Metastatic Castration-Resistant landscape

Clinical case and
evidence from literature

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Il sottoscritto Marco Messina in qualità di relatore

ai sensi dell'art. 76 sul Conflitto di Interessi, pag. 34 dell'Accordo Stato-Regione del 2 Febbraio 2017

dichiara

che negli ultimi due anni ha avuto i seguenti rapporti anche di finanziamento con soggetti portatori di interessi commerciali in campo sanitario:

Relationship	Company/Organization
Consulting	Sanofi, Elmaresearch, Iquvia
Congress Honoraria and Advisory board	Sanofi, Amgen, Novartis, AstraZeneca, Merck, Janssen, Archimedes Pharma, BMS
Congress Support and Sponsoring	Astellas, Janssen, Sanofi, Novartis, AstraZeneca, Eli Lilly, Roche, Amgen, Merk, BMS, Pfizer, Servier, BMS

Clinical case: 58 years old man with mCRPC

ECOG PS: 0 - PSA 120 ng/ml

Biopsy: Adenocarcinoma GS 4+5

➢ Bone scan: multiple metases (extra axial spread)
➢ CT scan: enlarged pelvic and retroperitoneal nodes

ADT + Docetaxel x 6 ⇨ ADT (*PSA nadir 1 ng/ml*)

After 14 months

➢ PSA 10 ng/ml; Serum testosterone < 50 ng/dl
➢ CT and Bone scan: nodal and bone PD (*4 new lesions*)

Genetic counseling

Somatic testing: BRCA2 biallelic mutation ⇨ **Germline testing**: mutation identified

Abiraterone Acetate + Prednisone and Donosumab (*PSA nadir 3 ng/ml*)

After 8 months

➢ PSA 28 ng/ml
➢ CT and Bone scan: bone PD

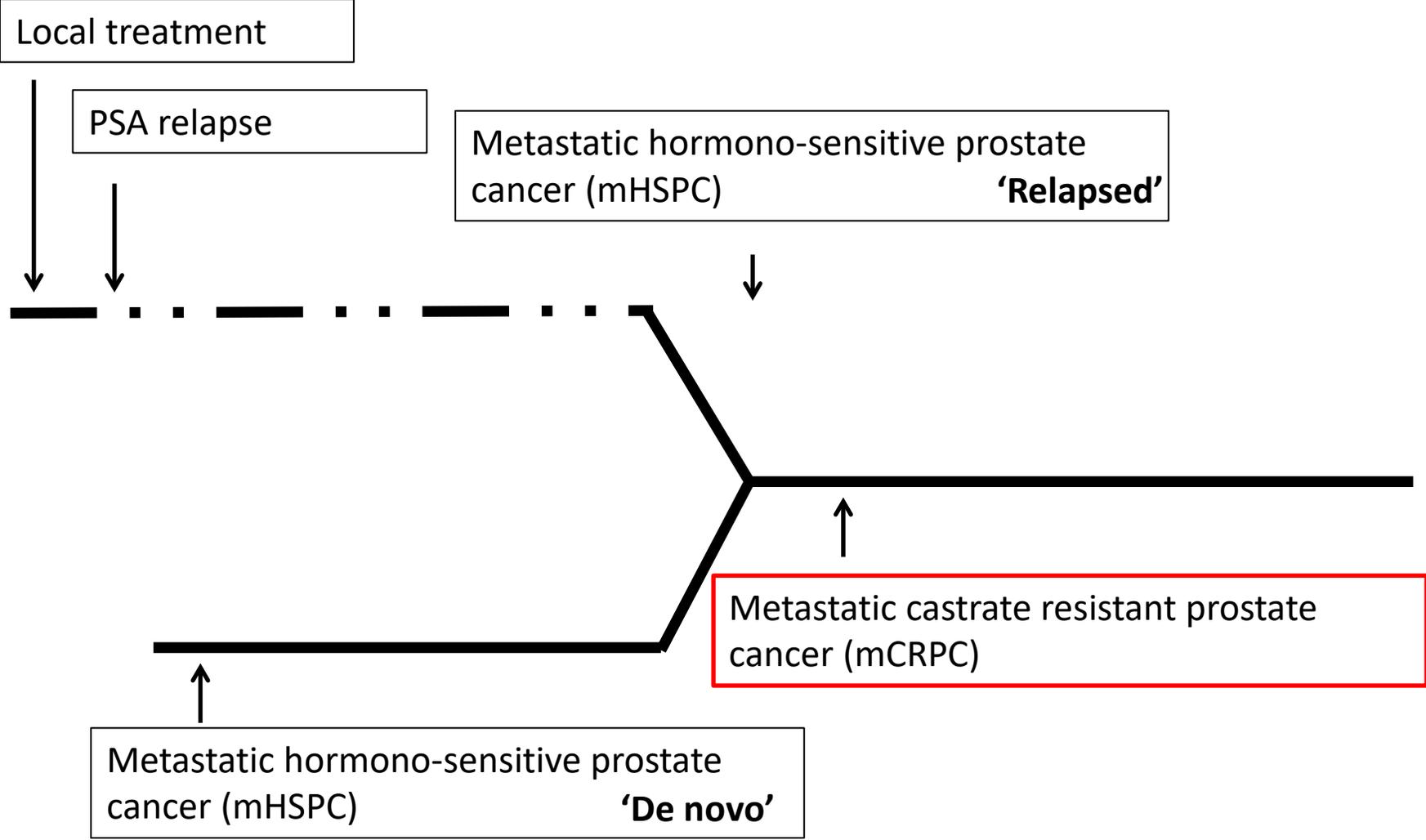**Olaparib** (*PSA nadir 10 ng/ml*)

After 10 months

➢ CT and Bone scan: Bone and nodal (*5 cm retroperitoneal*) PD

Cabazitaxel x 6 cycles

BSC for 3 months

Natural History of Prostate Cancer

Local treatment

PSA relapse

Metastatic hormono-sensitive prostate cancer (mHSPC)   **'Relapsed'**

Metastatic castrate resistant prostate cancer (mCRPC)

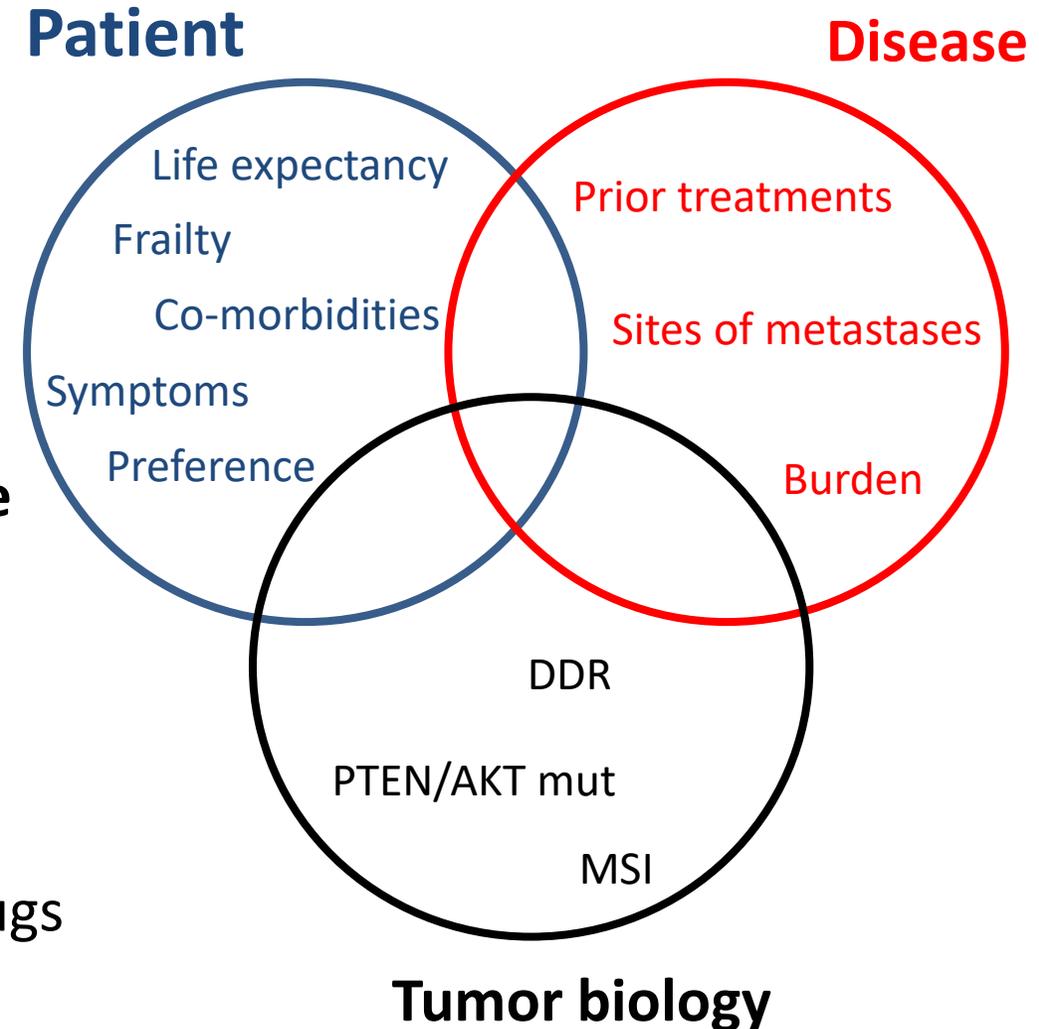Metastatic hormono-sensitive prostate cancer (mHSPC)   **'De novo'**

Survival prolonging therapies for mCRPC

- Abiraterone
- Cabazitaxel
- Docetaxel
- Enzalutamide
- Radium-223
- Sipuleucel-T *(USA only)*
- PARP inhibitors
- ^{177}Lu PSMA

Modified from K. Fizazi

Challanges for decision making in the mCRPC setting

- Most of the mCRPC trials **did NOT have a SOC arm** with a current, real word 'standard' therapy

- Most patients included in these trials **did NOT receive ADT based combination treatment** in the castration sensitive setting

- There is **no clear indication for sequencing** active drugs

Patient

Disease

Life expectancy

Frailty

Co-morbidities

Symptoms

Preference

Prior treatments

Sites of metastases

Burden

DDR

PTEN/AKT mut

MSI

Tumor biology

Clinical case: 58 years old man with mCRPC

ECOG PS: 0 - PSA 120 ng/ml

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➢ Bone scan: multiple metases (extra axial spread)

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ADT + Docetaxel x 6 ⇨ ADT (*PSA nadir 1 ng/ml*)

After 14 months **First Line**

➢ PSA 10 ng/ml

Genetic counseling

➢ CT and Bone scan: nodal and bone PD (*4 new lesions*)

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After 8 months

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➢ CT and Bone scan: bone PD

Olaparib (*PSA nadir 10 ng/ml*)

After 10 months

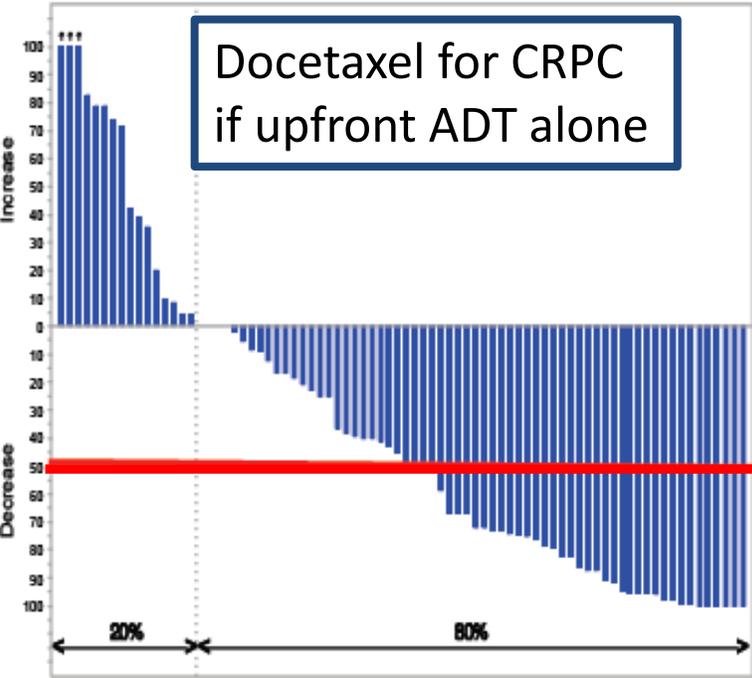➢ CT and Bone scan: Bone and nodal (*5 cm retroperitoneal*) PD

