Partnering for the Cure: An Innovative Role For Academia in Oncology Drug and Diagnostic Development

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An Innovative Role for Academia in Oncology Drug and Diagnostic Development

Howard I. Scher, M.D.

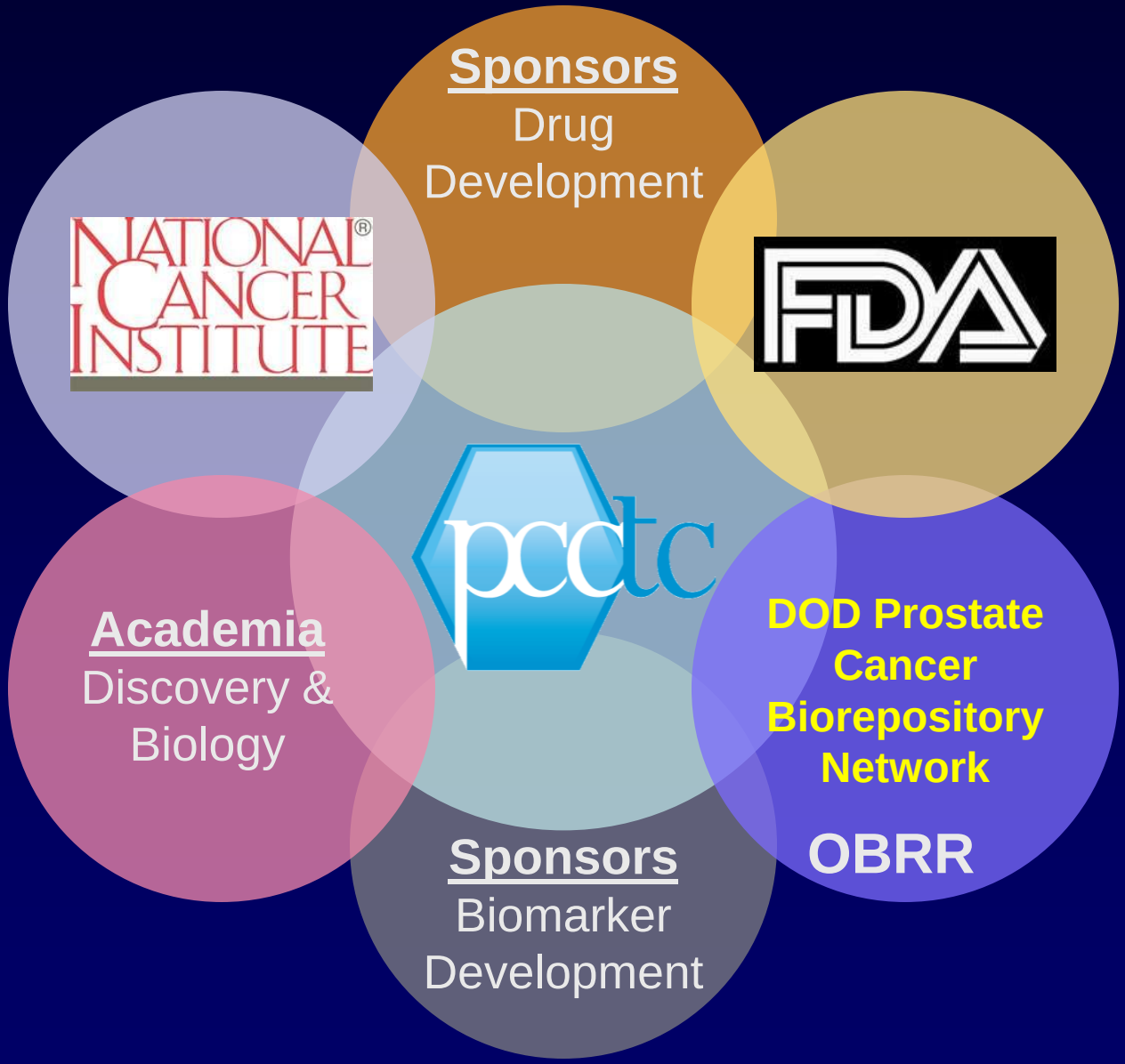
I have the following financial relationships to disclose:

Consultant:	Medivation (U), Veridex (U) Foundation Medicine (U). Janssen Pharmaceuticals
Grant/Research support:	Medivation (U), Veridex Janssen Pharmaceuticls

I will discuss the following off label use and/or investigational use in my presentation:

MDV3100, Abiraterone, TAK-700, Alpharadin

We Are Collaborating With Critical Stakeholders in Drug and Biomarker Development to Generate Evidence



Partnering for the Cure

1. **PCCTC: A platform for academic collaborations.**
2. Co-development with Sponsors and Regulators: a tale of two drugs.
3. The availability of analytically valid assays is rate limiting,
4. Implementation of a Precision Medicine Paradigm.

PCCTC:
The Prostate Cancer Clinical Trials Consortium:

Funding for the infrastructure to support collaboration.

Coordinating Center: MSKCC

Department of Defense and Prostate Cancer Foundation

The PCCTC mission is to design, implement, and complete hypothesis -driven phase I and phase II trials of novel agents and combinations that could prolong the lives of patients with prostate cancer.

Cancer Institute of New Jersey	Robert DiPaola
Chicago Prostate Cancer Association*	Walter Stadler
Dana-Farber/Harvard Cancer Center	Mary-Ellen Taplin
Duke Comprehensive Cancer Center	Daniel George
Johns Hopkins Prostate Cancer Program	Michael Carducci
Memorial Sloan-Kettering Cancer Center	Susan Slovin
Oregon Health and Science University**	Tomasz M. Beer
Univ. of California San Francisco	Charles Ryan
University of Michigan Cancer Center	Maha Hussain
University of Texas, MD Anderson CC	Paul Corn
University of Washington / Fred Hutchinson**	Tia Higano
University of Wisconsin Carbone CC	George Wilding
Wayne State University / Karmanos	Elisabeth Heath

Program Director: Mr. Jacob Vinson

Member institutions have scientific programs (e.g. SPOREs / PO1s / UO1s) to support biomarker discovery and a translational clinical research enterprise.

PCCTC Guiding Principles

1. **Centrally managed**, **harmonized** and **comprehensive** clinical trial processes will accelerate drug development an improve outcomes.

We are Doctor's first!

2. Achieved by **streamlining any** process that can impede trial activation, conduct, completion and analysis.

3. Aligned to member prescribed **scientific priorities**, teams of experts design **trials in a sequence,** each with "Go-No Go" metrics.

4. Embedded in the PCCTC, is an extensive effort to **discover, and validate biomarkers - analytically and clinically.**

PCCTC Members Led the Development of Standards for Trial Conduct That Synchronized Clinical Research With Clinical Practice

VOLUME 26 · NUMBER 7 · MARCH 1 2008

JOURNAL OF CLINICAL ONCOLOGY

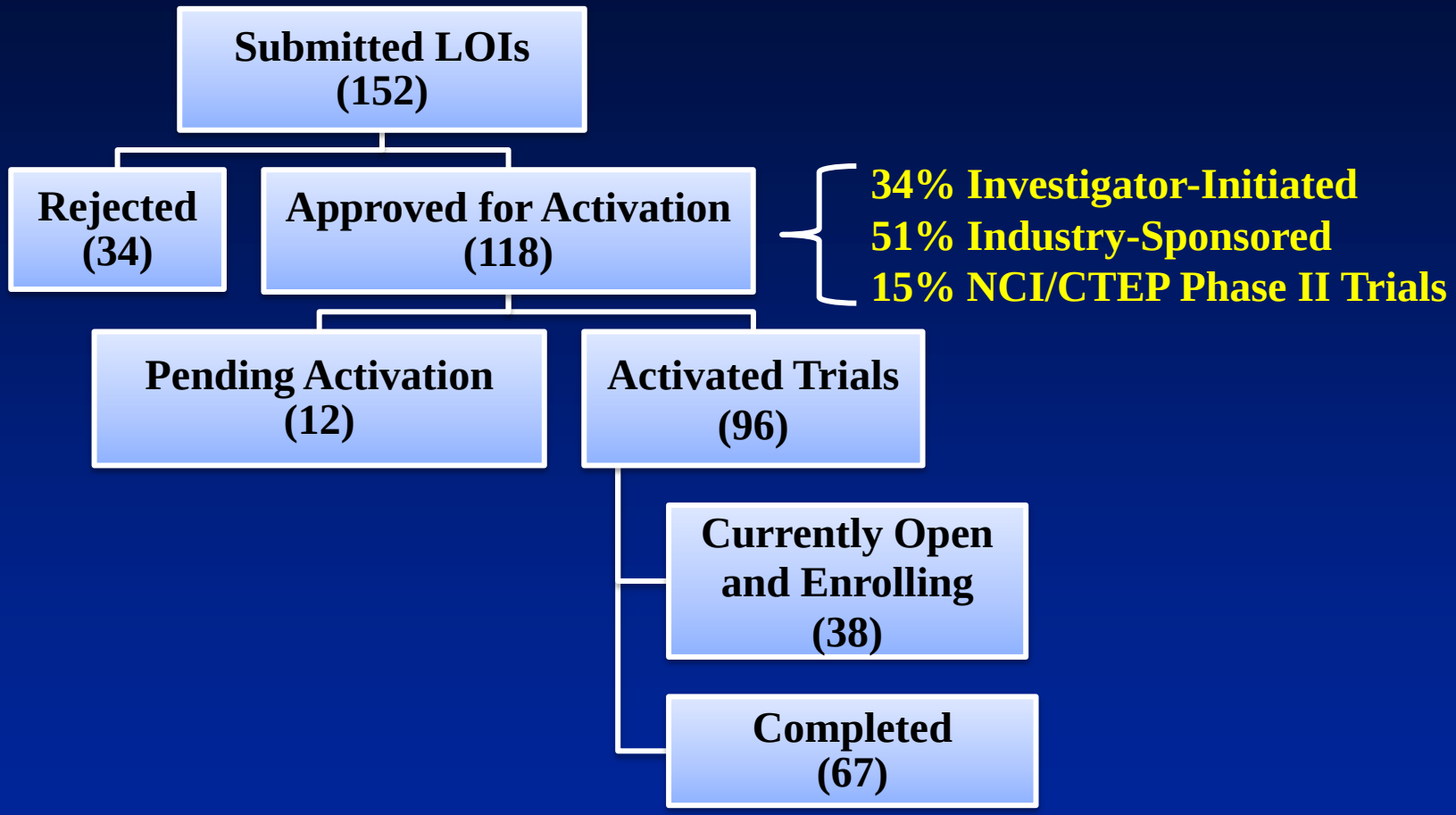
SPECIAL ARTICLE

Design and End Points of Clinical Trials for Patients With Progressive Prostate Cancer and Castrate Levels of Testosterone: Recommendations of the Prostate Cancer Clinical Trials Working Group

