FDA Briefing Document

NDA 208558/Supplement 25

Drug name: olaparib (Lynparza)

Applicant: AstraZeneca

Oncologic Drugs Advisory Committee Meeting

April 28, 2023

Division of Oncology 1

Office of Oncologic Diseases

DISCLAIMER STATEMENT

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

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Glossary

AA	Abiraterone acetate
AA/P	Abiraterone acetate and prednisone or prednisolone
AC	Advisory Committee
ADT	Androgen Deprivation Therapy
AE	Adverse Event
ARPI	Androgen Receptor Pathway Inhibitor
BD	Briefing Document
BICR	Blinded Independent Central Review
BRCA	Breast Cancer Gene
BRF	Benefit-Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDTL	Cross-Discipline Team Leader
CI	Confidence Interval
ctDNA	Circulating Tumor DNA
FDA	Food and Drug Administration
GI	Gastrointestinal
HR	Hazard Ratio
HRR	Homologous Recombination Repair
IA	Integrated Assessment
INV	Investigator
ITT	Intent to Treat
LDH	Lactate Dehydrogenase
mCRPC	metastatic Castration Resistant Prostate Cancer
NR	Not Reached
NE	Not Estimable
ORR	Objective Response Rate
OS	Overall Survival
PARP	poly-ADP Ribose Polymerase
PARPi	poly-ADP Ribose Polymerase inhibitor

PCWG3	Prostate Cancer Working Group 3
PSA	Prostate-specific Antigen
REMS	Risk Evaluation and Mitigation Strategy
rPFS	Radiographic Progression Free Survival
SAR	Serious Adverse Reaction
SAP	Statistical Analysis Plan
SD	Standard Deviation
sNDA	supplemental New Drug Application
SOC	Standard of Care
VTE	Venous Thromboembolic Events

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

1.1 Purpose/Objective of the AC Meeting

The FDA is convening this Oncologic Drugs Advisory Committee meeting to discuss concerns arising from PROpel, a randomized trial evaluating the combination of olaparib or placebo plus abiraterone in patients with metastatic castration-resistant prostate cancer (mCRPC). PROpel enrolled patients regardless of *BRCA* or HRR mutation status. However, despite lack of stratification and pre-specified analyses by biomarker, exploratory subgroup analyses demonstrate that efficacy is largely attributable to patients with tumor *BRCA* mutations, with modest benefit and possible harm for patients without tumor *BRCA* mutations.

AstraZeneca is the pharmaceutical company applying for this supplemental new drug application (sNDA) for olaparib and will be referred to throughout this document as "the Applicant". The Applicant is proposing a broad indication for this combination, i.e., as first-line therapy for patients with mCRPC unselected for the presence of *BRCA* or HRR mutations.

The FDA would like the Committee to discuss whether the indication for olaparib in combination with abiraterone should be restricted to patients with tumor *BRCA* mutations.

1.2 Context for Issues to Be Discussed at the AC

Olaparib is one of two PARP inhibitors currently FDA-approved as a single agent for the treatment of patients with mCRPC who have progressed on prior androgen-receptor pathway inhibitor (ARPI) therapy, a later line of therapy than that evaluated in PROpel. Rucaparib, sold under the brand name Rubraca, is a PARP inhibitor approved for the treatment of patients with *BRCA*-mutated mCRPC following both an ARPI and prior taxane-based chemotherapy. Each of these approvals was restricted to molecularly defined subsets of patients (olaparib for patients with tumor HRR gene mutations, including *BRCA* mutations; rucaparib for patients with tumor *BRCA* mutations), so both indications reference use of an FDA-approved companion diagnostic test to select patients for therapy.

Mutations in *BRCA* are the most prevalent HRR-related mutations in prostate cancer and the most sensitive to PARP inhibition across tumor types. In ovarian cancer, several PARP inhibitors were initially approved for all-comer populations. However, further follow-up of the clinical trials that originally led to approval of these PARP inhibitors demonstrated potential for detriment in overall survival (OS) in patients with ovarian cancer without tumor *BRCA* mutations. Therefore, FDA subsequently restricted indications for two PARP inhibitors in ovarian cancer to patients with tumor *BRCA* mutations in December 2022.

PROpel did not prospectively evaluate *BRCA* or HRR status, stratify by these biomarkers, or include pre-specified analyses by biomarker status. This design followed preliminary results of a small study of abiraterone with or without olaparib (Study 8) conducted by the Applicant in the all-comer 2nd-line mCRPC setting that demonstrated an improvement in investigator-assessed radiographic progression-free survival (rPFS) for the addition of olaparib that did not appear to differ based on retrospectively-assessed HRR status. However, subsequent evaluation of Study 8 by *BRCA* status and by BICR

assessment of rPFS indicate no rPFS benefit by BICR-assessment in the ITT population and potentially detrimental rPFS and OS in the population without tumor *BRCA* mutations.

FDA analyses of PROpel data similarly indicate that the efficacy demonstrated by the addition of olaparib is strongly attributable to patients with tumor *BRCA* mutations. FDA is therefore concerned for potential harm in the remaining and much larger population of patients with no identified *BRCA* mutations.

1.3 Brief Description of Issues for Discussion at the AC

PROpel, the randomized phase 3 trial on which this application is primarily based, compared abiraterone + olaparib to abiraterone + placebo in 796 patients with previously untreated mCRPC. This line of therapy and disease setting represents a large population (~45,000 patients diagnosed annually in the United States) despite the increasing use of ARPI therapy in the metastatic hormone sensitive setting. The primary outcome measure of PROpel was investigator-assessed (INV) rPFS, which differs from progression-free survival (PFS) due to the inclusion of disease progression by bone scan. OS was a key secondary endpoint. PROpel enrolled an ITT population that, as noted above, neither prospectively assessed BRCA or HRR status nor included pre-specified analyses for these subgroups. Based on contemporary understanding of the importance of *BRCA* status as a predictive biomarker for PARP inhibitor efficacy, this trial design would be considered inappropriate today as the biomarker should have been prospectively evaluated. Additionally, a prospective analysis plan for efficacy results should have been formulated, for example with stratification or enrollment into separate cohorts by biomarker status. This is a significant design flaw that other sponsors designing similar studies have more appropriately addressed.

In PROpel, the prespecified interim analysis of the primary efficacy endpoint of rPFS by INV in the ITT population was statistically significant (Table 1). Median rPFS was 25 vs. 17 months in the olaparib + abiraterone vs. placebo + abiraterone arms, respectively (HR 0.66 [95% CI 0.54, 0.81]). At the time of the prespecified final analysis there was no statistically significant OS difference between arms in the ITT population (HR 0.81 [95% CI 0.67, 1.00]). FDA considers rPFS to be a clinical endpoint that, with sufficient magnitude, may reflect benefit to patients if supported by other clinically meaningful endpoints such as favorable OS and an acceptable safety profile. However, because of the design issues noted previously, the ITT in PROpel represents a heterogeneous population, which complicates interpretability and applicability of overall trial results to unselected patients with mCRPC.

Patients enrolling on PROpel were required to submit a ctDNA and tumor tissue sample for retrospective mutational analysis. Results for at least one of these assays were available for 98% of patients enrolled. Despite limitations of post-hoc analysis, FDA analyzed PROpel data for subgroups based on likelihood of *BRCA* mutation. FDA considers this analysis clinically relevant due to the strong and consistent predictive effect of *BRCA* mutation status for PARP inhibitors in prostate cancer as well as other tumor types. For this analysis, FDA considered patients with positive results for *BRCA* by either tumor tissue or ctDNA testing to have a *BRCA* mutation (11% of ITT), as both tests have high specificity, those with negative results by both tests to not have a mutation (54% of ITT), and those with negative results by only one test or unknown results for both tests to have undetermined *BRCA* status (35% of ITT). The undetermined population, primarily composed of those with a negative ctDNA assay and a

failed tissue assay, was considered to have a low-intermediate likelihood of *BRCA* mutation given the low sensitivity of the ctDNA assay for detecting *BRCA* mutation.

