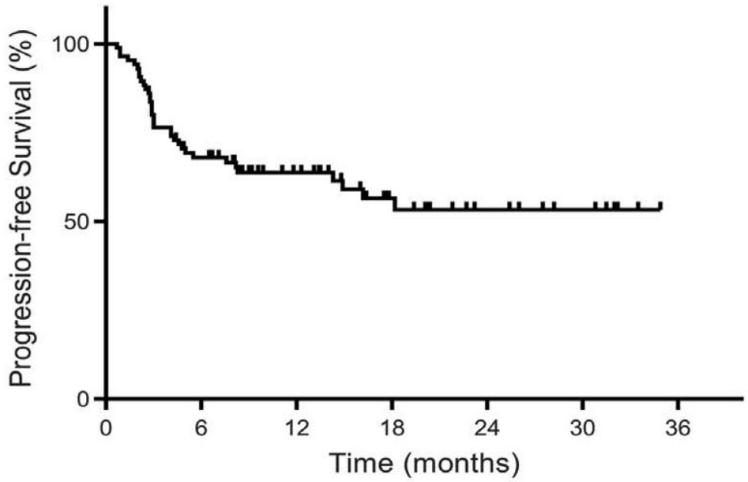
Clinical trials in prostate cancer - the data that populates the biomarker databases

Immunotherapy – the exception from the rule

- Advanced cancers.
- 12 different tumour types treated with PD-1 antibody.
- 53% with objective radiographic responses.
- 21% with complete responses.
- Lead to pan-cancer approval of pembrolizumab in the US.
  - Still not in the EU…



RESEARCH

CANCER BIOMARKERS

Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade

Dung T. Le,[1,2,3] Jennifer N. Durham,[1,2,3*] Kellie N. Smith,[1,3*] Hao Wang,[3*] Bjarne R. Bartlett,[2,4*] Laveet K. Aulakh,[2,4] Steve Lu,[2,4] Holly Kemberling,[3] Cara Wilt,[3] Brandon S. Luber,[3] Fay Wong,[2,4] Nilofer S. Azad,[1,3] Agnieszka A. Rucki,[1,3] Dan Laheru,[3] Ross Donehower,[3] Atif Zaheer,[5] George A. Fisher,[6] Todd S. Crocenzi,[7] James J. Lee,[8] Tim F. Greten,[9] Austin G. Duffy,[9] Kristen K. Ciombor,[10] Aleksandra D. Eyring,[11] Bao H. Lam,[11] Andrew Joe,[11] S. Peter Kang,[11] Matthias Holdhoff,[3] Ludmila Danilova,[1,3] Leslie Cope,[1,3] Christian Meyer,[3] Shibin Zhou,[1,3,4] Richard M. Goldberg,[12] Deborah K. Armstrong,[3] Katherine M. Bever,[3] Amanda N. Fader,[13] Janis Taube,[1,3] Franck Housseau,[1,3] David Spetzler,[14] Nianqing Xiao,[14] Drew M. Pardoll,[1,3] Nickolas Papadopoulos,[3,4] Kenneth W. Kinzler,[3,4] James R. Eshleman,[15] Bert Vogelstein,[1,3,4] Robert A. Anders,[1,3,15] Luis A. Diaz Jr.[1,2,3†‡]

Science, 2017

Immunomodulators in metastatic prostate cancer

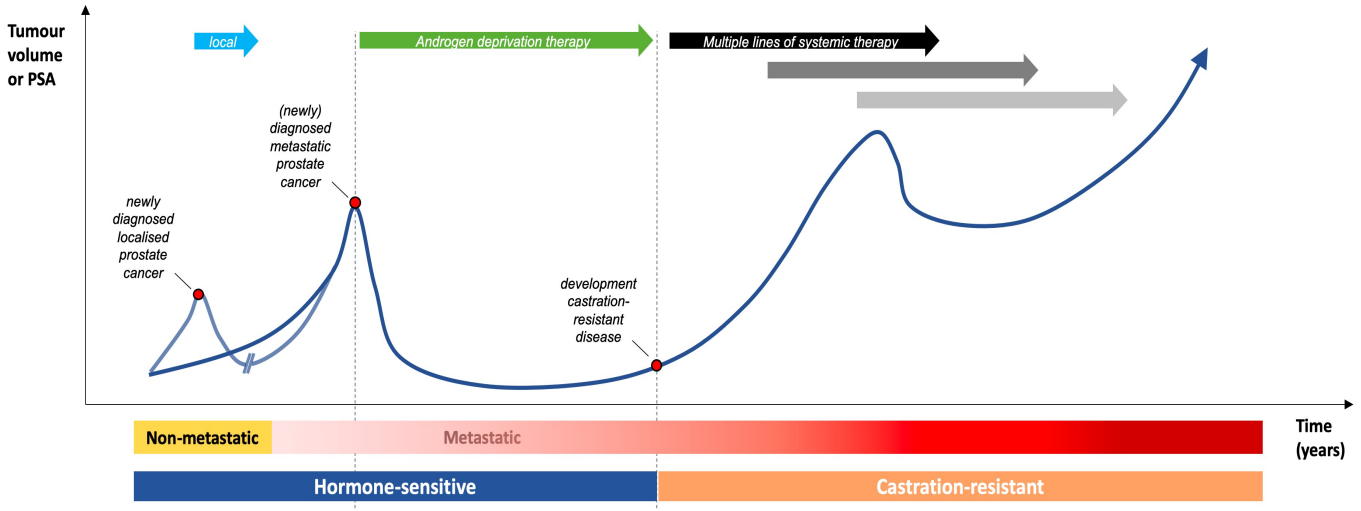
- Immunomodulators still not approved for MSI+ prostate cancer (4% of patients).
- MSI- prostate cancer patients do not gain from immunotherapy.
- Multiple phase III trials with pembrolizumab.
  - Unselected patients.
  - Combination of enzalutamide based on week small study data.
  - All negative.

February 28, 2023 6:45 am ET

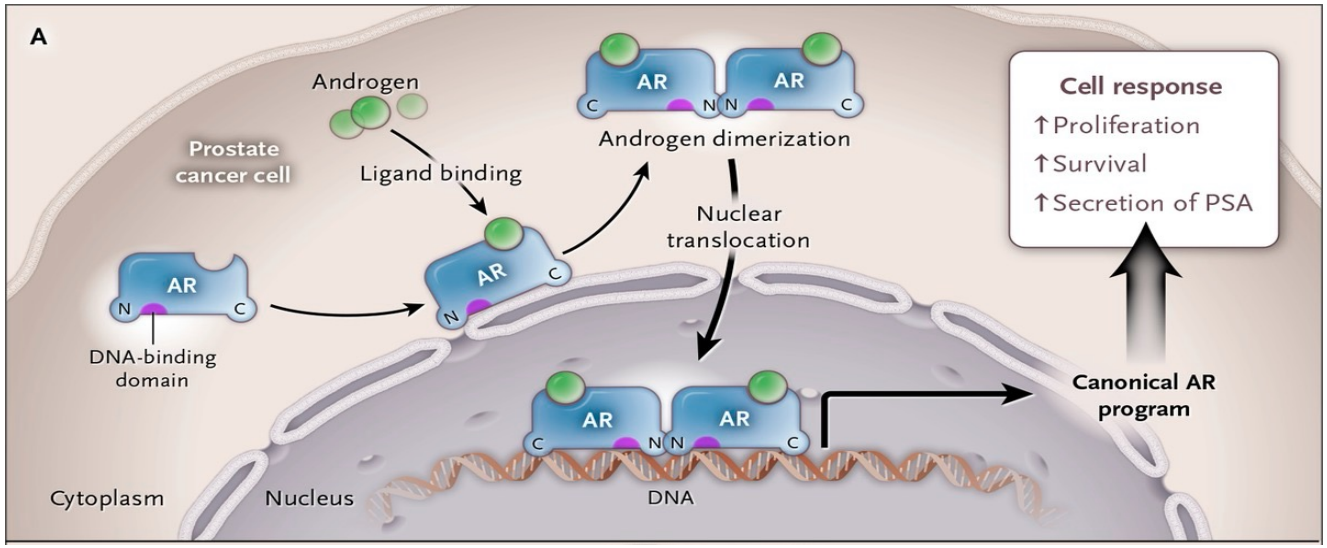
RAHWAY, N.J.--(BUSINESS WIRE)-- Merck (NYSE: MRK), known as MSD outside of the United States and Canada, today provided updates on two Phase 3 trials, KEYNOTE-641 and KEYNOTE-789. Merck is discontinuing the Phase 3 KEYNOTE-641 trial evaluating KEYTRUDA® (pembrolizumab), Merck's anti-PD-1 therapy, in combination with enzalutamide and androgen deprivation therapy (ADT) for the treatment of patients with metastatic castration-resistant prostate cancer (mCRPC) based on the recommendation of an independent Data Monitoring Committee. At an interim analysis, KEYTRUDA in combination with enzalutamide and ADT did not demonstrate an improvement in radiographic progression-free survival (rPFS) or overall survival (OS), the trial's dual primary endpoints, compared to placebo plus enzalutamide and ADT, and crossed a pre-specified futility boundary for OS. Merck is informing study investigators of the decision and advises patients in the study to speak to their physician regarding treatment.

