PARP INHIBITORS IN PROSTATE CANCER: WHO, WHEN, AND WHY (NOT)

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FDA Approvals for PARP Inhibitors in Prostate Cancer Prior to 2023

Agent	Indication	Required Mutations	Benefit
Olaparib	2nd line mCRPC (after first line Androgen Pathway Inhibitor)	Any HRR	OS
Rucaparib	2nd line mCRPC (after first line Androgen Pathway Inhibitor)	BRCA 1/2	OS

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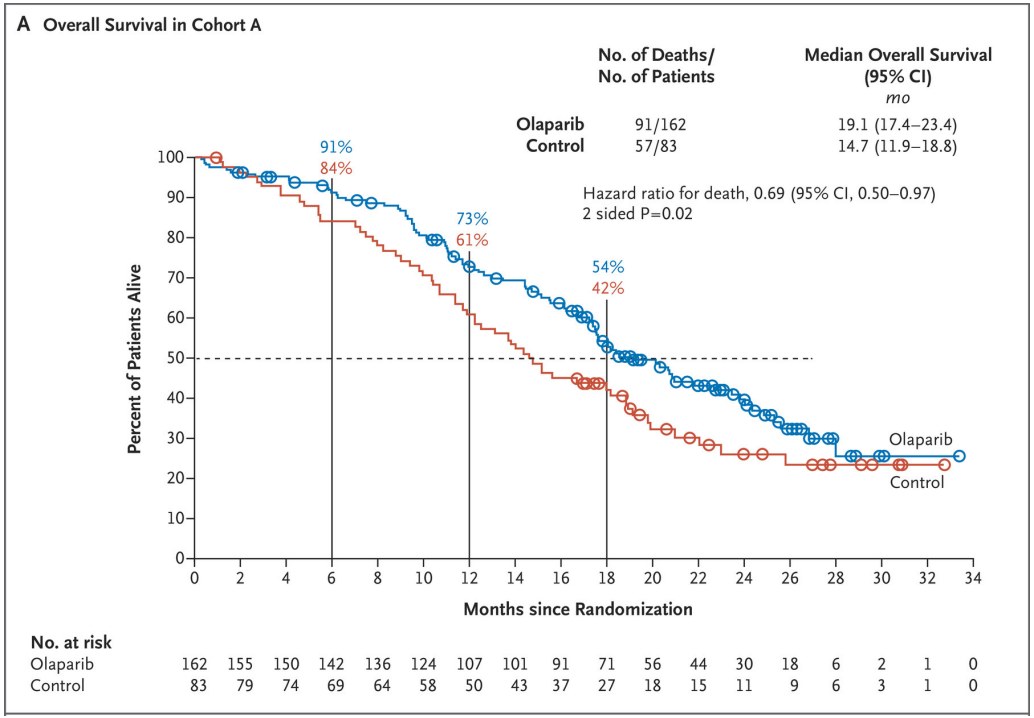
Olaparib Improves Survival in 2nd Line mCRPC vs. Abiraterone or Enzalutamide



Hussain, M et al. NEJM, 2020

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FDA Approvals for PARP Inhibitors in Prostate Cancer *in* 2023

Agent	Indication	Required Mutations	Benefit
Olaparib and Abiraterone (PROPEL)	1st line mCRPC	BRCA 1/2	PFS
Talazoparib and Enzalutamide (TALAPRO-2)	1st line mCRPC	All HRR+	PFS
Niraparib and Abiraterone (Magnitude)	1st line mCRPC	BRCA 1/2	PFS

2023 ASCO ANNUAL MEETING

CAPTURE

Hospital Universitario 12 de Octubre

Presence of somatic/germline homologous recombination repair (HRR) mutations and outcomes in metastatic castration-resistant prostate cancer (mCRPC) patients receiving first-line (1L) treatment stratified by BRCA status

David Olmos[1], David Lorente[2], Daniel Alameda[3], Carlo Cattrini[4], Nuria Romero-Laorden[5], Rebeca Lozano[6], Pedro P. Lopez-Casas[1], Camille Capone[7], Anne Marie Vanden Broecke[8], Marco Trevisan[9], Suzy Van Sanden[10], Alexandra Jürgens[11], Bernardo Herrera-Imbroda[3,12], Elena Castro[1,3]

1. Hospital Universitario 12 de Octubre, Instituto de Investigación Sanitaria Hospital 12 de Octubre, Madrid, Spain; 2. Hospital Provincial de Castellón, Castellón, Spain; 3. Instituto de Investigación Biomédica de Málaga, Málaga, Spain; 4. Maggiore della Carità University Hospital, Novara, Italy; 5. Hospital Universitario de la Princesa, Madrid, Spain; 6.Hospital Universitario de Salamanca, Salamanca, Spain; 7. Janssen Inc., Issy Les Moulineaux, France; 8. Janssen-Cilag B.V., Beerse, Belgium; 9. Janssen Pharmaceuticals, Zug, Switzerland; 10. Janssen Pharmaceutica NV, Beerse, Belgium; 11. Janssen, Neuss, Germany; 12. Hospital Universitario Virgen de la Victoria, Málaga, Spain

PRESENTED BY: David Olmos MD PhD @Dolmos77

ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY
KNOWLEDGE CONQUERS CANCER

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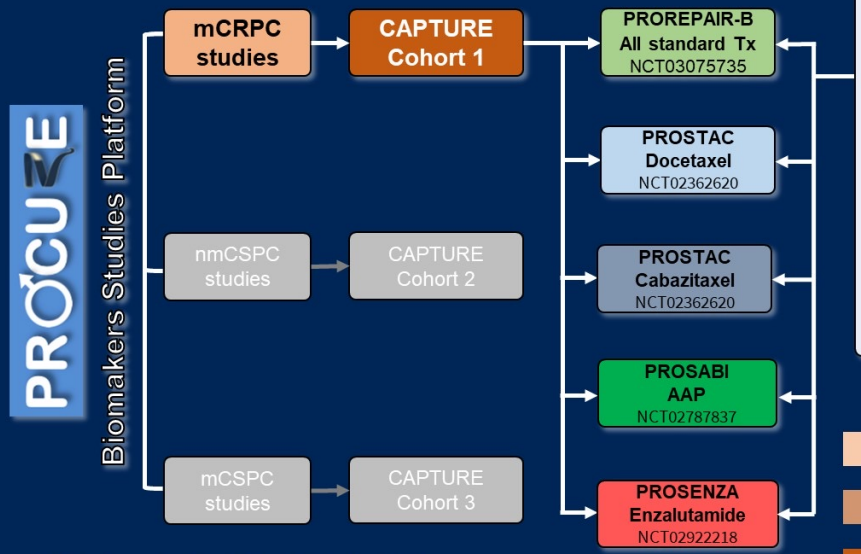
CAPTURE: Study design



Patient eligibility

- Enrolled prospectively in any PROCURE study at 1L mCRPC
- 1L with standard dose of docetaxel, cabazitaxel, AAP* or enzalutamide
- Availability of a DNA sample for germline variants analysis
- Archived FFPE sample with tumor tissue amenable for molecular analysis according to central pathologist
- No Prior PARPi or Alkylating agents
- ECOG 0-2
- Adequate Bone Marrow function

Gene Panel

ATM	*FANCA*
BRCA1	*HDAC2*
BRCA2	*PALB2*
BRIP1	*RAD51B*
CDK12	*RAD54L*
CHEK2	

Planned analyses groups

- *BRCA1/2* vs non-BRCA
- *BRCA1/2* vs HRR non-BRCA
- 1L ARSi vs Taxane
- Germline vs Somatic
- Biallelic vs Monoallelic
- *BRCA1* vs *BRCA2*

rPFS

PFS2

OS

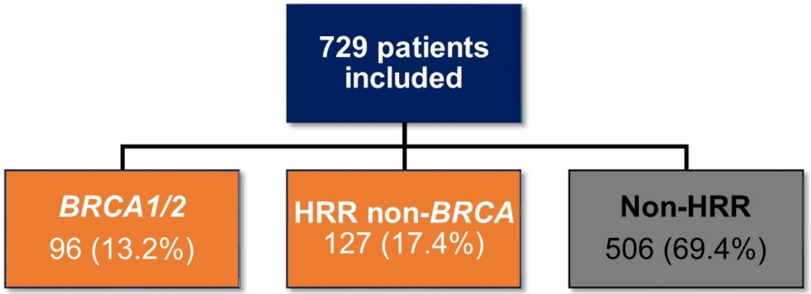
Data collection cut-off December 2021

FFPE: Formalin-Fixed Paraffin Embedded

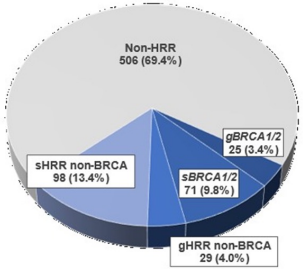
ARSi: Androgen Receptor Signalling inhibitors

