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Resistance mechanisms to ADT and androgen signaling agents

Philip Kantoff, MD

Chairman Department of Medicine

Memorial Sloan Kettering Cancer Center

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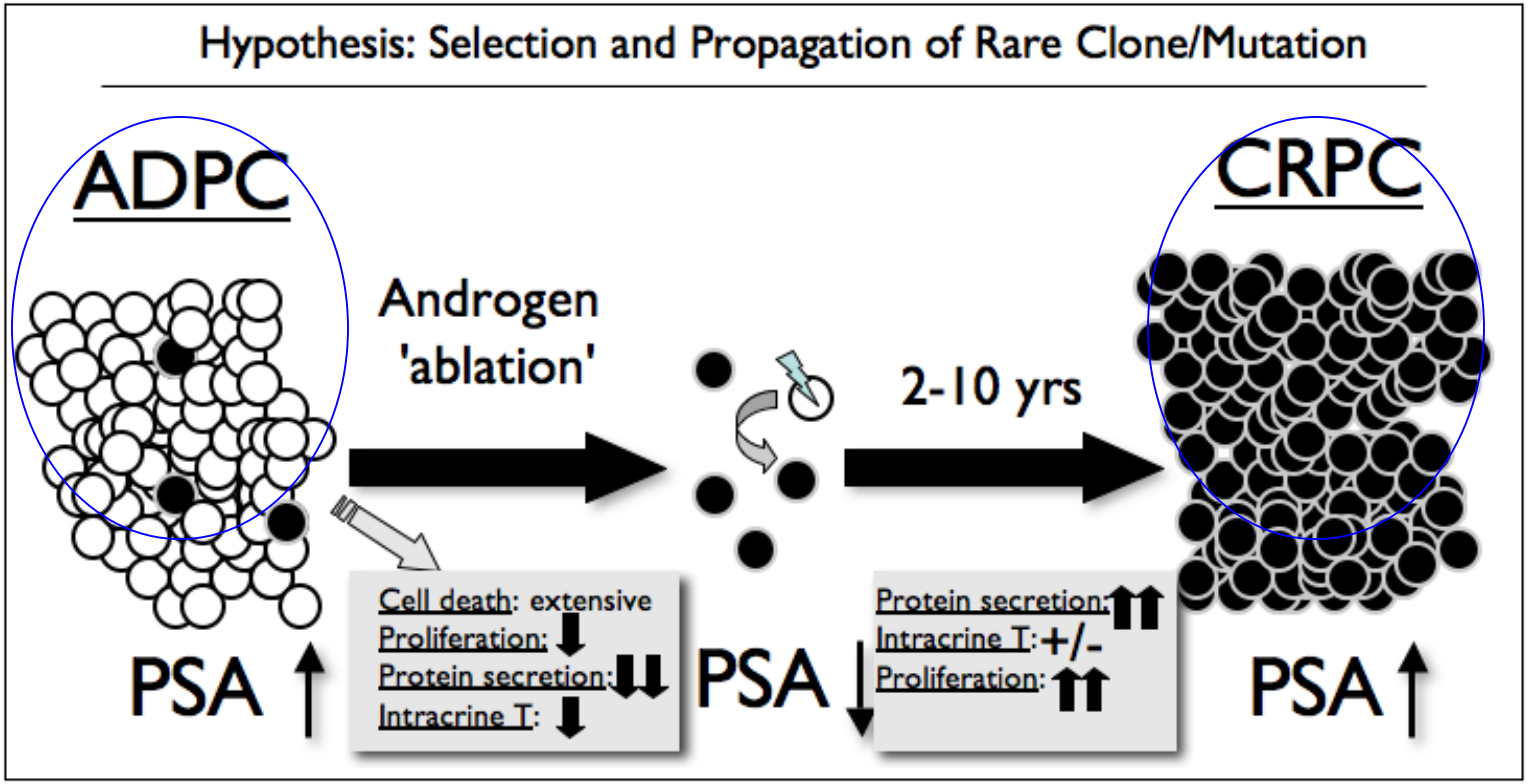
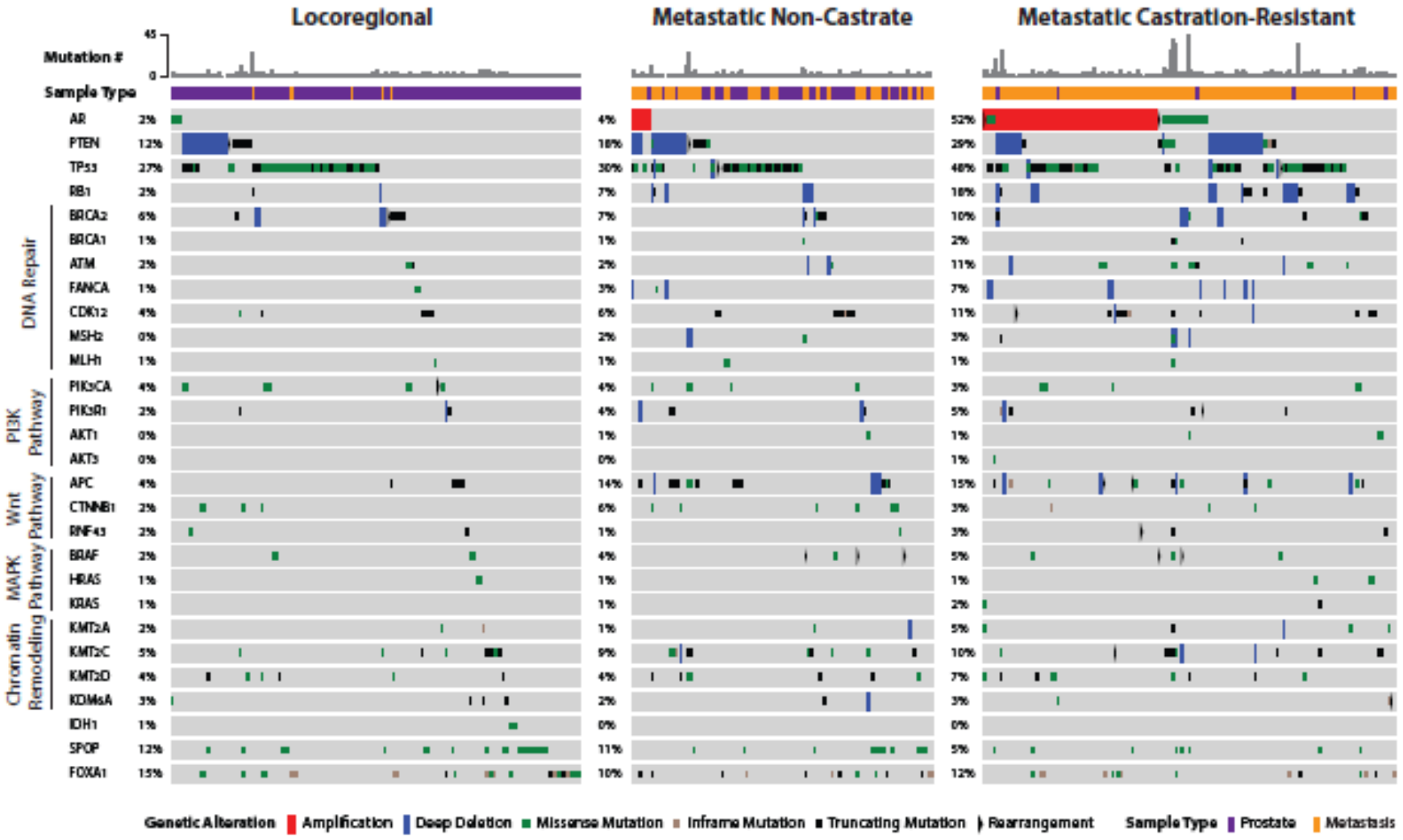


○	**androgen dependent cell**
●	**CRPC**

Mutational Landscape Across Disease States



Abida et al. JCO Precis Oncol. 2017

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HETEROGENEITY OF TREATMENT RESPONSE

