New Horizons in Prostate Cancer: Exploiting Disease Heterogeneity to Develop Marker Driven Curative Intent Treatment Strategies

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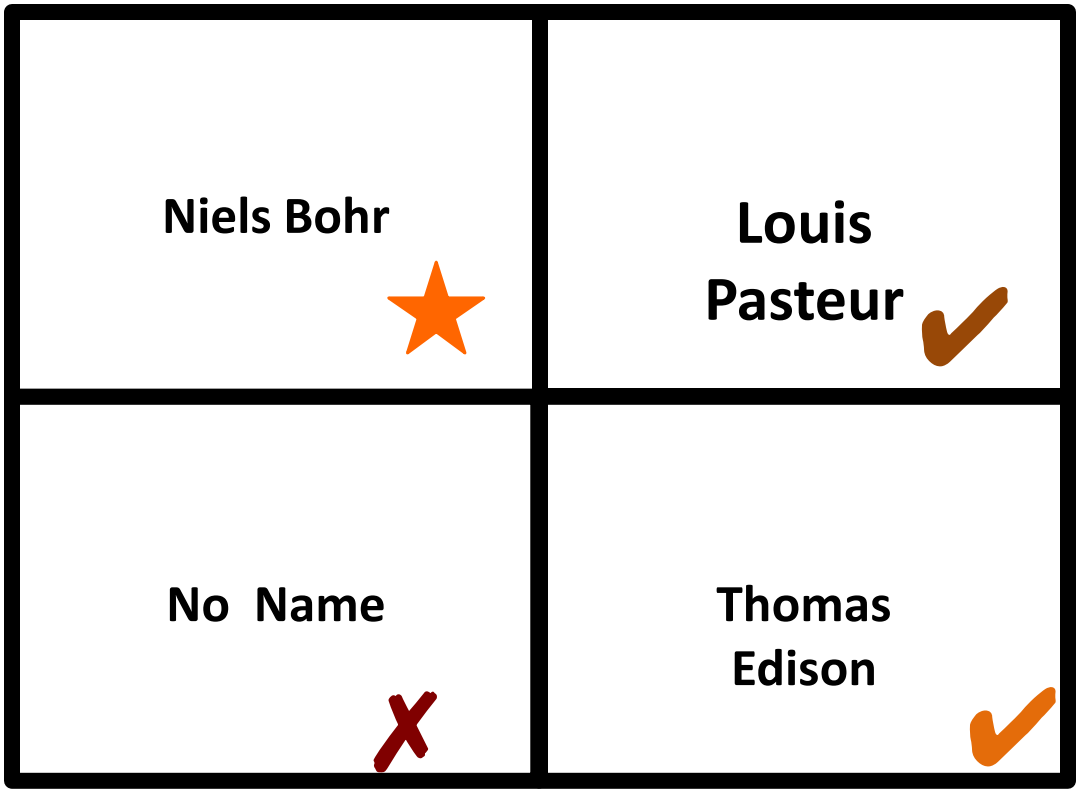
THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

Making Cancer History®

University of Athens
Medical School
Dept of Clinical Therapeutics

Precision Medicine Development
A matter of integration



Common Goal : Integration of Knowledge as a means to improve disease outcome and hence human lives

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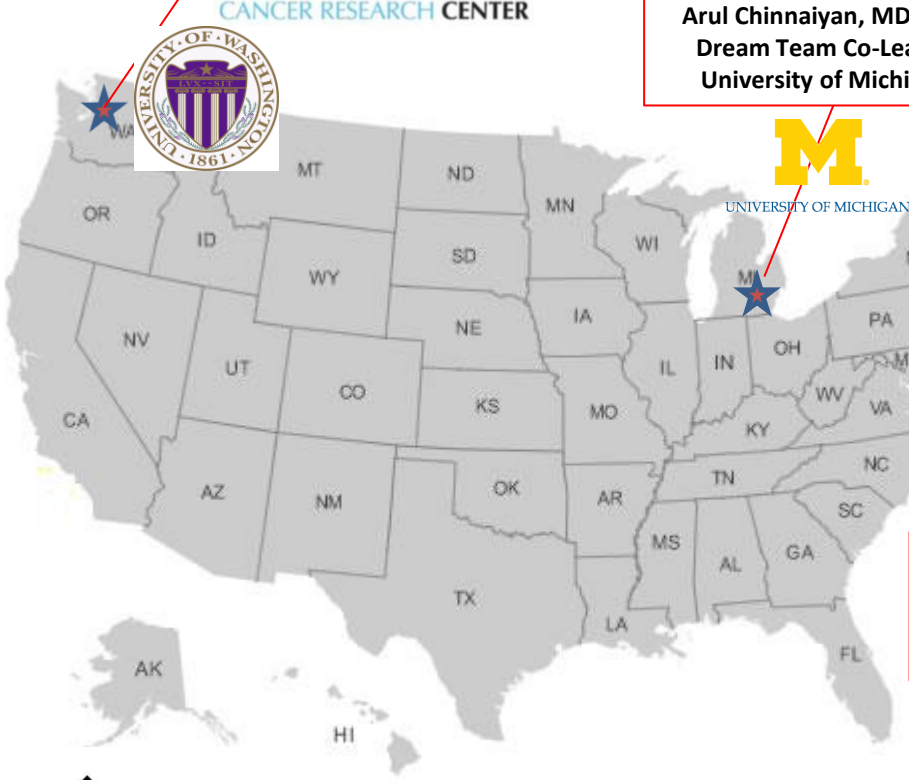

STAND UP TO CANCER

AACR American Association for Cancer Research

MEMORIAL SLOAN-KETTERING CANCER CENTER · ESTABLISHED 1884 ·

Prostate Cancer Foundation

ICR The Institute of Cancer Research

THE ROYAL MARSDEN

SU2C Prostate Dream Team Leaders and Principals

West Coast Dream Team Locations

Joshi Alumkal

OREGON HEALTH & SCIENCE UNIVERSITY

Tom Beer

Martin Gleave

RESEARCH TREATMENT

VANCOUVER PROSTATE CENTRE

A UBC & VGH Centre of Excellence

Kim Chi

Charles Ryan

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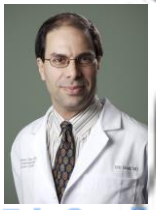

Eric Small

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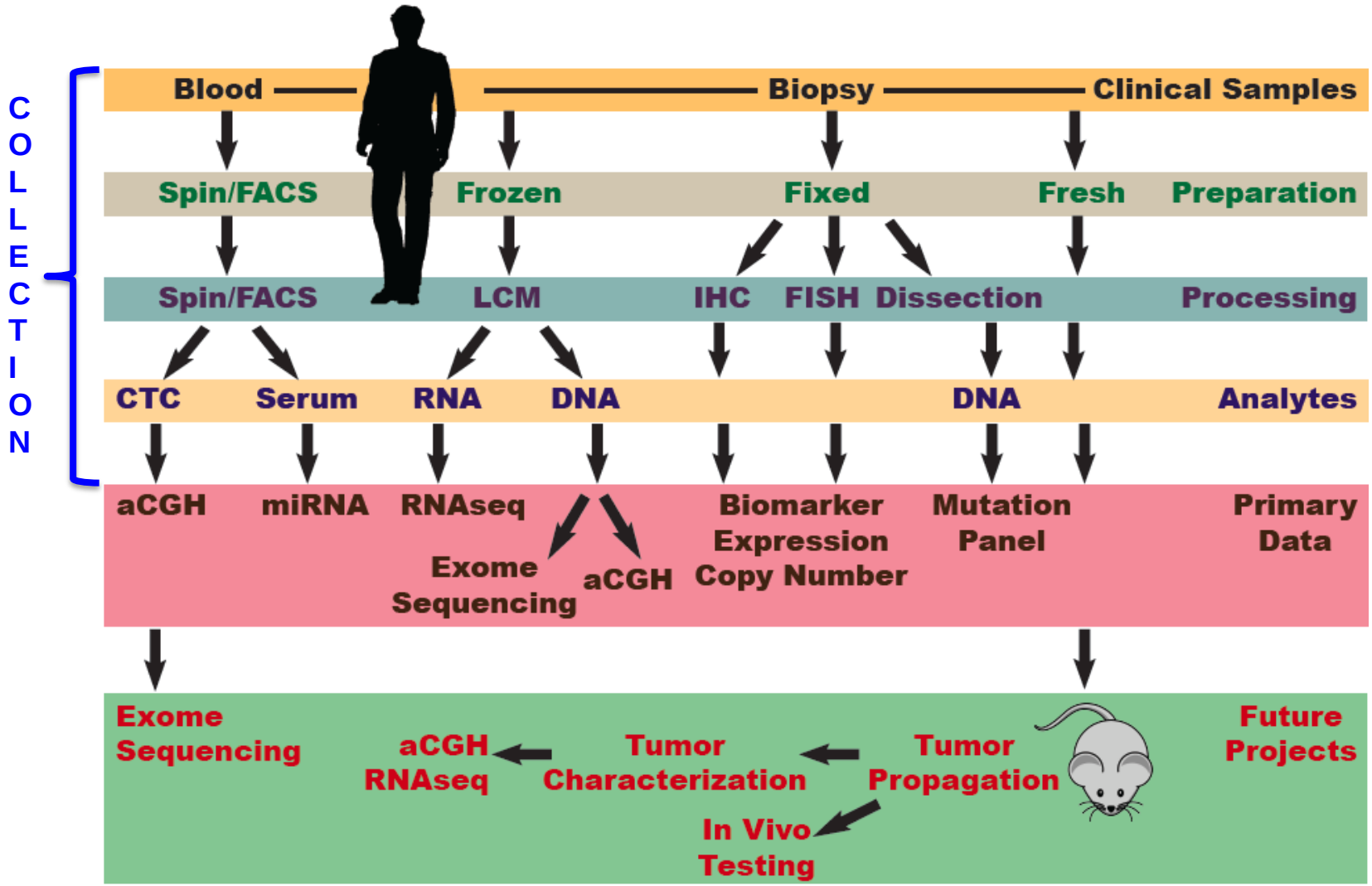
DAVID GEFFEN SCHOOL OF MEDICINE

UCLA

Robert Reiter

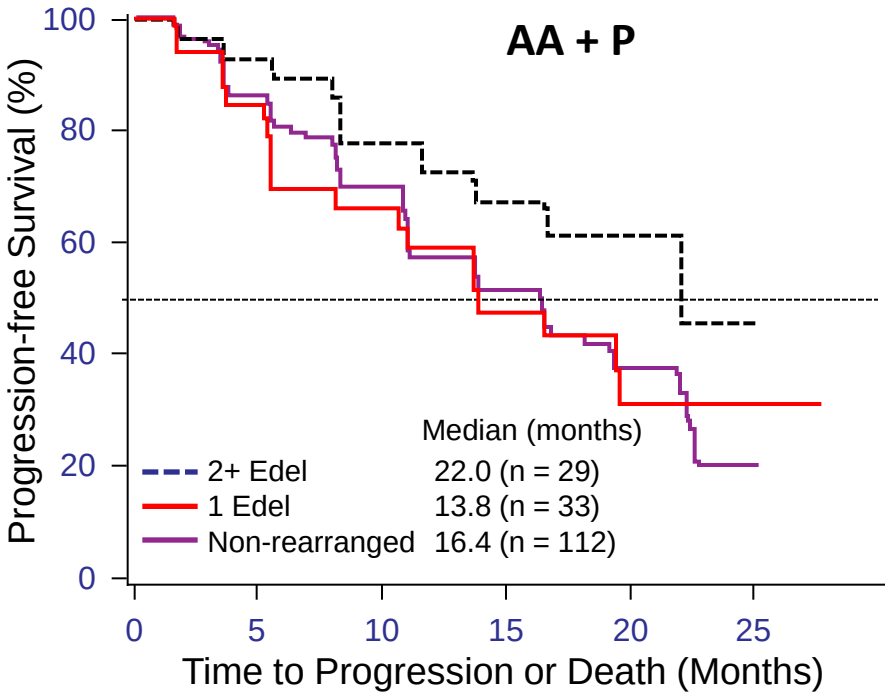
mCRPC Tissue Collection and Analysis

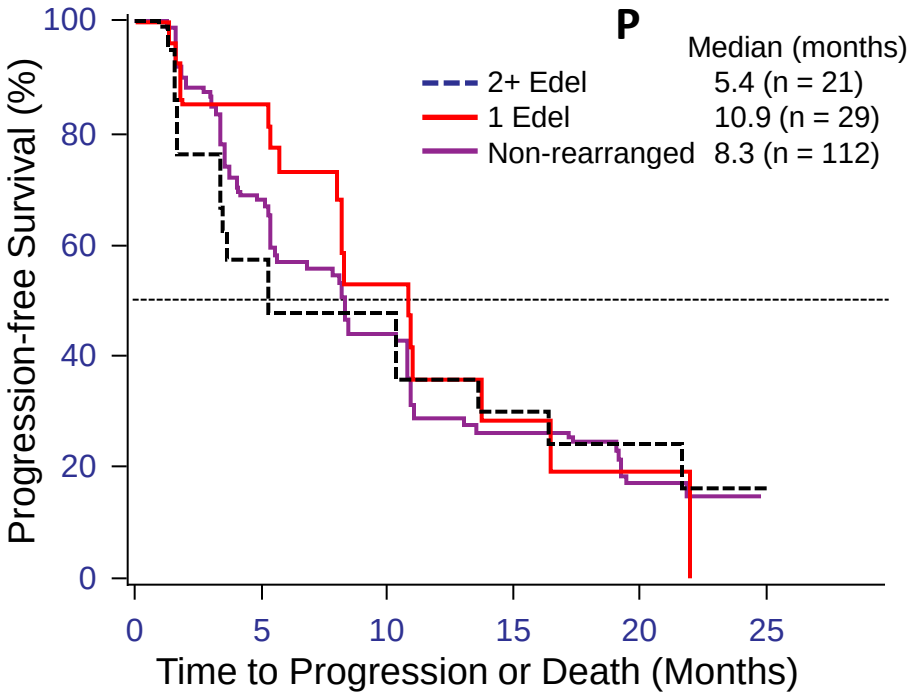


Efforts within phase III setting

Teaming up with Investigators creates a unique potential

Discovery :Study COU-AA-302:An Association of Improved rPFS in Pts with Tumors harboring Erg Rearrangements





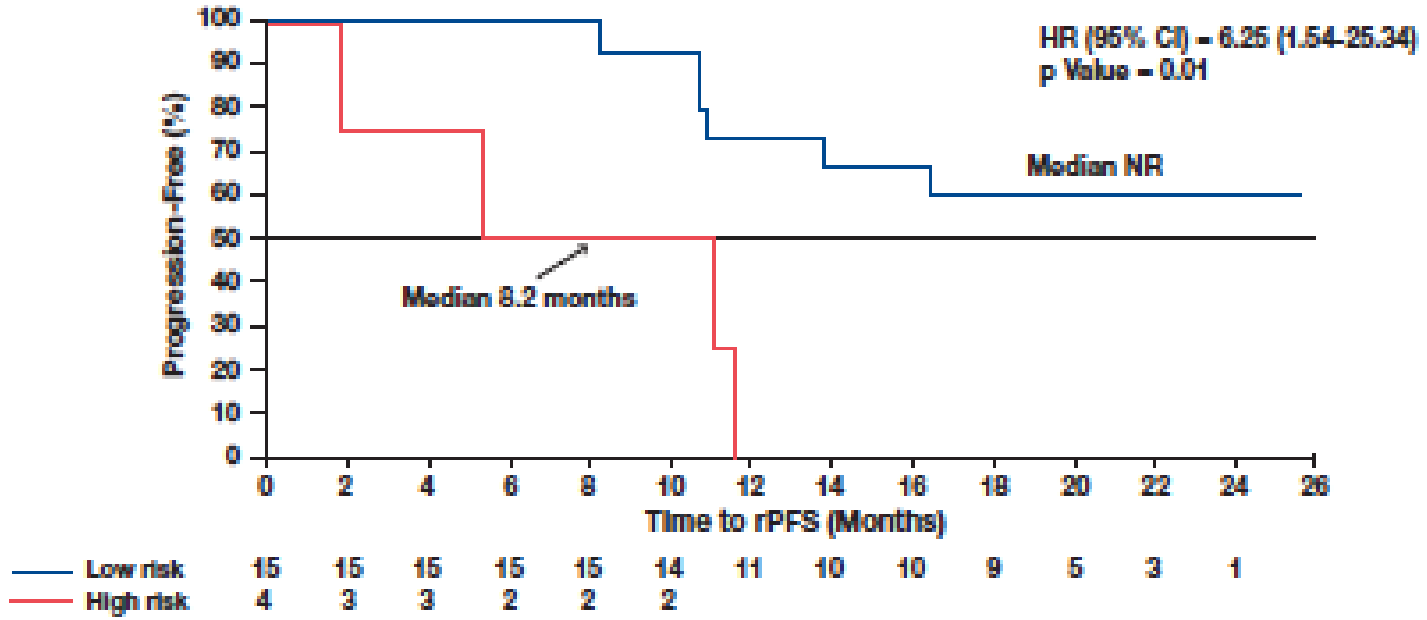
2+ Edel vs NR; HR (95% CI) = 0.54 (0.28, 1.06), p = 0.0744
1 Edel vs NR; HR (95% CI) = 1.04 (0.62, 1.73), p = 0.8924

2+ Edel vs NR; HR (95% CI) = 1.09 (0.63, 1.87), p = 0.7633
1 Edel vs NR; HR (95% CI) = 0.87 (0.51, 1.47), p = 0.5919

NR, *ERG* non-rearranged.

