UNIVERSITÄT BERN

Bern Center FOR PRECISION MEDICINE

1994 25 2019 DEPARTMENT FOR BIOMEDICAL RESEARCH

Molecular pathology to advance prostate cancer precision medicine

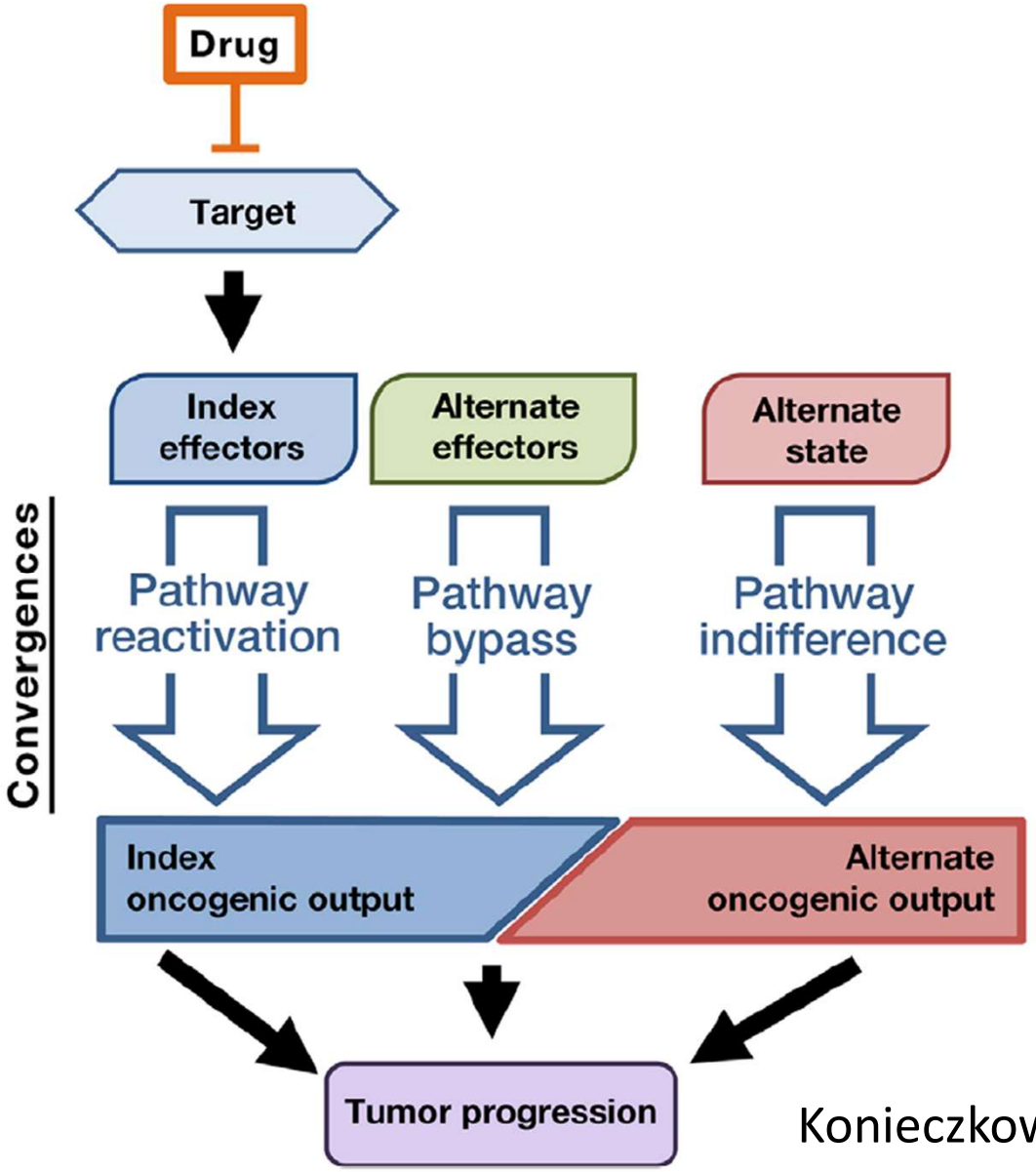
Mark A. Rubin | University of Bern, Switzerland
@ Rubinlab.unibe.ch *or* @MarkARubin1

Disclosures

FUNDING:
Janssen, Roche, Novartis

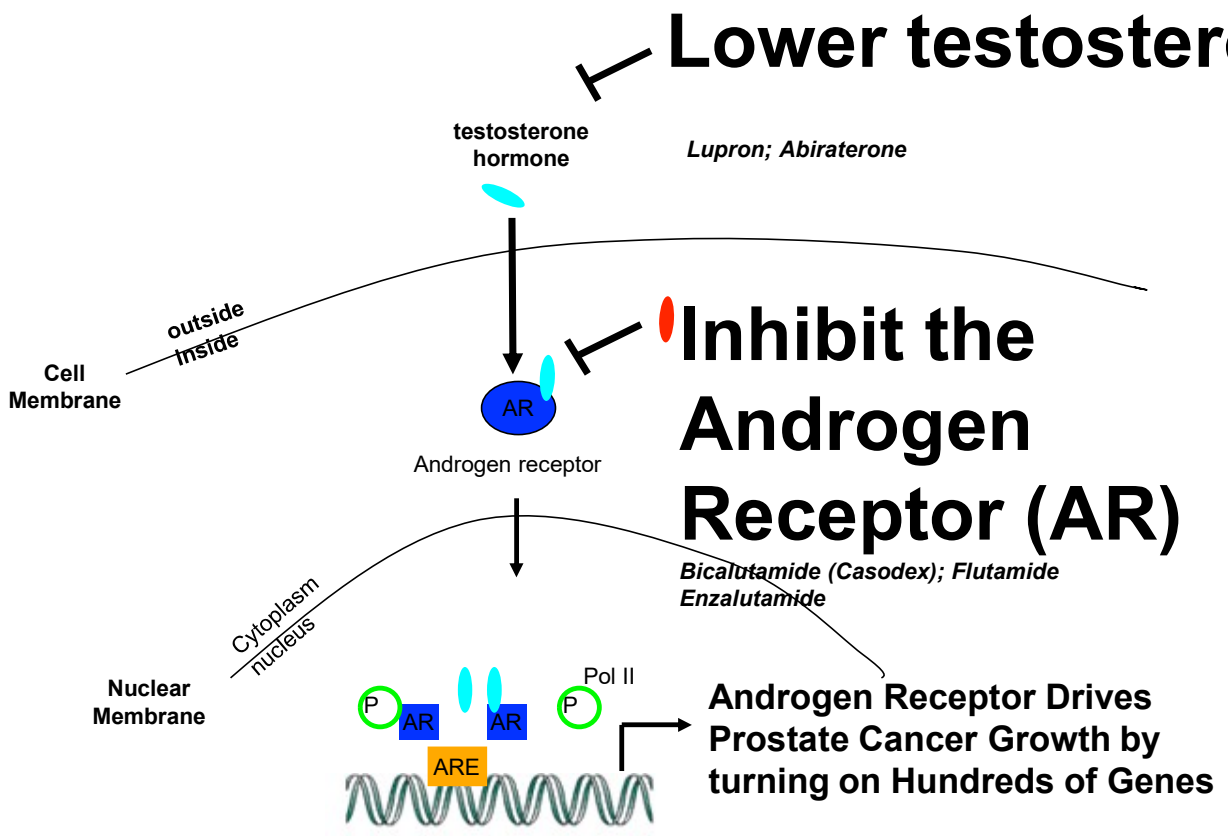
PATENTS:
Listed as co-inventor on patents in the diagnostic and treatment fields for ETS fusions (Harvard/Michigan),
EZh2 (Michigan), SPOP (Cornell) and AURKA / NMYC (Cornell), SWI/SNF

Scientific Board of Advisors:
NeoGenomics Labs

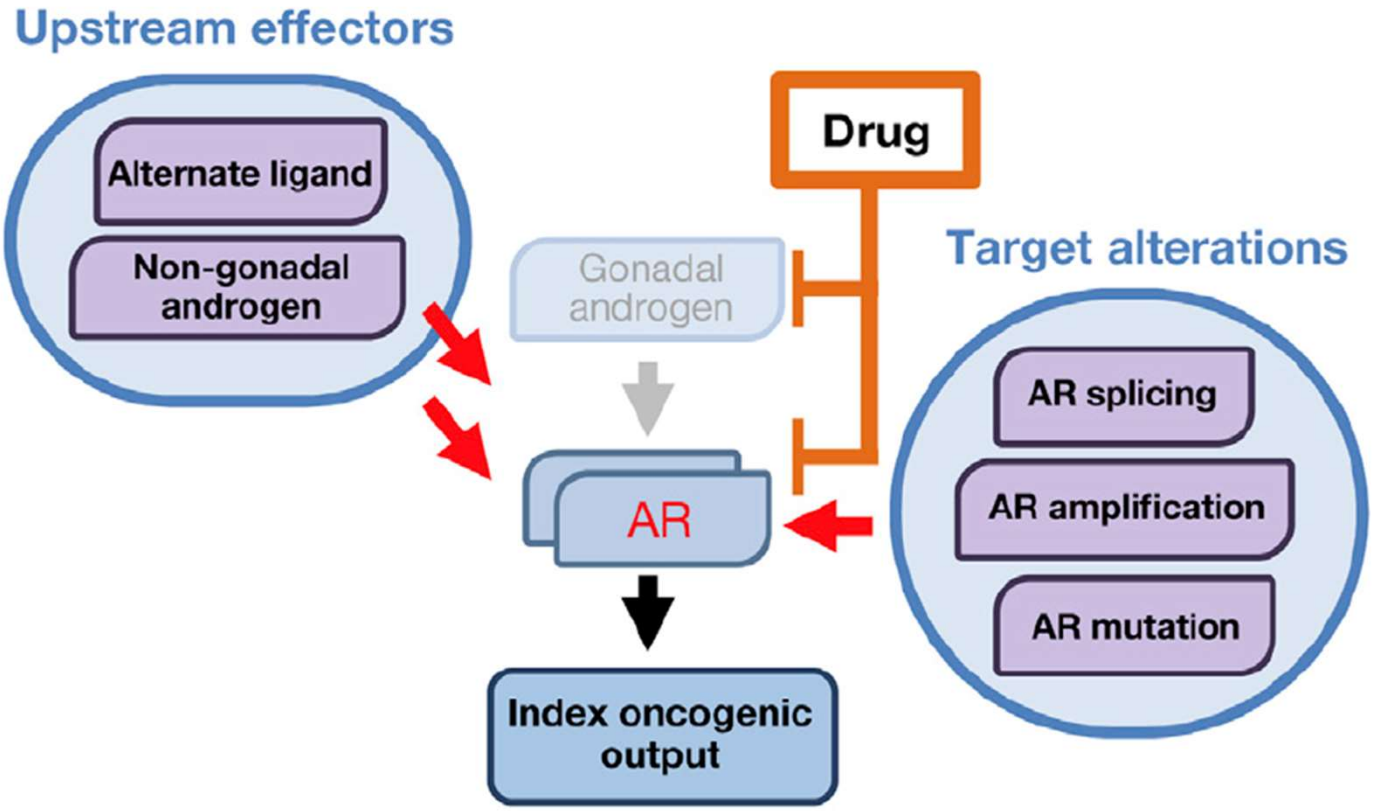


Konieczkowski et al, Cancer Cell 2018

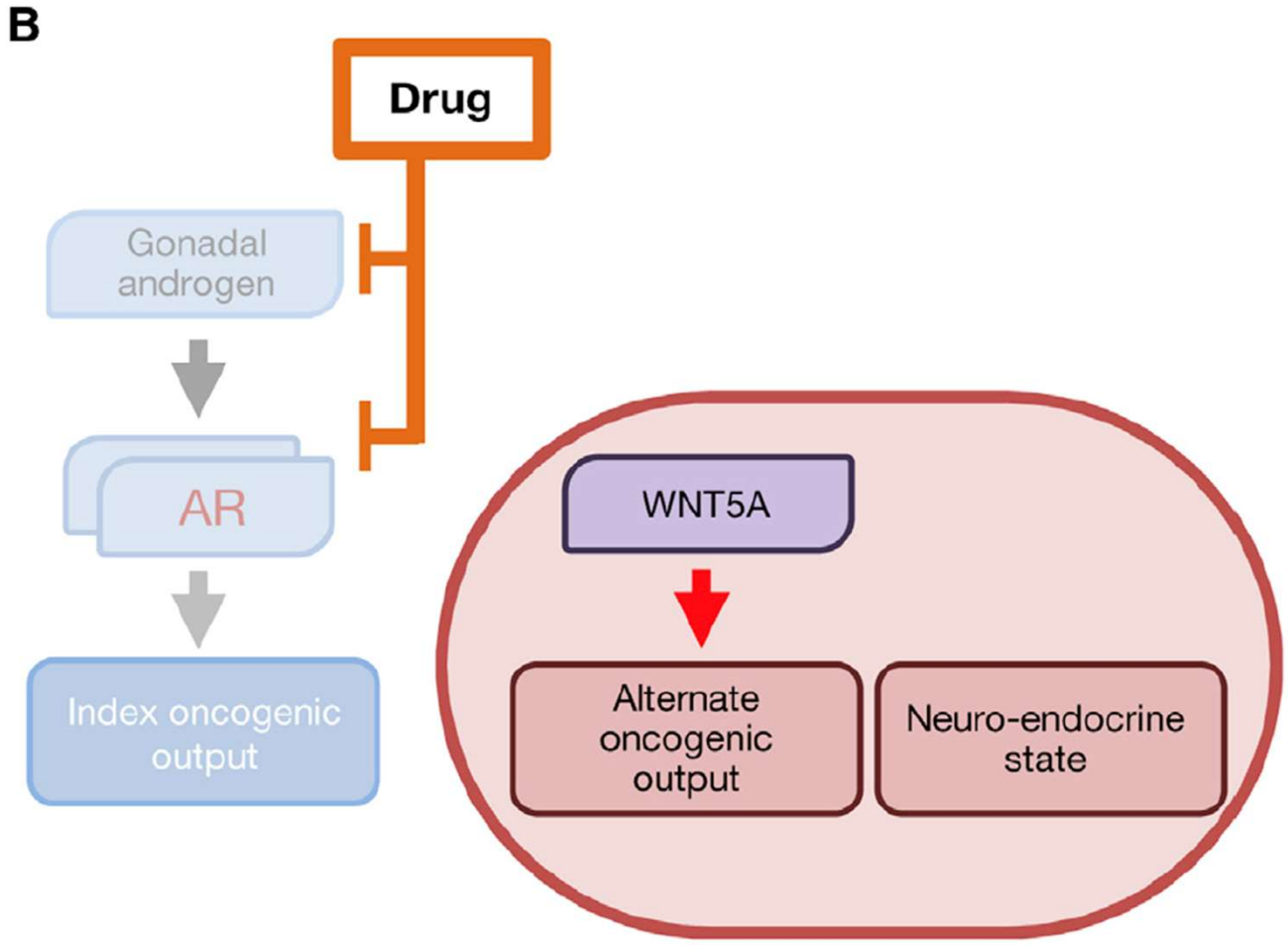
Androgen receptor signaling inhibitors (ARSi) major therapy



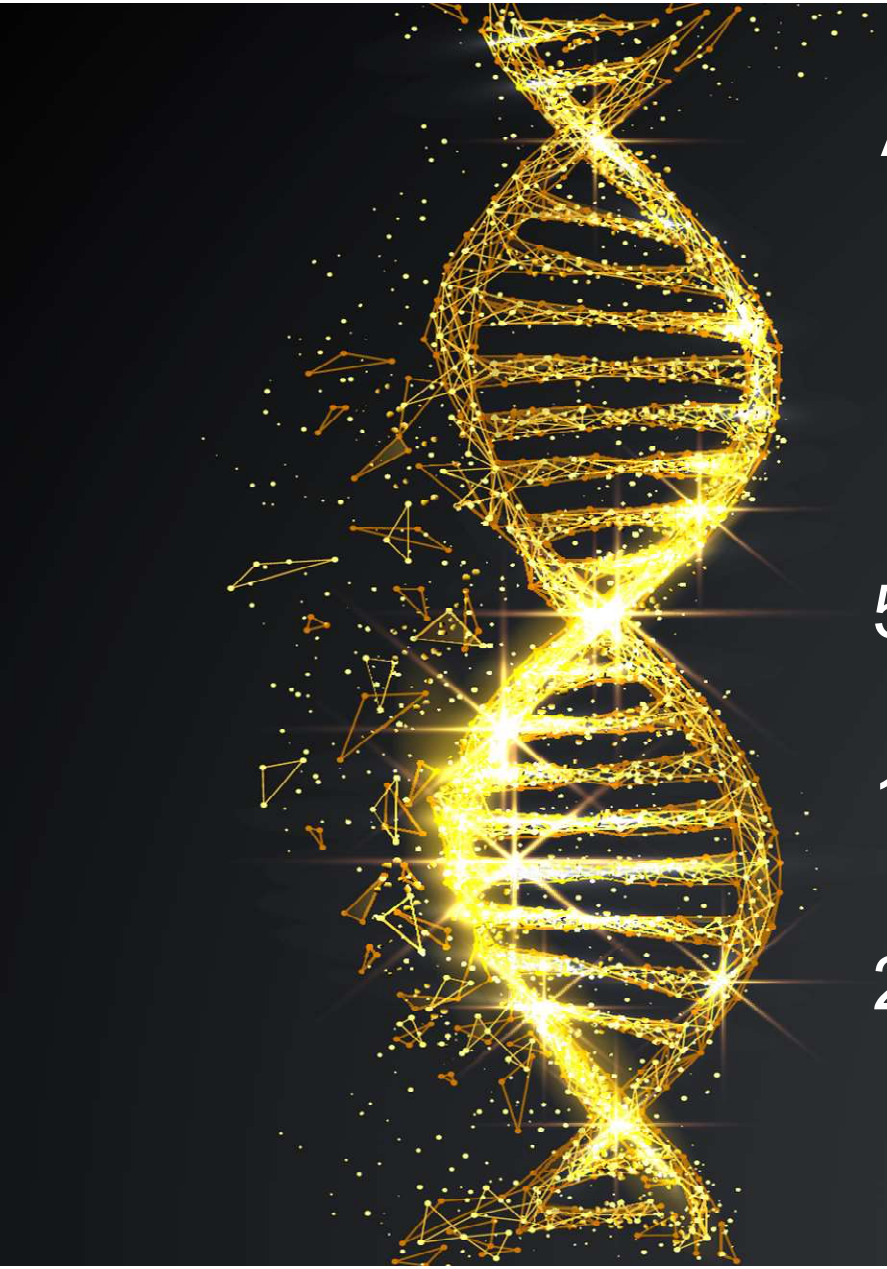
Modified from C. Sawyer



Konieczkowski et al, Cancer Cell 2018



Konieczkowski et al, Cancer Cell 2018



Advanced Prostate Cancer

5%, 10%, and 20%

5% have MSI or MMR alterations

Immunotherapy FDA

10% have germline DRM (e.g. BRCA)

PARPi or Platinum-based Tx/ Family implications

20% have DRM somatic-germline

PARPi or Platinum-based Tx

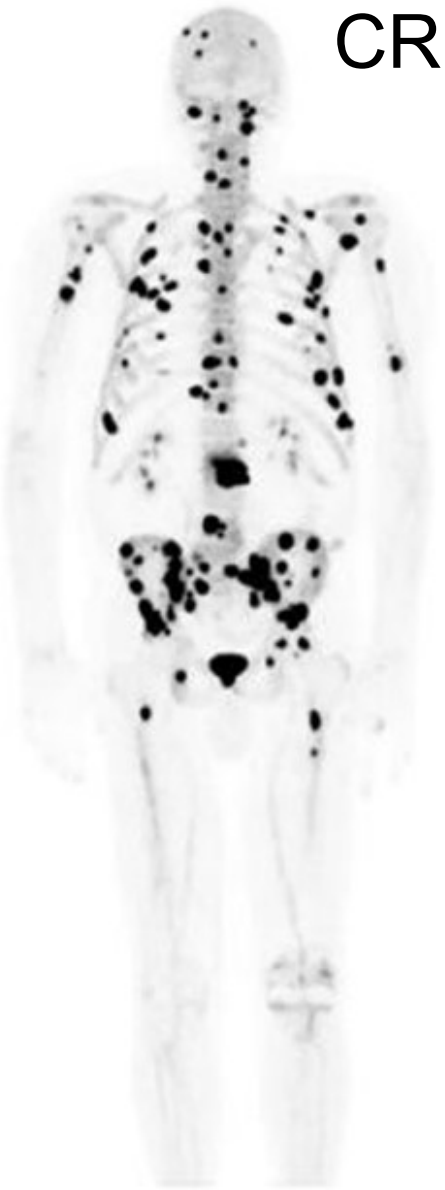
Definitions

A **prognostic biomarker** is one that indicates an increased (or decreased) likelihood of a future clinical event, disease recurrence or progression in an identified population. Prognostic biomarkers are measured at a defined baseline, which may include a background treatment

A **predictive biomarker** is used to identify individuals who are more likely to respond to exposure to a particular medical product or environmental agent. The response could be a symptomatic benefit, improved survival, or an adverse effect.

