Memorial Sloan Kettering
Cancer Center

Predictive biomarkers and new therapeutic targets

Philip Kantoff, MD
Chairman, Department of Medicine
Memorial Sloan Kettering

Overview

- Elephants and cancer-DNA Damage Repair

Overview

- Elephants and cancer

Potential Mechanisms for Cancer Resistance in Elephants and Comparative Cellular Response to DNA Damage in Humans

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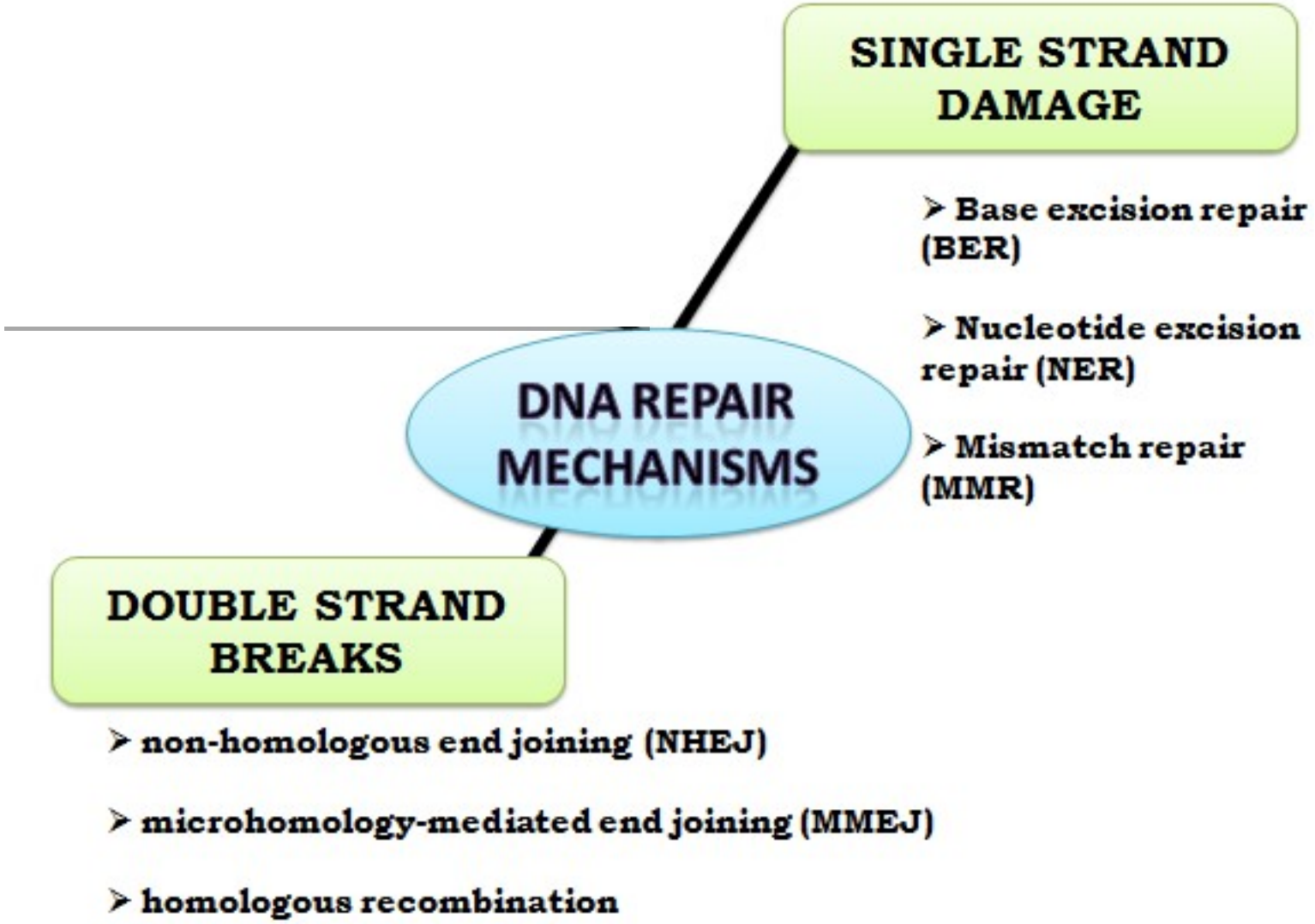
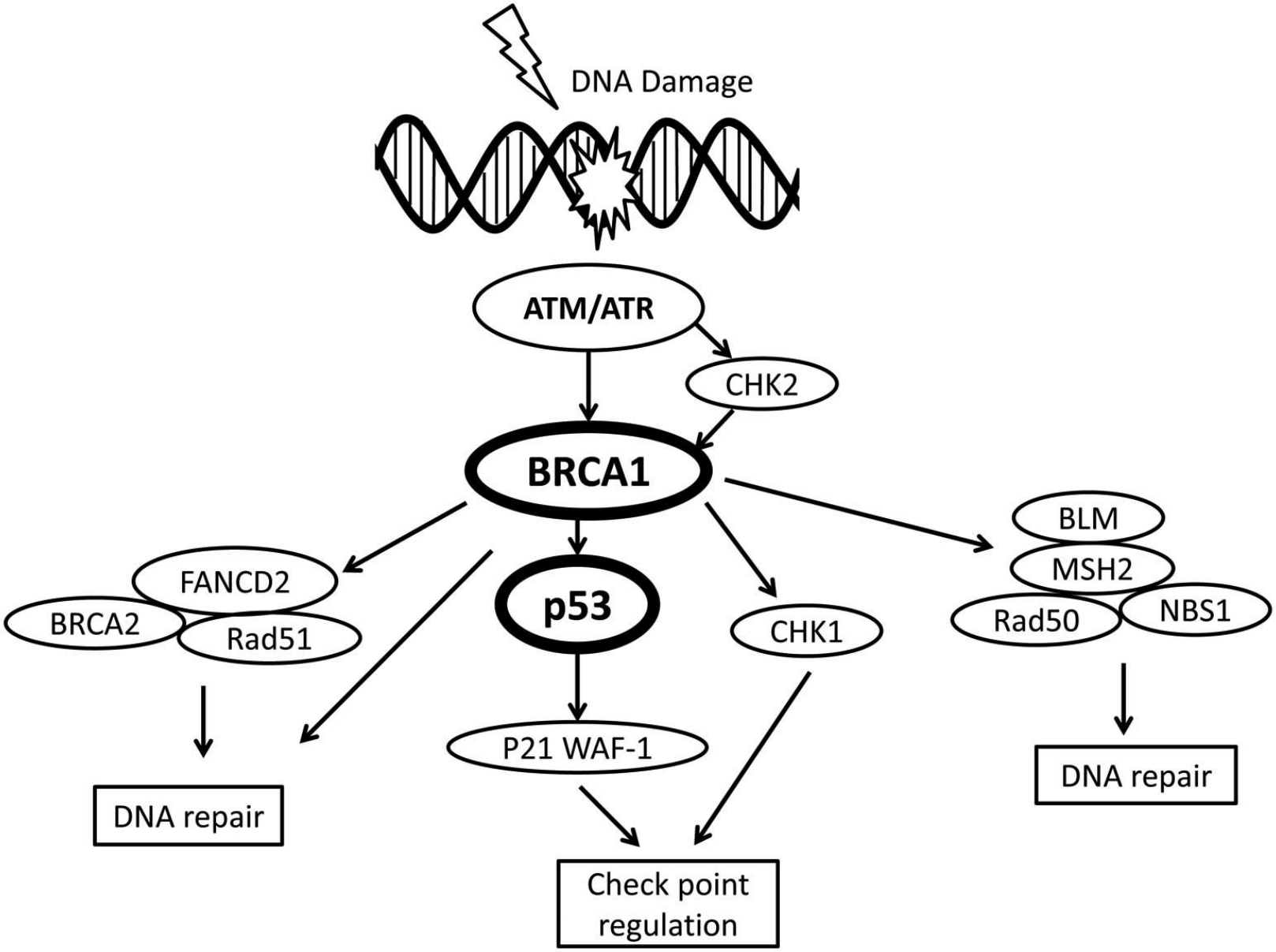
Cancer across species

- Across mammals, cancer mortality does not increase with body size and/or maximum life span;
- Despite their large body size and long life span, elephants are cancer resistant, with an estimated cancer mortality of 5%, compared with humans, who have up to a 25% cancer mortality;
- While humans have 1 copy of the gene p53, African elephants have at least 20 copies;

p53

- p53 prevents cancer formation and assists in DNA repair;
- p53 is called the “Guardian of the genome” because of its essential role in DNA repair;
- Every cell has 2 copies of it;
- Some people are born with only 1 normal copy- Li Fraumeni syndrome-develop multiple types of cancer; and
- p53 is the most commonly mutated gene in cancer (over 50% of cancers have a loss of p53).


