

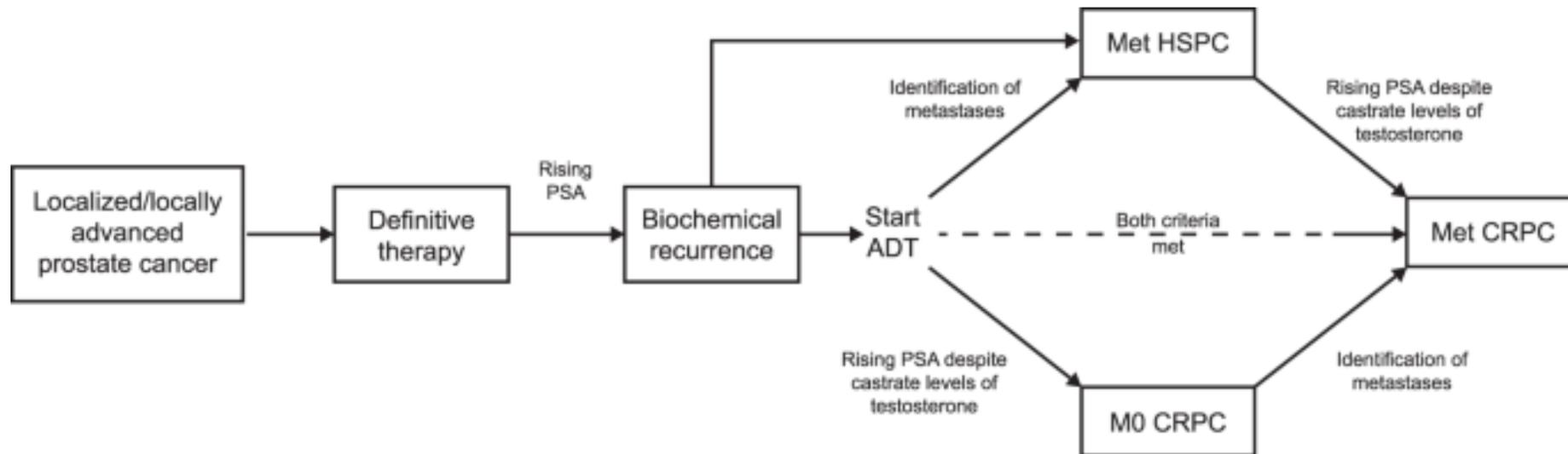
Prostate Cancer: Targeted Therapy, PSMA, and More

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MLS New Orleans: Updates in Oncology from the Masters



Progression of Prostate Cancer

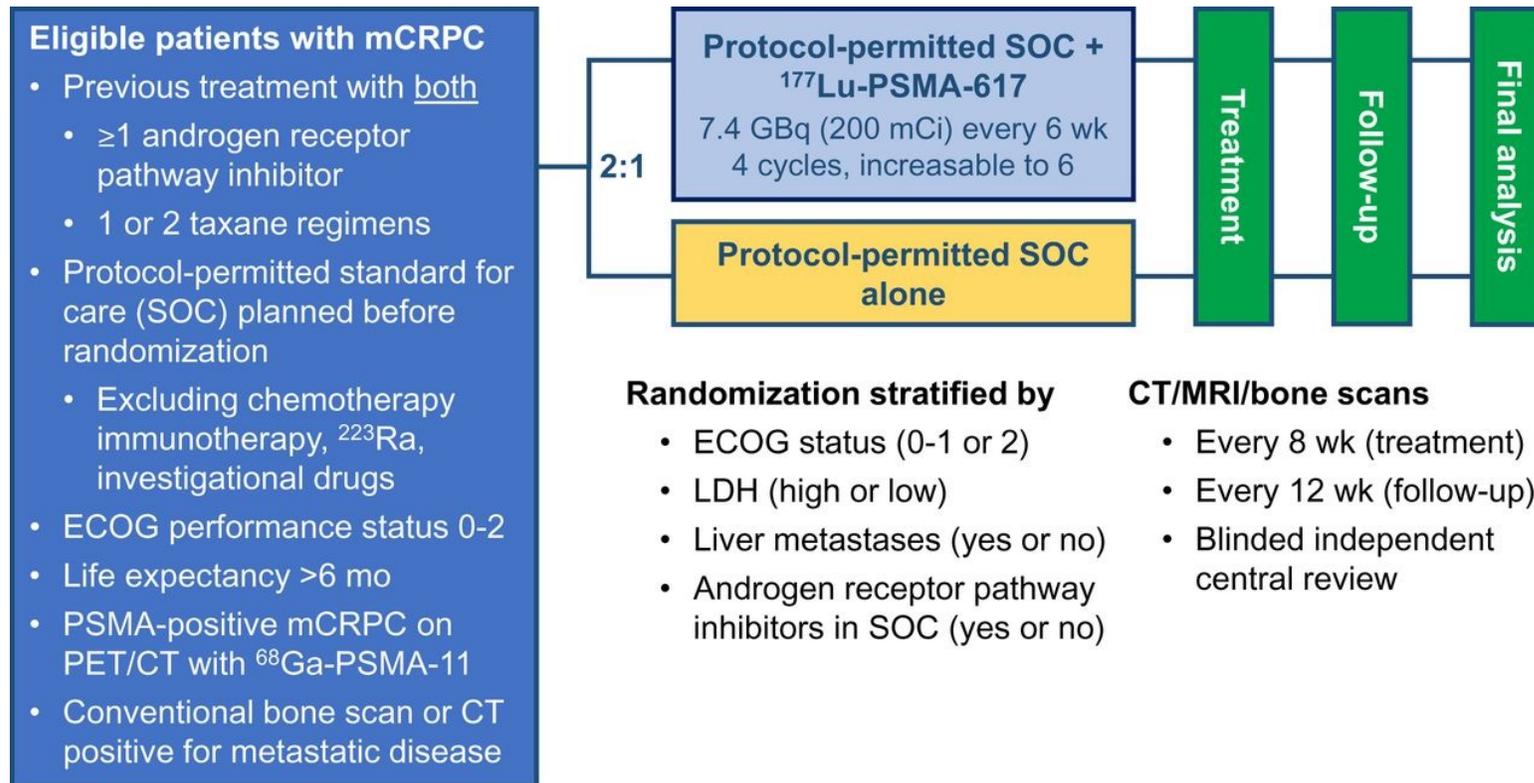


Advanced Imaging

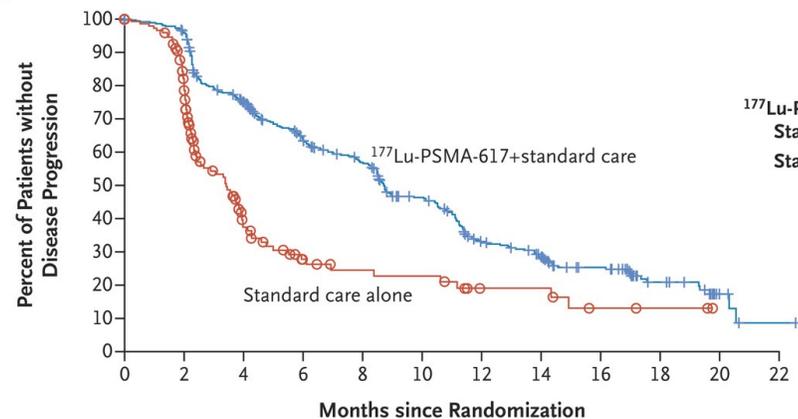
- PSMA PET-CT
 - Much more accurate (92% vs 65%) at detecting metastases than conventional imaging.
 - Decreasing non-metastatic, biochemical recurrence cases, and increasing oligometastatic disease.
 - EA8191 / INDICATE Trial – evaluating targeted XRT and apalutamide in this setting

