ARS #1

The practicing urologist plays a limited role in the management of advanced prostate cancer

1. True
2. False

ARS #2

The sequence and combination of therapies for patients with mCRPC has been well documented and supported by prospective randomized clinical trials.

1. True
2. False

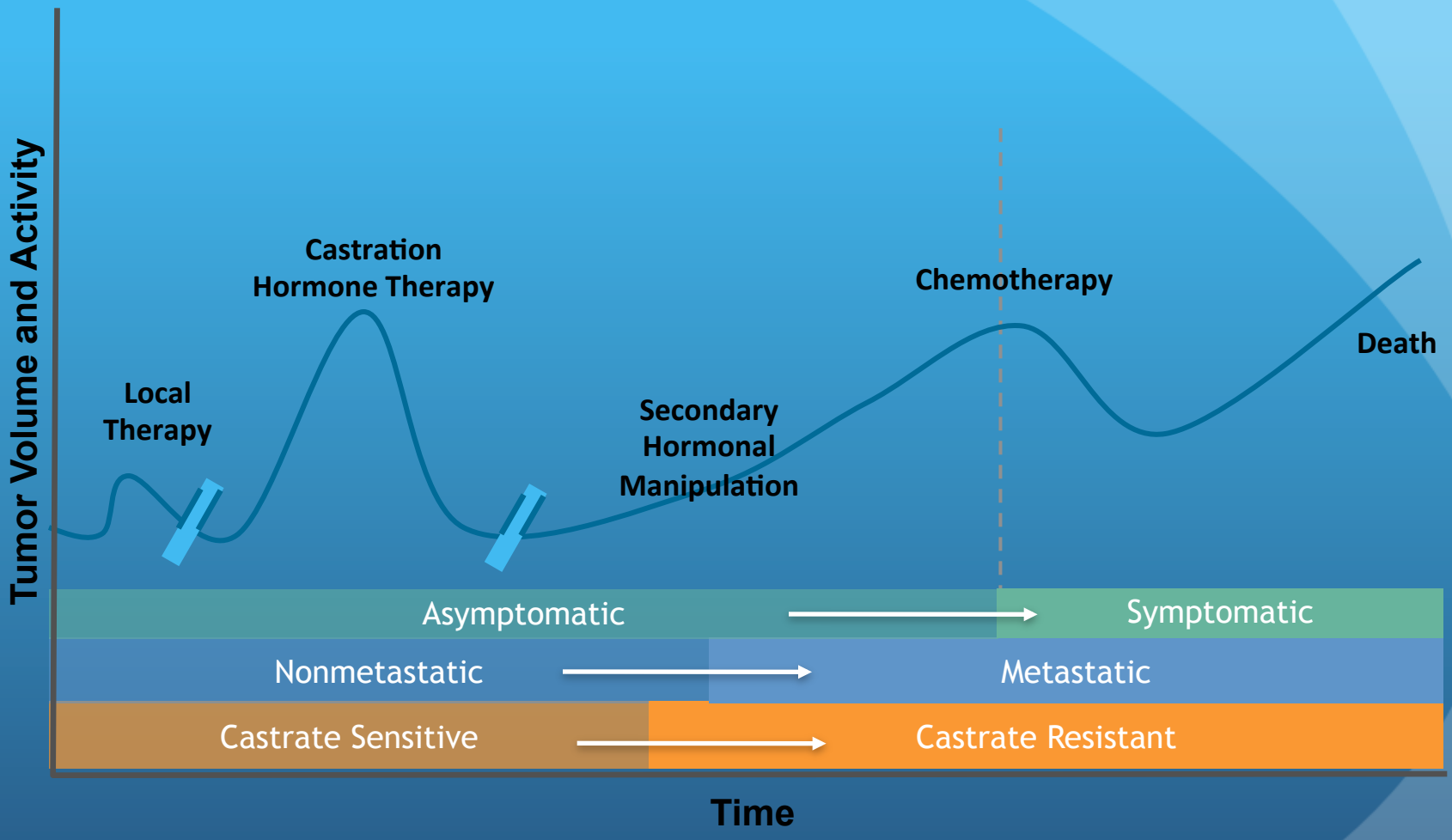
The Role of the Urologist in the Current Management of Advanced Prostate Cancer: 2016

Raoul S. Concepcion, M.D., F.A.C.S.
Vail CO
January 23, 2016

Disclosures

- Consultant: Cardinal Health, Genomic Health, CSSIAH, Myriad, CUSP, Ferring, Tolmar
- Speakers Bureau: Dendreon, Astellas, Bayer, Janssen, Sanofi, Medivation, Amgen
- Research Support: Janssen, Medivation, Dendreon, Bayer, SCRI

Natural History of Prostate Cancer



Adapted from Higano CS. In: Figg WD et al. *Drug Management of Prostate Cancer*. 2010:321.

STUDIES ON PROSTATIC CANCER

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

CHARLES HUGGINS, M.D.

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

AND

CLARENCE V. HODGES, M.D.

CHICAGO

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

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

From the Department of Surgery, University of Chicago.

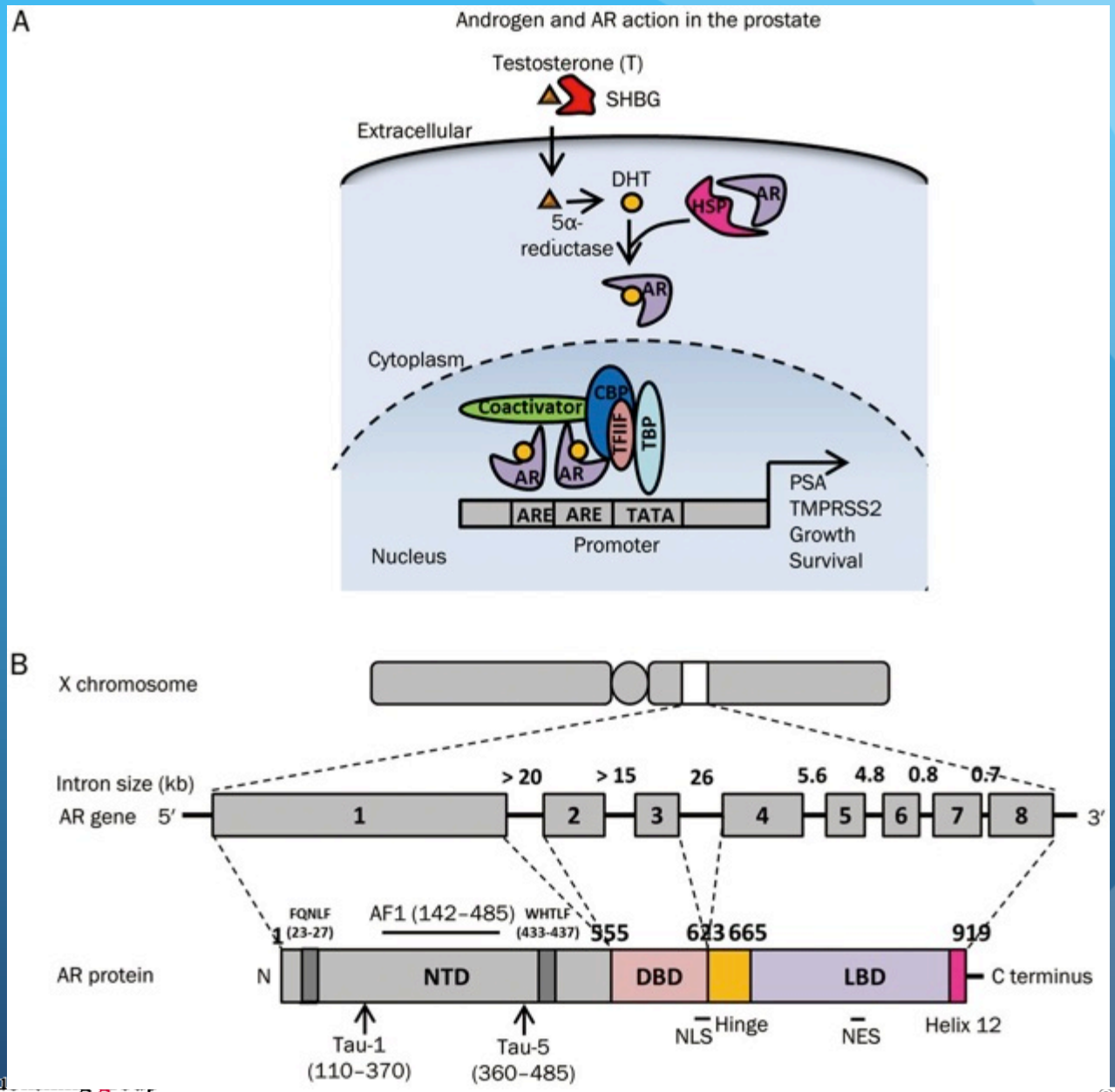
Dr. Hodges is a Fellow of the Douglas Smith Foundation for Medical Research of the University of Chicago.

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

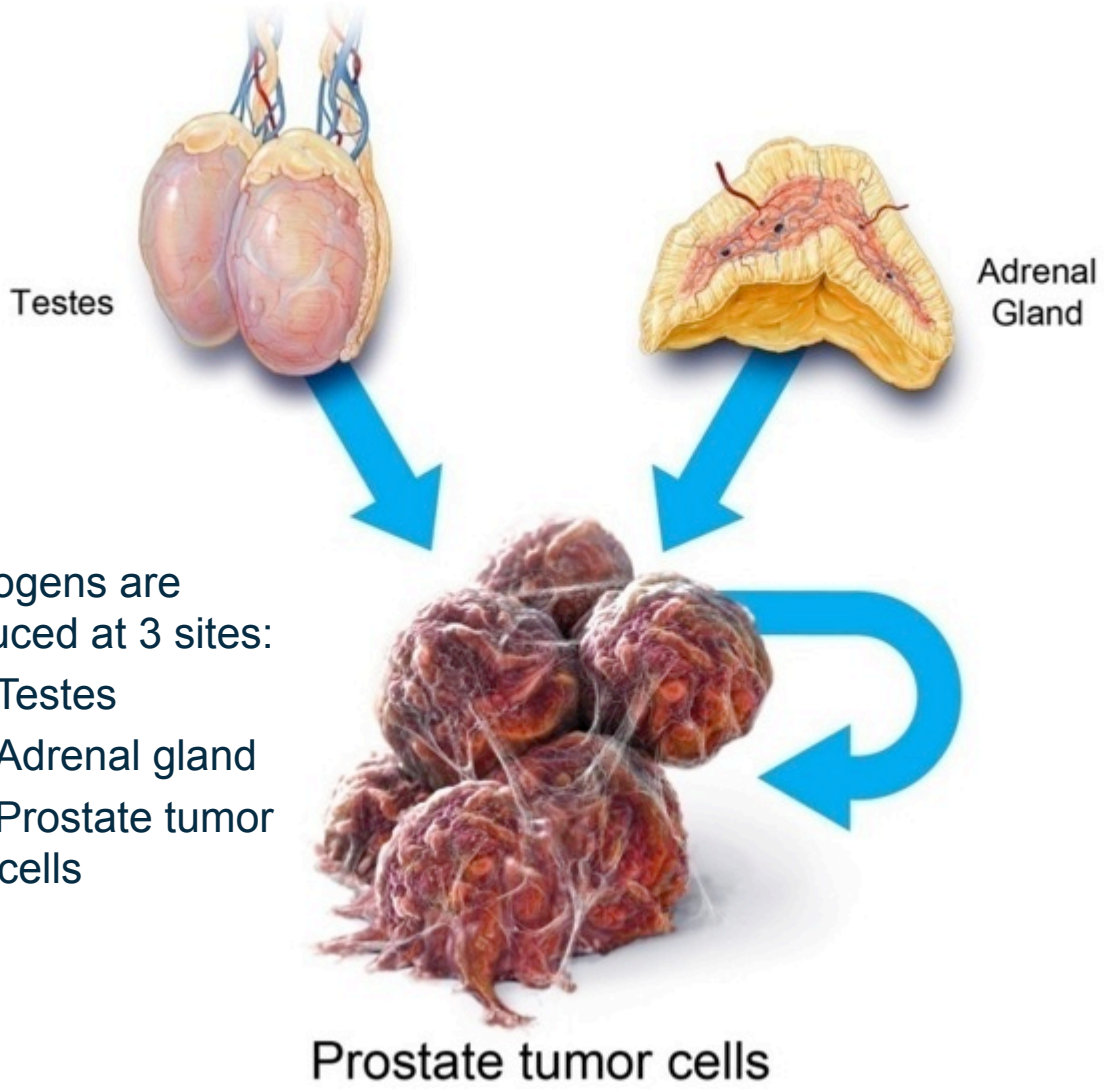
1. Kutscher, W., and Wolbergs, H.: Prostataphosphatase, Ztschr. f. physiol. Chem. **236**:237, 1935.

