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Trattamenti della malattia con mutazioni di BRCA e altro…

Background

- Prostate cancer is inheritable…but
- Important to know the family history
- A different type of genes are involved…BRCA1/2, Lynch Syndrome…others
- Pts with BRCA2 mutation have 3-9x risk of PC and more lethal
- Germline could be different from somatic mutation
- In advanced disease clinical management does not differ
- To whom should we offer germline genetic testing and when… because

Germline pathogenic alterations may have both familial and therapeutic implications

To whom should we *offer* germline genetic testing?

MEN with… (any of following)

- Metastatic prostate cancer, esp if interested in trials
- High or very high risk loco-regional PC
- Family history of *gBRCA1/2*, Lynch Syndrome, *HOXB13*
- Family history of cancers (prostate ca. AND others, esp breast, ovarian, pancreas, GI)*

*See also ASCO Education Article; NCCN Prostate Guidelines; NCCN Genetic/Familial High-Risk Assessment: Breast and Ovarian NCCN Prostate Cancer Early Detection

More recent genetic findings in advanced PC may also inform therapy

- ~5-10% of advanced prostate cancers have mismatch repair deficiency and/or MSI[1], candidates for immune checkpoint inhibitors.
- Germline *HSD3B1* 1245C variant associated with resistance to castration and response to CYP17A1 inhibitors (abiraterone)[2,3]
- *CDK12* loss may predict response to PD-1 inhibition[4]

1, Pritchard, et al (2014) Nat Commun
2, Hearn, et al. (2018) JAMA Oncol
3, Almassi, et al. (2018) JAMA Oncol
4 Wu, Cieslik, Robinson, et al. (*in press*) Cell

Table 1 – Prevalence of DNA repair gene mutations and deletions described in studies on localized and metastatic prostate cancer

Study	Disease status	Samples	Gene frequency							
		(*n*)	Homologous recombination				MMR		NER	
SU2C-PCF CRPC	CRPC metastasis	150	*BRCA1*	0.7%	*CDK12*	4.7%	*MLH1*	1.3%	*ERCC2*	1.3%
genomic landscape			*BRCA2*	13.3%	*CHEK2*	3.0%	*MSH2*	3.0%	*ERCC5*	1.3%
[12]			*ATM*	7.3%	*PALB2*	2.0%	*MSH6*	2.0%		
UM PC genomics	CRPC metastasis	50	*BRCA1*	0%	*CDK12*	6.0%	*MLH1*	2.0%	*ERCC2*	2.0%
[11]			*BRCA2*	12.0%	*CHEK2*		*MSH2*	2.0%	*ERCC5*	12.0%
			ATM	6.0%	*PALB2*	0%	*MSH6*	2.0%		
UM PC genomics	Treatment-naïve tumors	11	*BRCA1*	0%	*CDK12*	0	*MLH1*	0	*ERCC2*	0
[11]			*BRCA2*	1/11	*CHEK2*	0	*MSH2*	1/11	*ERCC5*	0
			ATM	1/11	*PALB2*	0	*MSH6*	1/11		
Weill Cornell/Broad	Prostatectomy for localized	109	*BRCA1*	1.8%	*CDK12*	0	*MLH1*	0	*ERCC2*	0
[6]	or locally advanced PC		*BRCA2*	0%	*CHEK2*	0	*MSH2*	0	*ERCC5*	0
	(somatic only)		*ATM*	2.8%	*PALB2*	1.8%	*MSH6*	0.9%		
TCGA localized PC	Localized PC	333	*BRCA1*	1.0%	*CDK12*	2.0%	*MLH1*	0.3%	*ERCC2*	0.6%
[8]			*BRCA2*	3.0%*	*CHEK2*	0%	*MSH2*	0.3%	*ERCC5*	0.3%
			ATM	4.0%	*PALB2*	0%	*MSH6*	1.5%		

MMR = mismatch repair; NER = nucleotide-excision repair; PC = prostate cancer; CRPC = castration-resistant PC; SU2C-PCF = Stand Up To Cancer-Prostate Cancer Foundation; UM = University of Michigan; TCGA = The Cancer Genome Atlas.

Outline

- The 6 DNA repair pathways
- Prevalence of DNA repair defects in prostate cancer
- DNA repair and therapeutic implications
  - **PARP inhibitors**
  - Hormonal therapy
  - Immune checkpoint inhibitors
  - Platinum chemotherapy

Single-Stranded (ss)DNA Repair Pathways

- Mismatch repair
  - Base errors from DNA replication and recombination
  - *MSH2, MSH6, MLH1, PMS2*
- Nucleotide excision repair
  - DNA damage from UV light, polycyclic aromatic hydrocarbons
  - *XPA-G, ERCC1-8, CSA/B, RPA, RAD23A/B*
- **Base excision repair**
  - **DNA damage from alkylation, oxidation/ROS, deamination**
  - ***PARP1/2/3, POLβ, MUTYH, XRCC1, MBD4, NTHL1***

Mateo J, et al. Eur Urol. 2017;71:417-425.

Double-Stranded (ds)DNA Repair Pathways

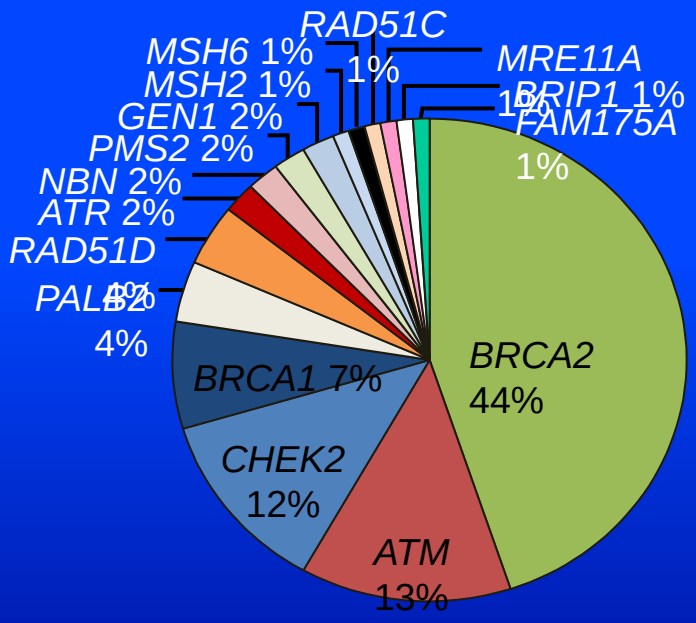
- **Homologous recombination**
  - **DNA damage from ionizing radiation or other dsDNA injury**
  - ***FANC* genes, *BRCA1/2, ATM, PALB2, RAD50, RAD51, NBN, GEN1, MRE11, BLM, ATR***
- Nonhomologous end joining
  - DNA damage from ionizing radiation or other dsDNA injury
  - *XRCC4/5/6, LIG4, DCLRE1C, PRKDC, NHEJ1, POLL/M*
- Translesion DNA synthesis
  - Error-prone recovery mechanism when no DNA template
  - *POLH, POLI, POLK, PCNA, REV1/3* (error-prone DNA polymerases)

Mateo J, et al. Eur Urol. 2017;71:417-425. Makridakis NM, et al. Front Genet. 2012;3:174.

Germline Mutations in Prostate Cancer: 1 in 10

- 11.8% (82/692) of men with metastatic prostate cancer inherited a germline DNA repair mutation vs 4.6% of 499 men with localized disease

Distribution of Presumed Pathogenic Germline Mutations



Presumed Pathogenic Germline Mutations in Metastatic Cases (N = 692)

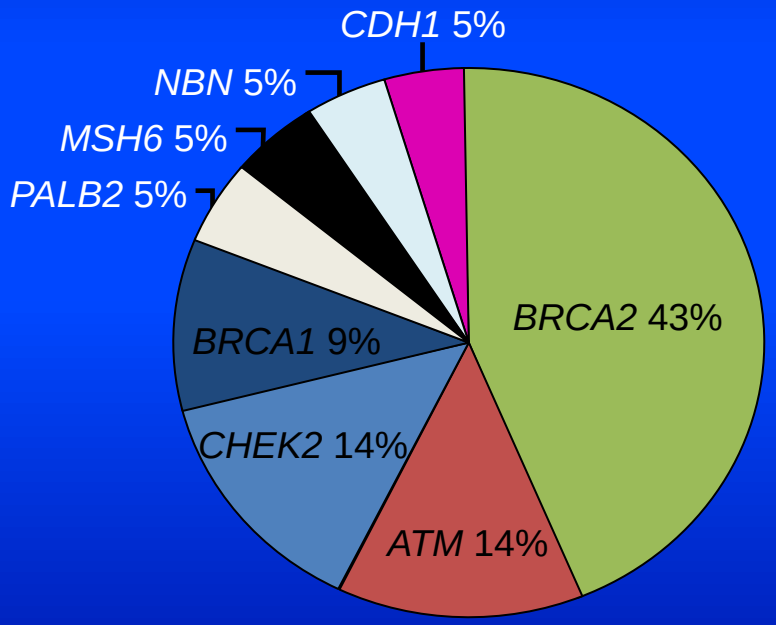
Gene	No. of Mutations	% of Men
BRCA2	37	5.35
ATM	11	1.59
*CHEK2**	10	1.87
BRCA1	6	0.87

*n = 534; data censored for metastatic cases with inadequate sequencing.

Pritchard CC, et al. N Engl J Med. 2016;375:443-453.