PRESENTED BY: David Olmos MD PhD @Dolmos77

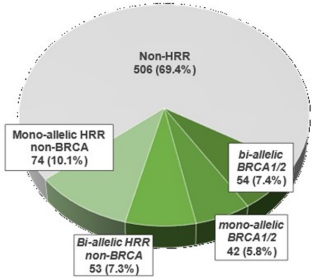
Prevalence and type of HRR alterations



Germline vs somatic



Bi-allelic vs Mono-allelic

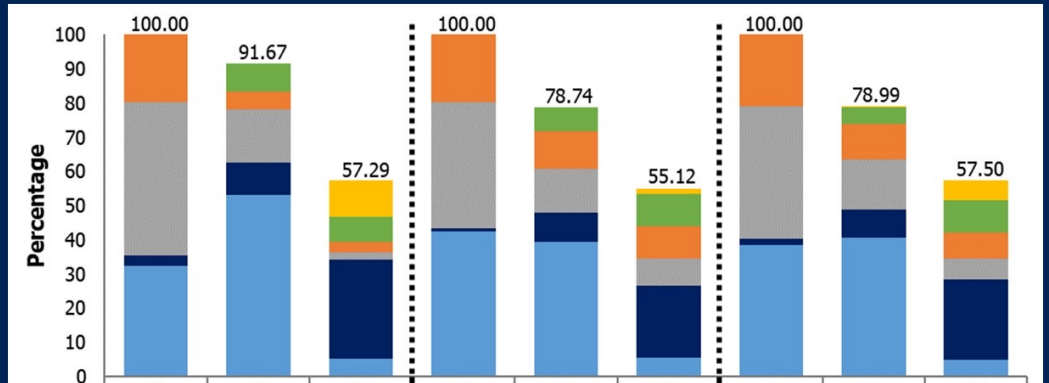


Gene by gene alterations*

Gene	n (%)
ATM	64 (8.8)
BRCA1	19 (2.6)
BRCA2	78 (10.7)
BRIP1	14 (1.9)
CDK12	15 (2.1)
CHEK2	11 (1.5)
FANCA	38 (5.2)
HDAC2	21 (2.9)
PALB2	4 (0.5)
RAD51B	3 (0.4)
RAD54L	5 (0.7)

*NOTE: 5.5% cases had alterations in >1 gene

Treatment exposure by subgroup

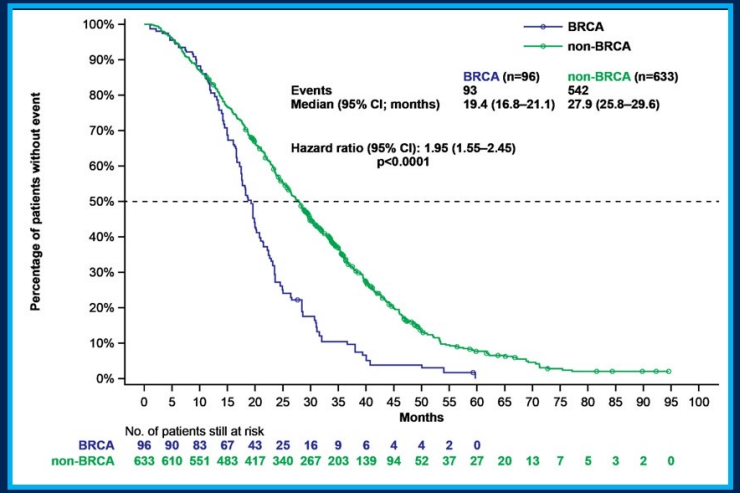


%	BRCA (n=96)			HRR non-BRCA (n=127)			non-BRCA (n=633)		
	1L	2L	3L	1L	2L	3L	1L	2L	3L
Other	0.00	0.00	10.42	0.00	0.00	1.57	0.00	0.16	5.85
Ra223	0.00	8.33	7.29	0.00	7.09	9.45	0.00	4.90	9.48
Enza	19.79	5.21	3.13	19.69	11.02	9.45	21.01	10.27	7.74
AAP	44.79	15.63	2.08	37.01	12.60	7.87	38.70	14.85	6.00
Caba	3.13	9.38	29.17	0.79	8.66	21.26	1.90	8.06	23.54
Doce	32.29	53.13	5.21	42.52	39.37	5.51	38.39	40.76	4.90

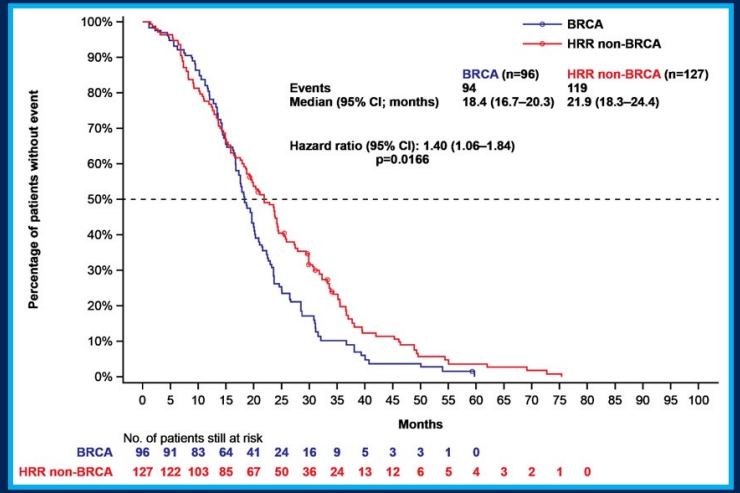
NOTE: among those with prior de novo/recurrent mHSPC: 8% recieved ADT+docetaxel, 1% ADT + ARSi and 0.1% ADT+Doc+ARSi

Overall Survival

BRCA1/2 vs non-*BRCA*



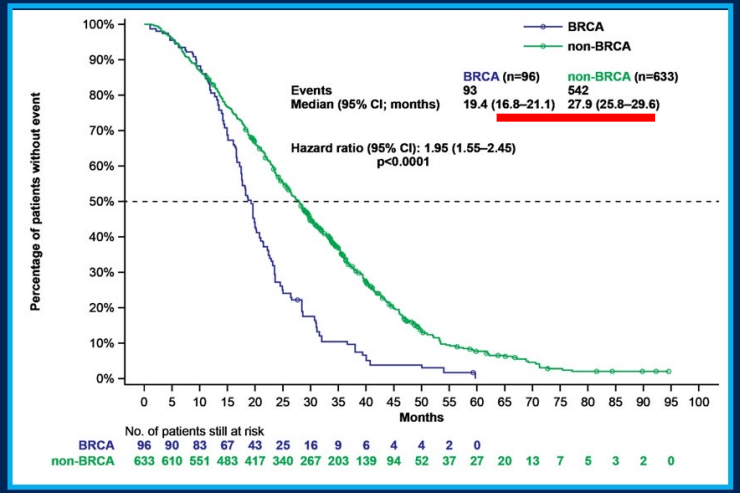
BRCA1/2 vs HRR non-*BRCA*



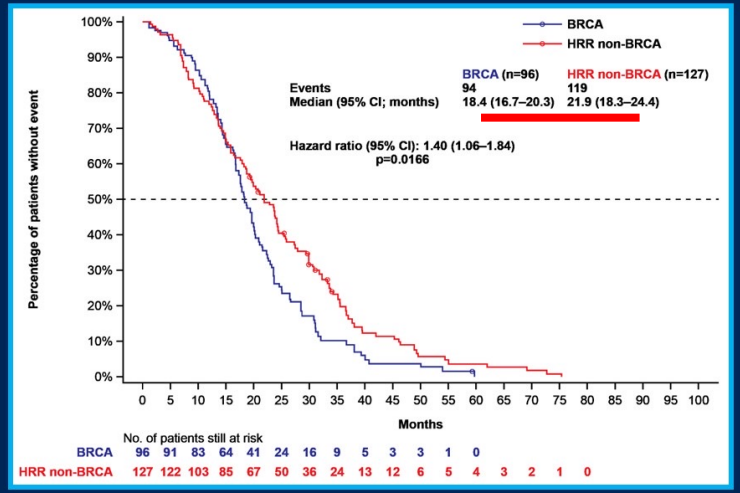
NOTE: propensity score weighted Kaplan Meier curves / Adjusted HR & p-values by Inverse probability weighted Cox models

Overall Survival

BRCA1/2 vs non-*BRCA*



BRCA1/2 vs HRR non-*BRCA*



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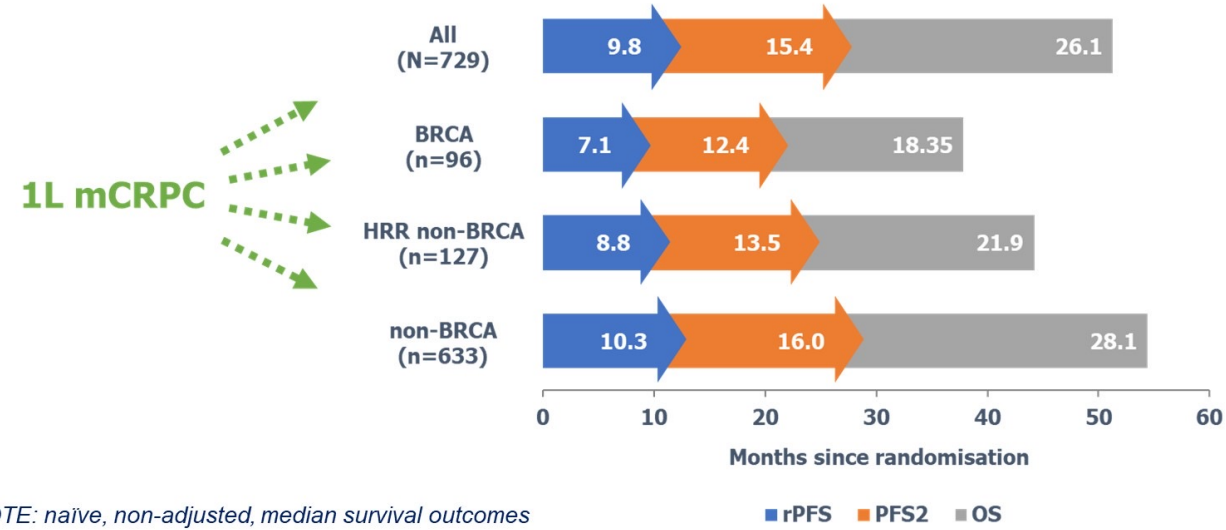
Summary of outcomes by subgroup