Overall Survival in M+ Patients as Determined by Nadir PSA 7 months after ADT

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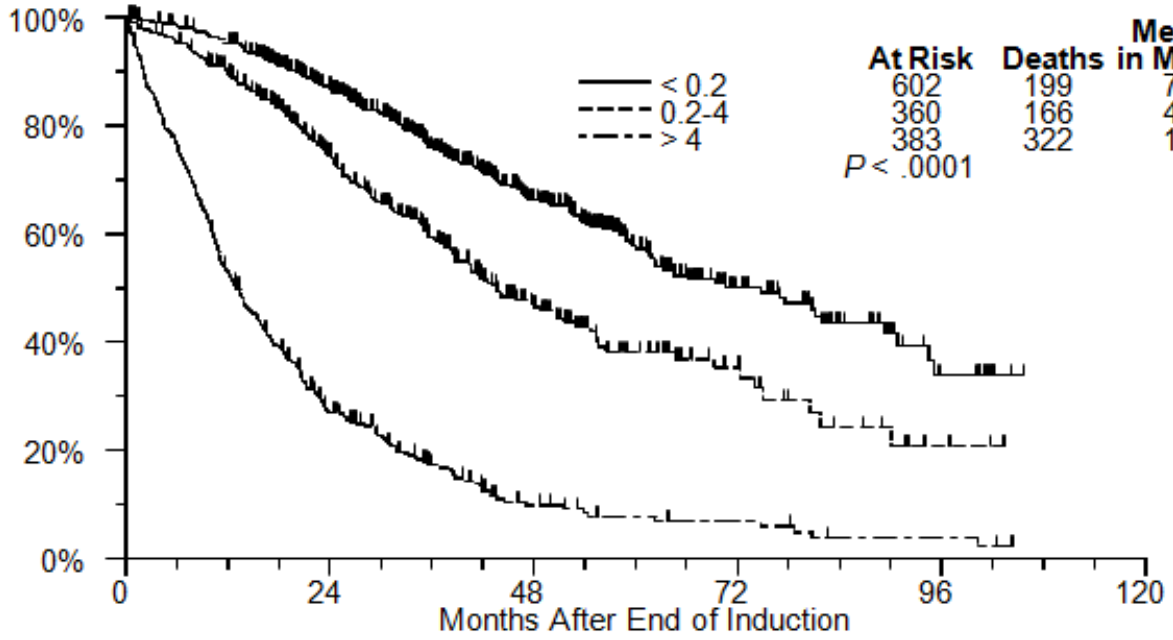

At Risk			
Undetected	453	206	60
Normalized	213	72	19
Neither	91	17	7

Hussain et al (JCO 2006)

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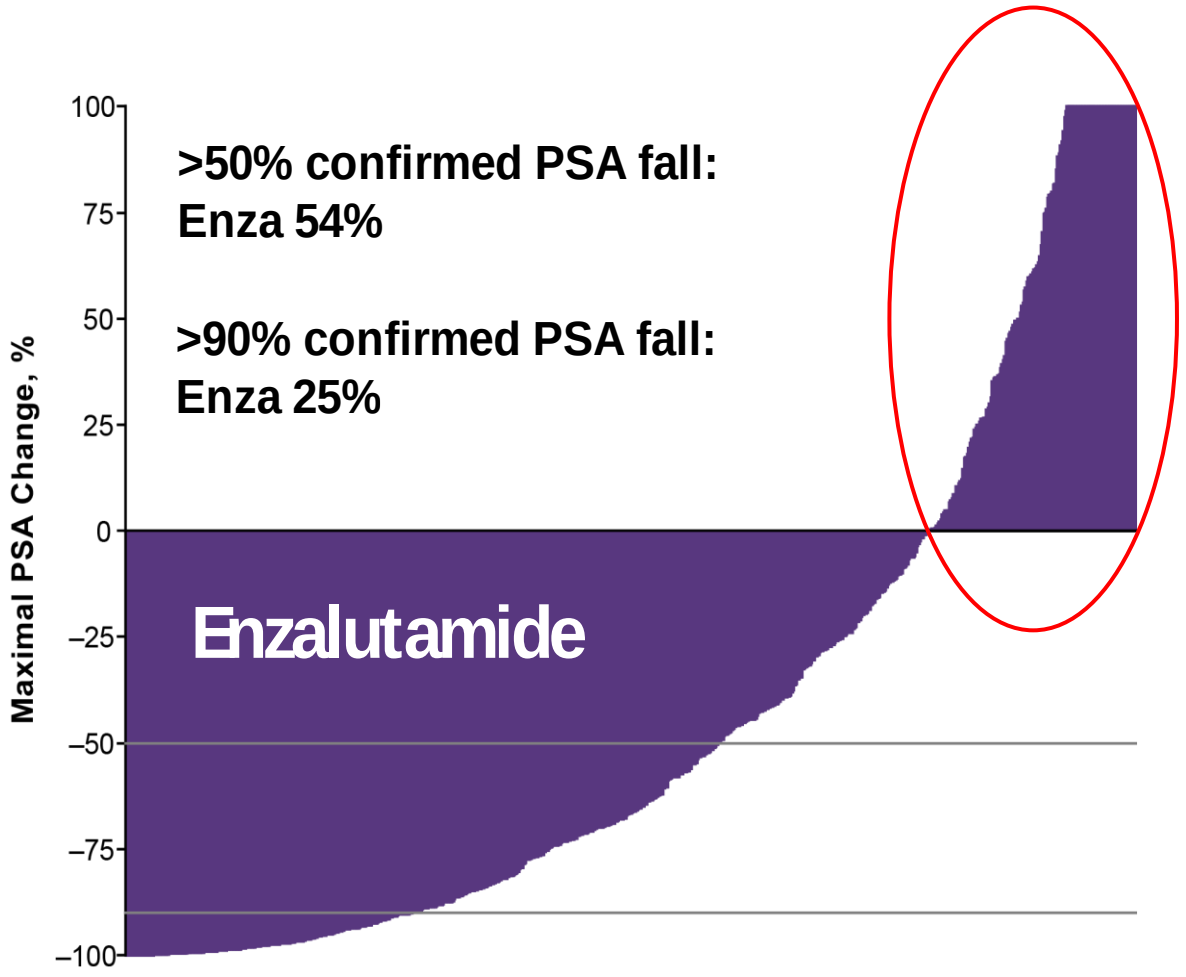
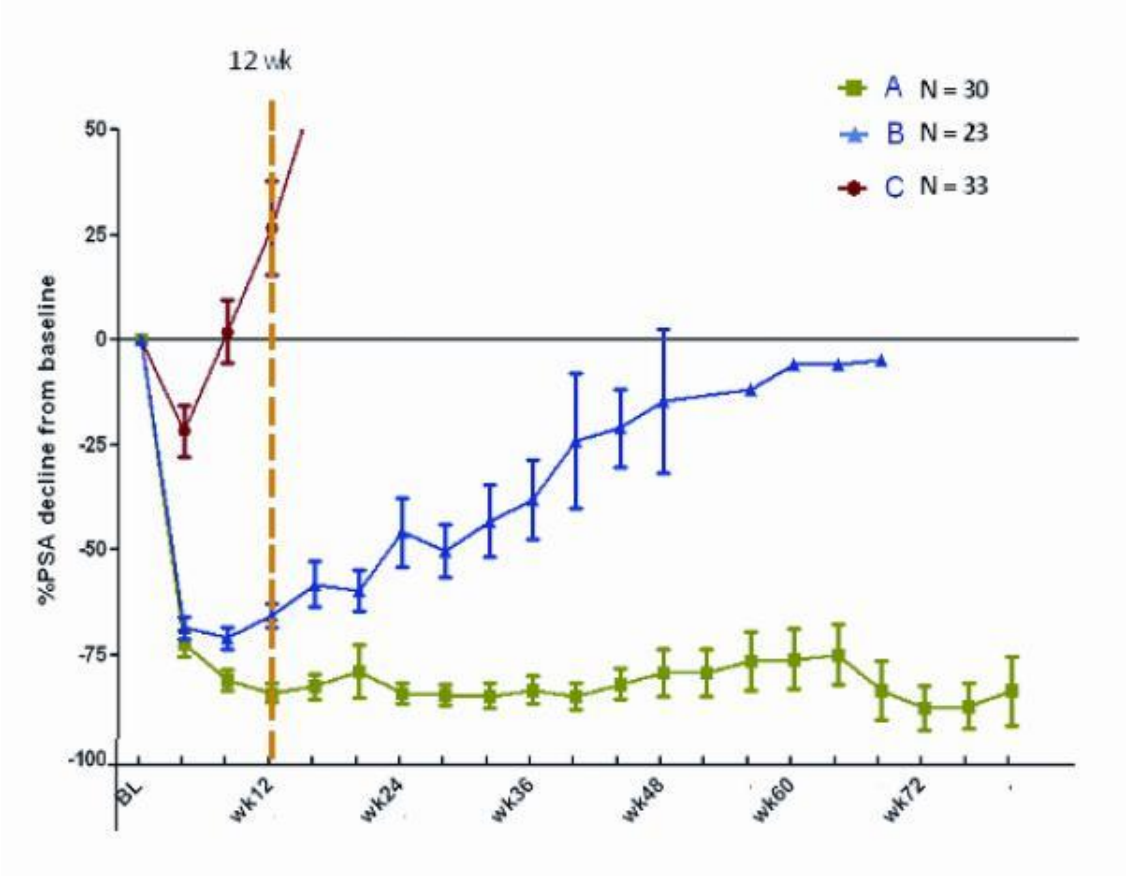
Response to enzalutamide: Phase 3 (AFFIRM)-Similar for apalutamide and abiraterone



21%
Never **had a PSA decline**

Two-Thirds of Patients With mCRPC Have Tumors With Intermediate or Full Resistance to AR-Targeting Agents

Post-therapy PSA change patterns in patients treated with AR targeting agents in mCRPC



A. Resistance (*nonresponse*: no significant durable decline in PSA)

B. Intermediate Resistance (*drifters*: rapid PSA decline, followed by slow increase)

C. AR Sensitive (*responders*: dramatic and durable PSA decline)

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Rathkopf D, Scher HI. *Cancer J*. 2013;19(1):43-49.

