Single Technology Appraisal

Olaparib with abiraterone for untreated hormone-relapsed metastatic prostate cancer [ID3920]
Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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Contents:

The following documents are made available to stakeholders:

Access the **final scope** and **final stakeholder list** on the NICE website.

1. **Company submission from AstraZeneca:**
   a. Full submission
   b. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**

3. **Patient group, professional group, and NHS organisation submissions** from:
   a. Prostate Cancer UK

4. **External Assessment Report** prepared by Centre for Reviews and Dissemination, University of York

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   a. Professor Suneil Jain, Professor of Clinical Oncology and Honorary Consultant in Clinical Oncology – clinical expert, nominated by AstraZeneca
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8. **Technical engagement responses from stakeholders:**
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Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

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Document B

Company evidence submission

April 2023

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ID3920_Olaparib_Company evidence submission_V1.0_[Redacted]	**1.0**	**Yes**	**17 April 2023**

Contents

Tables and Figures

List of abbreviations

Abbreviation	Definition
ABI	Abiraterone
ADT	Androgen deprivation therapy
AE	Adverse event
AIC	Akaike Information Criterion
AML	Acute myeloid leukaemia
AR	Androgen Receptor
ASCO	American Society of Clinical Oncology
ATM	Ataxia-telangiectasia mutated gene
BD	Twice daily
BIC	Bayesian Information Criterion
bid	Twice daily
BNF	British National Formulary
BPI-SF	Brief Pain Inventory-Short Form
BRCA1; BRAC2	Breast Cancer gene 1 ; Breast Cancer gene 2
CI	Confidence Interval
CR	Complete response
CrI	Credible interval
CSR	Clinical Study Report
CT	Computed Tomography
ctDNA	Circulating tumour DNA
CYP	Cytochrome P450
DCO	Data cut-off
DCR	Disease control rate
DOR	Duration of response
DSU	Decision support unit
dUCBT	Double umbilical cord blood transplantation
EAU	European Association of Urology
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EFR	Evaluable for response
EMA	European Medicines Agency
eMIT	Electronic Market Information Tool
Enz; Enza	Enzalutamide
EQ-5D-3L	European quality of life five-domain, three-level
EQ-5D-3L	European quality of life five-domain, three-level
ESMO	European Society for Medical Oncology

EWB	Emotional Wellbeing
FACT-G	Functional Assessment Of Cancer Therapy – General
FACT-P	Functional Assessment Of Cancer Therapy – Prostate
FAPSI-6	FACT Advanced Prostate Symptom Index 6
FAS	Full analysis set
FWB	Functional Wellbeing
GnRH	Gonadotropin releasing hormone
HR	Hazard Ratio
HRG	Healthcare resource group
HRQoL	Health Related Quality of Life
HRR	Homologous recombination repair pathway
HRRm	Homologous recombination repair pathway gene mutation
ICER	Incremental cost-effectiveness ratio
IQR	Interquartile range
ITC	Indirect treatment comparison
ITT	Intention To Treat
IWRS	Interactive Web Response System
KM; K-M	Kaplan Meier
LS mean	Least Squared mean
LYG	Life years gained
mCRPC	Metastatic castration-resistant prostate cancer
MDS	Myelodysplastic syndromes
mg	Milligram
MGUS	Monoclonal gammopathy of undetermined significance
mHSPC	Metastatic hormone-sensitive prostate cancer
MMRM	Mixed Models with Repeated Measures
MRI	Magnetic Resonance Imaging
NA	Not applicable
NC	Not calculated
NHS	National Health Service
NICE	National Institute of Health and Care Excellence
NMA	Network meta-analysis
NR	Not reported
o.d	Once daily
OLA	Olaparib
ORR	Objective response rate
OS	Overall Survival
OWSA	One way sensitivity analysis
PARP	Poly (ADP-ribose) polymerase

PAS	Patient Access Scheme
PCS	Prostate Cancer Scale
PCWG	Prostate Cancer Clinical Trials Working Group
PD	Progressive disease
PFS	Progression free survival
PFS2	Second progression free survival
PH	Proportional hazards
PLA	Placebo
PR	Partial response
Pred	Prednisone/prednisolone
PRO	Patient reported outcome
PSA	Probabilistic sensitivity analysis
PSA	Prostate Specific Antigen
PSSRU	Personal Social Services Research Unit
Pts	Patients
PWB	Physical Wellbeing
q.d	Once daily
QoL	Quality of Life
RCT	Randomised Clinical Trial
RECIST	Response Evaluation Criteria In Solid Tumors
rPFS	Radiological Progression-Free Survival
SAE	Serious adverse event
SE	Standard error
SmPC	Summary of product characteristics
SRE	Skeletal-related event
SWB	Social wellbeing
TA	Technology appraisal
TFST	Time to first subsequent therapy
TOI	Trial Outcome Index
TTD	Time to Treatment Discontinuation
TTDA	Time to Treatment Discontinuation with Abiraterone
TTPP	Time to progressive pain
UK	United Kingdom
VAS	Visual Analogue Scale

B.1 Decision problem, description of the technology and clinical care pathway

Background

- Prostate cancer is the most common cancer diagnosis in the UK, having over taken breast cancer in 2018 (1,2).
- An estimated 58,373 patients will be diagnosed with prostate cancer in the UK in 2023 (3). Of all incidences of prostate cancer, 2.22% of patients will develop mCRPC (4), with a 5-year survival rate of 49% (1).
- Prostate cancer cells are typically dependent on androgens for survival and growth and initially respond to androgen deprivation therapy (ADT). However, over time there is typically a loss of response to ADT. Metastatic disease that no longer responds to ADT is referred to as metastatic castration resistant prostate cancer (mCRPC).
- NICE-recommended first-line mCRPC treatment options include cyctotoxic chemotherapy with docetaxel in those with a Karnofsky performance status score $\geq$60%, per NICE TA101 (5), or the new hormonal agents (NHAs) enzalutamide or abiraterone (in combination with prednisone or prednisolone) in people with no or mild symptoms after ADT has failed and before chemotherapy is indicated, per NICE TA377 (6) and NICE TA387 (7).

Olaparib plus abiraterone (and prednisone or prednisolone)

- This appraisal relates to olaparib plus abiraterone for the treatment of adult patients with mCRPC in whom chemotherapy is not clinically indicated (8,9). The submission covers the full licensed indication.
- In line with the NICE scope, the relevant comparators are the NHAs enzalutamide and abiraterone (8). Given its far greater and increasing use in the first line mCRPC setting (10), enzalutamide is the primary comparator.
- The combination of olaparib (a PARP inhibitor) and abiraterone (a NHA androgen biosynthesis inhibitor) leads to an enhanced anti-tumour effect (9) that provides a step change in first-line therapy for patients with mCRPC in whom chemotherapy is not clinically indicated:
    - Olaparib plus abiraterone is the first combination therapy approach to be licensed for first line use in patients with mCRPC for whom chemotherapy is not clinically indicated. The combination was designated as innovative by the granting of an Innovation Passport in June 2022 as part of the MHRA-administered Innovative Licensing and Access Pathway (11).
    - In their phase 3 registrational trials, the NHAs enzalutaminde and abiraterone provided median progression-free survival (PFS) of approximately 16-20 months (12,13). In contrast, olaparib plus abiraterone provides a median PFS in the PROpel ITT population of 24.97 months at the last data cut, and so exceeds 2 years for the first time in this patient group (14) (see section B.2.6.1).
    - This improved efficacy of olaparib plus abiraterone is consistent across pre-specified subgroups, including patients with or without homologous recombination repair (HRR) mutations (14) (see section B.2.7).
    - This greater delay in disease progression can potentially delay the use of subsequent therapies that have diminishing efficacy, and may improve overall survival (15) (see section B.2.6.2). It was achieved without further impairing health-related quality of life.
    - Olaparib plus abiraterone therefore provides a much-needed new first-line therapeutic option to improve outcomes in first line mCRPC patients (irrespective of mutation their status) for whom chemotherapy is not clinically indicated.

B.1.1 Decision problem

Olaparib (Lynparza®) in combination with abiraterone (and prednisone or prednisolone) received a marketing authorisation by the UK Medicines and Healthcare products Regulatory Agency (MHRA) for the treatment of adult patients with metastatic castration resistant prostate cancer (mCRPC) in whom chemotherapy is not clinically indicated on 15th March 2023 (9).

This submission covers the full licensed indication for olaparib in combination with abiraterone (and prednisone or prednisolone) for first line use in adult patients with mCRPC in whom chemotherapy is not clinically indicated (9). This population is in line with the evidence base from the PROpel phase 3 clinical trial (NCT03732820) for olaparib plus abiraterone (14) and reflects its clinically appropriate positioning early in the mCRPC pathway to improve outcomes at this stage of the disease.

Please note that olaparib in combination with abiraterone (and prednisone or prednisolone) is referred to as olaparib plus abiraterone in this submission. Additionally, prednisone and prednisolone have been used interchangeably.

Full details of the decision problem addressed in the submission are summarised in Table 1.

Table 1. The decision problem

	Final scope issued by NICE (8)	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with hormone-relapsed metastatic prostate cancer for whom chemotherapy is not clinically indicated.	In line with scope and licensed indication	-
Intervention	Olaparib with abiraterone (and prednisone or prednisolone)	Olaparib with abiraterone (and prednisone or prednisolone)	-
Comparator(s)	• Enzalutamide • Abiraterone with prednisone or prednisolone	Main comparator: •Enzalutamide Secondary comparator: •Abiraterone with prednisone or prednisolone	Based on Blueteq requests in 2022 for their use in mCRPC before chemotherapy is indicated, enzalutamide accounts for twice as many initiations as abiraterone (67% vs 33%). Despite a 2-fold increase in total initiations of these therapies since 2020, abiraterone initiations have declined by 30% over the same period (10). Based on its far greater and growing use, enzalutamide is the main comparator for olaparib plus abiraterone, with abiraterone considered as a secondary comparator.
Outcomes	• Overall survival • Progression-free survival • Response rate • Adverse effects of treatment • Health-related quality of life.	• Overall survival (OS) • Progression-free survival (PFS; Primary endpoint: investigator-based. Sensitivity analysis: blinded independent central review) • Response rate • Adverse effects of treatment • Health-related quality of life (HRQoL) • Time to first subsequent therapy or death (TFST) • Time to second progression or death (PFS2) • Time to pain progression (TTPP) and time to first opiate use • Time to symptomatic skeletal-related events (SSRE) •Time to discontinuation of olaparib and abiraterone and time to discontinuation of abiraterone	The PROpel trial assessed additional important outcomes that contribute to the evidence base for olaparib plus abiraterone and may be used in the economic model.

	Final scope issued by NICE (8)	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Subgroups to be considered	If the evidence allows, the following subgroup will be considered: • homologous recombination repair (HRR) status including: -breast cancer gene (BRCA1 and BRCA2) -ataxia-telangiectasia mutated (ATM) gene.	Pre-specified subgroup analyses based on HRR mutation status (yes, no) are provided to demonstrate the consistent efficacy of olaparib plus abiraterone across patients with or without HRR mutations.	Enrolment into the PROpel trial was for an 'all comer' population and independent of HRR mutation status (14). The intention-to-treat population of the PROpel trial is aligned with the licensed indication (9). The trial population was stratified by type of distant metastases, and prior use of docetaxel in metastatic hormone sensitive stage of disease. Analyses in the HRR-mutated (HRRm) subgroup were pre-specified, but determination of HRRm status in the PROpel trial was conducted after randomisation had occurred. ~ 28% of enrolled participants were found to have HRR mutations (14), which is generalisable to the UK population. Pre-specified subgroup analyses based on HRRm status (yes, no) are provided only to demonstrate the consistent efficacy of olaparib in combination with abiraterone across patients irrespective of HRRm status. BRCA1, BRCA2 or ATM mutations are specific types of HRRm that are included in the HRRm subgroup but were not pre-specified for analysis in the PROpel trial. Participants with each of these mutations represent <10% of the enrolled population (14). Subgroup analyses by these specific mutations are not provided.
Special considerations including issues related to equity or equality	Not stated	Several potential equality issues relating to protected characteristics of age, sex and gender, race and religion require consideration: •Around 1 in 6 men develop prostate cancer and this disproportionately affects men of black ethnicity – around 1 in 4 black men will develop prostate cancer (1). •HRR mutations such as BRCA1 and BRCA2 increase the risk of developing prostate cancer and aggressive disease. Around 1 in 3-400 people in the population have a BRCA gene mutation, but people from Ashkenazi Jewish backgrounds have a 10-fold greater risk (1,16). •People who have a prostate and do not identify as male (e.g., people who have or are undergoing gender reassignment, those who identify as non-binary people) can develop prostate cancer (1). Olaparib plus abiraterone was designated as an innovative medicine by the granting of a Innovation Passport in June 2022 as part of the MHRA-administered Innovative Licensing and Access Pathway (11).	

B.1.2 Description of the technology being evaluated

B.1.2.1 Rationale for olaparib in combination with abiraterone

This appraisal relates to olaparib plus abiraterone in its full licensed indication for the treatment of adult patients with mCRPC in whom chemotherapy is not clinically indicated (8,9).

Olaparib was previously licensed as monotherapy for the treatment of adult patients with mCRPC and *BRCA 1* or 2 mutations (germline and/or somatic) who have progressed following prior therapy that included a new hormonal agent (NHA). When used in combination with abiraterone, olaparib exerts its anti-tumour effects in mCRPC irrespective of *BRCA1* or *2* or other homologous recombination repair (HRR) mutations.

Olaparib monotherapy is a potent inhibitor of human poly (ADP-ribose) polymerase enzymes (PARP-1, PARP-2, and PARP-3), which are required in the process of prostate cancer cell DNA repair. It inhibits the dissociation of PARP from DNA and so prevents subsequent access of base excision repair enzymes. In replicating cells this leads to formation of DNA double strand breaks (DSBs), which leads to prostate cancer cell death. In normal cells, the homologous recombination repair (HRR) pathway is effective at repairing DNA DSBs, but in prostate cancer cells carrying HRR mutations (such as BRCA1 or 2 mutations) these DNA DBSs cannot be repaired effectively (9,17).

Abiraterone is classed as a NHA and has a NICE recommendation as a first line treatment option in mCRPC before chemotherapy is indicated (TA387) (7) (and in later line use after chemotherapy treatment [TA259] (18)). It selectively inhibits the CYP17 enzyme which is required for androgen biosynthesis. As prostate cancer cells are dependent on androgens for survival and growth, this inhibition of androgen biosynthesis prevents proliferation of prostate cancer tumours (19).

Pre-clinical studies in prostate cancer models reported increased anti-tumour effect when PARP inhibitors and NHAs are administered together. In addition to its function in DNA repair, PARP-1 is involved in positive co-regulation of androgen receptor (AR) signalling, which leads to enhanced AR target gene suppression when PARP/AR signalling is co-inhibited. Other pre-clinical studies report that treatment with NHAs inhibits the transcription of some HRR genes, therefore, inducing HRR deficiency and increased sensitivity to PARP inhibitors via non-genetic mechanisms (9). The PROpel phase 3 randomised controlled trial discussed in section B.2, which demonstrates the efficacy of

olaparib plus abiraterone in patients who were enrolled irrespective of HRR mutation status (14), supports this theory.

Enzalutamide is also a NHA that inhibits androgen biosynthesis and has a NICE recommendation as a first line treatment option in mCRPC before chemotherapy is indicated (TA377) (6) (and in later line use after chemotherapy treatment [TA316] (20)). However, in contrast to abiraterone, enzalutamide is a strong inducer of CYP3A4 (21). As the hepatic cytochrome P450 enzymes CYP3A4 and CYP3A5 are predominantly responsible for the metabolic clearance of olaparib (9), co-administration of enzalutamide with olaparib could reduce plasma levels and therefore the potential efficacy of olaparib. Abiraterone was therefore added in combination with olaparib in the PROpel clinical trial due to its established safety profile and its reduced potential for interaction with olaparib compared with enzalutamide. Combining olaparib with abiraterone permits the use of their full monotherapy doses, thereby maximising the effectiveness of the combination (14,22).

B.1.2.2 Olaparib in combination with abiraterone is a much needed, innovative therapeutic approach

Olaparib in combination with abiraterone provides a step change in first line therapy for patients with mCRPC in whom chemotherapy is not clinically indicated:

- Olaparib plus abiraterone is the first combination therapy approach to be licensed for first line use in patients with mCRPC for whom chemotherapy is not clinically indicated. The combination was designated as innovative by the granting of an Innovation Passport in June 2022 as part of the MHRA-administered Innovative Licensing and Access Pathway (11).
- Current standard of care in the first line mCRPC setting when chemotherapy is not clinically indicated include NHAs (abiraterone or enzalutamide), which in their phase 3 registrational trials provided median progression-free survival (PFS) of approximately 16-20 months (12,13). In contrast, olaparib plus abiraterone provides a median PFS in the PROpel ITT population of 24.97 months at the last data cut, and so exceeds 2 years for the first time in this patient group (14) (see section B.2.6.1).
- This improved efficacy with olaparib plus abiraterone is observed irrespective of HRRm status (9,14) (see section B.2.7.1).
- The early use of olaparib in combination with abiraterone in mCRPC significantly delays disease progression, which can potentially delay the use of subsequent therapies that have diminishing efficacy and may improve overall survival (15,23) (see section B.2.6.2). Olaparib plus abiraterone therefore provides a much-needed new first-line therapeutic option to

improve outcomes in first line mCRPC patients (irrespective of mutation their status) for whom chemotherapy is not clinically indicated.

B.1.2.3 Further details of olaparib in combination with abiraterone

A summary of olaparib in combination with abiraterone, is provided in Table 2.

Table 2. Technology being evaluated

UK approved name and brand name	Olaparib (Lynparza®) in combination with abiraterone (and prednisone or prednisolone)
Mechanism of action	Olaparib is a potent PARP inhibitor, and abiraterone is a NHA that inhibits androgen biosynthesis. Pre-clinical studies in prostate cancer models reported an improved anti-tumour effect when PARP inhibitors and NHAs, are administered together. PARP is involved in positive co-regulation of androgen receptor (AR) signalling, which leads to enhanced AR target gene suppression when PARP/AR signalling is co-inhibited. Other pre-clinical studies reported that treatment with NHAs inhibits the transcription of some HRR genes, therefore, inducing HRR deficiency and increased sensitivity to PARP inhibitors via non-genetic mechanisms (9).
Marketing authorisation/CE mark status	Olaparib in combination with abiraterone was granted a UK marketing authorisation on 15th March 2023.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Olaparib 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 (9). A copy of the SmPC, which includes all other licensed indications for olaparib, is provided in Appendix C.
Method of administration and dosage	Olaparib is administered orally at a usual full recommended dose of 300 mg (2 × 150 mg tablets) twice daily with or without food, equivalent to a total daily dose of 600 mg (9). Abiraterone is administered orally at a usual full recommended dose of 1000mg (4 x 250mg tablets) once daily without food. In line with the abiraterone SmPC (9), all patients also take prednisone or prednisolone at a dose of 5mg twice daily. Treatment with a gonadotropin-releasing hormone (GnRH) analogue should be continued during treatment in all patients, or patients should have had prior bilateral orchiectomy (9). Treatment is continued until progression of disease or unacceptable toxicity.
Additional tests or investigations	As olaparib in combination with abiraterone is licensed for an all-comer population regardless of biomarker status, no specific genetic testing is required. There will be no further monitoring requirements beyond current clinical practice.
List price and average cost of a course of treatment	NHS indicative price: £2317.50: Olaparib (Lynparza) 150mg tablets x 56 (24). £190.00: Abiraterone acetate 500 mg tablets x 56 (24). £0.40: Prednisolone 5mg tablets x 12 (25). Average cost of a course of treatment (22.2 month) at list prices: Olaparib £51,448.50 + abiraterone £4,218.00 + prednisolone £8.88 = £55,675.38 total
Patient access scheme (if applicable)	A PAS provides a simple confidential discount on the list price of olaparib of [redacted]

B.1.3 Health condition and position of the technology in the treatment pathway

Prostate cancer is the most common cancer in men and is the most common cancer diagnosis in the UK having over taken breast cancer in 2018 (1,2). It mainly affects men over 50 years and the risk increases with age. Around 1 in 6 people born after 1960 will develop prostate cancer at some point in their lives (1); however, the lifetime risk is higher for people with a black-African family background (approximately 1 in 4), those with a family history of prostate cancer, and those who harbour specific homologous recombination repair mutations (HRRm), which include Breast Cancer gene 1 and 2 (*BRCA 1* and *BRCA 2*) mutations amongst others (1,16,26). Based on the population enrolled in the PROpel trial of olaparib plus abiraterone, approximately 28% of mCRPC patients harbour HRRm (14).

The National Prostate Cancer Audit (NPCA) 2020 reported there were 52,580 new diagnoses of prostate cancer in England and Wales in 2018/19 (27). In 2019/20 there were 45,885 newly diagnosed cases and in 2020/21 there were 32,426 newly diagnosed cases (28,29). The differences observed over these years are likely to reflect the impact of high-profile cases reported in the media in 2018/19, which increased the number of people presenting for diagnosis, followed by the impact of the COVID-19 pandemic in 2020/21, which reduced the number of people presenting for diagnosis. Nonetheless, an estimated 58,373 patients are anticipated will be diagnosed with prostate cancer in the UK in 2023 (3) and incidence rates are projected to rise such that by 2038-40 there could be as many as 85,100 new cases of prostate cancer each year (1).

Prostate cancer is amenable to curative therapy if detected early; however, advanced stages are incurable. The prognosis for people diagnosed with prostate cancer is therefore dependent on the stage of the disease at diagnosis (1) and its subsequent progression. NICE Clinical Guideline 131 (26) refers to the stages of prostate cancer as: localised disease (where the cancer is confined to the prostate gland); locally advanced disease (where the cancer has spread to adjacent tissues); or metastatic disease (where the cancer has spread to distant sites in the body, most often into bones but also lymph nodes, the liver, and lungs). Most cases are diagnosed with localised or locally advanced disease, and in these people 5-year survival rates are 100% and 96%, respectively. However, NPCA data indicate that 13-17% of people diagnosed between 2018-21 presented with metastatic disease (27–29). In these people treatment is given with palliative rather than curative intent, and the 5-year survival rate drops dramatically to 49% (1).

B.1.3.1 Metastatic castration resistant prostate cancer (mCRPC)

Prostate cancer cells are typically dependent on androgens for survival and growth. Therefore, androgen deprivation therapy (ADT) with luteinising hormone releasing hormone analogues or orchidectomy is usually initially effective at controlling metastatic disease. However, over time there is typically a loss of response to ADT, leading to disease progression. A further sub-categorisation of disease is therefore used according to whether the disease is currently sensitive to ADT, termed hormone-sensitive prostate cancer (HSPC) or is no longer responsive to ADT, termed castration resistant prostate cancer (CRPC, also known as hormone-relapsed or hormone-refractory prostate cancer) (26).

Metastatic disease that no longer responds to ADT is referred to as mCRPC. This is a more aggressive form of prostate cancer, which progresses rapidly and requires additional therapies to control the disease (30). Of all incidences of prostate cancer, 2.22% of patients will develop mCRPC (4). Median overall survival of people with mCRPC with current first line treatments is reported to be 19 to 36 months in clinical trials (12,13,30,31); however, survival outcomes in real world settings may be less (32). There is a significant drop off in patients receiving subsequent treatments and response to them diminishes. Data suggests only 50% of patients receive a second-line treatment in the mCRPC setting (32).

In addition to poor survival, people with metastatic disease often experience pain, fatigue and symptoms specific to the site of metastases, which can impact on mobility, sleep, and ability to perform normal activities of daily living (33–35). Bone metastases, which occur in over 90% of mCRPC cases (36), can lead to intractable pain and skeletal-related events (SREs) such as fractures and spinal cord compression, which severely impact functioning (37) and health-related quality of life (HRQoL) (38). But pain resulting from extra-skeletal metastasis, locoregional disease progression or treatment-associated adverse effects can also contribute to deteriorating HRQoL. Collectively, mCRPC has a profound impact on patient HRQoL and that of their caregivers and family (39,40).

A key aim of therapy in people with mCRPC is, therefore, to prolong survival and delay disease progression, whilst limiting treatment-related adverse effects to preserve HRQoL. Although there are several treatments for mCRPC, not all are available or appropriate for all patients. There remains a clear unmet need for further treatment options in the first line setting to achieve these aims.

B.1.3.2 Treatment Pathway

Treatment of prostate cancer is determined by the stage of the disease and its progression, prior therapies received, and individual patient characteristics and preferences (26). Treatment options based on NICE guidance are summarised below. Of note, the presence of HRR mutations, which includes mutations in BRCA1/2, ataxia-telangiectasia mutated (ATM) and a range of other genes in prostate cancer cells is associated with more aggressive disease and poorer prognosis with current standard of care therapy compared to those without such mutations (41–44). Testing for specific HRR mutations is included in the NHS Genomic Test Directory, although clinical expert opinion indicates that testing for such mutations is not routinely conducted and is variable across the UK (45). At the time of writing this submission, olaparib monotherapy is the only technology recommended by NICE for use in mCRPC patients based on BRCA1 or BRCA2 mutations (when a patient has progressed after a NHA such as abiraterone or enzalutamide) (46).

Localised or locally advanced disease therapy

As noted in the scope for this appraisal (8), treatment options for localised and locally advanced prostate cancer include active surveillance or radical treatment (surgery and radiotherapy) and ADT using orchidectomy or hormonal treatments such as luteinising hormone-releasing hormone agonists (e.g., goserelin) and antagonists (e.g., degarelix), and androgen receptor inhibitors (e.g., bicalutamide) (26).

Non-metastatic CRPC therapy

For patients diagnosed with non-metastatic CRPC (nmCRPC), treatment options include ADT alone, or in patients at high risk of developing metastatic disease the new hormonal agents (NHAs) apalutamide plus ADT per NICE TA740 (47) or darolutamide plus ADT per NICE TA660 (48).

Metastatic HSPC therapy

For newly diagnosed metastatic prostate cancer cases, docetaxel (chemotherapy) can be offered within 12 weeks of starting ADT (26). Enzalutamide (a NHA) plus ADT is recommended as an option for metastatic HSPC (mHSPC) per NICE TA712 (49). Interim guidance from NHS England in response to the COVID-19 pandemic allowed enzalutamide (or abiraterone when enzalutamide was not tolerated) plus ADT as an option instead of docetaxel in newly diagnosed metastatic disease to reduce toxicity and potential for hospital administration (50). NPCA data noted a rapid switch from docetaxel

to enzalutamide in this setting during this time, although the increasing use of enzalutamide has now plateaued (28,29).

mCRPC therapy

For patients with mCRPC, docetaxel is recommended in those with Karnofsky performance-status score ≥60%, per NICE TA101 (5). Enzalutamide and abiraterone (in combination with prednisone or prednisolone) are recommended in people with mCRPC who have no or mild symptoms after ADT has failed and before chemotherapy is indicated, per NICE TA377 (6) and NICE TA387 (7). Of note, retreatment with enzalutamide or abiraterone in patients who have previously received either agent at an earlier stage or line of therapy is not recommended in European Society for Medical Oncology (ESMO) prostate cancer guidelines (51) and is not offered in the NHS (45).

Following disease progression on docetaxel, treatment options include abiraterone (in combination with prednisone or prednisolone) (TA259) (18) or enzalutamide (TA316) (20) if not previously received, cabazitaxel (chemotherapy) (in combination with prednisone or prednisolone) (TA391) (52), or radium-223 dichloride in patients with symptomatic bone metastases and no known visceral metastases (TA412) (53).

B.1.3.3 Place in therapy of olaparib in combination with abiraterone

The licensed indication for olaparib plus abiraterone is for the treatment of adult patients with mCRPC in whom chemotherapy is not clinically indicated (9). The proposed positioning of olaparib plus abiraterone on the treatment pathway, in line with its licensed indication and the PROpel trial population, is as first line therapy in adult patients with mCRPC in whom chemotherapy is not clinically indicated.

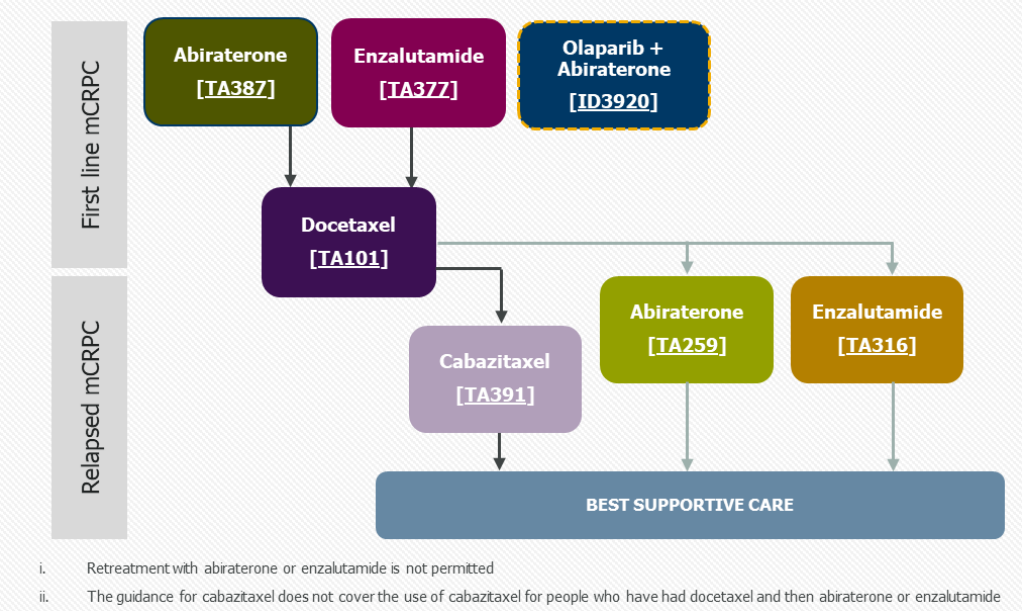
Based on the treatments recommended by NICE in mCRPC (see section B.1.3.2 above), and in line with the NICE scope for this appraisal (8), only enzalutamide and abiraterone are relevant comparators; olaparib plus abiraterone is only licensed for use in patients for whom chemotherapy is not clinically indicated, which excludes docetaxel and cabazitaxel as relevant comparators. Radium-233 dichloride is also available for treatment of mCRPC; however, clinical experts indicate it is recommended for use following failure of docetaxel primarily for palliation and control of symptomatic bone metastases.

Enzalutamide and abiraterone may be used as first line mCRPC options before docetaxel chemotherapy (per NICE TA377 and NICE TA387) (6,7) or, if not previously received, in the relapsed

mCRPC setting following docetaxel chemotherapy (per NICE TA259 and NICE TA316) (18,20) (see Figure 1). Data on Blueteq initiations of enzalutamide and abiraterone in the mCRPC setting in 2021-22 indicates an increasing majority (>70%) of use of these NHAs is as first line treatments (10). Given the clinically meaningful improvement in progression-free survival (PFS) observed with olaparib plus abiraterone demonstrated against abiraterone in the PROpel trial (14) (see section B.2.6.1), olaparib plus abiraterone is anticipated to displace NHAs as a first line therapy in mCRPC. This aligns with UK clinical expert opinion on its anticipated use in clinical practice (see section B.3.14).

The proposed positioning of olaparib in combination with abiraterone in the mCRPC treatment pathway is summarised in Figure 1.

Figure 1. Positioning of olaparib in combination with abiraterone in the mCRPC treatment pathway



Although olaparib is licensed for use in combination with abiraterone and was compared against abiraterone in the PROpel trial (14), both NHA treatments enzalutamide and abiraterone are recommended in the same first line position in the mCRPC treatment pathway. ESMO guidelines do not differentiate between enzalutamide and abiraterone based on efficacy (51) and UK clinical experts consider these to have equivalent efficacy, with the choice based on relevant comorbidities or clinician preference (see section B.3.14). Both enzalutamide and abiraterone in the first line setting are the relevant comparators for olaparib plus abiraterone, per the NICE scope for this appraisal (8). However, Blueteq requests in 2022 for their use in this setting indicate that enzalutamide accounts for twice as many initiations as abiraterone (67% vs 33%, respectively). Despite a 2-fold increase in total initiations of these NHAs in this setting since 2020, abiraterone initiations have declined by 30% over the same

period (10). Based on its far greater and growing use, enzalutamide is therefore considered to be the primary comparator for olaparib with abiraterone, with abiraterone considered as a secondary comparator.

B.1.4 Equality considerations

Several potential equality considerations exist relating to protected characteristics of age, sex and gender, race and religion:

- Around 1 in 6 men will develop prostate cancer (1).
- The risk of prostate cancer increases with age (1).
- Prostate cancer disproportionately affects men of black ethnicity – around 1 in 4 black men will develop prostate cancer (1).
- HRR mutations such as *BRCA1* or *2* mutations increase the risk of developing prostate cancer and, with existing standard of care therapies, are associated with more aggressive disease. Around 1 in 3-400 people in the population have a BRCA gene mutation, but people from Ashkenazi Jewish backgrounds have a 10-fold greater risk (1,16). The PROpel trial demonstrates olaparib plus abiraterone provides clinical benefit over current standard of care therapy with abiraterone for patients with or without HRRm. In providing this improved efficacy in all patients, olaparib in combination with abiraterone mitigates the inequity in treatment outcomes observed with current standard of care NHA therapy in those patients who unfortunately harbour HRR mutations.
- People who have a prostate and do not identify as men (e.g., people who have or are undergoing gender reassignment, those who identify as non-binary people) can develop prostate cancer (1).
- In patients for whom chemotherapy is not clinically indicated, olaparib plus abiraterone provides a more effective oral therapy option than would otherwise be available to them.

B.2 Clinical effectiveness

Summary of efficacy and safety data

- The efficacy and safety of olaparib plus abiraterone was determined in the phase 3 PROpel randomised controlled trial (RCT) (14).
- PROpel was a robust phase 3 trial, conducted in 796 mCRPC patients meeting the subsequent licensed indication for olaparib plus abiraterone (9). It was at low risk of bias and compared olaparib plus abiraterone against placebo plus abiraterone, a NICE-recommended standard of care first line therapy in patients with mCRPC who are not clinically indicated to receive chemotherapy.
- Olaparib plus abiraterone extended median radiological progression-free survival (rPFS, the primary endpoint) by approximately 8.2 months compared with placebo plus abiraterone (24.8 months vs 16.6 months, respectively; HR 0.66; 95% CI: 0.54–0.81; $p < 0.0001$), leading to a rPFS with olaparib plus abiraterone that exceeds 2 years for the first time in this patient population (14).
- rPFS improved across pre-specified subgroups, including in patients with homologous recombination repair mutations (HRRm) (HR 0.50; 95% CI: 0.34– 0.73) and those without (HR 0.76; 95% CI, 0.60 to 0.97) (14).
- Overall survival (OS) was a key secondary endpoint. Due to the additional benefit over placebo plus abiraterone, OS data for olaparib plus abiraterone were not fully mature at the time of the final OS analysis. However, at each data cut there was a trend towards an improvement in OS with olaparib plus abiraterone, and by the final analysis there was over a 7-month improvement in median OS compared to placebo plus abiraterone (42.1 vs 34.7 months, respectively; HR 0.81; 95% CI: 0.67–1.00; $p = 0.0544$) (15).
- These data are supported by positive trends towards median time to first subsequent therapy (24.6 vs 19.4 months; HR, 0.76 [95% CI,0.64-0.90]; nominal $p = 0.0025$), and second progression-free survival (PFS2; HR 0.76, 95% CI, 0.59–0.99; nominal $p = 0.0534$) (15), which indicate long-term benefit with first line olaparib plus abiraterone and its potential to delay use of subsequent line therapies that have diminishing efficacy.
- Adverse events with olaparib plus abiraterone were consistent with the known safety profiles for olaparib and abiraterone individually. No detriment in health-related quality of life was observed with the addition of olaparib to abiraterone.
- Due to data challenges, it is difficult to conduct a robust indirect treatment comparison of olaparib plus abiraterone vs enzalutamide; however, real-world data, clinical expert opinion and an exploratory network meta-analysis of OS data all indicate that abiraterone and enzalutamide are of equivalent efficacy in terms of the key outcomes of rPFS and OS. On this basis, the relative treatment effects of olaparib plus abiraterone vs abiraterone directly demonstrated in the PROpel trial are a reasonable proxy for the relative treatment effects of olaparib plus abiraterone versus enzalutamide.

B.2.1 Identification and selection of relevant studies

A systematic literature review of randomised controlled trials (RCTs) of first line therapies for mCRPC identified studies published upto December 2022 (see Appendix D). This confirmed the PROpel phase 3, double-blind RCT of olaparib plus abiraterone vs abiraterone (NCT03732820) (14) as the only

relevant RCT informing its proposed positioning for this appraisal. The marketing authorisation for olaparib plus abiraterone was also supported by Study 8, a phase 2, double-blind RCT of olaparib plus abiraterone in patients who had received up to 2 lines of prior chemotherapy in the mCRPC setting (54). As Study 8 is not aligned with the proposed positioning of olaparib plus abiraterone for this appraisal and does not inform the efficacy or safety of olaparib plus abiraterone in the economic model, it is not further discussed in this submission.

The systematic review identified the phase 3 trials of the comparators listed in the scope for this appraisal: PREVAIL (13) and PREVAIL Asia (55) trials of enzalutamide vs placebo and the COU-AA-302 trial of abiraterone (plus prednisone) vs prednisone (12). The PROpel trial provides the only direct comparative data for olaparib plus abiraterone against abiraterone; there are no direct comparative data for olaparib plus abiraterone vs enzalutamide.

B.2.2 List of relevant clinical effectiveness evidence

The phase 3 PROpel study providing the clinical evidence for olaparib plus abiraterone in its proposed positioning is summarised in Table 3.

Table 3. Clinical effectiveness evidence

Study	PROpel (Clarke et al 2022) (14)
Study design	Randomised (1:1), double-blind, placebo-controlled, multicentre, phase 3 clinical trial
Population	Patients with mCRPC who are treatment-naive in the metastatic castration-resistant setting (i.e., have not received any cytotoxic chemotherapy, NHAs or other systemic treatment in the mCRPC setting)
Intervention(s)	Olaparib 300 mg twice daily plus abiraterone 1000 mg once daily and prednisone or prednisolone 5 mg twice daily
Comparator(s)	Placebo twice daily plus abiraterone 1000 mg once daily and prednisone or prednisolone 5 mg twice daily
Indicate if study supports application for marketing authorisation	Yes – PROpel is the pivotal RCT supporting the marketing authorisation for Olaparib plus abiraterone in mCRPC
Indicate if study used in the economic model	Yes – PROpel provides the primary data source for the clinical efficacy and incidence of adverse events with olaparib plus abiraterone and abiraterone (plus prednisone or prednisolone), and health-related quality of life data
Rationale if study not used in model	N/A
Reported outcomes specified in the decision problem	• **Overall survival** • **Radiological progression-free survival** • Response rate • **Adverse effects of treatment** • **Health-related quality of life**
All other reported outcomes	• Time to first subsequent therapy or death (TFST) • Time to second progression or death (PFS2) • Time to pain progression (TTPP) and time to first opiate use •**Skeletal-related events (SSRE)**

mCRPC, metastatic castration-resistant prostate cancer; NHA, new hormonal agents
Bold outcomes included in the economic model

B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

A summary of the PROpel trial methodology is provided in Table 4.

Table 4. Summary of PROpel trial methodology

Trial number (acronym)	NCT03732820 (PROpel) (14,56)
Location	International (17 countries excluding separate cohort from China). Percentage of participants enrolled: 24.5% Asia, 44.0% in Europe, 31.5% in North and South America). 49 (6.1%) patients were enrolled in the UK.
Trial design	Randomised (1:1), double-blind, placebo-controlled, multicentre, phase 3 clinical trial
Eligibility criteria for participants	Adult patients with mCRPC who are treatment-naïve in the mCRPC setting. ADT and first-generation antiandrogen agents permitted with a 4-week washout period, but other systemic treatment in the mCRPC setting was not allowed. Prior docetaxel during neoadjuvant/ adjuvant treatment for localised prostate cancer and mHSPC was permitted.
Settings	Hospital outpatient
Trial drugs	Intervention: Olaparib 300 mg twice daily plus abiraterone 1000 mg once daily and prednisone or prednisolone 5 mg twice daily, all administered orally (n=399) Comparator: Placebo twice daily plus abiraterone 1000 mg once daily and prednisone or prednisolone 5 mg twice daily, all administered orally (n=397)
Primary outcomes (including scoring methods and timings of assessments)	rPFS, defined as the time from randomisation 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. Primary analysis is based on investigator assessed rPFS. Sensitivity analysis conducted using BICR assessment.
Other outcomes used in the economic model/specified in the scope	Outcomes used in economic model: • OS, defined as the time from randomisation to death from any cause. • AEs and SAEs, physical examination findings, vital signs (including BP and pulse rate), ECG findings and laboratory test results (including clinical chemistry and haematology parameters). Incidence of grade ≥3 AEs used in model. • Time to an SSRE: the time from randomisation to the first SSRE. An SSRE is defined as use of radiation therapy to bone in order to prevent or relieve skeletal complications, occurrence of new symptomatic pathological bone fractures (vertebral or non-vertebral, resulting from minimal or no trauma), occurrence of radiologically confirmed spinal cord compression or a tumour-related orthopaedic surgical intervention. Applied in the model as a probability of experiencing an SSRE for those experiencing disease progression. • Time to discontinuation of olaparib and abiraterone and time to discontinuation of abiraterone. Used in model. • HRQoL assessed by EQ-5D-5L (mapped to EQ-5D-3L) . Other outcomes specified in scope: • ORR, defined as the proportion of patients with measurable soft tissue disease at baseline who have a tumour response (CR and PR) using overall radiological response assessed by RECIST 1.1 (soft tissue) and PCWG-3 criteria (bone), by investigator and by BICR assessment (Exploratory endpoint). • HRQoL assessed by FACT-P and BPI-SF disease specific instruments. Other relevant outcomes: • TFST, defined as the time from randomisation to: 1) the start of the first subsequent anticancer therapy or 2) death from any cause. • TTPP, defined as time from randomisation to pain progression based on the BPI-SF Item 3 'worst pain in 24 hours and opiate analgesic use (AQA score). PFS2, defined as time from randomisation to second progression on next-line anticancer therapy by investigator assessment of radiological progression, clinical symptomatic progression, PSA progression, or death.