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

Figure 1 Androgen and AR action



Sources of Androgen Production



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

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

John Hunter
1780–castration

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

1904
First RP

1867
First perineal prostatectomy performed

1920s
RT for PC using radium

1960s
RT established as important treatment for PC

1970s
Steroidal and non-steroidal AAs available

Nobel Prize:
Andrzej Schally, Roger Guillemin

1960s and 70s
Synthetic estrogens developed

1980s
Long-acting synthetic LHRH agonists

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

2003
First GnRH blocker (abarelix) launched

2004
Docetaxel in combination with prednisone approved

2008
Degarelix approved in US

2009
ARSI Developed

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

1920 1940 1960 1980 2000 2020

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

Figure courtesy of Dr E. David Crawford

Hormone Therapy: Current Treatment Options

- Androgen deprivation therapy (ADT)
  - Estrogens
  - Surgical castration (bilateral orchiectomy)
  - LHRH agonists
  - GnRH antagonists
- Antiandrogens
- Combined androgen blockade (CAB)
- 17,20 Lyase Inhibitors

Complications of ADT

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

Early Chemotherapy in Metastatic PCa: E3805 CHAARTED trial

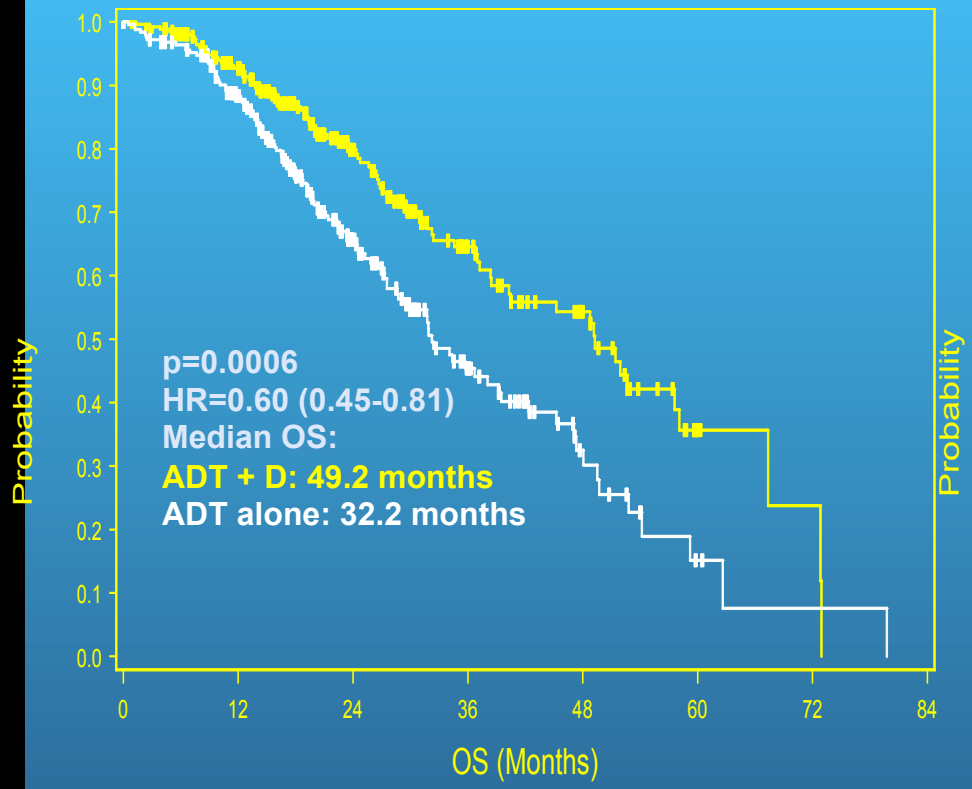
(ChemoHormonal therapy vs.Androgen Ablation Randomized Trial for Extensive Disease)

- Study design: multicenter, randomized phase 3
- Patients and treatment:
  - 790 men with metastatic PCa receiving androgen deprivation therapy (ADT) randomized to:
    - Continued ADT alone
    - ADT + docetaxel-based chemotherapy every 3 weeks for 18 weeks
- Primary endpoint: evaluation of the ability of early chemotherapy to improve OS in patients receiving ADT for metastatic PCa

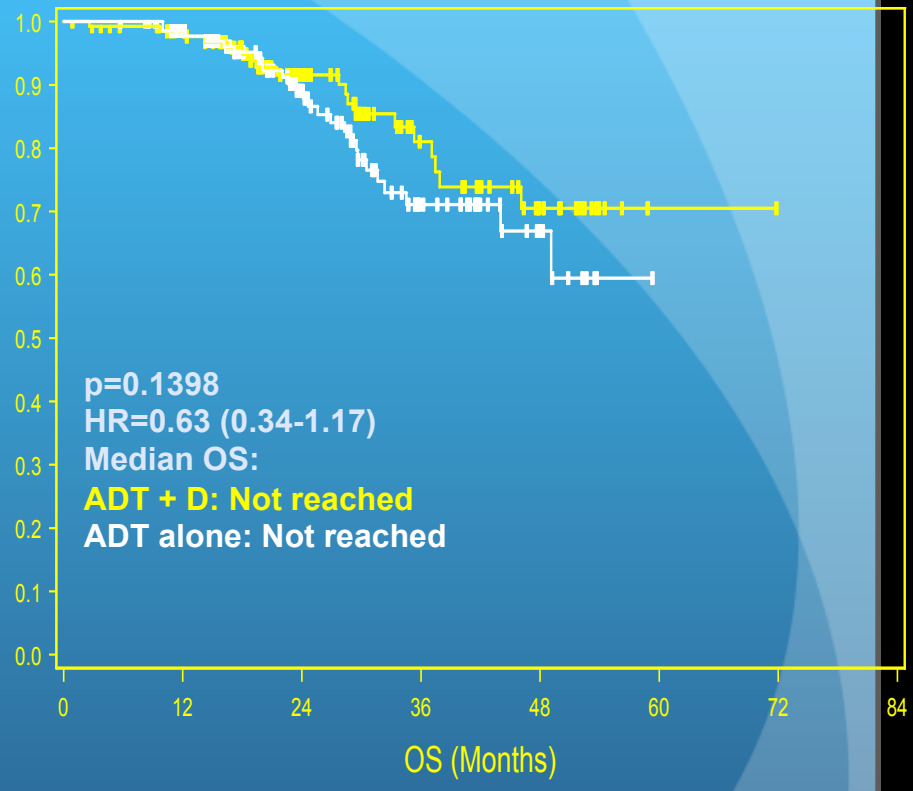
NIH. 2013. http://www.nih.gov/news/health/dec2013/nci-05.htm.

OS by extent of metastatic disease at start of ADT

High volume



Low volume



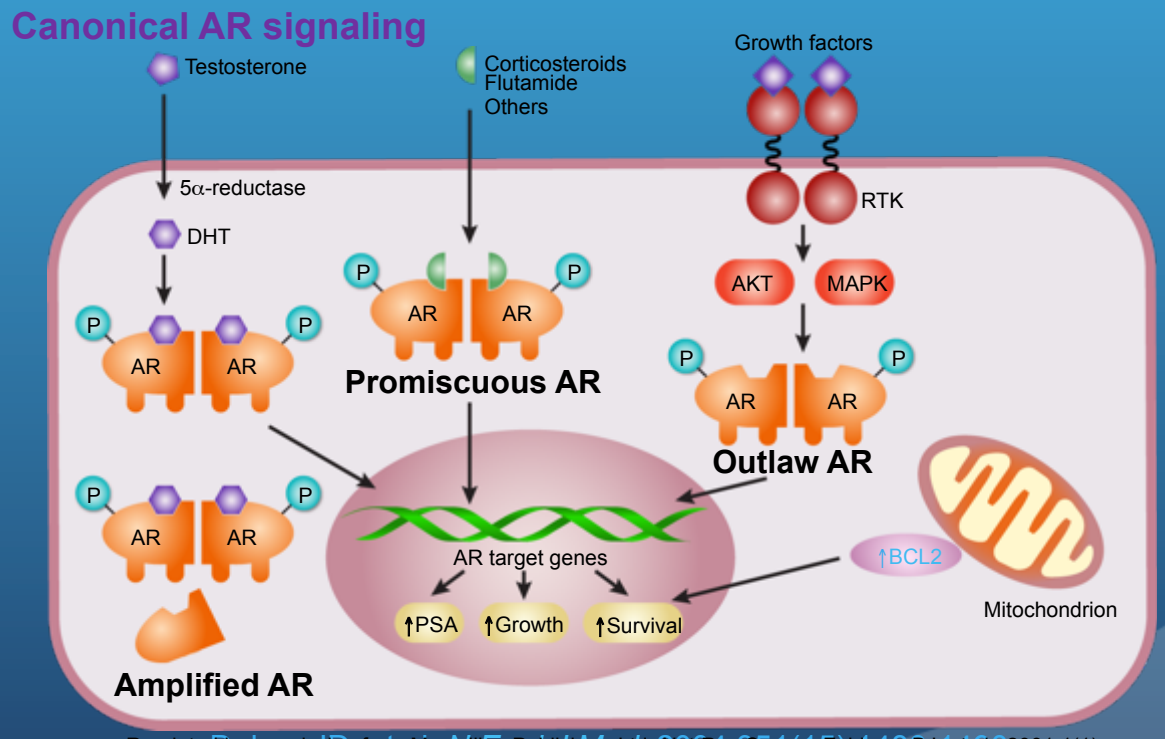
In patients with high volume metastatic disease, there is a 17 month improvement in median overall survival from 32.2 months to 49.2 months

We projected 33 months in ADT alone arm with collaboration of SWOG9346 team

Presented by: Christopher J. Sweeney, MBBS

Prostate Cancer Relies on Androgen Signaling for Progression

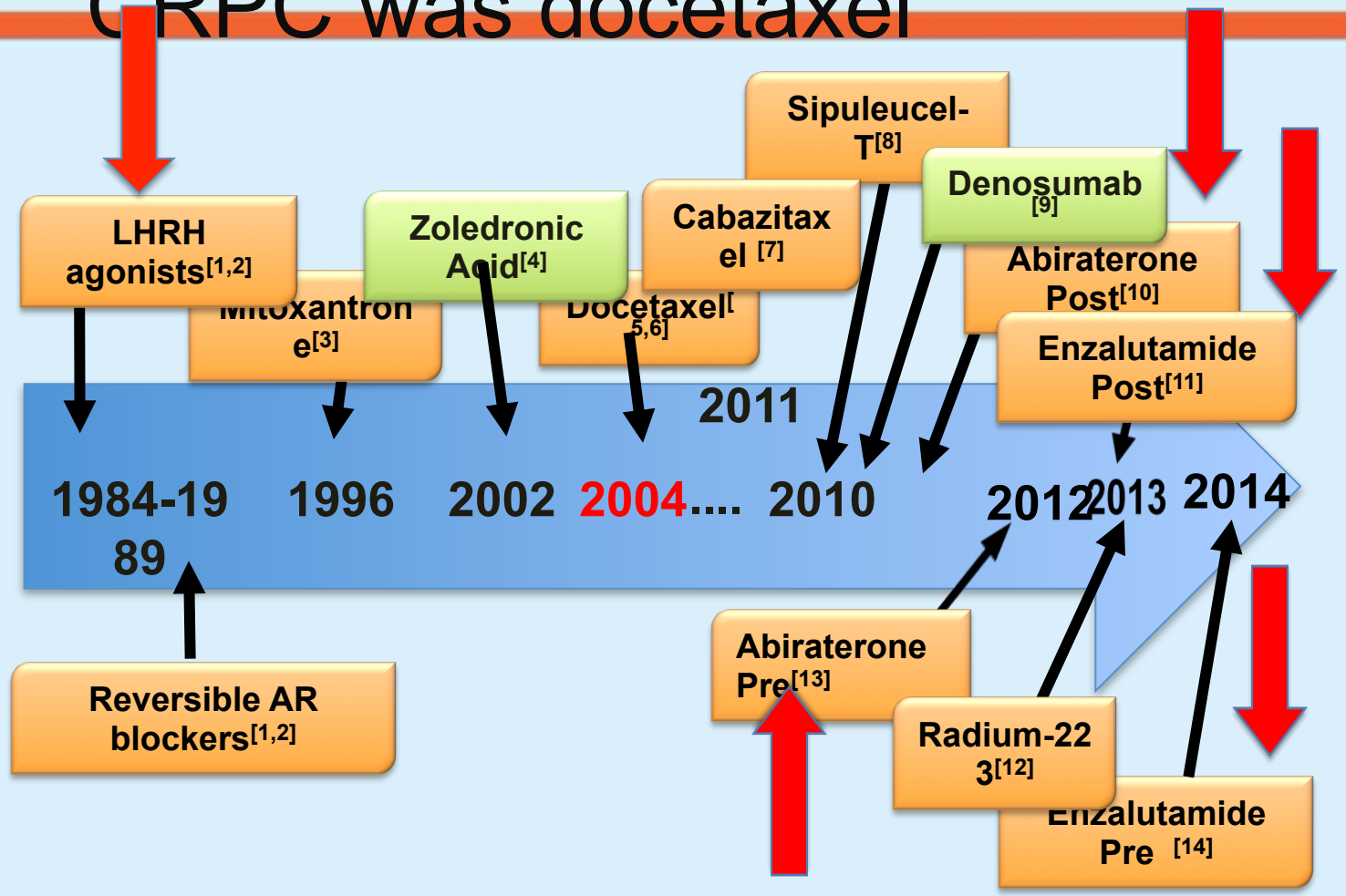
- Prostate cancer progression commonly relies on androgen signaling
- However, numerous adaptive mechanisms exist by which prostate cancer cells can bypass traditional androgen signaling pathways



Castration Resistant Prostate Cancer (CRPC)

- Androgen Deprivation Therapy
- Rising PSA
- Serum Testosterone < 50 ng/dl
- M0 Disease: (-) radiographic mets
- M1 Disease: (+) radiographic mets

