Targeting the Androgen Receptor: Implications and Resistance

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August 13, 2018

Disclosures

- Consultant: Dendreon, CUSP, Integra Connect, Cellay, Astellas
- Speakers Bureau: Dendreon, Astellas, Pfizer, Amgen

STUDIES ON PROSTATIC CANCER

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

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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

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From the Department of Surgery, University of Chicago.

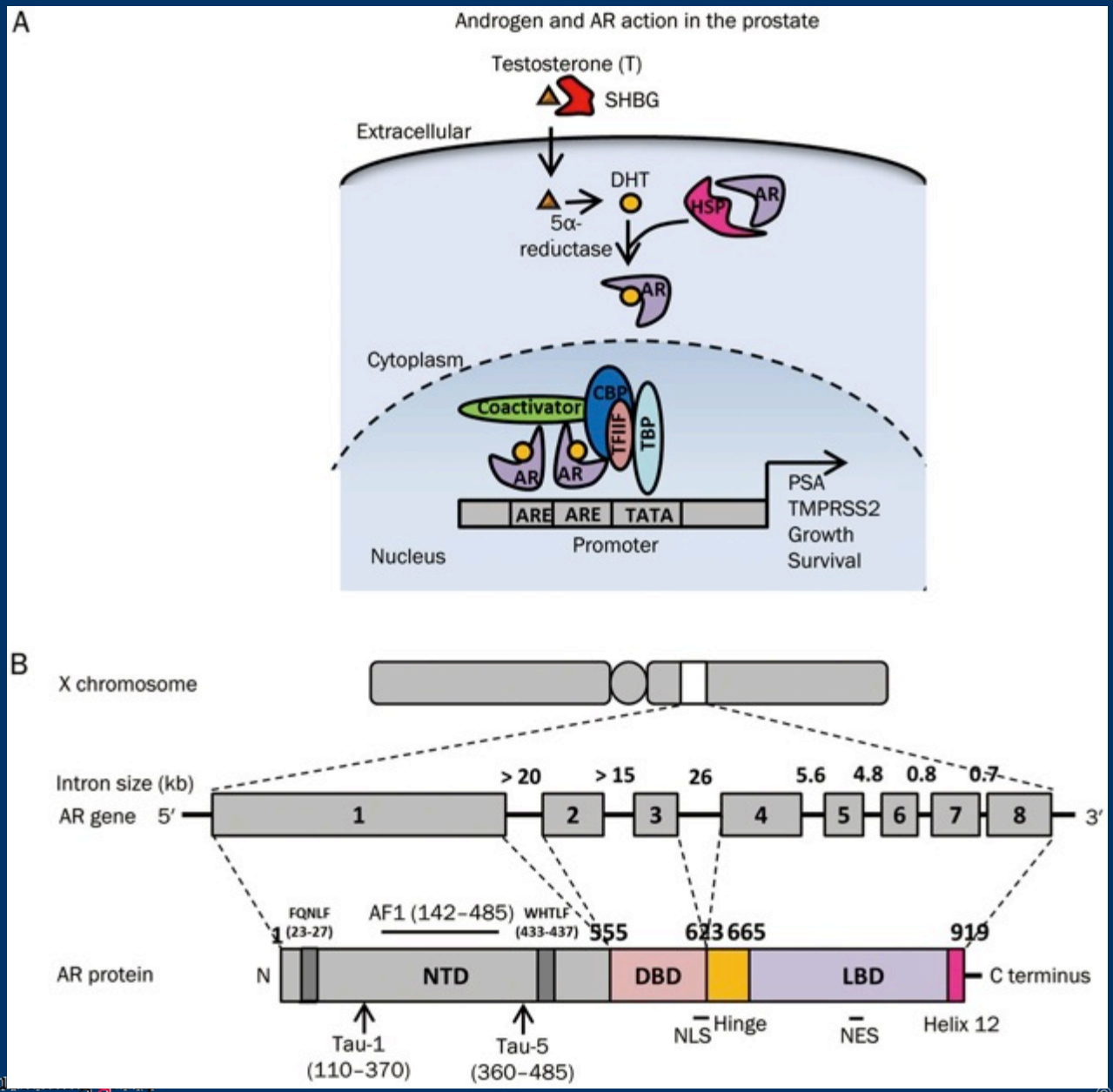
Dr. Hodges is a Fellow of the Douglas Smith Foundation for Medical Research of the University of Chicago.

