

***Combining an IL-12-based  
Immunocytokine (PDS0301) with  
Docetaxel in Metastatic Prostate  
Cancer: Preliminary Safety and  
Immune Data***

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*Genitourinary Malignancies Branch*

*Program Director, Physician-Scientist Early Investigator Program*

*Center for Cancer Research, NCI, NIH*



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National Cancer Institute

# Prostate Cancer Immunotherapy: *Current Research Approaches*

- Immune Checkpoints
- Bi/Tri-specific Antibodies
- Car-T Cells

# Prostate Cancer Immunotherapy: *Current Research Approaches*

- Immune Checkpoints
- Bi/Tri-specific Antibodies\*
- Car-T Cells\*
  - \*Cytokine-release syndrome are a toxicity to be minimized.

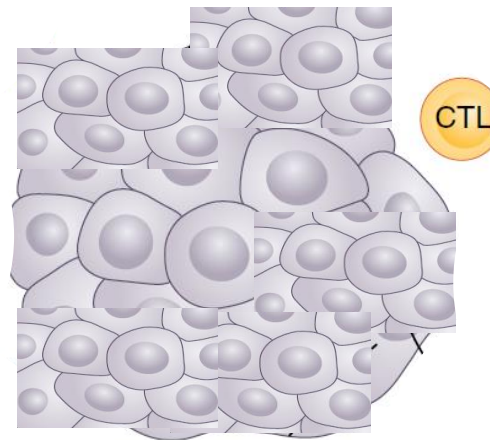
# Prostate Cancer Immunotherapy: *Current Research Approaches*

- Immune Checkpoints
- Bi/Tri-specific Antibodies
- Car-T Cells
- Can Cytokines be an *opportunity* rather than an obstacle?

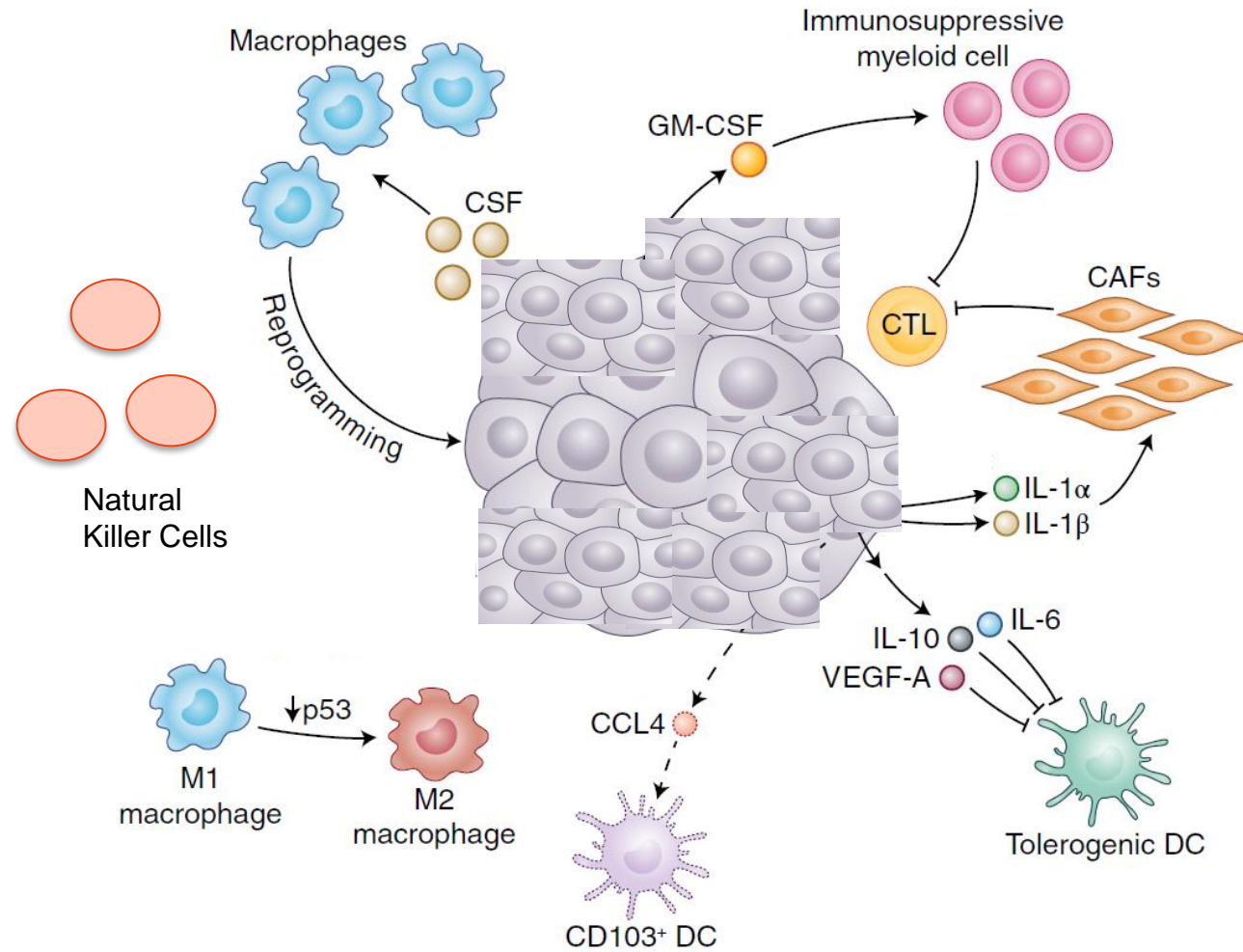
# Why has Immunotherapy in Prostate Cancer been less Successful than Other GU Tumors?

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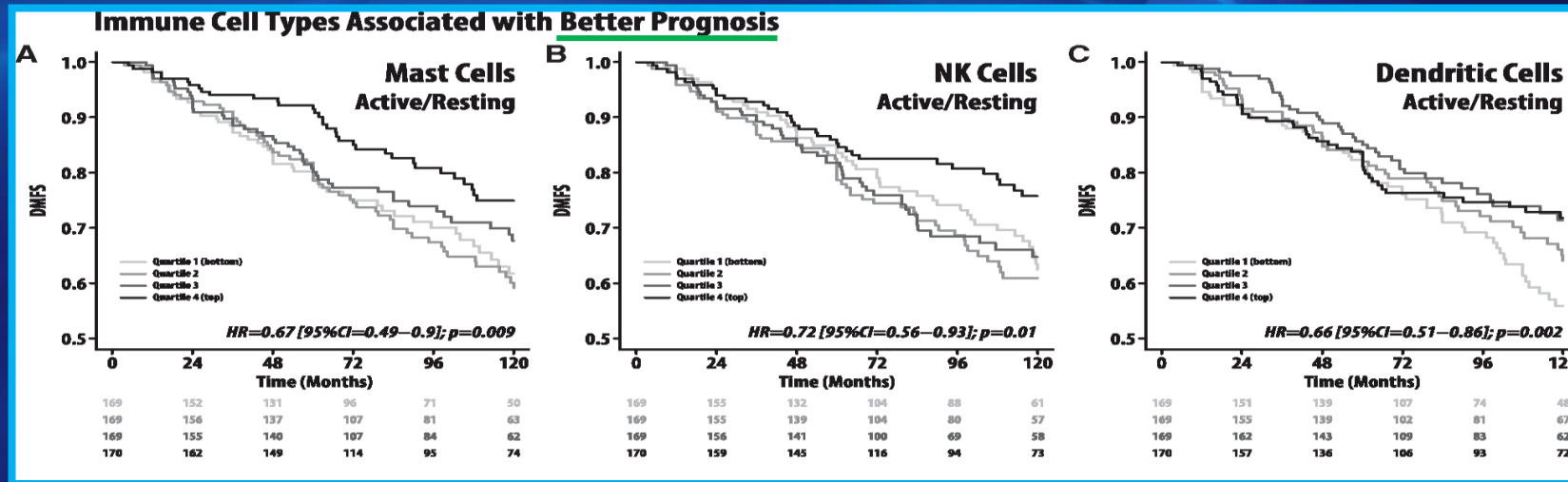
Current I/O Strategies are T-cell Centric



# Many other Components to the Tumor Immune Microenvironment



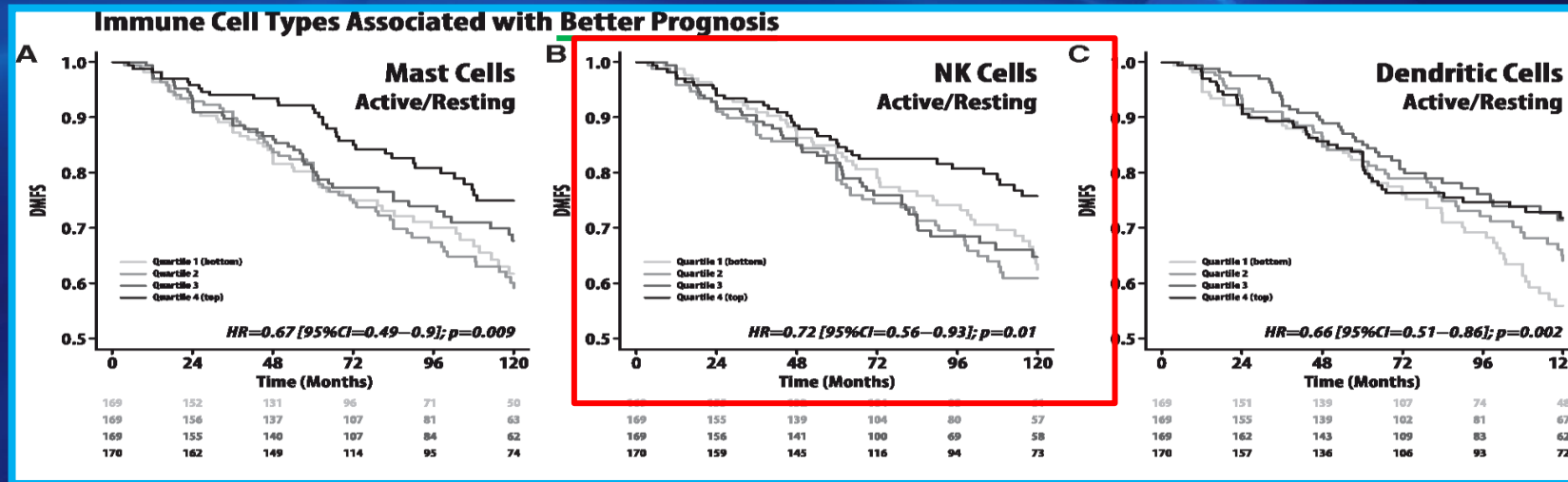
# Immune Analysis of 688 Prostatectomy samples with a median follow up of 10.2 years