Given for lab tests (CLIA/CLEP):
Accuracy
Reproducibility
Sensitivity
Specificity

FDA-NIH **Biomarker** Working Group.
Silver Spring (MD): Food and Drug Administration (US);
Bethesda (MD): National Institutes of Health (US); 2016

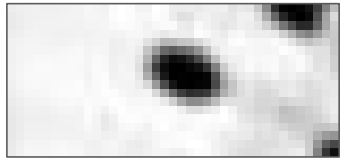


CRPC Patient and acquisition of samples for testing

Buccal sample

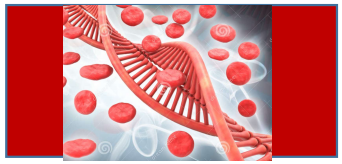
Germline DNA
Genetic testing (e.g., BRCA1/2)
Control normal sample for genomics

Tumor sample



Tumor DNA/RNA/Protein
For genomic sequencing, transcriptomic sequencing, etc.

Blood sample



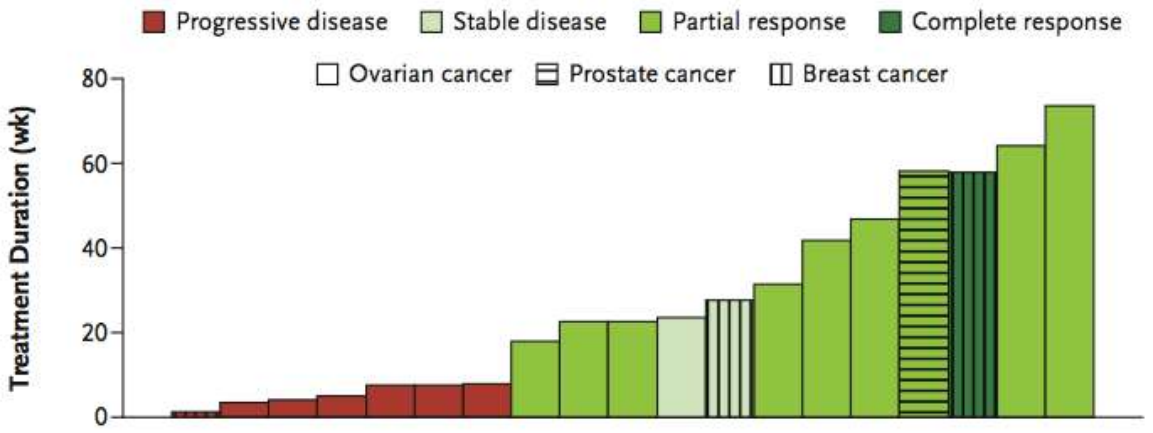
Tumor and normal DNA/RNA/Protein *fraction*
cfDNA, CTC, metabolites, etc.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 9, 2009 VOL. 361 NO. 2

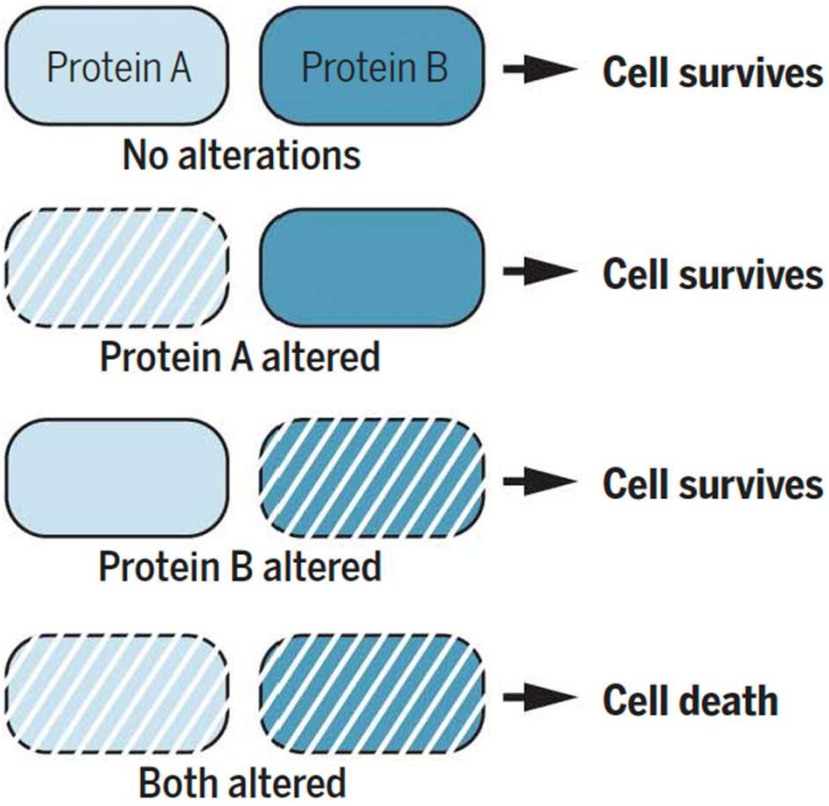
Inhibition of Poly(ADP-Ribose) Polymerase in Tumors from *BRCA* Mutation Carriers

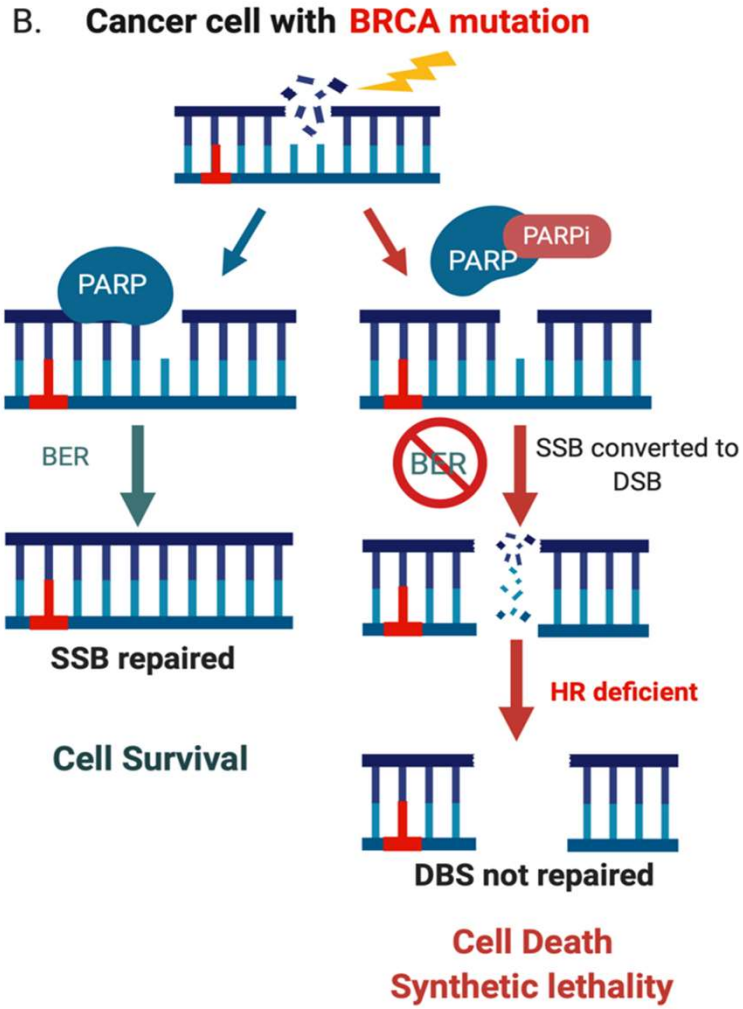
Peter C. Fong, M.D., David S. Boss, M.Sc., Timothy A. Yap, M.D., Andrew Tutt, M.D., Ph.D., Peijun Wu, Ph.D., Marja Mergui-Roelvink, M.D., Peter Mortimer, Ph.D., Helen Swaisland, B.Sc., Alan Lau, Ph.D., Mark J. O'Connor, Ph.D., Alan Ashworth, Ph.D., James Carmichael, M.D., Stan B. Kaye, M.D., Jan H.M. Schellens, M.D., Ph.D., and Johann S. de Bono, M.D., Ph.D.



19 BRCA mutated

Synthetic Lethality

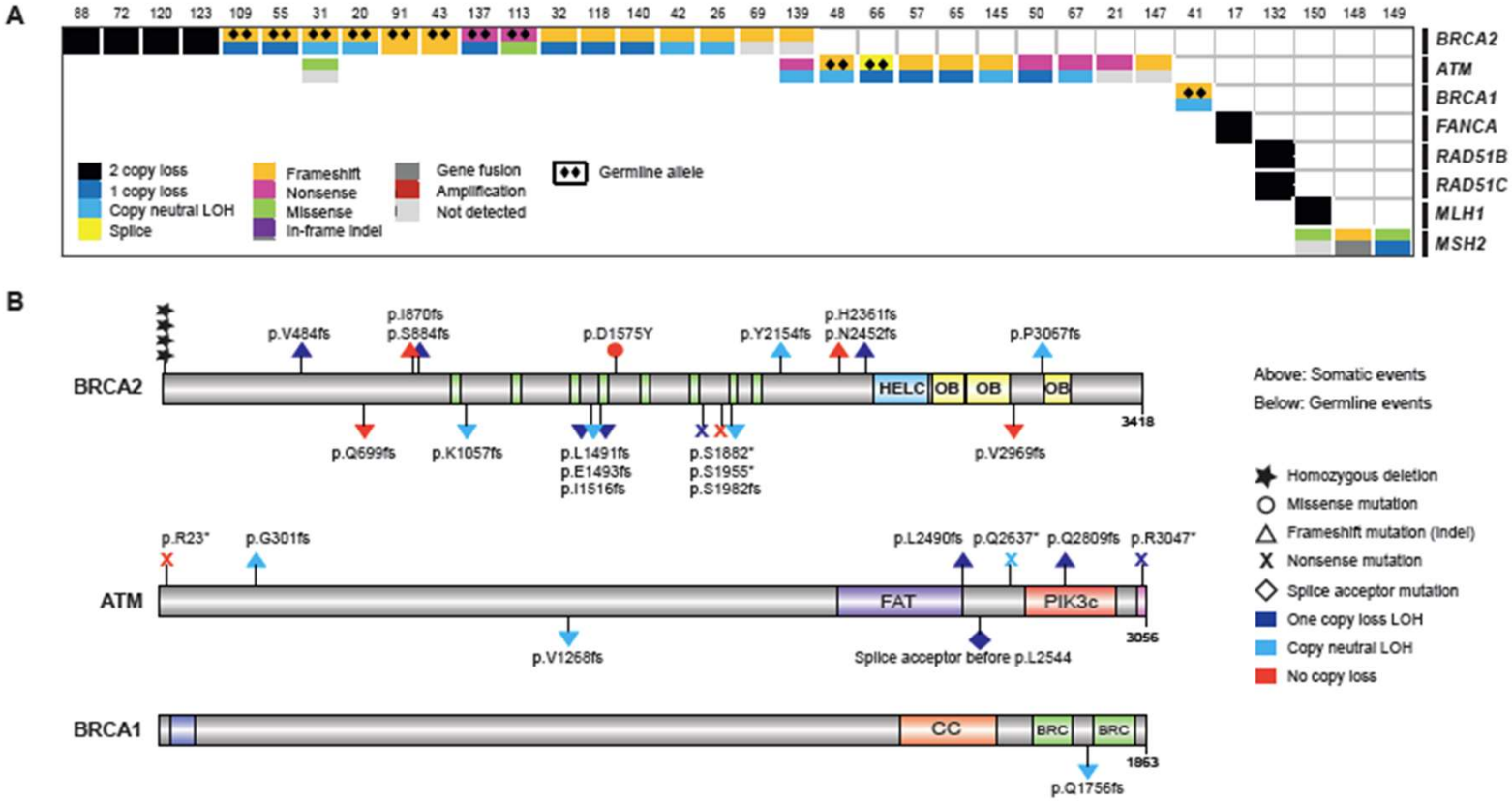




Lord and Ashworth, Science 355, 1152–1158 (2017)

Alexander von Werdt, unpublished

Significant alterations in DNA repair genes



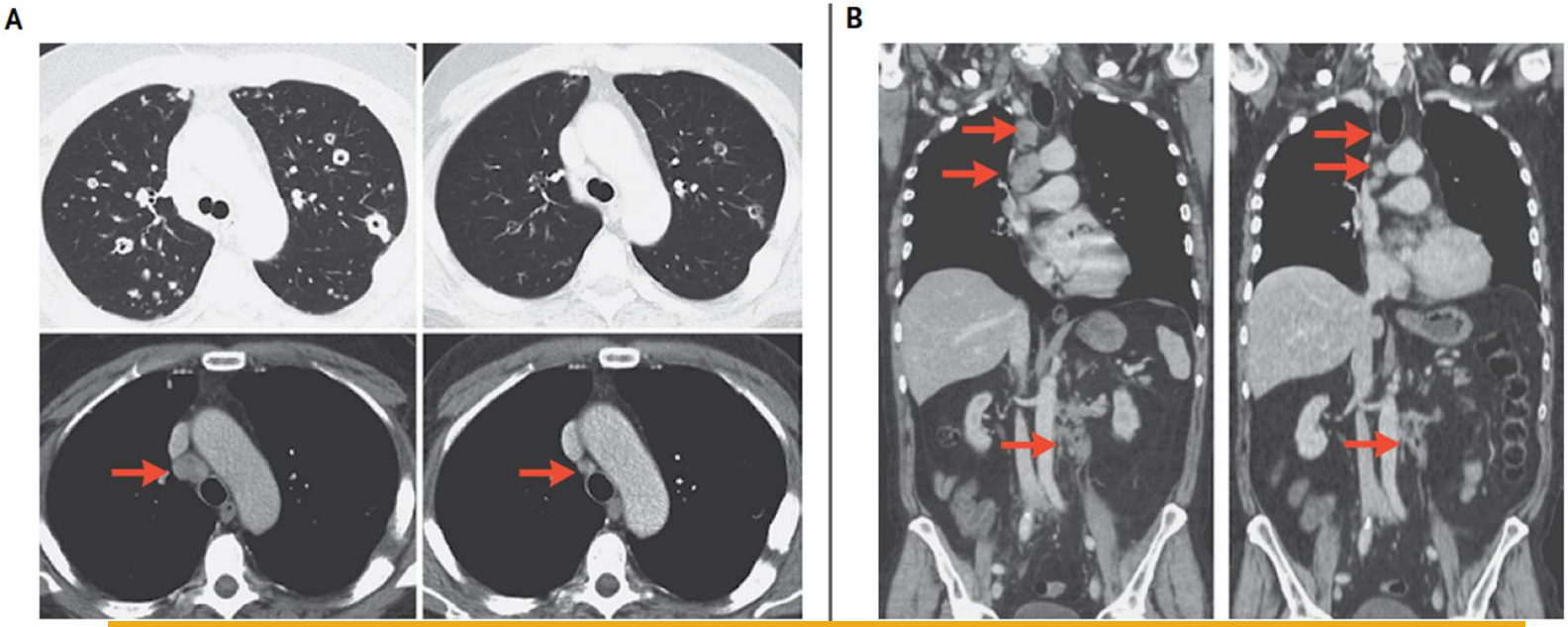
Robinson et al, Cell 2015

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 29, 2015 VOL. 373 NO. 18

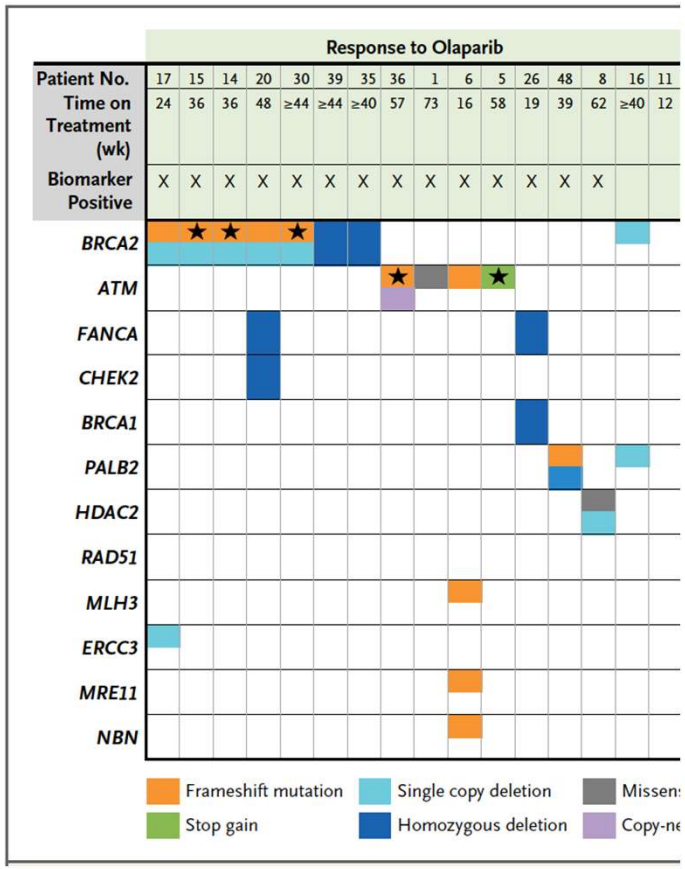
DNA-Repair Defects and Olaparib in Metastatic Prostate Cancer

