Management of m CRPC

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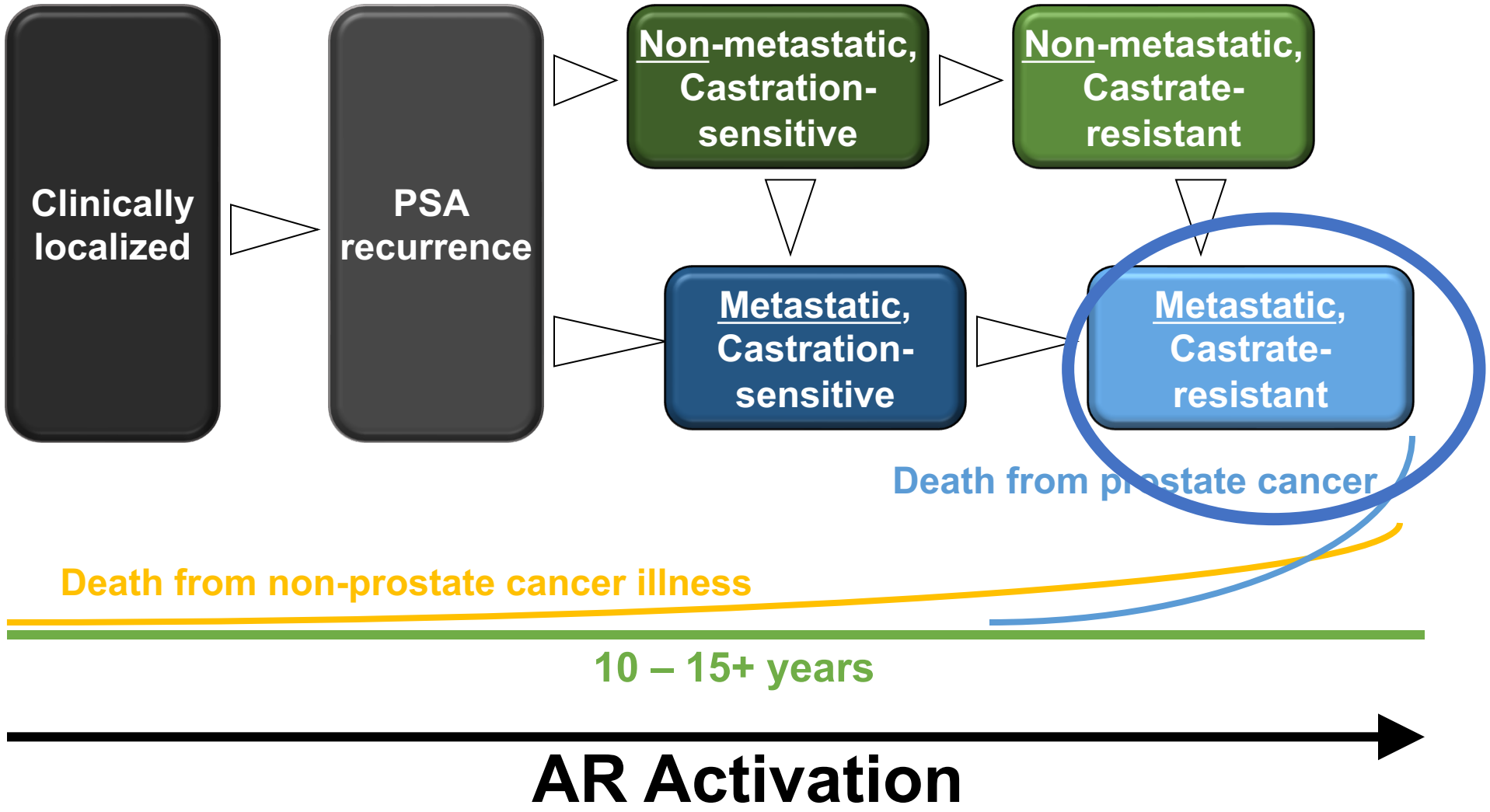
Stanford University

Clinical States of Prostate Cancer



National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: prostate cancer. Version 2.2017.

Classes of Approved Agents for CRPC

1. Hormonal Axis

- Enzalutamide
- abiraterone
- Apalutamide *
- Darolutamide *

2. Immunotherapeutic

- Sipuleucel –T
- Pembrolizumab for MSI-H/dMMR Cancer (not prostate-cancer specific)

3. Cytotoxic

- Docetaxel
- Cabazitaxel
- Mitoxantrone

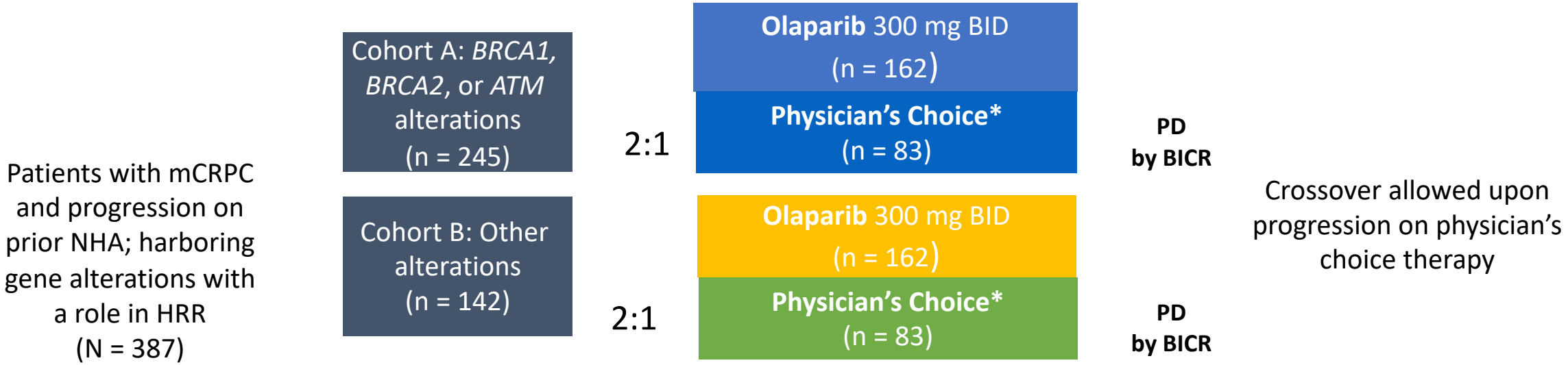
4. DNA Damage

- Radium 223 (radiopharmaceutical)
- Olaparib, rucaparib
- 617 PSMA-Lu177
- Abiraterone/Olaparib
- Enzalutamide/Talazoparib

*- approval in nmCRPC

Phase III PROfound: Olaparib vs Physician's Choice in Progressing Metastatic CRPC

Stratified by previous taxane (yes vs no) and measurable disease (yes vs no)



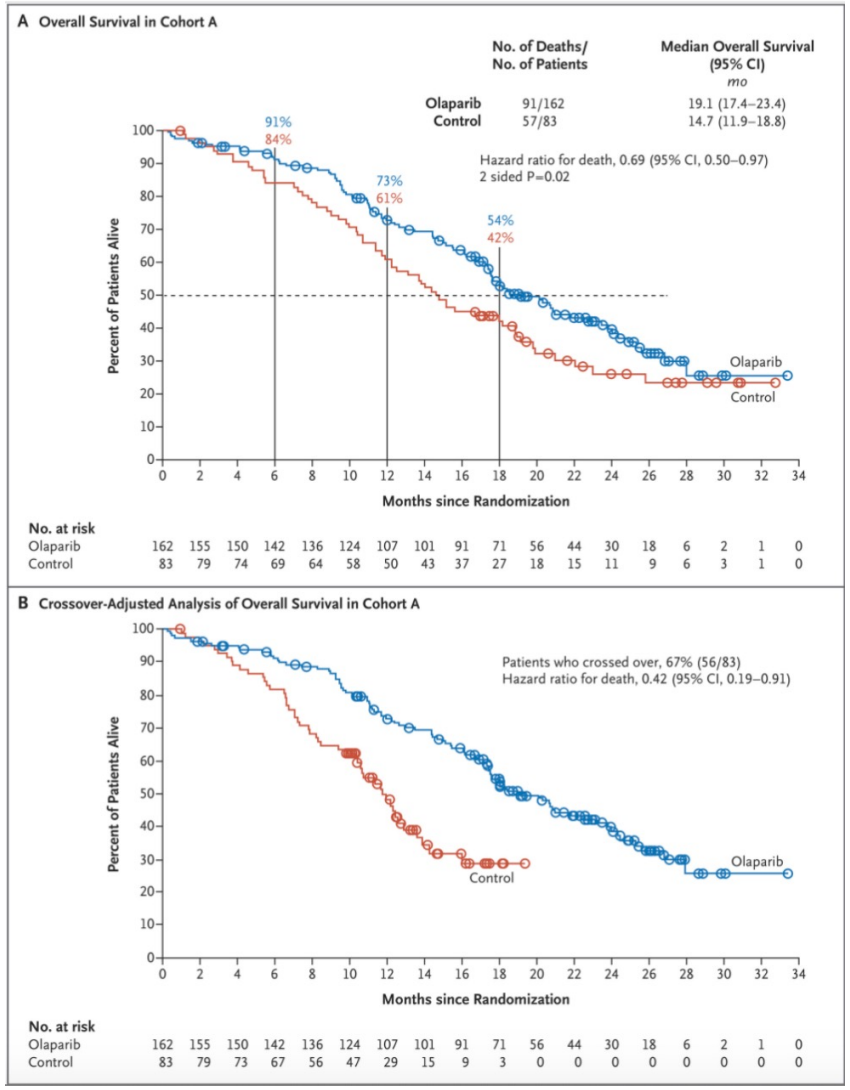
*Enzalutamide 160 mg QD or abiraterone acetate 100 mg QD plus prednisone 5 mg BID.

