# Targeting the Androgen Receptor in Prostate Cancer

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FDUS/Colorado Springs
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# Disclosures

- Consultant: GHI, CUSP, Tolmar, Integra Connect, Cellay, AZ
- Speakers Bureau: Dendreon, Astellas, Bayer, Janssen, Pfizer/Medivation, Amgen

# STUDIES ON PROSTATIC CANCER

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

CHARLES HUGGINS, M.D.

R. E. STEVENS JR., M.D.

AND

CLARENCE V. HODGES, M.D.

CHICAGO

The thesis of this work may be briefly summarized. In many instances a malignant prostatic tumor is an overgrowth of adult epithelial cells. All known types of adult prostatic epithelium undergo atrophy when androgenic hormones are greatly reduced in amount or inactivated. In this paper evidence is presented that significant improvement often occurs in the clinical condition of patients with far advanced cancer of the prostate after they have been subjected to castration. Conversely, the symptoms are aggravated when androgens are injected. We believe that this work provides a new concept of prostatic carcinoma.

The evidence that prostatic carcinoma is often composed of an adult type of epithelium derives from a study of such tissue with respect to the phosphatase which manifests optimum activity at $p_H$ 5. An important advance in the technic of investigation of the prostate gland was made by Kutscher and Wolbergs,[1] who found that this enzyme is present in large amounts in adult human and monkey prostate glands; indeed, this phosphatase is present in prostate tissue in larger amounts than any phosphatase in any other tissue. Gutman and Gutman[2] found that the enzyme is present in small amounts in infancy and childhood and is increased during puberty to the high values found in the adult. These

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From the Department of Surgery, University of Chicago.

Dr. Hodges is a Fellow of the Douglas Smith Foundation for Medical Research of the University of Chicago.

This investigation was supported by a grant from the Committee for Research in Problems of Sex of the National Research Council.

1. Kutscher, W., and Wolbergs, H.: Prostataphosphatase, Ztschr. f. physiol. Chem. **236**:237, 1935.

2. Gutman, A. B., and Gutman, E. B.: "Acid" Phosphatase and Functional Activity of the Prostate (Man) and Preputial Glands (Rat), Proc. Soc. Exper. Biol. & Med. **39**:529 (Dec.) 1938.

# Studies on Prostatic Cancer

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

Charles Huggins, M.D., and Clarence V. Hodges, M.D.

*(From the Department of Surgery, the University of Chicago, Chicago, Illinois)*

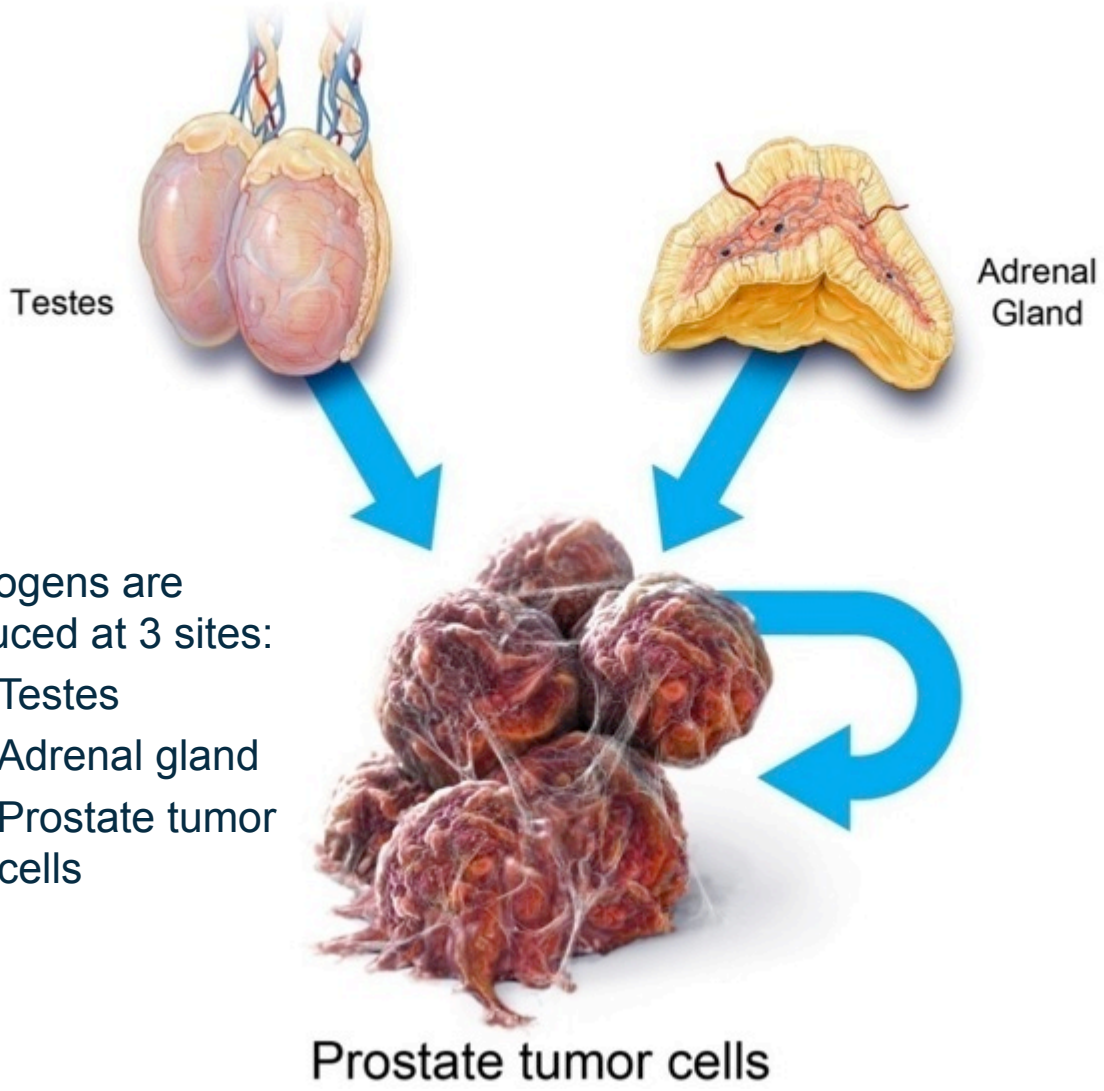
(Received for publication March 22, 1941)

Carcinoma of the prostate gland is peculiarly favorable for endocrine investigation since frequent serial observations of the activity of phosphatases in serum were found to provide objective indices of activity of the neoplasm when the enzymes were increased in amount above normal. In the present paper data are given for the values of serum phosphatases in carcinoma of the prostate and in normal men. We shall demonstrate that the acid phosphatase of serum is reduced in metastatic carcinoma of the prostate by decreasing the activity of androgens through castration or estrogenic injections and that this enzyme is increased by injecting androgens. We have been unable to find previous observations indicating any relationship of hormones to carcinoma of the prostate gland.

### Methods and Materials

The phosphatase activity of serum was determined by the method of King and Armstrong (10) using 0.005 M disodium monophenylphosphate as substrate. The buffers used were 0.05 M barbital-sodium at pH 9.3, and 0.1 M Sörensen's citrate-HCl or Walpole's 0.2 N sodium acetate-acetic acid buffers at pH 5. All serums were tested in duplicate and were added directly to buffer-substrate solutions without dilution; they were incubated at 37.5° C. for 30 minutes. Precautions were observed that all solutions were at this temperature before testing. Blanks were run by adding the protein precipitant to the buffer-substrate solution before adding serum. Colorimetric procedures were carried out with the Evelyn photoelectric colo-

# Sources of Androgen Production




- Androgens are produced at 3 sites:
  - Testes
  - Adrenal gland
  - Prostate tumor cells

# Historical Landmarks: 1st Effective Treatment, 1st Marker, 2 Nobel Prizes

John Hunter
1780–castration

1938–Acid Phos.
1940
Huggins –endocrine control
Advent of orchiectomy and estrogen treatment (Awarded Nobel Prize for this discovery)

1904
First RP

1867
First perineal prostatectomy performed

1920s
RT for PC using radium

1960s
RT established as important treatment for PC

1970s
Steroidal and non-steroidal AAs available

Nobel Prize:
Andrzej Schally, Roger Guillemin

1960s and 70s
Synthetic estrogens developed

1980s
Long-acting synthetic LHRH agonists

1995
Cryosurgery accepted as a treatment option for recurrent cancer after RT

2003
First GnRH blocker (abarelix) launched

2004
Docetaxel in combination with prednisone approved

2008
Degarelix approved in US

2009
ARSI Developed

The future
New androgen receptor–targeted drugs. AA vaccines, biomarkers, genetic research

1920 1940 1960 1980 2000 2020

ARSI = Androgen Receptor Signaling Inhibitor; AA = antiandrogen; LHRH = luteinizing hormone releasing hormone.

Figure courtesy of Dr E. David Crawford

# Hormone Therapy: Current Treatment Options

- Androgen deprivation therapy (ADT)
  - Estrogens (DES)
  - Surgical castration (bilateral orchiectomy)
  - LHRH/GnRH analogs (agonists/antagonists)
- Antiandrogens/Androgen receptor signaling inhibitors
  - Flutamide, Bicalutamide, Nilutamide
  - Enzalutamide
  - ? Apalutamide
- 17,20 Lyase Inhibitors/Androgen Synthesis inhibitors
  - Ketoconazole
  - Abiraterone Acetate

# Complications of ADT

1. Hot Flashes
2. Anemia
3. Sexual dysfunction
4. Cognitive dysfunction, ? Depression
5. Osteoporosis
6. Metabolic Syndrome
   - obesity
   - Insulin resistance
   - Dyslipidemia
   - Hypertension

Gaztanaga and Cook, JNCCN. 2012;10.

ARTICLE | April 1973

# A 25-Year Experience With Vagotomy-Antrectomy

J. Lynwood Herrington Jr., MD; John L. Sawyers, MD; H. William Scott Jr., MD

*Arch Surg.* 1973;106(4):469-474. doi:10.1001/archsurg.1973.01350160087014.