SINGLE STRAND DAMAGE
➢ Base excision repair (BER)
➢ Nucleotide excision repair (NER)
➢ Mismatch repair (MMR)
DNA REPAIR MECHANISMS
DOUBLE STRAND BREAKS
➢ non-homologous end joining (NHEJ)
➢ microhomology-mediated end joining (MMEJ)
➢ homologous recombination



Many genes involved in DNA repair

- Many of the DNA repair genes are mutated in cancer;
  - p53 (many cancers)
  - BRCA1 and BRCA2 (ovarian and breast but others as well)
  - The Fanconi genes (many cancers)
  - MSH2 (colon cancer)

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Dream Team Principal
University of Washington /
Fred Hutchinson Cancer Research Center

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DANA-FARBER CANCER INSTITUTE

Philip Kantoff, MD
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Mark Rubin, MD
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Johann de Bono, MD, PhD
Institute of Cancer Research/
Royal Marsden Hospital

Charles Sawyers, MD
Dream Team Co-Leader
Memorial Sloan Kettering
Cancer Center

ICR The Institute of Cancer Research

THE ROYAL MARSDEN

SU2C/PCF International Prostate Cancer Team

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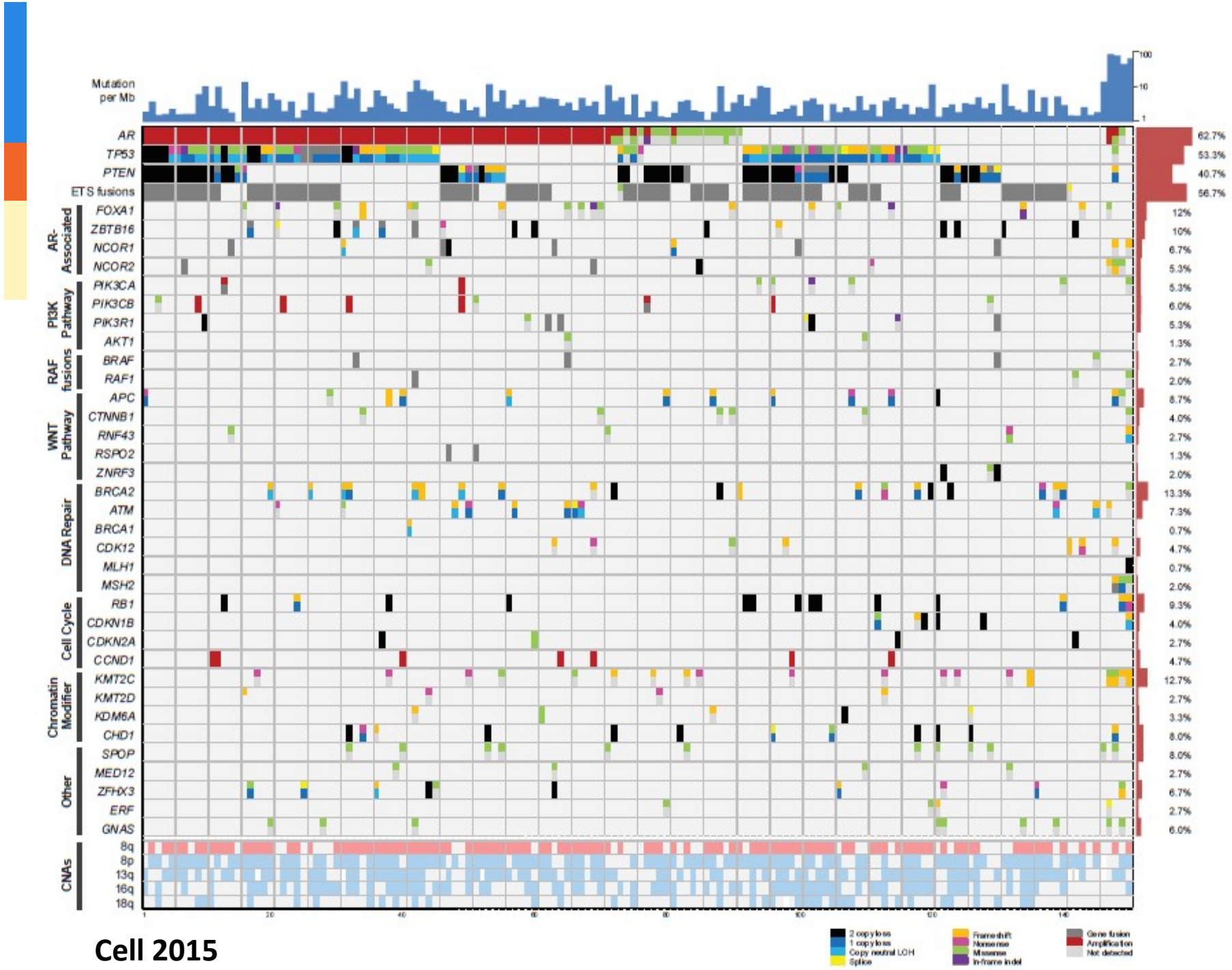
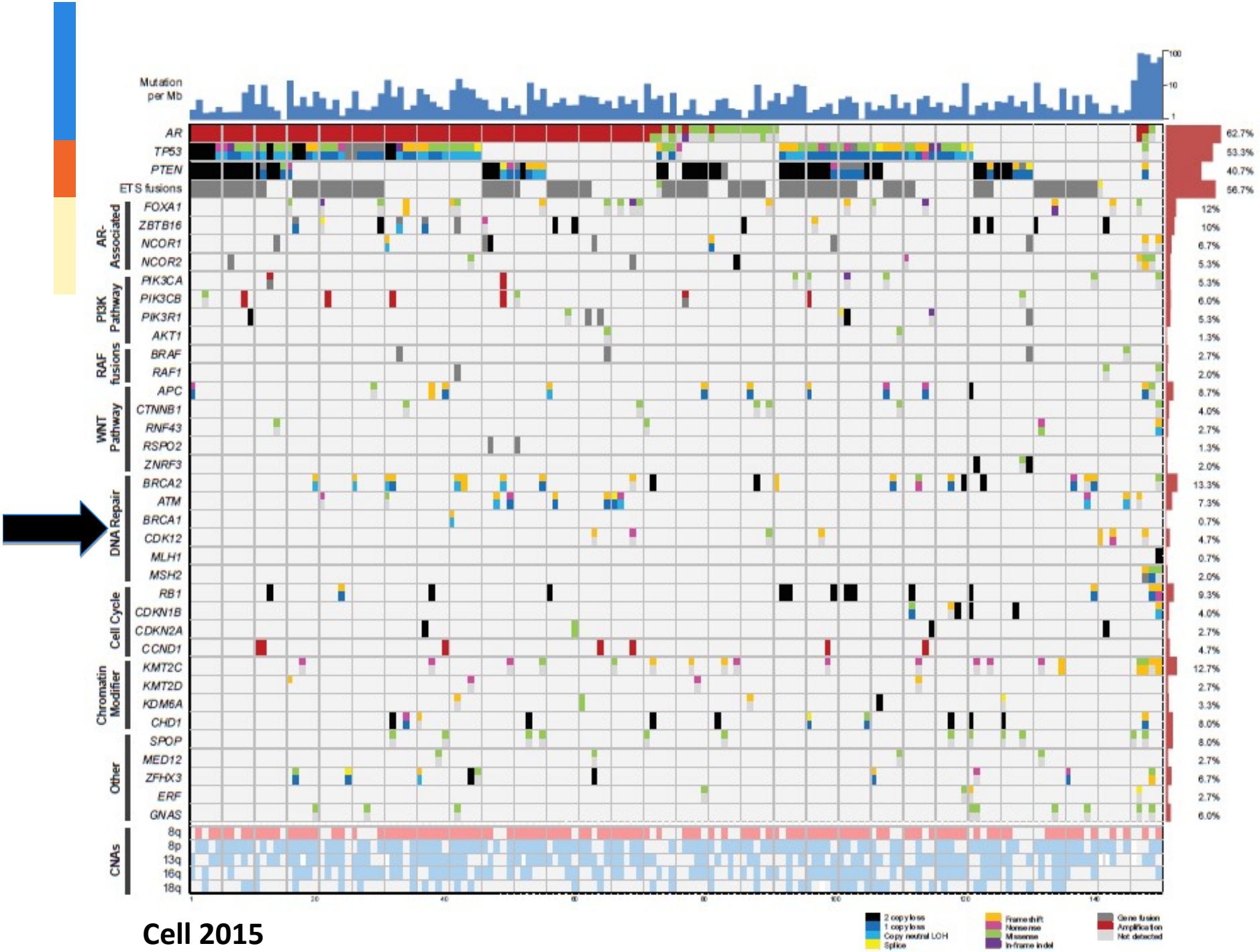

Mutation per Mb
100
10
1
AR
TP53
PTEN
ETS fusions
AR-Associated
FOXA1
ZBTB16
NCOR1
NCOR2
PI3K Pathway
PIK3CA
PIK3CB
PIK3R1
AKT1
RAF fusions
BRAF
RAF1
WNT Pathway
APC
CTNNB1
RNF43
RSPO2
ZNRF3
DNA Repair
BRCA2
ATM
BRCA1
CDK12
MLH1
MSH2
Cell Cycle
RB1
CDKN1B
CDKN2A
CCND1
Chromatin Modifier
KMT2C
KMT2D
KDM6A
CHD1
Other
SPOP
MED12
ZFHX3
ERF
GNAS
CNAs
8q
8p
13q
16q
18q
62.7%
53.3%
40.7%
56.7%
12%
10%
6.7%
5.3%
5.3%
6.0%
5.3%
1.3%
2.7%
2.0%
8.7%
4.0%
2.7%
1.3%
2.0%
13.3%
7.3%
0.7%
4.7%
0.7%
2.0%
9.3%
4.0%
2.7%
4.7%
12.7%
2.7%
3.3%
8.0%
8.0%
2.7%
6.7%
2.7%
6.0%
1
20
40
60
80
100
120
140
2 copy loss
1 copy loss
Copy neutral LOH
Splice
Frameshift
Nonsense
Missense
In-frame indel
Gene fusion
Amplification
Not detected