Howard I. Scher, Susan Halabi, Ian Tannock, Michael Morris, Cora N. Sternberg, Michael A. Carducci, Mario A. Eisenberger, Celestia Higano, Glenn J. Bubley, Robert Dreicer, Daniel Petrylak, Philip Kantoff, Ethan Basch, William Kevin Kelly, William D. Figg, Eric J. Small, Tomasz M. Beer, George Wilding, Alison Martin, and Maha Hussain

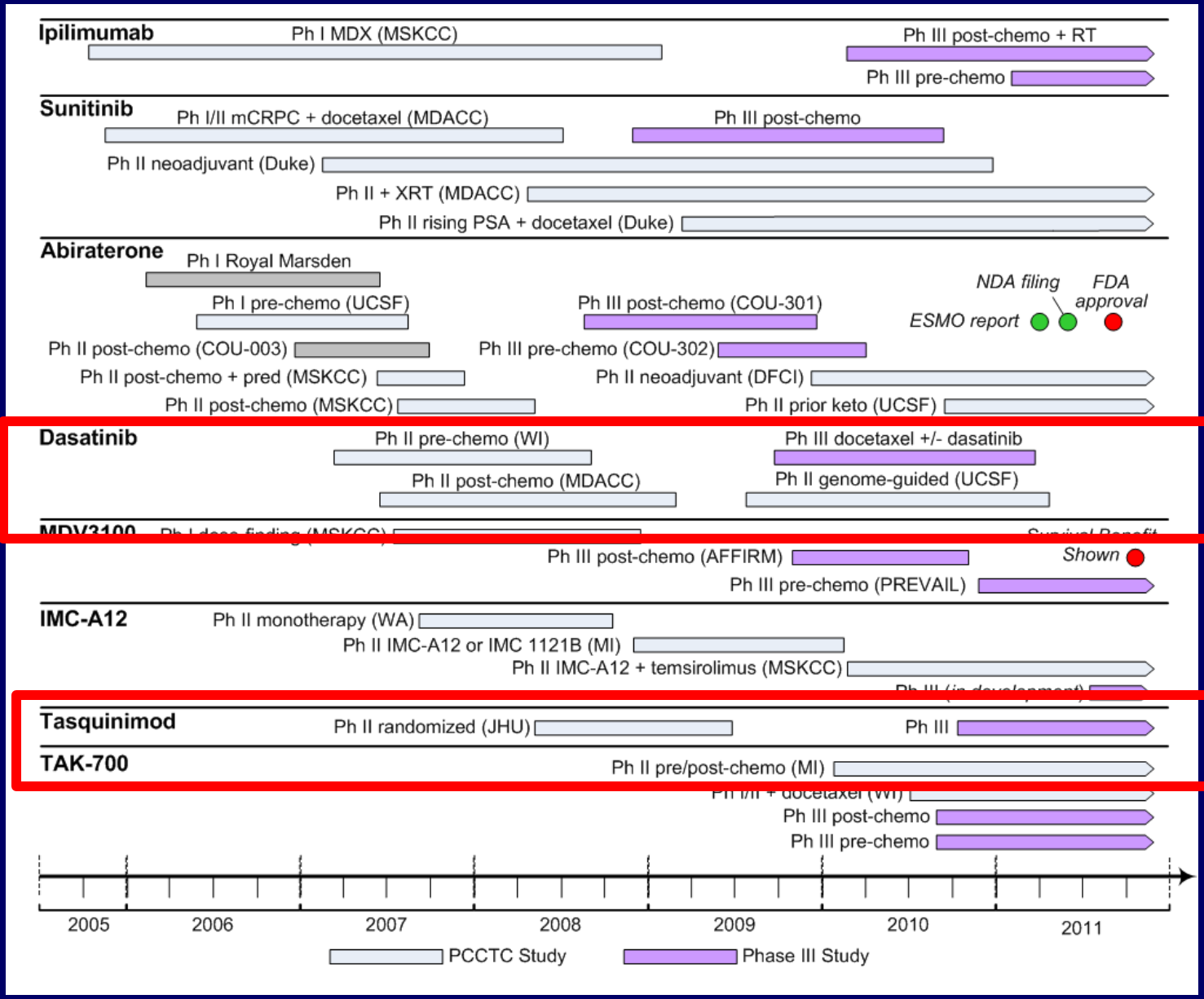
Meaningful endpoints to study biomarker associations and to design the series of prospective trials for a ***context of use.***

PCCTC Trial Activity: 2005-1Q 2012



Over 3265 men enrolled in trials of novel therapeutics.
Eight therapeutic candidates advanced to phase III study.

Collaborative Co-Development of PCCTC Members and Sponsors Enabled *8* Drugs To Reach Phase III Testing



OHSU, MSKCC

MDACC & Duke

UCSF & MSKCC, U WASH, DFCI

WIS, MDACC & UCSF

MSKCC

WASH & MICH

JHU, DUKE

MICH & WISC

Accomplishments of a Early Phase Clinical Research Collaborative: (2006-2012)

1. Many trials (118), many drugs (73) and many patients (>3265).

2. Field changing science leading to new drug approvals.

3. Evolved a research framework (co-development, operational logistics, endpoints and outcomes).

4. **Moved beyond our original charter to globally change the clinical research enterprise:**

   (e.g., biomarker – validation and qualification)

Partnering for the Cure

1. PCCTC: A platform for academic collaborations.

2. **Co-development with Sponsors and Regulators: a tale of two drugs giving biomarker access to large patient cohorts.**

3. The availability of analytically valid assays is rate limiting,

4. Implementation of a Precision Medicine Paradigm.

Prostate Cancer Therapeutics *Circa 2012*: A Changed Landscape As Six Phase 3 Trials Show a Survival Benefit

Noncastrate

Diagnoses: 217,730

Castration resistant

Deaths: 32,050

Clinically Localized Disease

Rising PSA

Clinical Metastases: Noncastrate

Non-Metastatic CRPC

Castration Resistant Metastatic Pre-Provenge 2010

Castration Resistant Metastatic 1st-Line Docetaxel 2004

Castration Resistant Metastatic Post-Cabazitaxel 2010

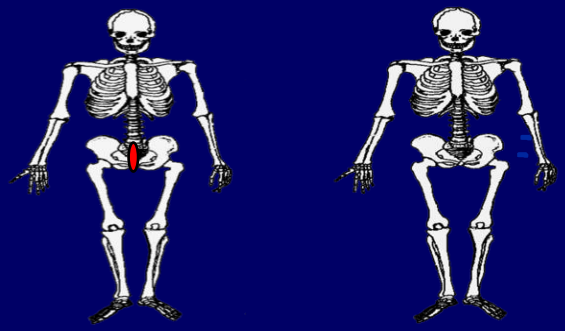
Abiraterone 2010

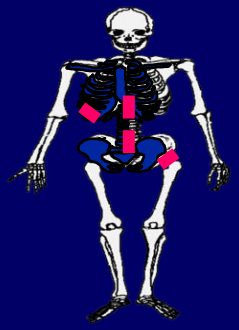
Alpharadin 2011

Alpharadin 2011

Abiraterone 2012

MDV3100 2011





Modified from Scher and Heller. *Urology*. 2000.

More Options Benefit Patients, but …

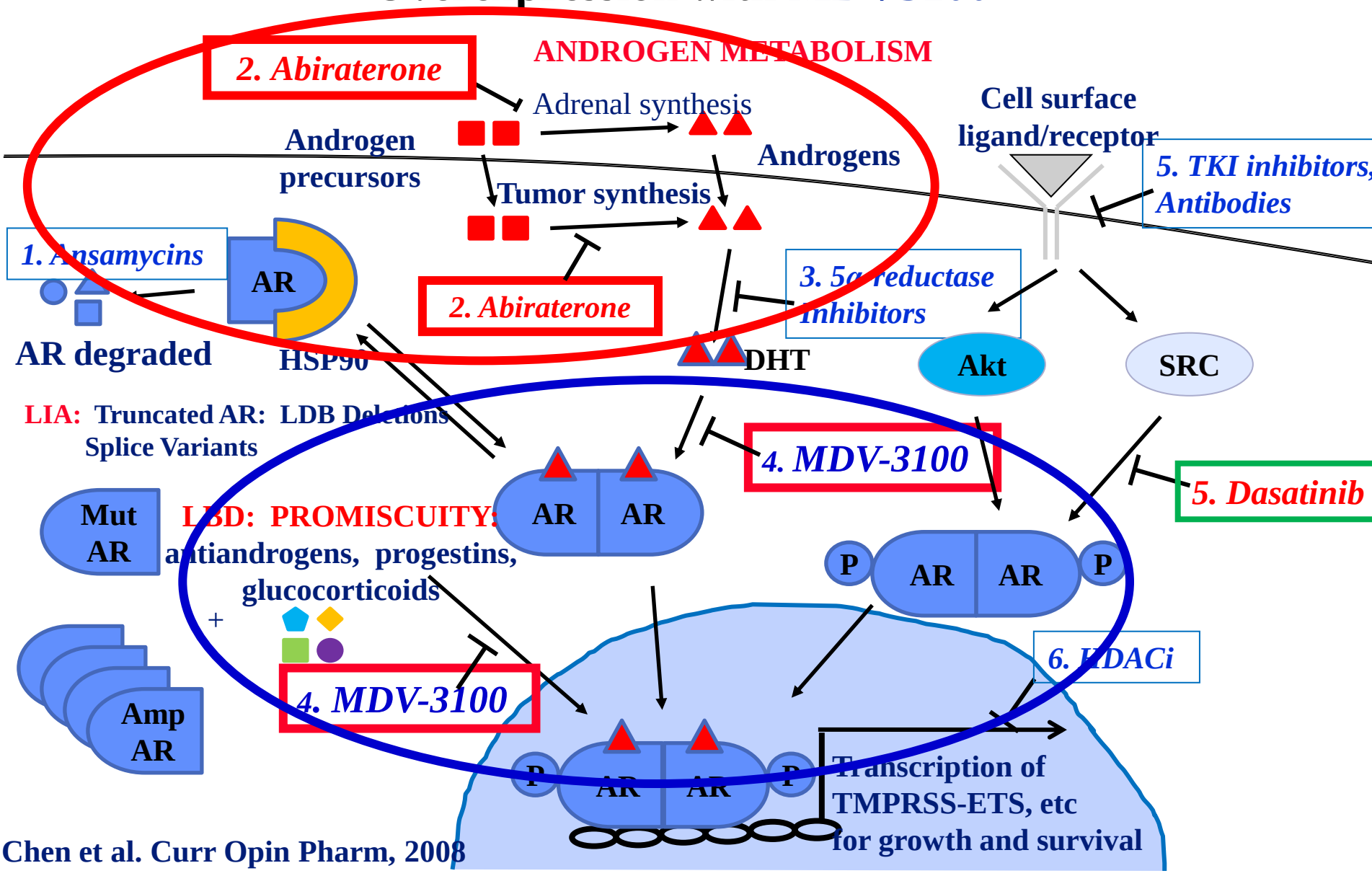
1. Make it more difficult to show a survival benefit for future drugs
   - Crossover to an effective treatment can confound a survival effect
   - Larger, longer studies and more costly studies will be required

2. Urgently needed are *qualified **surrogate** biomarkers* for survival that can be used for accelerated drug approvals.

