A Clinical Trial Combining a Tumor Targeting Immunocytokine (PDS01ADC) and Enzalutamide without Testosterone Lowering Therapy in PSMA+ Biochemically Recurrent Prostate Cancer

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Cytokines 2024
KAI 2024

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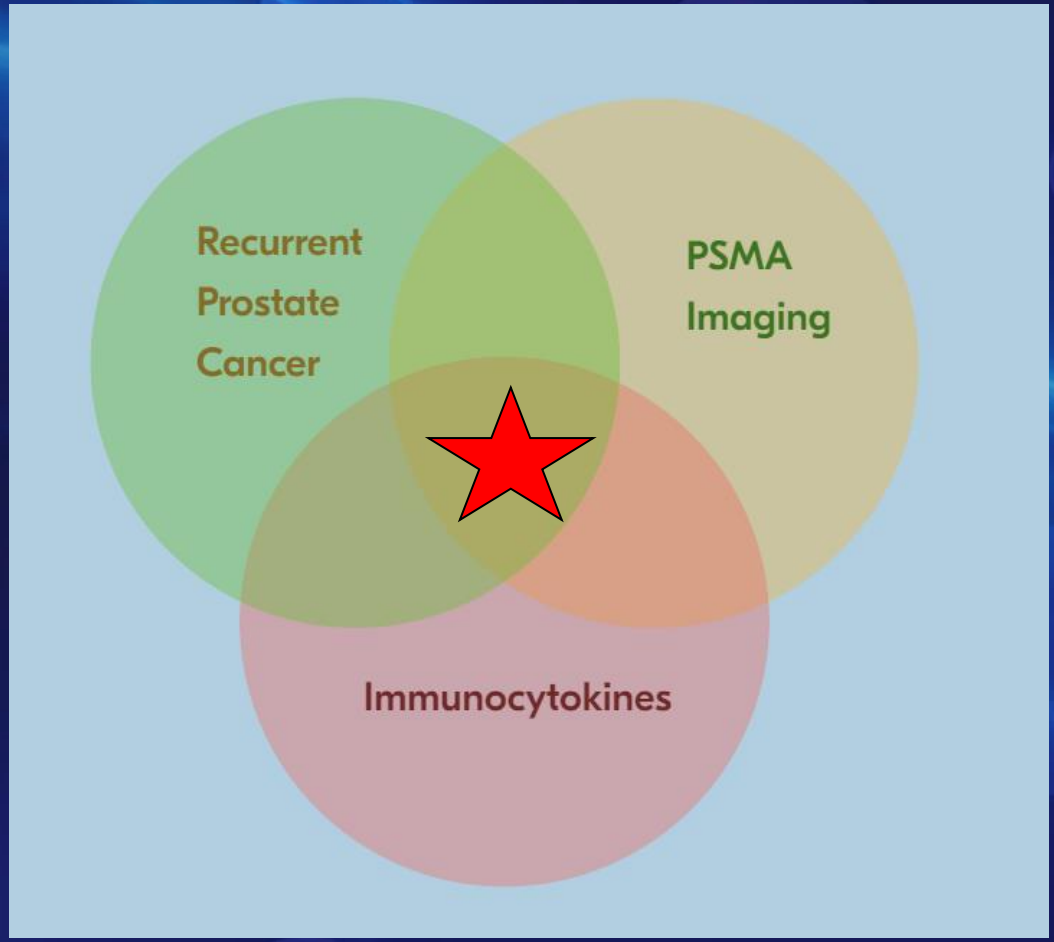
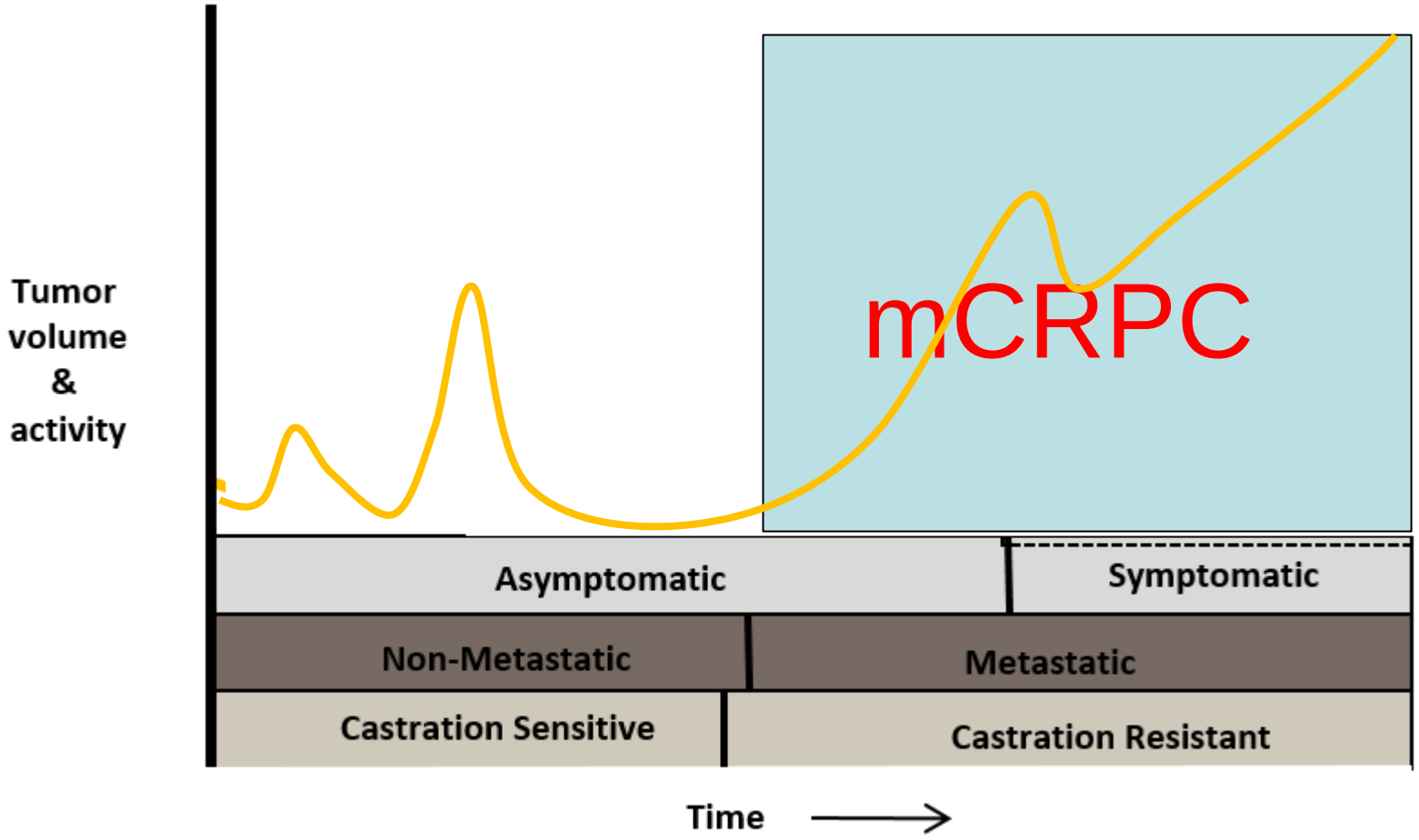
My Primary Areas of Research in Prostate Cancer

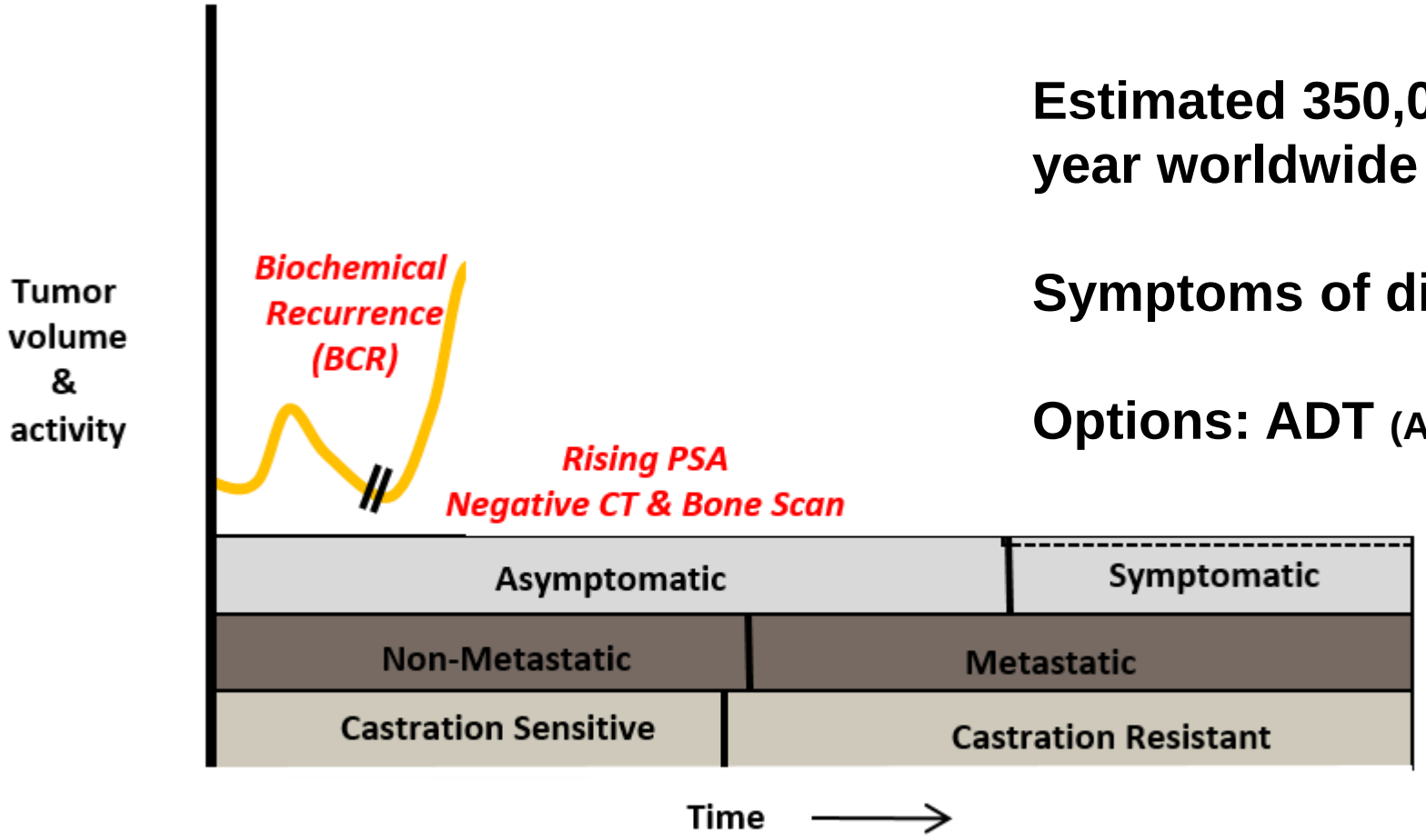
- Early Recurrence as a Population of Focus
- PSMA Imaging with a Novel Perspective
- *Immunocytokines as a Next-generation Immunotherapy Strategy*



Focus of Prostate Cancer Therapeutic Development Historically has Focused on Metastatic Disease



Biochemical Recurrence (BCR)



Estimated 350,000 men diagnosed each year worldwide

Symptoms of disease are absent*

Options: ADT (Androgen Deprivation Therapy) or Surveillance

***Therapies must have limited toxicity commensurate absent symptoms in this population**

Biologic Differences Between BCR and mCRPC

	Biochemically Recurrent Prostate Cancer	Metastatic Castration–Resistant Prostate Cancer
Testosterone levels	Normal physiologic levels	Castrate levels of testosterone
Predominant Sites of Disease	Lymph nodes (based on early PET imaging)	Bone
Tumor Burden	Minimal—not seen on conventional CT or Tc99 bone scan	Variable—but substantial enough to be seen on conventional imaging

This may improve responsiveness to immunotherapy relative to mCRPC

Bilusic M et al., Urol Clin North Am. 2020

Biochemical Recurrence Clinical Trial: Enzalutamide +/- Prostvac (NO ADT)

Population – Rising PSA after RT or Surgery (no mets)

Arm A: Enzalutamide for 3 months (n=17)

Arm B: Enzalutamide for 3 months with Prostvac (n=17) for 6 months

- Enzalutamide to be administered 160 mg daily for 3 months
- Prostvac given Day 1, 15, 29, and monthly to complete 6 months, consistent with Phase III Trial

Primary End Point: **Determine if vaccine alters tumor re-growth rate (PSA recovery) after discontinuation of enzalutamide**