Cell 2015


Mutation per Mb
AR
TP53
PTEN
ETS fusions
AR-Associated
FOXA1
ZBTB16
NCOR1
NCOR2
PI3K Pathway
PIK3CA
PIK3CB
PIK3R1
AKT1
RAF fusions
BRAF
RAF1
WNT Pathway
APC
CTNNB1
RNF43
RSPO2
ZNRF3
DNA Repair
BRCA2
ATM
BRCA1
CDK12
MLH1
MSH2
Cell Cycle
RB1
CDKN1B
CDKN2A
CCND1
Chromatin Modifier
KMT2C
KMT2D
KDM6A
CHD1
Other
SPOP
MED12
ZFHX3
ERF
GNAS
CNAs
8q
8p
13q
16q
18q
62.7%
53.3%
40.7%
56.7%
12%
10%
6.7%
5.3%
5.3%
6.0%
5.3%
1.3%
2.7%
2.0%
8.7%
4.0%
2.7%
1.3%
2.0%
13.3%
7.3%
0.7%
4.7%
0.7%
2.0%
9.3%
4.0%
2.7%
4.7%
12.7%
2.7%
3.3%
8.0%
8.0%
2.7%
6.7%
2.7%
6.0%
2 copy loss
1 copy loss
Copy neutral LOH
Splice
Frameshift
Nonsense
Missense
In-frame indel
Gene fusion
Amplification
Not detected

Cell 2015

Table 2: Germline DNA Repair Gene Mutation Frequencies

	Metastatic PC (n=692)		ExAC (without TCGA)		Metastatic PC vs. ExAC RR (95% CI)	*P*	Primary PC (n=499)		Metastatic PC vs. Primary PC RR (95% CI)	*P*†
Gene	Count	Freq (%)	Count	Freq (%)			Count	Freq (%)		
ATM	11	1.59%	153	0.25%	6.2 (3.1-11.1)	<0.001	5	1.00%	1.6 (0.8-2.8)	0.123
ATR	2	0.29%	45	0.08%	3.7 (0.4-13.3)	0.103	0	0.00%	-	<0.001
*BAP1**	0	0.00%	1	0.00%	-	-	0	0.00%	-	-
*BARD1**	0	0.00%	42	0.07%	-	-	1	0.20%	-	-
BRCA1	6	0.87%	133	0.27%	3.2 (1.2-6.9)	0.013	3	0.60%	1.4 (0.5-3.1)	0.320
BRCA2	37	5.35%	178	0.30%	17.6 (12.5-24.0)	<0.001	1	0.20%	26.7 (18.9-36.4)	<0.001
*BRIP1**	1	0.18%	116	0.19%	0.9 (0.0-5.1)	1.000	1	0.20%	0.9 (0.0-4.9)	1.000
*CHEK2**	10	1.87%	361	0.64%	2.9 (1.4-5.3)	0.003	2	0.40%	4.7 (2.2-8.5)	0.000
*FAM175A**	1	0.18%	57	0.09%	1.9 (0.0-10.5)	0.412	0	0.00%	-	<0.001
*GEN1**	2	0.46%	47	0.08%	5.8 (0.7-20.7)	0.048	0	0.00%	-	<0.001
MLH1	0	0.00%	12	0.02%	-	-	0	0.00%	-	-
MRE11A	1	0.14%	38	0.06%	2.3 (0.1-12.8)	0.353	1	0.20%	0.7 (0.0-4.0)	1.000
MSH2	1	0.14%	23	0.04%	3.5 (0.1-19.7)	0.246	1	0.20%	0.7 (0.0-4.0)	1.000
MSH6	1	0.14%	43	0.07%	2.0 (0.1-11.2)	0.390	1	0.20%	0.7 (0.0-4.0)	1.000
NBN	2	0.29%	78	0.14%	2.1 (0.3-7.6)	0.243	1	0.20%	1.4 (0.2-5.2)	0.404
PALB2	3	0.43%	78	0.13%	3.3 (0.7-9.7)	0.062	2	0.40%	1.1 (0.2-3.1)	0.760
PMS2	2	0.29%	61	0.11%	2.6 (0.3-9.4)	0.180	1	0.20%	1.4 (0.2-5.2)	0.404
RAD51C	1	0.14%	63	0.05%	2.8 (0.1-15.4)	0.303	2	0.40%	0.4 (0.0-2.0)	0.537
RAD51D	3	0.43%	48	0.05%	8.9 (1.8-25.9)	0.005	1	0.20%	2.2 (0.4-6.3)	0.163
*XRCC2**	0	0.00%	32	0.03%	-	-	0	0.00%	-	-

** Metastatic cases with inadequate sequencing for this gene are censored*

† Tests were one-sided for when mutation frequencies in primary PC patients were zero

We can take advantage of loss of DNA repair capability to treat cancer

- Through the concept of “synthetic lethality”, we take advantage of mutations in DNA repair genes that permit and do not repair single strand breaks and add drugs that facilitate breakage of second strand;
- PARP inhibitors do this and now approved for treatment of BRCA mutated ovarian cancer; and
- It is now apparent that these DNA repair gene mutations are common; and
- PARP inhibitors will be useful in a number of different cancers.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

DNA-Repair Defects and Olaparib in Metastatic Prostate Cancer

Joaquin Mateo, M.D., Suzanne Carreira, Ph.D., Shahneen Sandhu, M.D., Susana Miranda, B.Sc., Helen Mossop, M.Math.Stat., Raquel Perez-Lopez, M.D., Daniel Nava Rodrigues, M.D., Dan Robinson, Ph.D., Aurelius Omlin, M.D., Nina Tunariu, M.D.Res., Gunther Boysen, Ph.D., Nuria Porta, Ph.D., Penny Flohr, B.Sc., Alexa Gillman, B.Sc., Ines Figueiredo, B.Sc., Claire Paulding, B.Sc., George Seed, M.Sc., Suneil Jain, M.D., Christy Ralph, M.D., Andrew Protheroe, M.D., Ph.D., Syed Hussain, M.D., Robert Jones, M.D., Ph.D., Tony Elliott, M.D., Ph.D., Ursula McGovern, M.D., Ph.D., Diletta Bianchini, M.D., Jane Goodall, B.Sc., Zafeiris Zafeiriou, M.D., Chris T. Williamson, Ph.D., Roberta Ferraldeschi, M.D., Ph.D., Ruth Riisnaes, F.I.B.M.S., Bernardette Ebbs, B.T.E.C., Gemma Fowler, B.Sc., Desamparados Roda, M.D., Wei Yuan, Ph.D., Yi-Mi Wu, Ph.D., Xuhong Cao, M.S., Rachel Brough, Ph.D., Helen Pemberton, Ph.D., Roger A'Hern, Ph.D., Amanda Swain, Ph.D., Lakshmi P. Kunju, M.D., Rosalind Eeles, M.D., Ph.D., Gerhardt Attard, M.D., Ph.D., Christopher J. Lord, Ph.D., Alan Ashworth, Ph.D., Mark A. Rubin, M.D., Karen E. Knudsen, Ph.D., Felix Y. Feng, M.D., Ph.D., Arul M. Chinnaiyan, M.D., Ph.D., Emma Hall, Ph.D., and Johann S. de Bono, M.B., Ch.B., Ph.D.

N Engl J Med 2015; 373:1697-1708 | October 29, 2015 | DOI: 10.1056/NEJMoa1506859

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Olaparib in mCRPC

- 50 patients with mCRPC treated with Olaparib;
- Of the 16 patients who responded to Olaparib, 14 were found to have mutations in known DNA damage-repair genes, while only 2 of the 33 non-responders had mutations in any of these genes;
- Altered DNA damage-repair genes identified in the tumors of responders included BRCA2, BRCA1, ATM, FANCA, CHEK2, PALB2, HDAC2, MRE11, and NBN; and
- Germline or somatic alteration of DNA repair was 94% predictive of response.