Association Between Germline DNA-Repair Defects and Intraductal/Ductal Histology

Distribution of Pathogenic Germline Mutations



- Germline mutations in 14% (21/150) of men with recurrent/advanced prostate cancer
- Men with intraductal/ductal histology more likely to have germline mutations

Incidence of Pathogenic Germline Mutations

Intra/Ductal Histology	No Intra/Ductal Histology	*P* Value*
40% (10/25)	**9%** (11/125)	*P* = .003

Isaacsson Velho P, et al. The Prostate. 2018;[Epub ahead of print].

*Fisher's test.

Effect of DDR Mutation on Treatment Responses

Data emerging – may depend on assay / population

Annala 2017: Canadian cohort, ctDNA:

- Presence of DDR mutation associated with poorer outcomes on abiraterone/enzalutamide

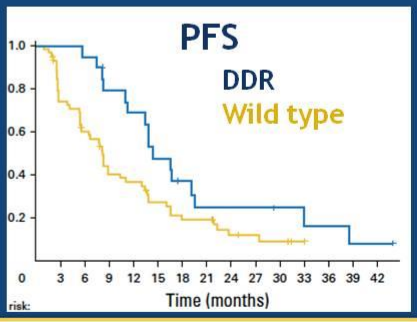
Similar trend reported by Castro for men with germline DDR mutations (ESMO 2017, LBA32)

Mateo 2018: UK / US / Australian cohort, n=390; 60 with germline DDR mutation:

- Similar response and survival rates on standard therapies

Hussain 2018: NCI 9012: randomized trial of abiraterone +/- veliparib

- Presence of DDR mutation associated with better outcomes



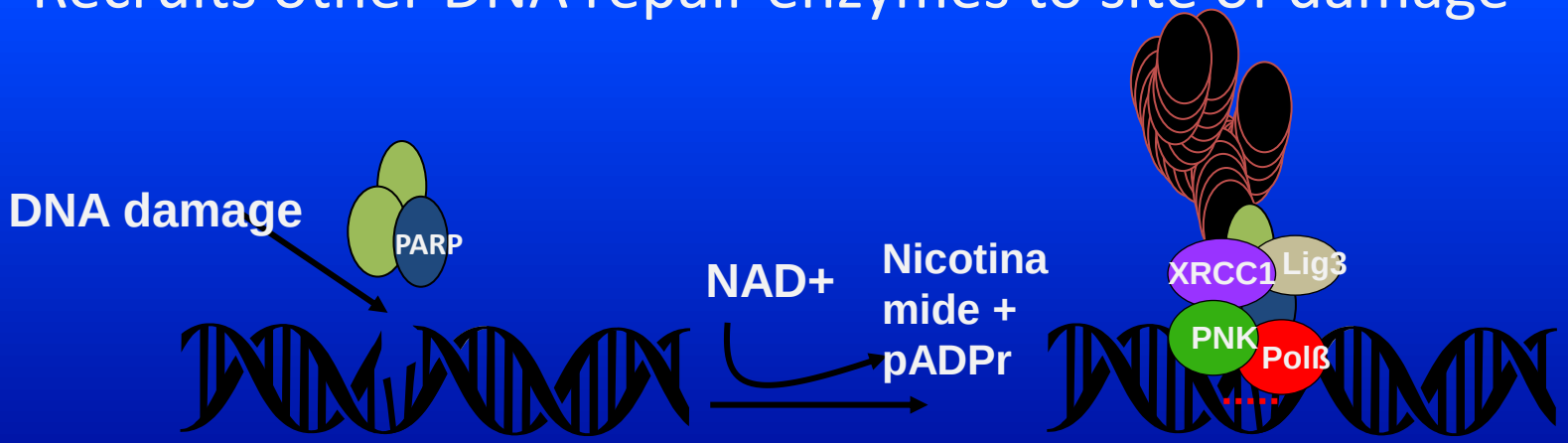
Annala Eur Urol 2017; Mateo Eur Urol 2018; Hussain J Clin Oncol 2018

Selected Trials for mCRPC with Relevance to DNA repair defects

Phase	Agent	Short Name	Clinicaltrials.gov
III	Rucaparib	TRITON3	NCT02975934
III	Olaparib	PROFOUND	NCT02987543
II	Niraparib	GALAHAD	NCT02854436
II	Talazoparib	TALAPRO	NCT03148795
II	Olaparib	BRCAaway	NCT03012321
II	Docetaxel and Carboplatin	(V) ABCD	NCT02598895 NCT02985021
II	Pembrolizumab	KEYNOTE-199	NCT02787005 NCT02312557
Ib/II	Pembrolizumab Combination Therapies	KEYNOTE-365	NCT02861573
II	Nivolumab Combination Therapies	CheckMate 9KD	NCT03338790

PARP Biology

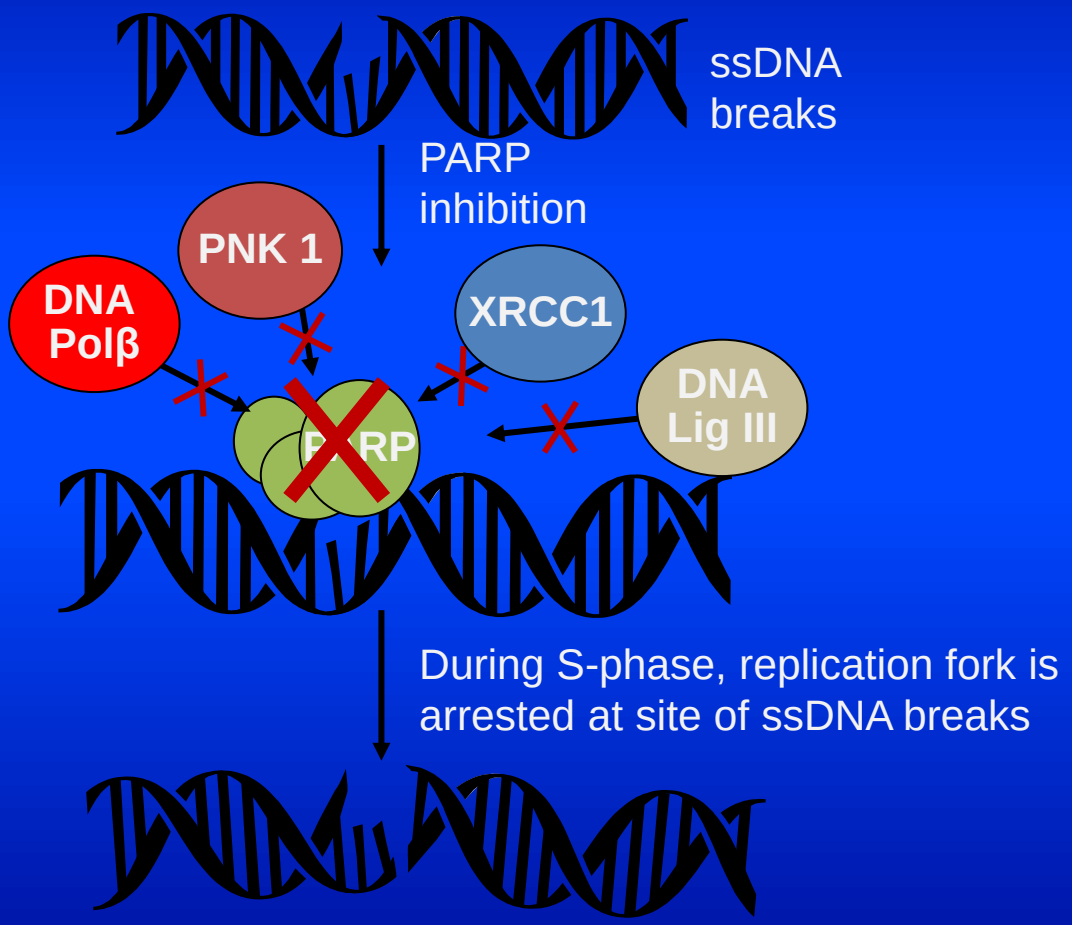
- A key role in the repair of ssDNA breaks via BER pathway
- Binds directly to sites of DNA damage
- Once activated, uses NAD as a substrate to add large, branched chains of poly(ADP-ribose) polymers (ie, PARylation) to itself and interaction partners
- Recruits other DNA repair enzymes to site of damage



Ohmoto A, et al. Onco Targets Ther. 2017;10:5195-5208.