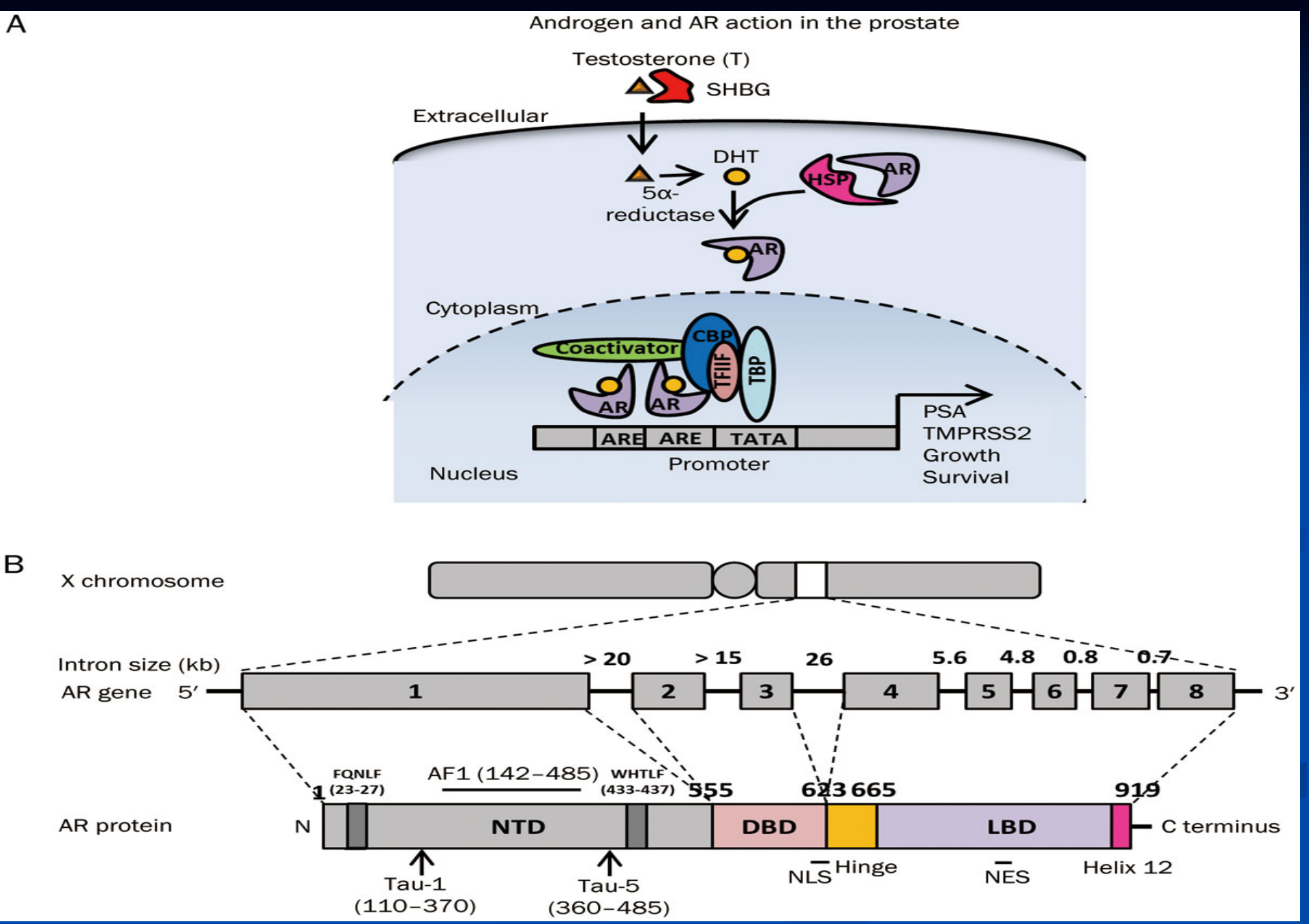


## ABSTRACT

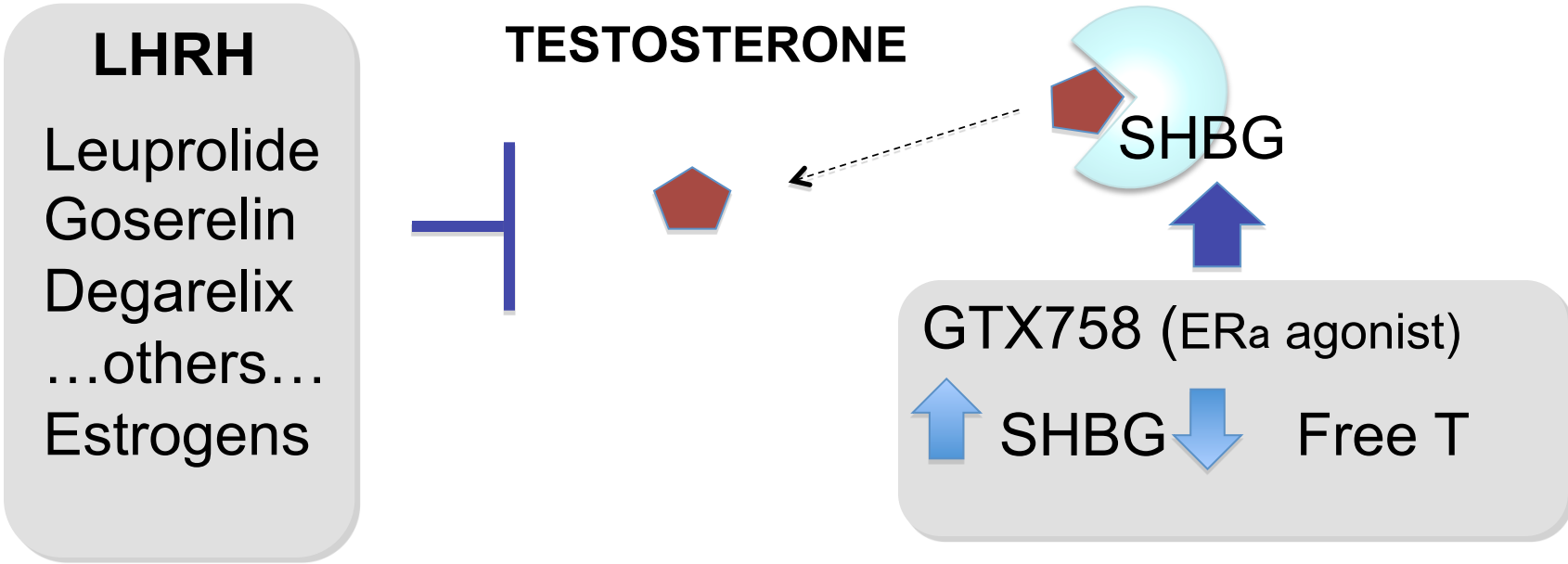


During the past 25 years our surgical group, utilizing three affiliated hospitals, has performed vagotomy-antrectomy on 3,584 patients. The follow-up has been 98%. The operative mortality has declined from 3.1% in the 1950s to the present mortality of 1.6%. The overall satisfactory results with the combined procedure has been 94% and the recurrent ulcer rate is 0.6%.

The clinical study supports the concept that vagotomy-antrectomy is the most effective operation to prevent recurrent ulceration. It can be performed with safety in most patients with complications of ulcer, but it is contraindicated in the high-risk individual and in circumstances where dissection about the duodenum would prove hazardous. Vagotomy-antrectomy remains the procedure of choice and lesser operations for ulcer are used in only certain selected cases.

