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- **ODAC@fda.hhs.gov**

Talazoparib with Enzalutamide
for
Metastatic Castration-Resistant Prostate Cancer (mCRPC)

Oncologic Drugs Advisory Committee (ODAC) Meeting

Opening remarks

May 21st, 2025

Jaleh Fallah, MD

U.S. Food and Drug Administration

HRR as a Predictive Biomarker of Treatment Effect for PARP Inhibitors

- PARP inhibitors (PARPi) exploit synthetic lethality to target DNA repair defects in cancer cells.
- Tumors with mutations in the homologous recombination repair (HRR) pathway appear especially susceptible to PARPi.
- HRR gene mutation (HRRm) in 20-30% of patients with mCRPC (**>70% without HRRm**).
- **Higher efficacy of PARPi in HRRm mCRPC**.

Non-Clinical Studies of PARPi + ARPI

- Non-clinical studies suggest an increased anti-tumor effect when combining PARPi with ARPI in treating prostate cancer, particularly in *BRCA*m or other HRRm tumors.

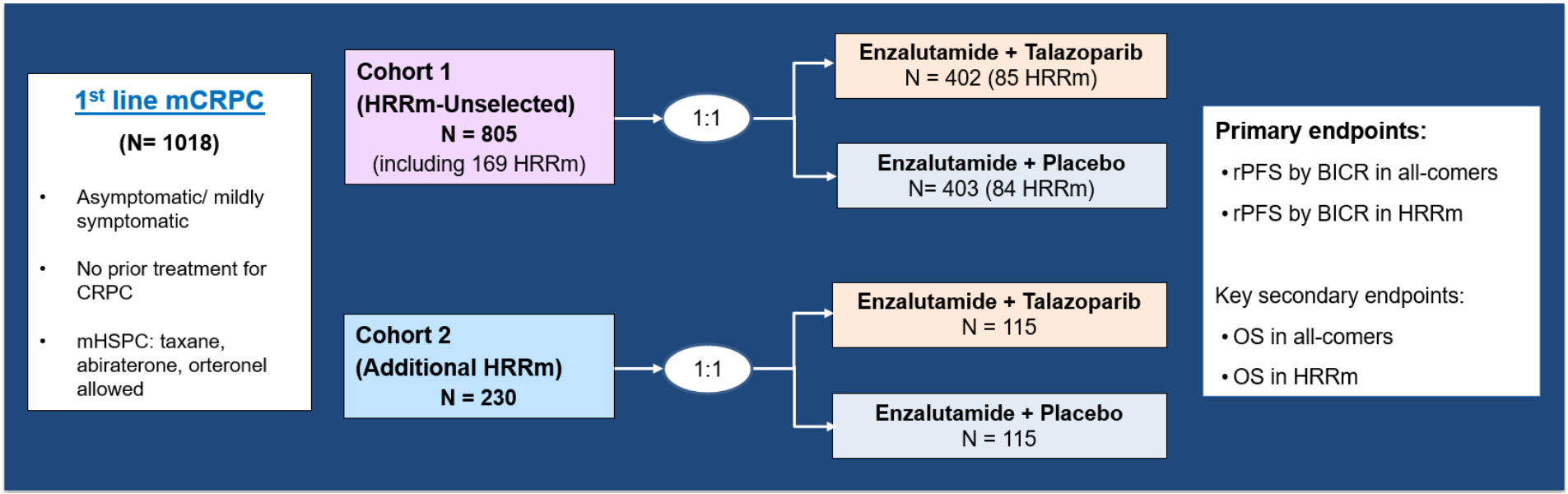
- Non-clinical studies suggest that treatment with ARPI can suppress HRR gene expression resulting in an HRR-deficient phenotype in prostate cancer tumors without an actual HRRm genotype.

- **Non-clinical studies** have provided **rationale for evaluation** of PARPi + ARPI **in clinical trials** of patients with and without HRRm tumors.

  - Several clinical trials of the combination of PARPi + ARPI has recently been conducted based on these findings, including TALAPRO-2.

ARPI: Androgen receptor pathway inhibitors; BRCAm: Breast cancer associated gene mutation.

TALAPRO-2



- Cohort 1 (HRRm-Unselected) stratification by HRRm vs non-HRR/Unknown → No stratification by HRR-negative (non-HRR)
- **HRRm analysis set** includes 399 patients total (169 from Cohort 1 + 230 Additional HRRm from Cohort 2)

N: number; CRPC: castration-resistant prostate cancer; HSPC: Hormone-sensitive prostate cancer; BICR: blinded independent central review; OS: overall survival.

June 2023: Approval of Talazoparib with Enzalutamide for HRRm Population

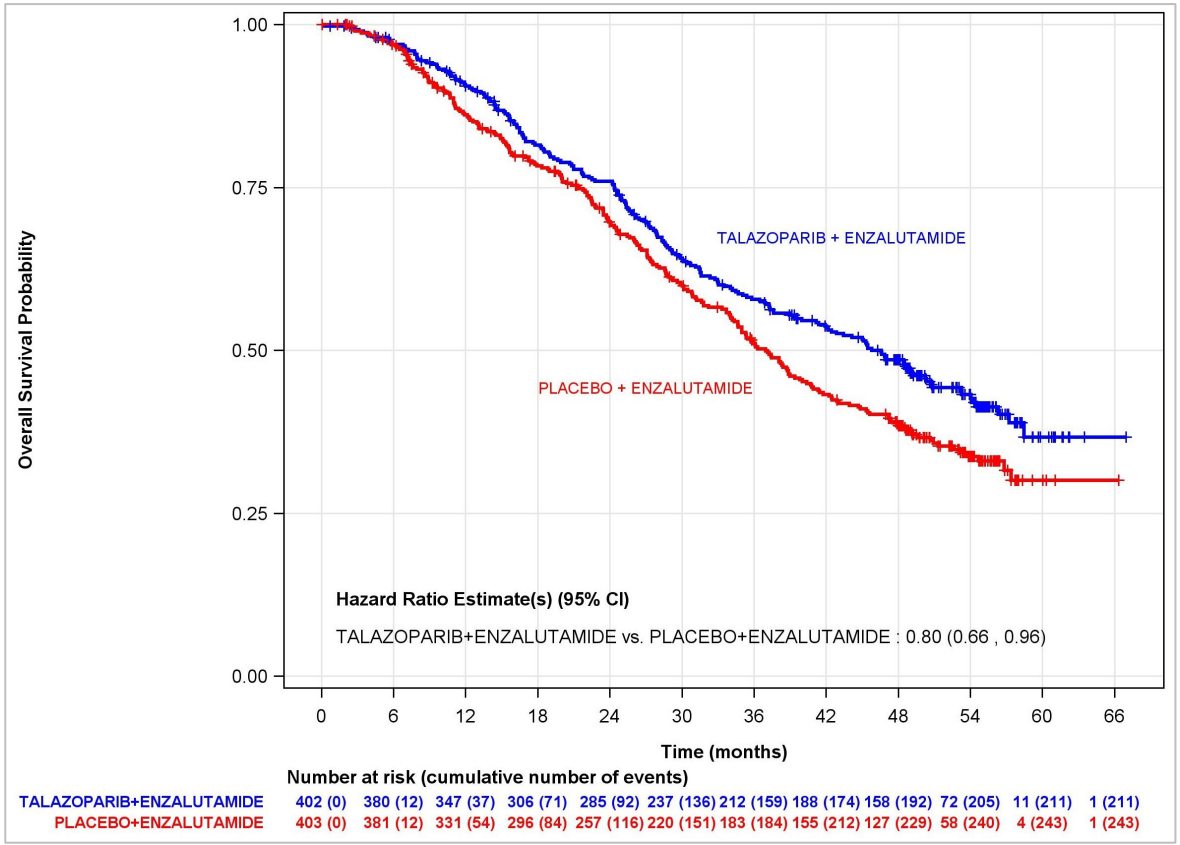
Endpoint	Non-HRR/Unknown (exploratory) N = 636	HRRm N = 399	**BRCAm** (exploratory) N = 155
rPFS HR (95% CI)	**0.70** (0.54, 0.89)	**0.45** (0.33, 0.61)	**0.20** (0.11, 0.36)
Interim OS HR (95% CI)	**0.93** (0.73, 1.19)	**0.69** (0.46, 1.03)	**0.61** (0.31, 1.23)

FDA approves talazoparib with enzalutamide for HRR gene-mutated metastatic castration-resistant prostate cancer

On June 20, 2023, the Food and Drug Administration approved talazoparib (Talzenna, Pfizer, Inc.) with enzalutamide for homologous recombination repair (HRR) gene-mutated metastatic castration-resistant prostate cancer (mCRPC).