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



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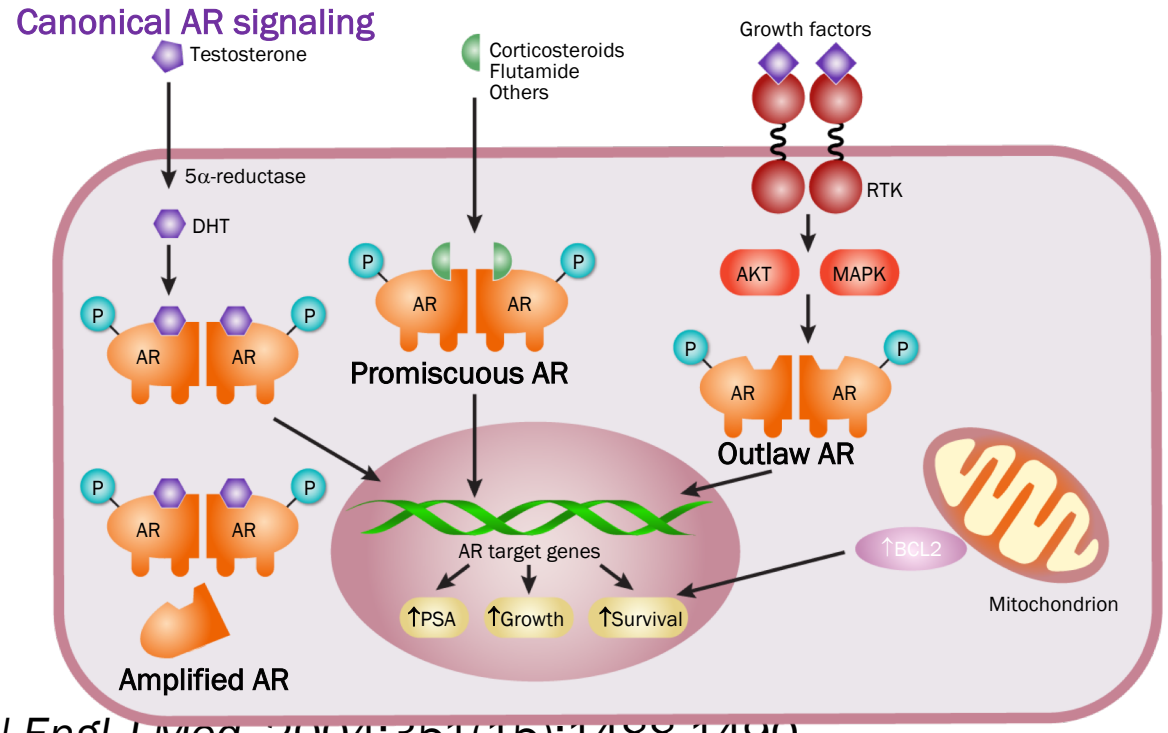
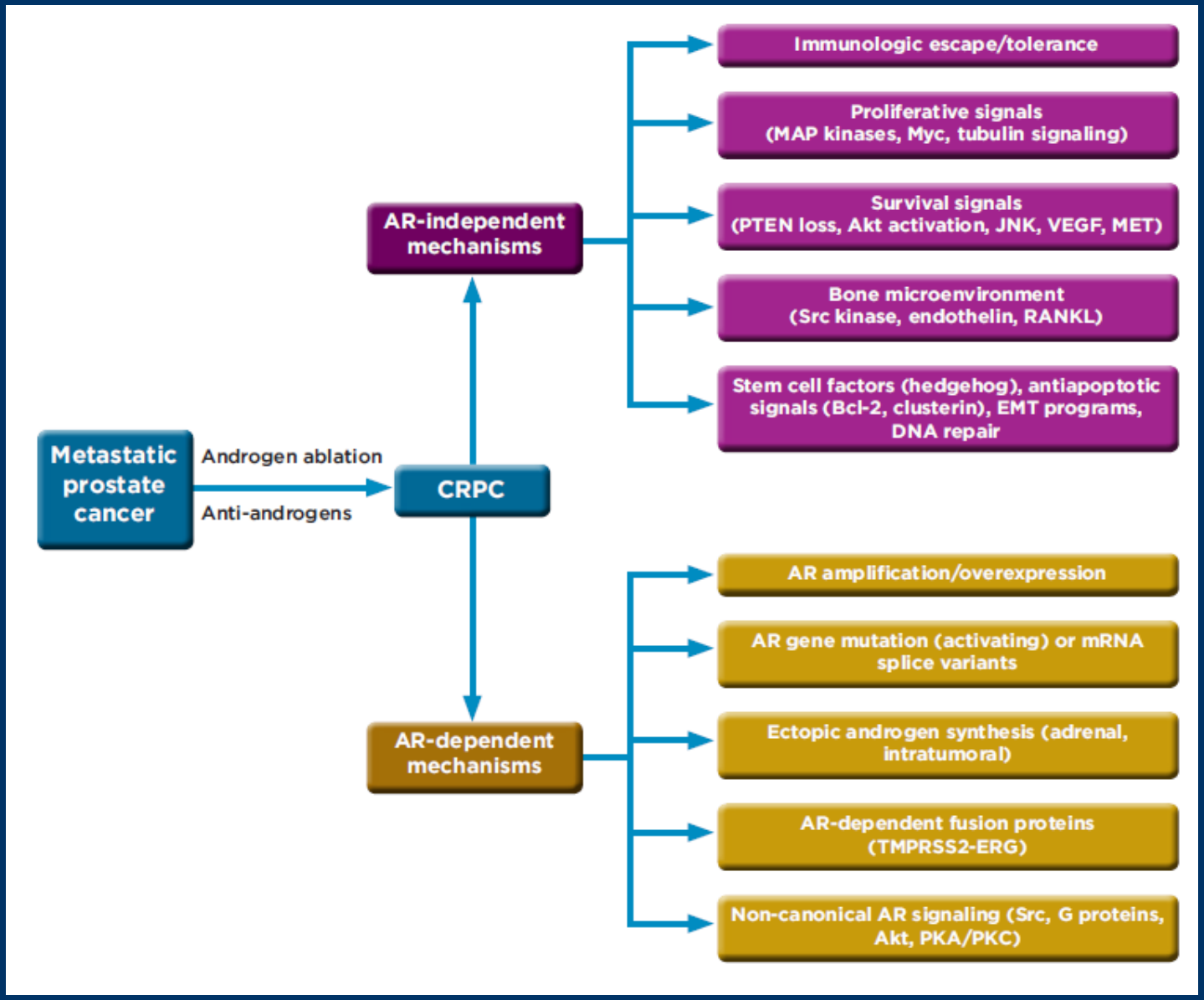
Prostate cancer relies on androgen signaling for progression

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



DebesJD, et al. *N Engl J Med.* 2004;351(15):1488-1490.

Biologic Mechanisms Driving CRPC



Antonarakis and Armstrong, Clin Oncol News 2011

Cell

Volume 154, Issue 5, 29 August 2013, Pages 1074–1084

Article

A Gain-of-Function Mutation in DHT Synthesis in Castration-Resistant Prostate Cancer

Kai-Hsiung Chang[1, 2, 3, 4], Rui Li[4], Barbara Kuri[1, 2, 3], Yair Lotan[5], Claus G. Roehrborn[5], Jiayan Liu[8], Robert Vessella[9], Peter S. Nelson[9, 10], Payal Kapur[6], Xiaofeng Guo[7], Hamid Mirzaei[7], Richard J. Auchus[8], Nima Sharifi[1, 2, 3, 4,]

Cell

Volume 155, Issue 6, 5 December 2013, Pages 1309–1322

Article

Glucocorticoid Receptor Confers Resistance to Antiandrogens by Bypassing Androgen Receptor Blockade

Vivek K. Arora[1,2], Emily Schenkein[1], Rajmohan Murali[1,3], Sumit K. Subudhi[2], John Wongvipat[1], Minna D. Balbas[1,4], Neel Shah[1,4], Ling Cai[1], Eleni Efstathiou[5], Chris Logothetis[5], Deyou Zheng[6], Charles L. Sawyers[1,7,]

VOLUME 31 · NUMBER 15 · MAY 20 2013

JOURNAL OF CLINICAL ONCOLOGY

REVIEW ARTICLE

Advancing Precision Medicine for Prostate Cancer Through Genomics

Sameek Roychowdhury and Arul M. Chinnaiyan

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

Supported by American Cancer Society Mentored Scholar Research Grant No. MRSG-12-194-01, a Landon Foundation American Association for Cancer Research Innovator Award for Personalized Cancer Medicine, and a Prostate Cancer Foundation Young Investigator Award (S.R.) and by the Prostate Cancer Foundation, National Institutes of Health Early Detection Research Network Grants No. UO1CA111275 and R01CA132874-01A1, Prostate Specialized Program of Research Excellence Grant No. P50CA69568, and by a Doris Duke Charitable Foundation Clinical Scientist Award (A.M.C.).

