XXIV SIMPOSIO DE REVISIONES EN CÁNCER

"Tratamiento médico del cáncer en el año 2022"

Integración de la medicina de precisión en la secuencia terapéutica del cáncer de próstata avanzado

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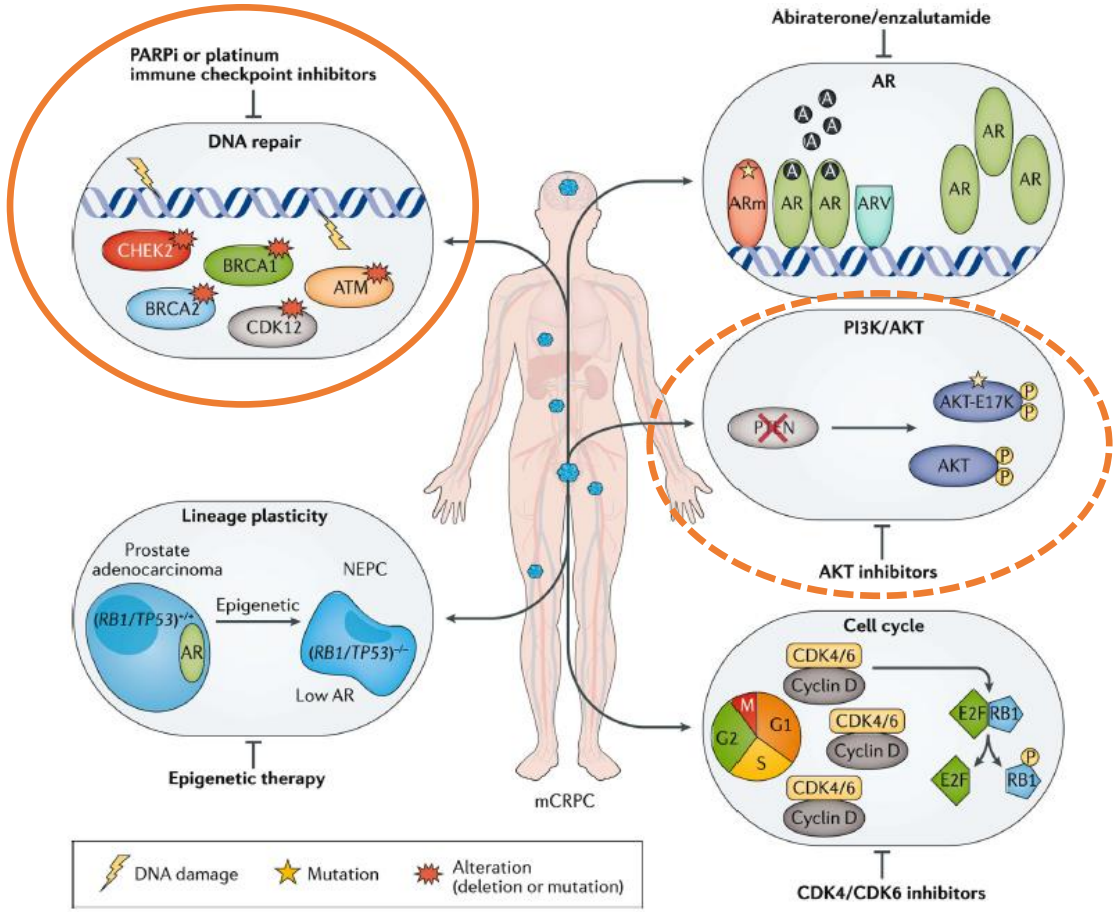
ARÁN

DISCLOSURE

I have the following potential conflicts of interest:

- Participation in advisory boards: *AstraZeneca, Bayer, Janssen, MSD, Pfizer*
- Research funding paid to my institution*: AstraZeneca, Bayer, Janssen, Synlab*
- Speaker fees: Astra Zeneca, Astellas, *Bayer, Clovis, Janssen, MSD, Pfizer*
- Travel, accomodation: *AstraZeneca, Astellas, Bayer, Janssen.*

Precision medicine for advanced prostate cancer



Drug	Ongoing clinical trials [a,b]	
PARP inhibitors [c]		
BGB-290	NCT03712930/EudraCT 2018-002587-28	NCT03150810/EudraCT 2017-001553-14
Niraparib	NCT03431350/EudraCT 2017-003552-23	
Rucaparib [d]	NCT02975934/EudraCT 2016-003163-20 NCT04179396 NCT04253262	NCT04276376/EudraCT 2018-001744-62 NCT04455750
Olaparib [d]	NCT03012321 NCT03317392 NCT03434158/EudraCT 2017-001469-26	NCT03787680 NCT03874884 NCT04556617
SC10914	NCT04486937	
SHR3162	NCT04108247	
Talazoparib	NCT03395197/EudraCT 2017-003295-31	NCT04019327
PD-1 inhibitors [e]		
Nivolumab	NCT03061539/EudraCT 2016-004091-21	NCT03570619
Pembrolizumab [d]	NCT02861573/EudraCT 2016-002312-41 NCT03248570 NCT03454451 NCT03506997/EudraCT 2017-000931-15 NCT03565445 NCT03658447 NCT03792841 NCT03799003	NCT03834493/EudraCT 2018-004117-40 NCT03834506/EudraCT 2018-004116-22 NCT03834519/EudraCT 2018-004118-16 NCT03805594 NCT03910660/EudraCT 2018-003734-32 NCT04090528 NCT04104893 NCT04471974
AKT inhibitors [f]		
Capivasertib	NCT02525068/EudraCT 2013-004091-34	NCT04087174
Ipatasertib	NCT04404140	
Other drugs/combinations being tested in patients with mCRPC with specific genomic characteristics [g]		
Cabazitaxel	NCT03050866/EudraCT 2016-002993-11	NCT03903835/EudraCT 2018-002350-78
Carboplatin + docetaxel	NCT02598895	NCT02985021
Carboplatin	EudraCT 2019-002104-40 NCT02955082/EudraCT 2016-000869-23	NCT03652493 NCT03903835/EudraCT 2018-002350-78
Docetaxel	NCT03903835/EudraCT 2018-002350-78	
Ipilimumab	NCT03061539/EudraCT 2016-004091-21 NCT03570619	NCT04388852

Ku et al, Nat Rev Urol, 2019; Merseburger et al, Eur Urol 2021

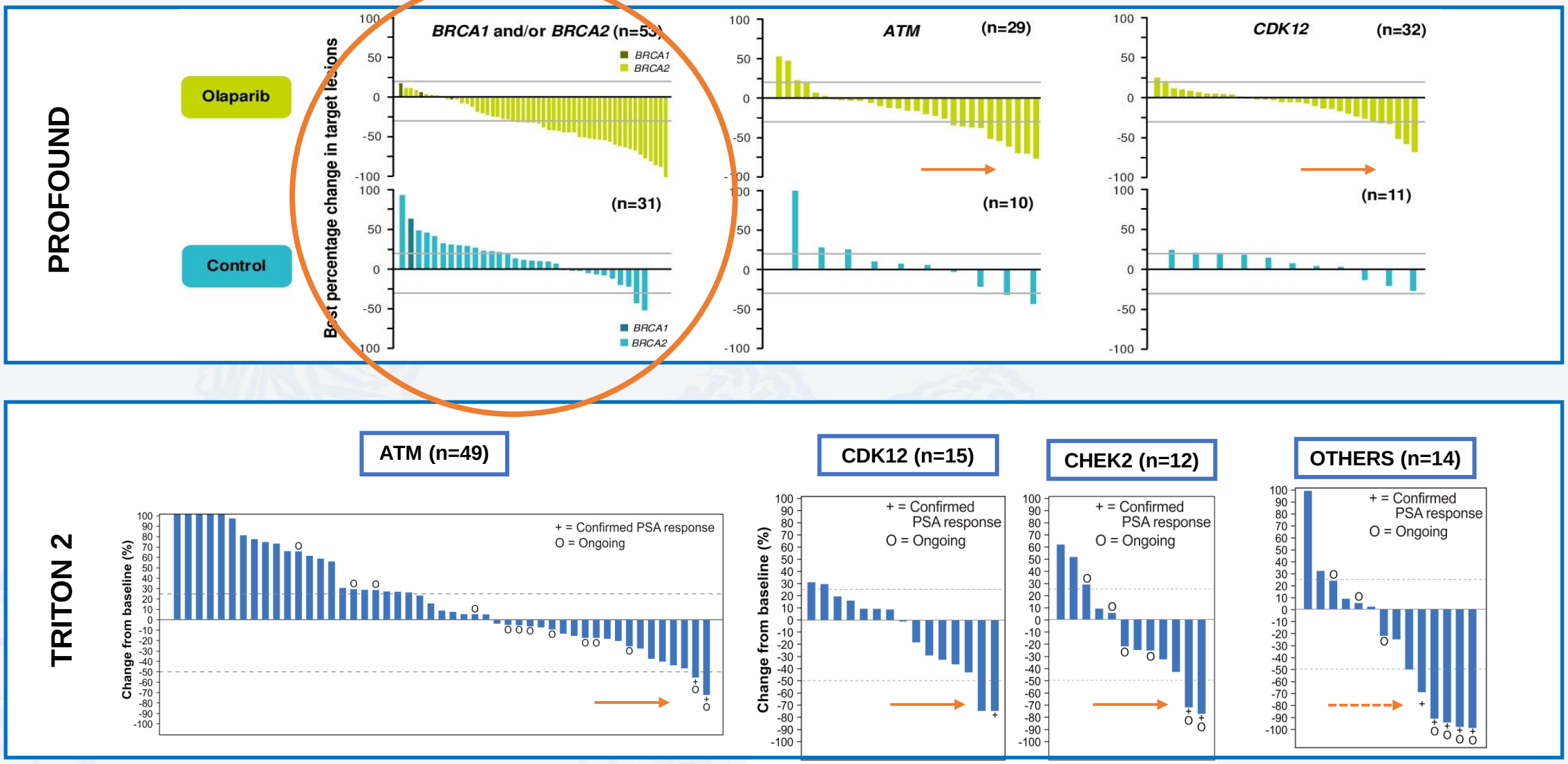
Trials of PARP inhibitor monotherapy in mCRPC