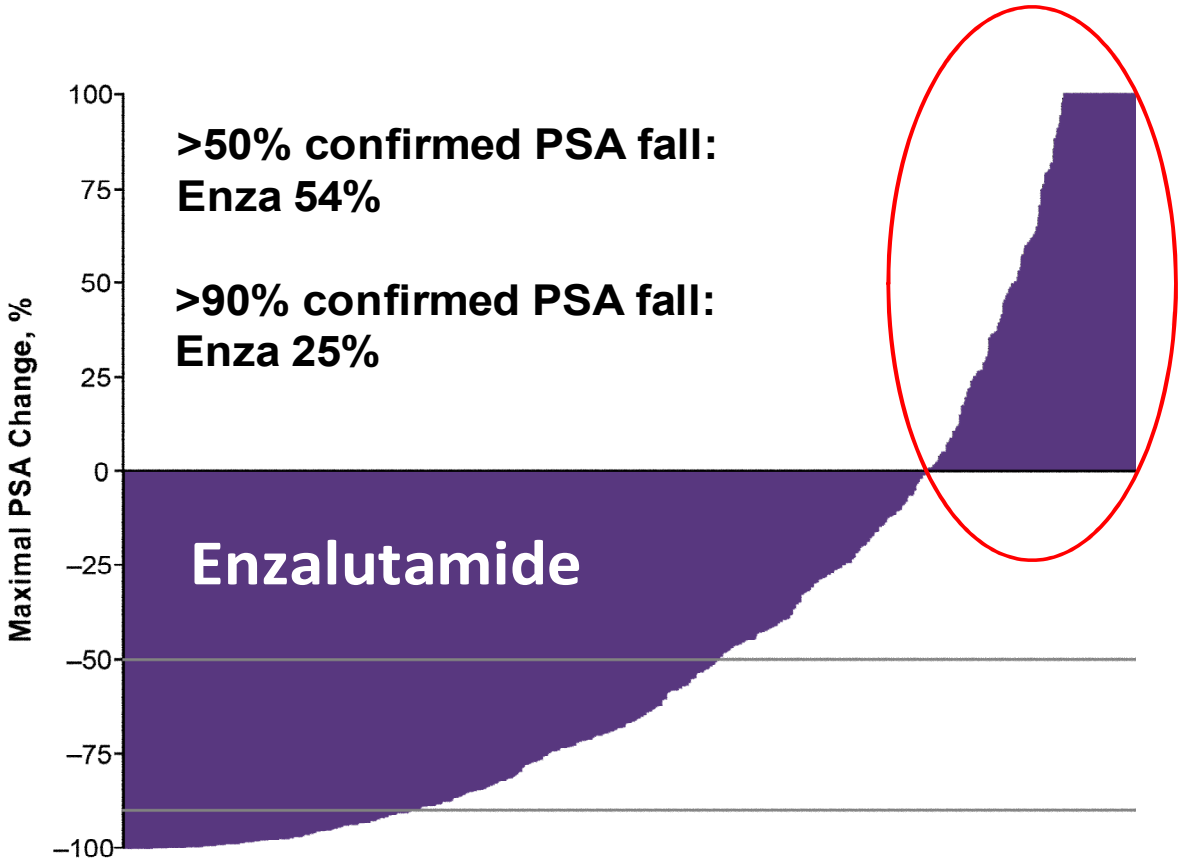
Overview

- Elephants and cancer-DNA Damage Repair
- Biomarkers of resistance to ADT

Persistent ligand in CRPC-The concept that led to new AR targeted agents

- Genetic evidence-AR-mutated or amplified AR ;
- Persistent AR expression and expression of androgen regulated genes; and
- Persistent intratumoral ligand-T or DHT or precursors.

Enzalutamide or Abiraterone responses:



21%
Never **had a PSA decline**

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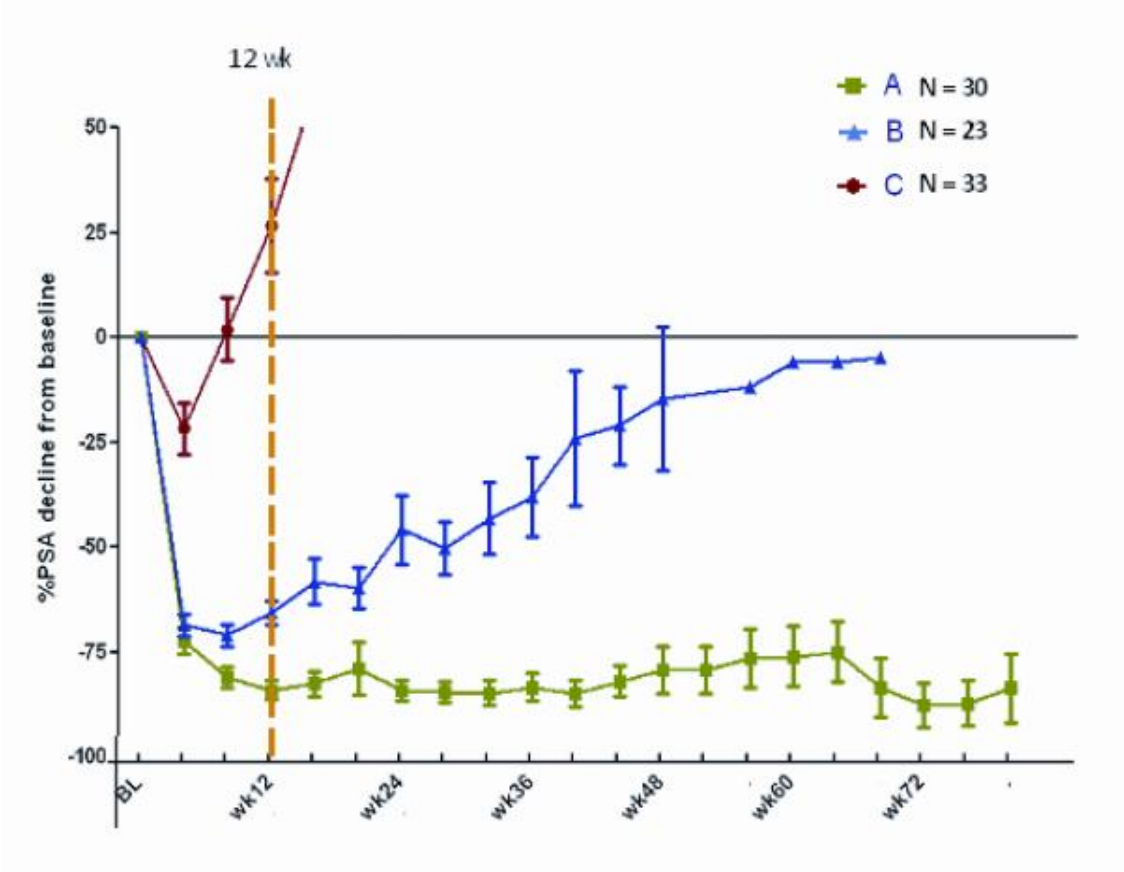
Types of responses to AR-Targeting agents

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 Sensitivity (*drifters*: rapid PSA decline, followed by slow increase)

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

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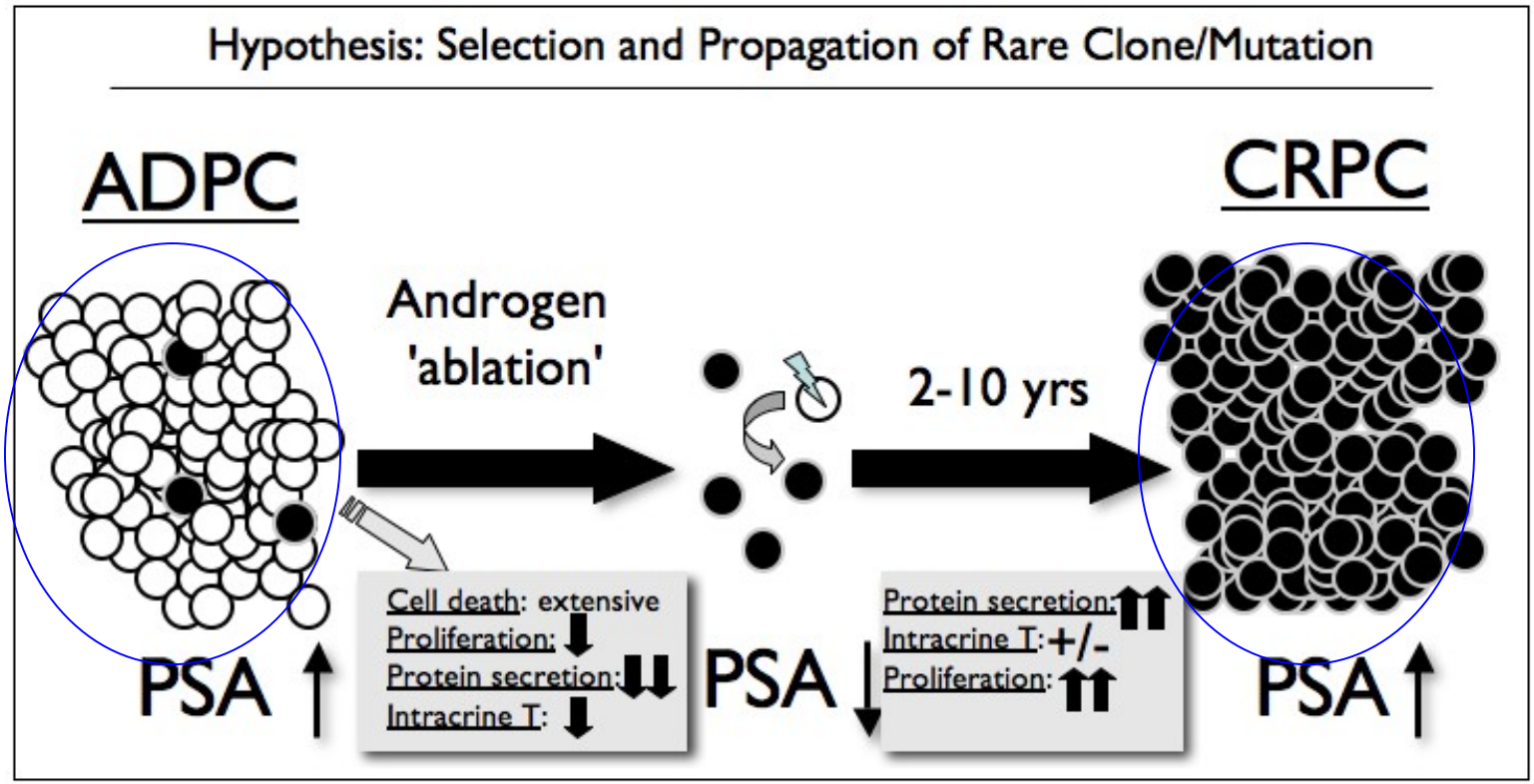
Rathkopf D, Scher HI. *Cancer J*. 2013;19(1):43-49.