N: number; rPFS: radiographic progression-free survival; HR: hazard ratio; OS: overall survival

December 2024: Request for Expansion of the Indication to All-comers with mCRPC

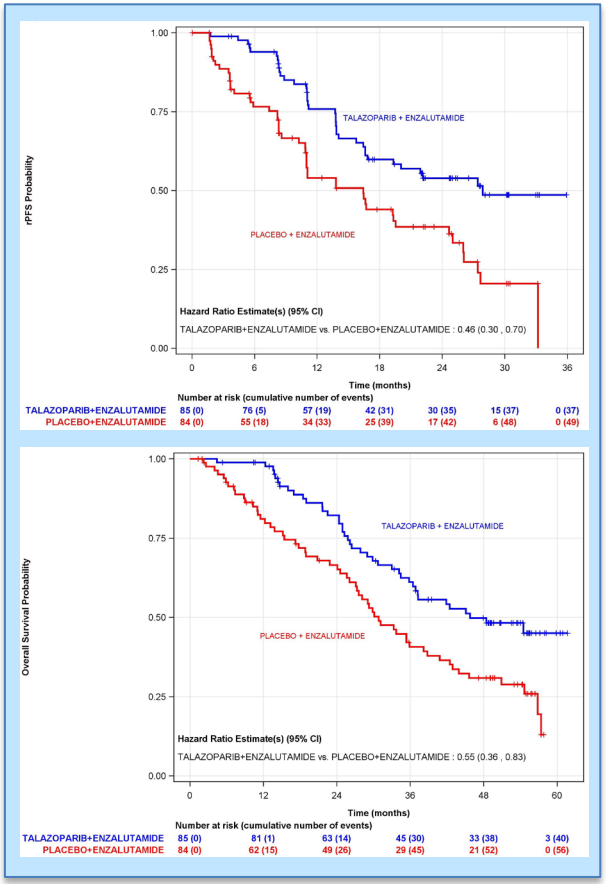
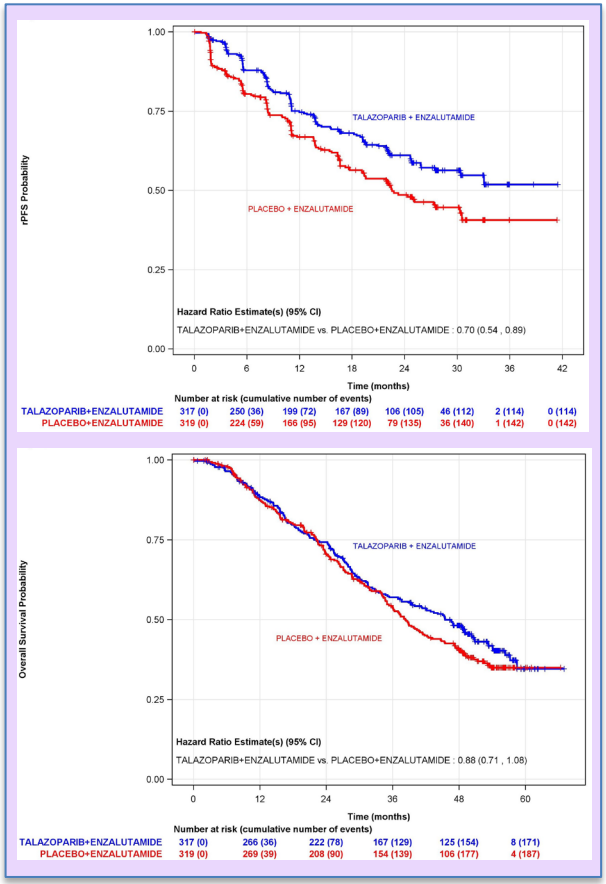


Overall Survival	Talazoparib + Enzalutamide N=402	Placebo + Enzalutamide N=403
Deaths, n (%)	211 (53)	243 (60)
Median months (95% CI)[a]	45.8 (39.4, 50.8)	37.0 (34.1, 40.4)
Hazard Ratio (95% CI)	**0.80 (0.66, 0.96)**	
p-value	0.0155	

www.fda.gov

TALAPRO-2 Results by HRR Status

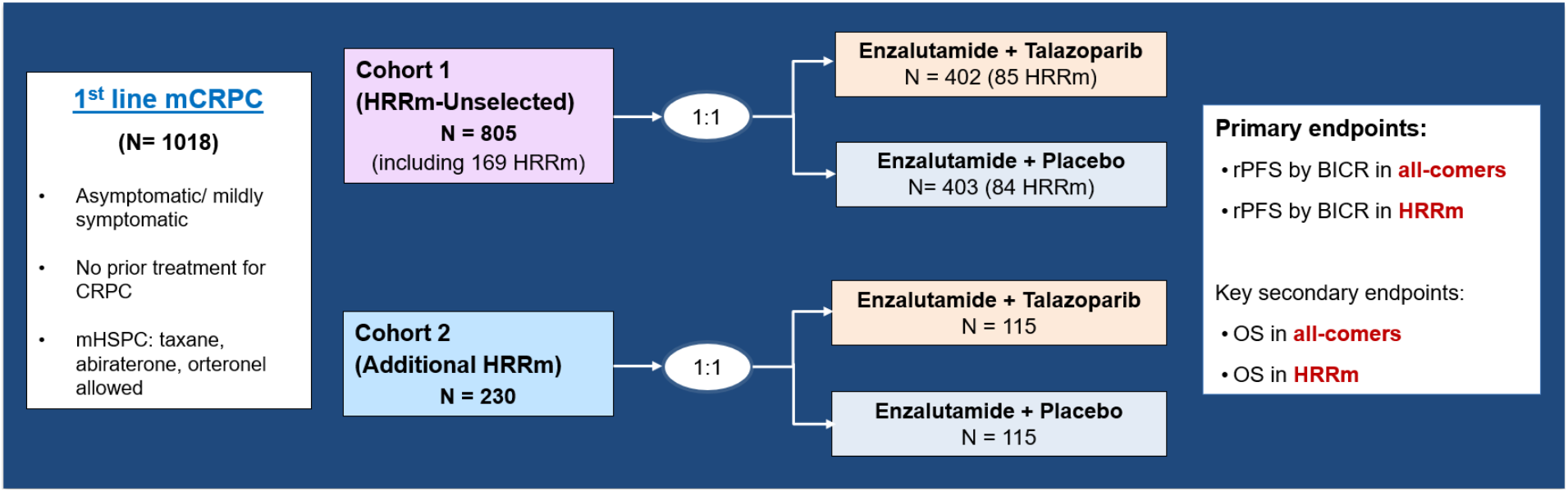
FDA

	HRRm	Non-HRRm/Unknown
rPFS		
OS		

Key Review Issues

- **Lack of pre-specified formal statistical testing** of efficacy in the non-HRR population
- **Lack of supportive data** from prior trials of PARPi for approval of non-HRR population

Lack of Pre-specified Formal Statistical Testing in Non-HRR Population



➢ **Potential for false-positive conclusions in HRR-negative population (Type I error)**

Lack of Supportive Data from Prior Trials of PARPi

Results from previous trials of PARPi in patients with mCRPC have demonstrated futility or unfavorable results in the non-HRR population.

Drug	Disease setting	Clinical trial	Key results
Olaparib + abiraterone	1L mCRPC	**PROpel**	• Efficacy primarily driven by *BRCA*m subgroup • Concern for OS detriment in non-*BRCA* population
Niraparib + abiraterone	1L mCRPC	**MAGNITUDE**	• Non-HRR cohort was stopped early for futility

➢ **Could the apparent effect in the exploratory analysis of non-HRR population in TALAPRO-2 be due to chance?**

Summary of Issues

- TALAPRO-2 demonstrated a statistically significant improvement in rPFS and OS in all-comers.
- The subgroup analysis shows a larger treatment effect in patients with an HRR gene alteration.
- OS results in the all-comers is primarily attributed to the HRRm population.

Key Issues:

- Lack of a prespecified formal analysis of efficacy in the non-HRR population.
- Lack of supportive data from other trials of PARPi for an all-comers indication.