PARPi	Study	Study Population	Selected Outcomes	Study Result
Olaparib	TOPARP-A Phase II,[24] single arm, start date 7/2012, enrollment 50 patients	mCRPC, unselected for HRD mutations, previously received taxane therapy	Composite RR (PSA decline by ≥ 50%, objective tumor response, CTC reduction)	- Composite RR 33% entire population - Composite RR 88% HRD mutations - Composite RR 6% no HRD mutation
	TOPARP-B Phase II,[25] single arm, start date 4/1/2015, enrollment 98 patients	mCRPC, HRD selected, previously received taxane therapy	Composite RR (PSA decline by ≥ 50%, objective tumor response, CTC reduction)	- Composite RR 54% at 400 mg dose level - Composite RR 39% for 300 mg dose level
	PROfound Phase III,[26] compared to enzalutamide or abiraterone, start date 2/6/2017, enrollment 387 patients	mCRPC, HRD selected (cohort A: BRCA1, BRCA2, ATM mut, cohort B: 12 other pre-specific HRD genes), received second-generation hormonal agent and up to one taxane (or taxane-unfit)	Primary outcome rPFS in cohort A, secondary pre-specified outcome rPFS in cohort A+B, OS cohort A	- rPFS cohort A vs control 7.4 vs 3.6 mo - rPFS cohort A+B vs control 5.8 vs 3.5 mo - OS cohort A vs control 18.5 mo vs 15.1 mo
Rucaparib	TRITON2 Phase II,[27,28] single arm, start date 2/15/2017, estimated enrollment 360 patients	mCRPC, HRD selected, received second-generation hormone agent and a taxane	ORR per RECIST/PCWG3 Secondary: PSA decline by ≥ 50%	- ORR for BRCA1/2 mut 43.5-50.8% - PSA response for BRCA1/2 mut 53.8% - ORR for ATM mut 10.5% - ORR for *CDK2* mut 0% - ORR for CHEK2 mut 11.1% - ORR for other HRD mut 28.6%
Niraparib	GALAHAD Phase II,[29] single arm, start date 8/31/2016, enrollment 291 patients	mCRPC, HRD selected bi-allelic, received second-generation hormone agent and a taxane	ORR by RECIST Composite RR (PSA decline by ≥ 50%, objective tumor response, CTC reduction)	- ORR for BRCA/2 mut 41% - Composite RR for BRCA1/2 mut 63% - ORR non-BRCA1/2 HRD mut 9% - Composite RR non-BRCA1/2 HRD mut 17%
Talazoparib	TALAPRO-1 Phase II,[30,31] single arm, start date 7/4/2017, estimated enrollment 100 patients	mCRPC, HRD selected, received second-generation hormone agent and a taxane	ORR per RECIST	- ORR: 30% - ORR for BRCA1/2 mut: 46% - Composite RR for BRCA1/2:72%

Abbreviations: PARPi, poly (ADP-ribose) polymerase inhibitors; mCRPC, metastatic castration-resistant prostate cancer; RR, response rate; HRD, homologous recombination deficiency; CTC, circulating tumor cells; Mut, mutation; rPFS, radiographic progression-free survival; OS, overall survival; mo, months; ORR, objective response rate.

Nizialek & Antonarakis. Cancer Manag Res, 2020

Sensitivity to PARP inhibitors depends on the gene altered



1. *Presented by Prof. de Bono at ASCO 2021; 2. Abida W, et al. J Clin Oncol.*

Current approvals of PARPi for prostate cancer

EMA, AEMPS

- OLAPARIB is indicated as monotherapy for the treatment of adult patients with mCRPC and ***BRCA1/BRCA2*** mutations (**germline and/or somatic**) who have progressed following prior therapy that included **an androgen receptor-directed therapy**

FDA

- OLAPARIB is a treatment option for patients with **mCRPC** and a pathogenic mutation (germline and/or somatic) in a HRR gene (***BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51C, RAD51D or RAD54L***) who have been treated previously with **androgen receptor-directed therapy**.

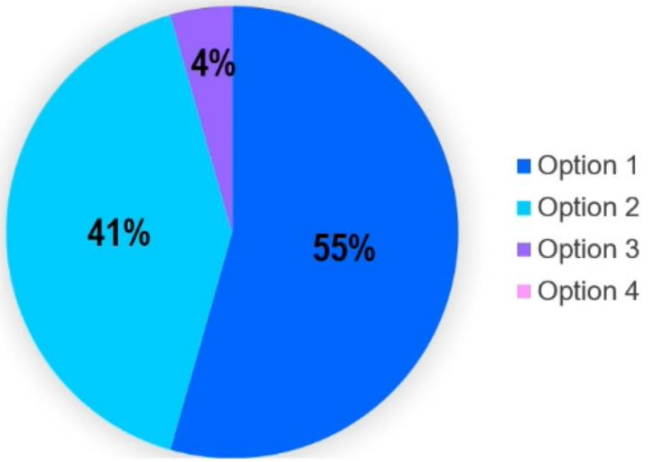
- RUCAPARIB is a treatment option of patients with mCRPC and a pathogenic ***BRCA1/BRCA2*** mutation (germline and/or somatic) who have been treated with **androgen receptor-directed therapy and a taxane based chemotherapy.** If the patients is not fit for chemotherapy, rucaparib can be considered even if taxane-based therapy has not been given.

Tumour (somatic) genomic profiling

APCCC ADVANCED PROSTATE CANCER CONSENSUS CONFERENCE www.apccc.org

101. In a patient with a pathogenic BRCA1/2 aberration (germline/somatic or somatic alone) when do you recommend introducing a PARP inhibitor therapy?

1. After one line of AR pathway inhibitor
2. After one line of AR pathway inhibitor and one line of chemotherapy
3. After one line of AR pathway inhibitor, one line of chemotherapy and Lutetium-PSMA
4. I don't recommend a PARP inhibitor in patients with BRCA1/2 aberration if another option is available
5. Abstain



Option	Votes
Option 1	37
Option 2	28
Option 3	3
Option 4	0
Abstain	4
Total votes	72

Preliminary results. For interpretation of results please refer to publication, which will follow shortly after APCCC 2021

PROfound study design

Documented evidence of mCRPC

Qualifying HRR mutation in tumour tissue (central review)

Investigator-assessed **radiographic progression on prior NHA** (e.g. abiraterone acetate and/or enzalutamide) **for mPC and/or CRPC**

ECOG PS 0–2

No prior treatment with a PARPi or any DNA-damaging cytotoxic chemotherapy for prostate cancer

Open-label

COHORT A*

BRCA1/2 or *ATM*

2:1

- Olaparib (300 mg BID tablets)
- Physician's choice†

→ Optional olaparib at BICR progression

COHORT B*

BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D, or *RAD54L*

2:1

- Olaparib (300 mg BID tablets)
- Physician's choice†

→ Optional olaparib at BICR progression

Second progression and survival follow-up
Subsequent anti-cancer therapy at investigator's discretion

Primary endpoint:

- rPFS by BICR in Cohort A, using RECIST 1.1 (soft tissue) and PCWG3 (bone) criteria

Key secondary endpoints:

- BICR-confirmed ORR (Cohort A)
- rPFS by BICR (Cohort A + B)
- Time to pain progression (Cohort A)
- Overall survival (Cohort A)
- Safety and tolerability

Patient randomisation will be stratified by:

- Prior taxane therapy (yes/no)
- Measurable disease at baseline (yes/no)

†Physician's choice of either enzalutamide (160 mg qd) or abiraterone (1000 mg qd plus prednisone [5 mg bid])