Metastatic prostate cancer

- A large proportion of prostate cancer patients will develop or are diagnosed with advanced **metastatic disease.**



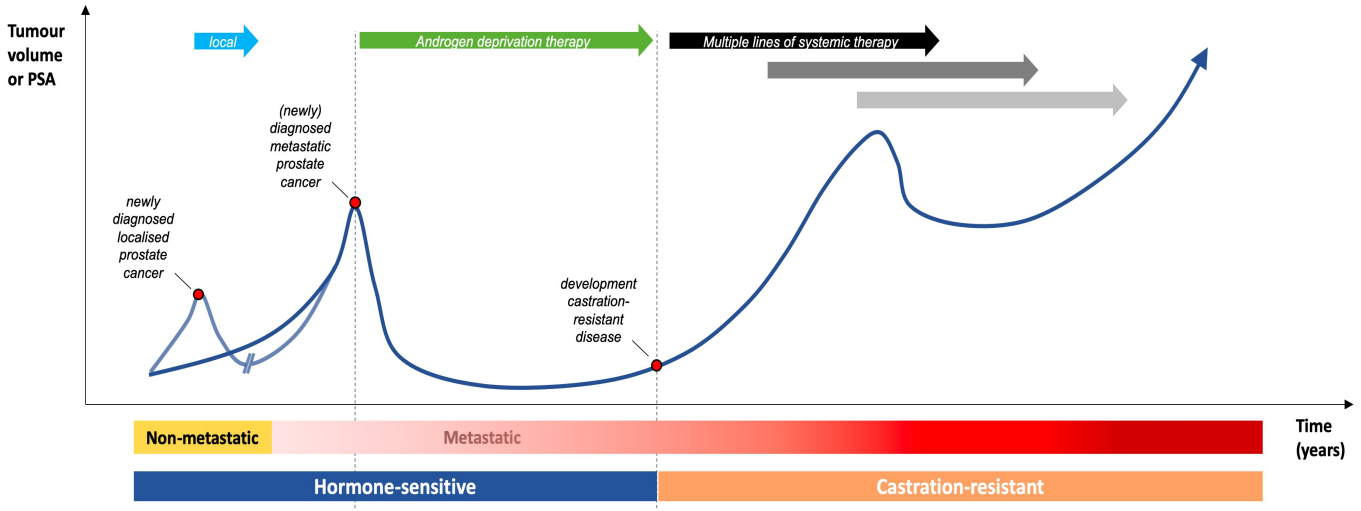
The Androgen Receptor



Nelson, New England Journal of Medicine, 2014

Metastatic prostate cancer

- A large proportion of prostate cancer patients will develop or are diagnosed with advanced **metastatic disease.**
- Many new drugs but without companion diagnostics.



ADT

Chemotherapy

Androgen receptor pathway inhibitors

Parp inhibitors

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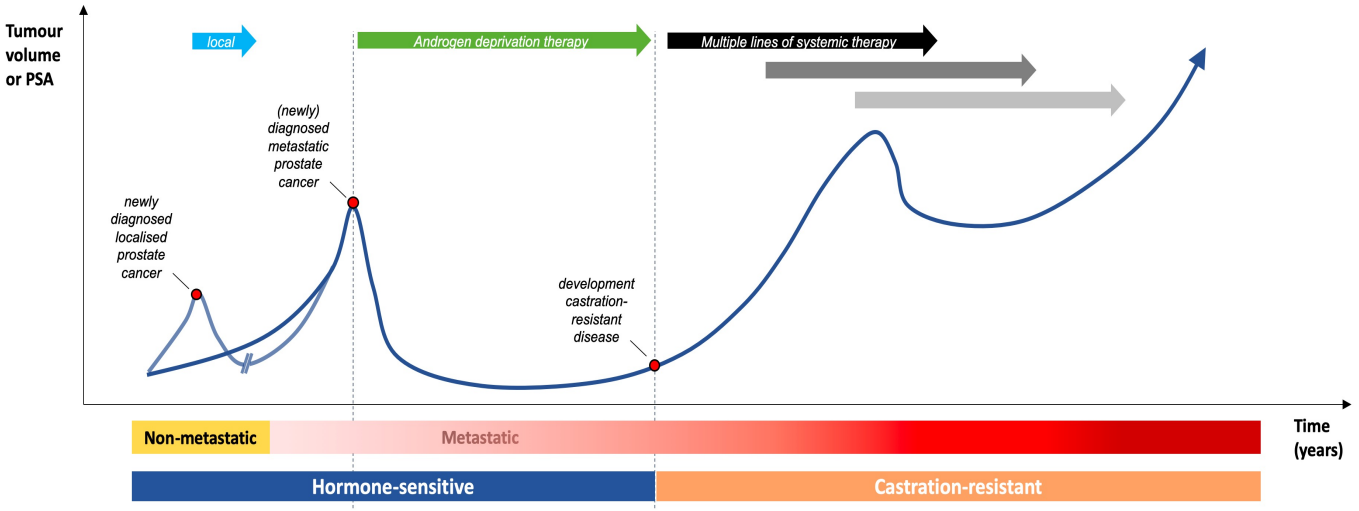