Attard et al ASCO 2013

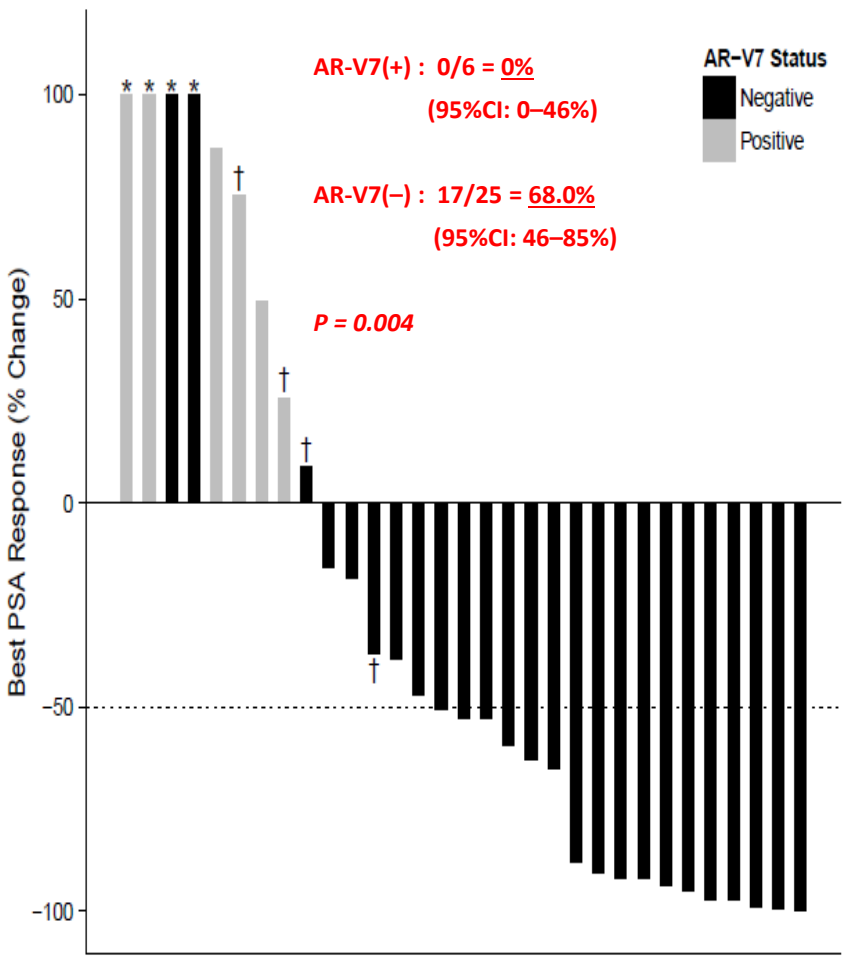
Discovery: Candidate (RNA) Androgen Signaling signature predictive of benefit with Abiraterone Acetate

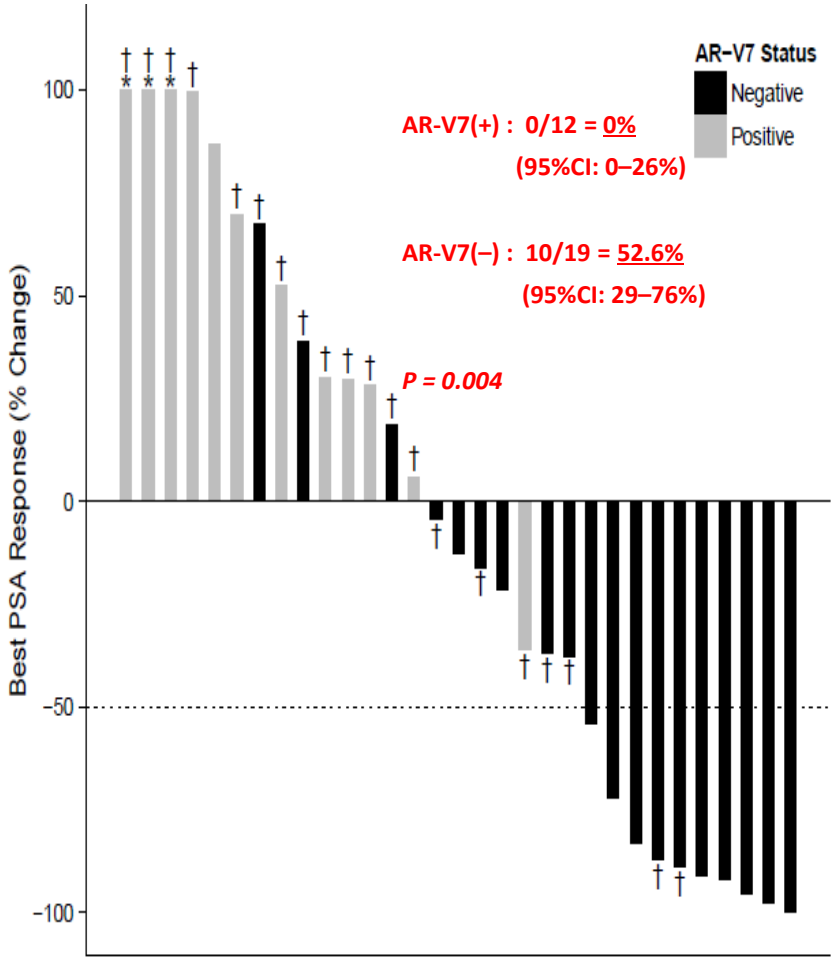


Ricci et al ASCO 2014

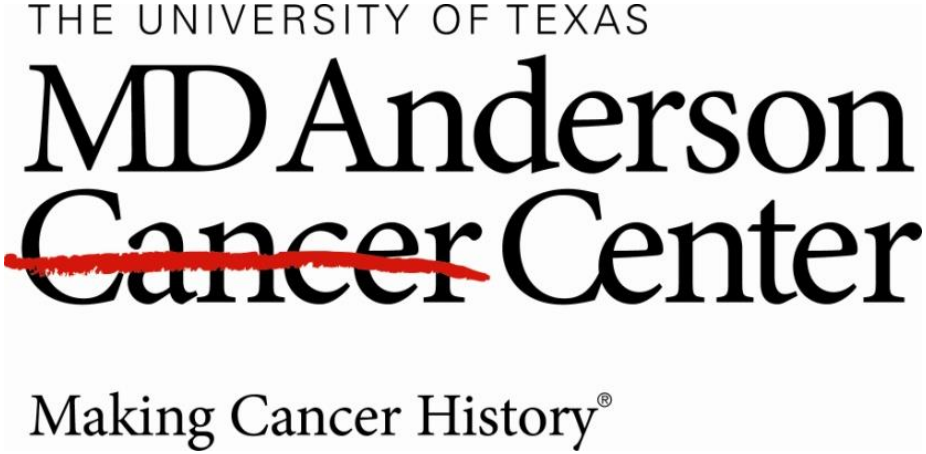
Single Institution Efforts

ARV7 detected in CTC associated with resistance to novel androgen signaling inhibition





Antonarakis et al NEJM 2014



Hypothesis: ***Optimum use of available prostate cancer 'agents' can lead to the Cure of "select" men with prostate cancer and secondary prevention in more advanced disease***

MDACC Efforts towards Precision Medicine

Prometheus

Integrating Molecular Characterisation & Clinical Data

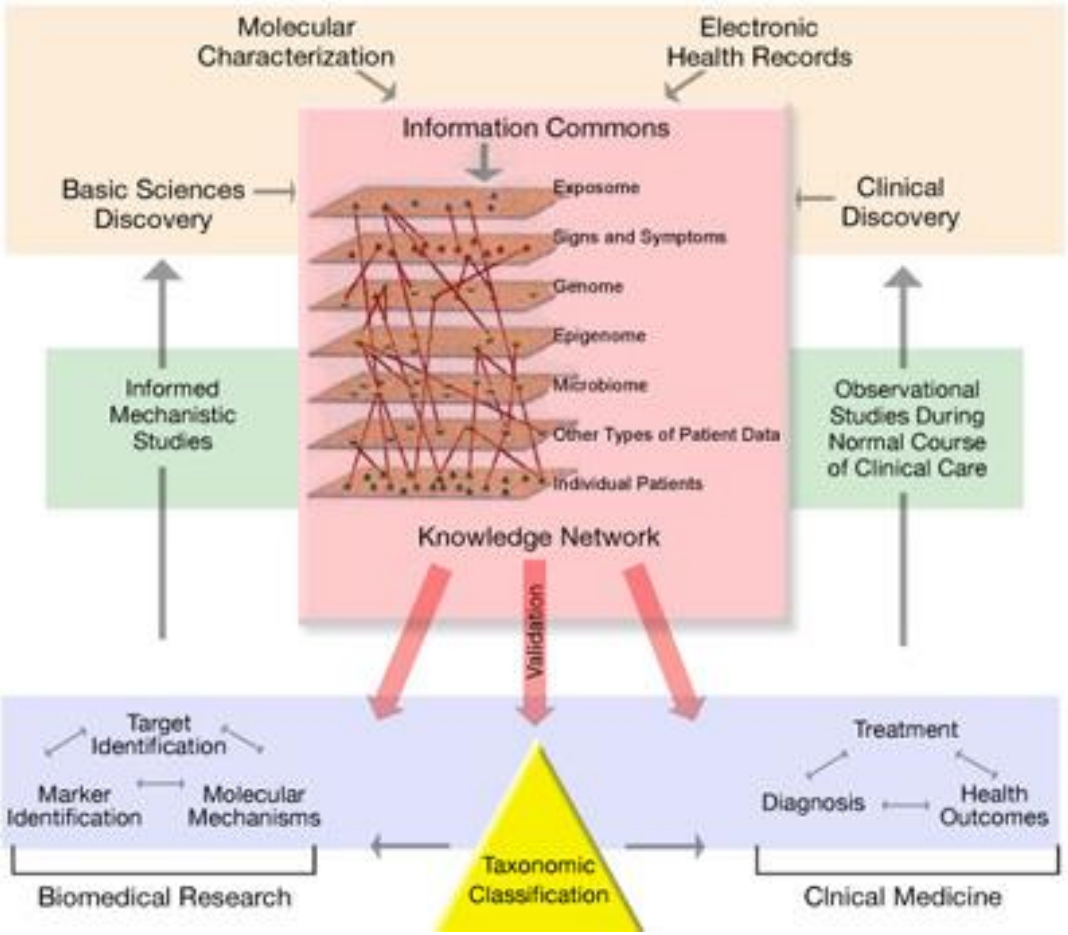
Tissue and Liquid Biopsy Based Clinical Research

Co-Clinical Research

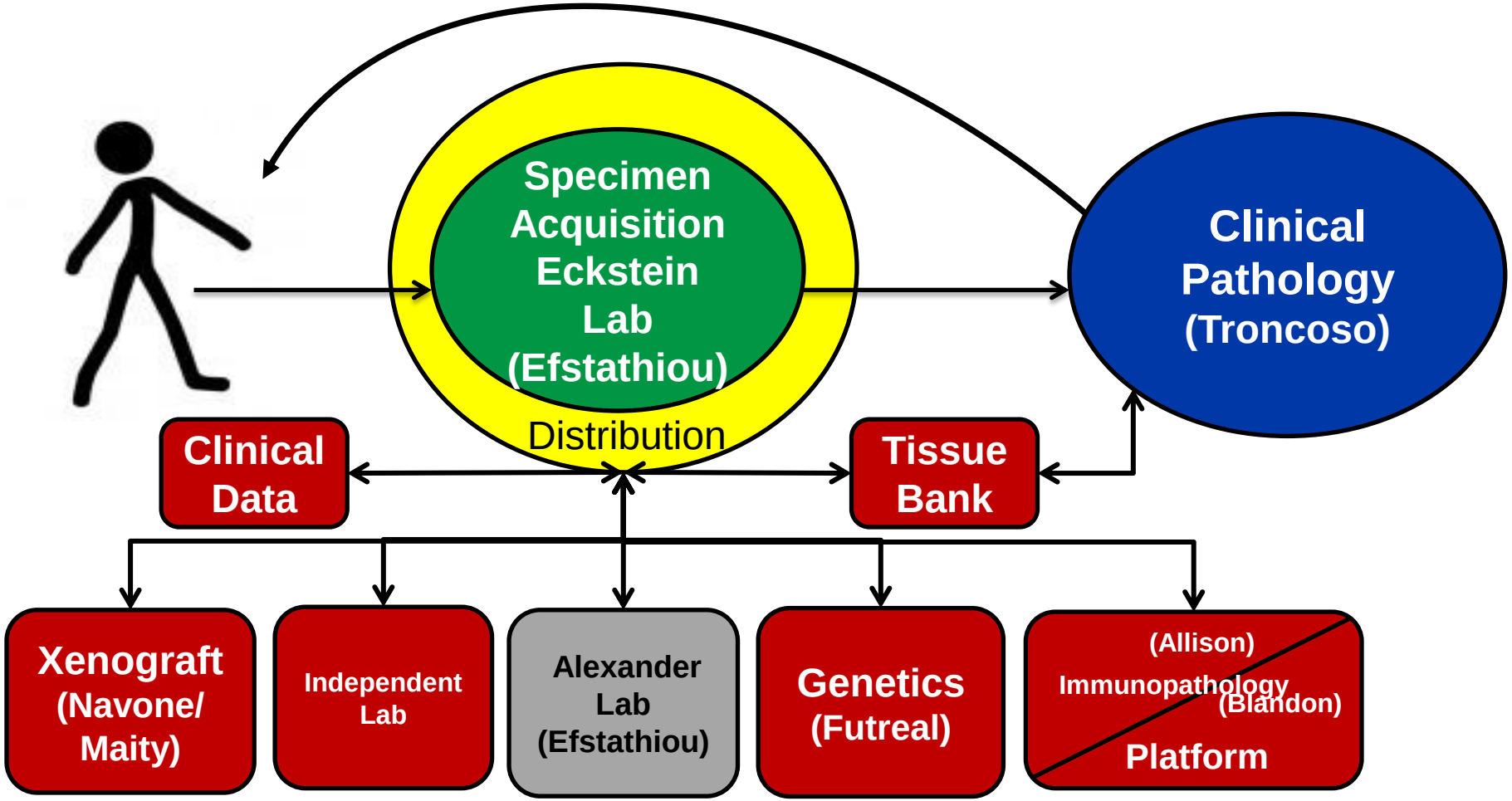
Discovery

Testing

Validation



Create Knowledge from Data



Estimate: *3 .5 million* analyses annually!