Resistance Mechanisms



○	Androgen dependent cell
●	CRPC

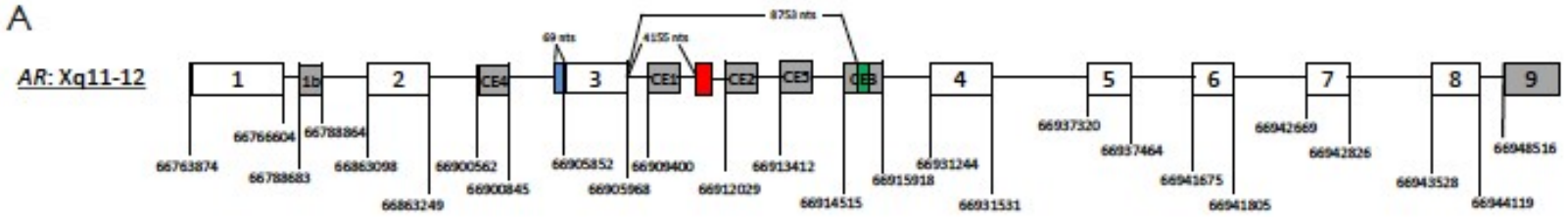
Overview of Mechanisms of Primary Resistance

- Adaptive mechanisms by which cells reprogram themselves
  - Probably epigenetic
- Acquired mechanisms
  - Usually genetic

Acquired Resistance to ADT/Abiraterone/Enzalutamide

- Androgen receptor mediated mechanisms
  - Activating mutations in AR
  - AR amplification-
  - AR splice variants

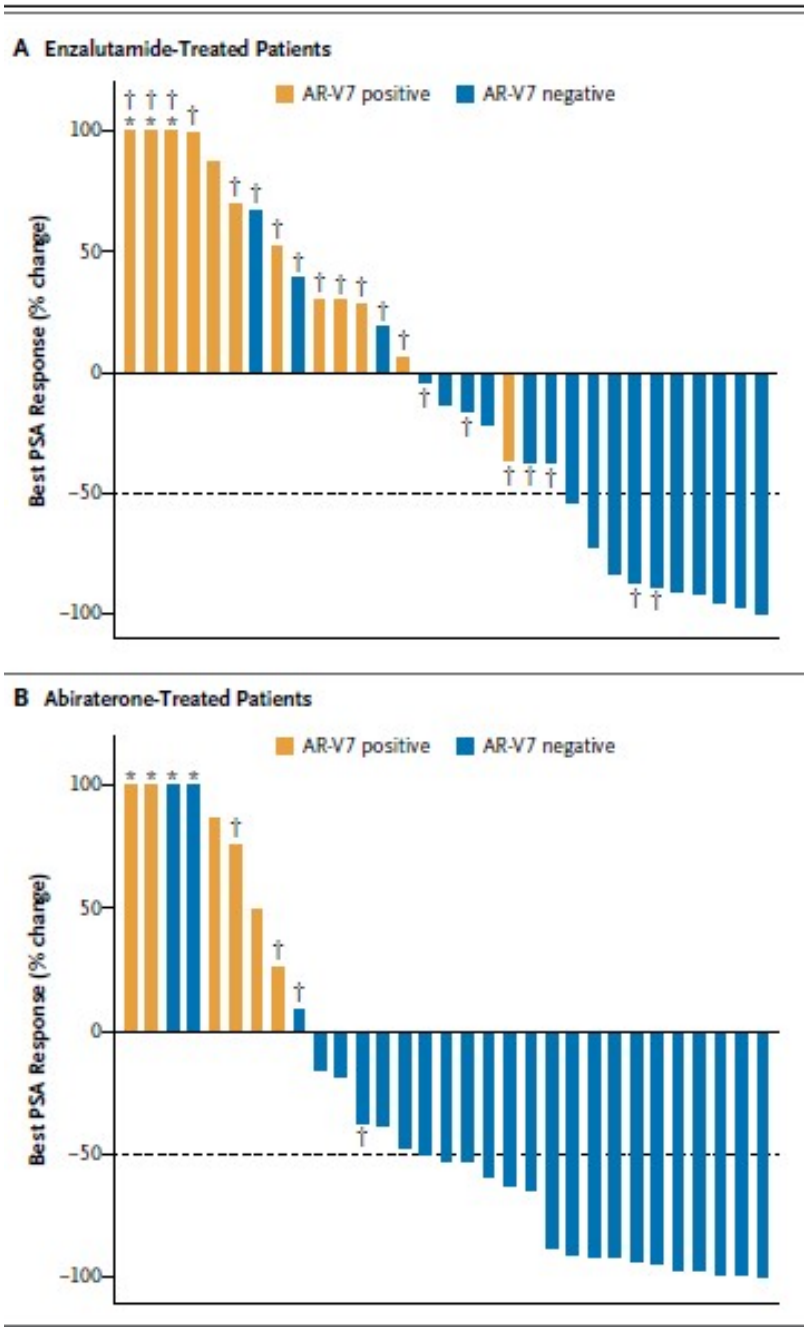
AR Splice Variants



B

AR-Vs	Alternative names	Transcriptional activity	Transcripts	Proteins
AR-FL		Ligand-stimulated	1 2 3 4 5 6 7 8	AR-FL:MTLGDNLPEQAAFWRHLHIFWDHVVKK stop
AR-45		Conditional	1b 2 3 4 5 6 7 8	AR45: start MILWLHSLETARDHVLPIDYY---FHTQ stop
AR-23		Ligand-stimulated	1 2 3 4 5 6 7 8	AR23: KVFFKRAAEEIPEERDSGNSCSELSTLVFVLPGKQKYLCA---FHTQ stop
AR-V1	AR4	Conditional	1 2 3 CE1	AR-V1:MTLGAVVVSERILRVFGVSEWOP stop
AR-V2		Unknown	1 2 3 3 CE1	AR-V2:MTLGAVVVSERILRVFGVSEWOP stop
AR-V3	AR1/2/2b	Constitutive	1 2 CE4 3 CE1	AR-V3:RAAEGFFRMNKLKESSDTNPKPYCMAAPMGLTENNRNRKKSYRETNLKAVSWPLNHT stop
AR-V4	AR1/2/3/2b, AR5	Constitutive	1 2 3 CE4 3 CE1	AR-V4:MTLGGFFRMNKLKESSDTNPKPYCMAAPMGLTENNRNRKKSYRETNLKAVSWPLNHT stop
AR-V5		Unknown	1 2 3 CE2	AR-V5:MTLGD stop
AR-V6		Unknown	1 2 3 CE2	AR-V6:MTLGAGSRVS stop
AR-V7	AR3	Constitutive	1 2 3 CE3	AR-V7:MTLGEKFRVGNCKHLKMTRP stop
AR-V8		Unknown	1 2 3	AR-V8:MTLGGFDNLCELSS stop
AR-V9		Conditional	1 2 3 CE5	AR-V9:MTLGDNLPEQAAFWRHLHIFWDHVVKK stop
AR-V10		Unknown	1 2 3	AR-V10:MTPSSGTNSVFLPHRDVVRTGCRSNSGYHSCSCEYHDYCFL stop
AR-V11		Unknown	1 2 3	AR-V11:MTLGGKILFFLFLLLPLSPFSLIF stop (EXON RUNON)
AR-V12	AR^{v567es}	Constitutive	1 2 3 4 8 9	AR-V12:KALPDCERAASVHF Stop
AR-V13		Inactive	1 2 3 4 5 6 9	AR-V13:LFSINHT Stop
AR-V14		Unknown	1 2 3 4 5 6 7 9	AR-V14:SVQPITPDAMYL Stop
AR-8		Inactive	1 3 CE3	AR8: YSGPYGDMRNTRRKRLWKLIIRSINSCICSPRETEVPVRQQK stop

