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FDA Briefing Document

NDA# 211651/Supplement 13
Drug name: talazoparib (Talzenna)
Applicant: Pfizer

Oncologic Drugs Advisory Committee Meeting
May 21, 2025
Division of Oncology 1
Office of Oncologic Diseases

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the Advisory Committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought a supplemental New Drug Application for talazoparib with enzalutamide for the treatment of patients with metastatic castration-resistant prostate cancer (mCRPC) to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the Advisory Committee. The FDA will not issue a final determination on the issues at hand until input from the Advisory Committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the Advisory Committee meeting.

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Glossary

Include any acronyms or abbreviations used four or more times in the AC BD. Each instance of terms appearing three or fewer times should be spelled out rather than abbreviated.

Acronyms and abbreviations should be spelled out at first use in the Executive Summary, main body (if not spelled out in the Executive Summary), and Appendix (if not spelled out in the Executive Summary or main body). The sample list below includes commonly used acronyms and may be used as a starting point.

AA	abiraterone acetate
AA/P	abiraterone acetate and prednisone or prednisolone
AC	Advisory Committee
AR	adverse reaction
ARPI	androgen receptor pathway inhibitor
BD	Briefing Document
BICR	blinded independent central review
BRCA	breast cancer gene
BRF	Benefit-Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDTL	Cross-Discipline Team Leader
CI	confidence interval
ctDNA	circulating tumor DNA
FDA	Food and Drug Administration
HR	hazard ratio
HRRm	Homologous recombination repair gene mutated
IA	integrated assessment
ITT	intention-to-treat
mCRPC	metastatic castration-resistant prostate cancer
NR	not reached
NE	not estimable
ORR	objective response rate
OS	overall survival
PARP	poly(ADP-ribose) polymerase
PARPi	poly(ADP-ribose) polymerase inhibitor
PCWG3	Prostate Cancer Working Group 3
PSA	Prostate-specific antigen
REMS	risk evaluation and mitigation strategy
rPFS	radiographic progression-free survival
RPM	Regulatory Project Manager

SAR	serious adverse reaction
SAP	Statistical Analysis Plan
SD	standard deviation
sNDA	supplemental New Drug Appliation

1 Executive Summary/Draft Points for Consideration by the Advisory Committee

1.1 Purpose/Objective of the AC Meeting

The FDA is convening this Oncologic Drugs Advisory Committee (ODAC) meeting to publicly discuss the potential expansion of the indication for the PARP inhibitor (PARPi) talazoparib in combination with enzalutamide to include patients with metastatic castration resistant prostate cancer (mCRPC) who do not have demonstrated tumor homologous recombination repair gene mutations (HRRm). The major justification provided for expansion of the indication is the final overall survival (OS) from the TALAPRO-2 trial, which showed a statistically significant benefit for the addition of talazoparib to enzalutamide in an all-comers mCRPC population.

The key review issue is that, although HRRm status is a predictive biomarker for PARPis, TALAPRO-2 did not formally assess the efficacy outcomes in the high-prevalence population of patients without tumor HRRm; this population represents the majority of patients with mCRPC. In the absence of statistically significant findings in the non-HRRm subgroup, the observed improvements in rPFS and OS in this subgroup may be a random finding due to chance, particularly as previous trials of PARPis in this setting have not supported a benefit in patients without tumor HRRm. An all-comers indication for talazoparib with enzalutamide would represent the first approval of a PARPi for patients with prostate cancer without tumor HRRm.

While the statistically significant OS improvement in the all-comers population provided the impetus for this application, interpretation of the OS result and its applicability to current US standard of care are unclear, given that few patients with *BRCA*m on the control arm received subsequent PARPi despite an OS benefit for treatment of patients with *BRCA*m with olaparib in that setting. Thus, consideration of the all-comers OS result may be misleading when interpreting efficacy in the non-HRRm population.

Furthermore, the observed rPFS and OS improvement of talazoparib appears to be attenuated in the patient subgroup without demonstrated tumor HRRm versus those with tumor HRRm, and adding talazoparib to enzalutamide results in greater toxicity, particularly anemia and other cytopenias. Due to the high efficacy of enzalutamide in this setting, patients may be exposed to the added toxicities of talazoparib for a median time of approximately 20 months with unclear benefit from adding talazopatib to enzalutamide.

Considering the high prevalence of patients without tumor HRRm, the long duration of exposure to the toxicities of talazoparib in this disease setting, and lack of formal statistical testing of the population without HRRm in TALAPRO-2 raising concern the findings may due to chance, the FDA has called this meeting to discuss whether the results from TALAPRO-2 are sufficient to conclude a favorable benefit-risk profile for adding talazoparib to enzalutamide in patients with mCRPC who do not have demonstrated tumor HRRm.

Pfizer is the pharmaceutical company applying for this supplemental new drug application (sNDA) for talazoparib and will be referred to throughout this document as “the Applicant”.

1.2 Context for Issues to Be Discussed at the AC

Talazoparib, sold under the brand name Talzenna, is one of three PARP inhibitors (PARPi) approved in combination with an androgen receptor pathway inhibitor (ARPI) for first-line treatment of biomarker-selected patients with mCRPC. Talazoparib is approved in combination with enzalutamide for the treatment of adult patients with HRRm mCRPC. Olaparib is approved in combination with abiraterone acetate (AA) for the treatment of adult patients with mCRPC and *BRCA* mutation (*BRCA*m). The fixed-dose combination of niraparib (another PARPi) and AA is approved for the treatment of adult patients with *BRCA*m.

Two PARPis are currently FDA-approved as single agents for the treatment of later-line mCRPC. Olaparib is approved as a single agent for the treatment of patients with HRRm mCRPC who have experienced disease progression on prior ARPI therapy. Rucaparib is approved for the treatment of patients with *BRCA*m mCRPC following both an ARPI and taxane-based chemotherapy. Each of these approvals was restricted to molecularly-defined subsets of patients based on the populations enrolled to each trial.

The proposed expanded indication for talazoparib being discussed at this meeting would be the first indication of a PARPi to include biomarker-unselected patients with mCRPC (including patients without a sensitizing gene mutation). The indications for the currently approved PARPis were generally narrowed to biomarker-selected populations based on the results of the pivotal trials that supported the approvals. The trials of PARPi with ARPI in first-line treatment of mCRPC suggested differential efficacy based on biomarker status, as well as uncertain or potentially unfavorable risk/benefit evaluation in biomarker-negative patients.

In ovarian cancer, several PARPi were initially approved for all-comer populations. However, further follow-up of the pivotal clinical trials demonstrated potential for detriment in overall survival (OS) in patients with ovarian cancer without tumor *BRCA* mutations. Therefore, FDA subsequently restricted indications for three PARP inhibitors in ovarian cancer to patients with tumor *BRCA* mutations between November 2022 and September 2023 [1].

Based on the available data, and depending on the definition of HRRm, it is estimated that 20-30% of patients with advanced prostate cancer have tumor HRRm, meaning that the majority (70-80%) of patients do not have tumor HRRm [2, 3]. Preclinical studies of PARPis have suggested that treatment of mCRPC tumors without HRRm can produce an HRRm phenotype in these tumors, sensitizing them to PARPi [4, 5]. However, the referenced studies did not specifically study talazoparib with enzalutamide and the strength of the biologic rationale for the activity of talazoparib with enzalutamide in patients non-HRRm tumors is unclear. The Applicant conducted a clinical mechanistic study using data from TALAPRO-2 which suggested potential crosstalk between the androgen receptor pathway and DNA damage repair pathways [6], however, the FDA review team notes that this is a retrospective and unvalidated analysis.

1.3 Brief Description of Issues for Discussion at the AC

TALAPRO-2, the randomized trial on which this sNDA is based, compared the combination of talazoparib with enzalutamide to placebo with enzalutamide in patients with mCRPC, with or without tumor HRRm. Cohort 1 (HRRm-Unselected) enrolled all-comers, regardless of HRR test result. Cohort 2 (HRRm-

Selected) only enrolled patients who had a positive HRR test result. Randomization in both cohorts was stratified by previous treatment with any ARPI or taxane-based chemotherapy (yes vs. no). Additionally, in Cohort 1, randomization was stratified by tumor HRRm status (HRRm vs. non-HRRm/unknown). The primary endpoint for TALAPRO-2 was radiographic progression-free survival (rPFS), assessed by blinded independent central review (BICR) in the HRRm-Unselected and HRRm-Selected populations. OS was a key secondary endpoint, to be statistically assessed in the HRRm-Unselected and HRRm-Selected populations.

TALAPRO-2 met its primary endpoint of rPFS at the primary rPFS analysis in HRRm-Unselected and HRRm-Selected populations. Despite a statistically significant rPFS improvement in the HRRm-Unselected cohort, it appeared that the results were primarily attributed to the treatment effect in patients with tumor HRRm. Thus, for patients without HRRm, the FDA did not consider the magnitude of rPFS improvement clinically meaningful in the context of the high prevalence of this population, add-on to an effective therapy, toxicity including severe anemia and need for blood transfusion in approximately 40% of patients, as well as the limited follow-up of OS. The approval of talazoparib with enzalutamide in June 2023 was therefore limited to patients with tumor HRRm, for whom there was a statistically significant and clinically meaningful improvement in rPFS [7].

At the time of the initial approval of talazoparib with enzalutamide for HRRm mCRPC, the OS results were immature. At the final OS analysis, TALAPRO-2 met the OS endpoint in the HRRm-Unselected (all-comers) population; subsequently, in December 2024, the Applicant submitted an application requesting the expansion of the indication for mCRPC from HRRm to all-comers.

However, the FDA review team have noted several issues arising from the suboptimal design of TALAPRO-2 for evaluation of the efficacy of talazoparib in patients without tumor HRRm:

1. Although the majority of patients with mCRPC do not have tumor HRRm, TALAPRO-2 did not define a pre-specified formal analysis plan for evaluation of efficacy results for patients with negative HRR test results. In the absence of a statistically significant difference, there may be false positive conclusions in the HRR-negative population. Of note, the Applicant was aware of the importance of HRRm as a predictive biomarker and designed the study in a way to enrich for and statistically test the efficacy results in the HRRm-Selected population.

   At the time of randomization, 26% (n=211) of patients in TALAPRO-2 had unknown HRR status, largely due to unknown tumor tissue results (e.g. due to failed assay quality control or limitations in sample quality) with no prospective ctDNA testing. Of these patients with unknown HRRm status, 29% (68 of 211) were later found to have positive results for HRRm on post-randomization testing. When a biomarker is strongly associated with treatment effect from a drug, the biomarker status should be prospectively determined prior to randomization in order to properly evaluate the efficacy results in biomarker-positive and -negative populations, with adequate power, sample size, and alpha control for each population. Thus, even though TALAPRO-2 stratified patients by prospectively-determined HRRm status, the large proportion of patients with unknown

status and the lack of alpha-controlled testing of a truly biomarker-negative population challenges interpretation of the results for this population.