Before 2010, the last agent approved for the treatment of CRPC was docetaxel

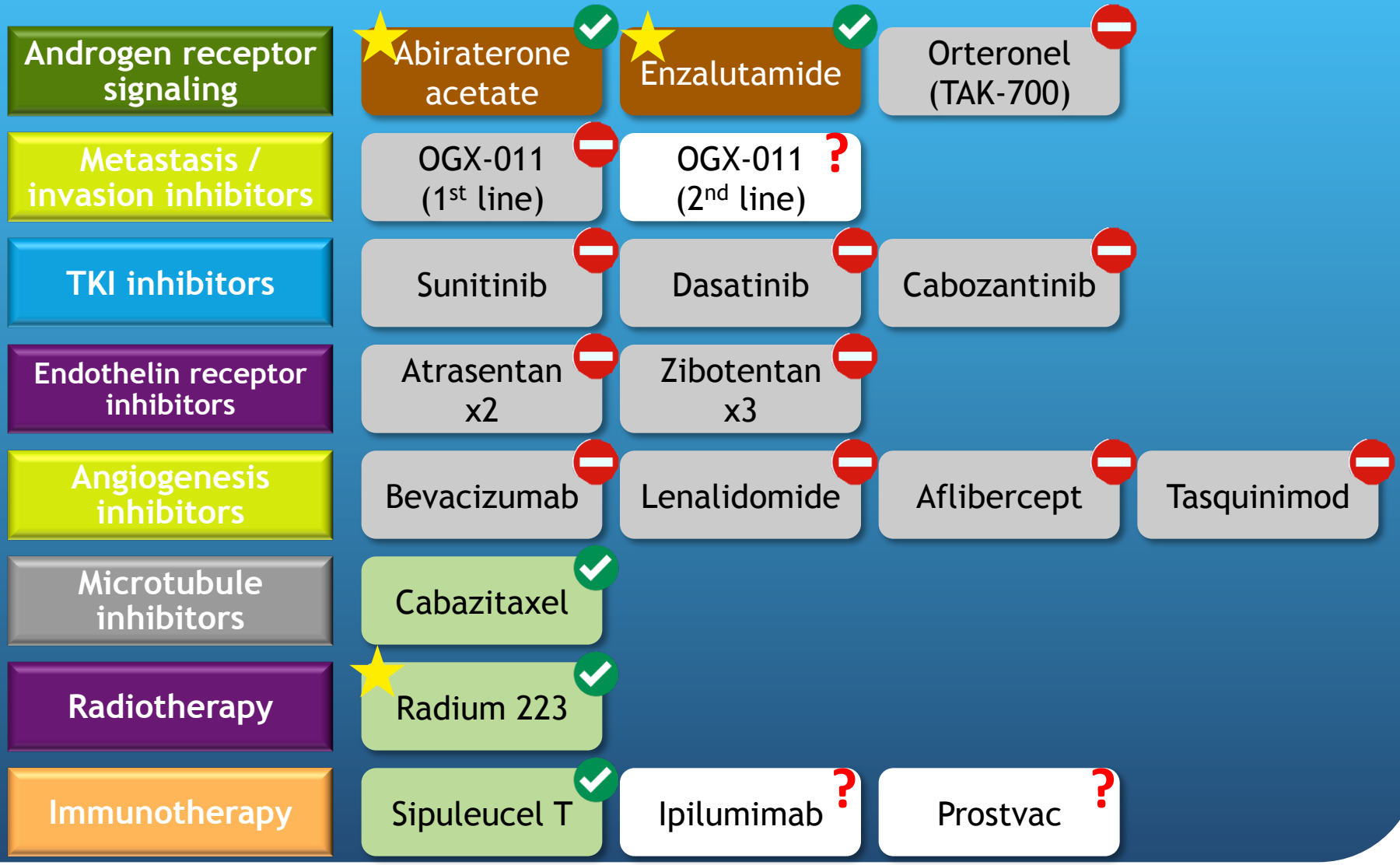


1. The Leuprolide Study Group. NEJM 1984;311:1281-1286. 2. Crawford ED, et al. NEJM. 1989;321:419-424. 3. Tannock IF, et al. J Clin Oncol. 1996;14:1756-1764. 4. Saad F, et al. JNCI 2002;94:1458-1468. 5. Petrylak DP, et al. NEJM. 2004;351:1513-1520. 6. Tannock IF, et al. NEJM. 2004;351:1502-1512. 7. de Bono JS, et al. Lancet. 2010;376:1147-1154. 8. Kantoff PW, et al. NEJM. 2010;363:411-422. 9. Fizazi K, et al. Lancet. 2011;377:813-822. 10. de Bono JS, et al. NEJM. 2011;364:1995-2005. 11. Scher HI, et al. NEJM. 2012 Sep 27;367(13):1187-97. 12. Parker et al. *NEJM*. 2013;369:213-223.13. Beer T et al. 2014 ASCO GU San Francisco, CA 14. Beer T NEJM 2014; 371:424-433

Key phase III clinical trials since 2004

Androgen receptor signaling	Abiraterone acetate	Enzalutamide	Orteronel (TAK-700)	
Metastasis / invasion inhibitors	OGX-011 (1st line)	OGX-011 (2nd line)		
TKI inhibitors	Sunitinib	Dasatinib	Cabozantinib	
Endothelin receptor inhibitors	Atrasentan	Zibotentan		
Angiogenesis inhibitors	Bevacizumab	Lenalidomide	Aflibercept	Tasquinimod
Microtubule inhibitors	Cabazitaxel			
Radiotherapy	Radium 223			
Immunotherapy	Sipuleucel T	Ipilumimab	Prostvac	

Key phase III clinical trials since 2004



Summary of clinical trial outcome (the monotherapy approach)

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

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

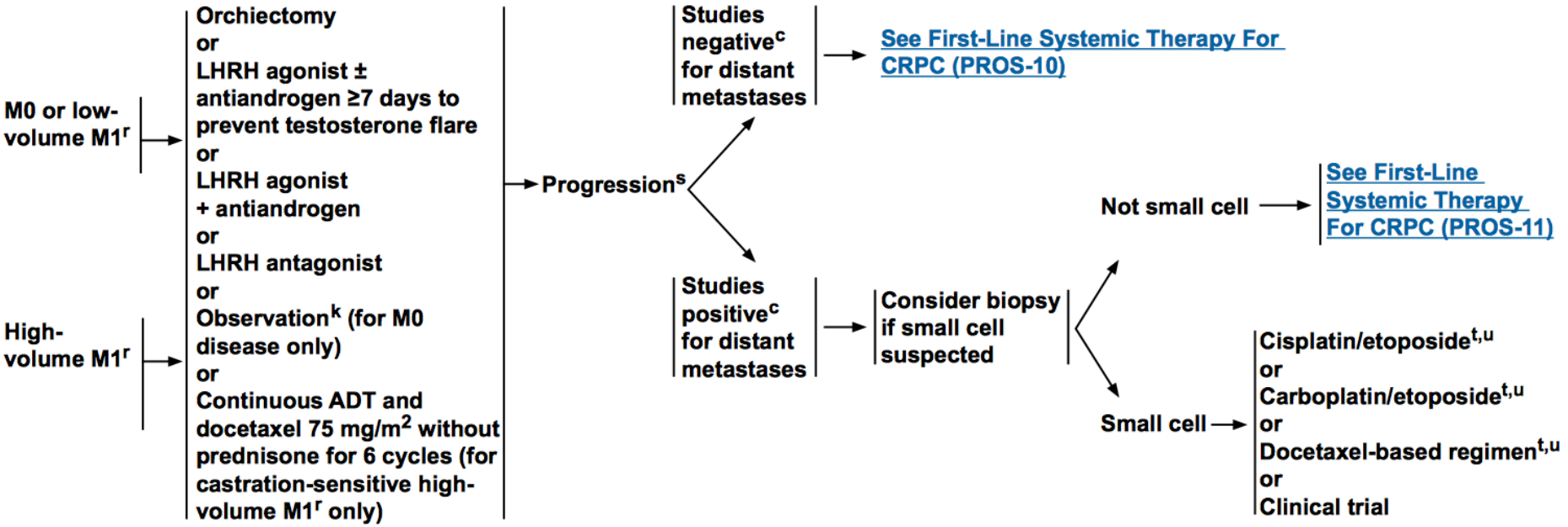
1. Berthold DR, et al. J Clin Oncol 2008;26:242-5; 2. de Bono JS, et al. Lancet 2010;76:1147-54;
3. Fizazi K, et al. Lancet Oncol 2012;13:983-92; 4. Rathkopf DE, et al. J Clin Oncol 2013;31(suppl. 6): abstract 5;
5. Scher HI, et al. N Engl J Med 2012;367:1187-97; 6. 12. Beer et al., J Clin Oncol 32,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

These studies are different (in type, population, inclusion/exclusion criteria, design and method, primary

AUA Guidelines: 2013

Index pt	Definition	Treatment
1	MO CRPC	observation
2	M1 CRPC, no prior chemo, minimal sx	Abiraterone, Sipuleucel-T or docetaxel
3	M1 CRPC, no prior chemo, moderate sx, good performance status	Docetaxel, or Abiraterone, ketoconazole, xofigo
4	M1 CRPC, no prior chemo, moderate sx, poor performance status	Abiraterone, ketoconazole, xofigo, docetaxol
5	M1 CRPC, prior chemo, good performance status	Abiraterone, cabazitaxel or Enzalutamide
6	M1 CRPC, prior chemo, poor performance status	Palliative treatment

ADVANCED DISEASE: SYSTEMIC THERAPY



[c] See Principles of Imaging (PROS-B).

[k] Observation involves monitoring the course of disease with the expectation to deliver palliative therapy for the development of symptoms or a change in exam or PSA that suggests symptoms are imminent.
See Principles of Active Surveillance and Observation (PROS-C).

[r] High-volume disease is differentiated from low-volume disease by visceral metastases and/or 4 or more bone metastases, with at least one metastasis beyond the pelvis vertebral column.

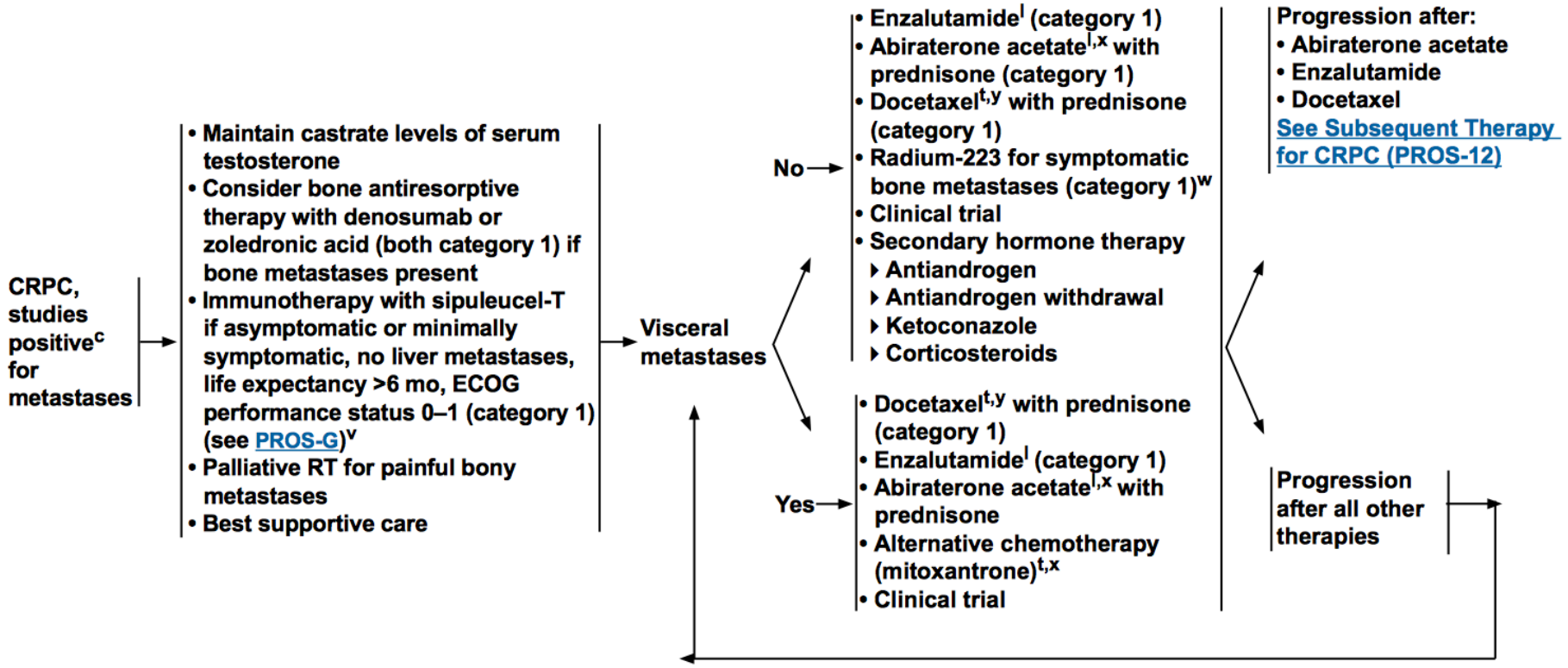
[s] Assure castrate level of testosterone.

[t] See Principles of Immunotherapy and Chemotherapy (PROS-G).

[u] See NCCN Guidelines for Small Cell Lung Cancer.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

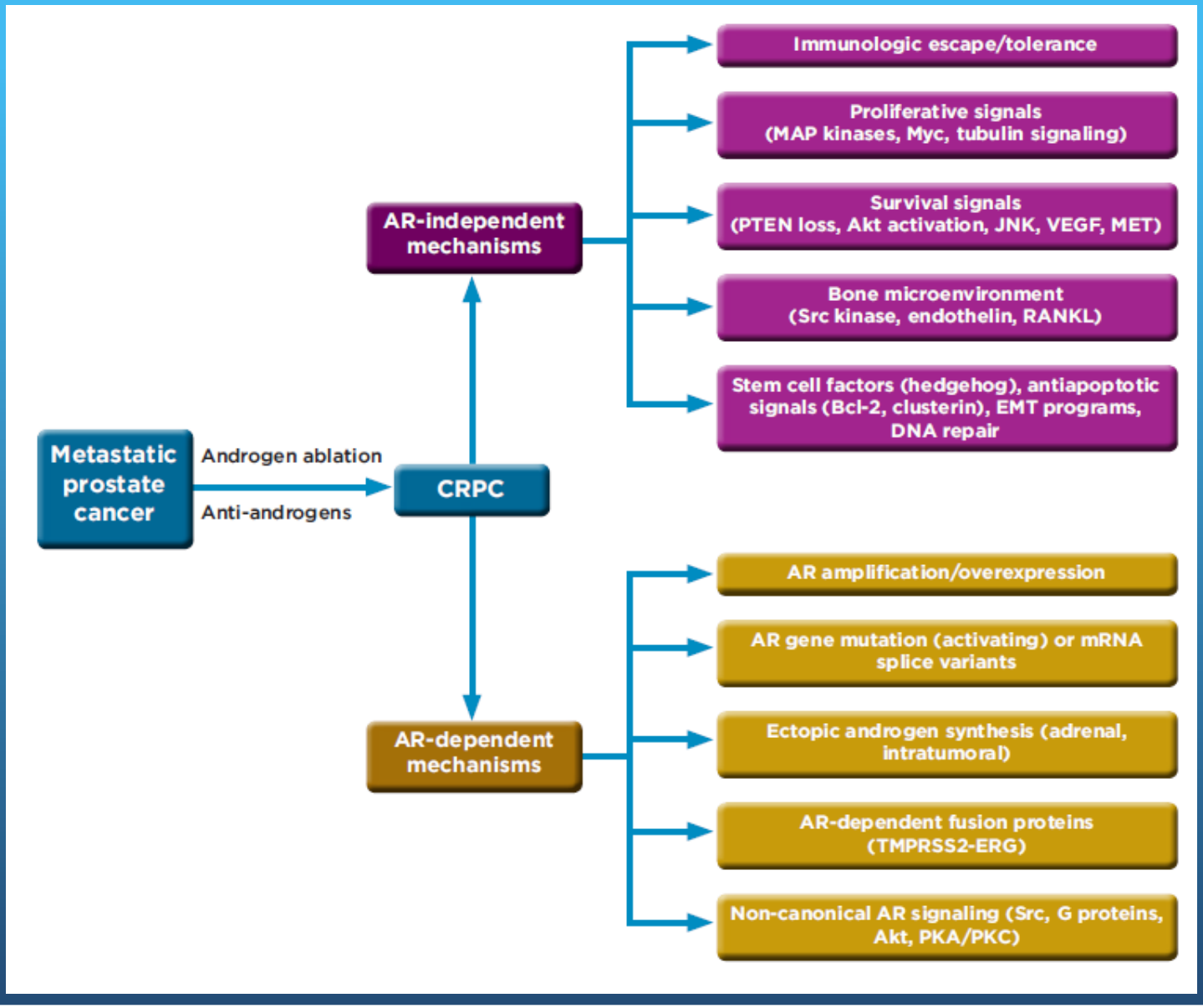
ADVANCED DISEASE: FIRST-LINE SYSTEMIC THERAPY FOR CRPC



[c] See Principles of Imaging (PROS-B).
[l] See Principles of Androgen Deprivation Therapy (PROS-F).
[t] See Principles of Immunotherapy and Chemotherapy (PROS-G).
[v] Sipuleucel-T has not been studied in patients with visceral metastases.
[w] Radium-223 is not approved for use in combination with docetaxel or any other chemotherapy. See Principles of Radiation Therapy (PROS-D, page 2 of 2).
[x] For patients who are not candidates for docetaxel-based regimens.
[y] Although most patients without symptoms are not treated with chemotherapy, the survival benefit reported for docetaxel applies to those with or without symptoms. Docetaxel may be considered for patients with signs of rapid progression or visceral metastases despite lack of symptoms.