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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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

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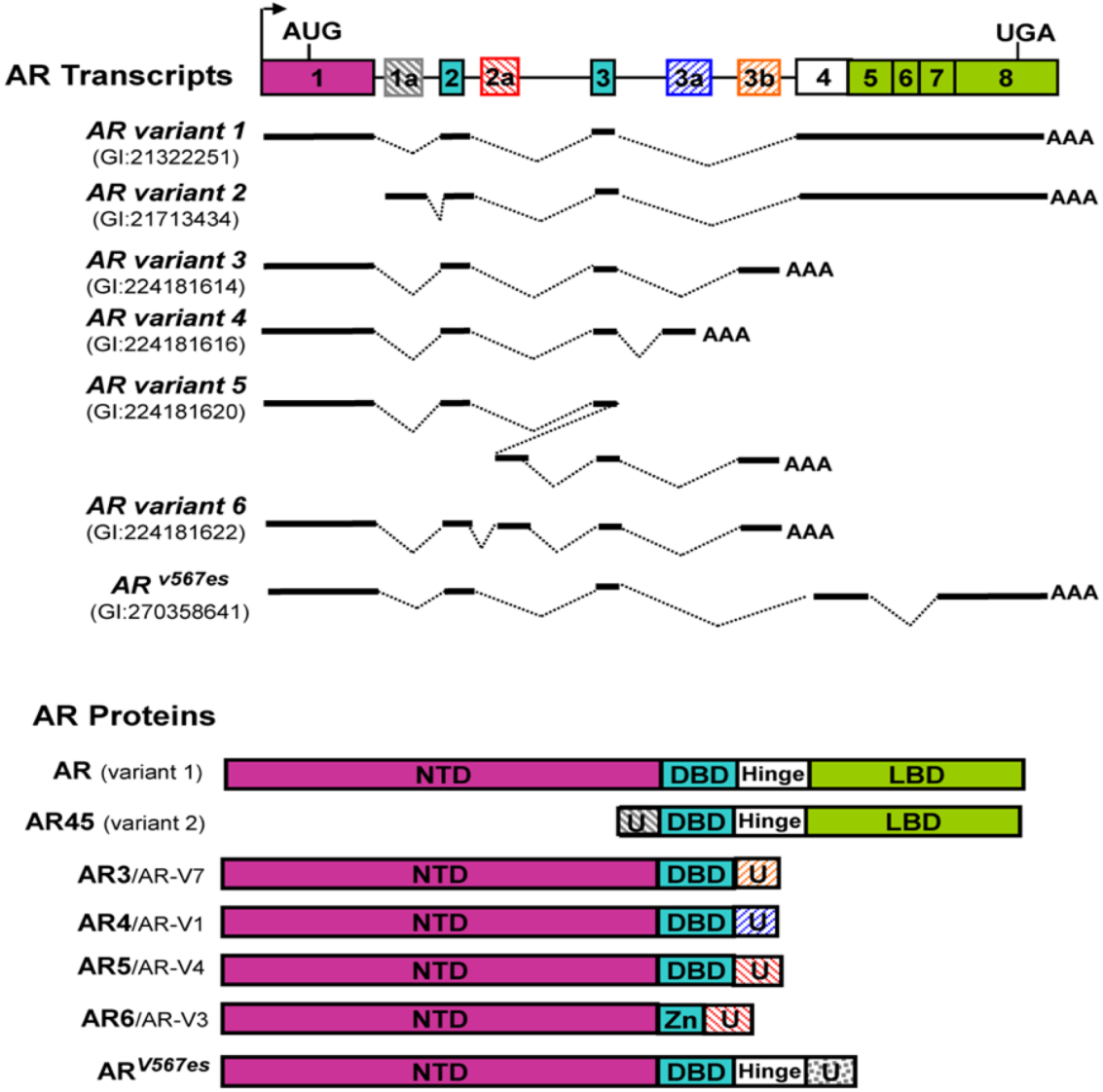
AR Splice Variants

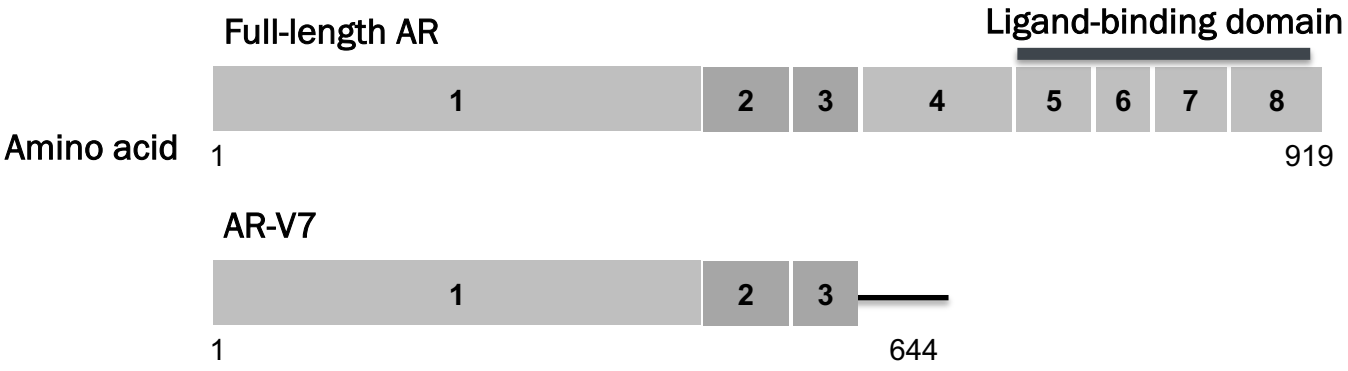


Guo Z and Qiu Y. *Int J Biol Sci.* 2011;7:815-822.

