FDA is committed to ensuring digital accessibility for people with disabilities. We are continually improving the user experience for everyone and applying the relevant accessibility standards. At the time of initial posting on **May 16, 2025**, the attached **Event Materials** may not be fully accessible to users using assistive technology. A fully accessible version of the **Event Materials** is in preparation and will be posted as soon as it is ready. We regret any inconvenience that this may cause our readers.

Please let us know if you encounter accessibility barriers by contacting **Division of Advisory Committee and Consultant Management (DACCM)** at:

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

ONCOLOGIC DRUGS ADVISORY COMMITTEE
SPONSOR BRIEFING DOCUMENT

TALZENNA® (TALAZOPARIB)

INDICATION: IN COMBINATION WITH ENZALUTAMIDE FOR THE TREATMENT OF ADULT PATIENTS WITH METASTATIC CASTRATION-RESISTANT PROSTATE CANCER (mCRPC)

DATE FINALIZED: APRIL 18, 2025

ADVISORY COMMITTEE BRIEFING MATERIALS:
AVAILABLE FOR PUBLIC RELEASE

Pfizer Inc.
66 Hudson Boulevard East
New York, NY 10001-2192
(212) 733-2323

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDIX TABLES

LIST OF APPENDIX FIGURES

LIST OF ABBREVIATIONS

The following abbreviations and special terms are used in this briefing document:

Abbreviation or special term	Definition
AE	adverse event
AESI	adverse event of special interest
AJCC	American Joint Committee on Cancer
AML	acute myeloid leukemia
AR	androgen receptor
ARPI	androgen receptor pathway inhibitors
ATM	ataxia-telangiectasia mutated gene
ATR	ataxia-telangiectasia- and Rad3-related
BICR	blinded independent central review
BMI	body mass index
BRCA	breast cancer gene
BRCA1	breast cancer gene 1
BRCA2	breast cancer gene 2
BRCAm	breast cancer gene mutated/mutation
CDK12	cyclin-dependent kinase 12
CDx	companion diagnostic
CHEK2	checkpoint kinase 2
CI	confidence interval
CLcr	creatinine clearance
CR	complete response
CRPC	castration-resistant prostate cancer
CSPC	castration-sensitive prostate cancer
CTC	circulating tumor cells
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor deoxyribonucleic acid
DDR	DNA damage response
DSB	double-strand break
ECOG PS	Eastern Cooperative Oncology Group performance status
F1CDx	FoundationOne® companion diagnostic
F1LCDx	FoundationOne® liquid companion diagnostic
FANCA	FA Complementation Group A
FDA	Food and Drug Administration
GHS	Global Health Status
HR	hazard ratio
HRD	homologous recombination deficiency
HRR	homologous recombination repair
HRRm	homologous recombination repair gene mutated
IND	Investigational New Drug
ITT	intent-to-treat
IWRS	Interactive Web Response System
mCRPC	metastatic castration-resistant prostate cancer
mCSPC	metastatic castration-sensitive prostate cancer
MDS	myelodysplastic syndrome
MLH1	MutL protein homolog 1
MRE11A	Meiotic recombination 11
NBN	nibrin
NE	not estimable

Abbreviation or special term	Definition
NGS	next-generation sequencing
ODAC	Oncologic Drugs Advisory Committee
ORR	objective response rate
OS	overall survival
PALB2	partner and localizer of BRCA2
PARP	poly (ADP-ribose) polymerase
PARPi	poly (ADP-ribose) polymerase inhibitor
PFS2	progression-free survival on next line therapy
PRO	patient-reported outcomes
PSA	prostate-specific antigen
PSA50	50% decline in prostate-specific antigen
QD	once daily
QoL	quality of life
RAD51C	RAD51 Paralog C
rPFS	radiographic progression-free survival
SAE	serious adverse event
sNDA	supplemental New Drug Application
SSB	single-strand break
TEAE	treatment-emergent adverse event
US	United States
USPI	United States Prescribing Information

1.0 EXECUTIVE SUMMARY

1.1 Purpose of Convening the Oncologic Drugs Advisory Committee

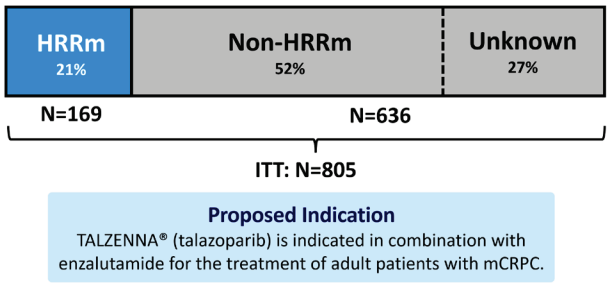
The Oncologic Drugs Advisory Committee (ODAC) has been convened to discuss the supplemental New Drug Application (sNDA) (NDA 211651/S-013, NDA 217439/S-003) for the proposed use of Talzenna® (talazoparib), a poly (ADP-ribose) polymerase (PARP) inhibitor, in combination with enzalutamide, for the treatment of adult patients with metastatic castration-resistant prostate cancer (mCRPC) unselected for homologous recombination repair (HRR) gene alterations (herein referred to as the HRRm-unselected population).

Despite therapeutic advances, mCRPC remains an aggressive and incurable disease with limited survival and substantial morbidity. Existing therapies have yielded only modest overall survival (OS) benefits in biomarker-unselected populations, and the majority of patients—approximately 75% [1]—do not have detectable HRR gene alterations and are therefore ineligible for current biomarker-restricted PARP inhibitor and androgen receptor pathway inhibitor (ARPI) combinations. This highlights a significant unmet clinical need for effective, broadly applicable first-line treatment strategies.

The focus of the sNDA and ODAC discussion is the final OS data from a prospectively defined, HRRm-unselected population of adult patients with mCRPC of the TALAPRO-2 study—referred to throughout this document as Cohort 1. This cohort was designed to reflect real-world clinical practice and evaluate the efficacy and safety of Talzenna in combination with enzalutamide (talazoparib + enzalutamide) compared to enzalutamide alone (placebo + enzalutamide) in mCRPC patients unselected for HRRm. Talzenna in combination with enzalutamide was approved by FDA on 20 June 2023, based on positive primary analysis results from Cohort 2, in the biomarker-selected population of patients with HRRm mCRPC (herein referred to as the HRRm-selected population).

In accordance with prior FDA feedback, randomization was prospectively stratified by HRRm status to ensure balance between treatment arms and to support prespecified subgroup analyses (Figure 1). Patients were categorized into two predefined strata: HRRm-positive (21%, N=169), and non-HRRm/HRRm-unknown (79%, N=636). The HRRm-unknown subgroup reflects patients whose HRRm status could not be ascertained, often due to limitations in genomic testing from tumor tissue—a common challenge in clinical practice.

Figure 1 Prospective Stratification by HRR Mutation Status in TALAPRO-2 Cohort 1—Basis for the Proposed Indication



HRRm = homologous recombination repair gene mutated; ITT = intent-to-treat; mCRPC = metastatic castration-resistant prostate cancer.

TALAPRO-2 met its primary endpoint, radiographic progression-free survival (rPFS) per blinded independent central review (BICR), in the intent-to-treat (ITT) population. The final analysis for OS, an alpha-protected key secondary endpoint, was conducted after an additional 2 years of follow-up beyond the primary analysis for rPFS. This mature analysis in the biomarker-unselected population demonstrated a statistically significant and clinically meaningful improvement in OS with talazoparib + enzalutamide compared with placebo + enzalutamide. The benefit was consistent across prespecified clinical and molecular subgroups, supporting the robustness of the treatment effect across the broader mCRPC population. These results, combined with a manageable safety profile, support the proposed indication in patients with mCRPC, unselected for HRRm, building upon the existing approval of Talzenna in combination with enzalutamide for patients with HRRm mCRPC.

Talazoparib enhances the antitumor activity of enzalutamide through complementary mechanisms that disrupt DNA repair and androgen receptor (AR) signaling [2], supporting its efficacy in patients unselected for HRRm. As the most potent PARP trapper among approved inhibitors, talazoparib forms stable PARP-DNA complexes that generate replication stress and cytotoxicity, contributing to antitumor effects even in HRR-proficient tumor cells [3].

In addition, enzalutamide suppresses expression of HRR genes such as breast cancer gene 1 (BRCA1), functionally reducing DNA repair capacity and sensitizing tumor cells to PARP inhibition [4-6]. Conversely, PARP1 activity is required for full AR transcriptional function; thus, PARP inhibition further attenuates AR signaling [7, 8]. These bidirectional effects support a biologically plausible mechanism by which the combination of talazoparib and enzalutamide exerts clinical benefit in a biomarker-unselected mCRPC population.

Together, the clinical efficacy, safety profile, and biologic rationale support the proposed expansion of the Talzenna indication. The ODAC discussion will focus on whether the data from Cohort 1 support a favorable benefit-risk assessment for use of this combination in patients with mCRPC unselected for HRR gene alterations.

1.2 Summary of Major Efficacy Findings From TALAPRO-2

Clinically Meaningful Efficacy in the Proposed Indication: HRRm-unselected mCRPC (Cohort 1)

The study met its primary endpoint at the primary analysis, demonstrating a statistically significant and clinically meaningful improvement in rPFS per BICR (Section 4.1).

In the final analysis for the key secondary endpoint of OS, treatment with talazoparib + enzalutamide demonstrated a statistically significant and clinically meaningful improvement in OS compared with placebo + enzalutamide (data cutoff date: 03 September 2024).

- The final analysis for OS showed a hazard ratio (HR) of 0.796 (95% confidence interval [CI]: 0.661, 0.958; 2-sided p=0.0155), representing a 20.4% reduction in the risk of death.
- Median OS was 45.8 (95% CI: 39.4, 50.8) months for the talazoparib + enzalutamide arm versus 37.0 (95% CI: 34.1, 40.4) months for the placebo + enzalutamide arm, an 8.8-month improvement.

- An updated descriptive rPFS analysis conducted at the time of the OS final analysis showed a 33.3% reduction in the risk of progression or death (HR=0.667; 95% CI: 0.551, 0.807), with median rPFS of 33.1 (95% CI: 27.4, 39.0) versus 19.5 (95% CI: 16.6, 24.7) months, confirming the durability of benefit.

A consistent treatment effect in OS and rPFS was observed across prespecified and exploratory clinical and molecular subgroups, including patients without HRR mutations.

- Median survival was similar across HRRm, non-HRRm, and HRRm-undetermined groups (i.e., patients with missing, inconclusive, or unevaluable HRR mutation status) who received the combination of talazoparib + enzalutamide (Sections 4.1.7.1 and 4.1.7.2).
- A consistent treatment effect in both OS and rPFS was observed in the most stringently defined non-HRRm subgroup—patients without detectable HRR alterations by both tumor and plasma (circulating tumor deoxyribonucleic acid [ctDNA]) testing (Section 4.1.7.3).

These findings demonstrate that the benefit of talazoparib + enzalutamide extends beyond biomarker-defined populations and support the use of the combination for treatment of patients with mCRPC unselected for HRR gene alterations.

Supportive Efficacy in the Current Indication: HRRm-Selected (Cohort 2)

In Cohort 2 (N=399), which enrolled patients with centrally confirmed HRRm, talazoparib + enzalutamide significantly improved both OS and rPFS compared with placebo + enzalutamide (Section 4.2).

- The final OS analysis showed an HR of 0.622 (95% CI: 0.475, 0.814); 2-sided p=0.0005, reflecting a 37.8% reduction in the risk of death and a 14-month improvement in median OS (45.1 vs. 31.1 months).
- A descriptive rPFS analysis conducted at the same time point (with 2 years of additional follow-up) demonstrated a 53.2% reduction in the risk of progression or death (HR=0.468; 95% CI: 0.359, 0.612), with a median rPFS which more than doubled from 12.3 to 30.7 months.
- The treatment effect was consistent across prespecified and exploratory subgroups, reinforcing the clinical benefit of talazoparib + enzalutamide in biomarker-selected patients and supporting the approved indication.

1.3 Summary of Major Safety Findings From TALAPRO-2

In Cohort 1 of TALAPRO-2, the safety findings with the combination were consistent with known profiles for talazoparib and enzalutamide, with no new safety signals identified after an additional 2 years of follow-up from the primary analysis (Section 5.0).

- Hematologic toxicities, particularly anemia, were common and manageable with dose modifications and supportive care, with few patients permanently discontinuing talazoparib due to anemia (8.5%).
- Both anemia and transfusions occurred early in the course of treatment, with decreasing incidence over time, thereby demonstrating that anemia was manageable with dose

modification and supportive care. Grade 3 anemia did not negatively impact global health status or quality of life, and no fatal anemia events were observed.

- Hematologic toxicities can be monitored with routine complete blood counts; recommendations for monitoring hematologic toxicities and dose modifications based on hemoglobin levels are reflected in the current Talzenna® United States Prescribing Information (USPI). With an additional 2 years of follow-up for safety, there have been no new cases of myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML; 1 case each previously reported at the primary analysis of TALAPRO-2).

1.4 Benefit-Risk Assessment Supports Proposed Indication in mCRPC

The benefit-risk profile for talazoparib + enzalutamide supports the proposed expansion of the current indication to include all patients with mCRPC, unselected for HRR gene alterations. In a prospectively randomized, biomarker-unselected population reflective of real-world clinical practice, the combination demonstrated statistically significant and clinically meaningful improvements in both rPFS (primary endpoint) and OS (key secondary endpoint).

The observed OS benefit represents the first statistically significant survival improvement in a randomized Phase 3 trial with an active comparator in the first-line mCRPC setting. These results were observed in the ITT population and were consistent across prespecified subgroups, including those defined by clinical and genomic characteristics, including patients without detectable HRR gene alterations by both tumor tissue and ctDNA testing.

The efficacy results are supported by a manageable safety profile, with no new safety signals identified after an additional 2 years of follow-up. Hematologic toxicities, particularly anemia, were generally observed early in treatment and declined in incidence over time with appropriate management.

Taken together, the data support the use of talazoparib in combination with enzalutamide for the treatment of patients with mCRPC, unselected for HRR gene alterations.

2.0 DESCRIPTION OF CLINICAL SETTING

2.1 Overview of Prostate Cancer

Prostate cancer is the second leading cause of cancer death in men worldwide. The American Cancer Society estimates that in 2025, up to 313,780 men in the United States will be diagnosed with prostate cancer, and approximately 35,770 will die of the disease [1, 9]. Prostate cancer typically progresses through a series of characteristic clinical states that represent both the natural history of the disease and response/resistance to treatment [10]. Prostate cancer may present as localized disease, locally advanced disease, or metastatic disease at initial diagnosis.

While localized disease may be amenable to curative primary intervention such as surgery or radiation therapy, the disease will recur and/or progress in approximately one-third of patients [11, 12]. Early in the disease, prostate cancers typically need androgens to survive; therefore, treatments that decrease androgen levels or block androgen activity can inhibit their growth. Initially, most patients are sensitive to androgen deprivation (castration/hormone-sensitive). Those whose disease recurs after primary treatment, and those who present with more advanced or metastatic disease, are typically treated with androgen deprivation therapy, with or without an ARPI.

Resistance to androgen deprivation therapy eventually develops over time, resulting in castration-resistant prostate cancer (CRPC). This is characterized by disease progression despite castrate serum testosterone levels (<50 ng/dL) [13] and represents an advanced disease stage associated with increased therapeutic challenges and poor prognosis, particularly once metastasis occurs.

2.2 Current Treatment Landscape

Currently approved therapies for the treatment of mCRPC (dependent on prior treatment exposure and/or biomarker status) include ARPIs, taxane-based chemotherapy, immunotherapies, radiopharmaceuticals, and PARP inhibitors, alongside ongoing ADT [14]. For first-line treatment of mCRPC, ARPIs, such as enzalutamide or abiraterone, are the most commonly used therapies [15]. Real-world data indicate treatment intensification with ARPIs in the castration-sensitive prostate cancer (CSPC) setting is increasing, yet approximately 50% of mCRPC patients remain ARPI-naive at diagnosis of mCRPC [16, 17], and only half receive subsequent treatment after progression on first-line therapy [18].

Biomarker testing has become increasingly important for identifying patients with poor prognosis and for guiding first-line use of PARP inhibitors in those with breast cancer gene mutations (BRCAm) or other HRR mutations [14, 19, 20]. These mutations may also have implications for hereditary cancer risk and family counseling. However, barriers to testing—such as tissue availability, access issues, and technical challenges with bone biopsies—can limit identification of eligible patients. Several PARP inhibitors are approved in combination with ARPIs for genomically-selected patients with mCRPC: talazoparib + enzalutamide for HRRm patients (TALAPRO-2 trial) [2, 21], olaparib + abiraterone with prednisone or prednisolone for BRCAm patients (PROpel trial) [22], and niraparib + abiraterone acetate with prednisone for BRCAm patients (MAGNITUDE trial) [23].

2.3 Unmet Need

Survival with prostate cancer declines considerably upon the development of metastases, with a 5-year survival rate of only 37% [24]. Patients progressing to mCRPC experience significant morbidity, including pain, cachexia, and deterioration in quality of life [25-28]. Despite recent advancements, mCRPC remains aggressive and incurable, with a reported median OS consistently less than 36 months among US patients [18, 22, 29-34].

Although genomic sequencing—including testing for HRR mutations—is increasingly important for prognostication and for identifying patients who may benefit from targeted therapies, real-world data indicate that testing rates remain low and typically occur late in the disease course [35-37]. Recent studies suggest that genetic testing rates have increased from <20% to nearly 50% of mCRPC patients in the United States [36], coinciding with the emergence of PARP inhibitor therapies. However, significant disparities persist in access to genomic testing, particularly among patients with Medicaid, lower functional status, older age, and those treated in community or rural settings [35]. Moreover, bone lesions—the most common metastatic sites in prostate cancer—pose a clinical challenge for obtaining sufficient tissue for genomic testing, further limiting the timely identification of patients eligible for precision therapies [37]. Overcoming these structural and logistical barriers is critical to expanding equitable access to effective targeted treatments [37].

Clinical trials evaluating current therapies highlight limitations in efficacy and underscore the urgent need for more effective treatment strategies. Most patients are treated with an ARPI, including enzalutamide or abiraterone. Their approval occurred more than a decade ago, based on the Phase 3 trials PREVAIL and COU-AA-302. The PREVAIL trial evaluated enzalutamide + gonadotropin-releasing hormone (GnRH) therapy and demonstrated an OS improvement versus placebo + GnRH therapy: median OS of 35.3 versus 31.3 months; HR 0.77; p=0.0002 [38]. Similarly, the COU-AA-302 trial demonstrated modest but statistically significant OS improvement with abiraterone acetate + prednisone compared to placebo + prednisone in chemotherapy-naive mCRPC patients (34.7 vs. 30.3 months; HR 0.81; p=0.0033) [30].

Recent trials investigating combination therapies have yielded minimal or statistically non-significant OS improvements over ARPI alone, further emphasizing limitations of current therapies in HRR-unselected populations. For example, the Alliance A031201 trial (enzalutamide + abiraterone/prednisone) showed no meaningful OS advantage compared to enzalutamide alone (34.2 vs. 32.7 months; HR 0.89; p=0.03) [31]. The ACIS trial (apalutamide + abiraterone/prednisone) also reported no meaningful OS improvement versus placebo + abiraterone/prednisone (36.2 vs. 33.7 months; HR 0.95, p=0.50) [39]. The PROpel trial (olaparib + abiraterone vs. placebo + abiraterone) demonstrated numerically longer but statistically non-significant OS improvement in unselected mCRPC patients (42.1 vs. 34.7 months; HR 0.81, p=0.054), with observed benefit largely limited to BRCAm subgroups (OS HR 1.06 for non-BRCA patients by two tests) [22]. In a subgroup analysis conducted by FDA, the non-BRCAm subgroup—composed of patients confirmed to be BRCA-negative by both ctDNA and tissue assays—demonstrated an OS HR of 1.06 (95% CI: 0.81, 1.39), favoring the control arm [40]. The PEACE-3 trial (radium-223 + enzalutamide) may offer potential benefit for select patients with bone-only disease; however, mature OS data remain pending [41].

These persistent challenges underscore the substantial unmet clinical need, especially among the approximately 75% of patients who do not harbor HRR gene alterations [42]. Novel therapeutic approaches that do not rely exclusively on genomic biomarker selection, such as the combination of talazoparib and enzalutamide, represent an opportunity to substantially improve clinical outcomes in the first-line mCRPC treatment setting.

2.4 The Role of PARP in DNA Repair

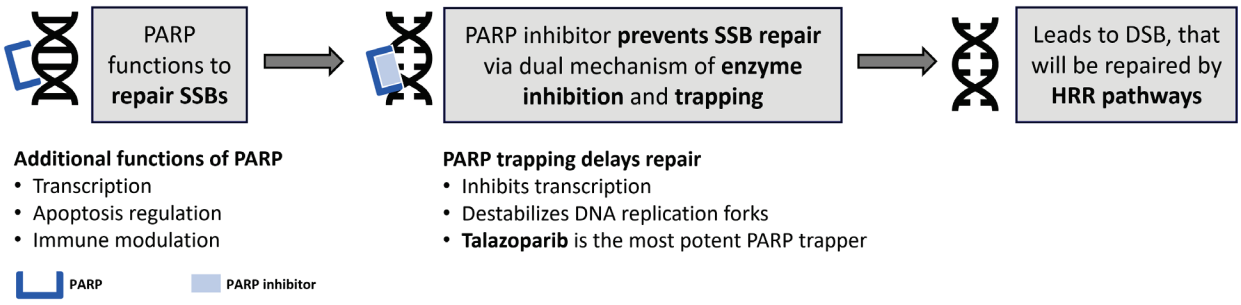
Given the therapeutic relevance of targeting HRR pathways in mCRPC, it is important to understand the biologic role of PARP enzymes in DNA repair. PARPs comprise a family of enzymes essential to the DNA damage response (DDR). They facilitate the repair of single-strand breaks (SSBs), thereby preventing their progression into more harmful double-strand breaks (DSBs). Among the PARP family, PARP1 and PARP2 are the most extensively characterized in terms of DNA repair functions, including the detection of DNA damage [43], recruitment of DNA repair factors [44], and regulation of alternative DNA repair pathways [45].

