POTENCIAIS ALVOS E BIOMARCADORES NO CÂNCER DE PRÓSTATA AVANÇADO

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Declaração sobre Potenciais Conflitos de Interesse

De acordo com a Resolução 1931/2009 do Conselho Federal de Medicina e com a RDC 96 / 2008 da ANVISA, declaro que:

- *Apresentações*: como palestrante convidado, participo dos eventos de: Janssen, Pfizer, Bayer, Novartis, Astra Zeneca, Astellas, Pierre-Fabre, Merck-Serono, Sanofi, Roche.
- *Consultoria*: como membro de *advisory boards*, participo de reuniões com: Astellas, Janssen, Roche, Bayer, Lilly, Astra Zeneca, Novartis, MSD, BMS.
- Apoio em pesquisa clínica: BMS

Não possuo ações de quaisquer destas companhias farmacêuticas.

Os meus pré-requisitos para participar destas atividades são a autonomia do pensamento científico, a independência de opiniões e a liberdade de expressão, aspectos que esta empresa respeita.

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The mCRPC landscape in 2019

	Relative reduction in risk of death, %	HR (95% CI; P-value)
Abiraterone/P vs. placebo/P[1] (post docetaxel)	26	0.74 (0.64–0.86; P < 0.001)
Abiraterone/P vs. placebo/P[2] (pre docetaxel)	19	0.81 (0.70-0.93; P < 0.001)
Enzalutamide vs. placebo[3] (post docetaxel)	37	0.63 (0.53–0.75; P < 0.0001)
Enzalutamide vs. placebo[4] (pre docetaxel)	29	0.77 (0.67–0.88; P 0.0002)
Docetaxel(q3w)/P vs. mitoxantrone/P[5]	24	0.76 (0.62–0.94; P = 0.009)
Cabazitaxel/P vs. mitoxantrone/P[6]	30	0.70 (0.59–0.83; P < 0.0001)
Sipuleucel-T* vs. placebo[7]	22	0.78 (0.61–0.98; P = 0.03)
Ra-223* vs. placebo[8]	31	0.70 (0.58–0.83; P < 0.0001)

P, prednisone; q3w, every 3 weeks;

1. Fizazzi K, et al. Lancet Oncol 2012;13:983–92; 2. Ryan et al. Lancet Oncol. 2015 Feb;16(2):152-60 3. Scher HI, et al. N Engl J Med 2012;367:1187–97; 4. Tombal et al. EAU 2015, Madrid 5. Tannock IF, et al. N Eng J Med 2004;2351:1502–12; 6. de Bono JS, et al. Lancet 2010;76:1147–54;7. Kantoff PW, et al. N Engl J Med 2010;363:411–22; 8. Parker et al. N Engl J Med. 2013 Jul 18;369(3):213-23.

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The mCSPC landscape in 2019

Study	Agents	N	Indication	HR (95% CI)	ΔOS (mo)
CHAARTED[1]	DOC vs ADT	790	Metastatic hormone –sensitive PCa (mHSPC)	0.72 (0.59-0.89)	**+10.0**
STAMPEDE[2]	DOC/P vs ADT	1,086	mHSPC	0.73 (0.59-0.89)	**+22.0**
LATITUDE[3]	ABI/P vs ADT	1,199	High-risk mHSPC	0.66 (0.56-0.78)	**+16.0**
STAMPEDE[4]	ABI/P vs ADT	1,002	mHSPC	0.61 (0.49-0.75)	Not reached

ABI: abiraterone; ADT: androgen deprivation therapy; CABA: cabazitaxel; DOC: docetaxel; ENZA: enzalutamide; mito: mitoxantrone; OS: overall survival; pbo: placebo; P: prednisone

1. Kyriakopoulos, J Clin Oncol 2018;36:1080-1087; 2. James, Lancet 2016; 387:1163-77&ASCO2015 (abs 5001); 3. J Clin Oncol 37, 2019 (suppl 7S; abstr 141); 4. James, NEJM 2017;377:338-51

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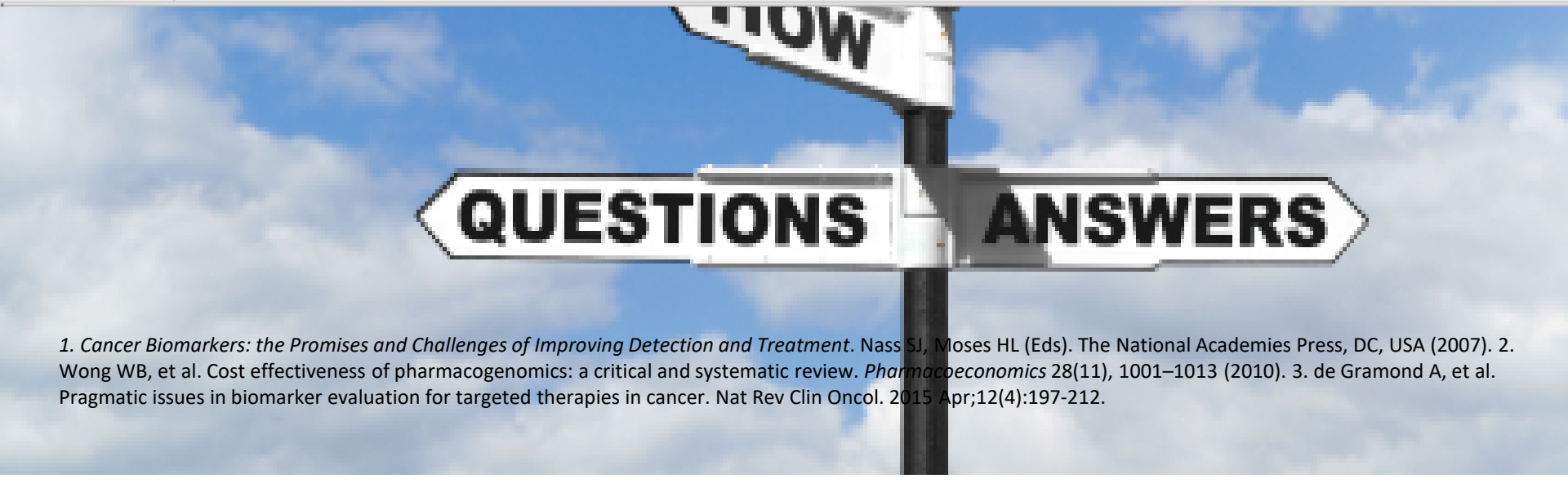
The M0CRPC landscape in 2019

	Relative reduction in risk of metastasis, %	HR (95% CI; P-value)
Apalutamide + ADT vs. placebo + ADT[1]	72	0.28 (0.23–0.35; P < 0.0001)
Enzalutamide + ADT vs. placebo + ADT[2]	71	0.29 (0.24-0.35; P < 0.0001)
Darolutamide + ADT vs. placebo + ADT[3]	59	0.41 (0.34–0.50; P < 0.000001)

1. Smith MR, et al. N Engl J Med. 2018 **2.** Hussain M, et al. N Engl J Med. 2018. **3.** N Engl J Med. 2019 Feb 14

1. **Who is the right patient for which novel therapy?**
2. **What is the optimal**

Biomarker use	Clinical objective	Economic considerations
Screening	Detect and treat early-stage cancers among the asymptomatic	Potential savings if total costs of treatment for patients diagnosed with early-stage cancer are less than costs for those diagnosed in later stages
Diagnosis	Accurately and quickly establish the presence of cancer	Potential savings from optimizing treatment approach† and timing
Monitoring	Determine whether treatment is having the intended effect; enable timely detection of post-treatment recurrence	Potential savings from optimizing treatment approach† and facilitating timely second-line treatment
Treatment optimization	Predict outcomes; determine aggressiveness of treatment; predict response to particular treatments ('stratified' medicine‡)	Potential savings from optimizing treatment approach† leading to improved outcomes, and minimizing costs of adverse events



1. Cancer Biomarkers: the Promises and Challenges of Improving Detection and Treatment. Nass SJ, Moses HL (Eds). The National Academies Press, DC, USA (2007). 2. Wong WB, et al. Cost effectiveness of pharmacogenomics: a critical and systematic review. *Pharmacoeconomics* 28(11), 1001–1013 (2010). 3. de Gramond A, et al. Pragmatic issues in biomarker evaluation for targeted therapies in cancer. Nat Rev Clin Oncol. 2015 Apr;12(4):197-212.

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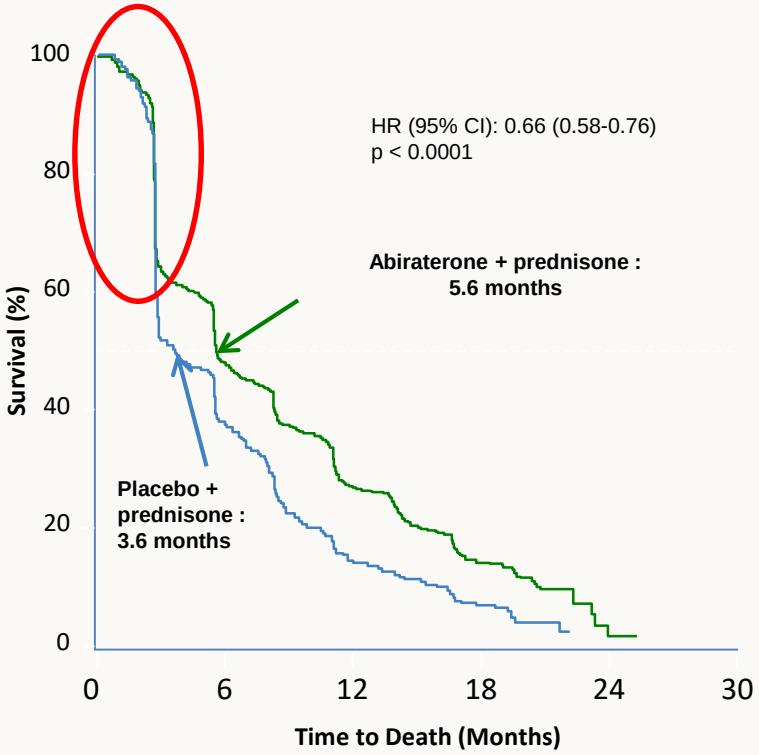
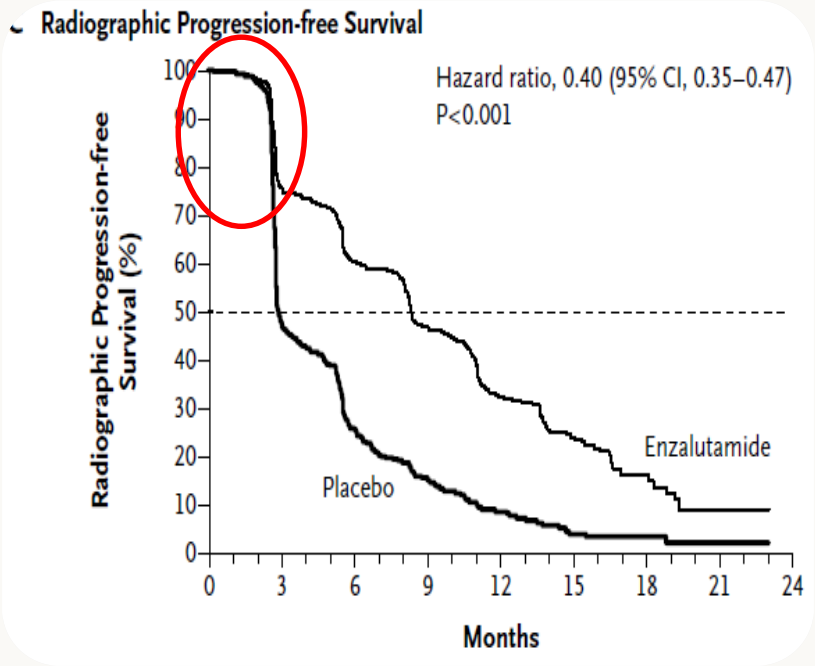
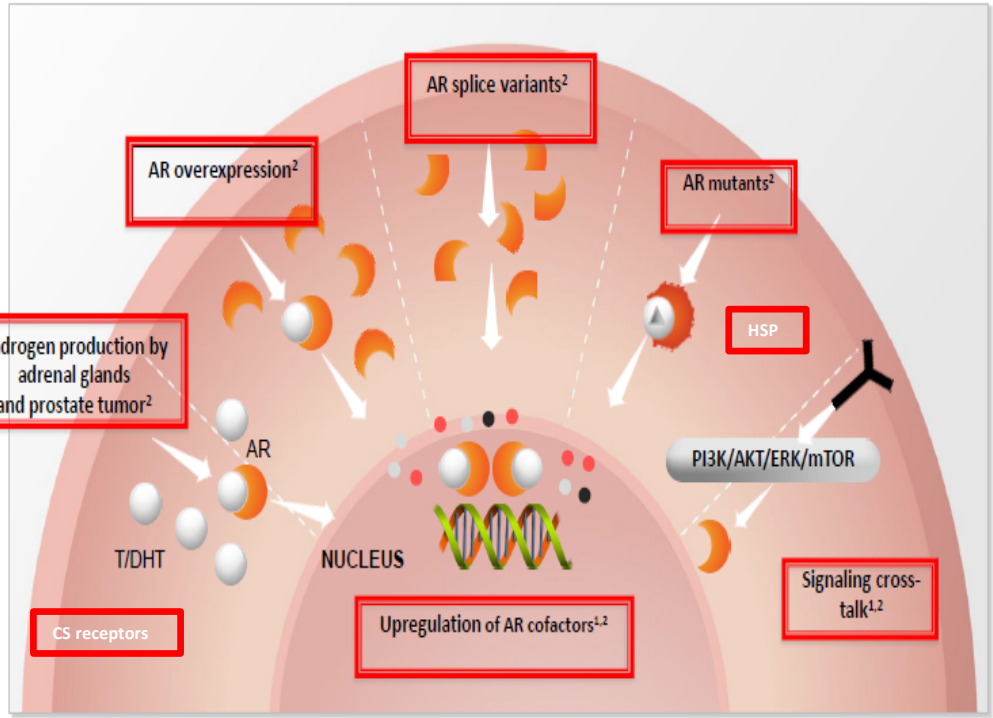
Abiraterone and Enzalutamide





1. de Bono et al. N Engl J Med 2011; 346(21): 1995-2005.
2. 2. Scher HI, et al. *N Engl J Med*. 2012;367:1187-1197.