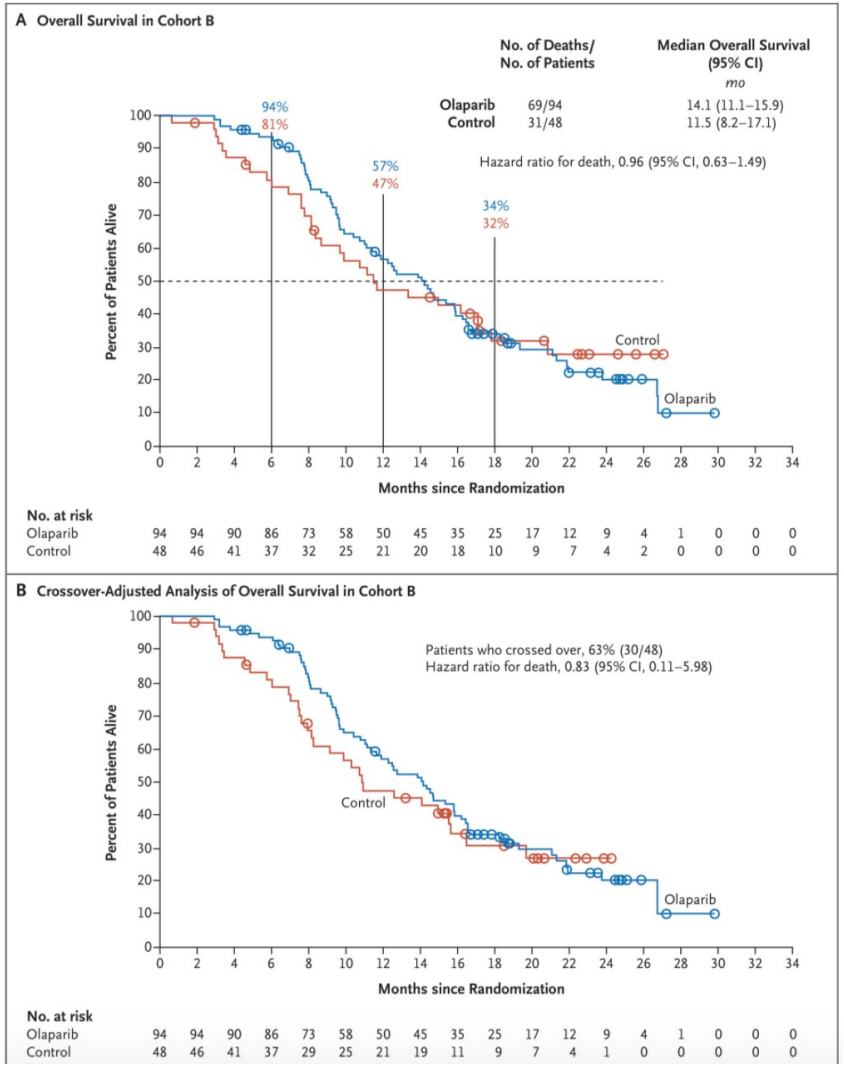
†***BRCA1/2, ATM, BRIP1, BARD1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RA51D, or RAD54L.***

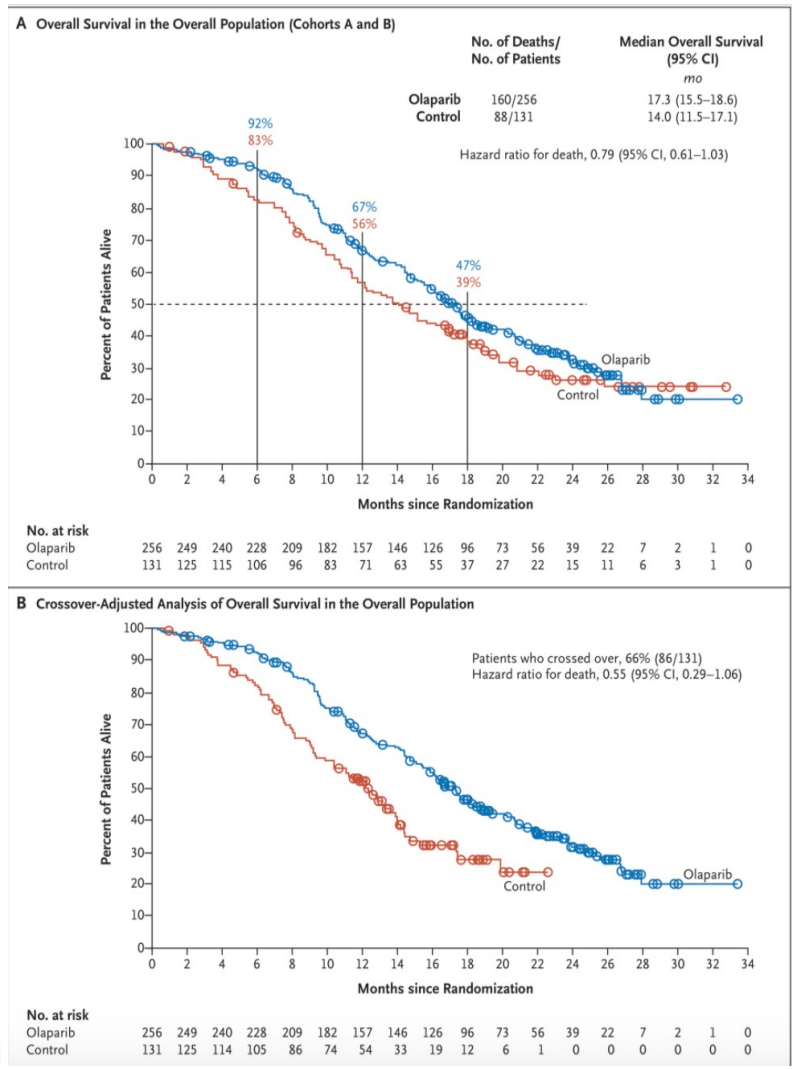
- Primary endpoint: radiographic PFS in Cohort A using RECIST 1.1 and PCWG3 by BICR
- Secondary endpoints: radiographic PFS in both cohorts, confirmed radiographic ORR in Cohort A, time to pain progression in Cohort A, OS in Cohort A

Hussain. NEJM 2020; de Bono. NEJM. 2020;382:2091.