Using the above grouping, subgroup analysis demonstrated the improved rPFS in PROpel to be heavily attributable to efficacy in the small subgroup of patients with tumor *BRCA* mutation (11% of ITT). In this subgroup, the estimated median rPFS was not reached (NR) vs. 8 months in the olaparib + abiraterone vs. placebo + abiraterone arms (HR 0.24 [95% CI 0.12 to 0.46]). OS results were also more favorable in this subgroup with median OS NR vs. 23 months in the olaparib + abiraterone vs. placebo + abiraterone arms (HR 0.30 [95% CI 0.15 to 0.60]). In contrast, there was marginal rPFS improvement in the subgroup of patients without *BRCA* mutation, comprising over half of the ITT population, with a point estimate for the OS hazard ratio that was above 1. FDA is thus concerned about the risk:benefit tradeoff and potential OS detriment in patients without tumor *BRCA* mutation. Specifically, for the non-*BRCA*m subgroup, comprised of patients confirmed to be tumor *BRCA* negative by both ctDNA and tissue assays, the HR for rPFS was 0.85 (95% CI 0.66 to 1.11) with median rPFS of 22 vs. 17 months in the olaparib+ abiraterone vs. placebo + abiraterone arms; the HR for OS was 1.06 (95% CI 0.81 to 1.39) with median OS of 37 vs. 38 months in the olaparib + abiraterone vs. placebo + abiraterone arms (Table 1).

A sensitivity analysis of rPFS by BICR showed similar results for the ITT population and for the three subgroups by *BRCA* status described above. The rPFS by BICR results in the subgroup of patients without *BRCA* mutation showed only a 3-month improvement in median rPFS, approximately equal to the imaging interval; thus, the actual rPFS difference may be even smaller than 3 months.

Table 1: PROpel: rPFS and OS by *BRCA* Mutation Status*

	ITT (N=796, 100%)		***BRCA*m[1] (N=85, 11%)**		**Undetermined *BRCA* status[2] (N=284, 35%)**		**non-*BRCA*m[3] (N=427, 54%)**	
	Olaparib + AA/P	**Placebo + AA/P**	**Olaparib + AA/P**	**Placebo + AA/P**	**Olaparib + AA/P**	**Placebo + AA/P**	**Olaparib + AA/P**	**Placebo + AA/P**
rPFS (INV)								
Median in months (range)	25 (20, 28)	17 (14, 19)	NR (19, NR)	8 (6, 15)	NR (10, NR)	19 (14, 22)	22 (17, 25)	17 (14, 19)
HR[4] (95%CI)	0.66 (0.54, 0.81)		0.24 (0.12, 0.46)		0.66 (0.46, 0.94)		0.85 (0.66, 1.11)	
rPFS (BICR)								
Median in months (range)	28 (20, NR)	16 (14,19)	NR (NR, NR)	8 (4,16)	NR (19, NR)	19 (14, 22)	20 (17,28)	17 (14,19)
HR[4] (95%CI)	0.61 (0.49, 0.74)		0.19 (0.1, 0.37)		0.59 (0.41, 0.85)		0.82 (0.62, 1.08)	
OS								
Median in months (range)	42 (38, NC)	35 (31, 39)	NR (NR, NR)	23 (18,34)	NR (40, NR)	38 (28, 39)	37 (33, NR)	38 (31, NR)
HR[4] (95%CI)	0.81 (0.67, 1.00)		0.3 (0.15, 0.6)		0.73 (0.52, 1.03)		1.06 (0.81, 1.39)	

*rPFS results were based on data from the pre-specified interim analysis of rPFS with 84% information fraction and OS results were based on pre-specified final OS analysis.

[1] either ctDNA or tissue test positive

[2] either ctDNA or tissue test negative and other test unknown or both tests unknown

[3] both ctDNA and tissue tests negative

[4] HR and CI for ITT analyses were based on Cox PH model adjusted by metastasis location and prior docetaxel for mHSPC. HR for subgroup analysis was based on Cox PH model without any adjustment and Wald type confidence intervals were reported for subgroup analyses.

The FDA also analyzed the efficacy data from PROpel as those with *BRCA* mutations (11% of the ITT population) vs all those without a demonstrated *BRCA* mutation (89% of the ITT population), i.e., a combination of the undetermined (35% of the ITT population) and non-*BRCAm* (54% of the ITT population) subgroups previously described. For the subgroup of all those without a demonstrated *BRCA* mutation (89% of the ITT), the HR of rPFS is 0.77 (95% CI 0.63 to 0.96) with a 5-month improvement in median rPFS (24 vs 19 months) and the HR of OS is 0.92 (0.74, 1.14). FDA considers a 5-month improvement in median rPFS for patients in this disease setting with no difference in OS to reflect modest efficacy for an add-on therapy. Further, due to the combination with a highly effective partner (abiraterone), patients without an identified *BRCA* mutation, for whom the added efficacy of olaparib is modest, would be exposed to the added toxicities of olaparib for a long duration without demonstration of early futility.

While the overall safety profiles of abiraterone and olaparib in PROpel study were consistent with known toxicities of the individual therapies, the combination therapy arm of PROpel was considerably more toxic than the abiraterone and placebo arm, with higher incidences of ≥ Grade 3 adverse reactions (56% vs 43%), nausea/vomiting (35% vs 21%), myelosuppression (57% vs 26%), blood transfusion (18% vs 4%), and thromboembolic events (9 vs 3.5%). The higher rate of bothersome symptoms such as nausea, vomiting, diarrhea, higher need for blood transfusion and risk of thromboembolic events can have meaningful adverse impacts on patients' lives, particularly in this early setting in mCRPC where patients are generally minimally symptomatic. While results of analyses of PROs are considered exploratory for PROpel, FDA noted that higher proportions of patients in the olaparib arm reported side effect bother compared to placebo.

Summary and conclusions

Despite the lack of stratification by *BRCA* mutation status in PROpel, the rPFS improvement demonstrated in the ITT population appears primarily attributable to the 11% of patients with identified *BRCA* mutations. Further, the addition of olaparib to abiraterone in patients with a high likelihood of no *BRCA* mutations (negative by two assays), which constituted the majority of patients in the ITT population, potentially results in a detriment in OS. Although these results are based on an un-preplanned subgroup analysis, they are supported by several factors including:

1. External consistency: Minimal efficacy and potential harm from PARP inhibitor treatment in patients without *BRCA* mutations have been demonstrated in another study of olaparib + abiraterone (Study 8), in studies of other PARP inhibitors in prostate cancer [1, 2], and in studies in patients with other cancers, including advanced ovarian cancer [3,4]. *BRCA* mutation status consistently appears to be a strong predictive biomarker for PARP inhibitor efficacy.

2. Internal consistency: Minimal efficacy was demonstrated for the non-*BRCAm* subgroup for the secondary endpoints of rPFS by BICR and ORR.

3. Minimal impact of lack of stratification: Given the large size of the undetermined and non-*BRCAm* subgroups there was minimal imbalance in baseline characteristics. Results were also consistent when adjusting for these characteristics based on a prognostic model for mCRPC.

The FDA is further concerned about the added toxicity in patients without *BRCA* mutations, particularly in an add-on treatment setting where the median duration of rPFS with abiraterone by itself is approximately 16-months. This differs from a monotherapy for a biomarker-unselected population, where there may be early progression if the drug is ineffective and the drug may be stopped, avoiding unnecessary toxicity. FDA is therefore concerned that olaparib may represent a toxic placebo in patients without tumor *BRCA* mutations. The FDA review team therefore asks the Committee to opine on whether the indication for olaparib in combination with abiraterone should be restricted to patients whose tumors have a *BRCA* mutation.

2 Introduction and Background

2.1 Background of the Condition/Standard of Clinical Care

Prostate cancer is the most commonly diagnosed cancer in men in the United States, with an estimated ~250,500 new cases in 2022 (American Cancer Society 2021, Siegel et al 2021). After initially responding to androgen deprivation therapy, most patients with advanced stages of prostate cancer develop mCRPC. Table A1 in the Appendix lists therapies that are FDA-approved for use in mCRPC. None of these therapies are curative, and mCRPC is an area of unmet medical need for development of new therapies and/or therapeutic combinations to improve clinical outcomes.