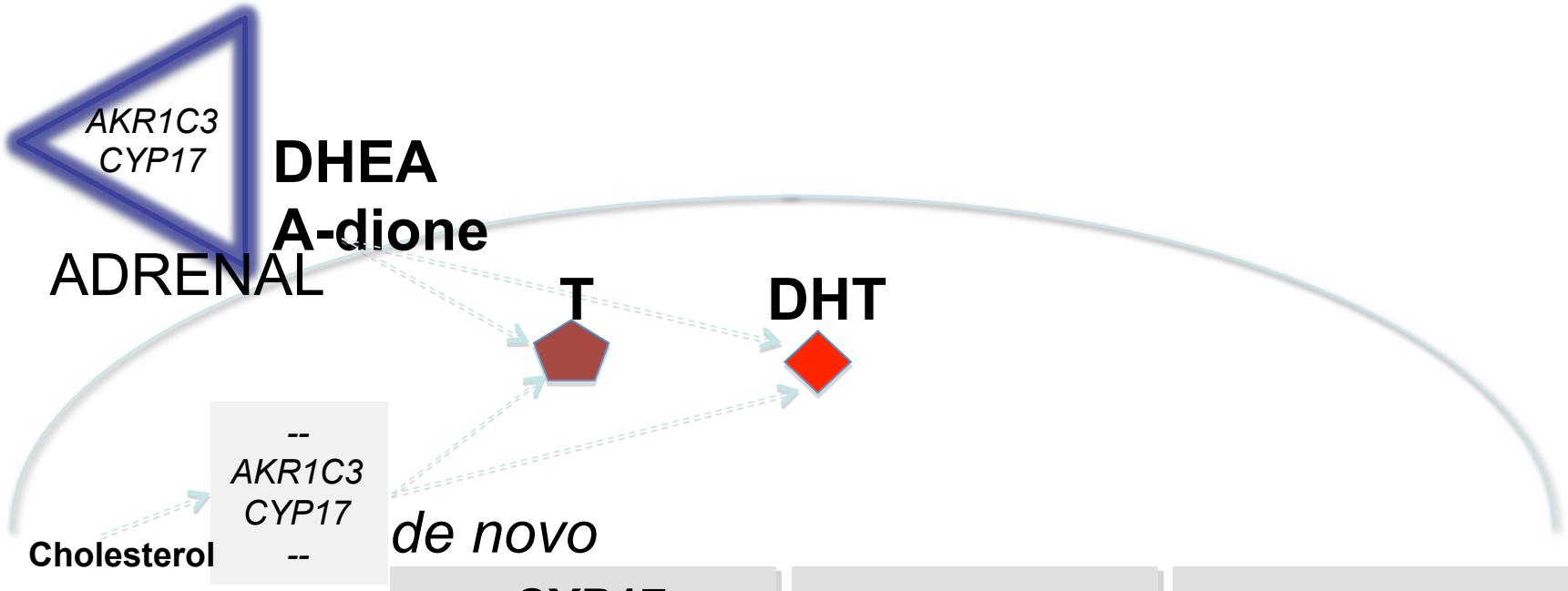


# Target 1: Gonadal/Circulating T




Modified from Peter Nelson, MD

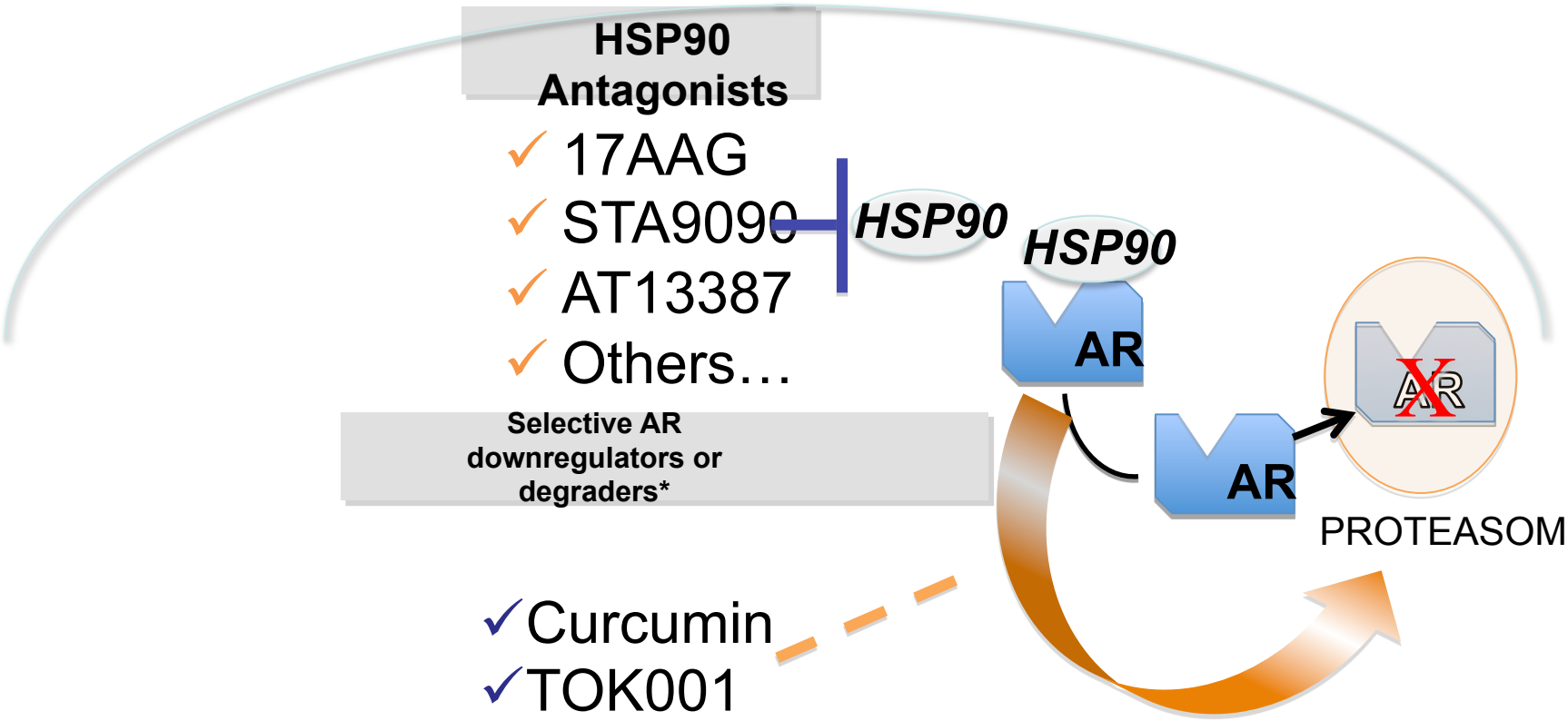
# Target 2: Adrenal/Intracrine Ligands




| CYP17 | AKR1C3 | 3bHSD |
|---|---|---|
| ✓ Ketoconazole | ✓ Indomethacin | ✓ Abiraterone-HD |
| ✓ Abiraterone | ✓ I-analogs | ✓ Trilostane |
| ✓ TAK700 | | |
| ✓ TOK001 | | |
| ✓ VT-464 | | |

Modified from Peter Nelson, MD

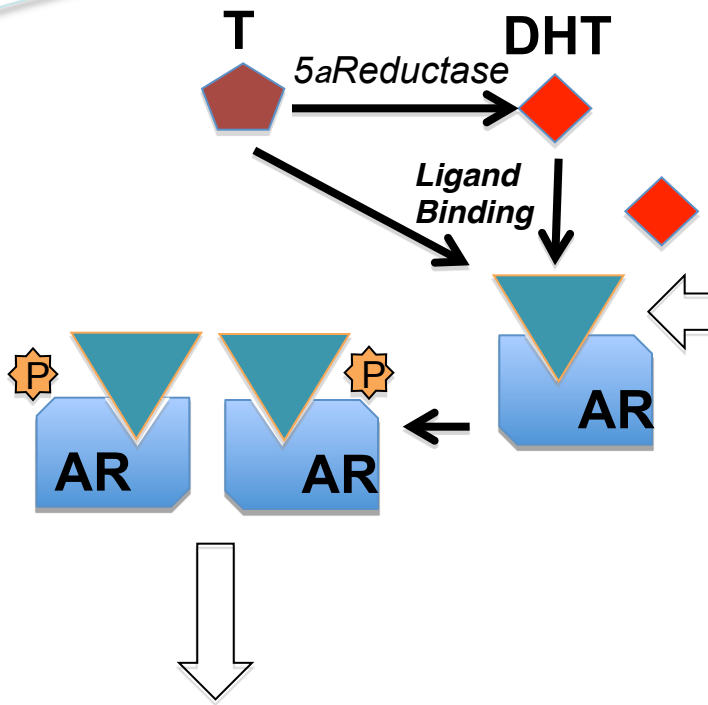
# Target 3: AR Degradation




*many others with low potency

Modified from Peter Nelson, MD

# Target 4: Androgen Receptor Blockade




**Competitive Antagonists**

Flutamide
Bicalutamide
Nilutamide
**Enzalutamide**
**ARN509**
**TOK001**

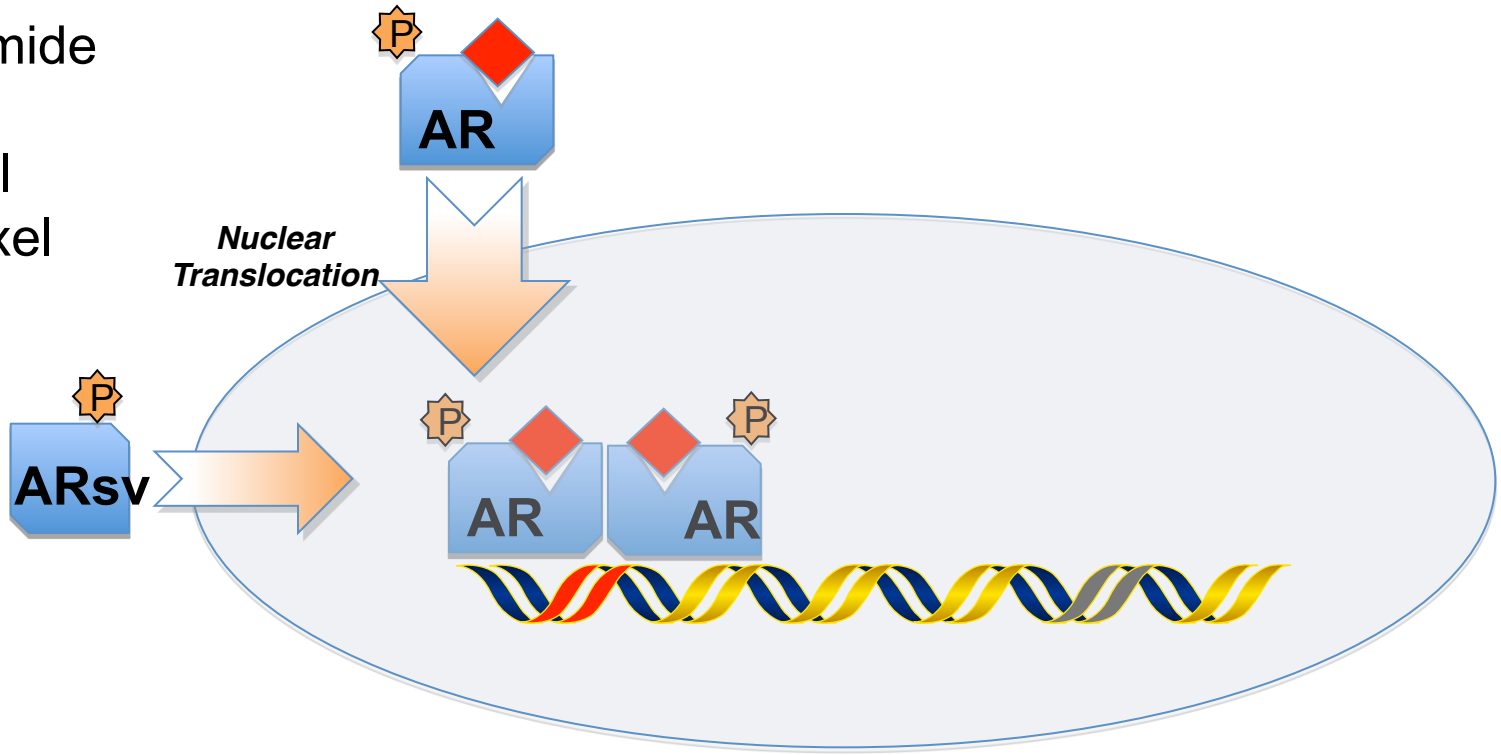
✓*enhanced degradation*
✓*translocation block*
✓*unproductive transcription*