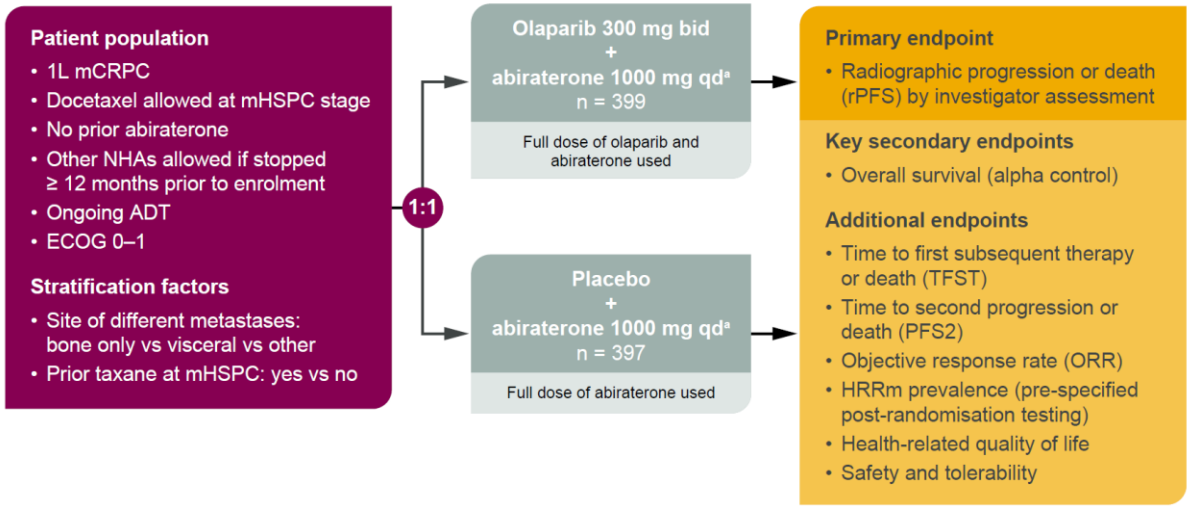
Pre-planned subgroups	Subgroups by stratification factors: • Metastases (bone only, visceral, or other) • Docetaxel treatment at mHSPC stage (yes or no) Pre-specified exploratory subgroup analyses: • HRRm status (HRRm, non-HRRm, unknown) based on ctDNA-based test and tissue test • ECOG performance status at baseline (0 or 1) • Age at randomisation (<65, ≥65) • Region (Asia, Europe, North and South America) • Race (White, Black/African-American, Asian, Other) Baseline PSA (above/below median baseline PSA of the patients across both treatment groups)

ADT, androgen deprivation therapy; AE, adverse event; BICR, blinded independent central review; AQA, Analgesic quantification algorithm; BPI-SF, brief pain inventory-short form; CR, complete response; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; EQ-5D-5L, Euroqol 5 dimension, 5 level instrument; FACT-P, Functional Assessment of Cancer Therapy – Prostate; HRQoL, health-related quality of life; HRRm, homologous recombination repair gene-mutated; mCRPC, metastatic castration resistant prostate cancer; mHSPC, metastatic hormone sensitive prostate cancer; ORR, objective response rate; OS, overall survival; PCWG-3, Prostate Cancer Working Group 3; PFS2, second progression free survival; PR, partial response; PSA, prostate specific antigen; RECIST, response evaluation criteria in solid tumours; rPFS, radiological progression free survival; SAE, serious adverse event; SSRE, symptomatic skeletal-related event; TFST, time to first subsequent therapy; TTPP, time to pain progression, with pain progression defined as: 1) for patients who were asymptomatic at baseline, a ≥ 2 point change from baseline in the average (4-7 days) BPI-SF Item 3 score observed at 2 consecutive evaluations (with ≥ 2 weeks between the end of the initial visit and start of the subsequent visit) OR initiation of opioid use for pain; 2) for patients who are symptomatic at baseline (average BPI-SF Item 3 score > 0 and/or currently taking opioids), a ≥ 2 point change from baseline in the average BPI-SF Item 3 score observed at 2 consecutive visits and average worst pain score ≥ 4, and no decrease in average opioid use (≥ 1-point decrease in AQA score from starting value of 2 or higher) OR any increase in opioid use (eg, 1-point change in AQA score) at 2 consecutive follow-up visits (with ≥ 2 weeks between the end of initial visit and start of subsequent visit). Any patient who had > 2 consecutive visits that were not evaluable for pain progression was to be censored at the last evaluable assessment.

B.2.3.1 PROpel Trial design

PROpel was a randomised, double-blind, placebo-controlled, multicentre phase 3 study that assessed the efficacy and safety of the combination of olaparib and abiraterone compared with placebo and abiraterone in patients with mCRPC who are previously untreated for mCRPC (i.e., in first line treatment). The trial design is summarised in Figure 2.

Figure 2. PROpel trial design



[a]In combination with prednisone or prednisolone 5 mg twice daily.
First patient randomised: November 2018. Last patient randomised: March 2020.
1L, first line; ADT, androgen deprivation therapy; b.i.d., twice daily; ECOG, Eastern Cooperative Oncology Group; HRRm, homologous recombination repair pathway gene mutation; mCRPC, metastatic castration-resistant prostate cancer; mHSPC, metastatic hormone-sensitive prostate cancer; NHA, new hormonal agent; q.d., once daily; PFS2, second progression-free survival; rPFS, radiological progression-free survival; TFST, time to first subsequent therapy.
Source: Clarke N. ASCO Oral Presentation Slides 2022 (15)

B.2.3.2 Eligibility criteria

Key inclusion and exclusion criteria for PROpel are summarised in Table 5. Following enrolment and randomisation, all patients underwent prospective assessment of tumour tissue and blood samples to assess for HRR gene mutations to enable exploratory HRR status subgroup analysis on outcomes (14).

Table 5. Key inclusion and exclusion criteria for the PROpel study

Inclusion criteria	Exclusion criteria

• Men aged ≥ 18 years (or ≥ 19 years of age in South Korea)
• Histologically or cytologically confirmed prostate adenocarcinoma
• First line mCRPC
  ○ Patients must be treatment naïve at mCRPC stage: patients should not have received any cytotoxic chemotherapy, NHAs, or other systemic treatment (approved drugs or experimental compounds) in the mCRPC setting; ADT is an exception
  ○ Docetaxel treatment is allowed during neoadjuvant/adjuvant treatment for localised prostate cancer and at mHSPC stage as long as no signs of failure or disease progression occurred during or immediately after such treatment
• Metastatic status defined as ≥ 1 documented metastatic lesion on either a bone or a CT/MRI scan
• ECOG performance status 0-1
• Eligible for abiraterone treatment with documented evidence of progressive disease
• Life expectancy of at least 6 months
• Availability of tumour tissue sample prior to or at screening to enable HRRm status to be determined
	• Any previous treatment with a PARP inhibitor, receipt of any systematic chemotherapy or radiotherapy (except for palliative care)
	• Any previous exposure to a CYP17 inhibitor (e.g., abiraterone or orteronel)
	• Concomitant use of a known strong or moderate CYP3A inhibitor; the required washout period prior to starting treatment is 2 weeks
	• Concomitant use of known strong or moderate CYP3A inducers; the required washout period prior to starting study treatment is 5 weeks for phenobarbital and enzalutamide and 3 weeks for other agents
	• Previous allogenic bone marrow transplant or dUCBT
	• Patients with brain metastases
	• Patients with spinal cord compression
	• Patients with MDS or AML or other malignancy (including MDS and MGUS) within the last 5 years, except for basal cell carcinoma of the skin and squamous cell carcinoma of the skin that has undergone potentially curative therapy

ADT, androgen deprivation therapy; AML, acute myeloid leukaemia; CT, computed tomography; CYP17, 17α-hydroxylase/17,20-lyase; CYP3A, cytochrome P450 3A; dUCBT, double umbilical cord blood transplantation; mCRPC, metastatic castration-resistant prostate cancer MDS, myelodysplastic syndromes; MGUS, monoclonal gammopathy of undetermined significance; mHSPC, metastatic hormone-sensitive prostate cancer; MRI, magnetic resonance imaging; NHA, new hormonal agent; PARP, poly(adenosine diphosphate)-ribose polymerase.
Source: PROpel CSR, Dec 2021(56)

B.2.3.3 Settings and location

PROpel was an international study, conducted in 17 countries (excluding China, which will be assessed as a separate cohort and not discussed further). The proportion of patients recruited from each region were: 24.5% from Asia, 44.0% from Europe, 31.5% from North and South America). Forty-nine (6.1%) patients were enrolled in the UK. As patients enrolled in the trial had mCRPC, the trial was conducted in the hospital setting, with therapy administered orally at home (14).

B.2.3.4 Trial drugs and concomitant medications

Eligible patients were randomly assigned (1:1) to abiraterone (1000mg once daily) plus either olaparib (300mg twice daily) or placebo. All patients received prednisone or prednisolone (5mg twice daily) per the abiraterone label requirement. Study treatment continued until objective radiological progressive disease as assessed by the investigator (using Response Evaluation Criteria in Solid Tumours [RECIST] 1.115 for soft tissue lesions and Prostate Cancer Working Group-316 [PCWG-3] criteria for bone lesions), unacceptable toxicity, or withdrawal of consent. Following objective disease progression, further treatment was at investigator discretion. Crossover from placebo to receive olaparib plus abiraterone was not allowed (14). Prohibited or restricted concomitant medications are as listed in Table 5.

B.2.3.5 Outcomes used in the economic model or specified in scope

All outcomes specified in the scope were assessed in the PROpel trial and are reported in this submission. See Table 4 for their definitions.

The primary endpoint in PROpel was radiological PFS (rPFS) as assessed by the investigator using RECIST 1.1 (soft tissue) and the Prostate Cancer Clinical Trials Working Group 3 (PCWG-3) criteria (bone) for all randomised patients (i.e., the intention-to-treat [ITT] population). The key secondary endpoint was overall survival (OS) (14,56). These outcomes are used to model the efficacy of olaparib plus abiraterone and the secondary economic comparator abiraterone in the economic model (see section B.3.). rPFS and OS observed with abiraterone in the PROpel trial is also used in the indirect treatment comparison to model the comparative efficacy of the primary economic comparator enzalutamide (see section B.2.9). Other outcomes used in the economic model include the incidence of grade 3 adverse events occurring in ≥5% of patients (see section B.2.10), time to symptomatic skeletal-related events (SSRE) (see section B.2.6.3.2) and health-related quality of life (HRQoL) assessed via the EQ-5D-5L instrument (see section B.2.6.5.3). Time to discontinuation of olaparib and abiraterone were not specified outcomes in the trial but are used to determine time on treatment with each agent in the model (see section B.3).

Additional outcomes assessed in PROpel but not specified in the scope or economic model included PFS2 (defined as the time from randomisation to second progression on next-line anticancer therapy by investigator assessment of radiological progression, clinical symptomatic progression, PSA progression, or death) (14). This was a secondary endpoint in PROpel and complements PFS and OS in settings where patients might experience prolonged PFS or post-progression survival following

multiple subsequent lines of therapies. Prolongation of PFS2 can demonstrate a potential benefit of study treatment beyond the initial disease progression. Other secondary endpoints in PROpel included time to pain progression (TTPP), and HRQoL assessed using validated, disease specific Brief Pain Inventory-Short Form (BPI-SF) and Functional Assessment of Cancer Therapy (FACT) – Prostate Cancer (FACT-P) questionnaire (14).

B.2.3.6 Baseline characteristics of PROpel trial participants

Baseline characteristics of participants in the PROpel trial were well balanced between treatment arms (14,56) (Table 6), and were generally in line with international registry data on first line mCRPC patients in real-world clinical practice (32,57). UK clinical expert opinion obtained via interviews with six oncologists indicates that the trial participants were broadly representative of patients anticipated to be eligible to receive olaparib plus abiraterone in clinical practice in the UK (see section B.3.14).

Patients were stratified by metastases (bone only vs visceral vs other) and docetaxel treatment at mHSPC stage (yes vs no) (14,56). Bone was the most common site for metastases. A quarter of patients in both trial arms had prior experience with docetaxel, and one patient in the olaparib arm had experience of prior use of NHA (enzalutamide) more than 12 months before enrolment. These prior therapies were all administered in the non-mCRPC setting. The proportion of patients with a HRRm was similar between treatment arms (olaparib plus abiraterone, 27.8%; placebo plus abiraterone, 29.0%) (14,56), and was consistent with what has been observed in real-world data and previous datasets, including the PROfound study of olaparib conducted in patients with previously treated mCRPC (58). UK clinicians have confirmed that the proportion of patients with HRRm in PROpel is representative of what they would expect to see in clinical practice (see section B.3.14). The most common HRRm was in the *BRCA2* gene, which occurred in fewer than 10% of participants.

Table 6. Baseline characteristics of PROpel trial participants

Baseline characteristic	Olaparib + Abiraterone (n = 399)	Placebo + Abiraterone (n = 397)
Age, years, median (range)	69 (43–91)	70 (46–88)
< 65 years, n (%)	[redacted]	[redacted]
≥ 65 years, n (%)	[redacted]	[redacted]
Gleason score ≥8, n (%)	265 (66.4)	258 (65.0)
Median PSA, ug/L (min–max)	17.90 (0.07–1869.5)	16.81 (0.01–1888.0)
Median time from mCRPC to randomisation (range), months	[redacted]	[redacted]
Prior treatment with second-generation antiandrogen agents (NHA), n (%)		
Yes (Enzalutamide)	1 (0.3)	0
Prior docetaxel treatment, n (%)		

Yes	97 (24.3)	98 (24.7)
At mHSPC stage	90 (22.6)	89 (22.4)
ECOG performance status, n (%)		
0	286 (71.7)	272 (68.5)
1	112 (28.1)	124 (31.2)
HRRm status[c], n (%)		
HRRm	111 (27.8)	115 (29.0)
BRCA1	9 (2.3)	3 (0.8)
BRCA2	38 (9.5)	35 (8.8)
Non-HRRm	279 (69.9)	273 (68.8)
HRRm unknown	9 (2.3)	9 (2.3)
Baseline pain score[a] (BPI-SF Item 3 worst pain score), n (%)		
0 (no pain)	133 (33.3)	137 (34.5)
> 0 - < 4 (mild pain)	151 (37.8)	173 (43.6)
4 - < 6 (moderate pain)	53 (13.3)	36 (9.1)
≥ 6 (severe pain)	32 (8.0)	28 (7.1)
Missing	30 (7.5)	23 (5.8)
Site of metastases, n (%)		
Bone	349 (87.5)	339 (85.4)
Distant lymph nodes	113 (33.3)	119 (30.0)
Locoregional lymph nodes	82 (20.6)	89 (22.4)
Lung/Respiratory	40 (10.0)	42 (10.6)
Liver	15 (3.8)	18 (4.5)

Stratification factors at randomisation

Site of distant metastases	Docetaxel treatment at mHSPC stage	Number of patients, n (%)	
		Olaparib + Abiraterone (n = 399)	Placebo + Abiraterone (n = 397)
As randomised (IWRS)			
Bone only	Yes	[redacted]	[redacted]
	No	[redacted]	[redacted]
Visceral	Yes	[redacted]	[redacted]
	No	[redacted]	[redacted]
Other	Yes	[redacted]	[redacted]
	No	[redacted]	[redacted]

[a]Patients with symptomatic pain at baseline: BPI-SF item #3 score ≥4 and/or opiate use at baseline
[b]As long as no signs of failure or disease progression occurred during or immediately after docetaxel treatment.
[c]The HRRm status of patients in PROpel was determined retrospectively using results from tumour tissue and plasma ctDNA HRRm tests. Patients were classified as HRRm if (one or more) HRR gene mutation was detected by either test; patients were classified as non-HRRm patients if no HRR gene mutation was detected by either test; patients were classified as unknown HRRm if no valid HRR test result from either test was achieved. Fourteen HRR genes were evaluated (*BRCA1, BRCA2, ATM, BRIP1, PALB2, RAD51C, BARD1, CDK12, CHEK1, CHEK2, FANCL, RAD51B, RAD51D, RAD54L*)
BPI-SF, Brief Pain Inventory – Short Form; ctDNA, circulating tumour DNA; ECOG, Eastern Cooperative Oncology Group; eCRF, electronic case report form; HRRm, homologous recombination repair pathway gene mutation; IQR, interquartile range; IWRS, Interactive Web Response System; mCRPC, metastatic castration-resistant prostate cancer; mHSPC, metastatic hormone-sensitive prostate cancer; PSA, prostate-specific antigen.
Source: Clarke et al, 2022 (14); PROpel CSR, Dec 2021(56)

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

B.2.4.1 Statistical analyses

The primary objective of the PROpel trial was to determine the efficacy of the combination of olaparib and abiraterone vs placebo and abiraterone by investigator assessment of rPFS in patients with mCRPC who had received no prior cytotoxic chemotherapy or NHA at the mCRPC stage (14). The primary endpoint of rPFS was formally analysed at two planned data cuts: first data cut (DCO1 – Primary PFS analysis; 30 July 2021) and second data cut (DCO2 – Final PFS analysis; 14 March 2022). OS, the key secondary endpoint, was analysed at three planned data cuts (DCO1 and DCO2 - interim OS analyses; DCO3 - Final OS analysis; 12 October 2022) (56). The relevant power calculations for each of these analyses is summarised in Table 7.

Table 7. Planned data cuts and power calculations

Data cut	Analysis
DCO1	**Primary rPFS analysis and interim OS analysis (30 July 2021)** At DCO1, the PROpel study had 94.1% power to detect a statistically significant difference in the primary endpoint at a one-sided alpha level of 0.014 based on a planned 379 rPFS events (47.6% maturity) occurring in 796 patients who were randomised 1:1 to receive olaparib or placebo with abiraterone, assuming a hazard ratio for progression or death of 0.68
DCO2	**Final rPFS analysis and interim OS analysis (14 March 2022)** At DCO2, the PROpel study had 98.2% power to detect a statistically significant difference in rPFS at a one-sided alpha level of 0.021 based on a planned 453 rPFS events (56.9% maturity) occurring in 796 patients who were randomised 1:1 to receive olaparib or placebo with abiraterone
DCO3	**Final OS analysis (12 October 2022)** DCO3 was planned to occur after 360 OS events, approximately 48 months after the first patient was randomised, when a minimum follow-up of 30 months was expected. The smallest treatment difference that would be statistically significant at the final analysis was an HR of 0.81

DCO1/2/3, data cut-off 1/2/3; HR, hazard ratio; OS, overall survival; rPFS, radiological progression-free survival. Sources: PROpel CSR, Dec 2021(56); PROpel CSR Addendum 1 (DCO2)(59); PROpel CSR Addendum2 (DCO3)(23)

Efficacy was analysed for the Full Analysis Set (FAS), which is defined as all patients randomised to receive olaparib or placebo with abiraterone irrespective of whether treatment was received (i.e., the intention-to-treat [ITT] population). The exception was response rates, which were analysed in the FAS in patients who had measurable disease at baseline as per RECIST 1.1 criteria (evaluable for response set, EFR). Safety was analysed in the Safety Analyses Set (SAS), defined as all patients who received any amount of abiraterone, olaparib, or placebo. Patients who received at least one dose of olaparib were included in the abiraterone and olaparib arm (14).

A multiplicity testing procedure, analogous to a simple sequential gatekeeping method, strongly controlled the overall familywise one-sided error rate of 2.5%. If the primary end point of rPFS was statistically significant, then OS would be tested in a hierarchical fashion. The O'Brien and Fleming

spending function, calculated on the basis of actual observed events, was used to control the overall type I error, with the restriction that alpha spend for the overall survival interim analysis at DCO1 would not exceed 0.0005. For time-to-event end points, a stratified log-rank test was used to calculate two-sided P-values. Hazard ratios and 95% confidence intervals (CIs) were calculated using the Cox proportional hazards model including the two stratification variables (metastases and prior docetaxel use at mHSPC stage) as covariates. Kaplan–Meier plots were used to calculate medians (14).

B.2.4.2 Patient disposition

Patient disposition in the PROpel trial from the final data cut off (DCO3, 12 October 2022), including number of patients enrolled to screening, number randomised, and discontinuations, is provided in Appendix D. Of 1103 screened patients, 796 met the inclusion criteria and were randomised (1:1) to olaparib plus abiraterone, or placebo plus abiraterone (14). Overall, 794 patients received study treatment; one patient from each treatment group did not receive study treatment.

A total of [redacted] patients ([redacted]) were ongoing in the study as of DCO3. The most frequent reason for withdrawal from the study was [redacted] ([redacted] patients [redacted]). In total, [redacted] patients [redacted] were still receiving treatment: [redacted] patients ([redacted]) on olaparib plus abiraterone and [redacted] on placebo plus abiraterone. The primary reason for treatment discontinuation was objective disease progression, which occurred more frequently in the placebo plus abiraterone arm than in the olaparib plus abiraterone arm: [redacted] patients versus [redacted] ([redacted]) patients, respectively (23).

A higher proportion of patients receiving olaparib gave [redacted] as the primary reason for treatment discontinuation compared with those receiving placebo: [redacted] patients [redacted] and [redacted] respectively. Similar proportions of patients in each treatment arm gave [redacted] as the primary reason for discontinuation of abiraterone: [redacted] patients[redacted] in the olaparib plus abiraterone arm and [redacted] patients [redacted] in the placebo plus abiraterone arm (23). Based on these data, there were no unexpected differences observed in withdrawals or discontinuations between the treatment arms.

B.2.5 Critical appraisal of the relevant clinical effectiveness evidence

Quality assessment of the PROpel trial was conducted using the NICE-recommended checklist adapted from the University of York Centre for Reviews and Dissemination's *Systematic reviews: CRD's guidance for undertaking reviews in health care* (60) (Table 8). This indicated that the PROpel trial design and execution was robust and the results are valid.

The baseline characteristics of the PROpel trial participants were well balanced (see section B.2.3.6), and UK clinical expert opinion indicates these are representative of patients in the first line mCRPC setting typically seen in clinical practice in the UK (see section B.3.14). 6.1% of patients in the PROpel trial were enrolled from the UK (14).

Olaparib plus abiraterone was dosed and used in line with their anticipated use in combination in clinical practice. The abiraterone comparator is a NICE-recommended standard of care NHA therapy in the first line mCRPC setting (7) and is a relevant comparator listed in the NICE scope for this appraisal (8). Of note, the median OS of 34.69 months (95%CI: 30.95–39.29) observed with placebo plus abiraterone in the PROpel trial is highly consistent with the median OS of 34.7 months (95% CI 32.7–36.8) observed with abiraterone in the phase 3 COU-AA-302 trial (12) that supported its regulatory licensing and its recommendation by NICE in the first line mCRPC setting (7,19).

The primary endpoint of rPFS in the PROpel trial was assessed by investigators, and results by blinded independent central review were highly consistent with these (14) (see section B.2.6.1), indicating that the investigator-based assessments were valid and reliable. Although a minority of patients in the PROpel trial received subsequent therapies that are not routinely used in UK clinical practice (see section B.2.6.3.1), these were well balanced between treatment arms, do not influence the primary endpoint of rPFS and UK clinical expert opinion indicates these are not anticipated to materially bias the OS estimates compared with what they would anticipate to see in practice (see section B.3.14).

Collectively, PROpel is a high-quality trial, at low risk of bias and the results are generalisable to its use in patients in clinical practice in the UK.

Table 8. Quality assessment of PROpel trial

Trial number (acronym)	NCT03732820 (PROpel) (14,56)
Was randomisation carried out appropriately?	Yes - Eligible patients were randomised (1:1 ratio) to receive either olaparib plus abiraterone, or placebo plus abiraterone.
Was the concealment of treatment allocation adequate?	Yes - Patients were centrally assigned to randomised study treatment using a Randomisation and Trial Supply Management System (Interactive Response Technology).
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes - Baseline characteristics were well balanced between treatment arms for known prognostic factors (see Table 6).
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes - The patient, the investigator, and study centre staff were blinded to study drug allocation.
Were there any unexpected imbalances in dropouts between groups?	No - See the patient disposition detail in Appendix D.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No – Based on the clinical study protocol and subsequent clinical study reports and manuscript there is no evidence to suggest that the authors measured more outcomes than were reported.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes – The efficacy analyses were appropriately conducted using the intention-to-treat principle.

B.2.6 Clinical effectiveness results: PROpel trial

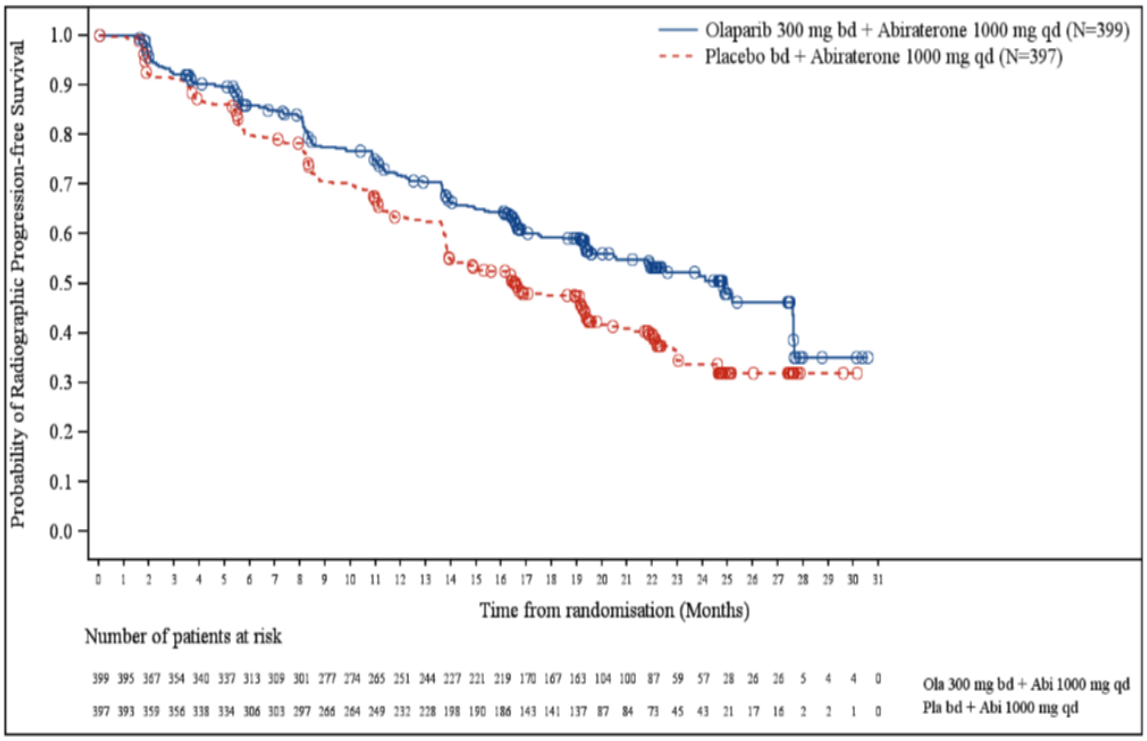
B.2.6.1 Primary endpoint of PROpel: investigator-assessed rPFS

The PROpel trial met its primary endpoint of investigator-assessed rPFS in the FAS (ITT) population primary analysis (DCO1, 30 July 2021) (14). Olaparib plus abiraterone demonstrated a statistically significant and clinically meaningful improvement in the risk of radiological disease progression or death when compared with placebo plus abiraterone as assessed by the investigator; median rPFS was 8.2 months longer with olaparib plus abiraterone (24.8 months in the olaparib plus abiraterone arm versus 16.6 months in the placebo plus abiraterone arm) with a 34% reduction in the risk of radiological disease progression or death (hazard ratio [HR] 0.66; 95% CI, 0.54 to 0.81; p<0.001) (Figure 3). The prespecified sensitivity analysis of rPFS by blinded independent central review (BICR) was consistent with and marginally improved compared with the results of the primary investigator-based data analysis (median, 27.6 vs. 16.4 months; HR 0.61; 95% CI, 0.49 to 0.74) (14), indicating that the investigator-based analyses are robust.

rPFS results at DCO2 (Final rPFS analysis, 14 March 2022) and a further, updated analysis at DCO3 (12 October 2022) are also consistent with the results of the primary analysis at DCO1, confirming the benefit of olaparib plus abiraterone over placebo plus abiraterone (Table 9). The DCO3 rPFS results are used in the economic model as these provide the longest available follow-up and for consistency with the follow up for the final OS analysis (see section B.3).

Olaparib plus abiraterone consistently demonstrated rPFS benefits across pre-specified subgroups (see section B.2.7).

Figure 3. Kaplan-Meier plot of rPFS in FAS population based on investigator assessment (Primary analysis at DCO1)



Circle indicates a censored observation, RECIST version 1.1 and PCWG-3.
Progression, as assessed by investigator, is defined by RECIST 1.1 and/or PCWG-3 or death (by any cause in the absence of progression) regardless of whether the patient withdraws from randomised therapy or receives another anticancer therapy prior to progression. DCO1 date: 30 July 2021.
Source: PROpel CSR, December 2021(56)

Table 9. Analyses of rPFS based on Investigator Assessment at different data cuts

	Median rPFS[b], Months (95% CI) Olaparib + Abiraterone (n = 399)	Median rPFS[b], Months (95% CI) Placebo + Abiraterone (n = 397)	HR (95% CI)[c]
DCO1 (Primary analysis, 30 July 2021)	24.84 (20.47–27.63)	16.59 (13.93–19.22)	0.66 (0.54–0.81) p<0.001[d]
DCO2 (Final analysis, 14 March 2022)[a]	[redacted]	[redacted]	[redacted]
DCO3 (Updated analysis, 12 October 2022)[a]	[redacted]	[redacted]	[redacted]

[a] As DCO1 was the primary analysis of rPFS. Analyses at DCO2 and DCO3 are necessarily considered to be exploratory.
[b]Progression defined by RECIST 1.1 (soft tissue) and 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 randomised therapy or receives another anticancer therapy prior to progression.
[c]HR and CI calculated using a Cox Proportional Hazards model adjusted for the variables selected in the primary pooling strategy: Metastases (bone only, visceral, other) and docetaxel treatment at mHSPC stage. The Efron approach was used for handling ties. A HR < 1 favours olaparib + abiraterone.
[d]Two-sided p-value calculated using the log-rank test stratified by the same variables selected in the primary pooling strategy. DCO2 and DCO3 p-value is labelled as nominal because the primary analysis was conducted at DCO1.
CI, confidence interval; DCO, data cut off; FAS, full analysis set; HR, hazard ratio; PCWG3, Prostate Cancer Working Group 3; RECIST, Response Evaluation Criteria in Solid Tumours; rPFS, radiological progression-free survival; mHSPC, metastatic hormone-sensitive prostate cancer; PFS, progression-free survival.
DCO1: 394 rPFS events (49.5% maturity); DCO2: 457 rPFS events (57.4% maturity); DCO3: 496 rPFS events (62.3% maturity).
Sources: PROpel CSR, Dec 2021(56); PROpel CSR Addendum 1 (DCO2)(59); PROpel CSR Addendum2 (DCO3)(23)

B.2.6.2 Key secondary endpoint of PROpel: OS

OS was the key secondary endpoint of PROpel. Analyses conducted at the different data cut-offs show a consistent trend towards an improving OS with olaparib plus abiraterone as the data became more mature (Table 10). Final analysis of OS was conducted at DCO3 (12 October 2022) when OS data was 47.9% mature (total, 381 events) with approximately 36.5 months follow-up in the FAS: 176 (44.1%) events in the olaparib plus abiraterone arm and 205 (51.6%) events in the placebo plus abiraterone, respectively. Olaparib plus abiraterone was associated with a numerical improvement in median OS (months) over placebo plus abiraterone of over 7 months (42.05 [95% CI, 38.41–NC] vs 34.69 [95% CI, 30.95–39.29]; HR 0.81; p=0.0544). Survival with olaparib plus abiraterone was improved from 18 months and the Kaplan−Meier curves clearly separated after approximately 22 months (
Figure 4). By 42 months 51.11% were still alive with olaparib plus abiraterone vs 42.99% with placebo plus abiraterone (23).

Given that abiraterone itself provided a median OS of 34.7 months and a benefit of 4.4 months over the prednisone comparator in the final analysis of study COU-AA-302 (median follow-up of 49.2 months) (12), the additional survival benefit of over 7 months with the addition of olaparib to abiraterone in PROpel (at DCO3, median follow-up 36.5 months) is noteworthy and clinically meaningful. Although the final OS analysis in PROpel was not powered to demonstrate statistically significant differences between the trial arms, the survival curves showed clear separation at 22 months and continued to separate (Figure 4). With a longer period of follow up it is plausible that the difference in OS between the trial arms would become more evident. Olaparib demonstrated numerical OS benefits across the pre-specified subgroups (see section B.2.7). The final (DCO3) analysis of OS is used in the economic model as this provides the longest available OS follow-up.

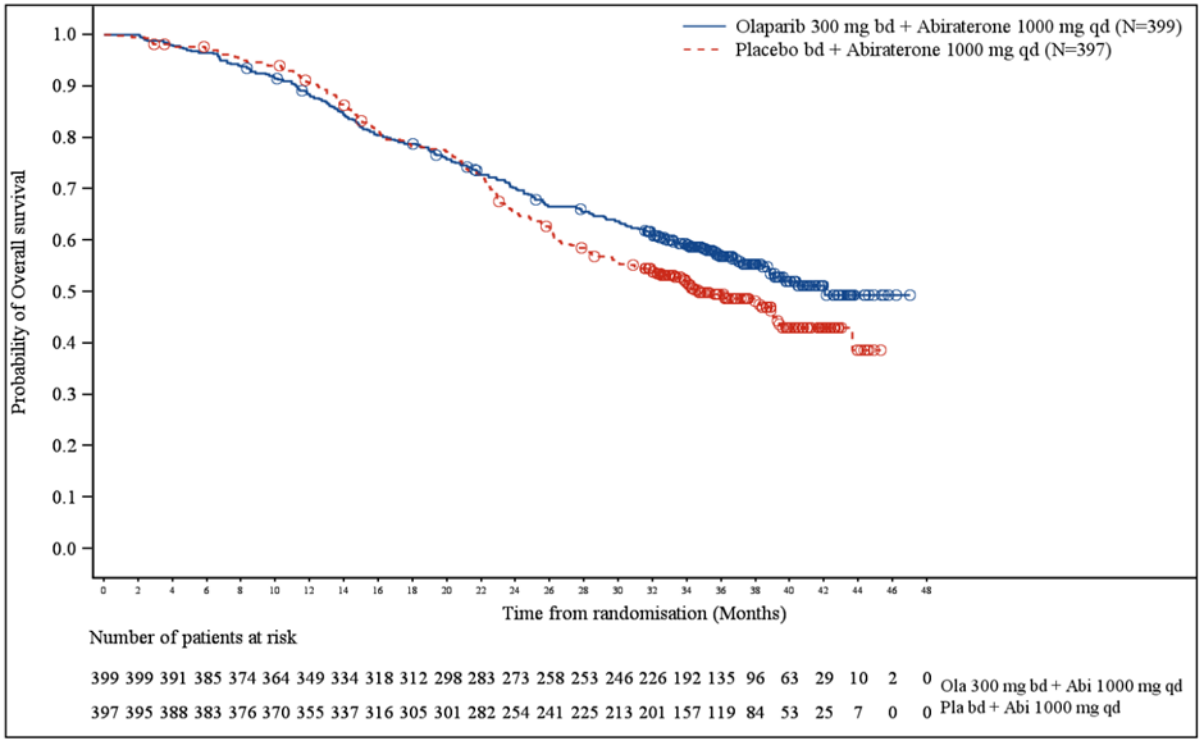
Table 10. Analyses of OS at different data cuts

	Median OS, Months (95% CI) Olaparib + Abiraterone (n = 399)	Median OS, Months (95% CI) Placebo + Abiraterone (n = 397)	HR (95% CI)[b]
DCO1 (Interim analysis, 30 July 2021)	NC	NC	0.86 (0.66–1.12); p = 0.2923[c]
DCO2 (Interim analysis, 14 March 2022)	NC	NC	0.83 (0.66–1.03); p = 0.1126[c]
DCO3 (Final analysis, 12 October 2022)[a]	42.05 [redacted]	34.69 [redacted]	0.81 (0.67–1.00); p=0.0544[c]

[a] DCO3 was the Final analysis. OS was formally tested as interim analyses failed to achieve statistical significance.
[b]HR and CI calculated using a Cox Proportional Hazards model adjusted for the variables selected in the primary pooling strategy: Metastases (bone only, visceral, other) and docetaxel treatment at mHSPC stage. The Efron approach was used for handling ties. A HR < 1 favours olaparib + abiraterone.
[c]Two-sided p-value calculated using the log-rank test stratified by the same variables selected in the primary pooling strategy.
CI, confidence interval; DCO, data cut off; FAS, full analysis set; HR, hazard ratio; NC, not calculated (median OS not reached); PCWG3, Prostate Cancer Working Group 3; RECIST, Response Evaluation Criteria in Solid Tumours; rPFS, radiological progression-free survival; mHSPC, metastatic hormone-sensitive prostate cancer; PFS, progression-free survival.

DCO1: 228 OS events (28.6% maturity); DCO2: 319 OS events (40.1% maturity); DCO3: 381 OS events (47.9% maturity).
Sources: PROpel CSR, Dec 2021(56); PROpel CSR Addendum 1 (DCO2)(59); PROpel CSR Addendum2 (DCO3)(23)

Figure 4. Final analysis of OS at DCO3



A circle indicates a censored observation.
bd, twice daily; DCO, data cut-off; OS, overall survival; qd, once daily.
Source: PROpel CSR Addendum 2 (DCO3)(23)

B.2.6.3 Other secondary endpoints of PROpel

Analyses of other secondary efficacy endpoints (TFST, TTPP, time to opiate use for cancer pain, time to first SSRE, and PFS2) at DCO3 are summarised in Table 11.

Table 11. Analyses of other secondary endpoints (FAS; DCO3, 12 October 2022)

	Olaparib + Abiraterone (n = 399)	Placebo + Abiraterone (n = 397)
TFST		
Number of events, n (%)	255 (63.9)	285 (71.8)
Median TFST (95% CI), months	24.6 (21.1–28.5)	19.4 (17.0–21.1)
HR (95% CI)[a]	0.76 (0.64–0.90); nominal p = 0.0025[b]	
TTPP (BPI-SF worst pain)		
Number of events, n (%)	[redacted]	[redacted]
Median TTPP (95% CI), months	[redacted]	[redacted]
HR (95% CI)[a]	[redacted]	
Time to opiate use for cancer-related pain		
Number of events, n (%)	[redacted]	[redacted]
Median time to opiate use for cancer pain (95% CI), months	[redacted]	[redacted]

HR (95% CI)[a]	[redacted]	
Time to first SSRE		
Number of events, n (%)	[redacted]	[redacted]
Median time to first SSRE	[redacted]	[redacted]
HR (95% CI)[a]	[redacted]	
PFS2		
Event, n (%)[a]	103 (25.8)	126 (31.7)
Median PFS2, months (95% CI)[a]	NC	NC
HR (95% CI)	0.76 (0.59–0.99); nominal p = 0.0534[b]	

[a] HR and CI were calculated using a Cox proportional hazards model adjusted for metastases and docetaxel treatment at mHSPC stage as covariates, with the Efron approach used for handling ties. HR < 1 favours olaparib + abiraterone.
[b] The 2-sided p-value was calculated using the log-rank test stratified by the same variables selected in the primary pooling strategy. The p-value presented is nominal as the endpoint is not alpha controlled.
[c] Calculated using the Kaplan-Meier technique.
TFST: Time to first subsequent therapy - defined as the time from randomisation to the earlier of start date of the first subsequent anti-cancer therapy (excluding radiotherapy) after discontinuation of randomised treatment or death from any cause.
TTPP: Time to progressive pain - time from randomisation to pain progression based on the BPI-SF Item 3 'worst pain in 24 hours' and opiate analgesic use (AQA score).
Time to first SSRE: Time to first symptomatic skeletal-related event – defined as time from randomisation to the first SSRE. An SSRE is defined as use of radiation therapy to bone in order to prevent or relieve skeletal complications, occurrence of new symptomatic pathological bone fractures (vertebral or non-vertebral, resulting from minimal or no trauma), occurrence of radiologically confirmed spinal cord compression or a tumour-related orthopaedic surgical intervention.
PFS2: Second progression free survival - defined as the time from randomisation to second progression on next-line of anticancer therapy as assessed by investigator assessment of radiological progression, clinical symptomatic progression, PSA progression, or death.
Source: PROpel CSR Addendum 2 (DCO3)(23)

B.2.6.3.1 Time to first subsequent therapy (TFST)

At DCO3 (12 October 2022), the time to first subsequent therapy (TFST) data were 67.8% mature (total, 540 events): 255 (63.9%) and 285 (71.8%) events had occurred in the olaparib plus abiraterone and placebo plus abiraterone arms, respectively. Olaparib plus abiraterone was associated with a nominally statistically significant and clinically meaningful 5.2-month improvement in TFST versus the placebo plus abiraterone (median 24.6 versus 19.4 months, respectively; HR 0.76, 95% CI, 0.64–0.90; nominal *p* = 0.0025) (15) (Table 11).

Following discontinuation of olaparib or placebo, [redacted] patients [redacted] in the olaparib plus abiraterone arm and [redacted] in the placebo plus abiraterone arm had received anticancer therapy (Table 12). This aligns with the lower proportion of patients who had disease progression on olaparib plus abiraterone versus placebo plus abiraterone. The therapies received were generally consistent with clinical practice. The most frequently used post-discontinuation anticancer therapy was [redacted] A higher proportion of patients received [redacted] in the placebo plus abiraterone arm than in the olaparib plus abiraterone arm [redacted] (23). A minority of patients received subsequent therapies that are not currently used routinely in mCRPC following first line therapy with NHA in the UK NHS; however, these were well balanced between the two arms of the PROpel trial and clinical expert opinion confirms these are unlikely to have materially impacted on the subsequent outcomes they would expect to see in these patients in UK clinical practice (see section B.3.14).

Table 12. Post-discontinuation anticancer therapy (FAS; DCO3, 12 October 2022)

Anticancer therapy[a]	Number (%) of patients		
	Olaparib + Abiraterone (n = 399)	Placebo + Abiraterone (n = 397)	Total (N = 796)
Patients with any post-discontinuation anticancer therapy	[redacted]	[redacted]	[redacted]
New hormonal agents			
Abiraterone[b]	[redacted]	[redacted]	[redacted]
Apalutamide	[redacted]	[redacted]	[redacted]
Bicalutamide	[redacted]	[redacted]	[redacted]
Darolutamide	[redacted]	[redacted]	[redacted]
Enzalutamide	[redacted]	[redacted]	[redacted]
Taxanes			
Cabazitaxel	[redacted]	[redacted]	[redacted]
Docetaxel	[redacted]	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]	[redacted]
PARP inhibitors			
Niraparib	[redacted]	[redacted]	[redacted]
Olaparib	[redacted]	[redacted]	[redacted]
Rucaparib	[redacted]	[redacted]	[redacted]
Talazoparib	[redacted]	[redacted]	[redacted]

[a]Patients can be counted in > 1 anticancer therapy.
[b]Includes abiraterone acetate.
[c]Includes one docetaxel patient counted under the Systemic Therapy category instead of Cytotoxic Chemotherapy.
bd, twice daily; FAS, full analysis set; PARP, polyadenosine 5'diphosphoribose polymerase; qd, once daily.
Source: PROpel CSR Addendum 2 (DCO3)(23)

B.2.6.3.2 Time to Pain Progression (TTPP), Opiate use, Time to first SSRE and PFS2

Data for the remaining secondary endpoints were not mature at DCO3 and so results should be interpreted with a degree of caution.

TTPP data were [redacted] mature (total, [redacted] events) and time to opiate use data were [redacted] mature (total, [redacted] events). There was no difference in the olaparib plus abiraterone arm versus the placebo plus abiraterone arm for TTPP ([redacted]) or time to opiate use [redacted]. Similarly, time to first SSRE data were [redacted] mature (total, [redacted] events). There was a numerical improvement (i.e., delay) in time to first SSRE in the olaparib plus abiraterone arm versus the placebo plus abiraterone arm ([redacted]) but the median time to first SSRE was not calculable for either treatment arm (Table 11) (23).

PFS2 data were [redacted] mature (total, 229 events): 103 (25.8%) and 126 (31.7%) events in the olaparib plus abiraterone and placebo plus abiraterone arms, respectively. Olaparib plus abiraterone was associated with a 24% reduction in the risk of second progression or death compared with placebo

plus abiraterone (median PFS2 non-calculable in both arms; HR 0.76, 95% CI, 0.59–0.99; p = 0.0534) (Table 11) (15).

B.2.6.4 Other endpoints specified in the NICE scope

The NICE scope specified response rates and health-related quality of life (HRQoL) as outcomes of interest (8).

B.2.6.4.1 Response rates

Response rates were assessed at DCO1 and DCO2 only. Analysis of radiological objective response rate (ORR) at each data cut is summarised in Table 13. ORR was (nominally) statistically significantly greater with olaparib plus abiraterone at each data cut, supporting the treatment benefit of the combination therapy over abiraterone and placebo (56,59).

