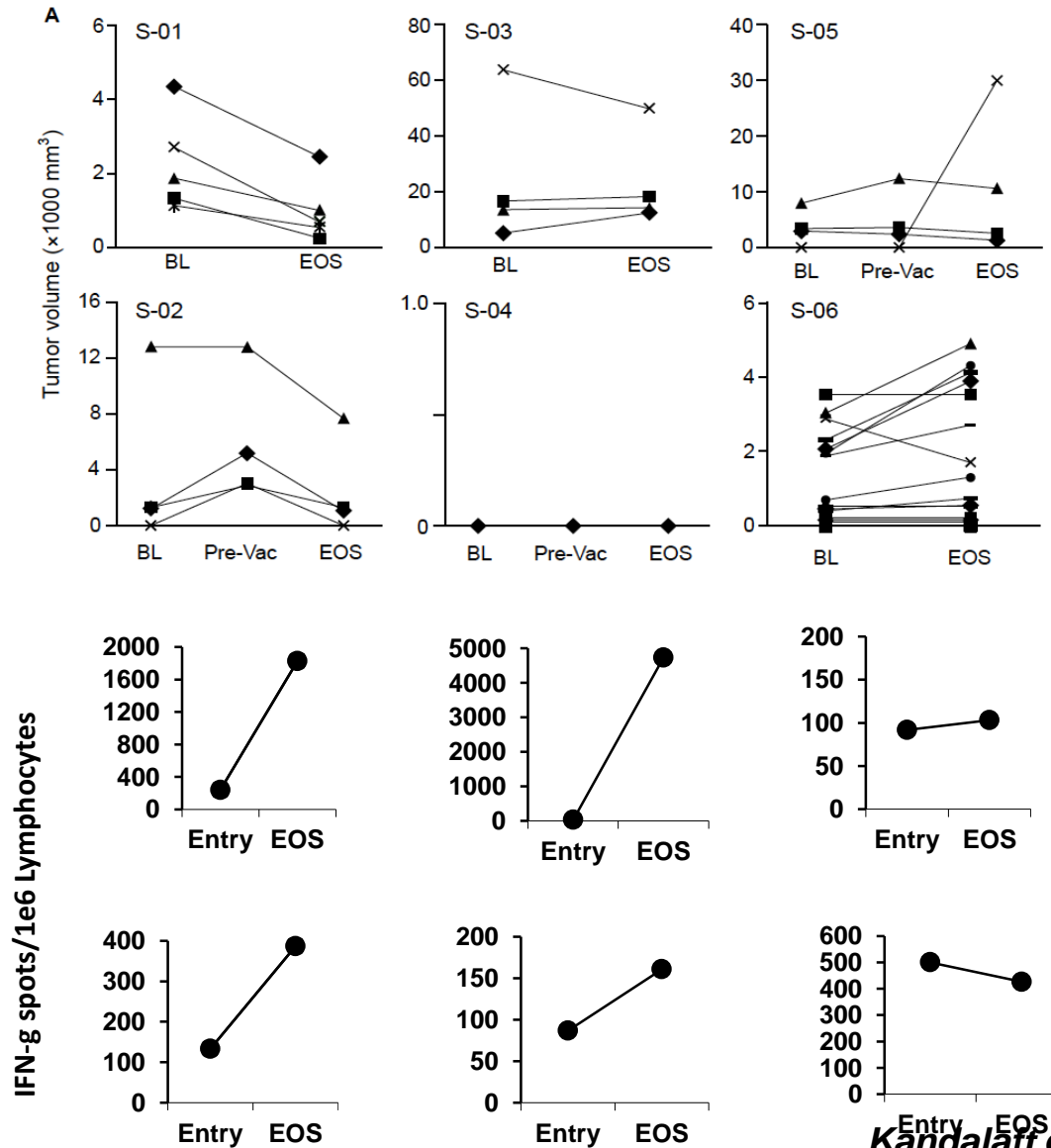
# Clinical Results of UPCC-11807

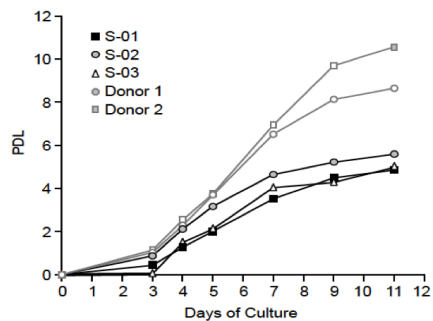
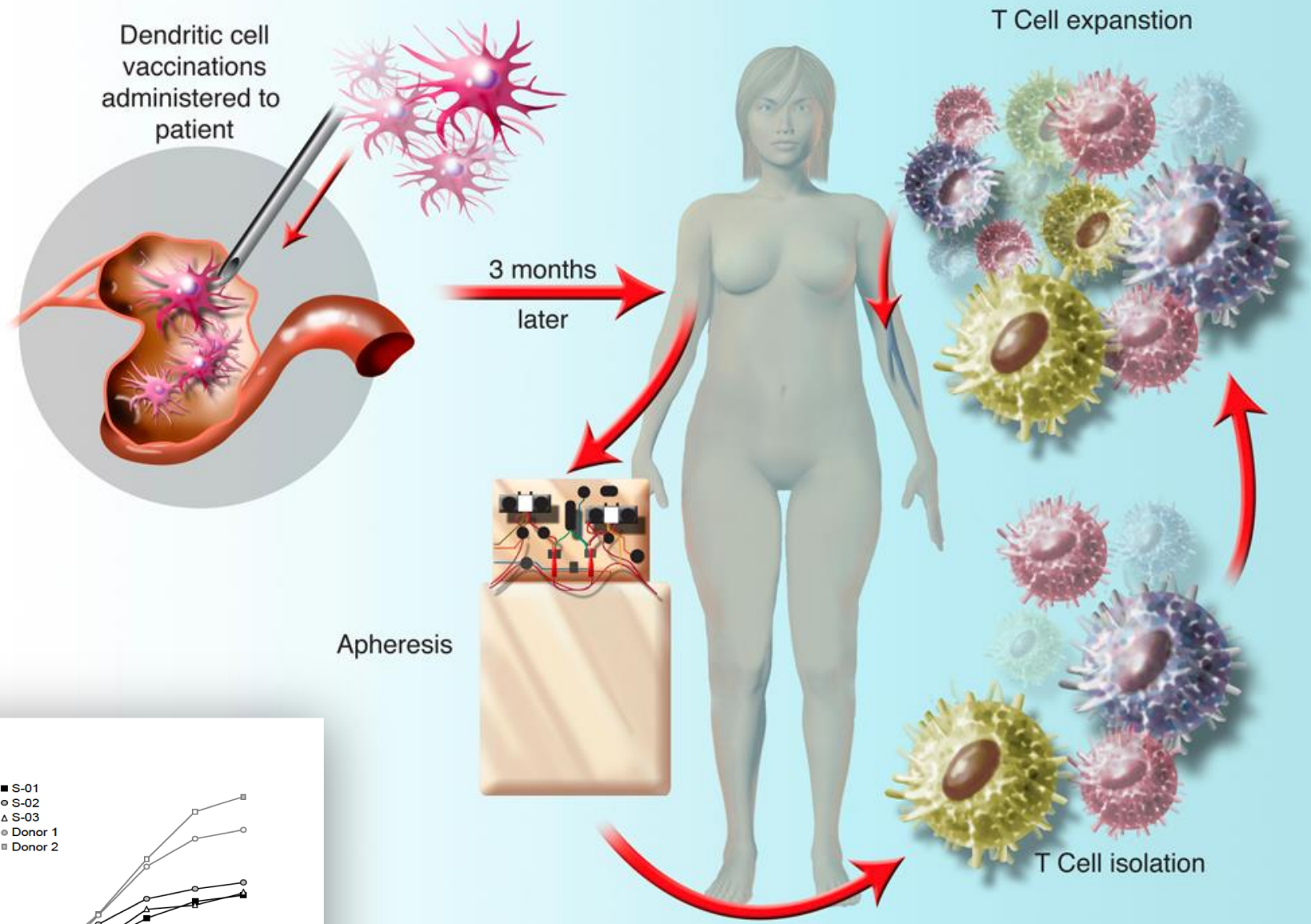
RESPONSE:

