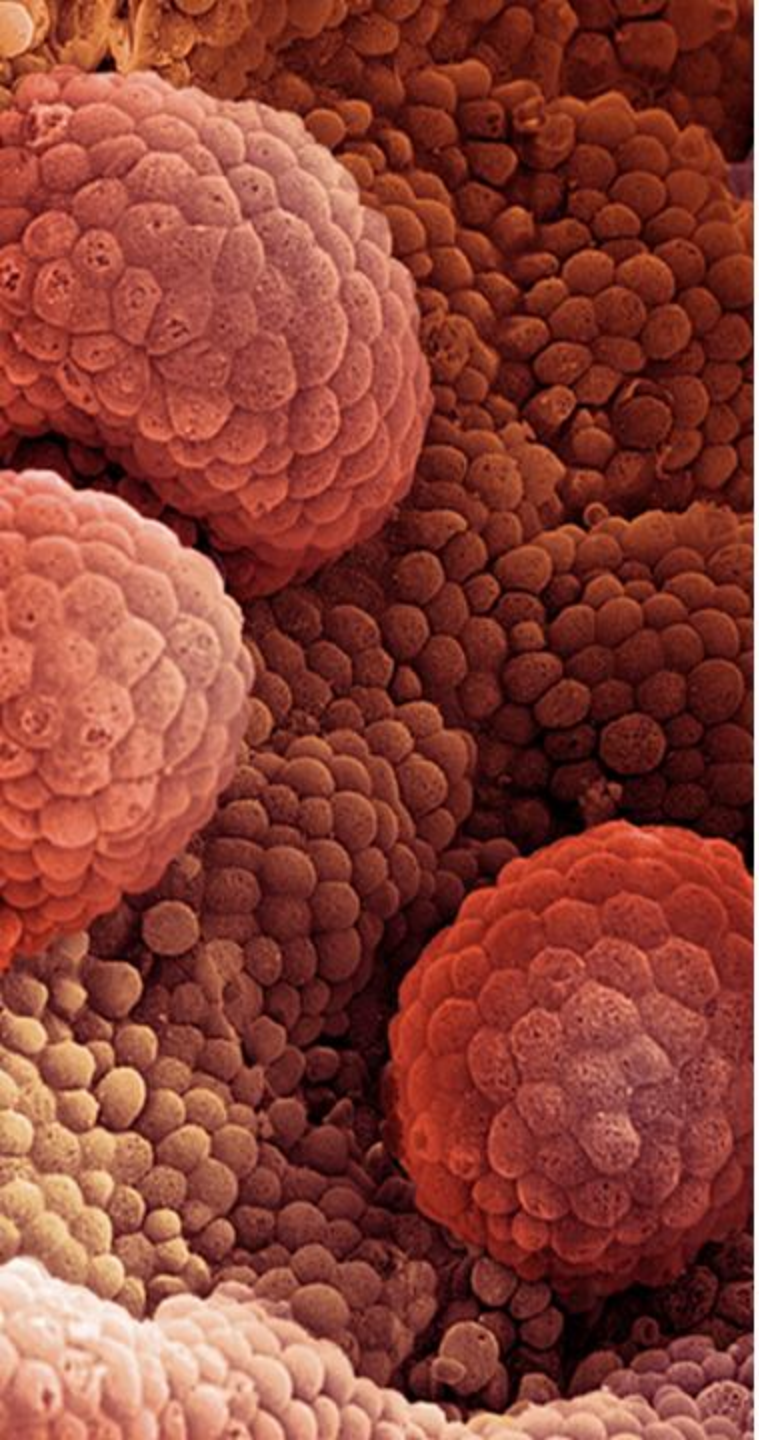


Metastatic Castration-Resistant Prostate Cancer

New Targets, New Therapeutic Approaches

Medscape EDUCATION Oncology

Faculty

Tomasz M. Beer, MD, FACP
Grover C. Bagby Endowed Chair for
Prostate Cancer Research
Deputy Director, OHSU Knight
Cancer Institute
Oregon Health & Science University
Portland, Oregon

Fred Saad, MD, FRCS
Professor and Chairman, Urology
Director, Urologic Oncology
U of M Endowed Chair, Prostate Cancer
CHUM/University of Montreal
Canada

Johann Sebastian de Bono, MB, ChB, FRCP, MSc, PhD
Professor of Experimental Cancer Medicine
Department of Medicine/ Drug Development Unit
Institute of Cancer Research
Honorary Consultant Medical Oncologist
Department of Medicine and Drug Development
Royal Marsden Hospital NHS Foundation Trust
Sutton, Surrey, United Kingdom

Chair

Christopher J. Logothetis, MD
Chairman/Professor
Department of Genitourinary
Medical Oncology
The University of Texas
MD Anderson Cancer Center
Houston, Texas

Medscape EDUCATION Oncology

Welcome and Introduction

Metastatic Castration-Resistant Prostate Cancer

New Targets,
New Therapeutic
Approaches

Purpose

The overall objective of this activity is to provide oncologists, urologists, and other healthcare professionals attending the 2012 Genitourinary Cancers Symposium with a comprehensive overview of new therapeutic approaches and the potential benefits of molecularly targeted therapies in patients with metastatic CRPC. This will allow for a more critical assessment of emerging clinical trial data and increased understanding of how molecularly targeted therapies might be effectively incorporated into future treatment paradigms to impact both survival and quality of life in men with metastatic CRPC.

Learning Objectives

Upon completion of this activity, participants will be able to:

- Recognize the benefits and limitations of current therapies for men with CRPC
- Outline the role of the Src signaling pathway in the development and progression of CRPC
- Evaluate clinical trial data on molecularly targeted agents in the management of patients with metastatic CRPC
- Describe how to target bone development and function to delay or avoid bone metastases (Src, RANKL, FGF, Met)
- Discuss challenges of integrating new therapies with distinct mechanisms of action (immunotherapy, bone targeting, chemotherapy, molecularly targeted agents) to maximize outcomes

Housekeeping Notes

The Symposium is Being Videotaped

An archive of the live event will be available to users on Medscape at a later date.

Turn Cell Phone Ringers to Silent or Off

Please set your ringers to "silent" or turn off your phone for the duration of the event. Phones that vibrate can still distract your fellow attendees.

Duration

The event is scheduled to last from 7:30 – 9:00 p.m.

Submitting Questions

At the end of the presentation the faculty will conduct a Q& A session. Audience members can submit a question through the iPad handed out as you walked in. We encourage you to submit a question at any time during the program. Due to time constraints unfortunately not all questions can be answered.

ARS iPads

At the end of the event **please return the iPad to the registration desk.** The iPads are not gifts and have a bar code to track lost units.

Polling Questions

Please take a moment to answer the following survey questions before the event begins. At the end of the program you will be prompted to answer some of the survey questions again based on what you learned from the faculty's presentations. A comparison of the results will be discussed by the panel.

Polling Question 1

- **How many new patients do you see each month diagnosed with a metastatic castration-resistant prostate cancer (mCRPC)?**

  a) 0

  b) 1–2

  c) 3–5

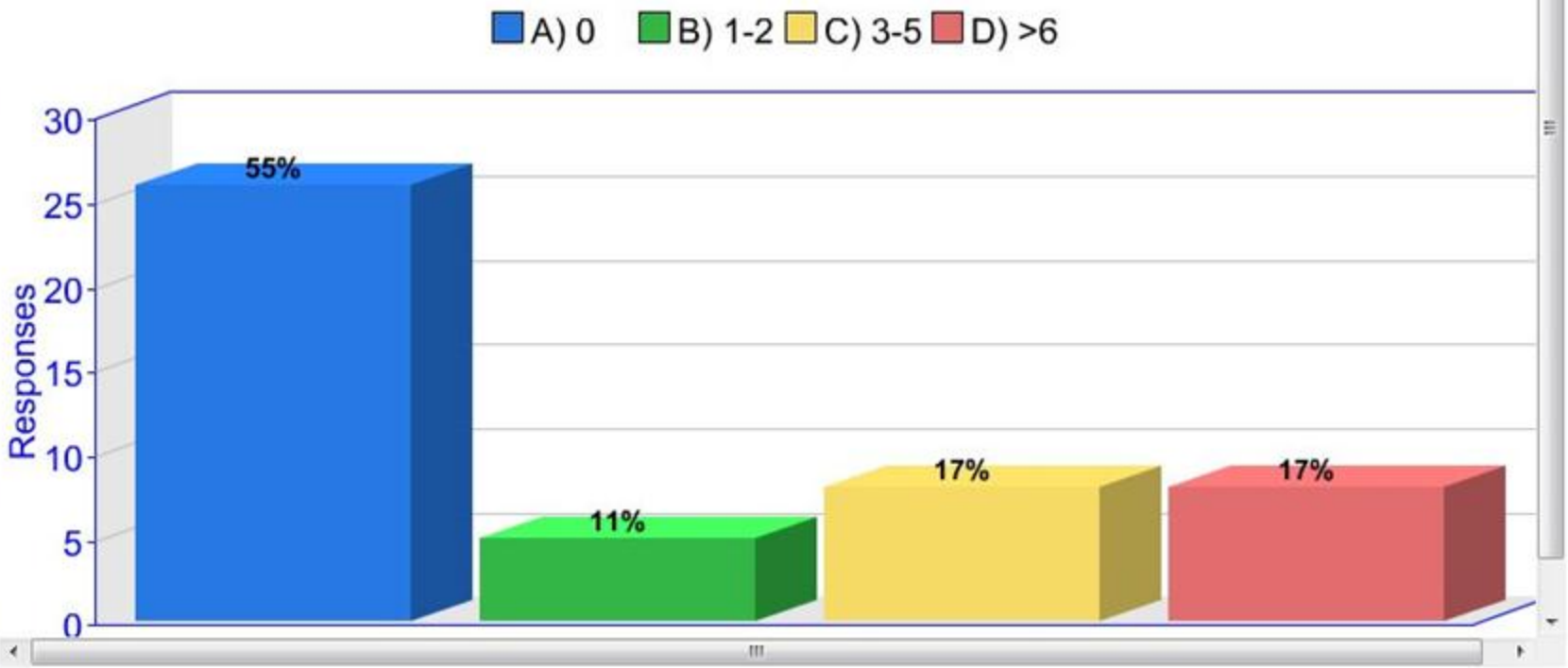
  d) > 6

Metastatic Castration-Resistant Prostate Cancer: New Targets, New Therapeutic Approaches CME

Reports

PreTest

1. How many new patients do you see each month diagnosed with a metastatic castration-resistant prostate cancer (mCRPC)?



Supported by an independent educational grant from Bristol-Myers Squibb Company

Polling Question 2

- **How confident are you that your knowledge about the management of mCRPC is up-to-date?**

  a) Not confident at all

  b) Slightly confident

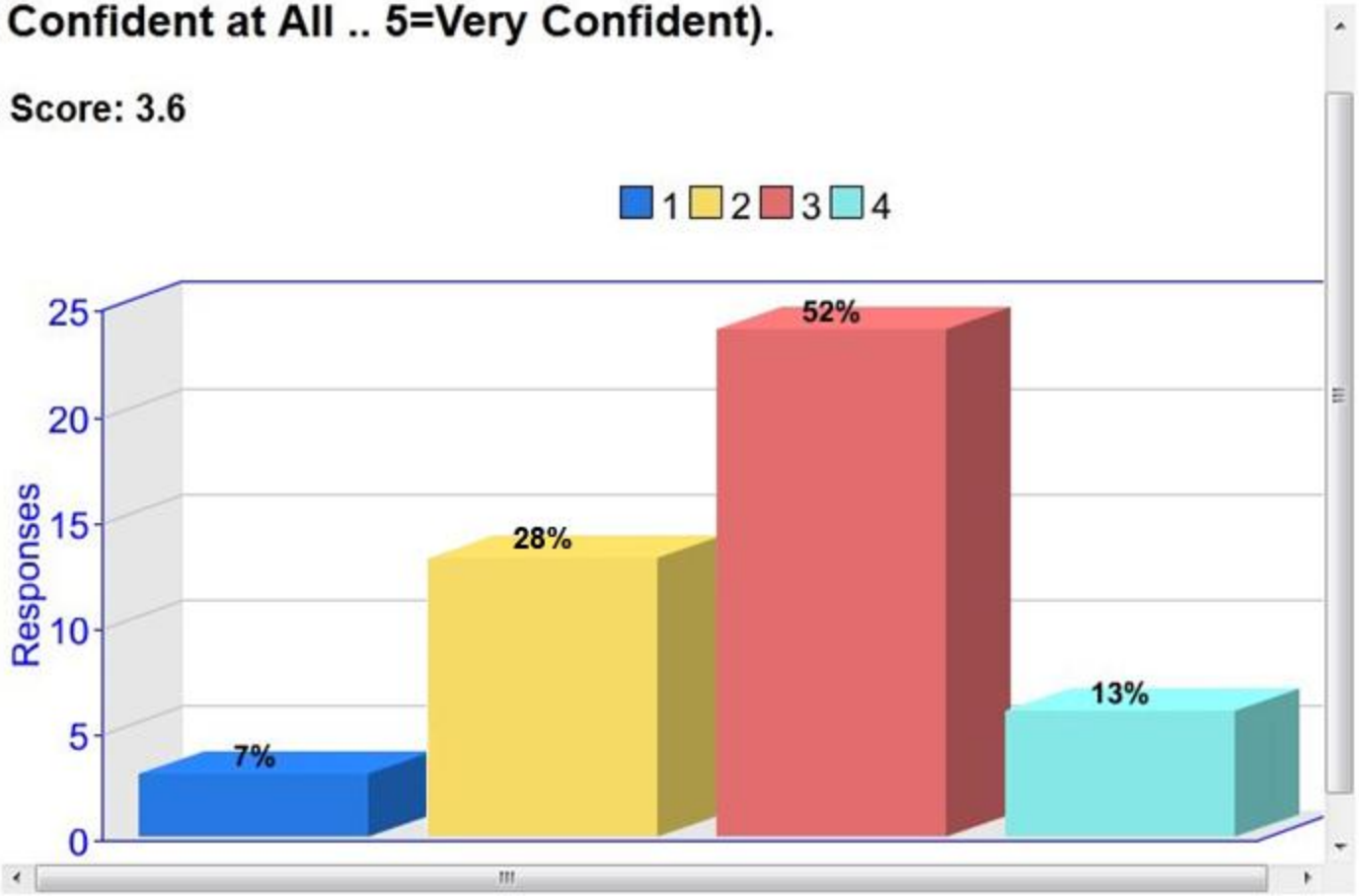
  c) Moderately confident

  d) Very confident

Metastatic Castration-Resistant Prostate Cancer: New Targets, New Therapeutic Approaches CME

2. How confident are you that your knowledge about the management of mCRPC is up-to-date?
(1=Not Confident at All .. 5=Very Confident).

Average Score: 3.6



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Polling Question 3

- **Which of the following is the most important barrier to the optimal management of mCRPC?**
  a) Current therapies incompletely suppress the androgen–AR axis
  b) Biologic heterogeneity of mCRPC and inability to tailor treatment based on individual tumor characteristics
  c) Genetic polymorphisms of proteins involved in drug metabolism and action
  d) Lack of consensus on how to sequence approved therapies in individual patients with CRPCs
  e) Not sure

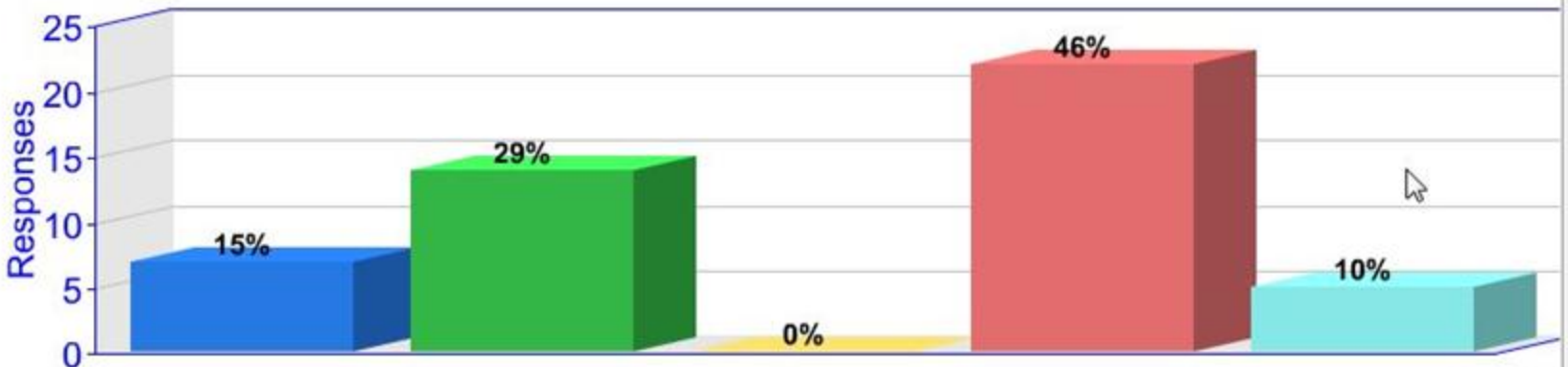
Metastatic Castration-Resistant Prostate Cancer: New Targets, New Therapeutic Approaches CME

Reports

PreTest

3. Which of the following is the most important barrier to the optimal management of mCRPC?

- A) Current therapies incompletely suppress the androgen–AR axis...
- B) Biologic heterogeneity of mCRPC and inability to tailor treatment based on ind...
- C) Genetic polymorphisms of proteins involved in drug metabolism and action...
- D) Lack of consensus on how to sequence approved therapies in individual patients...
- E) Not sure



Supported by an independent educational grant from Bristol-Myers Squibb Company

Polling Question 4

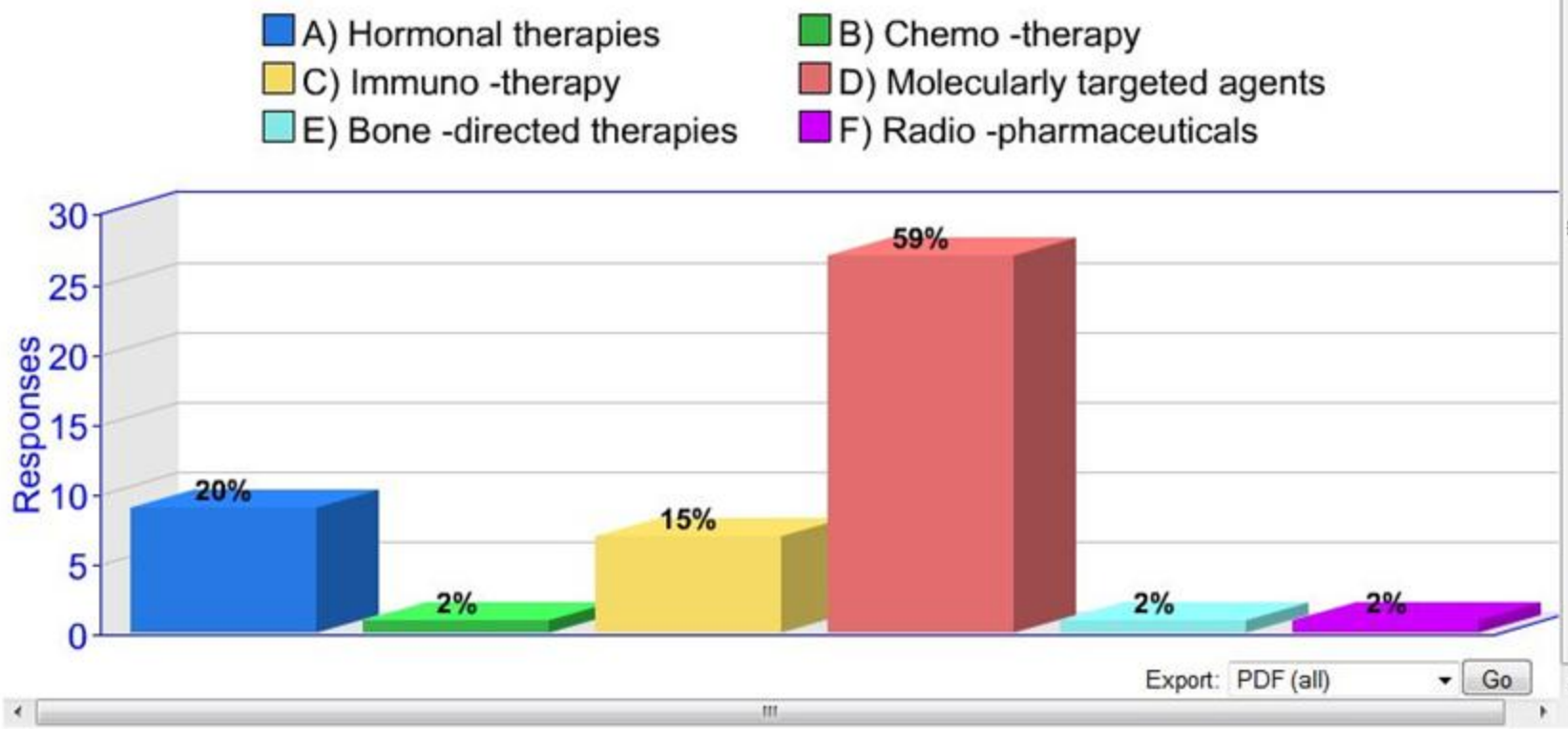
- **Which of the emerging treatment strategies holds most promise for the future management of mCRPC?**
  - a) Hormonal therapies
  - b) Chemotherapy
  - c) Immunotherapy
  - d) Molecularly targeted agents
  - e) Bone-directed therapies
  - f) Radiopharmaceuticals

Metastatic Castration-Resistant Prostate Cancer: New Targets, New Therapeutic Approaches CME

Reports

PreTest

4. Which of the emerging treatment strategies holds most promise for the future management of mCRPC?



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Polling Question 5

- **What is the role of Src/SFK signaling in CRPC?**
  a) Src/SFK signaling is associated with proliferative responses to androgens
  b) SFKs confer androgen-independence by mediating signals from various growth factors and chemokines
  c) Src/SFK signaling increases proliferation and promotes invasion and migration of prostate cancer
  d) Aberrant Src/SFK signaling leads to bone metastases
  e) All of the above

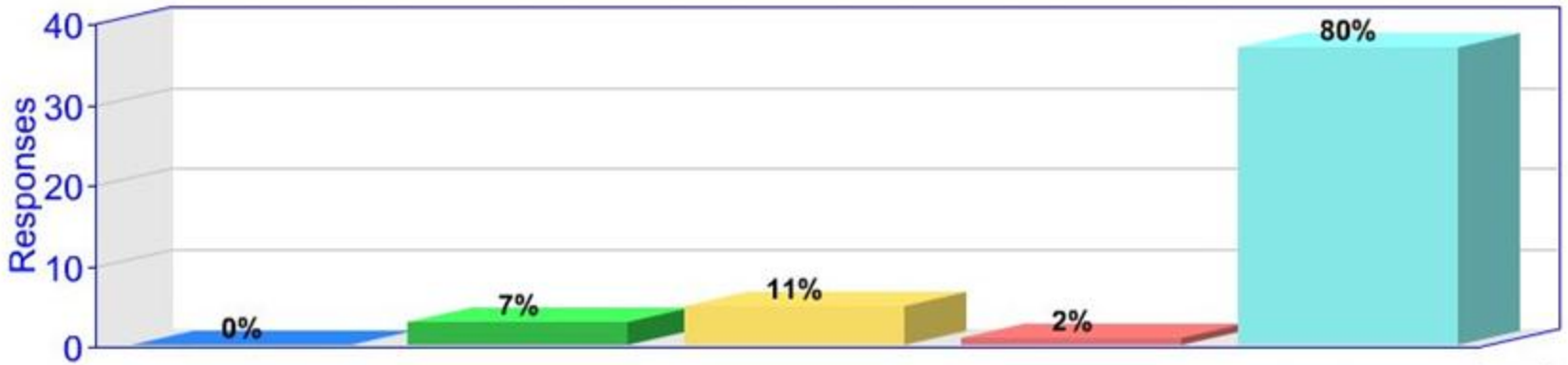
Metastatic Castration-Resistant Prostate Cancer: New Targets, New Therapeutic Approaches CME

Reports

PreTest

5. What is the role of Src/SFK signaling in CRPC?

- A) Src/SFK signaling is associated with proliferative responses to androgens...
- B) SFKs confer androgen-independence by mediating signals from various growth f...
- C) Src/SFK signaling increases proliferation and promotes invasion and migration...
- D) Aberrant Src/SFK signaling leads to bone metastases
- E) All of the above



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Polling Question 6

- **Which of the following biomarkers may lead to a more personalized approach to care that maximizes benefit and minimizes harm?**
  a) Circulating tumor cells
  b) Bone turnover biomarkers
  c) AR splice variants
  d) Androgen synthesis precursor levels
  e) c-Met/HGF activity
  f) Tubulin mutations
  g) None of the above

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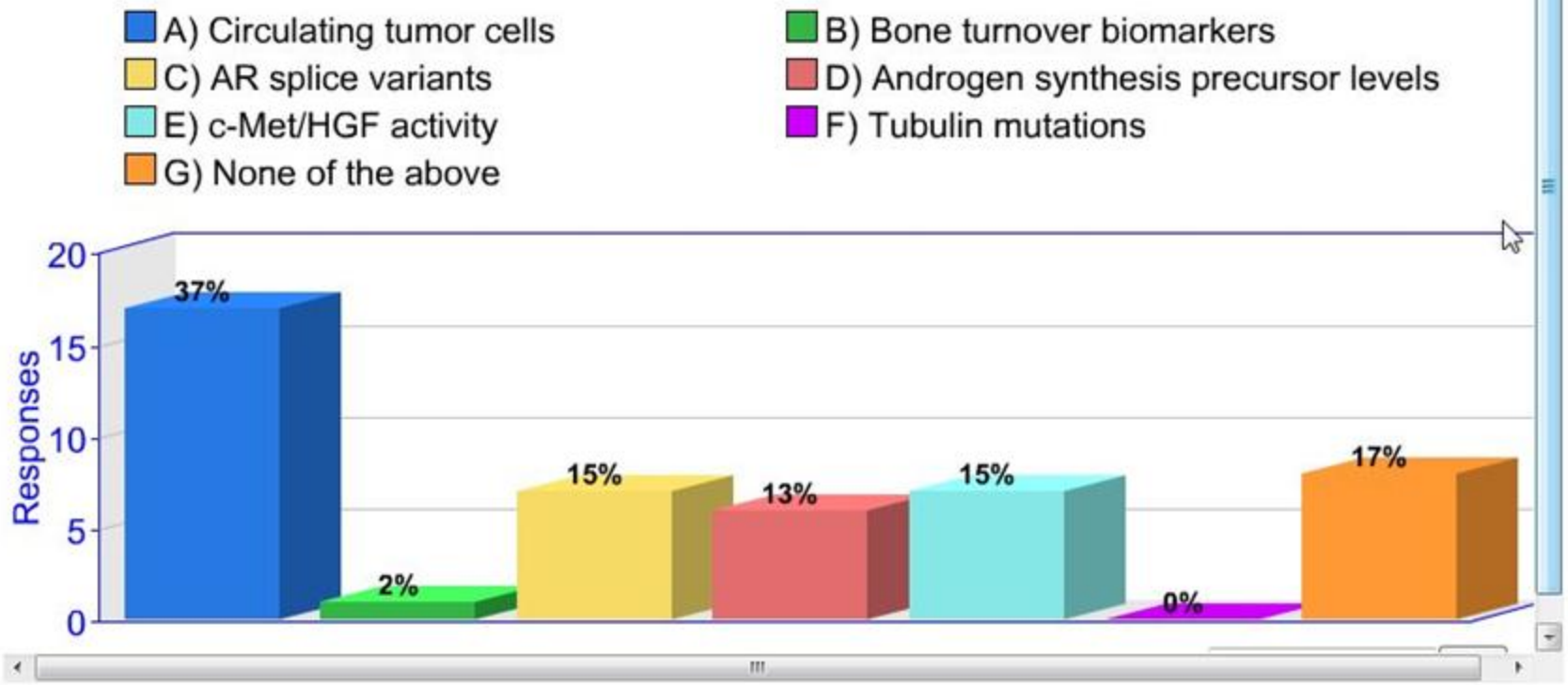
PreTest

6. Which of the following biomarkers may lead to a more personalized approach to care that maximizes benefit and minimizes harm?



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Polling Question 7

- **Abiraterone acetate inhibits which of the following enzymes?**
  a) 11β-hydroxylase
  b) 21 hydroxylase
  c) 5α-reductase
  d) 17alpha-hydroxylase
  e) C17,20-lyase
  f) 17α-hydroxylase and C17,20-lyase

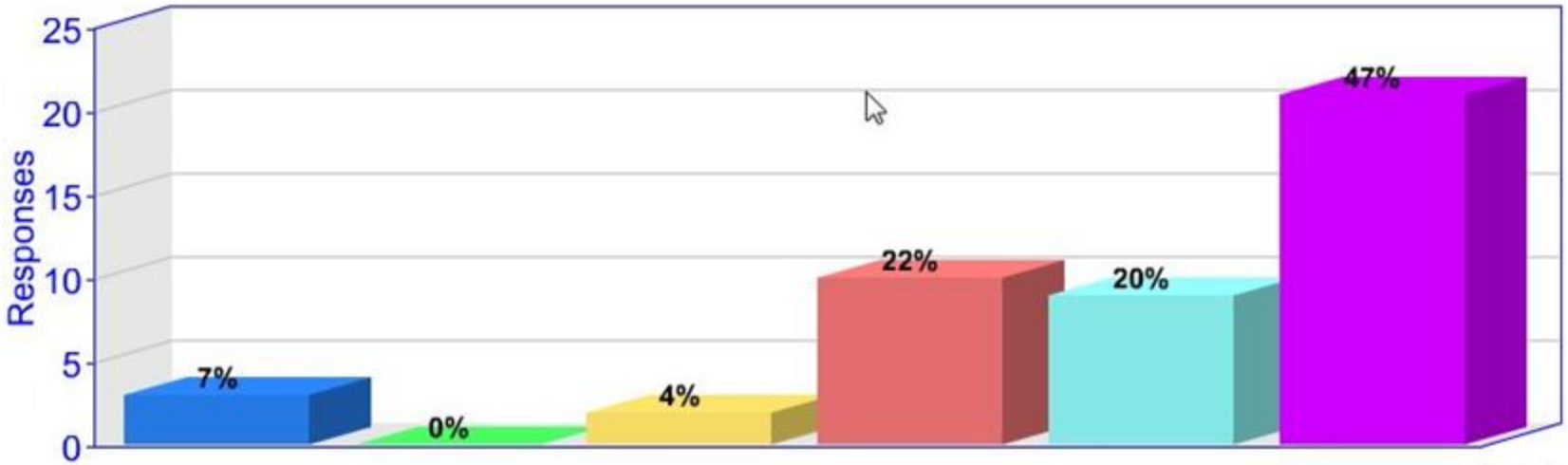
Metastatic Castration-Resistant Prostate Cancer: New Targets, New Therapeutic Approaches CME

Reports

PreTest

7. Abiraterone acetate inhibits which of the following enzymes?

A) 11β - hydroxylase
B) 21 hydroxylase
C) 5α - reductase
D) 17 alpha - hydroxylase
E) C17,20 - lyase
F) 17α - hydroxylase and C17,20-lyase



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Polling Question 8

- **Cabozatinib (XL184) is a small molecule inhibitor of:**
  a) VEGFR1
  b) VEGFR2
  c) MET
  d) VEGFR1 and MET
  e) VEGFR2 and MET

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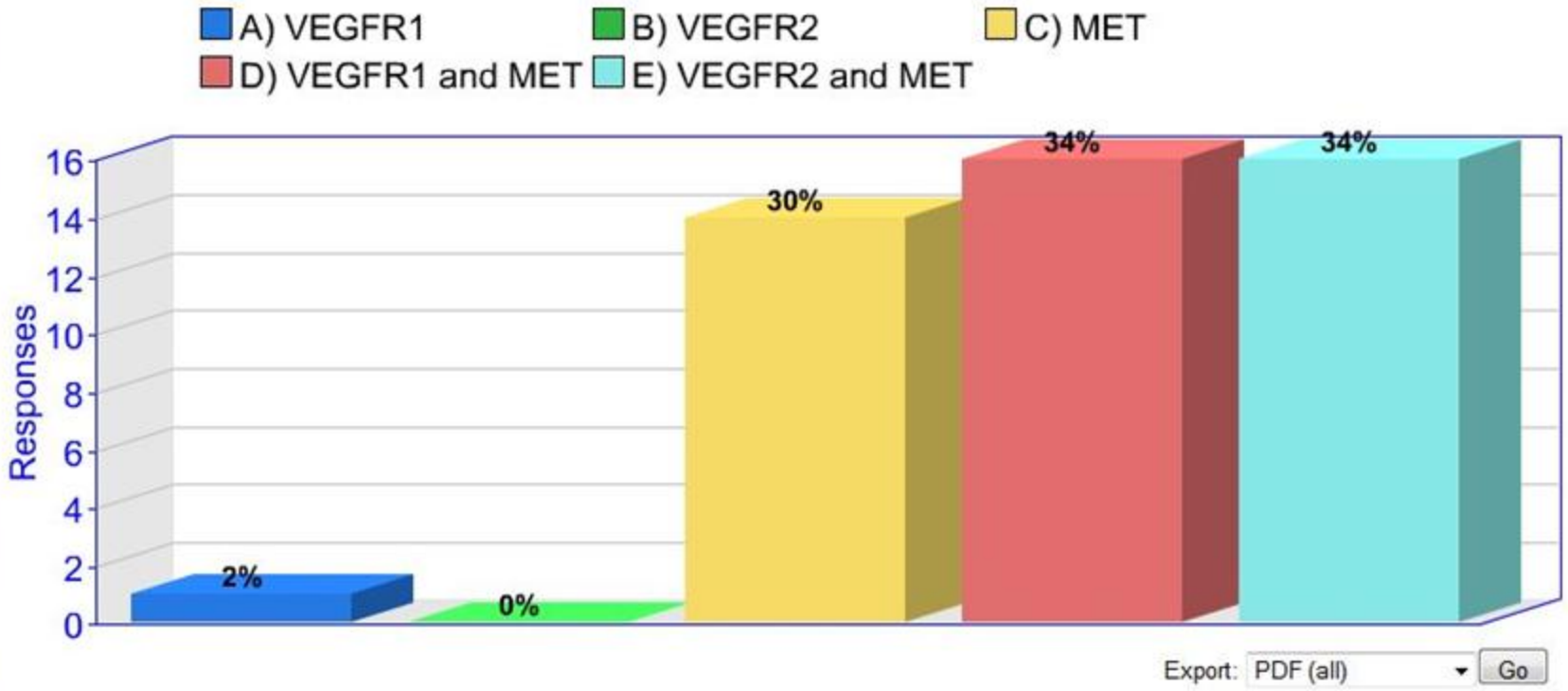
Reports

PreTest

8. Cabozatinib (XL184) is a small molecule inhibitor of:



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Polling Question 9

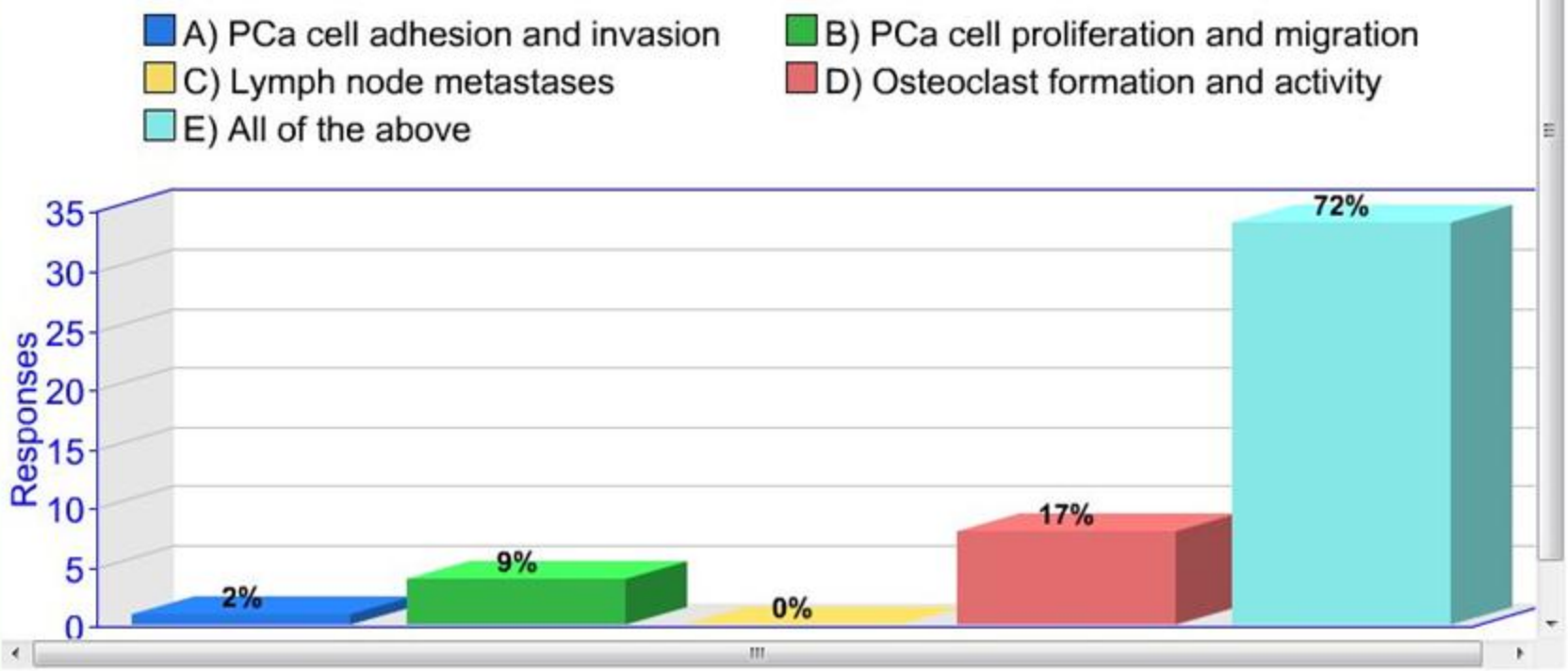
- **Dasatinib, a small molecule inhibitor of Src, Bcr-Abl, c-Kit, c-FMS, PDGFR, and EphA2 has been shown to inhibit:**
  a) PCa cell adhesion and invasion
  b) PCa cell proliferation and migration
  c) Lymph node metastases
  d) Osteoclast formation and activity
  e) All of the above

Metastatic Castration-Resistant Prostate Cancer: New Targets, New Therapeutic Approaches CME

Reports

PreTest

9. Dasatinib, a small molecule inhibitor of Src, Bcr-Abl, c-Kit, c-FMS, PDGFR, and EphA2 has been shown to inhibit:



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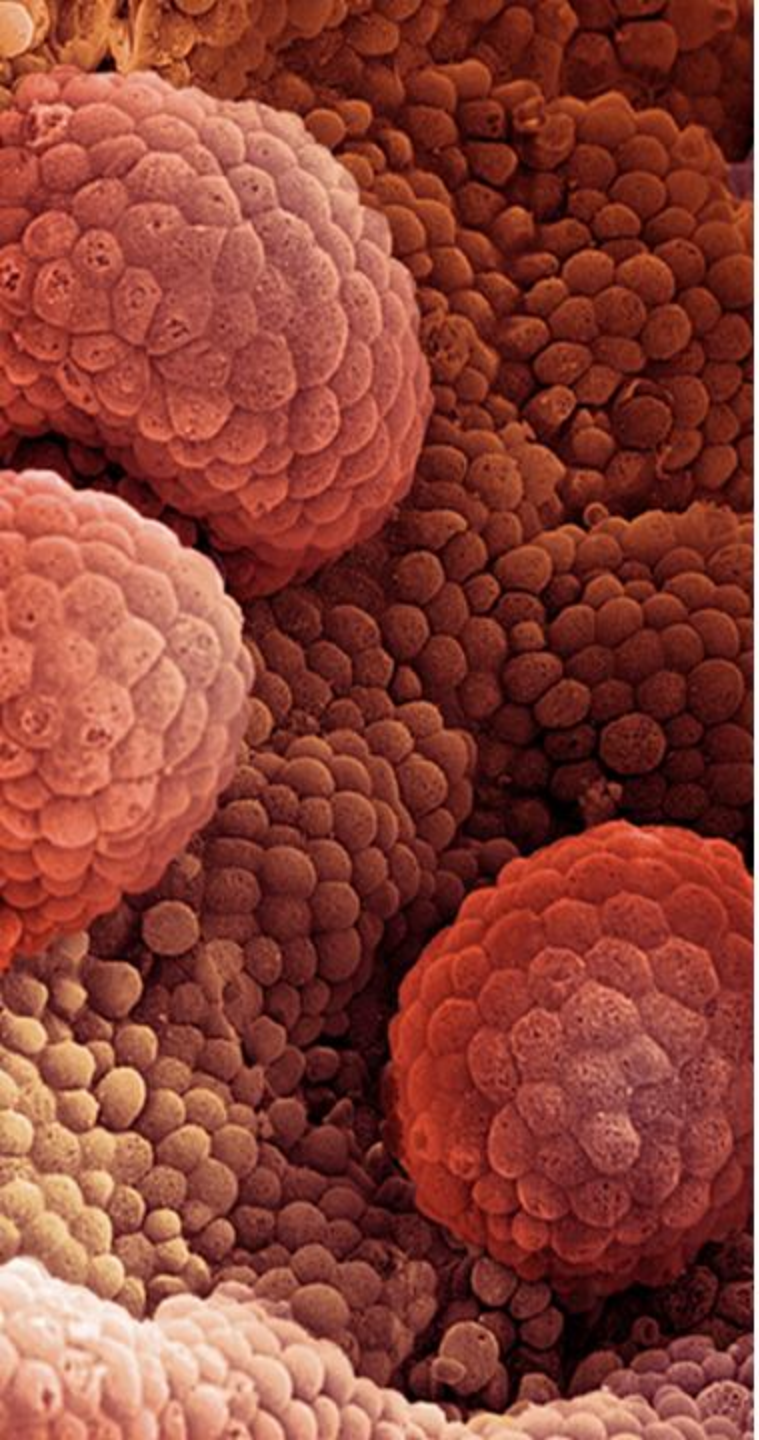


Metastatic CRPC: Biologic Framework

Christopher J. Logothetis, MD
Chairman/Professor
Department of Genitourinary Medical Oncology
The University of Texas
MD Anderson Cancer Center
Houston, Texas

Medscape Oncology
EDUCATION

Disclosure

Christopher J. Logothetis, MD

Served as an advisor or consultant for: Bristol-Myers Squibb Company; Amgen Inc.; Novartis Pharmaceuticals Corporation; Johnson & Johnson Pharmaceutical Research & Development, L.L.C.

Dr. Logothetis does intend to discuss off-label uses of drugs, mechanical devices, biologics, or diagnostics approved by the FDA for use in the United States.

Dr. Logothetis does intend to discuss investigational drugs, mechanical devices, biologics, or diagnostics not approved by the FDA for use in the United States.

Assumption

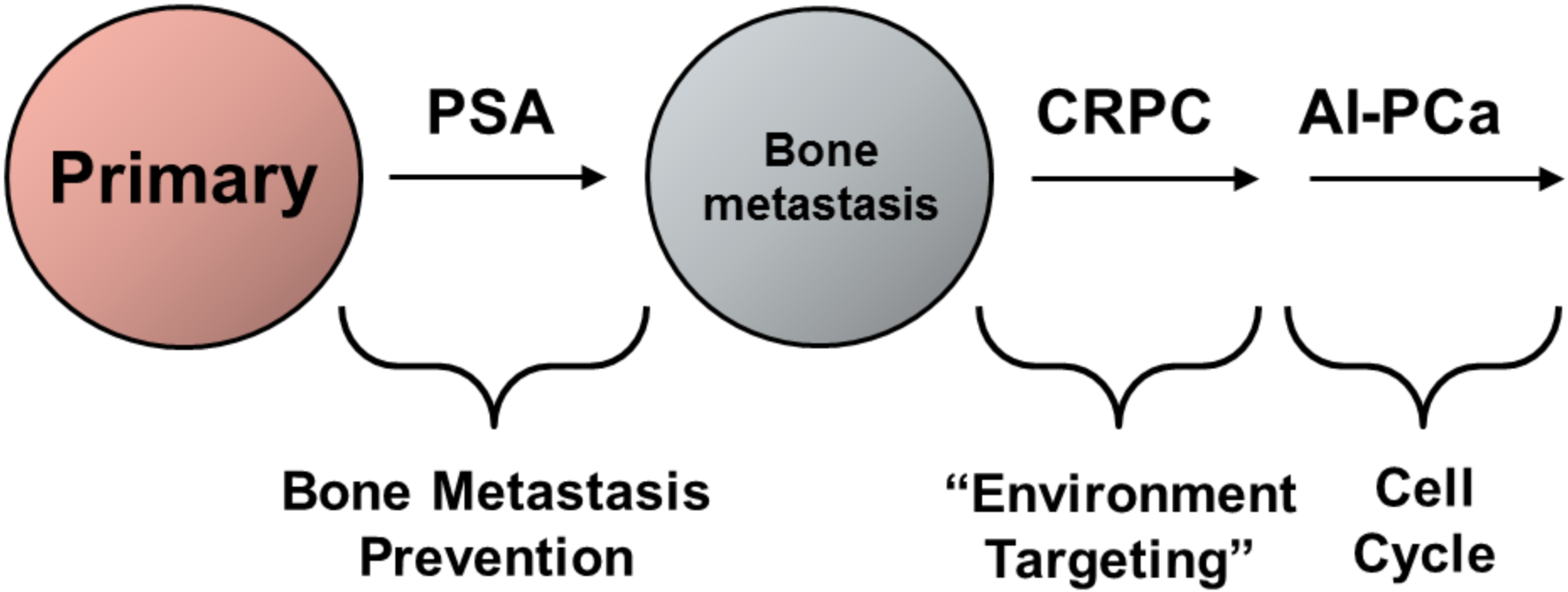
Optimum integration of therapies will further improve the survival of patients with prostate cancer.

Assumption

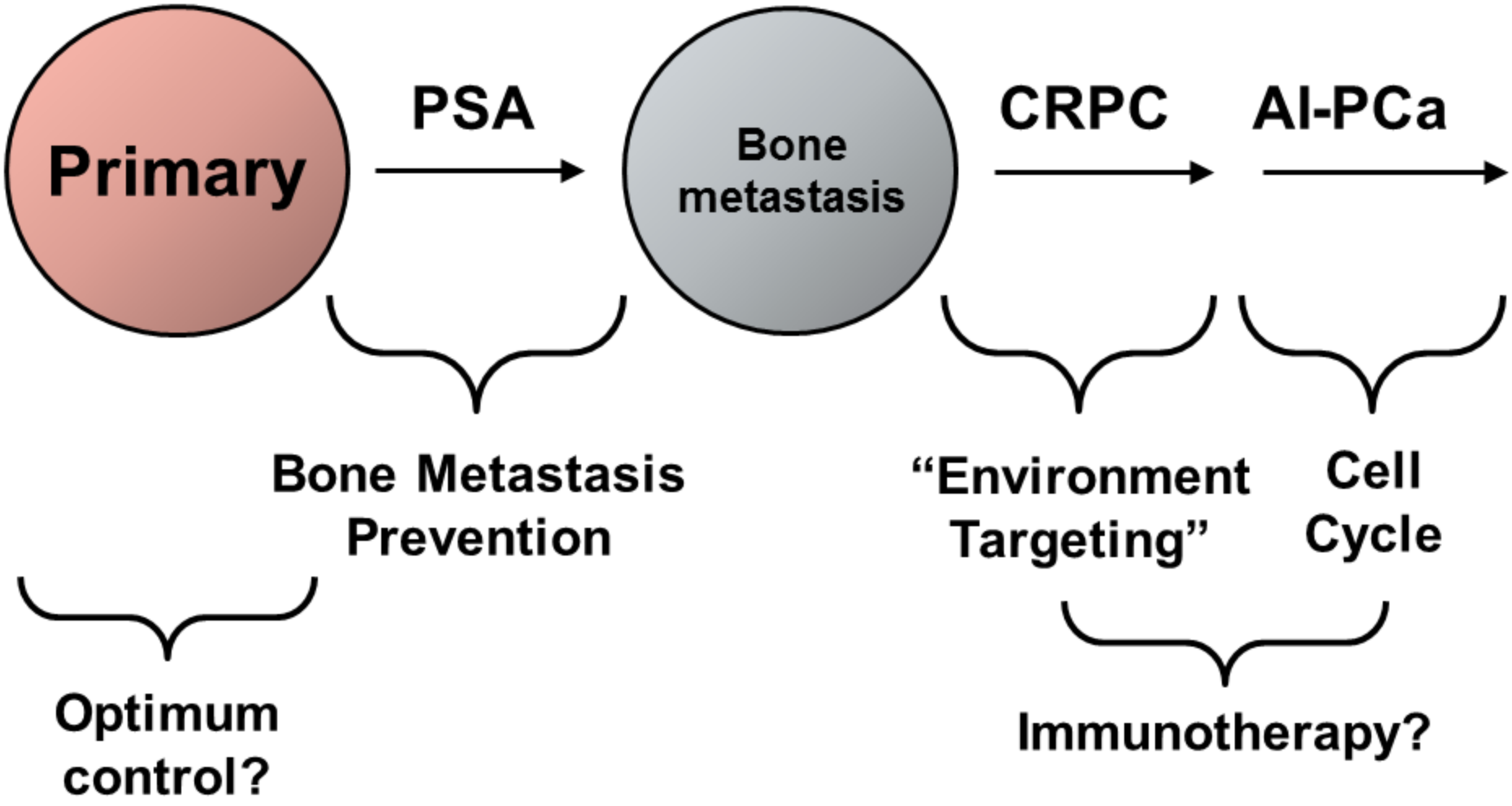
Optimum integration of therapies will further improve the survival of patients with prostate cancer.

An effective therapy strategy will need to be marker driven and founded on biology.

Milestone of PCa Progression

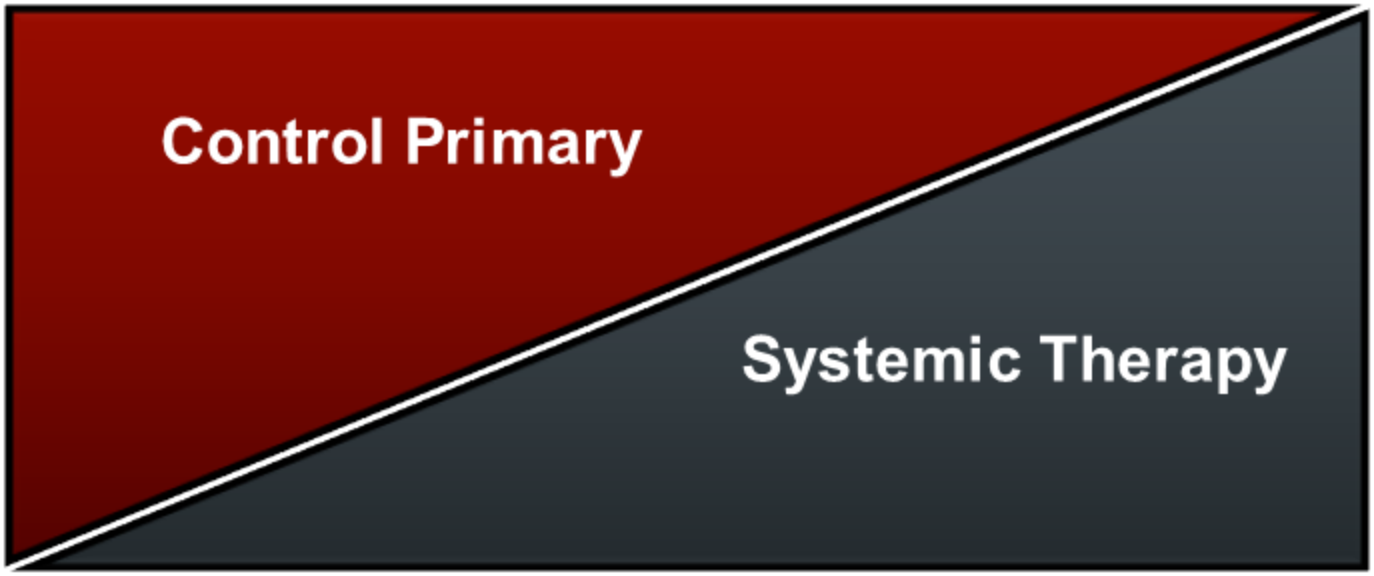


Milestone of PCa Progression



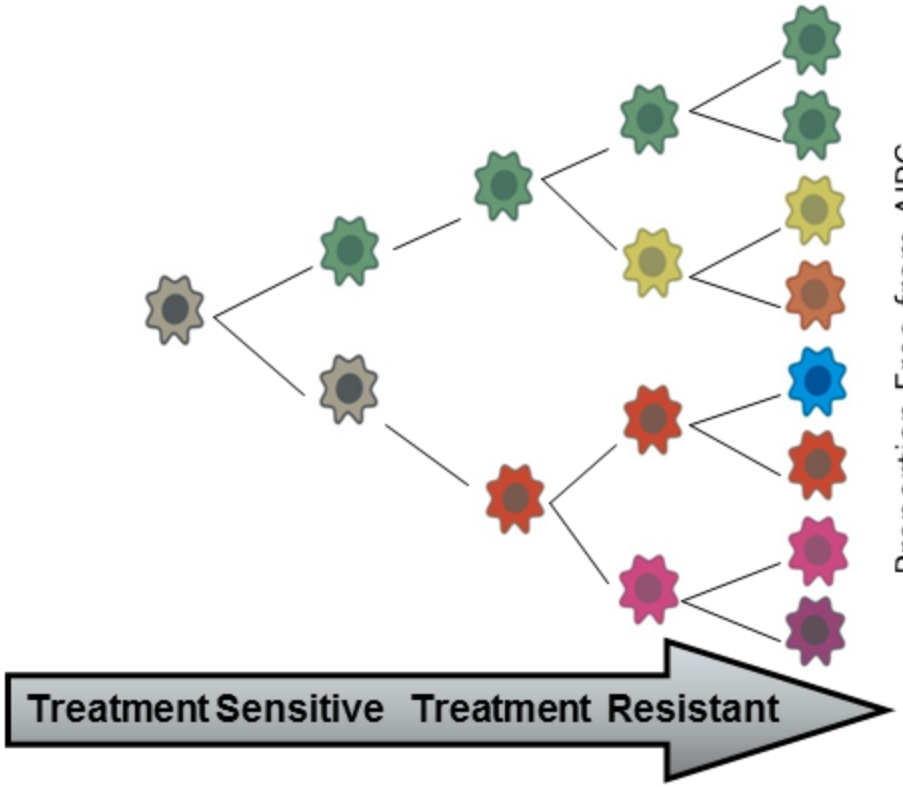
Solid Tumor Therapy Paradigm

Optimize therapy in advanced setting and apply early: paradigm assumes that biology of advanced cancer is similar to that in early cancers.