J. Mateo, S. Carreira, S. Sandhu, S. Miranda, H. Mossop, R. Perez-Lopez, D. Nava Rodrigues, D. Robinson, A. Omlin, N. Tunariu, G. Boysen, N. Porta, P. Flohr, A. Gillman, I. Figueiredo, C. Paulding, G. Seed, S. Jain, C. Ralph, A. Protheroe, S. Hussain, R. Jones, T. Elliott, U. McGovern, D. Bianchini, J. Goodall, Z. Zafeiriou, C.T. Williamson, R. Ferraldeschi, R. Riisnaes, B. Ebbs, G. Fowler, D. Roda, W. Yuan, Y.-M. Wu, X. Cao, R. Brough, H. Pemberton, R. A'Hern, A. Swain, L.P. Kunju, R. Eeles, G. Attard, C.J. Lord, A. Ashworth, M.A. Rubin, K.E. Knudsen, F.Y. Feng, A.M. Chinnaiyan, E. Hall, and J.S. de Bono

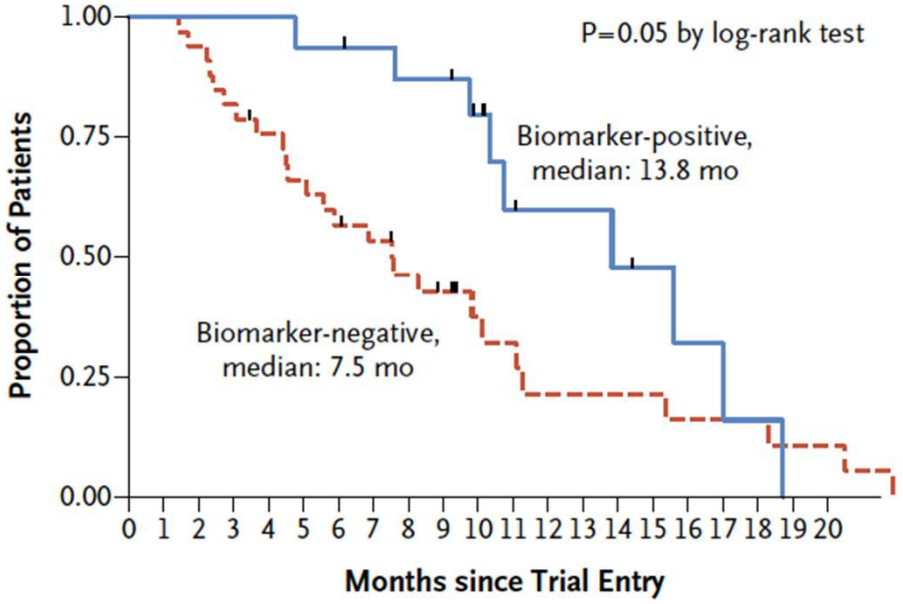


TOPARP Trial shows 30% Long Term Responders

NEJM, Oct 29 2015



B **Overall Survival**



No. at Risk

Biomarker-negative	33	33	31	27	24	21	18	16	13	11	7	6	4	4	4	4	3	3	3	2	2
Biomarker-positive	16	16	16	16	16	15	15	14	13	13	10	6	5	5	4	3	2	2	1	0	0

No. of Events

Biomarker-negative	0	2	4	2	3	3	1	2	1	1	1	2	0	0	0	1	0	0	1	0	–
Biomarker-positive	0	0	0	0	1	0	0	1	0	1	2	0	0	1	0	1	0	2	0	0	–

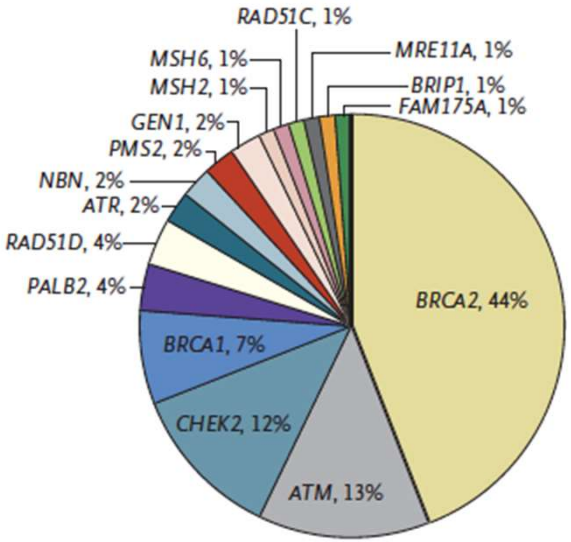
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Inherited DNA-Repair Gene Mutations in Men with Metastatic Prostate Cancer

Table 2. Germline Mutations in Metastatic Cases as Compared with the General Population and Primary Cases.

Gene	Metastatic Prostate Cancer (N=692)*	Exome Aggregation Consortium (N=53,105)†	TCGA Cohort with Primary Prostate Cancer (N=499)	Metastatic Prostate Cancer vs. Exome Aggregation Consortium		Metastatic Prostate Cancer vs. TCGA Cohort	
	No. of Mutations (% of Men)			Relative Risk (95% CI)	P Value	Relative Risk (95% CI)	P Value
ATM	11 (1.59)	133 (0.25)	5 (1.00)	6.3 (3.2–11.3)	<0.001	1.6 (0.8–2.8)	0.12
ATR	2 (0.29)	43 (0.08)	0	3.6 (0.4–12.8)	0.11	—	—
BAP1‡	0	1	0	—	—	—	—
BARD1‡	0	38 (0.07)	1 (0.20)	—	—	—	—
BRCA1	6 (0.87)	104 (0.22)	3 (0.60)	3.9 (1.4–8.5)	0.005	1.4 (0.5–3.1)	0.32
BRCA2	37 (5.35)	153 (0.29)	1 (0.20)	18.6 (13.2–25.3)	<0.001	26.7 (18.9–36.4)	<0.001
BRIP1‡	1 (0.18)	100 (0.19)	1 (0.20)	0.9 (0.02–5.3)	1.0	0.9 (0.0–4.9)	1.0
CHEK2‡	10 (1.87)	314 (0.61)	2 (0.40)	3.1 (1.5–5.6)	0.002	4.7 (2.2–8.5)	<0.001
FAM175A‡	1 (0.18)	52 (0.10)	0	1.8 (0.05–10.1)	0.42	—	—
GEN1‡	2 (0.46)	42 (0.08)	0	5.8 (0.7–20.8)	0.048	—	—
MLH1	0	11 (0.02)	0	—	—	—	—
MRE11A	1 (0.14)	36 (0.07)	1 (0.20)	2.1 (0.1–11.8)	0.38	0.7 (0.0–4.0)	1.0
MSH2	1 (0.14)	23 (0.04)	1 (0.20)	3.3 (0.1–18.5)	0.26	0.7 (0.0–4.0)	1.0
MSH6	1 (0.14)	41 (0.08)	1 (0.20)	1.9 (0.05–10.4)	0.41	0.7 (0.0–4.0)	1.0
NBN	2 (0.29)	61 (0.11)	1 (0.20)	2.5 (0.3–9.1)	0.19	1.4 (0.2–5.2)	0.40
PALB2	3 (0.43)	65 (0.12)	2 (0.40)	3.5 (0.7–10.3)	0.05	1.1 (0.2–3.1)	0.76
PMS2	2 (0.29)	56 (0.11)	1 (0.20)	2.7 (0.3–9.8)	0.17	1.4 (0.2–5.2)	0.40
RAD51C	1 (0.14)	59 (0.11)	2 (0.40)	1.3 (0.03–7.2)	0.54	0.4 (0.0–2.0)	0.54
RAD51D	3 (0.43)	40 (0.08)	1 (0.20)	5.7 (1.2–16.7)	0.02	2.2 (0.4–6.3)	0.16
XRCC2	0	23 (0.04)	0	—	—	—	—



Selected *DNA repair germline mutations from targeted panel and WES reveal 10-20% frequency* (Pritchard and Nelson, 2016)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Survival with Olaparib in Metastatic Castration-Resistant Prostate Cancer

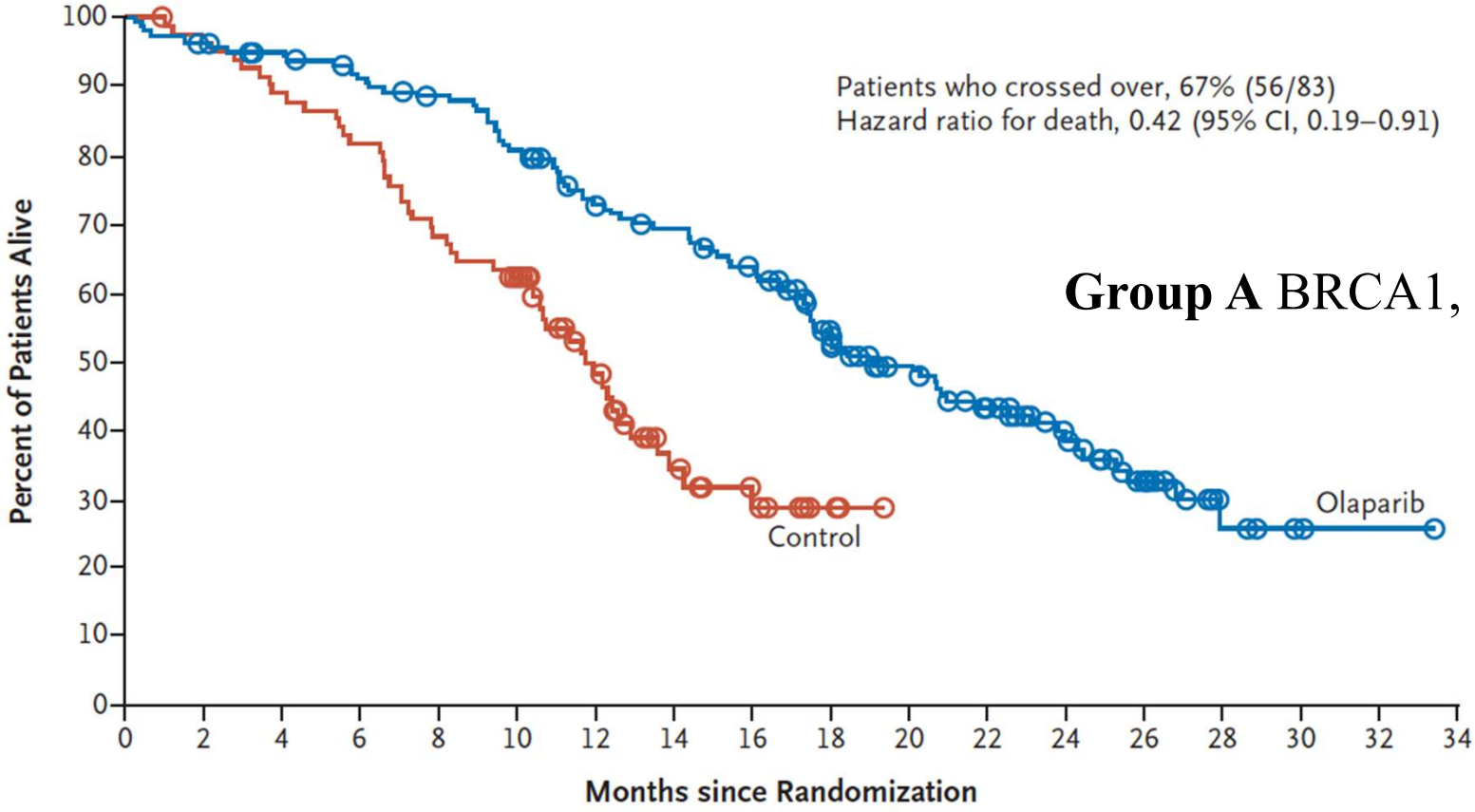
M. Hussain, J. Mateo, K. Fizazi, F. Saad, N. Shore, S. Sandhu, K.N. Chi, O. Sartor, N. Agarwal, D. Olmos, A. Thiery-Vuillemin, P. Twardowski, G. Roubaud, M. Özgüroğlu, J. Kang, J. Burgents, C. Gresty, C. Corcoran, C.A. Adelman, and J. de Bono, for the PROfound Trial Investigators*

Group A BRCA1, BRCA2, ATM

Group B: BRIP1, BARD1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D, and RAD54L

NEJM 2020

B Crossover-Adjusted Analysis of Overall Survival in Cohort A

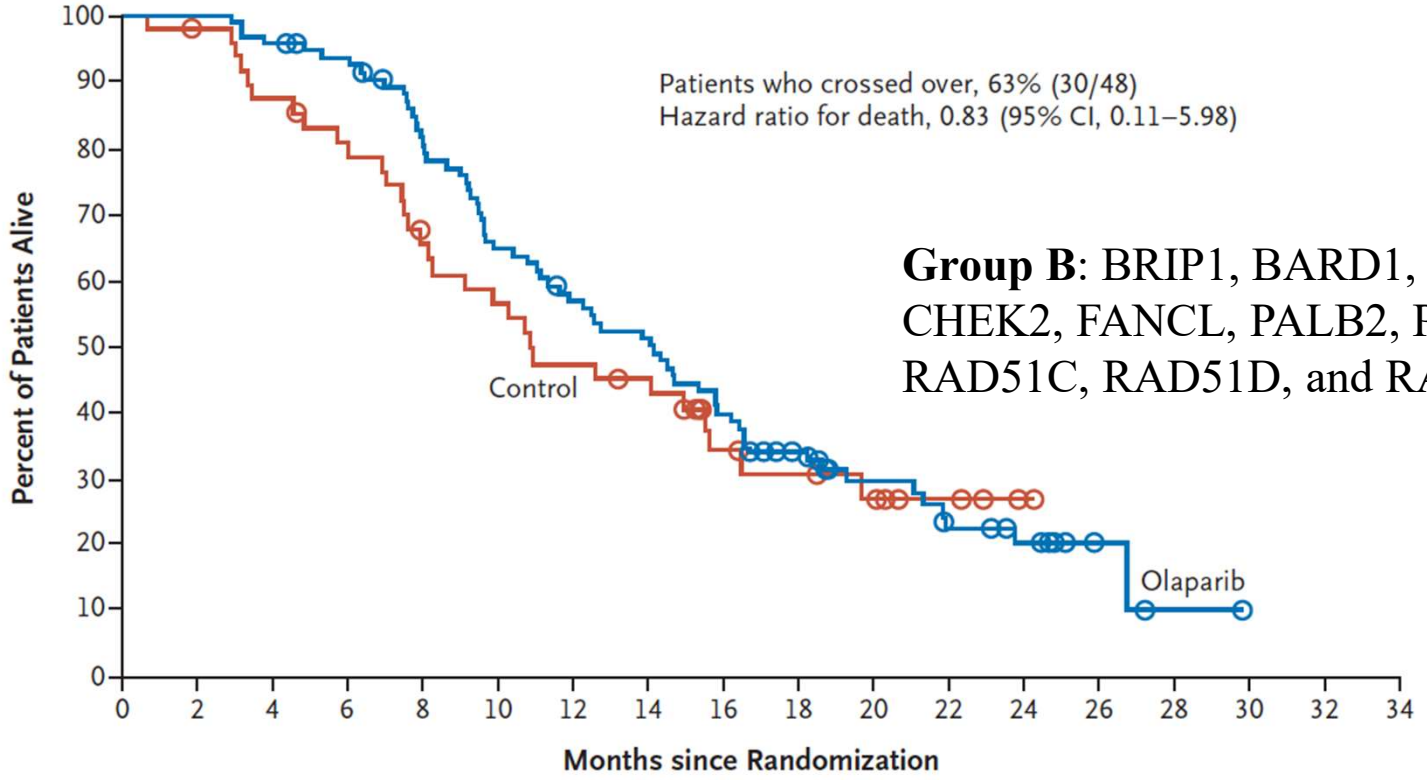


Group A BRCA1, BRCA2, ATM

No. at risk																		
Olaparib	162	155	150	142	136	124	107	101	91	71	56	44	30	18	6	2	1	0
Control	83	79	73	67	56	47	29	15	9	3	0	0	0	0	0	0	0	0

NEJM 2020

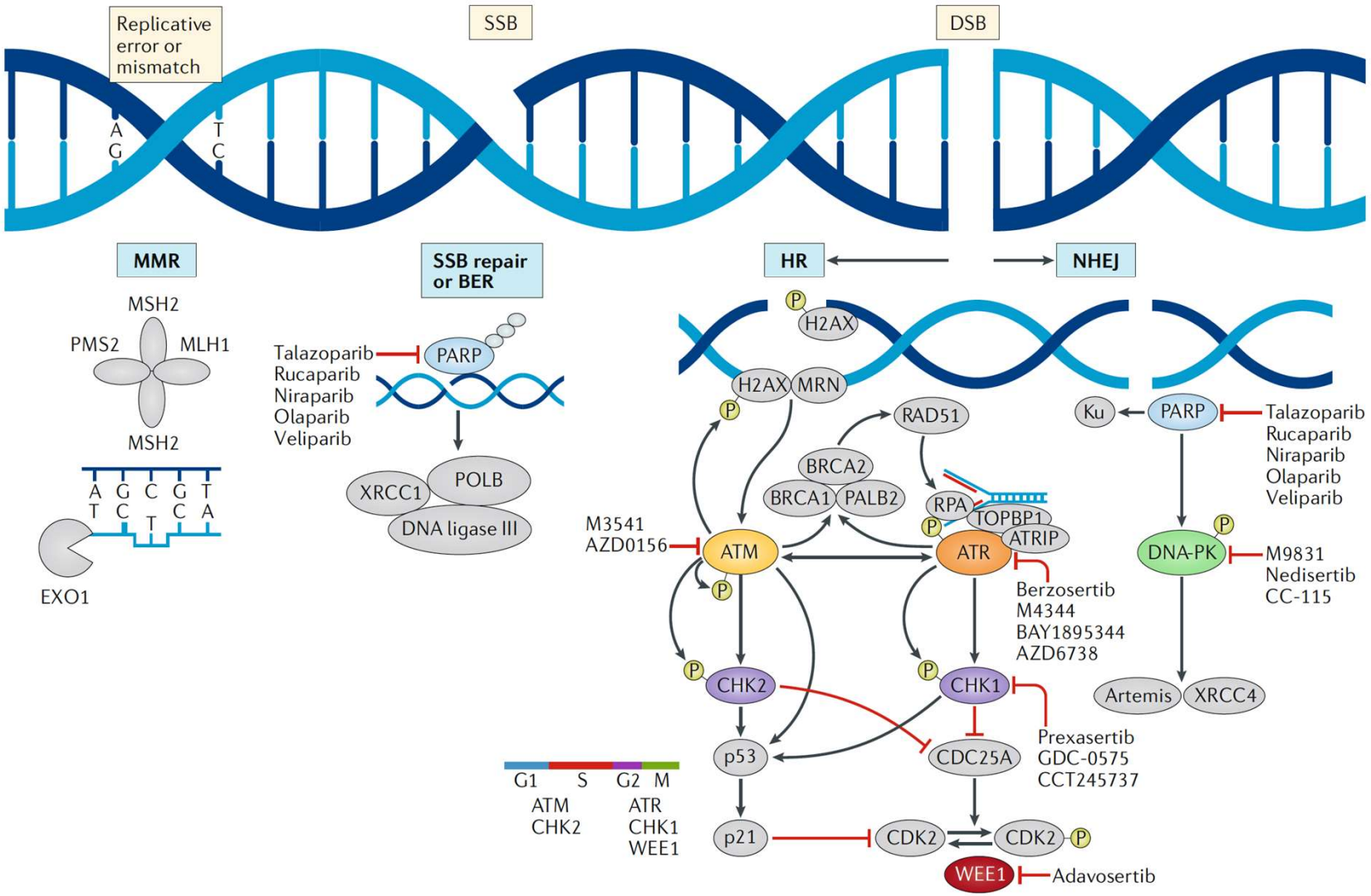
B Crossover-Adjusted Analysis of Overall Survival in Cohort B