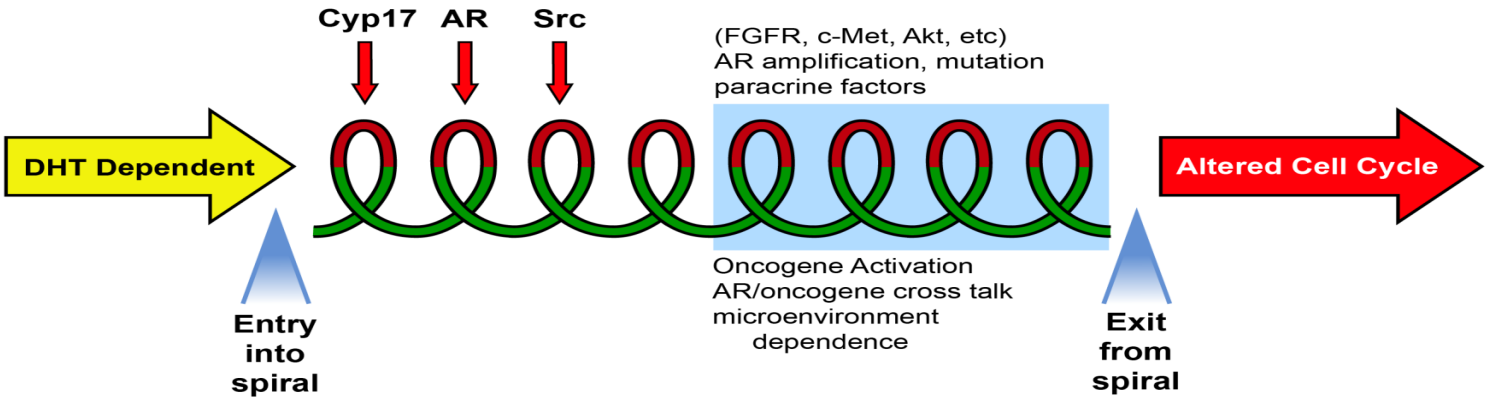
Prometheus Platform

Clinical Research Integration with molecular characterisation

- **Infrastructure "customized informatics"**
- **Acquire, chain of custody, inventory, distribute.**
- **Analytics platform**

From tissue to knowledge bank

A working Model for Reclassification of Prostate Cancer to incorporate intra patient and temporal disease heterogeneity



A Roadmap to New Taxonomy

Tools

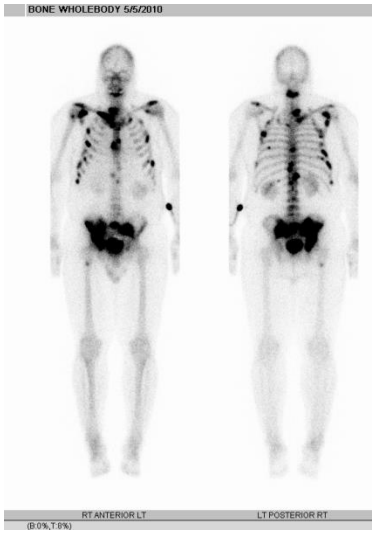
Prometheus : A Knowledge bank

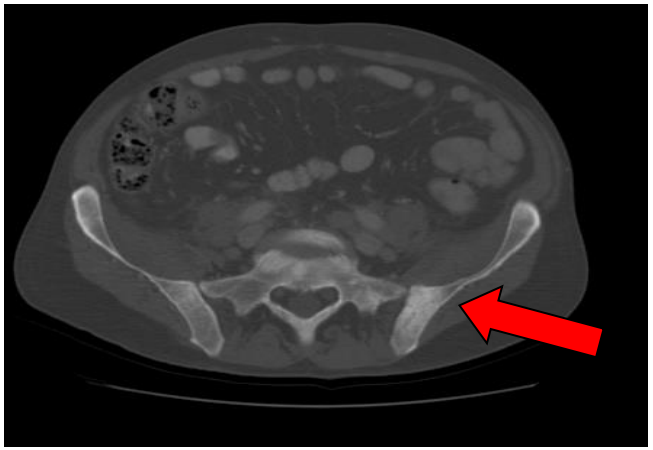
Tissue and Liquid Biopsy Based Clinical Research

Co-Clinical Research

Logothetis et al Cancer Discovery 2013

Informative Transilial Bone Marrow Biopsy



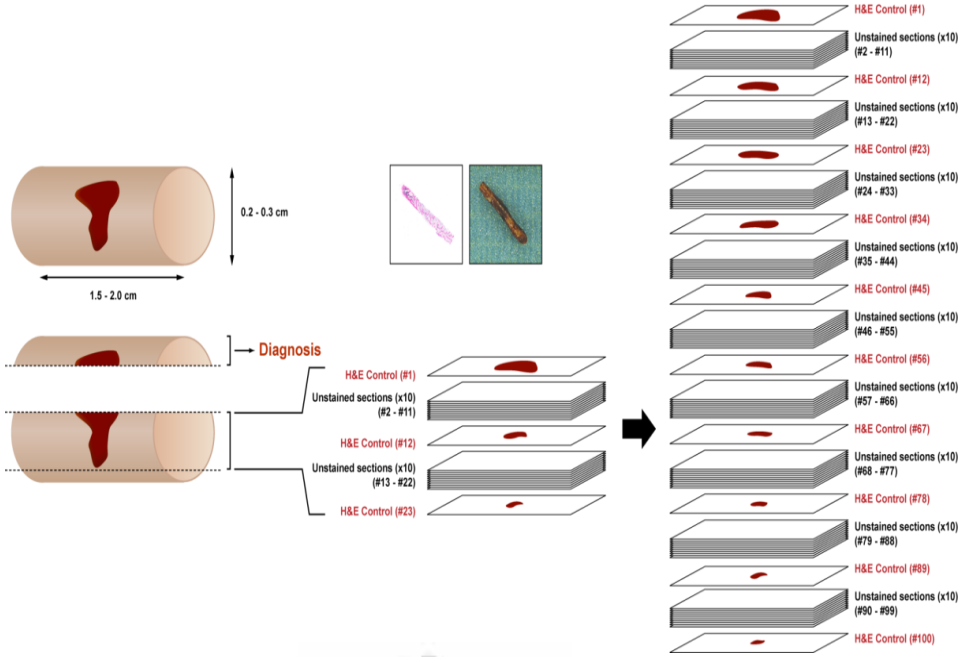


CT Directed

Efstathiou et al. J Clin Oncol 2012

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

Stanford Alexander Laboratory



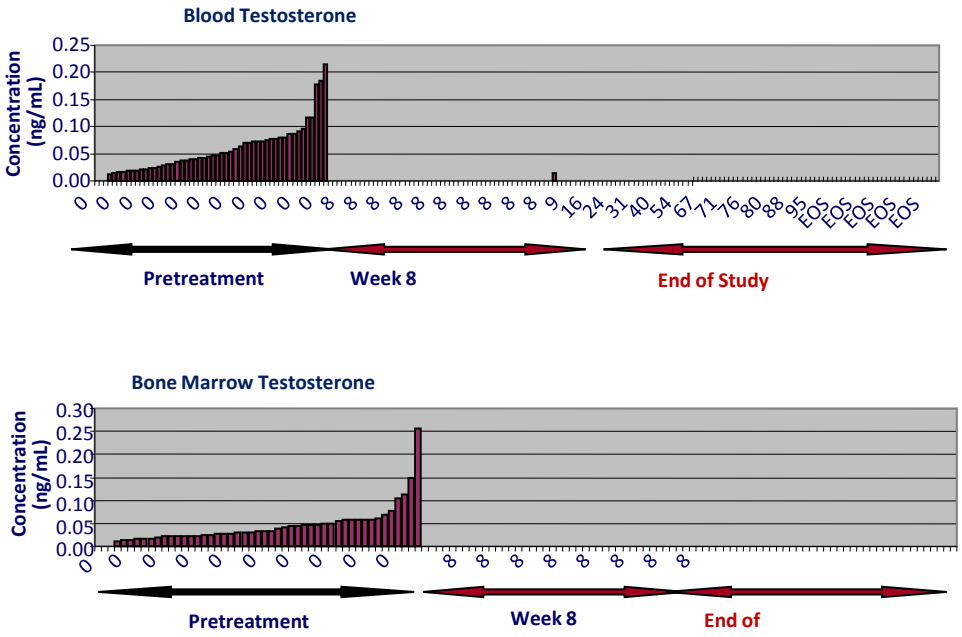
The MDACC Bone Biopsy Androgen Signaling mCRPC Program. Goal :Create Knowledge from Tissue based Clinical Research

	Study	Agents	mCRPC pts
Discovery	09-0590 (JCO 2012)	Abiraterone Acetate	60
Discovery	09-0886 (Eur Urol 2014)	Enzalutamide	60
Testing	12-0086 (ASCO 2014)	ABI +ENZA	60
Testing	10 -0070 (ESMO 2014)	ABI +randomization to Dasatinib or	170

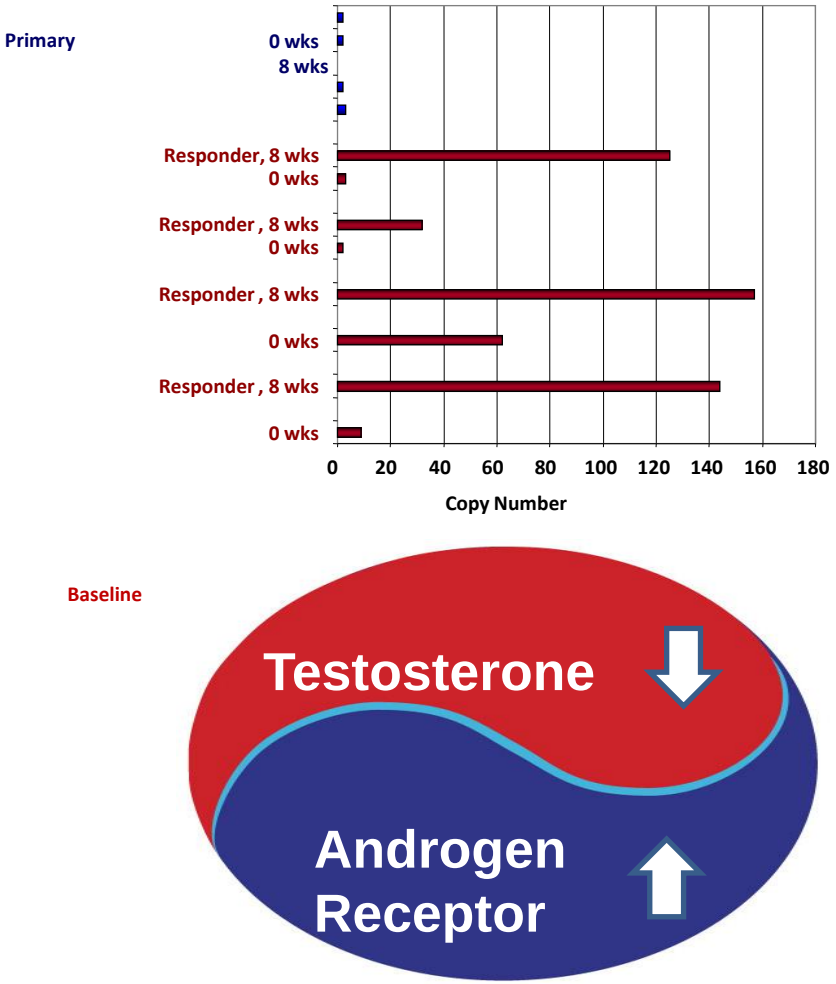
Endpoints:
Inform regarding Tumor microenvironment Impact of agents tested
Explore Identify Test and Validate predictive markers
Develop Assay Driven Therapy Strategies to guide treatment sequencing and combination

AR & Androgen Modulation Following Abiraterone Acetate (MDACC 09-0590)

Testosterone Depletion



AR Copy Number Modulation

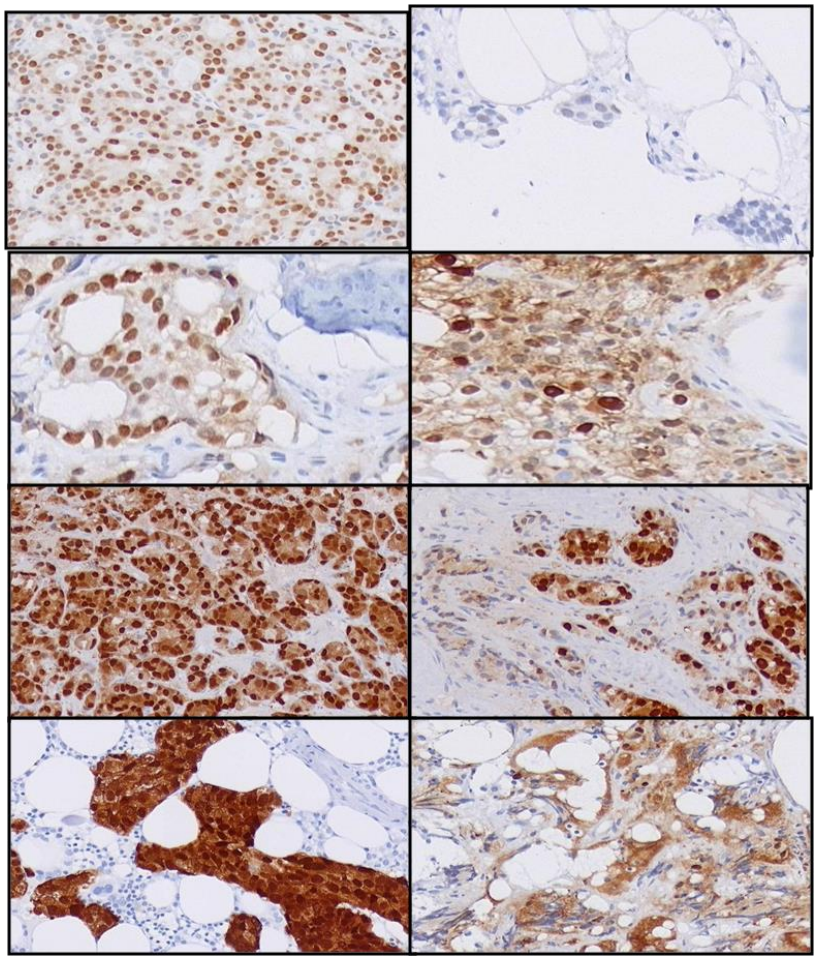


qPCR on ≥500 cells.

Efstathiou et al. J Clin Oncol 2012

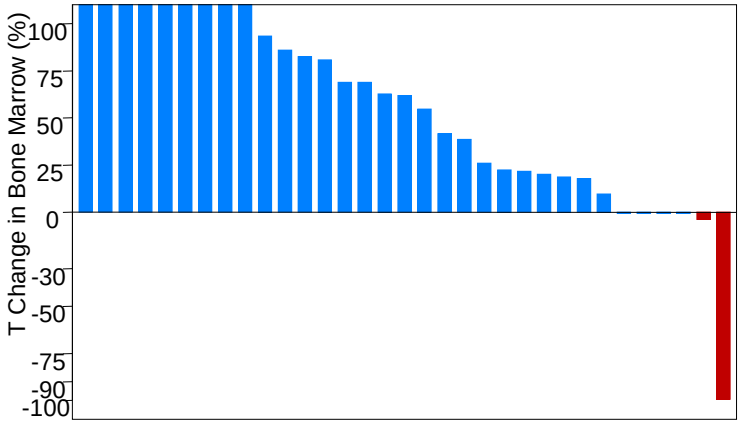
AR & Androgen Modulation Following Enzalutamide (MDACC 09-0886)

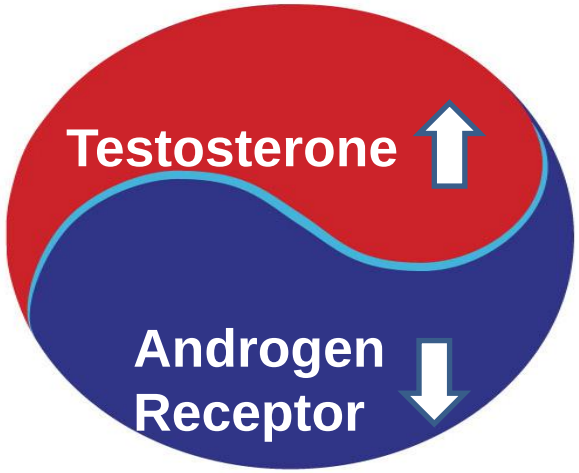
AR Shift in Subcellular Localization



Pretreatment Week 8

Marrow Testosterone Increase



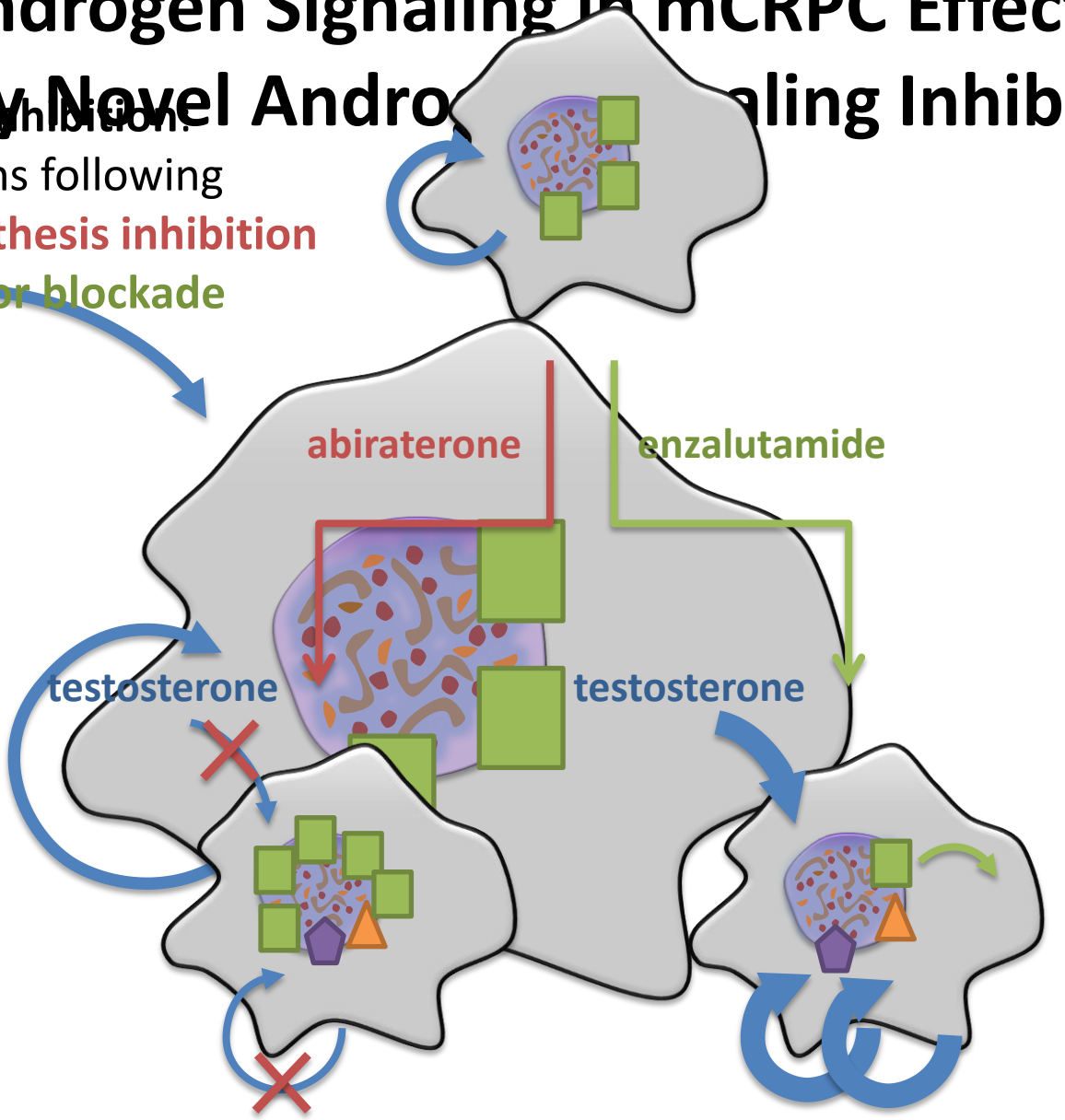


Efstathiou et al. Eur Urol 2014

Adaptive Androgen Signaling in mCRPC Effectively Targeted by Novel Androgen Signaling Inhibitors