RESISTANCE MECHANISMS

Importance of Persistent AR Pathway Signaling in CRPC-Persistent Ligand

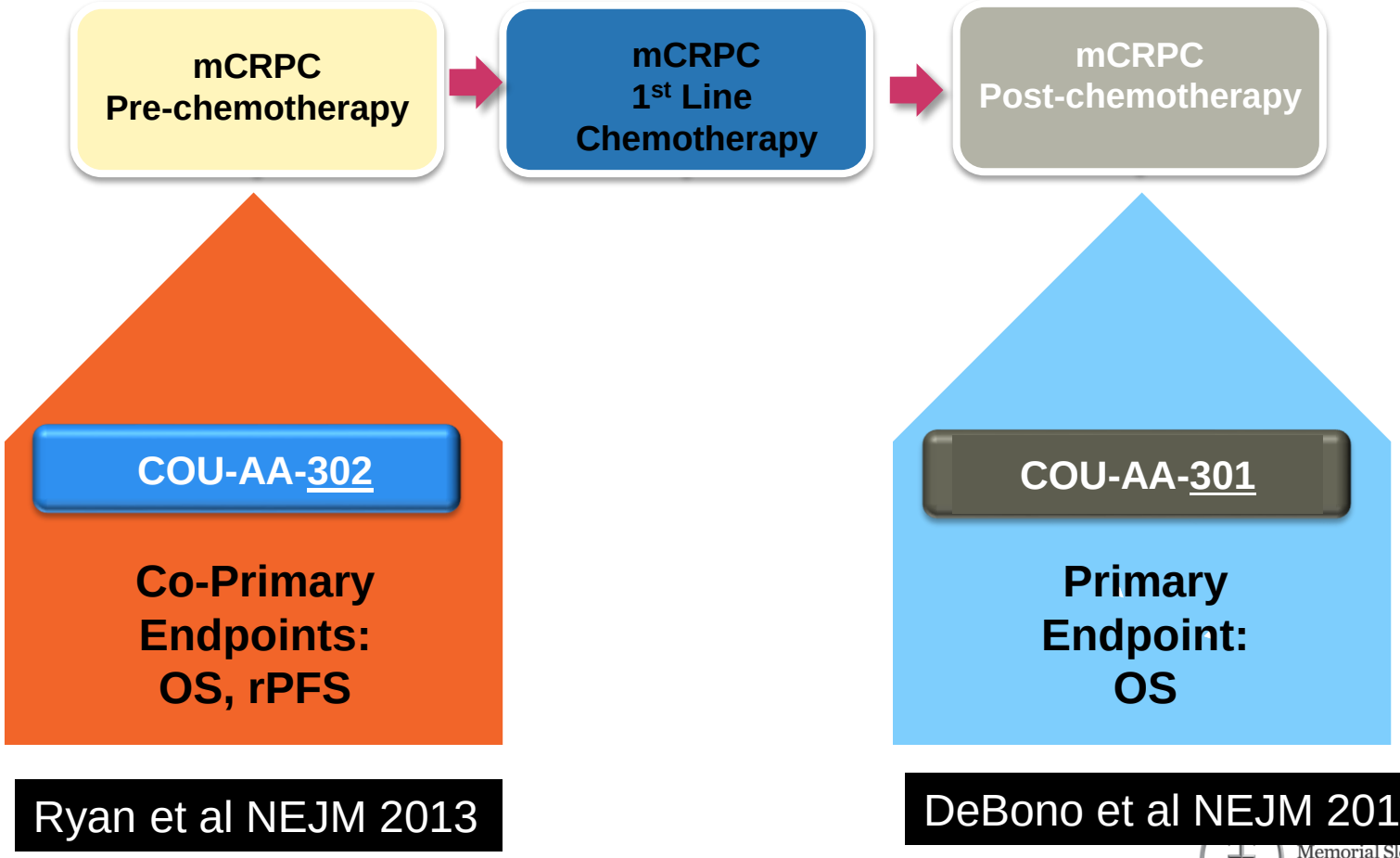
- Genetic evidence-AR-Mutated or amplified AR
- Persistent AR expression and expression of androgen regulated genes “androgen signature”
- “Persistent intratumoral ligand”-T or DHT or precursors

Androgen Signaling Pathway Inhibitors

- CYP 17, 20 lyase inhibitors-androgen biosynthesis inhibitors
  - Abiraterone acetate

- Antiandrogens-block AR action
  - Enzalutamide

Abiraterone acetate in mCRPC Pre and Post-Chemotherapy*



*FDA approved indications

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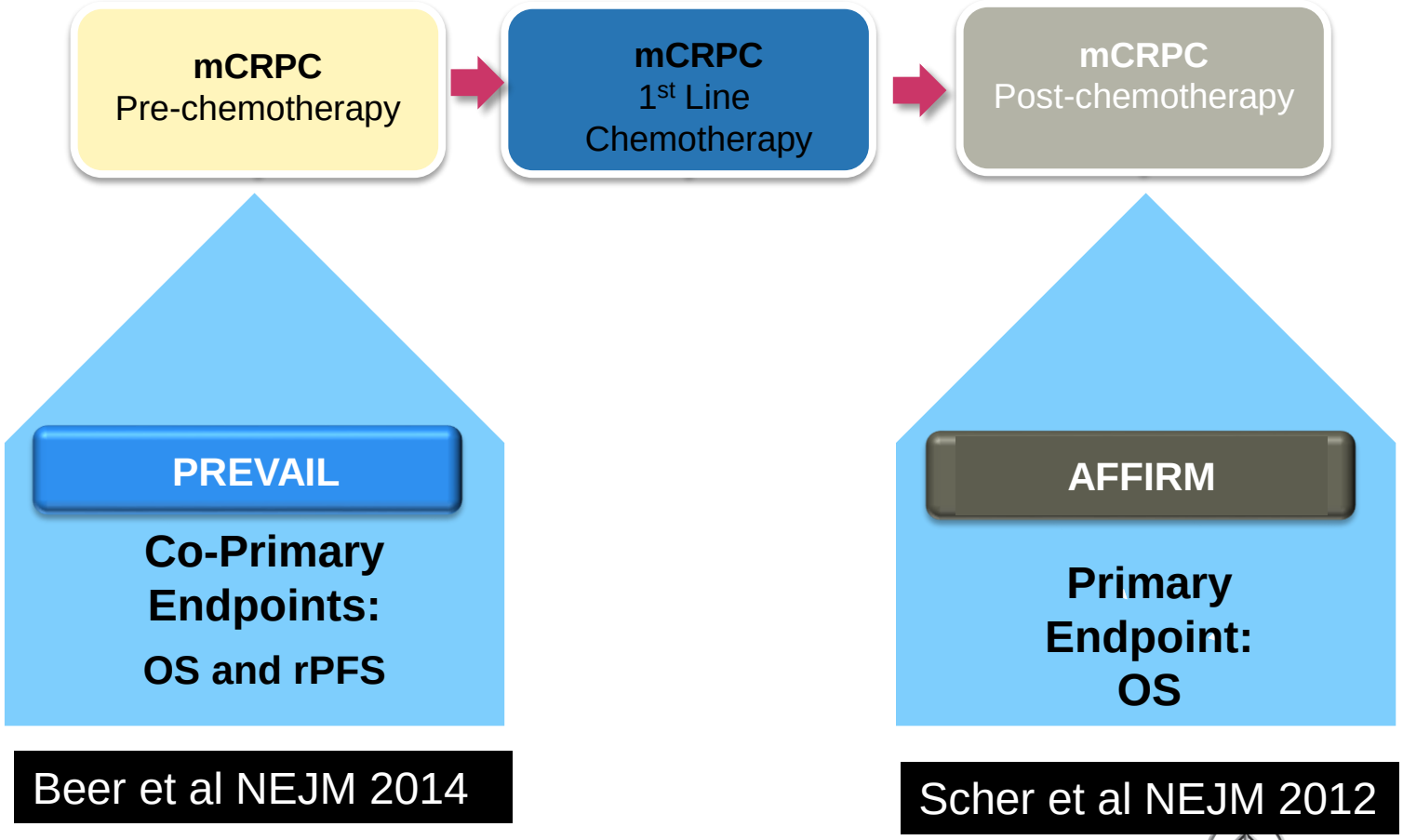
Enzalutamide in mCRPC Pre and Post-Chemotherapy*