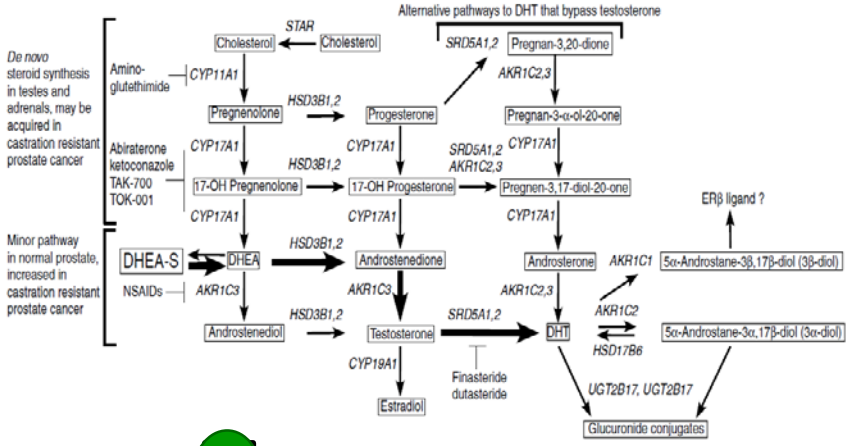
CRPC Remains Driven by Androgen Receptor Signaling – AR Alterations Selected During Therapy

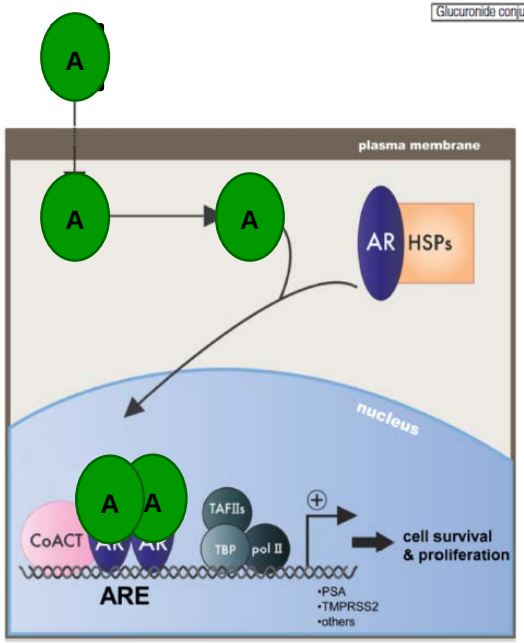


Up to 80% of CRPCs elevated AR gene copy number, 30% high-level amplification of the gene

AR mutations common10-30% of the CRPC treated with antiandrogens

¹Heinlein CA et al. Endocr Rev. 2004;25(2):276-308 ²Hu R et al. Expert Rev Endocrinol Metab. 2010;5(5):753-764





Knudsen KE, Penning TM. *Trends Endocrinol Metab.* 2010;21(5):315-324.

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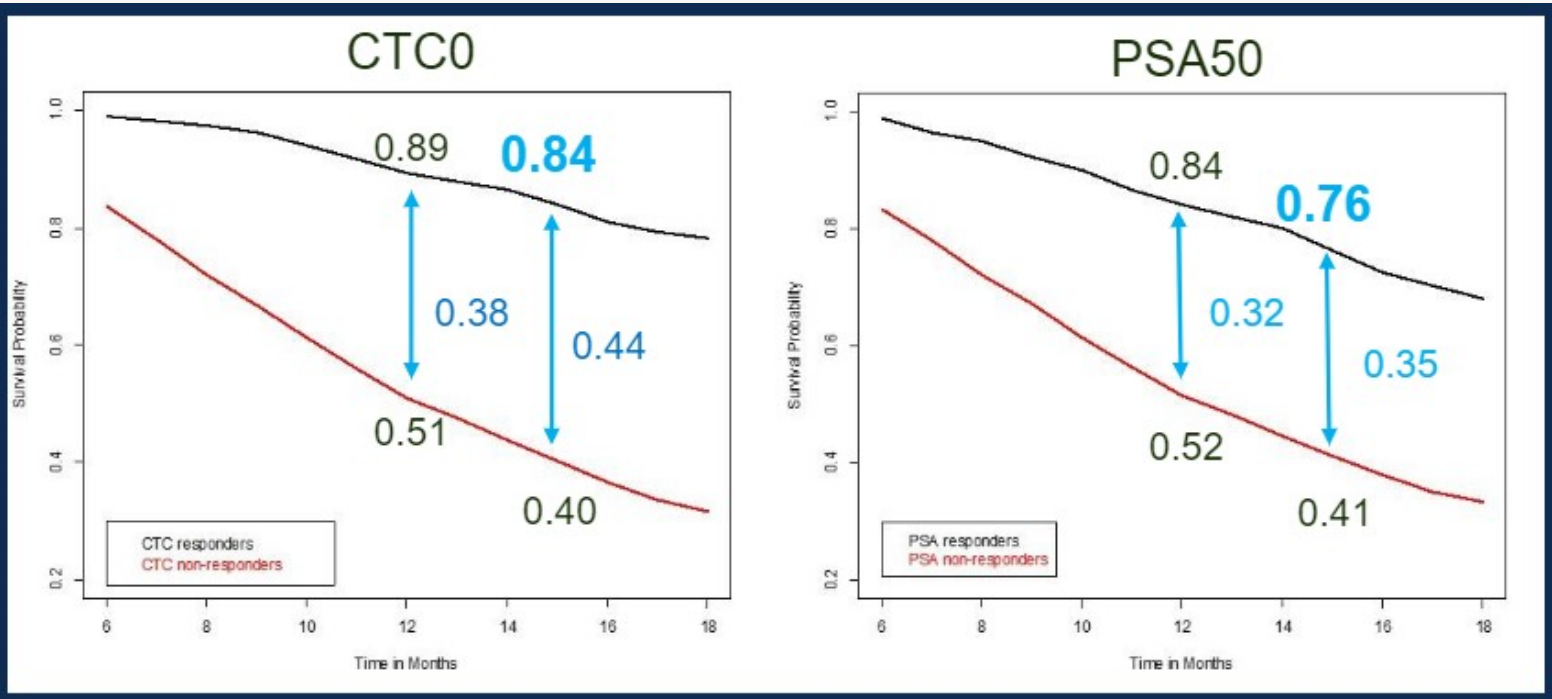
Survival probability estimates over months 6 to 18 with the difference in outcomes at the 12 and 15 month landmark



The primary driver of the difference is that CTC0 finds longer surviving patients better than PSA50.

J Clin Oncol. 2018 Feb 20;36(6):572-580

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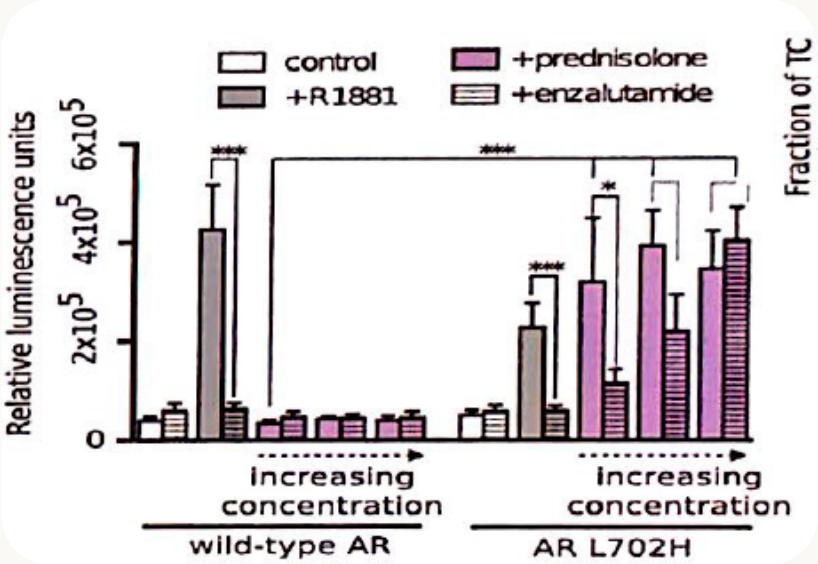
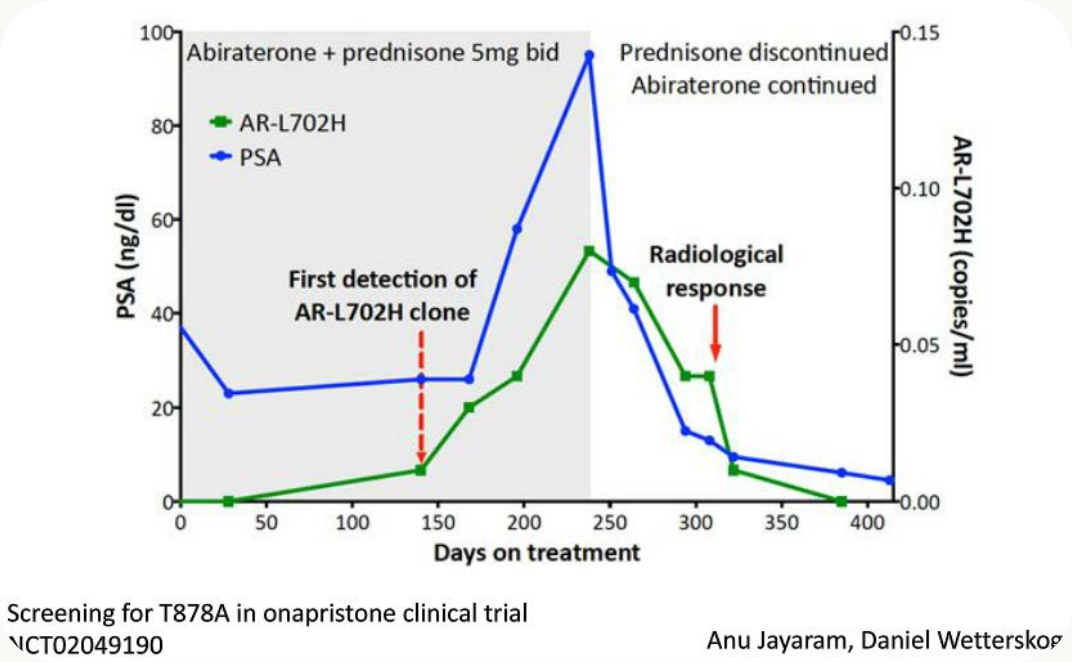
Abiraterone and L702H mutation





Screening for T878A in onapristone clinical trial
NCT02049190

Anu Jayaram, Daniel Wetterskog

Carreira S, et al. Sci Transl Med 2014;6:254ra125

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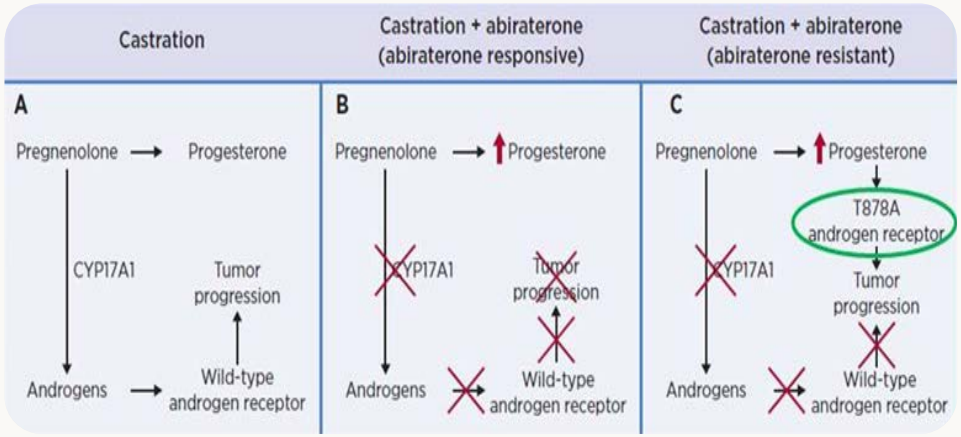
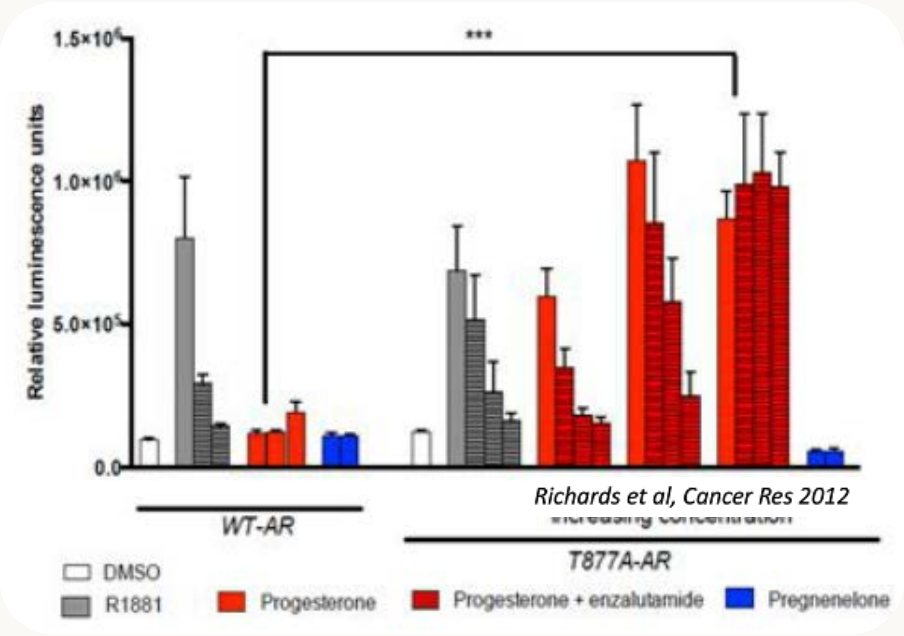
Abiraterone and T878A mutation





- ✓ AR was examined by targeted sequencing in 18 mCRPC pts, using metastatic tumor biopsies
- ✓ AR sequencing was performed before abi treatment, and upon progression
- ✓ The AR T878A mutation was found in 3/18 pts (17%) at progression, but was not detected at baseline

