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Lynparza® (Olaparib) in Combination with Abiraterone and Prednisone or Prednisolone for the Treatment of Adult Patients with Metastatic Castration-Resistant Prostate Cancer

SPONSOR BRIEFING DOCUMENT

ONCOLOGIC DRUGS ADVISORY COMMITTEE MEETING

MEETING DATE: 28 April 2023

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

Abbreviation or special term	Explanation
ADR(s)	Adverse drug reaction(s)
ADT	Androgen deprivation therapy
AE(s)	Adverse event(s)
AESI	Adverse events of special interest
AR	Androgen receptor
AML	Acute myeloid leukemia
bid	Twice daily
BICR	Blinded independent central review
BRCA	Breast cancer susceptibility gene (in accordance with scientific convention, gene and mutation is italicized whereas protein is not italicized)
BRCAm	*gBRCA* or *sBRCA* mutated
CDx	Companion diagnostic
CI	Confidence interval
COVID-19	Coronavirus disease 2019
CRPC	Castration-resistant prostate cancer
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating tumor DNA
DCO	Data cut-off
DDR	DNA damage response
DHT	Dihydrotestosterone
EMA	European Medicines Agency
FACT-P	Functional Assessment of Cancer Therapy – Prostate Cancer
FDA	Food and Drug Administration
gBRCA	Germline *BRCA*
GnRH	Gonadotropin releasing hormone
GSAT	Gene silencing-associated transcriptional
HR	Hazard ratio
HRQoL	Health-related quality of life
HRR	Homologous recombination repair
HRRm	Homologous recombination repair gene mutated
ITT	Intention-to-treat

Abbreviation or special term	Explanation
mCRPC	Metastatic castration-resistant prostate cancer
MDS	Myelodysplastic syndrome
mHSPC	Metastatic hormone-sensitive prostate cancer
MoA	Mechanism of action
MTP	Multiple testing procedure
NCCN	National Comprehensive Cancer Network
NHA(s)	New hormonal agent(s)
ORR	Objective response rate
OS	Overall survival
PARP	Polyadenosine 5'diphosphoribose polymerase
PARPi	PARP inhibitor
PCWG-2	Prostate Cancer Working Groups 2
PCWG-3	Prostate Cancer Working Groups 3
PFS2	Time from randomization to second progression or death
PSA	Prostate-specific antigen
PT(s)	Preferred term(s)
qd	Once daily
RECIST	Response Evaluation Criteria in Solid Tumors
RP	Radical prostatectomy
rPFS	Radiological progression-free survival
SAE(s)	Serious adverse event(s)
SAS	Safety analysis set
sBRCA	Somatic *BRCA* (*BRCA* variant found in the tumor but not in the germline)
sNDA	Supplemental new drug application
TFST	Time from randomization to start of first subsequent therapy or death
US	United States
USPI	United States prescribing information
vs	Versus
VTE	Venous thromboembolism

1 EXECUTIVE SUMMARY

The Oncologic Drugs Advisory Committee is convened to discuss the supplemental new drug application (sNDA) 208,558/S-025 for Lynparza® (olaparib) tablets (300 mg twice daily [bid]) in combination with abiraterone (1000 mg once daily [qd]) and prednisone or prednisolone 5 mg bid in support of the proposed indication:

Lynparza is indicated in combination with abiraterone and prednisone or prednisolone for the treatment of adult patients with metastatic castration-resistant prostate cancer.

This briefing document summarizes efficacy and safety data for olaparib in combination with abiraterone for the treatment of metastatic castration-resistant prostate cancer (mCRPC) in order to facilitate an assessment of benefit-risk in the proposed indication. The key points in the briefing document are summarized as follows:

Optimizing First-line Treatment for Patients With mCRPC is Critical to Improve Outcomes as it may be the Last Active Treatment for ~50% of Patients (Section 2.1.1 and Section 2.1.2)

- Metastatic castration-resistant prostate cancer is an incurable disease. Despite current standard of care treatment (eg, new hormonal agents [NHAs; abiraterone or enzalutamide], or chemotherapy), overall survival (OS) outcomes remain poor. Patients receiving first-line treatment for mCRPC have a median survival of approximately 2 to 3 years in clinical trial settings (Armstrong et al 2020, Beer et al 2014, Beer et al 2017, Berthold et al 2008, Francini et al 2019, Kanotff et al 2010, Parker et al 2013, Ryan et al 2013, Ryan et al 2015, Tannock et al 2004), and less than 2 years in clinical practice (George et al 2020).
- In mCRPC, giving the most effective treatment as early as possible matters, as only ~50% of patients with mCRPC will receive another treatment after their first progression. Hence there is need for a new first-line treatment option for patients with mCRPC that improves upon the current standard of care to prolong radiological progression-free survival (rPFS), delays initiation of subsequent therapy, and minimizes the impact on patients' health-related quality of life (HRQoL).

The Rationale for Assessing Olaparib + Abiraterone as a New Treatment Option in an All-comer Population of Patients With mCRPC is Underpinned by Supportive Pre-clinical Data Providing Insights into the Mechanism of Action and a Phase II Proof-of-Concept Study That Showed Benefit in Both the HRRm and Non-HRRm Patient Population (Section 3)

The initial scientific rationale for the combination of abiraterone and olaparib was based on pre-clinical published work demonstrating a role for polyadenosine 5'diphosphoribose polymerase (PARP) as a transcriptional co-factor for androgen receptor (AR) signaling (Schiewer et al 2012). In addition, AR inhibition was shown to down-regulate DNA damage response (DDR) gene transcription and increase sensitivity to DNA damaging agents, including PARP inhibitors (Asim et al 2017, Goodwin et al 2013, Li et al 2017, Polkinghorn et al 2013).

Additional pre-clinical data has subsequently been generated by AstraZeneca, providing insights into the mechanism of action (MoA) that explain the activity of olaparib in combination with abiraterone in an all-comer mCRPC population. The most relevant mechanistic readout for therapies based on inhibitors of the DNA damage response, such as PARP inhibitors, is the degree of DNA damage induction in tumor cells that results from treatment. The additional data provided in this briefing document extends our understanding of the combination MoA and focuses on the important DNA repair roles played by AR and PARP in prostate cancer in both homologous recombination repair gene mutated (HRRm) and non-HRRm prostate cancer cells.

The additional MoA insights are based on the observations that:

1 PARP facilitates the repair of DNA breaks (Chaudhuri and Nussenzweig 2017).

2 The AR facilitates DNA repair and its binding to damaged DNA is dependent on PARP.

3 The use of a PARP inhibitor (PARPi) such as olaparib, by trapping PARP on DNA, also leads to the generation of increased levels of DNA damage (Pommier et al 2016).

4 Olaparib and abiraterone together more effectively inhibit AR-dependent repair that extends beyond homologous recombination repair (HRR), leading to greater levels of DNA damage than abiraterone alone.

5 DNA damage generated by the olaparib and abiraterone combination will be greatest in tumor backgrounds with more profound DNA repair defects such as HRR deficiency resulting from breast cancer susceptibility gene (*BRCA*) mutations, but since AR-dependent repair extends beyond HRR, there is also increased DNA damage in non-HRRm prostate cancer cells.

Therefore, while *BRCA* mutant prostate cancer cells are expected to be the most sensitive to the increased levels of DNA damage resulting from the combination of olaparib and abiraterone, prostate cancer cells without a *BRCA* or other HRRm gene mutation will also accumulate more DNA damage resulting in the greater anti-cancer activity from the combination of olaparib and abiraterone compared to abiraterone alone (Asim et al 2017, Li et al 2017, AstraZeneca data on file).

Clinical evidence from a randomized, placebo-controlled Phase II proof-of-concept Study D081DC00008 (Study 8) supported initiation of the PROpel study (D081SC00001) to determine the benefit of adding olaparib to abiraterone in an all-comer population of patients with mCRPC.

- In Study 8, the combination of olaparib + abiraterone prolonged rPFS versus (vs) placebo + abiraterone in patients with mCRPC, who had received docetaxel; median rPFS was 5.6 months longer in the olaparib + abiraterone arm than in the placebo + abiraterone arm (13.8 months vs 8.2 months, respectively; hazard ratio [HR] = 0.65; 95% confidence interval [CI]: 0.44, 0.97; p = 0.034).
- There was also an rPFS improvement in both the HRRm (rPFS HR = 0.74 in the initial classification) and non-HRRm (rPFS HR = 0.52 in the initial classification) subpopulations (Clarke et al 2018).

PROpel is a Randomized, Placebo-controlled Phase III Study Assessing the Effect of Olaparib + Abiraterone as First-line Therapy for Patients With mCRPC (Sections 5.1 to 5.3 and 5.5)

- PROpel is global pivotal Phase III randomized, double-blind, placebo-controlled study (796 patients), evaluating olaparib plus abiraterone vs placebo plus abiraterone (each combined with prednisone or prednisolone), as first-line treatment for men with mCRPC. Abiraterone acetate, in conjunction with a corticosteroid, is a standard of care for the population in the proposed indication. The study design of PROpel was discussed and agreed with Food and Drug Administration (FDA) in 2018.
- The following stratification factors were used as they were known significant prognostic factors in mCRPC at the time of the PROpel design:
  - Site of distant metastases: bone only vs visceral vs other
  - Docetaxel treatment at metastatic hormone-sensitive prostate cancer (mHSPC) stage: yes vs no
- Biomarker status was not included as a stratification factor since PROpel was designed with the available data from Study 8, where HRR gene mutation status was not demonstrated to be predictive of benefit for the combination of olaparib + abiraterone in mCRPC, and at the time, there were limited evidence of prognostic value of HRRm or *BRCAm* in mCRPC.
- The primary endpoint chosen in PROpel (rPFS) is recommended by Prostate Cancer Working Groups 3 (PCWG-3) as an important endpoint for assessing clinical benefit in clinical studies in patients with mCRPC (Scher et al 2016); it provides assessment of benefit prior to the determination of survival and is not confounded by subsequent anti-cancer therapy. Additionally, rPFS was selected based on regulatory precedent as a primary endpoint in mCRPC registrational trials, FDA/European Medicines Agency (EMA) guidelines, feedback obtained during interactions with the FDA and EMA, and correlation between rPFS and OS in prior mCRPC trials.
  - A prolongation of rPFS has clinical relevance to patients with mCRPC, as delaying progression may result in a delay in the clinically important consequences such as bone pain, complications of visceral metastases, starting chemotherapy, and a deterioration of quality of life.
  - In PROpel, the primary endpoint of rPFS was derived from investigator assessment, as this was the most clinically relevant assessment of radiological progression. PROpel also included assessment of rPFS by blinded independent central review (BICR) as a sensitivity analysis.
- Overall survival was a pre-specified key secondary endpoint and was controlled for multiplicity. The study was powered for rPFS and aimed to show a trend of benefit in OS as it was not powered for OS.

The PROpel Study was Positive, Meeting its Primary Endpoint With a Statistically Significant and Clinically Meaningful Improvement in rPFS, and a Favorable Benefit-Risk Profile for the Olaparib + Abiraterone Combination Compared to Abiraterone Alone in an All-comer mCRPC Population (Sections 5.6 to 5.8.1 and Section 6)

- The PROpel study met its primary endpoint with a 34% reduction in the risk of radiological progression or death (HR = 0.66; 95% CI: 0.54, 0.81; $p < 0.0001$) and an 8.2-month improvement in median rPFS for the olaparib + abiraterone arm over the placebo + abiraterone arm (24.8 months vs 16.6 months, respectively).
- The sensitivity analysis of rPFS by BICR led to a 39% reduction in the risk of radiological progression or death (HR = 0.61; 95% CI: 0.49, 0.74; nominal $p < 0.0001$) and an 11.2-month improvement in median rPFS for the olaparib + abiraterone arm over the placebo + abiraterone arm (27.6 months vs 16.4 months, respectively), which was consistent with the investigator-assessed rPFS analysis.

- The benefit of olaparib + abiraterone over placebo + abiraterone in rPFS was maintained across all pre-defined subgroups based on the stratification factors, HRR gene mutation status, and clinical characteristics, with clinically meaningful reductions in the risk of radiological progression or death.
- At the final pre-specified OS analysis (data cut-off [DCO]3; OS = 47.9% mature), there was a 19% reduction in the risk of death in the olaparib + abiraterone arm compared to the placebo + abiraterone arm (HR = 0.81; 95% CI: 0.67, 1.00; p = 0.0544) and a median OS improvement of 7.4 months in the olaparib + abiraterone arm over the placebo + abiraterone arm (42.1 months vs 34.7 months, respectively) in the intention-to-treat (ITT) population, demonstrating the benefit of the combination in an all-comer mCRPC population. The results for OS did not reach the threshold for statistical significance.
- The clinical benefit in the all-comer population for olaparib + abiraterone vs placebo + abiraterone was supported by improvements in pre-specified secondary and exploratory endpoints (time to first subsequent therapy or death [TFST], time to second progression or death [PFS2], prostate-specific antigen [PSA] response, objective response rate [ORR], and time to PSA progression).
- Olaparib and abiraterone have well-characterized safety profiles, and the safety data from PROpel was generally consistent with the known monotherapy safety profiles.
  - No new safety signals were identified in PROpel.
  - The most common adverse events (AEs) in the olaparib + abiraterone arm were anemia, nausea, and fatigue, known adverse drug reactions (ADRs) for olaparib. They were primarily mild or moderate in intensity, non-serious, had a first occurrence within the first 3 months of treatment, and were well managed by dose modifications and/or supportive treatment. Other common AEs were consistent with the known safety profiles of olaparib and abiraterone as a monotherapy, or considered symptoms commonly reported in a mCRPC population.
  - As expected with the combination of 2 active treatments, the overall incidence of AEs was higher in the olaparib + abiraterone arm than in the placebo + abiraterone arm. However, the combination of olaparib + abiraterone had no clinically meaningful impact on patients' quality of life, as evidenced by the Functional Assessment of Cancer Therapy – Prostate Cancer (FACT-P) total score, which was similar between arms throughout the treatment period. Impact on HRQoL is an important consideration for patients with mCRPC.
- The median duration of exposure to standard of care abiraterone was increased by over 4 months when combined with olaparib, which is important as patients could discontinue olaparib or placebo and remain on abiraterone, or vice versa. This would result in delaying the time to the next therapy that patients would receive, which may be a taxane-based chemotherapy agent with an inherent increase in toxicity burden.
- Over 80% of patients were able to continue to receive olaparib until disease progression.

Genetic Testing is Important and Recommended But is Not Universally Implemented in Routine Clinical Practice (Section 5.4)

- Genetic testing is important in prostate cancer as it helps inform treatment decision making, for prognostic assessment, and assessment of familial risk. Genetic testing is recommended in the National Comprehensive Cancer Network (NCCN) guidelines and the American Urological Association/American Society for Therapeutic Radiology and Oncology/Society of Urologic Oncology guidelines (Lowrance et al 2021, NCCN Prostate Cancer Guidelines 2023).
- Tumor HRR gene testing showed a prevalence of 9.7% for mCRPC patients who had a *BRCA* mutation (de Bono et al 2019); HRR pathway alterations (including *BRCA*) can be detected in about 28% of patients with mCRPC (de Bono et al 2019, de Bono et al 2020).
- Rates of HRR gene mutation testing in the United States (US) have increased over time, but currently many patients are not tested. Before 2019, it was reported that in the US, only 13% of mCRPC patients had a documented genetic test (Shore et al 2021). Following the PROfound (D081DC0007; NCT02987543) and TRITON2 (NCT02952534) trials, HRR gene mutation testing rates in the US improved with reports of 38.2% of mCRPC patients tested in 2020. However, the data also showed that there was a disparity between those patients tested in an academic/cancer center (47.5%) vs in the community setting (27.9%) (Leith et al 2022), indicating that the HRR status is unknown for a majority of US patients with mCRPC.

Exploratory Aggregate Analyses Using Either Tissue or ctDNA Test Result Provides the Most Comprehensive Dataset; Closer to Real-life Clinical Practice (Sections 5.5, 5.8.2, and 6.2.6)

- In PROpel, biomarker testing was pre-planned and HRR gene mutation status were determined after randomization and before primary analysis using 2 sensitive, well-established, FDA-approved tests that are complementary to each other, the tumor tissue test (FoundationOne® companion diagnostic [CDx]) and a circulating tumor (ct)DNA-based test (FoundationOne® Liquid CDx). The reason 2 tests were used to define HRR gene mutation status in PROpel was to maximize the biomarker information and minimize the number of patients with an unknown status.
- To generate the most complete dataset of HRR and *BRCA* gene (a subset of HRR genes) mutation status, AstraZeneca conducted aggregate analyses, categorizing HRR and *BRCA* gene mutation status by either tumor tissue or ctDNA, thus minimizing the number of patients with an unknown HRR or *BRCA* gene mutation status; this reflects biomarker testing in clinical practice, as the majority of patients will be tested by only one test. Patients were categorized as HRRm or *BRCAm* if either test result detected a mutation. Patients were classified as non-HRRm or non-*BRCAm* if no mutation was detected by either test.

HRRm and *BRCAm* Subgroups:

- In the HRRm subgroup, a substantial clinically meaningful benefit was observed for both rPFS (HR = 0.50) and OS (HR = 0.66) in favor of the olaparib + abiraterone arm; medians in the olaparib + abiraterone arm for both endpoints were not reached.
- In the *BRCAm* subgroup, a substantial clinically meaningful benefit was observed for both rPFS (HR = 0.23) and OS (HR = 0.29) in favor of the olaparib + abiraterone arm; medians in the olaparib + abiraterone arm for both endpoints were not reached.

Non-HRRm and Non-*BRCAm* Subgroups:

- In the non-HRRm subgroup, a clinically meaningful benefit was observed for olaparib + abiraterone, with a 5.2-month improvement in median rPFS (investigator-assessed) over placebo + abiraterone (HR = 0.76) and an 8.5-month improvement in median rPFS (BICR-assessed) over placebo + abiraterone (HR = 0.72). There was no evidence of a detriment in OS (HR = 0.89) for the olaparib + abiraterone arm.
- Consistent with the primary analysis, the results from the secondary and exploratory endpoints of TFST, PFS2, ORR, PSA_{50} response, and time to PSA progression in the non-HRRm showed a benefit in favor of the olaparib + abiraterone arm compared with the placebo + abiraterone arm.
- In the non-*BRCAm* subgroup, a clinically meaningful benefit was observed for olaparib + abiraterone, with a 5.1-month improvement in median rPFS (investigator-assessed) over placebo + abiraterone (HR = 0.76). and an 11.0-month improvement in median rPFS (BICR-assessed) over placebo + abiraterone (HR = 0.72). There was no evidence of a detriment in OS (HR = 0.91) for the olaparib + abiraterone arm.
- Consistent with the primary analysis, the results from the secondary and exploratory endpoints of TFST, PFS2, ORR, PSA_{50} response, and time to PSA progression in the non-*BRCAm* subgroup showed a benefit in favor of the olaparib + abiraterone arm compared with the placebo + abiraterone arm.

- In safety analyses of the HRRm, *BRCAm*, non-HRRm, and non-*BRCAm* subgroups, the safety profile was shown to be generally consistent with the safety profile observed in the safety analysis set (SAS) and with the known monotherapy safety profiles. The data demonstrates a manageable safety profile in all subgroups.
- The safety data in the HRRm, *BRCAm*, non-HRRm, and non-*BRCAm* subgroups show that the addition of olaparib to the standard of care abiraterone had no clinically meaningful impact on patients' quality of life, as evidenced by the FACT-P total score, which was similar between arms throughout the treatment period in all subgroups.

Benefit-Risk Summary

PROpel was a positive study and met its primary endpoint of rPFS in the ITT population, with clinically meaningful benefit in the key secondary endpoint of OS and other secondary and exploratory endpoints (TFST, PFS2, PSA response, ORR, and time to PSA progression).

The safety data from PROpel was generally consistent with the known monotherapy olaparib and abiraterone safety profiles, and the AE data show that the addition of olaparib to the standard of care abiraterone had no clinically meaningful impact on patients' quality of life, as evidenced by the FACT-P total score, which was similar between arms throughout the treatment period.

A differential magnitude of benefit for olaparib + abiraterone was observed between the *BRCAm* and non-*BRCAm* subgroups, with the greatest benefit of olaparib + abiraterone seen in *BRCAm* patients. However, independent of this difference and considered on the merits of the data in this subgroup, the benefit-risk profile for the combination of olaparib + abiraterone in non-*BRCAm* patients is also positive. AstraZeneca considers that it is important to inform

prescribers of the differences between the *BRCAm* and non-*BRCAm* subgroups and proposes to include relevant biomarker subgroup data in the US prescribing information (USPI).

AstraZeneca recognizes the importance of testing in prostate cancer, and a complementary diagnostic may help inform physicians on the expected benefit-risk of the combination as a treatment option in *BRCAm* and non-*BRCAm* subgroups.

The totality of the data from PROpel demonstrates a favorable benefit-risk profile for the combination of olaparib plus abiraterone and prednisone or prednisolone in an all-comer mCRPC population and supports the approval of this new treatment option in the proposed indication: "*Lynparza is indicated in combination with abiraterone and prednisone or prednisolone for the treatment of adult patients with metastatic castration-resistant prostate cancer*".

2 BACKGROUND

Olaparib (Lynparza®) is a first-in-class, potent, oral PARPi (PARP-1, PARP-2 and PARP-3), that, as a monotherapy, exploits deficiencies in DNA repair pathways selectively targets cancer cells carrying such deficiencies.

In the US, olaparib was first approved in December 2014 and the olaparib tablet formulation is already registered for marketing for use in prostate, ovarian, breast, and pancreatic cancer. Table 1 shows the approved indications by tumor type for Lynparza in the US as of 01 January 2023.

Table 1 Olaparib FDA Approvals (Tablet Formulation)

Indications	Approved
PROSTATE CANCER	
Treatment of adult patients with deleterious or suspected deleterious germline or somatic homologous recombination repair gene-mutated metastatic castration-resistant prostate cancer who have progressed following prior treatment with enzalutamide or abiraterone.	19 May 2020
OVARIAN CANCER	
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.	17 August 2017
Treatment of adult patients with deleterious or suspected deleterious *gBRCA*-mutated advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy. [a]	17 August 2017
Maintenance treatment of adult patients with deleterious or suspected deleterious germline or somatic *BRCA*-mutated advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy.	19 December 2018
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 HRD-positive status defined by either: • a deleterious or suspected deleterious *BRCA* mutation, and/or • genomic instability.	08 May 2020
BREAST CANCER	
Treatment of adult patients with deleterious or suspected deleterious *gBRCA*-mutated, HER2-negative metastatic breast cancer, who have been treated with chemotherapy in the neoadjuvant, adjuvant, or metastatic setting.	12 January 2018
Adjuvant treatment of adult patients with deleterious or suspected deleterious *gBRCAm* human epidermal growth factor receptor 2 (HER2)-negative high risk early breast cancer who have been treated with neoadjuvant or adjuvant chemotherapy.	11 March 2022

Table 1 Olaparib FDA Approvals (Tablet Formulation)

Indications	Approved
PANCREATIC CANCER	
Maintenance treatment of adult patients with deleterious or suspected deleterious *gBRCA*-mutated metastatic pancreatic adenocarcinoma whose disease has not progressed on at least 16 weeks of a first-line platinum-based chemotherapy regimen.	27 December 2019

[a] AstraZeneca voluntarily withdrew this indication.
BRCA = breast cancer susceptibility gene; FDA = Food and Drug Administration; *gBRCA* = germline *BRCA*; *gBRCAm* = germline *BRCA* mutated; HER2 = human epidermal growth factor receptor 2; HRD = homologous recombination deficiency.

On 16 June 2022 AstraZeneca submitted an efficacy sNDA 208,558/S-025 for Lynparza (olaparib) tablets in combination with abiraterone and prednisone or prednisolone in support of the proposed indication and dose:

- Lynparza is indicated in combination with abiraterone and prednisone or prednisolone for the treatment of adult patients with metastatic castration-resistant prostate cancer.
- The recommended dose of Lynparza is 300 mg (two 150 mg tablets) taken orally bid, with or without food, for a total daily dose of 600 mg. The 100 mg tablet is available for dose reduction.

  When used with Lynparza, the recommended dose of abiraterone is 1000 mg taken orally qd. Abiraterone should be given in combination with prednisone or prednisolone 5 mg orally bid.

  Continue treatment until disease progression or unacceptable toxicity.

2.1 Unmet Medical Need in First-line mCRPC Treatment and the Importance of Offering the Best Treatment Upfront

2.1.1 Disease Background

In the US, prostate cancer is the leading male cancer diagnosis, ranking as the second most common cause of cancer death (American Cancer Society 2023). In a modelled analysis of US data, the incidence of mCRPC in 2020 was estimated to be 42970 cases, and all-cause mortality occurring in men with mCRPC was estimated at 42775 deaths (Scher et al 2015).

Metastatic castration-resistant prostate cancer is an incurable disease. Despite current standard of care treatment, OS outcomes remain poor. Patients receiving first-line treatment for mCRPC have a median survival of approximately 2 to 3 years in clinical trial settings (Armstrong et al 2020, Beer et al 2014, Beer et al 2017, Berthold et al 2008, Francini et al 2019, Kanotff et al 2010, Parker et al 2013, Ryan et al 2013, Ryan et al 2015). As patients with mCRPC experience disease progression having failed treatment on the current standard

of care, median survival has been reported as less than 2 years in clinical practice (George et al 2020).

In the real-world setting, only ~50% of patients with mCRPC will receive another FDA-approved treatment after their first progression. In a study by George et al assessing 2559 patients with mCRPC from the Flatiron Health database, 77% of patients received first-line therapy (abiraterone, enzalutamide, docetaxel, cabazitaxel, sipuleucel-T, or radium-223), but only 49% of these patients went on to receive second-line therapy, since a number of the patients died without receiving a subsequent therapy (George et al 2020). Therefore, optimizing therapies in the first-line treatment setting provides the greatest opportunity for delivering meaningful outcomes for mCRPC patients.

Metastatic castration-resistant prostate cancer is associated with a range of symptoms but is predominately characterized by bone pain, fatigue, and urinary dysfunction (Gater et al 2011, Lindqvist et al 2008). Around 90% of patients with mCRPC have bone metastases (de Bono et al 2010, de Bono et al 2011, Scher et al 2012), which leads to significant morbidity, including pain and skeletal-related events such as spinal cord compression and pathological fractures, which require interventions such as bone surgery or radiation therapy (El-Amm et al 2013). Existing bone-targeted therapies (zoledronic acid, denosumab) reduce the number of bone complications incompletely without a documented positive impact on OS (Fizazi et al 2011, Saad et al 2004).

Symptoms of mCRPC can have an impact on daily lives and contribute to diminished levels of HRQoL observed in this population (Eton and Lepore 2002). Since curative therapy is not possible in the metastatic setting, reducing disease burden and symptoms are critical objectives of any therapeutic intervention.

Hence, there is need for a new first-line treatment option for patients with mCRPC that improves upon the current standard of care to prolong rPFS. A prolongation of rPFS has clinical relevance to patients with mCRPC, as delaying progression may result in a delay in the clinically important consequences such as bone pain, complications of visceral metastases, starting chemotherapy, and deterioration of quality of life.

It is therefore proposed that the combination of olaparib with abiraterone represents an important addition to the treatment armamentarium for patients compared with existing standard of care in the first-line mCRPC treatment setting.

2.1.2 Currently Available Treatment Options for First-line Treatment of mCRPC

Available first-line therapy for patients with mCRPC in the US includes docetaxel, abiraterone, and enzalutamide. Cabazitaxel is approved in docetaxel-treated patients.

Radium-223 is only approved in bone-only disease in mCRPC. Sipuleucel-T is also approved but is only recommended for patients who are asymptomatic or minimally symptomatic, have no liver metastases, have a life expectancy > 6 months, and have an Eastern Cooperative Oncology Group performance status of 0 to 1.

For patients who have not received prior treatment with docetaxel or an NHA, the preferred NCCN regimen for systemic treatment for M1 castration-resistant prostate cancer (CRPC) include an NHA (abiraterone or enzalutamide) or docetaxel (NCCN Prostate Cancer Guidelines 2023). In the US, sipuleucel-T (Category 1) is only recommended for specific patients. Abiraterone and enzalutamide remain preferred Category 1 NHAs after systemic treatment with docetaxel in the M1 CRPC disease state. A Category 1 designation signifies that, based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Docetaxel was first approved in the US in 2004 in combination with prednisone for mCRPC based on improvements in OS. Docetaxel has safety and tolerability challenges, particularly hematological toxicity, hypersensitivity reactions, gastrointestinal toxicities, skin toxicity, neurotoxicity, and alopecia (Taxotere USPI 2020). Docetaxel (as administered by intravenous infusion) is a less convenient therapy for patients, which may further limit use. However, when patients present with signs of rapid progression and symptomatic or visceral metastatic disease, docetaxel-containing chemotherapy remains a valuable treatment option (NCCN Prostate Cancer Guidelines 2023).

New hormonal agents are potent, orally available treatment options with a favorable tolerability profile. Abiraterone and enzalutamide are authorized in the US for the treatment of patients with mCRPC who have received prior chemotherapy containing docetaxel and also for use in the first-line metastatic (pre-chemotherapy) setting. Both abiraterone and enzalutamide have demonstrated robust improvements of PFS and OS compared with placebo (Beer et al 2014, Ryan et al 2013). Although NHAs were studied in asymptomatic or mildly symptomatic patients with mCRPC in the first-line setting (COU-AA-302 [NCT00887198; Morris et al 2015] and PREVAIL [NCT01212991; Rathkopf et al 2018]), the NCCN guidelines do not limit their use to this specific patient population and, since their approval in the first-line setting, NHAs have increasingly replaced docetaxel globally as the preferred choice of first-line therapy for mCRPC (Flaig et al 2016, Parker et al 2020). However, following progression after first-line NHA therapy, the current treatment paradigm for the majority of patients is either to re-treat with another NHA or to use a taxane-based chemotherapy agent (docetaxel or cabazitaxel), with an inherent increase in toxicity burden. There is also evidence of significantly diminishing efficacy with subsequent lines of NHA therapy with no additional efficacy benefit of taxane-based therapies (Castro et al 2019, Romero-Laorden et al 2020, Swami et al 2020).

Treatment of patients who have developed mCRPC disease will vary depending on the regimens initially used in the early stage of disease. The NCCN guidelines (NCCN Prostate Cancer Guidelines 2023) recommend that patients with disease progression on a given therapy should not repeat that therapy, apart from docetaxel, which can be given as a rechallenge therapy in later stages of the disease, ie, if initially given in the hormone-sensitive setting. All approved therapy options for the first-line treatment of mCRPC are also available for later treatments.

3 RATIONALE FOR ASSESSING OLAPARIB PLUS ABIRATERONE AS A COMBINATION IN AN ALL-COMER POPULATION OF PATIENTS WITH MCRPC

The rationale for combining olaparib and abiraterone in an all-comer prostate cancer population was based on available pre-clinical and clinical data.

The initial scientific rationale for the combination of abiraterone and olaparib was based on published pre-clinical evidence indicating 2 plausible mechanisms that predicted PARP inhibitor-NHA combination activity in both HRRm and non-HRRm prostate cancer cells.

- The first evoked a potential transcriptional co-factor role for PARP, based on its ability to modify chromatin and thereby facilitate AR-dependent downstream signaling (reviewed in Schiewer and Knudsen 2014). PARP's transcriptional functions may be especially relevant in hormone-dependent cancers such as prostate cancer, as nuclear hormone receptors require catalytically active PARP as a positive co-regulator of target gene expression (Ju et al 2006). The proposed PARP co-regulation of the AR is supported by the observation that PARP inhibition may suppress transcription of several AR targets, in line with the observed improved efficacy in a prostate cancer xenograft model treated with PARP inhibitor accompanied by castration, when compared with castration or PARP inhibitor alone (Schiewer et al 2012).
- The second mechanistic rationale for activity of a PARP-NHA combination in non-HRRm prostate cancer cells, was the down-regulation of HRR gene expression following inhibition of AR signaling (Asim et al 2017, Goodwin et al 2013, Li et al 2017). If AR inhibition was accompanied by HRR loss of function, this could lead to increased sensitivity to PARP inhibitors such as olaparib through the process of induced synthetic lethality. Further data on the effects of AR inhibition in monotherapy or in combination with olaparib are provided in Appendix C.