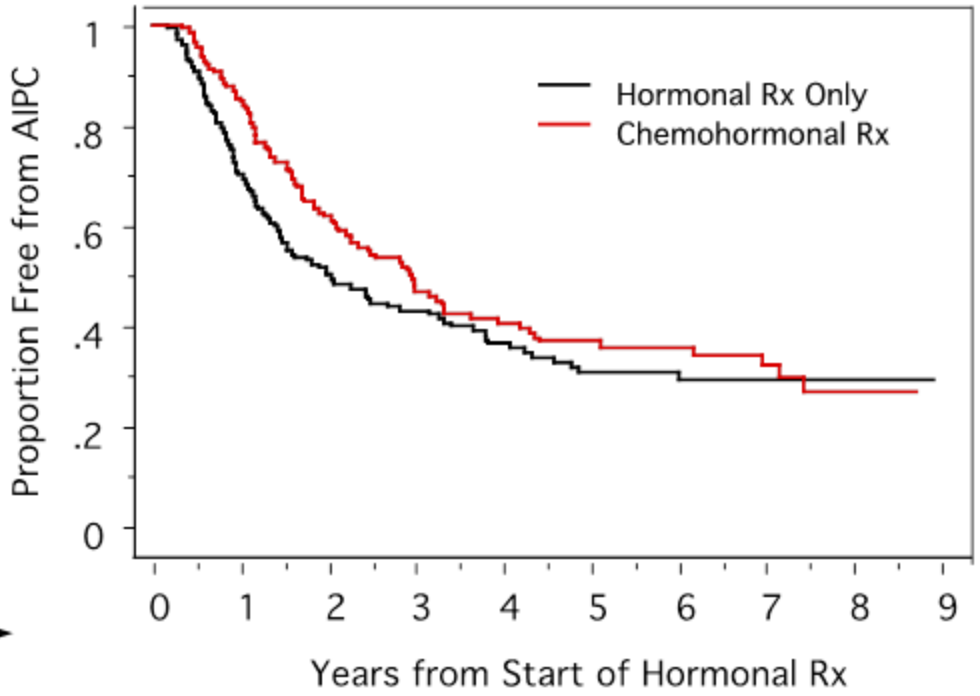


Timing of Chemotherapy

Accepted Model of Cancer Progression

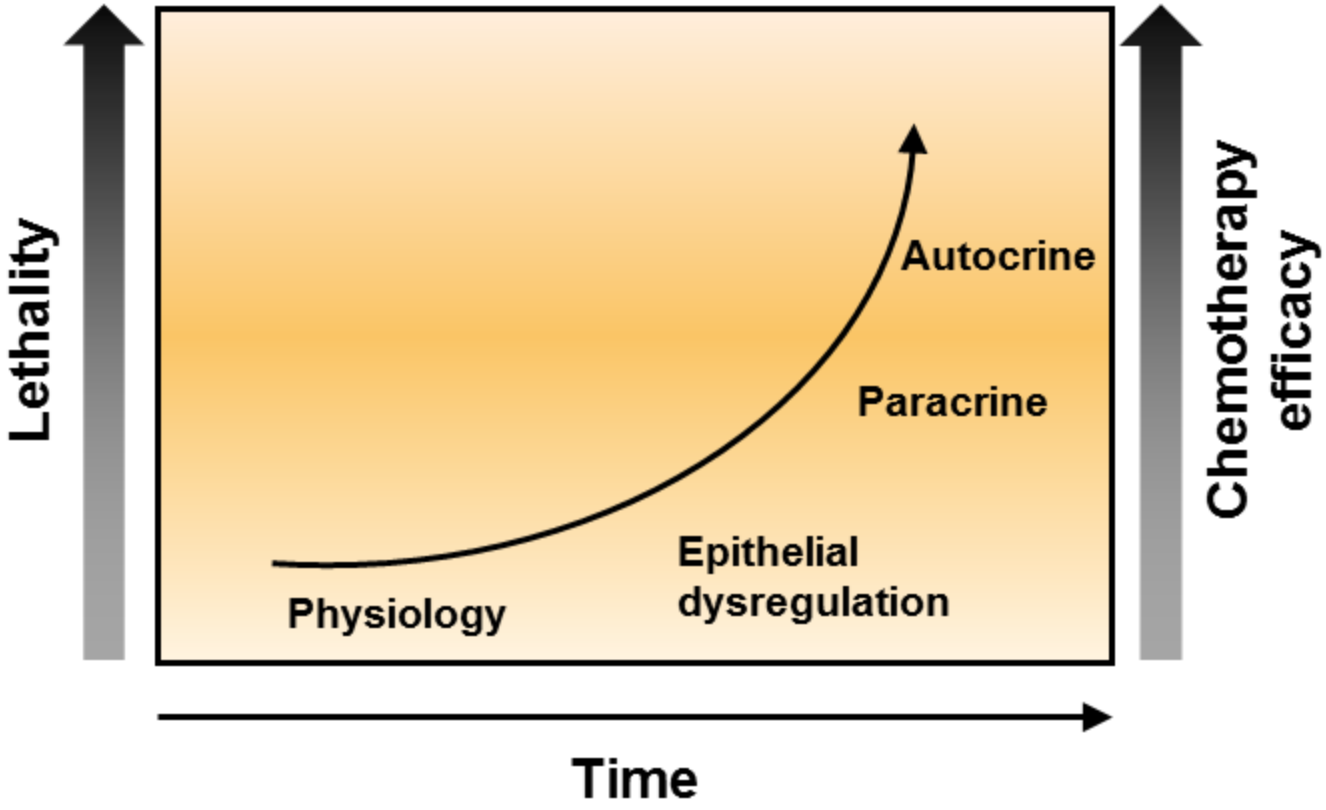


Earlier Chemotherapy Does Not Prolong Survival



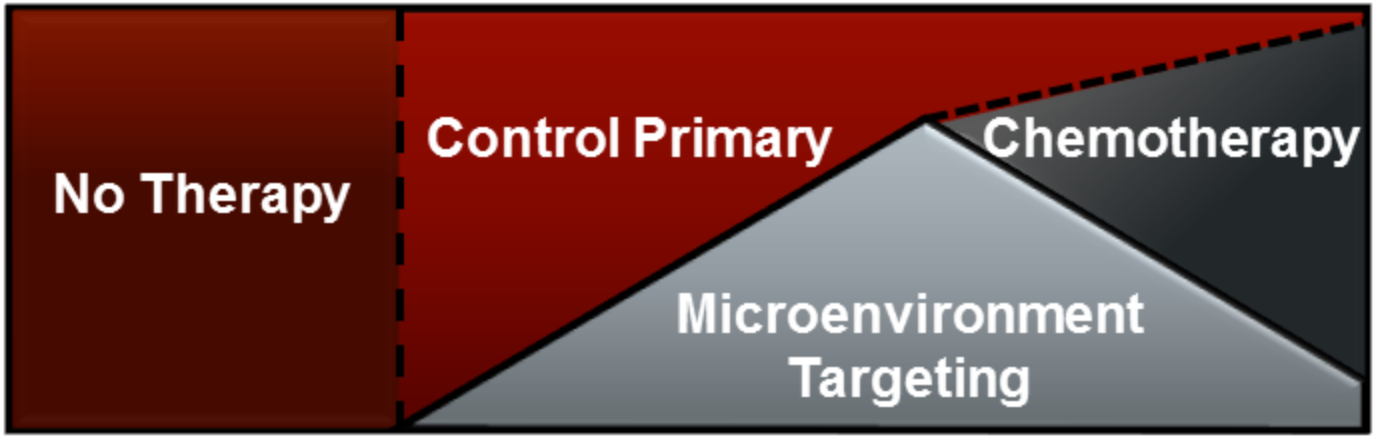
Millikan RE. *J Clin Oncol*. 2008;26:5936-5942.

Proposed Progression Model



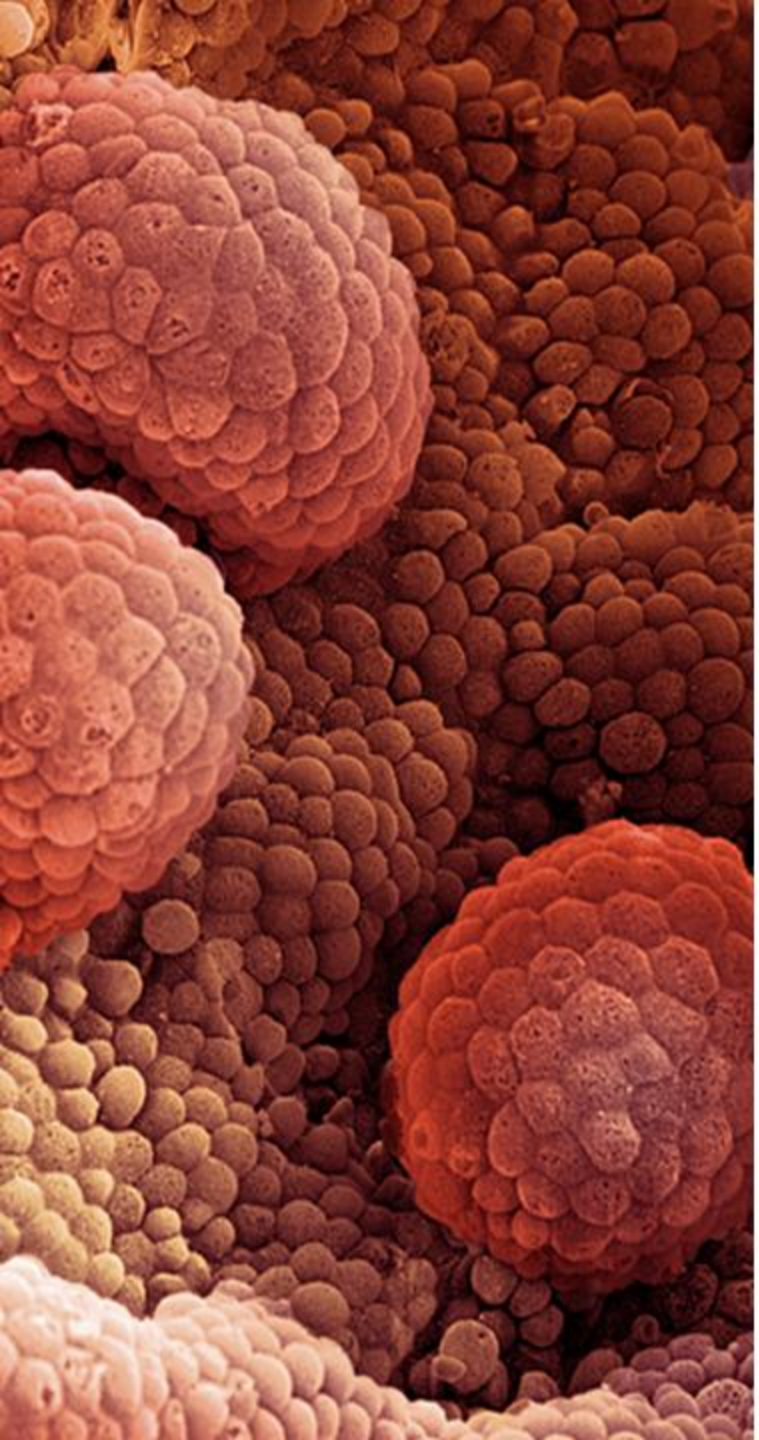
Efstathiou E, Logothetis CJ. *Clin Cancer Res*. 2010;16:1100-1107.

Paradigm Reconsidered



Milestones of PCa Progression

- Current Therapy, Integration of New Therapeutic Approaches (T. Beer)
- Inhibition of Altered AR Signaling (J. De Bono)
- Tumor Microenvironment & Src Family Kinases (F. Saad)
- Toward a Marker-Driven Treatment Strategy for CRPC (C. Logothetis)



Current Treatment Paradigm for CRPC: Integration of New Therapeutic Approaches

Tomasz M. Beer, MD, FACP
Grover C. Bagby Endowed Chair for
Prostate Cancer Research
Deputy Director, OHSU Knight Cancer Institute
Oregon Health & Science University
Portland, Oregon

Medscape Oncology
EDUCATION

Disclosure

Tomasz M. Beer, MD, FACP

Served as an advisor or consultant for: Centocor, Inc.; Ortho Biotech Products, L.P.; Dendreon Corp.; GTx, Inc.

Received grants for clinical research from: Bristol-Myers Squibb Company; Cell Therapeutics, Inc.; Cougar Biotechnology, Inc.; Dendreon Corp.; ImClone Systems Incorporated; Medivation, Inc.; Novartis Pharmaceuticals Corporation; OncoGenex Pharmaceuticals Inc.

Provided expert testimony for: Novartis Pharmaceuticals Corporation.

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CRPC
Targets and Therapy

- Molecular basis for targeting AR
- Current and emerging hormonal strategies
- Chemotherapy
- Immunologic therapy
- Targeted therapy
- Bone-directed therapy
- The evolving tool box

Targeting AR

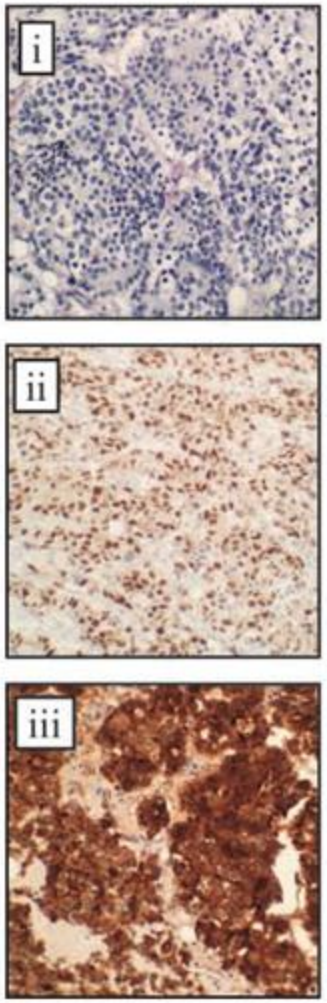
Molecular Basis

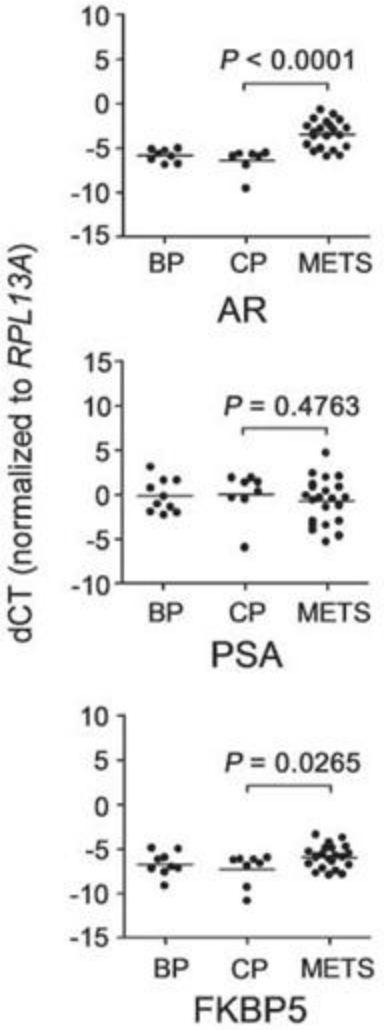
CRPC

Underlying Mechanism

Metastatic lymph node from a hormone-refractory patient

- ☑ AR expressed
- ☑ Prostate-specific antigen (PSA) expressed
- ☑ Androgen-responsive genes expressed





Montgomery RB, et al. *Cancer Res*. 2008;68:4447-4454.

Hormonal Therapy

Abiraterone and MDV3100

Standard 2nd-line Hormonal Therapy

Modest Response Rates

Androgen receptor antagonists

- Bicalutamide, flutamide, nilutamide

Androgen synthesis inhibitors

- Ketoconazole

Estrogens

- Diethylstilbestrol
- Conjugated estrogens
- Transdermal estradiol

Impact on Survival Unknown

Improving Hormonal Therapy
2 *Main Strategies*

Better suppression of testosterone (and related hormone) production

- Abiraterone, TAK-700

Better blockade of the androgen receptor

- MDV3100, ARN-509

Abiraterone
Current Status

- Survival improved in patients with metastatic prostate cancer resistant to both hormonal therapy and chemotherapy
  - Approved for use
- Phase 3 trial in patients with chemotherapy-naive metastatic CRPC accrues
  - Awaiting results

MDV3100
Current Status

Phase 3 trial in patients with metastatic prostate cancer resistant to both hormonal therapy and chemotherapy completed accrual

- Initial results announced November 2011
  - Median survival 18.4 vs 13.6 months
  - HR 0.63

Phase 3 trial in patients with metastatic CRPC accruing

Agents Targeting AR Signaling
Future Directions

Clinical questions
- Sequencing of therapy
- Combinations
- Place of the therapy in the continuum of care
  - Post-chemo, chemo-naive, first sign of castration resistance, front-line hormonal therapy?

Mechanistic questions
- Molecular consequence of treatment
  - Good and bad
- Molecular phenotype of response and resistance
- Opportunities for rational agent selection and co-targeting, including individualized care

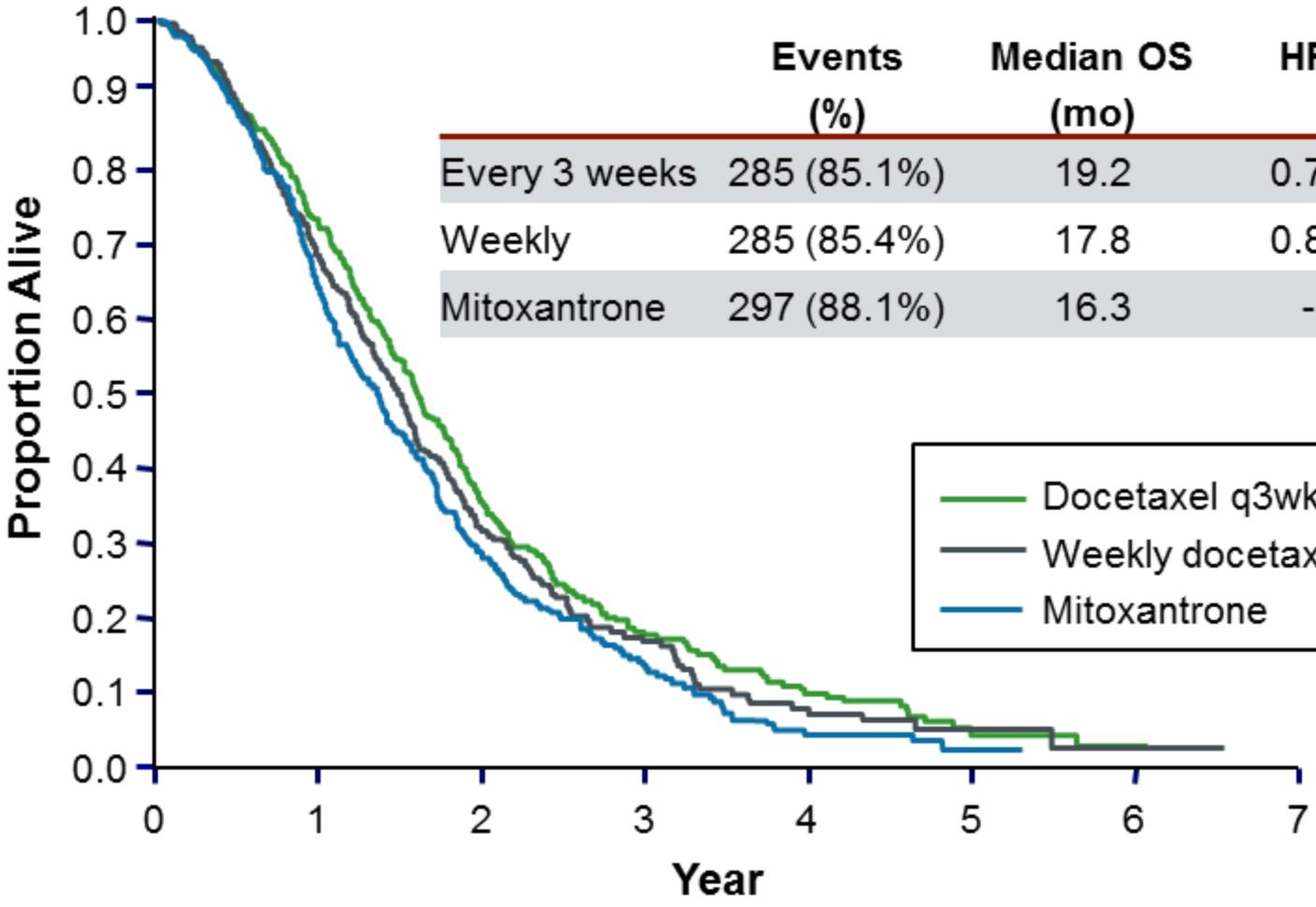
Linking knowledge of mechanism with clinical strategy

Chemotherapy

Docetaxel and Cabazitaxel

TAX 327 Study

Long-Term Overall Survival



	Events (%)	Median OS (mo)	HR	*P*
Every 3 weeks	285 (85.1%)	19.2	0.79	.004
Weekly	285 (85.4%)	17.8	0.87	.09
Mitoxantrone	297 (88.1%)	16.3	-	-

Berthold DR, et al. *J Clin Oncol*. 2008;26:242-245.

TROPIC

Phase 3 Registration Study

146 sites, 26 countries

Patients with metastatic CRPC that progressed during and after treatment with a docetaxel-based regimen
(N=755)

Stratification factors

ECOG PS (0, 1 vs 2); measurable vs nonmeasurable disease

Cabazitaxel 25 mg/m² q3wk + prednisone* for 10 cycles
(n=378)

Mitoxantrone 12 mg/m² q3wk + prednisone* for 10 cycles
(n=377)

Primary endpoint: OS

Secondary endpoints: PFS, response rate, and safety

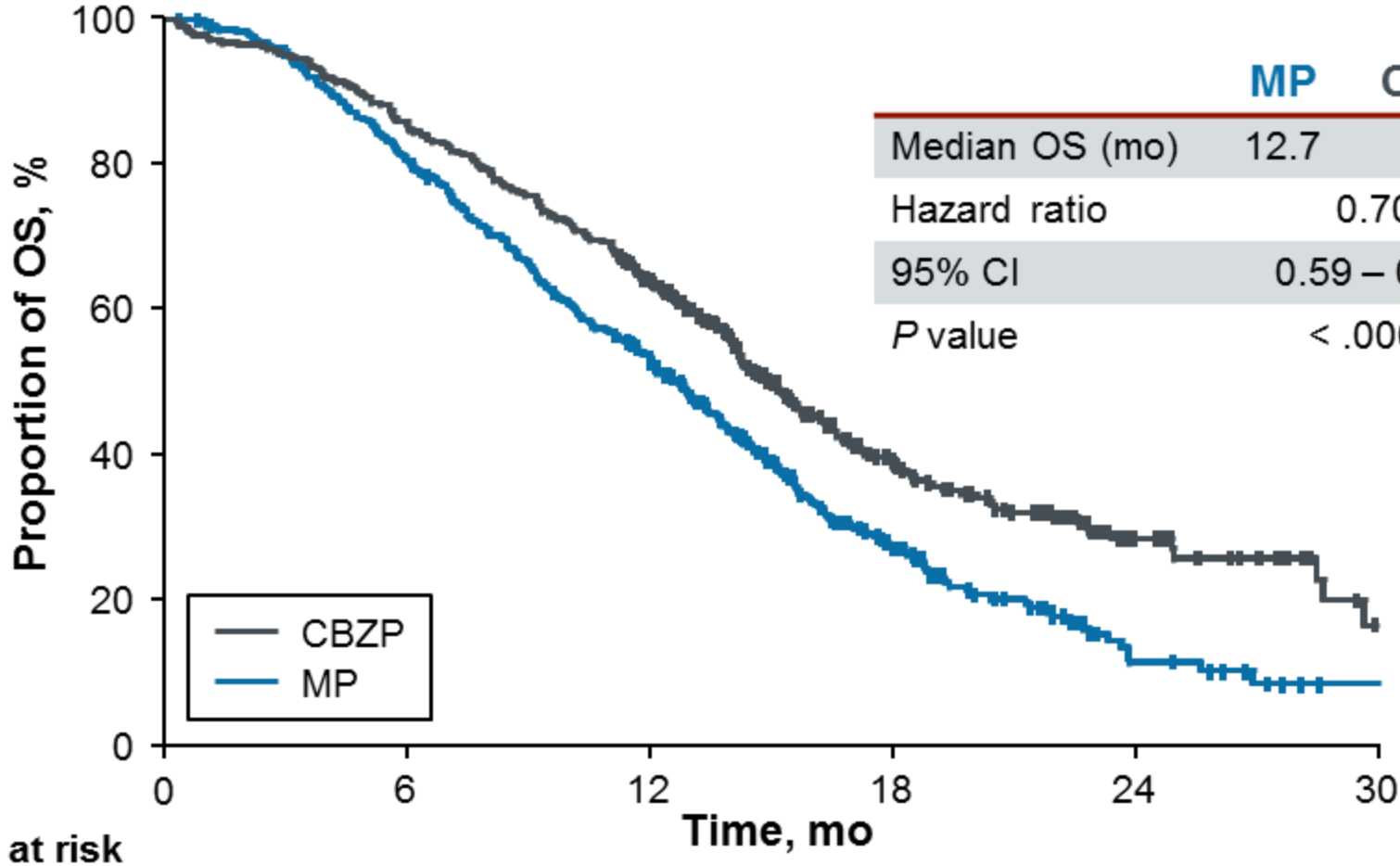
Inclusion: Patients with measurable disease must have had progression by RECIST; otherwise, must have had new lesions or PSA progression

*Oral prednisone/prednisolone: 10 mg daily

de Bono JS, et al. *Lancet*. 2010;376:1147-1154.

Primary Endpoint

Overall Survival (ITT Analysis)



	MP	CBZP
Median OS (mo)	12.7	15.1
Hazard ratio	0.70	
95% CI	0.59 – 0.83	
P value	< .0001	

Number at risk

MP	377	300	188	67	11	1
CBZP	378	321	231	90	28	4

de Bono JS, et al. *Lancet*. 2010;376:1147-1154.

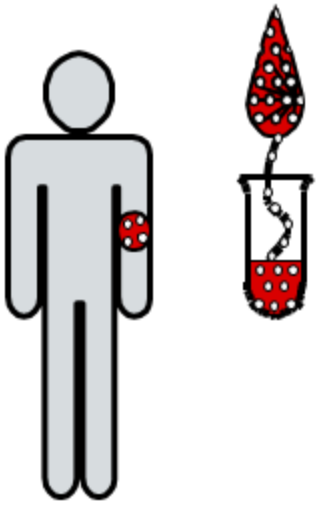
Immunotherapy

Sipuleucel-T and Ipilimumab

Sipuleucel-T

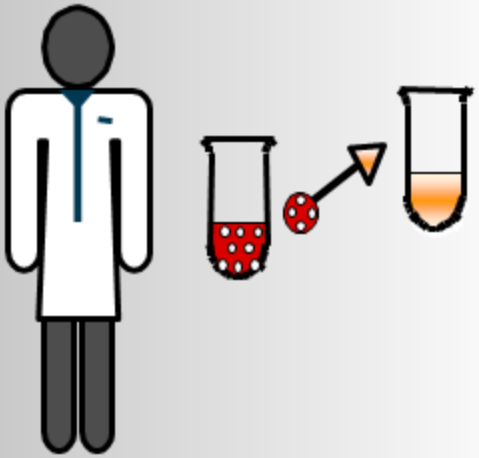
Patient-Specific Therapy

Day 1
Leukapheresis



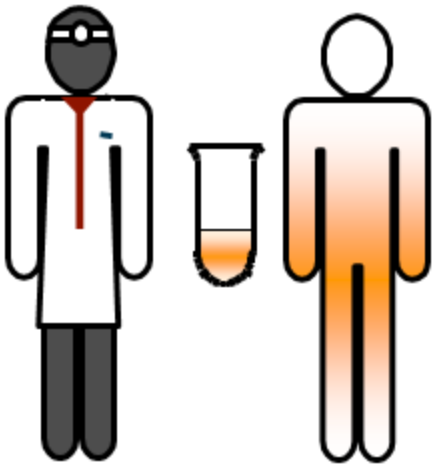
Apheresis Center

Day 2-3
Sipuleucel-T is manufactured



Central Processing

Day 3-4
Patient is infused

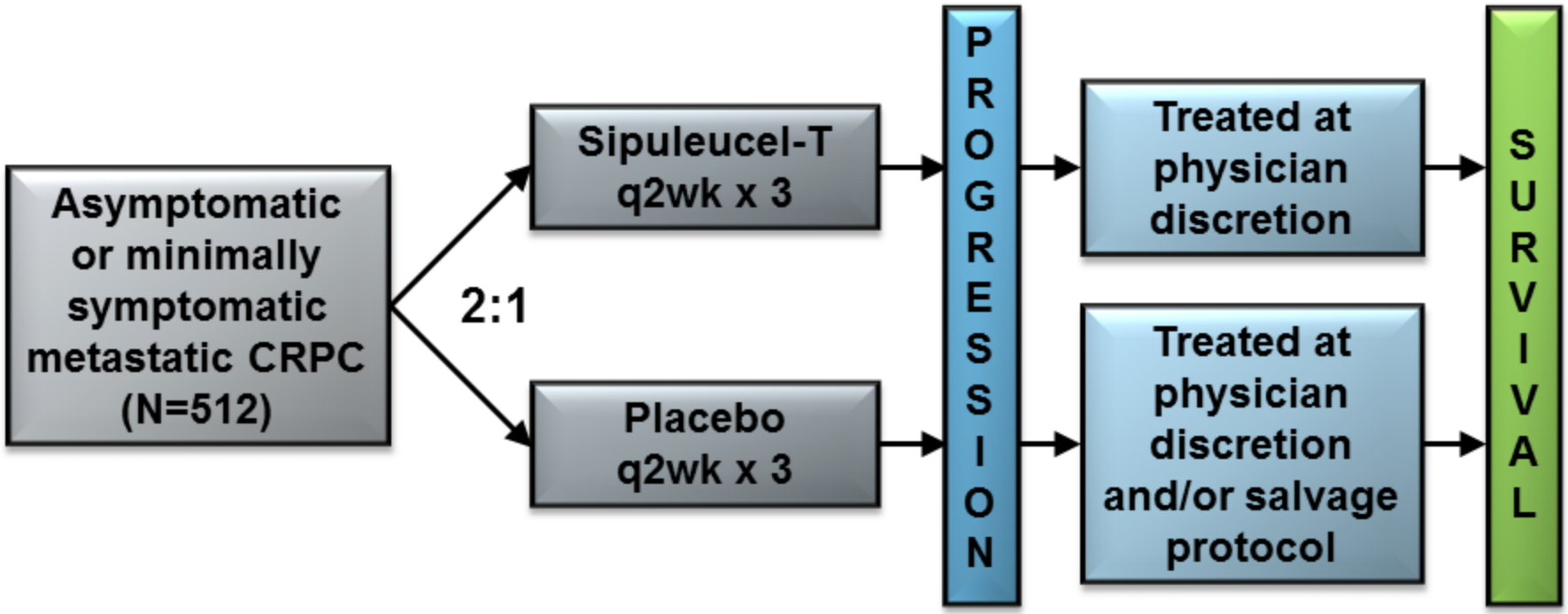


Physician's Office

Complete Course of Therapy:
Weeks 0, 2, 4

IMPACT

Randomized Phase 3 Trial



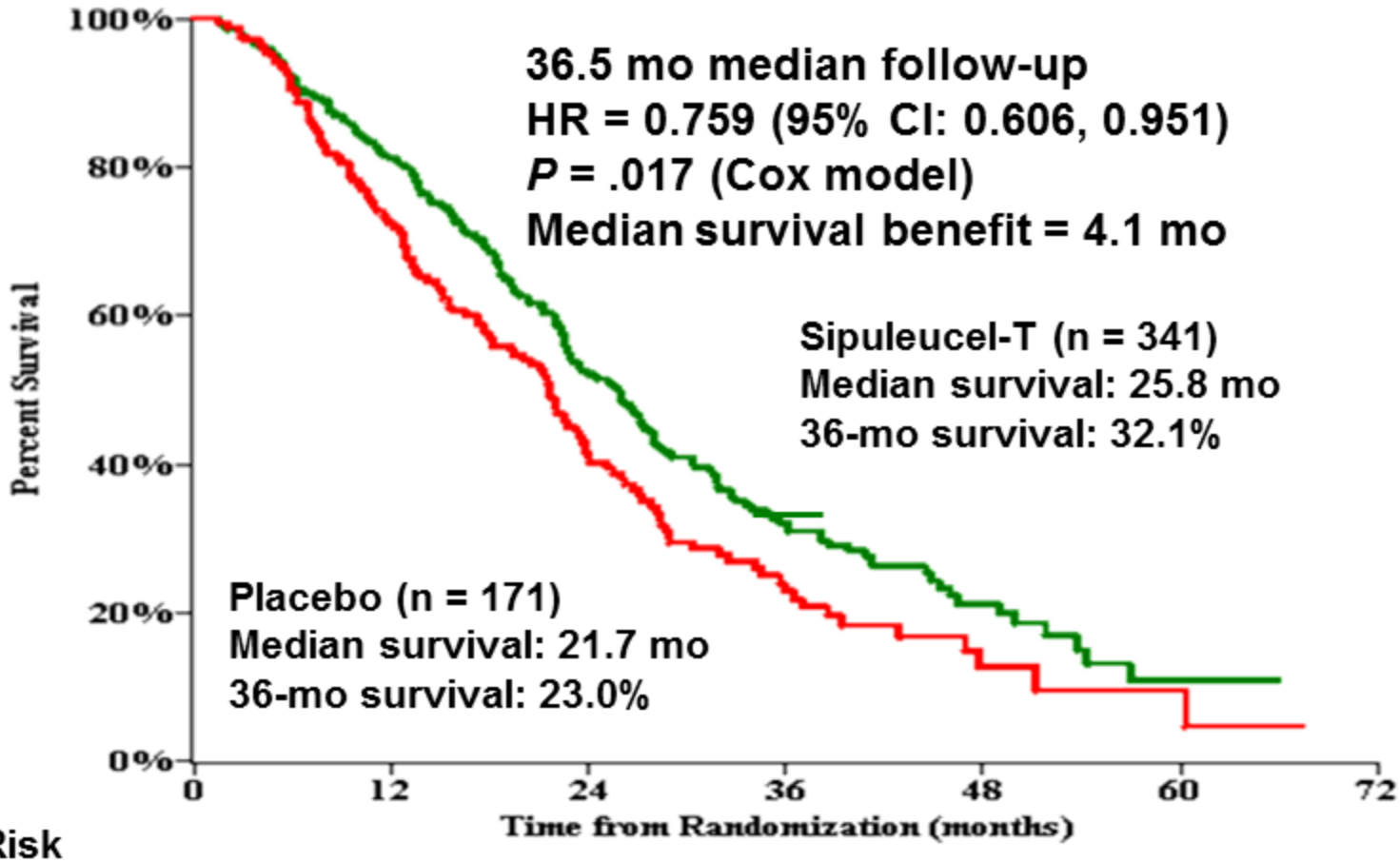
Primary Endpoint: Overall survival

Secondary Endpoint: Objective disease progression

Kantoff PW, et al. *N Engl J Med*. 2010;363:411-422.

IMPACT

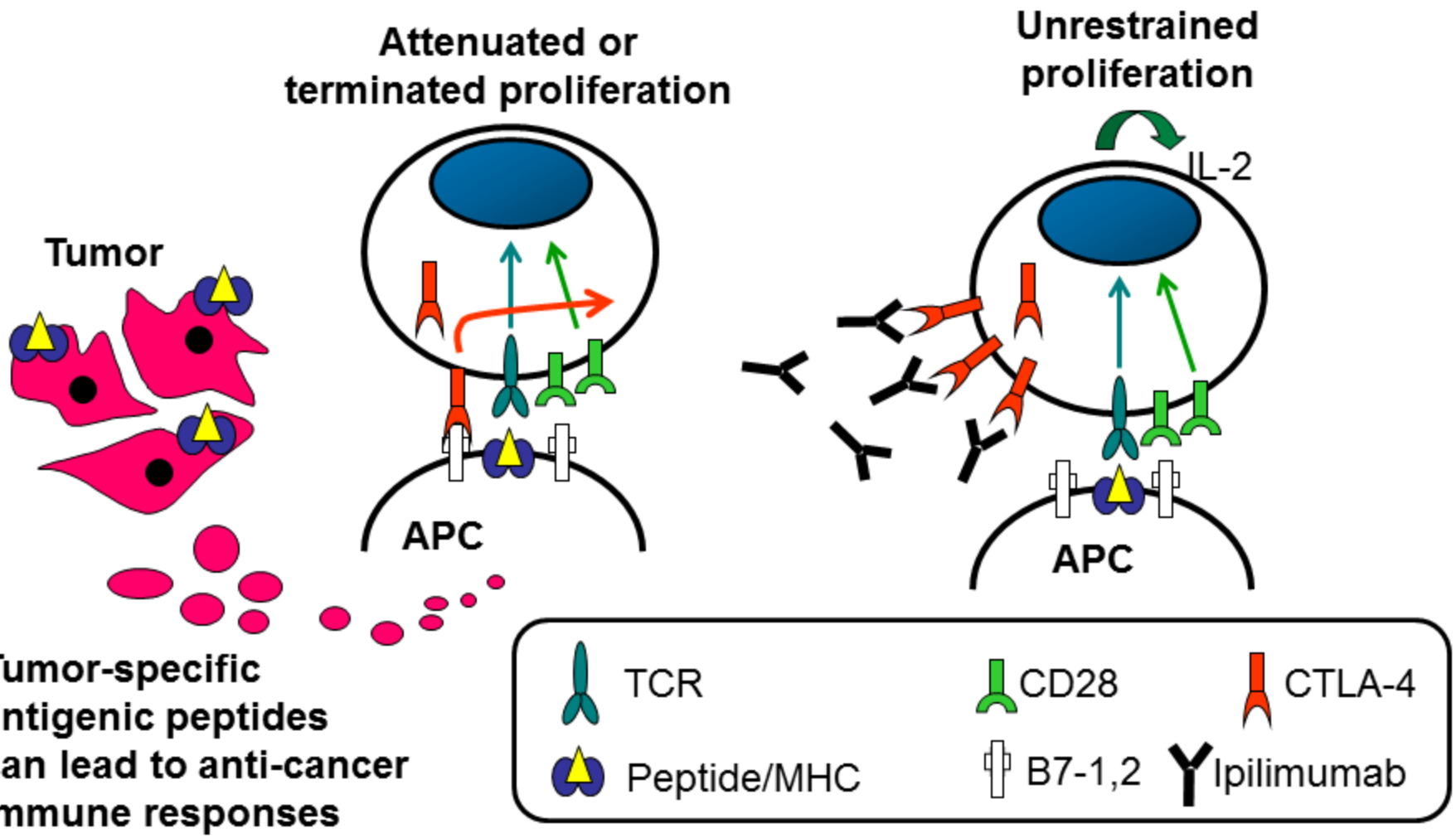
Overall Survival - Final Analysis



No. at Risk						
Sipuleucel-T	341	274	142	56	18	3
Placebo	171	123	59	22	5	2

Kantoff PW, et al. *N Engl J Med*. 2010;363:411-422.

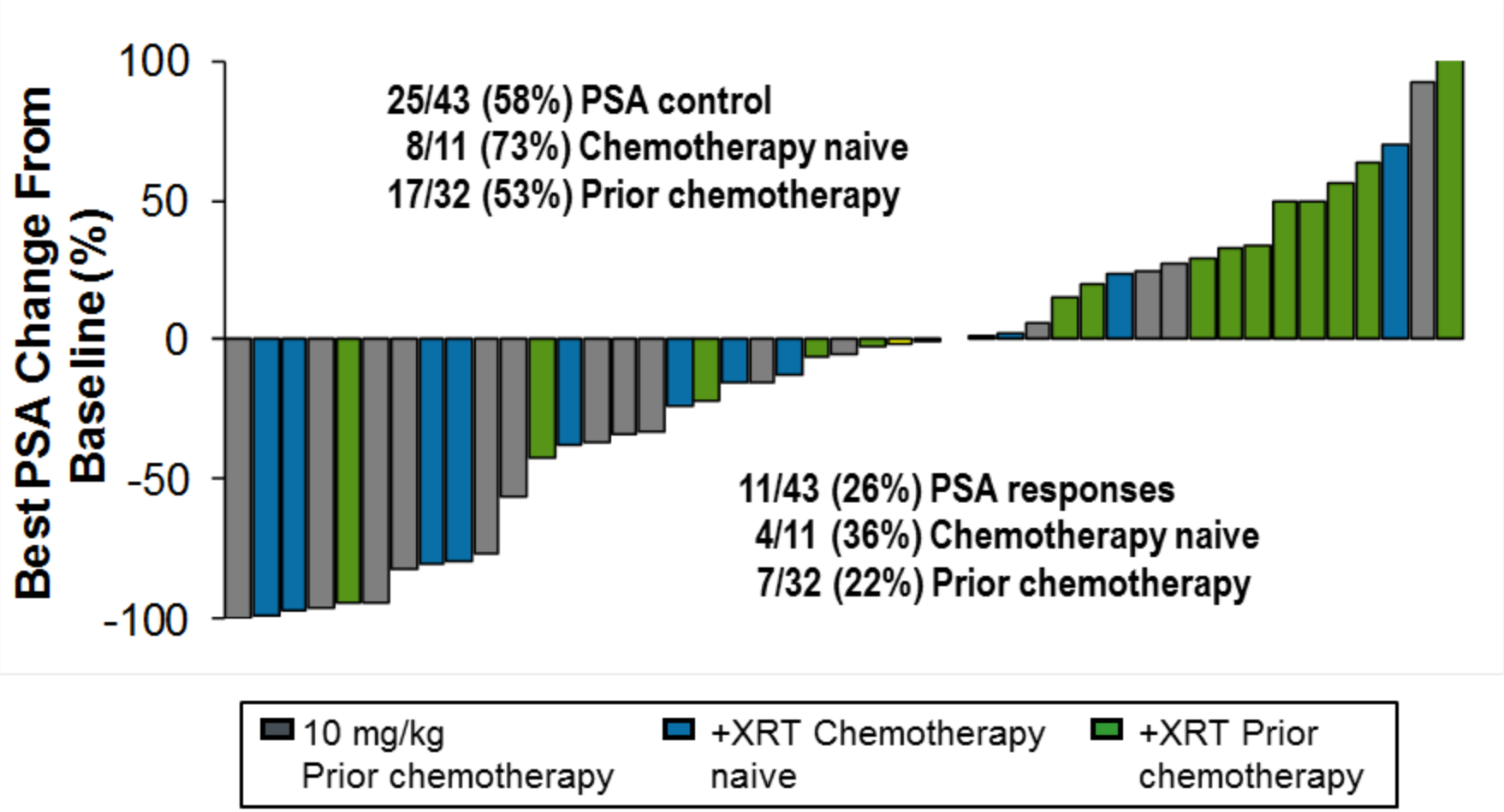
Ipilimumab
Mechanism of Action



Adapted from Chambers CA, et al. *Annu Rev Immunol.* 2001;19:565-594.

Ipilimumab

PSA Activity



Slovin SF, et al. 2009 ASCO®: Abstract 5138.

Sipuleucel-T and Ipilimumab
Current Status

Sipuleucel-T is approved for minimally symptomatic or asymptomatic CRPC

Ipilimumab

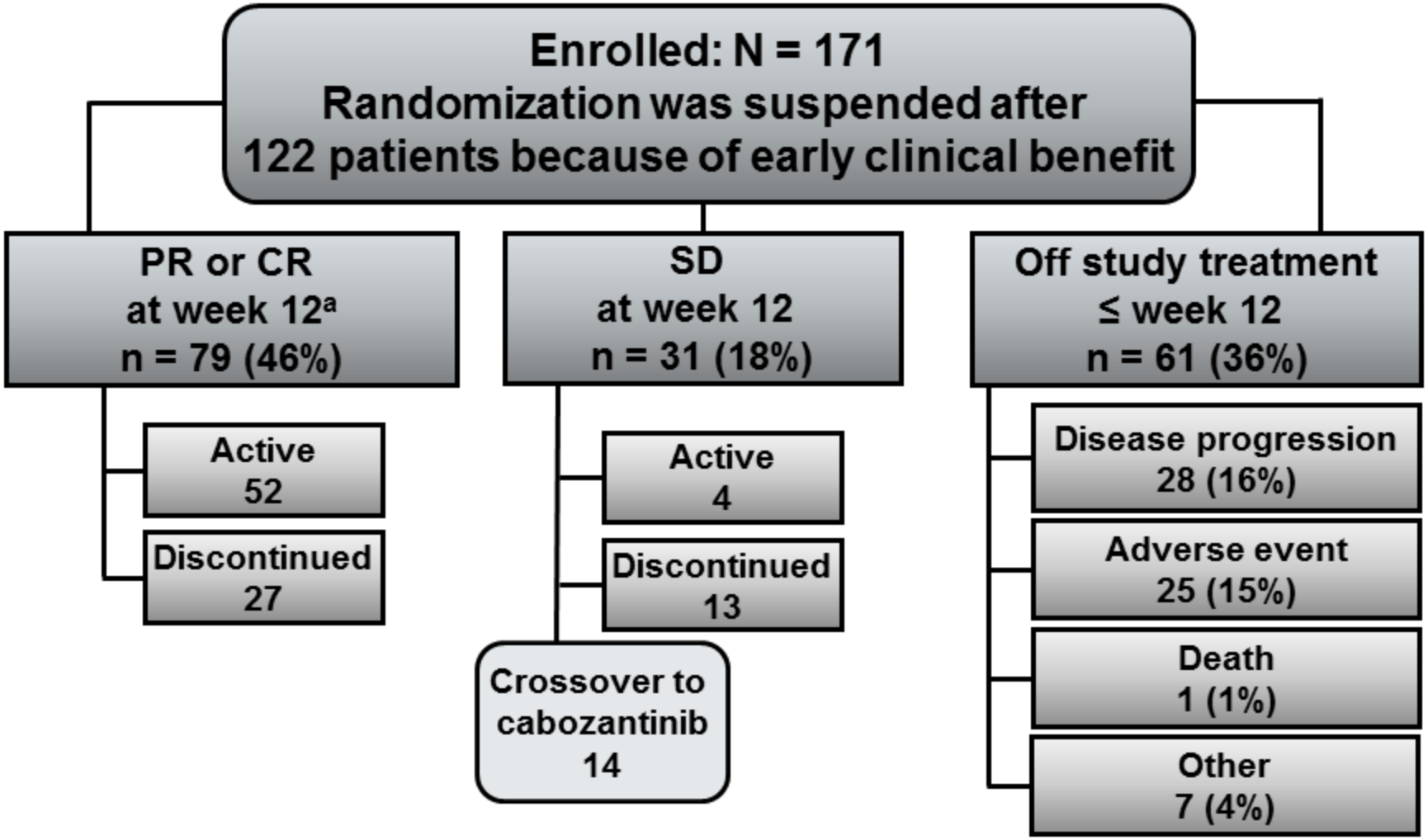
- Approved for the treatment of melanoma
- Phase 3 trial in patients with metastatic prostate cancer resistant to both hormonal therapy and chemotherapy under way
- Phase 3 trial in patients with chemotherapy-naive metastatic CRPC under way

Targeted Therapy

XL184

XL184 (MET + VEGFR2 Inhibitor)

Phase 2 Trial

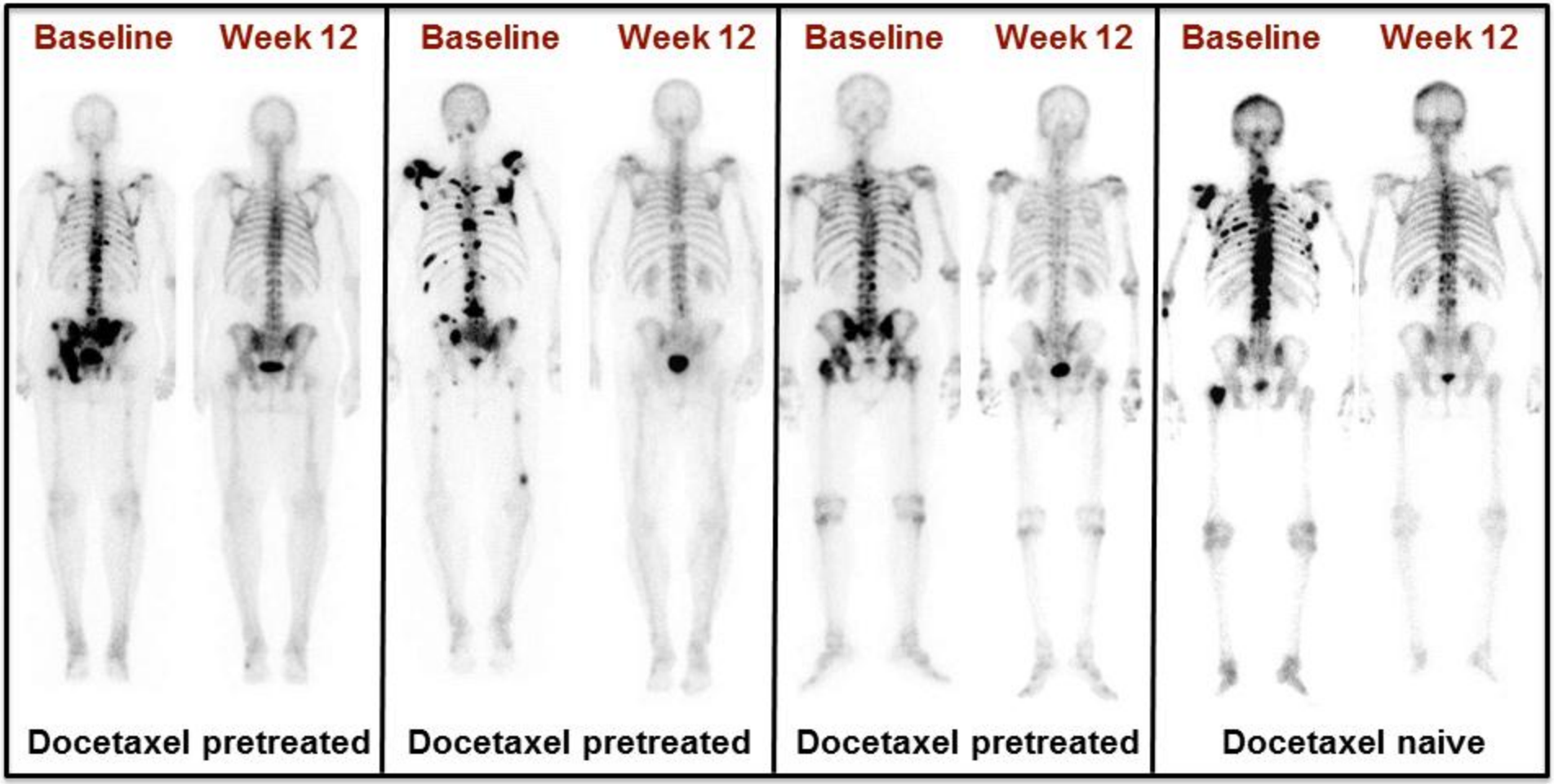


[a] Includes patients with SD at week 12 following suspension of randomization

Hussain M, et al. 2011 ASCO®: Abstract 4516.