2.4.1 PARP Inhibition and Synthetic Lethality

PARP1 detects SSBs and recruits repair proteins to seal the break using DNA ligases [46] (Figure 2). If left unrepaired, SSBs can progress into more dangerous DSBs during DNA replication [46]. HRR is one of the major pathways within the DDR that repairs DSBs [47]. Key HRR genes include BRCA1, breast cancer gene 2 (BRCA2), ataxia-telangiectasia mutated gene (ATM), and RAD51 Paralog C (RAD51C), which help maintain genomic stability [47]. HRR-deficient cells (e.g., BRCAm tumors) struggle to repair DSBs properly, making them vulnerable to treatments that further disrupt DNA repair (e.g., PARP inhibitors) [48].

PARP inhibitors block the repair of SSBs, causing them to escalate into DSBs, which HRR-deficient cancer cells cannot adequately repair—a concept termed “synthetic lethality,” which underpins the mechanism of action of this therapeutic class in oncology [48].

Figure 2 Antitumor Activity of PARP Inhibitors



DSB = double-strand break; HRR = homologous recombination repair; PARP = poly (ADP-ribose) polymerase; PARP = poly (ADP-ribose) polymerase; SSB = single-strand break.

In addition, trapping of catalytically inhibited PARP on DNA—resulting in replication fork collapse and disruption of transcription—has emerged as a key contributor to the efficacy of PARP inhibitors, including broadening efficacy to some HRR-proficient cancers [49, 50].

Talazoparib is differentiated from other clinically approved PARP inhibitors, as it is the most potent PARP trapper [51, 52]. Biophysical analyses demonstrated that catalytic inhibition of PARP by talazoparib or olaparib does not promote the release of inhibited PARP complexes from DNA, while catalytic inhibition of niraparib, rucaparib, and veliparib promotes release of such complexes from DNA, likely contributing to their relatively low potency in PARP trapping [53]. The relatively poor PARP trapping by niraparib may contribute to the generally weak efficacy seen in MAGNITUDE outside of BRCAm, most notably for CDK12m tumors (e.g., rPFS, HR=0.89 [95% CI: 0.34, 2.36]) [54], contrasting with TALAPRO-2 (e.g., rPFS by BICR, HR=0.49 [95% CI: 0.23, 1.02]) [21]. Detailed by-HRR gene breakdowns of efficacy beyond BRCAm have not been presented to date for PROpel, although it is noted that the OS HR for PROpel patients without BRCAm by two tests was 1.06 in favor of the abiraterone control [55].

The central importance of PARP trapping to the broad efficacy of talazoparib is supported by the identification of emergent PARP1 binding sites or truncating mutations predicted to abolish talazoparib binding to PARP1 as a frequent potential mechanism of acquired resistance to talazoparib in the Phase 2 TALAPRO-1 mCRPC study [56]. Such PARP1 mutations have not been reported clinically for other PARP inhibitors.

A recent mechanistic analysis [3] suggests that PARP trapping is primarily governed by the dissociation rate of the inhibitor, rather than physical stalling of PARP1 on DNA. Instead, PARP trapping reflects a high likelihood of PARP1 re-binding to damaged DNA in the absence of competing DNA-binding protein recruitment. Critically, talazoparib is substantially more potent in PARP1 trapping than other PARP inhibitors, including olaparib, niraparib, rucaparib, and veliparib, and in induction of the double-stranded DNA break marker γH2AX [50] (Figure 3).

Figure 3 Potent PARP Trapping by Talazoparib Is Associated With High Accumulation of DNA DS-Break Marker γH2AX

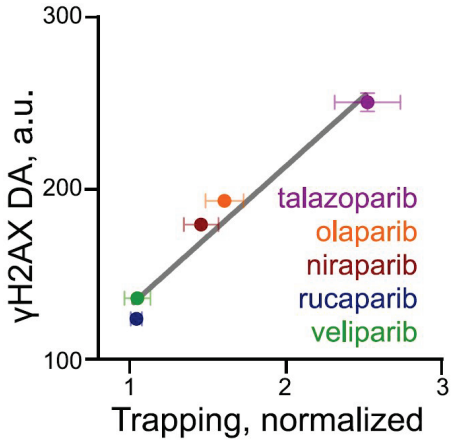
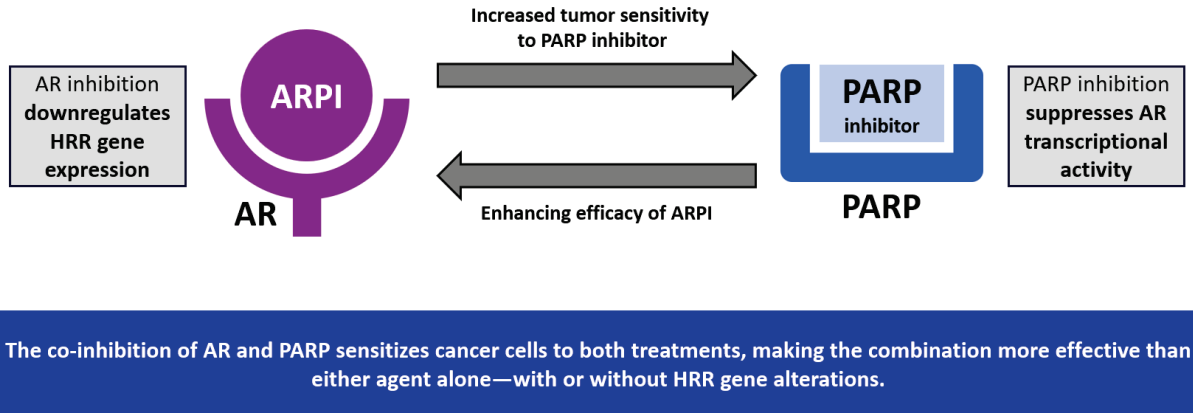


Image correlation spectroscopy DA of γH2AX aggregation in HT1080 cells treated with 1 µM PARP inhibitor overnight versus PARP1 trapping, with linear fit (gray line). Shown are average with SEM; trapping: n = 5; DA: n ≥ 536 cells; 3 biological repeats. DA = degree of aggregation; DS = double-strand; PARP = poly (ADP-ribose) polymerase; SEM = standard error of the mean.
Reprinted from *Cell Chemical Biology*, 31(7), Gopal, A.A., et al., PARP trapping is governed by the PARP inhibitor dissociation rate constant, 1373-1382 e10, Copyright 2024 with permission from Elsevier [3].

2.4.2 Biologic Rationale for Combining Talazoparib With Enzalutamide

Figure 4 illustrates the complementary mechanism of action of talazoparib (a PARP inhibitor) and enzalutamide (an AR inhibitor) in mCRPC [57]. The combination therapy disrupts tumor survival pathways at multiple levels, leading to enhanced tumor cell death.

Figure 4 Biologic Rationale of PARP Inhibitor and ARPI Combination



AR = androgen receptor; ARPI = androgen receptor pathway inhibitor; HRR = homologous recombination repair; PARP = poly (ADP-ribose) polymerase.

There is a three-fold rationale for combining PARP inhibitors with ARPI in CRPC, with or without HRRm, based on research in nonclinical models and clinical samples:

1. **Androgen receptor pathway inhibition suppresses the expression of HRR genes, including BRCA1, thereby increasing sensitivity to PARP inhibition [4-6].** In an analysis of 131 primary prostate cancer tumors, AR transcriptomic signatures were positively correlated with DNA repair gene expression [4]. Similarly, experimental studies in prostate cancer cells have shown that AR directly promotes the transcription of multiple DNA repair genes; treatment with antiandrogens reduces classical non-homologous end joining activity, potentially shifting reliance toward HRR pathways [4].

   Asim et al. (2017) demonstrated a direct requirement for AR signaling in maintaining HRR gene expression and functional DNA repair in prostate cancer cells. In ex vivo models, the combination of enzalutamide and PARP inhibition produced a greater antiproliferative effect than either agent alone [5].

   Further supporting these findings, Li et al. (2017) reported that CRPC cells exhibit increased expression of HRR genes, including BRCA1 [6]. Enzalutamide treatment suppressed these genes, inducing a state of homologous recombination deficiency and sensitizing cells to PARP inhibition [6].

   Together, these studies support the concept that AR signaling promotes HRR gene expression and that AR-directed therapies may enhance the susceptibility of prostate cancer cells to PARP inhibition.

2. **PARP1 activity is necessary for maximal AR function.** PARP inhibition not only reduces AR signaling but also enhances sensitivity to androgen receptor pathway inhibition [7, 8]. In

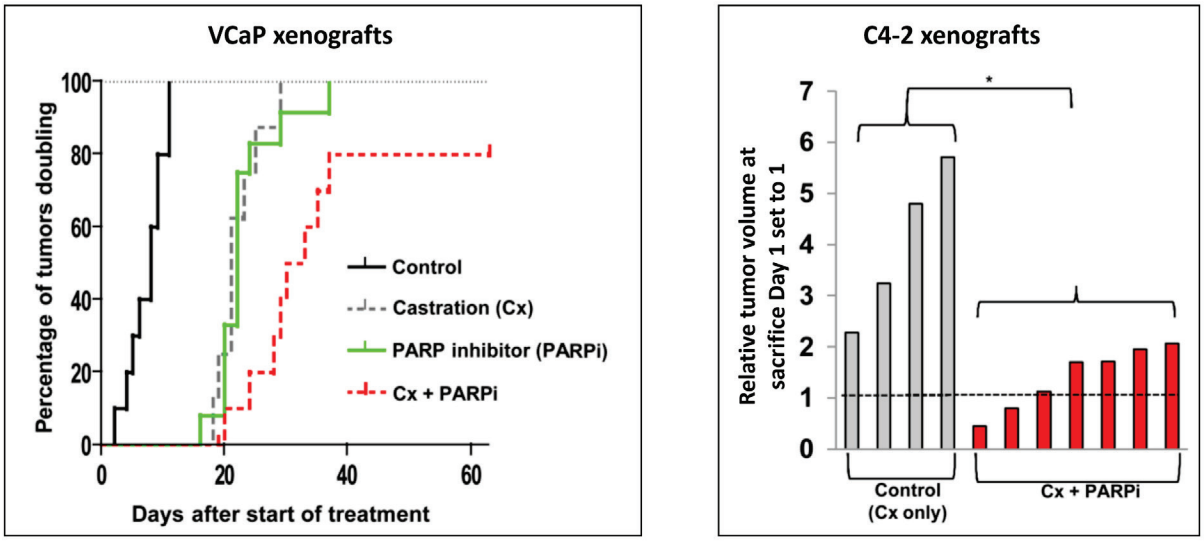
a mouse embryonic fibroblast model, Schiewer et al. (2012) demonstrated that the catalytic activity of PARP is required for full AR transcriptional function. In the VCaP xenograft model, combining castration with PARP inhibition significantly delayed tumor progression compared to either treatment alone, with similarly encouraging effects observed in the C4-2 model (Figure 5) [8].

Further mechanistic insight comes from studies showing that AR splice variants, which contribute to resistance in advanced prostate cancer, interact with both PARP1 and PARP2 and depend on their catalytic function to drive transcriptional activity [7].

Consistent with the role of PARP in facilitating AR signaling, data from TALAPRO-2 indicate that baseline AR tumor transcriptomic signatures—including expression of multiple AR target genes—were predictive of rPFS benefit in Cohort 1 for patients treated with talazoparib + enzalutamide but not for those treated with placebo + enzalutamide (Figure 6) [58].

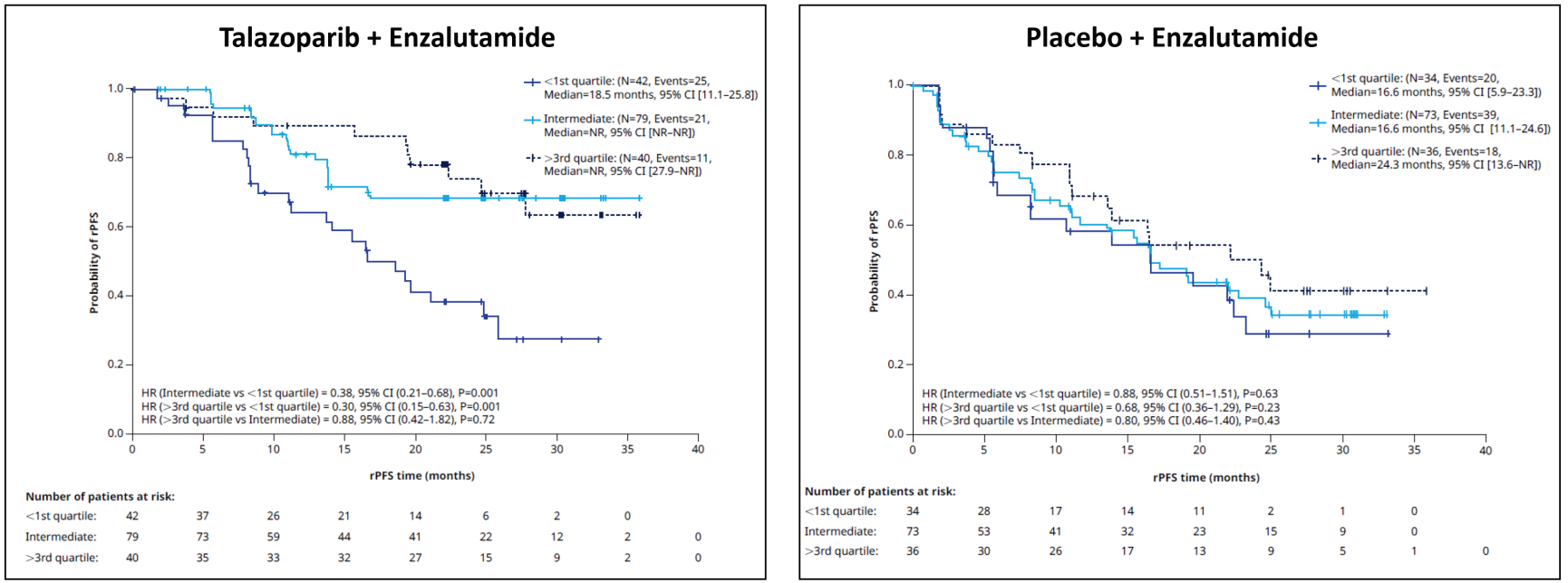
Together, these findings support the rationale that PARP inhibition may potentiate AR signaling suppression by enzalutamide.

Figure 5 AR Pathway Suppression (via Castration) Combined With PARP Inhibition Results in Enhanced Efficacy



VCaP: The combined treatment group is significantly different from the individual treatment groups, as determined by log-rank (Mantel–Cox) analysis. C4-2: Statistical significance was determined using Student *t* test. *p<0.05.
AR = androgen receptor; PARP = poly (ADP-ribose) polymerase; PARPi = poly (ADP-ribose) polymerase inhibitor; VCaP = vertebral-cancer of the prostate.
Reprinted from *Cancer Discovery*, Copyright 2012, 2(12), 1134-1149, Schiewer MJ, et al., Dual roles of PARP-1 promote cancer growth and progression, with permission from AACR [8].

Figure 6 Tumor Androgen Response Gene Expression Signature Is Associated With rPFS Benefit for Talazoparib + Enzalutamide

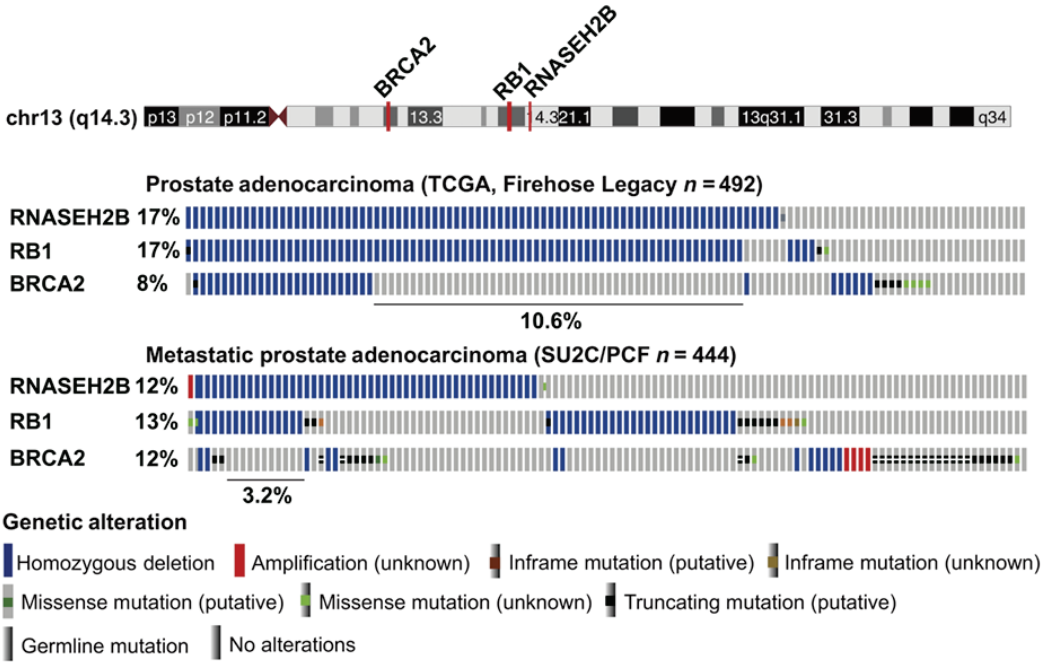


HR reference level is <1st quartile for comparison of Intermediate vs <1st quartile and >3rd quartile vs <1st quartile, and reference level is Intermediate for the comparison of >3rd quartile vs Intermediate. 2-sided p value is from log-rank test. A Cox proportional hazard model with two main effects (continuous gene expression and treatment arm), and an interaction effect (continuous gene expression by treatment arm) was fit to assess the significance of the interaction term. The p value associated with the interaction term is 0.19, calculated by likelihood ratio test.
CI = confidence interval; HR = hazard ratio; N = number of patients; NR = not reached; rPFS = radiographic progression-free survival.
Reprinted from Liu G, et al. Identification of a novel agnostic predictive multiomic signature via elastic net/machine learning in TALAPRO-2, a phase 3 study of talazoparib + enzalutamide vs placebo + enzalutamide as first-line treatment in patients with metastatic castration-resistant prostate cancer [poster]. Presented at the AACR 2024 Annual Meeting; April 5-10, 2024; San Diego, CA, USA. Abstract CT231 [58].
Provided courtesy of Glenn Liu, MD, University of Wisconsin Carbone Cancer Center, Madison, Wisconsin.

3. **Clinical resistance to AR blockade is sometimes driven by co-deletion of RB1 and BRCA2, a genomic alteration associated with increased sensitivity to PARP inhibition [59].** RNASEH2B, a gene whose deficiency also sensitizes cells to PARP inhibitors, is located in close proximity to RB1 and BRCA2 on the genome. As a result, RNASEH2B is frequently homozygously co-deleted with these genes—observed in approximately 8% of prostate adenocarcinoma cases in The Cancer Genome Atlas (TCGA) dataset Figure 7 [60].

   This pattern of co-deletion suggests a potential therapeutic vulnerability: tumors harboring deletions in RB1, BRCA2, and/or RNASEH2B may be particularly susceptible to combination treatment with talazoparib and enzalutamide. Such a combination may eliminate or suppress the expansion of enzalutamide-resistant clones in which resistance is mediated by RB1 loss.

Figure 7 BRCA2 and/or RNASEH2B Are Frequently Co-Deleted With RB1 in Prostate Cancer



Genomic alterations of *RNASEH2B*, *RB1*, and *BRCA2* genes on chromosome 13q in primary (TCGA cohort) and metastatic (SU2C/PCF cohort) prostate tumors. The *RNASEH2B/RB1* co-deletion accounts for 10.6 and 3.2% of cases in each cohort, respectively.
From Miao C, et al. *RB1* loss overrides PARP inhibitor sensitivity driven by *RNASEH2B* loss in prostate cancer. *Sci Adv.* 2022;8(7):eabl9794. doi: 10.1126/sciadv.abl9794. Reprinted with permission from AAAS [60].

Notably, the above-mentioned preclinical and clinical evidence suggest that co-inhibition of AR and PARP is a strategy that may provide therapeutic benefit in tumors without HRR gene alterations, broadening the potential mCRPC patient population that could derive clinical benefit from this combination.