2 PR

2 SD

2 PD





## 1. Leukapheresis



## 2. Elutriation



## 3. Wave Perfusion / Expansion



## 5. Resuspension



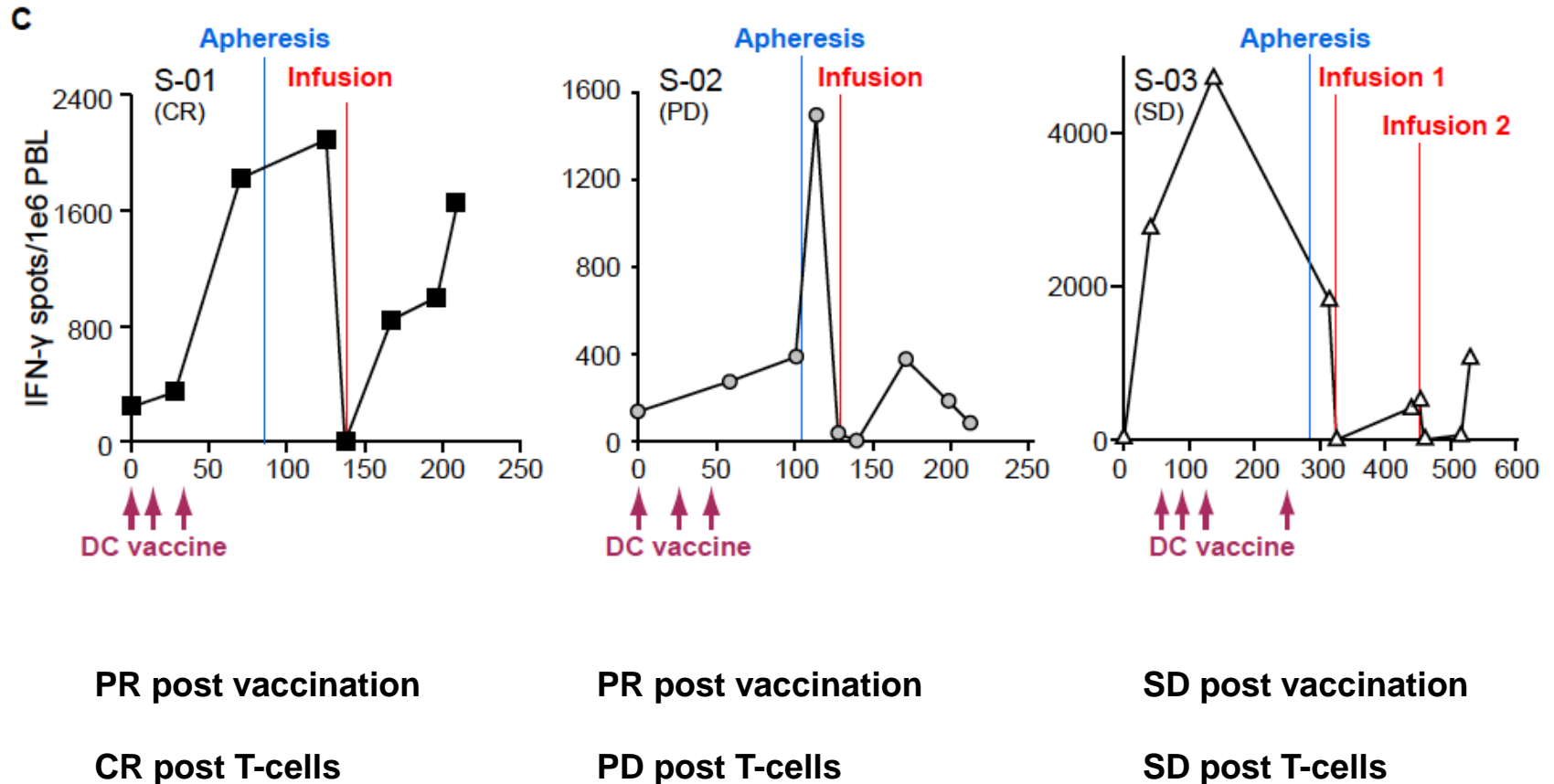
## 4. Bead Removal



## 6. Infusion



# Patients' Tumor Reactive T Cells Correlate with Clinical Outcome





# OPTIMIZING THE DENDRITIC CELL PLATFORM

OPEN ACCESS Freely available online



## Day-4 Myeloid Dendritic Cells Pulsed with Whole Tumor Lysate Are Highly Immunogenic and Elicit Potent Anti-Tumor Responses

Chiang *et al.* *Journal of Translational Medicine* 2011, **9**:198  
<http://www.translational-medicine.com/content/9/1/198>



JOURNAL OF  
TRANSLATIONAL MEDICINE

RESEARCH

Open Access

Optimizing parameters for clinical-scale production of high IL-12 secreting dendritic cells pulsed with oxidized whole tumor cell lysate

COMMENTARY

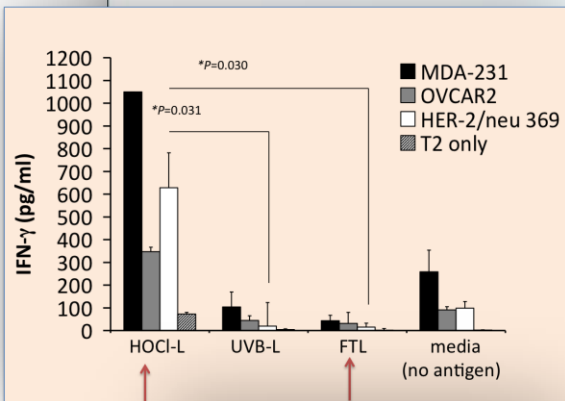
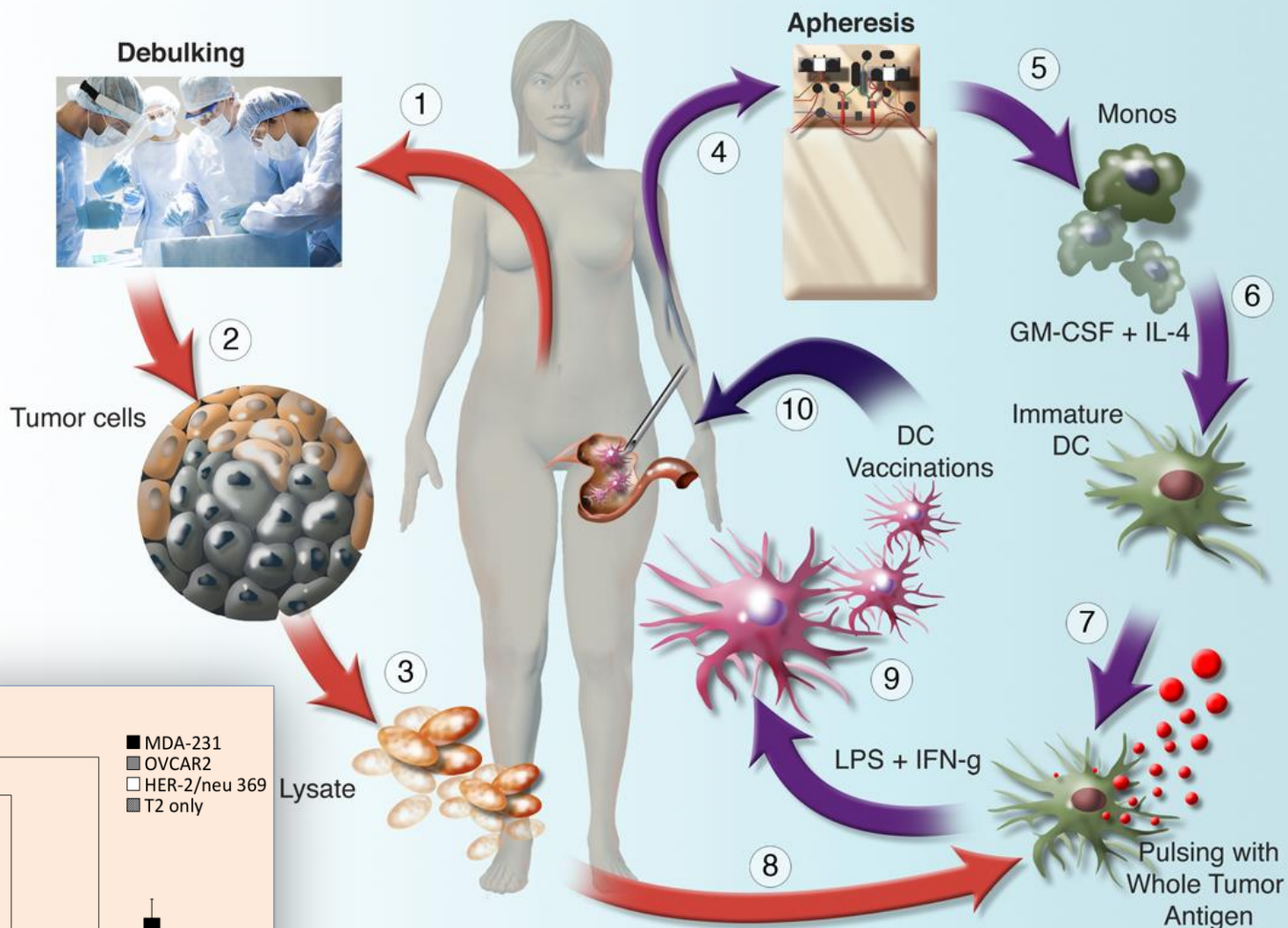
Open Access

A Phase I vaccine trial using dendritic cells pulsed with autologous oxidized lysate for recurrent ovarian cancer

