Bipolar Androgen Therapy (BAT) in men with prostate cancer

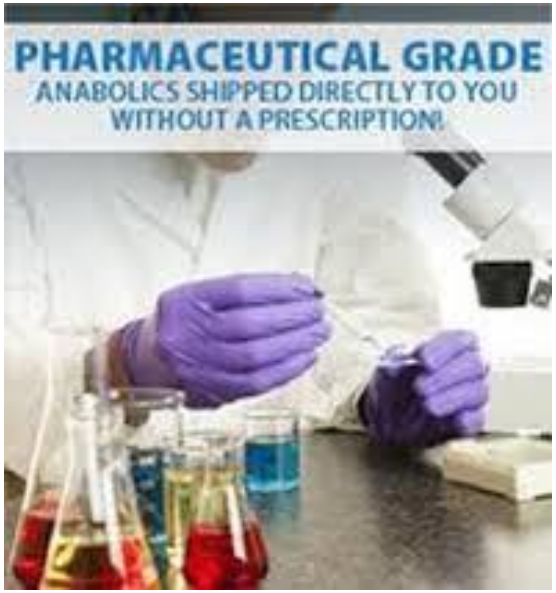
Samuel Denmeade, MD
Professor of Oncology, Urology and Pharmacology
The Johns Hopkins University School of Medicine, Baltimore, MD

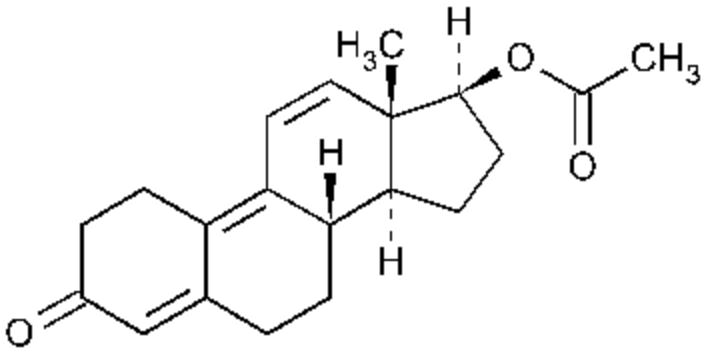
Presentation Overview

- **Androgen and Androgen Signaling 101**
- **Rationale For Bipolar Androgen Therapy (BAT)**
- **Results from the RESTORE study testing BAT in Castration Resistant Prostate Cancer**
- **The multi-center TRANSFORMER Trial**
- **Future Directions**
- **Results of BATMAN trial testing BAT as part of Intermittent Hormone Therapy strategy**

Testosterone Replacement

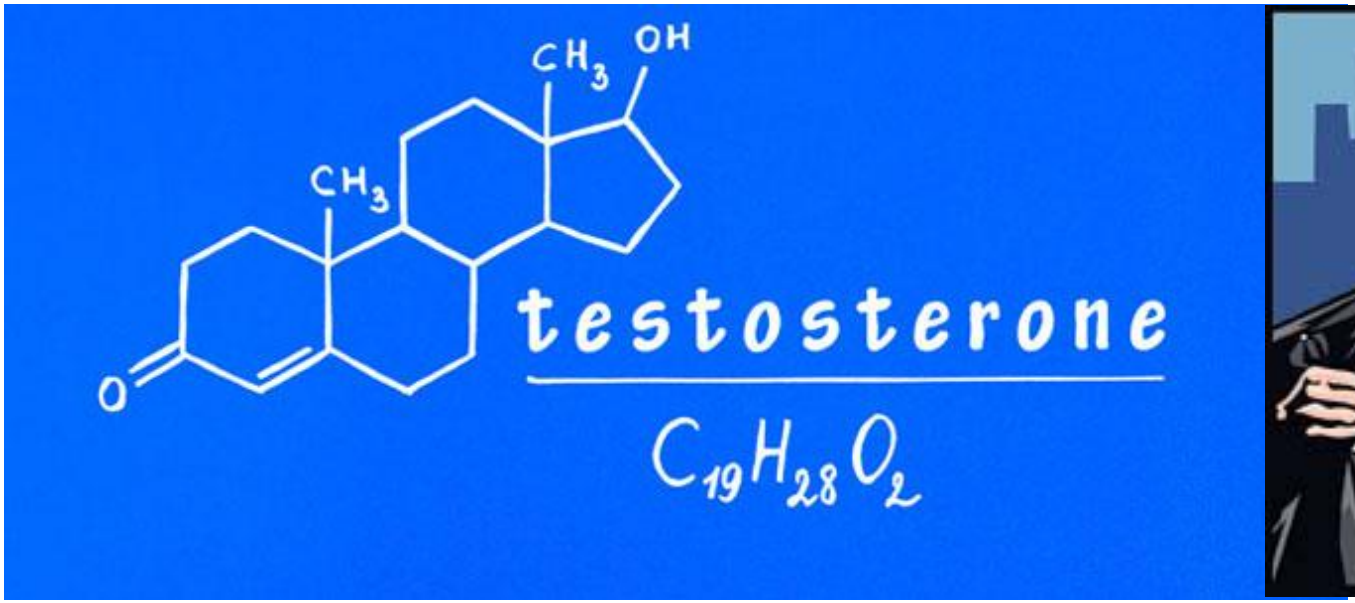
Anabolic Steroids





Trenbolone Acetate
(Fina-Finaplix H pellets)

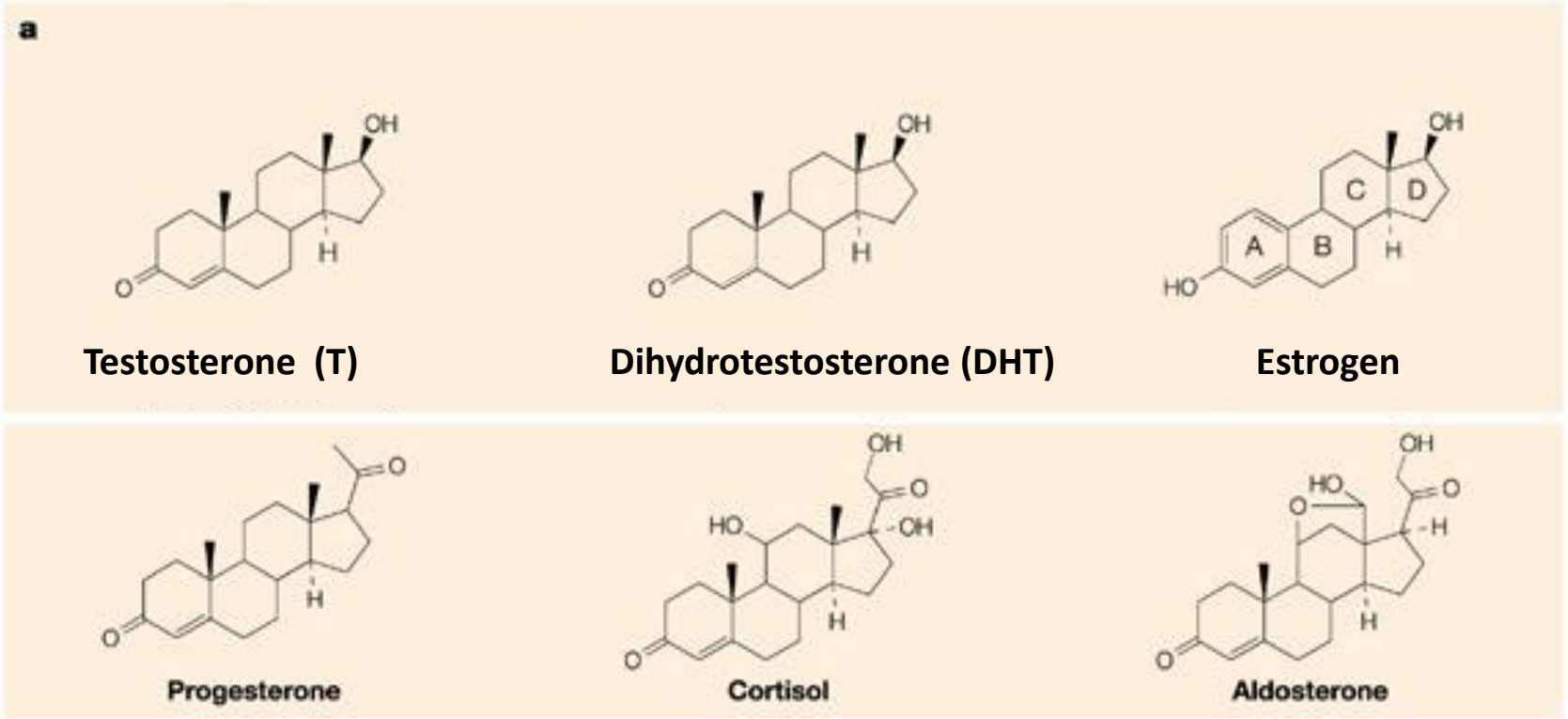
High Dose Testosterone as Treatment for Prostate Cancer



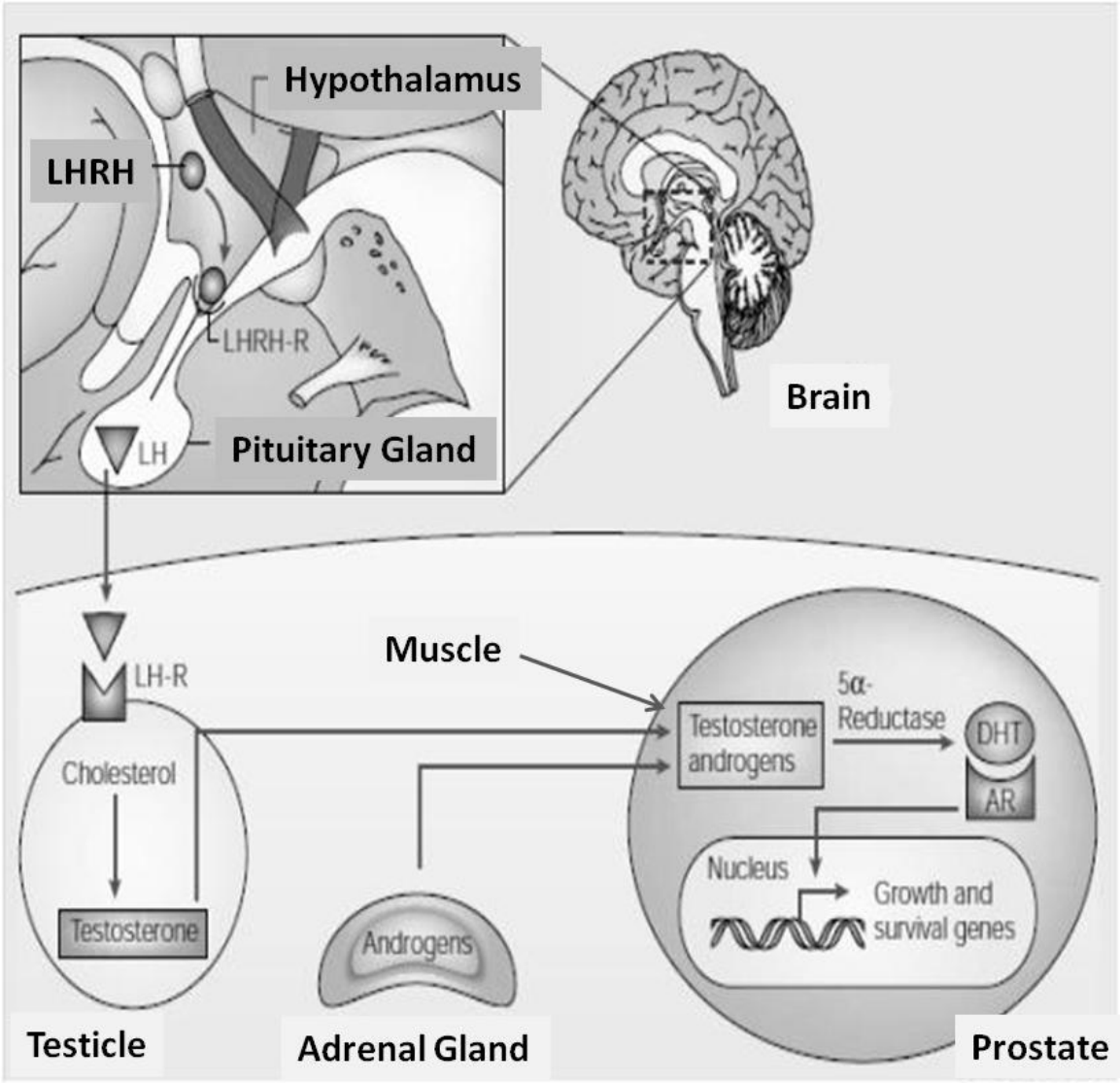
What Are Androgens?

- **Steroid hormone which can bind to Androgen Receptor**
  - Testosterone, Dihydrotestosterone (DHT), DHEA, Androstenedione…
- **Sexual Differentiation**
  - Needed to make a Male (Female is Default)
- **Primary Sex Characteristics**:
  - Spermatogenesis
  - Accessory Sex Tissue Maintenance
    - Penis, Prostate...
- **Secondary Sex Characteristics**:
  - Bone density
  - Muscle mass
  - Libido
  - Hair growth
  - Hematopoiesis

What is a Steroid Hormone?



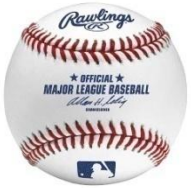
How are Androgens Made?