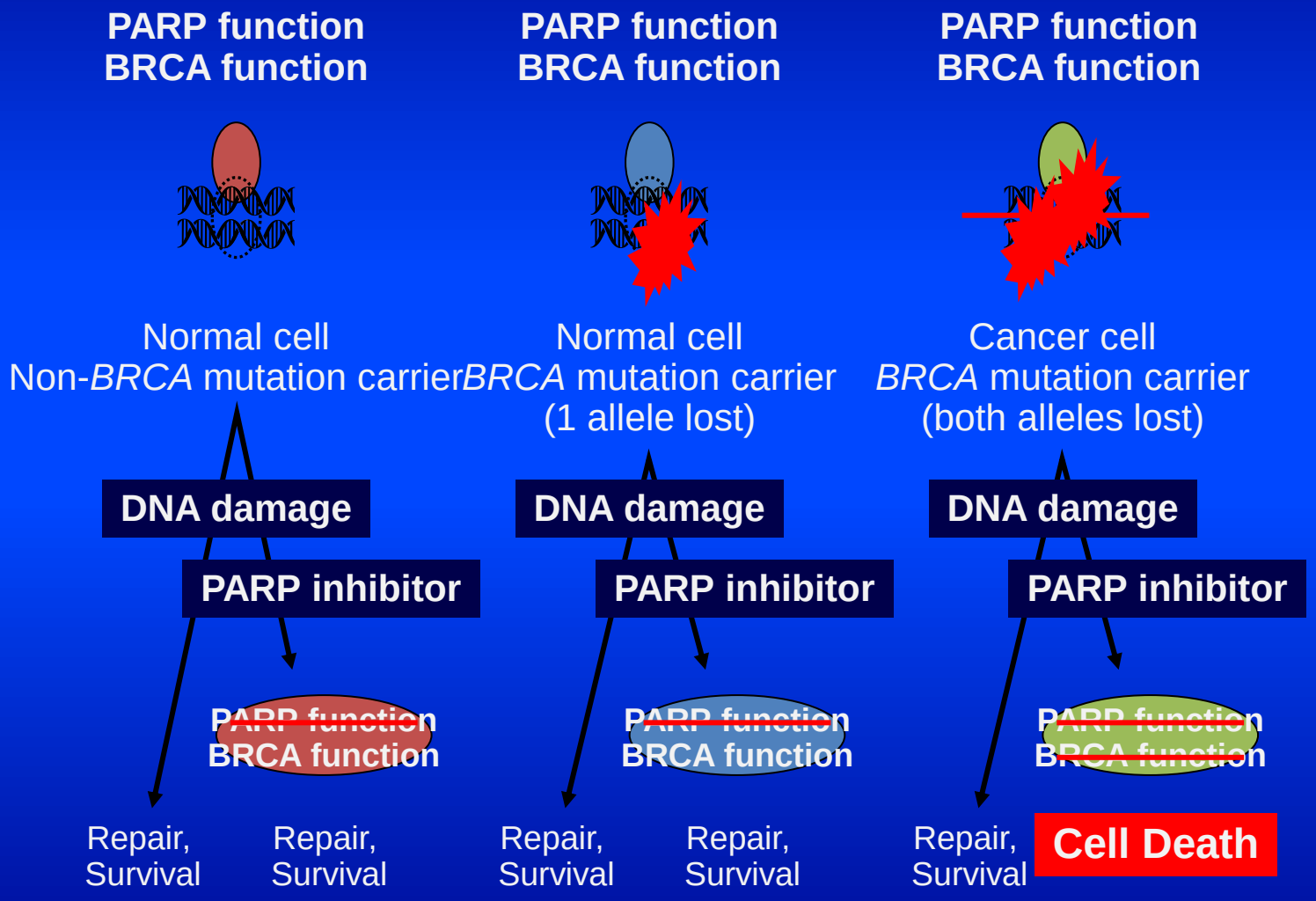
PARPi Leads to Increase in dsDNA Breaks

- Inhibition of PARP:
  - Prevents recruitment of DNA repair enzymes to ssDNA breaks, or traps PARP on DNA
  - Leads to failure of ssDNA repair and accumulation of ssDNA breaks
  - Replication fork is arrested at damage, produces dsDNA breaks



Ohmoto A, et al. Onco Targets Ther. 2017;10:5195-5208.

Synthetic Lethality Hypothesis



Farmer H, et al. Nature. 2005;434:917-921. Bryant et al. Nature. 2005;434:913-917.

TOPARP

Phase II trial in men with metastatic CRPC

-Disease progression after 1-2 lines of chemotherapy

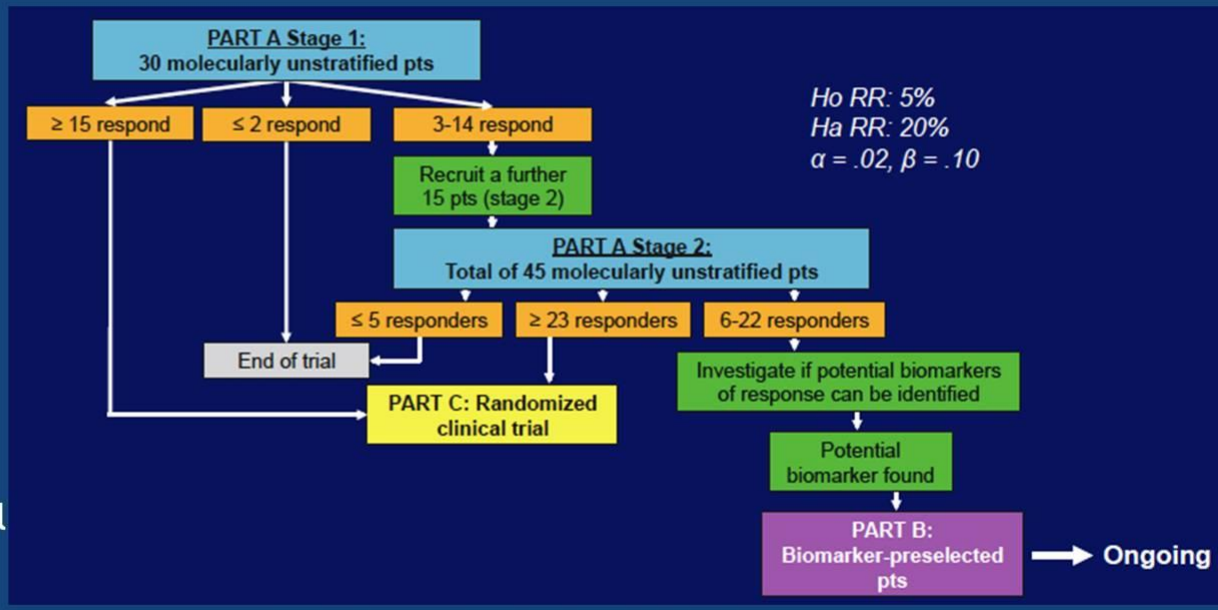
***80% of men ≥4 lines of treatment**

-ECOG PS 0-2

-Olaparib 400mg oral BD

Primary endpoint: Response

- Radiographic - RECIST 1.1
- PSA decline ≥50%
- CTC conversion (≥5 to <5 /7.5ml blood; confirmed)



N = 49 men evaluable in PART A

Figure: J de Bono; Mateo NEJM 2015

TOPARP Results: Response

ID	Max % Decline in PSA	Measurable Disease	Best RECIST Response	CTC / 7.5 mL Blood	Max % CTC Decline	Time on Tx, Wks
#1	85	No	--	87	100	73
#5	51	No	--	24	100	58
#6	29	Yes	SD	105	97.1	16
#8	47	No	--	38	94.7	62
#11	No decline	Yes	PD	6	83.3	12
#14	83	No	--	102	100	36
#15	80	Yes	PR	18	100	36
#16	88	Yes	PR	5	100	40 (ong)
#17	95	Yes	PR	8	100	24
#20	88	Yes	PR	< 5	100	48
#26	No decline	No	--	12	100	19
#30	70	No	--	100	100	44 (ong)
#35	96	Yes	PR	513	100	40 (ong)
#36	59	No	--	22	100	57
#39	68	Yes	PR	24	100	44 (ong)
#48	No decline	Yes	SD	9	100	39

ORR: 16 of 49 evaluable pts (33%)