BICR=blinded independent central review; BID=twice daily; CRPC=castration-resistant prostate cancer; EGOC PS=Eastern Cooperative Oncology Group Performance Score; HRRm=homologous recombination repair mutation; mCRPC=metastatic castration-resistant prostate cancer; mHSPC=metastatic hormone-sensitive prostate cancer; mPC=metastatic prostate cancer; NHA=new hormonal agent; nmCCRPC=non-metastatic castration-resistant prostate cancer; ORR=objective response rate; PARP=poly(ADP-ribose) polymerase; PARPi=poly(ADP-ribose) polymerase inhibitor; PCWG3=Prostate Cancer Working Group 3; PS=performance status; RECIST=Response Evaluation Criteria in Solid Tumours; rPFS=radiographic progression-free survival

1. de Bono J, et al. Presented at ESMO 2019, 27th September – 1st October, Barcelona. Abstract 847PD; 2. ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT02987543 (last accessed April 2020); 3. de Bono JS et al. Poster presented at: ASCO Annual Congress; June 2–6, 2017; Chicago, IL. Abstract TPS5091

PROfound study design

Documented evidence of mCRPC

Qualifying HRR mutation in tumour tissue (central review)

Investigator-assessed **radiographic progression on prior NHA** (e.g. abiraterone acetate and/or enzalutamide) **for mPC and/or CRPC**

ECOG PS 0–2

No prior treatment with a PARPi or any DNA-damaging cytotoxic chemotherapy for prostate cancer

65% had previously received taxanes

Control arm: 2nd ARTi

Open-label

COHORT A*

BRCA1/2 or *ATM*

2:1

- Olaparib (300 mg BID tablets)
- Physician's choice†

COHORT B*

BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D, or *RAD54L*

2:1

- Olaparib (300 mg BID tablets)
- Physician's choice†

Optional olaparib at BICR progression

Second progression and survival follow-up
Subsequent anti-cancer therapy at investigator's discretion

Primary endpoint:

- rPFS by BICR in Cohort A, using RECIST 1.1 (soft tissue) and PCWG3 (bone) criteria

Key secondary endpoints:

- BICR-confirmed ORR (Cohort A)
- rPFS by BICR (Cohort A + B)
- Time to pain progression (Cohort A)
- Overall survival (Cohort A)
- Safety and tolerability

Patient randomisation will be stratified by:

- Prior taxane therapy (yes/no)
- Measurable disease at baseline (yes/no)

†Physician's choice of either enzalutamide (160 mg qd) or abiraterone (1000 mg qd plus prednisone [5 mg bid])

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1. de Bono J, et al. Presented at ESMO 2019, 27th September – 1st October, Barcelona. Abstract 847PD; 2. ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT02987543 (last accessed April 2020); 3. de Bono JS et al. Poster presented at: ASCO Annual Congress; June 2–6, 2017; Chicago, IL. Abstract TPS5091

TRITON3: Rucaparib vs physician's choice therapy in mCRPC with HRR gene alterations

- Randomized, ongoing, multicenter, open-label phase III study

mCRPC patients
BRCA1/2* or *ATM alterations
Disease progression on ARTi†
No previous chemo for mCRPC
No previous PARPi
ECOG PS 0/1
(planned N = 400)

2:1

Rucaparib 600 mg BID x 28-day cycles (n = 267)

Physician's Choice* (n = 133)

Until radiographic progression or discontinuation for other reason

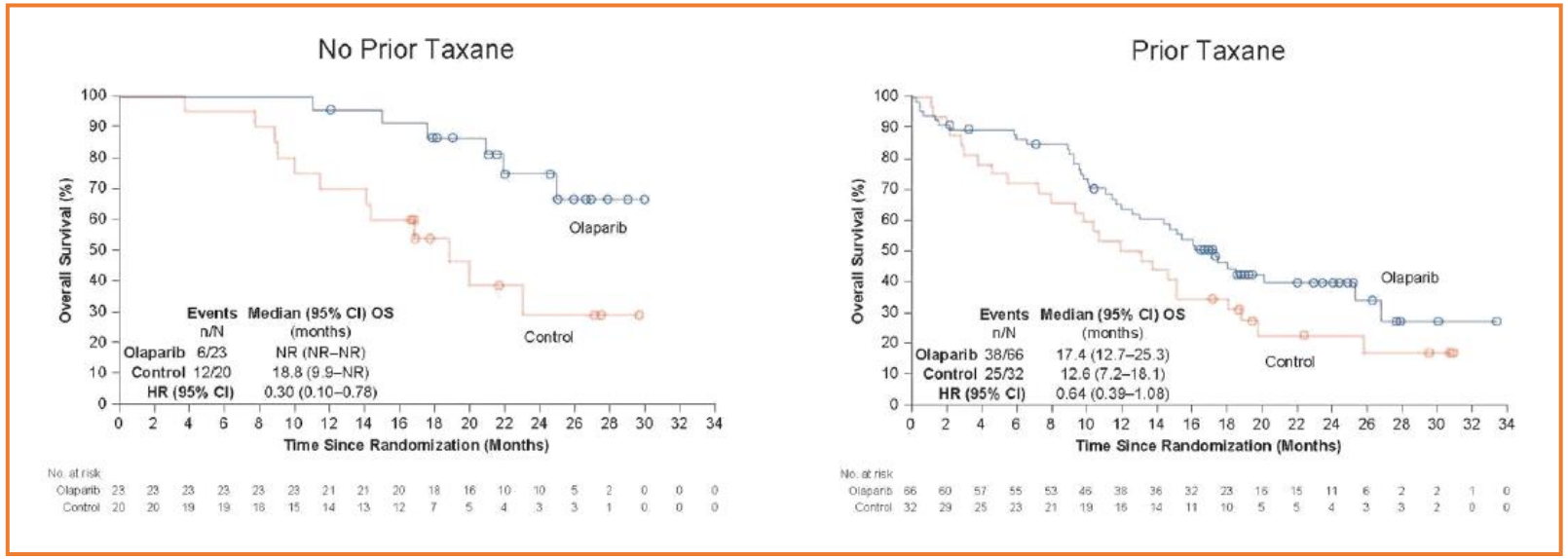
Crossover from CT to rucaparib optional following PD

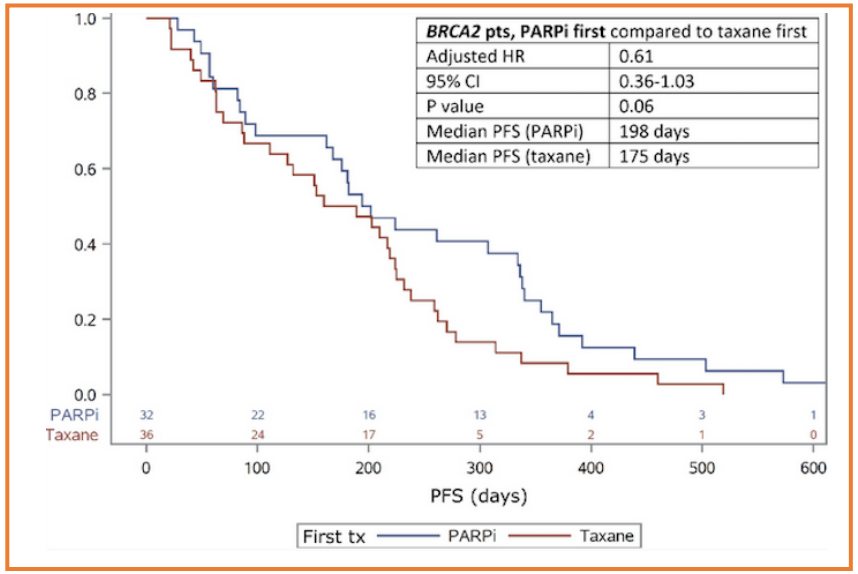
Primary endpoints: rPFS by IRR‡

*Docetaxel + prednisone 75 mg/m^2 in 21-day cycles (max 10 cycles) or abiraterone + prednisone 1000 mg QD or enzalutamide 160 mg QD.
†Abiraterone, enzalutamide, or investigational agent.
‡Modified RECIST to document soft tissue disease and PCCTWG v.3 criteria to document radiographic progression of bone lesions.

Ryan et al. ASCO GU 2018. Abstr TPS389. NCT02975934.