Androgen Receptor Signaling 101

Androgen Receptor

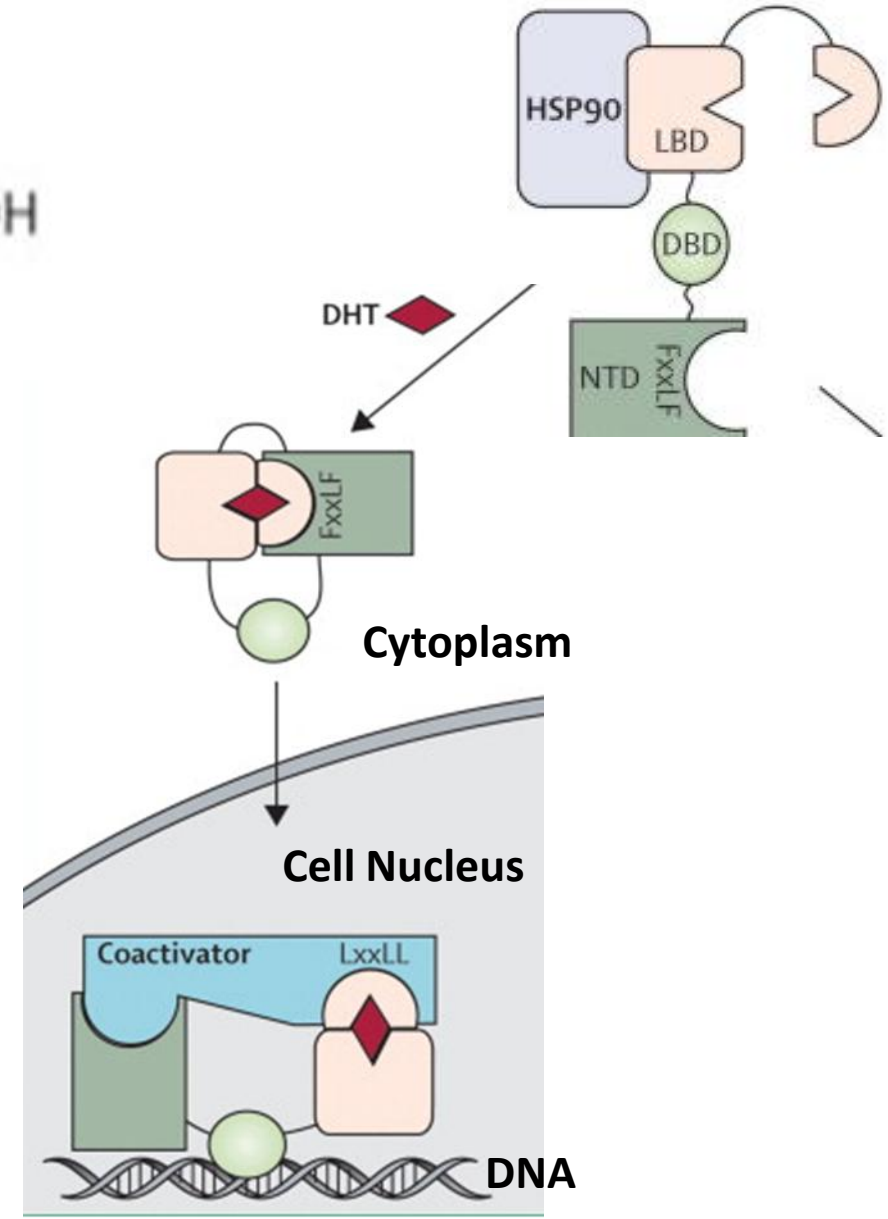
Androgen (Testosterone)



Active Androgen Receptor

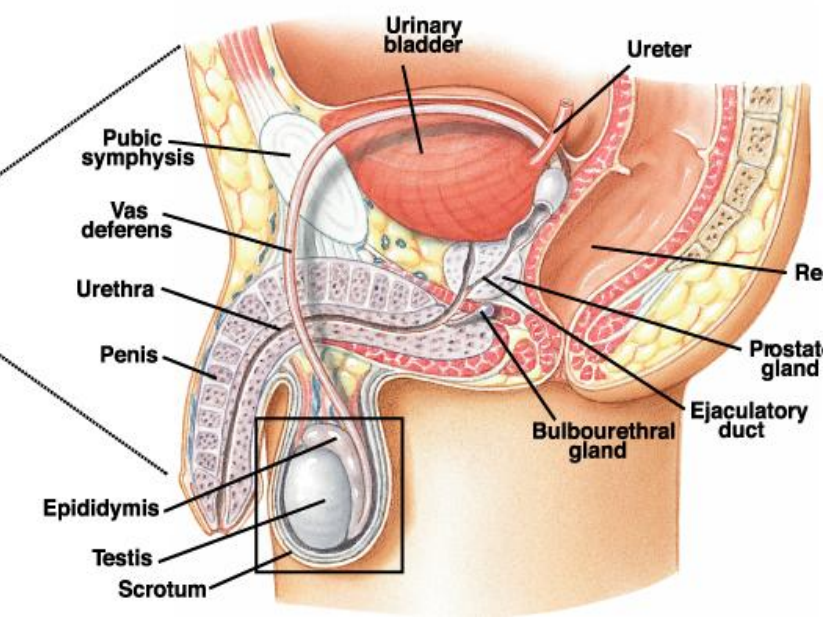
How Do Androgens Effect the Prostate Cell?

NTD- Signaling Part
DBD- DNA Binding Part
LBD- Androgen Binding Part

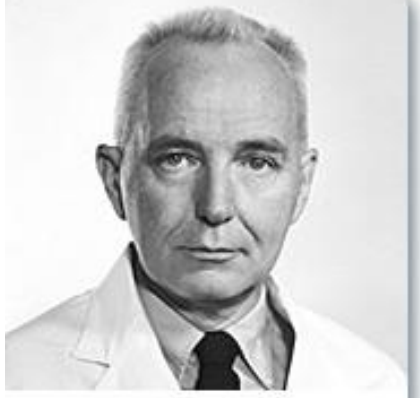


Binds and activates genes:
-Cell Growth
-Cell Survival
-Make prostate stuff like PSA, Acid Phosphatase, etc.

The Devilish Prostate



- Physiologic Function unknown
- 80% of American men develop benign prostatic hyperplasia (BPH) by age 80
- ~40% of 40 year olds in autopsy studies have microscopic prostate cancer
- In US ~220,000 annual new cases of clinical prostate cancer
- ~27,000 US deaths annually from prostate cancer



Charles Huggins
University of Chicago

Studies on Prostatic Cancer

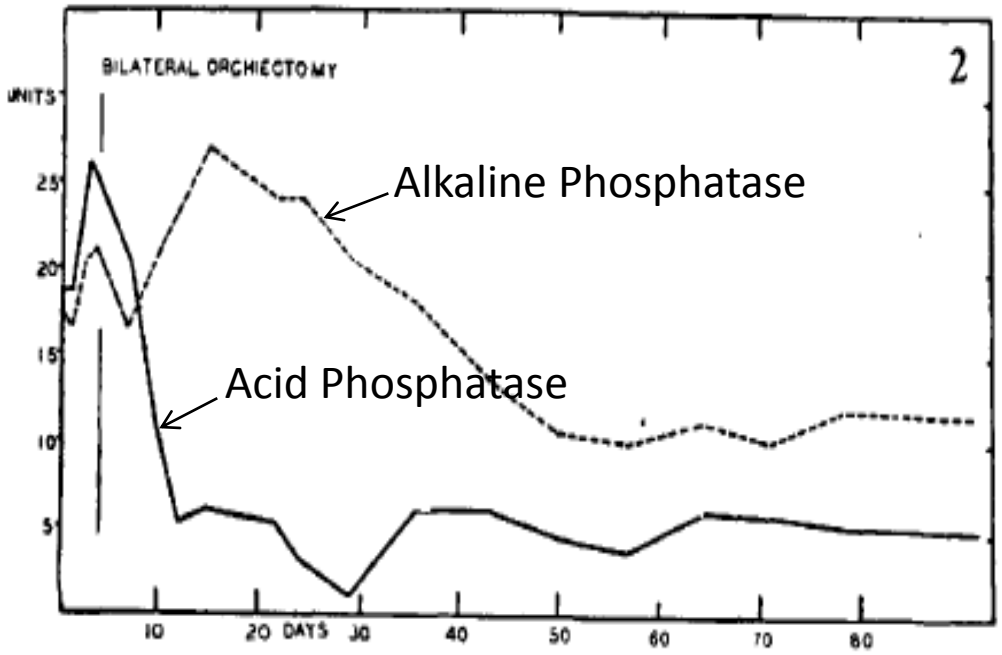
I. The Effect of Castration, of Estrogen and of Androgen Injection on Serum Phosphatases in Metastatic Carcinoma of the Prostate*

Huggins and Hodges Cancer Research 1:293, **1941**

STUDIES ON PROSTATIC CANCER

II. THE EFFECTS OF CASTRATION ON ADVANCED CARCINOMA OF THE PROSTATE GLAND

Huggins et al Archive of Surgery 43:209, **1941**



All Current Hormone Therapy for Prostate Cancer Involves Disrupting Androgen Interacting with its receptor

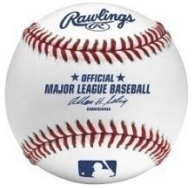
Androgen Receptor

Get Rid of Testosterone

-Orchiectomy

-Medical Castration

-Zytiga



Androgen Receptor

Block Testosterone Binding

-Antiandrogens

-Casodex

-Xtandi

75 years of Androgen Ablation

1940s-60s

Orchiectomy
Diethylstilbesterol
Adrenalectomy
Hypophysectomy

1970s-90s

LHRH agonists
Goserelin
Triptorelin
Buserelin
Histrelin
Nafarelin
Leuprolide…

LHRH antagonists
Degarelix
Abarelix

Antiandrogens
Cyproterone Acetate
Flutamide
Bicalutamide
Nilutamide

Adrenal Poisons
Aminoglutethimide
Ketoconazole

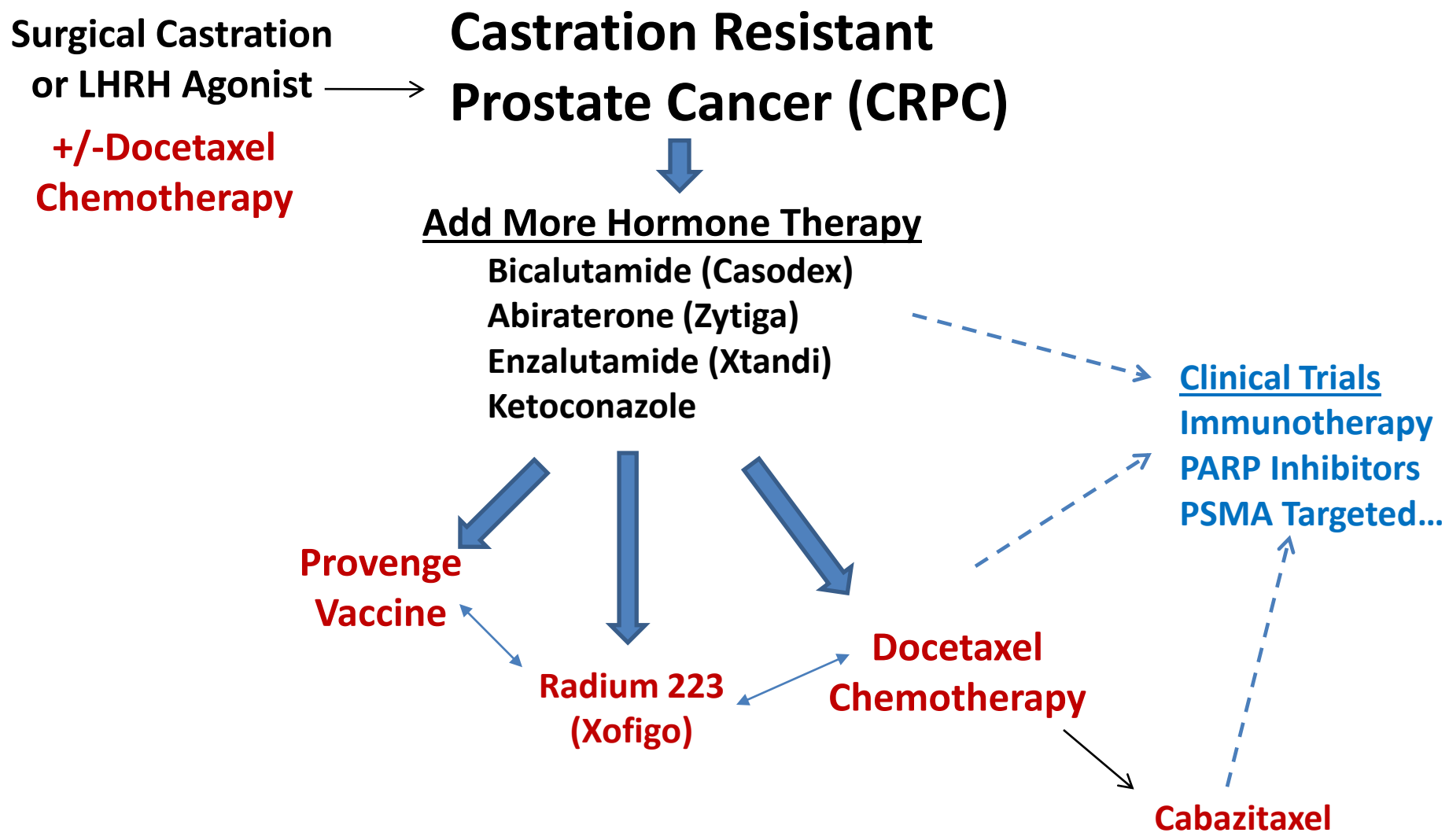
Combined Androgen Blockade

21st Century

Abiraterone
Enzalutamide

ARN-509
Galeterone
EPI-002…

Recurrent Prostate Cancer Treatment Paradigm



Back to the Future:
An Alternative Approach to Androgen Deprivation

Two Principles in Endocrine Therapy of Cancers: Hormone Deprival and Hormone Interference[1]

CHARLES HUGGINS

(The Ben May Laboratory for Cancer Research, University of Chicago, Chicago, Illinois)

…Two opposite sorts of change of the hormonal status can induce regression of hormone dependent cancers:

(a) deprivation of essential hormones

(b) hormone interference with large amounts of critical compounds (i.e. hormones) …

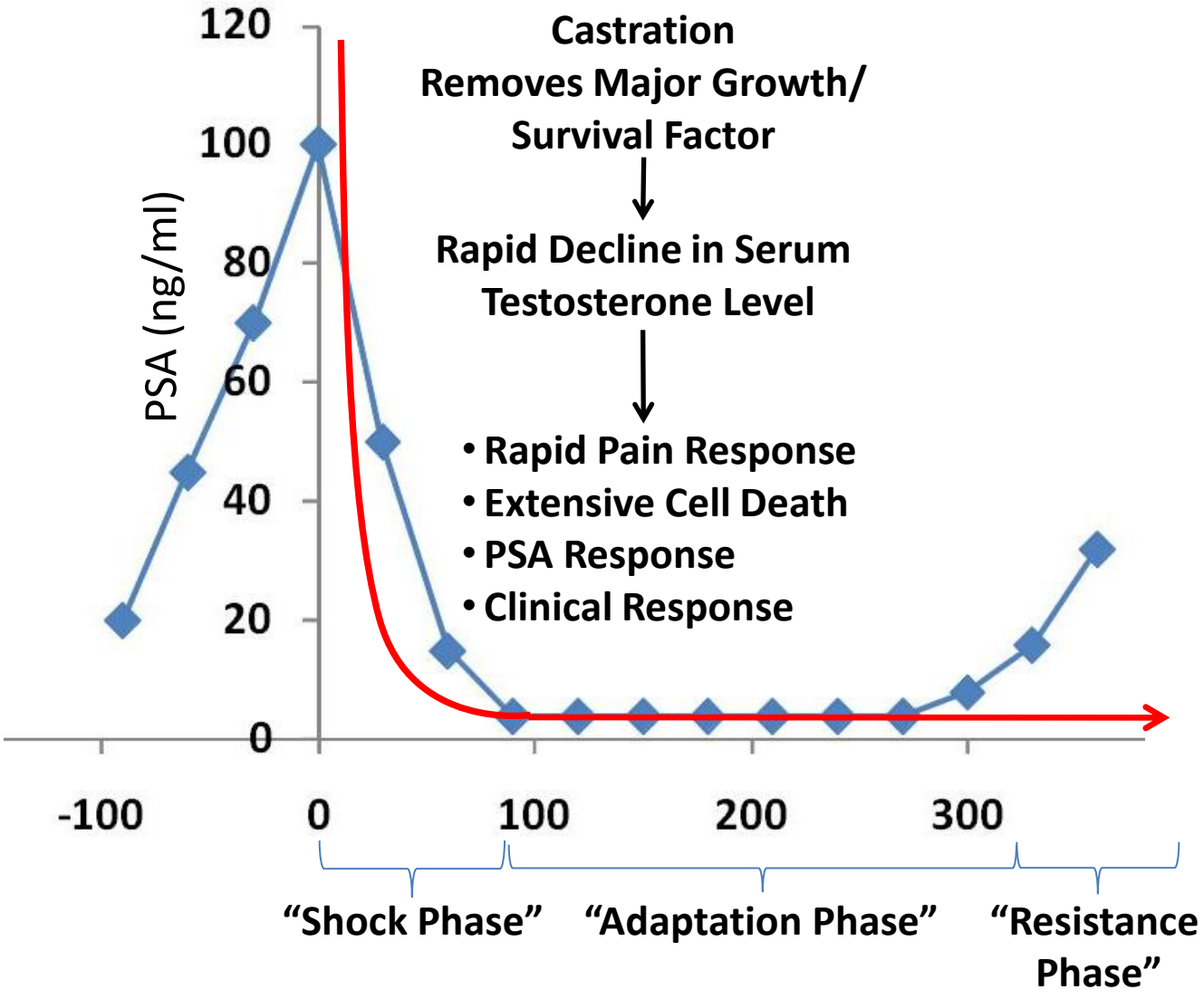
For an idea that does not first seem insane, there is no hope