Theranostics

- Lutetium-177 vipivotide tetraxetan PSMA therapy



A Imaging-Based Progression-free Survival



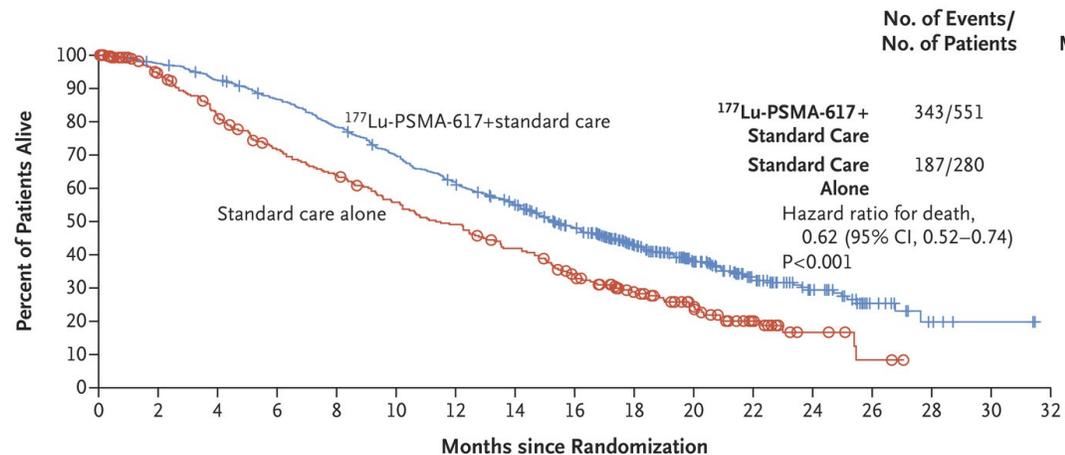
	No. of Events/ No. of Patients	Median <i>mo</i>
¹⁷⁷ Lu-PSMA-617+ Standard Care	254/385	8.7
Standard Care Alone	93/196	3.4

Hazard ratio for progression or death,
0.40 (99.2% CI, 0.29–0.57)
P<0.001

No. at Risk

¹⁷⁷ Lu-PSMA-617+standard care	385	362	272	215	182	137	88	71	49	21	6	1
Standard care alone	196	119	36	19	14	13	7	7	3	2	0	0

B Overall Survival



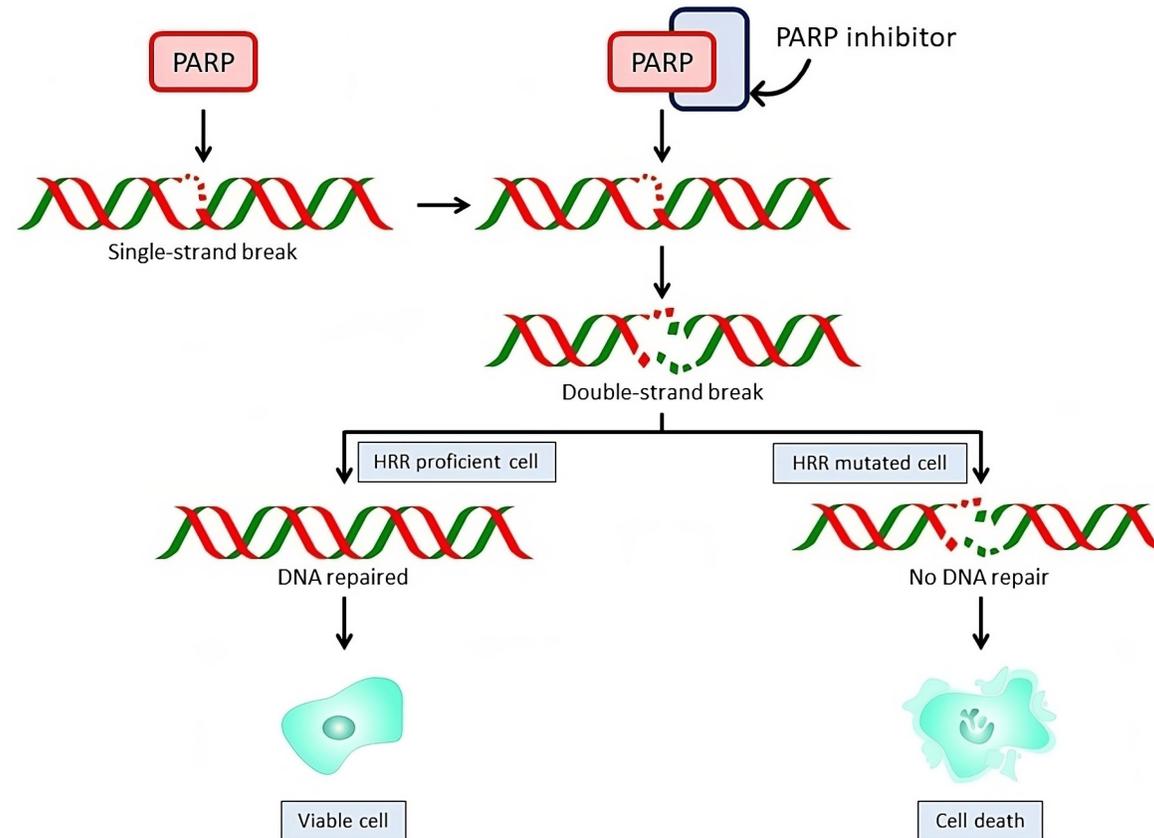
	No. of Events/ No. of Patients	Median <i>mo</i>
¹⁷⁷ Lu-PSMA-617+ Standard Care	343/551	15.3
Standard Care Alone	187/280	11.3