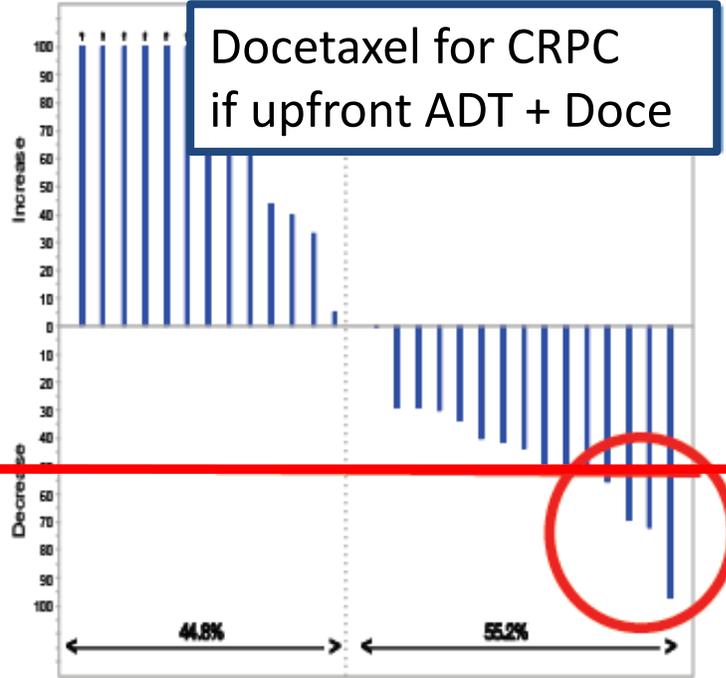**Cabazitaxel x 6 cycles**

BSC for 3 months

PSA response according to treatment for mCRPC patients previuously treated with ADT+Doce in the mHSPC setting
Data from the GETUG-15 trial

Best PSA variation % during treatment (n.80)

Docetaxel for CRPC
if upfront ADT alone

Best PSA variation % during treatment (n.29)

Docetaxel for CRPC
if upfront ADT + Doce

Best PSA variation % during treatment (n.15)

Abi/Enza for CRPC
if upfront ADT + Doce

20%

80%

44.8%

55.2%

13.3%

86.7%

Levaud, ESMO 2016
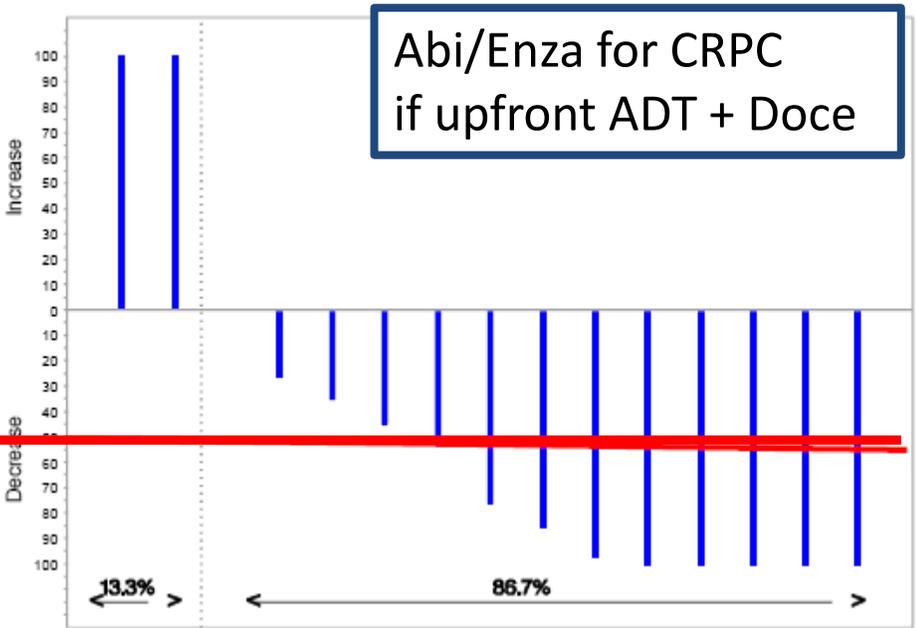
Bone protecting agents in mCRPC

Denosumab prevents symptomatic skeletal events
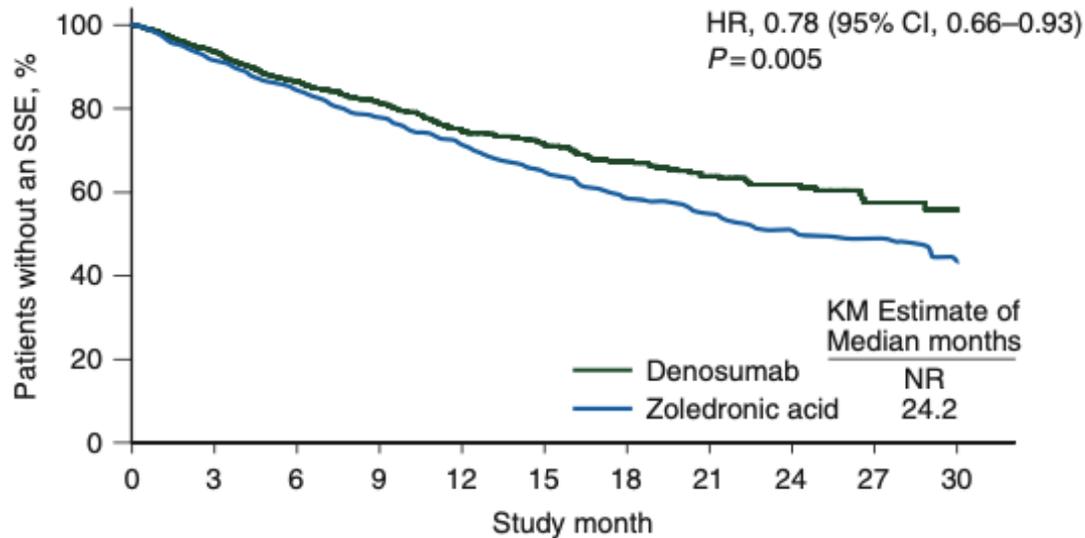
Abiraterone and Bone Targeting Agents in COU-AA-302: post hoc analysis

Overall survival
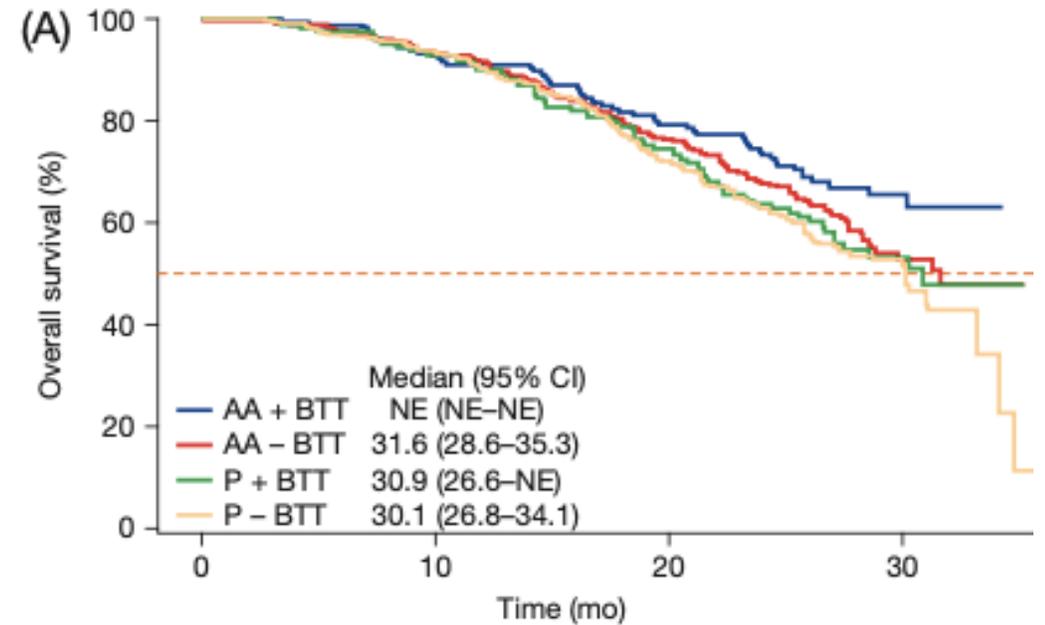
DNA repair and prostate cancer

Germline DNA repair mutations:

-**12%** in men with M1 prostate cancer

-5% in men with localized prostate cancer

-3% general population
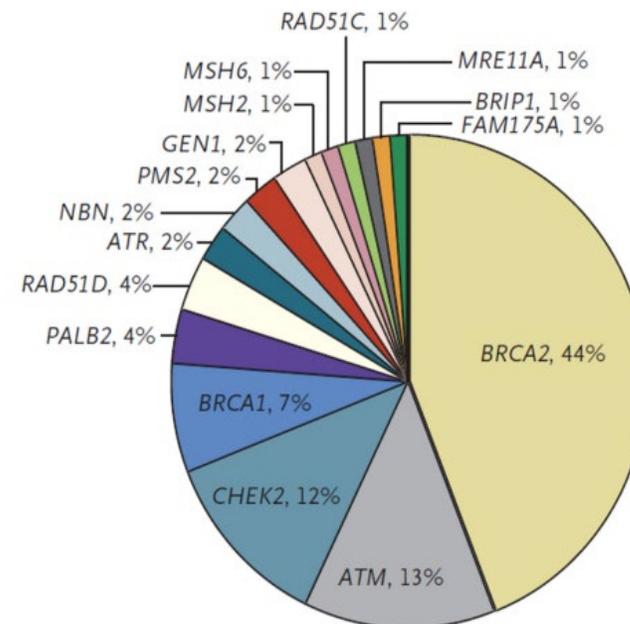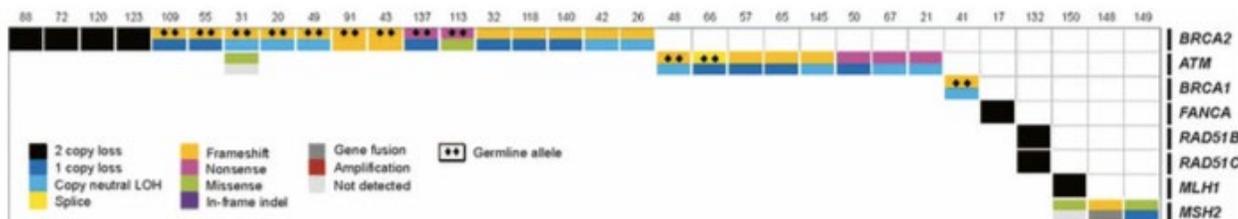
Somatic DNA repair mutations:

-**10%** in men with mCRPC

Pitchard, NEJM 2016
Robinson, Cell 2015

Prevalence of pathogenic germline variants in PC
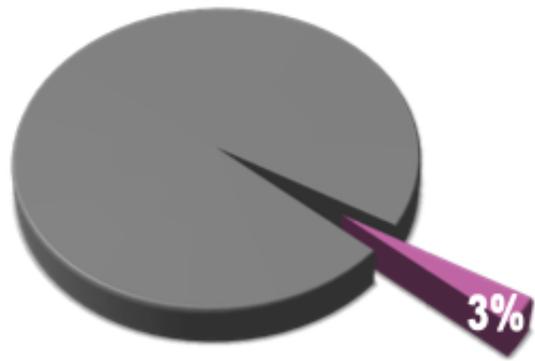
General Population — 3%
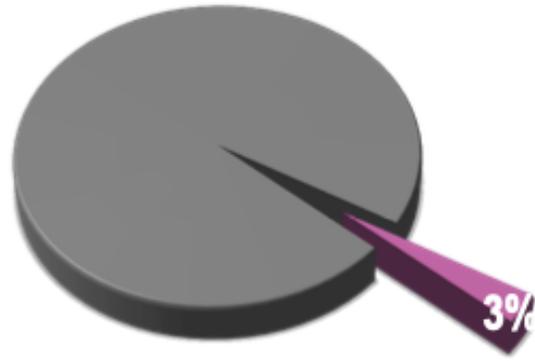
Low-Risk Localized PC — 3%

High-Risk Localized PC — 6%

Metastatic PC — 8-12%

Pritchard, NEJM 2016; Castro, JCO 2019; Nicolosi, JAMA 2019; Lee Eu Urol 2022
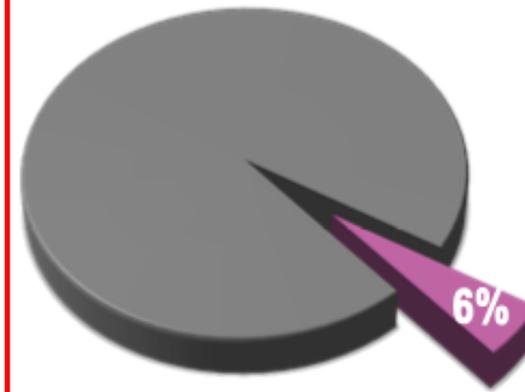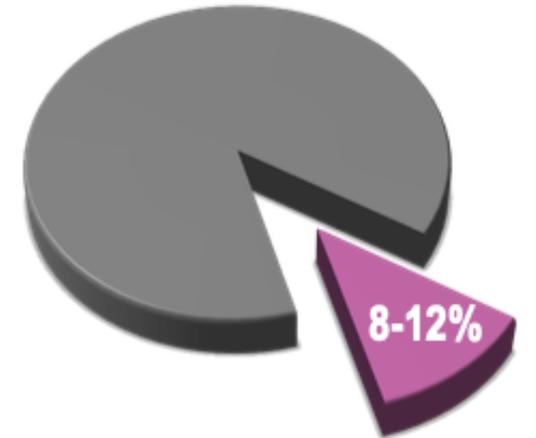
Genetic testing is standard of care in PC

Guidelines	Genomic testing recommendations	Germline testing for PC
NCCN Clinical Practice Guidelines in Oncology	✖	✖
ESMO 2020 Guidelines	✖	✖
AUA/ASTRO/SUO 2022 Guidelines	✖	✖
EAU2022 Guidelines	✖	✖
AIOM 2021 Guidelines	✖	✖

ESMO recommendations according to ESCAT

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

Mosele, Ann Onc 2020

HRR alterations: beyond predictive value

Cause Specific Survival in mCRPC

BRCA2 vs Non BRCA2

Impact of treatment sequencing in BRCA2 carriers

ASI-Tax

Tax-ASI

Prognostic information

Cancer prevention

prostate   breast   ovarian   pancreatic   skin cancers   colorectal   endometrial   stomach   sarcoma   others   ...