BRCA1/2: Improved outcomes with PARPi before taxanes

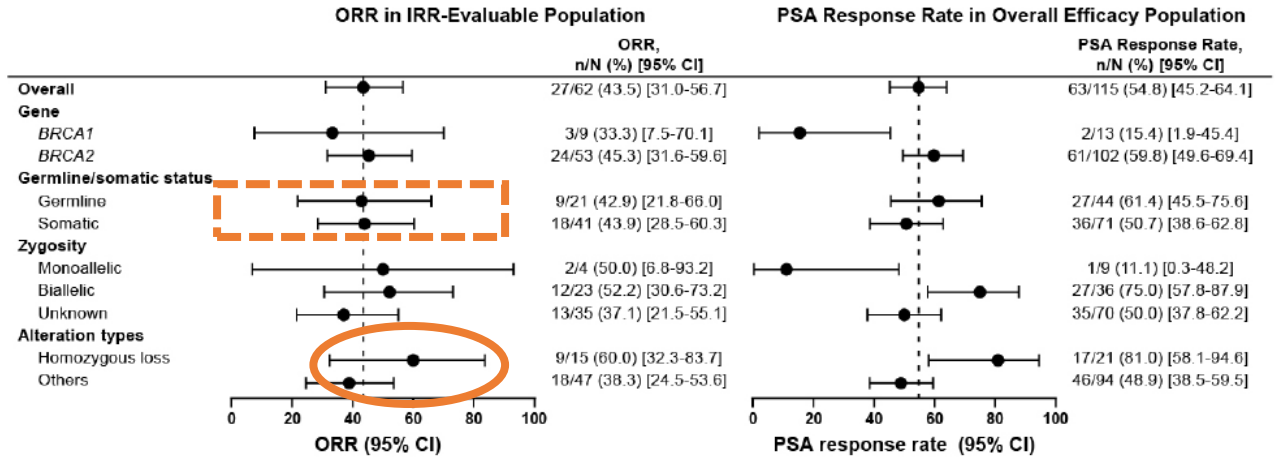




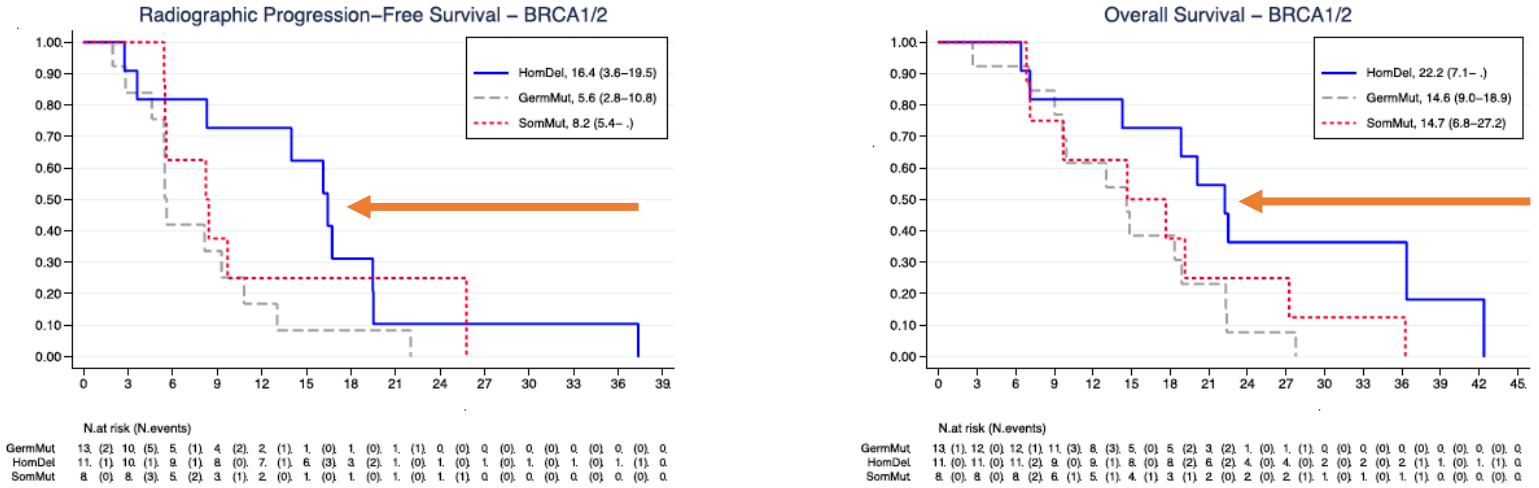
Hussain et al, NEJM, 2020; Presented by Dr Su at ASCO 2021

Response to PARP inhibitors in *BRCA1/2* patients may vary depending on the type of alteration

TRITON 2 (Rucaparib)



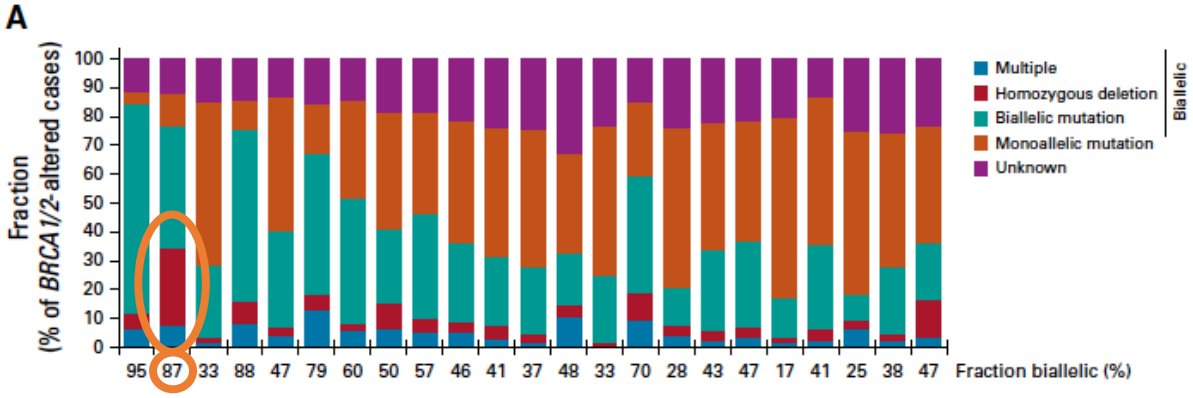
TOPARP-B (Olaparib)

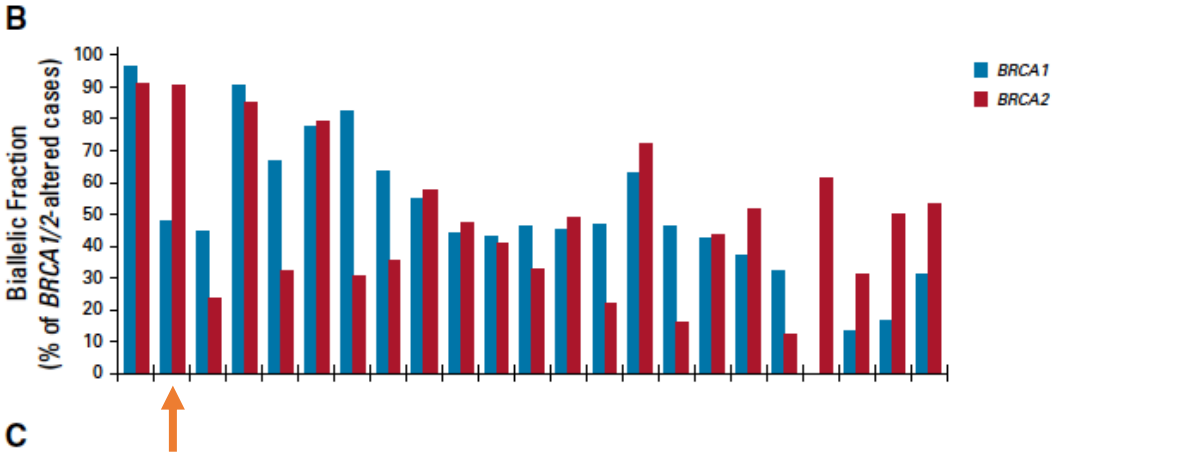


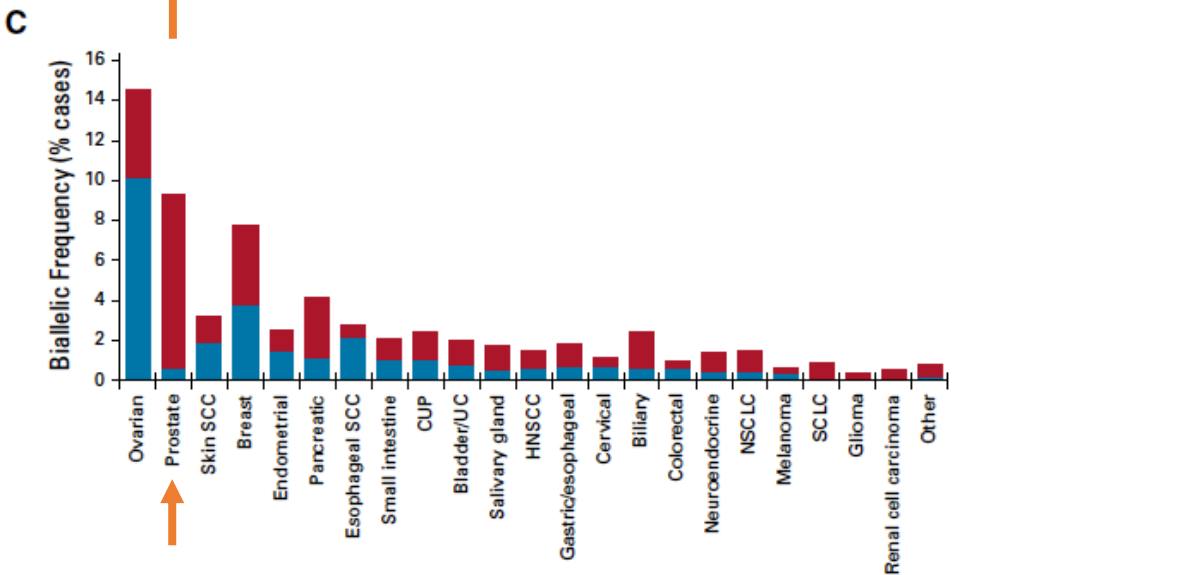
Abida et al, JCO, 2020; Carreira et al, Cancer Discov, 2021