Clin Cancer Res. 2015 Mar 15;21(6):1273-80

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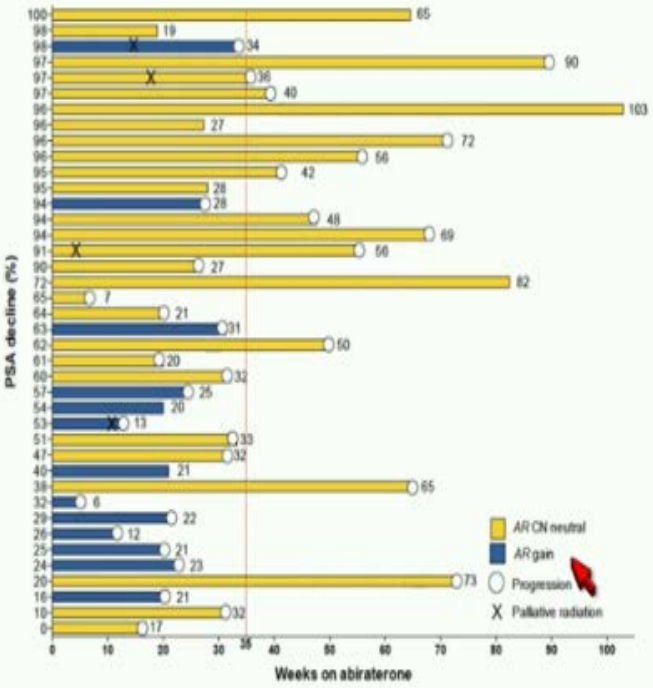
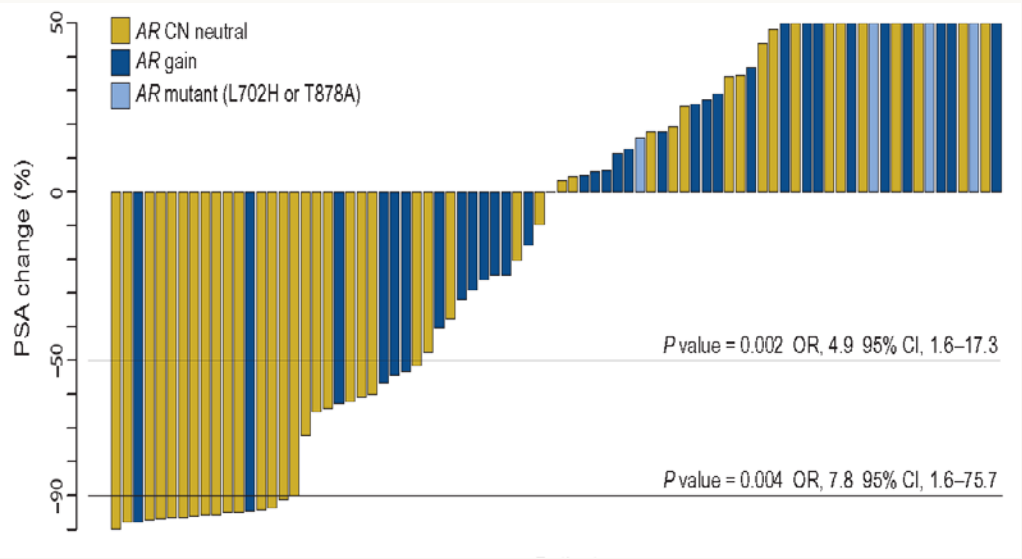
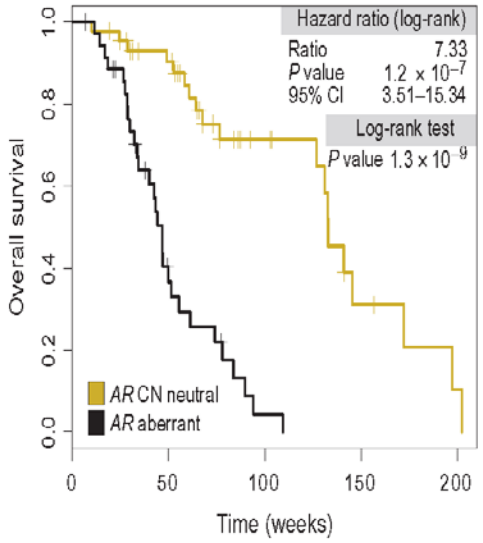
AR copy number – AR mutation

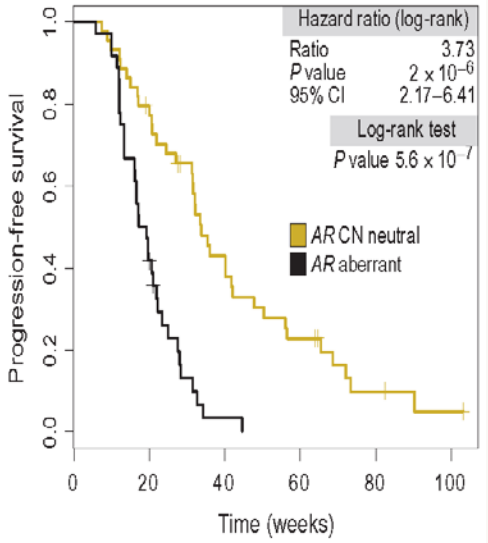
Plasma *AR* gain patients are characterized by early emergence of resistance



At 21 weeks, all patients with *AR* copy number gain had PSA progression







Romanel A, et al. Plasma AR and abiraterone-resistant prostate cancer. Sci Transl Med. 2015 Nov 4;7(312):312re10

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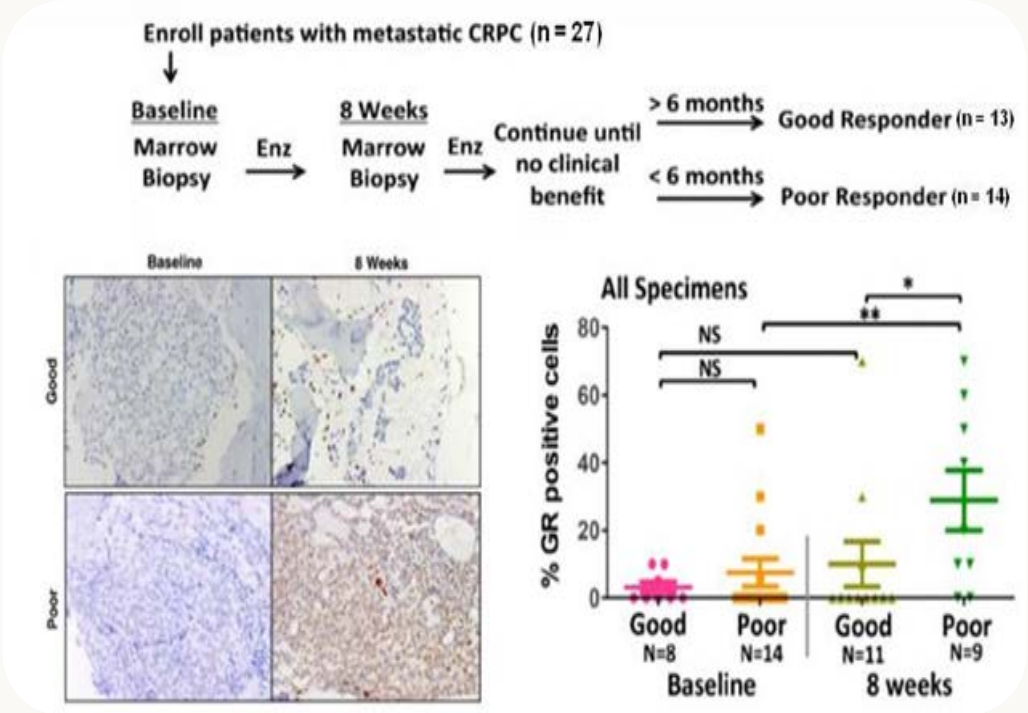
Enzalutamide and GR expression

- ✓ In the LNCaP/AR xenograft mouse model, induction of GR expression was suggested as a mechanism of acquired resistance to enza (and ARN-509)
- ✓ Potent AR inhibition, GR may co-opt AREs to maintain expression of androgen-related genes
- ✓ GR may bypass AR blocked



Cell. 2013 Dec 5;155(6):1309-22

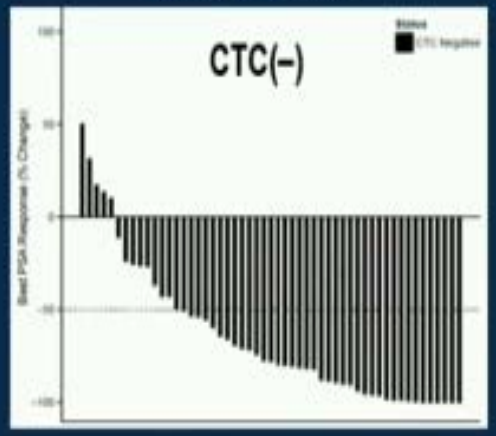
Updated JHU Analysis (N=202)

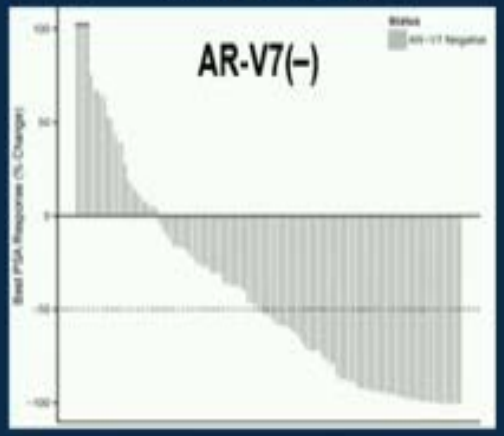
P < 0.001

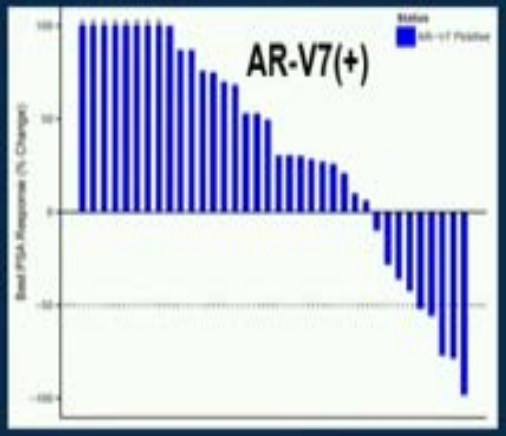
40/53 = 76%

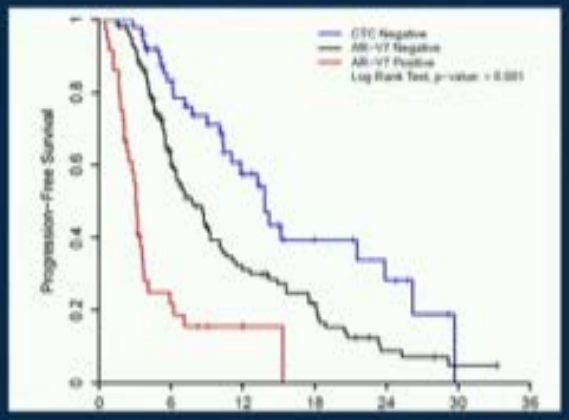
59/113 = 52%

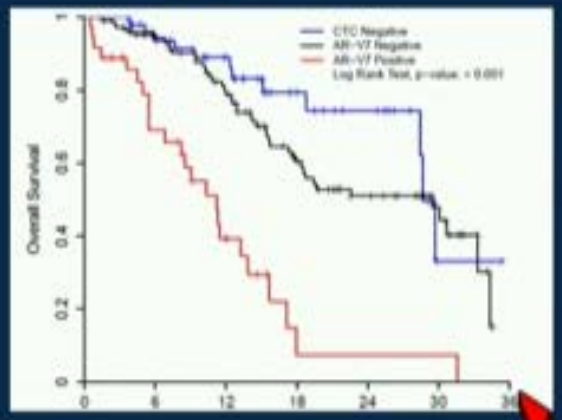
5/36 = 14%











Antonarakis ES et al. *ASCO 2016*; abstract 5012

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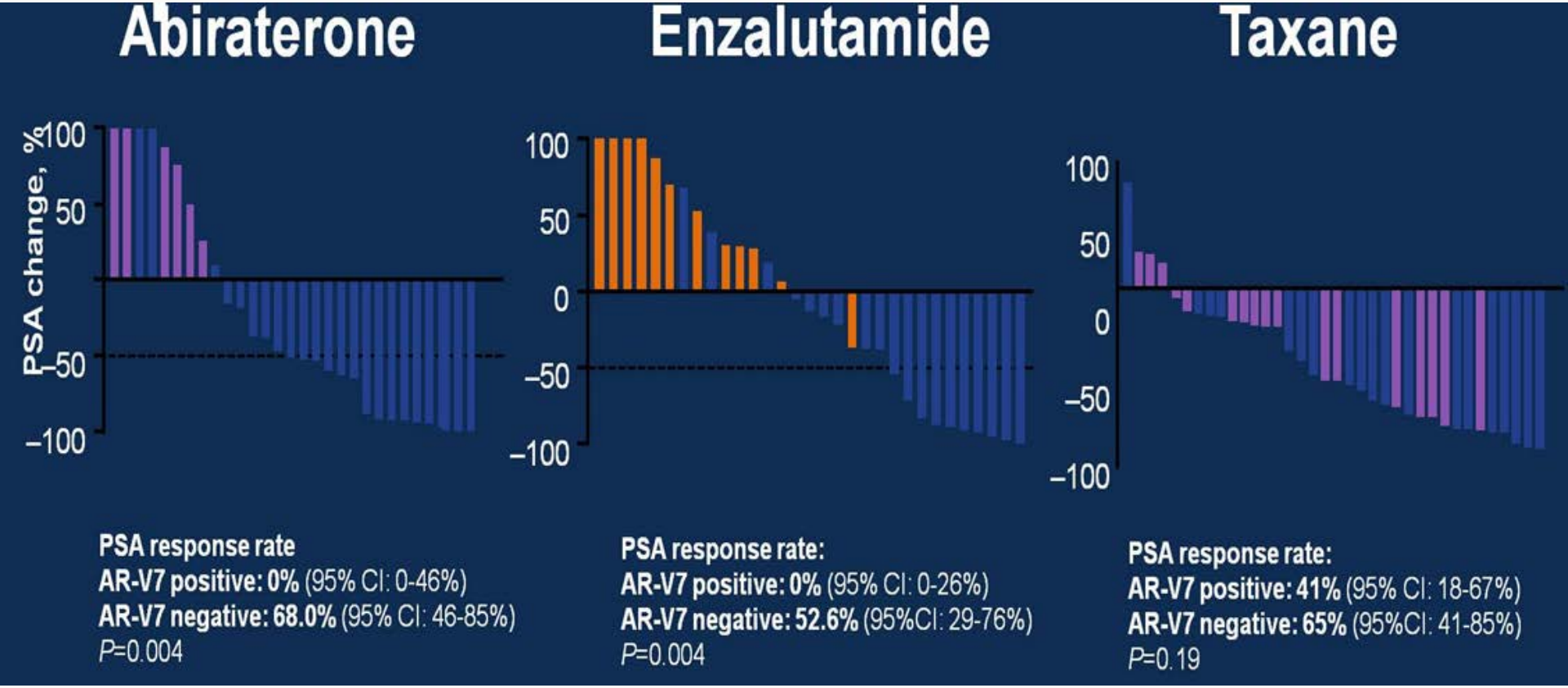
Taxanes x AR-V7



Antonarakis ES et al. N Engl J Med 2014;371:1028-38; Antonarakis ES et al. JAMA Oncol 2015;1:582-91