Table 13. Radiological ORR, investigator assessed in the EFR set

Treatment group	n	Number (%) of patients with response[a]	Comparison between groups		
			Odds ratio	95% CI	p-value (nominal)[b]
DCO1 – 30 July 2021					
Olaparib 300 mg bd + abiraterone 1000 mg qd	161	94 (58.4)	1.60	1.02 to 2.53	0.0409
Placebo bd + abiraterone 1000 mg qd	160	77 (48.1)			
DCO2 – 14 March 2022					
Olaparib 300 mg bd + abiraterone 1000 mg qd	161	[redacted]	[redacted]	[redacted]	[redacted]
Placebo bd + abiraterone 1000 mg qd	160	[redacted]			

[a] Radiological objective response rate assessed based on investigator assessed RECIST and bone scan data (using all scans regardless of whether they were scheduled or not) in patients with measurable disease. Response does not require confirmation. Radiological objective response rate compared using logistic regression adjusted for the variables selected in the primary pooling strategy: Metastases, Docetaxel treatment at mHSPC stage. An odds ratio > 1 favours olaparib + abiraterone. CI calculated using profile likelihood method.
[b] Where the number of patients with a response was ≥ 5 a 1-sided p-value was calculated based on twice the change in log-likelihood resulting from the addition of the treatment factor to the model that contains the specified covariates.
RECIST version 1.1 and PCWG-3.
bd, twice daily; CI, confidence interval; EFR, evaluable for response analysis set; mHSPC, metastatic hormone-sensitive prostate cancer; ORR, objective response rate; qd, once daily; RECIST, Response Evaluation Criteria in Solid Tumours.
Sources: PROpel CSR, Dec 2021(56); PROpel CSR Addendum 1 (DCO2)(59)

Based on DCO2 (the longest response rate follow-up), [redacted] patients ([redacted]) in the olaparib plus abiraterone arm and [redacted] patients ([redacted]) in the placebo plus abiraterone arm had a complete response (CR). Partial response (PR) was reported for [redacted] patients [redacted]) in the olaparib plus abiraterone arm and [redacted] patients ([redacted]X) in the placebo plus abiraterone arm. The proportion of patients with stable disease ≥ 11 weeks was similar between the two treatment arms: [redacted]% compared with [redacted] in olaparib plus abiraterone and placebo plus abiraterone, respectively (

Table 14).

Disease control rate (DCR) at 24 weeks was higher in the olaparib plus abiraterone arm; [redacted] patients had disease control in the olaparib plus abiraterone arm compared with [redacted] in the placebo plus abiraterone arm. Median duration of response (DoR) was [redacted] months longer in the olaparib plus abiraterone arm ([redacted] months) than in the placebo plus abiraterone arm ([redacted] months), with a similar median time to onset of response in both arms (

Table 14) (59).

Table 14. Best objective response, disease control rate, and duration of response, based on investigator assessment (FAS; DCO2, 14 March 2022)

	Olaparib + Abiraterone (n = 161)	Placebo + Abiraterone (n = 160)
Best objective response, n (%)[a]		
CR	[redacted]	[redacted]
PR	[redacted]	[redacted]
Non-response		
Stable disease ≥ 11 weeks	[redacted]	[redacted]
Progression	[redacted]	[redacted]
Non-PD	[redacted]	[redacted]
Not evaluable	[redacted]	[redacted]
DCR at 24 weeks[b]	[redacted]	[redacted]
Median DoR from randomisation (95% CI),[c] months	[redacted]	[redacted]
Median time to onset of response from randomisation (95% CI)[d], months	[redacted]	[redacted]

[a] Response did not require confirmation. Radiological objective response based on investigator assessment defined as the response recorded at one visit but either no confirmation assessment performed, or a confirmation assessment performed but response not confirmed. A responder is any patient with a BoR of PR or CR in soft tissue disease assessed by RECIST 1.1 and also bone scan status of non-PD or NE for their bone scans assessed by PCWG-3. BoR is defined as the best response up to progression or start of subsequent therapy. RECIST version 1.1 and PCWG-3.
[b] DCR at 24 weeks defined as the BoR of CR or PR and remaining on study without progression at 23 weeks (*) or having a duration of stable disease of ≥ 23 weeks (*) after randomisation. Duration of SD defined as (PD or death or censoring date - randomisation date + 1 in days). SD after the start of subsequent cancer therapy is not included in this duration.
(*) 24 weeks minus 1 week to allow for an early assessment within assessment window.
[c] DoR is the time from the first documentation of CR/PR until the date of radiological progression RECIST 1.1 or PCWG-3, as assessed by investigator, or death in the absence of disease progression. If a patient did not progress following a response, then their rPFS censoring date was used as the date at which the patient was censored for DoR.
Calculated using the Kaplan-Meier method.
[d] Distribution-free CI.
[e] Where the number of patients with a response was ≥ 5 a one-sided p-value was calculated based on twice the change in log-likelihood resulting from the addition of the treatment factor to the model that contains the specified covariates
bd, twice daily; BoR, best overall response; CI, confidence interval; CR, complete response; DCR, disease control rate; DoR, duration of response; EFR, evaluable for response analysis set; NC, not calculated; PR, partial response; qd, once daily.
Source: PROpel CSR Addendum 1 (DCO2)(59)

B.2.6.5 Disease-related symptoms and health-related quality of life (HRQoL)

Prostate cancer negatively affects patients' physical and mental HRQoL (33,61). It is important that treatment of prostate cancer, particularly in the mCRPC setting where treatment is non-curative, does not further negatively impact HRQoL. PROpel assessed the HRQoL and pain symptoms of participants using multiple instruments that demonstrate that the combination of olaparib with abiraterone does not negatively impact HRQoL compared with placebo plus abiraterone.

B.2.6.5.1 FACT-P

FACT-P is a multidimensional instrument designed to assess physical and functional HRQoL specifically in patients with prostate cancer. At DCO3, compliance rates for the completion of the FACT-P questionnaire at baseline were [redacted] and [redacted] for the olaparib plus abiraterone and placebo plus abiraterone arms, respectively, and overall were [redacted] and [redacted], respectively. The adjusted mean change from baseline in the FACT-P Total and its subscales showed no detriment for the olaparib and abiraterone compared with placebo and abiraterone (23) (Table 15).

Table 15. Overall adjusted mean change from baseline in FACT-P Total score and subscale scores, MMRM (FAS; DCO3, 12 October 2022)

FACT-P component	Summary statistic	Olaparib + Abiraterone (n = 399)	Placebo + Abiraterone (n = 397)
FACT-P Total[a]	LS mean (standard error)	[redacted]	[redacted]
	Difference in LS means (95% CI)	[redacted]	
	Two-sided p-value (nominal)	[redacted]	
FACT-G Total[b]	LS mean (standard error)	[redacted]	[redacted]
	Difference in LS means (95% CI)	[redacted]	
	Two-sided p-value (nominal)	[redacted]	
TOI[c]	LS mean (standard error)	[redacted]	[redacted]
	Difference in LS means (95% CI)	[redacted]	
	two-sided p-value (nominal)	[redacted]	
PWB[d]	LS mean (standard error)	[redacted]	[redacted]
	Difference in LS means (95% CI)	[redacted]	
	two-sided p-value (nominal)	[redacted]	
FWB[d]	LS mean (standard error)	[redacted]	[redacted]
	Difference in LS means (95% CI)	[redacted]	
	two-sided p-value (nominal)	[redacted]	
PCS[e]	LS mean (standard error)	[redacted]	[redacted]
	Difference in LS means (95% CI)	[redacted]	
	two-sided p-value (nominal)	[redacted]	
FAPSI-6[f]	LS mean (standard error)	[redacted]	[redacted]
	Difference in LS means (95% CI)	[redacted]	
	two-sided p-value (nominal)	[redacted]	

[a] FACT-P total score change from baseline values can be a minimum of -156 and a maximum of 156.
[b] FACT-G total score is the sum of PWB, SWB, EWB, and FWB, and can be a minimum of -108 and a maximum of 108.
[c] TOI score is the sum of PWB, FWB and PCS, and can be a minimum of -104 and a maximum of 104.
[d] PWB score and FWB score change from baseline values can be a minimum of -28 and a maximum of 28.
[e] PCS score change from baseline values can be a minimum of -48 and a maximum of 48.
[f] FAPSI-6 score change from baseline values can be a minimum of -24 and a maximum of 24.
Analysis was performed using a MMRM 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. The treatment by visit interaction remains in the model regardless of significance. An unstructured covariance matrix is used to model the within-patient error.
The Kenward-Roger approximation is used to estimate degrees of freedom.
DCO3 date: 12 October 2022.
bd, twice daily; CI, confidence interval; DCO, data cut-off; EWB, FACT-P Emotional Well-Being subscale; FACT-G, Functional Assessment of Cancer Therapy - General; FACT-P, Functional Assessment of Cancer Therapy – Prostate Cancer; FAPSI-6, FACT Advanced Prostate Symptom Index 6; FAS, full analysis set; FWB, FACT-P Functional Well-Being subscale; LS mean, least squares mean (estimated from model); mHSPC, metastatic hormone-sensitive prostate cancer; MMRM, mixed models for repeated measures; PCS, FACT-P Prostate Cancer Subscale; PWB, FACT-P Physical Well Being Subscale; qd, once daily; SWB, FACT-P Social/Family Well-Being Subscale; TOI, FACT-P Trial Outcome Index.
Source: PROpel CSR Addendum 2 (DCO3)(23)

B.2.6.5.2 BPI-SF

The Brief Pain Inventory – Short Form (BPI-SF) is a 9-item self-administered questionnaire used to evaluate the severity of a patient's pain and the impact on the patient's daily functioning (62). Compliance rates for completion of the BPI-SF questionnaire were high for both treatment arms: at baseline [redacted] and [redacted]; and overall [redacted] and [redacted], for the olaparib plus abiraterone and placebo plus abiraterone arms, respectively.

The mean change from baseline in BPI-SF scores (worst pain, pain severity, and pain interference) showed no overall differences over the treatment period between the olaparib plus abiraterone arm compared with the placebo plus abiraterone arm (Table 16), except for one visit where a difference was observed, which favoured the olaparib plus abiraterone arm, but this was considered an isolated occasion (23).

Table 16. Overall mean change from baseline pain interference scores in the PROpel trial (FAS; DCO3, 12 October 2022)

BPI-SF component	Summary statistic	Olaparib + Abiraterone (n = 399)	Placebo + Abiraterone (n = 397)
BPI-SF worst pain[a]	LS mean (standard error)	[redacted]	[redacted]
	Difference in LS means (95% CI)	[redacted]	
	2-sided p-value (nominal)	[redacted]	
BPI-SF pain severity score[a]	LS mean (standard error)	[redacted]	[redacted]
	Difference in LS means (95% CI)	[redacted]	
	2-sided p-value (nominal)	[redacted]	
BPI-SF pain interference score[a]	LS mean (standard error)	[redacted]	[redacted]
	Difference in LS means (95% CI)	[redacted]	
	2-sided p-value (nominal)	[redacted]	

[a] Displays the overall treatment effect across all visits.
Analysis was performed using a MMRM with treatment, visit, treatment by visit interaction, baseline BPI-SF total score and baseline score by visit interaction, Metastases and Docetaxel treatment at mHSPC stage as fixed effects. The treatment by visit interaction remains in the model regardless of significance. A Toeplitz with heterogeneity covariance matrix is used to model the within-patient error. The Kenward-Roger approximation is used to estimate degrees of freedom.
BPI-SF worst pain, pain severity and pain interference score changes can be a minimum of -10 and a maximum of 10. DCO3 date: 12 October 2022.
BPI-SF, Brief Pain Inventory - Short Form; CI, confidence interval; DCO, data cut-off; FAS, full analysis set; LS, least squares; mHSPC, metastatic hormone-sensitive prostate cancer; MMRM, mixed models for repeated measures; qd, once daily.
Source: PROpel CSR Addendum 2 (DCO3)(23)

B.2.6.5.3 EQ-5D-5L

EQ-5D-5L was collected in the PROpel trial at baseline, every 8 weeks, at week 52 and upon treatment discontinuation, and until 12 weeks after confirmed progressive disease. Overall compliance rates for completion of the EQ-5D-5L were [redacted] in the olaparib plus abiraterone arm and [redacted] in the placebo plus abiraterone arm. The data showed no detriment in dimension scores or visual analogue scale (VAS) over time for the olaparib plus abiraterone treatment arm compared with the placebo plus abiraterone arm (23). These data are referenced in Appendix M and were used to estimate health state utility values in the economic model (see section B.3.4).

B.2.7 Subgroup analysis

The PROpel study was powered for rPFS in the FAS (ITT) population, which meets the licensed indication for olaparib plus abiraterone in the first line mCRPC setting. Exploratory subgroup analyses of rPFS and OS based on investigator assessment were performed to investigate the consistency of the treatment effect across the following pre-defined subgroups in PROpel (14):

- Site of distant metastases (bone only vs visceral vs other)
- Docetaxel treatment at mHSPC stage (yes vs no)
- HRR gene mutation status
- ECOG performance status
- Age at randomisation
- Region
- Race
- Baseline PSA.

As the study was not powered to assess efficacy within individual subgroups and given the large number of comparisons without control for multiplicity, the subgroup analyses should be interpreted with caution.

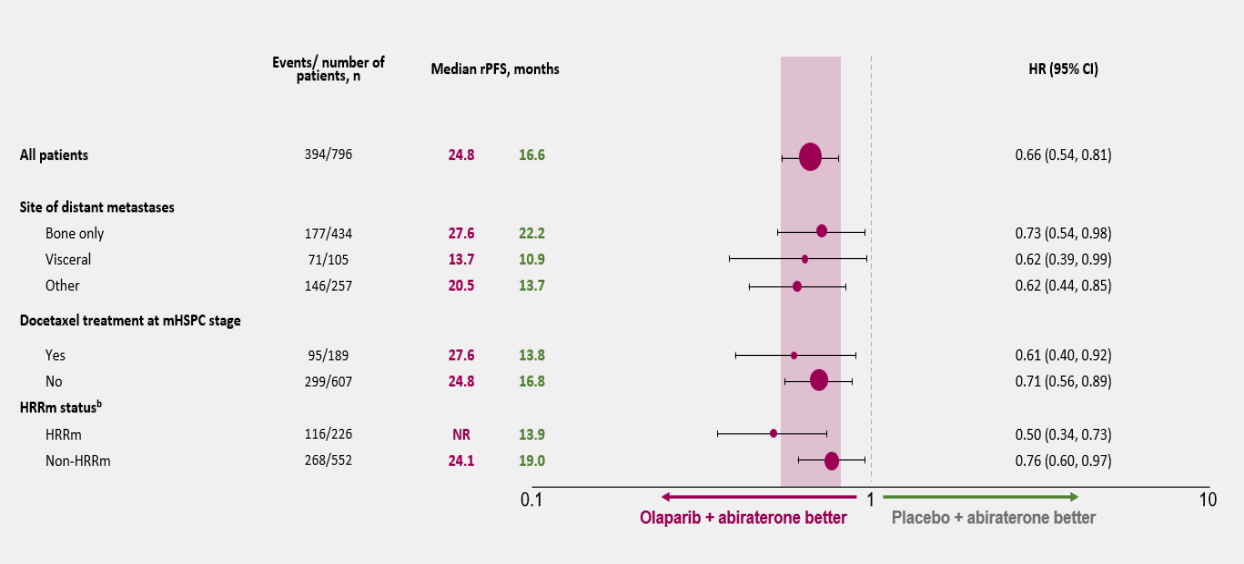
B.2.7.1 Subgroup analyses of rPFS

The benefit of olaparib plus abiraterone over placebo plus abiraterone was maintained across stratification factors (site of distant metastases and prior docetaxel use) and all other pre-defined subgroups in the primary analysis of rPFS (DCO1, 30 July 2021), with clinically meaningful reductions in the risk of radiological disease progression or death in patients receiving olaparib plus abiraterone (Figure 5 and Table 17). A global interaction test comparing the fit of a model with no interaction terms with a model with all subgroup interactions included was not significant at the 10% level (P=0.41), indicating a consistent treatment effect between subgroups (14).

The NICE scope requested subgroup analyses by HRRm status if data allowed, including *BRCA1, BRCA2* and *ATM* gene mutations (8). Patients' HRRm status was determined in PROpel retrospectively following randomisation by testing of ctDNA and tumour tissue samples provided at baseline for mutations in 14 genes: *ATM, BRCA1, BRCA2, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, and RAD54L*. The incidence of gene mutations was balanced between groups and aligned with the known epidemiology (58), with the most common mutations in *BRCA2* (9.5% in olaparib plus abiraterone; 8.8% in placebo plus abiraterone) (14).

Subgroup analyses by aggregate HRRm status (determined by either ctDNA or tumour tissue samples, for any of the 14 HRR gene mutations, or none), are provided in Figure 5 but subgroup analyses by individual gene mutation status are not appropriate due to their low prevalence.

Figure 5. Prespecified subgroup analysis of investigator-assessed rPFS: stratification factors and HRRm subgroups (FAS, DCO1)



[a] Primary analysis / DCO1: 30th July 2021; [b] The HRRm status of patients in PROpel was determined after randomisation and before primary analysis using aggregated results from tumour tissue and plasma ctDNA HRRm tests. Aggregate HRRm subgroup analyses are post-hoc exploratory analyses. Results shown are by investigator assessment.
CI, confidence interval; ctDNA, circulating tumour deoxyribonucleic acid; DCO, data cut-off; HR, hazard ratio; HRRm, homologous recombination repair gene mutation; mHSPC, metastatic hormone-sensitive prostate cancer; NR, not reached; rPFS, radiological progression-free survival.
Source: Clarke et al 2022(14); Clark N. ASCO presentation slides(15)

Table 17. Other prespecified subgroup analyses of rPFS (FAS, DCO1)

Subgroup	rPFS HR (95%CI)	Olaparib + Abiraterone (n/N)(%)	Placebo + Abiraterone (n/N)(%)
Age at random assignment: <65yr	0.51 (0.35-0.75)	47/130 (36.2)	59/97 (60.8)
Age at random assignment: ≥65yr	0.78 (0.62-0.98)	121/269 (45.0)	167/300 (55.7)
ECOG performance status at baseline = 0*	0.67 (0.52-0.85)	113/286 (39.5)	151/272 (55.5)
ECOG performance status at baseline = 1*	0.75 (0.53-1.06)	55/112 (49.1)	75/124 (60.5)
Baseline PSA: below median*	0.75 (0.55 to 1.02)	73/196 (37.2)	93/200 (46.5)
Baseline PSA: above or equal to median*	0.63 (0.48 to 0.82)	94/201 (46.8)	132/196 (67.3)
Asia region	0.57 (0.37 to 0.87)	34/91 (37.4)	53/104 (51.0)
Europe region	0.65 (0.49 to 0.87)	79/178 (44.4)	111/172 (64.5)
North and South America region	0.86 (0.60 to 1.23)	55/130 (42.3)	62/121 (51.2)
White race	0.67 (0.53 to 0.85)	124/282 (44.0)	166/275 (60.4)
Black/African American race	0.85 (0.24 to 3.06)	5/14 (35.7)	5/11 (45.5)
Asian race	0.62 (0.37 to 1.04)	24/66 (36.4)	35/72 (48.6)
Other race	NC	6/15 (40.0)	2/9 (22.2)

Subgroup	rPFS HR (95%CI)	Olaparib + Abiraterone (n/N)(%)	Placebo + Abiraterone (n/N)(%)
Data were derived from Interactive Voice/Web Response System stratification variables. Analysis performed included the stratification factors selected in the primary pooling strategy as covariates. Each subgroup analysis was performed using a Cox proportional hazards model that contained a term for treatment, factor, and treatment by factor interaction. A hazard ratio ,1 implies a lower risk of progression on olaparib. Subgroup categories with fewer than five events in either treatment group have NC presented. *Excludes patients with no baseline assessment. CI denotes confidence interval, ECOG Eastern Cooperative Oncology Group, HRRm homologous recombination repair gene mutation, NC noncalculable, and PSA prostate-specific antigen. Source: Clarke et al 2022(14)			

The HRRm status of patients at DCO3 was established to provide cost effectiveness analysis in the subgroup with HRRm. The HRRm population included 226 patients (90 positive both by tumour tissue and ctDNA, 28 positive by tumour tissue only and 108 positive by ctDNA only) and the non-HRRm population included 552 patients (328 negative both by tumour tissue and ctDNA, 38 negative by tumour tissue only and 186 negative by ctDNA only) (23,63).

There was a clinically meaningful rPFS improvement associated with olaparib plus abiraterone compared with placebo plus abiraterone in the HRRm subgroup (Figure 6) and non-HRRm subgroup (Source: patient-level data from DCO3 [data on file](64)

Table 18).

As with DCO1, all hazard ratio point estimates at DCO3 for the HRRm and non-HRRm populations favoured the combination of olaparib and abiraterone versus abiraterone and placebo (HRRm subgroup, HR=[redacted]; 95% CI, [redacted]; non-HRRm, HR=[redacted]; 95% CI, [redacted]) (64). Median rPFS results with olaparib plus abiraterone in both the HRRm and non-HRRm subgroups were broadly consistent with the FAS (ITT) population (see section B.2.6.1) and exceeded two years, indicating a clinically meaningful improvement in rPFS irrespective of HRRm status. The European Public Assessment Report noted the potential benefit of olaparib plus abiraterone in all HRRm subgroups, and considered these data support the use of the combination in all subgroups (65).

Figure 6. Kaplan-Meier plot of rPFS in HRRm subgroup based on investigator assessment (DCO3)

Source: patient-level data from DCO3 [data on file](64)

Table 18. Median rPFS estimates for HRRm subgroup analysis by investigator assessment (FAS; DCO3)

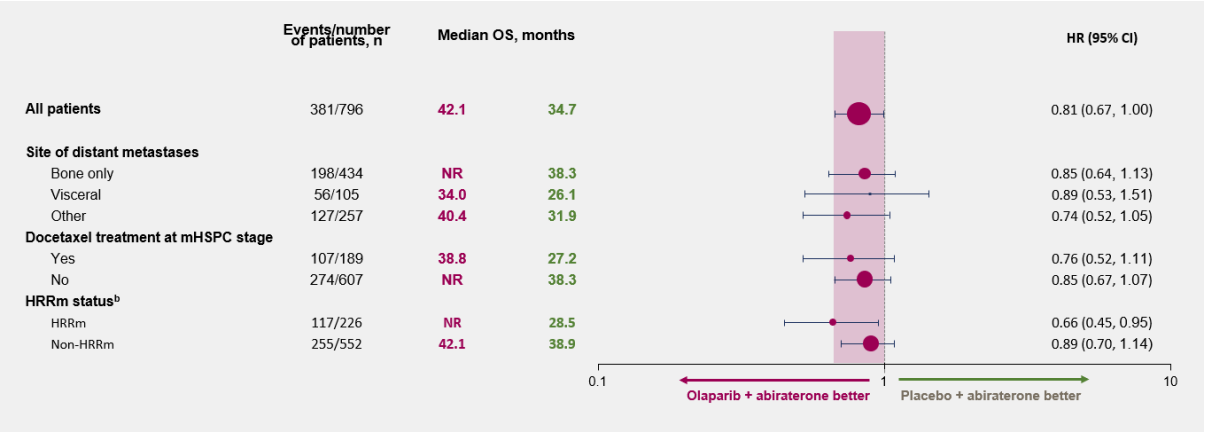
	Olaparib + Abiraterone	Placebo + Abiraterone
Investigator assessed – HRRm	n = 111	n = 115
Number of events, n (%)	[redacted]	[redacted]
Median PFS, months (95% CI)	[redacted]	[redacted]
HR (95% CI)	[redacted]	
Investigator assessed – non-HRRm	n = 279	n = 273
Number of events, n (%)	[redacted]	[redacted]
Median PFS, months (95% CI)	[redacted]	[redacted]
HR (95% CI)	[redacted]	

DCO, data cut-off; FAS, full analysis set; HR, hazard ratio; HRRm, homologous recombination repair gene mutation; PFS, progression free survival.
Aggregate data consistent with clinical trial protocol; HRRm was determined using ctDNA & tissue test
Source: patient-level data from DCO3 [data on file](64)

B.2.7.2 Subgroup analyses of OS

The numerical benefit in OS observed with olaparib plus abiraterone observed in the FAS (ITT) was maintained across stratification factors (site of distant metastases and prior docetaxel use) and the HRRm subgroup requested in the scope (Figure 7).

Figure 7. Forest plot of overall survival by subgroup (FAS; DCO3, 12 October 2022)



Final analysis / DCO3: 12th October 2022; [b]The pre-planned tumour tissue and plasma ctDNA testing was conducted after randomisation and before primary analysis. Results from tumour tissue and plasma ctDNA were combined to determine patients HRRm status.
CI, confidence interval; ctDNA, circulating tumour deoxyribonucleic acid; DCO, data cut-off; HR, hazard ratio; HRRm, homologous recombination repair gene mutation; ITT, intention-to-treat; mHSPC, metastatic hormone-sensitive prostate cancer; NR, not reached; OS, overall survival.
Source: Clark N. ASCO presentation slides (15)

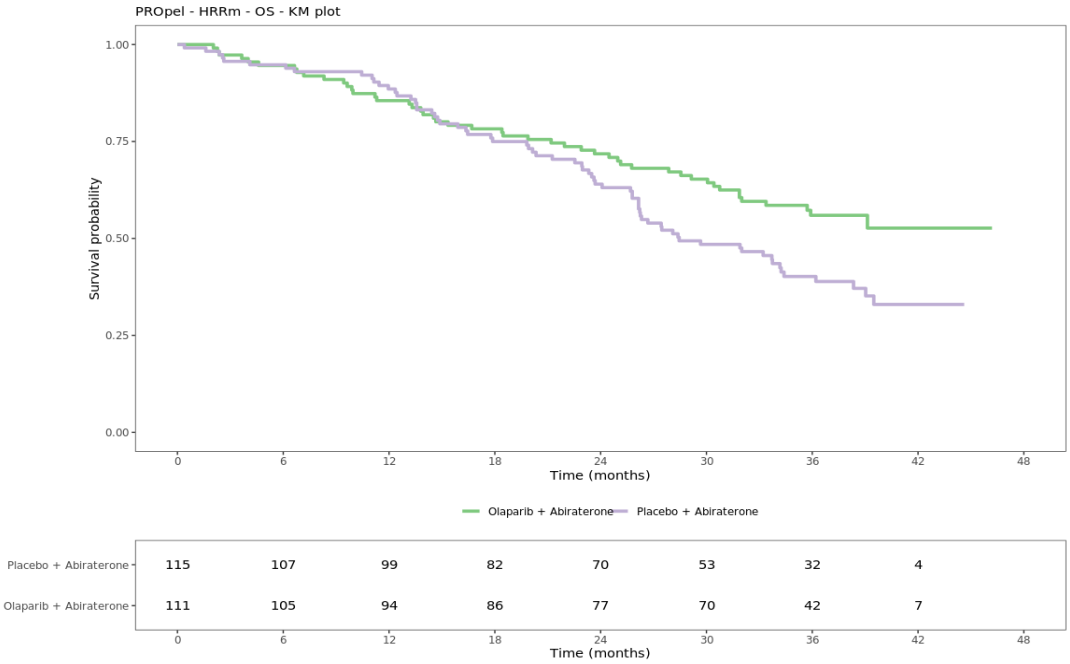
All hazard ratio point estimates for the HRRm and non-HRRm populations favoured the combination of olaparib plus abiraterone versus placebo plus abiraterone (HRRm subgroup, HR 0.66; 95% CI, 0.45– 0.95; non-HRRm, HR 0.89; 95% CI, 0.70–1.14). Median OS was not achieved with olaparib plus abiraterone, but available results in both the HRRm and non-HRRm populations indicate a clinically meaningful improvement of OS in these two populations (Table 19). The Kaplan-Meier curve for OS in the HRRm subgroup is provided in Figure 8.

Table 19. Median OS estimates for HRRm subgroup analysis by investigator assessment (FAS; DCO3, 12 October 2022)

	Olaparib + Abiraterone	Placebo + Abiraterone
Investigator assessed – HRRm	n = 111	n = 115
Number of events, n (%)	48 (43.2)	69 (60.0)
Median OS, months (95% CI)	NC (NC–NC)	28.45 [redacted]
HR (95% CI)	0.66 (0.45–0.95)	
Investigator assessed – non-HRRm	n = 279	n = 273
Number of events, n (%)	123 (44.1)	132 (48.4)
Median OS, months (95% CI)	42.05 (37.39–NC)	38.90 (32.53–NC)
HR (95% CI)	0.89 (0.70–1.14)	

DCO, data cut-off; FAS, full analysis set; HR, hazard ratio; HRRm, homologous recombination repair mutation; NC, not calculable; OS, overall survival.
Source: patient-level data from DCO3 [data on file](64); Clark N. ASCO presentation slides (15)

Figure 8. Kaplan-Meier plot of OS in HRRm subgroup based on investigator assessment (DCO3)



Source: patient-level data from DCO3 [data on file](64)

B.2.8 Meta-analysis

As the trial data for olaparib plus abiraterone is derived from a single phase 3 RCT, meta-analyses are not required.

B.2.9 Indirect and mixed treatment comparisons

The NICE scope stipulated the relevant comparators of interest for olaparib plus abiraterone for first-line mCRPC as enzalutamide and abiraterone (8). Based on its greater and growing use in clinical practice, enzalutamide is the primary comparator for olaparib plus abiraterone, with abiraterone the secondary comparator (see section B.1.3.3). The SLR detailed in Appendix D indicates that, whilst the PROpel trial provides direct comparative evidence for olaparib plus abiraterone against abiraterone (14), there are no direct comparative evidence for olaparib plus abiraterone against enzalutamide.

Real-world data (32,57) and clinical expert opinion (see section B.3.14) consistently indicate there is no difference in efficacy between abiraterone and enzalutamide in terms of rPFS or OS. In the absence of direct comparative data, it would, therefore, be reasonable to assume that the relative treatment effects of olaparib plus abiraterone versus abiraterone observed in the PROpel trial would apply to a comparison of olaparib plus abiraterone versus enzalutamide, and so pragmatically adopt the PROpel

trial results for abiraterone as a proxy for enzalutamide efficacy in the economic model. Nonetheless, for completeness, the feasibility of conducting indirect treatment comparisons to estimate the relative treatment effects of olaparib plus abiraterone against abiraterone and against enzalutamide has been explored.

B.2.9.1 Feasibility assessment

Studies investigating enzalutamide and abiraterone as the comparators of interest were considered for inclusion in the feasibility assessment, alongside the PROpel trial. The outcomes of interest for indirect comparison were rPFS and OS as these are key clinical outcomes for patients and clinicians, and data for these outcomes are required for the economic model (see sections B.3.2 and B.3.3). The SLR described in Appendix D identified the following studies as relevant to the decision problem and the indirect treatment comparison:

- PROpel trial for olaparib plus abiraterone versus abiraterone (14),
- COU-AA-302 trial of abiraterone (plus prednisone) versus placebo plus prednisone (12),
- PREVAIL trial of enzalutamide versus placebo (13),
- 9785-CL-0232 ('PREVAIL Asia') trial of enzalutamide versus placebo (66).

Given that four relevant studies were identified, the feasibility of conducting indirect comparisons using a network meta-analysis was undertaken. A qualitative evaluation of the studies was undertaken based on the study designs, baseline characteristics, and the following prognostic factors and treatment effect modifiers identified through a targeted literature search:

- ECOG performance status
- Gleason score
- Presence and extent of visceral, liver and bone metastasis
- Prostate specific antigen
- Time since diagnosis
- Pain score
- HRR mutation status.

Details of the designs, treatments received, sample size and type of endpoints available for the trials are summarised in the SLR report described in Appendix D, section D1.1.2.

B.2.9.1.1 Assessment of baseline characteristics

The baseline characteristics of the trial populations are summarised in Appendix D,section D1.1.2, Table 2. Similar eligibility criteria applied in all four trials, including patients with first-line mCRPC irrespective of their mutation status. Baseline characteristics were mostly similar between the studies; median age narrowly ranged between 69 to 72 years of age, all trials exclusively comprised patients with ECOG scores of 0-1, and similar high proportions of patients had bone metastases at baseline (83% of patients in PREVAIL, 93% in PREVAIL Asia, 81% in COU-AA-302 and 87% in PROpel). However, some potentially important differences exist between the trial populations:

- Gleason score tended to be higher in PROpel (14) and PREVAIL Asia (66) than in the COU-AA-302 (12) and PREVAIL(13) studies, with a higher number of patients scoring ≥8 at initial diagnosis (~66% for the former two studies vs. 52% for the latter two studies, respectively).
- Patients in COU-AA-302 and PREVAIL had a comparable median time since diagnosis (5.1 vs. 5.5 years) (12,13) but this was lower in the PROpel and PREVAIL Asia studies at 3 and 2.5 years, respectively (14,66), possibly due to the latter studies being more recent.
- Based on the brief pain inventory short form (BPI-SF), the PROpel population comprised of 19% of patients with moderate to severe pain scores at baseline (14), compared with 0-3% for the other trial populations (12,13,66).
- The presence of visceral metastasis was an exclusion criterion in COU-AA-302 (12) but in the PREVAIL, PREVAIL Asia and PROpel studies, patients with lung and/or liver metastases could be enrolled, with 10-15% of patients having visceral metastasis at baseline (13,14,66).
- All trials recruited patients irrespective of HRRm status, and only PROpel retrospectively determined HRRm status. Approximately 28% of patients in PROpel were subsequently determined to harbour HRR mutations (14), but it is unknown what proportion of the PREVAIL, PREVAIL Asia and COU-AA-302 trial populations harboured HRR mutations.

Other possible sources of heterogeneity between the studies included differences in the comparator arms of the studies, definition of rPFS and subsequent treatments received following disease progression, as discussed below.

B.2.9.1.2 Assessment of comparator arms

Despite being conducted in a similar disease setting, the studies of interest had distinct comparators arms:

- PROpel trial compared olaparib plus abiraterone (plus prednisone/prednisolone) versus placebo plus abiraterone (plus prednisone/prednisolone) (14),
- COU-AA-302 trial compared abiraterone (plus prednisone) versus placebo plus prednisone (12),
- PREVAIL and 'PREVAIL Asia' compared enzalutamide versus placebo (13,66).

There is therefore a difference in the proportion of patients receiving corticosteroid (prednisone/prednisolone) in the trials; 100% of patients in the placebo arms of COU-AA-302 and PROpel received corticosteroids, versus e.g. 30.2% in the placebo arm of PREVAIL (6). This can be explained by the licensing requirement for abiraterone to be taken with corticosteroids (19), which is not the case for enzalutamide. Whilst the incremental benefit of prednisone given with abiraterone is not known, there is evidence that when given alone, corticosteroids may have an impact on disease progression endpoints or the burden of symptoms (67,68). This evidence, alongside the imbalance in the use of prednisone across the control arms of COU-AA-302 and PREVAIL, suggests that grouping of placebo and prednisone as a common treatment arm, for the purpose of constructing a network between studies, may not be appropriate where the evidence suggest predisone has a therapeutic effect.

The difference in the comparator arms for the COU-AA-302, PREVAIL and PROpel introduces methodological heterogeneity, the extent and impact of which is difficult to quantify. This presents a challenge in constructing a network between the pivotal studies for the purposes of an indirect comparison.

Despite the inclusion of prednisone in the COU-AA-302 placebo arm, long-term OS outcomes from the final analyses for the comparator arms of COU-AA-302 and PREVAIL (based on a naïve comparison) were similar at a median of 30.3 months and 31.3 months, respectively. A difference was, however, observed in the naïve comparison of median PFS by investigator review; this was 8.3 months in the placebo plus prednisone group for COU-AA-302 (69), whereas it was 3.9 months for the placebo arm in PREVAIL (70).

The observed difference in PFS may be plausibly attributed to the addition of prednisone in COU-AA-302, given the evidence base which suggests corticosteroids may impact disease progression. However, no conclusions can be made about the potential impact of prednisone due to a lack of comparative data between prednisone and placebo, whilst cross-trial comparisons involve the presence of other heterogeneous factors which could be driving the differences in outcomes between the prednisone and placebo control arms. For example, the inclusion of patients with visceral disease in PREVAIL (and PROpel) may favour abiraterone in a naive comparison since patients with visceral

metastases were excluded from the COU-AA-302 study. The impact of the differences between the comparator arms, and the validity of assumptions required to facilitate a network of evidence for an NMA on PFS and OS are discussed further in sections B.2.9.2 and B.2.9.3, respectively.

B.2.9.1.3 Assessment of the definition of progression

In the COU-AA-302, PREVAIL and PREVAIL Asia studies, bone-related progression was assessed using the prostate cancer working group (PCWG) version 2 definition (66,69,70), whereas in PROpel the more contemporary PCWG version 3 definition was adopted (14). In PCWG2, progression was defined as at least two new lesions on the initial post-treatment bone scan, followed by at least two additional lesions on the subsequent scan (71). This rule was designed to control for tumour flare, a paradoxical worsening of the bone scan attributed to bone healing as a result of a favourable anti-tumour effect. PCWG3 updates PCWG2 by recommending that baseline patient assessment includes tumour histology, detailed records of prior systemic treatments and responses, and a detailed reporting of disease subtypes based on an anatomic pattern of metastatic spread. PCWG3 essentially introduced the concept of no longer clinically benefiting to underscore the distinction between first evidence of progression and the clinical need to terminate or change treatment, and the importance of documenting progression in existing lesions as distinct from the development of new lesions (72). Changes in imaging criteria between PCWG2 and 3, including increased nodal monitoring and recording of location of progression may impact on the cross-trial comparison of outcomes. To our knowledge, there is no comparative evidence on the impact of PCWG2 versus PCWG3 on outcomes, therefore any potential impact and the extent of these on an indirect comparison cannot be fully assessed.

B.2.9.1.4 Assessment of subsequent treatments

Since the initiation of the abiraterone study in first line mCRPC, the metastatic prostate cancer treatment landscape, and in particular the sequence of therapies, has rapidly evolved. Due to the different time points at which the relevant trials were conducted and the varied follow-up period, subsequent treatments received by patients following disease progression were also assessed as a potential source of heterogeneity between the studies.

COU-AA-302 was the first study to be initiated in April 2009 (73), 18 months prior to PREVAIL (September 2010) (74), followed by PREVAIL Asia (April 2014) (75) and PROpel almost a decade after COU-AA-302 (October 2018) (76). A *post-hoc* analysis of subsequent treatment patterns in the COU-AA-302 study based on the final OS data-cut off showed that 67.0% and 80.3% of patients in

the abiraterone and prednisone arms, respectively, received a subsequent therapy following discontinuation of study drug (77). Treatments received mainly comprised of taxane-based chemotherapy (~50%) and NHAs (~19%). In the published extended analysis of the PREVAIL study, 52.4% and 81.1% of patients in the enzalutamide and placebo arms, respectively, were given at least one subsequent therapy (13)[1]; the majority received taxane-based chemotherapy (56%) and to a greater extent than COU-AA-302, approximately 55% received a NHA across both study arms. In contrast, subsequent use of NHA following disease progression in the PREVAIL Asia trial was minimal, with only 2 patients (1%) in the placebo arm and none in the enzalutamide arm receiving NHA (abiraterone) (66). The overall subsequent treatments received in the PROpel study as reported at the final DCO3 were lower than both PREVAIL and COU-AA-302, with 44.9% and 54.4% of patients in the olaparib plus abiraterone, and abiraterone plus prednisone arms, respectively, receiving a post-discontinuation anti-cancer therapy (23). This difference maybe partially explained by changes in the treatment landscape but may also be driven by differences in follow-up period of the studies. Similar to the pattern observed in PREVAIL, the modalities of subsequent treatments received in PROpel mainly consisted of taxane-based chemotherapy (~43%) and NHA (~18%) (23).

The receipt of subsequent treatments would only impact the OS outcome. The main differences pertain to the proportion receiving NHAs, which was relatively lower in COU-AA-302 and PREVAIL Asia compared to the other studies. In the active treatment arms of COU-AA-302 and PREVAIL, and the comparator arm of PROpel, NHA retreatment is unlikely to have a significant impact on OS outcomes. There is strong evidence suggesting cross-resistance between abiraterone and enzalutamide and use of a second androgen receptor inhibitor (abiraterone for those with prior enzalutamide and vice versa) is likely to have only modest activity, hence current clinical guidelines do not recommend NHA retreatment (51). Clinical experts with experience in prostate cancer highlighted that NHA retreatment was not permitted or considered to have any meaningful impact on patients' survival outcomes and so the confounding bias on OS introduced due to this variability was highly unlikely to favour one treatment over another. The impact of the imbalance in the proportion crossing over in the placebo arms of COU-AA-302 versus PREVAIL cannot, however, be discounted given patients were naïve to treatment with an NHA and are therefore likely to experience clinical benefit. The relatively greater proportion of NHA usage in PREVAIL (38.8%) (13)[a] compared to the COU-AA-302 (7.7%) (77) in the

[a] The breakdown of the data was only available for the immediate next line (i.e., first subsequent treatment) rather than across all lines. However, this remains informative because the results are likely to be driven by the first subsequent therapy since the majority of patients with mCRPC receive only one subsequent line (32)

placebo arms of both studies may therefore bias survival estimates in favour of abiraterone over enzalutamide.

B.2.9.2 OS Network plot for olaparib plus abiraterone vs. enzalutamide

Due to distinct differences in the comparator arms between the four relevant trials, a network connection for olaparib plus abiraterone versus enzalutamide or via abiraterone and enzalutamide could not be established without grouping of placebo and prednisone, and assuming these regimens to have equivalent effect on OS.

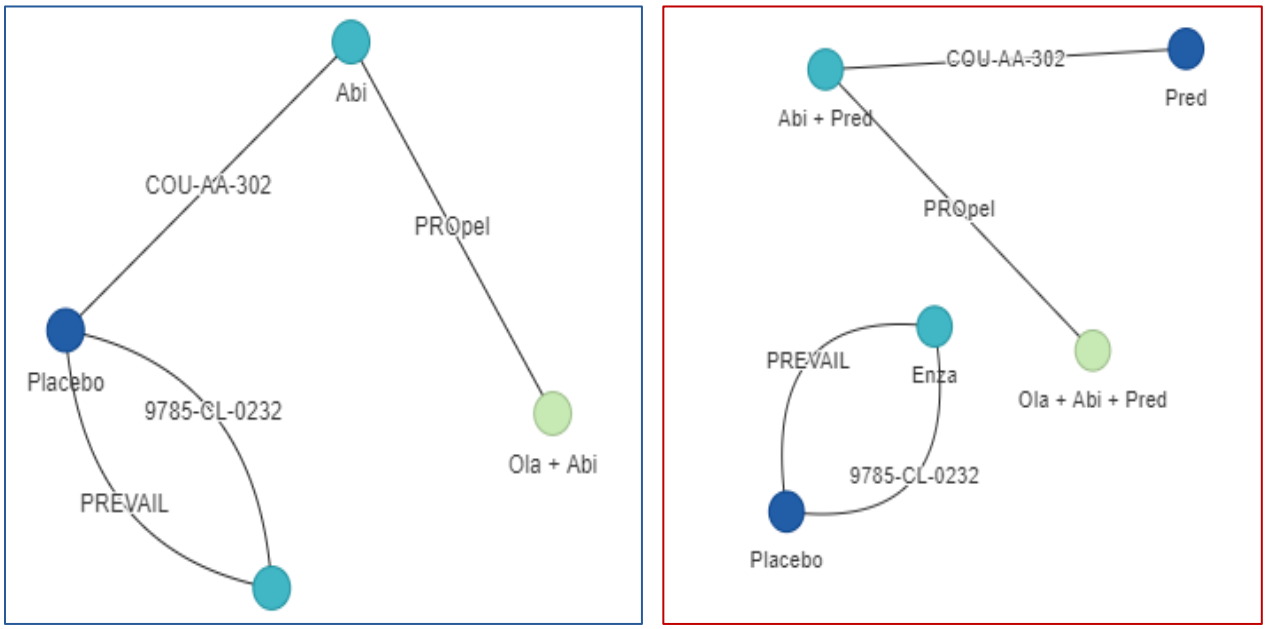
To our knowledge, there are no published head-to-head studies in the literature for prednisone versus placebo to directly estimate the effect of treatment with prednisone on OS. Corticosteroids inhibit prostate cancer growth through pleiotropic effects on suppression of adrenocorticotropic hormone (ACTH) secretion and downstream adrenal androgen production, as well as effects on cytokines and transcription factors. Thus, the incremental benefit of corticosteroids when given with abiraterone (which itself effectively suppresses adrenal androgen production) is not known. However, several studies have assessed the effect of prednisone alone on OS. Ghatalia et al conducted a pooled analysis of prospective studies exploring the impact of prednisone on outcomes based on the control arms of randomised studies that had or had not administered single agent prednisone. Data from 18 trials were considered, 9 of which had control arms that contained prednisone (n=2831) and, 9 without any prednisone (n=2784). The study reported that no significant differences were observed in relation to OS outcomes when treatments received with prednisone are compared to those that were administered without prednisone (78). Similarly, another prospective study based on a similar methodology of using pooled data from the control arms of two randomised studies, concluded that prednisone is not significantly associated with improvements in OS (79) . This is further substantiated by an earlier literature review and meta-analysis which also showed no significant effect of prednisone on overall survival (80).