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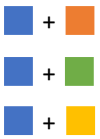
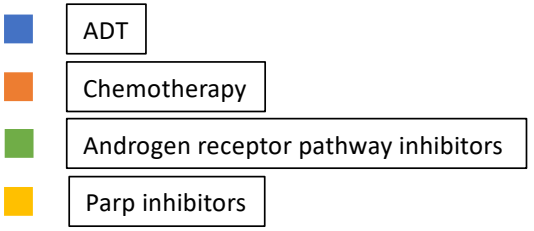
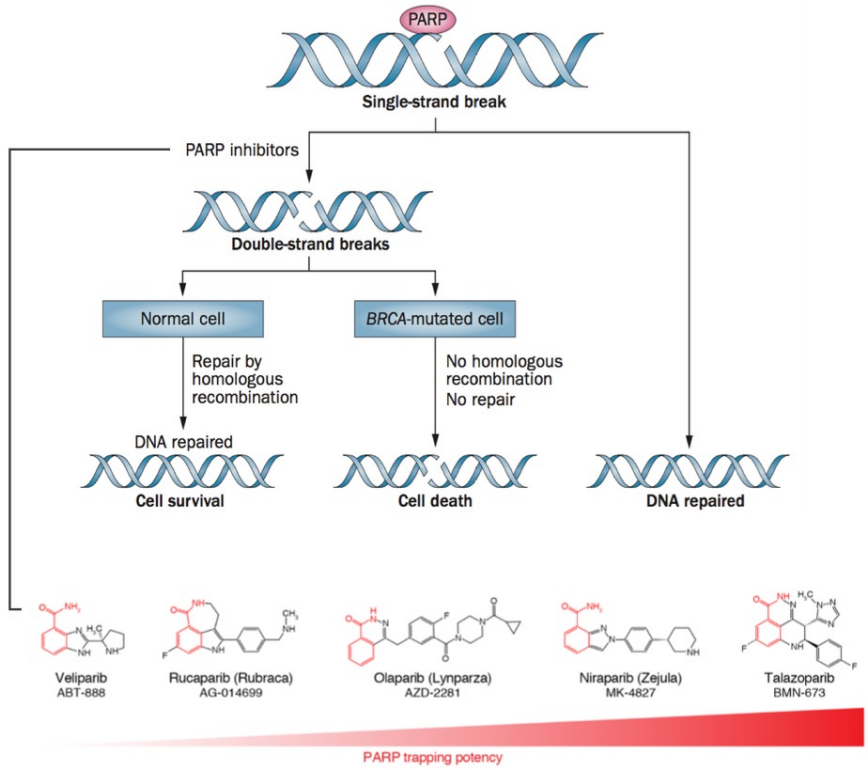




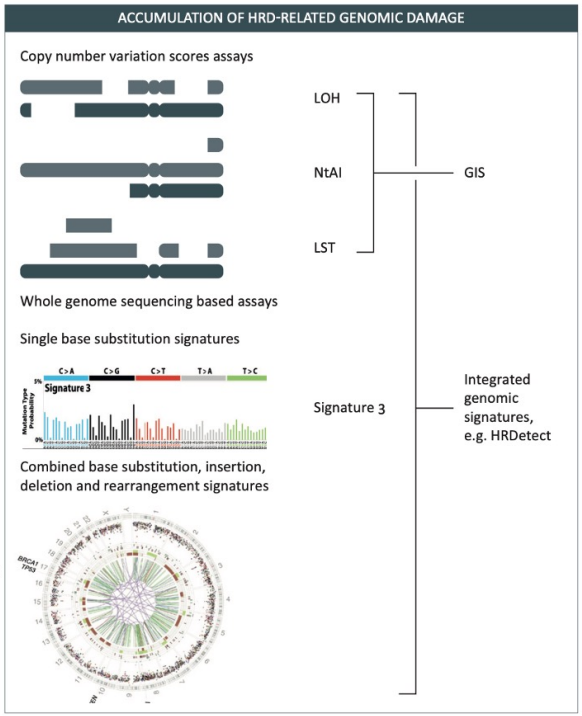
PARP-inhibitors ..

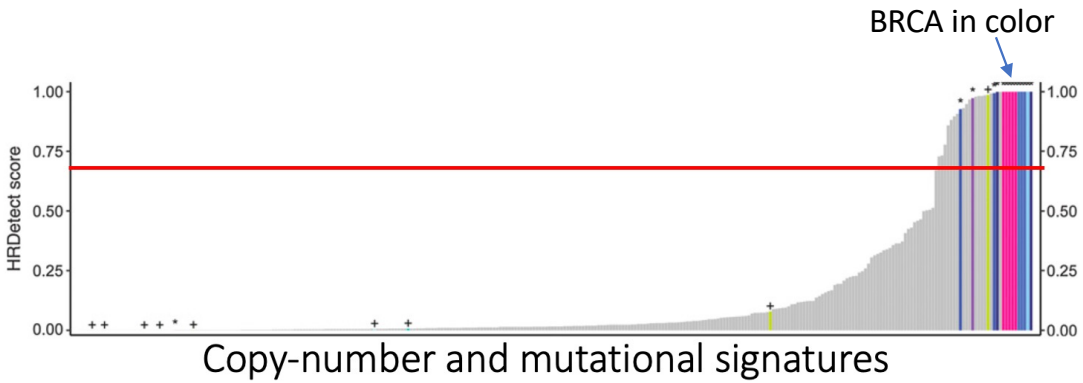


Postel-Vinay et al., Nat Rev Clin Onc, 2012 ; Sonnenblick et al, Nat. Rev., 2014; Anish et al., JCI, 2018

Who should be treated with PARP?

Phenotype





Copy-number and mutational signatures

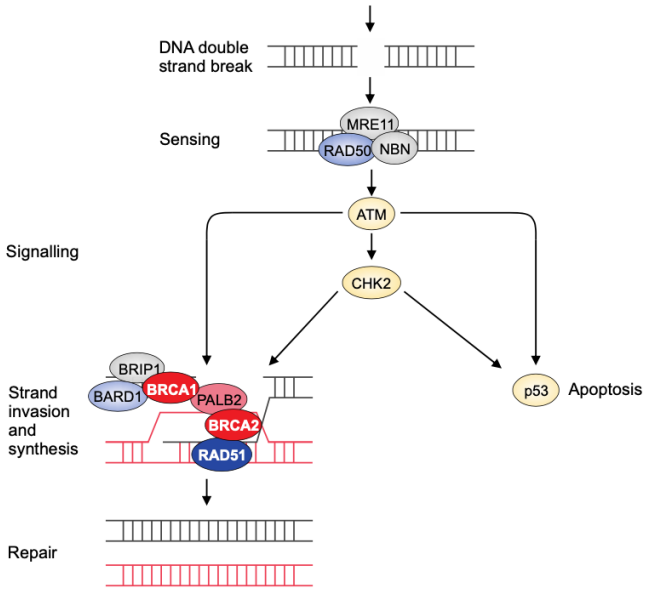
Combination of mutational signatures and genome instability score identifies 1.5x to 2x number of BRCA-patients that would benefit from PARP.

However – this requires exome or WGS for prostate cancer. Easier to identify mutations instead.

Detection of Molecular Signatures of Homologous Recombination Deficiency in Prostate Cancer with or without BRCA1/2 Mutations, CCR, 2020

Homologous repair deficiency - HRD

- A signalling cascade is triggered when a double strand break occurs.
- Multiple studies demonstrate that responses are confined to the BRCA-complex.



Polak, Nature Genetics, 2017

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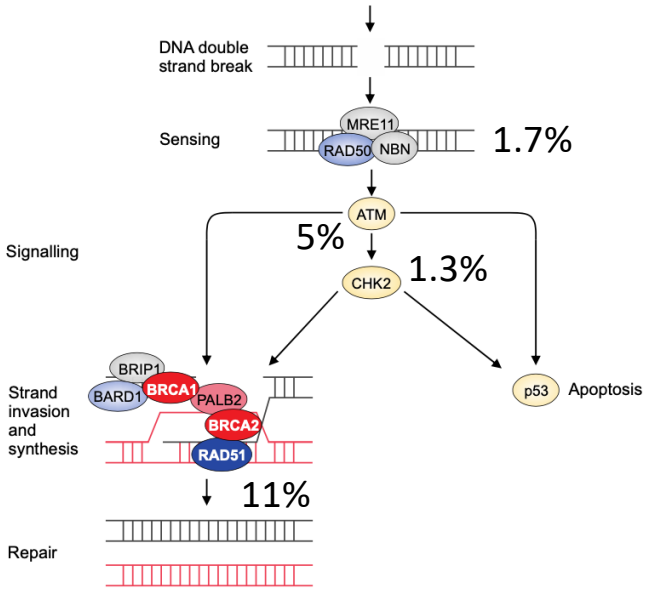