DMFS – Distant Metastasis Free Survival

Zhou SG, et al. JNCI, 2018  
 Strasner A et al. Fron Oncol, 2015  
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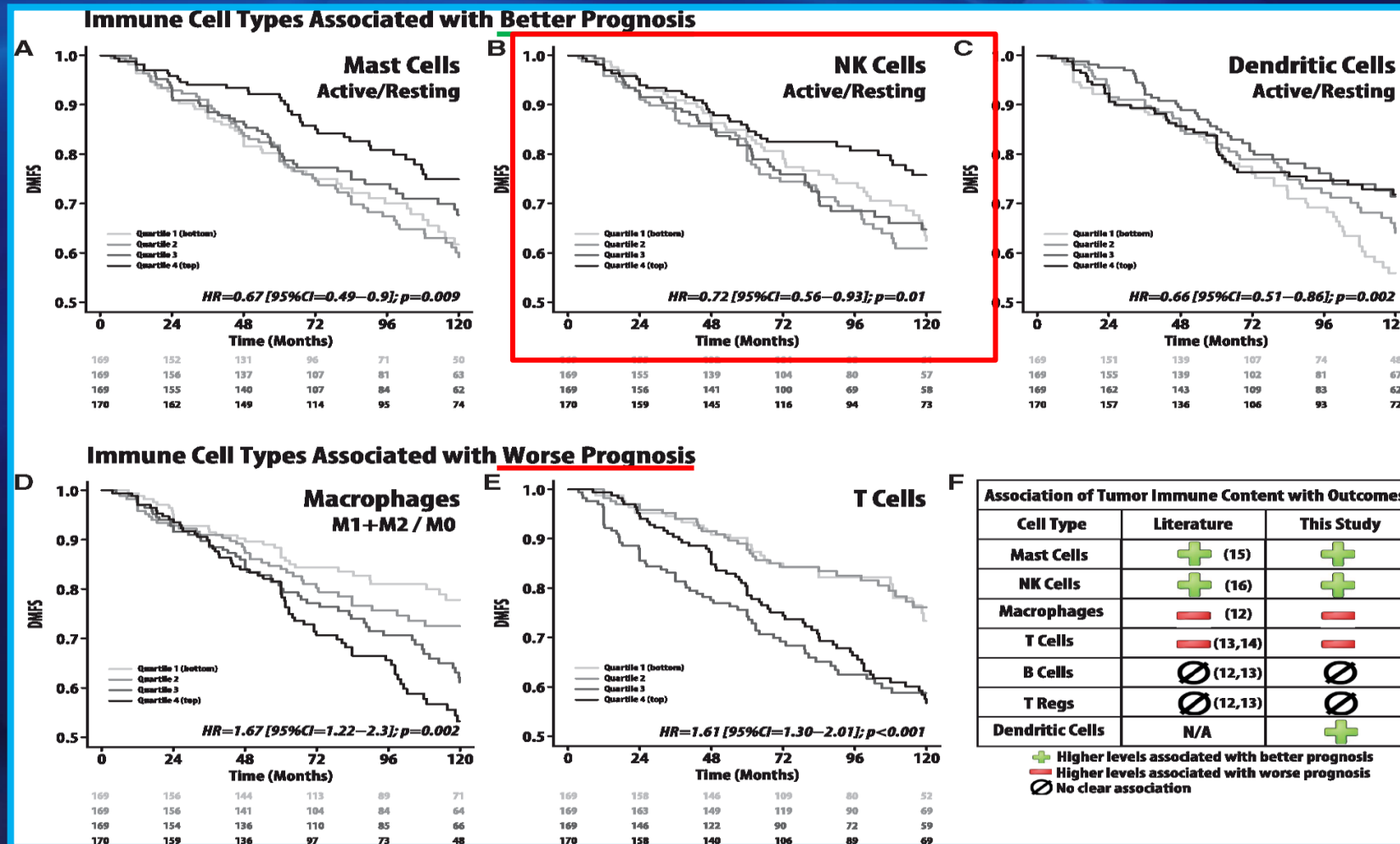


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# Standard of Care Therapies in Prostate Cancer Enhance Numbers and Activation of NK Cells

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- **Enzalutamide** without ADT (biochemically recurrent study )
- **Enzalutamide with ADT** (1<sup>st</sup> line mCRPC trial)
- **Docetaxel with ADT** in metastatic castration sensitive prostate cancer

# Cytokines

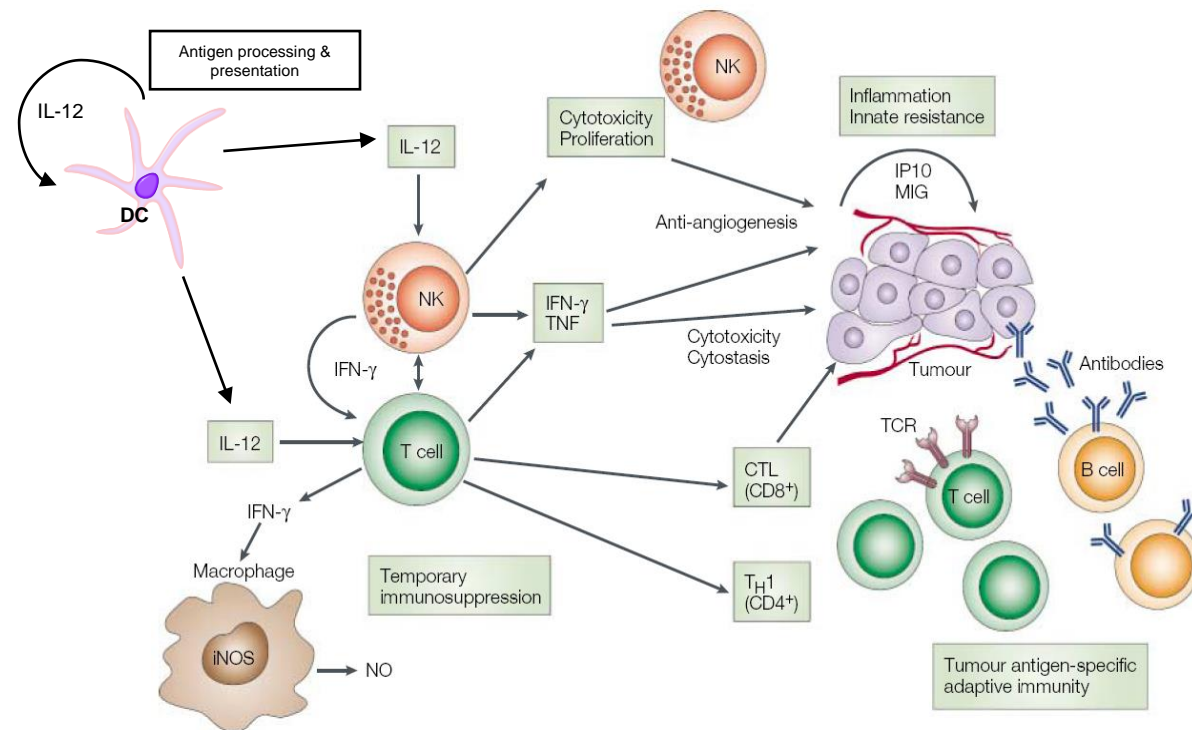
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- **Cytokines** have the potential to induce immune responses (historically in RCC and melanoma)
- Cytokines can **convert pleiotropic components** of the tumor microenvironment from immune-suppressive to anti-tumor
- ***Immunocytokines*** can minimize system toxicity

# IL-12

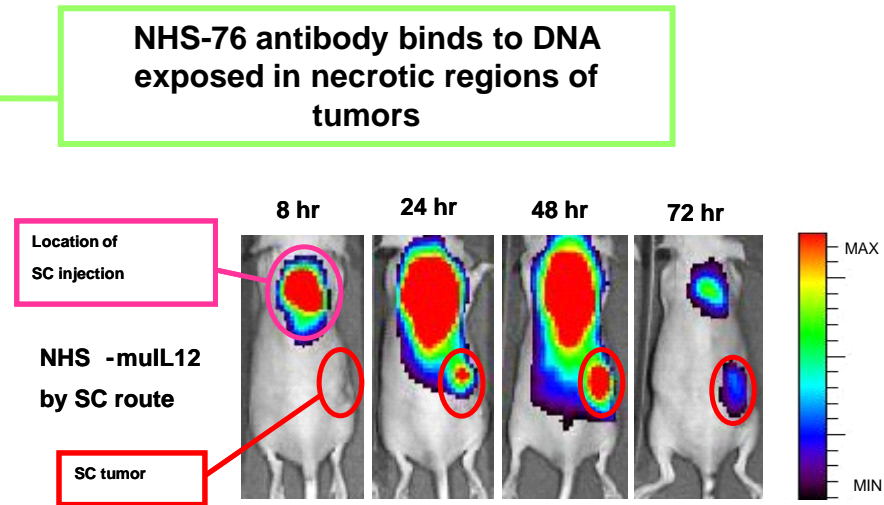
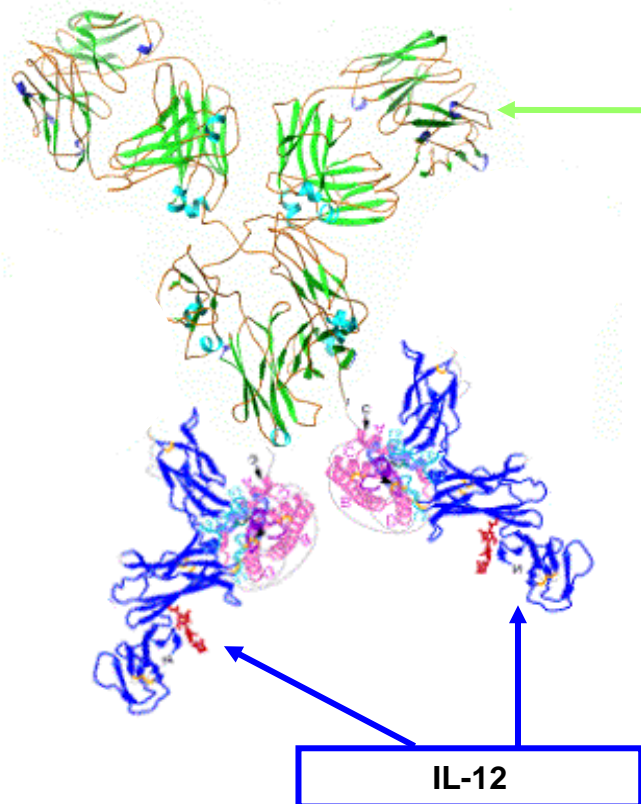
- Induces differentiation of naive CD4+ T-cells to the Th1 phenotype
- Increases proliferation and lytic capacity of CTL and NK
- Promotes IFN- $\gamma$  production by NK and T cells