2. The interpretation of OS results in TALAPRO-2 and their applicability to the current US standard of care remain unclear. While an OS improvement was demonstrated for the Cohort 1 all-comers population, this was attributable primarily to the HRRm stratum and any effect appeared substantially attenuated in the non-HRR/unknown stratum.

   Additionally, the applicability of TALAPRO-2 OS results to current US standard of care is unclear, given that only a small proportion of patients with tumor HRRm (7%) or tumor *BRCA*m (9%) received subsequent PARPi on the control arm of TALAPRO-2. This may have increased the observed OS difference in TALAPRO-2 versus what would be observed if appropriate subsequent therapy had been given. The heterogeneous all-comers population, which contains subpopulations with different expected sensitivities to PARPi, contributes to uncertainty in interpretation of the OS results in the non-HRRm subgroup.

3. Data both from TALAPRO-2 and from trials of other PARPis in prostate cancer provide a preponderance of evidence that there is reduced efficacy of PARPi in patients with biomarker-negative tumors. In the case of currently approved PARPis, this led to the restriction of the approved indications to patients with tumor HRRm or tumor *BRCA*m. While cross-trial comparisons should be interpreted with caution, the inconsistency between the results from the exploratory analysis of TALAPRO-2 in patients without HRRm and other trials of PARPi has raised the concern that the more favorable results of the exploratory analysis of TALAPRO-2 in patients without HRRm may be a random finding.

4. While the overall safety profiles of talazoparib and enzalutamide in TALAPRO-2 were consistent with known toxicities of the individual therapies, the combination was considerably more toxic than placebo with enzalutamide, with higher incidences of high-grade and serious adverse reactions, as well as adverse reactions resulting in dosage modifications. The additional toxicity primarily reflected a higher incidence of cytopenias, including a higher incidence of anemia and transfusion requirement, in patients receiving talazoparib versus patients receiving placebo. Although the incidence of anemia and need for blood transfusions decreased over time, presumably due to dose modifications, these adverse reactions can have adverse impacts on patients, particularly in this early setting in mCRPC where patients are generally minimally symptomatic, and will be exposed to the toxicities of the drug for approximately 20 months before disease progression and need for change of therapy. Furthermore, the additional toxicity of adding talazoparib to enzalutamide may be less acceptable in patients with non-HRRm tumors, given that the benefit in these patients is less certain than in biomarker-positive patients.

<u>Summary and conclusions</u>

Because of the issues with the design of TALAPRO-2, particularly the lack of a pre-specified plan for statistical testing of efficacy in patients with negative HRR status, as well as the results of other studies of PARPi in mCRPC that showed reduced or no benefit of PARPi in patients without tumor HRRm, there is uncertainty regarding the benefit/risk evaluation of talazoparib with enzalutamide in patients with mCRPC who do not have demonstrated tumor HRRm. These concerns and uncertainties could have been addressed by a dedicated trial that was adequately designed to assess patients with non-HRRm mCRPC.

1.4 Draft Points for Consideration

- Discuss whether FDA should require that new trial design proposals include adequate statistical power to assess the efficacy of a drug in the biomarker-negative group when the biomarker is predictive of response and the biomarker-negative group represents the largest population in the trial.
- Are the results from TALAPRO-2 sufficient to conclude a favorable benefit-risk profile for adding talazoparib to enzalutamide in patients with mCRPC who do not have demonstrated tumor homologous recombination repair (HRR) gene mutations?

2 Introduction and Background

2.1 Background of the Condition/Standard of Clinical Care

Prostate cancer is the most commonly diagnosed cancer in men in the United States, with an estimated ~313,780 new cases in 2025 [8]. After initially responding to androgen deprivation therapy, most patients with advanced stages of prostate cancer develop mCRPC. Table A1 in the Appendix lists therapies that are FDA-approved for use in mCRPC. None of these therapies is curative, and mCRPC is an area of unmet medical need for development of new therapies and/or therapeutic combinations to improve clinical outcomes.

2.2 Pertinent Drug Development and Regulatory History

Talazoparib is a PARPi currently FDA-approved in combination with enzalutamide for the treatment of adult patients with HRRm mCRPC, and as a single agent for the treatment of adult patients with deleterious or suspected deleterious germline *BRCA*-mutated (g*BRCA*m) HER2-negative locally advanced or metastatic breast cancer.

Enzalutamide is an ARPI currently approved for the treatment of patients with:

- castration-resistant prostate cancer
- metastatic castration-sensitive prostate cancer
- non-metastatic castration-sensitive prostate cancer with biochemical recurrence at high risk for metastasis

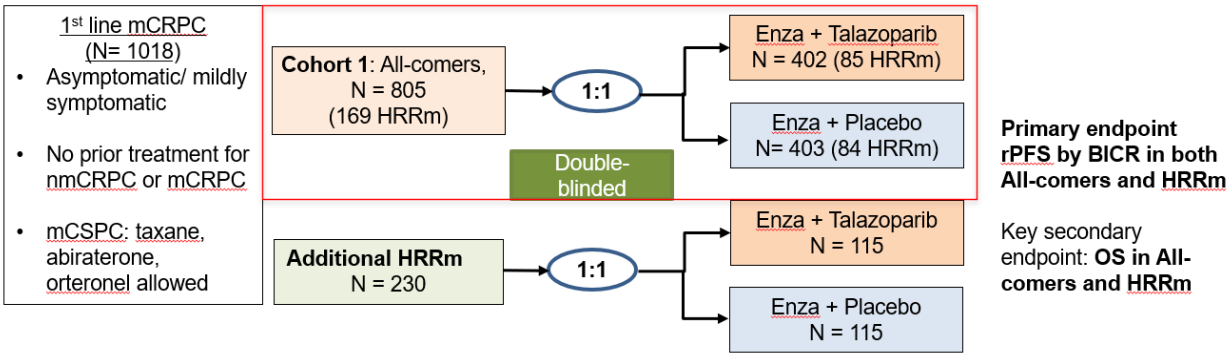
Clinical trial of talazoparib with enzalutamide in prostate cancer

The primary source of clinical data for the Applicant's sNDA for an expanded indication is Cohort 1 (all-comers population) of the TALAPRO-2 trial.

TALAPRO-2

TALAPRO-2 was a Phase 3 randomized (1:1), double-blind, placebo-controlled, multi-cohort study comparing the combination of talazoparib with enzalutamide to placebo with enzalutamide in patients with mCRPC (with or without tumor HRRm). Cohort 1 (HRRm-Unselected) enrolled all-comers , regardless of HRR test results. Cohort 2 (HRRm-Selected) only enrolled patients who had a positive HRR test result. Randomization in both cohorts was stratified by previous treatment with any ARPI or taxane-based chemotherapy (yes vs. no). Additionally, in the HRRm-Unselected cohort, randomization was stratified by tumor HRRm status (HRRm vs. non-HRRm/unknown). The primary endpoint for TALAPRO-2 was radiographic progression-free survival (rPFS) assessed by blinded independent central review (BICR) in the HRRm-Unselected and HRRm-Selected populations. OS was a key secondary endpoint, to be statistically assessed in the HRRm-Unselected and HRRm-Selected populations. The overall study design is shown in Figure 1.

Figure 1: TALAPRO-2 Study Design



Abbreviations: enza, enzalutamide; HRRm, homologous recombination repair mutation; mCRPC, metastatic castration-resistant prostate cancer; mHSPC, metastatic hormone-sensitive prostate cancer; nmCRPC, non-metastatic castration-resistant prostate cancer; OS, overall survival; rPFS, radiographic progression-free survival.

Mutation status was determined using a next generation sequencing (NGS)-based tumor tissue test or a ctDNA-based test. Tumor HRRm status, used as a stratification factor, was prospectively determined for some patients using samples (primarily tissue) that were available at the time of randomization; however, 26% of patients had unknown biomarker status at the time of randomization. Additional biomarker testing results (primarily from ctDNA samples) became available after randomization and were incorporated into the additional exploratory analyses conducted by the Applicant and the FDA. The details of biomarker status based on changing availability of test results are presented below in the context of Key efficacy issue 1.

TALAPRO-2 had five data cutoffs (DCO):

- DCO1 for an interim futility analysis of rPFS in the HRRm-Unselected Cohort (all-comers population);
- DCO2 for the final analysis of rPFS, and the first interim analysis of OS in the HRRm-Unselected Cohort, and an interim futility analysis of rPFS in the HRRm-Selected Cohort;
- DCO3 for the second interim analysis of rPFS and the first interim analysis of OS in the Cohort 2 HRRm population (no analysis for all-comers population);

- DCO4 for the second interim analysis of OS in the HRRm-Unselected Cohort (no analysis in the Cohort 2 HRRm population);
- DCO5 for the final OS analysis in the Cohort 1 all-comers population and the final rPFS and OS in the Cohort 2 HRRm population.

To control the overall type I error, the O'Brien and Fleming spending function was used.

On June 20, 2023, the FDA approved talazoparib with enzalutamide for treatment of adult patients with HRRm mCRPC based on the primary rPFS analysis at DCO3. Biomarker status appeared to predict both rPFS and OS results, with the largest rPFS and OS improvement seen in patients with tumor *BRCA*m, followed by tumor HRRm, followed by the subgroup of patients with non-HRR/unknown tumors. The OS endpoint was immature at the time of the primary rPFS analysis. Ultimately the review team concluded that the benefit-risk evaluation for subgroup of patients with non-HRRm/unknown tumors was not sufficiently favorable in the context of broad indication, increased toxicity of combination vs enzalutamide monotherapy, and immature OS [7]. Approval was therefore limited to patients with HRRm mCRPC.

Key efficacy results from HRRm-Unselected Cohort of TALAPRO-2 are shown in Table 1 below. TALAPRO-2 met its primary endpoint of rPFS per BICR with a HR of 0.63 (95% CI: 0.51, 0.78, 2-sided p-value < 0.0001) at the primary rPFS analysis (DCO2). The trial also met the key secondary endpoint of OS with a HR of 0.80 (95% CI: 0.66, 0.96, 2-sided p-value = 0.0155) at the final OS analysis (DCO5) in favor of talazoparib plus enzalutamide compared to placebo plus enzalutamide in the HRRm-Unselected Cohort (all-comers population). In December 2024, the Applicant submitted a new supplemental NDA which included the final OS results from TALAPRO-2 and requested the expansion of the indication for mCRPC from HRRm to all-comers.