2.2 Pertinent Drug Development and Regulatory History

Olaparib is a PARP inhibitor currently FDA-approved for the treatment of several solid tumors including prostate cancer in the 2nd-line mCRPC setting as well as ovarian, breast, and pancreatic cancers. See Table A2 in the Appendix for full listing.

Abiraterone is an androgen biosynthesis inhibitor that inhibits 17 α-hydroxylase/ C17,20-lyase (CYP17). Abiraterone is currently FDA-approved for the treatment of patients with mCRPC in combination with prednisone.

Clinical Trials of Olaparib in Prostate Cancer

The Applicant conducted several trials specifically evaluating olaparib either as monotherapy or in combination with abiraterone plus prednisone/prednisolone in patients with mCRPC. These trials include PROfound (monotherapy), and Study 8 and PROpel (combination therapy).

PROfound

In May 2020, FDA approved olaparib for the treatment of men with HRR gene-mutated mCRPC who progressed following prior enzalutamide or abiraterone. This was based on data from PROfound, which randomized 387 patients in a 2:1 ratio to olaparib 300 mg twice daily versus investigator's choice of enzalutamide or abiraterone acetate. Patients were assessed in one of 2 cohorts:

1. Cohort A (n= 245): mutations in either *BRCA*1, *BRCA*2, or *ATM*
2. Cohort B (n= 142): mutations in 12 other genes involved in the HRR pathway (*BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D, or RAD54L*)

PROfound demonstrated a statistically significant improvement in its primary outcome measure of BICR-assessed rPFS in Cohort A, with a HR of 0.34 (95% CI: 0.25, 0.47) for olaparib vs comparator arm. The

olaparib arm also demonstrated statistically significant improvements in confirmed ORR by BICR (33% vs 2%) and OS (HR 0.69 [95% CI 0.50, 0.97]).

There was also a statistically significant improvement in rPFS in Cohort A + B with HR of 0.49 (95% CI 0.38,0.63), however this was primarily attributable to the effects in Cohort A, composed predominantly of patients with *BRCA* mutations. In an exploratory analysis of Cohort B alone, median rPFS was 4.8 months for olaparib vs 3.3 months for the comparator (HR 0.88 [95% CI 0.58, 1.36]); ORR by BICR was 3.7% for olaparib vs comparator-treated patients.

Two companion diagnostic devices for patient selection were approved:

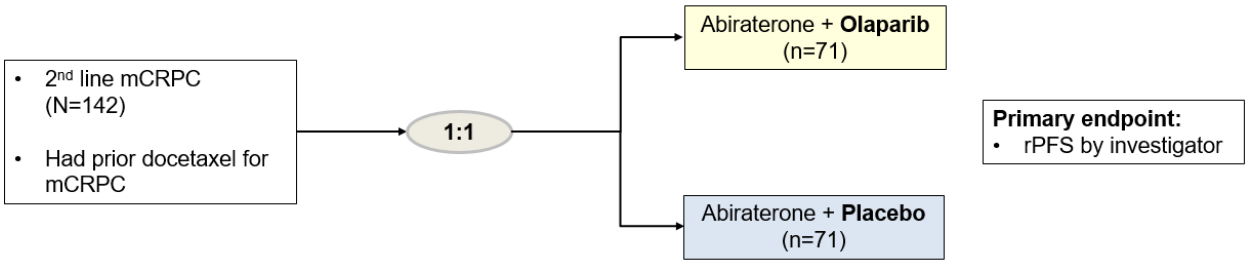
1. FoundationOne CDx (tumor tissue); and

2. FoundationOne Liquid CDx (circulating tumor DNA obtained from patient's plasma).

Study 8

To assess the combination of olaparib plus abiraterone (plus prednisone/prednisolone) in patients with mCRPC and with progression after docetaxel chemotherapy, the Applicant conducted Study 8, a small randomized, controlled phase 2 clinical trial in 142 patients. Randomization in Study 8 was not stratified by any predictive or prognostic factor, including HRRm or *BRCA*m status.

Figure 1: Study 8 Design



Both arms received prednisone/prednisolone.

Study 8 met its primary efficacy endpoint of rPFS by investigator assessment with an rPFS HR of 0.65 (95% CI: 0.44, 0.97). The median rPFS in the olaparib + abiraterone and control arm was 13.8 months vs 8.2 months, respectively. The HR for OS in the ITT population was 0.91 (95% CI: 0.60, 1.38). Subgroup analyses based on limited retrospective determination of HRR gene mutation status (15% HRRm, 25% non-HRRm, 61% unknown status), demonstrated similar rPFS (HRs of 0.74, 0.52, 0.67 respectively) in the three subgroups.

Based on these analyses, the Applicant concluded that there was benefit from olaparib in all enrolled patients, regardless of the presence of a sensitizing mutation in the tumor. However, the mutation status of the tumor was missing for more than half of patients enrolled. In 2018, the Applicant submitted the topline results of study 8 for FDA review, proposing an application seeking accelerated approval for olaparib in combination with abiraterone in an unselected population with mCRPC. In a meeting with the Applicant in May 2018, FDA discouraged submission and stated that the small size of Study 8 and the large proportion of patients with unknown HRR mutation status, which might lead to imbalances between the two arms, decreased confidence in the results. At the meeting, the Applicant

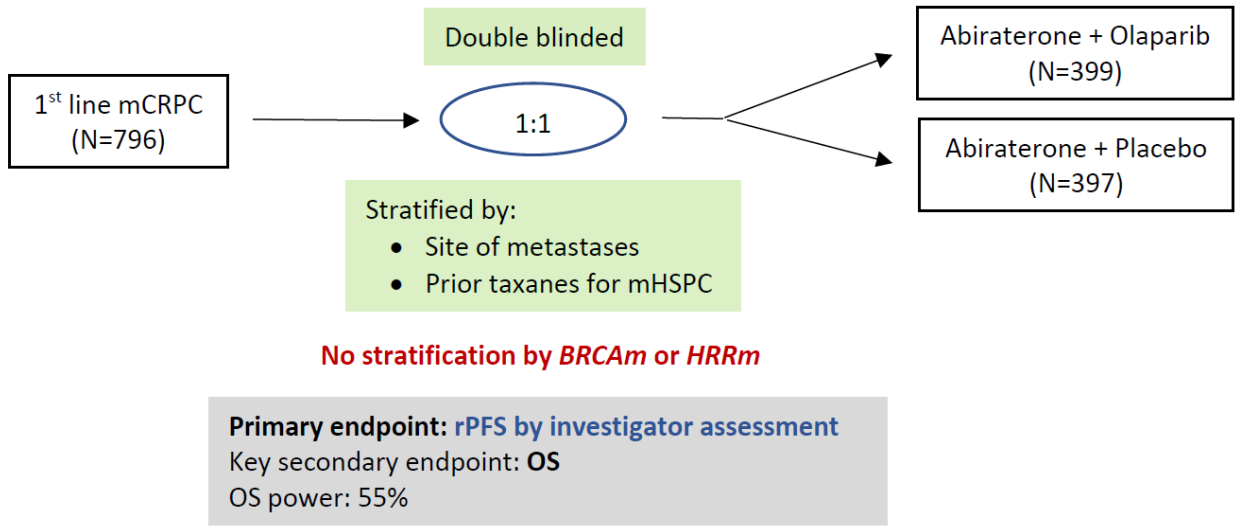
agreed to not pursue an accelerated approval based on Study 8 alone and acknowledged the need to assess the potential impact of HRR mutation on efficacy.

PROpel

To confirm the results of Study 8, the Applicant conducted PROpel, a study similar in design to Study 8 but with a larger sample size and conducted in an earlier line of therapy (pre-taxane chemotherapy) in patients with mCRPC (Figure 2).

PROpel was a phase 3 randomized, double-blind, placebo-controlled study comparing the combination of olaparib + abiraterone to placebo + abiraterone (plus prednisone or prednisolone in both arms) as first-line treatment for men with mCRPC, irrespective of HRR gene mutation status. Patients were randomized in a 1:1 ratio, stratified by site of metastases (bone only vs. visceral vs. other) and prior taxane for mHSPC (yes vs. no). The primary efficacy endpoint was investigator-assessed rPFS using RECIST 1.1 (soft tissue) and Prostate Cancer Working Group 3 (PCWG3) criteria (bone). Tumor imaging was performed every 8 weeks for the first 24 weeks, and then every 12 weeks. The key secondary endpoint was OS.