Group B: BRIP1, BARD1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D, and RAD54L

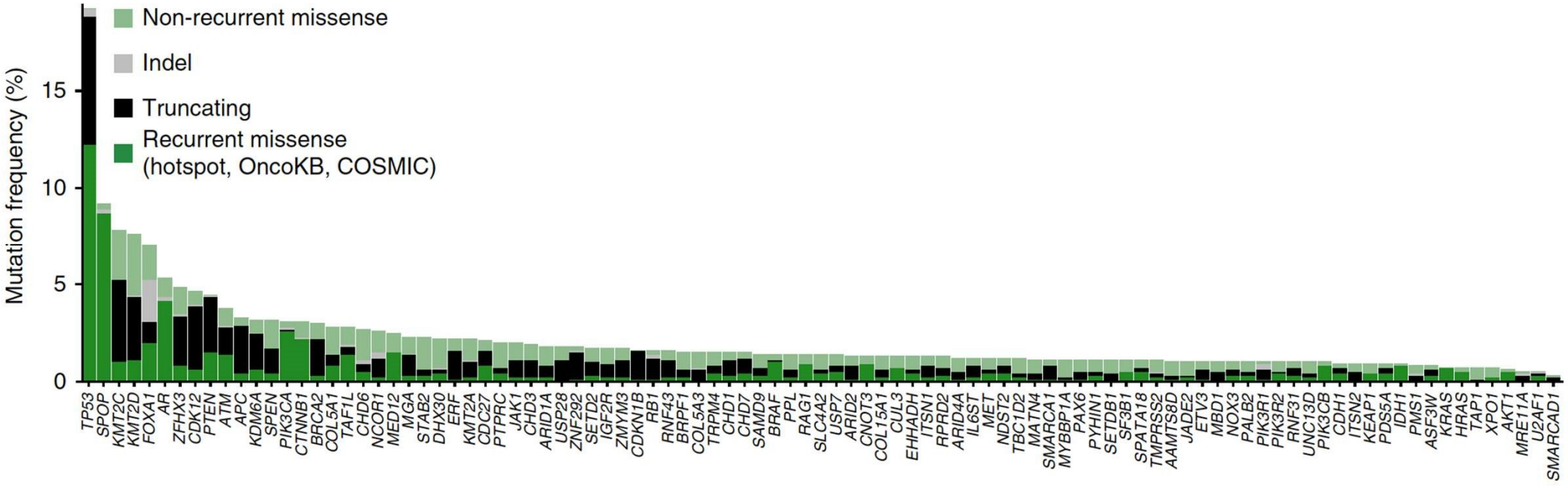
No. at risk																	
Olaparib	94	94	90	86	73	58	50	45	35	25	17	12	9	4	1	0	0	0
Control	48	46	41	37	29	25	21	19	11	9	7	4	1	0	0	0	0	0

NEJM 2020

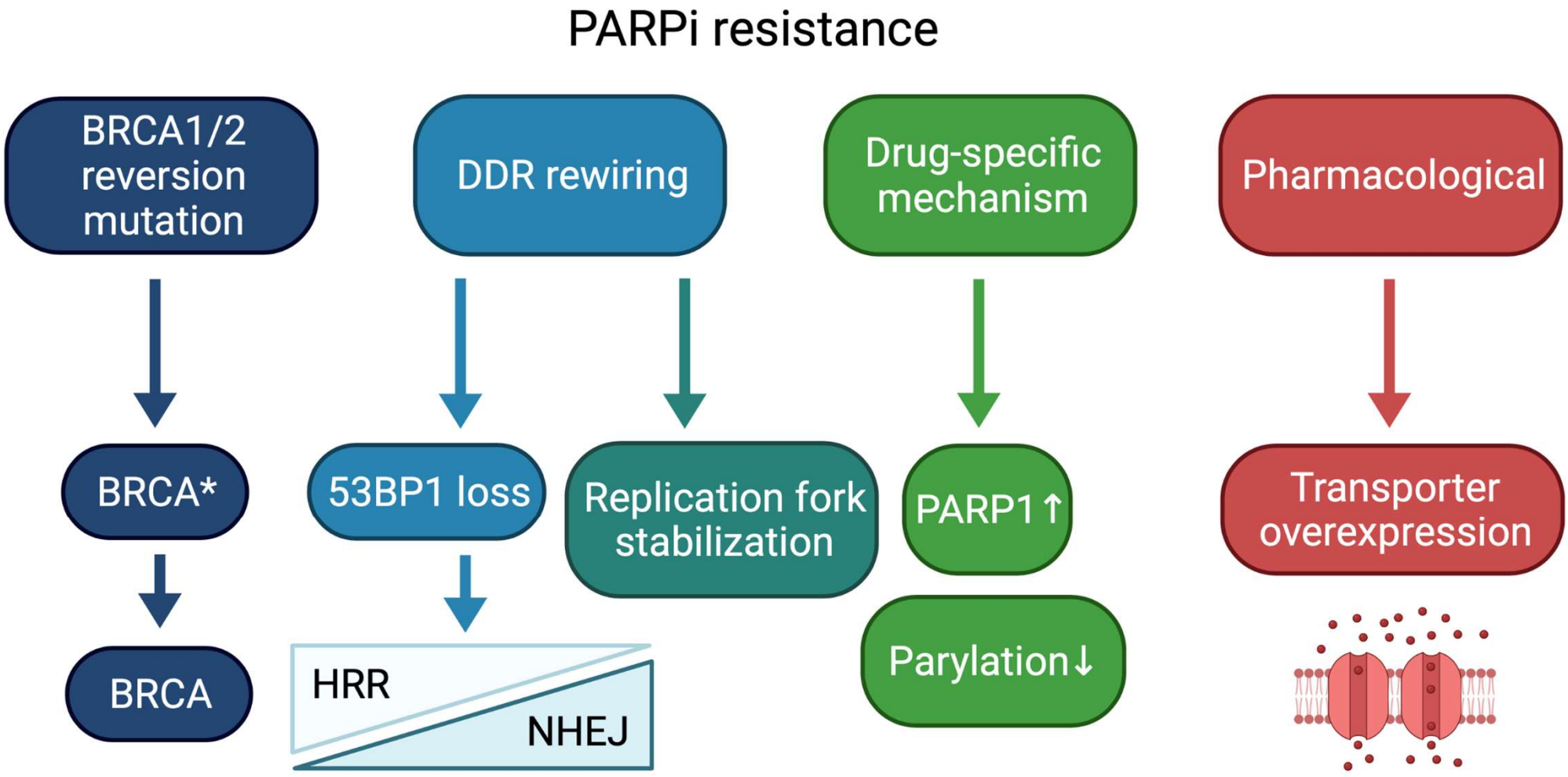


Pilié et al., Nature Reviews | Clinical Oncology 2019

long tail of prostate cancer mutations



Armenia et al, ***Nature Genetics***, 2018

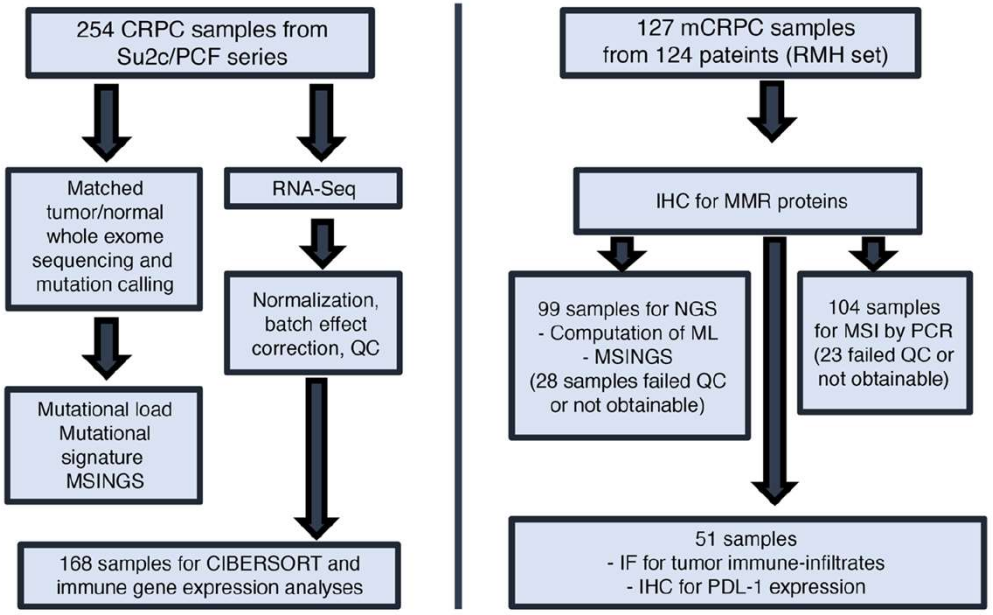


von Werdt et al, in revision

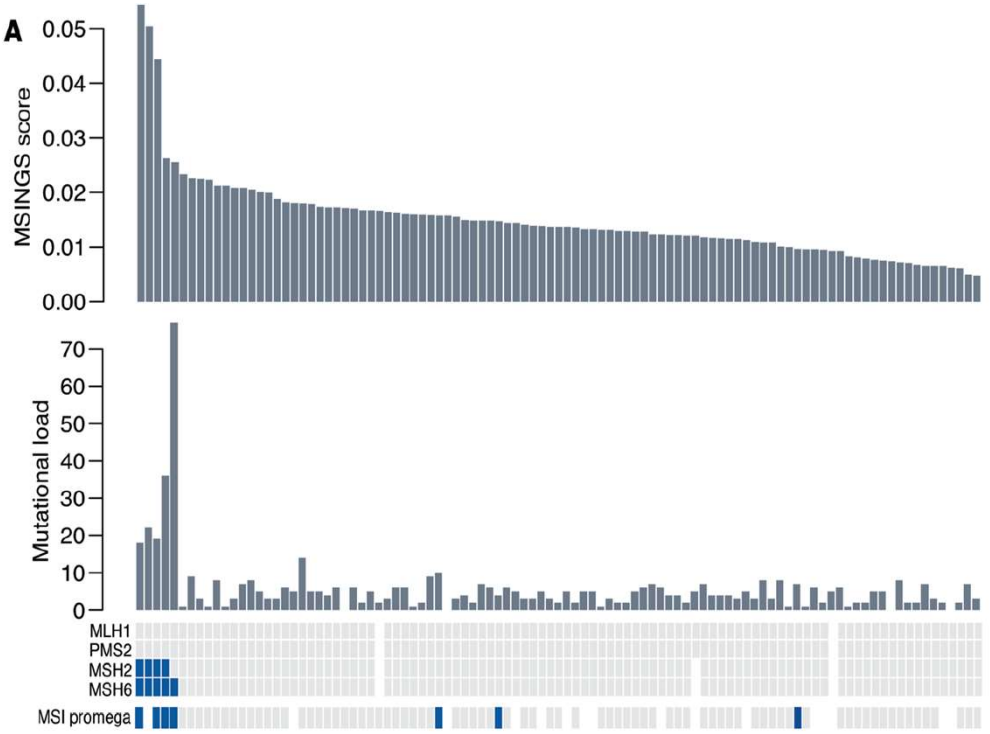
The Journal of Clinical Investigation CLINICAL MEDICINE

Immunogenomic analyses associate immunological alterations with mismatch repair defects in prostate cancer

Daniel Nava Rodrigues,[1,2] Pasquale Rescigno,[1,2,3] David Liu,[4,5] Wei Yuan,[1] Suzanne Carreira,[1] Maryou B. Lambros,[1] George Seed,[1] Joaquin Mateo,[1,2] Ruth Riisnaes,[1] Stephanie Mullane,[4,5] Claire Margolis,[4,5] Diana Miao,[4,5] Susana Miranda,[1] David Dolling,[1] Matthew Clarke,[1] Claudia Bertan,[1] Mateus Crespo,[1] Gunther Boysen,[1] Ana Ferreira,[1] Adam Sharp,[1] Ines Figueiredo,[1] Daniel Keliher,[4,5] Saud Aldubayan,[4,5] Kelly P. Burke,[4] Semini Sumanasuriya,[1] Mariane Sousa Fontes,[1,2] Diletta Bianchini,[1,2] Zafeiris Zafeiriou,[1,2] Larissa Sena Teixeira Mendes,[2] Kent Mouw,[4] Michael T. Schweizer,[6,7] Colin C. Pritchard,[6] Stephen Salipante,[6] Mary-Ellen Taplin,[3] Himisha Beltran,[8] Mark A. Rubin,[8] Marcin Cieslik,[9] Dan Robinson,[9] Elizabeth Heath,[10] Nikolaus Schultz,[11] Joshua Armenia,[11] Wassim Abida,[11] Howard Scher,[11] Christopher Lord,[1] Alan D'Andrea,[4] Charles L. Sawyers,[11] Arul M. Chinnaiyan,[9] Andrea Alimonti,[12] Peter S. Nelson,[6,7] Charles G. Drake,[13] Eliezer M. Van Allen,[4,5] and Johann S. de Bono[1,2]



Testing with a targeted NGS panel and WES of Tumor and Normal
Overall, 8.1% had evidence of MMR



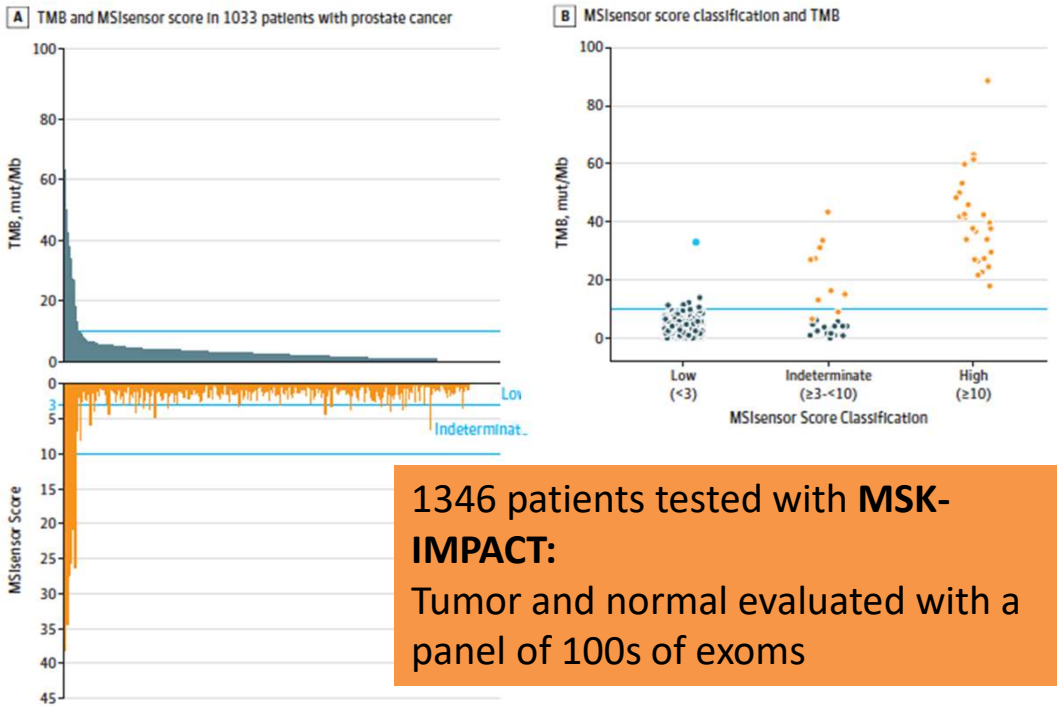
JCI Volume 128 Number 10 October 2018

JAMA Oncology | Original Investigation

Analysis of the Prevalence of Microsatellite Instability in Prostate Cancer and Response to Immune Checkpoint Blockade