3. Needed as well are *qualified **predictive** biomarkers* of sensitivity, to better match drugs to an individual patient's tumor.

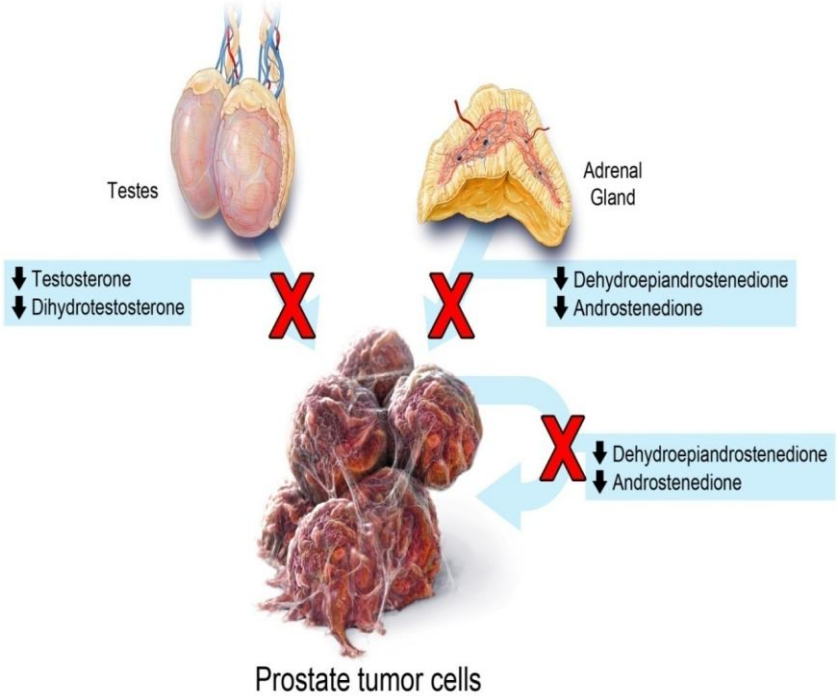
4. The era of the "all comers" trial will soon be ending.

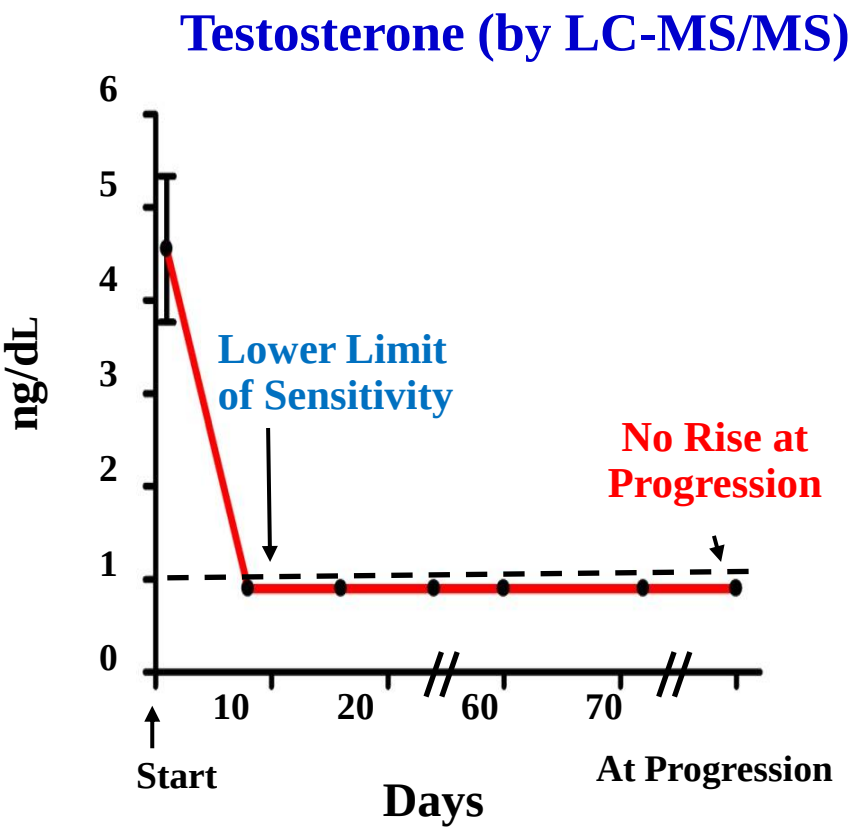
Restored AR Function in CRPC: *Targeting* Increased Androgen Biosynthesis with Abiraterone Acetate and Androgen Receptor Overexpression with MDV3100



Chen et al. Curr Opin Pharm, 2008

Prostate Cancers Acquire the Ability to Produce Androgens, Abiraterone Lowers Androgen Levels in in the Testis, Adrenal Glands and the Tumor

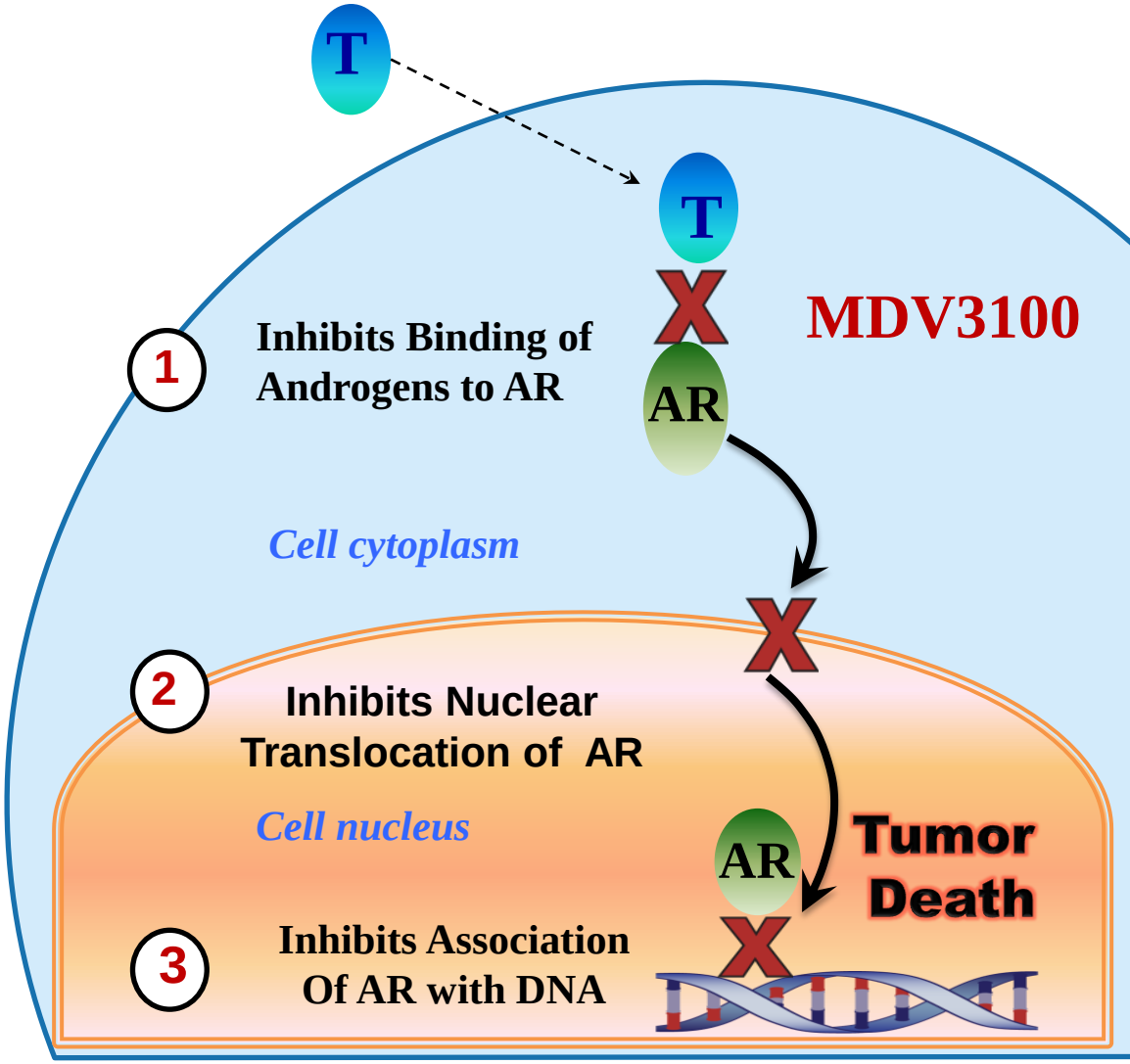




Attard et al. JCO 27:3742, 2009

The Androgen Receptor Signaling Inhibitor MDV3100 Is Unique From the Currently Available Anti-Androgens