ProFound OS: Cohort A/B/Overall

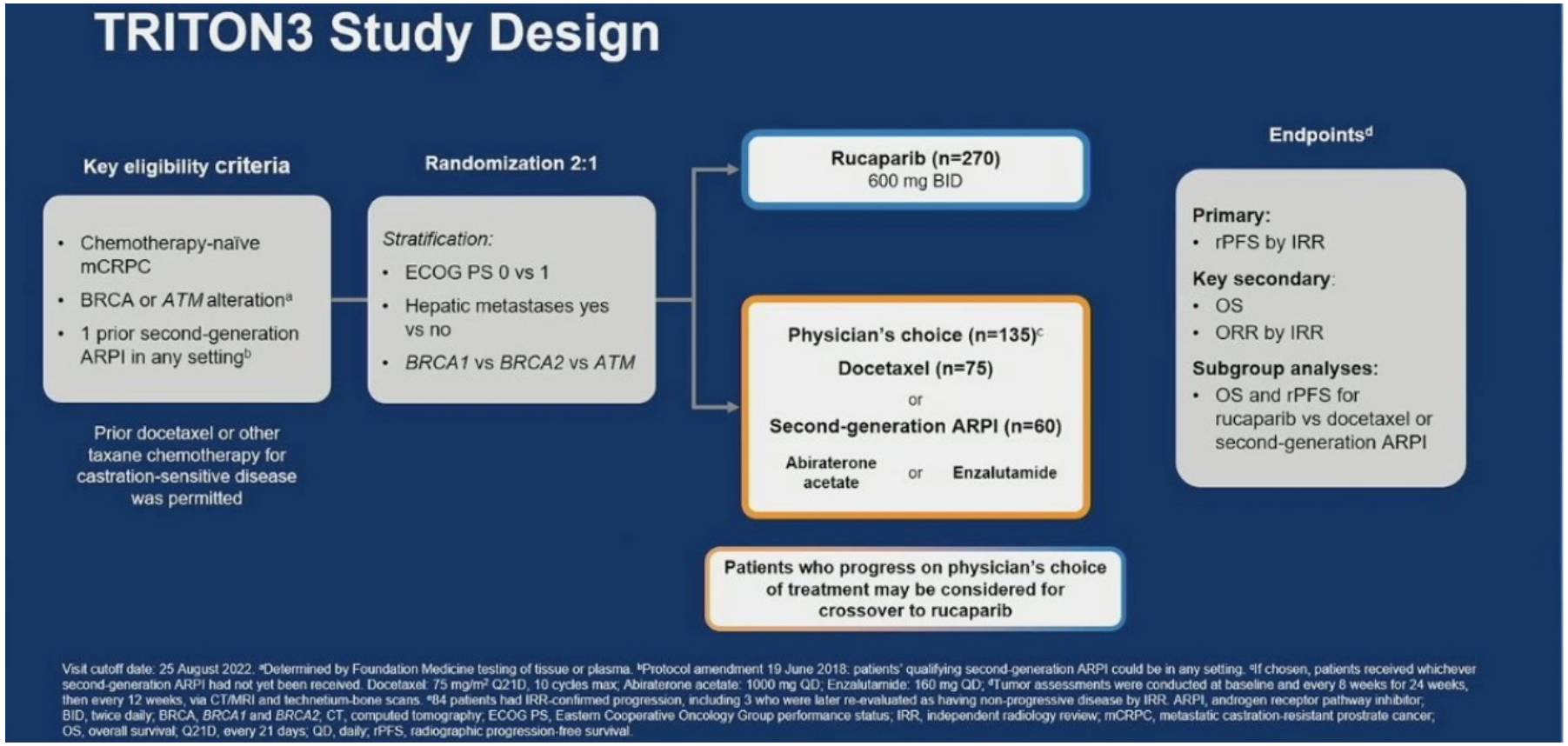




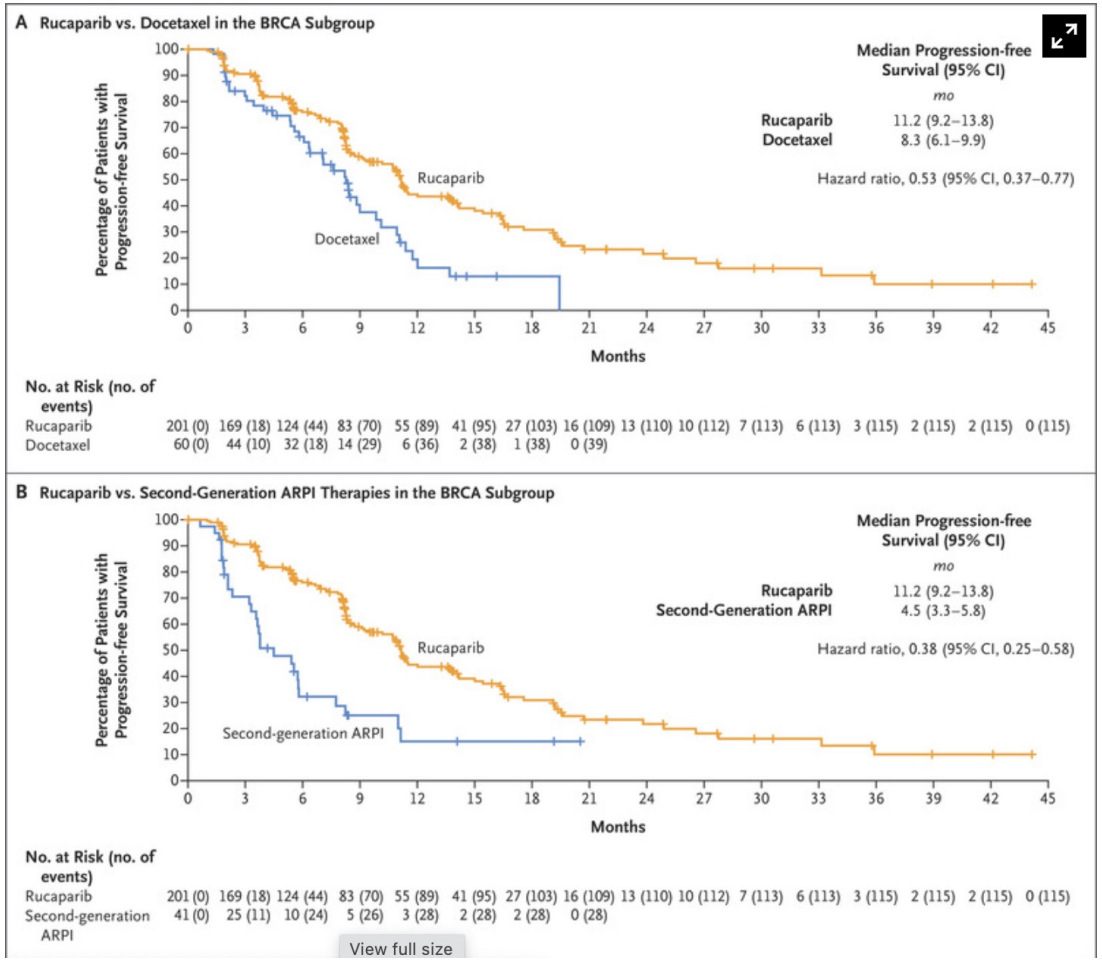


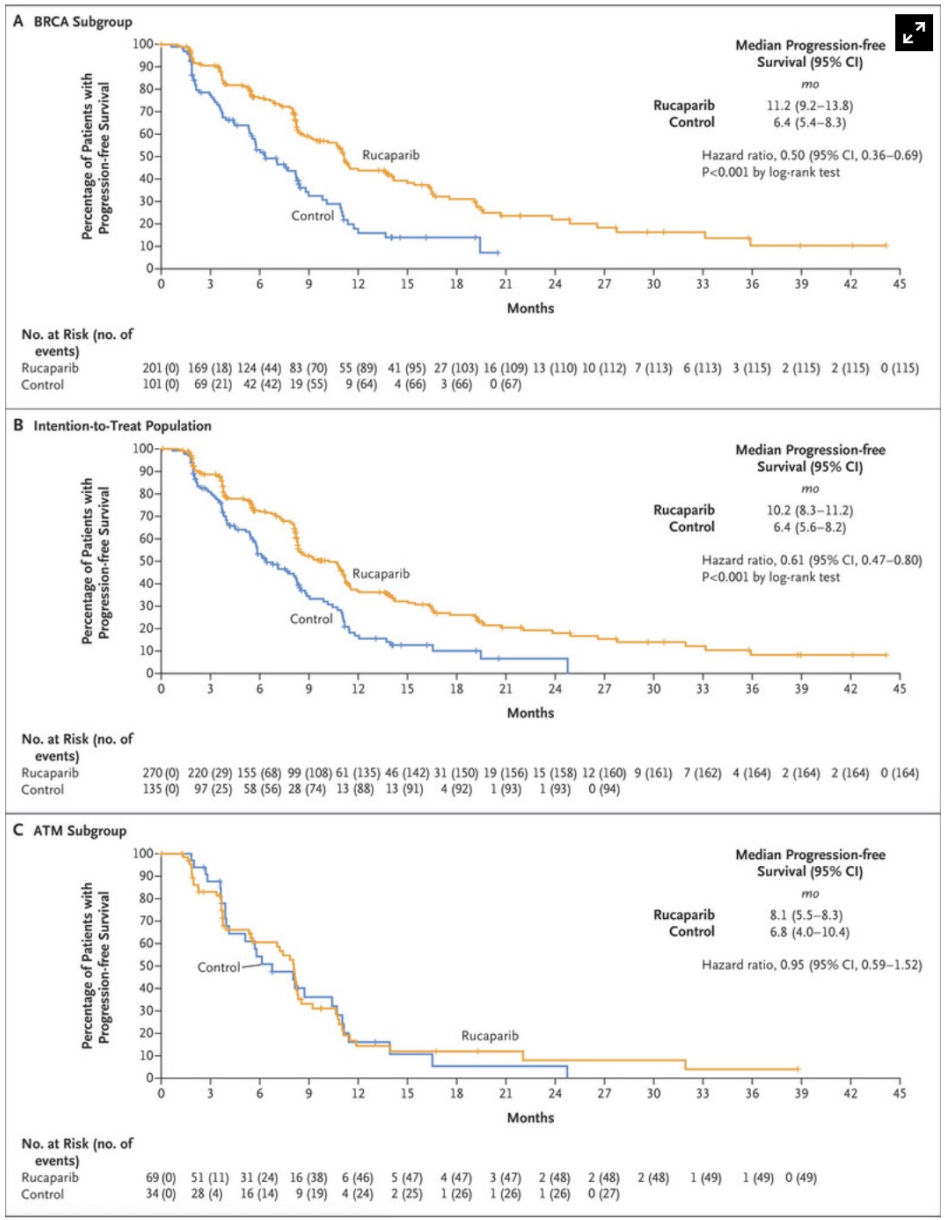
FDA approval May 19, 2020 for patients with HRR mutations who have progressed after abiraterone/enzalutamide

TRITON 3: Phase 3 study Rucaparib vs Physician Choice



TRITON 3 : Results

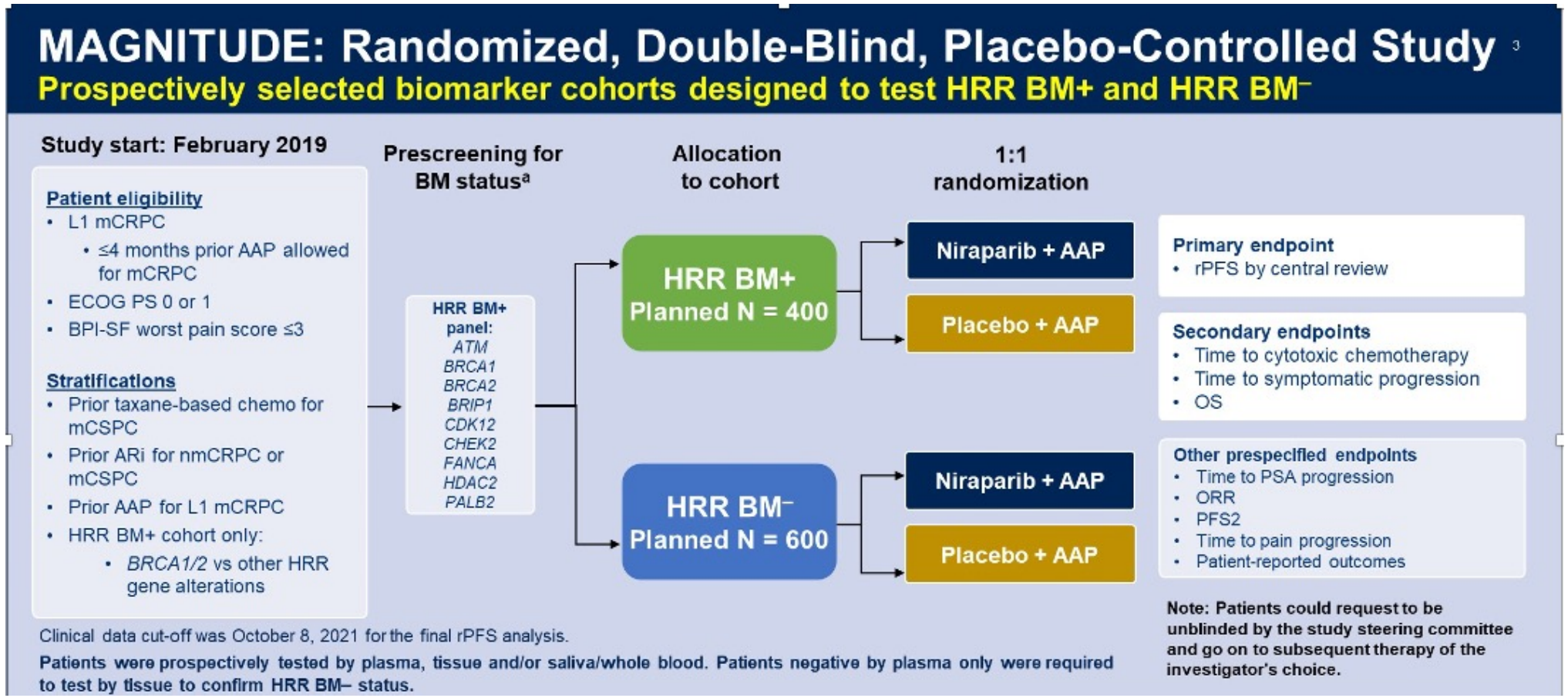




May 15 2020 approval in mCRPC post NHT/docetaxel with BRCA mutation

Fizazi NEJM 2023

Combinations of PARPI with NHT: Niraparib/Abiraterone



Results: NEGATIVE in Hrr neg : Closed for futility

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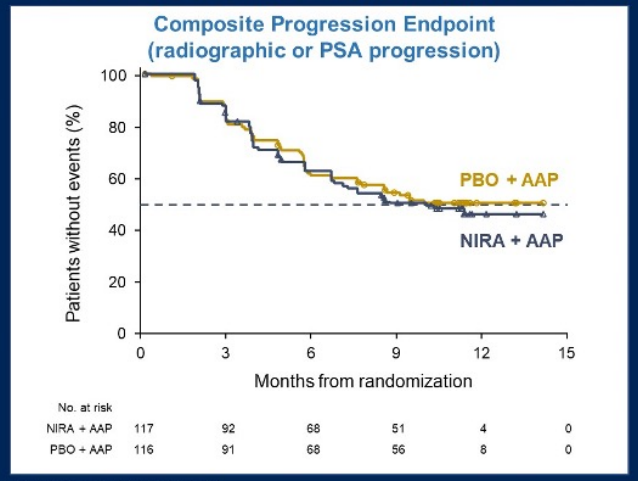
MAGNITUDE HRR BM⁻ : Prespecified Early Futility Analysis
No Benefit of NIRA + AAP in HRR BM⁻ Patients