-- Albert Einstein

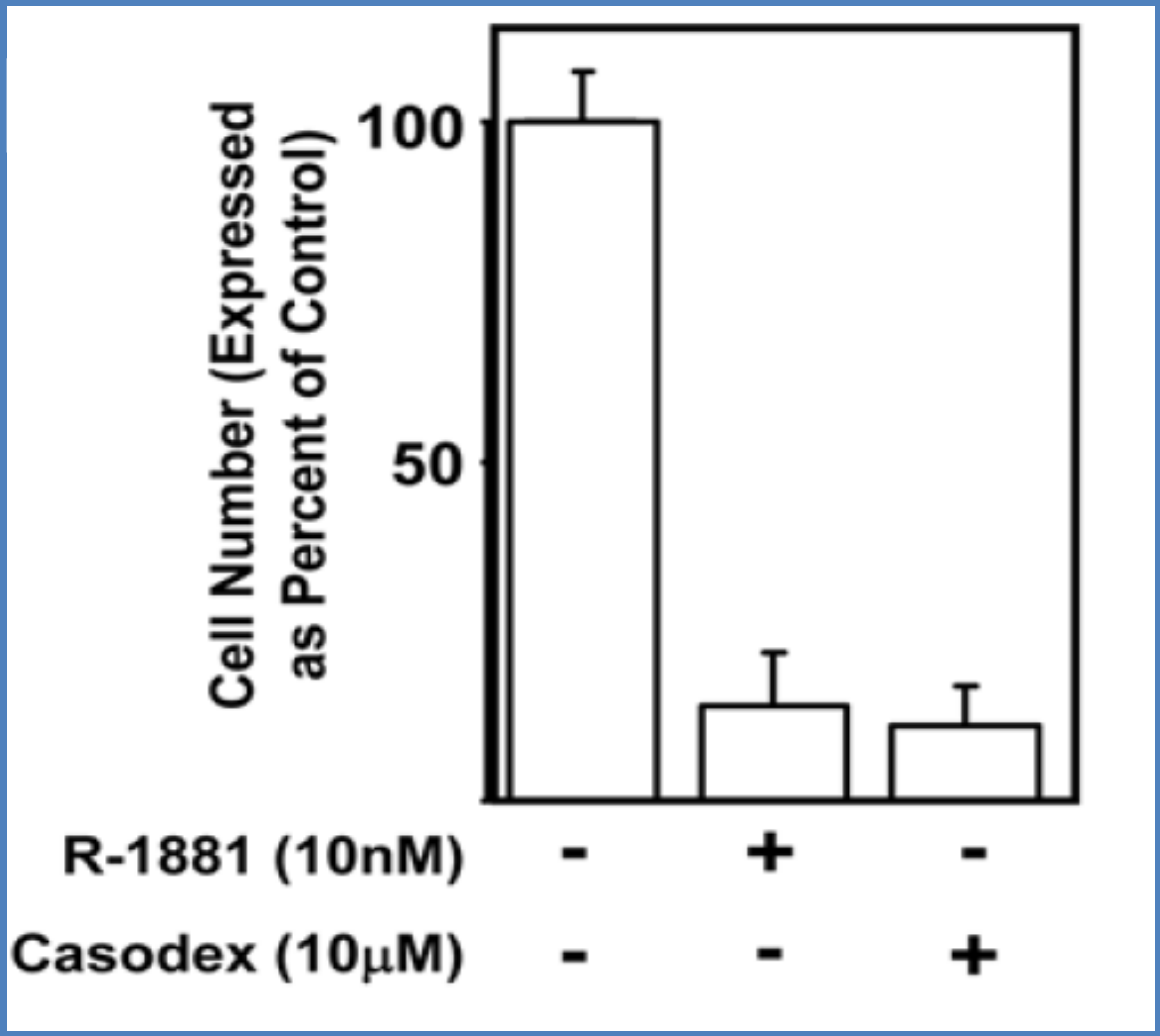
Brine Shrimp *Artemia salina*

- **Live in Great Salt Lake, Utah**
- **Can adapt to levels of salinity from 2.5% to 30% (seawater is 3.5%)**
- **DEATH by OSMOTIC SHOCK**
  - **Billions die from rapid change in salinity produced by runoff from melting snow from mountains**

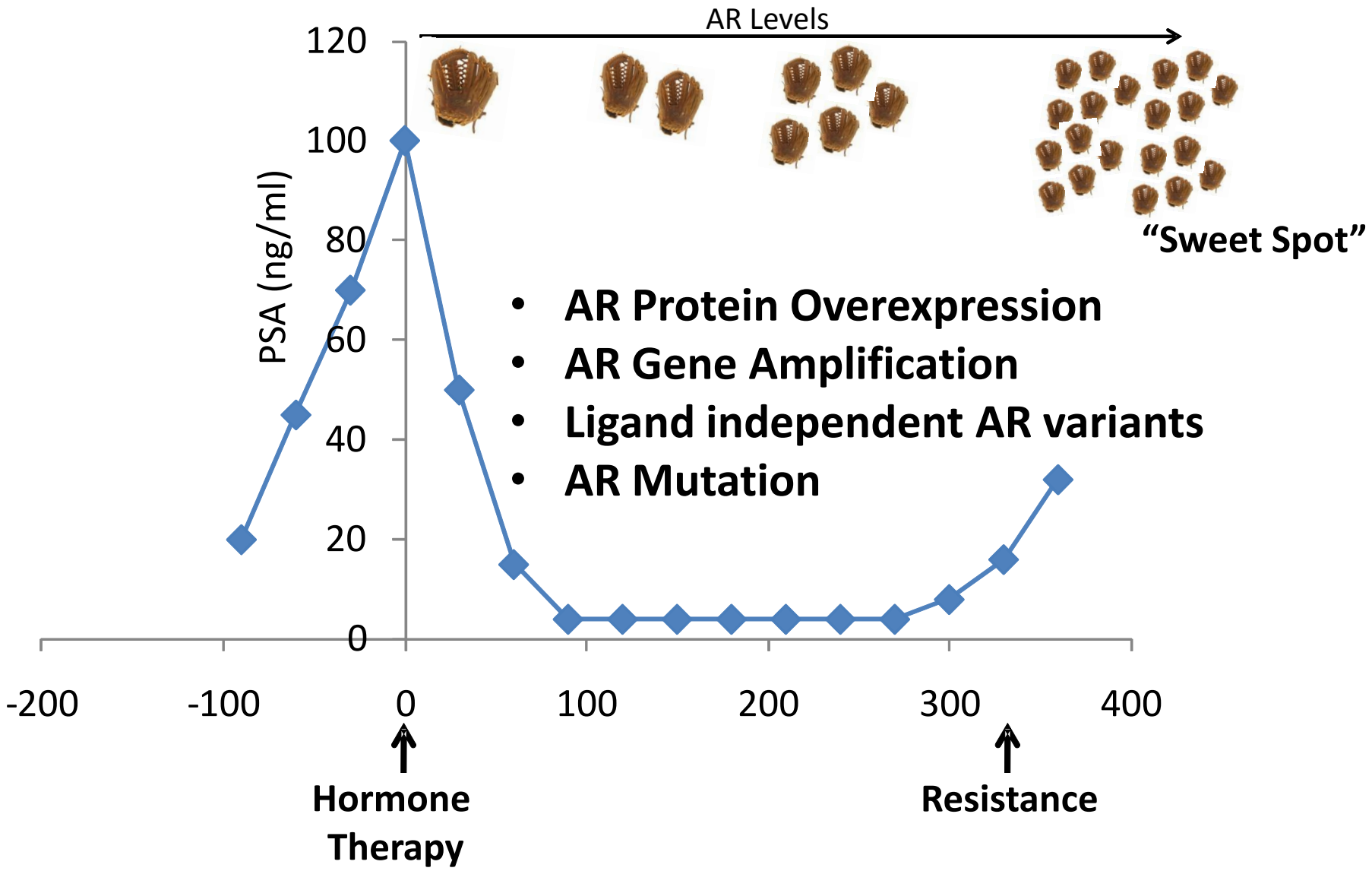
Castration is a form of "Shock Therapy" for Prostate Cancer



Prostate Cancer has an Androgen Receptor “Sweet Spot”

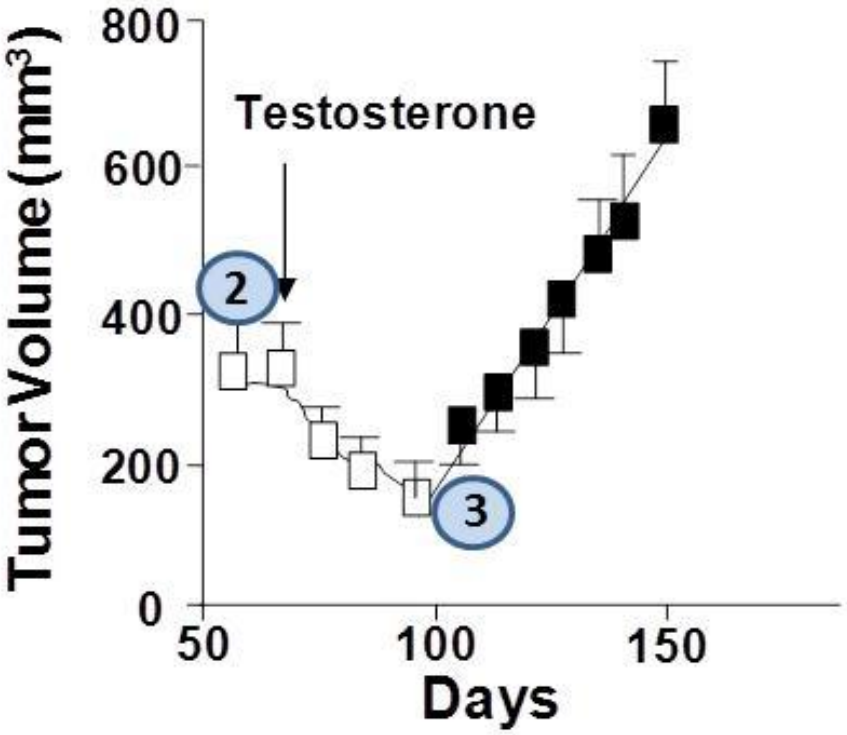


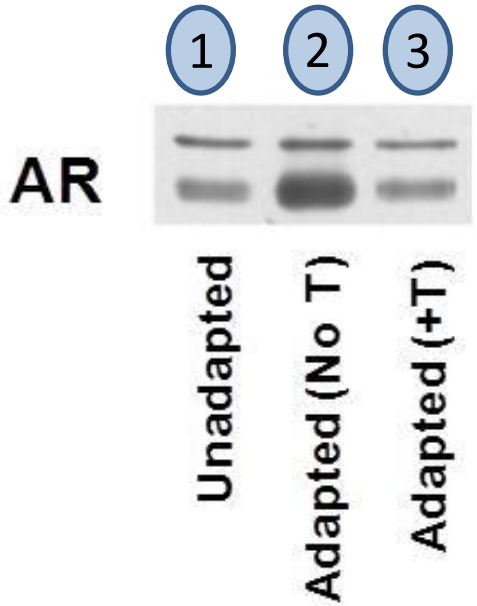
ADAPTATION:
Autoregulatory increase in Androgen Receptor activity leads to resistance to androgen ablative therapies



Dr. Shutsung Liao
Ben May U
Chicago

Growth of Castration Resistant AR-Positive Prostate Cancer Models is Inhibited by Androgen





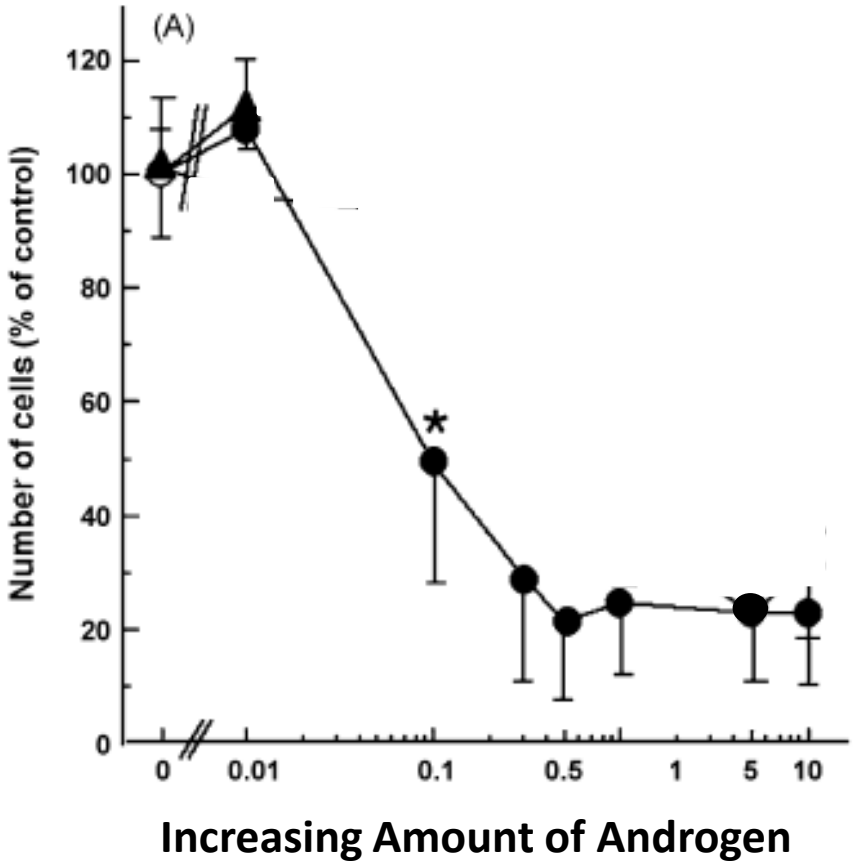
Chuu et al. Cancer Res. 2005;65:2082-4.