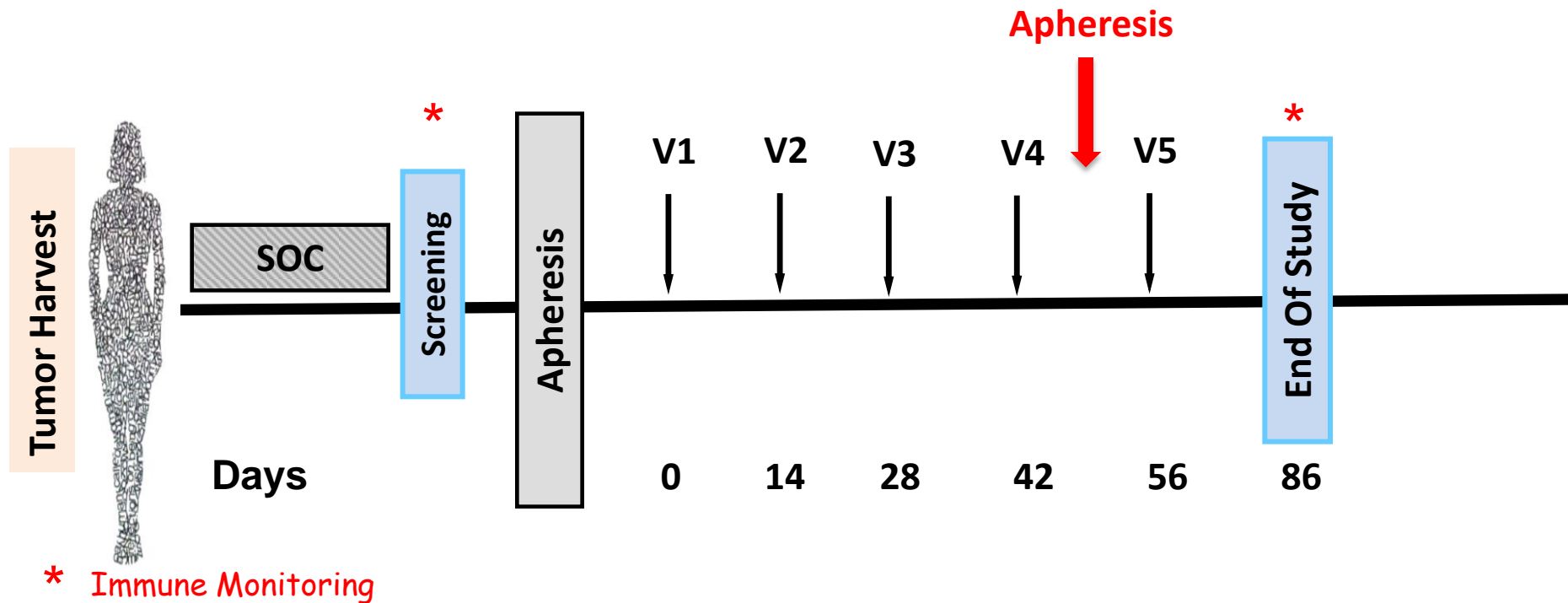
Lana E Kandalaft<sup>1\*</sup>, Cheryl L Chiang<sup>1</sup>, Janos Tanyi<sup>1</sup>, Greg Motz<sup>1</sup>, Klara Balint<sup>1</sup>, Rosemarie Mick<sup>2</sup> and George Coukos<sup>1</sup>



# Whole Tumor Antigen Dendritic Cell Vaccine Study



# A PILOT CLINICAL TRIAL OF DENDRITIC CELL VACCINE LOADED WITH AUTOLOGOUS TUMOR FOR RECURRENT OVARIAN, PRIMARY PERITONEAL OR FALLOPIAN TUBE CANCER



Cohort 1: OC-DC vaccine alone q 2 weeks

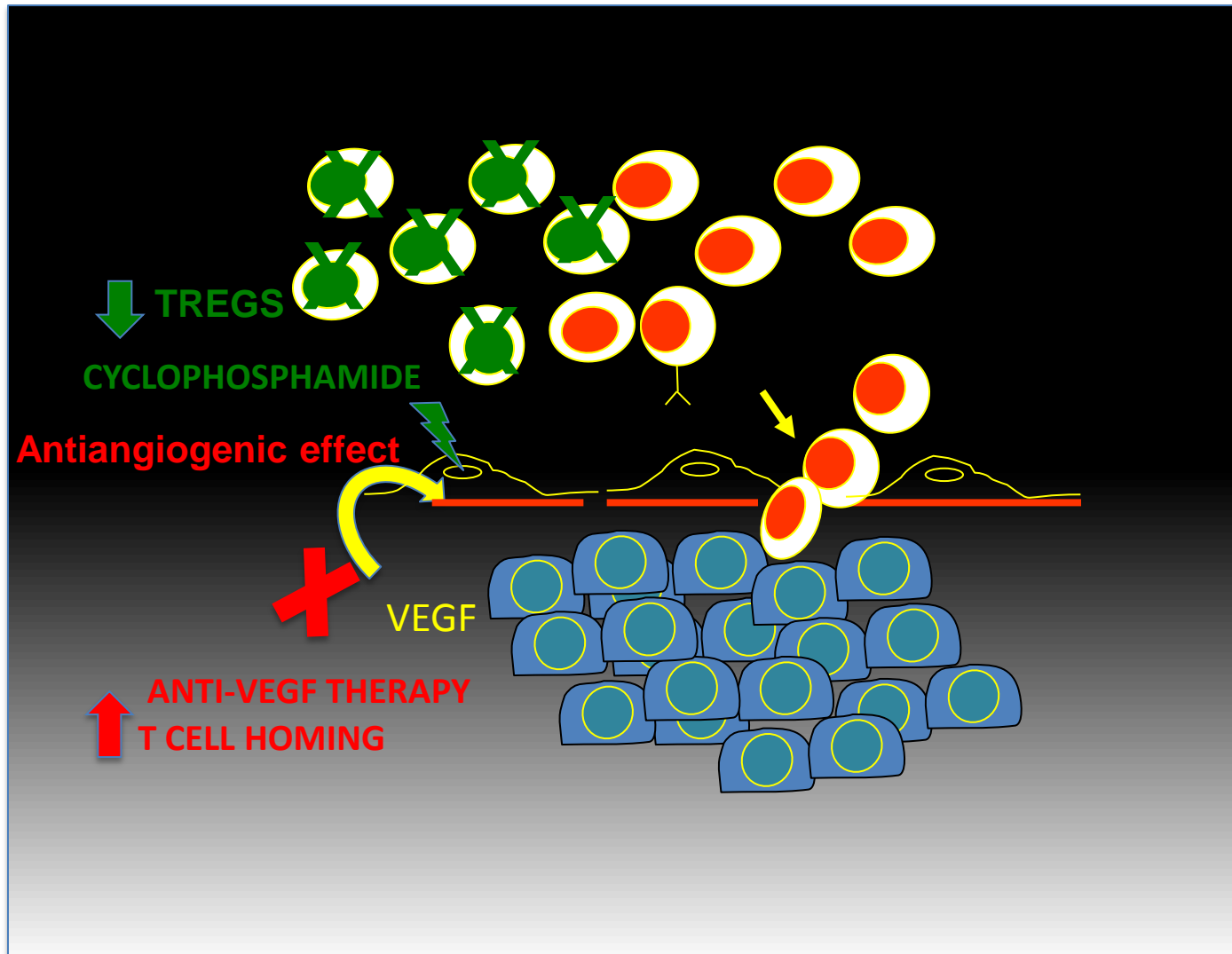
Cohort 2: OC-DC vaccine + Bevacizumab (10 mg/kg) q 2 weeks

Cohort 3: OC-DC vaccine + Bevacizumab (15 mg/kg) + Cyclophosphamide (200 mg/m<sup>2</sup>) q 3 weeks