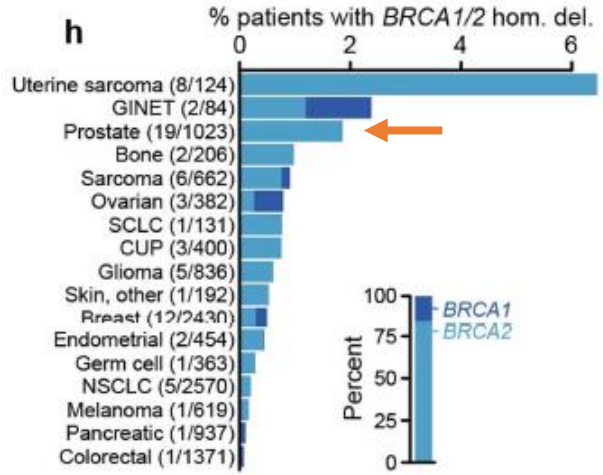
BRCA1/2 alterations in prostate cancer

- Most *BRCA1/2* alterations in PC are biallelic
- *BRCA2* > *BRCA1* in PC are biallelic
- Homozygous *BRCA1/2* deletions in **2%** of PC
- Homozygous *BRCA1/2* deletions in **≃30%** of *BRCA* altered PC





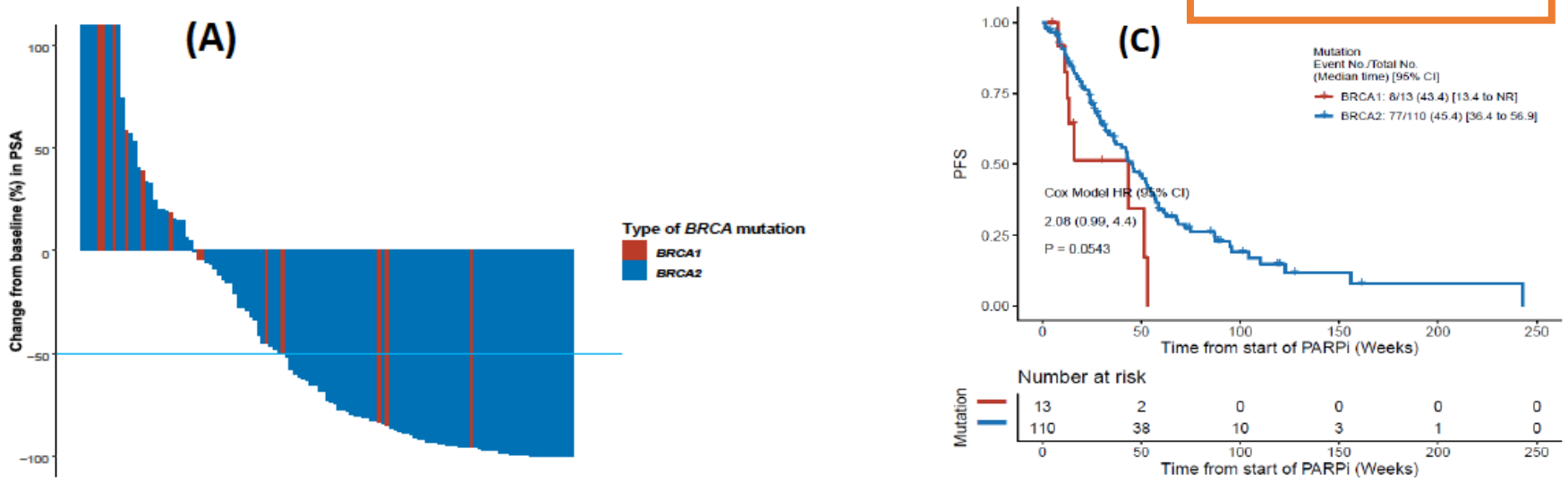




Jonsson, Nature, 2019; Sokol et al, JCO Precision Oncol, 2020

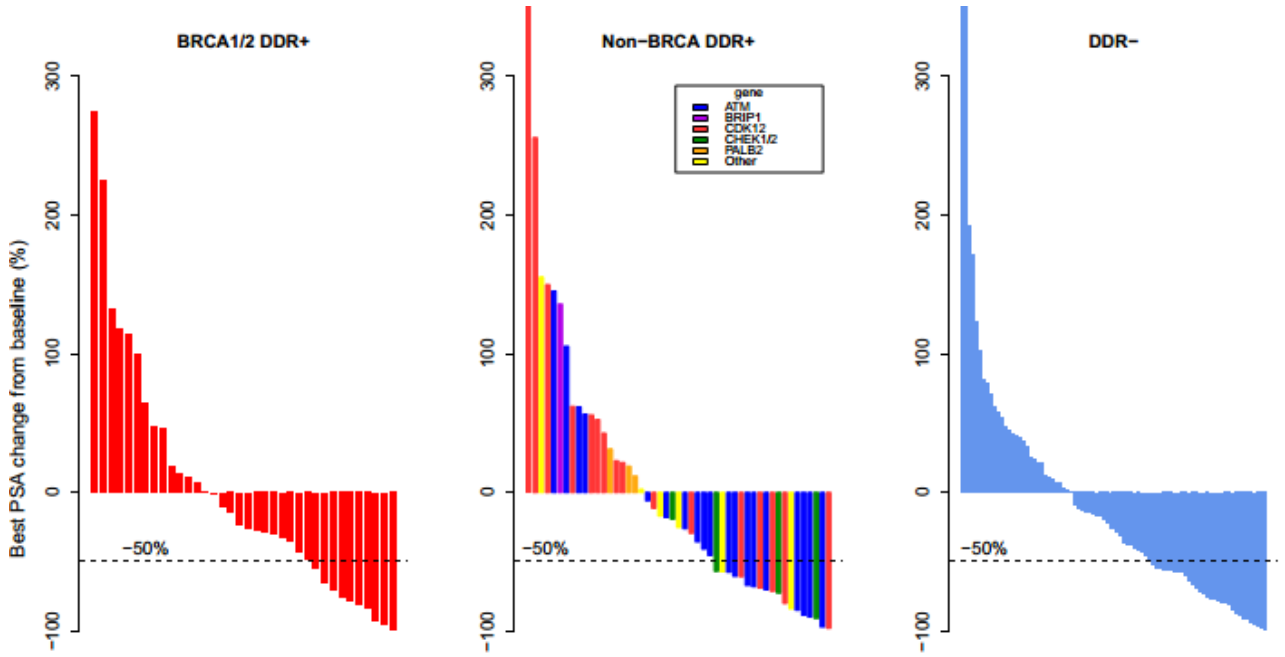
Differential activity of PARPi in *BRCA1* and *BRCA2* altered tumors

	TOPARP-A[14]		TOPARP-B[15]		PROfound[1]		TRITON2[2]		TALAPRO-1[16]		Pooled Data	
	BRCA1	*BRCA2*	*BRCA1*	*BRCA2*	*BRCA1*	*BRCA2*	*BRCA1*	*BRCA2*	*BRCA1*	*BRCA2*	*BRCA1*	*BRCA2*
Outcome	n/N	n/N	n/N	n/N (95% CI)	n/N (95% CI)	n/N (95% CI)	n/N (95% CI)	n/N (95% CI)	n/N	n/N (95% CI)	n/N (%) (95% CI)	n/N (%) (95% CI)
PSA_{50}	0/1	7/7	1/2	22/28	NR	NR	2/13	61/102	2/5	26/41	5/21 (23.8) (4.4 to 43.2)	116/178 (65.2) (58.2 to 72.2)
ORR	NE	5/5	0/1	11/20	0/5	24/43	3/9	24/53	2/4	15/37	5/19 (26.3) (5.1 to 47.5)	79/158 (50.0) (42.2 to 57.8)
rPFS, months	NE	NR	NE	8.2 (5.5 to 13.0)	2.1 (1.4 to 5.5)	10.8 (9.2 to 13.1)	8.7 (1.8 to 10.7)	9.7 (8.3 to 14.0)	NR	8.8 (5.6 to 19.2)	4.1 (1.0 to 16.8)	10.1 (8.9 to 11.6)
No. of patients evaluable for rPFS				30	8	81	13	102		41	21	254