Bone Scan Effects

Selected Images

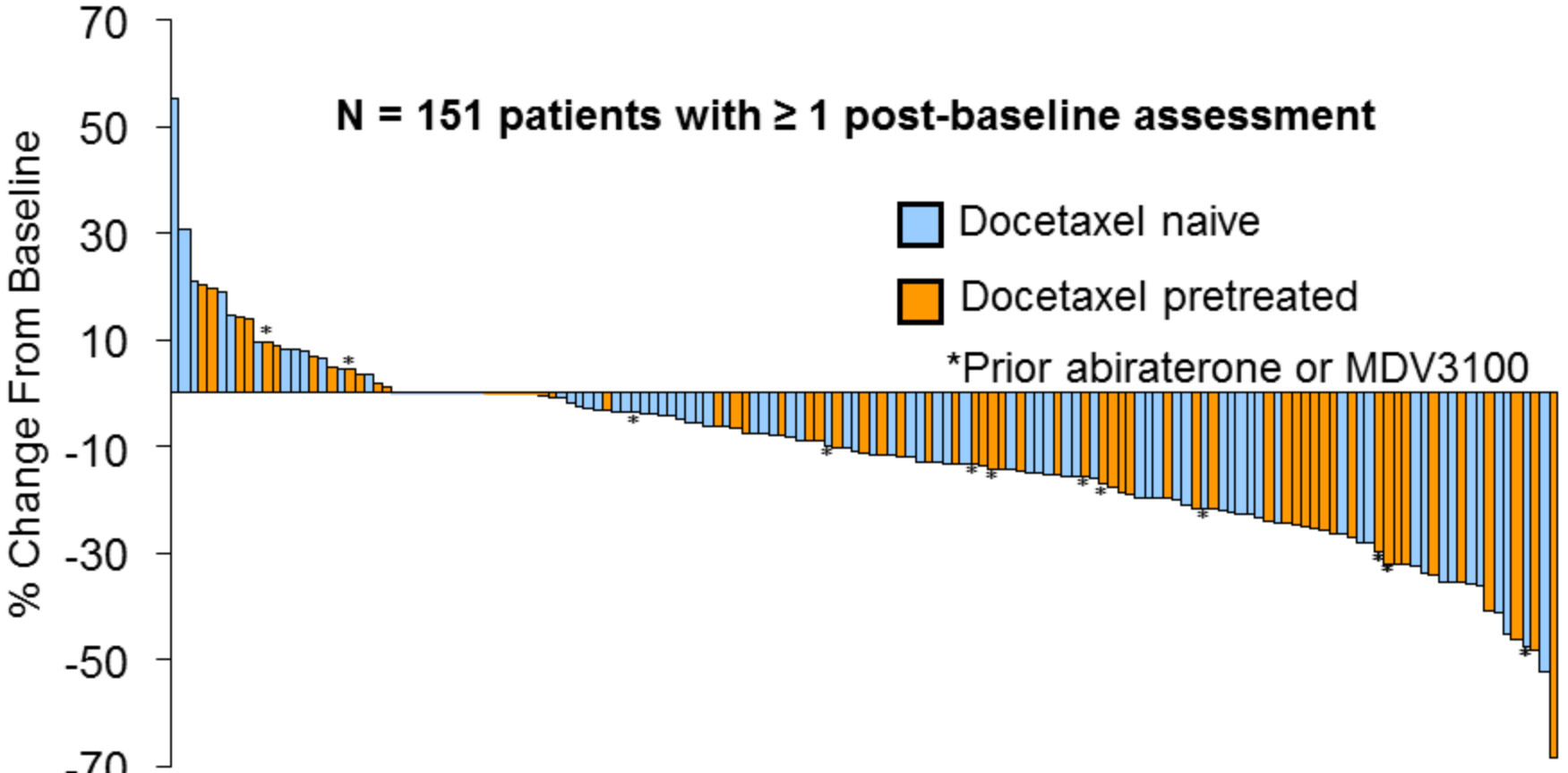


Each Patient had PR + Pain Improvement

Hussain M, et al. 2011 ASCO®: Abstract 4516.

XL184

Effects in Measurable Soft Tissue Lesions



- 74% of patients have shown evidence of tumor regression
- PSA changes did not correlate with radiographic changes

Hussain M, et al. 2011 ASCO®: Abstract 4516.

XL184

Effects on Bone Pain and Narcotic Use

	N (%)
Bone metastases and bone pain at baseline	83
Pain improvement at week 6 or 12	56 (67)
Narcotics for bone pain at baseline	67
Pain improvement at week 6 or 12	47 (70)
Evaluable for narcotics change	55
Decrease or discontinuation of narcotics	31 (56)

- Post-hoc investigator survey
- Limited to patients with ≥ 1 post-baseline assessment

Hussain M, et al. 2011 ASCO®: Abstract 4516.

XL184

Current Status

- Phase 3 trial in thyroid cancer under way
- Phase 3 trials in prostate cancer launching

Bone-Directed Therapy

Antiresorptive Agents and Radium-223

SRE Prevention in CRPC

Current Status of Antiresorptive Agents

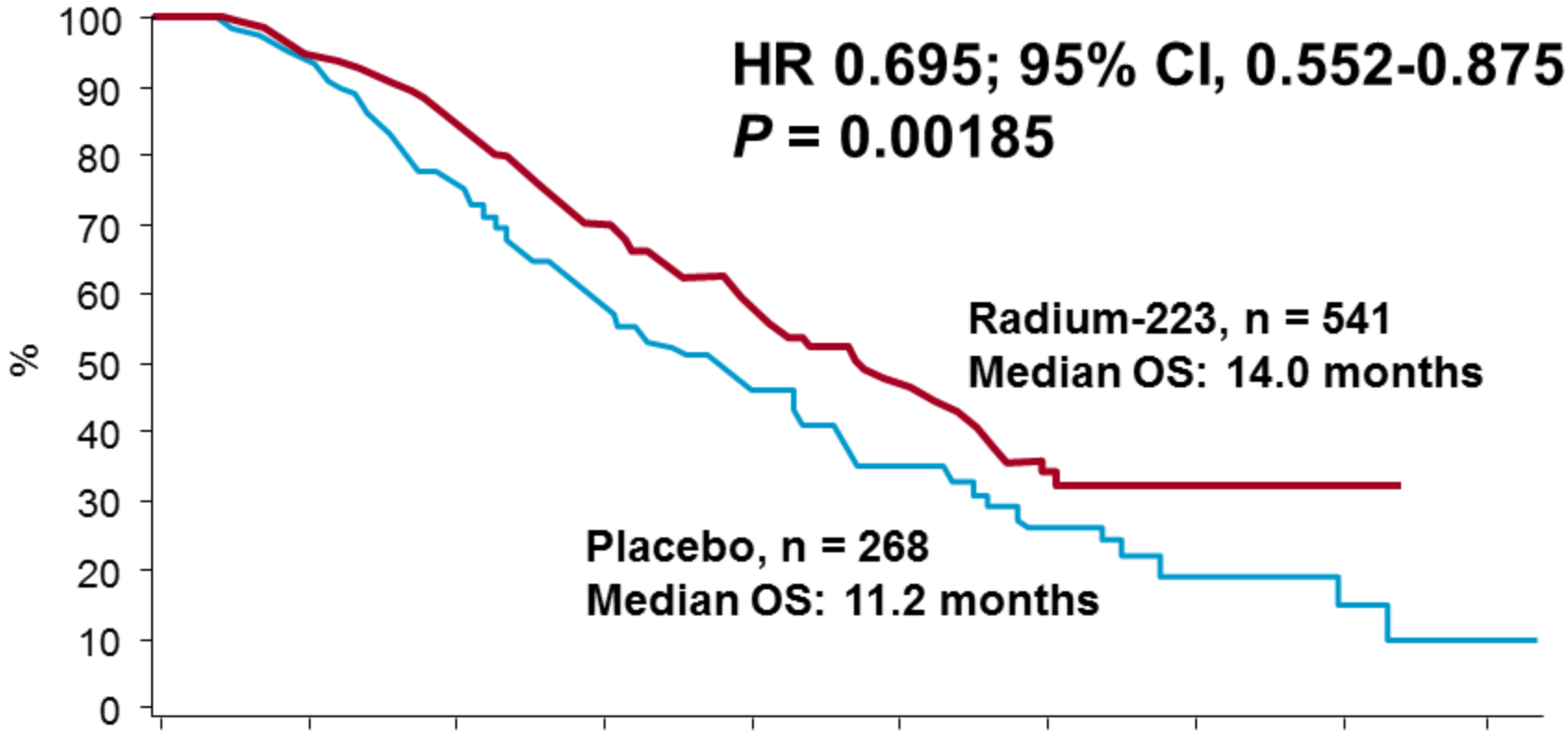
Agent	Study Duration (mo)	# Pts with SREs (%)	Median time to 1st SRE (mo)	HR/RR
ZOL (n=214) vs placebo (n=208)[a]	24	81 (38%) vs 101 (49%) *P* = .028	16.0 vs 10.5 *P* = .009	HR 0.64 *P* = .002
Pamidronate (n=169) vs placebo (n=181)[b]	6.8	42 (25%) vs 46 (25%) *P* = NA	NA	NA
Denosumab (n=950) vs ZOL (n=951)[c]	41	341 (36%) vs 386 (41%)	20.7 vs 17.1 *P* = .0002	RR 0.82 *P* = .008

Denosumab, a human monoclonal antibody against RANKL, proved better than zoledronic acid for SRE prevention

a. Saad F, et al. *J Natl Cancer Inst*. 2004;96:879-882.
b. Small EJ, et al. *J Clin Oncol*. 2003;21:4277-4284.
c. Fizazi K, et al. *Lancet*. 2011;377:813-822.

ALSYMPCA

Overall Survival

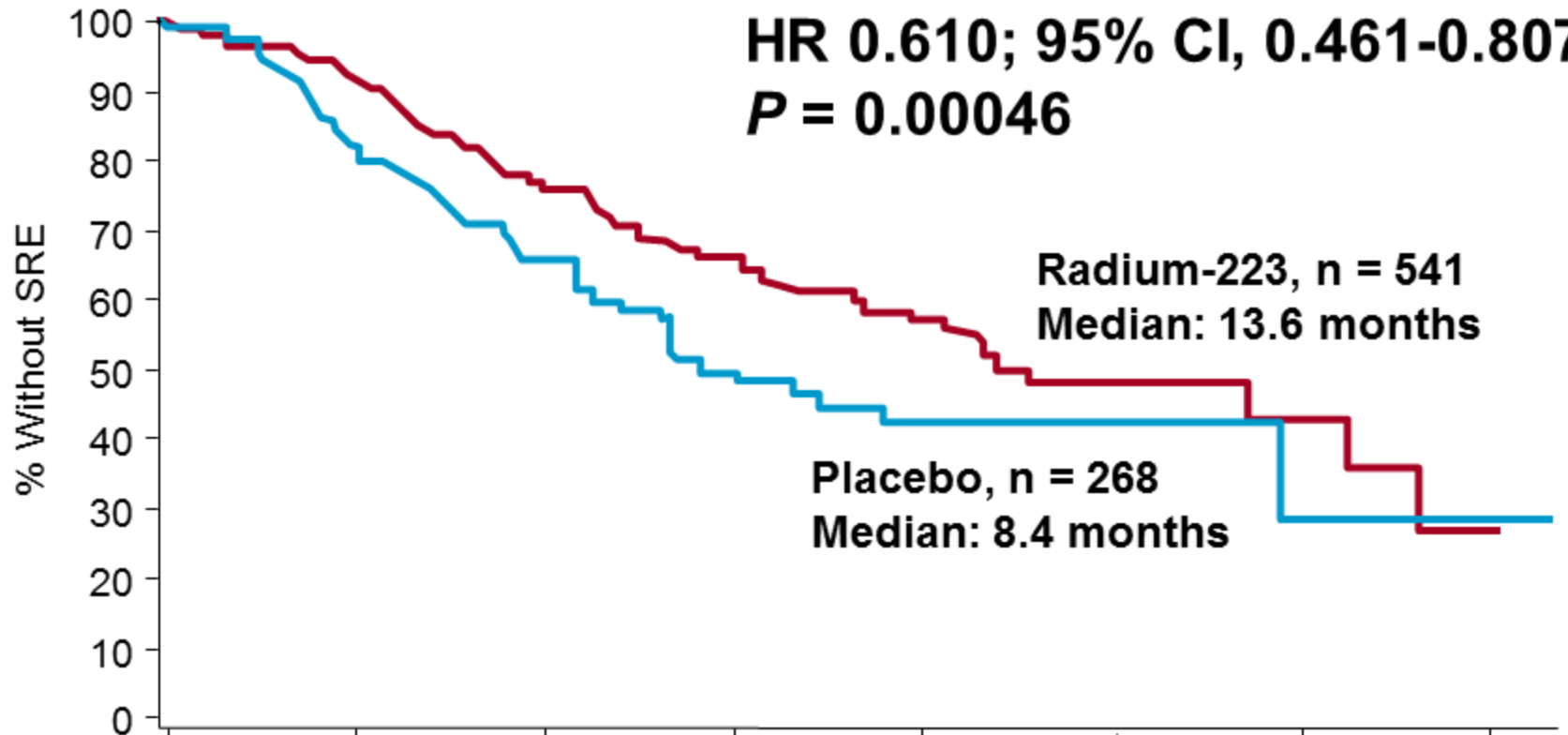


Month	0	3	6	9	12	15	18	21	24	27
Radium- 223	541	450	330	213	120	72	30	15	3	0
Placebo	268	218	147	89	49	28	15	7	3	0

Parker C, et al. 2011 EMCC: Abstract 1LBA.

ALSYMPCA

Time to First SRE



Month	0	3	6	9	12	15	18	21
Radium-223	541	379	214	111	51	22	6	0
Placebo	268	159	74	30	15	7	2	0

Parker C, et al. 2011 EMCC: Abstract 1LBA.

Radium-223
Current Status

- Overall survival advantage demonstrated in a phase 3 trial

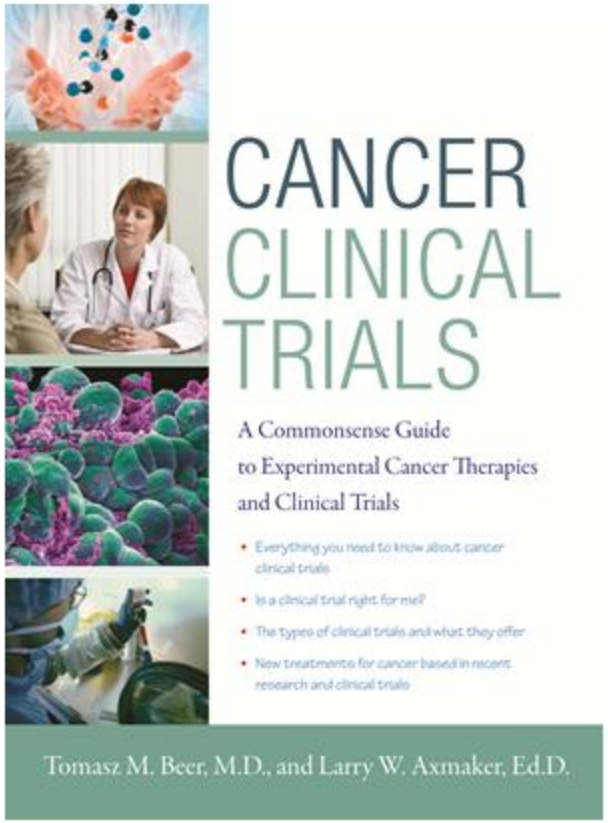
- The drug is before the FDA

Current Paradigm in CRPC

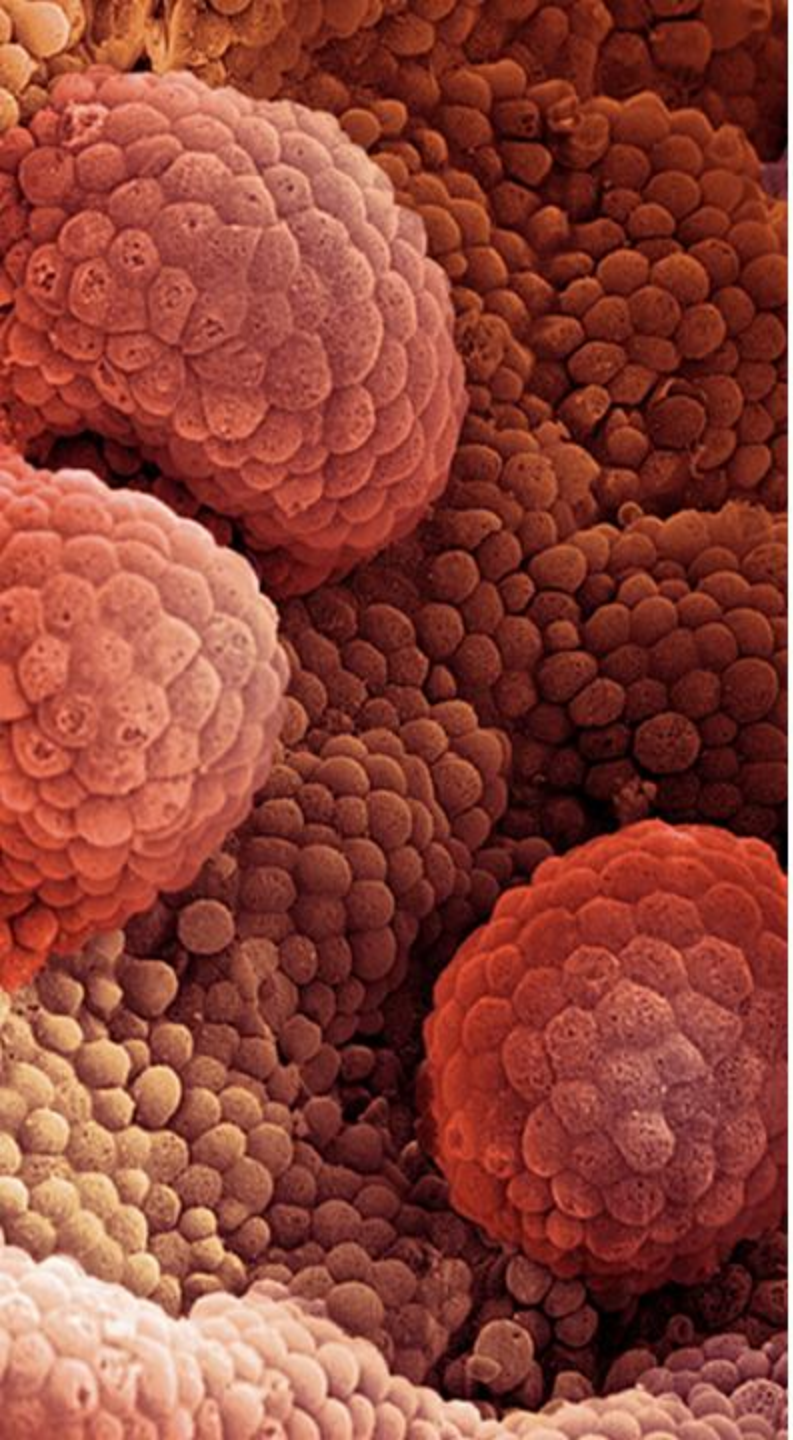
Bottom Line

- More novel promising agents under study for prostate cancer than ever before
  - Enabled by understanding of what drives tumor growth
- First time ever to have 3 new drugs that improve survival approved for prostate cancer in 18 months
- First-ever cancer-specific immunotherapy targets prostate cancer
  - Proof of principle that the immune system can be important in fighting prostate cancer
- Cooperation between leading institutions combined with scientific excellence is key to rapid progress
- Much more to come

Thank you



cancer-clinical-trials.com



Evolving Role of AR Signaling as Therapeutic Target

Johann Sebastian de Bono, MB, ChB, FRCP, MSc, PhD
Professor of Experimental Cancer Medicine
Department of Medicine/Drug Development Unit
Institute of Cancer Research
Honorary Consultant Medical Oncologist
Department of Medicine and Drug Development
Royal Marsden Hospital NHS Foundation Trust
Sutton, Surrey, United Kingdom

Medscape Oncology
EDUCATION

Disclosure

Johann Sebastian de Bono, MB, ChB, FRCP, MSc, PhD

Served as an advisor or consultant for: Cougar Biotechnology, Inc.; Johnson & Johnson Pharmaceutical Research & Development, L.L.C.; AstraZeneca Pharmaceuticals LP; Medivation, Inc.; Astellas Pharma, Inc.

Served as a speaker or a member of a speakers bureau for: Johnson & Johnson Pharmaceutical Research & Development, L.L.C.; sanofi-aventis
Received grants for clinical research from: Pfizer Inc.
Employed by a commercial interest: Institute of Cancer Research.

Dr. de Bono does intend to discuss off-label uses of drugs, mechanical devices, biologics, or diagnostics *approved* by the FDA for use in the United States.

Dr. de Bono does intend to discuss investigational drugs, mechanical devices, biologics, or diagnostics *not approved* by the FDA for use in the United States.

Advanced Prostate Cancer
Unprecedented Progress

In the last 2 years, 5 treatments shown to improve OS

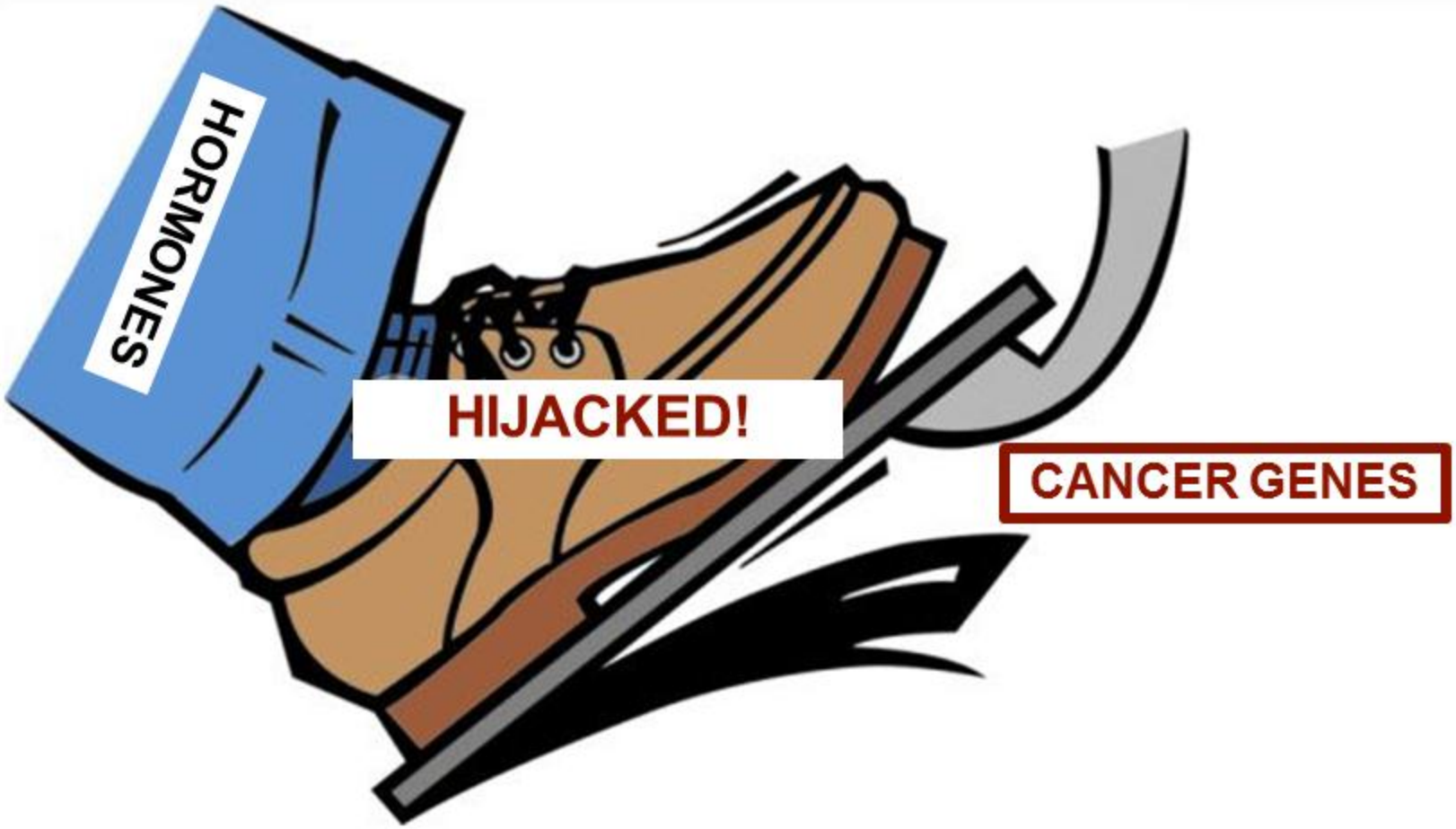
- Abiraterone[a]
- Sipuleucel-T[b]
- Cabazitaxel[c]
- Alpharadin[d]
- MDV3100[e]

a. de Bono J, et al. *N Engl J Med*. 2011;364:1995-2005.
b. Kantoff PW, et al. *N Engl J Med*. 2010;363:411-422.
c. de Bono JS, et al. *Lance*t. 2010;376:1147-1154.
d. Parker C, et al. ESMO 2011.
e. Scher HI & de Bono J, Press Release 11/2011; GU ASCO 2012

Presentation Overview

- **Insight into disease biology: key therapeutic targets**
- Improving treatment: changing landscape
- Future challenges

Hormone-Driven Genetic Switches



More than 20 different types of prostate cancers: all with different 'drivers'

Presentation Overview

- Insight into disease biology: Key therapeutic targets
- **Improving treatment: changing landscape**
- Future challenges

Androgen Receptor Addiction
Hard Habit to Break

Hormonal treatments continue to have antitumor activity

High levels of intratumoral androgens despite castration

- Preclinical and clinical evidence of intracrine synthesis

Castration resistance associated with

- AR amplification (increased gene dose)
- AR mutations that increase AR (transcriptional) activity
- ↑ AR (< 2x) expression (ligand driven) in isogenic resistant lines
- AR still switched on in Abiraterone- and MDV3100-resistant PCa

Identification of oncogenic translocations/fusions driven by androgens + estrogen-response elements (*ETS* genes; *TMPRSS2/ERG* in 50% to 70% of PCa)

Attard G, et al. *Cancer Cell*. 2009;16:458-462.

Abiraterone Acetate

Androgen Biosynthesis Inhibitor

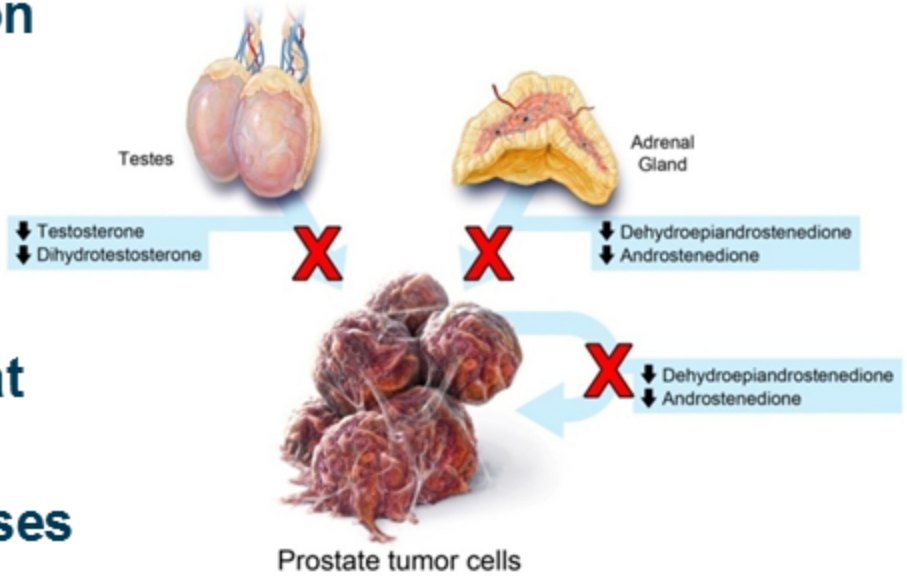
Androgens produced at 3 critical sites lead to tumor proliferation

- Testes
- Adrenal gland
- **Prostate tumor cells**

Abiraterone inhibits biosynthesis of androgens that stimulate tumor cell growth

PSA and radiographic responses in phase 1-2 studies

- Chemotherapy-naive and postchemotherapy patients[a-e]

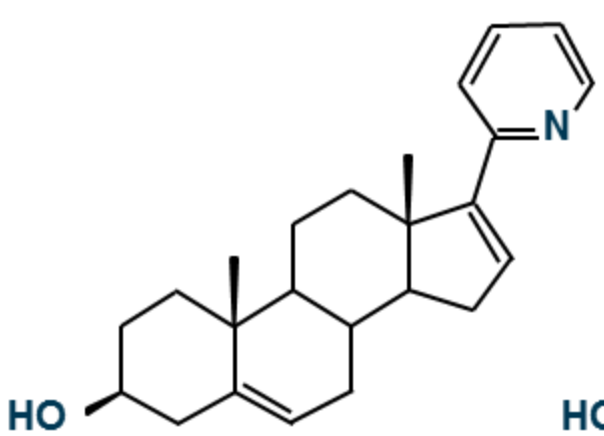


a. Attard G, et al. *J Clin Oncol*. 2008;26:4563-4571; b. Attard G, et al. *J Clin Oncol*. 2009;27:3742-3748; c. Reid AH, et al. *J Clin Oncol*. 2010;28:1489-1495; d. Ryan C, et al. *J Clin Oncol*. 2010;28:1481-1488; e. Danila D, et al. *J Clin Oncol*. 2010;28:1496-1501.

P450c17 Inhibitors

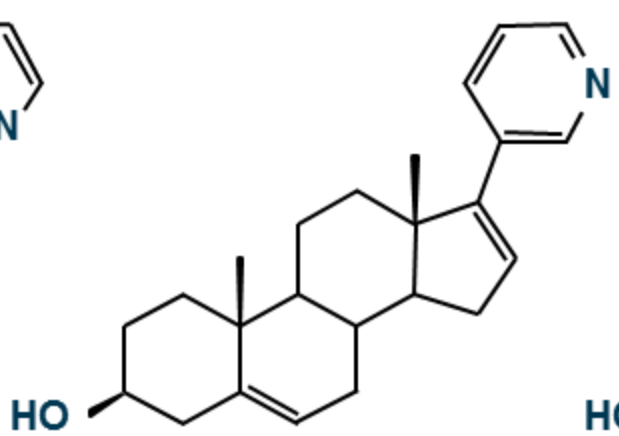
Chemical Development

Abiraterone



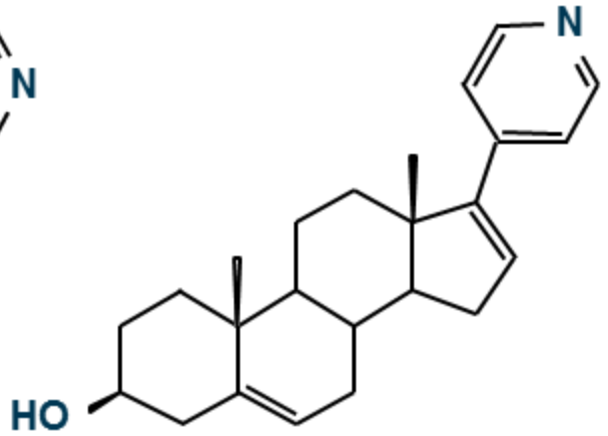
2-pyridyl

IC_{50} (nm)
lyase 76
hydroxylase 270



3-pyridyl

IC_{50} (nm)
lyase 2.9
hydroxylase 4



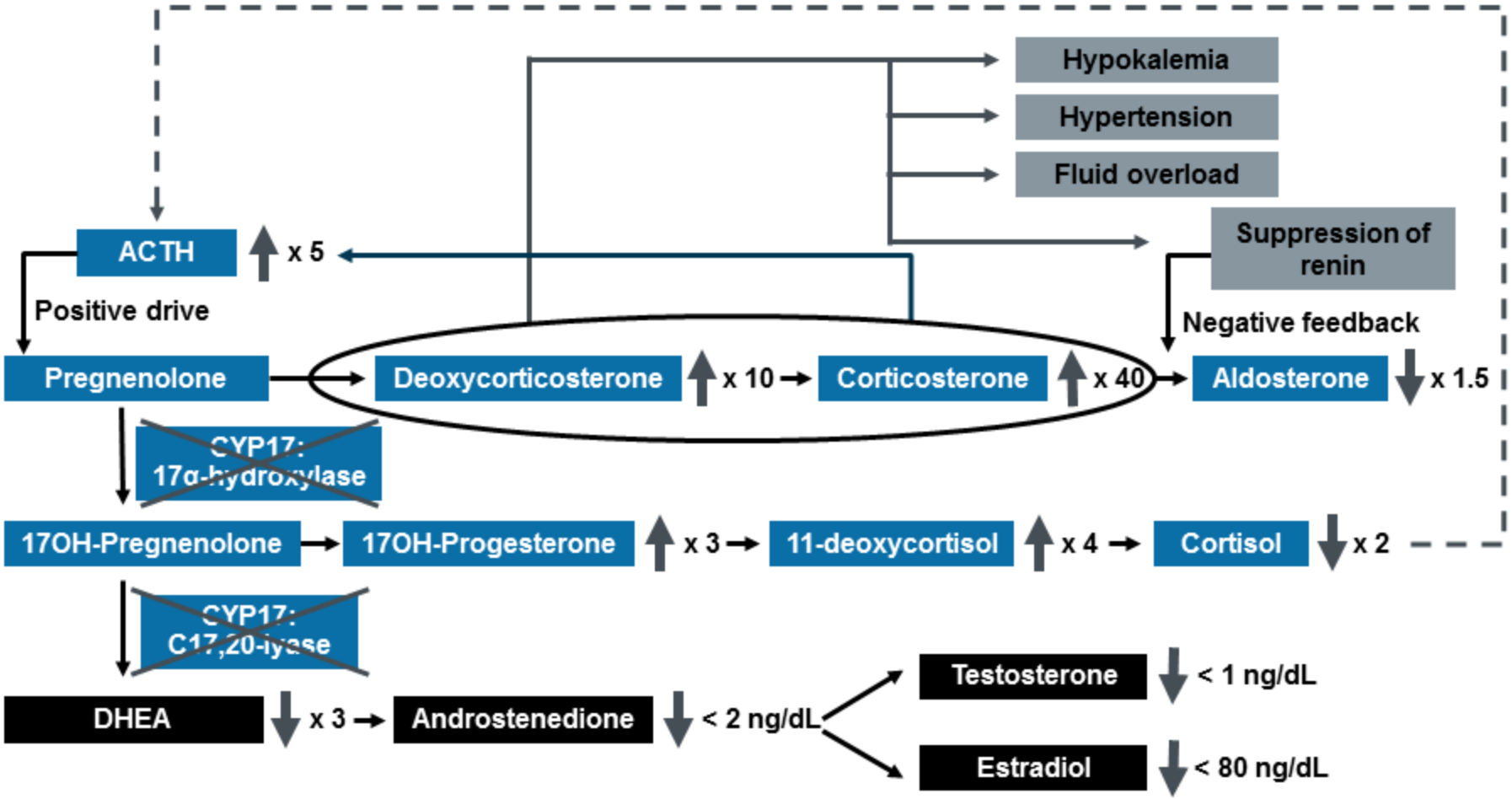
4-pyridyl

IC_{50} (nm)
lyase 1000
hydroxylase 4000

Designed at The Institute of Cancer Research: Jarman M, Potter G, Barrie E

Abiraterone

Mechanism of Action



Attard G, et al. *J Clin Oncol*. 2008;26:4563-4571.

Abiraterone
Phase 1 Study in CRPC

Continuous daily dosing (N = 21)

- 250-2000 mg daily to fasted chemotherapy-naive patients

Abiraterone administered without steroids

- Mineralocorticoid antagonist eplerenone utilized

No dose-limiting toxicity

Satisfactory dose-proportional pharmacokinetics

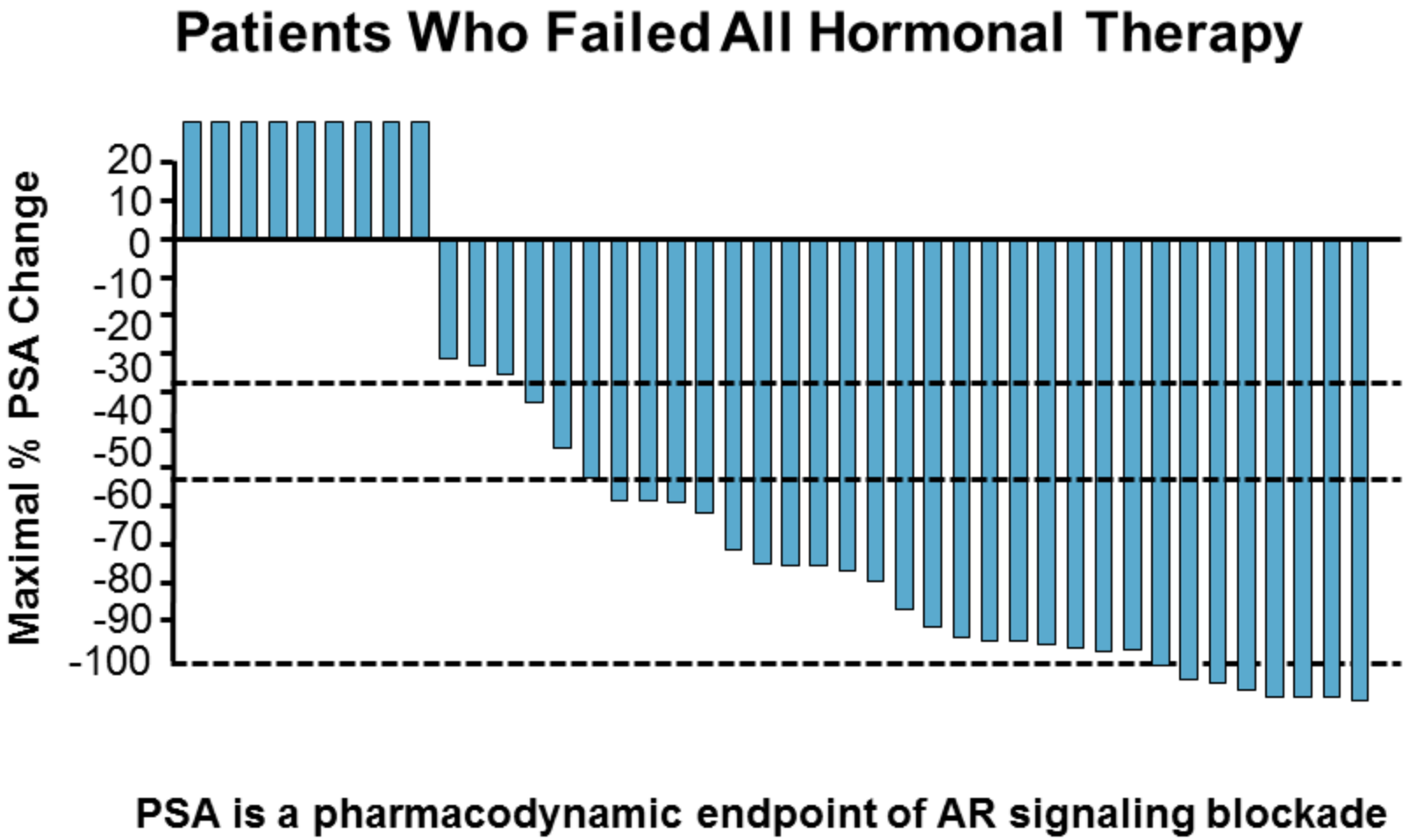
Pharmacodynamic endocrine data

- Suppression of hormone levels downstream of CYP17; increases in hormone levels upstream of CYP17; PSA decline; CTC decline

Attard G, et al. *J Clin Oncol*. 2008;26:4563-4571.

Abiraterone Acetate

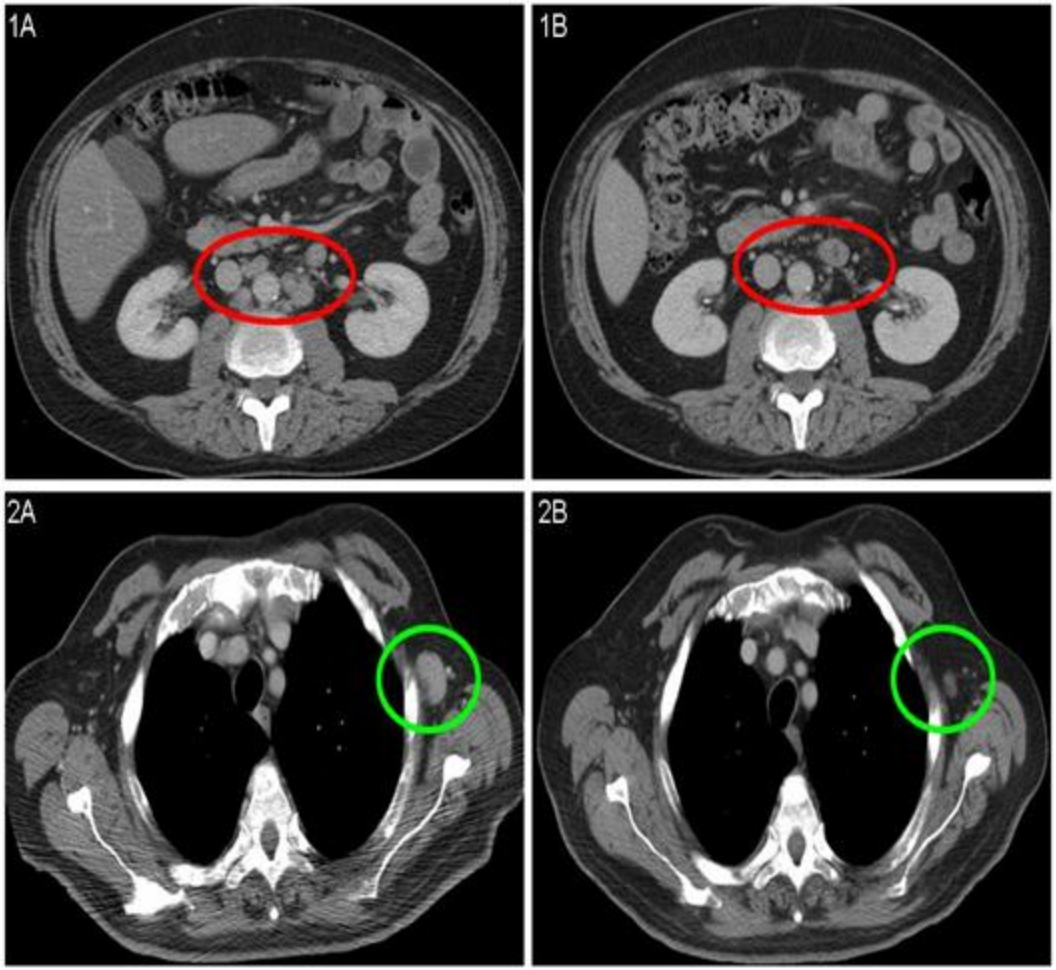
PSA Declines

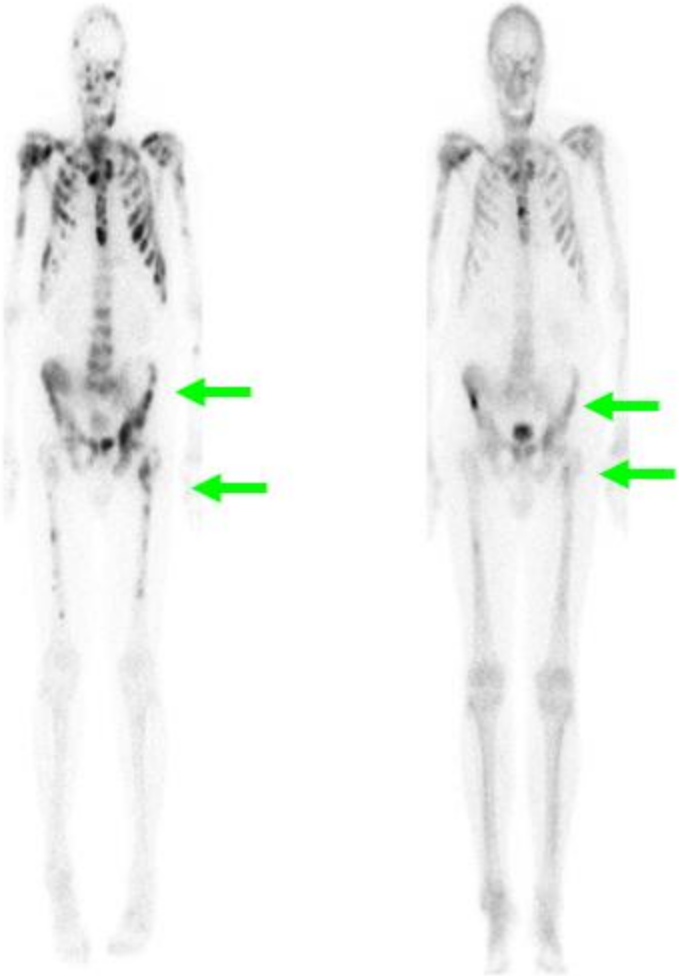


Attard G, et al. *J Clin Oncol*. 2009;27:3742-3748.

Abiraterone Acetate

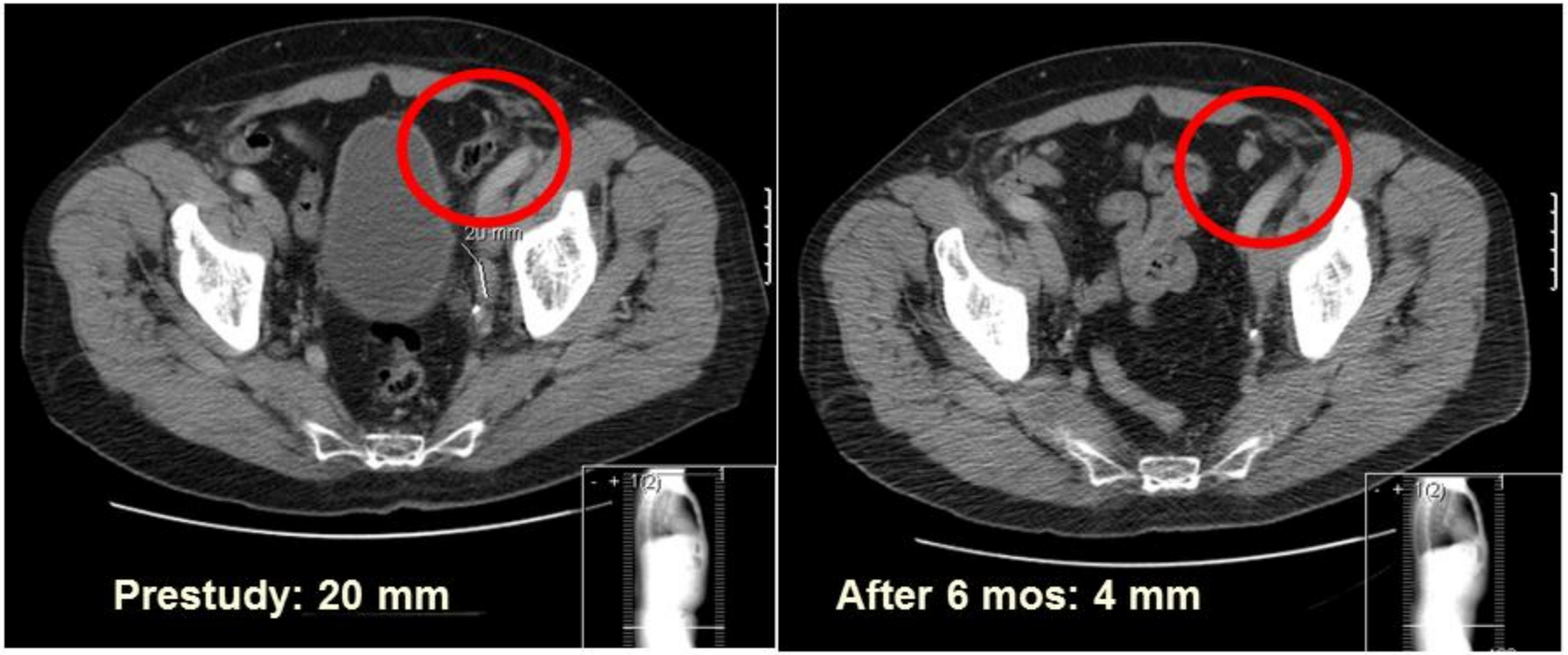
Antitumor Activity





Patient Receiving Abiraterone

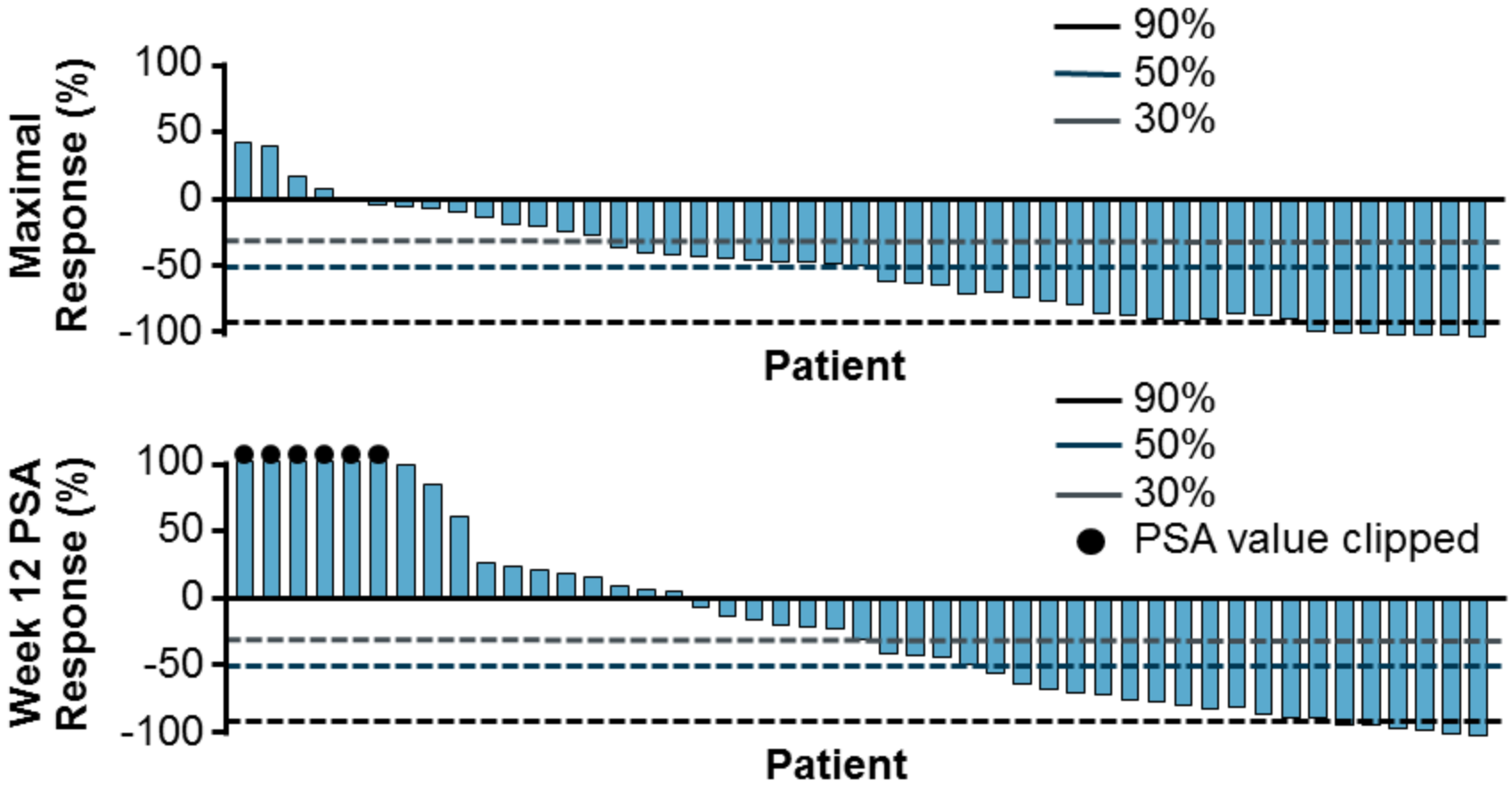
Regressing Pelvic Nodes



- Previous progression on several hormone treatments
- PSA decline from 34.3 ng/mL → 0.21 ng/mL (99%) within 3 mos
- Shrinkage of lymph glands shown above on CT scan

Postchemotherapy PSA Data

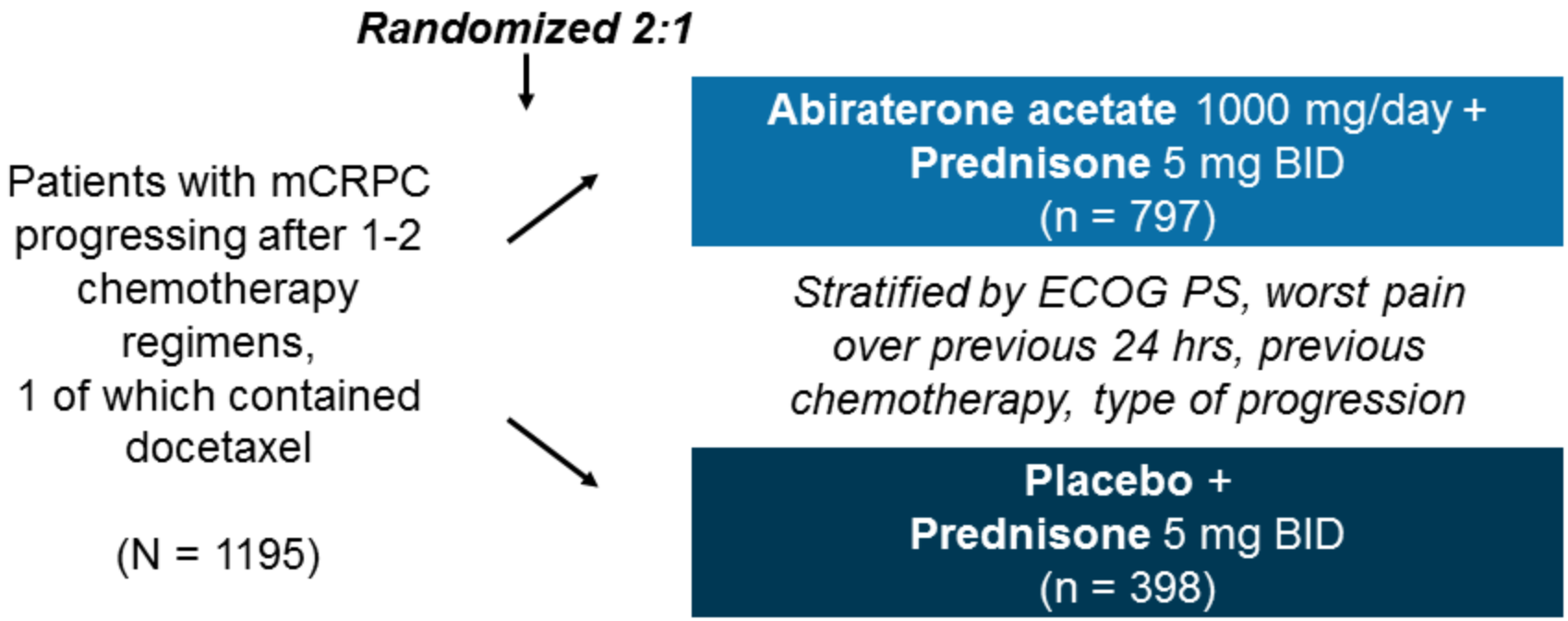
Abiraterone + Prednisolone 10 mg/day



Reid AH, et al. *J Clin Oncol*. 2010;28:1489-1495.