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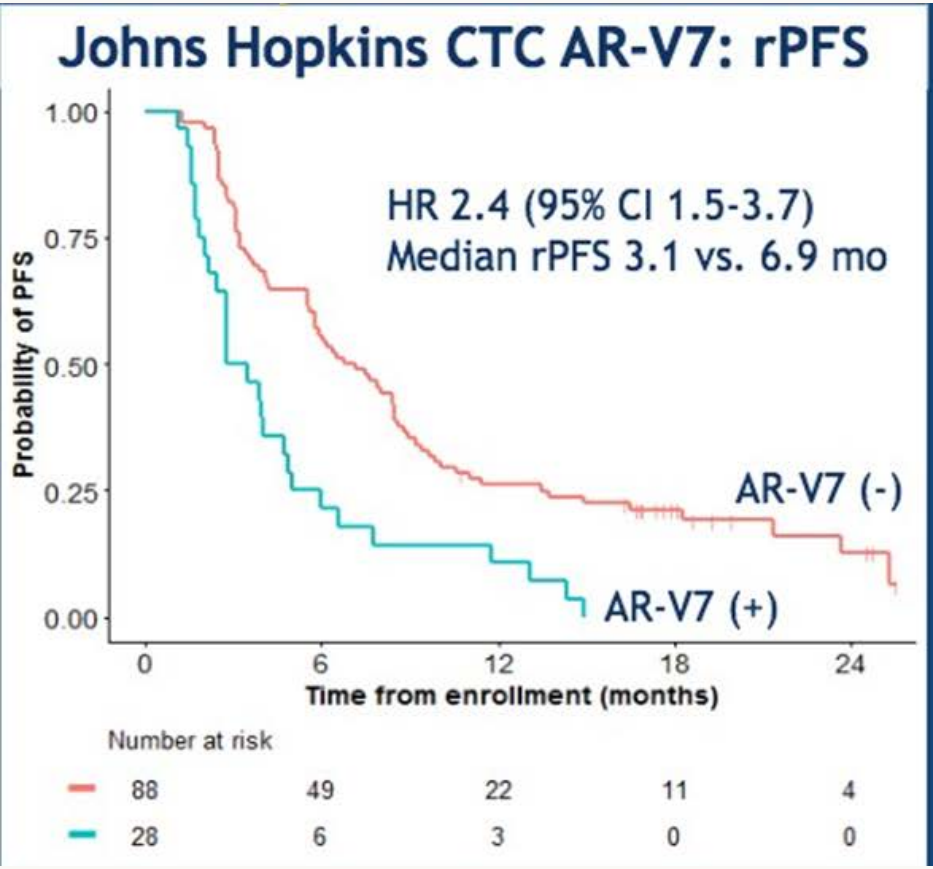
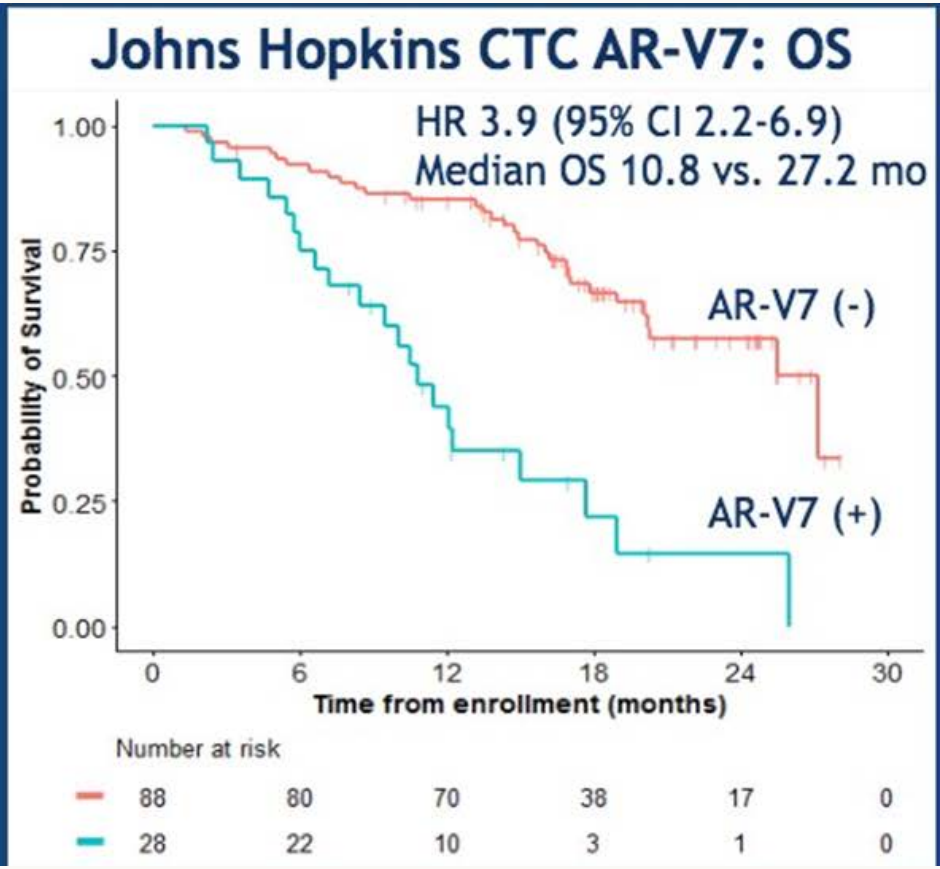
Johns Hopkins modified Adnatest AR-V7 efficacy prediction: rPFS and Overall Survival





J Clin Oncol. 2019 Mar 13

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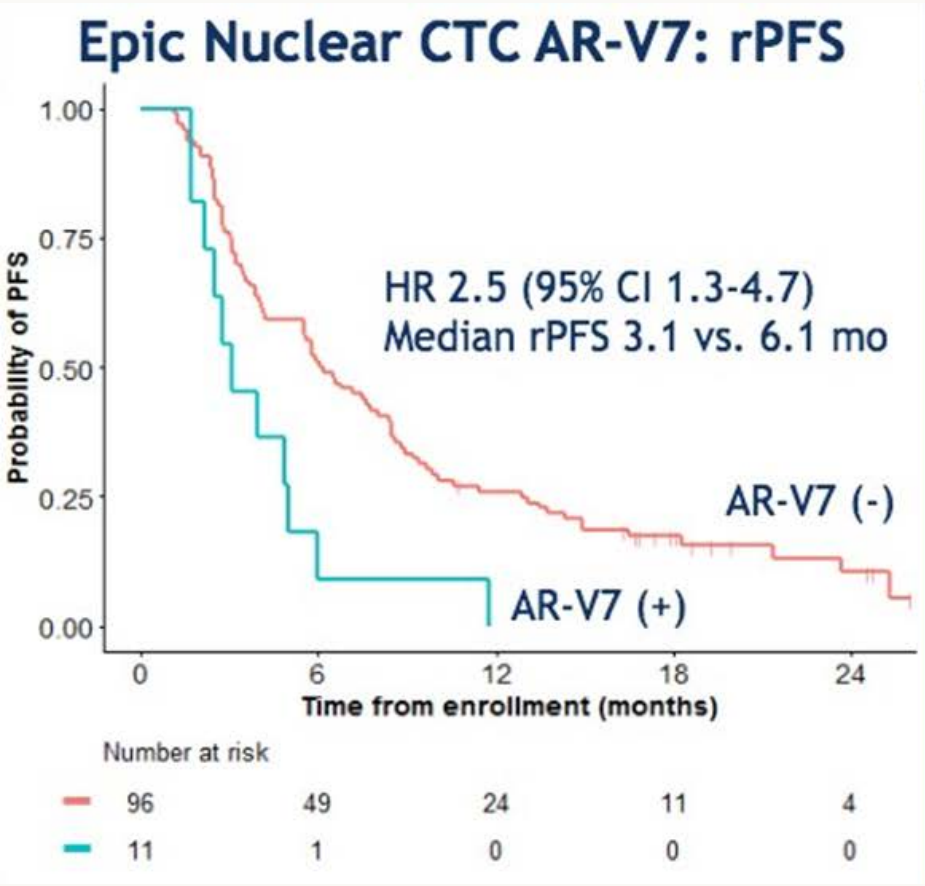
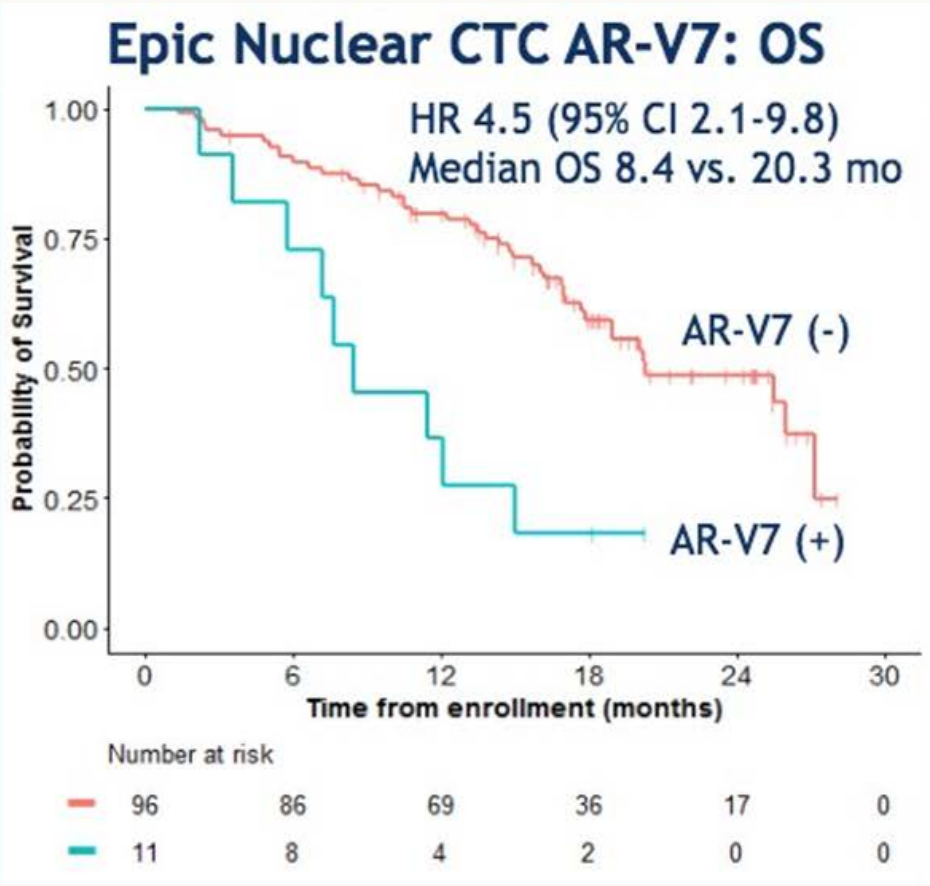
EPIC Nuclear CTC AR-V7 efficacy prediction: rPFS and Overall Survival





J Clin Oncol. 2019 Mar 13

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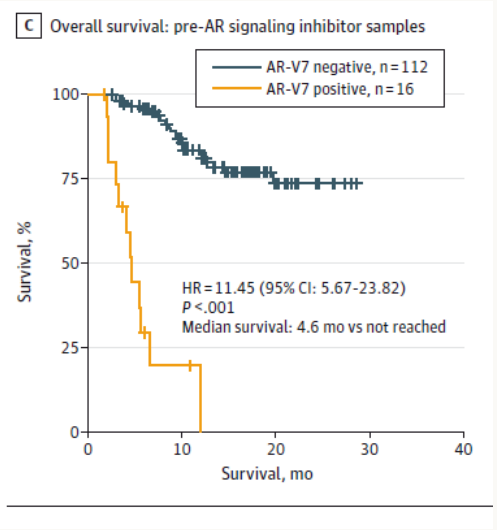
Research

Original Investigation

Association of AR-V7 on Circulating Tumor Cells as a Treatment-Specific Biomarker With Outcomes and Survival in Castration-Resistant Prostate Cancer

Howard I. Scher, MD; David Lu, PhD; Nicole A. Schreiber, BA; Jessica Louw, BS; Ryon P. Graf, PhD; Hebert A. Vargas, MD; Ann Johnson, MS; Adam Jendrisak, MBA; Richard Bambury, MB, BCh, BAO; Daniel Danila, MD; Brigit McLaughlin, BS; Justin Wahl, BS; Stephanie B. Greene, PhD; Glenn Heller, PhD; Dena Marrinucci, PhD; Martin Fleisher, PhD; Ryan Dittamore, MBA



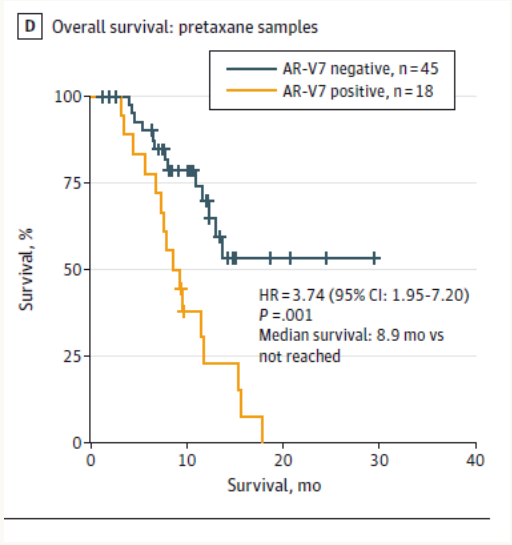
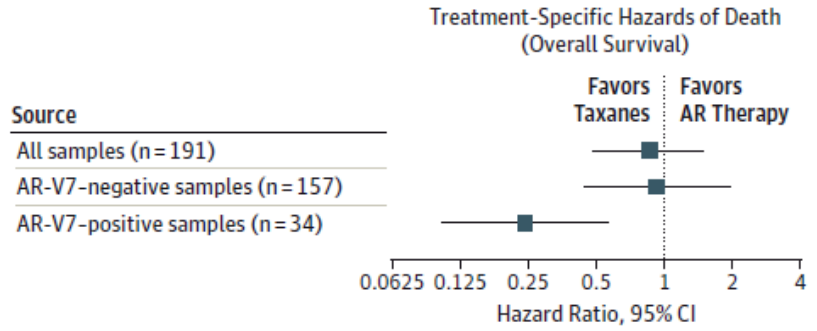


Figure 4. Patients With Pretherapy AR-V7–Positive CTCs and Overall Survival on Taxanes and/or AR Signaling Inhibitors.