- Composite endpoint[a] (N = 233)
  HR = 1.09[b] (95% CI 0.75-1.59)
  [futility was defined as ≥1]
- Additional grade 3/4 toxicity was observed using NIRA + AAP vs PBO + AAP
- With added toxicity and no added efficacy in patients with HRR BM⁻ mCRPC, the IDMC recommend stopping enrollment in this cohort

[b]Breakdown of composite endpoint events
83 PSA events (HR = 1.03, 95% CI 0.67-1.59)
65 rPFS events (HR = 1.03, 95% CI 0.63-1.67)

[a]rPFS or PSA progression, whichever occurred first
AAP, abiraterone acetate + prednisone/prednisolone; AE, adverse event; BM, biomarker; CI, confidence interval; HR, hazard ratio; HRR, homologous recombination repair; IDMC, independent data monitoring committee; mCRPC, metastatic castration-resistant prostate cancer; NIRA, niraparib; PBO, placebo; PSA, prostate specific antigen; rPFS, radiographic progression free survival

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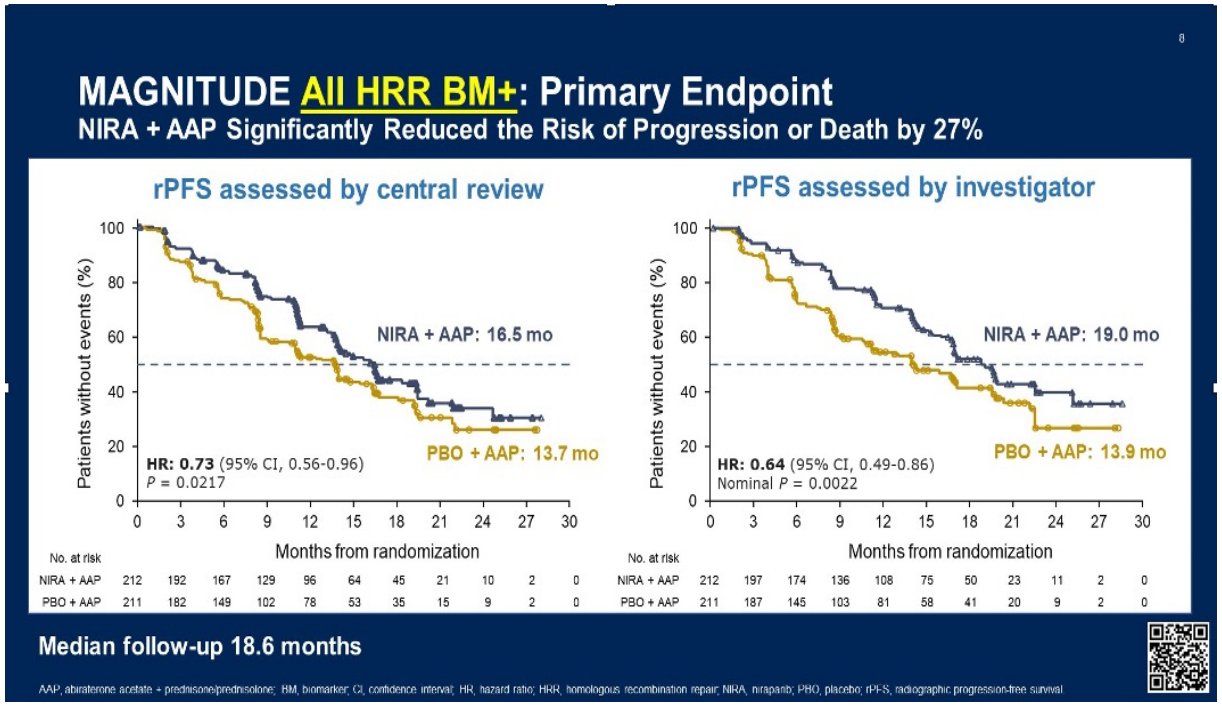
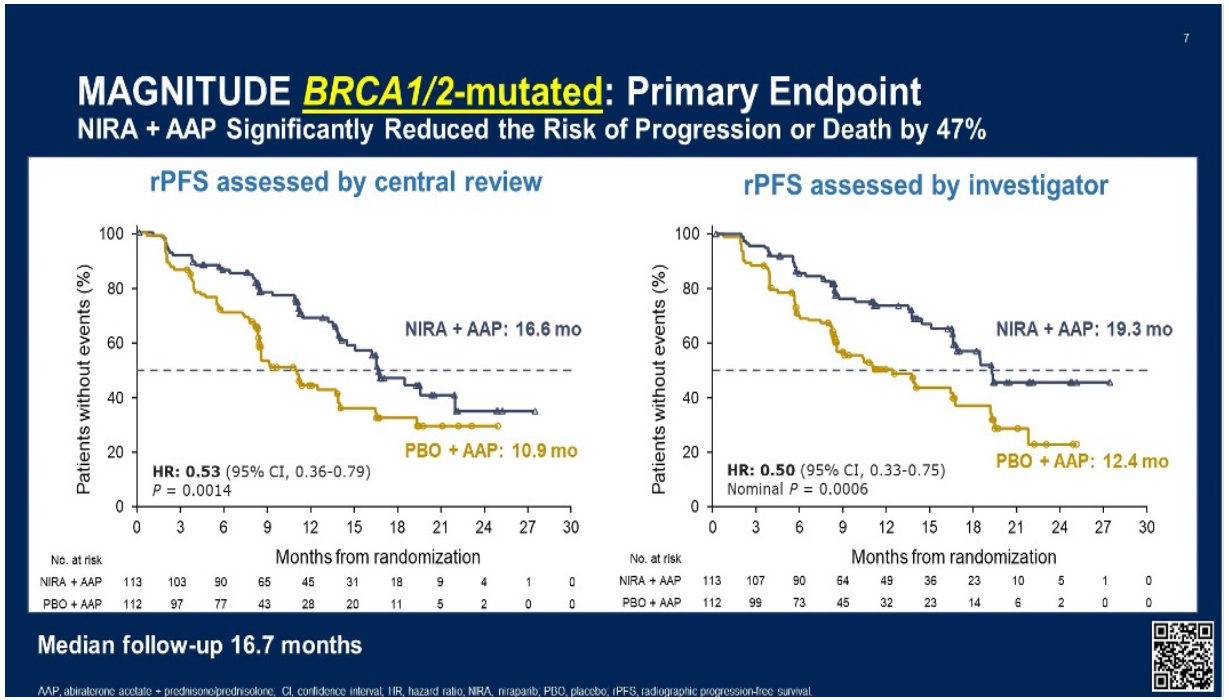
MAGNITUDE HRR BM+ Cohort: Patient Baseline Characteristics

	NIRA + AAP (n=212)	PBO + AAP (n=211)
Median age (range), yr	69 (45-100)	69 (43-88)
Biomarker alteration, n (%)		
BRCA2	86 (40.6)	88 (41.7)
BRCA1	12 (5.7)	4 (1.9)
ATM	43 (20.3)	42 (19.9)
CHEK2	18 (8.5)	20 (9.5)
PALB2	8 (3.8)	4 (1.9)
CDK12	5 (2.4)	8 (3.8)
FANCA, BRIP1 or HDAC2	11 (5.2)	13 (6.2)
Co-occurring alterations	29 (13.7)	32 (15.2)
BRCA containing co-occurring mutations	16 (7.5)	23 (10.9)
Median hemoglobin (range), g/L	129.0 (64.0-172.0)	131.0 (75.0-161.0)
Median LDH (range), enzyme U/L	199.0 (87.0-2959.0)	200.5 (77.0-1530.0)
ECOG, n (%) 0 / 1	130 (61.3) / 82 (38.7)	146 (69.2) / 65 (30.8)
Bone metastases, n (%)	183 (86.3)	170 (80.6)
Visceral metastases, n (%)	51 (24.1)	39 (18.5)
Liver	18 (8.5)	13 (6.2)
Lung	27 (12.7)	18 (8.5)
PSA at study entry (ug/L), median (range)	21.4 (0-4826.5)	17.4 (0.1-4400.0)
Prior taxane-based chemotherapy for nmCRPC/mCSPC, n (%)	41 (19.3)	44 (20.9)
Prior AR-targeted therapy for nmCRPC/mCSPC, n (%)	8 (3.8)	5 (2.4)
Prior AAP therapy for L1 mCRPC, n (%)	50 (23.6)	48 (22.7)

AAP, abiraterone acetate + prednisone/prednisolone; AR, androgen receptor; BM, biomarker; ECOG PS, Eastern Cooperative Oncology Group performance status; HRR, homologous recombination repair; L1, first line; LDH, lactate dehydrogenase; mCRPC, metastatic castration-resistant prostate cancer; mCSPC, metastatic castration-sensitive prostate cancer; NIRA, niraparib; nmCRPC, nonmetastatic castration-resistant prostate cancer; PBO, placebo; PSA, prostate-specific antigen

Biomarker Positive Cohorts:Improved rPFS in HRR + and in BRCA +





HR : Much better in the BRCA enriched population: BRCA prognostic biomarkers with worse outcome

Cougar 302: Abiraterone in mCRPC- PFS 16 months

Abiraterone/Olaparib: Phase 2 trial in unselected patients with mCRPC

N=171
Prior Docetaxel
HRR+=15%
HRR wildtype=21%
Partially characterized=63(neg by blood; not confirmed by tissue