Hazard ratio for death,
0.62 (95% CI, 0.52–0.74)
P<0.001

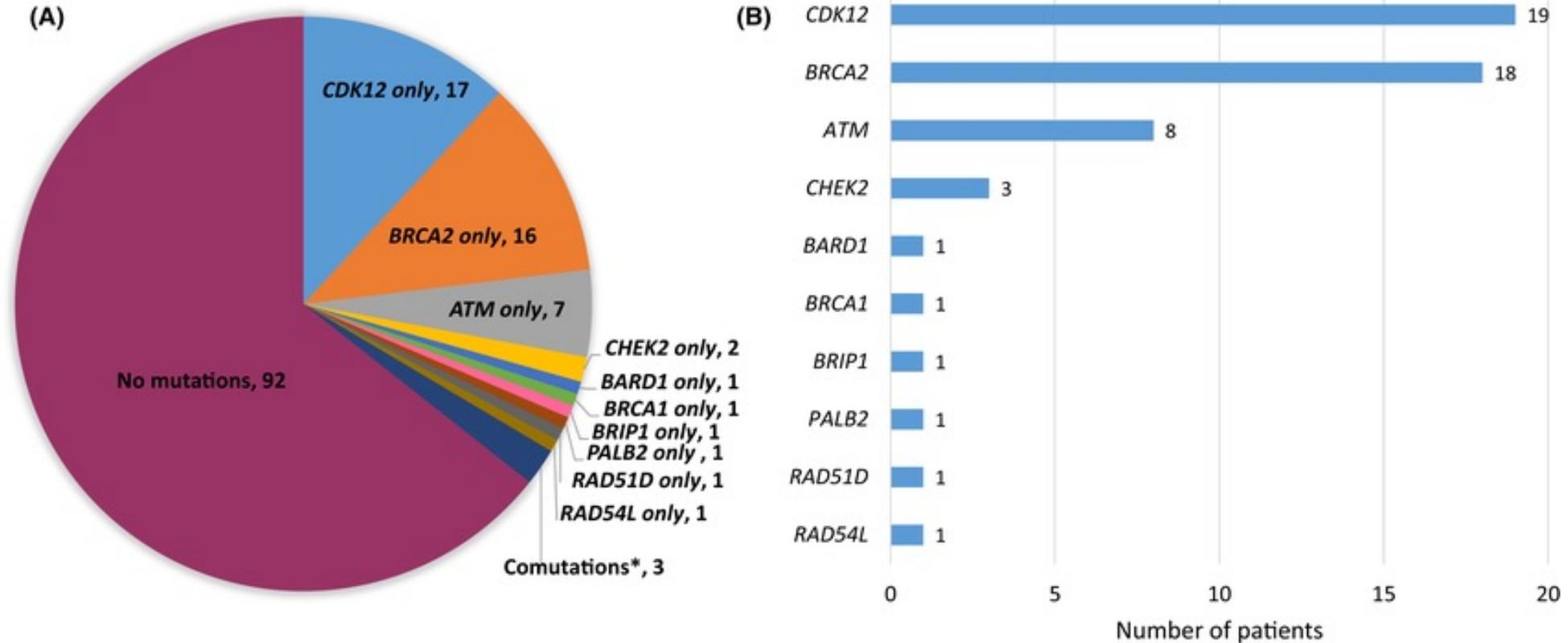
No. at Risk

¹⁷⁷ Lu-PSMA-617+standard care	551	535	506	470	425	377	332	289	236	166	112	63	36	15	5	2	0
Standard care alone	280	238	203	173	155	133	117	98	73	51	33	16	6	2	0	0	0