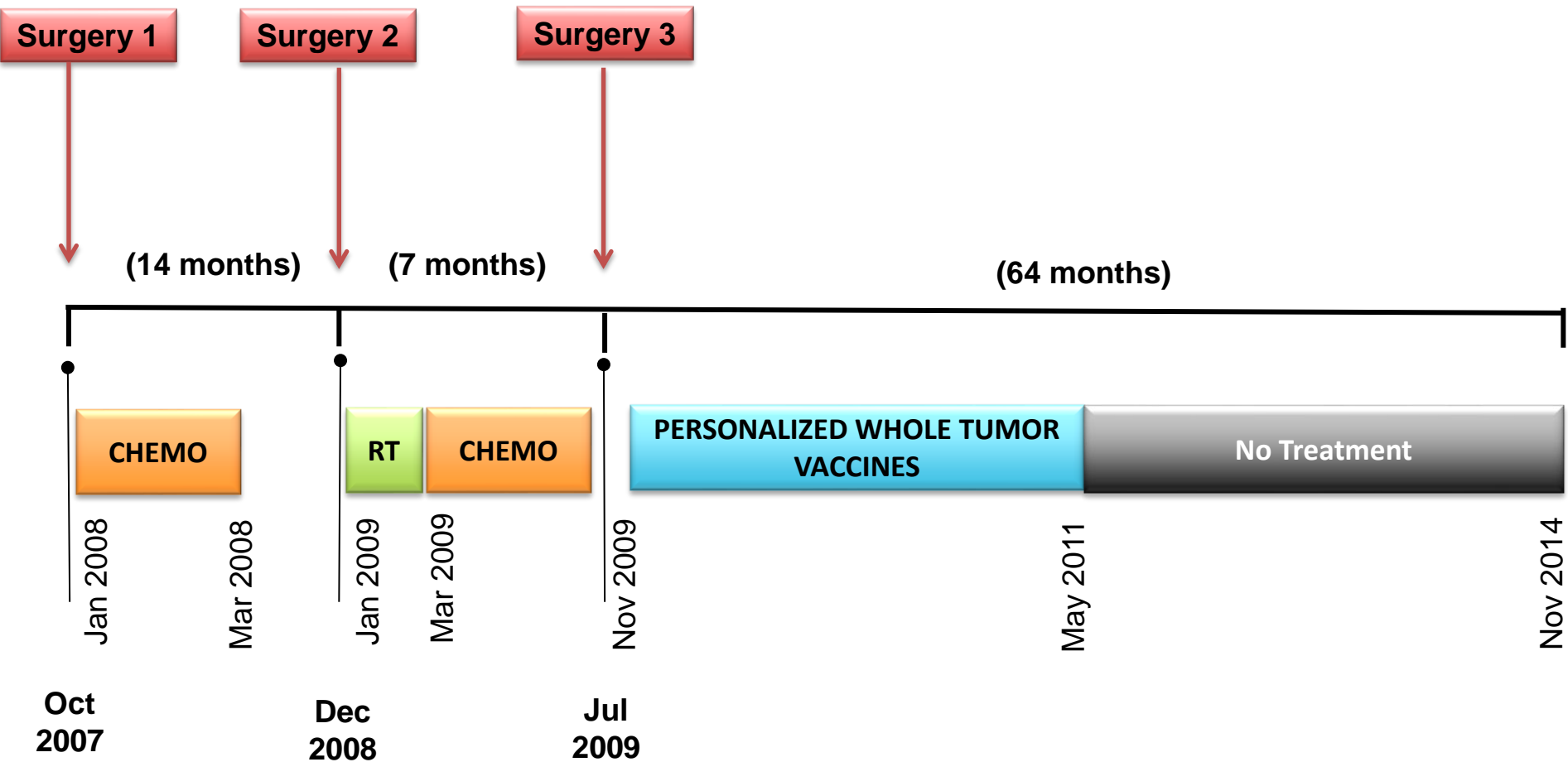
Cohort 4: OC-DC vaccine + Bevacizumab (15 mg/kg) + Cyclophosphamide (200 mg/m<sup>2</sup>) q 3 weeks + Daily 325 mg Enteric Coated Aspirin (currently enrolling)

Kandalaft et al, JTM 2013

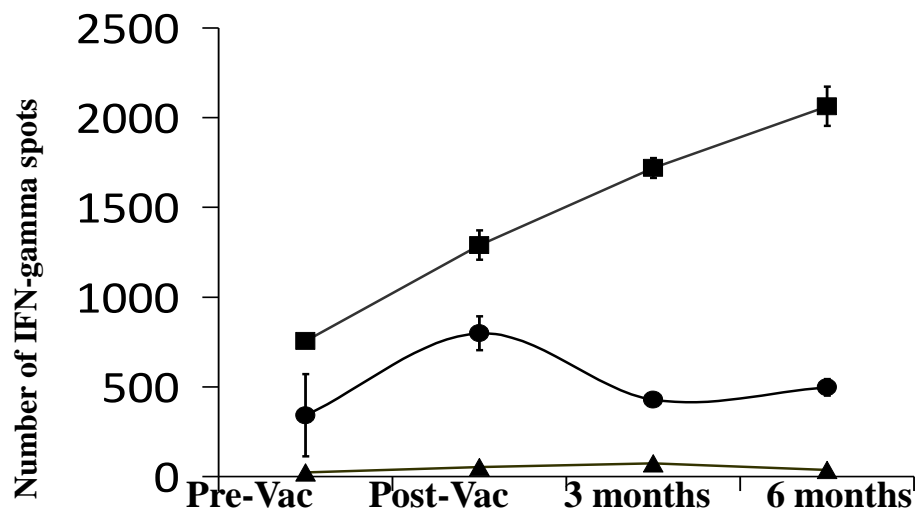
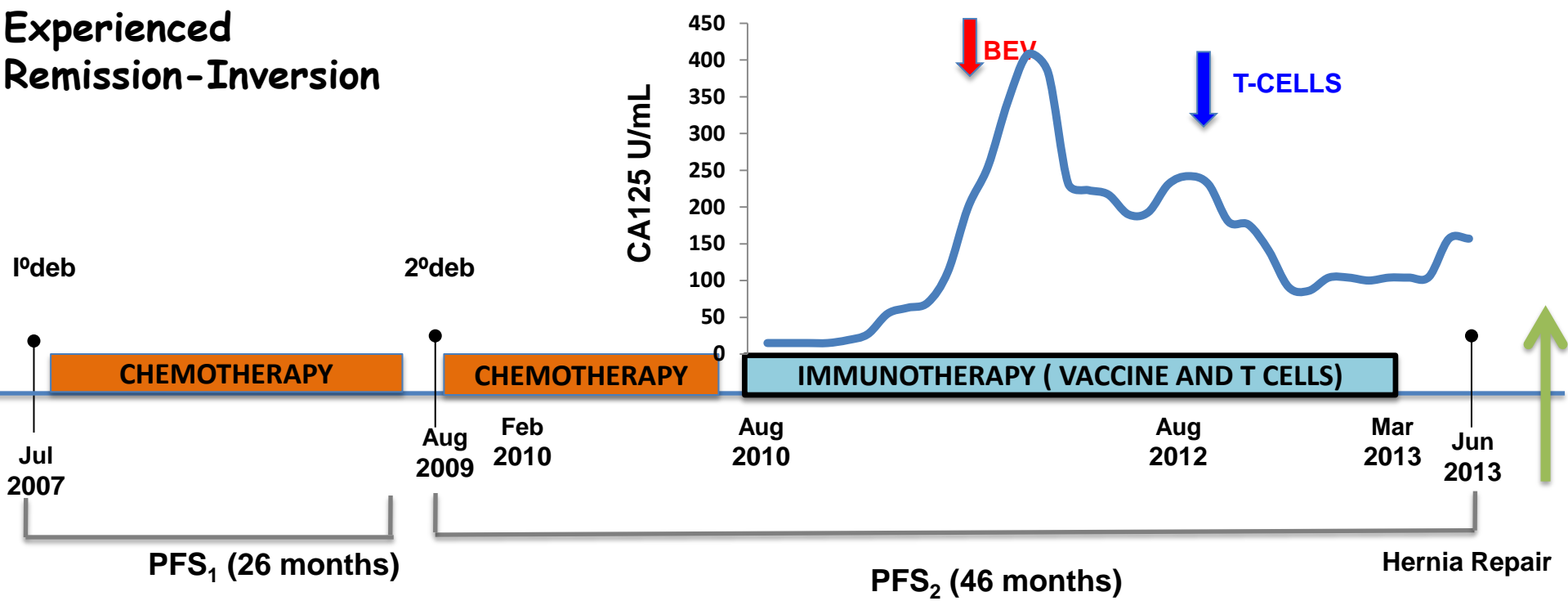
# Rationale of combining antiangiogenesis therapy and metronomic chemotherapy on the tumor microenvironment



# 19809-105 A Patient who has been cured after receiving vaccine



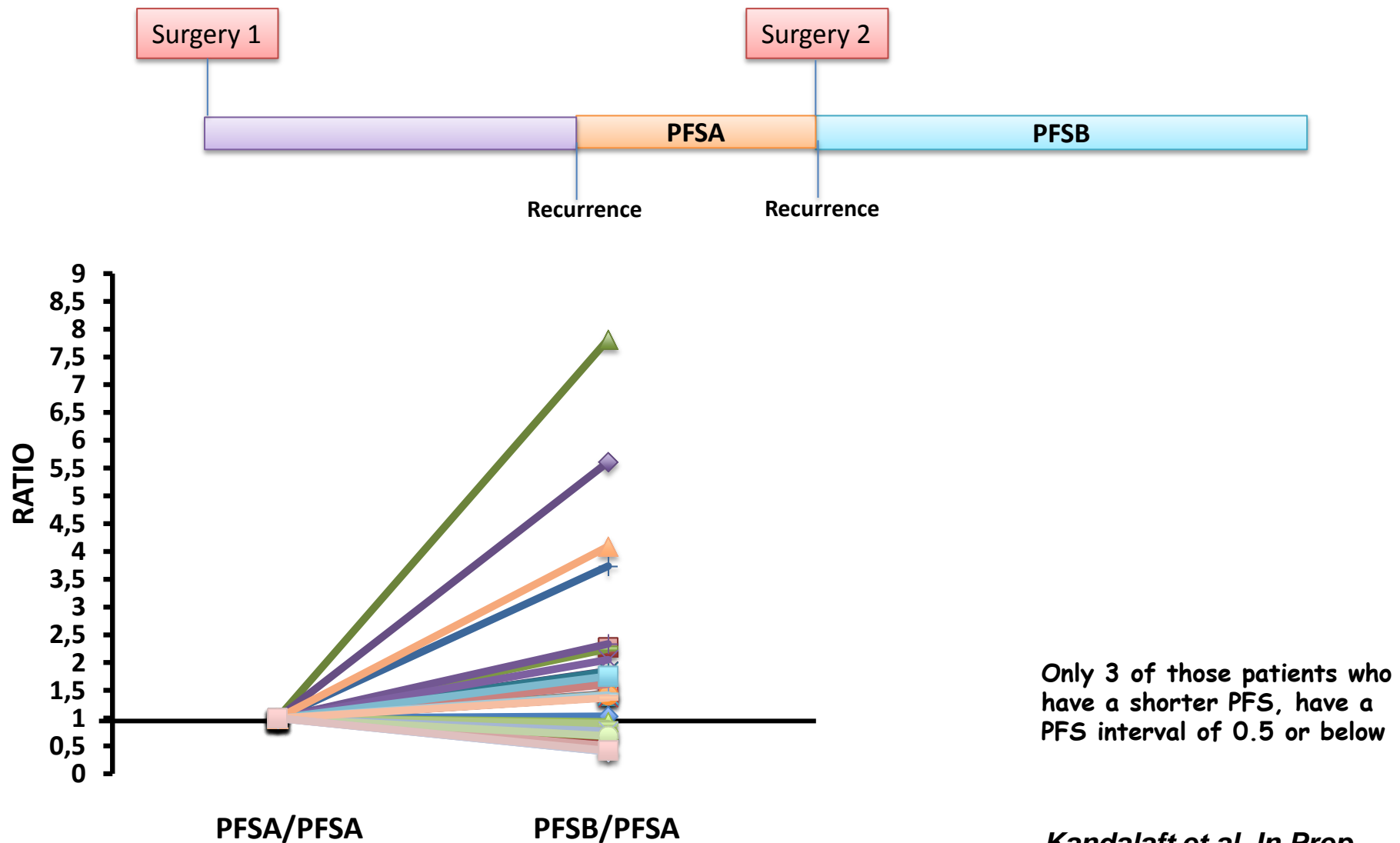
# 19809-203 Experienced Remission-Inversion



