A Path to Prostate Cancer Therapy Development

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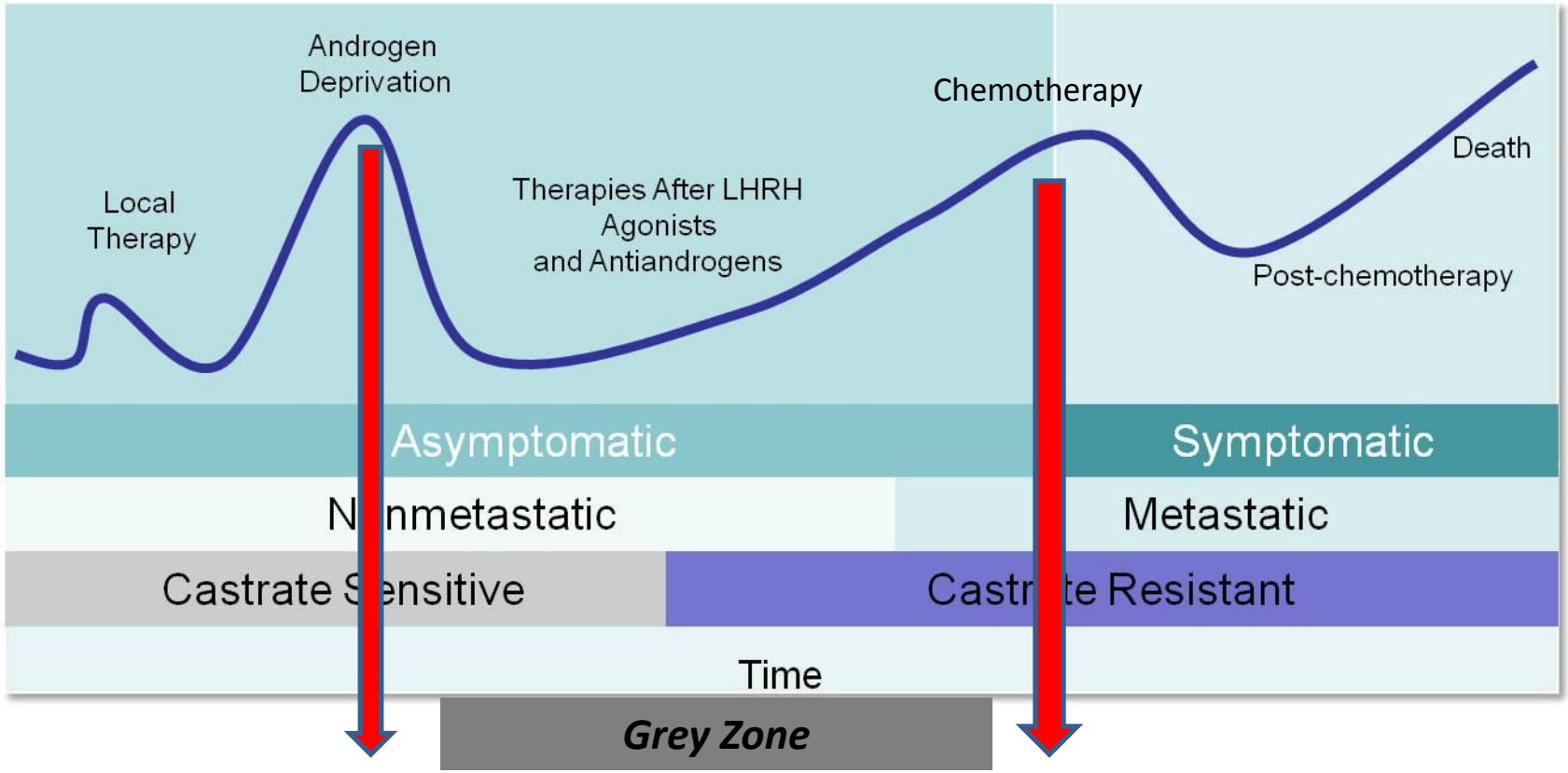
Medical School
Dept of Clinical Therapeutics

‘Discovery is our Business’

Charles Huggins (1902-1997)

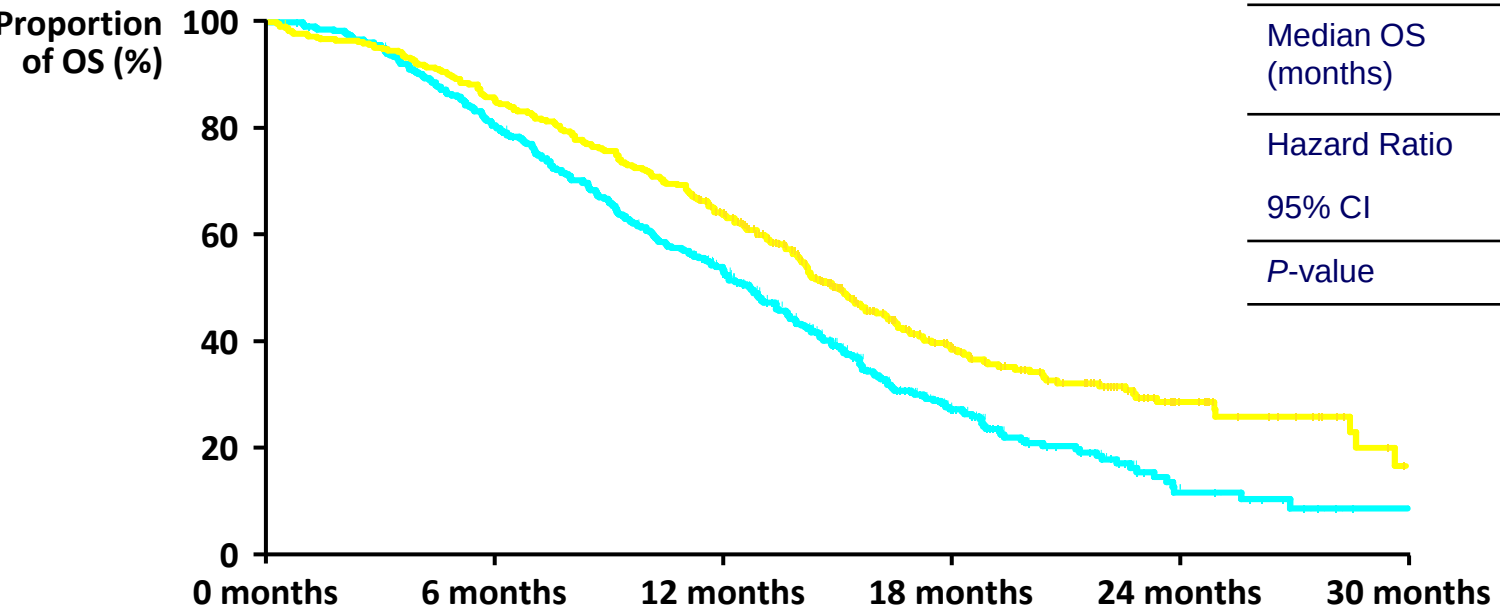
Nobel Prize in Medicine 1966

Prostate Cancer Therapeutics Evolution



March 2010

Cabazitaxel
Overall Survival Benefit in chemotreated mCRPC



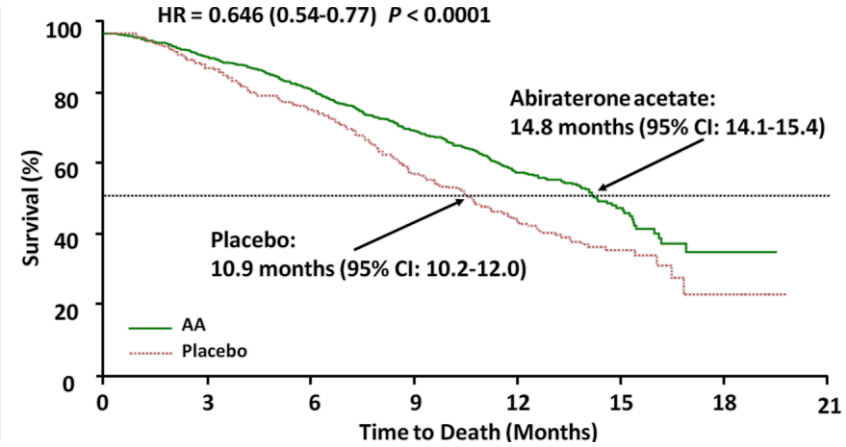
	CBZP	MP
Median OS (months)	15.1	12.7
Hazard Ratio	0.70	
95% CI	0.59-0.83	
P-value	< .0001	

Currently Investigating Known therapy Paradigm Survival Improvement over Docetaxel

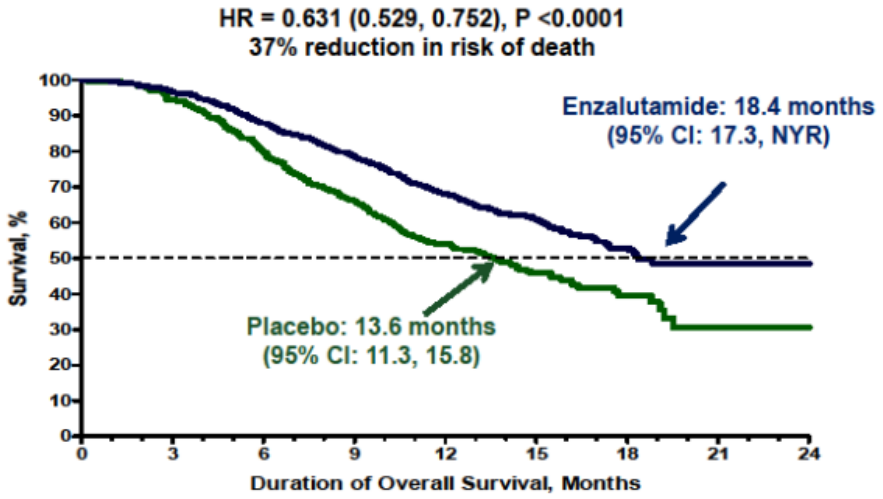
De Bono et al 2010.

Further androgen signaling inhibition prolongs life in chemotherapy-treated mCRPC

Abiraterone acetate + Prednisone

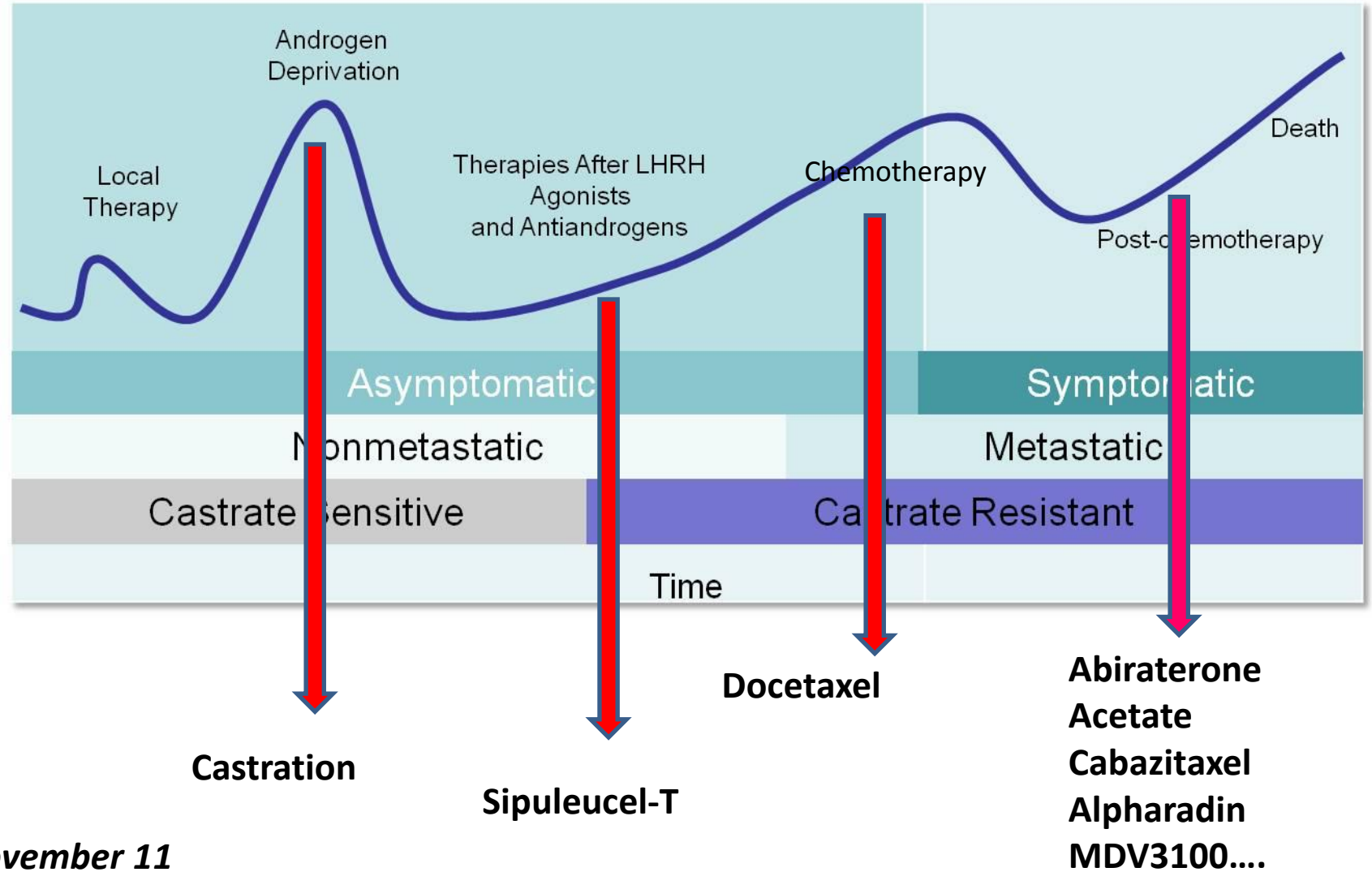


Enzalutamide



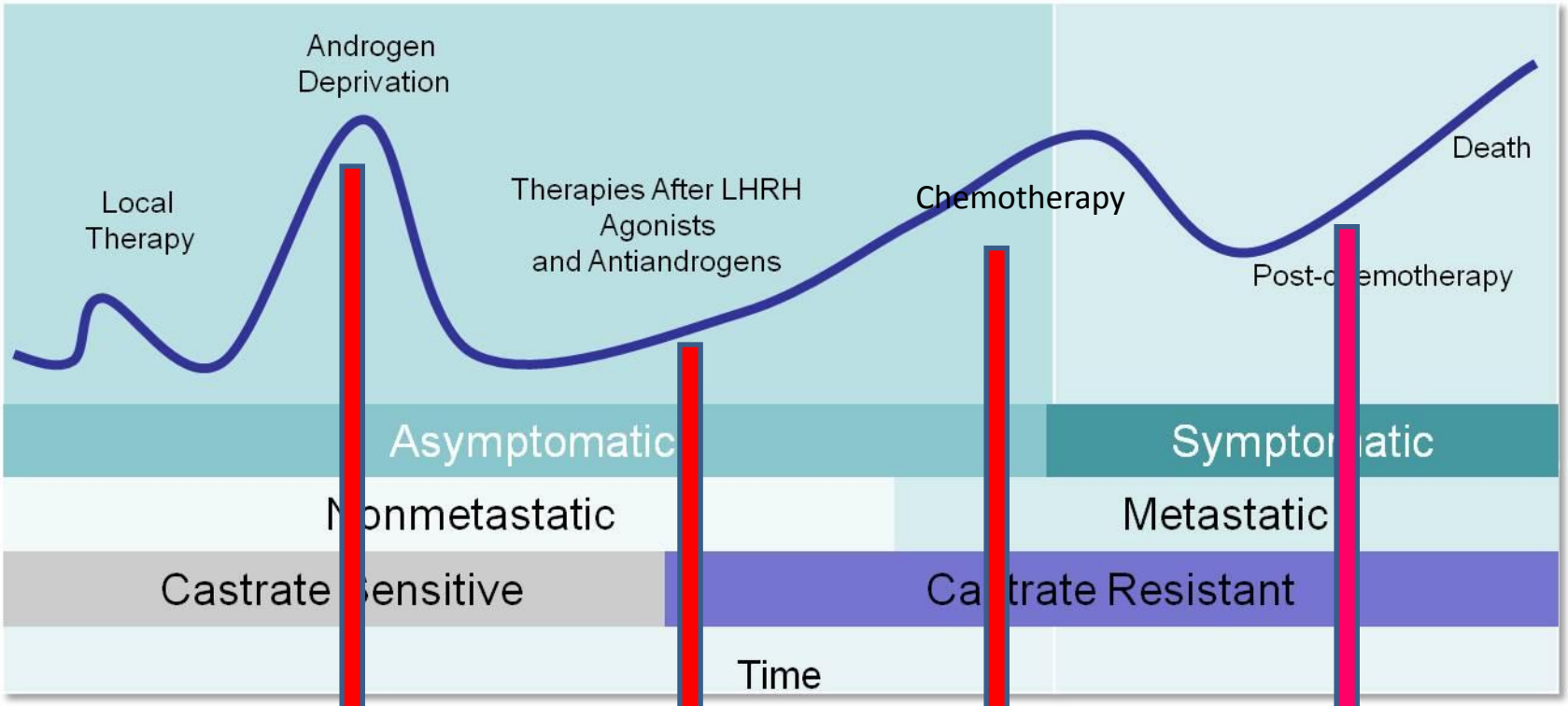
de Bono J et al. N Engl J Med 2011;364:1995-2005.
Scher HI et al. N Engl J Med 2012;367:1987-97.

Prostate cancer drug development



November 11

Prostate cancer drug development



Castration Intermittent for biochemical relapse

Continuous Castration mHSPC

Abiraterone Acetate
Sipeuleucel-T

Docetaxel

Abiraterone Acetate
Cabazitaxel
Alpharadin
Enzalutamide

June 12

Survival in patients with mCRPC

Trial	Regimen	Pts	HR	N	Survival (months)	Delta (mo's)
IMPACT	Sipuleucel-T	CRPC	0.78	512	25.8 vs. 21.7	4.1
Tax 327, Tannock NEJM, 2004	Docetaxel/pred vs. mito/pred	CRPC, chemo naïve	0.76	1006	18.9 vs. 16.5	2.4
TROPIC, Sartor Lancet 2010	CBZ/pred vs. mito/pred	CRPC, post-docetaxel	0.70	755	15.1 vs. 12.7	2.4
COUGAR 301 NEJM 2011	Abiraterone Acetate /pred vs. Pred	CRPC, post-docetaxel	0.64	1195	14.8 vs. 10.9	3.9
Alsympca	Alpharadin vs placebo	CRPC	0.695	809	14.0 vs 11.2	3.6
AFFIRM	Enzalutamide vs placebo	CRPC post docetaxel	0.63	1199	18.4 vs 13.6	4.8

Overall Survival increase: Can we add it up or do even better with the right sequence or combination

+ ≥21.2ms!!

We have a problem..

But it's a good one !!

More reagents than we knowledge on how to use them..

Therapy Development to be distinguished from Drug Development

Therapy approach

How we treat patients

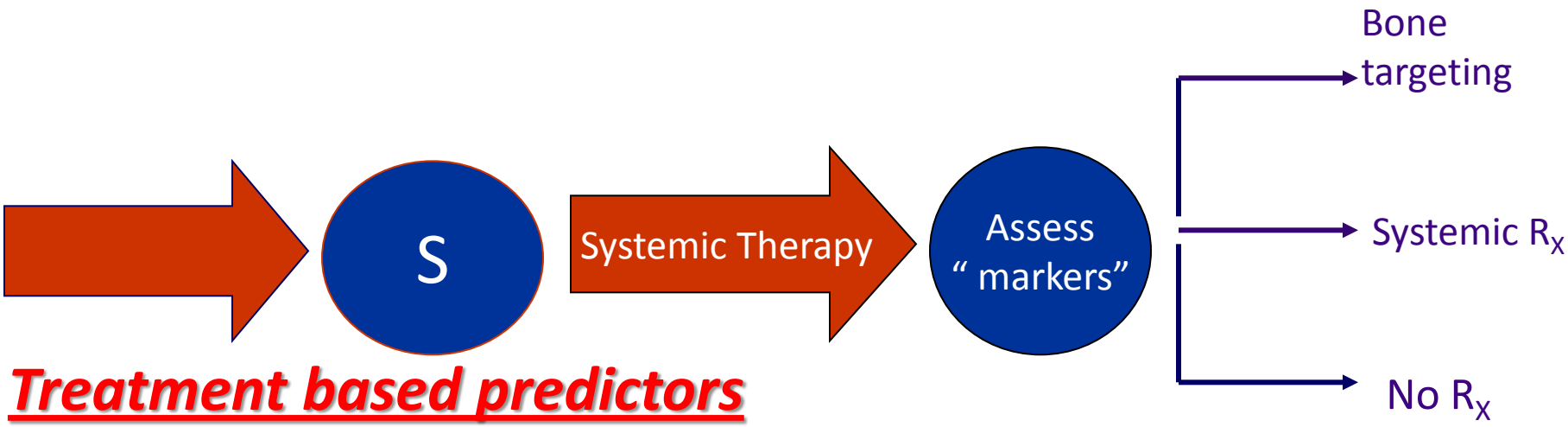
Vs

How we should treat patients!