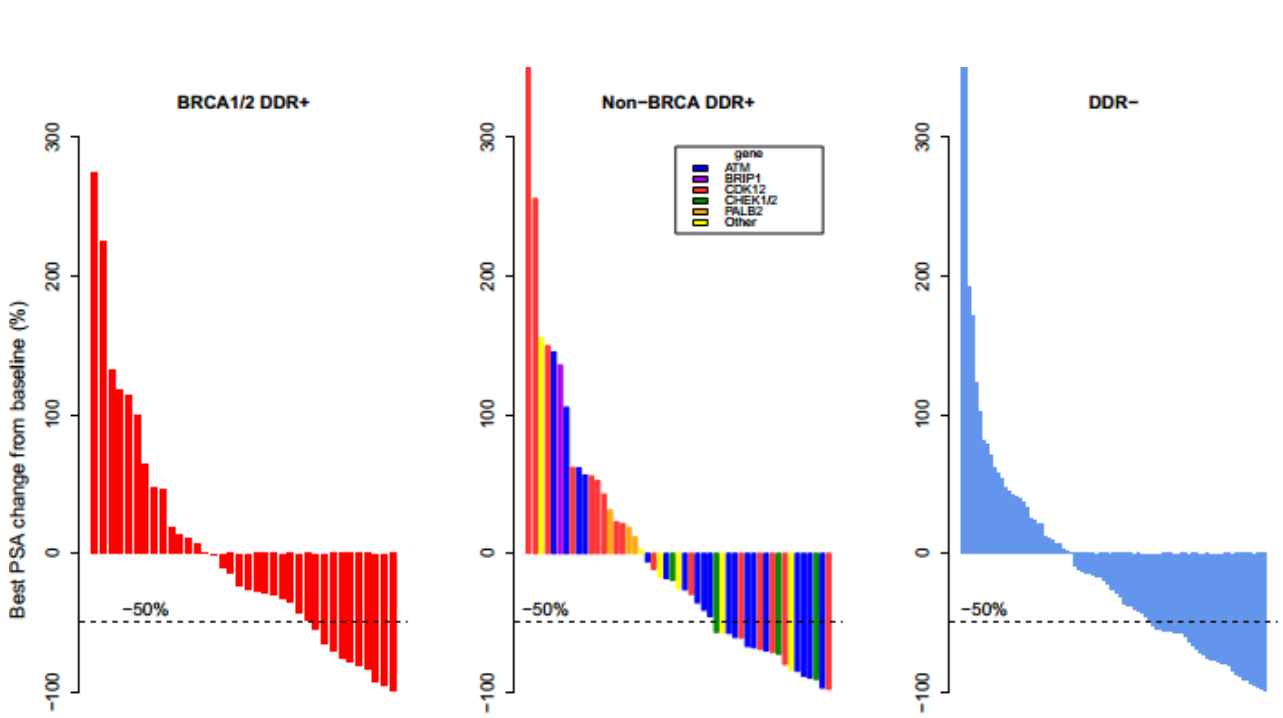
Markowski &Antonarakis, JCO, 2020; Taza et al JCO Precision Oncol, 2021

Cabazitaxel for patients with DDR alterations

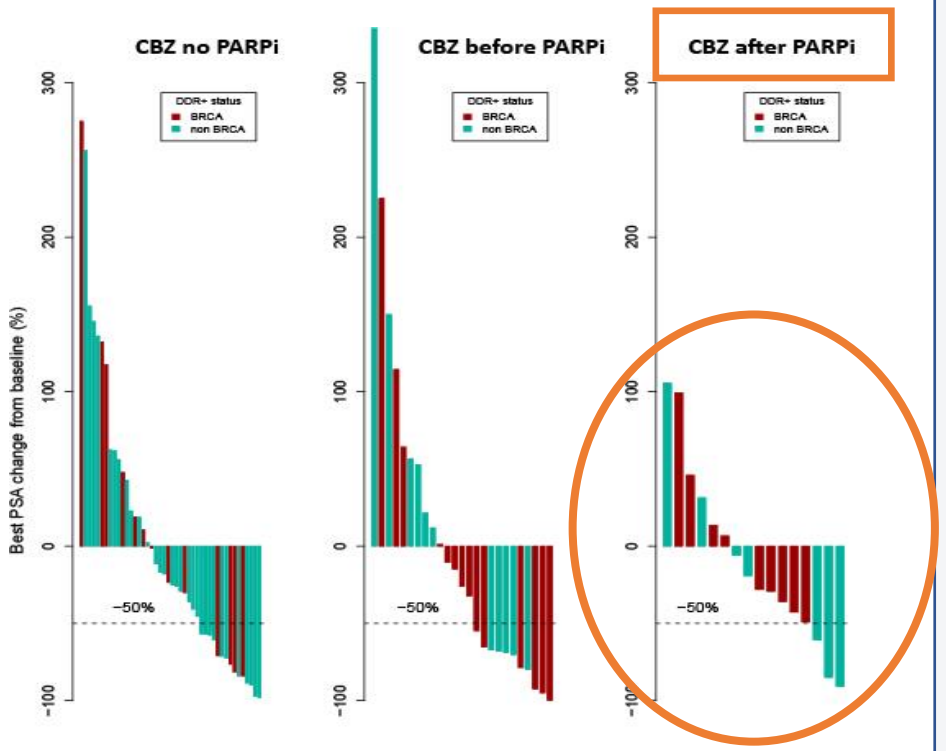


Similar response to Cabazitaxel in all groups by DDR status

Cabazitaxel for patients with DDR alterations



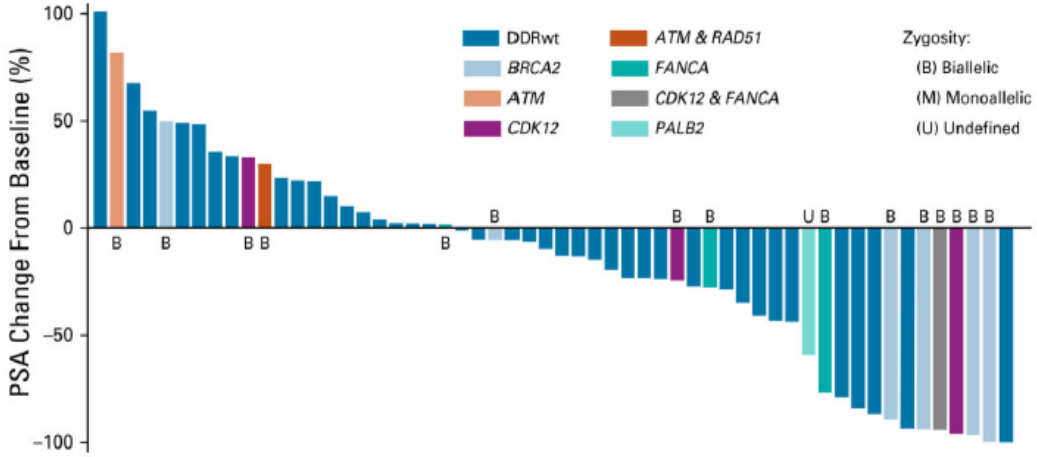
Similar response to Cabazitaxel in all groups by DDR status