Overall, there is a lack of evidence to suggest that treatment with prednisone directly impacts on OS outcomes. Therefore, it was considered reasonable to assume prednisone was equivalent to placebo for the purposes of building a network of evidence for OS. Figure 9 presents the network of evidence for OS based on this assumption – the prednisone plus placebo comparator arm of the COU-AA-320 study is labelled as placebo in the NMA plot presented.

This follows the approach adopted in a previously published NMA for enzalutamide versus abiraterone, which facilitated a network by assuming that corticosteroids (prednisone or prednisolone) were non-

therapeutic and therefore equivalent to the placebo arm from the enzalutamide PREVAIL study (81). Assuming the therapeutic equivalence of corticosteroids and placebo would facilitate a network connection for abiraterone and enzalutamide, anchored by placebo as a proxy for prednisone, an exploratory NMA for OS was conducted.

Figure 9: Network of evidence for OS with (left) and without (right) the assumption that prednisone is equivalent to placebo



Abi, abiraterone; Enza, enzalutamide; Ola, olaparib; Pred, prednisone

B.2.9.2.1 Methodology for OS NMA

The NMA was conducted in accordance with the National Institute for Health and Care Excellence Decision Support Unit Technical Support Document 2 (82).

The NMA for OS was conducted using Bayesian Markov Chain Monte Carlo (MCMC) methods. Hazard ratio (HR) data were synthesised on the log-HR scale. Mean and standard errors for the log HR were estimated from the published HRs and credible intervals (CrI). The standard errors (SE) were estimated as the range of the logged 95% CrI divided by 3.92. The mean log HR was estimated by the midpoint of the logged CrIs. Simulated data were sampled from the estimated normal distribution for the log HR and back transformed to HR to ensure the original central estimate and confidence intervals were recovered on back transformation. The latest HR reported in the published studies for enzalutamide (13), abiraterone (12) and the final data cut-off for PROpel (15,23) were used in the analyses.

Fixed treatment effects models presented in section B.2.9.2.2, which assume that the treatment effect estimates across studies are evaluating a common underlying treatment effect, i.e., that studies are homogeneous, were fitted in the first instance. These may not be plausible in the presence of heterogeneity across studies, so random treatment effects models were also fitted (see section B.2.9.2.3). Total residual deviance - the model's ability to predict the individual datapoints underlying it - were calculated to assess model fit. A comparison between the fit of the fixed effects and random effects models was assessed using the deviance information criterion (DIC); a lower DIC indicates a more parsimonious model. A vague Normal(0, 100) prior was used for the treatment effect in both the fixed and random effect models. For the between-study heterogeneity parameter in the random-effects models, suitable prior distributions were assessed.

Scenario analyses considering empirically-derived informative priors for the random treatment effects variance (83) specified for OS were also explored (see Section D1.1.2 in Appendix D).

B.2.9.2.2 Results of the fixed effects NMA for OS

A forest plot for a fixed effects NMA is provided in Figure 10 with abiraterone as the reference treatment. The HR point estimate for enzalutamide vs abiraterone ([redacted]) indicates that enzalutamide is not associated with clinically meaningful difference in OS compared to abiraterone. The 95% credible intervals overlaps unity, suggesting that the difference is not statistically significant at a 5% level.

For olaparib plus abiraterone compared to abiraterone, the NMA provides a HR of [redacted] which as expected is consistent with the efficacy observed in the PROpel study. As enzalutamide and abiraterone have similar antiandrogen modes of action and are considered by clinicians to be of equal efficacy, the hazards with enzalutamide are likely to be more closely aligned with the hazards for abiraterone than with the hazards for olaparib plus abiraterone for instance. It was therefore considered appropriate to estimate an OS hazard ratio for enzalutamide versus abiraterone in the exploratory NMA.

Figure 10: Forest plot for OS (fixed effects NMA), abiraterone as reference treatment

ABI, abiraterone; ENZ, enzalutamide; OLA, olaparib; PBO, placebo

B.2.9.2.3 Results of the random effects NMA for OS

A forest plot for a random effects NMA is provided in Figure 11 with abiraterone as the reference treatment. Consistent with the results based on the fixed effects NMA, the HR and 95% CrI indicate that enzalutamide is not associated with a clinically meaningful favourable OS outcome compared to abiraterone ( ). The 95% credible intervals are wide for the random effects NMA, strongly suggesting that the between-study variance is influenced by the vague prior, and that the models may not be providing a reasonable approximation of the between study heterogeneity. Only one comparison was informed by two studies, enzalutamide versus placebo, with all other comparisons being based on single studies, PROpel for olaparib plus abiraterone or COU-AA-302 for abiraterone. Thus, there was insufficient data in the network to reliably estimate between study heterogeneity. For this reason, random effects models with informative priors for between-study heterogeneity were explored, as discussed in section D1.1.3 in Appendix D. The HR and CrIs from this model ( ) are similarly consistent with the fixed effects model in indicating no meaningful difference in OS outcomes between abiraterone and enzalutamide.

Figure 11: Forest plot for OS (random effects NMA) abiraterone as reference

ABI, abiraterone; ENZ, enzalutamide; OLA, olaparib; PBO, placebo

B.2.9.2.4 Comparison of model fit for fixed vs. random effects NMA

The model fit summaries (residual deviance and DIC) for the fixed and random effects OS models are presented in Table 20. Both the fixed and random effects (vague priors) models fit the data reasonably well for OS. The random effects model with informative priors provides a similar model fit to the fixed and random effects model with non-informative priors (section D.1.1.3, Appendix D).

Table 20: Overall survival model fit summary

Model fit summary	Fixed effects model	Random effects model	Random effects model with informative priors
Residual deviance	[redacted]	[redacted]	[redacted]
DIC	[redacted]	[redacted]	[redacted]

DIC: deviance information criterion

B.2.9.2.5 Conclusions on OS for olaparib plus abiraterone vs enzalutamide

Notwithstanding the differences in trial patient populations, and the necessity to assume that prednisone is equivalent to placebo in terms of OS, the results of this exploratory NMA indicate no meaningful differences in OS between enzalutamide and abiraterone. This adds to the consistent evidence from real-world studies and clinical expert opinion that suggest enzalutamide and abiraterone are essentially of the same efficacy for OS. Therefore, the relative treatment effects of

olaparib plus abiraterone versus abiraterone directly observed in the PROpel trial are a reasonable proxy for the relative treatment effects of olaparib plus abiraterone versus enzalutamide. In the base case economic model, a hazard ratio of 1.0 for enzalutamide versus abiraterone was therefore applied to the abiraterone survival curves from PROpel to allow an estimate of the relative efficacy for olaparib plus abiraterone versus enzalutamide (see section B.3.3.1.2). This approach was validated with UK clinicians, as discussed in section B.3.14. Uncertainties in the indirect comparison of OS are discussed further in section B.2.12.4.2.

B.2.9.3 rPFS network plot for olaparib plus abiraterone vs. enzalutamide

As previously described for the OS NMA, the construction of an evidence network for an NMA of rPFS would require an assumption of equivalence between placebo and prednisone with respect to rPFS. The validity of the NMA is, therefore, partly dependent on the extent to which prednisone and placebo may be considered equivalent and interchangeable for the rPFS outcome when forming the evidence network.

B.2.9.3.1 Assessment of rPFS with prednisone vs placebo

The effect of prednisone on rPFS or response has been assessed in two studies. The pooled prospective study by Ghatalia et al (discussed above) reported on the impact of prednisone on PFS, and in contrast to their findings for OS, the authors reported that the median PFS was longer among the treatment arms including prednisone compared to arms where no prednisone treatment was given (78). In another retrospective study of two cohorts with mCRPC based upon whether prednisone was co-administered with docetaxel or not, prednisone with docetaxel was associated with reduced risk of progression on docetaxel (84). Expert feedback was also sought from UK clinicians on the clinical impact of prednisone and in particular, on PFS (see section B.3.14). Some of the experts viewed the role of corticosteroids as relevant for mitigating side effects that might occur whilst on abiraterone. However, other clinicians explained that corticosteroids were utilised in their clinical practice as a therapeutic treatment and reported a positive impact on prostate specific antigen (PSA) progression, which is regarded as an early indication of disease progression (85–87).

Overall, the available evidence in the literature and clinical opinion suggests that it is plausible that treatment with prednisone may have a therapeutic effect on rPFS. To adopt the control arm of the COU-AA-302 study as a proxy for placebo in the network may therefore lead to underestimation of the treatment benefit of abiraterone in the network and may benefit enzalutamide over abiraterone in any comparison of rPFS. It was therefore considered inappropriate to assume prednisone was equivalent to placebo for the purposes of the rPFS NMA, and therefore a connected network of trial data to enable

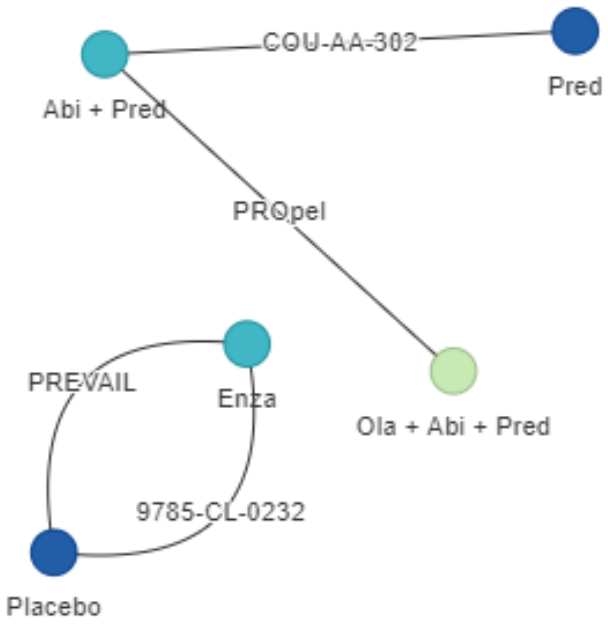
a NMA to be conducted for olaparib plus abiraterone or abiraterone versus enzalutamide for the rPFS outcome (Figure 12) could not be established.

Whilst not included in the network, a head-to-head Phase 2 sequencing study of abiraterone plus prednisone followed by enzalutamide, versus enzalutamide followed by abiraterone plus prednisone has been published (88). In this study, time to PSA progression on first line therapy was no different across the NHAs (HR=0.95, 95% confidence interval: 0.66-1.36). The study was excluded from the NMA because it did not report rPFS, and the cross-over design made the OS results incomparable to other trials.

Another prospective real-world multinational study including UK sites also found that there was no clinically meaningful difference in covariable-adjusted time to progression of abiraterone versus enzalutamide (HR=1.04; 95% credible interval: 0.85-1.27) (57). In contrast, the fixed effects PFS NMA by McCool et al, suggested that enzalutamide was superior to abiraterone (HR= 0.59; 95% credible interval: 0.48-0.72); however, the authors noted that the results should be interpreted with caution due to the limitation in the network construction which assumed prednisone was equivalent to placebo, and due to heterogeneity in the patient populations (81).

Six clinical experts with significant experience of using both abiraterone and enzalutamide were independently consulted to validate the impact of both therapies on PFS in the real-world setting (section B.3.14). All the experts agreed that they have observed no clinically meaningful differences in PFS for abiraterone plus prednisone versus enzalutamide in their clinical practice. They explained that abiraterone and enzalutamide are only differentiated in terms of their administration regimens, tolerability profiles, and interaction with other drugs, but are generally considered clinically equivalent with respect to efficacy.

Figure 12: Radiological progression free survival network plot



Abi, abiraterone; Enza, enzalutamide; Ola, olaparib; Pred, prednisone

B.2.9.3.2 Conclusions on rPFS for olaparib plus abiraterone vs enzalutamide

It is not possible to conduct an NMA (or other adjusted indirect treatment comparison) for olaparib plus abiraterone or abiraterone vs enzalutamide for the rPFS outcome. Based on the clinical feedback discussed above, and the results of the NMA for OS presented in Section B.2.9.2 that indicates equivalence, it was considered reasonable to assume that abiraterone and enzalutamide are also equivalent for rPFS. Similar to the approach for OS, a hazard ratio of 1.0, indicating no difference in PFS for abiraterone versus enzalutamide, was applied to the abiraterone rPFS survival curves from PROpel to permit estimation of relative efficacy for olaparib plus abiraterone versus enzalutamide within the base case economic model (see section B.3.3.2). This assumption is tested in the model in sensitivity analysis (see section B.3.11) using a HR for PFS estimated for abiraterone versus enzalutamide in a real-world study by Chowdury et al (57).

B.2.10 Adverse reactions

The adverse event (AE) profile of olaparib plus abiraterone in the PROpel trial was consistent with the known safety profiles of each agent used as monotherapy. There were no new safety concerns raised in the trial (9,14,65).

B.2.10.1 Exposure and dose intensity

At DCO3, the mean total duration of exposure to olaparib was [redacted] days versus [redacted] days with placebo. The mean total duration of exposure to abiraterone when combined with olaparib was [redacted] days versus [redacted] days when used with placebo (23) (Table 21). Combining olaparib with abiraterone did not, therefore, reduce the planned administration of abiraterone. It should be noted that patients who discontinued one study drug (e.g., olaparib without abiraterone or vice versa) continued in the study until both study treatments (i.e., olaparib and abiraterone) were permanently discontinued.

Table 21. Duration of exposure in PROpel (SAS; DCO3, 12 October 2022)

Treatment duration (days)	Olaparib + Abiraterone		Placebo + Abiraterone	
	Olaparib (n = 398)	Abiraterone[c] (n = 398)	Placebo (n = 396)	Abiraterone[d] (n = 396)
Total treatment duration[a]				
Mean (standard deviation)	[redacted]	[redacted]	[redacted]	[redacted]
Median (Min, Max)	[redacted]	[redacted]	[redacted]	[redacted]
Total number of treatment days	[redacted]	[redacted]	[redacted]	[redacted]
Actual treatment duration[b]				
Mean (standard deviation)	[redacted]	[redacted]	[redacted]	[redacted]
Median (Min, Max)	[redacted]	[redacted]	[redacted]	[redacted]
Total treatment days	[redacted]	[redacted]	[redacted]	[redacted]

[a]Total treatment duration = (last dose date - first dose date + 1).
[b]Actual treatment duration = (last dose date - first dose date + 1) excluding dose interruptions.
[c]Abiraterone for patients that received olaparib.
[d]Abiraterone for patients that received placebo.
DCO3 date: 12 October 2022.
bd, twice daily; DCO, data cut-off; Max, maximum; Min, minimum; N, number of patients in treatment; SAS, safety analysis set; qd, once daily.
Source: PROpel CSR Addendum 2 (DCO3)(23)

Treatment interruptions occurred more frequently with [redacted], and a higher proportion of patients required [redacted]. Similarly, dose reductions of [redacted] but the proportion of abiraterone dose reductions was similar in the combination and placebo arms ([redacted]) (Table 22).

The most frequently reported reason for treatment interruption or dose reduction was [redacted]. The median relative dose intensities were high for olaparib ([redacted]), placebo ([redacted]), and abiraterone ([redacted]), suggesting that dose intensity was not affected by dose interruptions or reductions. Median percentage intended dose exceeded [redacted] in all treatment arms (89). These data indicate that olaparib plus abiraterone was generally well tolerated.

Table 22. Treatment interruptions and dose reductions in PROpel (SAS; DCO3, 12 October 2022)

Number of patients, n (%)	Olaparib + Abiraterone		Placebo + Abiraterone	
	Olaparib (n = 398)	Abiraterone (n = 398)	Placebo (n = 396)	Abiraterone (n = 396)
Received planned starting dose	[redacted]	[redacted]	[redacted]	[redacted]
Number of patients with any dose interruption	[redacted]	[redacted]	[redacted]	[redacted]
Number of patients with a dose reduction	[redacted]	[redacted]	[redacted]	[redacted]
Number of patients with dose modification	[redacted]	[redacted]	[redacted]	[redacted]
RDI, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
RDI, median (IQR)	[redacted]	[redacted]	[redacted]	[redacted]
PID, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
PID, median (IQR)	[redacted]	[redacted]	[redacted]	[redacted]

IQR, interquartile range; PID, percentage intended dose; RDI, relative dose intensity; SD, standard deviation; SAS, safety analysis set
Source: PROpel DCO3 TLFs (Table 14.3.1.2)[data on file](89)

B.2.10.2 Overall safety and tolerability

The incidence of adverse events at DCO3 is summarised in (Table 23). The proportion of patients who experienced at least one AE of any grade was similar between treatment arms: olaparib plus abiraterone [redacted] and placebo and abiraterone [redacted]. Serious AEs and CTCAE Grade ≥ 3 events were reported for a higher proportion of patients in the olaparib plus abiraterone arm compared with the placebo plus abiraterone arm. The proportion of patients with AEs leading to discontinuation, dose reduction, or dose interruption of olaparib was higher in the olaparib plus abiraterone arm compared to placebo in the placebo plus abiraterone arm. The majority of AEs did not lead to discontinuation of study treatment. Adverse events with outcome of death were reported at a similar frequency in each treatment arm: [redacted] in the olaparib plus abiraterone arm and [redacted] in the placebo plus abiraterone arm; none were causally related to treatment with olaparib plus abiraterone (23) (Table 23).

Table 23. Adverse events in any category (SAS; DCO3; 12 October 2022)

AE category	Number of patients (%)[a]	
	Olaparib + Abiraterone (n = 398)	Placebo + Abiraterone (n = 396)
Any AE	389 (97.7)	380 (96.0)
Any AE causally related to olaparib + placebo	[redacted]	[redacted]
Any AE of CTCAE Grade 3 or higher	222 (55.8)	171 (43.2)
Any AE of CTCAE Grade 3 or higher, causally related to olaparib + placebo	[redacted]	[redacted]
Any AE with outcome of death	26 (6.5)	20 (5.1)
Any AE with outcome of death, causally related to olaparib + placebo	[redacted]	[redacted]
Any SAE (including events with outcome of death)	[redacted]	[redacted]

AE category	Number of patients (%)[a]	
	Olaparib + Abiraterone (n = 398)	Placebo + Abiraterone (n = 396)
Any SAE (including events with outcome of death), causally related to olaparib + placebo	[redacted]	[redacted]
Any AE leading to discontinuation of study treatment[b]	[redacted]	[redacted]
Any AE leading to discontinuation of olaparib + placebo[c]	69 (17.3)	34 (8.6)
Any AE leading to discontinuation of study treatment, causally related to olaparib + placebo	[redacted]	[redacted]
Any AE leading to dose reduction of study treatment[b]	[redacted]	[redacted]
Any AE leading to dose reduction of olaparib + placebo[d]	[redacted]	[redacted]
Any AE leading to dose reduction, causally related to olaparib + placebo	[redacted]	[redacted]
Any AE leading to dose interruption of study treatment[b]	[redacted]	[redacted]
Any AE leading to dose interruption of olaparib + placebo[e]	195 (49.0)	112 (28.3)
Any AE leading to dose interruption, causally related to olaparib + placebo	[redacted]	[redacted]

[a] Patients with multiple events in the same category are counted only once in that category. Patients with events in > 1 category are counted in each of those categories.
[b] 'Study treatment' refers to olaparib + placebo, and/or abiraterone, and/or prednisone/prednisolone.
[c]AEs leading to discontinuation of olaparib + placebo (regardless of any action taken with abiraterone).
[d]AEs leading to dose reduction of olaparib + placebo (regardless of any action taken with abiraterone).
[e]AEs leading to dose interruption of olaparib + placebo (regardless of any action taken with abiraterone).
Includes AEs with onset date, or worsening, on or after the date of first dose, up to and including 30 days after discontinuation of randomised treatment.
MedDRA version 25.0.
AE, adverse event; bd, twice daily; CTCAE, Common Terminology Criteria for Adverse Events (version 4.03); qd, once daily; SAE, serious adverse event; SAS, safety analysis set
Source: PROpel CSR Addendum 2 (DCO3)(23)

B.2.10.3 Most common AEs

The most frequently reported AEs of any grade in the olaparib plus abiraterone arm were [redacted]. In the placebo plus abiraterone arm, they were [redacted]. The full list of AEs occurring in ≥5% of trial participants at DCO3 is provided in Appendix F. The most commonly reported AEs in the olaparib plus abiraterone arm were consistent with the known adverse event profiles of olaparib or abiraterone or were considered to be attributable to the underlying disease (23).

Adverse events of Common Terminology Criteria for Adverse Events (CTCAE) Grade ≥ 3 at DCO3 were reported in [redacted] receiving olaparib plus abiraterone and [redacted] receiving placebo plus abiraterone. The most frequently reported CTCAE Grade ≥ 3 AEs reported in the olaparib plus abiraterone arm were [redacted], and in placebo plus abiraterone arm were [redacted](23). The full list of CTCAE Grade ≥ 3 AEs is provided in Appendix F.

B.2.10.4 Causally related adverse events

A higher proportion of patients had AEs of any grade considered to be causally related to olaparib/placebo in the olaparib plus abiraterone arm [redacted] than in the placebo plus abiraterone arm

[redacted]. The most frequently reported treatment-related AEs reported in the olaparib plus abiraterone arm were [redacted], and in the placebo plus abiraterone arm were [redacted] (23).

CTCAE Grade ≥ 3 AEs considered to be causally related to olaparib/placebo occurred in [redacted] patients in the olaparib plus abiraterone arm and in [redacted] in the placebo plus abiraterone arm. The most common AEs of CTCAE Grade ≥ 3, reported in the olaparib plus abiraterone arm were: [redacted]. The most common in the placebo plus abiraterone arm were: [redacted] (23). A full list of causally related, CTCAE Grade ≥ 3 AEs is provided in Appendix F.

B.2.10.5 Serious adverse events, discontinuations due to adverse events and deaths

Serious AEs (SAEs) were reported in [redacted] in the olaparib plus abiraterone arm and [redacted] in the placebo plus abiraterone arm. [redacted] was the most common SAE: [redacted] of patients in the olaparib plus abiraterone arm versus [redacted] in the placebo plus abiraterone arm. [redacted] was reported in [redacted] of patients on olaparib plus abiraterone and [redacted] on placebo plus abiraterone. COVID-19 was reported as an SAE in [redacted] of patients and [redacted] of patients in the olaparib plus abiraterone and placebo plus abiraterone arms, respectively. In addition, COVID-19 pneumonia was reported as an SAE in [redacted] of patients and [redacted] of patients in the olaparib plus abiraterone and placebo plus abiraterone arms, respectively (23). A full list of SAEs recorded in PROpel is provided in Appendix F.

Adverse events leading to discontinuation of study treatment (olaparib plus placebo, and/or abiraterone, and/or prednisone/prednisolone) were reported in [redacted] in the olaparib plus abiraterone arm and [redacted] in the placebo plus abiraterone arm. Adverse events leading to discontinuation were reported in [redacted] the olaparib plus abiraterone arm and [redacted] in the placebo plus abiraterone arm (Table 23). The most common AE leading to olaparib discontinuation (and dose reduction/interruption) was [redacted] (23).

B.2.10.6 Adverse events of special interest

The following were listed in the PROpel study protocol as AEs of special interest for patients with mCRPC receiving olaparib (90):

- myelodysplastic syndrome (MDS) or acute myeloid leukaemia (AML) events
- new primary malignancies

- pneumonitis.

From the start of the study up to DCO3 (12 October 2022), there were [redacted] cases of grade 4 MDS in the olaparib plus abiraterone arm (diagnosed during hospitalisation for COVID-19), and [redacted] of MDS or AML reported in the placebo plus abiraterone arm. The incidence of new primary malignancies and pneumonitis were similar between treatment arms: new primary malignancies were reported in [redacted] in the olaparib plus abiraterone arm and [redacted] in the placebo plus abiraterone arm; pneumonitis was reported in 5 patients (1.3%) in the olaparib plus abiraterone arm and [redacted] in the placebo plus abiraterone arm (23).

B.2.11 Ongoing studies

Further follow up analyses of the PROpel trial are anticipated in Q4 2023 and Q4 2024 (90).

B.2.12 Interpretation of clinical effectiveness and safety evidence

B.2.12.1 Context and decision problem

Olaparib plus abiraterone is indicated for the treatment of adult patients with mCRPC in whom chemotherapy is not clinically indicated (9). In this first line mCRPC setting, current treatment options include the NHAs abiraterone or enzalutamide, which in their phase 3 registrational trials provided median rPFS of approximately 16-20 months (12,13). In contrast, olaparib plus abiraterone provides a median PFS that exceeds 2 years for the first time in this patient group (14) (see section B.2.6.1), with consistent effects across all pre-specified subgroups, including patients with and without HRR mutations (9) (see section B.2.7.1). The early use of olaparib plus abiraterone in mCRPC therefore significantly delays disease progression, which can potentially delay the use of subsequent therapies that have diminishing efficacy (see section B.2.6.3) and improve overall survival (15) (see section B.2.6.3). Olaparib plus abiraterone therefore provides a much-needed new therapeutic option to improve outcomes in first line mCRPC irrespective of mutation status.

B.2.12.2 Summary of clinical evidence base

B.2.12.2.1 Efficacy and safety data in PROpel

Olaparib plus abiraterone provides unprecedented clinically meaningful improvements in disease progression and survival outcomes as a first line treatment for all patients meeting its licensed indication. It achieves this without detriment to patient health-related quality of life, and with a manageable safety and tolerability profile.

PROpel was a robust phase 3 trial, at low risk of bias and providing valid results for olaparib plus abiraterone against a NICE-recommended standard of care first line therapy (see section B.2.5). It met its primary endpoint, with olaparib plus abiraterone extending median rPFS by approximately 50% (8.2 months) compared with placebo plus abiraterone (24.8 months vs 16.6 months, respectively; HR 0.66; 95% CI: 0.54–0.81] $p < 0.0001$, primary analysis at DCO1) (14) (see section B.2.6.1). Results for rPFS were consistent across pre-specified subgroups, including in the HRRm subgroup (HR 0.50; 95% CI: 0.34– 0.73) and non-HRRm subgroup (HR 0.76; 95% CI, 0.60 to 0.97) (14) (DCO1, see section B.2.7.1).

At the final analysis of OS (DCO3), there was an improved OS compared with placebo plus abiraterone (median OS 42.1 vs 34.7 months, respectively; HR 0.81; 95% CI: 0.67–1.00; $p = 0.0544$) (15). Analyses at DCO1 and DCO2 showed OS improving over time (see section B.2.6.2). These data are supported by positive trends towards time to first subsequent therapy (TFST; 24.6 vs 19.4 months; HR, 0.76 [95% CI,0.64-0.90]; nominal p=0.0025) (section B.2.6.3.1), and second progression-free survival (PFS2; HR 0.76, 95% CI, 0.59–0.99; nominal p=0.0534) (15) (section B.2.6.3.2), which indicate long-term benefit with first line olaparib plus abiraterone and its potential to delay use of subsequent line therapies that have diminishing efficacy.

Adverse events with olaparib plus abiraterone were consistent with the known safety profiles for olaparib and abiraterone as individual treatments (14) (see section B.2.10). No detriment in health-related quality of life was observed with the addition of abiraterone to olaparib (see section B.2.6.5).

B.2.12.2.2 Comparative evidence vs enzalutamide

Real-world data (32,57) and clinical expert opinion (see section B.3.14) consistently indicate there is no difference in efficacy between abiraterone and enzalutamide in terms of rPFS or OS. In the absence of direct comparative data, it would, therefore, be reasonable to assume that the relative treatment effects of olaparib plus abiraterone versus abiraterone observed in the PROpel trial would apply to a comparison of olaparib plus abiraterone versus enzalutamide. For completeness, the feasibility of conducting adjusted indirect treatment comparisons using NMA to estimate the relative treatment effects of olaparib plus abiraterone against enzalutamide was explored using the PROpel trial of olaparib plus abiraterone vs abiraterone, the COU-AA-302 trial of abiraterone (plus prednisone) vs prednisone, and the PREVAIL and PREVAIL Asia trials of enzalutamide vs placebo (see section B.2.9).

As the COU-AA-320 trial used prednisone as a comparator, there are challenges in creating a trial network that connects to the placebo-controlled PREVAIL trial. Available evidence indicates that prednisone is unlikely to impact OS but may plausibly influence rPFS outcomes. Under a pragmatic but reasonable assumption that prednisone can be considered as a proxy for placebo in an analysis of OS, an exploratory NMA was conducted for OS. The results are aligned with the real-world evidence and clinical expert opinion that there is no meaningful difference in OS between enzalutamide and abiraterone (see section B.2.9.2). As it is not appropriate to make the same assumptions on prednisone for an analysis of rPFS, and to do so would bias the analysis against abiraterone, a NMA of rPFS was not feasible (see section B.2.9.3). However, given that all other available evidence (outside of analyses assuming therapeutic equivalence between the placebo arm of PREVAIL and the prednisone arm of COU-AA-302), indicates no differences in efficacy between enzalutamide and abiraterone for both rPFS and OS, it remains reasonable to assume equivalence between enzalutamide and abiraterone for both rPFS and OS. On this basis, the relative treatment effects of olaparib plus abiraterone vs abiraterone demonstrated in the PROpel trial are an appropriate proxy for the relative treatment effects of olaparib plus abiraterone vs enzalutamide. This approach was validated with UK clinicians, as discussed in section B.3.14.

B.2.12.3 Generalisability and relevance of clinical evidence base

The PROpel trial, participants and results are generalisable to the first line use of olaparib plus abiraterone in all mCRPC patients meeting its licensed indication in clinical practice in the UK.

B.2.12.3.1 Patient populations

Baseline characteristics of participants in the PROpel trial were generally in line with international registry data on first line mCRPC patients in real-world clinical practice (32,57). The trial enrolled patients who were naïve to cytotoxic chemotherapy or NHA in the mCRPC setting and irrespective of their HRRm status. The proportion of patients with HRR gene mutations (olaparib plus abiraterone, 27.8%; placebo plus abiraterone, 29.0%) (14) was consistent with what has been observed in real-world data and previous datasets, including the PROfound study of olaparib conducted in patients with previously treated mCRPC (58). 6.1% of participants were enrolled in the UK (14) and clinical expert opinion obtained via interviews with six UK oncologists indicates that the trial participants were broadly representative of patients in the first line mCRPC setting in clinical practice in the UK (see section B.3.14).

B.2.12.3.2 Intervention and comparators

In the PROpel trial, olaparib plus abiraterone was dosed and used in line with the subsequent licensed indication of the combination and their anticipated use of the combination in practice. The abiraterone comparator is a NICE-recommended standard of care NHA therapy in the first line mCRPC setting (7) and is a relevant comparator listed in the NICE scope for this appraisal (8).

Enzalutamide is also a relevant comparator. Based on its greater and growing use compared with abiraterone (10), enzalutamide is considered to be the main comparator for olaparib plus abiraterone, with abiraterone considered as a secondary comparator (see section B.1.3.3). Although there are no direct comparative data for olaparib plus abiraterone vs enzalutamide, evidence from real world studies and clinical experts consistently agrees that there is no meaningful difference in the efficacy of abiraterone and enzalutamide in terms of rPFS and OS. The exploratory NMA of OS discussed in section B.2.9.2 provides further evidence to support this conclusion. The evidence from PROpel is therefore a reasonable proxy for the relative effects of olaparib plus abiraterone vs abiraterone and vs enzalutamide.

B.2.12.3.3 Outcomes

The primary endpoint of the PROpel trial was rPFS assessed by investigators (14). rPFS is a well-accepted primary endpoint in oncology trials, was used as a primary endpoint in the key trials of NHAs in this setting (12,13) and was accepted by the regulatory authority as appropriate for the PROpel trial (9,65). rPFS assessed by blinded independent central review was conducted as a sensitivity analysis and demonstrated that the investigator assessment of rPFS was reliable and valid (see section B.2.6.1).

OS was a key secondary endpoint of PROpel. Due to the additional benefit over placebo plus abiraterone, OS data for olaparib plus abiraterone were not fully mature at the time of the final OS analysis. However, at each data cut there was a trend towards an improvement in OS with olaparib plus abiraterone, and by the final analysis there was over a 7-month improvement in median OS compared with placebo plus abiraterone (42.05 vs 34.69 months) (15) (see section B.2.6.2). Of note, the median OS of 34.69 months (95%CI: 30.95–39.29) observed with placebo plus abiraterone in the PROpel trial is highly consistent with the median OS of 34.7 months (95% CI 32.7–36.8) for abiraterone in the phase 3 COU-AA-302 trial that supported its regulatory licensing and its recommendation by NICE in the first line mCRPC setting (7,19). The consistency in abiraterone outcomes between the two trials provides a further degree of confidence in the validity of the PROpel trial outcomes.

Longer-term effects were additionally assessed by TFST, which showed that treatment with olaparib plus abiraterone resulted in a nominally significant delay in the use of subsequent therapies. PFS2 also showed a trend towards improvement with olaparib plus abiraterone (15) (see section B.2.6.3). Health-related quality of life, which is a particularly important outcome in the mCRPC setting where treatment is given with palliative rather than curative intent, was assessed using multiple instruments that consistently demonstrated no quality-of-life detriment from the use of olaparib plus abiraterone (23) (see section B.2.6.5).

Collectively, PROpel assessed a comprehensive, clinically relevant set of outcomes that are of direct relevance to patients with mCRPC and their management. Results across these outcomes consistently support the benefit of olaparib plus abiraterone, with no detriment to health-related quality of life. The use of rPFS and OS data from the abiraterone comparator arm of PROpel as a proxy for rPFS and OS with enzalutamide is reasonable and ensures appropriate outcomes are considered for all relevant comparators.

B.2.12.4 Strengths and limitations of clinical evidence

B.2.12.4.1 PROpel trial of olaparib plus abiraterone vs abiraterone

PROpel was a robust phase 3 trial, at low risk of bias and providing valid results for olaparib plus abiraterone against a NICE-recommended standard of care first line therapy (see section B.2.5). In the ITT population, the study demonstrated that olaparib plus abiraterone extended median investigator-assessed rPFS to over 2 years for the first time in mCRPC in whom chemotherapy is not clinically indicated (see section B.2.6.1). These clinically and statistically significant results were supported by the sensitivity analysis of rPFS by BICR, which indicates that the investigator-assessed rPFS is reliable. Results were also consistent across pre-specified subgroups, including patients with or without HRR mutations (see section B.2.7.1); however, the trial was not powered to assess efficacy within these subgroups, so results should be interpreted with caution.

OS data with olaparib plus abiraterone were not fully mature at the time of the final OS analysis; however, there was a clear trend towards improvement in OS over each of the pre-specified data cuts, and OS was extended by over 7 months at the final planned analysis (see section B.2.6.2). These results are supported by positive trends towards TFST (section B.2.6.3.1), and PFS2 (section B.2.6.3.2), which indicate long-term benefit with first line olaparib plus abiraterone and its potential to delay use of subsequent line therapies that have diminishing efficacy. Adverse events with olaparib plus abiraterone were consistent with the known safety profiles for olaparib and abiraterone as individual treatments (see section B.2.10) and no detriment in health-related quality of life was

observed with the addition of abiraterone to olaparib (see section B.2.6.5). The PROpel trial therefore provides compelling evidence of an improved clinical benefit of olaparib plus abiraterone over current standard of care in its full licensed indication.

All patients recruited to the PROpel trial were deemed eligible to receive abiraterone (14). Abiraterone, as a first line treatment in mCRPC, is only licensed and recommended for use by NICE in people who have no or mild symptoms (7) but over 20% of patients in PROpel had BPI-SF score ≥4, which is indicative of symptomatic disease. As there is evidence that BPI-SF score is predictive of OS in mCRPC (91), this could potentially impact the relative treatment effects observed in the trial. However, as the PFS and OS outcomes with abiraterone in the PROpel trial are highly consistent with those reported with abiraterone in its pivotal COU-AA-302 trial, the enrolment of a minority of patients with symptomatic disease in PROpel does not appear to be a significant source of bias.

Following discontinuation of the PROpel trial intervention and comparator, a minority of patients received subsequent therapies that are not routinely used in UK clinical practice (see section B.2.6.3.1); however, these were well balanced between treatment arms, do not influence the primary endpoint of rPFS and UK clinical expert opinion indicates these are not anticipated to materially bias the OS estimates compared with what they would anticipate to see in practice (see section B.3.14).

Collectively, despite some limitations, evidence from the PROpel is of high quality, at low risk of bias and is generalisable to the use of olaparib plus abiraterone in mCRPC patients meeting its licensed indication in clinical practice in the UK.

B.2.12.4.2 Indirect comparison of olaparib plus abiraterone vs enzalutamide

There are no direct comparative data for olaparib plus abiraterone versus enzalutamide; however, evidence from real-world studies, clinical expert opinion and the exploratory NMA for OS discussed in section B.2.9.2 are all consistent in indicating that enzalutamide and abiraterone have equivalent efficacy. From this, it is appropriate to infer the relative treatment effects of olaparib plus abiraterone versus enzalutamide from the relative treatment effects of olaparib plus abiraterone versus abiraterone directly observed in the PROpel trial.

The validity of the NMA for OS is contingent on the validity of the data contributing to the trial network. The trial network includes the most robust and relevant trial data possible; however, a key assumption required to construct the trial network was that the prednisone comparator of the COU-AA-302 abiraterone trial has no therapeutic effect on OS and is effectively equivalent to placebo. As discussed

in detail in section B.2.9.2, this is a reasonable and pragmatic assumption for OS, but was not for rPFS. An exploratory NMA for OS was therefore undertaken but it was not feasible to do this for rPFS.

As discussed in section B.2.9.1, there are some potentially important differences in prognostic factors in the trial populations that may impact on the resulting OS treatment effect estimates, including Gleason scores, time since diagnosis, proportion of enrolled patients with symptomatic disease, and inclusion or exclusion of patients with visceral disease. It is unknown what proportion of the PREVAIL, PREVAIL Asia and COU-AA-302 trials harboured HRR mutations. It is not possible to adjust for all these potential prognostic factors. Greater differences in these factors exist between the PROpel trial population versus the PREVAIL and COU-AA-302 trial populations, than between the PREVAIL and COU-AA-302 trial populations. However, rPFS and OS with the abiraterone comparator arm of PROpel are highly consistent with rPFS and OS observed with abiraterone in the COU-AA-302 trial. Therefore, despite differences in potential prognostic factors, on average they are not anticipated to be a significant source of bias in the NMA. Enzalutamide and abiraterone also have similar antiandrogen modes of action and are considered by clinicians to be of equal efficacy, the hazards with enzalutamide would be more closely aligned with the hazards for abiraterone than with the hazards for olaparib plus abiraterone. It is therefore appropriate to estimate an OS HR for enzalutamide versus abiraterone and apply this to the abiraterone arm of the economic model.

Differences exist in the in the receipt of subsequent treatments in the trials, which may impact on OS estimates; however, the overall proportion receiving subsequent treatments, and in particular, chemotherapy-based agents, is similar between studies. The main difference pertains to the proportion receiving retreatment with NHAs, which was relatively lower in the COU-AA-302 study compared to the PROpel and PREVAIL studies. In the active treatment arms of COU-AA-302 and PREVAIL, and the comparator arm of PROpel, NHA retreatment is unlikely to have a significant impact on OS outcomes; NHA retreatment is generally considered to be ineffective (51). However, there is an imbalance in the proportion crossing over in the comparator arms of COU-AA-302 vs PREVAIL, the impact of which cannot be discounted given patients in the comparator arms were naïve to treatment with an NHA and therefore likely to experience clinical benefit. The relatively greater proportion of NHA usage in the comparator arm of PREVAIL compared to the COU-AA-302 may therefore bias survival estimates in favour of abiraterone over enzalutamide in any comparison. Nonetheless, the resulting OS HR for enzalutamide vs abiraterone in the NMA (see section B.2.9.2) indicates no meaningful difference in OS for these agents, in line with real-world evidence and clinical expert opinion.

Despite clear limitations in the OS NMA, and the inability to conduct a rPFS NMA, all evidence to date supports the clinical expert opinion that enzalutamide and abiraterone have equivalent efficacy. Therefore, the relative treatment effects of olaparib plus abiraterone versus abiraterone directly observed in the PROpel trial are a reasonable proxy for the relative treatment effects of olaparib plus abiraterone versus enzalutamide. In the base case economic model, a HR of 1.0 for enzalutamide versus abiraterone was therefore applied to the abiraterone rPFS and OS survival curves from PROpel to allow an estimate of the relative efficacy for olaparib plus abiraterone versus enzalutamide (see section B.3.3.1.2). This approach was validated with UK clinicians, as discussed in section B.3.14.

B.2.12.5 Conclusions from clinical evidence

Based on robust phase 3 trial data, olaparib plus abiraterone provides clinically meaningful and statistically significant improvements in rPFS of over 8 months, with an improvement in median OS of over 7 months, compared with current standard of care therapy. The greater benefit of olaparib plus abiraterone observed in the ITT population of PROpel persisted across pre-specified subgroups, including patients with or without HRR mutations, and the results are applicable to comparisons against both abiraterone and enzalutamide. These data provide compelling support for the use of olaparib plus abiraterone in its full licensed indication as a first line therapy for patients with mCRPC in whom chemotherapy is not clinically indicated.

B.3 Cost effectiveness

Summary of cost effectiveness

- A three health-state partitioned survival model was developed in Microsoft Excel® to assess the cost effectiveness of olaparib plus abiraterone. The health states included progression-free, progressed disease and death states.
- The model is fully aligned with the NICE reference case and compares olaparib plus abiraterone in its full licensed indication against the comparators listed in the NICE scope: enzalutamide and abiraterone.
- The PROpel trial provides the OS and PFS data for olaparib plus abiraterone versus abiraterone. These data are extrapolated over a lifetime horizon using robust parametric modelling that was informed and validated by clinical experts and external data sources.
- Based on real world evidence sources, clinical expert opinion and exploratory network meta-analysis described in section B.2.9, OS and PFS with enzalutamide is reasonably assumed to be the same as observed for abiraterone.
- Health state utility values are derived from EQ-5D-5L data collected directly from patients in the PROpel trial and mapped to EQ-5D-3L.
- Enzalutamide is the primary comparator as described in section B.1.3.3. Compared with enzalutamide, olaparib plus abiraterone has a base case ICER of [redacted]
- Abiraterone has recently become available as a generic drug, resulting in a much reduced acquisition cost and a correspondingly greater ICER for olaparib plus abiraterone against this comparator.
- Extensive sensitivity and scenario analyses demonstrate that the base case model is robust to most parameters and assumptions. As may be expected, the model is most sensitive to the assumed OS and time on treatment for the enzalutamide comparator, which would drive its life years and costs.
- In the subgroup of patients harbouring HRR mutations, olaparib plus abiraterone had an ICER of [redacted] versus enzalutamide and [redacted] compared with abiraterone.
- Olaparib plus abiraterone is a plausibly cost effective therapy option in its licensed indication.

B.3.1 Published cost-effectiveness studies

A systematic literature review of economic evaluations of first line therapies for mCRPC was conducted to 01 December 2022 (see Appendix G). This identified a total of 30 published reports of 29 unique analyses. No published economic evaluations of olaparib in combination with abiraterone were identified. Fifteen previous HTAs of first line therapies for mCRPC were identified, including two NICE appraisals containing cost-effectiveness analyses of the relevant comparators of olaparib in combination with abiraterone: enzalutamide (TA377) (6) and abiraterone (TA387) (7). These relevant cost-effectiveness analyses are summarised in Table 24.

Table 24. Summary of published cost effectiveness analyses in HTAs relevant to this appraisal

NICE TA	Summary of model	Intervention / comparator	Patient population	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (per QALY gained)
TA377 (6)	**Model type:** Markov model with 3 health states: stable disease, progressed disease, and death. 3 further health states included in the progressed state: post progression 1, post progression 2 and palliative care. **Time horizon:** 10 years **Perspective:** NR **Cycle length:** 1 week **Discount rate for cost:** 3.5% **Discount rate for outcomes:** 3.5%	**Intervention:** Enzalutamide **Comparator:** Abiraterone; BSC	Patients with asymptomatic or mildly symptomatic mCRPC after failure of ADT and in whom chemotherapy is not yet clinically indicated.	NR	NR	Enzalutamide vs BSC: £27,036/QALY
TA387 (7)	**Model type:** DES model **Time horizon:** Lifetime **Perspective:** Payer **Cycle length: NR** **Discount rate for cost:** 3.5% **Discount rate for outcomes:** 3.5%	**Intervention:** Abiraterone followed by docetaxel followed by BSC **Comparator:** BSC followed by docetaxel followed by Abiraterone	Patients with mCRPC before chemotherapy is indicated.	Incremental costs: Abiraterone vs BSC: Original submission: £26,404 Resubmission: £16,055	Incremental health outcomes, abiraterone vs BSC: Original submission: QALYs: 0.57 LYGs: 0.62 Resubmission: QALYs: 0.56 LYGs: 0.62	Abiraterone vs BSC: Original submission: £46,722/QALY Resubmission: £28,563/QALY

BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; mCRPC, metastatic castration resistant prostate cancer; QALYs, quality-adjusted life years

B.3.2 Economic analysis

In the absence of published cost effectiveness analyses of olaparib in combination with abiraterone, a *de novo* cost effectiveness model was developed to conduct a cost-utility analysis in line with the NICE reference case. An overview of the model is provided in Table 25.