Androgen signaling inhibition:
Feedback mechanisms following

A. **Androgen biosynthesis inhibition**
B. **Androgen receptor blockade**



Efstathiou et al JCO 2012;
Efstathiou et al Eur Urology (in press).
mCRPC, metastatic castration-resistant prostate cancer

Efstathiou et al ASCO 2014

Study 12-0083

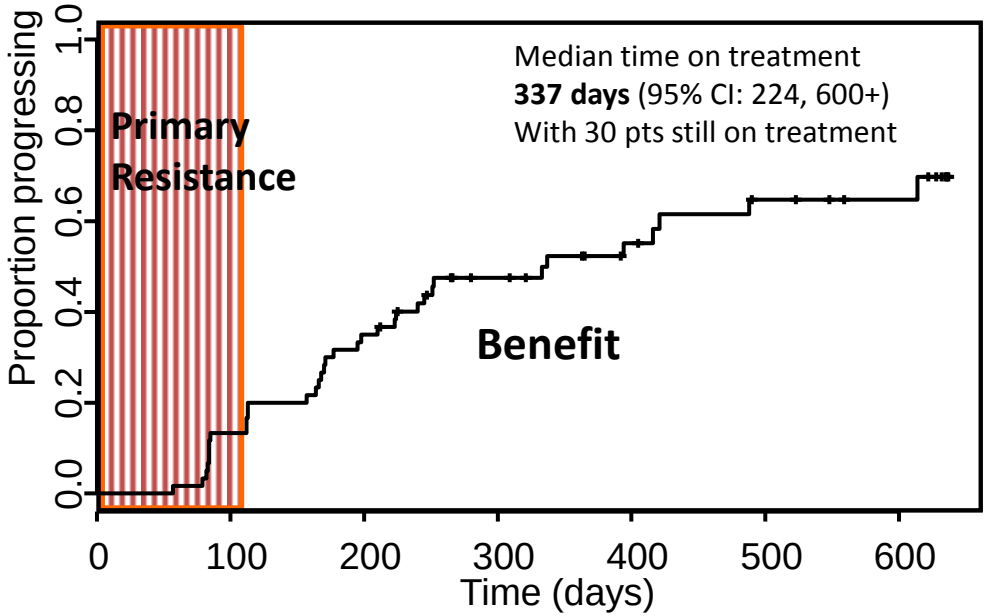
Enzalutamide 160 mg once daily + **Abiraterone acetate** 1 g once daily **(+ prednisone)** (5 mg twice daily)

Baseline

Bone marrow biopsy
Bone marrow aspirate
Blood collection

Week 9

Hypothesis Confirmed :
Combination of ABI +ENZA
will dissipate physiologic feedbacks
incurred by each agent alone

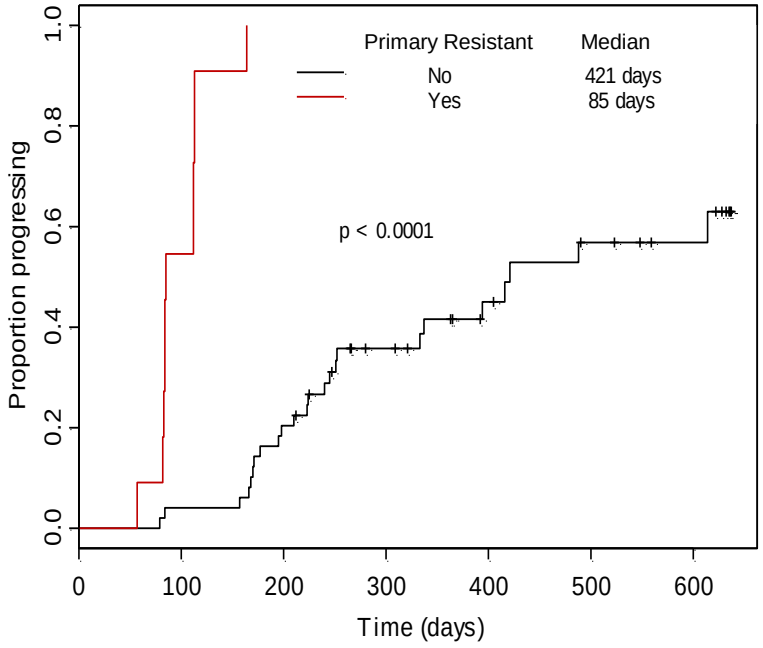


Primary Resistance :
Not related to feedback mechanisms
Ensuing Resistance :
maybe Affected as evidenced by time on combination

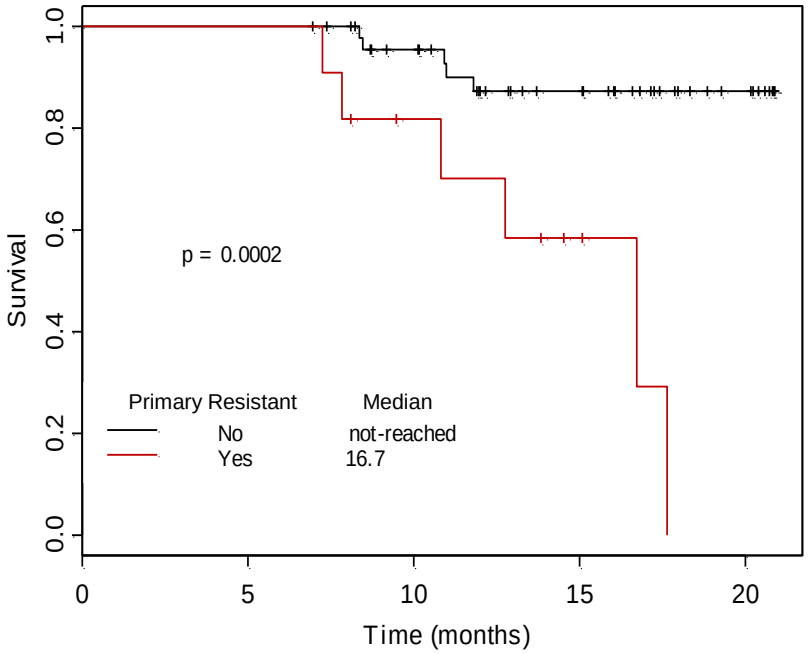
Efstathiou et al ASCO 2014

“Primary Resistance” as a Prognosticator in mCRPC

Time on treatment



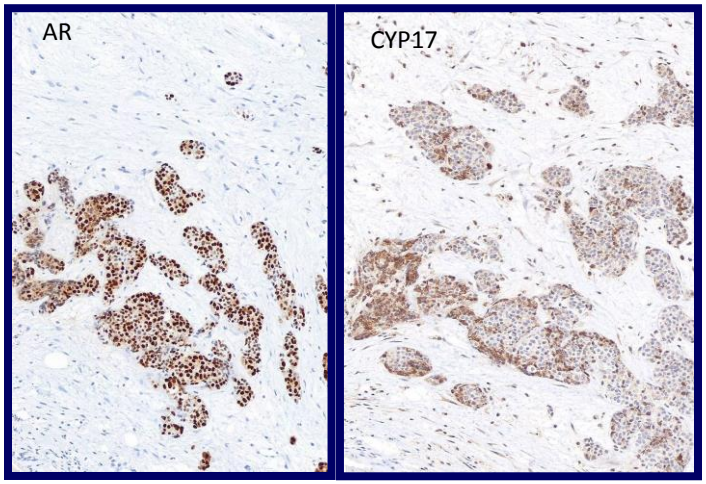
Overall survival

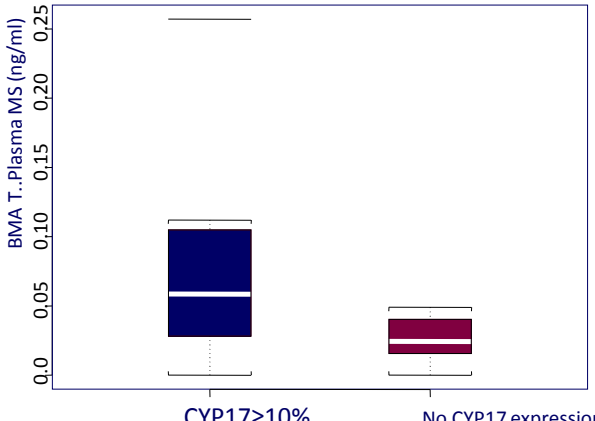


Efstathiou et al ASCO 2014

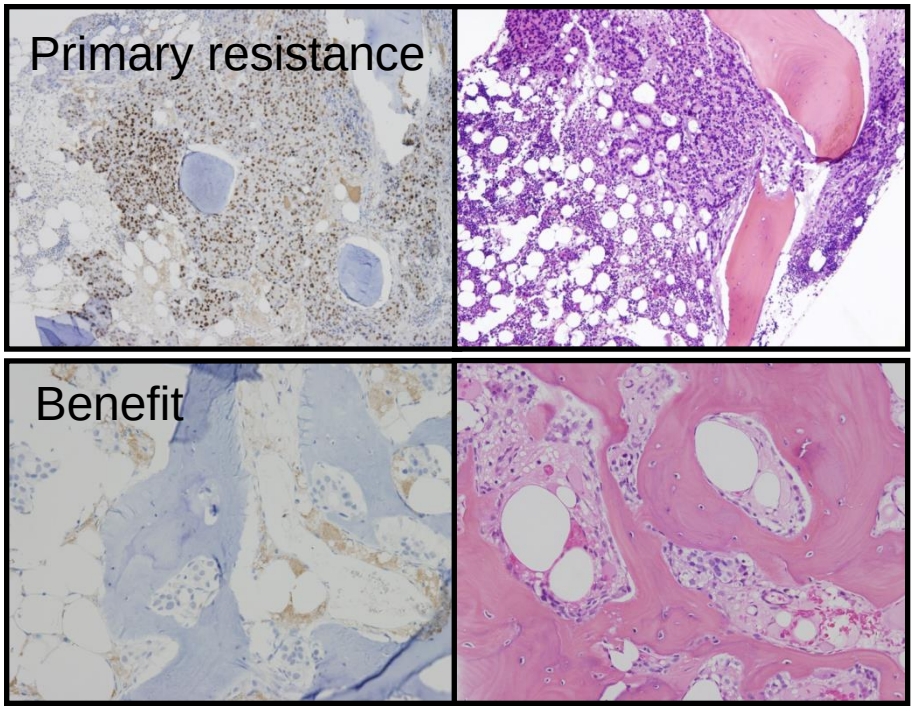
Androgen Signaling in mCRPC and association benefit

Nuclear over-expression of N terminal AR + CYP17 correlates with benefit (p<0.01)





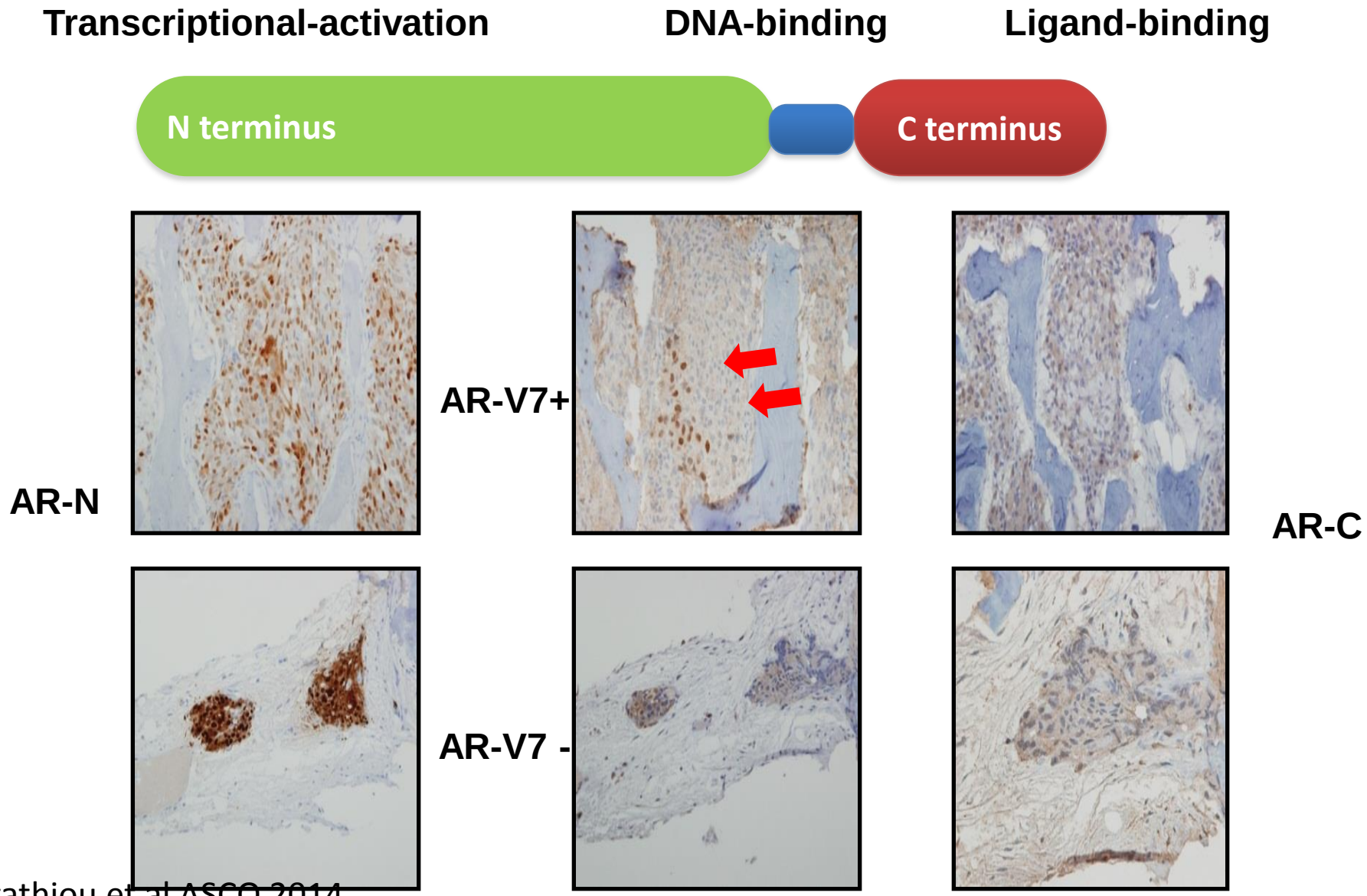
AR V7 expression linked primary resistance to enzalutamide (p=0.02)



Efstathiou et al JCO 2012;
Efstathiou et al Eur Urology 2014;
Antonarakis et al AACR 2014