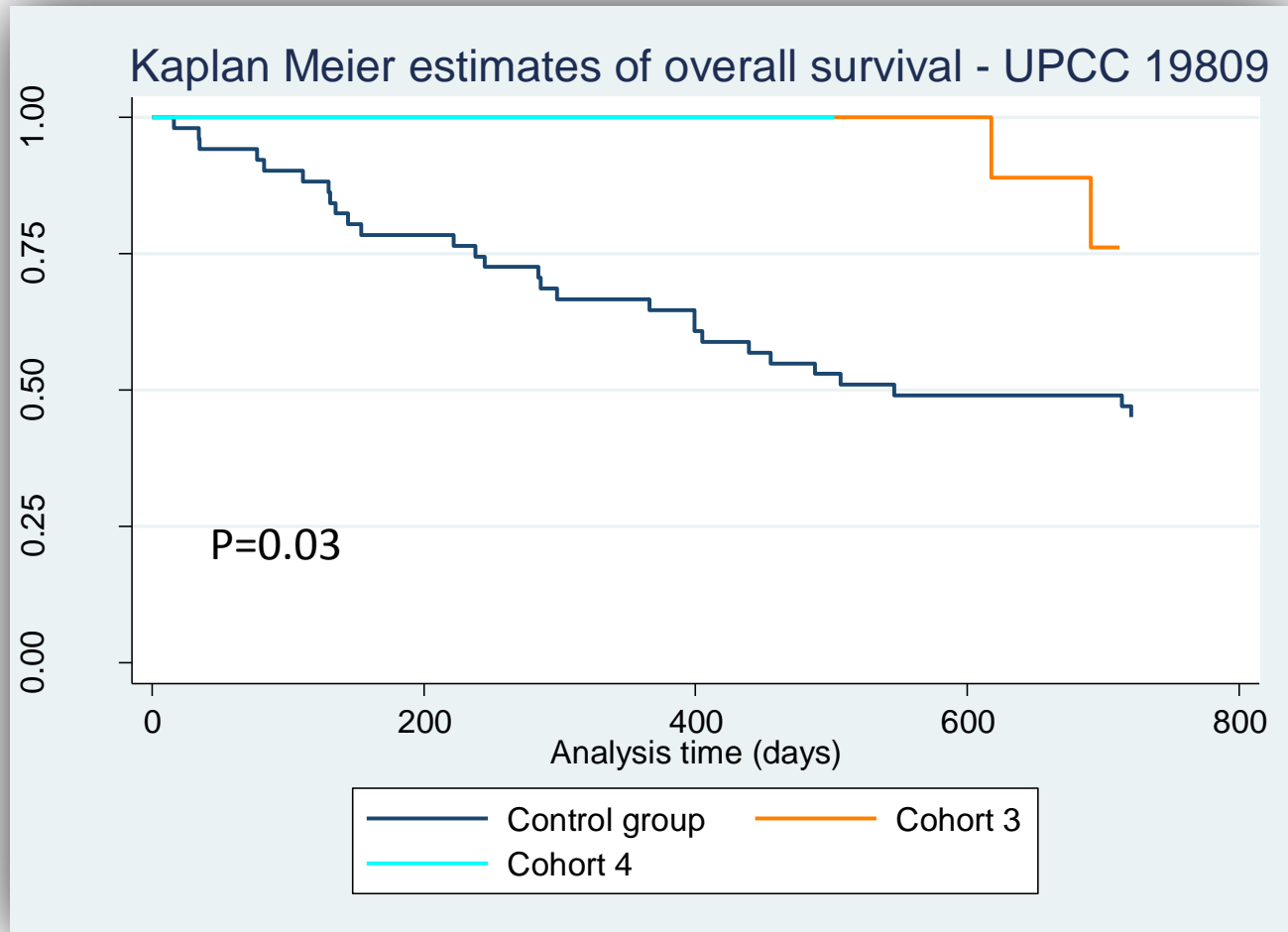
Aug 2013



# 71% OF PATIENTS HAVE A PROLONGED PROGRESSION FREE SURVIVAL ON IMMUNOTHERAPY



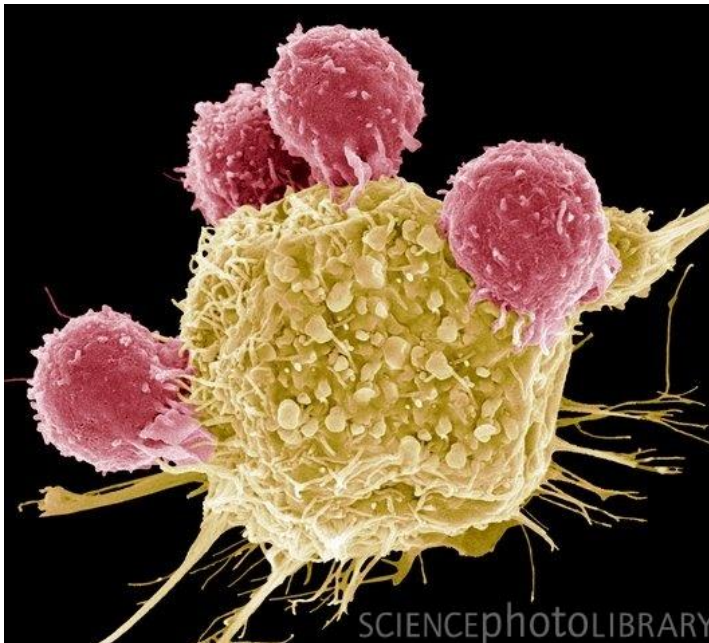
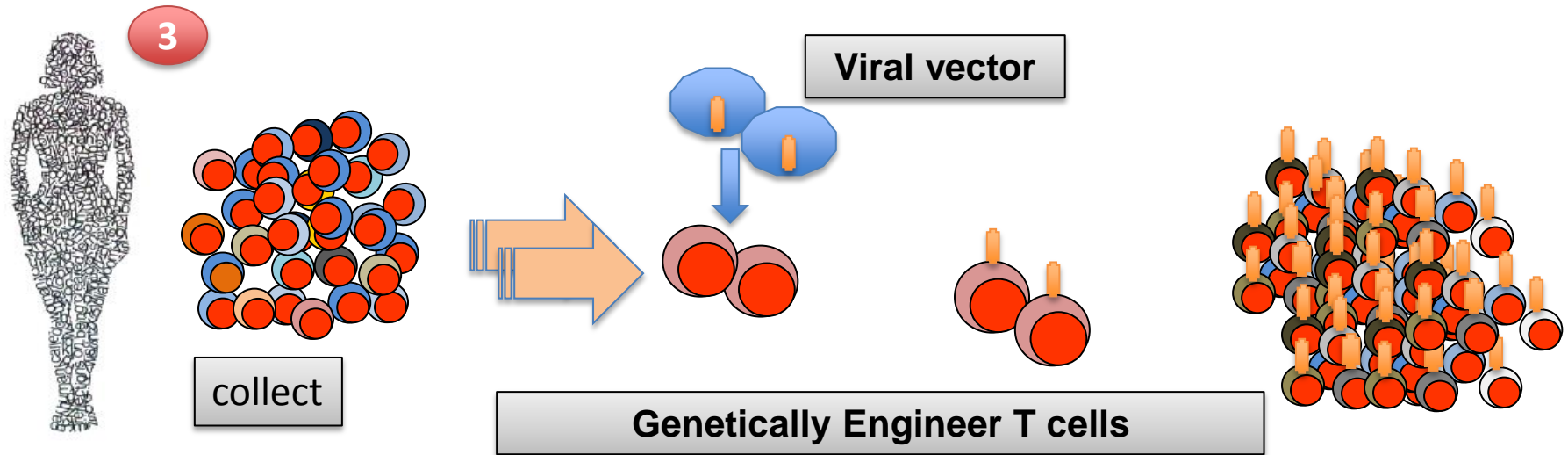
# Clinical Results: Comparison with a Control Group