PARP inhibitors



Rate of HRR gene mutations in men with metastatic prostate cancer



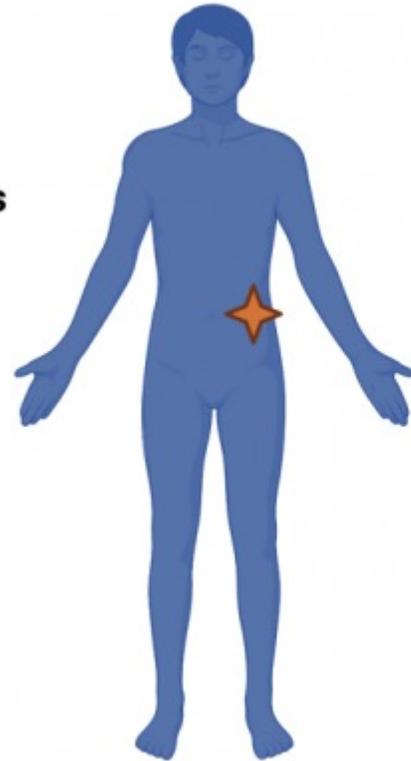
Somatic vs Germline Mutations

Somatic DNA changes

Acquired over a person's lifetime in single cells

Can lead to cancer

Can NOT be inherited

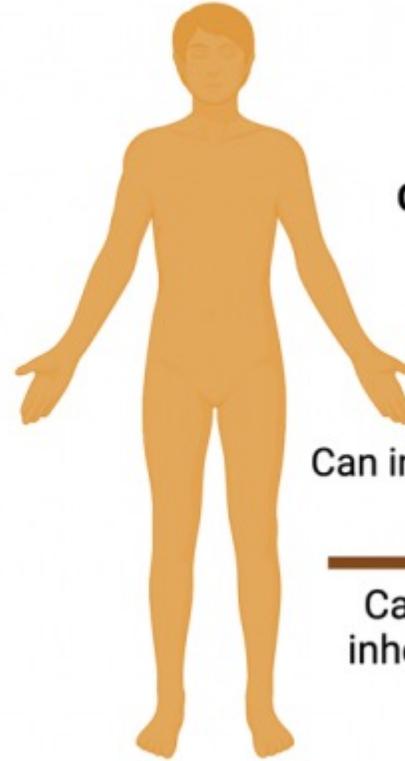


Germline DNA changes

Present in every cell of the body including egg and sperm

Can increase cancer susceptibility

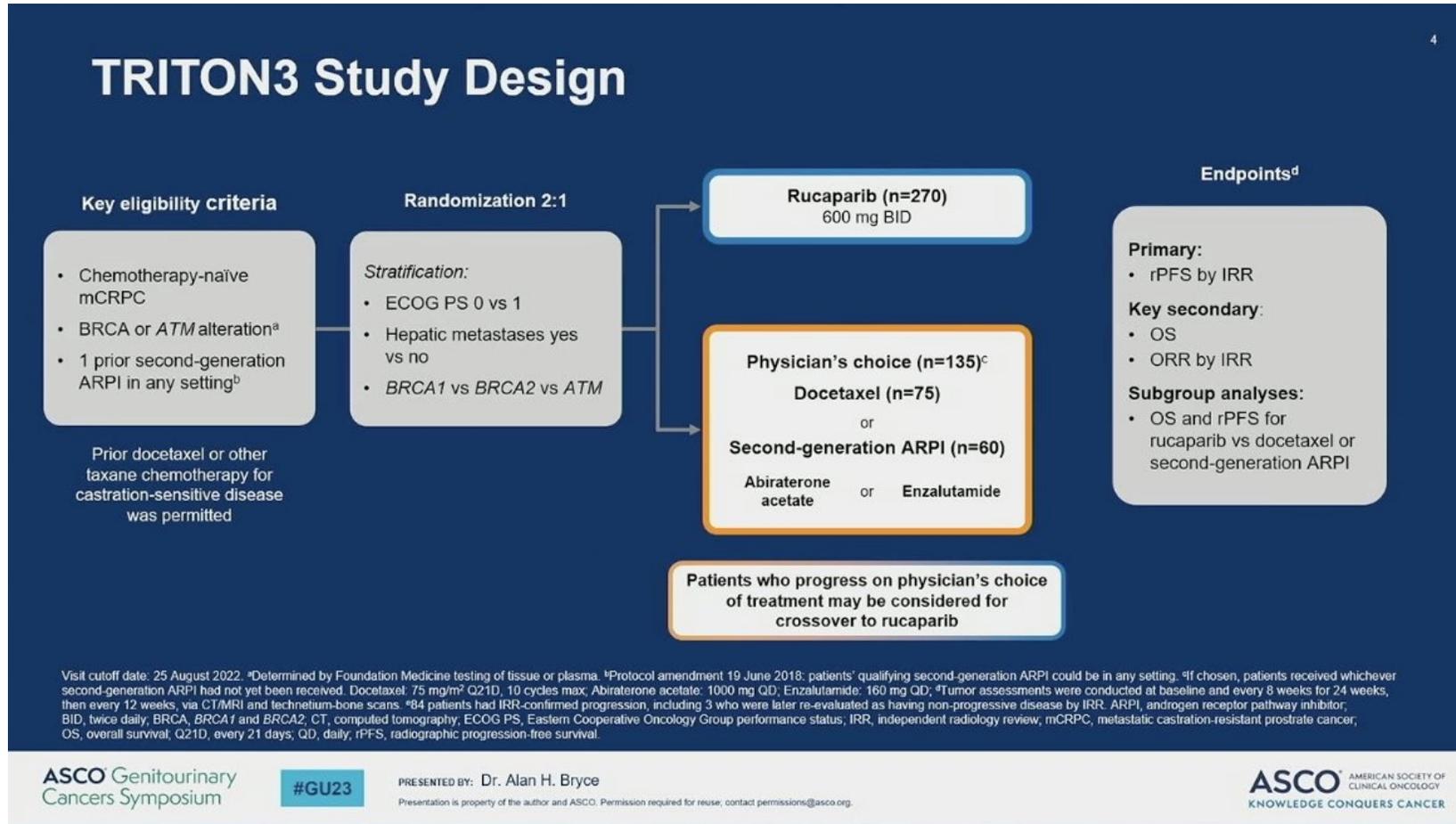
Can be inherited



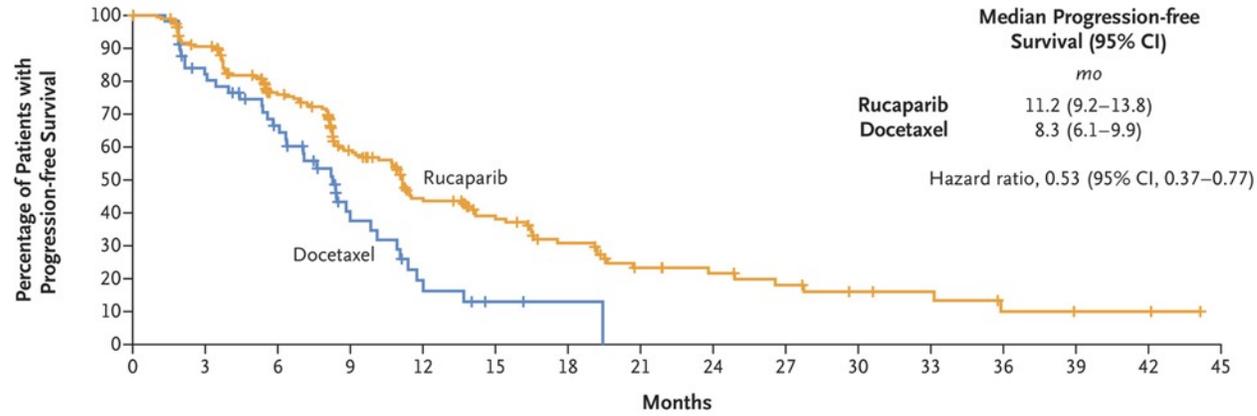
Single agent PARPi

- Rucaparib – BRCA mutations
- Olaparib – HRR gene mutations

Triton3 Study



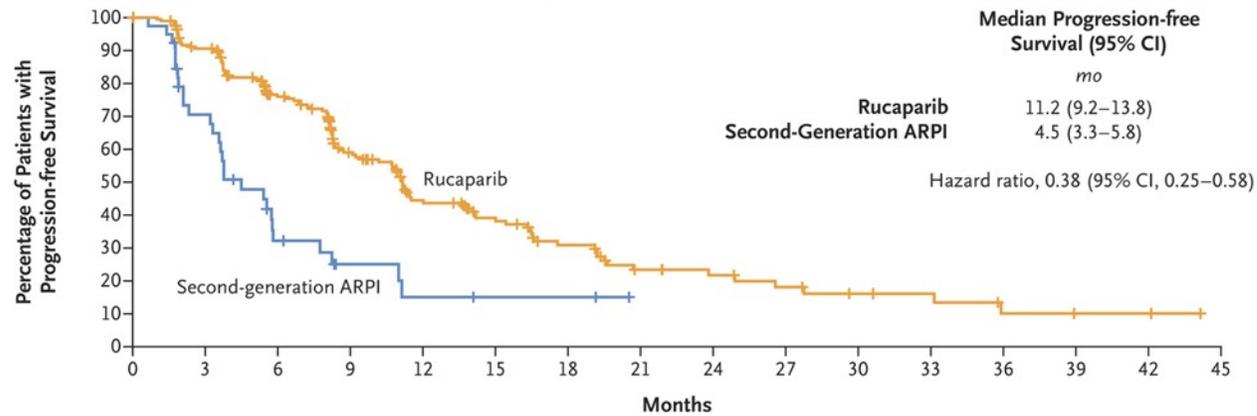
A Rucaparib vs. Docetaxel in the BRCA Subgroup



No. at Risk (no. of events)

Rucaparib	201 (0)	169 (18)	124 (44)	83 (70)	55 (89)	41 (95)	27 (103)	16 (109)	13 (110)	10 (112)	7 (113)	6 (113)	3 (115)	2 (115)	2 (115)	0 (115)
Docetaxel	60 (0)	44 (10)	32 (18)	14 (29)	6 (36)	2 (38)	1 (38)	0 (39)								