NOTE: naïve, non-adjusted, median survival outcomes

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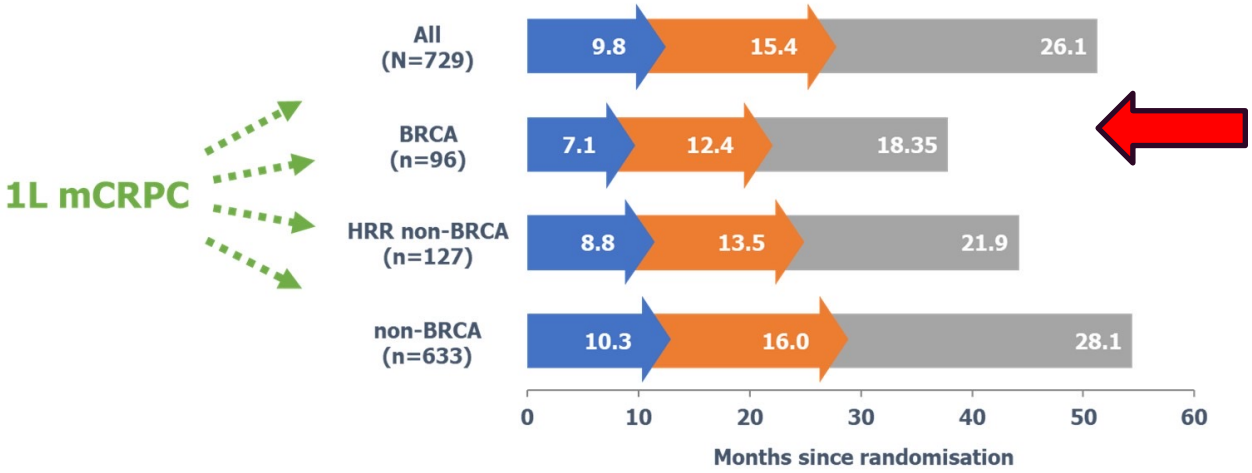
Summary of outcomes by subgroup



NOTE: naïve, non-adjusted, median survival outcomes

Data Leading to FDA 2023 Approvals

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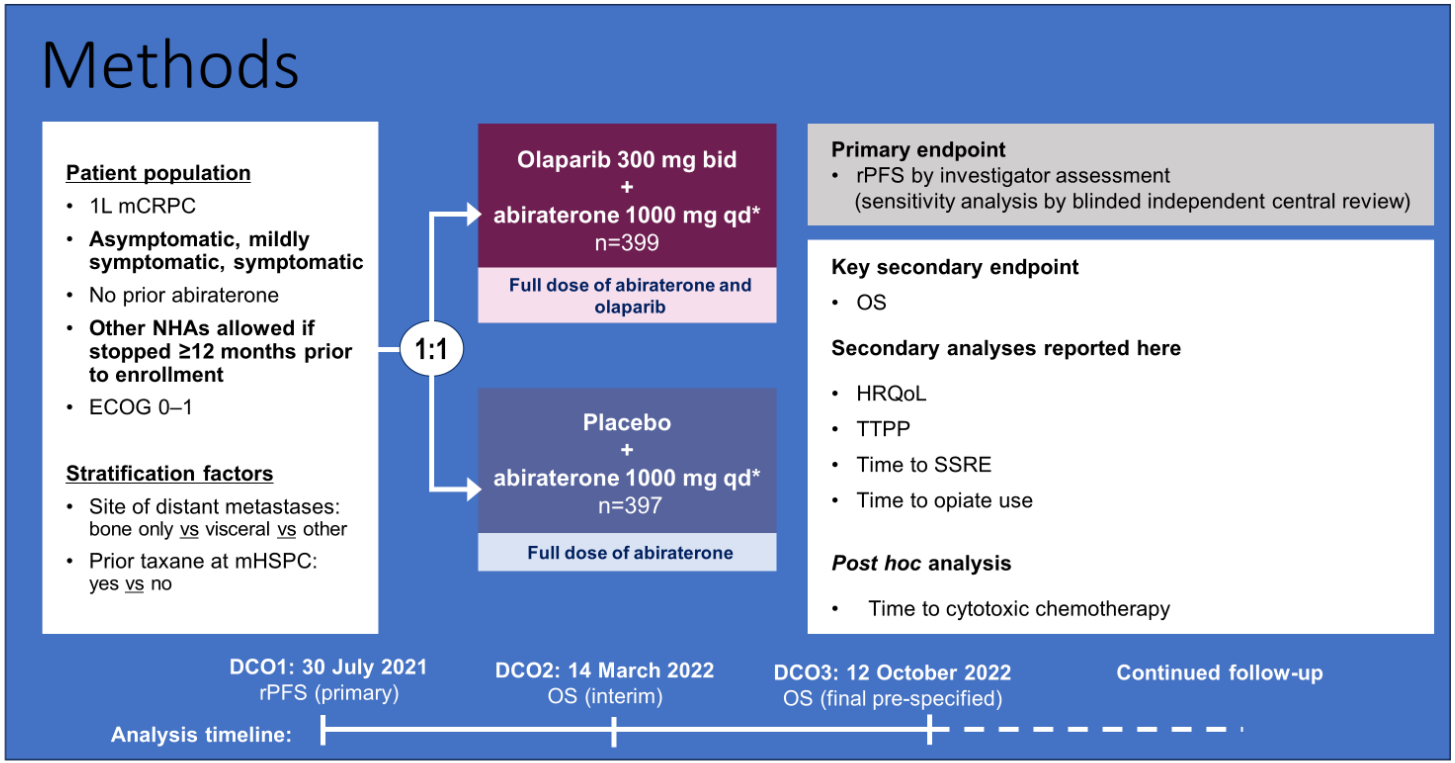
PROPEL: Abiraterone +/- Olaparib



Slide Courtesy of Dr. Andrew Armstrong via ASCO 2023, Abs 5102

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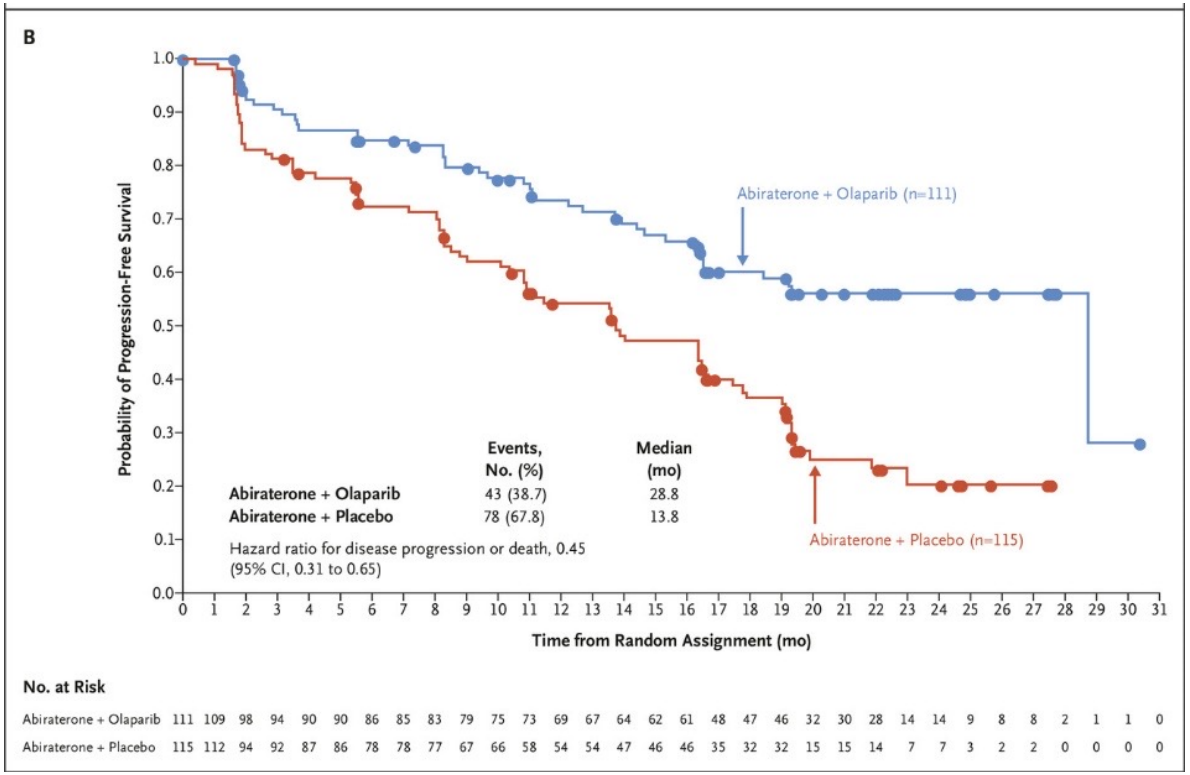
PROPEL: Abiraterone +/- Olaparib
(PFS in HRR+ Subgroup)