- **Uncertainty in benefit-risk assessment in patients with non-HRR mCRPC.**
- **The apparent effect in the non-HRR population can be due to randomness/chance.**
- **The approval decision affects a large patient population (>70% of mCRPC).**

Recommended Trial Design

Important considerations when biomarker-negative prevalence is expected to be high:

- **Separate pre-specified formal statistical analyses** with adequate control of type I error in each biomarker-defined populations
- **Adequate prospective diagnostic testing** for determination of the biomarker status

ODAC meeting on April 23, 2023 (olaparib with abiraterone for mCRPC):

- Importance of precision medicine and adequate trial design for biomarker-negative population
- Advisory committee voted in favor of restricting the indication to *BRCA*m group

Topic for Discussion

Discuss whether efficacy should be formally evaluated in a biomarker-negative population when the biomarker is predictive of response and the prevalence of the biomarker-negative group is high.

Voting Question

Are the TALAPRO-2 results sufficient to conclude a favorable benefit-risk profile for adding talazoparib to enzalutamide in patients with non-HRRm mCRPC?

Talazoparib With Enzalutamide for Metastatic Castration-Resistant Prostate Cancer (mCRPC)

Oncologic Drugs Advisory Committee (ODAC) Meeting

May 21, 2025

Will Maguire, MD, PhD

Clinical Reviewer, Genitourinary Malignancies

Division of Oncology 1, Office of Oncologic Diseases

FDA Review Team

Richard Pazdur, Director, Oncology Center of Excellence (OCE)	Vishal Bhatnagar, Associate Director for Patient Outcomes, OCE
Laleh Amiri-Kordestani, Director, Division of Oncology 1 (DO1)	Shenghui Tang, Division Director, Division of Biometrics V (DBV)
Daniel Suzman, Deputy Division Director, DO1	Mallorie Fiero, Supervisory Mathematical Statistician, DBV
Jaleh Fallah, Cross-Disciplinary Team Lead, DO1	Joyce Cheng, Statistical Team Lead, DBV
Will Maguire, Clinical Reviewer, DO1	Hee-Koung Joeng, Statistical Reviewer, DBV
Haw-Jyh (Brian) Chiu, Pharmacology/Toxicology Reviewer, Division of Hematology Oncology Toxicology (DHOT)	Tiffany Ricks, Pharmacology/Toxicology Team Lead, DHOT
Beatriz Sanchez-Solana, Reviewer, Center for Devices and Radiological Health (CDRH)	Shyam Kalavar, Deputy Branch Chief, Center for Devices and Radiological Health, CDRH
Anand Pathak, Medical Officer, CDRH	Yu Han, Diagnostic Devices Team Lead, CDRH

Applicant's Proposed Indication

Proposed indication for talazoparib, in combination with enzalutamide:

> Treatment of adult patients with metastatic castration-resistant prostate cancer (mCRPC)

Voting Question

Are the TALAPRO-2 results sufficient to conclude a favorable benefit-risk profile for adding talazoparib to enzalutamide in patients with non-HRRm mCRPC?

Why Did We Bring This to ODAC?

- TALAPRO-2 did not formally evaluate the biomarker-negative subgroup of the all-comers population → **increased uncertainty of effectiveness in biomarker-negative patients**.

- The proposed indication would be the first approval of a PARP inhibitor (PARPi) for unselected mCRPC:

PARPi	Approval year	Approved indication
Later-line mCRPC as monotherapy		
Rucaparib	2020	***BRCA*m** mCRPC post-ARPI and taxane (accelerated approval)
Olaparib	2020	**HRRm** mCRPC post-ARPI
First-line mCRPC in combination with ARPI		
Olaparib + abiraterone	2023	***BRCA*m** mCRPC
Talazoparib + enzalutamide	2023	**HRRm** mCRPC
Niraparib + abiraterone	2023	***BRCA*m** mCRPC

Risk of approving in a large patient subgroup without proper evaluation:

Approval in patients who **will not receive benefit** and therefore will experience **unnecessary toxicity.**

- **Over 70% of patients with mCRPC may be affected.**

Role of Preclinical Data in Evaluation of Talazoparib With Enzalutamide

- Preclinical studies provide **rationale for clinical evaluation** of talazoparib with enzalutamide in patients without tumor HRRm in clinical trials → **hypothesis generation**.

- **However,** mechanistic rationale alone is not adequate for drug approval.

- Unclear whether mechanistic rationale is sufficient to overcome clinical trial design issues with TALAPRO-2 and reduced/no efficacy of PARPi in non-HRRm mCRPC seen across all relevant trials.

Main Review Issues

1. Large (~70%), incompletely-defined non-HRRm subgroup was not formally tested for efficacy.

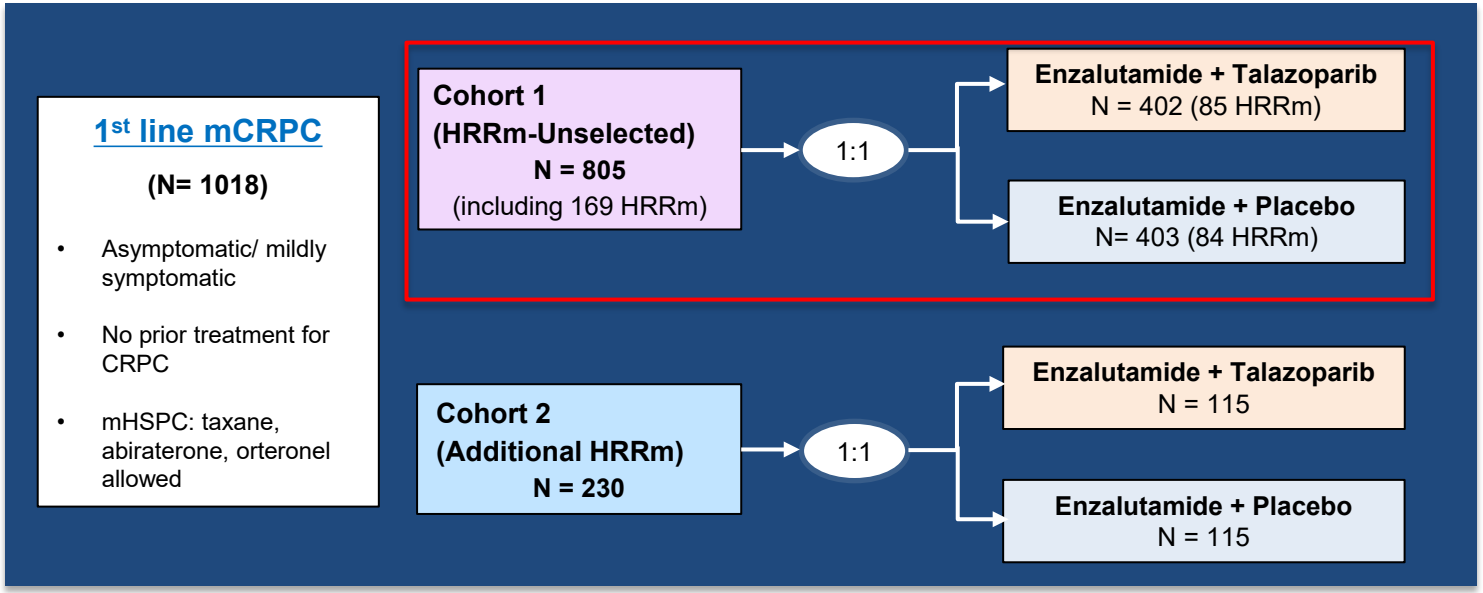
2. Interpretation of the overall survival (OS) results and applicability to current US standard of care are unclear.