COU-AA-301

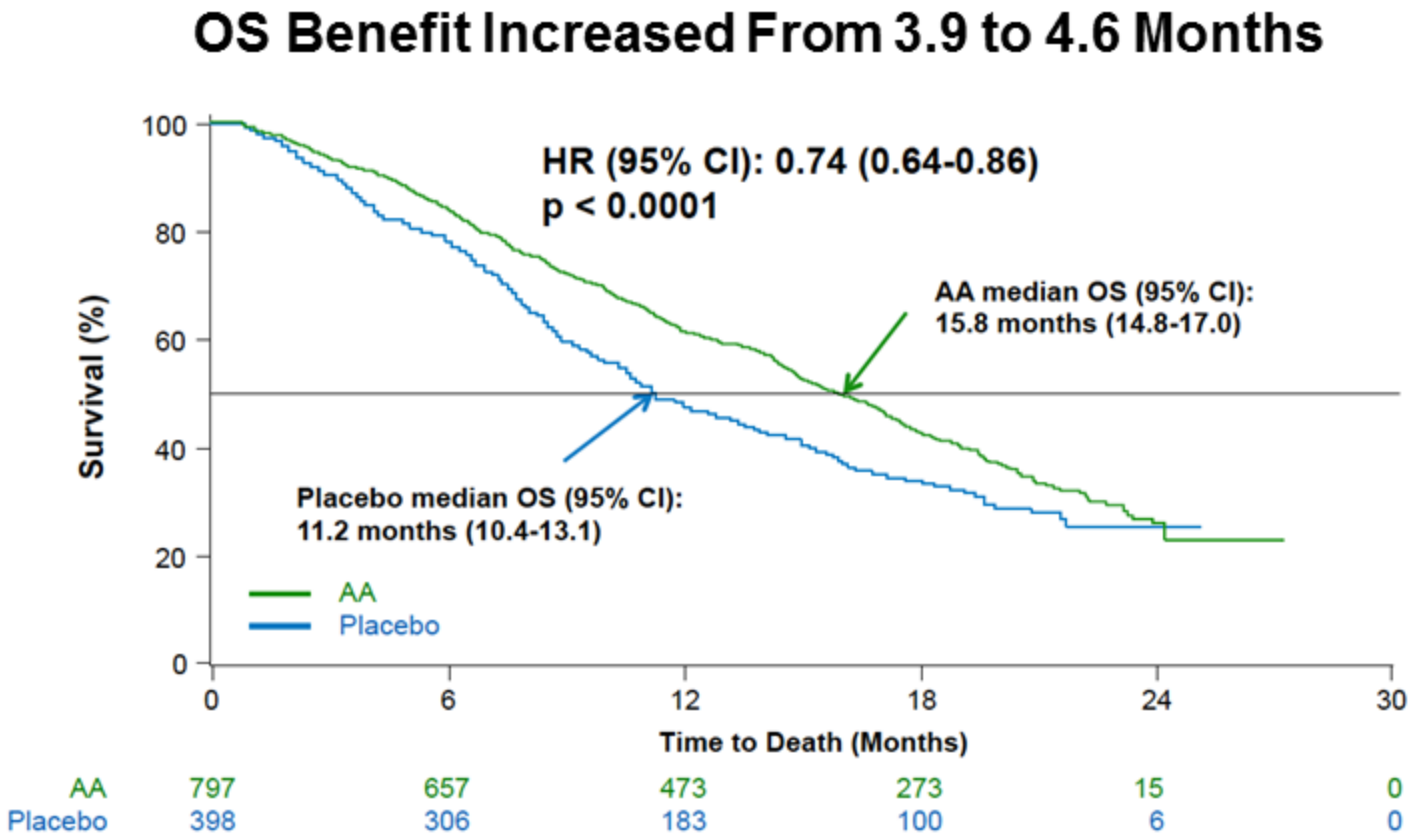
Phase 3 Study of Abiraterone in mCRPC



de Bono J, et al. *N Engl J Med*. 2011;364:1995-2005.

COU-AA-301

Updated Analysis (775 Events)

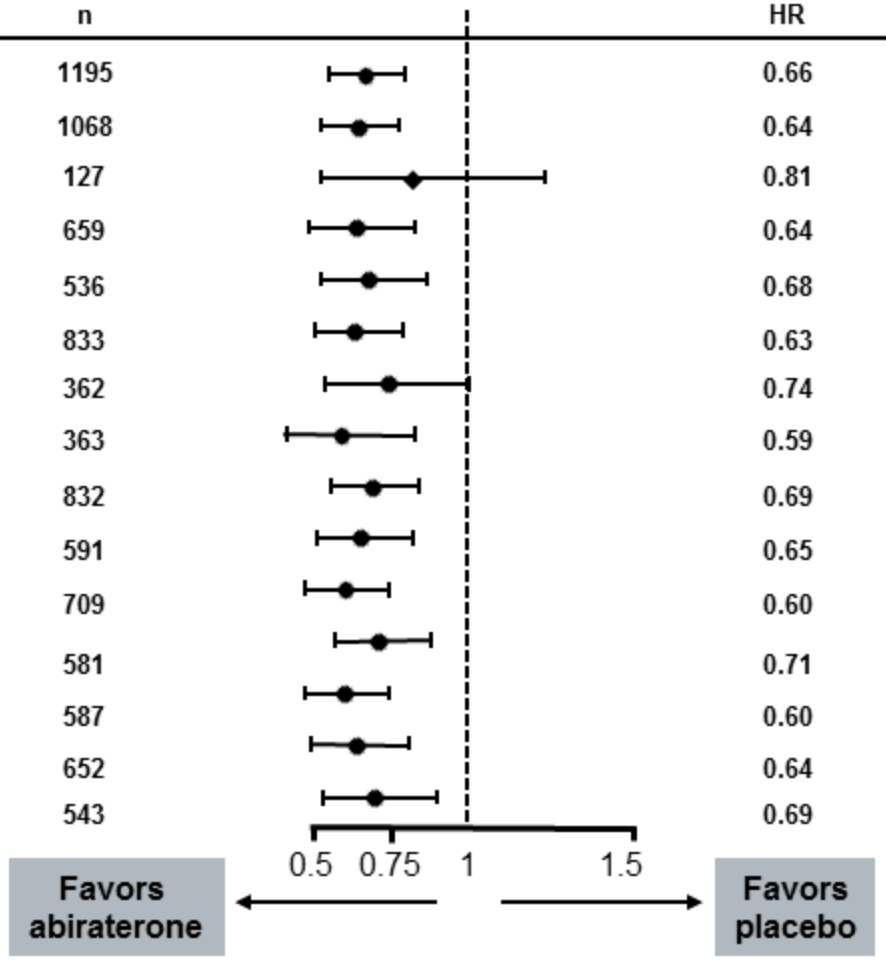


- Median duration of follow-up: 20.2 months
- Median duration of treatment: AA, 8 months vs placebo, 4 months

COU-AA-301

Survival Across Patient Subgroups

Variable	Subgroup	n	HR	95% CI
All subjects	All	1195	0.66	0.56-0.79
Baseline ECOG	0-1	1068	0.64	0.53-0.78
	2	127	0.81	0.53-1.24
Baseline BPI	< 4	659	0.64	0.50-0.82
	≥ 4	536	0.68	0.53-0.85
No. of prior chemo regimens	1	833	0.63	0.51-0.78
	2	362	0.74	0.55-0.99
Type of progression	PSA only	363	0.59	0.42-0.82
	Radiographic	832	0.69	0.56-0.84
Baseline PSA above median	Yes	591	0.65	0.52-0.81
Visceral disease at entry	Yes	709	0.60	0.48-0.74
Baseline LDH above median	Yes	581	0.71	0.58-0.88
Baseline ALK-P above median	Yes	587	0.60	0.48-0.74
Region	North America	652	0.64	0.51-0.80
	Other	543	0.69	0.54-0.90



de Bono J, et al. *N Engl J Med*. 2011;364:1995-2005.

COU-AA-301
Secondary Endpoints

Endpoint Characteristic	Abiraterone (n = 797)	Placebo (n = 398)	HR (95% CI)	*P* Value
TTPP, mos	10.2	6.6	0.58 (0.46-0.73)	< .0001
rPFS, mos	5.6	3.6	0.67 (0.59-0.78)	< .0001
PSA response rate, %				
• Total	38.0	10.1		< .0001
• Confirmed	29.1	5.5		< .0001

de Bono J, et al. *N Engl J Med*. 2011;364:1995-2005.

COU-AA-301
Summary of AEs

AE, %	Abiraterone (n = 791)		Placebo (n = 394)	
	All Grades	Grades 3/4	All Grades	Grades 3/4
All treatment-emergent AEs	98.9	54.5	99.0	58.4
Serious AEs	37.5	32.1	41.4	35.3
AEs leading to discontinuation	18.7	10.5	22.8	13.5
AEs leading to death	11.6		14.7	
Deaths within 30 days of last dose	10.5		13.2	
• Underlying disease	7.5		9.9	
• Other specified cause	2.9		3.3	

de Bono J, et al. *N Engl J Med*. 2011;364:1995-2005.

COU-AA-301

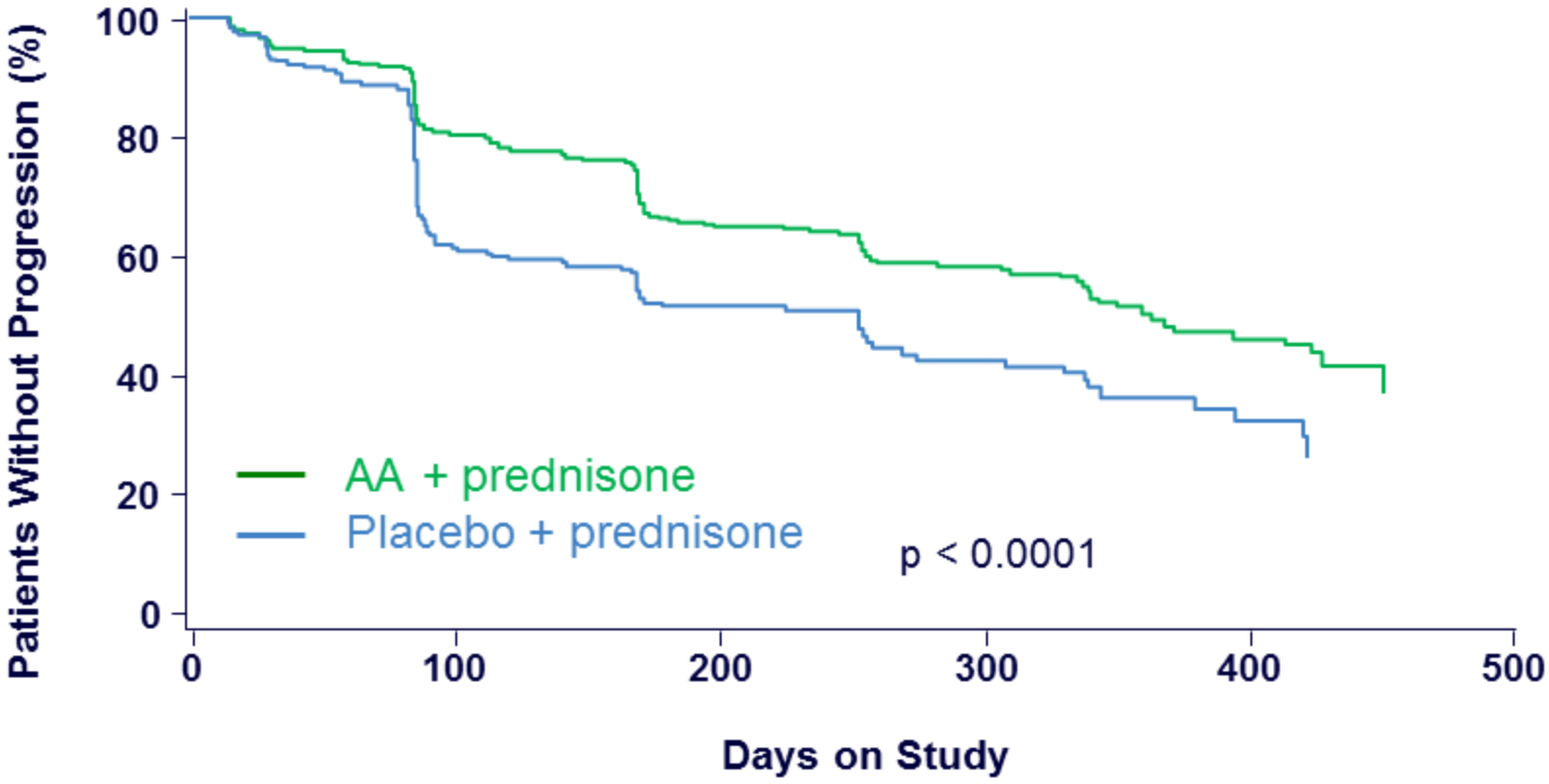
AEs of Special Interest

	Abiraterone (n = 791)		Placebo (n = 394)	
AE, %	**All Grades**	**Grades 3/4**	**All Grades**	**Grades 3/4**
Fluid retention	30.5	2.3	22.3	1.0
Hypokalemia	17.1	3.8	8.4	0.8
LFT abnormalities	10.4	3.5	8.1	3.0
Hypertension	9.7	1.3	7.9	0.3
Cardiac disorders	13.3	4.1	10.4	2.3

de Bono J, et al. *N Engl J Med*. 2011;364:1995-2005.

QOL

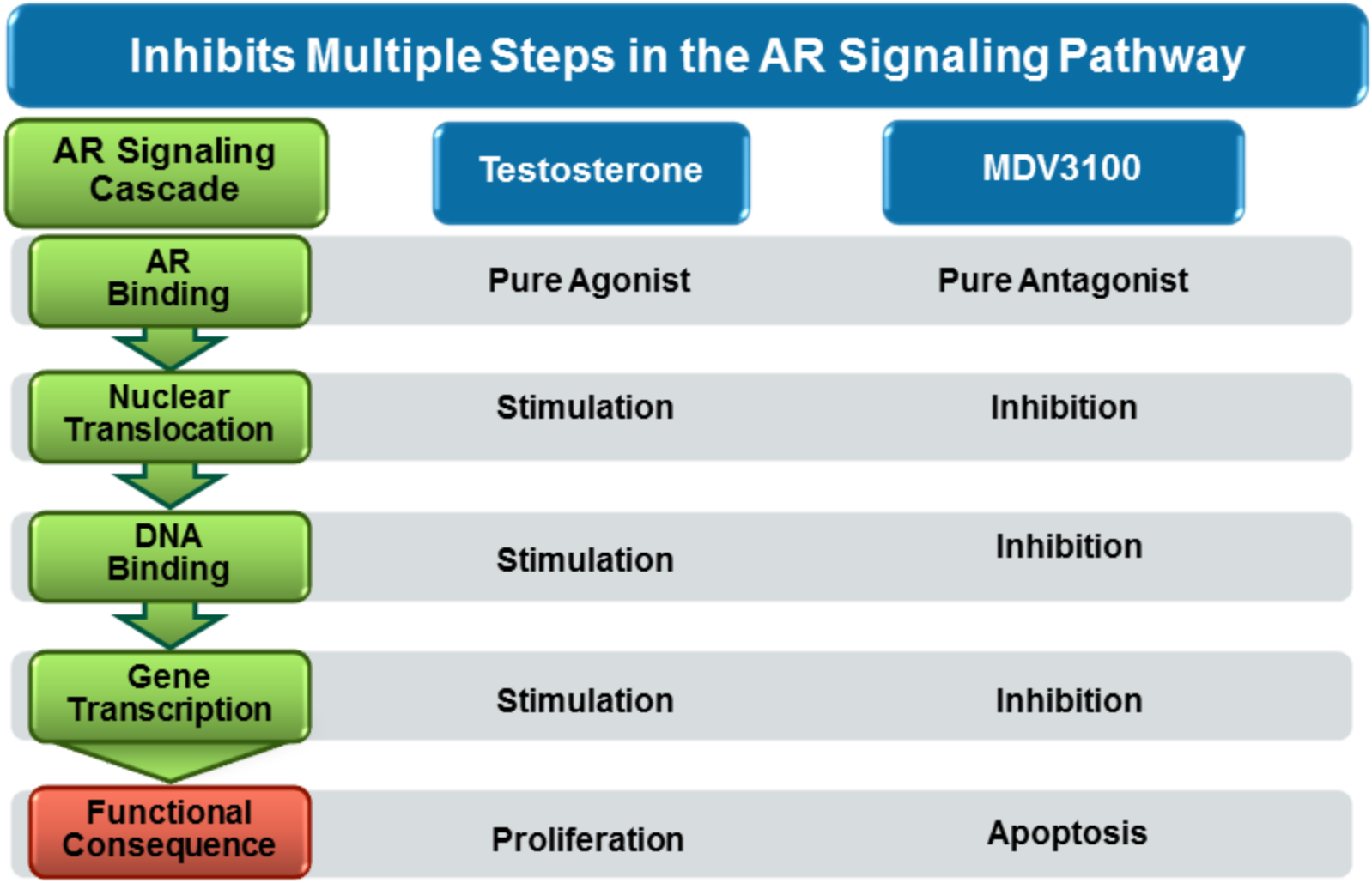
Time to FACT-P Deterioration



- The median time to functional status degradation (FACT-P total score) was 12.1 months in the AA + prednisone group vs 8.4 months in the placebo + prednisone group

MDV3100

Novel, Oral AR antagonist



Mukherji D, et al. *Expert Opin Investig Drugs*. 2012;21:227-233.

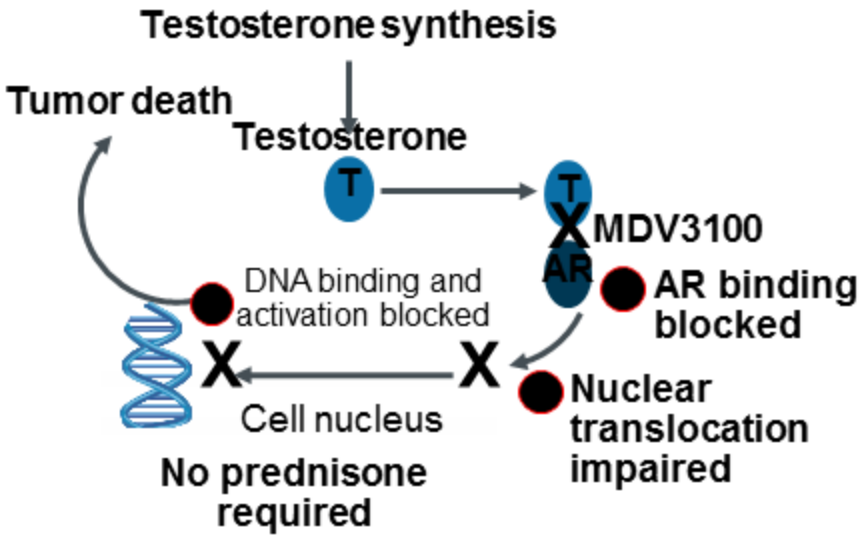
MDV3100

Phase 1/2 Study in Advanced PCa

Phase 1/2 trial conducted to determine safety, PK, and antitumor activity of MDV3100[b]

- N = 140 patients with progressive CRPC, pre- or postchemotherapy
- Cohorts treated with sequentially escalating doses of MDV3100 (30-600 mg/day)

Slows tumor growth and causes cell death in cancers resistant to bicalutamide[a]



a. Tran C, et al. *Science*. 2009;324:787-790.
b. Scher HI, et al. *Lancet*. 2010;375:1437-1446.

MDV3100

Long-term Follow-up

Antitumor activity durable both before and after chemotherapy

Outcome	Chemotherapy Naive (n = 65)	Post Chemotherapy (n = 75)
≥ 50% PSA decline from baseline, %	62	51
Median time to PSA progression, days		
• Per protocol*	NYR	316
• PCCTWG 2 criteria†	281	148
Median time to radiographic progression, days	392	175

*≥ 25% increase in PSA from baseline with increase ≥ 5 ng/mL.

†≥ 25% increase in PSA from nadir with increase ≥ 2 ng/mL.

Higano CS, et al. ASCO GU 2011. Abstract 134.

MDV3100

AFFIRM: Study Design

Phase 3, multinational, double-blind, placebo-controlled

MDV3100 160 mg/day vs placebo (2:1 randomization)

Enrollment completed November 2010

N = 1,199 enrolled

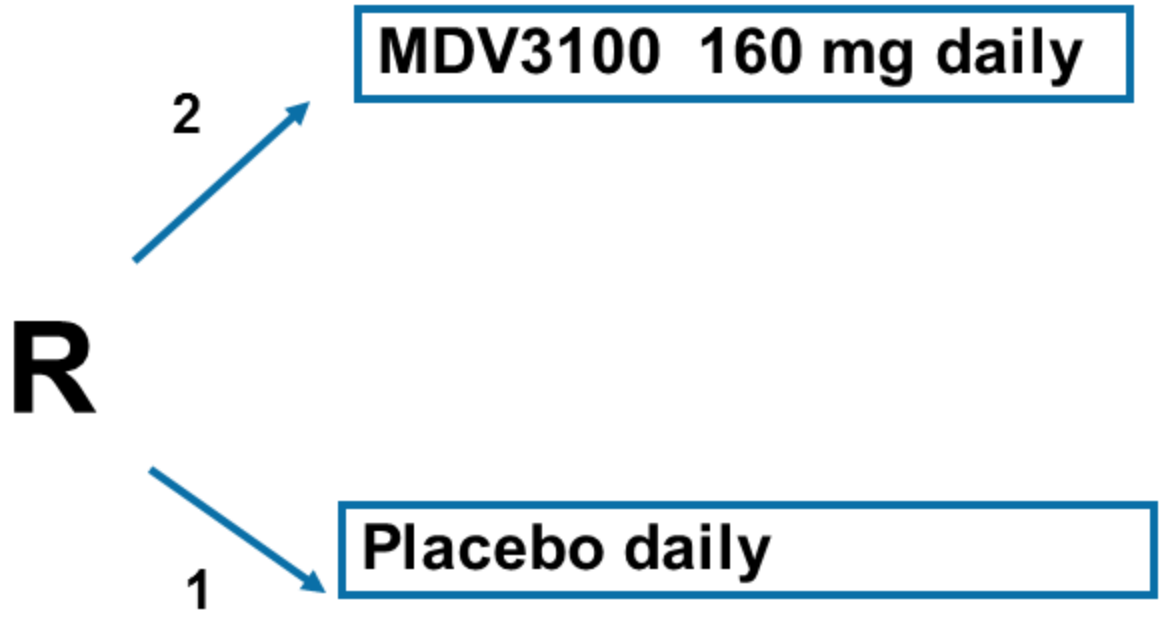
Patient population:

- Progressive mCRPC
- Ongoing ADT or orchiectomy
- Previously treated with chemotherapy (≤ 2 regimens) at least one of which was docetaxel-based
- ECOG Performance Status 0-2

ClinicalTrials.gov Identifier: NCT00974311.

AFFIRM

Post-Chemotherapy Phase 3 trial



OS primary endpoint

Interim analyses after 520 deaths

Steroid use was optional for MDV3100

ClinicalTrials.gov Identifier: NCT00974311.

AFFIRM
Study Objectives

Primary objective

- Overall survival

Key Secondary objectives

- Radiographic progression-free survival
- Time to first skeletal-related event
- QoL – FACT-P and EQ-5D
- PSA Progression
- Pain Palliation
- Safety
- Pharmacokinetics

ClinicalTrials.gov Identifier: NCT00974311.

AFFIRM

Planned Interim Analysis

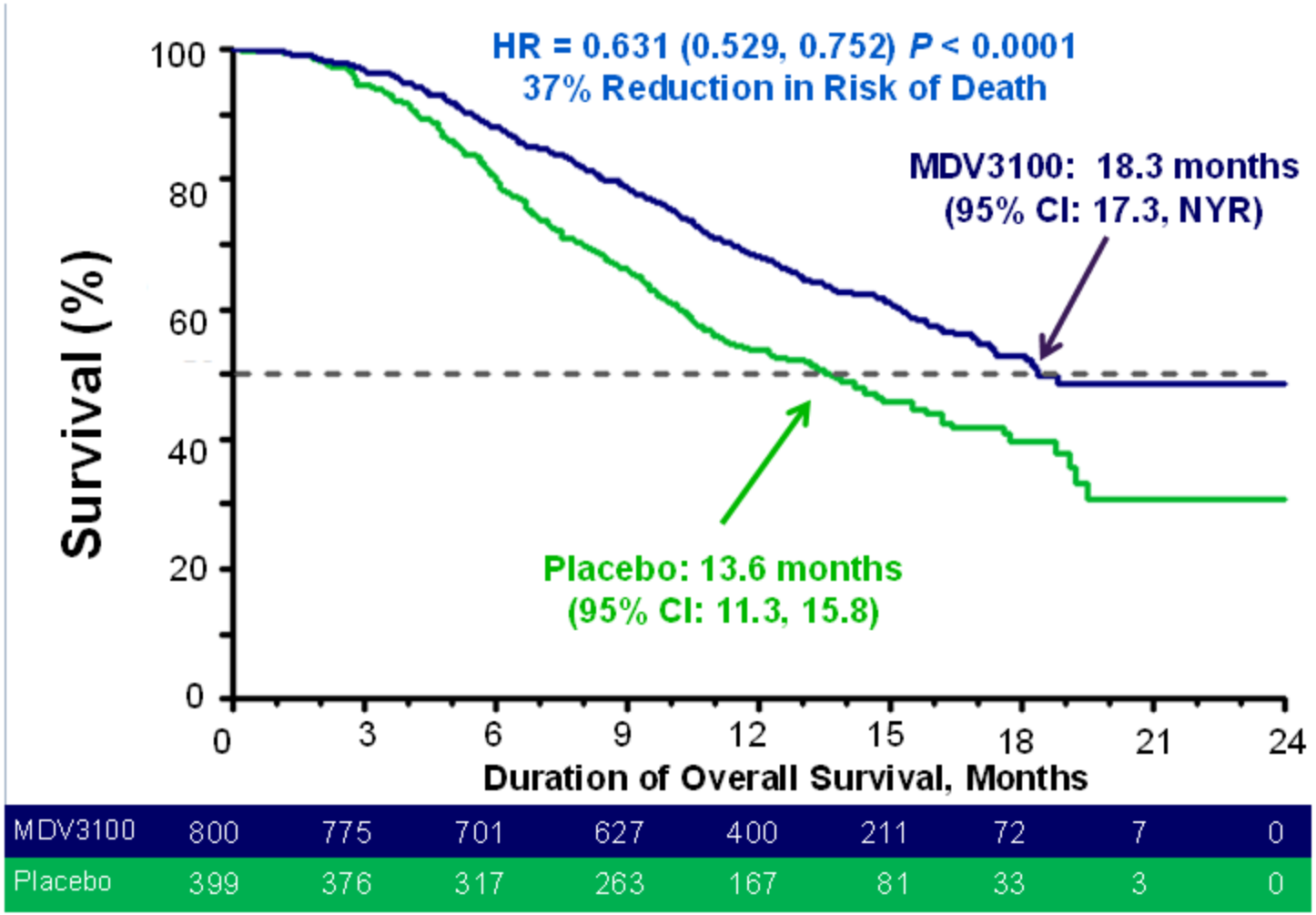
Independent Data Monitoring Committee recommended stopping the study early:

- 520 events at the time of the interim analysis
- Statistically significant improvement in overall survival MDV3100 compared to placebo
- Met pre-determined stopping criteria
- Favorable benefit-risk ratio
- Placebo patients should be crossed over to MDV3100

ClinicalTrials.gov Identifier: NCT00974311.

AFFIRM

MDV3100 Prolongs Survival



Scher HI, et al. ASCO GU 2012. LBA1.

Presentation Overview

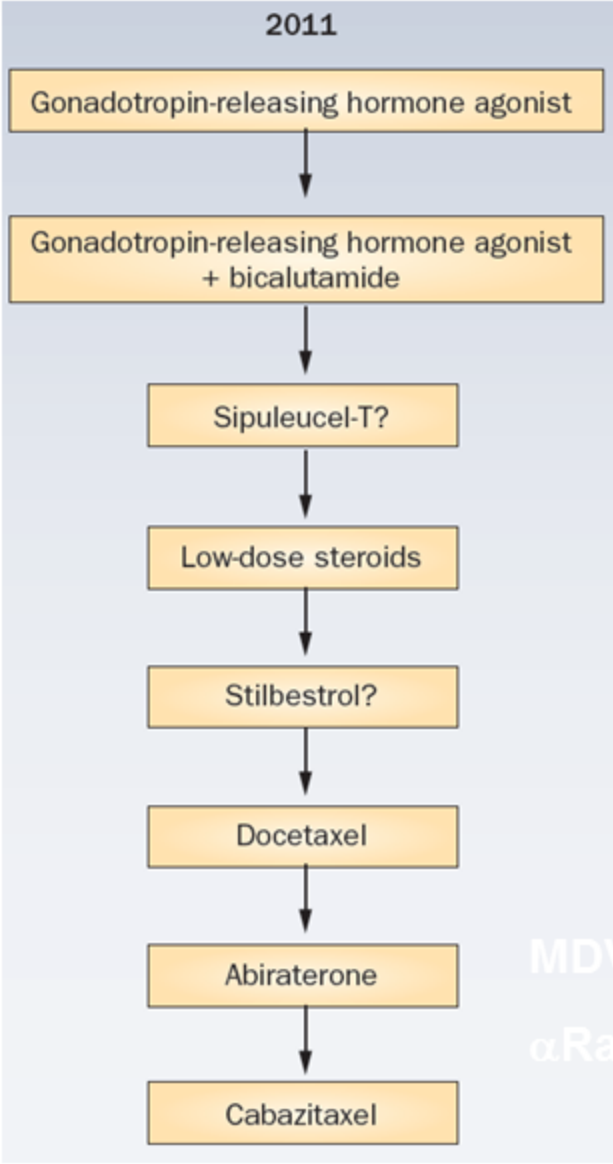
- Insight into disease biology: Key therapeutic targets
- Improving treatment: Changing landscape
- **Future challenges**

CRPC

Current Landscape

Multiple lines of treatment for advanced prostate cancer that improve OS: Sipuleucel-T, docetaxel, abiraterone, cabazitaxel, MDV3100, alpharadin

- Optimal sequence of administration now needs defined: Combinations!
- Cross-resistance: taxanes, abiraterone and MDV3100?
- Abiraterone now being evaluated in large adjuvant trial (STAMPEDE)



Yap TA, et al. *Nat Rev Clin Oncol*. 2011;8:597-610.

AR Signaling as Therapeutic Target
Conclusion

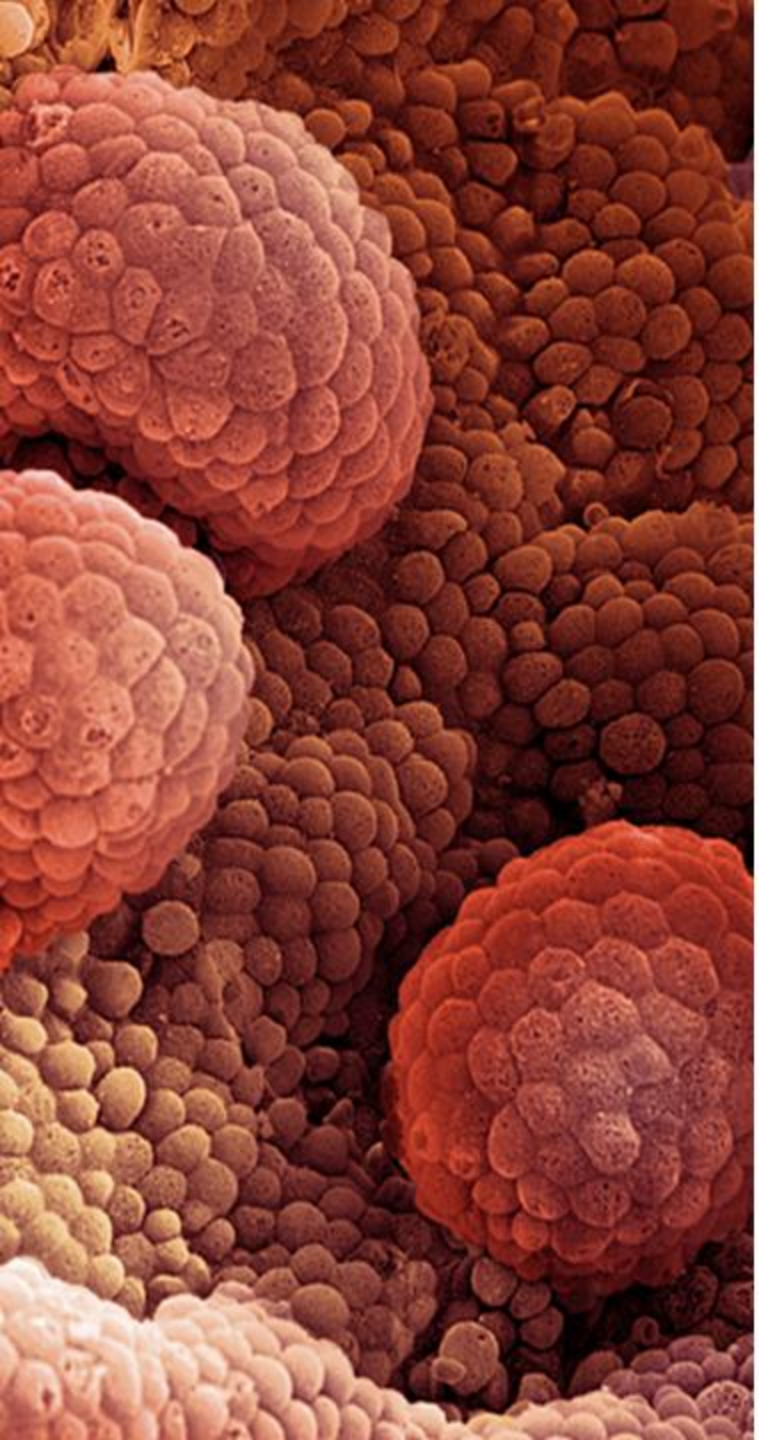
Advanced prostate cancer

- Not hormone refractory
- Nor androgen independent
- Remains nuclear steroid receptor driven even after AA and MDV3100

Hormone therapy works after chemotherapy

- Important since OS remains only robust registration endpoint

Maximal androgen blockade is a misnomer



Preclinical and Early Clinical Validation of Targeting Src/SFKs in Prostate Cancer:

A Review of The Evidence

Fred Saad, MD
Professor and Chairman of Urology
Director, Urologic Oncology
U of M Endowed Chair in Prostate Cancer
CHUM/University of Montreal
Canada

Medscape Oncology
EDUCATION

Disclosure

Fred Saad, MD, FRCS

Served as an advisor or consultant for: Amgen Inc.; Novartis Pharmaceuticals Corporation; Janssen Pharmaceutica Products, LP; sanofi-aventis

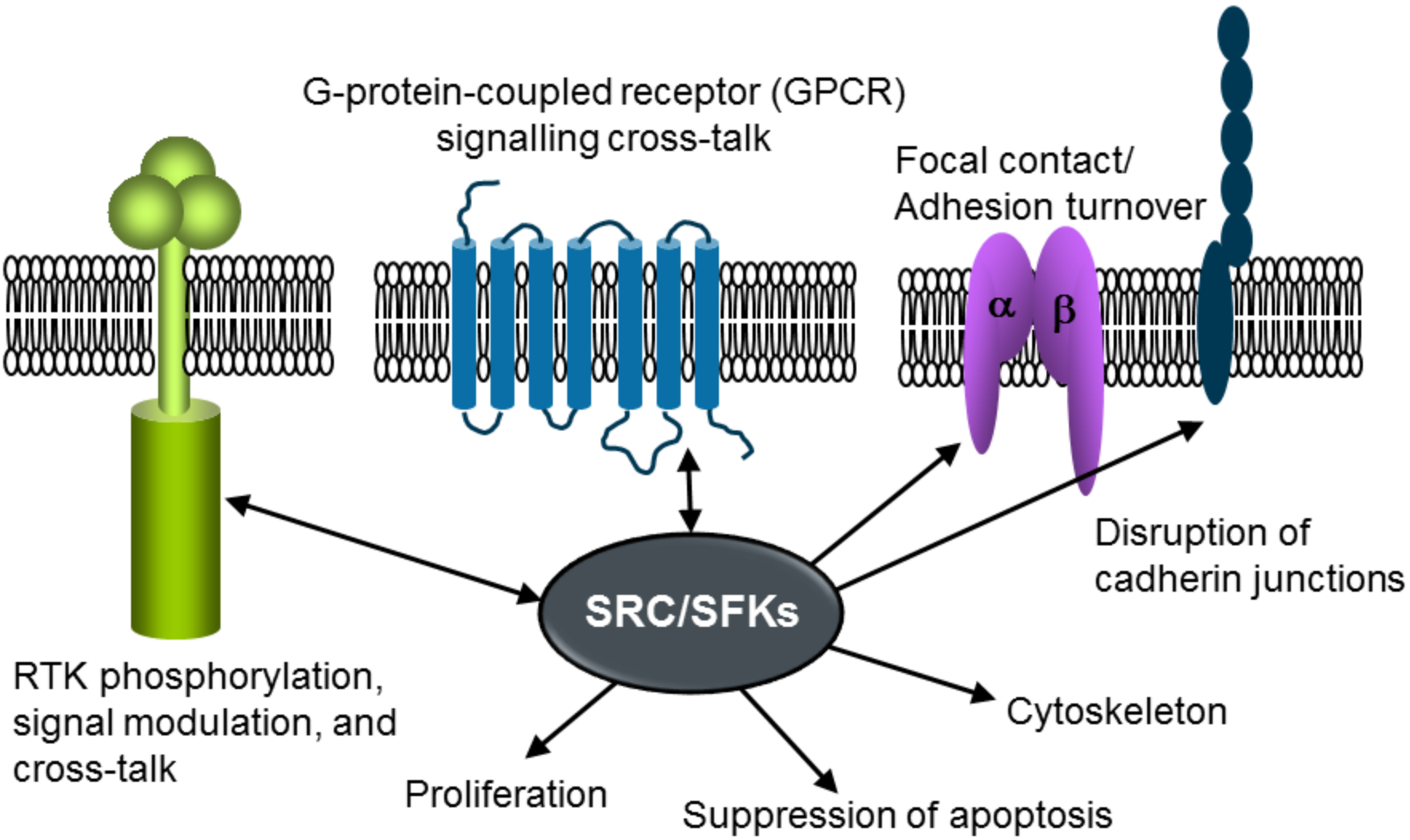
Served as a speaker or a member of a speakers bureau for: Amgen Inc.; Novartis Pharmaceuticals Corporation; Janssen Pharmaceutica Products, L.P; sanofi-aventis

Received grants for clinical research from: Amgen Inc.; Cougar Biotechnology, Inc.; Medivation, Inc.; Bristol-Myers Squibb Company

Dr. Said does not intend to discuss off-label uses of drugs, mechanical devices, biologics, or diagnostics approved by the FDA for use in the United States.

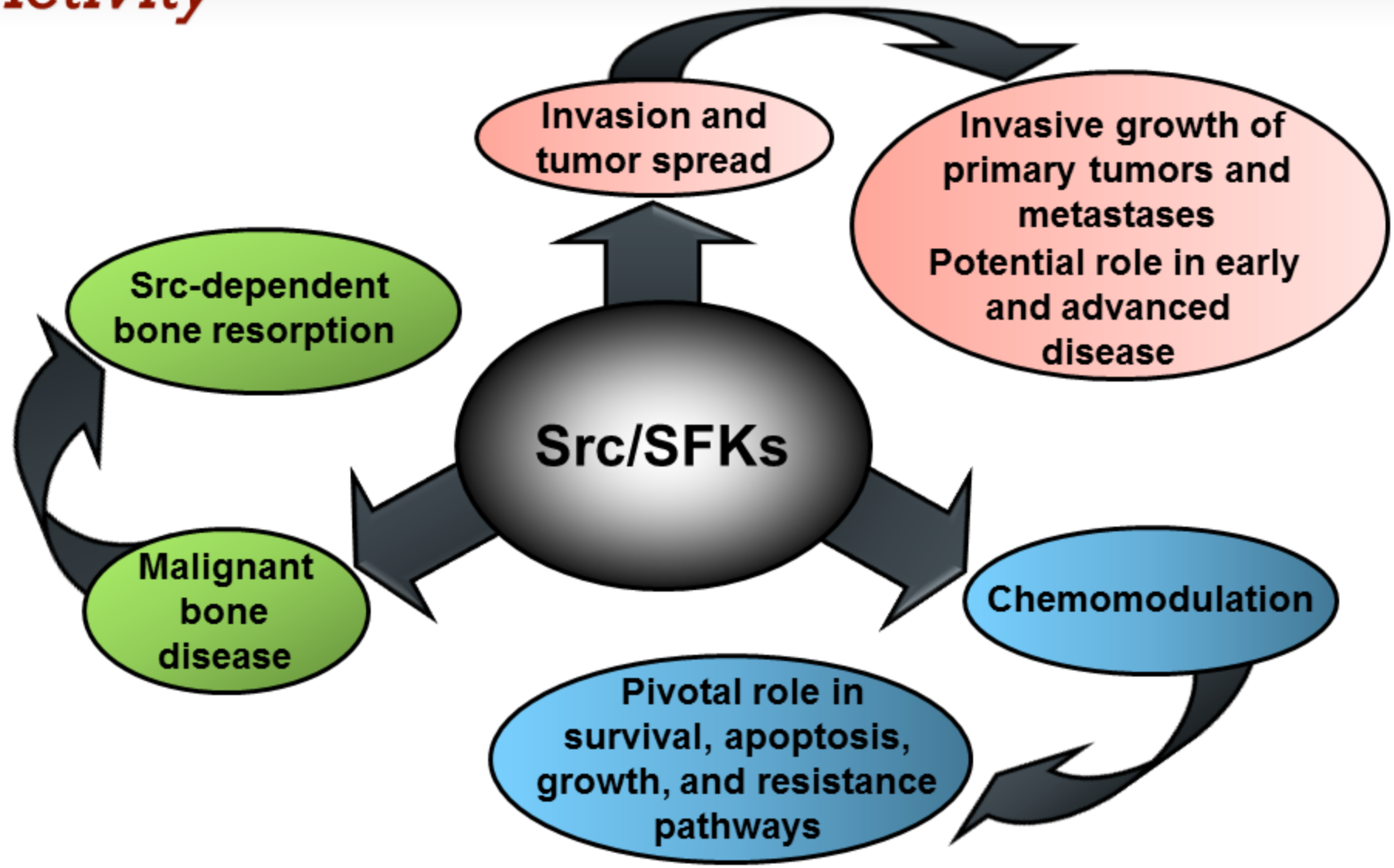
Dr. Saad does not intend to discuss investigational drugs, mechanical devices, biologics, or diagnostics not approved by the FDA for use in the United States.

Src/SFKs
Key Role in Cancer Signalling Pathways



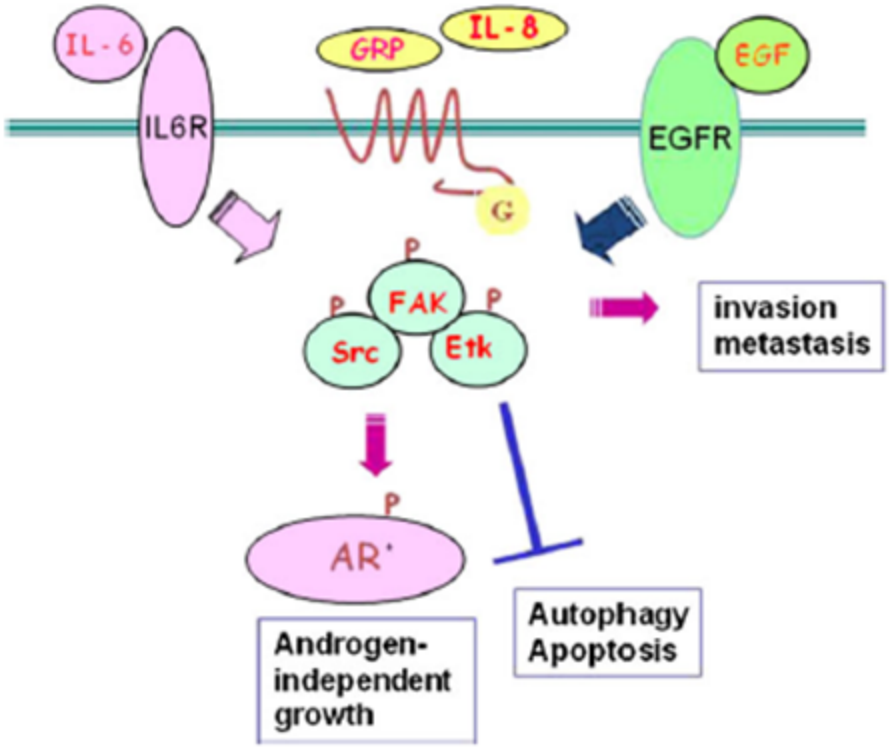
Fizazi K. *Ann Oncol.* 2007;18:1765-1773.

Src/SFKs
Activity

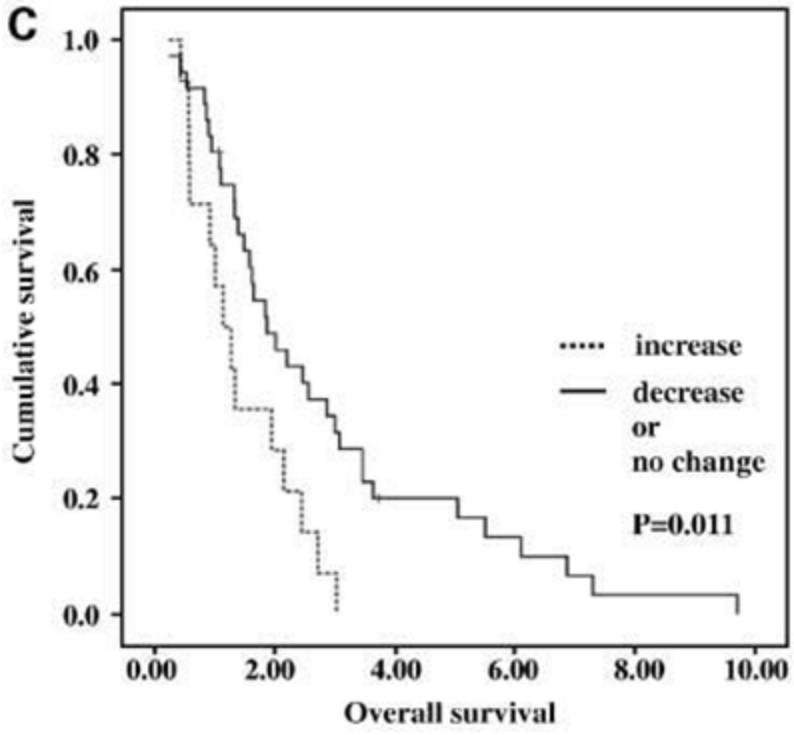


Fizazi K. *Ann Oncol.* 2007;18:1765-1773.

Increased Src/SFK Activity
Transition From ASPC to CRPC



Antibody	Histoscores	
	ASPC	AIPC
Phospho-Src Y^{419}		
Cytoplasm	45 (18.75-80)	70 (40-90)
Membrane	20 (0-60)	50 (0-90)
Phospho-Src Y^{527}		
Cytoplasm	80 (50-112.5)	50 (20-90)
Membrane	50 (20-80)	20 (0-70)



Kung HJ. *Horm Cancer.* 2011;2:38-46.
Tatarov O. *Horm Cancer.* 2011;2:38-46.

mCRPC

Rationale for Src/SFKs Inhibition

- Src/SFK activity increased in PCa
- Src/SFK regulate osteoclast and osteoblast function
- Src/SFK inhibitors target:
  - Tumor cells and microenvironment
  - Deregulated pathways, both locally and at the site of metastatic disease

Inhibition should lead to reduction in

Tumor growth
Tumor metastasis
Bone resorption/complications
Tumor angiogenesis

Fizazi K. *Ann Oncol.* 2007;18:1765-1773.
Chang YM, et al. *Neoplasia*. 2007;9:90-100.

mCRPC

Current Status of Src/SFKs Inhibitors

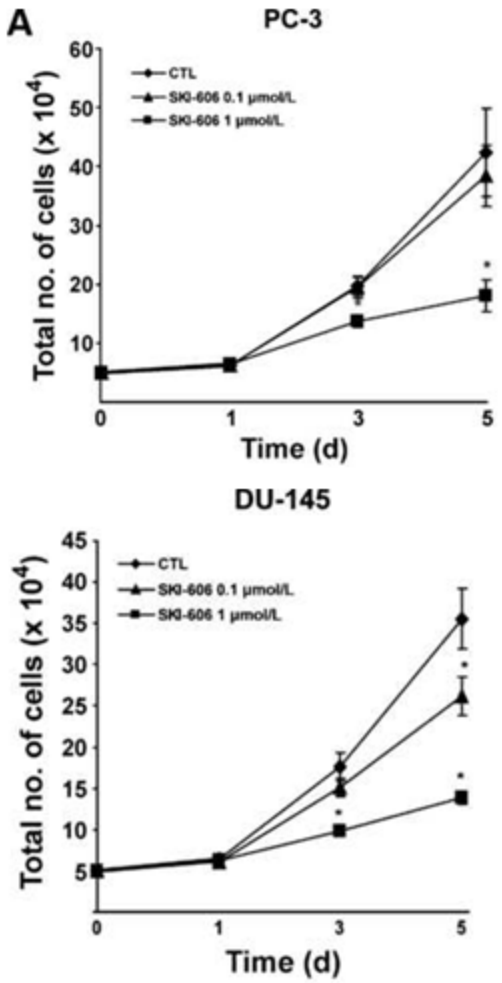
Agent	Target(s)	Development Stage
Bosutinib (SKI-606)	Src, Bcr-Abl	• Preclinical
KX2–391	Src	• Phase 2
Saracatinib (AZD0530)	Src, Bcr-Abl	• Phase 1 and 2 as monotherapy and in combinations
Dasatinib (BMS-354825)	Src/SFKs, Bcr-Abl, c-Kit, PDGFR, c-FMS, EphA2	• Phase 1 and 2 as monotherapy and in combinations • Phase 3 completed

Puls LN, et al. *Oncologist.* 2011;16:566-578.

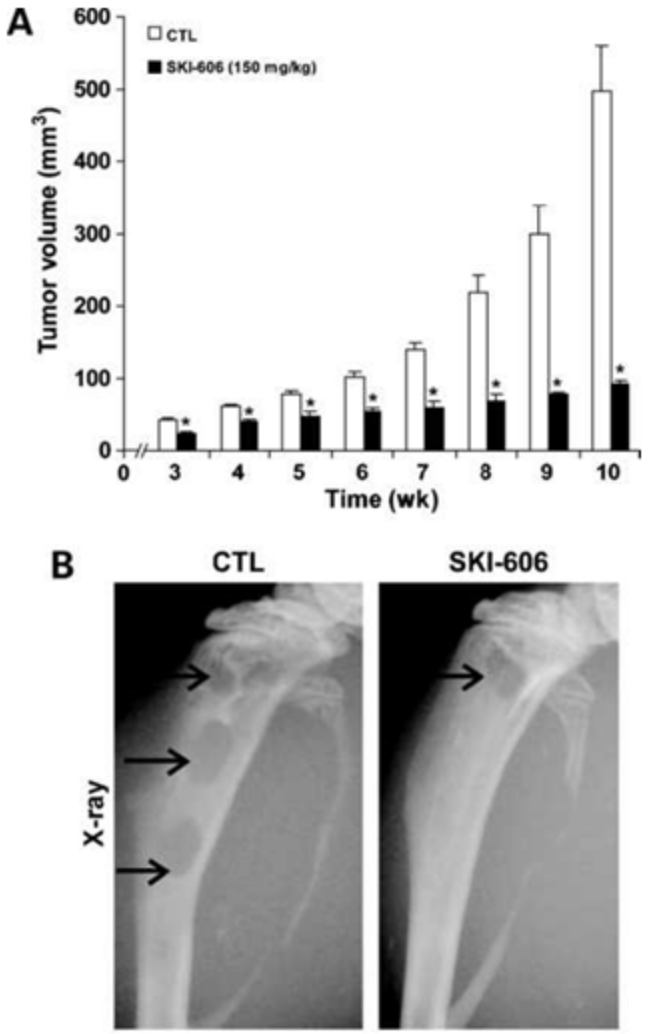
Bosutinib (SKI-606)

Blocks PCa Growth and Bone Metastasis

In vitro



In vivo



Rabbani SA, et al. *Mol Cancer Ther.* 2010;9:1147-1157.