Castro E. J Clin Oncol. 2019
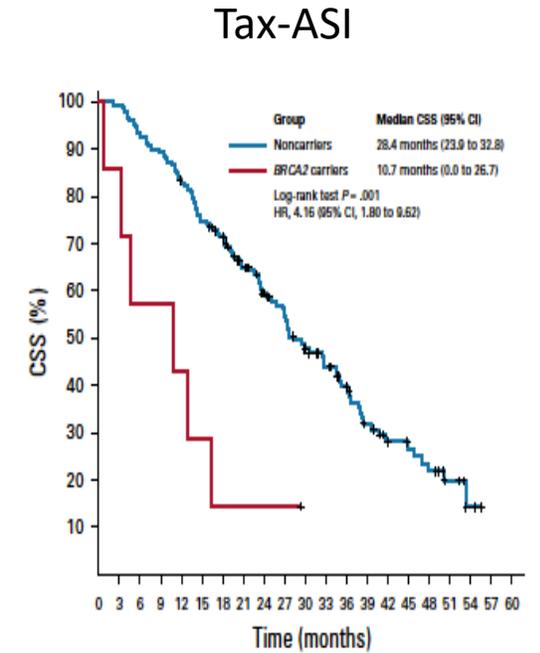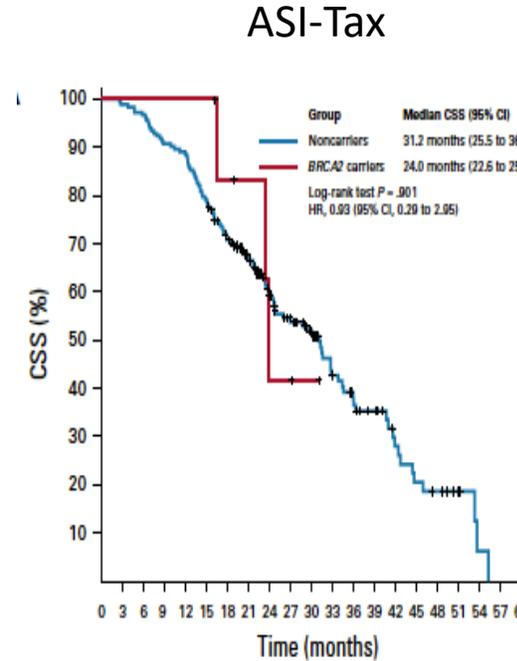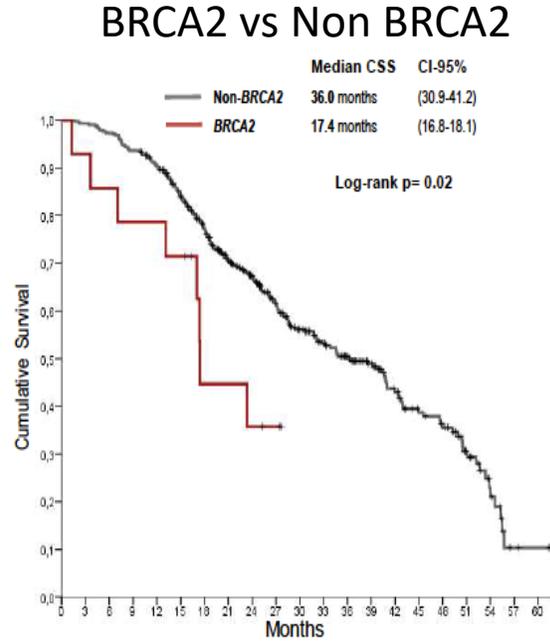
Tissue is the issue

PROfound
N 4047 samples

n (%)
2792 (69%)

n (%)
1255 (31%)

- Successful
- Failed
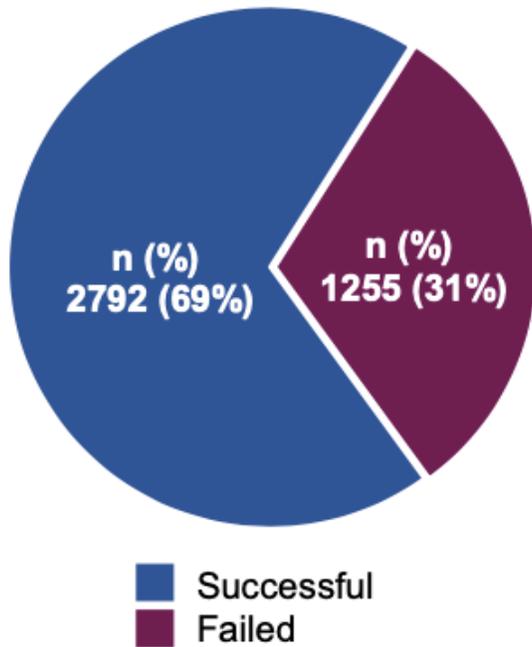
NGS Testing: 30-40%
failure with PC samples

Collection time

56.9 — Archival (n = 4,365)
63.9 — Recently obtained (n = 438)

Collection site

56.2 — Primary prostate gland (n = 4,022)
63.9 — Overall metastatic sites (n = 809)
42.6 — Bone (n = 204)
56.3 — Liver (n = 87)
60.5 — Lung (n = 43)
74.7 — Lymph node (n = 328)
74.8 — Other (not specified; n = 147)

Age of samples

68.1 — <1 year (n = 923)
62.5 — 1–3 years (n = 1,134)
56.4 — 3–5 years (n = 934)
50.4 — 5–10 years (n = 1,275)
47.3 — >10 years (n = 548)

Tumor content

48.5 — 20–30% (n = 937)
60.1 — 30–40% (n = 952)
67.0 — 40–60% (n = 1,134)
68.3 — 60–80% (n = 1,034)
77.5 — ≥80% (n = 387)
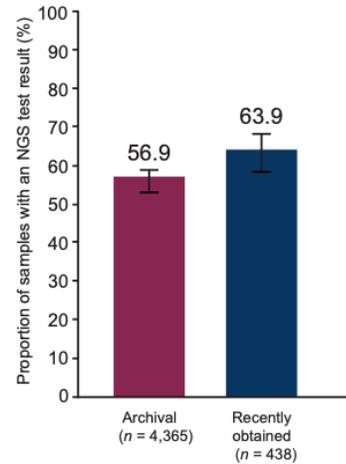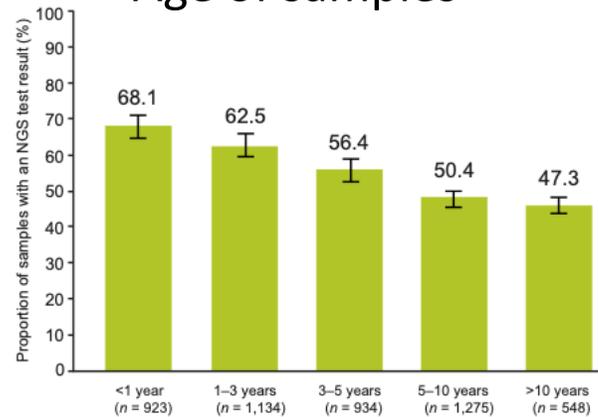
Sample selection and optimisation of tissue collection in critical

De Bono, Ann Onc 2019

Hussain, Clin Canc Res 2022

Somatic vs Germline testing

BRCA1/2 analysis workflow in mPC
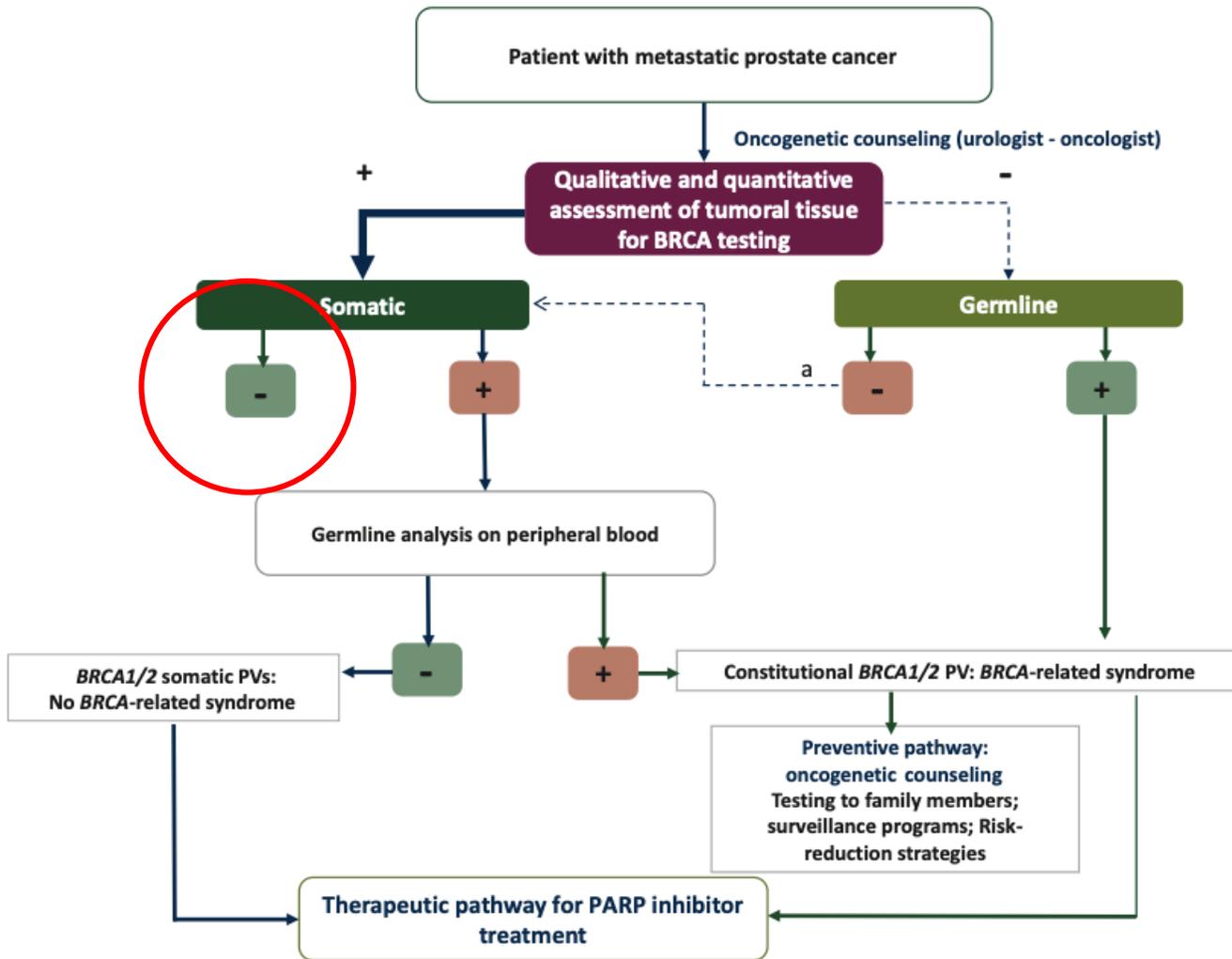
Comprehensive assessment of germline pathogenic variant detection in tumor-only sequencing

21.333 cancer patients

Intervention: Tumor and 'Clinical' germline testing

Results:

Tumor-only sequencing failed to detect **10.5%** of pathogenic germline variants (7.5% HRD)

Tumor only sequencing detection rate:
- 100% nonsense and missense SNV and indels
- **55% deletion/duplication**

CONSIDER CLINICAL GENETIC TESTING
High Risk patients with negative tumor only sequencing results

AIOM Pos. Paper - Russo , ESMO Open 2022

Terraf, Ann Onc 2022

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➤ Bone scan: multiple metases (extra axial spread)

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Genetic counseling

Abiraterone Acetate + Prednisone and Donosumab (*PSA nadir 3 ng/ml*)