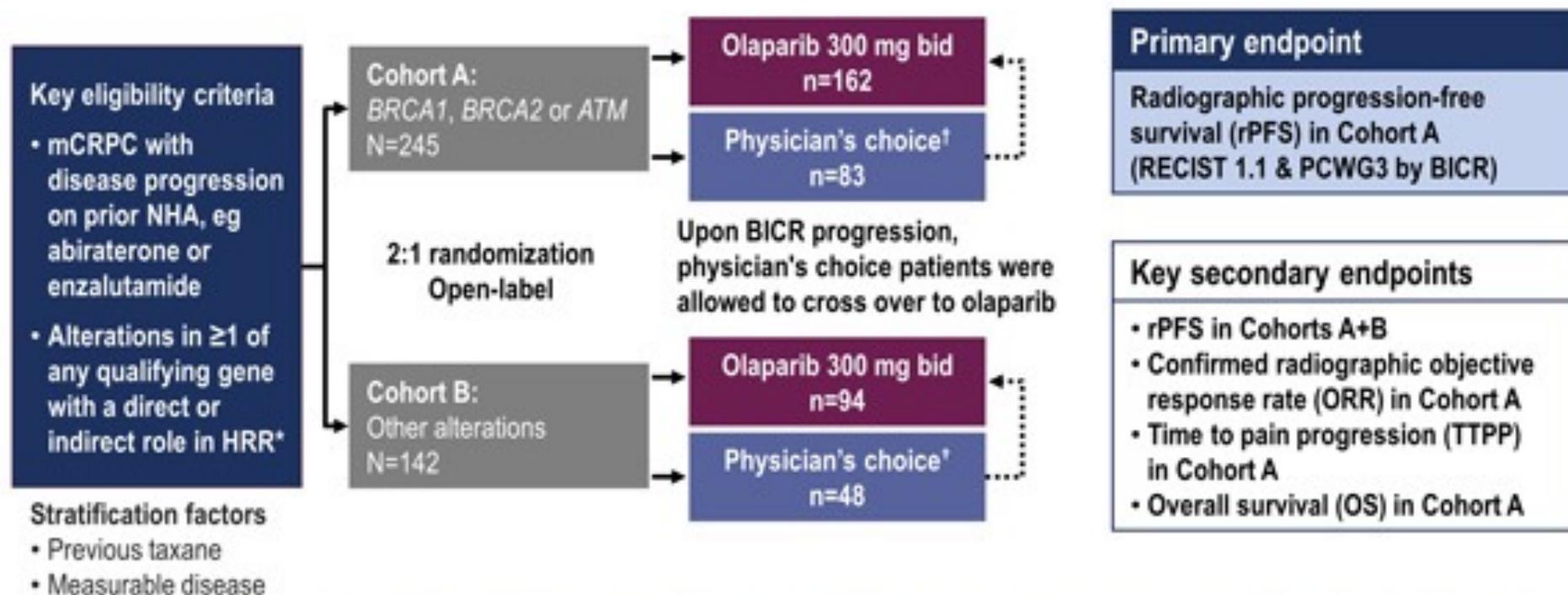
B Rucaparib vs. Second-Generation ARPI Therapies in the BRCA Subgroup



No. at Risk (no. of events)

Rucaparib	201 (0)	169 (18)	124 (44)	83 (70)	55 (89)	41 (95)	27 (103)	16 (109)	13 (110)	10 (112)	7 (113)	6 (113)	3 (115)	2 (115)	2 (115)	0 (115)
Second-generation ARPI	41 (0)	25 (11)	10 (24)	5 (26)	3 (28)	2 (28)	2 (28)	0 (28)								

PROfound STUDY DESIGN

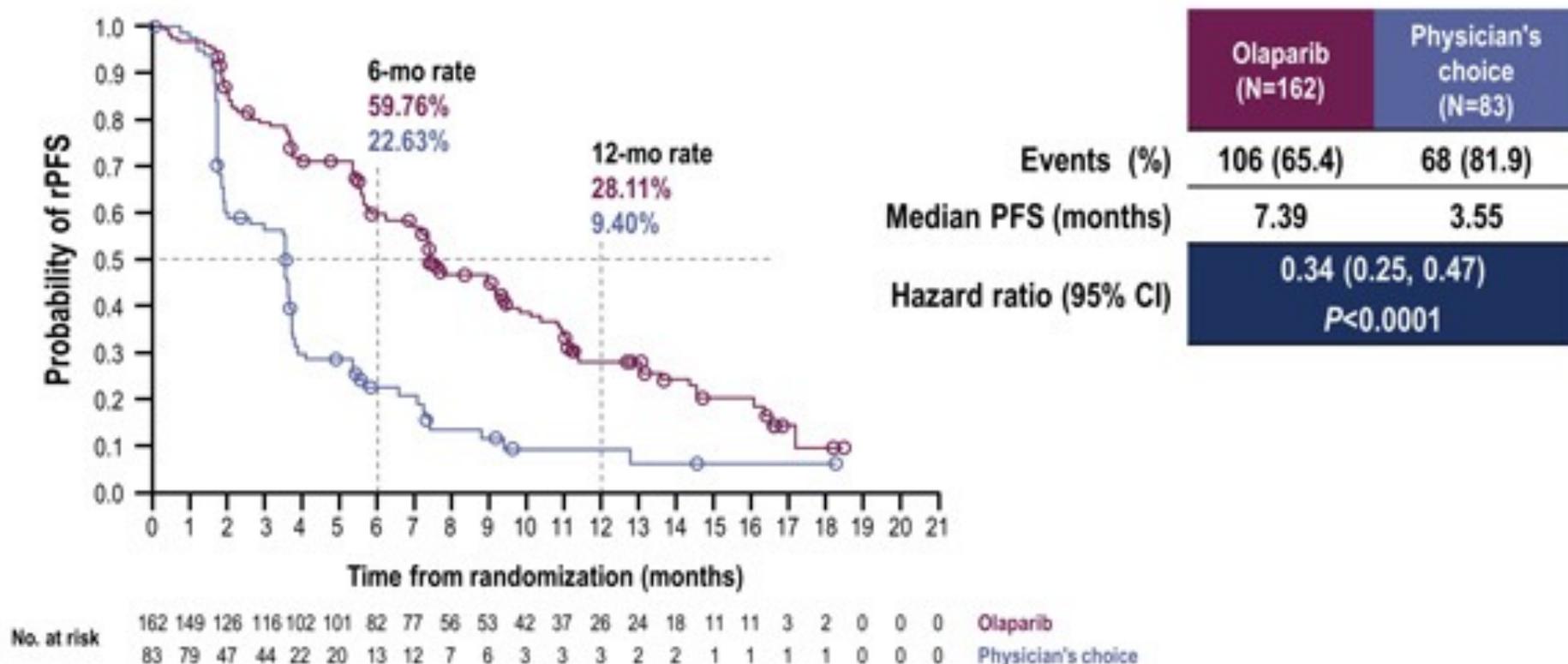


*An investigational Clinical Trial Assay, based on the FoundationOne CDx next-generation sequencing test, and developed in partnership with Foundation Medicine Inc, was used to prospectively select patients harboring alterations in the following genes in their tumor tissue: *BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D or RAD54L*

†Physician's choice of either enzalutamide (160 mg qd) or abiraterone (1000 mg qd plus prednisone [5 mg bid])
BICR, blinded independent central review; PCWG3, Prostate Cancer Working Group 3;
RECIST, Response Evaluation Criteria in Solid Tumors
NCT02987543