AR splice variants are associated with poor prognosis and Treatment resistance

- The translation of splice variants results in proteins with altered activity and regulation[1]

- Exons 4-8 of AR are not required for transcriptional activity and splice variants lacking this region may be constitutively active[2]
- In one study, expression of AR variants lacking the ligand-binding domain in CRPC bone metastases was associated with poor prognosis[2]
- Detection of AR-V7 in tumor cells is associated with treatment resistance[3,4]



Thadani-Mulero M, et al. *Cancer Res.* 2014;74(8):2270-2282. © 2014 American Association for Cancer Research.

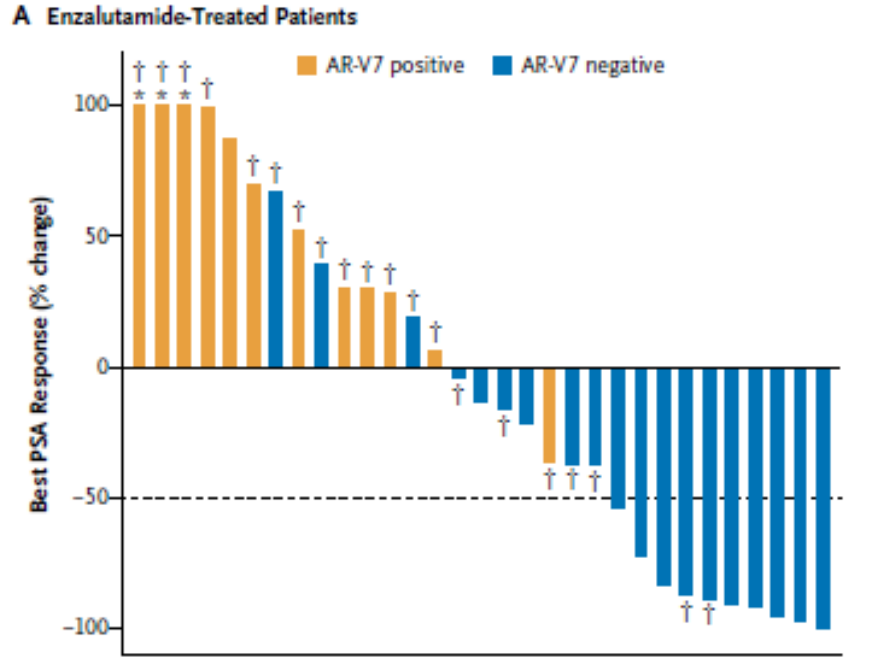
Lack of Response Associated with AR-V7 (Johns Hopkins University)

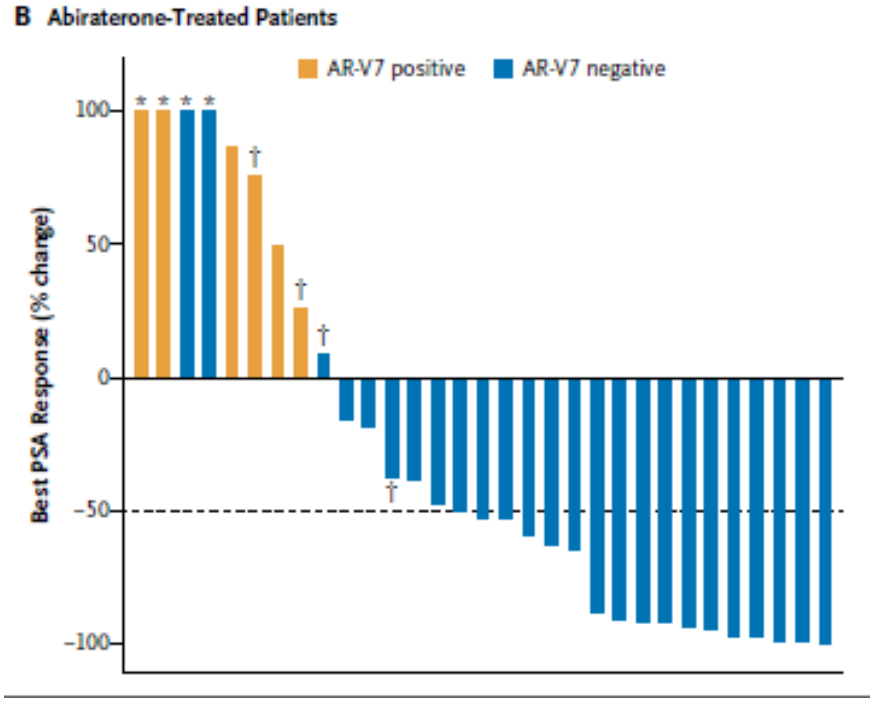
- Prospective study of M1 CRPC patients eligible for abiraterone (N=31) and enzalutamide (N=31) treatment; AR-V7 identified in CTC samples pretreatment
- None (0/18) of the AR-V7 positive patients achieved a PSA50
  - Only 1 AR-V7 positive patient showed any PSA reduction (enzalutamide)
- AR-V7 prevalence increased post additional treatments

Treatment[1]	Baseline AR-V7+	Response						
		AR-V7 status	PSA50	P- value	rPFS	P- value	OS (95% CI)	P value
Abiraterone (N=31)	19% (6/31)	+	0% (0/6)	.004	2.3 mos	<.001	10.6 mos (8.5–NR)	.002
		–	68% (17/25)		>6.3 mos		>11.9 mos (11.9–NR)	
Enzalutamide (N=31)	39% (12/31)	+	0% (0/12)	.004	2.1 mos	<.001	5.5 mos (3.9–NR)	.006
		–	53% (10/19)		6.1 mos		NR (NR–NR)	