Figure 2: PROpel Study Design



mHSPC: metastatic hormone-sensitive prostate cancer; OS: overall survival. Both arms received prednisone/prednisolone.

PROpel enrolled patients regardless of tumor HRRm or *BRCA*m status. After randomization, both tumor tissue and blood samples were collected for retrospective evaluation of HRRm and *BRCA*m status. Mutation status was then determined using a ctDNA-based test (FoundationOne Liquid CDx), a tumor tissue test (FoundationOne CDx). These ctDNA and tumor tissue tests assessed for mutations in the following 14 genes: *ATM, BRCA1, BRCA2, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D*, and *RAD54L.*

PROpel had three data cut-offs (DCOs): DCO1 for the first interim analysis of rPFS (84% information fraction), DCO2 for the final analysis of rPFS, and DCO3 for the final OS analysis. Interim OS analyses were also performed at time of each rPFS analysis. For each interim analysis, the O'Brien and Fleming spending function was used to control the overall type I error.

PROpel met its primary endpoint of rPFS at the interim analysis. There was a statistically significant improvement of rPFS with olaparib in combination with abiraterone over placebo and abiraterone in the ITT population (HR 0.66 [95% CI: 0.54,0.81]; p<0.0001) and an 8-month improvement of median rPFS. The final OS analysis did not show a statistically significant difference in OS between two arms (Table 2).

Table 2: PROpel: Topline Results (ITT Population)

ITT (N=796)	Olaparib + abiraterone (n=399) vs placebo + abiraterone (n=397)	HR[a] (95%CI)	p-value
Median rPFS[b] (months)	25 vs 17	0.66 (0.54, 0.81)	<0.0001
Median OS[c] (months)	42 vs 35	0.81(0.67, 1.00)	0.054*

[a] HR and CI were based on Cox PH model adjusted by metastasis location and prior docetaxel for mHSPC;
[b] Interim analysis of rPFS by investigator with 83.7% information fraction.
[c] Final OS analysis, OS difference was not statistically significant (two-sided p-value cut-off = 0.038, using O'Brien-Fleming boundary).

2.3 Efficacy Issues

The Applicant is proposing a broad indication for the combination of olaparib plus abiraterone as first-line therapy for patients with mCRPC unselected for the presence of *BRCA* or HRR mutations. The FDA is therefore asking the Committee to discuss whether the indication should be restricted to patients selected for the presence of a tumor *BRCA* mutation. Considering this question in the context of PROpel and other applicable trial results, the key efficacy issues are as follows:

Efficacy Issue #1: Heterogeneous population enrolled in PROpel, unstratified by *BRCA* mutation status

Efficacy Issue #2: Inadequate determination of *BRCA* mutation status for patients on PROpel

Efficacy Issue #3: Potential harm in patients with confirmed *BRCA* mutation negative status across trials

2.3.1 Efficacy Issues in Detail

Efficacy Issue #1: *BRCA*m is a strong predictive biomarker of response to PARP inhibitors (PARPi) but PROpel enrolled a heterogenous population, unstratified by *BRCA* status.

Large randomized controlled trials of PARP inhibitors as monotherapy or in combination with ARPIs in patients with prostate cancer have consistently shown a strong correlation between the presence of *BRCA* mutation and observed benefit. Table 3 summarizes public results from these clinical trials. Both 2nd line trials administered olaparib as monotherapy versus investigator's choice (PROfound: abiraterone or enzalutamide, TRITON-3: abiraterone, enzalutamide, or docetaxel) whereas MAGNITUDE randomized patients to abiraterone with or without niraparib and TALAPRO-2 randomized patients to enzalutamide with or without talazoparib. The rPFS benefit for subgroups with *BRCA*m is consistently greater than that

in other subgroups, which suggests that efficacy is strongly attributable to the effect in these patients. For MAGNITUDE, enrollment into the cohort of patients with non-HRR tumor was stopped early due to futility in demonstrating efficacy for the addition of niraparib to abiraterone. In addition, all trials in Table 3 included *BRCA*m or HRRm as a stratification factor and/or selected patients based on their tumor mutation status.

Table 3: rPFS Analysis in Other Trials of PARPi in mCRPC

Clinical Trial	PARPi	Line	Stratified by HRRm or *BRCA*m	HR for rPFS (PARPi arm vs. control)		
				***BRCA*m**	**HRRm**	**Non-HRRm**
PROfound[a]	Olaparib	2nd	All patients selected for tumor HRRm	0.22	0.49	None Enrolled
TRITON-3[b]	Rucaparib	2nd	Yes	0.50	0.61 (*BRCA* + ATM)	None Enrolled
MAGNITUDE[b]	Niraparib	1st	Yes	0.55	0.76	Stopped early for futility
TALAPRO-2[b]	Talazoparib	1st	HRRm only	Not Presented	0.46	0.69

[a] sNDA submission for Olaparib; [b] ASCO GU 2023

The strength of *BRCA* mutation as a predictive biomarker for PARP inhibitors, including lack of benefit in patients without tumor *BRCA* mutations, has also been demonstrated across other solid tumors such as ovarian cancer (Table 4). In two trials (NOVA and ARIEL3) for patients with metastatic ovarian cancer where PARP inhibitors were used for maintenance treatment in the frontline setting, the rPFS benefit was more pronounced in the *BRCA*m subgroup. The hazard ratio (HR) estimates for final OS analysis for the non-*BRCA*m subgroup in both trials were above 1. Due to concern for potential OS detriment from treatment with PARP inhibitors in non-*BRCAm* subgroups, the FDA subsequently restricted both indications to patients with *BRCA* mutated tumors.

Table 4: Selected Clinical Trials of PARPi in Ovarian Cancer

Clinical Trial	PARPi	Setting	Endpoint	HR (PARPi vs. control arm)		Change to Labeling Non-*BRCA*m
				***BRCA*m**	***Non-BRCA*m**	
NOVA[a-c]	Niraparib	2nd-line maintenance	PFS	0.26	0.45	Restricted indication to g*BRCA*m[g] (Dec 8, 2022)
			Final OS	0.85	1.06	
ARIEL3[d, e]	Rucaparib	2nd-line maintenance	PFS	0.23	0.44 and 0.58 (high and low LOH[f])	Restricted indication to t*BRCA*m (Dec 21st, 2022)
			Final OS	0.83	1.08	

[a] Mirza et al. NEJM 2016; [b] USPI for niraparib; [c] www.gsk.com; [d] Coleman et al. Lancet 2017;
[e] https://clovisoncology.com; [f] LOH = loss of heterozygosity; [g] g*BRCA*: germline *BRCA* mutation; [h] t*BRCA*: tumor *BRCA* mutation.

PROpel enrolled patients with mCRPC irrespective of their *BRCA*m or HRRm status. The biomarker status of the patient's tumors was determined retrospectively. There was no prespecified plan for subgroup analysis by *BRCA*m or HRRm status in PROpel and randomization was not stratified by tumor biomarker

status. Thus, there is concern around interpreting trial results in a heterogeneous patient population where efficacy is likely to be primarily attributable to a small biomarker-defined subgroup.

Summary of Efficacy Issue #1: *Heterogeneous population enrolled in PROpel, unstratified by BRCA mutation status*

- *BRCA*m status has been consistently shown to be a strong predictor of benefit from PARP inhibitors.
- There is accumulating clinical evidence across trials of solid tumors showing lack of benefit and potential OS detriment from treatment with PARP inhibitors in patients without *BRCA*m tumors.
- While FDA might otherwise consider the 8-month improvement in median rPFS and no detriment in OS (HR for OS <1) as supportive of a favorable benefit-risk assessment in mCRPC, this would only apply to a homogenous patient population. However, PROpel enrolled a heterogenous patient population in terms of *BRCA*m status and thus sensitivity to PARP inhibitors. This raises the concern that the results in the ITT are attributable to the small subgroup with tumor *BRCA* mutations.
- FDA considers this to be a flaw of trial design that other sponsors have overcome when designing trials evaluating PARP inhibitors in this setting.