After 8 months

➤ PSA 28 ng/ml

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Second Line

Olaparib (*PSA nadir 10 ng/ml*)

After 10 months

➤ CT and Bone scan: Bone and nodal (*5 cm retroperitoneal*) PD

Cabazitaxel x 6 cycles

BSC for 3 months

PARP inhibitors in pretreted molecularly selected mCRPC: Phase II trials

Study Drugs	Study	Population	Primary Endpoint	Efficacy data
Olaparib	TOPARP-B	DDR	Composite OR	54 %
Rucaparib	TRITON-2	BRCA1-2	ORR	43.5%
Niraparib	GALAHAD	DDR	ORR	41%
Talazoparib	TALAPRO-1	DDR	ORR	26.7

Mateo, Lancet Oncol 2020; Abida, J Clin Onc 2020; Smith, ESMO 2019; De Bono, ASCO 2020

PROfound phase III: Trial design
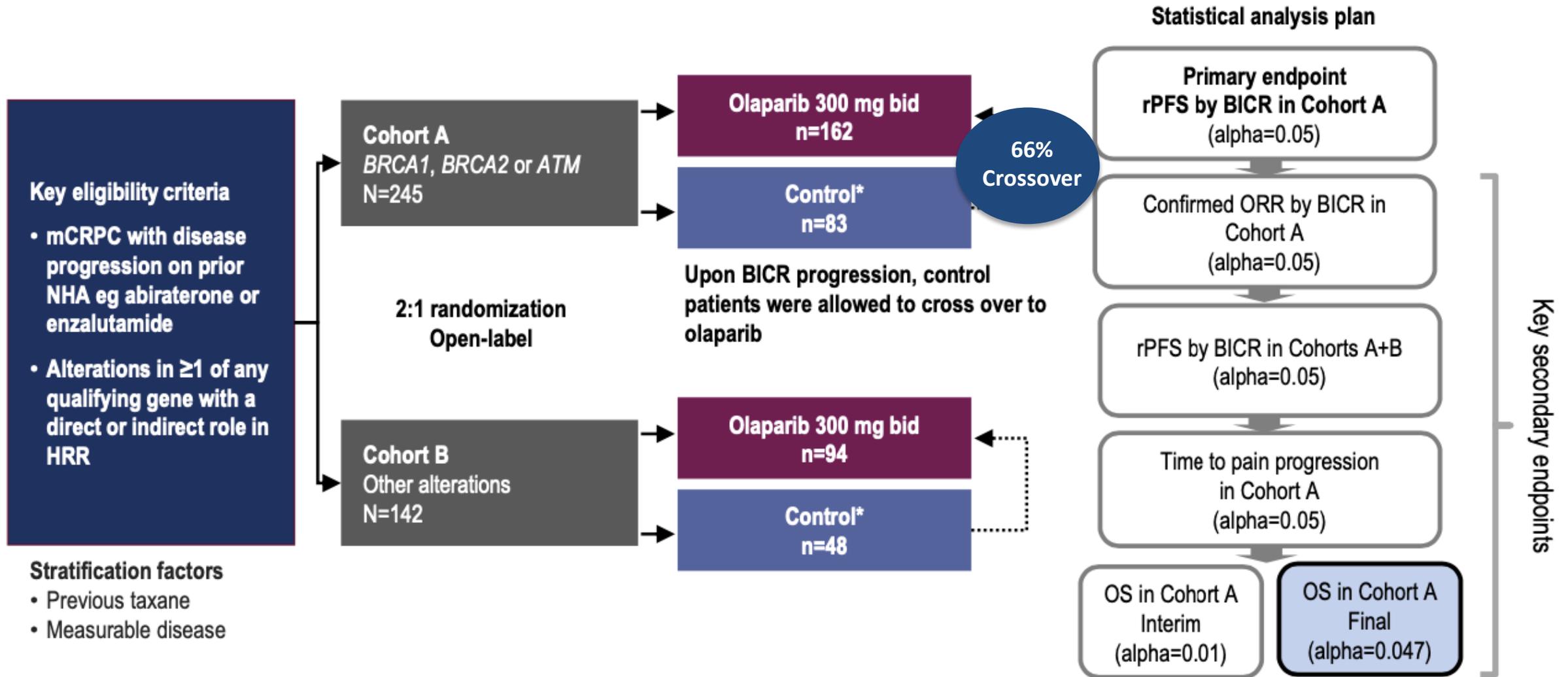
De Bono, ESMO 2020

PROfound phase III: primary end ponit

rPFS in COHORT A

Objective response rate

De Bono, ESMO 2020

De Bono, ESMO 2019
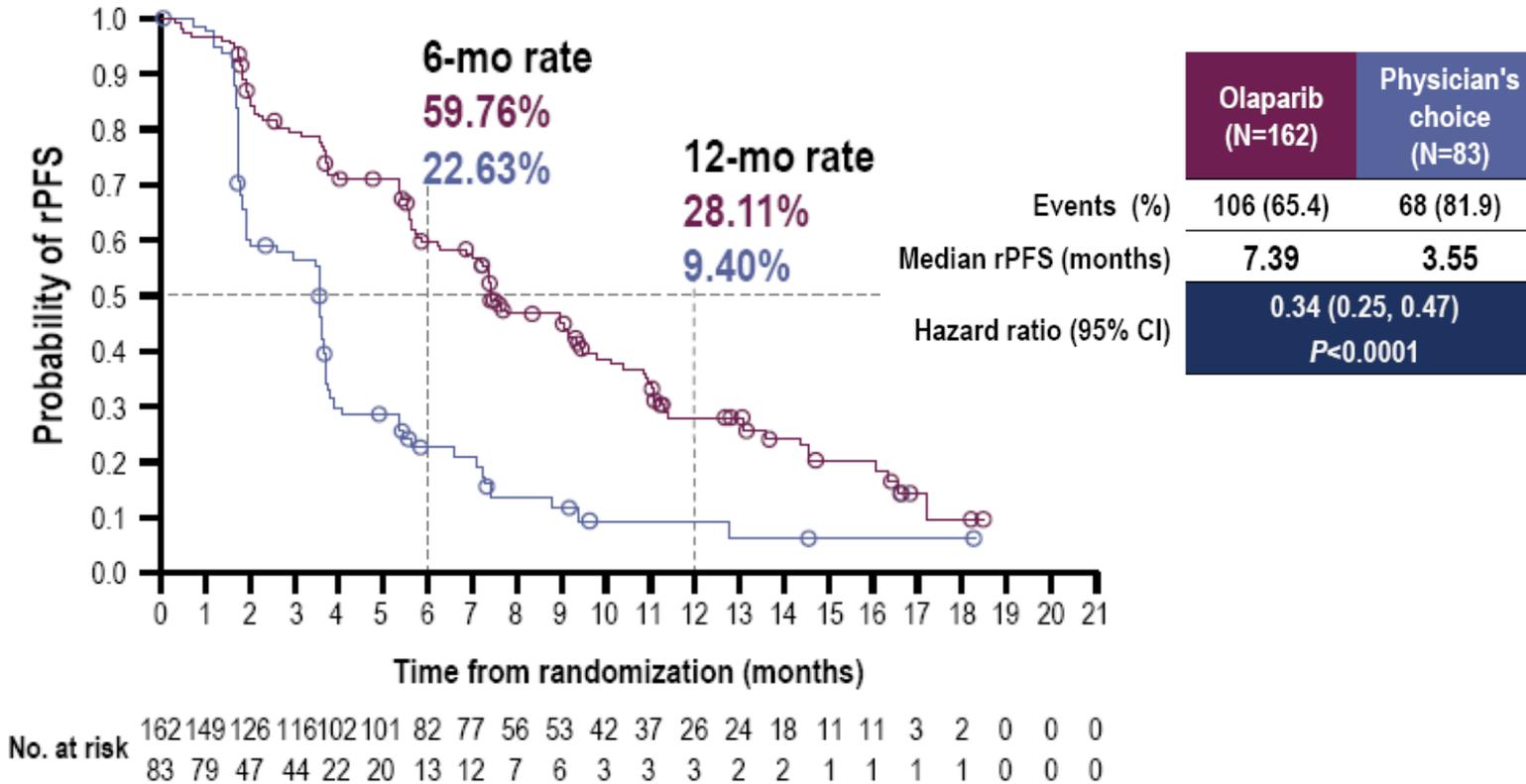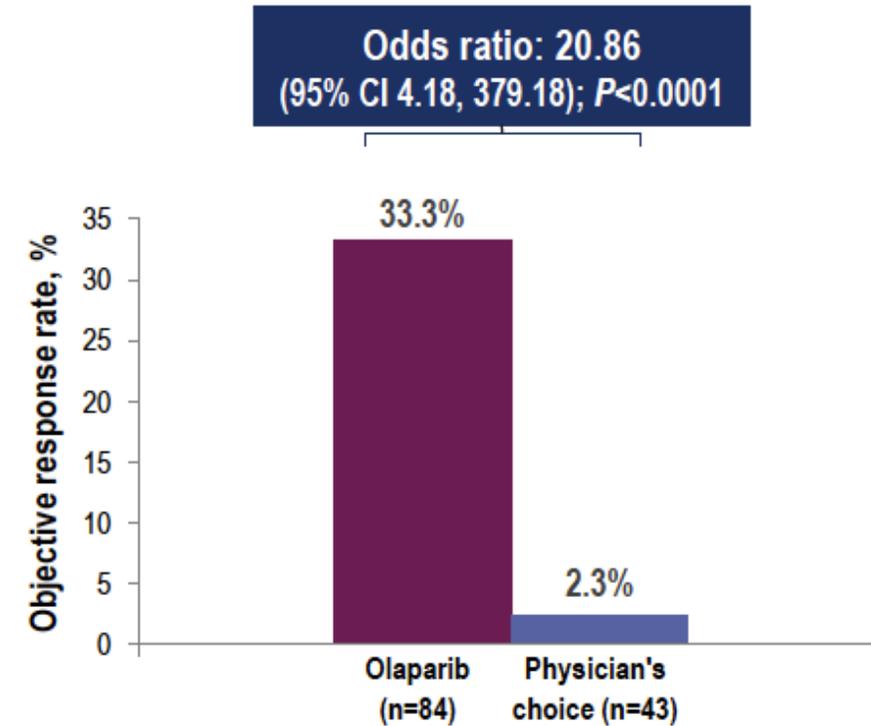
PROfound phase III: Overall Survival

Cohort A

	Olaparib (N=162)	Control (N=83)
Events, n (%)	91 (56)	57 (69)
Median OS	19.1 months	14.7 months
HR (95% CI)	0.69	
	(0.50–0.97); P=0.0175	

+ 4.4 mo

Overall survival (%)

Time since randomization (months)

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   74   69   64   58   50   43   37 27 18 15 11   9 6 3 1 0

Cohort A with adjustment for crossover*

Crossover rate†	67% (56/83)
HR (95% CI)	0.42
	(0.19–0.91)

Overall survival (%)

Time since randomization (months)

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

De Bono, ESMO 2020

PROfound phase III: Exploratory gene-level analysis of final OS

Subgroup	Olaparib n/N	Control n/N	Overall population	HR (95% CI)
Alteration in any single HRR gene	148/239	81/120		0.79 (0.60–1.04)
Cohort A				
BRCA1 (n=13)	5/8	5/5		0.42 (0.12–1.53)
BRCA2 (n=128)	39/81	32/47		0.59 (0.37–0.95)
ATM (n=86)	39/62	15/24		0.93 (0.53–1.75)
Cohort B				
BARD1 (n=1)	0/0	1/1	NC	NC
BRIP1 (n=3)	1/2	1/1	NC	NC
CDK12 (n=89)	47/61	18/28		0.97 (0.57–1.71)
CHEK1 (n=2)	1/1	0/1	NC	NC
CHEK2 (n=12)	4/7	3/5		0.87 (0.19–4.44)
PALB2 (n=4)	2/3	1/1	NC	NC
PPP2R2A (n=10)	5/6	2/4		5.11 (1.10–35.73)
RAD51B (n=5)	2/4	1/1	NC	NC
RAD51D (n=1)	1/1	0/0	NC	NC
RAD54L (n=5)	2/3	2/2	NC	NC

0.06 0.25 1 4 16 64

← Olaparib better   Control better →

Patients with tumours harbouring a *BRCA1* or *BRCA2* alteration appeared to derive the greatest OS benefit from olaparib

Data are reported only for patients with an alteration in a single gene. HR and CI values were not calculated for subgroups in which fewer than five survival events occurred; none of the enrolled patients harboured alterations in *FANCL* or *RAD51C*. The sizes of the circles are proportional to the number of events.

De Bono, ESMO 2020

BRCA1 Versus *BRCA2* and PARP Inhibitor Sensitivity in Prostate Cancer: More Different Than Alike?