*FDA approved indications

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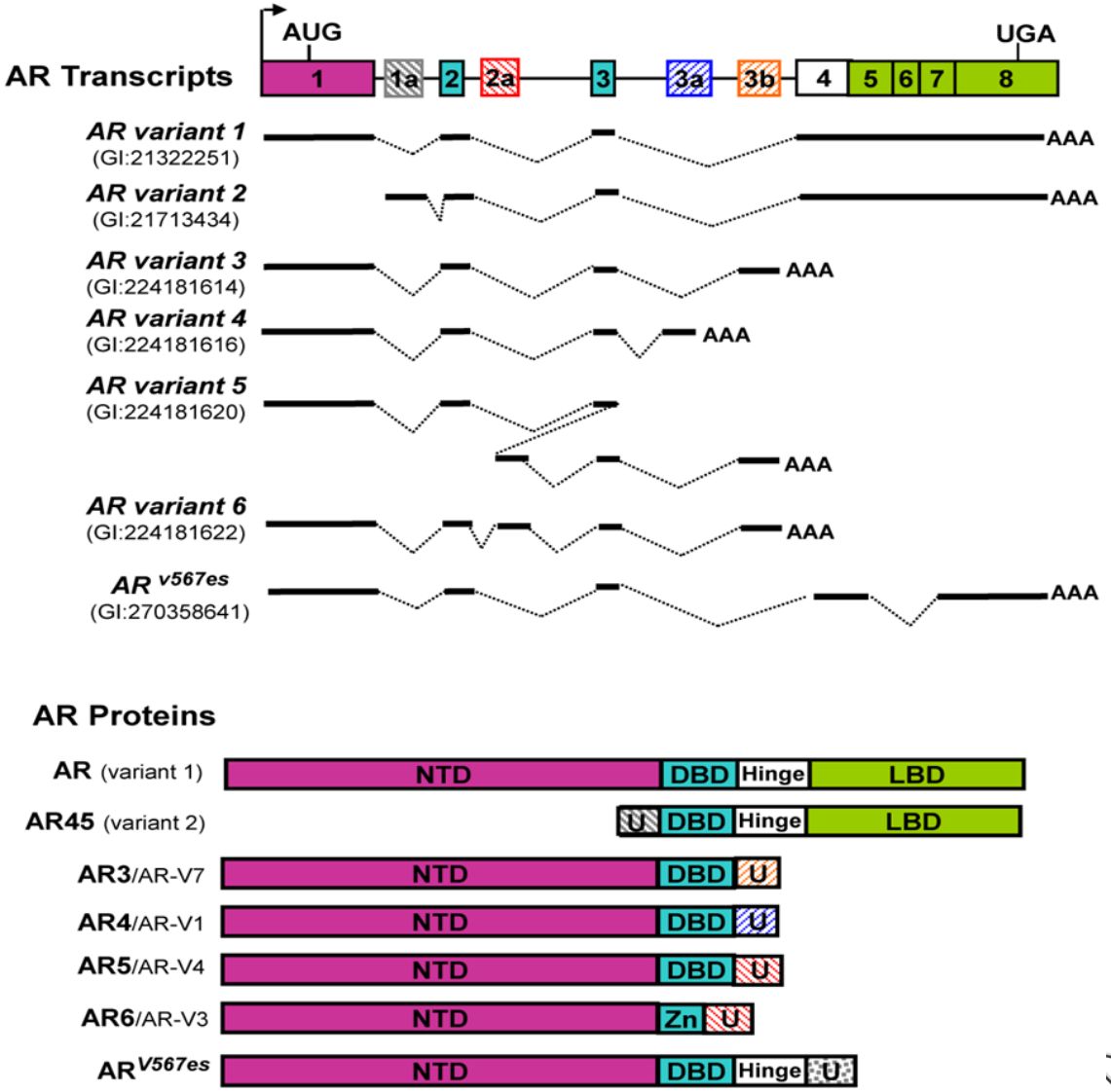
Acquired Resistance to ADT/Abiraterone/Enzalutamide

- Androgen receptor mediated mechanisms
  - AR amplification-
  - AR splice variants
  - Activating mutations in AR
    - F876L with enzalutamide
    - AR mutants responsive to progesterone after abiraterone

AR Splice Variants



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

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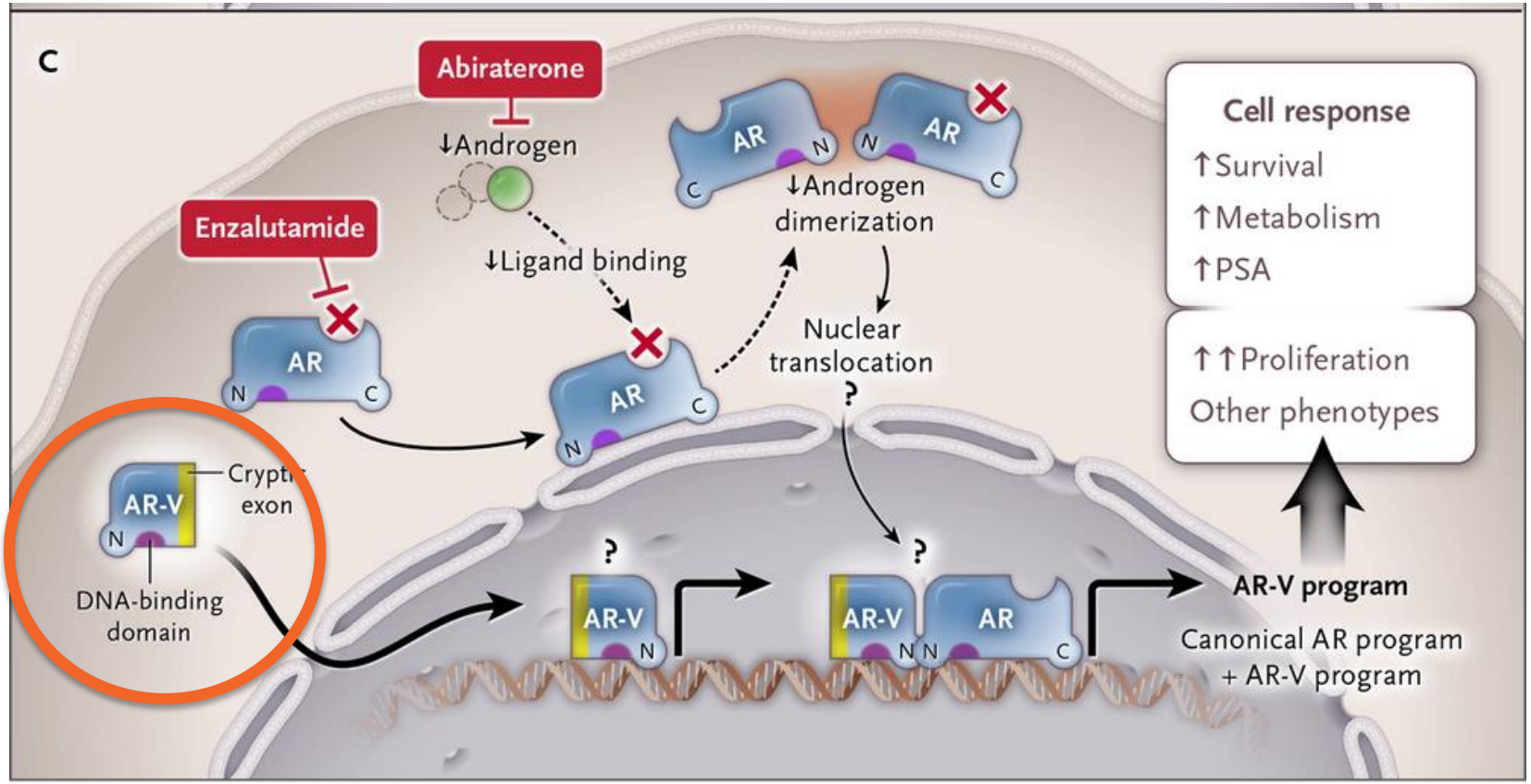
AR Variants associated With Resistance to AR-Targeted Therapy