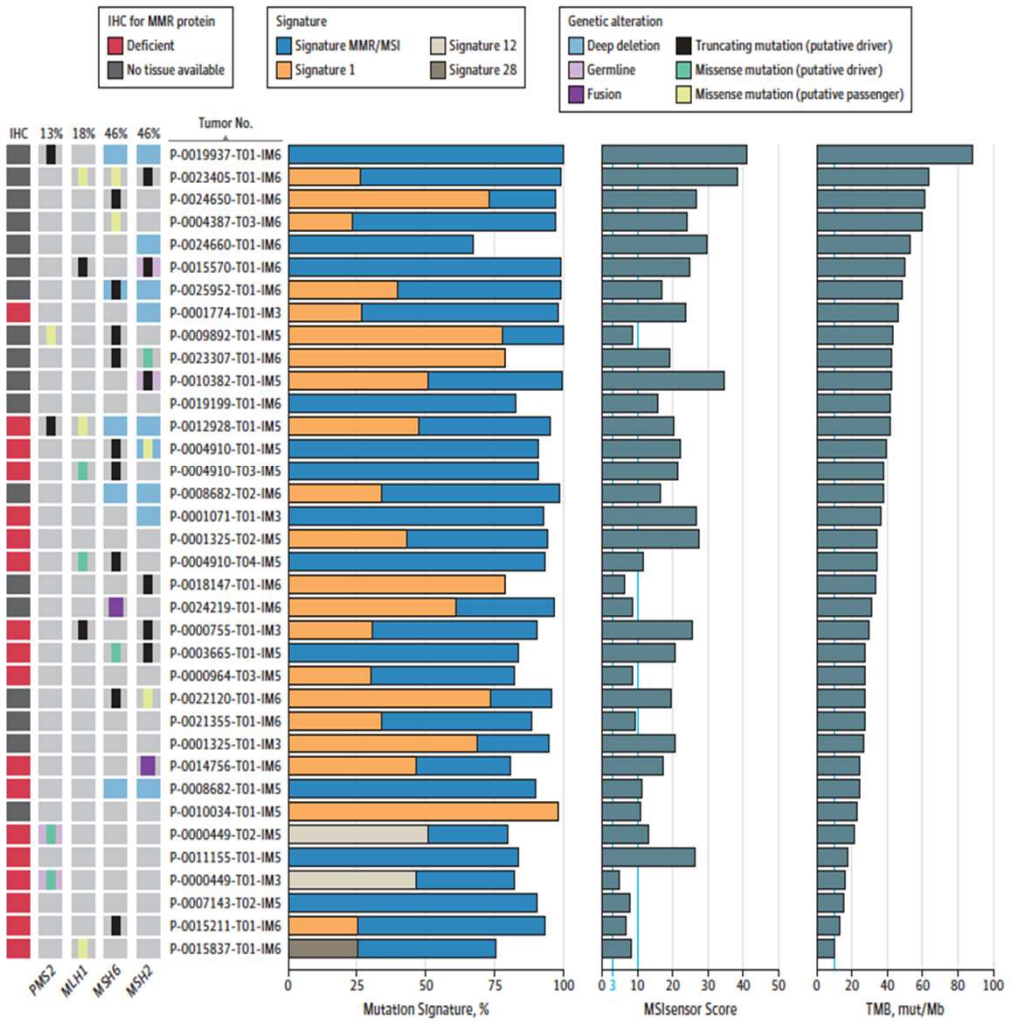
Wassim Abida, MD, PhD; Michael L. Cheng, MD; Joshua Armenia, PhD; Sumit Middha, PhD; Karen A. Autio, MD; Hebert Alberto Vargas, MD; Dana Rathkopf, MD; Michael J. Morris, MD; Daniel C. Danila, MD; Susan F. Slovin, MD, PhD; Emily Carbone, BA; Ethan S. Barnett, MS; Melanie Hullings, BA; Jaclyn F. Hechtman, MD; Ahmet Zehir, PhD; Jinru Shia, MD; Philip Jonsson, PhD; Zsofia K. Stadler, MD; Preethi Srinivasan, BA; Vincent P. Laudone, MD; Victor Reuter, MD; Jedd D. Wolchok, MD, PhD; Nicholas D. Socci, PhD; Barry S. Taylor, PhD; Michael F. Berger, PhD; Philip W. Kantoff, MD; Charles L. Sawyers, MD; Nikolaus Schultz, PhD; David B. Solit, MD; Anuradha Gopalan, MD; Howard I. Scher, MD

Figure 1. Tumor Mutation Burden (TMB) and Microsatellite Instability (MSI) in Prostate Cancer



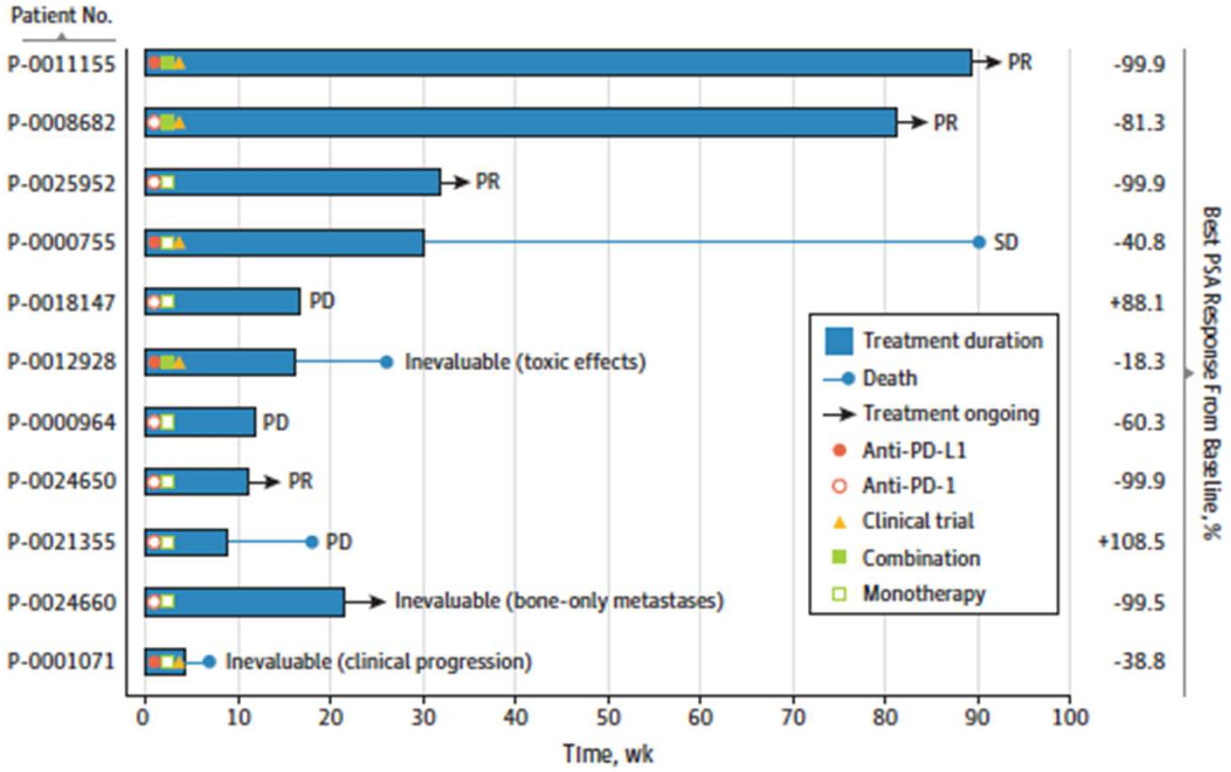
1346 patients tested with **MSK-IMPACT:**
Tumor and normal evaluated with a panel of 100s of exoms

Figure 2. Integrative Analysis of Microsatellite Instability (MSI), Tumor Mutation Burden (TMB), Mutational Signature Decomposition, and Mismatch Repair (MMR) Gene and Protein Status



JAMA Oncology Published online December 27, 2018

Figure 4. Responses to Immune Checkpoint Blockade in Microsatellite Instability–High and Mismatch Repair Deficient (MSI-H/dMMR) Prostate Cancer



JAMA Oncology Published online December 27, 2018

color Health Systems Employers Individuals Providers Giving Back Help Activate Kit Sign In

A new model for data-driven healthcare

Color helps create an end-to-end delivery model that links precision data to risk, risk to decisions, and decisions to behavior change across populations.

- Quickly engage your population through clinical-grade genetics and digital tools.
- Efficiently collect rich phenotypic and genotypic (whole genome) information across your population and their families while protecting individual privacy.
- Translate precision clinical data into an understanding of risk for individuals, providers, and systems to help inform appropriate health interventions
- Drive behavior changes such as adherence, compliance, and lifestyle choices to impact outcomes.

Color Extended: The most relevant genes for common hereditary cancers

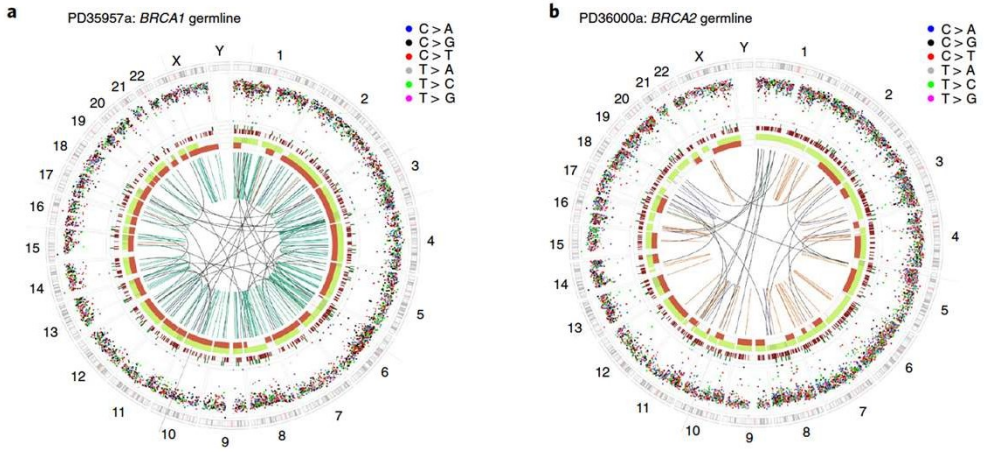
Gene	Breast	Ovarian	Uterine	Colorectal	Melanoma	Pancreatic	Stomach	Prostate*
BRCA1	●	●				●		●
BRCA2	●	●			●	●		●
MLH1		●	●	●		●	●	●
MSH2		●	●	●		●	●	●
MSH6		●	●	●			●	●
PMS2***		●	●	●				●
EPCAM**		●	●	●		●	●	●
APC				●		●	●	
MUTYH				●				
MITF**					●			
BAP1					●			
CDKN2A					●	●		
CDK4**					●			
TP53	●	●	●	●	●	●	●	●
PTEN	●		●	●	●			
STK11	●	●	●	●		●	●	
CDH1	●						●	
BMPR1A				●		●	●	
SMAD4				●		●	●	
GREM1**				●				
POLD1**				●				
POLE**				●				
PALB2	●	●				●		
CHEK2	●			●				●
ATM	●					●		●
NBN	●							●
BARD1	●							
BRIP1	●	●						
RAD51C		●						
RAD51D		●						

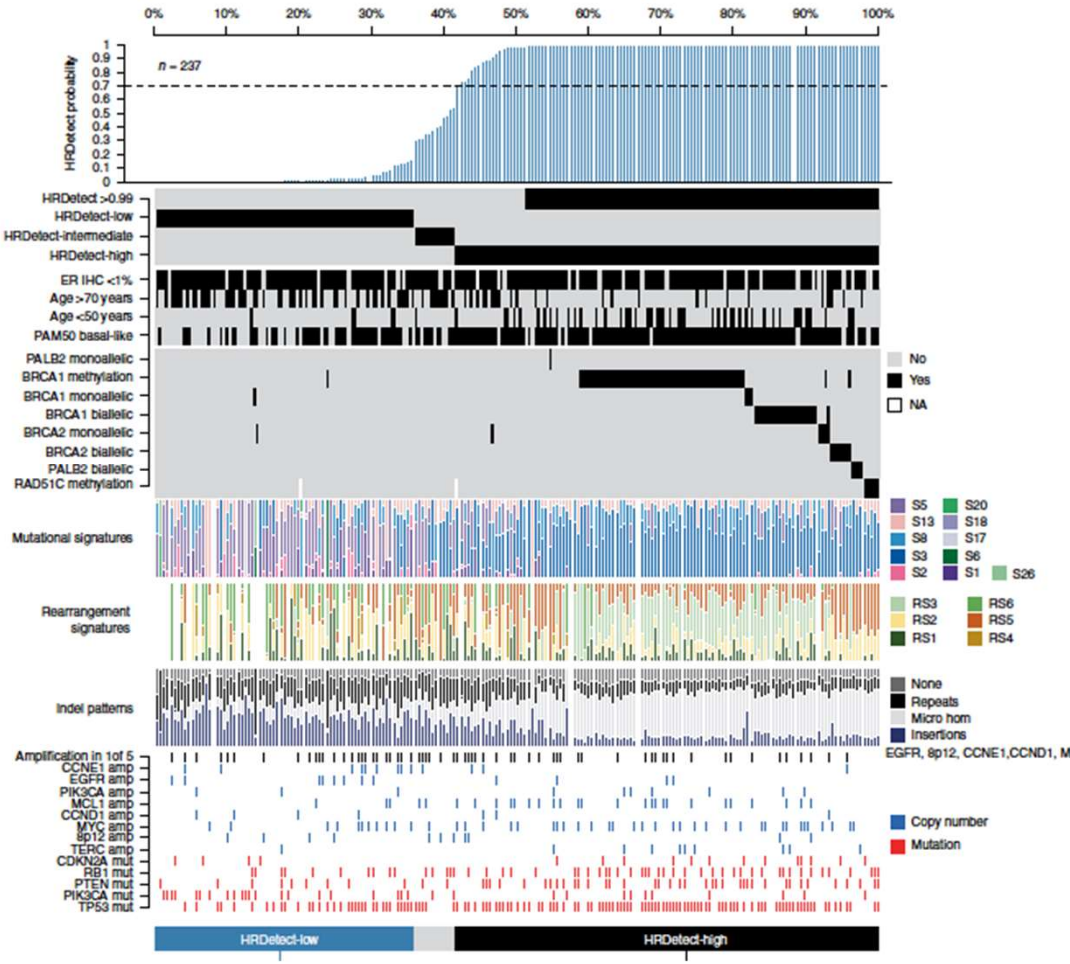
Many tests available – need test that is designed to address clinically relevant alterations. For advanced PCa, combining somatic and germline will be critical

LETTERS
https://doi.org/10.1038/s41591-019-0582-4
nature medicine

Whole-genome sequencing of triple-negative breast cancers in a population-based clinical study

Johan Staaf[1,13*], Dominik Glodzik[1,2,3,13], Ana Bosch[1,4], Johan Vallon-Christersson[1], Christel Reuterswärd[1], Jari Häkkinen[1], Andrea Degasperi[3,5], Tauanne Dias Amarante[3,5], Lao H. Saal[1], Cecilia Hegardt[1], Hilary Stobart[6], Anna Ehinger[1,7], Christer Larsson[8], Lisa Rydén[9,10], Niklas Loman[1,4], Martin Malmberg[1,4], Anders Kvist[1], Hans Ehrencrona[7,11], Helen R. Davies[3,5,12], Åke Borg[1,13] and Serena Nik-Zainal[5,12,13*]





ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

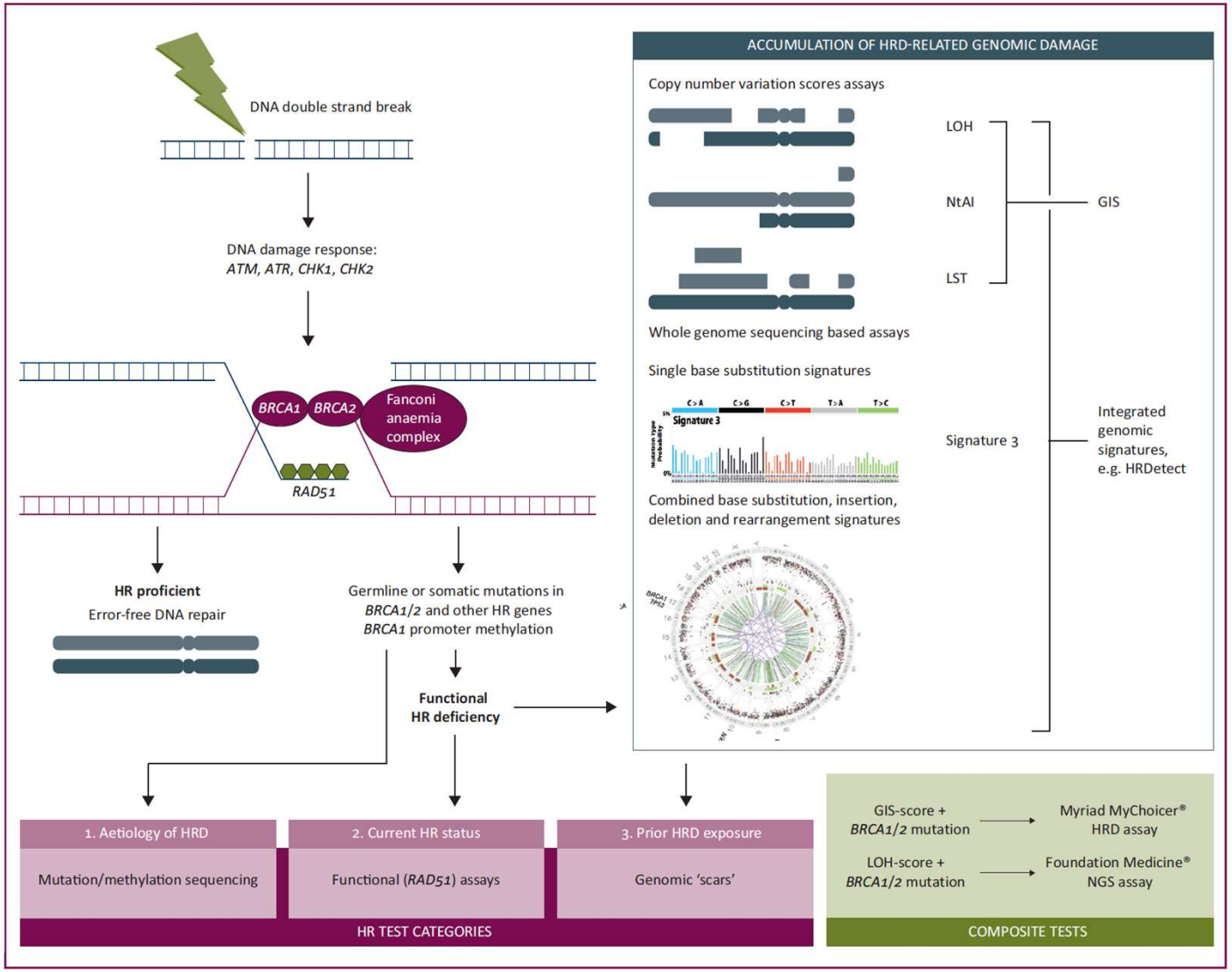
ANNALS OF ONCOLOGY driving innovation in oncology

SPECIAL ARTICLE

ESMO recommendations on predictive biomarker testing for homologous recombination deficiency and PARP inhibitor benefit in ovarian cancer

R. E. Miller[1,2], A. Leary[3], C. L. Scott[4,5], V. Serra[6], C. J. Lord[7,8], D. Bowtell[4,5], D. K. Chang[9,10], D. W. Garsed[4,5], J. Jonkers[11], J. A. Ledermann[12], S. Nik-Zainal[13,14], I. Ray-Coquard[15,16], S. P. Shah[17], X. Matias-Guiu[18], E. M. Swisher[19] & L. R. Yates[20,21*]

Annals of Oncology, 2020



Annals of Oncology, 2020

Genomic Characterization of Prostatic Ductal Adenocarcinoma Identifies a High Prevalence of DNA Repair Gene Mutations