2.4.3 Distinct Mechanistic and Clinical Rationale for Talazoparib Plus Enzalutamide Versus Other PARP Inhibitor Combinations

Additional evidence supporting the differentiated efficacy of talazoparib + enzalutamide beyond HRRm tumors is provided by exploratory clinical biomarker analyses of TALAPRO-2 using tumor transcriptomic data and screening ctDNA, retrospectively analyzed using FoundationOne® liquid companion diagnostic testing (F1LCDx), which identified multiple genomic and multiomic signatures associated with efficacy irrespective of HRRm gene alteration status. These include TMPRSS2 ERG and RB1 mutations [61] and AR target gene expression signatures [58]. A 33-feature (3 genes, 30 transcripts) elastic net signature was identified that was predictive of rPFS with talazoparib + enzalutamide [58]: TP53 and AR short variant alteration status were each prognostic and associated with worse rPFS. Expression of multiple AR target genes, including ALDH1A3 (top selected feature) and CAMKK2, was positively associated with rPFS. For talazoparib + enzalutamide, this multiomic signature was predictive of rPFS irrespective of HRR gene alterations, and to a lesser extent for placebo + enzalutamide. Strikingly, none of the 12 HRR genes used for stratification in TALAPRO-2 were included in the signature. Overall, these additional biomarker analyses also support the potential for efficacy of talazoparib + enzalutamide extending beyond HRR12m tumors.

In addition, enzalutamide and abiraterone acetate have different mechanisms of action, which may contribute to observed differences in combination with PARP inhibitors. Enzalutamide is an AR inhibitor that acts on different steps in the AR signaling pathway [62]. Enzalutamide has been shown to competitively inhibit androgen binding to AR and, consequently, inhibits nuclear translocation of AR and their interaction with DNA. This mechanism of action has been demonstrated to cooperate with PARP inhibition in preclinical models, underpinning the biologic rationale for extension of activity beyond tumors that bear HRR gene alterations. Clinical evidence of benefit with talazoparib + enzalutamide in patients with non-HRRm tumors has also been convincingly demonstrated in TALAPRO-2, with improvements in rPFS, OS, and other secondary endpoints.

In contrast, abiraterone acetate is converted in vivo to abiraterone, an androgen biosynthesis inhibitor, that inhibits 17 α-hydroxylase/C17,20-lyase (CYP17) [63]. This enzyme is expressed in testicular, adrenal, and prostatic tumor tissues and is required for androgen biosynthesis. Abiraterone augments the activity of androgen deprivation therapy, which decreases androgen production in the testes, by also decreasing androgen production in the adrenals and tumor. This "more potent" androgen deprivation approach has not been demonstrated to cooperate or synergize with PARP inhibition in preclinical models and has failed to demonstrate clinical activity in combination with PARP inhibitors in patients with non-HRRm tumors in multiple Phase 3 clinical trials (PROpel, MAGNITUDE).

In summary, the biologic rationale for the combination of talazoparib and enzalutamide is distinct from the other PARP inhibitor and abiraterone acetate combinations. The consistent treatment effect of talazoparib + enzalutamide across prespecified and exploratory subgroups in TALAPRO-2 demonstrates clinical proof of principle of the biologic rationale for this combination to benefit patients with or without HRR gene alterations.

3.0 PRODUCT OVERVIEW

3.1 Indication

3.1.1 Currently Approved mCRPC Indication

Talzenna (talazoparib) is indicated in combination with enzalutamide for the treatment of adult patients with HRR gene-mutated mCRPC.

3.1.2 Proposed mCRPC Indication

The Sponsor submitted an sNDA based on updated efficacy and safety results, including the final OS analysis, from the TALAPRO-2 trial to support the following proposed indication:

Talzenna (talazoparib) is indicated in combination with enzalutamide for the treatment of adult patients with mCRPC.

3.2 Dosage and Administration

For patients with HRRm mCRPC, the approved dose of talazoparib is 0.5 mg once daily (QD) in combination with enzalutamide 160 mg QD. For patients with mild renal impairment (creatinine clearance [CLcr] 60 to 89 mL/min), no dose adjustment is recommended. For patients with moderate renal impairment (CLcr 30 to 59 mL/min), the recommended dose of talazoparib is 0.35 mg QD in combination with enzalutamide. For patients with severe renal impairment (CLcr 15 to 29 mL/min), the recommended dose of talazoparib is 0.25 mg QD in combination with enzalutamide.

There are no proposed changes to the approved dosing regimen for patients with mCRPC.

3.2.1 Patient Selection

In the United States, patients with HRRm mCRPC are selected for treatment with talazoparib + enzalutamide based on the presence of alterations in genes directly or indirectly involved in HRR (ATM, ATR, BRCA1, BRCA2, CDK12, CHEK2, FANCA, MLH1, MRE11A, NBN, PALB2, or RAD51C), based on the current indication. HRR mutation status has prognostic importance and should be taken into consideration when making treatment decisions in order to optimize patient care. Therefore, while the proposed indication is for adult patients with mCRPC unselected for HRRm, genomic testing is expected to remain a critical and complementary component of treatment planning.

3.3 Regulatory History

The FDA approval of Talzenna in combination with enzalutamide for HRRm mCRPC (20 June 2023) was based on Cohort 2 of the TALAPRO-2 study, which enrolled patients with HRR gene mutations. The focus of the sNDA and ODAC discussion is the final OS data from Cohort 1, supporting the proposed indication of patients with mCRPC, unselected for HRR gene alterations. Key regulatory interactions leading up to the HRRm mCRPC approval and those supporting the current application are summarized in Table 1 and Table 2, respectively.

Table 1 Key US FDA Regulatory History Prior to HRRm mCRPC Approval

IND / NDA Date	Activity
July 2017 IND 129642	Type B Pre-Phase 3 Meeting was held to discuss the proposed talazoparib mCRPC development plan. • Agreement was reached on key aspects of Study C3441021 TALAPRO-2, including the primary endpoint of rPFS, patient population, control arm and overall study design.
March 2019 IND 129642	Type B Meeting was held to discuss key elements of the revised Phase 3 C3441021 TALAPRO-2 study. • Agreement was reached on addition of a new cohort of mCRPC participants without selection for HRR deficiencies (Cohort 1 "HRRm-unselected population") to the previously proposed HRRm-selected population (Cohort 2), with appropriate modifications to allow independent testing of hypotheses in both populations while maintaining an overall 1-sided alpha of 0.025. • Based on meeting discussion, the protocol was also revised to introduce the use of liquid biopsies to assess HRR status and add the concordance of HRR testing results between liquid and tissue biopsies as an exploratory endpoint.
August to December 2021 IND 129642	FDA Written Responses were provided for a Type C Meeting agreeing on the format and content of the planned sNDA in August 2021. FDA also provided responses to Sponsor follow-up questions in November and December 2021. • Agreement was reached that use of retrospective ctDNA testing to reduce the proportion of HRR-unknown patients was reasonable but retrospective classification of HRR-mutation status would be exploratory only and may not be used to support labeling for a CDx.
November 2022 IND 129642	FDA Preliminary Comments were provided for a Type B Pre-sNDA Meeting. Sponsor responses to the preliminary comments were submitted and the following feedback was provided during the meeting: • OS is both an efficacy and a safety endpoint and an rPFS benefit alone in the context of a potential decrement in OS in the non-HRR subgroup is unlikely to support a favorable benefit-risk assessment for the HRRm-unselected population (Cohort 1) at the interim analysis. • FDA requested more mature data and supportive results from OS data in the stratified subgroup of patients without HRR deficiency.
December 2022 NDA 211651 (S-010)	sNDA submitted based primarily on data from the pivotal Phase 3 study C3441021 (TALAPRO-2).
February 2023 NDA 211651 (S-010)	Priority Review granted by FDA.
20 June 2023 NDA 211651 (S-010)	FDA approval for talazoparib in combination with enzalutamide for adult patients with HRR gene-mutated mCRPC. Issuance of Postmarketing Commitments (PMCs):

IND / NDA Date	Activity
	1. PMC 4460-1: Complete the trial, "A phase 3, randomized, double-blind, placebo-controlled study of talazoparib with enzalutamide in metastatic castration-resistant prostate cancer (TALAPRO-2)," and include final OS analyses of patients with HRRm mCRPC (including HRRm patients enrolled in Cohort 1 and Cohort 2) and patients in Cohort 1 (unselected for HRRm). 2. PMC 4460-2: Conduct an analytical and clinical validation study using clinical trial data, adequate to support the availability of an *in vitro* diagnostic device using tissue samples that is essential to the safe and effective use of talazoparib for patients diagnosed with mCRPC, whose tumors harbor Homologous Recombination Repair (HRR) gene alterations, with HRR genes defined as: ATM, ATR, BRCA1, BRCA2, CDK12, CHEK2, FANCA, MLH1, MRE11A, NBN, PALB2 and RAD51C. 3. PMC 4460-3: Conduct an analytical and clinical validation study using clinical trial data, adequate to support the availability of an *in vitro* diagnostic device using ctDNA samples from plasma that is essential to the safe and effective use of talazoparib for patients diagnosed with mCRPC, whose ctDNA samples harbor HRR gene alterations, with HRR genes defined as: ATM, ATR, BRCA1, BRCA2, CDK12, CHEK2, FANCA, MLH1, MRE11A, NBN, PALB2 and RAD51C.

CDx=companion diagnostic; ctDNA = circulating tumor deoxyribonucleic acid; FDA = US Food and Drug Administration; HRR = homologous recombination repair; HRRm = homologous recombination repair gene mutated; IND = Investigational New Drug; mCRPC = metastatic castration-resistant prostate cancer; OS = overall survival; rPFS = radiographic progression-free survival; sNDA = supplemental New Drug Application.

Table 2 US FDA Regulatory History Following HRRm mCRPC Approval

IND / NDA Date	Activity
April 2024 IND 129642	FDA Written Responses were provided for a Type C Meeting agreeing on the format and content of a planned sNDA based on final analysis results from TALAPRO-2. Sponsor follow-up questions were addressed by FDA and written responses were updated in May 2024. • In addition to providing updated clinical data for both cohorts, the Agency recommended submitting updated efficacy results (rPFS, OS, and ORR) for patients with two negative HRR test results.
November 2024 IND 129642	FDA Preliminary Comments were provided for a Type B Pre-sNDA Meeting. Sponsor responses to the preliminary feedback were submitted and the pre-sNDA meeting was subsequently canceled.
December 2024 NDA 211651 (S-013) NDA 217439 (S-003)	sNDA submitted based on updated efficacy and safety results from TALAPRO-2, including final OS data, to support the proposed indication for talazoparib in combination with enzalutamide in adult patients with mCRPC, unselected for HRR gene alterations. A submission was also made to NDA 217439, talazoparib soft-gel capsules, to cross-reference the above sNDA.
February 2025 NDA 211651 (S-013)	Priority Review granted by FDA.

FDA = US Food and Drug Administration; HRR = homologous recombination repair; HRRm = homologous recombination repair gene mutated; IND = Investigational New Drug; mCRPC = metastatic castration-resistant prostate cancer; ORR = objective response rate; OS = overall survival; rPFS = radiographic progression-free survival; sNDA = supplemental New Drug Application.

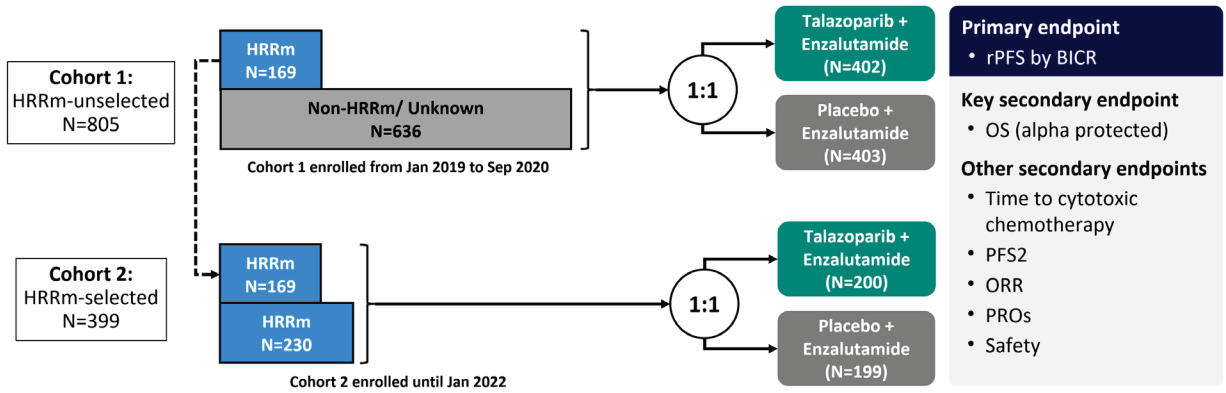
3.4 TALAPRO-2

3.4.1 Study Design and Methods

TALAPRO-2 is a Phase 3, multicenter, randomized, double-blind, placebo-controlled trial designed to evaluate the efficacy and safety of talazoparib + enzalutamide versus placebo + enzalutamide in patients with mCRPC.

The trial enrolled two cohorts (Figure 8) [57]. Cohort 1 included mCRPC patients with or without HRRm (the HRRm-unselected population), while Cohort 2 enrolled patients with HRRm (the HRRm-selected population). Importantly, the term "unselected" as used in this document refers to the inclusion of all patients unselected for HRRm—including HRRm, non-HRRm (non-deficient), and HRRm-unknown individuals—not exclusively patients without HRRm.

Figure 8 TALAPRO-2 Study Design



Stratification Factors
- Prior abiraterone[a] or docetaxel for CSPC (yes vs no)
- HRR gene alteration status (deficient vs non-deficient or unknown)[b]

[a]Prior orteronel was received by two patients in each treatment arm in Cohort 1 and one patient in each treatment arm in Cohort 2.
[b]Unselected cohort only.
BICR = blinded independent central review; CSPC = castration-sensitive prostate cancer; HHR = homologous recombination repair; HRRm = homologous recombination repair gene mutated; ORR=objective response rate; OS = overall survival; PFS2 = progression-free survival on next line therapy; PRO = patient-reported outcomes; rPFS = radiographic progression-free survival.
Data from Agarwal N, et al. Poster presented at: 2025 ASCO Genitourinary Cancers Symposium Meeting; San Francisco, CA; February 13-15, 2025. Abstract LBA18 [57].

Eligible patients had not received prior systemic cancer therapies for mCRPC, though prior treatment with taxane-based chemotherapy or an ARPI in the CSPC setting was permitted. Patients in each cohort were randomized (1:1) to receive either talazoparib 0.5 mg QD + enzalutamide 160 mg QD or placebo + enzalutamide 160 mg QD.

Cohort 1 (N=805) enrolled patients between January 2019 and September 2020. Cohort 2 (N=399), which included only HRRm-selected patients, continued enrollment until January 2022 (after Cohort 1 completed enrollment). Importantly, the 169 HRRm-selected patients in Cohort 1 were also part of Cohort 2 with no re-randomization.

Patients were stratified by prior receipt of abiraterone or docetaxel for CSPC (yes vs. no) as well as by HRR gene alteration status (HRRm vs. non-HRRm or unknown) in the HRRm-unselected cohort. For enrollment and stratification, assessment of HRR mutation status was by prospective analysis of tissue or historical analysis, per F1CDx (Tissue CDx). In a minority of cases, assessment of HRR mutation status by prospective analysis of blood (liquid biopsy) was also performed. Patients were categorized as HRRm if at least one pathogenic mutation was detected in any of 12 prespecified genes (ATM, ATR, BRCA1, BRCA2, CDK12, CHEK2, FANCA, MLH1, MRE11A, NBN, PALB2, RAD51C), with positivity in either tumor tissue or blood sufficient for this classification.

The primary endpoint of the trial was rPFS as assessed by BICR. Overall survival was an alpha-protected key secondary endpoint. Other secondary endpoints included time to cytotoxic chemotherapy, second progression-free survival (PFS2), objective response rate (ORR), patient-reported outcomes (PROs), and safety. TALAPRO-2 aimed to evaluate the potential benefit of combined PARP inhibition and AR blockade in both HRRm-selected and HRRm-unselected mCRPC populations.

3.4.1.1 Statistical Analysis Methods

For rPFS by BICR in the HRRm-unselected population (Cohort 1), approximately 333 rPFS events were required to provide 85% power to detect an HR of 0.696 using a 1-sided stratified log-rank test at a significance level of 0.0125 and an interim analysis for futility using a Lan-DeMets β–spending function to determine the futility boundary. For rPFS by BICR in the HRRm-selected population (Cohort 2), approximately 224 events were needed to provide 85% power to detect an HR of 0.64. The primary analysis of rPFS was completed for both cohorts in 2022 (data cutoff date: 16 August 2022 for Cohort 1 and 03 October 2022 for Cohort 2).

For the final OS analysis in Cohort 1 (data cutoff date: 03 September 2024), approximately 438 OS events were required to provide 78% power to detect an HR of 0.75 using a 1-sided log-rank test at a 1-sided significance level of 0.0125 and a 3-look group sequential design with Lan-DeMets (O'Brien-Fleming) α-spending function to determine the efficacy boundaries. The final OS analysis in Cohort 2 was performed at the time of the final OS analysis for Cohort 1.

3.4.2 Disposition

In the HRRm-unselected population (Cohort 1), 805 patients were randomized to treatment with either talazoparib + enzalutamide or placebo + enzalutamide based on Interactive Web Response System (IWRS); 169 patients (21.0%) were HRRm, and 636 patients (79.0%) were non-HRRm or unknown. Patient disposition is provided in Appendix Figure 1 (Section 8.1).

In the HRRm-selected population (Cohort 2), 399 HRRm patients were randomized to treatment with either talazoparib + enzalutamide or placebo + enzalutamide (Appendix Figure 2; Section 8.1).

3.4.3 Demographic and Baseline Characteristics

In both Cohorts, the distribution of demographic characteristics (age, race, ethnicity, and pooled geographic region) and physical measurements (weight and body mass index [BMI]) was similar across treatment arms.

The distribution of baseline disease characteristics (time since initial diagnosis, Eastern Cooperative Oncology Group performance status [ECOG PS], renal impairment at baseline, histopathological classification, initial American Joint Committee on Cancer [AJCC] M stage, Gleason score, baseline serum prostate-specific antigen [PSA], bone metastases and number of bone metastases at baseline, distribution of disease, type of progression at study entry, baseline circulating tumor cells [CTC] count [cells/7.5 mL blood], and baseline HRR tissue source) was similar across treatment arms. Alterations of specific HRR genes (including BRCA1/2) were generally well balanced between the two treatment arms.

Patient demographic and baseline characteristics for Cohorts 1 and 2 are provided in Appendix Table 1 and Appendix Table 2, respectively (Section 8.2).

4.0 CLINICAL EFFICACY

The TALAPRO-2 efficacy results presented in the sNDA included the final OS results (alpha-protected key secondary endpoint) and updated descriptive results from the primary endpoint, rPFS, and other secondary endpoints from Cohorts 1 and 2 (data cutoff date: 03 September 2024).

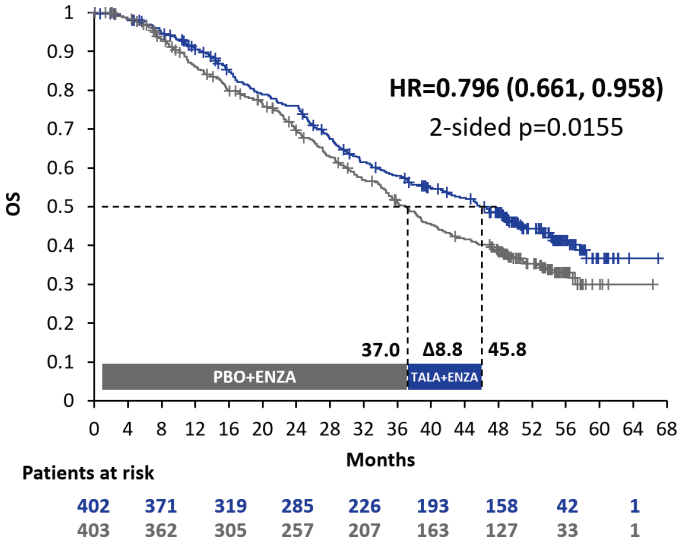
This section presents efficacy results from the TALAPRO-2 study, with a primary focus on Cohort 1, which enrolled a biomarker-unselected mCRPC population reflective of real-world clinical practice (Section 4.1). Efficacy was evaluated across prespecified HRR mutation subgroups and expanded molecular subgroups defined using both tumor tissue and plasma ctDNA testing. Particular emphasis has been placed on the non-HRRm population—specifically, patients with no detectable HRR gene alterations in both tissue and plasma—representing the most stringent molecular definition of non-HRRm patients. Data from Cohort 2, which enrolled only patients with HRR gene mutations, formed the basis of the June 2023 FDA approval. Updated data for Cohort 2 from the final OS cutoff are summarized separately in Section 4.2.

4.1 Proposed Indication Supported by Efficacy in the HRRm-unselected Population (Cohort 1)

4.1.1 Final OS Analysis: HRRm-unselected (Cohort 1)

As of the final OS analysis cutoff date (03 September 2024), a total of 454 events had occurred in the HRRm-unselected (Cohort 1) population. At this time point, talazoparib + enzalutamide demonstrated a statistically significant and clinically meaningful improvement in OS compared with placebo + enzalutamide. The observed OS HR was 0.796 ([95% CI: 0.661, 0.958]; 2-sided p=0.0155), corresponding to a 20.4% reduction in the risk of death (Figure 9).

Figure 9 Kaplan-Meier Plot of OS: HRRm-unselected (Cohort 1)



ENZA = enzalutamide; HR = hazard ratio; HRRm = homologous recombination repair gene mutated; OS = overall survival; PBO = placebo; TALA = talazoparib.