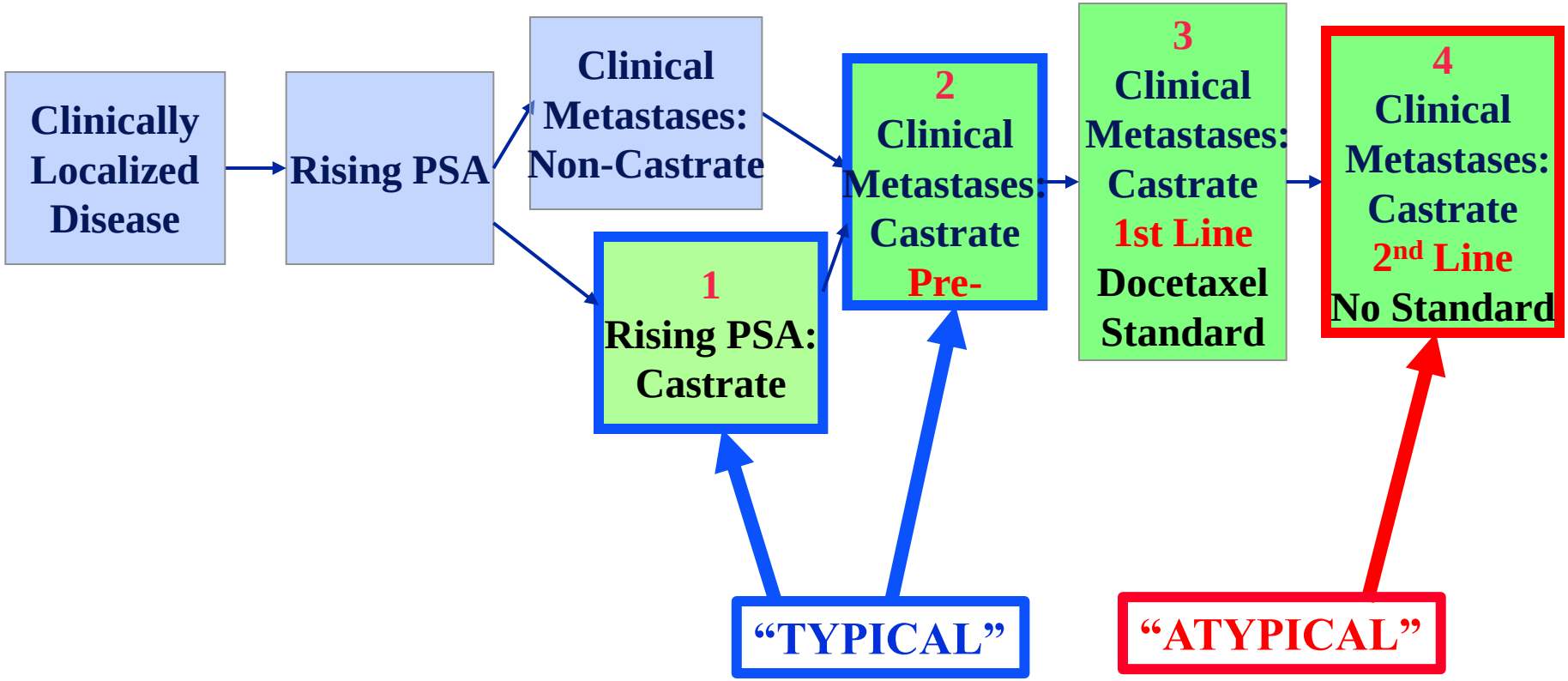
NDA filed May 21, 2012



Scher et al., GU ASCO, 2012

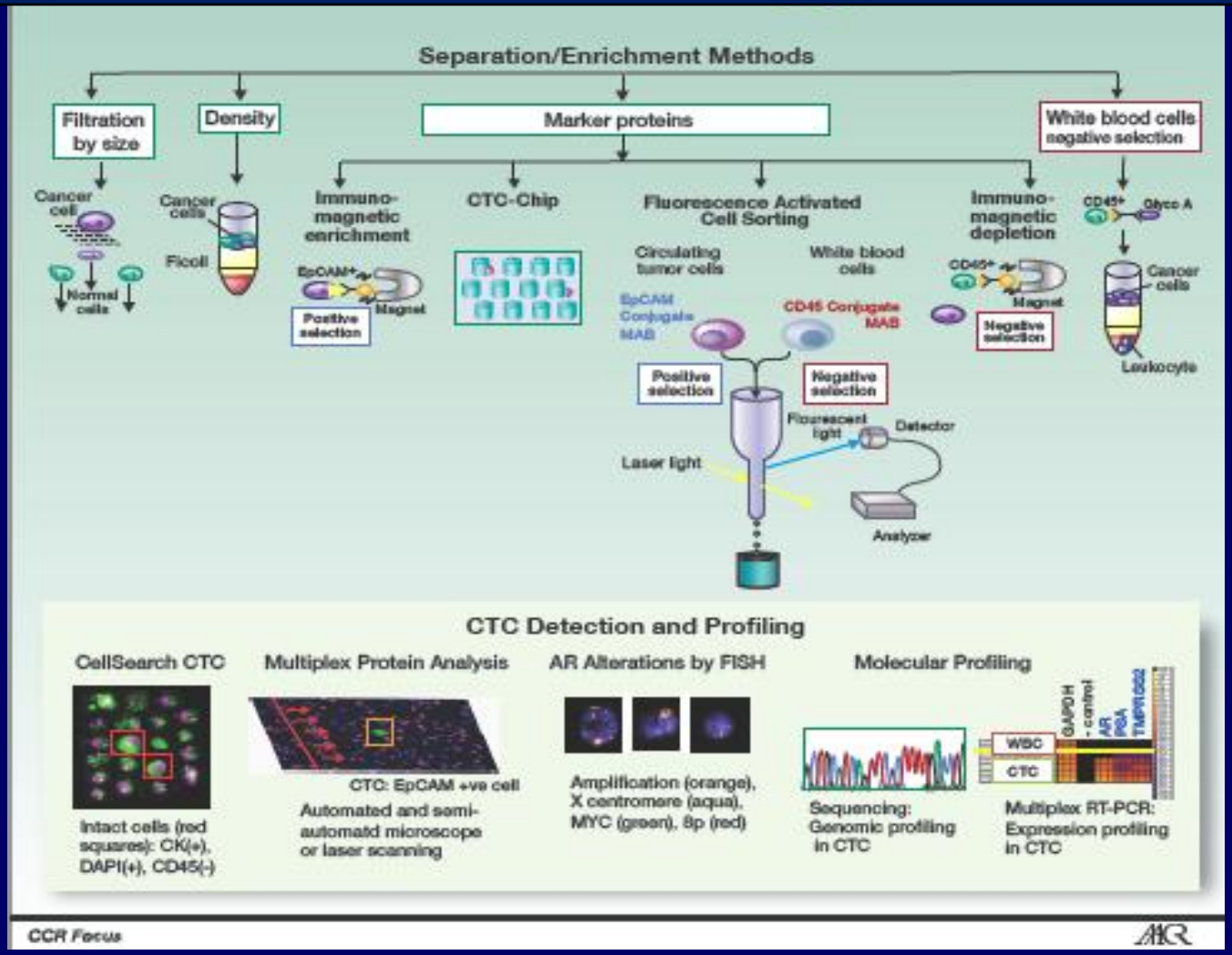
Tran et al. Science 224:787, 2009.

Both Abiraterone Acetate and MDV3100 Were Studied In *Pre-* and *Post-* Chemotherapy Treated CRPC: Prospective Biomarker Testing in a Defined Setting



With a shared investment (Drug and Biomarker Sponsor, Grants, Foundations, Academia) Circulating Tumor Cell number (CellSearch) was included as an endpoint.

We Hypothesize that Circulating Tumor Cell Biomarkers Could Fulfill These Unmet Needs but Before a Platform is Used in a Trial, It Undergoes Our Own Analytical Testing



Danila et al., CCR, 17:3903, 2011.

All Technologies Undergo Validation On Site or with Patient Samples: Fleisher's Principles

Assay:

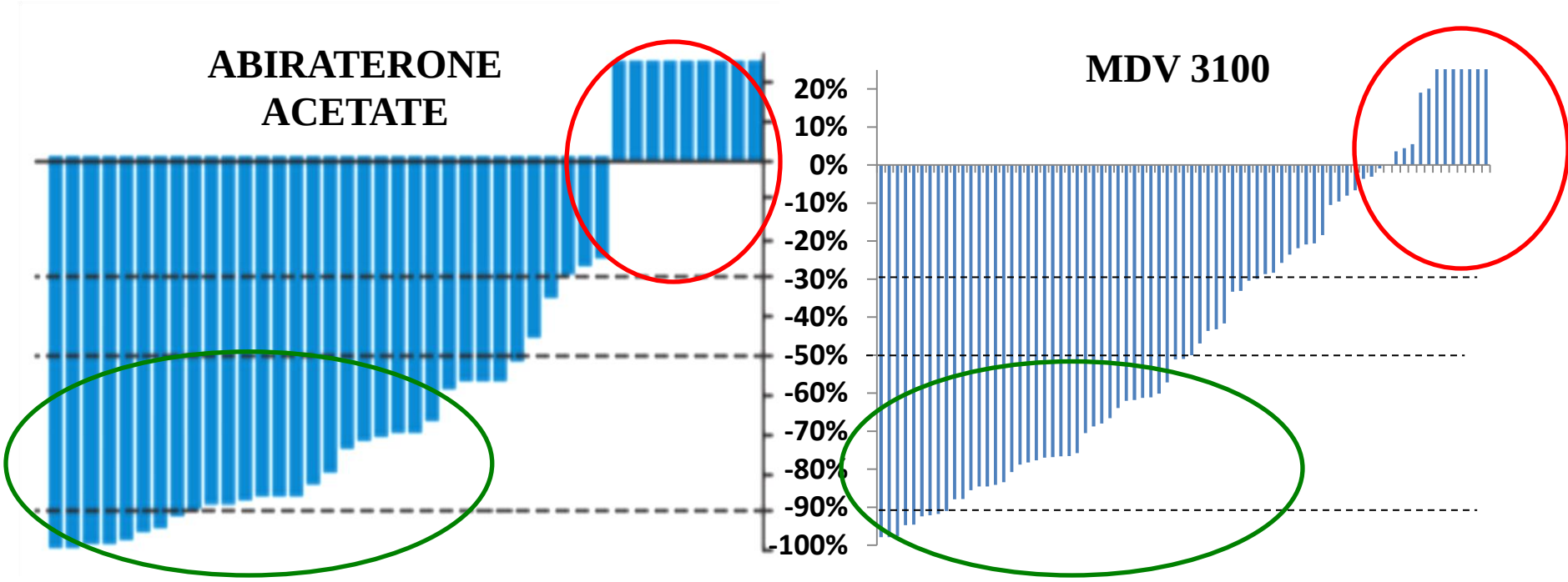
1. To establish the minimum performance characteristics for an **assay/test** to **justify/warrant** clinical testing.
2. To achieve **analytical validity** across laboratories/centers.

Most "new" technologies simply fail.

Clinical Evaluation:

3. To develop **performance metrics in the clinic** to justify further testing.
4. To design trials in a sequence to qualify a "biomarker" for a specific "context of use" (label) that will **affect/impact/guide medical decision** making.

Abiraterone Acetate and MDV3100 Produced Similar Patterns of Decline in PSA and Similar CTC Conversion Rates



	No. Patients	≥ 50% PSA Decline	Baseline CTC ≥ 5	CTC Conversion ≥ 5 to < 5
Abiraterone[1]	47	51% (24)	27	41% (11)
Abiraterone[2]	58	43% (25)	29	34% (10)
MDV3100[3]	68	34 (50%)	35	37% (13)

[1]Reid et al., JCO 27: 1489, 2010; [2]Danila et al. JCO 27:1496, 2010; [3]Scher et al., Lancet 75:1437, 2010.