Secondary End Points: PSA-Response, TTP, Immune Responses

Collaboration with astellas

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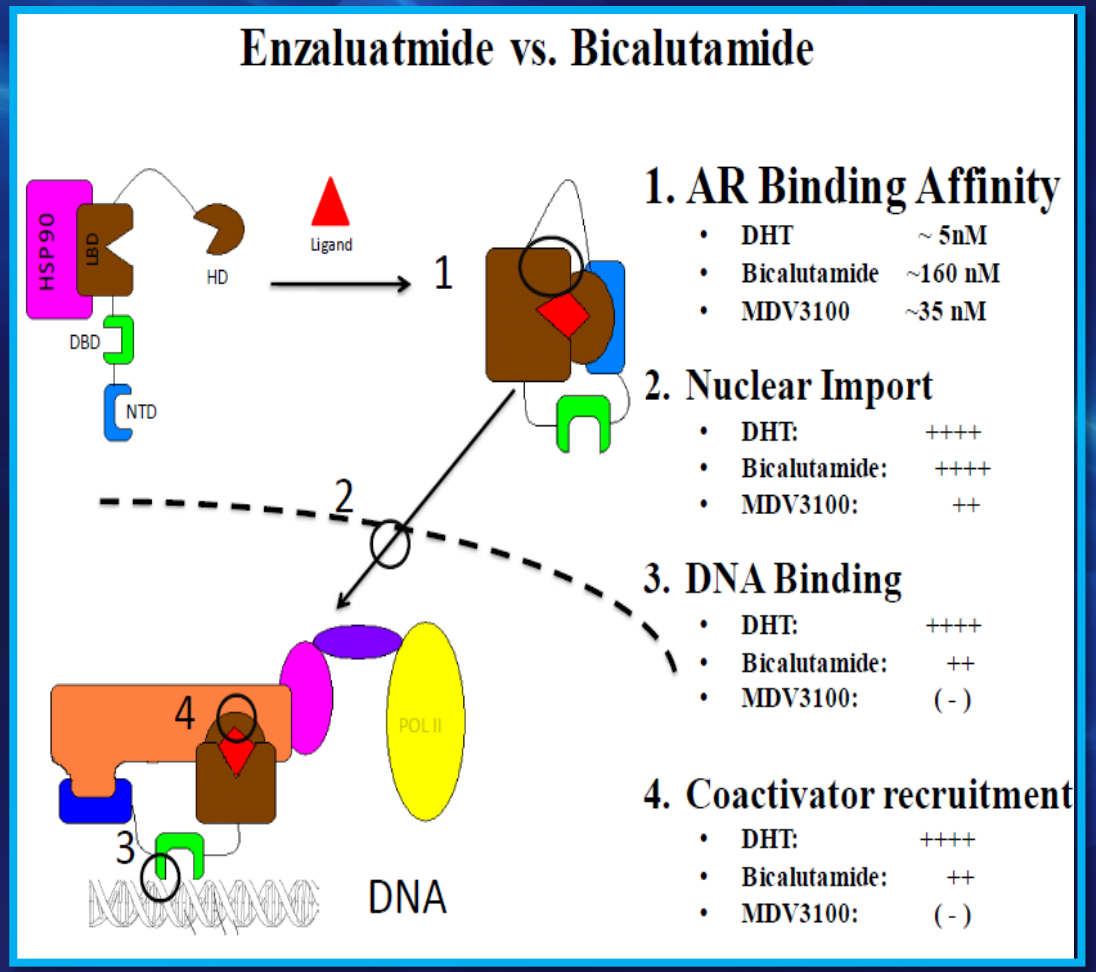
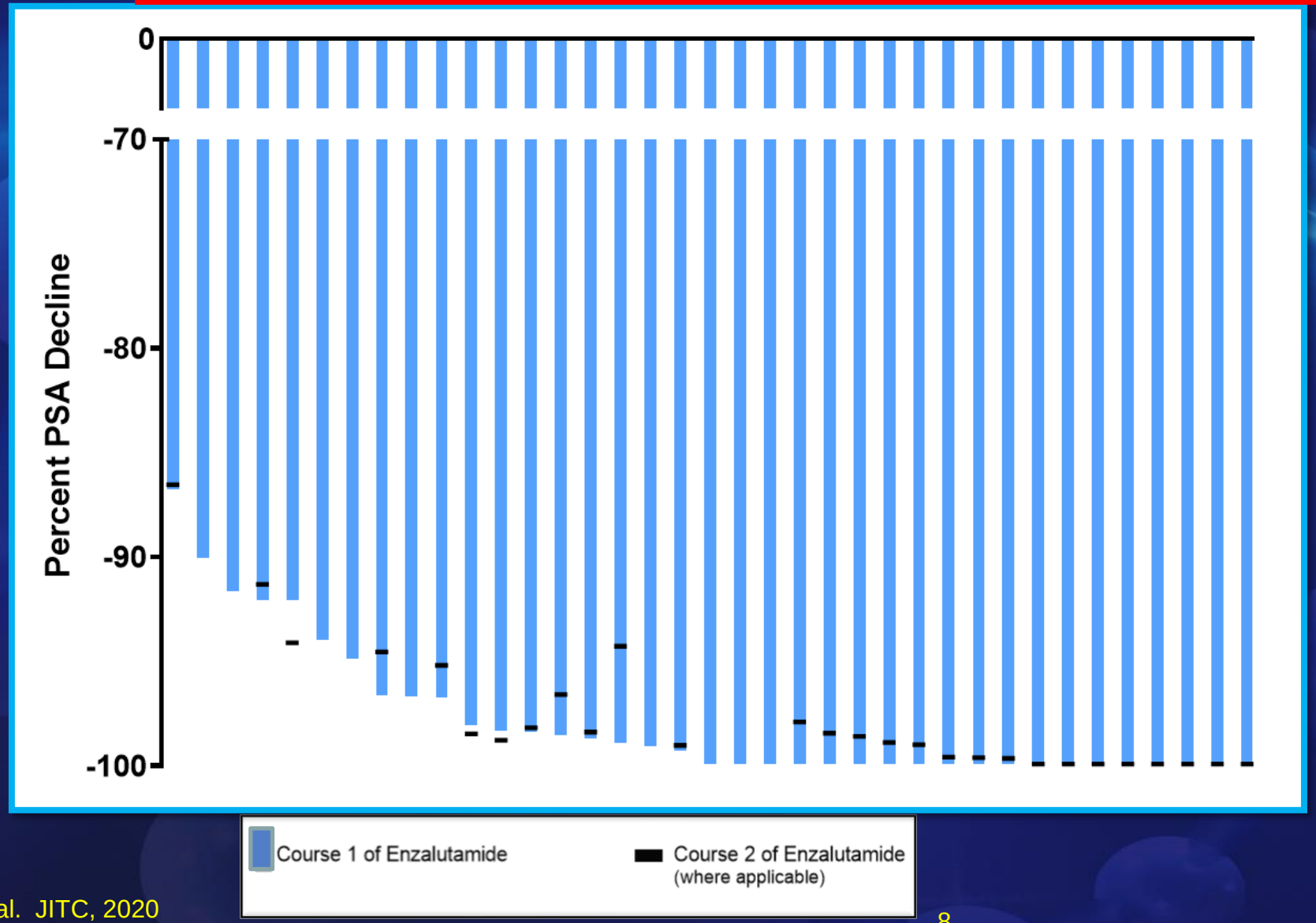
Enzalutamide

- Androgen receptor pathway inhibitor
- Approved for treatment of prostate cancer in multiple stages of disease



Tran et al. Science. 2009.

PSA Declines after 3 Months of Enzalutamide for Biochemically Recurrent Prostate Cancer (no ADT)



Median PSA decline >99% for both courses of therapy

Madan RA, et al. JITC, 2020

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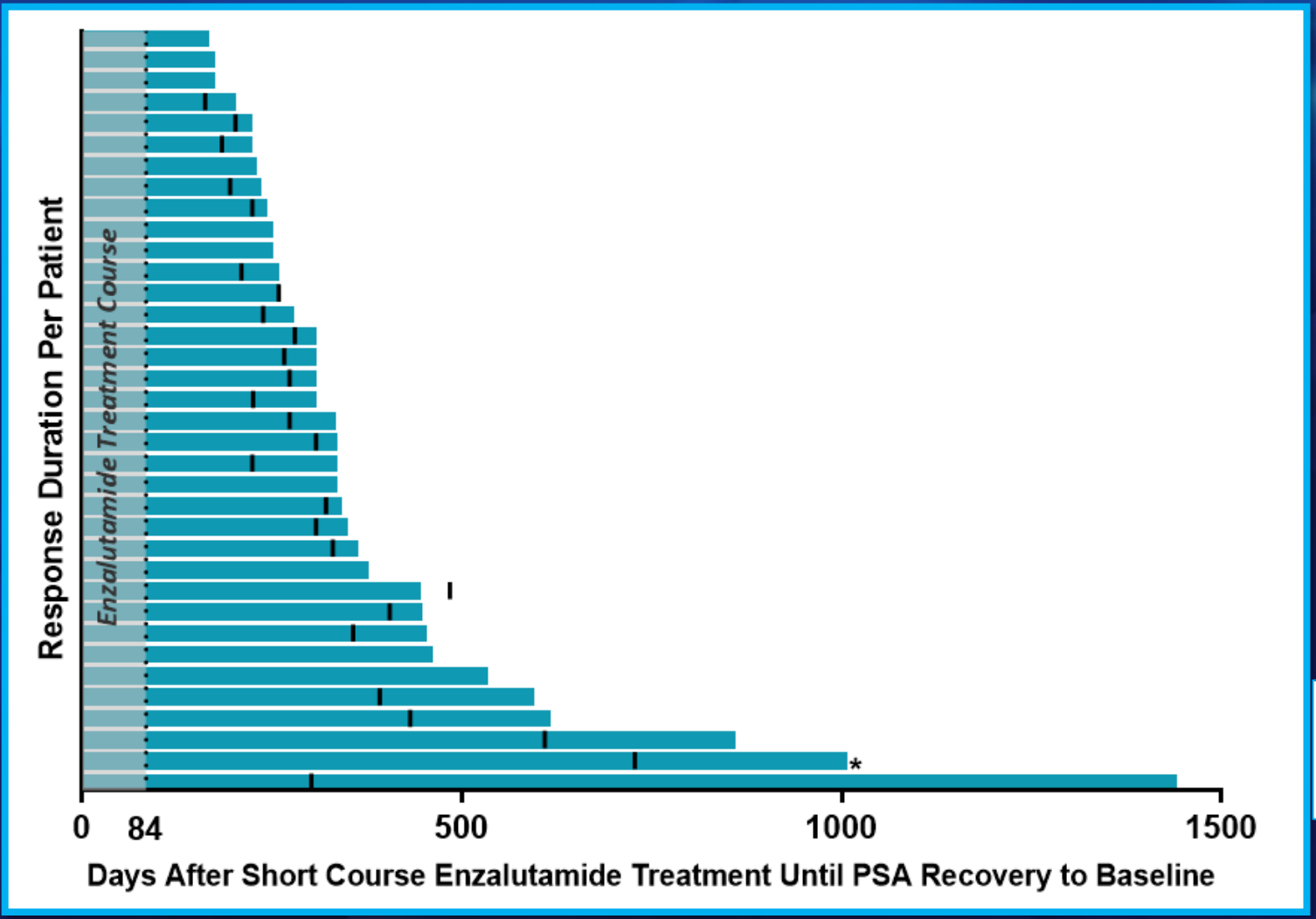
Time until PSA Recovery to Baseline after 3 months of Enzalutamide for BCR (no ADT)



Median Days Until PSA Recovery to Baseline

Course 1: 308 (224 after 84 days of enzalutamide)
Course 2: 273 (189 after 84 days of enzalutamide)