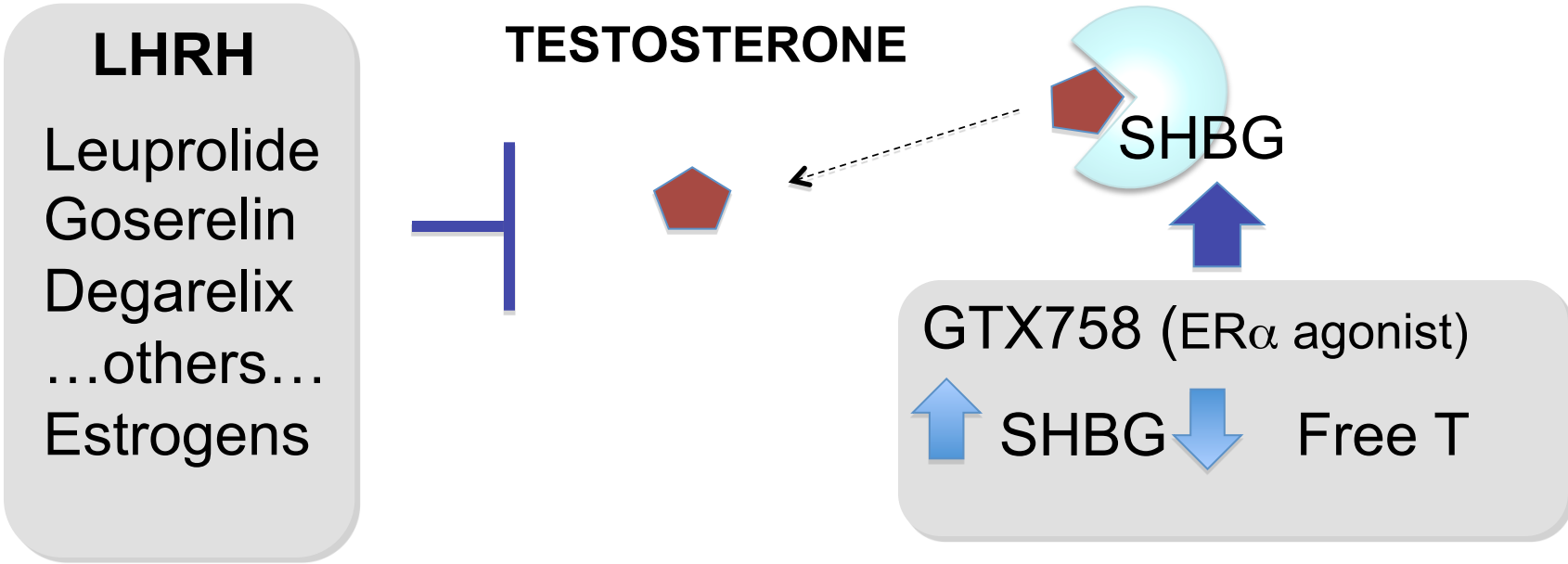
Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Biologic Mechanisms Driving CRPC



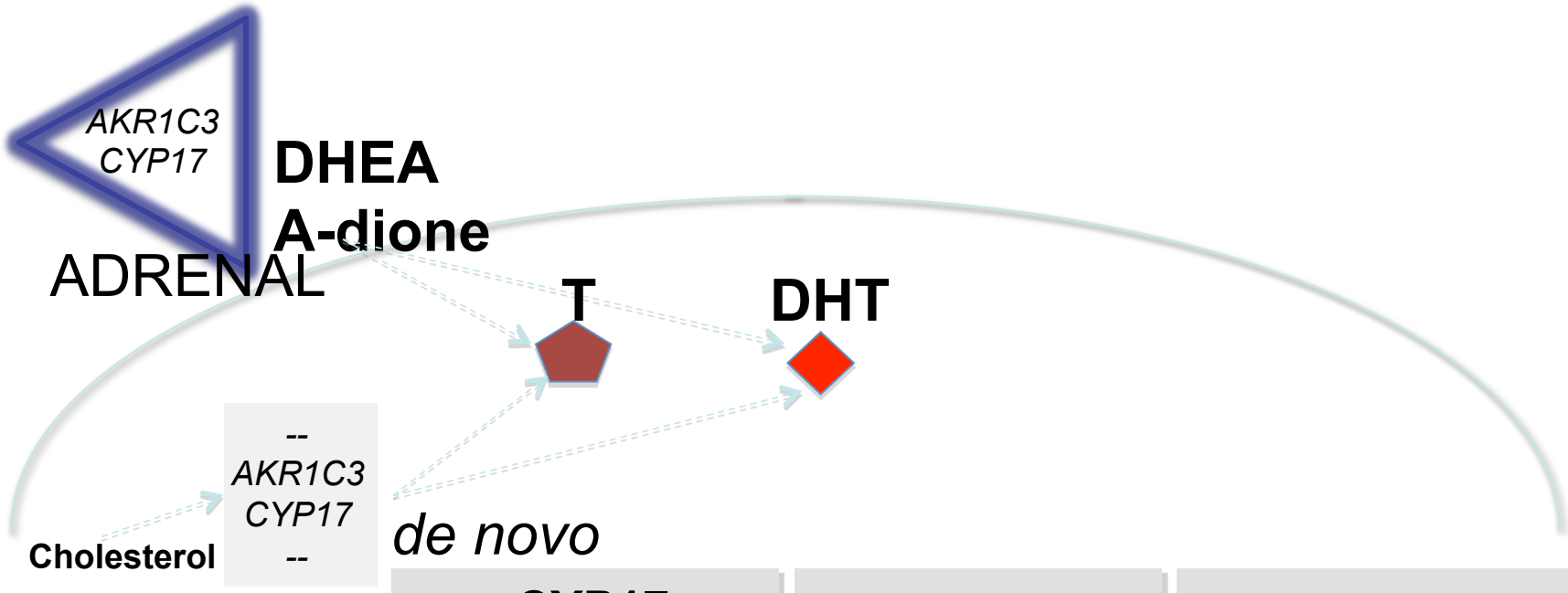
Antonarakis and Armstrong, Clin Oncol News 2011

Target 1: Gonadal/Circulating T



Modified from Peter Nelson, MD

Target 2: Adrenal/Intracrine Ligands



CYP17

- ✓ Ketoconazole
- ✓ Abiraterone
- ✓ TAK700
- ✓ TOK001
- ✓ VT-464

AKR1C3

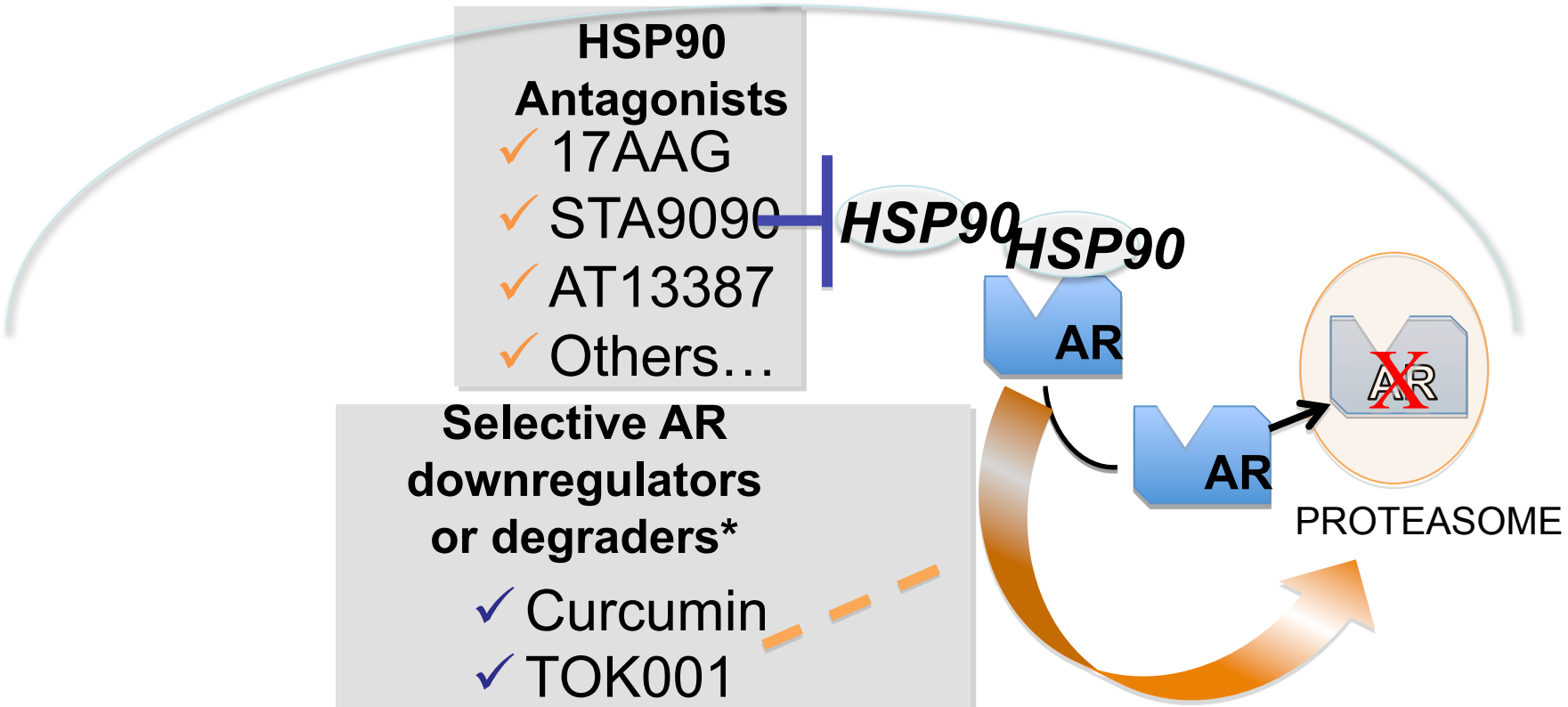
- ✓ Indomethacin
- ✓ I-analogs

3βHSD

- ✓ Abiraterone-HD
- ✓ Trilostane

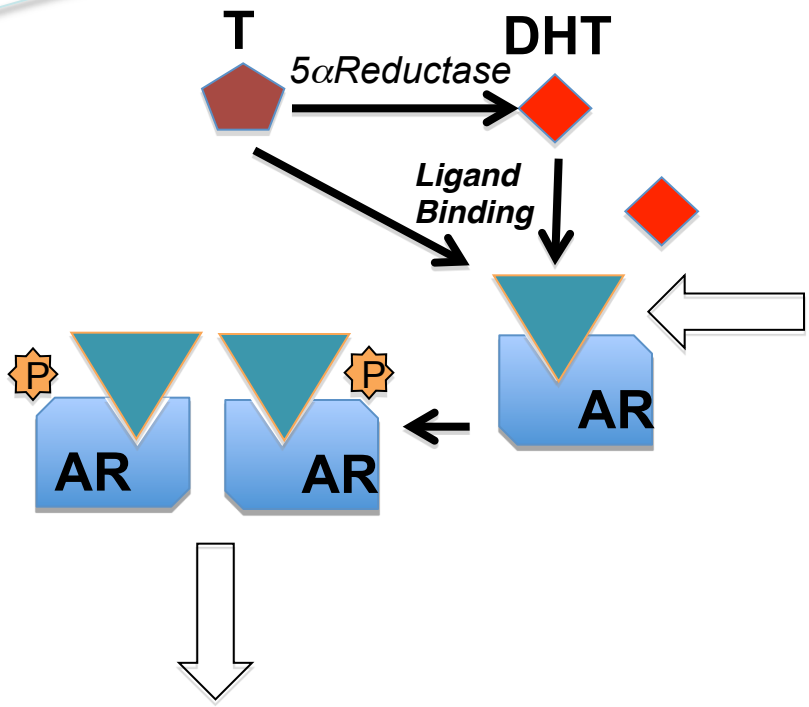
Modified from Peter Nelson, MD

Target 3: AR Degradation



Modified from Peter Nelson, MD

Target 4: Androgen Receptor Blockade



Competitive Antagonists

Flutamide
Bicalutamide
Nilutamide
Enzalutamide
ARN509
TOK001

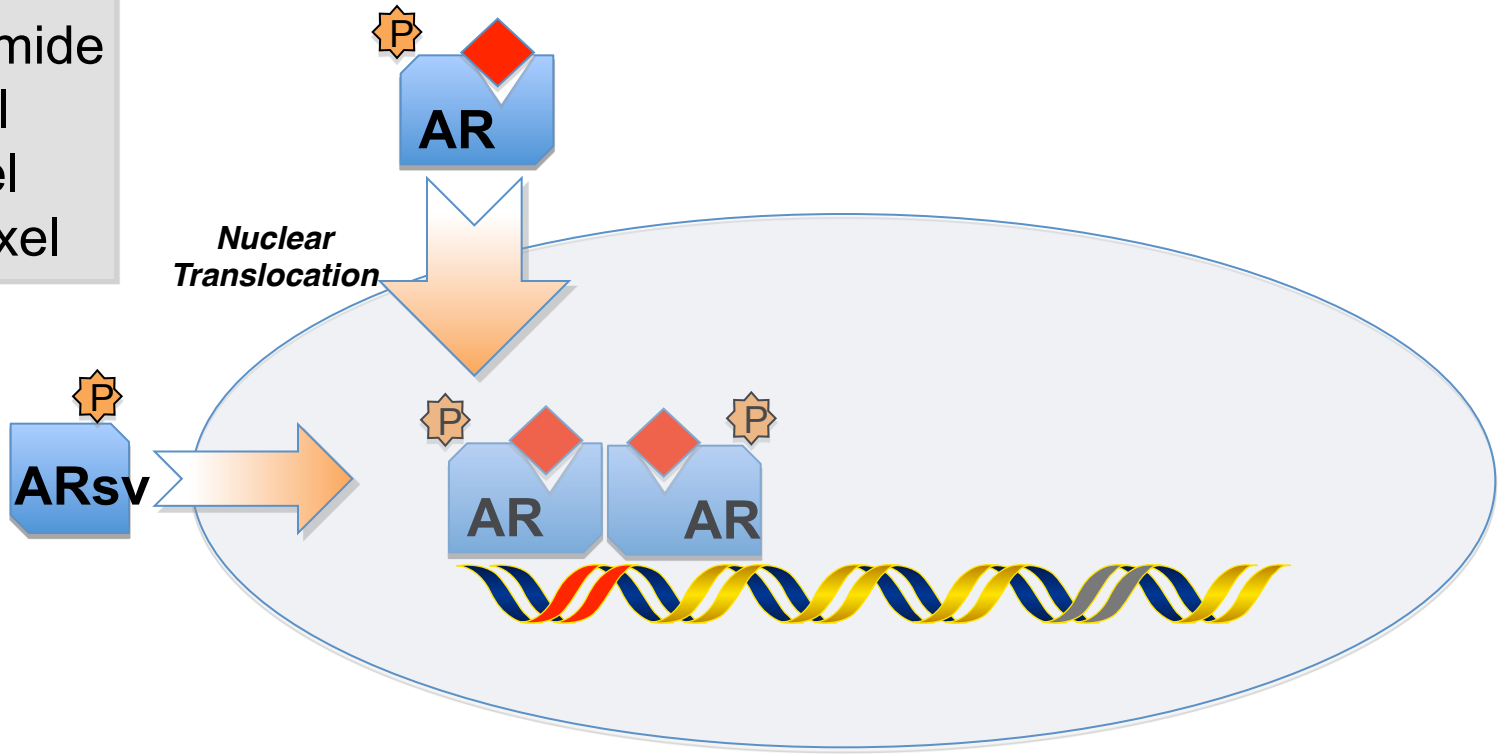
- ✓ *enhanced degradation*
- ✓ *translocation block*
- ✓ *unproductive transcription*