# Clinical Results

Parameters	Chemotherapy + Vaccine	Chemotherapy
Progression Free Survival at 6 months	75%	45%
Time to progression	15 months	6 months
1-year survival	100%	60%
2-year survival	75%	47%

# Cellular Immunotherapy Approaches

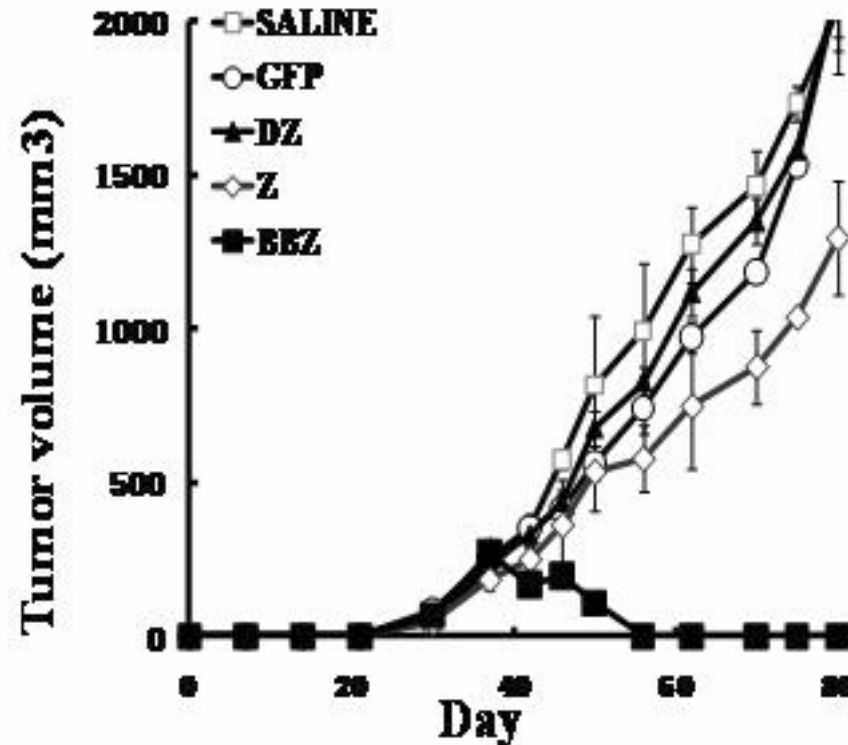
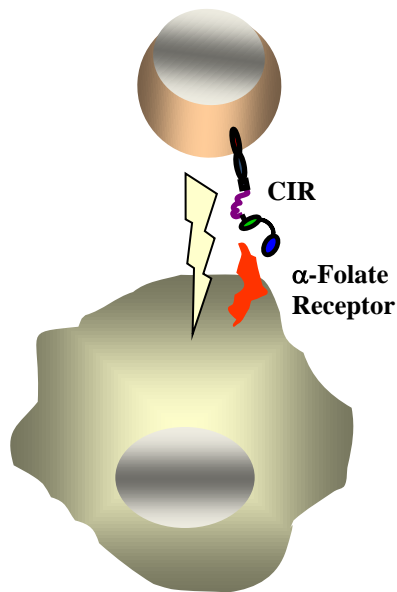


**A T-cell attacking a tumor**

# CAR Based Immunotherapy



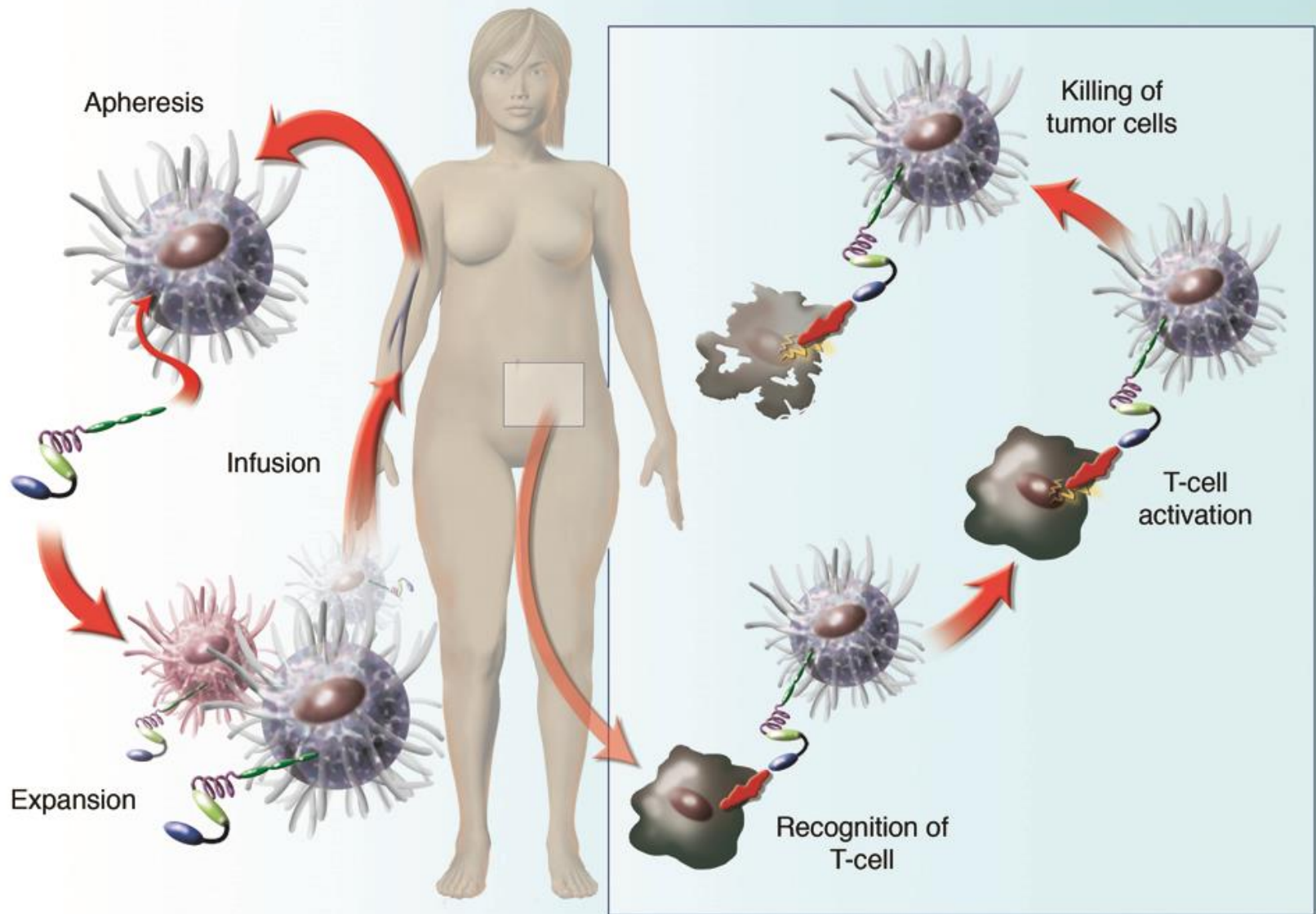
Treatment of large, established human ovarian cancer using Folate Receptor alpha CAR gene therapy



Dan Powell, PhD, Cancer Res 2011



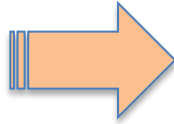
# Engineering T cells Against aFR Tumors



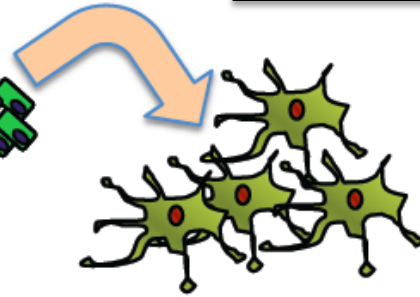
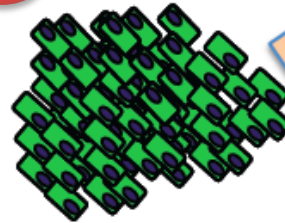
# Cellular Immunotherapy Approaches