Course 1 of Enzalutamide

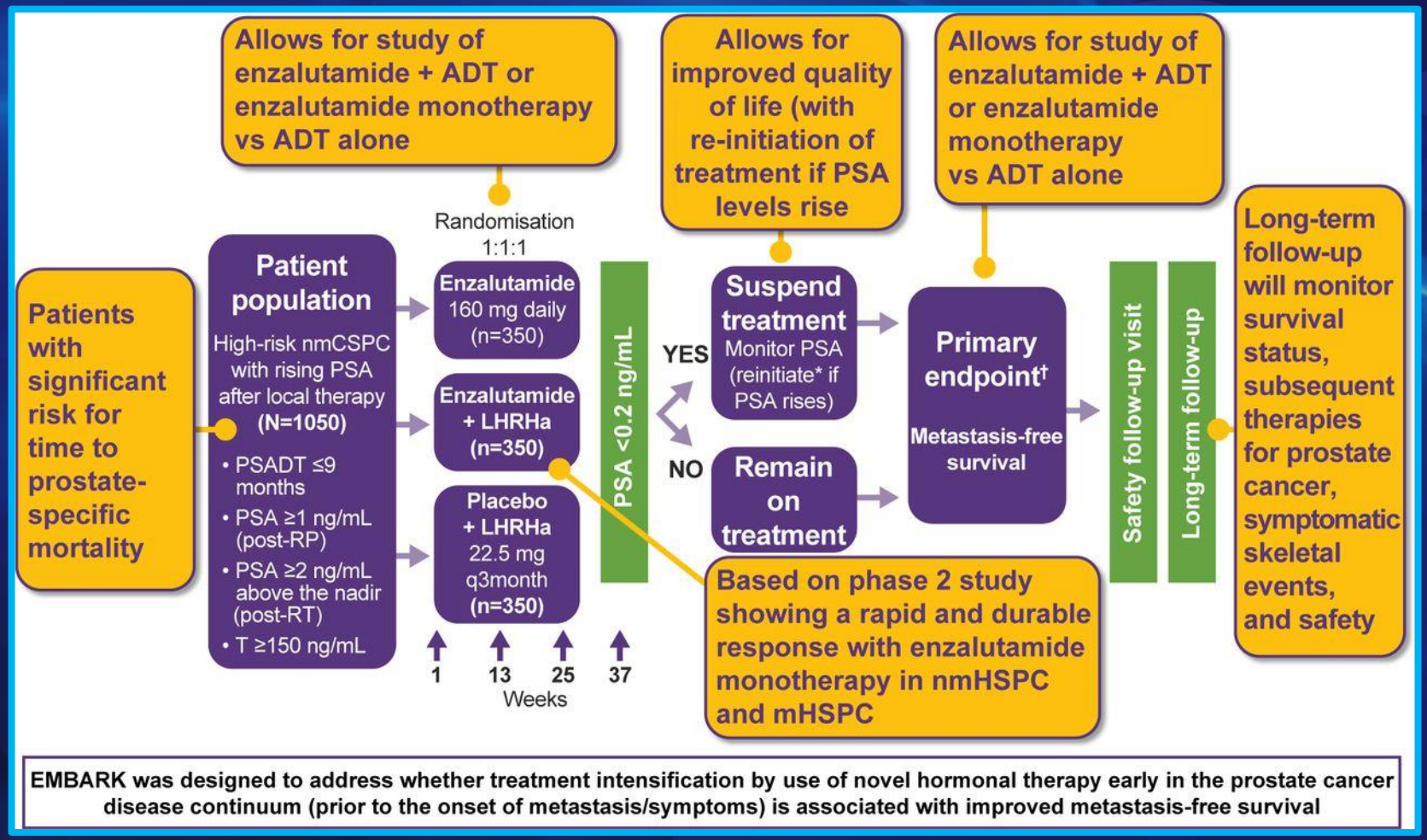
Course 2 of Enzalutamide (where applicable)

*Ongoing - PSA remains below baseline

Madan RA, et al. JITC, 2020

National Cancer Institute

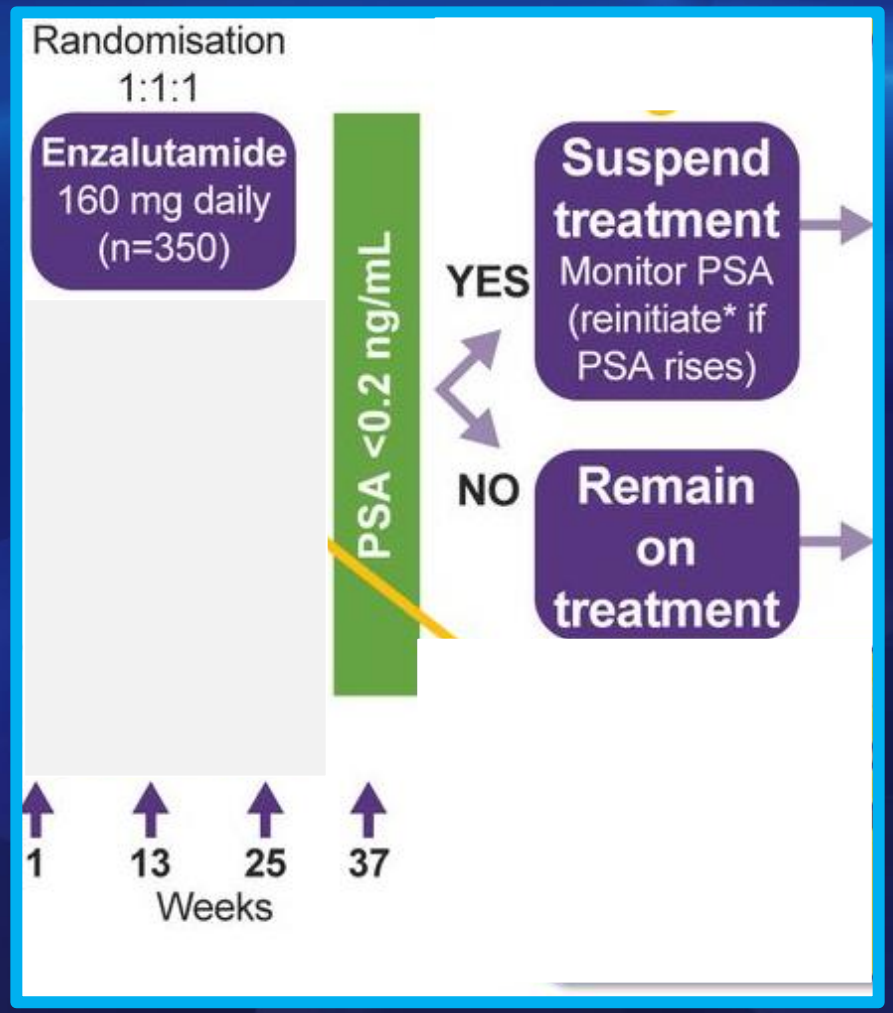
EMBARK – Study of ADT and Enzalutamide in BCR



Freedland SJ et al. BMJ Open 2021

National Cancer Institute

EMBARK - Short Course Enzalutamide Improves Metastasis Free Survival vs ADT



Pfizer Science Products Stories Newsroom About

Phase 3 Study Shows XTANDI® (enzalutamide) plus Leuprolide Significantly Improves Metastasis-Free Survival in Men with Non-Metastatic Prostate Cancer

Thursday, March 16, 2023 - 07:30pm

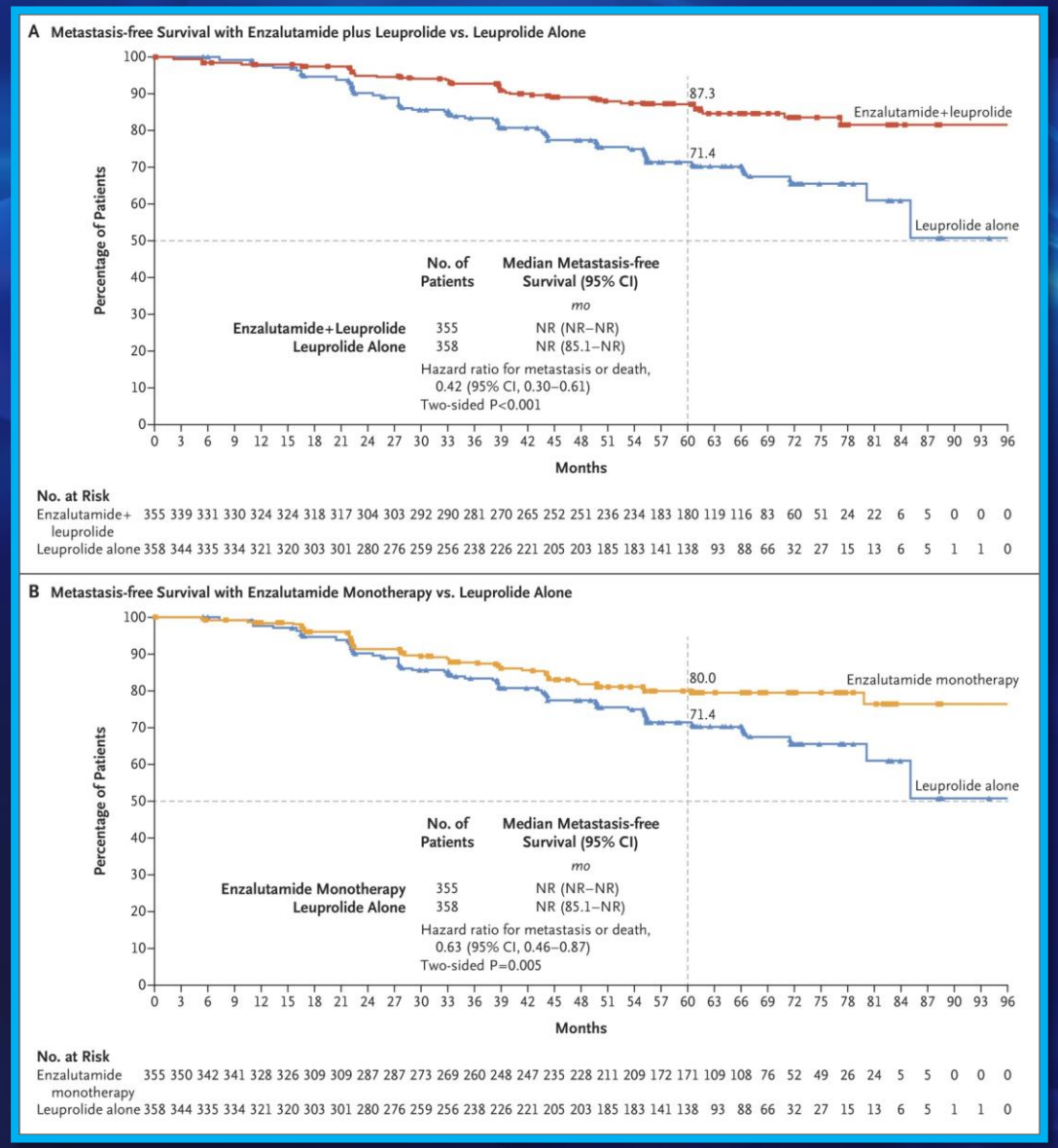
Pfizer and Astellas announce positive topline results from Phase 3 EMBARK trial

NEW YORK and TOKYO, March 16, 2023 – Pfizer Inc. (NYSE: PFE) and Astellas Pharma Inc. (TSE: 4503, President and CEO: Kenji Yasukawa, Ph.D., "Astellas") today announced positive topline results from the Phase 3 EMBARK trial evaluating XTANDI® (enzalutamide) in men with non-metastatic hormone-sensitive prostate cancer (nmHSPC; also known as non-metastatic castration-sensitive prostate cancer or nmCSPC) with high-risk biochemical recurrence (BCR). Patients enrolled in the trial were randomized to one of three study arms: XTANDI plus leuprolide, placebo plus leuprolide, or XTANDI monotherapy. The study met its primary endpoint with a statistically significant and clinically meaningful improvement in metastasis-free survival (MFS) for patients treated with XTANDI plus leuprolide versus placebo plus leuprolide.

At the time of the analysis, a positive trend in the key secondary endpoint of overall survival (OS) was also observed, but these data were not yet mature. Patients in the trial will be followed for a subsequent final OS analysis. The study also met a key secondary endpoint with a statistically significant and clinically meaningful improvement in MFS for patients treated with XTANDI monotherapy versus placebo plus leuprolide. Additional key secondary endpoints reached statistical significance, including time to prostate-specific antigen (PSA) progression