Clarke NW at al., NEJM Evidence, 2022

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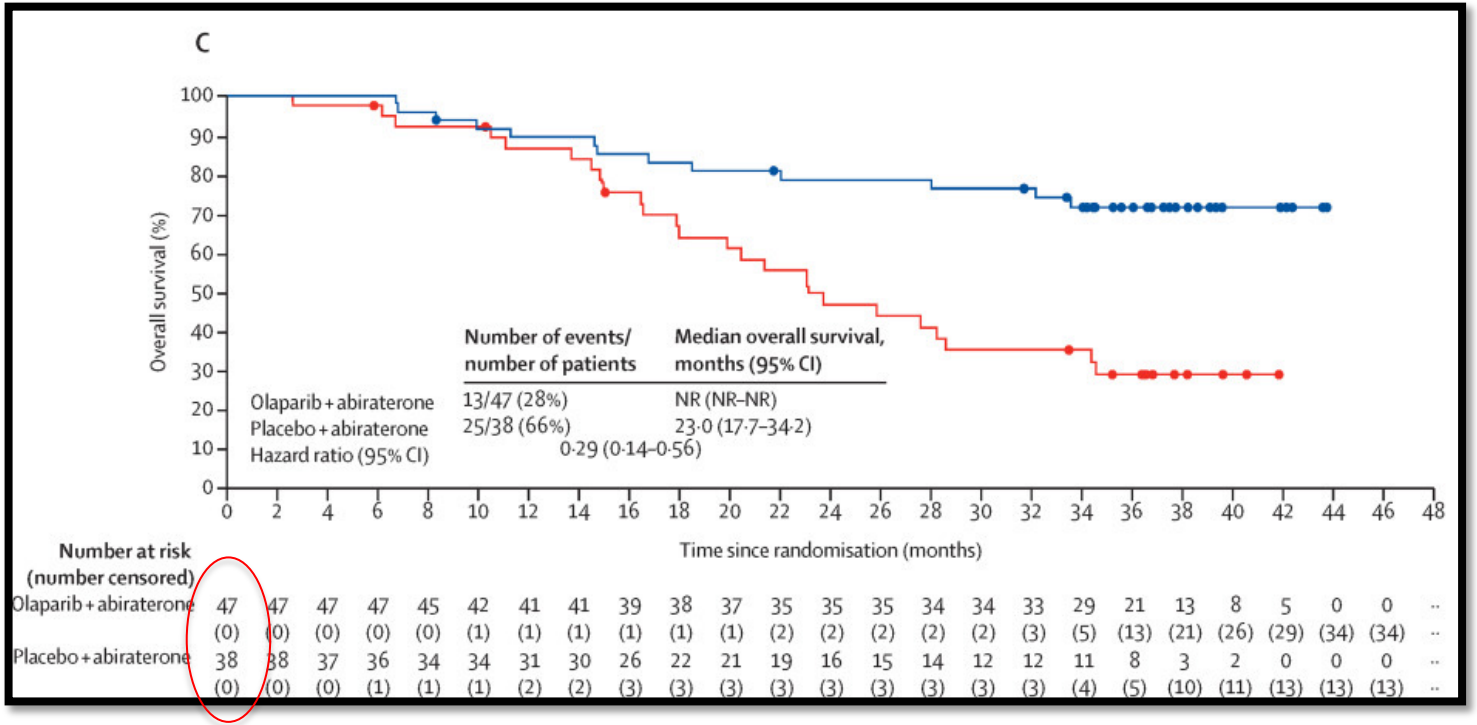
PROPEL: Abiraterone +/- Olaparib

(OS in BRCA Subgroup – the FDA Approved Subgroup)



Saad F at al., NEJM Evidence, 2022

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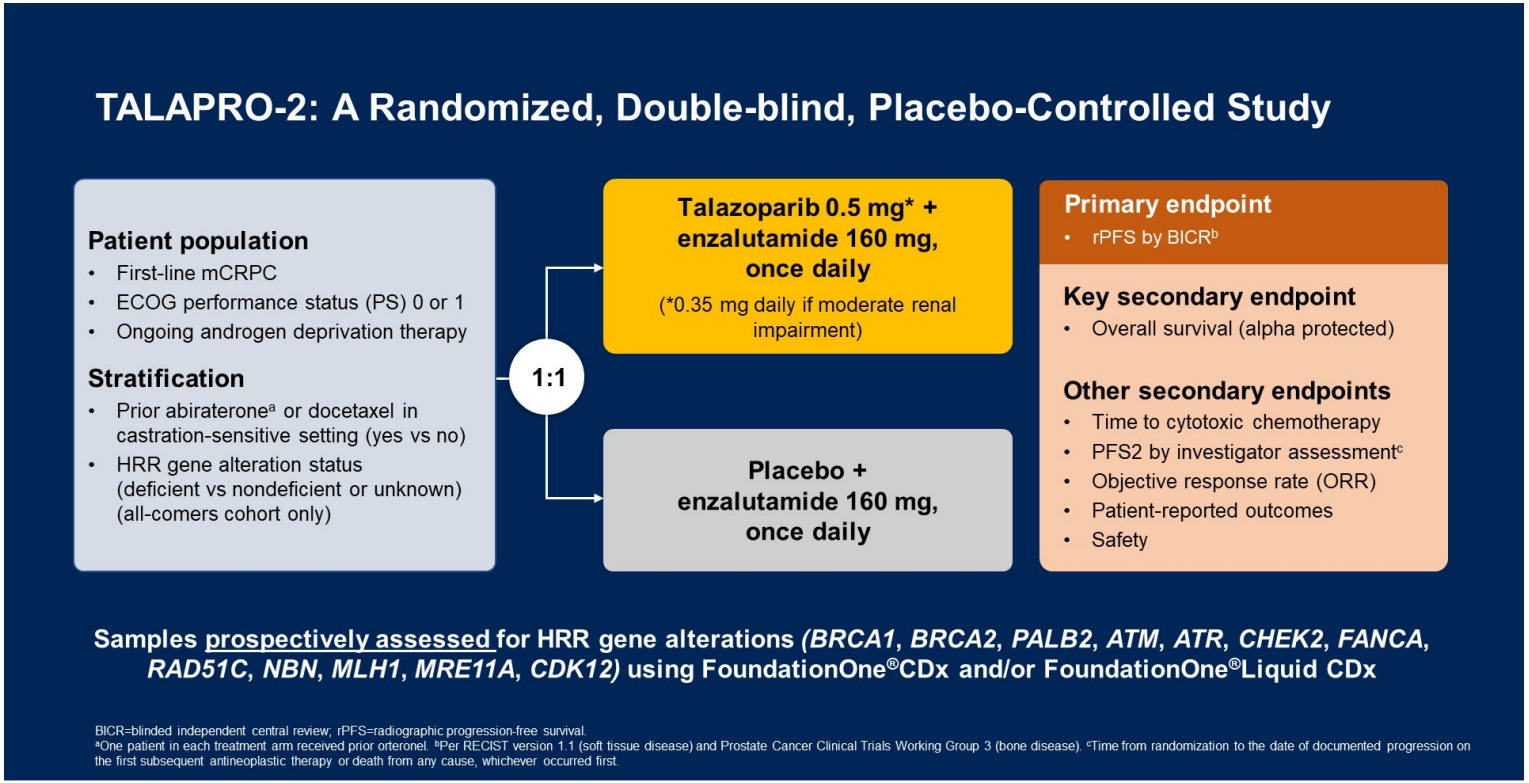
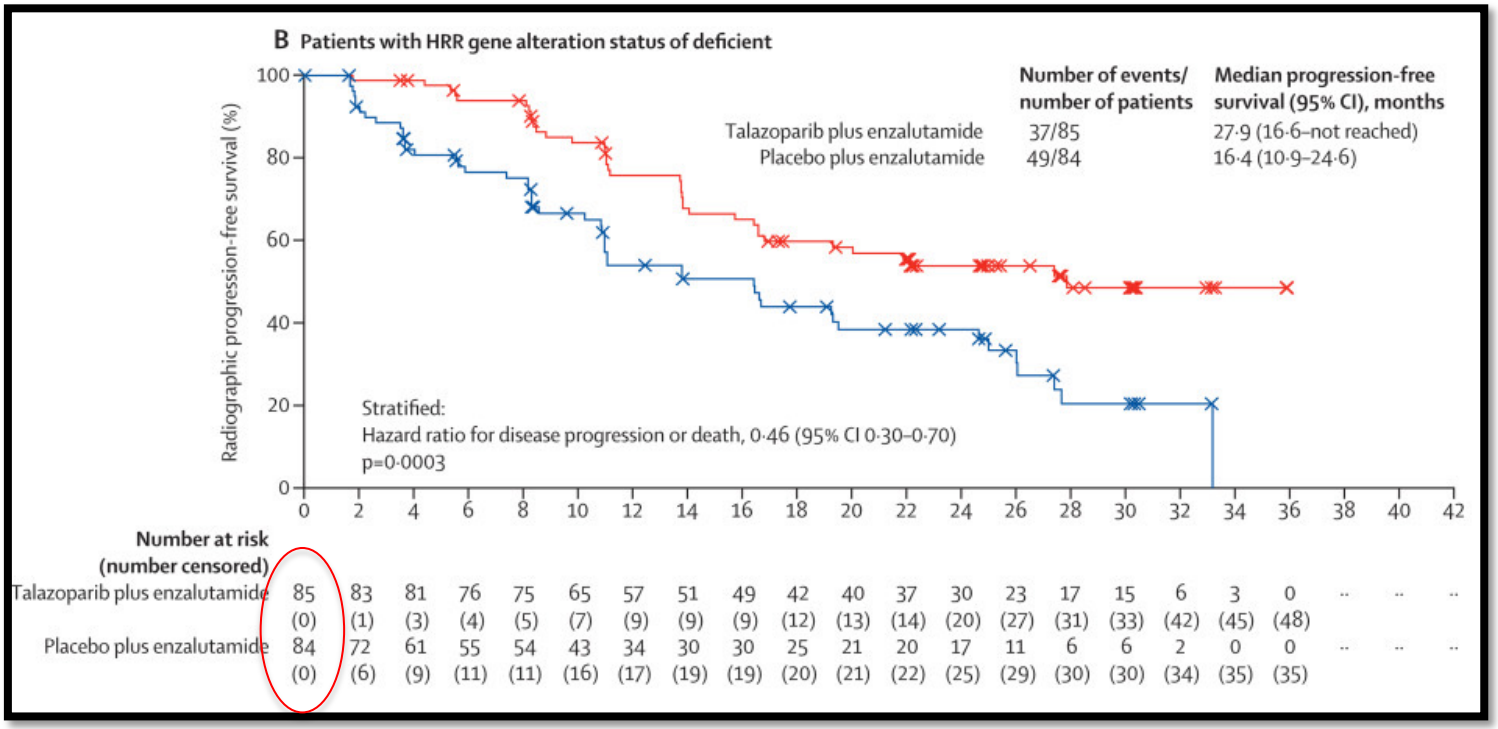
TALAPRO-2: Enzalutamide +/- Talazoparib