Current Treatment Approach

- Access to reagents
- Reimbursement Status/ Ease to prescribe
- Discipline / Physician *(urology/ medical oncology/ radiation oncology)*
- Experience/ Evidence Driven- Solid Tumor Therapy Paradigm
- Disease Characteristics (bone tropism / anaplastic features)
- Patient Characteristics
- Safety Profile
- Patient Preference *(need to build on this)*

Integrated Management of Advanced Prostate Cancer



Treatment based predictors of outcome are required

Disease Heterogeneity may require combinatorial approach or guided sequencing

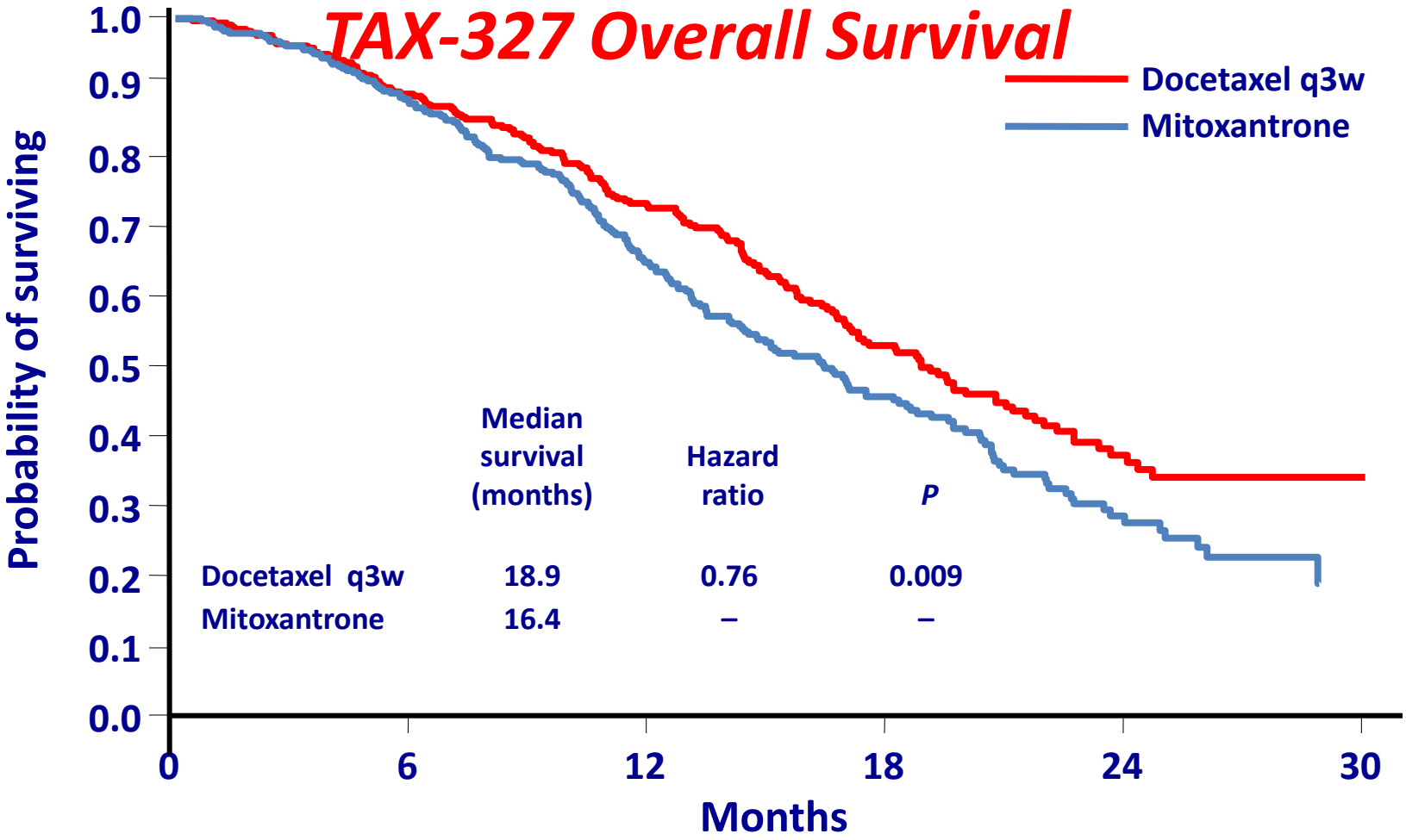
- ✓ ***The significance of Prostate Cancer Chemotherapy Response Profile***
- ✓ ***Proposed New Therapy Paradigm***
- ➢ ***Transition from endocrine to paracrine androgen signaling***
- ➢ ***microenvironment driven resistance to androgen signaling inhibition***
- ➢ ***Epitheliocentric progression : Altered cell cycle***

Solid Tumor Therapy Paradigm

Therapeutic agents effective in far-advanced disease states will be more effective in earlier states.

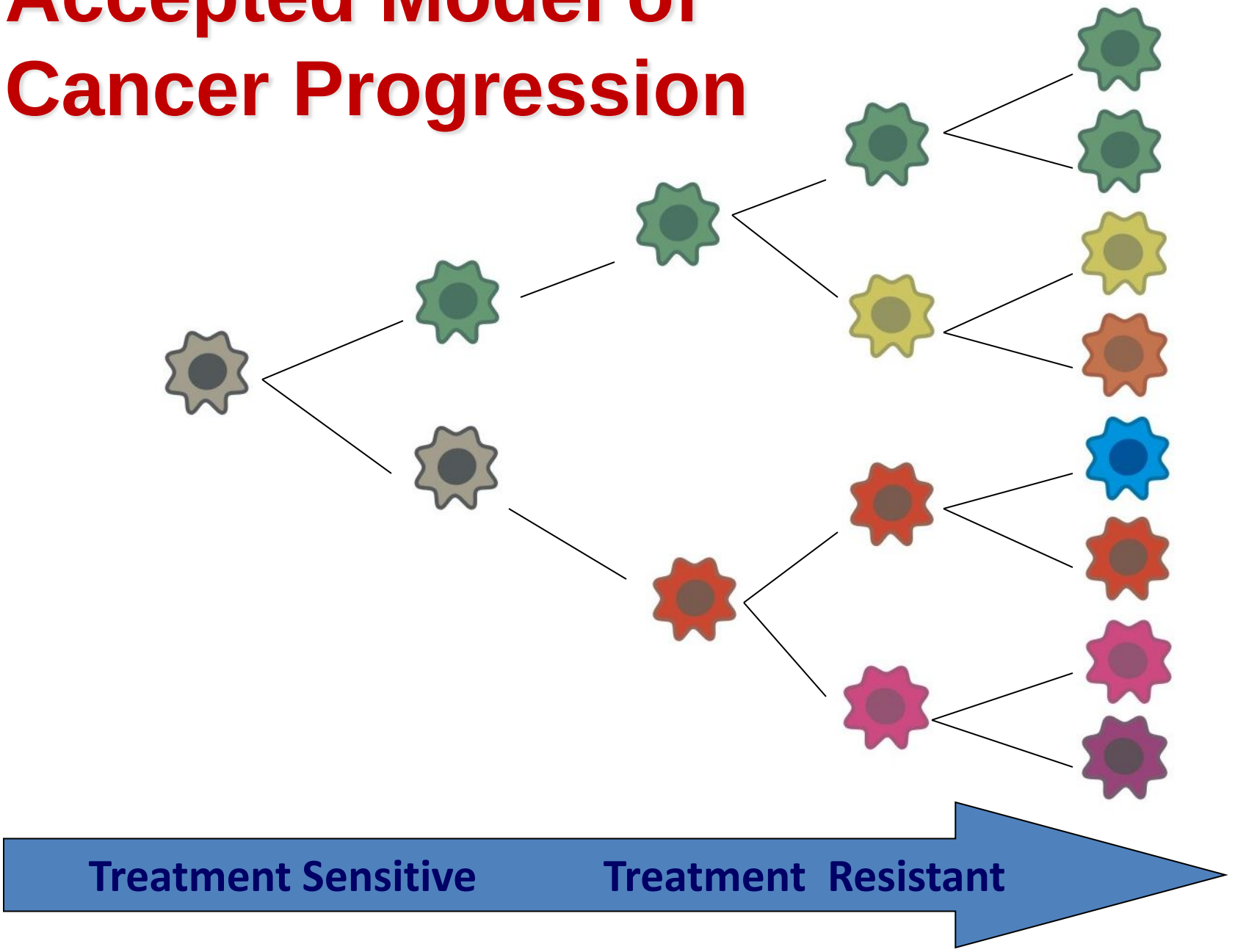
Chemotherapeutic Standard of Care in Metastatic Castrate Resistant Prostate Cancer

Docetaxel



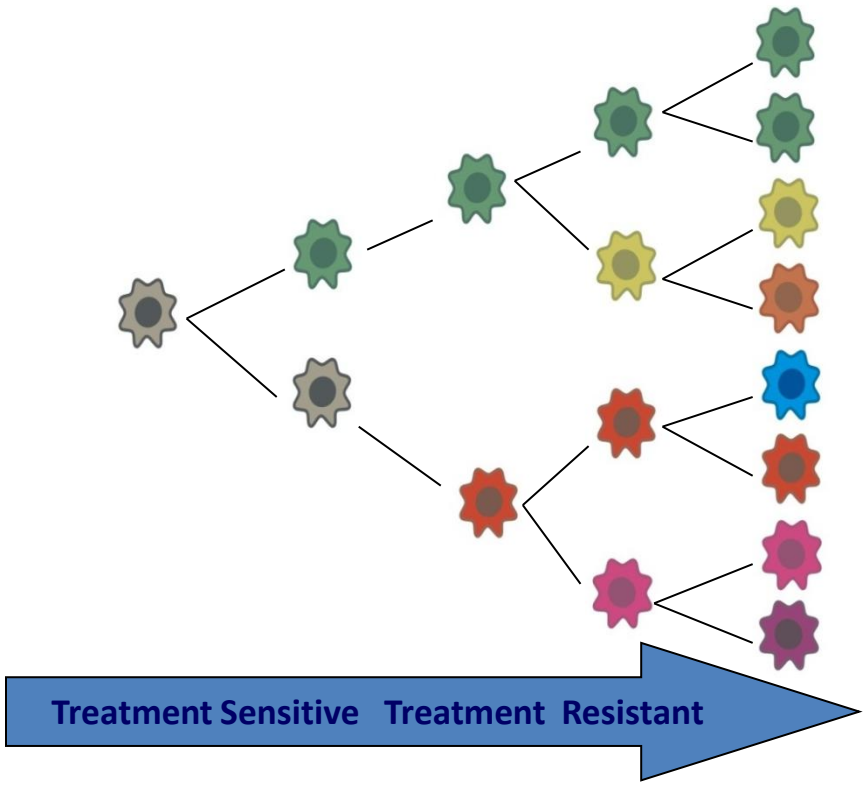
Tannock et al NEJM 2004

Accepted Model of Cancer Progression

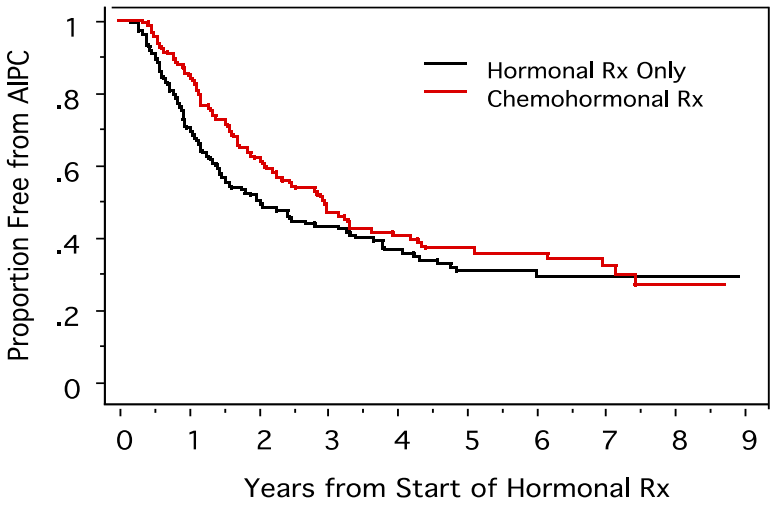


Therapeutic agents effective in far-advanced disease states will be more effective in earlier states.

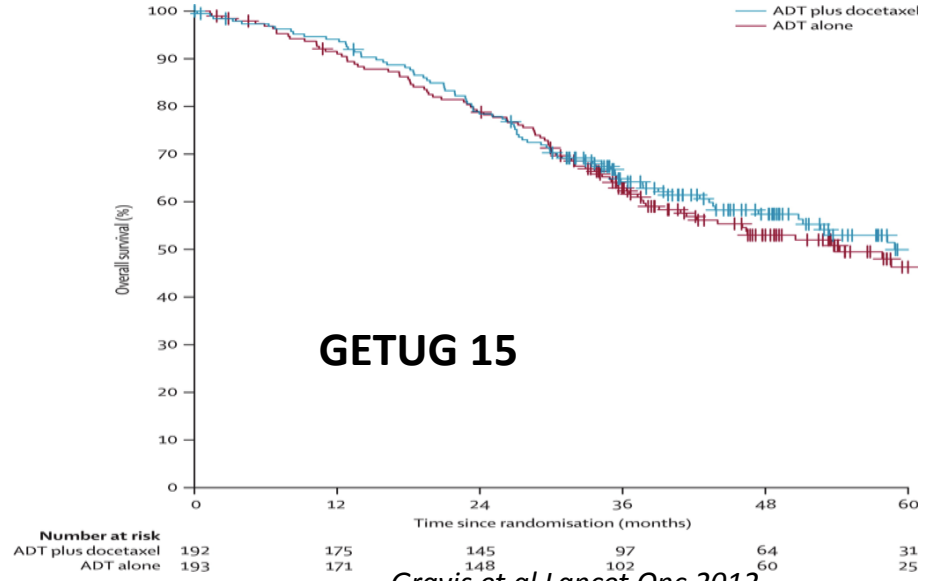
Accepted Model of Cancer Progression



Earlier Chemotherapy Does Not Prolong Survival !