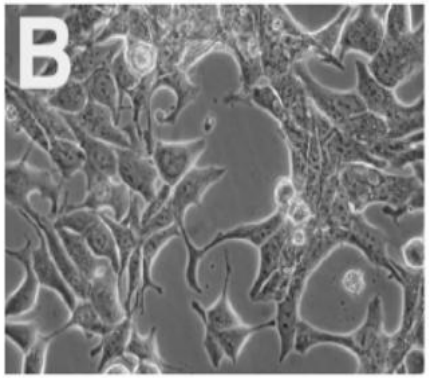
Why does BAT work against Prostate Cancer?

- **Disrupt new DNA production preventing cell division**
- **Induce breaks in DNA**
- **Turn off important cell growth signals**
- **Stop cells from making the AR-V7 variant**
- **Prevent cells from becoming more aggressive in growth in response to potent hormone blockade**
- **Induce Cell Stress that can activate cell death**

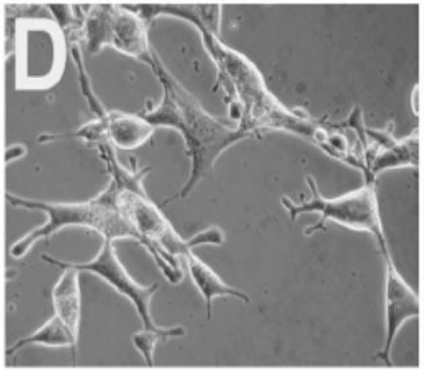
Pharmacology: Dose Matters

Androgen Dose-Response

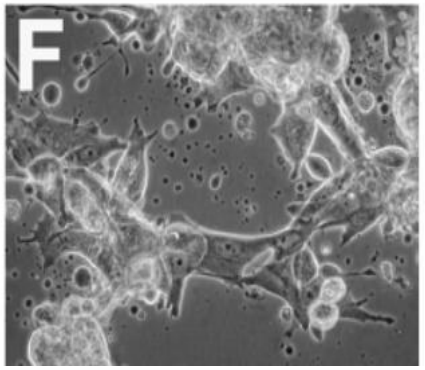




Control



Physiologic Androgen (0.1 nM R1881)



Supra-Physiologic Androgen (10 nM R1881)

Foury et al. 1998;66: 235; Joly-Pharaboz et al. 2008;111:50-J Steroid Biochem Molec Biol

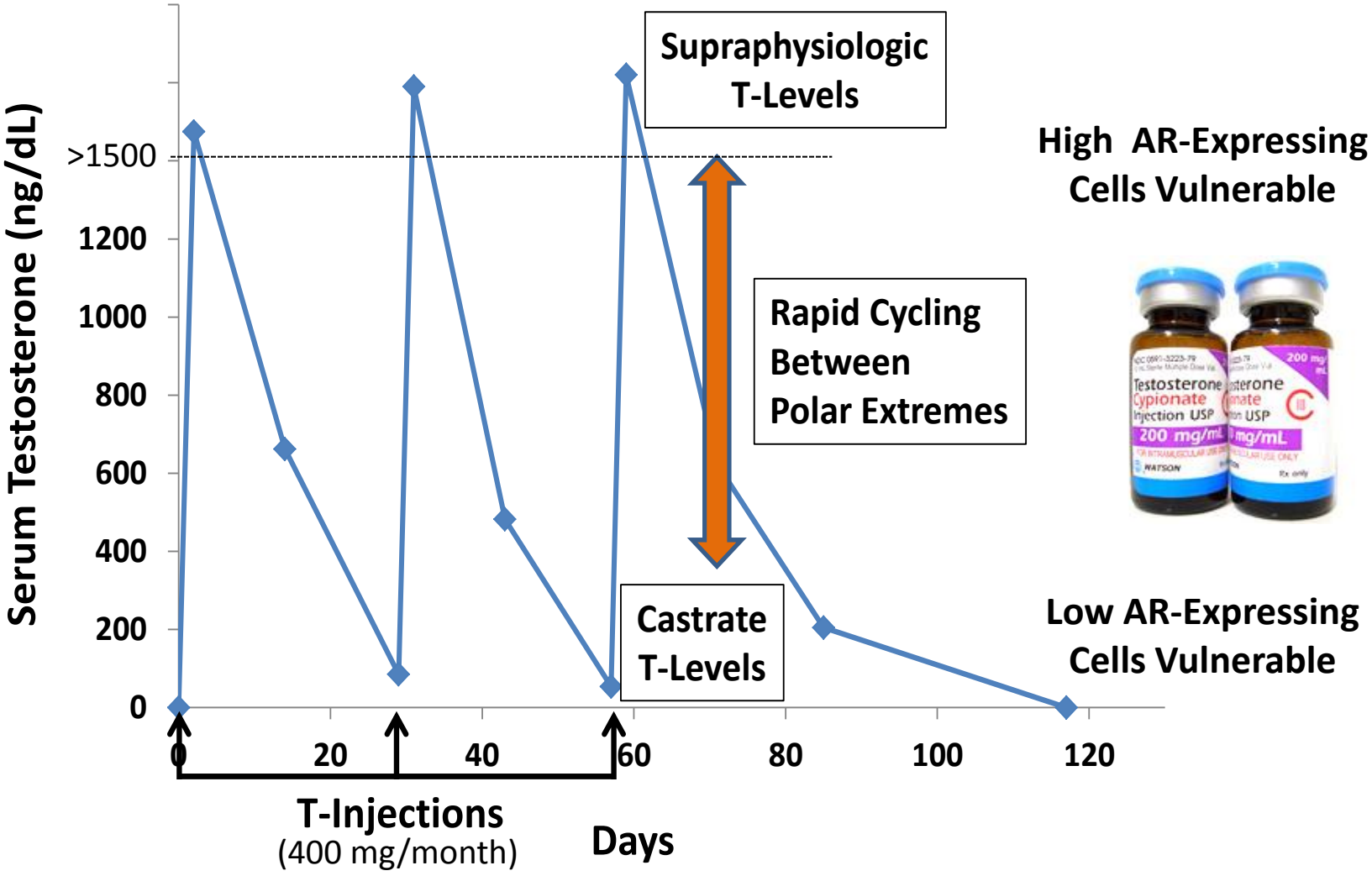
Hypotheses:

- **Men with Castration Resistant Prostate Cancer could respond to rapid cycling between polar extremes of supraphysiologic and castrate testosterone levels [Bipolar Androgen Therapy (BAT)].**

- **Rapid cycling disrupts adaptive autoregulation of the Androgen Receptor.**

- **Adaptive decrease in the amount of Androgen Receptor may re-sensitize CRPC to androgen ablative therapies**

"Bipolar Androgen Therapy"



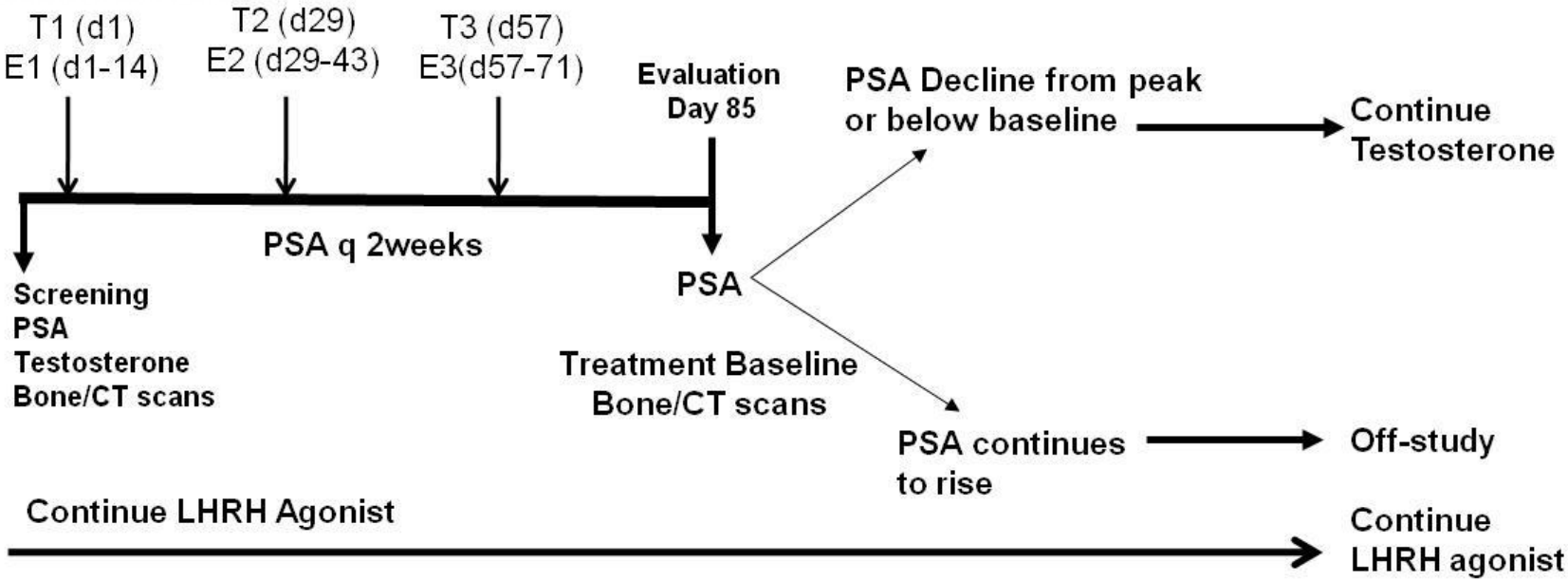
THE ONE-IN-SIX FOUNDATION

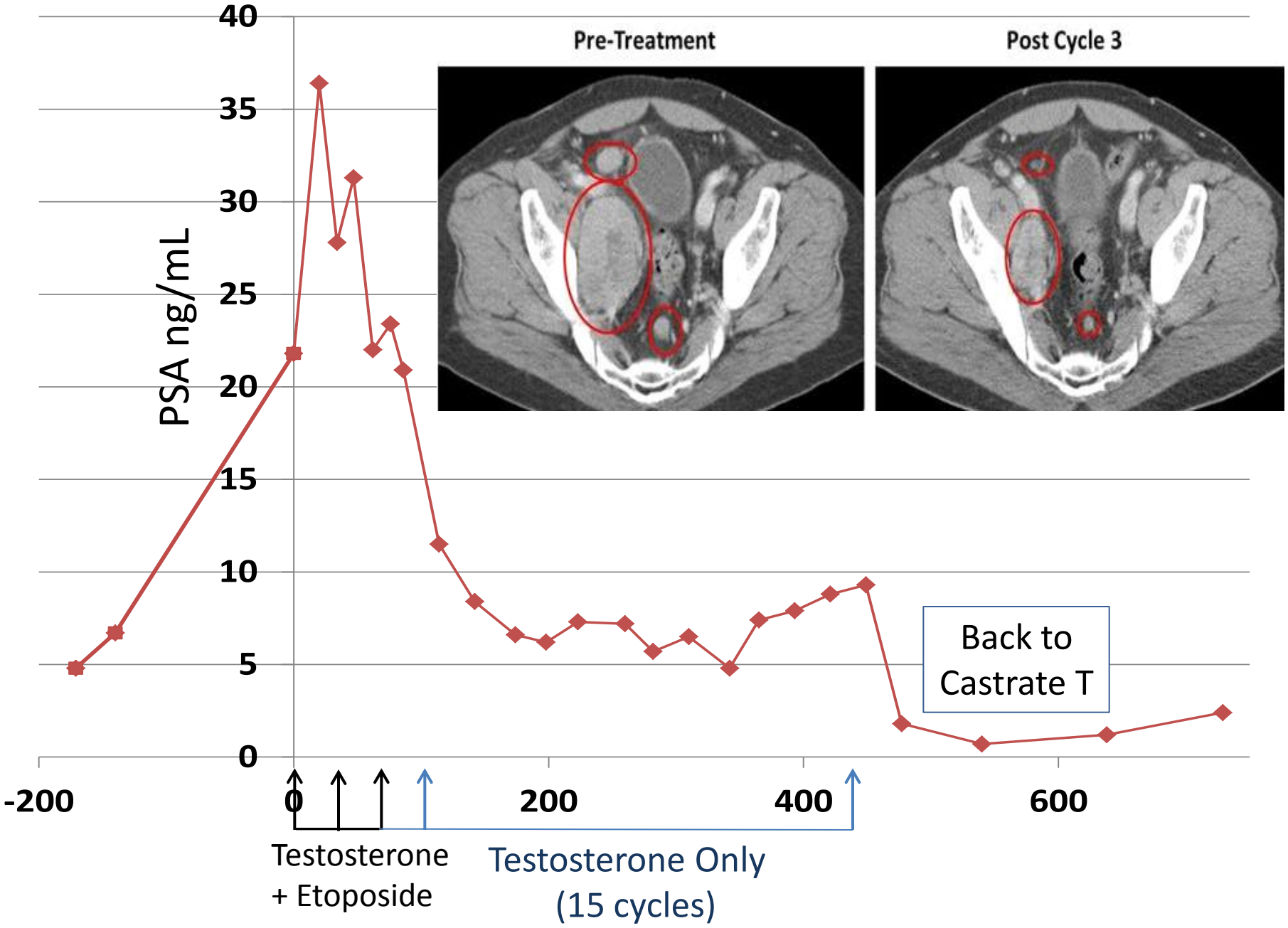
Funding the research that's finding a cure.