Specimens have been Stored for Future Retrospective-Prospective Analyses

Special Report

Clinical Cancer Research

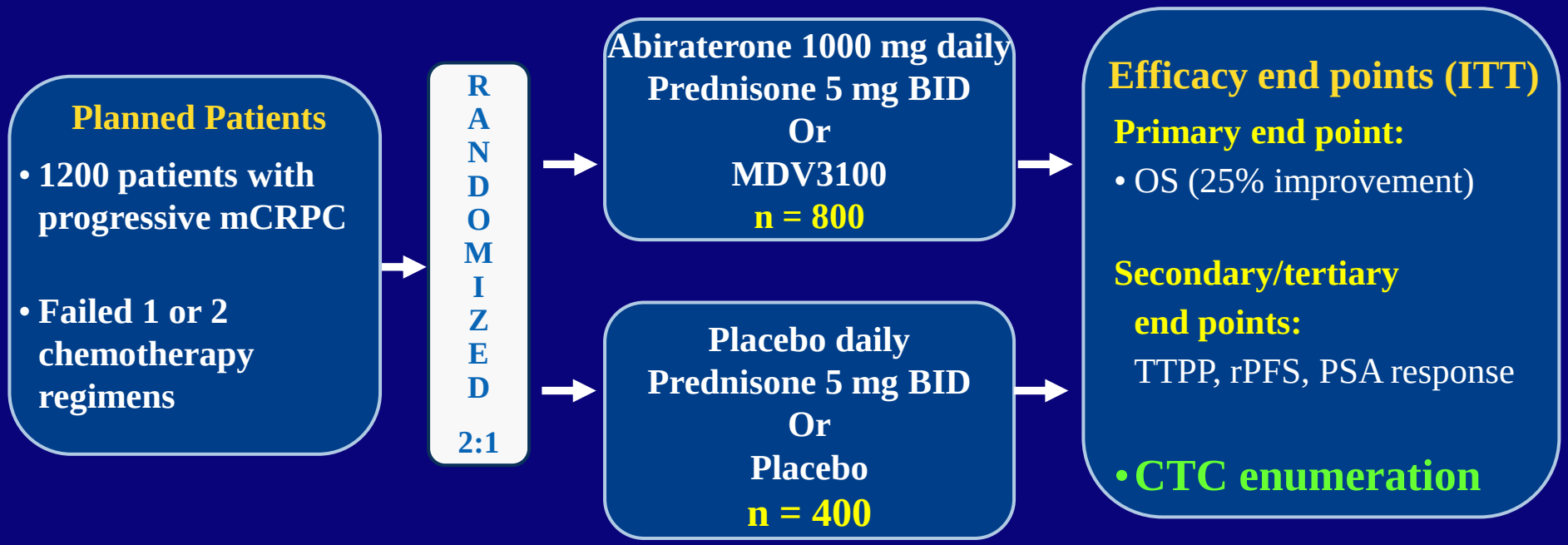
Adaptive Clinical Trial Designs for Simultaneous Testing of Matched Diagnostics and Therapeutics

Howard I. Scher[1], Shelley Fuld Nasso[2], Eric H. Rubin[3], and Richard Simon[4]

Clinical Cancer Res 17: 6634, 2011

FOCR and Brookings Institute, October, 2010

Based on the Phase II Results, Two Phase 3 Registration Trials of Similar Design Were Conducted (COU-AA-301 and AFFIRM) with Biomarker Questions Embedded



This designs was discussed with CDRH of the FDA: November 7, 2007; August 27, 2009

HR, hazard ratio; ITT, intent to treat;

As the Second Phase 3 Trial Was Designed A Briefing Documented Was Requested and Submitted to FDA To Generate the Evidence to Support Accelerated Approvals

A Voluntary Data Submission to Support the Qualification of Circulating Tumor Cells (CTCs) as an Efficacy-response Biomarker in Castration Resistant Prostate Cancer (CRPC)

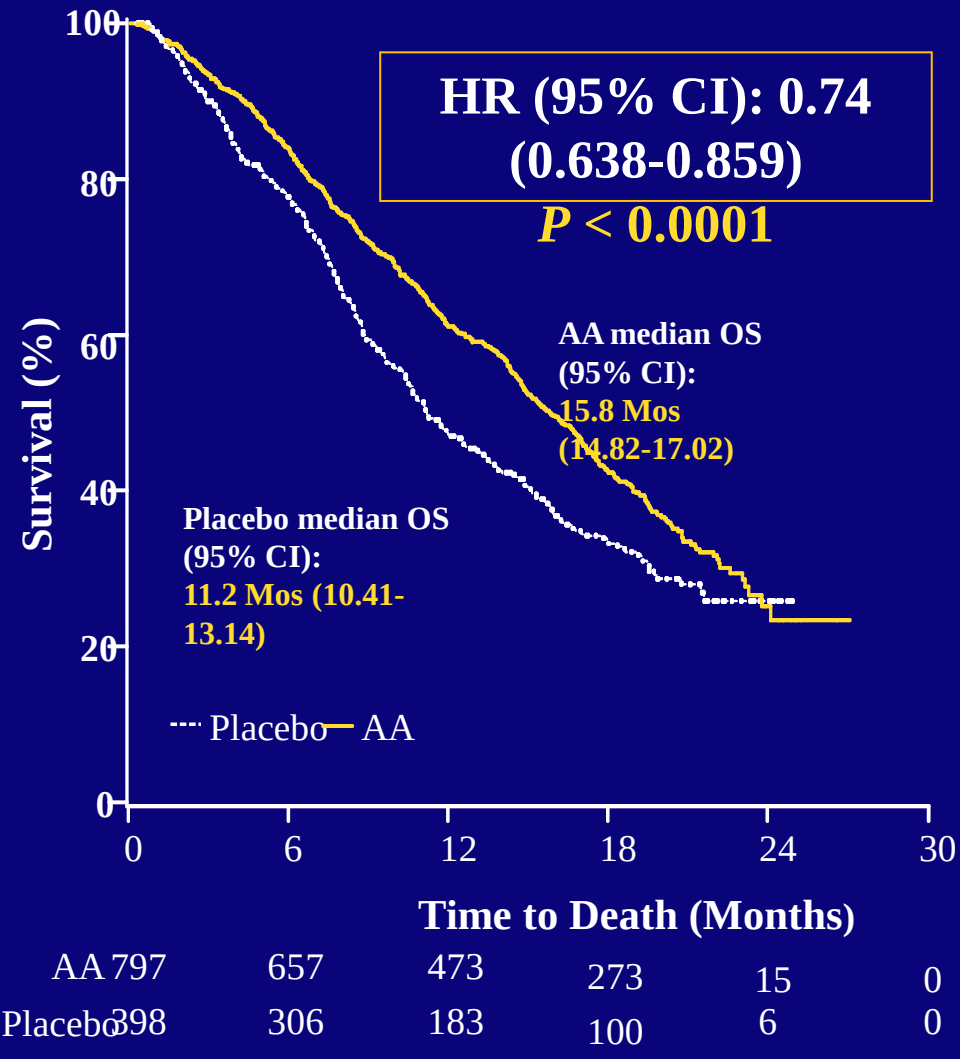
Submitted by:

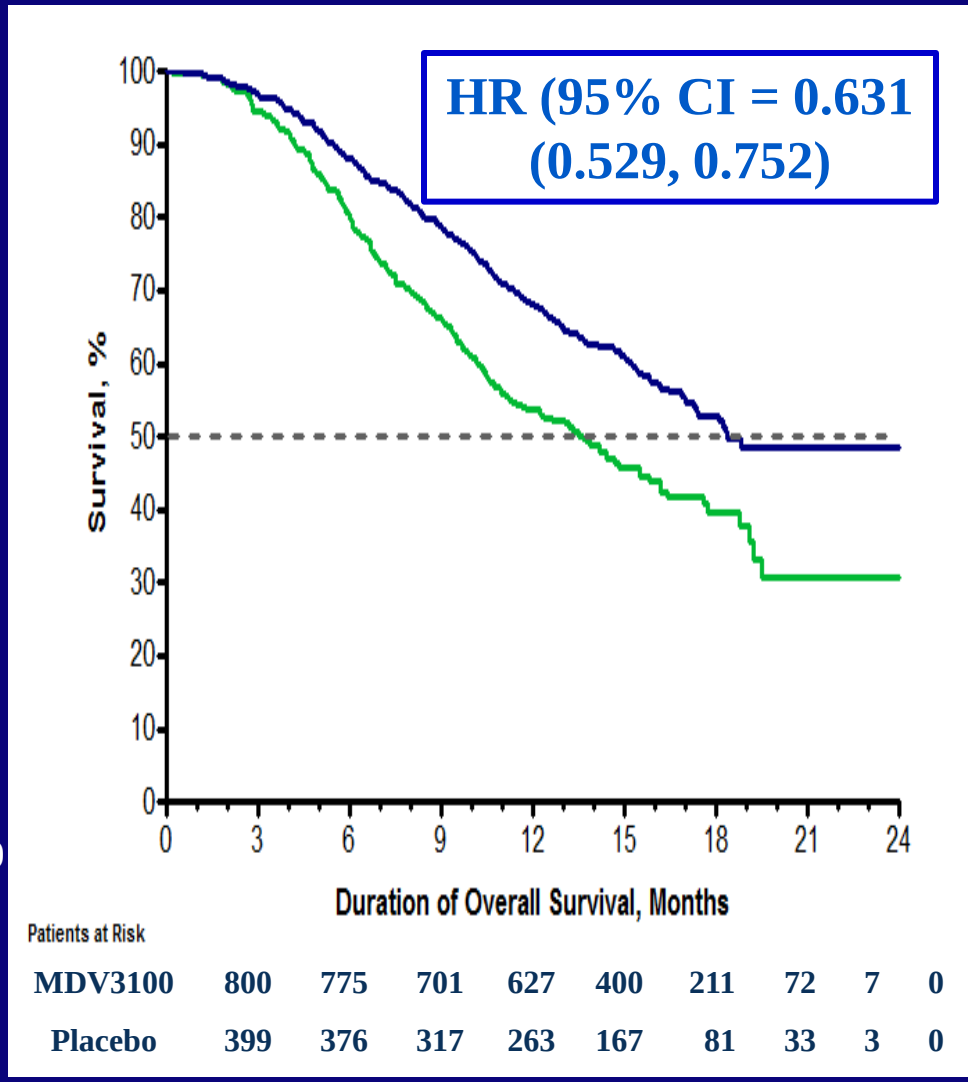
Dr. Howard Scher (Memorial-Sloan Kettering Cancer Center)
OrthoBiotech Oncology Research and Development (A Unit of Cougar Biotechnology)
Medivation, Inc.
Centocor OrthoBiotech Pharmaceuticals
and
Veridex, LLC