1

Tumor



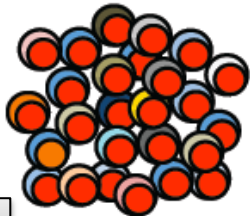
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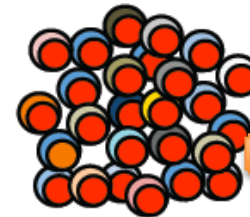
Dendritic Cell Vaccines

vaccination

Extract,  
activate and  
expand

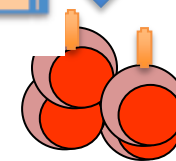


Administer

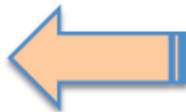
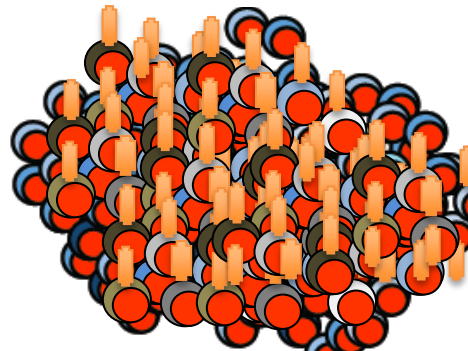
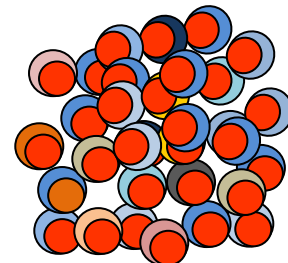


3

Genetically Engineer T cells



Viral vector



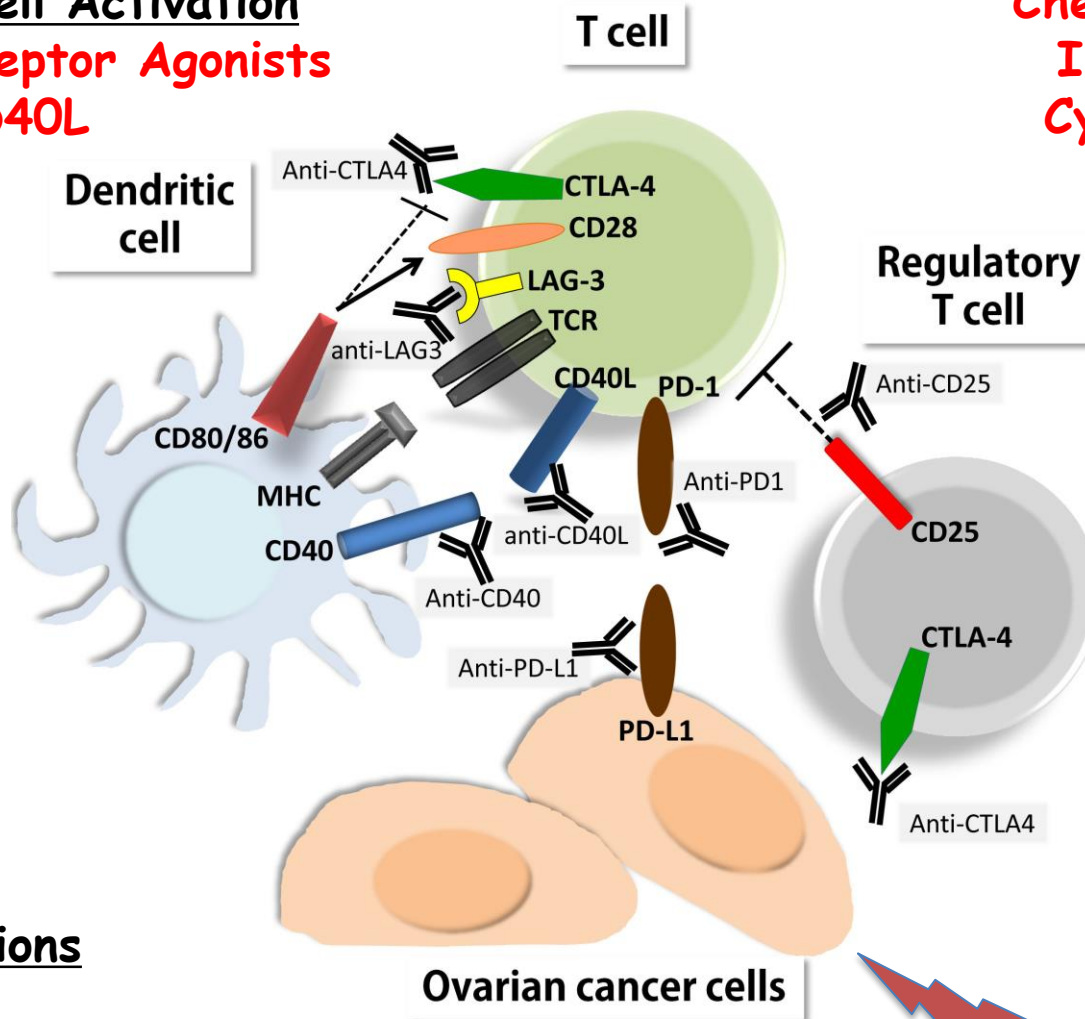
# Drug-based Immunotherapy for Ovarian cancer