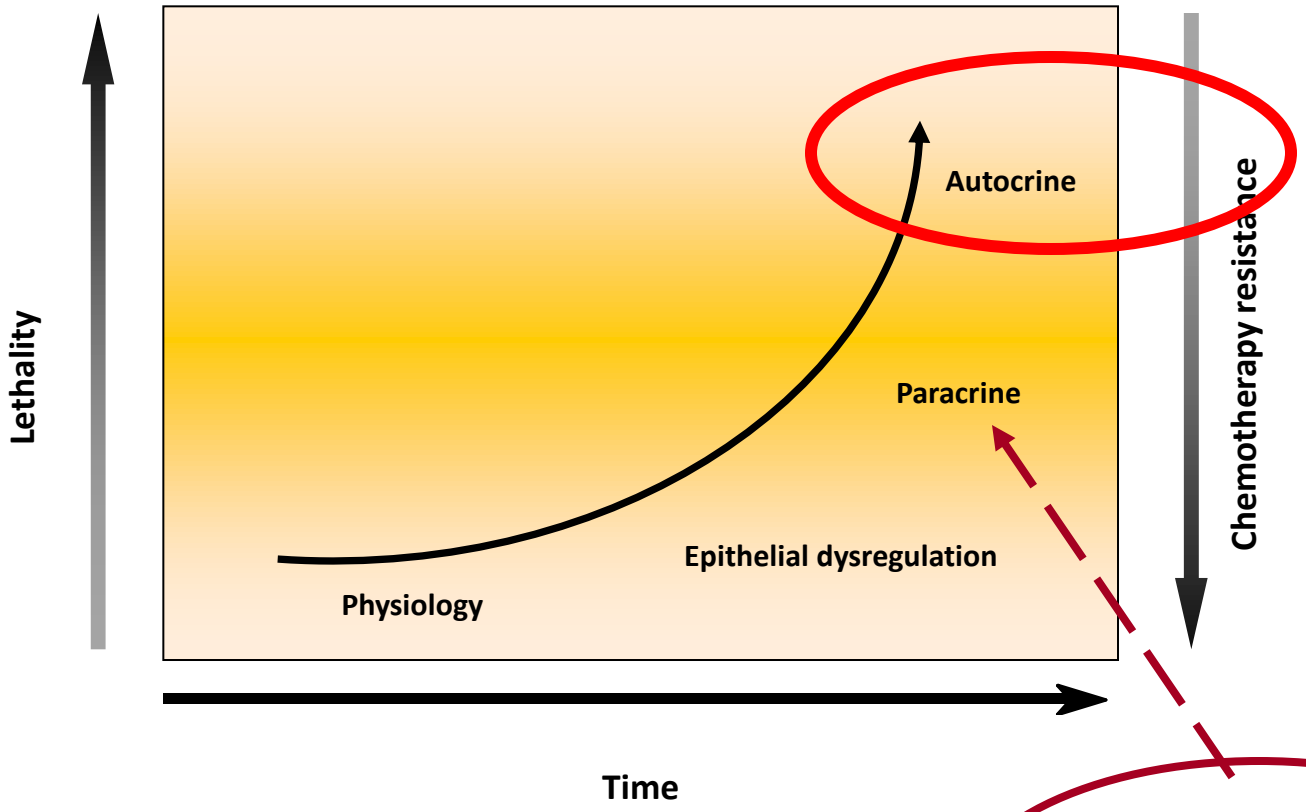
Millikan et al JCO 2008



GETUG 15

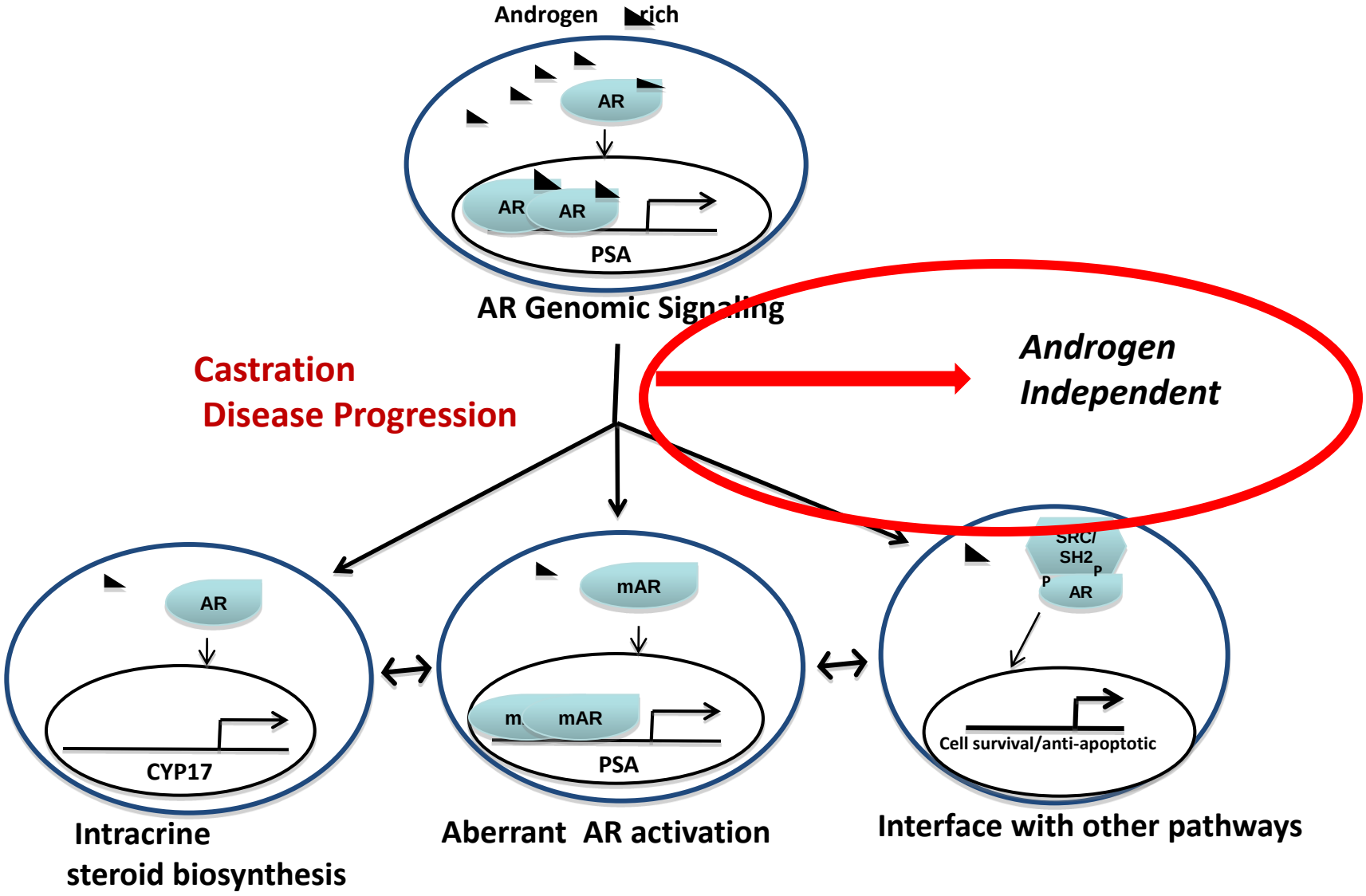
Gravis et al Lancet Onc 2012

Proposed Progression Model

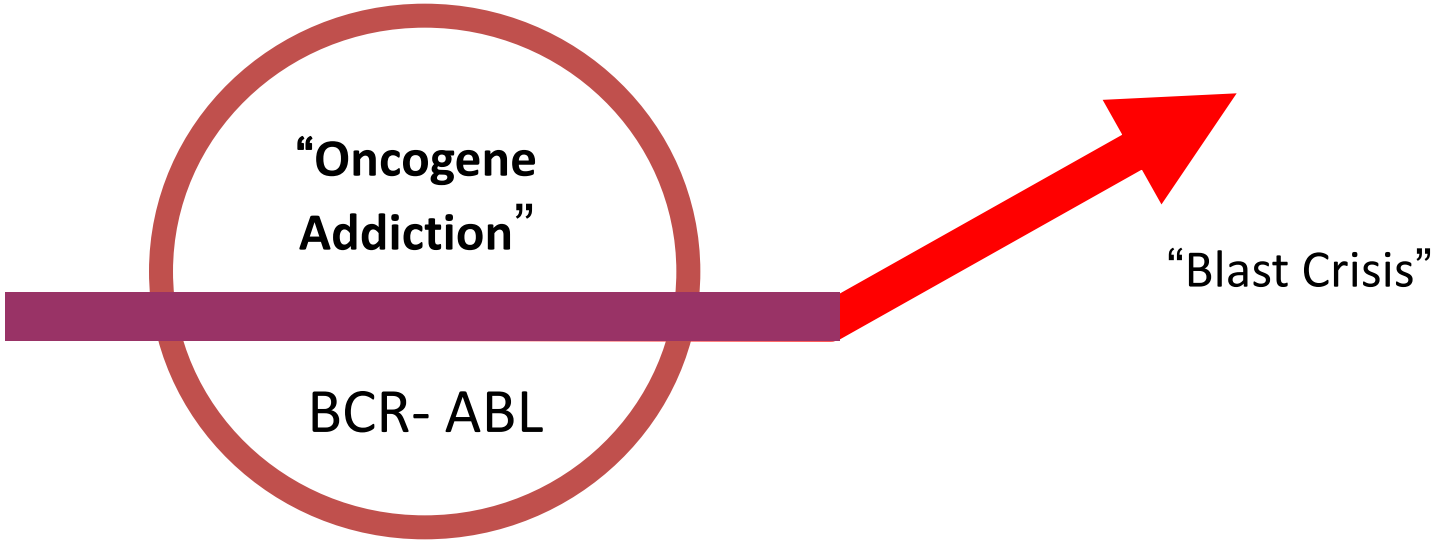


Efstathiou et al CCR 2010

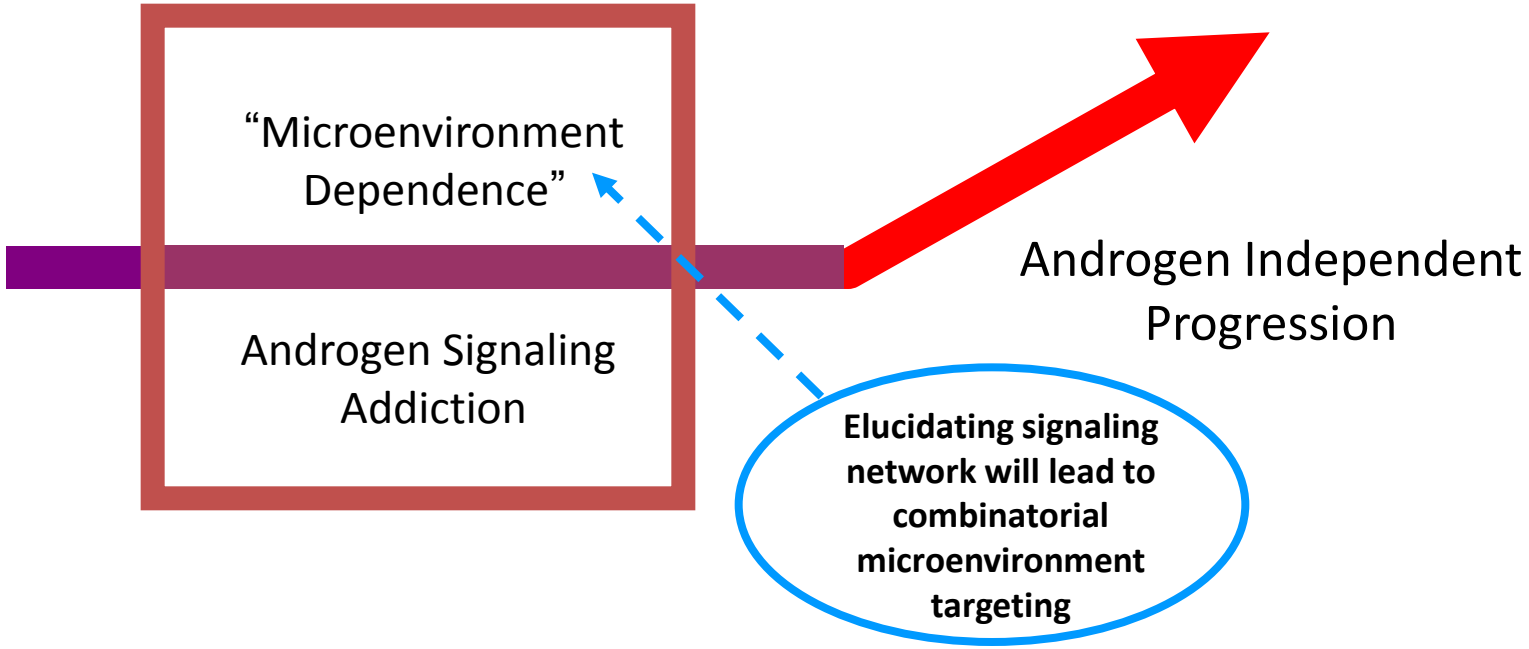
Adaptive Response of Androgen Signaling in CRPC



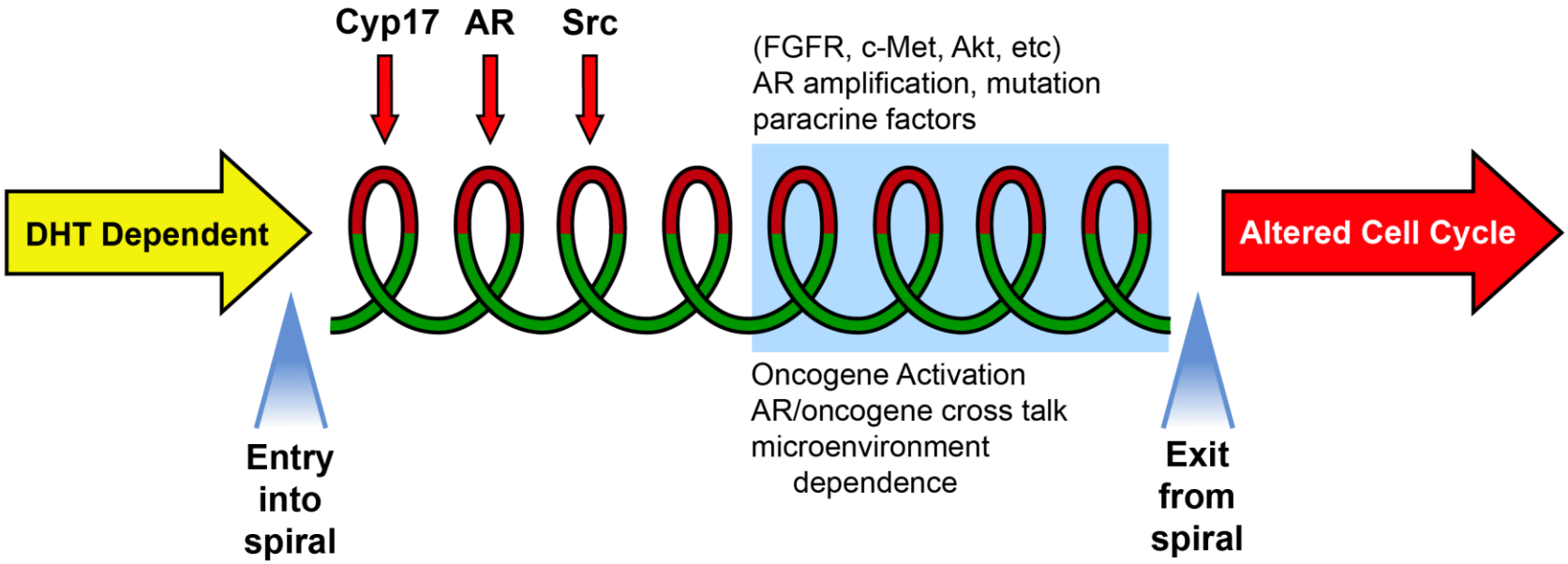
Chronic Myelogenous Leukemia



Prostate Cancer



Model for Reclassification of Prostate Cancer



Logothetis et al Cancer Discovery in press.

Imagine if we knew how to prioritize or/and combine agents to *effectively* and *anticipate* need before clinically apparent!

Do we have any predictors of outcome or resistance to proposed treatments?

Being Pragmatic!

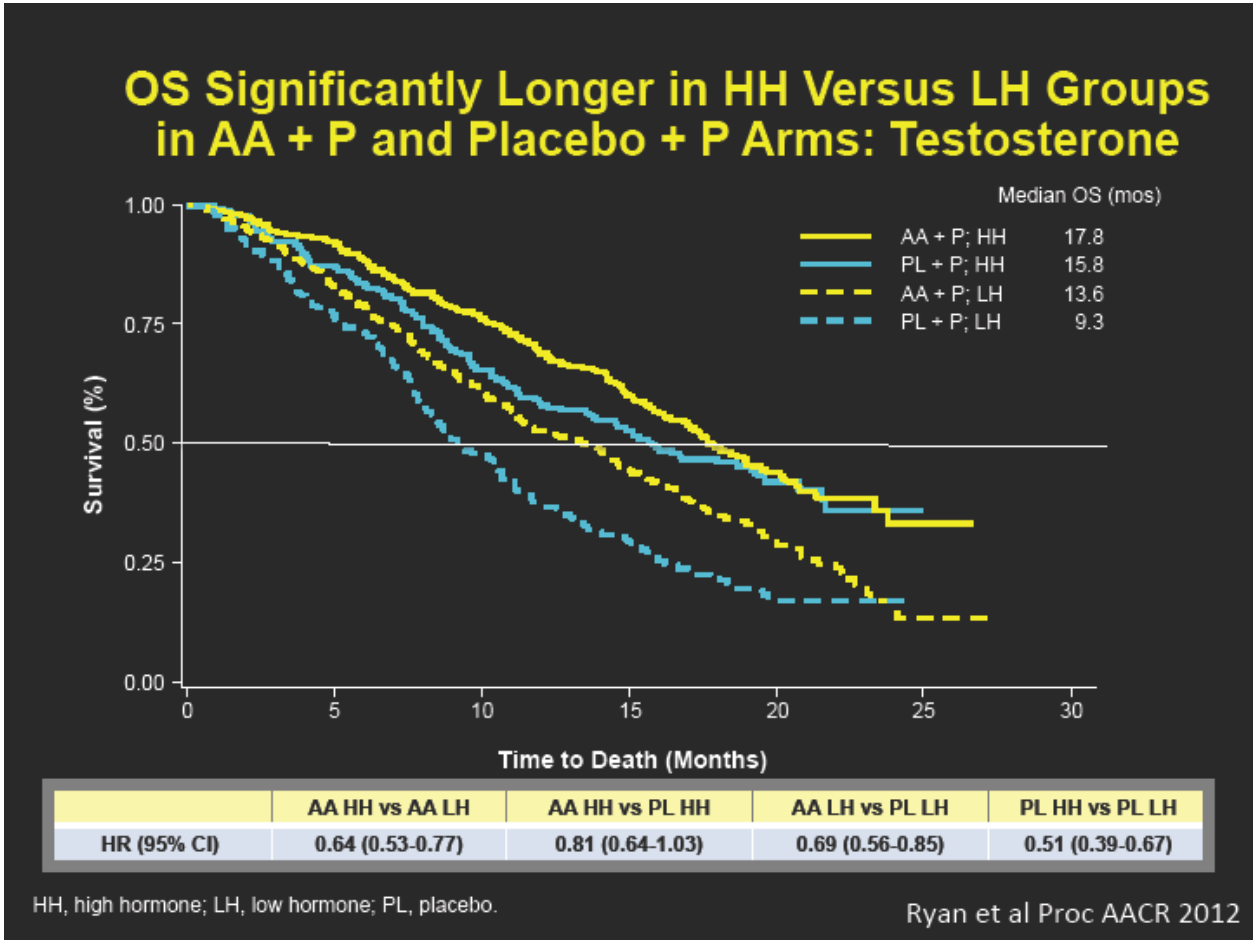
Do we have any predictors of outcome or resistance to proposed treatments?

NO!

We only have some prognosticators of outcome

- Predictor of outcome or resistance to a specific treatment
- Prognosticator : provides prognosis of outcome irrespective of treatment used

Abiraterone Acetate chemonaive mCRPC: Patients with *Low SerumTestosterone* perform poorly…

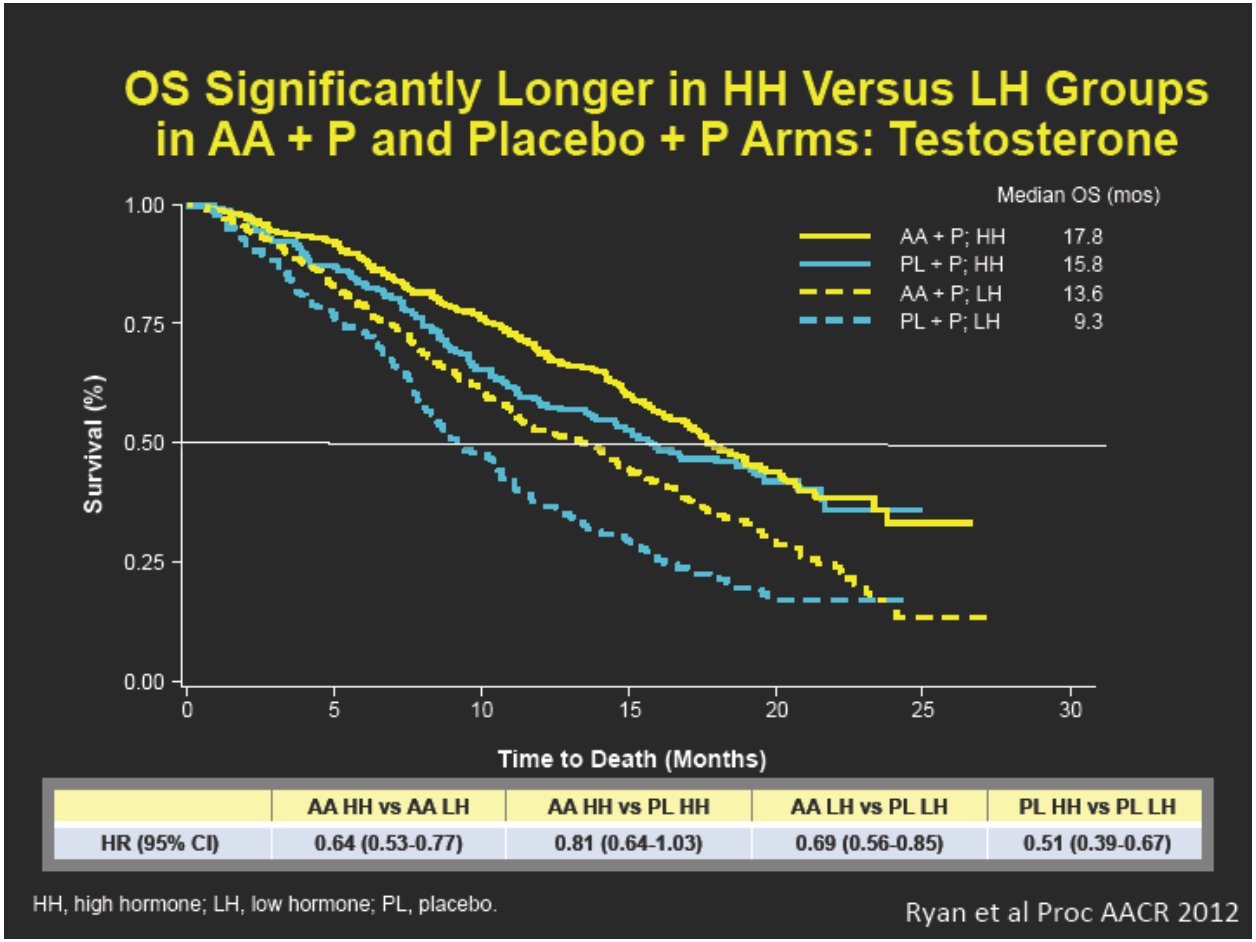


Ryan et al AACR 2012

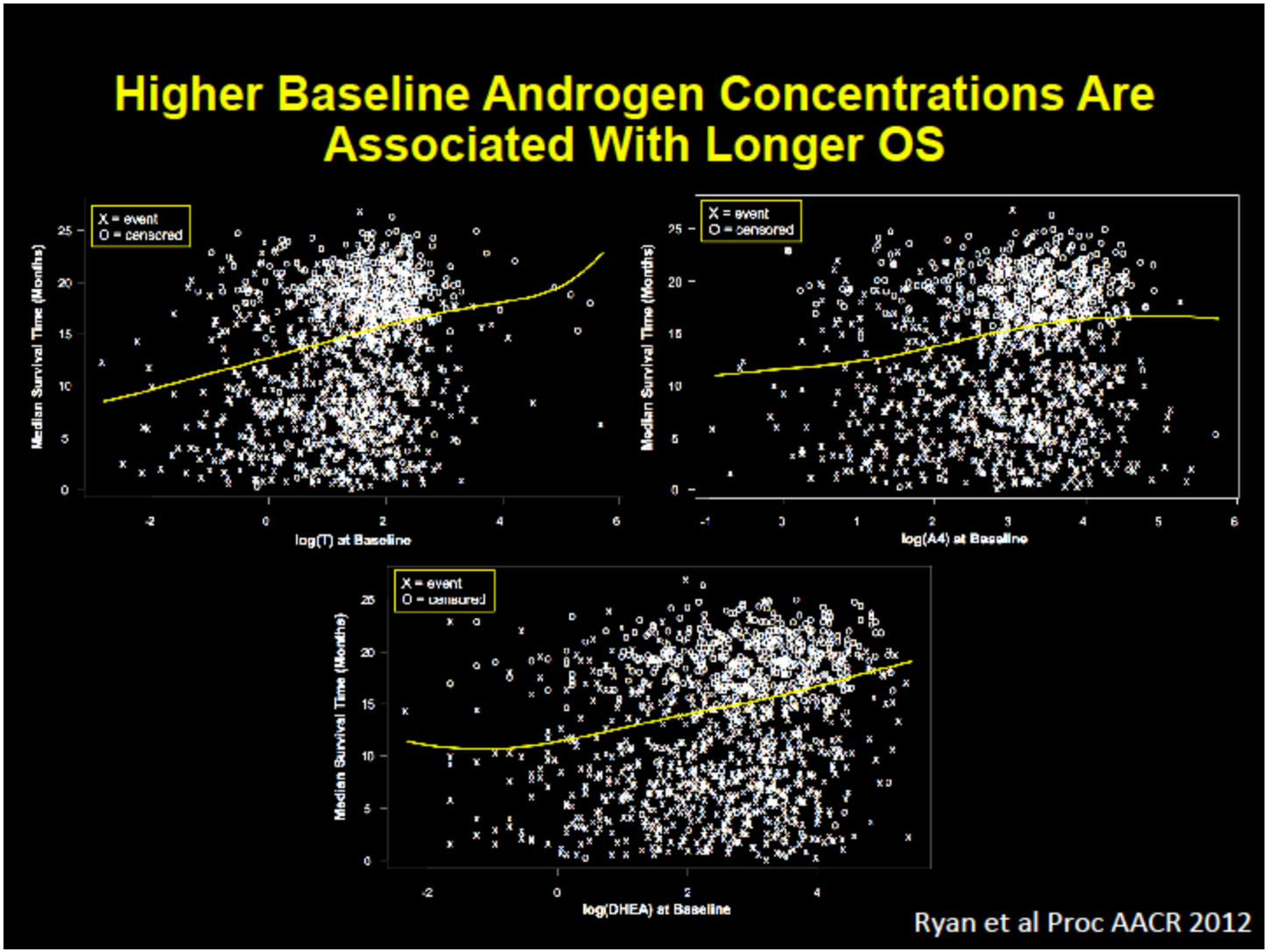
Prognostic: Patients with *Low SerumTestosterone* perform poorly… but

Still Abiraterone better than Prednisone alone!!