Efficacy Issue #2: Inadequate determination of tumor *BRCA*m status for patients enrolled in PROpel.

Determination of *BRCA*m status

Two diagnostic tests were used to determine the status of *BRCA*m and other HRRm in PROpel:

1. FoundationOne CDx (uses tumor tissue); and
2. FoundationOne Liquid CDx (uses circulating tumor DNA obtained from the patient's plasma).

The FDA previously approved both tests for selection of patients with HRRm or *BRCA*m for treatment with olaparib or rucaparib in more advanced settings of mCRPC.

Table 5 below summarizes the positive percent agreement (PPA) and negative percent agreement (NPA) for ctDNA *BRCA* assays compared to tumor tissue assays across clinical trials. These PPA and NPA values reflect, respectively, the probability of the ctDNA assay being positive when a *BRCA* mutation is detected by tissue testing or negative when the tissue test is negative for *BRCA* mutation. The PPA of ctDNA testing is relatively low, suggesting that a negative ctDNA test result in the absence of a valid negative tissue assay result is insufficient to rule out the presence of a *BRCA* mutation. This is consistent with the labeled recommendation for the FoundationOne Liquid CDx (ctDNA assay) which states that "A negative

result does not rule out the presence of a mutation in the patient's tumor" and that a negative ctDNA test result should be confirmed by a tumor tissue test.

Table 5: PPA and NPA of ctDNA *BRCA* Assays

Study	Tumor type(s)	ctDNA Assay	PPA % (95% CI)	NPA % (95% CI)
PROpel (olaparib)	Prostate cancer	*BRCA1/2*	**74** (59, 86)	**96** (94, 98)
PROfound (olaparib)	Prostate cancer	*BRCA1/2, ATM*	**80** (72, 86)	**92** (87, 95)

***BRCA* test results in PROpel:**

Table 6 summarizes the concordance for ctDNA and tumor tissue *BRCA* tests in PROpel. The *BRCA*m status of each patient's tumor in PROpel was assessed retrospectively. Because patients with mCRPC tend to have bone-predominant disease, obtaining fresh tissue for biopsy is often impractical. As a result, archival prostate biopsies or prostatectomy specimens were the source of tissue for *BRCA* testing for 93% of patients enrolled in PROpel. However, test failure rates in this setting were high; in 33% of the ITT population, *BRCA* mutation status by tumor tissue test was unknown. As a result, in 28% of the ITT population (N=226), negative ctDNA test results could not be confirmed by tissue test.

Table 6: Concordance Between Tumor Tissue and ctDNA Assays (PROpel)

***BRCA* test results in PROpel**		**Tumor tissue test, n (%)**			
		Yes	**No**	**Unknown**	**Total**
ctDNA assay, n (%)	**Yes**	34 (4)	18 (2)	17 (2)	69 (9)
	No	12 (2)	427 (54)	226 (**28**)	665 (84)
	Unknown	4 (1)	40 (5)	18 (2)	62 (8)
	Total	50 (6)	485 (61)	**261 (33)**	796 (100)

Ultimately, the retrospective analysis of *BRCAm* status may have impacted adequate characterization of *BRCA* status in patients on PROpel given reliance on archival tissue samples. It is likely that had PROpel required prospective evaluation of *BRCA* status, a substantial proportion of the 35% of patients whom the FDA considered to have undetermined tumor BRCA status may have been more accurately characterized by obtaining and evaluating an adequate tissue sample.

***BRCA*m-based subgroups:**

To assess the correlation between the results of PROpel and patients' *BRCA* mutation status, FDA defined three exploratory subgroups based on the likelihood of having a *BRCA* mutation:

a. ***BRCA*m** (11% of the ITT): Patients with *BRCA* mutation identified via either ctDNA or tumor tissue testing. The relatively high specificity of both tests leads to high certainty that these patients have *BRCA* mutated disease.

b. ***Non-BRCA*m** (54% of the ITT): Patients with negative *BRCA* mutation status confirmed by *both* ctDNA and tumor tissue testing, leading to high certainty that patients *do not* have *BRCA* mutated disease.

c. **Undetermined** *BRCA* status (35% of the ITT): Patients who had one negative *BRCA* mutation test result that was not confirmed by the other test, or for whom results of both tests were indeterminate. Based on the demonstrated prevalence of BRCA mutations in PROpel and in other

studies of metastatic prostate cancer and the rate of non-concordance between the ctDNA and tissue results, the FDA estimates the incidence of underlying BRCA mutations in this undetermined BRCA group to likely be small (approximately 2% and 7%).

Summary of efficacy issue #2: *Inadequate determination of BRCA status for patients on PROpel*

- A negative ctDNA assay result for *BRCA* without a confirmatory tissue assay result does not definitively rule out the presence of a *BRCA* mutation. Patients with negative ctDNA assay results and tissue assay failure on PROpel did not undergo further confirmatory testing, leading to substantial uncertainty regarding *BRCAm* status in these patients.
- Use of archival tissue from prostate biopsy or prostatectomy specimens in a disease where bone metastases predominate results in frequent test failure. This led to about one-third of patients having unknown tumor tissue *BRCA* results.
- A large percentage of enrolled patients (~35% of the ITT) had undetermined *BRCA* mutational status, in part due to the retrospective PROpel testing strategy. This population likely included patients with unidentified *BRCA* mutations.

Efficacy Issue #3: Potential harm in non-*BRCAm* subgroup across trials (PROpel, Study 8, and others)

PROpel subgroup analysis by *BRCA*m status: primary and secondary endpoints

Table 7 shows the exploratory subgroup analysis of primary and secondary endpoints by *BRCA* subgroup in PROpel. The efficacy results in the ITT population were largely attributable to a strong treatment effect in patients with tumor *BRCA* mutations. For the non-BRCAm subgroup, the upper bound of the 95% confidence interval for rPFS HR crosses 1, and the point estimate for the OS HR is above 1, indicating at best a modest improvement in rPFS and a potential for OS detriment. This non-*BRCA*m subgroup represented the majority of patients in PROpel (54%).

A sensitivity analysis of rPFS by BICR assessment was consistent with the investigator-assessed rPFS. Of note, the median rPFS difference in the non-*BRCA* subgroup by BICR assessment is only 3 months, which is approximately equal to the imaging interval, suggesting that the true rPFS difference may be smaller in this subgroup.

The difference in confirmed ORR by BICR between arms at the time of the final rPFS analysis was 32% for the *BRCAm* subgroup and only 4% for those in the non-*BRCA*m subgroup. Although assessment of ORR is limited by the small number of patients with prostate cancer who have measurable disease, this

finding also suggests efficacy with the addition of olaparib largely isolated to those with *BRCA* mutated disease and a concern for lack of efficacy in the non-*BRCA*m subgroup.

Table 7: Primary and Selected Secondary Endpoints Analysis by *BRCA* Mutation Status (PROpel)

	BRCAm N= 85 (11%) Olaparib vs Placebo	**Undetermined *BRCAm* status** N= 284 (35%) Olaparib vs Placebo	**Non-*BRCAm*** N= 427 (54%) Olaparib vs Placebo
rPFS by INV			
Median, months	NR vs 8	NR vs 19	22 vs 17
HR (95% CI)	0.24 (0.12, 0.46)	0.66 (0.46, 0.94)	0.85 (0.66, 1.11)
rPFS by BICR			
Median, months	NR vs 8	NR vs 19	20 vs 17
HR (95% CI)	0.19 (0.1, 0.37)	0.59 (0.41, 0.85)	0.82 (0.62, 1.08)
OS			
Median, months	NR vs 23	NR vs 38	37 vs 38
HR (95% CI)	0.3 (0.15, 0.6)	0.73 (0.52, 1.03)	1.06 (0.81, 1.39)
ORR by BICR			
Patients with evaluable disease at baseline	N= 20 vs 18	N= 50 vs 51	N= 92 vs 81
ORR % (95% CI)	60% (36, 81) vs 28% (10, 53) (Δ = 32%)	60% (45, 74) vs 43% (29, 58) (Δ = 17%)	52% (42, 63) vs 48% (37, 60) (Δ = 4%)

N: number; NR: not reached

Exploratory post-hoc subgroup analyses with small sample sizes create the potential for imbalance in baseline covariates. The FDA therefore used a prognostic model developed by Halabi et al in 2014[3] to assess overall balance among baseline prognostic risk factors for patients in the three subgroups by *BRCA* mutation status. This model uses eight identified prognostic factors (opioid use, disease site, ECOG performance status, LDH, albumin, hemoglobin, alkaline phosphatase, and PSA) to calculate a composite risk score for each patient that predicts OS in the first-line chemotherapy setting for patients with mCRPC. Using the regression coefficients of this model and baseline values of prognostic factors, FDA calculated a risk score (i.e., exp [$\Sigma\beta X$]) for each patient in PROpel. The median scores for ITT and the three *BRCA*-based subgroups are shown in Table 8.