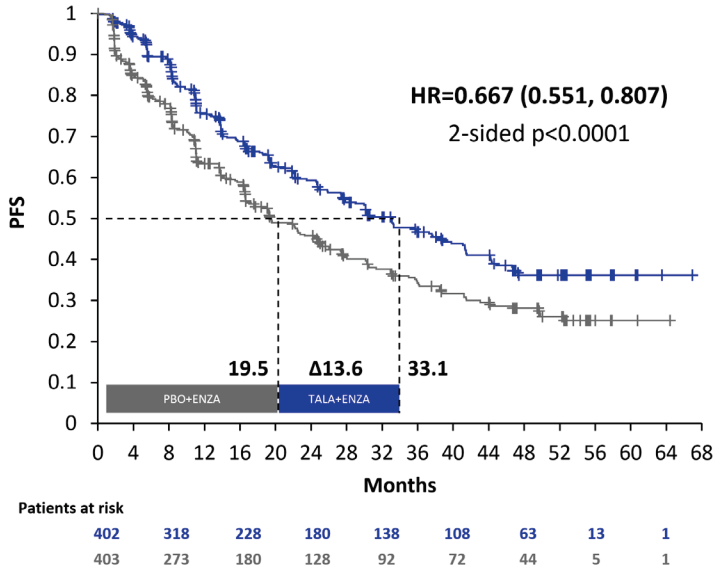
Median OS was 45.8 months (95% CI: 39.4, 50.8) for patients treated with talazoparib + enzalutamide compared with 37.0 months (95% CI: 34.1, 40.4) for those treated with placebo + enzalutamide—a difference of nearly 9 months. These final OS results in Cohort 1 reflect the first statistically significant improvement in survival demonstrated in a randomized Phase 3 study in the first-line mCRPC setting against an active control.

Consistent with the primary rPFS analysis (16 August 2022), the OS benefit was maintained across prespecified and exploratory clinical subgroups, including those defined by prognostic and treatment history factors (e.g., Gleason score, ECOG PS, prior taxane or abiraterone). A consistent treatment effect was also observed across HRR-defined molecular subgroups, with consistent median OS of ~45 months with the combination across the ITT population, and the stratified subgroups of HRRm or non-HRRm and unknown. Differences in HRs were largely attributable to variability in the performance of the active control across subgroups. These results support a consistent survival benefit with talazoparib + enzalutamide in patients with mCRPC unselected for HRR gene alterations.

4.1.2 rPFS Updated Descriptive Analysis: HRRm-unselected (Cohort 1)

At the time of the final OS analysis, the rPFS benefit in the HRRm-unselected (Cohort 1) population was maintained in favor of talazoparib + enzalutamide. The updated HR for rPFS was 0.667 ([95% CI: 0.551, 0.807]; 2-sided p<0.0001), representing a 33.3% reduction in the risk of radiographic progression or death (Figure 10). Median rPFS was 33.1 months (95% CI: 27.4, 39.0) for the talazoparib + enzalutamide arm versus 19.5 months (95% CI: 16.6, 24.7) for the placebo + enzalutamide arm, reflecting a median improvement of 13.6 months.

Figure 10 Kaplan-Meier Plot of rPFS: HRRm-unselected (Cohort 1)



ENZA = enzalutamide; HR = hazard ratio; HRRm = homologous recombination repair gene mutated; PBO = placebo; rPFS = radiographic progression-free survival; TALA = talazoparib.

These results confirm the durability of the primary rPFS findings and further reinforce the clinical benefit of talazoparib + enzalutamide in the first-line mCRPC setting. The rPFS benefit was consistently observed across prespecified clinical and genomic subgroups, including HRRm, non-HRRm, and HRRm-undetermined patients, as well as subgroups defined by baseline disease characteristics and prior therapies.

4.1.3 Secondary Endpoints: HRRm-unselected (Cohort 1)

Benefit was consistently maintained across secondary endpoints at this final analysis (Table 3). Clinically important improvements were observed in confirmed 50% decline in prostate-specific antigen (PSA50, 84.6% vs. 72.2%), ORR (60.5% vs. 43.8%), and complete response (CR, 37.0% vs. 20.8%) for talazoparib + enzalutamide versus placebo + enzalutamide, respectively. Additionally, talazoparib + enzalutamide treatment delayed median time to PSA progression (28.1 vs. 17.5 months), initiation of first antineoplastic therapy (not estimable [NE] vs. 28.5 months), and first cytotoxic chemotherapy (NE vs. 56.1 months). Additionally, PFS2 was notably prolonged (43.4 vs. 34.2 months), further confirming sustained clinical benefit with talazoparib + enzalutamide.

Table 3 Benefit Across Secondary Endpoints: HRRm-unselected (Cohort 1)

	Intent-to-Treat (N=805)		
	Talazoparib + Enzalutamide (N=402)	**Placebo + Enzalutamide (N=403)**	**HR (95% CI)**
Confirmed PSA50 response	84.6%	72.2%	–
Confirmed ORR	60.5%[a]	43.8%[b]	–
Confirmed CR	37.0%[c]	20.8%[d]	–
Median time to (months):			
PSA progression	28.1	17.5	0.69 (0.57, 0.84)
First antineoplastic therapy	NE	28.5	0.57 (0.47, 0.71)
First cytotoxic chemotherapy	NE	56.1	0.57 (0.45, 0.72)
PFS2	43.4	34.2	0.79 (0.66, 0.94)

[a]Value represents 72/119 patients.
[b]Value represents 57/130 patients.
[c]Value represents 44/119 patients.
[d]Value represents 27/130 patients.
CI = confidence interval; CR = complete response; HR = hazard ratio; HRRm = homologous recombination repair gene mutated; NE = not estimable; ORR = objective response rate; PFS2 = progression-free survival on next line therapy; PSA = prostate-specific antigen; PSA50 = 50% decline in prostate-specific antigen.

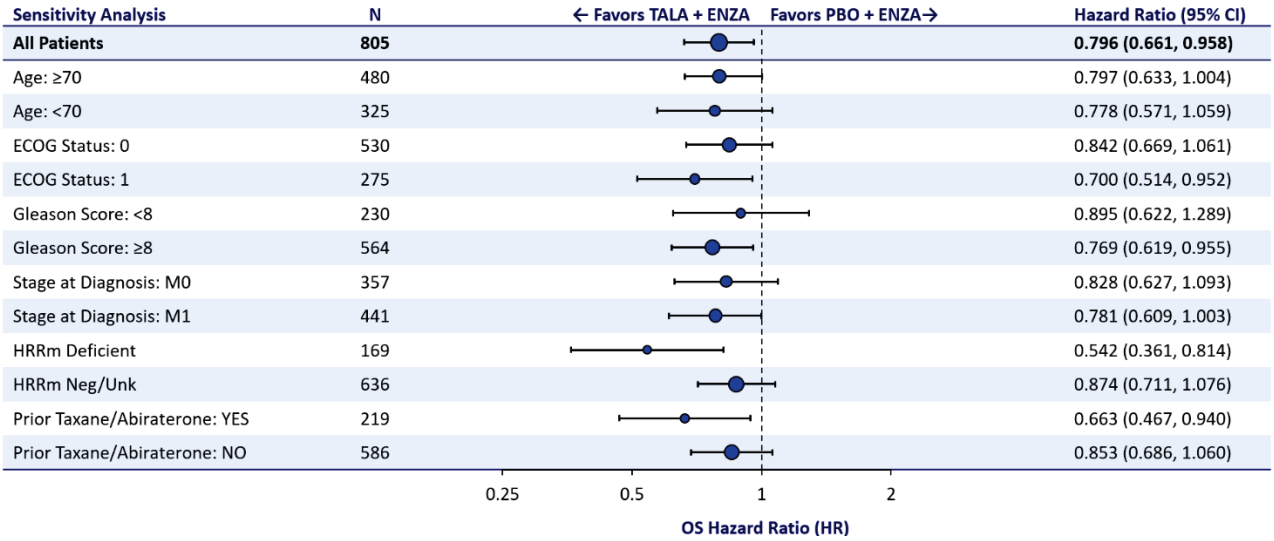
4.1.4 Consistent Benefit Across Prespecified HRR Subgroups: HRRm-unselected (Cohort 1)

Efficacy by prespecified HRR subgroups—HRRm and non-HRRm or HRR-unknown—was evaluated primarily based on tumor testing. The benefit of talazoparib + enzalutamide was consistent across these subgroups, including patients without known HRR mutations.

4.1.4.1 OS for Prespecified Subgroups: HRRm-unselected (Cohort 1)

A clinically meaningful and consistent improvement in OS was observed across all prespecified clinical and genomic subgroups in the HRRm-unselected (Cohort 1) population, including patients with or without detectable HRR gene alterations (Figure 11). The HRs for these subgroups consistently favored talazoparib + enzalutamide. These findings support the use of talazoparib + enzalutamide beyond HRRm-selected patients, reinforcing benefit across a broad range of baseline characteristics and treatment histories.

Figure 11 Forest Plot of OS for Prespecified Subgroups: HRRm-unselected (Cohort 1)



CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; ENZA = enzalutamide; HRRm = homologous recombination repair gene mutated; Neg = negative; OS = overall survival; PBO = placebo; TALA = talazoparib; Unk = unknown.

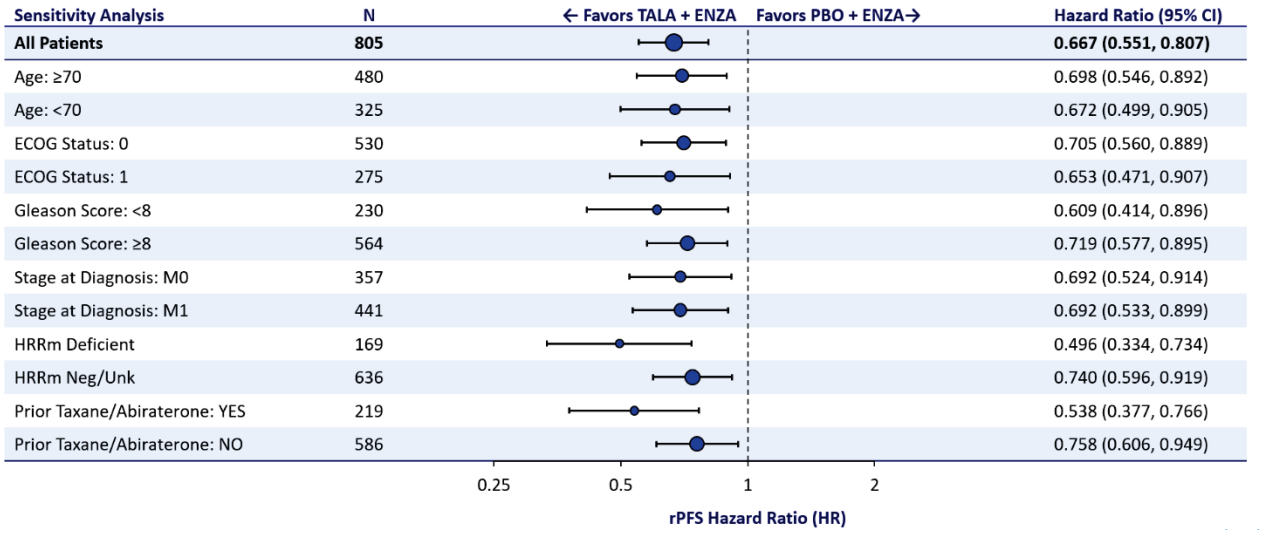
4.1.4.2 rPFS for Prespecified Subgroups: HRRm-unselected (Cohort 1)

Subgroup analyses of rPFS in the HRRm-unselected population demonstrated a consistent and clinically meaningful treatment effect across all prespecified clinical and genomic subgroups, including patients with and without detectable HRR gene alterations (Figure 12). These analyses reinforce the robustness of the rPFS findings in the ITT population.

HRs consistently favored talazoparib + enzalutamide across age (<70, ≥70), ECOG PS (0, 1), Gleason score (<8, ≥8), disease stage at diagnosis (M0, M1), and prior exposure to taxane or abiraterone (yes, no). Notably, HRRm and non-HRRm/unknown subgroups also demonstrated consistent treatment effect, with HRs of 0.496 (95% CI: 0.334, 0.734) and 0.740 (95% CI: 0.596, 0.919), respectively.

These results provide further evidence for the consistent efficacy of the combination across clinically and molecularly diverse subgroups and support the applicability of talazoparib + enzalutamide across a broad patient population unselected for HRR gene alterations.

Figure 12 Forest Plot of rPFS for Prespecified Subgroups: HRRm-unselected (Cohort 1)



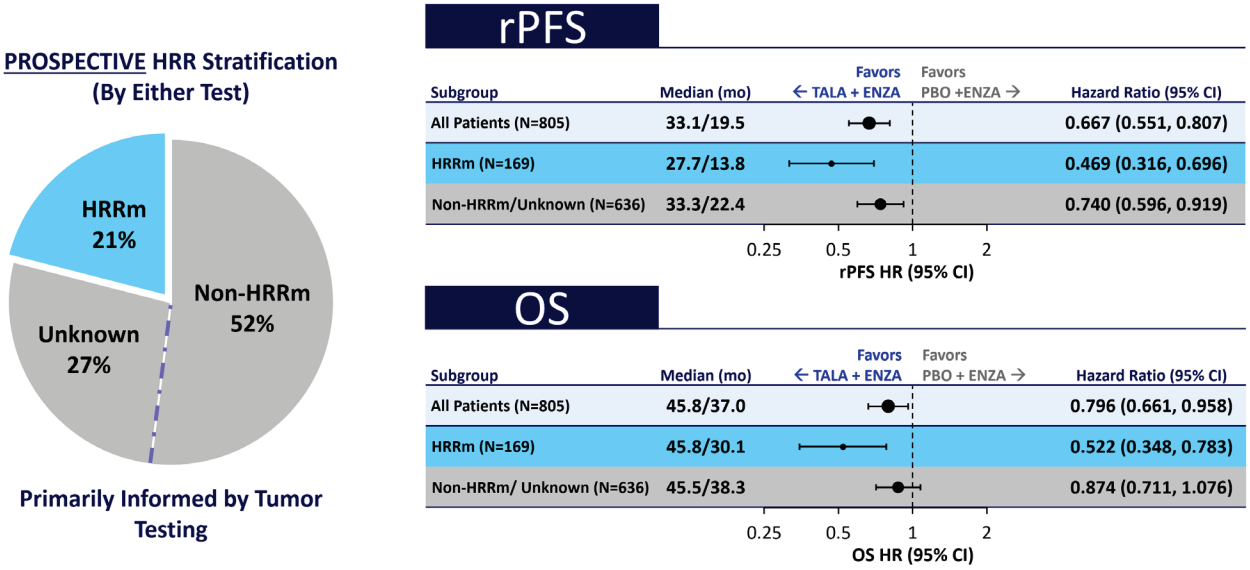
CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; ENZA = enzalutamide; HRRm = homologous recombination repair gene mutated; Neg = negative; PBO = placebo; rPFS = radiographic progression-free survival; TALA = talazoparib; Unk = unknown.

4.1.5 Efficacy in Molecular Subgroups Primarily Informed by Tumor Testing, Prospective Only: HRRm-unselected (Cohort 1)

In the TALAPRO-2 study, all patients underwent prospective next-generation sequencing (NGS) testing of tumor tissue, and approximately 6% of patients also underwent prospective ctDNA testing to assess HRR status. This approach, in which HRR status was determined prospectively and used for stratification, represents a strength of the study design. As illustrated in Figure 13, 21% of patients had detectable HRR gene alterations, while 79% either had no detectable HRR alterations or their HRR status remained unknown. The majority of unknown cases (27% of the total population) reflected unknown results from tumor tissue testing, consistent with the performance characteristics of the F1CDx used for HRR detection.

Subgroup analyses of rPFS and OS are depicted in the forest plots on the right side of Figure 13. Treatment with talazoparib + enzalutamide showed a consistent benefit across both patients with detectable HRR alterations and those without detectable HRR alterations, primarily reflecting HRR status determined by tumor tissue testing.

Figure 13 Molecular Subgroup Efficacy, Prospective HRR Stratification Primarily Informed by Tumor Testing: HRRm-unselected (Cohort 1)



CI = confidence interval; ENZA = enzalutamide; HR = hazard ratio; HRR = homologous recombination repair; HRRm = homologous recombination repair gene mutated; OS = overall survival; PBO = placebo; rPFS = radiographic progression-free survival; TALA = talazoparib.

4.1.6 Efficacy in Molecular Subgroups Informed by Prospective and Retrospective ctDNA Testing: HRRm-unselected (Cohort 1)

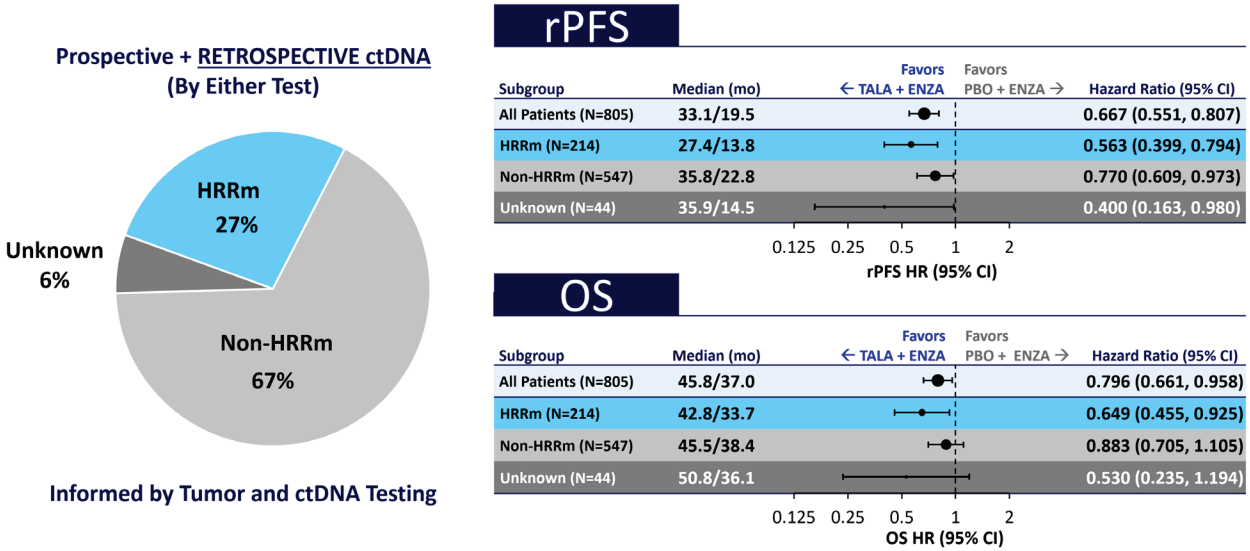
To further refine HRRm subgroup classification and resolve unknown results arising from tumor tissue testing alone, additional retrospective ctDNA analyses of baseline samples were conducted, based on FDA agreement during study planning. The goal of this extended molecular

characterization was to create a more complete molecular characterization, representative of real-world clinical practice and incorporating all available testing results.

When combining tumor and ctDNA data—by using the results from both tests—the proportion of patients classified as HRRm was 27%, non-HRRm increased to 67%, and the unknown population decreased to 6% (Figure 14). This distribution highlights the utility of ctDNA as a complementary tool to resolve previously unknown cases by tissue testing and more accurately identify biomarker-defined subgroups.

Subgroup analyses for both rPFS and OS using this updated classification demonstrate a consistent treatment effect in favor of talazoparib + enzalutamide in both HRRm and non-HRRm patients. The rPFS HR in the non-HRRm population (N=547) was 0.770 (95% CI: 0.609, 0.973), while the corresponding OS HR was 0.883 (95% CI: 0.705, 1.105), supporting a treatment effect beyond patients selected for HRR gene alterations. These results align with and reinforce the ITT population findings.

Figure 14 Molecular Subgroup Efficacy, Based on Combined Prospective and Retrospective ctDNA Testing: HRRm-unselected (Cohort 1)



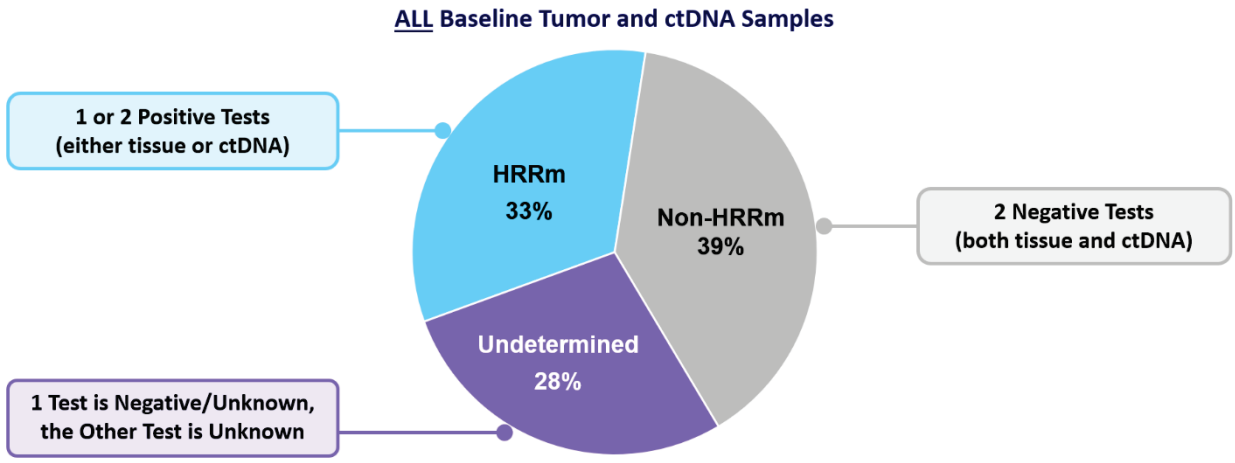
CI = confidence interval; ctDNA, circulating tumor deoxyribonucleic acid; ENZA = enzalutamide; HR = hazard ratio; HRRm = homologous recombination repair gene mutated; OS = overall survival; PBO = placebo; rPFS = radiographic progression-free survival; TALA = talazoparib.