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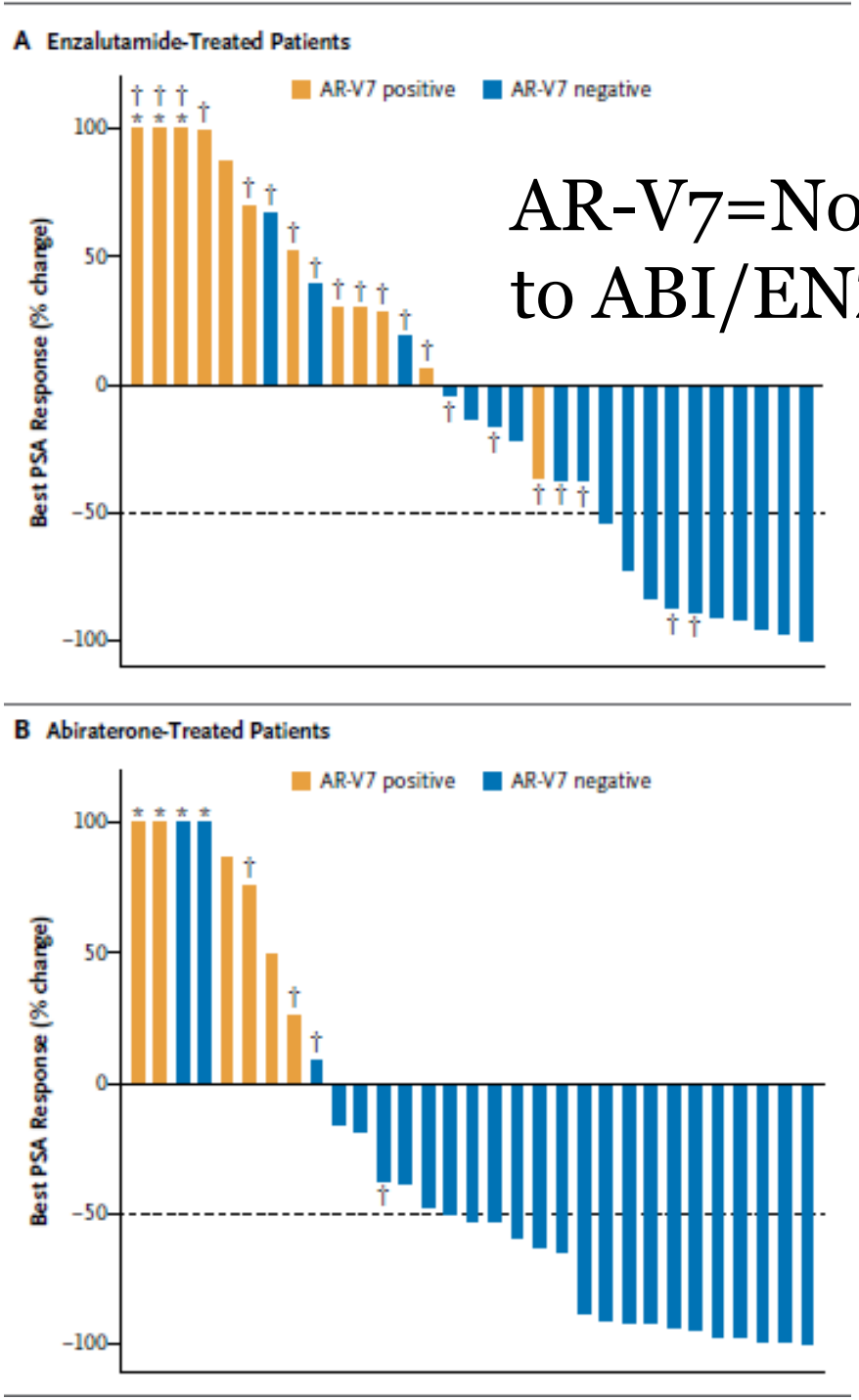
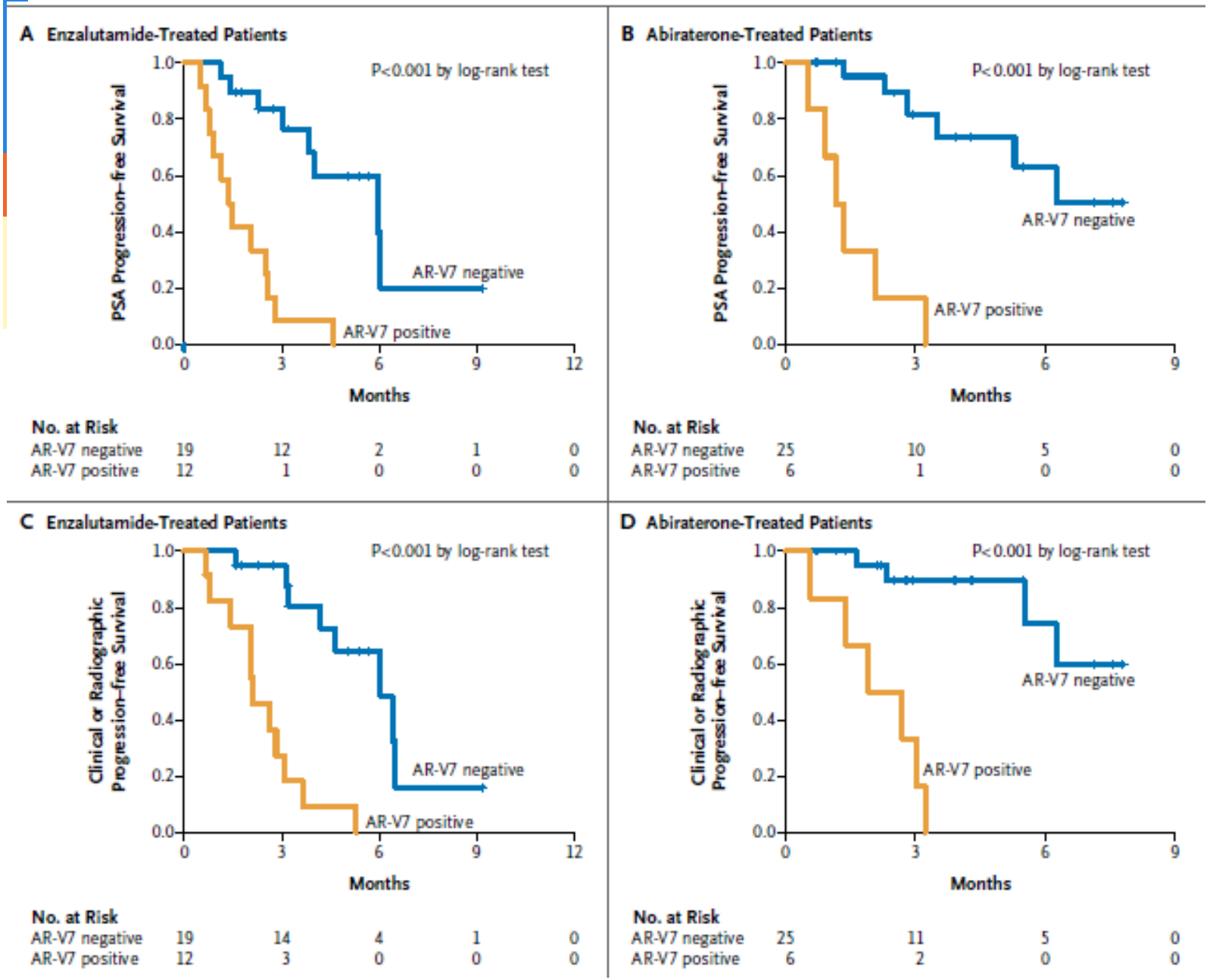


AR-V7=Non-Responders to ABI/ENZA

Antonarakis et al NEJM 2014



Antonarakis et al
NEJM 2014

Epigenetic Mechanism-Androgen Receptor Targets are Distinct in HSPC and CRPC

Cell

Androgen Receptor Regulates a Distinct Transcription Program in Androgen-Independent Prostate Cancer

Qianben Wang,[1,2,3,4,*] Wei Li,[3,14] Yong Zhang,[4] Xin Yuan,[5] Kexin Xu,[1] Jindan Yu,[6] Zhong Chen,[2] Rameen Beroukhim,[1,7] Hongyun Wang,[8] Mathieu Lupien,[1,13] Tao Wu,[8] Meredith M. Regan,[4] Clifford A. Meyer,[4] Jason S. Carroll,[9] Arjun Kumar Manrai,[4] Olli A. Jänne,[10] Steven P. Balk,[5] Rohit Mehra,[6] Bo Han,[6] Arul M. Chinnaiyan,[6] Mark A. Rubin,[11] Lawrence True,[12] Michelangelo Fiorentino,[1] Christopher Fiore,[1] Massimo Loda,[1] Philip W. Kantoff,[1] X. Shirley Liu,[4,*] and Myles Brown[1,*]

Wang Q, et al. *Cell.* 2009;138(2):245-256.

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Acquired Resistance to ADT/Abiraterone/Enzalutamide

- Androgen receptor mediated mechanisms
  - AR amplification-
  - AR splice variants
  - Activating mutations in AR
    - F876L with enzalutamide
    - AR mutants responsive to progesterone after abiraterone

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- Androgen receptor mediated mechanisms
  - Activating mutations in AR
  - AR amplification
  - AR splice variants
- **Up-regulation of other steroidogenic enzymes**