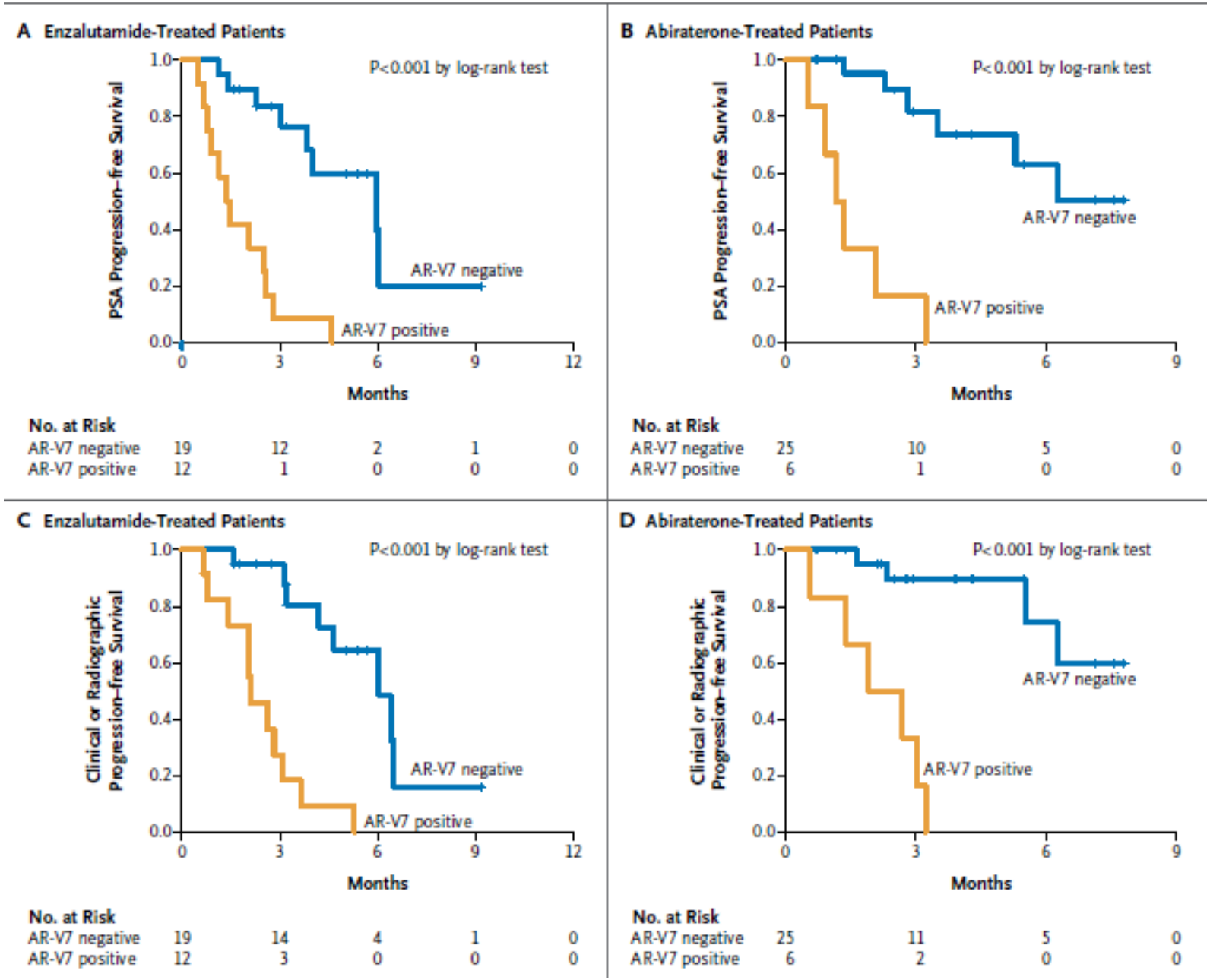
Patient Treatment Status[2]	Before enzalutamide or abiraterone	Post enzalutamide	Post abiraterone	Post abiraterone & enzalutamide
AR-V7 Prevalence	12%	25%	51%	67%

CRPC=castration-resistant prostate cancer; CTC=circulating tumor cell; M1=metastatic disease; NR=not reached; OS=overall survival; PSA=prostate specific antigen; rPFS=radiographic progression-free survival. 1. Antonarakis ES et al. NEJM. 201410.1056/NEJMoa1315815. 2.. Antonarakis ES et al. ASCO 2014





Antonarakis et al
NEJM 2014



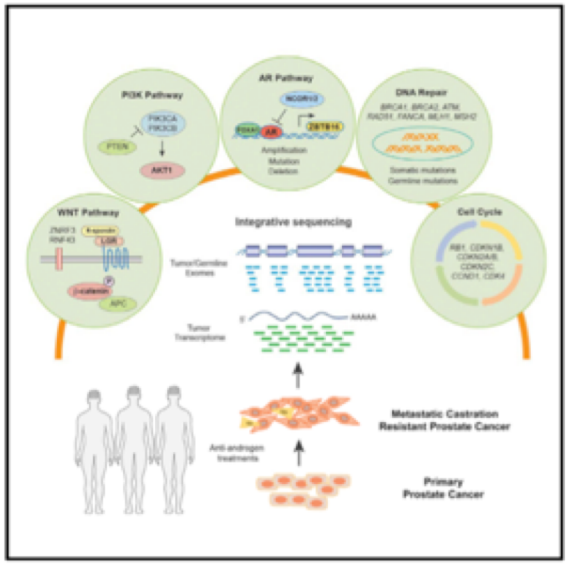
Antonarakis et al
NEJM 2014

Resource

Cell

Integrative Clinical Genomics of Advanced Prostate Cancer

Graphical Abstract



Authors

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In Brief

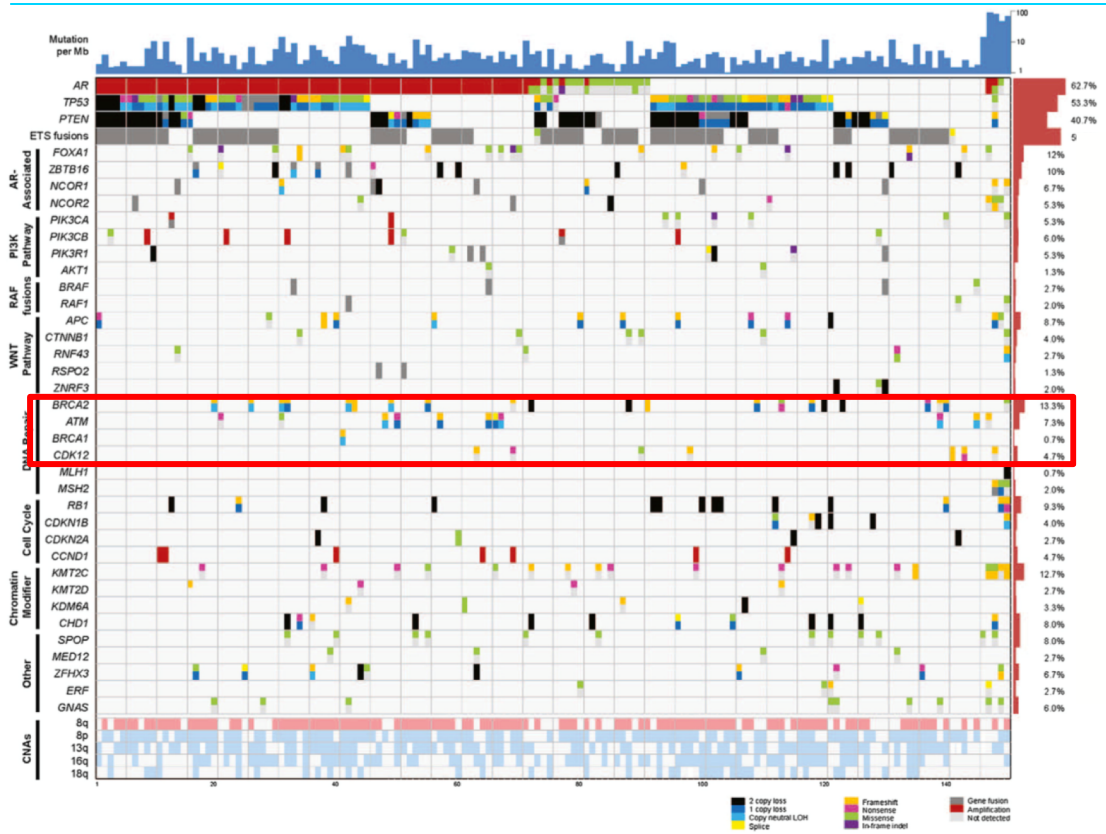
A multi-institutional integrative clinical sequencing analysis reveals that the majority of affected individuals with metastatic castration-resistant prostate cancer harbor clinically actionable molecular alterations, highlighting the need for genetic counseling to inform precision medicine in affected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