**Systemic IL-12 hampered by severe systemic toxicity**



Modified from Trinchieri G, *Nature Reviews Immunology* 2003

# Immunocytokine: PDS0301



Dorsal imaging of SC Lewis Lung Carcinoma tumors on right rear flank

# PDS0301 Phase 1 Study

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- Enrolled 59 patients
- Established safety and 16.8 ug/kg as the monthly dose

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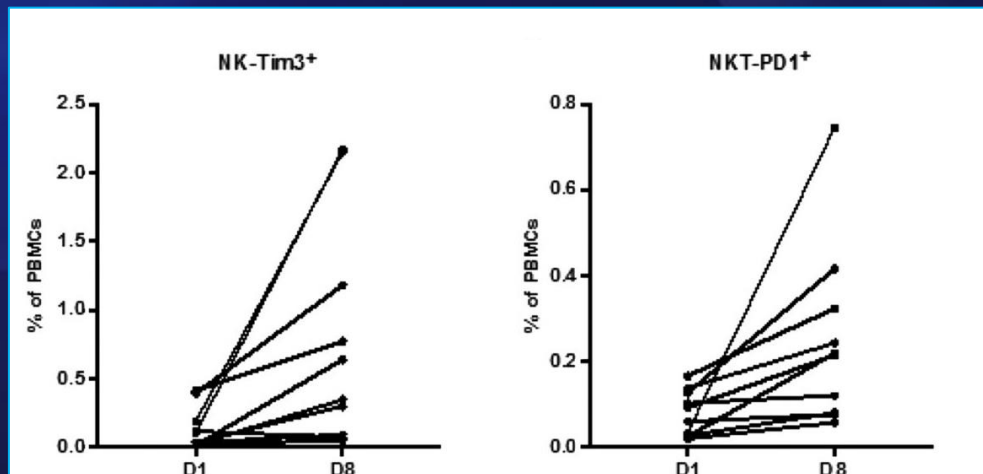
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Immune Cell Subset	Day 1	Day 8	delta	p	Adjusted p
NK-Tim3+	0.07 (0.02-0.024)	0.49 (0.09-1.42)	Increase	0.0059	0.047
NK-Mature Tim3+	0.07 (0.03-0.021)	0.93 (0.25-1.53)	Increase	0.002	0.018
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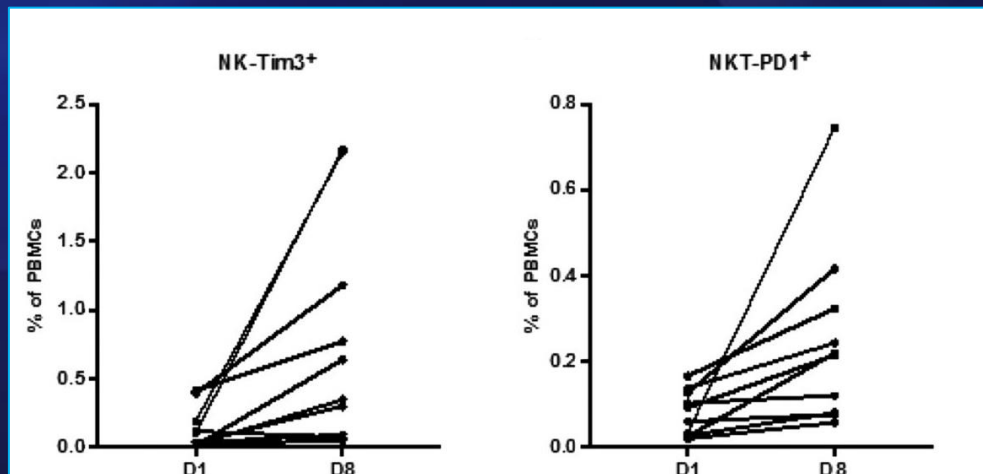


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*Immune Responses are **Dose Dependent** when Used as Monotherapy*

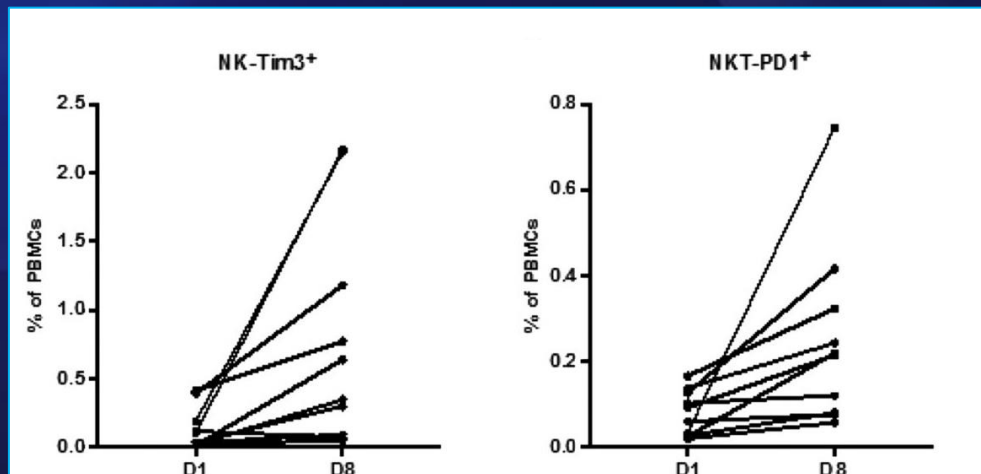


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**Most Common Toxicity:**

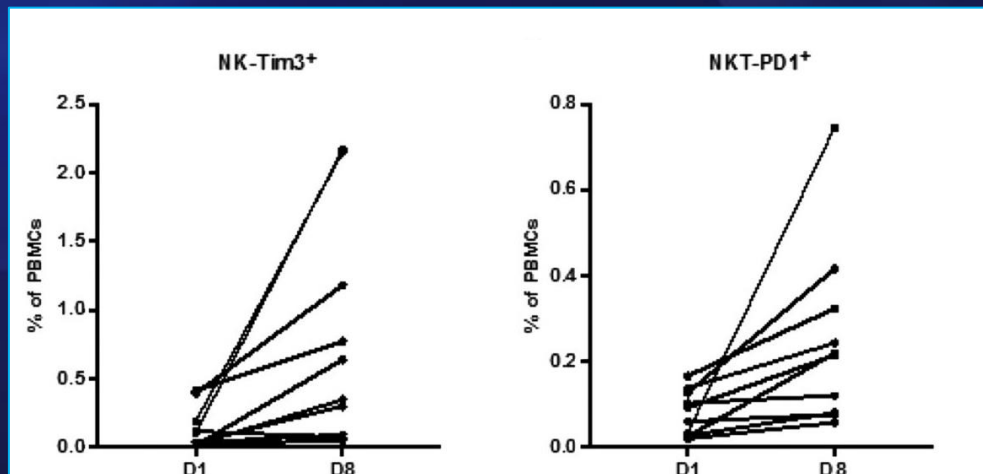
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- Fatigue (peaks w/in 48 hours)

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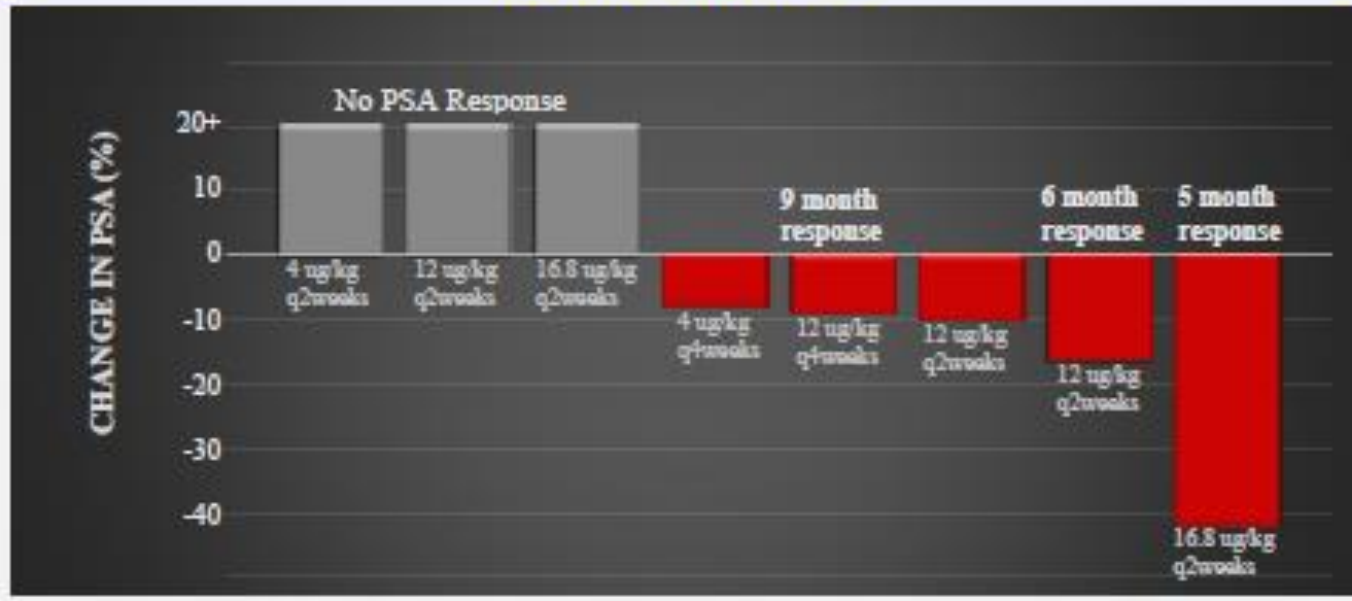