KX2-391

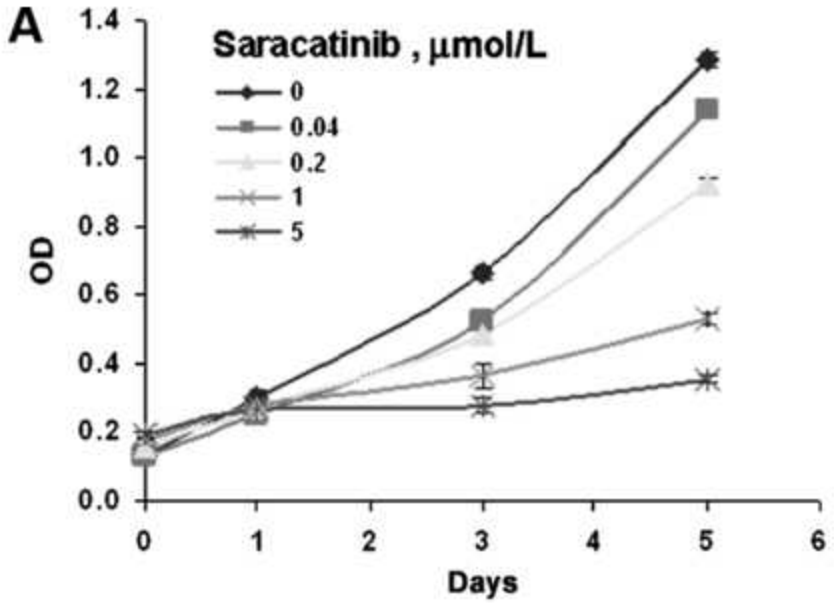
Substrate-Binding Pocket Inhibitor

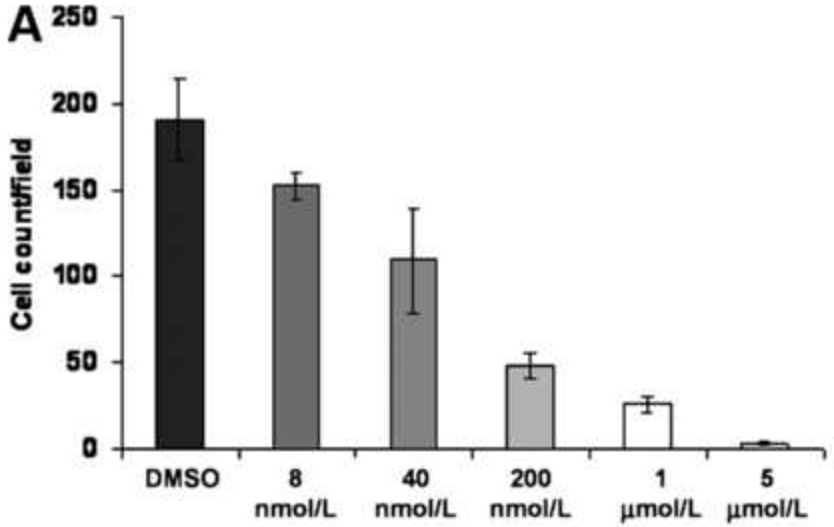
- Wider spectrum of *in vitro* activity in solid tumors
- More potent in mouse xenografts models than other Src/SFK/Abl kinase inhibitors
- Also inhibits microtubule polymerization
- Phase 1 data demonstrated biologic activity in a patient with PCa (PSA: 205 ng/ml → 39 ng/ml)
- DLTs (eg, elevated transaminases, neutropenia, and fatigue) were reversible within 7 days
- Phase 2 study completed; data pending

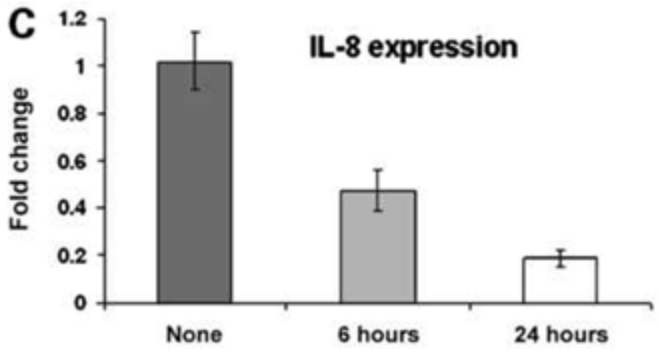
Puls LN, et al. *Oncologist.* 2011;16:566-578.
Adjei AA, et al. *J Clin Oncol.* 2009;27(15 suppl):Abstract 3511.
ClinicalTrials.gov Identifier: NCT00646139.

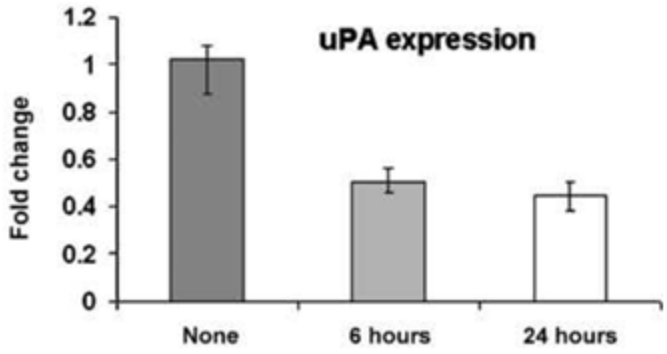
Saracatinib (AZD0530)

Inhibits PC-3 Cell Growth and Invasion





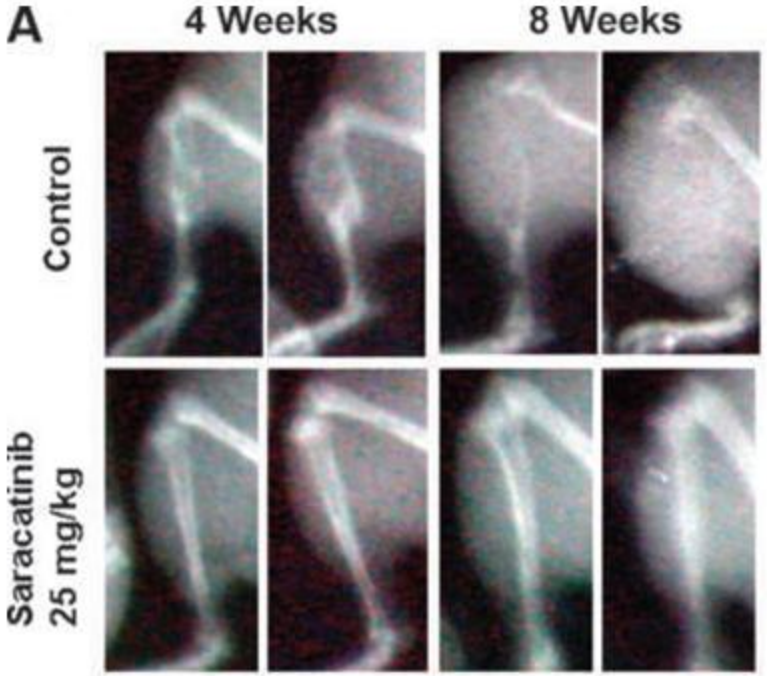


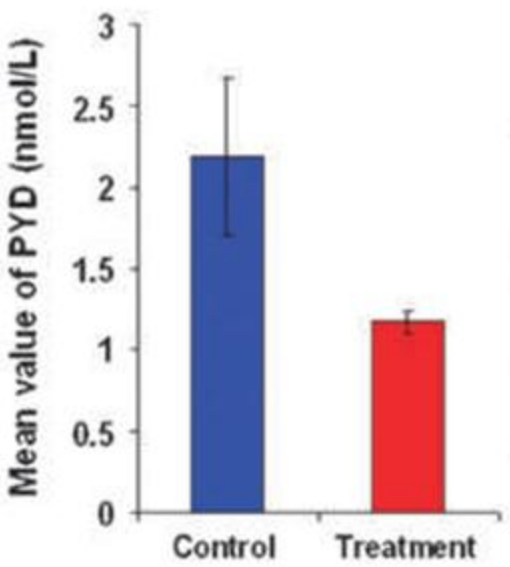


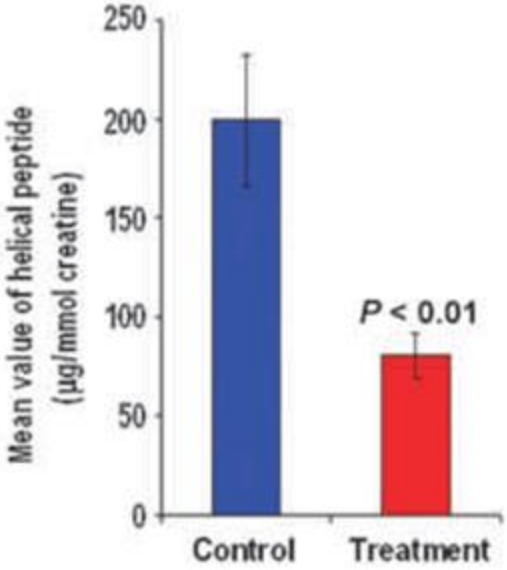
Yang JC, et al. *Mol Cancer Ther.* 2010;9:1629-1637.

Saracatinib (AZD0530)

Inhibits Osteolysis







- sCTX changed in the 50, 125 and 175 mg/d groups by -36%, -64% and -75%, respectively
- uNTX/Cr changed in the 50, 125 and 175 mg/d groups by; -13%, -48% and -50%, respectively

Yang JC, et al. *Mol Cancer Ther.* 2010;9:1629-1637.

Hannon RA, et al. *Bone.* 2012; Jan 8. [Epub ahead of print].

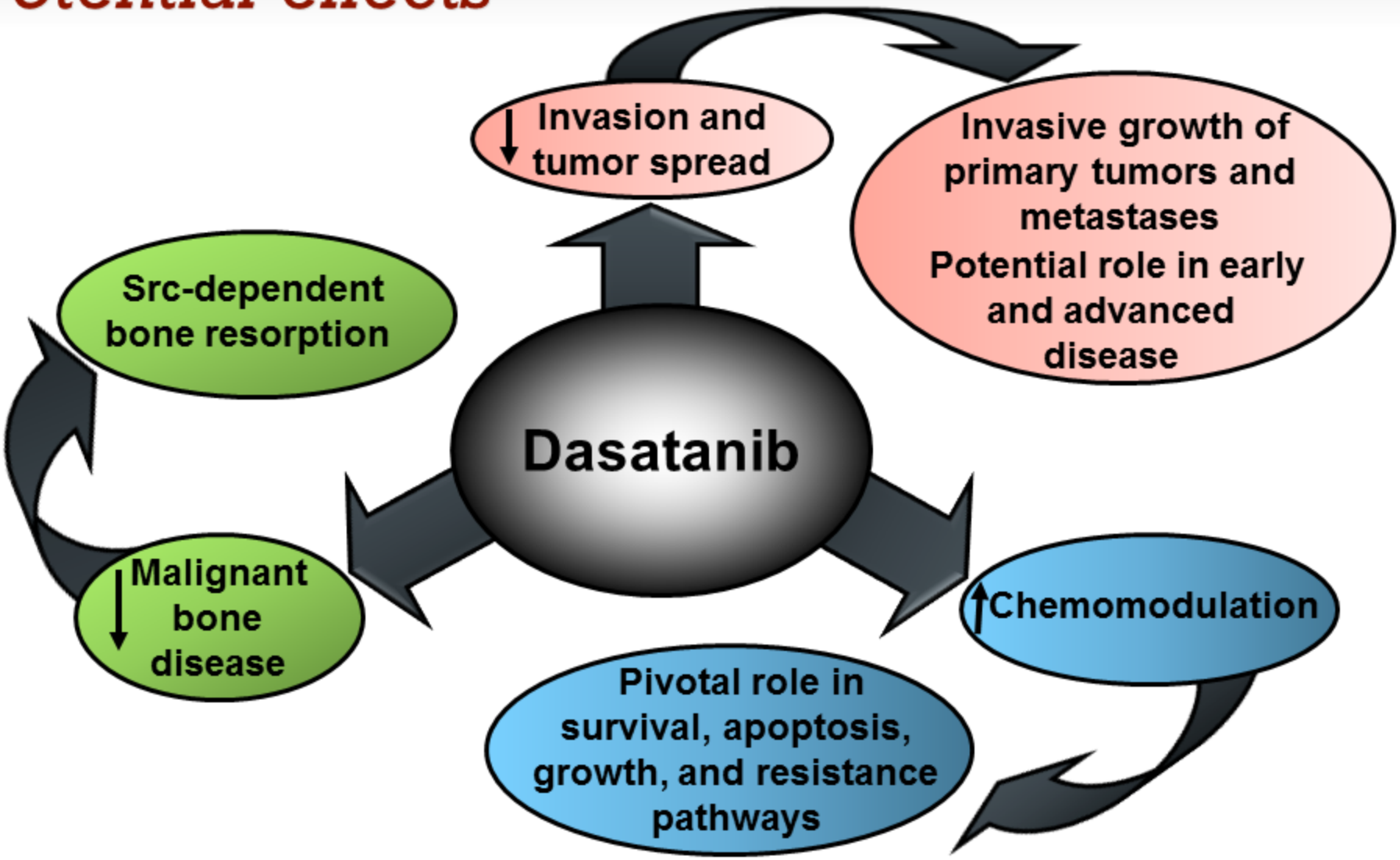
Saracatinib (AZD0530)
Phase 2 Trial in Advanced CRPC

- Single-arm, Simon two-stage trial of saracatinib monotherapy
- Five of 28 patients had a decline in PSA, however no patient achieved 30% decline
- Median PFS was 8 weeks
- Preclinical evidence warrants further investigation of saracatinib in earlier stage PCa or as combination therapy

Lara PN Jr., et al. *Anticancer Drugs.* 2009;20:179-184.

Dasatanib

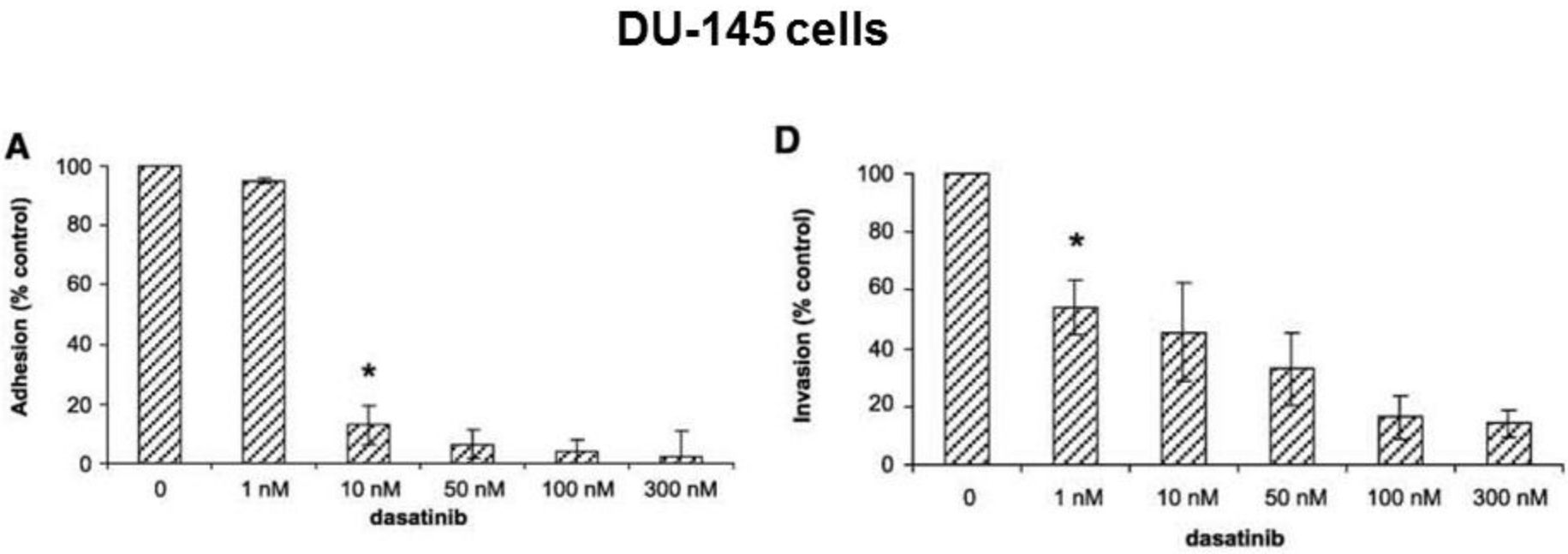
Potential effects



Adapted Fizazi K. *Ann Oncol.* 2007;18:1765-1773.

Dasatinib (BMS-354825)

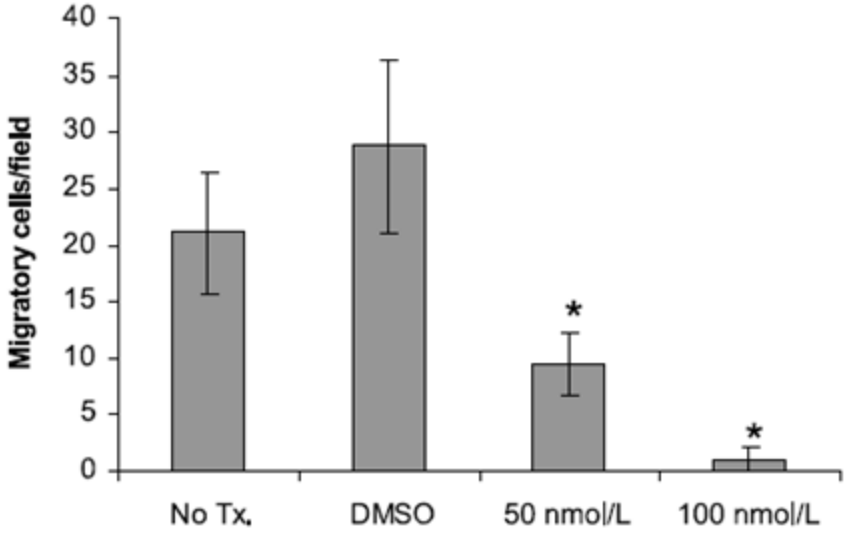
Inhibits PCa Cell Adhesion and Invasion

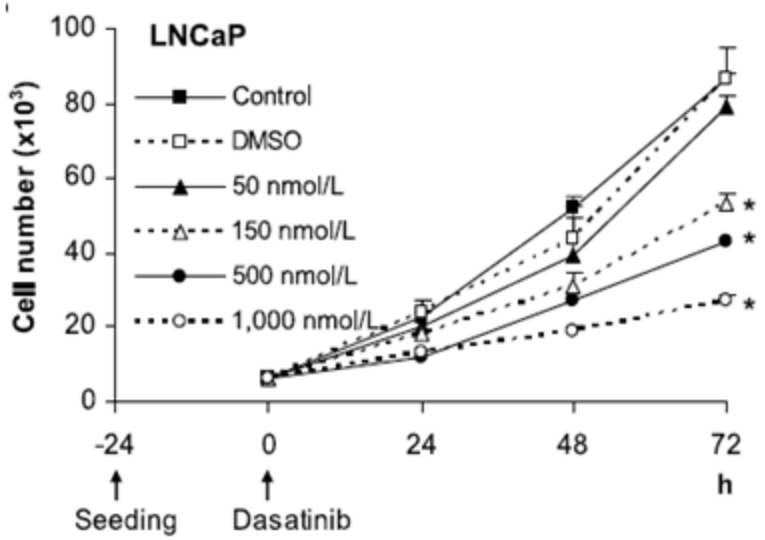


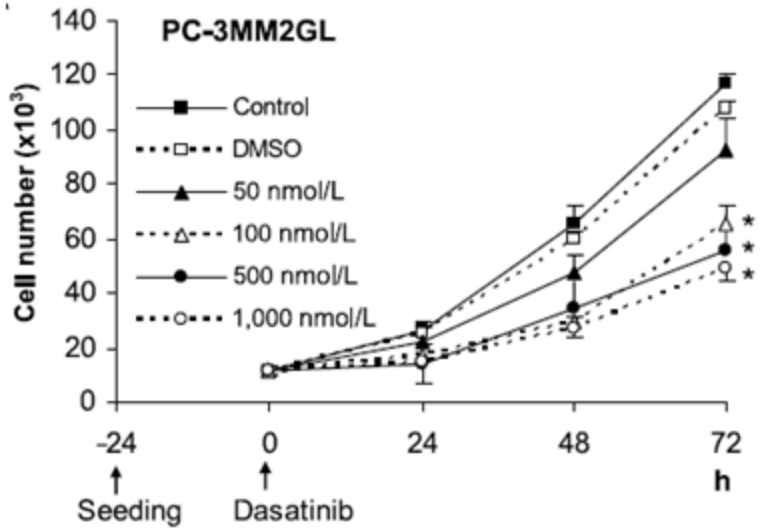
Nam S, et al. *Cancer Res.* 2005;65:9185-9189.

Dasatinib (BMS-354825)

Inhibits PCa Proliferation and Migration



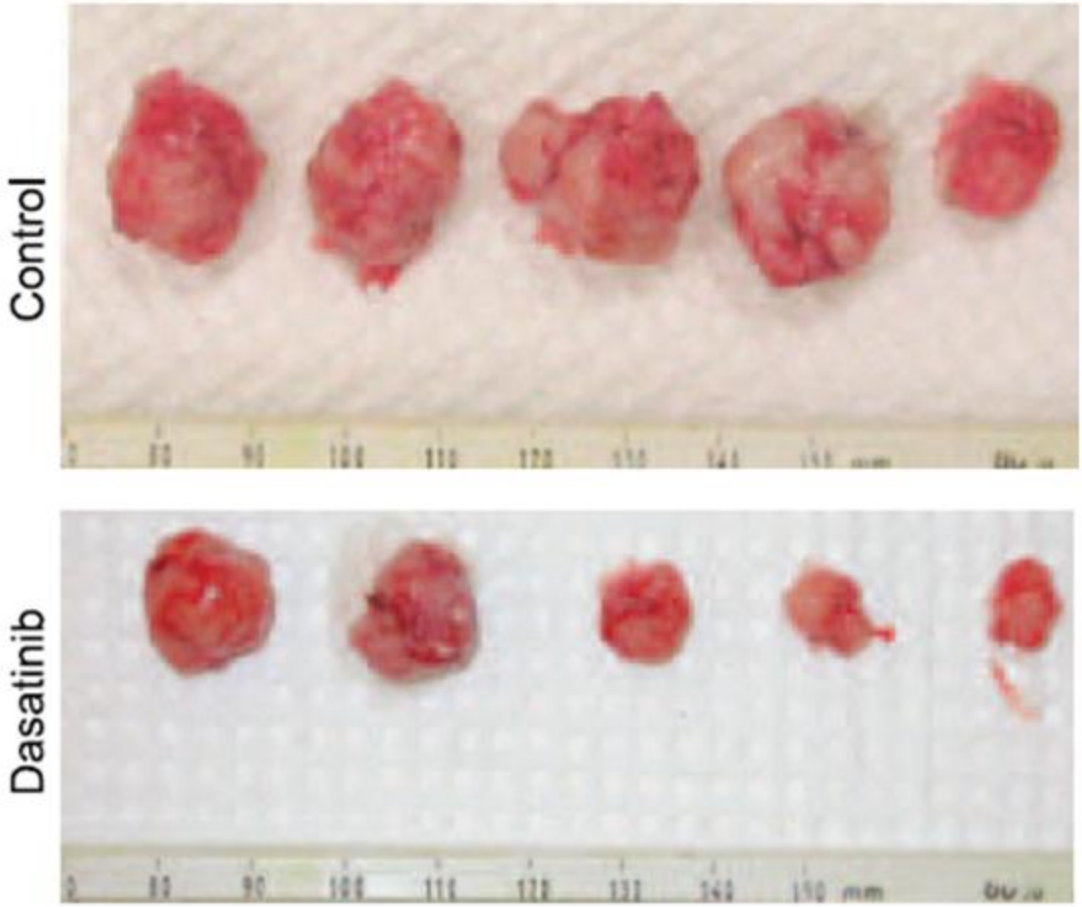




Park SI, et al. *Cancer Res.* 2008;68:3323-3333.

Dasatinib (BMS-354825)

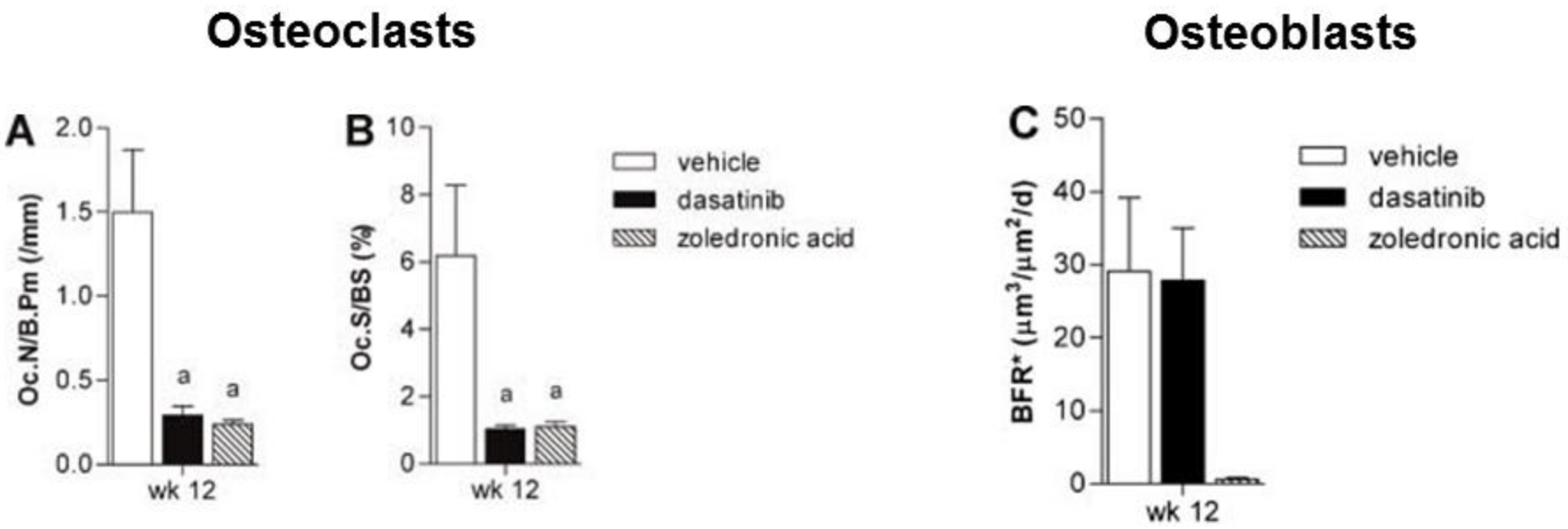
Inhibits Lymph Node Metastases



Park SI, et al. *Cancer Res.* 2008;68:3323-3333.

Dasatinib (BMS-354825)

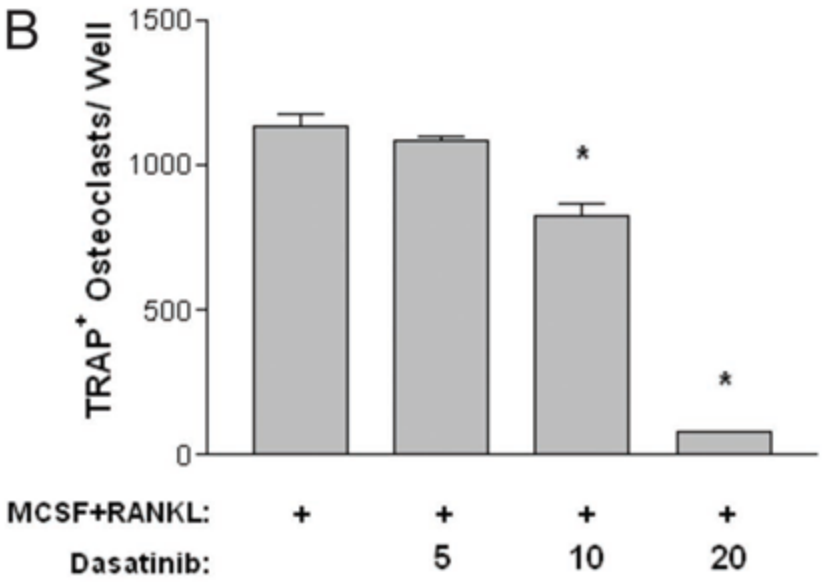
Effects on Osteoclasts vs Osteoblasts

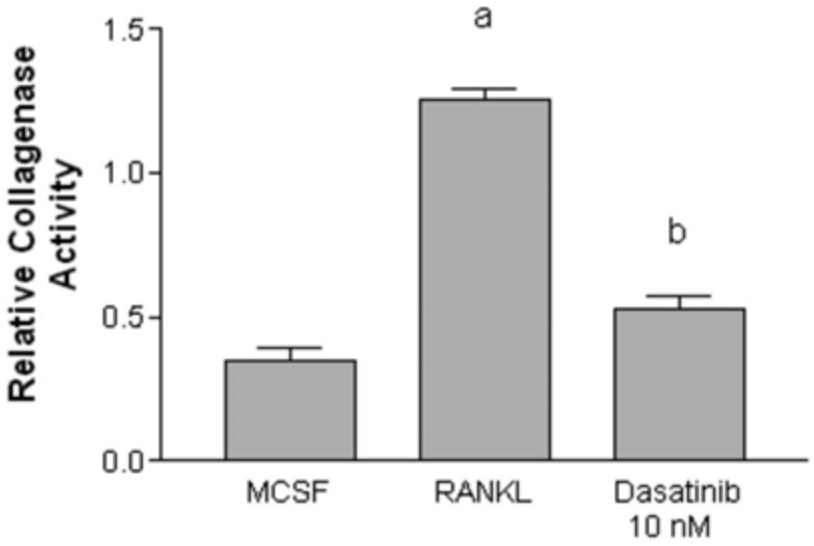


Vandyke K, et al. *J Bone Miner Res.* 2010;25:1759-1770.

Dasatinib (BMS-354825)

Blocks Osteoclast Formation and Activity

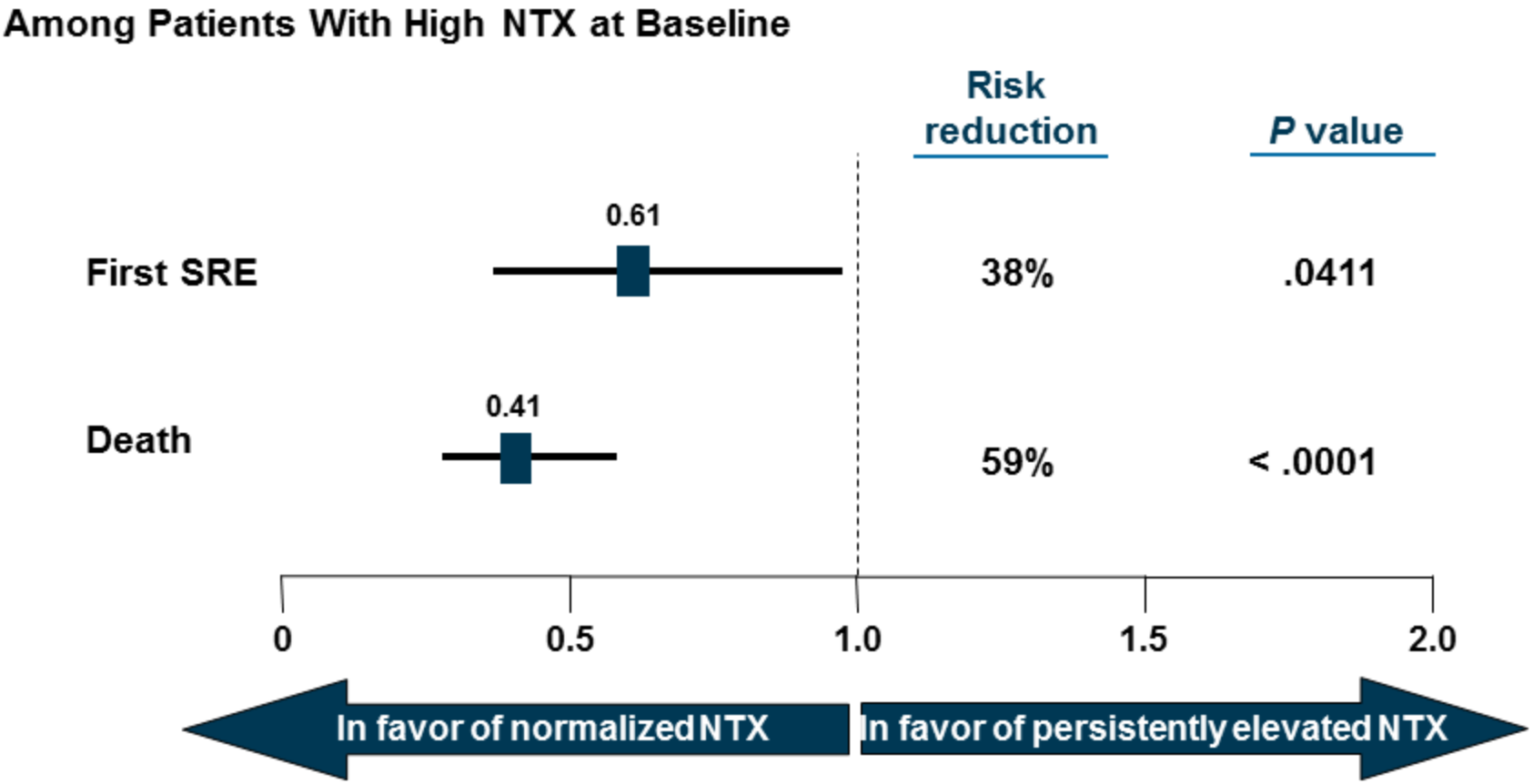




Araujo J, et al. *Cancer Biol Ther.* 2009;8:2153-2159.

Importance of Osteoclast Inhibition

Impact of NTX Levels in mCRPC



Saad F, et al. *Urol Oncol.* 2010 Dec 15. [Epub ahead of print].

Dasatinib as Monotherapy in CRPC

Results

25% of patients responded or had stable disease

PSA doubling time improved in 88% of evaluable patients

- 1 patients had a PSA response

51% of patients experienced a ≥40% decrease in uNTX levels

- 50% of patients who received bisphosphonates
- 52% of patients who did not receive bisphosphonates

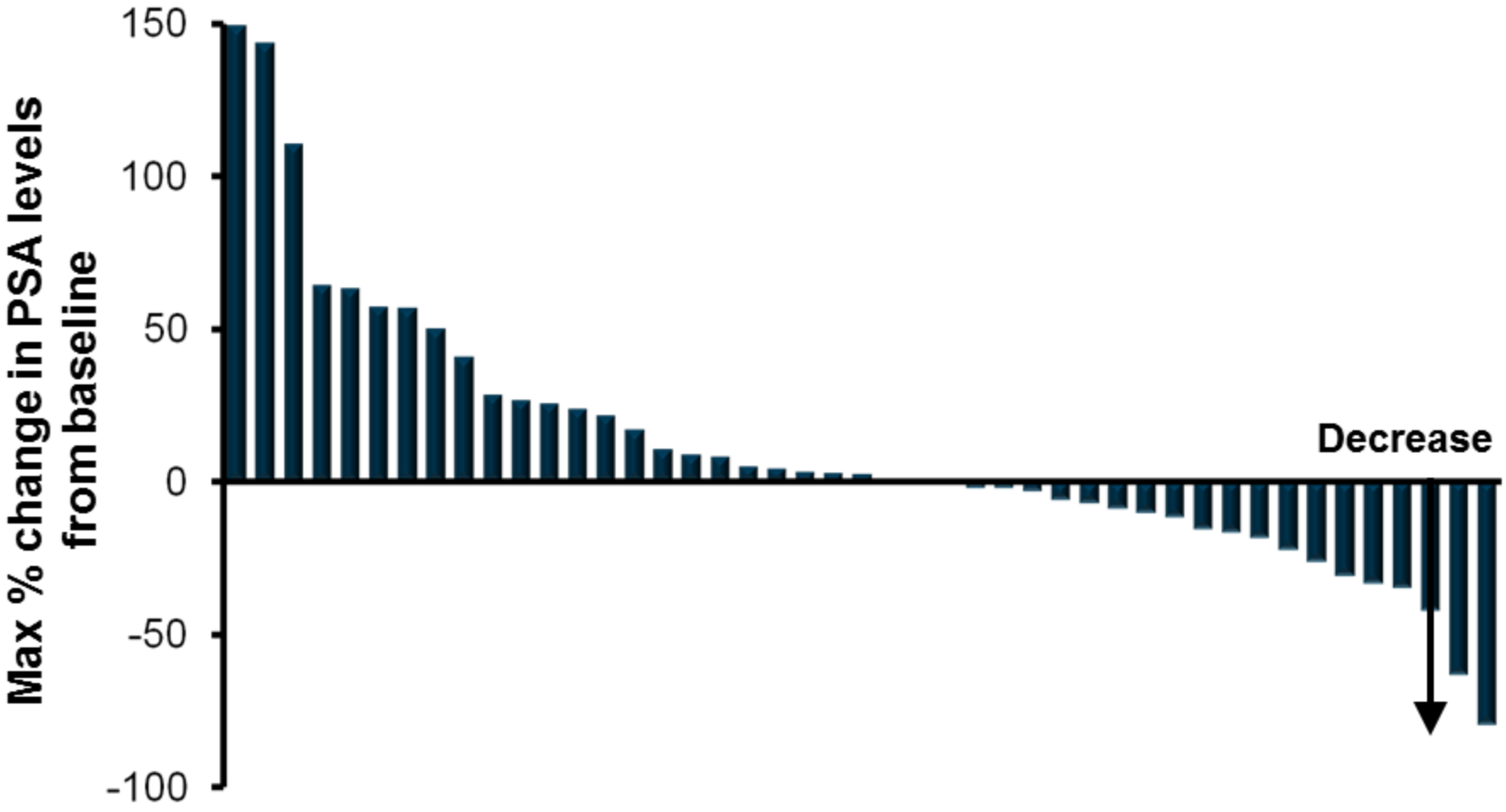
59% patients experienced a decrease in BAP levels

- 7 of 12 (58%) who received bisphosphonates
- 19 of 32 (59%) who did not receive bisphosphonates

Yu EY et al. Clin Cancer Res. 2009 Dec 1;15(23):7421-8

Dasatinib as Monotherapy in CRPC

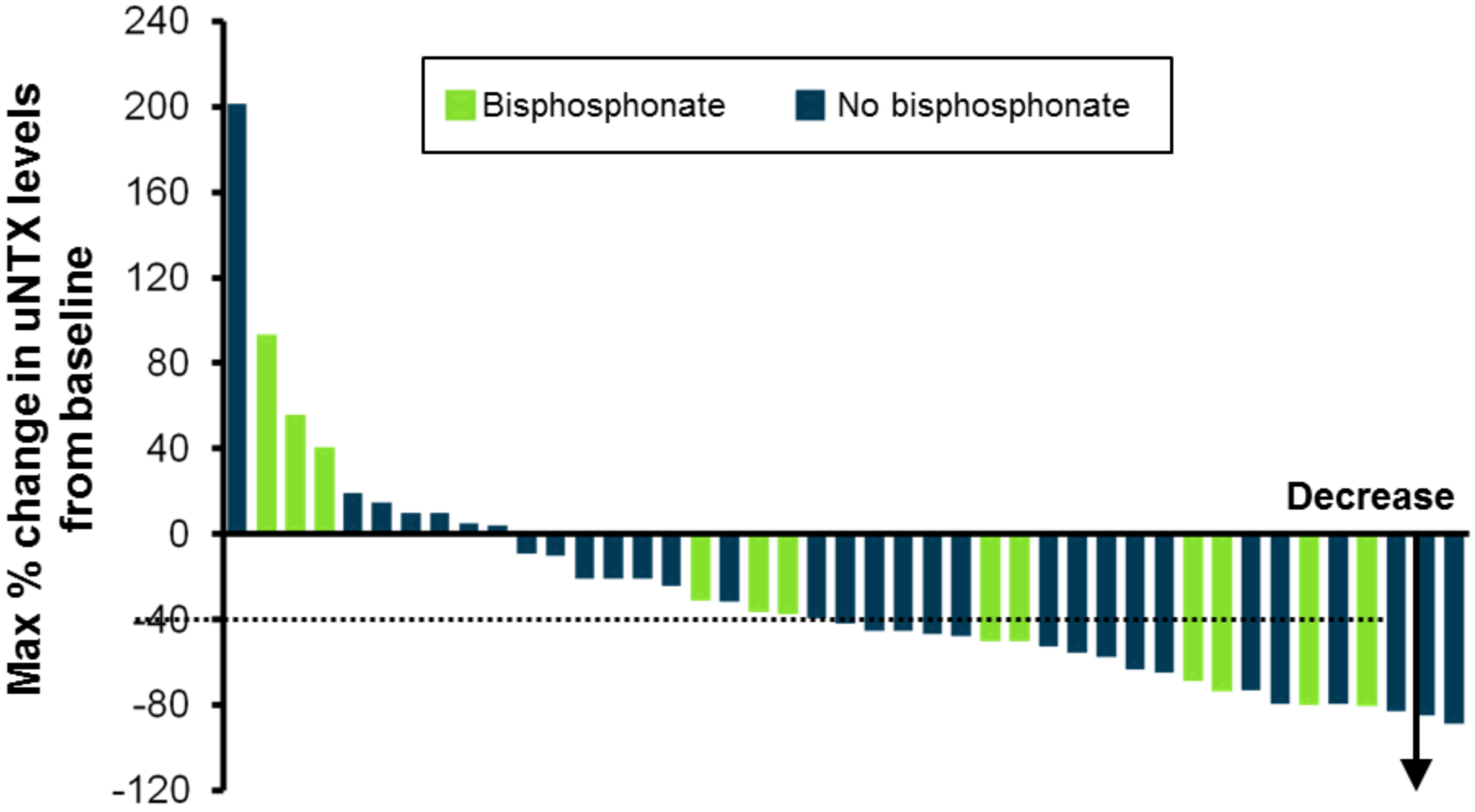
PSA Change



Yu EY et al. Clin Cancer Res. 2009 Dec 1;15(23):7421-8

Dasatinib as monotherapy in CRPC

uNTX Change



Yu EY et al. Clin Cancer Res. 2009 Dec 1;15(23):7421-8

Dasatinib as Monotherapy in CRPC

Treatment-Related AEs

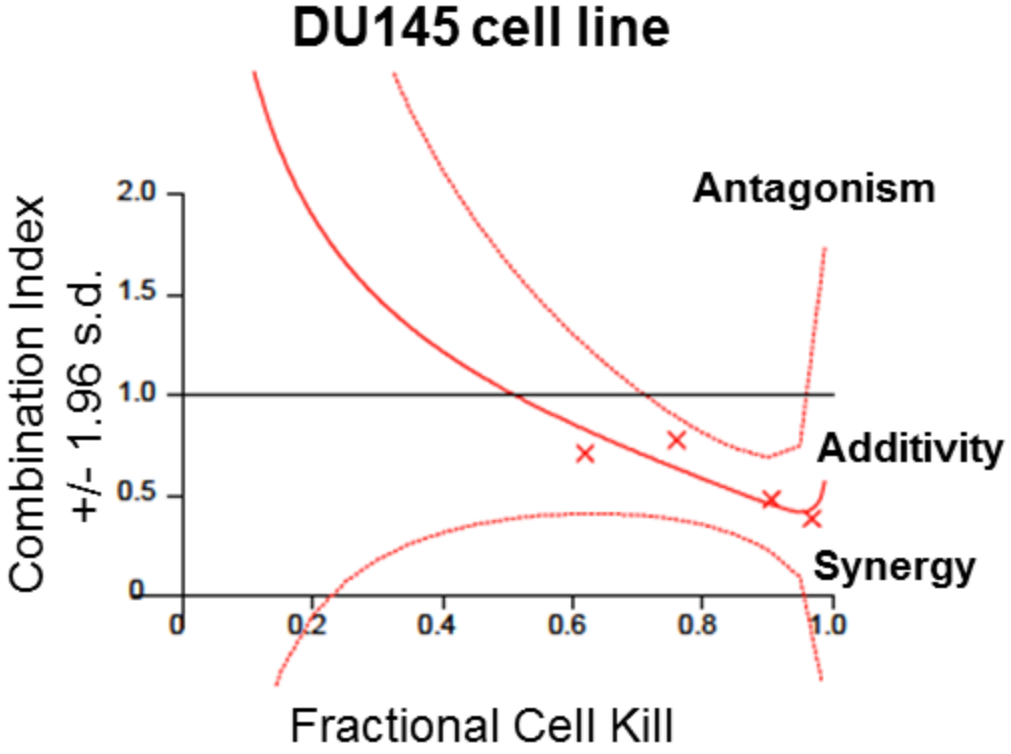
	100 mg QD (n=48)		BID dosing (n=47)[8]	
	Grade 1/2 (%)	Grade 3/4 (%)	Grade 1/2 (%)	Grade 3/4 (%)
Pleural effusion	17	2	49	2
Dyspnea	15	2	30	6
Asthenia	17	2	23	4
Constipation	15	2	4	0
Diarrhea	27	0	57	4
Nausea	27	0	45	2
Fatigue	44	0	34	11
Rash	13	0	34	0
Anorexia	21	0	36	0
Headache	27	0	38	0
Peripheral edema	8	0	21	0
Prolonged QT interval	4	0	19	0
Flushing	2	0	17	0
Pericardial effusion	2	0	23	0
Weight decrease	6	0	17	0
Any AE	77	13	68	32

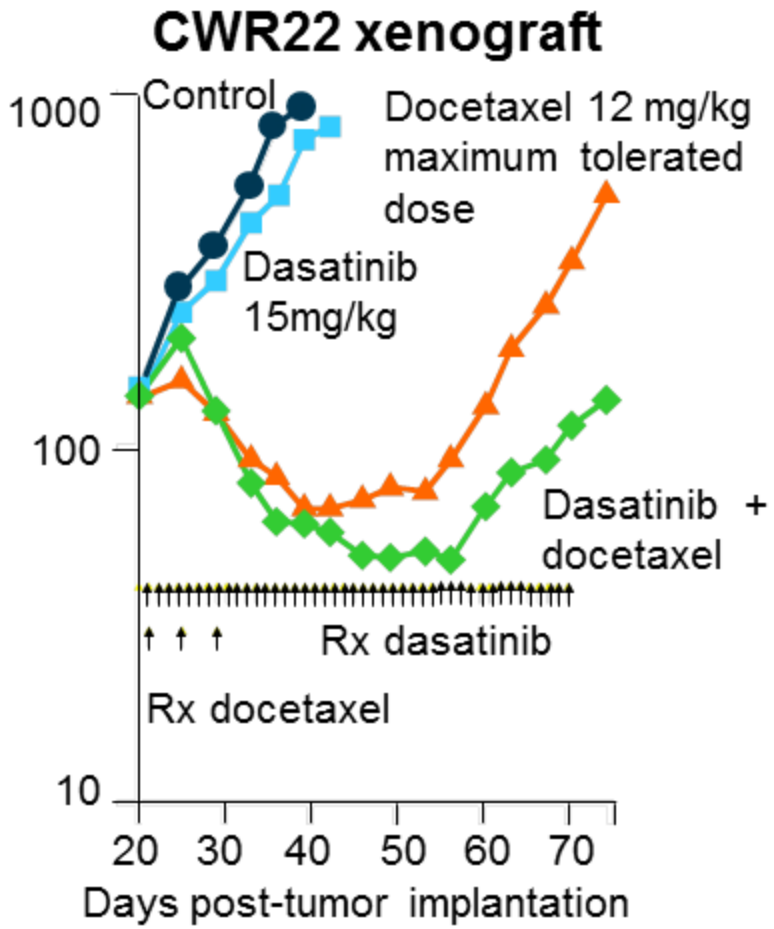
Yu EY et al. Clin Cancer Res. 2009 Dec 1;15(23):7421-8

Dasatinib Plus Docetaxel

Synergistic in Prostate Cancer Models

Improved tumor inhibition compared with single agent docetaxel in human CRPC cell lines and xenografts[a]





Das = dasatinib

a. BMS (Data on file).

Dasatinib Plus Docetaxel

Phase 1/2 Results

Phase I/II study of combination in patients with mCRPC

- Phase I: (dose-finding) 16 patients - 5 dose cohorts
- Phase II: additional 30 patients enrolled for treatment with dasatinib 100 mg QD and docetaxel 75 mg/m^2 Q21D

Araujo J, et al. *Cancer.* 2012;118:63-71.

Dasatinib Plus Docetaxel

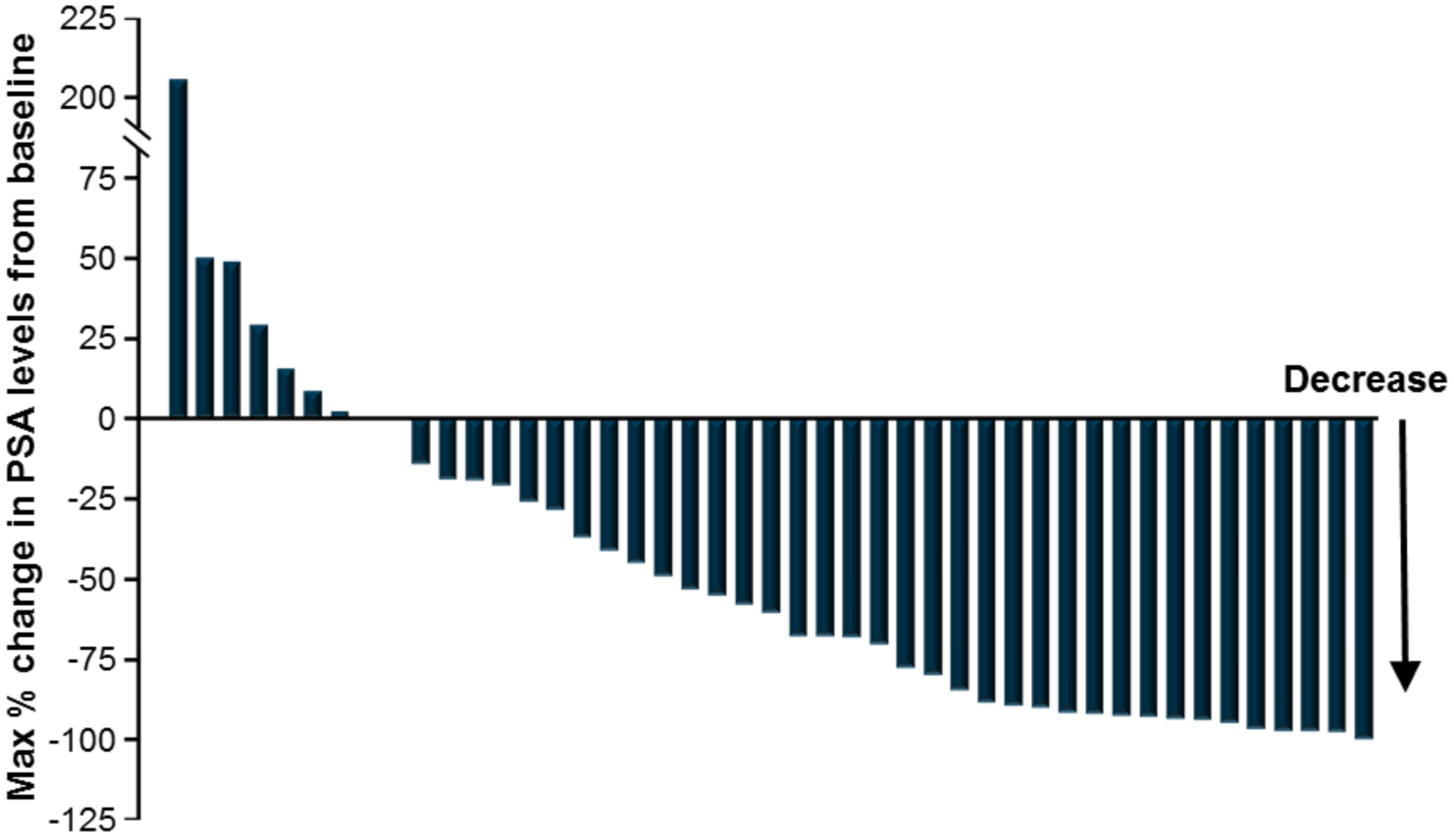
PSA Data

- 37 patients (80%) had a decrease in PSA from baseline
- 26 patients (57%) had a confirmed PSA response (sustained 50% decline for 6 weeks)

Araujo J, et al. *Cancer.* 2012;118:63-71.

Dasatinib Plus Docetaxel

PSA Change



Araujo J, et al. *Cancer.* 2012;118:63-71.

Dasatinib Plus Docetaxel

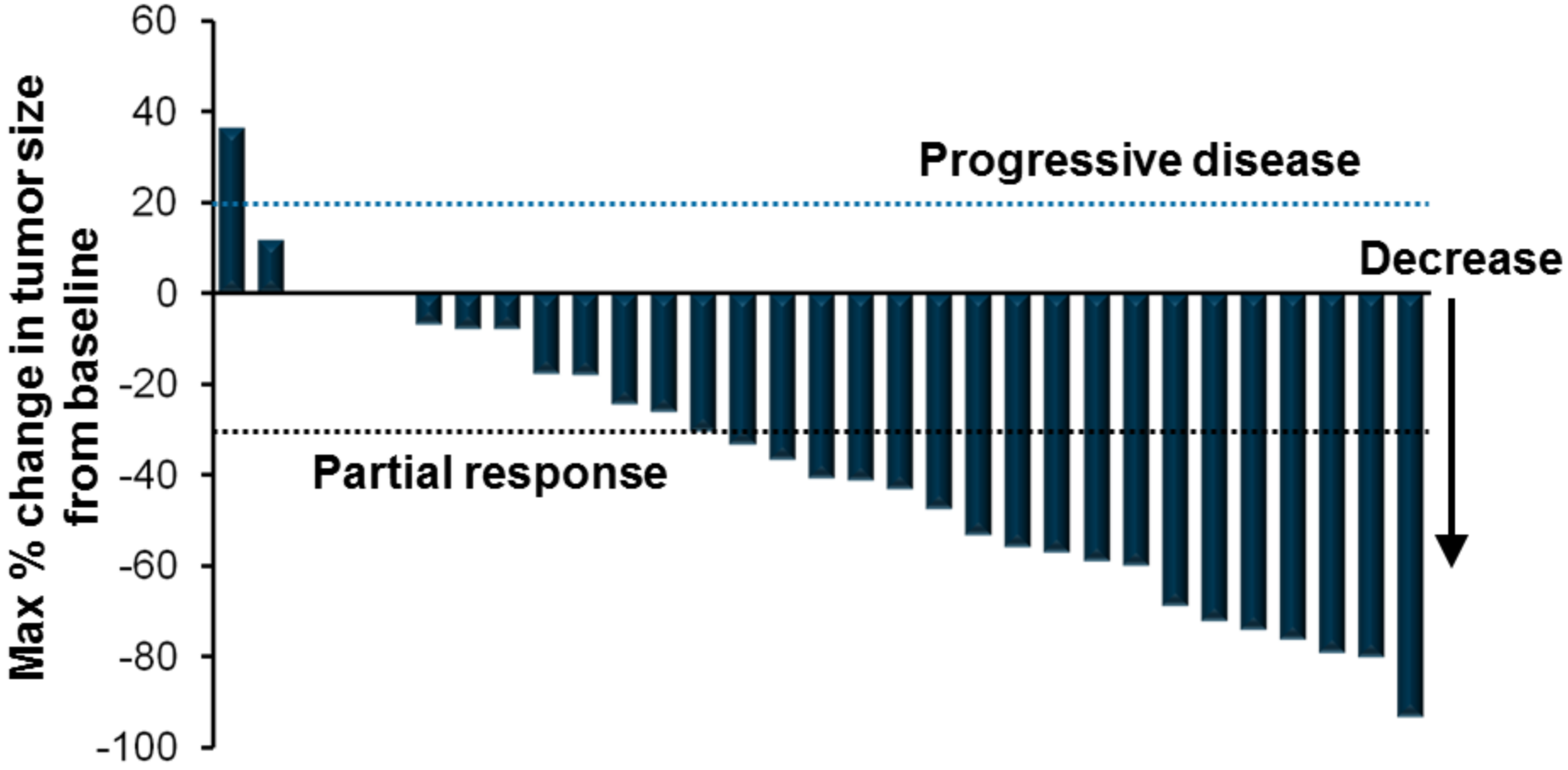
Best Tumor Response by RECIST

Patients	
RECIST-evaluable disease at baseline, n	30
On-study assessment, n	30
Responses, n/N (%)	
PR	18/30 (60)
SD (≥18 weeks)	5/30 (17)
Overall disease control rate (%)	**77**

Araujo J, et al. *Cancer.* 2012;118:63-71.