Outcome	TOPARP-A[14] BRCA1 n/N	TOPARP-A[14] BRCA2 n/N	TOPARP-B[15] BRCA1 n/N	TOPARP-B[15] BRCA2 n/N (95% CI)	PROfound[1] BRCA1 n/N (95% CI)	PROfound[1] BRCA2 n/N (95% CI)	TRITON2[2] BRCA1 n/N (95% CI)	TRITON2[2] BRCA2 n/N (95% CI)	TALAPRO-1[16] BRCA1 n/N	TALAPRO-1[16] BRCA2 n/N (95% CI)	Pooled Data BRCA1 n/N (%) (95% CI)	Pooled Data BRCA2 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

NOTE. n/N denotes the number of patients who achieved a given end point out of the total number of evaluable patients for that end point.

Abbreviations: NE, not evaluable; NR, not reported; ORR, objective response rate; PSA$_{50}$, confirmed 50% or greater PSA response rate; rPFS, radiographic progression-free survival.

Markowski, J Clin Oncol 2020

Should we move PARP inhibitors in I line for **Biomerker +** mCRPC?
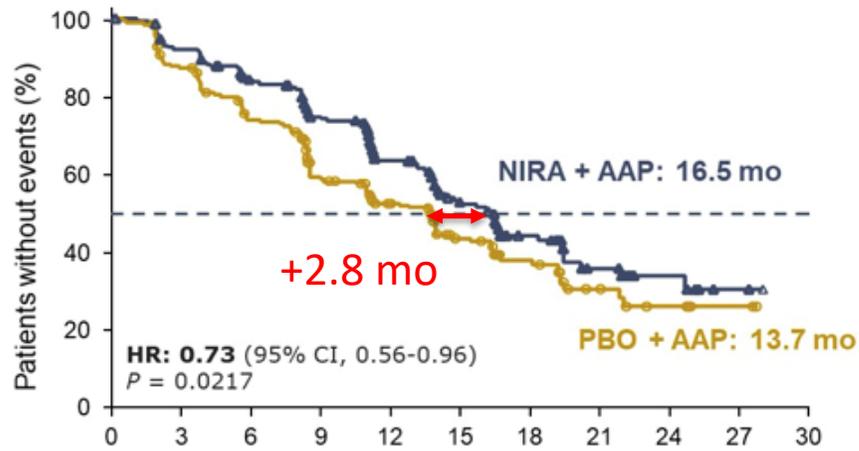
Magnitude phase III: Niraparib + AAP vs Placebo + AAP

All HRR biomarker +

BRCA1/2 Mutated

Overall Response Rate
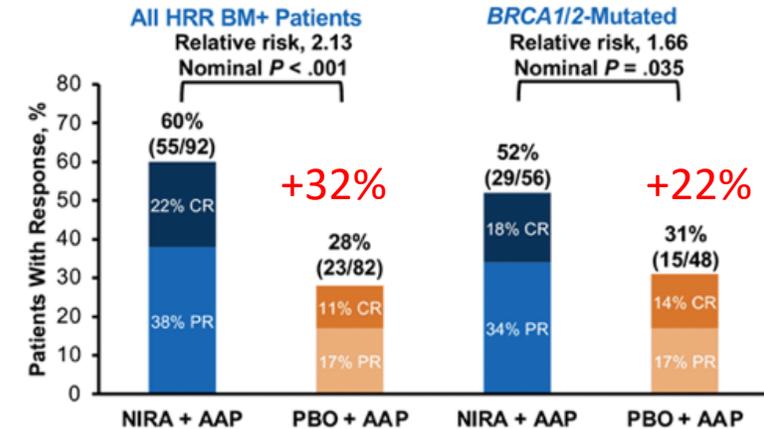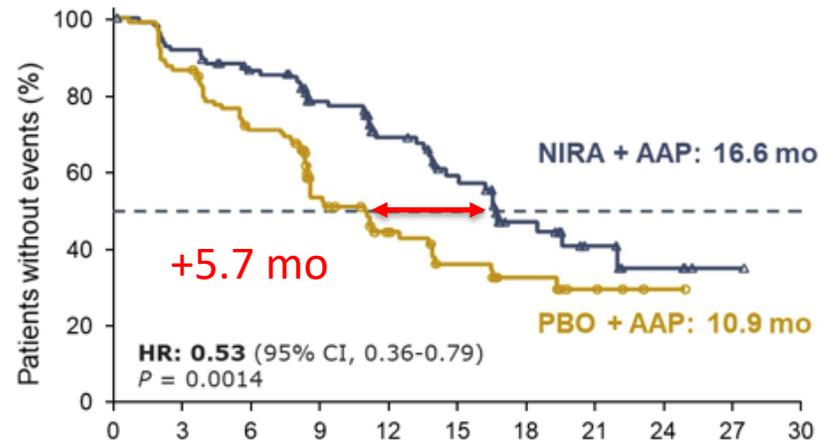
- Two distinct cohorts: with or without HRR genes alterations
- Prior ARTA, Docetaxel for mHSPC allowed

Overall survival awaited

Is PARP monotherapy enough?

Chi, ASCO GU 2022

Should we move PARP inhibitors in I line for **unselected** mCRPC?

PROpel phase III: Olaparib + AAP vs Placebo + AAP

Radiographic Progression free survival

	Abiraterone + olaparib (n=399)	Abiraterone + placebo (n=397)
Events, n (%)	168 (42.1)	226 (56.9)
Median rPFS (months)	24.8	16.6
HR (95% CI)	0.66 (0.54–0.81); *P*<0.001	
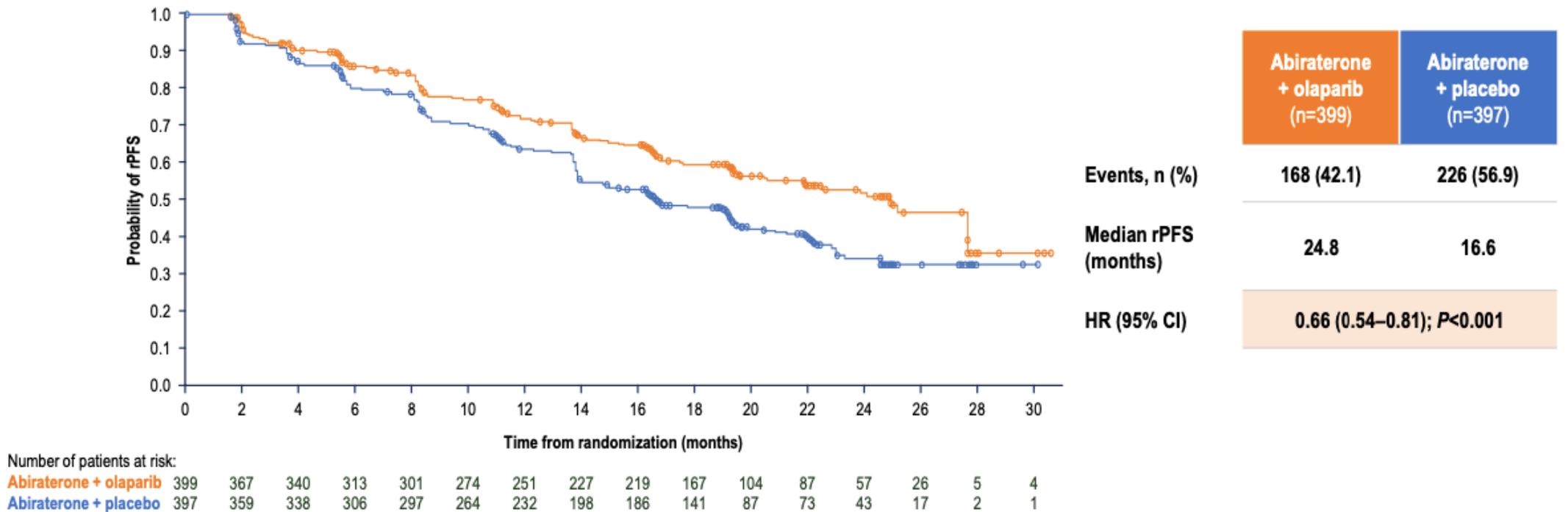
- Unselected population (HRR testing prospectively evaluated, tissue + ctDNA)
- Prior Docetaxel for mHSPC allowed (ARTA not allowed)

Saad, ESMO 2022

Should we move PARP inhibitors in I line for **unselected** mCRPC?

PROpel phase III: Olaparib + AAP vs Placebo + AAP

Radiographic Progression free survival

Saad, ESMO 2022
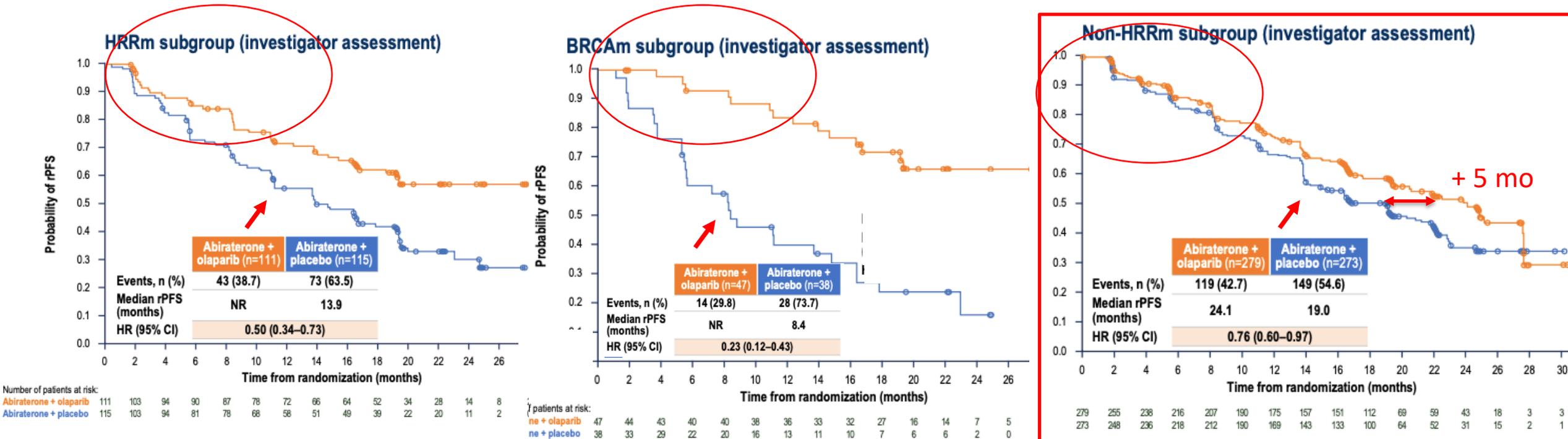
PARP inhibitors and NHA in I line for **non HRRm** mCRPC subgroup…
…..ready for primetime??

External consistency

Slightly 'incremental' activity with PARP combination

Overall response rate in the PROpel trial

Saad, ESMO 2022

Methodological considerations

- HRR is not a stratification factor

- Subgroup analysis

- Potential 'folse negative results' in the Non HRRm subgroup

- OS data immature

MAGNITUDE

Chi, ASCO GU 2022
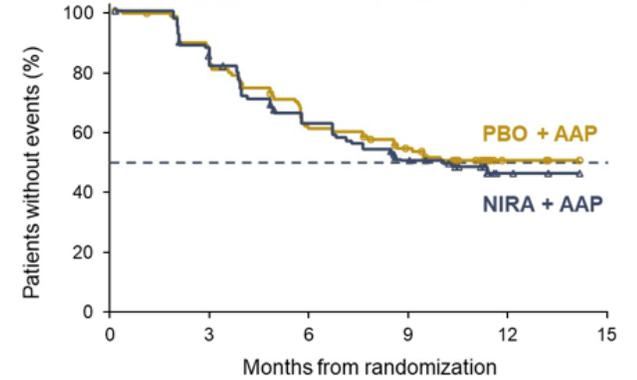
NCI918

Response	Abiraterone	Abiraterone + Veliparib	P	Interaction P
PSA	(n = 26)	(n = 34)		
PSA response	12 (46.2)	22 (64.7)	.15	.97
95% CI, %	27.0 to 65.3	48.6 to 80.8		
Measurable disease	(n = 19)	(n = 25)		
RECIST response	7 (36.8)	10 (40.0)	.83	.64
95% CI, %	15.2 to 58.5	20.8 to 59.2		

DNA-Repair WT/Monoallelic (n = 60) — No. (%)

...more evidence needed

Hussain, J clin Onc 2018
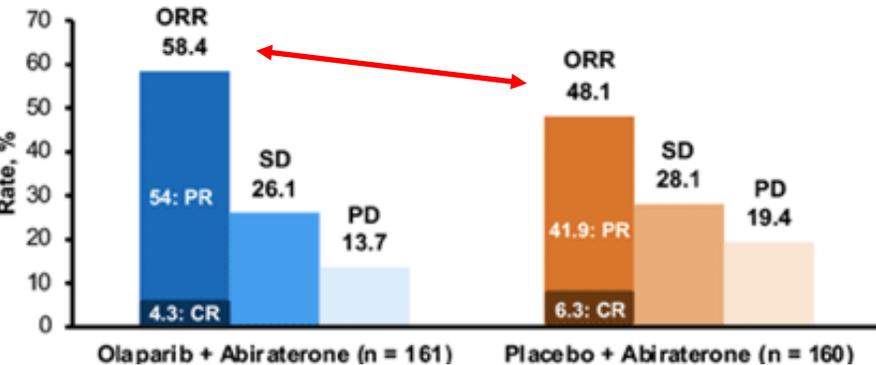
PARP inhibitors + NHA in first-line mCRPC: ongoing phase III trials

Talapro-2
First-line Talazoparib + Enzalutamide

International, 2-part phase III trial
- Part 1: nonrandomized
- Part 2: randomized, double-blind placebo controlled study

Stratification factors:
- Prior
- DDR

Primary end points: rPFS in DDR unselected and DDR mutant

Agarwal. ASCO 2020. Abstr TPS5598. NCT03395197.