AR, androgen receptor

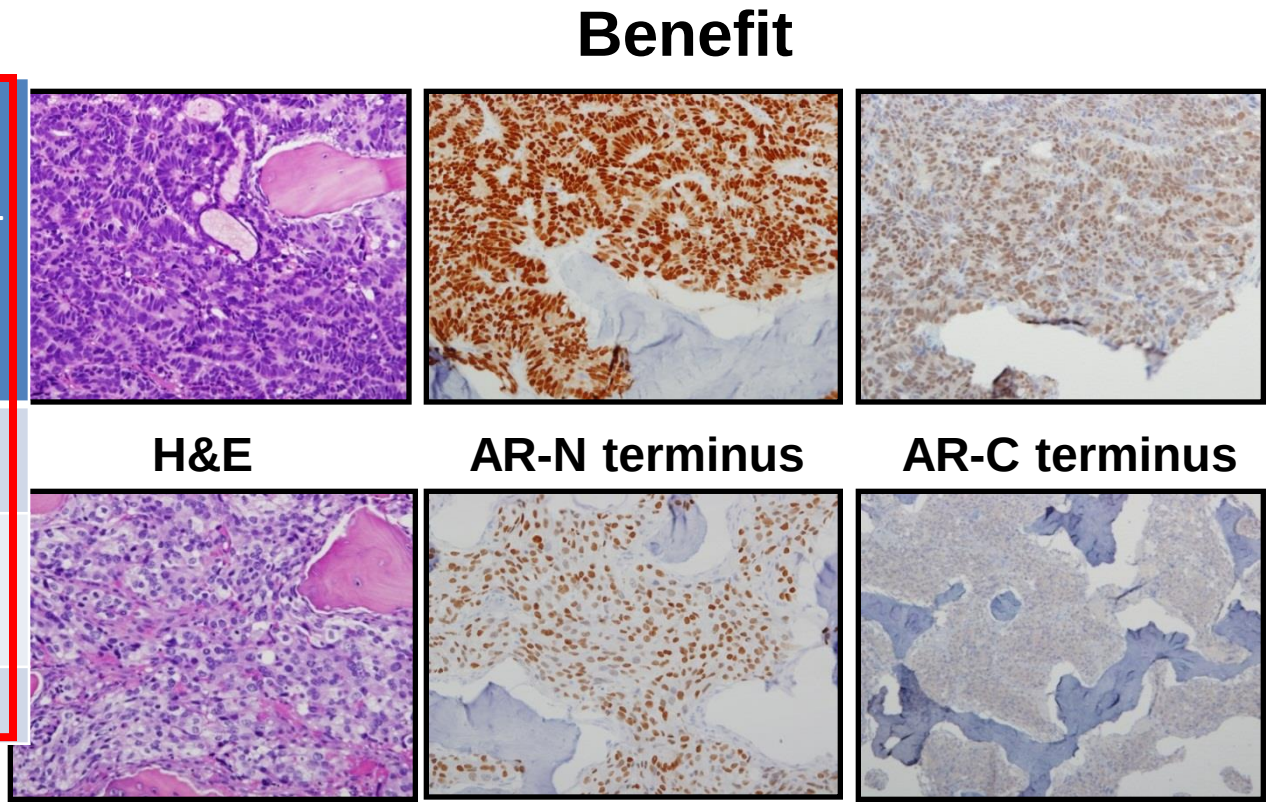
Androgen Receptor Expression & Alterations



Efstathiou et al ASCO 2014

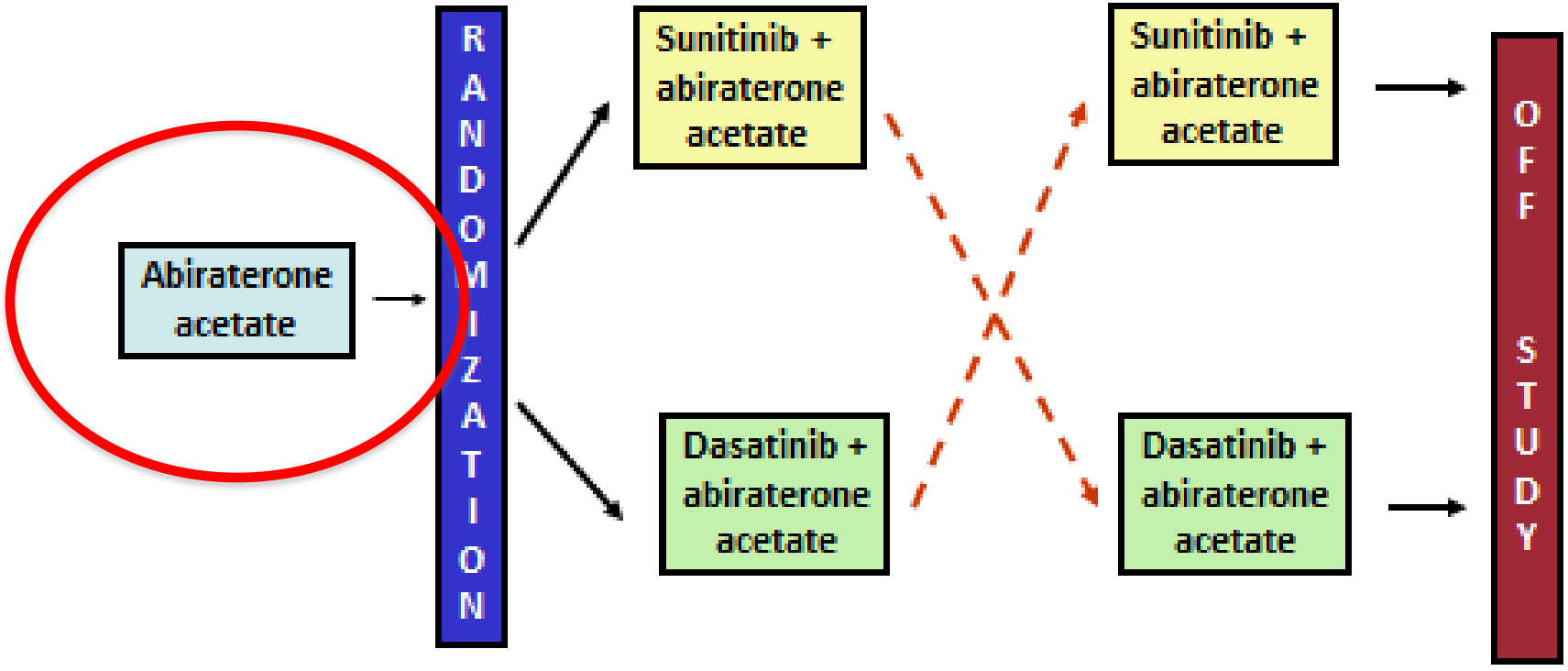
C Terminal / N Terminal Ratio AR Expression May Enhance Predictive Performance

Marker	ARN (n3+)+CYP 17	ARC/ARN (n) ~1 +ARN(n3)+ CYP17
Benefit (n=9)	9	9
Primary resistance (n=6)	2	0
P value	0.03	**0.0002**



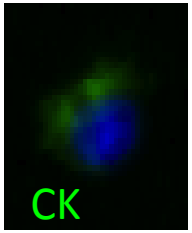
Efstathiou et al ASCO 2014

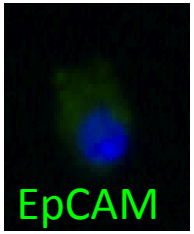
MDACC 10-0070 Testing Primary Resistance associations with androgen signaling molecular signature

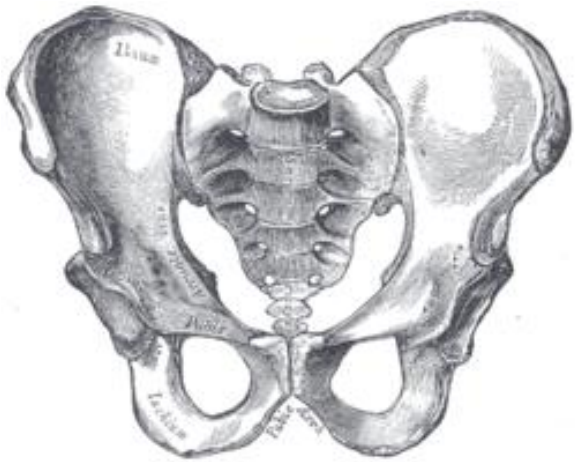


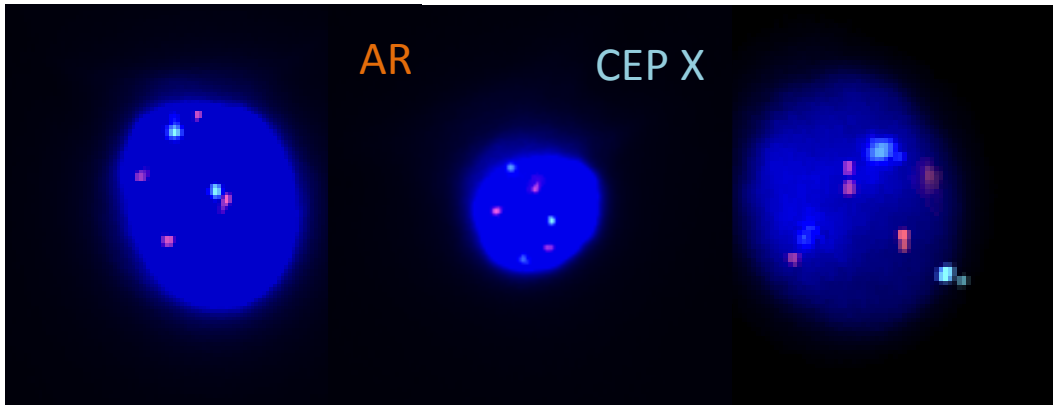
Efstathiou et al ESMO 2014

Prostate Cancer in the Bone Marrow



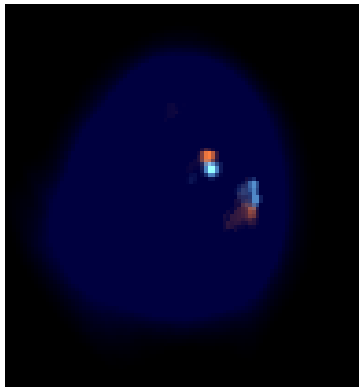






AR amplification (17/37 CK+ cells)

3 months on abiraterone and enzalutamide



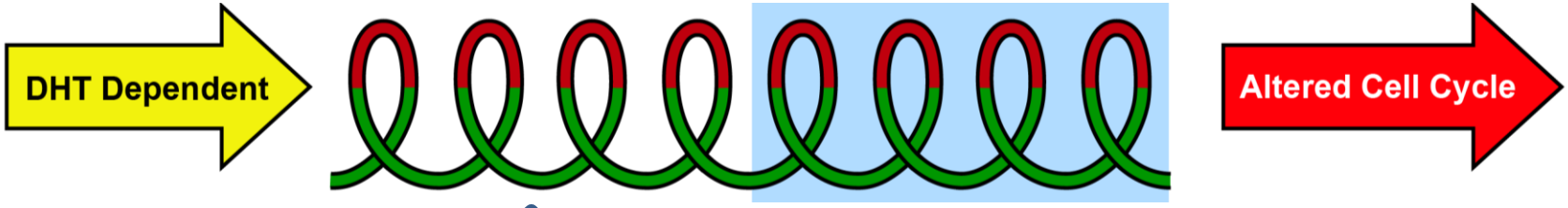
AR gain (5/5 cells)

Progressing to abiraterone

Negative BM (path)

Zurita et al

Acquiring Knowledge with a Curative Intent
The preoperative high risk model

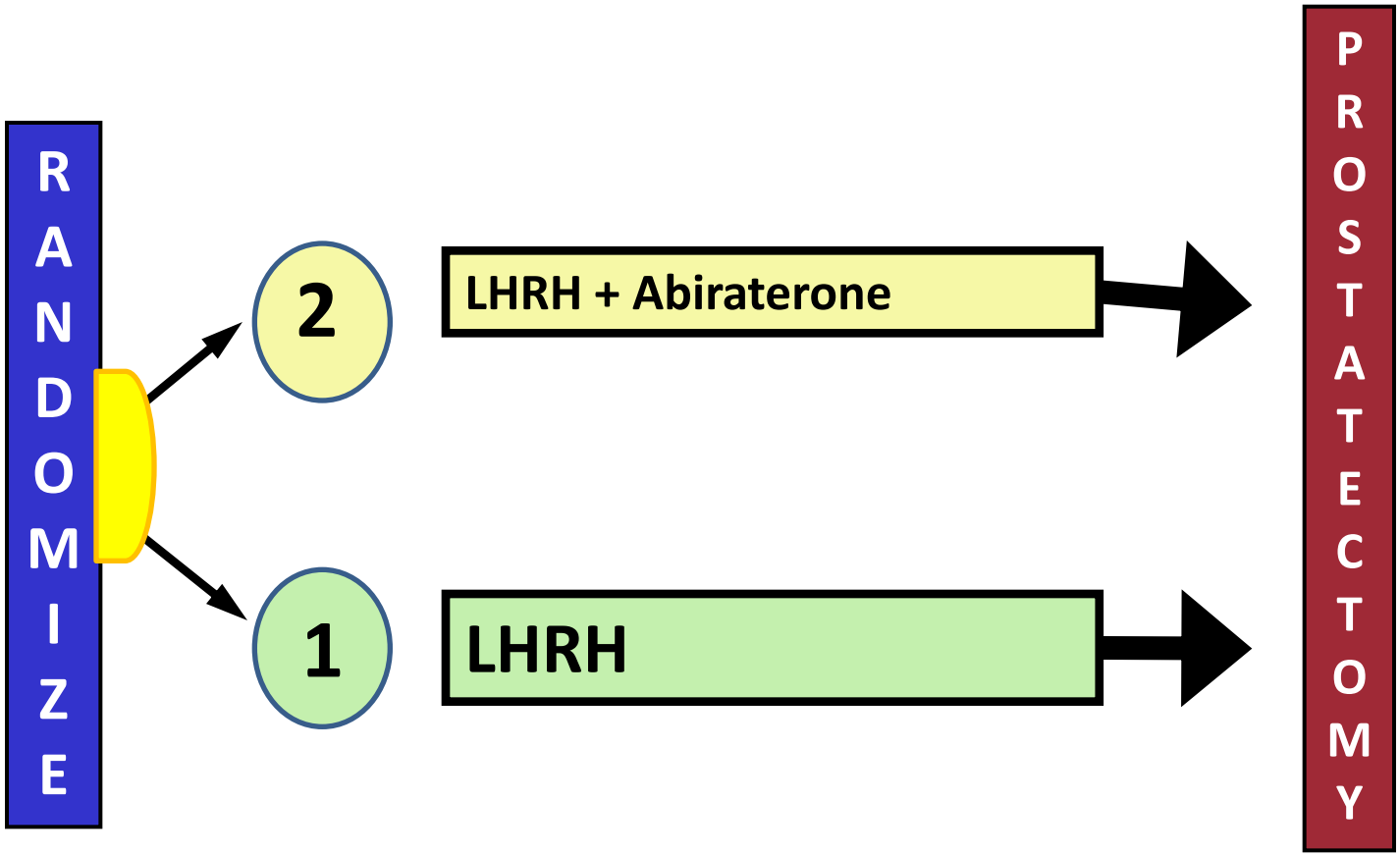


Cancer early in spiral does not possess "plasticity" to resist therapy!