Modified from Peter Nelson, MD

# Target 5: Prevent AR Nuclear Translocation

**Microtubule Inhibitors**

- ✓ Enzalutamide
- ✓ Paclitaxel
- ✓ Docetaxel
- ✓ Cabazitaxel

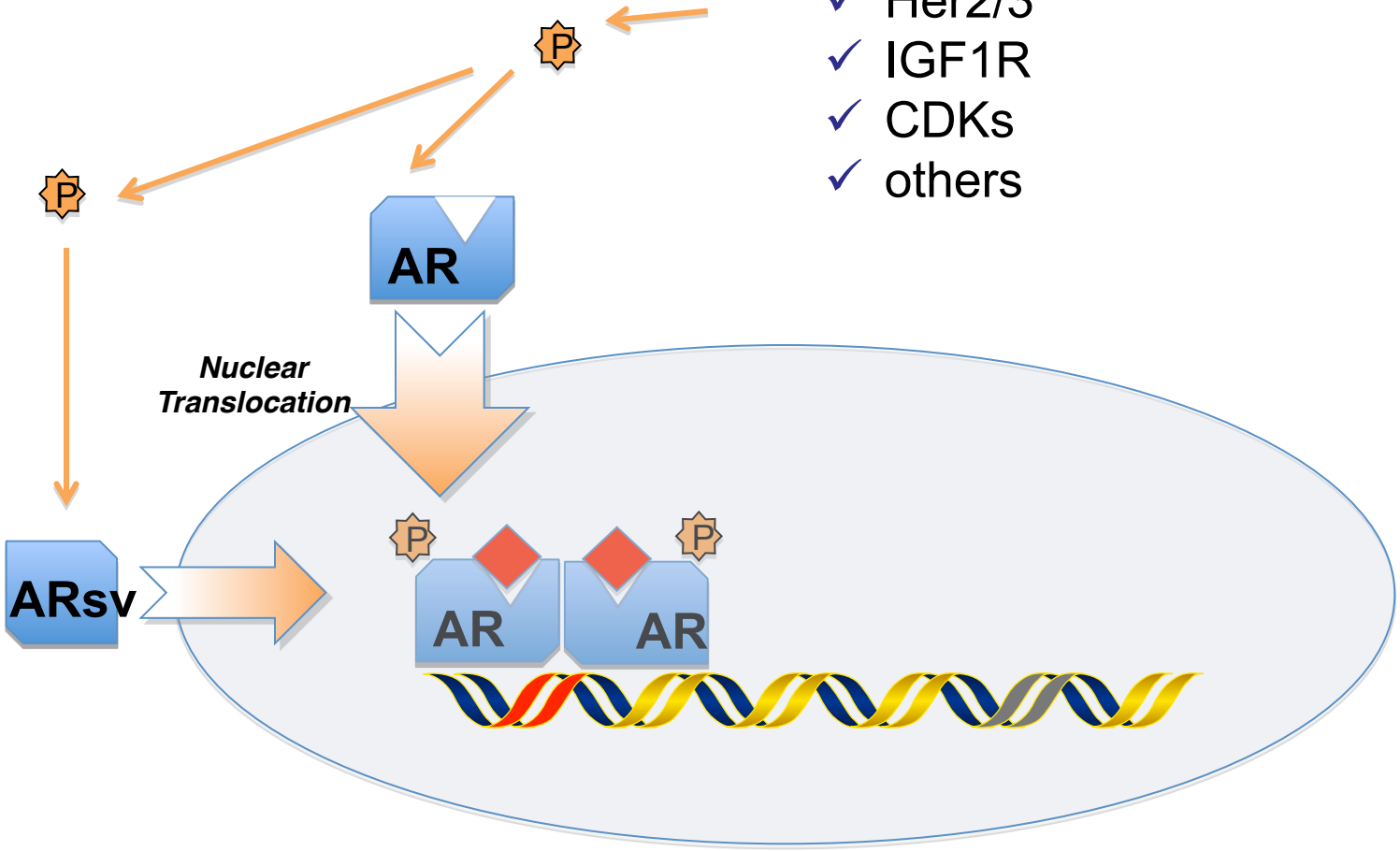



Modified from:Peter Nelson, MD

# Target 6: Interfere With AR 'Enablers'

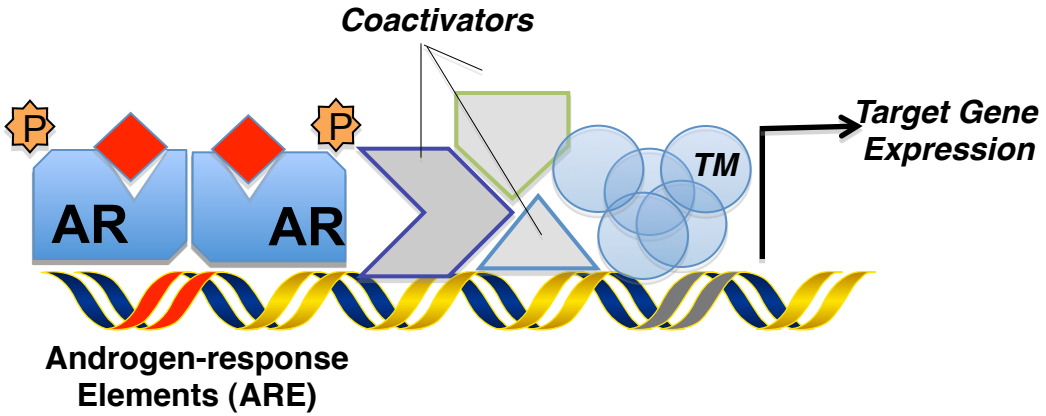
**Signaling Pathways**

- ✓ Her2/3
- ✓ IGF1R
- ✓ CDKs
- ✓ others




Modified from:Peter Nelson, MD

# Target 7: Block AR–DNA/Co-Activator Interaction




***Important as they may target ARsv***

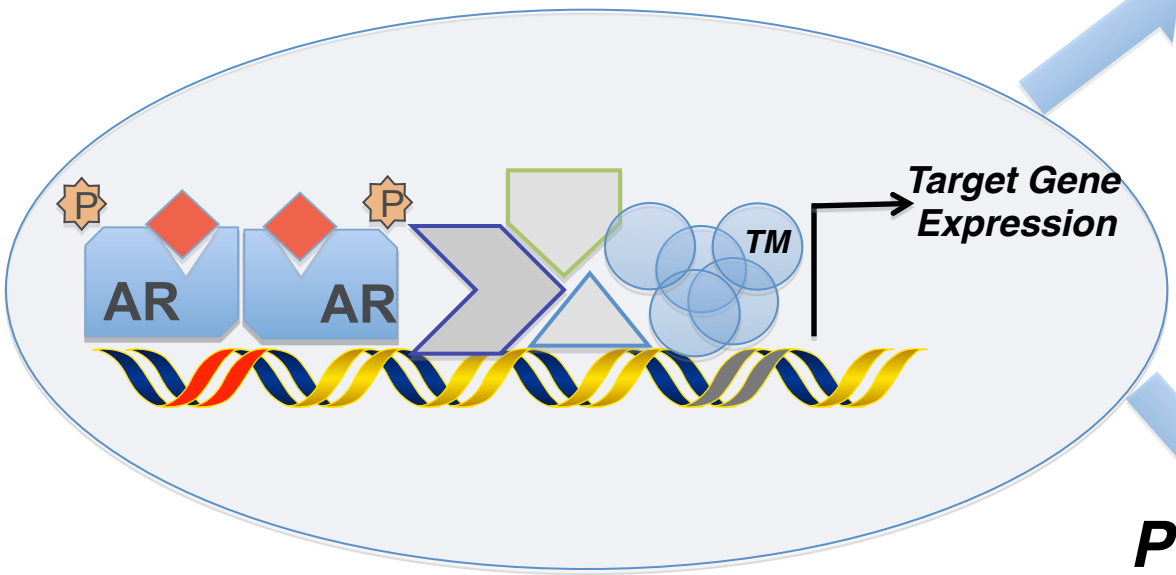
**Non-Competitive Antagonists***

**EPI-001**
**'D2'**
**Pyrivinium**
**Harmol HCL**
**Others**

*N-C interactions
Nuclear translocations
AR AF2-LXXLL Interactions
Co-factor inhibition

Modified from Peter Nelson, MD

# Target 8: AR Downstream ‘Effectors’




**PI3K-Pathway Inhibitors**

**ETS-family Inhibitors**

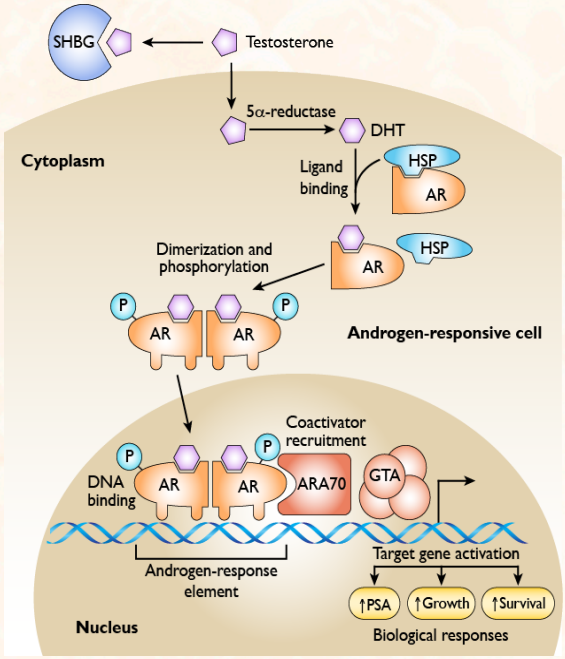
***Proliferation***
***Survival***
***Metabolism***

**CAMKK2 inhibitor (STO-609)**

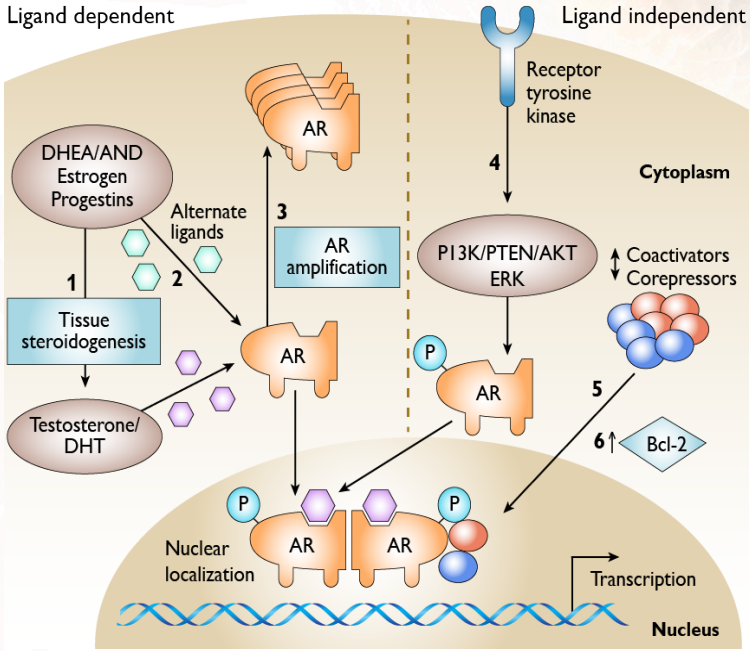
Modified from Peter Nelson, MD

# The Development of mCRPC Involves Alterations in AR-Signaling

## Androgen Signaling[1]




## Pathways to Castration Resistance[1]




Aggressive forms of CRPC, such as neuroendocrine, and small-cell carcinomas often lack AR expression[2,3]


1. HARRIS WP, ET AL. *NAT CLIN PRACT UROL.* 2009;6(2):76-85.
2. DEBES JD, TINDALL DJ. *N ENGL J MED.* 2004;351(15):1488-1490.
3. APARICIO A, TZELEPI V. *ONCOLOGY (WILLISTON PARK).* 2014;28(10):831-838.

# Summary of clinical trial outcome

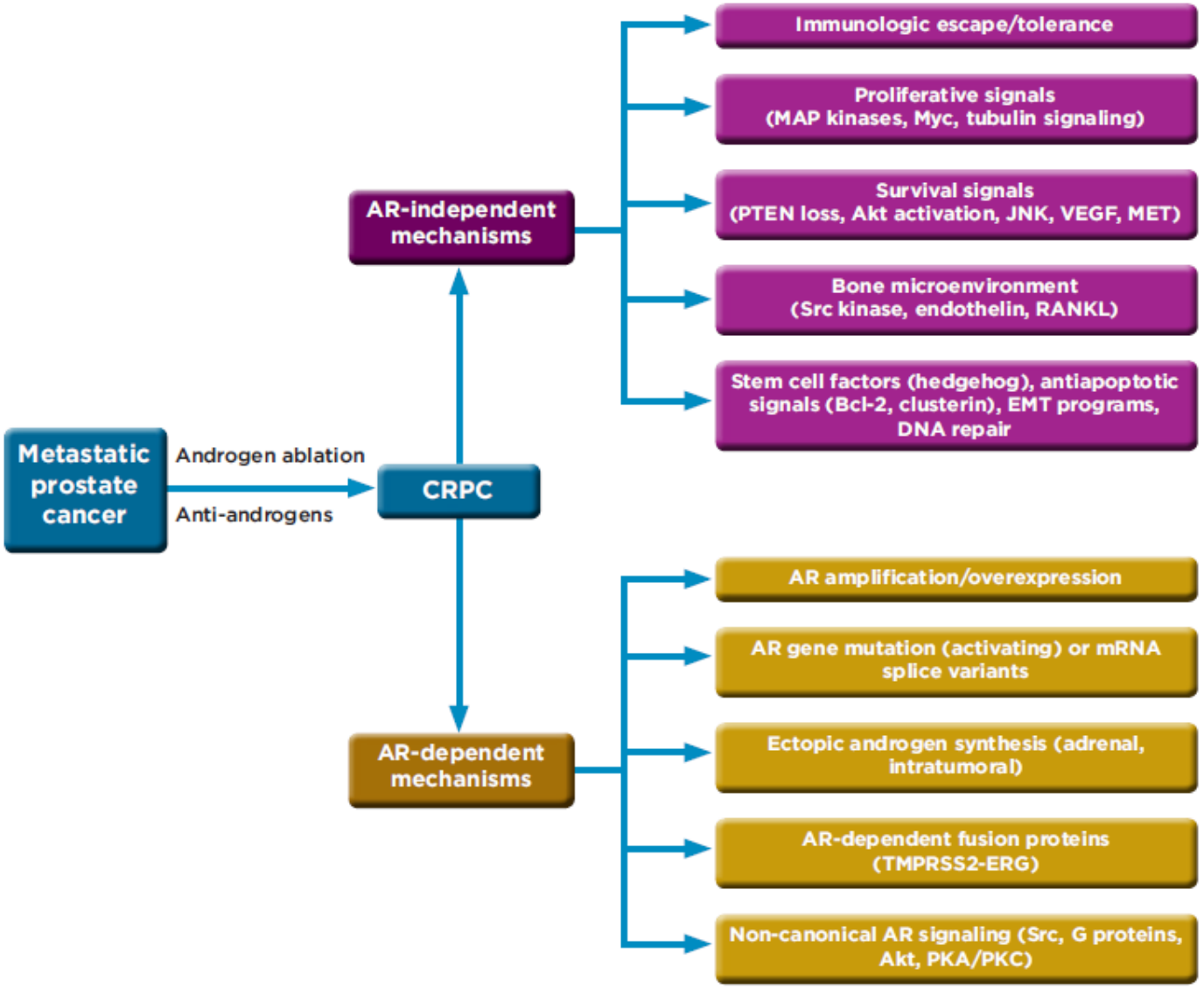
| | Patient setting | Control | OS | | |
|---|---|---|---|---|---|
| | | | Increase in median, months | HR | p value |
| **Docetaxel/P**[1] | First-line | Mitoxantrone/P | 2.9 | 0.79 | 0.004 |
| **Cabazitaxel/P**[2] | Post-docetaxel | Mitoxantrone/P | 2.4 | 0.70 | <0.0001 |
| **Abiraterone/P**[3] | Post-docetaxel | Placebo/P | 4.6 | 0.74 | <0.0001 |
| **Abiraterone/P**[4] | Chemo-naïve | Placebo/P | 5.2 | 0.81 | 0.0033* |
| **Enzalutamide**[5] | Post-docetaxel | Placebo | 4.8 | 0.63 | <0.001 |
| **Enzalutamide**[6] | Chemo-naïve | Placebo | 2.2 | 0.71 | <0.0001 |
| **Radium-223**[7] | Bone metastases, Pre- and post docetaxel | Placebo | 3.6 | 0.70 | <0.001 |