TALAPRO-2: Enzalutamide +/- Talazoparib PFS in HRR+ Subgroup



Agarwal N at al., Lancet, 2023

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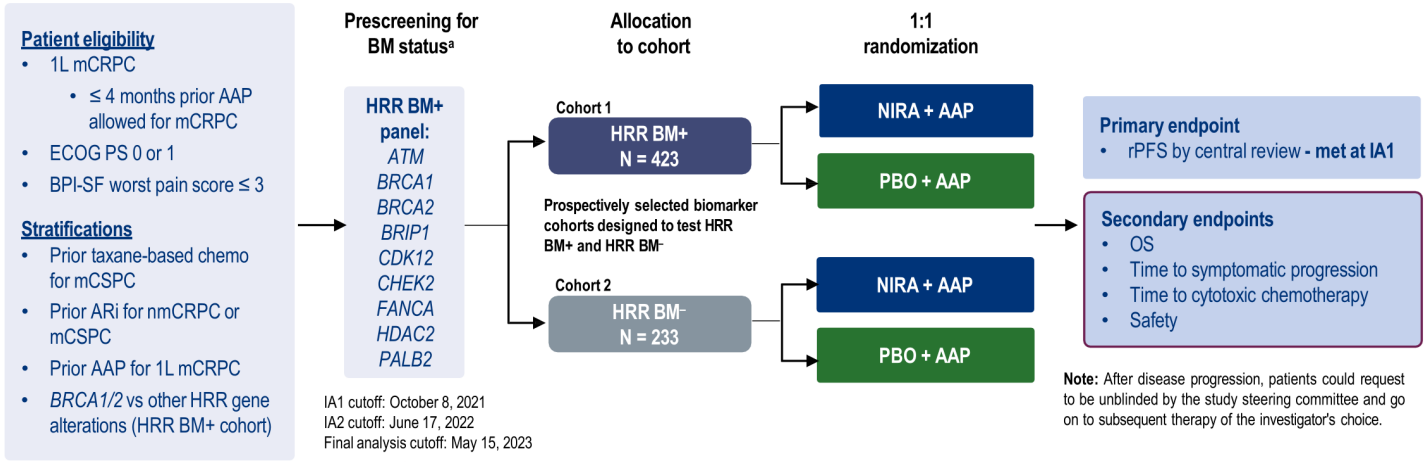
MAGNITUDE: Abiraterone +/- Niraparib

MAGNITUDE

Phase 3, randomized, double-blind, placebo-controlled study enrolling a population representative of patients treated in clinical practice today



[a]Tissue and plasma assays: FoundationOne tissue test (F… CDx), Resolution Bioscience liquid test (circulating tumor [ct]DNA), AmoyDx blood and tissue assays, Invitae germline testing (blood/saliva), local lab biomarker test results demonstrating a pathogenic germ… ation listed in the study BM gene panel. AR, androgen receptor; ARi, androgen receptor inhibitor; BM, biomarker; BPI-SF, Brief Pain Inventory-Short Form; ECOG PS, Eastern Cooperative Oncology Group per… tatus; IA, interim analysis; mCSPC, metastatic castration-sensitive prostate cancer; nmCRPC, nonmetastatic castration-resistant prostate cancer.

MADRID 2023 ESMO congress

Original Slide Presented by Dr. Kim N. Chi, ESMO 2023

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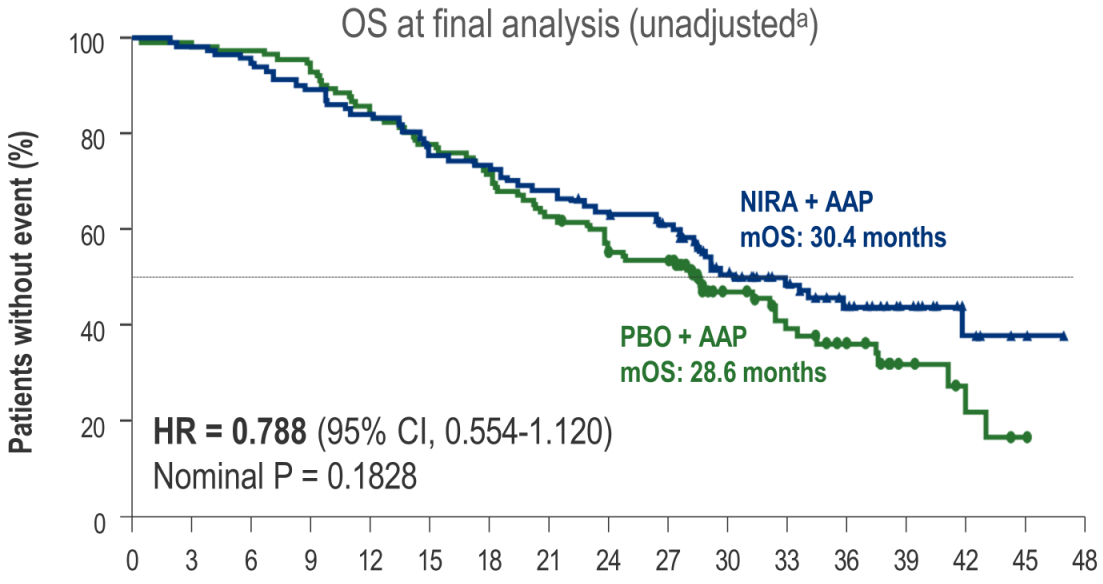
MAGNITUDE Final Analysis

Secondary endpoint: OS favored NIRA + AAP over PBO + AAP in *BRCA*+ patients



[a]Does not account for baseline imbalances. mOS, median overall survival.

Preplanned multivariate analysis (MVA) using prespecified prognostic factors supported an OS benefit of NIRA + AAP

MVA: HR = 0.663 (95% CI, 0.464-0.947); nominal P = 0.0237

How Do 2023 Approvals of ARPI + PARP Inhibitor Inform Practice in 2024?

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- In 2024, I can sequence ARPI and PARP inhibitor

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How Do 2023 Approvals of ARPI + PARP Inhibitor Inform Practice in 2024?

- In 2024, I can sequence ARPI and PARP inhibitor
- *The question asked in the ARPI/PARPi combo trials was essentially combo or never*

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Limited Functional Cross-Over an Issue with All PARPi + ARPI Trials

Trial	Agents	Reported % of HRRM+ Pts who Received Subsequent PARPi from Control Arms
MAGITUDE	Niraparib + Abiraterone	25-33%

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Limited Functional Cross-Over an Issue with All PARPi + ARPI Trials

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MAGITUDE	Niraparib + Abiraterone	**25-33%**
TALAPRO-2	Talazoparib + Enzalutamide	**17%**

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PROPEL	Olaparib + Abiraterone	

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Talapro-2	Talazoparib + Enzalutamide	**17%**
PROPEL	Olaparib + Abiraterone	**2%**

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Rationale to Use Combination ARPI and PARP Inhibitor

- Biologic Synergy!