Freedland SJ et al. BMJ Open 2021

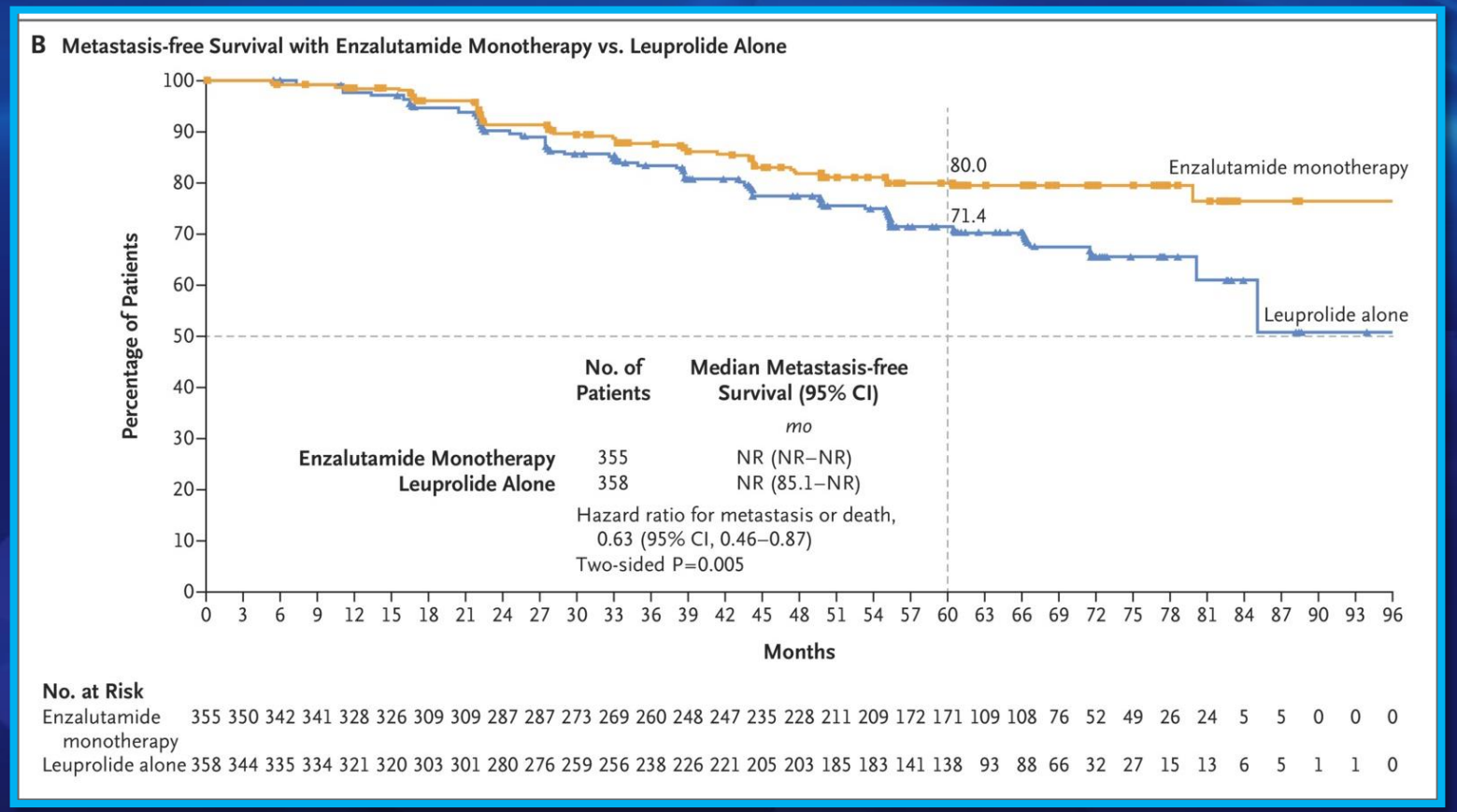
EMBARK – Study of Enzalutamide +/- ADT in BCR



Freedland SJ et al. N Engl J Med, 2023

National Cancer Institute

EMBARK – Study of Enzalutamide +/- ADT in BCR



Questions about EMBARK

- Toxicity
  - ~20% discontinuation
  - Fatigue
  - Gynecomastia

Freedland SJ et al. N Engl J Med, 2023

ARTICLE IN PRESS

EUROPEAN UROLOGY ONCOLOGY xxx (xxxx) xxx

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journal homepage: euoncology.europeanurology .com

European Association of Urology

EUO Priority Article – Editorial

Referring to the article published on pp. x-y of this issue

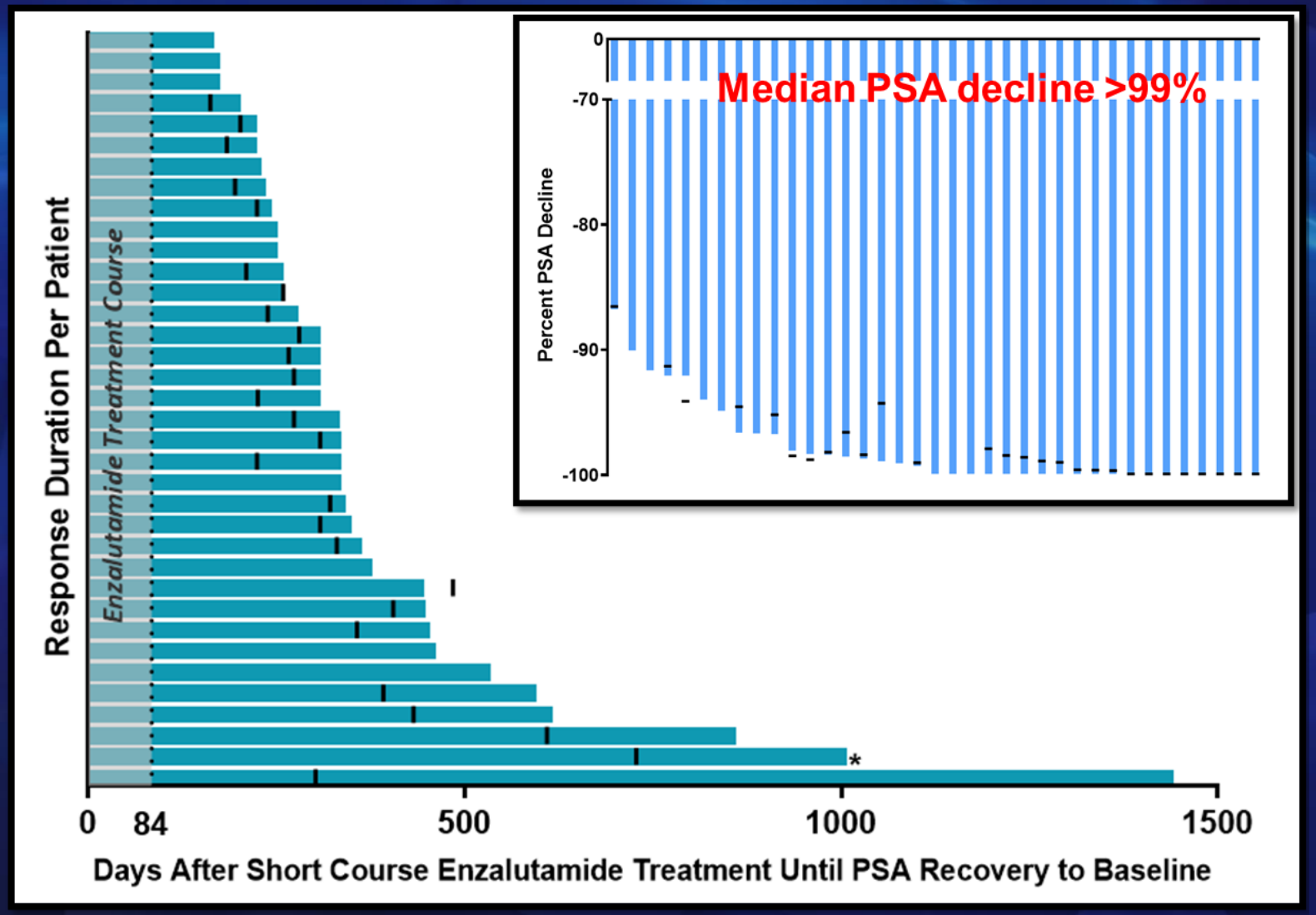
Enzalutamide Monotherapy in the EMBARK Trial Should Be Practice-changing and Existing Data Suggest How to Mitigate Toxicity

Lisa M. Cordes, Fatima Karzai, Ravi A. Madan *

Genitourinary Malignancies Branch, National Cancer Institute, Bethesda, MD, USA

"While enzalutamide monotherapy offers the greatest therapeutic novelty and opportunity to preserve quality of life, much concern has been raised about associated Toxicities… Existing data may highlight a path forward on how to optimize enzalutamide monotherapy."

3 Months of Enzalutamide in BCR With NO ADT



Madan RA, et al. JITC, *2021*

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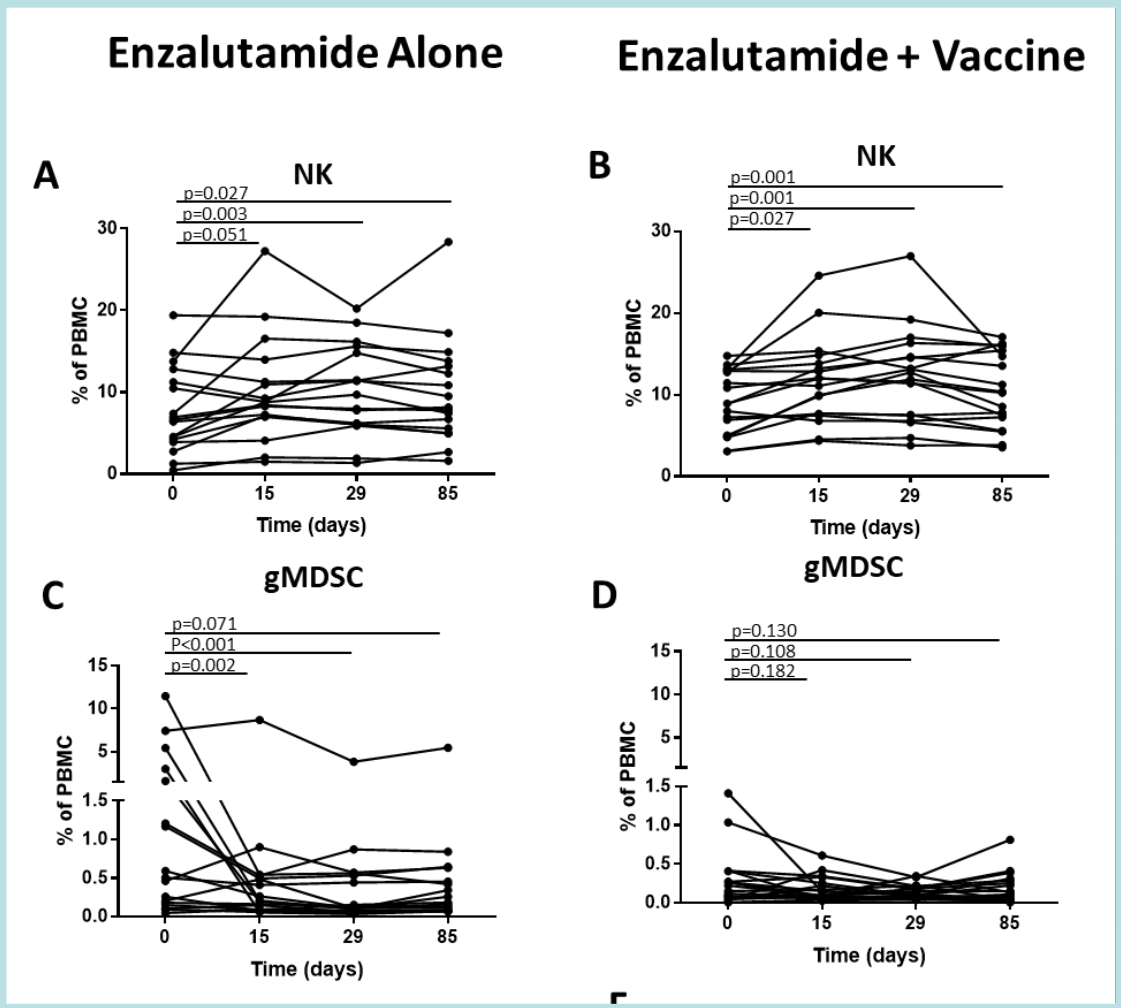
Enzalutamide Increases NK Cells and Decreases MDSCs in BCR



Center for Immuno-Oncology

Renee N. Donahue, Ph.D.