Table 1: TALAPRO-2 Analysis of Primary and Key Secondary Endpoints in Cohort 1 (HRRm-Unselected)

	Number of events (%)		**Median, months (95% CI)**		**Hazard Ratio (95% CI)** [†]	**p-value**[‡]
	Talazoparib + Enzalutamide N=402	**Placebo + Enzalutamide** N=403	**Talazoparib + Enzalutamide** N=402	**Placebo + Enzalutamide** N=403		
rPFS per BICR	151 (37.6%)	191 (47.4%)	NR (27.5, NE)	21.9 (16.6, 25.1)	0.63 (0.51, 0.78)	<0.0001
OS	211 (52.5%)	243 (60.3%)	45.8 (39.4, 50.8)	37.0 (34.1, 40.4)	0.80 (0.66, 0.96)	0.0155

[†] HR and CI based on stratified Cox PH model

[‡] two-sided p-value based on stratified log-rank test

NR: not reached; NE: not evaluable

DCO: 08/16/2022 for rPFS per BICR at the final rPFS analysis (DCO2) and 09/03/2024 for OS at the final OS analysis (DCO5)

3 Summary of Issues for the AC

3.1 Efficacy Issues

The Applicant is proposing to expand the indication for talazoparib with enzalutamide, which is currently indicated as first-line therapy for patients with HRRm mCRPC, to include patients regardless of their tumor HRRm status. The FDA is therefore asking the advisory committee to discuss whether the indication should be extended to include those without a tumor HRR gene alteration based on the TALAPRO-2 trial results or whether an additional trial is needed to adequately define the benefit-risk profile in this population.

- Key efficacy issue 1: Large, incompletely-defined non-HRRm subgroup was not formally tested for efficacy.
- Key efficacy issue 2: Interpretation of the OS result and applicability to current US standard of care are unclear
- Key efficacy issue 3: Trials of other PARPis did not support an all-comers indication.

3.1.1 Sources of Data for Efficacy

The primary source of clinical data for the Applicant's sNDA for an expanded indication is HRRm-Unselected Cohort (all-comers population) of the TALAPRO-2 trial. The formal prespecified efficacy analyses include patients who were randomized to one of the two treatment arms, regardless of whether or not they received study treatment.

3.1.2 Efficacy Summary

The statutory standard for drug approval is substantial evidence of effectiveness [9]. This requirement may be satisfied in one of three ways:

- two adequate and well-controlled clinical investigations;
- a single large multicenter trial with "clinically meaningful and statistically very persuasive effect" such that confirmation in a second trial would be impracticable or unethical;
- one adequate and well-controlled trial plus confirmatory evidence.

Regarding the first option, the Applicant has not presented results from two adequate and well-controlled clinical investigations for any mCRPC population, including patients with non-HRRm tumors. The ongoing TALAPRO-3 trial in metastatic hormone sensitive prostate cancer (mHSPC), which is also evaluating the combination of talazoparib with enzalutamide, is limited to patients with HRRm mCRPC and therefore could not serve as a second adequate and well-controlled trial for patients with non-HRRm prostate cancer.

Regarding the second and third options, the advisory committee should discuss whether TALAPRO-2 constitutes an adequate and well-controlled clinical investigation for patients with non-HRRm mCRPC. The FDA review team has concerns about the study design and results of TALAPRO-2, as detailed in the following efficacy issues. In short, TALAPRO-2 studied a large, incompletely-defined non-HRRm subgroup that was not formally tested for efficacy (Key efficacy issue 1). This raises the possibility that the apparently favorable efficacy results in the non-HRR/unknown stratum or the exploratory HRR "double-

negative" subgroup (defined below) might be due to chance. Furthermore, the interpretation of the OS results in TALAPRO-2 and applicability to current US standard of care are unclear (Key efficacy issue 2).

Even if TALAPRO-2 is considered to be an adequate and well-controlled trial for patients with non-HRRm tumors, it is unclear whether it has a "clinically meaningful and statistically very persuasive effect" such that confirmation in a second trial in patients with non-HRRm tumors would be impracticable or unethical. Furthermore, regarding the confirmatory evidence criteria for the third option, the available confirmatory evidence is conflicting. Examples of potential confirmatory evidence are strong mechanistic support and scientific knowledge about the effectiveness of other drugs in the same pharmacologic class [9]. Preclinical and clinical mechanistic studies appear to support the effectiveness of the combination of PARPi and ARPI in non-HRRm mCRPC, although the strength of this support is debatable. However, clinical trials of other drugs in the same pharmacologic class, and data from TALAPRO-2 itself, suggest reduced or no efficacy of PARPi in patients with non-HRRm mCRPC (Key efficacy issue 3).

3.1.3 Efficacy Issues in Detail

Key efficacy issue 1: A large, incompletely-defined non-HRRm subgroup was not formally tested for efficacy.

Conducting an all-comers analysis provides the average treatment effect across all randomized patients. However, the treatment effect can vary when assessing subgroups. Subgroup results may vary due to chance, smaller sample sizes, expected differential efficacy, and other potential confounding factors. Since the all-comers population includes subgroups identifiable by demographics, clinical histories, and disease characteristics, the overall treatment effect observed in the all-comers population may mask lack of benefit or potential harm in certain subgroups, or positive results may be primarily attributable to one or more specific subgroups.

Tumor HRRm status is expected to be a predictor of response to PARPi treatment in mCRPC, including in patients treated with the combination of a PARPi and ARPI. Thus, patients who have non-HRRm status may have a lower magnitude of treatment effect relative to the HRRm subgroup. Further, it is known that the estimated prevalence of mCRPC without detected HRRm (including non-HRRm status and unknown status) is larger than that of HRRm mCRPC (70-80% compared to 20-30%) [2, 3].

In the all-comers cohort of TALAPRO-2, HRRm status was used as a stratification factor with only two categories: (1) HRRm and (2) a combined group of patients identified as having non-HRRm or unknown status (non-HRR/unknown). The majority (79%) of patients were stratified in the non-HRR/unknown stratum at randomization. However, TALAPRO-2 did not require complete prospective HRRm determination prior to randomization, resulting in a large proportion of patients with unknown status, and the analysis plan did not prespecify formal testing of the primary and key secondary endpoints in patients without tumor HRRm, resulting in challenges with interpreting the results in this population.

Efficacy results of TALAPRO-2 by HRR stratification factor

Table 2 and Figure 2 summarize the analysis of rPFS and OS in the all-comers population (i.e. the HRRm-Unselected Cohort) and in the subgroups by tumor HRRm status according to the stratification factor.

The primary endpoint of rPFS per BICR was met at the final rPFS analysis (DCO2) by demonstrating a statistically significant improvement of rPFS in favor of talazoparib with enzalutamide compared to placebo with enzalutamide in the HRRm-Unselected Cohort (all-comers population) (HR=0.63 [95% CI: 0.51, 0.78]; 2-sided p-value < 0.0001). In addition, the key secondary endpoint of OS was met, with a HR of 0.80 (95% CI: 0.66, 0.96, 2-sided p-value = 0.0155) and a difference in median OS of 9 months at the final OS analysis in the HRRm-Unselected Cohort (all-comers population).

Exploratory subgroup analyses of patients in the non-HRRm/Unknown stratum showed results generally consistent with those seen in all-comers for both rPFS per BICR and OS. However, the treatment effect for patients in the non-HRRm/Unknown stratum appeared smaller than for patients in the HRRm stratum. The HR of rPFS in the non-HRRm/Unknown stratum subgroup was 0.70 (95% CI: 0.54, 0.89). The median rPFS was not reached in the talazoparib plus enzalutamide arm and 22.5 months in the placebo plus enzalutamide arm. The HR for OS in the non-HRRm/Unknown stratum subgroup was 0.88 (95% CI: 0.71, 1.08) and the addition of talazoparib to enzalutamide yielded a 7-month median improvement for OS. However, the Kaplan-Meier curves for OS in this subgroup crossed and overlapped multiple times indicating a violation of the proportional hazards assumption and further challenging interpretation of the treatment effect on OS beyond the issue with lack of formal testing in a well-defined biomarker-negative subgroup discussed above (Figure 3).

Table 2: TALAPRO-2 Subgroup Analysis of rPFS per BICR and OS by Stratification Factor of HRRm Status in Cohort 1 (HRRm-Unselected)

		All-comers (N=805)		**HRRm (N=169)**		**Non-HRRm/Unknown (N=636)**	
		Talazoparib + Enzalutamide N=402	**Placebo + Enzalutamide** N=403	**Talazoparib + Enzalutamide** N=85	**Placebo + Enzalutamide** N=84	**Talazoparib + Enzalutamide** N=317	**Placebo + Enzalutamide** N=319
rPFS	**Number of events (%)**	151 (37.6%)	191 (47.4%)	37 (43.5%)	49 (58.3%)	114 (36%)	142 (44.5%)
	Median, months (95% CI)	NR (27.5, NE)	21.9 (16.6, 25.1)	27.9 (16.6, NE)	16.4 (10.9, 24.6)	NR (27.5, NE)	22.5 (19.1, 30.5)
	Hazard Ratio (95% CI) [†]	0.63 (0.51, 0.78)		0.46 (0.30, 0.70)		0.70 (0.54, 0.89)	
	p-value[‡]	<0.0001					
OS	**Number of events (%)**	211 (52.5%)	243 (60.3%)	40 (47.1%)	56 (66.7%)	171 (53.9%)	187 (58.6%)
	Median, months (95% CI)	45.8 (39.4, 50.8)	37.0 (34.1, 40.4)	45.8 (35.8, NE)	30.8 (26.1, 38.8)	45.5 (37.6, 50.8)	38.3 (34.7, 42.4)
	Hazard Ratio (95% CI) [†]	0.80 (0.66, 0.96)		0.55 (0.36, 0.83)		0.88 (0.71, 1.08)	
	p-value[‡]	0.0155					

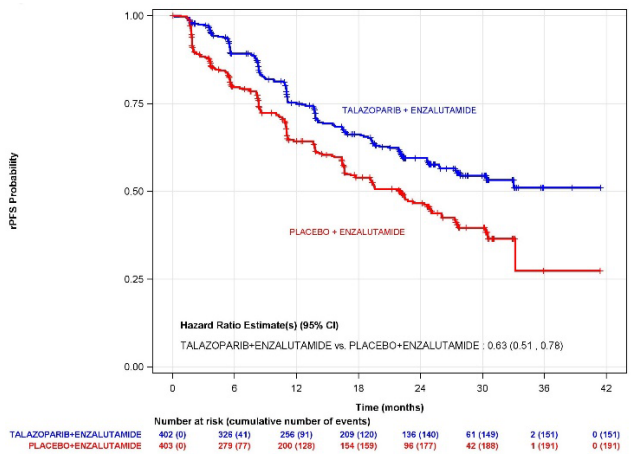
[†] HR and CI based on stratified Cox PH model