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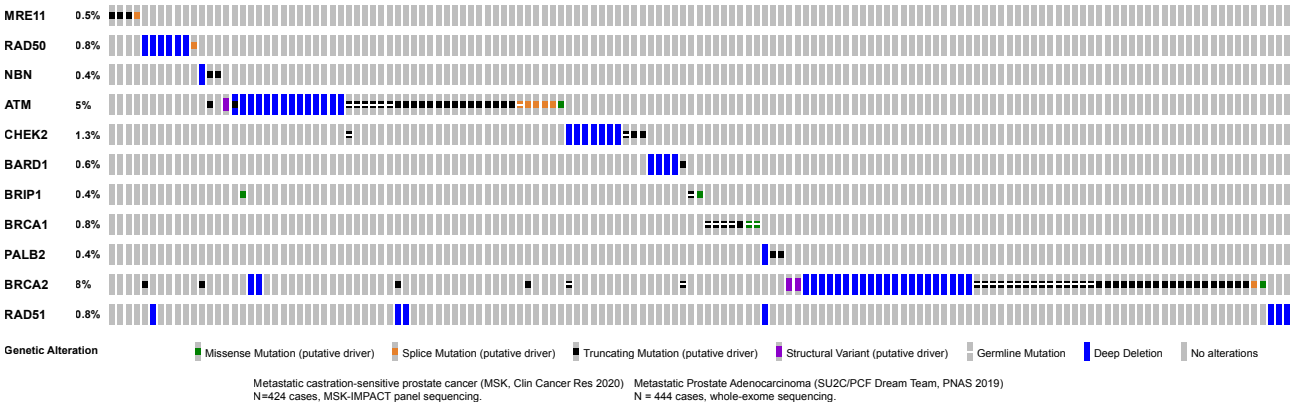


Profound trial – profoundly unethical

ORIGINAL ARTICLE

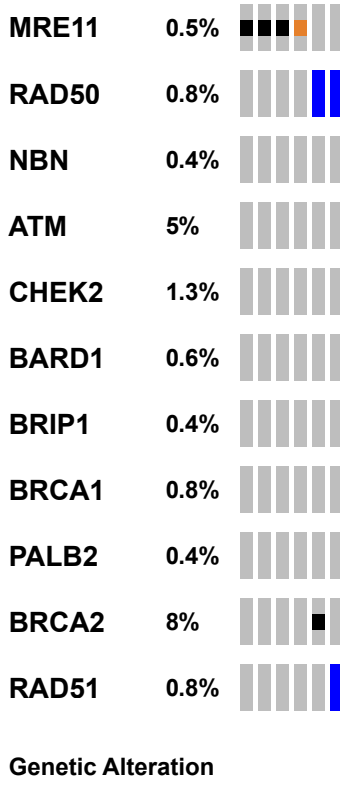
Olaparib for Metastatic Castration-Resistant Prostate Cancer

J. de Bono, J. Mateo, K. Fizazi, F. Saad, N. Shore, S. Sandhu, K.N. Chi, O. Sartor, N. Agarwal, D. Olmos, A. Thiery-Vuillemin, P. Twardowski, N. Mehra, C. Goessl, J. Kang, J. Burgents, W. Wu, A. Kohlmann, C.A. Adelman, and M. Hussain

Listen to the podcast of Vinay Prasad
https://soundcloud.com/plenarysession/ep252

Profound trial – profoundly unethical

- The profound trial, led to Olaparib approval in Europe and US.
- Phase III trial
- Biomarker driven:
  - Genes with a ”direct” or ”indirect” role in homologous recombination repair.
  - Cohort A (n=245): Patients with at least one alteration in BRCA1, BRCA2, or ATM.
  - Cohort B (n=142): Patients with alterations in any of the other 12 specified genes.
- Why ATM?



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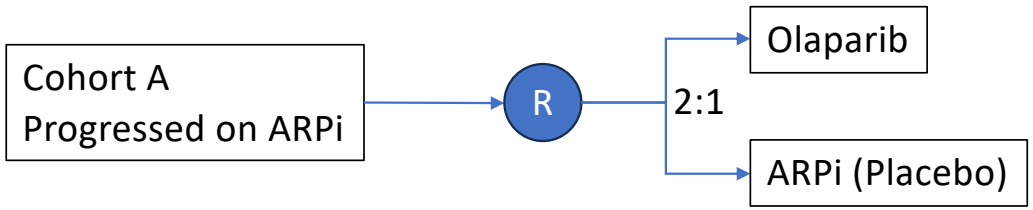
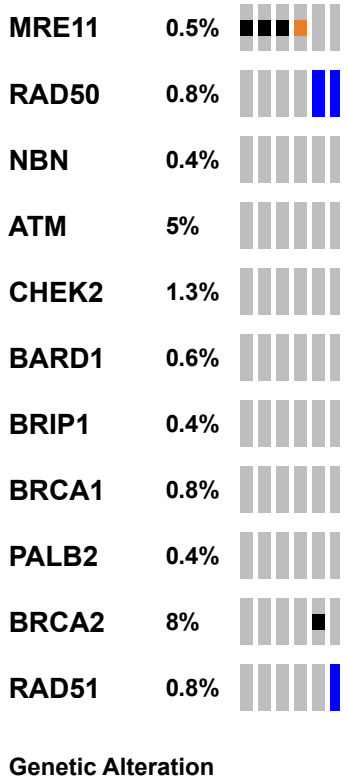
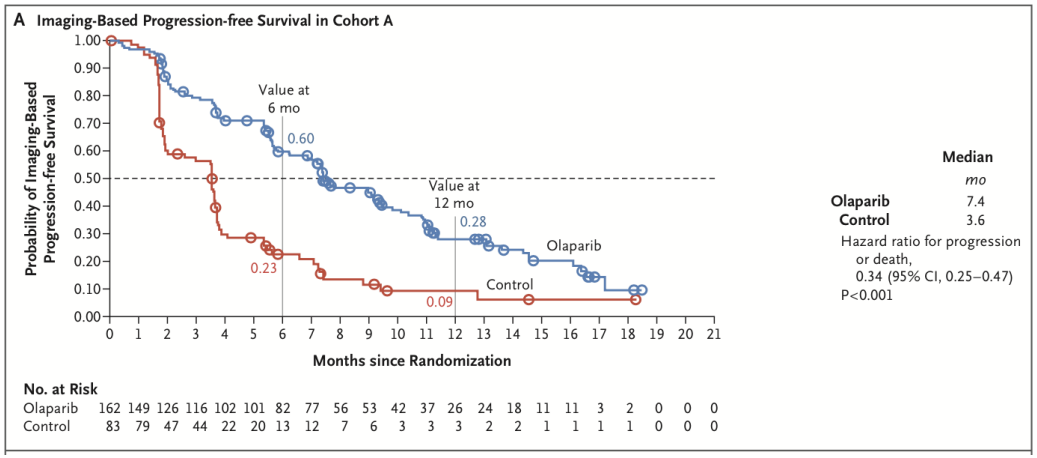
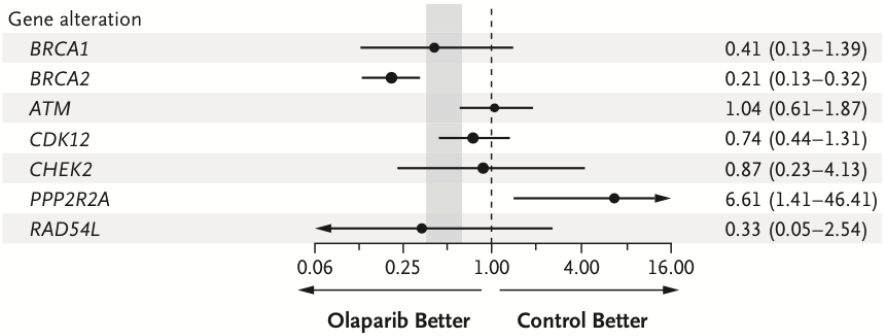
  - Cohort A (n=245): Patients with at least one alteration in BRCA1, BRCA2, or ATM.
  - Cohort B (n=142): Patients with alterations in any of the other 12 specified genes.
- Patients: Second-line mCRPC, progressed on ARPi