Table 25. Overview of cost effectiveness model

	Details	Rationale
Population	Patients meeting the licensed indication for olaparib in combination with abiraterone in the UK, i.e., adult patients with mCRPC in whom chemotherapy is not clinically indicated. An exploratory subgroup analysis based on HRRm status is provided to demonstrate the cost effectiveness of olaparib in combination with abiraterone across its licensed indication.	In line with scope
Intervention	Olaparib in combination with abiraterone (with prednisone or prednisolone)	In line with scope
Comparators	Primary comparator: Enzalutamide Secondary comparator: Abiraterone (with prednisone or prednisolone)	In line with scope and NICE reference case
Perspective on costs	NHS and PSS	In line with NICE reference case
Perspective on outcomes	All health effects for patients	In line with NICE reference case

	Details	Rationale
Type of economic evaluation	Cost utility analysis	In line with NICE reference case
Model type	A three health-state partitioned survival model (progression-free [PF], progressed disease [PD] and death)	In line with recent NICE TAs of prostate cancer therapies (TA580, TA660, TA712, TA740, TA741)
Time horizon	Lifetime horizon (set at 30 years in the base case)	Sufficient to capture all important differences in costs and outcomes In line with NICE reference case
Cycle length	1 month (30.44 days) with half-cycle correction	Sufficient granularity to capture costs and effects
Discounting	3.5% in the base case for both costs and outcomes	In line with NICE reference case
Synthesis of evidence on health effects	Systematic literature review identified PROpel trial providing direct RCT evidence for rPFS and OS with olaparib plus abiraterone vs abiraterone. NMA of RCTs provides indirect comparative OS data for olaparib plus abiraterone vs enzalutamide based on studies identified in the systematic literature review.	In line with NICE reference case
Measuring and valuing health effects	Health effects expressed in terms of QALYs using EQ-5D-3L	EQ-5D is preferred measure of HRQoL, in line with NICE reference case.
Source of data for measurement of HRQoL	EQ-5D-5L measured directly in patients in the PROpel trial were mapped to derive EQ-5D-3L	In line with NICE reference case
Source of preference data for valuation of changes in HRQoL	Hernandez Alava et al value set estimated in a representative sample of UK population	In line with NICE reference case
Equity considerations	QALYs relate only to patients. No severity weighting is applied	In line with NICE reference case
Evidence on resource use and costs	Costs relate to NHS resource use and drug costs, and are valued using recent NHS reference costs, eMIT and BNF drug prices	In line with NICE reference case

AE, adverse event; HRQoL, health-related quality of life; HRRm, homologous recombination repair pathway gene mutation; ICER, incremental cost-effectiveness ratio; LY, life-year; mCRPC, metastatic castration-resistant prostate cancer; NHA, new hormonal agent; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; OS, overall survival; PD, progressed disease; PF, progression free; PSS, Personal Social Services; QALY, quality-adjusted life-year; rPFS, radiological progression-free survival; SRE, skeletal-related event; TTD, time to treatment discontinuation.

B.3.2.1 Patient population

The patient population in the base-case model reflects the full UK licensed indication under appraisal: adult patients with mCRPC in whom chemotherapy is not clinically indicated (9). This is aligned with the population of the PROpel trial (see section B.2.3).

The scope for this appraisal requested subgroup analyses in patients with HRR mutations, where the data allows (8). The PROpel trial pre-specified subgroup analyses based on HRRm status; mutation status was retrospectively determined after enrolment and randomisation in the trial (14). An exploratory cost utility analysis in the subgroup of patients with HRRm is provided in line with the request in the scope (see Appendix E.1.1).

B.3.2.2 Model structure

A three health-state partitioned survival model was developed in Microsoft Excel® to assess the cost effectiveness of olaparib plus abiraterone versus abiraterone and enzalutamide. This is a widely used and accepted approach to modelling the cost effectiveness of oncology therapies, which avoids the need for more complex methods, such as discrete event simulation (DES) or models with greater numbers of health states. The NICE appraisal of abiraterone in first-line mCRPC (TA387) utilised DES model which was referred to as "*complex and lacked transparency, which made it difficult for the evidence review group (ERG) to validate and critique, and for the committee to determine the plausibility of the model outcomes*" (7). As per the NICE Decision Support Unit (DSU) Technical Support Document (TSD) 19 (92), partitioned survival modelling is well understood, intuitive and easy to communicate, hence, this was adopted as the most appropriate modelling methodology. The three-state structure with a monthly cycle reflects the natural disease course and the primary objectives of treatment for patients with mCRPC in the form of delaying progression, with its associated treatment costs and impact on quality of life, and in extending survival (see section B.1.3.1). The model structure directly leverages the primary and key secondary time-to-event endpoints in the PROpel study, namely OS and PFS. The structure is also consistent with previous approaches adopted in recent NICE technology appraisals for prostate cancer therapies (47–49,93,94).

Mutually exclusive health states in the model included:

- **Progression free (PF):** patients who are alive with no disease progression; patients can remain in this state, or progress to the progressed disease (PD) or death states at the end of each cycle.
- **Progressed disease (PD):** patients who are alive with PD; patients in the PD state can either remain in this state or enter the death state
- **Death:** patients who transition from PF and PD to death from any cause; patients remain in the death state for the time horizon.

The structure of the model is summarised in Figure 13. All patients entered the model in the PF health state and were assumed to initiate first line treatment for mCRPC. In each model cycle, patients could either remain in the health state, progress, or die. The proportion of patients who are progression free are calculated directly from the cumulative survival probabilities for rPFS from the PROpel trial. Although the PROpel trial included analysis of rPFS by blinded independent central review, the primary endpoint was rPFS based on investigator-assessed progression (14). The model uses this investigator-assessed progression as it better represents how progression would be assessed in clinical practice (i.e., by the treating physician).

The PD health state consists of patients who are alive but whose disease has progressed. Consistent with the natural history of progressive mCRPC, it was assumed that disease progression is irreversible, meaning patients could move from the PF to PD health state but were not able to move from PD to PF. In each model cycle, the proportion of patients with progressed disease was calculated as the difference between the cumulative survival probabilities of OS and rPFS (i.e., patients who are alive but not progression-free) (Figure 14).

The death state is an absorbing state; patients who entered the death state remain in that state until the end of the time horizon. The state occupancy for death was calculated as 1 – OS (i.e., all patients who are not alive). A one-time end-of-life cost was applied at the time of death. Extrapolated OS curves were adjusted for general population mortality informed by life tables for the UK (95) to ensure that the disease-specific probability of death never falls below that of the general population.

Outcomes in the model included life years and QALYs accrued in the PF and PD health states. The PF state represents the period of relatively better quality of life while the disease is under control and PD represents the period with new and worsening symptoms. The efficacy of subsequent treatment post-discontinuation of initial therapy is not explicitly captured in the model; however, as OS is fully captured in the model, varying the composition of subsequent treatment only impacts subsequent treatment costs, an approach that is consistent with other Health Technology Assessment (HTA) submissions for mCRPC.

The costs of drug therapy are based on the proportion of patients receiving olaparib and abiraterone over time. These calculations were modelled independently of rPFS and OS, using data on the time to discontinuation (TTD) of study drug (olaparib only) and the TTDA of abiraterone (for both arms) from PROpel. These data represent the actual duration of individual treatments in the trial which, importantly, captures the impact of both tolerability and progression on treatment persistence. Disease monitoring and follow-up costs were accrued based on whether a patient was receiving first-line treatment or in post-first line care. Data from the PROpel study was used to model the health outcomes for olaparib versus abiraterone, and enzalutamide (assumed to have equivalent efficacy as abiraterone, as discussed in section B.2.9.2).

As is standard practice for developing partitioned survival models in oncology, the following structural assumptions were applied in the model to ensure logical patient flow:

- The risk of death in the modelled population was always at least equal to or greater than the all-cause risk of death of the UK general population, as determined by published life tables. In each cycle, the risk of death was assumed equal to or greater than that of the general population matched on age and male gender.
- The cumulative survival probabilities for rPFS and time to discontinuation of treatment were constrained to be less than or equal to the cumulative survival of OS, such that the number of patients who are in the PF health state or receiving treatment could not exceed the total number of patients alive (i.e., the sum of patients who are in the PF and PD health states)

Figure 13. Health states of the partitioned survival model

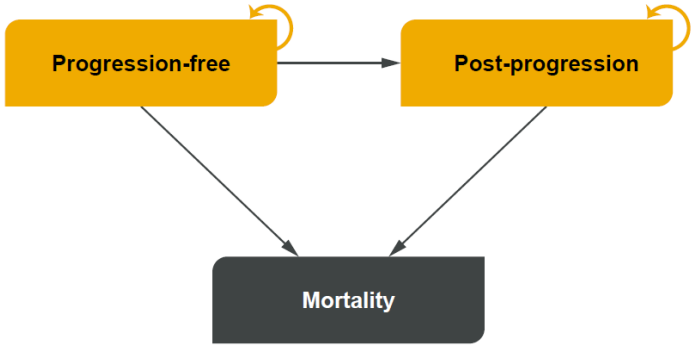
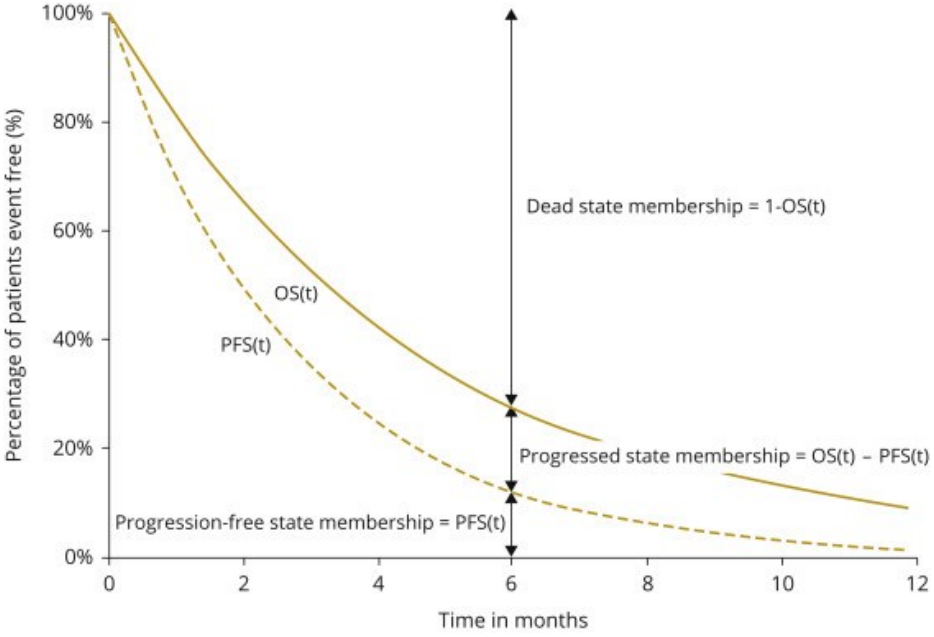


Figure 14. Partitioned survival model estimation of health state occupancy



OS, overall survival; PFS, progression-free survival; (t), time

A comparison of key features of the current model and earlier models used to support the NICE appraisals of enzalutamide (TA377) and abiraterone (TA388) in the first line mCRPC setting, which are the relevant comparators for this appraisal (8), is provided in Table 26. In the base-case analysis, cost and health outcomes were modelled over an appropriate lifetime horizon, which was assumed to be 30 years (i.e., lifetime, aged 100 years) and discounted at an annual rate of 3.5% as per the NICE reference case. The model also uses the most robust sources of utilities data and costs and adopts the same appropriate assumptions on persistence of treatment effects as the relevant comparators in this disease setting.

Table 26. Comparison of features of the economic analysis vs other models of first line comparator therapies in mCRPC

	Previous evaluations		Current evaluation	
Factor	**TA377**(6)	**TA387**(7)	**Chosen values**	**Justification**
Time horizon	10 years	Lifetime	Lifetime	Lifetime horizon appropriate for disease associated with risk of death
Treatment waning effect	Not employed	Not employed	Not employed	No evidence of waning effect with olaparib in combination with abiraterone. No waning of effect assumed by NICE for the relevant comparators for this appraisal.
Source of utilities	Literature (EQ-5D data collected in PREVAIL trial could not be used)	UK patient survey and literature	EQ-5D-5L data collected directly from patients in PROpel trial mapped to EQ-5D-3L	Using directly collected data from the trial participants is more robust than using external sources
Source of costs	NHS reference costs (EAG preferred analysis)	Unclear	NHS reference costs, eMIT and BNF	Relevant sources used to reflect costs perspective of NHS and PSS

B.3.2.3 Intervention technology and comparators

Olaparib in combination with abiraterone is modelled in line with its full licensed indication in adult patients with mCRPC in whom chemotherapy is not clinically indicated. It is compared in the model against enzalutamide (primary comparator, see section B.1.3.3) and abiraterone (secondary comparator, see section B.1.3.3). These comparators reflect the decision problem defined by the NICE scope (8). All technologies are administered and dosed in the model in line with their summaries of product characteristics and clinical trials, and are continued until either disease progression, discontinuation due to intolerability, adverse events, or death. No other clinical continuation or stopping rules are employed.

B.3.3 Clinical parameters and variables

The clinical parameters included in the economic analysis include:

- Overall survival
- Radiological progression-free survival assessed by the study investigator
- Time to discontinuation of olaparib and abiraterone

Adverse events and skeletal-related events are considered in terms of their impact on costs and health-related quality of life in section B.3.4.

B.3.3.1 Overall survival modelling for base case analyses

B.3.3.1.1 OS for olaparib in combination with abiraterone vs abiraterone

OS for olaparib in combination with abiraterone and the abiraterone comparator is modelled using patient-level data from the final OS data cut (DCO3, 12 October 2022) of the PROpel RCT (described in section B.2.3-B.2.6).

At DCO3, the OS data were 47.9% mature (381 events/796 patients) after a median follow-up of approximately 36.5 months. In the olaparib plus abiraterone arm, 44.1% of patients had died compared with 51.6% of patients in the placebo plus abiraterone arm. The median OS was 42.1 months in the olaparib plus abiraterone arm, and 34.7 months in the placebo plus abiraterone arm. The hazard ratio for OS was 0.81 (95% CI: 0.67, 1.00; p = 0.0544) in favour of the olaparib plus abiraterone arm (see section B.2.6.2).

Diagnostic Assessment

To determine the appropriate method of extrapolation of the OS data over the lifetime time horizon, the methods outlined in NICE DSU Technical Support Document (TSD) 14 (96) were followed. First, assessment of proportional hazards between the two arms was undertaken using Schoenfeld residuals and log-cumulative hazards plots. The Schoenfeld residuals plot shows a non-linear and non-zero gradient for residuals against time, indicating that an assumption of proportional hazards between the two trial arms may not hold (Figure 15). This was supported by the log-cumulative hazards plot, which showed non-parallel trendlines between arms (Figure 16) indicating that individual fitted models may be more appropriate for extrapolating each arm rather than jointly fitted models.

Figure 15. Schoenfeld residuals plot for OS

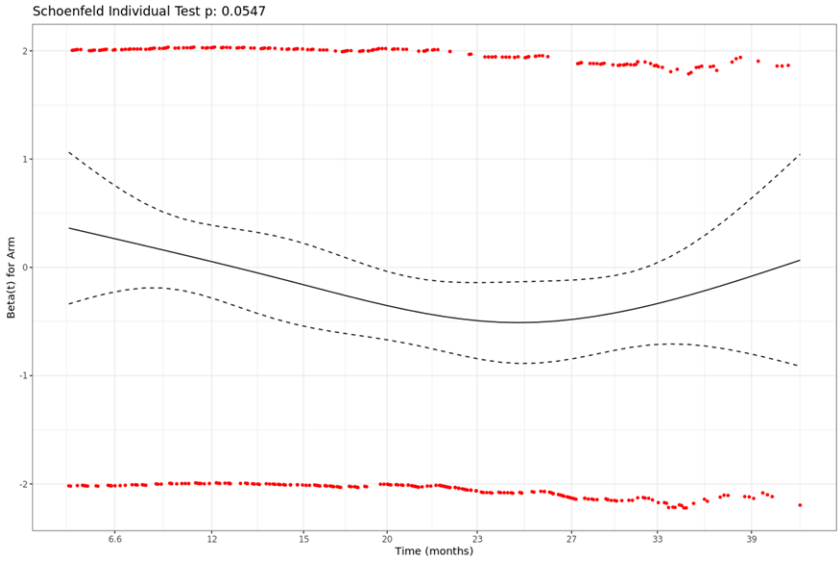
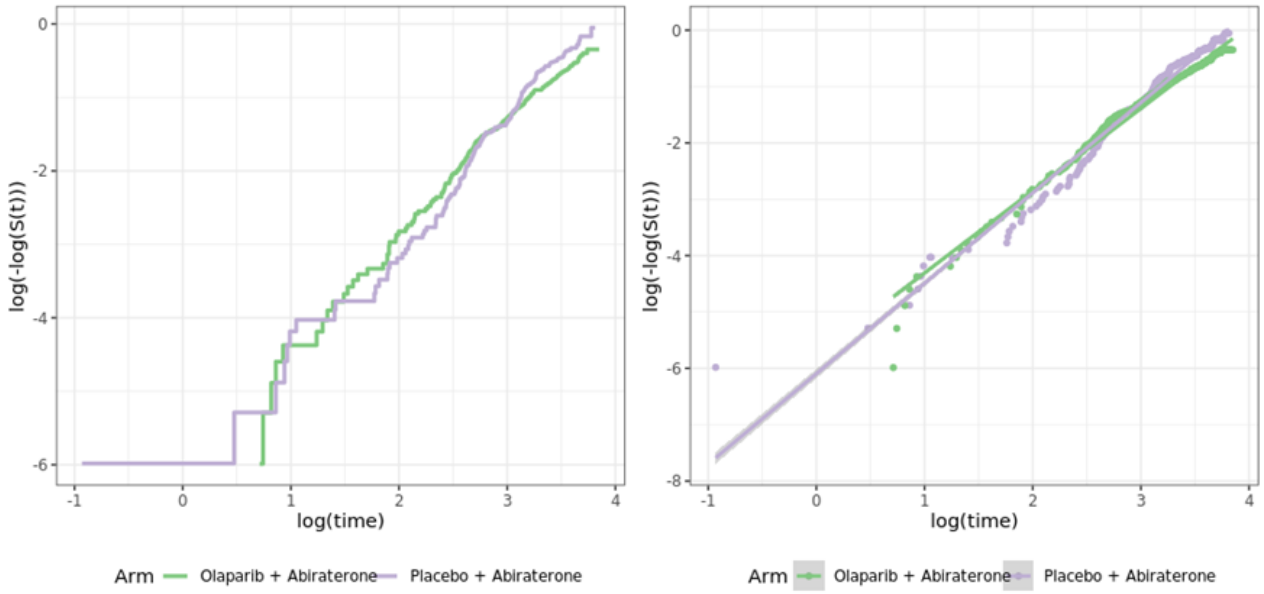


Figure 16. Log-cumulative hazard plot for OS



Visual and Statistical fit

Next, parametric survival models were fitted to patient-level OS data for each arm of PROpel and assessed for goodness of fit. In line with NICE DSU TSD 14 (96), the standard parametric functions (exponential, Weibull, log logistic, lognormal, generalised gamma and Gompertz) were considered, (Figure 17 for olaparib plus abiraterone; Figure 18 for abiraterone).

Figure 17. OS parametric extrapolation for olaparib plus abiraterone

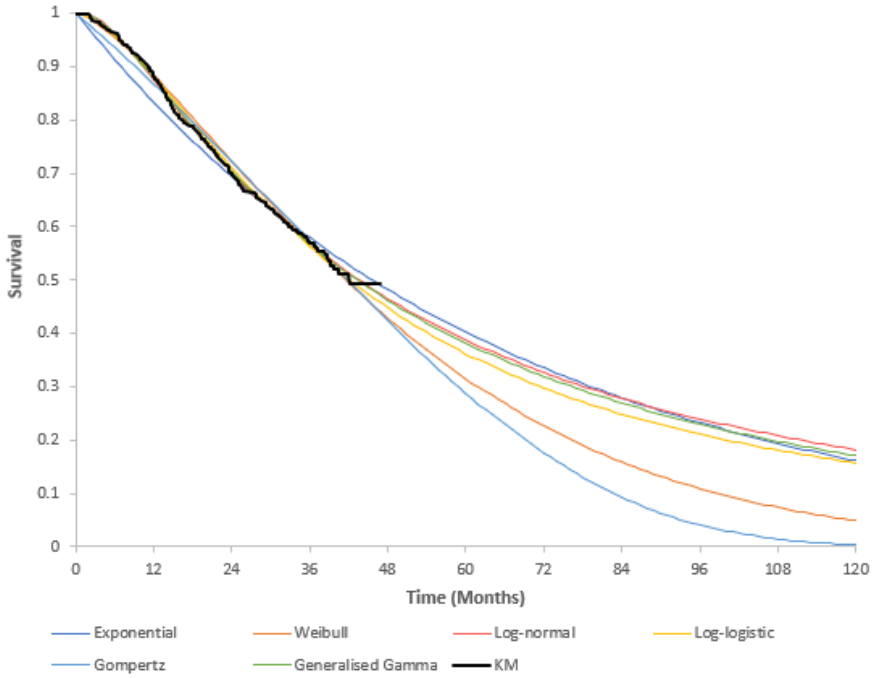
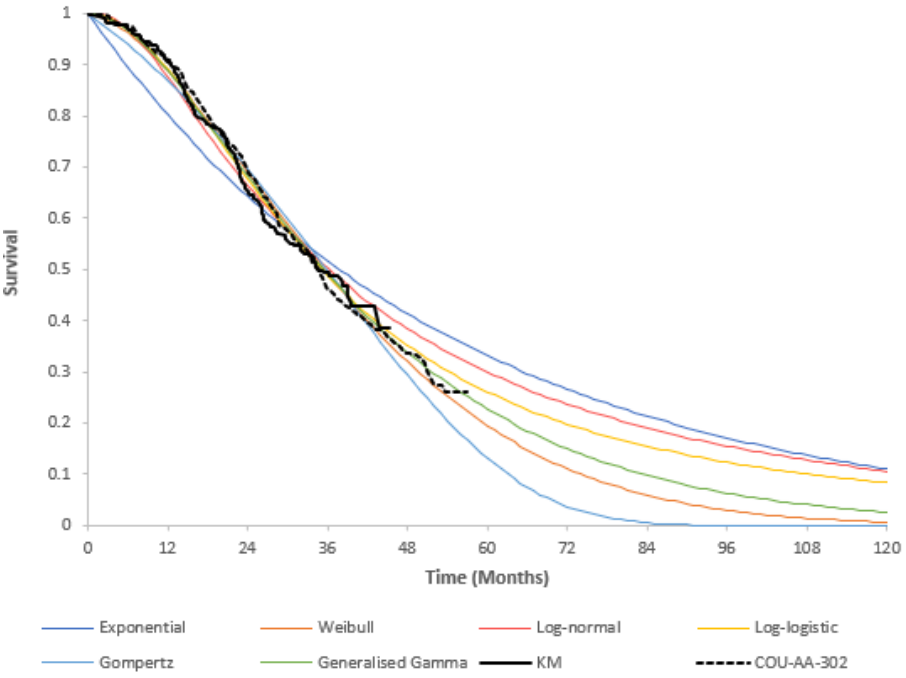


Figure 18. OS parametric extrapolation for abiraterone



With the exception of the exponential and Gompertz extrapolations, most of the distributions fit the observed data well for both treatment arms based on a visual inspection alone (Figure 17 and Figure

18). The exponential shows significant underestimation over the first 24 months with overestimation of survival towards the tail of the KM whereas the Gompertz underestimates survival in the near and longer term.

The statistical fit of each distribution was assessed using both the Akaike information criterion (AIC) and the Bayesian information criterion (BIC) goodness-of-fit statistics, with the results summarised in Table 27. The best statistical fits are distributions with the lowest values indicating the most parsimonious fit to the data. To aid interpretation, the average of the AIC and BIC scores were considered when assessing model fit. In ascending order for the olaparib plus abiraterone arm, this includes the lognormal, log logistic, generalised gamma and Weibull which have combined average AIC and BIC scores with a difference of 10 or less. The Gompertz and exponential curves with higher combined AIC and BIC scores were considered the worst fit to the observed olaparib plus abiraterone data. For the abiraterone arm, the log logistic, Weibull and generalised gamma curves were the best fit with scores of 10 or less; the remaining distributions namely lognormal, Gompertz, and exponential models were relatively worse fits to the data. In alignment with the guidance in NICE DSU TSD 14 (96), the same distribution was preferred across both treatment arms therefore, curve selection was based on those that provided a good fit across these. Consistent with the visual assessment, the Gompertz and exponential were excluded based on statistical fit, with the lognormal and Weibull distributions also performing less well across the treatment arms.

Table 27. Goodness-of-fit test on OS parametric distributions of each treatment arm

	Olaparib + Abiraterone				Placebo + Abiraterone			
	AIC	BIC	AIC+BIC	Rank	AIC	BIC	AIC+BIC	Rank
Exponential	1828	1832	1830	6	2051	2055	2053	6
Weibull	1810	1818	1814	4	2003	2011	2007	2
Lognormal	1803	1811	1807	1	2012	2020	2016	4
Log logistic	1806	1814	1810	2	1999	2007	2003	1
Gompertz	1821	1829	1825	5	2020	2028	2024	5
Generalised Gamma	1805	1817	1811	3	2003	2015	2009	3

Landmark and External Validation

To externally validate modelled OS estimates, the landmark and median OS from PROpel and digitised data from COU-AA-302 were compared to the remaining distributions that performed well across both treatment arms in the visual and statistical assessment (i.e., log logistic and generalised gamma) (Table 28). Based on the latest available landmark at approximately 4 years for COU-AA-302 (12) and PROpel (15,23), the generalised gamma and log logistic distributions both provided reasonable predictions, with slight underestimations across both treatment arms. Survival estimates predicted by the generalised gamma model were, however, more aligned to predicted OS estimates versus both datasets and across both treatment arms (~33.8% vs. ~33.7% [COU-AA-302] and 38.7%

[PROpel] for placebo plus abiraterone, and ~46.2% vs. 49.3% [PROpel] for the olaparib combination at ~4 years). The modelled median OS associated with the generalised gamma was also highly consistent with the observed data from the PROpel study (42.1 vs. 43.0 months, respectively, for the olaparib combination, and 34.7 vs. 35.0 months for the placebo plus abiraterone arm).

Table 28. Landmark and median OS with different parametric models

	Olaparib + Abiraterone					Placebo + Abiraterone				
	Year 1	Year 2	Year 4	Year 10	Median (month)	Year 1	Year 2	Year 4	Year 10	Median (month)
PROpel (15,23)	88.2%	70.2%	49.3%	-	42.1	90.6%	65.5%%	38.7%	-	34.7
COU-AA-302 (12)	-	-	-	-	-	91.3%	69.7%	33.7%	-	34.7
Exponential	83.3%	69.5%	48.2%	16.2%	45.0	80.2%	64.3%	41.4%	11.0%	37.0
Weibull	88.4%	72.4%	42.9%	4.9%	41.0	88.7%	69.2%	32.1%	0.6%	35.0
Lognormal	87.6%	70.4%	46.6%	18.2%	43.0	87.5%	66.6%	38.5%	10.6%	36.0
Log-logistic	88.3%	71.2%	44.8%	15.7%	42.0	89.0%	67.7%	35.3%	8.4%	35.0
Gompertz	86.8%	72.3%	42.4%	0.4%	41.0	86.8%	69.7%	29.4%	0.0%	35.0
Generalised Gamma	87.7%	70.5%	46.2%	17.1%	43.0	88.7%	68.3%	33.8%	2.6%	35.0

PREVAIL, the study investigating enzalutamide versus placebo, had the longest available follow-up data amongst the pivotal studies for first-line mCRPC (97) . Digitised data was available for ~6.5 years, which is at least 30 more months of follow-up than was available for COU-AA-302 and PROpel. Given abiraterone and enzalutamide were concluded to have equivalent efficacy for OS based on expert opinion and the results of the NMA (see section B.2.9), the long-term data for enzalutamide was considered relevant in validating OS for the abiraterone arm beyond the follow-up period of PROpel. At the 6.5-year landmark, approximately 13.3% of patients in the enzalutamide arm from PREVAIL were shown to be alive. Comparing this to the modelled estimates for abiraterone, the Weibull and Gompertz curves had the most pessimistic predictions at 6.5 years (~1.5% and ~8.2%, respectively) whilst the exponential, lognormal and log logistic were optimistic with cumulative survival estimates ranging from ~17.5% to 23.8%. Consistent with the landmark and median estimates based on the observed data, the generalised gamma remained the most consistent, predicting 11.9% of patients were alive at 6.5 years.

Assessment of Hazard Functions

The hazard functions for each treatment arm was also assessed to aid understanding of the shape of the hazards (or risk of an event) during the observed trial period and to support model choice through inspection of the patterns of extrapolated hazards made by each parametric model.

The smoothed hazard plots alongside the model extrapolations are shown in Figure 19 and Figure 20. The smoothed hazards from the empirical data (dotted line) suggest differences in the pattern of the hazard function over time between the olaparib plus abiraterone and placebo plus abiraterone arms of PROpel. With olaparib plus abiraterone, the hazard rate appears to increase initially, before peaking at approximately 12 months and then remaining either constant or decreasing at a shallow rate thereafter. For placebo plus abiraterone, the general trend is for a slowly increasing hazard over the entire follow-up time of PROpel. To use the same type of parametric model, as recommended by NICE DSU TSD 14 (96), a more flexible model was deemed necessary to account for the differing shapes of the hazard function in each arm. The generalised gamma distribution is a three-parameter survival model, and therefore more flexible than the lognormal and log logistic models, allowing it to better capture differences in the underlying hazard functions.

Figure 19: Smoothed hazard function for OS for olaparib plus abiraterone (dotted line) with hazards function for parametric model extrapolations

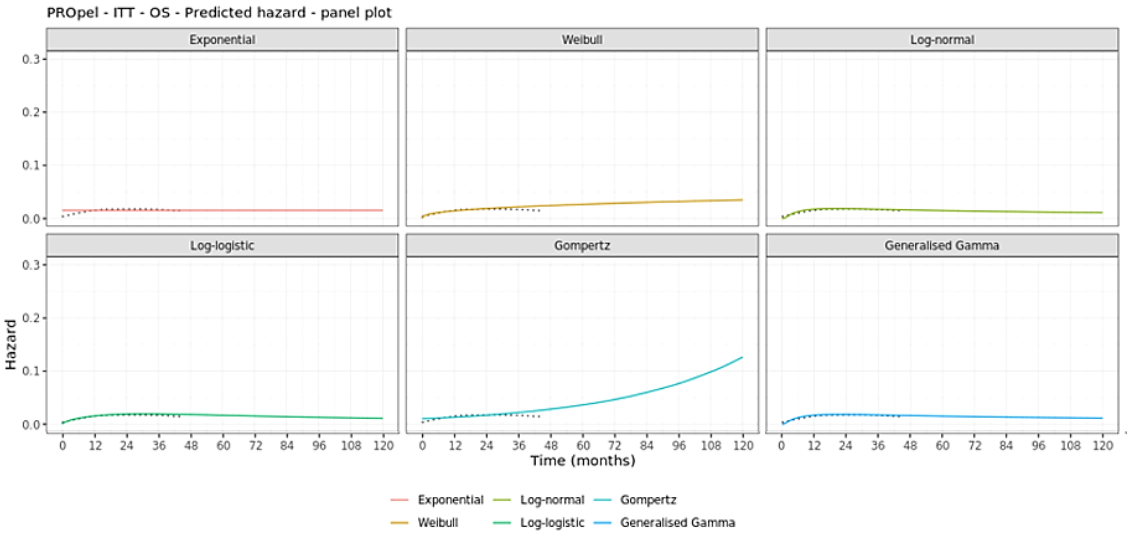
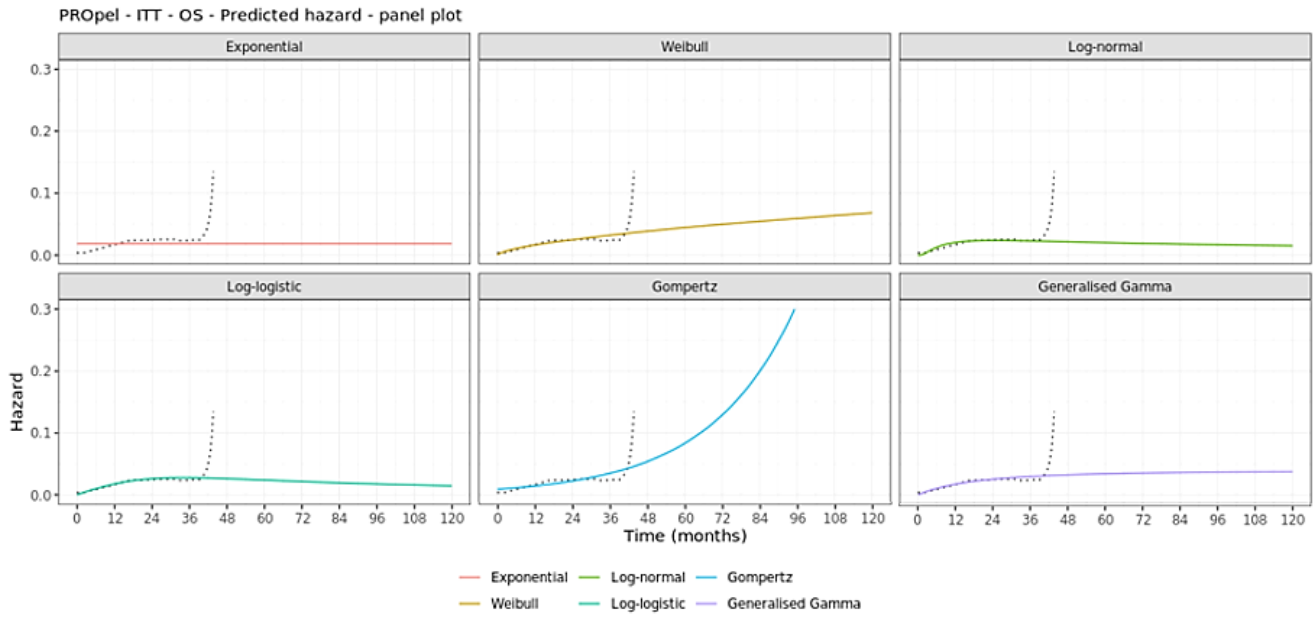


Figure 20: Smoothed hazard function for OS for placebo + abiraterone (dotted line) with hazards function for parametric model extrapolations



Clinical Validation

Lastly, six UK clinical experts with experience of using abiraterone for treating first-line mCRPC were consulted to clinically validate the appropriate choice of extrapolation. The method of eliticing clinical expert viewpoint is summarised in section B.3.14. The Gompertz and Weibull model predictions were unanimously excluded in the first instance because they predicted that nearly all patients treated with abiraterone would not be alive by the 10-year timepoint. The experts explained that this was an overly pessimistic projection of survival for patients who are NHA-naïve and received an NHA as their first-line treatment in mCRPC. The exponential and lognormal, distributions were conversely ruled out as optimistic estimations based on their 10-year predictions for OS in the abiraterone arm. The generalised gamma which predicted ~2-3% would be alive at 10 years was considered to produce the most reasonable 10-year estimates of OS for the abiraterone arm. For the olaparib in combination with abiraterone arm, the Gompertz curve was similarly excluded by experts because it predicted that almost no patients would be alive by 10 years. In alignment with the observed OS benefit in the PROpel trial for the combination arm, a clinical benefit for the olaparib combination over abiraterone monotherapy could be expected in the first-line mCRPC.

Conclusion on OS extrapolation

The base-case model, therefore, uses the generalised gamma distribution to extrapolate OS for both treatment arms because it provided a good fit to the observed data from both the PROpel and digistised COU-AA-302 study and median OS estimates for both treatment arms, it is flexible to account for the differing shapes of the hazard function, and it performed well according to AIC and BIC statistics. A scenario analysis using the log logistic curve for extrapolation of overall survival is provided in section B.3.11.

Figure 21: Base-case OS extrapolation using generalised gamma for olaparib plus abiraterone vs. abiraterone

ABI, abiraterone; KM, Kaplan-Meier; OLA, olpaparib

B.3.3.1.2 OS for olaparib in combination with abiraterone vs enzalutamide

Enzalutamide is the primary comparator for olaparib plus abiraterone, as discussed in section B.1.3.3. Based on real-world data, clinical expert opinion and the exploratory NMA described in section B.2.9, OS with enzalutamide is considered to be equivalent to that with abiraterone. Therefore, for the base case analysis, OS with enzalutamide treatment is assumed to be the same as for abiraterone. Clinical experts have confirmed this assumption is reasonable (see section B.3.14). A scenario analysis in which the OS hazard ratio for enzalutamide versus abiraterone estimated in the exploratory NMA in section B.2.9 is applied to the abiraterone survival curves to model OS with enzalutamide, has been conducted to explore the sensitivity of model to this assumption.

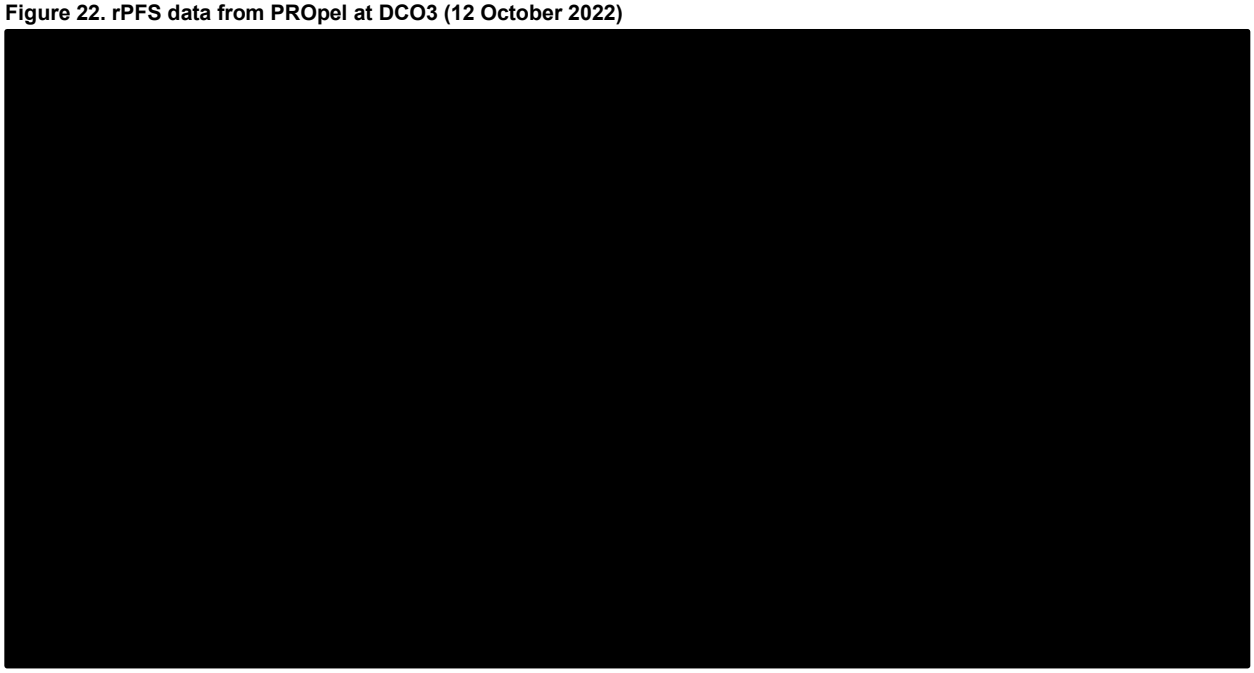
B.3.3.2 Progression-free survival modelling for base case analyses

B.3.3.2.1 rPFS for olaparib in combination with abiraterone vs abiraterone

Investigator-assessed rPFS was the primary endpoint of the PROpel trial (14) and reflects the assessment of PFS in clinical practice (see section B.2.3- B.2.6). rPFS is therefore appropriately modelled based on patient-level investigator-assessed rPFS data for olaparib plus abiraterone and the abiraterone comparator. These data are taken from the final data cut (DCO3, 12 October 2022) of the PROpel RCT described in section B.2.3-B.2.6. Although the primary analysis of rPFS occurred at DCO1 (30 July 2021), DCO3 provides the longest available follow up of rPFS data and is aligned with the data used for the longest available follow up, and final analysis, of OS data.

At DCO3, the rPFS data from PROpel were [redacted] mature (496 events/796 patients) after a median follow up (in censored patients) of approximately 36.5 months. In the olaparib plus abiraterone arm, progression events (including death prior to progression) were observed in 54.9% of patients versus 69.8% of patients in the placebo plus abiraterone arm. The median rPFS was [redacted] months for olaparib plus abiraterone versus [redacted] months for placebo plus abiraterone. The hazard ratio for rPFS was [redacted] (23) (see section B.2.6.1). The Kaplan-Meier curve for these data is provided in Figure 22.

Figure 22. rPFS data from PROpel at DCO3 (12 October 2022)



Source: PROpel CSR Addendum 2 (DCO3) (23)

Diagnostic Assessment

Following the same approach as used for OS modelling, and in line with NICE DSU TSD 14 (96), assessment of proportional hazards for rPFS in the PROpel trial was undertaken, followed by consideration of the best fitting parametric models for long-term extrapolation.

The Schoenfeld residuals plot for PFS is shown in Figure 23. The plot shows a non-linear trend line and a non-zero gradient for residuals against time indicating that the proportional hazards assumption may not hold. This was also supported by the log-cumulative hazards plot (Figure 24) showing non-parallel trendlines between arms. This indicates that individual fitted models should be preferred to joint models.

Figure 23. Schoenfeld residuals plot for rPFS

Figure 24. Log-cumulative hazard plot for rPFS

Visual and Statistical fit

Standard parametric functions, namely exponential, Weibull, log logistic, lognormal, generalised gamma, and Gompertz were fitted to the rPFS data (Figure 25 for olaparib plus abiraterone; Figure 26 for abiraterone).

Figure 25. rPFS parametric extrapolation models for olaparib plus abiraterone

Figure 26. rPFS parametric extrapolation models for abiraterone

Based on visual inspection of the extrapolations in Figure 25 and Figure 26**Error! Reference source not found.**, all the parametric distributions seem to fit the observed PFS data well. However, the best statistical fit for both olaparib plus abiraterone and placebo plus abiraterone arms based on lowest AIC and BIC combined scores were the lognormal, generalised gamma and log logistic distributions with comparable scoring across both treatment arms (Table 29). Similar to the approach for OS, a single best-fitting curve choice for PFS was sought given the similar underlying disease; the Gompertz, exponential and Weibull distributions with higher combined AIC and BIC scores were the worst fit to the observed data for both treatment arms and were therefore excluded for extrapolating rPFS.