[‡] two-sided p-value based on stratified log-rank test

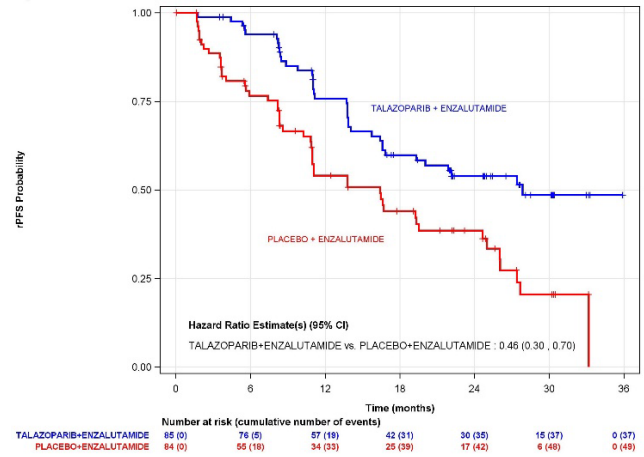
NR: not reached; NE: not evaluable

DCO: 08/16/2022 for rPFS per BICR at the final rPFS analysis (DCO2) and 09/03/2024 for OS at the final OS analysis (DCO5)

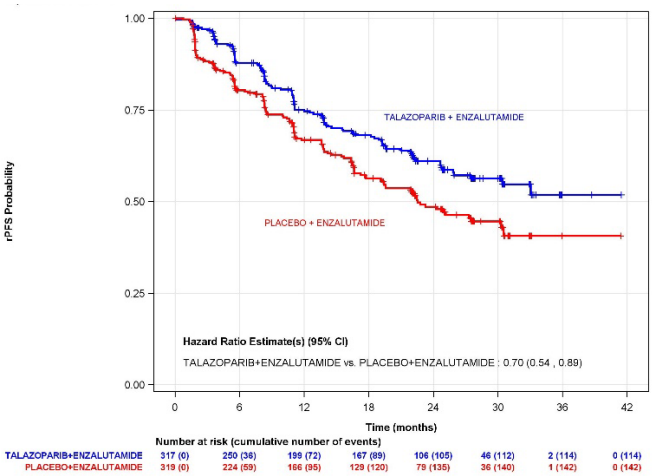
Figure 2: TALAPRO-2 Kaplan-Meier Plot of rPFS per BICR by Stratification Factor of HRRm Status in Cohort 1 (HRRm-Unselected)



a) All-comers population



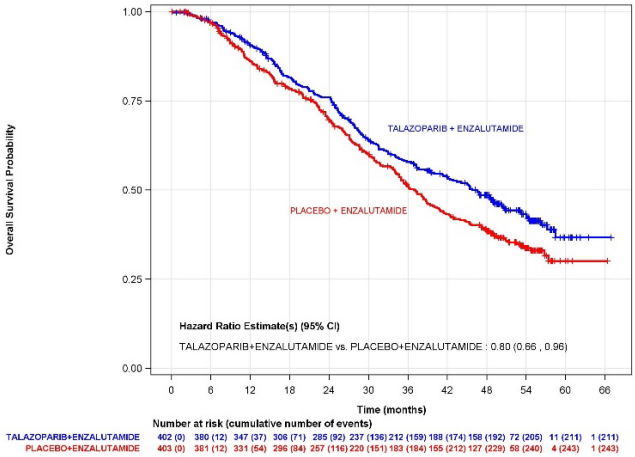
b) HRRm



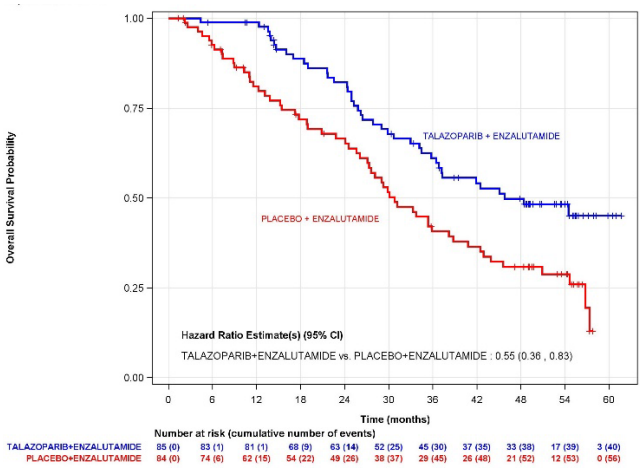
c) Non-HRRm/Unknown

DCO: 08/16/2022 at the final rPFS analysis (DCO2)
Source: FDA analysis

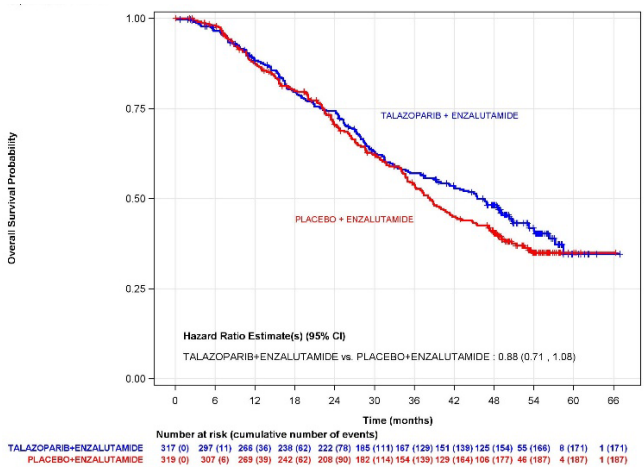
Figure 3: TALAPRO-2 Kaplan-Meier Plot of OS by Stratification Factor of HRRm Status in Cohort 1 (HRRm-Unselected)



a) All-comers population



b) HRRm



c) Non-HRRm/Unknown

DCO: 09/03/2024 at the final OS analysis (DCO5)
Source: FDA analysis

Incomplete prospective determination of biomarker status

Incomplete assessment of biomarker status at randomization further challenges interpretation of efficacy for patients without demonstrated tumor HRRm. Notably, 26% (211 of 805) of the all-comers population had unknown HRRm status based on prospective testing results. Furthermore, 26% of the patients (163 of 636) who were stratified to the non-HRR/ unknown HRRm subgroup at randomization were later found to have tumor HRRm on subsequent testing.

At the time of randomization, 798 of the 805 patients in Cohort 1 (99%) had prospective tumor tissue testing results available. ctDNA testing was added after the start of the overall study via protocol amendment, and only 55 patients (7%) had prospective ctDNA testing results available at the time of randomization. A large number of additional patients had results that became available after randomization but before treatment started categorized as "prescreening/screening results": 7 additional patients had available tissue results (for a total of 805 patients or 100% of Cohort 1), and 685 additional patients had ctDNA results available (for a total of 740 total patients or 92% of Cohort 1 who had at least 1 ctDNA test result) in the "prescreening/screening results" category.

Finally, 10 additional patients had ctDNA results that were obtained on-study, for a total of 750 patients or 93% of Cohort 1 who had at least 1 ctDNA test result in the "all results" category. Some patients who had ctDNA results available at earlier timepoints had additional ctDNA testing on-study, such that the biomarker status of numerous patients changed between the "prescreening/screening results" category and the "all results" category.

To address this, the FDA defined the following HRRm status categories based on both the tumor tissue and ctDNA tests, and further subgroup analyses were performed based on these categories:

a) Positive: patients with positive HRRm identified by at least one testing type (either tissue or ctDNA)
b) Double-negative: patients with negative HRRm by at least two tests, including at least one tissue and ctDNA test
c) Single-negative: patients with negative HRRm by only one testing type (either tissue or ctDNA) and unknown HRRm by the other type
d) Unknown: unknown HRRm by all tissue and ctDNA tests

The shifting biomarker status of patients based on the obtained testing results is presented in Table 3.

Table 3: TALAPRO-2 Summary of HRRm Status in Cohort 1 (HRRm-Unselected)

All Patients (N = 805)	**HRRm**	**Non-HRRm/Unknown**	**Comment**
Prospectively assessed (pre-randomization) tumor tissue and ctDNA	**169 (21.0%)**[a]	**636 (79.0%)**[b] -Unknown: 211 (26.2%) -"Single-negative"[c]: 409 (50.8%) -"Double-negative"[d]: 14 (1.7%) -Positive: 2 (0.2%) [b]	Basis of Applicant's stratification/prespecified testing plan

Using prescreening/screening results	**266 (33.0%)**	**539 (67.0%)** -Unknown: 42 (5.2%) -"Single-negative"[c]: 183 (22.7%) -"Double-negative"[d]: 314 (39.0%)	Basis of Applicant's exploratory analyses of HRR "double-negative"
Using all available results	**328 (40.7%)**	**477 (59.3%)** -Unknown: 28 (3.5%) -"Single-negative"[c]: 155 (19.3%) -"Double-negative"[d]: 294 (36.5%)	Basis of FDA's exploratory analyses of HRR "double-negative"

[a]Only 165 patients had HRRm. Four patients were mis-stratified into this subgroup.
[b]Two patients with HRRm were mis-stratified into this subgroup.
[c]Negative HRRm by one testing type (either tissue or ctDNA).
[d]Negative HRRm by at least two tests, including at least one tissue and ctDNA test.
Source: FDA analysis

The above table illustrates that 26% of patients in TALAPRO-2 had unknown biomarker status (testing failure or test not performed) at the time of randomization, some of whom were later found to have tumor HRRm on subsequent testing. Patients with unknown biomarker status are a heterogeneous group with no known inherent biologic significance, and the inclusion of some patients with tumor HRRm in this subgroup adds noise to the results in the non-HRRm/unknown stratum. The number of patients identified as having tumor HRRm nearly doubled when all samples were used instead of prospectively assessed (pre-randomization) samples. One caveat is that some of the HRR gene mutations identified through subsequent testing are not anticipated to confer particular sensitivity to PARPi, for example *ATM* and *CHEK2* mutations [10]. However, the later testing also identified some patients with tumor *BRCA*m (N=33) or other mutations that are expected to be sensitive to PARPi, and therefore the subsequent results are still relevant to the discussion. Table A2 (appendix) provides a summary of specific HRR mutations that were identified in the different testing groups.