National Cancer Institute

Madan RA, et al. JITC, *2021*

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

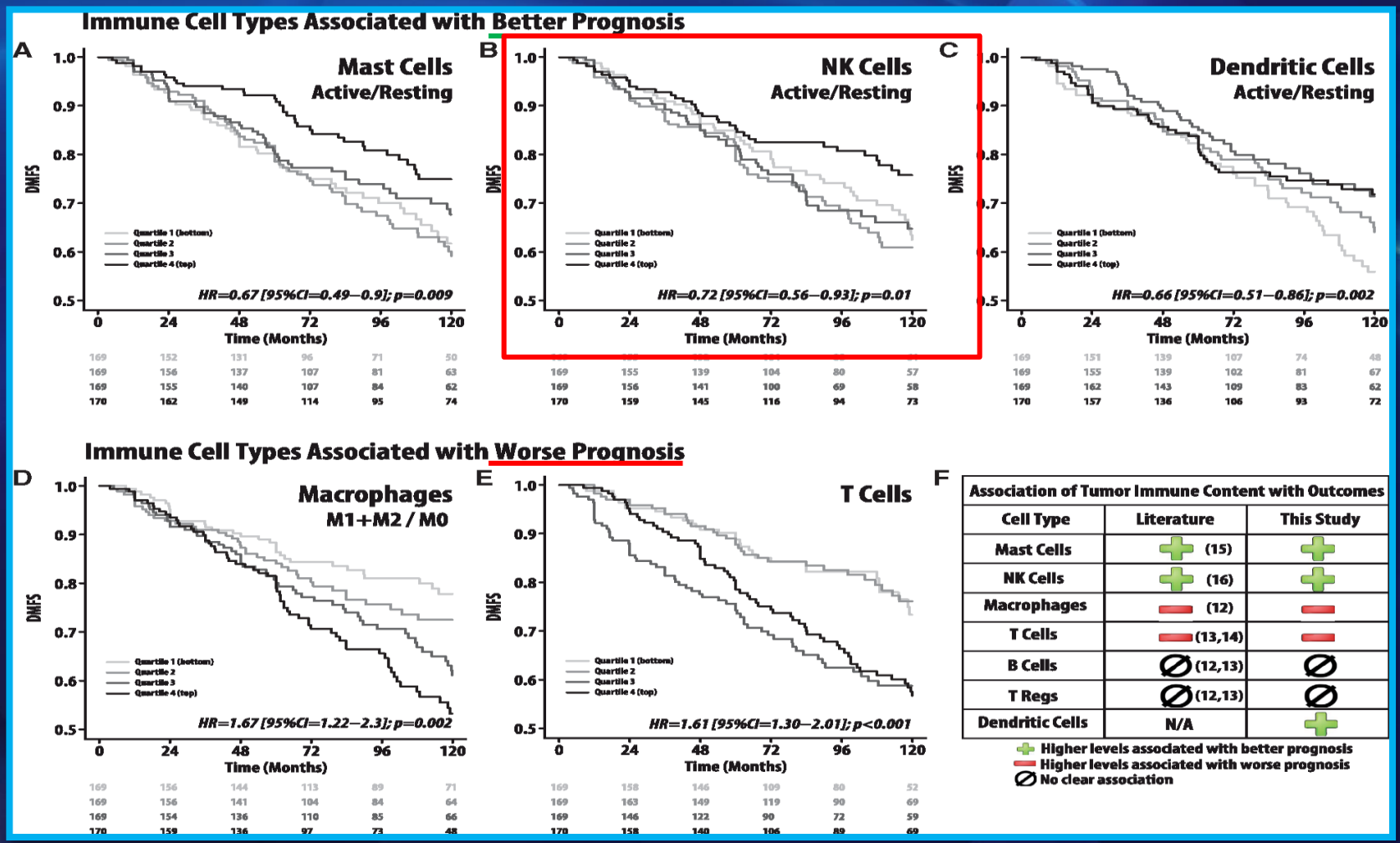
- Enzalutamide without ADT (biochemically recurrent study)
- Enzalutamide with ADT (1st line mCRPC trial)
- Docetaxel with ADT in mCSPC *(unpublished)*

- *No other consistent changes in other peripheral immune subsets including T-cells.*

Madan RA et al. JITC, 2021
Madan RA et al. ESMO, 2022
Chandran E at al. ASCO GU, 2023

Collaboration with Dr. Rene Donahue, CIO, NCI

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
Flammiger A et al. APMIS 2012
McArdle PA et al. J Cancer, 2004
Lancotti M. et al.. Bio Res Int 2104
Gannon PO et al.J Immunol Methods, 2009

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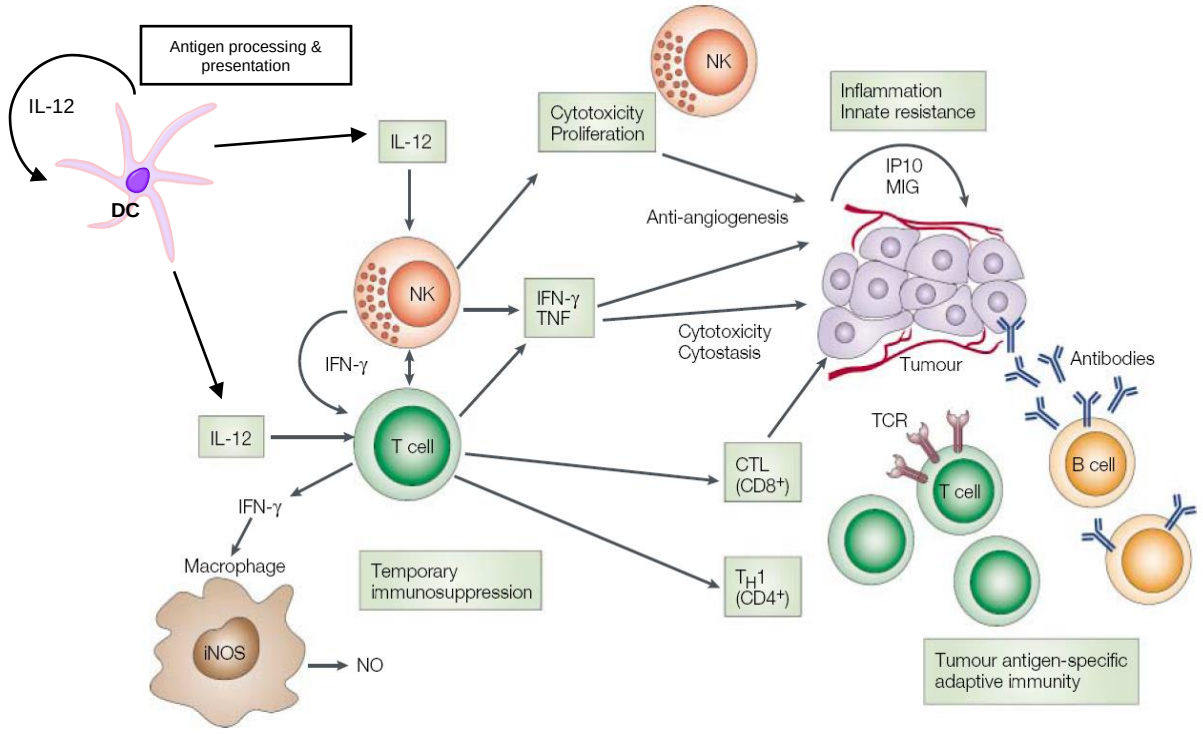
IL-12

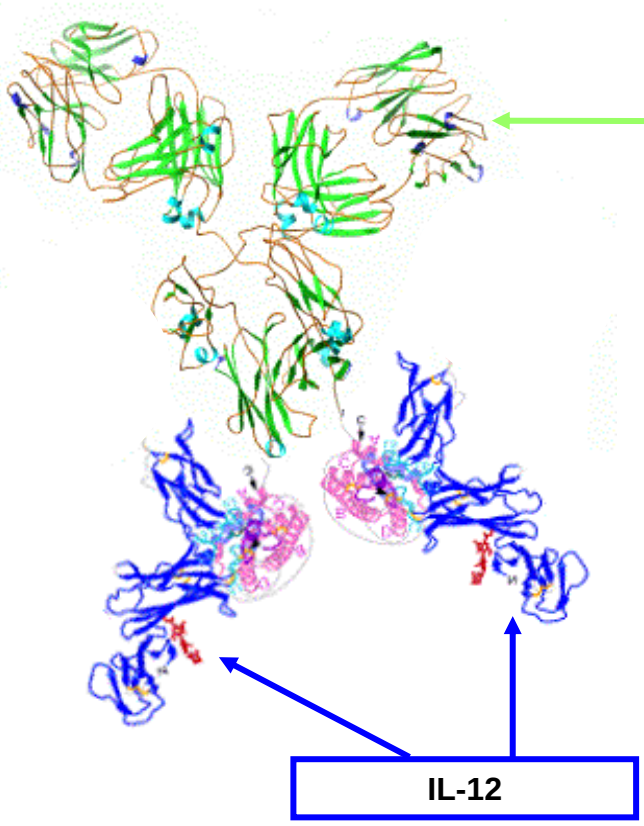
- Induces differentiation of naive CD4+ T-cells to the Th1 phenotype
- Increases proliferation and lytic capacity of CTL and NK
- Promotes IFN-γ production by NK and T cells

Systemic IL-12 hampered by severe systemic toxicity

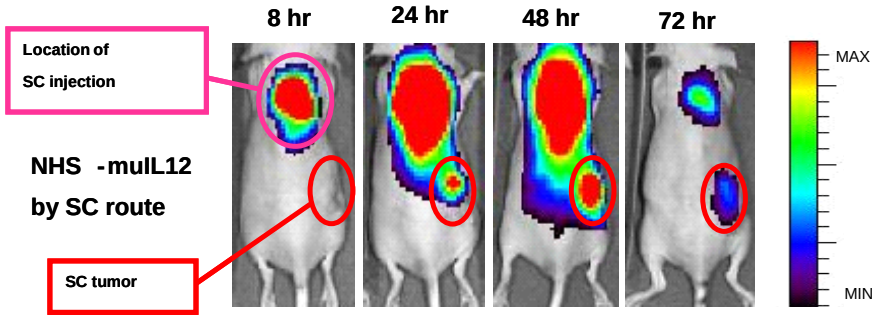


Modified from Trinchieri G, *Nature Reviews Immunology* 2003

Immunocytokine: PDS01ADC



NHS-76 antibody binds to DNA exposed in necrotic regions of tumors

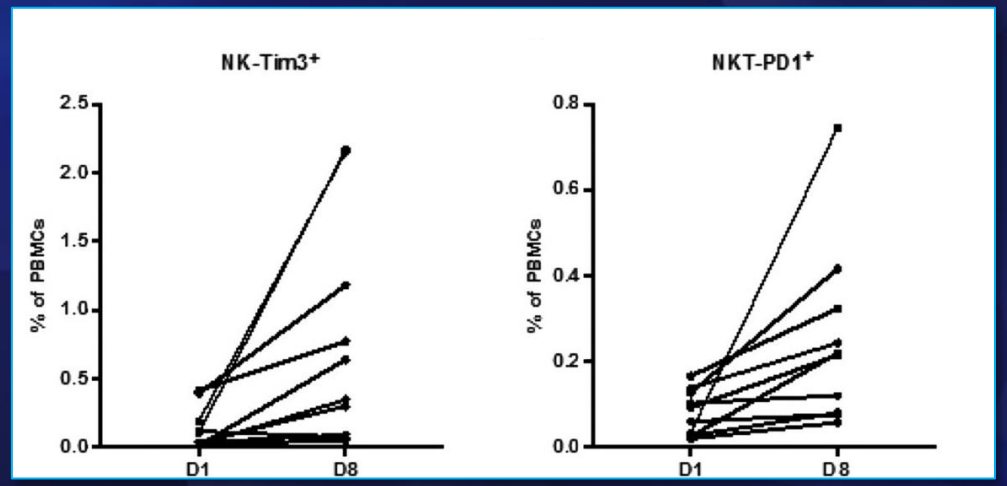


Dorsal imaging of SC Lewis Lung Carcinoma tumors on right rear flank of a mouse

PDS01ADC Phase 1 Study

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

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
NKT-PD1+	0.08 (0.03-0.013)	0.22 (0.08-0.35)	Increase	0.002	0.008

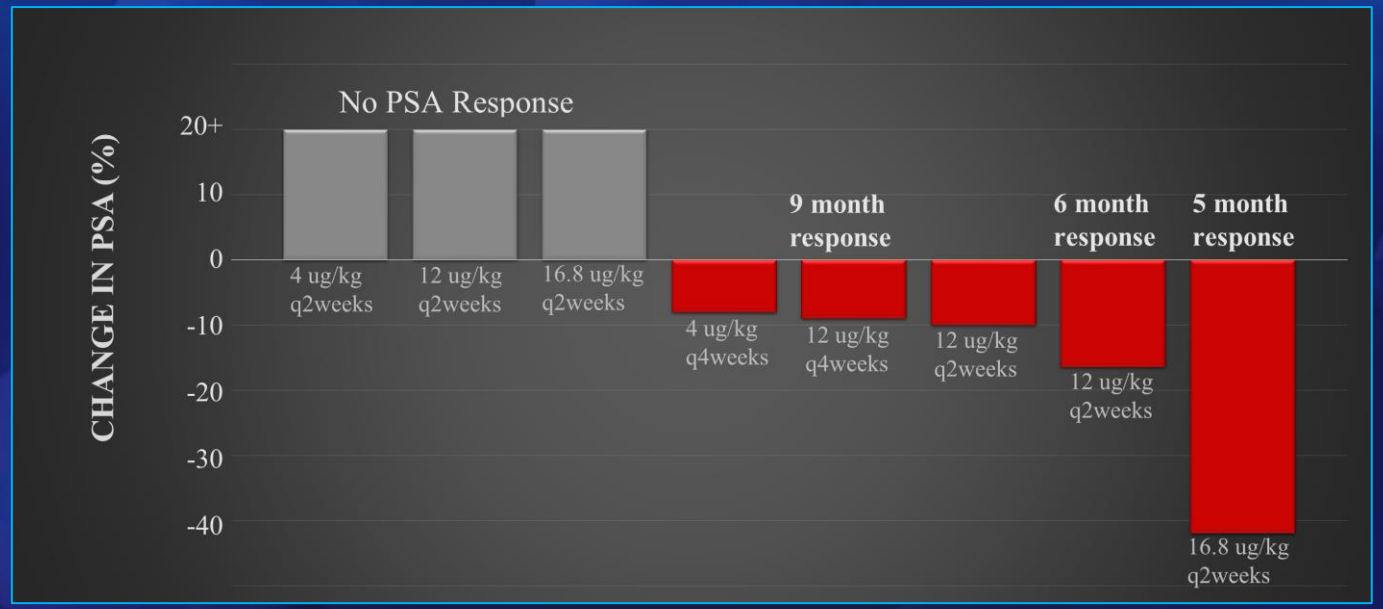


Most Common Toxicity:
- Fevers (~48 hours)
- Fatigue (peaks w/in 48 hours)