Michael T. Schweizer, MD[1,2]; Emmanuel S. Antonarakis, MD[3]; Tarek A. Bismar, MD[4]; Liana B. Guedes, MD[3]; Heather H. Cheng, MD, PhD[1,2]; Maria S. Tretiakova, MD, PhD[1]; Funda Vakar-Lopez, MD[1]; Nola Klemfuss, MHA[2]; Eric Q. Konnick, MD, MS[1]; Elahe A. Mostaghel, MD, PhD[1,2]; Andrew C. Hsieh, MD[2]; Peter S. Nelson, MD[2]; Evan Y. Yu, MD[1,2]; R. Bruce Montgomery, MD[1]; Lawrence D. True, MD[1]; Jonathan I. Epstein, MD[3]; Tamara L. Lotan, MD[3]; and Colin C. Pritchard, MD, PhD[1]

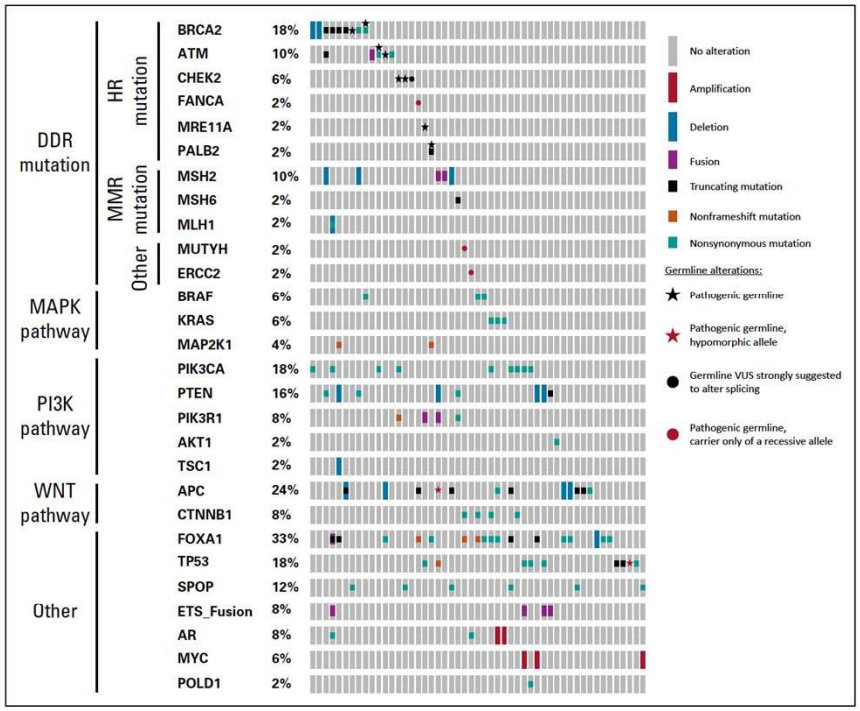


TABLE 2. Recurrent Genomic Alterations in Patients With Ductal Prostate Cancer Compared With Men With Spora Prostate Cancer [22,23]

	No. of Mutations (% of men)			Ductal Cohort Versus TCGA		Ductal Cohort Versus SU2C	
Gene/Pathway	Ductal Cohort (n = 51)	TCGA (n = 333)*	SU2C (n = 150)†	RR (95% CI)	*P*	RR (95% CI)	*P*
Any DDR	25 (49)	62 (19)	34 (23)	2.63 (1.84 to 3.77)	< .001	2.16 (1.44 to 3.25)	< .001
MMR alteration	7 (14)	11 (3)	3 (2)	4.16 (1.69 to 10.23)	.002	6.86 (1.84 to 25.55)	.004
MSH2	5 (10)	5 (2)	3 (2)	6.53 (1.96 to 21.77)	.002	4.90 (1.21 to 19.79)	.026
MLH1	1 (2)	1 (0.3)	1 (0.7)	6.53 (0.41 to 102.76)	.182	2.94 (0.18 to 46.17)	.443
MSH6	1 (2)	6 (2)	0	1.09 (0.13 to 8.85)	.937	—	.254
PMS2	0	4 (1)	0	—	1.00	—	—

2018

ANALYSIS

nature medicine

Classification and characterization of microsatellite instability across 18 cancer types

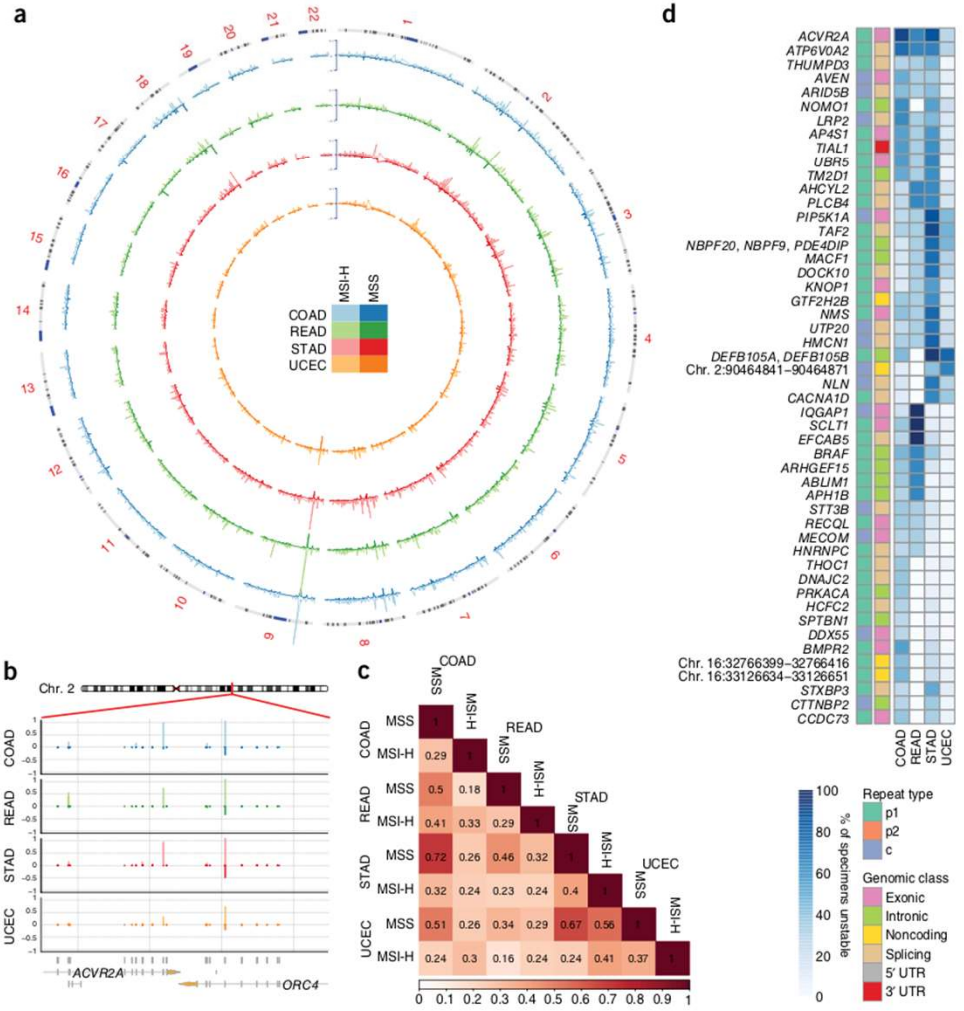
Ronald J Hause[1], Colin C Pritchard[2], Jay Shendure[1,3] & Stephen J Salipante[2]

Microsatellite instability (MSI), the spontaneous loss or gain of nucleotides from repetitive DNA tracts, is a diagnostic phenotype for gastrointestinal, endometrial, and colorectal tumors, yet the landscape of instability events across a wider variety of cancer types remains poorly understood

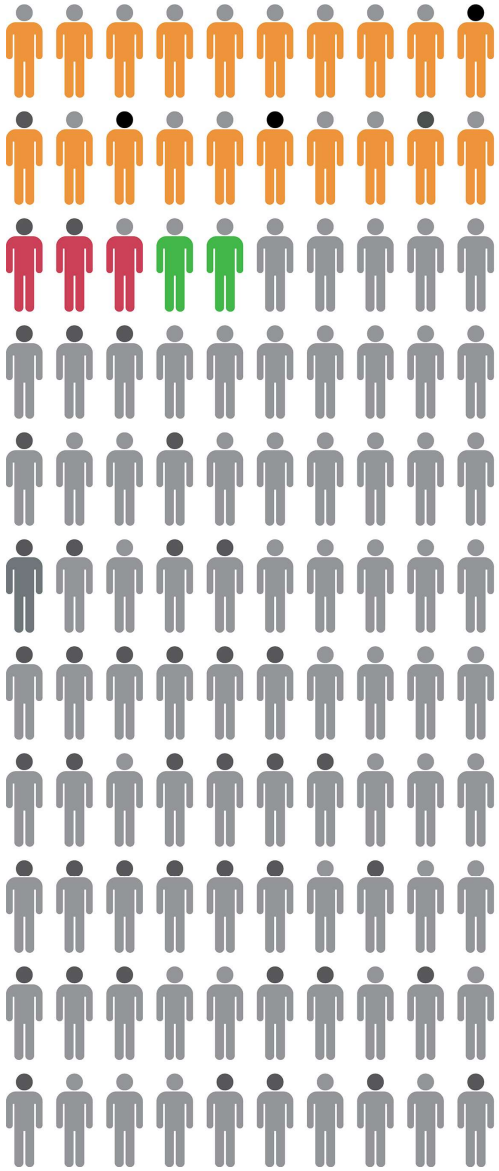
have demonstrated improved outcomes for patients with MSI-positive tumors treated with inhibitors of programmed cell death 1 (PD-1), presumably as a result of T lymphocyte recognition of neoantigens produced by somatic mutations[7,8]. However, mutations resulting from MSI can also drive oncogenesis, by inactivating tumor suppressor

MSI calling using WES demonstrates that each cancer
May require slightly different approaches.

There is no one perfect **small panel** for all cancer



2016



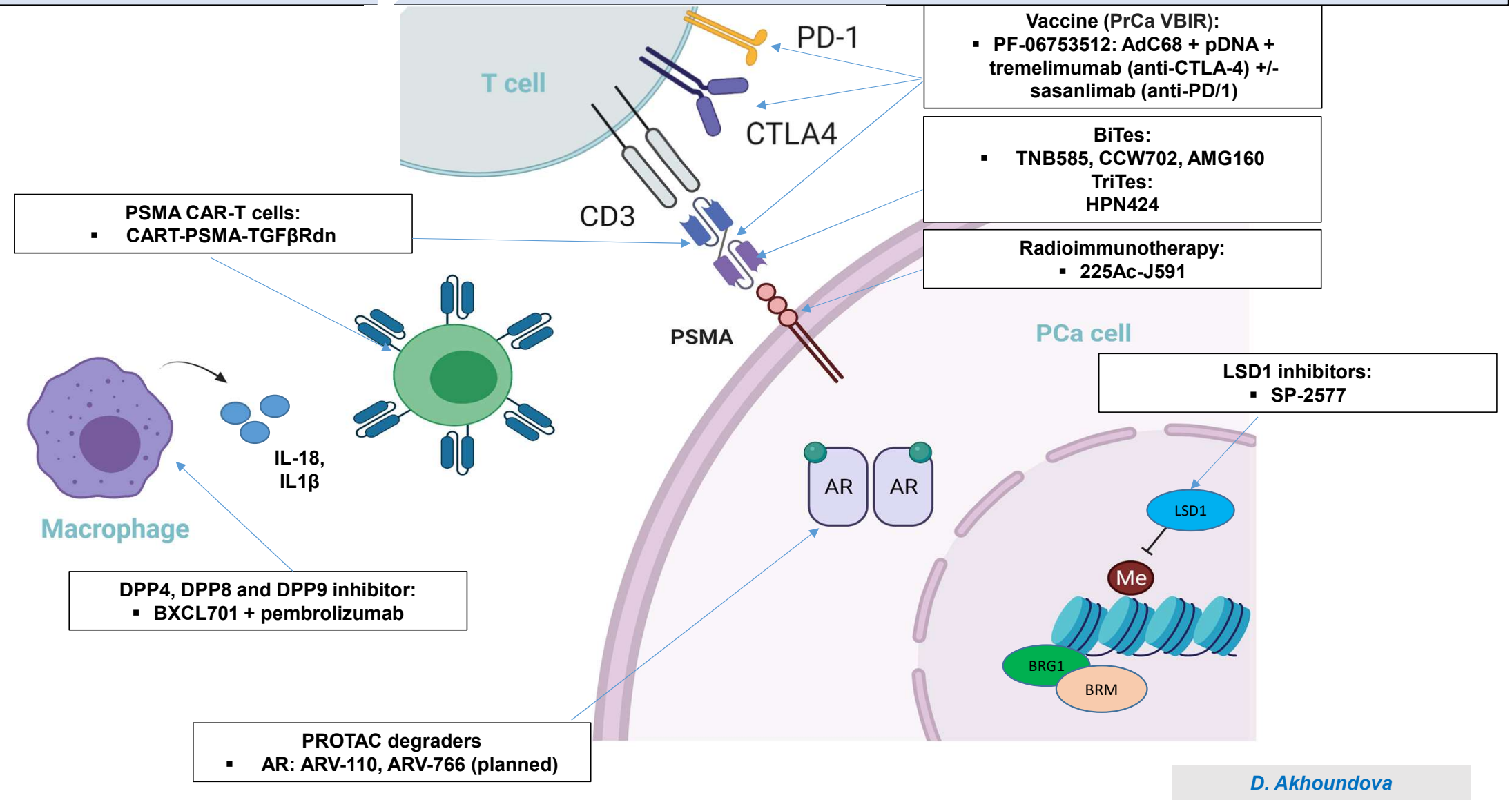
DNA Repair (BRCA1/2, ATM, etc.) 20%

MMR /MSI 5%

The remaining 75%

What is Needed Next?

Novel targeting strategies in advanced PCa



Vaccine (PrCa VBIR):
- **PF-06753512: AdC68 + pDNA + tremelimumab (anti-CTLA-4) +/- sasanlimab (anti-PD/1)**

BiTes:
- **TNB585, CCW702, AMG160**

TriTes:
HPN424

Radioimmunotherapy:
- **225Ac-J591**

PSMA CAR-T cells:
- **CART-PSMA-TGFβRdn**

LSD1 inhibitors:
- **SP-2577**

DPP4, DPP8 and DPP9 inhibitor:
- **BXCL701 + pembrolizumab**

PROTAC degraders
- **AR: ARV-110, ARV-766 (planned)**

D. Akhoundova

Novel targeting strategies in advanced PCa

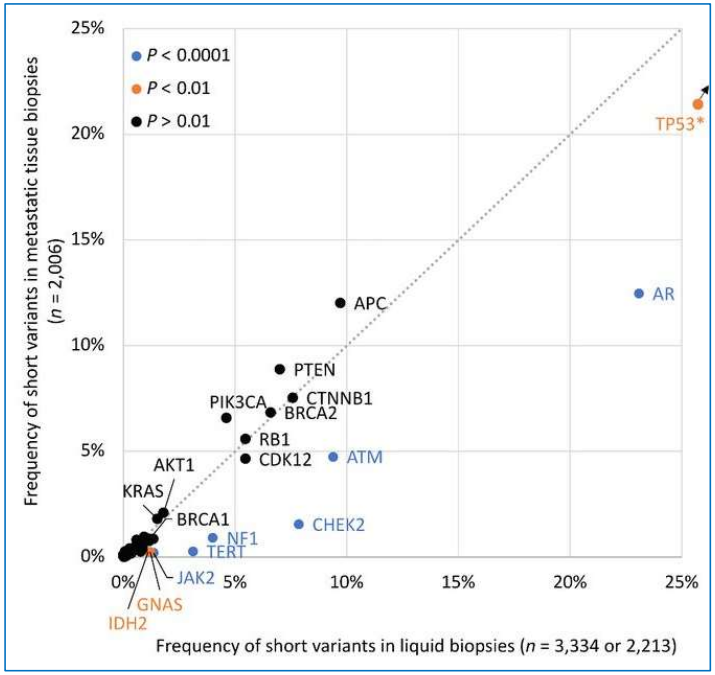
Drug	Target	CT ID	Phase	Status
PF-06753512 [1]	PSA, PSMA, PSCA CTLA-4, PD-1	NCT02616185	Phase 1	Completed
TNB585 [2]	PSMA, CD3	NCT04740034	Phase 1	Recruiting
CCW702 [3]	PSMA, CD3	NCT04077021	Phase 1	Recruiting
AMG160 [4]	PSMA, CD3	NCT03792841	Phase 1	Recruiting
HPN424 [5]	PSMA, CD3, Albumin	NCT03577028	Phase 1/2a	Recruiting
CART-PSMA-TGFβRdn [6]	PSMA, TGFβ	NCT04227275	Phase 1	Active, not recruiting
225Ac-J591 [7]	PSMA	NCT03276572	Phase 1	Active, not recruiting
ARV-110 [8]	AR	NCT03888612	Phase 1/2	Recruiting
Seclidemstat (SP-2577) [9]	LSD1	NCT03895684	Phase 1	Recruiting
Talabostat Mesylate (BXCL701)+ pembrolizumab [10]	DPP4, DPP8, DPP9 (macrophages), PD-1	NCT03910660	Phase 1b/2	Recruiting

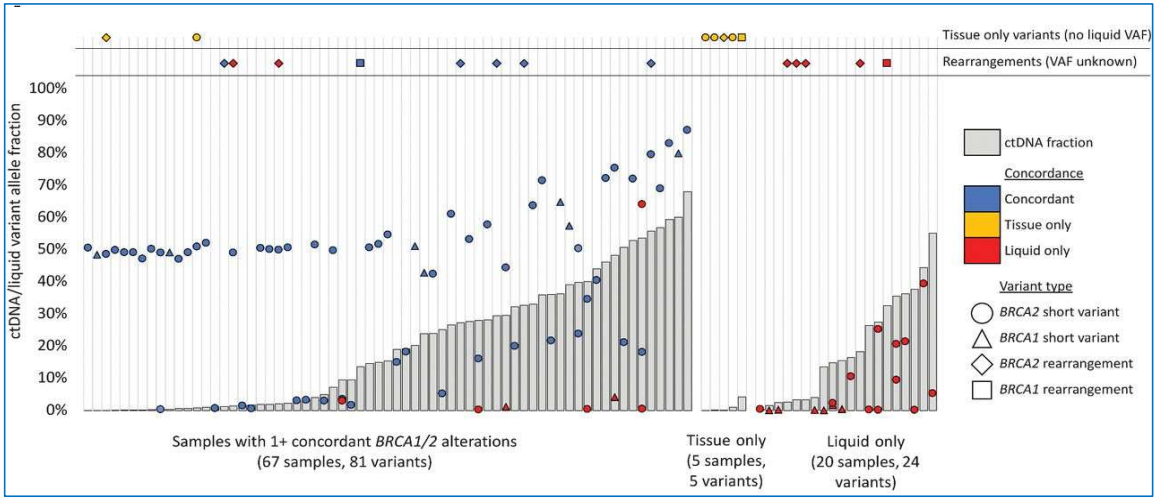
[1] Autio K.A. et al. JCO 2021; [2] Buelow B. et al. JCO 2021; [3] Markowski M.C. et al. JCO 2021; [4] Sumit K.S. et al. JCO 2021; [5] De Bono J.S. et al. JCO 2021; [6] Narayan V.et al. JCO 2021; [7] Tagawa S.T. et al. JCO 2021; [8]Petrylak D.P. et al. JCO 2020; [9] Chawla S.P et al. JCO 2021; [10] Aggarwal R.R et al. JCO 2021