Exploratory sensitivity analyses using all available biomarker testing results

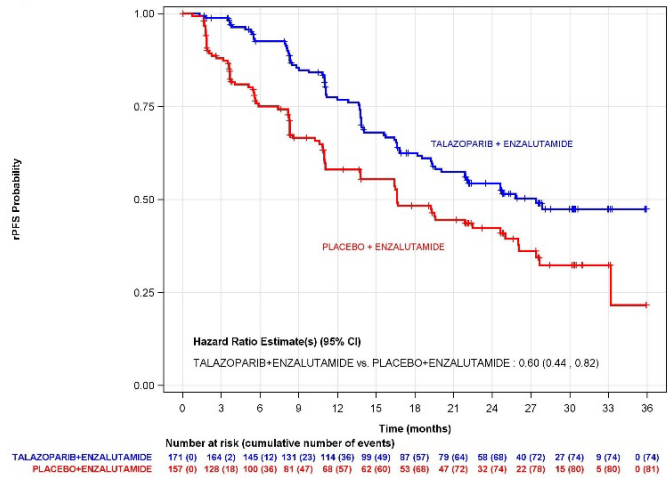
To estimate the potential efficacy of the addition of talazoparib to enzalutamide in patients without tumor HRRm, the Applicant and FDA conducted exploratory sensitivity analyses in a "double-negative" non-HRR subgroup, who had negative tumor HRRm results from at least two tests, including at least one tissue and ctDNA test. While two negative results do not guarantee the absence of tumor HRRm, and the presence of even small numbers of patients with undetected, highly sensitive mutations such as *BRCA2*m may affect the subgroup results, the FDA considered the "double-negative" population in TALAPRO-2 to more accurately represent a true non-HRRm population than the non-HRR/unknown stratum, given the inadequate prospective determination of HRR status. The Applicant's analysis used the results of prescreening/screening samples, and the FDA's analysis incorporated all available results (including results obtained after randomization). The table and figure below summarize the FDA's exploratory subgroup analyses for rPFS (Table 4 and Figure 4) and OS (Table 4 and Figure 5) based on all available results.

Table 4: TALAPRO-2 Subgroup Analyses for HRRm and Non-HRRm Subgroups Using All Results in Cohort 1 (HRRm-Unselected)

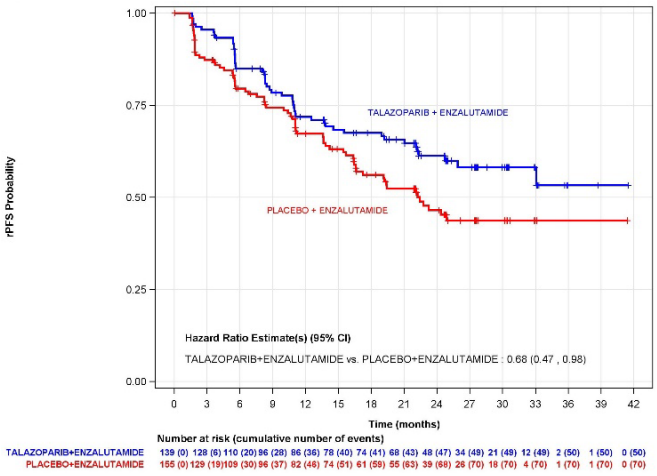
Endpoint	Variable	HRRm (N=328)		Non-HRRm "double-negative" (N=294)	
		Talazoparib + Enzalutamide N=171	Placebo + Enzalutamide N=157	Talazoparib + Enzalutamide N=139	Placebo + Enzalutamide N=155
rPFS	Number of events (%)	74 (43.3%)	81 (51.6%)	50 (36.0%)	70 (45.2%)
	Median rPFS, months (95% CI)	27.4 (19.6, NE)	16.6 (11.1, 24.6)	NR (25.9, NE)	22.4 (16.4, NE)
	rPFS Hazard Ratio (95% CI) †	**0.60** (0.44, 0.82)		**0.68** (0.47, 0.98)	
OS	Number of events (%)	90 (52.6%)	100 (63.7%)	73 (52.5%)	93 (60.0%)
	Median OS, months (95% CI)	42.4 (34.2, 54.5)	33.7 (28.8, 40.8)	50.2 (35.1, 54.1)	38.0 (33.7, 41.8)
	OS Hazard Ratio (95% CI) †	**0.72** (0.54, 0.95)		**0.77** (0.56, 1.04)	

† HR and CI based on unstratified Cox PH model
Abbreviations: NE: not evaluable; NR, not reached.
DCO: 08/16/2022 for rPFS per BICR at the final rPFS analysis (DCO2) and 09/03/2024 for OS at the final OS analysis (DCO5)
Source: FDA analysis

Figure 4: TALAPRO-2 Kaplan-Meier Plot of rPFS per BICR for HRRm and Non-HRRm Subgroups Using All Results in Cohort 1 (HRRm-Unselected Cohort)



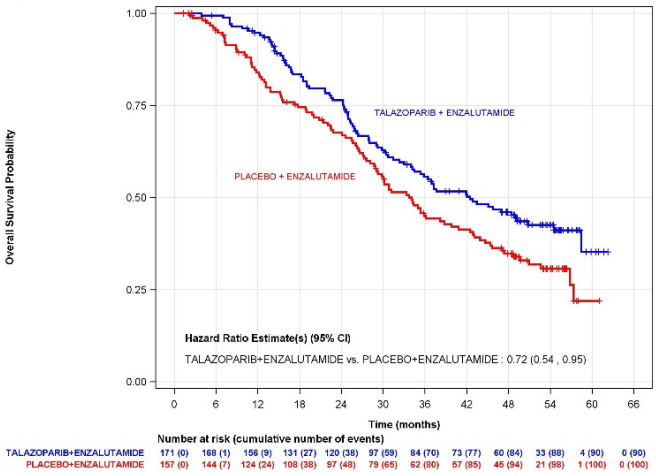
a) HRRm



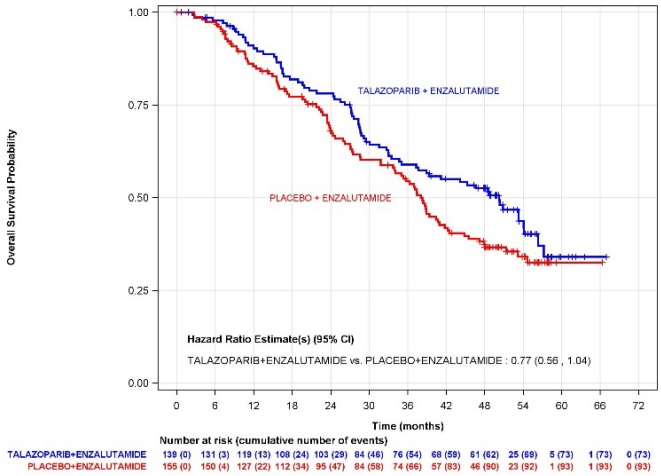
b) Non-HRRm "double-negative"

DCO: 08/16/2022 at the final rPFS analysis (DCO2)
Source: FDA analysis

Figure 5 TALAPRO-2 Kaplan-Meier Plot of OS for HRRm and Non-HRRm Subgroups Using All Results in Cohort 1 (HRRm-Unselected Cohort)



a) HRRm



b) Non-HRRm "double-negative"

DCO: 09/03/2024 at the final OS analysis (DCO5)
Source: FDA analysis

Overall, these analyses demonstrated an attenuated treatment effect for the "double-negative" subgroup of the non-HRRm/unknown stratum compared to the HRRm population. Given that this exploratory "double-negative" subgroup was not stratified, and baseline characteristics may have differed between treatment arms, the FDA conducted additional sensitivity analyses based on adjusted hazard ratio using the Halabi prognostic risk score and matched patients using a propensity score approach to adjust for differences in baseline characteristics. These sensitivity analyses are not shown here, but were supportive of the above analyses, suggesting that the observed results did not appear due to baseline imbalances in known prognostic factors. However, as discussed later, the OS results for the "single-negative/unknown" subgroup were numerically worse than for the "double-negative" subgroup, raising concern for imbalance of confounding baseline factors in these post-hoc analyses and increasing uncertainty regarding the reliability of the results in the "double-negative" subgroup.

While these exploratory analyses detailed above were generally supportive of efficacy in patients without tumor HRRm, these were not part of the formal prespecified statistical analysis plan and should be interpreted with caution, as discussed further in the next section.

Lack of formal statistical testing for Type I error in biomarker negative population

Despite the expected differential effect based on tumor HRRm status and high prevalence of the unselected biomarker subgroup, the non-HRRm subgroup of TALAPRO-2 was not formally powered or tested in the formal testing plan. The lack of a prespecified alpha-controlled testing plan to reduce Type I error in the non-HRR population in TALAPRO-2 raises the concern that the favorable trend in rPFS and OS in this subgroup can be a random false positive conclusion.

The risk of a false positive conclusion should be a major concern when interpreting biomarker subgroup analyses without pre-specified alpha-controlled statistical testing. Prespecifying the analyses to control for type I error helps prevent misinterpretation caused by post hoc, data-driven, exploratory analyses

[11, 12]. Even in a case where only one or two exploratory analyses are presented, if the analyses were not pre-specified in the protocol, type I error probability is difficult or impossible to control because many tests or other influences could have motivated the selections of the presented results [13].

Finally, a large magnitude of effect in an exploratory subgroup analysis does not guarantee that the result is true or reproducible. Two historical examples of this are presented in Table 5. In both cases, an initial seemingly favorable treatment effect in an exploratory subgroup analysis was followed by subsequent dedicated trials that failed to confirm that effect.

Table 5: Examples of Subgroup Analyses Suggestive of Large Treatment Effects That Were not Replicated in Subsequent Dedicated Trials

Drug	Disease indication	Initial trial	Initial subgroup result	Subsequent trial	Key result
Histamine dihydrochloride	Metastatic melanoma (combination with IL-2)	Randomized Phase 3 (n=305) (ODAC 2001) No formal testing for patients with liver involvement [14]	HR 0.46 (95% CI: 0.29 -0.750), nominal p = 0.004, median OS of 9.4 months compared to 5.1 months in subgroup with liver involvement (n=129), [14]	Dedicated Phase 3 in patients with liver metastases [15]	Negative trial (detailed results not published) [15]
				Phase 3: IL-2 + IFN-α-2b + histamine dihydrochloride vs DTIC, stratified by liver metastases [15]	Negative trial in overall population and patients with liver metastases (latter not formally tested) [15]
Olaratumab	Metastatic soft tissue sarcoma (combination with doxorubicin)	Randomized, open-label Phase 2 (n=133) No formal testing [16]	HR 0.46, (95% CI 0.30-0.71), nominal p=0.0003, median OS of 26.5 months compared to 14.7 months [16]	ANNOUNCE trial Randomized, double-blinded, placebo-controlled Phase 3 trial [17]	Negative trial. Total STS: OS hazard ratio, 1.05; median, 20.4 vs 19.7 months; leiomyosarcoma: OS hazard ratio, 0.95; median, 21.6 vs 21.9 months [17]

Abbreviations: DTIC, dacarbazine; IFN-α-2b, interferon- α-2b; IL-2, interleukin-2; STS, soft tissue sarcoma.
Source: FDA analysis

While the treatment effects on rPFS and OS in the exploratory "double-negative" subgroup of TALAPRO-2 appear to have clinically meaningful magnitude, the analysis plan for TALAPRO-2 did not pre-specify rPFS and OS to be formally tested in the "double-negative" subgroup, in which formal statistical testing should be feasible given the high prevalence. Therefore, the treatment effect observed in the exploratory analyses of non-HRRm population in TALAPRO-2 is uncertain and subject to bias and chance from the statistical perspective. The presence or absence of a treatment effect in the non-HRRm

population would be best assessed in a dedicated cohort or trial with adequate power, sample size, and alpha control.