Table 8: Median Prognostic Risk Score by Subgroup (PROpel)

Population		**Median risk score (Higher score indicates worse prognosis)**	
		Olaparib + Abiraterone	**Placebo + Abiraterone**
ITT	N=796	0.68	0.66
BRCAm	N=85 (11%)	0.63	0.80
Undetermined *BRCAm* status	N=284 (35%)	0.68	0.64
Non-*BRCAm*	N=427 (54%)	0.69	0.65

Despite lack of stratification, summarized baseline prognostic risk scores were well-balanced between treatment arms in the undetermined *BRCA*m subgroup and in the non-*BRCAm* subgroup, likely due to

large sample size of these subgroups. The level of imbalance in baseline characteristics was higher in the *BRCAm* subgroup likely due to the small sample size. After adjustment for risk score, there were no overall changes in the conclusions for rPFS and OS subgroup analyses.

The FDA also analyzed the efficacy data from PROpel as those with *BRCA* mutations (11% of the ITT population) vs all those without a demonstrated BRCA mutation (89% of the ITT population), i.e., a combination of the undetermined and non-*BRCAm* subgroups previously described. In the 89% of patients without a demonstrated *BRCA* mutation, the addition of olaparib to abiraterone yielded a 5-month improvement in median rPFS (24 vs 19 months; HR 0.77; 95% CI: 0.63, 0.96) and the HR for OS was 0.92 (95% CI 0.74, 1.14). FDA considers a 5-month improvement in median rPFS for patients in this disease setting with no difference in OS to reflect modest efficacy for an add-on therapy with a 20-month median duration of exposure. In addition, it is not clear to what extent the 5-month improvement in rPFS may be attributed to patients with unidentified *BRCA* mutations.

The Applicant has noted that the median rPFS improvement by BICR in the population of patients defined by the Applicant as negative for *BRCAm* (similar to the FDA-defined population of 89% of the ITT population without a demonstrated *BRCA* mutation but excluding 18 patients with unknown results for both assays) was 11 months. The FDA considers this an overestimation of the treatment effect in this population for several reasons. First, rPFS by INV was the primary endpoint and thus rPFS by BICR should be considered as supportive. The hazard ratios were similar (0.76 vs 0.72 for rPFS by INV vs BICR respectively) with the difference in median rPFS largely reflecting an unstable median due to no rPFS events by BICR proximate to the olaparib arm median. Further, the difference was almost entirely attributable to the Undetermined *BRCAm* status subgroup, which may include patients with *BRCA* mutation, and the median rPFS difference in the non-*BRCAm* subgroup was only 3 months, as previously discussed.

Table 9: Efficacy by *BRCAm* vs No Demonstrated *BRCA* Mutation (PROpel)

		BRCAm **N= 85 (11%) Olaparib vs Placebo**	**No Demonstrated BRCA Mutation N= 711 (89%) Olaparib vs Placebo**
rPFS by INV	HR (95% CI)	0.24 (0.12, 0.46)	0.77 (0.63, 0.96)
	Median (months)	NR vs 8	24 vs 19 (Δ: 5 mo)
OS	HR (95% CI)	0.3 (0.15, 0.6)	0.92 (0.74, 1.14)
	Median (months)	NR vs 23	40 vs 38

Study 8 Final Results

As mentioned previously, Study 8 met its primary efficacy endpoint by demonstrating an improvement in rPFS by investigator assessment with olaparib + abiraterone (N=68) compared to placebo + abiraterone (N=68) (HR 0.65 [95% CI 0.44, 0.97); median rPFS was 13.8 months with olaparib + abiraterone vs 8.2 months with placebo + abiraterone. However, a subsequent sensitivity analysis of rPFS by BICR assessment submitted to the FDA during review of PROpel demonstrated a median rPFS of only 11.1 months in the olaparib + abiraterone arm vs 8.2 months with placebo + abiraterone; this difference was not statistically significant (HR 0.95 [95% CI: 0.62, 1.44]). There was also no statistically significant difference in OS between the two treatment arms in the ITT population (HR 0.91 [95% CI: 0.60,1.38]).

Study 8 subgroup analysis by *BRCAm* status

In an exploratory analysis by the three *BRCAm* status subgroups defined by the FDA for analysis of PROpel and described previously, 23 (16%) of 142 patients in Study 8 were found to have non-*BRCAm* status. In this subgroup, there was no statistically significant difference in rPFS by investigator assessment between arms. The HRs for rPFS by BICR assessment and for OS for olaparib + abiraterone vs. placebo + abiraterone in the non-*BRCAm* subgroup were both above 1, which raises concern for potential harm from the addition of olaparib in patients with non-*BRCAm* status (Table 10). Although not shown in the table, the HR of OS was consistently over 1 for non-*BRCAm* subgroups when two other classification methods proposed by Applicant were used to combine the tumor tissue, ctDNA and germline test results.

Table 10: Final Efficacy Results of Study 8

	ITT (N=142) Olaparib vs Placebo	***BRCAm* (5%) Olaparib vs Placebo**	**Undetermined *BRCAm* status (79%) Olaparib vs Placebo**	**Non-*BRCAm* (16%) Olaparib vs Placebo**
N (Olaparib vs Placebo)	71 vs 71	2 vs 5	56 vs 56	13 vs 10
rPFS by INV				
Median, in months	14 vs 8	20 vs 3	15 vs 8	12 vs 11
HR (95% CI)	0.65 (0.44, 0.97)	NE[a]	0.62 (0.39, 0.98)	0.88 (0.33, 2.37)
rPFS by BICR				
Median, in months	11 vs 8	20 vs 3	11 vs 8	12 vs 11
HR (95% CI)	0.95 (0.62, 1.44)	NE	0.89 (0.56, 1.41)	1.72 (0.56, 5.76)
OS				
Median, in months	23 vs 21	23 vs 17	26 vs 21	**12 vs 25**
HR (95% CI)	0.91 (0.60 ,1.38)	NE	0.71 (0.43, 1.16)	**2.77 (1.06, 8.06)**

[a] Not estimable

Although interpretation of Study 8 results is limited by its small sample size, the efficacy results by exploratory subgroups based on *BRCA* mutation status are consistent with those of PROpel. Notably, the results of both trials point to a possible OS detriment in patients with non-*BRCA*m tumors. When findings from two separate trials are consistent, they are less likely to be merely due to chance. This further raises the concern for lack of benefit and potential harm of treatment with olaparib for patients without *BRCAm* tumors.

Considering the results of both PROpel and Study 8, as well as the consistency of modest or no efficacy for non-*BRCAm* populations in trials of olaparib and other PARP inhibitors across tumor types (Table 4), FDA is concerned about the Applicant's proposed broad indication for olaparib + abiraterone in mCRPC. Since the Applicant is seeking an "all-comers" indication, no companion diagnostic device (CDx) is proposed for contemporaneous approval for patient selection for treatment with olaparib + abiraterone. Thus, patients in a real-world setting may not be identified as lacking a tumor *BRCA*

mutation, which may expose them to the toxicity of olaparib for more than a year (the median rPFS for abiraterone alone) without demonstration of futility.