Modified from Peter Nelson, MD

Target 5: Prevent AR Nuclear Translocation

Microtubule Inhibitors

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

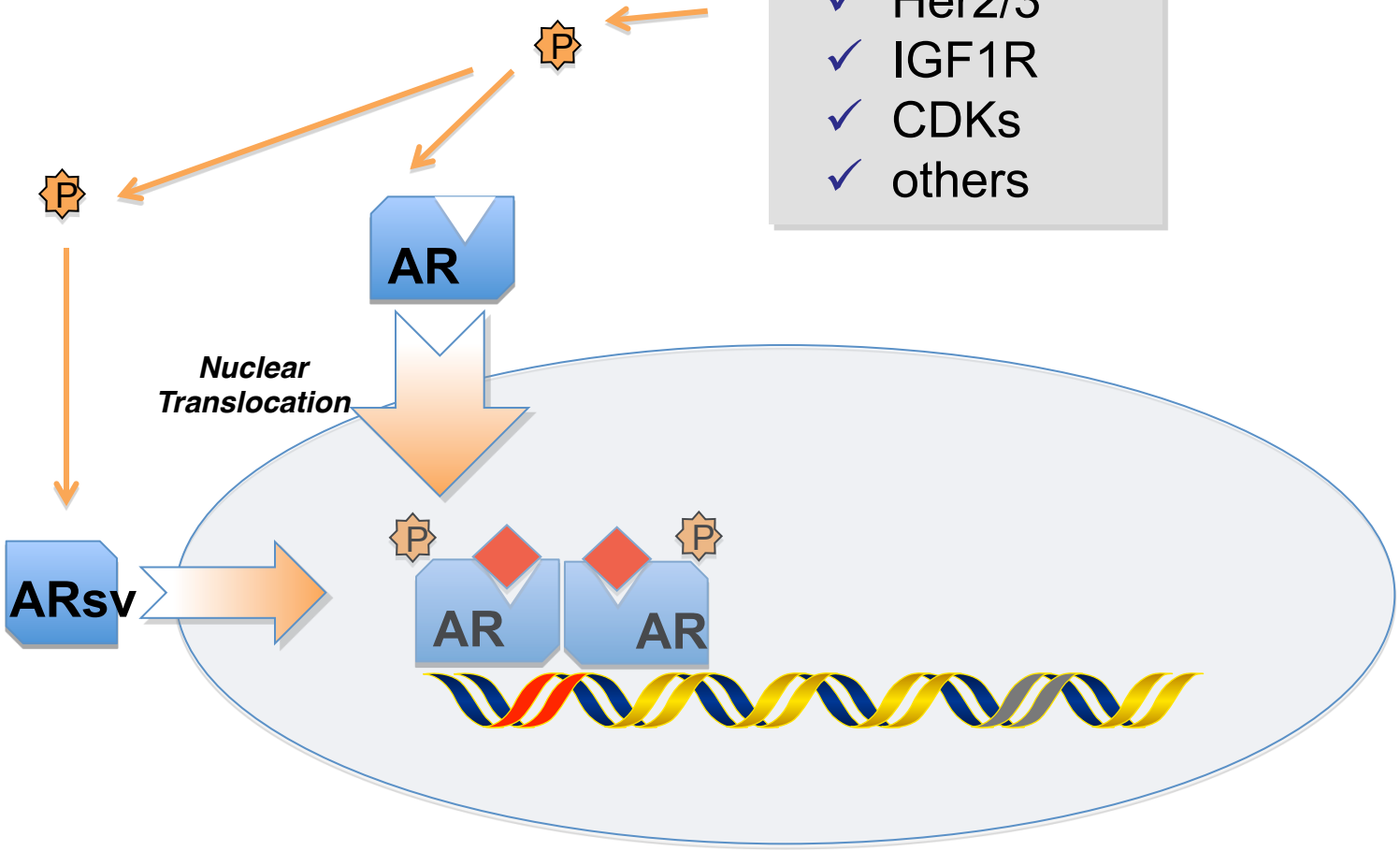


Modified from:Peter Nelson, MD

Target 6: Interfere With AR 'Enablers'

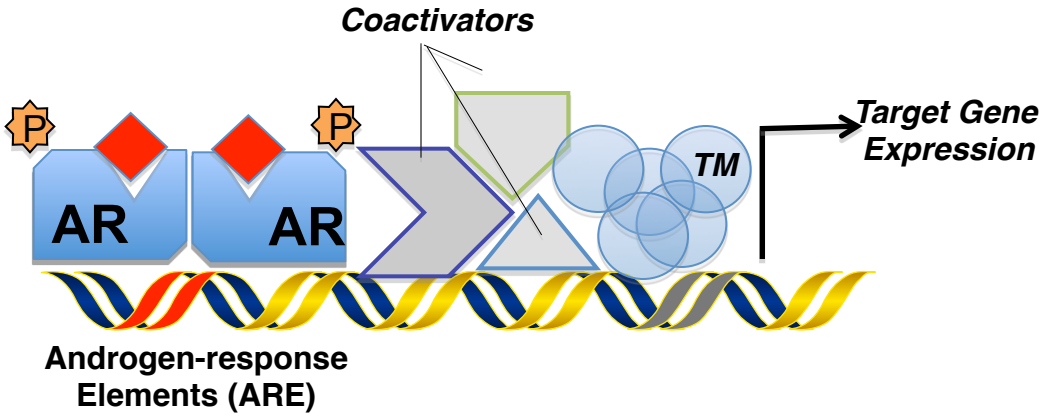
Signaling Pathways

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



Modified from:Peter Nelson, MD

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



Important as they may target ARsv

Non-Competitive Antagonists*

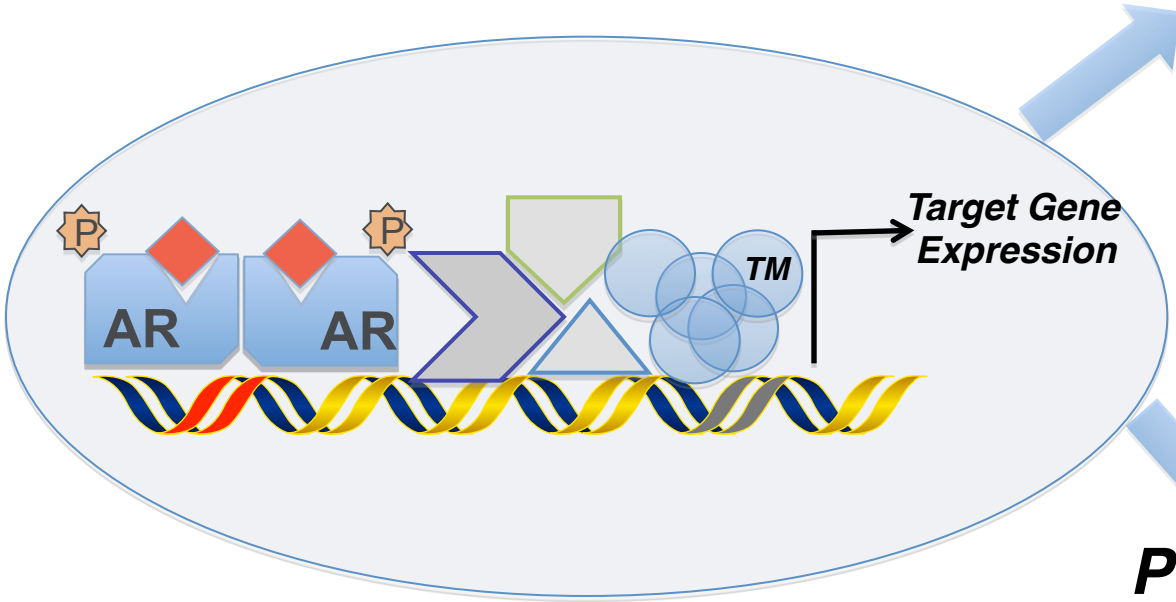
EPI-001
'D2'
Pyrivinium
Harmol HCL
Others

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

Modified from Peter Nelson, MD

Target 8: AR Downstream ‘Effectors’

PI3K-Pathway Inhibitors



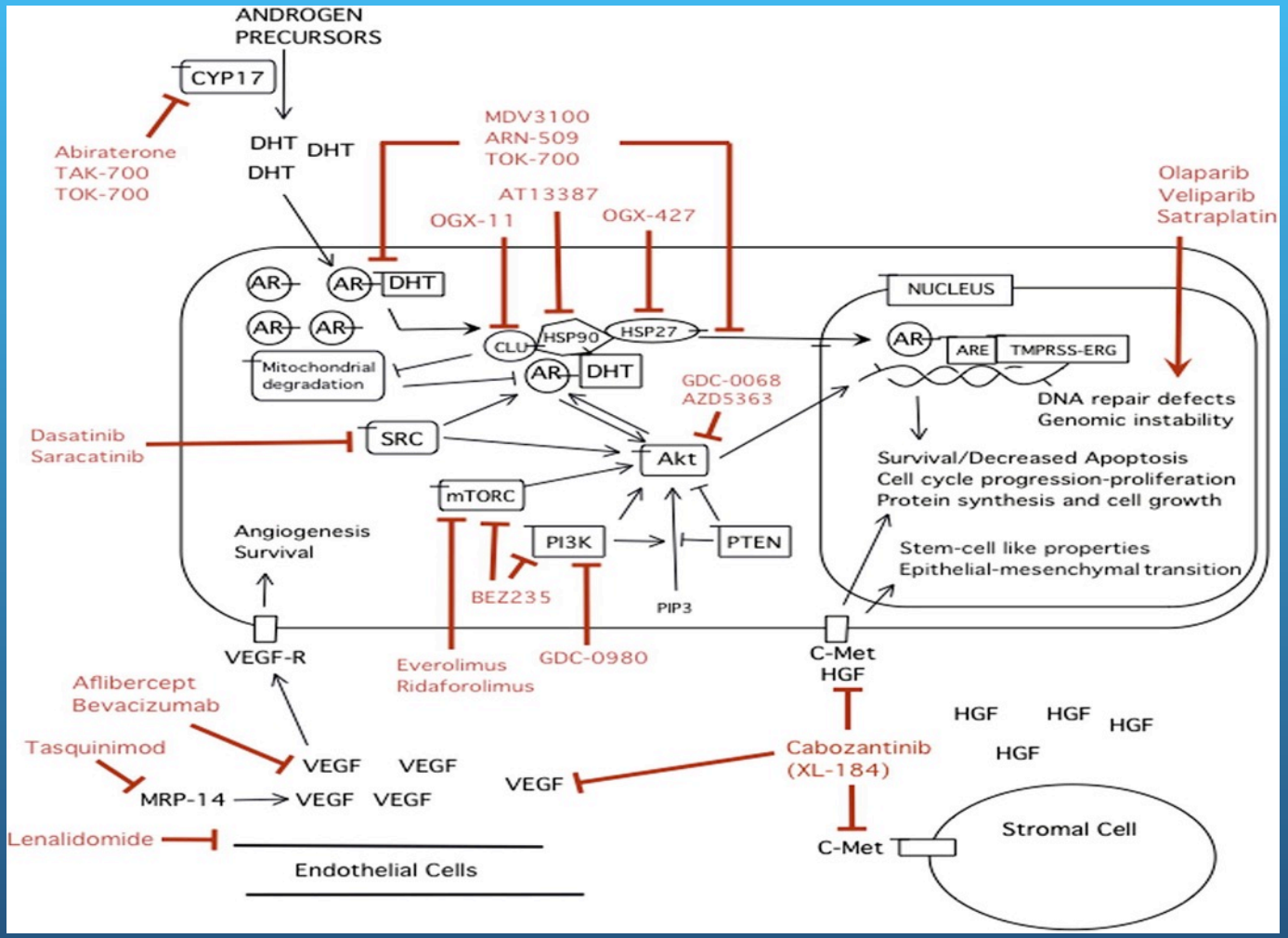
ETS-family Inhibitors

Proliferation
Survival
Metabolism

CAMKK2 inhibitor (STO-609)