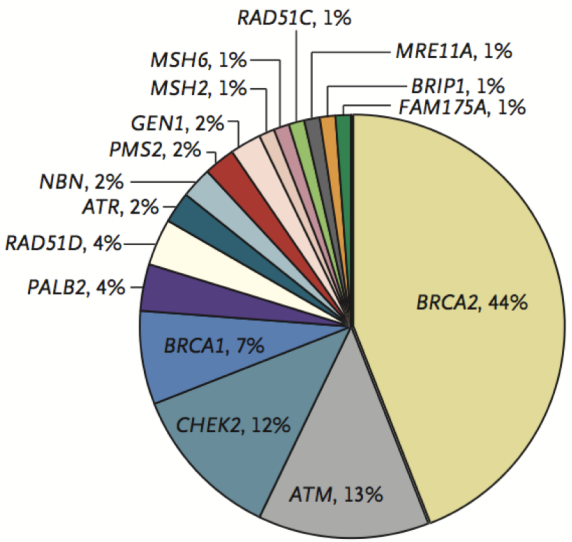
Highlights

- 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

CellPress



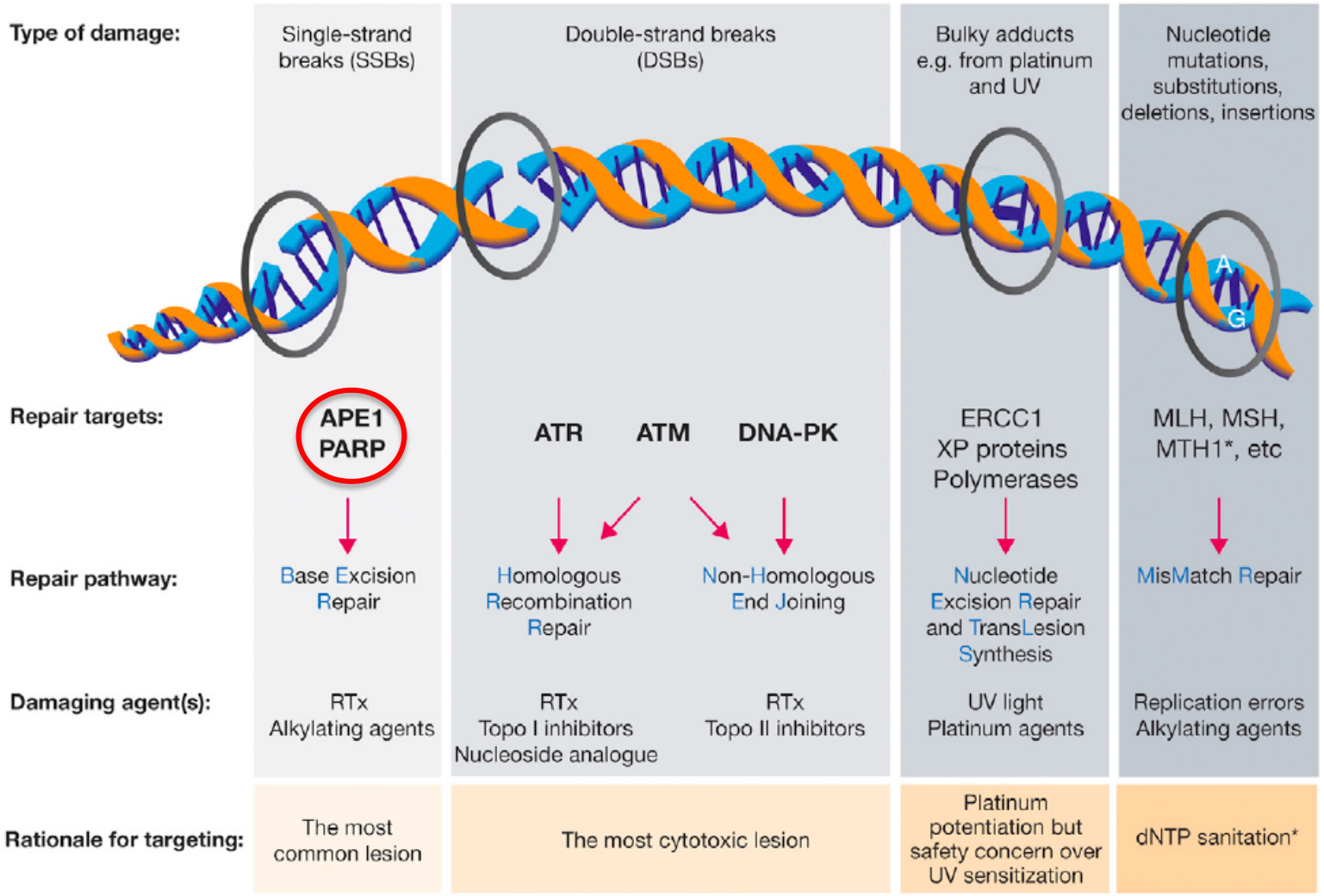


- 23% of metastatic castration-resistant prostate cancers harbor DNA repair alterations
- The frequency of DNA repair alterations increases with disease progression