Transl Androl Urol. 2013

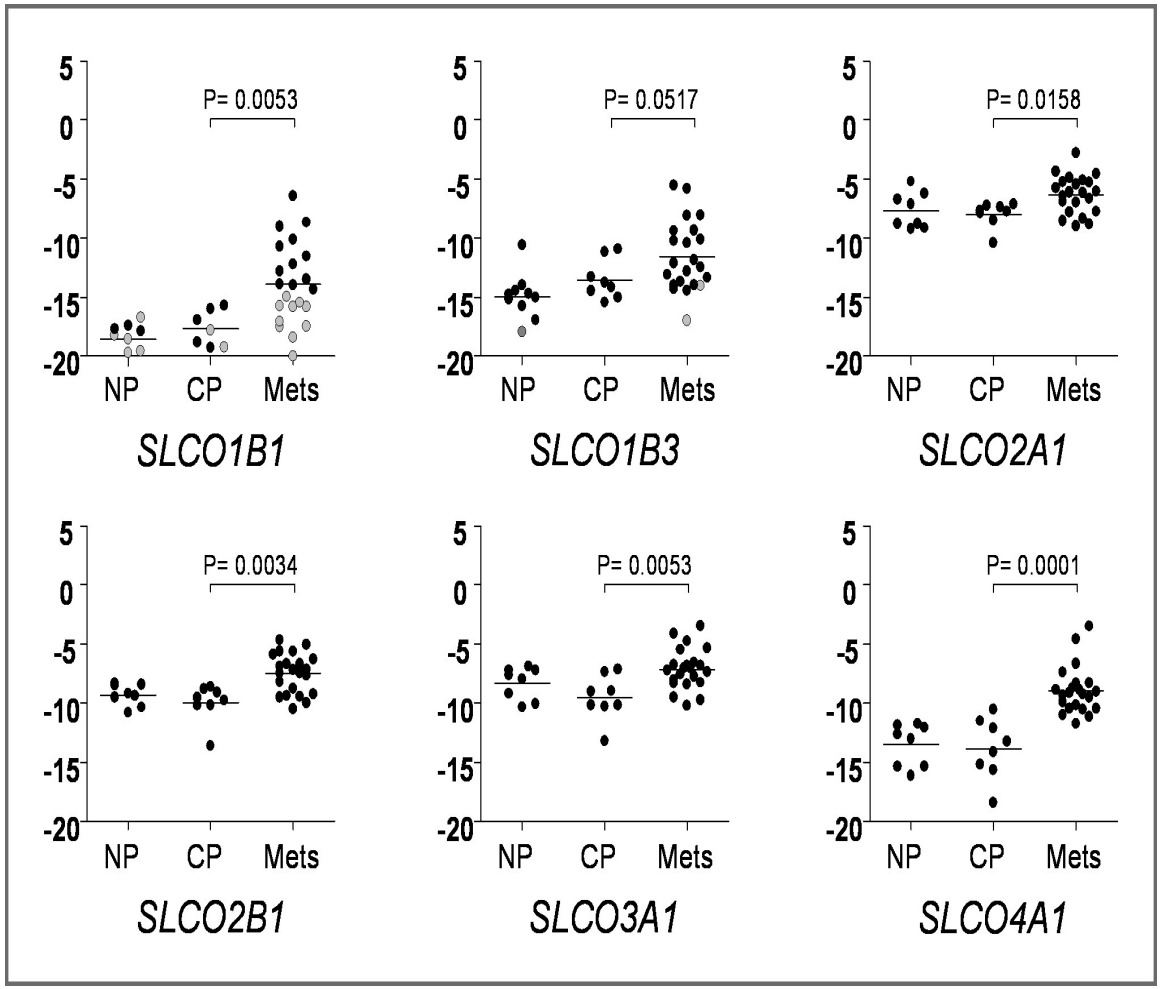


Antonarakis, et. al NEJM 2014

Resistance to ADT/Abiraterone/Enzalutamide

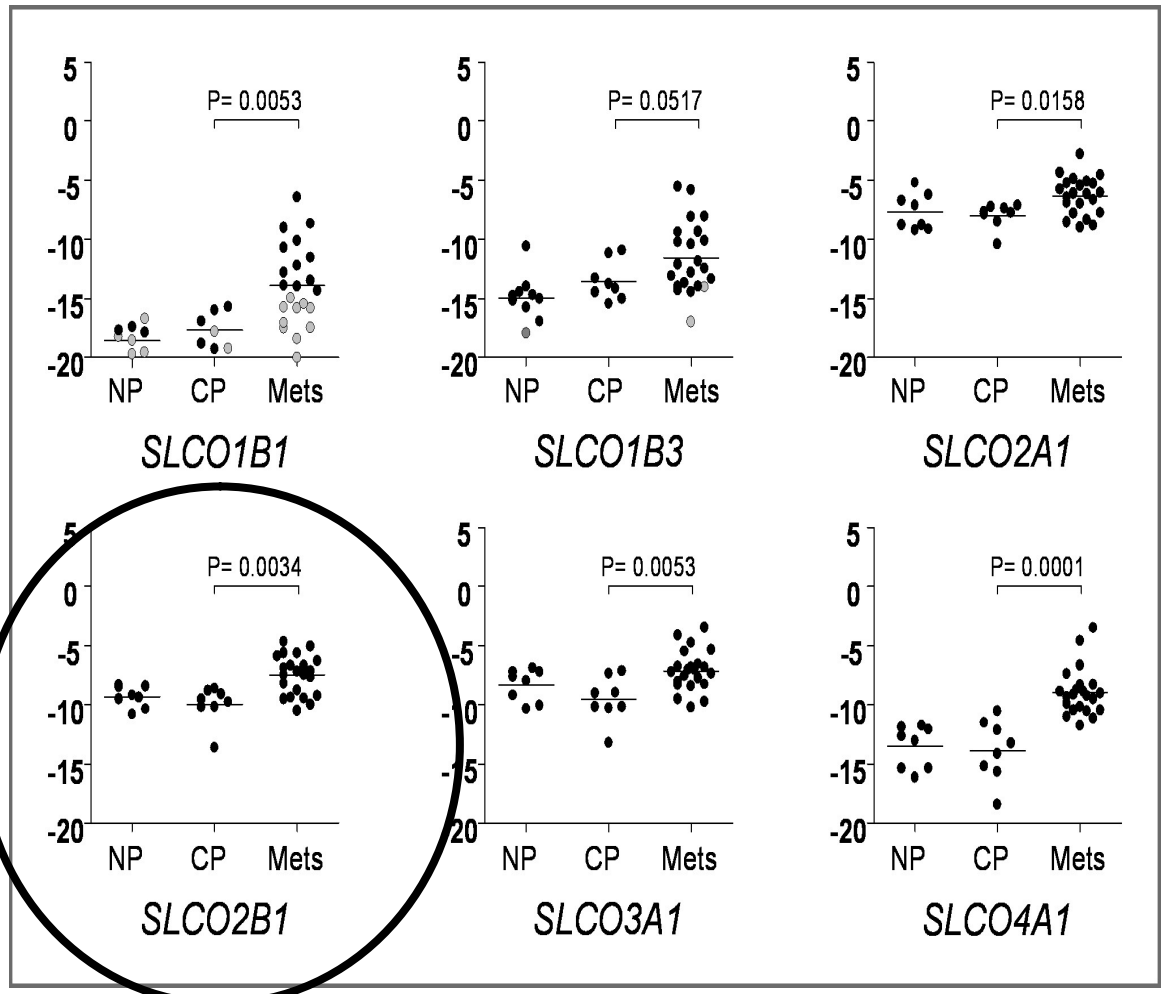
- Androgen receptor mediated mechanisms
  - Activating mutations in AR
  - AR amplification
  - AR splice variants
- Mutation of other pathways eg. P53, PTEN loss
- Activation of other pathways
  - Androgen transporters

CRPC Metastases Showed Significantly Increased Expression of 6 *SLCO* Family Members



Wright JL, et al., CEBP. 2011

CRPC Metastases Showed Significantly Increased Expression of 6 *SLCO* Family Members