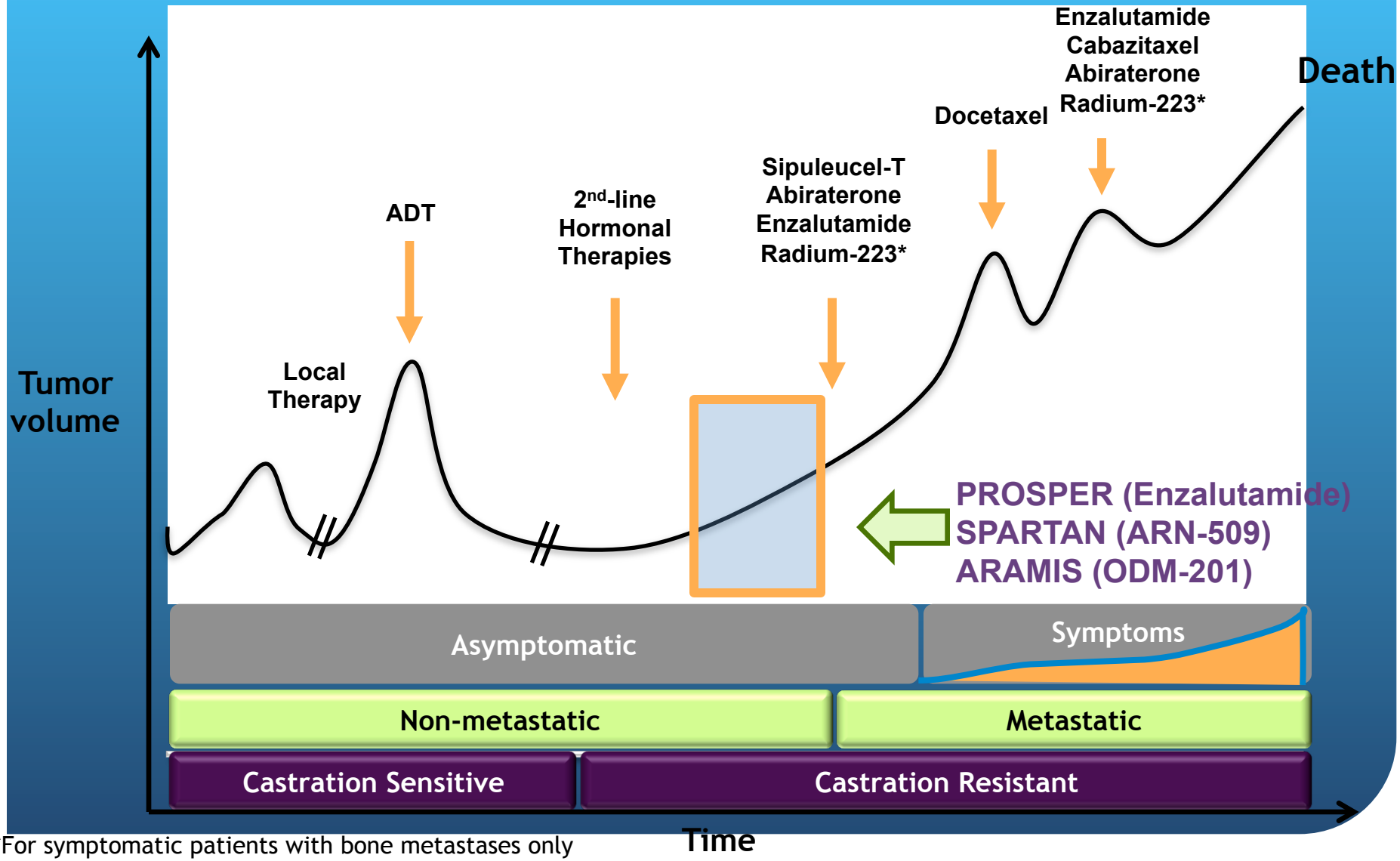
Modified from Peter Nelson, MD

Sequence or Layering?



D. Lorente, J.S. De Bono, Eur J Cancer 2014;50:753

M0 CRPC
An unmet need in Prostate Cancer



*For symptomatic patients with bone metastases only

Sequencing Trials

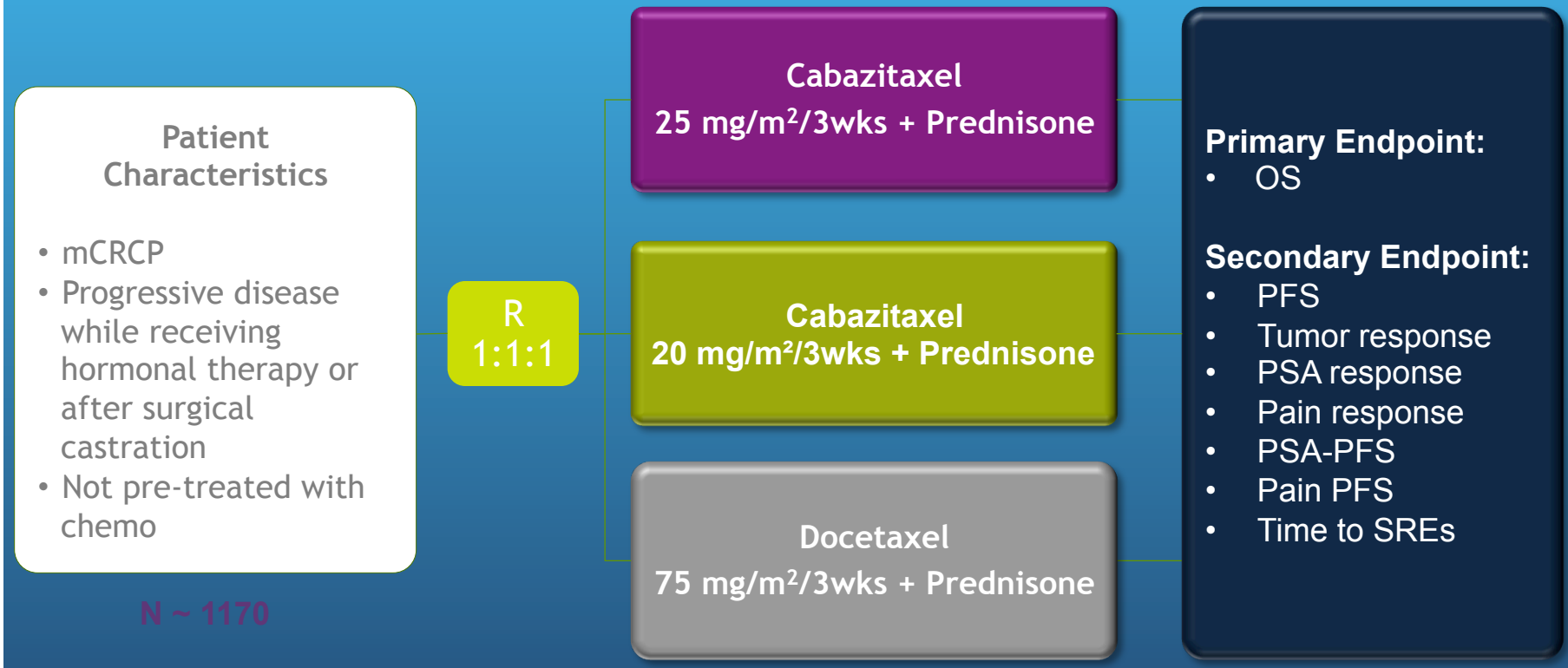
Dendreon-sponsored Trials

Trial	Ph	Basic Design	Findings to date
STAND: A randomized, open-label, phase 2 trial examining the sequencing of sipuleucel-T and androgen deprivation therapy in men with non-metastatic prostate cancer and a rising serum prostate specific antigen after primary therapy[1]	2	• Randomized • Non-metastatic hormone-sensitive PCa with rising PSA • 1° outcome measure– immune responses following sipuleucel-T → ADT vs. ADT → sipuleucel-T	• Feasible and tolerable • Sipuleucel-T → ADT appeared to induce stronger T cell responses than ADT → sipuleucel-T • However, Both treatment sequences resulted in strong, sustained immune memory 2 years after sipuleucel-T (*Manuscript in progress)*
STAMP: A randomized, open-label, phase 2 trial of sipuleucel-T with concurrent versus sequential administration of abiraterone acetate plus prednisone in men with metastatic castrate resistant prostate cancer[2]	2	• Randomized • Asymptomatic to minimally symptomatic mCRPC • 1° outcome measure- effect of AA + P on sipuleucel-T manufacture	• Sipuleucel-T can be manufactured during concurrent administration • No blunting of immunologic effects or immune parameters that correlate with sipuleucel-T clinical benefit • No new safety signals from combination *(Published in CCR)*
STRIDE: A randomized, open label, phase 2 study of sipuleucel-T with concurrent versus sequential administration of enzalutamide in men with metastatic castrate-resistant prostate cancer[3]	2	• Randomized • Asymptomatic to minimally symptomatic mCRPC • 1° outcome measure – immune responses following sipuleucel-T with concurrent or sequential ENZ	• Order of Sipuleucel-T and ENZ had no effect on sipuleucel-T manufacture or immune responses • No new safety signals associated with the combination *(Trial still in progress)*

AA=abiraterone acetate; AA + P=abiraterone acetate plus prednisone; ADT=androgen deprivation therapy; ENZ=enzalutamide; mCRPC=metastatic castration-resistant prostate cancer; PCa=Prostate cancer; PSA=prostate specific antigen

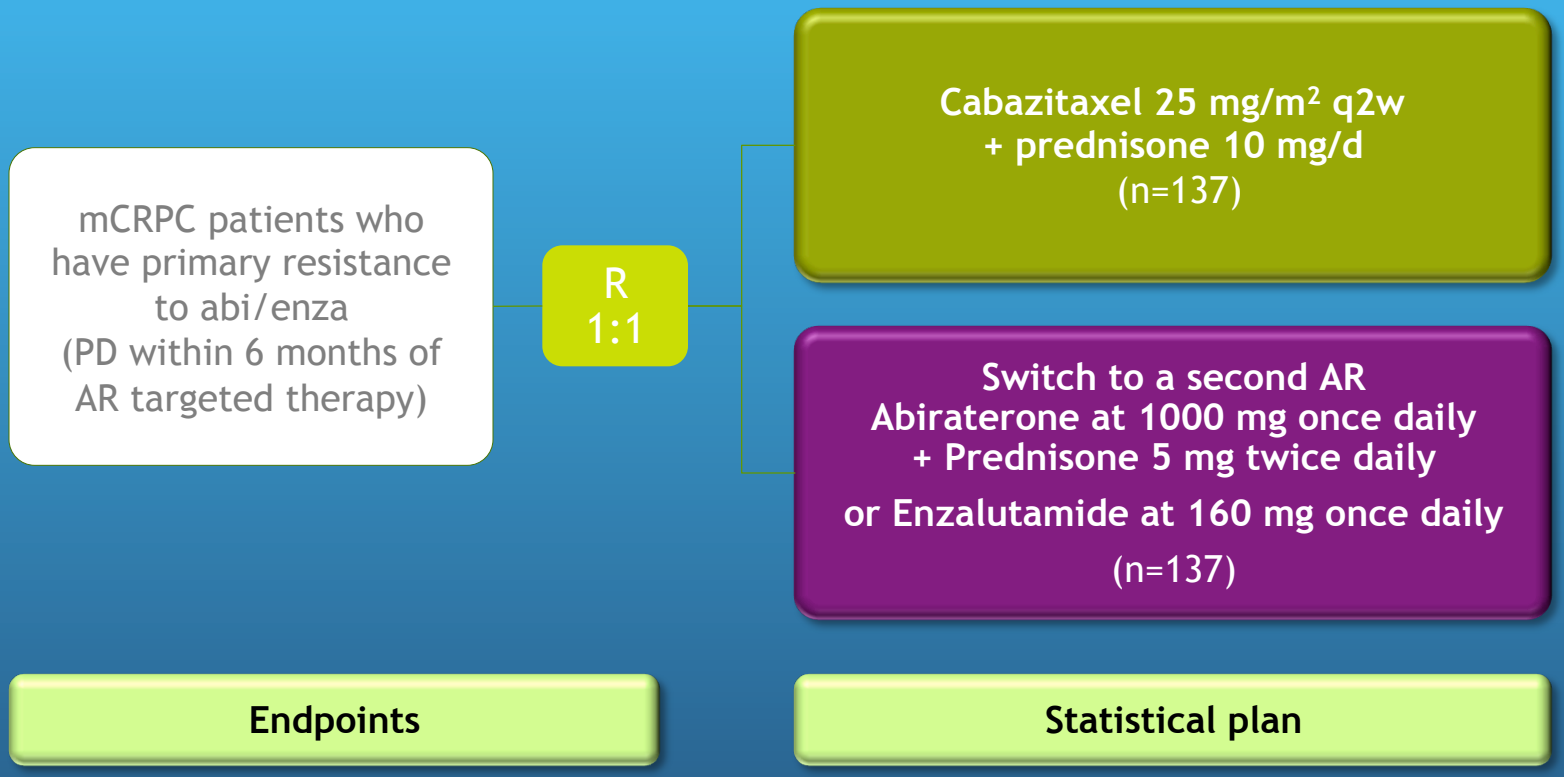
1) Drake, et al. ESMO 2014, Abstract. 2) Small, et al. Clinical Cancer Research, 2015. 3) Pieczonka, et al. Abstract. SUO, 2015.