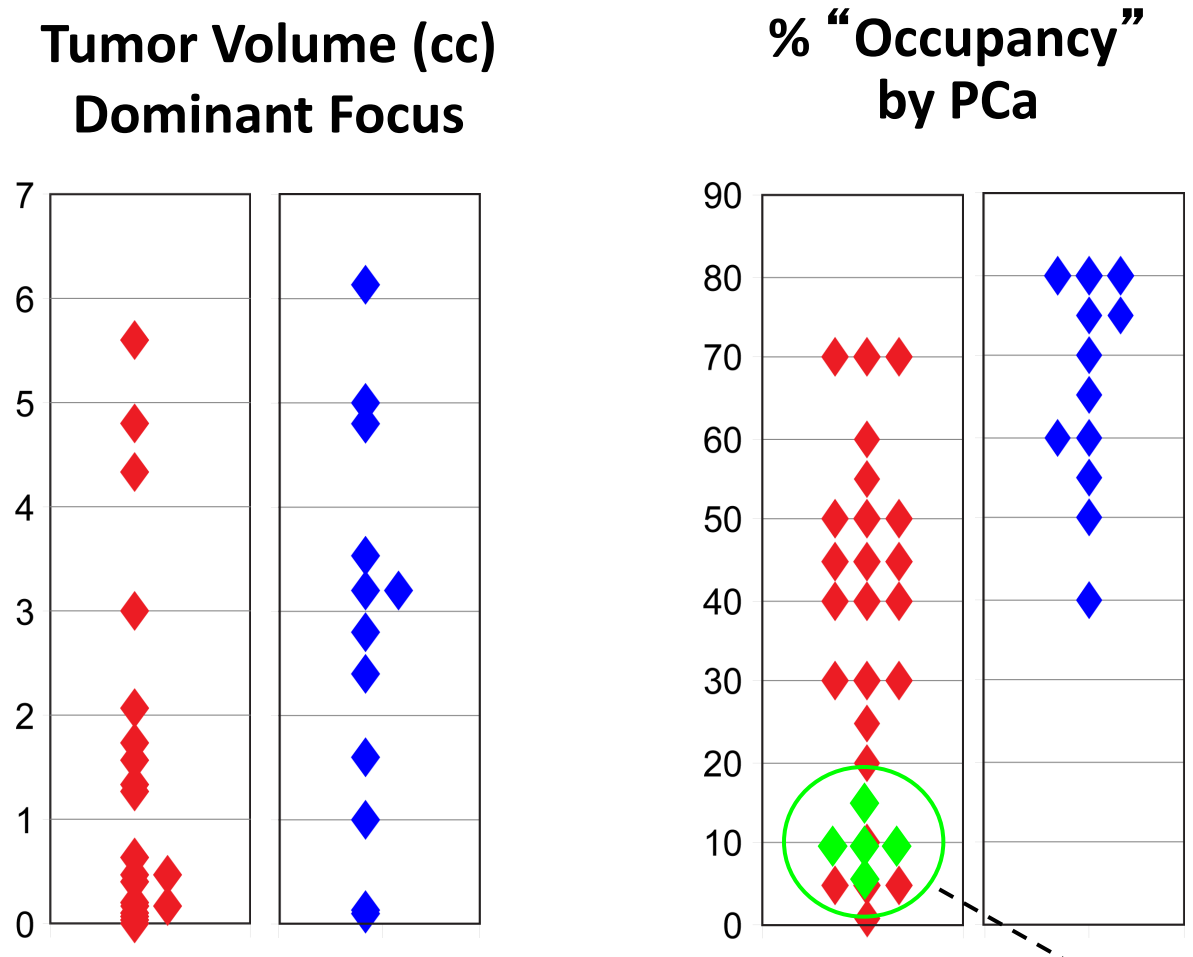
Preoperative High Risk Platform

Protocol #	Protocol	Years	#RP	Frozen Tissue (FT) % of cases	% FT with Ca
	KAVE	97-98	30	13	50
DM97-095	p-53	98-99	25	36	100
DM96-140	TNP	98-00	24	46	100
99-063	KAVE vs Horm. Abl. *(Prostate 12)*	99-03	60	67	73
01-079	Thalidomide *(CCR 07)*	2001-02	16	75	100
ID03-0112	Docetaxel &LHRH. (JCO 12)	2003-05	36	92	77*
2003-0492	CCI 779 (ASCO 09)	2004-07	34	100	97*
2004-0273	Horm. Abl. & Docetaxel*	2006-09	32	81	**
2005-0903	Sutent	2007-09	39	100	**
2008-0069	Sutent (Multi-Center)	2009-09	1	100	**
2009-0293	LHRH +Abiraterone (Multi-Center)	2010-11	13	92	**
2009-0473	LHRH +/- GDC-0449 (Single-Center) pending	2009-12	12		**
2009-0322	LHRH +/- Abiraterone Acetate (ASCO 12)	2010-13	66	88	**
2012-0922	LHRH+Abi+/-Enza	2013			

High Risk Pre–op Model (Curative Intent)

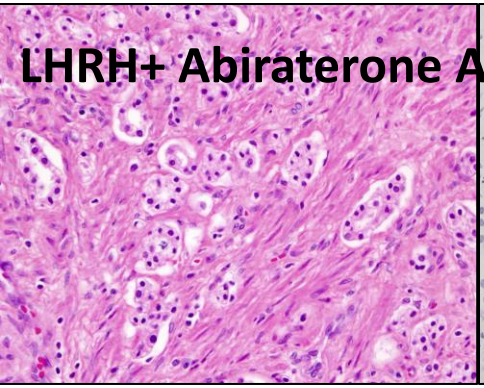


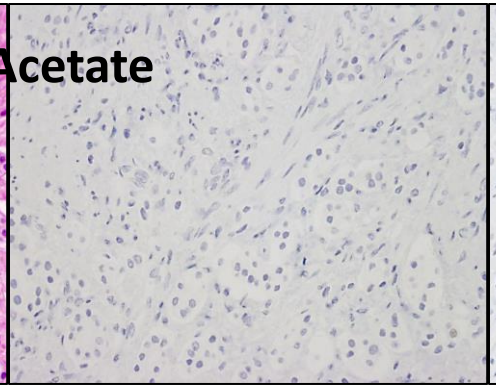
Primary Resistance in high risk locally advanced disease

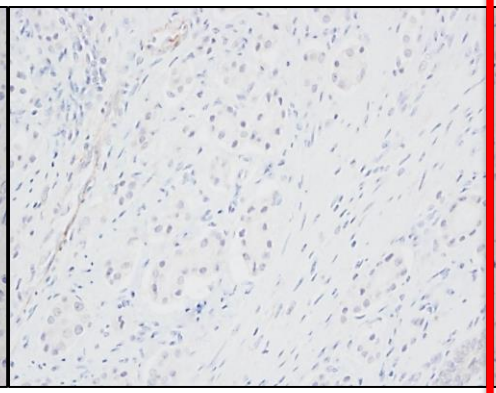


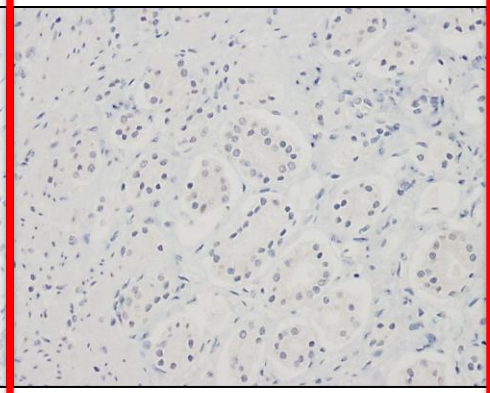
Efstathiou et al ASCO 2013

Androgen Receptor Expression and lack of Splice Variant detection

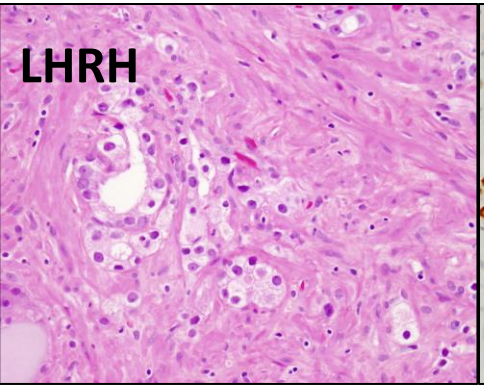


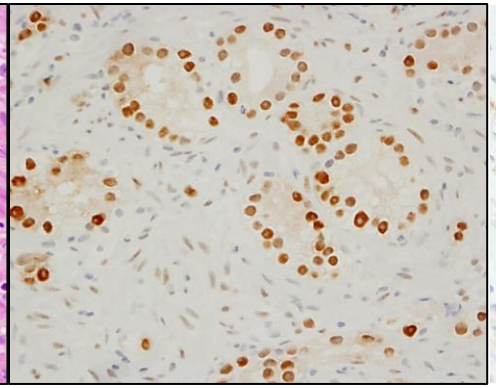


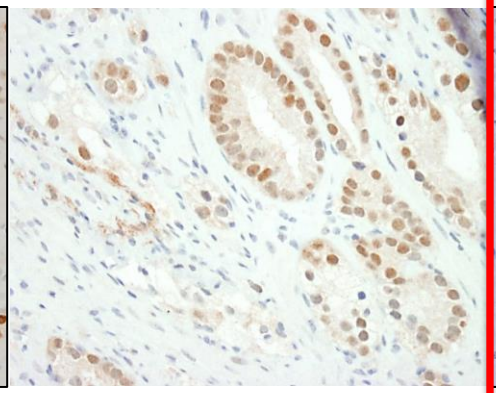


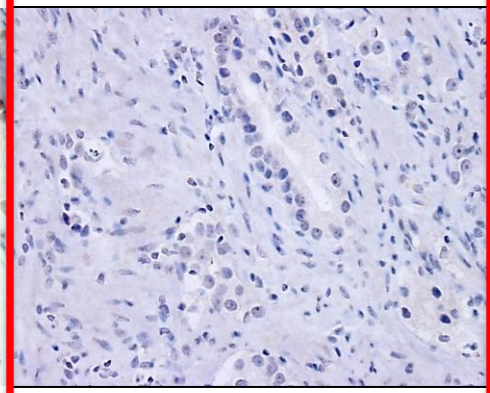


H&E AR-N AR-C19 ARV7









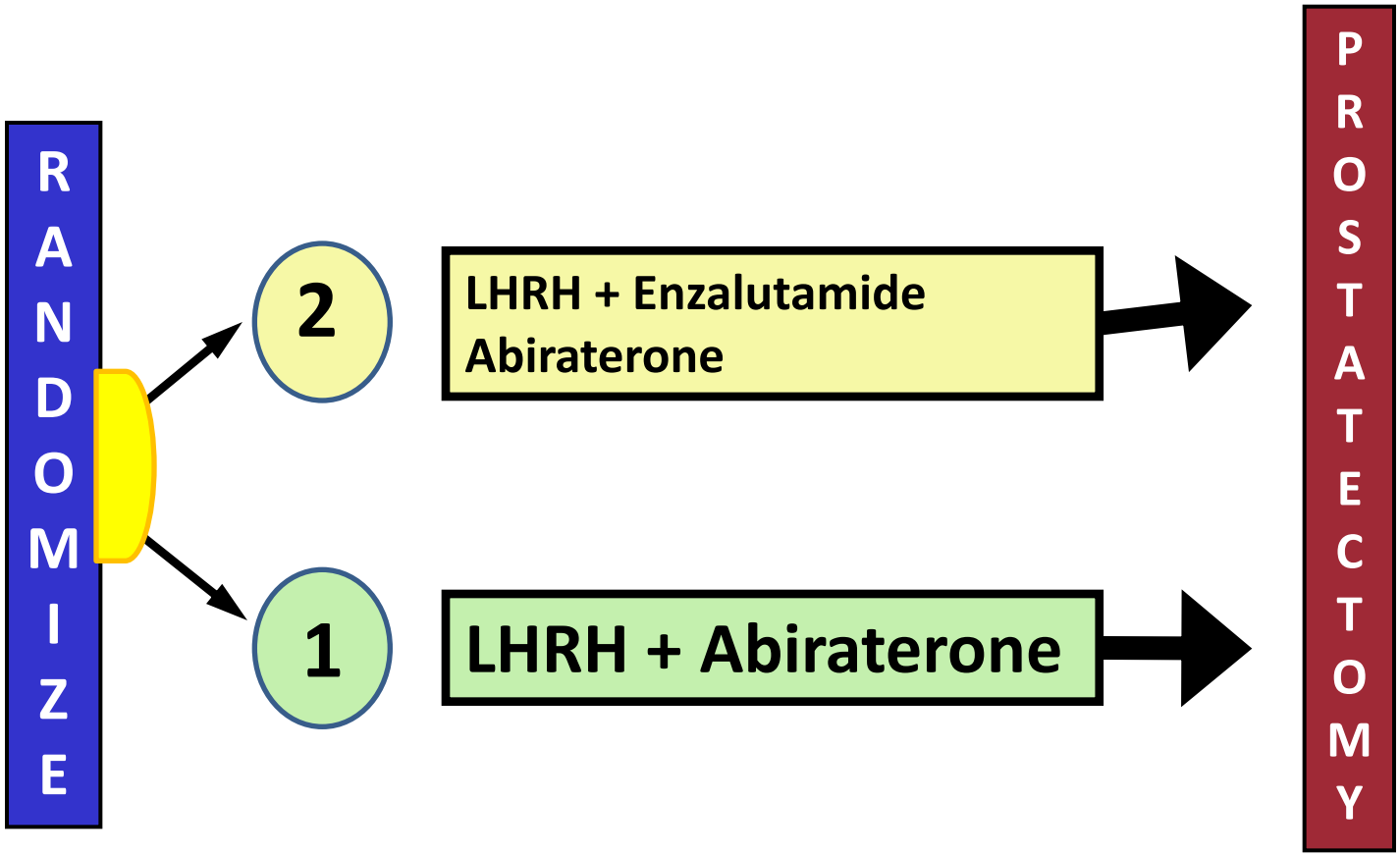
AR-C/AR-N≈≈ 1

NO ARV7 DETECTED

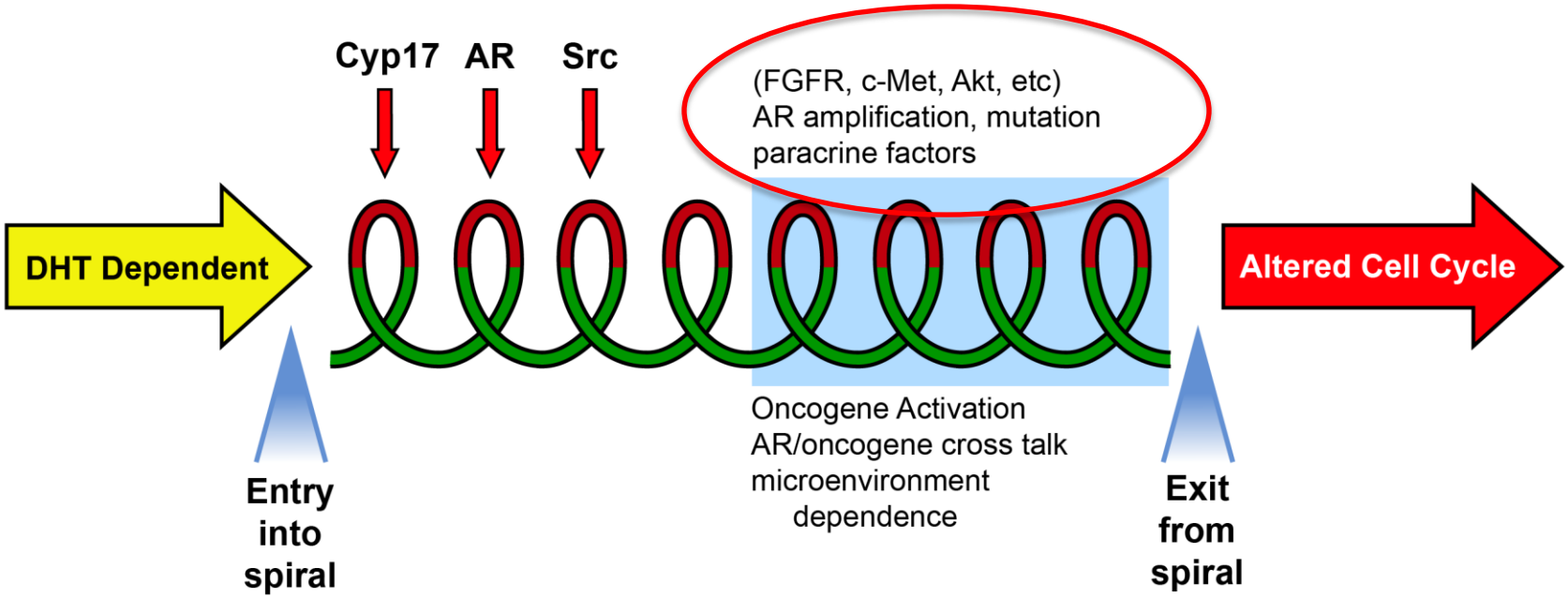
In line with data on untreated primary PCA Plymate et al

Efstathiou et al ASCO 2013

High Risk Pre–op Model (Curative Intent)