Submitted December 22, 2009

Face-to-Face Meeting May 7, 2010

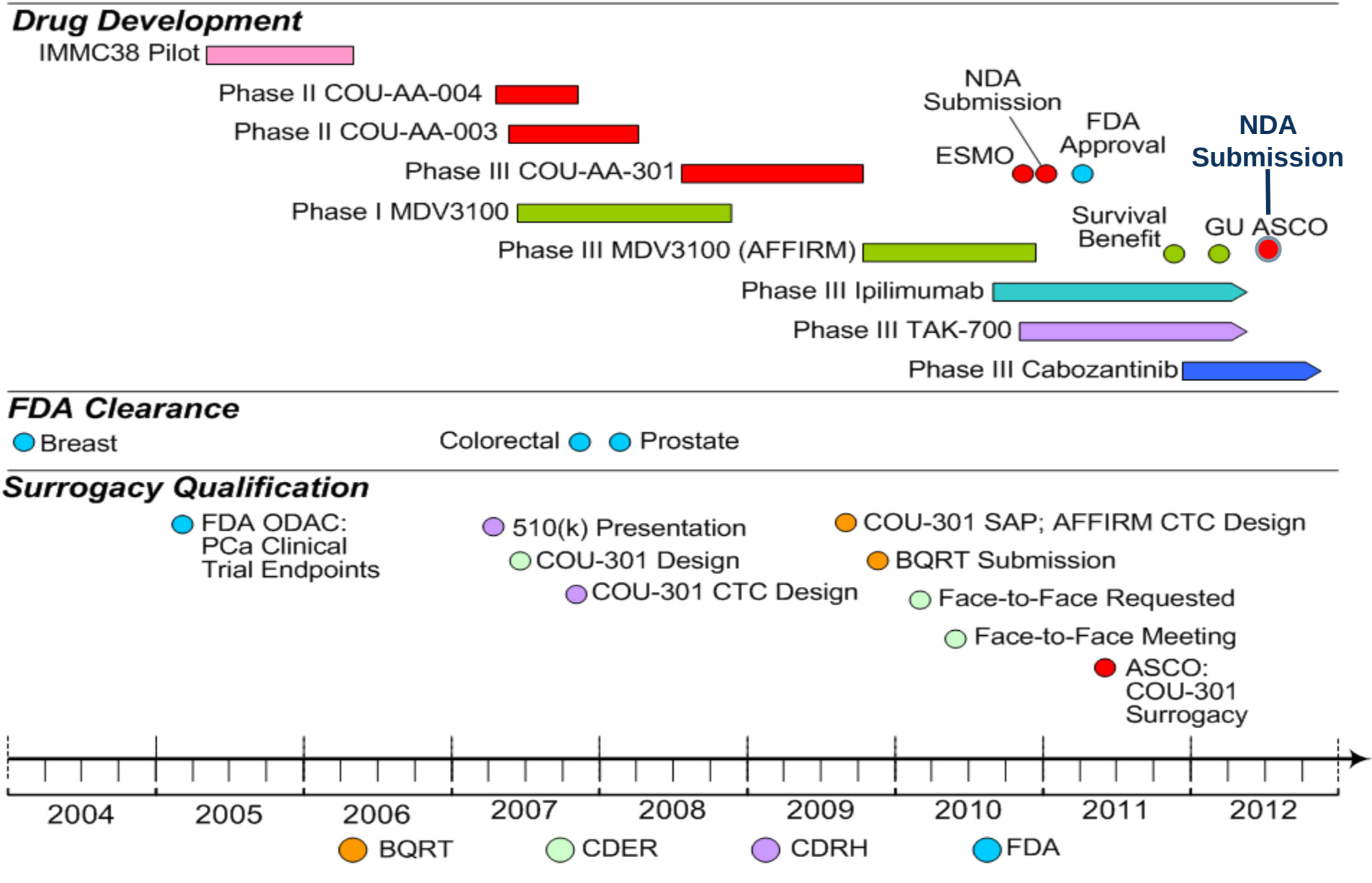
Abiraterone Acetates Prolongs Survival Relative to Placebo in Post-Chemotherapy Treated CRPC





Scher et al., ASCO, 2011

The Early and Ongoing Engagement of the CDRH at FDA Enabled A Collaboration toward Qualification of an Efficacy Response Surrogate For Survival



Partnering for the Cure

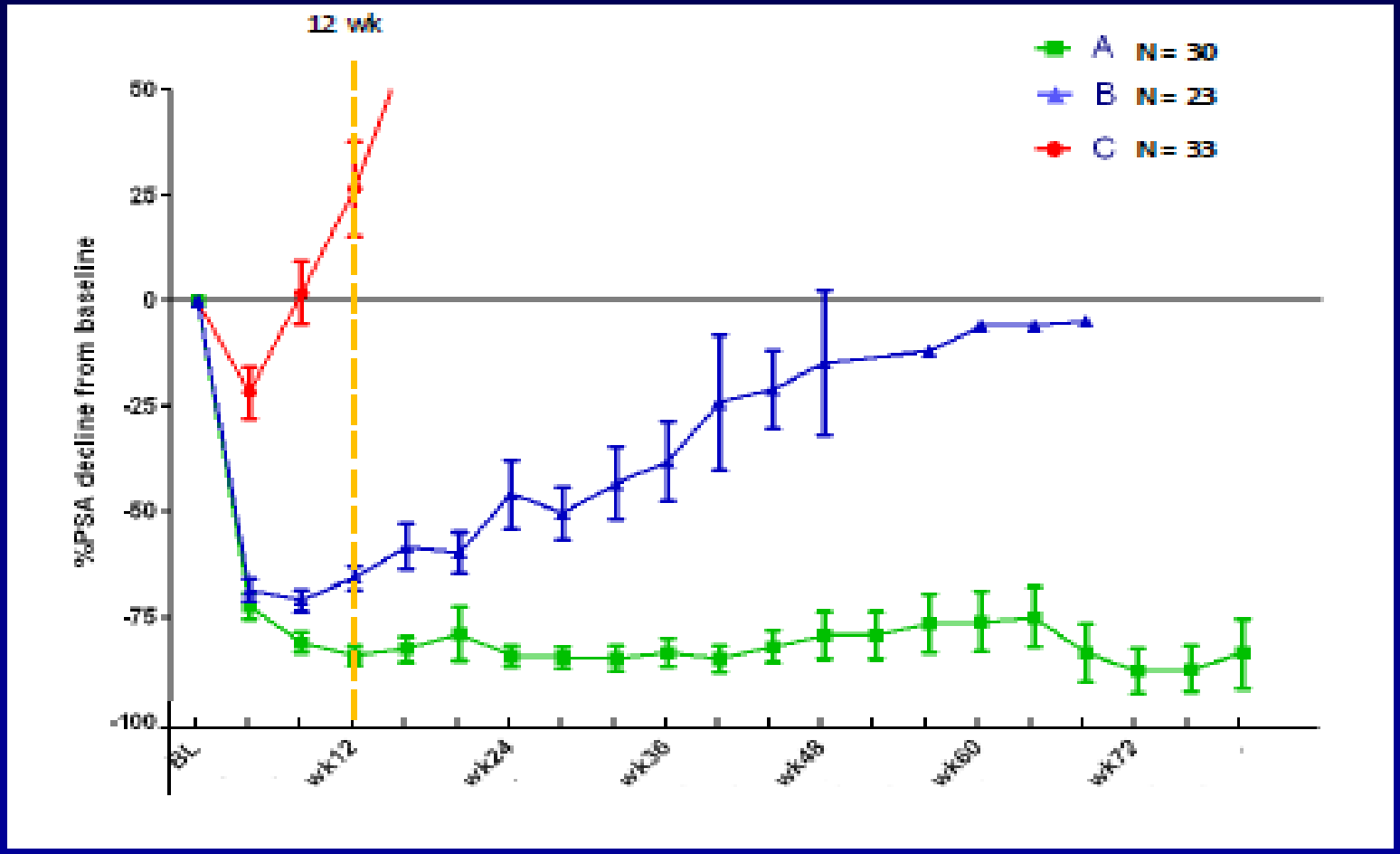
1. PCCTC: A platform for academic collaborations.

2. Co-development with Sponsors and Regulators: a tale of two drugs.

3. **The availability of analytically valid assays is rate limiting,**

4. **I**mplementation of a Precision Medicine Paradigm.

The Patterns of Post-Therapy PSA Change With Abiraterone and MDV3100: Some Tumors are Resistant *de novo* and Others *Acquire* Resistance



Which materials should be used for assay development?

Several biomarkers have been postulated, but none have been definitively established as predictive.

Specimens have been stored for future analysis.

As an Investigator, what do you do?

Develop assays for putative markers and study associations with clinical outcomes using those that are "close" to analytical validation.

Rationale for Developing Assays for Biomarkers for which Preclinical Data Support Prediction

1. We have identified pathways and targets:

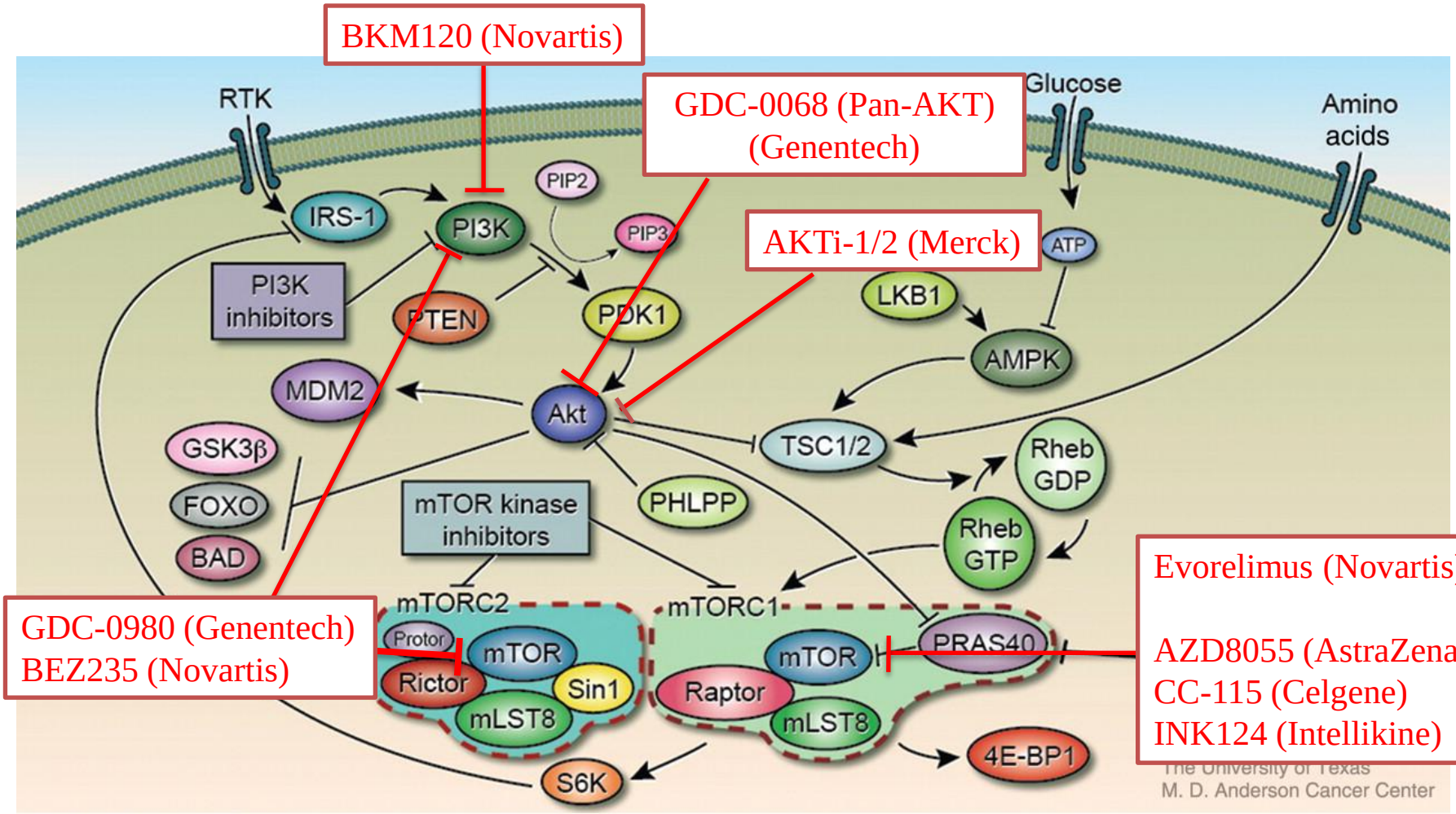
   e.g. AR and PI3K signaling axes.