Docetaxel or Cabazitaxel FIRST ?
FIRSTANA Trial



https://clinicaltrials.gov; Identifier: NCT01308567

POST ABI/ENZA
PRIMCAB: Study design



Endpoints

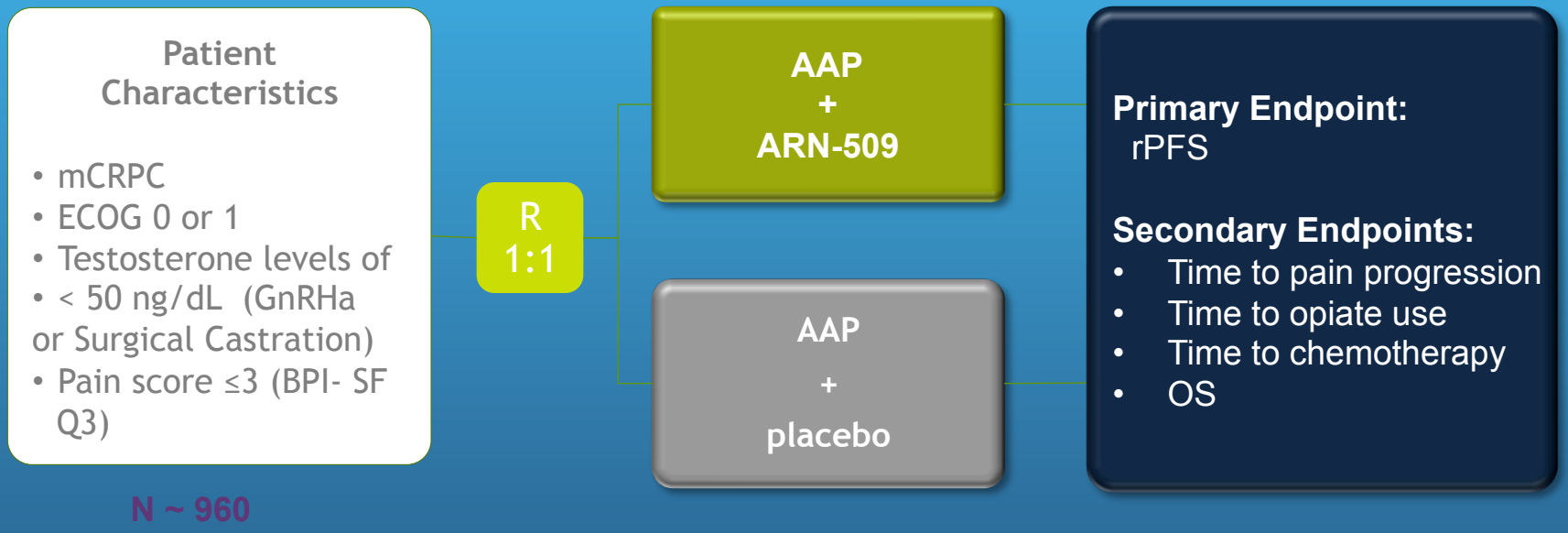
- Primary : rPFS
- Main Secondary : OS, TTPP, Safety

Statistical plan

- *Superiority design with assumption of HR=0.67*

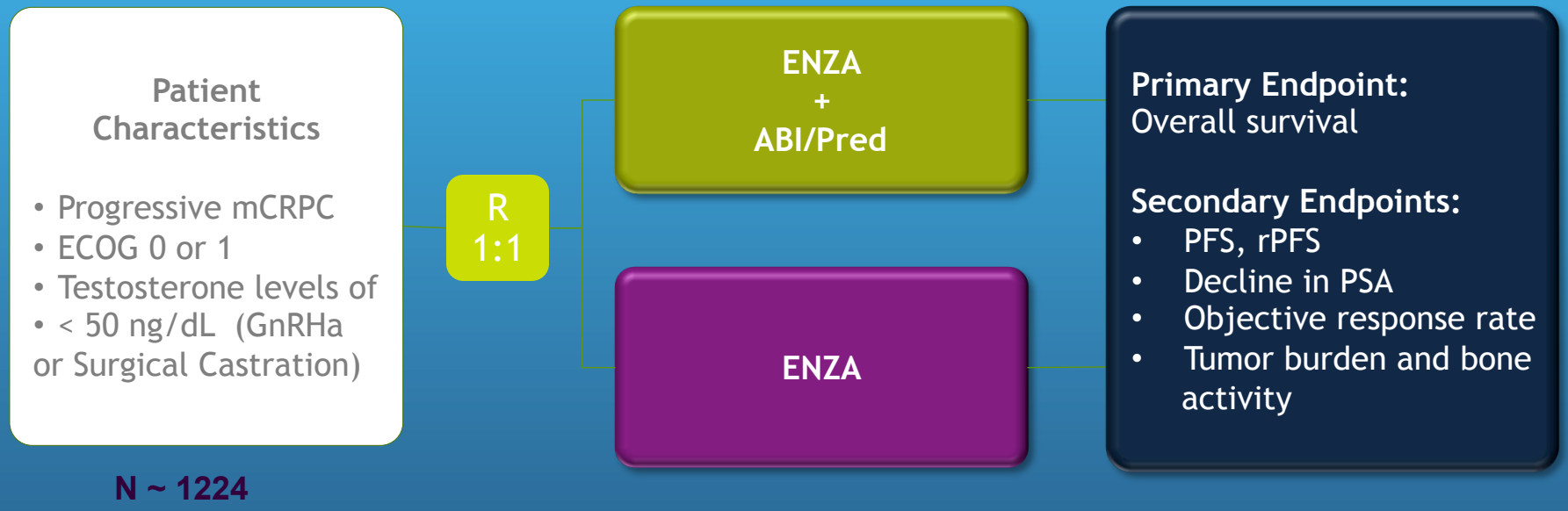
https://clinicaltrials.gov/ct2/show/NCT02379390

Targeting androgen production and AR
Abiraterone +/- ARN-509 in mCRPC



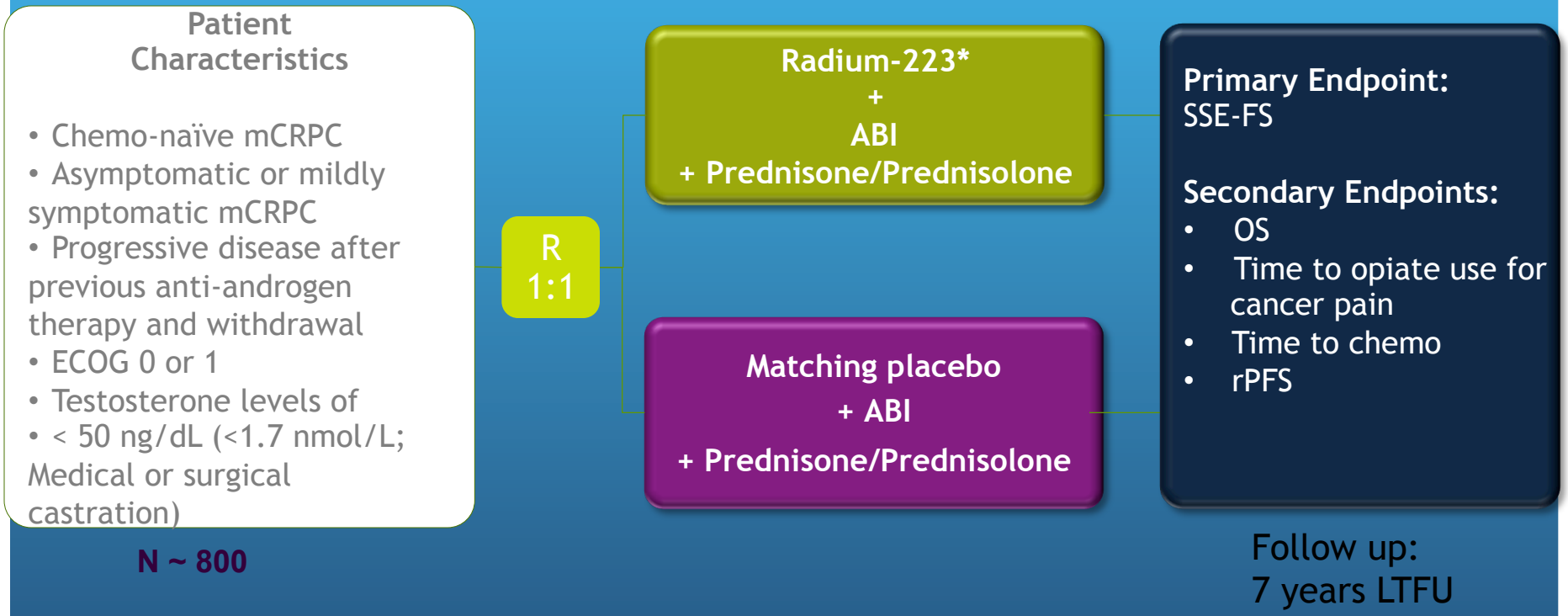
Slide courtesy of Dr. Fred Saad; trial info not yet publicly available

Targeting androgen production and AR: Enza +/- Abiraterone/Pred in mCRPC



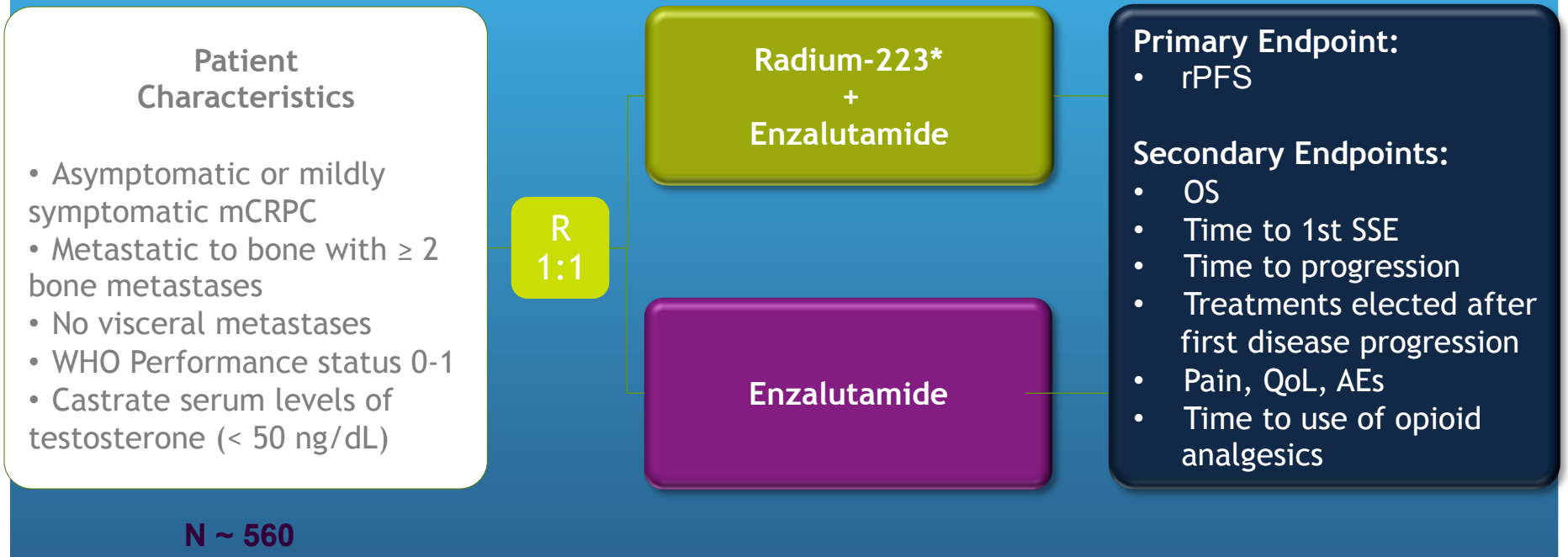
https://clinicaltrials.gov; Identifier: NCT01949337

Targeting Androgen Production and Bone: Abiraterone +/- Radium 223 (ERA-223 trial)



Abi, abiraterone; Enza, Enzalutamide; SSE-FS, Symptomatic skeletal event free survival, time frame 3 years
*50 KBq/Kg/4wks X 6 IV
https://clinicaltrials.gov; Identifier: NCT02043678

Targeting the Androgen Receptor and Bone
Enzalutamide +/- Radium 223 (PEACE III trial)



SSE, symptomatic skeletal event
*50 KBq/Kg/4wks X 6 IV
https://clinicaltrials.gov; Identifier: NCT02194842

Novel Therapies in Clinical Trials

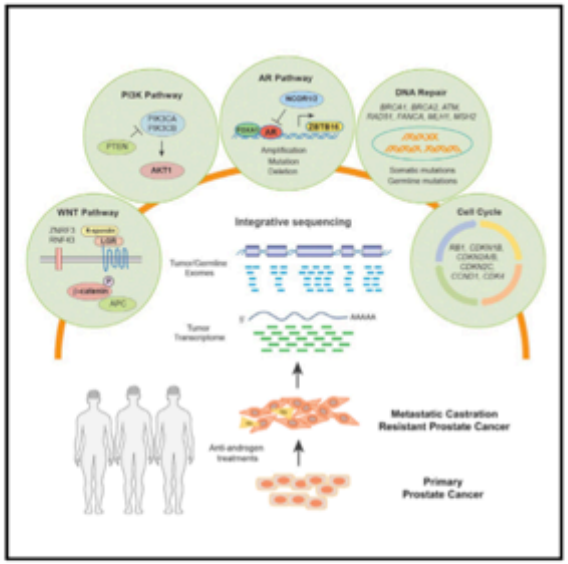
Estimated	~2017	~2015/16	~2017	~2015	~2017/18	~2019
	tōkai	Active Biotech / IPSEN	BAVARIAN NORDIC	Bristol-Myers Squibb	janssen	Sotio
Compound	**Galeterone***	**Tasquinimod[1]**	**PROSTVAC[2]**	**Ipilimumab[3]**	**ARN 509[4]**	**DCVAC/PCa[5]**
Brand	TBD	TBD	TBD	Yervoy	TBD	TBD
MOA	CYP17 inhibition, AR antagonism, AR degradation	Angiogenesis inhibitor, immunomodulator	Active immunotherapy	Immune checkpoint inhibitor	Hormonal agent	Active immunotherapy
Potential Label	mCRPC (AR-SV positive)	mCRPC (asymptomatic)	mCRPC (asymptomatic or minimally symptomatic)	mCRPC (chemother-apy naive)	M0 CRPC	mCRPC (with chemotherapy)
Key Clinical Benefits (phase 2) (median PFS, OS [mPFS, mOS])	• PSA response mCRPC: 85% PSA30; 77% PSA50 • PSA50 in 6 of 7 patients with AR C-term loss	• mPFS 7.6 m vs 3.3 m • 6-month PFS 69% vs 37%	• mOS 25.1 m vs 16.6 m • PFS 3.8 m vs 3.7 m	• mOS 26.3 m vs 17.2 m predicted	• 91% PSA response rate in high-risk M0 CRPC	• mOS 19 m vs 12 m predicted
Delivery	Oral	Oral	SC injections	IV	Oral	SC injections
Frequency	Daily	Daily	7 SC injections over 5 months	≤4 doses at 3-week intervals; q12 week maintenance	Daily	12 SC injections over 11 months (based on phase 2)

AR, androgen receptor; IV, intravenous; SC, subcutaneous.; *study details phase III trial not yet publicly available;

Cell

Integrative Clinical Genomics of Advanced Prostate Cancer

Graphical Abstract



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In Brief

A multi-institutional integrative clinical sequencing analysis reveals that the majority of affected individuals with metastatic castration-resistant prostate cancer harbor clinically actionable molecular alterations, highlighting the need for genetic counseling to inform precision medicine in affected individuals with advanced prostate cancer.

Highlights

- A multi-institutional integrative clinical sequencing of mCRPC
- Approximately 90% of mCRPC harbor clinically actionable molecular alterations
- mCRPC harbors genomic alterations in *PIK3CA/B*, *RSPO*, *RAF*, *APC*, β-catenin, and *ZBTB16*
- 23% of mCRPC harbor DNA repair pathway aberrations, and 8% harbor germline findings

Robinson et al., 2015, Cell *161*, 1215–1228
May 21, 2015 ©2015 Elsevier Inc.
http://dx.doi.org/10.1016/j.cell.2015.05.001

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JOURNAL OF CLINICAL ONCOLOGY

REVIEW ARTICLE

Advancing Precision Medicine for Prostate Cancer Through Genomics

Sameek Roychowdhury and Arul M. Chinnaiyan

All authors: University of Michigan and Michigan Center for Translational Pathology, Ann Arbor, MI.