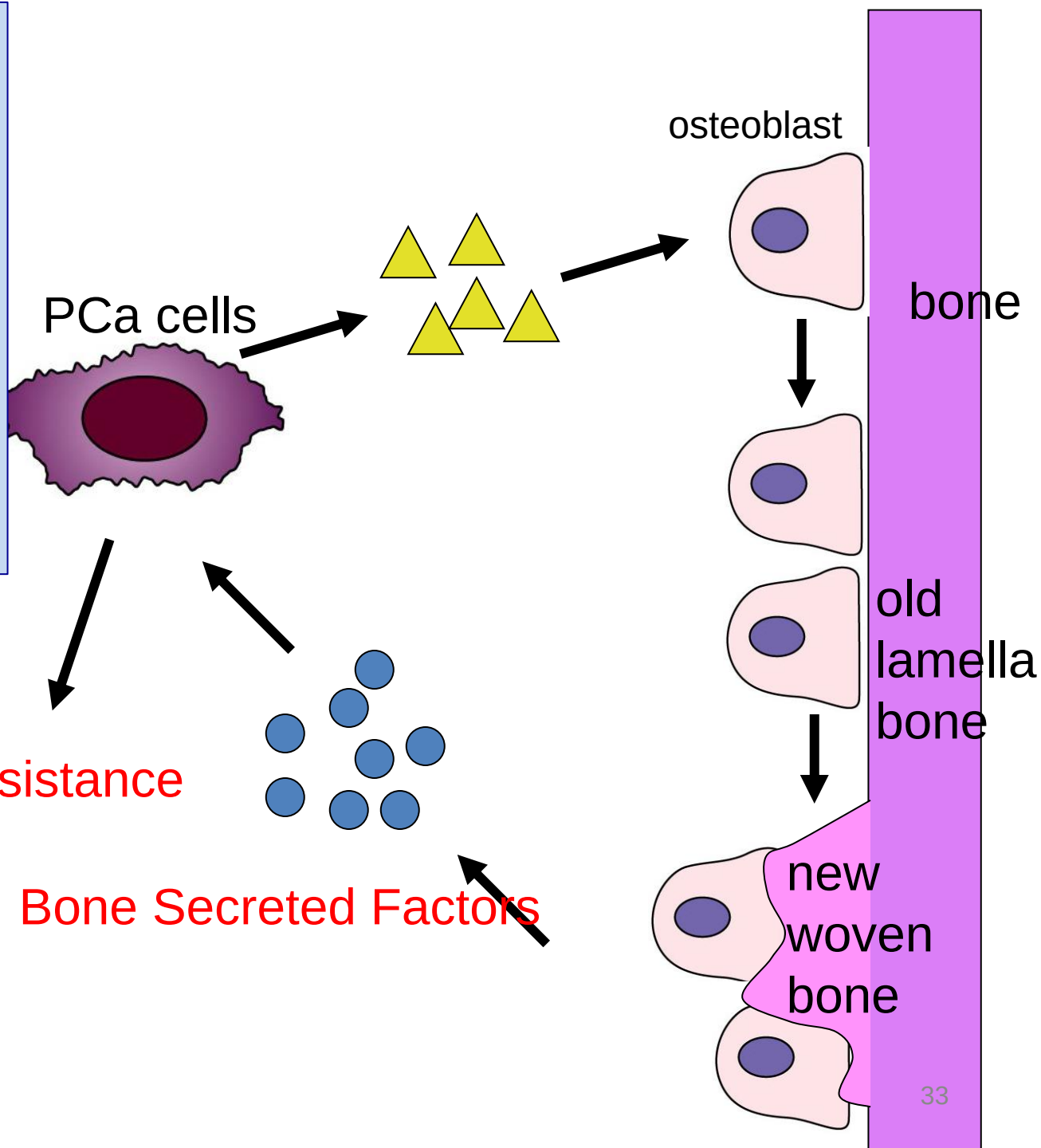


Model for Reclassification of Prostate Cancer

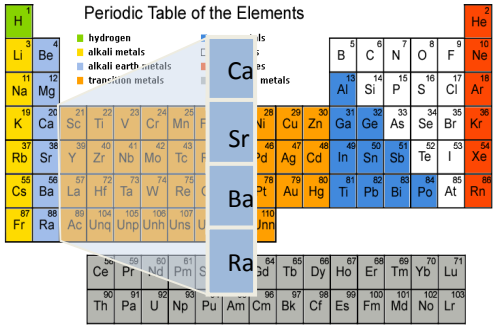


Microenvironment Dependence

Osteoblasts secrete factors (osteocrines) in the tumor microenvironment thus mediating therapy resistance of PCa bone metastasis.



Lin et al 2012

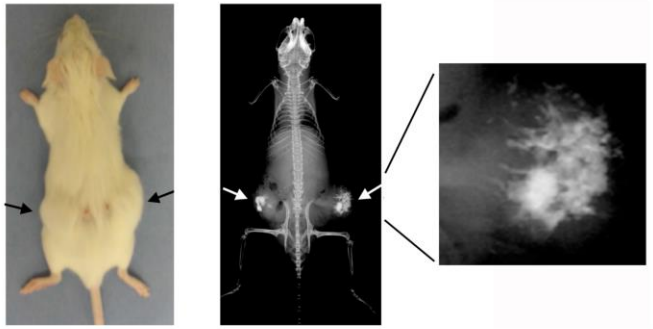


Rad-223 efficacy attributed to microenvironment targeting;

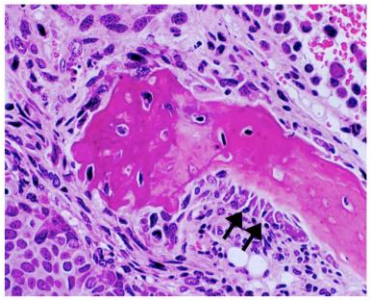
Determining bone marrow secretome of patients treated will identify candidate predictive markers

MDA-PCa-118b

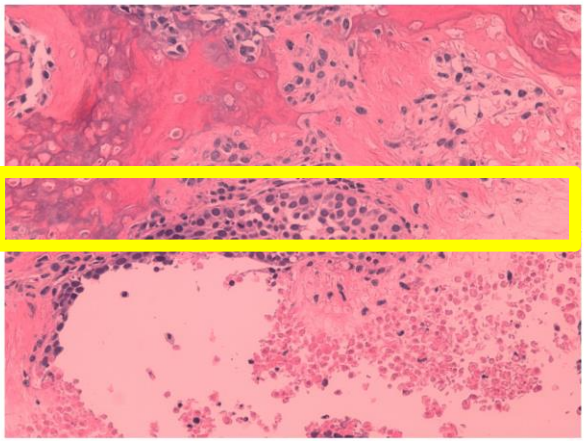
X-ray



Histology



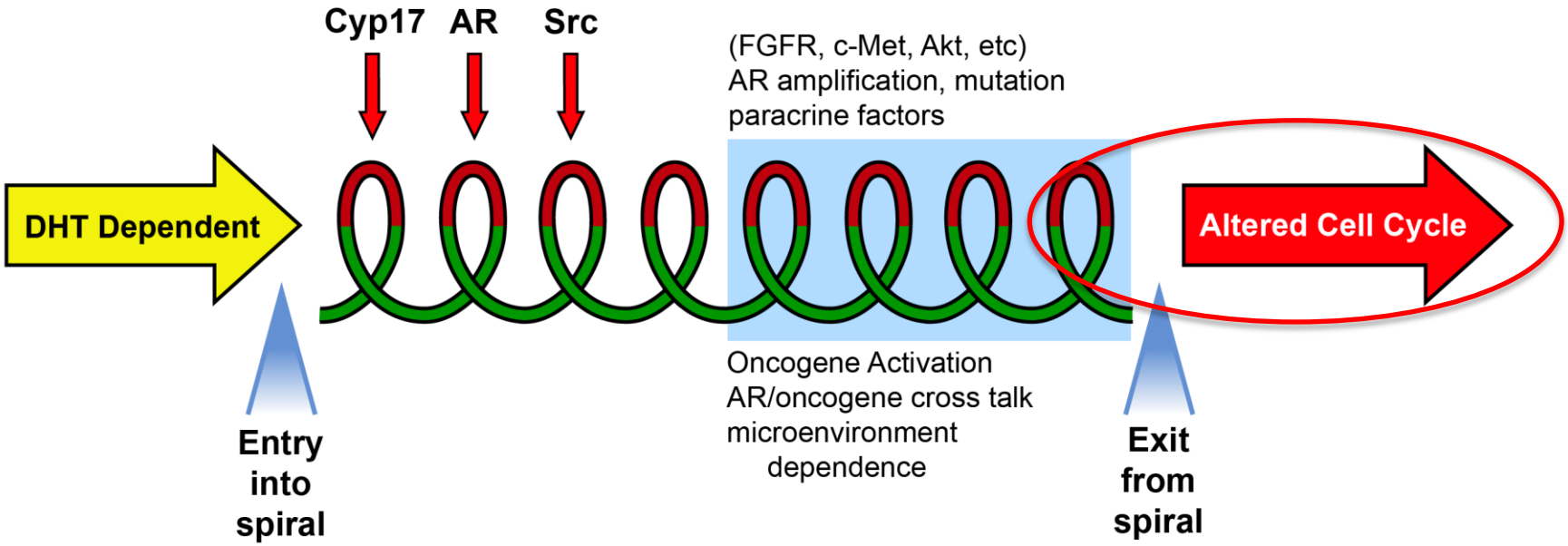
Prostate cancer xenograft MDA-PCa-118b secretes bone forming soluble factors



Resistant Tumor Cells Are Found Close to Newly Formed Bone Matrix

J Araujo, S Lin

Model for Reclassification of Prostate Cancer



From SCPC to "*Anaplastic*"

0022-5347/92/1473-0935$03.00/0
THE JOURNAL OF UROLOGY
Vol. 147, 935-937, March 1992
Printed in U.S.A.

CHEMOTHERAPY FOR SMALL CELL CARCINOMA OF PROSTATIC ORIGIN

ROBERT J. AMATO,* CHRISTOPHER J. LOGOTHETIS, REBECCA HALLINAN, JAE Y. RO, AVISHAY SELLA AND FRANCISCO H. DEXEUS

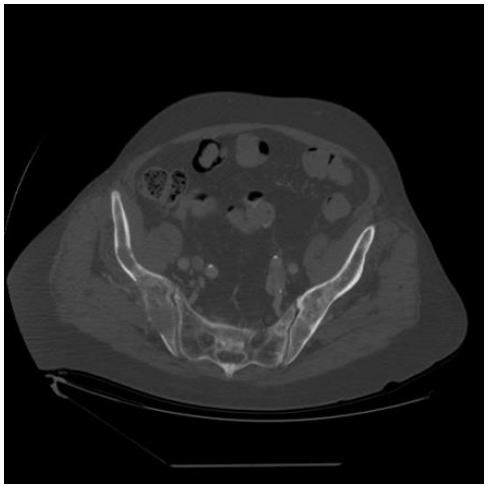
From the Department of Medical Oncology, University of Texas M. D. Anderson Cancer Center, Houston, Texas

Results of a Phase II Study With Doxorubicin, Etoposide, and Cisplatin in Patients With Fully Characterized Small-Cell Carcinoma of the Prostate

By Christos N. Papandreou, Danai D. Daliani, Peter F. Thall, Shi-Ming Tu, Xuemei Wang, Adriana Reyes, Patricia Troncoso, and Christopher J. Logothetis

Journal of Clinical Oncology, Vol 20, No 14 (July 15), 2002: pp 3072-3080

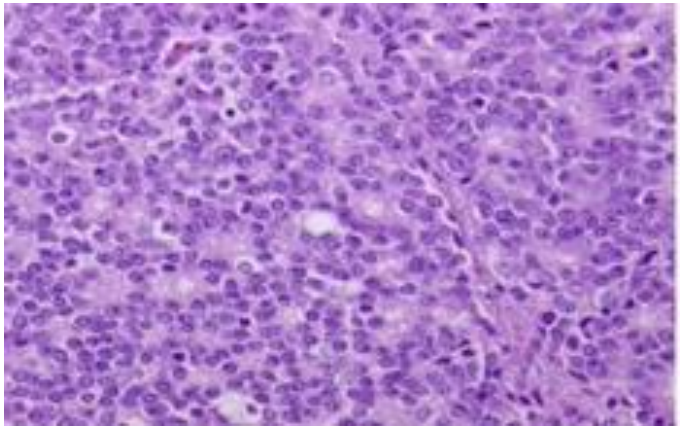
Liver



Lytic bone

Chemotherapy Responsive

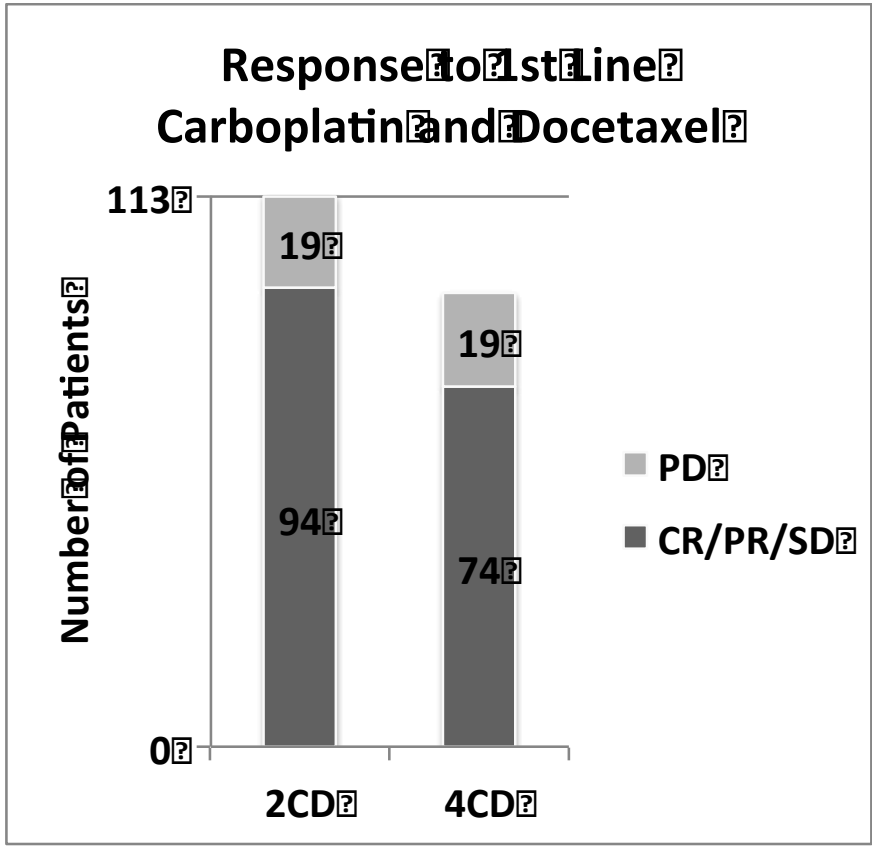
Hypothesis
Clinically defined *"anaplastic" prostate cancers share the* ***chemotherapy responsiveness*** *of the small cell prostate carcinomas (despite* ***morphologic heterogeneity****)*



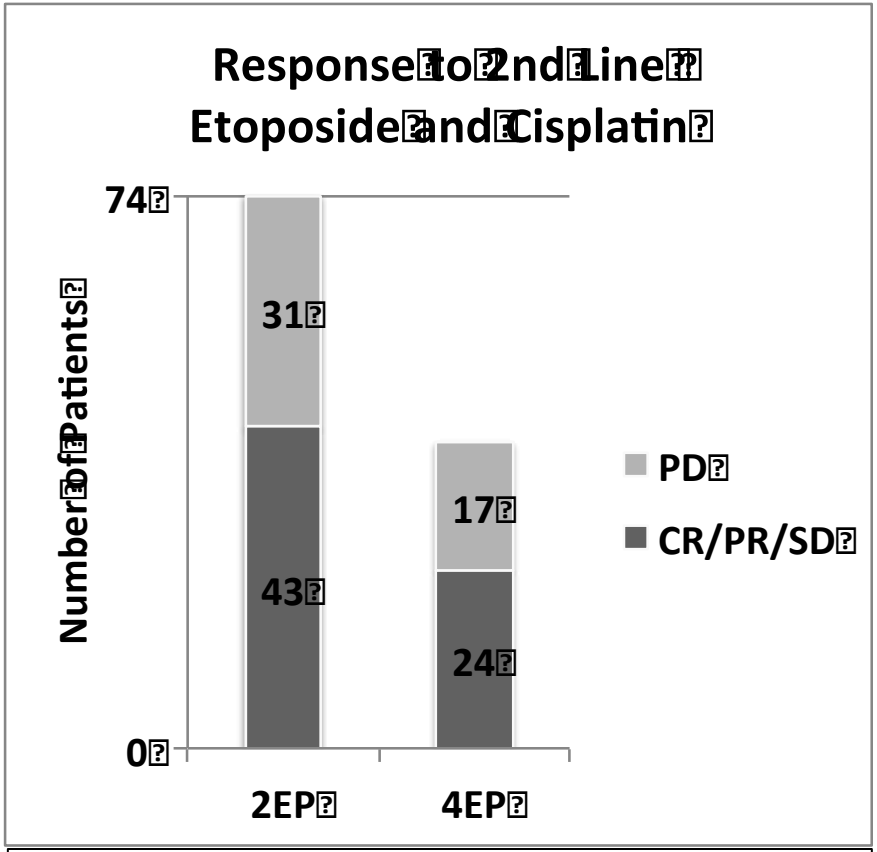
Adenocarcinoma

PCCTC 05-015:

*Morphologically heterogeneous CRPC with variant **clinical features** have a **chemotherapy response** profile similar to that observed in SCPC*



Median PFS = 5.1mo (95%CI 4.2-6.0mo)