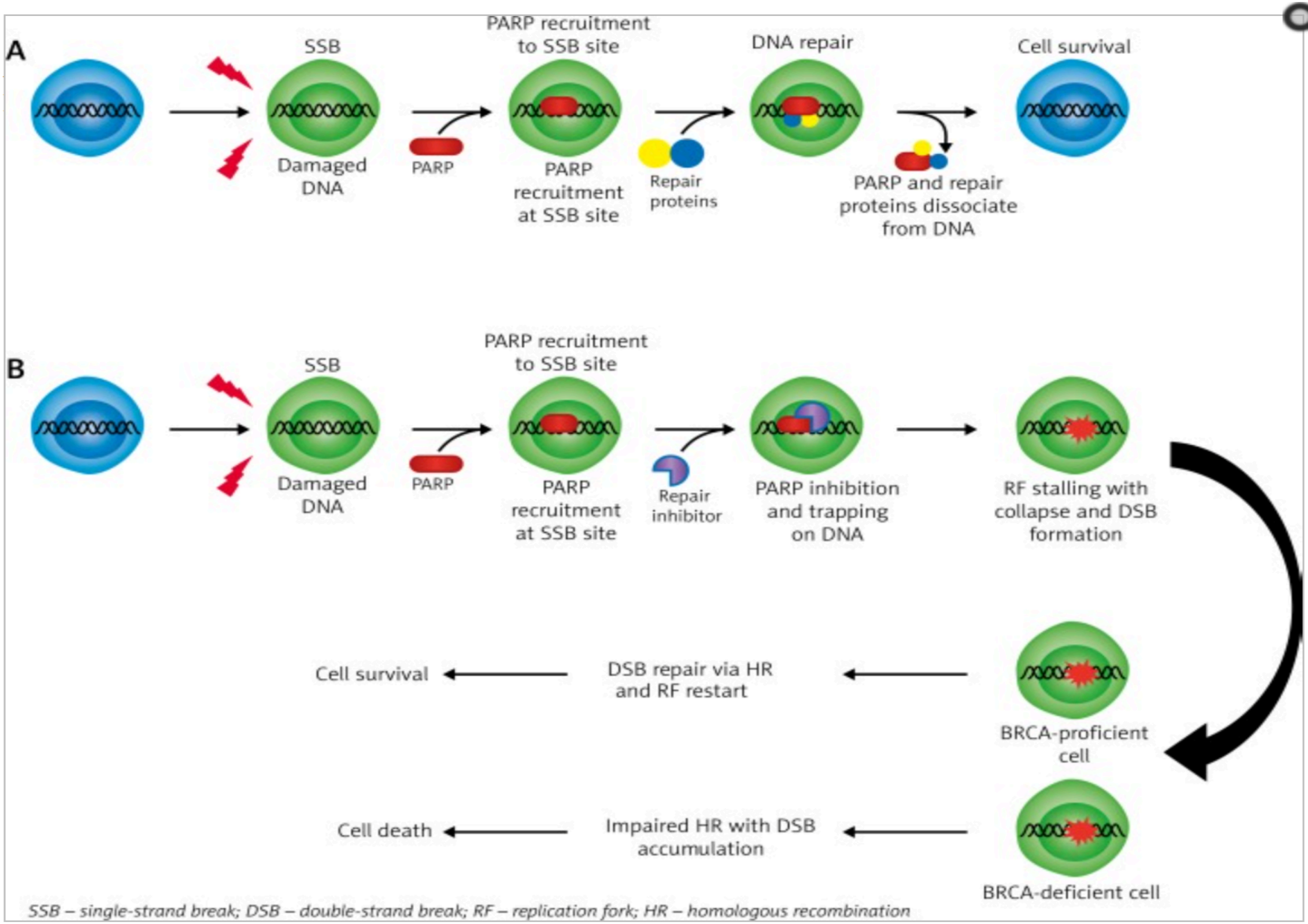
- 11.8% of men with metastatic prostate cancer have a germline alteration in 16 DNA damage repair genes
- Age and family history did not affect mutation frequency

Robinson D et al. *Cell* 2015; 161:1215-28.

Pritchard CC et al. *N Engl J Med.* July 6,2016.