AR-V7 Therapy Interaction: Multivariable Cox PH Model		
	Comparison	Hazard Ratio (95% CI)
AR-V7 Status and Therapy	AR-V7 positive: Taxane vs AR	0.24 (0.10 to 0.57)
	AR-V7 negative: Taxane vs AR	0.92 (0.44 to 1.95)

Scher et al. JAMA Oncol 2016

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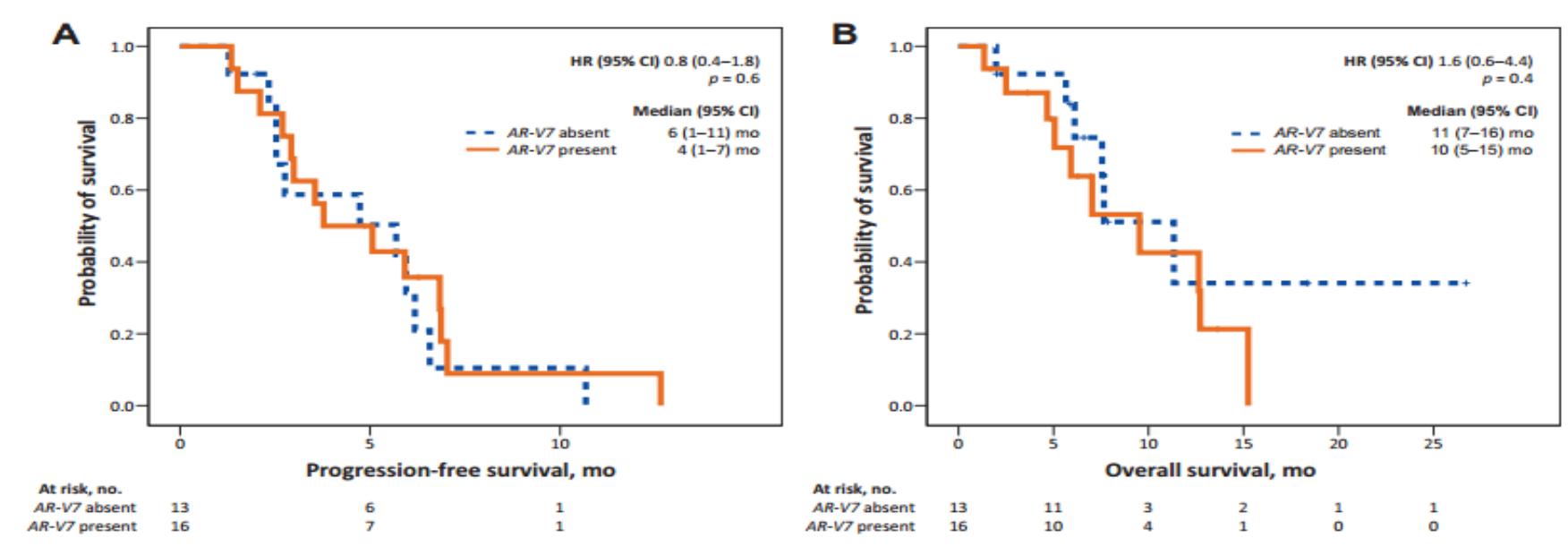
Platinum Priority – Prostate Cancer
Editorial by Archana Anantharaman and Terence W. Friedlander on pp. 946–948 of this issue

Efficacy of Cabazitaxel in Castration-resistant Prostate Cancer Is Independent of the Presence of *AR-V7* in Circulating Tumor Cells

Wendy Onstenk[a,], Anieta M. Sieuwerts[a], Jaco Kraan[a], Mai Van[a], Annemieke J.M. Nieuweboer[a], Ron H.J. Mathijssen[a], Paul Hamberg[b], Hielke J. Meulenbeld[c], Bram De Laere[d,e], Luc Y. Dirix[d,e], Robert J. van Soest[f], Martijn P. Lolkema[a], John W.M. Martens[a], Wytske M. van Weerden[f], Guido W. Jenster[f], John A. Foekens[a], Ronald de Wit[a], Stefan Sleijfer[a]*



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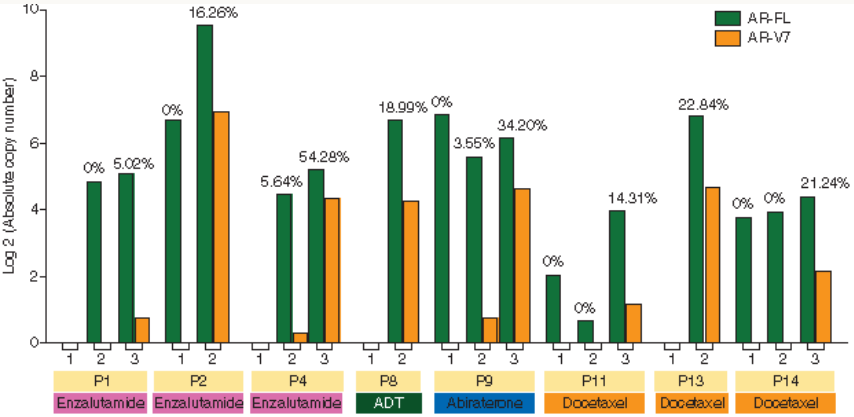
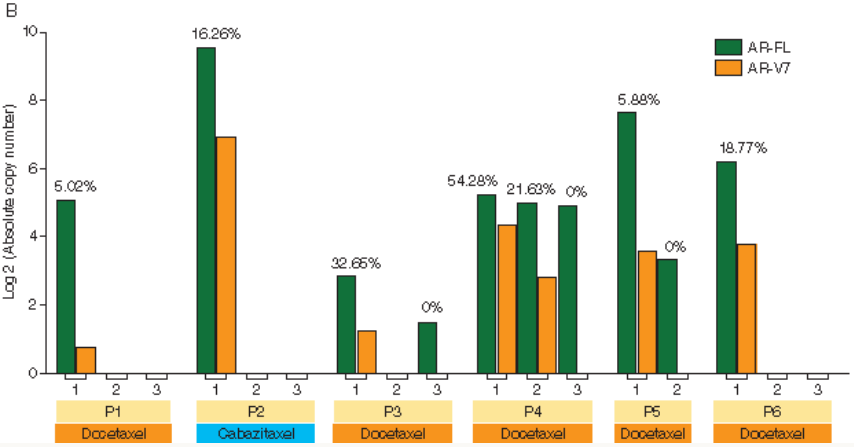
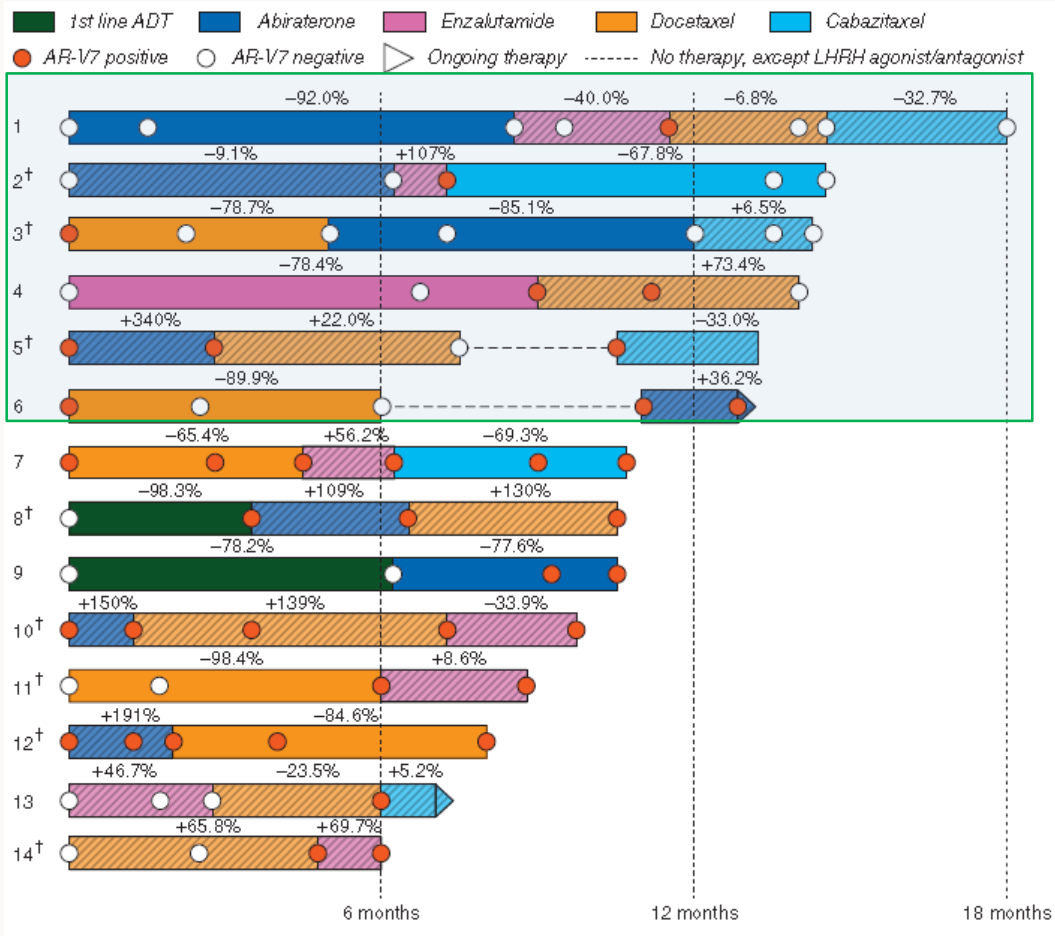
AR-V7 Conversion







Nakazawa M, et al. Serial blood-based analysis of AR-V7 in men with advanced prostate cancer. Ann Oncol. 2015 Sep;26(9):1859-65

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International Stand Up to Cancer – PCF Prostate Cancer Dream Team

- ✓ 150 metastatic CRPC biopsies
- ✓ DNA repair alterations found in 22%
  - ✓ HRD genes: BRCA (13.3%), ATM (7.3%), CHEK2 (3%), PALB2 (2%), BRCA1 (0.7%)
  - ✓ MMR genes: MLH1 (1.3%), MSH2 (3%), MSH6 (2%)
  - ✓ 11.8% with germline alterations
- ✓ Prognostic, therapeutic and family implications

Cell. 2015 May 21;161(5):1215-1228
N Engl J Med. 2016 Aug 4;375(5):443-53

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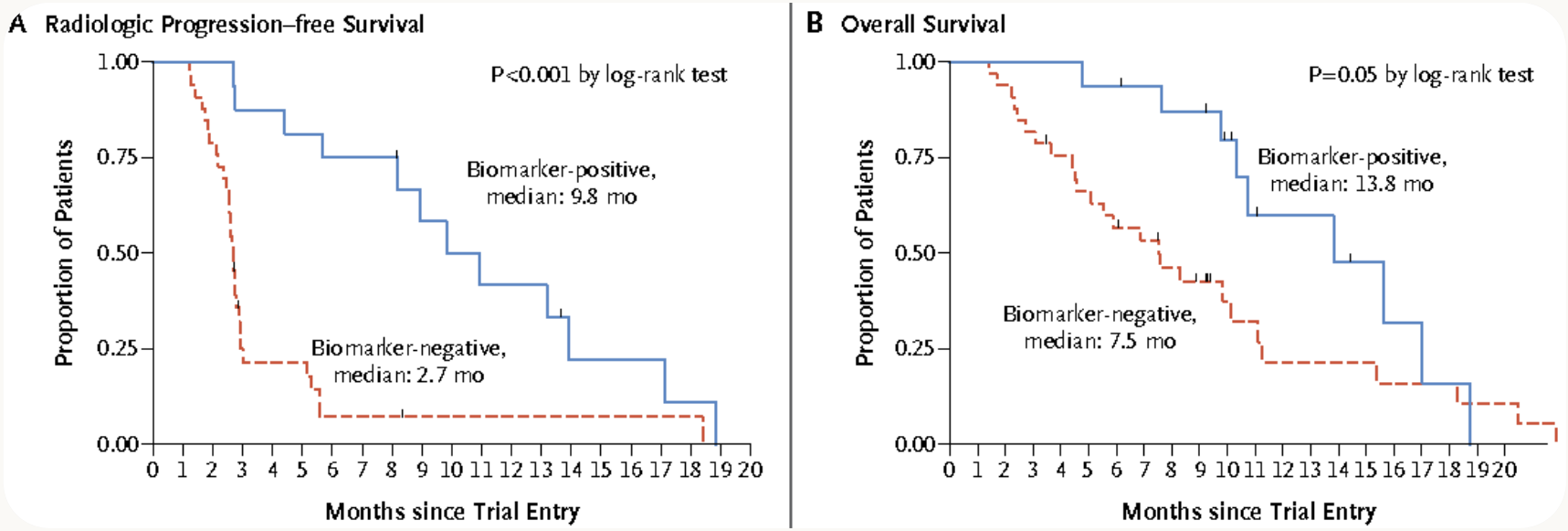
Olaparib and DNA repair defects

- ✓ 16/49 responded (ORR – 33%)
- ✓ 14/16 responders with DNA repair defect (BRAC2 and ATM) – ORR 88%



N Engl J Med. 2015 Oct 29;373(18):1697-708.