4.1.7 Efficacy in Molecular Subgroups Informed by All Baseline Tumor and ctDNA Records: HRRm-unselected (Cohort 1)

Based on FDA feedback prior to the sNDA submission, an expanded molecular subgroup analysis was undertaken to further evaluate efficacy in patients without detectable HRR gene alterations (Figure 15). This approach leveraged all tumor and ctDNA baseline samples to generate the most robust possible categorization of HRRm status.

The HRRm subgroup included patients with an alteration detected by either tumor or ctDNA testing (33% of the population). The non-HRRm subgroup—representing patients with no HRR mutation detected by both tests—comprised 39% of the population and represented the most stringently defined non-HRRm group. The remaining 28% of patients were classified as molecularly "undetermined" due to an unknown result in tumor tissue and/or ctDNA. This framework enabled a nuanced understanding of efficacy across HRRm subgroups and provided the highest degree of certainty for isolating the treatment effect in the non-HRRm population.

Figure 15 Distribution of Stringently Defined Molecular Subgroups Using Tumor and ctDNA Testing: HRRm-unselected (Cohort 1)



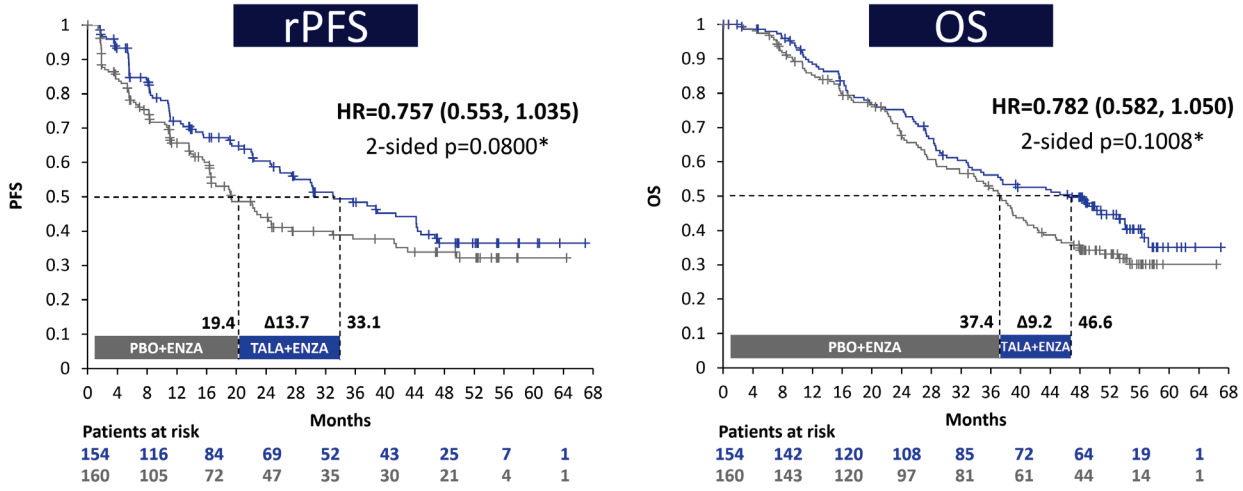
ctDNA = circulating tumor deoxyribonucleic acid; HRRm = homologous recombination repair gene mutated.

4.1.7.1 Efficacy in Non-HRRm Subgroup, by Both ctDNA and Tissue: HRRm-unselected (Cohort 1)

The non-HRRm subgroup in Cohort 1 of TALAPRO-2 refers to patients with no detectable HRR gene mutations by both tumor tissue and ctDNA testing, representing the most stringent definition of non-HRRm. This group was distinct from the HRRm and HRR-undetermined populations, representing 314 patients (39% of the Cohort 1 population) without detectable HRRm across both testing methodologies.

For rPFS, treatment with talazoparib + enzalutamide resulted in a median improvement of 13.7 months over placebo + enzalutamide (33.1 vs. 19.4 months) with an HR of 0.757 (Figure 16). A robust OS treatment effect was also observed, with a 22% reduction in the risk of death (HR=0.782; [95% CI: 0.582, 1.050]), corresponding to an improvement of 9.2 months in median OS (46.6 vs. 37.4 months).

Figure 16 Consistent Treatment Effect in the Non-HRRm Subgroup by Two Tests: (Cohort 1)



*Nominal p value.
ENZA = enzalutamide; HR = hazard ratio; HRRm = homologous recombination repair gene mutated; OS = overall survival; PBO = placebo; rPFS = radiographic progression-free survival; TALA = talazoparib.

The consistent rPFS and OS treatment effect favoring talazoparib + enzalutamide demonstrates a clinically meaningful improvement in patients with no detectable HRRm by two tests. These findings reinforce the broader efficacy of the combination therapy and support the proposed indication in mCRPC, unselected for HRR gene alterations.

The results in Table 4 show that talazoparib + enzalutamide led to deeper and more durable treatment responses compared to placebo + enzalutamide in patients without HRR mutations. The combination therapy resulted in higher PSA response rates, higher confirmed ORR, and more CRs, indicating benefit over the active control. Additionally, patients receiving talazoparib + enzalutamide experienced delayed PSA progression and a longer time before requiring additional treatments, including chemotherapy, suggesting a prolonged treatment effect. These findings further support the combination of talazoparib + enzalutamide providing meaningful clinical benefit beyond HRRm patients in a broader mCRPC population.

Table 4 Benefit Across Secondary Endpoints in the Non-HRRm Subgroup by Two Tests: (Cohort 1)

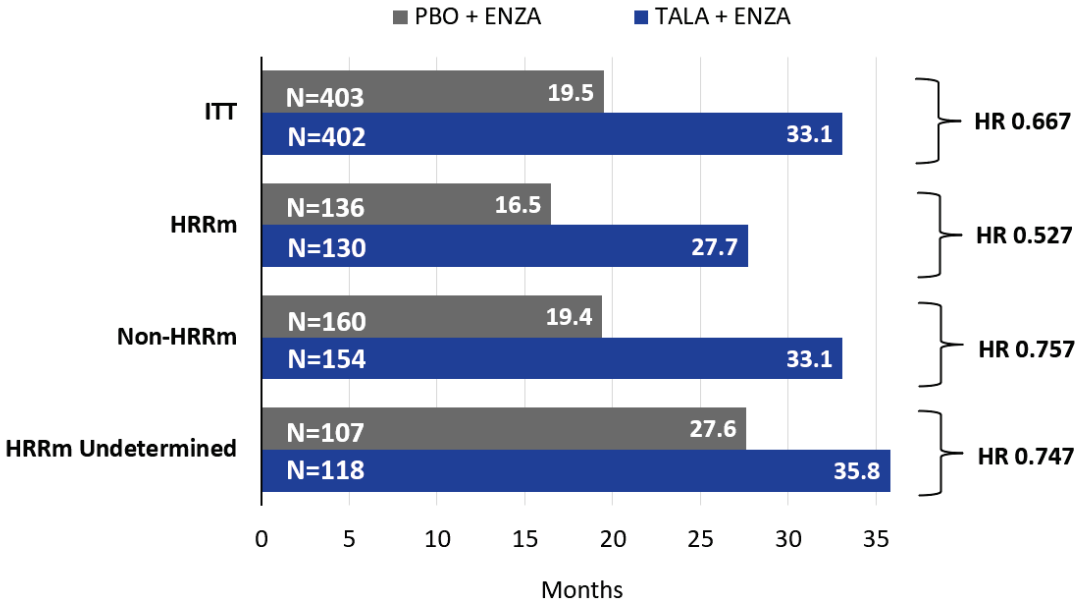
	No HRRm by Two Tests (N=314)		
	Talazoparib + Enzalutamide (N=154)	**Placebo + Enzalutamide (N=160)**	**HR (95% CI)**
Confirmed PSA50 response	84.3%	71.2%	–
Confirmed ORR	54.0%[a]	35.7%[b]	–
Confirmed CR	32.0%[c]	14.3%[d]	–
Median time to (months):			
PSA progression	28.6	17.5	0.78 (0.56, 1.08)
First antineoplastic therapy	NE	25.6	0.49 (0.34, 0.69)
First cytotoxic chemotherapy	NE	36.2	0.40 (0.27, 0.60)
PFS2	44.1	35.0	0.75 (0.56, 1.00)

[a]Value represents 27/50 patients.
[b]Value represents 20/56 patients.
[c]Value represents 16/50 patients.
[d]Value represents 8/56 patients.
CI = confidence interval; CR = complete response; HR = hazard ratio; HRRm = homologous recombination repair gene mutated; NE = not estimable; ORR = objective response rate; PFS2 = progression-free survival on next line therapy; PSA = prostate-specific antigen; PSA50 = 50% decline in prostate-specific antigen.

4.1.7.2 Median rPFS by Subgroup, by Both Tissue and ctDNA: HRRm-unselected (Cohort 1)

Exploratory analyses of median rPFS across the ITT population and molecular subgroups defined by integrated tumor and ctDNA testing confirm a consistent treatment effect in favor of talazoparib + enzalutamide (Figure 17). Median rPFS was 33.1 versus 19.5 months in the ITT population (HR=0.667), 27.7 versus 16.5 months in HRRm patients (HR=0.527), and 33.1 versus 19.4 months in non-HRRm patients (HR=0.757). In the HRRm-undetermined group, median rPFS was 35.8 versus 27.6 months (HR=0.747), which reflects a more favorable outcome with enzalutamide in this subgroup. Collectively, these results support the conclusion that the rPFS benefit of talazoparib + enzalutamide extends across molecularly defined populations.

Figure 17 Median rPFS by Subgroup, Based on Two Tests: HRRm-unselected (Cohort 1)



ENZA = enzalutamide; HR = hazard ratio; HRRm = homologous recombination repair gene mutated; ITT = intent-to-treat; PBO = placebo; rPFS = radiographic progression-free survival; TALA = talazoparib.

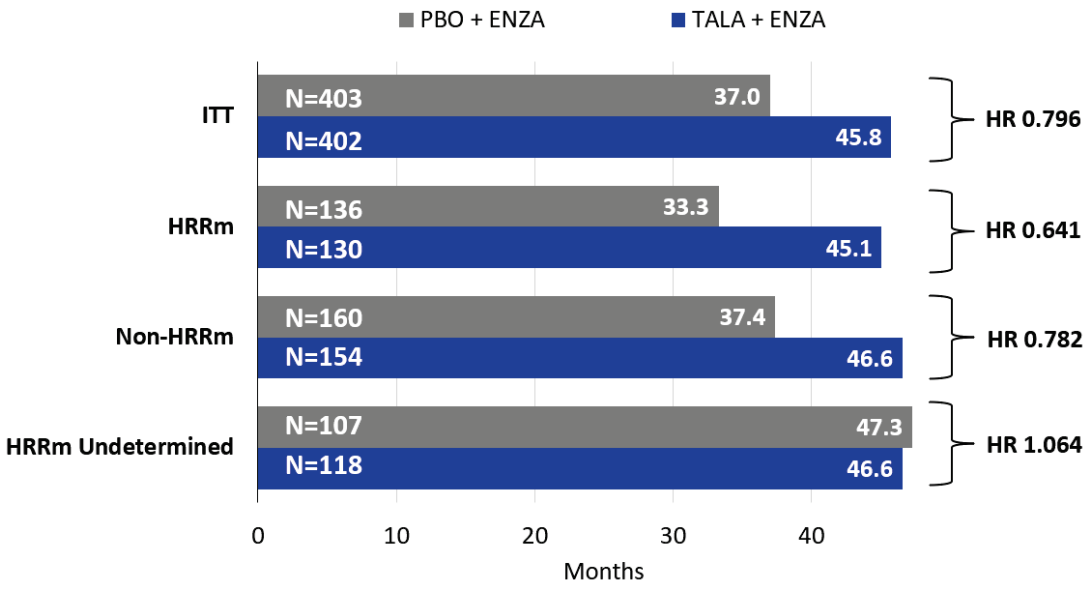
4.1.7.3 Median OS by Subgroup, by Both Tissue and ctDNA: HRRm-unselected (Cohort 1)

Median OS was consistent across the ITT population and molecular subgroups defined by integrated tumor and ctDNA testing (Figure 18). Median OS in the ITT population was 45.8 versus 37.0 months (HR=0.796). In HRRm patients, median OS was 45.1 versus 33.3 months (HR=0.641), and in non-HRRm patients, OS was 46.6 versus 37.4 months (HR=0.782). Among patients with HRRm-undetermined status, median OS was 46.6 versus 47.3 months (HR=1.064).

Among patients receiving talazoparib + enzalutamide, median OS values were notably similar across groups—45.1 months in HRRm, 46.6 months in non-HRRm, and 45.8 months in the ITT population—supporting the robustness of the OS benefit across molecular subgroups. These subgroup analyses demonstrate that the observed benefit is not driven exclusively by patients with HRRm.

Differences in HRs may reflect underlying prognostic heterogeneity. Specifically, HRRm patients receiving enzalutamide alone experienced poorer outcomes (33.3 months). In contrast, the OS in the HRRm-undetermined subgroup of the control arm (47.3 months) was unexpectedly favorable. These findings support the hypothesis that talazoparib + enzalutamide may mitigate the adverse prognostic effect of HRR gene alterations when treated with enzalutamide alone and extend survival benefit across biomarker-defined groups.

Figure 18 Median OS by Subgroup, Based on Two Tests: HRRm-unselected (Cohort 1)



ENZA = enzalutamide; HR = hazard ratio; HRRm = homologous recombination repair gene mutated; ITT = intent-to-treat; PBO = placebo; TALA = talazoparib.

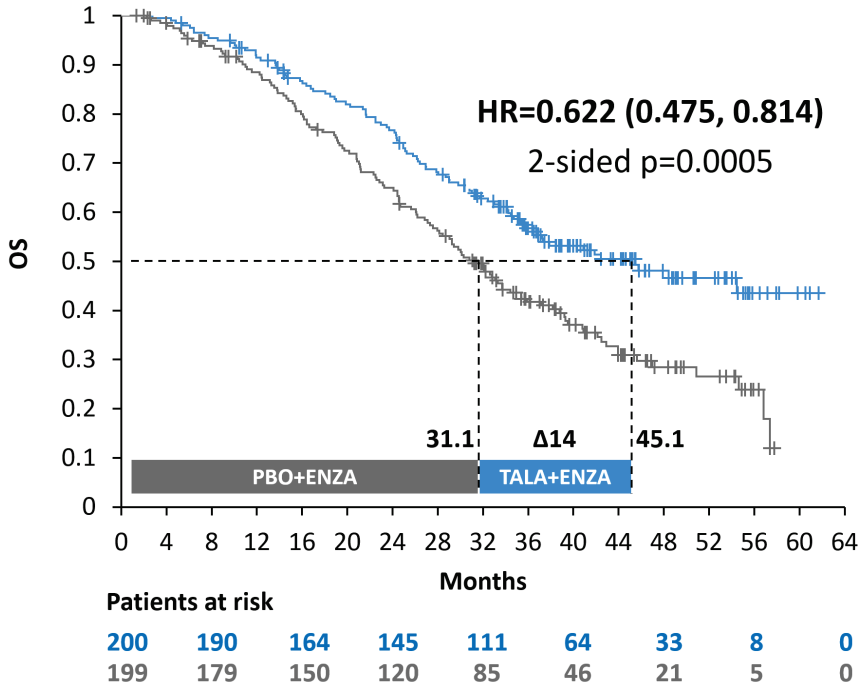
4.2 Efficacy in the HRRm-selected Population (Cohort 2): Reflective of the Current Indication

Cohort 2 enrolled 399 patients with confirmed HRR gene mutations and formed the basis of the June 2023 FDA approval of Talzenna + enzalutamide for the treatment of HRRm mCRPC. As previously reported, the combination significantly improved both rPFS and OS compared to placebo + enzalutamide.

4.2.1 Final OS Analysis: HRRm-selected (Cohort 2)

As of the final OS analysis cutoff date (03 September 2024), at which time 219 events had occurred, there was a clinically meaningful and statistically significant improvement in OS in favor of patients treated with talazoparib + enzalutamide compared with placebo + enzalutamide. The observed HR was 0.622 (95% CI: 0.475, 0.814) in favor of talazoparib + enzalutamide, representing a 37.8% reduction in the risk of death compared with the placebo (Figure 19). Median OS was 45.1 (95% CI: 35.4, NE) months for the talazoparib + enzalutamide arm and 31.1 (95% CI: 27.3, 35.4) months for the placebo + enzalutamide arm.

Figure 19 Kaplan-Meier Plot of OS: HRRm-selected (Cohort 2)

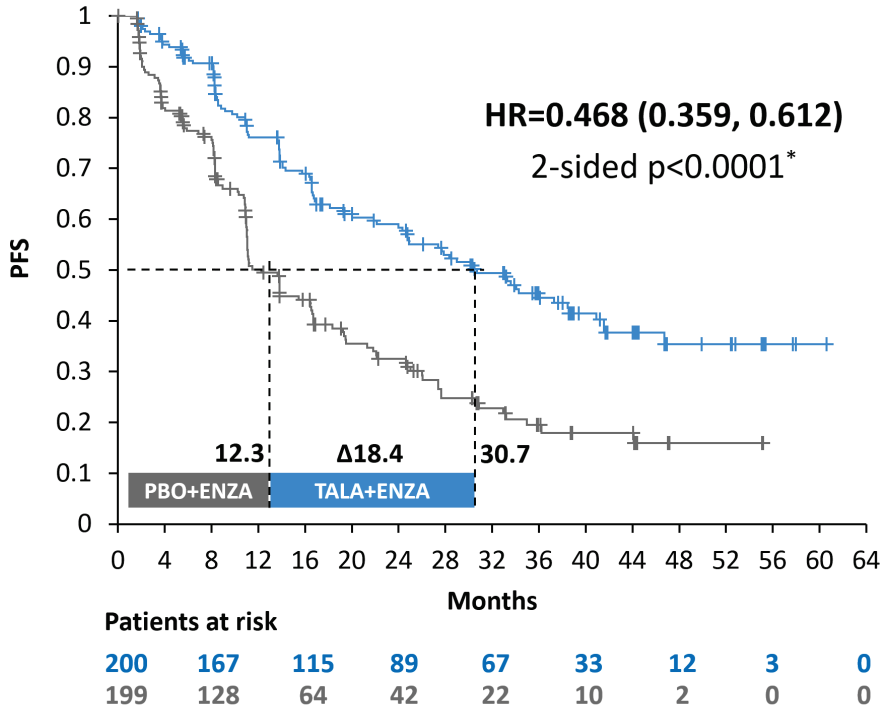


ENZA = enzalutamide; HR = hazard ratio; HRRm = homologous recombination repair gene mutated; OS = overall survival; PBO = placebo; TALA = talazoparib.

4.2.2 rPFS Updated Descriptive Analysis: HRRm-selected (Cohort 2)

As of the final OS analysis cutoff date (03 September 2024), the clinically meaningful improvement in rPFS per BICR was maintained with an HR of 0.468 (95% CI: 0.359, 0.612), representing a 53.2% reduction in the risk of disease progression or death in the talazoparib + enzalutamide arm compared with the placebo + enzalutamide arm (Figure 20). At this descriptive analysis, median rPFS was reached for the talazoparib + enzalutamide arm (30.7; [95% CI: 24.3, 38.5] months for patients who received talazoparib + enzalutamide and 12.3 [95% CI: 11.0, 16.5] months for patients who received placebo + enzalutamide).

Figure 20 Kaplan-Meier Plot of rPFS: HRRm-selected (Cohort 2)



*Nominal p value.
ENZA = enzalutamide; HR = hazard ratio; HRRm = homologous recombination repair gene mutated; PBO, placebo; rPFS = radiographic progression-free survival; TALA = talazoparib.

Across all prespecified and exploratory subgroup analyses, the rPFS benefit was consistent with the clinically significant results of the primary analysis in the HRRm population in favor of talazoparib + enzalutamide versus placebo + enzalutamide.

4.3 Overall Efficacy Conclusions

Talazoparib + Enzalutamide Demonstrates Broad Clinical Benefit in mCRPC

Final data from TALAPRO-2 confirm that talazoparib + enzalutamide improves both OS and rPFS in patients with mCRPC, including those unselected for HRRm.

Consistent Benefit in the HRRm-unselected Population (Cohort 1)

In Cohort 1—the population reflective of real-world practice—talazoparib + enzalutamide showed a durable OS and rPFS benefit. These improvements were consistently observed across prespecified and molecularly defined subgroups, including patients without detectable HRR mutations. Secondary endpoints also demonstrated deeper and more durable responses, with delayed time to subsequent therapy, further supporting the clinical benefit of the combination.

Reinforced Efficacy in the HRRm-selected Population (Cohort 2)

In Cohort 2, composed of patients with HRR mutations, talazoparib + enzalutamide improved OS and rPFS over the active control. These results validate the benefit in biomarker-selected patients and support the existing FDA-approved indication.