Cell

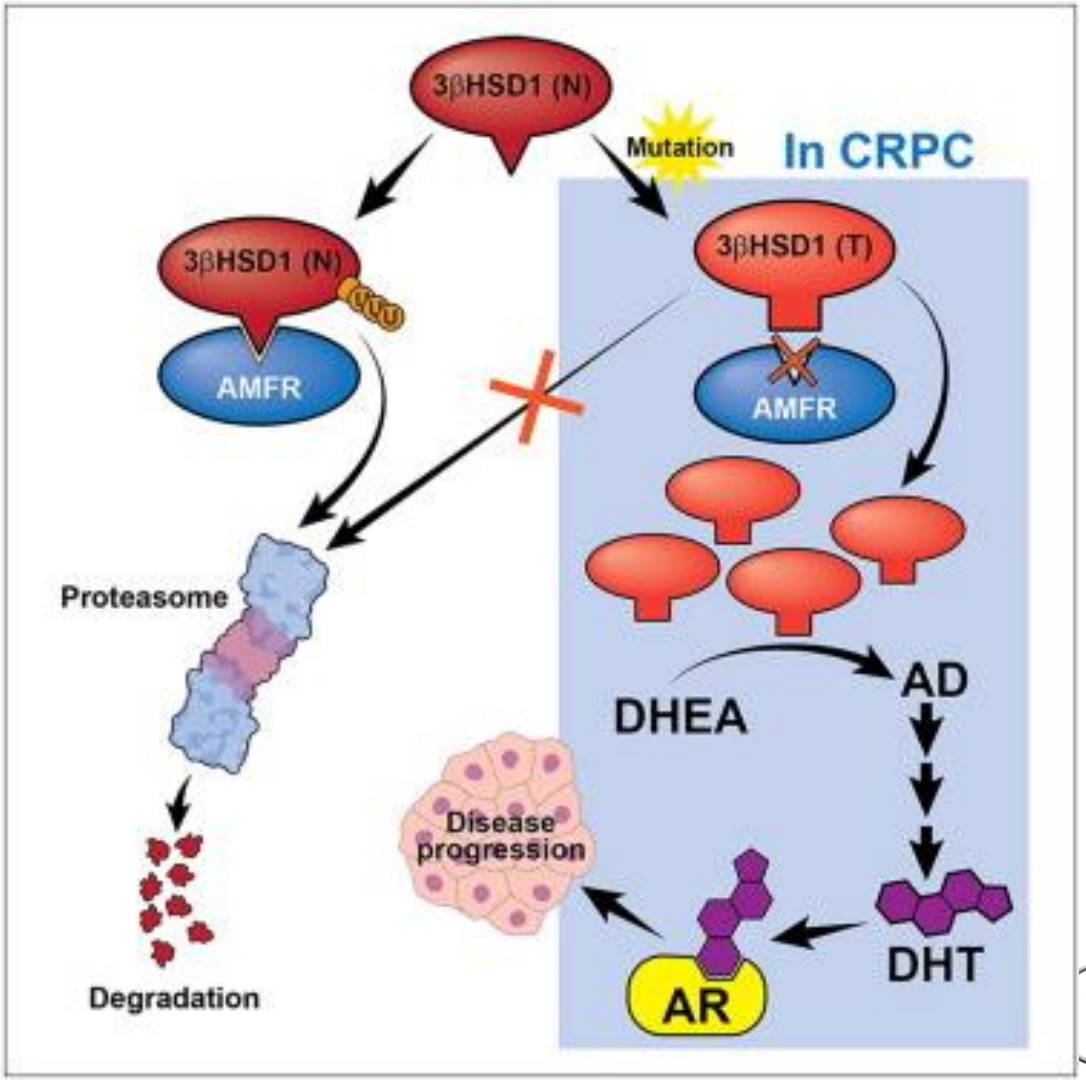
Volume 154, Issue 5, 29 August 2013, Pages 1074–1084

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,]

Mutation in 3BHSD1 Facilitates Conversion of Precursors to DHT



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Resistance to ADT/Abiraterone/Enzalutamide

- Androgen receptor mediated mechanisms
  - Activating mutations in AR
  - AR amplification
  - AR splice variants
- Up-regulation of other steroidogenic enzymes
- **GR- (or PR-) mediated transcriptional activation**

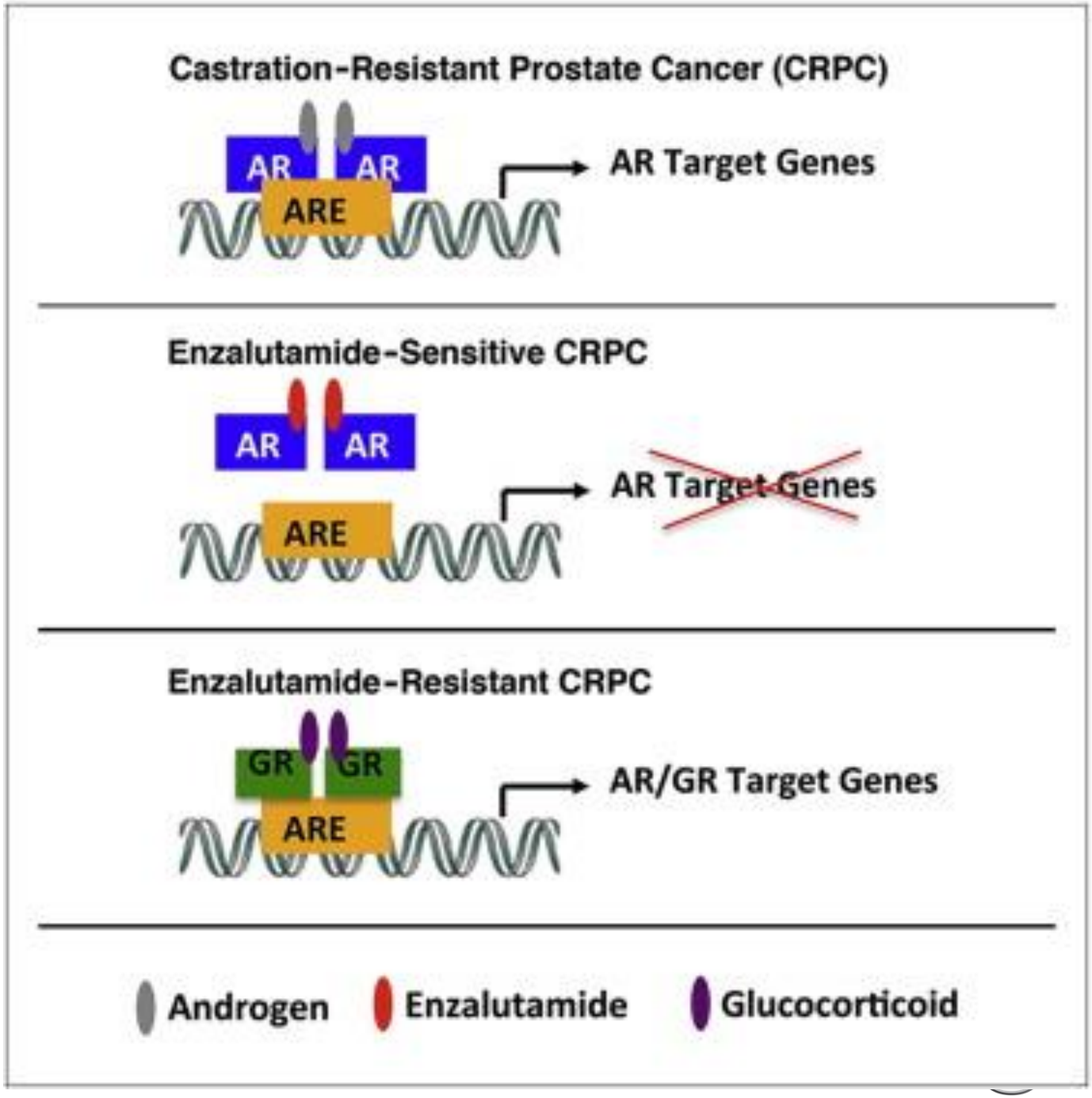
Cell

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

Article

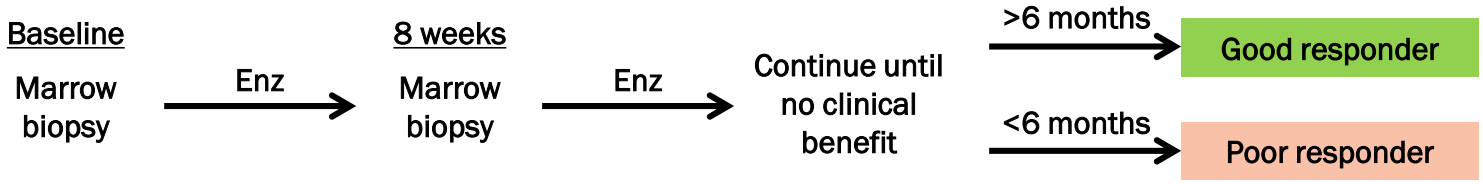
Glucocorticoid Receptor Confers Resistance to Antiandrogens by Bypassing Androgen Receptor Blockade

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,]

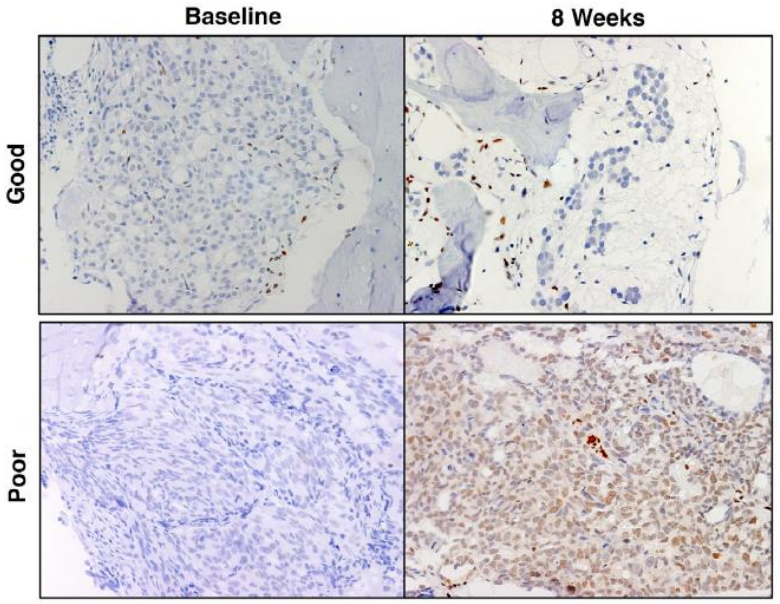

Castration-Resistant Prostate Cancer (CRPC)
AR
AR
ARE
AR Target Genes
Enzalutamide-Sensitive CRPC
AR
AR
ARE
AR Target Genes
Enzalutamide-Resistant CRPC
GR
GR
ARE
AR/GR Target Genes
Androgen
Enzalutamide
Glucocorticoid

Glucocorticoid Receptor Activation Post-Enzalutamide Treatment

- Acquired resistance to enzalutamide can be associated with increased expression of the glucocorticoid receptor (GR)



PSA decline	Good	Poor
>50%	11	1
<50%	2	13



Arora VK, et al. *Cell* .2013;155:1309–22.