3. Addition of talazoparib increases hematologic toxicity versus enzalutamide alone.

4. Trials of other PARP inhibitors did not support an all-comers indication.

Background: Overall Design of TALAPRO-2 and Initial Approval

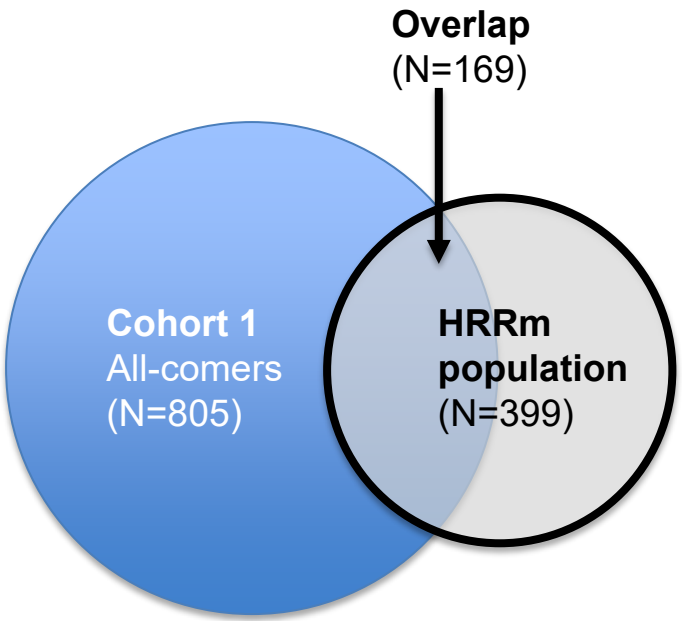
TALAPRO-2 Cohort 1 (All Comers Population) is the Basis of the Proposed Expanded Indication

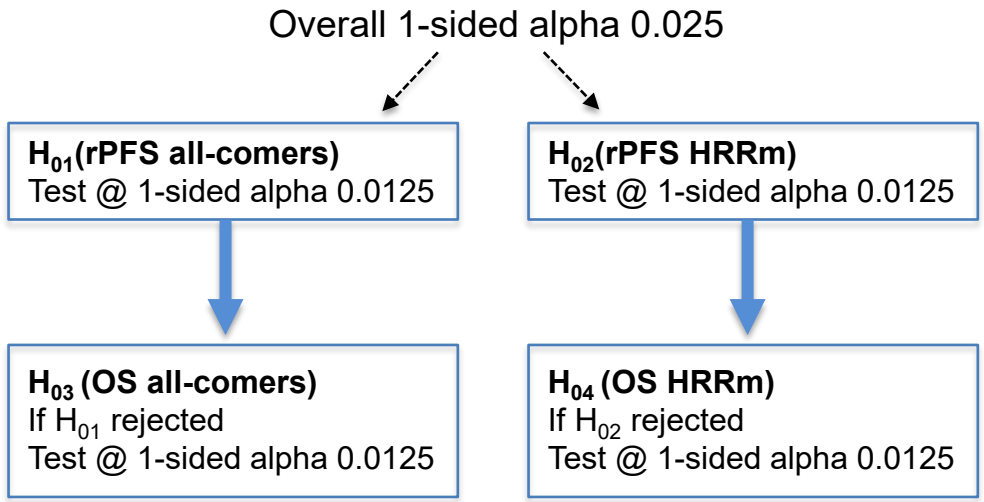


- Cohort 1 was stratified by HRRm status (HRRm vs non-HRRm/unknown), but **did not separately stratify non-HRRm vs unknown.**

Abbreviations: HRRm, homologous recombination repair mutation; mCRPC, metastatic castration-resistant prostate cancer; mHSPC, metastatic hormone-sensitive prostate cancer.

TALAPRO-2: Key Efficacy Endpoints and Statistical Testing Plan





No pre-specified formal statistical testing of rPFS or OS in non-HRR population

Initial Approval June 20, 2023 Was Limited to Patients With Tumor HRRm

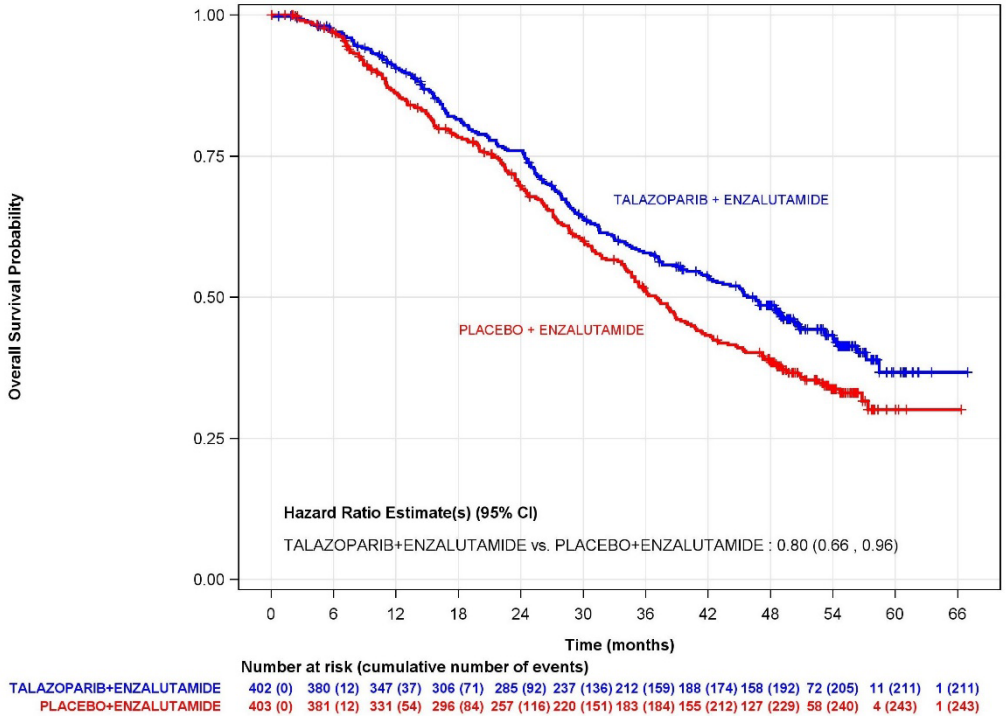
- Primary rPFS analysis: Biomarker status appears to predict rPFS and OS benefit.

	Cohort 1 All-comers N = 805	**Cohort 1 Non-HRRm/Unknown* N = 636**	**HRRm (combined) N = 399**	***BRCA*m (combined)* N = 155**
rPFS HR (95% CI) p-value (2-sided)	**0.63** (0.51, 0.78) <0.0001	**0.70** (0.54, 0.89)	**0.45** (0.33, 0.61) <0.0001	**0.20** (0.11, 0.36)
OS HR (95% CI) (**Immature** at interim analysis)	**0.84** (0.67, 1.04)	**0.93** (0.73, 1.19)	**0.69** (0.46, 1.03)	**0.61** (0.31, 1.23)

*Exploratory

- Safety: increased toxicity of combination vs enzalutamide monotherapy

TALAPRO-2: Statistically Significant Final OS Results in All-comers Population



	Cohort 1 all-comers (N=805)	
	Talazoparib + Enzalutamide N=402	**Placebo + Enzalutamide** N=403
Number of events (%)	211 (52.5%)	243 (60.3%)
Median, months (95% CI)	45.8 (39.4, 50.8)	37.0 (34.1, 40.4)
Hazard Ratio (95% CI) †	**0.80 (0.66, 0.96)**	
p-value‡	0.0155	

†, HR and CI based on stratified cox PH model
‡, two-sided p-value based on stratified log-rank test

Main Review Issues

1. **Large (~70%), incompletely-defined non-HRRm subgroup was not formally tested for efficacy.**