Totality of Data Supports Expanded Use in mCRPC

TALAPRO-2 is the first Phase 3 trial in more than a decade to demonstrate a survival advantage in mCRPC against an active comparator. The consistent efficacy across clinical and genomic subgroups—including those without detectable HRR mutations by two tests—supports the proposed expansion of the indication to all patients with mCRPC.

5.0 CLINICAL SAFETY

5.1 Safety Populations

Updated safety data from the final analysis of the TALAPRO-2 trial was submitted in the sNDA (data cutoff date: 03 September 2024). Safety data from Cohort 1 and Cohort 2 were generally consistent and aligned with the known safety profiles of the individual agents.

The safety information that follows focuses mainly on the HRRm-unselected population (Cohort 1), which is the basis for the proposed indication. Cohort 1 includes 398 patients treated with talazoparib + enzalutamide and 401 patients treated with placebo + enzalutamide. The Cohort 2 population includes 399 patients with HRRm: 169 patients with HRRm enrolled in Cohort 1, and 230 additional patients enrolled after Cohort 1 enrollment was complete (197 treated with talazoparib + enzalutamide and 199 treated with placebo + enzalutamide). The integrated safety population includes 1028 patients: 512 patients treated with talazoparib + enzalutamide and 516 patients treated with placebo + enzalutamide.

With 2 additional years of follow-up from the primary analysis of TALAPRO-2, the safety profile for talazoparib + enzalutamide remained consistent with that observed at the primary analyses for both Cohort 1 and Cohort 2, and no new safety signals were identified.

5.2 Extent of Exposure in the HRRm-unselected Population (Cohort 1)

The median duration of exposure to both talazoparib/placebo and enzalutamide was longer in the combination arm compared with the control arm (Table 5). The median relative dose intensity was over 80% with talazoparib, and nearly 100% with enzalutamide. Importantly, patients treated with talazoparib + enzalutamide benefitted from enzalutamide longer when administered with talazoparib as reflected by their being able to stay on enzalutamide for a median of approximately 6 months longer than placebo + enzalutamide patients.

Table 5 Longer Exposure With Talazoparib and Enzalutamide: HRRm-unselected (Cohort 1)

	Talazoparib + Enzalutamide (N=398)	**Placebo + Enzalutamide (N=401)**
Talazoparib/Placebo		
Median duration of treatment, months	19.75	16.07
Median average daily dose administered, mg/day	0.38	0.50
Median relative dose intensity, %	81.78	100.00
Enzalutamide		
Median duration of treatment, months	22.36	16.56
Median average daily dose administered, mg/day	159.42	160.00
Median relative dose intensity, %	99.64	100.00

HRRm = homologous recombination repair gene mutated.

5.3 Adverse Events in the HRRm-unselected Population (Cohort 1)

Overall, 99.0% and 95.8% of patients in the talazoparib + enzalutamide and placebo + enzalutamide treatment arms, respectively, experienced at least one treatment-emergent adverse event (TEAE) (Table 6).

Grade 3 or Grade 4 TEAEs were reported more frequently for patients in the talazoparib + enzalutamide arm (75.9%) than in the placebo + enzalutamide arm (44.6%). 45.7% and 31.4% of patients experienced a serious adverse event (SAE) in the talazoparib + enzalutamide arm and in the placebo + enzalutamide arms, respectively. Grade 5 TEAEs were reported at a similar frequency for patients in the talazoparib + enzalutamide arm (3.5%) and placebo + enzalutamide arm (5.0%). Dose modifications (reductions, interruptions, and discontinuations) due to TEAEs were reported for more patients in the talazoparib + enzalutamide arm compared to the placebo + enzalutamide arm. Most patients were able to continue talazoparib, with 21.6% permanently discontinuing talazoparib due to TEAEs.

Table 6 Overview of TEAEs (All Causalities): HRRm-unselected (Cohort 1)

	Talazoparib + Enzalutamide (N=398)	**Placebo + Enzalutamide (N=401)**
Any TEAE, n (%)	394 (99.0)	384 (95.8)
Maximum Grade 3 or 4 TEAEs, n (%)	302 (75.9)	179 (44.6)
Maximum Grade 5 TEAEs, n (%)	14 (3.5)	20 (5.0)
Any serious TEAE, n (%)	182 (45.7)	126 (31.4)
TEAEs leading to discontinuation, n (%)		
Talazoparib/Placebo	86 (21.6)	52 (13.0)
Enzalutamide	53 (13.3)	48 (12.0)
TEAEs leading to dose reduction, n (%)		
Talazoparib/Placebo	217 (54.5)	29 (7.2)
Enzalutamide	61 (15.3)	33 (8.2)
TEAEs leading to dose interruptions, n (%)		
Talazoparib/Placebo	260 (65.3)	99 (24.7)
Enzalutamide	175 (44.0)	91 (22.7)

HRRm = homologous recombination repair gene mutated; TEAE = treatment-emergent adverse event.

5.3.1 Common All-Causality AEs: HRRm-unselected (Cohort 1)

All Grade and Grade 3 or higher all-causality TEAEs were reported more frequently in the talazoparib + enzalutamide arm compared to the placebo + enzalutamide arm (Table 7).

The most frequently reported TEAEs (occurring in ≥20% of patients) in the talazoparib + enzalutamide arm included anemia (67.8%), neutrophil count decreased (37.7%), fatigue (34.9%), back pain (26.9%), platelet count decreased (25.6%), white blood cell count decreased (24.1%), decreased appetite (22.4%), fall (22.4%), and nausea (21.4%). The most frequent TEAEs (occurring in ≥20% of patients) in the placebo + enzalutamide arm included fatigue (30.2%), arthralgia (21.7%), back pain (20.7%), and anemia (20.0%).

Table 7 Summary of TEAEs by Preferred Term and CTCAE Grade (All Grade and Grade 3 or Higher; ≥10% of Patients): HRRm-unselected (Cohort 1)

Number (%) of patients: by preferred term	Talazoparib + Enzalutamide (N=398)[a]		Placebo + Enzalutamide (N=401)[a]	
	All Grade	Grade ≥3	All Grade	Grade ≥3
With any adverse event	378 (95.0)	277 (69.6)	347 (86.5)	89 (22.2)
Anemia	270 (67.8)	195 (49.0)	80 (20.0)	18 (4.5)
Neutrophil count decreased	150 (37.7)	77 (19.3)	29 (7.2)	6 (1.5)
Fatigue	139 (34.9)	17 (4.3)	121 (30.2)	8 (2.0)
Back pain	107 (26.9)	13 (3.3)	83 (20.7)	4 (1.0)
Platelet count decreased	102 (25.6)	29 (7.3)	16 (4.0)	4 (1.0)
WBC count decreased	96 (24.1)	27 (6.8)	19 (4.7)	0
Decreased appetite	89 (22.4)	6 (1.5)	67 (16.7)	4 (1.0)
Fall	89 (22.4)	11 (2.8)	68 (17.0)	8 (2.0)
Nausea	85 (21.4)	2 (0.5)	53 (13.2)	3 (0.7)
Constipation	78 (19.6)	1 (0.3)	73 (18.2)	2 (0.5)
Arthralgia	69 (17.3)	2 (0.5)	87 (21.7)	2 (0.5)
Diarrhea	63 (15.8)	1 (0.3)	60 (15.0)	1 (0.2)
Asthenia	61 (15.3)	12 (3.0)	38 (9.5)	4 (1.0)
Hypertension	61 (15.3)	25 (6.3)	68 (17.0)	33 (8.2)
Dizziness	55 (13.8)	4 (1.0)	25 (6.2)	2 (0.5)
Weight decreased	53 (13.3)	4 (1.0)	43 (10.7)	3 (0.7)
Hot flush	51 (12.8)	0	56 (14.0)	0
Lymphocyte count decreased	51 (12.8)	25 (6.3)	23 (5.7)	4 (1.0)
Edema peripheral	47 (11.8)	0	27 (6.7)	0
Dyspnea	45 (11.3)	2 (0.5)	25 (6.2)	2 (0.5)
Pain in extremity	43 (10.8)	1 (0.3)	35 (8.7)	1 (0.2)
Headache	40 (10.1)	1 (0.3)	39 (9.7)	1 (0.2)

[a]Number of patients evaluable for adverse events.
CTCAE = Common Toxicity Criteria for adverse event; HRRm = homologous recombination repair gene mutated; TEAE = treatment-emergent adverse event; WBC = white blood cell.

5.3.2 Serious Adverse Events: HRRm-unselected (Cohort 1)

All-causality SAEs were reported more frequently for patients in the talazoparib + enzalutamide arm (45.7%) than for patients in the placebo + enzalutamide arm (31.4%).

Anemia was the most commonly reported SAE in the talazoparib + enzalutamide arm (14.8%; versus 0.2% in the placebo + enzalutamide arm).

All-causality SAEs reported in ≥2% of patients are summarized in Table 8.

Table 8 Summary of SAEs by Preferred Term and Max CTCAE Grade (≥2% of Patients): HRRm-unselected (Cohort 1)

Number (%) of patients: by preferred term	Talazoparib + Enzalutamide (N=398)[a]		Placebo + Enzalutamide (N=401)[a]	
	All Grade	Grade ≥ 3	All Grade	Grade ≥ 3
Anemia	59 (14.8)	53 (13.3)	1 (0.2)	1 (0.2)
Hematuria	10 (2.5)	10 (2.5)	5 (1.2)	5 (1.2)
Urinary tract infection	10 (2.5)	8 (2.0)	5 (1.2)	5 (1.2)
Pulmonary embolism	8 (2.0)	8 (2.0)	2 (0.5)	2 (0.5)

[a]Number of patients evaluable for adverse events.
CTCAE = Common Terminology Criteria for Adverse Events; HRRm = homologous recombination repair gene mutated; max = maximum; SAE = serious adverse event.

5.3.3 Adverse Events Leading to Dosing Interruption: HRRm-unselected (Cohort 1)

There were differences in the frequencies of AEs leading to dose interruption between treatment arms, primarily due to differences in the incidence of anemia.

5.3.3.1 Talazoparib/Placebo Interruptions

Dose interruptions of talazoparib/placebo due to an AE were reported for 65.3% of patients in the talazoparib + enzalutamide arm and 24.7% of patients in the placebo + enzalutamide arm.

In both treatment arms, dose interruptions of talazoparib/placebo were most frequently reported due to the hematologic AEs of anemia, neutrophil count decreased, and platelet count decreased. Anemia was the most common reason for dose interruption (46.5%) in the talazoparib + enzalutamide arm. Nonhematologic AEs that led to a dose interruption of talazoparib/placebo included fatigue, nausea, and decreased appetite.

5.3.3.2 Enzalutamide Interruptions

Dose interruptions of enzalutamide due to an AE were reported for 44.0% of patients in the talazoparib + enzalutamide arm and 22.7% of patients in the placebo + enzalutamide arm.

Anemia and neutrophil count decreased were the most frequently reported AEs leading to an enzalutamide dose interruption, and both AEs were reported at a higher incidence in the talazoparib + enzalutamide arm than in the placebo + enzalutamide arm. Nonhematologic AEs that led to a dose interruption of enzalutamide included decreased appetite, nausea, and fatigue.

5.3.4 Adverse Events Leading to Dose Reductions: HRRm-unselected (Cohort 1)

There were differences in the frequencies of AEs leading to dose reductions between treatment arms, primarily due to differences in the incidence of anemia.

5.3.4.1 Talazoparib/Placebo Reductions

Dose reductions of talazoparib/placebo due to an AE were reported for 54.5% of patients in the talazoparib + enzalutamide arm and 7.2% of patients in the placebo + enzalutamide arm.

Anemia was the most commonly reported AE leading to a dose reduction of talazoparib/placebo (44.5%).

5.3.4.2 Enzalutamide Reductions

Dose reductions of enzalutamide due to an AE were reported for 15.3% of patients in the talazoparib + enzalutamide arm and 8.2% of patients in the placebo + enzalutamide arm.

Anemia and fatigue were the most frequently reported AEs leading to a dose reduction of enzalutamide.

5.3.5 Adverse Events Leading to Permanent Treatment Discontinuation: HRRm-unselected (Cohort 1)

Dose modifications were used effectively to manage AEs, allowing most patients to remain on talazoparib + enzalutamide treatment.

5.3.5.1 Talazoparib/Placebo Discontinuations

Adverse events leading to permanent treatment discontinuation of talazoparib/placebo were reported for 21.6% of patients in the talazoparib + enzalutamide arm and 13.0% of patients in the placebo + enzalutamide arm. Anemia was the most commonly reported AE leading to permanent discontinuation of talazoparib/placebo—8.5% of patients in the talazoparib + enzalutamide arm discontinued talazoparib due to anemia.

5.3.5.2 Enzalutamide Discontinuations

Adverse events leading to permanent discontinuations of enzalutamide were reported for 13.3% of patients in the talazoparib + enzalutamide arm and 12.0% of patients in the placebo + enzalutamide arm. Anemia was the most frequently reported AE leading to permanent discontinuation of enzalutamide.

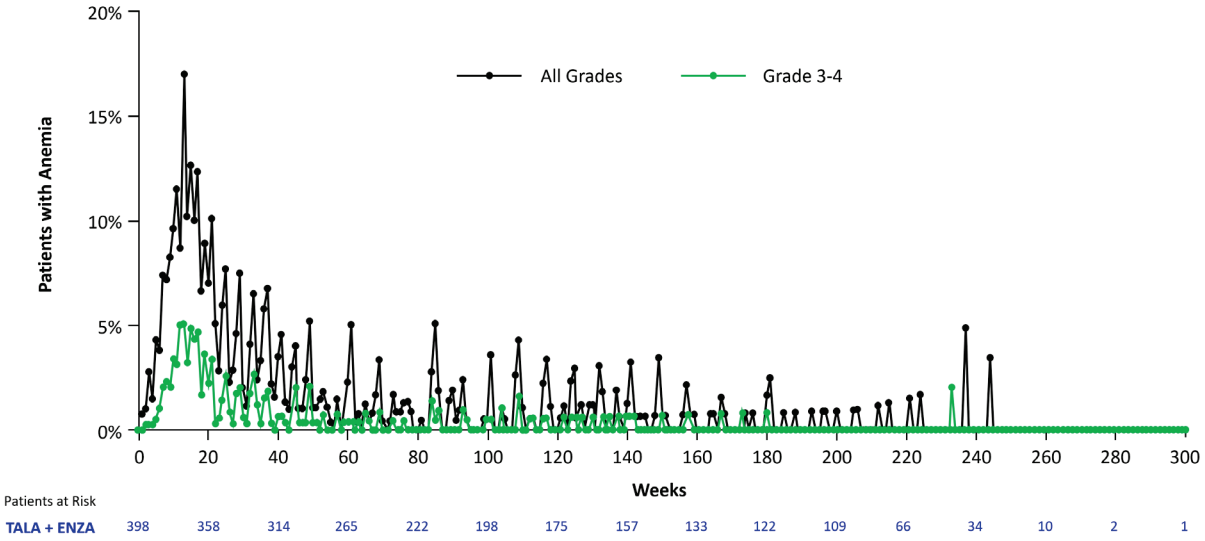
5.3.6 Anemia: HRRm-unselected (Cohort 1)

Anemia is an expected and on-target effect of talazoparib.

Grade ≥3 hematologic AEs were more frequent in the talazoparib + enzalutamide arm than the placebo + enzalutamide arm (60.3% and 7.5%, respectively), primarily due to the higher incidence of anemia. Anemia was the most frequent all-causality AE and SAE reported in the talazoparib + enzalutamide arm (67.8% and 14.8%, respectively) and occurred at a higher incidence than in the placebo + enzalutamide arm (20.0% and 0.2%, respectively).

Anemia was most frequently reported between 15 to 20 weeks after the initiation of talazoparib + enzalutamide treatment (N=398); however, it was manageable, and its incidence subsequently decreased over time with appropriate management (Figure 21).

Figure 21 Incidence of Anemia Decreased Over Time, Talazoparib + Enzalutamide Arm Only: HRRm-unselected (Cohort 1)



ENZA = enzalutamide; HRRm = homologous recombination repair gene mutated; TALA = talazoparib.

With appropriate management, few patients (8.5%) permanently discontinued talazoparib treatment due to anemia, and events were manageable through dosing interruption, dose reduction, and/or standard supportive care (e.g., blood transfusion) (Table 9). There were no reports of fatal anemia.

Table 9 Incidence and Management of Anemia-Related Dose Modifications: HRRm-unselected (Cohort 1)

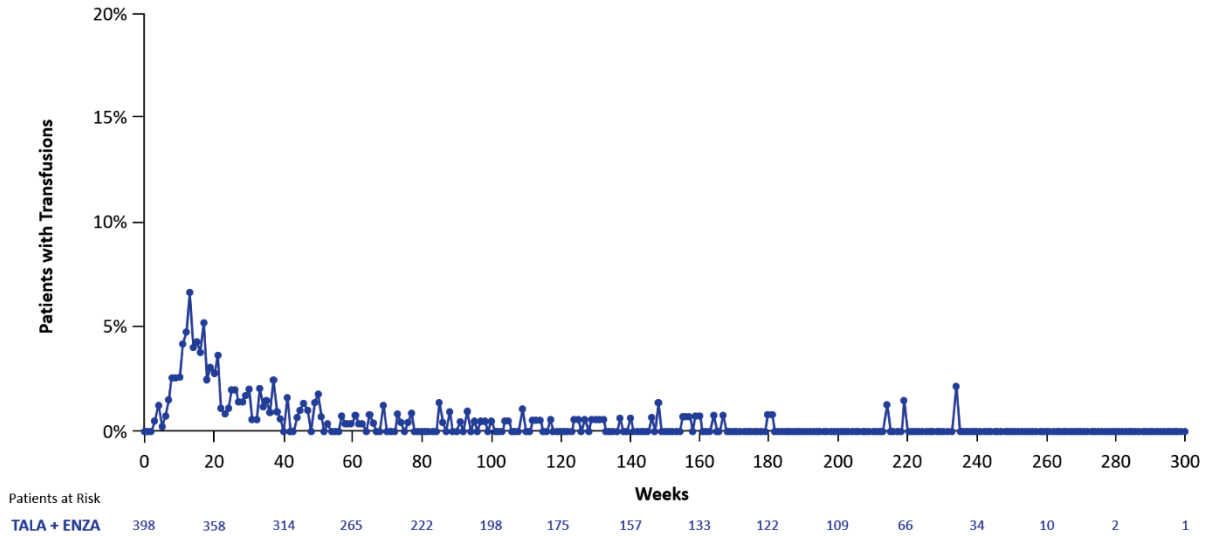
	Talazoparib + Enzalutamide (N=398)	Placebo + Enzalutamide (N=401)
Talazoparib or placebo dose discontinuation due to anemia,[a] n (%)	34 (8.5)	6 (1.5)
Talazoparib or placebo dose reduction due to anemia, n (%)	177 (44.5)	6 (1.5)
Talazoparib or placebo dose interruption due to anemia, n (%)	185 (46.5)	10 (2.5)

[a]Refers to permanent discontinuation.
HRRm = homologous recombination repair gene mutated.

5.3.7 Transfusions: HRRm-unselected (Cohort 1)

Mirroring the rate of Grade 3 or 4 anemia over time, the proportion of treatment-emergent transfusions peaked by 20 weeks and subsequently decreased over time (Figure 22).

Figure 22 Incidence of Transfusions Decreased Over Time, Talazoparib + Enzalutamide Arm Only: HRRm-unselected (Cohort 1)



ENZA = enzalutamide; HRRm = homologous recombination repair mutated; TALA = talazoparib.

Transfusions are summarized in Table 10. More patients in the talazoparib + enzalutamide treatment arm (45.2%) received at least one blood transfusion compared with the placebo + enzalutamide treatment arm (5.7%). Red blood cells were the most common transfused blood product, reported for 42.2% and 4.5% of patients in the talazoparib + enzalutamide and placebo + enzalutamide arm, respectively.

Table 10 Summary of Blood Transfusion by Blood Products: HRRm-unselected (Cohort 1)

	Talazoparib + Enzalutamide (N=398)	Placebo + Enzalutamide (N=401)
Patients with at least 1 blood transfusion, n (%)	180 (45.2)	23 (5.7)
Packed RBCs, n (%)	168 (42.2)	18 (4.5)
Platelets, n (%)	12 (3.0)	1 (0.2)
Whole blood cells, n (%)	13 (3.3)	3 (0.7)
Plasma, n (%)	3 (0.8)	1 (0.2)
Other, n (%)	5 (1.3)	1 (0.2)

HRRm = homologous recombination repair gene mutated; RBC = red blood cell.

5.3.8 Adverse Events of Special Interest: HRRm-unselected (Cohort 1)

With an additional 2 years of follow-up from the primary analysis of TALAPRO-2, there were no clinically significant changes in the TEAEs of special interest (Table 11). The frequencies of adverse events of special interest remained low with no new safety signals identified.

Table 11 Summary of TEAEs of Special Interest for Talazoparib/Placebo by Preferred Term: HRRm-unselected (Cohort 1)

Number (%) of patients: by preferred term	Talazoparib + Enzalutamide (N=398)	Placebo + Enzalutamide (N=401)
	Grade ≥3	Grade ≥3
Venous thrombotic/embolic events	13 (3.3)	3 (0.7)
Second primary malignancies	11 (2.8)	17 (4.2)
Pneumonitis	1 (0.3)	0
Myelodysplastic syndrome/ Acute myeloid leukemia	2 (0.5)[a]	0

[a]Includes one case of AML reported outside of safety reporting period.
AML = acute myeloid leukemia; HRRm = homologous recombination repair gene mutated; TEAE, treatment-emergent adverse event.