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PARP inhibitors and DNA repair defects

Niraparib

Response n % (95% CI)	All Biallelic DRD (N = 39)	
	BRCA1/2 (n = 23)	Non-BRCA (n = 16)
Composite RR	15/23	5/16
	65%	31%
	(43%, 84%)	(11%, 59%)
Objective RR	5/13	1/9
	38%	11%
	(14%, 68%)	(0%, 48%)
PSA_{50}	13/23	1/16
	57%	6%
	(34%, 77%)	(0%, 30%)
CTC Conversion	11/23	5/16
	48%	31%
	(27%, 69%)	(11%, 59%)

Rucaparib

Journal of Clinical Oncology 37, no. 7_suppl (March 1 2019) 202-202
Annals of Oncology (2018) 29 (suppl_8)

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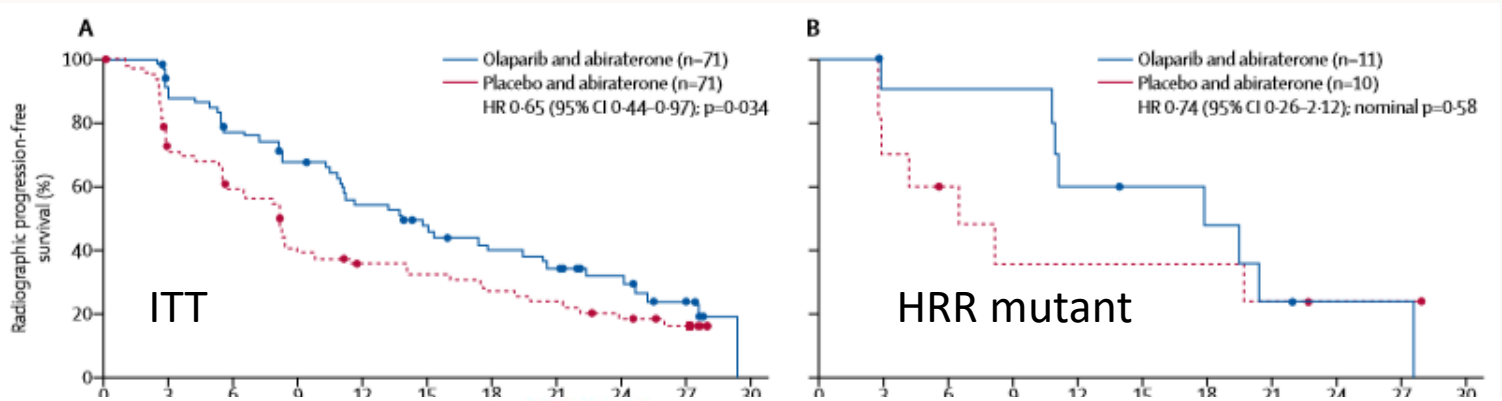
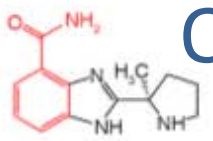


PARPis

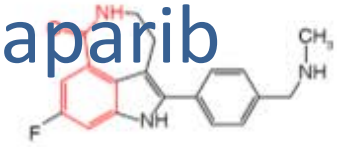
Approved for ovarian, fallopian, and peritoneal cancers

Approved for breast cancer

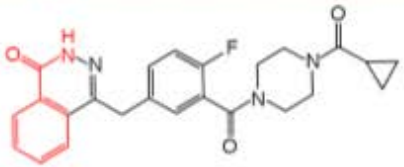
Olaparib



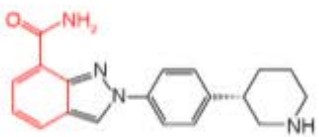
Veliparib
ABT-888



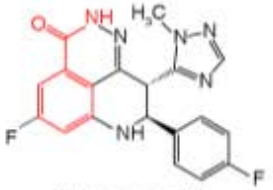
Rucaparib (Rubraca)
AG-014699



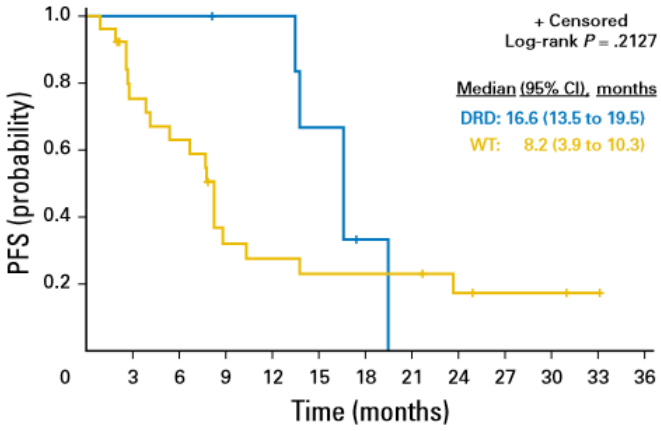
Olaparib (Lynparza)
AZD-2281

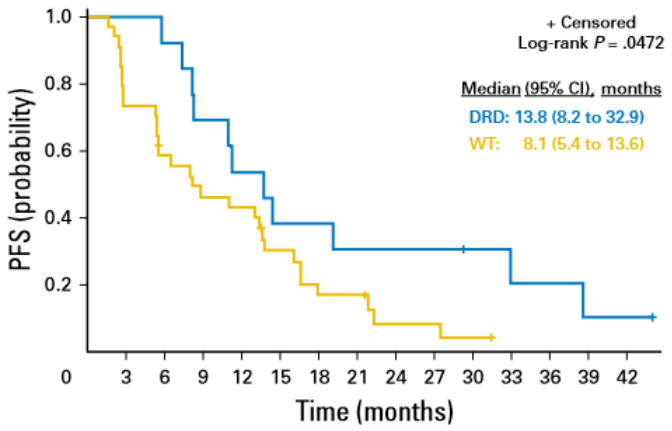


Niraparib (Zejula)
MK-4827



Talazoparib
BMN-673





Veliparib

Lancet Oncol. 2018 Jul;19(7):975-986
J Clin Oncol. 2018 Apr 1;36(10):991-999
J Clin Invest. 2018;128(5):1727-1730

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Pembrolizumab and prostate cancer

Response by Presence of Somatic Aberrations in DNA Repair Genes: Cohorts 1+2+3

	BRCA1/2 or *ATM* 19/153	Other DDR Genes[a] 10/153	Negative 124/153
RECIST v1.1			
ORR	2 (11%)[b]	0	4 (3%)
DCR (any duration)	4 (22%)	0	22 (18%)
CR	0	0	2 (2%)
PR	2 (11%)	0	2 (2%)
SD (any duration)	2 (11%)	2 (20%)	18 (15%)
NonCR/nonPD	1 (5%)	0	7 (6%)
PD	12 (63%)	5 (50%)	80 (65%)
NE or missing	2 (11%)	3 (30%)	15 (12%)
PSA responders	2 (11%)	1 (10%)	4 (3%)

[a]*BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *PPP2R2A*, *RAD51C*, *RAD51B*, *RAD51D*, and *RAD54L*. [b]1 patient each from cohorts 1 and 2.
Presence of somatic alterations in DNA repair genes was derived from whole exome sequencing. Data cutoff date: Oct 13, 2017.

Journal of Clinical Oncology 36, no. 15_suppl (May 20 2018) 5007

Durvalumab + Olaparib

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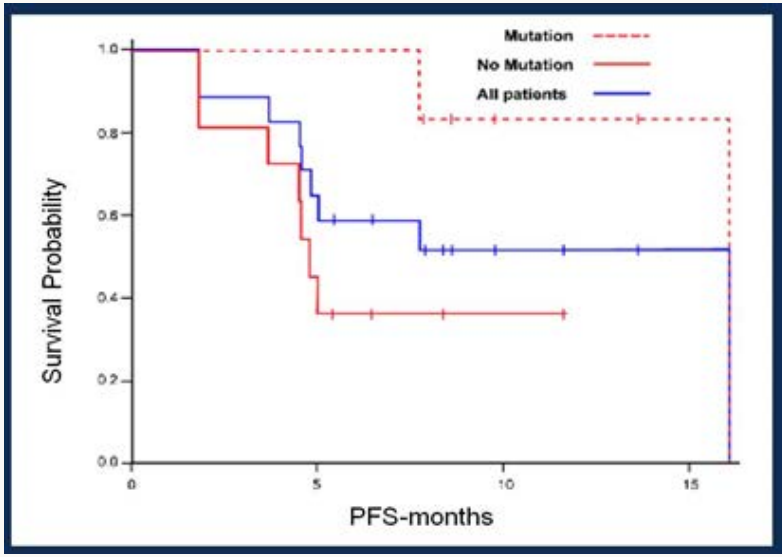
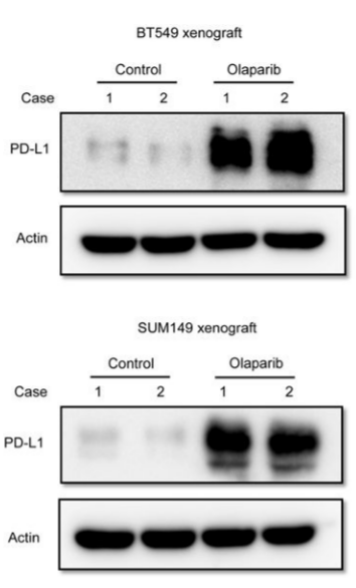


- All patients: 16.1 months (95% CI: 4.5-16.1 months)
- Non-mutated/unknown: 4.8 months (95% CI: 1.8 months- cannot be calculated)
- Mutated: 16.1 months (95% CI: 7.8-18.1 months)

Patient Number	DNA Damage Repair (DDR) Pathway Mutation(s)	Other Genomic Aberration(s)	Maximum % PSA Decline
1	BRCA2	None	-79%
2	BRCA2	ASXL1	-99%
3	None	TP53, RB1	15%
4	None	AR amplification	35%
5	None	MYD88, CCND3, BIRC3	-79%
6	BRCA2 (germline)	SPOP, 13q deletion, AR amplification	-89%
7	Insufficient specimen	Insufficient specimen	-99%
8	BRCA2 (germline)	13q deletion, PKP2	-93%
9	Insufficient specimen	Insufficient specimen	-23%
10	BRCA2	TP53, KAT6A	-85%
11	BRCA2 (germline)	Copy number loss and allelic imbalance on 13q	-50%
12	None	RYR2, PIK3CA	37%
13	Insufficient specimen	Insufficient specimen	9%
14	BRCA2	HRAS	-80%
15	None	PIK3CA, ADGRB3, TP53	4%
16	None	TP53, STAG1	-46%
17	None	BRAF, AR amplification, ASXL1, MYH11	-10%



J Immunother Cancer. 2018 Dec 4;6(1):141
Clin Cancer Res . 2017 July 15; 23(14): 3711–3720

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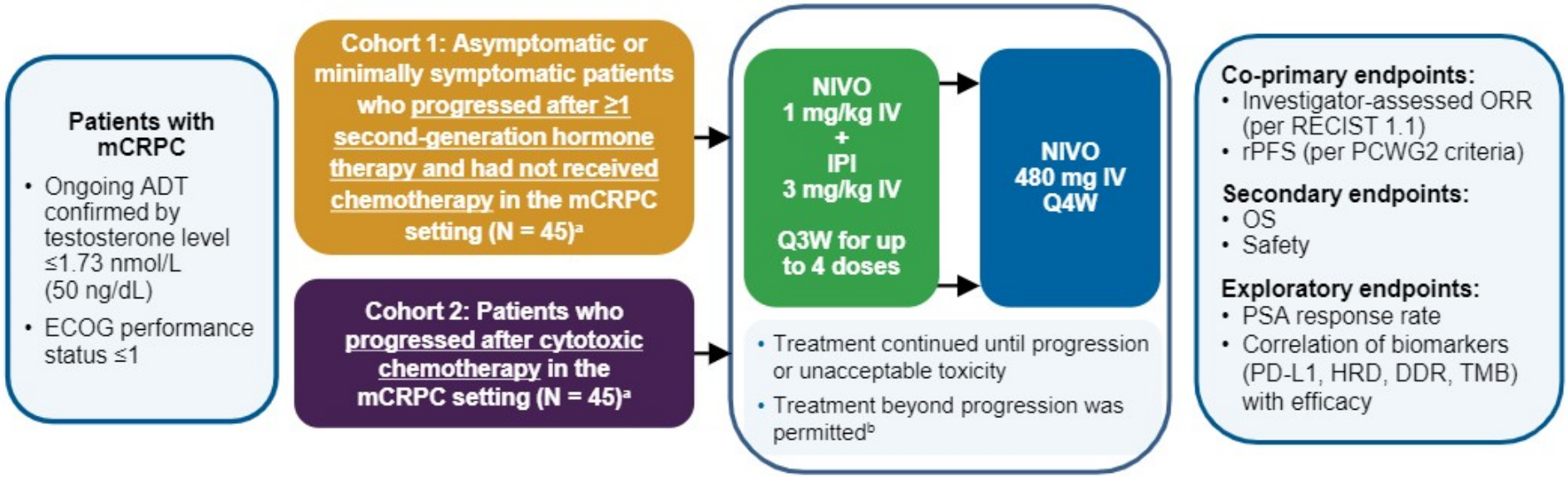
Study design

Open-label, multicenter, phase 2 study (NCT02985957)



- Patients who had received ≥1 combination dose and who had toxicity that did not meet discontinuation criteria were permitted to begin NIVO maintenance before completion of all 4 combination doses

J Clin Oncol 37, 2019 (suppl 7S; abstr 142)

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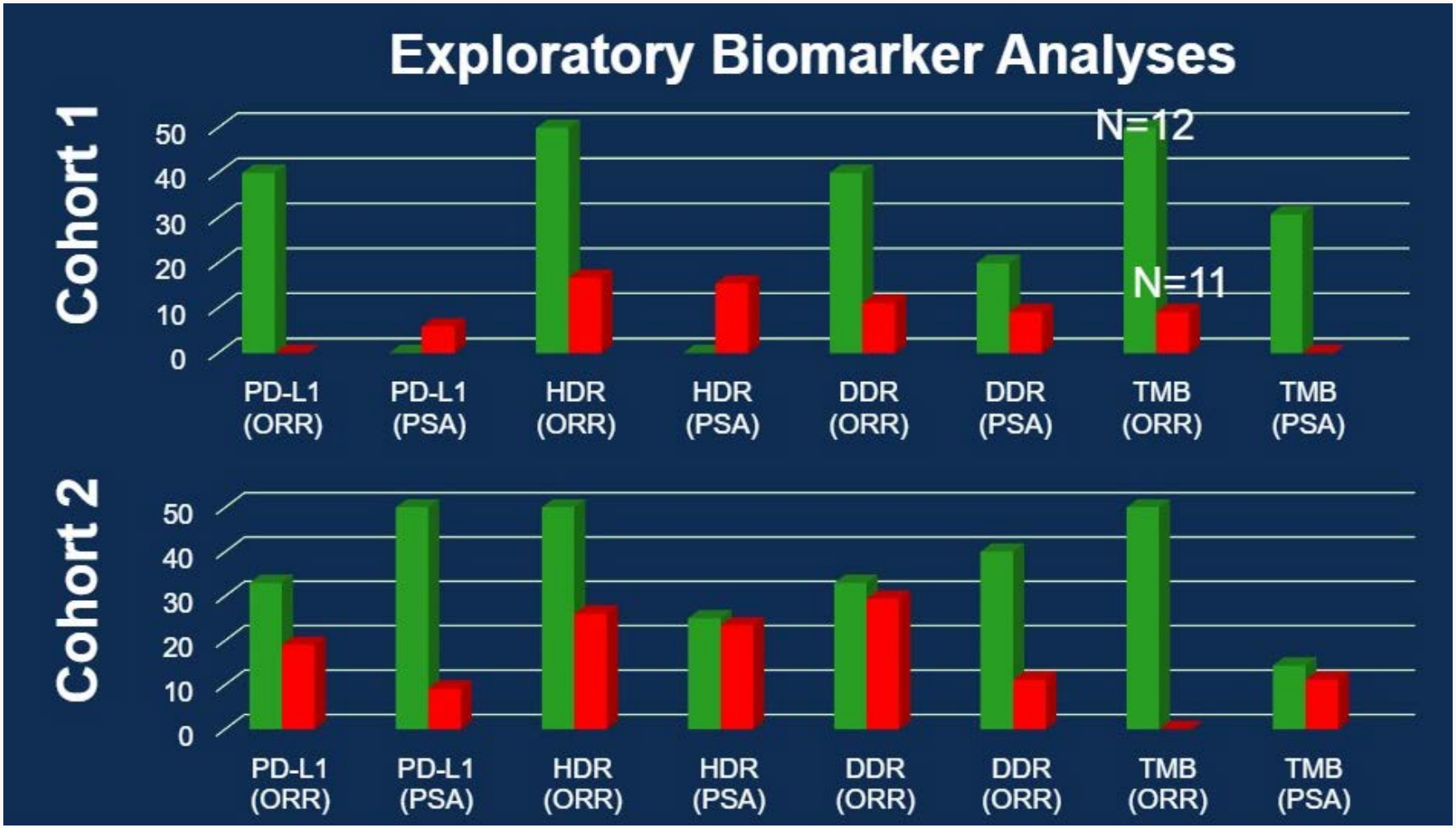
Nivolumab plus Ipilimumab