- 14 of 16 (88%) biomarker-positive pts
- 2 of 33 (6%) biomarker-negative pts

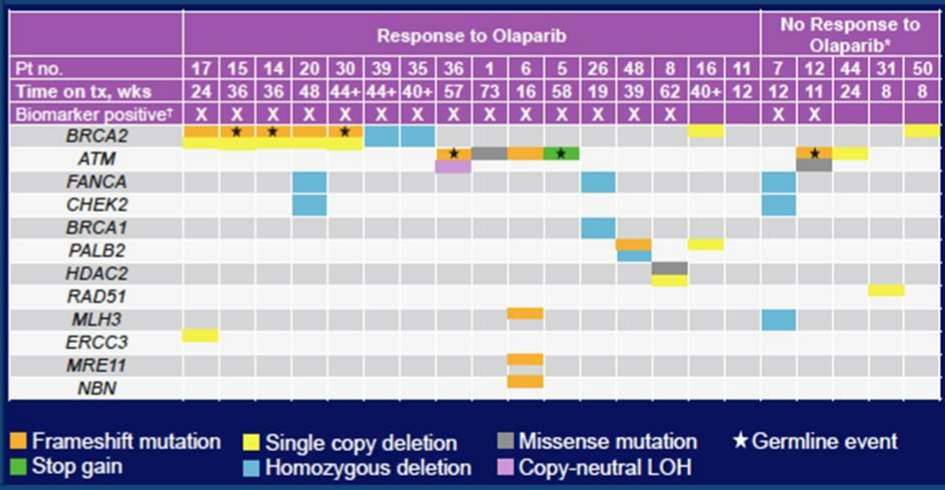


Figure: J de Bono; Mateo NEJM 2015

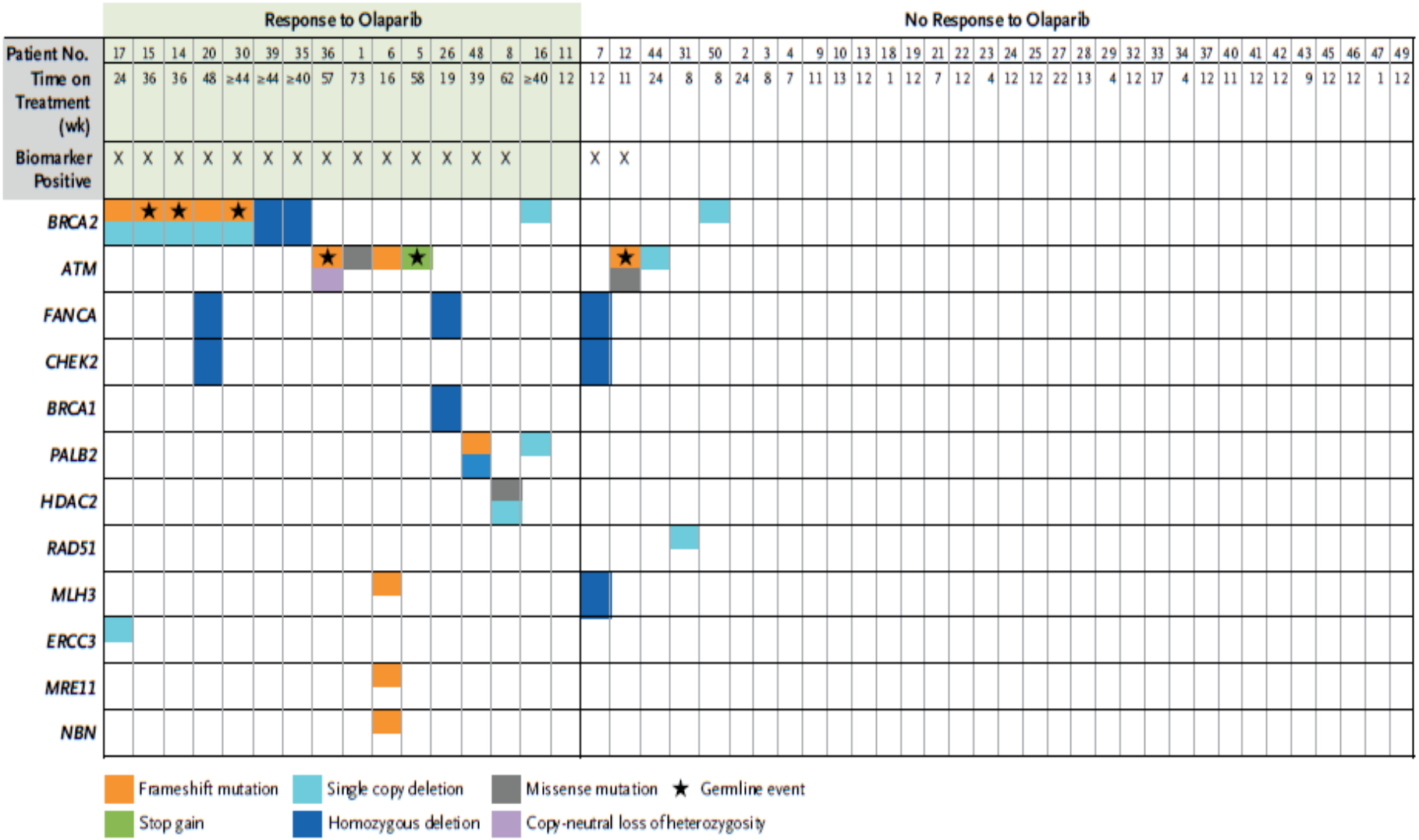
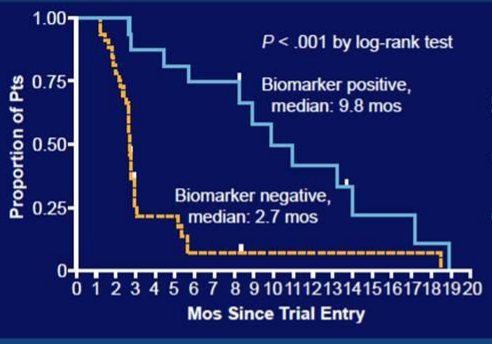


Figure 1. Genomic Aberrations in DNA Repair in Patients with Metastatic, Castration-Resistant Prostate Cancer.

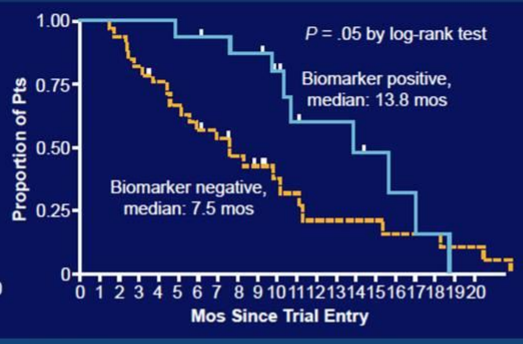
Data are shown for the 49 patients who could be evaluated for a response. Mutations and deletions in DNA-repair genes were identified through next-generation sequencing studies. Green shading indicates patients who were classified as having a response to olaparib in the clinical trial. Patients were considered to be biomarker-positive if homozygous deletions, deleterious mutations, or both were detected in DNA-repair genes (but not single copy deletions without events detected in the second allele). A star indicates that a particular genomic event was detected in germline DNA. Archival tumor samples were used for the sequencing studies in Patients 13, 18, 21, 40, 41, and 49 because the biopsy samples obtained during the trial were negative for tumor content.

TOPARP Results

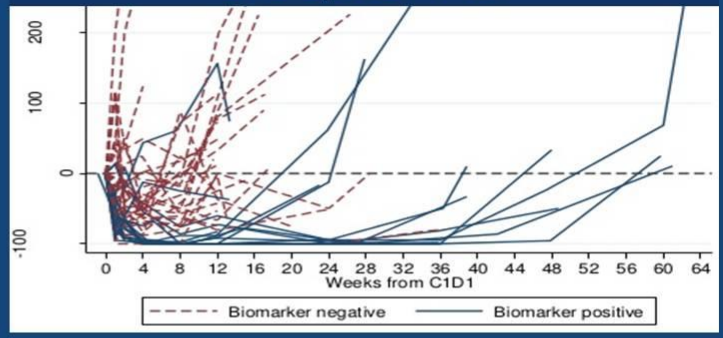
Radiographic PFS



Overall Survival



CTC Spider Plot



AEs in ≥ 20% of Patients, n (%)	All Grade	Grade ≥ 3
Anemia	38 (76)	10 (20)
Fatigue	29 (58)	6 (12)
Nausea	18 (36)	0
Arthralgia	15 (30)	1 (2)
Anorexia	14 (28)	1 (2)
Dyspnea	14 (28)	1 (2)
Back pain	11 (22)	1 (2)
Vomiting	10 (20)	0

Figure: J de Bono; Mateo NEJM 2015

Single Agent Trials In Progress

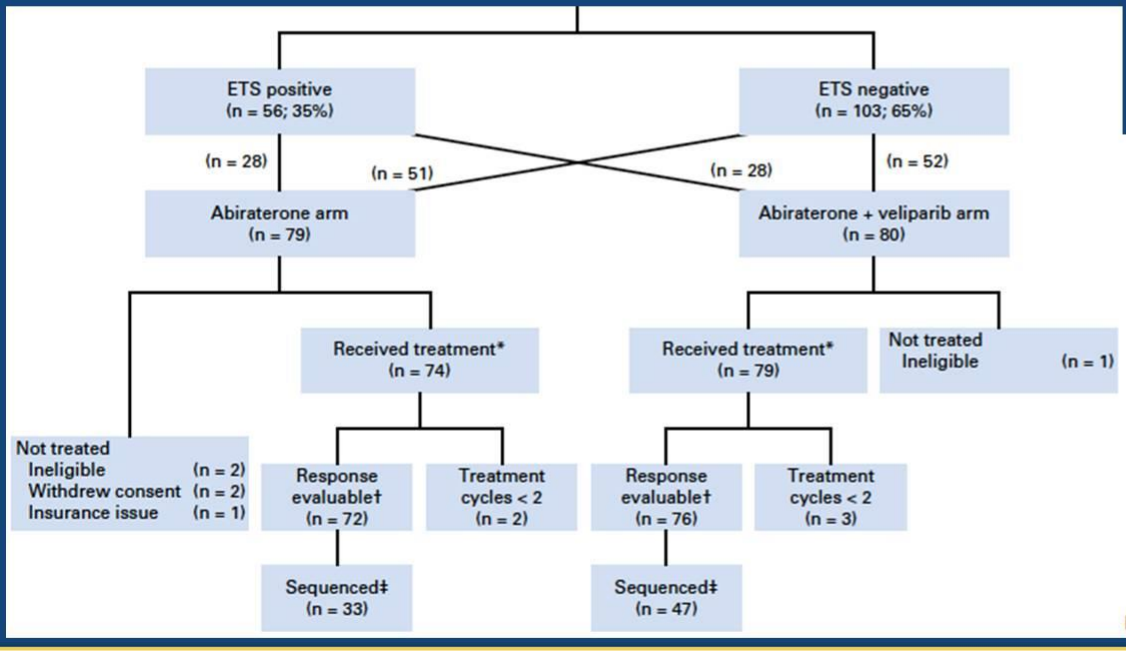
Drug	Clinicaltrials.gov ID; Trial name	Phase; Study size	Setting; Comparator (if applicable)	Primary Endpoint
Phase II in CRPC				
Olaparib **PART A COMPLETED**	NCT01682772	II N~89 (adaptive design)	mCRPC, post 1-2 taxane chemotherapy(ies)	RR
Niraparib	NCT02854436 Galahad	II N=160	mCRPC, post 1+ chemotherapy and 1+ AR-targeting agent(s)	ORR
Rucaparib	NCT02952534 TRITON2	II N=160	mCRPC, post 1+ chemotherapy and 1-2 AR-targeting agent(s)	ORR + PSA response
Talazoparib	NCT03148795	II N=100	mCRPC, post 1-2 chemotherapy and 1+ AR-targeting agent(s)	ORR
Olaparib	NCT03263650	II Randomized N=96	mCRPC with aggressive features; maintenance after 6 cycles cabazitaxel + carboplatin Olaparib vs. observation	PFS
Phase II in HSPC				
Olaparib	NCT03047135	II N=50	Biochemical recurrence post-RP; PSA doubling ≤6 months	PSA response
Rucaparib	NCT03413995 TRIUMPH	II N=30	mHSPC, not on ADT	PSA response
Phase III in CRPC				
Olaparib	NCT02987543 PROfound	III N=340	mCRPC, post 1+ AR-targeting agent(s) vs. Investigator choice (abiraterone / enzalutamide	rPFS
Rucaparib	NCT02975934 TRITON3	III N=400	mCRPC, chemotherapy-naïve vs. Investigator choice (abiraterone / enzalutamide / docetaxel)	rPFS