Wright JL, et al., CEBP. 2011

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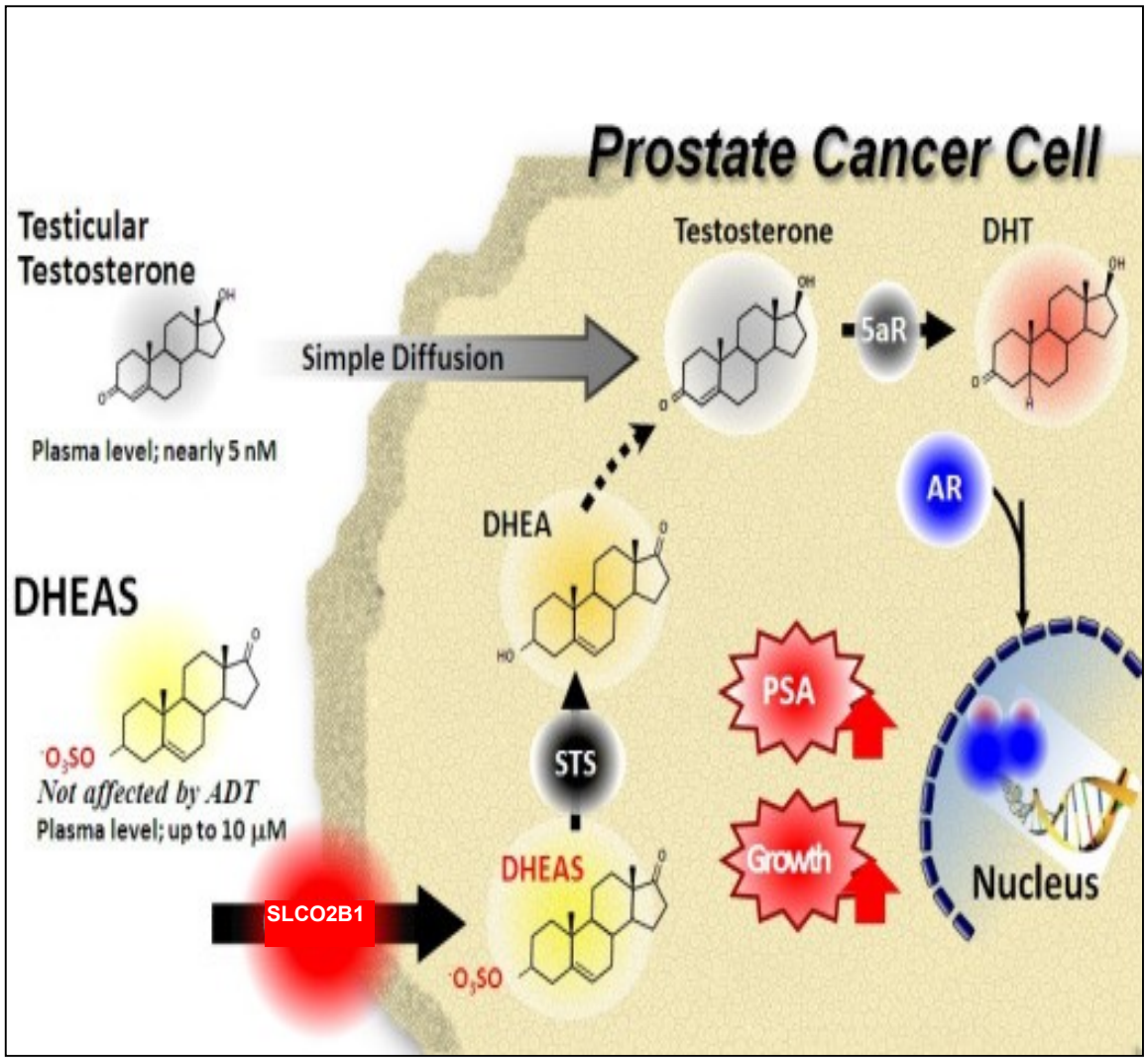
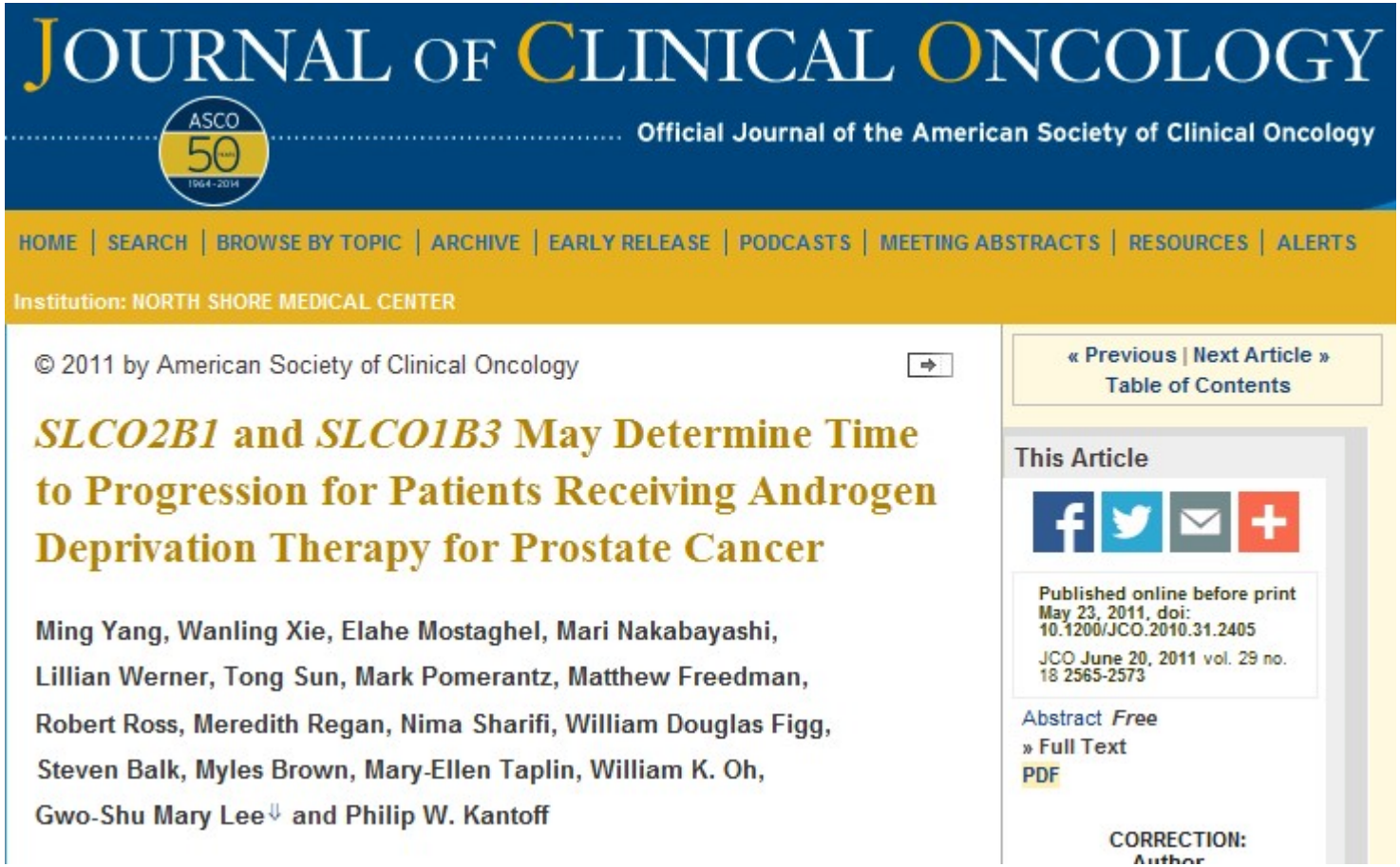

Prostate Cancer Cell
Testicular Testosterone
Plasma level; nearly 5 nM
Simple Diffusion
Testosterone
5aR
DHT
AR
DHEA
DHEAS
Not affected by ADT
Plasma level; up to 10 μM
STS
SLCO2B1
DHEAS
PSA
Growth
Nucleus

Androgen Transporters



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Institution: NORTH SHORE MEDICAL CENTER

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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:

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

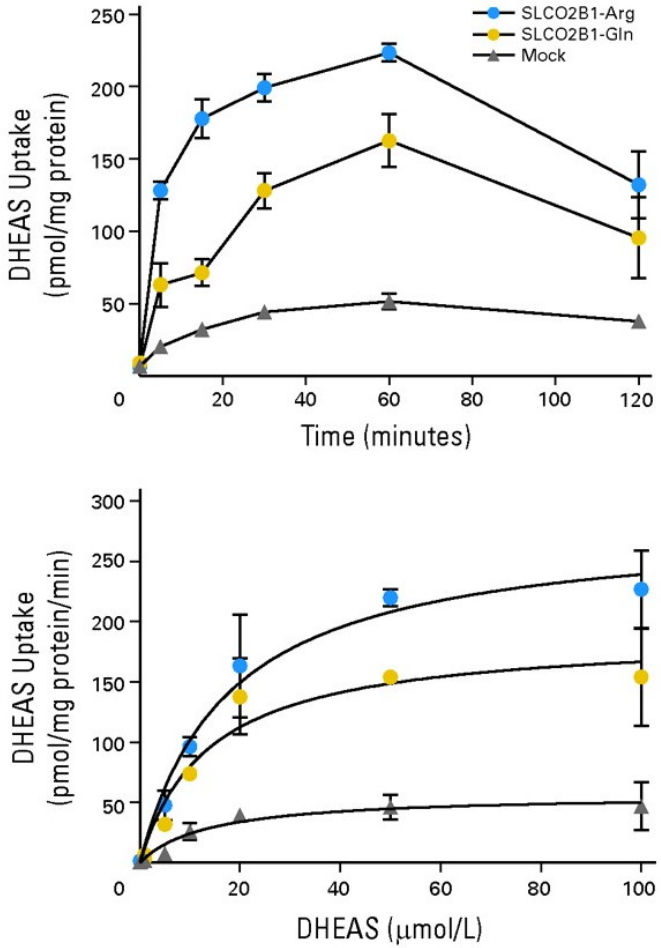
Ming Yang, Wanling Xie, Elahe Mostaghel, Mari Nakabayashi, Lillian Werner, Tong Sun, Mark Pomerantz, Matthew Freedman, Robert Ross, Meredith Regan, Nima Sharifi, William Douglas Figg, Steven Balk, Myles Brown, Mary-Ellen Taplin, William K. Oh, Gwo-Shu Mary Lee and Philip W. Kantoff

SLCO2B1 Genotype Distribution and Its Association With TTP on ADT N=538

Gene and Genotype	No.	Median TTP (months)	95% CI	Univariate Model HR	95% CI	P	FDR	$P_{permutation}$	Multivariate Model* HR	95% CI	P
SLCO2B1 rs12422149											
AA/AG	98	31.5	18.1 to 42.6	1.00	Reference	.029	0.17	.33	1.00	Reference	.018
GG	434	20.9	17.5 to 25.2	1.35	1.03 to 1.77				1.40	1.06 to 1.84	
SLCO2B1 rs1789693											
AA	215	21.5	16.7 to 29.0	1.00	Reference	.007	0.08	.11	1.00	Reference	.051 (.018†)
AT	228	26.3	19.0 to 31.1	1.07	0.86 to 1.34				1.08	0.86 to 1.34	
TT	82	14.5	10.9 to 22.0	1.60	1.19 to 2.16				1.46	1.07 to 1.98	
SLCO2B1 rs1077858											
AA	188	28.1	22.7 to 36.6	1.00	Reference	.009	0.08	.13	1.00	Reference	.008
AG	231	19.3	15.7 to 25.5	1.25	1.00 to 1.58				1.33	1.05 to 1.68	
GG	73	16.4	12.0 to 27.5	1.59	1.17 to 2.17				1.57	1.15 to 2.14	
SLCO2B1, No. of risk genotype											
≤ 1	235	30.9	25.0 to 36.9	1.00	Reference	< .001			1.00	Reference	< .001
2	204	19.0	15.5 to 25.0	1.44	1.15 to 1.80				1.56	1.24 to 1.97	
3	50	12.8	9.0 to 22.0	2.01	1.42 to 2.85				1.91	1.34 to 2.71	

Yang, et. al., JCO 2011

Sulfated Dehydroepiandrosterone (DHEAS) Uptake by *SLCO2B1* Variants (rs12422149)



Yang, et al. JCO 2011

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Association of *SLCO2B1* Genotypes With Time to Progression and Overall Survival in Patients Receiving Androgen-Deprivation Therapy for Prostate Cancer

Xiaodong Wang, Lauren C. Harshman, Wanling Xie, Mari Nakabayashi, Fangfang Qu, Mark M. Pomerantz, Gwo-Shu Mary Lee and Philip W. Kantoff

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JCO February 1, 2016 vol. 34 no. 4 352-359