Dasatinib Plus Docetaxel

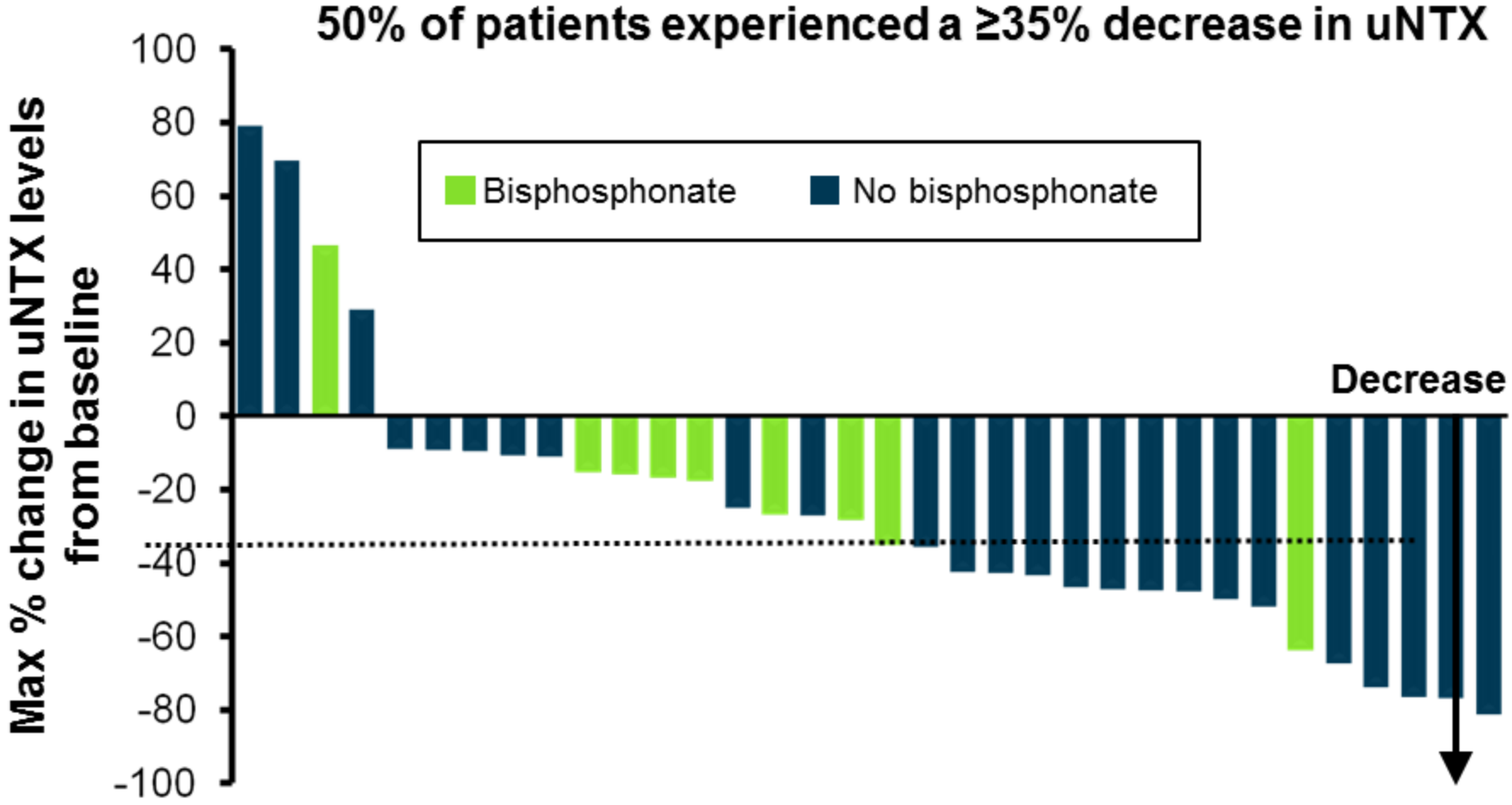
Tumor Size Change



Araujo J, et al. *Cancer.* 2012;118:63-71.

Dasatinib Plus Docetaxel

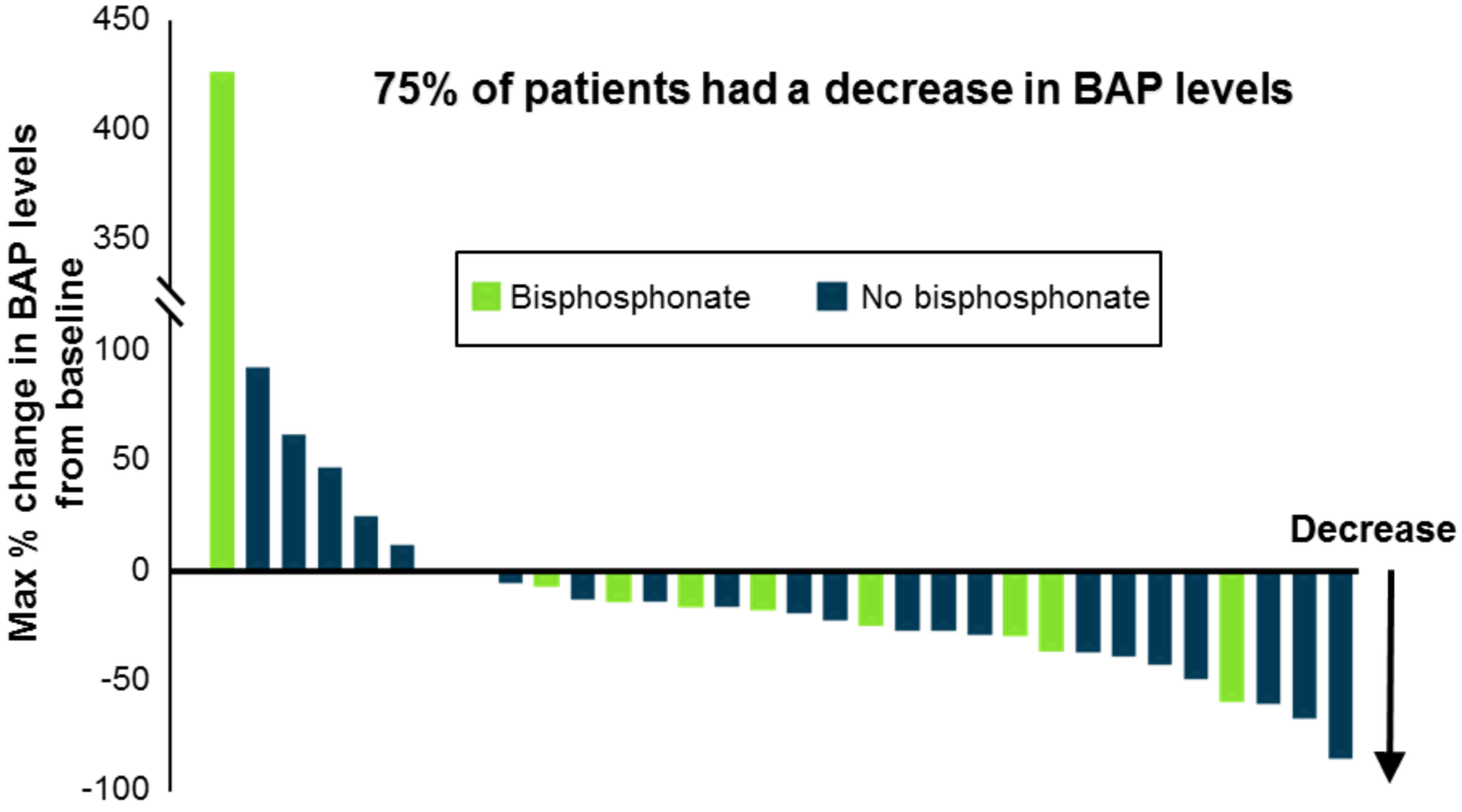
uNTX Change



Araujo J, et al. *Cancer.* 2012;118:63-71.

Dasatinib Plus Docetaxel

BAP change

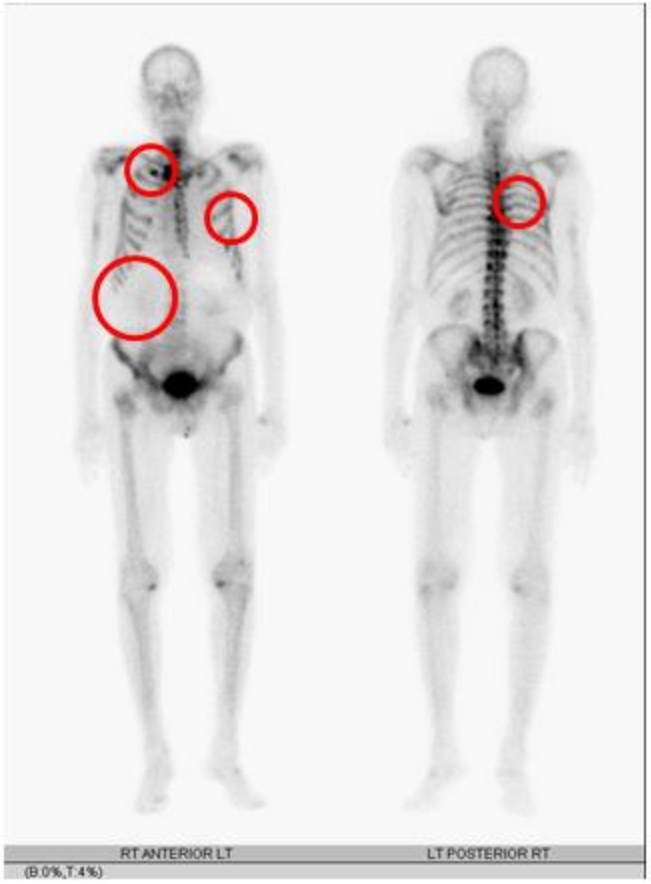


Araujo J, et al. *Cancer.* 2012;118:63-71.

Dasatinib Plus Docetaxel

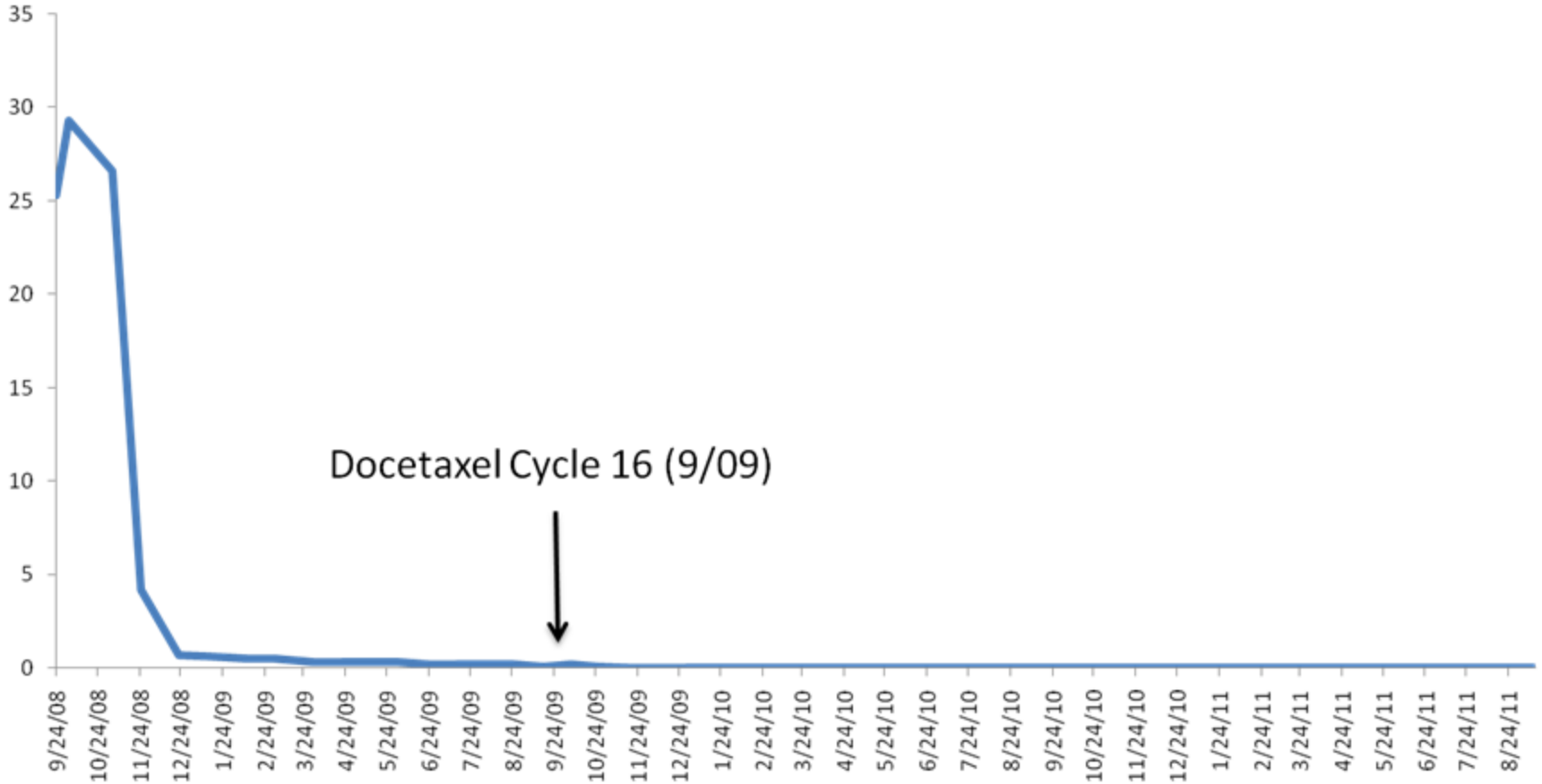
Bone Scan Improvement and Stabilization

> 2 years



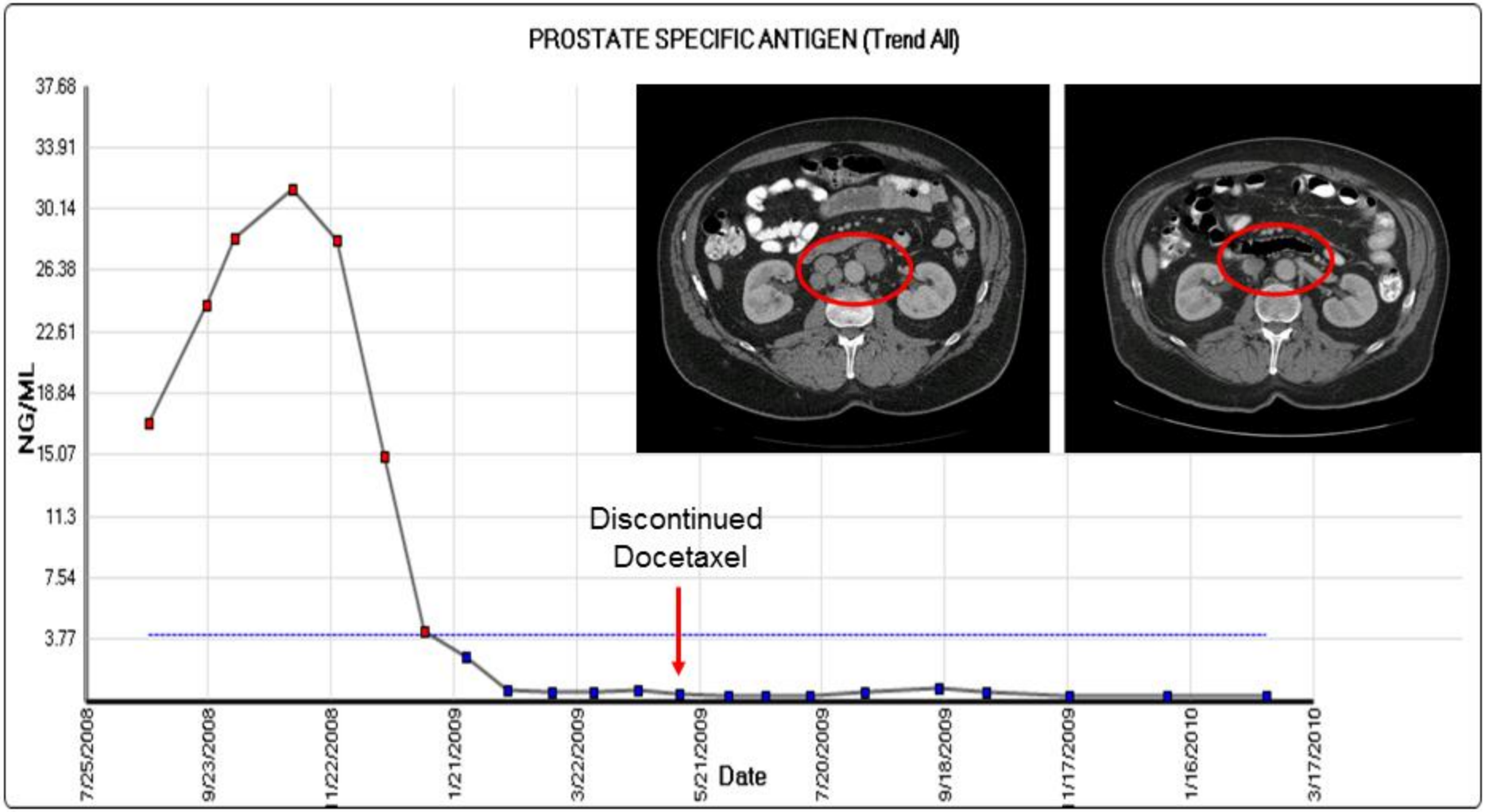
Dasatinib Plus Docetaxel

Prolonged PSA Response



Dasatinib Plus Docetaxel

CT-Scan Improvement and Stabilization



Dasatinib Plus Docetaxel

Summary

Dasatinib and docetaxel combination treatment was well tolerated

Responses demonstrate the anti-tumor activity of dasatinib in combination with docetaxel

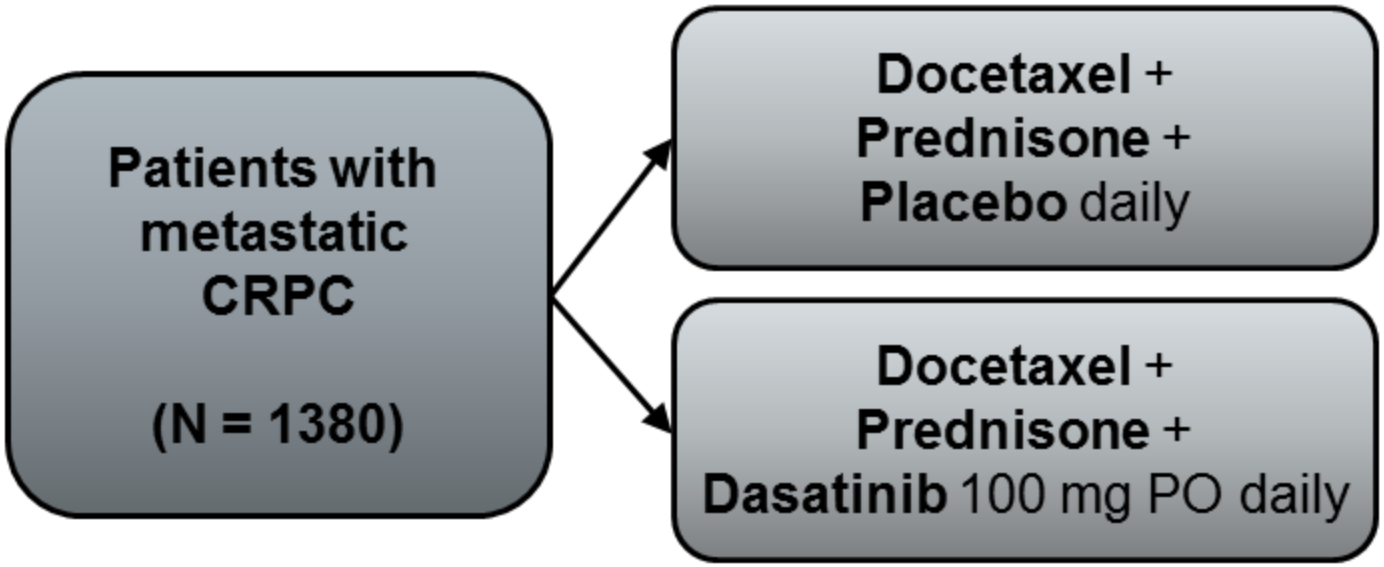
- 30% had reduction in size and/or number of bone lesions
- 60% had confirmed PR (RECIST)

Dasatinib favourably modulates bone turnover as a single agent and in combination with chemotherapy

- 76% had decrease in BAP from baseline
- 47% had ≥35% uNTX decrease from baseline

Docetaxel ± Dasatinib in CRPC

Phase 3 study (READY)



- **Primary endpoint:** OS
- **Secondary endpoints:** change in uNTx, time to first SRE, change in pain intensity, time to PSA progression, tumour response rate, SD, safety/tolerability

Available at: http://www.clinicaltrials.gov/ct2/show/NCT00744497

Targeting Src/SFKs in PCa
Conclusion

SRC family kinases (SFKs) have a critical role in prostate cancer

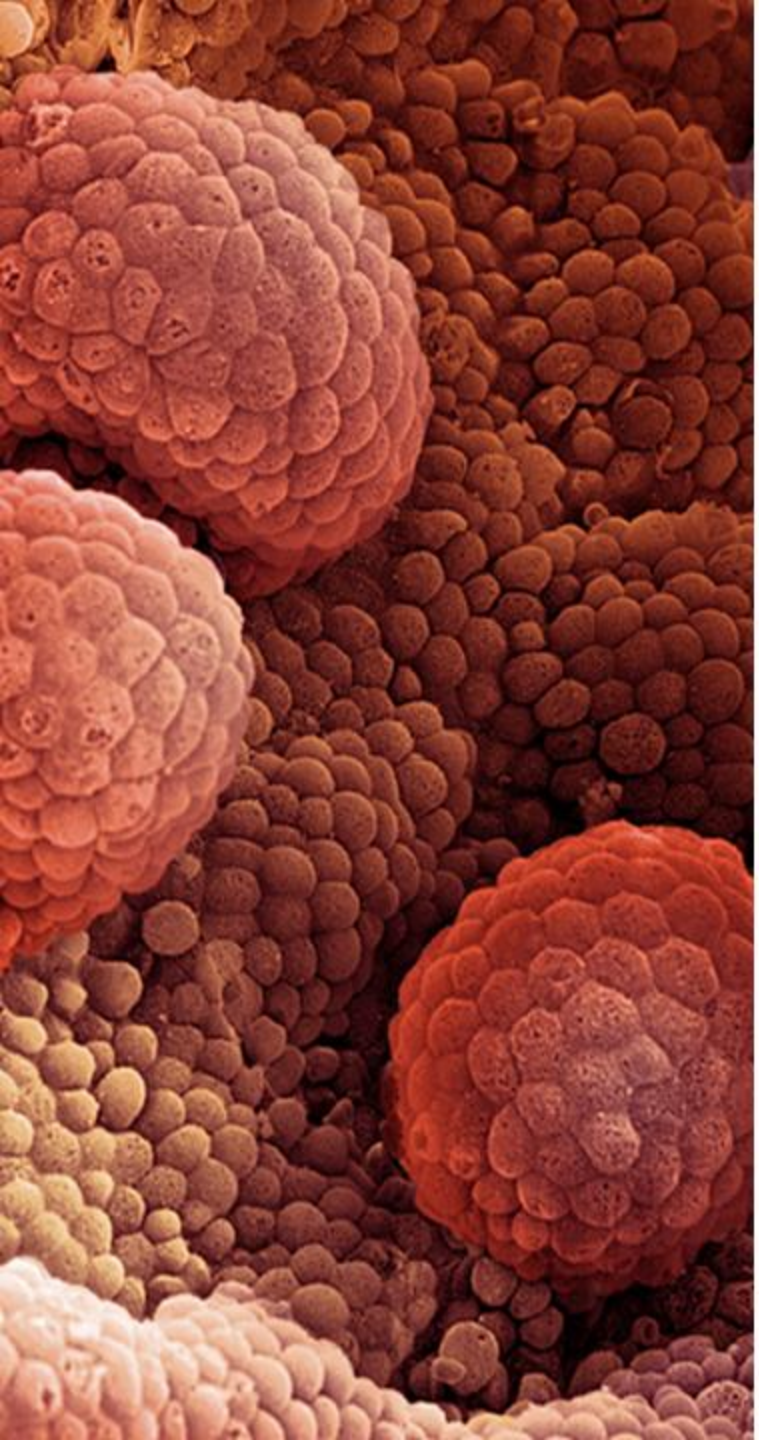
- Tumor proliferation
- Metastatic bone disease

Dasatinib is a potent inhibitor of multiple SFKs with

- Direct antitumor activity
- Synergy with tubulin-binding drugs
- Osteoclast inhibition

Phase II evidence of activity in mCRPC

Randomized Phase III trial completed and results pending



Toward a Marker-Driven Treatment Strategy for CRPC

Christopher J. Logothetis, MD
Chairman/Professor
Department of Genitourinary Medical Oncology
The University of Texas
MD Anderson Cancer Center
Houston, Texas

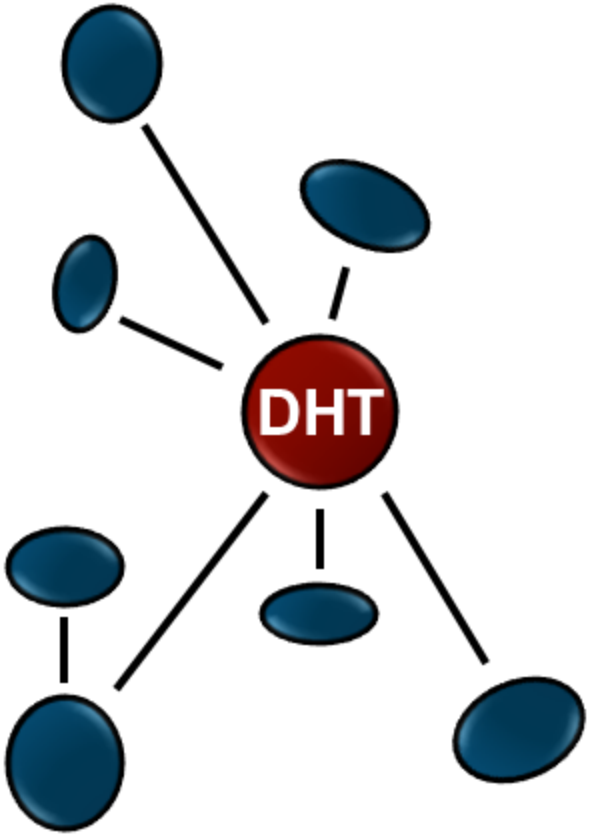
Medscape Oncology
EDUCATION

Topics

- Prostate cancer therapeutics
- The role of bone
- Marker-driven combinations
- Therapy
- Summary

Genetic Networks

Anticipated Outcome



Dihydrotestosterone

Cancer Detection in REDUCE

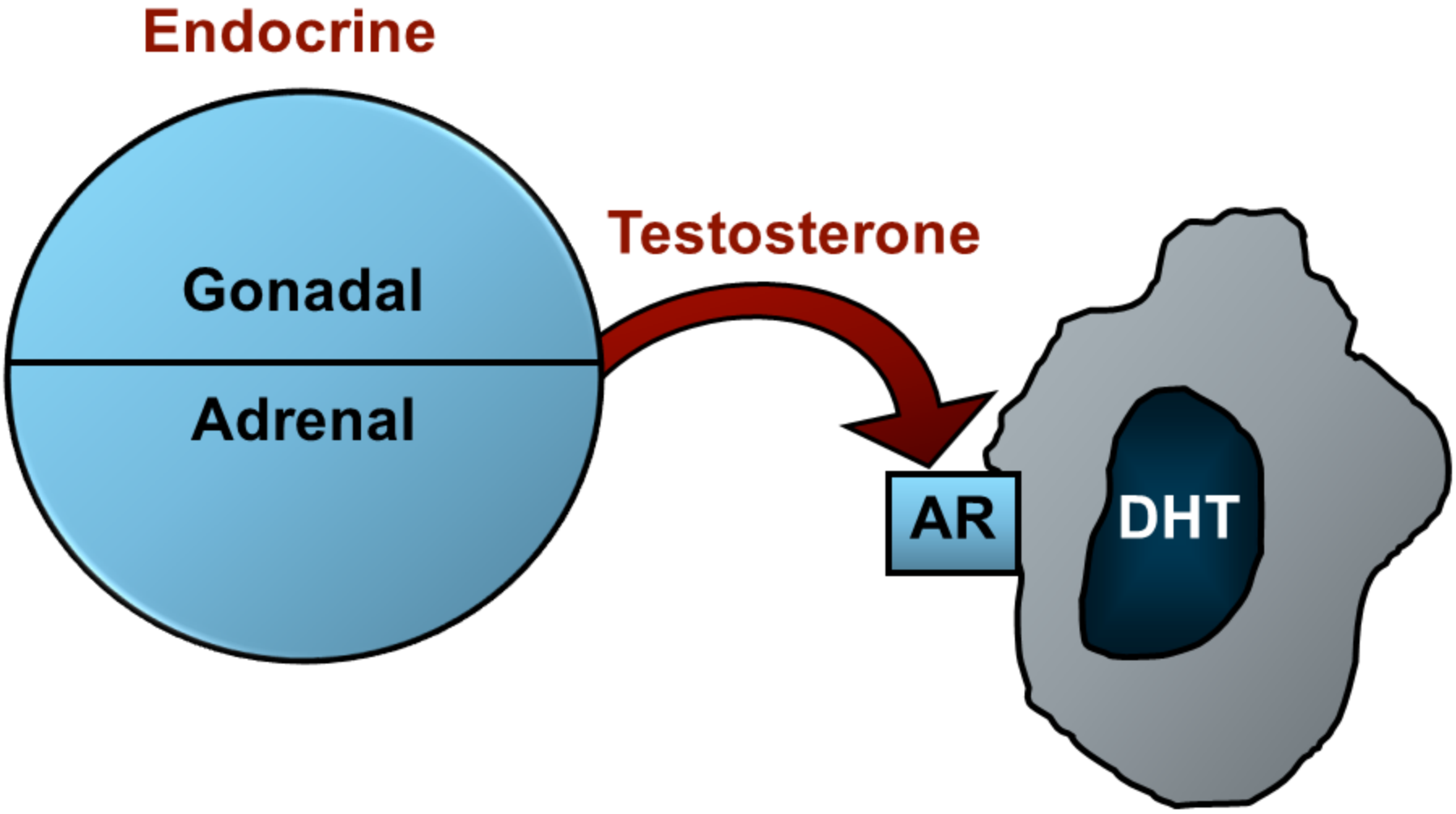
By Time, Treatment and Gleason Score

	Years 1-2		Years 3-4	
	Placebo	**Dutasteride**	**Placebo**	**Dutasteride**
No. subjects biopsied	3345	3929	2342	2446
Gleason 5-6	401	290	216	147
Gleason 7 (3+4)	125	99	51	47
Gleason 7 (4+3)	32	28	6	17
Gleason 8-10	18 (0.5%)	17 (0.5%)	1 (0.04%)	12 (0.5%)

Andriole GL, et al. *N Engl J Med*. 2010;362:1192-1202.

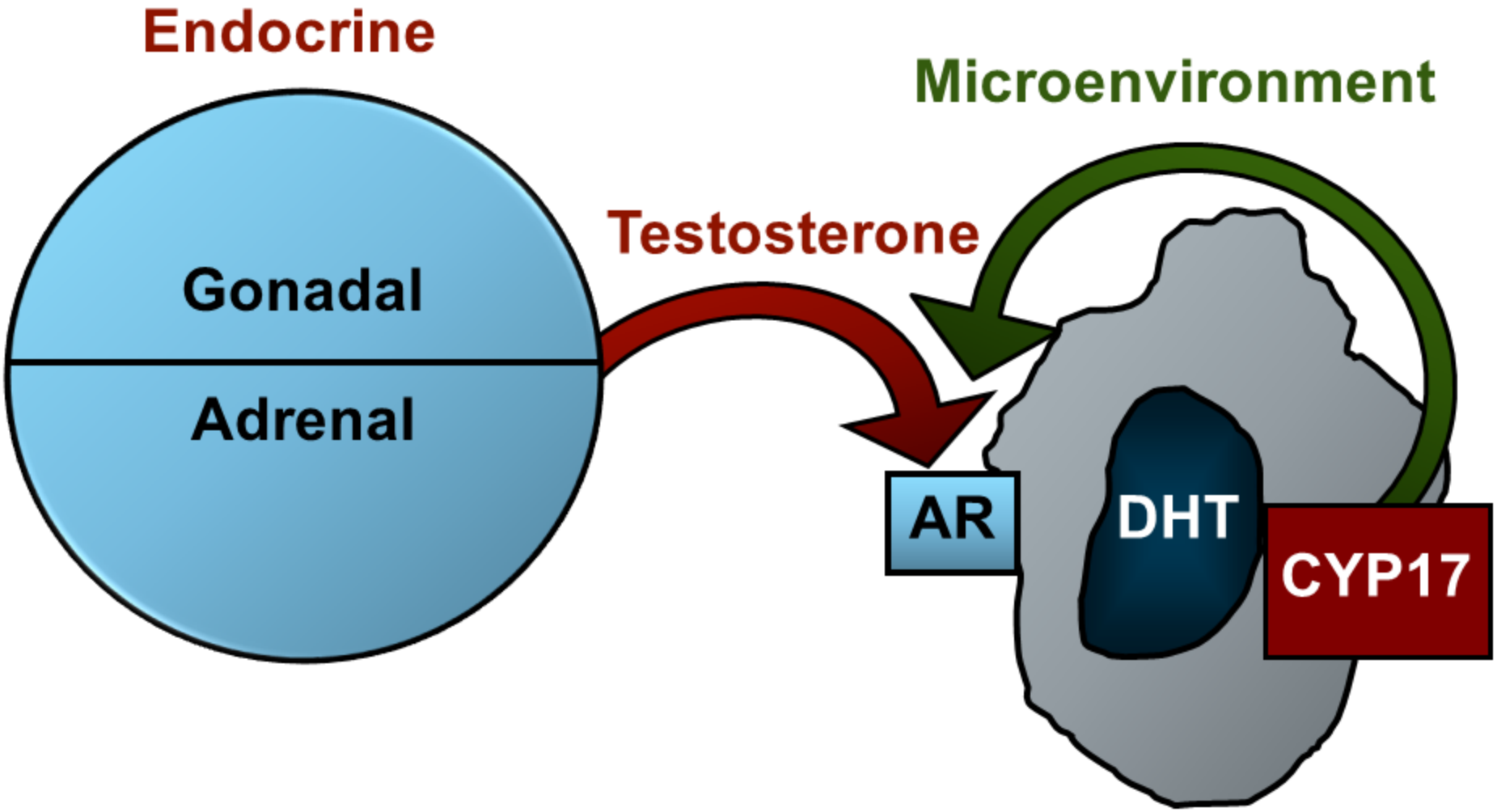
Prostate Cancer

Androgen-Mediated Progression

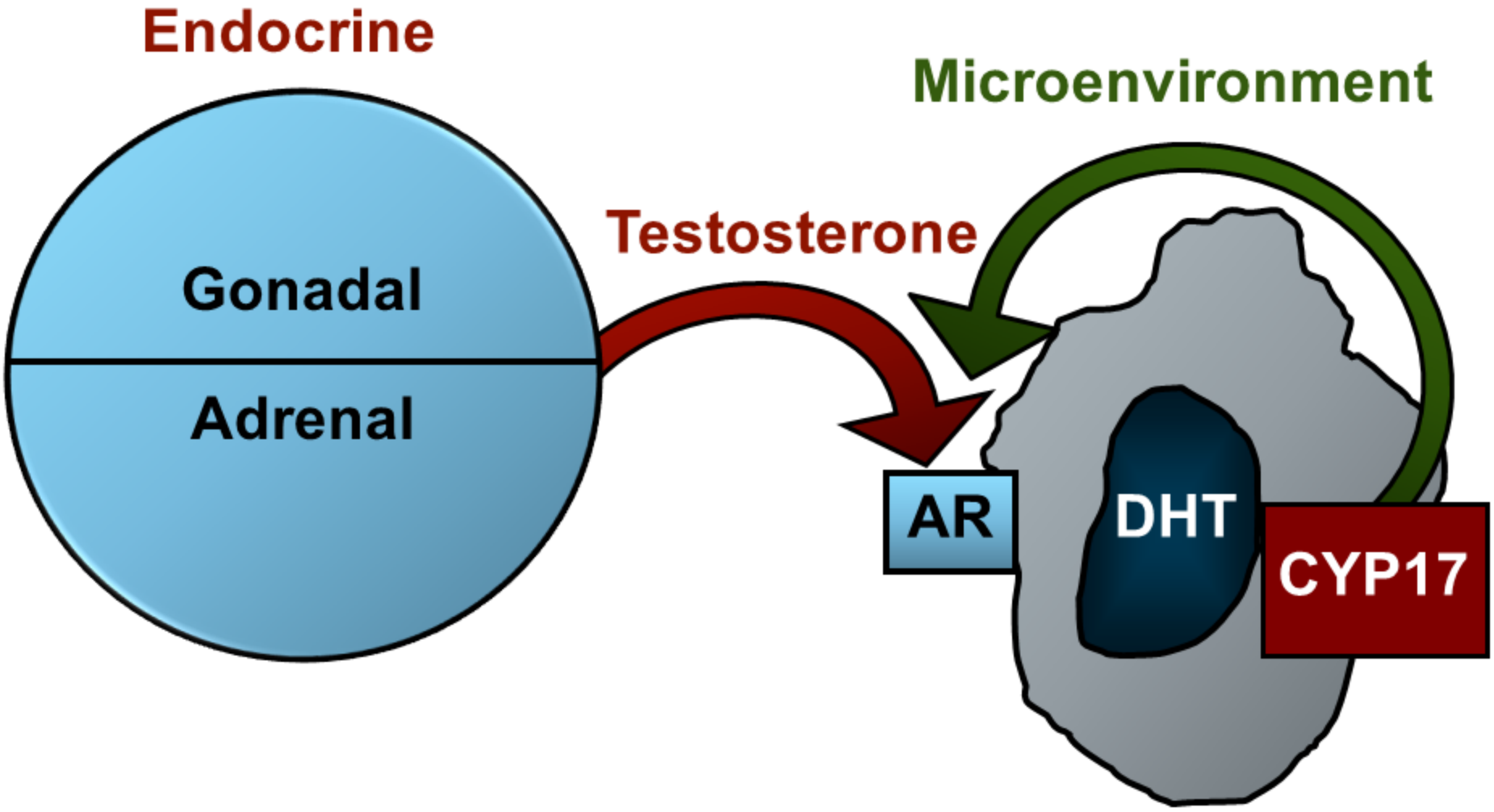


Prostate Cancer

Androgen-Mediated Progression

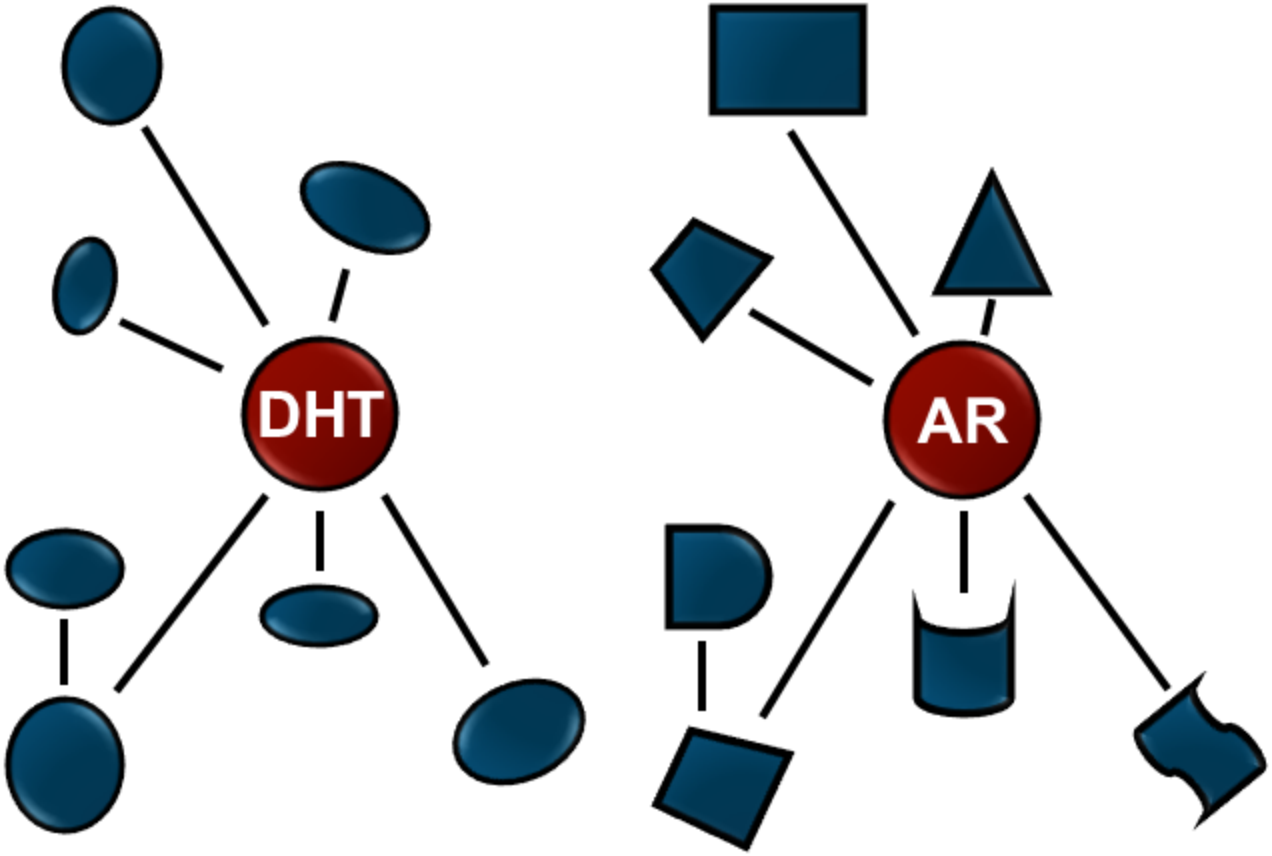


Where Androgen Signaling and Tumor Microenvironment Transect



Genetic Networks

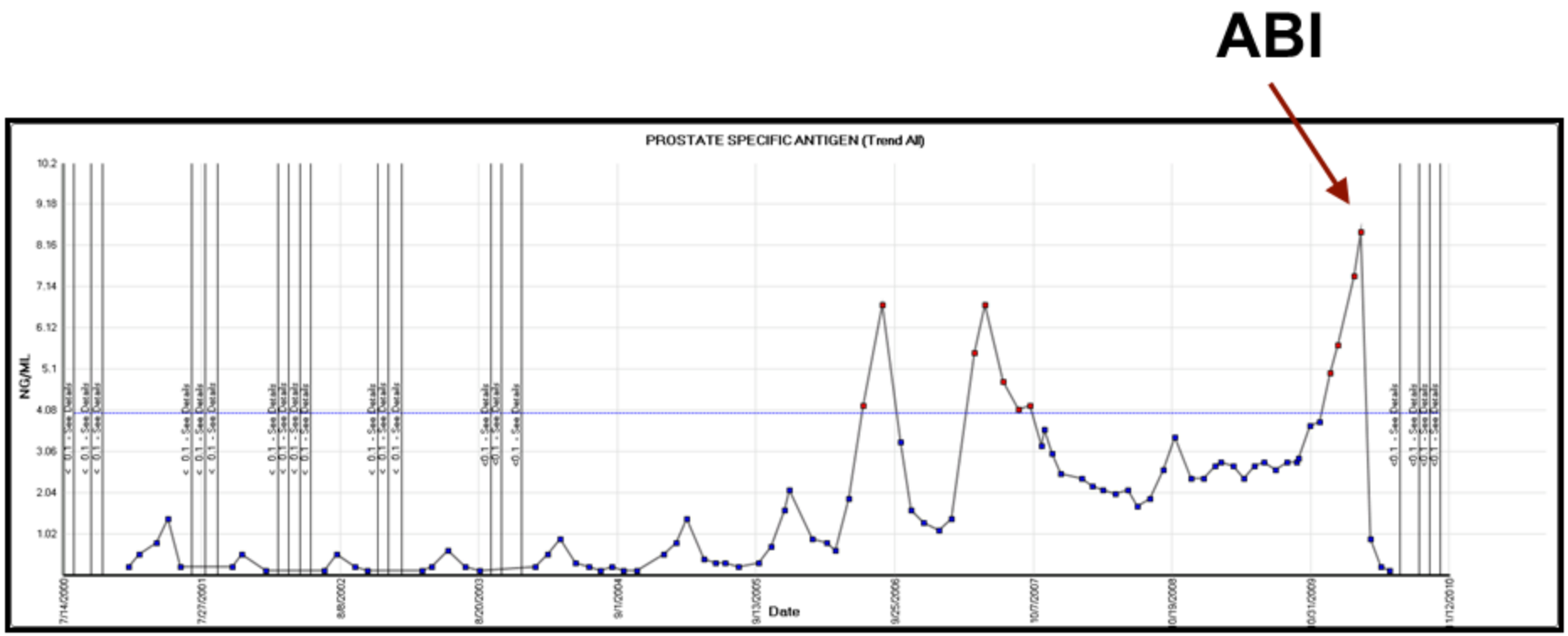
Anticipated Outcome



Dihydrotestosterone

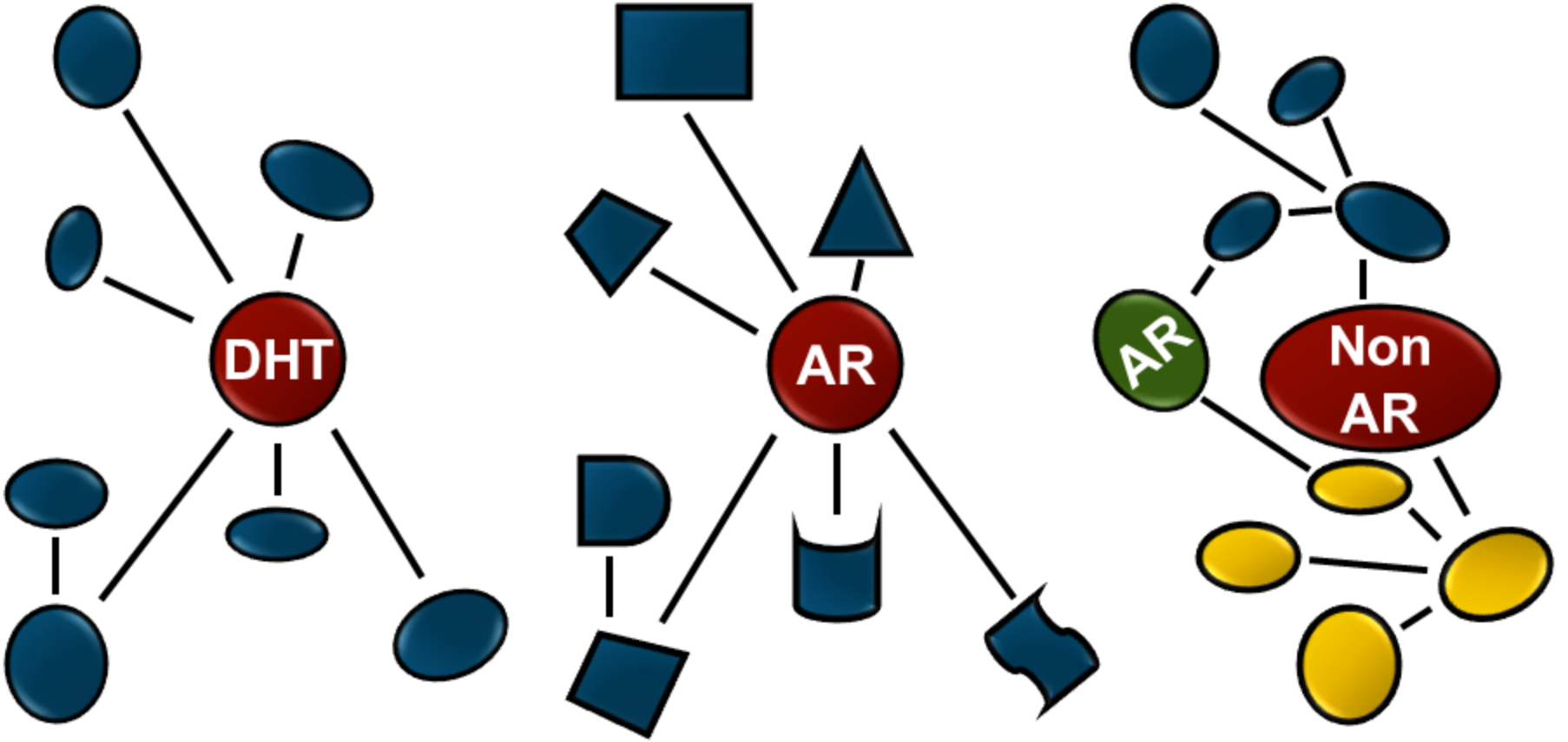
Androgen Signaling

“Earlier” Use of Androgen Biosynthesis Inhibitor



Genetic Networks

Anticipated Outcome



Dihydrotestosterone

Androgen Signaling

Microenvironment Dependent

SFK Expression and PCa Progression

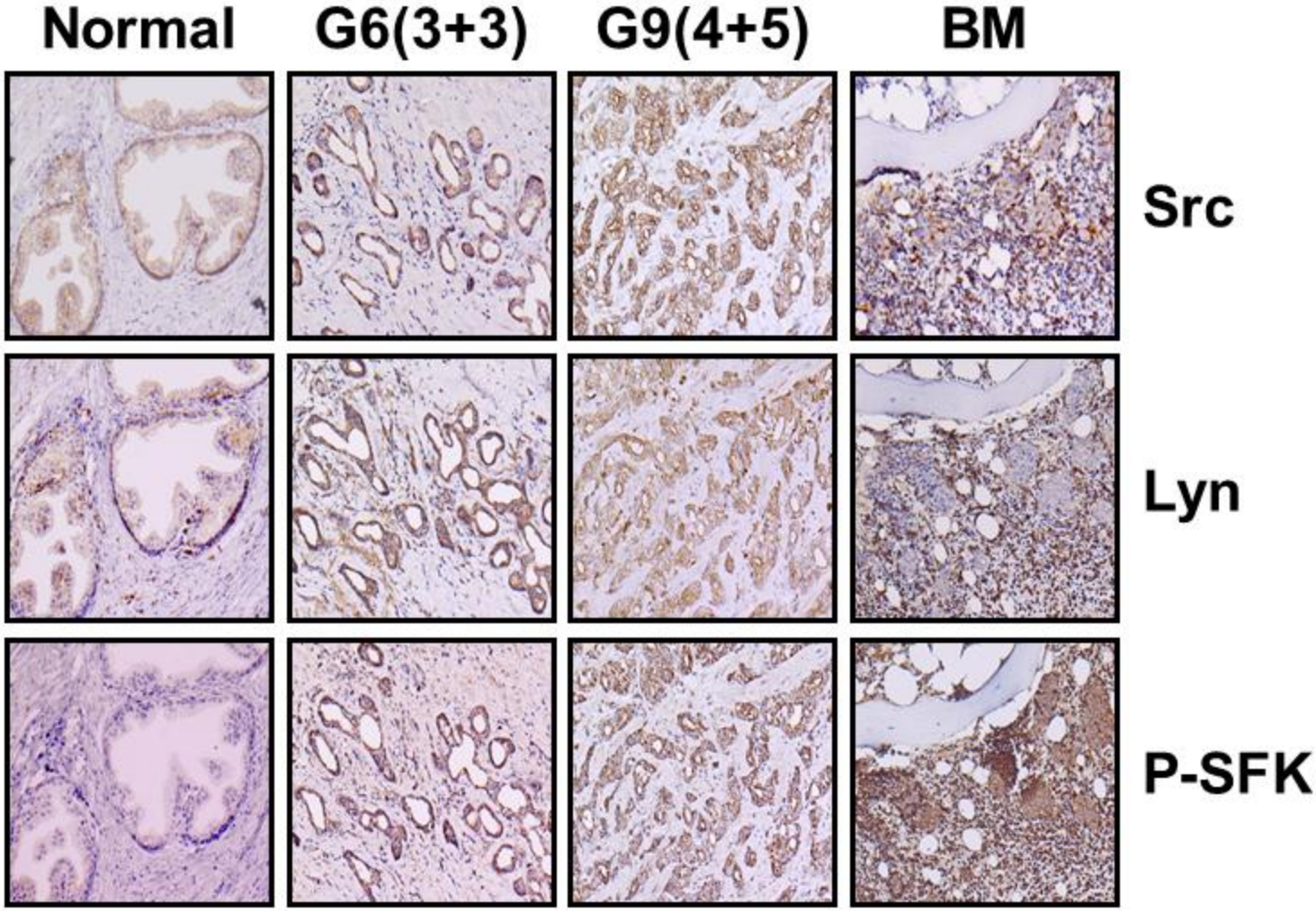


Image courtesy of G. Gallick, PhD.