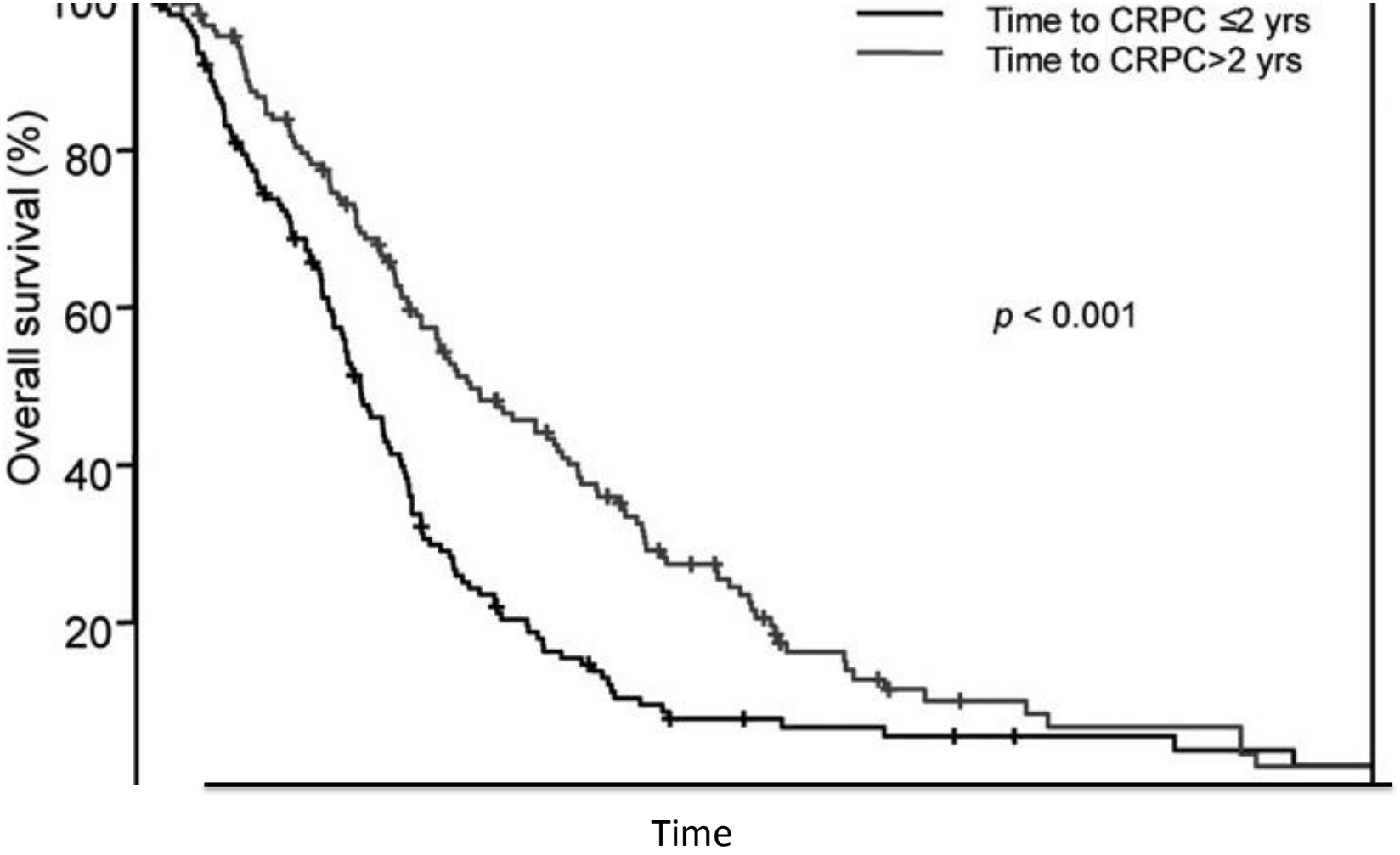
Maybe Predictive of resistance to Hormonal Treatments…to be proven



….Sometimes we need to prove the Obvious…



Short Time to CRPC prognostic of poor outcome



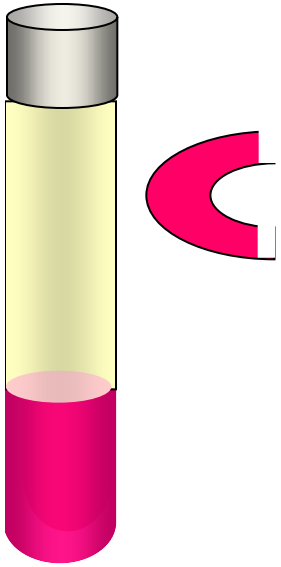
Bournakis et al 2012

Circulating Tumor Cell Allures

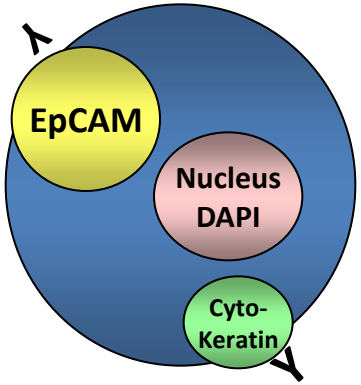
- CTC a step for haematogenous metastatic spread Mechanism unclear
- CTC enumeration:
  - Might represent a prognostic tool
    - Identifying patients for adjuvant therapy- *is it adjuvant??*
  - *Accelerate confirmation of treatment efficacy in trials?*
- Molecular characterisation of CTC could be more representative than profile of primary tumor
  - Real-time
- Minimally invasive

Veridex CellSearch® is the only test Analytically Valid and FDA Cleared (Breast, Colorectal, and Prostate)

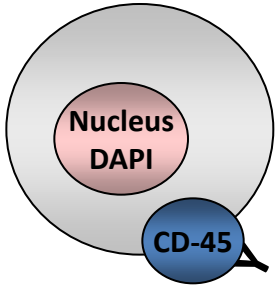
Immunomagnetic Selection



EpCAM Ferromagnetic Conjugate MAB



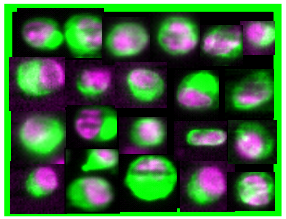
CK-6, 8, 18-PE



CD-45-APC

Digital Image Analysis

Digital Image Analysis™



Intact CTC

The Biomarker:

The "number" of intact; DAPI (+), EpCAM (+), CD45 (-)

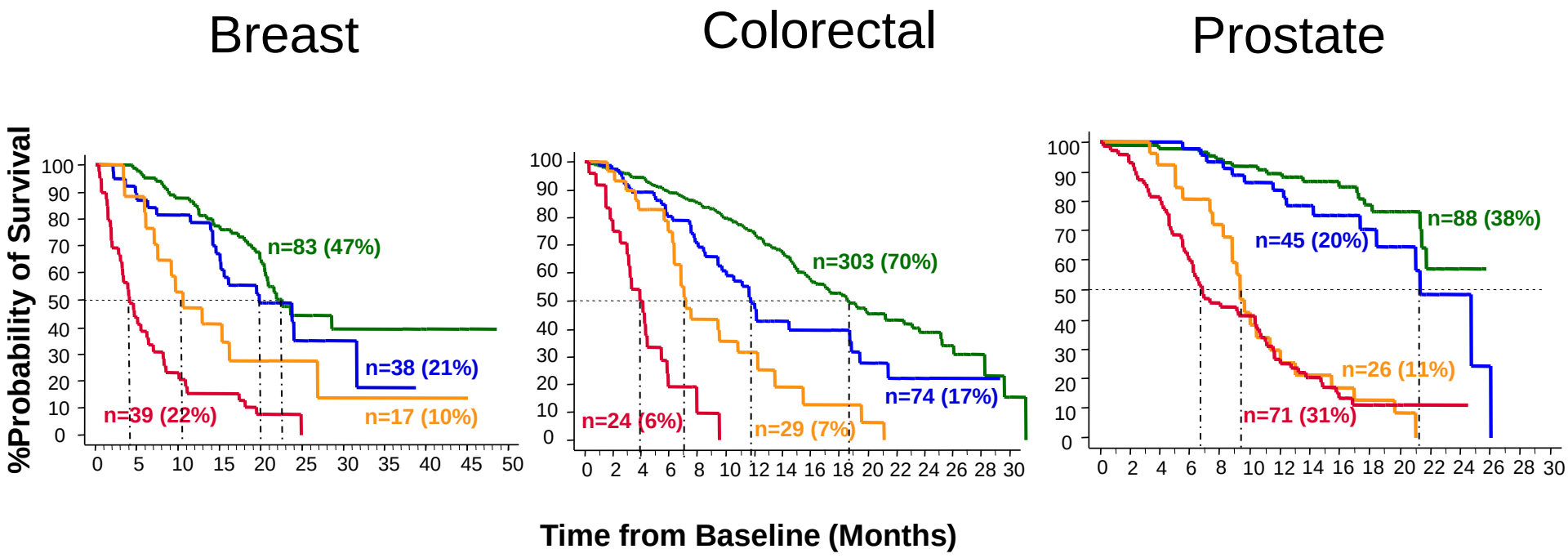
Reported as number of cells/7.5 mL of blood

Favorable: < 5 CTC

Unfavorable: ≥ 5 CTC

must be analysed within 96 hours

CTC counts are ***prognostic*** & identify response to treatment in chemotherapy-treated pts



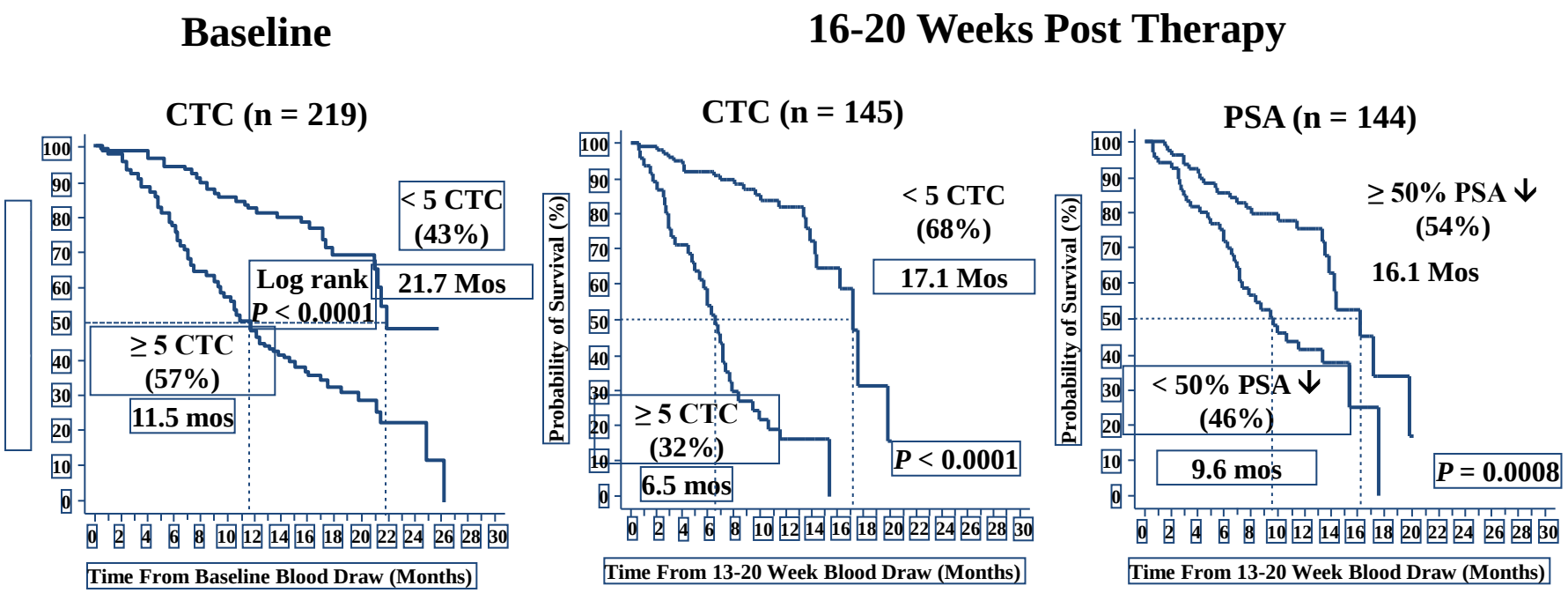
Remain Favorable

Convert to Unfavorable

Remain Unfavorable

Convert to Favorable

In Chemotherapy-Treated Patients, CTC Number is Prognostic for Survival at Baseline

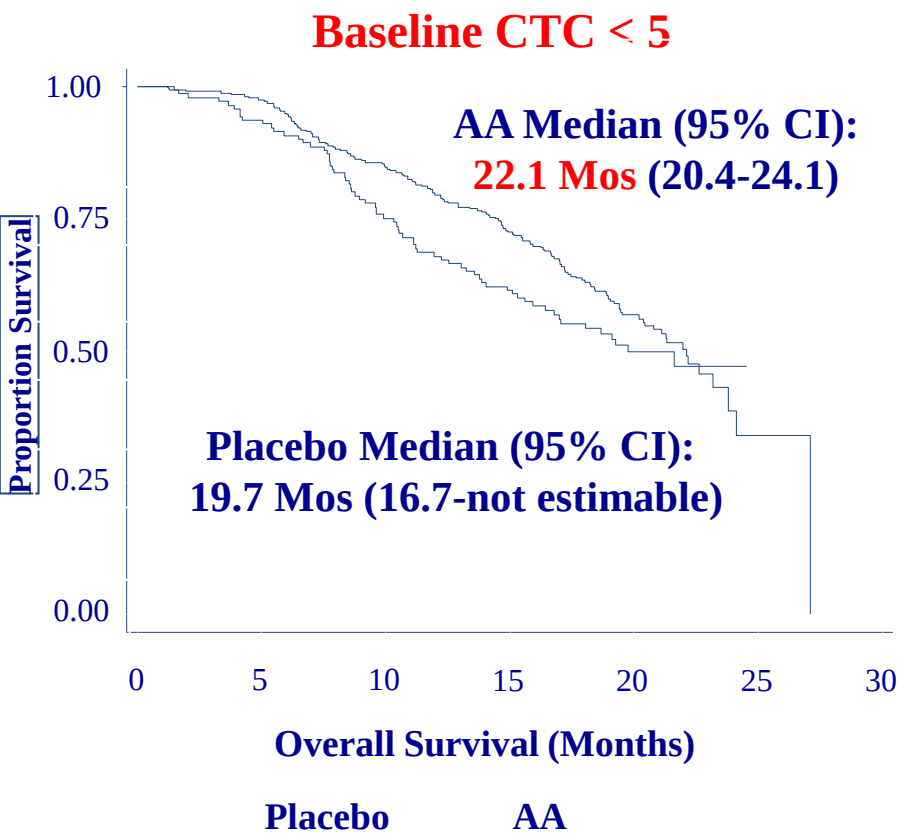


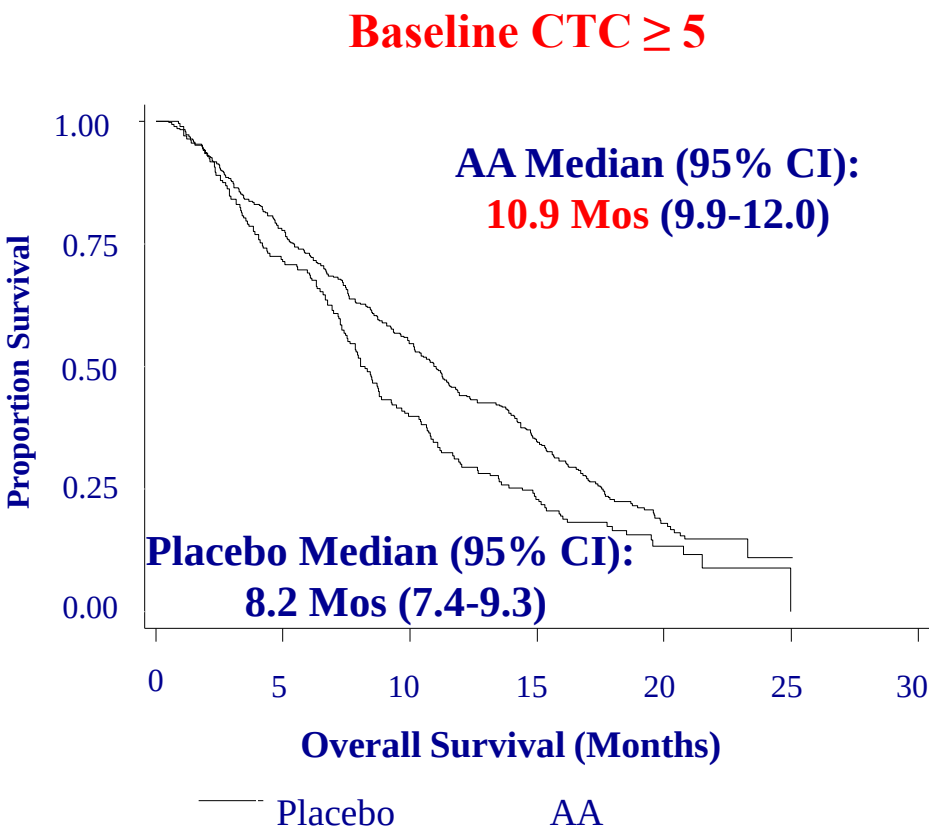
The results lead to a 510K clearance, but did not establish surrogacy as an efficacy-response biomarker

1. de Bono JS, et al. *Clin Cancer Res.* 2008. 2. Scher H, et al. *Lancet Oncology.* 2009.

COUAA301: AA Improves Overall Survival in ***Patients with Favorable and Unfavorable CTC Counts at Baseline***

No predictor there!





Scher et alASCO2011

Treatment, Baseline LDH and CTC Count Were Prognostic for Survival in the Multivariate Model While PSA Was Not

	Baseline (n = 949, CPE = 0.70 [SE = 0.008])	
Biomarker	**HR (95% CI)**	**p Value**
Treatment	**0.70 (0.59, 0.828)**	**< 0.0001**
LDH	**2.98 (2.496, 3.565)**	**< 0.0001**
CTC count	**1.19 (1.137, 1.245)**	**< 0.0001**
Hgb	0.95 (0.891, 1.001)	0.0574
ALP	0.98 (0.874, 1.097)	0.7218
PSA	**1.04 (0.983, 1.093)**	**0.1797**

PSA, prostate-specific antigen; Hgb, hemoglobin; LDH, lactase dehydrogenase; ALP, alkaline phosphatase.