PROSTATE CANCER RESEARCH

A Pilot Study of Parenteral Testosterone and Oral Etoposide as Therapy for Men with Castration Resistant Prostate Cancer

Schweizer et al. Sci Transl Med. 2015;7(269):269ra2



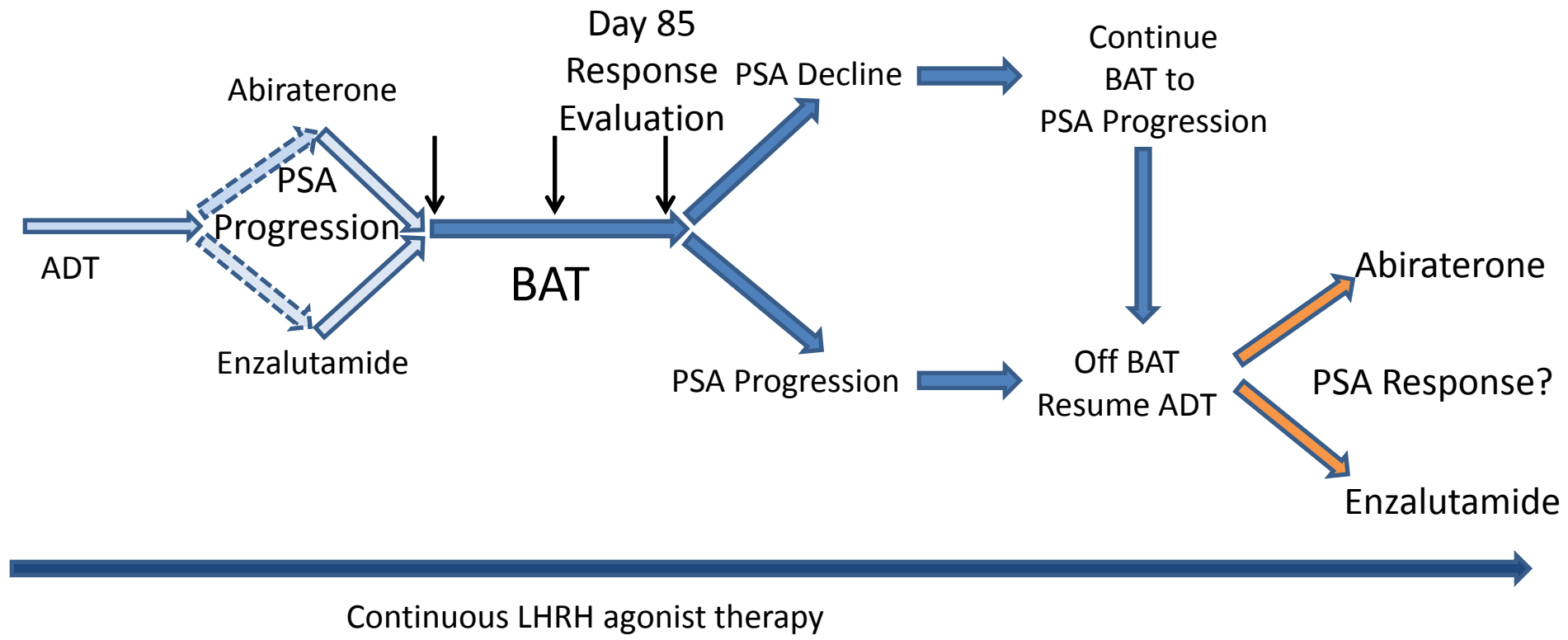

Pre-Treatment
Post Cycle 3
PSA ng/mL
40
35
30
25
20
15
10
5
0
-200
0
200
400
600
Back to Castrate T
Testosterone + Etoposide
Testosterone Only (15 cycles)

Pilot Study Response Summary

- **8 of 14 men had some PSA decline**
- **30% had >50% PSA decline**
- **Median Response was 248 Days**
- **4 men received ≥ 12 cycles of T**
- **50% Objective Response by RECIST**
- **10/10 patients had some PSA decline on abiraterone or anti-androgens post-BAT**

Subject #	Cycles (N)	Max PSA change relative to baseline %	RECIST Response
15	9	-39	PR
8	3	-46	SD
6	13	-48	PR
3	6	-60	SD
9	18	-78	NA
4	15	-86	PR
13	36	-97	PR
16	6	-98	CR

RE-sensitizing with Supraphysiologic Testosterone to Overcome REsistance (The RESTORE Study)

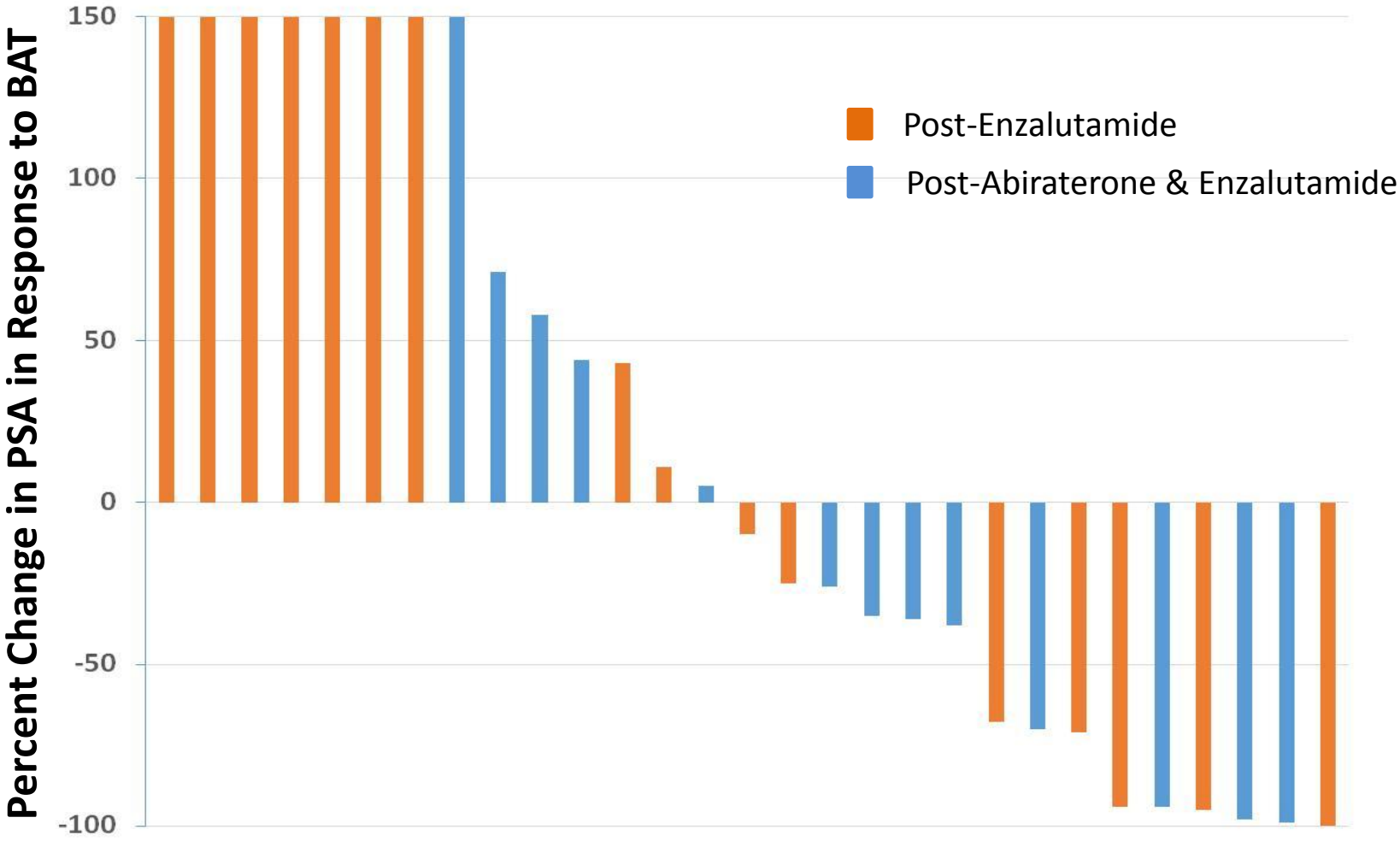


NIH-RO1 funded

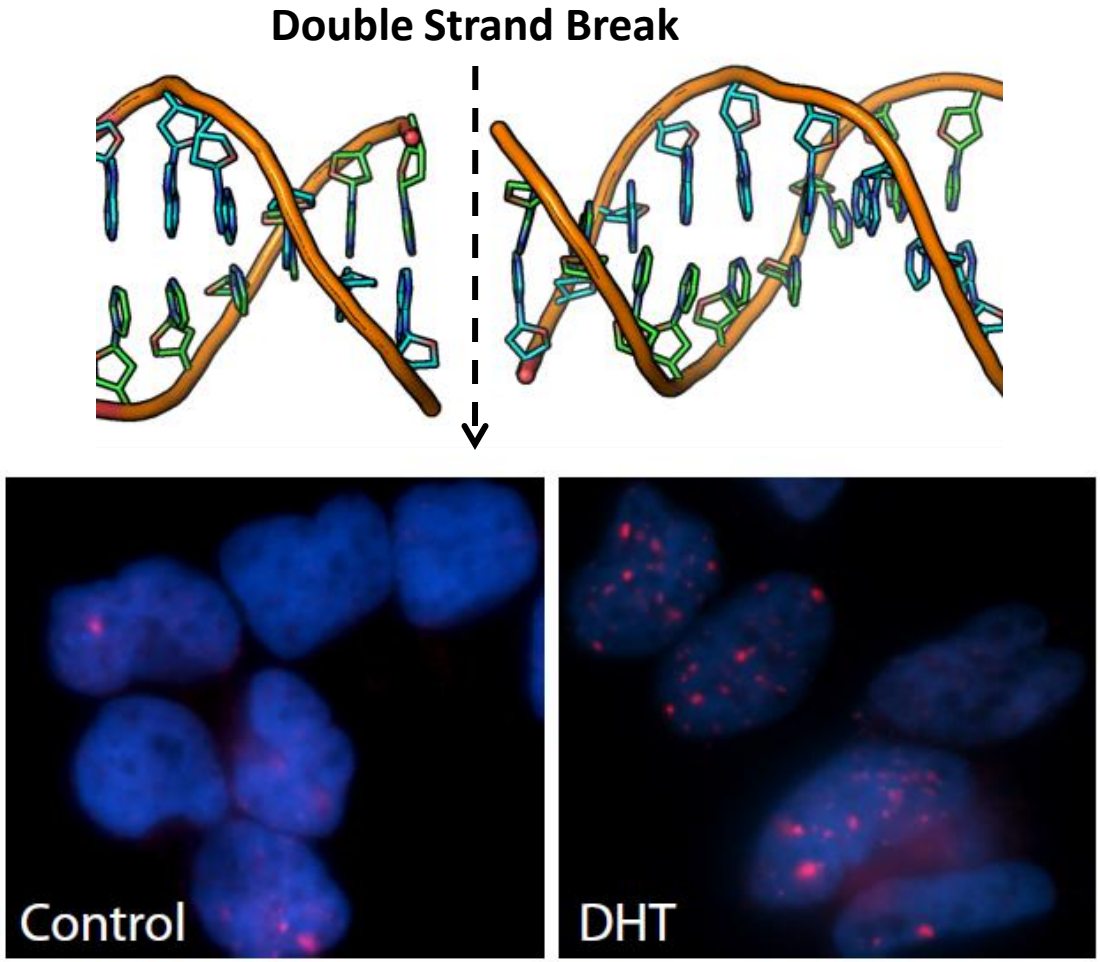
Trial Eligibility

- Maintained on continuous ADT
- Progression on either Abiraterone, Enzalutamide or both
  - Rising PSA
  - Measurable bone metastases, lymph node or soft tissue metastasis
- No worrisome lesions (spinal cord compression, urinary tract obstruction)
- No pain due to prostate cancer

PSA Response to BAT in Post-Enzalutamide Patients

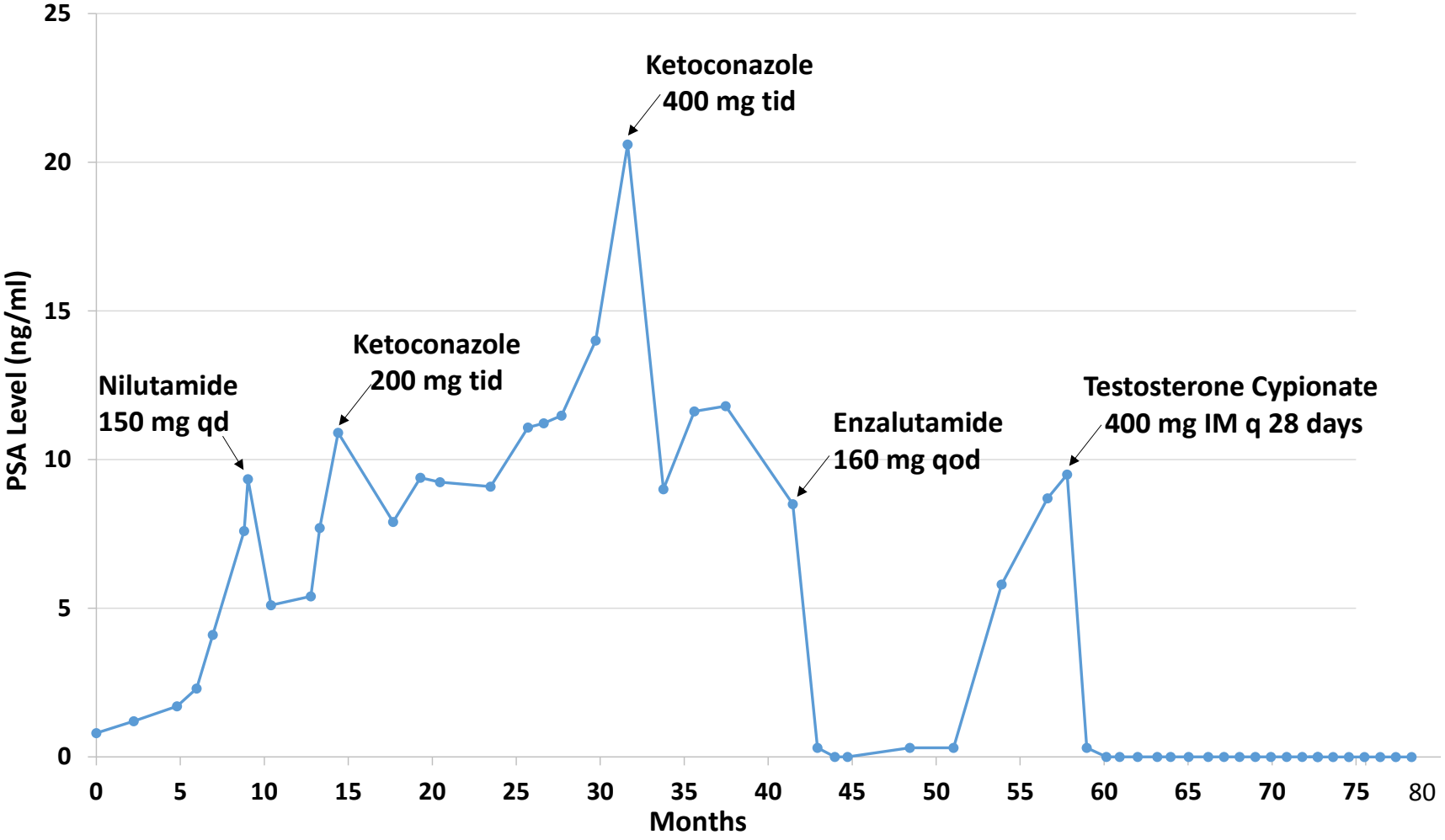


Androgen Produces Double Strand DNA Breaks in Prostate Cancer Cells



Haffner M, et al. Nat Genet. 2010 Aug;42(8):668-75.