2. The drugs are already in development.

3. The availability of analytically valid assay is rate limiting.

4. Assay development takes time and resources.

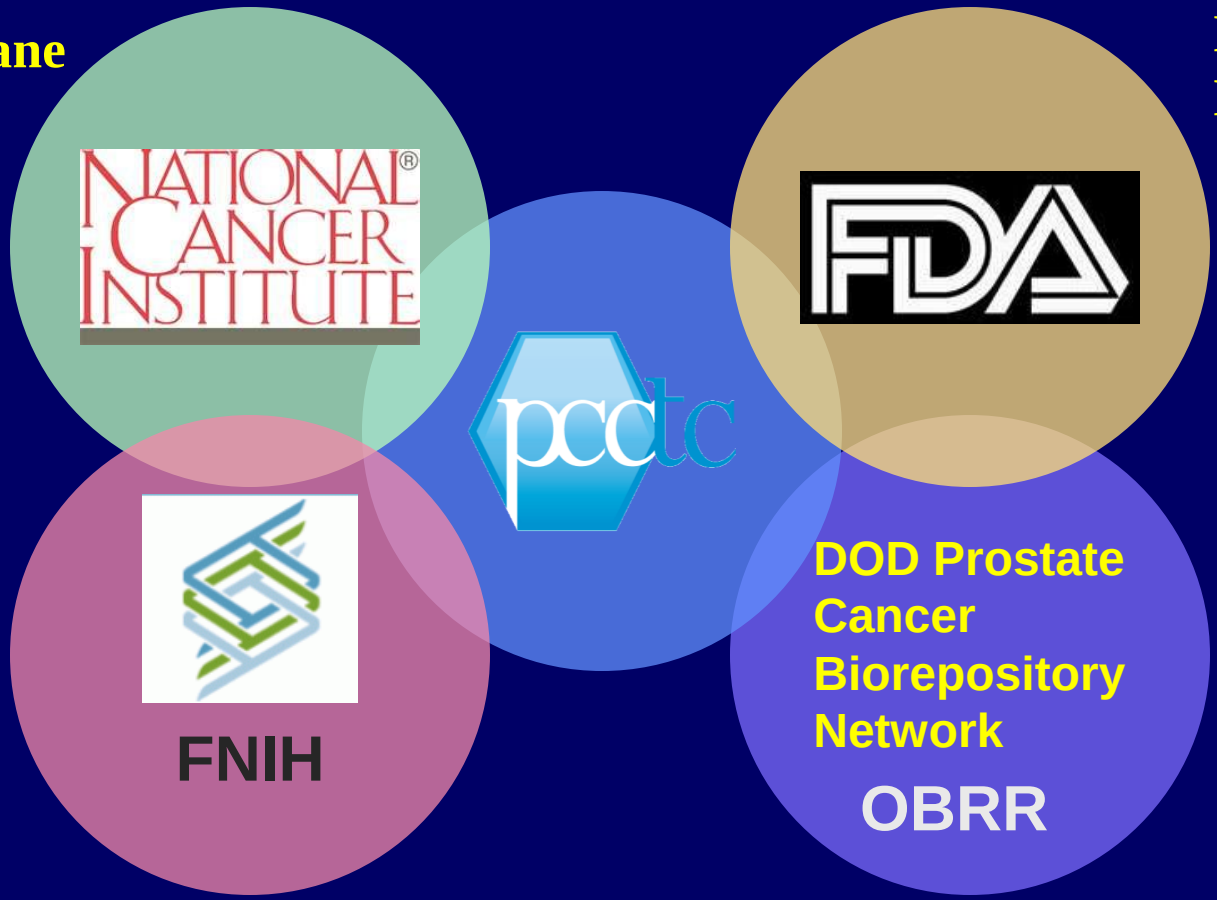
A partial list of agents targeting the PI3K signaling axis in clinical development



Adapted from Emerling et al. Cancer Res 2011

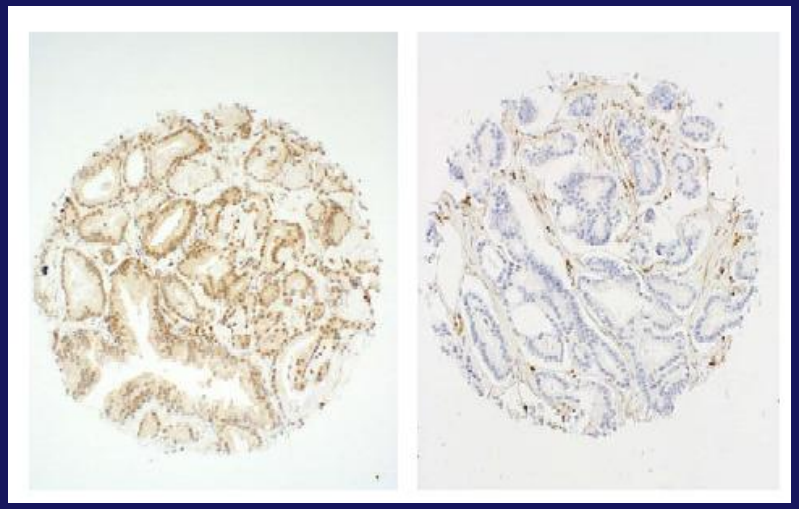
American Association for Cancer Research

We Know the Guidance for Integral Predictive Assays and Are Collaborating With Critical Stakeholders of the Biomarker Qualification Pathway



To Test This Hypothesis Clinically Requires Validated Assays: A Proposed Clinical Trial Includes an Analytically Valid IHC Assay for PTEN: "Null" or "Any"

PTEN expression in tumors from two different patients on a tissue microarray



Present in tumor and stroma

"Null" in tumor Present in stroma

DeMarzo (JHU) Loda (DFCI) and Reuter (MSKCC).

MSKCC, JHU, DFCI SPORE

1. Validation in cell lines.
2. **IHC in primary and metastatic tissue**: "**Null**" or any; H-score
3. qPCR.
4. **CNA (Exploratory)**
5. Output signatures.

What Tumor Material and What Assay Will be Most Informative for Predictive Biomarkers?

Primary tumor, metastatic site biopsy, CTC, Cell Free ……

1. AR. MYC PTEN and TMPRSS2/ERG status.
2. Genetic analysis (FISH).
3. Protein (IHC)
4. Copy number alterations (CNA) .
5. Transcriptome (qRT-PCR or Microarray profiling0.
6. Mutational analysis of key components of the PI3K pathway.
7. PD-given preclinical evidence of reciprocal feedback.

Others …….

There is no validated assay for the androgen receptor!

Partnering for the Cure

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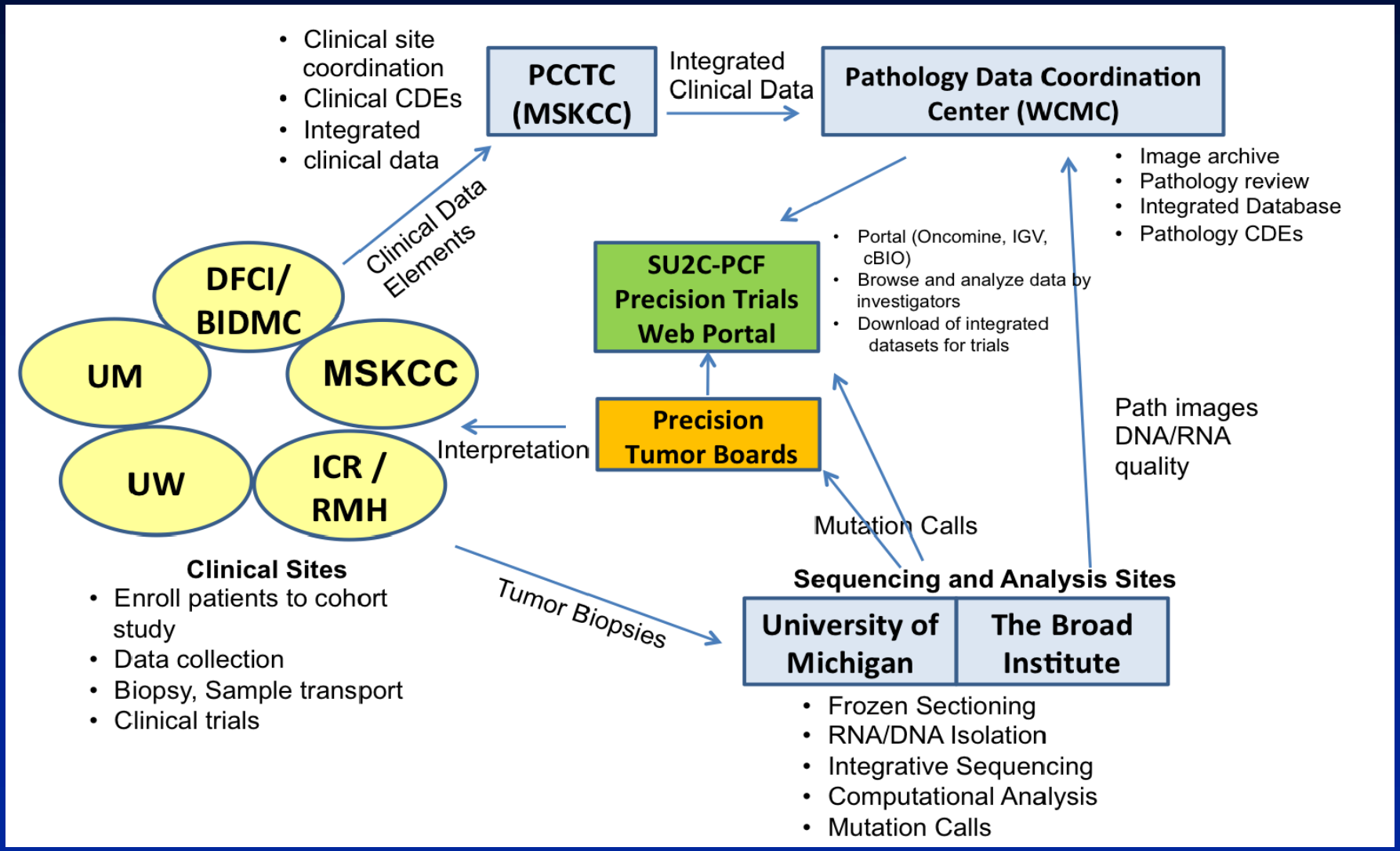
3. The availability of analytically valid assays is rate limiting,