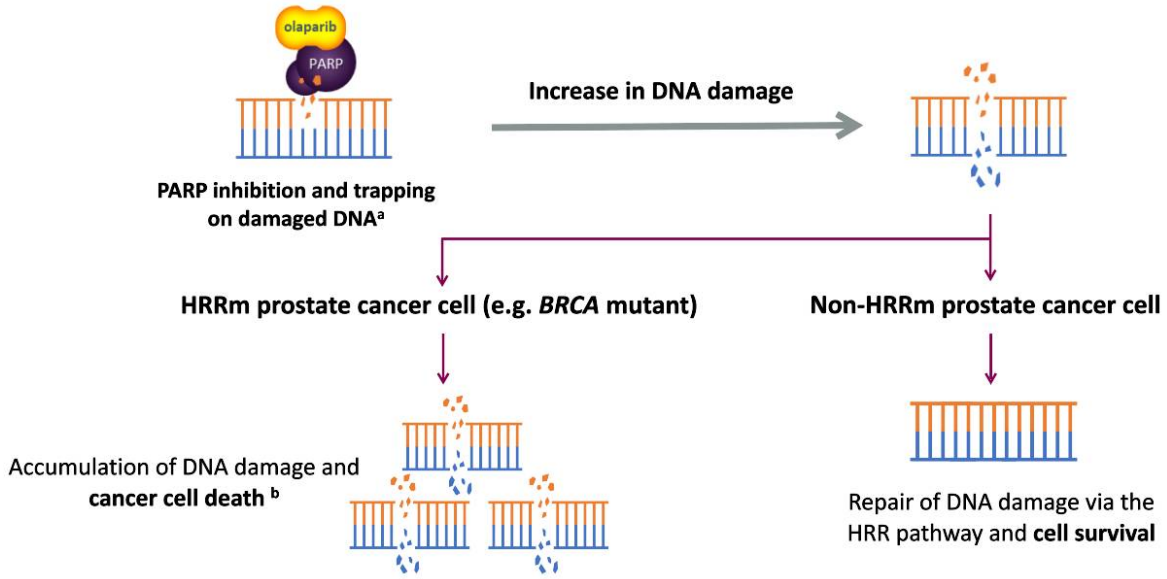
Both of the scientific rationales outlined above could explain how the activity of olaparib and abiraterone in mCRPC extends beyond that for olaparib and abiraterone monotherapies alone. Additional relevant information about the individual DNA repair roles of PARP and AR also

contribute to our understanding of the potential combination efficacy of olaparib and abiraterone.

3.1 The Role of PARP in DNA Repair

Polyadenosine 5'diphosphoribose polymerase (PARP) is a DNA damage response protein that facilitates the repair of different forms of DNA damage (Chaudhuri and Nussenzweig 2017) and inhibition of PARP impairs DNA repair. Moreover, a PARPi (such as olaparib) has the capability of stabilizing PARP binding to DNA (also referred to as trapping), and this will induce DNA damage (Pommier et al 2016). Inhibition and trapping of PARP proteins by olaparib treatment in cancers harboring HRR gene mutations results in tumor cell death by synthetic lethality (Lord and Ashworth 2017; Figure 1).

Figure 1 Olaparib Monotherapy Mechanism of Action in HRRm mCRPC



[a] Murai et al 2012, Murai et al 2014, and Pommier et al 2016
[b] Farmer et al 2005, Fong et al 2009

BRCA = breast cancer susceptibility gene; *BRCAm* = *gBRCA* or *sBRCA* mutated; *gBRCA* = germline *BRCA;* HRR = homologous recombination repair; HRRm = homologous recombination repair gene mutated; mCRPC = metastatic castration-resistant prostate cancer; PARP = polyadenosine 5'diphosphoribose polymerase; *sBRCA* = somatic *BRCA.*

3.2 The Role of the Androgen Receptor in DNA Repair

The AR, in addition to its role in binding androgen and stimulating prostate cancer cell growth (Westaby et al 2022), also contributes towards the general repair of DNA damage, including damage not normally repaired by HRR (Goodwin et al 2013, Polkinghorn et al 2013, Tarish et al 2015). In patients with early prostate cancer, this is thought to be the basis of the

AR-mediated radiation resistance and the rationale for the potentiation effect of radiotherapy-induced DNA damage when coupled with androgen deprivation therapy (ADT) (Polkinghorn et al 2013, Tarish et al 2015).

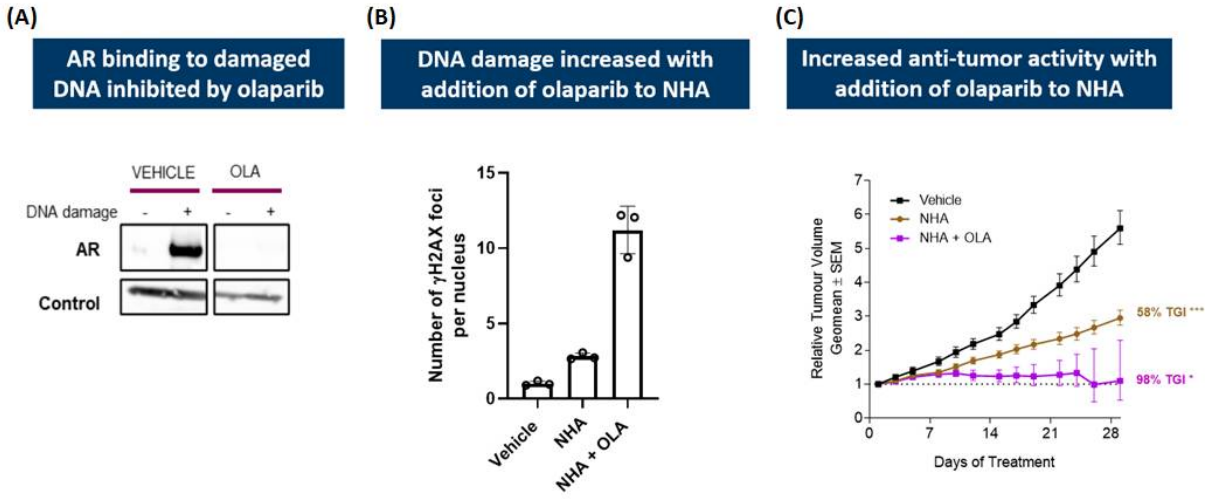
3.3 Additional Supportive Pre-clinical Data for Combining Olaparib and Abiraterone

PARP and the AR have previously been shown to interact at the protein level (Kounatidou et al 2019). Following the initiation of PROpel, AstraZeneca has generated data that provide additional evidence that the AR and PARP are both important for DNA repair in non-HRRm prostate cancer cells and highlight the importance of cross-talk (interaction) between them. These data provide further scientific rationale for targeting both proteins in order to treat mCRPC and support a combination mechanism of action in which:

1. PARP facilitates the repair of DNA breaks (Chaudhuri and Nussenzweig 2017).
2. The AR facilitates DNA repair and its binding to damaged DNA is dependent on PARP (Figure 2A).
3. The use of a PARPi such as olaparib, by trapping PARP on DNA, also leads to the generation of increased levels of DNA damage (Pommier et al 2016).
4. Olaparib and abiraterone together more effectively inhibit AR-dependent repair leading to greater levels of DNA damage than abiraterone alone (Figure 2B) and this in turn translates in vivo into greater anti-tumor activity (Figure 2C).
5. Therefore, while *BRCA* mutant prostate cancer cells are expected to be the most sensitive to the increased levels of DNA damage resulting from the combination of olaparib and abiraterone, prostate cancer cells without a *BRCA* or other HRRm gene mutation will also be exposed to increased DNA damage, resulting in greater anti-cancer activity from the combination compared to abiraterone alone.

Figure 2 highlights some of the new data that support the mechanism of action model for the combination of olaparib and abiraterone (outlined in Figure 3). More details of the experimental work presented in Figure 2 are provided in Appendix A. The technical reasons for using the NHA enzalutamide in pre-clinical experiments, rather than abiraterone, are provided in Appendix B.

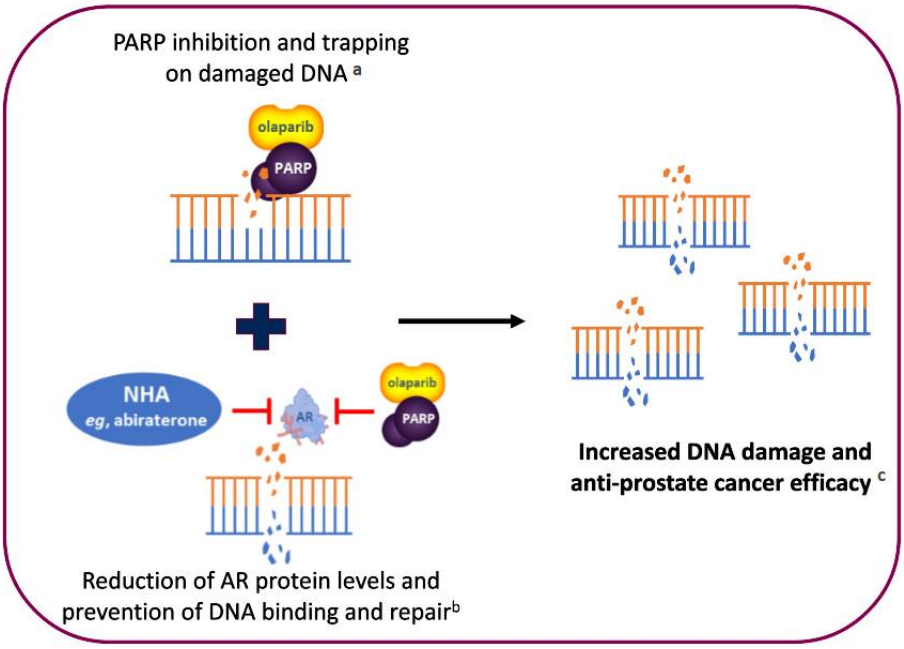
Figure 2 Olaparib Plus an NHA Results in More DNA Damage and More Anti-tumor Activity Than an NHA in a Non-HRRm Prostate Model



(A) Western blot from the chromatin fraction showing that nuclear AR protein associates with DNA following DNA damage induction but this is prevented in the presence of the PARP inhibitor olaparib (also see Appendix A, Figure A3).
(B) Western blot analysis of the DNA damage biomarker γH2AX showing the addition of olaparib to the NHA enzalutamide in a metastatic prostate cancer cell line model results in greater levels of DNA damage (also see Appendix A, Figure A2).
(C) In vivo tumor response data in the xenograft model LnCAP showing increased DNA damage observed with the addition of olaparib to the NHA enzalutamide in Figure 2B translates into greater anti-tumor activity in vivo.
AR = androgen receptor; HRRm = homologous recombination repair gene mutated; NHA = new hormonal agent; OLA = olaparib; PARP = polyadenosine 5'diphosphoribose polymerase; TGI = tumor growth inhibition; SEM = standard error of the mean.

In the model depicted in Figure 3, a PARP inhibitor such as olaparib will both prevent the repair of DNA damage and trap PARP onto the DNA, leading to the accumulation of more DNA damage. While the majority of this damage will be repaired by HRR, PARP inhibitor treatment will result in an increase in DNA damage even in cells with functional HRR (Appendix A, Figure A2). The AR normally contributes to the repair of DNA damage by binding to damaged DNA and activating DDR gene expression that includes HRR genes but also non-HRR DDR genes. The new data shown in Figure 2A and Appendix A, Figure A3, demonstrate that PARP inhibition with olaparib impairs nuclear AR binding to damaged DNA. Consequently, the combination of an NHA, such as abiraterone and a PARP inhibitor such as olaparib will result in increased levels of DNA damage, as seen in Figure 2B. This increased DNA damage translates into greater anti-tumor activity as shown in Figure 2C.

Figure 3 Mechanism of Action Model: Increased DNA Damage Results from the Addition of Olaparib to Abiraterone in Non-HRRm mCRPC Cells



[a] Pommier et al 2016.
[b] AstraZeneca data on file.
[c] Asim et al 2017, Li et al 2017.
AR = androgen receptor; HRRm = homologous recombination repair gene mutated; NHA = new hormonal agent; mCRPC = metastatic castration-resistant prostate cancer; PARP = polyadenosine 5'diphosphoribose polymerase.

These new data show that combined inhibition of PARP (by olaparib) and AR (by NHAs such as abiraterone) results in increased accumulation of DNA damage, that can enhance the anti-tumor efficacy of the combination compared to either agent alone in non-HRRm, non-*BRCAm* metastatic prostate cancer models. While the increased DNA damage resulting from trapped PARP and the inhibition of AR DNA repair will be expected to have the greatest effect in prostate tumors harboring *BRCA* mutations, it also explains why the addition of olaparib to abiraterone will have enhanced activity in non-HRRm prostate cancer cells.

3.4 Clinical Evidence from a Phase II Proof-of-Concept Study for Combining Olaparib and Abiraterone in an All-comer Population

The pre-clinical data were the basis for initiation of Study D081DC00008 (Study 8; NCT01972217), a randomized, double-blind, placebo-controlled, multicenter 2-part Phase II study of olaparib in combination with abiraterone and prednisone or prednisolone vs placebo in combination with abiraterone and prednisone or prednisolone, in patients with mCRPC (an all-comer population) who had received up to 2 lines of prior chemotherapy including docetaxel (in Part B) (Clarke et al 2018).

Study 8 Overview

Study 8 was a 2-part Phase II study in an all-comer population of patients with mCRPC:

- Part A was an open-label safety run-in study for olaparib dose selection designed to assess the safety, tolerability, and pharmacokinetics of olaparib when given in addition to abiraterone 1000 mg qd and prednisone or prednisolone 5 mg bid. A total of 16 patients were assigned to Part A (3 patients in Cohort 1 received olaparib 200 mg bid and abiraterone 1000 mg qd; 13 patients in Cohort 2 received olaparib 300 mg bid and abiraterone 1000 mg qd).
- Part B was a randomized, double-blind, placebo-controlled comparison of the efficacy, safety, and tolerability of the dose of olaparib selected from Part A (300 mg bid) when given in addition to abiraterone vs placebo and abiraterone. A total of 142 patients were randomized and received olaparib + abiraterone (N = 71) or placebo + abiraterone (N = 71) in Part B.

Overall, the demographic and baseline disease characteristics were representative of the intended patient population in Parts A and B of this study.

Efficacy and Safety Summary (Part B)

A summary of the rPFS and OS outcomes from Study 8 are presented in Table 2.

Table 2 Study 8: Summary of rPFS and OS Outcomes (ITT) – DCO 22 September 2017

	Olaparib + Abiraterone (N = 71)	**Placebo + Abiraterone (N = 71)**
rPFS by investigator assessment (70.4% maturity)		
Number of events (%) [a]	46 (64.8)	54 (76.1)
Median rPFS (months) [a, b]	13.8	8.2
HR (95% CI)	0.65 (0.44, 0.97)	
p-value	0.034	
OS (62.0% maturity)		
Number of events (%)	43 (60.6)	45 (63.4)
Median OS (months) [b]	22.7	20.9
HR (95% CI)	0.91 (0.60, 1.38)	
p-value	0.662	

[a] Progression defined by RECIST 1.1 (soft tissue) and/or PCWG-2 (bone) criteria as assessed by investigator or death (by any cause in the absence of progression).

[b] Calculated using the Kaplan-Meier technique.

The analysis was performed using the log rank test with treatment group as a factor.

The HR and CI were estimated from the U and V statistics obtained directly from the LIFETEST model (using the Breslow approach for handling ties). An HR < 1 favors olaparib + abiraterone.
CI = confidence interval; DCO = data cut-off; HR = hazard ratio; ITT = intention-to-treat; N = total number of patients; OS = overall survival; PCWG-2 = Prostate Cancer Working Groups-2; RECIST = Response Evaluation Criteria in Solid Tumors; rPFS = radiological progression-free survival.

- As shown in Table 2, Study 8 met its primary objective with a statistically significant and clinically meaningful improvement in rPFS (by investigator assessment) for olaparib + abiraterone vs the placebo + abiraterone in an ITT population of patients with mCRPC.
- A summary of the rPFS outcomes in pre-specified analyses by HRR gene mutation status are presented in Table 3 and show a clinical benefit in rPFS in both the HRRm and non-HRRm subgroups that was consistent with that observed in the ITT.
- As shown in Table 2, there was no OS detriment in olaparib + abiraterone-treated patients.
- Other secondary endpoints (TFST, PFS2, and time to second subsequent therapy or death) all favored the olaparib + abiraterone arm over the placebo + abiraterone.
- The nature and severity of the observed AEs were consistent with the known monotherapy safety profiles of olaparib and abiraterone.
- Although *BRCA* was assessed as part of the HRR panel in Study 8, only 7 patients were *BRCAm* on the final classification. It was therefore not possible to assess subgroups based on *BRCAm* status in this study.

Taken together, the rationale for the PROpel study was based on available pre-clinical and clinical (Study 8) data to combine 2 effective treatments in an all-comer population of patients with mCRPC, where improvement in clinical outcomes can be most impactful to patients by significantly delaying progression, and initiation of subsequent therapy.

Table 3 Study 8: Summary of rPFS by HRR Gene Mutation Status – DCO 22 September 2017

Classification	Subgroup	Treatment arm	N	Number of events (%) [a]	Median rPFS (months) [a, b]	HR (95% CI)
Initial HRR classification	HRRm	Olap + Abi	11	8 (72.7)	17.8	0.74 (0.26, 2.12)
		Pla + Abi	10	7 (70.0)	6.5	
	Non-HRRm	Olap + Abi	15	8 (53.3)	15.0	0.52 (0.24, 1.15)
		Pla + Abi	20	17 (85.0)	9.7	
	HRRm unknown	Olap + Abi	45	30 (66.7)	13.1	0.67 (0.40, 1.13)
		Pla + Abi	41	30 (73.2)	6.4	
Final HRR classification	HRRm	Olap + Abi	11	8 (72.7)	17.8	0.62 (0.23, 1.65)
		Pla + Abi	12	9 (75.0)	6.5	
	Non-HRRm	Olap + Abi	35	24 (68.6)	11.6	0.54 (0.32, 0.93)
		Pla + Abi	38	32 (84.2)	5.5	
	HRRm unknown	Olap + Abi	25	14 (56.0)	15.3	0.95 (0.44, 2.04)
		Pla + Abi	21	13 (61.9)	13.9	

[a] Progression defined by RECIST 1.1 (soft tissue) and/or PCWG-2 (bone) criteria as assessed by investigator or death (by any cause in the absence of progression).

[b] Calculated using the Kaplan-Meier technique.

Final classification HRR15 takes into account all initial data and further test results subsequently available.
The analysis was performed using the log rank test with treatment group as a factor.
The HR and CI were estimated from the U and V statistics obtained directly from the LIFETEST model (using the Breslow approach for handling ties). An HR < 1 favors olaparib + abiraterone.
Abi = abiraterone; CI = confidence interval; DCO = data cut-off; HR = hazard ratio; HRR = homologous recombination repair; HRRm = HRR gene mutated; N = total number of patients; Olap = olaparib; PCWG-2 = Prostate Cancer Working Groups-2; Pla = placebo; RECIST = Response Evaluation Criteria in Solid Tumors; rPFS = radiological progression-free survival.

4 OLAPARIB REGULATORY HISTORY

A summary of the key advice received in relation to the PROpel study is provided in Table 4.

Table 4 Summary of FDA Advice on the PROpel Study Design

Date	Communication
24 May 2018	FDA Type B meeting to obtain feedback on the results of Study 8 as a basis for an accelerated approval and on the study design for a proposed Phase III study (PROpel) as confirmatory evidence of the benefit of the combination of olaparib and abiraterone in mCRPC. The Agency agreed with AstraZeneca's proposal for the PROpel study eligibility criteria, the monitoring plan to characterize the safety of the olaparib and abiraterone combination, and the drug-drug interaction package. The Agency also agreed with rPFS as the primary endpoint but noted the requirement for demonstration of sufficient magnitude of effect, internal consistency of efficacy endpoints, and the need for BICR sensitivity analysis. The Agency indicated the importance of demonstrating a trend towards improved OS to ensure no treatment detriment in the ITT population.
24 July 2018	PROpel study protocol submitted in the US.
29 September 2020	FDA Type C meeting to obtain feedback on revisions to the PROpel study design and SAP, and registrational plans for olaparib and abiraterone in first-line mCRPC.
26 January 2021	PROpel study protocol version 2 and SAP submitted.
24 March 2021	FDA provided feedback to incorporate formal testing for OS at DCO1.
28 May 2021	PROpel study protocol version 3 and SAP (incorporating formal testing for OS at DCO1) submitted.
09 November 2021	Type B pre-submission meeting to obtain feedback on suitability of the proposed submission package.
04 February 2022	Type B Written Responses Only to obtain feedback on the format and content of the planned sNDA.
18 May 2022	Type B pre-submission meeting to obtain feedback on suitability of the proposed submission package.
16 June 2022	AstraZeneca submitted the sNDA application (S-025) to NDA 208,558.
15 August 2022	FDA granted the sNDA application (NDA 208,558/S-025) a priority review classification.

BICR = blinded independent central review; DCO = data cut-off; FDA = Food and Drug Administration; ITT = intention to treat; mCRPC = metastatic castration-resistant prostate cancer; NDA = new drug application; OS = overall survival; rPFS = radiological progression-free survival; SAP = statistical analysis plan; sNDA = supplemental new drug application; US = United States.

Status of Worldwide PROpel Regulatory Submissions as of 16 March 2023

Based on the data from the PROpel study, the European Commission decision (approval) was received on 16 December 2022, for the following indication:

Lynparza is indicated in combination with abiraterone and prednisone or prednisolone for the treatment of adult patients with mCRPC in whom chemotherapy is not clinically indicated (see Section 5.1).

Approvals for PROpel (with full ITT indications) have also been received from Chile, Brazil, Russia, South Korea, Great Britain, and Singapore (12 September 2022, 23 January 2023, 06 February 2023, 23 February 2023, 15 March 2023, and 16 March 2023, respectively).

Regulatory reviews of PROpel are ongoing globally.

5 PROPEL: THE PIVOTAL STUDY FOR OLAPARIB IN COMBINATION WITH ABIRATERONE AS FIRST-LINE TREATMENT FOR PATIENTS WITH MCRPC

5.1 Study Design

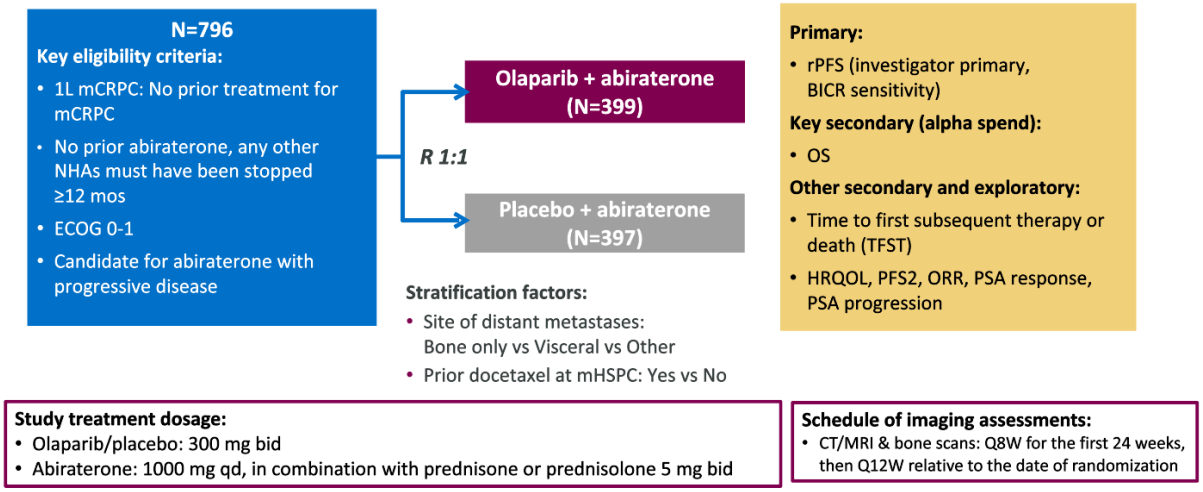
PROpel (NCT03732820) is a Phase III randomized, double-blind, placebo-controlled multicenter study of olaparib in combination with abiraterone vs placebo in combination with abiraterone, each combined with prednisone or prednisolone, as first-line treatment for men with mCRPC.

All patients had to have evidence of histologically or cytologically confirmed prostate adenocarcinoma and metastatic status defined as at least one documented metastatic lesion on either a bone or computed tomography/magnetic resonance imaging scan. At the mCRPC stage (first-line setting), patients had to have no prior cytotoxic chemotherapy or NHA treatment. Prior to the mCRPC stage, treatment with second-generation antiandrogen agents (except abiraterone) without PSA progression/clinical progression/radiological progression during treatment was allowed, provided the treatment was stopped at least 12 months before randomization. Treatment with first-generation antiandrogen agents was also allowed provided there was a washout period of 4 weeks. Patients could have received prior docetaxel treatment during neoadjuvant/adjuvant treatment for localized prostate cancer and at the mHSPC stage.

Both symptomatic and asymptomatic/mildly symptomatic patients were eligible as well as patients with visceral metastases (except brain metastases) as long as they were considered candidates for abiraterone by the investigator.

Patients received either olaparib (300 mg bid) or placebo in combination with abiraterone (1000 mg qd). Treatment with abiraterone was given as per label indication and included prednisone or prednisolone 5 mg bid for both treatment groups. Patients continued to receive study treatment until objective radiological disease progression by investigator assessment or until they were unable to tolerate study treatment.

Figure 4 PROpel Overview



1L = first-line; bid = twice daily; BICR = blinded independent central review; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; HRQOL = health-related quality of life; mHSPC = metastatic hormone-sensitive prostate cancer; N = total number of patients; NHAs = new hormonal agents; mCRPC = metastatic castration-resistant prostate cancer; mos = months; MRI = magnetic resonance imaging; ORR = objective response rate; OS = overall survival; PFS2 = time from randomization to second progression or death; PSA = prostate-specific antigen; Q8W = every 8 weeks; Q12W = every 12 weeks; qd = once daily; R = randomization; rPFS = radiological progression-free survival; TFST = time to first subsequent therapy or death; vs = versus.

Randomization and Blinding

Patients were randomized 1:1 and both investigators and patients remained blinded to randomized treatment for the study duration. Randomization was stratified by site of distant metastases at baseline (bone only vs visceral vs other) and docetaxel treatment at the mHSPC stage (yes vs no). Unblinding to treatment allocation was permitted in cases of medical emergency.

Stratification Factors at Randomization

The following stratification factors were used as they were known significant prognostic factors in mCRPC at the time of the PROpel design:

- Site of distant metastases: bone only vs visceral vs other
- Docetaxel treatment at mHSPC stage: yes vs no

These 2 stratification factors were chosen because:

1 Patients with visceral metastases have been shown to have a shorter survival time compared to patients without visceral metastases from the PREVAIL study, and patients

with bone-only metastases have been shown to have longer survival compared to patients with other metastases at baseline from the COU-AA-302 study.

2 Docetaxel treatment is only indicated in patients with high disease burden (high volume disease) or with high-risk features at mHSPC based on 2 randomized controlled Phase III trials, CHAARTED (NCT00309985; Kyriakopoulos et al 2018) and STAMPEDE (NCT00268476; James et al 2016). Hence patients with prior docetaxel at mHSPC by default have a poor prognosis compared to patients without prior docetaxel at mHSPC (mostly like low disease burden or low-risk patients).

Biomarker status was not included as a stratification factor since PROpel was designed with the available data from Study 8, where HRR gene mutation status was not demonstrated to be predictive of benefit for the combination of olaparib + abiraterone in mCRPC, and at the time, there were limited evidence of prognostic value of HRRm or *BRCAm* in mCRPC. Therefore, clinical factors with known significant prognostic value were prioritized and selected as stratification factors for the study.

Biomarker testing in PROpel was pre-planned and was performed after randomization and before primary analysis. This approach ensured that the PROpel study enrolled a true all-comer population of first-line mCRPC patients, as there was no bias caused by patients or investigators knowing the biomarker status of the tumor.

5.2 Study Endpoints

The PROpel study design was discussed with the FDA (May 2018) and the sole primary endpoint of rPFS was deemed acceptable. It was also stated by FDA that at least a trend toward OS benefit would need to be demonstrated in the study in the ITT population.

Primary Endpoint

The primary endpoint in PROpel is rPFS as assessed by the investigator using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 (soft tissue) and PCWG-3 criteria (bone) for all randomized patients (ie, the ITT population). Radiological progression-free survival was chosen as it is recommended by PCWG-3 as an important endpoint in assessing clinical benefit in clinical studies in patients with mCRPC (Scher et al 2016), since it provides an assessment of benefit prior to determination of survival and is not confounded by subsequent anti-cancer therapy. A prolongation of rPFS has clinical relevance to patients with mCRPC, as delaying progression may result in a delay in the clinically important consequences such as bone pain, complications of visceral metastases, starting chemotherapy, and deterioration of quality of life.

The primary endpoint was investigator-assessed rPFS which is the most clinically relevant assessment of radiological progression. As PROpel was double-blind, the risk of bias to this

endpoint was assessed to be minimal, though the study also included assessment of rPFS by BICR as a sensitivity analysis. The use of investigator-assessed rPFS and a sensitivity analysis by BICR was agreed with the FDA (Table 4).

Radiological progression-free survival was defined as the time from randomization to 1) radiological progression, assessed by investigator per RECIST 1.1 (soft tissue) and PCWG-3 criteria (bone), or 2) death from any cause, whichever occurs first.

Tumor assessments by computed tomography/magnetic resonance imaging using RECIST 1.1 for soft tissue and bone scintigraphy scans using the PCWG-3 criteria for bone lesions were performed every 8 weeks (± 7 days) until Week 24, and every 12 weeks (± 7 days) thereafter following randomization until objective radiological disease progression was confirmed by the investigator. The tumor assessment schedule was based on the recommendation from PCWG-3 (Scher et al 2016). After the initial assessment of progression, whether the patient received a subsequent therapy or not, the patient was to have a follow-up scan collected preferably at (and no later than) the next scheduled imaging visit, and no less than 6 weeks after the prior assessment of disease progression.

Radiological progression-free survival based on Prostate Cancer Working Groups 2 (PCWG-2) or PCWG-3 has been increasingly used as a meaningful imaging-based endpoint in patients with mCRPC. In randomized Phase III trials, rPFS showed a good correlation with OS at the individual trial level, eg, COU-AA-302 (Morris et al 2015) and PREVAIL (Rathkopf et al 2018) studies. A recent meta-analysis assessed the correlation between the HR of imaging-based intermediate endpoints and OS among PCWG-2-based randomized trials. Twenty-eight Phase II to III randomized trials (16,511 patients) were included, in which 18 trials used rPFS as an imaging-based endpoint. The correlation between OS and rPFS was good (R^2 = 0.58, 95% CI, 0.32 to 0.82 vs 0.00, 95% CI, -0.01 to 0.01) (Woo et al 2022).

Key Secondary Endpoint

Overall survival was defined as the time from randomization until date of death (due to any cause) for all randomized patients (ie, the ITT population). Any patient not known to have died at the time of analysis was censored based on the last recorded date on which the patient was known to be alive.

Other Secondary Endpoints

Additional secondary endpoints included TFST, PFS2, time to pain progression, time to opiate use for cancer pain, and time to first symptomatic skeletal-related event, HRQoL (assessed using Functional Assessment of Cancer Therapy – Prostate Cancer questionnaire), safety and tolerability.

Exploratory Endpoints

Exploratory endpoints included ORR, PSA_{50} response, and time to PSA progression.

5.3 Statistical Methodology

The primary analysis was based on rPFS programmatically derived based on investigator recorded assessments using RECIST 1.1 (soft tissue) and PCWG-3 criteria (bone) for all randomized patients. A sensitivity analysis based on BICR assessments was also performed.

Patients who had not progressed (ie, who had a complete response, partial response, or stable disease by RECIST 1.1, non-progressive disease by PCWG-3) and not died at the time of analysis were censored at the earliest date of their last evaluable RECIST assessment (taking the latest target lesion, non-target lesion or new lesion scan date) or bone scan assessment that showed no disease progression (compared to Week 8 or compared to baseline at the Week 8 visit) (if the RECIST and bone scans were at different visits). If the RECIST and bone scan assessments were performed at the same visit, then the patient was censored at the latest of the previous RECIST1.1 and bone scan assessments.