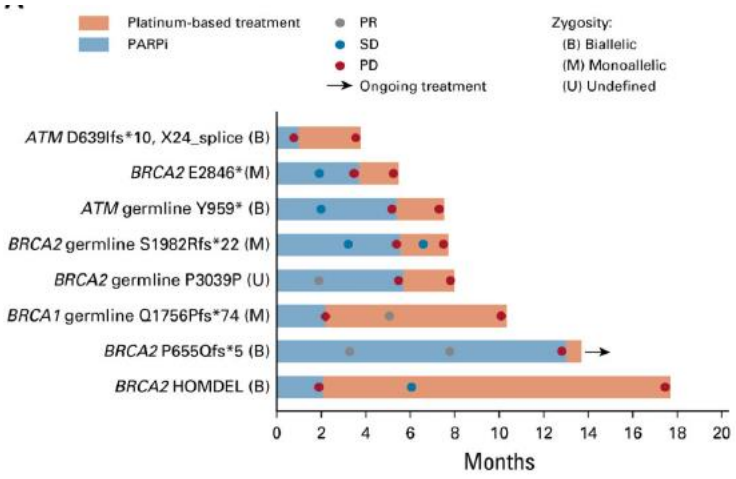


Limited responses **after PARPi**

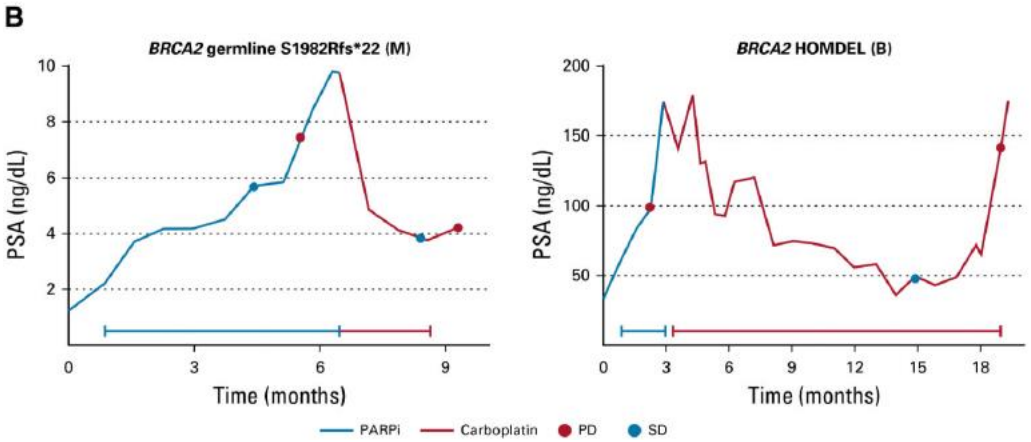
Aldea et al, EJC, 2021

Platinum-based chemotherapy for patients with DDR alterations



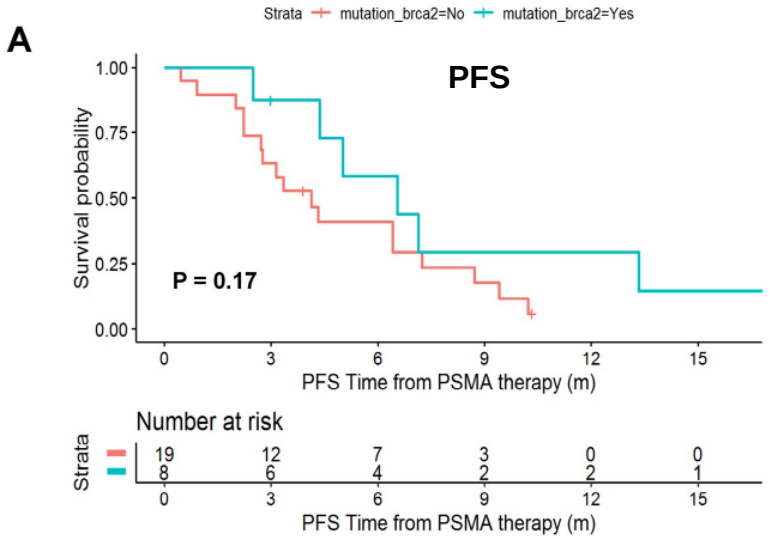


Best radiographic response (RECIST)		PSA decline from baseline (%)	
PARPi	*Platinum*	*PARPi*	*Platinum*
PD	PD	+34	-40
SD	PD	+2	+49
SD	PD	+154	-5
SD	SD	+67	-61
PR	PD	-68	-23
PD	PR	N/A	N/A
PR	N/A	-77	-5
PD	SD	+34	-79



Mota et al, JCO Precis Oncol, 2020

PSMA-targeted radionuclide therapy for patients with *BRCA1/2* alterations



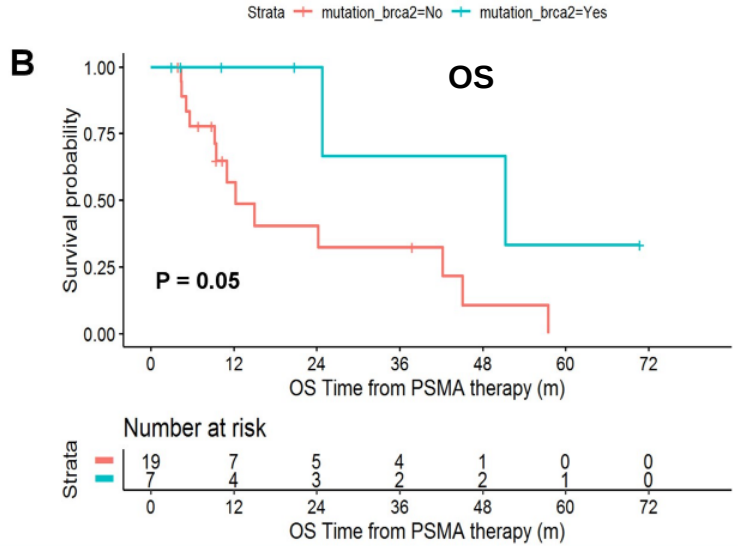
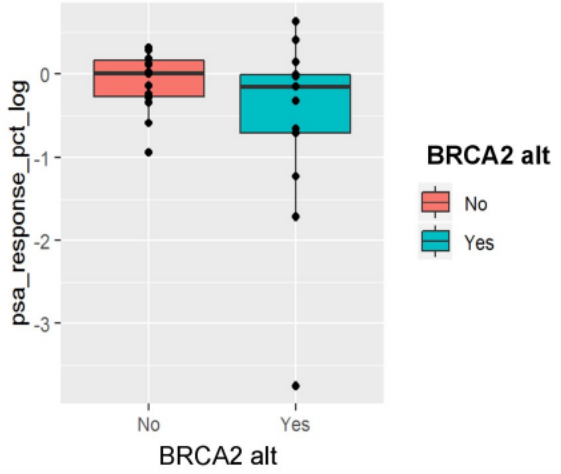


Table 2. Predictors of PFS and OS in patients treated with PSMA-TRT

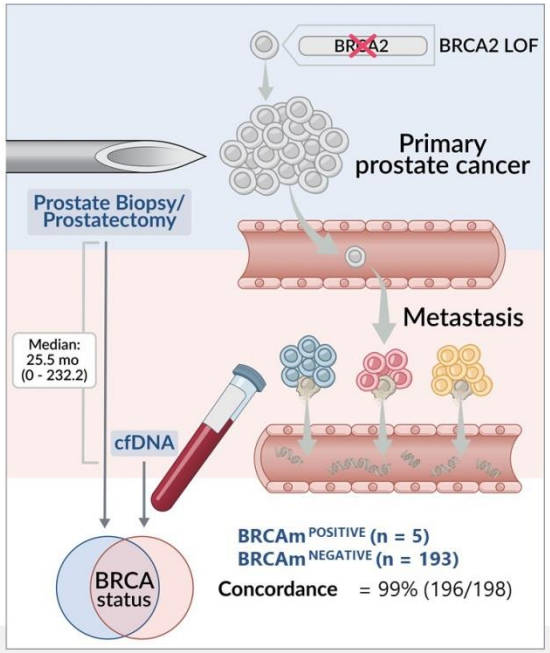
Backward stepwise selection for PFS			Backward stepwise selection for OS		
Variable	**HR (95% CI)**	**P**	**Variable**	**HR (95% CI)**	**P**
Narcotic use	0.28 (0.08,0.91)	0.035	Baseline ALP	1.02 (1.00, 10.3)	0.024
Baseline ALP	1.02 (1.01,1.03)	0.003	**BRCA2 alt**	0.09 (0.01,0.91)	0.041
BRCA1 alt	0.02 (0.0,0.32)	0.004			
BRCA2 alt	0.26 (0.08,0.85)	0.026			
TP53 alt	4.82 (1.24,18.7)	0.023			



Presented by Dr Conteduca at ASGO GU 2019

BRCA1/2 and other DDR alterations are likely early events

High concordance in DDR mutational status between primary prostate and metastatic tissue/ctDNA



BRCA1/2: 99% Overall concordance

Table 1. Patients with BRCA mutation in primary tumor

Pt #	BRCAm primary	Interval	BRCAm cfDNA 1
1	Detected	3.13 months	Not Detected
2	Detected	0.93 months	Detected
3	Detected	0.2 months	Detected
4	Detected	97.93 months	Not Detected
5	Detected	40.77 months	Detected

Table 2. Patients with no BRCA mutation in primary tumor

Matched CGP	Median (range)	New BRCA1	New BRCA2
Primary test to 1st cfDNA (n=191)	23.6 months (0.1 - 232)	None	None
Primary test to 2nd cfDNA (n=27)	58.9 months (7.23 - 211)	None	None
Primary test to 3rd cfDNA (n=2)	65.5 months (21.9 - 109)	None	None