*OS did not reach the prespecified efficacy boundary (p=0.0035)

1. Berthold DR, et al. J Clin Oncol 2008;26:242–5; 2. de Bono JS, et al. Lancet 2010;76:1147–54;
3. Fizazi K, et al. Lancet Oncol 2012;13:983–92; 4. Rathkopf DE, et al. J Clin Oncol 2013;31(suppl. 6): abstract 5;
5. Scher HI, et al. N Engl J Med 2012;367:1187–97; 6. 12. Beer et al., J Clin Oncol 32, 2014 (suppl 4; abstr LBA1^); 7. Parker C, et al. N Engl J Med 2013;369:213–23

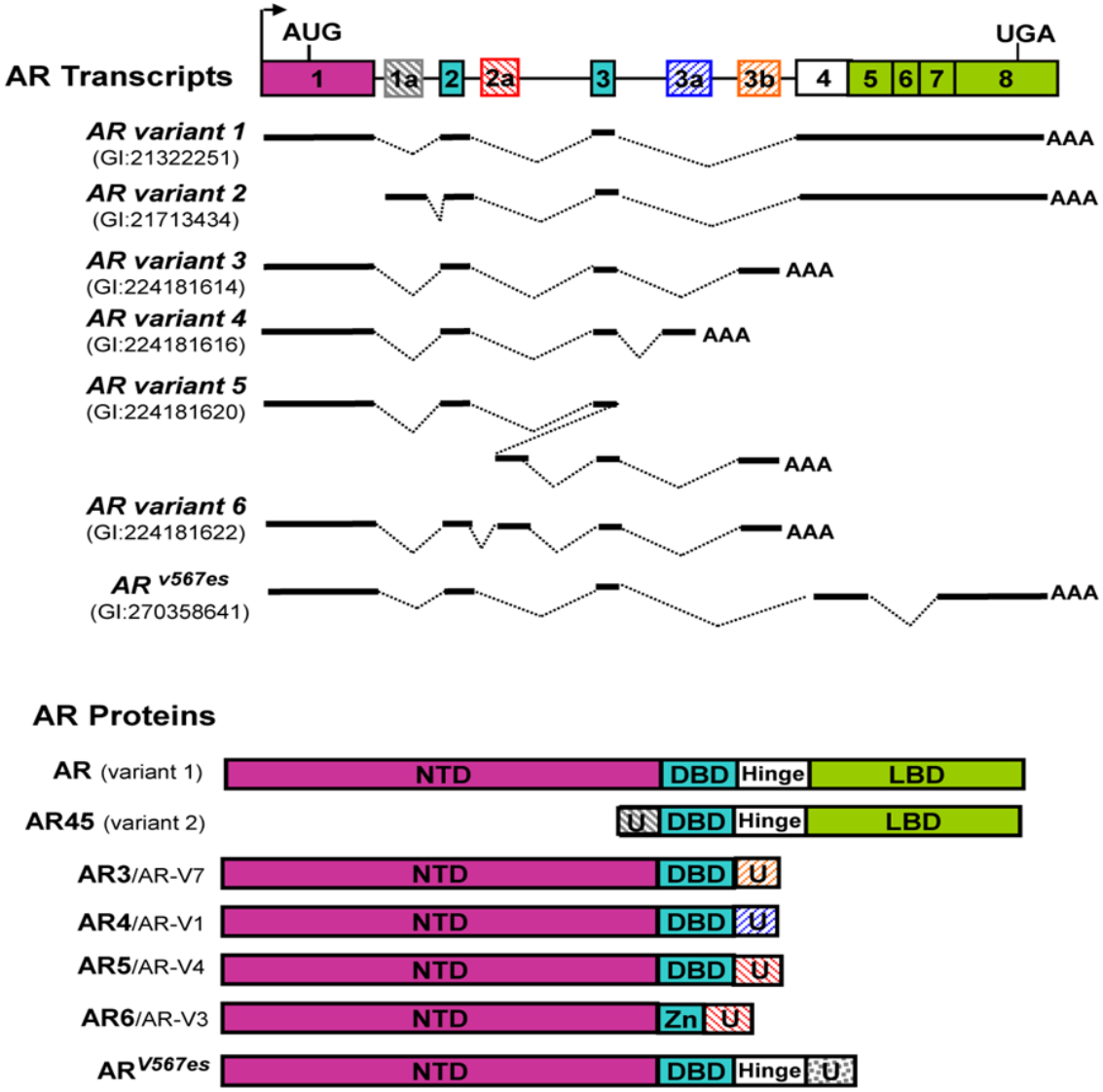
These studies are different (in type, population, inclusion/exclusion criteria, design and method, primary objectives) and therefore a comparison cannot be made.

# Biologic Mechanisms Driving CRPC




Antonarakis and Armstrong, Clin Oncol News 2011

# AR Splice Variants

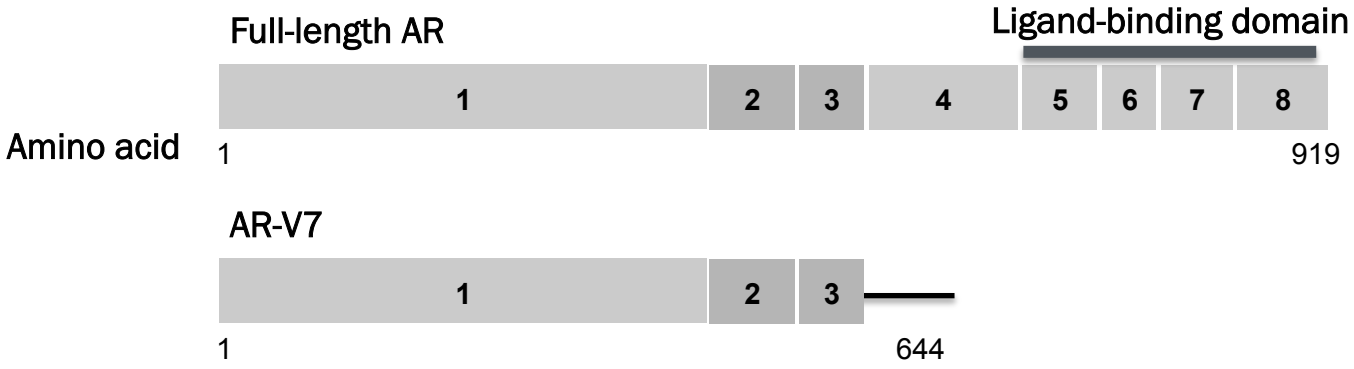



Guo Z and Qiu Y. *Int J Biol Sci.* 2011;7:815-822.

# AR splice variants are associated with poor prognosis and Treatment resistance

- The translation of splice variants results in proteins with altered activity and regulation[1]

- Exons 4-8 of AR are not required for transcriptional activity and splice variants lacking this region may be constitutively active[2]
- In one study, expression of AR variants lacking the ligand-binding domain in CRPC bone metastases was associated with poor prognosis[2]
- Detection of AR-V7 in tumor cells is associated with treatment resistance[3,4]




Thadani-Mulero M, et al. *Cancer Res.* 2014;74(8):2270-2282. © 2014 American Association for Cancer Research.

# Lack of Response Associated with AR-V7 (Johns Hopkins University)

- Prospective study of M1 CRPC patients eligible for abiraterone (N=31) and enzalutamide (N=31) treatment; AR-V7 identified in CTC samples pretreatment
- None (0/18) of the AR-V7 positive patients achieved a PSA50
  - Only 1 AR-V7 positive patient showed any PSA reduction (enzalutamide)
- AR-V7 prevalence increased post additional treatments

| Treatment[1] | Baseline AR-V7+ | Response | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | AR-V7 status | PSA50 | P- value | rPFS | P- value | OS (95% CI) | P value |
| Abiraterone (N=31) | 19% (6/31) | + | 0% (0/6) | .004 | 2.3 mos | <.001 | 10.6 mos (8.5–NR) | .002 |
| | | – | 68% (17/25) | | >6.3 mos | | >11.9 mos (11.9–NR) | |
| Enzalutamide (N=31) | 39% (12/31) | + | 0% (0/12) | .004 | 2.1 mos | <.001 | 5.5 mos (3.9–NR) | .006 |
| | | – | 53% (10/19) | | 6.1 mos | | NR (NR–NR) | |

| Patient Treatment Status[2] | Before enzalutamide or abiraterone | Post enzalutamide | Post abiraterone | Post abiraterone & enzalutamide |
|---|---|---|---|---|
| AR-V7 Prevalence | 12% | 25% | 51% | 67% |

CRPC=castration-resistant prostate cancer; CTC=circulating tumor cell; M1=metastatic disease; NR=not reached; OS=overall survival; PSA=prostate specific antigen; rPFS=radiographic progression-free survival. 1. Antonarakis ES et al. NEJM. 201410.1056/NEJMoa1315815. 2.. Antonarakis ES et al. ASCO 2014