Table 29. Goodness-of-fit test on rPFS parametric distributions of each treatment arm

	Olaparib + Abiraterone				Placebo + Abiraterone			
	AIC	BIC	AIC+BIC	Rank	AIC	BIC	AIC+BIC	Rank
Exponential	2008	2012	2010	4	2345	2349	2347	5
Weibull	2006	2014	2010	5	2342	2350	2346	4
Lognormal	1998	2006	2002	1	2331	2339	2335	1
Log logistic	2002	2010	2006	3	2332	2340	2336	2
Gompertz	2009	2017	2013	6	2347	2355	2351	6
Generalised Gamma	2000	2012	2006	2	2332	2344	2338	3

Landmark and External Validation

Following the visual and statistical inspection, landmark and median rPFS estimates from PROpel were then assessed. Digitised data for the abiraterone arm from the COU-AA-302 study was also included in the external validation exercise which showed rPFS estimates for COU-AA-302 and PROpel were highly consistent (Table 30). The final DCO from PROpel provides at least an additional 12 months of follow-up for rPFS than the latest available KM estimates from COU-AA-302 study. Based on the latest available landmark for rPFS at approximately 4 years from PROpel, Weibull was the most pessimistic, whereas lognormal and log logistic had marginally more optimistic projections of 4-year rPFS.

There was however no clear preference between the statistically best-fitting curves, namely lognormal, generalised gamma and log logistic, as they all closely matched the predicted rPFS estimates compared to the observed dataset for both treatment arms. Although the lognormal and log logistic offered a simpler model, they were marginally more optimistic than the generalised gamma at the 4-year timepoint. Given that the longer-term extrapolations with generalised gamma are not as optimistic as the lognormal and log logistic, and it provides a reasonable balance between statistical fit and a reasonable estimate of long-term extrapolation, the generalised gamma was selected as the most appropriate choice based on an assessment of landmark estimates. The predicted rPFS estimates with generalised gamma at 4 years compared to the observed dataset for both treatment arms were

~28.2% versus [redacted], respectively, for olaparib, and ~16.5% versus [redacted], respectively, for placebo plus abiraterone. The median rPFS indicates that the generalised gamma distributions may be conservative for olaparib plus abiraterone (median rPFS with olaparib plus abiraterone in PROpel at DCO3 was 25.0 months vs. 23.0 months with the generalised gamma; median rPFS with placebo plus abiraterone was [redacted] months in PROpel and COU-AA-302 vs. 16.0 months for generalised gamma) (Table 30).

Table 30. Landmark and median rPFS with different parametric distributions

	Olaparib + Abiraterone					Placebo + Abiraterone				
	Year 1	Year 2	Year 4	Year 10	Median (month)	Year 1	Year 2	Year 4	Year 10	Median (months)
PROpel (15,23)	[redacted]									
COU-AA-302 (98)	-	-	-	-	-	58.0%	37.4%	-	-	16.5
Exponential	[redacted]									
Weibull										
Log-normal										
Log-logistic										
Gompertz										
Generalised Gamma										

Assessment of Hazard Functions

The hazard functions based on PFS for each treatment arm was also assessed to aid understanding of the shape of the hazards (or risk of an event) during the observed trial period and to support model choice through inspection of the patterns of extrapolated hazards made by each parametric model.

The smoothed hazard plots alongside the model extrapolations are shown in Figure 27 and Figure 28. Similar to the pattern observed for OS, the smoothed hazards from the empirical data (dotted line) suggest differences in the pattern of the hazard function over time between the olaparib plus abiraterone and placebo plus abiraterone arms of PROpel. To use the same type of parametric model, as recommended by NICE DSU TSD 14 (96), a more flexible model was deemed necessary to account for the differing shapes of the hazard function in each arm. The generalised gamma distribution is a three-parameter survival model, and therefore more flexible than the lognormal and log logistic models, allowing it to better capture differences in the underlying hazard functions.

Figure 27: Smoothed hazard function for PFS for olaparib plus abiraterone (dotted line) with hazards function for parametric model extrapolations

Figure 28: Smoothed hazard function for PFS for placebo plus abiraterone (dotted line) with hazards function for parametric model extrapolations

Clinical Validation

Similar to the approach for validating OS, six UK clinical experts with experience of using abiraterone for treating first-line mCRPC were consulted to clinically validate the appropriate choice of extrapolating rPFS. The lognormal and logistic model predictions were unanimously excluded in the first instance because they predicted that approximately [redacted] of patients treated with abiraterone would be progression-free and alive by the 10-year timepoint. The experts explained a small minority of patients who receive NHAs in the first-line do perform well; however, this was likely to be less than 5%. A few of the clinicians also excluded Gompertz, exponential and Weibull distributions, which estimate that almost no patients remain progression-free and alive, on the basis that these are too pessimistic to capture the small minority of exceptional responders. Based on the statistical, landmark assessments and expert feedback, the generalised gamma was selected as the most appropriate distribution for the extrapolation of rPFS for both treatment arms. A scenario analysis using the lognormal and logistic curves for extrapolation of rPFS is provided in section B.3.11.

Figure 29: Base-case PFS extrapolation using generalised gamma for olaparib plus abiraterone vs. abiraterone

ABI, abiraterone; KM, Kaplan-Meier curve; OLA+ABI, olaparib plus abireaterone

B.3.3.2.2 rPFS for olaparib in combination with abiraterone vs enzalutamide

As noted in section B.3.3.1.2, in the absence of direct comparative data for olaparib plus abiraterone versus enzalutamide, an NMA was considered to provide relative treatment effects for rPFS data versus enzalutamide in the model. However, as detailed in section B.2.9, due to the lack of a true placebo-controlled trial for abiraterone (the COU-AA-302 trial compared abiraterone plus prednisone/prednisolone against prednisone/prednisolone (12)) it was not possible to form a connected network without an assumption of therapeutic equivalence between prednisone and placebo. If prednisone impacts upon tumour progression, as suggested by the evidence discussed in section B.2.9, then any network created under this assumption would be subject to bias. Therefore, a NMA of rPFS data for olaparib plus abiraterone versus enzalutamide could not be performed.

In contrast, the same sources of evidence around prednisone activity did not identify any impact of prednisone on OS; hence, an exploratory NMA for OS was deemed possible, although it remains subject to limitations. Real-world data (57) and clinical expert opinion (section B.3.14), and the exploratory NMA of OS data described in section B.2.9, consistently indicate there is no difference in efficacy between abiraterone and enzalutamide in terms of either rPFS or OS. Therefore, a pragmatic but reasonable assumption is made in the model that rPFS with enzalutamide is the same as the rPFS for abiraterone from the PROpel trial.

B.3.3.3 Time to treatment discontinuation for the base case analysis

Time to treatment discontinuation (TTD) is derived from the clinical trials of olaparib plus abiraterone and the comparators and is used to determine their total costs in the model. The use of TTD results in drug cost estimates that reflect the impact of delayed disease progression and tolerability on treatment duration.

B.3.3.3.1 TTD for olaparib and abiraterone

The time on treatment for olaparib and abiraterone were modelled using data from two endpoints for PROpel:

- TTD: time from randomisation to discontinuation of olaparib plus abiraterone (presented separately for each regimen)
- TTDA: time from randomisation to discontinuation of abiraterone.

TTDA and TTD were modelled independently to ensure that the treatment costs of both abiraterone and olaparib reflected actual treatment duration in PROpel and included the observed differences in durations for each individual component of the combination regimen.

At DCO3, [redacted] of patients in the olaparib plus abiraterone arm had discontinued olaparib treatment ([redacted] events/399 patients, TTD), with a median duration of treatment of [redacted] months. The median duration of abiraterone treatment in the olaparib arm (TTDA) was [redacted] months ([redacted] events/399 patients) (23).

In the placebo plus abiraterone arm, [redacted] of patients had discontinued abiraterone treatment ([redacted] events/397 patients) with a median duration of treatment of [redacted] months (TTDA) (23). The Kaplan-Meier data for TTD and TTDA are presented in Figure 30 and Figure 31, respectively.

Figure 30. TTD for olaparib alone in the olaparib plus abiraterone arm

Source: patient-level data from DCO3 [data on file](64)

Figure 31. TTD for abiraterone alone in the olaparib plus abiraterone and TTDA for abiraterone comparator arm

Source: patient-level data from DCO3 [data on file](64)

TTD and TTDA were extrapolated beyond the trial follow-up period therefore a similar process to that followed for OS and rPFS was used to determine the appropriate approach to extrapolation of these TTD and TTDA data.

The proportional hazards assumption was assessed for the endpoint of TTDA only. For TTD, the cost effectiveness model utilises data from the olaparib arm only of PROpel for which no assessment of proportional hazards is required. The Schoenfeld residuals plot for TTDA is shown in Figure 32. The plot shows a non-linear trend with non-zero gradient for residuals against time, indicating that the proportional hazards assumption may not hold. This was also supported by the log-cumulative hazards plot (Figure 33) showing non-parallel trendlines between arms. This indicates that individual fitted models should be preferred over jointly fitted models.

Figure 32. TTDA Schoenfeld plot (abiraterone in both arms)

Figure 33. Log-cumulative hazard plot for TTDA (abiraterone in both arms)

Standard parametric functions (namely exponential, Weibull, log logistic, lognormal, generalised Gamma, and Gompertz) were fitted to the TTD and TTDA data, (Figure 34 for olaparib within the olaparib plus abiraterone arm; Figure 35 for abiraterone within the olaparib plus abiraterone arm; Figure 36 for abiraterone within the placebo plus abiraterone arm of PROpel).

Figure 34. TTD extrapolation curves for olaparib within the olaparib + abiraterone arm

Figure 35. TTD extrapolation curves for abiraterone within the olaparib + abiraterone arm

Figure 36. TTDA parametric extrapolation curves for the abiraterone arm

Based on a visual assessment, most of the curves fit the observed data well. The curves with the best statistical fit based on the lowest combined AIC and BIC values as shown in Table 31 were lognormal and log logistic distributions for both regimens in the olaparib plus abiraterone combination arm and for TTDA in the placebo plus abiraterone arm. However, both curves were not selected in the base case because in the long-term the TTDA in the placebo plus abiraterone arm marginally exceeded PFS.

Table 31. Goodness-of-fit test on TTD parametric extrapolations for each treatment arm

	Olaparib + Abiraterone (TTD OLA)				Olaparib + Abiraterone (TTD ABI)				Placebo + Abiraterone (TTDA)			
	AIC	BIC	AIC + BIC	Rank	AIC	BIC	AIC + BIC	Rank	AIC	BIC	AIC + BIC	Rank
Exponential	2540	2544	2542	4	2525	2529	2527	5	2630	2634	2632	5
Weibull	2542	2550	2546	5	2523	2531	2527	4	2624	2632	2628	4
Lognormal	2527	2535	2531	1	2508	2516	2512	1	2606	2614	2610	2
Log logistic	2534	2542	2538	3	2515	2523	2519	3	2606	2614	2610	1
Gompertz	2542	2550	2546	6	2527	2535	2531	6	2632	2640	2636	6
Generalised Gamma	2529	2541	2535	2	2510	2522	2516	2	2607	2619	2613	3

Given that the summary of product characteristics for olaparib plus abiraterone, and abiraterone plus prednisone recommend that treatment is continued until either disease progression or due to toxicity (9,19), the Weibull distribution for treatment discontinuation, which does not exceed rPFS extrapolation over the time horizon, was deemed appropriate to use in the base case. A cap was also applied to all treatment discontinuation curves in the model such that time on treatment does not exceed PFS over the time horizon. A scenario analysis using the generalised gamma curve, which is a statistically better fit for extrapolation of time on treatment, is provided in section B.3.11.

The final curve selections for olaparib plus abiraterone versus abiraterone for PFS versus treatment discontinuation curves is provided below in Figure 37.

Figure 37: Extrapolation of treatment discontinuation and PFS for olaparib plus abiraterone vs. abiraterone

ABI, abiraterone; OLA, olaparib; PFS, progression-free survival; TTD, time to discontinuation; TTDA, time to discontinuation with abiraterone

B.3.3.3.2 TTD for enzalutamide

TTD for enzalutamide was not publicly available from the RCTs of enzalutamide identified in the systematic review. As rPFS (and OS) with enzalutamide is appropriately assumed to be the same as with abiraterone, TTD for enzalutamide in the base case model is appropriately assumed to be the

same as TTD with abiraterone. This pragmatic assumption has been confirmed to be reasonable by clinical experts (see section B.3.14).

B.3.3.4 Clinical parameters for the subgroup of patients with HRRm

OS, rPFS and TTD for the subgroup of patients in the PROpel trial with HRRm are provided in Appendix E.1.1.

B.3.4 Measurement and valuation of health effects

B.3.4.1 Health-related quality-of-life data from clinical trials

In PROpel, HRQoL for both treatment arms was measured using the EQ-5D-5L questionnaires. EQ-5D-5L was collected in the PROpel trial at baseline, every 8 weeks, at week 52 and upon treatment discontinuation, and until 12 weeks after confirmed progressive disease. Overall compliance rates for completion of the EQ-5D-5L were [redacted] in the olaparib plus abiraterone arm and [redacted] in the placebo plus abiraterone arm. The data showed no detriment in dimension scores or visual analogue scale (VAS) over time for the olaparib plus abiraterone treatment arm compared with the placebo plus abiraterone arm (see Appendix M). These data were used to estimate health state utility values in the economic model.

B.3.4.2. Mapping

In line with NICE methods guidance (99), the EQ-5D-5L responses collected in PROpel were 'cross walked' to produce EQ-5D-3L derived UK utility values using the Hernández Alava et al., 2017 algorithm (100). The economic model uses the mapped EQ-5D-3L values to estimate the health state utility of patients in the progression-free and progressed disease states.

To estimate health state utility (HSU) inputs to the cost-effectiveness model, a mixed effects model for repeated measures (MMRM) analysis was performed. This method was used to estimate the mean HSU for each state in the economic model. The MMRM analysis provides valid estimates of the mean and standard error of repeated measures data that considers the correlation that exists between the repeated measurements of HSU by subject. It provides valid results under the assumption that missing data are missing at random. The MMRM analysis was used to determine the impact of randomised group and progression status (investigator-based rPFS) on the HSU of patients in PROpel, according to the following specifications:

- Model 1: HSU ~ treatment arm
- Model 2: HSU ~ progression state

- Model 3: HSU ~ treatment arm + progression state
- Model 4: HSU ~ treatment arm x progression state + treatment arm + progression state.

The best fitting model was judged based on Akaike Information Criterion (AIC) score, with lower scores indicating an improved (and more parsimonious) fit to the trial data. For input to the cost-effectiveness model, the mean HSU was derived from the best fitting regression analysis using the least squares mean or estimated marginal mean method. According to AIC score, the best fitting MMRM was model 2 (HSU ~ progression status) (Table 32).

Table 32. Utility model fits based for PROpel ITT population, EQ-5D-5L values

Parameter	Model 1	Model 2	Model 3	Model 4
Intercept	[redacted]	[redacted]	[redacted]	[redacted]
Randomised treatment - Olaparib versus placebo	[redacted]	[redacted]	[redacted]	[redacted]
Progression state – PD vs PF	[redacted]	[redacted]	[redacted]	[redacted]
Interaction term (Olaparib and PD)	[redacted]	[redacted]	[redacted]	[redacted]
AIC score	[redacted]	[redacted]	[redacted]	[redacted]

SE= robust standard errors

Across models, only progression status was consistently associated with a significant ($p<0.01$) impact on HSU. Consistent with the analysis of FACT-P and BPI-SF in PROpel, the HSU analysis did not show a significant or meaningful difference in utility weight across treatment arms (see section B.2.6.5). These data showed no detriment in HRQoL or HSU from the addition of olaparib to abiraterone. The same HSU was therefore applied across all arms of the model. The HSU values used in the base case model are presented in Table 33.

Table 33. Utility values used in the base case model

Population	Health state	Estimate	Standard error	Lower 95%	Upper 95%
All comers	Progression-free	[redacted]	[redacted]	[redacted]	[redacted]
	Progressed disease	[redacted]	[redacted]	[redacted]	[redacted]

B.3.4.3 Health-related quality-of-life studies

The systematic review described in Appendix H identified 20 studies and publications making reference to HSU values in the first line mCRPC setting. Of these, 15 were HTA reports, of which 2 were considered most relevant to the current decision problem on the basis of their alignment with the NICE reference case and as the relevant comparators for olaparib plus abiraterone: NICE TA377 for enzalutamide (6) and NICE TA387 for abiraterone (7). These provide health state utility values for the

progression free state of 0.844 based on the PREVAIL trial and 0.830 based on the COU-AA-302 trial, respectively, but do not provide progressed disease state utility values. The progression free state values are explored in scenario analyses (section B.3.11).

B.3.4.4 Adverse reactions

Whilst the HRQoL data from PROpel showed no detriment from treatment with olaparib (see section B.2.6.5), it is possible that adverse events (AEs) experienced outside of the scheduled collection of patients reported outcomes may have impacted on HRQoL. Additionally, the distinct tolerability profile of enzalutamide may lead to an increase in AEs that are not captured in the HSU values obtained from PROpel. Hence, for all therapies in the model, the potential impact of AEs on HSU was considered.

Treatment-related adverse event prevalence data were obtained from the literature or from the clinical trials used to inform the regulatory approval of each therapy (PROpel for olaparib plus abiraterone and comparator abiraterone (23), PREVAIL for enzalutamide (13)). AE prevalence for secondary (subsequent) therapy was assumed to be equal to that of docetaxel. Only the Common Terminology Criteria for Adverse Events (CTCAE) ≥3 that were reported in 5% of patients or greater in any comparator were included, as lower grade AEs were assumed to have a negligible impact on patient quality of life and costs.

The prevalence and duration of AEs and their associated disutilities are displayed in Table 34 and Table 35. The QALY losses associated with the AEs of each therapy were applied as a one-time decrement at the start of the model on the basis that serious AEs likely occurred soon after commencing treatment. The QALY loss associated with subsequent (secondary) therapy was applied as a one-time decrement at the cycle disease progression was experienced. For each treatment the total mean QALY loss was calculated as a weighted sum of the prevalence of each AE and its associated QALY losses. The QALYs lost with each AE was pragmatically based on disutility values from a published catalogue of UK EQ-5D scores (101) multiplied by an assumed duration of two weeks.

Table 34. Adverse event prevalence and associated disutility (applied as a one-time event at model initiation)

Adverse Event	Olaparib(23)	Abiraterone(23)	Enzalutamide (13)
Anaemia	[redacted]	[redacted]	3.3%
Leukopenia	[redacted]	[redacted]	0.0%
Pneumonia	[redacted]	[redacted]	1.3%
Pulmonary Embolism	[redacted]	[redacted]	0.0%
Hypertension	[redacted]	[redacted]	6.8%

Myocardial Infarction	[redacted]	[redacted]	0.0%
Neutropenia	[redacted]	[redacted]	0.0%
Total disutility	[redacted]	[redacted]	[redacted]

Source for AE prevalence: Olaparib and abiraterone from PROPel CSR Addendum 2 (DCO3)(23); Enzalutamide from PREVAIL trial(13)

Table 35. Treatment-related adverse event disutilities

Adverse event	Disutility estimate	Duration of AE (days)
Anaemia	-0.020	14.00
Leukopenia	-0.020	14.00
Pneumonia	-0.079	14.00
Pulmonary embolism	-0.051	14.00
Hypertension	-0.037	14.00
Myocardial infarction	-0.056	14.00
Neutropenia	-0.020	14.00

Source for disutilities: Sullivan (2011) (101). Duration was assumed to be two weeks.

B.3.4.5 Skeletal-related events

Disutilities related to skeletal-related events (SREs) were also included in the model and were applied as a one-time decrement during the cycle of disease progression. This assumption was based on the occurrence of SREs being associated with disease progression. As such, the rates of SREs upon progression were assumed to be equivalent between the comparators. Patients had a [redacted] probability of experiencing an SRE based on the overall PROpel trial data ([redacted] SRE events and [redacted] non-fatal progression events) (23). The distribution of type of SRE was based on data from the NICE submission for olaparib in previously treated mCRPC (TA831) (45). The SRE rates and disutilities are presented in Table 36 below. The utility decrement associated with SRE events is assumed to last for the whole cycle in which disease progression occurs.

Table 36. Skeletal-related event occurrence and associated disutility

Skeletal-related event	Utility decrement estimate*	Duration of SRE (days)	Olaparib	Abiraterone	Enzalutamide
Probability of at least one SRE occurring			[redacted]	[redacted]	[redacted]
Spinal cord compression	-0.555	30.44	15.5%	15.5%	15.5%
Radiation to bone	-0.070	30.44	67.7%	67.7%	67.7%
Surgery to bone	-0.130	30.44	4.1%	4.1%	4.1%
Pathologic bone fractures	-0.130	30.44	12.9%	12.9%	12.9%
		Total disutility	[redacted]	[redacted]	[redacted]

**Utility decrement values within the model are positive, so that they can be sampled from the beta distribution in probabilistic analyses.*

Source: NICE submission for TA831 (Table 37) (23)

Source for SRE distribution and duration: Olaparib for previously treated hormone-relapsed metastatic prostate cancer (NICE submission: ID1640, Table 33)

B.3.4.6 Summary of HRQoL data used in the cost-effectiveness analysis

HRQoL of patients based on whether they are in progression-free and progressed disease health states are derived directly from the PROpel trial. HRQoL of patients with mCRPC deteriorates upon disease progression, as observed in the patient-level data providing utility values for these health states. Of note, there was no additional deterioration in HRQoL in patients receiving olaparib plus abiraterone in the PROpel trial compared with those receiving the placebo plus abiraterone comparator (see section B.2.6.5); however, to ensure the model fully reflects the impact of mCRPC and its treatment on HRQoL of patients, utility decrements are applied for AEs and SREs that may not have been captured fully in the scheduled HRQoL assessments in the trial. A summary of the utility values used in the model is provided in Table 37. No differences in HRQoL are assumed for patients with HRRm explored in subgroup analysis and no additional health effects were identified for any mCRPC patients in the literature or clinical trials.

Table 37. Summary of utility values for cost-effectiveness analysis

State	Utility value: mean (standard error)	95% confidence interval	Reference in submission (section and page number)	Justification
Health states				
Progression free	[redacted]	[redacted]	B.3.4.2, page 105	Mapped EQ-5D-3L values directly measured from the PROpel study population
Progressed disease	[redacted]	[redacted]		
Death	-	-		
Adverse events				
Anaemia	-0.020 (0.009)	0.002-0.038	B.3.4.4, page 107	Values were not available in the PROpel study therefore published data based on catalogue EQ-5D index scores for the UK were utilised as the most robust source (101)
Leukopenia	-0.020 (0.009)	0.002-0.038		
Pneumonia	-0.079 (0.042)	0.000-0.161		
Pulmonary embolism	-0.051 (0.013)	0.026-0.076		
Hypertension	-0.037 (0.004)	0.029-0.046		
Myocardial infarction	-0.056 (0.011)	0.034-0.078		
Neutropenia	-0.020 (0.009)	0.002-0.038		
Skeletal-related events				
Spinal cord compression	-0.555 (0.0111)	0.337-0.773	B.3.4.5, page 108	Values derived from NICE submission for Olaparib in previously treated BRCA mutation-positive hormone-relapsed metastatic prostate cancer [TA831] (45)
Pathologic bone fractures disutility estimate	-0.130 (0.026)	0.079-0.181		
Radiation to bone	-0.070 (0.014)	0.043-0.097		
Surgery to bone	-0.130 (0.026)	0.079-0.181		
Pathologic bone fractures	-0.130 (0.026)	0.079-0.181		

B.3.5 Cost and healthcare resource use identification, measurement and valuation

A systematic literature review of health care resource use (HCRU) and costs in the first line mCRPC setting was undertaken as detailed in Appendix I. This identified a wide range of studies providing HCRU and cost estimates across many different countries but few in the UK. Due to difficulties in translating costs and HCRU across different jurisdictions, the current model adopted HCRU from the previous NICE submission of enzalutamide in first line mCRPC (TA377) (6), with unit costs taken from relevant NHS reference costs (102). Drug costs were based on those reported in the electronic market information tool (eMIT) (25) where available or from the British National Formulary (BNF) (24), while dosing was based on the respective SmPC labels.

B.3.5.1 Intervention and comparator drug costs

First line therapy drug dosing information and costs for olaparib, abiraterone, and enzalutamide are displayed in Table 38 and Table 39. All regimens are administered orally, which is assumed to have no administration costs, and olaparib in combination with abiraterone are given at their full licensed doses. Patients were assumed to receive 100% of their targeted dose for each comparator.

Table 38. Drug acquisition costs (at list prices) and dosing schedule

Regimen	Drug	Route	Dose per admin	Days (per cycle)	Admin per day	Dose (mg) per cycle	Unit strength (mg)	Cost per pack (£)	Unit per pack	Pack per cycle
Olaparib + Abiraterone	Olaparib	Oral	300 mg	30.44	2	18,263	150	2,317.50	56.00	2.17
	Abiraterone	Oral	1,000 mg	30.44	1	30,438	500	190.00	56.00	1.09
	Prednisolone	Oral	5.00 mg	30.44	2	304	5	0.40	28.00	2.17
Abiraterone	Abiraterone	Oral	1000.00 mg	30.44	1	30,438	500	190.00	56.00	1.09
	Prednisolone	Oral	5.00 mg	30.44	2	304	5	0.40	28.00	2.17
Enzalutamide	Enzalutamide	Oral	160.00 mg	30.44	1	4,870	40	2,734.67	112.00	1.09

mg: milligram; admin: administration

Table 39. Drug costs per cycle in model (using PAS price for olaparib and list prices for other drugs)

Regimen	Drug	Cost per cycle (£)	Dose distribution	Dosing source	Cost source	Dosing rule
Olaparib + Abiraterone	Olaparib	[redacted]	100%	PROpel	BNF	300 mg twice daily
	Abiraterone	206.54	100%		BNF	1000 mg once daily
	Prednisolone	0.87	100%		eMIT	5 mg twice daily
Abiraterone	Abiraterone	206.54	100%	PROpel	BNF	1000 mg once daily
	Prednisolone	0.87	100%		eMIT	5 mg twice daily
Enzalutamide	Enzalutamide	2,972.73	100%	Xtandi SmPC	BNF	160 mg (four 40 mg film-coated tablets or two 80 mg film-coated tablets) as a single oral daily dose. once daily

Xtandi SmPC available at: https://www.medicines.org.uk/emc/product/10318/smpc ; BNF: British National Formulary; eMIT: electronic market information tool; mg: milligram

B.3.5.2 Subsequent line therapy acquisition and administration costs

After progressing on initial treatment, [redacted] of patients that entered the progressed disease state receive subsequent therapy (based on [redacted] patients in PROpel receiving subsequent therapies, with [redacted] progression events). Market share and cost information on subsequent therapies are displayed in Table 40 and Table 41.

Respective market shares of subsequent therapies varied depending on the primary therapy received. Data for subsequent treatments in the olaparib plus abiraterone and abiraterone monotherapy were derived from the PROpel trial data (103) and, for enzalutamide, these was based on a real-world publication by Leith 2022 (104). The values presented in the model derived from the PROpel study were reweighted to ensure they equal to 100%. Although several PARP inhibitors were used as subsequent therapies in the PROpel trial, the model assumed all PARP inhibitors as a subsequent therapy would be olaparib monotherapy since this is the only one approved for use in the mCRPC setting at present (46). This has a minimal impact on the analysis due to very small number of patients receiving this.

Due to the fact that PROpel is a multinational trial, some subsequent treatments received are not available in the UK. Of note, NHA retreatment with abiraterone and enzalutamide, which currently is not permitted in the UK following disease progression, was observed in PROpel across both treatment arms. Experts consulted (section B.3.14) highlighted that NHA retreatment was not considered an effective treatment strategy and was therefore highly unlikely to have any meaningful impact on patient's survival outcomes in the PROpel study. As there is also strong evidence suggesting cross-resistance between abiraterone (51), this variability is not anticipated to impact the generalisability of the benefits from PROpel study to UK clinical practice.

To ensure generalisability to UK clinical practice, six clinical experts with experience of treating patients with mCRPC were consulted to elicit subsequent treatments used in UK clinical practice (section B.3.14). These were utilised to model subsequent therapies in the base case; however, values based on PROpel are also presented in a scenario analysis. Docetaxel and cabazitaxel consisted of the majority of subsequent treatments used by the experts in the UK which is broadly similar to what was reported in PROpel. The key differences were relating to NHA retreatment as explained above, and the use of olaparib monotherapy following disease progression on abiraterone or enzalutamide, which is currently available in the UK (46). The duration of each available regimen was based on the

treatment durations reported in their respective clinical trials. If durations were not reported, a treatment duration of the therapy deemed most similar was used.

Table 40. Proportion of subsequent therapies based on PROpel

	Market share (post-olaparib + abiraterone)	Market share (post-abiraterone)	Market share (post-enzalutamide)
Olaparib monotherapy	[redacted]	[redacted]	0.0%
Abiraterone	[redacted]	[redacted]	0.0%
Docetaxel	[redacted]	[redacted]	65.4%
Enzalutamide	[redacted]	[redacted]	0.0%
Cabazitaxel	[redacted]	[redacted]	34.6%
Mitoxantrone	[redacted]	[redacted]	0.0%
Carboplatin	[redacted]	[redacted]	0.0%
Sipuleucel-T	[redacted]	[redacted]	0.0%
Radium-223	[redacted]	[redacted]	0.0%
Total	100.0%	100.0%	100.0%

Source: olaparib plus abiraterone and abiraterone: PROpel DCO3 TLFs Table 14.1.15 (103); enzalutamide: Leith 2022 - Table 3 (104); Values are rebalanced to 100%

Table 41: Market share of subsequent therapies based on UK clinical practice

	Market share (post-olaparib + abiraterone)	Market share (post-abiraterone)	Market share (post-enzalutamide)
Olaparib monotherapy	[redacted]	[redacted]	14.9%
Abiraterone	[redacted]	[redacted]	0.0%
Docetaxel	[redacted]	[redacted]	42.6%
Enzalutamide	[redacted]	[redacted]	0.0%
Cabazitaxel	[redacted]	[redacted]	24.8%
Mitoxantrone	[redacted]	[redacted]	0.0%
Carboplatin	[redacted]	[redacted]	3.0%
Sipuleucel-T	[redacted]	[redacted]	0.0%
Radium-223	[redacted]	[redacted]	14.9%
Total	100.0%	100.0%	100.0%

The individual cost components used to derive the final costs of subsequent therapies are displayed in Table 42 and Table 43. All regimens are administered orally or via intravenous infusion and were assumed to receive 100% of the targeted dose. In the model, the mean patient weight and body surface area (BSA) at baseline were 82.7kg and 1.90m^2, respectively. These inputs were used to derive dosing for weight- and BSA-based treatments. Average patient weight was sourced from the PROpel trial, while the average BSA was based on the value reported in the cabazitaxel NICE

submission (TA255) (105). A calculation for wastage, which assumes that any unused drug in a vial is discarded, was included in the base case analysis and applied on a per administration basis (i.e., upon administration, if an administered dose required was less than that contained in the vial, the remaining contents were assumed to be discarded, therefore the cost of the entire vial is incurred for the administration). Infusion cost per hour was inflation-adjusted to £311.61 (based on NHS Reference Cost: Code SB13Z) and applied at the time of intravenous administration.

Table 42. Drug acquisition costs (at list prices) and dosing schedule

Drug regimen	Drug	Administration	Dose Per Administration (mg)	Days Administered (per Cycle)	Administrations per Day	Dose (mg) per Cycle	Vial Size/Unit Strength (mg)	Cost per Pack (£)	Unit per Pack	Vials/Pack per Cycle
Olaparib	Olaparib	Oral	300	30.44	2	18,262.50	150	2,317.00	56	2.17
Abiraterone	Abiraterone	Oral	1000	30.44	1	206.54	500	190	56	1.09
	Prednisolone	Oral	5.00	30.44	2	304.38	5	0.40	28	2.17
Docetaxel	Docetaxel	IV	142	1.45	1	206.54	160	17.95	1	1.45
	Prednisolone	Oral	5	30.44	2	304.38	5	0.40	28	2.17
Enzalutamide	Enzalutamide	Oral	160	30.44	1	4,870.00	40	2,734.67	112	1.09
Sipuleucel-T	Sipuleucel-T	IV	1	3.00	1	3.00	1	18,403.47	1	3.00
Cabazitaxel	Cabazitaxel	IV	48	1.45	1	68.85	60	3,696.00	1	1.45
	Prednisolone	Oral	10	30.44	1	304.38	5	0.40	28	2.17
Mitoxantrone	Mitoxantrone	IV	27	1.45	1	38.55	20	61.67	1	2.90
	Prednisolone	Oral	5	30.44	2	304.38	5	0.40	28	2.17
Radium-233	Radium-233	IV	4548	1.09	1	4,944.46	6,000	4,606.19	1	1.09
Carboplatin	Carboplatin	IV	760	1.09	1	826.16	600	24.11	1	2.17

IV: intravenous; mg: milligram

Table 43. Drug cost per cycle of subsequent therapies

Drug regimen	Drug	Cost per Cycle (£)	Dose Distribution	Total drug cost per cycle (£)	Dosing Source	Cost Source	Dosing Rule
Olaparib	Olaparib	[redacted]	100%	[redacted]	PROpel	BNF	300 mg twice daily
Abiraterone	Abiraterone	190	100%	207.41	PROpel	BNF	1000 mg once daily
	Prednisolone	0.87	100%			eMIT	5 mg twice daily
Docetaxel	Docetaxel	477.66	100%	478.53	a	eMIT	Docetaxel 75 mg/m^2 every 3 weeks for 10 cycles
	Prednisolone	0.87	100%			eMIT	5 mg twice daily
Enzalutamide	Enzalutamide	2,972.73	100%	2,972.73	b	BNF	160 mg (four 40 mg film-coated tablets or two 80 mg film-coated tablets) as a single oral daily dose. once daily
Sipuleucel-T	Sipuleucel-T	56,145.22	100%	56,145.22	c	NICE TA322	3 times over a 1 month time frame (once every 1-2 weeks)
Cabazitaxel	Cabazitaxel	5,808.64	100%	5,809.51	d	BNF	25 mg/m^2 administered as a 1 hour intravenous infusion every 3 weeks
	Prednisolone	0.87	100%			eMIT	10 mg once daily
Mitoxantrone	Mitoxantrone	630.41	100%	631.28	e	eMIT	12 to 14 mg/m^2 given as a short intravenous infusion every 21 days, in combination with low oral doses of corticosteroids.
	Prednisolone	0.87	100%			eMIT	5 mg twice daily
Radium-233	Radium-233	5,345.91	100%	5,345.91	f	NICE	55 kBq per kg body weight, given at 4 week intervals for 6 injections
Carboplatin	Carboplatin	391.15	100%	391.15	g	eMIT	400 mg/m2 every 28 days

a. https://www.medicines.org.uk/emc/product/7206/smpc
b. https://www.medicines.org.uk/emc/product/10318/smpc#PRECLINICAL_SAFETY
c. http://chemocare.com/chemotherapy/drug-info/SipuleucelT.aspx
d. https://www.medicines.org.uk/emc/product/12332/smpc#PHARMACOLOGICAL_PROPSzoo
e. https://www.medicines.org.uk/emc/product/1694/smpc;
f. https://www.medicines.org.uk/emc/product/5204#PHARMACODYNAMIC_PROPS;
g. https://www.medicines.org.uk/emc/product/3787/smpc#gref

BNF: British National Formulary; eMIT: electronic market information tool; m: metre; mg: milligram; NICE: National Institute for Health and Care Excellence

The final costs of subsequent therapies used in the model, based on UK clinical practice estimates of use, dosing scehdules and costs, are presented in Table 44.

Table 44. Final cost of subsequent therapies (based on UK clinical practice)

	Dose duration (number of cycles)	Cost (post- olaparib + abiraterone) (£)	Cost (post-abiraterone) (£)	Cost (post-enzalutamide) (£)
Olaparib monotherapy	7.40	0.00	[redacted]	[redacted]
Abiraterone	7.40	0.00	0.00	0.00
Docetaxel	6.90	1,650.78	1,405.61	1,405.61
Enzalutamide	8.30	0.00	0.00	0.00
Cabazitaxel	5.06	1,373.46	1,169.48	1,169.48
Mitoxantrone	5.06	0.00	0.00	0.00
Carboplatin	5.06	69.04	58.78	58.78
Sipuleucel-T	1.00	0.00	0.00	0.00
Radium-223	5.52	5,146.53	4,382.19	4, 382.19
Total		**8,239.80**	**11,611.08**	**11,611.08**

Duration sources: Olaparib monotherapy; Abiraterone; Canabzitaxel; Enzalutamide: Company submission (Table 45) for NICE TA381; Docetaxel: SmPC; Mitoxantrone, Carboplatin: Assumed same as Cabazitaxel; Sipuleucel-T: SmPC; Radium-22: SmPC

B.3.5.3 Health-state unit costs and resource use

The costs of ongoing disease monitoring / patient follow-up are determined by the treatment status of the population, which is modelled using the time to discontinuation curves described in section B.3.3.3. In this way, a change in treatment would determine the follow-up and disease monitoring patterns.

Disease monitoring frequency and costs, stratified by treatment regimen (olaparib plus abiraterone, abiraterone, enzalutamide and secondary therapy) are displayed in Table 45. Utilisation rates were based on the rates reported in the Enzalutamide NICE submission (TA377) (6) and were assumed to be equivalent between the olaparib plus abiraterone and abiraterone arms.

Health care resource items consist of outpatient visits (consultation and nurse visits), CT scans, radiological/MRI scans, ECGs, ultrasounds, bone scans, full blood counts, liver function tests, kidney function tests, treatment toxicity monitoring, and PSA tests. A higher weekly frequency use is applied over the first three months of treatment, and then reduced from four months onwards for olaparib, abiraterone, and enzalutamide, and at any time for docetaxel and secondary therapy. The unit costs associated with ongoing disease monitoring over patients' lifetime were sourced from the NHS Schedule of Reference Costs 2019/2020 (102), which, along with the total costs per cycle, are displayed in Table 46. Note that these costs have been inflated to 2020/21 prices before the Covid-19

pandemic using the most recent inflation index from the PSSRU Unit Costs of Health and Social Care 2022 report (106).

Table 45. Monitoring frequency (per week) and resource use with olaparib plus abiraterone, comparators and subsequent therapies

	Olaparib + Abiraterone*				Abiraterone				Enzalutamide				Subsequent therapy*	
	First 3 Months		Months 4+		First 3 Months		Months 4+		First 3 Months		Months 4+		Any Time	
Resource	**Frequency**	**% Pts**	**Frequency**	**% Pts**	**Frequency**	**% Pts**	**Frequency**	**% Pts**	**Frequency**	**% Pts**	**Frequency**	**% Pts**	**Frequency**	**% Pts**
Outpatient visit (consultation)	0.50	50%	0.25	50%	0.50	50%	0.25	50%	0.25	50%	0.13	50%	0.17	50%
Outpatient visit (nurse)	0.50	50%	0.25	50%	0.50	50%	0.25	50%	0.25	50%	0.13	50%	0.17	50%
CT scan	0.05	100%	0.05	100%	0.05	100%	0.05	100%	0.04	100%	0.04	100%	0.14	100%
Bone Scan	0.08	20%	0.08	20%	0.08	20%	0.08	20%	0.08	20%	0.08	20%	0.08	20%
Full blood count	0.50	100%	0.25	100%	0.50	100%	0.25	100%	0.25	100%	0.13	100%	0.17	100%
Liver function test	0.50	100%	0.25	100%	0.50	100%	0.25	100%	0.25	50%	0.13	50%	0.17	100%
Kidney function test	0.50	100%	0.25	100%	0.50	100%	0.25	100%	0.25	100%	0.13	100%	0.17	100%
Treatment toxicity monitoring (first 12 months)**	0.23	100%	0.23	100%	0.00	0%	0.00	0%	0.00	0%	0.00	0%	0.00	0%
PSA	0.50	100%	0.25	100%	0.50	100%	0.25	100%	0.25	100%	0.13	100%	0.17	100%

Source: NICE TA377 (Enzalutamide submission, 2015) (6); *Assumed same frequency as Abiraterone applied per week
CT: computerised tomography; PSA: prostate-specific antigen

Table 46. Monitoring costs per cycle

Code for items		Unit Cost £ (Inflation-Adjusted)	Olaparib + Abiraterone		Abiraterone		Enzalutamide		Subsequent Therapy
			First 3 Months	Months 4+	First 3 Months	Months 4+	First 3 Months	Months 4+	Any Time
Out-patient visit (consultation)	Per hour of GMS activity	156.00	169.58	84.79	169.58	84.79	84.79	42.40	56.53
Out-patient visit (nurse)	Per hour visit	42.00	45.66	22.83	45.66	22.83	22.83	11.41	15.22
CT scan	RD22Z**	120.57	23.83	23.83	23.83	23.83	19.42	19.42	74.89
Bone scan	RN15A**	316.49	22.94	22.94	22.94	22.94	22.94	22.94	22.94
Full blood count	DAPS05**	2.58	5.61	2.80	5.61	2.80	2.80	1.40	1.87

Code for items		Unit Cost £ (Inflation-Adjusted)	Olaparib + Abiraterone		Abiraterone		Enzalutamide		Subsequent Therapy
			First 3 Months	Months 4+	First 3 Months	Months 4+	First 3 Months	Months 4+	Any Time
Liver function test	DAPS04**	6.09	13.24	6.62	13.24	6.62	3.31	1.66	4.41
Kidney function test	DAPS04**	12.18	26.48	13.24	26.48	13.24	13.24	6.62	8.83
Treatment toxicity monitoring*	Per hour visit	2.58	2.58	2.58	0.00	0.00	0.00	0.00	0.00
PSA test	DAPS04**	1.22	2.65	1.33	2.65	1.33	1.33	0.66	0.88
		Total	**309.99**	**178.38**	**309.99**	**178.38**	**170.65**	**106.50**	**185.57**

**Based on full blood count; **from NHS Reference Costs 2019-2020 (National Cost Collection for the NHS) (102), inflated to 2020/21 prices*
CT: computerised tomography; PSA: prostate-specific antigen

B.3.5.4 Adverse reaction unit costs and resource use

The prevalence of adverse events included in the model is as described in section B.3.4.4. The unit costs and inflation-adjusted unit costs of adverse events are displayed in Table 47, sourced from the NHS Schedule of Reference Costs 2019/2020 (102) and inflation adjusted to 2020/21 prices. Total AE costs were calculated as the sum–product of the unit cost and treatment-specific probability of AEs occurring for each intervention and were applied as a one-off cost at the start of the model. The aggregated costs of adverse events by treatment regimen (olaparib plus abiraterone, abiraterone, enzalutamide, and secondary therapy) are displayed in Table 48.

Table 47. Treatment-related adverse event costs

Treatment-emergent Adverse Events	Unit Cost (£)	Unit Cost (inflation-adjusted) (£)	Code	Source
Anaemia	1,453.86	1,497.48	SA01G-K	*NHS Reference Costs 2019-2020: weighted average of SA01G, SA01H, SA01J, SA01K; Total HRGs*
Leukopenia	135.00	139.05		*No HRG, so assumed same as outpatient visit (PSSRU unit costs of health and social care 2020)*
Pneumonia	1,909.34	1,966.62	DZ11K-V	*NHS Reference Costs 2019-2020: weighted average of DZ11K, DZ11L, DZ11M. DZ11N, DZ11P, DZ11Q, DZ11R, DZ11S, DZ11T, DZ11U, DZ11V; Total HRGs*
Pulmonary embolism	1,498.57	1,543.53	LB09D	*NHS Reference Costs 2019-2020: LB09D; Total HRGs "Intermediate Endoscopic Ureter Procedures, 19 years and older"*
Hypertension	639.00	658.17	EB04Z	*NHS Reference Costs 2019-2020: EB04Z; Total HRGs "Hypertension"*
Myocardial infarction	1,596.39	1,644.28	EB10A-E	*NHS Reference Costs 2019-2020: weighted average of EB10A-EB10E; Total HRGs*
Neutropenia	161.00	165.83		*Enzalutamide manufacturer submission revised 2015*

National Health Service (NHS) Reference Costs 2019-2020(102)

Table 48. Final costs of adverse events by treatment arm

Treatment-emergent Adverse Events	Olaparib (£)	Abiraterone (£)	Enzalutamide (£)
Anaemia	[redacted]	[redacted]	49.42
Leukopenia	[redacted]	[redacted]	0.00
Pneumonia	[redacted]	[redacted]	25.57
Pulmonary embolism	[redacted]	[redacted]	0.00
Hypertension	[redacted]	[redacted]	44.76
Myocardial infarction	[redacted]	[redacted]	0.00
Neutropenia	[redacted]	[redacted]	0.00

Treatment-emergent Adverse Events	Olaparib (£)	Abiraterone (£)	Enzalutamide (£)
Total (£)	[redacted]	[redacted]	**119.74**

B.3.5.5 Miscellaneous unit costs and resource use

B.3.5.5.1 Skeletal-related event costs

Skeletal-related events (SREs) are a key clinical aspect of mCRPC due to the high susceptibility for prostate cancer to metastasise to bone tissue. These events were therefore included in the economic model as a one-off cost and SRE-specific utility decrement for patients upon progression.