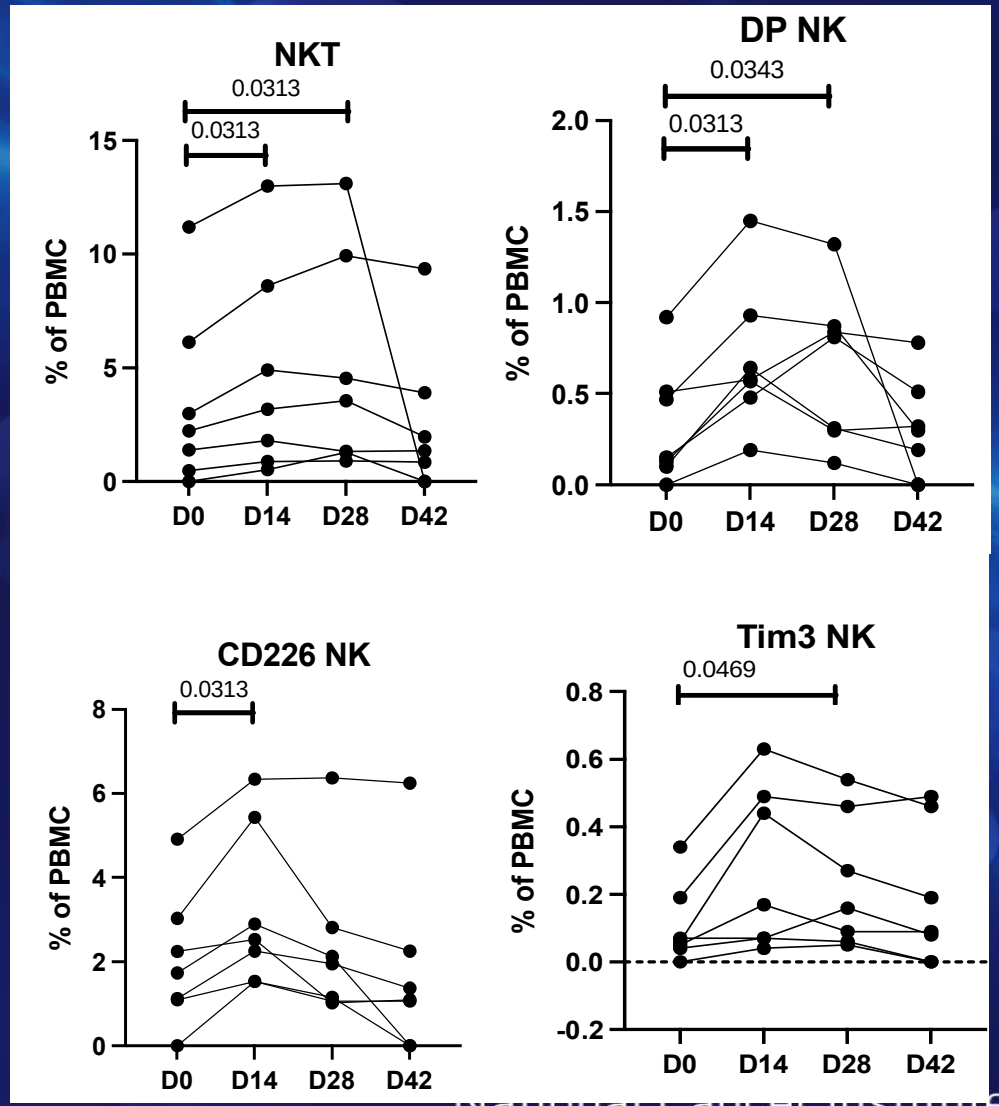
Strauss J et al, Clin Cancer Res 2019

PDS01ADC Phase 1 Study: Prostate Cancer Patients

Confirmed PSA Responses



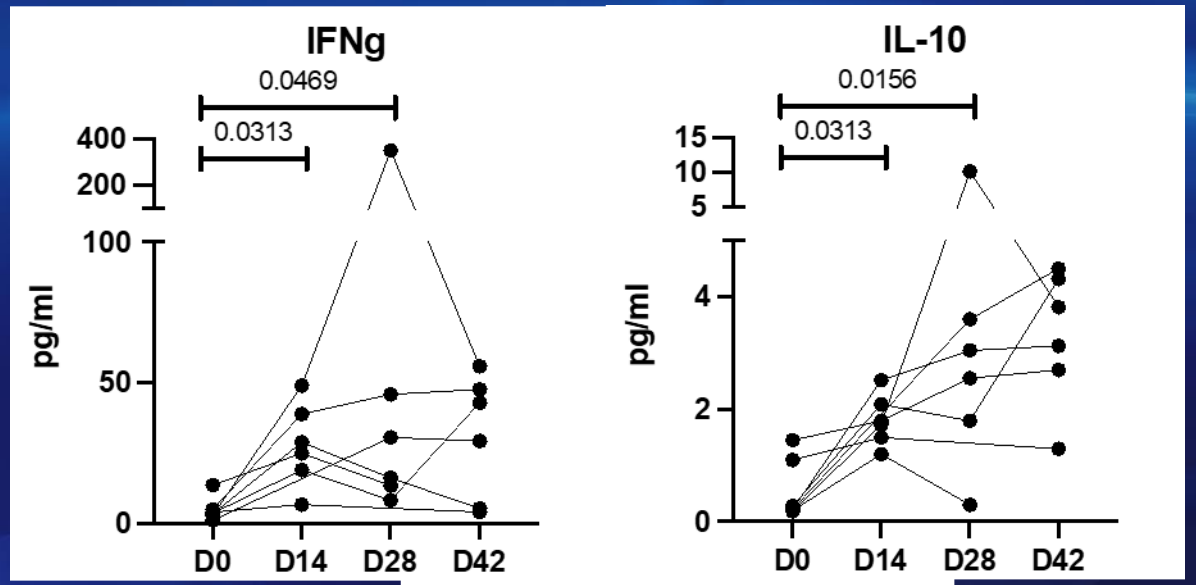
NK Cell Subpopulations

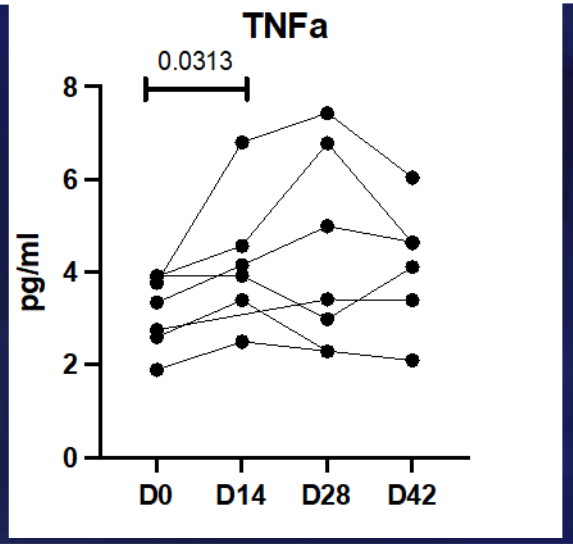


Meininger L. et al, ASCO GU, 2022

PDS01ADC Phase 1 Study: Prostate Cancer Patients

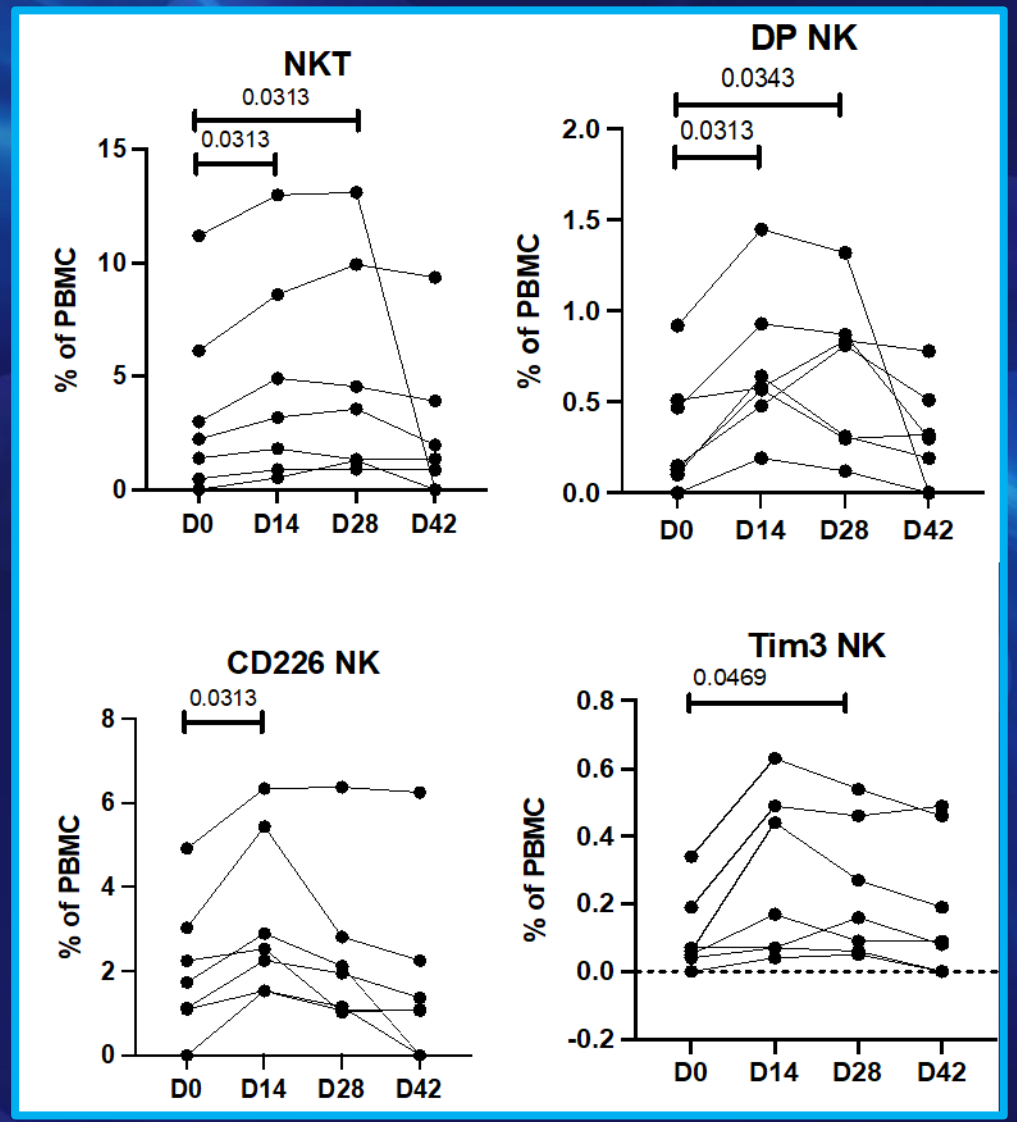
NHS-Il12 Enhances Systemic Cytokines c/w Immune Activation





Collaboration with
Dr. Donahue, CIO

NK Cell Subpopulations



Meininger L. et al, ASCO GU, 2022

Docetaxel + PDS01ADC

Phase I Trial Design

Safety Cohort Metastatic Prostate Cancer (Cohort 1)