Cell

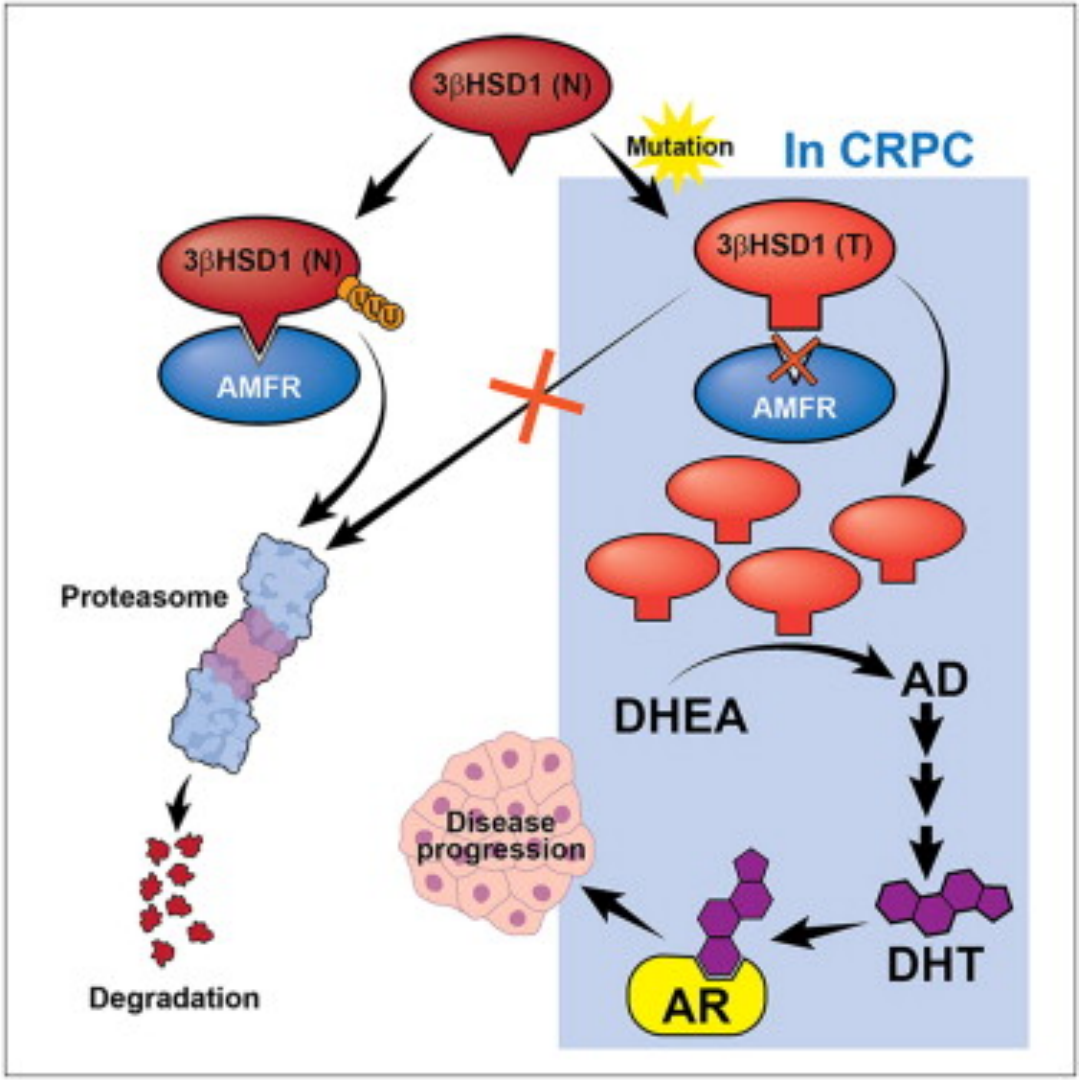
Volume 154, Issue 5, 29 August 2013, Pages 1074–1084

Article

# A Gain-of-Function Mutation in DHT Synthesis in Castration-Resistant Prostate Cancer

Kai-Hsiung Chang[1, 2, 3, 4], Rui Li[4], Barbara Kuri[1, 2, 3], Yair Lotan[5], Claus G. Roehrborn[5], Jiayan Liu[8], Robert Vessella[9], Peter S. Nelson[9, 10], Payal Kapur[6], Xiaofeng Guo[7], Hamid Mirzaei[7], Richard J. Auchus[8], Nima Sharifi[1, 2, 3, 4,]

# Mutation in 3BHSD1 Facilitates Conversion of Precursors to DHT



Cell

Volume 155, Issue 6, 5 December 2013, Pages 1309–1322

Article

# Glucocorticoid Receptor Confers Resistance to Antiandrogens by Bypassing Androgen Receptor Blockade

Vivek K. Arora[1,2], Emily Schenkein[1], Rajmohan Murali[1,3], Sumit K. Subudhi[2], John Wongvipat[1], Minna D. Balbas[1,4], Neel Shah[1,4], Ling Cai[1], Eleni Efstathiou[5], Chris Logothetis[5], Deyou Zheng[6], Charles L. Sawyers[1,7,]

# ENACT: Enzalutamide in Patients with Localized Prostate Cancer Undergoing Active Surveillance

**Recruiting**

**N=230**
**Key Eligibility Criteria:**
- Clinically localized, histologically proven adenocarcinoma of prostate
- Not received any treatment for prostate cancer ever and has chosen active surveillance (low/ intermediate risk)
- ECOG PS ≤ 2

R
1:1

**Enzalutamide 160mg QD x 1 year then active surveillance for year 2**

**Active Surveillance x 2 years**

Stratification factors:
- low vs intermediate risk
- mpMRI biopsy vs non mpMRI biopsy

**Primary endpoint:**
- Time to progression (pathological or therapeutic)

**Key Secondary endpoints:**
- Safety
- Proportion of patients with negative biopsy for PC at 1 and 2 years
- Percent of cancer positive cores at 1 year and 2 years
- Time to PSA progression (secondary rise in serum PSA>25% above baseline or >25% above nadir or absolute increase > 2 ng/ mL)
- Proportion of patients with secondary rise in PSA at 1 year and 2 years
- Quality of life by BFI, SF-12, EPIC, MAX-PC

**low risk = T1c-T2a, PSA<10, N0, M0, GS ≤ 6 ; intermediate risk = T2b-T2c, PSA<20, N0, M0, GS ≤7 (3+4 pattern only). ‡PC progression defined as either pathologic or therapeutic progression. Pathologic progression: increase in primary or secondary Gleason pattern by ≥ 1 or higher proportion of cancer positive cores (≥15% increase). Therapeutic progression: the earliest occurrence of primary therapy for PC (prostatectomy/ radiation/focal therapy/systemic therapy). EPIC = Expanded PC Index Composite questionnaire – urinary, sexual and hormonal domains; MAX-PC = Memorial Anxiety scale for PC questionnaire; SF-12 = Medical outcomes study 12-item short form survey.*

www.clinicaltrials.gov (NCT02799745)

# EMBARK: A Study of Enzalutamide in Patients With High-Risk Nonmetastatic Prostate Cancer Progressing After Definitive Therapy

**Recruiting**

Patients with high-risk nonmetastatic prostate cancer progressing after definitive therapy*

N = 1860

1:1:1 Randomization stratification

R

- Enzalutamide 160 mg qd
- Enzalutamide 160 mg qd + Leuprolide q12wk
- Placebo qd + Leuprolide q12wk

**Additional inclusion criteria include: PSA doubling time ≤ 9 months; PSA ≥ 2.0 ng/mL for patients who had radical prostatectomy as primary treatment or ≥ 5.0 ng/mL and greater than or equal to the nadir + 2 ng/mL for patients who had radiotherapy as primary treatment; serum testosterone ≥ 150 ng/dL*

## Objectives

- **Primary Endpoint:**
  - Metastasis-free survival
- **Key Secondary Endpoints:**
  - Overall survival
  - Proportion of patients treatment-free 2 years after treatment suspension at week 37 due to undetectable PSA
  - Time to castration resistance[#]
  - Safety[‡]

- Phase 3 multinational randomized study

*[#]Time from randomization to first PSA increase that is ≥ 25% and ≥ 2 µg/L above the nadir or screening value, whichever is lower, and that is confirmed by a second consecutive value obtained at least 3 weeks later*

*[‡]Composite measure of incidence and severity of adverse events, serious adverse events, incidence of treatment discontinuation due to adverse events, and incidence of new clinically significant changes in clinical laboratory values and vital signs*

*PSA = prostate-specific antigen; R = randomization*

www.clinicaltrials.gov (NCT02319837).

# ARCHES: Multinational, Phase 3, Randomized, Double-blind, Placebo-controlled Efficacy and Safety Study of Enzalutamide +ADT vs Placebo + ADT in HSPC Patients

**Ongoing**

**N=1100**
- Patients with mHSPC
- ECOG PS 0-1

- Stratified by:
  - volume of disease
    - Low vs. high
  - prior docetaxel therapy for prostate cancer
    - No prior
    - 1-5 cycles
    - 6 cycles

R 1:1

- Enzalutamide + ADT 160 mg/d
- Placebo daily + ADT

**Primary Endpoint**
- rPFS (based on central review)

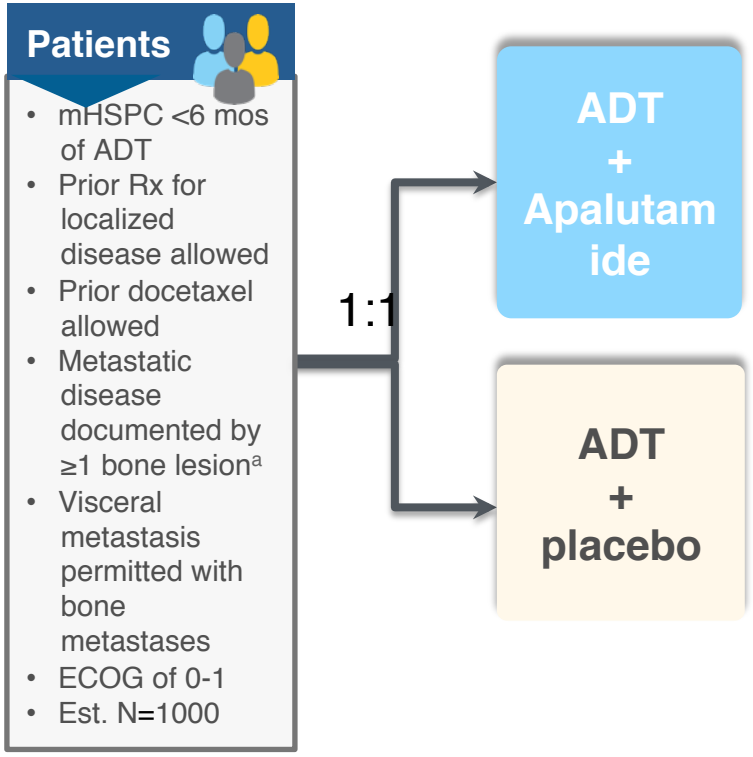
**Key Secondary Endpoints**
- OS
- Time to first SSE
- Time to castration resistance
- Time to deterioration of QoL
- Time to initiation of new antineoplastic therapy
- Time to PSA progression (≥ 2 ng/mL) (Prostate Cancer Clinical Trials Working Group 2 criteria)
- PSA undetectable rate (< 0.2 ng/mL)
- ORR
- Time to pain progression
- Safety

**High-volume disease = metastases involving viscera or ≥4 bone lesions with at least 1 of which in a bony structure beyond the vertebral column & pelvic bone*

*ADT = androgen deprivation therapy; BPI-SF = Brief Pain Inventory-Short Form; ECOG PS = Eastern Cooperative Oncology Group performance status; EQ-5D-5L = European Quality of life-5 Dimensions-5 Levels; FACT-P = Functional Assessment of Cancer Therapy-Prostate; GnRHa = gonadotropin releasing hormone analogue (agonist or antagonist) or prior bilateral orchiectomy (medical or surgical castration); mHSPC = metastatic hormone sensitive prostate cancer; PC = prostate cancer; PSA = prostate-specific antigen; QLQ-PR25 = Quality of Life Questionnaire-Prostate 25; R = randomization; rPFS = radiographic progression-free survival*

www.clinicaltrials.gov (NCT02677896)

# TITAN: Hormone Sensitive M1 Study Design




[a]Subjects with 1 bone lesion on scan must have CT / MRI confirmation.