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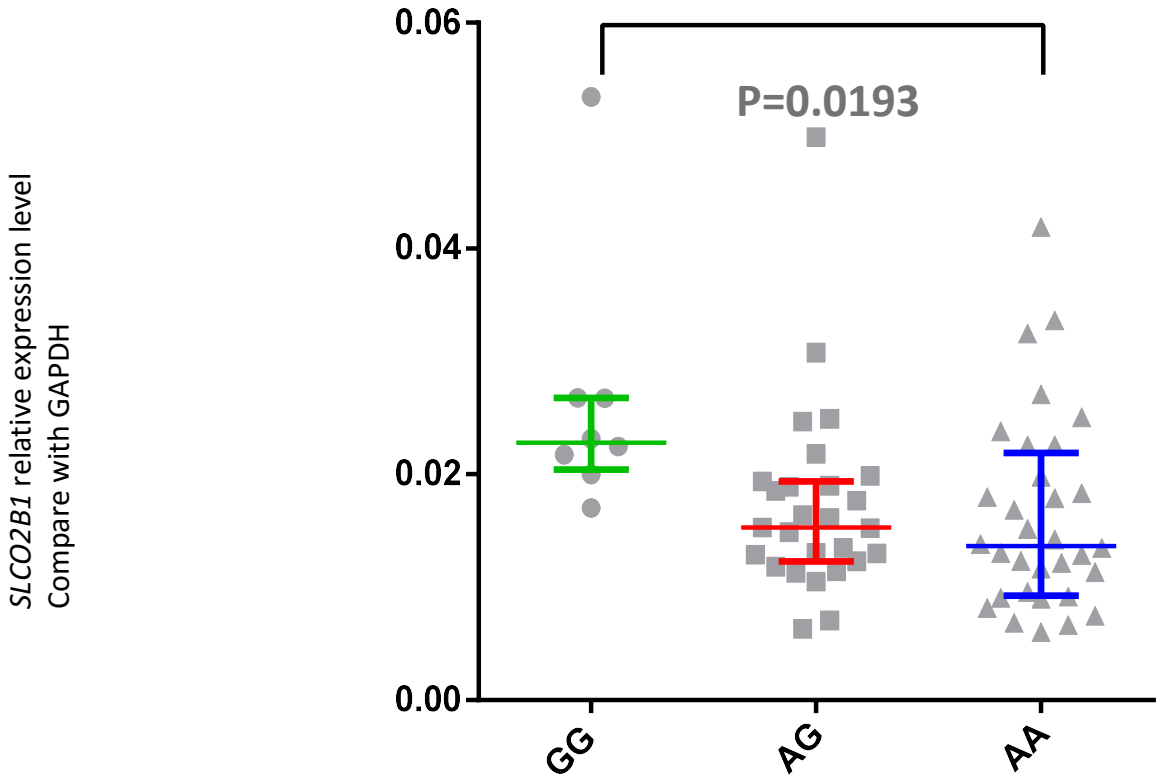
SLCO2B1 Intronic SNP (rs1077858) Associated with Expression Differences in *SLCO2B1*



Wang, Harshman, et al., JCO 2015

Statin Use and *SLCO2B1*

- Given that both statins and DHEAS utilize the same transporter, we evaluated possible interaction between statins and DHEAS influx into PC cells; and
- Preclinical data drove us to investigate outcomes of patients taking statins at time of ADT initiation.

JAMA Oncology

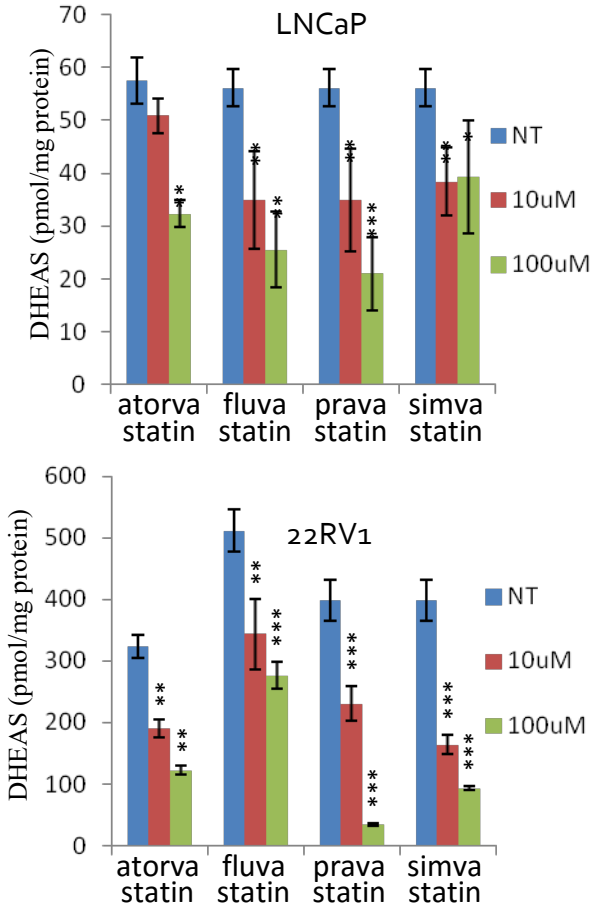
Original Investigation | July 2015

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

FREE

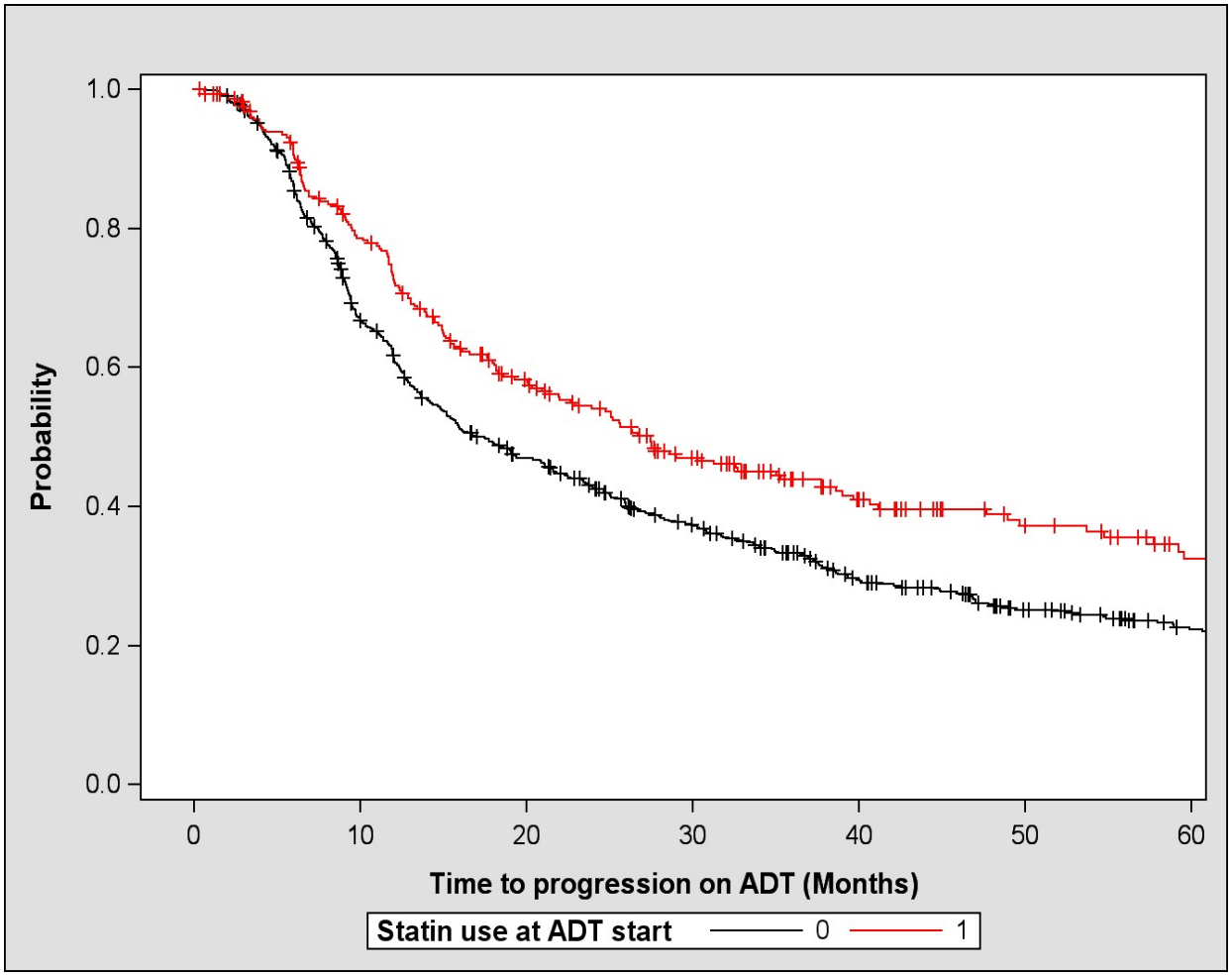
Lauren C. Harshman, MD[1]; Xiaodong Wang, PhD[2]; Mari Nakabayashi, MD[1]; Wanling Xie, MS[2]; Loana Valenca, MD[1]; Lillian Werner, MS[2]; Yongjiang Yu, PhD[2,4]; Aaron M. Kantoff, BS[3]; Christopher J. Sweeney, MBBS[1]; Lorelei A. Mucci, ScD[5]; Mark Pomerantz, MD[1]; Gwo-Shu Mary Lee, PhD[2]; Philip W. Kantoff, MD[1,2]

Statins decrease DHEAS Uptake Efficiency



Harshman, et al. JAMA ONC 2015

Statins (Utilize Androgen Transporter) and Duration of Response to ADT



Harshman ,et al. JAMA ONC 2015

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Conclusions

- Understanding the genetics of prostate cancer has been transformative;
- Two new agents targeting androgen pathway extend survival and delay progression;
- DNA repair pathway frequently mutated and the recognition will lead to new treatments