2. Interpretation of the OS results and applicability to current US standard of care are unclear.

3. Addition of talazoparib increases hematologic toxicity versus enzalutamide alone.

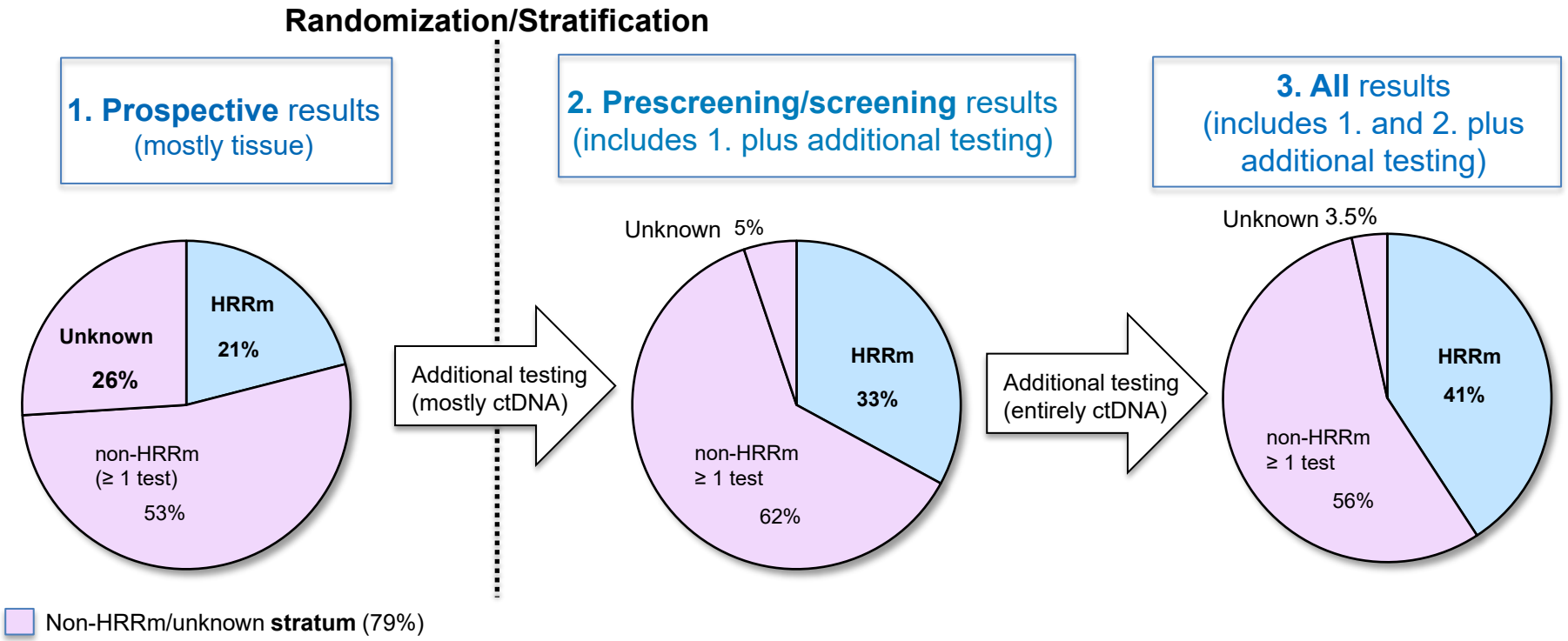
4. Trials of other PARP inhibitors did not support an all-comers indication.

The Biomarker-undetected Population Is a High Proportion of the All-comers Population

- 20-30% of patients with mCRPC are estimated to have HRR mutations (HRRm); **70-80% do not have documented HRR mutations**.[1,2]
- A preponderance of data, including from TALAPRO-2, provide strong biological rationale that PARPi are more efficacious in biomarker+ tumors (more later).
- Important, and feasible, to reliably characterize benefit-risk ratio in a large subgroup of biomarker-negative patients who are expected to benefit less than biomarker-positive patients.

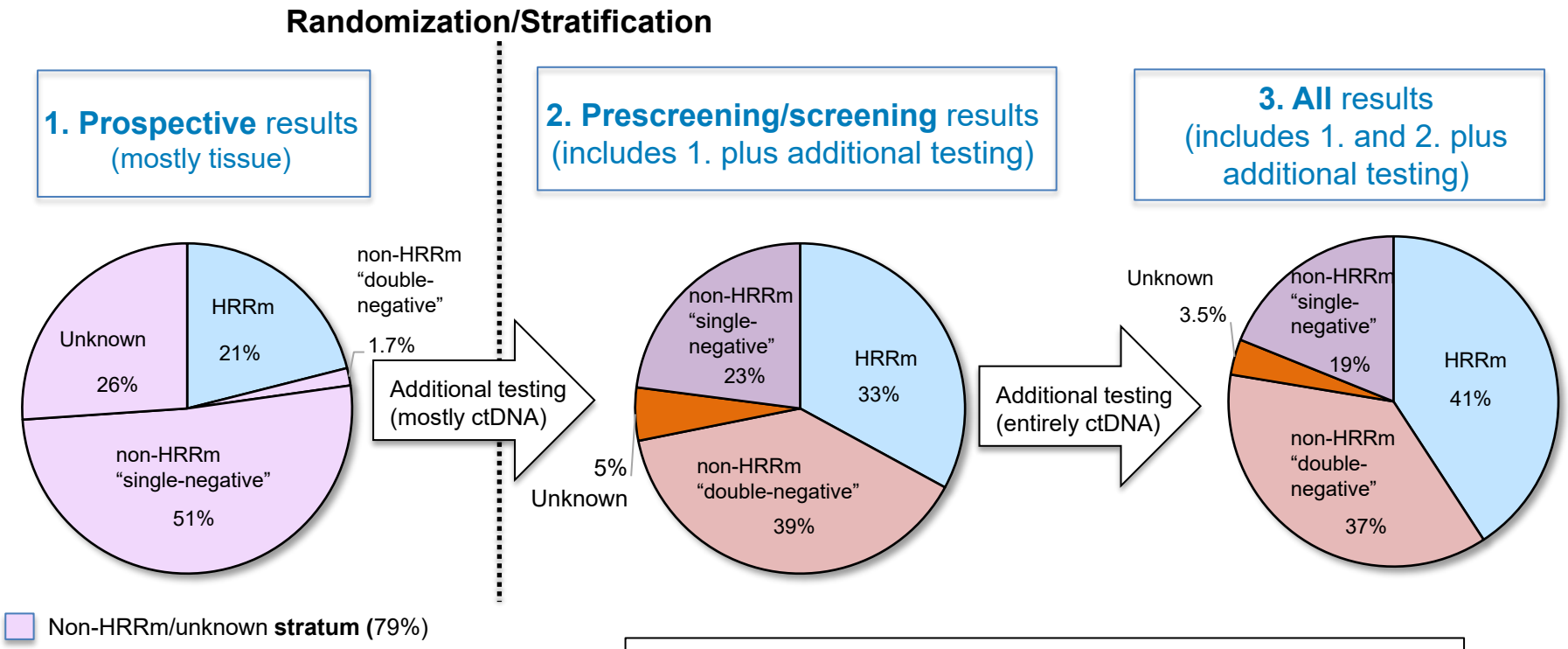
1. Walsh, C. Clin Obstet Gynecol, 2024. 67(4): p. 711-719; 2. Mateo, J., et al., Eur Urol, 2017. 71(3): p. 417-425.

Non-HRRm/unknown Stratum Was Not a True "Biomarker-negative" Population



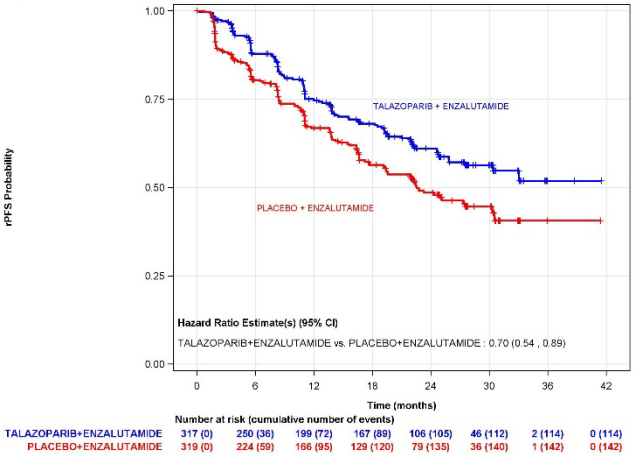
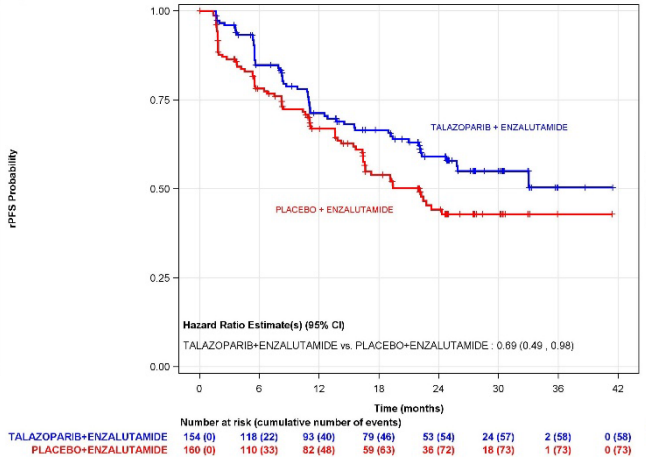
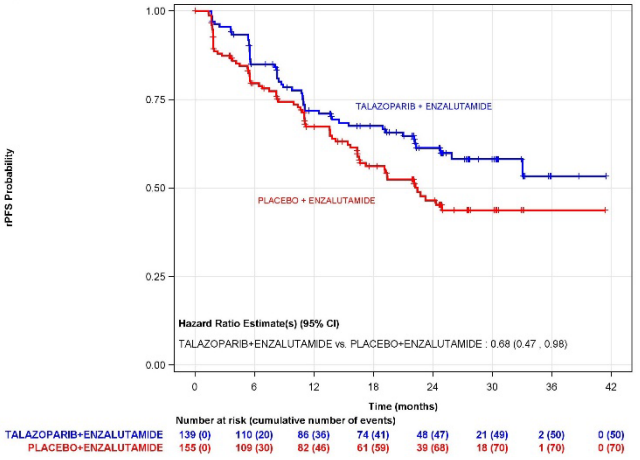
Results in non-HRRm/unknown stratum should be interpreted with caution.