Results





- Cohort A was predefined in the protocol (BRCA1, BRCA2, or ATM) = Led to approval in US for ATM/BRCA1/BRCA2

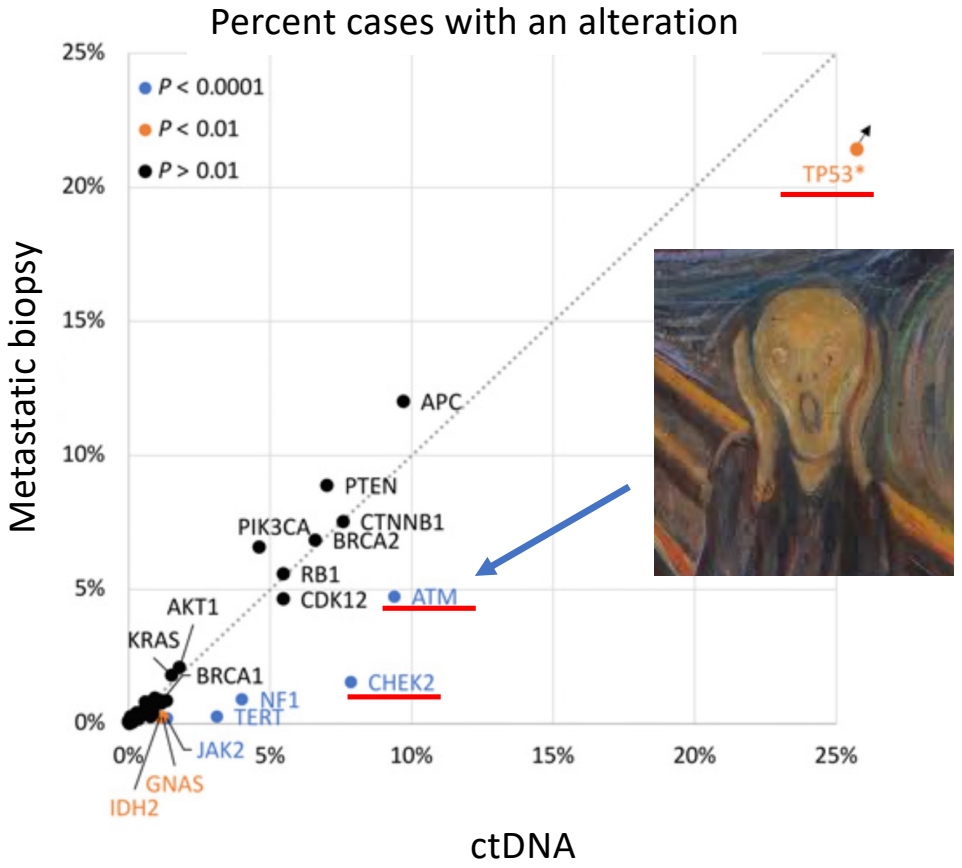
- www.oncokb.org

FMI says “there is nothing to do about it” ..

CLINICAL CANCER RESEARCH | PRECISION MEDICINE AND IMAGING

Genomic Analysis of Circulating Tumor DNA in 3,334 Patients with Advanced Prostate Cancer Identifies Targetable BRCA Alterations and AR Resistance Mechanisms

Hanna Tukachinsky[1], Russell W. Madison[1], Jon H. Chung[1], Ole V. Gjoerup[1], Eric A. Severson[1], Lucas Dennis[1], Bernard J. Fendler[1], Samantha Morley[1], Lei Zhong[1], Ryon P. Graf[1], Jeffrey S. Ross[1,2], Brian M. Alexander[1], Wassim Abida[3], Simon Chowdhury[4], Charles J. Ryan[5], Karim Fizazi[6], Tony Golsorkhi[7], Simon P. Watkins[7], Andrew Simmons[7], Andrea Loehr[7], Jeffrey M. Venstrom[1], and Geoffrey R. Oxnard[1]



- Triton2/3 + routine testing
- Foundation ACT + FoundationOne Liquid
- No deletions

Metastatic prostate cancer

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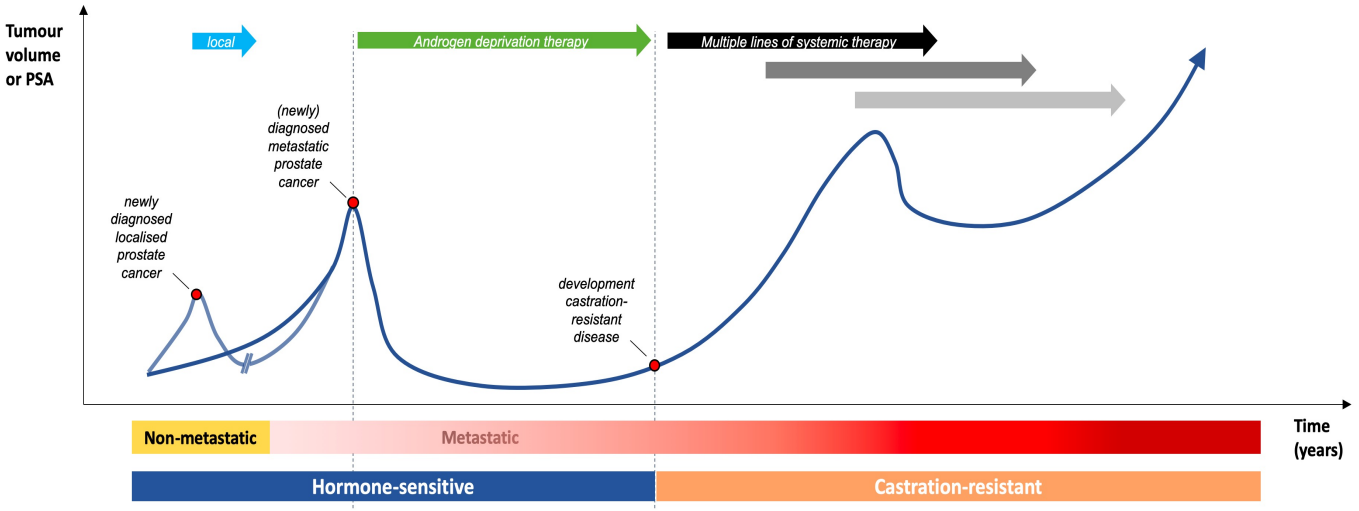
- Many new drugs but without companion diagnostics.