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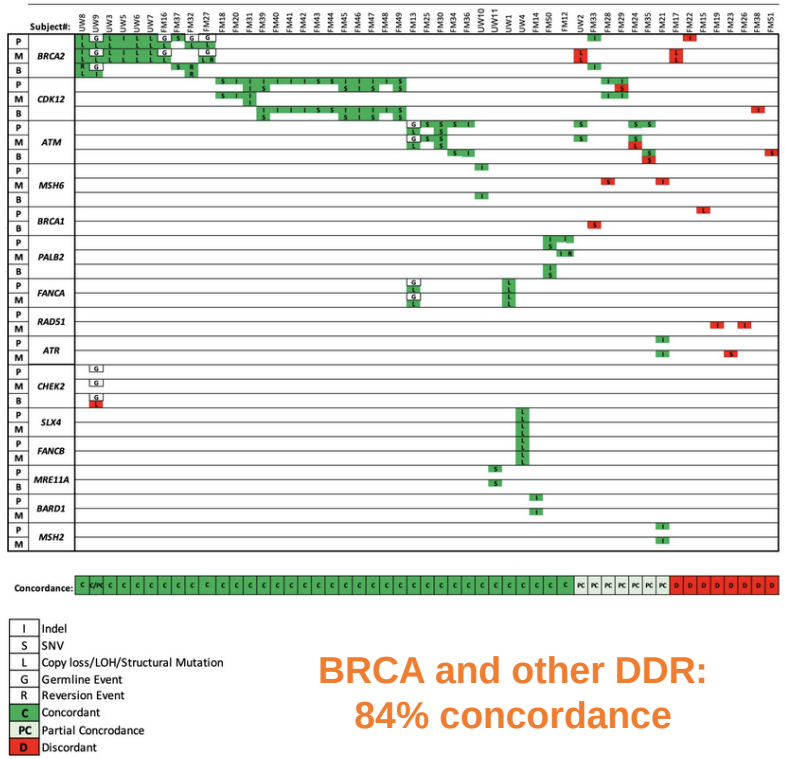


BRCA and other DDR: 84% concordance

Presented By Dr McFarland at 2021 Genitourinary Cancers Symposium ; Presented by Dr Schweizer at al JAMA Oncol, 2021

ESMO Precision Medicine Working Group recommendations

Gene	Alteration	Prevalence	ESCAT
BRCA1/2	Somatic mutations/delectations	9%	IA
PTEN	Deletions/mutations	40%	IIA*
ATM	Mutations/deletions	5%	IIA
PALB2	Mutations	1%	IIB
PIK3CA	Hotspot mutations	3%	IIIA
AKT1^{E17K}	Mutations	1%	IIIA
	MSI-H	1%	IC

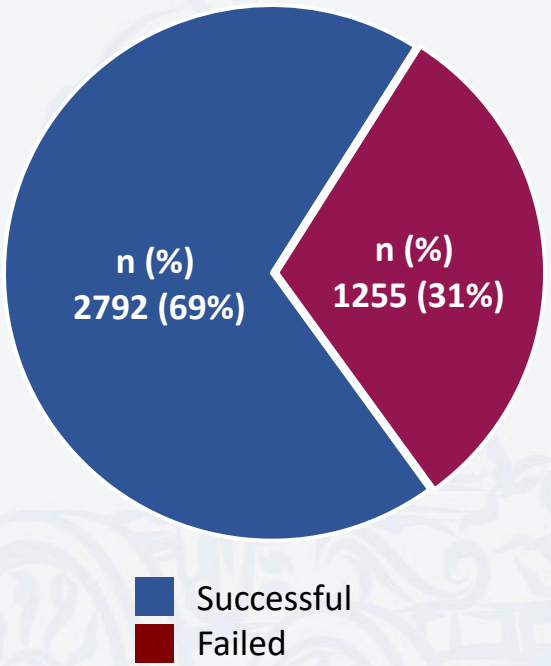
ESCAT is a framework that ranks a match between drug and genomic alterations, according to their actionability

Mosele et al, Ann Oncol, 2019

Challenge of molecular diagnosis in PC: TISSUE is the ISSUE

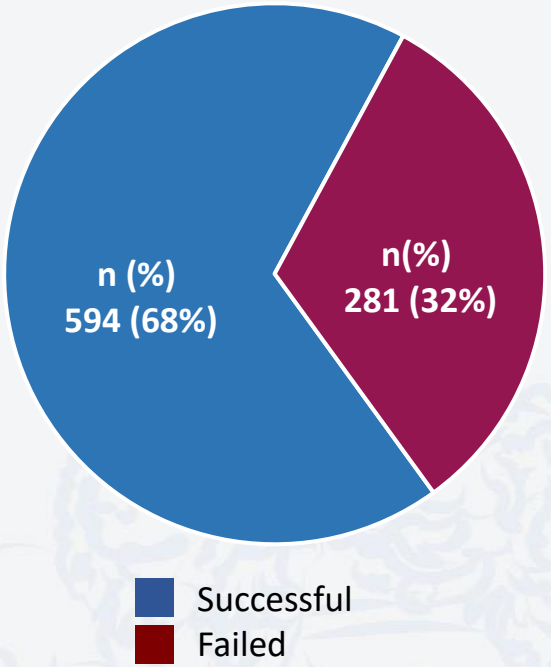
PROfound[1]

N = 4047 samples



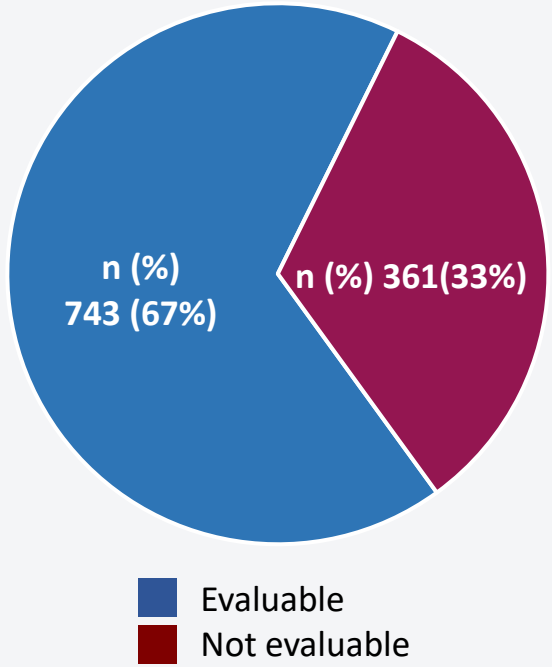
TRITON2[2*]

N = 875 samples



IPATential150[3]

N = 1104 samples



Sample selection and optimisation of tissue collection is critical, since 30–50% of prostate cancer samples fail NGS[1–3]

*Prostate cancer samples are shown for TRITON2.

mCRPC, metastatic castration-resistant prostate cancer; NGS, next-generation sequencing.

1. de Bono J, et al. Ann. Oncol. 2019; 30 (suppl_5): v325-v355. (ESMO 2019, #5118); 2. Green F, et al. AACR 2019; (#727); 3. de Bono JS, et al. Journal of Clinical Oncology. 2021;39 (suppl_6):13-13.

Different diagnostic strategies can be considered to assess for HR alterations

	Advantages	Disadvantages
Tumour tissue testing	**Gold standard** (High clinical sensitivity) **Fresh or archival** tumour samples can be used (but older samples can have lower success rates) Can detect both **germline and somatic** mutations	High failure rate, especially for older samples Tissues for sampling may be in locations that are not safe or amenable to biopsy Single-site biopsies do not capture intra-individual heterogeneity (across metastases in an individual or changes over time or with disease progression)
Plasma ctDNA testing	**Non-invasive**, safer, serial analysis Can detect both **germline and somatic** mutations Useful where no tissue is available or when re-biopsy is undesirable Capture relative **contribution of metastases** in different anatomical sites	Low levels of tumour fraction can lead to false negative results Blood collection must be timed in order to evaluate progressive disease Relative sensitivity at a prospective cohort level is unknown (clinical validation in PC still limited)
Germline testing (Blood or saliva)	Assess **familial risk** **Easy to obtain** samples from blood, saliva or buccal swabs	Misses alterations of somatic origin (≃ 50% of HR alterations)

Wyatt 2016; Pellegrino 2019; Moreno 2019; Merker 2019; Hennigan 2019; Hussain 2020; Gilson 2020; Mateo 2020

TAKE HOME MESSAGES

- Drugs targeting the pathways more frequently altered in prostate cancer are being developed
  - *PARPi are the first targeted therapies approved for mCRPC.*
- PARPi are approved for the treatment of patients with *BRCA1/2* alterations after progression to ARTi.
  - *Best treatment sequence for BRCA1/2 altered patients is unclear*
- Consider assessing HR status early
  - *Retrieve blocks, consider re-biopsy,…*
  - *BRCA1/2 mutations rarely change status over tike*
- Use a targeted next generation sequencing (NGS) panel
  - *BRCA1* and *BRCA2*
  - Other HRR genes if possible *(reimbursement, treatment options, etc…)*
  - MMR genes/MSI
- When possible, analyze a recent tissue sample (metastatic biopsy)
  - *Sequencing of primary tissue is also possible, but consider sample age, fixation, etc..*
  - *Liquid biopsy may help overcome difficulties of tissue analysis, but also has limitations*
  - *Germline testing only will miss about 50% of patients eligible for PARPi*
- All patients with metastatic prostate cancer should be offered germline testing
  - *Somatic tests are not validated for germline assessment*
  - *Analyze potential germline origin of mutations in cancer-related genes found in tumor*

XXIV SIMPOSIO DE REVISIONES EN CÁNCER

"Tratamiento médico del cáncer en el año 2022"

Gracias

ARÁN