Candidate Clinical Predictors of Response (post hoc analyses)

- Gleason Score <8 vs high risk(baseline evaluation):

Conflicting data Loriot et al /vs Oudard et al

- prior lines of chemo (>1 vs 1) –stating the obvious!
- time to crpc (jury still out- shortcoming : definition of CRPC/retrospective data)

in line with protracted androgen signaling addiction vs autocrine/epitheliocentric progression

Gleason Score Criterion

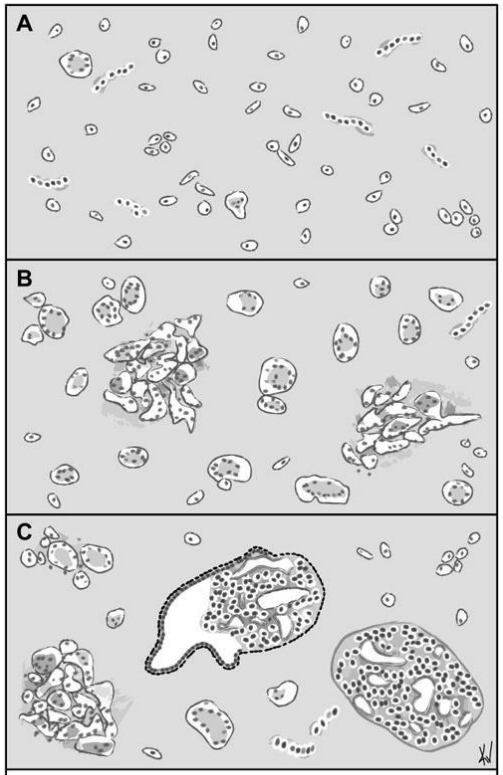
Beware:

This is a morphology criterion

1. Gleason Grade 4 includes distinct morphologies with different behavior

2. Temporal heterogeneity and heterogeneity within disease warrants rebiopsy

Presence of Cribriform Gleason Score 4 predicts for relapse



Proposed Grouping of Treated Prostate Cancer

Group	Dominant Architectural Pattern	Cribriform Pattern or Intraductal Spread
A	Cell clusters/cords, isolated cells	Absent
B	Small glands, fused glands	Absent
C	Any	Present

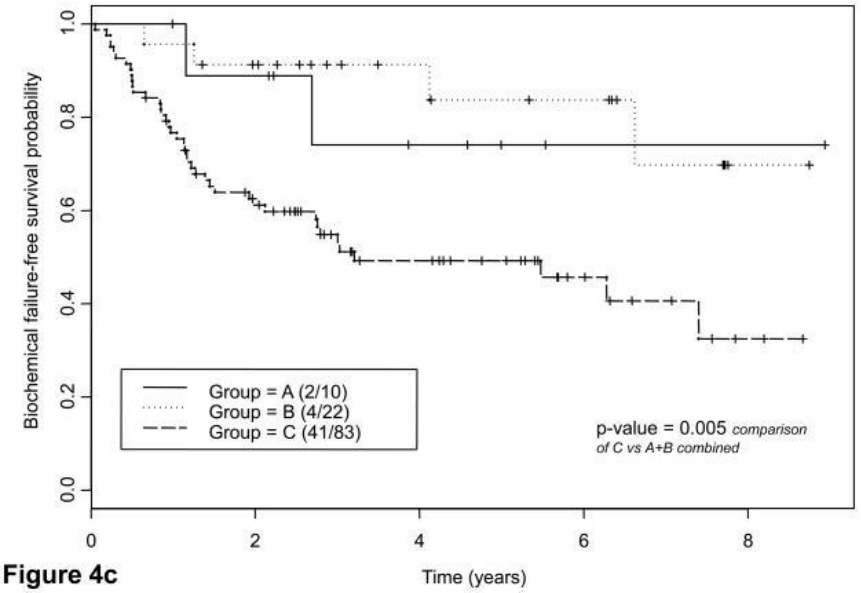


Figure 4c

Efstathiou et al 2010 Eur Urology

What do we know ..?

Making a decision in the clinic- Based on clinical information-'physician algorithm'

Age vs Frailty-other comorbidities (Droz et al)

Disease Related Symptoms- Rapid Progression

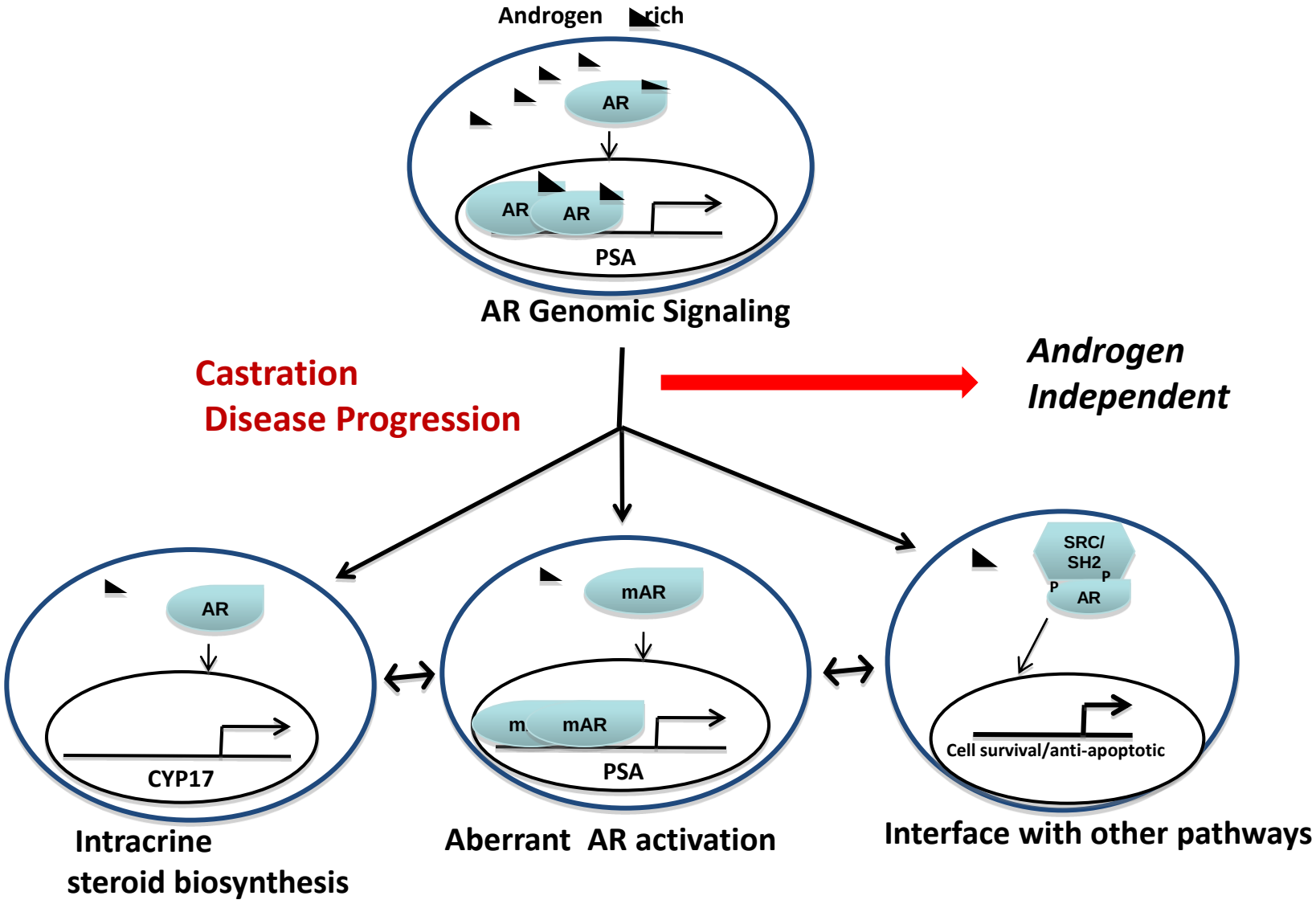
Rapid radiologic progression

Presence of visceral metastases

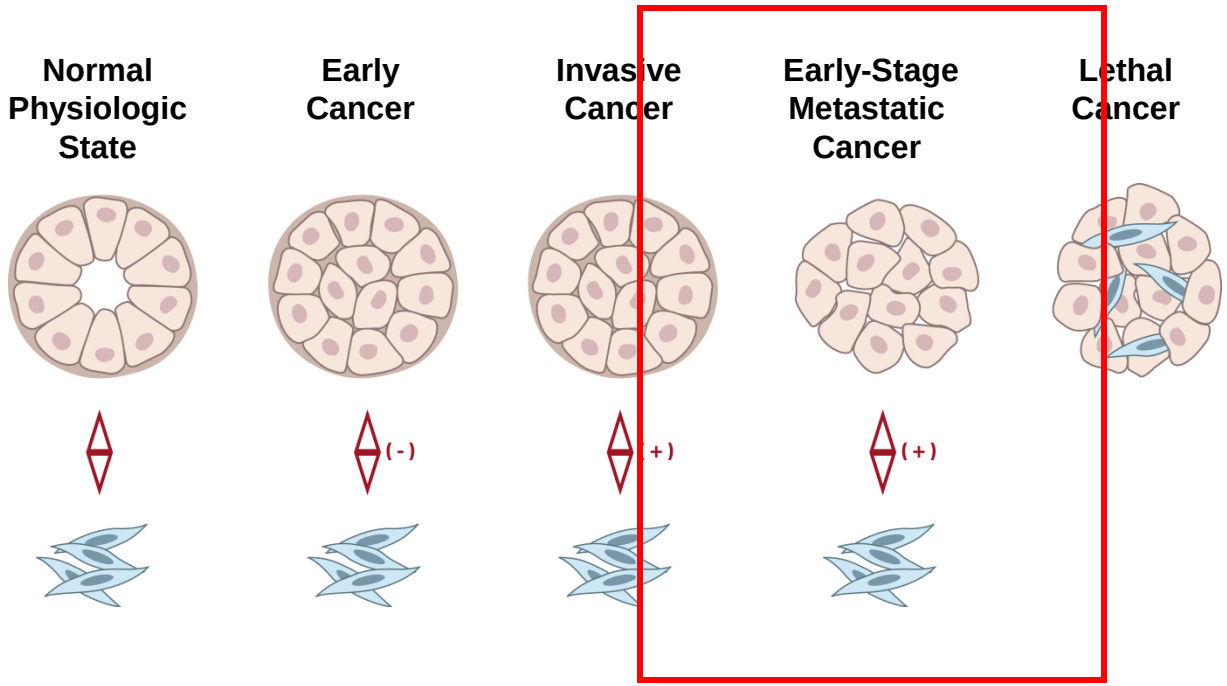
Whatever happened to characterizing the tumor?

Facilitated by the advent of drugs that actually do work!

Adaptive Response of Androgen Signaling in Bone mCRPC



Endocrine-to-Paracrine Androgen Signaling Transition



Proposed Model of Prostate Cancer Progression

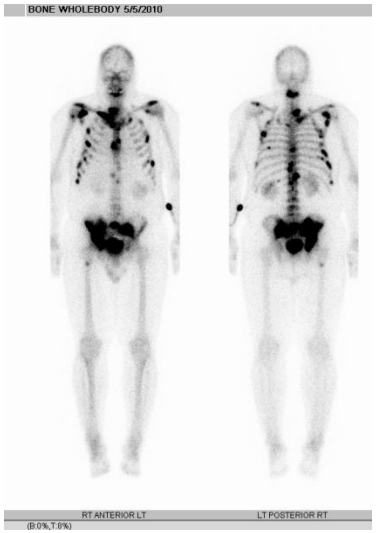
Role of endocrine-to-paracrine androgen signaling transition

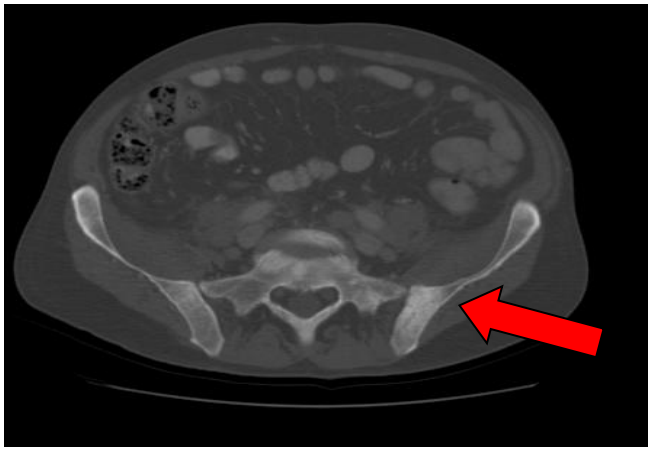
Efstathiou et al. Clin Cancer Res. 2010.

Elucidating the link of androgen signaling to milestones of prostate cancer progression will serve as the foundation for the individualized microenvironment targeted therapies

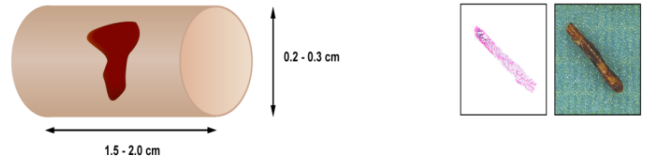
AND THUS 'PRECISION THERAPY' DEVELOPMENT

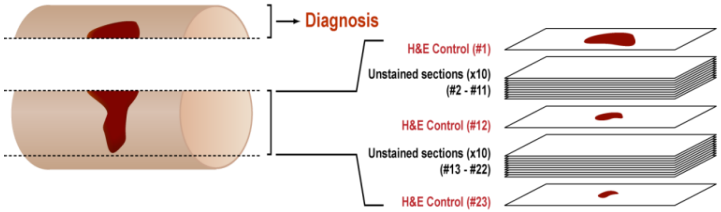
Informative Transilial Bone Marrow Biopsy