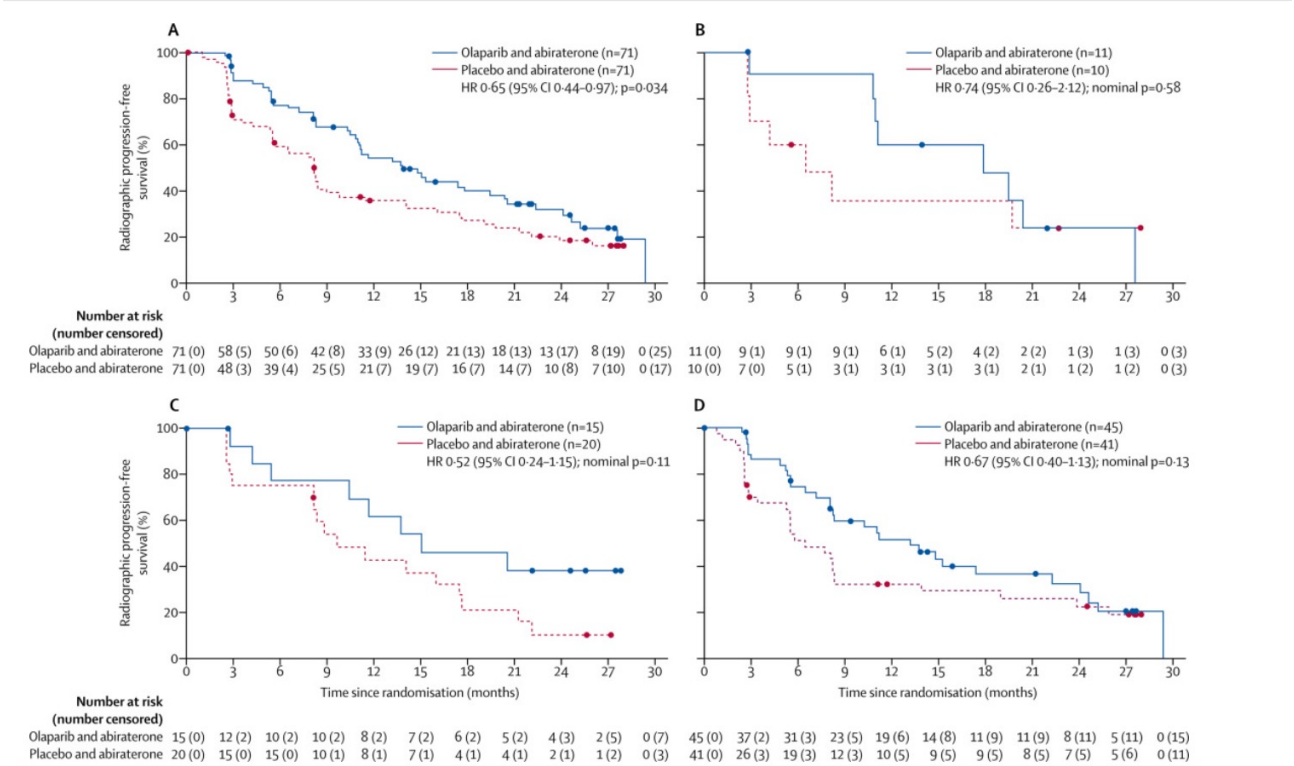


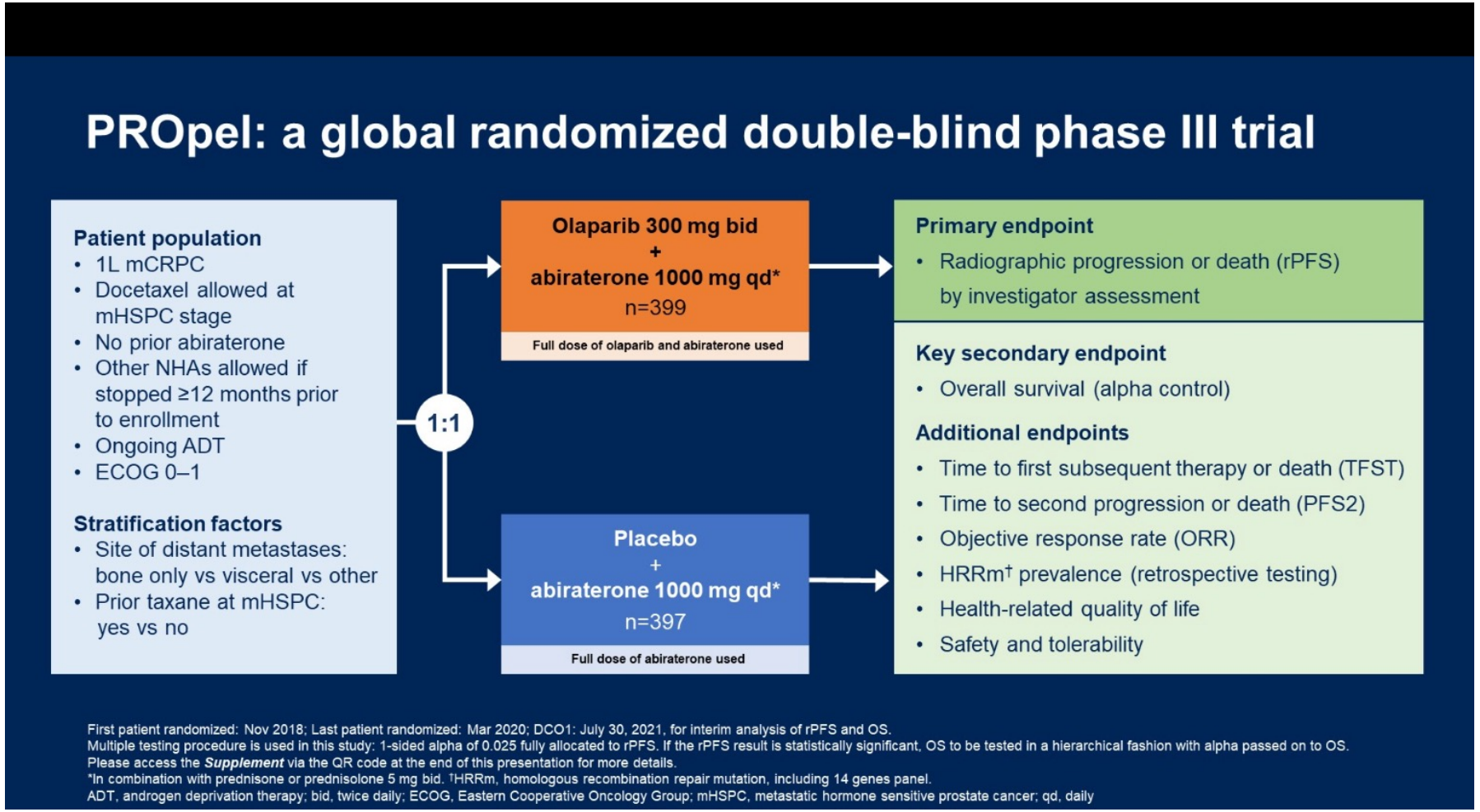
Figure 2

Radiographic progression-free survival in the (A) intention-to-treat population, (B) HRR mutation-positive subgroup, (C) wild-type HRR subgroup, and (D) partially characterised HRR status subgroup

HRR=homologous recombination repair. HR=hazard ratio.

Clarke Lancet Oncol 2018

Combination #2: Abiraterone/Olaparib



Patient Characteristics: RESULTS;rPFS improved in all comers

PROpel: baseline patient characteristics

Well-balanced between treatment arms

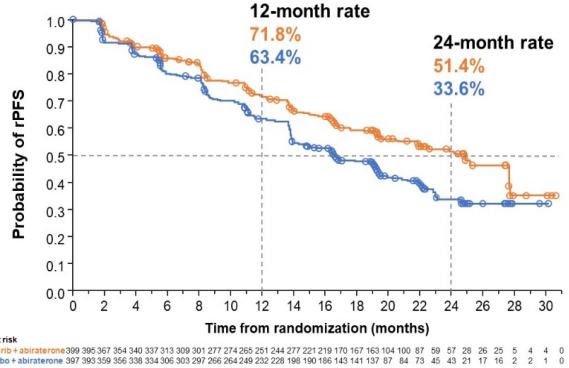
	Olaparib + abiraterone (n=399)	Placebo + abiraterone (n=397)
Median (range) age, years	69.0 (43–91)	70.0 (46–88)
ECOG performance status, n (%)		
0	286 (71.7)	272 (68.5)
1	112 (28.1)	124 (31.2)
Symptomatic (BPI-SF ≥ 4 and/or opiate use), n (%)	**103 (25.8)**	**80 (20.2)**
Site of metastases, n (%)		
Bone	349 (87.5)	339 (85.4)
Distant lymph nodes	133 (33.3)	119 (30.0)
Locoregional lymph nodes	82 (20.6)	89 (22.4)
Lung	40 (10.0)	42 (10.6)
Liver	15 (3.8)	18 (4.5)
Docetaxel treatment at mHSPC stage, n (%)	**90 (22.6)**	**89 (22.4)**
Median PSA, ug/L (IQR)	17.90 (6.09–67.00)	16.81 (6.26–53.30)
HRRm status†		
HRRm	**111 (27.8)**	**115 (29.0)**
Non-HRRm	**279 (69.9)**	**273 (68.8)**
HRRm unknown	**9 (2.3)**	**9 (2.3)**

†The HRRm status of patients in PROpel was determined retrospectively using results from tumor tissue and plasma ctDNA HRRm tests. Patients were classified as HRRm if (one or more) HRR gene mutation was detected by either test; patients were classified as non-HRRm if no HRR gene mutation was detected by either test; patients were classified as unknown HRRm if no valid HRR test result from either test was achieved. Please access the Supplement via the QR code at the end of this presentation for more details.

BPI-SF, Brief Pain Inventory – Short Form; ctDNA, circulating tumor DNA; IQR, interquartile range; PSA, prostate-specific antigen.