Extreme Responder Case #1



- **Biochemical and Radiographic Complete Response**
- **Inactivating Germline Mutations in DNA Repair-BRCA2 and ATM**

Summary of Response to BAT in Post-Enzalutamide Patients

>50% PSA Response	30% (9/29)
Any PSA decline	51% (15/29)
Median Cycles of BAT/Patient	6 cycles (3-22+)
Response Rate after 3 cycles BAT	14% (4/29)
Complete Response	4% (1)
Partial Response	10% (3)
Stable Disease	62% (18)
Progression	21% (6)

Side Effects from BAT

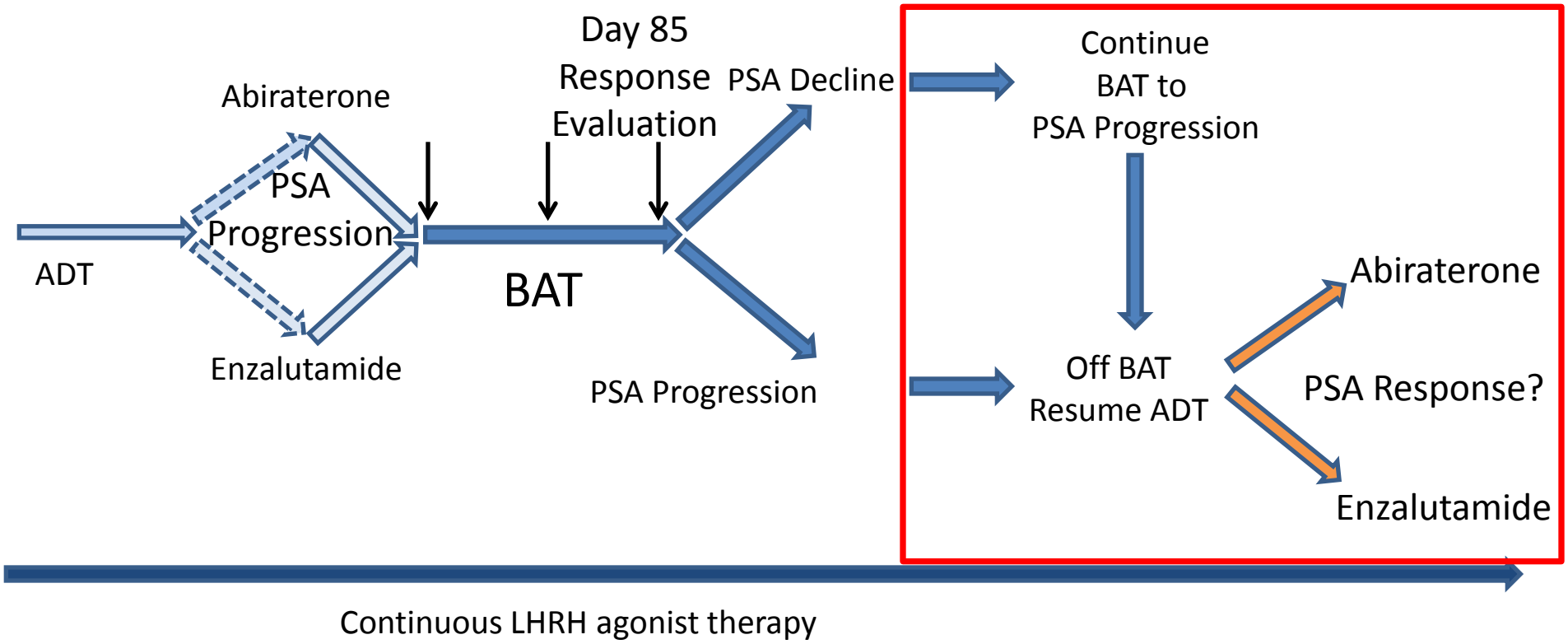
Adverse Events (n=29 pt) All are Grade 1-2	n=	Percent
Anorexia	2	7
Breast Tenderness	6	21
Gynecomastia	2	7
Lower Extremity Edema	3	10
Fatigue	6	21
Headache	2	7
Hot flashes	4	14
Nausea	4	14
Decreased Urine Flow	1	3
Pain	5	17
Grade 1	4	14
Grade 2	1	3

Serious Adverse Events	Grade	Relationship to BAT
Urinary retention	2	Probable
Disseminated intravesicular coagulation	4	Possible
Hyponatremia, fluid retention, hydronephrosis & ureteral obstruction	4	Possible
Pulmonary embolism	3	Possible
Non-ST elevation myocardial infarction	3	Possible

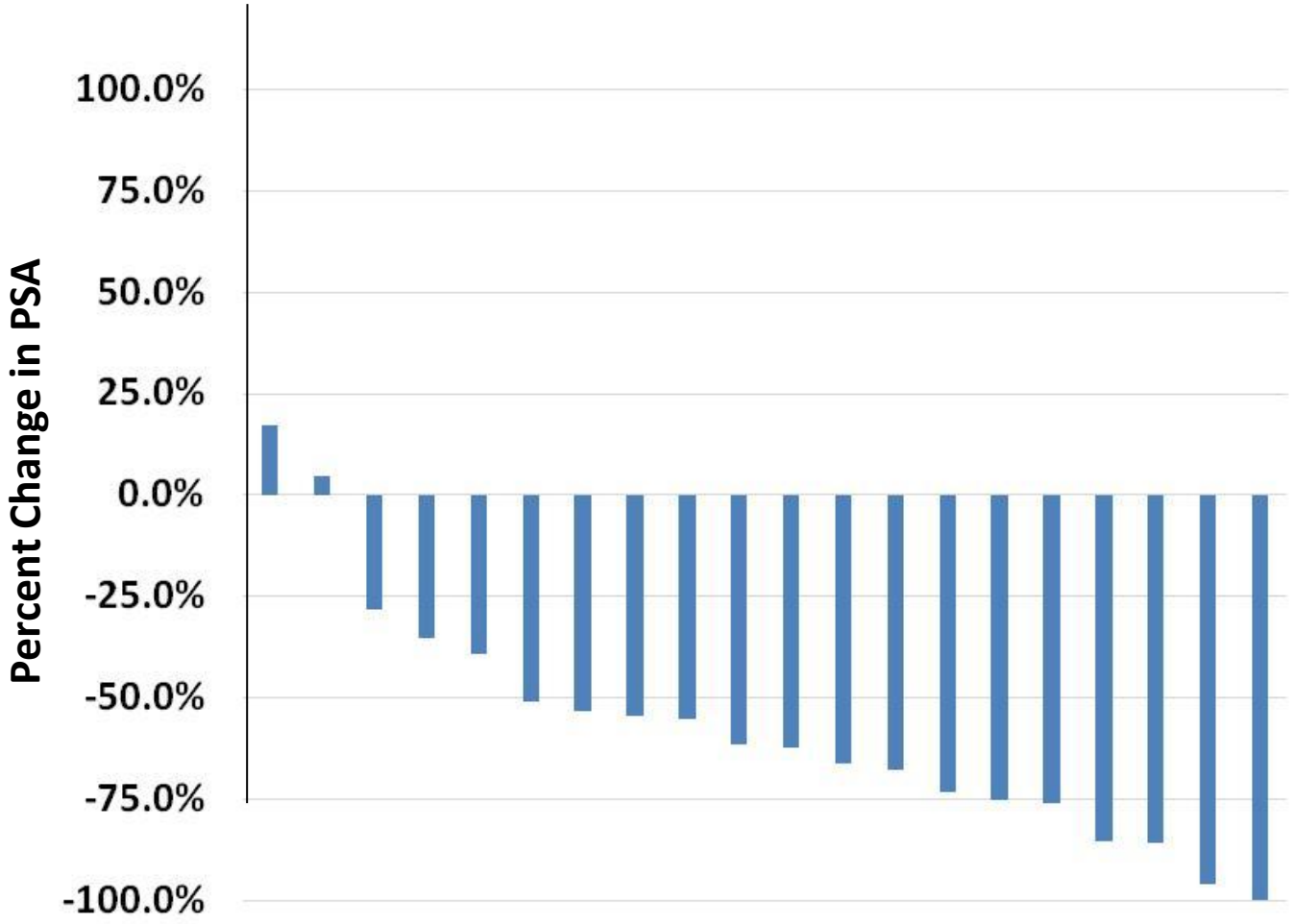
Potential Positive Effects

- **Subjective improvement in energy levels, functional activity**
- **Increased Hemoglobin**
- **Renewed Sexual Potency**
- **Increased Libido**

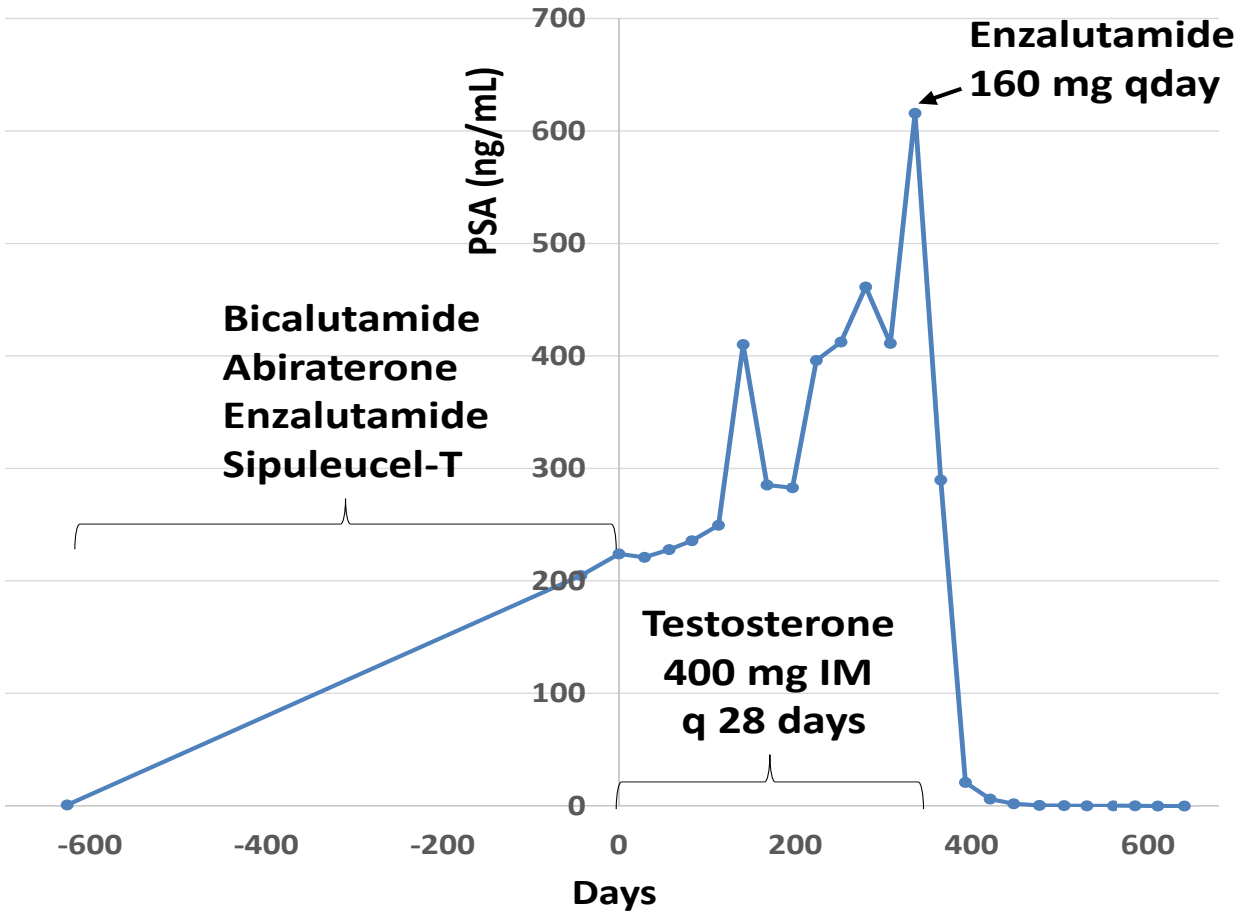
Do we RESTORE Sensitivity to Hormone Therapy?



Changes in PSA Levels After Re-Treatment with Enzalutamide



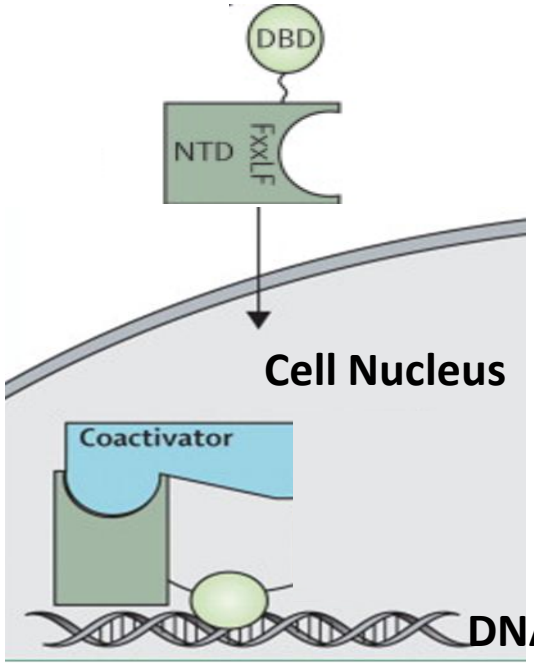
Extreme Responder Case #2

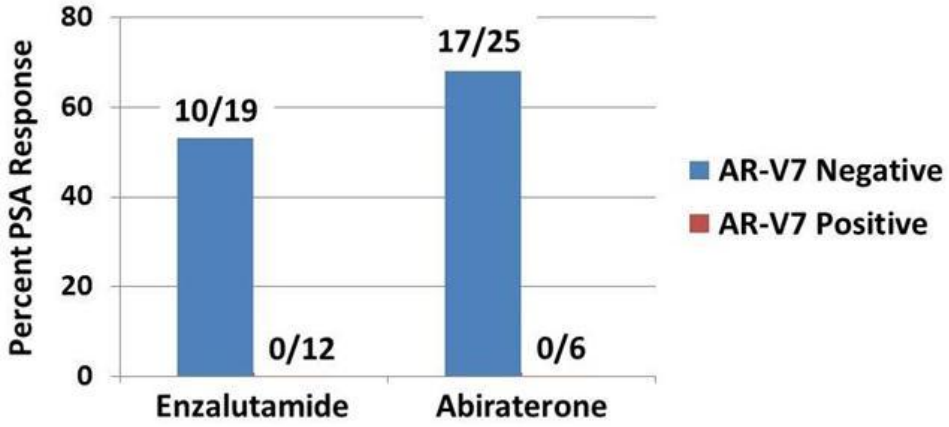


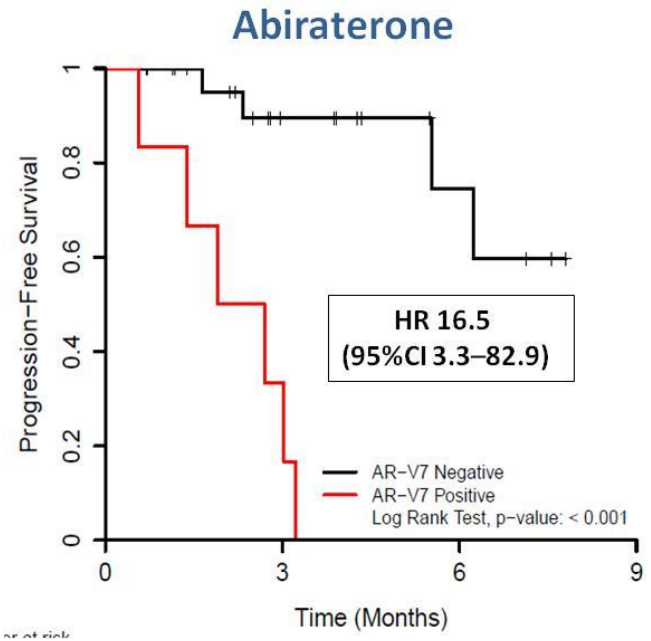
- Undetectable PSA on Enzalutamide Rechallenge
- Stable Bone-Only Disease for 19 months
- Somatic Mutations of unclear significance in BRCA2 and FANCA