PROfound Primary endpoint

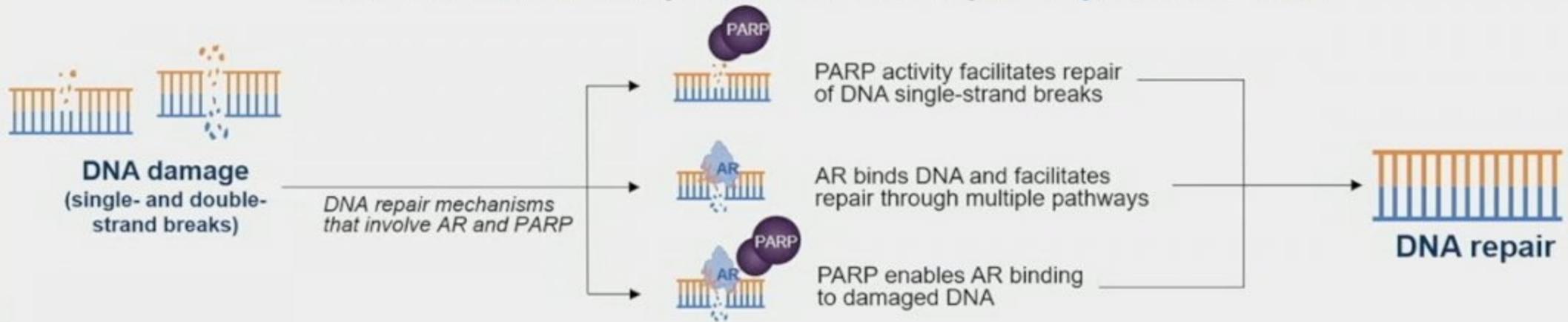
rPFS BY BICR IN PATIENTS WITH ALTERATIONS IN *BRCA1*, *BRCA2*, OR *ATM* (COHORT A)



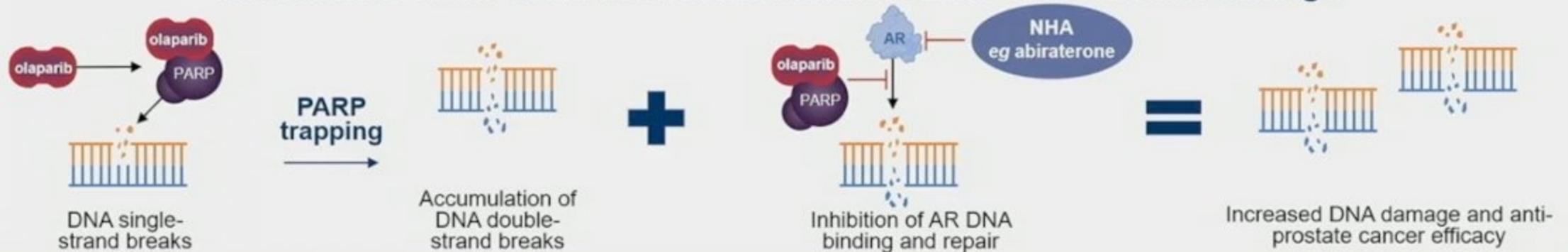
NCT02987543

Prespecified sensitivity analysis based on investigator assessment: Hazard ratio 0.24 (95% CI 0.17, 0.34); P<0.0001

PARP and AR are important for DNA repair in prostate cancer



Inhibition of PARP and AR in combination results in more DNA damage

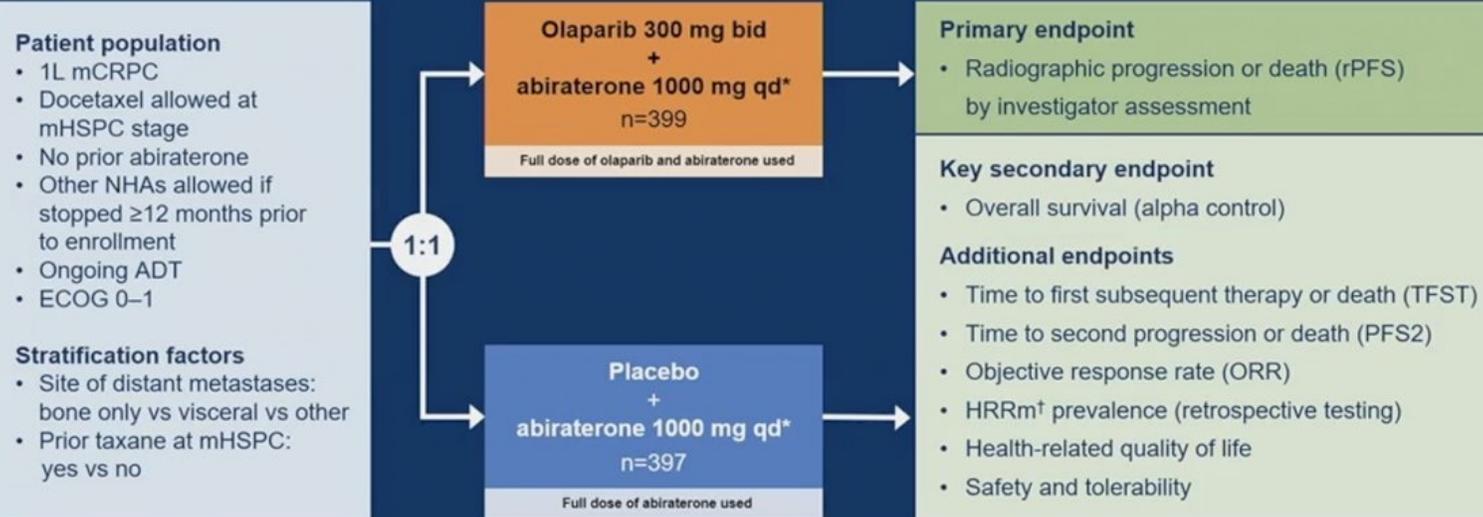


PARPi+NHT Combos

- Olaparib/abiraterone – BRCA mutations
- Niraparib/abiraterone – BRCA mutations
- Talazoparib/enzalutamide – HRR gene mutations

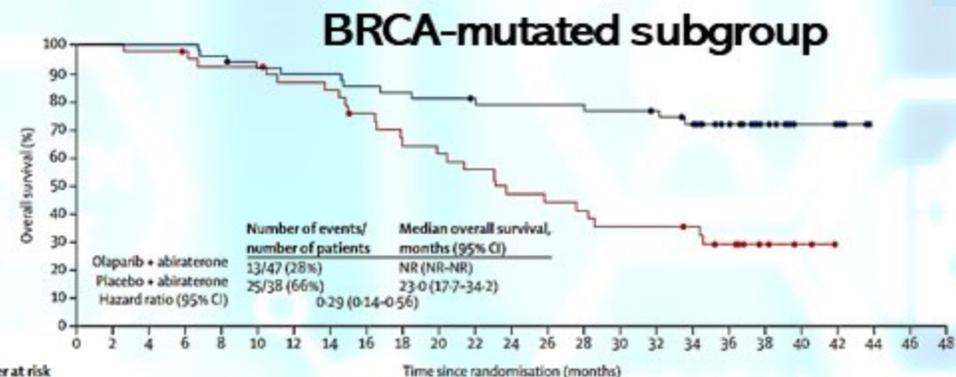
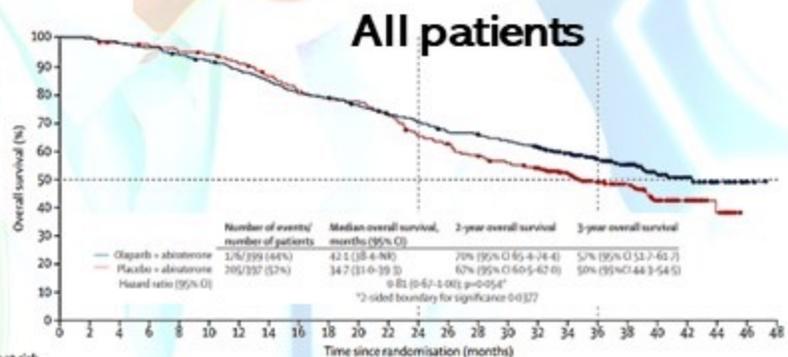
PROpel Study