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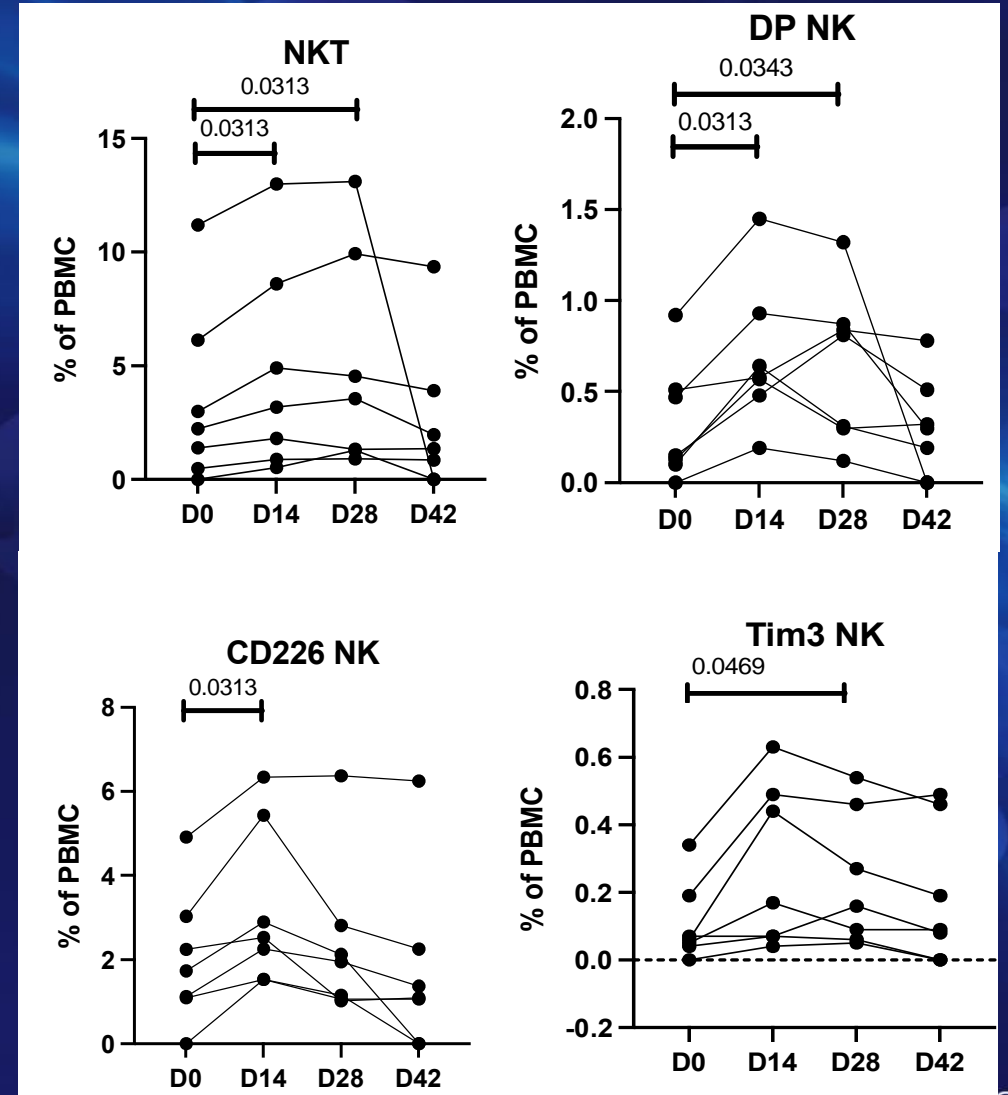
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# PDS0301 Phase 1 Study: Prostate Cancer Patients

## PSA Responses



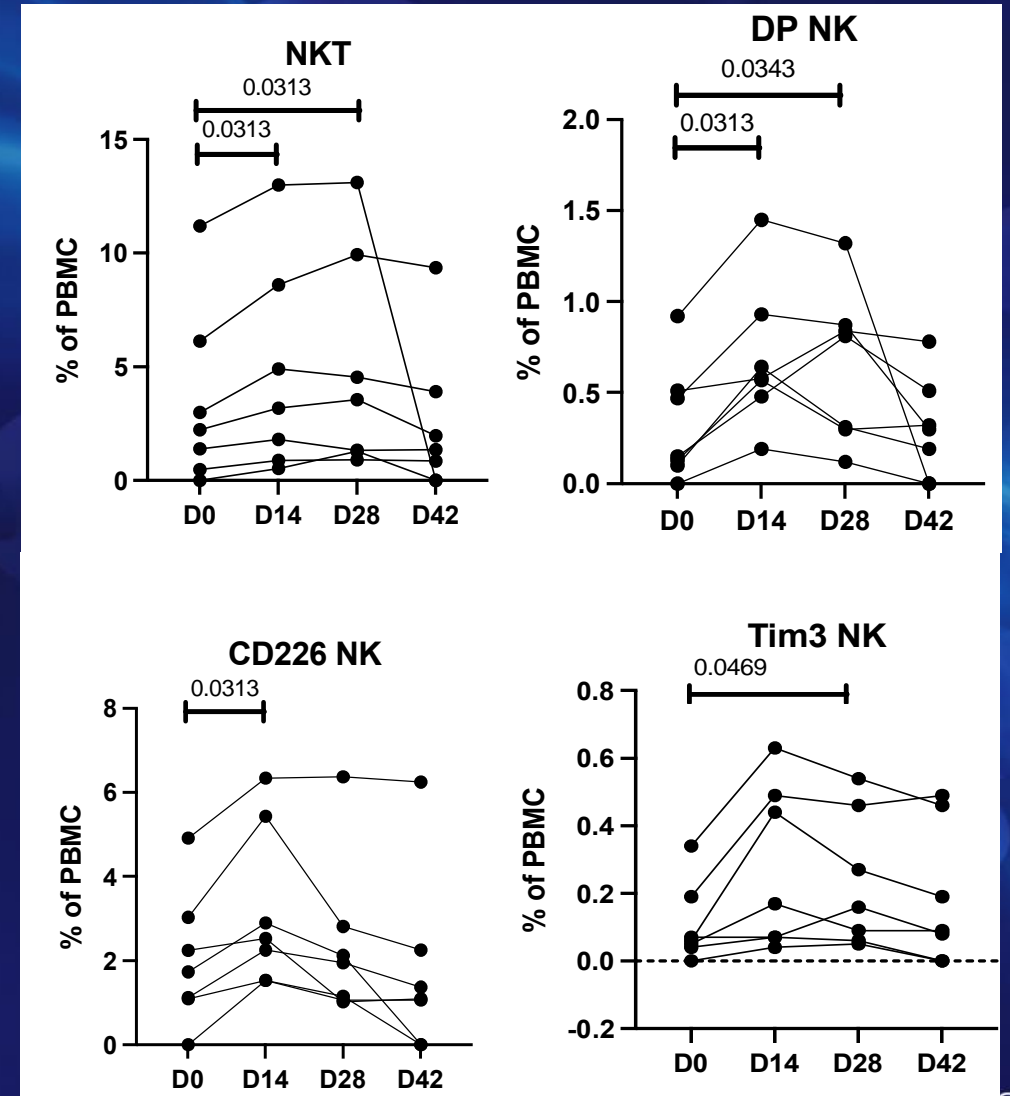
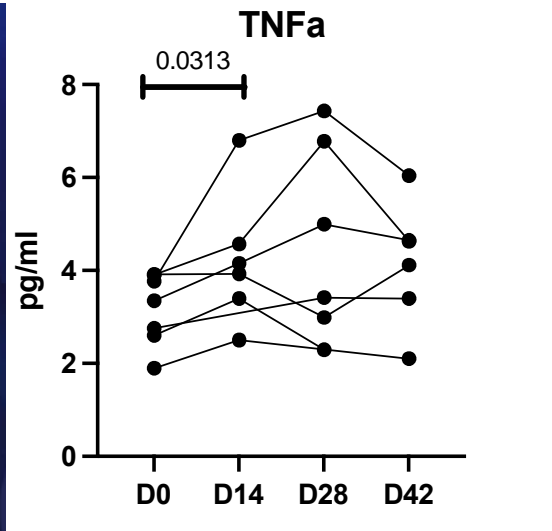
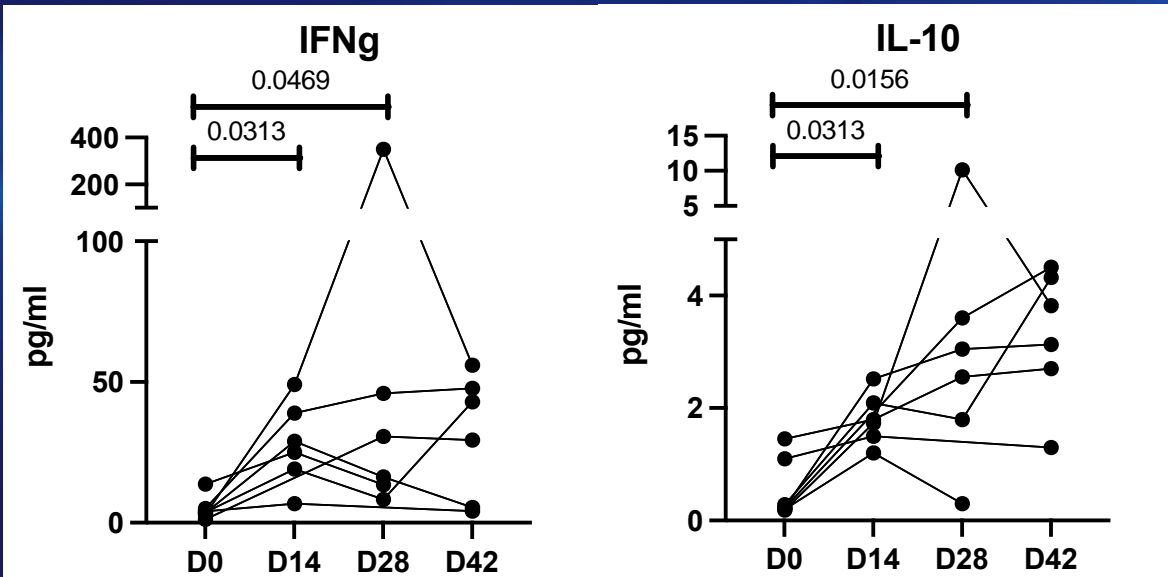
## NK Cell Subpopulations