Rationale to Use Combination ARPI and PARP Inhibitor

- Biologic Synergy?
  - Not clearly been demonstrated a clinical trial

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Rationale to Use Combination ARPI and PARP Inhibitor

- Biologic Synergy?

- Toxicity is high, but no impact on quality of life!

TALAPRO-2 HRR-Deficient: Summary of TEAEs

TEAEs, n (%)	TALA + ENZA (N=198)	PBO + ENZA (N=199)
Any TEAE	196 (99.0)	191 (96.0)
Treatment-related	180 (90.9)	144 (72.4)
SAEs	60 (30.3)	40 (20.1)
Treatment-related	27 (13.6)	0
Grade 3–4 TEAEs	131 (66.2)	74 (37.2)
Grade 5 TEAEs	3 (1.5)	5 (2.5)
Treatment-related	0	0
Dose interruption of talazoparib or placebo due to AE	133 (67.2)	39 (19.6)
Dose reduction of talazoparib or placebo due to AE[a]	110 (55.6)	12 (6.0)
Discontinuation of talazoparib or placebo due to AE	20 (10.1)	14 (7.0)

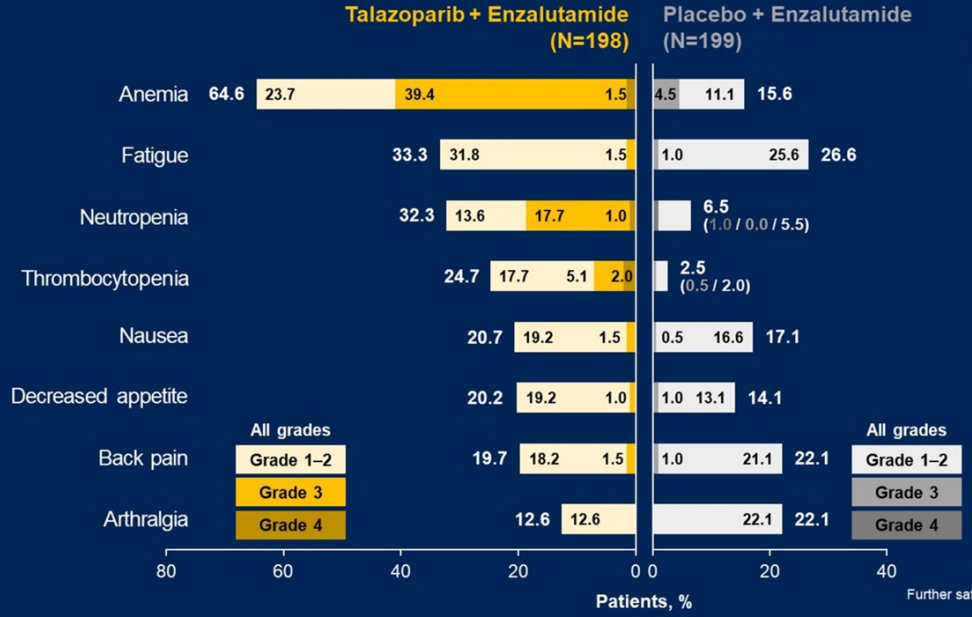
TEAEs of special interest for talazoparib

- There were no cases of myelodysplastic syndrome or acute myeloid leukemia
- Pulmonary embolism was reported in 4 (2.0%) patients (grade 3 in 3 patients; grade 2 in the other) in the talazoparib plus enzalutamide arm and in 2 (1.0%) patients (both grade 3) in the placebo plus enzalutamide arm

[a]The median relative dose intensity of talazoparib remained >80%.

Further safety details can be found by accessing abstract No. 5053 (poster No. 147)

TALAPRO-2 HRR-Deficient: Most Common All-Cause TEAEs



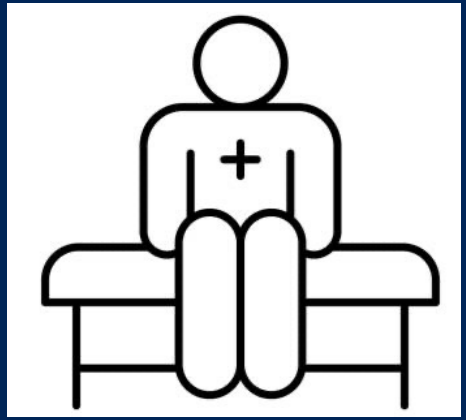
In the talazoparib arm:

- Most common TEAEs leading to a dose reduction of talazoparib were:
  - Anemia (42.9%)
  - Neutropenia (15.2%)
  - Thrombocytopenia (5.6%)
- 55.6% had grade 1–2 anemia at baseline
- Grade 3–4 anemia
  - Median time to onset was 3.2 months
  - Reported in 40.9% of patients
- 4.0% discontinued talazoparib due to anemia
- The median relative dose intensity of talazoparib remained >80%

Further safety details can be found by accessing abstract No. 5053 (poster No. 147)