ASCO 2018 Education Book
As at Jan 2018

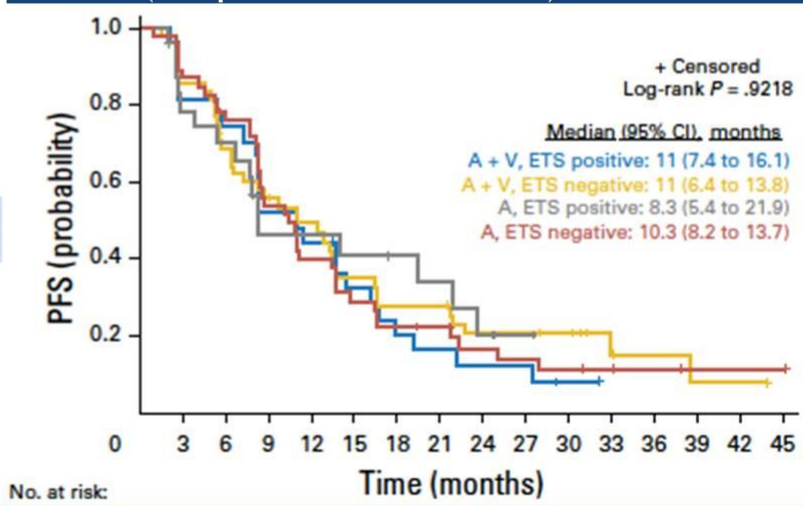
Combination Abiraterone +/- Veliparib (NCI 9012)

Randomised Phase II trial; biomarker stratified

Preclinical data supports synergy for AR targeting + PARP inhibition, especially in presence of an ETS fusion-positive tumor



No difference in response rate or PFS, irrespective of ETS status or treatment arm (despite DDR mutation):



Asim Nature Comm 2017; Hussain J Clin Oncol 2018

Combination Trials In Progress

Drug	Clinicaltrials.gov ID; Trial name	Phase; Study size	Setting; Comparator (if applicable)	Primary Endpoint
Veliparib	NCT01576172	II Randomized N=148	mCRPC, prior chemotherapy allowed Randomized: abiraterone +/- veliparib	PSA response
Olaparib	NCT01972217	II Randomized N=159	mCRPC, post docetaxel Randomized: abiraterone +/- olaparib	rPFS
Olaparib	NCT02893917	II Randomized N=90	mCRPC, post 1+ therapy for CRPC Randomized: olaparib +/- cediranib	rPFS
Olaparib	NCT03317392	I/II Randomized N=112	mCRPC with bone metastases Randomized: Ra-223 +/- olaparib	(Phase II) rPFS
Olaparib	NCT03012321	II Randomized N=70	mCRPC, post docetaxel Randomized to abiraterone / olaparib / combination	PFS
Rucaparib	NCT03338790 CheckMate 9KD	II Randomized N=300	mCRPC, prior chemotherapy allowed Randomized to nivolumab + one of: rucaparib / docetaxel / enzalutamide	ORR + PSA response
Talazoparib	NCT03395197 TALAPRO-3	III N=444	mCRPC, chemotherapy-naïve Randomized to AR-targeting agent +/- talazoparib	rPFS

PLUS:

Other DDR targets being tested in Phase I-II trials:

Chk1/2 (Prexasertib), DNA-PK (LY-3023414), WEE1, ATR, ATM, MTH1...

Clinical Data Extrapolations

	Olaparib	Niraparib	Rucaparib	Talazoparib	Veliparib
Relative PARP-trapping potency	1	~2	1	~100	<0.02

Olaparib, Rucaparib, Niraparib have FDA approval in ovarian cancers

Similar magnitudes of efficacy shown

- Differed by mutation status; number of prior therapies

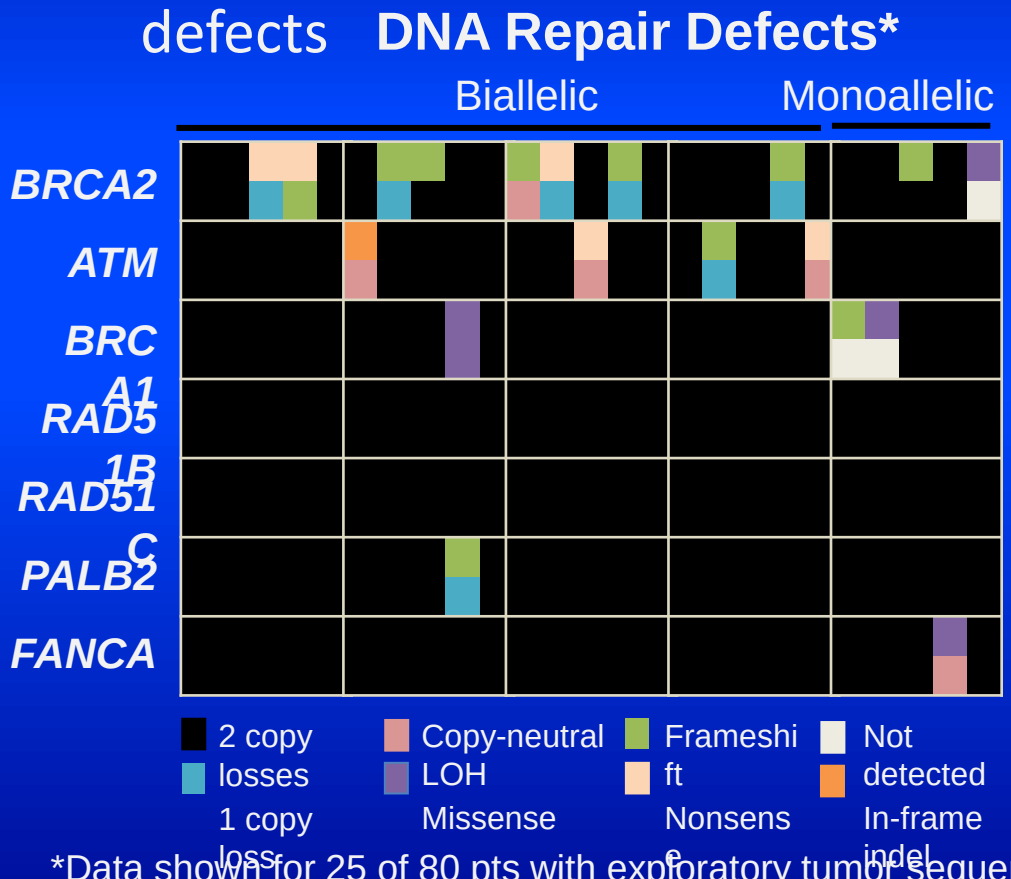
Similar AE profiles [SOLO2, NOVA, ARIEL2 trials]:

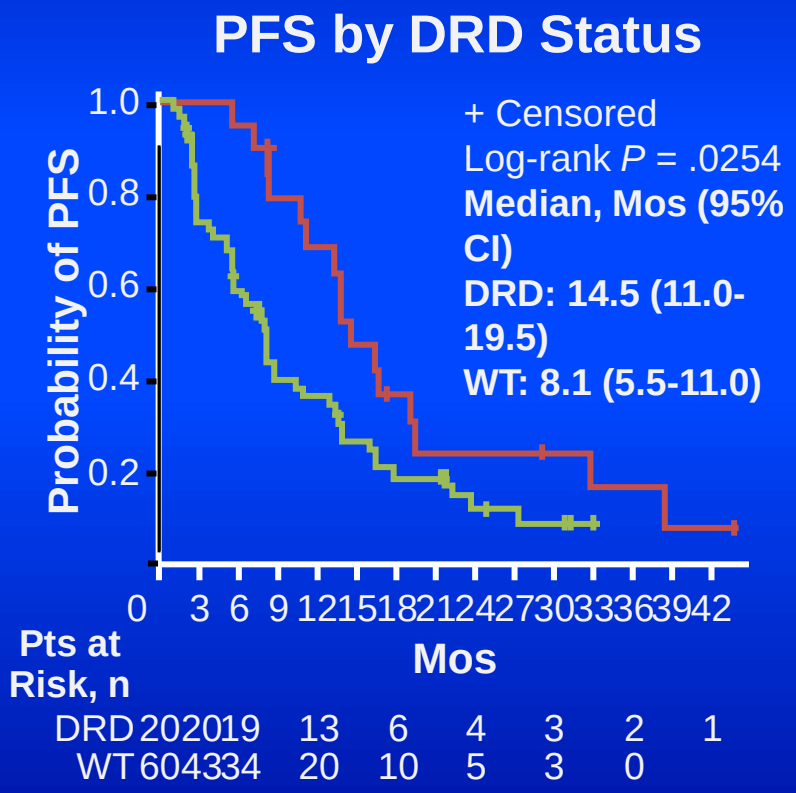
	All Grade	Grade 3-4
Anemia	37-50%	19-25%
Neutropenia	18-30%	5-20%
Nausea	74-75%	3-4%
Fatigue	60-69%	4-8%