PROpel primary endpoint: rPFS by investigator-assessment

34% risk reduction of progression or death with olaparib + abiraterone



	Olaparib + abiraterone (n=399)	Placebo + abiraterone (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*<0.0001	

Pre-specified 2-sided alpha: 0.0324

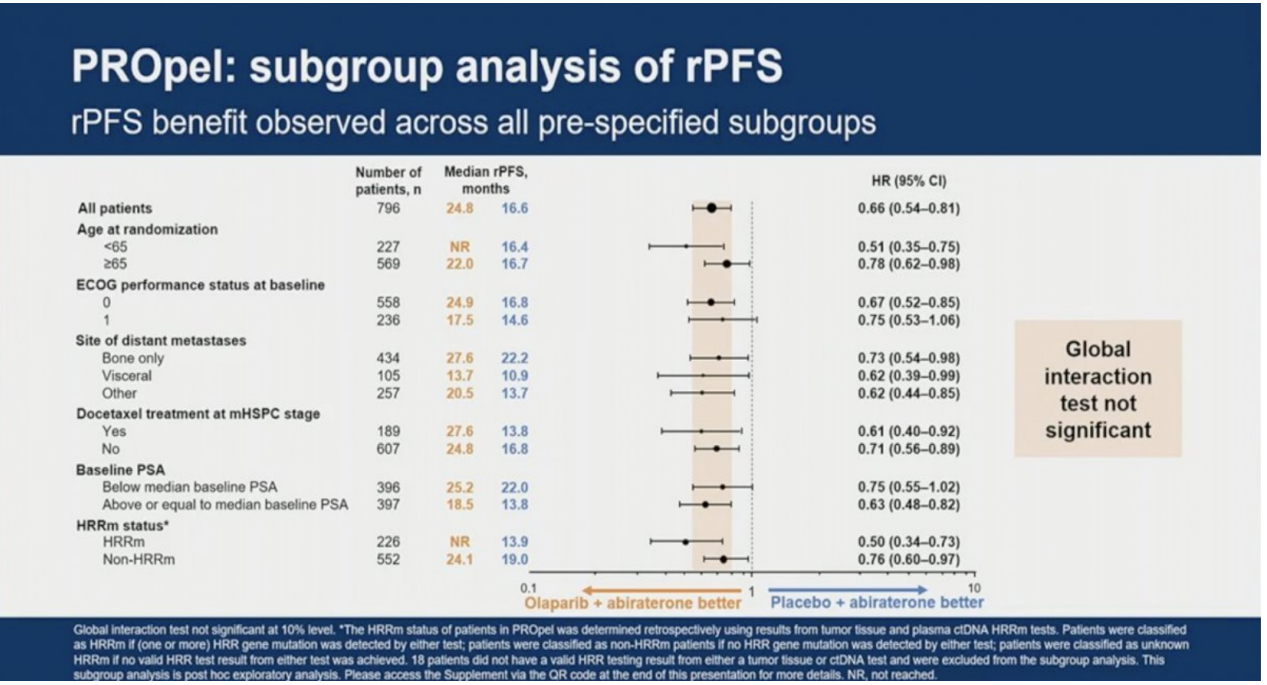
Median rPFS improvement of 8.2 months favors olaparib + abiraterone*

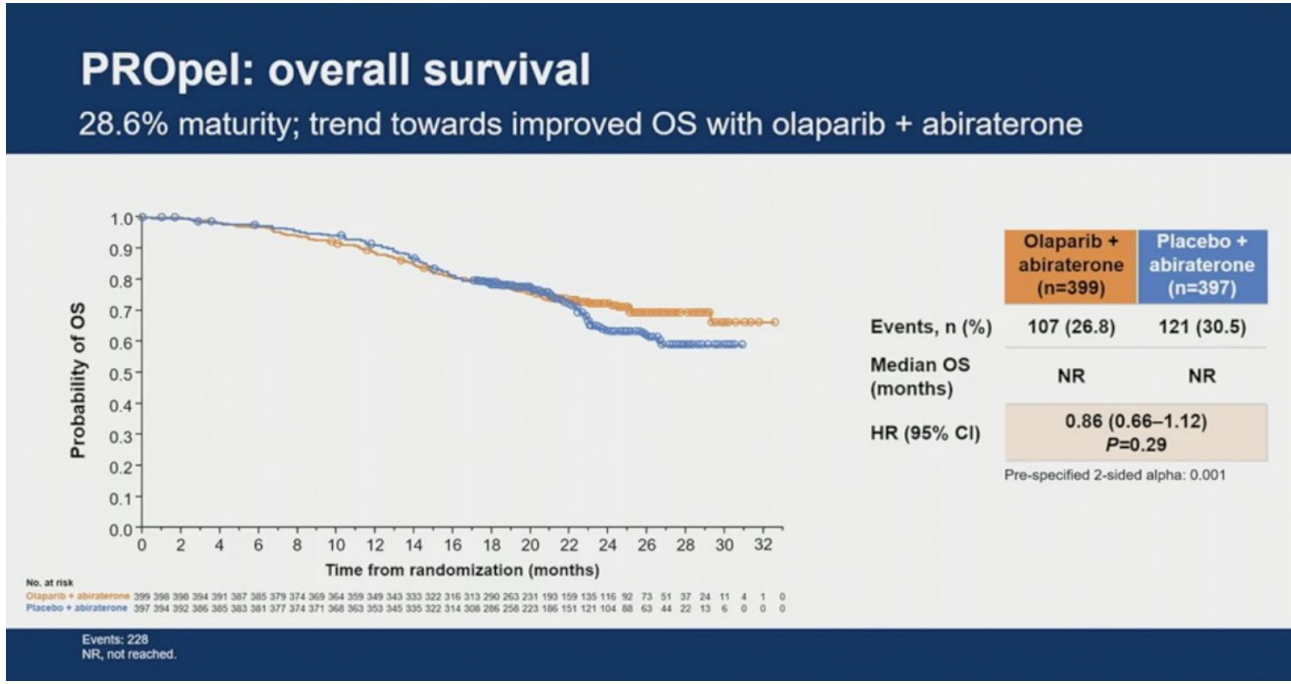
Events: 394; Maturity 49.5%

*In combination with prednisone or prednisolone

CI, confidence interval; HR, hazard ratio.

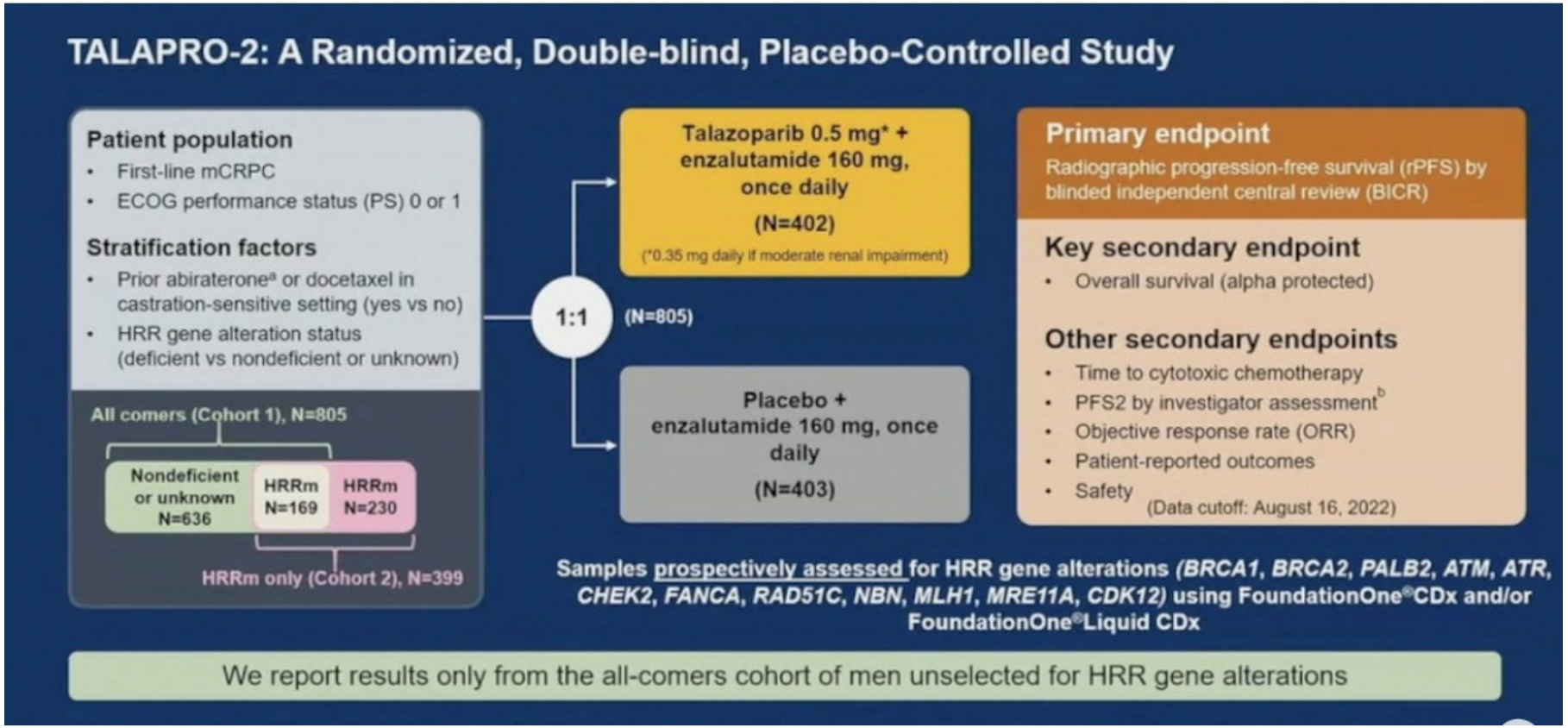
All groups benefit from the combo: HR better for HRRm