SFKs

Stromal/Tumor Interaction Paradigms

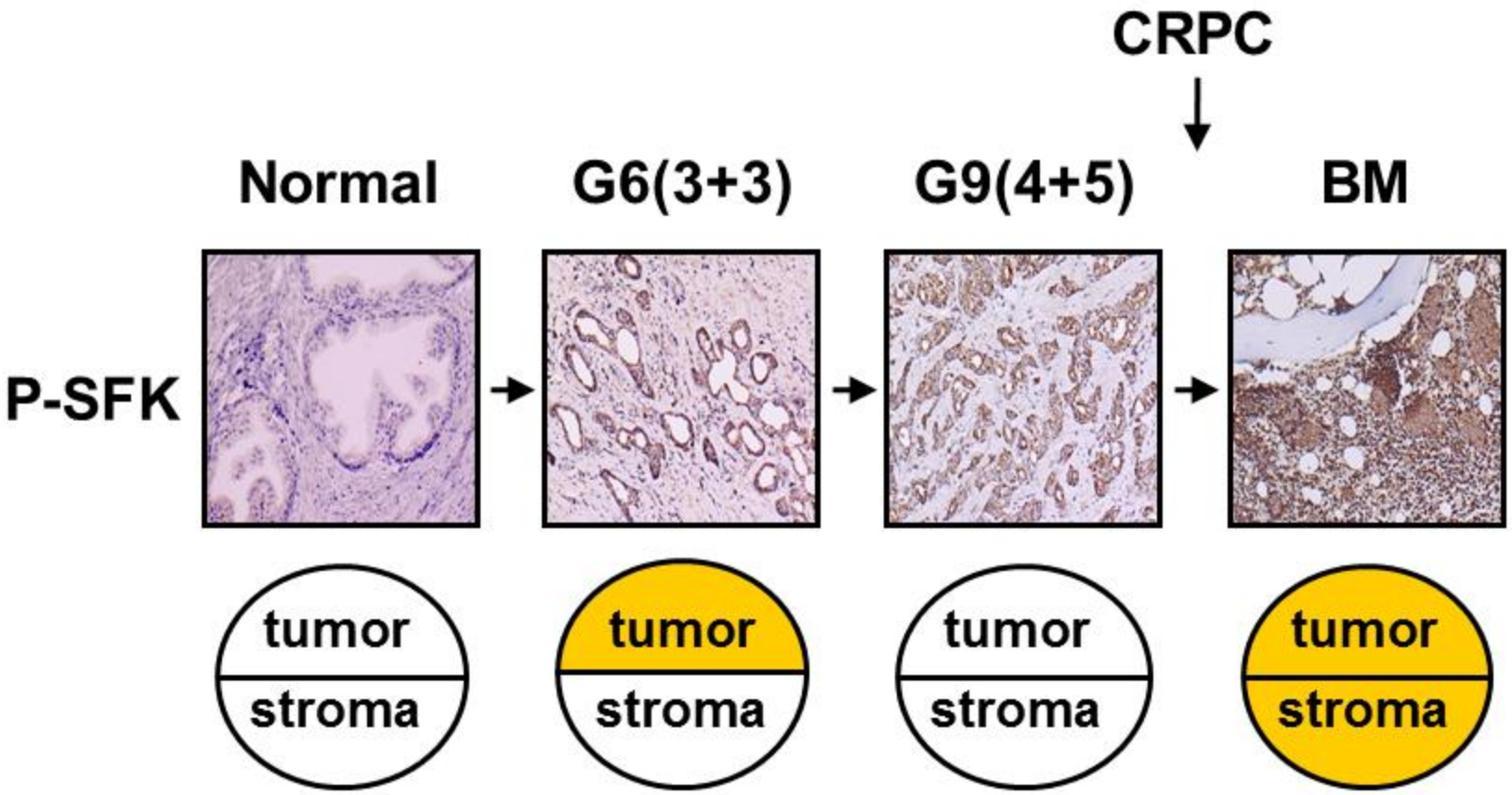


Image courtesy of G. Gallick, PhD.

Lethal Variant of Prostate Cancer

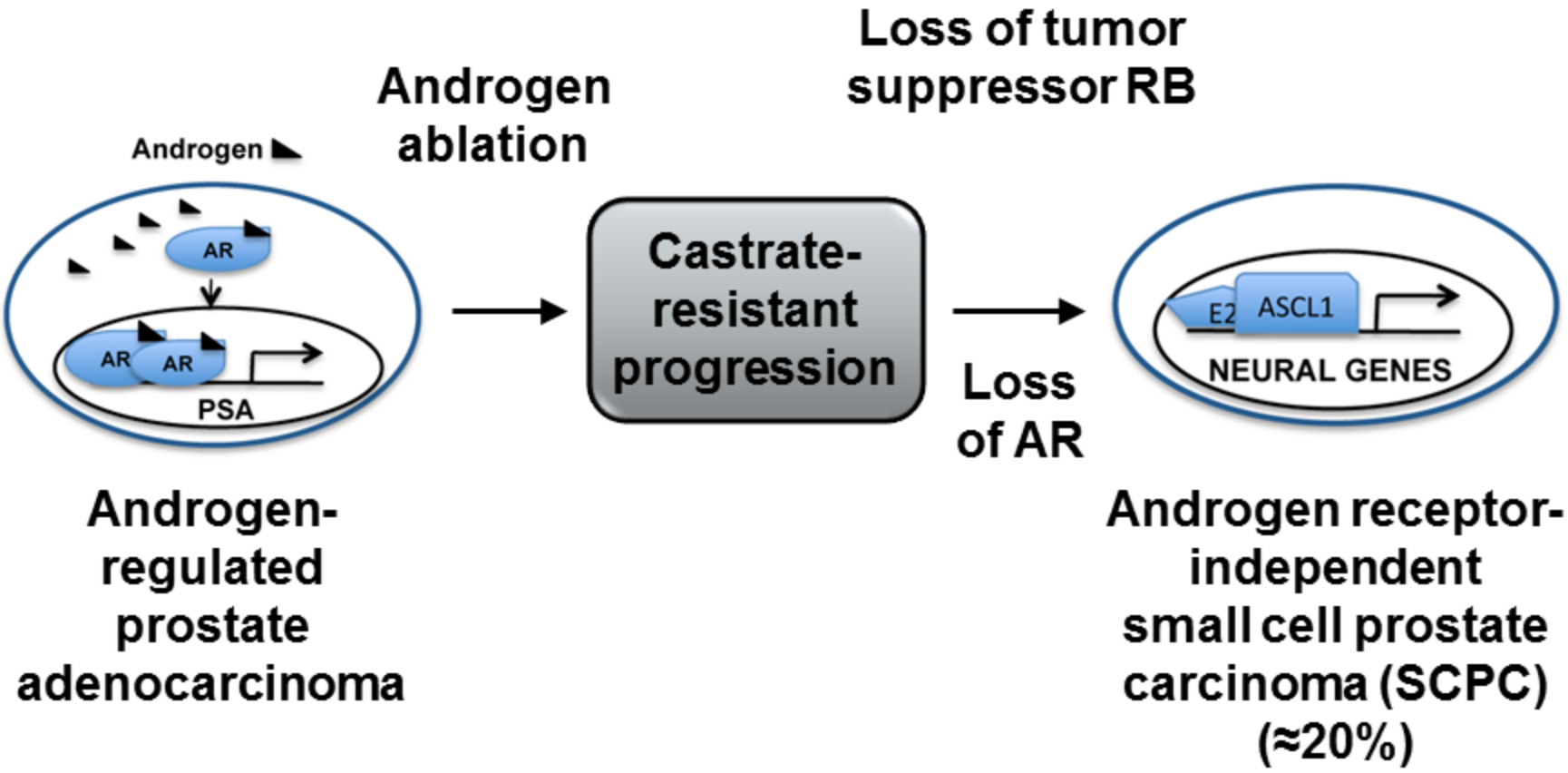


Image courtesy of A. Aparicio and S. Maity.

Xenograft Models of SCPC

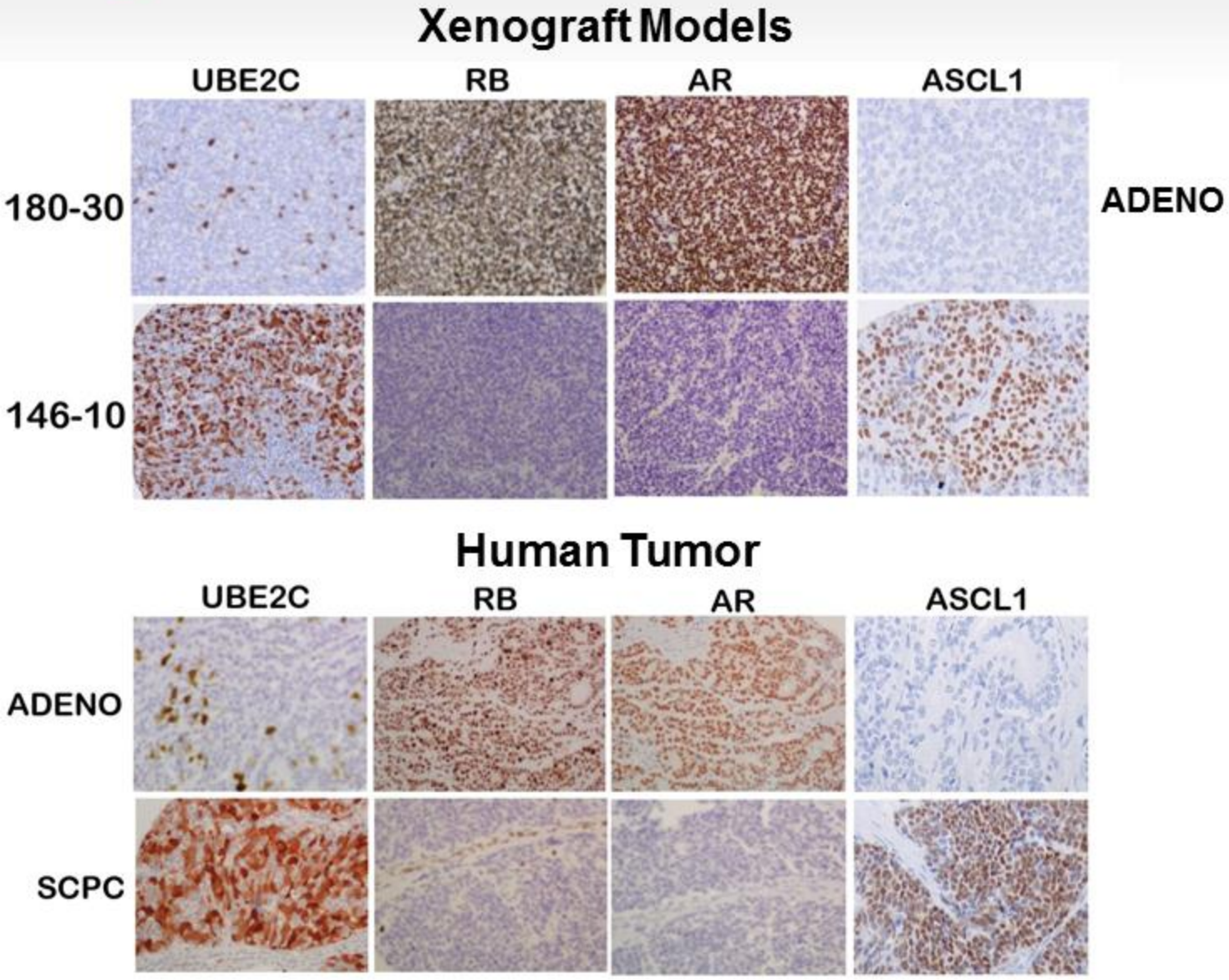
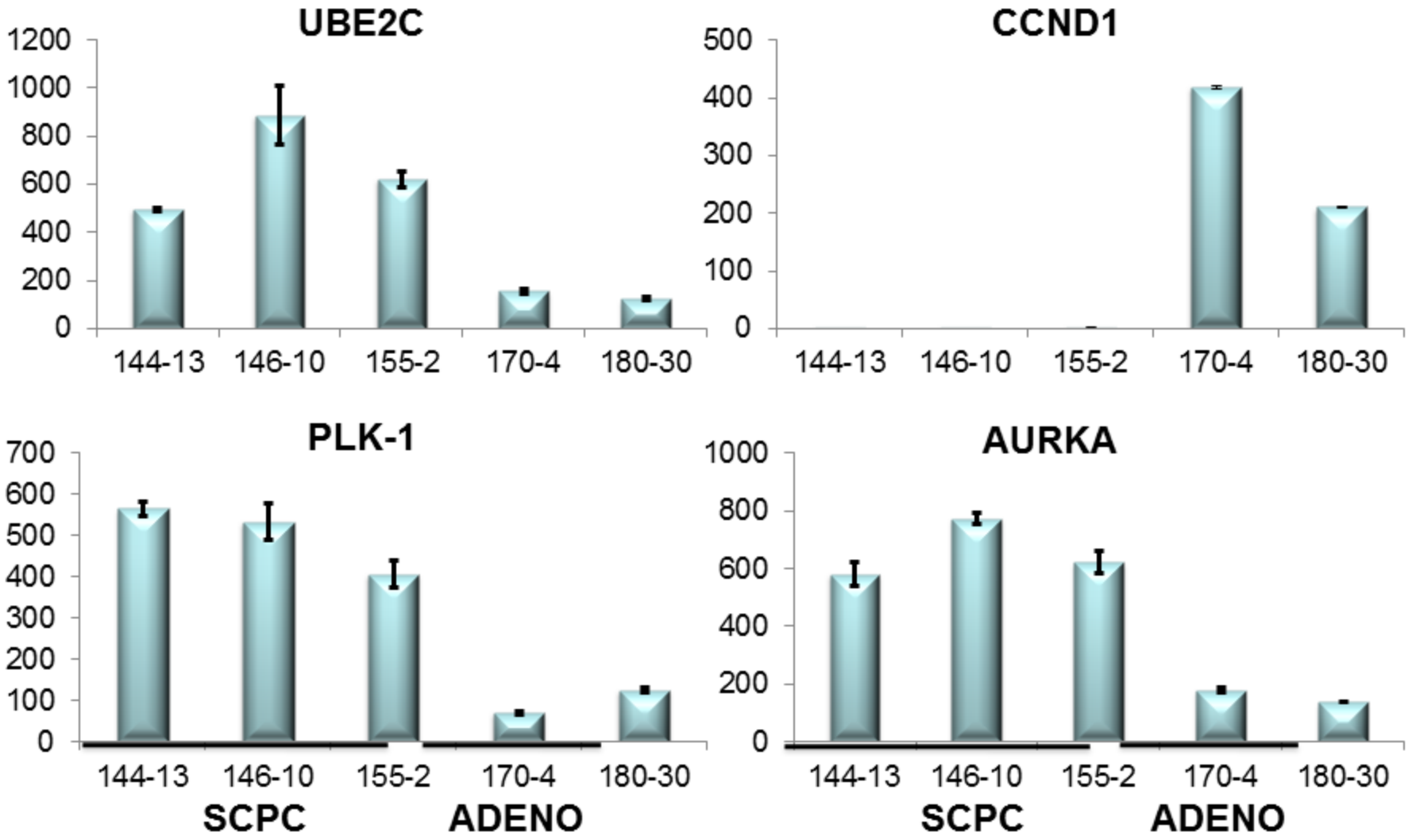


Image courtesy of A. Aparicio and S. Maity.

SCPC

Activation of Mitotic (Program) Kinases



Maity S, et al. Clinical Cancer Research (CCR-11-1867)

Targeting SCPC

Selective Inhibition of Aurora Kinase A

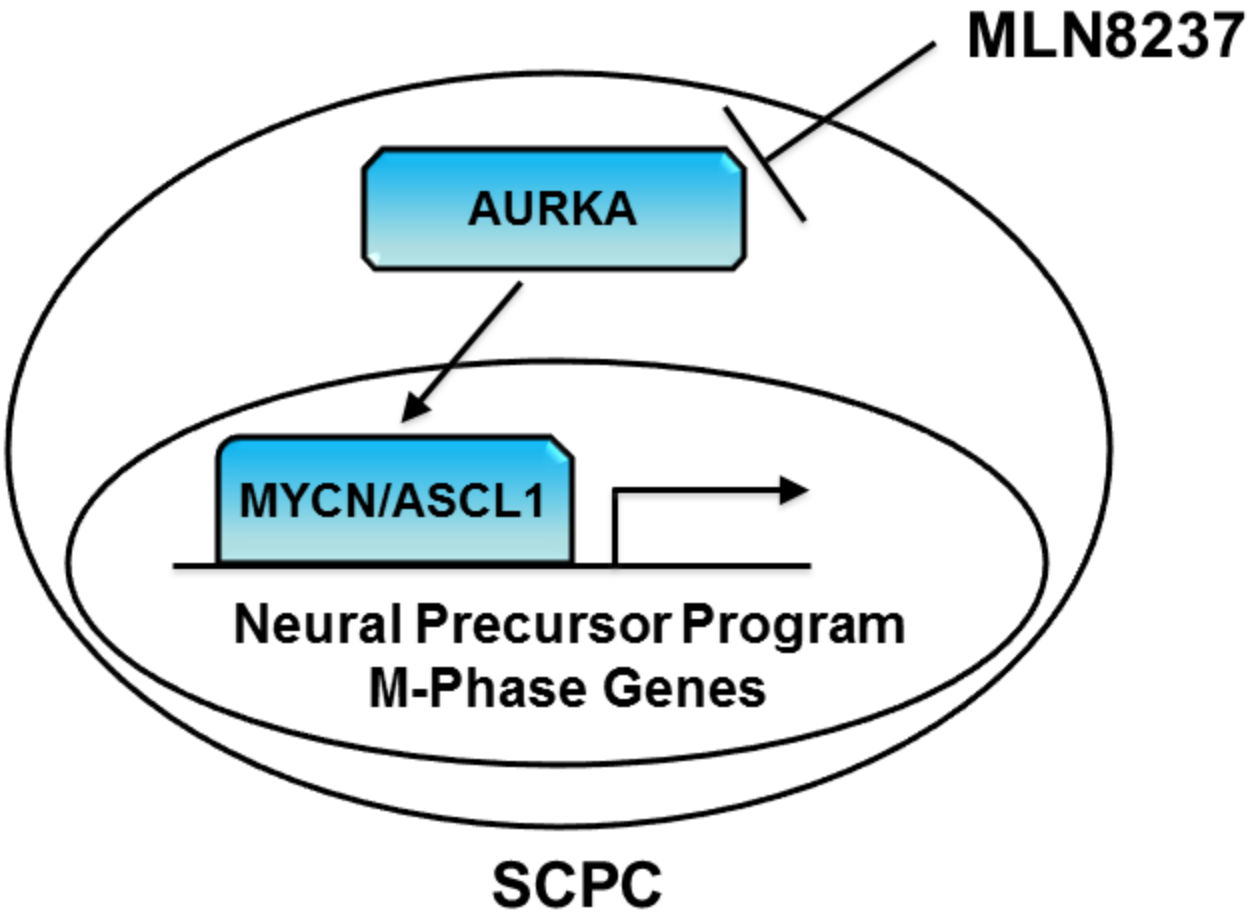
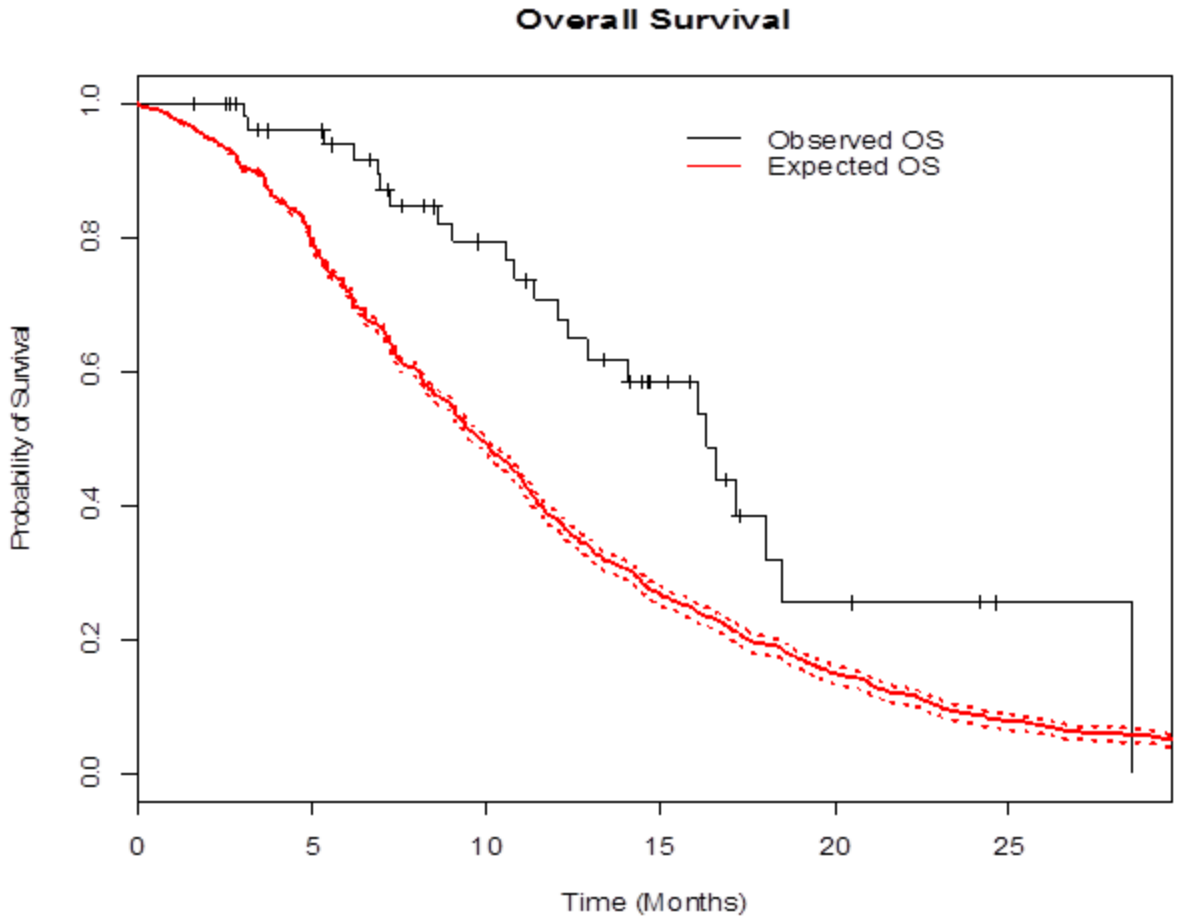


Image courtesy of A. Aparicio and S. Maity.

Anaplastic Cancers are "Carboplatin Sensitive"

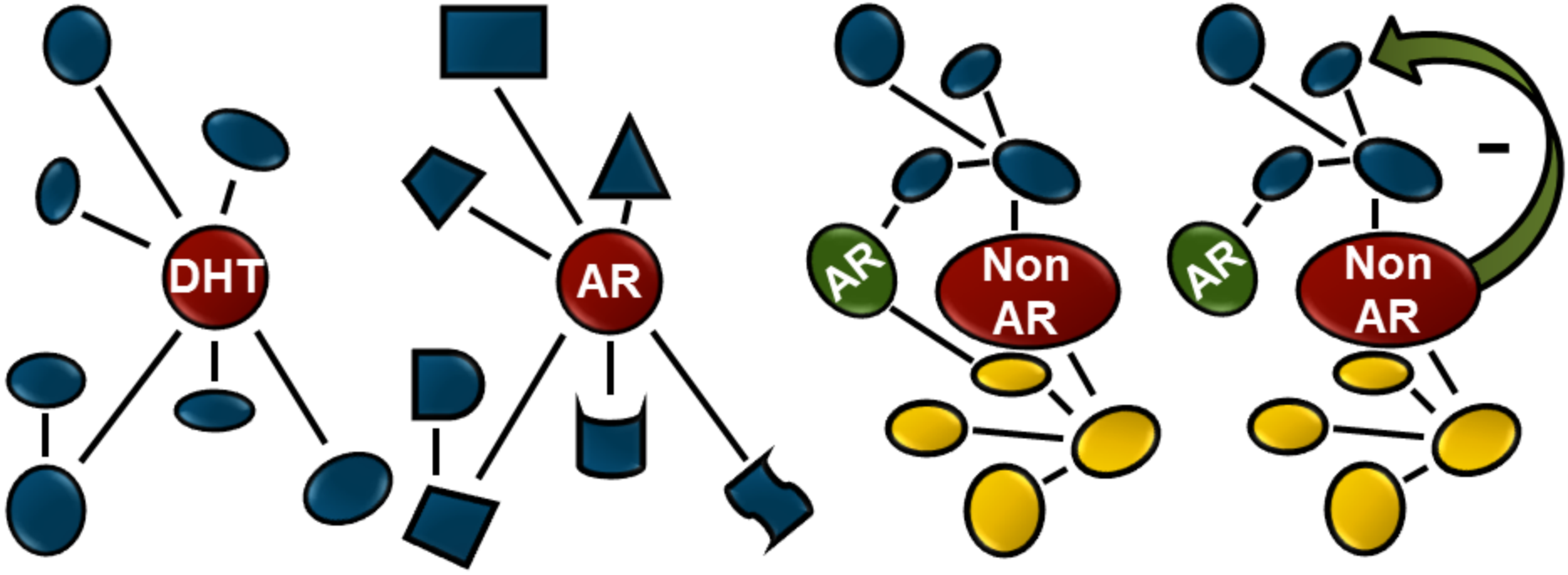
Observed OS versus expected OS based on TAX327 model



A. Aparicio, unpublished data.

Androgen Signaling Networks

Progression



Dihydrotestosterone

Androgen Signaling

Microenvironment Dependent

AR Interference

Prostate Cancer

Challenge of "Temporal Heterogeneity"

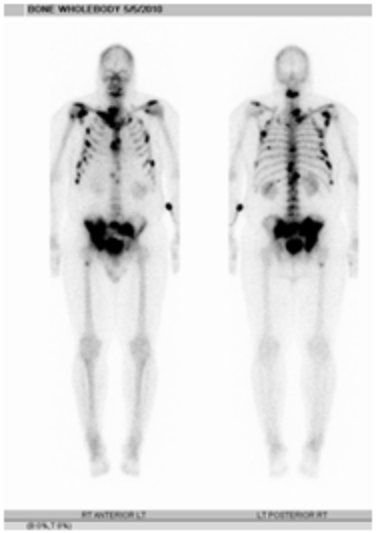
If therapeutically meaningful differences emerge over time:

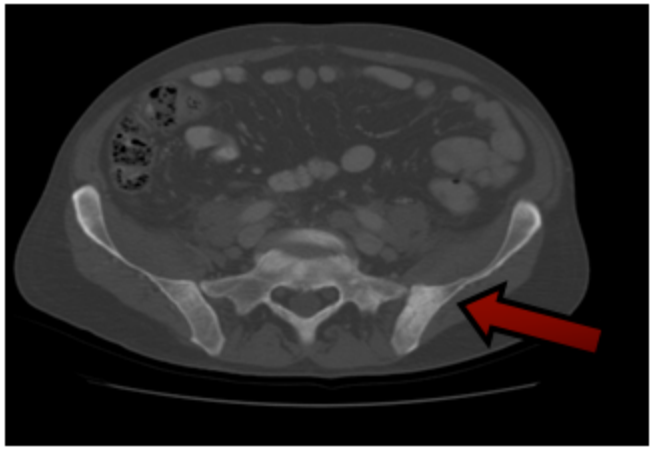
Prostate Cancer

Challenge of "Temporal Heterogeneity"

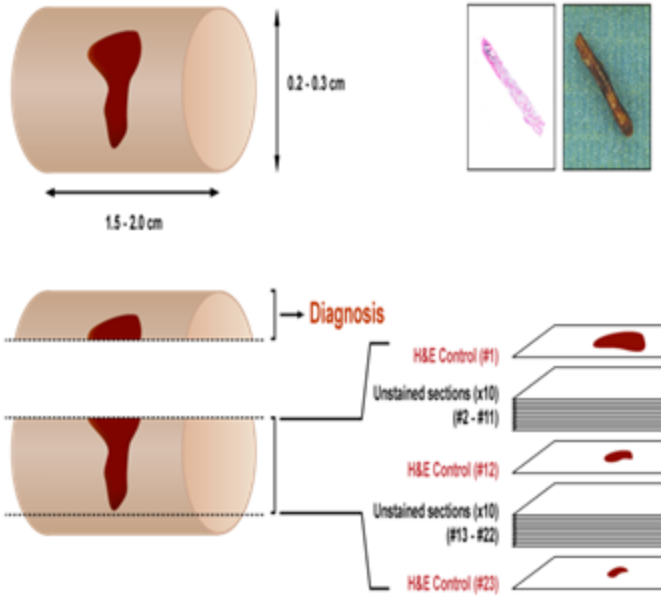
If therapeutically meaningful differences emerge over time:
then only tissue collected proximate to planned intervention can be predictive.

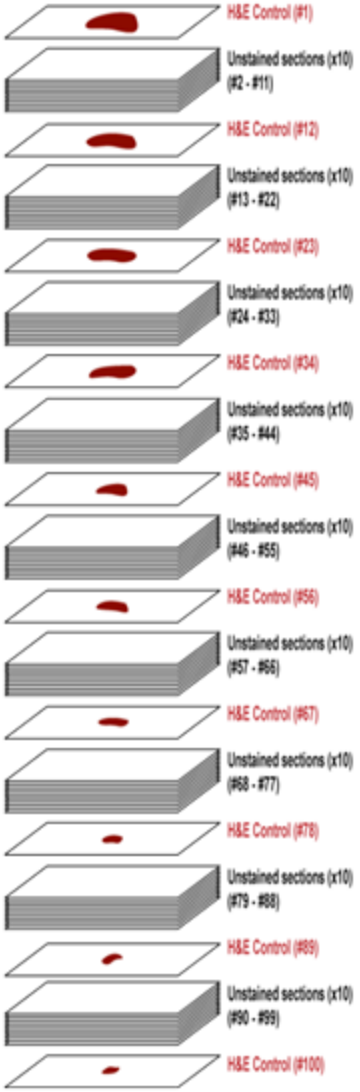
Maximizing Yield of "Blind" Transilial Bone Marrow Biopsy





CT directed

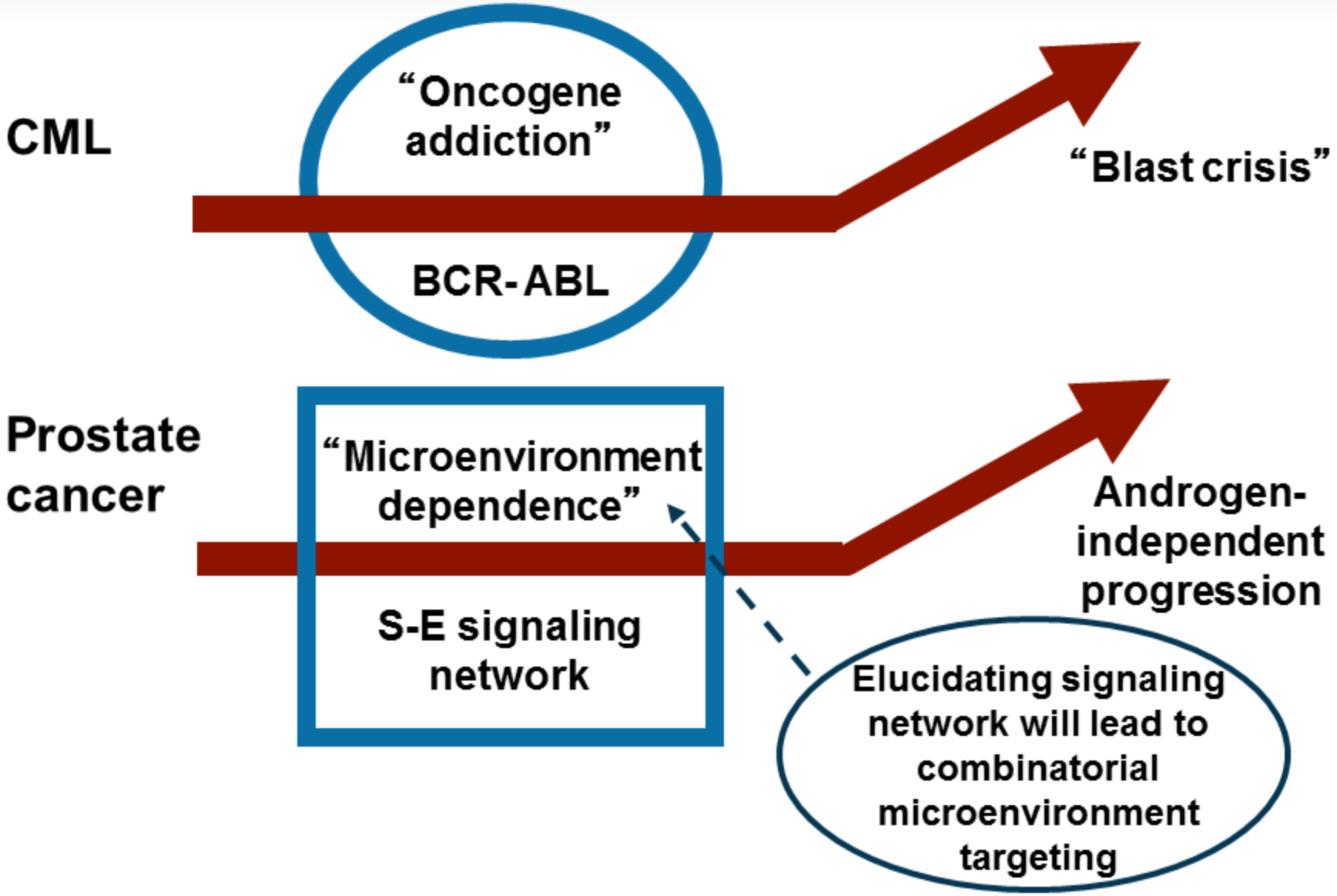




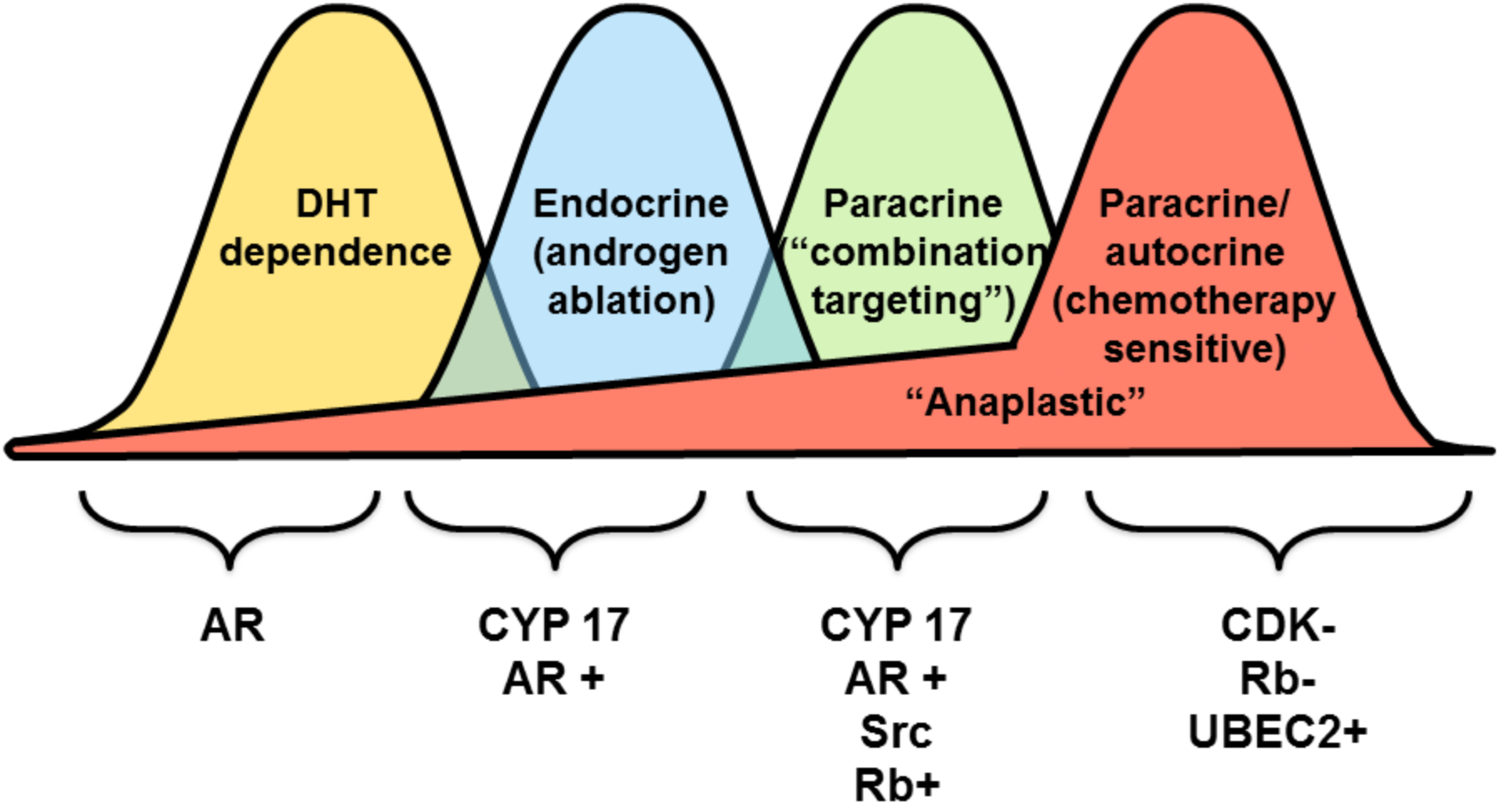
Therapy Targets
A Land of Plenty

- Novel microtubular poison
- Alkylating agent(s)
- Bone-homing radiopharmaceutical immunotherapy (vaccine checkpoint blockade)
- Stromal-epithelial interacting pathways (Src family kinases, Hedgehog, FGF)
- Signaling networks: (IGF, PI3K,GSK3b, PARP)
- AR signaling: (androgen biosynthesis inhibition, AR blockade)

Temporal Heterogeneity of PCa

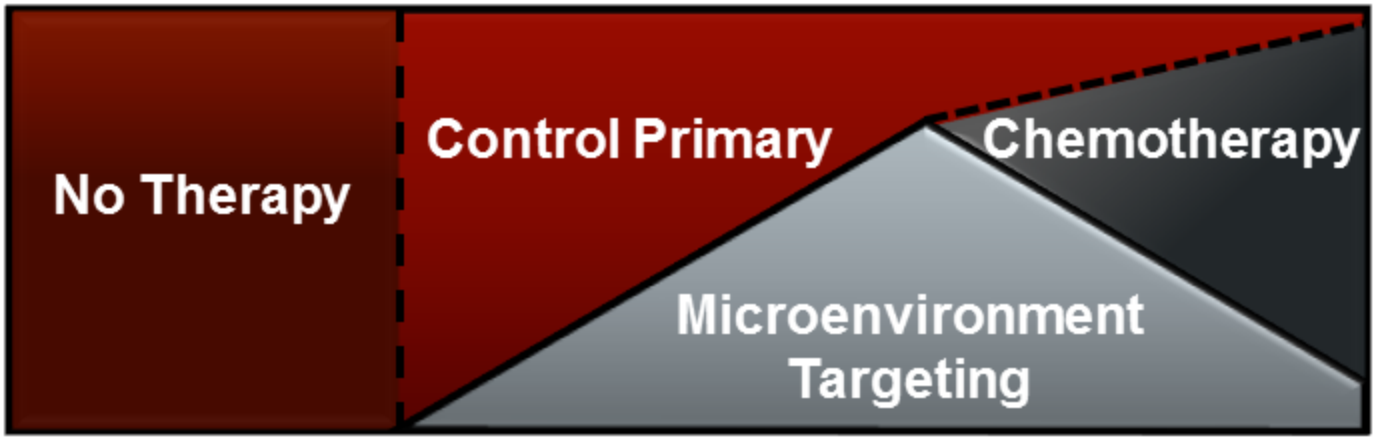


Prostate Cancer Progression

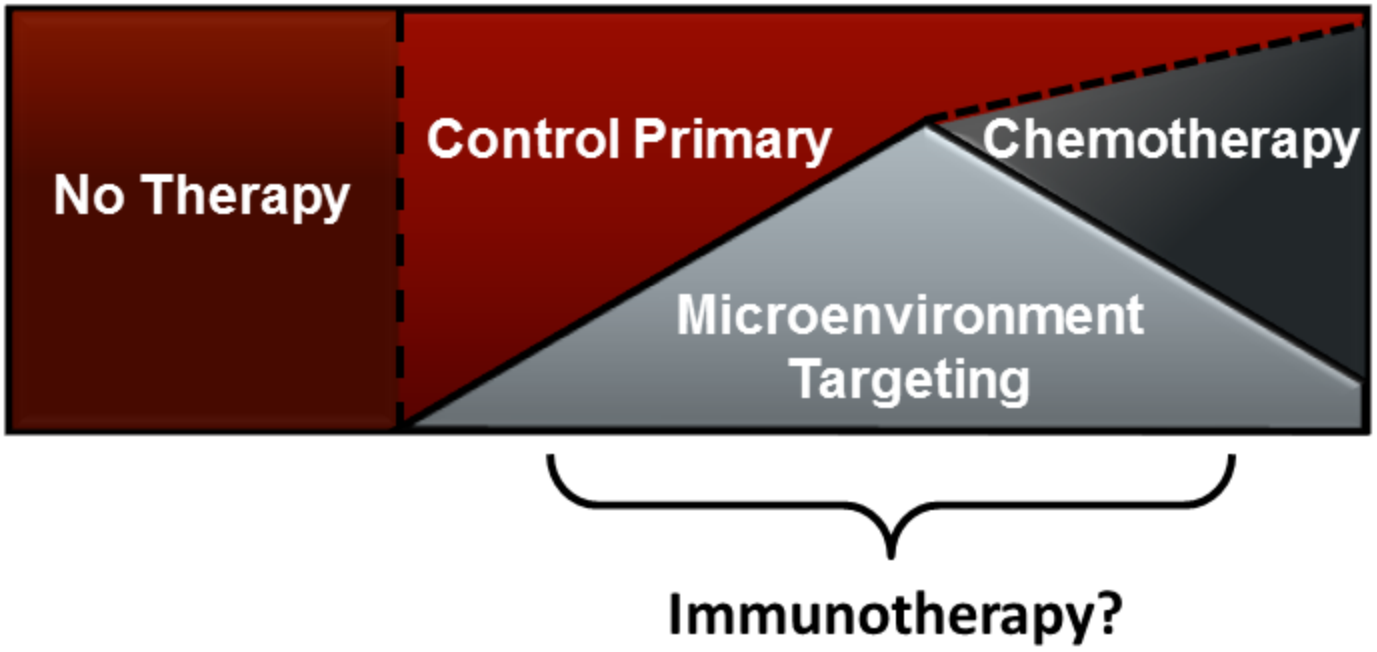


Control Primary
Systemic Therapy

Control Primary
Systemic Therapy


No Therapy
Control Primary
Chemotherapy
Microenvironment
Targeting

Control Primary
Systemic Therapy


No Therapy
Control Primary
Chemotherapy
Microenvironment
Targeting
Immunotherapy?

Acknowledgments

MD Anderson Cancer Center

Genitourinary Medical Oncology

W. Arap
J. Araujo
A. Aparicio
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S. Maity
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D Tsavachidou
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P. Troncoso

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V. Kundra

Texas A& M University

W. L. McKeehan
F. Wang

Nijmegen

P. Friedl*

University of Athens

E. Efstathiou*

Polling Questions

Please take a moment to answer again the survey questions. A comparison of the results will be discussed by the panel.

Polling Question 2

- **How confident are you that your knowledge about the management of mCRPC is up-to-date?**

  a) Not confident at all

  b) Slightly confident

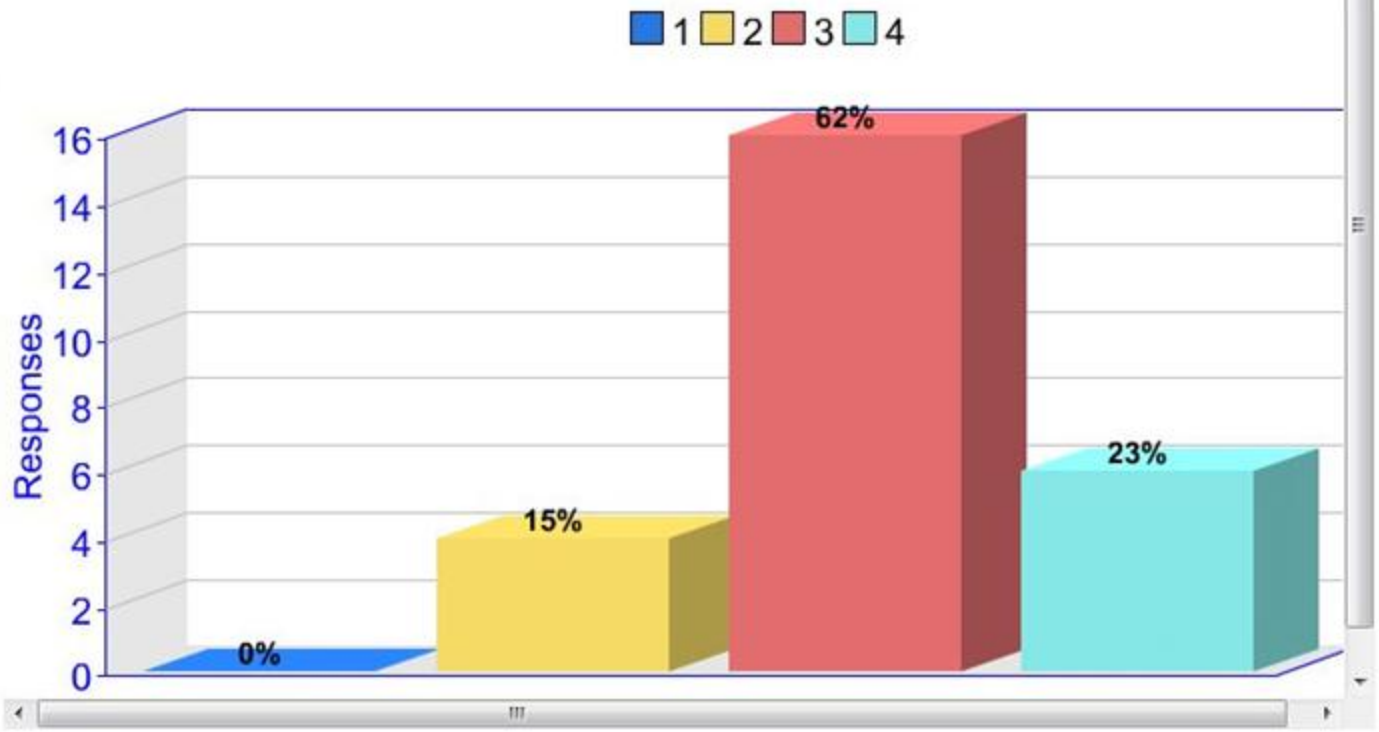
  c) Moderately confident

  d) Very confident

Metastatic Castration-Resistant Prostate Cancer: New Targets, New Therapeutic Approaches CME

2. Following the presentations, how confident are you that your knowledge about the management of mCRPC is up-to-date?
(1=Not Confident at All .. 5=Very Confident).

Average Score: 4.1



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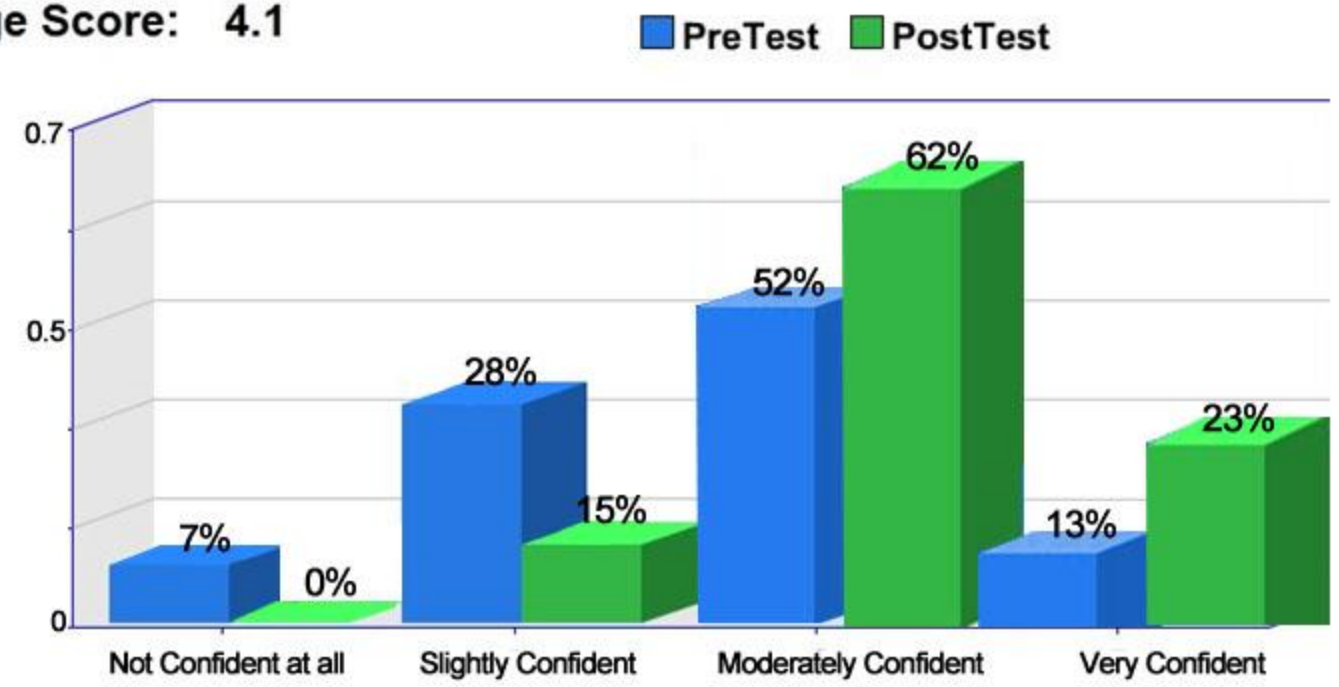
Compare Reports

2. How confident are you that your knowledge about the management of mCRPC is up-to-date?

(1=Not Confident at All .. 4=Very Confident).