However, if the patient progressed or died immediately after 2 or more consecutive missed visits, the patient was censored at the time of the earliest of either the previous RECIST 1.1 assessment (taking the latest target lesion, non-target lesion or new lesion scan date) or previous bone scan assessment prior to the 2 consecutive missed visits (if RECIST and bone scan done at different visits). If the RECIST and bone scan assessments were performed at the same visit, then the patient was censored at the latest of the previous RECIST 1.1 and bone scan assessments. If the patient had no evaluable visits or did not have baseline data they were censored at Day 1 unless they died within 2 visits of baseline (2 visits of baseline equates to Day 120 based on 16 weeks plus 1 week allowing for a late assessment within the visit window), in which case their date of death was used.

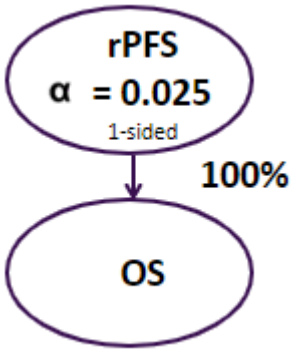
For OS, if patients were confirmed to be alive or if the death date was after the DCO date, these patients were censored at the date of DCO.

Radiological progression-free survival was analyzed using a log-rank test stratified by site of distant metastases (bone only vs visceral vs other) and docetaxel treatment at the mHSPC stage (yes vs no) to calculate a 2-sided p-value. The HR and corresponding 95% CI were estimated using a Cox proportional hazards model including the stratification variables as covariates with the CI calculated using a profile likelihood approach.

Analyses of secondary endpoints (eg, OS, TFST, PFS2, HRQoL) used the same method as used for the analysis of rPFS, stratified in accordance with the primary pooling strategy.

The multiple testing procedure (MTP) was based on analyses at 3 DCOs. To strongly control the Type I error at 2.5% (1-sided), an MTP was used across the primary (rPFS) and key secondary (OS) endpoints in the ITT population (Figure 5). Following a hierarchical testing strategy, rPFS was tested first and then OS was tested only if statistical significance was shown for rPFS. For each endpoint with an interim analysis, the O'Brien and Fleming spending function (Lan and DeMets 1983, O'Brien and Fleming 1979), calculated based on actual observed events, was used to strongly control the overall Type I error, with the restriction that alpha spend for the OS interim analysis at DCO1 would not exceed 0.0005 (1-sided). It was assumed that for the primary endpoint of rPFS, the true treatment effect was an HR of 0.68, corresponding to an assumed increase in median rPFS from 16.5 months in the placebo + abiraterone arm to 24.3 months in the olaparib + abiraterone arm. PROpel was not powered for OS, based upon a priori assumptions of the treatment effect for this endpoint, specifically a median OS of 36 months in the control arm and an underlying HR of 0.8.

Figure 5 Multiplicity Strategy in PROpel



OS = overall survival; rPFS = radiological progression-free survival.

Radiological PFS analyses were formally planned at DCO1 and DCO2, however, as the rPFS comparison was statistically significant at DCO1 (p-value of < 0001 from the log-rank test below the controlled alpha spending allocation of 0.0324 [2-sided]), formal rPFS analysis at DCO2 was not performed and analysis of this endpoint at DCO2 was considered descriptive only (with nominal p-values provided); a final exploratory analysis of rPFS was performed at DCO3. Overall survival was formally analyzed at DCO1 (interim analysis; alpha spend restricted to not exceed 0.001 [2-sided]), DCO2 (interim analysis; alpha threshold of 0.0338 [2-sided]), and DCO3 (final analysis; alpha threshold of 0.0377 [2-sided]).

A summary of the information for the 3 DCOs is presented in Table 5.

Table 5 Summary of DCO Information in PROpel

Analysis number	Type of analysis	Planned number of rPFS events (% maturity)	Information fraction (%)	DCO date	Actual number of rPFS events at DCO (% maturity)	Months after first patient randomized	Months after last patient randomized	Planned number of OS events (% maturity)	Actual number of OS events at DCO (% maturity)
DCO1	Event driven	379/796 (47.6)	83.7	30 July 2021	394/796 (49.5)	33	17	230/796 (28.9)	228/796 (28.6)
DCO2	Event driven	453/796 (56.9)	100	14 March 2022	457/796 (57.4)	40	25	295/796 (37.1)	319/796 (40.1)
DCO3	Time driven (~48 months after first patient randomized	NA	NA	12 October 2022	496/796 (62.3) [a]	47	32	360/796 (45.2)	381/796 (47.9)

[a] rPFS analysis at DCO3 was descriptive.
DCO = data cut-off; NA = not applicable; OS = overall survival; rPFS = radiological progression-free survival.

5.4 Genetic Testing in Clinical Practice

Metastatic castration-resistant prostate cancer is a biologically heterogenous disease. The HRR pathway alterations can be detected in about 28% of patients with mCRPC (de Bono et al 2019, de Bono et al 2020) and pertains to patients who have an underlying somatic or germline gene mutation. Tumor HRR gene testing showed a prevalence of 9.7% for mCRPC patients who had a *BRCA* mutation, of which *BRCA2* mutations represented 8.7% (de Bono et al 2019).

Genetic testing is important in prostate cancer to support informed patient-physician shared treatment decision making, for prognostic assessment (determination of how aggressive a tumor may be or assessment on survival), management of risk of other cancers, and/or potential risk of cancer in family members (detected through germline testing). Genetic testing is recommended in the NCCN guidelines and the American Urological Association/American Society for Therapeutic Radiology and Oncology/Society of Urologic Oncology guidelines (Lowrance et al 2021, NCCN Prostate Cancer Guidelines 2023).

There are different techniques that are used to identify patients with underlying HRR gene mutations, such as a tumor tissue test, ctDNA-based test, or germline testing using whole blood. Further details about the tumor tissue test and ctDNA-based test, which can detect both germline and somatic mutations, are provided in Section 5.5.

Rates of HRR gene mutation testing in the US have increased over time, but currently many patients are not tested. Before 2019, it was reported that in the US, only 13% of mCRPC patients (674/5213) had a documented genetic test (Shore et al 2021). Following the PROfound (D081DC0007; NCT02987543) and TRITON2 (NCT02952534) trials, HRR gene mutation testing rates in the US improved with reports of 38.2% of mCRPC patients (132/346) tested in 2020. However, the data also showed that there was a disparity between those patients tested in an academic/cancer center (47.5%) vs lower rates in the community setting (27.9%) (Leith et al 2022), indicating that the majority of patients in the US would have an unknown HRR gene mutation status and therefore would not have the option of a therapy that required genetic testing.

Although HRR gene mutation testing has increased over time (Leith et al 2022, Shore et al 2021), it is uncommon for patients to have valid testing results from both tumor and ctDNA tests. A recent study reported that out of 3889 prostate cancer patients who were tested as a part of clinical care, only 233 patients had both tumor tissue and ctDNA testing results, indicating that < 6% patients with prostate cancer had results from both tests (Tukachinsky et al 2021).

5.5 Biomarker Testing Strategy

PROpel is an all-comer study and patient enrollment was not based on HRR gene mutation status (HRR gene panel consisted of 14 genes[1] [including *BRCA1* and *BRCA2*] that were included in the FDA approval of olaparib monotherapy based on the PROfound trial). These 14 HRR genes were initially selected based on mechanistic role in HRR (direct or indirect), pre-clinical evidence of sensitivity to PARP inhibition, clinical efficacy data, hereditary cancer risk, prevalence across solid tumor types and genetic reversion events that restore gene function in tumors from patients who have developed clinical resistance to PARP inhibitors. However, HRR gene mutation testing was pre-planned for all patients. Both archival tumor tissue and blood samples at baseline were collected from > 98% of randomized patients so that HRR gene mutation status by both tumor tissue test (FoundationOne® CDx) and a ctDNA-based test (FoundationOne® Liquid CDx) could be determined blinded to treatment arm, after randomization and before primary analysis. Both tests are sensitive, well-established, FDA-approved and are complementary to each other.

- The tumor tissue test detects gene mutations present in the cancer cells regardless of whether or not the tumor sheds cancer cells into the bloodstream.
- ctDNA is derived from the shedding of a pool of cancer cells at different disease sites.

Tumor testing is considered the reference standard, but is dependent on high-quality tissue availability, which is challenging for many mCRPC patients. Despite best efforts, the failure rate of the tumor tissue gene mutation testing in prostate cancer is approximately 30% mainly due to small and poor-quality tumor tissue samples (Abida et al 2017). Of the 782 patients in PROpel that provided a tumor sample for analysis with the tissue tumor test, 535 patients (68.4%) had a valid test result while 247 patients (31.6%) had samples that failed testing. The tumor tissue test failure rate (31.6%) observed in PROpel was in line with what was observed in PROfound (31%, de Bono et al 2019) and published literature (32%, Abida et al 2017).

In order to maximize the biomarker information available for all patients, the ctDNA test was used to complement the tissue testing, as this identifies mutations from any tumor lesion shed into the blood. In contrast to the tumor tissue test, of the 794 patients who provided a blood sample for ctDNA testing, 92.4% (734 patients) had a valid ctDNA test result; the ctDNA gene mutation test failure rate was only 7.6% (60 patients).

In PROpel the prevalence of *BRCAm* was 11% which is similar to the that of previously published studies (9 to 12%) indicating that PROpel is representative of the mCRPC patient

[1] 14 genes in HRR panel are: *ATM*, *BARD1*, *BRCA1*, *BRCA2*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *RAD51B*, *RAD51C*, *RAD51D*, and *RAD54L*.

population (Abida et al 2017, Abida et al 2019, Armenia et al 2018, Chung et al 2019, de Bono et al 2019).

Rationale for Exploratory Aggregate Analyses Using Either Test Result

AstraZeneca conducted aggregate analysis, categorizing HRR and *BRCA* gene mutation status by either tumor tissue or ctDNA test in order to:

- Generate the most complete dataset of HRR and *BRCA* gene mutation status, maximizing the biomarker information in the study and thus minimizing the number of patients with an unknown biomarker gene mutation status.
- Use either ctDNA-based or tumor tissue testing within PROpel to determine patients' HRR gene mutation or *BRCA* mutation status reflect clinical practice, as the majority of patients will be tested by only one test.

In PROpel, 98% of patients had samples assessed by both tests and only 18 patients did not have a valid result by any test.

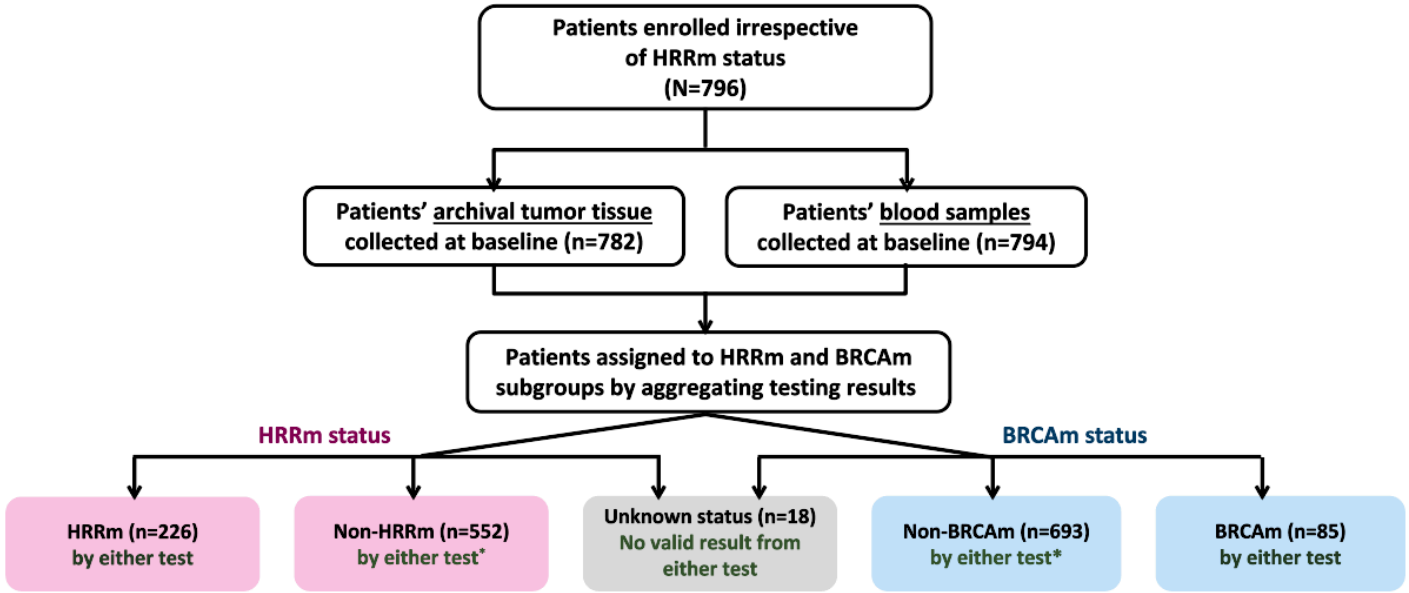
Concordance analyses showed a high overall agreement between tumor tissue and ctDNA tests (94%) and a low probability of missing a sample that could be HRRm (~12 potential HRRm patients) or *BRCAm* (~6 *BRCAm* patients) by tissue test (Figure 6), when assessed successfully by ctDNA test only, supporting the robustness for aggregate analyses.

The aggregate HRRm subgroup comprised patients with an HRR gene mutation detected by either test. The non-HRRm subgroup comprised patients who were not HRRm and who did not have a HRR gene mutation detected by either test. Finally, the HRRm unknown group comprised patients who did not have valid results from both tests.

Similarly, the aggregate *BRCAm* subgroup comprised patients with *BRCAm* detected by either test. The non-*BRCAm* subgroup comprised patients who were not *BRCAm* and who did not have a *BRCA* mutation detected by either test. Finally, the *BRCAm* unknown group comprised patients who did not have valid results from both tests.

A schematic of the assignments in the aggregate HRR and *BRCA* subgroups is shown in Figure 6.

Figure 6 Aggregate Analysis: HRR and *BRCA* Assignment Data to Generate the Most Complete Dataset



* Excludes patients tested positive by either test.
Negative predictive value of ctDNA test = 97.3% (427/[427+12]*100). Approximately 6 *BRCAm* patients could be misclassified as non-*BRCAm* by the ctDNA test.
Negative predictive value of tumor test = 96.0% (427/[427+18]*100). Approximately 2 *BRCAm* patients could be misclassified as non-*BRCAm* by the tumor test.
BRCA = breast cancer susceptibility gene; *BRCAm* = *gBRCA* or *sBRCA* mutated; ctDNA = circulating tumor DNA; *gBRCA* = germline *BRCA*; HRR = homologous recombination repair; HRRm = HRR gene mutated; N = total number of patients; n = number of patients; *sBRCA* = somatic *BRCA*.

Limitations of Requiring Two Test Results to Define the Non-HRRm and Non-*BRCAm* Populations

An alternative approach to delineate the non-*BRCAm* population would require results from both tests to be negative.

There are a number of limitations to this methodology:

- Double testing is not warranted due to the low risk of misclassification by either test.
  - Based on the high negative predictive values (~96 to 97%) observed in PROpel for both the ctDNA and tumor tissue tests, the AstraZeneca aggregate method (mutation status by either the ctDNA-based test or tumor tissue-based test) could potentially misclassify ~8 *BRCAm* patients as non-*BRCAm*, and such a small number of *BRCAm* patients would have limited impact to the study results in the 693 non-*BRCAm* aggregate population. Hence the treatment effect observed in the aggregate non-*BRCAm* population is a reliable estimation.
- Introduction of potential bias.
  - The biomarker dataset would be the most incomplete of all those available due to the high rate of testing failure.
  - The large missing proportion (~36% of all patients with unknown status) of the population would likely introduce unknown bias to the analyses.
- The requirement to have used both tests in clinical testing practice for determination of *BRCA* mutation status is likely to be challenging for all patients, where it is very uncommon for patients to receive 2 tests.
  - Despite the best efforts and resources in a Phase III study like PROpel, approximately one third of the patients could not have valid test results by both tumor tissue and ctDNA to determine the non-*BRCAm* status by negative result from both tests.

Conclusion

AstraZeneca therefore considers that the aggregate method presented herein (non-*BRCAm* subgroup defined by negative mutation status by either the ctDNA-based test or tumor tissue-based test) represents the most complete and clinically relevant dataset for estimation of a treatment effect in the biomarker subgroups (HRRm, *BRCAm*, non-HRRm, and non-*BRCAm*) within PROpel that will support patient/physician's discussion on the expected benefit/risk.

5.6 Patient Disposition

Patient disposition is summarized in Table 6. The most common primary reason for discontinuation from study treatment was objective disease progression, which occurred more frequently in the placebo + abiraterone arm than in the olaparib + abiraterone arm.

Table 6 Patient Disposition (All Patients) at DCO3 (12 October 2022)

	Number (%) of patients		
	Olaparib + Abiraterone (N = 399)	**Placebo + Abiraterone (N = 397)**	**Total**
Patients enrolled [a]			1103
Patients randomized	399 (100)	397 (100)	796 (100)
Patients who were not randomized			307
Screen failure			284
Patient decision			20
Incorrect enrolment			2
Other			1
Full analysis set	399 (100)	397 (100)	796 (100)
Patients who received treatment	398 (99.7)	396 (99.7)	794 (99.7)
Patients who did not receive treatment	1 (0.3)	1 (0.3)	2 (0.3)
Failure to meet randomization criteria	1 (0.3)	0	1 (0.1)
Screen failure	0	1 (0.3)	1 (0.1)
Patients ongoing treatment at DCO3 [b]	110 (27.6)	79 (19.9)	189 (23.8)
Patients ongoing both olaparib/placebo and abiraterone [b]	103 (25.9)	77 (19.4)	180 (22.7)
Patients who discontinued olaparib/placebo alone [b]	7 (1.8)	2 (0.5)	9 (1.1)
Patient decision	1 (0.3)	0	1 (0.1)
Adverse event	6 (1.5)	2 (0.5)	8 (1.0)
Due to COVID-19 pandemic	0	0	0
Patients who discontinued treatment [b]	288 (72.4)	317 (80.1)	605 (76.2)
Olaparib/Placebo [b]			
Patient decision	29 (7.3)	19 (4.8)	48 (6.0)
Adverse event	61 (15.3)	29 (7.3)	90 (11.3)
Severe non-compliance to protocol	3 (0.8)	3 (0.8)	6 (0.8)
Objective disease progression	125 (31.4)	186 (47.0)	311 (39.2)
Patient lost to follow-up	0	1 (0.3)	1 (0.1)
Other [c]	70 (17.6)	79 (19.9)	149 (18.8)
Due to COVID-19 pandemic	0	0	0
Abiraterone [b]			
Patient decision	30 (7.5)	22 (5.6)	52 (6.5)

Table 6 Patient Disposition (All Patients) at DCO3 (12 October 2022)

	Number (%) of patients		
	Olaparib + Abiraterone (N = 399)	**Placebo + Abiraterone (N = 397)**	**Total**
Adverse event	37 (9.3)	30 (7.6)	67 (8.4)
Severe non-compliance to protocol	4 (1.0)	3 (0.8)	7 (0.9)
Objective disease progression	137 (34.4)	183 (46.2)	320 (40.3)
Patient lost to follow-up	0	1 (0.3)	1 (0.1)
Other [c]	80 (20.1)	78 (19.7)	158 (19.9)
Due to COVID-19 pandemic	0	0	0
Patients ongoing study at DCO3	210 (52.6)	178 (44.8)	388 (48.7)
Patients who terminated study	189 (47.4)	219 (55.2)	408 (51.3)
Death	168 (42.1)	203 (51.1)	371 (46.6)
Failure to meet randomization criteria	1 (0.3)	1 (0.3)	2 (0.3)
Screen failure	0	1 (0.3)	1 (0.1)
Patient decision	14 (3.5)	10 (2.5)	24 (3.0)
Patient lost to follow-up	4 (1.0)	2 (0.5)	6 (0.8)
Other	2 (0.5)	2 (0.5)	4 (0.5)
Due to COVID-19 pandemic	0	0	0

[a] Informed consent received.

[b] Percentages are calculated from number of patients who received treatment.

[c] "Other" reason for discontinuation as provided by investigator includes clinical progression, PSA progression, death, etc.

Unless otherwise stated, percentages are calculated from the number of patients randomized.
Full analysis set: All randomized patients with treatment groups assigned in accordance with the randomization, regardless of the treatment actually received.
"Due to COVID-19 pandemic" refers to site closure due to pandemic impacting all patients at affected sites.
COVID-19 = Coronavirus disease 2019; DCO = data cut-off; N = total number of patients; PSA = prostate-specific antigen.

5.7 Study Population

The patient population treated in PROpel was a prospectively defined population with a high unmet medical need, reflecting current treatment practices for patients with mCRPC globally, including in the US. The entry criteria were designed to define a study population who could receive benefit from the combination of olaparib + abiraterone treatment. Baseline, demographic, tumor characteristics, and stratification factors were generally well-balanced between the treatment arms (Table 7).

The first patient was enrolled onto the study (ie, provided signed informed consent) on 31 October 2018 and the last patient was enrolled on 11 March 2020. Patients were randomized at 126 centers in 17 countries.

Table 7 Summary of Selected Demographic and Disease Characteristics at Baseline (ITT) - DCO1 (30 July 2021)

		Patients, %	
		Olap + Abi (N = 399)	**Pla + Abi (N = 397)**
Demographics			
Age, yrs	Median (Min, Max)	69.0 (43, 91)	70.0 (46, 88)
	< 65	32.6	24.4
	≥ 65	67.4	75.6
Disease Characteristics			
ECOG PS	(0) Normal activity	71.7	68.5
	(1) Restricted activity	28.1	31.2
Total Gleason Score	≤ 7	30.4	33.8
	8 to 10	66.4	64.9
Baseline S-Prostate Specific Antigen (µg/L)	Median	17.9	16.8
Prior docetaxel at mHSPC	Yes	22.6	22.4
Site of metastases	Bone only	54.4	54.7
	Visceral (eg, lung/liver)	13.3	13.1
	Other	32.3	32.2
Baseline pain score (BPI-SF Item 3 score)	0 to < 4 (No/Mild pain)	71.1	78.1
	4 to ≥ 6 (Moderate/Severe pain)	21.3	16.2

Abi = abiraterone; BPI-SF = Brief Pain Inventory-Short Form; DCO = data cut-off; ECOG = Eastern Cooperative Oncology Group; ITT = intention-to-treat; Max = maximum; mHSPC = metastatic hormone-sensitive prostate cancer; Min = minimum; N = total number of patients; Olap = olaparib; Pla = placebo.

5.8 PROpel Key Efficacy Data

5.8.1 PROpel ITT Data

A summary of the key efficacy outcomes from PROpel is presented in Table 8.

Table 8 PROpel: Summary of Key Efficacy Outcome Variables (ITT)

	Olaparib + Abiraterone (N = 399)	**Placebo + Abiraterone (N = 397)**
rPFS by investigator assessment (49.5% maturity) DCO1 (30 July 2021)		
Number of events (%) [a]	168 (42.1)	226 (56.9)
Median rPFS (months)	24.84	16.59

	Olaparib + Abiraterone (N = 399)	Placebo + Abiraterone (N = 397)
HR (95% CI) [b]	0.66 (0.54, 0.81)	
p-value [c]	< 0.0001	
Type of progression events		
RECIST progression only	73 (18.3)	111 (28.0)
Bone scan PCWG-3 criteria progression only	65 (16.3)	81 (20.4)
RECIST and bone scan PCWG-3 progression [i]	2 (0.5)	6 (1.5)
Death [j]	28 (7.0)	28 (7.1)
rPFS by BICR (47.1% maturity) DCO1 (30 July 2021)		
Number of events (%) [d]	157 (39.3)	218 (54.9)
Median rPFS (months) [e]	27.60	16.39
HR (95% CI) [b]	0.61 (0.49, 0.74)	
p-value [f]	< 0.0001	
OS (47.9% maturity) DCO3 (12 October 2022)		
Number of events (%)	176 (44.1)	205 (51.6)
Median OS (months) [e]	42.05	34.69
HR (95% CI) [b]	0.81 (0.67, 1.00)	
p-value [c]	0.0544	
TFST DCO3 (12 October 2022)		
Number of events (%)	255 (63.9)	285 (71.8)
Median TFST (months) [e]	24.6	19.4
HR (95% CI) [b]	0.76 (0.64, 0.90)	
p-value [c, g]	0.0025	
PFS2 DCO3 (12 October 2022)		
Number of events (%)	103 (25.8)	126 (31.7)
Median PFS2 (months) [e]	NC	NC
HR (95% CI) [b]	0.76 (0.59, 0.99)	
p-value [c, g]	0.0534	
Time to PSA progression DCO1 (30 July 2021)		
Number of events (%)	152 (38.1)	223 (56.2)
Median (months) [e]	NC	12.02
HR (95% CI) [b]	0.55 (0.45, 0.68)	
p-value [c, g]	< 0.0001	

	Olaparib + Abiraterone (N = 399)	Placebo + Abiraterone (N = 397)
Confirmed ORR DCO1 (30 July 2021)		
Number of patients with a response/total number of patients with measurable disease at baseline (%)	84/161 (52.2)	70/160 (43.8)
Confirmed PSA_{50} Response DCO1 (30 July 2021)		
Number of patients with a response/total number of patients with a PSA result at baseline (%)	315/397 (79.3)	274/396 (69.2)
FACT-P total score [h] DCO3 (12 October 2022)		
Overall change from baseline (LS means)	-5.84	-5.30

[a] Progression defined by RECIST 1.1 (soft tissue) and/or PCWG-3 (bone) criteria as assessed by investigator or death (by any cause in the absence of progression), regardless of whether the patient withdraws from randomized therapy or receives another anti-cancer therapy prior to progression.
[b] The HR and CI were calculated using a Cox proportional hazards model adjusted for the variables selected in the primary pooling strategy: metastases, docetaxel treatment at mHSPC stage. The Efron approach was used for handling ties. An HR < 1 favors olaparib + abiraterone.
[c] Two-sided p-value calculated using the log-rank test stratified by the same variables selected in the primary pooling strategy.
[d] The 2-sided p-value was calculated using the log-rank test stratified by the same variables selected in the primary pooling strategy, using the Breslow method for handling ties.
[e] Calculated using the Kaplan-Meier technique.
[f] Progression defined by BICR assessment of RECIST 1.1 (soft tissue) and PCWG-3 (bone) criteria.
[g] The p-value presented is nominal as the endpoint is not alpha controlled.
[h] The analysis was performed using a mixed model for repeated measures with treatment, visit, treatment by visit interaction, baseline FACT-P total score and baseline score by visit interaction, Metastases and Docetaxel treatment at mHSPC stage as fixed effects.
[i] Defined as RECIST and PCWG-3 progression at the same visit.
[j] Death in the absence of radiological progression.

FACT-P total score change from baseline values can be a minimum of -156 and a maximum of 156.
A clinically meaningful change value of 10 points was implemented in PROpel for the FACT-P total score-based endpoint based on the work of Cella et al 2009.
BICR = blinded independent central review; CI = confidence interval; DCO = data cut-off; FACT-P = Functional Assessment of Cancer Therapy – Prostate Cancer; HR = hazard ratio; ITT = intention-to-treat; LS = least squares; mHSPC = metastatic hormone-sensitive prostate cancer; N = total number of patients; NC = not calculable/calculated; ORR = objective response rate; OS = overall survival; PFS2 = time from randomization to second progression or death; PCWG-3 = Prostate Cancer Working Groups-3; PSA = prostate-specific antigen; PSA_{50} = A ≥ 50% decline in PSA from baseline; RECIST = Response Evaluation Criteria in Solid Tumors; rPFS = radiological progression-free survival; TFST = time to first subsequent therapy or death.

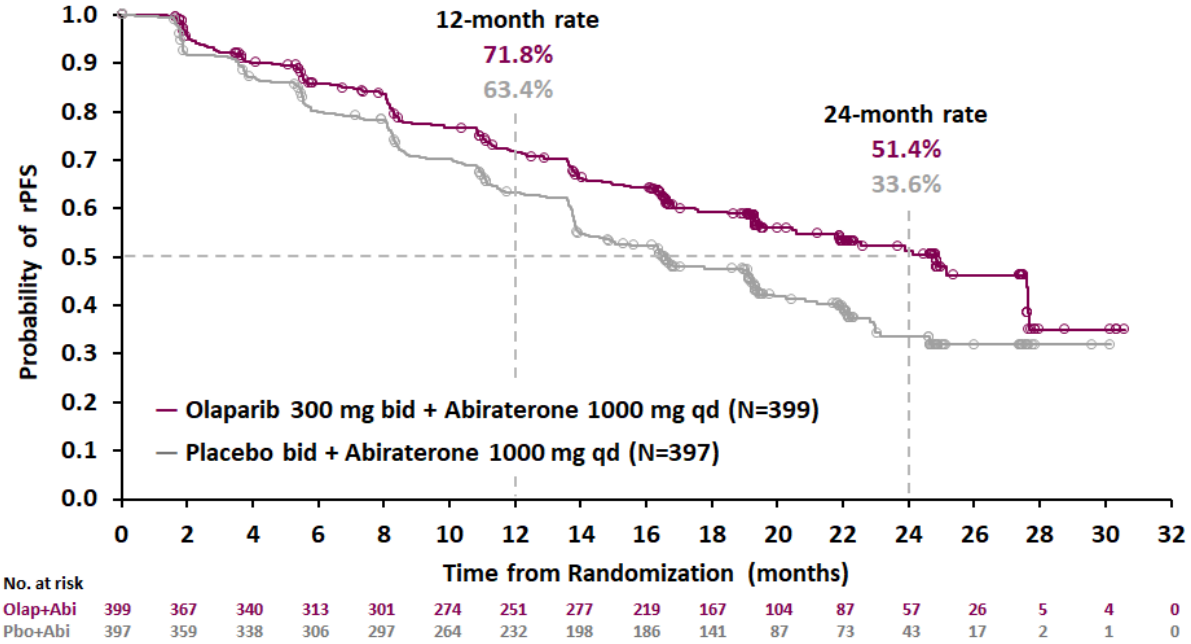
The primary rPFS analysis DCO1 in PROpel was 30 July 2021, at which time 394 rPFS events (49.5% maturity) were observed.

PROpel met its primary endpoint in the ITT patient population, with olaparib + abiraterone providing a statistically significant and clinically meaningful improvement in rPFS over the current standard of care (placebo + abiraterone).

The treatment benefit in PROpel was evidenced by:

- At DCO1, a statistically significant and clinically meaningful 34% reduction in the risk of radiological disease progression or death (HR = 0.66; 95% CI 0.54, 0.81; p < 0.0001) as assessed by the investigator, with a median rPFS improvement of 8.2 months in the olaparib + abiraterone arm over the placebo + abiraterone arm (24.8 months vs 16.6 months, respectively; Figure 7). This benefit was maintained at DCO2 and DCO3.
  - A greater percentage of patients were alive and progression-free at 12 and 24 months in the olaparib + abiraterone arm compared with the placebo + abiraterone arm, respectively.

Figure 7 Kaplan-Meier Plot of rPFS (Investigator Assessment) in the ITT - DCO1 (30 July 2021)

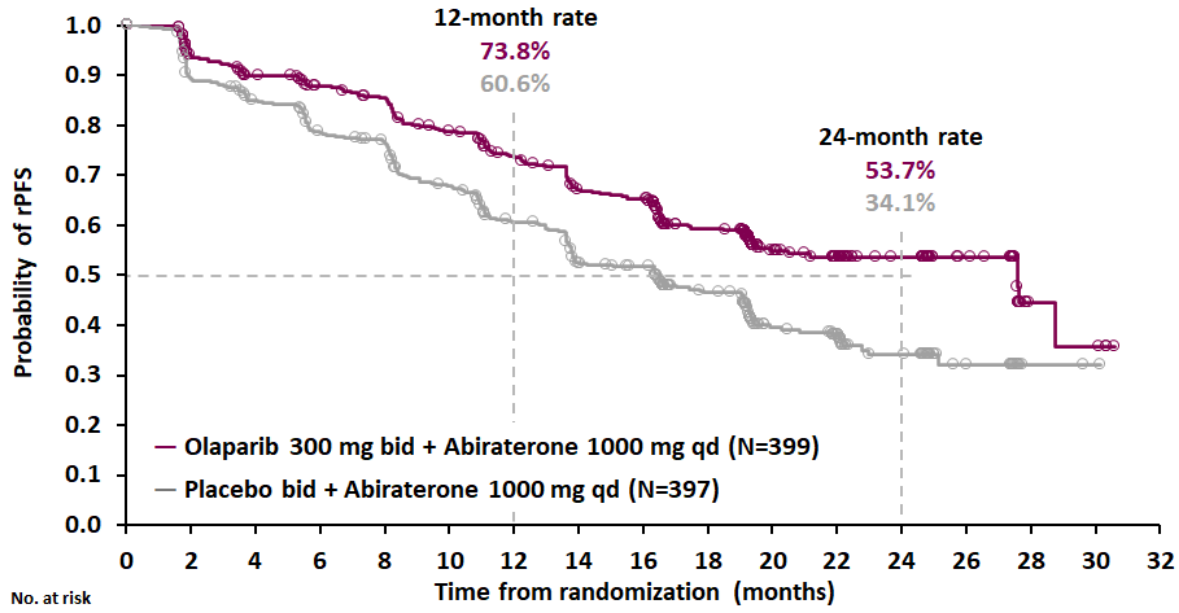


	Olaparib + Abiraterone N=399	Placebo + Abiraterone N=397
Events (%)	168 (42.1)	226 (56.9)
Median, mo	24.8	16.6
Median improvement	8.2 months	
HR (95% CI)	0.66 (0.54, 0.81)	
p-value	<0.0001	

Abi = abiraterone; bid = twice daily; CI = confidence interval; DCO = data cut-off; HR = hazard ratio; ITT = intention-to-treat; mo = months; N = total number of patients; No = number; Olap = olaparib; Pbo = placebo; qd = once daily; rPFS = radiological progression-free survival.