Skeletal-related events were applied as a one-time cost at disease progression, with the proportions of the specific SREs assumed to be equivalent between therapies (i.e., it was assumed that SREs were a result of disease progression, rather than the therapy received). Based on this approach, patients had a [redacted] probability of experiencing an SRE ([redacted] SRE events divided by [redacted] non-fatal progression events in PROpel). The distribution of type of SRE was based on data from NICE TA831 (Olaparib for previously treated hormone relapsed metastatic prostate cancer) (45). Radiation to bone had the greatest prevalence.

The probability of skeletal-related events and costs are displayed in Table 49. Spinal cord compression had the greatest inflation-adjusted cost, at £7,099, followed by pathologic bone fractures, at £6,294. Radiation to bone had the lowest inflation-adjusted cost, at £830.

Table 49. Frequency of skeletal-related events and associated unit costs

Event	Probability	Unit cost (£)	Cost source and description
Probability of at least one SRE occurring	[redacted]		*PROpel DCO3 TLFs*
Spinal cord compression	15.5%	7,099	*NHS Reference Costs (2020): Spinal Cord Conditions without Interventions, with CC Score 7+ (HC28J)*
Radiation to bone	67.7%	830	*NHS Reference Costs (2020): All HRGs (SC21Z-SC28Z) - Assumed 5 fractions*
Surgery to bone	4.1%	3,983	*NHS Reference Costs (2020): Pathological Fractures with CC Score 8-10, Non-elective long stay (HD39E)*
Pathologic bone fractures	12.9%	6,294	*Assumed fractures were 50% non-vertebral and 50% vertebral. 61% of non-vertebral fractures were also assumed to require 3 months outpatient follow up. Assumptions based on NICE TA377 (weighted combination from rows below)*
Total cost applied at progression (£)		**604.18**	

Sources: PROpel DCO3 TLFs *(Table 14.2.1.1.1)* (107); National Health Service (NHS) Reference Costs 2019-2020(102)

B.3.5.5.2 End-of-life costs

End-of-life costs used in the model are displayed in Table 50. The estimated total per-patient inflation-adjusted end-of-life cost was £2,170. This cost was applied as a one-off cost for patients upon death.

Table 50. End-of-life cost per patient

Inflated End-of-Life Cost (£)	Source
2,170	Cabazitaxel NICE Submission (TA391)(52)

B.3.5.5.3 Diagnostic genetic testing for subgroup analysis in HRRm

The base-case analysis positions olaparib in combination with abiraterone in all patients meeting its licensed indication. As the licensed indication does not require diagnostic biomarker testing for HRRm, there are no costs to include such testing in the base case model.

The NICE scope requests subgroup analysis based on HRRm status where data allows (8). Subgroup analysis has been provided for patient with HRRm (see section B.3.12). As testing for specific HRR mutations is included in the NHS Genomic Test Directory, this should be considered as a routine cost of the diagnostic work up of patients with mCRPC. No costs of testing for HRRm are therefore assumed in the subgroup analysis.

B.3.6 Severity

This technology does not meet the criteria for consideration of a severity weight.

B.3.7 Uncertainty

First line treatment of mCRPC is a rapidly evolving area. The PROpel trial provides high quality evidence against a comparator that is relevant to clinical practice in the UK.

B.3.8 Managed access proposal

This submission proposes olaparib plus abiraterone is commissioned for routine use in patients meeting the licensed indication under appraisal. A managed access proposal is not provided.

B.3.9 Summary of base-case analysis inputs and assumptions

B.3.9.1 Summary of base-case analysis inputs

A summary of the key variables included in the model are provided in Table 51.

Table 51: Key model variables

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
General model parameters			
Time horizon	Lifetime (30 years)	Not applicable	B.3.2
Cycle length	30.44 days	Not applicable	B.3.2
Discount rate	3.5%	Not applicable	B.3.2
Population characteristics			
Weight	82.7	81.58-83.82 (Lognormal)	B.3.2
Body surface area (m^2)	1.90	1.49-2.31 (Lognormal)	B.3.2
Glomerular filtration rate	61.0	37.10-84.94 (Lognormal)	NA
Extrapolation of outcomes			
OS – OLA+ABI	Generalised gamma	Covariance matrices	B.3.3.1
OS – ABI / ENZA	Generalised gamma	Covariance matrices	B.3.3.1
PFS – OLA+ABI	Generalised gamma	Covariance matrices	B.3.3.1
PFS – ABI / ENZA	Generalised gamma	Covariance matrices	B.3.3.1
TTD – Olaparib (OLA+ABI)	Weibull	Covariance matrices	B.3.3.1
TTD – Abiraterone (OLA+ABI)	Weibull	Covariance matrices	B.3.3.1
TTDA – Abiraterone (ABI / ENZA)	Weibull	Covariance matrices	B.3.3.1
OS – HR for ABI vs. ENZA	1.00	0.61-1.39 (Lognormal)	B.3.3.1
PFS – HR for ABI vs. ENZA	1.00	0.61-1.39 (Lognormal)	B.3.3.1
TTD – HR for ABI vs. ENZA	1.00	0.61-1.39 (Lognormal)	B.3.3.1
Health-related quality of life			
Progression-free	[redacted]	0.80-0.83 (Beta)	B.3.4.2
Post-progression	[redacted]	0.75-0.80 (Beta)	B.3.4.2
Adverse event disutility			
Anaemia	-0.020	-0.002, -0.038 (Beta)	B.3.4.4
Leukopenia	-0.020	-0.002, -0.038 (Beta)	B.3.4.4
Pneumonia	-0.079	-0.000, -0.161 (Beta)	B.3.4.4
Pulmonary embolism	-0.051	-0.026, -0.076 (Beta)	B.3.4.4
Hypertension	-0.037	-0.029, -0.046 (Beta)	B.3.4.4
Myocardial infarction	-0.056	-0.034, -0.078 (Beta)	B.3.4.4
Neutropenia	-0.020	-0.002, -0.038 (Beta)	B.3.4.4
Spinal cord compression	-0.555	-0.337, -0.773 (Beta)	B.3.4.4
Radiation to bone	-0.070	-0.043, -0.097 (Beta)	B.3.4.4
Surgery to bone	-0.130	-0.079, -0.181 (Beta)	B.3.4.4
Pathologic bone fractures	-0.130	-0.079, -0.181 (Beta)	B.3.4.4

Costs			
Olaparib | 150mg (56 pack)	[redacted]	Not applicable	B.3.5
Abiraterone | 500mg (56 pack)	£190.00	Not applicable	B.3.5
Prednisolone | 5mg (28 pack)	£0.40	Not applicable	B.3.5
Docetaxel | 160mg per pack	£17.95	Not applicable	B.3.5.2
Enzalutamide | 40mg (112 pack)	£2,734.67	Not applicable	B.3.5.2
Cabazitaxel | 60mg per pack	£332.07	Not applicable	B.3.5.2
Ra-223 | 6,000 kBq per pack	£4,606.19	Not applicable	B.3.5.2
Cost of resources (prior to inflation)			
Outpatient visit (consultation)	£156.00	Not applied	B.3.5.5
Outpatient visit (Nurse)	£42.00	Not applied	B.3.5.5
CT scan	£120.57	Not applied	B.3.5.5
Radiographic/MRI scan	£306.40	Not applied	B.3.5.5
ECG	£61.86	Not applied	B.3.5.5
Ultrasound	£75.50	Not applied	B.3.5.5
Bone Scan	£316.49	Not applied	B.3.5.5
Full blood count	£2.58	Not applied	B.3.5.5
Liver function test	£6.09	Not applied	B.3.5.5
Kidney function test	£12.18	Not applied	B.3.5.5
PSA	£1.22	Not applied	B.3.5.5
Anaemia	£1453.86	£883.95-£2023.77 (Gamma)	B.3.5.5
Leukopenia	£135.00	£82.08-£187.92 (Gamma)	B.3.5.5
Pneumonia	£1,909.34	£1160.88-£2,657.8 (Gamma)	B.3.5.5
Pulmonary embolism	£1498.57	£911.13-£2,086.01 (Gamma)	B.3.5.5
Hypertension	£639.00	£388.51-£889.49 (Gamma)	B.3.5.5
Myocardial infarction	£1,596.39	£970.60-£2,222.17 (Gamma)	B.3.5.5
Neutropenia	£161.00	£97.89-£224.11 (Gamma)	B.3.5.5
Spinal cord compression	£6,892.00	£4190.34-£9,593.7 (Gamma)	B.3.5.5
Radiation to bone	£806.00	£490.05-£1,121.95 (Gamma)	B.3.5.5
Surgery to bone	£3,867.00	£2351.14-£5,382.9 (Gamma)	B.3.5.5
Pathologic bone fractures	£6,110.79	£3715.36-£8,506.2 (Gamma)	B.3.5.5
Administration of intravenous	£311.61	Not applicable	NA
End-of-life costs (prior to inflation)			
Mortality cost	£1,952	£1,186-£2,717 (Gamma)	B.3.5.5.2
Utilisation of resource use for olaparib + abiraterone & placebo + abiraterone (<3 months)			
Outpatient visit (consultation)	0.50 per week	0.30-0.70 (Lognormal)	B.3.5.5
Outpatient visit (Nurse)	0.50 per week	0.30-0.70 (Lognormal)	B.3.5.5
CT scan	0.05 per week	0.03-0.06 (Lognormal)	B.3.5.5
Radiographic/MRI scan	0.00	Not applied	B.3.5.5
ECG	0.00	Not applied	B.3.5.5
Ultrasound	0.00	Not applied	B.3.5.5
Bone Scan	0.08 per week	0.05-0.12 (Lognormal)	B.3.5.5
Full blood count	0.50 per week	0.30-0.70 (Lognormal)	B.3.5.5
Liver function test	0.50 per week	0.30-0.70 (Lognormal)	B.3.5.5
Kidney function test	0.50 per week	0.30-0.70 (Lognormal)	B.3.5.5
PSA	0.50 per week	0.30-0.70 (Lognormal)	B.3.5.5
Utilisation of resource use for enzalutamide (<3 months)			
Outpatient visit (consultation)	0.25 per week	0.15-0.35 (Lognormal)	B.3.5.5
Outpatient visit (Nurse)	0.25 per week	0.15-0.35 (Lognormal)	B.3.5.5

CT scan	0.05 per week	0.03-0.06 (Lognormal)	B.3.5.5
Radiographic/MRI scan	0.00 per week	Not applicable	B.3.5.5
ECG	0.00 per week	Not applicable	B.3.5.5
Ultrasound	0.00 per week	Not applicable	B.3.5.5
Bone Scan	0.08 per week	0.05-0.12 (Lognormal)	B.3.5.5
Full blood count	0.25 per week	0.15-0.35 (Lognormal)	B.3.5.5
Liver function test	0.25 per week	0.15-0.35 (Lognormal)	B.3.5.5
Kidney function test	0.25 per week	0.15-0.35 (Lognormal)	B.3.5.5
PSA	0.25 per week	0.15-0.35 (Lognormal)	B.3.5.5
Probability of at least one SRE	23%	0.19-0.27 (Gamma)	B.3.5.5.1
Subsequent treatment options			
% receiving secondary therapy	93.6%	0.91-0.96 (Beta)	NA
Following progression on olaparib + abiraterone			
Docetaxel	[redacted]	Not applied	B.3.5.5.2
Cabazitaxel	[redacted]	Not applied	B.3.5.5.2
Carboplatin	[redacted]	Not applied	B.3.5.5.2
Radium-223	[redacted]	Not applied	B.3.5.5.2
Following progression on abiraterone			
Olaparib monotherapy	[redacted]	Not applied	B.3.5.5.2
Docetaxel	[redacted]	Not applied	B.3.5.5.2
Cabazitaxel	[redacted]	Not applied	B.3.5.5.2
Carboplatin	[redacted]	Not applied	B.3.5.5.2
Radium-223	[redacted]	Not applied	B.3.5.5.2
Following progression on enzalutamide			
Olaparib monotherapy	[redacted]	Not applied	B.3.5.5.2
Docetaxel	[redacted]	Not applied	B.3.5.5.2
Cabazitaxel	[redacted]	Not applied	B.3.5.5.2
Carboplatin	[redacted]	Not applied	B.3.5.5.2
Radium-223	[redacted]	Not applied	B.3.5.5.2
Duration of subsequent therapy (number of cycles)			
Olaparib monotherapy	7.40	4.50-10.30 (Lognormal)	B.3.5.5.2
Docetaxel	6.90	4.19-9.60 (Lognormal)	B.3.5.5.2
Cabazitaxel	5.06	3.08-7.04 (Lognormal)	B.3.5.5.2
Carboplatin	5.06	3.08-7.04 (Lognormal)	B.3.5.5.2
Radium-223	5.52	3.36-7.68 (Lognormal)	B.3.5.5.2

B.3.9.2 Assumptions

A summary of all the model assumptions and justifications is provided in Table 52.

Table 52: Key model assumptions

Model input	Assumption	Rationale / Justification
Perspective	NHS and PSS	NICE reference case
Discounting	3.5% per annum for costs and health outcomes	NICE reference case
Time horizon	Lifetime	A lifetime horizon consistent with NICE reference case
Cycle length	30.44 days	The cycle length is 30.44 days to capture the costs and events associated with the rapid progression of disease
Efficacy	Direct extrapolation of PROpel efficacy endpoints for olaparib + abiraterone	Uses available data from a head-to-head randomised control trial. Validated by clinical experts as the preferred approach.

Model input	Assumption	Rationale / Justification
	versus abiraterone (OS and PFS) for the base case	
	Assumed efficacy for olaparib + abiraterone versus enzalumatide is equivalent to what is observed in PROpel for olaparib + abiraterone versus abiraterone (OS and PFS)	Supported by an exploratory NMA presented for OS, clinical expert opinion and real-world evidence sources, where available.
	Independent models are fitted for OS, PFS and TTD.	Inspection of the Schoenfeld residual and log-cumulative hazards plots indicate the proportional hazards assumption was systematically violated between the two treatment arms. Independent models capture different shapes of the hazards between the two arms.
Utilities	Utility values are assumed to differ by health state, but not by treatment arm.	Consistent with the observed HrQoL in the PROpel study.
Costs	Olaparib is aligned to the existing simple PAS. Costs for abiraterone and enzalutamide are presented based on list prices.	Reflects cost of olaparib in current UK clinical practice and available costs for other regimens.
	Health state costs are based on time to treatment discontinuation individually derived directly from PROpel for: • Olaparib (OLA+ABI) • Abiraterone (OLA+ABI) • Abiraterone (PLA+ABI) These are capped to prevent treatment time from exceeding PFS.	The UK marketing authorisation for olaparib is treat to progression, therefore no patients are expected to be on treatment after progression.
Subsequent treatment	Approximately [redacted], [redacted] and [redacted] were assumed to have received docetaxel, cabazitaxel and radium-223, respectively following progression across all treatment arms. [redacted] were assumed to have received olaparib monotherapy after progressing on either enzalutamide or abiraterone.	The overall proportion receiving chemotherapy, radium-223 and new hormonal agents were based on UK clinical opinion validated through expert validation meetings. Please note that the values presented here were reweighted in the model to ensure they equal to 100%.
	The duration of subsequent treatment was dependent on the specific treatment.	The duration of each subsequent treatment was taken from relevant previous NICE appraisals.
Inclusion of end-of-life care cost	End-of-life care cost were derived from a published NICE submission for cabazitaxel (TA391)(52)	Inclusion of these costs reflects the additional care required in the months prior to death, borne by the NHS/PSS. End-of-life costs were applied as a one-off cost at the time of mortality

B.3.10 Base-case results

Total costs, life year gained (LYG), QALYs, and incremental cost per QALY gained for olaparib in combination with abiraterone versus enzalutamide and abiraterone are presented in Table 53.

The ICER is presented at base case as probabilistic as per NICE guidance. All key parameters were assigned appropriate probability distributions, point estimates were derived using Monte Carlo simulation techniques. In the base-case analysis 1000 iterations were run.

Olaparib plus abiraterone is associated with an incremental QALY gain of 1.27 and an incremental cost of [redacted], when compared to enzalutamide. This translates to an incremental cost per QALY of [redacted]. When compared to abiraterone, olaparib plus abiraterone is associated with an incremental QALY gain of 1.27 and an incremental cost of [redacted]. This represents an incremental cost per QALY gained of [redacted]. The net health benefit at cost effectiveness thresholds of £20,000 and £30,000 per QALY are presented in Table 54.

Table 53: Probabilistic base-case results (at list prices for comparators and confidential PAS price for olaparib)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER for Olaparib + Abiraterone vs comparator (£/QALY)
Olaparib + Abiraterone	[redacted]	4.93	3.95	-	-	-	-
Enzalutamide	[redacted]	3.34	2.67	[redacted]	1.59	1.27	[redacted]
Abiraterone	[redacted]	3.34	2.67	[redacted]	1.59	1.27	[redacted]

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 54: Net health benefit

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £30,000
Olaparib + Abiraterone	[redacted]	3.95	-	-		
Enzalutamide	[redacted]	2.67	[redacted]	1.27	[redacted]	[redacted]
Abiraterone	[redacted]	2.67	[redacted]	1.27	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; NHB, net health benefit for Olaparib + Abiraterone vs comparator

Clinical outcomes estimated from the model, and disaggregated results of the cost-effectiveness analysis are presented in Appendix J.

B.3.11 Exploring uncertainty

B.3.11.1 Probabilistic sensitivity analysis

As the base case presented is probabilistic no further PSA was conducted. The cost effectiveness plane and cost effectiveness acceptability curve from the base case for both comparators is presented below.

Figure 38. Cost-effectiveness plane (versus Enzalutamide)

Figure 39: Cost-effectiveness threshold (versus Enzalutamide)

Figure 40: Figure 36: Cost-effectiveness plane (versus Abiraterone)

Figure 41: Cost-effectiveness threshold (versus Abiraterone)

B.3.11.2 Deterministic sensitivity analysis

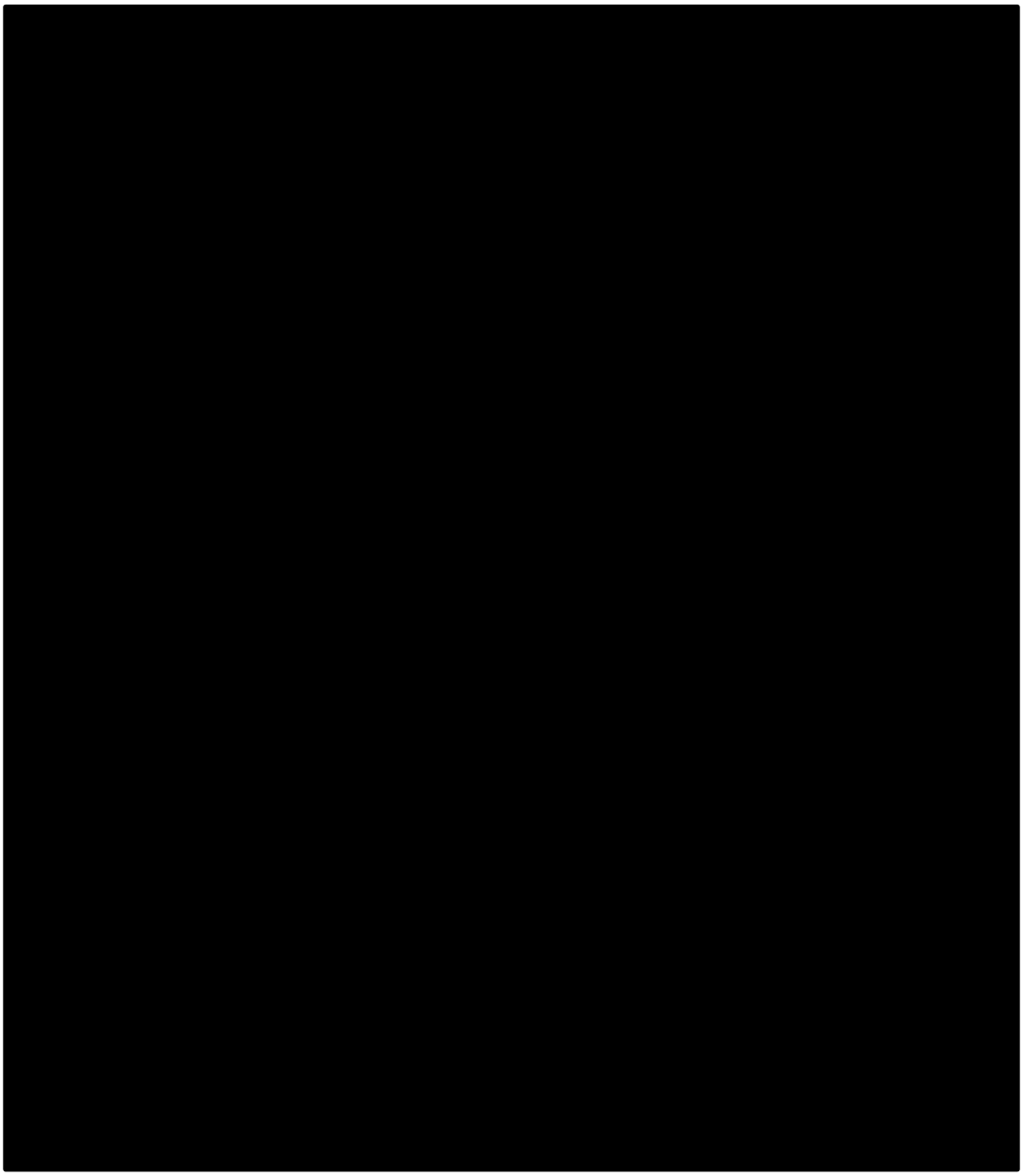
To identify key model drivers, one-way deterministic sensitivity analysis (DSA) was conducted. Parameters were varied one at a time between an upper and lower 95% confidence interval, which were determined using standard errors when available. Where measures of variance were not available, a +/- 20% variation around the mean was used as an estimated standard error. A variation of +/- 10% around the mean was used to estimate standard errors for NMA HR scenarios.

The tornado plots displayed in Figure 42 and Figure 43 showing the top ten parameters that had the biggest impact on the ICER for enzalutamide and abiraterone, respectively. The full detailed output of the DSA for each parameter and each comparator are provided in Appendix M1.2. Overall, the DSAs

show that the model was robust to most parameter values in the base case. As may be expected, in the comparison of olaparib plus abiraterone against enzalutamide, the results of the analysis were most sensitive to the assumed OS and time on treatment for enzalutamide (reflected by the sensitivity of the results to the hazard ratios for OS and time to discontinuation for enzalutamide vs. abiraterone). There was little sensitivity to parameter uncertainty in the comparison of olaparib plus abiraterone vs abiraterone.

Figure 42: DSA tornado graph (versus Enzalutamide)

Figure 43: DSA tornado graph (versus Abiraterone)



B.3.11.3 Scenario analysis

A wide range of scenario analyses were explored to test the assumptions of the base case model. A summary of all scenario analyses is provided in Table 55 and Table 56. For both comparators the model was most sensitive to the parametric distributions assumed for extrapolation of OS and TTD beyond the trial follow up period. It should be noted that the selection of the base case parametric distributions followed recommended guidance and was validated against external data and by clinical expert opinion (see section B.3.3).

Table 55: Summary of Scenario Analysis (versus Enzalutamide)

Scenario	Olaparib + Abiraterone		Enzalutamide		Difference		Estimated ICER (£)	ABS diff
	Cost (£)	QALYs	Cost (£)	QALYs	Cost (£)	QALYs		
Deterministic base case	[redacted]	***3.90***	[redacted]	***2.64***	[redacted]	***1.26***	[redacted]	
Time horizon								
20 years	[redacted]	3.83	[redacted]	2.64	[redacted]	1.19	[redacted]	2067
Abiraterone vs. Enzalutamide HR								
PFS = 0.962 (Chowdhury et al)(57)	[redacted]	3.90	[redacted]	2.64	[redacted]	1.25	[redacted]	1,508
NMA, OS fixed effects	[redacted]	3.90	[redacted]	2.62	[redacted]	1.27	[redacted]	480
NMA, OS random effects inc. informative priors	[redacted]	3.90	[redacted]	2.67	[redacted]	1.22	[redacted]	1,019
OS extrapolation (olaparib+abiraterone arm)								
Log Logistic	[redacted]	3.80	[redacted]	2.64	[redacted]	1.16	[redacted]	2968
PFS extrapolation (olaparib+abiraterone arm)								
Lognormal	[redacted]	3.90	[redacted]	2.64	[redacted]	1.26	[redacted]	147
Log Logistic	[redacted]	3.90	[redacted]	2.64	[redacted]	1.26	[redacted]	135
OS extrapolation (abiraterone arm – proxy for enzalutamide)								
Log Logistic	[redacted]	3.90	[redacted]	3.04	[redacted]	0.86	[redacted]	17130
PFS extrapolation (abiraterone arm – proxy for enzalutamide)								
Lognormal	[redacted]	3.90	[redacted]	2.64	[redacted]	1.25	[redacted]	339
Log Logistic	[redacted]	3.90	[redacted]	2.64	[redacted]	1.25	[redacted]	7
TTD extrapolation								
Generalised Gamma	[redacted]	3.90	[redacted]	2.64	[redacted]	1.26	[redacted]	12329
Cost inclusion								
Administration cost excluded	[redacted]	3.90	[redacted]	2.64	[redacted]	1.26	[redacted]	54
Secondary therapy cost excluded	[redacted]	3.90	[redacted]	2.64	[redacted]	1.26	[redacted]	2673
Routine medical care costs excluded	[redacted]	3.90	[redacted]	2.64	[redacted]	1.26	[redacted]	4095
Adverse event costs excluded	[redacted]	3.90	[redacted]	2.64	[redacted]	1.26	[redacted]	265
Mortality costs excluded	[redacted]	3.90	[redacted]	2.64	[redacted]	1.26	[redacted]	94
Wastage excluded	[redacted]	3.90	[redacted]	2.64	[redacted]	1.26	[redacted]	27
Utility								
Disutility excluded (all)	[redacted]	3.90	[redacted]	2.64	[redacted]	1.26	[redacted]	0.15
AE disutility excluded	[redacted]	3.90	[redacted]	2.64	[redacted]	1.26	[redacted]	9
SRE disutility excluded	[redacted]	3.90	[redacted]	2.64	[redacted]	1.26	[redacted]	9
Source of utility values: COU-AA-302	[redacted]	3.95	[redacted]	2.67	[redacted]	1.27	[redacted]	545
Source of utility values: PREVAIL	[redacted]	3.95	[redacted]	2.67	[redacted]	1.27	[redacted]	545
Source of subsequent treatment market share								
PROpel trial	[redacted]	3.90	[redacted]	2.64	[redacted]	1.26	[redacted]	5135.40
Enzalutamide Discount								
20% discount	[redacted]	3.90	[redacted]	2.64	[redacted]	1.26	[redacted]	10063
50% discount	[redacted]	3.90	[redacted]	2.64	[redacted]	1.26	[redacted]	25159

Table 56: Summary of Scenario Analysis (versus Abiraterone)

Scenario	Olaparib + Abiraterone		Abiraterone		Difference		Estimated ICER (£)	ABS diff
	Cost (£)	QALYs	Cost (£)	QALYs	Cost (£)	QALYs		
Deterministic base case	[redacted]	3.90	[redacted]	2.64	[redacted]	1.26	[redacted]	
Time horizon								
20 years	[redacted]	3.83	[redacted]	2.64	[redacted]	1.19	[redacted]	4,738
Abiraterone vs. Enzalutamide HR								
PFS = 0.962 (Chowdhury et al)(57)	[redacted]	3.90	[redacted]	2.64	[redacted]	1.25	[redacted]	0
NMA, OS fixed effects	[redacted]	3.90	[redacted]	2.62	[redacted]	1.27	[redacted]	0
NMA, OS random effects inc. informative priors	[redacted]	3.90	[redacted]	2.67	[redacted]	1.22	[redacted]	0
OS extrapolation (olaparib+abiraterone arm)								
Log Logistic	[redacted]	3.80	[redacted]	2.64	[redacted]	1.16	[redacted]	6,633
PFS extrapolation (olaparib+abiraterone arm)								
Lognormal	[redacted]	3.90	[redacted]	2.64	[redacted]	1.26	[redacted]	293
Log Logistic	[redacted]	3.90	[redacted]	2.64	[redacted]	1.26	[redacted]	268
OS extrapolation (abiraterone arm)								
Log Logistic	[redacted]	3.90	[redacted]	3.04	[redacted]	0.86	[redacted]	38,240
PFS extrapolation (abiraterone arm)								
Lognormal	[redacted]	3.90	[redacted]	2.64	[redacted]	1.25	[redacted]	204
Log Logistic	[redacted]	3.90	[redacted]	2.65	[redacted]	1.25	[redacted]	164
TTD/TDA extrapolation								
Generalised Gamma	[redacted]	3.90	[redacted]	2.64	[redacted]	1.26	[redacted]	17,236
Cost inclusion								
Administration cost excluded	[redacted]	3.90	[redacted]	2.64	[redacted]	1.26	[redacted]	54
Secondary therapy cost excluded	[redacted]	3.90	[redacted]	2.64	[redacted]	1.26	[redacted]	2,673
Routine medical care costs excluded	[redacted]	3.90	[redacted]	2.64	[redacted]	1.26	[redacted]	2,749
Adverse event costs excluded	[redacted]	3.90	[redacted]	2.64	[redacted]	1.26	[redacted]	242
Mortality costs excluded	[redacted]	3.90	[redacted]	2.64	[redacted]	1.26	[redacted]	94
Wastage excluded	[redacted]	3.90	[redacted]	2.64	[redacted]	1.26	[redacted]	27
Utility								
Disutility excluded (all)	[redacted]	3.90	[redacted]	2.60	[redacted]	1.26	[redacted]	2
AE disutility excluded	[redacted]	3.90	[redacted]	2.64	[redacted]	1.26	[redacted]	17
SRE disutility excluded	[redacted]	3.90	[redacted]	2.64	[redacted]	1.26	[redacted]	19
Source of utility values: COU-AA-302	[redacted]	3.95	[redacted]	2.67	[redacted]	1.27	[redacted]	1,171
Source of utility values: PREVAIL	[redacted]	3.95	[redacted]	2.67	[redacted]	1.27	[redacted]	1,171
Source of subsequent treatment market share								
PROpel Trial	[redacted]	3.90	[redacted]	2.64	[redacted]	1.26	[redacted]	2,250

B.3.12 Subgroup analysis

As requested in the NICE scope (8), deterministic results for the subgroup of patients harbouring HRR mutations are provided in Table 57. The difference in ICERs for olaparib plus abiraterone in this subgroup compared with the ICERs in the base case 'all comer' population is driven primarily by the lower efficacy of standard of care enzalutamide and abiraterone in this subgroup. Full details of the analysis in the HRRm subgroup are provided in Appendix E1.1-E1.6.

Table 57: Deterministic results in HRRm subgroup (at list prices for comparators and confidential PAS price for olaparib)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER for Olaparib + Abiraterone vs comparator (£/QALY)
Olaparib + Abiraterone	[redacted]	5.10	4.06	-	-	-	-
Enzalutamide	[redacted]	2.63	2.10	[redacted]	2.47	1.97	[redacted]
Abiraterone	[redacted]	2.63	2.10	[redacted]	2.47	1.97	[redacted]

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

B.3.13 Benefits not captured in the QALY calculation

The model is unlikley to fully capture the HRQoL benefits of delaying treatment with cytotoxic chemotherapy, including the psychological impact and inconvenience or its administration. See also equality related issues in section B.1.4.

B.3.14 Validation

B.3.14.1 Clinical expert validation of clinical evidence and cost-effectiveness analysis

Two rounds of individual clinical expert interviews were conducted to validate the clinical assumptions underpinning the economic model: round 1 & 2 took place between March and April 2023. There were six clinical experts and their areas of practice and working location are summarised in Table 58.

Table 58: Summary of clinical validation interviews supporting this submission

	Interview round 1	Interview round 2
Number of clinical experts	6	
Area of practice	Oncology/urology	
Geographical spread	Surrey London Belfast Glasgow Manchester	

The following topics were included in the pre-specified interview agendas:

1. The UK clinical pathway and management of mCRPC, including:
    - Real world experience with comparators enzalutamide and abiraterone
    - Subsequent therapies after first line mCRPC
    - Biomarker testing
2. PROpel study design and generalisibility to current UK clinical landscape
3. Extrapolation of PROpel progression/survival outcomes in the all comer and HRRm subgroups

Real world experience with comparators enzalutamide and abiraterone

- Both enzalutamide and abiraterone are currently used in the same first line position in the mCRPC treatment pathway.
- Clinicians considered them to be equally efficacious based on their real world observed progression and survival outcomes, irrespective of biomarker mutation status.
- Treatment choice is dependent on patient comorbidities or contraindications. For example, abiraterone is typically avoided in diabetic patients, where as enzalutamide is typically avoided in patients with cognitive impairment.
- Clinical experts highlighted that NHA retreatment was not permitted as it was not considered to positively impact patients' survival outcomes.
- Some of the experts viewed the role of corticosteroids as relevant for mitigating tolerability effects that might occur whilst on abiraterone. However, other clinicians explained that corticosteroids were utilised in their clinical practice as a therapeutic treatment and reported a positive impact on prostate specific antigen (PSA) progression, which is regarded as an early indication of disease progression (i.e. PFS).

Subsequent therapies after first line mCRPC

- Clinical experts indicated that docetaxel and cabazitaxel were the main subsequent treatments used by experts in the UK after patient progression on a NHA; olaparib monotherapy was identified as a subsequent treatment for BRCA mutated patients, as well as radium-233 dichloride for patients with symptomatic bone metastases following docetaxel failure.
- The quantitative subsequent treatment results from the six clincians were used to calculate the average proportion of subsequent treatments in UK clinical practice.
- None of the clinicians supported NHA retreatment, as this was considered to have no clinical benefit on patients' survival outcomes.

- Although a minority of patients in the PROpel trial received subsequent therapies that are not routinely used in UK clinical practice, the clinical opinion suggested that these were well balanced between treatment arms and were not anticipated to materially bias the OS or PFS estimates compared with what they would anticipate to see in practice.

Biomarker testing

- Clinical opinion indicates that testing for specific HRR mutations (including BRCA) is not currently part of routine practice, and the amount of testing is variable across the UK.
- Clinical experts suggested that following the approval of olaparib monotherapy in the BRCA mutated group (46), biomarker testing is likely to become routine clinical practice.

PROpel study design and generalisibility to current UK clinical landscape

- The clinical experts highlighted that NHAs are now increasingly used in the mHSPC space, but where patients are naïve to an NHA in the first line mCRPC setting they would be eligible to receive enzalutamide or abiraterone, and therefore olaparib plus abiraterone would be used in this setting as a first line therapy in mCRPC.
- The baseline characteristics of the PROpel trial participants were well balanced and broadly representative of patients that the UK clinical experts typically see in the first line mCRPC setting.
- Clinicians flagged that the proportion of people excluded with an ECOG score ≥2 are likely to be individuals who may not be eligible to receive a combination therapy in real world clinical practice.

B.3.14.2 External validation of outcomes

As described in section B.3.1, the modelling approach and structure adopted considering a range of factors, including to:

- accurately reflecting the primary (PFS) and key secondary outcomes (OS) in PROpel
- maintain consistency with approaches accepted in previous appraisals
- to capture the important aspects of the clinical and treatment pathway (e.g., patients are expected to unilaterally progress, and cure is not considered clinically plausible with current therapies)
- ensure the model intuitive and easy to validate

Clinical validation of extrapolated outcomes versus external sources is discussed in detail in Section B.3.3. The plausibility of model projections for OS in the abiraterone arm of PROpel was assessed through comparison with the final OS analysis of the COU-AA-302 registrational trial for abiraterone

in first line mCRPC. At final analysis, the OS for the abiraterone arm of COU-AA-302 was 68% mature with median follow-up of 49.2 months. At a median follow-up of approximately 33 months, PROpel was less mature than COU-AA-302 with 51.6% of patients having had an event in the abiraterone arm of PROpel. However, the median OS was for the abiraterone arm was 34.7 months in both the COU-AA-302 study and the PROpel trial. The final rPFS data from COU-AA-302 was less mature than the abiraterone arm of PROpel (59% versus 69.8% for PROpel at DCO3) and hence of little use in validating model extrapolations for rPFS. Median rPFS was also equal for Abiraterone across both studies at 16.5 months. Overall, the COU-AA-302 study was therefore considered a reliable benchmark for the extrapolation of survival data for the control arm of PROpel. For olaparib plus abiraterone, the PROpel trial is the only available data source for the survival modelling of rPFS and OS. In the absence of external data, the choice of optimal model for the base case was based on fit to the data and the plausibility of extrapolation.

B.3.14.3 Quality assurance of model

The model was subject to review and quality control before finalisation. Two health economists not involved in the model development reviewed the model for coding errors, inconsistencies, and plausibility of inputs and outputs. A range of extreme value and logic tests were conducted to examine the behavior of the model and ensure that the results were logical.

B.3.15 Interpretation and conclusions of economic evidence

[redacted]

Enzalutamide is the primary comparator based on its far greater and increasing use in the first line mCRPC setting compared with abiraterone, as discussed in section B.1.3.3. Against this primary comparator, olaparib (at its existing confidential PAS price) plus abiraterone has an ICER of [redacted] gained. Abiraterone has recently become available as a generic drug, resulting in a much reduced acquisition cost and a corresepondingly greater ICER for olaparib plus abiraterone against this comparator. All available evidence indicates that enzalutamide and abiraterone are of equivalent efficacy (see section B.2.9), and so the far lower acquisition cost of abiraterone would, from a theoretical health economics perspective, suggest that abiraterone dominates enzalutamide. However, both enzalutamide and abiraterone are recommended by NICE as cost effective therapy options in the same first-line mCRPC setting, and the greater and increasing use of enzalutamide in

practice suggests that enzalutamide remains the most relevant clinical and economic comparator for olaparib plus abiraterone.

Extensive sensitivity and scenario analyses demonstrate that the base case model is robust to most parameters and assumptions. As may be expected, in the comparison of olaparib plus abiraterone against enzalutamide, the results of the analysis were most sensitive to the assumed OS and time on treatment for enzalutamide, which would drive its accrued QALYs and costs. There was little sensitivity to parameter uncertainty in the comparison of olaparib plus abiraterone vs abiraterone, which was modelled based on direct comparative data from the PROpel trial. Whilst scenario analyses indicate that the models are sensitive to the choice of parametric distributions used to extrapolate OS and TTD data over the long term, it should be noted that the selection of the base case parametric distributions followed recommended guidance and was validated against external data and by clinical expert opinion (see section B.3.3). The parametric distributions adopted in the base case models are therefore the most plausible and appropriate.

Of note, progression-free survival, during which patients experience their greatest quality of life, is not a key driver of the model. This demonstrates the relative PFS with enzalutamide versus olaparib plus abiraterone (detailed in section B.2.9) does not present significant uncertainties in the model results.

In the subgroup of patients harbouring HRR mutations, olaparib plus abiraterone had an ICER of [redacted] compared with enzalutamide and [redacted] compared with abiraterone. Whilst these ICERs are lower than in the base-case population meeting the full licensed indication, the differences are driven primarily by the lower efficacy of standard of care enzalutamide and abiraterone in this subgroup. This lower efficacy leads to greater disease progression and faster treatment discontinuation, resulting in their lower accrual of QALYs and lower total costs compared to the base case. In contrast, as olaparib plus abiraterone at least maintains its efficacy in this subgroup, its accrued QALYs and costs are more similar to those in the base case than is observed for enzalutamide and abiraterone. The higher total costs for olaparib plus abiraterone is therefore driven not only by higher acquisition costs, but also its superior efficacy that permits patients be treated for longer with first-line treatment than is the case with standard of care enzalutamide and abiraterone.

Due to differences in modelling approaches and incomplete information, it is not possible to directly compare the current model outputs for enzalutamide and abiraterone against the outputs of previous models supporting their NICE recommendations in TA377 and TA387. However, we can be confident that a robust approach, using the most robust data possible, has been adopted to model the cost effectiveness of olaparib plus abiraterone in its licensed indication. The model is aligned with the NICE

reference case and the NICE methods manual, has undergone extensive validation with clinical experts, and compares olaparib plus abiraterone against both the relevant comparators listed in the NICE scope.

Notwithstanding the fact that [redacted], olaparib plus abiraterone is a plausibly cost effective therapy option in its licensed indication.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Olaparib with abiraterone for untreated hormone-relapsed metastatic prostate cancer [ID3920]

Summary of Information for Patients (SIP)

June 2023

File name	Version	Contains confidential information	Date
ID3920_Olaparib in combination with abiraterone for mCRPC_NICE SIP	1.0	No	28th June 2023

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you. The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

Olaparib (Lynparza®)

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

- Olaparib in combination with abiraterone and prednisolone/prednisone is intended for the treatment of adult patients with metastatic castration-resistant prostate cancer (mCRPC) in whom chemotherapy is not clinically indicated.

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

- Olaparib in combination with abiraterone and prednisolone/prednisone was granted a UK marketing authorisation by the MHRA (Medicines and Healthcare products Regulatory Agency) on 15th March 2023.
- The link to the MHRA approval can be accessed in via the following link.

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

- AstraZeneca UK engages with the following patient groups relevant to this medicine with the aims of strengthening patient insights and responding to requests for information: Prostate Cancer UK, Prostate Cancer Research and Tackle.
- AstraZeneca UK publishes funding provided to UK patient groups on our website annually.
- Since the most recent publication, a hands-off payment of £10,000 has been made to Prostate Cancer UK as a grant funding for their clinical champions training and education programme.

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England. Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.
• Prostate cancer is the most common cancer diagnosis in the UK, having over taken breast cancer in 2018 (1,2). • An estimated 58,373 patients will be diagnosed with prostate cancer in the UK in 2023 (3). Of all incidences of prostate cancer, 2.22% of patients will develop mCRPC (4), with a 5-year survival rate of 49% (1). • Prostate cancer cells are typically dependent on androgens (a type of hormone) for survival and growth, and they initially respond to androgen deprivation therapy (ADT). However, over time there is typically a loss of response to ADT. Metastatic disease (cancer that has spread beyond the prostate) that no longer responds to ADT is referred to as metastatic castration resistant prostate cancer (mCRPC); this is sometimes also referred to as metastatic hormone relapsed prostate cancer (mHSPC). • In addition to poor survival, people with metastatic disease often experience pain, fatigue and symptoms specific to the site of metastases, which can impact on mobility, sleep, and ability to perform normal activities of daily living (5–7). Collectively, mCRPC has a profound impact on a patient's health-related quality of life (HRQoL) and that of their caregivers and family (8,9).

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?
• There is no national prostate cancer screening programme in the UK. • Initial tests for prostate cancer are usually conducted at GP surgeries and may include a prostate specific antigen (PSA) test (a blood test), a digital rectal examination (DRE), and urine tests to rule out urine infections. • Men over 50 can ask for a PSA test at any time, and men of black ethnicity or those with a family history of prostate cancer, who are at increased risk, can ask for a PSA test from 45. • Some men may be offered a PSA test as part of a general check-up. Some men may also be offered a PSA test if they are experiencing symptoms of a possible prostate problem, such as more urgency to urinate, needing to urinate more often than usual at night time,

difficulty starting to urinate or to maintain urine flow, or feeling the bladder has not emptied properly. Any such changes should be discussed with a GP.

- But a PSA test is not definitive, and the PSA level can be influenced by many other factors, such as non-cancerous enlarged prostate, urinary infection, and recent sexual activity.
- A DRE involves a doctor or nurse examining your prostate gland by sliding a finger gently into the back passage. They are testing for the size and texture of the prostate gland.
- Based on the PSA results and DRE findings the GP will decide whether to refer the patient to a hospital for further tests by a urologist (a specialist in the male genitourinary tract).
- Tests at the hospital may include another PSA test or DRE, or further tests e.g., a MRI (magnetic resonance imaging) or CT (computerised tomography) scan, or a prostate biopsy.
- If cancer is found, other tests may be conducted to determine the best course of treatment.
- Prostate Cancer UK is a charity that provides patient-friendly information on the diagnosis and treatment of prostate cancer – this can be accessed at: www.prostatecanceruk.org.