AR-Variant 7 is associated with poor response to hormonal therapies and decreased progression free survival

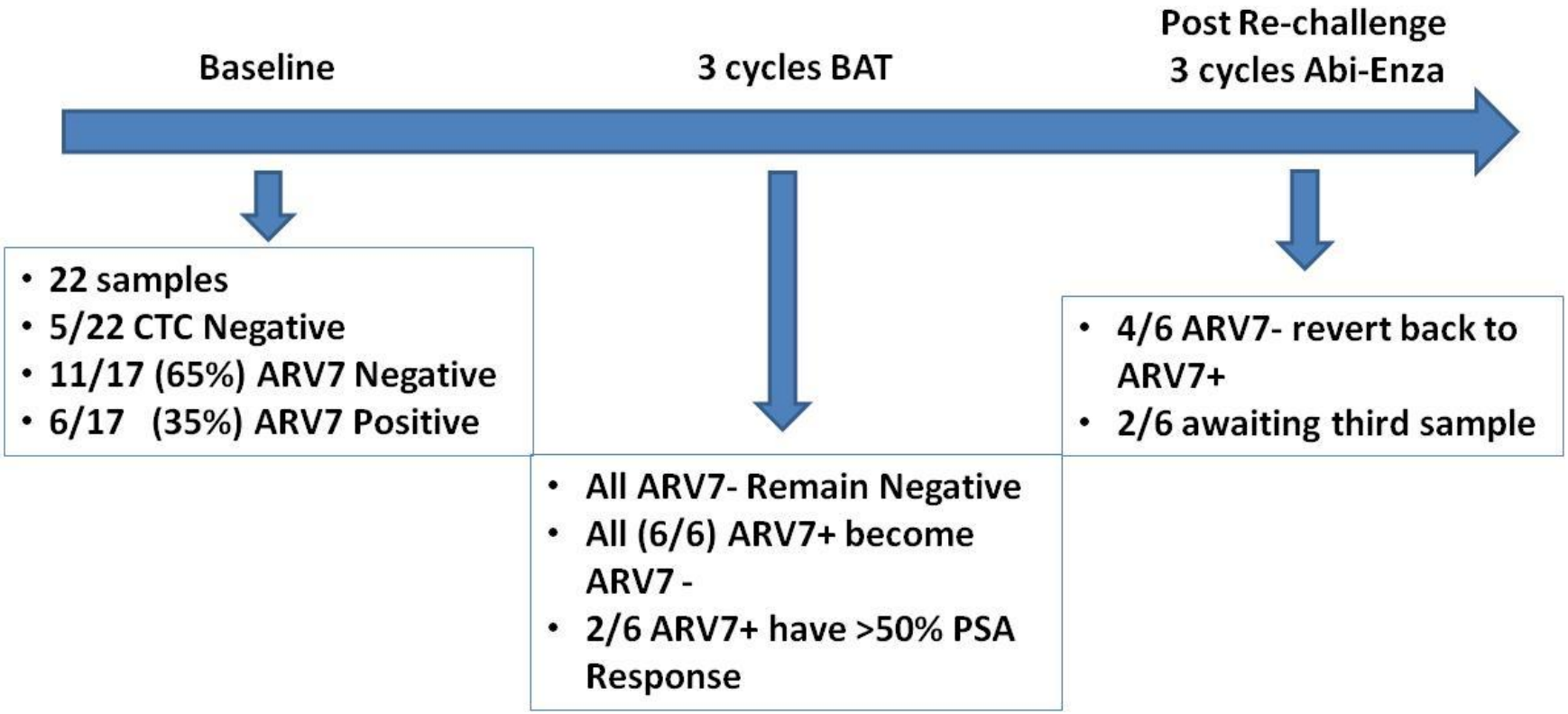
No ball needed



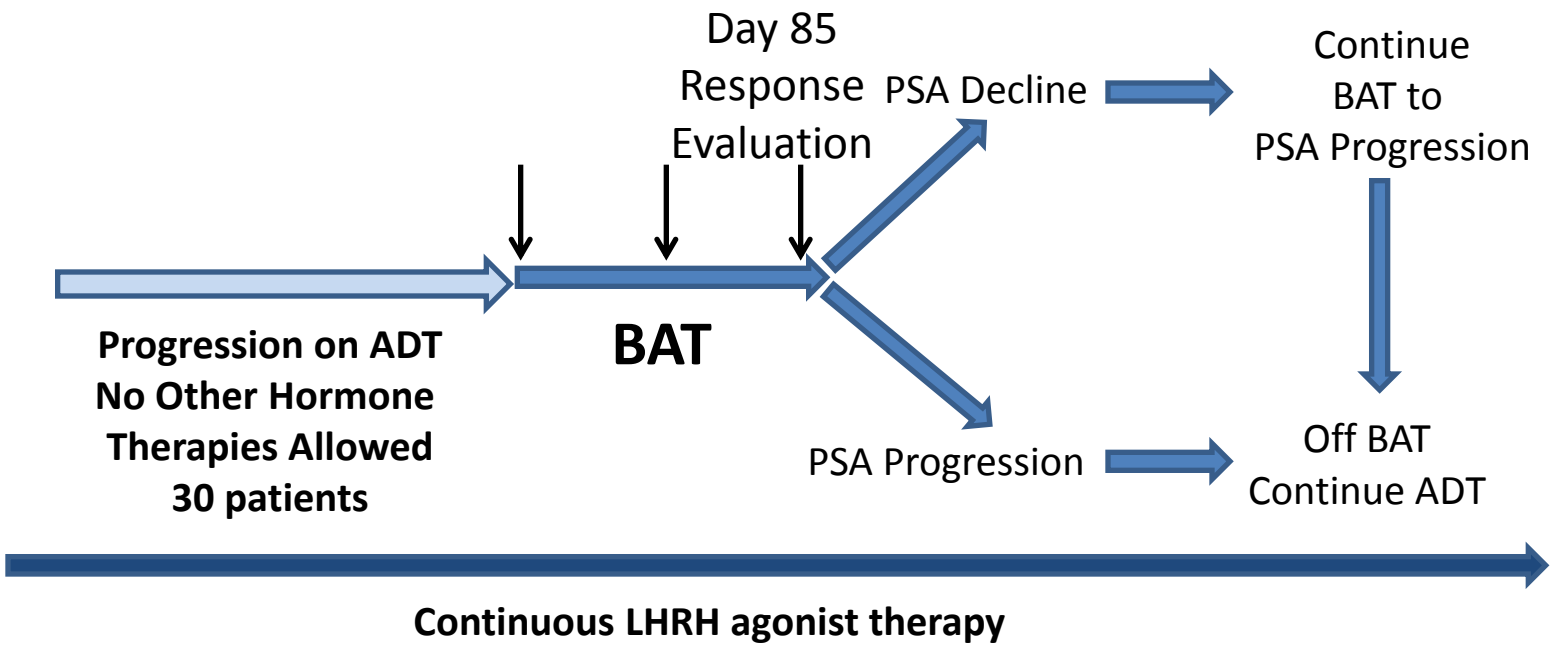




Preliminary AR-V7 Results from RESTORE Study



The RESTORE Study
New Castration-Only Study Arm Opening March 2017

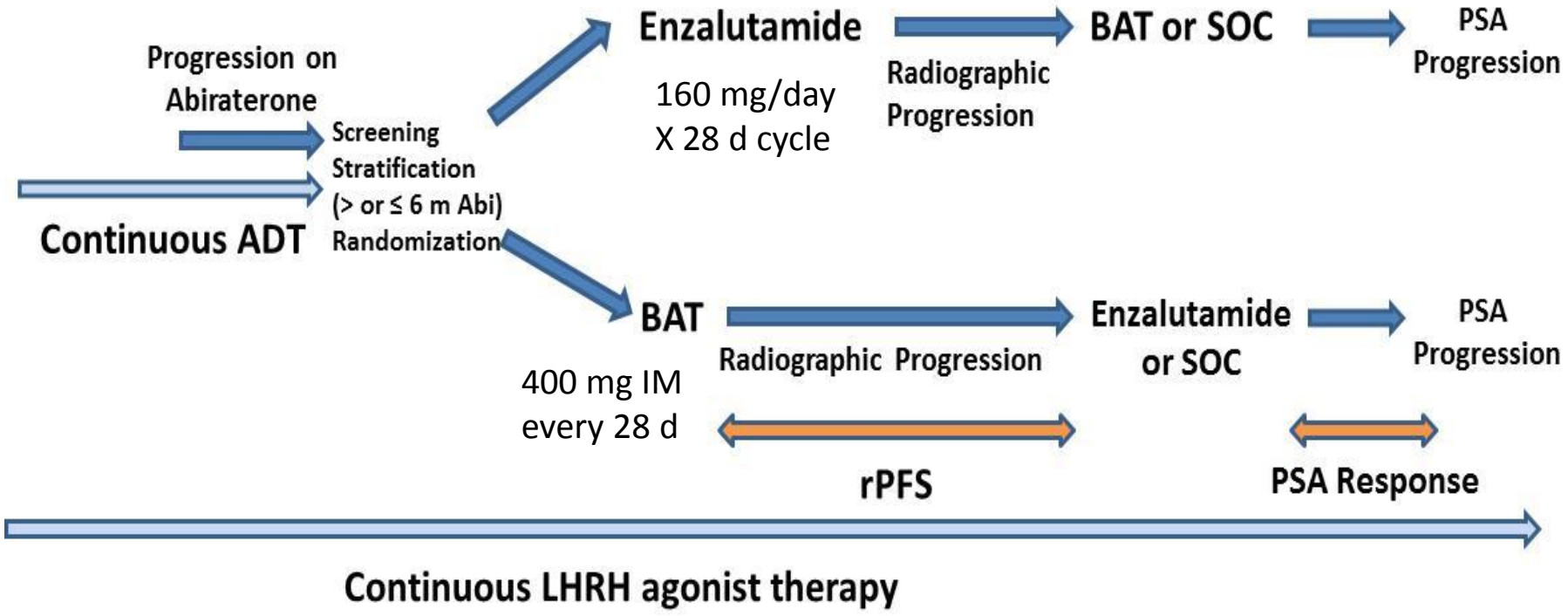


NIH-RO1 funded

A Randomized Phase II Study Comparing Bipolar Androgen Therapy vs. Enzalutamide in Asymptomatic Men with Castration Resistant Metastatic Prostate Cancer:

The TRANSFORMER Trial
(Testosterone Revival Abolishes Negative Symptoms, Fosters Objective Response and Modulates Enzalutamide Resistance)

Randomized Trial Design



- **Designed to detect 50% improvement in Progression Free survival for BAT vs. Enzalutamide**
- **Number of Patients: 180 (1:1 randomization)**
- **17 US sites**
- **143 patients enrolled to date**

Key Eligibility Criteria

- **Good Performance Status**
- **Treated with continuous hormone therapy**
- **No prior enzalutamide or other investigational AR targeted therapy**
- **Documented metastatic disease on scans**
- **Must have had disease progression while on abiraterone alone or abiraterone in combination with other investigational agents based on:**
  - **PSA progression And/Or**
  - **Cancer progression on scans**

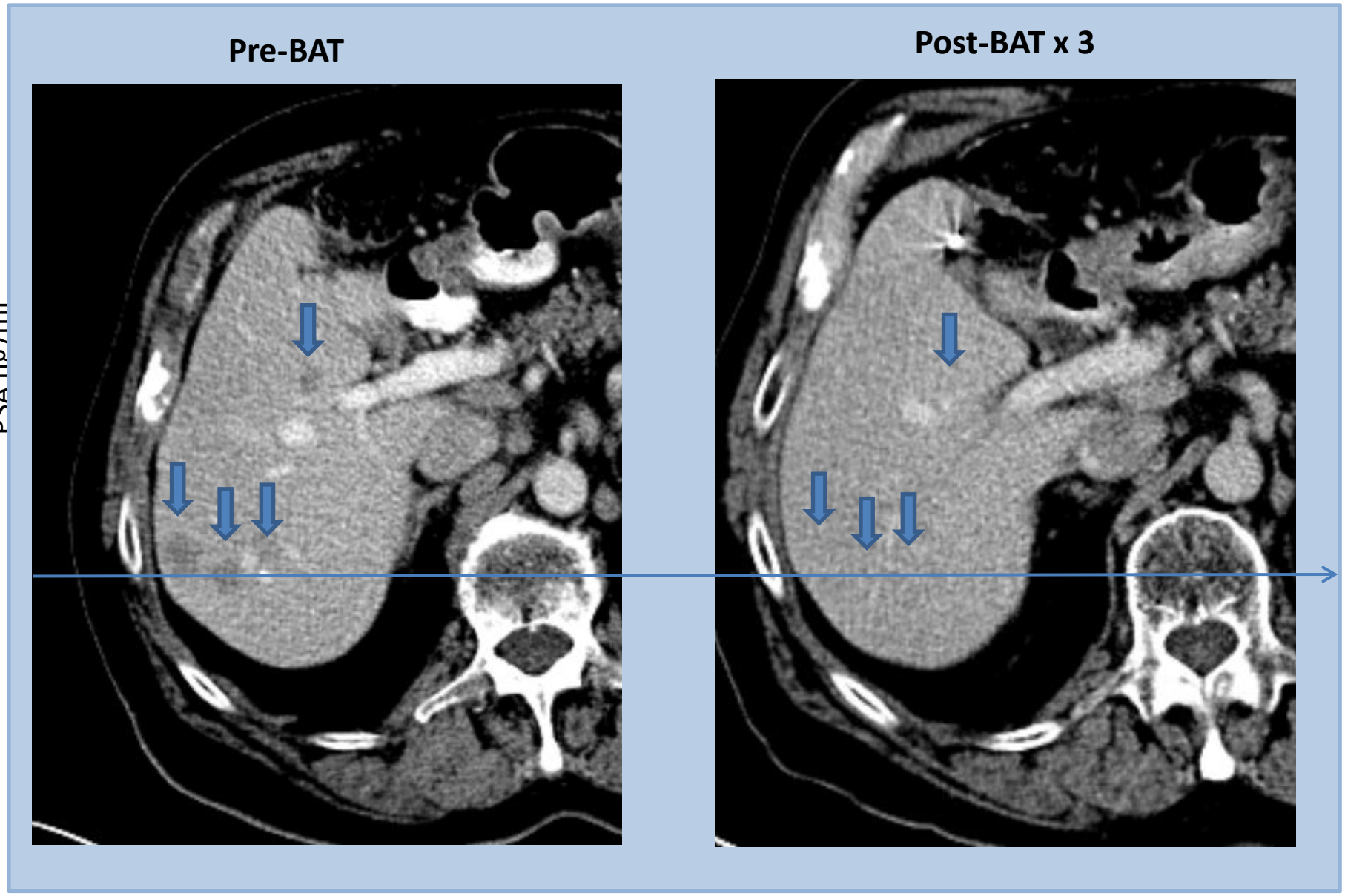
Exclusion Factors

- **PAIN due to metastatic prostate cancer requiring treatment intervention**
- **Prior treatment with docetaxel or cabazitaxel for metastatic CRPC**
- **Require urinary catheterization for voiding due to obstruction from prostatic enlargement**
- **Evidence of disease in sites or extent that, in the opinion of the investigator, would put the patient at risk from therapy with testosterone**