Pfizer Announces Positive Topline Results from Phase 3 TALAPRO-2 Trial

Tuesday, October 04, 2022 - 06:45am

- TALZENNA® first PARP inhibitor to demonstrate clinical benefit in combination with XTANDI® in metastatic castration-resistant prostate cancer (mCRPC)
- Study achieves primary endpoint of radiographic progression-free survival
- Robust, highly consistent efficacy demonstrated in mCRPC both with or without homologous recombination repair gene mutations

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CASPAR
First-line Rucaparib + Enzalutamide

Randomized, open-label phase III

mCRPC
No prior therapy for mCRPC
Prior treatment for mHSPC or nmCRPC allowed
No screening for mutated HRR
Genes required for trial entry

→ Rucaparib + Enzalutamide

→ Placebo + Enzalutamide

Stratification factors:
- HRR status

Primary end points: rPFS, OS

Alliance for Clinical Trials in Oncology. NCT04455750.

Clinical case: 58 years old man with mCRPC

ECOG PS: 0 - PSA 120 ng/ml

Biopsy: Adenocarcinoma GS 4+5

➤ Bone scan: multiple metases (extra axial spread)

➤ CT scan: enlarged pelvic and retroperitoneal nodes

ADT + Docetaxel x 6 ⇨ **ADT** (*PSA nadir 1 ng/ml*)

After 14 months

➤ PSA 10 ng/ml

➤ CT and Bone scan: nodal and bone PD (*4 new lesions*)

Genetic counseling

Somatic testing: BRCA2 biallelic mutation ⇨ **Germline testing**: mutation identified

Abiraterone Acetate + Prednisone and Donosumab (*PSA nadir 3 ng/ml*)

After 8 months

➤ PSA 28 ng/ml

➤ CT and Bone scan: bone PD

Olaparib (*PSA nadir 10 ng/ml*)

After 10 months

➤ CT and Bone scan: Bone and nodal (*5 cm retroperitoneal*) PD

Cabazitaxel x 6 cycles

BSC for 3 months

Later Lines

Sequencing of AR pathway Inhibitors

	[1]CARD Trial Abi/Enza after Enza/Abi	[2]PLATO trial Abi after Enza	[3]Canadian Abi after Enza	[3]Canadian Enza Afer Abi	[4]NCT02116582 Enza after Abi
Patient selection	PD ≤ 12 mo on NHA	pts witout PSA rise on ≥ 21 wks of Enza	PD on 1L Enza for mCRPC	PD on 1L Abi for mCRPC	≥ 24 wks of prior Abi
PSA decline ≥ 50%	13.5%	2%	4%	36%	19%
Time to PSA prog. (months)	1.7 (PFS)	2.8	1.7	3.5	5.7
rPFS (months)	3.7 Enza after Abi 4.8 Abi after Enza 3.4	5.6 (rPFS or Clin PFS)	NR	NR	8.1

1.de Wit, NEJM 2019; 2.Attard, J Clin Onc 2018; 3.Khaaf, Lanc Onc 2019; 4.De Bono, Eur Urol 2018

CARD Trial: Cabazitaxel vs NHA after prior NHA

- 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

R A N D O M I Z E

1:1
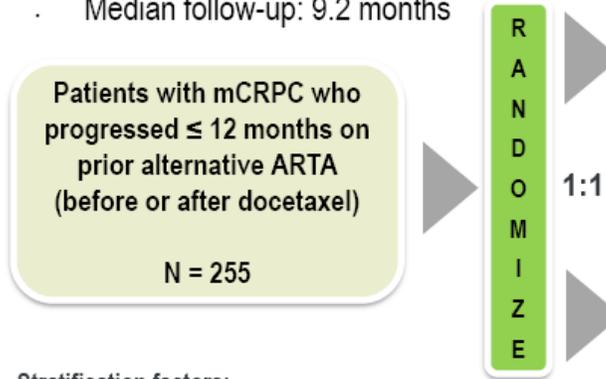
Cabazitaxel (25 mg/m^2 Q3W) + prednisone + G-CSF
n = 129

Abiraterone (1000 mg QD) + prednisone OR Enzalutamide (160 mg QD)
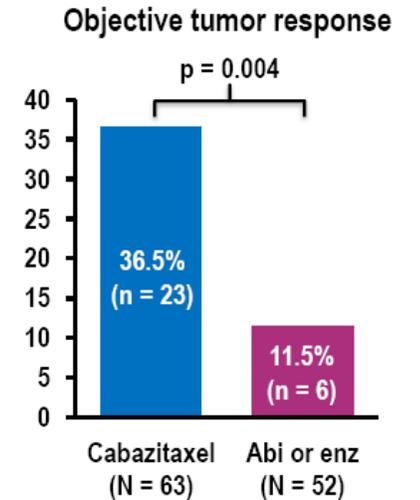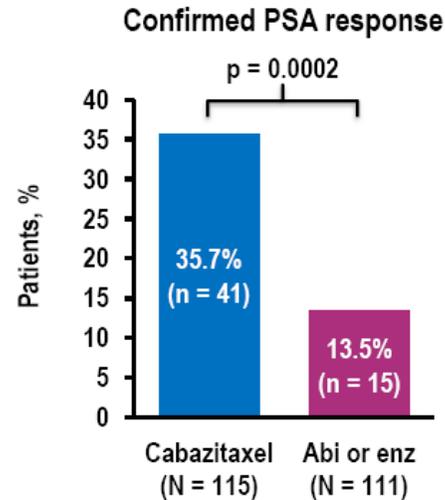**n = 126**

Endpoints

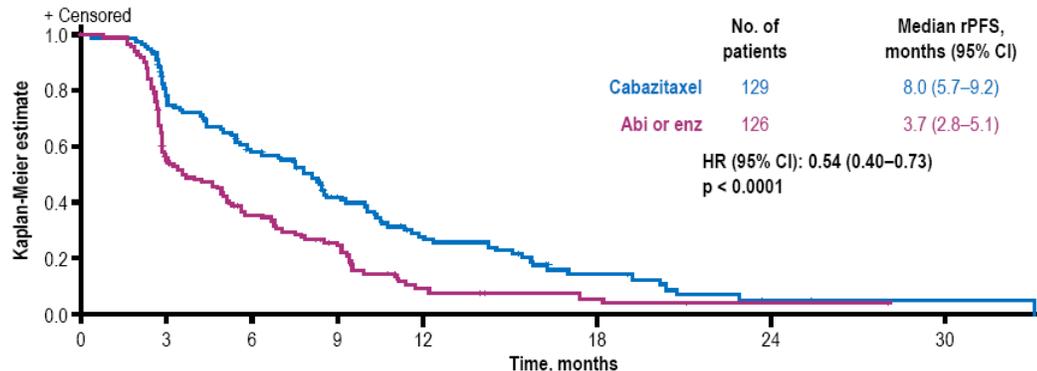Primary: rPFS

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

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

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)

Confirmed PSA response

p = 0.0002

- Cabazitaxel (N = 115): 35.7% (n = 41)
- Abi or enz (N = 111): 13.5% (n = 15)

Objective tumor response

p = 0.004

- Cabazitaxel (N = 63): 36.5% (n = 23)
- Abi or enz (N = 52): 11.5% (n = 6)

Radiographic progression free survival

	No. of patients	Median rPFS, months (95% CI)
Cabazitaxel	129	8.0 (5.7–9.2)
Abi or enz	126	3.7 (2.8–5.1)

HR (95% CI): 0.54 (0.40–0.73)
p < 0.0001

No. at risk
Cabazitaxel	129	91	64	41	23	9	2	1
Abi or enz	126	61	36	22	7	3	1	0

Overall survival

	No. of patients	Median OS, months (95% CI)
Cabazitaxel	129	13.6 (11.5–17.5)
Abi or enz	126	11.0 (9.2–12.9)

HR (95% CI): 0.64 (0.46–0.89)
p = 0.0078
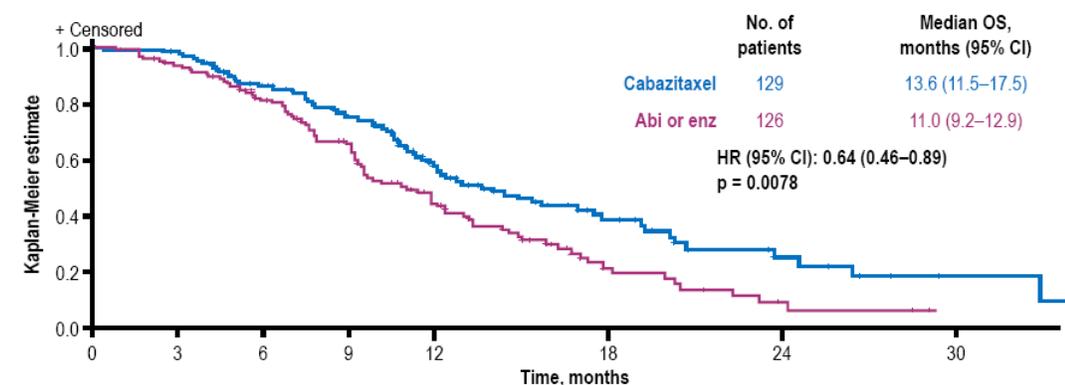
No. at risk
Cabazitaxel	129	122	96	77	51	21	8	2
Abi or enz	126	116	88	64	39	11	3	0

de Wit, ESMO 2019

Cabazitaxel in DDR+ and DDR- mCRPC

PSA decline on cabazitaxel DDR+ vs DDR- 32% vs 36%, p = 0.64

BRCA1/2 vs **non-BRCA** vs **DDR-** 27% vs 35% vs 36%, p=0.62.

Aldea, ESMO 2020
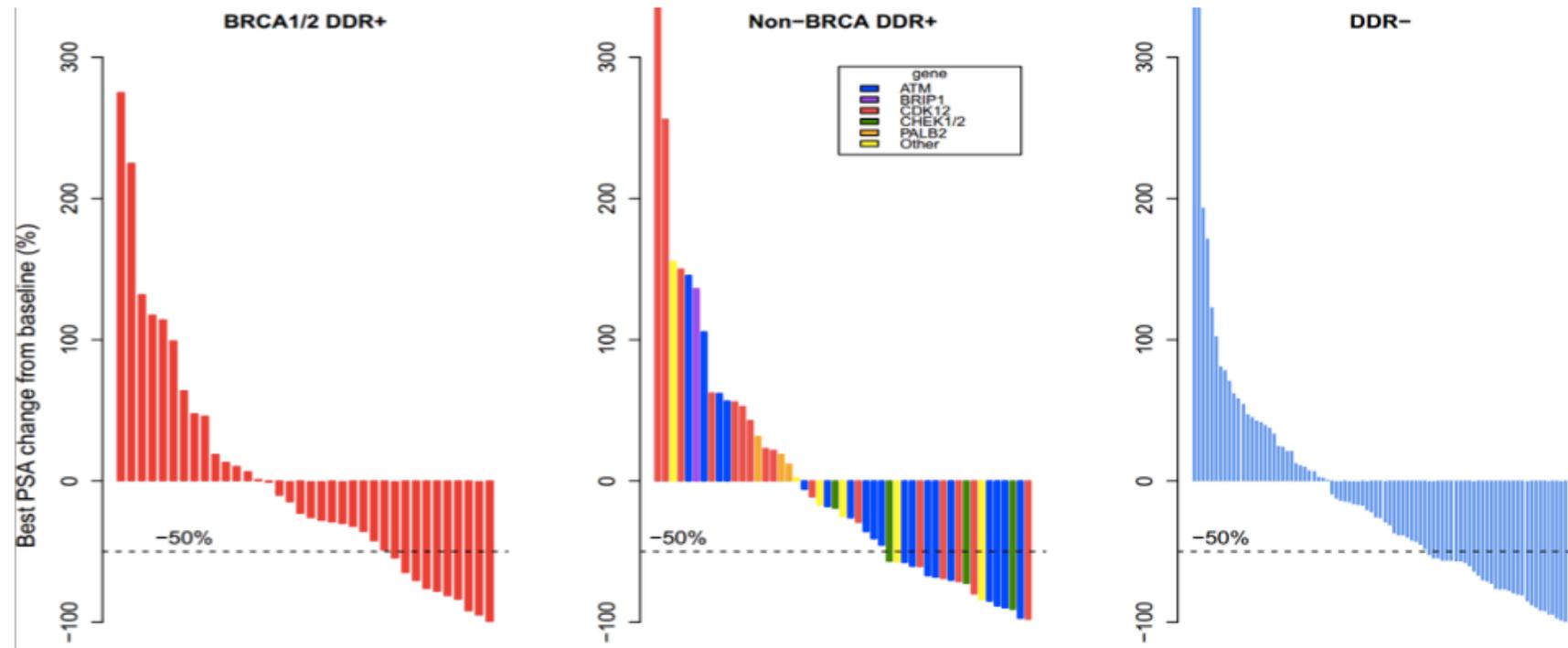
Radium-223 radioligand therapy