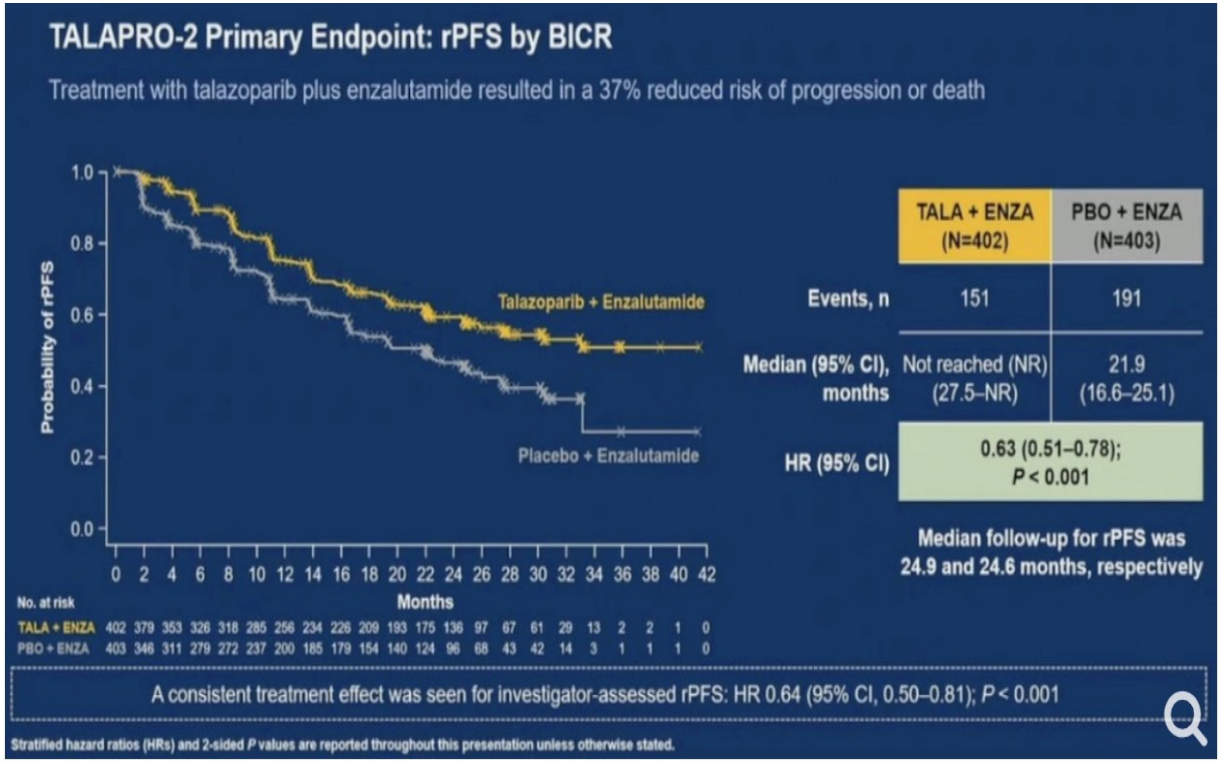
FDA did a post hoc analysis: 11% BRCA positive
BRCA Positive: HR 0.30; BRCA uncertain: 0.73; BRCA negative: 1.06
ODAC 4/28- unanimous vote for narrow indication
FDA approval for the combination 5/31/2023 for BRCA mutated patients

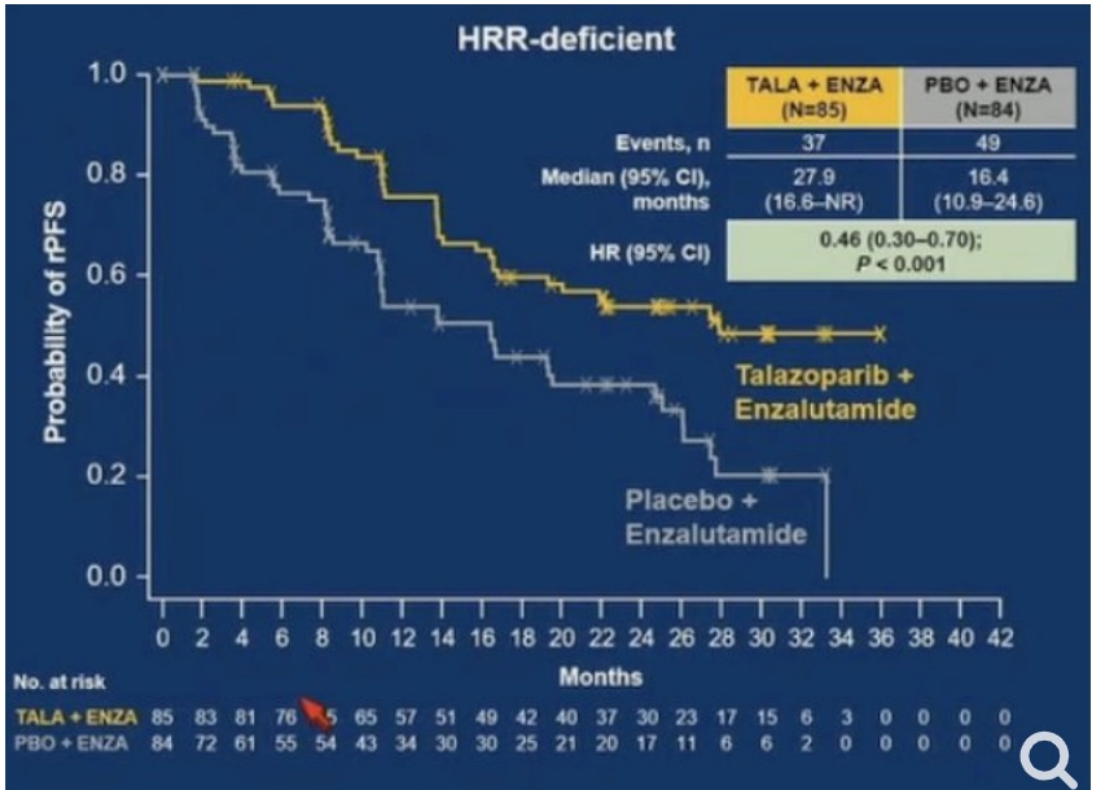
Combination #3: TALAPRO 2: Talazoparib



Agarwal GU ASCO 2023

Improvement in rPFS in ITT and in HRR





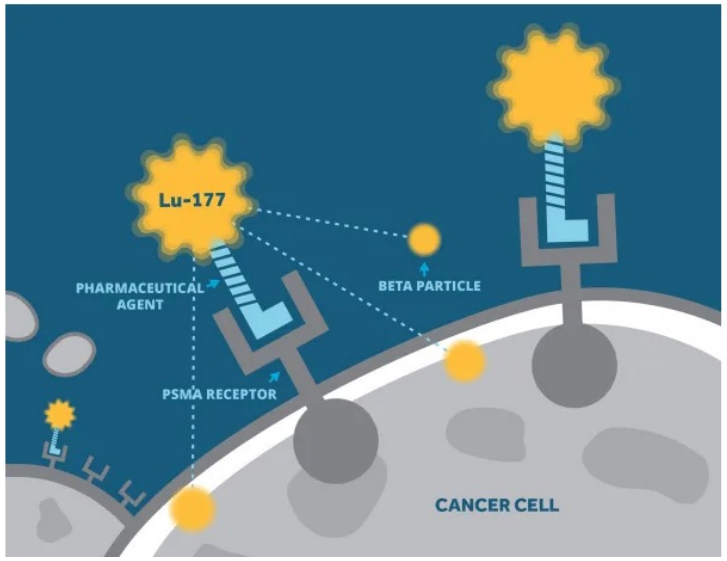
On 6/20/23 FDA approved the combination for HRRm+ patients

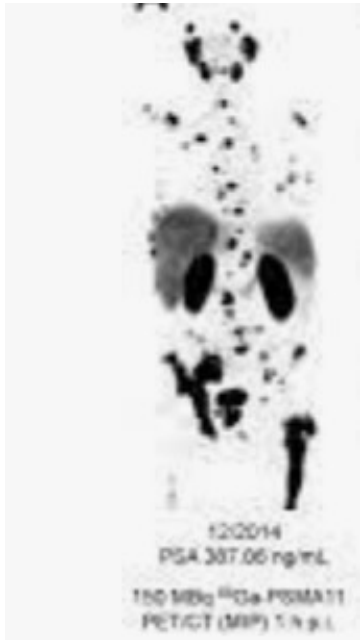
PARP combinations: Conclusions

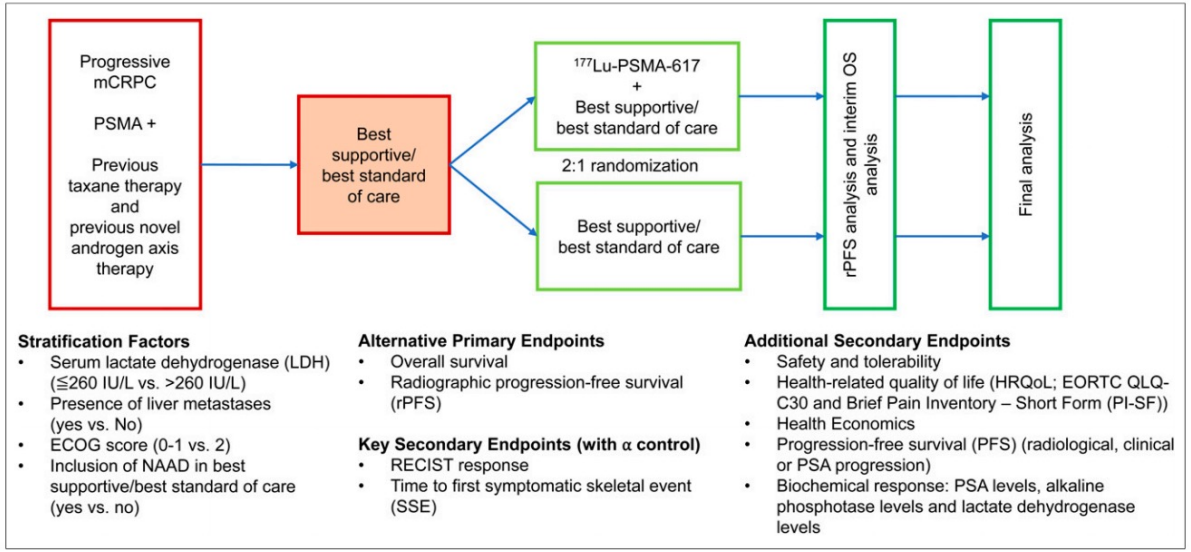
	rPFS	OS	HRR+	BRCA+	FDA Approval
PROPEL Abiraterone/Olaparib vs abi	27.6 vs 16.4 HR-0.61		28.8 vs 13.8 HR- 0.45	HR 0.29	BRCA only
MAGNITUDE Abiraterone/niraparib vs abi	16.7 mos vs 13.7 HR- 0.76			19.5 vs10.9 HR 0.5	
TALAPRO-2 Enzalutamide/talazoparib vs enza	NR vs 21.9 HR-0.63		27.9 vs 16.4 HR-0.46		HRRm+ only

Not all PARP's are the same
No OS benefit with combinations yet
Just like monoRx: benefit higher in HRR and even higher in BRCA populations
Use of NHT in earlier lines: do these patients exist?
BRCA is prognostic/predictive
If a BRCA pt who has never had NHT and in CRPC- combo very reasonable