**Primary Endpoints**

- rPFS, OS

**Secondary Endpoint**

- Time to symptomatic progression (pain progression or SRE)
- Time to chronic opioid use
- Time to initiation of chemotherapy
- Time to PSA progression

**Patient Reported Outcomes**

- BPI-SF, BFI, FACT-P, EQ-5D-5L

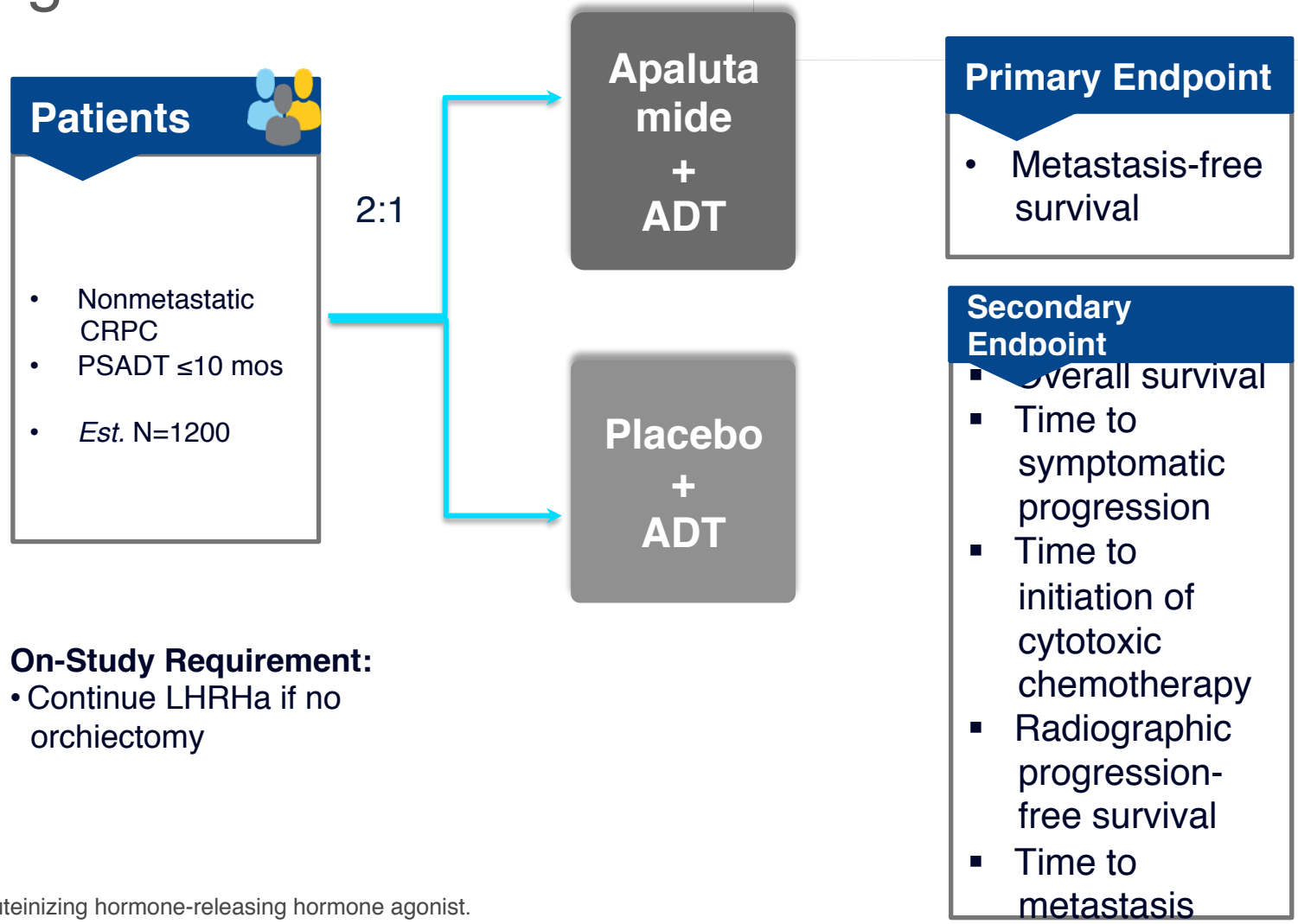
**Stratifications:**

- Gleason Score at Diagnosis (≤7, >7)
- Geographic Regions (NA, EU, Other countries)

mHSPC, metastatic hormone sensitive prostate cancer; SRE, skeletal-related events.

www.clinicaltrials.gov NCT02489318.

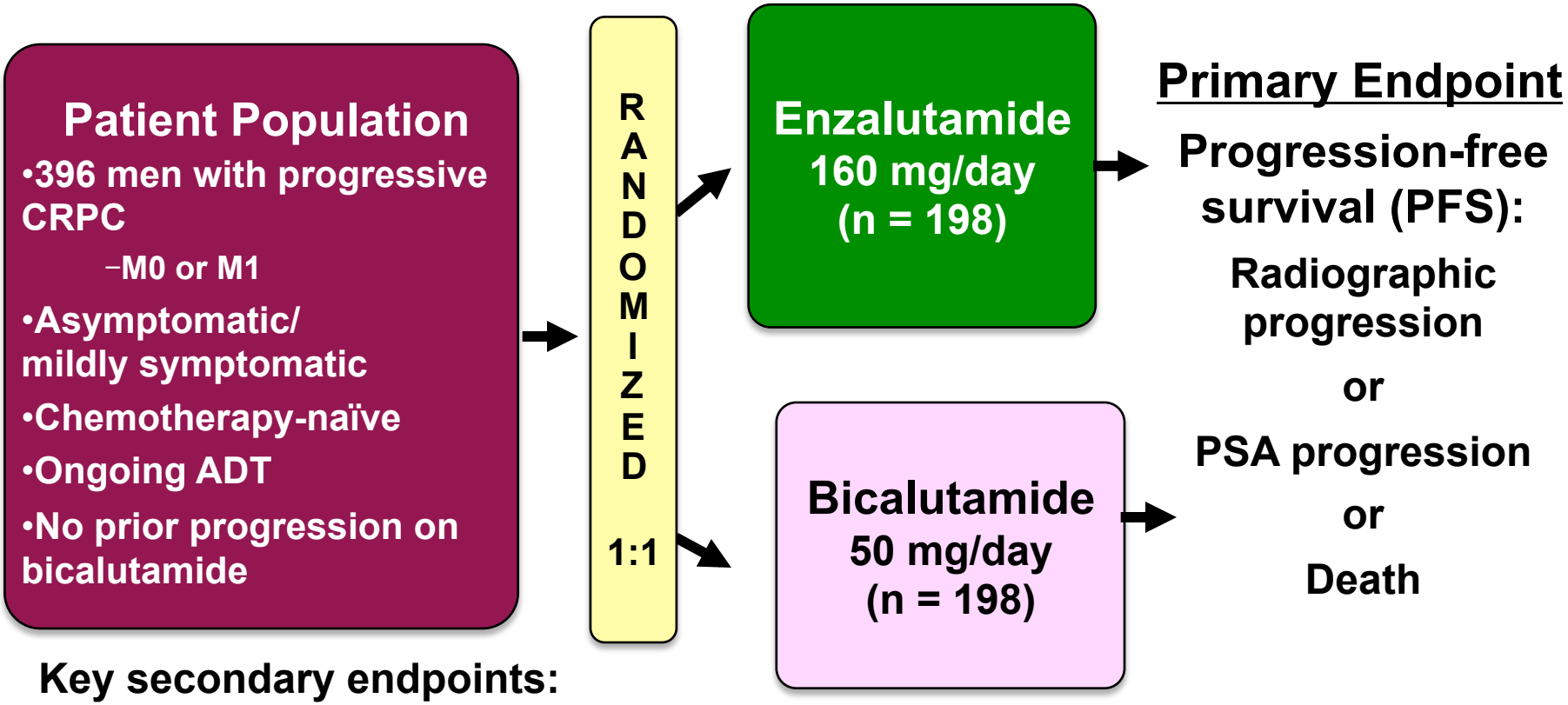
# SPARTAN: High-Risk nmCRPC Phase 3 – Study Design




**On-Study Requirement:**
- Continue LHRHa if no orchiectomy

LHRHa, luteinizing hormone-releasing hormone agonist.

# STRIVE: Study Design



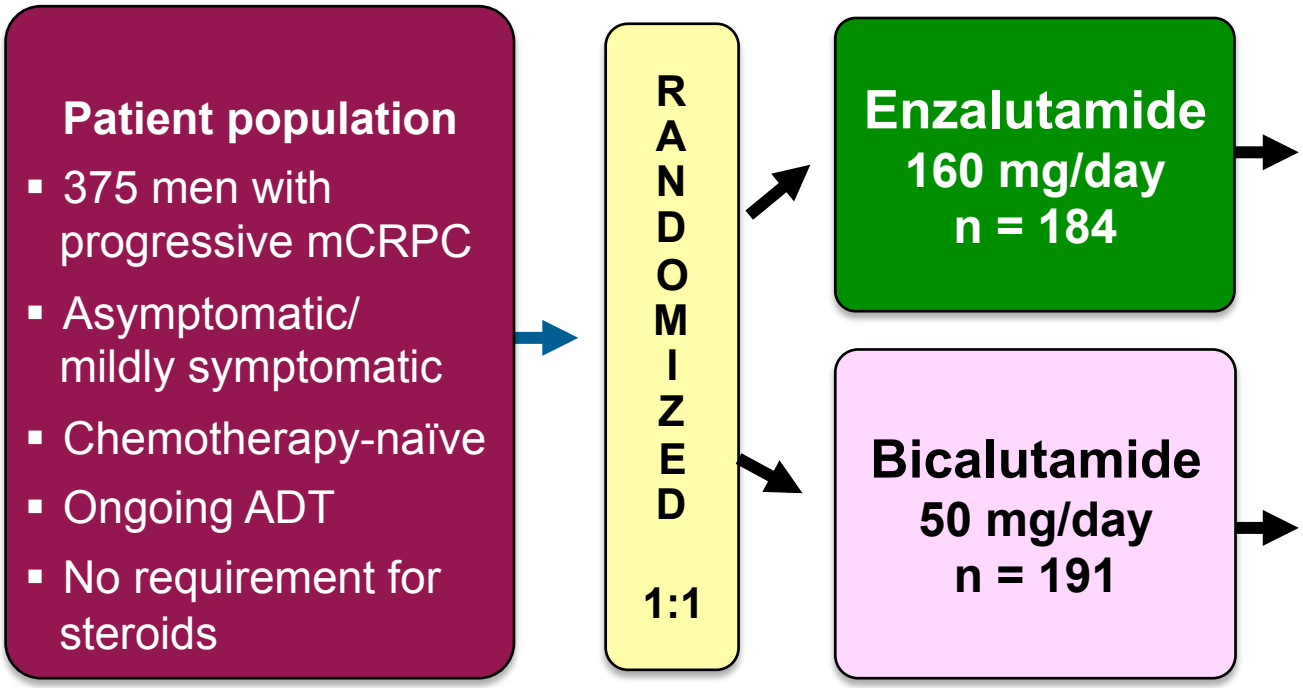

- **Key secondary endpoints:**
  - **Time to PSA progression**
  - **PSA response**
  - **rPFS (M1 population only)**

ClinicalTrials.gov identifier: NCT01664923

ADT = androgen deprivation therapy; CRPC = castration-resistant prostate cancer; M0 = nonmetastatic; M1 = metastatic; PSA = prostate-specific antigen; rPFS = radiographic PFS..