[1]ALSYMPCA Eligibility Criteria

- Symptomatic mCRPC
- ≥ 2 bone metastases
- No known visceral mets
- *Post docetaxel, unfit for docetaxel or refused docetaxel*

N = 901   2:1

R

Best SOC +
Radium-223
50 kBq/kg Q4W
up to 6 cycles

Placebo

Primary end point: OS

Overall Survival

Hazard ratio, 0.70 (95% CI, 0.58−0.83)
P<0.001

Radium-223
(median overall
survival, 14.9 mo)

Placebo
(median overall
survival, 11.3 mo)

Months since Randomization

No. at Risk

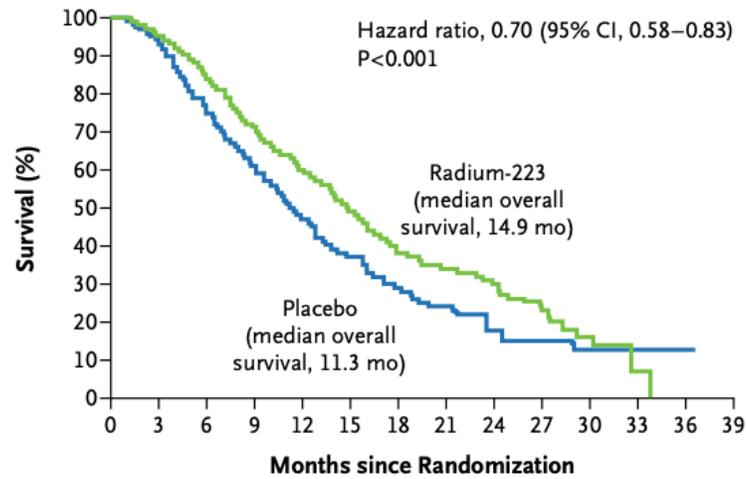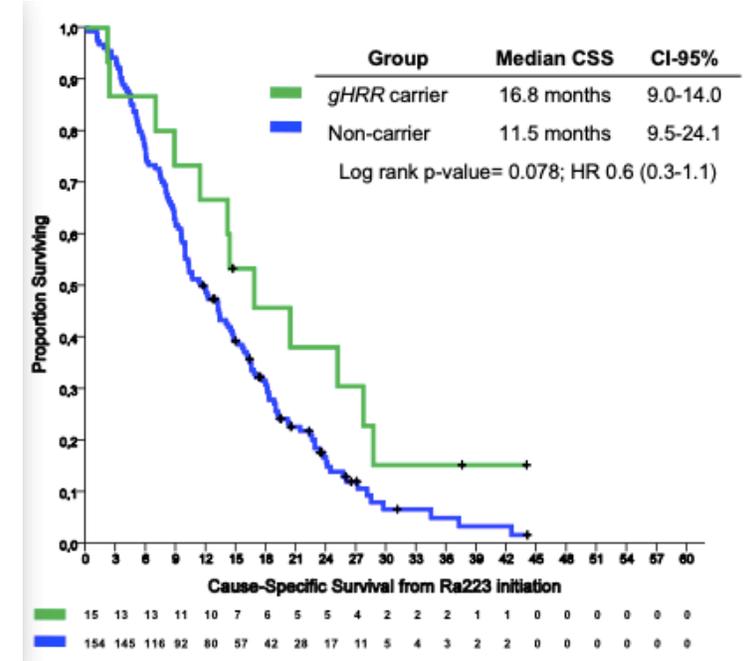|	0	3	6	9	12	15	18	21	24	27	30	33	36
Radium-223	614	578	504	369	274	178	105	60	41	18	7	1	0	0
Placebo	307	288	228	157	103	67	39	24	14	7	4	2	1	0

[2]PRORADIUM phase II trial

Cause spec. Survival by HRR status

Group	Median CSS	CI-95%
gHRR carrier	16.8 months	9.0-14.0
Non-carrier	11.5 months	9.5-24.1

Log rank p-value= 0.078; HR 0.6 (0.3-1.1)

Cause-Specific Survival from Ra223 initiation

15	13	13	11	10	7	6	3	2	2	1	1	1	0	0	0	0	0	0	0	0
154	145	116	92	80	57	42	28	17	11	5	4	3	2	2	0	0	0	0	0	0

Greater benefit in HRRm patients

1.Parker, NEJM 2013; 2.Castro, ESMO 2021

^{177}LU-PSMA-617 radioligand therapy: VISION phase III trial

Morris, ASCO 2021

VISION phase III trial: coprimary end points

Radiographic progression free survival

Hazard ratio: 0.40
(99.2% CI: 0.29, 0.57)
$p < 0.001$ (one-sided)

Median 8.7 vs 3.4 months

Overall survival

Hazard ratio: 0.62
(95% CI: 0.52, 0.74)
$p < 0.001$ (one-sided)

Median 15.3 vs 11.3 months

Morris, ASCO 2021

TheraP phase II trial: [177]LU-PSMA-617 vs Cabazitaxel
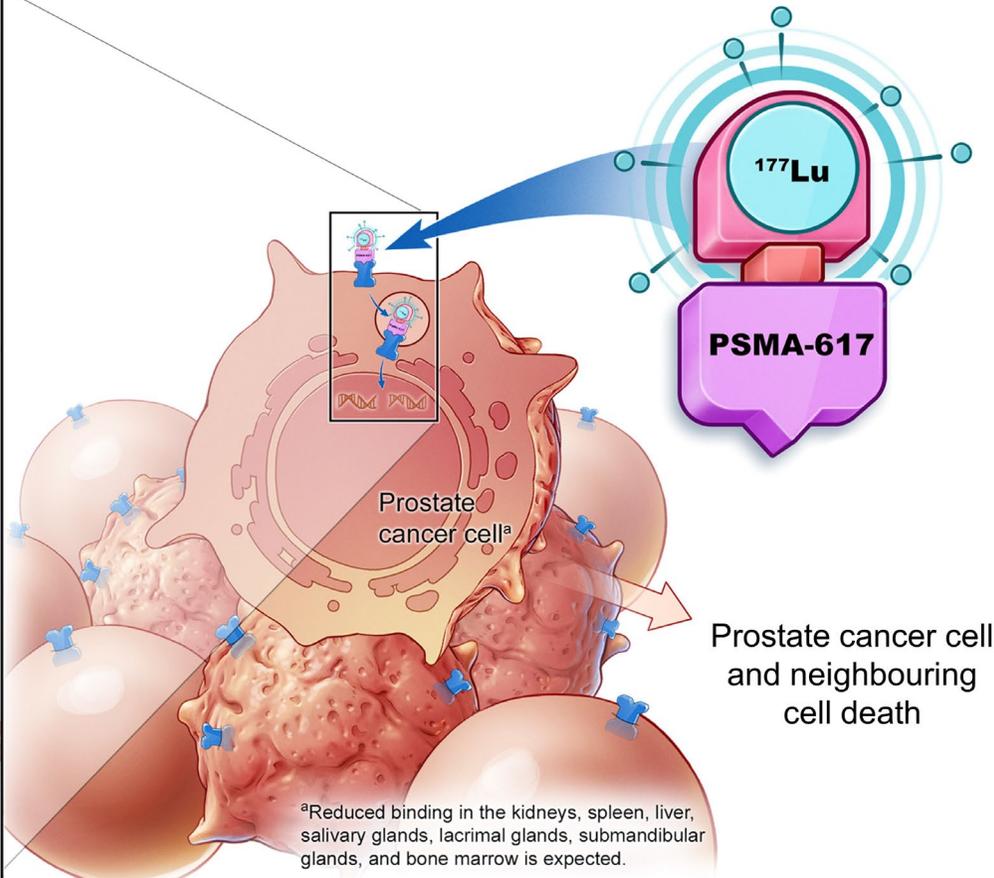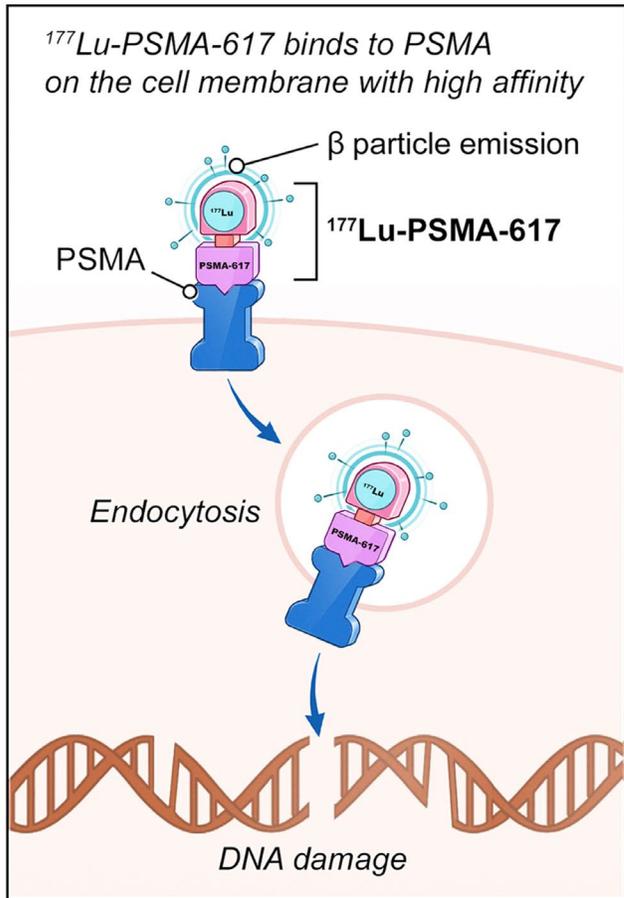
TheraP Eligibility Criteria

- mCRPC
  - Prior treatments
    - ➤ Progression on Docetaxel
  - PS of 0-2
  - PSMA PET+ and FDG PET+

  (no discordant results)

N = 200   1:1

R

Best SOC
[177]LU-PSMA-617
8.5 GBq Q6W
up to 6 cycles

Cabazitaxel
20 mg/mq
up to 10 cycles

Primary end point: PSA>50% Response rate

PSA >50% Response rate

PSA or rPFS
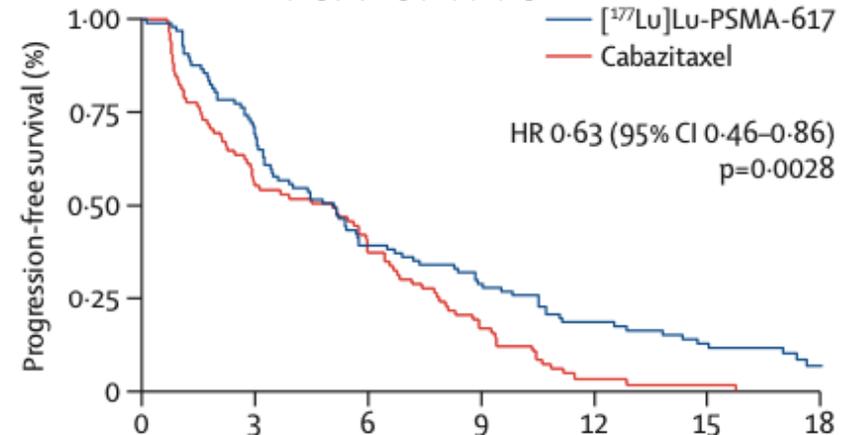
Number at risk							
Cabazitaxel	101	46	31	14	2	1	0
[177Lu]-PSMA-617	99	67	38	28	17	11	4