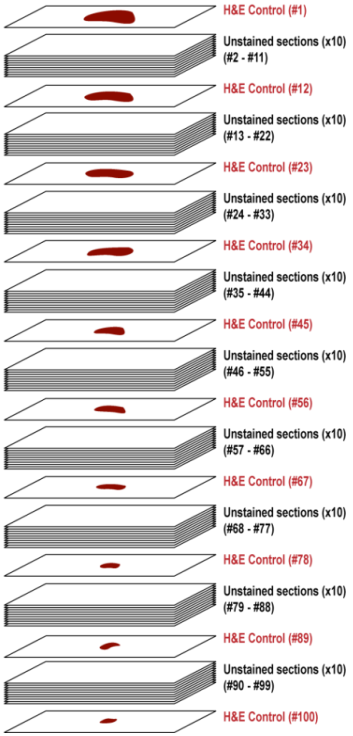


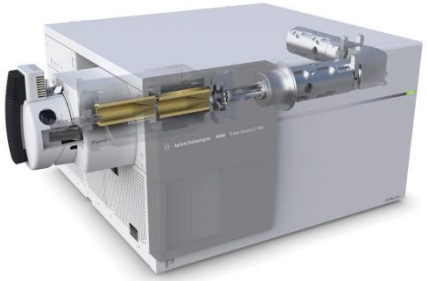


CT Directed





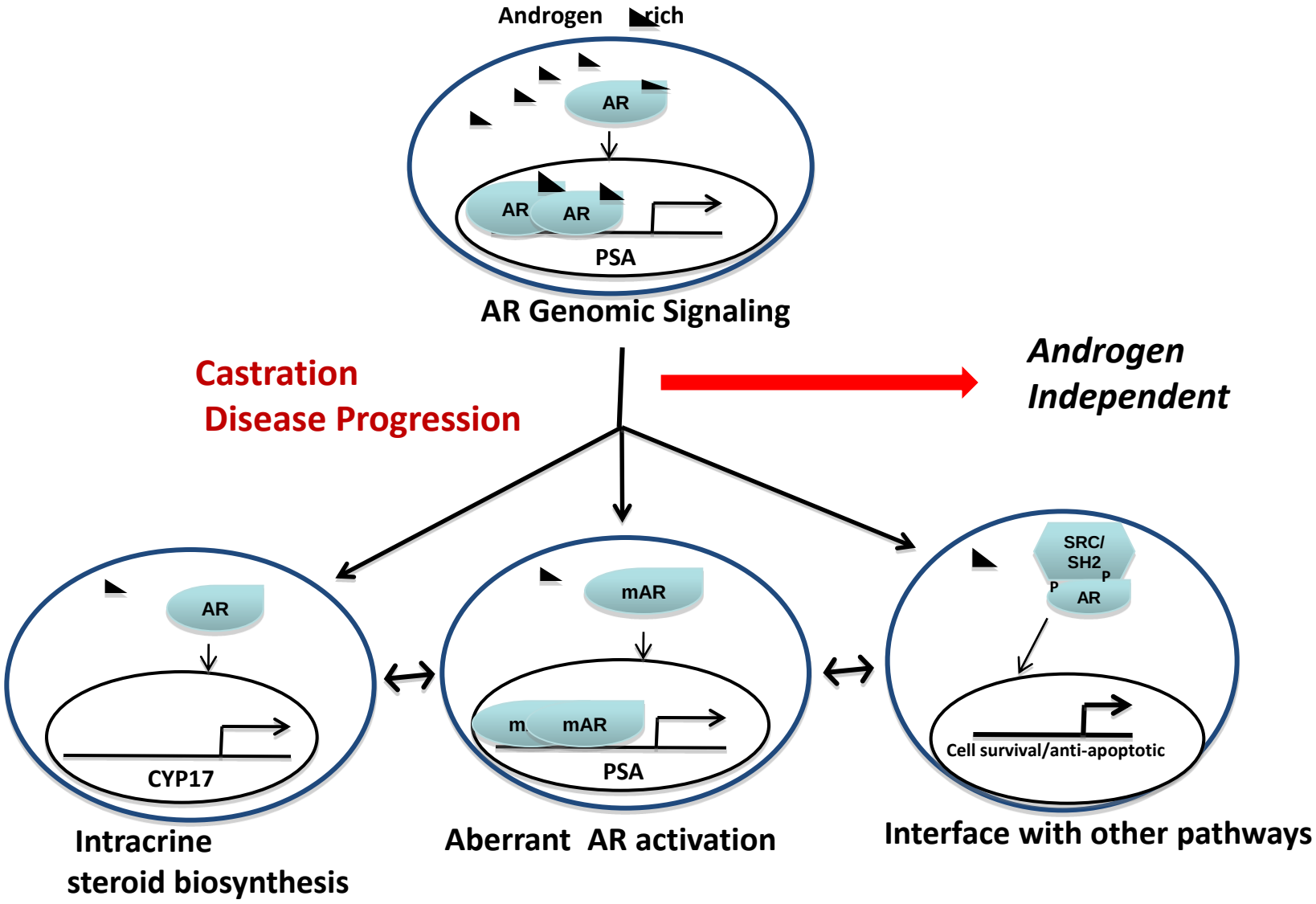




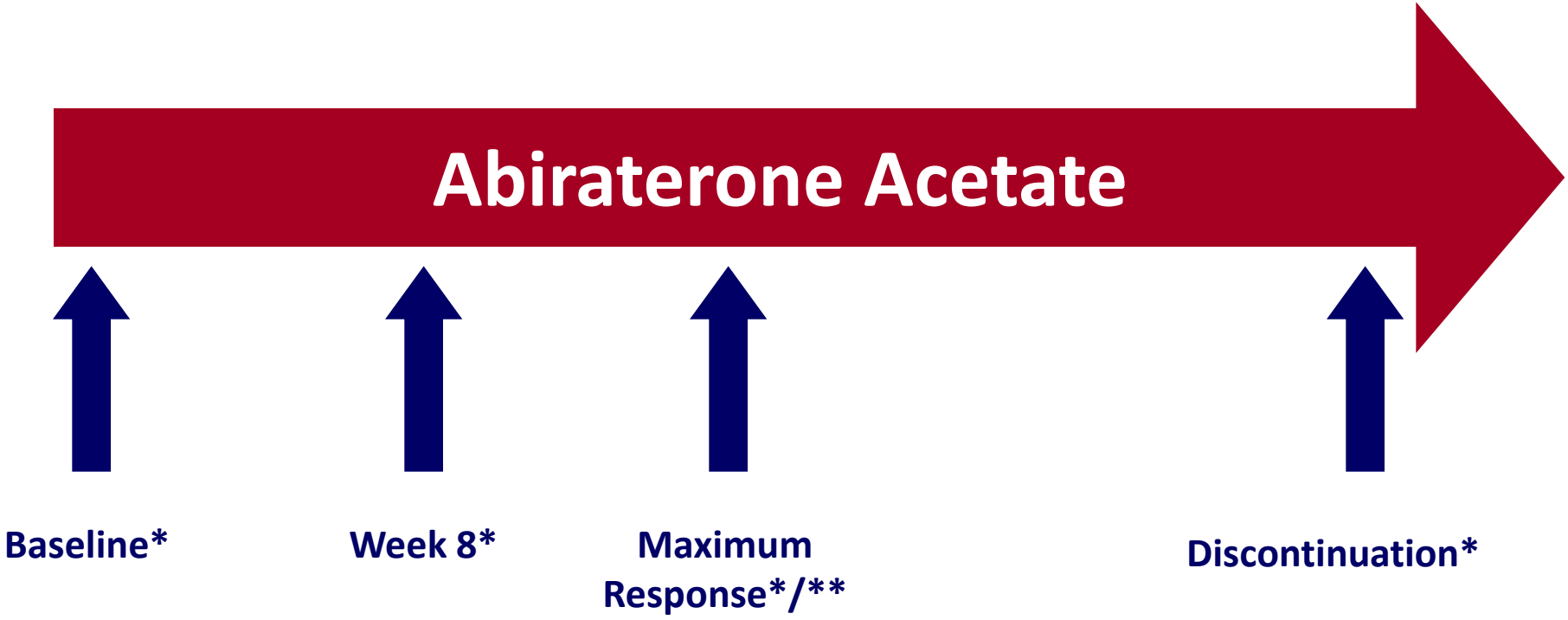
Efstathiou et al. J Clin Oncol 2012

Efstathiou et al. J Clin Oncol 2011; 29(Suppl): Abstract 4501

Adaptive Response of Androgen Signaling in Bone mCRPC



BMA Abiraterone Acetate Study

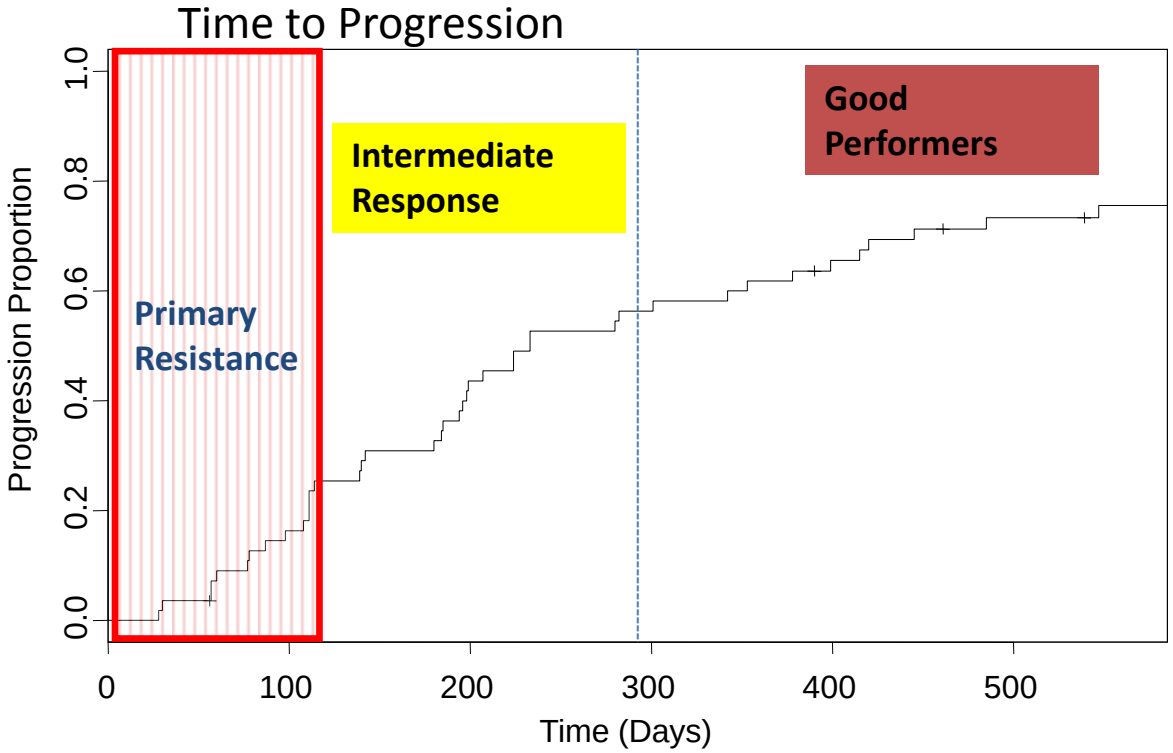


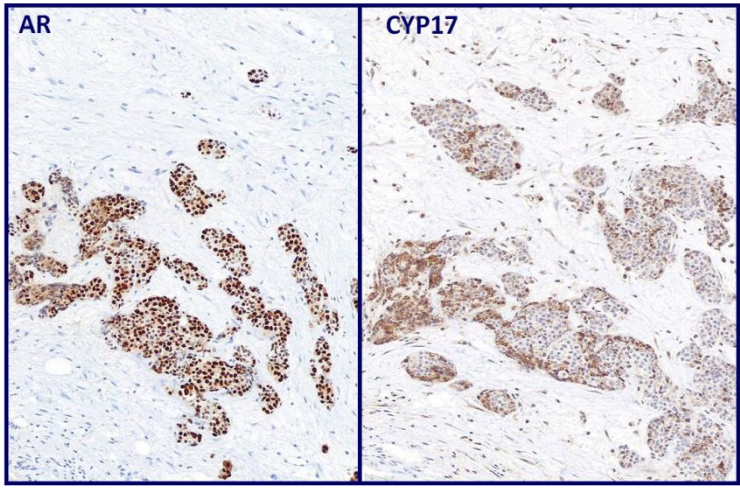
*Tissue:
1) Serum and plasma blood and bone marrow aspirate
2) Transilial bone marrow biopsy

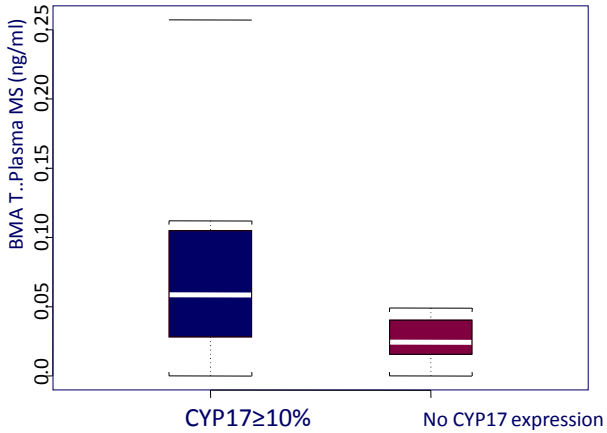
**Variable time point/optional

Efstathiou et al. J Clin Oncol

Predicting Outcome of Androgen Signaling Inhibition





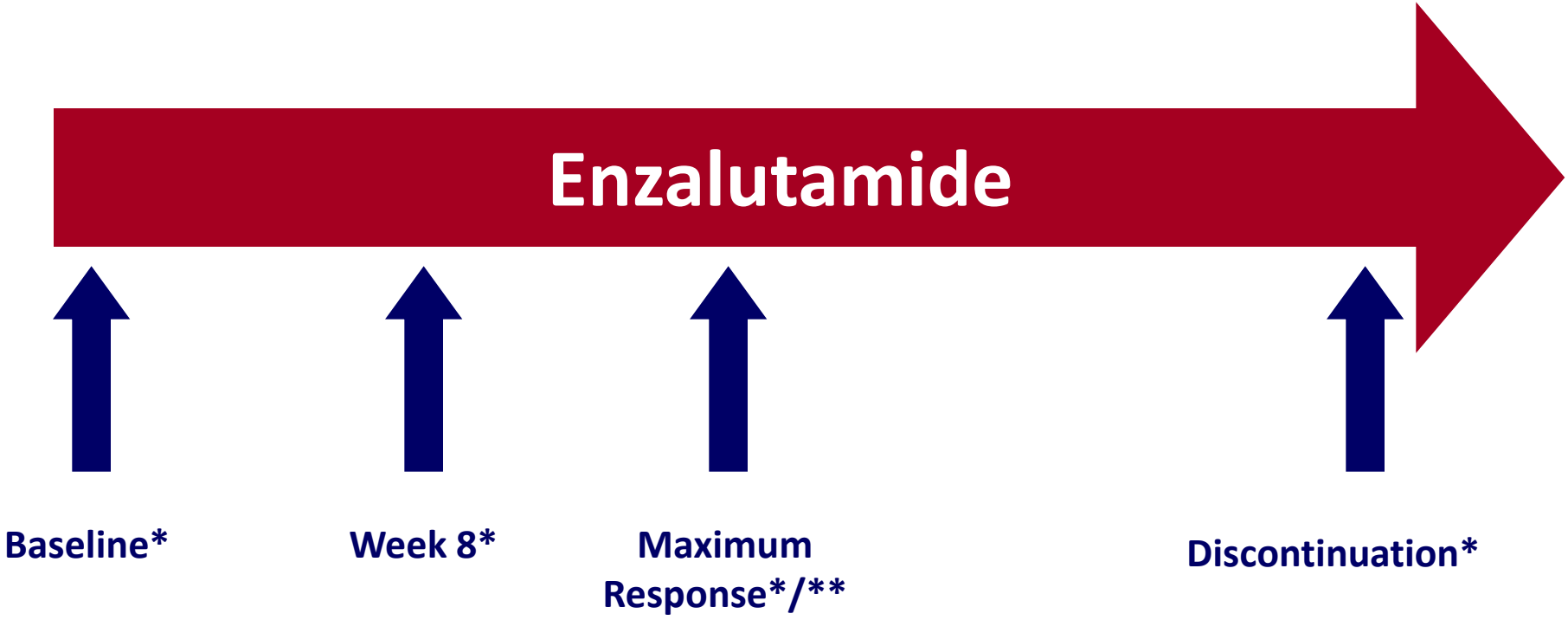


Androgen Signaling Signature predictive of benefit: Overexpression of nuclear AR + CYP17 expression

Correlation of CYP17 expression to intracrine androgens

Efstathiou et al JCO 2012

BMA Study



*Tissue:
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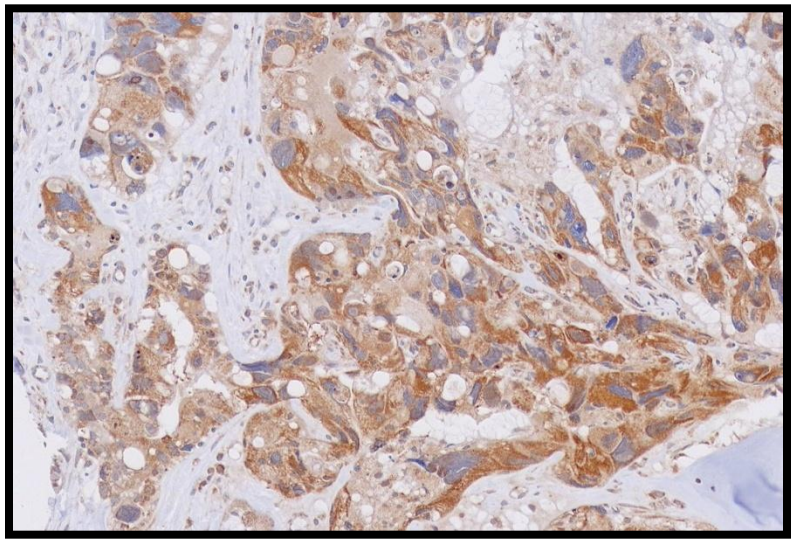
2) Transilial bone marrow biopsy

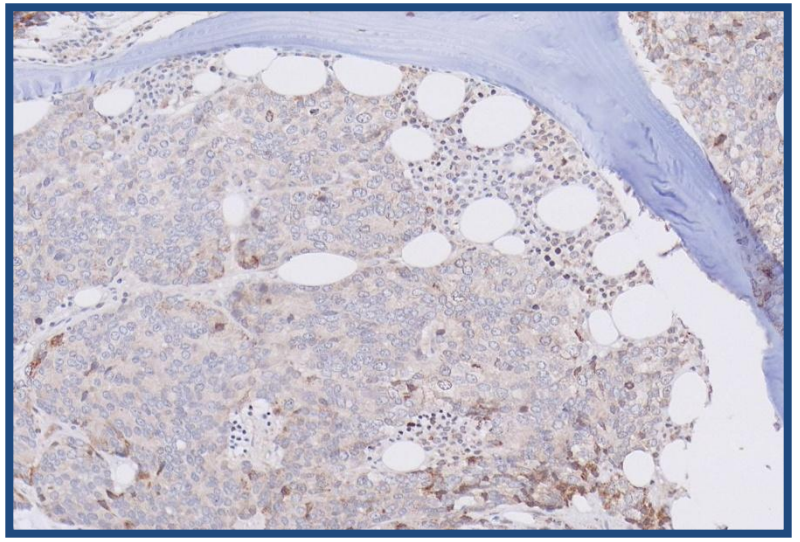
**Variable time point/optional

Efstathiou et al. in review

Increased pretreatment CYP17 expression and bone marrow testosterone concentration predict for benefit in the background of AR nuclear overexpression



Benefit



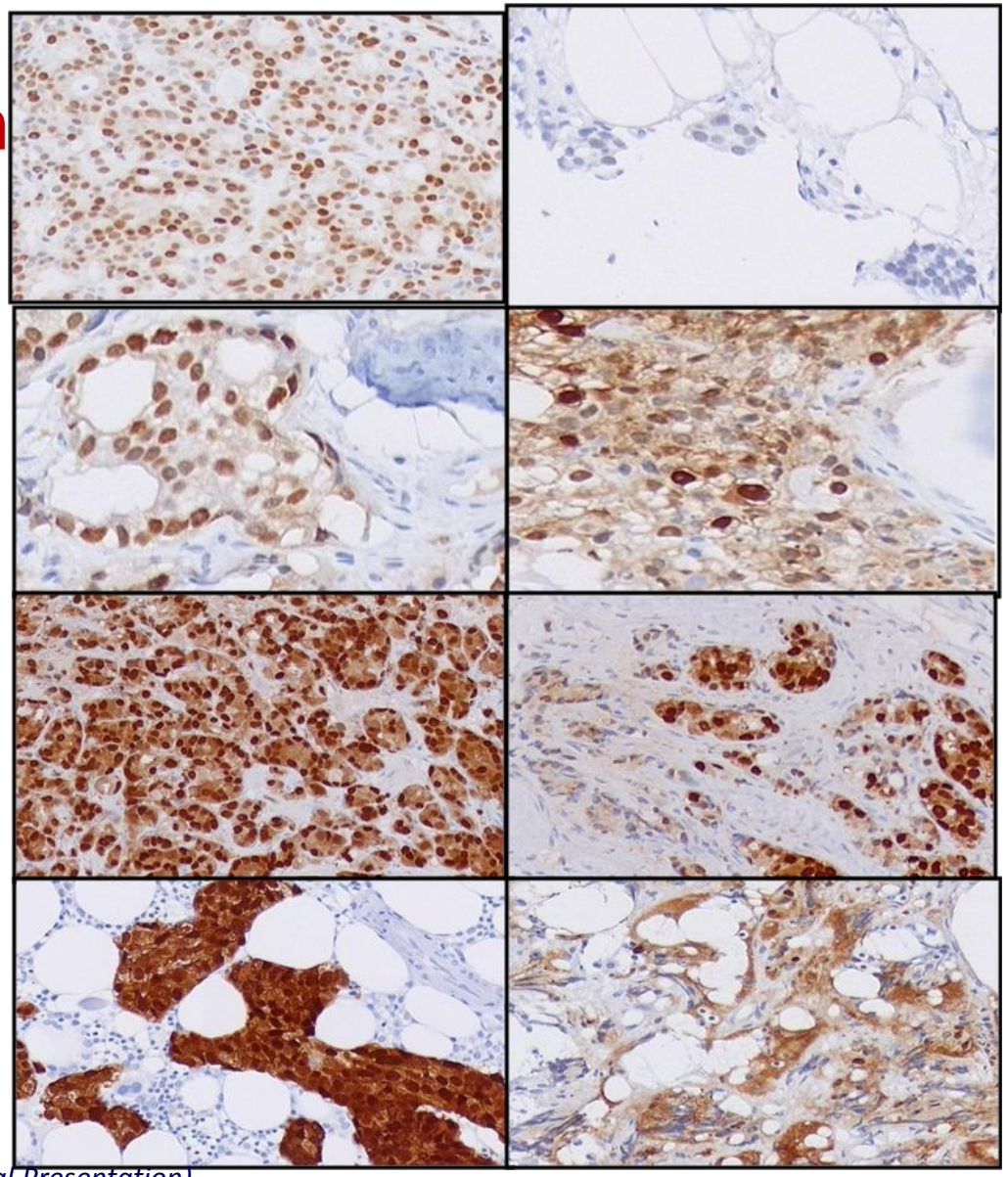
Primary Resistance

Suggestive of overlap Between reagents	Primary Resistance	Benefit	P value Wilcoxon's rank test
Mean CYP17 Expression (%) (Range)	10 (0-30)	70 (0-90)	0.002
Mean Bone Marrow Aspirate Testosterone (Range)(ng/ml)	0.016 (0-0.077)	0.033 (0-0.105)	0.019

Efstathiou et al. J Clin Oncol 2011; 29(Suppl): Abstract 4501 (Oral Presentation)

Androgen Receptor Subcellular Localization Shift following Enzalutamide

	Decrease in Nuclear AR (>20%)	No Change	P value
≥50%PSA decline	6	2	0.05
No PSA decline	2	8	

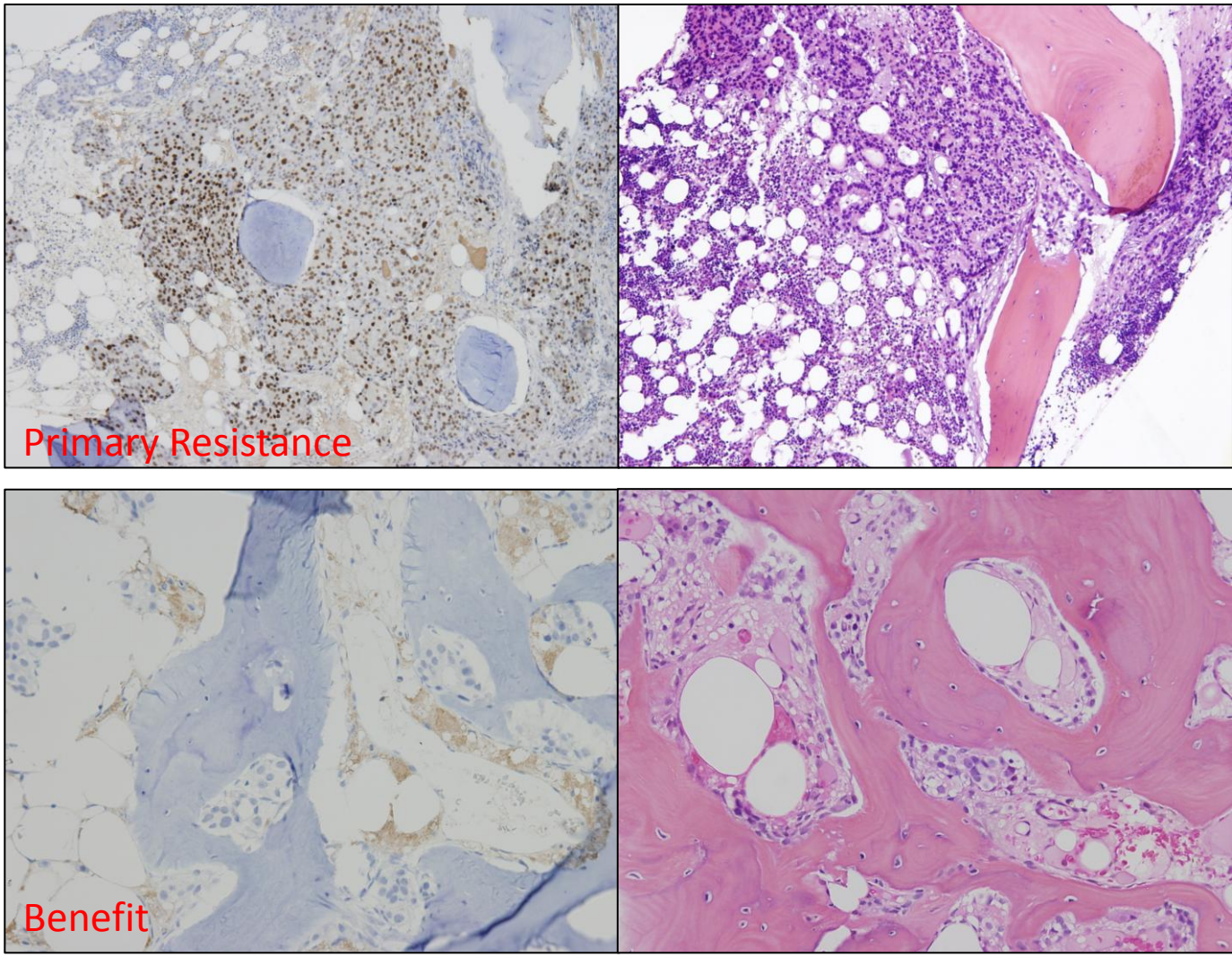


Pretreatment Week 8

Efstathiou et al. J Clin Oncol 2011; 29(Suppl): Abstract 4501 (Oral Presentation)
Efstathiou et al under review