# PDS0301 Phase 1 Study: Prostate Cancer Patients

PDS0301 Enhances Systemic Cytokines c/w Immune Activation

NK Cell Subpopulations



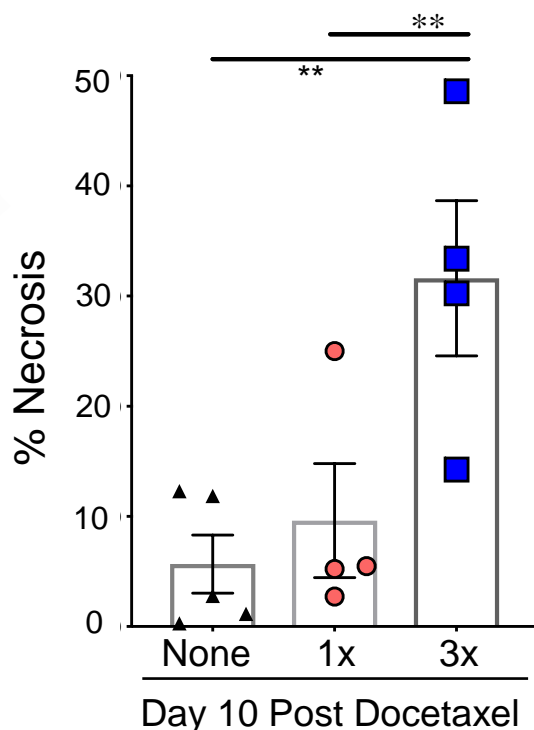
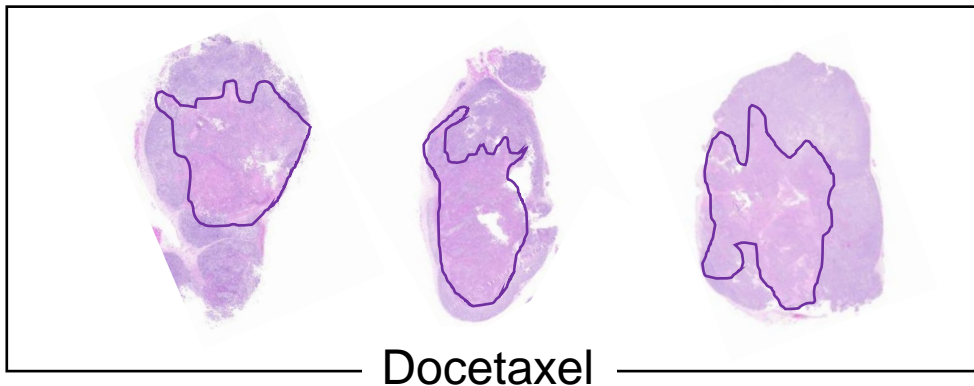
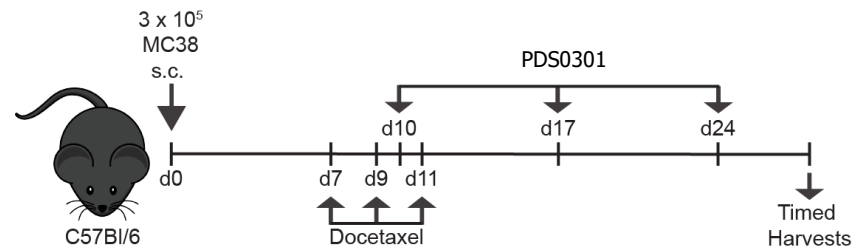
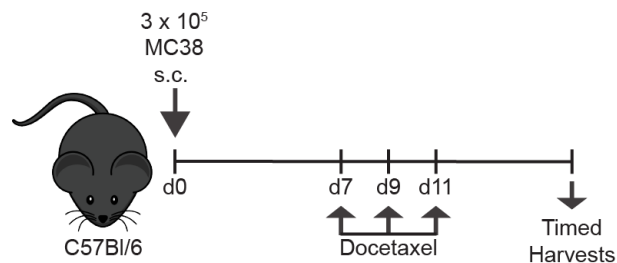
# How Best to Develop A Necrosis Targeting Immunocytokine?

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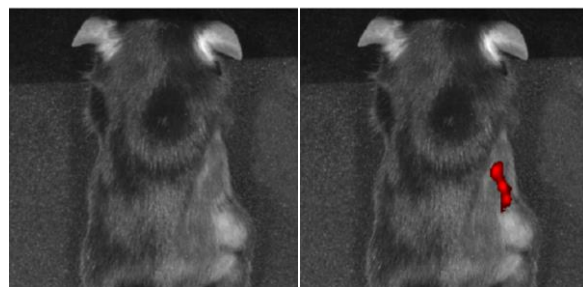


**James W. Hodge, Ph.D., M.B.A.,  
Senior Investigator, CIO**

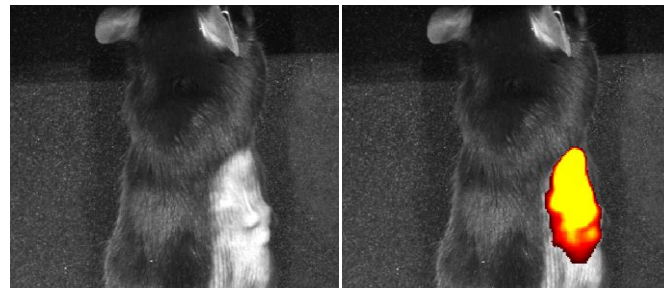
# Docetaxel induces necrosis and PDS0301 retention in MC38



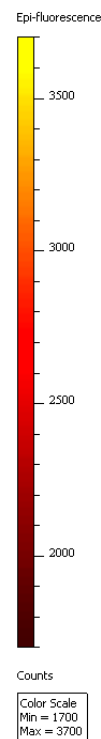
## PDS0301 Alone



## PDS0301 + Docetaxel



2ug PDS0301 labeled with AF647 – far red  
24hr post PDS0301 treatment



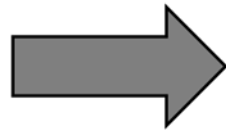
In-Progress -- Preliminary Data

\* Untreated tumors have detectable levels of baseline necrosis

# Docetaxel + PDS0301

## Phase I Trial Design

**Safety Cohort  
Metastatic  
Prostate  
Cancer  
(Cohort 1)**



**Docetaxel 75 mg/m<sup>2</sup>  
PDS0301 Starts Cycle 2**

**Safety 3+3 Design**

**PDS301  
Dose Levels**

**8 mcg/kg**

**12 mcg/kg**

**16.8 mcg/kg**

**Eligible patients include both mCSPC and mCRPC**



# Docetaxel + PDS0301: Phase I Study

## Baseline Characteristics

Category	Value
Age Range (yrs)	39-82
Median Age (yrs)	69
Race	
White	50%
Black	44%
Hispanic	6%

Category	Value
Disease State	
CSPC	61% (11)
CRPC	39% (7)
CSPC Volume	
Low	55% (6)
High	45% (5)