FDA's preferred study designs for biomarker-negative subpopulation with high prevalence

Instead of an all-comers trial design, a preferred approach when there is an expected differential effect based on biomarker status is to assess the biomarker-positive and biomarker-negative subpopulations separately. A major risk of not properly evaluating biomarker-negative patients for a targeted therapy is approval in patients who will not receive benefit and therefore may experience unnecessary toxicity. As noted in the 2019 FDA Guidance on Enrichment Trial Designs, characterization of benefit in the biomarker-negative subpopulation is of particular concern when this subpopulation has high prevalence [18].

Based on a scenario where only biomarker-positive and biomarker-negative status are detected, two clinical trial designs may be considered. Both of these designs should require adequate prospective determination of biomarker status prior to randomization to avoid heterogeneous "unknown" populations where efficacy is difficult to interpret.

Formal testing for each biomarker population can be performed with full alpha allocated to each biomarker-defined subgroup, so that the possibility of false-positive results is lessened while still maintaining adequate power to detect a true effect. Two preferred designs would include:

1) Two-trial approach: The biomarker-positive and biomarker-negative populations are each evaluated in a standalone trial.
2) Separate cohort approach: Patients enroll into separate cohorts based on biomarker status, and then are randomized to the investigational or control arm, in one overarching trial protocol.

In the two-trial approach, separate trials could be developed with independent timelines for clinical development and potential regulatory submissions. Trial designs and potential adaptive features may be entirely different from each other. In the separate cohort approach, the two cohorts would be pre-specified to be individually powered and tested in an overall, more streamlined, statistical analysis plan. Although trial conduct for the two cohorts would not be entirely independent, this may be more efficient from an operational perspective.

Summary of Efficacy Issue 1: Large, inadequately-defined non-HRRm subgroup was not formally tested for efficacy.

- Biomarker status should be adequately determined at baseline for all patients; however prospective biomarker determination was incomplete in TALAPRO-2.
- Exploratory subgroup results in TALAPRO-2 suggest efficacy in the non-HRR "double-negative" subgroup, but these results may be due to chance.
- Analyses should be specified for biomarker-negative populations, particularly those that are high prevalence, with adequate power, sample size, and alpha control. The HRR-negative population was not formally tested in TALAPRO-2.

- It is the Applicant's responsibility to provide rationale for why the safety and efficacy demonstrated in a biomarker-based subgroup is sufficient to include in a broad indication.

Key efficacy issue 2: Interpretation of OS result and applicability to current US standard of care are unclear.

The statistically significant final OS result in the all-comers population was a major reason for the submission of this sNDA to expand the indication to include an all-comers population. However, there are at least three caveats to interpretation of the OS results, as described below.

OS benefit was not clearly established for patients without positive HRRm status in Cohort 1

In the exploratory subgroup analysis of patients with undetected HRRm status (including non-HRRm and unknown), the Kaplan-Meier curves crossed multiple times, overlapping for the first 36 months and crossing again at the tail end of the curves at approximately 58 months. There was heavy censoring at the tail end of the curves. The curves indicate that the hazard ratio may be difficult to interpret since this estimate relies on the proportional hazards assumption, which was not followed here. The estimated median OS improvement of 7 months in the exploratory analysis may also be an over-estimate. Thus, while interpretation of efficacy in biomarker-negative patients is limited given the lack of prospective adequate biomarker status and formal testing, exploratory OS results for the non-HRRm/unknown stratum do not clearly support any OS improvement in this population.

Low proportion of patients in the placebo with enzalutamide arm received subsequent PARPi

A low proportion of patients in the placebo with enzalutamide arm (4%; 16/403) received subsequent PARPi, including those with documented tumor HRRm (7%; 11/157) or tumor *BRCA*m (9%; 8/92). The positive biomarker definitions used here are based on all available testing results, as was done with the FDA's sensitivity analyses for efficacy described above.

Olaparib was approved in 2020 as monotherapy for HRRm mCRPC after progression on an ARPI and was thus available for most patients on TALAPRO-2 after progression. In the PROfound trial, olaparib treatment resulted in both an rPFS benefit in the overall HRRm population and a statistically significant OS benefit attributable to the *BRCA*m population and is a standard of care for patient with these tumor mutations. If patients with tumor HRRm, particularly those with *BRCA*m, had received subsequent olaparib, the statistically significant all-comers OS improvement observed in TALAPRO-2, largely driven by patients with HRRm, might have been abrogated.

In a dedicated trial in patients with non-HRRm tumors, interpretation of OS would not be affected by receipt or non-reciept of subsequent PARPi, since patients with non-HRRm tumors are not indicated to receive subsequent PARPi monotherapy. Therefore, a dedicated trial in patients with non-HRRm tumors could provide a more certain estimate of any potential OS benefit in this subpopulation.

Exploratory biomarker subgroups based on all available HRR test results show counterintuitive results for OS

OS in the FDA-defined non-HRR "double-negative" subgroup appears numerically more favorable than the results for patients with one negative test result or unknown HRR status ("single-negative"/unknown subgroup) (Table 6 and Figure 6). This biologically counterintuitive result increases uncertainty that results in these exploratory subgroups are truly indicative of a biologic effect, rather than reflective of imbalances in unknown prognostic factors due to loss of randomization. This further highlights the issue with interpretation of biomarker-based subgroup results in the setting of incomplete prospective biomarker assessment; the interpretation that efficacy was maintained in the "double-negative" subgroup must be made with caution.

Table 6: TALAPRO-2 Exploratory Analyses of OS for Non-HRRm and Unknown Subgroups (FDA definition) Using All Results in Cohort 1 (HRRm-Unselected)

	Non-HRRm "double-negative" (N=294)		**Non-HRRm "single-negative"/Unknown (N=183)**	
	Talazoparib + Enzalutamide N=139	**Placebo + Enzalutamide** N=155	**Talazoparib + Enzalutamide** N=92	**Placebo + Enzalutamide** N=91
Number of events (%)	73 (52.5%)	93 (60.0%)	48 (52.2%)	50 (54.9%)
Median OS, months (95% CI)	50.2 (35.1, 54.1)	38.0 (33.7, 41.8)	46.6 (31.6, NE)	41.3 (34.6, 53.6)
OS Hazard Ratio (95% CI) [†]	**0.77** (0.56, 1.04)		**0.99** (0.67, 1.47)	

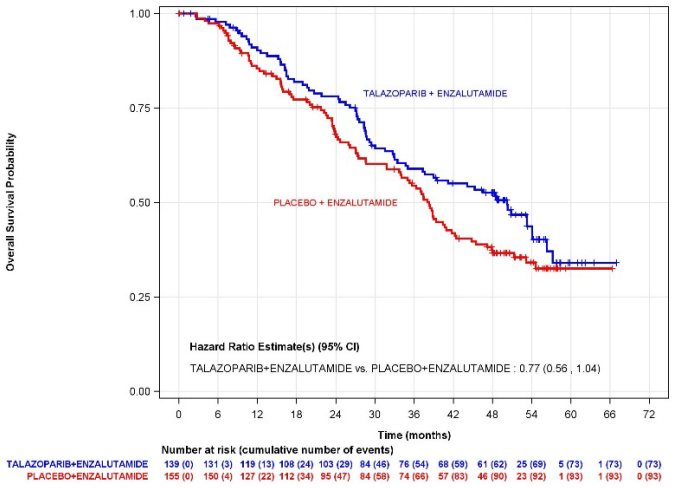
[†] HR and CI based on unstratified Cox PH model

NE: not evaluable

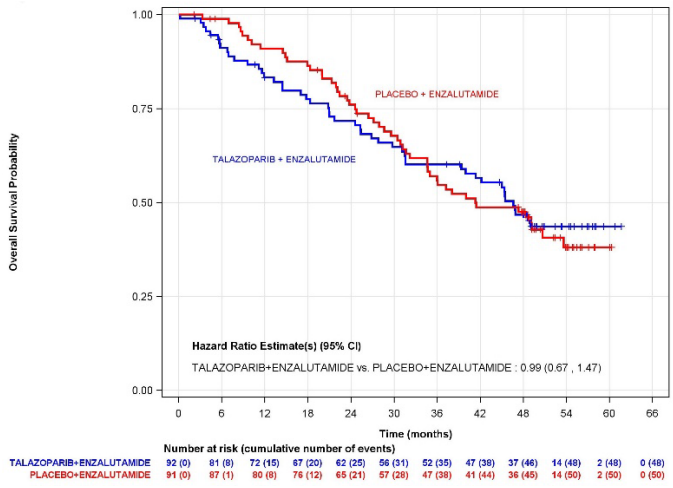
DCO: 09/03/2024 for OS at the final OS analysis (DCO5)

Source: FDA analysis

Figure 6: TALAPRO-2 Kaplan-Meier Plot of OS for Non-HRRm and Unknown Subgroups (FDA definition) in Cohort 1 (HRRm-Unselected)



a) Non-HRRm "double-negative"



b) Non-HRRm "single-negative"/Unknown

DCO: 09/03/2024 for OS at the final OS analysis (DCO5)
Source: FDA analysis

Summary of Efficacy Issue 2: Interpretation of OS result and applicability to current US standard of care are unclear.

- OS benefit was not clearly established in the exploratory subgroup of patients with non-detected tumor HRRm in Cohort 1 (non-HRRm/unknown stratum).
- Only a small proportion of patients with HRRm or *BRCA*m received subsequent PARPi on the control arm of TALAPRO-2. This may have increased the observed OS difference in TALAPRO-2 versus what would be observed if adequate subsequent therapy had been given.
- The heterogeneous all-comers population, which contains subpopulations with expected different sensitivities to PARPi, contributes to uncertainty in interpretation of the OS results in the non-HRRm subgroup.
  A dedicated trial in non-HRRm patients could provide a more certain estimate of any potential OS benefit in this subpopulation.

Key efficacy issue 3: Trials of other PARP inhibitors did not support an all-comers indication.

If the proposed all-comers indication were approved, it would be the first approval of a PARPi for treatment of a biomarker-unselected prostate cancer population. However, a preponderance of data, both external and within TALAPRO-2, provide strong biological rationale that PARPi are more efficacious in patients with biomarker-positive tumors than those with biomarker-negative tumors, and that the statistically significant rPFS and OS improvement in all-comers is primarily attributed to the stronger treatment effect in the biomarker-positive population.

The Applicant has provided non-clinical data that talazoparib may be differentiated from other PARPis due to differences in the mechanism of action, e.g. differences in PARP1 trapping. However, the adequacy of these data to consider the results of TALAPRO-2 entirely separately from trials of other PARPis is unclear. The FDA acknowledges that the non-clinical data provided by the Applicant may serve as adequate rationale for conducting clinical trials of the combination of talazoparib with enzalutamide in patients with non-HRRm mCRPC. However, any claims of differential efficacy for talazoparib with enzalutamide compared to other PARPi + ARPI combinations cannot be proven in the absence of head-to-head randomized comparisons. Further, while the FDA agrees that the Applicant's provided non-clinical and translational studies provide support for evaluating talazoparib with enzalutamide in patients without tumor HRRm, ultimately data from randomized clinical trials are needed to determine efficacy in this population.