PROpel: a global randomized double-blind phase III trial



First patient randomized: Nov 2018; Last patient randomized: Mar 2020; DCO1: July 30, 2021, for interim analysis of rPFS and OS. Multiple testing procedure is used in this study: 1-sided alpha of 0.025 fully allocated to rPFS. If the rPFS result is statistically significant, OS to be tested in a hierarchical fashion with alpha passed on to OS. Please access the [Supplement](#) via the QR code at the end of this presentation for more details.
*In combination with prednisone or prednisolone 5 mg bid. [†]HRRm, homologous recombination repair mutation, including 14 genes panel.
ADT, androgen deprivation therapy; bid, twice daily; ECOG, Eastern Cooperative Oncology Group; mHSPC, metastatic hormone sensitive prostate cancer; qd, daily

Olaparib plus abiraterone in metastatic castration-resistant prostate cancer

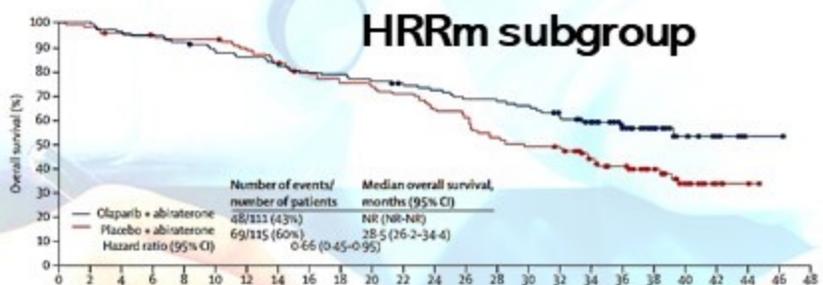


Number at risk (number censored)

Time since randomisation (months)	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48
Olaparib + abiraterone	399	399	391	385	374	364	349	334	318	312	298	283	273	258	253	246	226	192	135	96	63	29	10	2	0
Placebo + abiraterone	397	395	388	383	376	370	355	337	316	305	301	282	254	241	235	213	201	157	119	84	53	25	7	0	0

Number at risk (number censored)

Time since randomisation (months)	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48
Olaparib + abiraterone	47	47	47	47	45	42	41	41	39	38	37	35	35	35	34	34	33	29	21	13	8	5	0	0	--
Placebo + abiraterone	38	38	37	36	34	34	31	30	26	22	21	19	16	15	14	12	12	11	8	3	2	0	0	0	--



Number at risk (number censored)

Time since randomisation (months)	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48
Olaparib + abiraterone	111	111	107	105	102	96	94	90	87	86	83	79	77	73	70	62	55	42	22	14	7	1	1	0	0
Placebo + abiraterone	115	113	109	107	105	105	99	92	86	82	80	77	70	66	57	53	51	40	32	22	12	4	1	0	0

	Median overall survival	Olaparib + abiraterone	Placebo + abiraterone	Hazard ratio
All patients		42.1 months	34.7 months	0.81
HRRm subgroup		NR	28.5 months	0.66
BRCA-mutated subgroup		NR	23.0 months	0.29

In the phase 3 PROpel trial, a significant improvement in overall survival is observed for olaparib with abiraterone compared to placebo with abiraterone in patients with mCRPC. The improvement observed was primarily attributable to patients with BRCA mutation.

MAGNITUDE Study

Patient eligibility

- 1L mCRPC
 - ≤ 4 months prior AAP allowed for mCRPC
- ECOG PS 0 or 1
- BPI-SF worst pain score ≤ 3

Stratifications

- Prior taxane-based chemo for mCSPC
- Prior ARi for nmCRPC or mCSPC
- Prior AAP for 1L mCRPC
- *BRCA1/2* vs other HRR gene alterations (HRR BM+ cohort)

Prescreening for BM status^a

HRR BM+ panel:
ATM
BRCA1
BRCA2
BRIP1
CDK12
CHEK2
FANCA
HDAC2
PALB2

IA1 cutoff: October 8, 2021
IA2 cutoff: June 17, 2022
Final analysis cutoff: May 15, 2023

Allocation to cohort

Cohort 1

HRR BM+
N = 423

Prospectively selected biomarker cohorts designed to test HRR BM+ and HRR BM-

Cohort 2

HRR BM-
N = 233

1:1 randomization

NIRA + AAP

PBO + AAP

NIRA + AAP

PBO + AAP

Primary endpoint

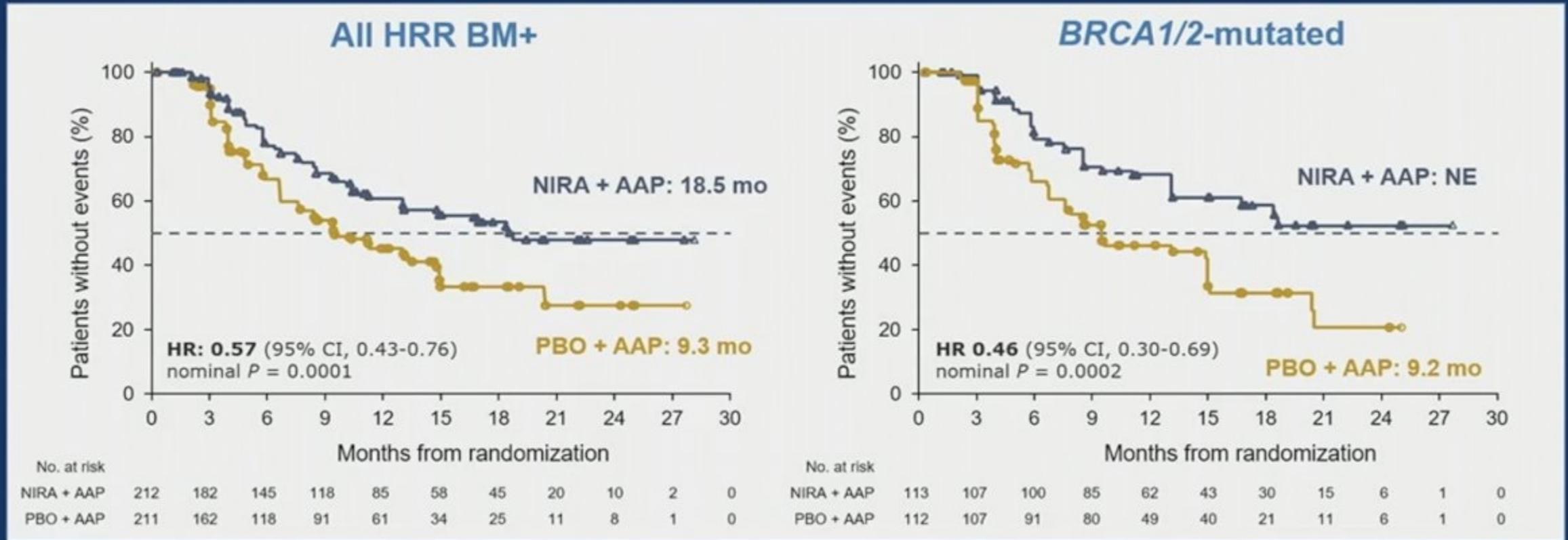
- rPFS by central review - met at IA1

Secondary endpoints

- OS
- Time to symptomatic progression
- Time to cytotoxic chemotherapy
- Safety

Note: After disease progression, patients could request to be unblinded by the study steering committee and go on to subsequent therapy of the investigator's choice.