Summary of Efficacy Issue #3: Potential harm in patients with confirmed BRCA negative status

- In both PROpel and Study 8, improvement in rPFS was modest for patients with non-*BRCAm* tumors and the HR estimate for OS was >1, raising concern for a potential OS detriment. In PROpel, this subgroup represented the majority of enrolled patients.
- Results for other secondary endpoints (rPFS by BICR, ORR) also suggested diminished efficacy in this subgroup
- Consistency of these results in both PROpel and Study 8 suggest they are less likely due to chance. These results are externally consistent with other trials of PARP inhibitors in prostate cancer as well as other solid tumors, including ovarian cancer.

Regulatory Precedent for Restricting Indications based on Potential Harm in Un-prespecified Analyses

Subgroup analysis has an important role in regulatory decision-making to ensure there is consistency of treatment effect across the study subgroups [6]. Although subgroup analyses are generally considered exploratory, FDA may restrict an indication to a biomarker-defined subgroup based on subgroup analysis when there are safety/efficacy concerns and a strong biologic rationale. Selected examples of restricting an indication based on lack of efficacy, added toxicity, and concern for OS detriment based on unstratified subgroup analysis are listed below [7-10]:

1. Limitation of use for pemetrexed in patients with squamous cell non-small cell lung cancer (2008).
2. Limitations of use for the cetuximab (2012) and panitumumab (2014) in patients with RAS mutant metastatic colorectal cancer.
3. Restriction of the indication of olaparib in combination with bevacizumab for the maintenance treatment of ovarian cancer to patients with homologous recombination deficiency as defined by a *BRCA* mutation or a high tumor genomic instability score (2020).

2.4 Safety Issues

2.4.1 Sources of Data for Safety

The safety of olaparib + abiraterone for the proposed indication was evaluated based on analysis of safety in all patients enrolled and treated on PROpel. This included both investigator-reported adverse reactions (ARs) and patient-reported outcomes (PROs). Data from Study 8 were considered supportive due to its smaller sample size and different line of therapy.

2.4.2 Safety Summary

The overall summary of observed safety data in patients enrolled on PROpel is presented in Table 11. Overall, observed toxicities were in line with those expected based on previous clinical experience with olaparib and abiraterone as monotherapies, with no new safety signal observed with the combination.

Median exposure duration for patients on the olaparib + abiraterone arm was 17.5 months vs 15.7 months for those on the placebo + abiraterone arm. This represents a relatively prolonged duration of exposure for patients, primarily due to the efficacy of abiraterone.

Table 11: Summary of Safety Data (PROpel ITT population)

Toxicity	**Olaparib + abiraterone (N=398)**	**Placebo + abiraterone (n=396)**
Grade 3-4 adverse reactions (ARs) (%)	56	43
Serious ARs (%)	41	32
Fatal ARs (%)	7	5
All Grade ARs leading to discontinuation of olaparib vs placebo (%)	17	9
All Grade myelosuppression* (%)	57	26
Received blood transfusion (%)	18	4
All Grade nausea/vomiting (%)	35	21
All Grade diarrhea (%)	21	11
All Grade venous thromboembolic events (%)	9	3.5

* Anemia, thrombocytopenia, neutropenia, lymphopenia

Patients randomized to treatment with olaparib + abiraterone experienced a higher frequency of total, high-grade, serious, and fatal adverse reactions than those on the placebo + abiraterone arm. Specific adverse events noted to occur with greater frequency for patients on the olaparib + abiraterone arm were thromboembolic events, myelosuppression, nausea/vomiting, and diarrhea.

The most common causes of fatal adverse reactions in patients treated with olaparib + abiraterone were COVID-19 (n=4) and pneumonia (n=1). The most common serious adverse reactions in > 2% of patients were anemia (6%), COVID-19 (6%), pneumonia (4.5%), pulmonary embolism (3.5%), and urinary tract infection (3%). The most common adverse reactions which resulted in permanent discontinuation of olaparib were anemia (4.3%) and pneumonia (1.5%).

Overall, the most common adverse reactions (≥10%) in patients who received olaparib + abiraterone were anemia (48%), fatigue (38%), nausea (30%), diarrhea (19%), decreased appetite (16%), lymphopenia (14%), abdominal pain (13%), and dizziness (14%).

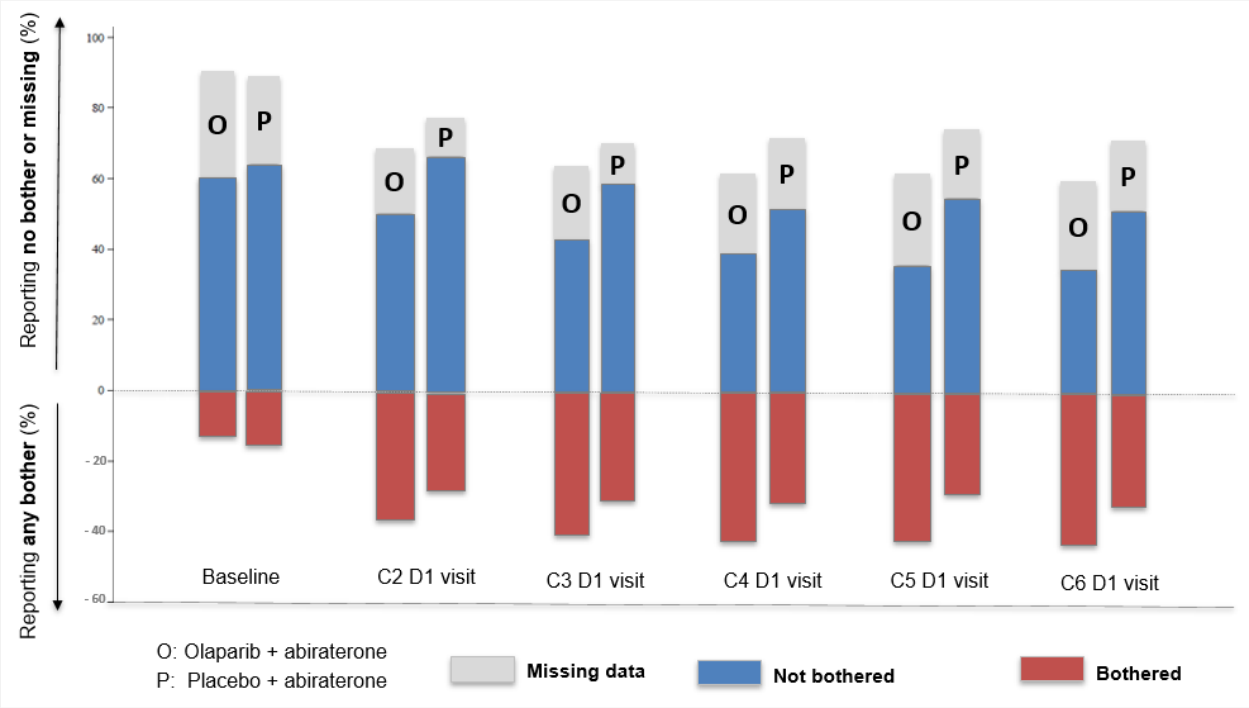
Patient Reported Outcomes (PROs)

Patient-reported outcomes were collected in PROpel using the Functional Assessment of Cancer Therapy – Prostate (FACT-P) instrument [(11)]. FDA specifically focused on the descriptive results of the FACT GP5 overall side effect impact item to assess tolerability of the treatment regimen. This GP5 item asks patients if they are "bothered by side effects of treatment" and rates the level of bother from 0 to 4 (0: Not at all; 1: A little bit; 2: Somewhat; 3: Quite a bit; 4: Very much). Previous experience in the literature (Saad, et al) suggested minimal ARPI side effect impact compared to placebo using a patient-reported side effect bother item in patients with non-metastatic CRPC[(12)]. In PROpel, PROs were included as exploratory and descriptive information and the adequate completion rate (greater than70% at most timepoints in the first six cycles) allowed for analysis and interpretation of these results.

Patient-generated responses to GP5 question in FACT-P tool are shown in Figure 3. Although a formal comparative tolerability endpoint was not included in the PROpel study, FDA noted higher proportions

of patients in the olaparib arm who reported side effect bother compared to placebo. Although the number of patients reporting bother was consistently higher in the olaparib arm, there were few patients who reported severe bother (score 3 or 4) in both arms at all time points.