Table 8 summarizes key trials of other PARPis in prostate cancer that tested both biomarker-negative and biomarker-positive patients and supported restrictions of the respective indications to patients with either tumor HRRm or tumor *BRCA*m.

Table 7: Key Trials of PARPi in Prostate Cancer Supporting Restriction of Indications to Biomarker-Positive Populations

Drug	Disease setting	Trial	Key results	Approved indication
Olaparib	mCRPC post-chemo	TOPARP-A Single-arm Phase 2 study [19]	Composite response rate 14/16 (88%) in HRRm vs 2/33 (6%) in non-HRRm [19]	N/A
	1L mCRPC in combination with abiraterone acetate	PROpel Randomized Phase 3 trial of olaparib+AAP vs placebo+AAP in all-comers population [20]	Efficacy primarily driven by *BRCA*m subgroup [20]	*BRCA*m mCRPC
Niraparib	1L mCRPC in combination with abiraterone acetate	MAGNITUDE Randomized Phase 3 trial [21] (see Figure 7)	Lack of added efficacy in non-HRRm [21] (see Figure 7)	*BRCA*m mCRPC

Source: FDA analysis

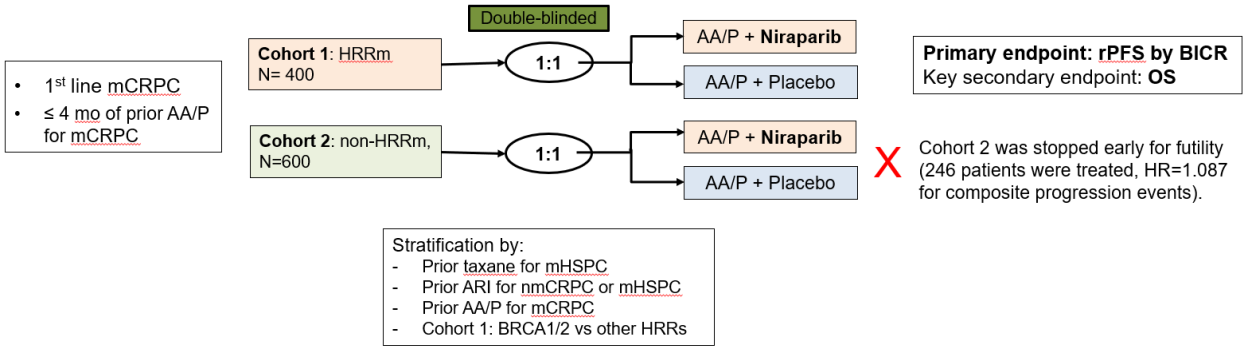
Olaparib was studied in two trials that included both patients with HRRm and non-HRRm tumors and showed differential efficacy by biomarker status:

- TOPARP-A was a single-arm Phase 2 study of olaparib monotherapy in patients with mCRPC who had previously been treated with chemotherapy. The primary endpoint was a composite response endpoint that comprised either an objective response according to Response Evaluation Criteria in Solid Tumors, version 1.1, or as a reduction of at least 50% in the prostate-specific antigen level or a confirmed reduction in the circulating tumor-cell count from 5 or more cells per 7.5 ml of blood to less than 5 cells per 7.5 ml. The composite response rate was 14/16 (88%) in patients with tumor HRRm vs 2/33 (6%) in patients without tumor HRRm [19].

- PROpel was a randomized Phase 3 trial of olaparib with AAP versus placebo with AAP for first-line treatment of mCRPC in an all-comers population. As was discussed at ODAC on April 28, 2023, this trial had critical design issues including the lack of prospective determination of biomarker status and the lack of prespecified alpha-controlled subgroup analyses by tumor *BRCA*m or tumor HRRm status. Ultimately, the FDA concluded that the efficacy of the combination of olaparib plus abiraterone was primarily attributed to the treatment effect in the *BRCA*m subgroup. For patients without tumor *BRCA*m, the FDA determined that the modest rPFS improvement, combined with clinically significant toxicities and exploratory OS HR >1, did not demonstrate a favorable benefit/risk assessment. Therefore, although PROpel met the primary end point of rPFS in the all-comers population, the FDA restricted the indication to patients with *BRCA*m mCRPC [20].

The fixed-dose combination of niraparib with AA was studied in the MAGNITUDE trial, whose design was generally consistent with FDA's preferred trial design for a biomarker-negative population with high prevalence. The schema is shown in Figure 7.

Figure 7: MAGNITUDE study design



Abbreviations: AA/P, abiraterone acetate with prednisone or prednisolone; ARI, androgen receptor inhibitor; HR, hazard ratio; HRRm, homologous recombination repair mutation; mCRPC, metastatic castration-resistant prostate cancer; mHSPC, metastatic hormone-sensitive prostate cancer; mo, months; nmCRPC, non-metastatic castration-resistant prostate cancer; OS, overall survival; rPFS, radiographic progression-free survival; tx, treatment

Cohort 2 was a dedicated cohort studying niraparib with AA versus placebo with AA in patients without HRRm tumors (defined as at least one negative test result from tissue or ctDNA testing with no positive results, or testing failure of or no reportable result for both tissue and ctDNA tests), which had appropriate power, sample size, and alpha control to assess efficacy in the biomarker-negative subpopulation. Cohort 2 (non-HRR cohort) was stopped early due to futility after 246 patients were treated, with a HR of 1.087 for composite progression events (defined as the first of either PSA progression, radiographic progression, or death). Ultimately, based on the results of Cohort 1 (HRRm cohort), the approved indication was further limited to patients with *BRCA*m tumors [21].

A caveat with applying these external trial results directly to TALAPRO-2 is that these are cross-trial comparisons, and there may be many differences between trials that might contribute to different results. For example, both the PARPi and the ARPI are different between TALAPRO-2 and the other trials in first-line treatment of mCRPC. Although enzalutamide and AA are both considered ARPIs, they have different mechanisms of action, with enzalutamide primarily acting directly on the androgen receptor while AA acts primarily on androgen biosynthesis. Still, the differences between TALAPRO-2 and similar trials should at least raise the question of whether additional data are needed to further substantiate the apparent added efficacy of talazoparib in patients with non-HRRm tumors.

Of note, other clinical trials of PARPi in mCRPC (PROfound for olaparib and TRITON2 for rucaparib) limited enrollment to patients with tumor HRRm [22, 23]. The Applicant's own ongoing trial of talazoparib with enzalutamide in mHSPC, TALAPRO-3, is limiting enrollment to patients with tumor HRRm [24]. Furthermore, we note that the Applicant designed TALAPRO-2 to statistically test the treatment effect in patients with HRRm in a separate cohort. These restricted eligibility criteria suggest a broad understanding in the field, including by the Applicant, that there is differential sensitivity to PARPi based on biomarker status, with reduced or no sensitivity in patients with non-HRRm tumors.

Finally, the results from TALAPRO-2 itself support differential sensitivity to PARPi based on biomarker status. Table 9 presents key efficacy results from TALAPRO-2 in the Cohort 1 all-comers population, the Cohort 1 non-HRRm/unknown stratum, the Cohort 2 HRRm analysis set, and the exploratory subset of

patients with tumor *BRCA*m in Cohort 2. The Cohort 2 analyses include patients with tumor HRRm or tumor *BRCA*m from Cohort 1, plus additional patients with tumor HRRm or tumor *BRCA*m.

Table 8: TALAPRO-2 Subgroup Key Efficacy Results of TALAPRO-2 by Biomarker Status

TALAPRO-2 **Key efficacy**	**Cohort 1 all-comers (HRRm-Unselected)** **N = 805**	**Cohort 1 Non-HRR/Unknown** **N = 636**	**Cohort 2 HRRm analysis set** **N = 399**	**Cohort 2 *BRCA*m analysis set (exploratory)** **N = 155**
rPFS HR (95% CI) 2-sided p-value* (initial approval)	**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) 2-sided p-value* (final OS results)	**0.80** (0.66, 0.96) † 0.0155	**0.88** (0.71, 1.08) †	**0.62** (0.48, 0.81) † 0.0005	**0.48** (0.31, 0.75) ‡

† HR and CI based on stratified Cox PH model
‡ HR and CI based on unstratified Cox PH model
* two-sided p-value based on stratified log-rank test
DCO: 08/16/2022 for rPFS per BICR at the final rPFS analysis in Cohort 1 (DCO2) and 10/3/2022 for rPFS per BICR at the second interim analysis of rPFS in Cohort 2(DCO3); and 09/03/2024 for OS at the final OS analysis in Cohort 1 and 2 (DCO5)

There is a clear trend of differential efficacy according to biomarker status, with greatest efficacy seen in patients with tumor *BRCA*m, followed by tumor HRRm, followed by patients with non-HRRm/unknown status.

Taken together, the external trial data and differential efficacy by biomarker status in TALAPRO-2 contribute to uncertainty regarding whether the addition of talazoparib to enzalutamide has a true beneficial effect in patients without tumor HRRm. This could be addressed with a separate dedicated trial of talazoparib with enzalutamide in patients without tumor HRRm.

Summary of Efficacy Issue 3: Trials of other PARP inhibitors did not support an all-comers indication.

- Data from trials of other PARPi in prostate cancer and differential efficacy by biomarker status in TALAPRO-2 strongly indicate that efficacy of PARPi is attenuated, if not absent, in biomarker-negative patients.
- In the case of currently approved PARPis, this led to the restriction of the approved indications to patients with tumor HRRm or *BRCA*m.
- Cross-trial comparisons indicating less activity of PARPi with ARPI in patients without HRRm tumors contribute to uncertainty regarding whether the addition of talazoparib to enzalutamide has a favorable benefit-risk profile in this population.

3.2 Safety Issues

Key safety issue 1: Addition of talazoparib increases hematologic toxicity versus enzalutamide alone.

3.2.1 Sources of Data for Safety

The safety of talazoparib with enzalutamide for the proposed indication was evaluated based on analysis of safety in all patients enrolled and treated on TALAPRO-2, including the additional patients with tumor HRRm that were included in Cohort 2. There were no substantial differences in overall safety based on biomarker status (not shown), supporting the pooling of these heterogeneous biomarker subgroups into a larger safety population.

3.2.2 Safety Summary

An overall summary of exposure and safety data in patients enrolled on TALAPRO-2 is presented in Table 10.