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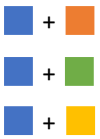

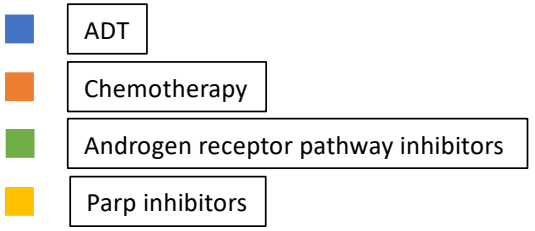

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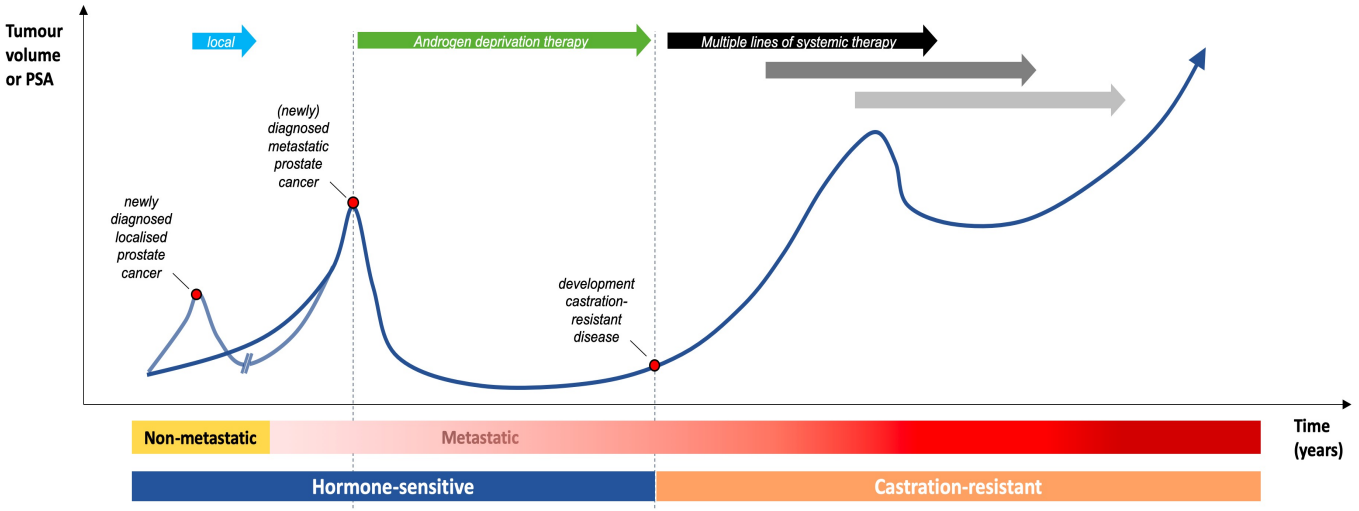

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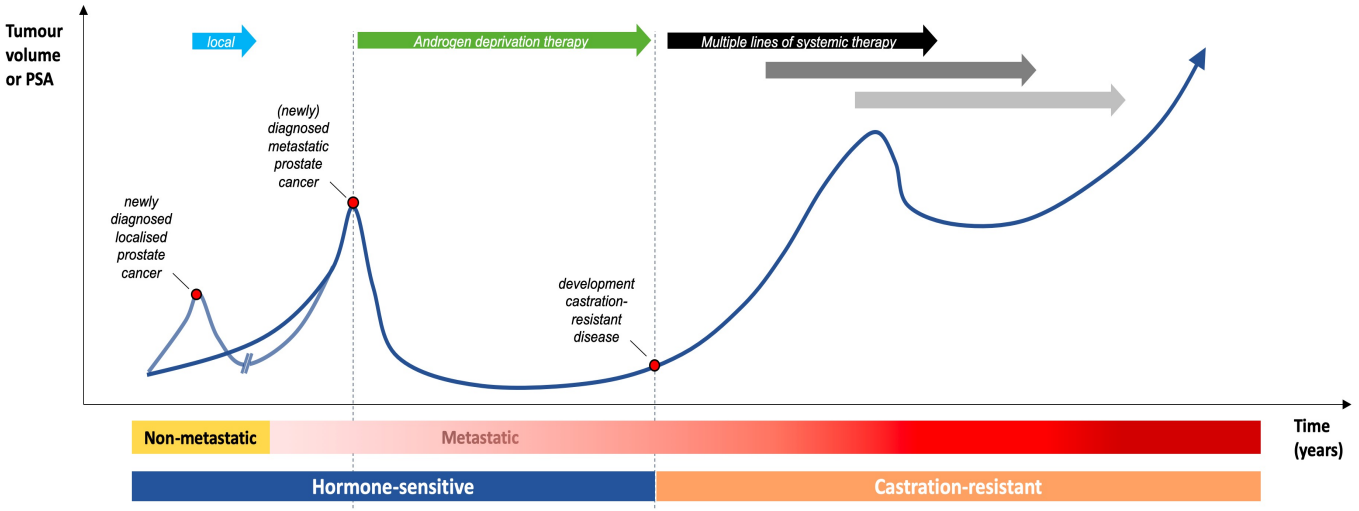

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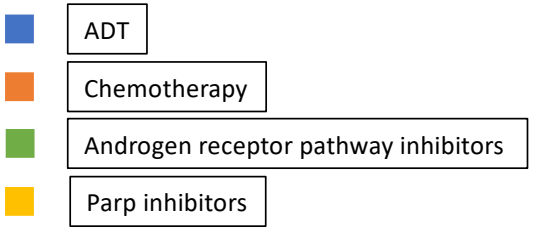
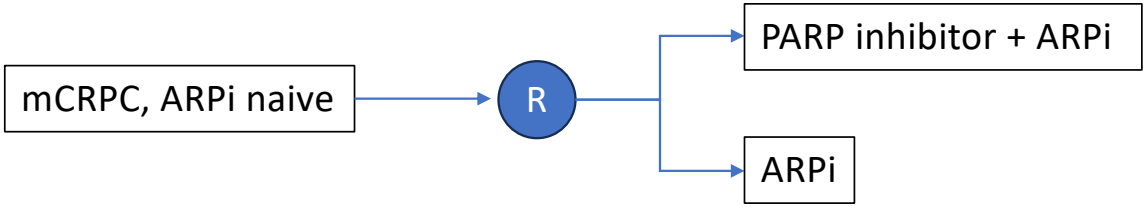
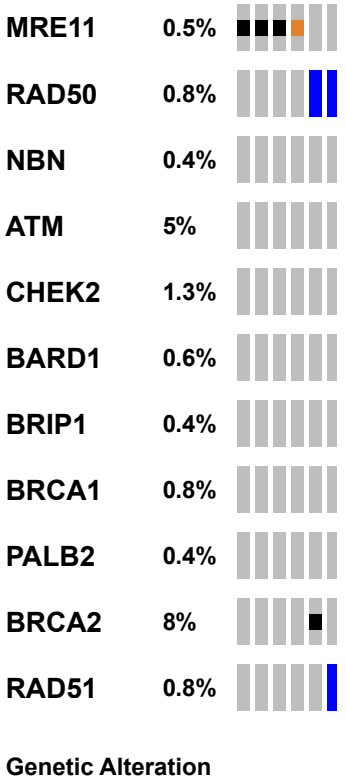


PROpel/TALAPRO-2 – in first line mCRPC

- Phase III trials
- Hypothesis: poor functional data suggests that ARPi induces HRD in prostate cancer cells, therefore all patients ($$$) may be treated.
- Biomarkers are identified, predefined subgrops.
- Patients: first line mCRPC.