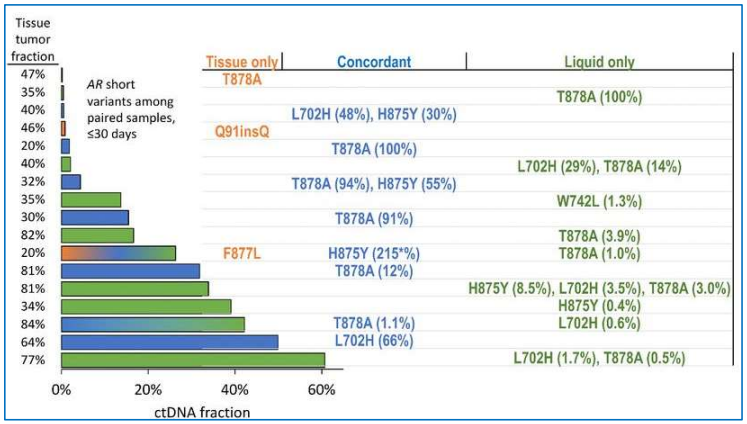
D. Akhoundova

Genomic Analysis of Circulating Tumor DNA in 3,334 Patients with Advanced Prostate Cancer Identifies Targetable BRCA Alterations and AR Resistance Mechanisms. *Tukachinsky H. et al. Clin Cancer Res. 2021.*

- **Aim:** to assess agreement between ctDNA and tissue genomic profiling in mCRPC
- **Methods:** plasma ctDNA (Foundation ACT™, FoundationOne® Liquid) and tissue genomic analysis (70 genes, ≥500× coverage) in 3,334 pts with mCRPC (including 1,674 samples from TRITON2/3 trials)







- High agreement between genomic analysis of ctDNA and tissue samples in patients with mCRPC, high concordance in *BRCA1/2* mutations
- Higher detection of acquired resistance alterations in ctDNA

Tukachinsky H. et al. Clin Cancer Res. 2021

D. Akhoundova

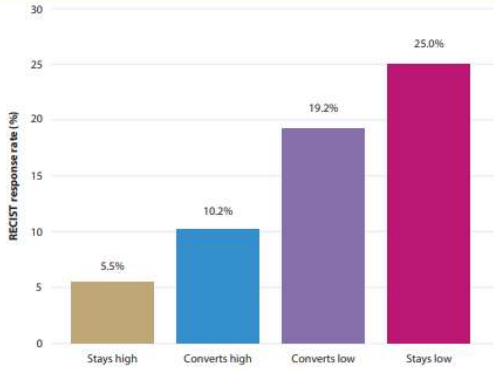
CTC counts as a biomarker of prognosis and response in metastatic castration-resistant prostate cancer (mCRPC) from the CARD trial. *De Bono J.S. et al. JCO 2021.*

- **Aim:** to analyze CTC counts as a biomarker of prognosis and response in mCRPC patients from the CARD trial.
- **Methods:** CTC analysis (Epic Sciences) from blood samples at screening, Cycle 2 day 1, and therapy end.

ASSOCIATION OF CTC CHANGES WITH OS, rPFS AND RECIST RESPONSE

- Patients that maintain low CTCs at C2D1 have longer OS and a higher rate of Partial Response (PR)

Tumor response (all arms combined)



Multivariable Risk Adjusted Hazard Ratios

	rPFS		OS	
	HR[a] (95% CI)	*P*	HR[a] (95% CI)	*P*
CTC conversion over median[b]				
Stays high (n = 69)	(reference)		(reference)	
Converts low (n = 33)	0.89 (0.52–1.52)	0.67	0.66 (0.37–1.20)	0.18
Converts high (n = 45)	0.81 (0.49–1.33)	0.40	0.52 (0.30–0.90)	0.02
Stays low (n = 51)	0.79 (0.51–1.25)	0.32	0.46 (0.27–0.79)	0.004

De Bono J.S.. et al. JCO 2021

CARD: STUDY DESIGN

- Multicenter, randomized, open-label study
- Enrollment: Nov 2015 – Nov 2018
- Median follow-up: 9.2 months

Patients with mCRPC who progressed ≤ 12 months on prior alternative ARTA (before or after docetaxel)

N = 255

RANDOMIZE 1:1

- Cabazitaxel (25 mg/m² Q3W) + prednisone + G-CSF, n = 129
- Abiraterone (1000 mg QD) + prednisone OR Enzalutamide (160 mg QD), n = 126

Stratification factors:
- ECOG PS (0/1 vs 2)
- Time to progression on prior alternative ARTA (0–6 vs > 6–12 months)
- Timing of ARTA (before vs after docetaxel)

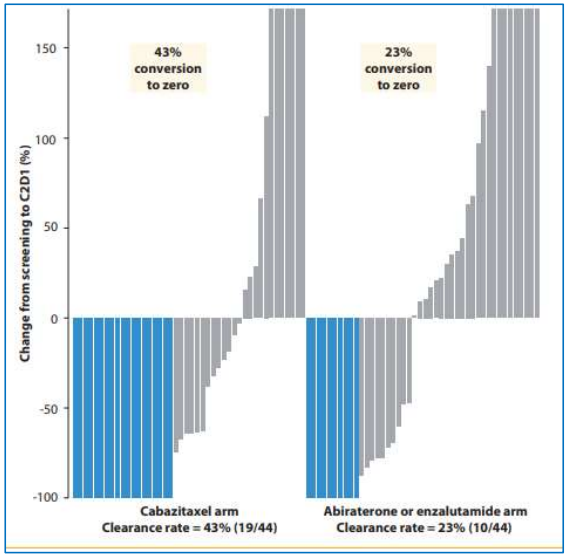
Endpoints

Primary: rPFS

Key secondary: OS, PFS, PSA response, tumor response

Other secondary: Pain response, time to symptomatic skeletal event, safety, HRQoL, biomarkers

De Wit R. et al. ESMO 2019



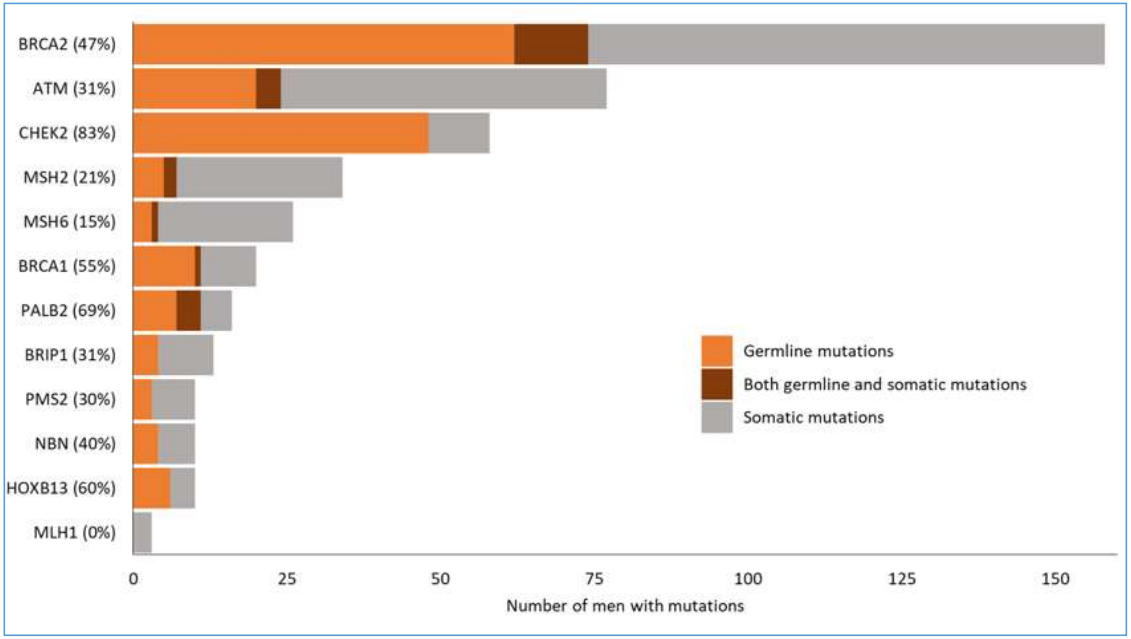
De Bono J.S.. et al. JCO 2021

- Baseline CTCs have prognostic value in mCRPC
- Early decrease correlates with therapeutic response

D. Akhoundova

Characterization of findings on prostate cancer tumor sequencing that should prompt consideration for germline testing. *Truong H. et al. JCO 2021.*

- **Aim:** to determine the overall and gene-specific probability of pathogenic/likely pathogenic germline mutations based on tumor-only sequencing.
- **Methods:** matched tumor-normal sequencing (n=1883)



Gene	Germline probability (%)
CHEK2	83
PALB2	69
HOXB13	60
BRCA1	55
BRCA2	47
NBN	40
ATM	31
BRIP1	31
PMS2	30
MSH2	21
MSH6	15

Truong H. et al. JCO 2021

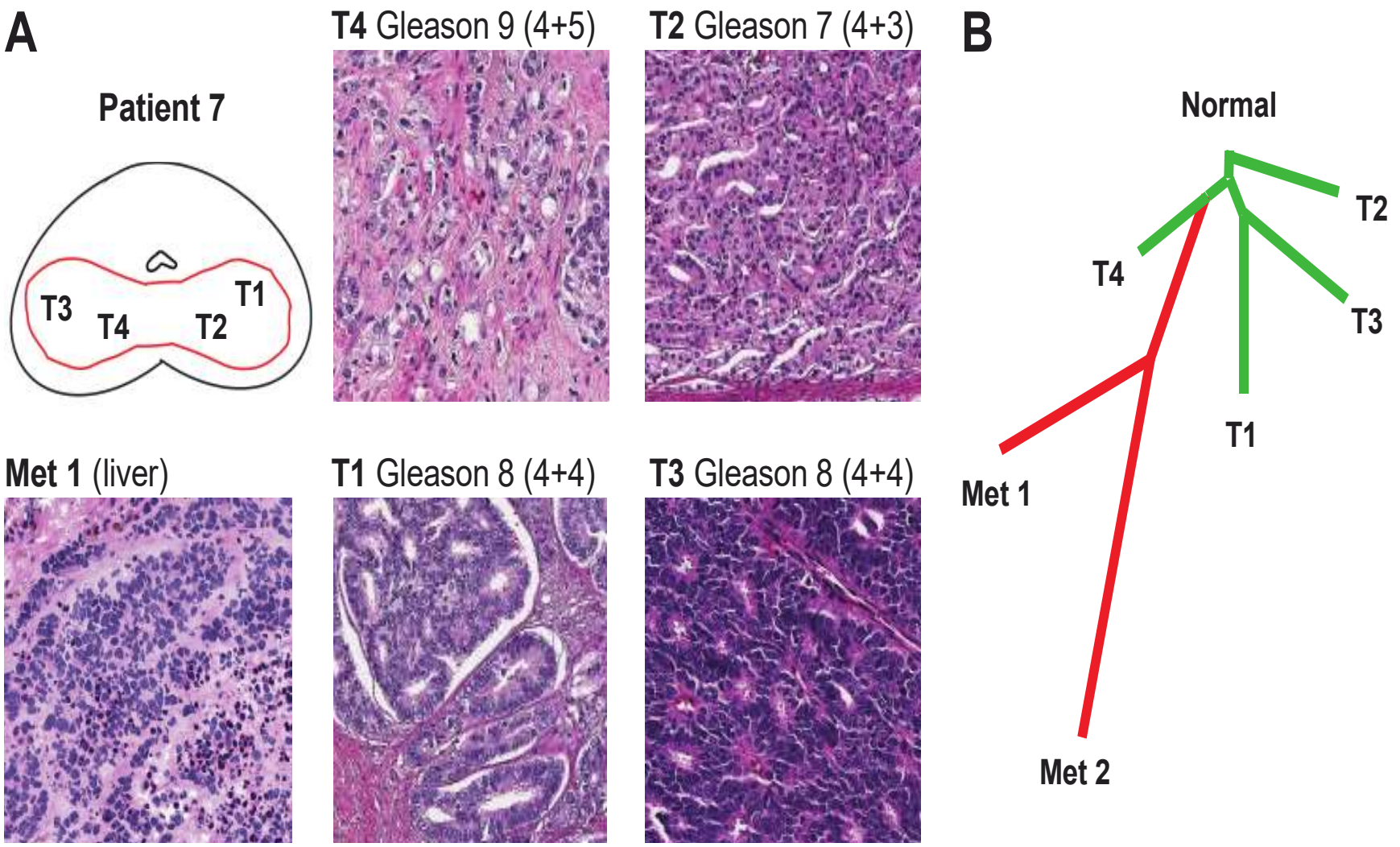
Results:

- 19% patients presented at least one mutation (somatic or germline) in PCa genes. 10% pathogenic germline variants (PGV). 46% PGV undetected based on family or personal history
- Average of 40% of mutations found in cancer susceptibility genes on PCa tumor sequencing were germline mutations.

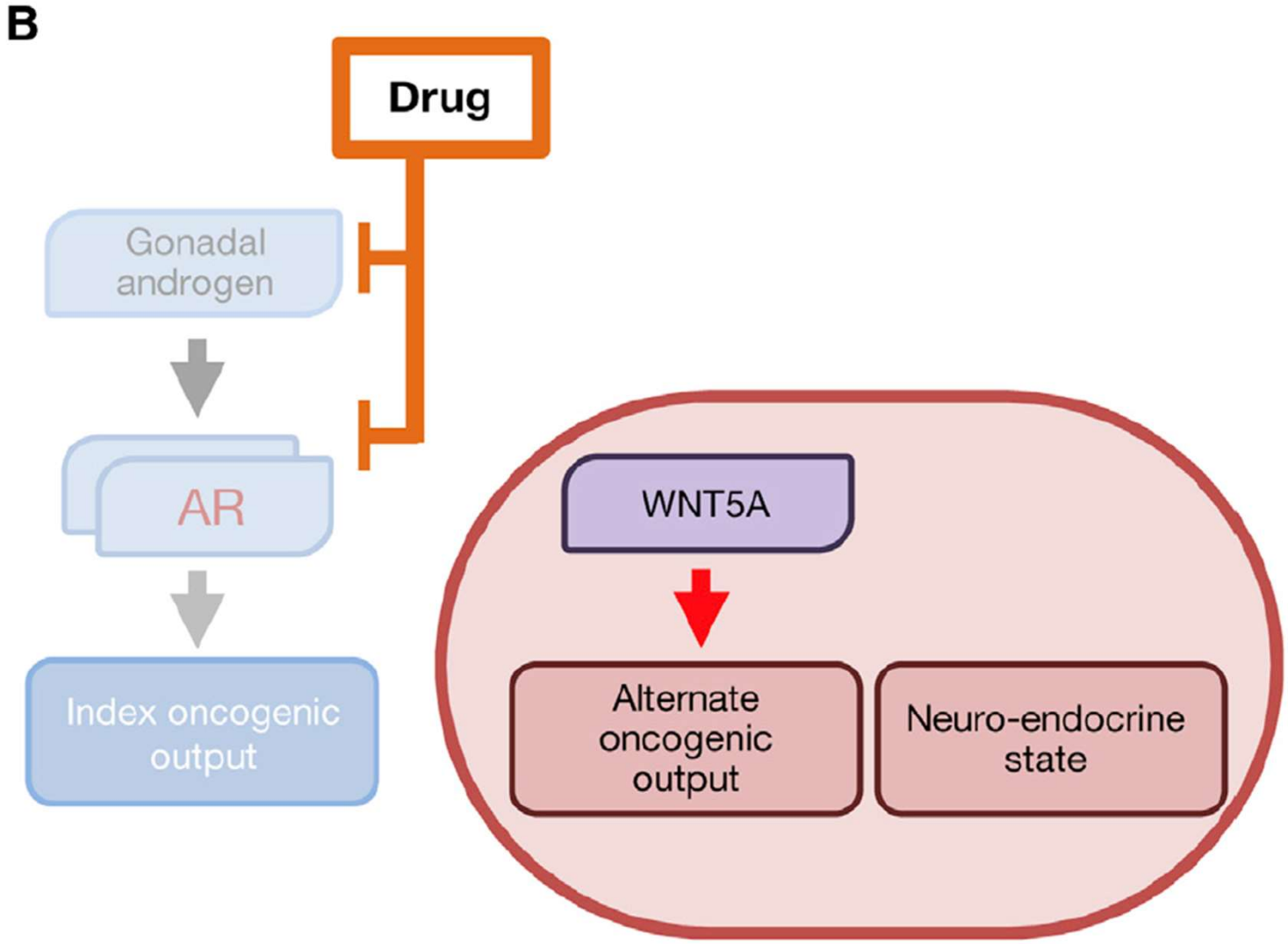
Confirmatory germline testing should be considered in patients with mutations in *CHEK2, PALB2, HOXB13, BRCA1/2, NBN, ATM, BRIP1, PMS2, MSH2 and MSH6*