Penson DF, et al. *J Clin Onc*ol. 2016 Jun 20;34(18):2098-2106.

# TERRAIN: A Phase 2 Efficacy and Safety Study of Enzalutamide vs Bicalutamide in mCRPC: Study Design[1]




## Primary endpoint

- Progression-free survival (PFS), defined as time from randomization to (whichever occurs first):
  - Radiographic progression
  - SRE
  - Initiation of new antineoplastic therapy
  - Death

## Secondary endpoints

- PSA response
- Time to PSA progression
- Safety

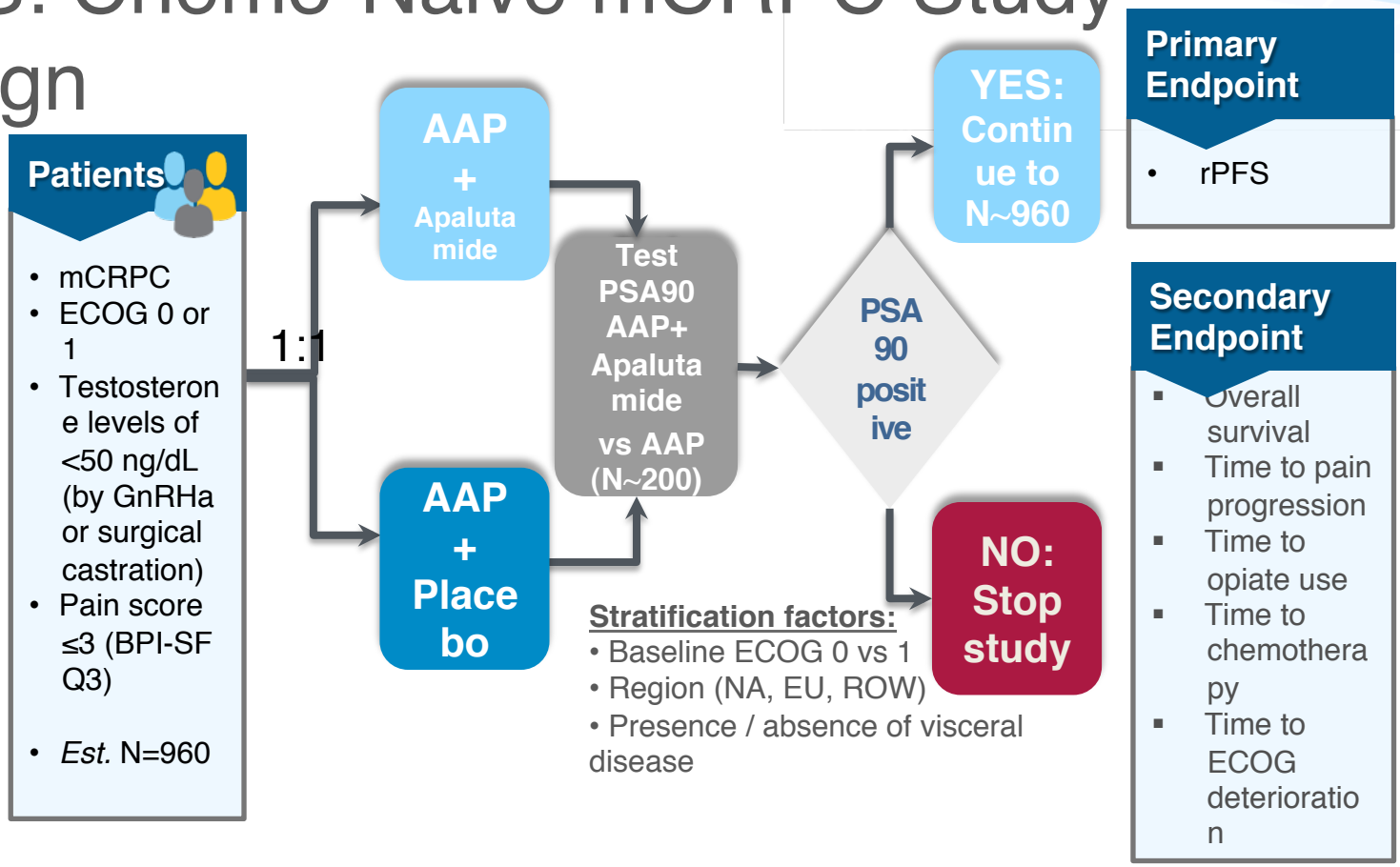
## Statistical design

- Final analysis planned at ≥ 220 progression events with 85% power to detect a target hazard ratio of 0.67 (assuming a median PFS of 9 months versus 6 months[2])
- Data cutoff date was 19 October 2014 with 240 events for the primary efficacy endpoint

*mCRPC = metastatic castration-resistant prostate cancer; PSA = prostate-specific antigen; SRE = skeletal-related event*


1. Shore ND, et al. *Lancet Oncol*. 2016;17:153-163.
2. Kucuk O, et al. *Urology*. 2001;58:53-58.

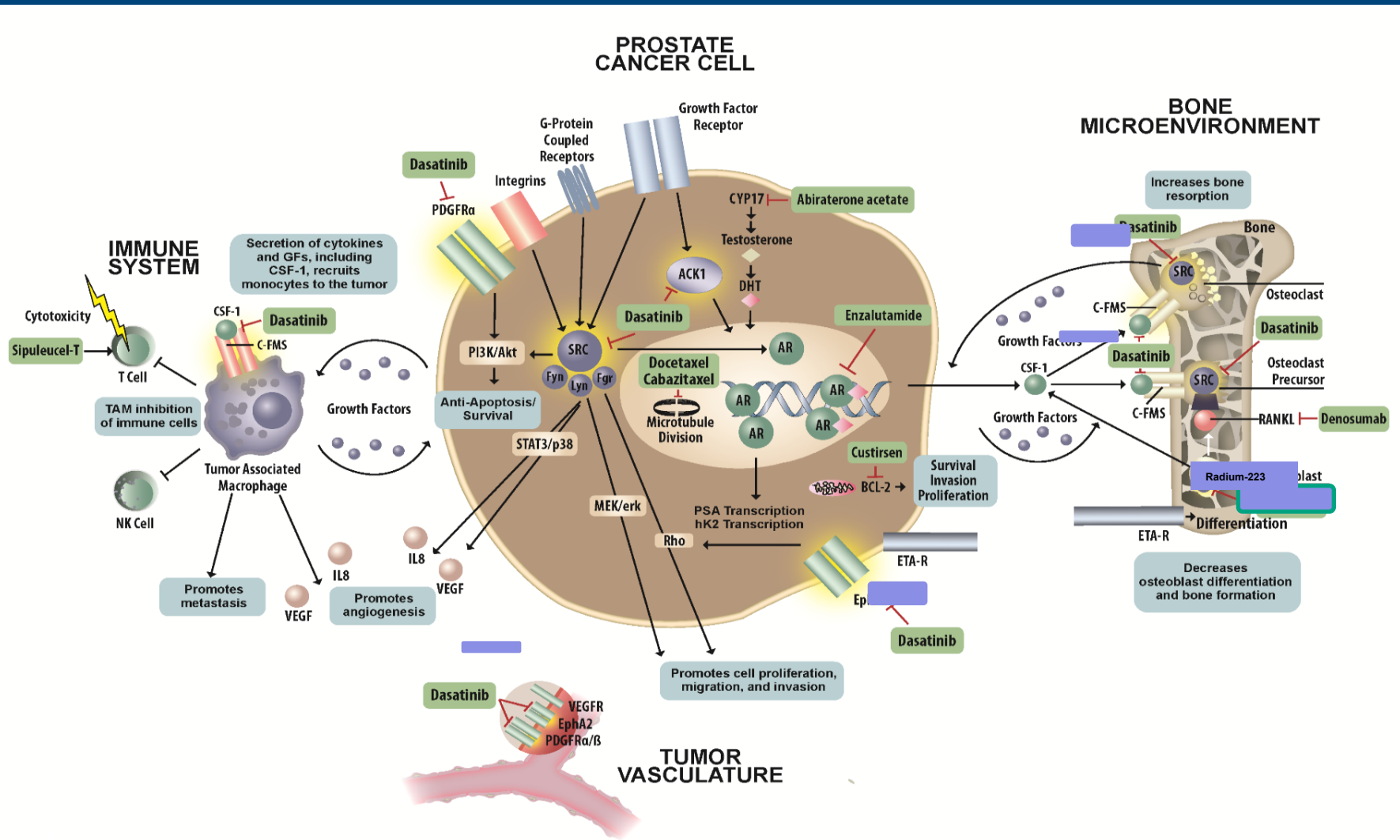
# ACIS: Chemo-Naive mCRPC Study Design




AAP, abiraterone acetate plus prednisone; BPI-SF Q3, patient reported outcome survey for pain; ECOG, Eastern Cooperative Oncology Group;
EU, European Union; GnRHa, gonadotropin releasing-hormone agonist; NA, North America; PSA90, PSA response defined as ≥90% reduction;
rPFS, time from randomization to first evidence of radiographic disease progression or death from any cause; ROW, rest of world.

clinicaltrials.gov, NCT NCT02123758.

# FUTURE
# Novel and Multi Modal Therapy



# Conclusions

- The AR continues to be a major driver in the growth and survival of prostate CA cells, even in the CRPC patient
- As urologists, we need to understand the nuances of resistance mechanisms and genomic alterations
- Despite all the recent advances, there remains multiple challenges and opportunities for researchers to better understand the disease and possible development of novel targeted agents

Thank you

rsconcepcion@me.com

- Blue Earth Imaging -> Blue Earth County MN
- Blue Tooth Technology -> ?????

- **HARALD BLUETOOTH**
  - King of Denmark (940 – 981)
  - Unified Danish tribes into a single kingdom