DNA Repair Defects and Hormonal Therapy

Abiraterone in mCRPC With HR Deficiency

- 20/80 (25%) evaluable pts with mCRPC had DNA repair defects

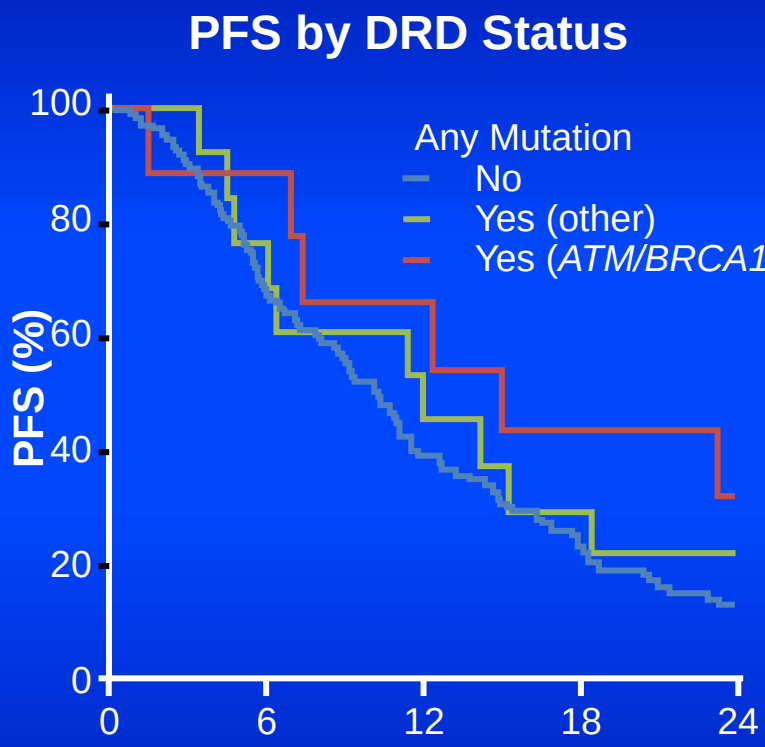




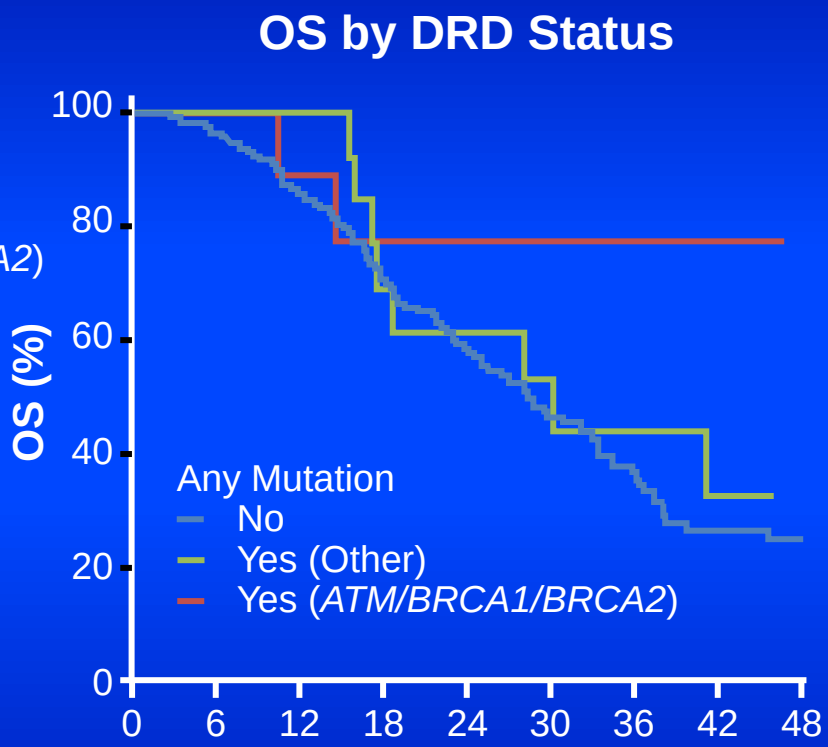
*Data shown for 25 of 80 pts with exploratory tumor sequencing.

Hussain M, et al. J Clin Oncol. 2017;[Epub ahead of print].

Abiraterone or Enzalutamide and HR Deficiency



Pts at Risk, n					
No	150	102	60	38	18
Yes (other)	13	9	6	4	3
Yes (*ATM/BRCA1/BRCA2*)	9	8	6	4	3

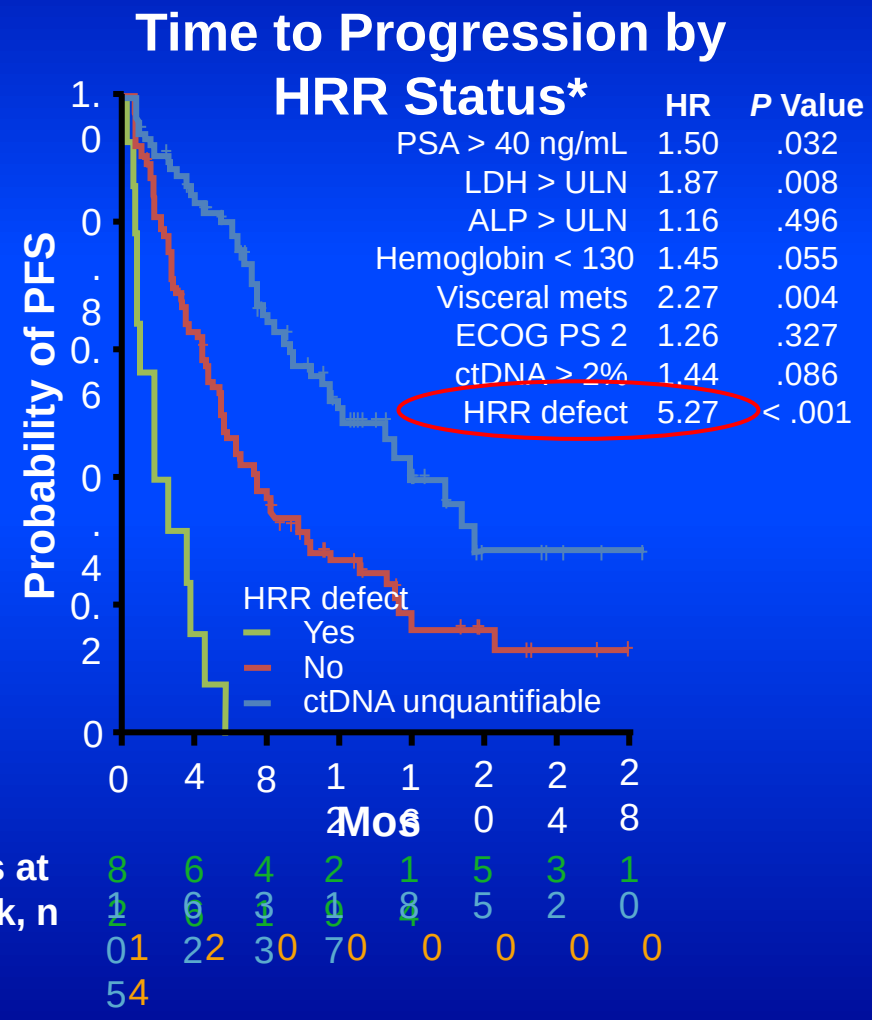


Pts at Risk, n									
No	150	145	128	75	75	52	35	22	11
Yes (other)	13	13	13	9	8	6	5	3	0
Yes (*ATM/BRCA1/BRCA2*)	9	9	8	7	6	4	4	4	0

Antonarakis ES, et al. Eur Urol. 2018. In press.

Abiraterone vs Enzalutamide and HR Deficiency

- Randomized phase II crossover study in treatment-naive pts with mCRPC (N = 202)
- *BRCA2*- or *ATM*-truncating mutations or rearrangements:
  - Somatic (ctDNA): 6/115 (5.2%)
  - Germline (WBC): 8/202 (4.0%)
- Monoallelic *BRCA2* or *ATM* deletion in 21 pts
  - No TTP differences (*P* = .205)