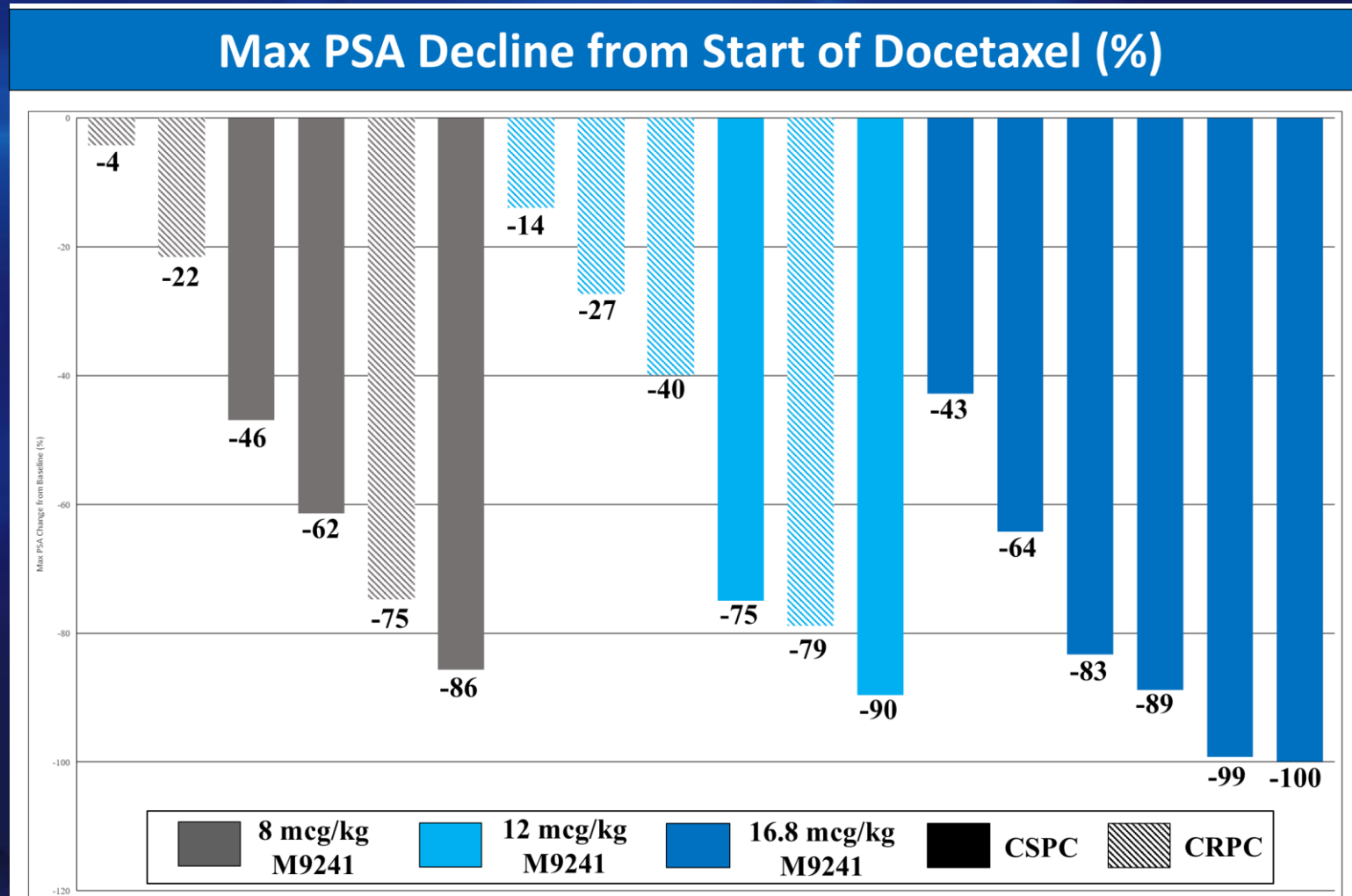
# Docetaxel + PDS0301: Phase I Study

## Adverse Events

Toxicity	PDS0301 16.8 mcg/kg N = 6			PDS0301 12.0 mcg/kg N = 6			PDS0301 8.0 mcg/kg N = 6		
	Grade 2	Grade 3	Grade 4	Grade 2	Grade 3	Grade 4	Grade 2	Grade 3	Grade 4
Fatigue	3 (60%)	0	0	1 (17%)	1 (17%)	0	2 (33%)	0	0
Anemia	0	1 (20%)	0	2 (33%)	1 (17%)	0	0	0	0
Lymphopenia	0	0	0	4 (67%)	0	0	0	0	0
Diarrhea	1 (20%)	1 (20%)	0	1 (17%)	0	0	0	0	0
Neutropenia	1 (20%)	0	0	0	0	1 (17%)	0	1 (17%)	0
Leukopenia	1 (20%)	0	0	0	1 (17%)	0	1 (17%)	0	0
Febrile Neutropenia	0	1 (20%)	0	0	0	0	0	0	0

Number of patients experiencing AEs of interest separated by M9241 dose and AE grade. The percentage of patients experiencing an AE per dose level is in parentheses.

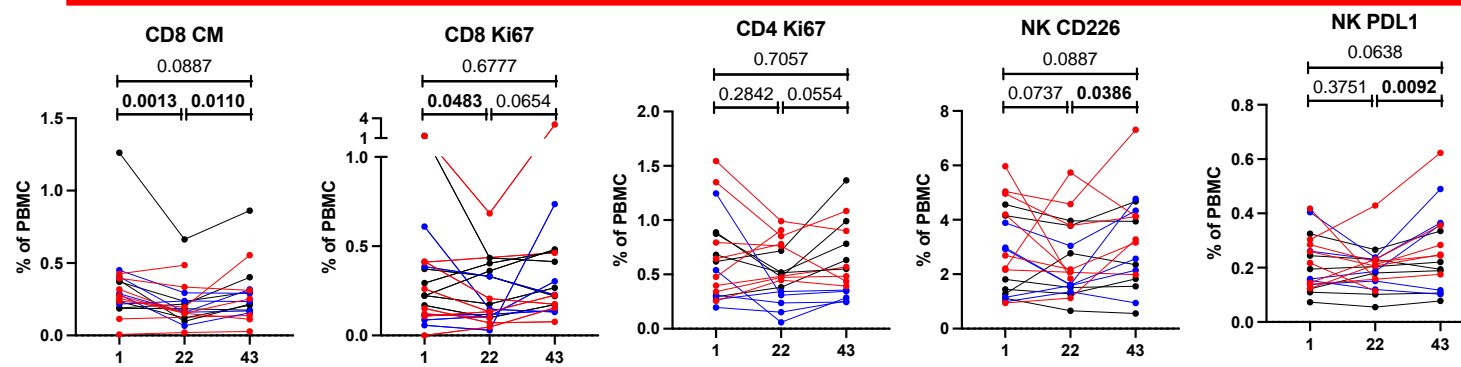
# Docetaxel + PDS0301: Phase I Study and PSA Responses



*All mCRPC pts on study beyond 6 months*

# Adding PDS0301 to Docetaxel at Day 22 Increases Immune Activation in a Dose-Independent Fashion

*Increases*



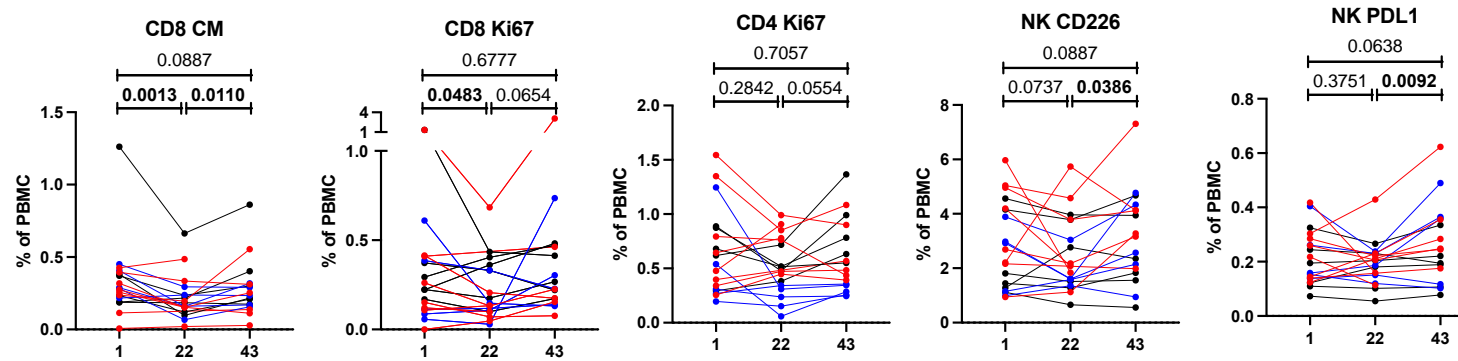
## Treatment Schedule

D1: Docetaxel  
D22: Docetaxel + PDS0301

- Addition of PDS0301 decreases Treg subsets and ki67+ NK
- Addition of PDS0301 increases CM CD8, proliferative CD4 and CD8, and increases activated NK

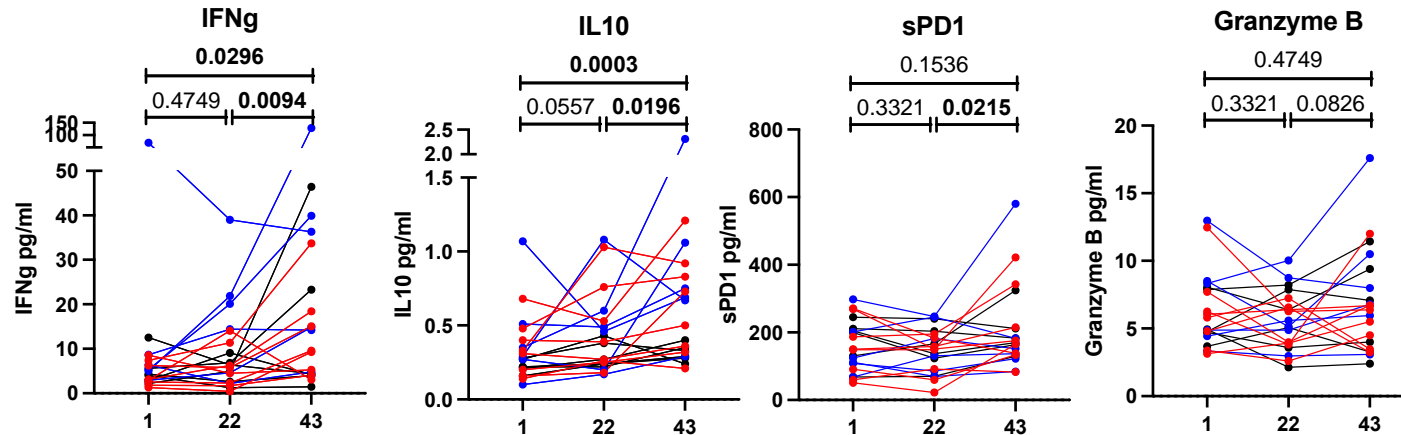
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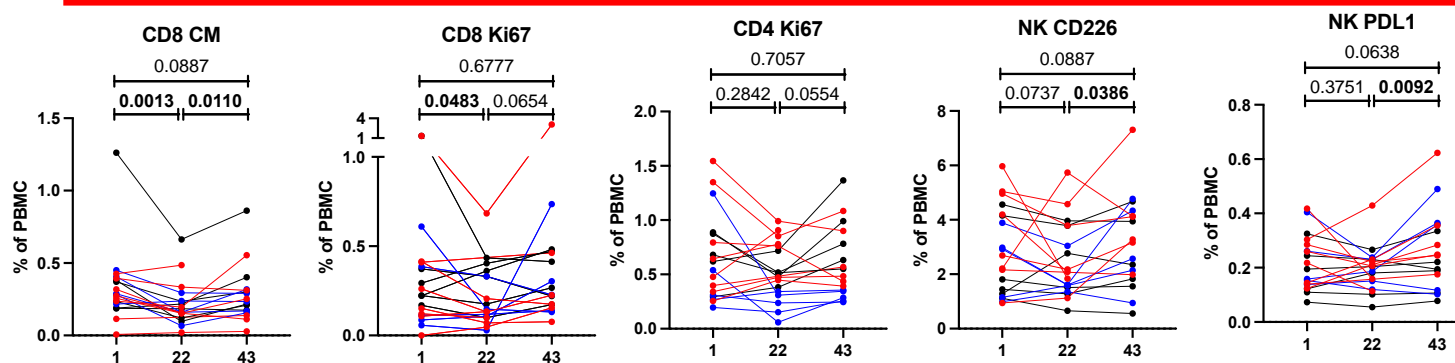