Published online ahead of print at www.jco.org on April 15, 2013.

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0732-183X/13/3115w-1866w/$20.00

DOI: 10.1200/JCO.2012.45.3662

ABSTRACT

Prostate cancer is the most common type of cancer in men and the second leading cause of cancer death in men in the United States. The recent surge of high-throughput sequencing of cancer genomes has supported an expanding molecular classification of prostate cancer. Translation of these basic science studies into clinically valuable biomarkers for diagnosis and prognosis and biomarkers that are predictive for therapy is critical to the development of precision medicine in prostate cancer. We review potential applications aimed at improving screening specificity in prostate cancer and differentiating aggressive versus indolent prostate cancers. Furthermore, we review predictive biomarker candidates involving *ETS* gene rearrangements, *PTEN* inactivation, and androgen receptor signaling. These and other putative biomarkers may signify aberrant oncogene pathway activation and provide a rationale for matching patients with molecularly targeted therapies in clinical trials. Lastly, we advocate innovations for clinical trial design to incorporate tumor biopsy and molecular characterization to develop biomarkers and understand mechanisms of resistance.

J Clin Oncol 31:1866-1873. © 2013 by American Society of Clinical Oncology

INTRODUCTION

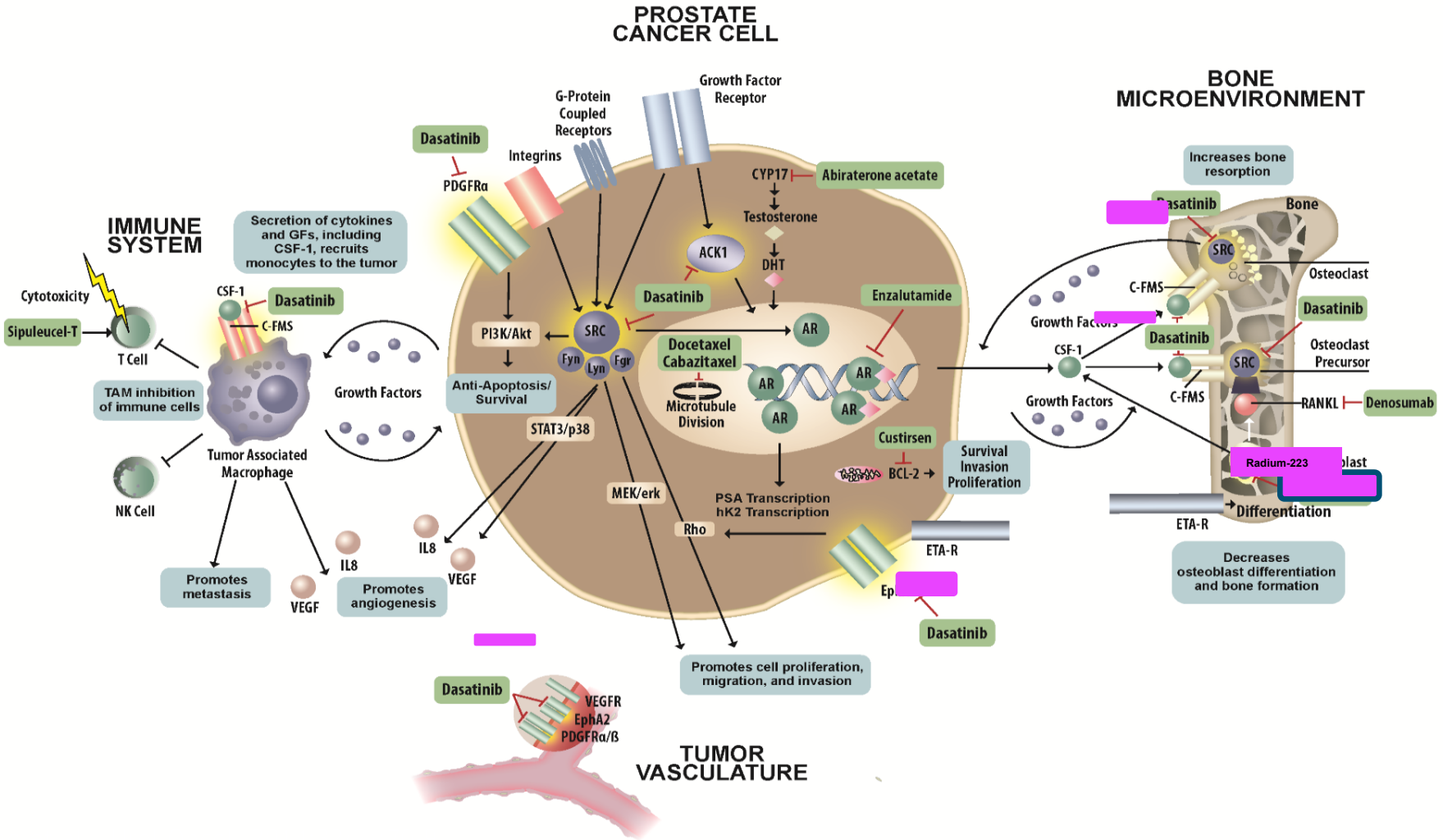
Prostate cancer is the most common nonskin cancer and the second leading cause of cancer death in men in the United States.[1,2] Although there has been significant progress in the treatment of prostate cancer, with the approval of three new therapies for metastatic prostate cancer[3] this year, several challenges persist such as a means to match patients with targeted therapies and the implementation of rational combination therapies. The Institute of Medicine recently critiqued the cooperative clinical trial groups in oncology and recommended innovative trial design through the incorporation of predictive biomarker stratification for patient selection.[4] A molecular classification of cancer has the potential benefits of improving response, minimizing the time and adverse effects of treating patients with ineffective therapies, and reducing the sample size needed to show efficacy. High-throughput sequencing technologies have accelerated the molecular characterization of prostate cancer and positioned opportunities for development of precision medicine for therapeutic decision making in this disease. Here we examine the current data on molecular alterations in prostate cancer, the progress in translating these findings into the clinic, and the challenges that lay ahead for translational genomics in prostate cancer.

Genomic results have the potential to be translated clinically as diagnostic, prognostic, or predictive biomarkers. Diagnostic biomarkers facilitate obtaining an accurate cancer diagnosis as part of screening or confirmatory testing. Prognostic biomarkers provide data on risk of disease progression or morbidity and thereby help determine which patients need additional treatment, such as Gleason score 6 (low risk) versus 8 (high risk) prostate cancer. Predictive biomarkers suggest a course of therapeutic action. Here we provide examples, including early potential of *ETS* gene rearrangements as a diagnostic biomarker, and comment on novel approaches to prognostic biomarker development. Germline line mutations have the potential to be diagnostic, prognostic, or predictive and are discussed in another review in *Journal of Clinical Oncology*. Finally, we focus our attention on an in-depth review of putative predictive biomarkers for molecularly targeted therapies in clinical trials.

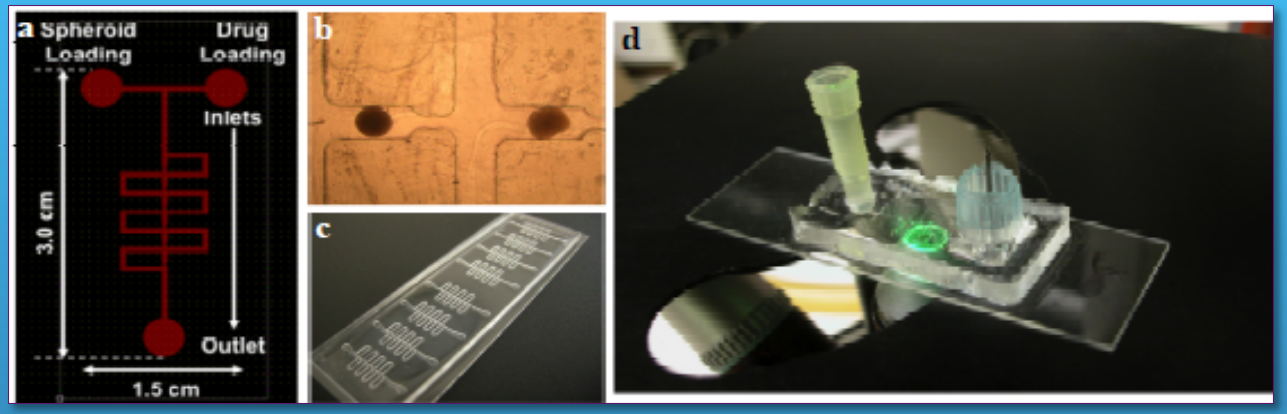
ETS GENE FUSIONS AND URINE TESTING

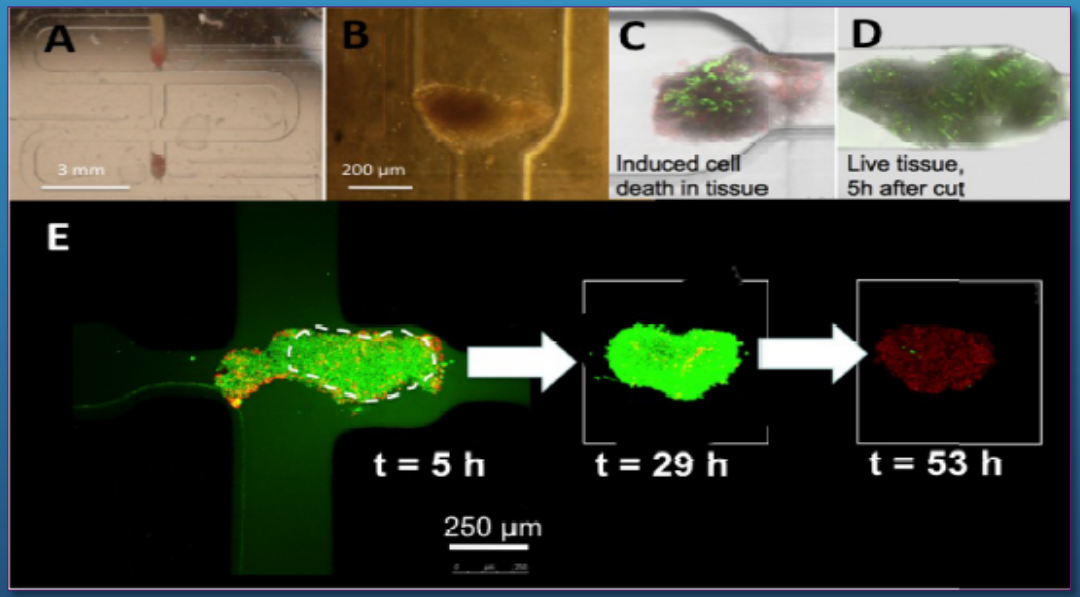
Gene fusions in prostate cancer were first described in 2005 using a bioinformatics approach that detected outlier transcript expression of genes with microarrays.[5,6] The most common chromosomal rearrangements involve the 5′ untranslated region of the androgen-regulated gene *TMPRSS2* and

FUTURE
Novel and Multi Modal Therapy



Predicting response to therapy
Microfluidic platform

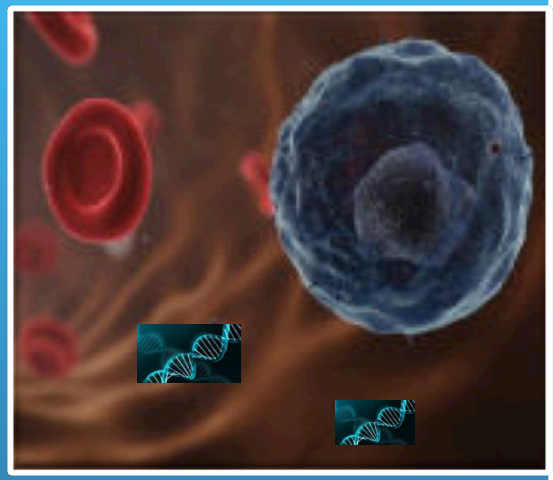


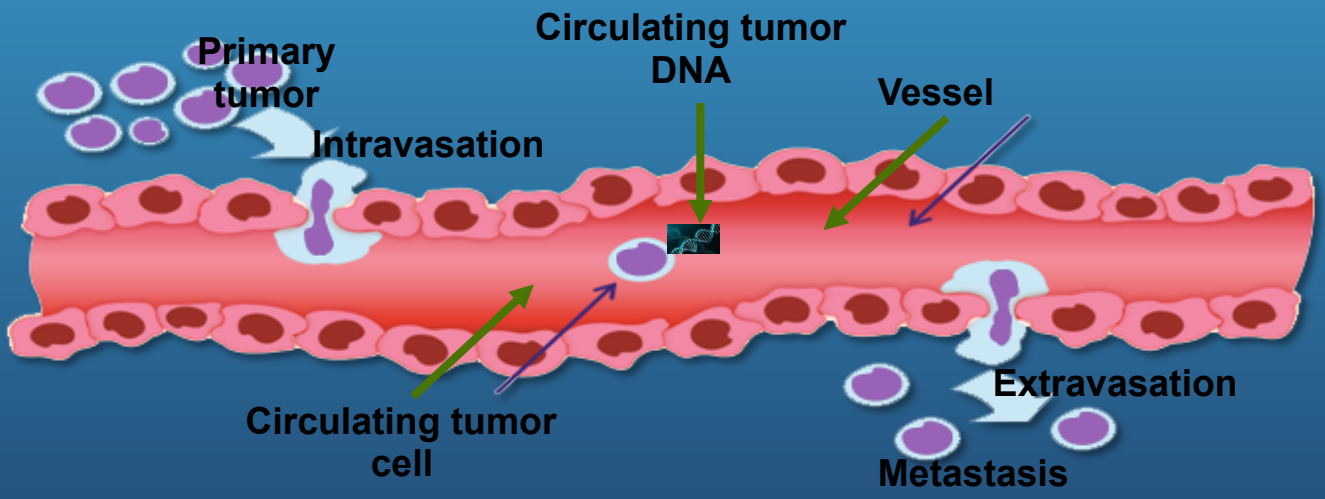


Images courtesy of Dr. Fred Saad

Circulating Tumor Cells and Circulating DNA: The future ?

- Cancer phenotyping
- Personalizing therapy
- Treatment response marker





Medical management of mCRPC– 2016

- Where we have been
  - 1 modern chemotherapy drug with a clear survival benefit (docetaxel, 2004)
- Where we are
  - 5 newly approved PCA agents in 24-month period
- Where we are going
  - Optimal timing and use (combination) of these new therapies

ARTICLE | April 1973

A 25-Year Experience With Vagotomy-Antrectomy

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

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

ABSTRACT

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

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