Definitions of “Biomarker-negative” Vary



non-HRRm / “double-negative”: at least two negative tests (must have available negative results from both tissue and ctDNA)

Sensitivity Analyses of rPFS in Non-HRR Population

non-HRRm/unknown stratum N = 636 (79%)	**"Double-negative" non-HRRm (Applicant)** N = 314 (39%)	**"Double-negative" non-HRRm (FDA)** N = 294 (37%)
		
HR = **0.70** (95% CI:0.54, 0.89)	HR = **0.69** (95% CI: 0.49, 0.98)	HR = **0.68** (95% CI: 0.47, 0.98)

<u>However</u>, these are all exploratory analyses.

TALAPRO-2 Did Not Formally Control for False-positive Conclusions in the Large Non-HRRm Subgroup

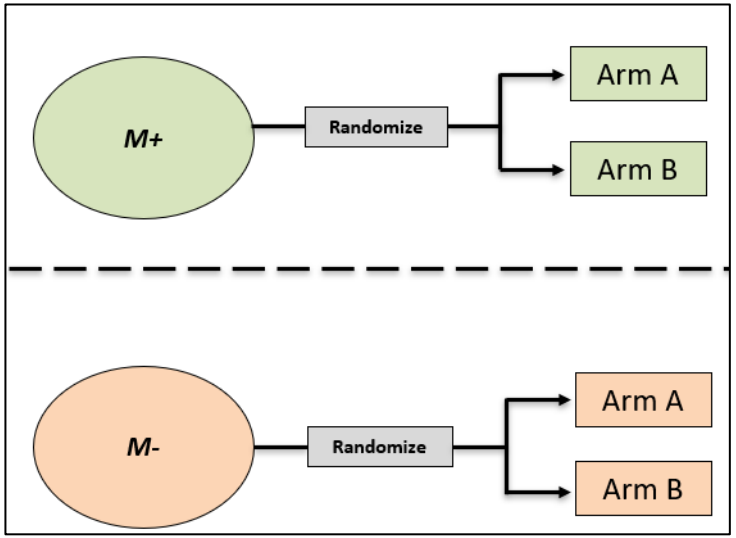
- Interpretation of subgroup analyses is limited without a prespecified formal statistical testing plan and α-control to reduce **the risk of making a false positive conclusion** (i.e. type-1 error).

Could the apparent effect in the exploratory analysis of non-HRR population in TALAPRO-2 be due to chance?

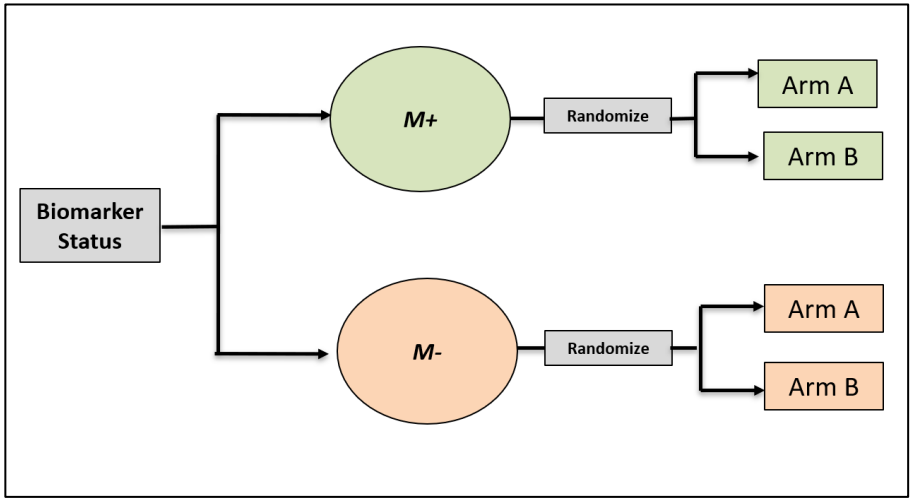
- **All exploratory subgroup analyses should be interpreted with caution**. This is especially true here given the large proportion of non-HRRm mCRPC patients who might be exposed to toxicity from talazoparib without a statistically convincing result, and who are expected to have less efficacy than HRRm mCRPC patients.

Prospective Trial Design Options to Assess Biomarker Populations

Two Separate Trials



One Trial, Separate Cohorts



- Adequately determine biomarker status prior to randomization.
- Assess biomarker subgroups separately with adequate power and sample size.
- Full alpha (eg, 2-sided 0.05) can be used for testing M+ and M- in either trial design.

Main Review Issues

1. Large (~70%), incompletely-defined non-HRRm subgroup was not formally tested for efficacy.

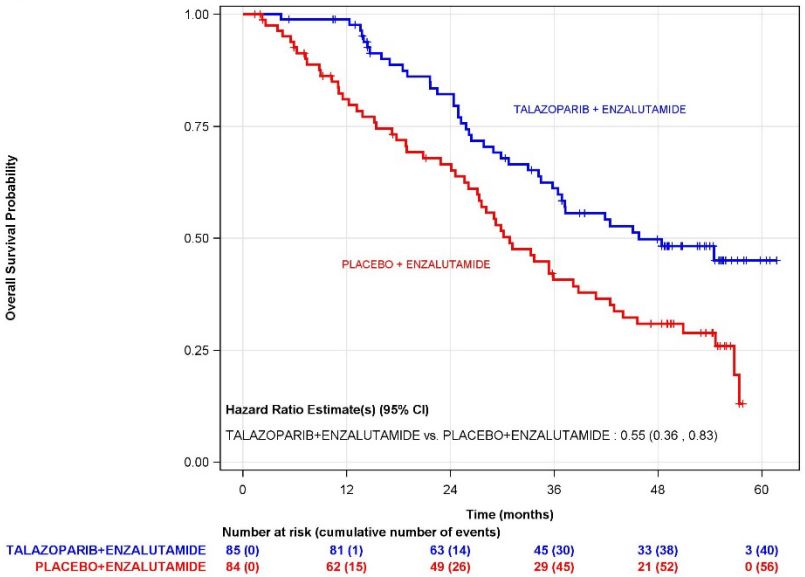
2. **Interpretation of the OS results and applicability to current US standard of care are unclear.**

3. Addition of talazoparib increases hematologic toxicity versus enzalutamide alone.

4. Trials of other PARP inhibitors did not support an all-comers indication.

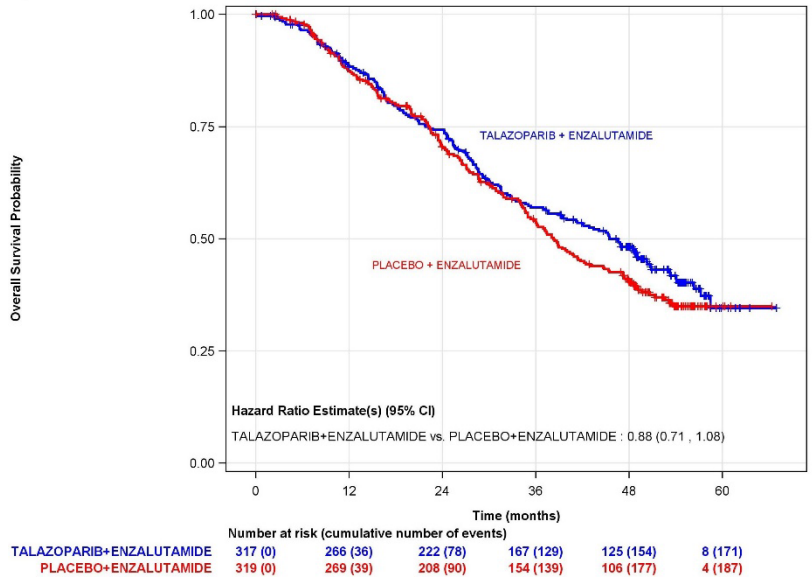
OS Benefit is Primarily Attributed to HRRm Stratum and is Not Clearly Established in the HRRm/unknown Stratum

HRRm
N = 169 (21%) (85 vs. 84)



HR = 0.55
(95% CI: 0.36, 0.83)