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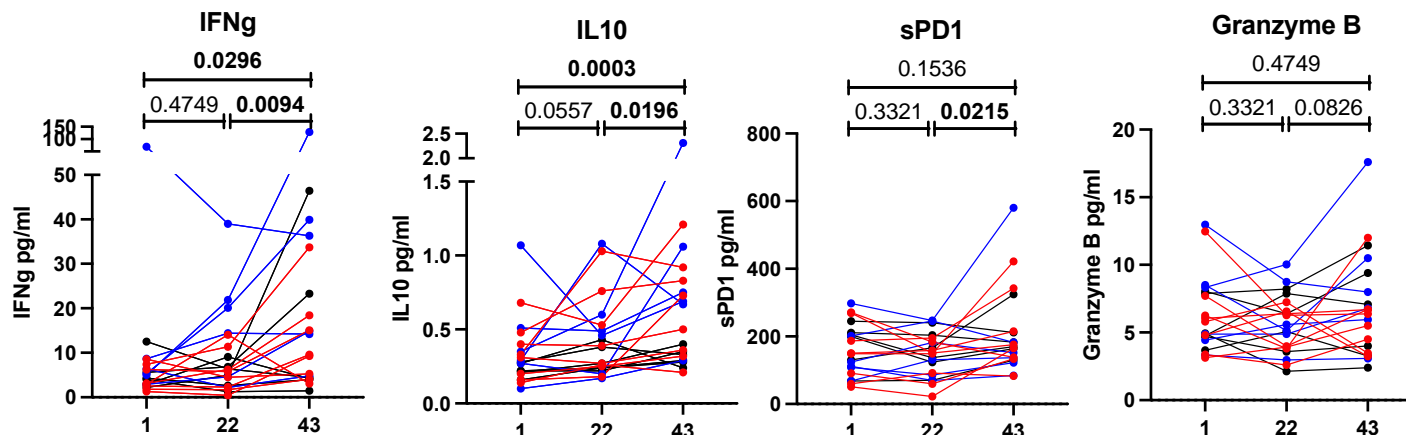
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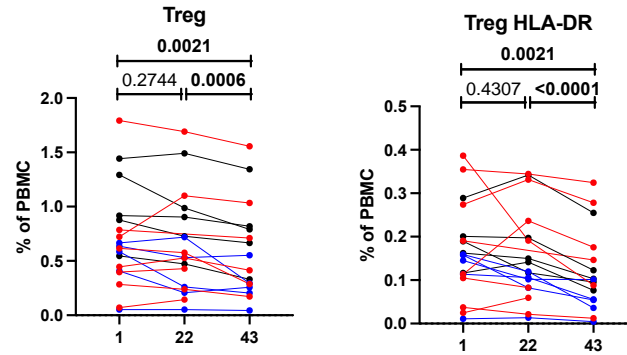
Unlike single agent PDS0301, there did not appear to be a dose-response to immune changes, consistent with increased IL-12 delivery when combined with a necrosis-inducing agent

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# Adding PDS0301 to Docetaxel at Day 22 Decreases Regulatory T-cells

## Decreases

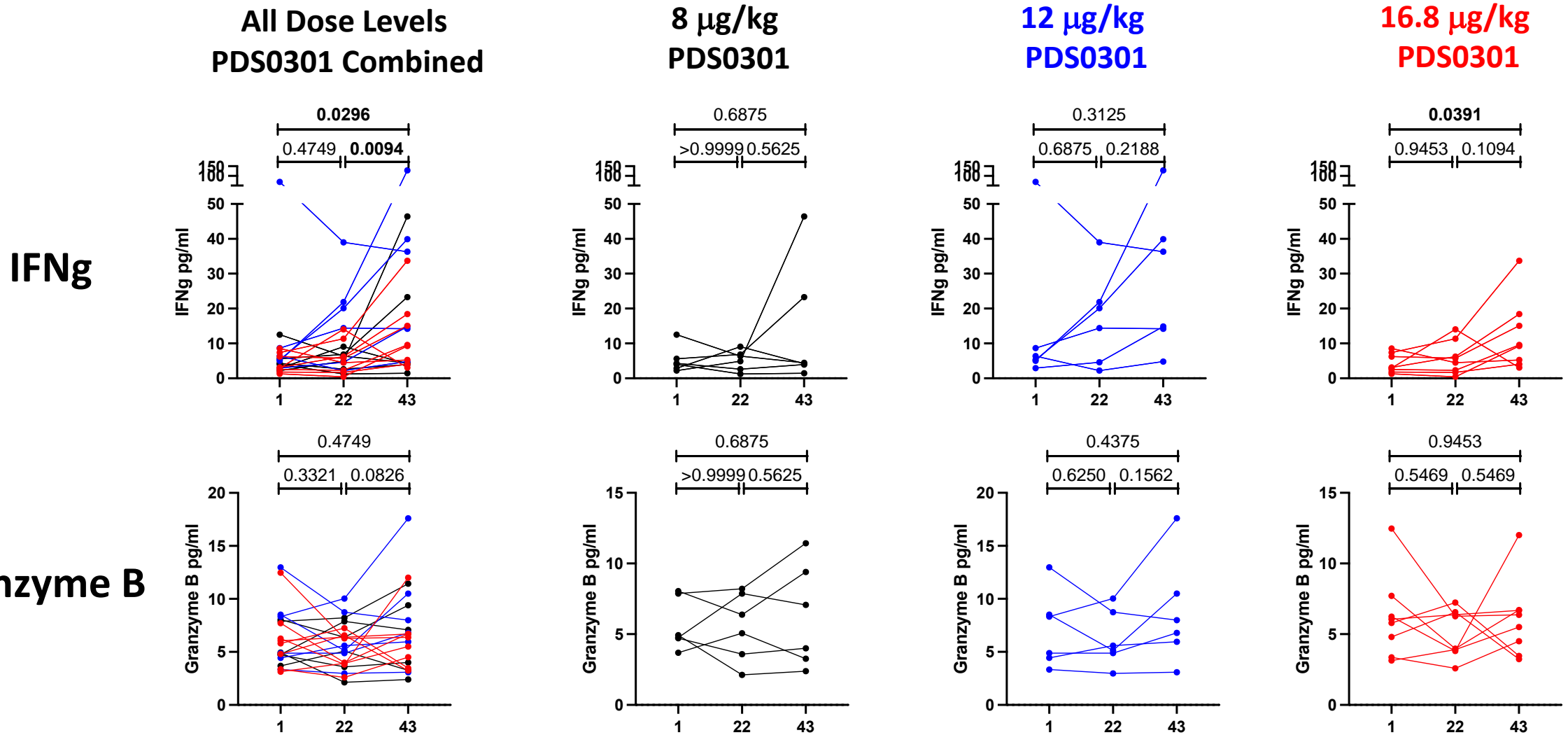


Black: PDS0301 8 mcg/kg; Blue: PDS0301: 12 mcg/kg; Red: PDS0301: 16.8 mcg/kg

## Treatment Schedule

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# Comparison of Changes Induced by the Addition of Docetaxel Followed by Docetaxel + PDS0301 (By 3 Dose Levels)



- There are not obvious differences seen in the levels of IFN $\gamma$  and Granzyme B among the different dose levels of PDS0301



# Preliminary Conclusion of Immune Analysis of Docetaxel and PDS0301

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- Consistent with pre-clinical synergy, increasing necrosis with chemotherapy leads to consistent immune activation at all dose levels

# Docetaxel + PDS301: Phase I Study

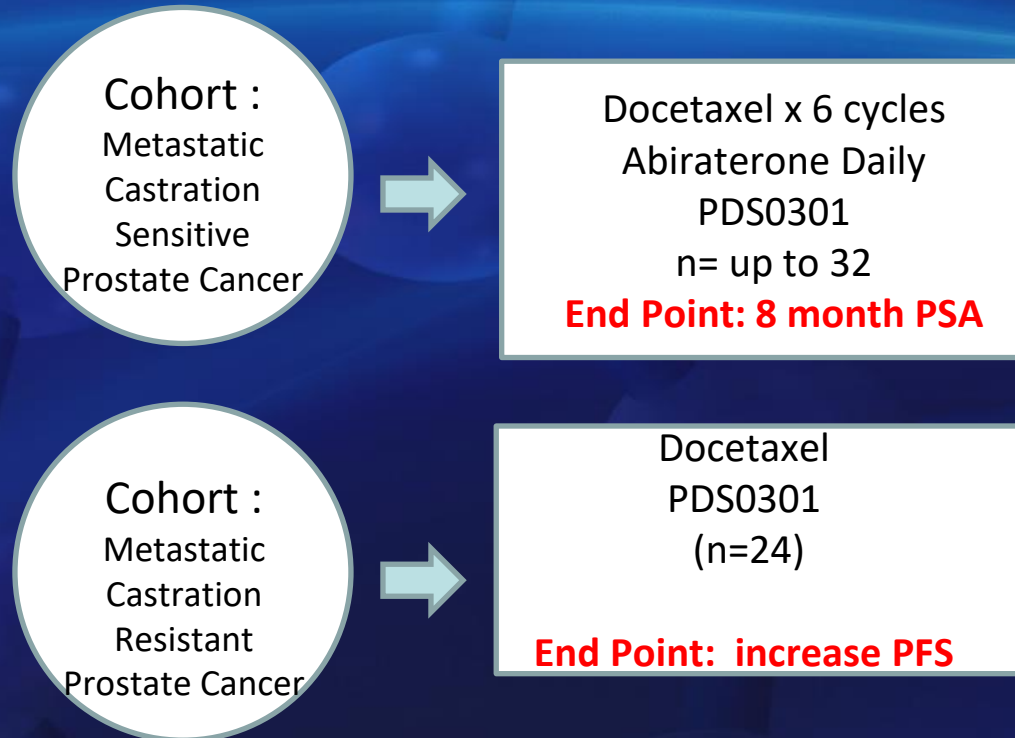
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# Chemo-Immunotherapy in Metastatic Prostate Cancer