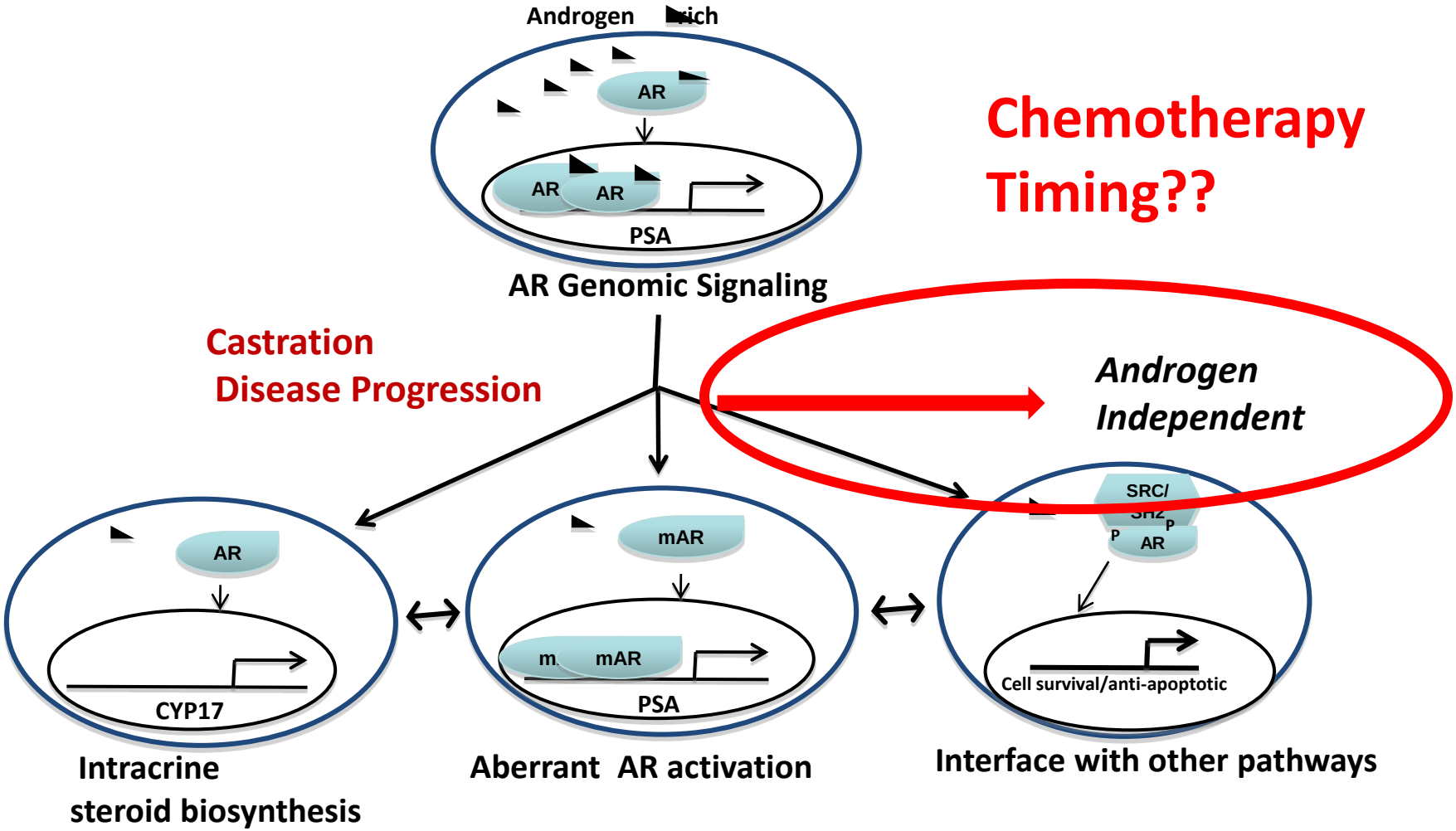
Candidate Predictors of primary resistance to Enzalutamide: ARV7 splice variant

	ARV7	No ARV 7	P value
Primary Resistance	7	3	0.04
Benefit	0	8	



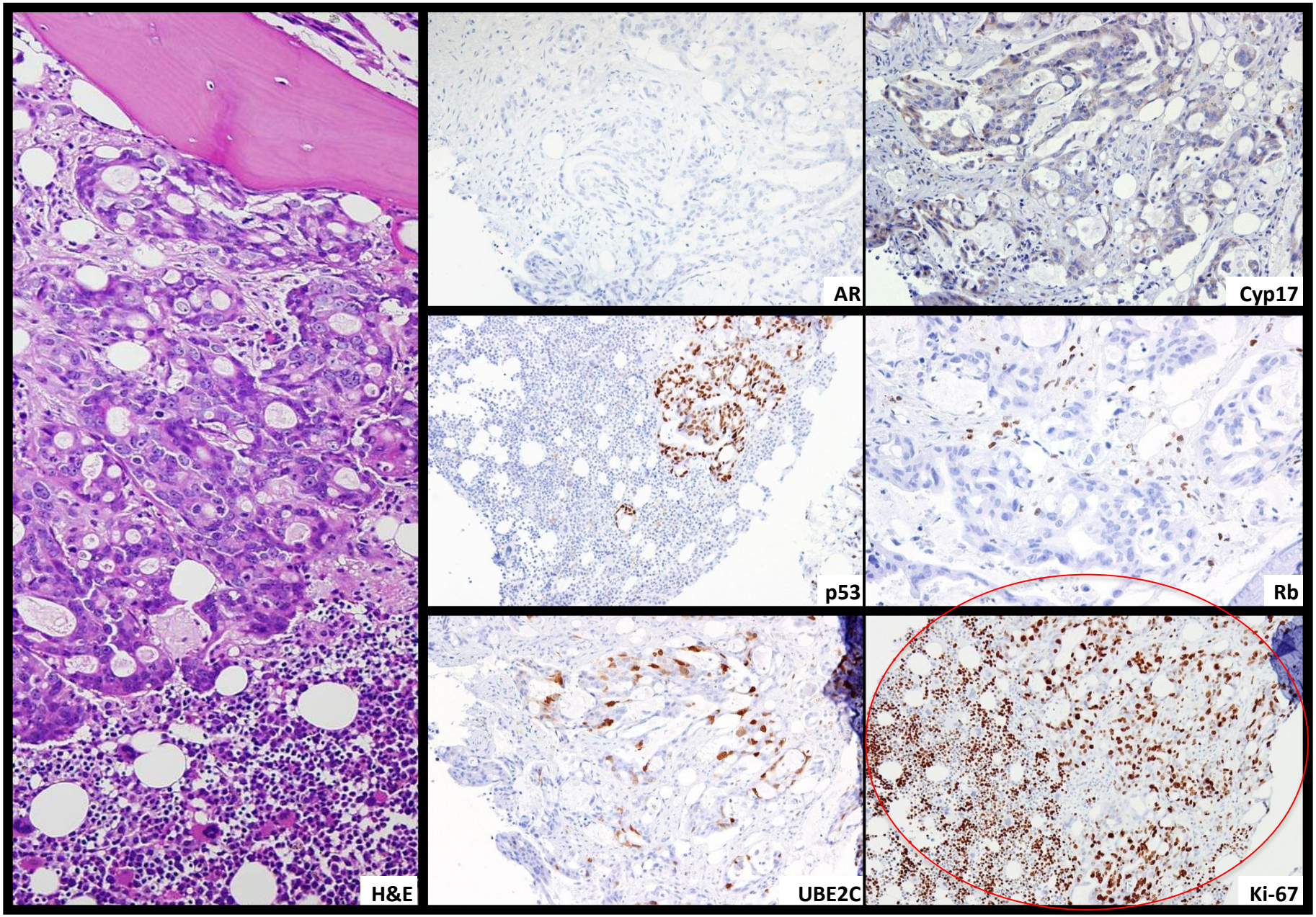
Efstathiou et al under review

Adaptive Response of Androgen Signaling in CRPC



Halabi et al: Neither PSA decline (≥30% and ≥50%) nor PSA velocity within the first three months of therapy are surrogate endpoints for OS in pts receiving second line chemotherapy. (ASCO 2012)

“Altered Cell Cycle” & Adenocarcinoma



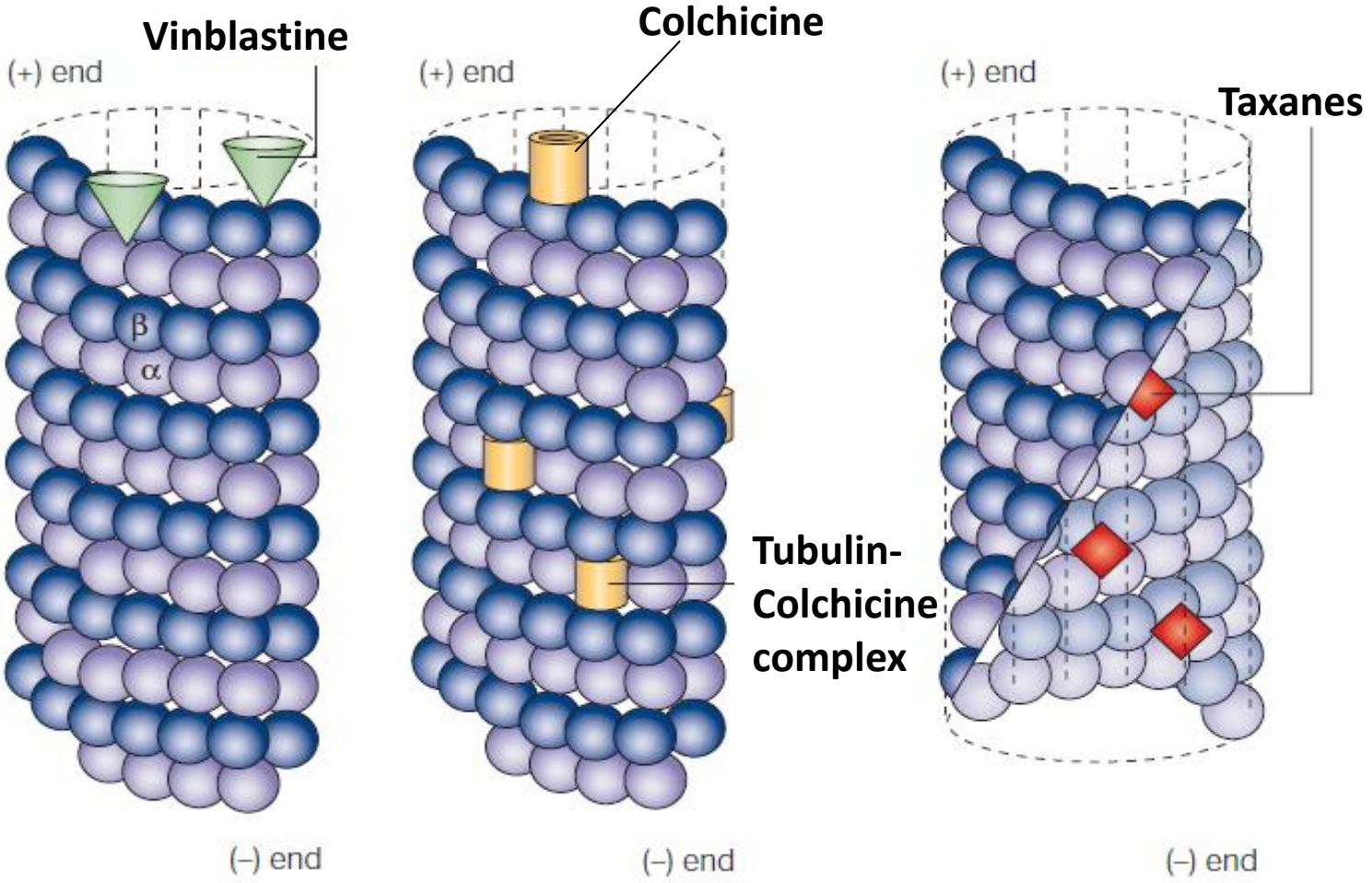
BMA Study

*Tissue:
1) Serum and plasma blood and bone marrow aspirate
2) Transilial bone marrow biopsy

**Variable time point/optional

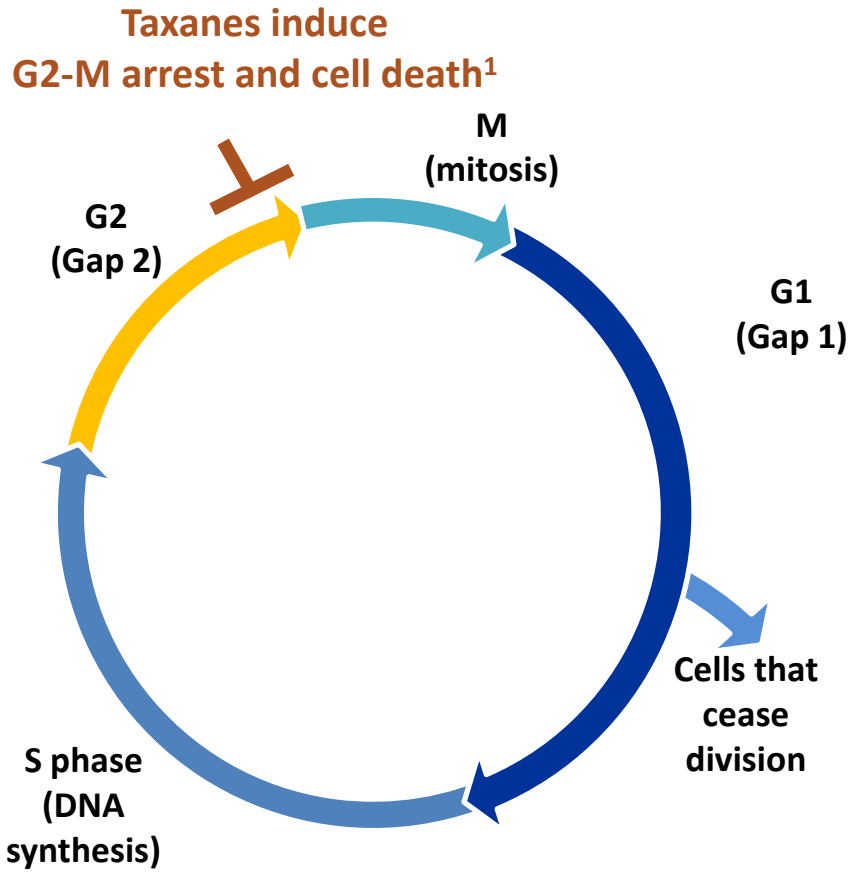
Efstathiou et al. in review

Antimitotic drugs bind to microtubules at diverse sites



Jordan MA & Wilson L. Nature Reviews Cancer 2004;4:253-265.

Impact of taxanes on cell cycle

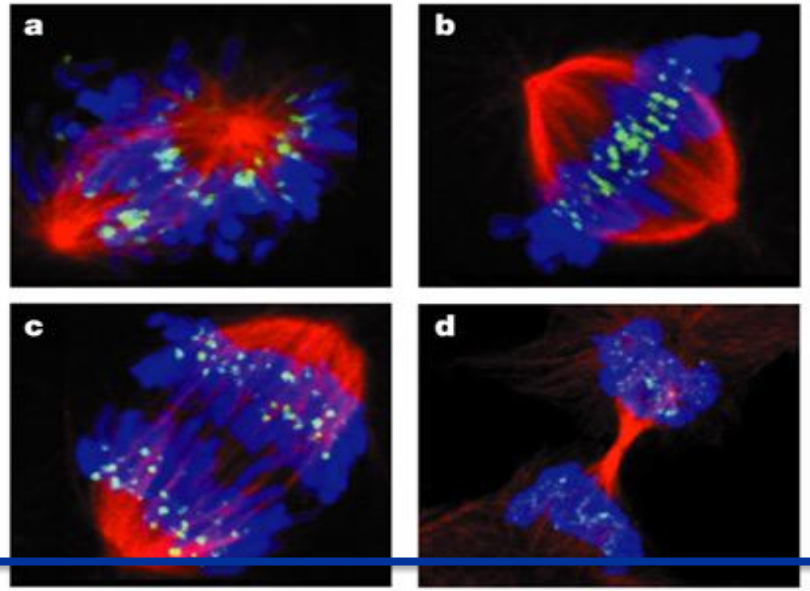


- Androgens act earlier than taxanes in cell cycle
- Androgens given before taxanes will prevent their action

1. Moos PJ & Fitzpatrick FA. Cell Growth and Differentiation 1998; 9:687-97

Taxanes stabilize microtubules leading to cell-cycle arrest in metaphase-anaphase

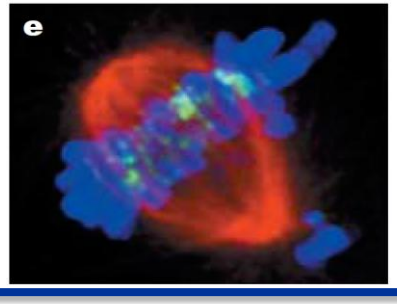
Normal cell cycle



a. Prometaphase
b. Metaphase

c. Anaphase
d. Telophase

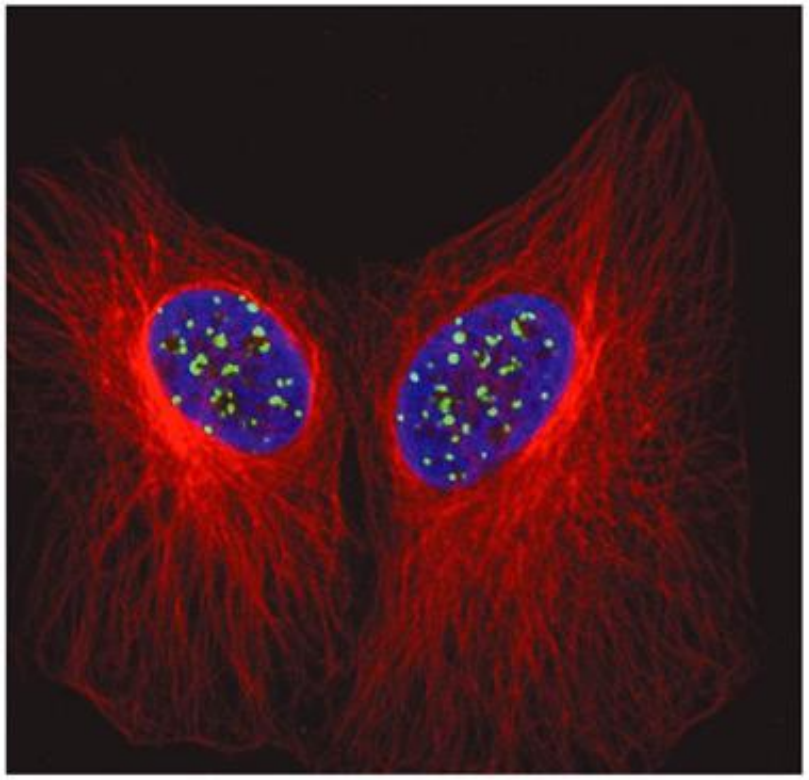
Taxanes



Taxanes stabilize microtubules and inhibit disassembly: cell-cycle signal to pass from metaphase to anaphase is blocked and cells eventually die by apoptosis

Jordan MA & Wilson L. Nature Reviews Cancer 2004;4:253-265.

Function of microtubules



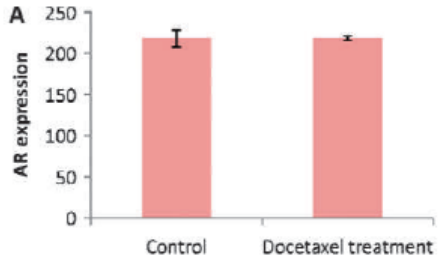
Nature Reviews | Cancer

- Cell shape
- Transport of vesicles
- Mitochondrial function
- Cell signalling
- Cell division and mitosis

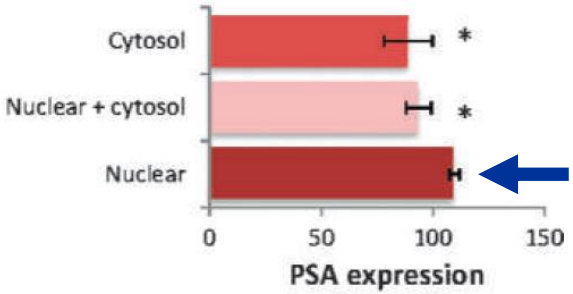
Jordan MA & Wilson L. Nature Reviews Cancer 2004;4:253-265.