D. Akhoundova

Overcome Heterogeneity

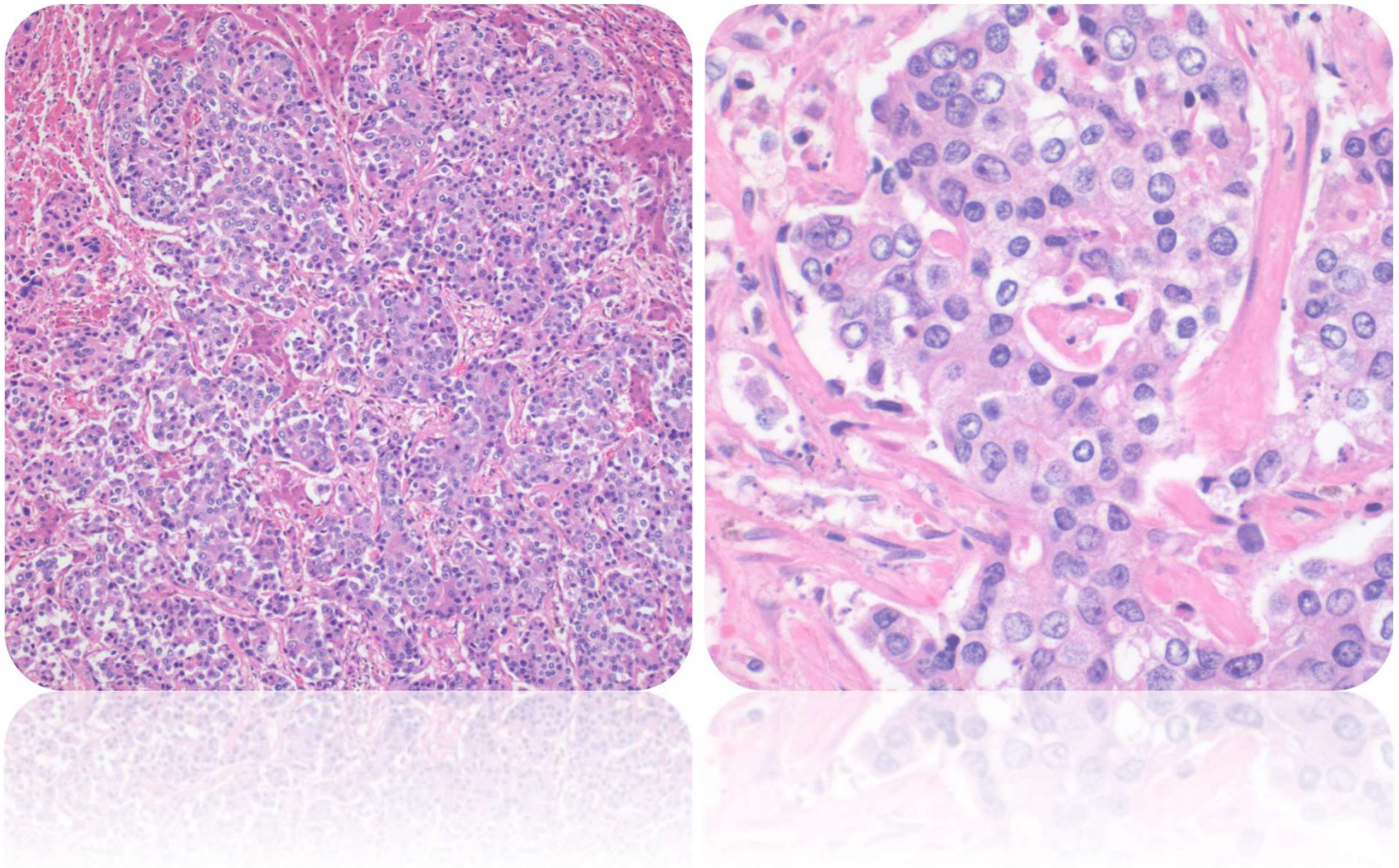


Cyrta, Prandi, et al., in preparation

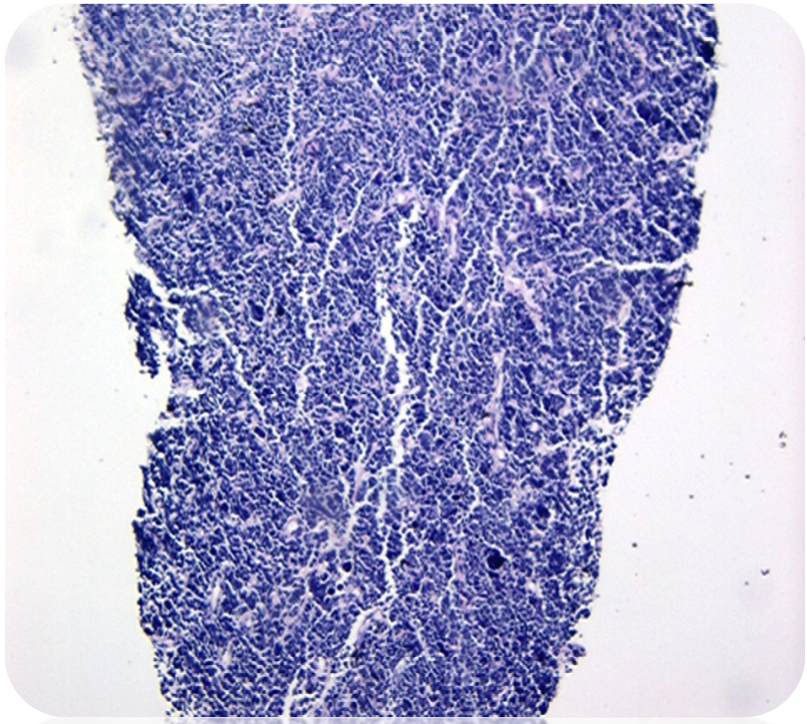


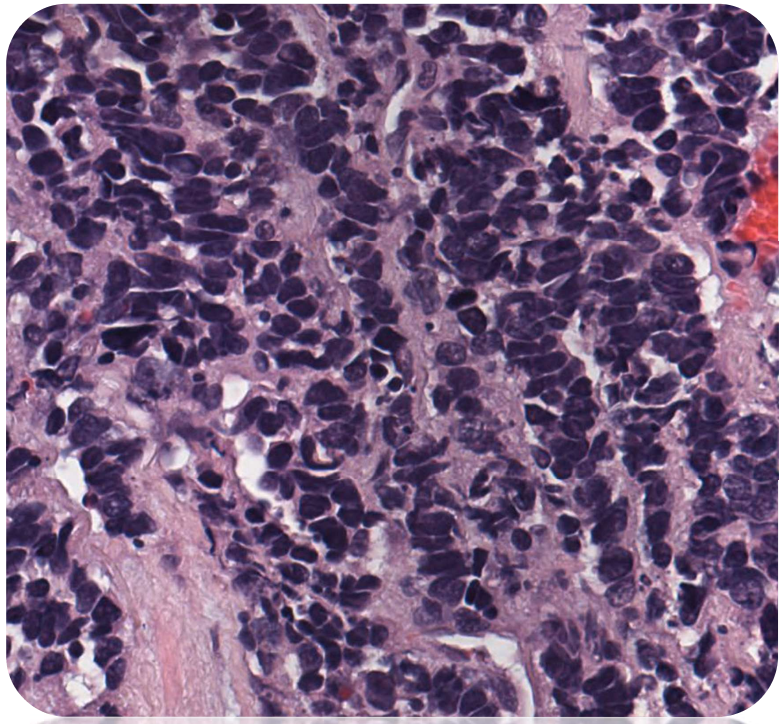
Konieczkowski et al, Cancer Cell 2018

Diagnosis: Prostate Cancer, adenocarcinoma

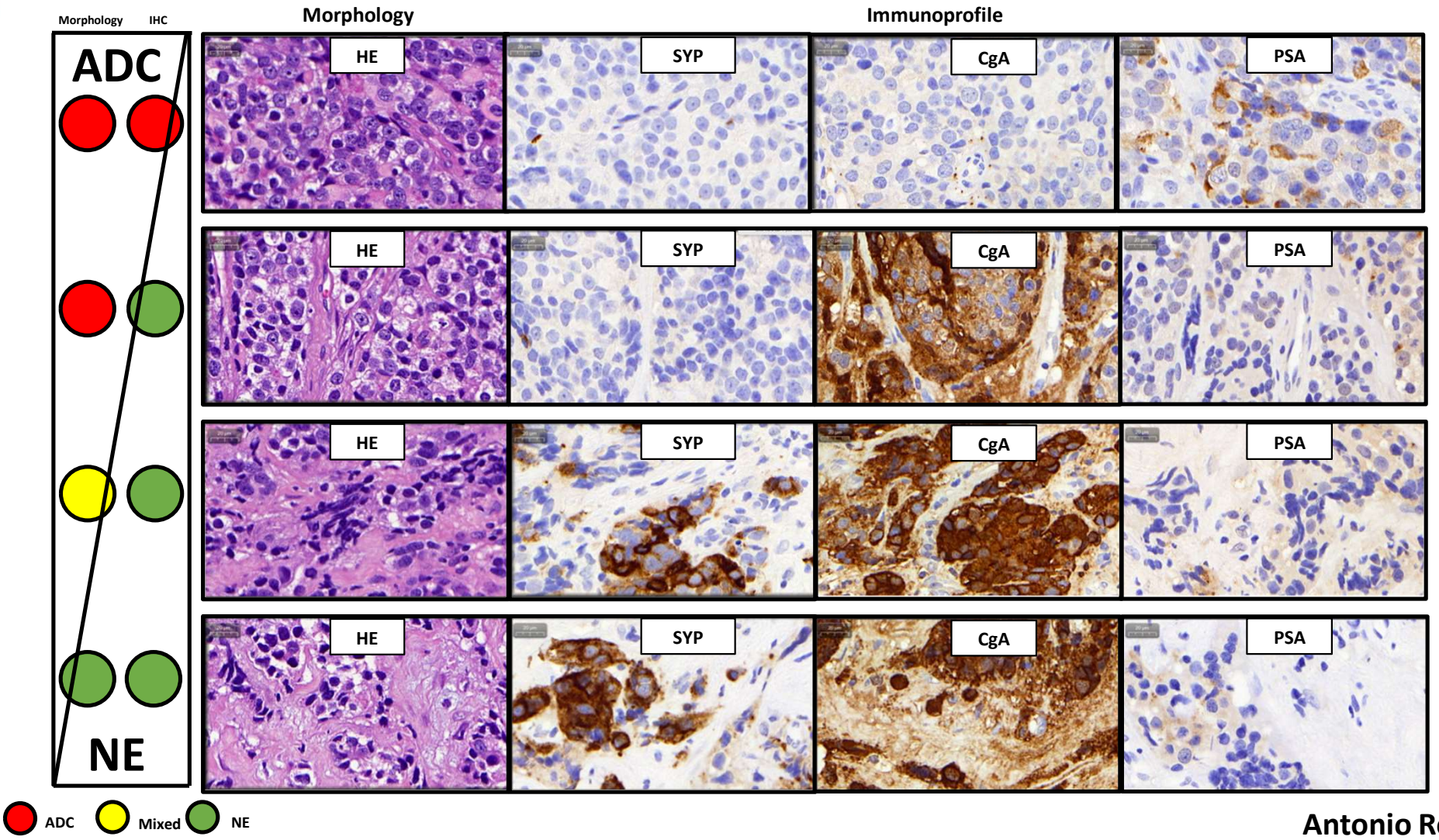


Diagnosis: Small Cell/Neuroendocrine Prostate Cancer





Sample: Spectrum adenocarcinoma-NE differentiation



Antonio Rodríguez

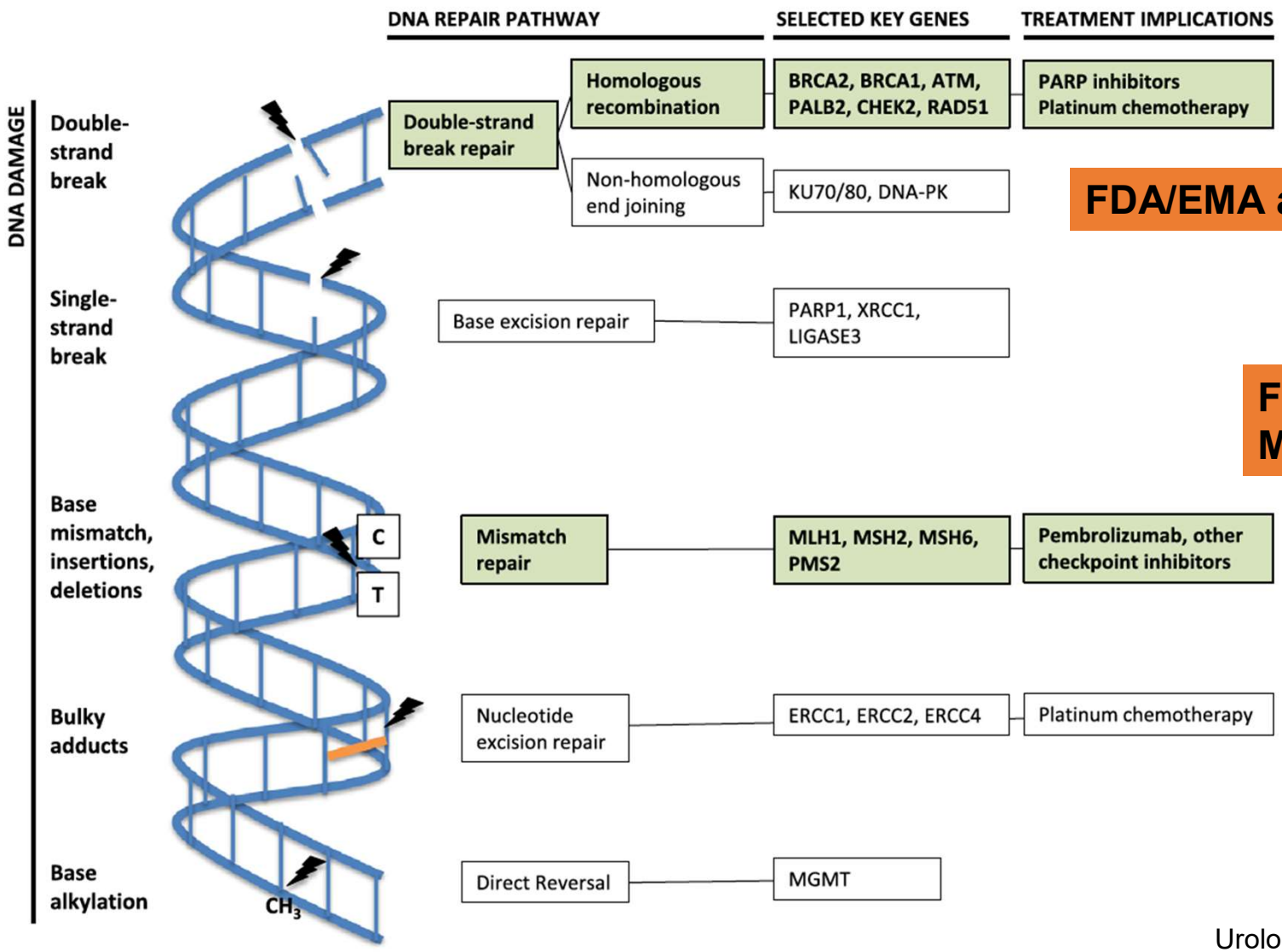
In conclusion:

What is "*actionable*" or ready for clinical use?

Promising/Need prospective validation

-Biopsy or cfDNA for DNA fraction, AR, others

-CTC for CN, AR, AR v7



20%

FDA/EMA approval for BRCA1/2, ATM

FDA (May 2017) approval for MSI and MMR deficiency

5%

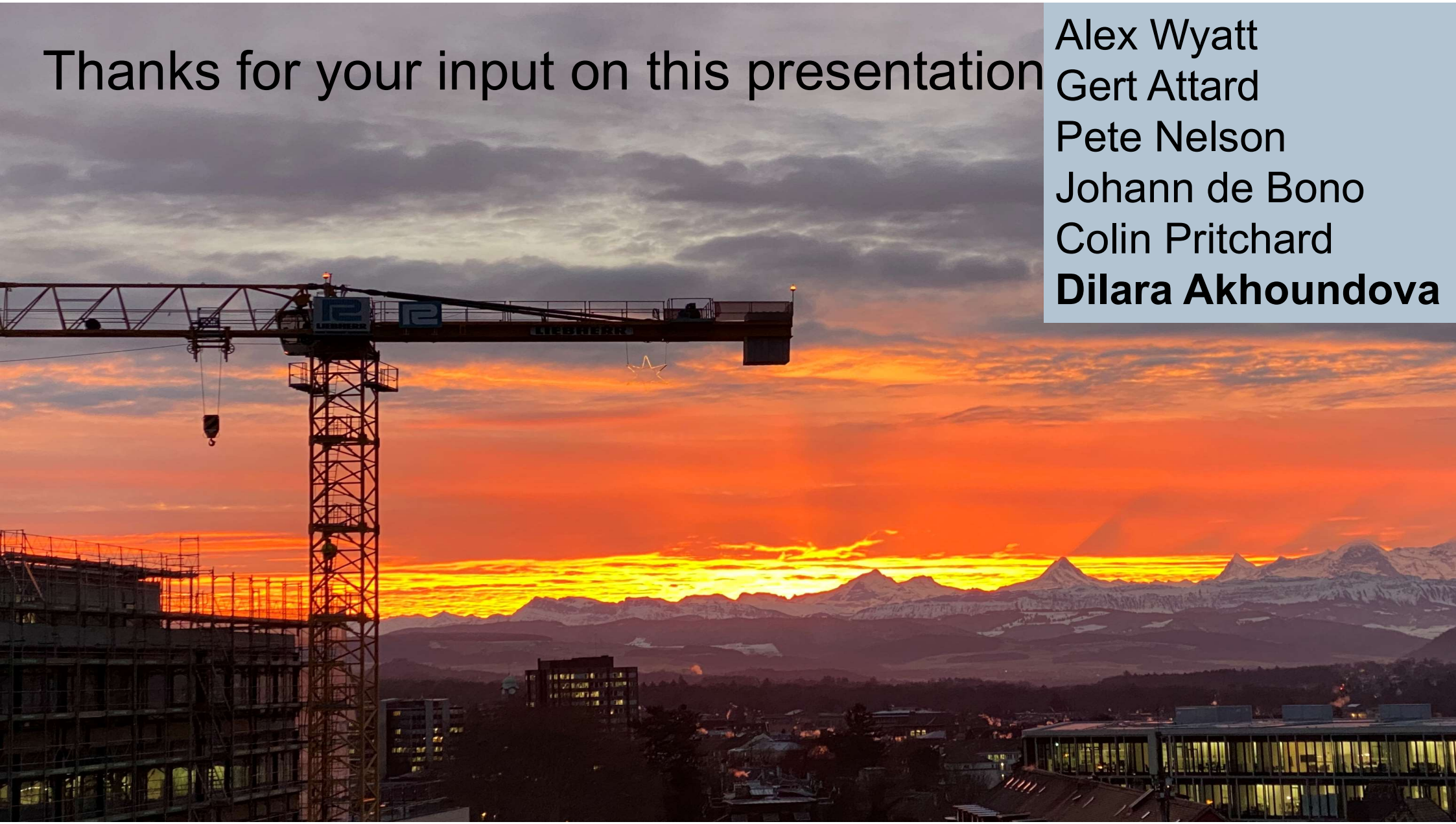
Urologic Oncology: Sem. and Orig. Invest. 36(2018)385–388

Recommendations for Genomic Testing for mCRPC

1) BRCA1/2 and ATM mutation tests: germline, somatic/germline, somatic exhibit clinical validity consistently identifying the subgroup of prostate cancer patients who derive benefit from PARPi therapy. (i.e., tissue, cfDNA)
2) HRD mutation signature suggested –especially useful in cases on mono-allelic loss

N.B. Currently an insufficient quantity of evidence to determine the clinical validity of individual or panels of non-BRCA HRR genes for predicting a PARPi response

3) Determination of mismatch repair (MMR) tumor mutation burden (TMB), (e.g. MSI high/dMMR/high TMB)



Thanks for your input on this presentation

Alex Wyatt
Gert Attard
Pete Nelson
Johann de Bono
Colin Pritchard
Dilara Akhoundova