5.3.8.1 MDS/AML: HRRm-unselected (Cohort 1)

With an additional 2 years of follow-up from the primary analysis of TALAPRO-2, no new cases of MDS or AML have been reported. MDS and AML are recognized class effects of PARP inhibitors and are included in the Warnings and Precautions section of the approved Talzenna USPI.

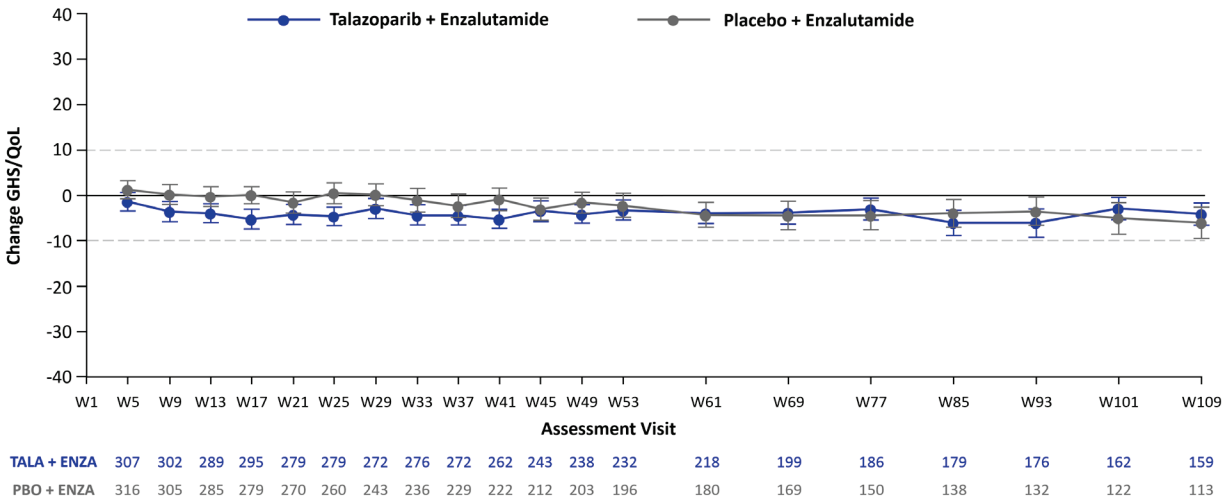
Overall, a total of one case of MDS (Grade 3) and one case of AML have been reported in the talazoparib + enzalutamide arm. The MDS event occurred in an 82-year-old male within the treatment-emergent period (Day 1 through 28 days after the last dose), approximately 1 year after starting treatment. The AML event occurred in a 73-year-old male during the post-treatment follow-up period, approximately 14 months after treatment initiation; the patient subsequently died. No patients in the placebo + enzalutamide arm experienced MDS or AML during the study.

5.4 PROs: HRRm-unselected (Cohort 1)

PROs were collected every 4 weeks during the first year of the study and then every 8 weeks thereafter until disease progression. PRO analyses were exploratory and not adjusted for multiplicity.

No clinically meaningful differences were observed between the talazoparib + enzalutamide and placebo + enzalutamide arms in mean change from baseline scores in Global Health Status/ Quality of Life (GHS/QoL) (Figure 23), function and symptom scales. The difference in the estimated mean change from baseline in GHS/QoL score between arms, based on longitudinal mixed effect model, was –2.2 (–4.3, –0.1), which did not reach the prespecified clinically meaningful threshold of >10 points.

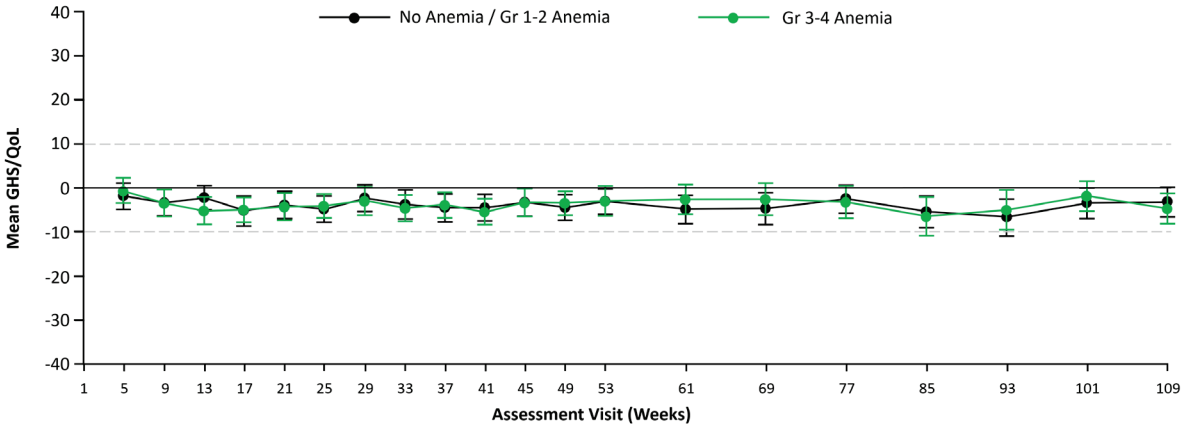
Figure 23 Mean Change From Baseline in GHS/QoL Scores Over Time: HRRm-unselected (Cohort 1)



ENZA = enzalutamide; GHS = Global Health Status; HRRm = homologous recombination repair gene mutated; PBO = placebo; QoL = quality of life; TALA = talazoparib.

To understand the role of anemia on QoL, exploratory analyses were conducted in patients in the talazoparib + enzalutamide arm who experienced either no anemia or Grade 1-2 anemia, compared to patients who experienced Grade 3-4 anemia. Mean changes from baseline over time in GHS/QoL scores were similar while on treatment. Consistent findings were observed for physical and role function, as well as symptom scales (Figure 24).

Figure 24 Mean Change From Baseline in GHS/QoL Scores Over Time by Anemia Status, Talazoparib + Enzalutamide Arm Only: HRRm-unselected (Cohort 1)

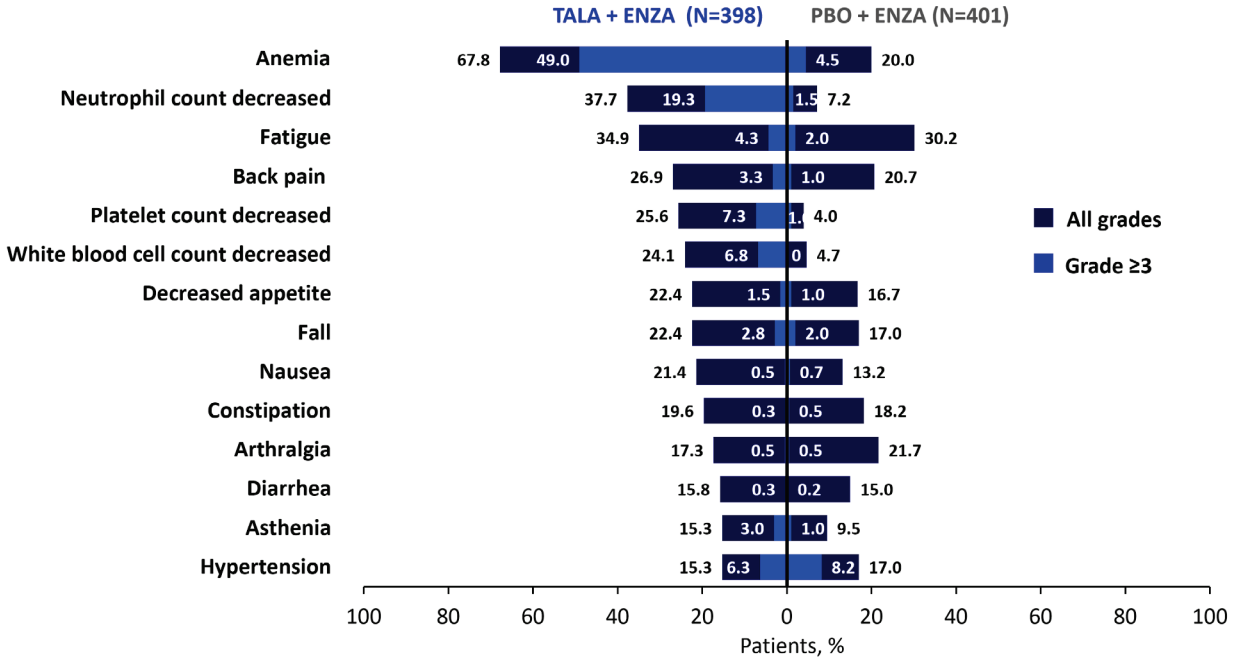


GHS = Global Health Status; Gr = Grade; HRRm = homologous recombination repair gene mutated; QoL = quality of life.

5.5 Consistency in Safety Profile Between Cohorts

The safety profile of talazoparib + enzalutamide was generally consistent between the HRRm-unselected (Cohort 1) and HRRm-selected (Cohort 2) populations and aligned with the known safety profiles of the individual agents (Figure 25).

Figure 25 Summary of TEAEs (≥15% of Patients): HRRm-unselected (Cohort 1) and HRRm-selected (Cohort 2)



ENZA = enzalutamide; HRRm = homologous recombination repair gene mutated; PBO=placebo; TALA = talazoparib; TEAE = treatment-emergent adverse event.

Common Adverse Events

Across both Cohort 1 and Cohort 2, the most frequently reported adverse events in the talazoparib + enzalutamide arm were hematologic (e.g., anemia), followed by nonhematologic events, primarily gastrointestinal and constitutional symptoms. The incidence of all-causality nonhematologic AEs (Any Grade and Grade ≥3) was generally similar across cohorts.

Grade ≥3 Adverse Events

Higher rates of Grade ≥3 AEs were observed in the talazoparib + enzalutamide arm in both cohorts, mainly due to anemia. However, anemia was manageable with dose modifications and standard supportive care. Importantly, its incidence decreased over time, indicating manageable toxicity with appropriate dose modifications and standard supportive care.

Integrated Safety Analysis

Safety analyses were performed on an integrated safety population that included patients from both cohorts, allowing for a comprehensive assessment of the safety profile of talazoparib + enzalutamide. No new safety signals were identified; the safety data from the combination of

talazoparib + enzalutamide in the integrated population were consistent with that observed for Cohort 1 and Cohort 2 (Table 12). As expected, based on the known safety profile of talazoparib, TEAEs—particularly hematologic events such as anemia—were more frequent with the combination regimen. However, these TEAEs were generally manageable with dose modifications and supportive care and infrequently led to permanent treatment discontinuation. The frequency and severity of TEAEs were broadly consistent between cohorts and with prior analyses.

Table 12 Overview of TEAEs (All Causalities): Cohorts 1 and 2 (Integrated Safety Population)

	Cohort 1 and 2 Integrated (N=1028)	
	Talazoparib + Enzalutamide (N=512)	**Placebo + Enzalutamide (N=516)**
Any TEAE, n (%)	508 (99.2)	497 (96.3)
Maximum Grade 3 or 4 TEAEs, n (%)	389 (76.0)	222 (43.0)
Maximum Grade 5 TEAEs, n (%)	18 (3.5)	22 (4.3)
Any serious TEAE, n (%)	227 (44.3)	152 (29.5)
TEAEs leading to discontinuation, n (%)		
Talazoparib/Placebo	102 (19.9)	60 (11.6)
Enzalutamide	69 (13.5)	56 (10.9)
TEAEs leading to dose reduction, n (%)		
Talazoparib/Placebo	283 (55.3)	33 (6.4)
Enzalutamide	84 (16.4)	39 (7.6)
TEAEs leading to does interruptions, n (%)		
Talazoparib/Placebo	333 (65.0)	119 (23.1)
Enzalutamide	222 (43.4)	110 (21.3)

TEAE = treatment-emergent adverse event.

5.6 Overall Safety Conclusions

With 2 additional years of follow-up from the primary analysis from TALAPRO-2, the safety profile for talazoparib in combination with enzalutamide remained consistent with that observed at the primary analyses for both Cohort 1 and Cohort 2 and with the known safety profiles of each individual agent. The safety profile of talazoparib + enzalutamide was generally manageable and no new safety signals were identified at the final analysis.

The most frequent all-causality AEs in the talazoparib + enzalutamide arm were hematologic; nonhematologic AEs were primarily gastrointestinal and constitutional, and mild to moderate in severity. Adverse events associated with talazoparib + enzalutamide were generally manageable with dose modifications (including interruptions and reductions) and/or standard supportive care.

The frequencies of all-causality Any Grade and Grade ≥3 nonhematologic AEs were generally balanced between treatment arms. Grade ≥3 AEs were higher in the talazoparib + enzalutamide arm, primarily due to the higher incidence of anemia. Anemia was the most common SAE and was generally well-managed with appropriate dose modifications and/or standard supportive medical therapy, with a low percentage of patients permanently discontinuing talazoparib due to anemia and no reports of fatal anemia. Importantly, anemia occurred most frequently in the first several months of treatment, and the incidence decreased over time.

PRO data further support the tolerability of talazoparib + enzalutamide, with no clinically meaningful deterioration in global health status or cancer-related symptoms observed in the HRRm-unselected population. Functional and symptom scales remained stable over time, consistent with a manageable safety profile and preserved quality of life.

Hematologic toxicities can be monitored with routine complete blood counts; recommendations for monitoring, and dose modifications based on hemoglobin level are reflected in the approved Talzenna USPI [64]. No new cases of MDS or AML have been reported at the final analysis, from the one case each previously reported at the primary analysis of TALAPRO-2.

6.0 OVERALL BENEFIT RISK CONCLUSIONS

6.1 Benefits of Talazoparib

As of the final OS analysis (data cutoff date: 03 September 2024), treatment with talazoparib + enzalutamide demonstrated a clinically meaningful and statistically significant improvement in OS in patients with mCRPC, including those unselected for HRR gene alterations. In the ITT population of Cohort 1, the observed OS HR was 0.796 ([95% CI: 0.661, 0.958]; 2-sided p=0.0155), corresponding to a 20.4% reduction in the risk of death, and a median improvement of 8.8 months (45.8 vs. 37.0 months) compared with placebo + enzalutamide.

This OS benefit was consistent across prespecified and exploratory subgroups, including a stringently defined non-HRRm population—patients without detectable HRR mutations by both tumor and ctDNA tests. In this non-HRRm subgroup, the OS HR was 0.782 ([95% CI: 0.582, 1.050]; 2-sided p=0.1008), with a median OS of 46.6 months in the talazoparib + enzalutamide arm and 37.4 months in the placebo + enzalutamide arm—demonstrating a favorable treatment effect against the placebo + enzalutamide active control, supporting consistent treatment effect in stringently defined non-HRRm patients.

rPFS also demonstrated sustained benefit. The HR for rPFS was 0.667 ([95% CI: 0.551, 0.807]; 2-sided p<0.0001), a 33.3% reduction in risk, with a median improvement of 13.6 months (33.1 vs. 19.5 months). This benefit was consistently observed across prespecified clinical subgroups and molecularly defined genomic categories.

Additionally, clinically meaningful benefit with talazoparib + enzalutamide was observed across multiple secondary endpoints, including ORR, PSA response, time to PSA progression, time to first antineoplastic and cytotoxic therapy, and PFS2. The benefit across these secondary measures further supports the robustness of the treatment effect in patients with and without HRR gene alterations.

Taken together, these data confirm and extend the clinical benefit previously observed at the primary analysis and support the use of talazoparib + enzalutamide in patients with mCRPC unselected for HRR gene alterations.

6.2 Risks of Talazoparib

As of the final OS analysis, no new safety signals were identified. The safety profile of talazoparib + enzalutamide remained consistent with the known profiles of each agent individually. Anemia was the most common TEAE; however, it was manageable, and the incidence subsequently decreased over time with appropriate dose modifications and supportive care. GHS/QoL scores were similar among patients experiencing Grade 3 anemia and those who did not. There were no fatal cases of anemia, and no new cases of MDS or AML were reported.

6.3 Benefit-Risk Conclusions

The final OS results from TALAPRO-2 support the benefit previously observed at the primary analysis and demonstrate survival benefit in patients with mCRPC, selected or unselected for HRR gene alterations. In the ITT population of Cohort 1, talazoparib + enzalutamide

demonstrated a statistically significant OS benefit over enzalutamide alone, with consistent benefit observed across clinical and genomic subgroups.

Notably, in the stringently defined non-HRRm population (patients negative for HRR gene alterations by both ctDNA and tumor tissue testing), a favorable OS treatment effect was observed, reinforcing the relevance of this combination therapy for patients without detectable HRR gene alterations.

These clinically meaningful efficacy results were observed on a background of active control, and with a well-characterized and manageable safety profile. Talazoparib + enzalutamide offers a favorable benefit-risk profile and represents an important treatment option for adult patients with mCRPC, unselected for HRR gene alterations.

7.0 REFERENCES

1. Key Statistics for Prostate Cancer. 2025a January 16, 2025 [cited 2025 March 6]; Available at: https://www.cancer.org/cancer/types/prostate-cancer/about/key-statistics.html.
2. Agarwal, N., et al., The biology behind combining poly [ADP ribose] polymerase and androgen receptor inhibition for metastatic castration-resistant prostate cancer. Eur J Cancer, 2023. 192: p. 113249.
3. Gopal, A.A., et al., PARP trapping is governed by the PARP inhibitor dissociation rate constant. Cell Chem Biol, 2024. 31(7): p. 1373-82 e10.
4. Polkinghorn, W.R., et al., Androgen receptor signaling regulates DNA repair in prostate cancers. Cancer Discov, 2013. 3(11): p. 1245-53.
5. Asim, M., et al., Synthetic lethality between androgen receptor signalling and the PARP pathway in prostate cancer. Nat Commun, 2017. 8(1): p. 374.
6. Li, L., et al., Androgen receptor inhibitor-induced "BRCAness" and PARP inhibition are synthetically lethal for castration-resistant prostate cancer. Sci Signal, 2017. 10(480).
7. Kounatidou, E., et al., A novel CRISPR-engineered prostate cancer cell line defines the AR-V transcriptome and identifies PARP inhibitor sensitivities. Nucleic Acids Res, 2019. 47(11): p. 5634-47.
8. Schiewer, M.J., et al., Dual roles of PARP-1 promote cancer growth and progression. Cancer Discov, 2012. 2(12): p. 1134-49.
9. ECIS - European Cancer Information System© European Union, 2021. 2021 [cited 2021 27 Nov].
10. Scher, H.I. and Heller, G., Clinical states in prostate cancer: toward a dynamic model of disease progression. Urology, 2000. 55(3): p. 323-7.
11. Shore, N.D., et al., Biochemical recurrence in patients with prostate cancer after primary definitive therapy: treatment based on risk stratification. Prostate Cancer Prostatic Dis, 2024. 27(2): p. 192-201.
12. Simon, N.I., et al., Best approaches and updates for prostate cancer biochemical recurrence. Am Soc Clin Oncol Educ Book, 2022. 42: p. 1-8.
13. Cornford, P., et al., EAU-ESTRO-SIOG Guidelines on Prostate Cancer. Part II: Treatment of Relapsing, Metastatic, and Castration-Resistant Prostate Cancer. Eur Urol, 2017. 71(4): p. 630-42.
14. Lowrance, W., et al., Updates to Advanced Prostate Cancer: AUA/SUO Guideline (2023). J Urol, 2023. 209(6): p. 1082-90.
15. Ferretti, S., et al., Metastatic castration-resistant prostate cancer: insights on current therapy and promising experimental drugs. Res Rep Urol, 2023. 15: p. 243-59.
16. Swami, U., et al., MP68-16: Real world treatment patterns and outcomes of patients with metastatic castration-resistant prostate cancer stratified by prior novel hormonal therapy and taxane use. J Urol, 2024. Vol. 211, No. 5S: p. e1115.
17. Brown, J.R., Shore, N., and Barata, P.C., In the era of treatment intensification for prostate cancer, why are some living in the past? JAMA Netw Open, 2024. 7(12): p. e2448660.