Docetaxel suppresses androgen receptor nuclear translocation in PCa tumors

A. Similar AR levels in controls & docetaxel-treated PCa patients

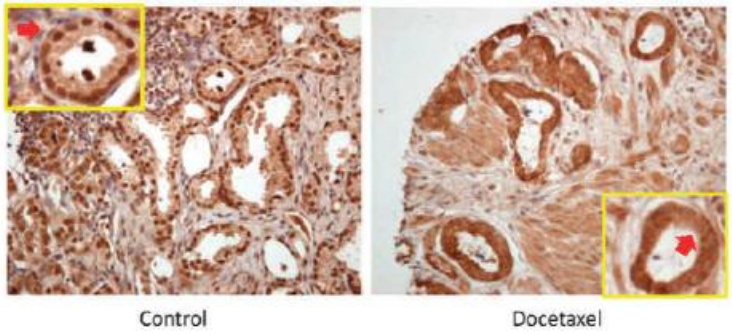


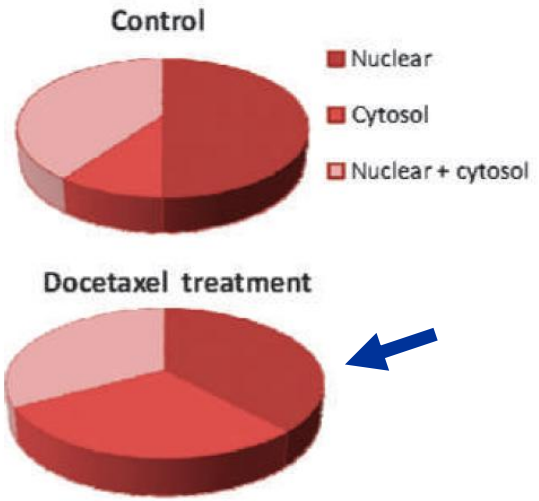
D. Hi ells with AR nuclear localization



Marked reduction of AR nuclear translocation with docetaxel

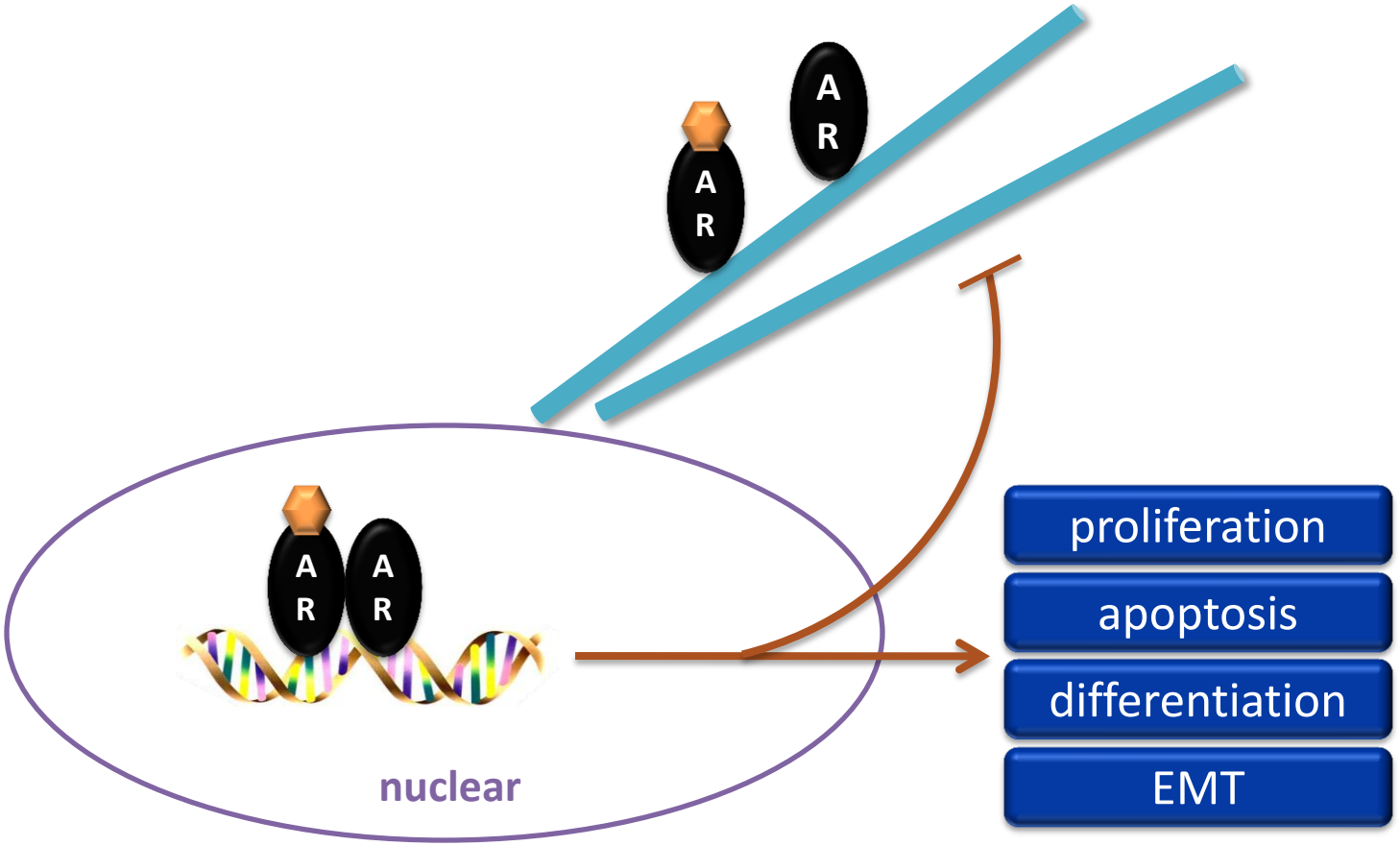
C.





Zhu ML et al. Cancer Res 2010;70:7992-8002.

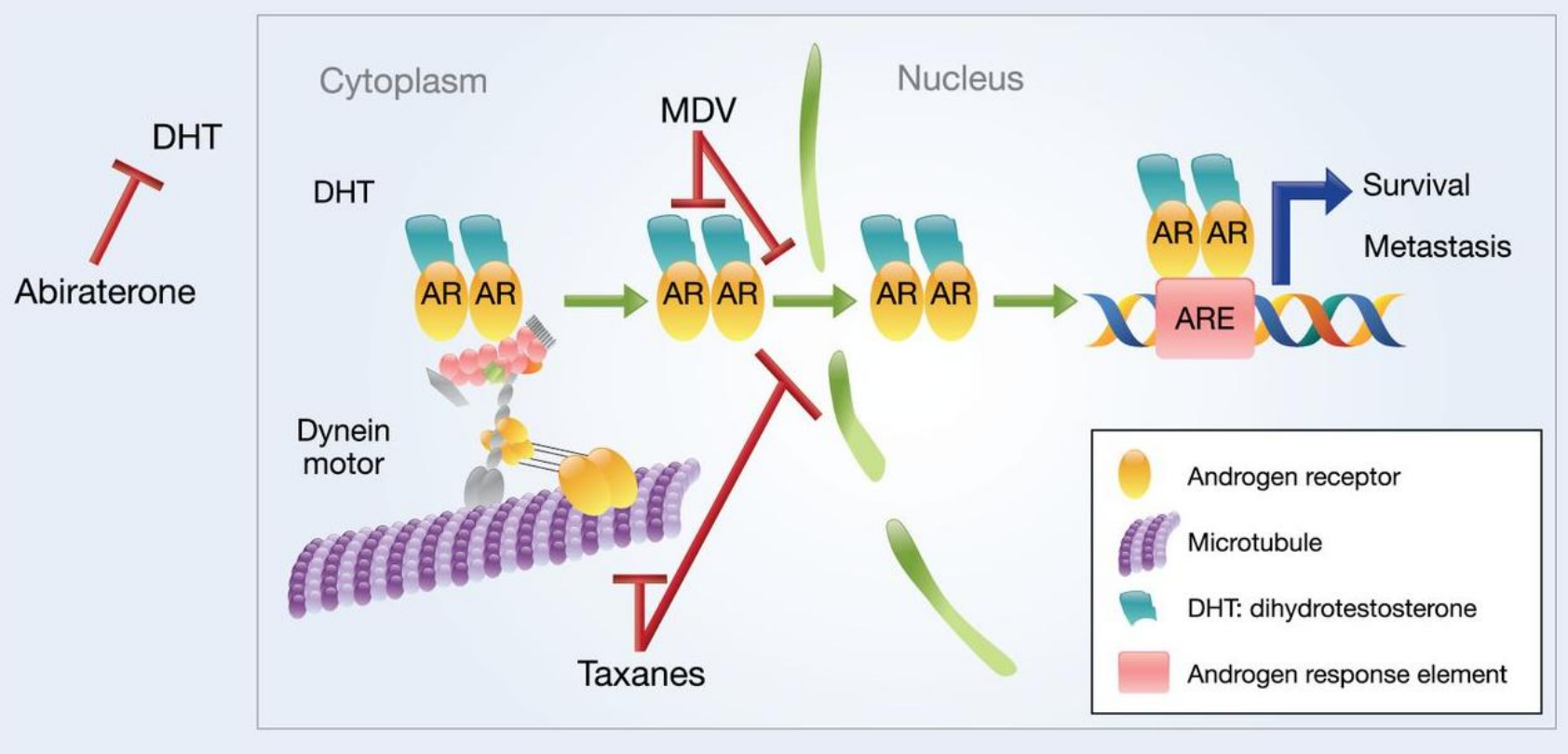
Microtubules facilitate AR nuclear translocation



Microtubules facilitate AR nuclear translocation
and enhance downstream AR transcriptional activity

Zhu ML et al. Cancer Res 2010;70:7992-8002.

Alternative taxane mechanism of action in prostate cancer Beyond Cell Cycle Arrest



Non clinical data

Thadani-Mulero M et al. Cancer Res 2012;72:4611-4615.

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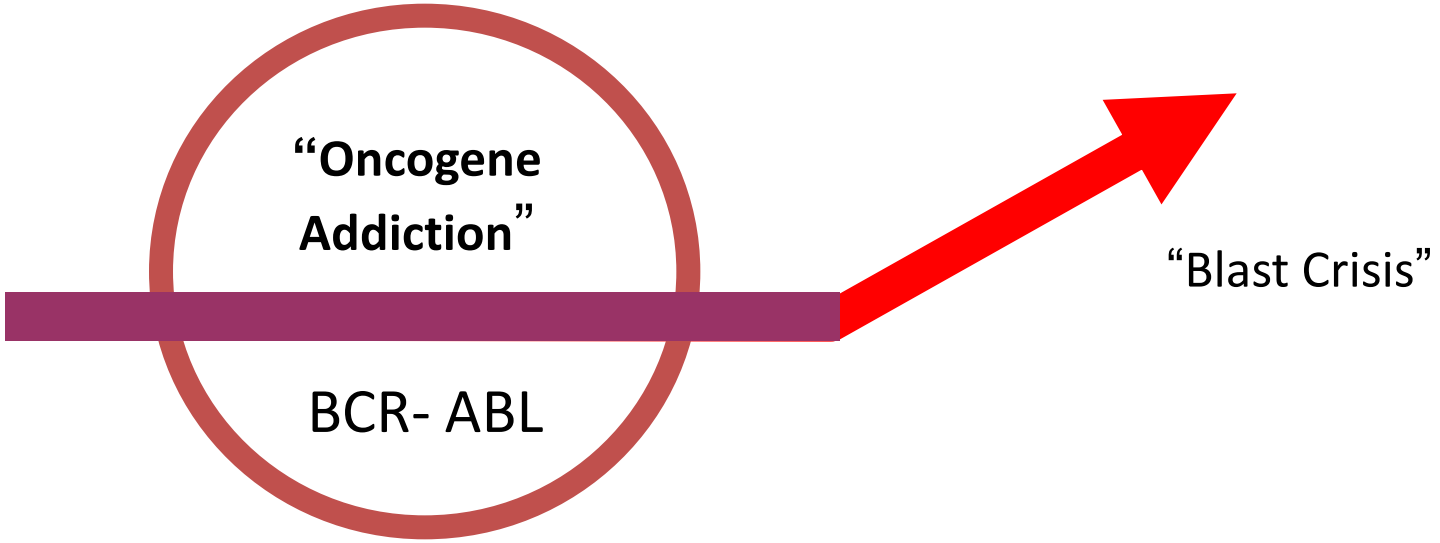
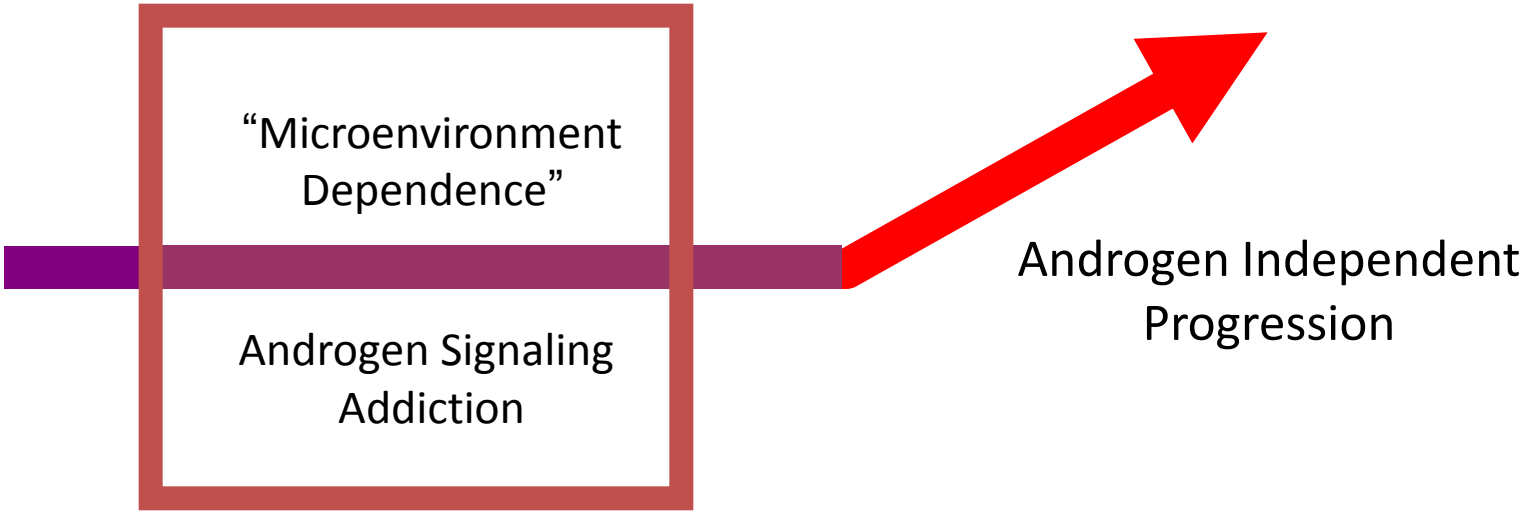
Chronic Myelogenous Leukemia

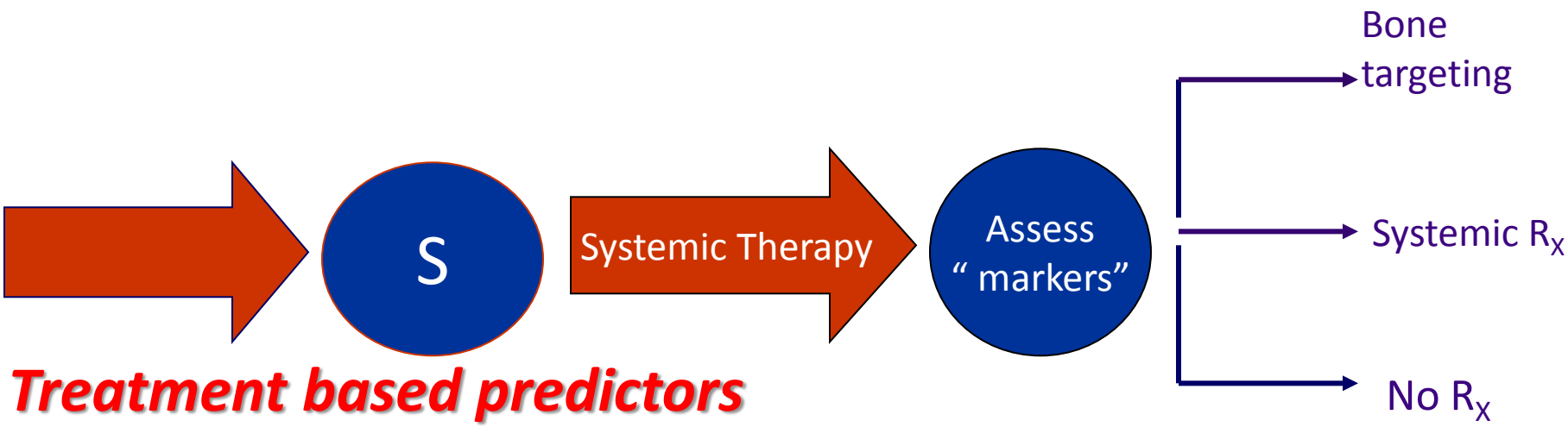


Prostate Cancer



Identifying Predictors of Outcome and Resistance to therapy is essential to therapy development

Integrated Management of Advanced Prostate Cancer

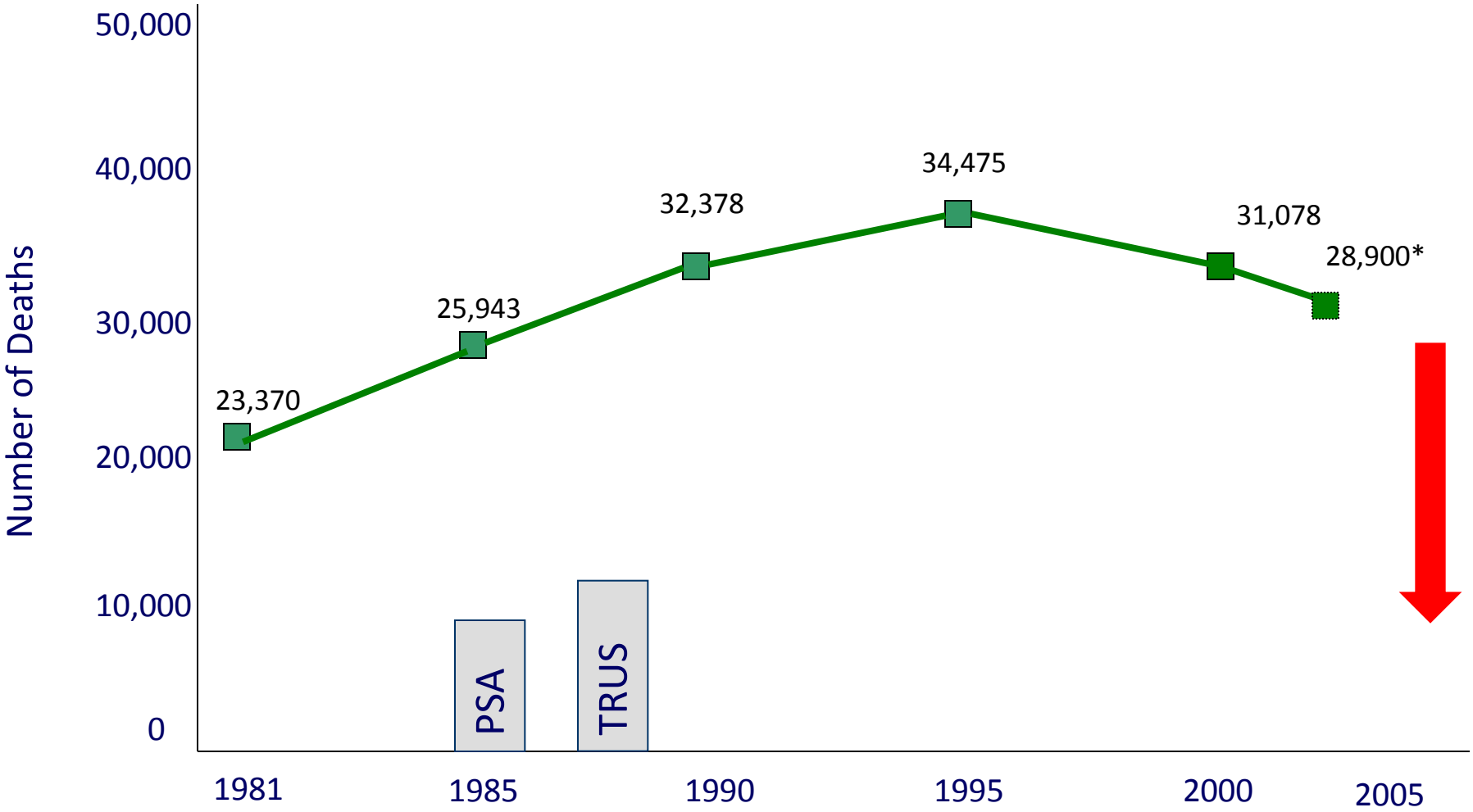


Treatment based predictors of outcome are required

Disease Heterogeneity may require combinatorial approach or guided sequencing

WHAT IS “CURING” PROSTATE CANCER!

Prostate Cancer Mortality



*estimated for 2003

Sources: Ca-A Cancer Journal for Clinicians (ACS);
Vital Statistics of the United States; SEER

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DOD Therapy Consortium

Patients & Families