PROpel/TALAPRO-2 – a biomarker testing perspective

PROpel, NEJM 2022

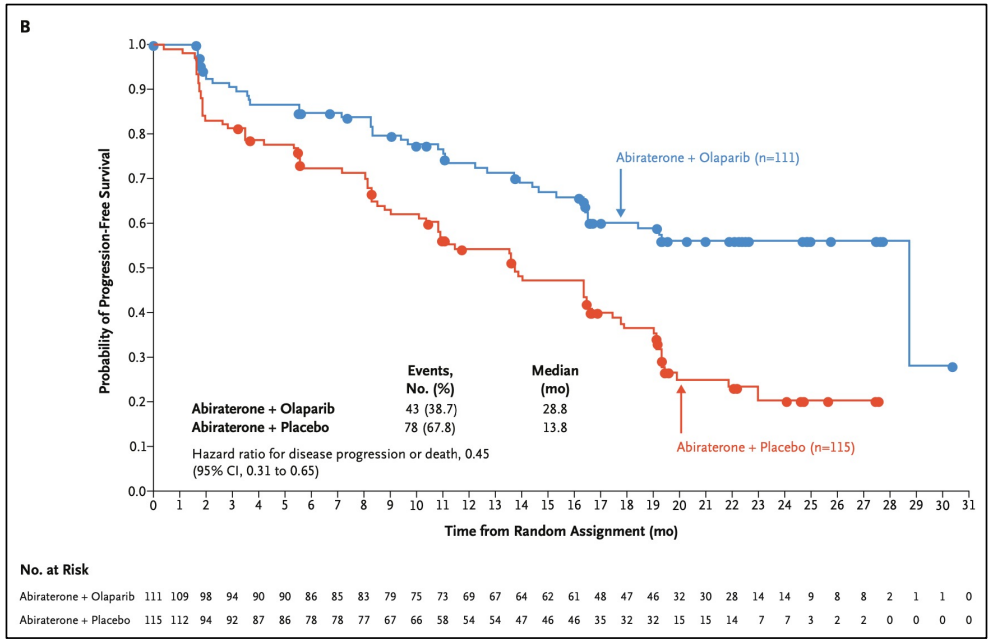


Image-based PFS on **HRR** group

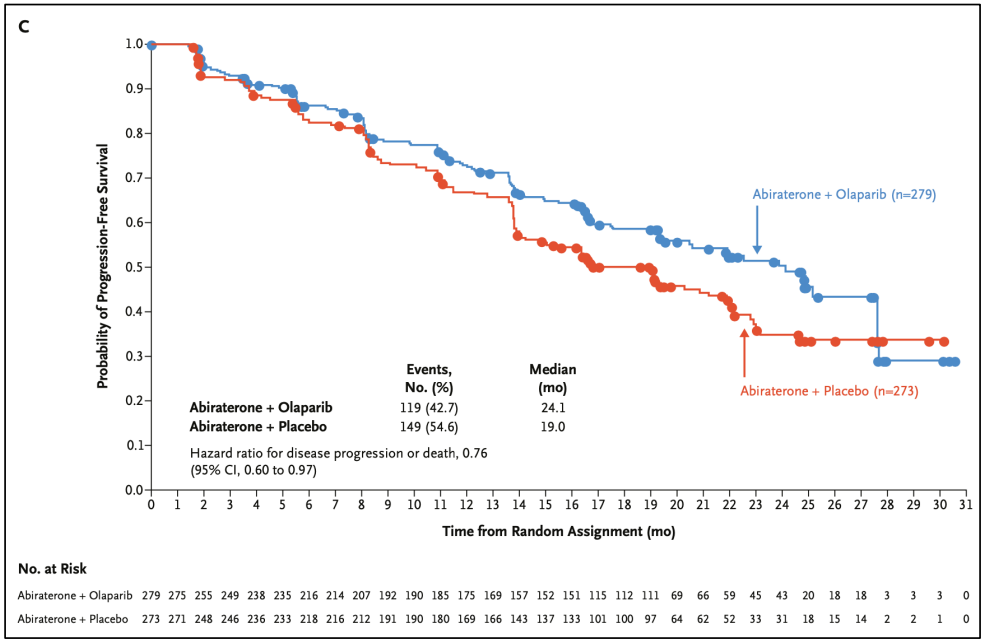


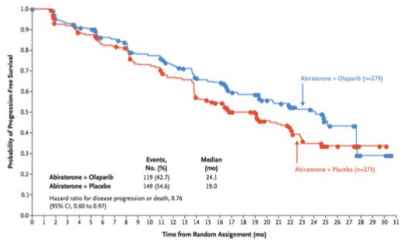
Image-based PFS on **HRR-negative** group

Difference due to abiraterone-induced “BRCAness” or not detected HRD+ patients?

PROpel/TALAPRO-2 – a biomarker testing perspective

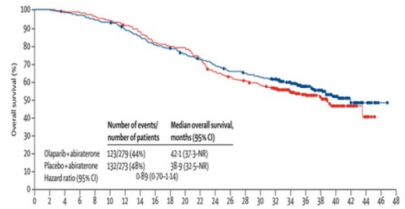
non-HRR

rPFS



HR 0.76 (0.6-0.97)

OS



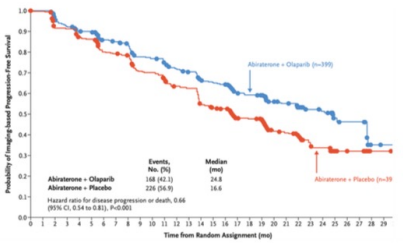
HR 0.89 (0.7-1.14)

PROpel, NEJM 2022

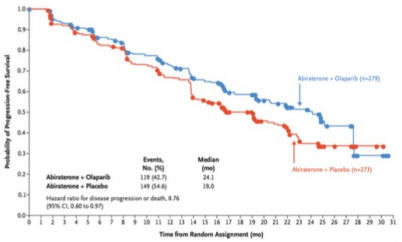
PROpel/TALAPRO-2 – a biomarker testing perspective

unselected > non-HRR

rPFS

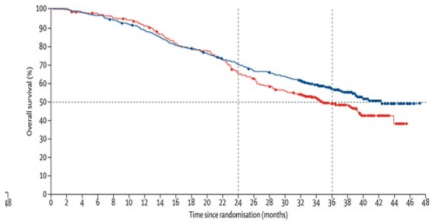


HR 0.66 (0.54-0.81)

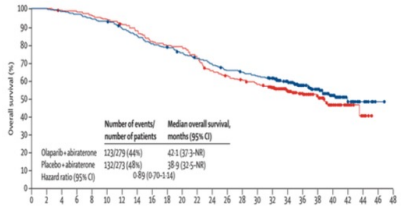


HR 0.76 (0.6-0.97)

OS



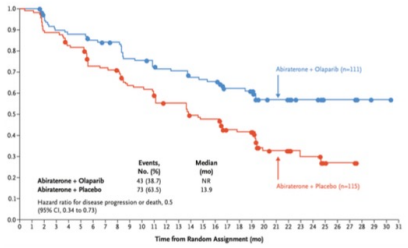
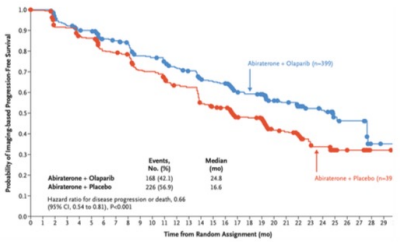
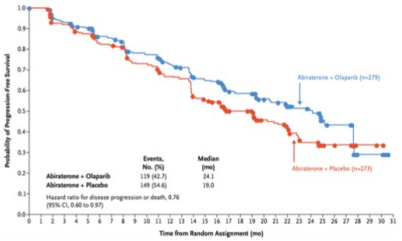
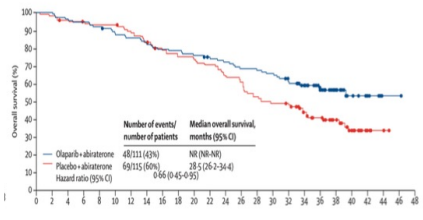
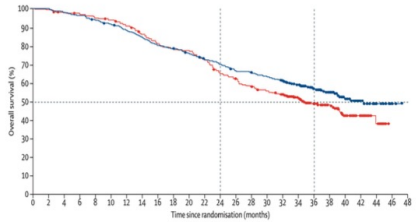
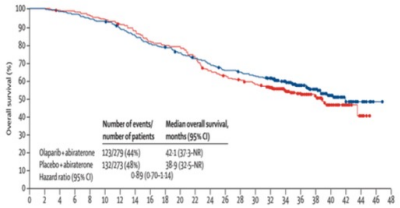
HR 0.8 (0.67-1.0)