Resistance to ADT/Abiraterone/Enzalutamide

- Androgen receptor mediated mechanisms
  - Activating mutations in AR
  - AR amplification
  - AR splice variants
- Upregulation of other steroidogenic enzymes
- GR- (or PR-) mediated transcriptional activation
- **Activation of other pathways**
  - **Androgen transporters**

Androgen Transporters

JOURNAL OF CLINICAL ONCOLOGY

ASCO 50 1964-2014

Official Journal of the American Society of Clinical Oncology

SLCO2B1 and *SLCO1B3* May Determine Time to Progression for Patients Receiving Androgen Deprivation Therapy for Prostate Cancer

Ming Yang, Wanling Xie, Elahe Mostaghel, Mari Nakabayashi, Lillian Werner, Tong Sun, Mark Pomerantz, Matthew Freedman, Robert Ross, Meredith Regan, Nima Sharifi, William Douglas Figg, Steven Balk, Myles Brown, Mary-Ellen Taplin, William K. Oh, Gwo-Shu Mary Lee and Philip W. Kantoff

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This Article

Published online before print May 23, 2011, doi: 10.1200/JCO.2010.31.2405

JCO June 20, 2011 vol. 29 no. 18 2565-2573

Abstract *Free*
» Full Text
PDF

CORRECTION:
Author

Statins block androgen transporters

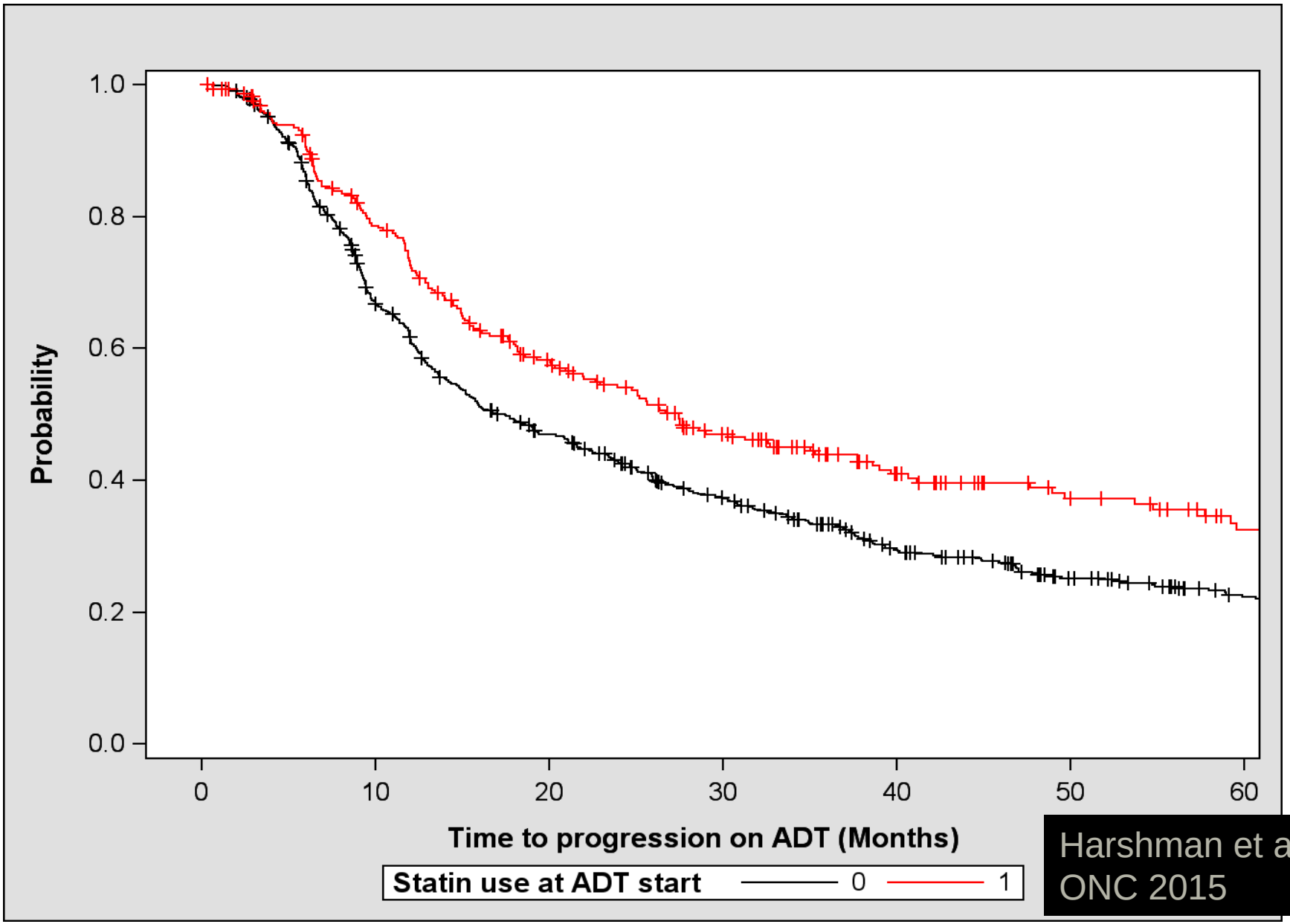
Original Investigation

Statin Use at the Time of Initiation of Androgen Deprivation Therapy and Time to Progression in Patients With Hormone-Sensitive Prostate Cancer

Lauren C. Harshman, MD; Xiaodong Wang, PhD; Mari Nakabayashi, MD; Wanling Xie, MS; Loana Valenca, MD; Lillian Werner, MS; Yongjiang Yu, PhD; Aaron M. Kantoff, BS; Christopher J. Sweeney, MBBS; Lorelei A. Mucci, ScD; Mark Pomerantz, MD; Gwo-Shu Mary Lee, PhD; Philip W. Kantoff, MD

JAMA Onc 2015

Statins (utilize androgen transporter) and duration of response to ADT



Harshman et al JAMA ONC 2015

Ligand and AR Independent Mechanisms-The Latest Stages

- Alternative molecular signaling pathways

A randomized phase II cross-over study of abiraterone + prednisone vs enzalutamide for patients with metastatic, castration-resistant prostate cancer

Kim N. Chi, Matti Annala, Katherine Sunderland, Daniel Khalaf, Daygen Finch, Conrad D. Oja, Joanna Vergidis, Muhammad Zulfiqar, Kevin Beja, Gillian Vandekerkhove, Martin Gleave, Alexander W. Wyatt

British Columbia Cancer Agency, Vancouver, BC; Institute of Biosciences and Medical Technology, Tampere, Finland; BC Cancer Agency - Vancouver Centre, Vancouver, BC; BC Cancer Agency - Centre for the Southern Interior, Kelowna, BC; British Columbia Cancer Agency, Fraser Valley Centre, Vancouver, BC; British Columbia Cancer Agency, Vancouver Island Centre, Victoria, BC; BC Cancer Agency, Abbotsford, BC; Vancouver Prostate Centre, Department of Urologic Sciences, University of British Columbia, Vancouver, BC; Vancouver Prostate Centre, University of British Columbia, Vancouver, BC