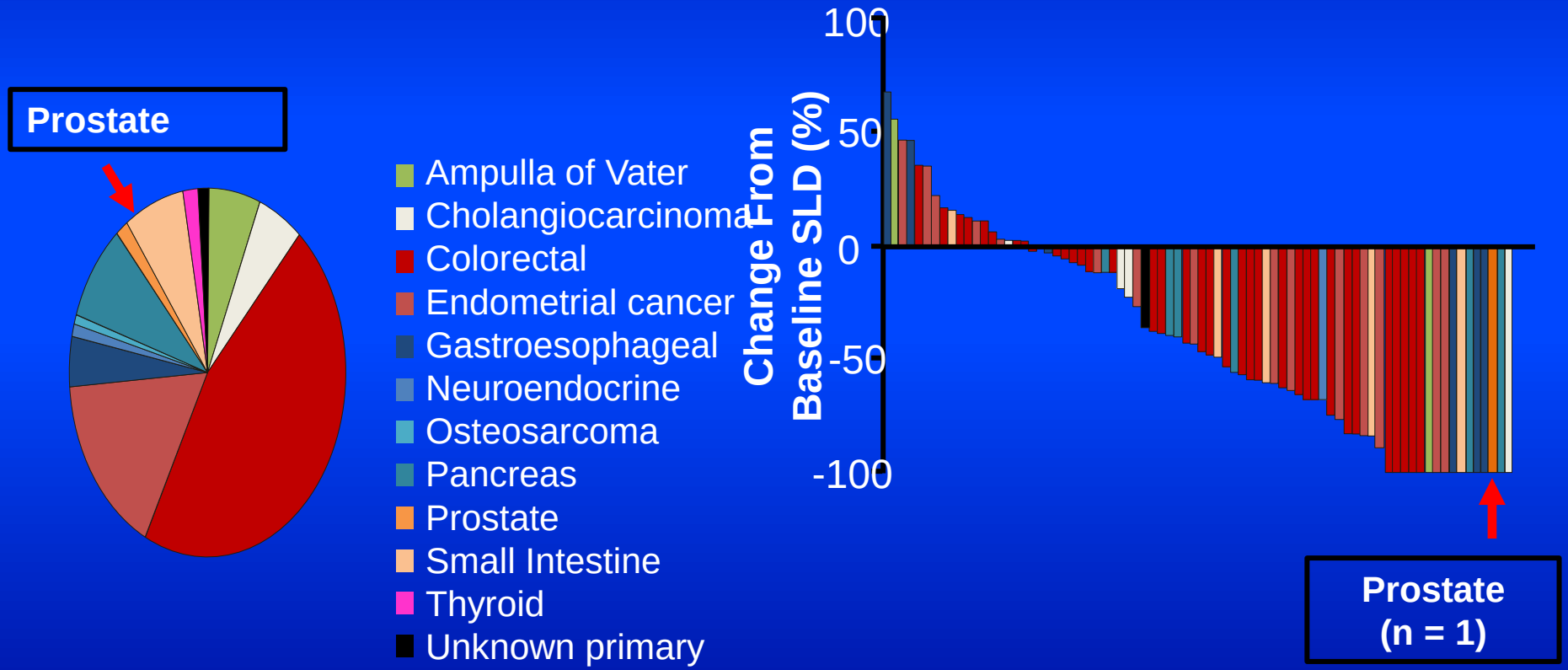
Annala M, et al. Cancer Discov. 2018;[Epub ahead of print].

*Abiraterone + enzalutamide arms combined.

DNA Repair Defects and Immune Checkpoint Inhibitors

KEYNOTE-016: Responses to Pembrolizumab in MMR-Deficient Tumors

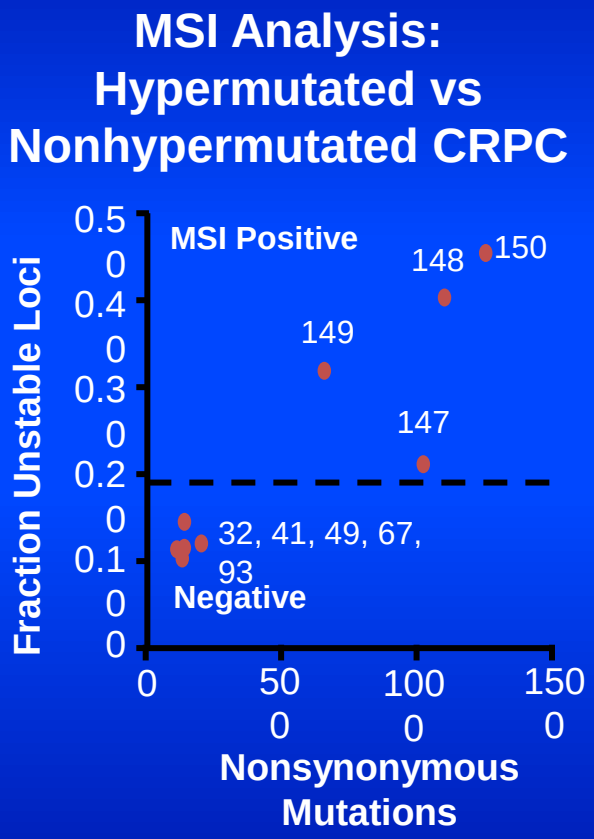
- Radiographic responses across 12 tumor types at 20 wks (N = 86)



Le DT, et al. Science. 2017;357:409-413.

MMR Mutations in mCRPC

- 4/150 (2.7%) mCRPC pts were MSI-high, 3 of whom had MMR mutations (2%)
  - 13 mut/Mb (Pt #149) – *MSH2*
  - 21 mut/Mb (Pt #147) – no MMR mutation
  - 23 mut/Mb (Pt #148) – *MSH2*
  - 25 mut/Mb (Pt #150) – *MSH2* and *MLH1*



Robinson D, et al. Cell. 2015;161:1215-1228.

MMR Mutations Can Cause HRD Mutations

Patient Case	Gene	Mutation
Primary MMR mutation	▪ MSH2	E809X* + LOH = MSI-high (> 100 mut/Mb)
Secondary DNA-repair mutations	▪ BRCA2 ▪ ERCC4 ▪ ERCC5 ▪ FANCM ▪ MSH6	▪ E1646fs* ▪ M361fs* ▪ E474fs* ▪ V1336fs* ▪ F1104fs*

*Protein truncation by stop codon (X) or frameshift (fs).

- This patient should be treated with a PD-1 inhibitor, not a PARP inhibitor

MMR Defects in Prostatic Ductal Carcinoma

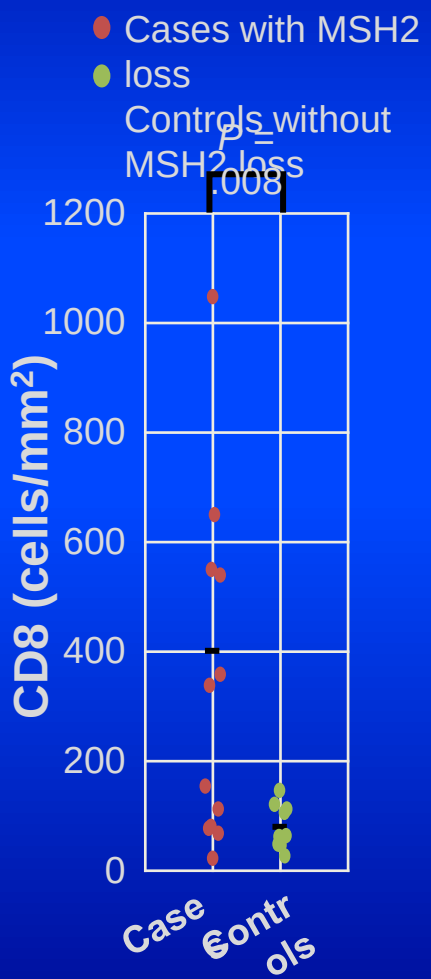
- 4/10 (40%) had MMR mutations; 3/10 (30%) had MSI and hypermutation

Pt No.	Ductal Component for NGS, %	Est. Tumor Content From NGS, %	MMR Gene Alteration	HR Gene Alteration	Hyper-mut	Total Coding Muts/1.2 Mb Sequenced
1	71	30	No	CHEK2 c.1100delC + LOH	No	4
2	45	40	MSH2 inversion	No	No	4
3	65	60	No	No	No	4
4	30	60	MSH6 c.1900_1901del + LOH	No	Yes	29
5	97	50	MSH2-GRHL2 rearrangement + LOH	No	Yes	34
6	99	50	No	No	No	5
7	25	0	--	--	--	--
8	31	70	No	No	No	5
9	35	10	No	BRCA2 c.594delT + likely LOH	No	3
10	--	60	MLH1 exon 19+ 3'UTR homozygous deletion	No	Yes	32

Schweizer MT, et al. Oncotarget. 2016;7:82504-82510.

MMR Defects and Gleason Grade

- 1.2% (14/1176) of primary adenocarcinomas and NEPC had MSH2 protein loss by IHC
- Pathology and MSH2 loss
  - Primary Gleason pattern 5 enriched for MSH2 loss: 8% (7/91)
  - MSH2 loss in pts with any other Gleason score: < 1% (5/1042)
  - $P < .05$

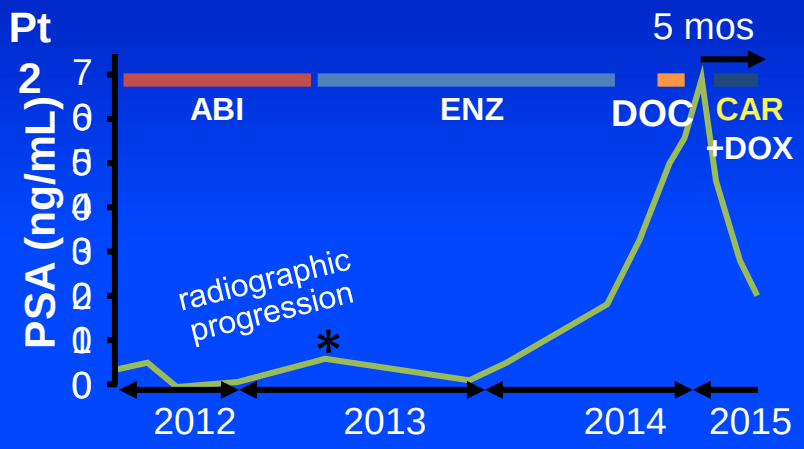


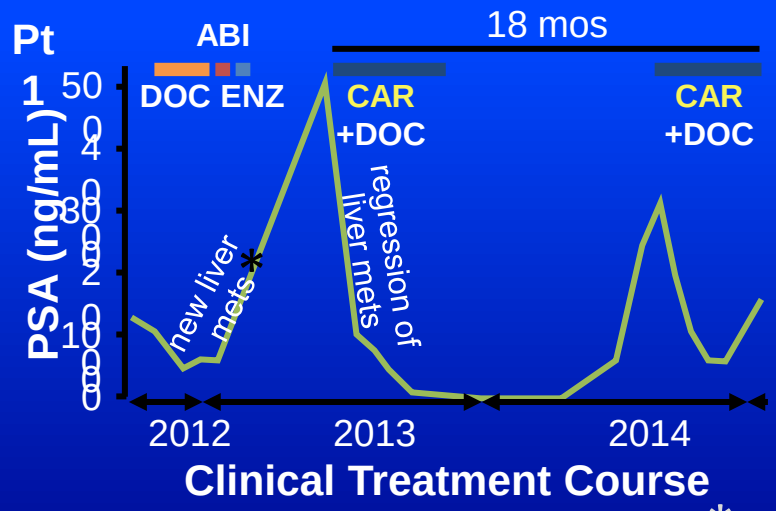
Guedes LB, et al. Clin Cancer Res. 2017;23:6863-6874.