4. **Implementation of a Precision Medicine Paradigm.**

SU2C-PCF Prostate Dream Team: Precision Therapy of Advanced Prostate Cancer
Arul Chinnaiyan and Charles Sawyers (Co-PI)

- Establish a "Rosetta Stone" resource of mutation profiles of advanced prostate cancer for researchers and patients
- Establish advanced prostate cancer as a model tumor type for the precision medicine paradigm and facilitate the use of clinical sequencing for cancer management
- Establish the use of *Precision Tumor Boards* to help guide the management of advanced prostate cancer
- Identify resistance mechanisms and sensitivity biomarkers for new prostate cancer therapies
- Identify rare "actionable" mutations in advanced prostate cancer and provide rational clinical trial options to patients

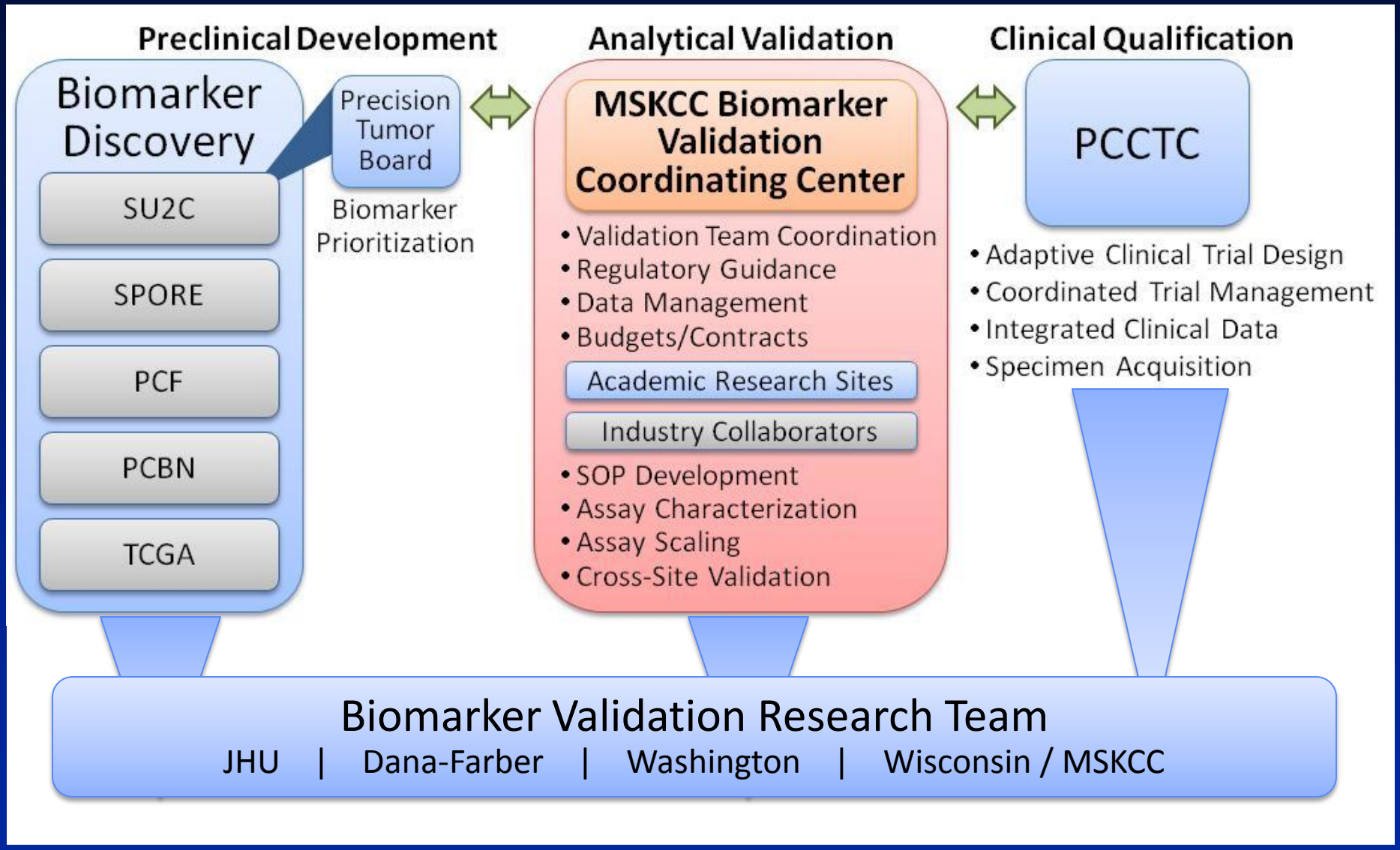
Stand Up 2 Cancer (SU2C) – Prostate Cancer Foundation Precision Clinical Trials



Arul Chinnaiyan and Charles Sawyers, Co-P.I.'s

SU2C

To Practice of Precision Medicine Requires Analytically Valid Assays When the Trials Are Ready to Begin



Toward the Practice of Precision Medicine: A Biomarker Validation Coordinating Center

Objective: To form a centralized infrastructure to coordinate biomarker development, specifically validation.

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1. Select and prioritize biomarkers in conjunction with the SU2C Precision Tumor Board
2. Coordinate validation teams to analytically validate assays
3. Partner with industry collaborators
4. Execute clinical trials with integral biomarker assays embedded

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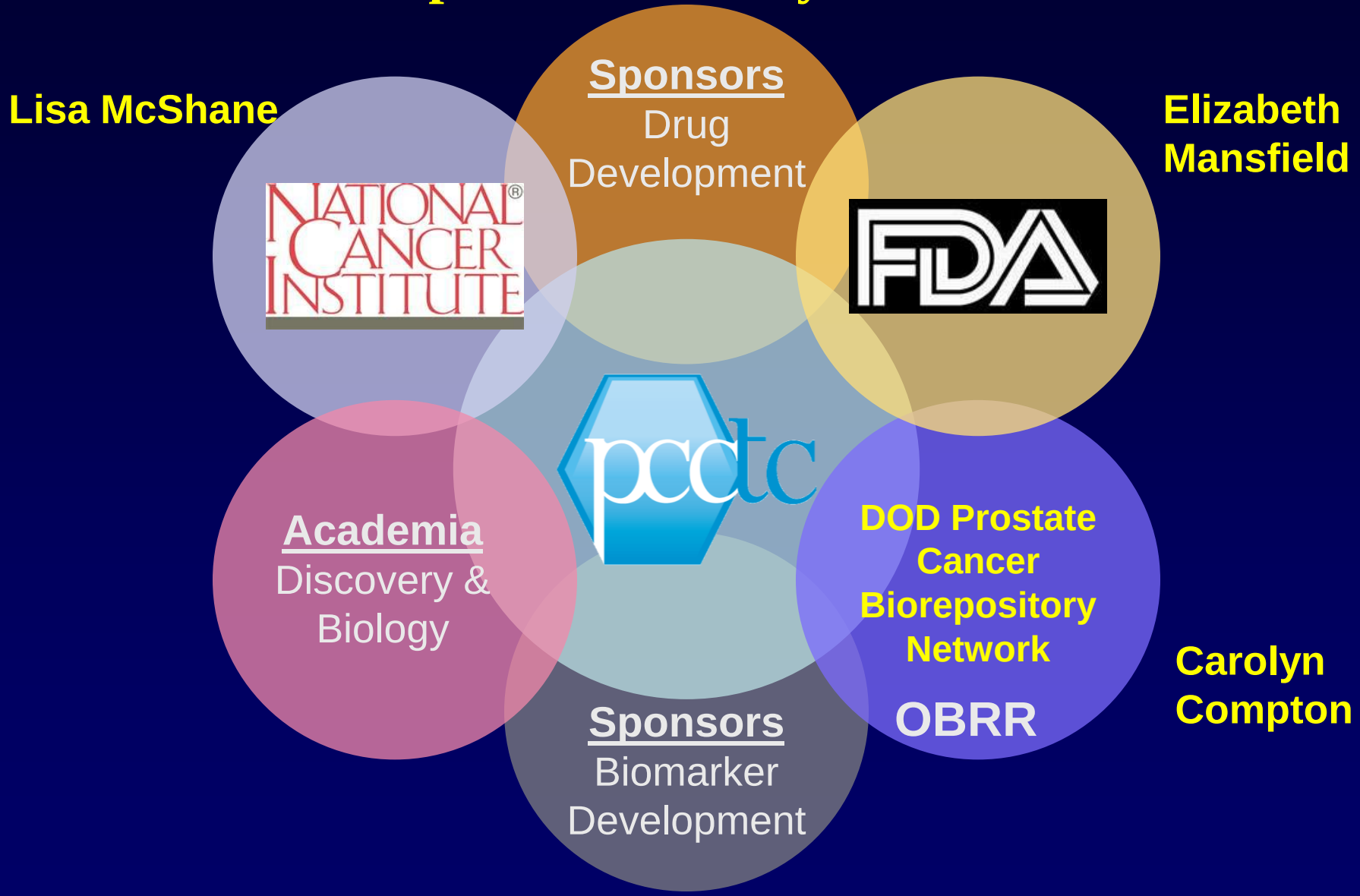
We Are Collaborating With Critical Stakeholders of the Biomarker Qualification Pathway: Our Group Welcomes Payors to the Mix



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Vivek Arora

Adriana Heguy
Agnes Viale
Katia Manova

Anu Gopalan
Victor Reuter
Ying-Bai Chen

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Nikki Schultz
Nick Socci

Neal Rosen
David Solit

Glenn Heller

Royal Marsden:
Johann deBono
Gerhard Attard

UCSF: Charles Ryan
OHSU: Tom Beer
U Washington: Tia Higano
MDACC: Chris Logothetis
DFCI: Mary-Ellen Taplin
BIDMC: Glenn Bubley
U Mich: Maha Hussain

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Thian Keough
Veridex
Robert McCormack
Medivation:
Lynn Seely
Mohammed Hirmand

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Lisa McShane
Carolyn Compton
Gary Kelloff
FDA:
Liz Mansfield
Mark Walter
Robert Becker

NIH SPORE, DOD PCCTC, Prostate Cancer Foundation