Docetaxel 75 mg/m^2
And
PDS01ADC Starts Cycle 2

Safety 3+3 Design

PDS01ADC Dose Levels
8 mcg/kg
12 mcg/kg
16.8 mcg/kg

Eligible patients include both mCSPC and mCRPC

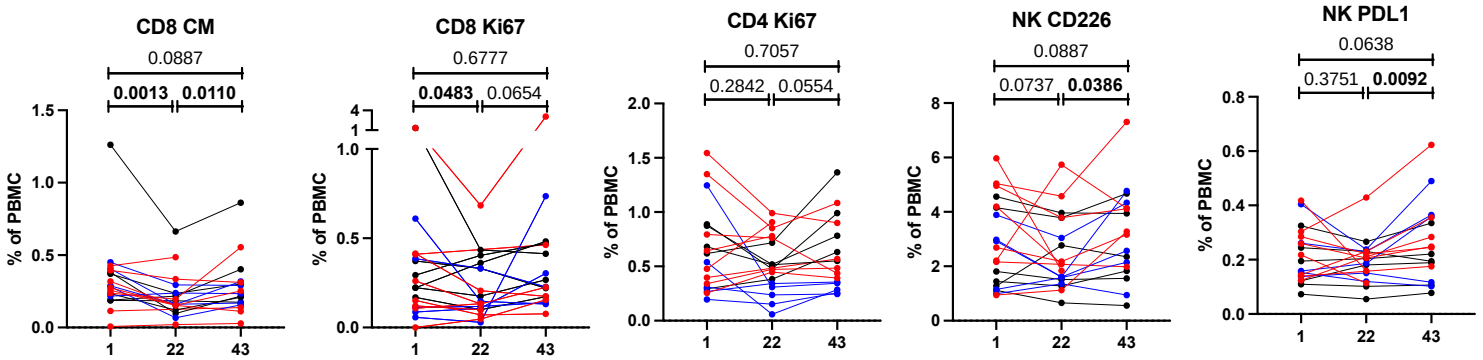
Cytokines 2023
International Cytokine & Interferon Society ICIS

Atiq M. et al, ASCO GU, 2022

National Cancer Institute

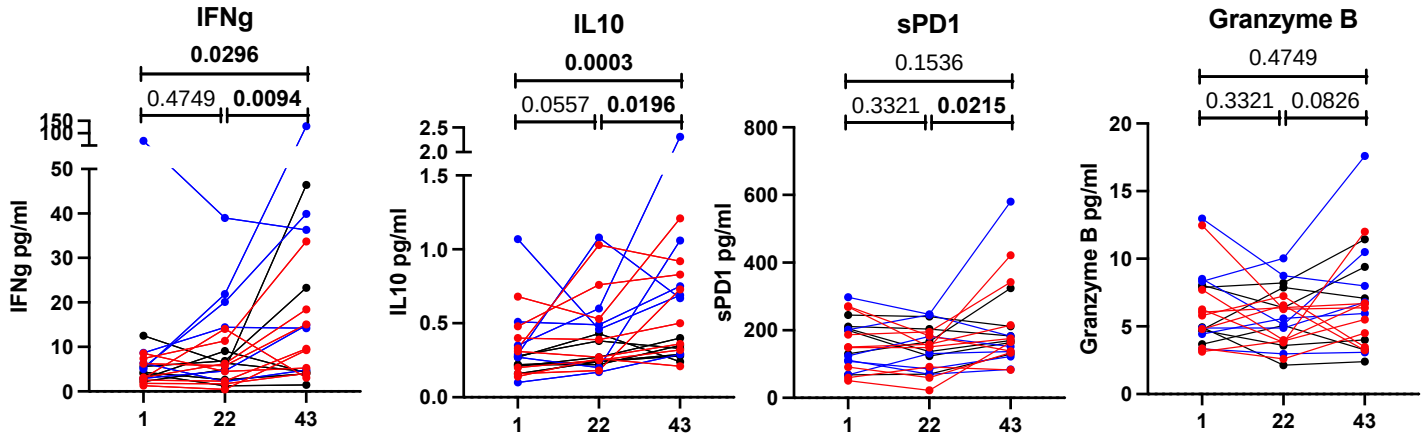
Adding PDS01ADC to Docetaxel at Day 22 Increases Immune Activation in a Dose-Independent Fashion

Increases



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

Increases

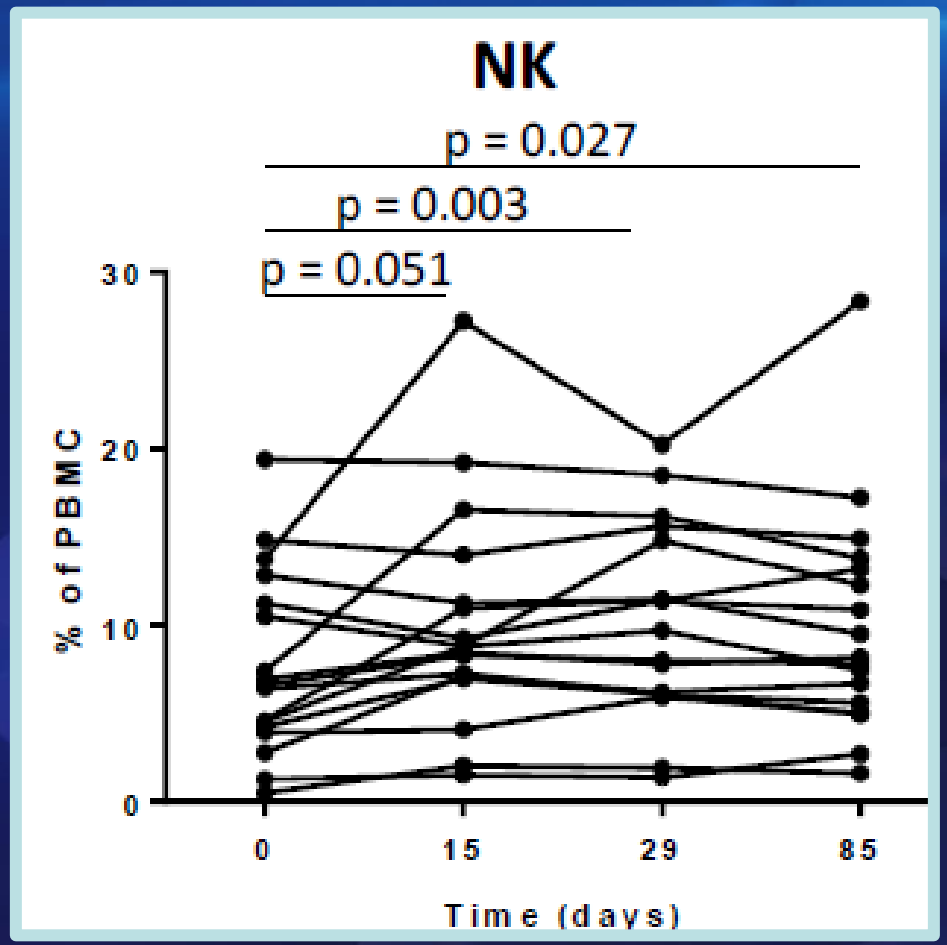


Treatment Schedule

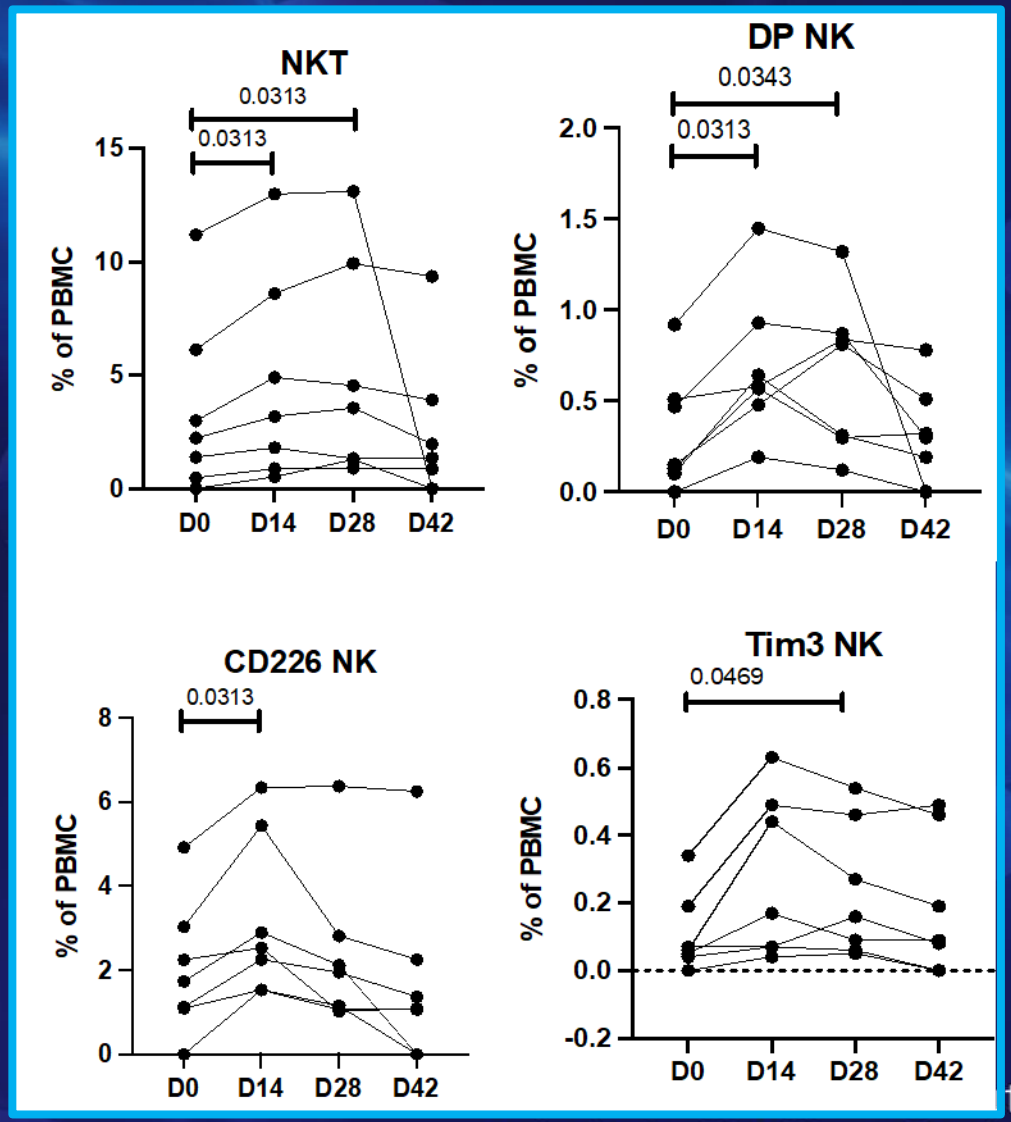
D1: Docetaxel
D22: Docetaxel + PDS01ADC

Unlike single agent PDS01ADC, 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

Enzalutamide Increases NK Cells in BCR



PDS01ADC Enhances NK Cells in Prostate Cancer Patients



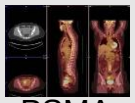
Madan RA, et al. JITC, *2021*

3 months Enzalutamide With NO ADT in BCR +/- PDS01ADC

Study Now Accruing at the NCI

Enroll (n=50)

Key Eligibility
PSA DT <12 mos
PSA >1.0 ng/ml
Testosterone > 100
PSMA+
Negative CT and Bone Scan

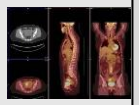


PSMA

Randomize

Enzalutamide+ PDS01ADC for 3 months

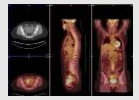
Enzalutamide for 3 months



PSMA

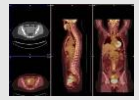
Monitor off Treatment as PSA Recovers to Baseline

Restage: CT Bone Scan PSMA



PSMA

Course 2 Enzalutamide for 3 months



PSMA

Primary Endpoint: Time to PSA Recovery

Secondary Endpoints: Immune Response
PSMA Imaging Responses
PSA Responses

National Cancer Institute

PSA Responses and PSMA Scan Changes after Immunotherapy for Biochemically Recurrent Prostate Cancer (BCR) Without Androgen Deprivation Therapy (ADT)

Ravi A. Madan[1], Esther Mena[2], Elias Chandran[1], Jeanny Aragon-Ching[3], Philip M. Arlen[1], Liza Lindenberg[2], Clara C. Chen, Lisa Cordes[1], Sheri McMahon[1], Elizabeth Lamping[1], Amy Hankin[1], Monique Williams[1], Yolanda McKinney, William D. Figg[1], James L. Gulley[4], Peter Choyke[2], Fatima Karzai[1]

[1]Genitourinary Malignancies Branch, [2]Molecular Imaging Branch, Molecular Imaging Program, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD, [3]Inova Schar Cancer Institute, Fairfax, VA, [4]Center for ImmunoOncology, National Cancer Institute, National Institutes of Health, Bethesda, MD

Abstract

Background:

Patients (pts) with BCR have a rising PSA after definitive therapy but negative CT/Tc99 scans. Regardless of PSMA scan findings, no treatments have extended survival in BCR. Biologically, BCR has less tumor burden, less bone-based disease and pts have normal testosterone (T) relative to late stage disease. These key differences could lead to different clinical outcomes of immunotherapy in BCR relative to previous immunotherapy trials in metastatic pts.

Methods:

This study (NCT03315871) enrolled pts with negative CT/Tc99 scans, T>100, PSA> 0.8 ng/ml after surgery or 2.0 ng/ml after radiation. Pts had a PSA doubling time (PSADT) of 5-15 months. Treatment was 2 pox viral-based therapeutic cancer vaccines targeting PSA and MUC1/CEA respectively for 7 months. Pts were monitored thereafter. PSA declines were noted based on multiple confirmed PSA declines from an intra-study apex PSA (ISAP; Madan ASCO GU 2018). Serial PSMA imaging was done in most pts.