Average Score: 3.6

Average Score: 4.1



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Polling Question 3

- **Which of the following is the most important barrier to the optimal management of mCRPC?**
  a) Current therapies incompletely suppress the androgen–AR axis
  b) Biologic heterogeneity of mCRPC and inability to tailor treatment based on individual tumor characteristics
  c) Genetic polymorphisms of proteins involved in drug metabolism and action
  d) Lack of consensus on how to sequence approved therapies in individual patients with CRPCs
  e) Not sure

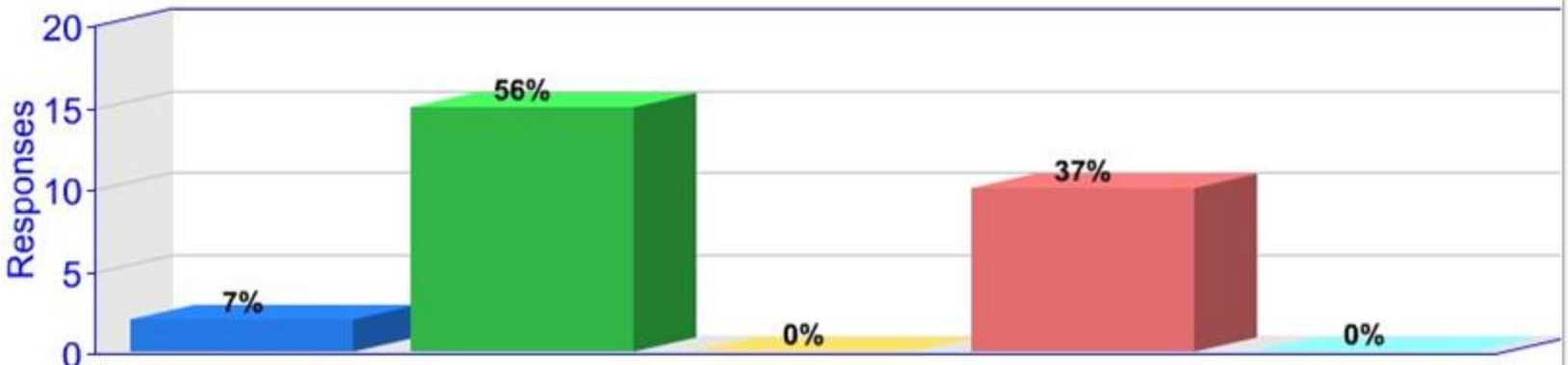
Metastatic Castration-Resistant Prostate Cancer: New Targets, New Therapeutic Approaches CME

Reports

PostTest

3. Which of the following is the most important barrier to the optimal management of mCRPC?

- A) Current therapies incompletely suppress the androgen–AR axis...
- B) Biologic heterogeneity of mCRPC and inability to tailor treatment based on ind...
- C) Genetic polymorphisms of proteins involved in drug metabolism and action...
- D) Lack of consensus on how to sequence approved therapies in individual patients...
- E) Not sure



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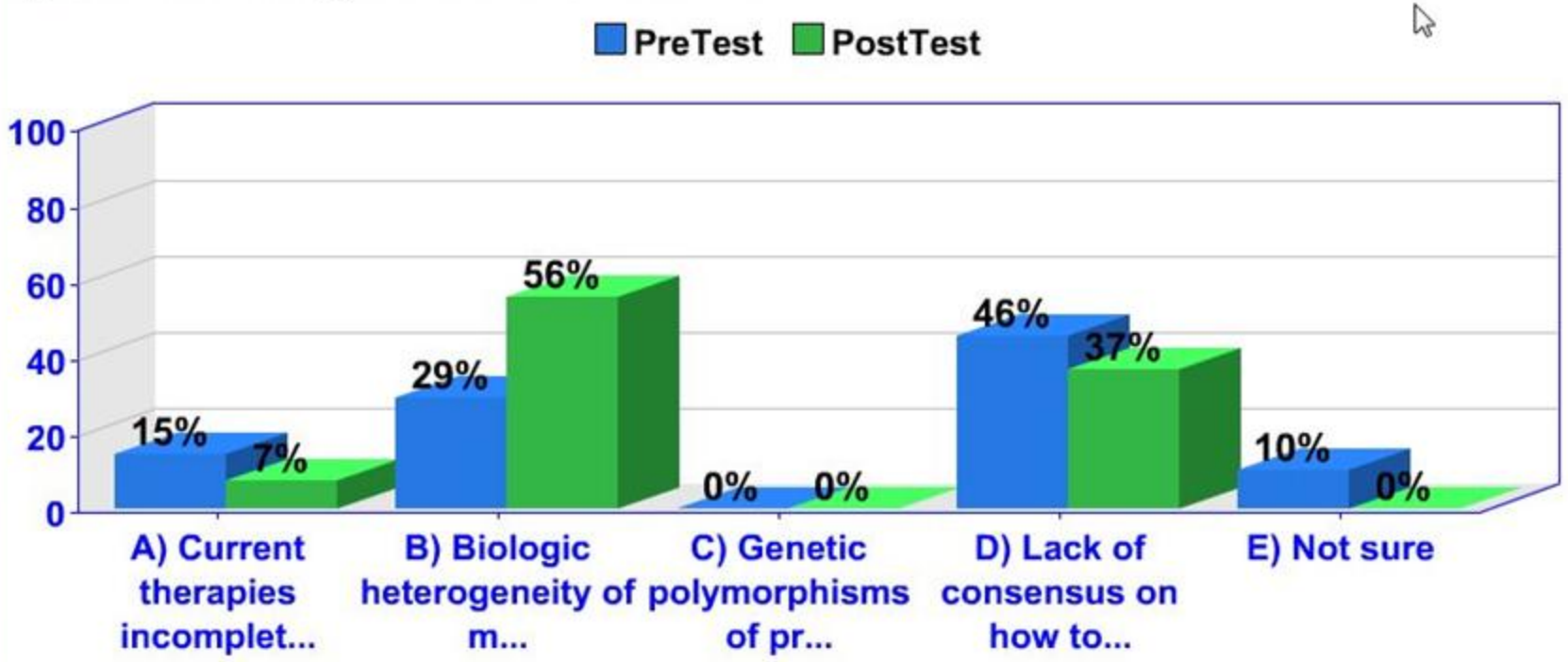
Compare Reports

3. Which of the following is the most important barrier to the optimal management of mCRPC?



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Polling Question 4

- **Which of the emerging treatment strategies holds most promise for the future management of mCRPC?**
  - a) Hormonal therapies
  - b) Chemotherapy
  - c) Immunotherapy
  - d) Molecularly targeted agents
  - e) Bone-directed therapies
  - f) Radiopharmaceuticals

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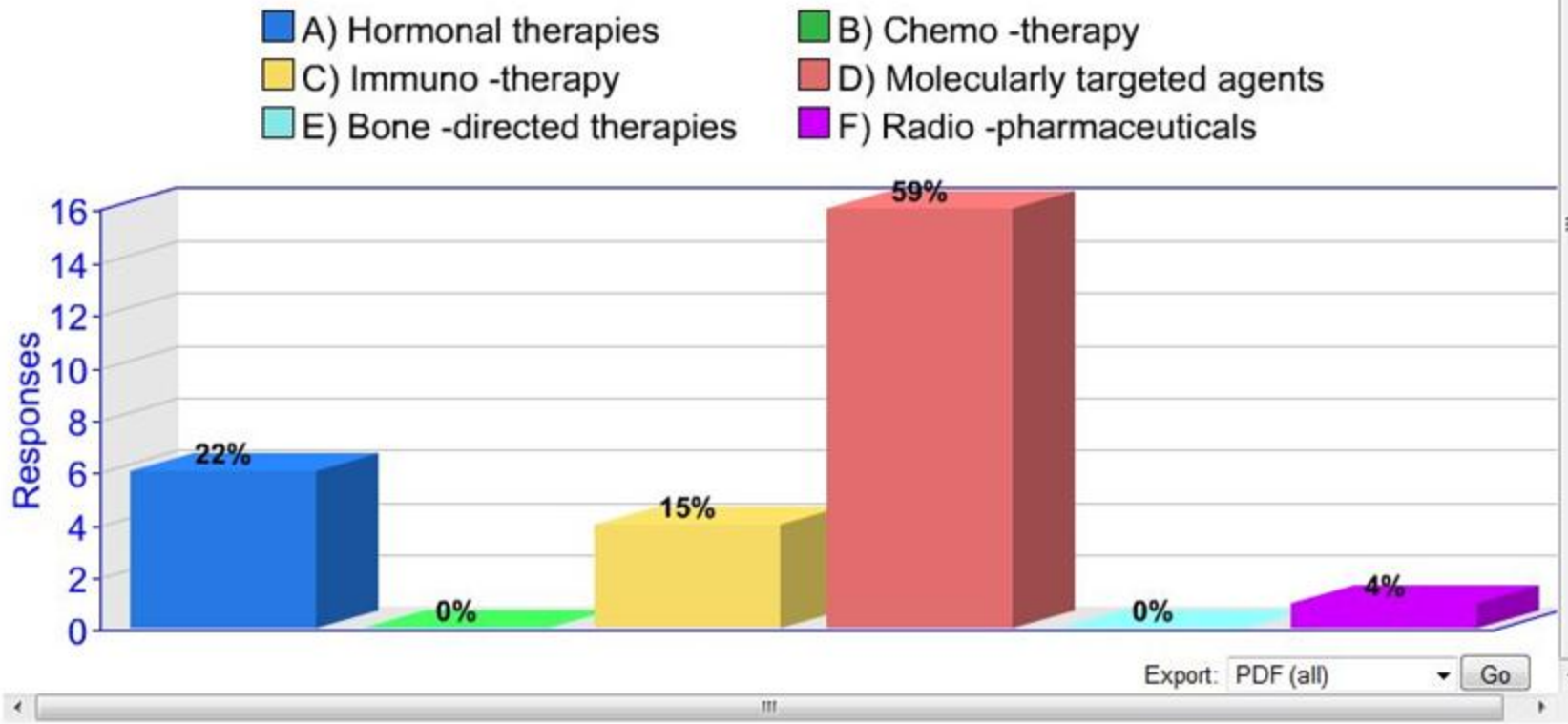
Reports

PostTest

4. Which of the emerging treatment strategies holds most promise for the future management of mCRPC?



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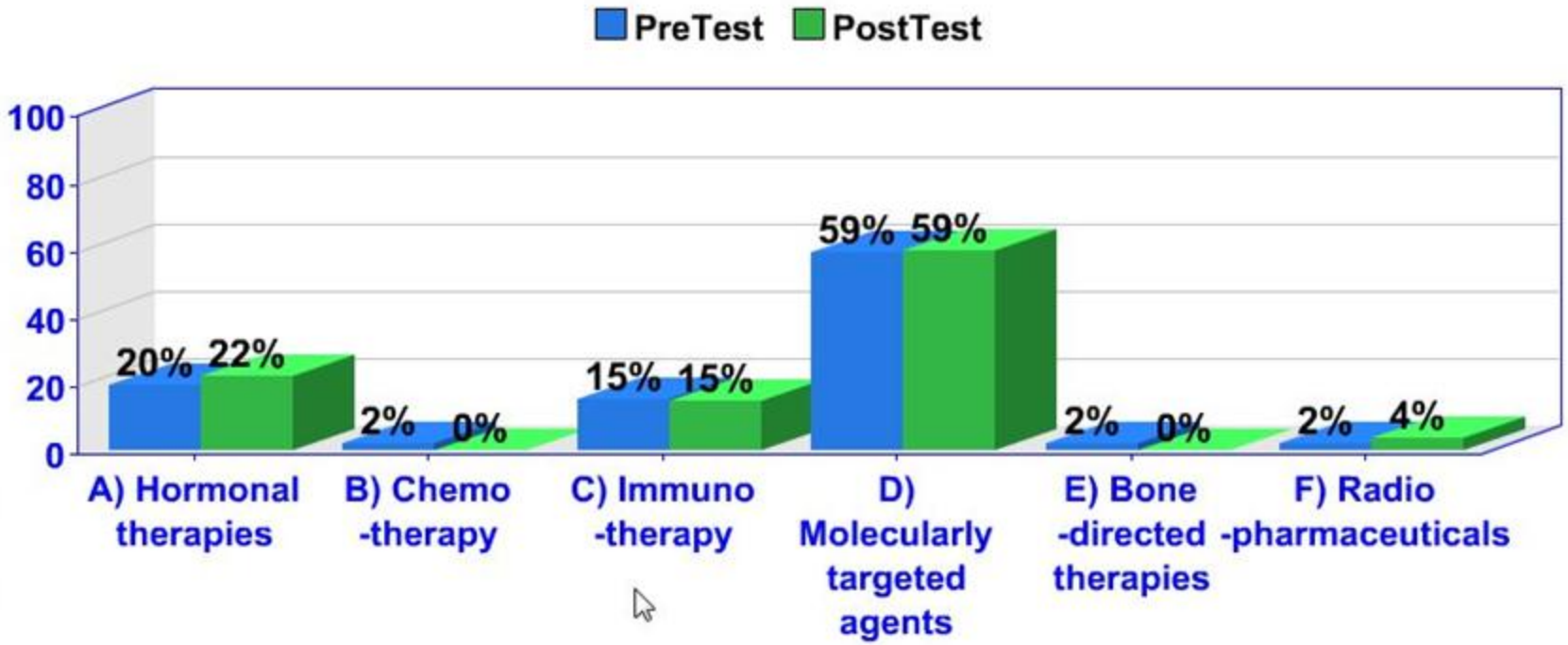
Compare Reports

4. Which of the emerging treatment strategies holds most promise for the future management of mCRPC?



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Polling Question 5

- **What is the role of Src/SFK signaling in CRPC?**
  a) Src/SFK signaling is associated with proliferative responses to androgens
  b) SFKs confer androgen-independence by mediating signals from various growth factors and chemokines
  c) Src/SFK signaling increases proliferation and promotes invasion and migration of prostate cancer
  d) Aberrant Src/SFK signaling leads to bone metastases
  e) All of the above

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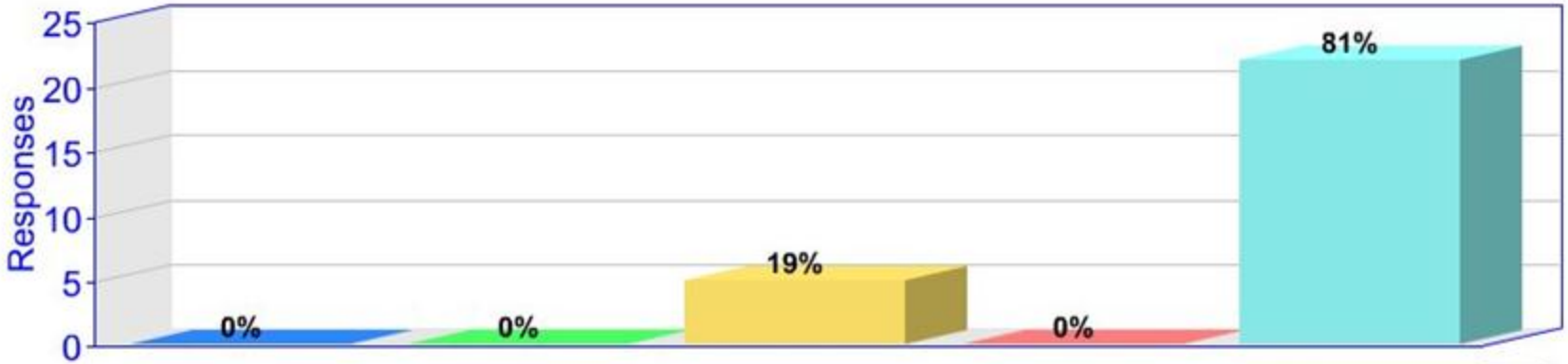
Reports

PostTest

5. What is the role of Src/SFK signaling in CRPC?

- A) Src/SFK signaling is associated with proliferative responses to androgens...
- B) SFKs confer androgen-independence by mediating signals from various growth f...
- C) Src/SFK signaling increases proliferation and promotes invasion and migration...
- D) Aberrant Src/SFK signaling leads to bone metastases
- E) All of the above



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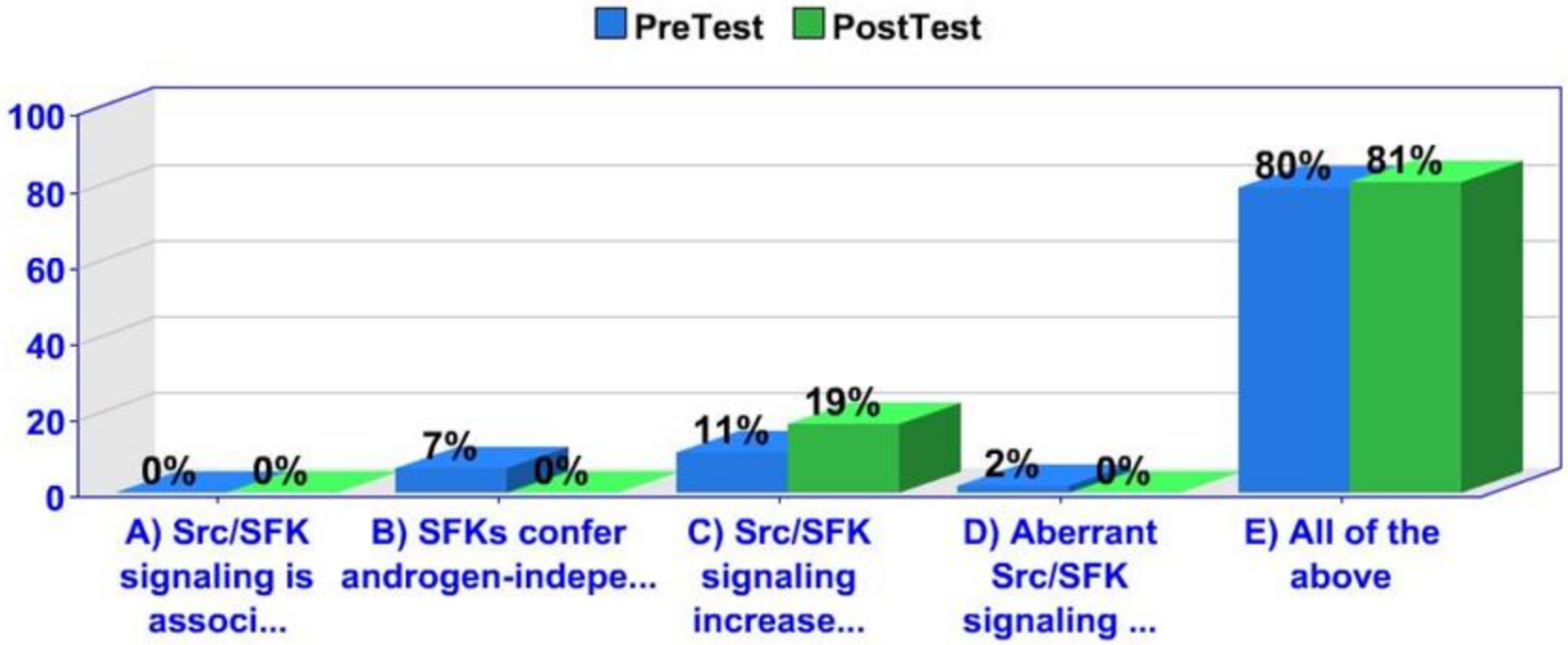
Compare Reports

5. What is the role of Src/SFK signaling in CRPC?



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Polling Question 6

- **Which of the following biomarkers may lead to a more personalized approach to care that maximizes benefit and minimizes harm?**
  a) Circulating tumor cells
  b) Bone turnover biomarkers
  c) AR splice variants
  d) Androgen synthesis precursor levels
  e) c-Met/HGF activity
  f) Tubulin mutations
  g) None of the above

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6. Which of the following biomarkers may lead to a more personalized approach to care that maximizes benefit and minimizes harm?

- A) Circulating tumor cells
- B) Bone turnover biomarkers
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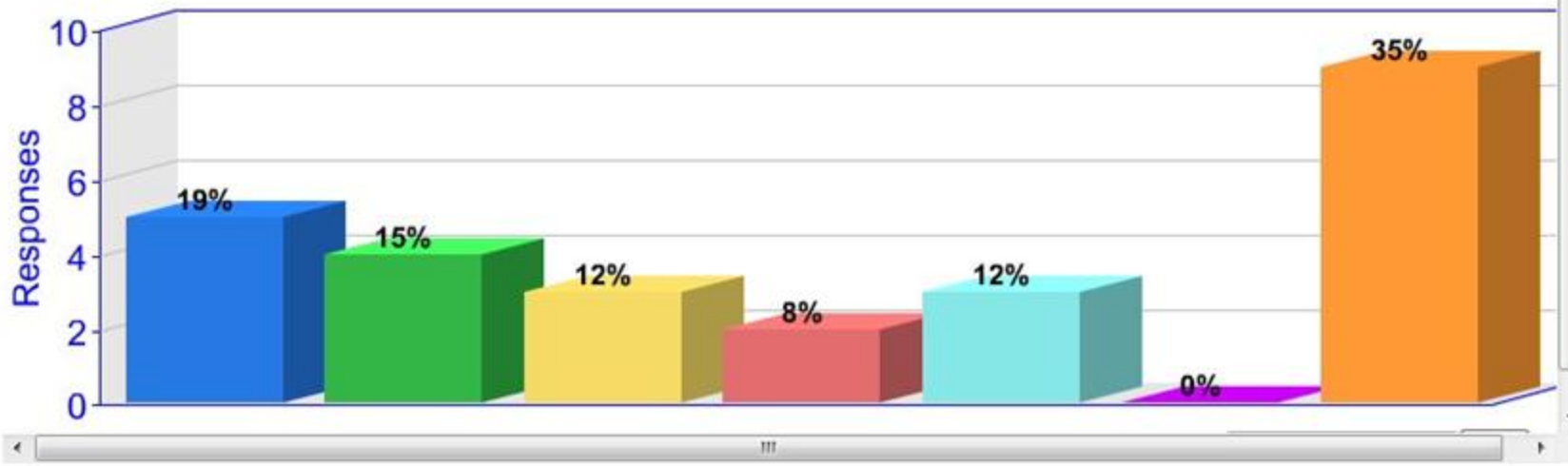

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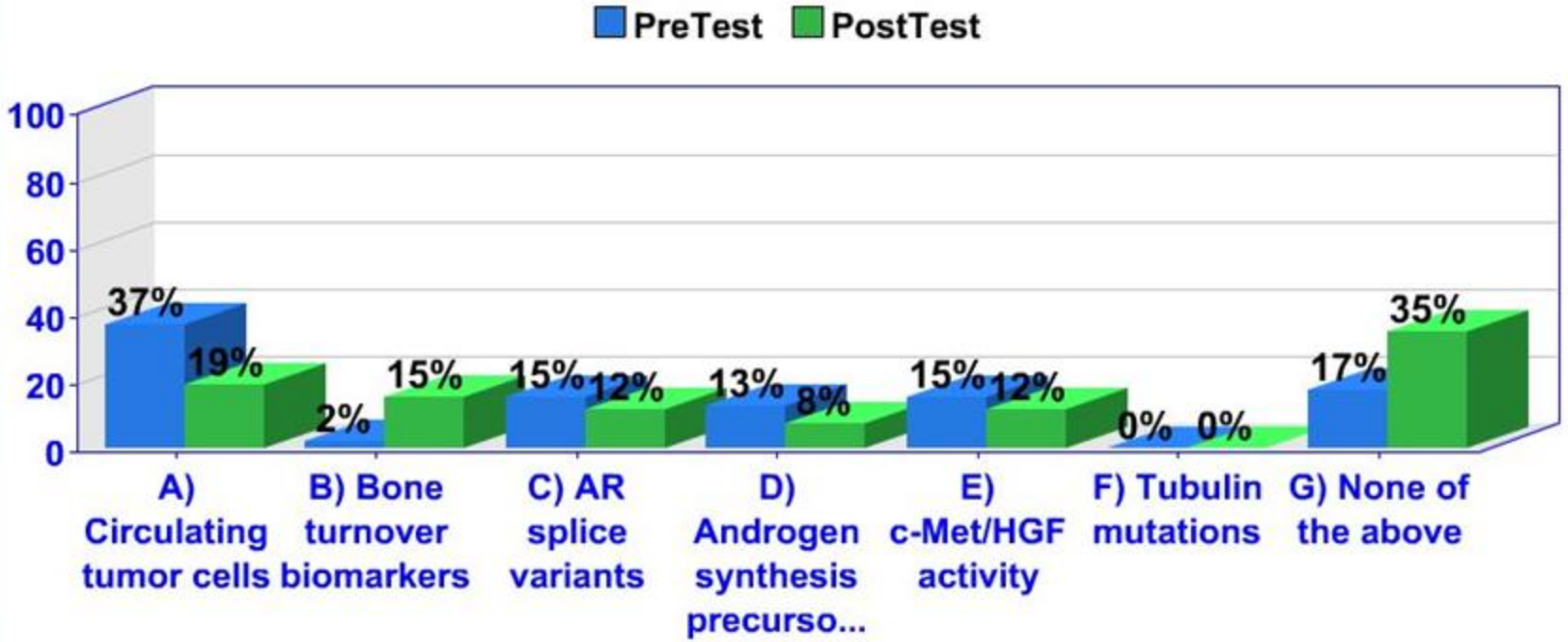
6. Which of the following biomarkers may lead to a more personalized approach to care that maximizes benefit and minimizes harm?



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Polling Question 7

- **Abiraterone acetate inhibits which of the following enzymes?**
  a) 11β-hydroxylase
  b) 21 hydroxylase
  c) 5α-reductase
  d) 17alpha-hydroxylase
  e) C17,20-lyase
  f) 17α-hydroxylase and C17,20-lyase

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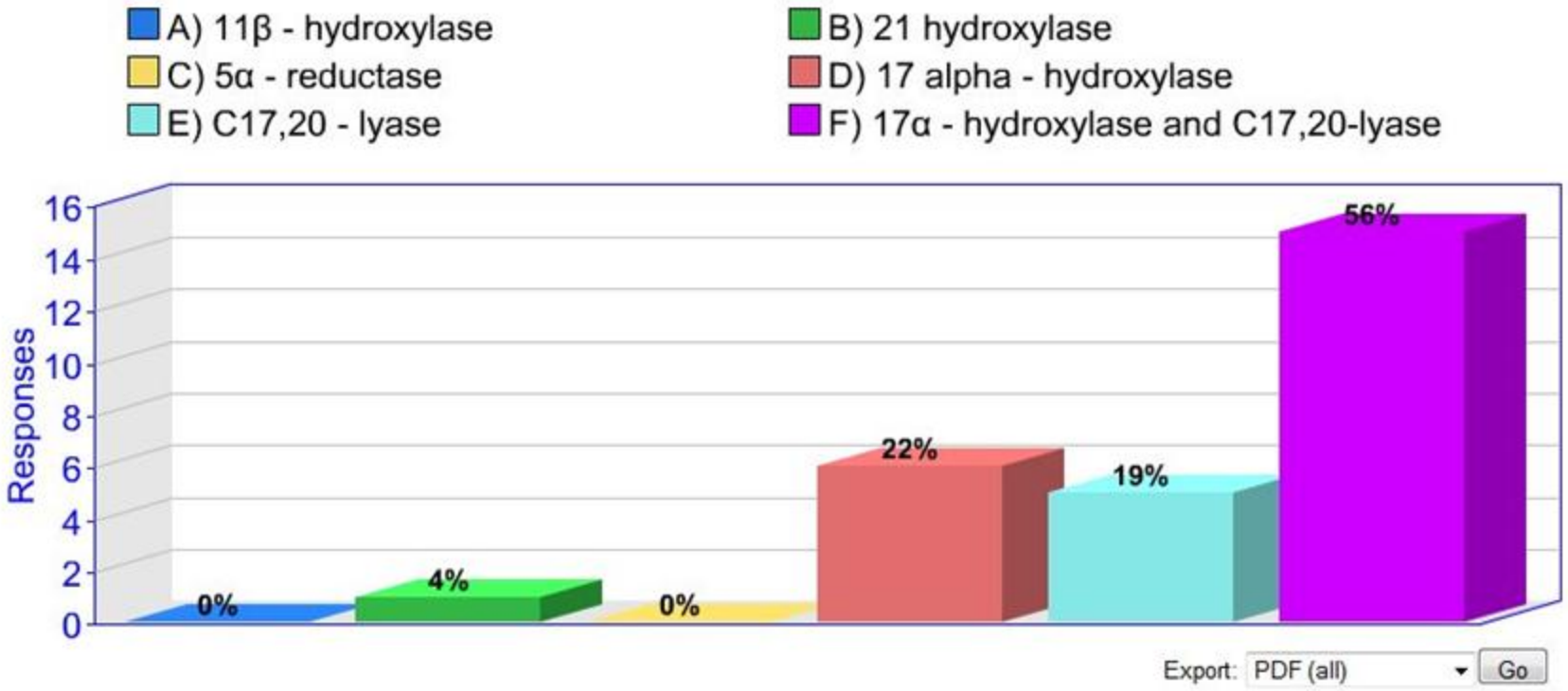
7. Abiraterone acetate inhibits which of the following enzymes?



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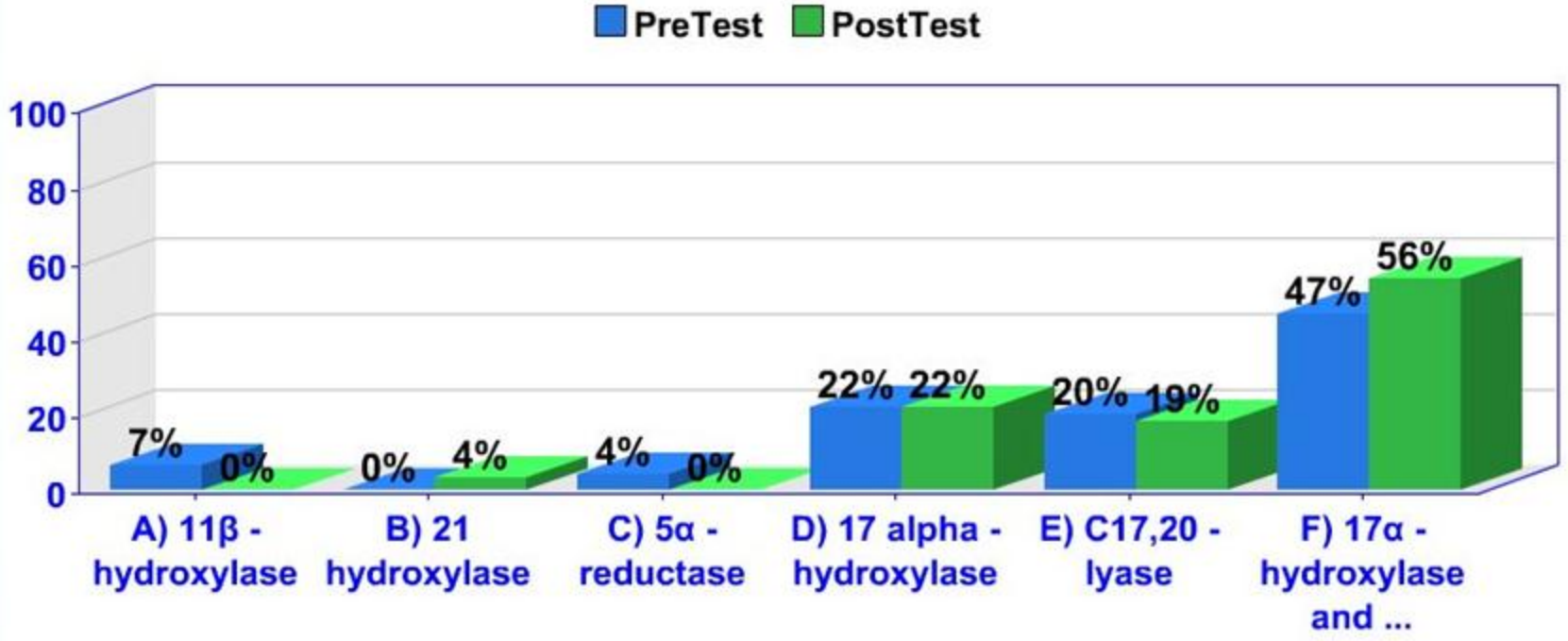

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Polling Question 8

- **Cabozatinib (XL184) is a small molecule inhibitor of:**
  a) VEGFR1
  b) VEGFR2
  c) MET
  d) VEGFR1 and MET
  e) VEGFR2 and MET

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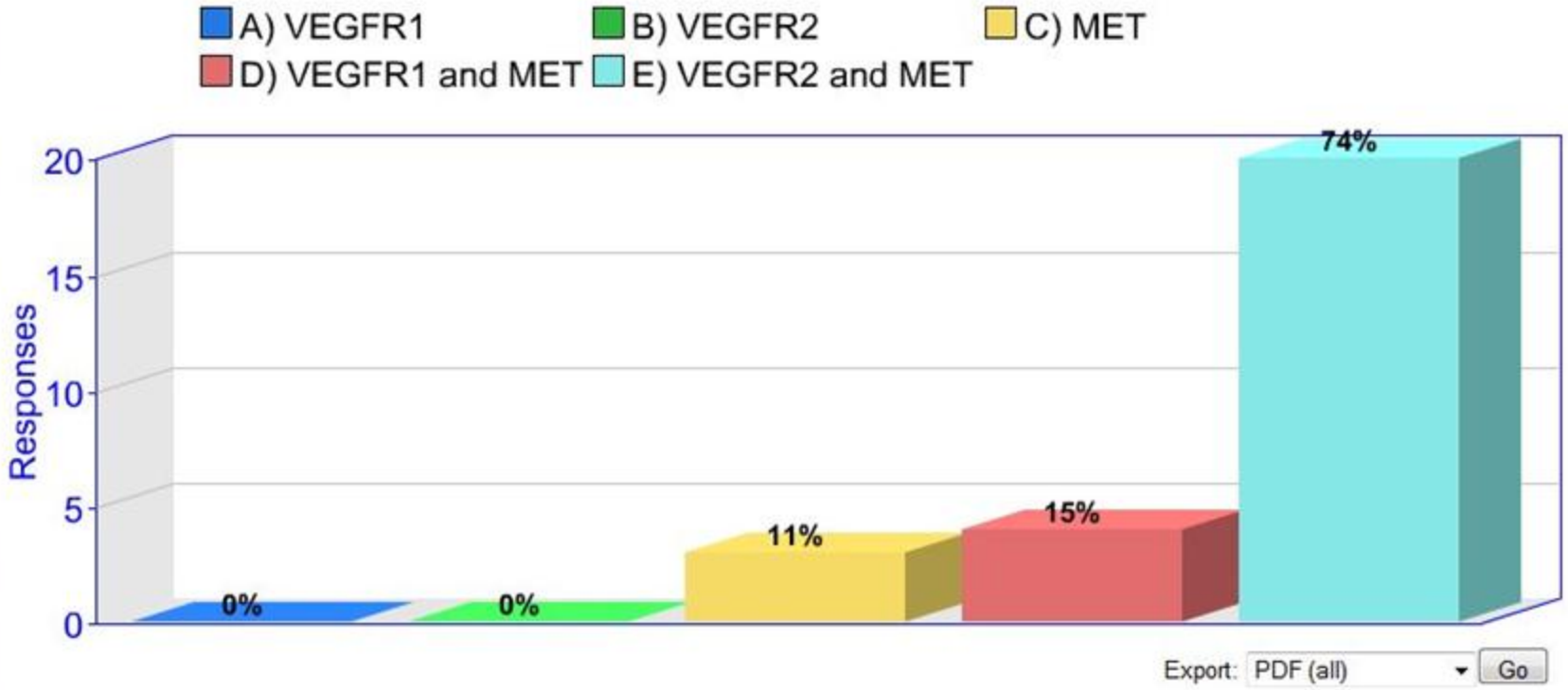
8. Cabozatinib (XL184) is a small molecule inhibitor of:



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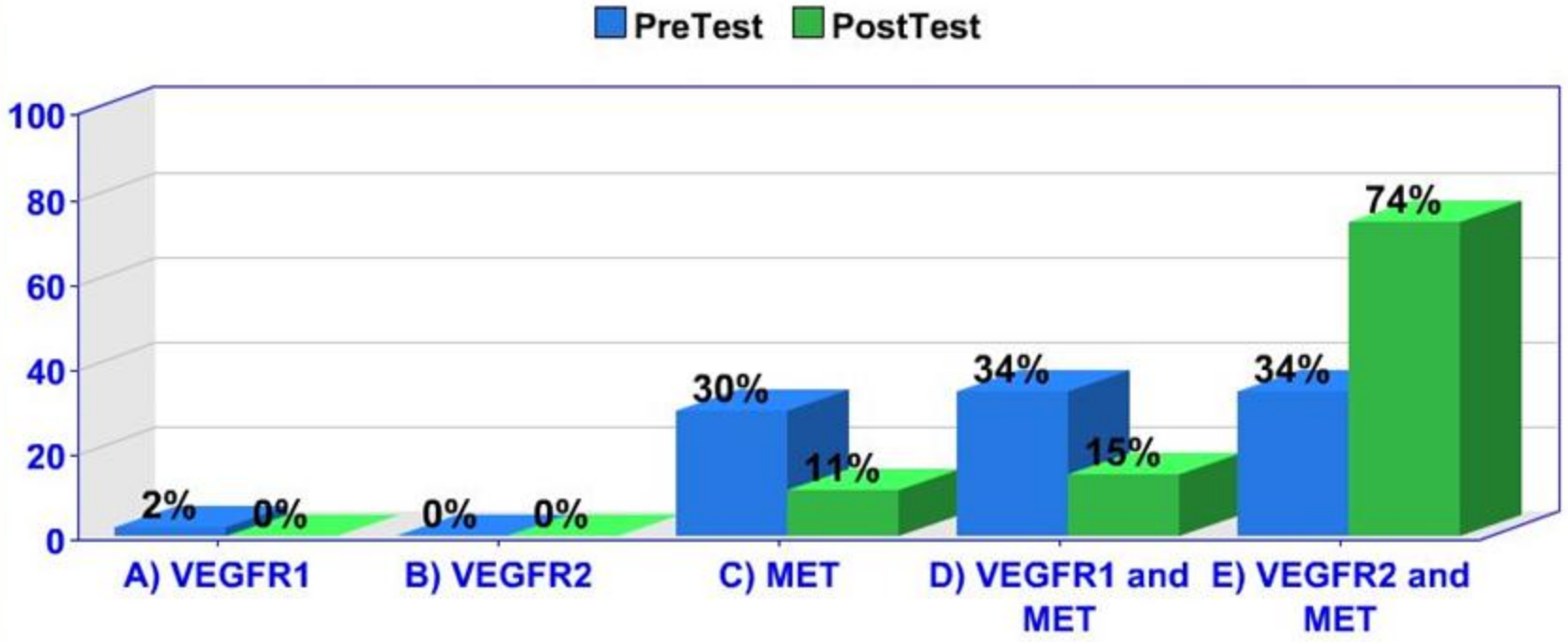

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Polling Question 9

- **Dasatinib, a small molecule inhibitor of Src, Bcr-Abl, c-Kit, c-FMS, PDGFR, and EphA2 has been shown to inhibit:**
  a) PCa cell adhesion and invasion
  b) PCa cell proliferation and migration
  c) Lymph node metastases
  d) Osteoclast formation and activity
  e) All of the above

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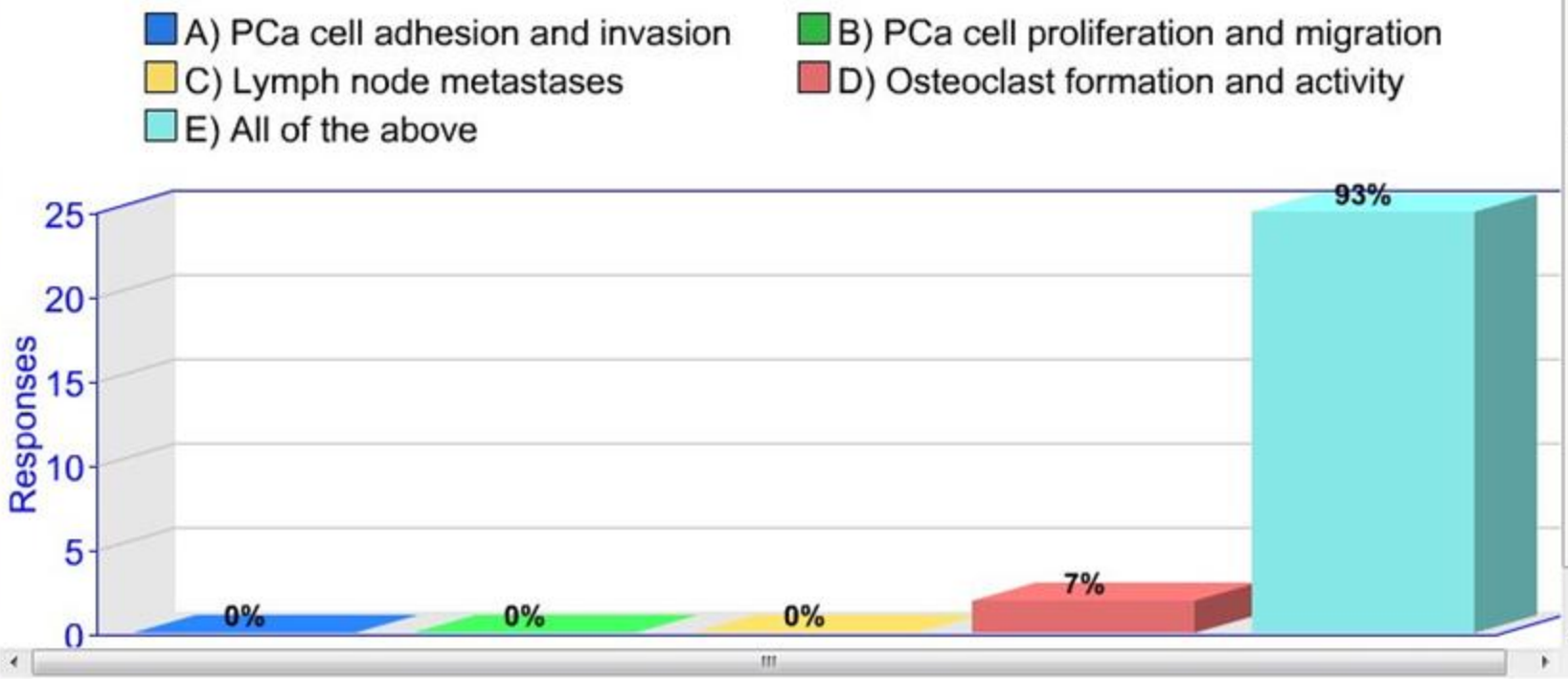
9. Dasatinib, a small molecule inhibitor of Src, Bcr-Abl, c-Kit, c-FMS, PDGFR, and EphA2 has been shown to inhibit:



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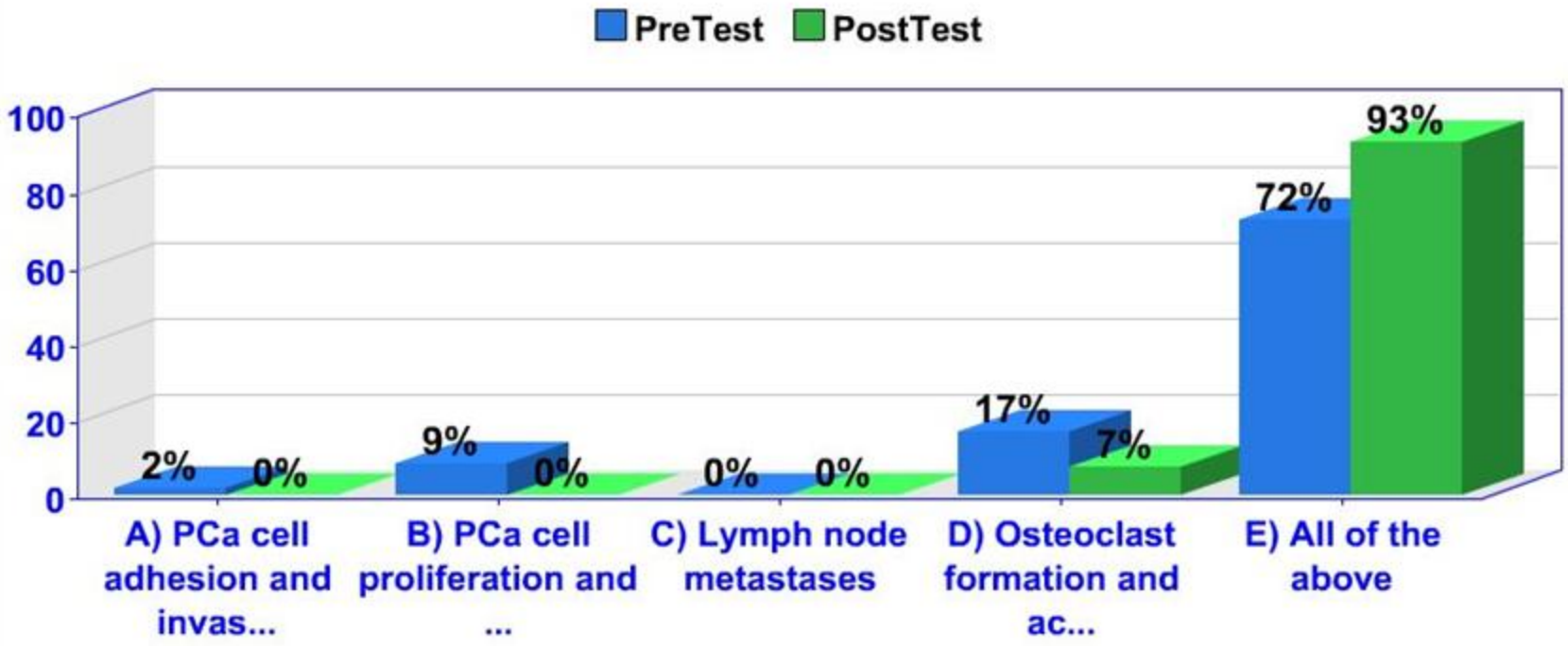

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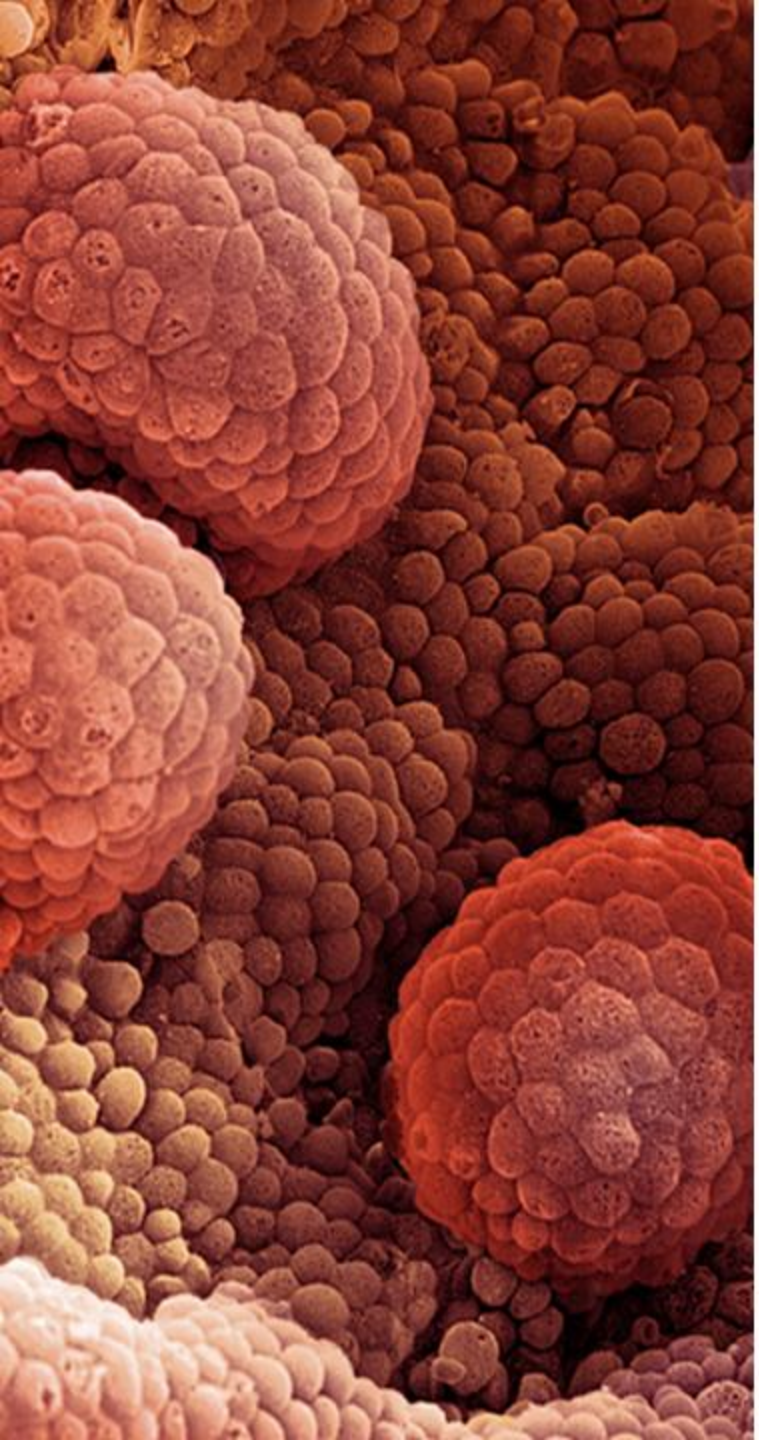

Q & A

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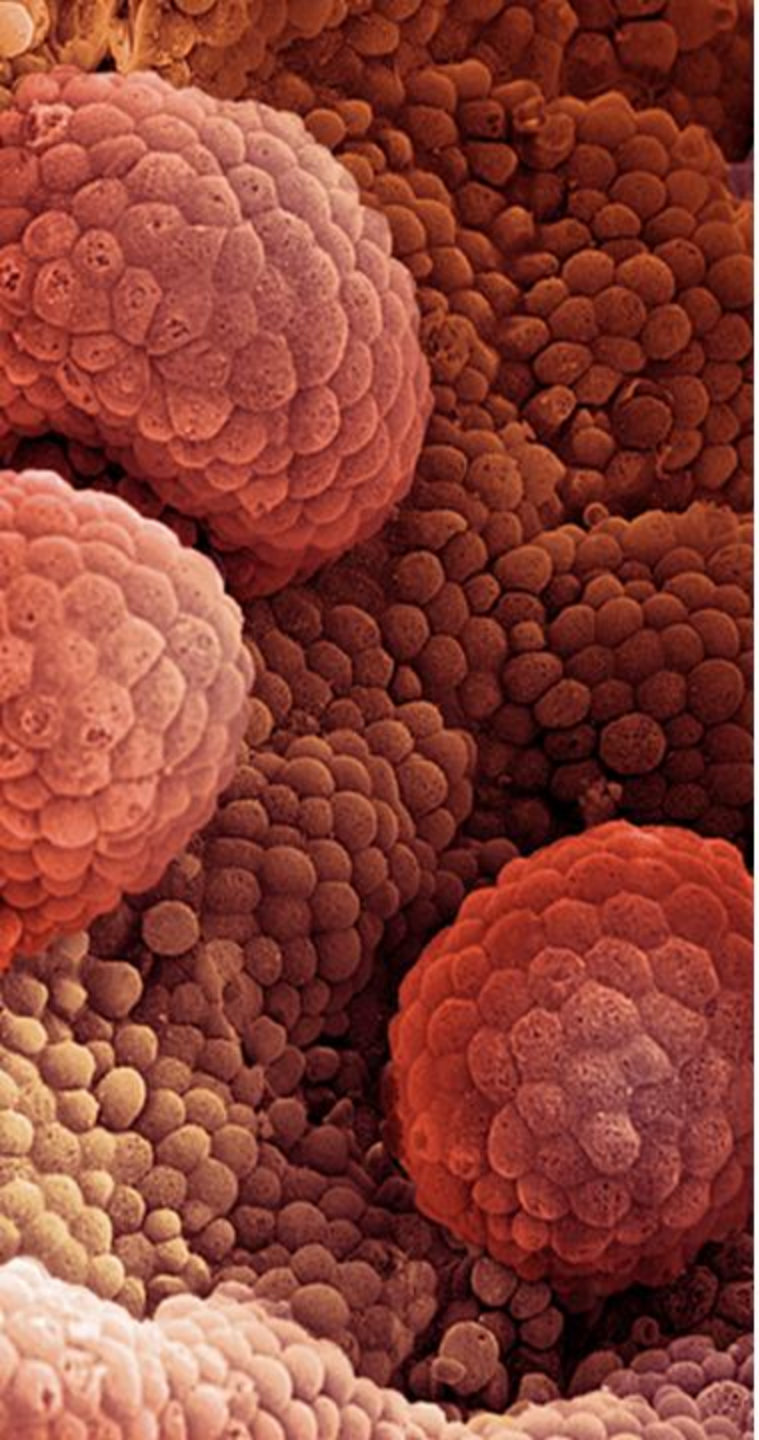

Panel Discussion

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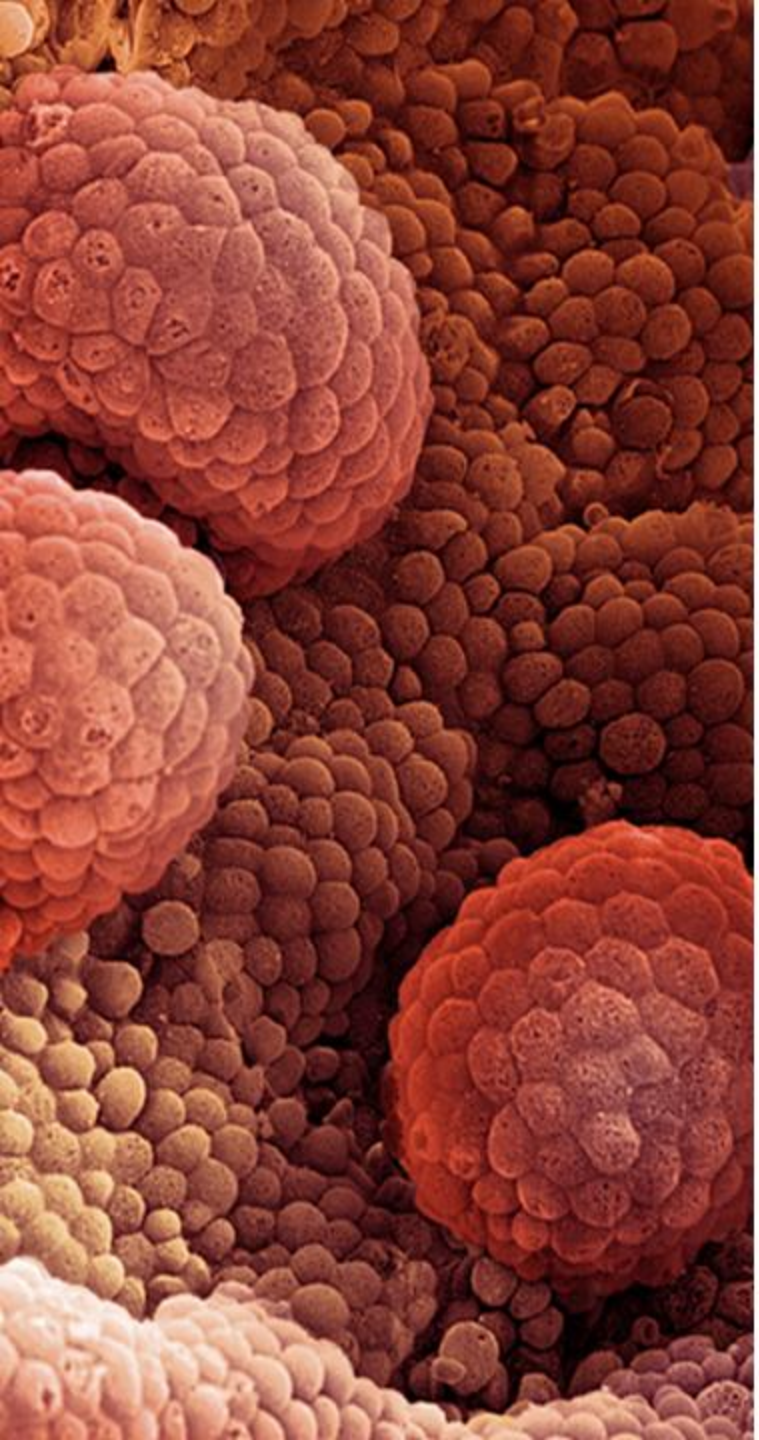

Concluding Remarks, Future Directions

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Thank You

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