HR 0.89 (0.7-1.14)

PROpel, NEJM 2022

PROpel/TALAPRO-2 – a biomarker testing perspective

	HRRm	>>	unselected	>	non-HRR
rPFS					
	HR 0.5 (0.34-0.73)		HR 0.66 (0.54-0.81)		HR 0.76 (0.6-0.97)
OS					
	HR 0.66 (0.45-0.95)		HR 0.8 (0.67-1.0)		HR 0.89 (0.7-1.14)

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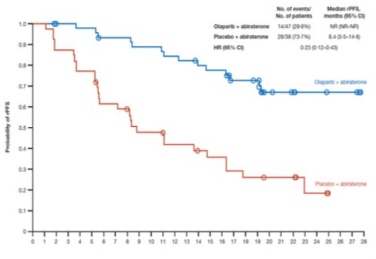
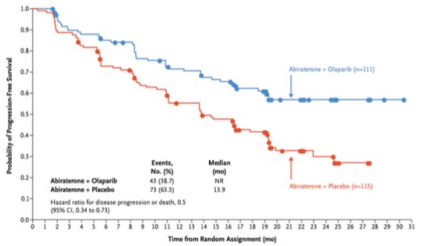
BRCA >>> HRRm >> unselected > non-HRR

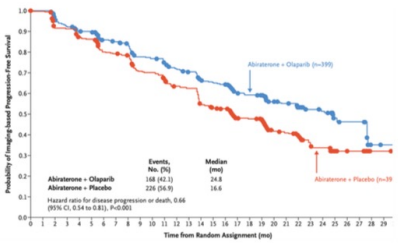
rPFS



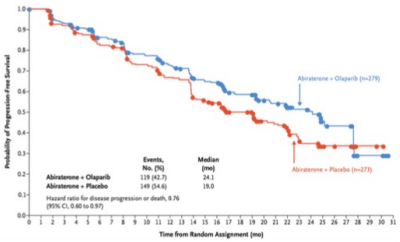
HR 0.23 (0.12-0.43)



HR 0.5 (0.34-0.73)

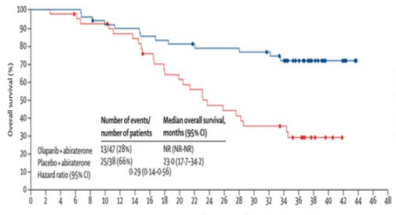


HR 0.66 (0.54-0.81)

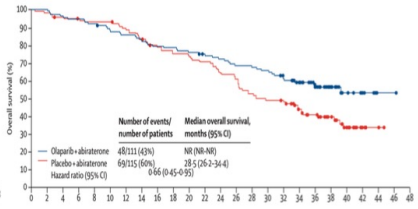


HR 0.76 (0.6-0.97)

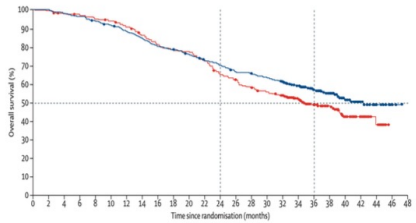
OS



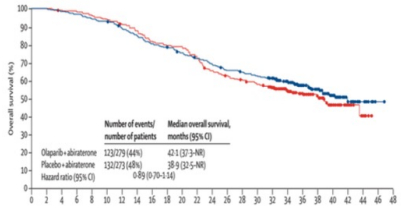
HR 0.29 (0.14-0.56)



HR 0.66 (0.45-0.95)



HR 0.8 (0.67-1.0)



HR 0.89 (0.7-1.14)

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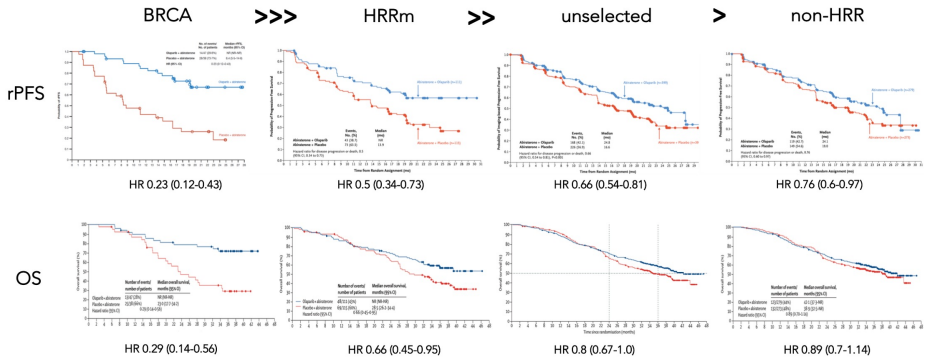
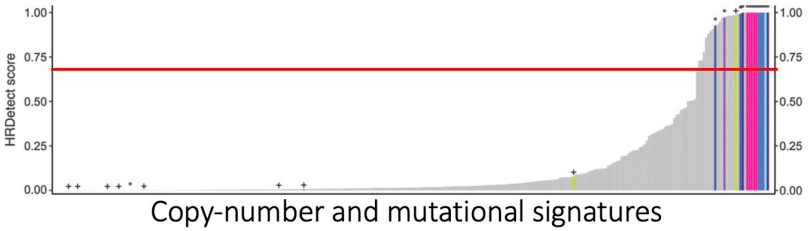
PROpel/TALAPRO-2 – a biomarker testing perspective

What happens if a fraction in the non-HRR are in fact HRD-p?





Combination of mutational signatures and genome instability score identifies 1.5x to 2x number of patients that would benefit from PARP.

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PROpel/TALAPRO-2 – a biomarker testing perspective

nature medicine

Article https://doi.org/10.1038/s41591-023-02704-x

First-line talazoparib with enzalutamide in HRR-deficient metastatic castration-resistant prostate cancer: the phase 3 TALAPRO-2 trial

- 399 patients with HRR alterations
- If a HRR/DRD driver is found: very low probability of unknown BRCA-variant
- Variable response is expected for non-BRCA HRR genes. Additional research needed …

Modified table for simplicity

Subgroup		Hazard ratio (95% CI)	Two-sided *P* value
All HRR-deficient	N=396	0.44 (0.32–0.60)	<0.0001
Only *BRCA1*	N=17	0.17 (0.02–1.51)	0.07
Only *BRCA2*	N=115	0.19 (0.10–0.38)	<0.0001
Only *PALB2*	N=11	0.56 (0.12–2.51)	0.44
Only *CDK12*	N=58	0.49 (0.23–1.02)	0.05
Only *ATM*	N=57	0.76 (0.30–1.94)	0.58
Only *CHEK2*	N=48	0.90 (0.34–2.39)	0.83
BRCA cluster	N=155	0.20 (0.11–0.36)	<0.0001
PALB2 cluster	N=15	0.46 (0.12–1.87)	0.27
CDK12 cluster	N=71	0.38 (0.19–0.76)	0.004
ATM cluster	N=72	0.90 (0.39–2.04)	0.80
Other gene cluster	N=82	1.51 (0.73–3.15)	0.26

Hierarchy

0.01 0.10 1.00 10.00

Favors talazoparib + enzalutamide Favors placebo + enzalutamide

PROpel/TALAPRO-2 – a biomarker testing perspective

- PROpel/TALAPRO-2 led to variable approvals in different countries
- This is just prostate cancer ..

The end