## Dendritic Cell Activation

**Toll-like Receptor Agonists**  
**CD40L**

## T cell Activation

**Checkpoint Blockade**  
**IDO-1 Blockade**  
**Cytokine Therapy**

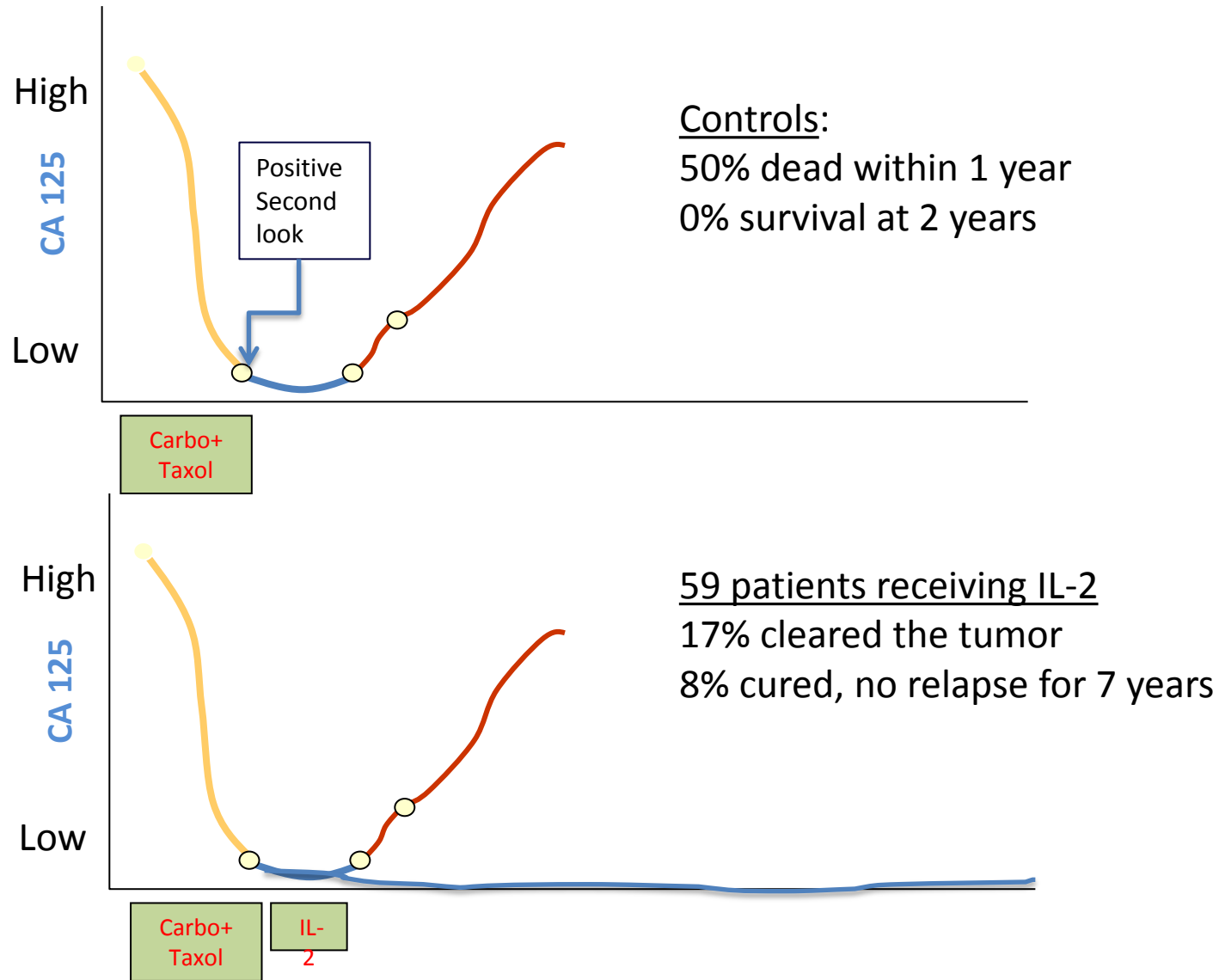


## Combinations

**Immunogenic Cell Death**

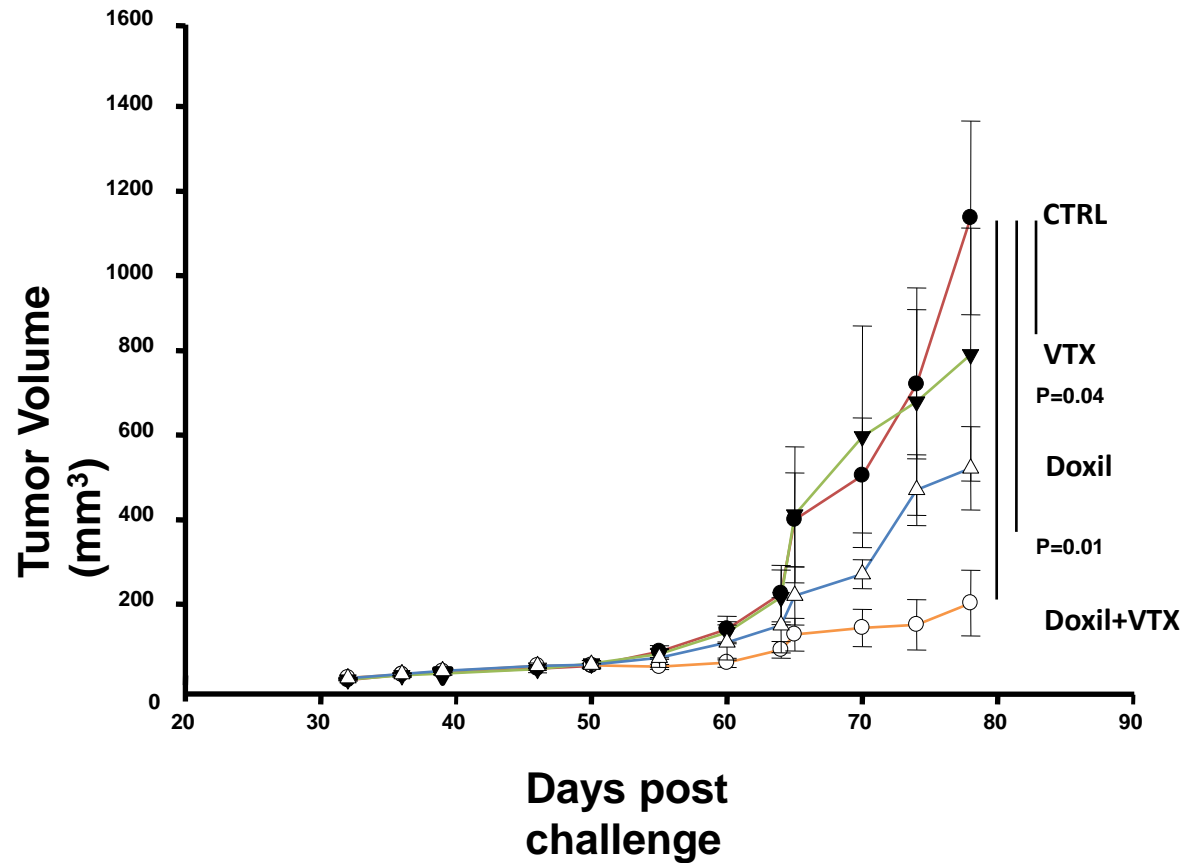
**Immunogenic chemotherapy**  
**Radiation**

## Chemotherapy Resistant Ovarian Cancer Cured by IL-2



# DC Activation and Immunogenic Cell Death

VTX-2337 (A TLR8 agonist) in combination with Doxil Abrogate Tumors in mice



(G. Coukos and A. Facciabene)



# GOG-9925: VTX-2337 + PLD

## Preliminary Data\*

VTX-2337 Dose	No. of Cycles	Best Response
2.5 mg/m <sup>2</sup>	2	Stable Disease
2.5 mg/m <sup>2</sup>	2	Stable Disease
2.5 mg/m <sup>2</sup>	6	Complete Response*
3.0 mg/m <sup>2</sup>	4	Stable Disease
3.0 mg/m <sup>2</sup>	6	Complete Response*
3.0 mg/m <sup>2</sup>	2	Progressive Disease
3.5 mg/m <sup>2</sup>	1	Progressive Disease
3.5 mg/m <sup>2</sup>	3	Stable Disease
3.5 mg/m <sup>2</sup>	5	Stable Disease
3.5 mg/m <sup>2</sup>	4	Stable Disease
3.5 mg/m <sup>2</sup>	8	Stable Disease
3.5 mg/m <sup>2</sup>	2	TBD

\* presented by Monk et al. at ASCO 2013

# Phase 2 Ovarian Study: VTX-2337 + PLD (GOG-3003)

## Phase 2 Randomized Placebo-Controlled Trial

Population	Study Design	Objectives
Patients with platinum resistant ovarian cancer n=300	28-day dose cycle: PLD (40 mg/m <sup>2</sup> ): Day 1 VTX-2337 (3.0 mg/m <sup>2</sup> ): Day 3, 10*, and 17*  *Starting with Cycle 5, dosing with VTX-2337 is on Day 3 <u>only</u>  Repeat cycles until confirmed disease progression  Tumor assessment starting at week 12 and Q8 weeks thereafter	Primary: Overall Survival  Secondary: PFS (irRECIST), tolerability  Other: Response rate, DCR, biomarkers (including TruCulture, Immune Score), TLR8 SNPs

**A Phase 1/2 Study of Chemo-immunotherapy with Toll-like Receptor 8 Agonist  
Motolimod (VTX-2337) and anti-PD-L1 Antibody MEDI4736 in Subjects with Ovarian  
Cancer After Failure of Platinum-Based Chemotherapy .**

**Sponsor: Ludwig Institute for Cancer Research, New York, NY**

**PI : George Coukos**

**Multisite clinical trial run in The US and in Lausanne**

**George Coukos**

Clinical Team

Janos Tanyi

Sureya Sufian

Vijaya Dandamudi

Kathleen Steacker

Jessica Marchesi

Dina Sharhan

Klara Balint

Daniel Schullary

Andrew Best

Gabor Kari

Qunrui Ye



**Perelman**  
School of Medicine  
UNIVERSITY of PENNSYLVANIA

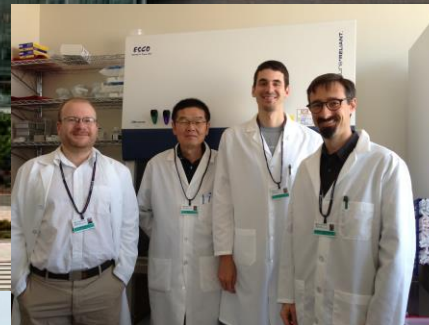
Laboratory

**Cheryl Chiang**

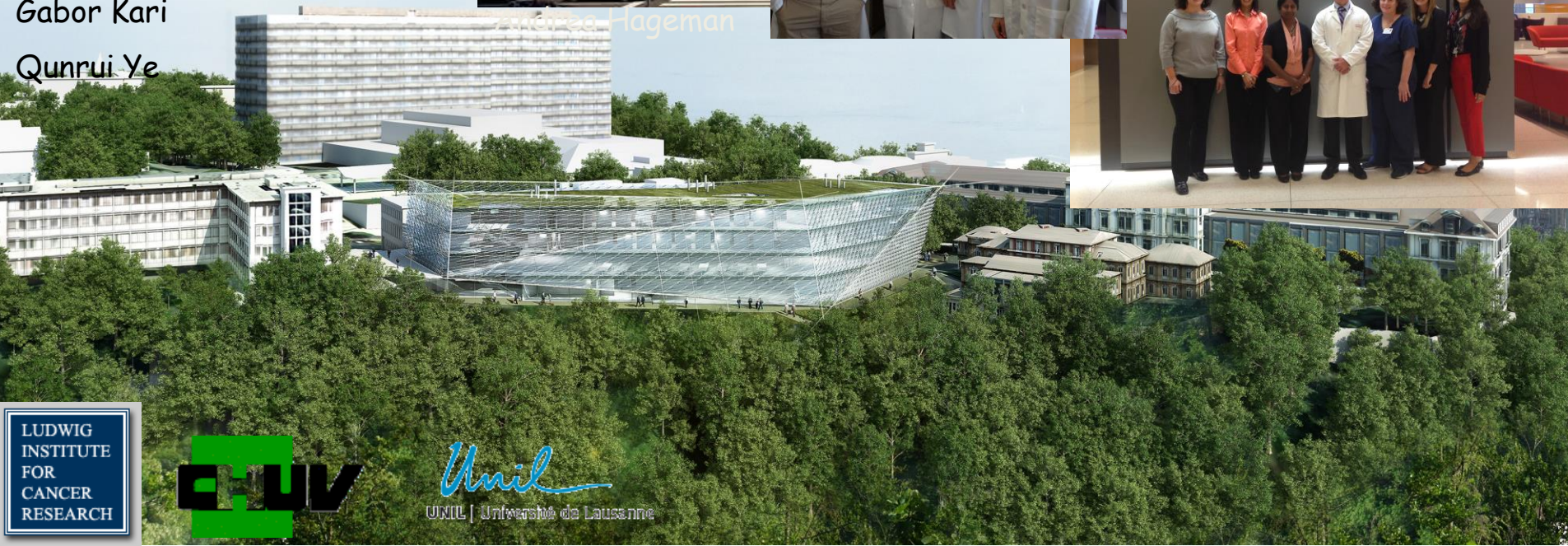
**Raphael Genolet**

**Eran Ophir**

**Andrea Hageman**



**Smilow Center for Translational Research**  
Penn Medicine



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