Non-HRRm/Unknown stratum
(Exploratory analysis)
N = 636 (79%) (317 vs. 319)



HR = 0.88
(95% CI: 0.71, 1.08)

Only a Small Proportion of Patients in the Cohort 1 Control Arm Received a Subsequent PARP Inhibitor

Placebo + Enzalutamide arm of Cohort 1 (HRRm-Unselected)			
Patient population	Total N=403	HRRm* N=157	*BRCA*m* N=51
Subsequent PARPi	**16 (4%)**	**11 (7%)**	**8 (16%)**

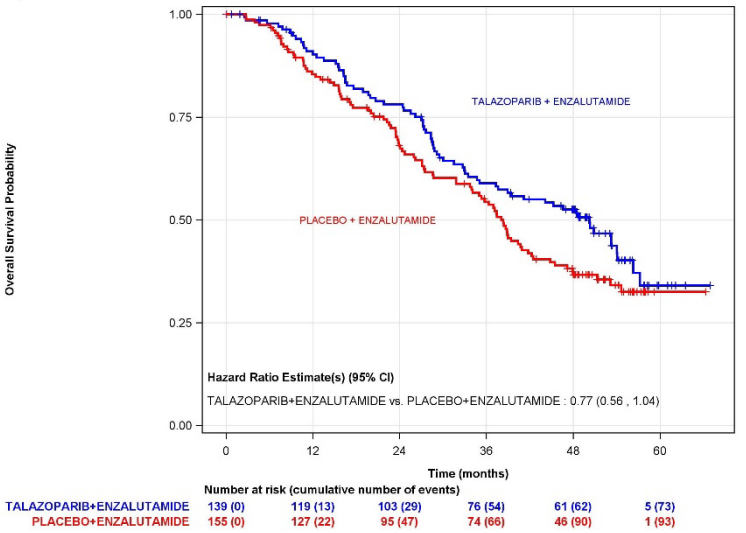
* FDA definition using all tested samples; includes patients with HRR co-mutations

- Olaparib monotherapy was approved **May 19, 2020** for treatment of patients with **HRRm mCRPC post-ARPI** based on PROfound trial:
  - Cohort A (***BRCA*m** + *ATM*m*): significant improvements in rPFS, **OS**, and ORR
  - Cohort A + B (all-HRRm): Significant improvement in rPFS

**ATM*, Ataxia-telangiectasia gene mutated

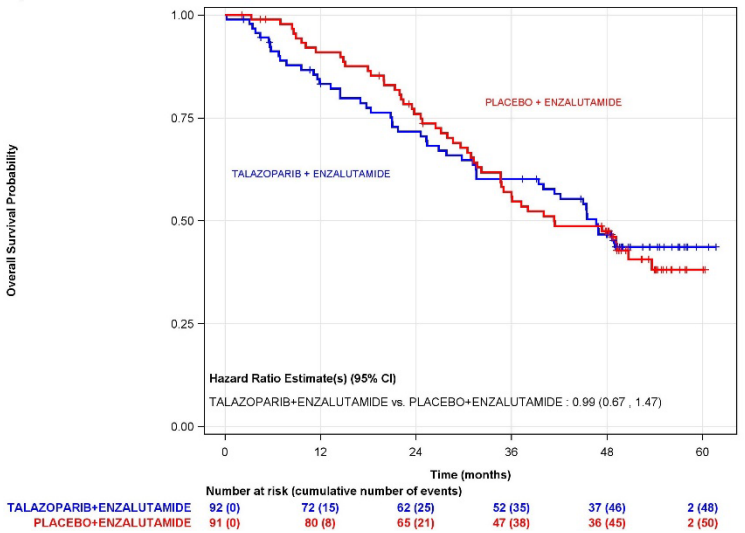
Counterintuitive OS Results in Exploratory Non-HRRm Subgroups in TALAPRO-2: Which is More Accurate?

non-HRRm "Double-negative"*
N = 294 (37%) (139 vs. 155)



HR = 0.77 (0.56, 1.04)

"Single-negative"/ Unknown*
N = 183 (23%) (92 vs. 91)



HR = 0.99 (0.67, 1.47)

* FDA definition using all available testing results

Main Review Issues

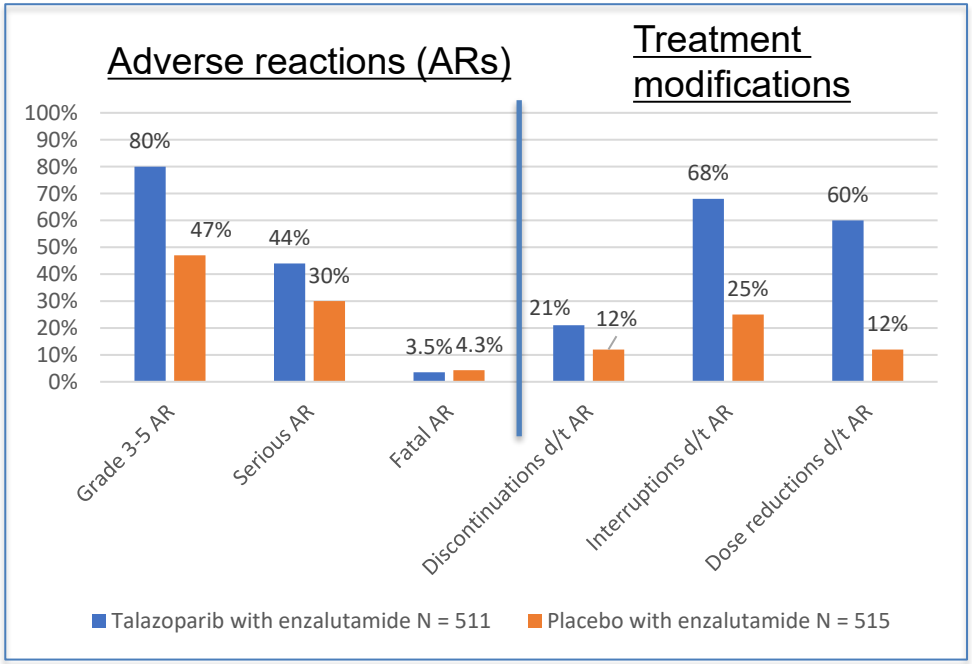
1. Large (~70%), incompletely-defined non-HRRm subgroup was not formally tested for efficacy.

2. Interpretation of the OS results and applicability to current US standard of care are unclear.

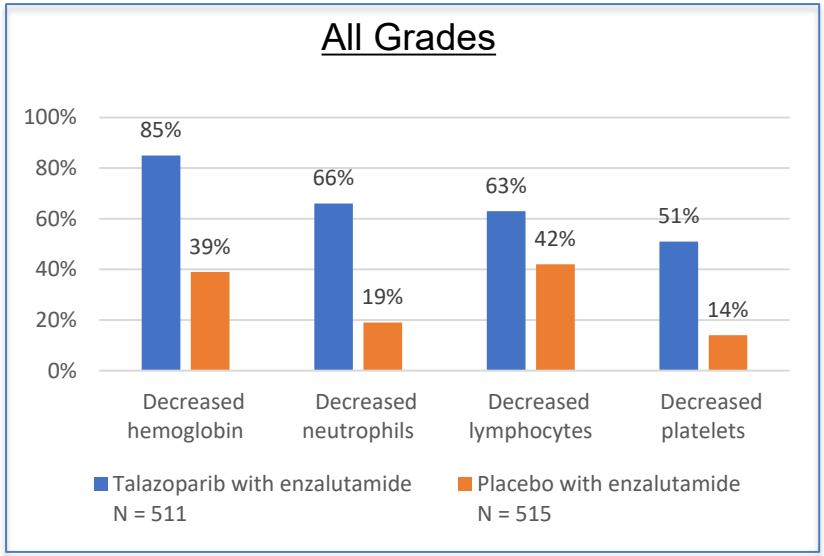
3. **Addition of talazoparib increases hematologic toxicity versus enzalutamide alone.**

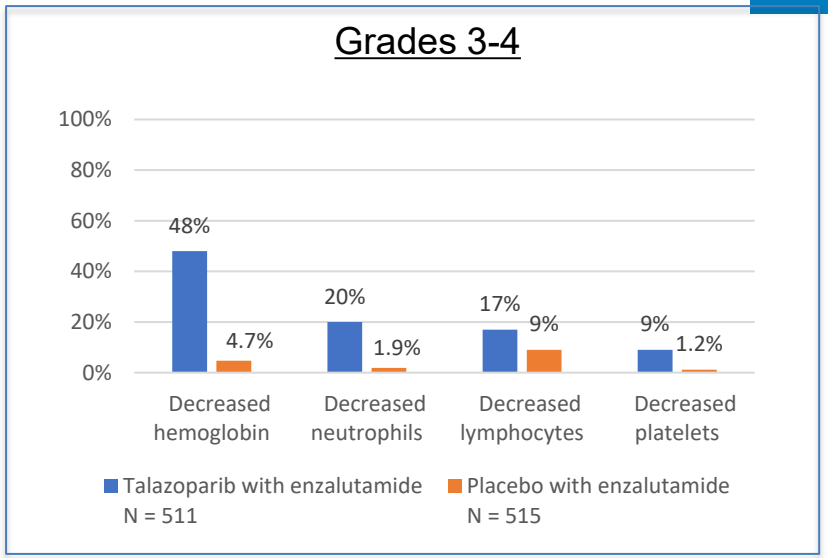
4. Trials of other PARP inhibitors did not support an all-comers indication.