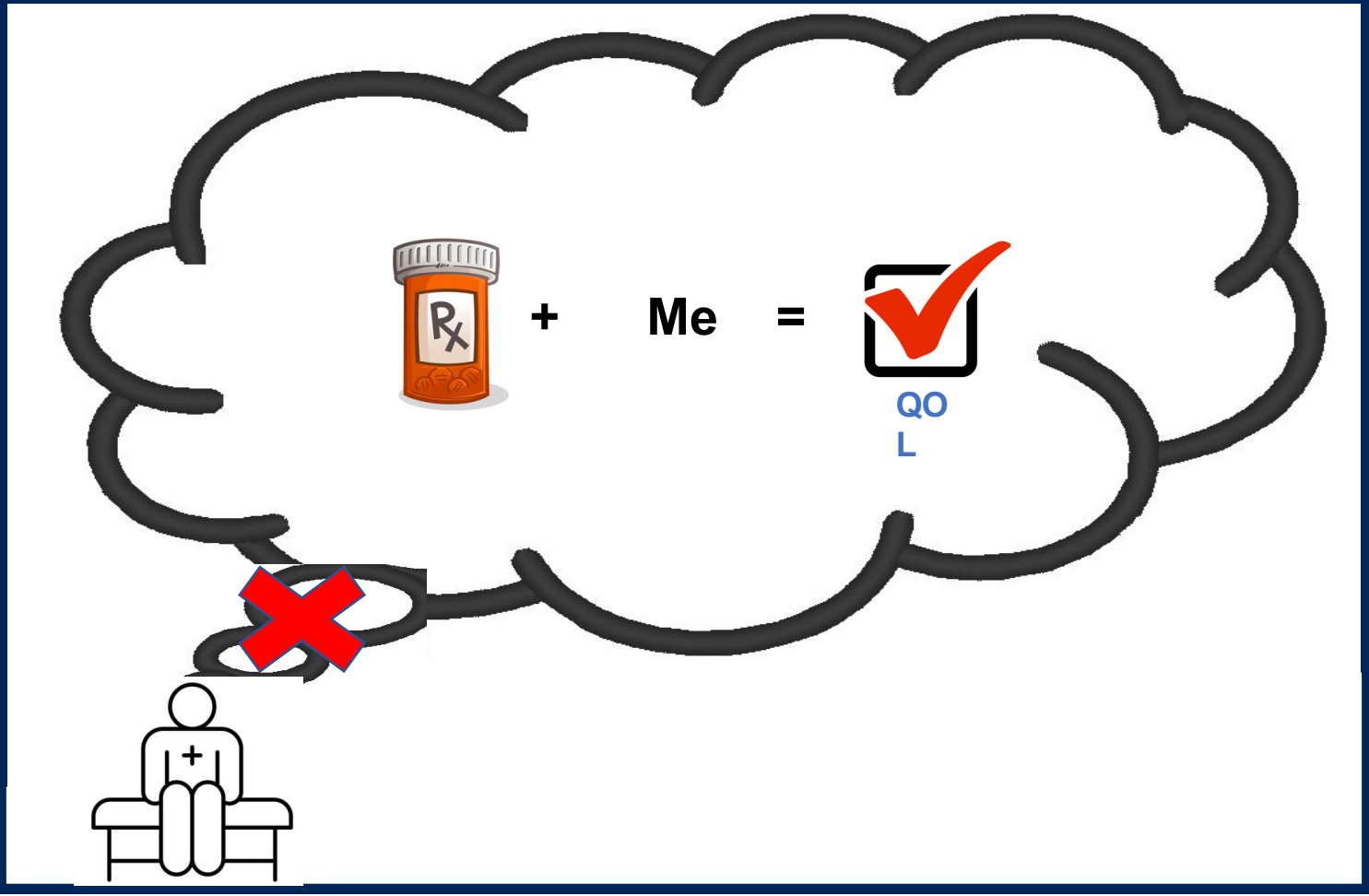
PRESENTED BY: Professor Karim Fizazi

Patient Reported Outcomes are a Product of a Complex Calculus

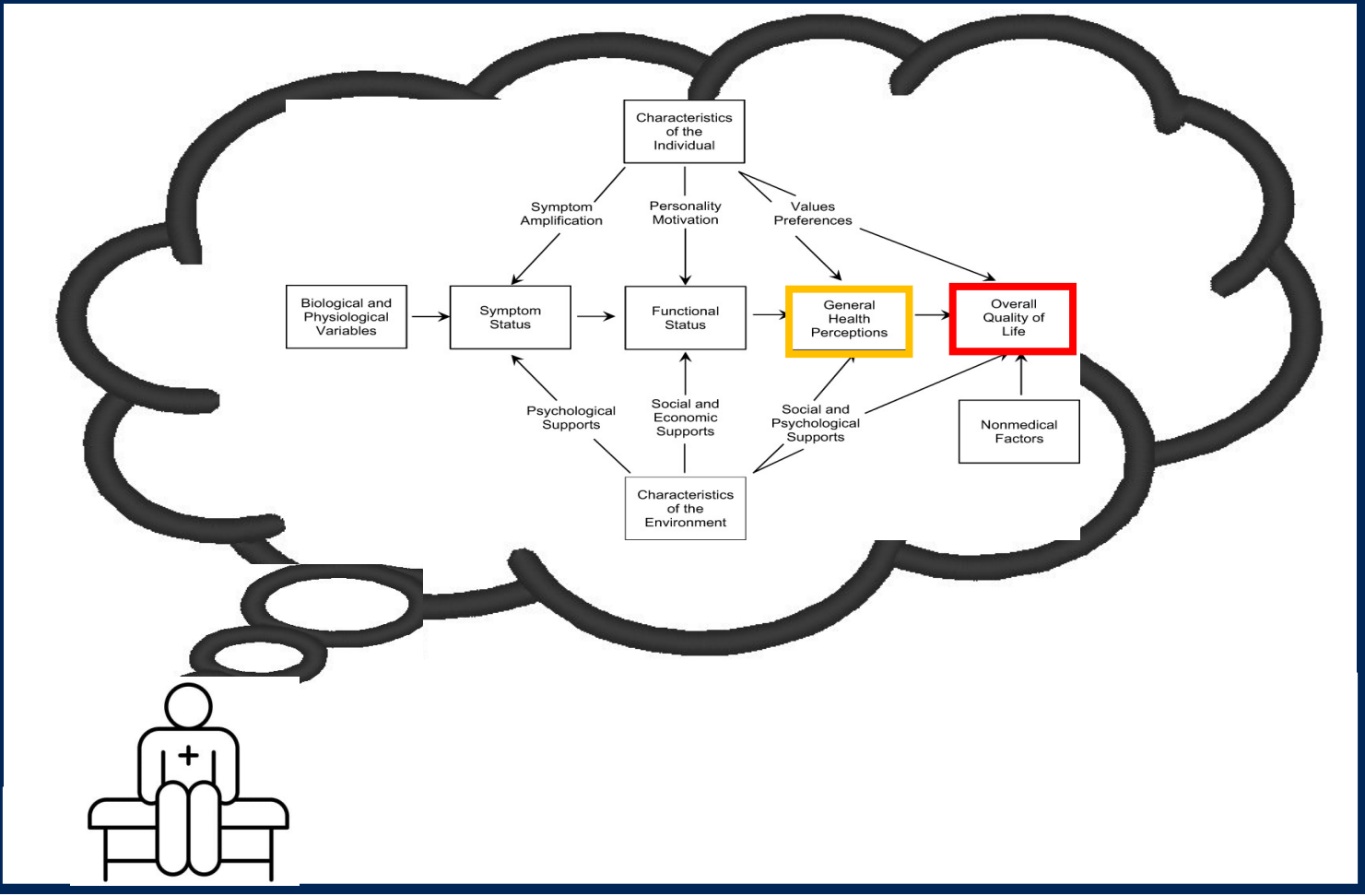


Patient

Patient Reported Outcomes are a *More Complex* than the Treatment



Patient Reported Outcomes are a *More Complex* than the Treatment



Wilson IB and Cleary PD, JAMA, 1995

My Perspective on Patient Reported Outcomes & *Role in Informing Clinical Practice*

PROs and QOL assessments ***best*** inform clinical practice when:

My Perspective on Patient Reported Outcomes & *Role in Informing Clinical Practice*

PROs and QOL assessments ***best*** inform clinical practice when:

- Two or more treatment options have *negligible* toxicity
- Two or more treatment options appear to have *equivalent* toxicity

My Perspective on Patient Reported Outcomes & *Role in Informing Clinical Practice*

PROs and QOL assessments ***best*** inform clinical practice when:

- Two or more treatment options have *negligible* toxicity
- Two or more treatment options appear to have *equivalent* toxicity

(PROs/QOL will provide an added dimension to our understanding of toxicity or the patient impact of a treatment)

Perspective on Patient Reported Outcomes & *Role in Informing Clinical Practice*

Dilemma for clinicians regarding 1st line Parp Inhibitor Combinations in mCRPC:

How do PRO or QOL data factor into treatment decisions when there is objective discrepancy between the toxicity of two different treatment options?

Rationale to Use Combination ARPI and PARP Inhibitor

- Biologic Synergy?
- Toxicity is high, but no impact on quality of life?

- “Patients rarely get more than one line of therapy!”

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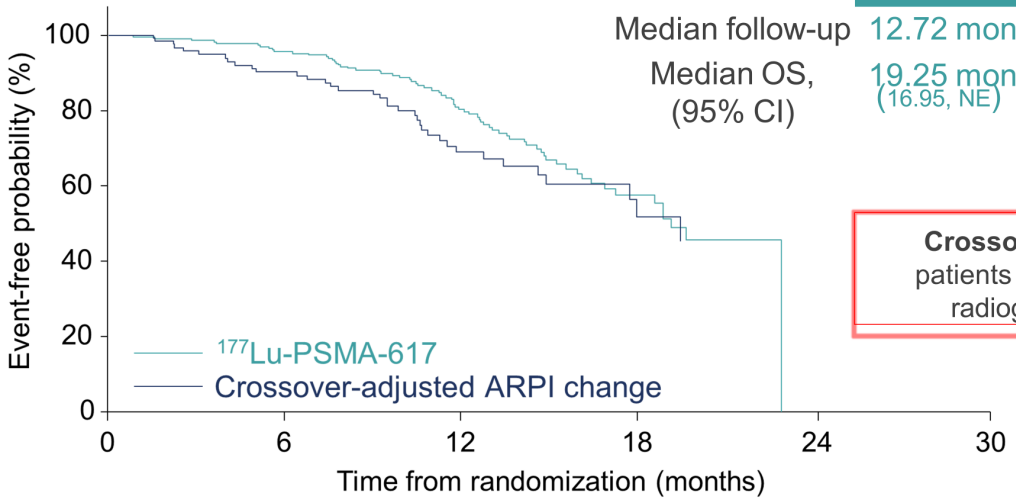
PSMAfore: Lu-PSMA in 2nd line mCRPC

2nd interim OS: prespecified crossover-adjusted analysis

HR: 0.80 (95% CI: 0.48, 1.33)



	177Lu-PSMA-617 (n = 234)	ARPI change (n = 234)
Median follow-up	12.72 months	13.08 months
Median OS, (95% CI)	19.25 months (16.95, NE)	19.55 months (14.95, NE)

Crossover: 123/146 (84.2%) patients who discontinued with radiographic progression

Original Slide Presented by Dr. Oliver Sartor, ESMO 2023

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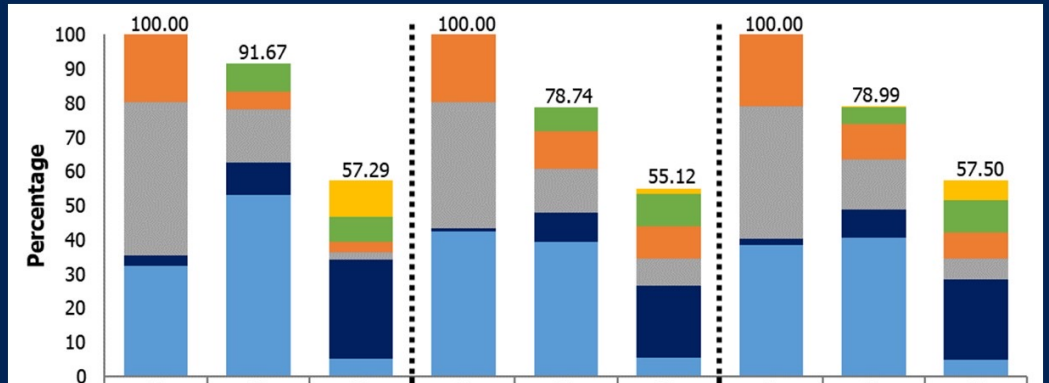
Treatment exposure by subgroup



%	BRCA (n=96)			HRR non-BRCA (n=127)			non-BRCA (n=633)		
	1L	2L	3L	1L	2L	3L	1L	2L	3L
Other	0.00	0.00	10.42	0.00	0.00	1.57	0.00	0.16	5.85
Ra223	0.00	8.33	7.29	0.00	7.09	9.45	0.00	4.90	9.48
Enza	19.79	5.21	3.13	19.69	11.02	9.45	21.01	10.27	7.74
AAP	44.79	15.63	2.08	37.01	12.60	7.87	38.70	14.85	6.00
Caba	3.13	9.38	29.17	0.79	8.66	21.26	1.90	8.06	23.54
Doce	32.29	53.13	5.21	42.52	39.37	5.51	38.39	40.76	4.90

NOTE: among those with prior de novo/recurrent mHSPC: 8% recieved ADT+docetaxel, 1% ADT + ARSi and 0.1% ADT+Doc+ARSi

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Rationale to Use Combination ARPI and PARP Inhibitor

- Biologic Synergy?
- Toxicity is high, but no impact on quality of life?
- Patients rarely get more than one line of therapy?