Figure 3: FACT-P GP5 Reports at Baseline and First 6 Months on Treatment (PROpel)



These descriptive and exploratory GP5 results support the observed increased clinician-reported adverse reactions observed when olaparib is added to abiraterone.

2.4.3 Summary of Safety Issues

- Patients treated with olaparib + abiraterone experienced greater toxicity than patients treated with placebo + abiraterone in terms of higher rates of overall ARs, high-grade, serious, and fatal adverse reactions.
- Specific ARs experienced with higher frequency in patients treated with olaparib included venous thromboembolic events, myelosuppression, requirement for blood transfusions, nausea/vomiting, and diarrhea.
- PROpel evaluated an early line of therapy and a minimally symptomatic population at baseline, so toxicity may be particularly impactful given prolonged treatment duration in a setting where standard of care is ARPI monotherapy, which is generally well-tolerated.
- As olaparib will be given as an add-on therapy to a very effective partner drug, patients may be exposed to treatment for a prolonged duration without demonstration of futility. This is different than a monotherapy setting, where lack of efficacy may be clear much earlier and therapy could be stopped for early disease progression.
- PRO data, although exploratory, demonstrated a higher level of side effect burden in patients treated with olaparib + abiraterone vs. patients treated with placebo + abiraterone.

2.5 Benefit: Risk Assessment

PROpel enrolled a heterogenous population in terms of tumor *BRCA*m status and sensitivity to PARPi. Therefore, although subgroup analyses are generally considered exploratory, they are performed to ensure consistency of treatment effect across the study subgroups and results of subgroup analyses can impact regulatory decision making.

Below is the FDA's benefit: risk assessment in the three subgroups defined based on probability of having tumor *BRCAm* in PROpel:

- ***BRCA*m subgroup:** There is evidence of clinical benefit (clinically meaningful improvement in time to disease progression and overall survival) from adding olaparib to abiraterone in patients who had 1-2 positive *BRCA* test(s). Despite lack of stratification and a prespecified analysis plan for this very small subgroup, adjustment by a known prognostic model in mCRPC did not produce overall divergent results from unadjusted results. This subgroup likely accounts for much of the overall efficacy benefit observed on PROpel.

- **Non-*BRCA*m subgroup:** Despite modest improvement in rPFS by investigator in this subgroup, this is of questionable clinical meaningfulness and lessens in magnitude when reviewed by BICR. Olaparib is an add-on to abiraterone, a highly effective treatment with a median rPFS as monotherapy of over a year. Thus, patients in whom olaparib has a very small likelihood of efficacy may be exposed to its toxicities (e.g., myelosuppression, gastrointestinal toxicities, thromboembolic events, increased symptom burden) for a prolonged duration due to the efficacy of abiraterone. Additionally, the HR for OS for patients without tumor *BRCAm* in both PROpel and in Study 8 was above 1, which is concerning for potential OS detriment and harm from the addition of olaparib.

- **Undetermined *BRCA*m status:** This subgroup is a heterogenous mixture of a very small number of patients with undetected *BRCA* mutation and a much larger population (> 90% of this subgroup) whose tumors are likely truly negative for *BRCA* mutation. Given the potential toxicity and worsened survival demonstrated in patients with confirmed non-*BRCA* status, FDA is concerned that adding olaparib to abiraterone in patients with unknown or an undetermined negative test result may harm the great majority of this population that is truly negative for *BRCA*m.

3 Summary

The Applicant has submitted a supplementary new drug application for olaparib in combination with abiraterone and prednisone or prednisolone, for treatment of adult patients with mCRPC, which includes patients with and without tumor *BRCA* mutations. However, FDA is concerned that efficacy and safety have not been demonstrated outside of the small population of patients with tumor *BRCA* mutations and that the addition of olaparib to abiraterone may cause harm in patients who are definitively negative for tumor *BRCA* mutations. Despite the suboptimal trial design of PROpel, which did not prospectively assess *BRCA* status and neither stratified by, nor specified analyses based on, this important predictive biomarker, the results indicating decreased efficacy with the addition of olaparib in patients without tumor *BRCA* mutations were consistent with results in Study 8 and in studies of other

PARP inhibitors in prostate cancer as well as other tumor types. Further, the maintenance indications for two other PARP inhibitors in metastatic ovarian cancer were recently restricted after extended follow-up due to concern for OS detriment and harm in patients without *BRCA*m. Consistency across trials increases the robustness of the finding that OS may be negatively impacted in patients without *BRCA*m.

Patients treated in the first-line mCRPC setting are generally minimally symptomatic at baseline with a median rPFS of approximately 16 months with abiraterone alone. Added toxicity may be particularly impactful in this setting given the prolonged treatment duration and generally well-tolerated backbone of ARPI. For patients with non-*BRCAm*, in whom olaparib is unlikely to be highly effective, the addition of olaparib may represent prolonged exposure to a toxic placebo as the efficacy of abiraterone may effectively mask an ineffective add-on therapy.

Given the FDA's concern for harm from adding olaparib to abiraterone in patients without tumor *BRCA*m, FDA asks the ODAC to consider whether the indication for olaparib in combination with abiraterone in mCRPC should be restricted to patients whose tumors have a *BRCA* mutation.

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5 Appendix

Table A1. FDA-approved therapies for the treatment of mCRPC

Drug (+ ADT)	**Approved Indication**
Abiraterone	1+ line mCRPC (+ prednisone)
Docetaxel	1+ line mCRPC (+ prednisone)
Enzalutamide	1+ line mCRPC
Radium-223	1+ line mCRPC (with symptomatic bone mets and no known visceral mets)
Sipuleucel-T	1+ line mCRPC (asymptomatic or minimally symptomatic)
Cabazitaxel*	2+ line mCRPC (+ prednisone) (post-docetaxel)
^{177}Lu-PSMA-617	3+ line PSMA(+) mCRPC (post-ARPI and post-taxane)
Olaparib	2+ line, HRRm mCRPC (previously treated with enzalutamide or abiraterone)
Rucaparib (accelerated approval)	3+ line, *BRCA*m mCRPC (post-ARPI and post-taxane)
Pembrolizumab	2+ line, unresectable/metastatic MSI-H, dMMR, or TMB-H solid tumors (with PD following prior treatment and no satisfactory alternative treatment options)

Table A2. Approved indications of Olaparib

Tumor type	**Approved indication**
Ovarian cancer	for the maintenance treatment of adult patients with **deleterious or suspected deleterious germline or somatic *BRCA*m** advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy.
	in combination with bevacizumab for the maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy and whose cancer is associated with homologous recombination deficiency (HRD)-positive status defined by either: • a **deleterious or suspected deleterious *BRCA* mutation**, and/or • **genomic instability**.
	for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer, who are in complete or partial response to platinum-based chemotherapy
Breast cancer	for the adjuvant treatment of adult patients with **deleterious or suspected deleterious g*BRCA*m** human epidermal growth factor receptor 2 (HER2)-negative high risk early breast cancer who have been treated with neoadjuvant or adjuvant chemotherapy.

	for the treatment of adult patients with **deleterious or suspected deleterious g*BRCA*m**, HER2-negative metastatic breast cancer who have been treated with chemotherapy in the neoadjuvant, adjuvant or metastatic setting. Patients with hormone receptor (HR)-positive breast cancer should have been treated with a prior endocrine therapy or be considered inappropriate for endocrine therapy.
Pancreatic cancer	for the maintenance treatment of adult patients with **deleterious or suspected deleterious g*BRCA*m** metastatic pancreatic adenocarcinoma whose disease has not progressed on at least 16 weeks of a first-line platinum-based chemotherapy regimen.
Prostate cancer	for the treatment of adult patients with **deleterious or suspected deleterious germline or somatic HRRm** mCRPC who have progressed following prior treatment with enzalutamide or abiraterone (PROfound, the trial leading to this approval, is described and discussed more fully in the next section).

*BRCA*m: *BRCA*-mutated; g*BRCA*: germline *BRCA* mutation; *HRR*: homologous recombination repair; *HRR*m: *HRR*-mutated