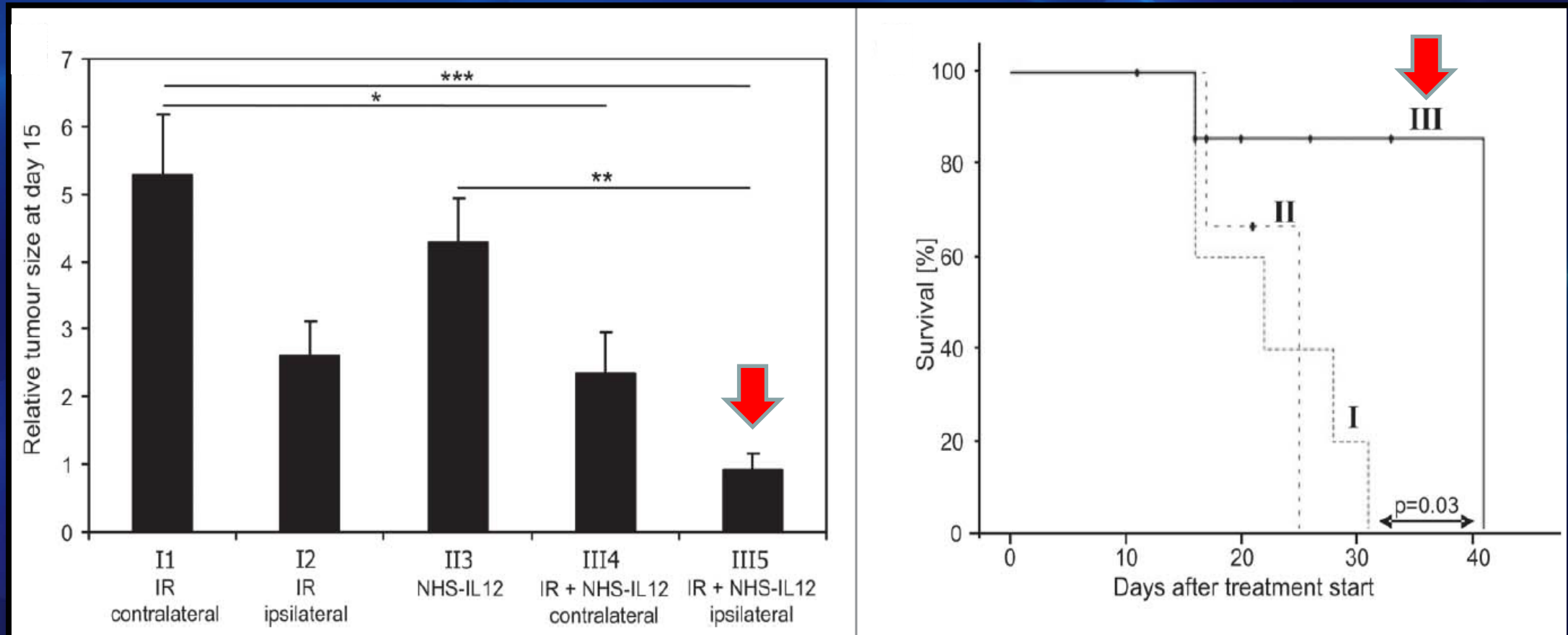
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## Key Correlatives:

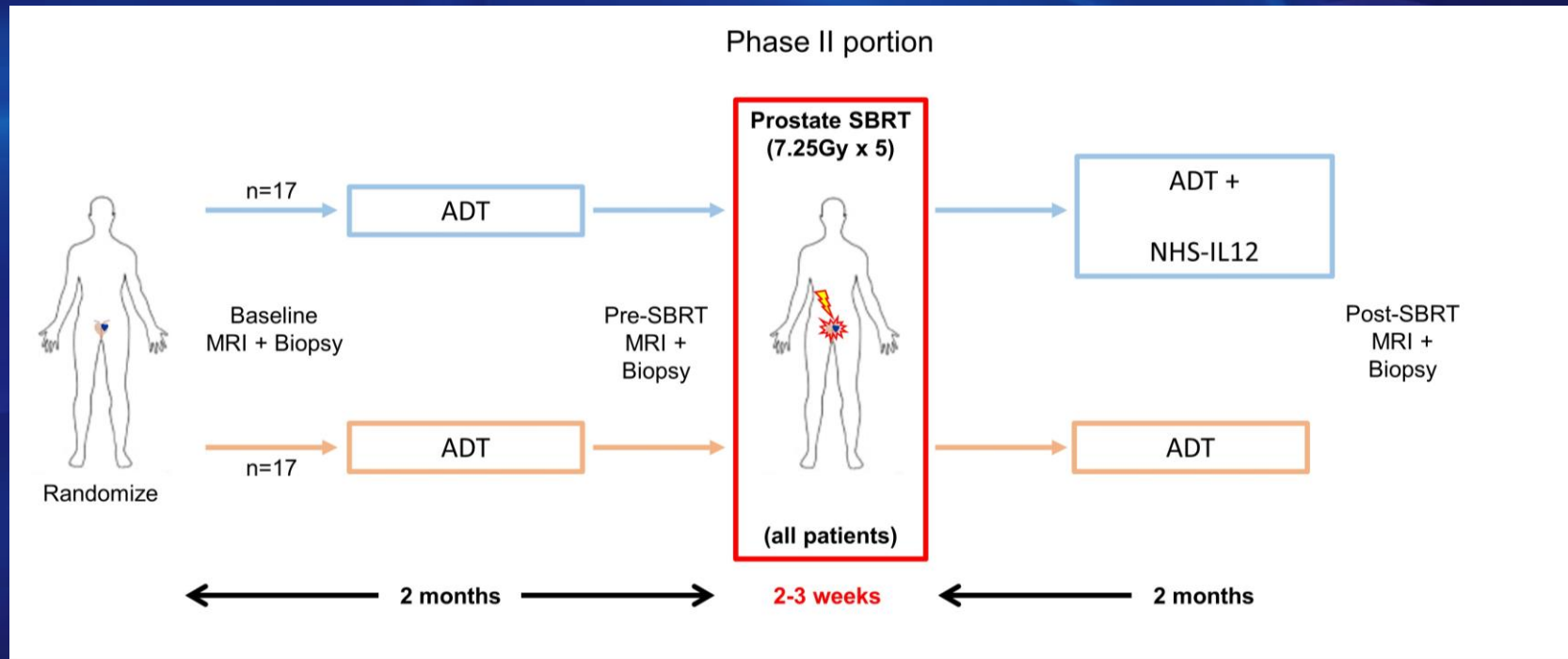
- 150+ circulating immune cell subsets (CIO Collaboration)
- Pre and post treatment biopsies
- Evolution of Neuroendocrine Prostate Cancer Cells (U01 Grant with Mass General and Daniel Haber, MD, PHD)

# PDS0301 Enhances Radiation Anti-Tumor Impact and Survival



Anti-tumor effect and survival was greatest in the mice treated with radiation (IR) and PDS0301 (group III; note group III4 evaluates the tumor contralateral to IR and the group III5 evaluates the tumor ipsilateral to the IR.)

# Definitive Radiation + PDS0301 in Intermediate and High Risk Prostate Cancer



Study Now  
Enrolling at  
the NCI

## Primary Endpoints:

- Safety
- Changes in T-cell Clonality

## Secondary/Exploratory Endpoints:

- Changes in Immune Cell Subsets
- Changes in T-cell Clonality (periphery vs. tumor)

ROB Collaborators:  
Dr. Deborah Citrin  
Dr. Krishnan Patel

National Cancer Institute

# Can Cytokines Make an Impact in Prostate Cancer?

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- Preclinical data supports potential **synergy of PDS0301 in combination with necrosis-inducing therapies**
- Clinical data demonstrates the **safety of PDS0301 with docetaxel**
- Correlative immune data suggests **immune synergy** of docetaxel and PDS0301
- **On-going and planned studies** at the NCI will further evaluate PDS0301 in prostate cancer

# Acknowledgments:

## *Clinical Trial Patients & Their Families*

### Genitourinary Malignancies Branch

- William D. Figg PharmD
- **Fatima Karzai MD**
- Philip Arlen MD
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- **Amy Hankin PA**
- **Nikki Williams CRNP**
- **Megan Hausler RN**
- Kathy Lee-Wisdom RN
- Elizabeth Lamping RN
- Lisa Cordes, PharmD
- Moniquea Smith

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- **Peter Choyke MD**
- Baris Turkbey MD
- Liza Lindenberg MD
- Esther Mena MD

### Radiation Oncology Branch

- **Deborah E. Citrin, MD**
- **Krishnan Patel, MD**

### Center for ImmunoOncology

- James L. Gulley, MD PhD
- Jeffrey Schlom PhD
- **James Hodge PhD**
- Julius Strauss MD
- John Greiner PhD
- Claudia Palena PhD
- **Renee Donahue PhD**
- Sofia Gameiro PhD