PRESENTED AT: ASCO ANNUAL MEETING '17 | #ASCO17

Chi et al Canc Disc 2018

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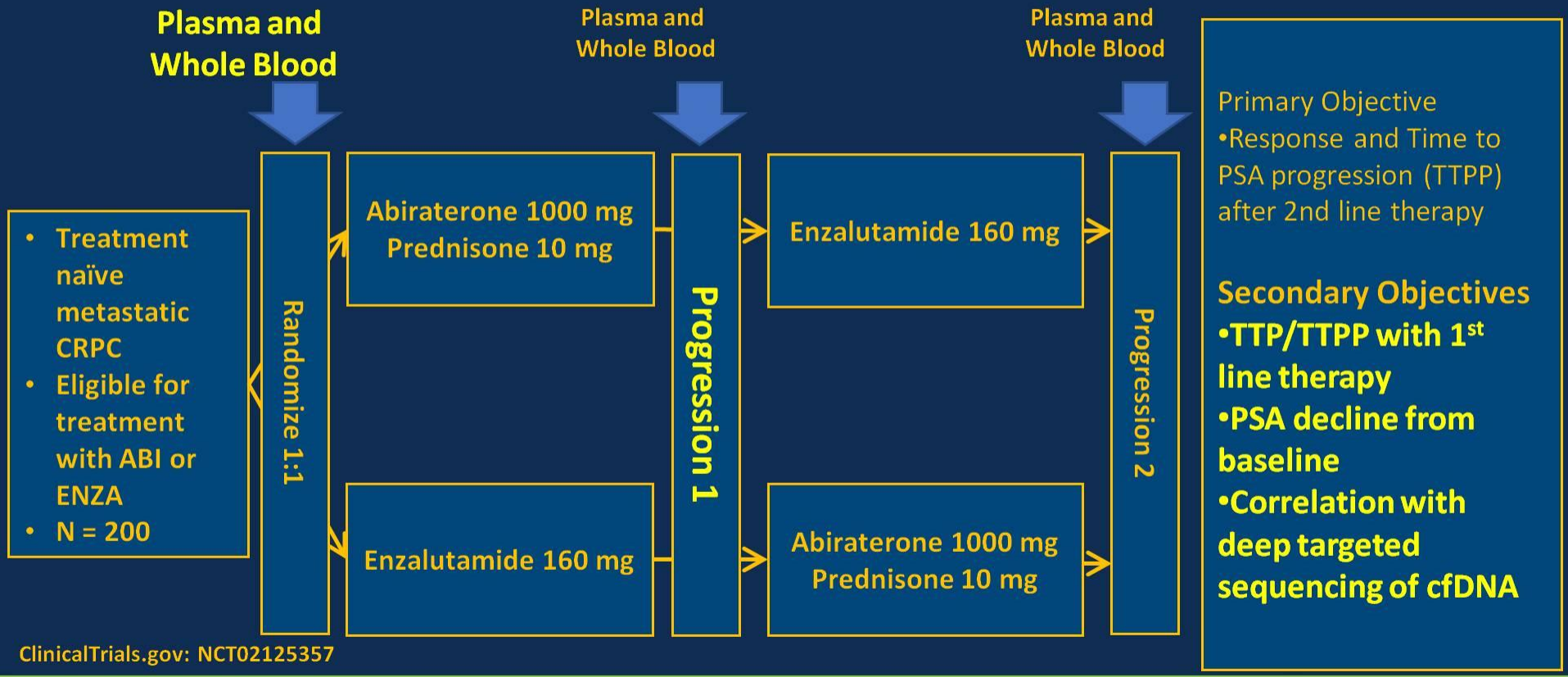
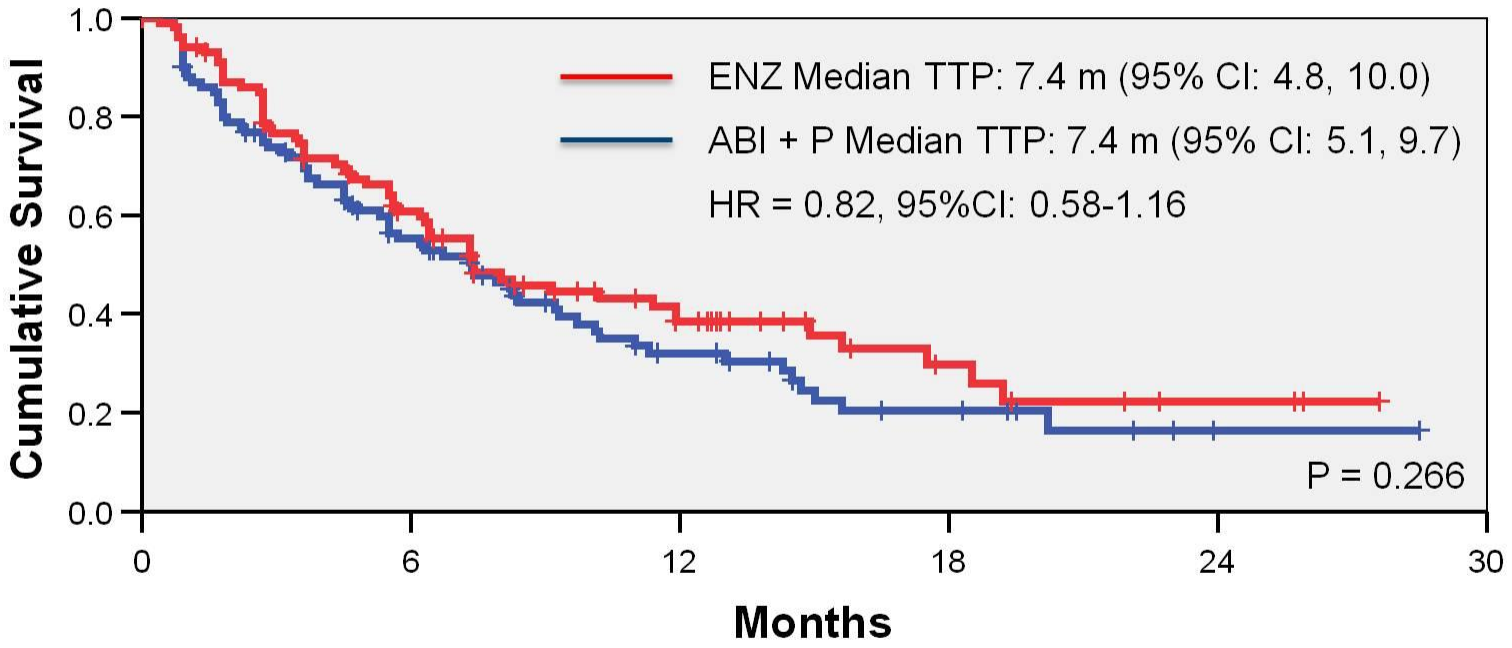
Study Schema



Chi et al Canc Disc 2018

Time to Progression



*First of confirmed PSA progression (PCWG3), clinical or radiological progression, or death from disease

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Genomic Correlates with TTP

Genomic Alteration	Median TTP Positive vs Negative* (months)	Univariate		Multivariate***	
		HR	P-value	HR	P-value
BRCA2/ATM truncating mutation	**1.8 vs 8.0**	**6.14 (3.35-11.26)**	**<0.001**	**5.34 (2.84-10.03)**	**<0.001**
TP53 inactivation**	**3.3 vs 10.2**	**2.78 (1.92-4.03)**	**<0.001**	**2.21 (1.38-3.55)**	**0.001**
PI3K pathway	**3.3 vs 10.4**	**2.73 (1.91-3.90)**	**<0.001**	**1.95 (1.31-2.90)**	**<0.001**
AR amplification	**5.0 vs 9.3**	**2.05 (1.43-2.93)**	**<0.001**	1.29 (0.85-2.09)	0.271
RB1 inactivation**	**3.6 vs 8.2**	**2.03 (1.36-3.04)**	**<0.001**	1.45 (0.95-2.21)	0.08
SPOP mutation	7.3 vs 7.4	1.00 (0.51-1.97)	1.00		
AR mutation	6.2 vs 7.4	1.02 (0.53-1.95)	0.95		

Includes patients without detectable ctDNA; ** Mutation, deletion, or rearrangement
*** MVA includes trial arm, presence of quantifiable ctDNA, and clinical prognostic factors (LDH, ALP, Visceral Mets, ECOG PS)

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Chi et al Canc Disc 2018

Ligand and AR Independent Mechanisms-The Latest Stages

- Alternative molecular signaling pathways
- Evolution of AR and PSA negative cells
- Acquisition of neuroendocrine differentiation

CROSS RESISTANCE

Cross-Resistance: Abiraterone and Enzalutamide

	Therapy	Prior Therapy	PSA_{50}	ORR	PFS
Noonan et al 2013	Abiraterone	Enzalutamide	4%	0%	3.9 mo
Loriot et al 2013	Abiraterone	Enzalutamide	8%	8%	2.7 mo
Smith et al 2014	Abiraterone	Enzalutamide			2.8 mo
Schrader et al 2013	Enzalutamide	Abiraterone	28%	3%	–
Badrising et al 2013	Enzalutamide	Abiraterone	21%	–	3.0 mo
Cheng et al 2014	Enzalutamide	Abiraterone	20%	–	–

Noonan KL, et al. *Ann Oncol.* 2013;24(7):1802-1807.
Loriot Y, et al. *Ann Oncol.* 2013;24(7):1807-1812.
Smith, et al., ASCO GU. 2014
Schrader AJ, et al. *Eur Urol.* 2014;65(1):30-36.
Badrising S, et al. *Cancer.* 2014;120(7):968-975
Cheng et al. ASCO 2014

PSA Responses Diminish With Second-Line AR Therapy

	ENZA → ABI		ABI→ ENZA	
	First Line	Second Line	First Line	Second Line
≥50% PSA Decline	55-60%	4-8%	38-46%	13-29%

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Conclusions

- Understanding the persistence of the androgen signaling pathway in CRPC has been transformative
- Cross resistance occurs between agents
- Numerous mechanisms of resistance
- We need validated and easily accessable biomarkers to guide therapy

Thank you