- PARPi/ARPI combos delay time to chemotherapy!

Is Time to Chemo a Relevant Endpoint in 2023 in mCRPC for HRRm Patients?

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- Phase 3 data demonstrates an OS benefit of Olaparib as second-line therapy

- Phase 3 data with Rucabarib shows PFS benefit vs. chemotherapy in second line mCRPC (Fizazi et al. NEJM, 2023)

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- Phase 3 data with Rucabarib shows PFS benefit vs. chemotherapy in second line mCRPC (Fizazi et al. NEJM, 2023)

- Would we use 2nd line chemo in mCRPC in HRRm patients?

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What is the Implied Benefit of Deferring Chemotherapy?

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- *Do Patients Need added Toxicity of PARPi in first line mCRPC?*

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UPDATE From ASCO GU 2024

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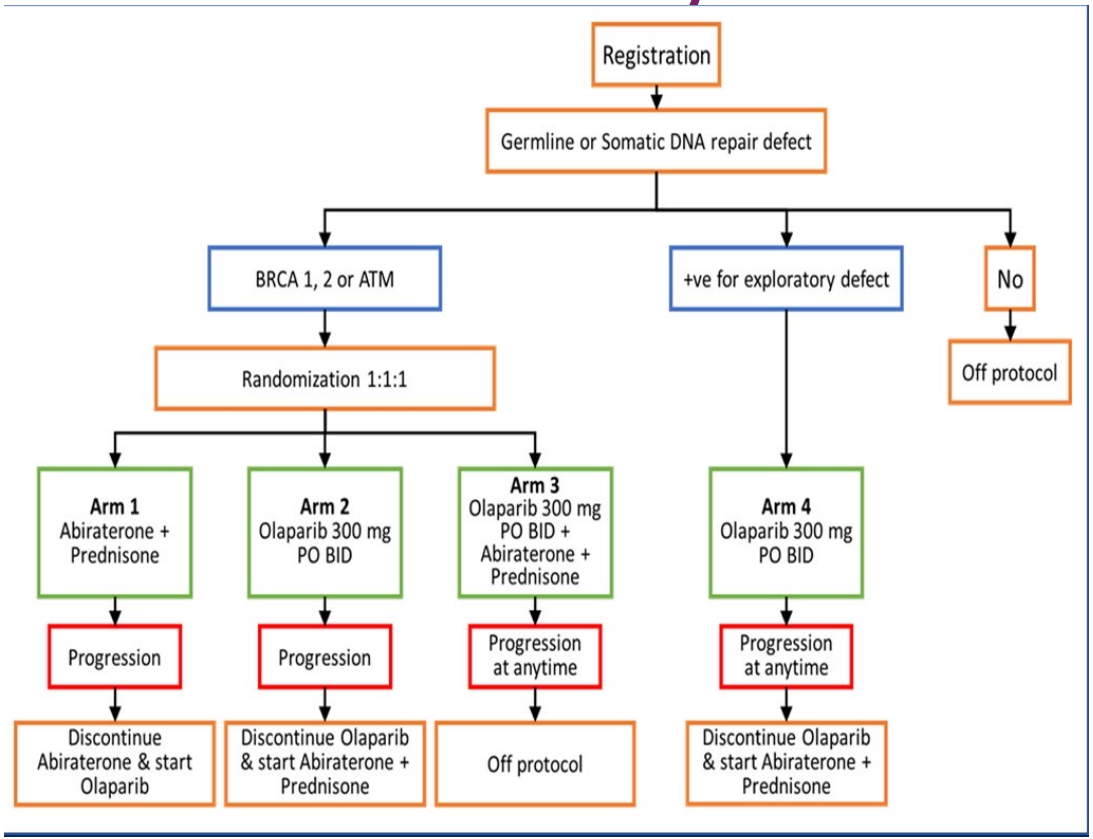
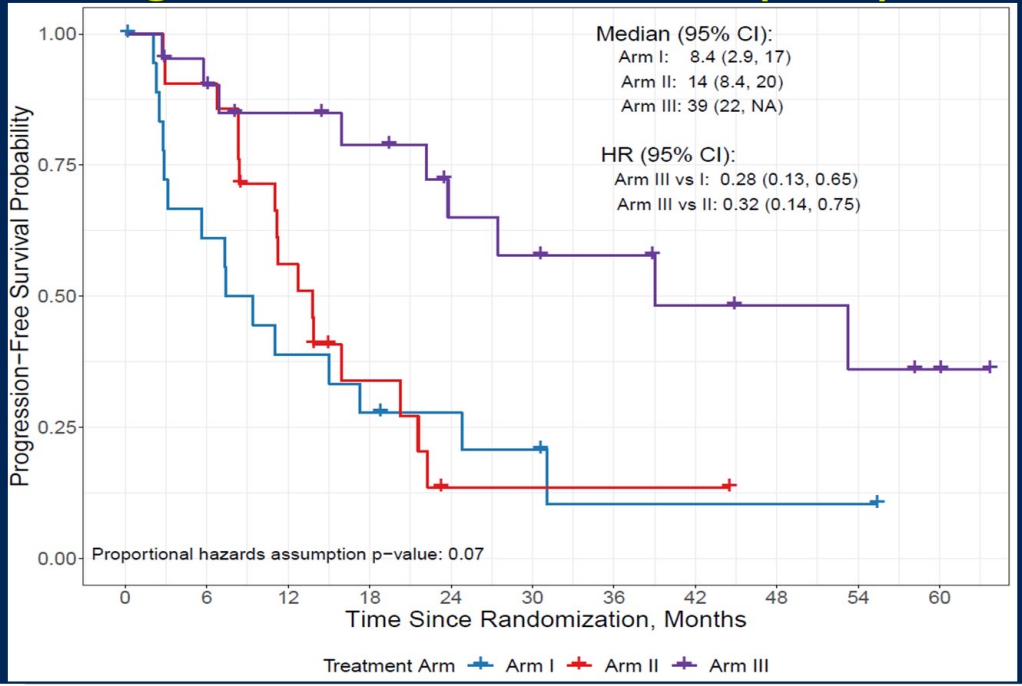
ASCO GU24: BRCAAway Trial



PRESENTED BY: Maha Hussain, MD, FACP, FASCO

ASCO GU24: BRCAAway Trial

Progression-Free Survival (PFS)



PFS: time from randomization until first progression or death.

Proportional hazards assumption was not met for Arm I versus II comparison.

ASCO GU24: BRCAAway Trial

Crossover

- At progression 8/19 pts crossed over from abiraterone/prednisone to olaparib and 8/21 pts vice versa.

	Crossover to Olaparib (n = 8)	Crossover to Abiraterone (n = 8)
Median PFS from crossover, months (95% CI)	**8.3 (5.5, 15)**	**7.2 (2.8, NR)**
Median PFS from randomization, months (95% CI)	**16 (7.8, 25)**	**16 (11, NR)**

NR, Not Reached

- RR to crossover treatment: olaparib 38% and abiraterone 25%.
- PSA RR to crossover treatment: olaparib 50% and abiraterone 63%.

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Comments and Controversies

Poly(ADP-ribose) Polymerase Inhibitor Combinations in First-Line Metastatic Castration-Resistant Prostate Cancer: Increasing Toxicity With Unclear Benefits

Ravi A. Madan, MD[1]; Fatima Karzai, MD[1]; David J. VanderWeele, MD, PhD[2]; Heather H. Cheng, MD, PhD[3]; and Johann S. de Bono, MD, PhD, MSc, FRCP, FMedSci[4,5]

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Since 2015, it has been clear that a small but meaningful percentage of patients with prostate cancer harbor homologous recombination repair mutations (HRRms) and may benefit from treatment with a poly(ADP-ribose) polymerase (PARP) inhibitor.[1,2] Multiple clinical trials have demonstrated the efficacy of PARP inhibitor monotherapy in patients with HRRms in metastatic castration-resistant prostate cancer (mCRPC) in the second-line setting after androgen receptor pathway inhibitors (ARPIs).[3,4] Over the past year, emerging data from several trials have reported that ARPIs (either enzalutamide or abiraterone) combined with a PARP inhibitor have a progression-free survival (PFS) advantage relative to enzalutamide or abiraterone alone.[5-7] The scientific rationale for these studies comes from limited investigations suggesting potential synergy when cotargeting the androgen receptor and DNA repair mechanisms, which to date have not been fully validated in the clinic to our knowledge.[8,9] The clinical trials have culminated with the approvals by the US Food and Drug Administration (FDA) of abiraterone with olaparib (in *BRCA1/2m* prostate cancer) and enzalutamide with talazoparib (in HRRm prostate cancer) as first-line therapeutic options for mCRPC on the basis of data from the PROpel and TALAPRO-2 trials, respectively, without any postapproval requirements.[10,11] Despite the regulatory

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THANK YOU!

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