MAGNITUDE: NIRA + AAP Consistently Prolongs Time to PSA Progression Across Gene Alterations



NIRA + AAP nearly doubles the median time to PSA progression with 43% improvement

AAP, abiraterone acetate plus prednisone; CI, confidence interval; HR, hazard ratio; HRR, homologous recombination repair; NE, not estimable; PSA, prostate-specific antigen.



TALAPRO-2: A Randomized, Double-blind, Placebo-Controlled Study

Patient population

- First-line mCRPC
- ECOG performance status (PS) 0 or 1
- Ongoing androgen deprivation therapy

Stratification

- Prior abiraterone^a or docetaxel in castration-sensitive setting (yes vs no)
- HRR gene alteration status (deficient vs nondeficient or unknown) (all-comers cohort only)

1:1

**Talazoparib 0.5 mg* +
enzalutamide 160 mg,
once daily**

(*0.35 mg daily if moderate renal impairment)

**Placebo +
enzalutamide 160 mg,
once daily**

Primary endpoint

- rPFS by BICR^b

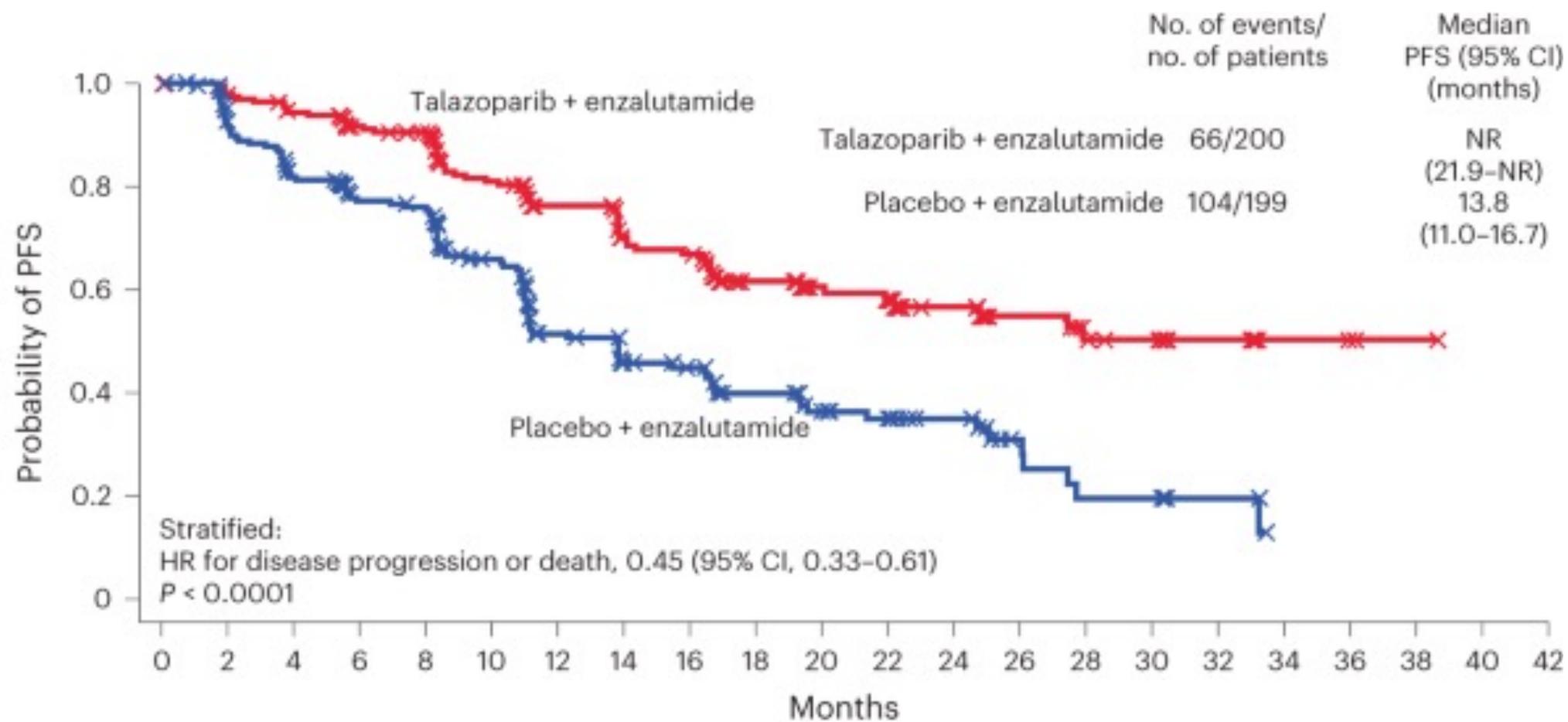
Key secondary endpoint

- Overall survival (alpha protected)

Other secondary endpoints

- Time to cytotoxic chemotherapy
- PFS2 by investigator assessment^c
- Objective response rate (ORR)
- Patient-reported outcomes
- Safety

Samples prospectively assessed for HRR gene alterations (*BRCA1, BRCA2, PALB2, ATM, ATR, CHEK2, FANCA, RAD51C, NBN, MLH1, MRE11A, CDK12*) using FoundationOne[®]CDx and/or FoundationOne[®]Liquid CDx



No. at risk		0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42
Talazoparib + enzalutamide	200	191	180	168	163	131	107	86	82	60	49	45	34	26	21	19	9	4	2	1	0	0	0
Placebo + enzalutamide	199	171	149	131	126	96	67	51	47	38	29	25	21	11	7	7	4	0	0	0	0	0	0

Immunotherapy for advanced prostate cancer

- Pembrolizumab for MSI-H, dMMR, or TMB ≥ 10 mut/Mb

Immunotherapy for advanced prostate cancer

- Combination immunotherapy in prostate cancer:
 - Phase 3 KEYNOTE-641 and KEYNOTE-789 (pembrolizumab + enzalutamide) were discontinued early due to lack of efficacy
 - Phase III KEYLYNK-010 (pembrolizumab + olaparib) did not meet PFS or OS endpoints
 - Phase II trial of pembrolizumab + Lu177 is currently enrolling

Conclusions

- New treatment modalities (theranostics, targeted therapy, and immunotherapy) offer new hope to patients with advanced prostate cancer.
- Defining novel molecular targets and new biomarkers of response will allow us to better personalize innovative treatments options for patients with advanced prostate cancer.