J Clin Oncol 37, 2019 (suppl 7S; abstr 142)

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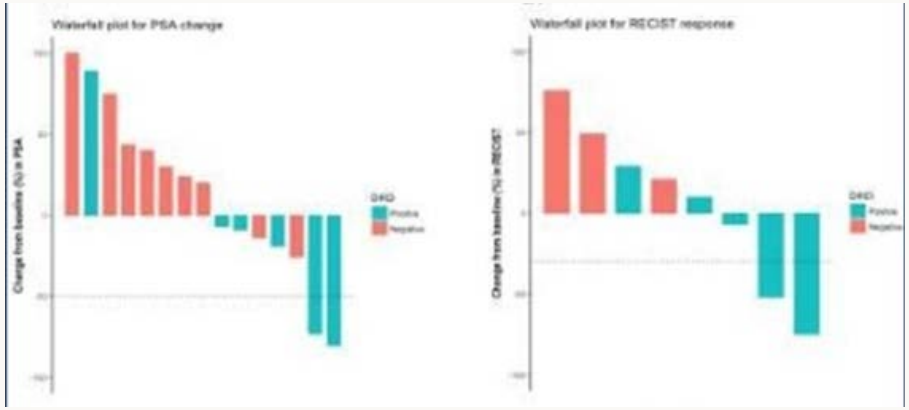
Ipilimumab plus nivolumab and DNA-repair defects in AR-V7-expressing metastatic prostate cancer

- ✓ 15 patients
  - ✓ 6/15 (40%) positive for DDR
- ✓ Outcomes: DRD+ vs. DRD-
  - ✓ PSA response (33% vs 0%; p=0.14)
  - ✓ ORR (40% vs 0%; p=0.46)
  - ✓ PSA-PFS (HR 0.19; p<0.01)
  - ✓ PFS (HR 0.31; p=0.01)
  - ✓ OS (HR 0.41; p0.11)



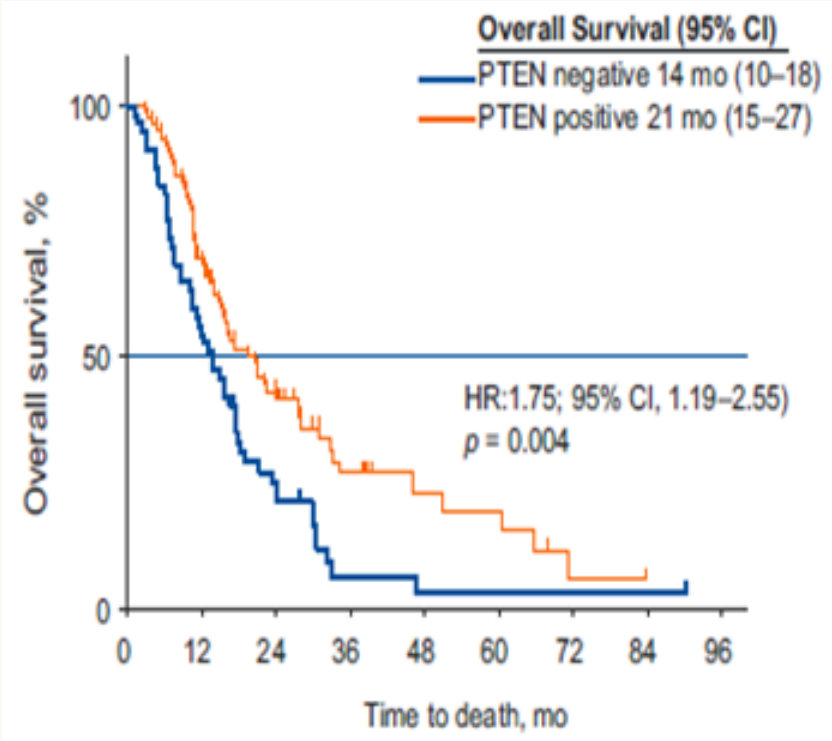
Oncotarget. 2018 Jun 19;9(47):28561-28571

Prostate Cancer

PTEN Protein Loss and Clinical Outcome from Castration-resistant Prostate Cancer Treated with Abiraterone Acetate

Roberta Ferraldeschi[a], Daniel Nava Rodrigues[a], Ruth Riisnaes[a], Susana Miranda[a], Ines Figueiredo[a], Pasquale Rescigno[a], Praful Ravi[a], Carmel Pezaro[a], Aurelius Omlin[a], David Lorente[a], Zafeiris Zafeiriou[a], Joaquin Mateo[a], Amelia Altavilla[a], Spyridon Sideris[a], Diletta Bianchini[a], Emily Grist[a], Khin Thway[a], Raquel Perez Lopez[a], Nina Tunariu[a], Chris Parker[b], David Dearnaley[b], Alison Reid[a], Gerhardt Attard[a], Johann de Bono[a,]*

[a] *Prostate Cancer Targeted Therapy Group and Drug Development Unit, The Royal Marsden NHS Foundation Trust and The Institute of Cancer Research, Sutton, Surrey, UK;* [b] *Academic Urology Unit, The Royal Marsden NHS Foundation Trust, London, UK*



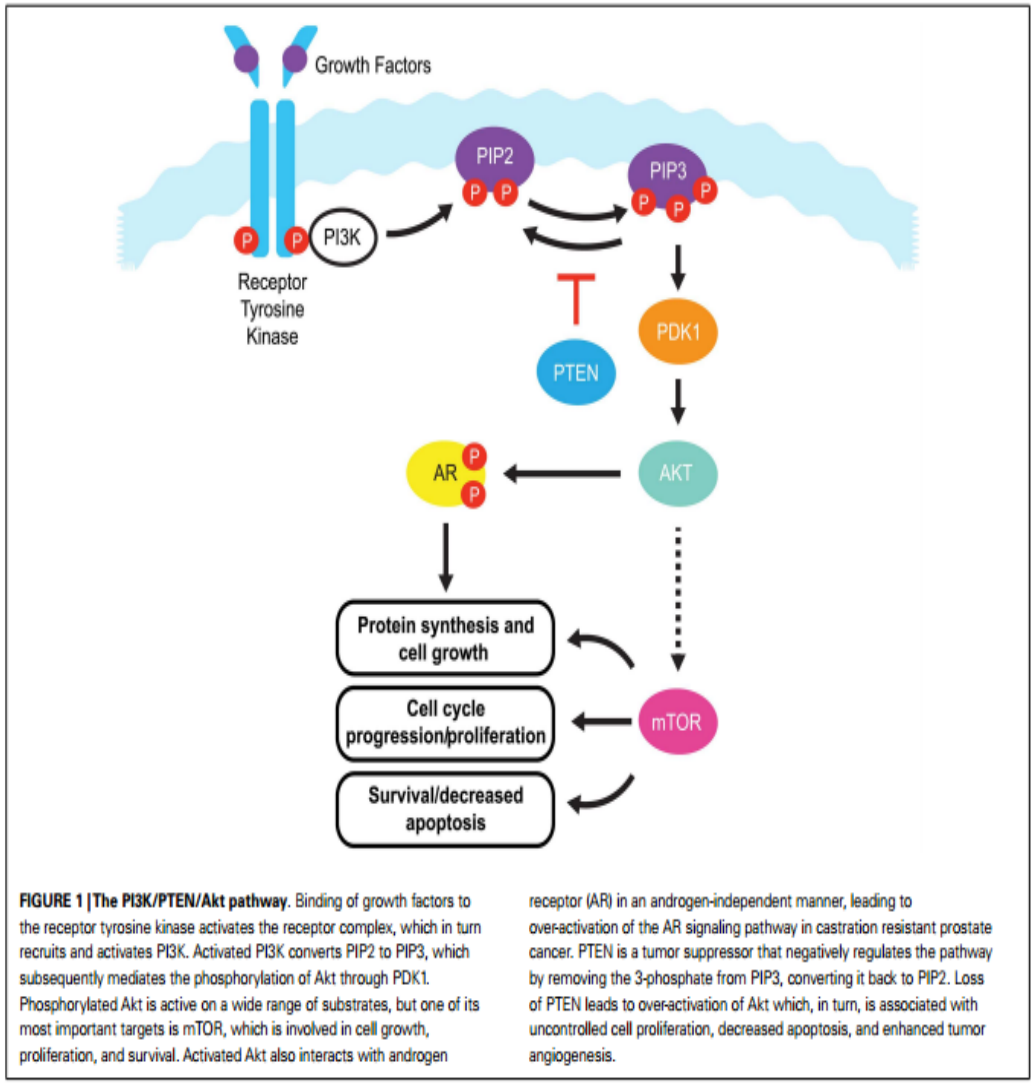


FIGURE 1 | The PI3K/PTEN/Akt pathway. Binding of growth factors to the receptor tyrosine kinase activates the receptor complex, which in turn recruits and activates PI3K. Activated PI3K converts PIP2 to PIP3, which subsequently mediates the phosphorylation of Akt through PDK1. Phosphorylated Akt is active on a wide range of substrates, but one of its most important targets is mTOR, which is involved in cell growth, proliferation, and survival. Activated Akt also interacts with androgen receptor (AR) in an androgen-independent manner, leading to over-activation of the AR signaling pathway in castration resistant prostate cancer. PTEN is a tumor suppressor that negatively regulates the pathway by removing the 3-phosphate from PIP3, converting it back to PIP2. Loss of PTEN leads to over-activation of Akt which, in turn, is associated with uncontrolled cell proliferation, decreased apoptosis, and enhanced tumor angiogenesis.

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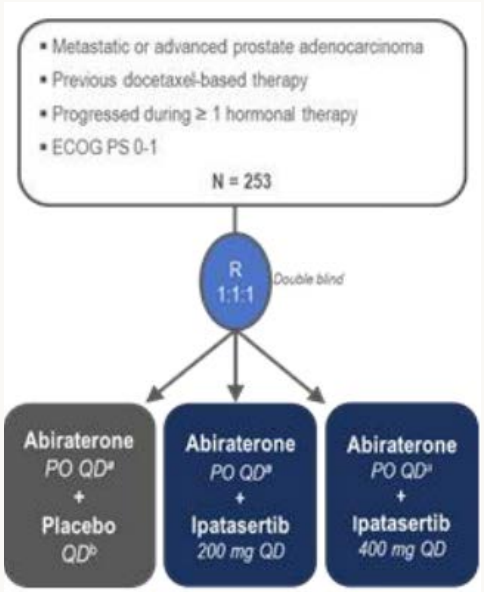
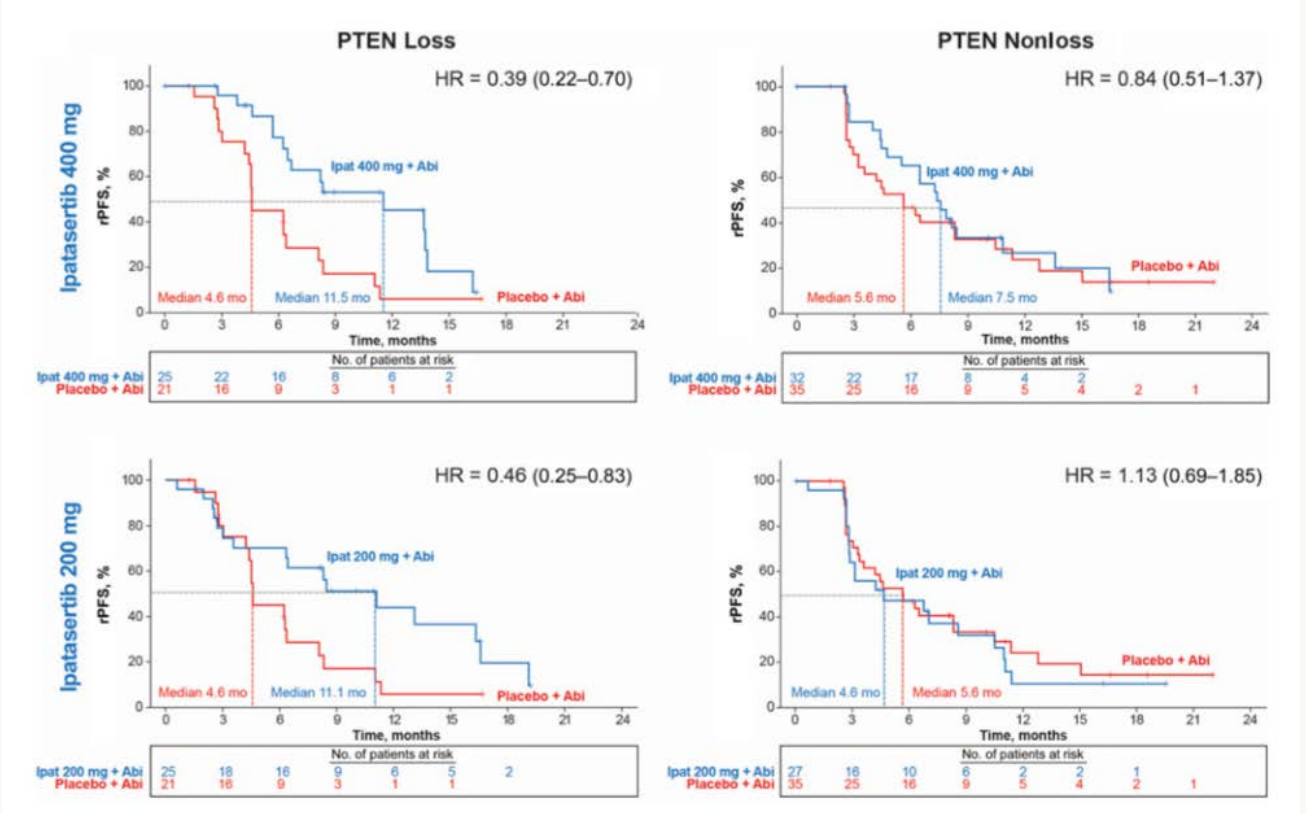
Ipatasertib and PTEN loss