- The sensitivity analysis of rPFS by BICR had an HR of 0.61 (95% CI 0.49, 0.74) and extended rPFS benefit by 11.2 months for olaparib + abiraterone compared to placebo + abiraterone (27.6 months vs 16.4 months, respectively) and was consistent with the investigator-assessed rPFS analysis (Figure 8). The results of these 2 rPFS analyses demonstrate consistency (investigator-assessed rPFS = 0.66; BICR-assessed rPFS = 0.61) and the overall concordance of rPFS between the investigator and BICR analyses was 83%.

Figure 8 **Kaplan-Meier Plot of rPFS (Blinded Independent Central Review) in the ITT - DCO1 (30 July 2021)**



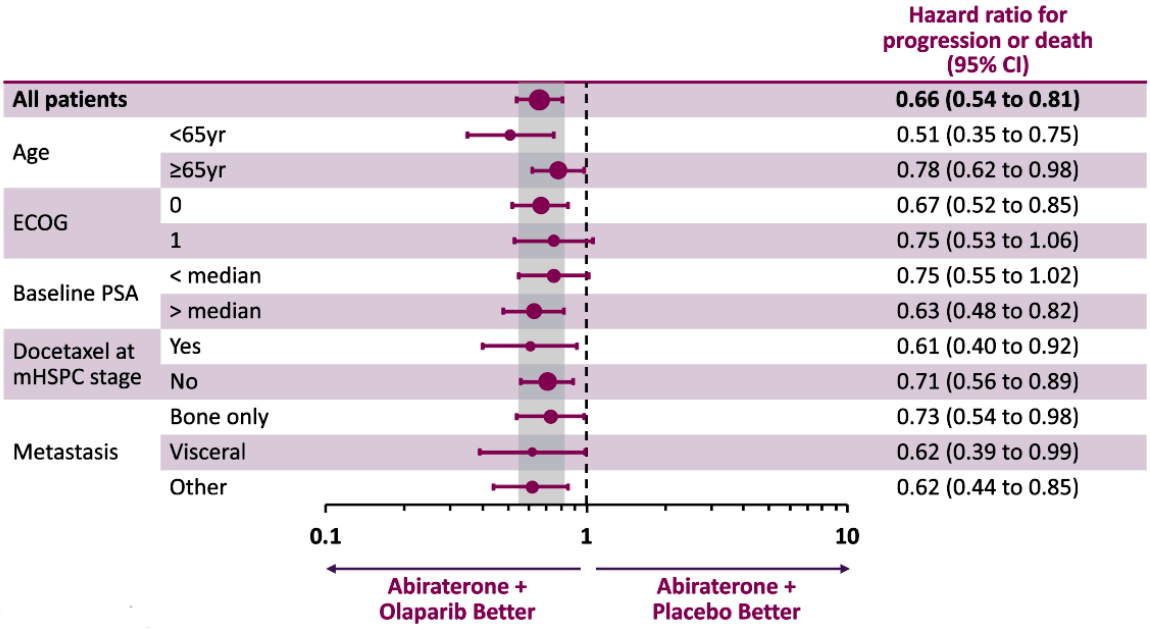
	Olaparib + Abiraterone N=399	Placebo + Abiraterone N=397
Events (%)	157 (39.3)	218 (54.9)
Median, mo	27.6	16.4
Median improvement	**11.2 months**	
HR (95% CI)	**0.61** (0.49, 0.74)	
p-value	<0.0001	

Abi = abiraterone; bid = twice daily; CI = confidence interval; DCO = data cut-off; HR = hazard ratio; ITT = intention-to-treat; mo = months; N = total number of patients; No = number; Olap = olaparib; Pbo = placebo; qd = once daily; rPFS = radiological progression-free survival.

- The benefit of olaparib + abiraterone over placebo + abiraterone in rPFS was maintained across all pre-defined subgroups based on the stratification factors, HRR gene mutation

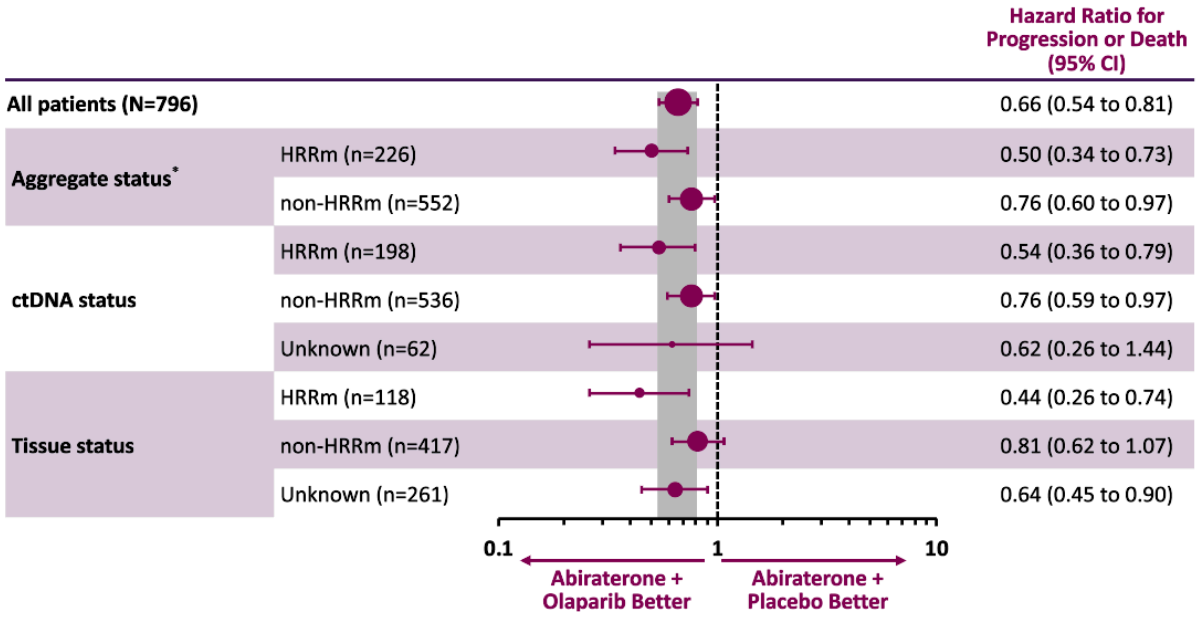
status, and clinical characteristics, with clinically meaningful reductions in the risk of radiological progression or death (Figure 9 and Figure 10). The global interaction test was not significant at the 10% level (p = 0.4129) indicating that overall, the treatment effect was consistent across the stratification factors.

Figure 9 Radiological Progression-free Survival Across Key Pre-specified Clinical Subgroups (ITT) - DCO1 (30 July 2021)



CI = confidence interval; DCO = data cut-off; ECOG = Eastern Cooperative Oncology Group; ITT = intention-to-treat; mHSPC = metastatic hormone-sensitive prostate cancer; PSA = prostate-specific antigen; yr = years.

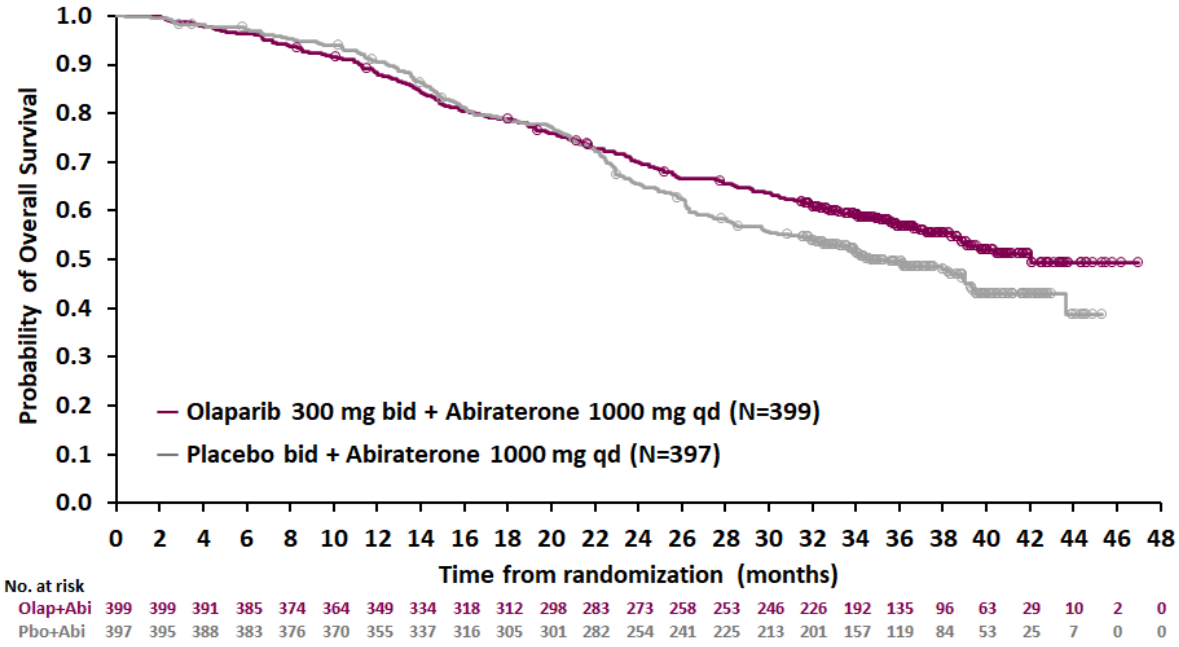
Figure 10 Radiological Progression-free Survival Across HRR Gene Mutation Subgroups (ITT) - DCO1 (30 July 2021)



* Only 18 patients had an unknown status by aggregate and were not included in the analysis.
HRR status by ctDNA and tissue test were pre-specified analyses; aggregate analyses were post-hoc.
CI = confidence interval; ctDNA = circulating tumor DNA; DCO = data cut-off; HRR = homologous recombination repair; HRRm = HRR gene mutated; ITT = intention-to-treat.

- At the final pre-specified OS analysis (DCO3 12 October 2022, OS = 47.9% mature), there was a 19% reduction in the risk of death in the olaparib + abiraterone arm compared to the placebo + abiraterone arm (HR = 0.81; 95% CI: 0.67, 1.00; p = 0.0544; Figure 11). The results for OS did not reach the threshold for statistical significance.
  - There was a median OS improvement of 7.4 months in the olaparib + abiraterone arm over the placebo + abiraterone arm (42.1 months vs 34.7 months, respectively) and survival rates at 24, 36, and 42 months were higher in the olaparib + abiraterone arm vs the placebo + abiraterone arm.

Figure 11 Kaplan-Meier Plot of OS in the ITT - DCO3 (12 October 2022)



	Olaparib + Abiraterone N=399	Placebo + Abiraterone N=397
Events (%)	176 (44.1)	205 (51.6)
Median, mo	42.1	34.7
Median improvement	**7.4 months**	
HR (95% CI)	**0.81** (0.67, 1.00)	
p-value	0.0544	
Alpha boundary	0.0377	

Abi = abiraterone; bid = twice daily; CI = confidence interval; DCO = data cut-off; HR = hazard ratio; ITT = intention-to-treat; mo = months; N = total number of patients; No = number; Olap = olaparib; OS = overall survival; Pbo = placebo; qd = once daily.

As of DCO3, subsequent anti-cancer therapies following study treatment discontinuation were received by a lower percentage of patients (44.9% [179 patients]) in the olaparib + abiraterone arm compared with the placebo + abiraterone arm (54.4% [216 patients]), which is in line with the lower proportion of patients who had disease progression on olaparib + abiraterone versus placebo + abiraterone. The most common post-discontinuation anti-cancer therapy included cytotoxic chemotherapy (290 patients [36.4%]), which was received by a higher percentage of patients in the placebo + abiraterone arm (42.1%) compared with the olaparib + abiraterone arm (30.8%), or hormonal therapy which was received by a similar percentage of patients in both arms (approximately 18%). Treatment with a subsequent PARPi occurred in 2 patients (0.5%) in the olaparib + abiraterone arm (both patients received olaparib), and 5 patients (1.3%) in the placebo + abiraterone arm (of which 2 patients received olaparib).

As shown in Table 8, results from other pre-specified secondary and exploratory endpoints support the clinical benefit of olaparib + abiraterone observed in PROpel:

- Results of TFST, PFS2, ORR, PSA_{50} response, and time to PSA progression all show improvements for olaparib +abiraterone compared with placebo + abiraterone in the ITT, supporting results from the primary rPFS analysis and demonstrating the clinical benefit of treatment with the combination of olaparib + abiraterone.
- As shown in Table 8, the FACT-P total score was similar between treatment arms throughout the treatment period. Compliance rates for completion of the FACT-P questionnaire were 70.9% for the olaparib + abiraterone arm and 75.6% for the placebo + abiraterone arm at baseline; and 69.8% for the olaparib + abiraterone arm and 74.5% for the placebo + abiraterone arm, overall.
  - PROpel data show that the combination of olaparib + abiraterone prolonged rPFS and had no clinically meaningful impact on patients' HRQoL. This is an important consideration for patients, since current anti-cancer treatments maybe expected to impact HRQoL because of the adverse effects associated with mCRPC regimens (Section 2.1.1).

5.8.2 Efficacy Analyses in Aggregate HRR and *BRCA* Subgroups

Baseline, demographic, tumor characteristics, and stratification factors in the HRRm and *BRCAm* subgroups are presented in Appendix D, Table D1 and for the non-HRRm and non-*BRCAm* subgroups are presented in Appendix D, Table D2.

There was no stratification by HRR gene mutation or *BRCA* mutation status in PROpel. Nevertheless, generally in the HRRm, non-HRRm and non-*BRCAm* subgroups, clinically important baseline characteristics were balanced similarly to the ITT population. Given the small size of the *BRCAm* subgroup (n = 85), there were some imbalances between treatment arms within this subgroup. As described in Section 5.5, analyses of efficacy data were performed on a combination of results from both tumor tissue and ctDNA-based tests (aggregate) as they represent the most accurate and comprehensive dataset for estimation of HRRm, *BRCAm*, non-HRRm, and non-*BRCAm* treatment effects.

A clinically meaningful benefit with olaparib + abiraterone was observed in the HRRm, *BRCAm*, non-HRRm, and non-*BRCAm* subgroups, with the greatest benefit of olaparib + abiraterone seen in the *BRCAm* and HRRm subgroups.

5.8.2.1 Efficacy in Patients who are HRRm or *BRCAm*

A summary of efficacy data in the HRRm and *BRCAm* subgroups is shown in Table 9.

Table 9 PROpel: Summary of Key Efficacy Outcome Variables (HRRm and *BRCAm* Subgroups)

	HRRm subgroup		*BRCAm* subgroup	
	Olaparib + Abiraterone (N = 111)	**Placebo + Abiraterone (N = 115)**	**Olaparib + Abiraterone (N = 47)**	**Placebo + Abiraterone (N = 38)**
rPFS by investigator assessment DCO1 (30 July 2021)				
Number of events (%) [a]	43 (38.7)	73 (63.5)	14 (29.8)	28 (73.7)
Median rPFS (months)	NC	13.86	NC	8.38
HR (95% CI) [b]	0.50 (0.34,0.73)		0.23 (0.12, 0.43)	
rPFS by BICR DCO1 (30 July 2021)				
Number of events (%) [d]	43 (38.7)	78 (67.8)	12 (25.5)	31 (81.6)
Median rPFS (months) [c]	28.75	13.77	NC	8.38
HR (95% CI) [b]	0.45 (0.31, 0.65)		0.18 (0.09, 0.34)	
OS DCO3 (12 October 2022)				
Number of events (%)	48 (43.2)	69 (60.0)	13 (27.7)	25 (65.8)
Median OS (months) [c]	NC	28.45	NC	22.97
HR (95% CI) [b]	0.66 (0.45, 0.95)		0.29 (0.14, 0.56)	
TFST DCO3 (12 October 2022)				
Number of events (%)	68 (61.3)	88 (76.5)	24 (51.1)	30 (78.9)
Median TFST (months) [c]	25.76	15.70	37.39	14.75
HR (95% CI) [b]	0.62 (0.45, 0.85)		0.35 (0.21, 0.61)	
PFS2 DCO3 (12 October 2022)				
Number of events (%)	32 (28.8)	43 (37.4)	9 (19.1)	15 (39.5)
Median PFS2 (months) [c]	NC	NC	NC	22.97
HR (95% CI) [b]	0.66 (0.41, 1.04)		0.31 (0.13, 0.69)	
Time to PSA progression DCO3 (12 October 2022)				
Number of events (%)	54 (48.6)	79 (68.7)	19 (40.4)	30 (78.9)
Median (months) [c]	25.10	9.17	40.61	5.59

	HRRm subgroup		*BRCAm* subgroup	
	Olaparib + Abiraterone (N = 111)	**Placebo + Abiraterone (N = 115)**	**Olaparib + Abiraterone (N = 47)**	**Placebo + Abiraterone (N = 38)**
HR (95% CI) [b]	0.41 (0.29, 0.59)		0.14 (0.08, 0.25)	
Confirmed ORR DCO1 (30 July 2021)				
Number of patients with a response/total number of patients with measurable disease at baseline (%)	26/53 (49.1)	24/49 (49.0)	10/20 (50.0)	4/15 (26.7)
Confirmed PSA_{50} Response DCO1 (30 July 2021)				
Number of patients with a response/total number of patients with a PSA result at baseline (%)	86/110 (78.2)	72/114 (63.2)	40/47 (85.1)	19/37 (51.4)
FACT-P total score [e] DCO3 (12 October 2022)				
Overall change from baseline (LS means)	-4.34	-2.04	2.43	-1.21

[a] Progression defined by RECIST 1.1 (soft tissue) and/or PCWG-3 (bone) criteria as assessed by investigator or death (by any cause in the absence of progression), regardless of whether the patient withdraws from randomized therapy or receives another anti-cancer therapy prior to progression.

[b] The HR and CI were calculated using a Cox proportional hazards model adjusted for the variables selected in the primary pooling strategy: metastases, docetaxel treatment at mHSPC stage. The Efron approach was used for handling ties. An HR < 1 favors olaparib + abiraterone.

[c] Calculated using the Kaplan-Meier technique.

[d] Progression defined by BICR assessment of RECIST 1.1 (soft tissue) and PCWG-3 (bone) criteria.

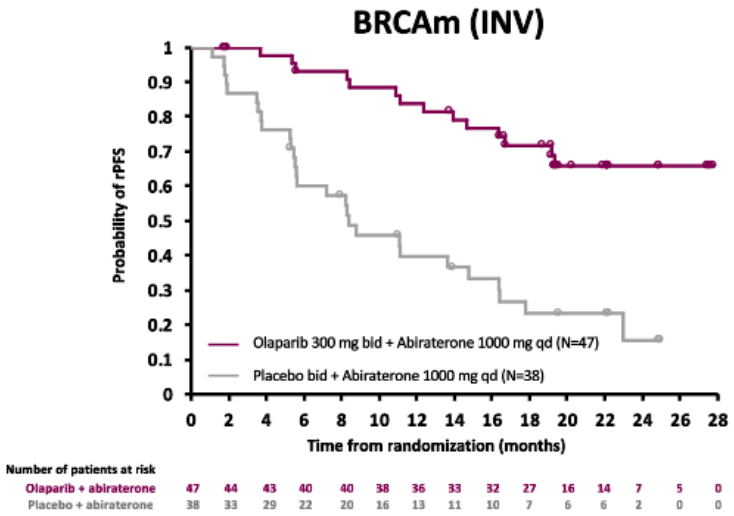
[e] The analysis was performed using a mixed model for repeated measures with treatment, visit, treatment by visit interaction, baseline FACT-P total score and baseline score by visit interaction, Metastases and Docetaxel treatment at mHSPC stage as fixed effects.

FACT-P total score change from baseline values can be a minimum of -156 and a maximum of 156.
A clinically meaningful change value of 10 points was implemented in PROpel for the FACT-P total score-based endpoint based on the work of Cella et al 2009.
Time to pain progression, time to first SSRE, and time to opiate use for cancer-related pain are not shown in Table 9 as data maturity for these endpoints was low (< 25%).
BICR = blinded independent central review; *BRCA* = breast cancer susceptibility gene; *BRCAm* = *gBRCA* or *sBRCA* mutated; CI = confidence interval; DCO = data cut-off; FACT-P = Functional Assessment of Cancer Therapy – Prostate Cancer; *gBRCA* = germline *BRCA*; HR = hazard ratio; HRRm = homologous recombination repair gene mutated; LS = least squares; mHSPC = metastatic hormone-sensitive prostate cancer; N = total number of patients; NC = not calculable/calculated; ORR = objective response rate; OS = overall survival; PFS2 = time from randomization to second progression or death; PCWG-3 = Prostate Cancer Working Groups-3; PSA = prostate-specific antigen; PSA_{50} = A ≥ 50% decline in PSA from baseline; RECIST = Response Evaluation Criteria in Solid Tumors; rPFS = radiological progression-free survival; *sBRCA* = somatic *BRCA*; SSRE = symptomatic skeletal-related event; TFST = time to first subsequent therapy or death.

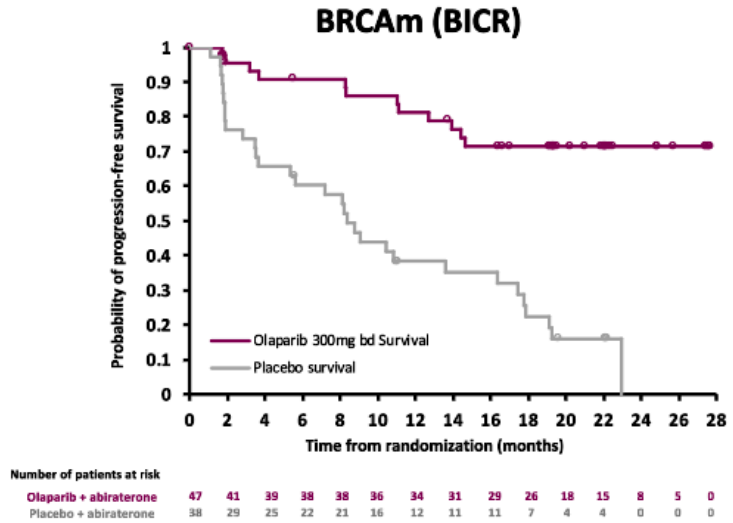
Primary Endpoint: rPFS in the HRRm and *BRCAm* Subgroups

- At DCO1, results from analyses in the HRRm subgroup showed a substantial clinically meaningful benefit in investigator-assessed rPFS in favor of the olaparib + abiraterone arm (HR = 0.50; see Appendix D, Figure D1); the median rPFS was not reached in the olaparib + abiraterone arm and was 13.9 months in the placebo + abiraterone arm.
- The rPFS results by individual tumor test and by ctDNA test in the HRRm subgroup are shown in Figure 10.
- At DCO1, results from analyses in the *BRCAm* subgroup showed a substantial clinically meaningful benefit in rPFS in favor of the olaparib + abiraterone arm.
  - The investigator-assessed rPFS had an HR of 0.23; median rPFS was not reached in the olaparib + abiraterone arm and was 8.4 months in the placebo + abiraterone arm (Figure 12).
  - The BICR-assessed rPFS had an HR of 0.18; median rPFS was not reached in the olaparib + abiraterone arm and was 8.4 months in the placebo + abiraterone arm (Figure 12).
- The rPFS results by individual tumor test and by ctDNA test in the *BRCAm* subgroup are shown in Appendix D, Figure D2.

Figure 12 Radiological Progression-free Survival Analyses for the *BRCAm* Subgroup (Investigator Assessment vs BICR) - DCO1 (30 July 2021)



	Olaparib + Abiraterone N=47	Placebo + Abiraterone N=38
Events (%)	14 (29.8)	28 (73.7)
Median, m	NC	8.4
Median Improvement	NC	
HR (95% CI)	**0.23** (0.12–0.43)	



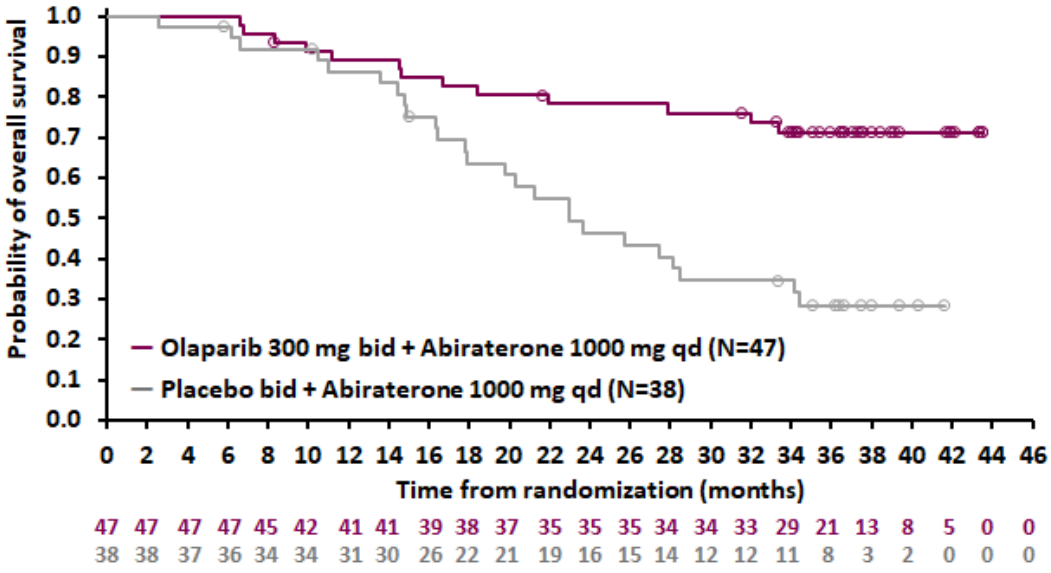
	Olaparib + Abiraterone N=47	Placebo + Abiraterone N=38
Events (%)	12 (25.5)	31 (81.6)
Median, m	NC	8.4
Median improvement	NC	
HR (95% CI)	**0.18** (0.09, 0.34)	

BICR = blinded independent central review; bid = twice daily; *BRCA* = breast cancer susceptibility gene; *BRCAm* = *gBRCA* or *sBRCA* mutated; CI = confidence interval; DCO = data cut-off; *gBRCA* = germline *BRCA*; HR = hazard ratio; INV = investigator; m = months; N = total number of patients; NC = not calculable/calculated; qd = once daily; rPFS = radiological progression-free survival; *sBRCA* = somatic *BRCA*.

Key Secondary Endpoint: OS in the HRRm and *BRCAm* Subgroups

- At DCO3, results from analyses in the HRRm subgroup showed a clear clinically meaningful benefit in OS in favor of the olaparib + abiraterone arm (HR = 0.66; see Appendix D, Figure D3); the median OS was not reached in the olaparib + abiraterone arm and was 28.5 months in the placebo + abiraterone arm.
- The OS results by individual tumor test and by ctDNA test in the HRRm subgroup are shown in Appendix D, Figure D4.
- At DCO3, results from analyses in the *BRCAm* subgroup showed a clear clinically meaningful benefit in OS in favor of the olaparib + abiraterone arm (HR = 0.29; Figure 13); the median OS was not reached in the olaparib + abiraterone arm and was 23.0 months in the placebo + abiraterone arm.
- The OS results by individual tumor test and by ctDNA test in the *BRCAm* subgroup are shown in Appendix D, Figure D5.

Figure 13 Overall Survival Analysis in the *BRCAm* Subgroup - DCO3 (12 October 2022)



	Olaparib + Abiraterone N=47	Placebo + Abiraterone N=38
Events (%)	13 (27.7)	25 (65.8)
Median, mo	NC	23.0
Median improvement	**NC**	
HR (95% CI)	**0.29** (0.14, 0.56)	

bid = twice daily; *BRCA* = breast cancer susceptibility gene; *BRCAm* = *gBRCA* or *sBRCA* mutated; CI = confidence interval; DCO = data cut-off; *gBRCA* = germline *BRCA*; HR = hazard ratio; mo = months; N = total number of patients; NC = not calculable/calculated; OS = overall survival; qd = once daily; *sBRCA* = somatic *BRCA*.

Other Efficacy Endpoints in the HRRm and *BRCAm* Subgroups

As shown in Table 9, results from other analyses of TFST, PFS2, ORR, PSA_{50} response, and time to PSA progression in the HRRm and *BRCAm* subgroups showed a substantial benefit in favor of the olaparib + abiraterone arm compared with the placebo + abiraterone arm, with the greatest benefit of olaparib + abiraterone seen in *BRCAm* patients.

As shown in (Table 9), in the *BRCAm* subgroup, the FACT-P total score was similar between treatment arms throughout the treatment period, indicating that the combination of olaparib + abiraterone had no clinically meaningful impact on patients' HRQoL within this subgroup.

5.8.2.2 Efficacy in Patients who are Non-HRRm or Non-*BRCAm*

A summary of efficacy data in the non-HRRm and non-*BRCAm* subgroups is shown in Table 10.

Table 10 PROpel: Summary of Key Efficacy Outcome Variables (Non-HRRm and Non-*BRCAm* Subgroups)

	Non-HRRm subgroup		Non-*BRCAm* subgroup	
	Olaparib + Abiraterone (N = 279)	**Placebo + Abiraterone (N = 273)**	**Olaparib + Abiraterone (N = 343)**	**Placebo + Abiraterone (N = 350)**
rPFS by investigator assessment DCO1 (30 July 2021)				
Number of events (%) [a]	119 (42.7)	149 (54.6)	148 (43.1)	194 (55.4)
Median rPFS (months)	24.11	18.96	24.11	18.96
HR (95% CI) [b]	0.76 (0.60,0.97)		0.76 (0.61, 0.94)	
rPFS by BICR DCO1 (30 July 2021)				
Number of events (%) [d]	110 (39.4)	136 (49.8)	141 (41.1)	183 (52.3)
Median rPFS (months) [c]	27.60	19.12	27.60	16.62
HR (95% CI) [b]	0.72 (0.56, 0.93)		0.72 (0.58, 0.90)	
OS DCO3 (12 October 2022)				
Number of events (%)	123 (44.1)	132 (48.4)	158 (46.1)	176 (50.3)
Median OS (months) [c]	42.05	38.90	39.62	37.95
HR (95% CI) [b]	0.89 (0.70, 1.14)		0.91 (0.73, 1.13)	
TFST DCO3 (12 October 2022)				
Number of events (%)	180 (64.5)	192 (70.3)	224 (65.3)	250 (71.4)
Median TFST (months) [c]	24.11	20.27	23.95	19.91
HR (95% CI) [b]	0.84 (0.69, 1.03)		0.84 (0.70, 1.01)	
PFS2 DCO3 (12 October 2022)				
Number of events (%)	69 (24.7)	80 (29.3)	92 (26.8)	108 (30.9)
Median PFS2 (months) [c]	NC	NC	NC	NC
HR (95% CI) [b]	0.83 (0.60, 1.15)		0.86 (0.65, 1.14)	
Time to PSA progression DCO3 (12 October 2022)				
Number of events (%)	132 (47.3)	166 (60.8)	167 (48.7)	215 (61.4)
Median (months) [c]	23.10	13.83	22.01	13.08

	Non-HRRm subgroup		Non-*BRCAm* subgroup	
	Olaparib + Abiraterone (N = 279)	**Placebo + Abiraterone (N = 273)**	**Olaparib + Abiraterone (N = 343)**	**Placebo + Abiraterone (N = 350)**
HR (95% CI) [b]	0.67 (0.53, 0.84)		0.67 (0.55, 0.82)	
Confirmed ORR DCO1 (30 July 2021)				
Number of patients with a response/total number of patients with measurable disease at baseline (%)	54/104 (51.9)	44/107 (41.1)	70/137 (51.1)	64/141 (45.4)
Confirmed PSA_{50} Response DCO1 (30 July 2021)				
Number of patients with a response/total number of patients with a PSA result at baseline (%)	222/278 (79.9)	197/273 (72.2)	268/341 (78.6)	250/350 (71.4)
FACT-P total score [e] DCO3 (12 October 2022)				
Overall change from baseline (LS means)	-5.44	-5.40	-6.27	-5.27

[a] Progression defined by RECIST 1.1 (soft tissue) and/or PCWG-3 (bone) criteria as assessed by investigator or death (by any cause in the absence of progression), regardless of whether the patient withdraws from randomized therapy or receives another anti-cancer therapy prior to progression.