Table 9: TALAPRO-2 Summary of Overall Exposure and Safety by Treatment (Safety Population)

	Talazoparib with enzalutamide N = 511	**Placebo with enzalutamide N = 515**
Median duration of exposure to talazoparib/placebo, months (range)	20 (0.07, 67)	15 (0.5, 67)
Median duration of exposure to enzalutamide, months (range)	22 (0.07, 67)	15 (0.5, 67)
Patients with any treatment-emergent AR	508 (99%)	497 (97%)
Patients with any grade 3-5 AR	407 (80%)	244 (47%)
Patients with any serious AR	227 (44%)	152 (30%)
Patients with fatal AR	18 (3.5%)	22 (4.3%)
Patients with discontinuations* due to AR	106 (21%)	60 (12%)
Patients with treatment delay* due to AR	346 (68%)	129 (25%)
Patients with dose reductions* due to AR	309 (60%)	60 (12%)

Abbreviations: AR, adverse reaction.

*Any study drug.

The median duration of exposure to both study drugs was longer in patients receiving talazoparib with enzalutamide versus placebo with enzalutamide, which may have been due to improved rPFS with the addition of talazoparib. In any case, the overall duration of exposure to either study drug did not appear to be compromised by added toxicity from combination treatment.

Patients receiving talazoparib with enzalutamide experienced increased toxicity compared to patients receiving placebo with enzalutamide, including a higher rates of anemia with need for blood transfusion, leukopenia, infection, gastrointestinal toxicity, and pulmonary thromboembolism. There was a

substantially higher incidences of Grade 3-5 and serious adverse reactions, as well as adverse reactions leading to treatment discontinuations, delays, and dose reductions. The incidence of fatal adverse reactions was similar between treatments.

Subgroup analyses of patients who received talazoparib with enzalutamide demonstrated a trend towards decreasing exposure and increasing overall toxicity based on patient age, as shown in Table A3.

Of note, 170/511 = 33% of patients who received talazoparib on TALAPRO-2 were ages 75 or greater. For reference, the median age at diagnosis of mCRPC is 76 ; therefore, elderly patients may have been underrepresented on TALAPRO-2, resulting in an underestimate of toxicity versus a real-world patient population.

The primary reason for the increased toxicity in patients receiving talazoparib with enzalutamide was an increase in cytopenias, as shown in Table 12.

Table 10: Common Cytopenias Observed in TALAPRO-2, by Treatment

Laboratory abnormalitity	**Talazoparib with enzalutamide N = 511**		**Placebo with enzalutamide N = 515**	
	All Grades, n (%)	Grade 3-4, n (%)	All Grades, n (%)	Grade 3-4, n (%)
Decreased hemoglobin	432 (85%)	243 (48%)	200 (39%)	24 (4.7%)
Decreased neutrophils	335 (66%)	100 (20%)	96 (19%)	10 (1.9%)
Decreased lymphocytes	324 (63%)	85 (17%)	216 (42%)	44 (9%)
Decreased platelets	263 (51%)	44 (9%)	71 (14%)	6 (1.2%)

Forty-two percent of patients receiving talazoparib with enzalutamide required a red blood cell transfusion, including 25% who required more than one transfusion.

Overall, the incidence of both anemia and transfusions appeared to decrease over time, as noted by the Applicant. This was likely due at least in part to dose reductions, which occurred in 55% of patients who received talazoparib with enzalutamide and were frequently due to anemia.

Myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) are class effects for PARPi; two cases of MDS/AML were reported on TALAPRO-2.

Although the additional hematologic toxicity of adding talazoparib to enzalutamide may be acceptable for whom a well-established and robust efficacy benefit has been demonstrated, the added toxicity may be less acceptable in patients with non-HRRm tumors, where the benefit is less certain and of lower magnitude.

The Applicant collected patient-reported outcomes in TALAPRO-2, and claims no clinically meaningful difference between arms in global health status. Although the difference between arms was not large in

magnitude, mean change from baseline was numerically worse in the talazoparib arm at most timepoints. Furthermore, similar scores over time are not sufficient evidence of tolerability. A more robust assessment of patient-reported side effects, such as a more frequent assessment of fatigue and overall side effect impact, could have provided additional details about the tolerability of talazoparib with enzalutamide.

3.2.3 Summary of Safety Issues

- The combination of talazoparib with enzalutamide was more toxic than placebo with enzalutamide, with higher incidences of high-grade and serious adverse reactions , as well as adverse reactions resulting in dosage modifications.
- The additional toxicity was primarily due to a higher incidence of cytopenias, including anemia and transfusion requirement
- Although the incidence of anemia and transfusions in the overall safety population decreased over time, presumably due to dose modifications, the higher rate of adverse reactions can still have meaningful adverse impacts on patients' lives, particularly in this first-line disease setting where patients are generally minimally symptomatic.
- MDS/AML are class effects of PARPi, however only 2 cases were reported on TALAPRO-2.
- The additional toxicity of adding talazoparib to enzalutamide may be less acceptable in patients with non-HRRm tumors, given that any benefit in these patients is less certain than in biomarker-positive patients.

4 Benefit-Risk Framework (Optional)

Benefit-Risk Framework

Disclaimer: This pre-decisional Benefit-Risk Framework does not represent the FDA's final benefit-risk assessment or regulatory decision.

Considerations favoring a broad all-comers approval based on TALAPRO-2 or retaining a restricted indication are presented in Table 13.

Table 11: Summary of Benefit-Risk Framework for All-comers Approval Based on TALAPRO-2

Favors broad approval based on TALAPRO-2	**Favors restriction to HRRm mCRPC**
Trial demonstrated a statistically significant rPFS and OS improvement in the all-comers population.	Unclear whether all-comers OS benefit would remain with appropriate second-line therapy for patients with tumor HRRm/*BRCA*m, or whether it translates to patients with non-HRRm tumors.
rPFS result appears favorable in non-HRR (double-negative) subgroup in exploratory sensitivity analyses.	No formal testing in large, incompletely-defined biomarker-negative subgroup. Positive subgroup results could be due to chance.
Incidence of anemia and transfusion requirements decreases over time, potentially due to dose modifications.	Added toxicity in patients receiving talazoparib with enzalutamide vs placebo with enzalutamide, that increases with patient age, may be less acceptable for biomarker-negative patients.
Both the PARPi and the ARPI in TALAPRO-2 differ from prior studies; are differences in the mechanism of action of talazoparib and/or enzalutamide sufficient to consider the results of TALAPRO-2 as distinct from those studies?	Trials of other PARP inhibitors did not support an all-comers indication. TALAPRO-2 also demonstrated differential efficacy based on biomarker status.

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6 Appendix

Table A1. FDA-Approved Therapies for the Treatment of mCRPC

Drug (+ ADT)	**Approved Indication**
Abiraterone	1+ line mCRPC (+ prednisone)
Docetaxel	1+ line mCRPC (+ prednisone)
Enzalutamide	1+ line mCRPC
Radium-223	1+ line mCRPC (with symptomatic bone mets and no known visceral mets)
Sipuleucel-T	1+ line mCRPC (asymptomatic or minimally symptomatic)
Cabazitaxel	2+ line mCRPC (+ prednisone) (post-docetaxel)
^{177}Lu-PSMA-617	2+ line PSMA(+) mCRPC (post-ARPI in patients considered appropriate to delay taxane-based therapy; and post-ARPI post-taxane)
Olaparib	1+ line *BRCA*m mCRPC (with abiraterone)
	2+ line, HRRm mCRPC as monotherapy (previously treated with enzalutamide or abiraterone)
Niraparib + abiraterone fixed-dose combination	1+line *BRCA*m mCRPC
Talazoparib	1+ line HRRm mCRPC (with enzalutamide)
Rucaparib (accelerated approval)	3+ line, *BRCA*m mCRPC (post-ARPI and post-taxane)
Pembrolizumab	2+ line, unresectable/metastatic MSI-H, dMMR, or TMB-H solid tumors (with disease progression following prior treatment and no satisfactory alternative treatment options)

Table A2. TALAPRO-2 Shifts in HRRm Gene Designations Based On Availability of Testing Results in Cohort 1 (HRRm-Unselected)

Gene mutation **(single-gene unless listed as co-occurring)**	**Prospective results** **(pre-randomization)** **N = 169**	**Prescreening/** **Screening results** **N = 266**	**All results** **N = 328**
BRCA (with/without other co-mutations)	59 (34.9%)	84 (31.6%)	92 (28.0%)
BRCA2	40 (23.7%)	48 (18.0%)	43 (13.1%)
BRCA1	7 (4.1%)	9 (3.4%)	9 (2.7%)

ATM	31 (18.3%)	61 (22.9%)	89 (27.1%)
ATR	1 (0.6%)	6 (2.3%)	5 (1.5%)
CDK12	44 (26.0%)	44 (16.5%)	42 (12.8%)
CHEK2	8 (4.7%)	25 (9.4%)	42 (12.8%)
FANCA	5 (3.0%)	6 (2.3%)	5 (1.5%)
MLH1	2 (1.2%)	1 (0.4%)	1 (0.3%)
MRE11A	1 (0.6%)	1 (0.4%)	1 (0.3%)
NBN	4 (2.4%)	5 (1.9%)	4 (1.2%)
PALB2	3 (1.8%)	4 (1.5%)	5 (1.5%)
RAD51C	2 (1.2%)	3 (1.1%)	3 (0.9%)
Co-occurring with at least one *BRCAm*	12 (7.1%)	27 (10.2%)	40 (12.2%)
Co-occurring without *BRCA*m	5 (3.0%)	26 (9.8%)	39 (11.9%)
No detected HRRm	4	N/A	N/A

Table A3: Summary of Overall Exposure and Safety on TALAPRO-2 Patients Receiving Talazoparib with Enzalutamide, by Age Group

Talazoparib with enzalutamide	Overall safety population N = 511	<65 N = 102	65 ≤ Age < 75 N = 239	≥ 75 N = 170
Median duration of exposure to talazoparib, months (range)	20 (0.07, 67)	26 (0.3, 58)	22 (0.1, 67)	15 (0.7, 64)
Median duration of exposure to enzalutamide, months (range)	22 (0.07, 67)	26 (2.0, 58)	25 (0.1, 67)	18 (1.3, 64)
Patients with any treatment- emergent AR	508 (99%)	102 (100%)	236 (99%)	170 (100%)
Patients with any grade 3-5 AR	407 (80%)	64 (63%)	190 (79%)	153 (90%)
Patients with any serious AR	227 (44%)	33 (32%)	105 (44%)	89 (52%)
Patients with fatal AR	18 (3.5%)	2 (2.0%)	8 (3.3%)	8 (4.7%)
Patients with discontinuations* due to AR	102 (20%)	12 (12%)	32 (13%)	58 (34%)
Patients with treatment delay* due to AR	333 (65%)	52 (51%)	156 (65%)	125 (74%)

Patients with dose reductions* due to AR	283 (55%)	35 (34%)	137 (57%)	111 (65%)

Abbreviations: AR, adverse reaction.

*Any study drug.