18. Shore, N.D., et al., Real-world treatment patterns and overall survival of patients with metastatic castration-resistant prostate cancer in the US prior to PARP inhibitors. Adv Ther, 2021. 38(8): p. 4520-40.
19. National Comprehensive Cancer Network., (2024), NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Prostate Cancer, Version 1.2025; December 4, 2024.
20. Yu, E.Y., et al., Germline and Somatic Genomic Testing for Metastatic Prostate Cancer: ASCO Guideline. J Clin Oncol, 2025. 43(6): p. 748-58.
21. Fizazi, K., et al., First-line talazoparib with enzalutamide in HRR-deficient metastatic castration-resistant prostate cancer: the phase 3 TALAPRO-2 trial. Nat Med, 2024. 30(1): p. 257-64.
22. Saad, F., et al., Olaparib plus abiraterone versus placebo plus abiraterone in metastatic castration-resistant prostate cancer (PROpel): final prespecified overall survival results of a randomised, double-blind, phase 3 trial. Lancet Oncol, 2023. 24(10): p. 1094-1108.
23. Chi, K.N., et al., Niraparib and abiraterone acetate for metastatic castration-resistant prostate cancer. J Clin Oncol, 2023. 41(18): p. 3339-51.
24. Survival Rates for Prostate Cancer. 2025b January 16, 2025 [cited 2025 March 6]; Available at: https://www.cancer.org/cancer/types/prostate-cancer/about/key-statistics.html.
25. Devlin, N., et al., Health-related quality of life effects of enzalutamide in patients with metastatic castration-resistant prostate cancer: an in-depth post hoc analysis of EQ-5D data from the PREVAIL trial. Health Qual Life Outcomes, 2017. 15(1): p. 130.
26. Basch, E., et al., Abiraterone acetate plus prednisone versus prednisone alone in chemotherapy-naive men with metastatic castration-resistant prostate cancer: patient-reported outcome results of a randomised phase 3 trial. Lancet Oncol, 2013. 14(12): p. 1193-9.
27. Moul, J.W. and Dawson, N., Quality of life associated with treatment of castration-resistant prostate cancer: a review of the literature. Cancer Invest, 2012. 30(1): p. 1-12.
28. Holmstrom, S., et al., Symptoms and impacts in metastatic castration-resistant prostate cancer: qualitative findings from patient and physician interviews. Patient, 2019. 12(1): p. 57-67.
29. Armstrong, A.J., et al., Five-year survival prediction and safety outcomes with enzalutamide in men with chemotherapy-naive metastatic castration-resistant prostate cancer from the PREVAIL trial. Eur Urol, 2020. 78(3): p. 347-57.
30. Ryan, C.J., et al., Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naive men with metastatic castration-resistant prostate cancer (COU-AA-302): final overall survival analysis of a randomised, double-blind, placebo-controlled phase 3 study. Lancet Oncol, 2015. 16(2): p. 152-60.
31. Morris, M.J., et al., Randomized phase III study of enzalutamide compared with enzalutamide plus abiraterone for metastatic castration-resistant prostate cancer (Alliance A031201 trial). J Clin Oncol, 2023. 41(18): p. 3352-62.

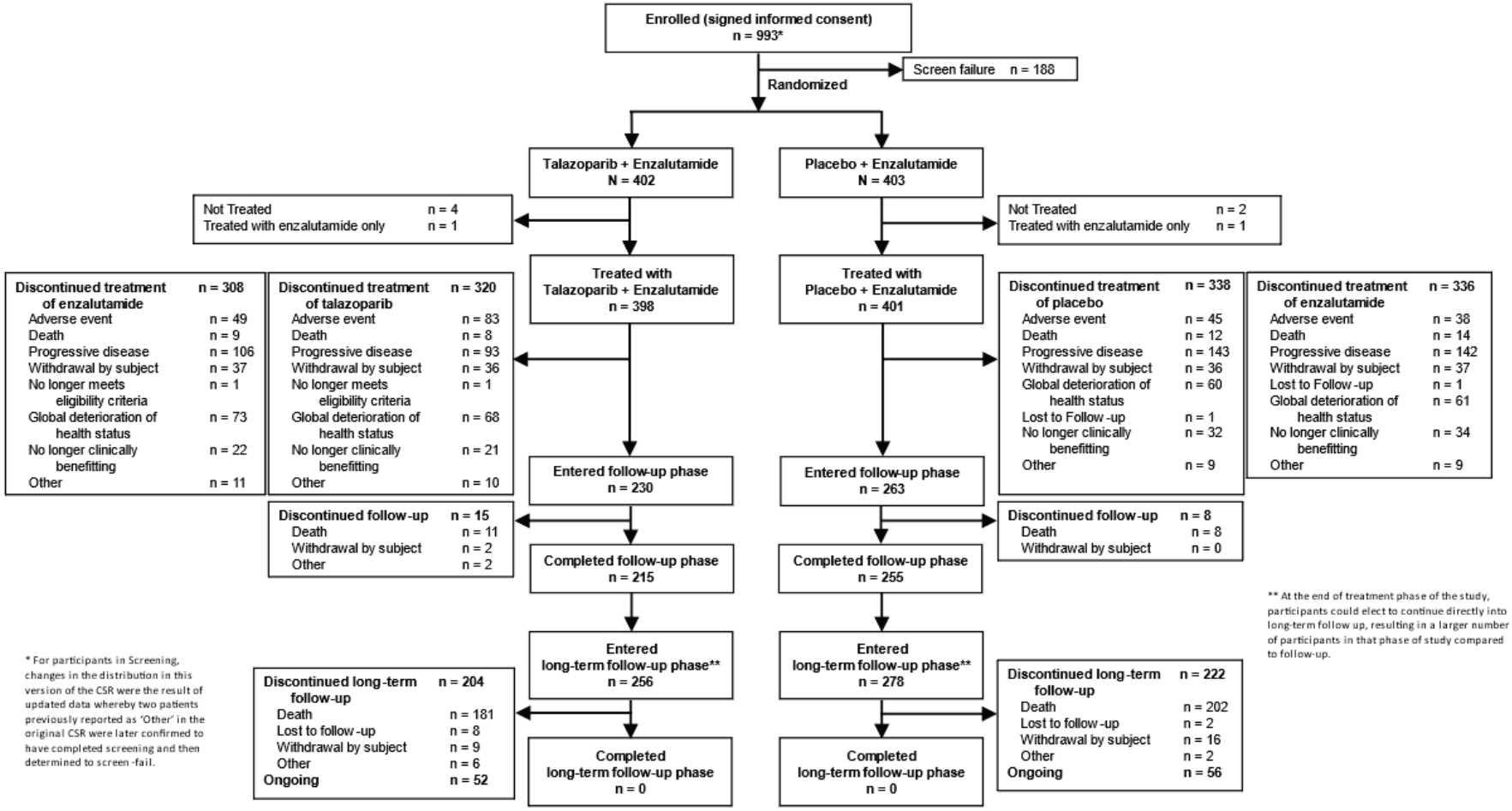
32. Tagawa, S.T., et al., Survival outcomes in patients with chemotherapy-naive metastatic castration-resistant prostate cancer treated with enzalutamide or abiraterone acetate. Prostate Cancer Prostatic Dis, 2021. 24(4): p. 1032-40.
33. Freedland, S.J., et al., Real-world treatment patterns and overall survival among men with Metastatic Castration-Resistant Prostate Cancer (mCRPC) in the US Medicare population. Prostate Cancer Prostatic Dis, 2024. 27(2): p. 327-33.
34. Swami, U., et al., Treatment patterns, clinical outcomes, health care resource utilization and costs in older patients with metastatic castration-resistant prostate cancer in the united states: an analysis of SEER-Medicare data. Clin Genitourin Cancer, 2023. 21(5): p. 517-29.
35. Barata, P.C., et al., Genetic testing in men with metastatic castration-resistant prostate cancer. JAMA Oncol, 2024. 10(7): p. 975-7.
36. Hage Chehade, C., et al., Trends and disparities in next-generation sequencing in metastatic prostate and urothelial cancers. JAMA Netw Open, 2024. 7(7): p. e2423186.
37. Armstrong, A.J., et al., Germline and somatic testing for homologous repair deficiency in patients with prostate cancer (part 1 of 2). Prostate Cancer Prostatic Dis, 2024.
38. Beer, T.M., et al., Enzalutamide in men with chemotherapy-naive metastatic castration-resistant prostate cancer: extended analysis of the phase 3 PREVAIL study. Eur Urol, 2017. 71(2): p. 151-4.
39. Saad, F., et al., Apalutamide plus abiraterone acetate and prednisone versus placebo plus abiraterone and prednisone in metastatic, castration-resistant prostate cancer (ACIS): a randomised, placebo-controlled, double-blind, multinational, phase 3 study. Lancet Oncol, 2021. 22(11): p. 1541-59.
40. FDA Briefing Document: NDA 208558/Supplement 25 (Lynparza [olaparib]); Oncologic Drugs Advisory Committee Meeting; April 28, 2023. US FDA.
41. Gillessen, S., et al., Decrease in fracture rate with mandatory bone-protecting agents in the EORTC 1333/PEACE-3 trial comparing radium-223 combined with enzalutamide versus enzalutamide alone: a safety analysis. Eur Urol, 2025. 87(3): p. 285-8.
42. Lukashchuk, N., et al., Impact of DNA damage repair alterations on prostate cancer progression and metastasis. Front Oncol, 2023. 13: p. 1162644.
43. Pascal, J.M., The comings and goings of PARP-1 in response to DNA damage. DNA Repair (Amst), 2018. 71: p. 177-82.
44. Pandey, N. and Black, B.E., Rapid detection and signaling of DNA damage by PARP-1. Trends Biochem Sci, 2021. 46(9): p. 744-57.
45. Fouquin, A., et al., PARP2 controls double-strand break repair pathway choice by limiting 53BP1 accumulation at DNA damage sites and promoting end-resection. Nucleic Acids Res, 2017. 45(21): p. 12325-39.
46. Ray Chaudhuri, A. and Nussenzweig, A., The multifaceted roles of PARP1 in DNA repair and chromatin remodelling. Nat Rev Mol Cell Biol, 2017. 18(10): p. 610-21.
47. Zhang, J. and Powell, S.N., The role of the BRCA1 tumor suppressor in DNA double-strand break repair. Mol Cancer Res, 2005. 3(10): p. 531-9.
48. Lord, C.J. and Ashworth, A., PARP inhibitors: synthetic lethality in the clinic. Science, 2017. 355(6330): p. 1152-8.

49. Krastev, D.B., Wicks, A.J., and Lord, C.J., PARP inhibitors - trapped in a toxic love affair. Cancer Res, 2021. 81(22): p. 5605-7.
50. Onji, H. and Murai, J., Reconsidering the mechanisms of action of PARP inhibitors based on clinical outcomes. Cancer Sci, 2022. 113(9): p. 2943-51.
51. Murai, J., et al., Trapping of PARP1 and PARP2 by clinical PARP inhibitors. Cancer Res, 2012. 72(21): p. 5588-99.
52. Murai, J., et al., Stereospecific PARP trapping by BMN 673 and comparison with olaparib and rucaparib. Mol Cancer Ther, 2014. 13(2): p. 433-43.
53. Zandarashvili, L., et al., Structural basis for allosteric PARP-1 retention on DNA breaks. Science, 2020. 368(6486).
54. Chi, K.N., et al., Niraparib plus abiraterone acetate with prednisone in patients with metastatic castration-resistant prostate cancer and homologous recombination repair gene alterations: second interim analysis of the randomized phase III MAGNITUDE trial. Ann Oncol, 2023. 34(9): p. 772-82.
55. U.S. FDA. April 28, 2023 Meeting of the Oncologic Drugs Advisory Committee - AstraZeneca Presentations. 2023.
56. Castro, E.D., et al., 1815P - Emergent circulating tumor DNA (ctDNA) variants and ctDNA burden dynamics with potential associations with talazoparib antitumor activity in TALAPRO-1, Presented at the 2023 Congress of the European Society for Medical Oncology: Madrid, Spain.
57. Agarwal, N., et al., Final overall survival (OS) with talazoparib (TALA) + enzalutamide (ENZA) as first-line treatment in unselected patients with metastatic castration-resistant prostate cancer (mCRPC) in the phase 3 TALAPRO-2 trial. J ClinOncol, 2025. 43(5 suppl).
58. Liu, G., et al., Abstract and Poster CT231: Identification of a novel agnostic predictive multiomic signature via elastic net/machine learning in TALAPRO-2 (TP-2), a phase 3 study of talazoparib (TALA) + enzalutamide (ENZA) vs placebo (PBO) + ENZA as first-line (1L) treatment in pat. Cancer Res, 2024. 84(7 suppl): p. CT231.
59. Chakraborty, G., et al., Significance of BRCA2 and RB1 co-loss in aggressive prostate cancer progression. Clin Cancer Res, 2020. 26(8): p. 2047-64.
60. Miao, C., et al., RB1 loss overrides PARP inhibitor sensitivity driven by RNASEH2B loss in prostate cancer. Sci Adv, 2022. 8(7): p. eabl9794.
61. Piulats, J.M., et al., Abstract CT018: TMPRSS2-ERG and RB1 as candidate predictive biomarkers for efficacy in TALAPRO-2: Phase 3 study of talazoparib (TALA) + enzalutamide (ENZA) vs placebo (PBO) + ENZA as first-line (1L) treatment in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC). Cancer Res, 2024. 84(7 suppl): p. CT018.
62. U.S. FDA. Xtandi (enzalutamide) Prescribing Information. 2012.
63. U.S. FDA. Zytiga (abiraterone acetate) Prescribing Information. 2011.
64. U.S.P.I. Prescribing information for TALZENNA™ (talazoparib) capsules.

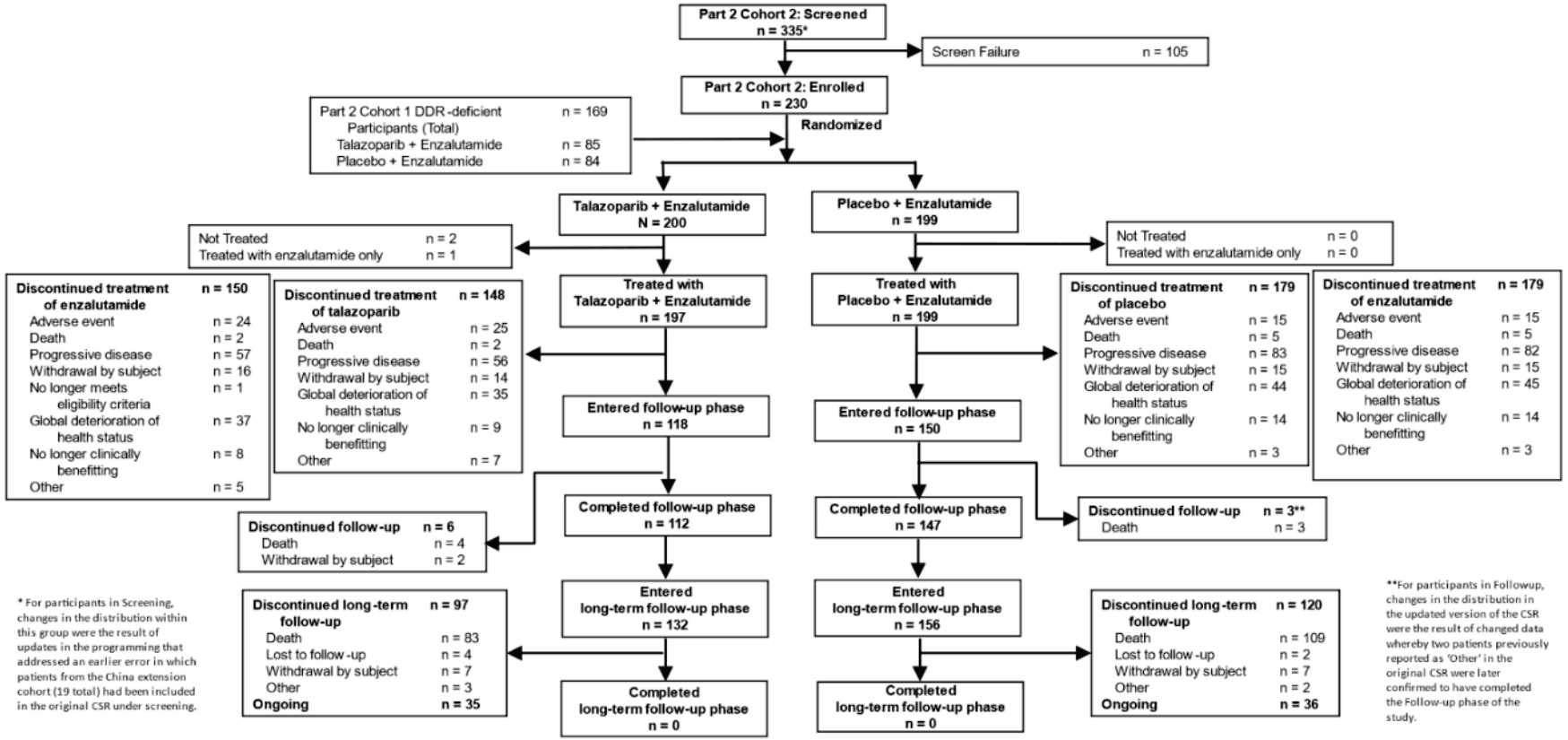
8.0 APPENDICES

8.1 Appendix A: Disposition

Appendix Figure 1 Participant Disposition – HRRm-unselected (Cohort 1)



Appendix Figure 2 Participant Disposition – HRRm-selected (Cohort 2)



8.2 Appendix B: Demographics

Appendix Table 1 Demographic Characteristics – HRRm-unselected (Cohort 1)

	TALAZOPARIB + ENZALUTAMIDE (N=402)	PLACEBO + ENZALUTAMIDE (N=403)	Total (N=805)
Age, (years) n (%)			
Age < 65	79 (19.7)	94 (23.3)	173 (21.5)
Age 65 to < 75	188 (46.8)	175 (43.4)	363 (45.1)
Age ≥ 75	135 (33.6)	134 (33.3)	269 (33.4)
Unspecified	0	0	0
n	402	403	805
Median	71.00	71.00	71.00
Mean	70.92	70.35	70.63
Standard deviation	7.99	8.19	8.09
Range (min, max)	(41, 90)	(36, 91)	(36, 91)
Geographical region, n (%)			
North America	59 (14.7)	63 (15.6)	122 (15.2)
European Union/Great Britain	150 (37.3)	155 (38.5)	305 (37.9)
Asia	124 (30.8)	117 (29.0)	241 (29.9)
Rest of the world	69 (17.2)	68 (16.9)	137 (17.0)
Race, n (%)			
White	243 (60.4)	255 (63.3)	498 (61.9)
Black or African American	11 (2.7)	5 (1.2)	16 (2.0)
Asian	127 (31.6)	120 (29.8)	247 (30.7)
American Indian or Alaska Native	0	0	0
Native Hawaiian or other Pacific Islander	2 (0.5)	1 (0.2)	3 (0.4)
Not reported	19 (4.7)	21 (5.2)	40 (5.0)
Unknown	0	0	0
Multiracial	0	1 (0.2)	1 (0.1)
Not collected due to local data privacy laws	0	0	0
NA	0	0	0
Ethnicity, n (%)			
Hispanic or Latino or of Spanish origin	39 (9.7)	46 (11.4)	85 (10.6)
Not Hispanic or Latino or of Spanish origin	341 (84.8)	327 (81.1)	668 (83.0)
Unknown	0	0	0
Not reported	22 (5.5)	30 (7.4)	52 (6.5)
Weight at baseline, kg			
n	402	402	804
Median	79.25	81.00	80.00
Mean	82.56	82.51	82.54
Standard deviation	18.66	17.50	18.08
Range (min, max)	(45, 169)	(48, 178)	(45, 178)
BMI at baseline, kg/m^2			
n	401	396	797
Median	27.00	27.35	27.20
Mean	27.70	27.84	27.77
Standard deviation	5.04	5.11	5.08
Range (min, max)	(16, 51)	(16, 59)	(16, 59)

BMI = body mass index; NA = not applicable.

Appendix Table 2 Demographic Characteristics – HRRm-selected (Cohort 2)

	TALAZOPARIB + ENZALUTAMIDE (N=200)	PLACEBO + ENZALUTAMIDE (N=199)	Total (N=399)
Age (years), n (%)			
Age < 65	48 (24.0)	53 (26.6)	101 (25.3)
Age 65 to < 75	92 (46.0)	88 (44.2)	180 (45.1)
Age ≥ 75	60 (30.0)	58 (29.1)	118 (29.6)
Unspecified	0	0	0
n	200	199	399
Median	70.00	71.00	70.00
Mean	69.83	69.76	69.79
Standard deviation	8.43	8.52	8.47
Range (min, max)	(41, 90)	(44, 90)	(41, 90)
Geographical region, n (%)			
North America	22 (11.0)	27 (13.6)	49 (12.3)
European Union/Great Britain	93 (46.5)	100 (50.3)	193 (48.4)
Asia	44 (22.0)	36 (18.1)	80 (20.1)
Rest of the world	41 (20.5)	36 (18.1)	77 (19.3)
Race, n (%)			
White	137 (68.5)	136 (68.3)	273 (68.4)
Black or African American	6 (3.0)	5 (2.5)	11 (2.8)
Asian	45 (22.5)	39 (19.6)	84 (21.1)
American Indian or Alaska Native	0	0	0
Native Hawaiian or other Pacific Islander	1 (0.5)	1 (0.5)	2 (0.5)
Not reported	10 (5.0)	17 (8.5)	27 (6.8)
Unknown	1 (0.5)	0	1 (0.3)
Multiracial	0	1 (0.5)	1 (0.3)
Not collected due to local data privacy laws	0	0	0
NA	0	0	0
Ethnicity, n (%)			
Hispanic or Latino or of Spanish origin	21 (10.5)	26 (13.1)	47 (11.8)
Not Hispanic or Latino or of Spanish origin	164 (82.0)	152 (76.4)	316 (79.2)
Unknown	0	0	0
Not reported	15 (7.5)	21 (10.6)	36 (9.0)
Weight at baseline, kg			
n	200	199	399
Median	80.65	83.90	81.70
Mean	83.22	85.09	84.15
Standard deviation	16.75	18.50	17.65
Range (min, max)	(45, 135)	(49, 178)	(45, 178)
BMI at baseline, kg/m^2			
n	199	196	395
Median	27.20	27.80	27.40
Mean	27.61	28.33	27.97
Standard deviation	4.65	5.51	5.10
Range (min, max)	(17, 45)	(18, 59)	(17, 59)

BMI = body mass index; NA = not applicable.