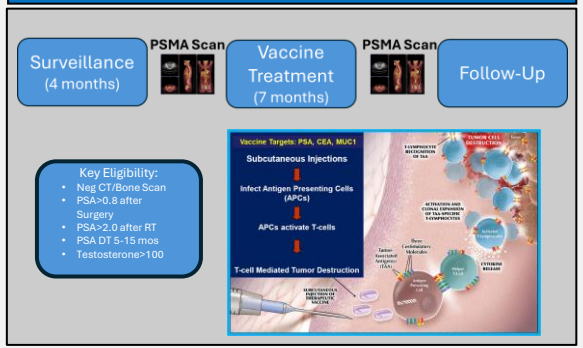
Results:

27 pts enrolled and 23 were treated/evaluable for response. Baseline medians include age of 69.5 years (58-84), PSA 5.1 ng/ml (0.9-32.9) and PSA DT 8.1 months (5-14.4). The treatment was well tolerated with grade 1/2 injection site reactions and rare transient flu-like symptoms. 11/23 (48%) pts had >30% slowing of the PSADT while on treatment, 7/23 (30%) were stable. 8/23 (35%) evaluable pts had confirmed ISAP PSA declines after treatment with a median decline of 19% (11-66%) lasting a median of 140 days (56-375). 21 pts had baseline and follow-up PSMA imaging with 9 having declines in PSMA tumor volume (PSMA-TV). 5/9 pts with declines in PSMA-TV also had PSA declines. The other 4 had stable PSA values prior to PSMA. Of interest, a pt with rising PSA for 553 days after therapy before a 66% confirmed PSA decline had a PSMA-TV decline that mirrored the PSA trend.

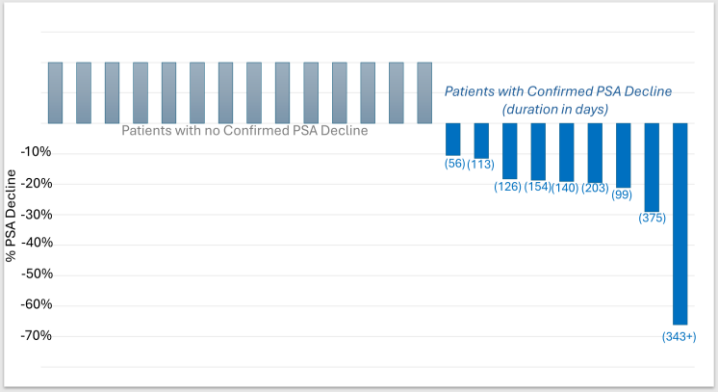
Conclusions:

This is the first study in BCR to show PSA declines after immunotherapy without ADT that are associated with decreased PSMA-TV. The data further support the potential of immunotherapy in BCR without ADT despite negative immunotherapy trials in metastatic prostate cancer. Additional BCR immunotherapy studies are ongoing/planned at the NCI with serial PET imaging.

Trial Design



Confirmed PSA Declines From Intra-Study Peak



CONCLUSIONS

- This is the second trial in BCR to suggest a subset of patients can have delayed PSA responses to vaccine-based immunotherapy without ADT
- This is the *first* trial in PSMA+ BCR to describe PSA declines and changes in total volume on PSMA imaging
- This study provides proof of concept that immunotherapy may be effective in controlling PSMA+ BCR over time without ADT and its accompanying side effects
- This study is part of a programmatic approach at the NCI to explore ADT-sparing strategies in BCR, including PSMA+ BCR

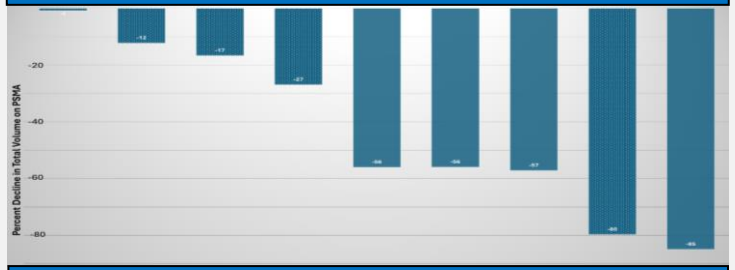
Patient Characteristics at Baseline

	N= 23	
Median Age	69.5 years	(58-84)
PSA (ng/ml)	5.1 ng/ml	(0.9-32.9)
PSA Doubling Time	8.1 months	(5.0-14.4)
Evaluable Patients with PSMA+ Disease and Serial Scans	21 patients	

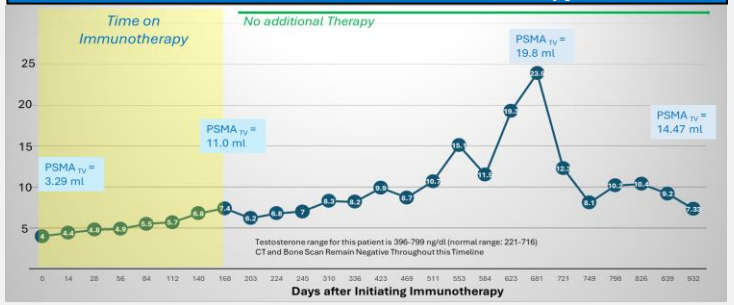
Changes in PSA DT after Treatment

	N= 23	
>30% Improvement or decrease in PSA DT	11 of 23 patients	48%
Stabilization of PSA DT	7 of 23	30%
>30% Improved or Stable PSA DT	8.1 months	(5.0-14.4)

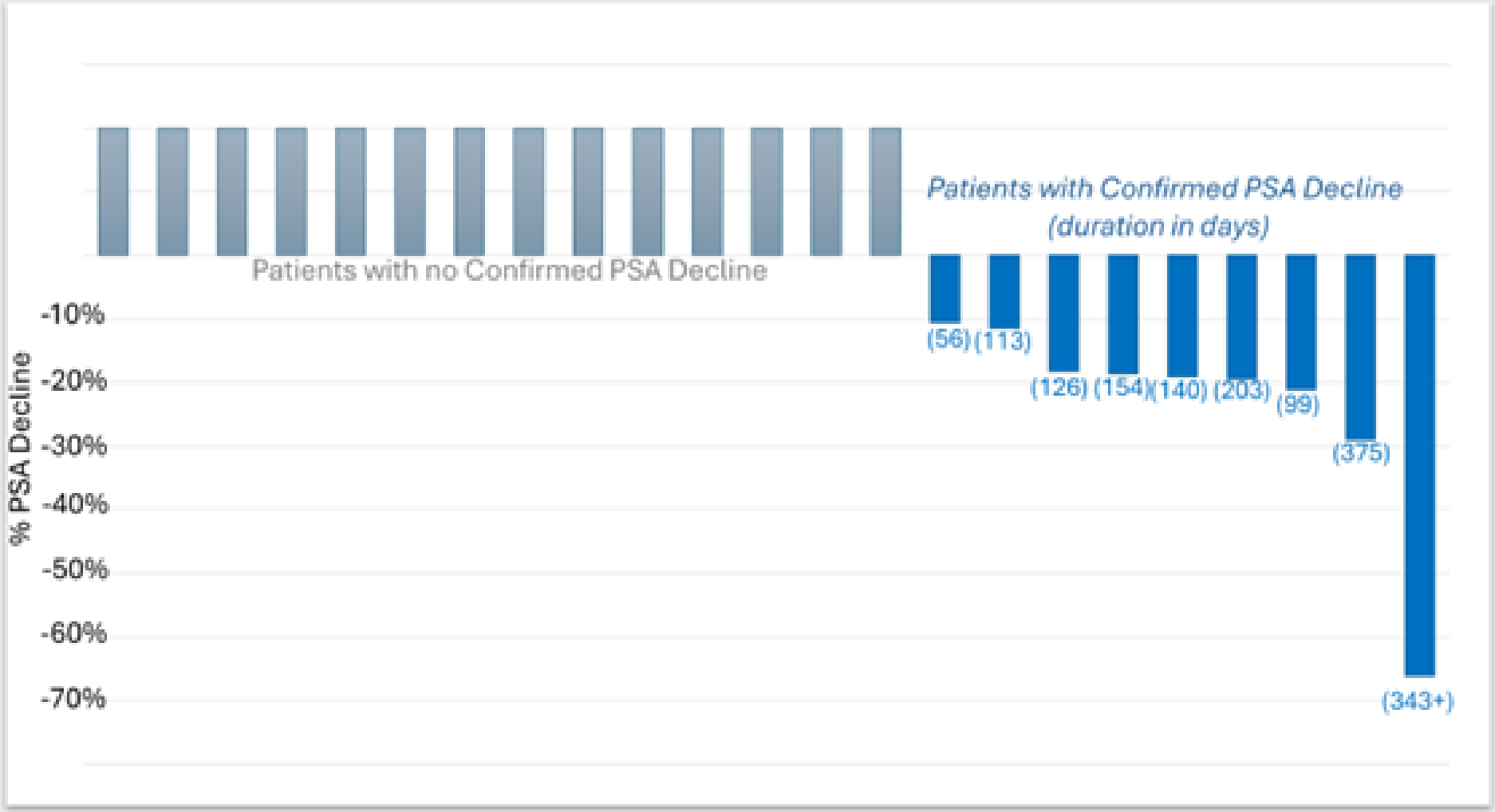
Patients with Declines in Total Volume on PSMA



Case Study of Delayed PSA and $PSMA_{TV}$ Response



Confirmed PSA Declines From Intra-Study Peak after Vaccine



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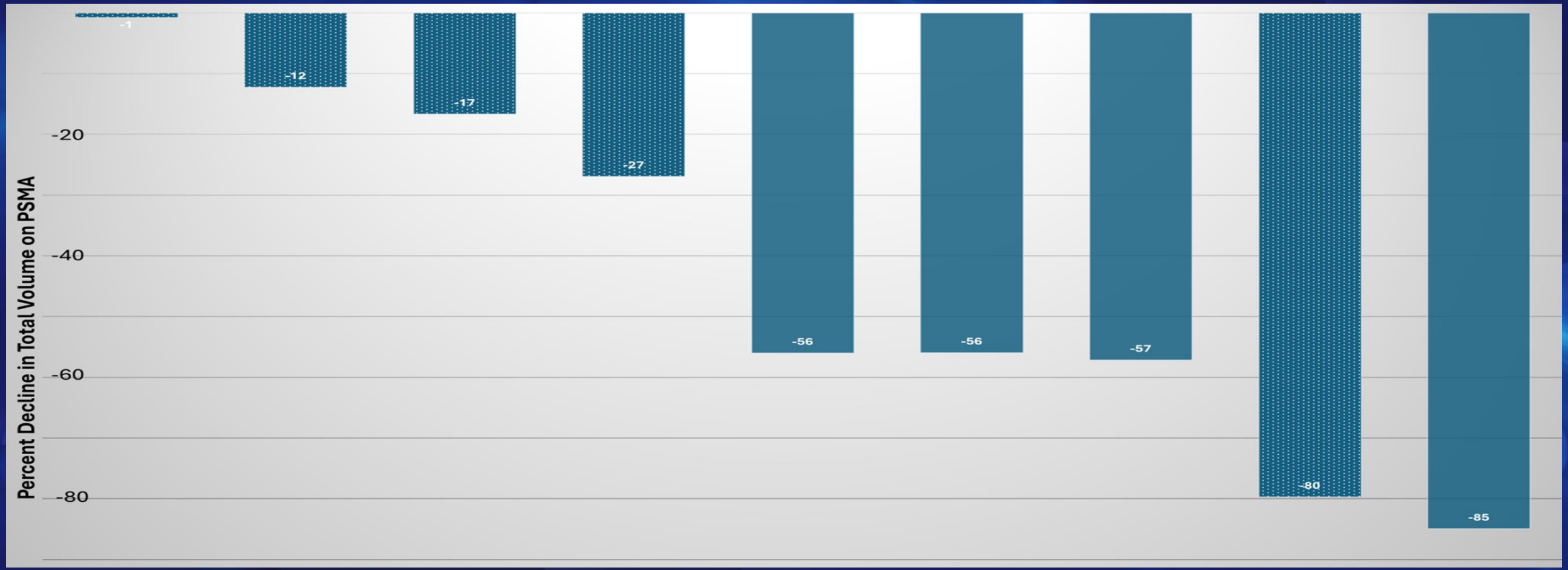
Patients with Declines in Total Volume on PSMA After Vaccine



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Conclusions

- Enzalutamide is an option for patients with BCR prostate cancer
- Enzalutamide enhances NK cells in BCR
- PDS01ADC can enhance NK cells and has been associated with PSA declines in prostate cancer
- The current study will evaluate enzalutamide and PDS01ADC in BCR

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