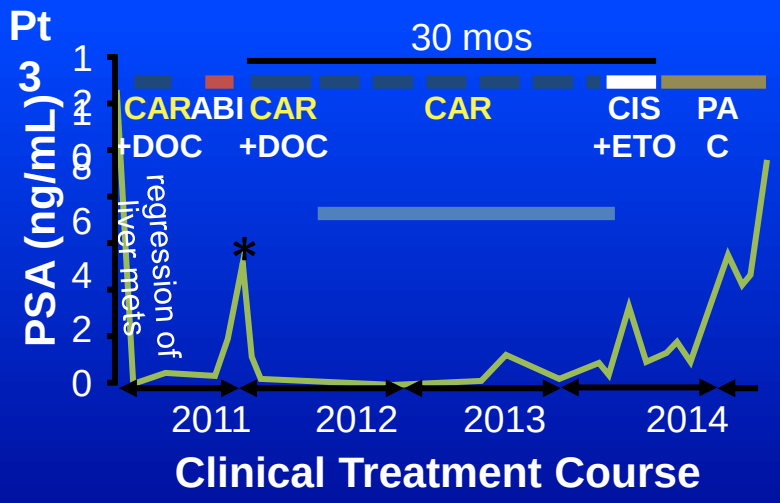
DNA Repair and Platinum Chemotherapy

Platinum Response in mCRPC With HR Deficiency

Pt	Allele	BRCA2 Mutation	Mutation Type
1	1	c.9196C>T; p.Q3066X	Premature stop
	2	127 bp del in exon 11	Fs deletion
2	1	c.8904delC; p.V2969Cfs *7	Fs deletion
	2	c.2611delT; p.S871Qfs *3	Fs deletion
3	1	Homozygous copy loss	Copy loss
	2	Homozygous copy loss	Copy loss







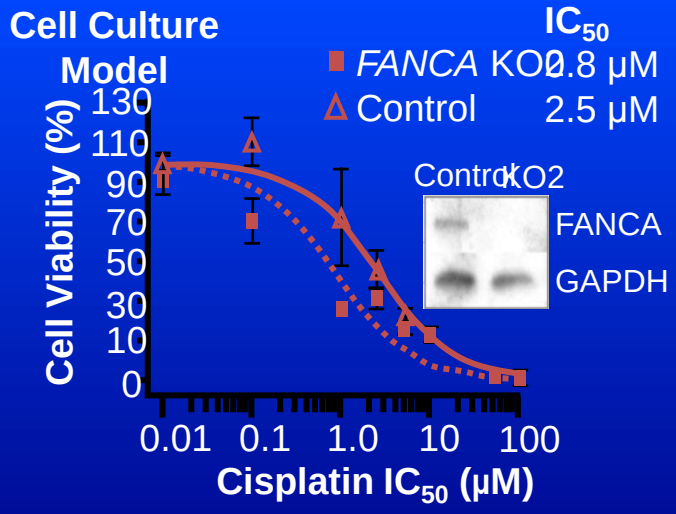
Cheng H, et al. Eur Urol. 2016;69:992-995.

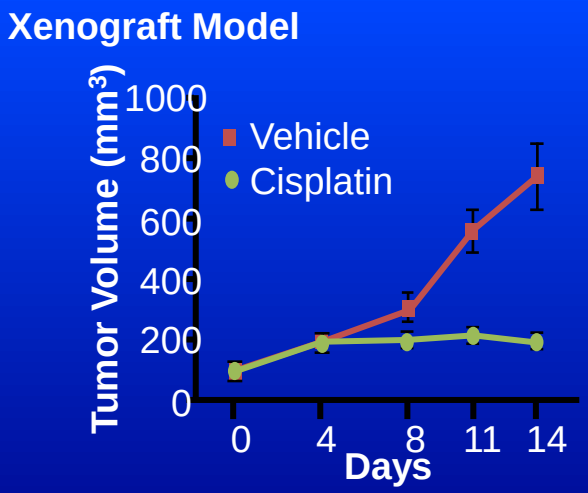
*Time of metastatic biopsy.

Platinum Response in mCRPC With *FANCA* Deficiency

- Near-CR to cisplatin/docetaxel in a pt with metastatic NEPC, lasting 12 mos
  - Genome of metastatic tumor found to be highly altered; germline *FANCA* mutation (S1088F) with somatic LOH also identified
  - In preclinical studies, loss of *FANCA* associated with increased cisplatin sensitivity

Increased Cisplatin Sensitivity With Loss of *FANCA*



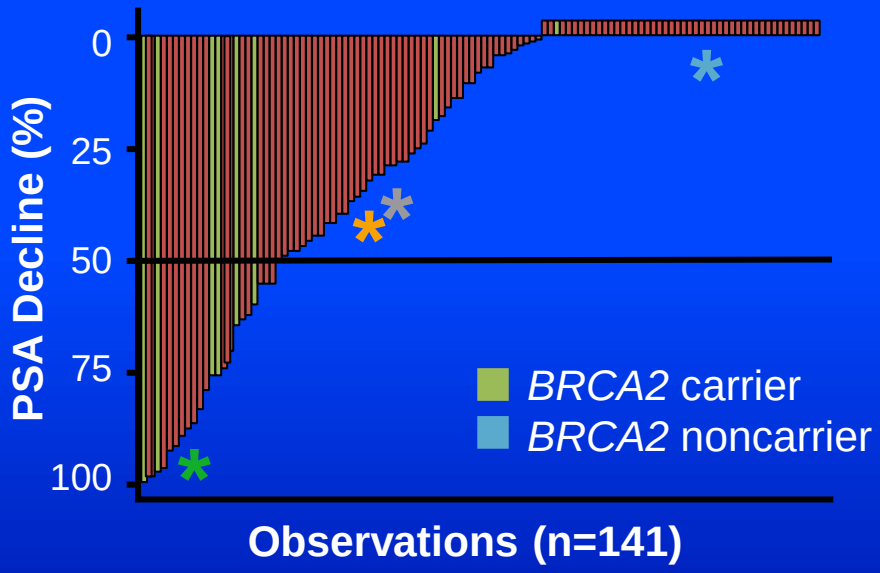


Beltran H, et al. JAMA Oncol. 2015;1:466-474.

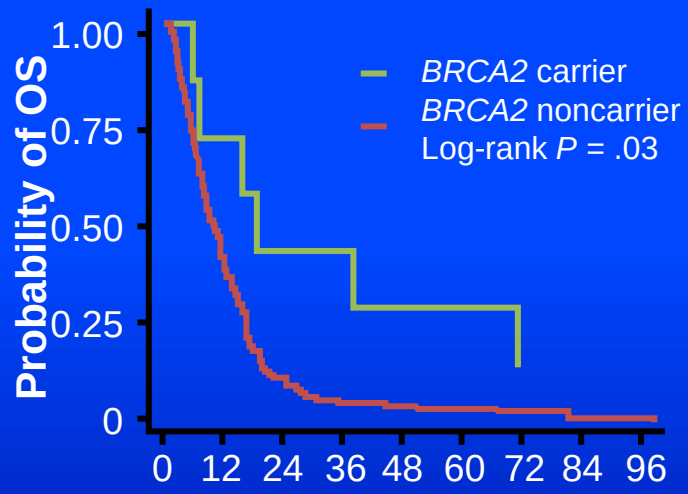
HR Deficiency and Response to Carboplatin

- 8/141 (5.7%) men with mCRPC had pathogenic germline *BRCA2* variants

PSA Response With Carboplatin/Docetaxel by *BRCA2* Carrier Status



OS With Carboplatin/Docetaxel by *BRCA2* Carrier Status



Pts at Risk, n									
BRCA2 noncarrier	133	51	14	6	5	3	2	1	1
BRCA2 carrier	8	5	3	3	2	2	0	0	0

*Carriers of pathogenic germline variants in other DNA repair genes (*MSH2*, *ATM*, *BLM*, *FANCA*).

Pomerantz MM, et al. Cancer. 2017;123:3532-3539.

Conclusions

- Not all DNA repair lesions are created equal
- Somatic (and germline) DNA repair mutations are common in prostate cancer, particularly mCRPC
- HRD mutations may sensitize to PARP inhibitors, platinum agents
- MMR mutations may sensitize to immune checkpoint inhibitors
- The role of germline vs somatic, and single- vs double-copy inactivation, remains unclear

Grazie!!!!!