Talazoparib with Enzalutamide is Substantially More Toxic Than Placebo with Enzalutamide



Myelosuppression (Particularly Anemia) is Common With Talazoparib





- **42%** of patients required red blood cell transfusion, including **25%** who required more than one transfusion.

- Myelodysplastic syndrome/acute myeloid leukemia are class effects of PARP inhibitors and were reported in in 2/511 patients (0.4%) treated with talazoparib in TALAPRO-2.

Is **Any** Additional Toxicity Acceptable in Non-HRRm mCRPC if Benefit is Uncertain?

- Talazoparib is given as an **add-on** to effective therapy in enzalutamide
- Not possible to establish added effectiveness of talazoparib on an individual patient level; **toxic placebo?**
- Certainty about trial-level results is particularly important to determine whether added toxicity is acceptable.

Main Review Issues

1. Large (~70%), incompletely-defined non-HRRm subgroup was not formally tested for efficacy.

2. Interpretation of the OS results and applicability to current US standard of care are unclear.

3. Addition of talazoparib increases hematologic toxicity versus enzalutamide alone.

4. **Trials of other PARP inhibitors did not support an all-comers indication.**

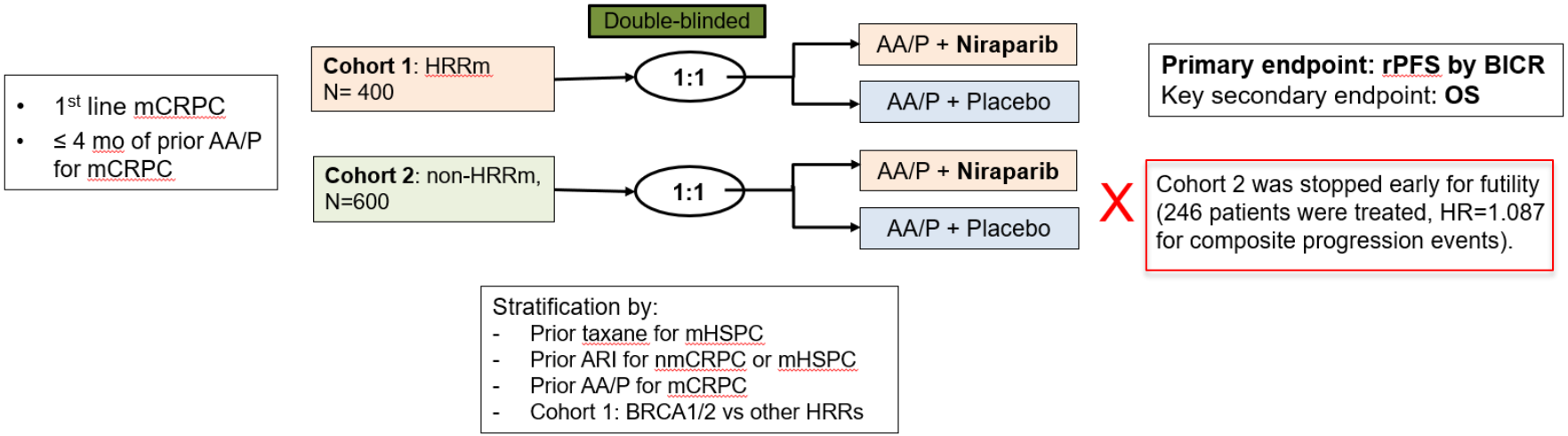
Other Trials of PARPi + ARPI Suggested Limited or No Efficacy of PARPi in Non-HRRm mCRPC

Drug	Disease setting	Trial	Key results	Approved indication
Olaparib	mCRPC post-chemo	TOPARP-A Single-arm Phase 2 study[1]	Composite response rate* 14/16 (88%) in HRRm vs 2/33 (6%)	N/A
	1L mCRPC in combination with abiraterone acetate	PROpel Randomized Phase 3 trial of olaparib+AAP vs placebo+AAP (all-comers)[2]	rPFS benefit primarily driven by *BRCA*m subgroup	*BRCA*m mCRPC
Niraparib	1L mCRPC in combination with abiraterone acetate	MAGNITUDE Randomized Phase 3 trial (see next slide)[3]	Lack of added efficacy in non-HRRm (see next slide)	*BRCA*m mCRPC

*Defined as any of radiographic response, PSA response, or reduction in circulating tumor-cell count
AAP, abiraterone acetate and prednisone or prednisolone

1. Mateo, J., et al. N Engl J Med, 2015. 373(18): p. 1697-708.
2. Fallah, J., et al. J Clin Oncol, 2024. 42(5): p. 605-613.
3. Chi, K.N., et al. J Clin Oncol, 2023. 41(18): p. 3339-3351.

MAGNITUDE Was Formally Designed to Test the Non-HRRm Population, Showing Lack of Added Efficacy



- **Caveat**: cross-trial comparisons, including that other trials of PARPi + ARPI used different PARPi and ARPI from TALAPRO-2

Some Trials Enrolled Only Patients With Tumor HRRm, Including the Applicant's Own Ongoing Trial TALAPRO-3

Drug	Disease setting	Trial	Biomarker eligibility
Olaparib	2nd line mCRPC (post-ARPI)	PROfound (Randomized Phase 3)	**HRRm**
Rucaparib	3rd line mCRPC (post-ARPI and taxane)	TRITON2 (Single-arm Phase 2)	**HRRm**
	2nd line mCRPC (pose-ARPI)	TRITON3 Randomized Phase 3	***BRCA*m and *ATM*m**
Talazoparib with enzalutamide	mHSPC	**TALAPRO-3 (Randomized Phase 3)**	**HRRm**

Broad understanding in field that PARPi are more effective in patients with tumor HRRm (and particularly tumor *BRCA*m)

Data From TALAPRO-2 Itself Support Differential Sensitivity to PARPi Based On Biomarker status

Endpoint	Cohort 1 All-comers N = 805	Cohort 1 Non-HRR/Unknown Stratum* N = 636	Cohort 1 HRRm stratum* N = 169	***BRCA*m** (within HRRm stratum)* N = 59
rPFS HR (95% CI) (Primary analysis)	**0.63** (0.51, 0.78)	**0.70** (0.54, 0.89)	**0.46** (0.30, 0.70)	**0.22** (0.10, 0.50)
OS HR (95% CI) (Final analysis)	**0.80** (0.66, 0.96)	**0.88** (0.71, 1.08)	**0.55** (0.36, 0.83)	**0.52** (0.27, 1.02)

*Exploratory analysis

Summary: Uncertainty for Talazoparib With Enzalutamide in Non-HRRm mCRPC

TALAPRO-2 evaluated a heterogeneous all-comers population with a suboptimal design for biomarker-negative patients.
Large (~70%), incompletely-defined non-HRRm subgroup was not formally tested for efficacy.
Interpretation of the OS results and applicability to current US standard of care are unclear.
Addition of talazoparib increases hematologic toxicity versus enzalutamide alone.
Supporting data are conflicting and of unclear strength.
Unclear whether mechanistic rationale is sufficient to overcome clinical trial design issues and differences in efficacy by biomarker status across all trials of PARPi in mCRPC.

Topic for Discussion

Discuss whether efficacy should be formally evaluated in a biomarker-negative population when the biomarker is predictive of response and the prevalence of the biomarker-negative group is high.

Voting Question

Are the TALAPRO-2 results sufficient to conclude a favorable benefit-risk profile for adding talazoparib to enzalutamide in patients with non-HRRm mCRPC?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