Clin Cancer Res. 2019 Feb 1;25(3):928-936

Molecular states framework for androgen receptor (AR) activation in prostate cancer

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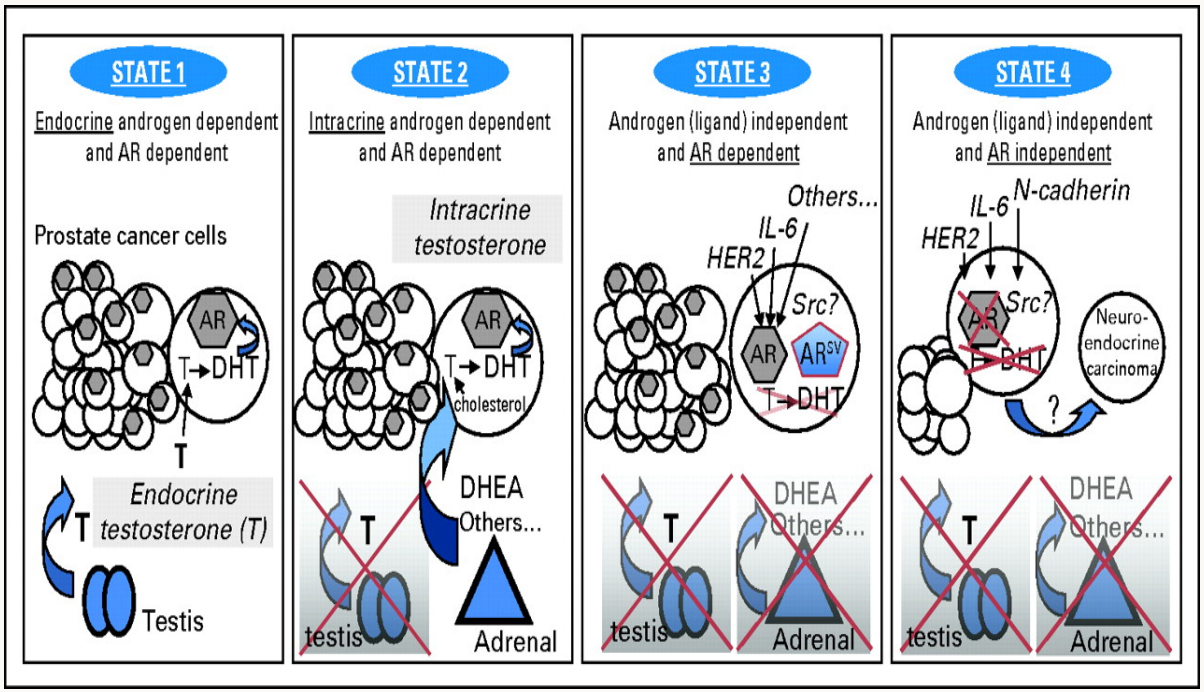
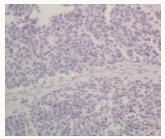
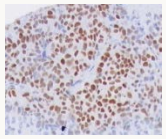
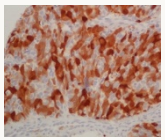
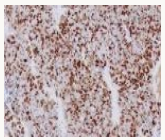
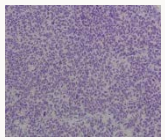
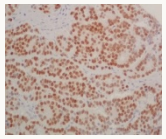
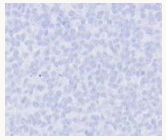
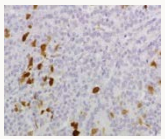
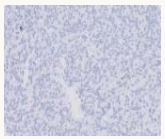
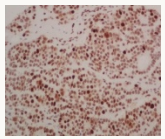


	AR	ASCL1	UBE2C	p53	RB
SCPC					
ADENO					

1. Nelson PS, et al. JCO 2012;30:644-646. 2. Tzelepi V. et al. Clin Cancer Res. 2012 Feb 1;18(3):666-77

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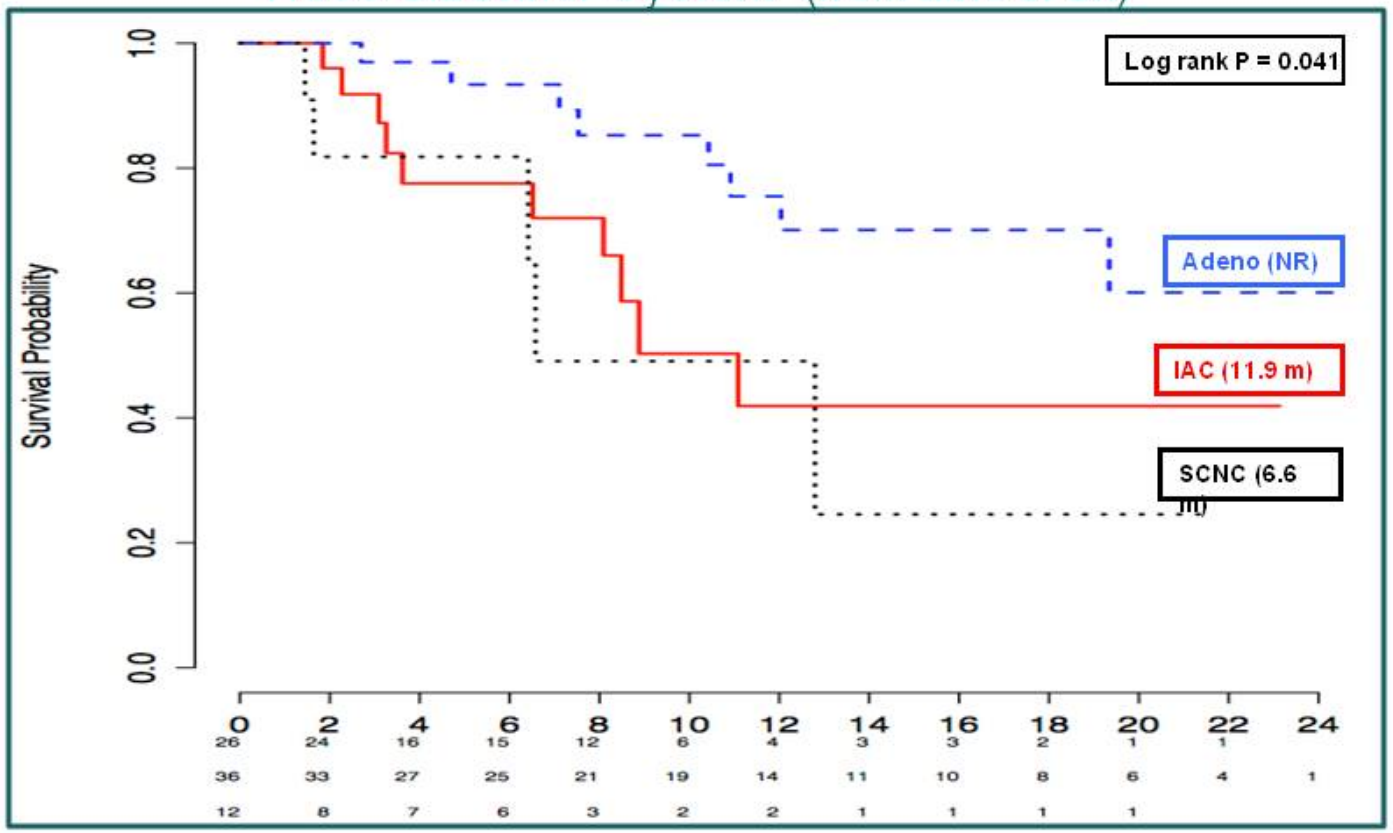
Characterization of neuroendocrine prostate cancer (NEPC) in patients with metastatic castration resistant prostate cancer (mCRPC) resistant to abiraterone (Abi) or enzalutamide (Enz): Preliminary results from the SU2C/PCF/AACR West Coast Prostate Cancer Dream Team (WCDT).

Small E. J Clin Oncol 33, 2015 a5003

2015 ASCO Annual Meeting
Illumination&Innovation
transforming data into learning

Overall survival as function of biopsy pathology Three-classifier System (from time of bx)



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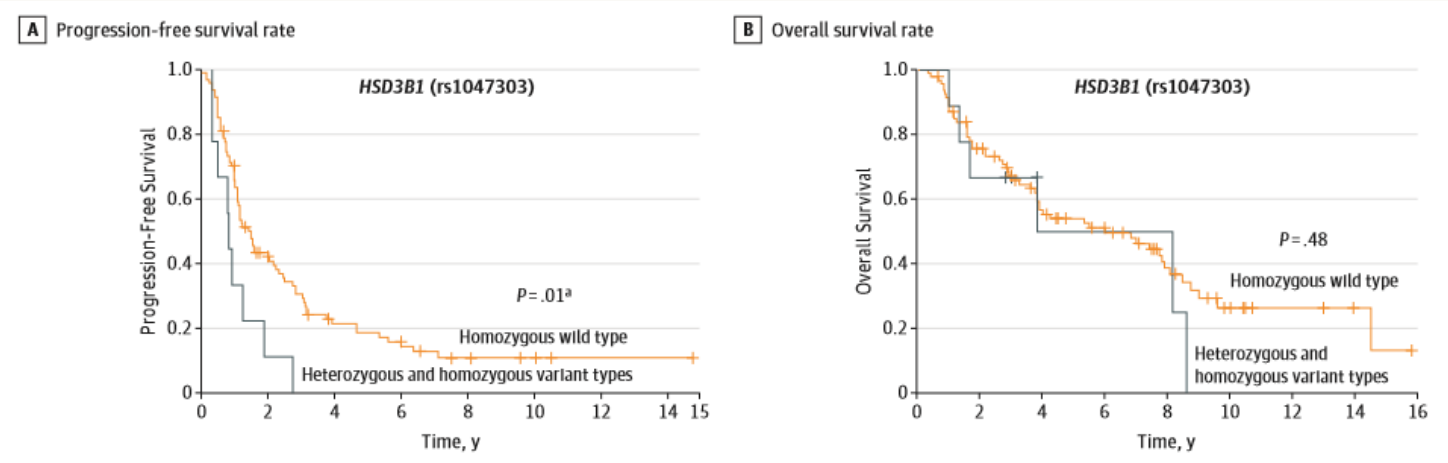

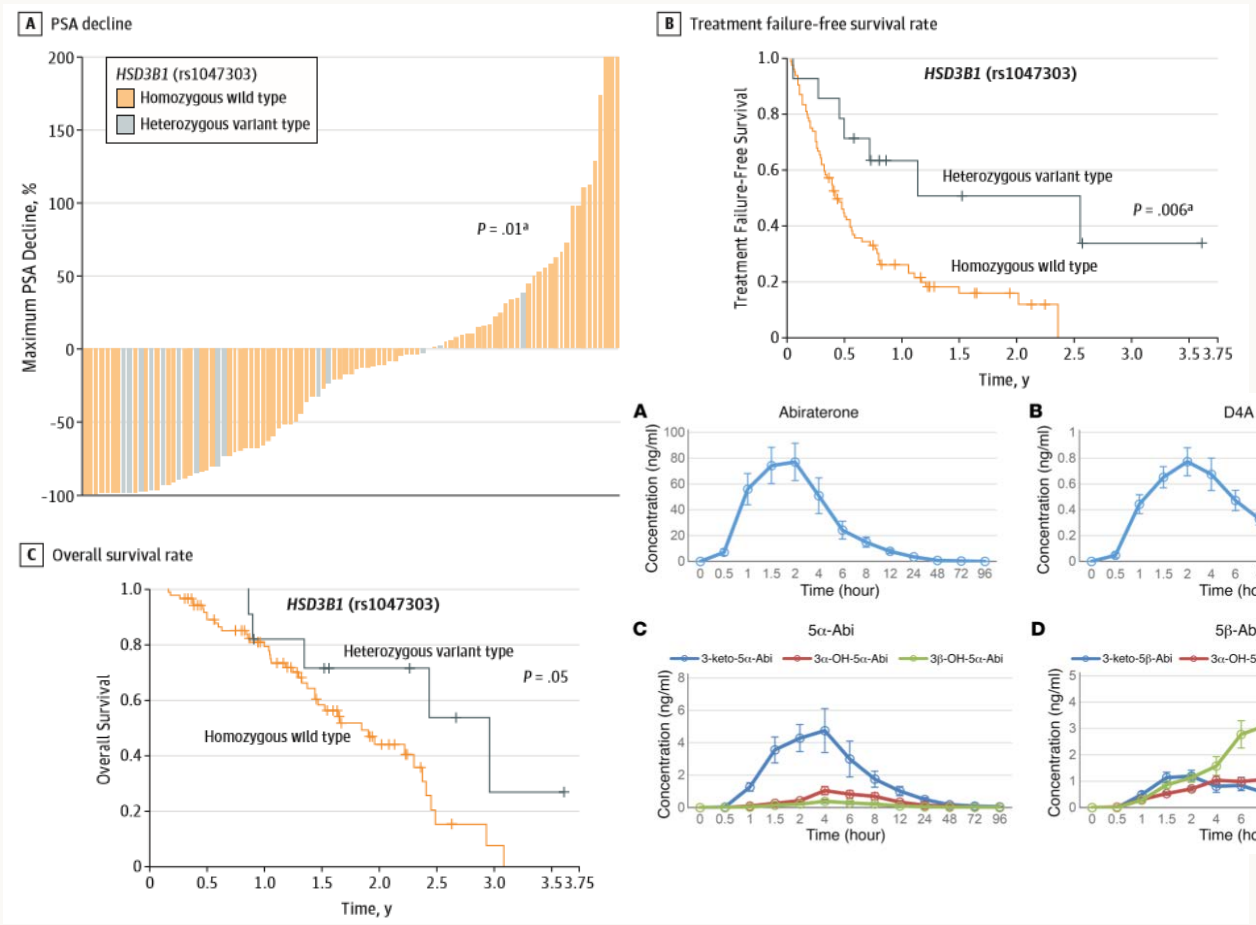

HSD3B1

Nat Rev Urol. 2018 Mar;15(3):191-196
J Clin Invest. 2018 Aug 1;128(8):3333-3340
JAMA Netw Open. 2019 Feb 1;2(2):e190115

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Conclusions

- ✓ Biomarkers are useful to guide the treatment
- ✓ AR-V7 seems to be the closest marker to be used in clinical practice
- ✓ AR-V7 positive patients are sensitive to taxane
- ✓ Taxanes can convert AR-V7 positive patients in to AR-V7 negative
- ✓ AR point mutations, DNA repair defects, AR null, RB1 mutation, p53 mutation and PTEN mutation are promising

SAVE THE DATE

III SIMPÓSIO INTERNACIONAL

GU - REVIEW 2019 - LACOG

29 E 30/11 DE 2019

SÃO PAULO

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THANK YOU

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@SoaresAndrey