[b] The HR and CI were calculated using a Cox proportional hazards model adjusted for the variables selected in the primary pooling strategy: metastases, docetaxel treatment at mHSPC stage. The Efron approach was used for handling ties. An HR < 1 favors olaparib + abiraterone.

[c] Calculated using the Kaplan-Meier technique.

[d] Progression defined by BICR assessment of RECIST 1.1 (soft tissue) and PCWG-3 (bone) criteria.

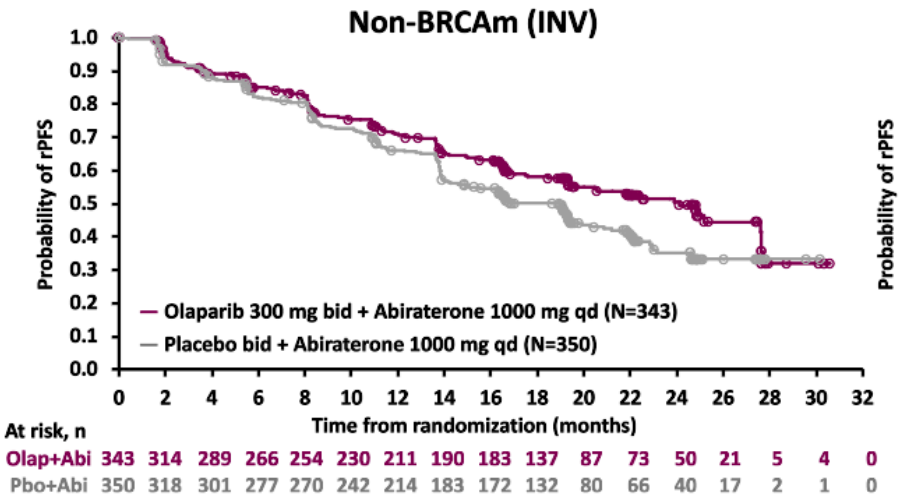
[e] The analysis was performed using a mixed model for repeated measures with treatment, visit, treatment by visit interaction, baseline FACT-P total score and baseline score by visit interaction, Metastases and Docetaxel treatment at mHSPC stage as fixed effects.

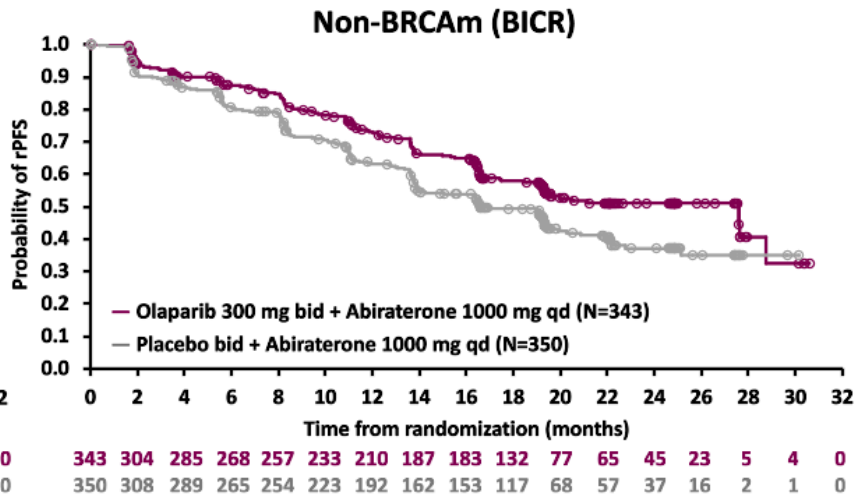
FACT-P total score change from baseline values can be a minimum of -156 and a maximum of 156.
A clinically meaningful change value of 10 points was implemented in PROpel for the FACT-P total score-based endpoint based on the work of Cella et al 2009.
Time to pain progression, time to first SSRE, and time to opiate use for cancer-related pain are not shown in Table 10 as data maturity for these endpoints was low (< 25%).
BICR = blinded independent central review; *BRCA* = breast cancer susceptibility gene; *BRCAm* = *gBRCA* or *sBRCA* mutated; CI = confidence interval; DCO = data cut-off; FACT-P = Functional Assessment of Cancer Therapy – Prostate Cancer; *gBRCA* = germline *BRCA*; HR = hazard ratio; HRRm = homologous recombination repair gene mutated; LS = least squares; mHSPC = metastatic hormone-sensitive prostate cancer; N = total number of patients; NC = not calculable/calculated; ORR = objective response rate; OS = overall survival; PFS2 = time from randomization to second progression or death; PCWG-3 = Prostate Cancer Working Groups-3; PSA = prostate-specific antigen; PSA_{50} = A ≥ 50% decline in PSA from baseline; RECIST = Response Evaluation Criteria in Solid Tumors; rPFS = radiological progression-free survival; *sBRCA* = somatic *BRCA*; TFST = time to first subsequent therapy or death.

Primary Endpoint: rPFS in the Non-HRRm and Non-*BRCAm* Subgroups

- At DCO1, results from analyses in the non-HRRm subgroup showed a clinically meaningful benefit in rPFS in favor of the olaparib + abiraterone arm.
  - The investigator-assessed rPFS had an HR of 0.76 with a median rPFS improvement of 5.2 months in favor of the olaparib + abiraterone arm vs the placebo + abiraterone arm (see Appendix D, Figure D6).
  - The BICR-assessed rPFS had an HR of 0.72 with a median rPFS improvement of 8.5 months in favor of the olaparib + abiraterone arm vs the placebo + abiraterone arm.
- The rPFS results by individual tumor test and by ctDNA test in the non-HRRm subgroup are shown in Figure 10.
- At DCO1, results from analyses in the non-*BRCAm* subgroup showed a clinically meaningful benefit in rPFS in favor of the olaparib + abiraterone arm.
  - The investigator-assessed rPFS had an HR of 0.76 with a median rPFS improvement of 5.1 months in favor of the olaparib + abiraterone arm vs the placebo + abiraterone arm (Figure 14).
  - The BICR-assessed rPFS had an HR of 0.72 with a median rPFS improvement of 11.0 months in favor of the olaparib + abiraterone arm vs the placebo + abiraterone arm (Figure 14).
- The rPFS results by individual tumor test and by ctDNA test in the non-*BRCAm* subgroup are shown in Appendix D, Figure D2.

Figure 14 Radiological Progression-free Survival Analyses for the Non-*BRCAm* Subgroup (Investigator Assessment vs BICR) - DCO1 (30 July 2021)





	Olaparib + Abiraterone N=343	Placebo + Abiraterone N=350
Events (%)	148 (43.1)	194 (55.4)
Median, mo	24.1	19.0
Median improvement	**5.1 months**	
HR (95% CI)	**0.76** (0.61, 0.94)	

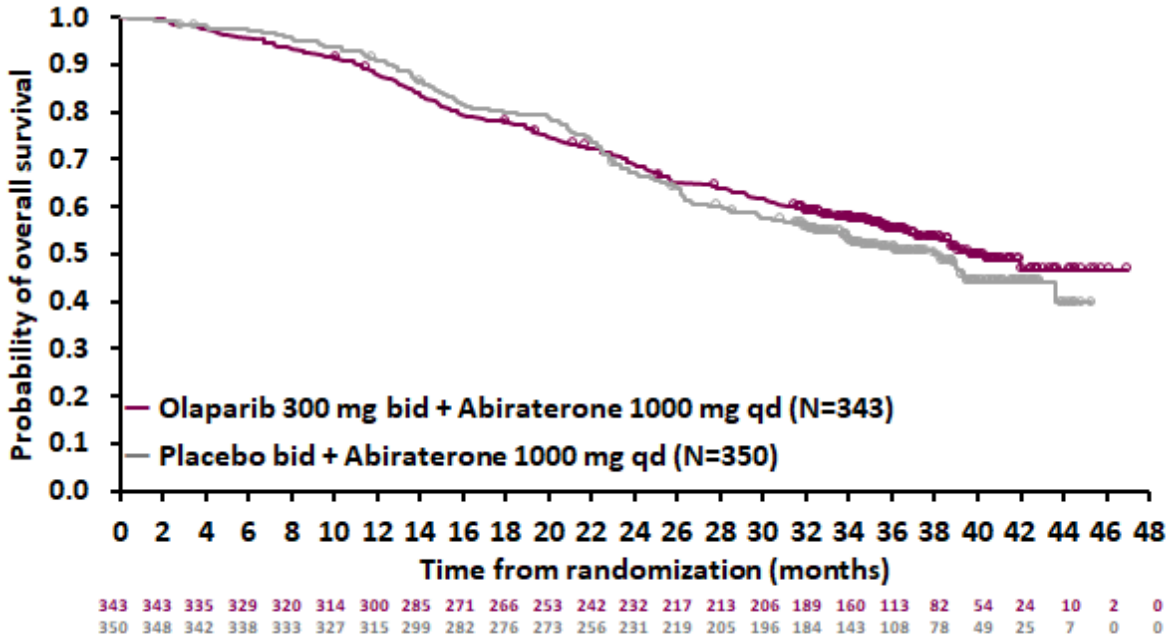
	Olaparib + Abiraterone N=343	Placebo + Abiraterone N=350
Events (%)	141 (41.1)	183 (52.3)
Median, mo	27.6	16.6
Median improvement	**11.0 months**	
HR (95% CI)	**0.72** (0.58, 0.90)	

Abi = abiraterone; BICR = blinded independent central review; bid = twice daily; *BRCA* = breast cancer susceptibility gene; *BRCAm* = *gBRCA* or *sBRCA* mutated; CI = confidence interval; DCO = data cut-off; *gBRCA* = germline *BRCA*; HR = hazard ratio; INV = investigator; mo = months; N = total number of patients; n = number of patients; Olap = olaparib; qd = once daily; rPFS = radiological progression-free survival; *sBRCA* = somatic *BRCA*.

Key Secondary Endpoint: OS in the Non-HRRm and Non-*BRCAm* Subgroups

- At DCO3, results from analyses in the non-HRRm subgroup showed no evidence of detriment in OS (HR = 0.89; see Appendix D, Figure D7).
- The OS results by individual tumor test and by ctDNA test in the non-HRRm subgroup are shown in Appendix D, Figure D4.
- At DCO3, results from analyses in the non-*BRCAm* subgroup showed no evidence of detriment in OS (HR = 0.91; Figure 15).
- The OS results by individual tumor test and by ctDNA test in the non-*BRCAm* subgroup are shown in Appendix D, Figure D5.

Figure 15 Overall Survival Analysis in the Non-*BRCAm* Subgroup - DCO3 (12 October 2022)



	Olaparib + Abiraterone N=343	Placebo + Abiraterone N=350
Events (%)	158 (46.1)	176 (50.3)
Median, mo	39.6	38.0
Median improvement	**1.7 months**	
HR (95% CI)	**0.91** (0.73, 1.13)	

bid = twice daily; *BRCA* = breast cancer susceptibility gene; *BRCAm* = *gBRCA* or *sBRCA* mutated; CI = confidence interval; DCO = data cut-off; *gBRCA* = germline *BRCA*; HR = hazard ratio; mo = months; N = total number of patients; OS = overall survival; qd = once daily; *sBRCA* = somatic *BRCA*.

Other Efficacy Endpoints in the Non-HRRm and Non-*BRCAm* Subgroups

As shown in Table 10, results from other analyses of TFST, PFS2, ORR, PSA_{50} response, and time to PSA progression in the non-HRRm and the non-*BRCAm* subgroup showed a benefit in favor of the olaparib + abiraterone arm compared with the placebo + abiraterone arm.

The TFST results in the non-*BRCAm* subgroup (Table 10) showed a median 4.1-month improvement in the olaparib + abiraterone arm over the placebo + abiraterone arm, which is meaningful for patients as there is a delay in an important clinical event, ie when a patient may receive their next anti-cancer treatment.

As shown in (Table 10), in the non-*BRCAm* subgroup, the FACT-P total score was similar between treatment arms throughout the treatment period, indicating that the combination of olaparib + abiraterone had no clinically meaningful impact on patients' HRQoL within this subgroup.

Taken together, the data demonstrated internal consistency with the primary results of the study, supporting meaningful clinical benefit in the non-HRRm and non-*BRCAm* subgroups.

6 CLINICAL SAFETY

Across the entire clinical program, as of 15 December 2022, approximately 20,000 patients are estimated to have received treatment with olaparib. There have been > 140,000 patient-years exposure from post-marketing use.

The 300 mg bid dose of olaparib has demonstrated a consistent and well-defined safety profile suitable for use as a monotherapy treatment (including as a maintenance therapy) or combination therapy (with bevacizumab in ovarian cancer) in different cancer types and disease setting. Hematological side effects (predominantly anemia), gastrointestinal disturbances (nausea and vomiting) and fatigue/asthenia are the most commonly reported adverse events (reported by ≥ 15% of patients) with olaparib treatment. These adverse events are predominantly mild or moderate in severity and infrequently lead to discontinuation of treatment.

In the US, abiraterone (1000 mg qd) in combination with prednisolone (5 mg bid) was approved for use in mCRPC in 2011 and is the most commonly used NHA in mCRPC. Bone/muscle pain, cardiovascular effects (hypertension, edema, hypokalemia, heart failure,

and arrhythmia), and infections (upper respiratory tract infections, urinary tract infections) are commonly reported adverse events (Zytiga USPI 2021).

Olaparib and abiraterone have well-characterized safety profiles, and safety data from PROpel was consistent with the known monotherapy safety profiles (Section 6.1 to Section 6.2.6). There were no new safety signals observed in PROpel with the combination of olaparib + abiraterone, and the effect of the combination did not result in any additive toxicity of the 2 agents combined (eg, the rate of anemia was not higher than observed with olaparib monotherapy in other studies or conversely the rate of hypertension in the olaparib + abiraterone arm in PROpel was not higher than in the placebo + abiraterone arm, indicating no impact with the addition of olaparib on to abiraterone).

In Section 6.1 to Section 6.2.6, all safety data are presented from DCO3 (12 October 2023) unless stated otherwise.

6.1 Exposure in PROpel

- As shown in Table 11, the median total duration of exposure to olaparib (18.5 months) was approximately 3 months longer than the duration of exposure to placebo (15.7 months).
- The median total duration of exposure to abiraterone was over 4 months longer (20.1 months) in the olaparib + abiraterone arm compared with the placebo + abiraterone arm (15.7 months; Table 11).
  - The longer median duration of exposure for both olaparib and abiraterone in the combination arm compared with placebo and abiraterone exposure in the comparator arm suggests that patients were tolerating the combination treatment without progression; this was evidenced in an exploratory rPFS analyses at DCO3 (12 October 2023) which showed a median rPFS improvement of 8.5 months in the olaparib +abiraterone arm compared with placebo + abiraterone arm.
- A higher proportion of patients in the olaparib +abiraterone arm remained on study treatment at 12, 24, and 36 months compared with the placebo + abiraterone arm (Table 11).

Table 11 Duration of Exposure and Cumulative Exposure Over Time (SAS) - DCO3 (12 October 2022)

		Olaparib + Abiraterone		Placebo + Abiraterone	
		Olaparib (N = 398)	Abiraterone (N = 398)	Placebo (N = 396)	Abiraterone (N = 396)
Median total treatment duration (months)		18.5	20.1	15.7	15.7
Cumulative exposure over time (% patients on treatment)	≥ 12 months	62.3	66.1	59.8	60.1
	≥ 24 months	40.2	43.5	30.8	31.6
	≥ 36 months	16.1	17.8	14.6	14.9

DCO = data cut-off; N = total number of patients; SAS = safety analysis set.

6.2 Adverse Events

The patients experiencing AEs in any category are summarized in Table 12. The majority of patients experienced 1 or more AEs during the course of the study. As expected with a combination of 2 active treatments versus a monotherapy, serious AEs (SAEs) and Common Terminology Criteria for Adverse Events (CTCAE) Grade ≥ 3 events were reported for a higher percentage of patients in the olaparib + abiraterone arm compared with the placebo + abiraterone arm. Dose interruptions, and if needed, dose reductions are the main strategies for managing AEs with olaparib. The percentage of patients with AEs leading to discontinuation, dose reduction, or dose interruption of olaparib was higher in the olaparib + abiraterone arm compared to placebo in the placebo + abiraterone arm, primarily driven by anemia (a known adverse drug reaction [ADR] of olaparib) which was the most common AE in these categories. The percentage of patients with AEs leading to discontinuation of abiraterone were similar between treatment arms. Overall, the combination of olaparib + abiraterone was well-tolerated, as over 80% of patients were able to continue to receive olaparib until disease progression.

Adverse events with outcome of death were reported at a similar frequency in each treatment arm.

Table 12 Number (%) of Patients with Adverse Events in any Category in PROpel – Patient Level (SAS) - DCO3 (12 October 2022)

	Patients, n (%)	
	Olaparib + Abiraterone (N = 398)	Placebo + Abiraterone (N = 396)
Any AE	389 (97.7)	380 (96.0)
Any AE of CTCAE Grade ≥ 3	222 (55.8)	171 (43.2)
Any SAE	161 (40.5)	126 (31.8)

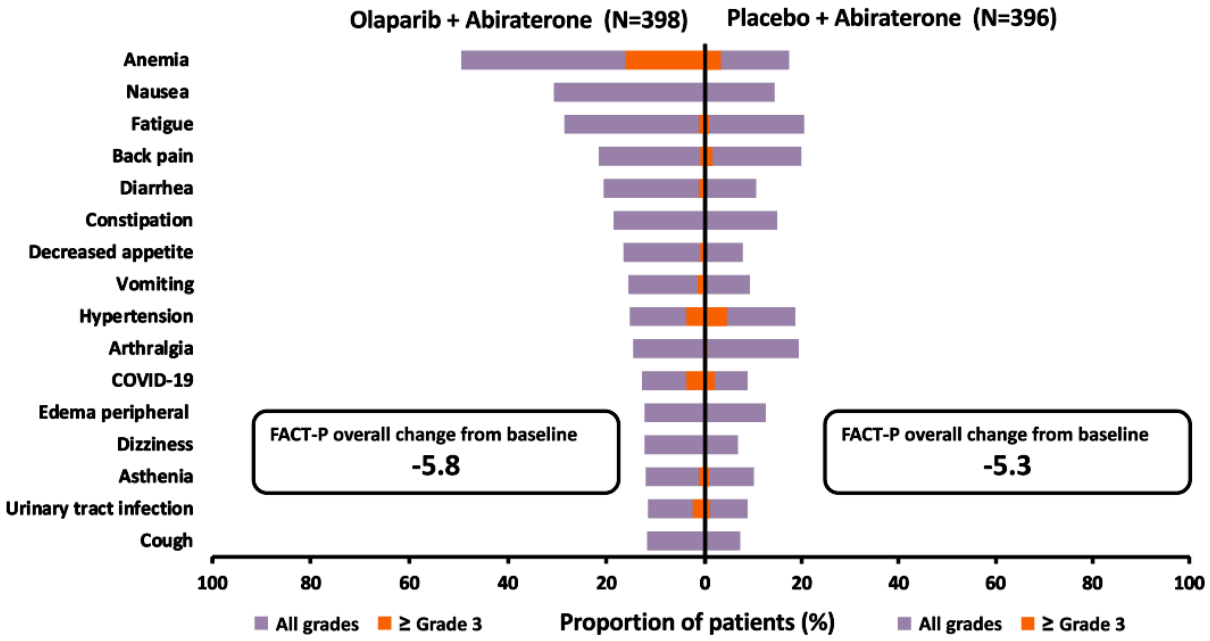
	Patients, n (%)	
	Olaparib + Abiraterone (N = 398)	**Placebo + Abiraterone (N = 396)**
Any AE with outcome of death	26 (6.5)	20 (5.1)
Any AE leading to dose interruption of olaparib/placebo	195 (49.0)	112 (28.3)
Any AE leading to dose reduction of olaparib/placebo	90 (22.6)	24 (6.1)
Any AE leading to discontinuation of olaparib/placebo	69 (17.3)	34 (8.6)
Any AE leading to dose interruption of abiraterone	145 (36.4)	95 (24.0)
Any AE leading to dose reduction of abiraterone	10 (2.5)	17 (4.3)
Any AE leading to discontinuation of abiraterone	45 (11.3)	37 (9.3)

AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; DCO = data cut-off; N = total number of patients; n = number of patients with an event; SAE = serious adverse event; SAS = safety analysis set.

6.2.1 Most Common Adverse Events by Preferred Term (any Grade) and Grade ≥ 3

In the olaparib + abiraterone arm, the 3 most commonly reported AEs of anemia, nausea, and fatigue, are known ADRs for olaparib (Figure 16; Table 13). The median time to onset of the first event of these AEs was 0.95 months (nausea), 1.91 months (anemia), and 1.94 months (fatigue/asthenia), indicating these events were observed early. Other common AEs were consistent with the known ADR profiles for olaparib and abiraterone, or considered symptoms commonly reported in a mCRPC population.

Figure 16 **PROpel: Most Common AEs (≥ 10%) and Grade ≥ 3 AEs (SAS) - DCO3 (12 October 2022)**



FACT-P total score change from baseline values can be a minimum of -156 and a maximum of 156.
A clinically meaningful change value of 10 points was implemented in PROpel for the FACT-P total score-based endpoint based on the work of Cella et al 2009.
AEs = adverse events; COVID-19 = Coronavirus disease 2019; DCO = data cut-off; FACT-P = Functional Assessment of Cancer Therapy – Prostate Cancer; N = total number of patients; SAS = safety analysis set.

Table 13 **Number (%) of Patients [b] with Most Common Adverse Events (Frequency ≥ 10% in either Treatment Arm), by Preferred Term (SAS) - DCO3 (12 October 2022)**

MedDRA PT [a]	Olaparib + Abiraterone (N = 398)	Placebo + Abiraterone (N = 396)
Patients with any AE	389 (97.7)	380 (96.0)
Anemia	197 (49.5)	69 (17.4)
Nausea	122 (30.7)	57 (14.4)
Fatigue	114 (28.6)	81 (20.5)
Back pain	86 (21.6)	79 (19.9)
Diarrhea	82 (20.6)	42 (10.6)
Arthralgia	58 (14.6)	77 (19.4)
Hypertension	61 (15.3)	74 (18.7)
Constipation	74 (18.6)	59 (14.9)

MedDRA PT [a]	Olaparib + Abiraterone (N = 398)	Placebo + Abiraterone (N = 396)
Decreased appetite	66 (16.6)	31 (7.8)
Vomiting	62 (15.6)	37 (9.3)
Hot flush	35 (8.8)	51 (12.9)
COVID-19	51 (12.8)	35 (8.8)
Edema peripheral	49 (12.3)	50 (12.6)
Dizziness	49 (12.3)	27 (6.8)
Asthenia	48 (12.1)	40 (10.1)
Cough	47 (11.8)	29 (7.3)
Urinary tract infection	46 (11.6)	35 (8.8)

[a] Multiple occurrences of a MedDRA PT for a patient are only counted once for the patient.
[b] Sorted by descending frequency in either arm.
Includes AEs with onset date or worsening, on or after the date of first dose and up to and including 30 days following discontinuation of randomized treatment.
MedDRA version 25.0.
AE = adverse event; COVID-19 = Coronavirus disease 2019; DCO = data cut-off; MedDRA = Medical Dictionary for Regulatory Activities; N = total number of patients; PT = preferred term; SAS = safety analysis set.

A higher percentage of all patients in the olaparib + abiraterone arm reported AEs of CTCAE Grade ≥ 3 (55.8%) compared with the placebo + abiraterone arm (43.2%) (Figure 16; Table 14). The most common CTCAE Grade 3 or 4 AEs in the olaparib + abiraterone arm were anemia (16.1%) and pulmonary embolism (7.3%); the most common CTCAE Grade 3 or 4 AE in the placebo + abiraterone arm was hypertension (4.5%). Anemia, pulmonary embolism (as part of the venous thromboembolic events [VTE] grouped term) and hypertension are all known ADRs for either olaparib or abiraterone. All other CTCAE Grade ≥ 3 AEs were reported in < 4% of patients in either treatment arm.

An imbalance in VTE was noted in PROpel, which were reported more frequently in the olaparib + abiraterone arm (8.5%) compared with the placebo + abiraterone arm (4.0%). The most common VTE was pulmonary embolism, reported in 29 patients (7.3%) in the olaparib + abiraterone arm and 9 patients (2.3%) in the placebo + abiraterone arm. The majority of pulmonary embolism events were CTCAE Grade ≥ 3 and detected incidentally on radiographic imaging in both treatment arms. The majority of patients who reported an event of pulmonary embolism recovered with standard medical care and were able to continue on study treatment. There was one Grade 5 event of pulmonary embolism in an 80-year-old patient who had a cardiovascular medical history. Venous thromboembolism is a common comorbidity in patients with metastatic prostate cancer, especially in those receiving ADT (O'Farrell et al 2016). Venous thromboembolism was included in the USPI Section 5

Warnings and Precautions on 19 May 2020 when the S-014 was approved based on PROfound study data.

Importantly, despite the higher incidence of CTCAE Grade ≥ 3 AEs and SAEs, the addition of olaparib to the standard of care abiraterone had no clinically meaningful impact on patients' quality of life, as evidenced by the FACT-P total score which was similar between arms throughout the treatment period (Figure 16).

Table 14 Number (%) of Patients [b] with Adverse Events of CTCAE Grade 3 or Higher (Frequency ≥ 2% in Either Treatment Arm), by Preferred Term (SAS) - DCO3 (12 October 2022)

MedDRA PT [a]	Olaparib + Abiraterone (N = 398)	Placebo + Abiraterone (N = 396)
Patients with any AE CTCAE Grade 3 or higher	222 (55.8)	171 (43.2)
Anemia	64 (16.1)	13 (3.3)
Pulmonary embolism	29 (7.3)	9 (2.3)
Hypertension	15 (3.8)	18 (4.5)
COVID-19	15 (3.8)	8 (2.0)
Lymphocyte count decreased	15 (3.8)	6 (1.5)
Neutrophil count decreased	11 (2.8)	3 (0.8)
Pneumonia	10 (2.5)	4 (1.0)
Urinary tract infection	10 (2.5)	4 (1.0)
White blood cell count decreased	9 (2.3)	2 (0.5)
Alanine aminotransferase increased	4 (1.0)	9 (2.3)
Hyperglycemia	8 (2.0)	6 (1.5)

[a] Patients with multiple AEs of CTCAE Grade 3 or higher are counted once for each PT.
[b] Sorted by descending frequency in either arm.
Includes AEs with onset date or worsening, on or after the date of first dose and up to and including 30 days following discontinuation of randomized treatment.
MedDRA version 25.0.
AE = adverse event; COVID-19 = Coronavirus disease 2019; CTCAE = Common Terminology Criteria for Adverse Events; DCO = data cut-off; MedDRA = Medical Dictionary for Regulatory Activities; N = total number of patients; PT = preferred term; SAS = safety analysis set.

6.2.2 Serious Adverse Events

In PROpel, a higher percentage of patients reported SAEs in the olaparib + abiraterone arm (40.5%) compared with the placebo + abiraterone arm (31.8%) (Table 15). Most SAE preferred terms (PTs) were reported in < 3% of patients in each arm. The most commonly reported SAEs (> 3%) in the olaparib + abiraterone arm were anemia, coronavirus disease 2019 (COVID-19), and pulmonary embolism. In addition, COVID-19 pneumonia was

reported in 1.8% of patients in the olaparib + abiraterone arm and 0.8% of patients in the placebo + abiraterone arm.

The imbalance in serious COVID-19 events is reflective of a higher proportion of patients with 2 or more risk factors for mortality from COVID-19 in the olaparib + abiraterone arm than in the placebo + abiraterone arm (Table 17).

Table 15 Number (%) of Patients [b] with SAEs (> 1% in the Olaparib Arm) in PROpel (SAS) - DCO3 (12 October 2022)

MedDRA PT [a]	Patients, n (%)	
	Olaparib + Abiraterone (N = 398)	Placebo + Abiraterone (N = 396)
Any SAE	161 (40.5)	126 (31.8)
Anemia	23 (5.8)	3 (0.8)
COVID-19	15 (3.8)	10 (2.5)
Pulmonary embolism	15 (3.8)	3 (0.8)
Pneumonia	11 (2.8)	5 (1.3)
Urinary tract infection	9 (2.3)	3 (0.8)
COVID-19 pneumonia	7 (1.8)	3 (0.8)
Back pain	5 (1.3)	3 (0.8)
Sepsis	5 (1.3)	3 (0.8)
Febrile neutropenia	5 (1.3)	2 (0.5)
Syncope	5 (1.3)	2 (0.5)
Urosepsis	5 (1.3)	2 (0.5)

[a] Patients with multiple events are counted once for each PT.
[b] Sorted by descending frequency in the olaparib + abiraterone arm.
COVID-19 = Coronavirus disease 2019; DCO = data cut-off; N = total number of patients; n = number of patients with an event; PT = preferred term; SAE = serious adverse event; SAS = safety analysis set.

6.2.3 Adverse Events Leading to Discontinuation of Olaparib or Placebo

In PROpel, AEs leading to discontinuation of olaparib were reported in 17.3% of patients in the olaparib + abiraterone arm and AEs leading to discontinuation of placebo were reported in 8.6% of patients in the placebo + abiraterone arm.

The most common AEs leading to discontinuation of olaparib were anemia (4.3%) and fatigue (1.3%). The most common AEs leading to discontinuation of placebo were anemia and arthralgia (both 0.8%). All other AEs were reported in < 1% of patients (≤ 3 patients each).

The percentage of patients with AEs leading to discontinuation of abiraterone were similar between treatment arms; the most common AE leading to discontinuation of abiraterone in the olaparib + abiraterone arm was anemia, and in the placebo + abiraterone arm was alanine aminotransferase increased.

6.2.4 Deaths

In PROpel, at the time of the final OS analysis (DCO3; 12 October 2022), there were 176 deaths (44.1%) in the olaparib + abiraterone arm and 205 deaths (51.6%) in the placebo + abiraterone arm). The majority of deaths (76% [289/381]) were due to the disease under investigation only.

Table 16 All Deaths (ITT) - DCO3 (12 October 2022)

Category	Number (%) of patients	
	Olaparib + Abiraterone (N = 399)	Placebo + Abiraterone (N = 397)
Total number of deaths	176 (44.1)	205 (51.6)
Death related to disease under investigation only	127 (31.8)	162 (40.8)
AE with outcome of death only	23 (5.8)	13 (3.3)
AE with outcome of death only (AE start date after 30-day follow-up period)	1 (0.3)	0
Number of patients with death related to disease under investigation and an AE with outcome of death	3 (0.8)	7 (1.8)
Other deaths [a]	22 (5.5)	23 (5.8)

[a] Patients who died and are not captured in the earlier categories.
Death related to disease under investigation is determined by the investigator.
Rows are mutually exclusive; patients are only reported in one category.
AE = adverse event; DCO = data cut-off; ITT = intention-to-treat; N = total number of patients.

Adverse events with an outcome of death (during study treatment or within the 30-day follow-up period) were reported at a similar frequency between treatment arms (6.5% in the olaparib + abiraterone arm and 5.1% in the placebo + abiraterone arm). None were considered related to olaparib by the reporting investigator.