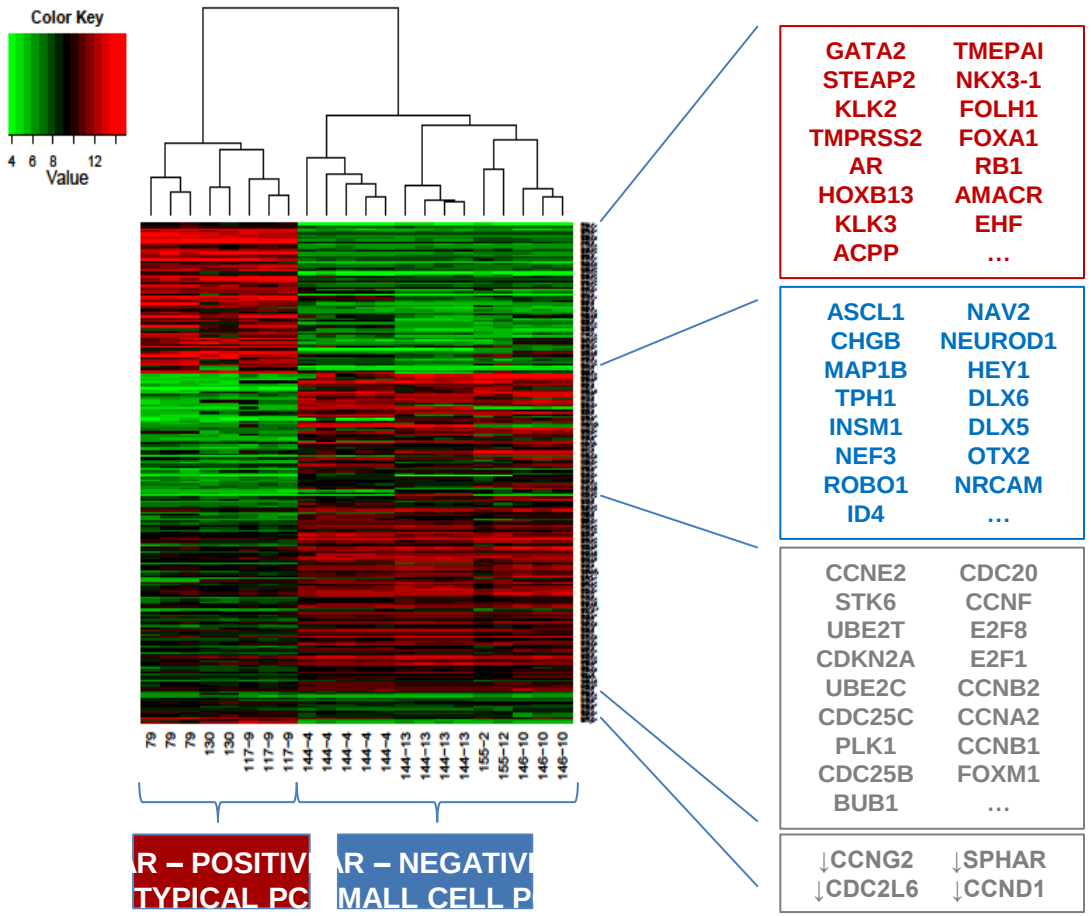
Median PFS = 3.0mo (95%CI 1.6-3.5mo)

Aparicio et al *Clin Cancer Res* 2013;19:3621-3630

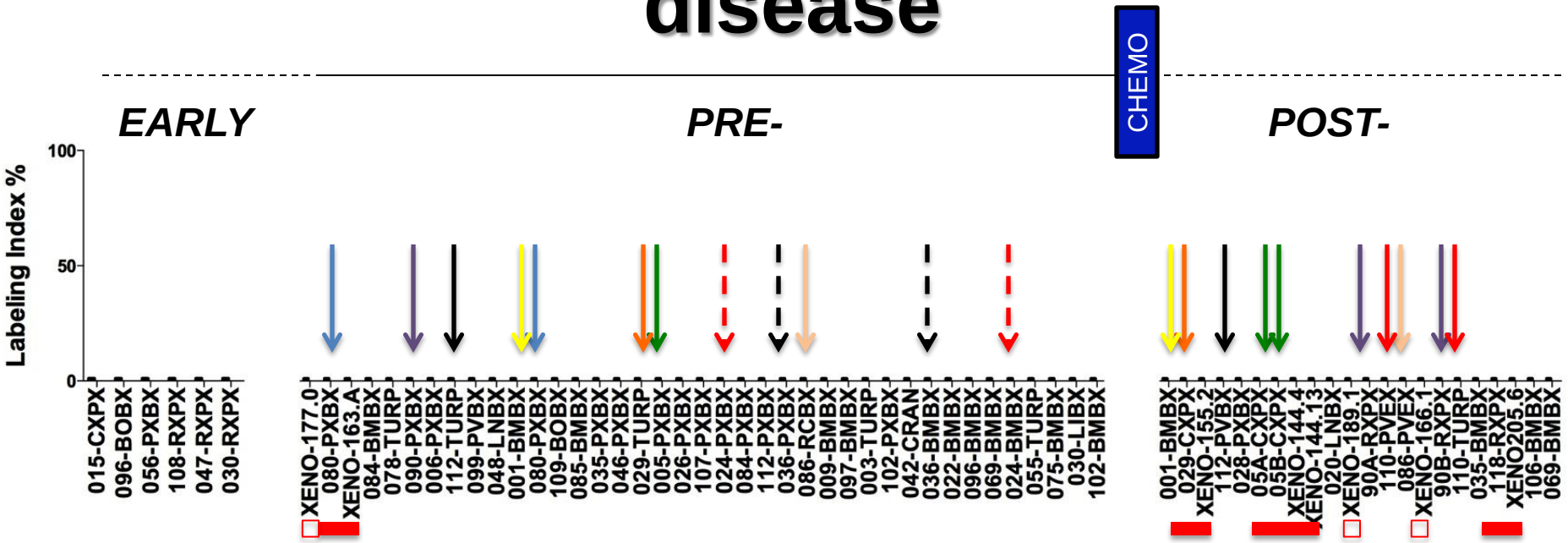
Activation of the Mitotic and Neural Precursor Programs in Small Cell Prostate Carcinomas

Hypothesis

Functional characterization of patient derived xenografts (PDX) from men with 'anaplastic' prostate cancers will enable the identification of predictive markers and therapy targets



Molecular Profiling of Anaplastic disease

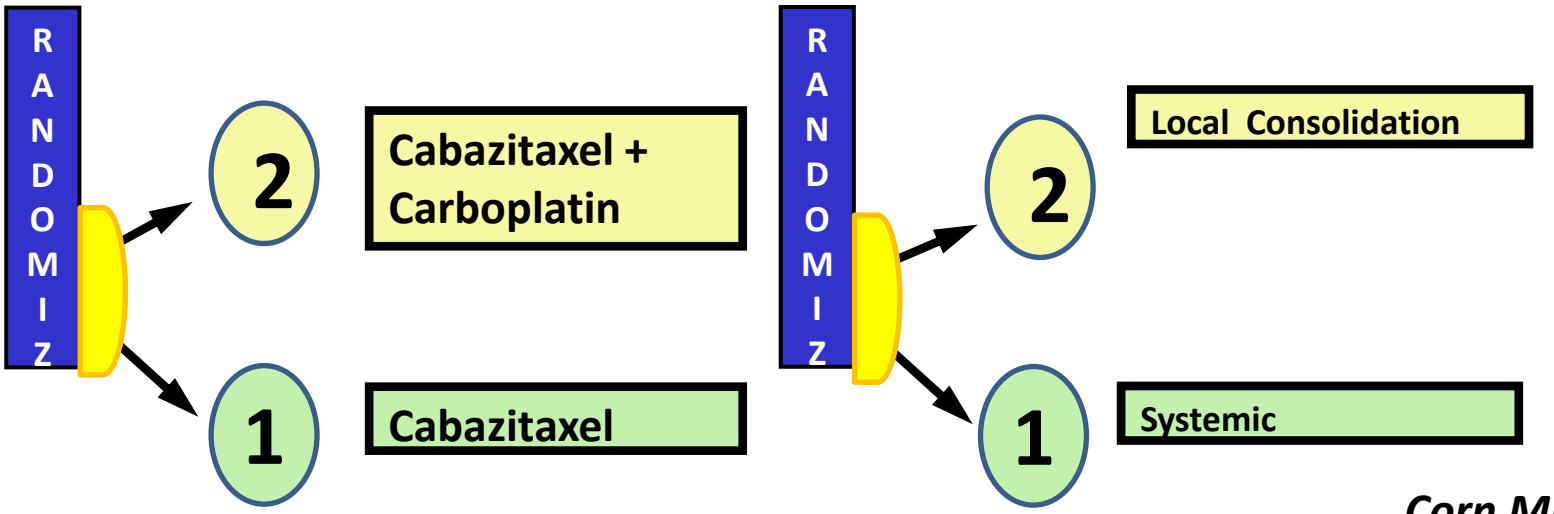


The **Clinical** "**anaplastic**" **tumors show alterations in 3 domains:**

1. Loss of tumor suppressors (RB, p53 and/or REST)
2. Gain of neural development program
3. Alteration of the mitotic apparatus

The transitions and mixed profiles observed are consistent with the presence of a **biologic continuum**.

Translational Chemotherapy Trials



Corn MDACC

CT Guided Biopsy/BMB – Cabazitaxel Trial

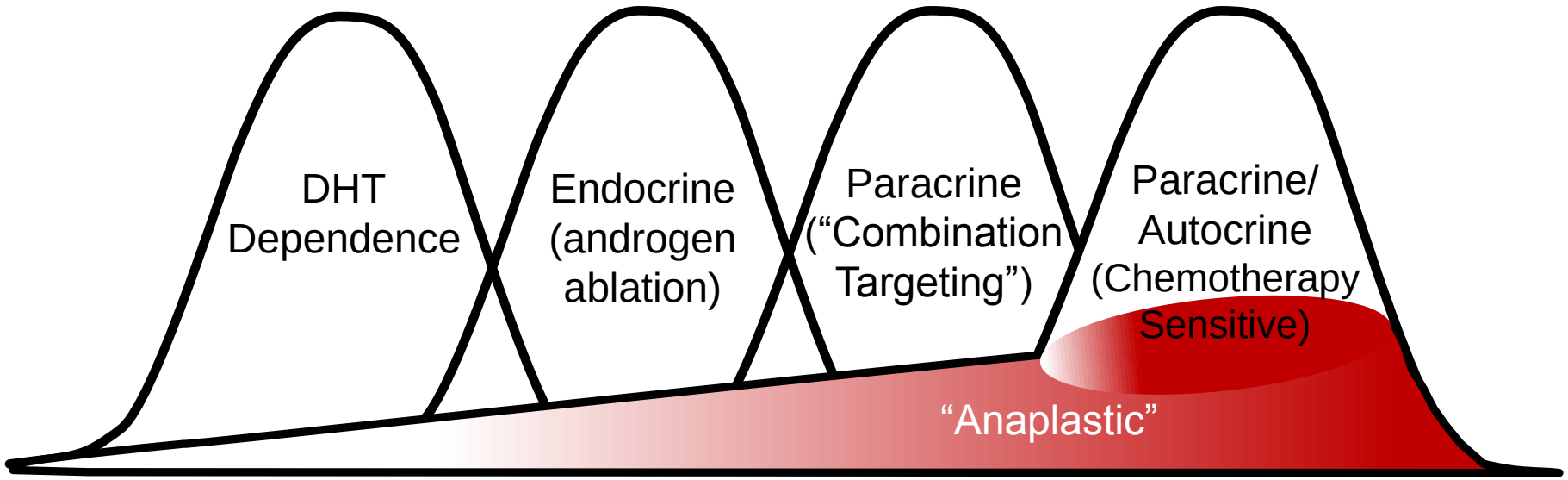
Week 8*

Maximum Response*/**

Discontinuation*

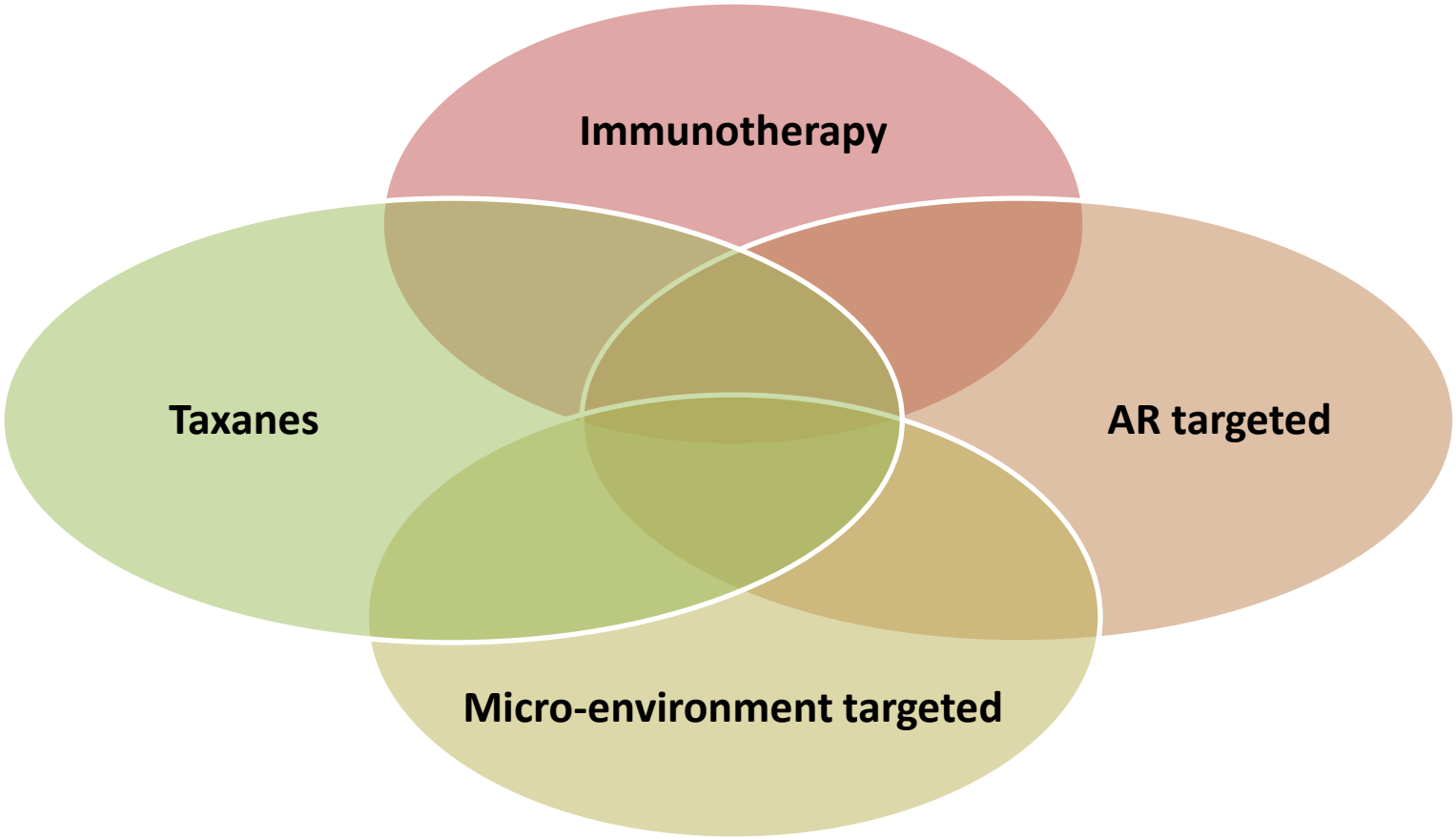
Efstathiou HeCoG- MDACC

Building on Findings



Discovery → Testing → Validation

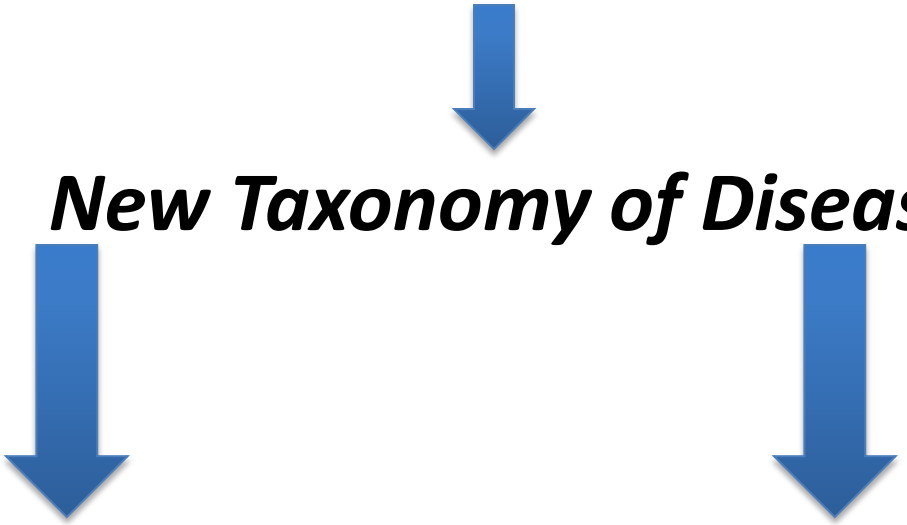
Drug Sequencing and Combination era WARRANTS Integration of Knowledge towards a BIOMARKER STRATEGY



Precision Medicine Requirements

Knowledge Network for Biomedical Research

integrating :
Molecular Characterisation
& Clinical Data



New Taxonomy of Disease

Biomedical Research → ***Clinical Medicine***

Precision Medicine delivered

Right *treatment strategy at the* ***right*** *dose at the* ***right*** *time, with minimum ill consequences and maximum efficacy*

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DOD Therapy Consortium

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