VISION: Phase 3 randomized study Lu177



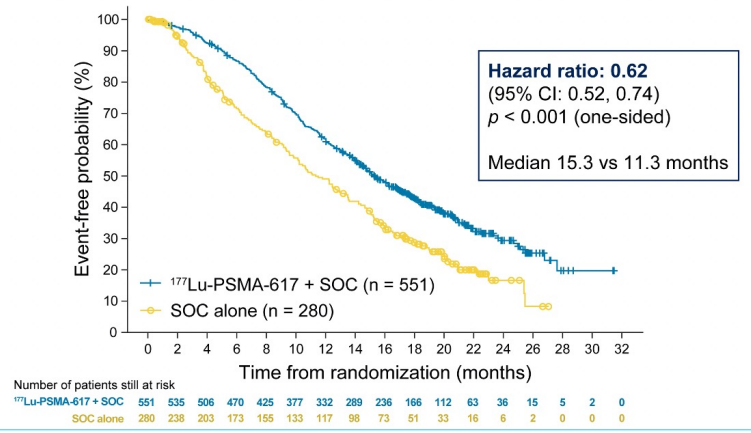




Primary Endpoints: Improved Overall survival/rPFS

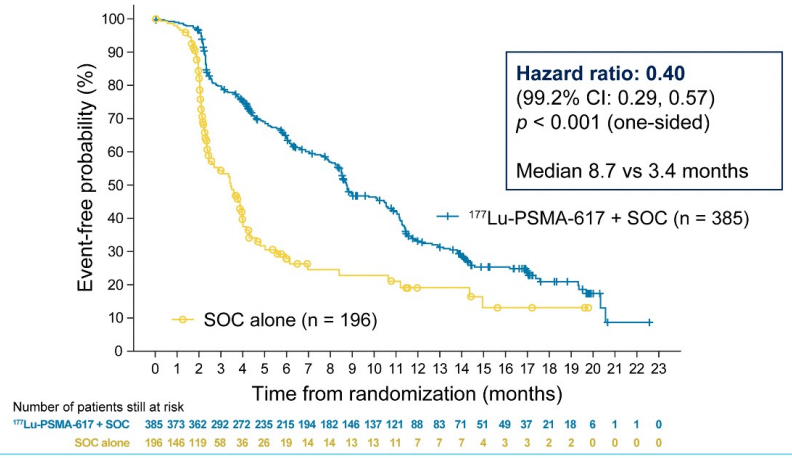
Primary endpoints: ^{177}Lu-PSMA-617 prolonged OS

Primary analysis
All randomized patients
(N = 831)



Primary endpoints: ^{177}Lu-PSMA-617 improved rPFS

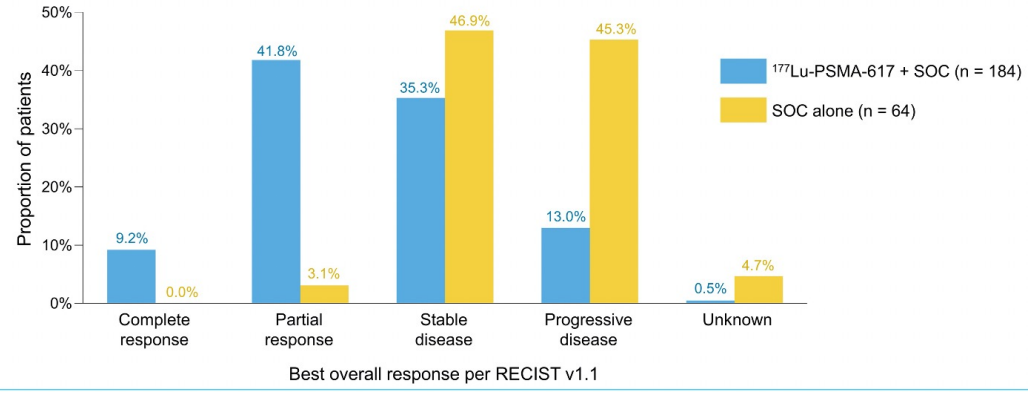
Primary analysis
rPFS analysis set
(n = 581)



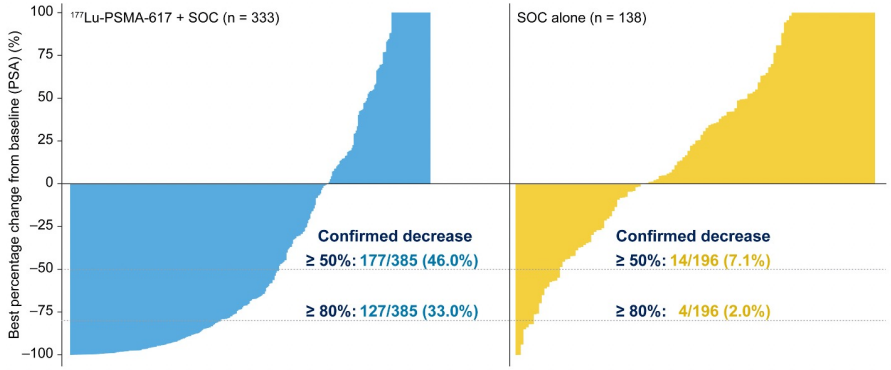
Morris, ASCO 2021

Secondary Endpoints: Measurable Disease and PSA responses

Secondary endpoint: RECIST v1.1 responses favored the ^{177}Lu-PSMA-617 arm in patients with measurable disease



Secondary endpoint: PSA responses favored the ^{177}Lu-PSMA-617 arm among evaluable patients



Summary of Approved Therapies with Survival Benefit for mCRPC

Agent	Indication	Route Schedule	Cortico-steroids	Symptoms	Contra-indications	PSA Response	Median OS Benefit, Mos
Sipuleucel-T	Pre/post docetaxel	IV every 2 wk x 3	no	asymptomatic, minimally sx	narcotics for pain, liver mets	No	4.1
Abiraterone	Pre/post docetaxel	oral, empty stomach	yes*	not specified	severe liver dysfx, low K, heart failure	Yes	Post-doc: 4.6 Pre-doc: 4.4
Enzalutamide	Pre/post docetaxel	oral	no	not specified	seizures	Yes	Post-doc: 4.8 Pre-doc: 4.0
Docetaxel	mCRPC	IV every 3 wk	yes*	not specified	moderate liver dysfx, cytopenias	Yes	2.4
Cabazitaxel	Post docetaxel	IV every 3 wk	yes*	not specified	moderate liver dysfx, cytopenias	Yes	2.4
Radium-223	Post docetaxel or not fit for docetaxel	IV, every 4 wks for 6 doses	not required	symptomatic bone metastases	visceral mets	NR	3.6
Lu 177	Post ARI/Chemo	IV q 6 weeks x 4-6 doses	Not reqd	Not specified	PSMA negative disease	yes	4.0

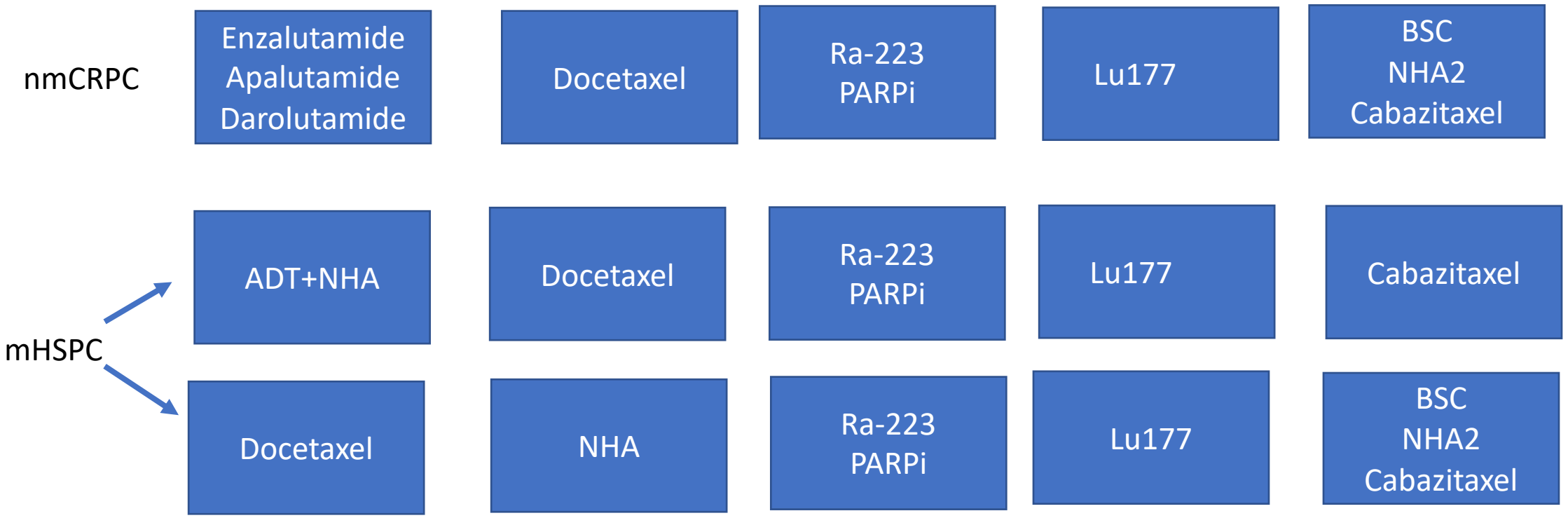
Sequencing Drugs in CRPC remains a challenge

- Lack of level 1 evidence
- Cross resistance between NHA
- Cross resistance with chemotherapeutics
- Many of the existing drugs/classes used in earlier lines of Rx

Selection based on:

- Time between the agents
- Symptomatic vs asymptomatic
- Bone disease vs non bone disease
- Presence or absence of visceral metastases
- Presence or absence of Genomic aberrations
- Oral vs IV
- Distance from the center
- Patient preference
- PS /Frailty
- Prior duration of response to ADT

Sequencing Examples



Conclusions

- Strive to give as many life prolonging therapy as possible
- Sequence tumors to identify PARP inhibitors and Check point inhibitors
- Consider Radium in patients with just bone disease without PSMA uptake
- Consider NHT with PARP in patients with BRCA mutations/HRRm
- Consider Sip-T in patients with low burden of disease, black men

Questions? Thank You

@sandysrimd