Twelve patients (3.0%) died due to COVID-19 (includes PTs of COVID-19 pneumonia and suspected COVID-19) on the olaparib + abiraterone arm compared with 3 patients (0.8%) in the placebo + abiraterone arm. An imbalance was noted among all 10 fatal cases of COVID-19, where patients in the olaparib + abiraterone arm had significantly more risk factors (which include hypertension, diabetes mellitus, cardiovascular disease, chronic obstructive pulmonary disease/asthma/bronchitis,

hypercholesterolemia/hyperlipidemia/hypertriglyceridemia, obesity, smoker, and chronic/acute kidney disease; Dessie and Zewotir 2021) (Table 17). The observed imbalance of risk factors for mortality from COVID-19 between arms, with a higher proportion of patients with 2 or more risk factors in the olaparib + abiraterone arm, is likely to account for the increased number of fatal cases in that arm.

Table 17 PROpel: Risk Factors [a] in Patients With COVID-19 Grouped Term (SAS) - DCO3 (12 October 2022)

Category	Number (%) of patients					
	Any COVID-19 AE		Any COVID-19 SAE		Any fatal COVID-19 AE	
	Olap + Abi (N = 63)	Pla + Abi (N = 63)	Olap + Abi (N = 24)	Pla + Abi (N = 13)	Olap + Abi (N = 12)	Pla + Abi (N = 3)
No risk factor	18 (28.6)	13 (33.3)	7 (29.2)	6 (46.2)	2 (16.7)	2 (66.7)
Any risk factor	45 (71.4)	26 (66.7)	17 (70.8)	7 (53.8)	10 (83.3)	1 (33.3)
1 risk factor	17 (27.0)	16 (41.0)	5 (20.8)	6 (46.2)	3 (25.0)	1 (33.3)
2 risk factors	16 (25.4)	9 (23.1)	8 (33.3)	1 (7.7)	4 (33.3)	0
3 risk factors	8 (12.7)	0	3 (12.5)	0	3 (25.0)	0
> 3 risk factors	4 (6.3)	1 (2.6)	1 (4.2)	0	0	0

[a] The risk factors included in this analysis are based on a meta-analysis of mortality related risk factors of COVID-19 (Dessie and Zewotir 2021), these include hypertension, diabetes mellitus, cardiovascular disease, chronic obstructive pulmonary disease/asthma/bronchitis, hypercholesterolemia/hyperlipidemia/hypertriglyceridemia, obesity, smoker, and chronic/acute kidney disease.

Preferred terms include: COVID-19, COVID-19 pneumonia, and suspected COVID-19.
Abi = abiraterone; AE = adverse event; COVID-19 = Coronavirus Disease 2019; N = total number of patients; Olap = olaparib; Pla = placebo; SAE = serious adverse event; SAS = safety analysis set.

Two patients (0.5%) in the placebo + abiraterone arm died due to acute pulmonary edema vs zero patients in the olaparib + abiraterone arm. All other PTs were reported for one patient each. For 6 patients (2 in the olaparib + abiraterone arm and 4 in the placebo + abiraterone arm), the reported PT was *death* or *sudden death*.

6.2.5 Adverse Events of Special Interest

Adverse events of special interest (AESI) for olaparib include myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML), new primary malignancies, and pneumonitis. A summary of AESIs in PROpel is shown in Table 18.

Table 18 PROpel: Summary of AESIs (SAS) - DCO3 (12 October 2022)

	Patients, n (%)		
	Olaparib + Abiraterone (N = 398)	**Placebo + Abiraterone (N = 396)**	**Olaparib Combined Monotherapy Pool [a] [Capsules + Tablets] (N = 4499)**
MDS/AML	2 (0.5)	0	46 (1.0)
Other new primary malignancies	18 (4.5)	14 (3.5)	46 (1.0)
Pneumonitis	5 (1.3)	3 (0.8)	44 (1.0)

[a] Olaparib combined monotherapy pool (N = 4499) DCO for MDS/AML and Other New Primary Malignancies = 15 December 2022; DCO for pneumonitis = 12 October 2022.
AESIs = adverse events of special interest; AML = acute myeloid leukemia; DCO = data cut-off; MDS = myelodysplastic syndrome; N = total number of patients; n = number of patients with an event; SAS = safety analysis set.

Myelodysplastic Syndrome/Acute Myeloid Leukemia

In PROpel, there were 2 patients with events of MDS in the olaparib + abiraterone arm and no events of MDS/AML in the placebo + abiraterone arm (Table 18). Both patients who reported events of MDS were HRRm and had received prior docetaxel.

The incidence of MDS/AML in the olaparib + abiraterone arm of PROpel is consistent with the larger olaparib combined monotherapy pool (capsule + tablets) (Table 18).

Other New Primary Malignancies

In PROpel, the incidence of new primary malignancies were balanced between treatment arms, with events reported in 18 patients (4.5%) in the olaparib + abiraterone arm and 14 patients (3.5%) in the placebo + abiraterone arm. The incidence of new primary malignancies in the olaparib + abiraterone arm of PROpel is higher than in the larger olaparib combined monotherapy pool (capsule + tablets) (Table 18), however this may reflect the higher background rate of new primary malignancies in an older prostate cancer population compared to the combined monotherapy pool population of predominantly younger, female patients.

Pneumonitis

In PROpel, pneumonitis was reported at a similar frequency in both treatment arms (5 patients [1.3%] in the olaparib + abiraterone arm and 3 patients [0.8%] in the placebo + abiraterone arm). The incidence of pneumonitis in the olaparib + abiraterone arm of PROpel is consistent with the larger olaparib combined monotherapy pool (capsule + tablets) (Table 18).

6.2.6 Safety Analyses in *BRCA* and HRR Subgroups

6.2.6.1 Safety Data in Patients who are *BRCAm*

In the safety analyses of the *BRCAm* subgroup (Table 19), the incidences of AEs of CTCAE ≥ 3, SAEs, AEs leading to an outcome of death, and AEs leading to treatment discontinuation in the olaparib + abiraterone arm of the *BRCAm* subgroup were lower compared with those observed in the SAS. The lower incidence of AEs of CTCAE ≥ 3 in the *BRCAm* subgroup is largely driven by a lower incidence of anemia CTCAE ≥ 3 AEs in the *BRCAm* subgroup vs the SAS (10.6% vs 16.1%, respectively). The incidence of CTCAE ≥ 3 AEs of anemia in the SAS is similar to that observed in other olaparib studies (monotherapy pool anemia CTCAE ≥ 3 AEs = 14.2%). This difference is likely due to the small size of the *BRCAm* subgroup, where a 6% incidence of an AE reflects an absolute difference of only 2 to 3 patients.

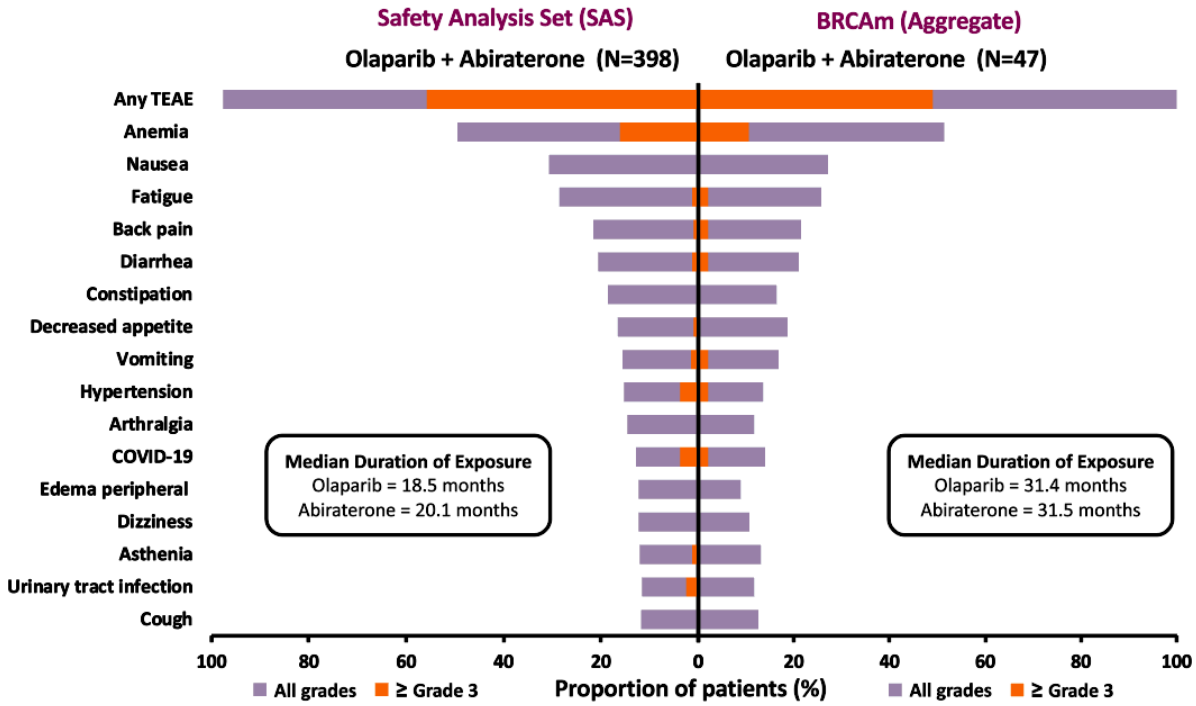
Table 19 PROpel: Safety Data in the SAS and *BRCAm* Subgroup - DCO3 (12 October 2022)

	SAS		*BRCAm* subgroup	
	Olap + Abi (N = 398)	**Pla + Abi (N = 398)**	**Olap + Abi (N = 47)**	**Pla + Abi (N = 38)**
Median total duration of exposure (days)				
Olaparib/Placebo	564.0	476.5	957.0	300.0
Abiraterone	612.0	477.0	960.0	300.0
Patients, n (%)				
Any AE	389 (97.7)	380 (96.0)	47 (100)	34 (89.5)
Any AE of CTCAE Grade ≥ 3	222 (55.8)	171 (43.2)	23 (48.9)	15 (39.5)
Any SAE	161 (40.5)	126 (31.8)	14 (29.8)	12 (31.6)
Any AE with outcome of death	26 (6.5)	20 (5.1)	1 (2.1)	2 (5.3)
Any AE leading to discontinuation of olaparib/placebo	69 (17.3)	34 (8.6)	6 (12.8)	4 (10.5)
Any AE leading to discontinuation of abiraterone	45 (11.3)	37 (9.3)	3 (6.4)	4 (10.5)

Abi = abiraterone; AE = adverse events; *BRCA* = breast cancer susceptibility gene; *BRCAm* = *gBRCA* or *sBRCA* mutated; CTCAE = Common Terminology Criteria for Adverse Events; DCO = data cut-off; *gBRCA* = germline *BRCA*; N = total number of patients; n = number of patients with an event; Olap = olaparib; Pla = placebo; SAE = serious adverse events; SAS = safety analysis set; *sBRCA* = somatic *BRCA*.

Figure 17 and Table 20 summarize the most common AEs and AEs of CTCAE Grade 3 or higher in the *BRCAm* subgroup vs the SAS. The most common AEs in the *BRCAm* subgroup were the same as those observed in the SAS (anemia, fatigue, and nausea in the olaparib + abiraterone arm; hypertension was one of the most common AEs in the placebo + abiraterone arm). The most common AE of CTCAE Grade 3 or higher in olaparib + abiraterone arm of the *BRCAm* subgroup was the same as observed in the SAS (anemia).

Figure 17 **PROpel: Most Common AEs (≥ 10%) and Grade ≥ 3 AEs in the SAS and *BRCAm* Subgroup - DCO3 (12 October 2022)**



AEs = adverse events; *BRCA* = breast cancer susceptibility gene; *BRCAm* = *gBRCA* or *sBRCA* mutated; COVID-19 = Coronavirus disease 2019; DCO = data cut-off; *gBRCA* = germline *BRCA;* N = total number of patients; TEAE = treatment-emergent adverse event; SAS = safety analysis set; *sBRCA* = somatic *BRCA*.

Table 20 Number (%) of Patients [b] with Most Common AEs (Frequency ≥ 10% in Either Treatment Arm of the SAS) or AEs of CTCAE Grade 3 or Higher (Frequency ≥ 2% in Either Treatment Arm of the SAS), in the SAS and *BRCAm* Subgroup, by Preferred Term – DCO3 (12 October 2022)

MedDRA PT [a]	SAS				*BRCAm* subgroup			
	All grades		Grade 3 or higher		All grades		Grade 3 or higher	
	Olap + Abi (N = 398)	Pla + Abi (N = 396)	Olap + Abi (N = 398)	Pla + Abi (N = 396)	Olap + Abi (N = 47)	Pla + Abi (N = 38)	Olap + Abi (N = 47)	Pla + Abi (N = 38)
Patients with any AE	389 (97.7)	380 (96.0)	222 (55.8)	171 (43.2)	47 (100.0)	34 (89.5)	23 (48.9)	15 (39.5)
Anemia	197 (49.5)	69 (17.4)	64 (16.1)	13 (3.3)	19 (40.4)	7 (18.4)	5 (10.6)	2 (5.3)
Nausea	122 (30.7)	57 (14.4)	1 (0.3)	1 (0.3)	13 (27.7)	3 (7.9)	0	0
Fatigue	114 (28.6)	81 (20.5)	5 (1.3)	3 (0.8)	19 (40.4)	5 (13.2)	1 (2.1)	0
Back pain	86 (21.6)	79 (19.9)	4 (1.0)	6 (1.5)	13 (27.7)	8 (21.1)	1 (2.1)	2 (5.3)
Diarrhea	82 (20.6)	42 (10.6)	5 (1.3)	1 (0.3)	7 (14.9)	3 (7.9)	1 (2.1)	0
Arthralgia	58 (14.6)	77 (19.4)	0	2 (0.5)	11 (23.4)	7 (18.4)	0	0
Hypertension	61 (15.3)	74 (18.7)	15 (3.8)	18 (4.5)	6 (12.8)	8 (21.1)	1 (2.1)	0
Constipation	74 (18.6)	59 (14.9)	0	1 (0.3)	7 (14.9)	6 (15.8)	0	0
Decreased appetite	66 (16.6)	31 (7.8)	4 (1.0)	0	5 (10.6)	3 (7.9)	0	0
Vomiting	62 (15.6)	37 (9.3)	6 (1.5)	1 (0.3)	4 (8.5)	3 (7.9)	1 (2.1)	0
Hot flush	35 (8.8)	51 (12.9)	0	0	2 (4.3)	5 (13.2)	0	0
COVID-19	51 (12.8)	35 (8.8)	15 (3.8)	8 (2.0)	5 (10.6)	3 (7.9)	1 (2.1)	0
Edema peripheral	49 (12.3)	50 (12.6)	0	1 (0.3)	6 (12.8)	3 (7.9)	0	0
Dizziness	49 (12.3)	27 (6.8)	0	0	4 (8.5)	5 (13.2)	0	0
Asthenia	48 (12.1)	40 (10.1)	5 (1.3)	3 (0.8)	2 (4.3)	3 (7.9)	0	0
Cough	47 (11.8)	29 (7.3)	0	0	6 (12.8)	4 (10.5)	0	0
Urinary tract infection	46 (11.6)	35 (8.8)	10 (2.5)	4 (1.0)	8 (17.0)	4 (10.5)	0	1 (2.6)
Lymphocyte count decreased	34 (8.5)	17 (4.3)	15 (3.8)	6 (1.5)	5 (10.6)	0	2 (4.3)	0
Hyperglycemia	30 (7.5)	28 (7.1)	8 (2.0)	6 (1.5)	2 (4.3)	1 (2.6)	2 (4.3)	0

MedDRA PT [a]	SAS				*BRCAm* subgroup			
	All grades		Grade 3 or higher		All grades		Grade 3 or higher	
	Olap + Abi (N = 398)	Pla + Abi (N = 396)	Olap + Abi (N = 398)	Pla + Abi (N = 396)	Olap + Abi (N = 47)	Pla + Abi (N = 38)	Olap + Abi (N = 47)	Pla + Abi (N = 38)
Pulmonary embolism	29 (7.3)	9 (2.3)	29 (7.3)	9 (2.3)	5 (10.6)	0	5 (10.6)	0
White blood cell count decreased	26 (6.5)	10 (2.5)	9 (2.3)	2 (0.5)	3 (6.4)	0	1 (2.1)	0
Pneumonia	25 (6.3)	13 (3.3)	10 (2.5)	4 (1.0)	3 (6.4)	0	1 (2.1)	0
Neutrophil count decreased	18 (4.5)	7 (1.8)	11 (2.8)	3 (0.8)	3 (6.4)	0	1 (2.1)	0
Alanine aminotransferase increased	15 (3.8)	28 (7.1)	4 (1.0)	9 (2.3)	0	5 (13.2)	0	1 (2.6)

[a] Patients with multiple events are counted once for each PT.
[b] Sorted by descending frequency of all grades in either arm of the SAS.
Includes AEs with onset date or worsening, on or after the date of first dose and up to and including 30 days following discontinuation of randomized treatment.
MedDRA version 25.0.
Abi = abiraterone; AE = adverse event; *BRCA* = breast cancer susceptibility gene; *BRCAm* = *gBRCA* or *sBRCA* mutated; COVID-19 = Coronavirus disease 2019; CTCAE = Common Terminology Criteria for Adverse Events; DCO = data cut-off; *gBRCA* = germline *BRCA*; MedDRA = Medical Dictionary for Regulatory Activities; Olap = olaparib; Pla = placebo; PT = preferred term; SAS = safety analysis set; *sBRCA* = somatic *BRCA*.

6.2.6.2 Safety Data in Patients Who Are Non-*BRCAm*

In the safety analyses of the non-*BRCAm* subgroup (Table 21), the safety profile was generally consistent with the safety profile observed in the SAS and the olaparib monotherapy pool.

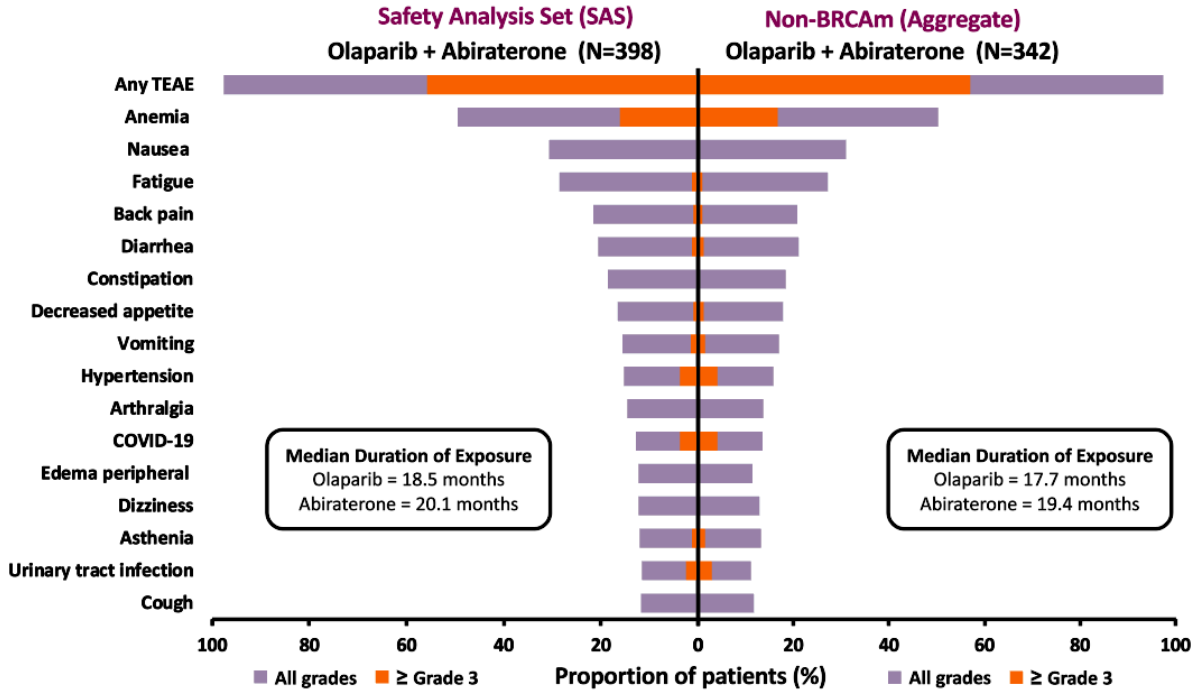
Table 21 PROpel: Safety Data in the SAS and Non-*BRCAm* Subgroup - DCO3 (12 October 2022)

	SAS		Non-*BRCAm* subgroup	
	Olap + Abi (N = 398)	**Pla + Abi (N = 398)**	**Olap + Abi (N = 342)**	**Pla + Abi (N = 350)**
Median total duration of exposure (days)				
Olaparib/Placebo	564.0	476.5	538.5	502.5
Abiraterone	612.0	477.0	590.5	503.5
Patients, n (%)				
Any AE	389 (97.7)	380 (96.0)	333 (97.4)	339 (96.9)
Any AE of CTCAE Grade ≥ 3	222 (55.8)	171 (43.2)	195 (57.0)	153 (43.7)
Any SAE	161 (40.5)	126 (31.8)	144 (42.1)	112 (32.0)
Any AE with outcome of death	26 (6.5)	20 (5.1)	24 (7.0)	17 (4.9)
Any AE leading to discontinuation of olaparib/placebo	69 (17.3)	34 (8.6)	60 (17.5)	28 (8.0)
Any AE leading to discontinuation of abiraterone	45 (11.3)	37 (9.3)	40 (11.7)	31 (8.9)

Abi = abiraterone; AE = adverse events; *BRCA* = breast cancer susceptibility gene; *BRCAm* = *gBRCA* or *sBRCA* mutated; DCO = data cut-off; *gBRCA* = germline *BRCA*; N = total number of patients; n = number of patients with an event; Olap = olaparib; Pla = placebo; SAE = serious adverse events; SAS = safety analysis set; *sBRCA* = somatic *BRCA*.

Figure 18 and Table 22 summarize the most common AEs and AEs of CTCAE Grade 3 or higher in the non-*BRCAm* subgroup vs the SAS. The most common AEs in the non-*BRCAm* subgroup were the same as those observed in the SAS (anemia, fatigue, and nausea in the olaparib + abiraterone arm; hypertension was one of the most common AEs in the placebo + abiraterone arm). The most common AE of CTCAE Grade 3 or higher in olaparib + abiraterone arm of the non-*BRCAm* subgroup was the same as observed in the SAS (anemia).

Figure 18 **PROpel: Most Common AEs (≥ 10%) and Grade ≥ 3 AEs in the SAS and Non-*BRCAm* Subgroup - DCO3 (12 October 2022)**



AEs = adverse events; *BRCA* = breast cancer susceptibility gene; *BRCAm* = *gBRCA* or *sBRCA* mutated; COVID-19 = Coronavirus disease 2019; DCO = data cut-off; *gBRCA* = germline *BRCA;* N = total number of patients; TEAE = treatment-emergent adverse event; SAS = safety analysis set; *sBRCA* = somatic *BRCA*.

Table 22 Number (%) of Patients [b] with Most Common AEs (Frequency ≥ 10% in Either Treatment Arm of the SAS) or AEs of CTCAE Grade 3 or Higher (Frequency ≥ 2% in Either Treatment Arm of the SAS), in the SAS and Non-*BRCAm* Subgroup, by Preferred Term – DCO3 (12 October 2022)

MedDRA PT [a]	SAS				Non-*BRCAm* subgroup			
	All grades		Grade 3 or higher		All grades		Grade 3 or higher	
	Olap + Abi (N = 398)	Pla + Abi (N = 396)	Olap + Abi (N = 398)	Pla + Abi (N = 396)	Olap + Abi (N = 342)	Pla + Abi (N = 350)	Olap + Abi (N = 342)	Pla + Abi (N = 350)
Patients with any AE	389 (97.7)	380 (96.0)	222 (55.8)	171 (43.2)	333 (97.4)	339 (96.9)	195 (57.0)	153 (43.7)
Anemia	197 (49.5)	69 (17.4)	64 (16.1)	13 (3.3)	172 (50.3)	60 (17.1)	57 (16.7)	11 (3.1)
Nausea	122 (30.7)	57 (14.4)	1 (0.3)	1 (0.3)	106 (31.0)	54 (15.4)	1 (0.3)	1 (0.3)
Fatigue	114 (28.6)	81 (20.5)	5 (1.3)	3 (0.8)	93 (27.2)	75 (21.4)	3 (0.9)	3 (0.9)
Back pain	86 (21.6)	79 (19.9)	4 (1.0)	6 (1.5)	71 (20.8)	68 (19.4)	3 (0.9)	4 (1.1)
Diarrhea	82 (20.6)	42 (10.6)	5 (1.3)	1 (0.3)	72 (21.1)	38 (10.9)	4 (1.2)	1 (0.3)
Arthralgia	58 (14.6)	77 (19.4)	0	2 (0.5)	47 (13.7)	67 (19.1)	0	2 (0.6)
Hypertension	61 (15.3)	74 (18.7)	15 (3.8)	18 (4.5)	54 (15.8)	63 (18.0)	14 (4.1)	15 (4.3)
Constipation	74 (18.6)	59 (14.9)	0	1 (0.3)	63 (18.4)	53 (15.1)	0	1 (0.3)
Decreased appetite	66 (16.6)	31 (7.8)	4 (1.0)	0	61 (17.8)	28 (8.0)	4 (1.2)	0
Vomiting	62 (15.6)	37 (9.3)	6 (1.5)	1 (0.3)	58 (17.0)	34 (9.7)	5 (1.5)	1 (0.3)
Hot flush	35 (8.8)	51 (12.9)	0	0	32 (9.4)	46 (13.1)	0	0
COVID-19	51 (12.8)	35 (8.8)	15 (3.8)	8 (2.0)	46 (13.5)	31 (8.9)	14 (4.1)	8 (2.3)
Edema peripheral	49 (12.3)	50 (12.6)	0	1 (0.3)	39 (11.4)	46 (13.1)	0	1 (0.3)
Dizziness	49 (12.3)	27 (6.8)	0	0	44 (12.9)	22 (6.3)	0	0
Asthenia	48 (12.1)	40 (10.1)	5 (1.3)	3 (0.8)	45 (13.2)	37 (10.6)	5 (1.5)	3 (0.9)
Cough	47 (11.8)	29 (7.3)	0	0	40 (11.7)	24 (6.9)	0	0
Urinary tract infection	46 (11.6)	35 (8.8)	10 (2.5)	4 (1.0)	38 (11.1)	31 (8.9)	10 (2.9)	3 (0.9)
Lymphocyte count decreased	34 (8.5)	17 (4.3)	15 (3.8)	6 (1.5)	29 (8.5)	17 (4.9)	13 (3.8)	6 (1.7)
Hyperglycemia	30 (7.5)	28 (7.1)	8 (2.0)	6 (1.5)	28 (8.2)	26 (7.4)	6 (1.8)	6 (1.7)

MedDRA PT [a]	SAS				Non-*BRCAm* subgroup			
	All grades		Grade 3 or higher		All grades		Grade 3 or higher	
	Olap + Abi (N = 398)	Pla + Abi (N = 396)	Olap + Abi (N = 398)	Pla + Abi (N = 396)	Olap + Abi (N = 342)	Pla + Abi (N = 350)	Olap + Abi (N = 342)	Pla + Abi (N = 350)
Pulmonary embolism	29 (7.3)	9 (2.3)	29 (7.3)	9 (2.3)	24 (7.0)	9 (2.6)	24 (7.0)	9 (2.6)
White blood cell count decreased	26 (6.5)	10 (2.5)	9 (2.3)	2 (0.5)	23 (6.7)	10 (2.9)	8 (2.3)	2 (0.6)
Pneumonia	25 (6.3)	13 (3.3)	10 (2.5)	4 (1.0)	21 (6.1)	13 (3.7)	9 (2.6)	4 (1.1)
Neutrophil count decreased	18 (4.5)	7 (1.8)	11 (2.8)	3 (0.8)	15 (4.4)	7 (2.0)	10 (2.9)	3 (0.9)
Alanine aminotransferase increased	15 (3.8)	28 (7.1)	4 (1.0)	9 (2.3)	15 (4.4)	23 (6.6)	4 (1.2)	8 (2.3)

[a] Patients with multiple events are counted once for each PT.
[b] Sorted by descending frequency of all grades in either arm of the SAS.
Includes AEs with onset date or worsening, on or after the date of first dose and up to and including 30 days following discontinuation of randomized treatment.
MedDRA version 25.0.
Abi = abiraterone; AE = adverse event; *BRCA* = breast cancer susceptibility gene; *BRCAm* = *gBRCA* or *sBRCA* mutated; COVID-19 = Coronavirus disease 2019; CTCAE = Common Terminology Criteria for Adverse Events; DCO = data cut-off; *gBRCA* = germline *BRCA*; MedDRA = Medical Dictionary for Regulatory Activities; Olap = olaparib; Pla = placebo; PT = preferred term; SAS = safety analysis set; *sBRCA* = somatic *BRCA*.

Deaths

In the non-*BRCAm* subgroup, adverse events with an outcome of death (during study treatment or within the 30-day follow-up period) were reported at a similar frequency between treatment arms (7.0% in the olaparib + abiraterone arm and 4.9% in the placebo + abiraterone arm). The small differences observed were driven by an imbalance in the number of COVID-19 related deaths. In the olaparib + abiraterone arm 7 patients died from COVID-19 vs 2 patients in the placebo + abiraterone arm. As discussed in Section 6.2.4, the observed imbalance of risk factors for mortality from COVID-19 between arms, with a higher proportion of patients with 2 or more risk factors in the olaparib + abiraterone arm, is likely to account for the increased number of fatal cases in that arm.

6.2.6.3 Safety Data in Patients who are HRRm

In the safety analyses of the HRRm subgroup (see Appendix D, Table D3), the incidences of AEs of CTCAE ≥ 3, SAEs, and AEs leading to an outcome of death in the olaparib + abiraterone arm of the HRRm subgroup were slightly lower compared with those observed in the SAS.

6.2.6.4 Safety Data in Patients who are Non-HRRm

In the safety analyses of the non-HRRm subgroup (see Appendix D, Table D4), the safety profile was generally consistent with the safety profile observed in the SAS and the olaparib monotherapy pool.

6.2.6.5 Conclusion on Safety Data in *BRCAm*, Non-*BRCAm*, HRRm, and Non-HRRm Subgroups

Overall, the safety data demonstrates a manageable safety profile in the *BRCAm*, non-*BRCAm*, HRRm, and non-HRRm subgroups, that is generally consistent with the established safety profiles of the monotherapies. This is supported by data showing that the addition of olaparib to the standard of care abiraterone in all these subgroups had no clinically meaningful impact on patients' quality of life, as evidenced by the FACT-P total score which was similar between treatment arms throughout the treatment period (Table 9 and Table 10).

7 BENEFIT-RISK ASSESSMENT

7.1 Unmet Medical Need

Metastatic castration-resistant prostate cancer is an incurable disease and is one of the leading causes of male cancer deaths in the US. Despite current standard of care treatment, OS outcomes remain poor. Patients receiving first-line treatment for mCRPC have a median survival of approximately 2 to 3 years in clinical trial settings (Armstrong et al 2020, Beer et al 2014, Beer et al 2017, Berthold et al 2008, Francini et al 2019, Kanotff et al 2010, Parker et

al 2013, Ryan et al 2013, Ryan et al 2015) and less than 2 years in clinical practice (George et al 2020).

In the real-world setting, only ~50% of patients with mCRPC will receive another FDA-approved treatment after their first progression. Therefore, optimizing therapies in the first-line treatment setting provides the greatest opportunity for delivering meaningful outcomes for mCRPC patients.

Metastatic castration-resistant prostate cancer is associated with a range of symptoms but is predominately characterized by bone pain, fatigue, and urinary dysfunction (Gater et al 2011, Lindqvist et al 2008). Symptoms of mCRPC can have an impact on daily lives and contribute to diminished levels of HRQoL observed in this population (Eton and Lepore 2002). Since curative therapy is not possible in the metastatic setting, delaying disease progression, and reducing disease burden and symptoms are critical objectives of any therapeutic intervention.

New hormonal agents such as abiraterone and enzalutamide are the preferred treatment option in the US for patients with mCRPC who have received prior chemotherapy containing docetaxel and also for use in the first-line metastatic (pre-chemotherapy) setting. However, following progression after first-line NHA therapy, the current treatment paradigm is either to re-treat with another NHA or to use a taxane-based chemotherapy agent (docetaxel or cabazitaxel), with an inherent increase in toxicity burden. There is also evidence of significantly diminishing efficacy with subsequent lines of NHA therapy with no additional efficacy benefit of taxane-based therapies (Castro et al 2019, Romero-Laorden et al 2020, Swami et al 2020).