PI and Site
Dr. Agarwal --- Huntsman Cancer Institute, Salt Lake City, UT
Dr. Smith --- University of Michigan, Ann Arbor, MI
Dr. Denmeade --- Johns Hopkins and Sibley, Washington DC.
Dr. Stein --- Cancer Institute of New Jersey, New Brunswick, NJ
Dr. Flaig --- University of Colorado, Denver, CO
Dr. Schweizer --- University of Washington, Seattle, WA
Dr. Assikis--- Piedmont Cancer Institute, Atlanta, GA
Dr. Twardowski --- City of Hope, Duarte, CA
Dr. Szmulewitz --- University of Chicago, Chicago, IL
Dr. Holzbeierlein--- Kansas University, Kansas City, KS
Dr. Sonpavde --- University Alabama, Birmingham, AL
Dr. Garcia --- Cleveland Clinic, Cleveland OH
Dr. Hussain --- University of Maryland, Baltimore, MD
Dr. Sartor--- Tulane University, New Orleans, LA
Dr. Hauke --- Nebraska Cancer Specialists, Omaha, ME
Dr. Mao--- Allegheny Hospital, Pittsburgh, PA

Study Enrollment

- 16 sites have enrolled patients
- 143 patients signed consents
  - 15 patients failed screening
  - 120 patients have received treatment
  - Two Safety Board meetings held with no concerns
  - Recommend continue the study


Pre-BAT
Post-BAT x 3
PSA ng/ml

Many Questions to Answer

- Should we move forward?
- How can we move forward? $$$
- How to Identify Responders?
- Optimize Dosing Schedule
- Mechanism of Re-Sensitization?
- Combination therapy?
  - DNA repair inhibitors
  - Other hormones
  - Immunotherapy
  - Bone Marrow Transplant

Points to Take Home

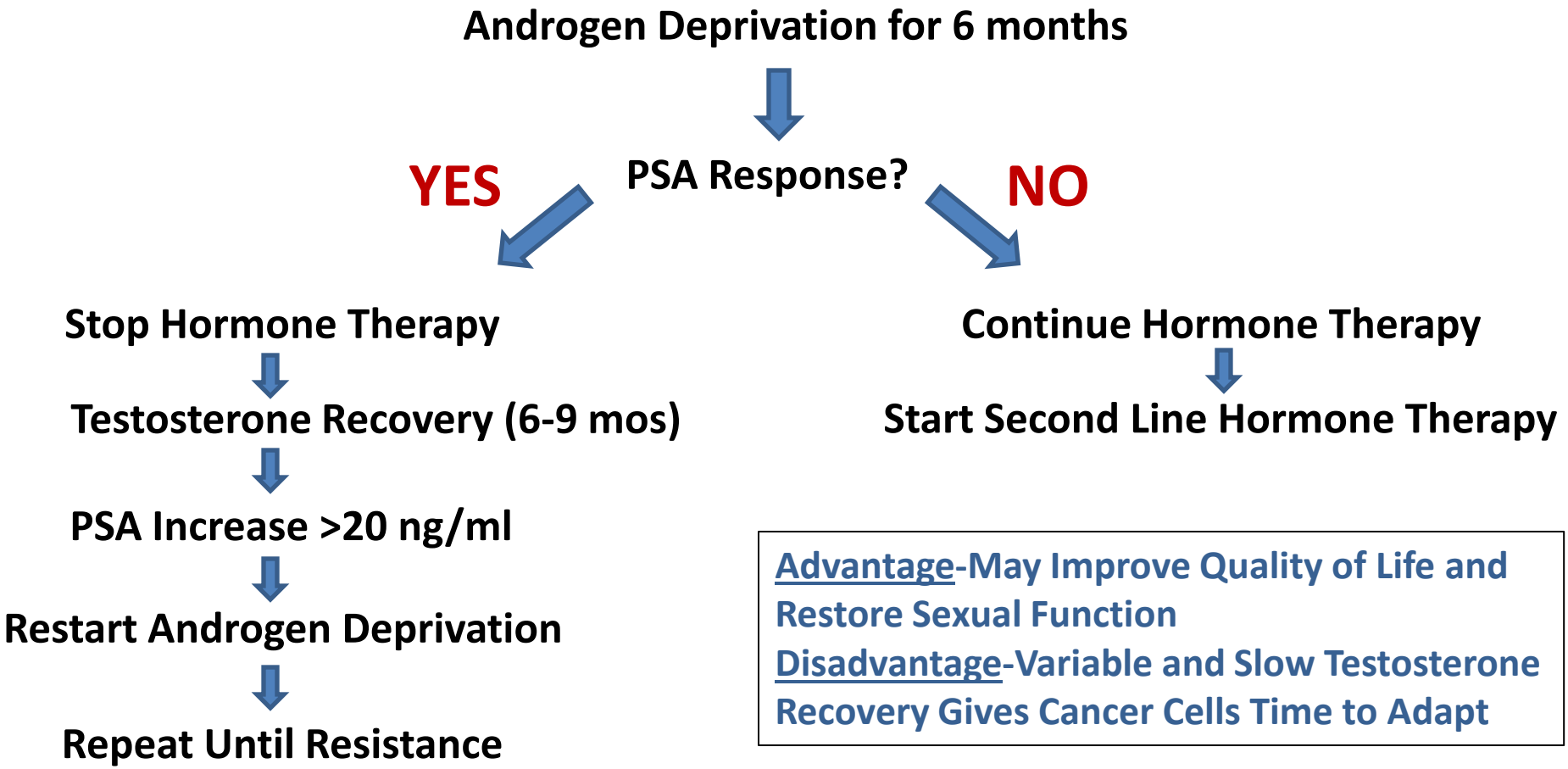
- **Pharmacologic testosterone (BAT) can be given safely to asymptomatic men with castrate resistant prostate cancer**
- **Radiographic Response and PSA response observed in some men**
- **BAT may re-sensitize CRPC to androgen ablative therapies**
- **BAT improves Quality of Life in some men**

Can BAT be Incorporated into an Intermittent Androgen Deprivation Strategy?

- **Prolong Response to Hormonal Therapies?**
- **Delay Development of Castration Resistance?**
- **Mitigate Side Effects of Hormone Therapy?**
- **Positive Effects on Quality of Life?**

Hormone Therapy Side Effects

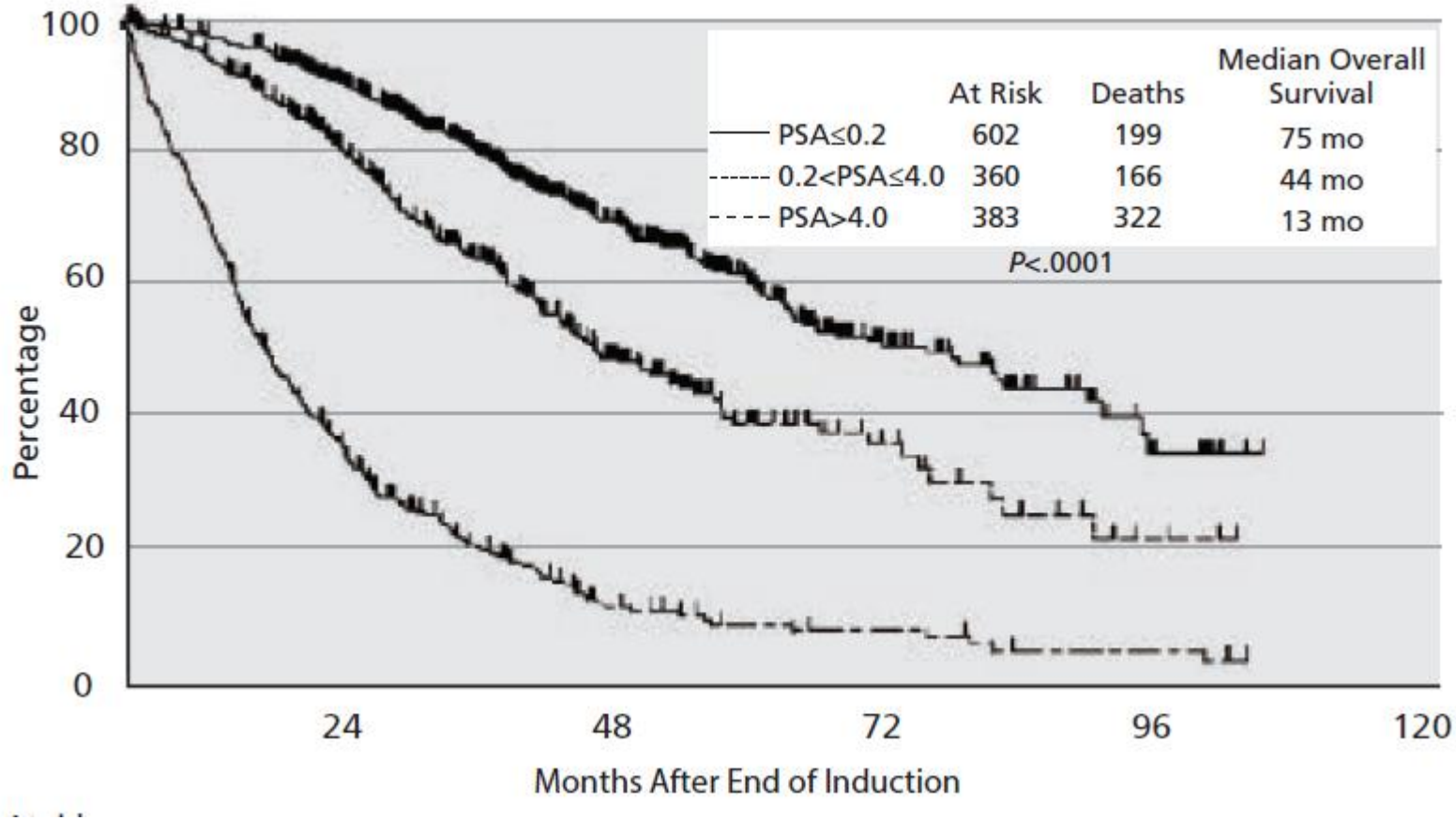
Standard Intermittent Hormone Therapy



Advantage-May Improve Quality of Life and Restore Sexual Function

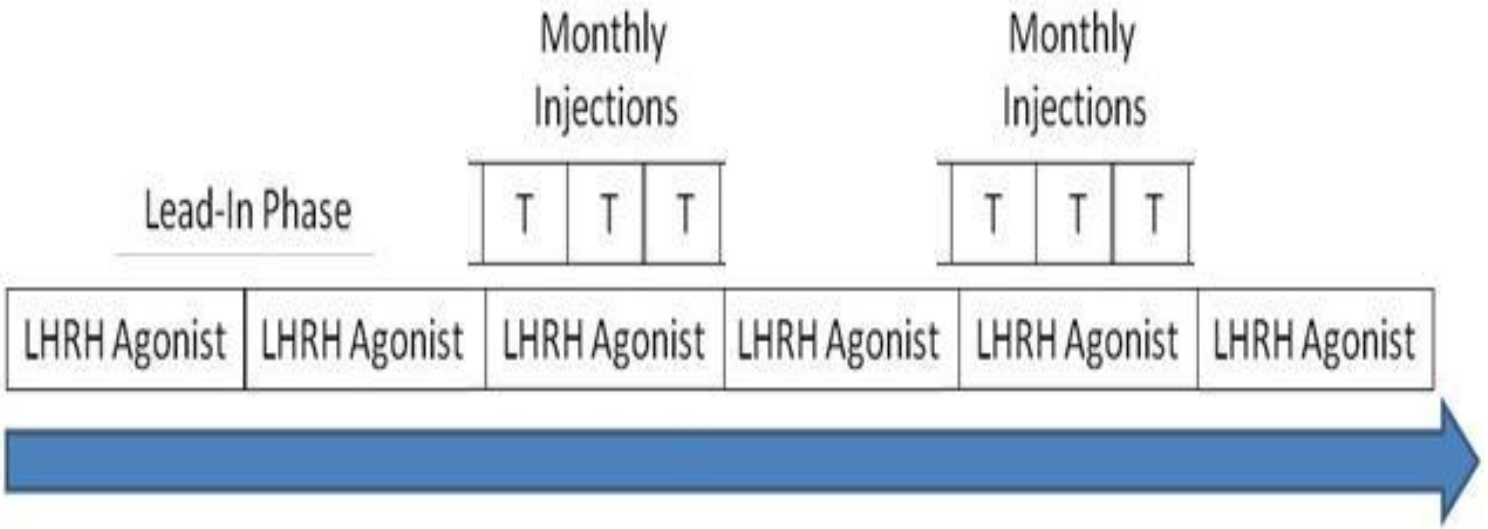
Disadvantage-Variable and Slow Testosterone Recovery Gives Cancer Cells Time to Adapt

PSA Level after 7 months of ADT Predicts for Survival



(SWOG 9346: Hussain et al. JCO 2006;24:3984)

Bipolar Androgen Therapy in Men with Androgen-ablation Naive Prostate Cancer: The "BATMAN" Study



- **Androgen Ablation Naive men with no or minimal metastatic disease and asymptomatic**
- **First Line Therapy**
- **N= 33 men, Baseline Avg. PSA 49.7 (5.6-257.3)**

BATMAN Study

- **Primary endpoint is percentage of men with PSA ≤ 4 ng/ml after 18 months of therapy**
- **We estimated 40% would have PSA < 4 (IADT studies)**
- **We predicted 60% would have PSA <4 with addition of BAT cycling**
- **33 men completed trial from Jan 2013 to Feb 2014**
- **Trial Completed May 2015**

BATMAN Results

- **29/33 men had declining PSA after 6 months ADT lead-in and allowed to proceed to BAT**
- **21/29 (72%) men reached PSA < 4 after 18 months**
- **Most common side effect low grade swelling in lower legs**
- **Significantly improved Quality of Life and sexual function**

Schweizer et al. Prostate. 2016 Sep;76(13):1218-26.

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Mario Eisenberger
Channing Paller
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Founder- One-in-Six Foundation

Thank You for Your Attention and Your Advocacy

For information about clinical trial enrollment contact Dr. Denmeade

Email: denmesa@jhmi.edu
Phone: 410-955-8875