Hofman, Lancet Onc 2021

^{177}LU-PSMA-617 radioligand therapy: ptient selection

Activity in randomised trials

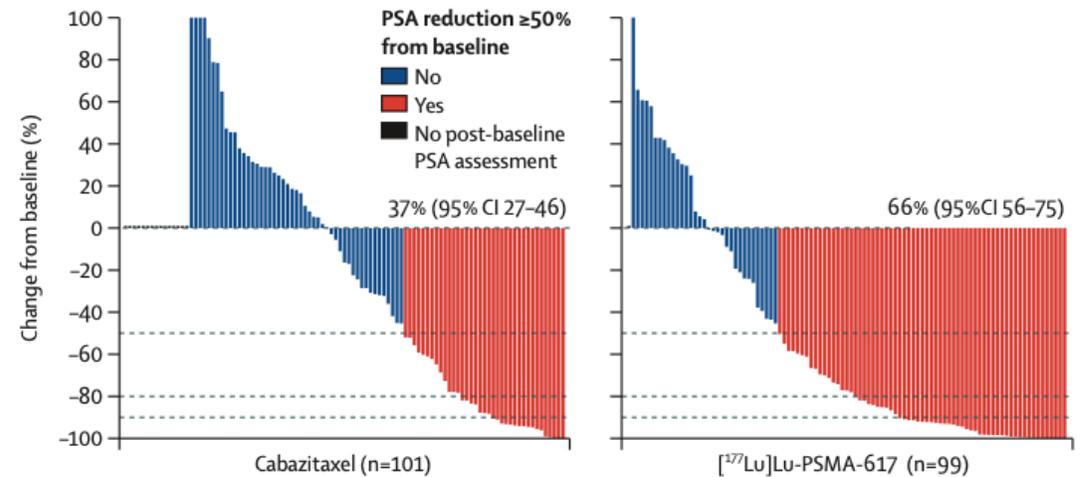|	[1]TheraP	[2]VISION	Δ
CONTROL ARM	Cabazitaxel	SOC	
Patient selection	PSMA PET + FDG PET	PSMA PET	
PSA ≥ 50% response	66%	46%	20%
ORR (RECIST)	49%	51%	2%

The narrower the selection the higher the response

Feaseability of double PET selection is an issue

[3]PSA response according to PSMA-PET SUV

Minor benefit in patients with PSMA SUVmean < 10

	Cabazitaxel (n/N)	Cabazitaxel, % (95% CI)	[177Lu]Lu-PSMA-617 (n/N)	[177Lu]Lu-PSMA-617, % (95% CI)	OR (95% CI)
PSMA SUVmean <10	23/71	32% (22–45)	33/64	52% (39–64)	2·22 (1·11–4·51)
PSMA SUVmean ≥10	14/30	47% (29–65)	32/35	91% (76–98)	12·19 (3·42–58·76)
Q1: PSMA SUVmean <6·9	12/28	43% (25–63)	6/21	29% (12–52)	0·53 (0·15–1·74)
Q2: PSMA SUVmean ≥6·9 to <8·5	3/20	15% (4–39)	18/29	62% (42–79)	9·27 (2·44–46·68)
Q3: PSMA SUVmean ≥8·5 to <10·8	11/30	37% (21–56)	17/22	77% (54–91)	5·87 (1·79–22·15)
Q4: PSMA SUVmean ≥10·8	11/23	48% (27–69)	24/27	89% (70–97)	8·73 (2·25–44·37)

0·25 1·0 2·0 4·0 8·0 16·0

Favours cabazitaxel → ← Favours [177Lu]Lu-PSMA-617

1.Sartor, NEJM 2021; 2.Hofman, Lanc Onc 2021; 3. Buteau, Lancet Onc 2022

^{177}Lu-PSMA-617 vs a chenage
in androgen receptor pathway inhibitor
in taxane naive patients with mCRPC
the PSMAfore phase III trial

www.clinicaltrials.gov: NCT04689828

^{177}Lu-PSMA-617 in combination
with standard of care vs SOC alone
in mHSPC: a phase III trial

www.clinicaltrials.gov: NCT04720157

Patient population
- mCRPC with disease pre...
  on previ...

Novartis Pluvicto™ shows statistically significant and clinically meaningful radiographic progression-free survival benefit in patients with PSMA–positive metastatic castration-resistant prostate cancer
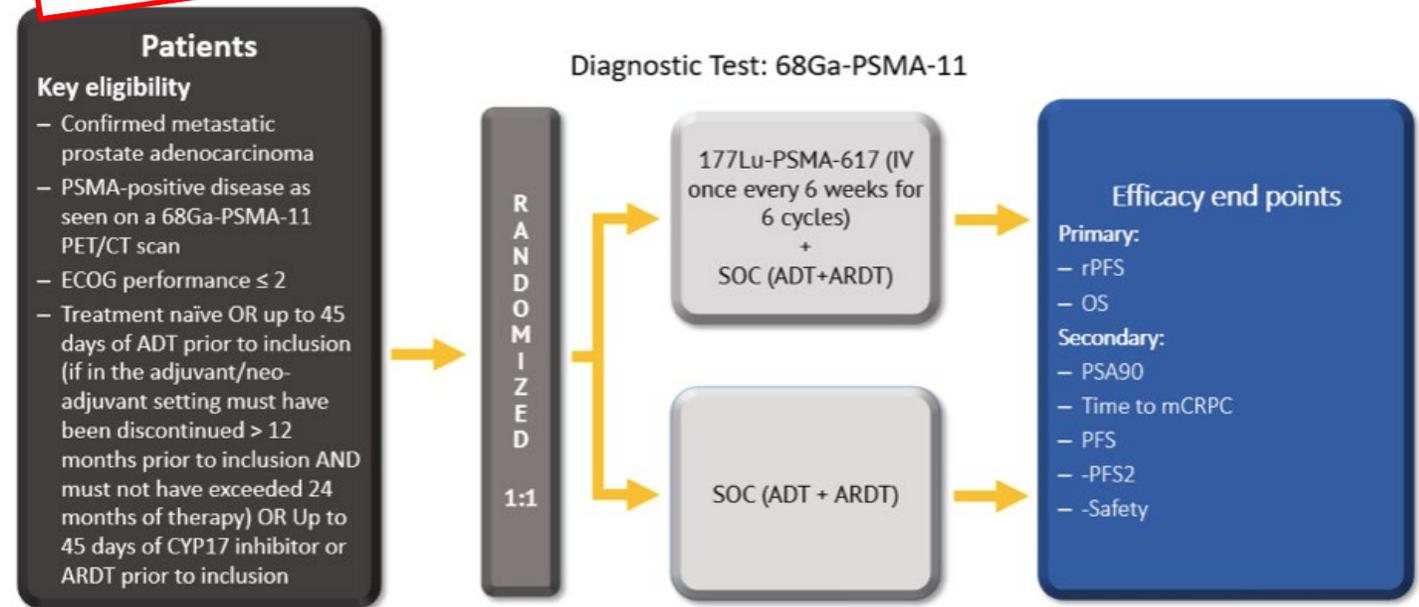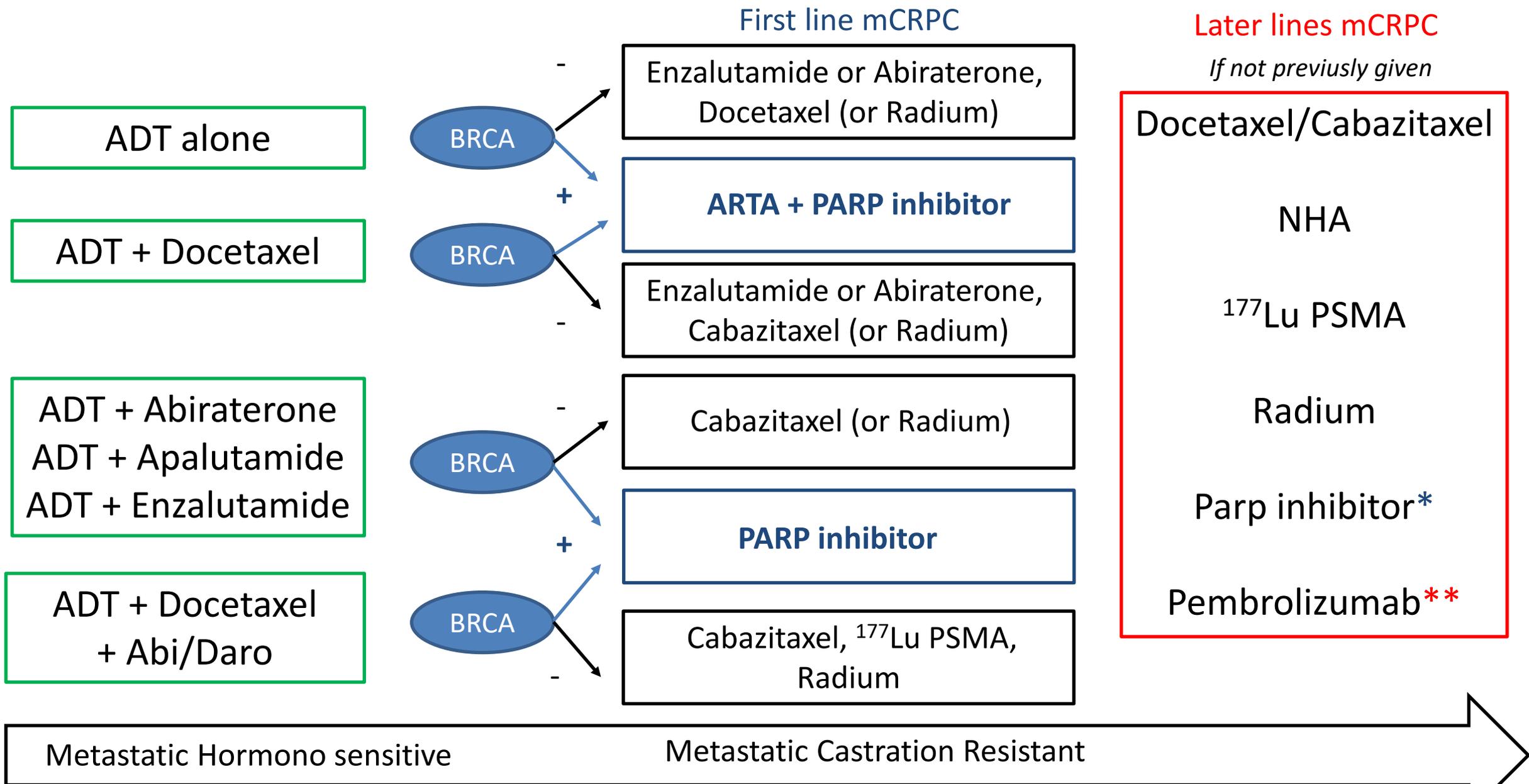
Dec 05, 2022

Ad hoc announcement pursuant to Art. 53 LR

- Phase III PSMAfore trial with Pluvicto™ met the primary endpoint of radiographic progression-free survival (rPFS) in PSMA–positive mCRPC who have been treated with androgen-receptor pathway inhibitor (ARPI) therapy[1]

- Pluvicto becomes the first PSMA-targeted radioligand therapy to demonstrate clinical benefit in mCRPC patients before receiving taxane-based chemotherapy[1], addressing a significant unmet need[2]

- Findings to be presented at an upcoming medical meeting and submitted to regulatory authorities for approval in 2023

- Novartis is advancing a broad portfolio of radioligand therapies to treat cancer and is investing in manufacturing capacity to meet the growing global demand for treatment

QoL (FACT-P, EQ-5D-5L, BPI-SF)

Patients
Key eligibility
- Confirmed metastatic prostate adenocarcinoma
- PSMA-positive disease as seen on a 68Ga-PSMA-11 PET/CT scan
- ECOG performance ≤ 2
- Treatment naïve OR up to 45 days of ADT prior to inclusion (if in the adjuvant/neo-adjuvant setting must have been discontinued > 12 months prior to inclusion AND must not have exceeded 24 months of therapy) OR Up to 45 days of CYP17 inhibitor or ARDT prior to inclusion

Diagnostic Test: 68Ga-PSMA-11

RANDOMIZED 1:1

177Lu-PSMA-617 (IV once every 6 weeks for 6 cycles) + SOC (ADT+ARDT)

SOC (ADT + ARDT)

Efficacy end points
Primary:
– rPFS
– OS
Secondary:
– PSA90
– Time to mCRPC
– PFS
– -PFS2
– -Safety

Treatment options in the evolving scenario of mCRPC

First line mCRPC

Later lines mCRPC

If not previusly given

ADT alone

ADT + Docetaxel

ADT + Abiraterone
ADT + Apalutamide
ADT + Enzalutamide

ADT + Docetaxel
+ Abi/Daro

BRCA

− Enzalutamide or Abiraterone, Docetaxel (or Radium)

+ **ARTA + PARP inhibitor**

BRCA

− Enzalutamide or Abiraterone, Cabazitaxel (or Radium)

BRCA

− Cabazitaxel (or Radium)

+ **PARP inhibitor**

BRCA

− Cabazitaxel, ^{177}Lu PSMA, Radium

Docetaxel/Cabazitaxel

NHA

^{177}Lu PSMA

Radium

Parp inhibitor*

Pembrolizumab**

Metastatic Hormono sensitive

Metastatic Castration Resistant

* if BRCA Mut   ** if MSI-H

Final remarks for mCRPC

Several life prolonging agents, seqence is unclear

Lack of data after combo treatment for mHSPC

BRCA testing **as soon as possible** ➡ New data in 1L mCRPC for BRCA Mutant

Don't forget bone protecting agents

Later lines:
  ➢ ARTA cross resistance well defined
  ➢ Cabazitaxel, Radium-223, ^{177}LU-PSMA, PARP Inhibitors, Pembro are options

Enroll your patients in clinical trials whenever possible