Hence there is need for a new treatment option for patients with mCRPC that improves upon the current standard of care to prolong rPFS. A prolongation of rPFS has clinical relevance to patients with mCRPC, as delaying progression may result in a delay in the clinically important consequences such as bone pain, complications of visceral metastases, starting chemotherapy, and deterioration of quality of life.

7.2 Results from the PROpel Study

PROpel, a Phase III, randomized, double-blind, placebo-controlled study in patients with mCRPC, met its primary endpoint (rPFS) with a 34% reduction in the risk of radiological progression or death and an 8.2-month difference in median rPFS for the olaparib + abiraterone arm over the placebo + abiraterone arm.

The clinical benefit of the olaparib + abiraterone in PROpel was further supported by:

- Results of the rPFS assessment by BICR showing a median improvement in rPFS of 11.2 months for olaparib + abiraterone vs placebo + abiraterone.

- An rPFS improvement for olaparib + abiraterone was maintained across all pre-defined subgroups based on the stratification factors, HRR gene mutation status, and clinical characteristics.
- At the final pre-specified OS analysis (DCO3 12 October 2022, OS = 47.9% mature), a 19% reduction in the risk of death and a median OS improvement of 7.4 months in the olaparib + abiraterone arm over the placebo + abiraterone arm in the ITT population, demonstrating the trend towards OS benefit of the combination in an all-comer mCRPC population. The results for OS did not reach the threshold for statistical significance.
- Results of TFST, PFS2, ORR, PSA_{50} response, and time to PSA progression all show improvements for olaparib + abiraterone compared with placebo + abiraterone in the ITT, and support results from the primary rPFS analysis.
- At DCO3 (12 October 2022), the FACT-P total score was similar between treatment arms throughout the treatment period.
  - This shows that the combination of olaparib + abiraterone prolonged rPFS and had no clinically meaningful impact on patients' HRQoL. This is an important consideration for patients, since current anti-cancer treatments may be expected to impact HRQoL because of the adverse effects associated with mCRPC regimens.
- Results of efficacy analyses in the HRR and *BRCA* subgroups showed the greatest magnitude of benefit in the *BRCAm* and HRRm subgroups.
- Results in the non-*BRCAm* subgroup showed clinically meaningful rPFS improvements of 5.1 months (investigator-assessed), and 11.0 months (BICR), with no evidence of detriment in OS (HR = 0.91). Internal consistency of benefit with other secondary and exploratory endpoints (TFST, PFS2, ORR, PSA_{50} response, and time to PSA progression) was also observed in the non-*BRCAm* subgroup.

Olaparib and abiraterone have well-characterized safety profiles. Approximately 20,000 patients are estimated to have received treatment with olaparib and there have been > 140,000 patient-years exposure from post-marketing use. Abiraterone was approved for use in mCRPC in 2011, and it is the most commonly used NHA in mCRPC.

Safety data from PROpel was consistent with the known monotherapy safety profiles and demonstrate that overall, the combination of olaparib + abiraterone has a manageable safety profile for the treatment of patients with mCRPC. This is evidenced by:

- No new safety signals were identified in PROpel.
- The median duration of exposure to standard of care abiraterone was increased by combination treatment with olaparib.
- The median duration of exposure to olaparib was longer compared with placebo.

- A higher proportion of patients in the olaparib + abiraterone arm remained on study treatment at 12, 24, and 36 months compared with the placebo + abiraterone arm.
- The most common AEs in the olaparib + abiraterone arm were anemia, nausea, and fatigue, all known ADRs for olaparib. Other common AEs were consistent with the known safety profiles of olaparib and abiraterone as a monotherapy, or considered symptoms commonly reported in a mCRPC population.
- The AE data show that the addition of olaparib to the standard of care abiraterone had no clinically meaningful impact on patients' quality of life, as evidenced by the FACT-P total score which was similar between arms throughout the treatment period.
- AEs leading to discontinuation of olaparib were reported in 17.3% of patients in the olaparib + abiraterone arm; the most commonly report AE leading to discontinuation of olaparib was anemia.
- The incidence of MDS/AML and pneumonitis were generally consistent with the known olaparib safety profile. The incidence of NPMs was balanced between treatment arms but higher than in the larger combined monotherapy pool (capsule + tablets), however this may reflect the higher background rate of new primary malignancies in an older prostate cancer population.
- Imbalances were noted in VTE and COVID-19-related events, which were more frequently reported with the olaparib + abiraterone arm compared with the placebo + abiraterone arm.
  - VTE was included in the USPI Section 5 Warnings and Precautions on 19 May 2020 when the S-014 was approved based on PROfound study data. VTE is now an ADR for olaparib but is generally manageable with standard medical care.
  - The imbalance in serious COVID-19 events was reflective of a higher proportion of patients with 2 or more risk factors for mortality from COVID-19 in the olaparib + abiraterone arm than in the placebo + abiraterone arm.
- In the safety analyses of the non-HRRm and non-*BRCAm* subgroups, the safety profile was shown to be generally consistent with the safety profile observed in the SAS and with the known monotherapy safety profiles.
- The median duration of exposure to standard of care abiraterone was increased when combined with olaparib in both the non-HRRm and non-*BRCAm* subgroups.
- With the exception of COVID-19 related events, the percentage of deaths due to an AE was similar between the olaparib + abiraterone and the placebo + abiraterone arms of the non-HRRm and non-*BRCAm* subgroups, and none were considered to be related to olaparib by the reporting investigator.

7.3 Conclusions on the Benefit-Risk Assessment

PROpel was a positive study and met its primary endpoint of rPFS in the ITT population, with clinically meaningful benefit in the key secondary endpoint of OS and other secondary and exploratory endpoints (TFST, PFS2, PSA response, ORR, and time to PSA progression).

The safety data from PROpel was generally consistent with the known monotherapy olaparib and abiraterone safety profiles, and the AE data show that the addition of olaparib to the standard of care abiraterone had no clinically meaningful impact on patients' quality of life, as evidenced by the FACT-P total score, which was similar between arms throughout the treatment period.

A differential magnitude of benefit for olaparib + abiraterone was observed between the *BRCAm* and non-*BRCAm* subgroups, with the greatest benefit of olaparib + abiraterone seen in *BRCAm* patients. However, independent of this difference and considered on the merits of the data in this subgroup, the benefit-risk profile for the combination of olaparib + abiraterone in non-*BRCAm* patients is also positive. AstraZeneca considers that it is important to inform prescribers of the differences between the *BRCAm* and non-*BRCAm* subgroups and proposes to include relevant biomarker subgroup data in the USPI.

AstraZeneca recognizes the importance of testing in prostate cancer, and a complementary diagnostic may help inform physicians on the expected benefit-risk of the combination as a treatment option in *BRCAm* and non-*BRCAm* subgroups.

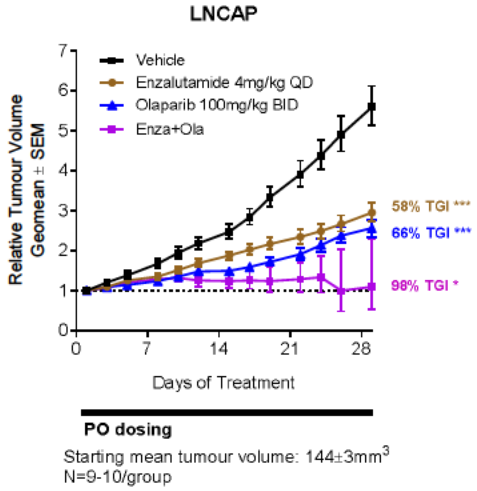
The totality of the data from PROpel demonstrates a favorable benefit-risk profile for the combination of olaparib plus abiraterone and prednisone or prednisolone in an all-comer mCRPC population and supports the approval of this new treatment option in the proposed indication: "*Lynparza is indicated in combination with abiraterone and prednisone or prednisolone for the treatment of adult patients with metastatic castration-resistant prostate cancer*".

Appendix A Data Supporting the Mechanistic Rationale for Olaparib and Abiraterone Combination Treatment in Prostate Cancer

AstraZeneca provides new data to support the mechanistic rationale for treatment of olaparib and the NHA abiraterone in an all-comer mCRPC patient population. These new data show that combined inhibition of PARP (by olaparib) and AR (by NHAs such as abiraterone) results in increased accumulation of DNA damage, leading to enhanced efficacy of the combination compared to the NHA alone.

To model the HRR wild-type, mCRPC population, AstraZeneca explored combination activity of olaparib and enzalutamide in the LNCAP cell line, which was isolated from a metastatic lesion of human prostatic cancer (Horoszewicz et al 1983) and has no biallelic genetic alterations in *BRCA* or HRR genes (https://www.cbioportal.org/patient?studyId=cellline_ccle_broad&caseId=LNCaP_clone_FGC). Details of why abiraterone was not used to generate the data in pre-clinical models are presented in Appendix B. When used as a tumor xenograft in vivo, LNCAP responded poorly, with a murine RECIST classification of progressive disease (Schwartz et al 2016), to either enzalutamide or olaparib single agent treatments, but showed a better response (stable disease) when both agents were used in combination (Figure A1). Thus, LNCAP could be considered a good representative model of the HRR wild-type, mCRPC population in the PROpel clinical trial.

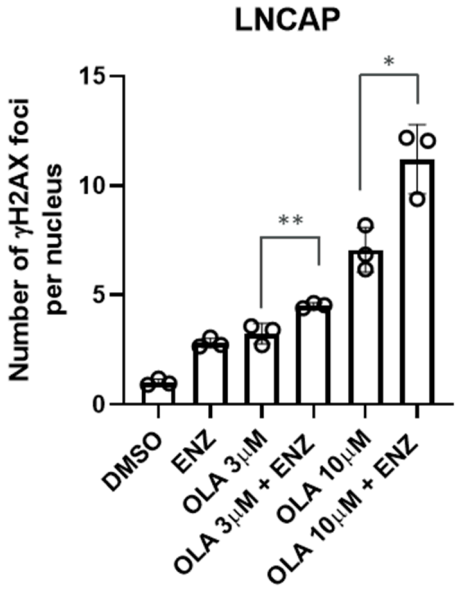
Figure A1 Anti-tumor Efficacy in Vivo in LNCAP Xenograft Tumor Model Treated Orally (PO Dosing) with Olaparib (100 mg/kg BID) or Enzalutamide (4 mg/kg QD) as Monotherapies or in Combination



Number of mice = 9-10 per group.
BID = twice daily; Enza = enzalutamide; N = total number; Ola = olaparib; PO = orally; QD = once daily; SEM = standard error of the mean; TGI = tumor growth inhibition.

To understand the cause of the additional benefit of the combination of enzalutamide and olaparib in the LNCAP cell line, AstraZeneca explored the accumulation of DNA damage in cells treated with either monotherapy or the combination, by assessing the presence of phosphorylated histone variant H2A.X on residue Ser-139 (also known as γH2AX), a well-described biomarker of DNA damage and genome instability (Ciccia and Elledge 2010). As shown in Figure A2, accumulation of γH2AX signal increases in cells treated with the olaparib and enzalutamide combination, suggesting an increase in unrepaired DNA damage when both PARP and AR activities are blocked in a cell line that is HRR wild-type. Increased DNA damage accumulation in the olaparib plus enzalutamide treatment condition could thus be an important factor in the increased benefit of the combination in the mCRPC population.

Figure A2 **Immunofluorescence-based Quantification of γH2AX Nuclear Accumulation (Foci) in LNCAP Cells Treated with Olaparib (3 or 10 µM), Enzalutamide (3 µM), Their Combination or Vehicle Control (DMSO) for 72 h**

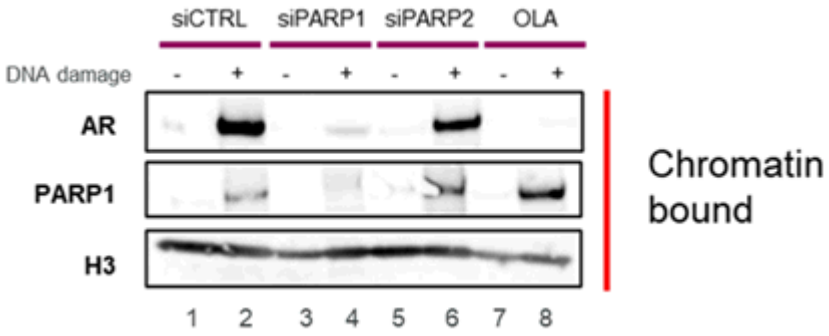


Results are shown as mean number of foci per nucleus ± SD (N = 3 technical replicates).
Statistical significance was calculated by unpaired t test analysis (* p-value 0.019; ** p-value 0.009).
DMSO = dimethyl sulfoxide; ENZ = enzalutamide; h = hours; Ola = olaparib; SD = standard deviation.

The data presented above indicate a role for the AR in the repair of PARPi-induced DNA damage. As the best characterized function of the AR is its activity at promoting gene expression in prostate cancer, for which binding to DNA is essential (Schmidt et al 2021), AstraZeneca explored whether DNA binding of the AR is influenced by PARP activity,

particularly in the presence of DNA damage. To perform the experiment in these conditions, mCRPC cells were treated with a well-known inducer of DNA breaks and an activator of PARP (hydrogen peroxide; Hegedűs and Virág 2014). As shown in Figure A3, induction of DNA damage by hydrogen peroxide (as measured by the increase of γH2AX signal) causes recruitment of PARP-1 to DNA but also a substantial increase in AR DNA binding (compare lane 2 vs lane 1). Importantly, AR DNA binding was impaired by treatment with olaparib (compare lane 2 vs lane 8) or depletion of PARP-1 (compare lane 2 vs lane 4). Collectively, these data show that there is enhanced DNA binding of the AR in response to DNA damage, and that enhanced binding requires the activity of PARP-1.

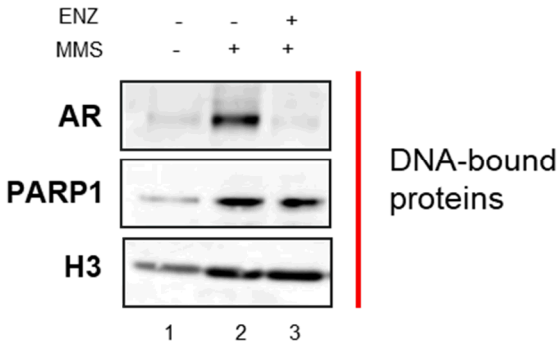
Figure A3 **Recruitment of the AR to DNA Chromatin is Blocked by Inhibition of PARP1 in the Presence of DNA Damage**



AR and PARP1 enrichment in the chromatin fraction in C4-2 cells (mCRPC cell line; Thalmann et al 1994) treated with siRNA (to cause down-regulation of the mentioned proteins) against PARP1, PARP2 or a control sequence, and (+) treated with H_2O_2 (1 mM) for 30 min to induce DNA damage. In lanes 7 and 8, cells were pre-treated with olaparib (3 µM) for 2 h. Down-regulation of PARP1 (compare lane 2 to lane 4) or inhibition of PARP activity with olaparib (compare lane 2 to lane 8) impair recruitment of the AR to DNA chromatin. Histone H3 was used as loading control for DNA-bound proteins.
AR = androgen receptor; h = hours; mCRPC = metastatic castration-resistant prostate cancer; OLA = olaparib; PARP = polyadenosine 5'diphosphoribose polymerase; siRNA = small interfering RNA.

DNA binding of the AR requires its nuclear localization, an event that is prevented by treatment of prostate cancer cells with NHAs (eg, abiraterone or enzalutamide) (Schmidt et al 2021). To understand whether NHA treatment could also prevent DNA-damage induced AR DNA binding, DNA damage was induced in mCRPC cells in the presence or absence of enzalutamide treatment. As shown in Figure A4, DNA damage induction resulted in increased DNA binding of both AR and PARP-1 (compare lane 2 vs lane 1), as observed previously (Figure A3). Enzalutamide treatment prevented the increased AR DNA binding in the presence of DNA damage (compare lane 3 vs lane 2).

Figure A4 Induction of DNA Damage in mCRPC Cells in the Presence or Absence of Enzalutamide Treatment



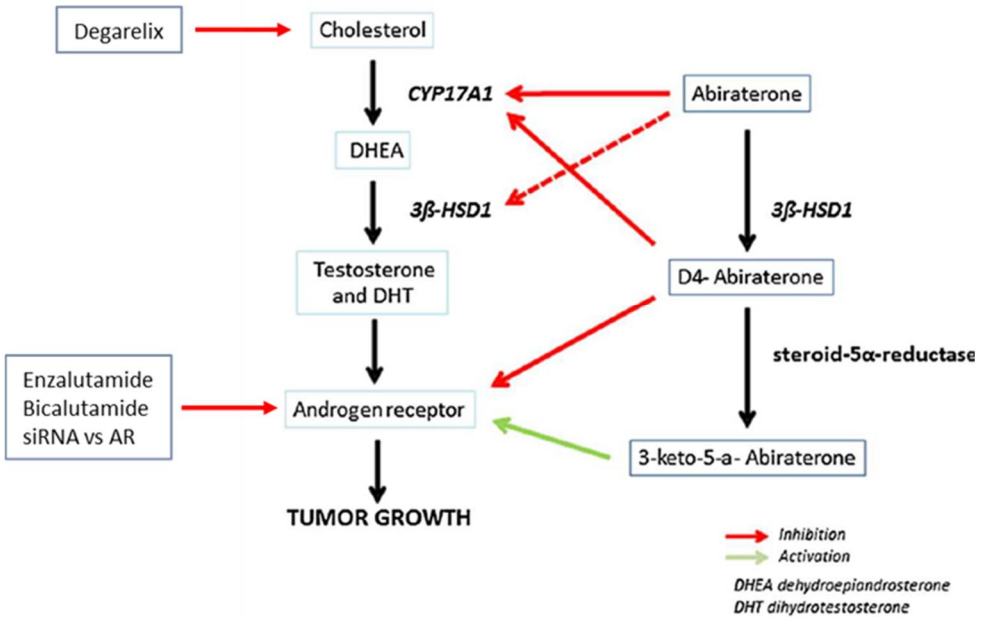
AR and PARP-1 enrichment in the chromatin fraction of C4-2 cells (mCRPC cell line; [Thalmann et al 1994]) treated with methyl-methane sulfonate (MMS; 0.01%) for 3 h and pre-treated with enzalutamide (ENZ; 3 µM) or vehicle control for 16 h. Histone H3 was used as loading control for DNA-bound proteins.
AR = androgen receptor; ENZ = enzalutamide; h = hours; mCRPC = metastatic castration-resistant prostate cancer; PARP = polyadenosine 5'diphosphoribose polymerase.

All the data presented provide support for a mechanism of action model that can explain the increased efficacy of the combination of PARPi with NHA therapies (eg, abiraterone, enzalutamide) in mCRPC patients with non-HRRm tumors. In this model, a PARPi that can induce PARP trapping, such as olaparib, can cause DNA damage in mCRPC tumor cells (Figure A2), thus driving combination benefit with NHAs. This benefit of the combination can be explained by the observation that repair of the DNA damage caused by PARP trapping requires AR activity (Figure A2), most likely through its ability to bind DNA, an event that is dependent on both PARP activity and AR nuclear localization (Figure A3 and Figure A4). This model is summarized in Figure 3, and provides a plausible explanation for the observed benefit of the combination of PARPi with NHA treatment in the non-HRRm mCRPC population of the PROpel clinical trial.

Appendix B Use of Abiraterone in Pre-clinical Models of Prostate Cancer

Abiraterone is a structural analog of pregnenolone that inhibits CYP17A1, an enzyme necessary for androgen synthesis (Figure B1) (Blanchet et al 2018, Rehman and Rosenberg 2012). The pre-clinical in vitro use of NHAs has been limited by the need to use serum-supplemented media (that itself contains testosterone) to culture tumor cell lines. To circumvent the confounding effect of the presence of hormones in culture medium, specialized serum preparations (such as charcoal-stripped serum; https://www.thermofisher.com/uk/en/home/life-science/cell-culture/mammalian-cell-culture/fbs/specialty-serum/charcoal-stripped-fbs.html) can be used and hormones or hormonal precursors to stimulate cell growth added in a controlled manner. The metabolite of choice in the androgen production pathway for addition in charcoal-stripped serum medium is dihydrotestosterone (DHT). Given that DHT is a cholesterol metabolite that enters the testosterone production pathway downstream of the enzymatic step governed by abiraterone's main target, CYP17A1 (Figure B1), researchers have focused on the use of NHAs that directly target AR. To be able to study the effect on NHAs in the AR pathway both in charcoal-stripped and testosterone-containing serum conditions (such as in Asim et al 2017, Li et al 2017), the AR targeted agents used include enzalutamide or bicalutamide (Casodex), or alternatively, small-interfering RNAs that downregulate AR expression (Figure B1).

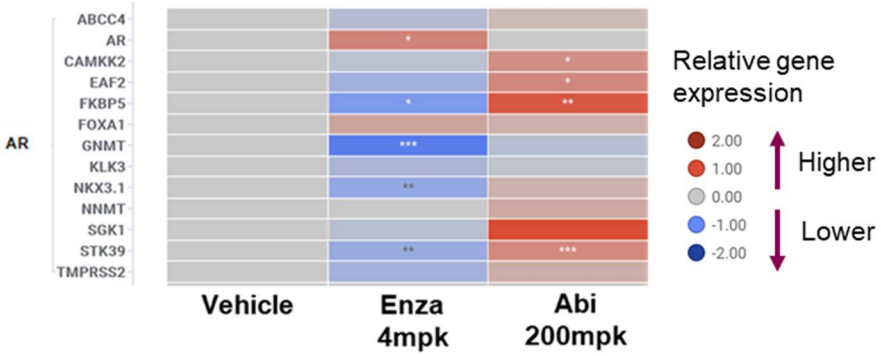
Figure B1 Pathways of Androgen Synthesis and Abiraterone Metabolism



Adapted from: Blanchet et al 2018
3βHSD1 = 3β-hydroxysteroid dehydrogenase/Δ5→4 isomerase 1; AR = androgen receptor; CYP17A1 = 17α-hydroxylase/17,20-lyase; DHEA = dehydroepiandrosterone; DHT = dehydrotestosterone; siRNA = small interfering RNA.

Abiraterone has also not been the NHA of choice for in vivo work in pre-clinical rodent models due to the differences in androgenic hormone biosynthesis between humans and rodents - there is a lack of androgen synthesis by the adrenal glands of mouse and rat (van Weerden et al 1992) due to the lack of expression of abiraterone's target, CYP17A1 in rodent adrenal glands (Luu-The et al 2005). Consequently, while in humans, castration-resistant prostate cancer androgen production can be both adrenal and intra-tumoral, in rodent models it is exclusively intra-tumoral. Consistent with the published literature, these androgen production differences between humans and rodents are reflected in AstraZeneca internal data that show treatment with enzalutamide effectively downregulates expression of AR-driven genes in a xenograft model of metastatic prostate cancer, while no inhibition was observed using abiraterone (Figure B2).

Figure B2 **Relative RNA Expression Level Compared to Vehicle Control of a Panel of AR Target Genes in the Prostate Cancer LNCAP Xenograft Model**



Mice (n = 6 per treatment group) were dosed for 5 days with either vehicle, enzalutamide (4 mg/kg QD) or abiraterone (200 mg/kg QD) and samples were collected 1 h after the last dose. Each sample was normalized to housekeeping genes (ACTB, GAPDH, PORL2A, IPO8, YWHAZ) and then to the average of the vehicle. Values of + 1 and - 1 correspond to 2-fold increase and 2-fold decrease, respectively. Statistical significance was calculated using pairwise two-sided t test (*p-value < 0.05; **p-value < 0.01).
Abi = abiraterone; AR = androgen receptor; Enza = enzalutamide; h = hours; QD = once daily.

It is because of these technical issues that pre-clinical data for NHAs as single agents or in combination with PARP inhibitors use enzalutamide or bicalutamide rather than abiraterone (Asim et al 2017, Li et al 2017, Schiewer et al 2012). Despite this, abiraterone, enzalutamide, bicalutamide, degarelix or RNAi knockdown of AR expression are all expected to work on the same pathway and have the same effect on androgen receptor activity (Figure B1).

Appendix C Clinical and Pre-clinical Data Reporting the Effect of Inhibition of the Androgen Receptor Pathway on a HRR Gene Silencing-Associated Transcriptional Signature

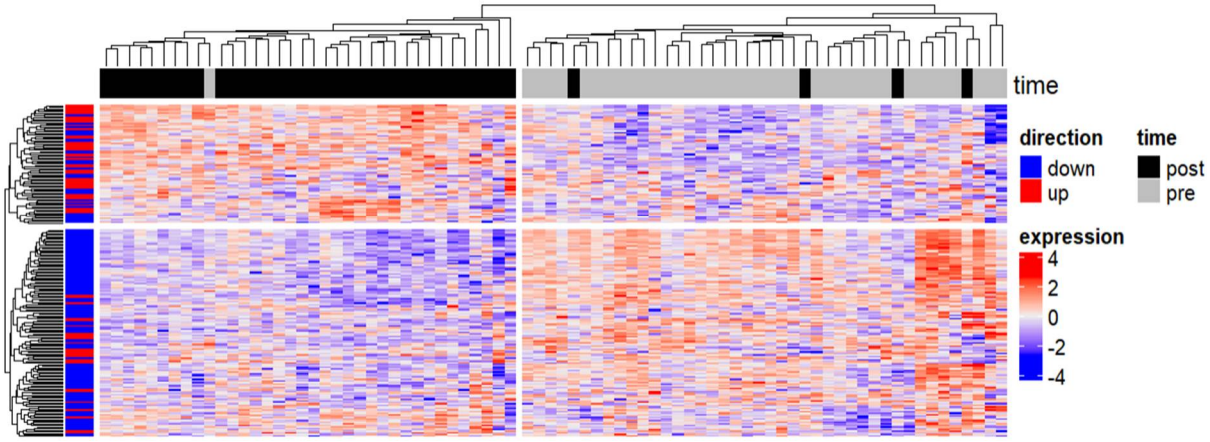
Emerging data have been generated in October/November 2022 from 2 new clinical trials and pre-clinical data. These new data demonstrate that treatment of prostate cancer patients with NHA, or degarelix (a gene silencing associated transcriptional [GnRH] antagonist that suppresses androgen production [Zengerling et al 2021]) in combination with olaparib, induces significant changes in a published HRR gene silencing-associated transcriptional (GSAT) signature that is reported to be increased upon independent knockdown of genes associated with HRR in pre-clinical models (Peng et al 2014).

To evaluate whether NHA treatment leads to changes in this gene signature, AstraZeneca analyzed the recently published RNA sequencing (RNA seq) dataset from the DARANA clinical trial (Dynamics of Androgen Receptor Genomics and Transcriptomics After Neoadjuvant Androgen Ablation; ClinicalTrials.gov identifier, NCT03297385; Linder et al 2022). In this study, 56 men with primary high-risk (Gleason score ≥ 7) prostate cancer received neoadjuvant NHA (enzalutamide) treatment for 3 months, followed by prostatectomy.

To measure effects on gene expression, AstraZeneca utilized a published gene signature, described to be linked to common molecular changes associated with defective HRR (Peng et al 2014). The HRR GSAT signature is composed of 230 genes of which 148 are down-regulated (HRR GSAT-down) and 82 up-regulated (HRR GSAT-up) in cells following independent knockdown of genes associated with HRR.

Using this gene signature, pattern-based classification (hierarchical clustering) from the DARANA study dataset was conducted, and it was observed that the samples clustered in 2 main groups composed of either NHA-pre-treatment or post-treatment samples (Figure C1). Moreover, lower expression of HRR GSAT-down genes and higher expression of HRR GSAT-up genes in the post-treatment samples was observed, indicating that NHA treatment changes expression of the HRR GSAT signature (AstraZeneca data on file).

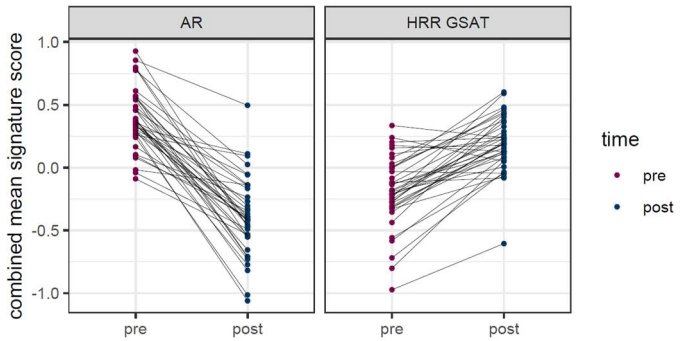
Figure C1 **Heatmap Showing the Expression of HRR GSAT Signature Genes in Tumor Samples Taken Pre or Post NHA (Enzalutamide) Treatment in the DARANA Clinical Trial**



GSAT = gene silencing-associated transcriptional; HRR = homologous recombination repair; NHA = new hormonal agent.

To directly compare pre- and post-NHA-treatment paired samples from the DARANA clinical trial, AstraZeneca generated gene expression score for the HRR GSAT signature. Following treatment with NHA, a significant up-regulation of the gene signatures score was observed (Wilcoxon, paired test, p-value 8.9e-8) (Figure C2; AstraZeneca data on file). As control, AstraZeneca calculated an AR signaling score, using a published AR gene signature (Hieronymus et al 2006). As expected, significant down-regulation of the AR scores following NHA treatment was observed (Wilcoxon, paired test, p-value 3.6e-12) (Figure C2) (AstraZeneca data on file). These data demonstrate that NHA treatment significantly inhibits AR signaling and changes the HRR GSAT gene signature (Peng et al 2014).

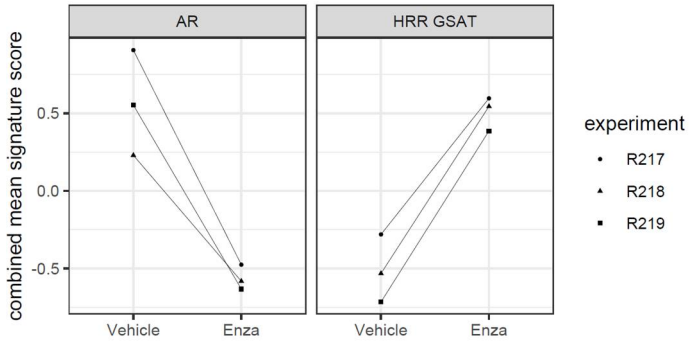
Figure C2 **Combined Mean Signature Scores for the AR Signaling and HRR GSAT Signature in Pre and Post NHA (Enzalutamide) Treatment from the DARANA Clinical Trial**



Gene values of each sample were converted to a Z score by $Z = (x - \mu)/\sigma$, where μ is the average $\log_2$ (expr) across all samples of a gene and σ is the standard derivation of the $\log_2$ expression value. The Z scores were then averaged across all genes for each sample.
AR = androgen receptor; GSAT = gene silencing-associated transcriptional; HRR = homologous recombination repair; NHA = new hormonal agent.

To provide further evidence that inhibition of AR signaling changes the HRR GSAT gene signature, the effects of NHA (enzalutamide) treatment were evaluated in a prostate cancer cell line (LNCAP) in vitro. New hormonal agent treatment changed the gene signature and inhibited AR signaling (Figure C3) (AstraZeneca data on file). These data are consistent with the data from the DARANA clinical study, providing further evidence that NHA treatment changes the HRR GSAT signature (Peng et al 2014).

Figure C3 **Combined Mean Signature Scores for the AR Signaling and HRR GSAT for LNCAP Cells Treated In Vitro with NHA (3 µm Enzalutamide) for 72 Hours**



AR = androgen receptor; GSAT = gene silencing-associated transcriptional; HRR = homologous recombination repair; NHA = new hormonal agent.

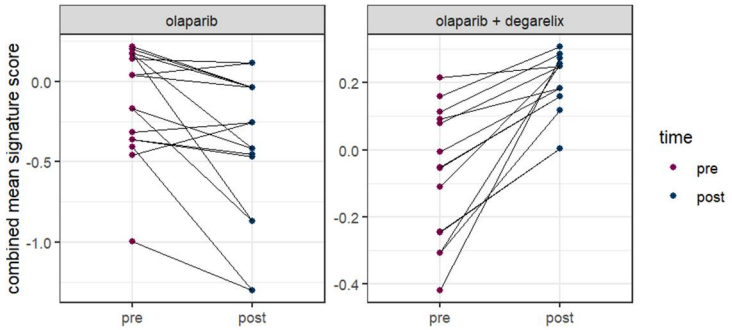
AstraZeneca has demonstrated that the effects of AR signaling inhibition on the HRR GSAT signature are also observed in prostate cancer patients treated with degarelix in combination with olaparib. Degarelix is a GnRH antagonist that competitively binds to receptors in the pituitary gland, leading to immediate castration and suppression of androgen production (Zengerling et al 2021). These data provide further evidence that AR signaling inhibition affects the HRR GSAT signature in prostate cancer patients and demonstrates that the effects are not only restricted to AR signaling inhibition induced by enzalutamide treatment.