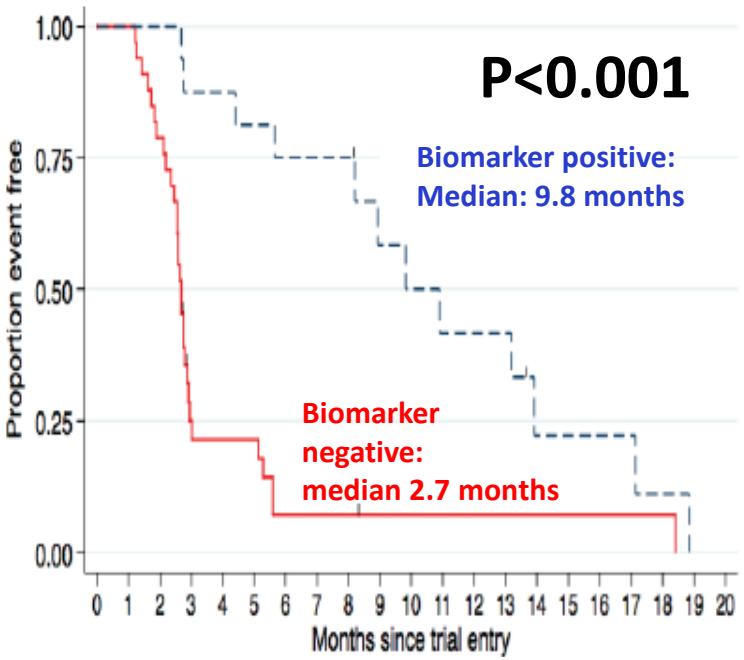


O'Connor MJ, *Molecular Cell*, 2015

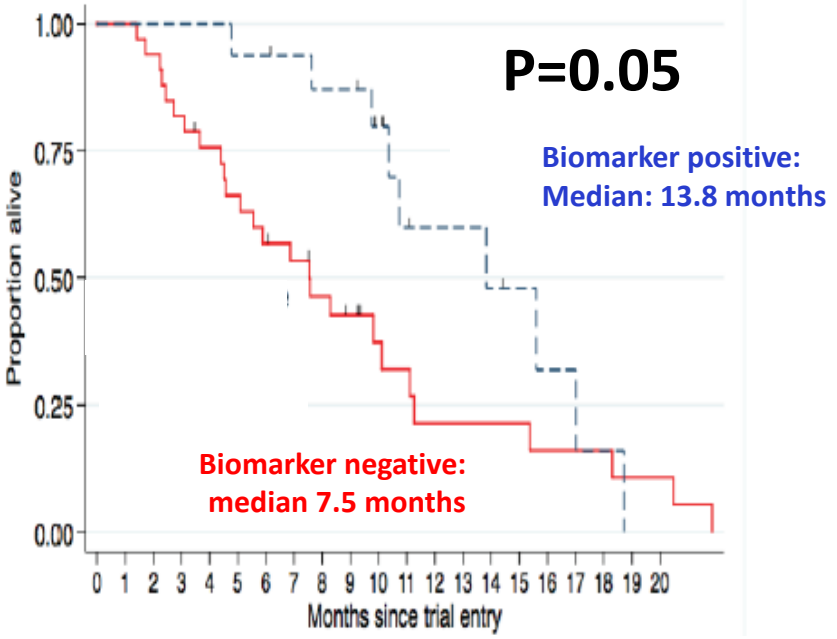

A
SSB
Damaged DNA
PARP
PARP recruitment to SSB site
PARP recruitment at SSB site
Repair proteins
DNA repair
PARP and repair proteins dissociate from DNA
Cell survival
B
SSB
Damaged DNA
PARP
PARP recruitment to SSB site
PARP recruitment at SSB site
Repair inhibitor
PARP inhibition and trapping on DNA
RF stalling with collapse and DSB formation
BRCA-proficient cell
DSB repair via HR and RF restart
Cell survival
BRCA-deficient cell
Impaired HR with DSB accumulation
Cell death
SSB – single-strand break; DSB – double-strand break; RF – replication fork; HR – homologous recombination

Olaparib (PARPi) with Superior Outcomes in mCRPC Patients with DNA Repair Gene Alterations

rPFS by presence of genomic defects in DNA repair genes



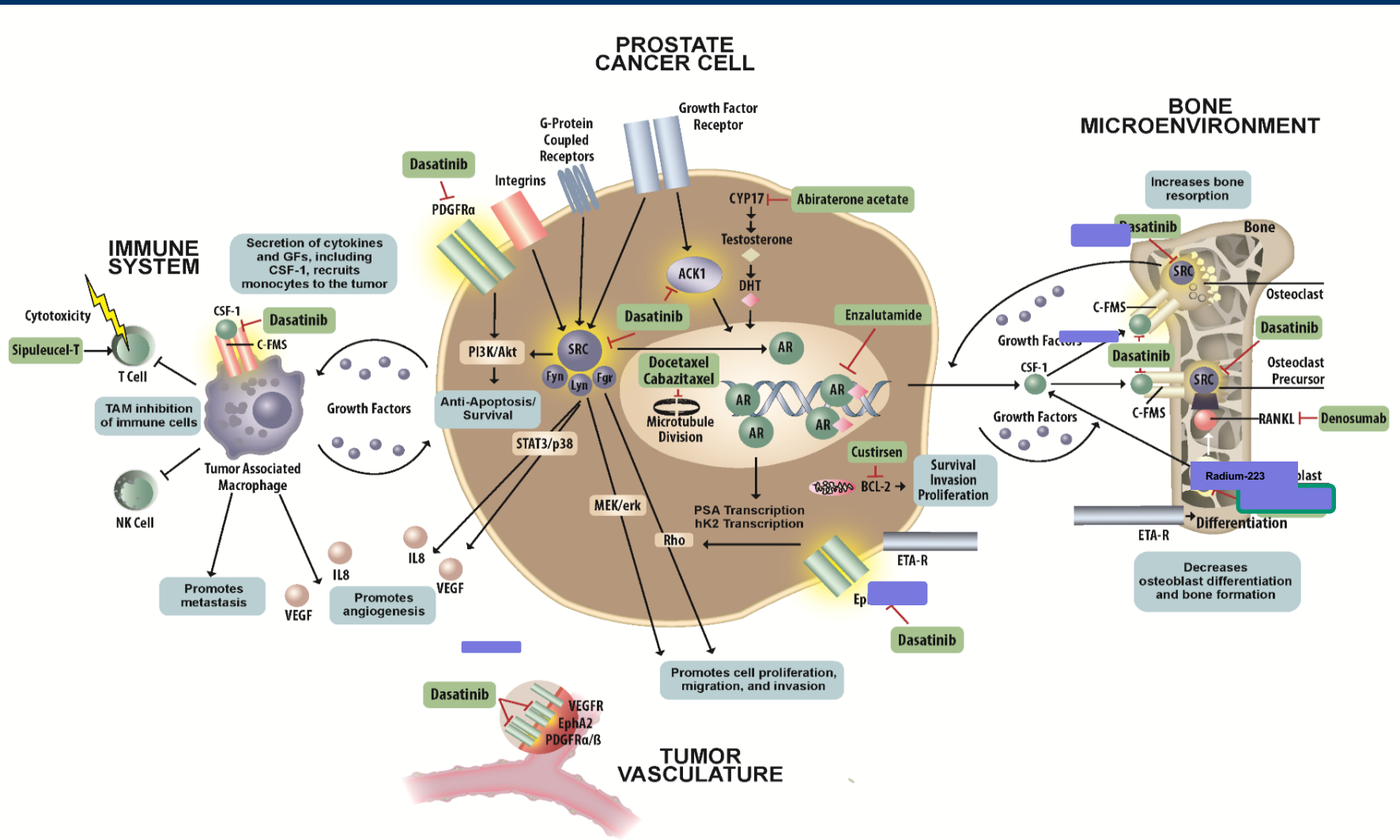
OS by presence of genomic defects in DNA repair genes



- **Overall response rate of 32.7% -- median duration of response ~ 9 months**
- **14/16 (88%) of patients with a DNA repair alteration had a response**
- **2/33 (6%) of patients without a DNA repair alteration had a response**

Mateo J. et al, *N Engl J Med* 2015; 373:1697-708.

FUTURE
Novel and Multi Modal Therapy



Conclusions

- The AR continues to be a major driver in the growth and survival of prostate CA cells, even in the CRPC patient
- As urologists, we need to understand the nuances of resistance mechanisms and genomic alterations
- Despite all the recent advances, there remains multiple challenges and opportunities for researchers to better understand the disease and possible development of novel targeted agents

Thank you