To assess the effect of treatment of degarelix in combination with olaparib, the HRR GSAT signature in tumor samples from prostate cancer patients from the CANCAP03 clinical trial was evaluated. CANCAP03 was an investigator-led (Coordinating investigator Simon Pacey, University of Cambridge/Cambridge University Hospitals NHS Foundation Trust; NCT02324998) window of opportunity study of the biomarker effects from olaparib (PARP inhibitor) ± degarelix (GnRH antagonist) given for 2 weeks prior to radical prostatectomy (RP). Using a "window" trial, olaparib ± degarelix were given to men before RP. Men with localized prostate cancer (intermediate or high-risk recurrence) were recruited prior to RP and patients received olaparib 300 mg bid for 2 weeks and were randomized (1:1) to degarelix (240 mg subcutaneous) or not.

RNA sequencing data were generated for 41 tumor samples from 14 patients from the CANCAP03 study. The HRR GSAT combined mean signature scores were calculated as described above.

Comparison of paired pre- and post-treatment samples showed that treatment with degarelix in combination with olaparib significantly affects the expression of the HRR GSAT signature (Wilcoxon, paired test, p-value 0.000122) (Figure C4) (AstraZeneca data on file). In this 2-arm clinical trial the clinical effect of degarelix treatment alone was not evaluated.

Figure C4 **Effects of Olaparib ± Degarelix on HRR GSAT Signature in the CANCAP03 Clinical Trial**



GSAT = gene silencing-associated transcriptional; HRR = homologous recombination repair.

Additional PROpel Data in HRR and *BRCA* Subgroups

Appendix D Additional PROpel Data in HRR and *BRCA* Subgroups

Table D1 Summary of Selected Demographic and Disease Characteristics at Baseline in the HRRm and *BRCAm* Subgroups (ITT) - DCO1 (30 July 2021)

		Number (%) of patients			
		HRRm subgroup (N = 226)		*BRCAm* subgroup (N = 85)	
		Olaparib + Abiraterone (N = 111)	Placebo + Abiraterone (N = 115)	Olaparib + Abiraterone (N = 47)	Placebo + Abiraterone (N = 38)
Demographics					
Age (years)	Median (Min, Max)	68.0 (43, 89)	70.0 (46, 86)	67.0 (43, 83)	70.0 (46, 85)
	< 65	40 (36.0)	29 (25.2)	17 (36.2)	11 (28.9)
	≥ 65	71 (64.0)	86 (74.8)	30 (63.8)	27 (71.1)
Disease Characteristics					
ECOG performance status	0 (Normal activity)	79 (71.2)	74 (64.3)	36 (76.6)	20 (52.6)
	1 (Restricted activity)	32 (28.8)	41 (35.7)	11 (23.4)	18 (47.4)
Total Gleason Score	≤ 7	24 (21.6)	34 (29.6)	10 (21.3)	12 (31.6)
	8 to 10	83 (74.8)	80 (69.6)	34 (72.4)	25 (65.8)
Baseline S-Prostate Specific Antigen (µg/L)	Median	27.2	21.8	29.0	22.5
Prior docetaxel at mHSPC	Yes	26 (23.4)	25 (21.7)	8 (17.0)	10 (26.3)
Sites of metastases	Bone only	55 (49.5)	64 (55.7)	25 (53.2)	20 (52.6)
	Visceral (eg, lung/liver)	15 (13.5)	18 (15.7)	5 (10.6)	8 (21.1)
	Other	41 (36.9)	33 (28.7)	17 (36.2)	10 (26.3)
Baseline pain score (BPI-SF Item 3 score)	0 to < 4 (no pain to mild pain)	72 (64.9)	89 (77.4)	31 (66.0)	26 (68.4)
	4 to ≥ 6 (moderate pain to severe pain)	35 (31.5)	20 (17.4)	15 (31.9)	10 (26.3)

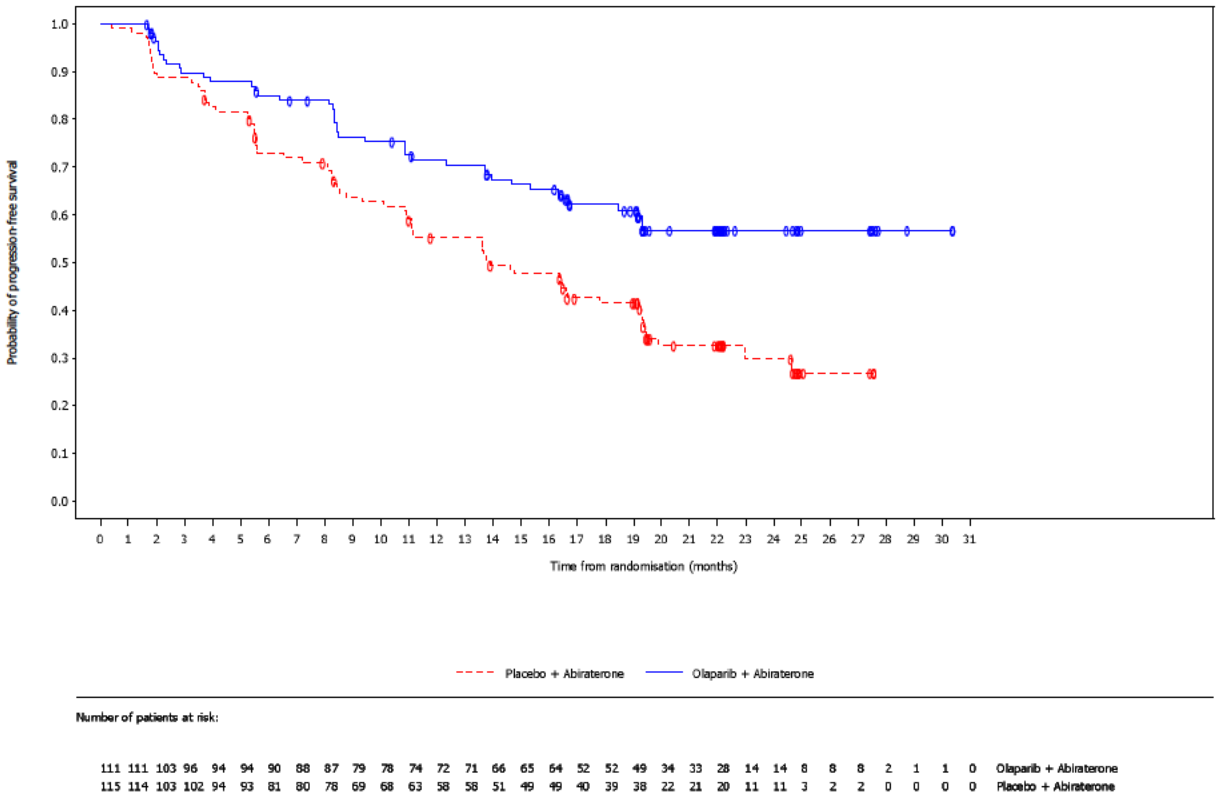
BPI-SF = Brief Pain Inventory-Short Form; *BRCA* = breast cancer susceptibility gene; *BRCAm* = *gBRCA* or *sBRCA* mutated; DCO = data cut-off; ECOG = Eastern Cooperative Oncology Group; *gBRCA* = germline *BRCA*; HRRm = homologous recombination repair gene mutated; ITT = intention-to-treat; Max = maximum; mHSPC = metastatic hormone-sensitive prostate cancer; Min = minimum; N = total number of patients; *sBRCA* = somatic *BRCA*.

Table D2 Summary of Selected Demographic and Disease Characteristics at Baseline in the Non-HRRm and Non-*BRCAm* Subgroups (ITT) - DCO1 (30 July 2021)

		Number (%) of patients			
		Non-HRRm subgroup (N = 552)		Non-*BRCAm* subgroup (N = 693)	
		Olaparib + Abiraterone (N = 279)	Placebo + Abiraterone (N = 273)	Olaparib + Abiraterone (N = 343)	Placebo + Abiraterone (N = 350)
Demographics					
Age (years)	Median (Min, Max)	69.0 (45, 91)	70.0 (50, 88)	69.0 (45, 91)	70.0 (49, 88)
	< 65	88 (31.5)	66 (24.2)	111 (32.4)	84 (24.0)
	≥ 65	191 (68.5)	207 (75.8)	232 (67.6)	266 (76.0)
Disease Characteristics					
ECOG performance status	0 (Normal activity)	202 (72.4)	193 (70.7)	245 (71.4)	247 (70.6)
	1 (Restricted activity)	76 (27.2)	80 (29.3)	97 (28.3)	103 (29.4)
Total Gleason Score	≤ 7	95 (34.1)	96 (35.2)	109 (31.8)	118 (33.7)
	8 to 10	175 (62.7)	173 (63.4)	224 (65.3)	228 (65.1)
Baseline S-Prostate Specific Antigen (µg/L)	Median	16.8	15.9	17.7	16.8
Prior docetaxel at mHSPC	Yes	61 (21.9)	61 (22.3)	79 (23.0)	76 (21.7)
Sites of metastases	Bone only	157 (56.3)	149 (54.6)	187 (54.5)	193 (55.1)
	Visceral (eg, lung/liver)	34 (12.2)	32 (11.7)	44 (12.8)	42 (12.0)
	Other	88 (31.5)	92 (33.7)	112 (32.7)	115 (32.9)
Baseline pain score (BPI-SF Item 3 score)	0 to < 4 (no pain to mild pain)	207 (74.2)	213 (78.0)	248 (72.3)	276 (78.9)
	4 to ≥ 6 (moderate pain to severe pain)	48 (17.2)	44 (16.1)	68 (19.8)	54 (15.4)

BPI-SF = Brief Pain Inventory-Short Form; *BRCA* = breast cancer susceptibility gene; *BRCAm* = *gBRCA* or *sBRCA* mutated; DCO = data cut-off; ECOG = Eastern Cooperative Oncology Group; *gBRCA* = germline *BRCA*; HRRm = homologous recombination repair gene mutated; ITT = intention-to-treat; Max = maximum; mHSPC = metastatic hormone-sensitive prostate cancer; Min = minimum; N = total number of patients; *sBRCA* = somatic *BRCA*.

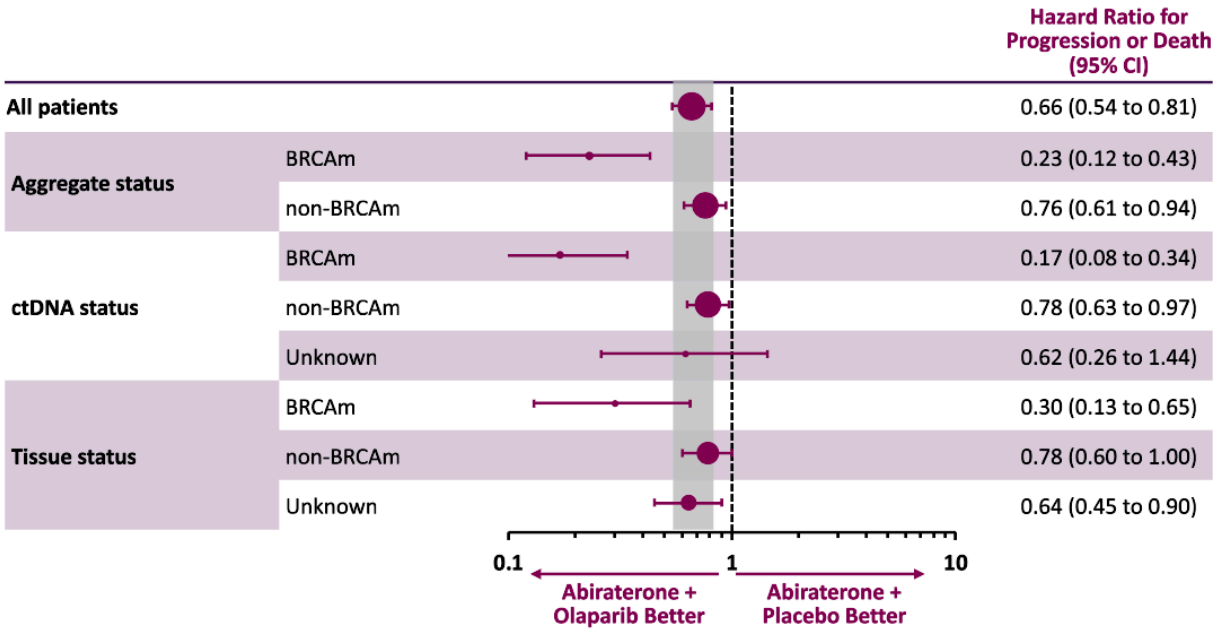
Figure D1 **Radiological Progression-free Survival Analysis (Investigator Assessment) in the HRRm Subgroup - DCO1 (30 July 2021)**



	Olaparib + Abiraterone N=111	Placebo + Abiraterone N=115
Events (maturity)	43 (38.7)	73 (63.5)
Median, m	NC	13.86
HR (95% CI)	**0.50** (0.34, 0.73)	

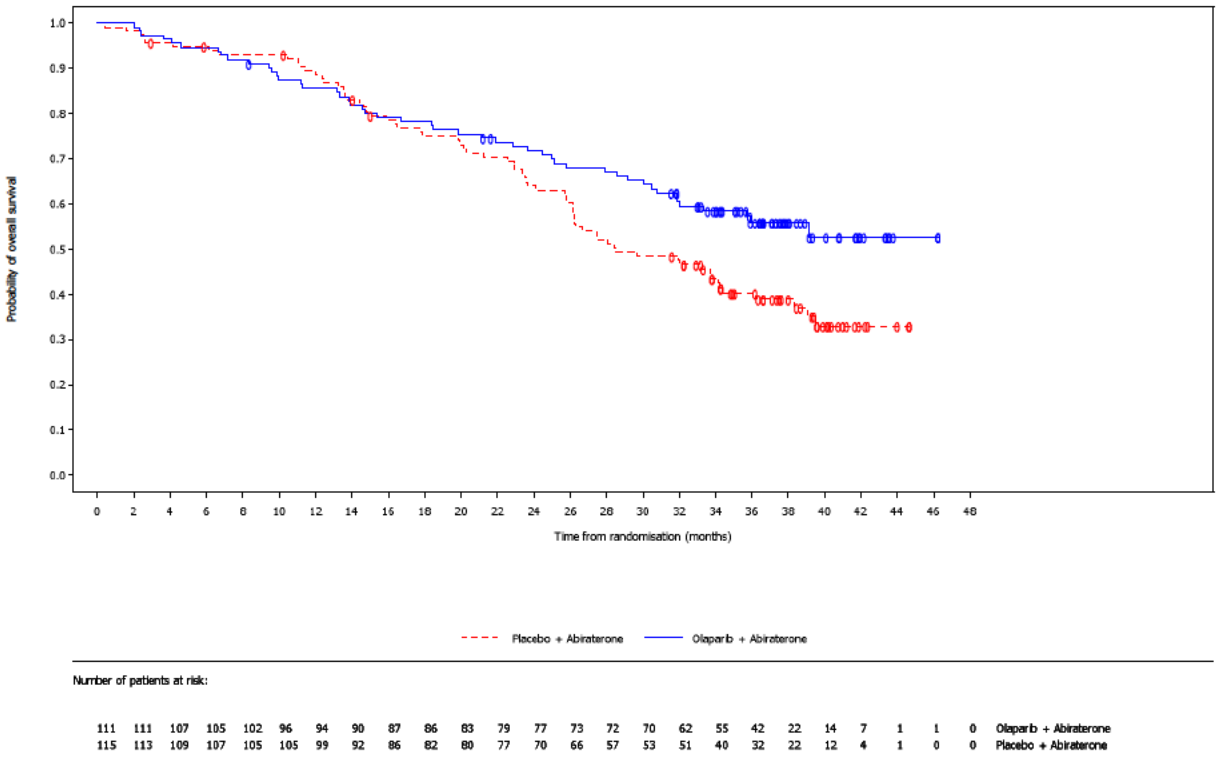
CI = confidence interval; DCO = data cut-off; HR = hazard ratio; HRRm = homologous recombination repair gene mutated; m = months; N = total number of patients; NC = not calculable/calculated; rPFS = radiological progression-free survival.

Figure D2 **Radiological Progression-free Survival Across *BRCA* Subgroups (ITT) - DCO1 (30 July 2021)**



BRCA = breast cancer susceptibility gene; *BRCAm* = *gBRCA* or *sBRCA* mutated; CI = confidence interval; ctDNA = circulating tumor DNA; DCO = data cut-off; *gBRCA* = germline *BRCA*; ITT = intention-to-treat; *sBRCA* = somatic *BRCA*.

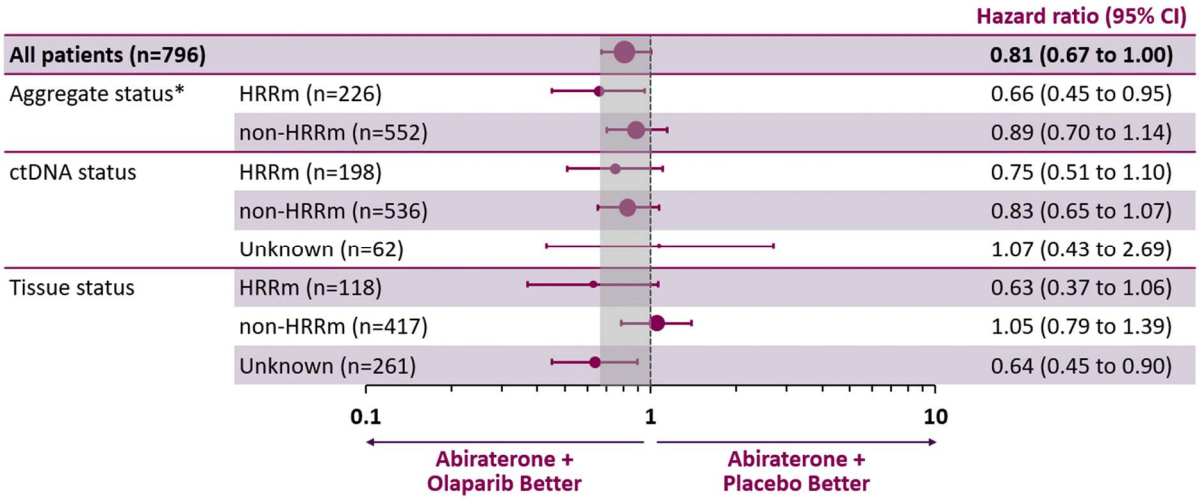
Figure D3 **Overall Survival Analysis in the HRRm Subgroup - DCO3 (12 October 2022)**



	Olaparib + Abiraterone N=111	Placebo + Abiraterone N=115
Events (maturity)	48 (43.2)	69 (60.0)
Median, m	NC	28.45
HR (95% CI)	**0.66** (0.45, 0.95)	

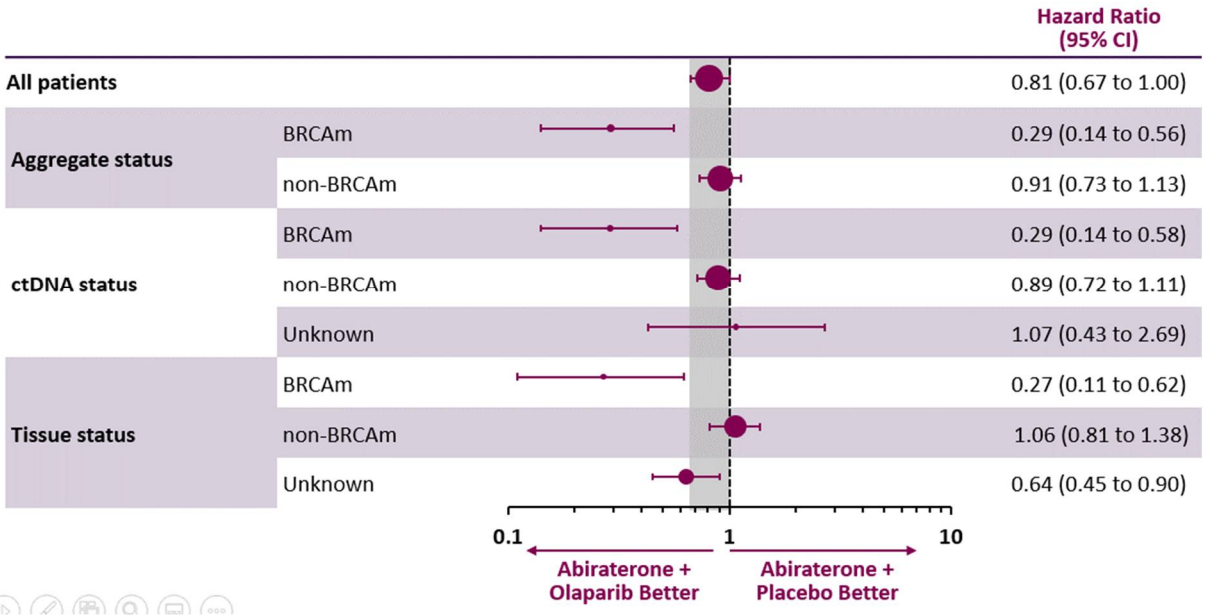
CI = confidence interval; DCO = data cut-off; HR = hazard ratio; HRRm = homologous recombination repair gene mutated; m = months; N = total number of patients; NC = not calculable/calculated; OS = overall survival.

Figure D4 Overall Survival Across HRR Gene Mutation Subgroups (ITT) - DCO3 (12 October 2022)



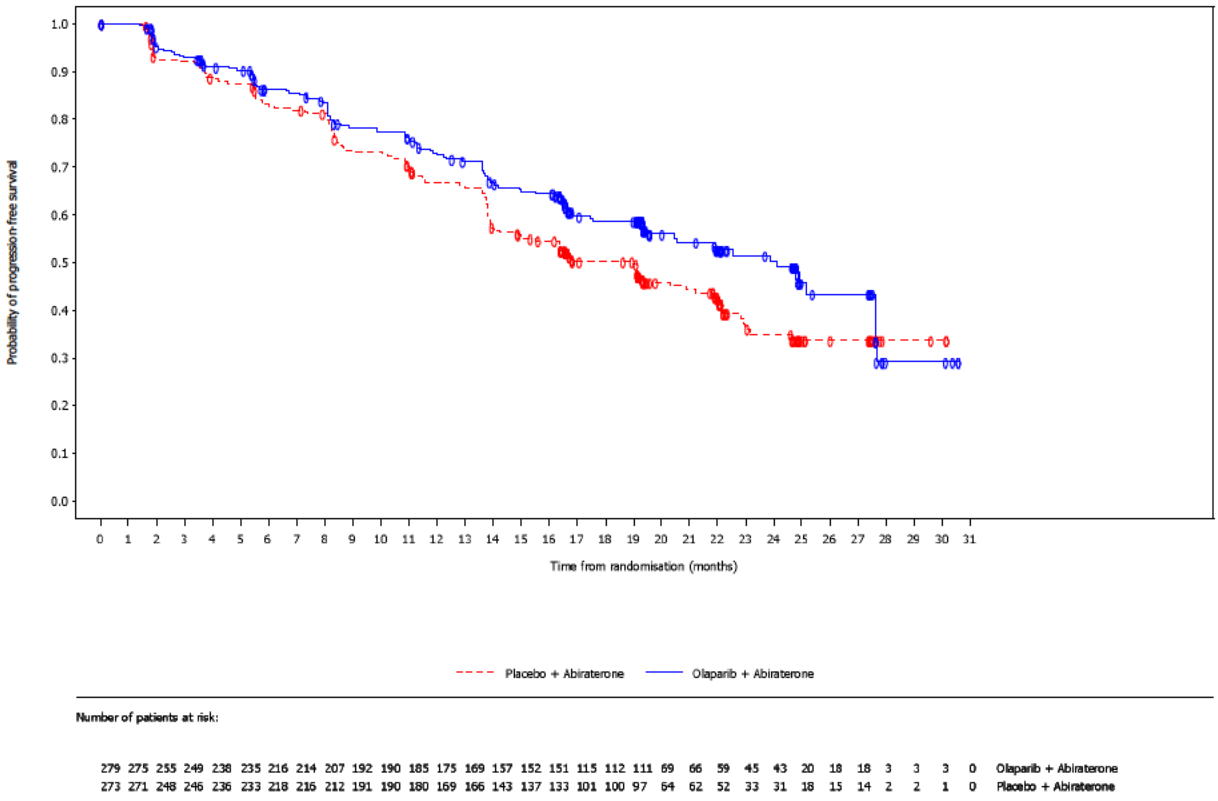
* Only 18 patients had an unknown status by aggregate and were not included in the analysis.
HRR status by ctDNA and tissue test were pre-specified analyses; aggregate analyses were post-hoc.
CI = confidence interval; ctDNA = circulating tumor DNA; DCO = data cut-off; HRR = homologous recombination repair; HRRm = HRR gene mutated; ITT = intention-to-treat.

Figure D5 Overall Survival Across *BRCA* Subgroups (ITT) - DCO3 (12 October 2022)



BRCA = breast cancer susceptibility gene; *BRCAm* = *gBRCA* or *sBRCA* mutated; CI = confidence interval; ctDNA = circulating tumor DNA; DCO = data cut-off; *gBRCA* = germline *BRCA*; ITT = intention-to-treat; *sBRCA* = somatic *BRCA*.

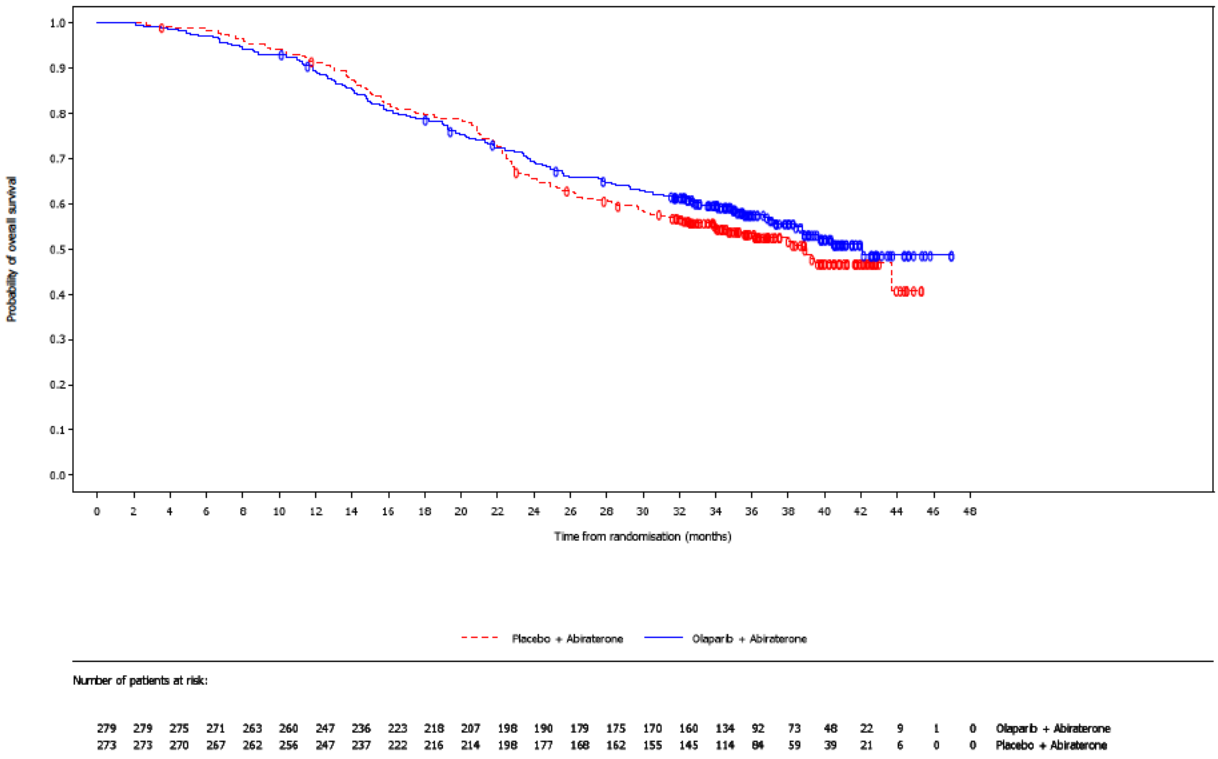
Figure D6 **Radiological Progression-free Survival Analysis (Investigator Assessment) in the Non-HRRm Subgroup - DCO1 (30 July 2021)**



	Olaparib + Abiraterone N=279	Placebo + Abiraterone N=273
Events (maturity)	119 (42.7)	149 (54.6)
Median, m	24.11	18.96
HR (95% CI)	**0.76** (0.60, 0.97)	

CI = confidence interval; DCO = data cut-off; HR = hazard ratio; HRRm = homologous recombination repair gene mutated; m = months; N = total number of patients; rPFS = radiological progression-free survival.

Figure D7 Overall Survival Analysis in the Non-HRRm Subgroup - DCO3 (12 October 2022)



	Olaparib + Abiraterone N=279	Placebo + Abiraterone N=273
Events (maturity)	123 (44.1)	132 (48.4)
Median, m	42.05	38.90
HR (95% CI)	**0.89** (0.70, 1.14)	

CI = confidence interval; DCO = data cut-off; HR = hazard ratio; HRRm = homologous recombination repair gene mutated; m = months; N = total number of patients; OS = overall survival.

Table D3 PROpel: Safety Data in the SAS and HRRm Subgroup - DCO3 (12 October 2022)

	SAS		HRRm subgroup	
	Olap + Abi (N = 398)	**Pla + Abi (N = 398)**	**Olap + Abi (N = 111)**	**Pla + Abi (N = 115)**
Median total duration of exposure (days)				
Olaparib/Placebo	564.0	476.5	593.0	418.0
Abiraterone	612.0	477.0	644.0	418.0
Patients, n (%)				
Any AE	389 (97.7)	380 (96.0)	110 (99.1)	106 (92.2)
Any AE of CTCAE Grade ≥ 3	222 (55.8)	171 (43.2)	56 (50.5)	49 (42.6)
Any SAE	161 (40.5)	126 (31.8)	39 (35.1)	37 (32.2)
Any AE with outcome of death	26 (6.5)	20 (5.1)	5 (4.5)	6 (5.2)
Any AE leading to discontinuation of olaparib/placebo	69 (17.3)	34 (8.6)	21 (18.9)	10 (8.7)
Any AE leading to discontinuation of abiraterone	45 (11.3)	37 (9.3)	10 (9.0)	11 (9.6)

Abi = abiraterone; AE = adverse events; CTCAE = Common Terminology Criteria for Adverse Events; DCO = data cut-off; HRRm = homologous recombination repair gene mutated; N = total number of patients; n = number of patients with an event; Olap = olaparib; Pla = placebo; SAE = serious adverse events; SAS = safety analysis set.

Table D4 PROpel: Safety Data in the SAS and Non-HRRm Subgroup - DCO3 (12 October 2022)

	SAS		Non-HRRm subgroup	
	Olap + Abi (N = 398)	**Pla + Abi (N = 398)**	**Olap + Abi (N = 278)**	**Pla + Abi (N = 273)**
Median total duration of exposure (days)				
Olaparib/Placebo	564.0	476.5	542.0	502.0
Abiraterone	612.0	477.0	594.5	503.0
Patients, n (%)				
Any AE	389 (97.7)	380 (96.0)	270 (97.1)	267 (97.8)
Any AE of CTCAE Grade ≥ 3	222 (55.8)	171 (43.2)	162 (58.3)	119 (43.6)
Any SAE	161 (40.5)	126 (31.8)	119 (42.8)	87 (31.9)
Any AE with outcome of death	26 (6.5)	20 (5.1)	20 (7.2)	13 (4.8)
Any AE leading to discontinuation of olaparib/placebo	69 (17.3)	34 (8.6)	45 (16.2)	22 (8.1)
Any AE leading to discontinuation of abiraterone	45 (11.3)	37 (9.3)	33 (11.9)	24 (8.8)

Abi = abiraterone; AE = adverse events; CTCAE = Common Terminology Criteria for Adverse Events; DCO = data cut-off; HRRm = homologous recombination repair gene mutated; N = total number of patients; n = number of patients with an event; Olap = olaparib; Pla = placebo; SAE = serious adverse events; SAS = safety analysis set.

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