2c) Current treatment options:

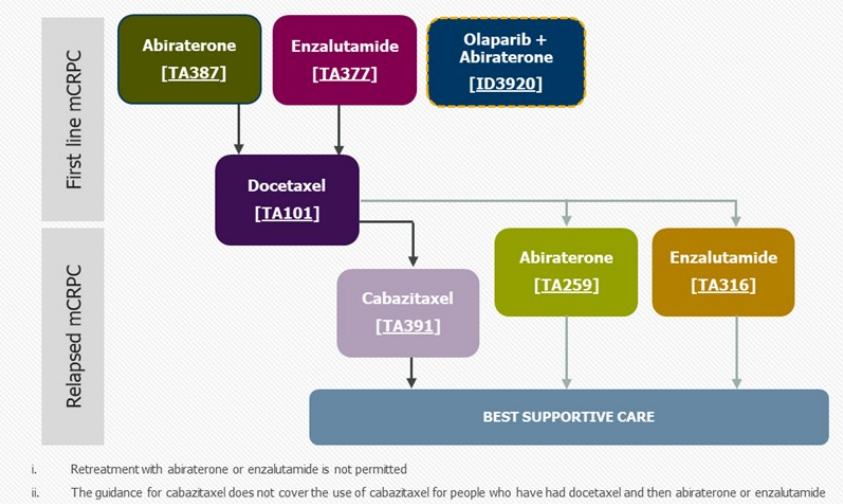
The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
  - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
  - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

- Treatment options for prostate cancer are determined by the stage of the disease.
- In early-stage disease that is localised or locally advanced, treatment may include active surveillance or radical treatment (surgery and radiotherapy). Most patients would at some point receive androgen deprivation therapy (ADT), which reduces the amount of testosterone circulating in the body. This is because testosterone often stimulates the growth of prostate cancer. ADT may be given as drugs or by removal of the testes (castration, also known as orchiectomy).
- In people with cancer that has spread beyond the prostate (metastatic prostate cancer), chemotherapy (using a drug called docetaxel) may be offered if the patient is fit enough.
- People with metastatic disease that no longer responds to ADT (metastatic castration-resistant prostate cancer – mCRPC) who have not had chemotherapy and have no, or only

mild symptoms may receive treatment with either enzalutamide or abiraterone, which are androgen receptor inhibitors, are also known as new hormone agents (NHAs). Enzalutamide is the most used NHA at this stage of the disease (used in approximately two-thirds of these patients).

- This appraisal is for olaparib in combination with abiraterone. It would be used in patients with mCRPC who are not clinically indicated to receive chemotherapy, as an alternative to enzalutamide or abiraterone, as shown below. Note, enzalutamide and abiraterone can be used in several places in the treatment pathway, but this appraisal is only for olaparib plus abiraterone as an alternative to enzalutamide or abiraterone when used as first line therapies in patients with mCRPC.



2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

- The PROpel clinical trial that supported the licensing of olaparib plus abiraterone in patients with mCRPC specifically sought to assess the health-related quality of life of enrolled patients and assessed pain and symptoms. PROpel was conducted in 796 mCRPC patients meeting the subsequent licensed indication for olaparib plus abiraterone (10).

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment? Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities. If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.
• Olaparib and abiraterone have different modes of action, and their combined effect increases their effectiveness compared with either agent alone. Olaparib was originally licensed for use in prostate cancer in patients carrying specific gene mutations (called BRCA1 and 2 mutations); however, the combination of olaparib plus abiraterone is effective in patients with or without these gene mutations. • Olaparib plus abiraterone is the first combination therapy approach to be licensed for first line use in patients with mCRPC for whom chemotherapy is not clinically indicated. • The combination was designated as innovative by the UK licensing authority (11). • Current standard of care treatments in the first line mCRPC setting when chemotherapy is not clinically indicated include NHAs (abiraterone or enzalutamide), which in their phase 3 clinical trials provided median progression-free survival (PFS) of approximately 16-20 months (12,13). In contrast, olaparib plus abiraterone provided a median PFS in the PROpel clinical trial of 24.97months, exceeding 2 years for the first time in this patient group (14). • The early use of olaparib in combination with abiraterone in mCRPC significantly delays disease progression, which can potentially delay the use of subsequent therapies that have diminishing effectiveness and may improve overall survival (15,16). • Olaparib plus abiraterone therefore provides a much-needed new first line therapeutic option to improve outcomes in mCRPC patients for whom chemotherapy is not clinically indicated. • Olaparib plus abiraterone is taken orally as tablets daily. It is taken along with corticosteroid tablets called prednisolone/prednisone. • Like many medicines used in the treatment of cancers, it may cause some side effects. • Full details of olaparib in combination with abiraterone, including how it works, how to take the medicine, list of known side effects and people who should not take olaparib plus abiraterone, are available in the Summary of Product Characteristics at: https://www.medicines.org.uk/emc/product/9488/smpc and the Patient Information Leaflet at: https://www.medicines.org.uk/emc/product/9488/pil.

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines? If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together. If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects. **If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.**
• This appraisal refers to olaparib in combination with abiraterone (plus corticosteroid). • Olaparib works by blocking the action of enzymes that repair DNA in cancer cells. In this way it inhibits the growth of the cancer cells. It also blocks androgen signalling inside the tumour cells. • Abiraterone inhibits the production of androgens (e.g., testosterone). As testosterone stimulates the growth of prostate cancer cells, abiraterone inhibits the growth of prostate cancer cells. • Combining olaparib with abiraterone leads to an improved anti-tumour effect. • See the olaparib Summary of Product Characteristics at: https://www.medicines.org.uk/emc/product/9488/smpc and the abiraterone Summary of Product Characteristics at: https://www.medicines.org.uk/emc/product/2381/smpc.

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for. How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?
• As olaparib and abiraterone (and the corticosteroid) are both taken orally as tablets, this treatment regimen can be taken at home. • Olaparib is administered orally at a usual full recommended dose of 300 mg (2 × 150 mg tablets) twice daily with or without food, equivalent to a total daily dose of 600 mg (10). • Abiraterone is administered orally at a usual full recommended dose of 1000mg (4 x 250mg tablets) once daily without food. • In line with the abiraterone Summary of Product Characteristics (17), all patients should also take prednisone or prednisolone at a dose of 5mg twice daily. Treatment with a gonadotropin-releasing hormone (GnRH) analogue should be continued during treatment in all patients, or patients should have had prior bilateral orchiectomy. • Treatment is continued until progression of disease or unacceptable toxicity.

- For full administration details see the olaparib Summary of Product Characteristics at: https://www.medicines.org.uk/emc/product/9488/smpc and the Patient Information Leaflet at: https://www.medicines.org.uk/emc/product/9488/pil.

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

- The safety and efficacy of olaparib were studied in adult patients with metastatic castration-resistant prostate cancer (mCRPC) in a Phase III randomised, double-blind, placebo-controlled, multicentre study called PROpel (14).
- PROpel evaluated the efficacy of olaparib (300 mg [2 x 150 mg tablets] twice daily) in combination with abiraterone (1000 mg [2 x 500 mg tablets] once daily) versus a comparator arm of placebo plus abiraterone. Patients in both arms also received either prednisone or prednisolone 5 mg twice daily.
- The study randomised 796 patients (1:1 randomisation; 399 olaparib plus abiraterone:397 placebo plus abiraterone) who had confirmed mCRPC and who had not received chemotherapy or an NHA in the mCRPC setting. Prior to the mCRPC stage, treatment with NHAs (except abiraterone) without PSA progression (clinical or radiological) during treatment was allowed, provided the treatment was stopped at least 12 months before randomisation. Chemotherapy using docetaxel treatment was allowed during earlier stages of the disease, as long as no signs of disease progression occurred during or immediately after such treatment. All patients received ADT as drugs or had prior bilateral orchiectomy. Patients were stratified by metastases (bone only, visceral or other) and docetaxel treatment at the metastatic hormone-sensitive prostate cancer (mHSPC) stage (yes or no). Treatment was continued until radiological progression of the underlying disease or unacceptable toxicity.
- Demographic and baseline characteristics were balanced between the two trial arms. The median age of patients was 69 years overall, and the majority (71%) of patients were in the ≥65 years age group. 189 (24%) patients had prior docetaxel (chemotherapy) treatment at earlier stage disease. In total, 434 (55%) patients had bone metastases (metastases in the bone and no other distant site), 105 (13%) patients had visceral metastases (distant soft tissue metastases in an organ e.g., liver, lung) and 257 (32%) patients had other metastases (this could include, for example, patients with bone metastases and distant lymph nodes or patients with disease present only in distant lymph nodes). Most patients in both arms (70%) had an ECOG performance status of 0 (ECOG is a scale from 0 to 5 used to describe a patient's level of functioning i.e., their ability to care for themself, daily activity, and physical

ability, a lower score suggests a higher level of functioning). There were 103 (25.8%) symptomatic patients in the olaparib group and 80 (20.2%) patients in the placebo group; symptomatic patients were characterized by Brief Pain Inventory-Short Form (BPI-SF) item #3 score ≥ 4 and/or use of opiate pain relief at baseline.

- Patient enrolment was not based on genetic status. Testing for important gene mutations that may increase the risks of prostate cancer was reviewed retrospectively and after randomisation (by blood and/or tumour tissue tests) to assess the consistency of treatment effect within the overall population. Of the patients tested, 198 and 118 had one or more genetic mutations as determined by blood tests and tumour tissue tests, respectively. The distribution of genetic mutations in patients was well balanced between the two trial arms.
- Full PROpel trial details are provided in the published manuscript available at: https://evidence.nejm.org/doi/full/10.1056/EVIDoa2200043 and in the Summary of Product Characteristics available at: https://www.medicines.org.uk/emc/product/9488/smpc.

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.
In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

PROpel trial of olaparib plus abiraterone vs abiraterone

- The primary endpoint of PROpel was investigator assessed radiological progression-free survival (rPFS), assessed at the first data-cut off (DCO1) after a median follow up of ~19.4 months. rPFS assessed by blinded independent central review (BICR) was analysed in a sensitivity analysis (14).
- Olaparib plus abiraterone extended median investigator-assessed rPFS by approximately 8.2 months compared with placebo plus abiraterone (24.8 months vs 16.6 months, respectively; hazard ratio [HR] 0.66; 95% CI: 0.54–0.81; p < 0.0001), leading to a rPFS with olaparib plus abiraterone that exceeded 2 years for the first time in this patient population. Results for BICR assessed rPFS were highly consistent (27.6 months vs 16.4 months, respectively; HR 0.61; 95% CI: 0.49–0.74; nominal p < 0.0001), confirming the validity of the investigator assessed data (14).
- rPFS improved across stratification factors (prior docetaxel at earlier stage of disease and site of distant metastases) and all pre-specified subgroups, including in patients with genetic mutations that increase the risk of prostate cancer development and progression (homologous recombination repair mutations, HRRm) (HR 0.50; 95% CI: 0.34–0.73) and

those without (HR 0.76; 95% CI, 0.60 to 0.97) (14) (see section B.2.7.1 of the company submission).

- Overall survival (OS) was a key secondary endpoint, formally assessed at the final data-cut off (DCO3) after a median follow up of ~36.5 months (16).
- Due to the additional benefit over placebo plus abiraterone, OS data for olaparib plus abiraterone were not fully mature at the time of the final OS analysis. However, at each data cut there was an increasing trend towards an improvement in OS with olaparib plus abiraterone. By the final analysis there was over a 7 month improvement in median OS compared with placebo plus abiraterone (42.1 vs 34.7 months, respectively; HR 0.81; 95% CI: 0.67–1.00; p = 0.0544) (16).
- The numerical benefit in OS observed with olaparib plus abiraterone observed in the whole trial population was maintained across stratification factors and pre-specified subgroups, including in patients with HRRm (HR 0.66; 95% CI, 0.45– 0.95) and those without (HR 0.89; 95% CI, 0.70–1.14) (see section B.2.7.2 of the company submission).
- Other secondary outcomes assessed in the PROpel trial supported the rPFS and OS data. There were positive trends towards median time to first subsequent therapy (24.6 vs 19.4 months; HR, 0.76 [95% CI,0.64-0.90]; nominal p = 0.0025), and second progression-free survival (PFS2; HR 0.76, 95% CI, 0.59–0.99; nominal p = 0.0534) (22) (see B.2.6.3 of the company submission). These indicate a long-term benefit with first line olaparib plus abiraterone and its potential to delay use of subsequent line therapies that have diminishing efficacy.

Efficacy compared with enzalutamide:

- As the PROpel trial did not compare olaparib plus abiraterone vs enzalutamide, indirect treatment comparisons using a statistical technique called network meta-analysis (NMA) were explored for the key outcomes of rPFS and OS.
- An extensive feasibility assessment (see company submission section B.2.9.1) identified data challenges relating to the comparator arms of the relevant trials of olaparib plus abiraterone and enzalutamide. In contrast to the placebo arms of the enzalutamide PREVAIL trials, all patients in the comparator arms of the COU-AA-302 trial of abiraterone and the PROpel trial of olaparib plus abiraterone were taking corticosteroids (18), due to the licensing requirement for abiraterone to be taken with corticosteroids (17). Whilst there is little evidence that corticosteroids impact OS, there is evidence they may impact disease progression endpoints (19,20). It was therefore not feasible to conduct a robust NMA of olaparib plus abiraterone vs enzalutamide for rPFS, but an exploratory NMA for OS was possible.
- The exploratory NMA indicated that there is no meaningful difference in OS with enzalutamide and abiraterone (see company submission section B.2.9.2.3).

- Given that real-world data (21,22), clinical expert opinion (company submission section B.3.14) and the exploratory NMA of OS data (company submission section B.2.9.2.3) all indicate that abiraterone and enzalutamide are of equivalent efficacy, the relative treatment effects of olaparib plus abiraterone vs abiraterone directly demonstrated in the PROpel trial (20,22) are a reasonable proxy for the relative treatment effects of olaparib plus abiraterone versus enzalutamide.

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information? Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

Prostate cancer negatively affects patients' health-related quality of life (HRQoL) (5,27). It is important that the treatment of prostate cancer, particularly in the mCRPC setting where treatment is non-curative, does not further negatively impact HRQoL. PROpel assessed the HRQoL and pain symptoms of participants using multiple instruments, including EQ-5D-5L, that demonstrated that combining olaparib with abiraterone does not negatively impact HRQoL compared with placebo plus abiraterone (see section B.2.6.5 of the company submission).

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

- The side effects observed with olaparib plus abiraterone in the PROpel trial were consistent with the known side effect profile of each agent used as monotherapy. There were no new safety concerns raised in the trial (10,14).

- The most common side effects in the PROpel trial for olaparib plus abiraterone arm were anaemia, fatigue/weakness, and nausea. Anaemia was the most common grade 3 or higher side effect, occurring in 60 patients (15.1%) in the olaparib plus abiraterone arm and 13 patients (3.3%) in the abiraterone and placebo arm (14).

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

- Olaparib plus abiraterone is the first combination therapy approach to be licensed for first line use in patients with mCRPC in whom chemotherapy is not clinically indicated.
- All available evidence indicates that olaparib in combination with abiraterone provides clinically meaningful improvements in efficacy compared with enzalutamide or abiraterone, which are the current standards of care for the first line treatment of mCRPC in people for whom chemotherapy is not clinically indicated.
- The increase in median rPFS of over 8 months compared with standard of care abiraterone, means patients can delay the use of subsequent therapies for longer. The observed numerical improvement in median OS of over 7 months indicates patients are likely to live for longer with combination therapy than with current standard of care therapy.
- Efficacy has been demonstrated in patients with or without genetic mutations that increase the risk of disease development and progression, which increases the potential treatment options for a broader range of mCRPC patients.
- These improvements in efficacy were achieved without negatively impacting HRQoL, which is ever important when treatment is not curative.
- In contrast to some other therapies (e.g., chemotherapy) used in mCRPC, olaparib plus abiraterone is an all-oral therapy, which means patients can take therapy at home.

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

- Like all anticancer therapies, olaparib plus abiraterone is associated with some side effects. The most common side effects are anaemia, fatigue/weakness, and nausea, but a minority of patients may experience other side effects. See the Summary of Product Characteristics at: https://www.medicines.org.uk/emc/product/9488/smpc and the Patient Information Leaflet at: https://www.medicines.org.uk/emc/product/9488/pil for the full list of known side effects.
- Patients receiving olaparib plus abiraterone would typically need to take 10 tablets per day, split over 2 doses each day. This compares with 6 tablets per day over two doses for abiraterone and 4 tablets taken once per day with enzalutamide.

3i) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

What are the comparators?

The economic model compares olaparib plus abiraterone against enzalutamide (the most used NHA in England) and abiraterone.

What is the structure of the model? Explain how the model reflects the experience of having the condition over time.

A three health-state partitioned survival model was developed in Microsoft Excel® to assess the cost effectiveness of olaparib plus abiraterone over a lifetime horizon. The health states included progression-free, progressed disease and death. The costs associated with each health state, and the HRQoL patients experiencing each of the health states are included. This is a standard model structure used to model cancer treatments.

Does the treatment extend life? If so, please explain how (for example. by delaying disease progression, reducing disease severity or complications, reducing disease relapses or life-limiting side effects).

Treatment with olaparib plus abiraterone delays disease progression and extends life compared with abiraterone monotherapy, as demonstrated by the longer rPFS and OS observed in the PROpel trial. As explained in response to question 3e above, the efficacy of enzalutamide is assumed to be the same as with abiraterone.

Describe briefly which trial outcomes feed into the economic model. If trial data used for a certain length of time followed by extrapolation, please note how long the trial data was used for and briefly how the data has been extrapolated.

The key clinical parameters included in the economic analysis include OS, rPFS and time to discontinuation of olaparib and abiraterone taken from the longest available follow up of data from the PROpel trial. OS was assessed after a median follow up of approximately 36.5 months. The OS and rPFS data are extrapolated over a lifetime horizon using NICE-recommended modelling approaches, with the resulting survival curves validated by UK clinical experts.

How is the treatment modelled to change a person's quality of life compared with the treatments already in use? This should include after stopping treatment if relevant. For example, say if the treatment improves quality of life because of improving symptoms or decreases quality of life because of side effects.

HRQoL is captured in the model using utility values derived from data collected in the PROpel trial. The utility values are specific to the health states and are not dependent on treatment received. The utility values are used to model quality adjusted life years (QALYs) with each treatment, as recommended by NICE. The differences in QALYs between the models arises from the differences in time spent in each health state between the treatments. For example, as olaparib plus abiraterone delays time to disease progression compared with the comparators, patients treated with olaparib plus abiraterone in the model stay in the progression free health state for longer than patients treated with the comparators. As patients who are progression free have a higher quality of life than patients who have progressive disease, patients treated with olaparib plus abiraterone stay in a higher quality of life state for longer than patients treated with the comparators. Over the lifetime of the model, patients treated with olaparib plus abiraterone on average live for longer than patients treated with the comparators, and so they accrue more QALYs than patients treated with the comparators.

Which quality of life measure(s) did you use to estimate a person's quality of life over time and on treatments? Are there any aspects of the condition or its treatments affecting quality of life which may not have been fully captured by the methods used to estimate quality of life?

Utility values in the model are derived from the HRQoL data collected directly from patients using the EQ-5D-5L instrument in the PROpel trial. In line with NICE's preferred approach, these data were first mapped to EQ-5D-3L data using the appropriate mapping algorithms. The EQ-5D instruments are generic quality of life tools and so it is possible that they are less sensitive to some aspects of the disease compared with disease specific quality of life instruments. However, NICE prefers the use of the EQ-5D instrument.

Does the medicine lead to any cost implications (positive or negative) for the health service (e.g., drug costs, number of days in hospital)?

The model reflects acquisition costs of all drugs, plus the costs associated with resource use in each of the modelled health states. As enzalutamide and olaparib are made available to the NHS at a confidential discount, we are unable to report the total costs. It should be noted that any additional costs of olaparib plus abiraterone are also accompanied by clinically meaningful improvements in efficacy, leading to more QALYs.

Are there any important differences in the way the medicine is given compared with those already in use that will affect the experience of the patient or costs to the health service or patients (e.g., where it is given or the monitoring that is needed)?

As olaparib plus abiraterone and the comparators are all given as oral therapies there are no costs associated with administration in the model, and there is no data suggesting the differences in pill burden will have a meaningful difference in quality of life. The model does account for the costs of monitoring and the quality-of-life impacts and costs of management of adverse events, but these have very little impact on the total cost and total QALY estimates.

Are there any key assumptions you have made in your model about the medicine's benefits or costs because of lack of data?

As explained in response to question 3e, there are no direct comparative data for olaparib plus abiraterone vs enzalutamide; however, real world data, clinical expert opinion and the indirect treatment comparison all suggest there are no differences between abiraterone and enzalutamide. We therefore assume in the model that the efficacy of olaparib plus abiraterone vs abiraterone observed in the PROpel trial would reflect the efficacy of olaparib plus abiraterone vs enzalutamide.

Did you test using alternative assumptions or data in your model? Which had the largest effect on your cost effectiveness estimates?

A wide range of sensitivity and scenario analyses were conducted around parameter values and assumptions, which indicated that the base case model estimates were generally robust. As may be expected, in the comparison of olaparib plus abiraterone against enzalutamide, the assumptions having the largest effect on the cost effectiveness estimates was the assumed OS and time on treatment for enzalutamide. In comparisons against abiraterone, the cost effectiveness estimates were affected minimally across the broad range of parameters tested.

Are there any data you have presented to support your modelled outcomes being plausible?

Model outputs were tested against the observed data in relevant clinical trials and were shown to be a good match. Clinical experts validated the modelled survival.

What is the modelled benefit in overall survival, quality adjusted life years and the incremental cost effectiveness ratio?

Over the modelled lifetime, olaparib plus abiraterone generated an additional 1.56 years of survival and 1.26 QALYs compared with the comparators. These are discounted values assuming an annual discount rate of 3.5% in line with NICE requirements. As the costs are confidential, we are unable to report the incremental cost effectiveness ratio here.

Have you made a case for a severity modifier being relevant for this condition? If so, please summarise the data presented

No case is made for a severity modifier to be applied.

Are there any benefits or disadvantages of the treatment not captured in the modelling?

The model is unlikely to fully capture the HRQoL benefits of delaying treatment with cytotoxic chemotherapy, including the psychological impact and inconvenience or its administration.

3j) Innovation

NICE considers how innovative a new treatment is when making its recommendations.
If the company considers the new treatment to be innovative, please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

Olaparib in combination with abiraterone provides a step change in first line therapy for patients with mCRPC in whom chemotherapy is not clinically indicated:

- Olaparib plus abiraterone is the first combination therapy approach to be licensed for first line use in patients with mCRPC for whom chemotherapy is not clinically indicated. The combination was designated as innovative by the granting of an Innovation Passport in June 2022 as part of the UK regulatory authority (MHRA)-led Innovative Licensing and Access Pathway (11).
- Current standard of care in the first line mCRPC setting when chemotherapy is not clinically indicated include NHAs (abiraterone or enzalutamide), which in their phase 3 registrational trials provided median progression-free survival (PFS) of approximately 16-20 months (12,13). In contrast, olaparib plus abiraterone provides a median PFS in the PROpel ITT population of 24.97 months at the last data cut, and so exceeds 2 years for the first time in this patient group (14) (see company submission section B.2.6.1).
- Improved efficacy with olaparib plus abiraterone is observed irrespective of whether patients have genetic mutations associated with high risk of disease development and progression (10,14) (see company submission section B.2.7.1).
- The early use of olaparib in combination with abiraterone in mCRPC significantly delays disease progression, which can potentially delay the use of subsequent therapies that have diminishing efficacy and may improve overall survival (15,16) (see company submission section B.2.6.2). The economic model is unlikely to fully capture the HRQoL benefits of delaying treatment with cytotoxic chemotherapy, including the psychological impact and inconvenience or its administration.
- Olaparib plus abiraterone therefore provides a much-needed new first-line therapeutic option to improve outcomes in first line mCRPC patients (irrespective of their genetic mutation status) for whom chemotherapy is not clinically indicated.

3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics.

More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.

Several potential equality considerations exist relating to protected characteristics of age, sex and gender, race and religion:

- Around 1 in 6 men will develop prostate cancer (1).
- The risk of prostate cancer increases with age (1).

- Prostate cancer disproportionately affects men of black ethnicity – around 1 in 4 black men will develop prostate cancer (1).
- Genetic (HRR) mutations such as BRCA1 or 2 mutations increase the risk of developing prostate cancer and are associated with more aggressive disease. Around 1 in 3-400 people in the population have a BRCA gene mutation, but people from Ashkenazi Jewish backgrounds have a 10-fold greater risk (1,23). The PROpel trial demonstrates olaparib plus abiraterone provides clinical benefit over current standard of care therapy with abiraterone for patients with or without genetic mutations.
- People who have a prostate and do not identify as men (e.g., people who have or are undergoing gender reassignment, those who identify as non-binary people) can develop prostate cancer (1).
- In patients for whom chemotherapy is not clinically indicated, olaparib plus abiraterone provides a more effective oral therapy option than would otherwise be available to them.

SECTION 4: Further information, glossary and references

4a) Further information

Useful patient information on prostate cancer is available from:

- Prostate Cancer UK: https://prostatecanceruk.org/
- Cancer Research UK: https://www.cancerresearchuk.org/about-cancer/prostate-cancer.

Further information on NICE and the role of patients**:**

- Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE
- NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE
- EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/
- EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf
- National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/
- INAHTA: http://www.inahta.org/
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

- **Double-blind.** Design feature of a robust randomised controlled trial (RCT) that ensures neither the patient nor the person assessing the patient knows which treatment the patient has received.
- **DRE – digital rectal examination.** Used to see if you might have a prostate problem or prostate cancer. It involves your doctor or nurse feeling your prostate through the wall of the back passage (rectum).
- **EQ-5D-3L/5L.** A validated generic quality of life instrument that may be used to assess HRQoL across a range of different diseases. From this utility values can be estimated.
- **HR - hazard ratio.** The hazard or chance of an event occurring in the treatment arm of a study as a ratio of the chance of an event occurring in the control arm over time.

- **HRQoL – health-related quality of life.** A combination of a person's physical, mental and social well-being; not merely the absence of disease. Can be assessed using validated questionnaires or surveys (e.g., EQ-5D-5L instrument), or using quantitative experiments where people reveal their preferences for different situations.
- **HRRm – homologous recombination repair mutations.** Specific genetic mutations (e.g., BRCA1 or 2) that increase the chances of development or progression of prostate cancer (or some other cancers).
- **mCRPC – metastatic castration-resistant prostate cancer.** Prostate cancer that has spread beyond the prostate gland is no longer responsive to or continues to progress despite androgen deprivation therapy with drugs or castration. Sometimes also called hormone-relapsed metastatic prostate cancer.
- **NMA – network meta-analysis.** A statistical technique for comparing multiple treatments simultaneously in a single analysis by combining data from randomised controlled trials.
- **OS – overall survival.** Typically defined as the time from randomisation in the trial to death from any cause.
- **Patient information leaflet.** Document that provides information for patients on using a medicine safely and correctly.
- **Primary endpoint/outcome.** The main outcome for which a clinical trial is designed to evaluate the effects of a treatment.
- **PSA – prostate specific antigen.** A protein produced by normal cells in the prostate and also by prostate cancer cells. Abnormally high levels of PSA in the blood may indicate the presence of prostate cancer, but may also be caused by other, non-cancer-related problems such as enlarged prostate (benign prostatic hyperplasia) or inflammation of the prostate gland (prostatitis).
- **PSA test – prostate specific antigen test.** A blood test to measure the levels of PSA.
- **QALYs – quality adjusted life years.** A measure of the state of health of a person or group in which the benefits, in terms of length of life, are weighted using utility values to reflect the quality of life. One quality-adjusted life year (QALY) is equal to 1 year of life in perfect health.
- **RCT – randomised controlled trial.** A type of clinical trial to compare the effects of treatments such as drugs against each other by assigning participants randomly to each of the treatments. This is the most scientifically robust type of clinical trial.
- **rPFS – radiographic progression free survival.** Typically defined as the time from randomisation in the trial to the first objective evidence of disease progression as assessed using radiography, or death, whichever occurs first.
- **Real-world data.** Data collected in real world settings or real clinical practice rather than in a clinical trial.

- **Secondary endpoint(s)/outcome(s).** Specified key outcomes a trial will evaluate that are not the primary endpoint. This does not necessarily mean the secondary endpoints are less important than the primary endpoint; it relates to the ability of the trial design to test for any differences between treatments in their effects on the outcome(s) in the trial.
- **Summary of Product Characteristics.** A document describing the properties and the officially approved conditions of use of a medicine. Forms the basis of information for healthcare professionals on how to use the medicine safely and effectively.
- **Utility values.** A measure of the preference or value that an individual or society gives a particular health state. It is generally a number between 0 (representing death) and 1 (perfect health). Can be used to weight the length of time spent in a given health state to generate QALYs.

4c) References

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Olaparib with abiraterone for untreated hormone-relapsed metastatic prostate cancer [ID3920]

Clarification questions

May 2023

File name	Version	Contains confidential information	Date
ID3920_Olaparib_CompanyResponse to CQs_v1.0	1.0	Yes	24 May 2023

Section A: Clarification on effectiveness data

Population

A1. Priority Question: Olaparib 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. However, the patients in the PROpel trial seem fit enough to receive chemotherapy (i.e. chemotherapy is a clinical option). Please clarify why the authorisation wording is not "…. in whom chemotherapy is not yet clinically indicated", as is seen in the abiraterone and enzalutamide authorisations.

At the time that abiraterone and enzalutamide recieved marketing authorisations for mCRPC, docetaxel was not routinely available at the earlier mHSPC setting. When the European Medicines Agency (EMA) granted an authorisation for olaparib in combination with abiraterone to treat mCRPC, docetaxel had become a routine treatment choice at mHSPC. Therefore, the authorisation was consistent with the abiraterone and enzalutamide labels, with a minor amendment to improve the clarity of the licensed population reflecting these outlined changes in the treatment landscape. This label is also as per the PROpel clinical trial which underpins the licensing of olaparib in combination with abiraterone in the first-line mCRPC setting.

PROpel enrolled patients that were both docetaxel naïve and docetaxel experienced from the pre-mCRPC setting - 97 (24.3%) and 98 (24.7%) patients had received prior docetaxel treatment in the olaparib plus abiraterone arm and placebo plus abiraterone arm, respectively (1). It is also worth noting that patients in PROpel were stratified by prior docetaxel experience. Based on these trial data, it would be inappropriate for the licensed indication to stipulate use in patients for whom chemotherapy is not *yet* clinically indicated, as this suggests that patients will proceed to become clinically indicated. Given that a proportion of patients in PROpel had already received docetaxel in the pre-mCRPC setting, they would be ineligible for repeated docetaxel treatment as NICE NG131 outlines that this is not permitted (2). Additionally, patients who have not received prior docetaxel could still be ineligible, i.e., due to contraindications or their level of 'fitness'. This therefore demonstrates that the

wording ‘in whom chemotherapy is not clinically indicated’ is appropriate and the qualifier of not *yet* clinically indicated is therefore inappropriate.

PROpel Trial

A2. Please provide the protocol and statistical analysis plan documents for the PROpel trial.

A copy of the protocol and statistical analysis plan for the PROpel clinical study have been included in the files submitted by the company.

A3. For Figure 2 of the appendices (CONSORT diagram) please provide more detailed data on why patients discontinued for ‘other’ reasons.

In the PROpel study, only one of the following reasons could be selected as the main reason for investigational product discontinuation:

- Adverse event
- Development of study specific discontinuation criteria
- Objective disease progression
- Severe non-compliance to protocol
- Patient decision
- Patient lost to follow-up
- Other

“Other” reasons for discontinuation of olaparib or placebo were not further classified in the clinical study report. The proportion of patients discontinuing treatment for ‘other’ reasons was comparable for olaparib plus abiraterone (n = 70, 17.6%), and placebo plus abiraterone (n = 79, 19.9%).

A4. Priority Question: Section B.2.7 presents subgroup analyses and results for a global interaction test.

a) **Please provide results for interaction tests for all the individual subgroup analyses.**

Interaction tests for individual subgroups are provided in the accompanying references: SubgroupAnalysis_DCO3_rPFS_interaction_CONFIDENTIAL.pdf and SubgroupAnalysis_DCO3_OS_interaction_CONFIDENTIAL.pdf.

The pre-specified analysis of interaction effects between treatment and subgroup was assessed by means of an overall global interaction test. No adjustment to the significance level for testing of subgroups was made since all subgroup analyses were considered exploratory of the primary rPFS analysis. The analysis of individual-level interaction effects was performed post-hoc and without control for multiplicity and therefore should be viewed with caution.

A nominally significant interaction ($p<0.05$) was observed for only the age at randomisation subgroups (<65 yrs; ≥65 yrs) in the rPFS subgroup analyses. No significant interaction was noted for any other subgroup for either rPFS or OS, including for age in OS. We therefore do not believe this reflects a true differential treatment effect based on age. These data support the clinical benefit of olaparib plus abiraterone in all patients meeting its licensed indication.

b) The EAG is cognisant that olaparib monotherapy is only recommended in BRCA 1 and 2 patients. Although not pre-specified, exploring subgroup effects within this subgroup of HRRm patients may therefore be useful. Please provide these results (OS and rPFS) where possible.

As requested by the EAG, subgroup analyses of OS and rPFS (at DCO3 – the latest data cut) in patients harbouring BRCA1 and 2 mutations in the PROpel trial at DCO3 (latest data cut) are provided below (Table 1, Figure 1, Table 2, Figure 2). It should be noted that, in contrast to the PROfound study that supported the licensing of olaparib as monotherapy in BRCA1 and 2, NHA-exposed mCRPC patients, the PROpel trial enrolled patients irrespective of HRR-mutation status and only determined HRR-mutation status after randomisation. The subgroup analysis of BRCA1 and 2 is therefore a non-stratified, post-hoc analysis hence the results should be interpreted with caution.

Table 1. OS BRCAm (DCO3)(3)

Arm	N	Events	Maturity	Median OS (95% CI)	HR (95% CI)
Placebo + abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Olaparib + abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Figure 1 . OS KM curve for BRACm subgroup (DCO3)

Table 2. PFS BRCAm (Investigator DCO3)(3)

Arm	N	Events	Maturity	Median rPFS (95% CI)	HR (95% CI)
Placebo + abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Olaparib + abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Figure 2. rPFS KM curve for BRCAm subgroup (DCO3)

A5. Section B.2.6.5.3 reports on EQ-5D-5L. Please explain why data were available for only around two-thirds of the trial cohort (compliance rates for completion of the BPI-SF questionnaire were much higher). Please comment on the likelihood of these missing data resulting in biased results.

As outlined in the study protocol, patients in the PROpel trial completed the questionnaires in a sequential order; first BPI-SF, followed by FACT-P and finally the EQ-5D-5L.

As noted by the EAG, the completion rates for patient reported outcomes (PROs) were much higher for BPI-SF which was the first instrument to be completed, and lower for instruments collected second and third in the planned sequence of PRO collection (see Table 3).

Table 3: Overall compliance rate by sequential order in PROpel

Sequence of administration	Instrument	Overall compliance rate	
		Olaparib + abiraterone	***Placebo + abiraterone***
1st	BPI-SF	[redacted]	[redacted]
2nd	FACT-P	[redacted]	[redacted]
3rd	EQ-5D-5L	[redacted]	[redacted]

The reasons for not completing an individual questionnaire were not recorded; only information relating to failure to complete any of the PRO instruments was reported. However, based on the trend observed in Table 3, compliance rates decreased with each additional PRO, suggesting that the compliance rates potentially were impacted by the sequence of data collection.

An exploratory analysis of missing baseline EQ-5D-5L was performed to understand whether the probability of having a missing EQ-5D-5L questionnaire was associated with poor quality of life. This was analysed according to age, ECOG performance status and pain score, all of which are characteristics associated with health-related quality of life. The analysis was limited to baseline measures as not all relevant measures (e.g., ECOG) were routinely collected at study follow-up visits.

The results shown below (Table 4) indicate that missingness was not related to any of the baseline characteristics that are likely to be associated with lower utility values, including factors related to frailty (age, ECOG score) or pain (BPI-SF). These findings suggest that the missing EQ-5D-5L in PROpel may be either missing at random (MAR) or, missing completely at random (MCAR). Under these assumptions, the mixed effects repeated measures analysis of EQ-5D-5L can be expected to provide a valid estimate of health state utility.

Table 4. Missing EQ-5D-5L data by baseline characteristics

Baseline characteristics		Baseline EQ-5D	Olaparib + abiraterone (N=399)	Placebo + abiraterone (N=397)	Total (N=796)
Age	Median (Min, Max)	Present	[redacted]	[redacted]	[redacted]
		Missing	[redacted]	[redacted]	[redacted]
Baseline WHO performance status n (%)	ECOG 0	Present	[redacted]	[redacted]	[redacted]
		Missing	[redacted]	[redacted]	[redacted]
	ECOG 1	Present	[redacted]	[redacted]	[redacted]
		Missing	[redacted]	[redacted]	[redacted]
	Missing	Present	[redacted]	[redacted]	[redacted]
		Missing	[redacted]	[redacted]	[redacted]
Baseline pain score, BPI-SF n (%)	0-4	Present	[redacted]	[redacted]	[redacted]
		Missing	[redacted]	[redacted]	[redacted]
	≥4	Present	[redacted]	[redacted]	[redacted]
		Missing	[redacted]	[redacted]	[redacted]
	Missing	Present	[redacted]	[redacted]	[redacted]
		Missing	[redacted]	[redacted]	[redacted]

A6. Please present a table which compares the number (and percentages) of Grade≥ 3 AEs for the PROpel, COU-AA-302, PREVAIL, and PREVAIL Asia trials.

As requested by the EAG, the below Table 5 compares the grade≥ 3 adverse events from the PROpel, COU-AA-302, PREVAIL, and PREVAIL Asia clinical studies. However, this should be interpreted with caution due to the differences in the maturity of the four data sets. PROpel data from DCO1 (Primary PFS analysis; 30 July 2021)) has been used so that the maturity is as similar as possible to the other data sets; please refer to Appendix F in the company submission submission to access Grade≥ 3 adverse event reporting from DCO3 (final OS analysis; 12 October 2022).

It is also worth noting that the COU-AA-302 clinical study reported grade 3-4 adverse events only (not including grade 5) (4), whereas the other studies reported all grade≥ 3 adverse events. Additionally, PREVAIL Asia only reported the 'most frequent' grade≥ 3 adverse events occurring in ≥ 2% patients (5), in contrast to the other studies which reported all grade≥ 3 adverse events occurring in ≥ 1% patients.

Table 5: Comparison of Grade≥ 3 AEs for the PROpel, COU-AA-302, PREVAIL, and PREVAIL Asia trials

	COU-AA-302		PREVAIL		PREVAIL Asia		PROpel	
	Abiraterone + prednisone (N=542)	**Placebo + prednisone (N=540)**	**Enzalutamide (N=871)**	**Placebo (N=844)**	**Enzalutamide (N=198)**	**Placebo (N=190)**	**Olaparib + abiraterone (N=398)**	**Placebo + abiraterone (N=396)**
Total Grade ≥ 3 AEs	267 (49.3%) *Grade 3-4 only	235 (43.5%)	374 (42.9%)	313 (37.1%)	49 (24.7%)	56 (29.5%)	188 (47.2%)	152 (38.4%)
Metabolism and nutrition disorders	61 (11.3%)	42 (7.8%)	-	-	-	-	30 (7.5%)	21 (5.3%)
Hyperglycaemia	14 (2.6%)	11 (2.0%)	-	-	-	-	7 (1.8%)	6 (1.5%)
Hypokalaemia	14 (2.6%)	10 (1.9%)	-	-	-	-	7 (1.8%)	2 (0.5%)
Hyponatraemia	9 (1.7%)	8 (1.5%)	-	-	-	-	-	-
Dehydration	7 (1.3%)	3 (0.6%)	-	-	-	-	-	-
Anorexia	6 (1.1%)	1 (0.2%)	-	-	-	-	-	-
Hypophosphataemia	5 (0.9%)	7 (1.3%)	-	-	-	-	-	-
Investigations	51 (9.4%)	27 (5.0%)	-	-	9 (4.5%)	8 (4.2%)	38 (9.5%)	33 (8.3%)
ALT increased	30 (5.5%)	4 (0.7%)	-	-	-	-	4 (1.0%)	9 (2.3%)
AST increased	17 (3.1%)	5 (0.9%)	-	-	-	-	2 (0.5%)	6 (1.5%)
Blood ALP increased	6 (1.1%)	5 (0.9%)	-	-	-	-	-	-
Amylase	-	-	-	-	-	-	3 (0.8%)	5 (1.3%)
Lymphocyte count decreased	-	-	-	-	-	-	13 (3.3%)	5 (1.3%)
Neutrophil count decreased	-	-	-	-	-	-	9 (2.3%)	3 (0.8%)
White blood cell count decreased	-	-	-	-	-	-	7 (1.8%)	2 (0.5%)
Musculoskeletal and connective tissue disorders	48 (8.9%)	60 (11.1%)	68 (7.8%)	78 (9.2%)	7 (3.5%)	14 (7.4%)	-	-
Back pain	15 (2.8%)	21 (3.9%)	22 (2.5%)	25 (3.0%)	-	-	-	-
Arthralgia	10 (1.8%)	10 (1.9%)	12 (1.4%)	9 (1.1%)	-	-	-	-
Bone pain	7 (1.3%)	11 (2.0%)	12 (1.4%)	20 (2.4%)	3 (1.5%)	7 (3.7%)	-	-
Musculoskeletal pain	7 (1.3%)	6 (1.1%)	-	-	-	-	-	-
Muscular weakness	3 (0.6%)	6 (1.1%)	-	-	-	-	-	-
Pathological fracture	-	-	9 (1.0%)	7 (0.8%)	-	-	-	-
Infections and infestations	43 (7.9%)	35 (6.5%)	45 (5.2%)	37 (4.4%)	9 (4.5%)	7 (3.7%)	47 (11.8%)	35 (8.8)

Urinary tract infection	9 (1.7%)	3 (0.6%)	13 (1.5%)	11 (1.3%)	-	-	8 (2.0%)	4 (1.0)
Pneumonia	7 (1.3%)	4 (0.7%)	11 (1.3%)	7 (0.8%)	4 (2.0%) “lung infection”	1 (0.5%) “lung infection”	7 (1.8%)	3 (0.8)
COVID-19	-	-	-	-	-	-	12 (3.0%)	7 (1.8)
Nervous system disorders	36 (6.6%)	23 (4.3%)	73 (8.4%)	53 (6.3%)	6 (3.0%)	1 (0.5%)	-	-
Syncope	9 (1.7%)	6 (1.1%)	14 (1.6%)	8 (0.9%)	-	-	-	-
Spinal cord compression	-	-	33 (3.8%)	24 (2.8%)	-	-	-	-
Vascular disorders	36 (6.6%)	31 (5.7%)	69 (7.9%)	26 (3.1%)	7 (3.5%)	2 (1.1%)	18 (4.5%)	13 (3.3%)
Hypertension	23 (4.2%)	17 (3.1%)	59 (6.8%)	19 (2.3%)	-	-	14 (3.5%)	13 (3.3%)
Deep vein thrombosis	8 (1.5%)	6 (1.1%)	-	-	-	-	-	-
Renal and urinary disorders	31 (5.7%)	28 (5.2%)	49 (5.6%)	68 (8.1%)	4 (2.0%)	9 (4.7%)	-	-
Haematuria	7 (1.3%)	4 (0.7%)	9 (1.0%)	11 (1.3%)	2 (1.0%)	4 (2.1%)	-	-
Urinary retention	7 (1.3%)	3 (0.6%)	8 (0.9%)	14 (1.7%)	-	-	-	-
Hydronephrosis	1 (0.2%)	8 (1.5%)	5 (0.6%)	16 (1.9%)	-	-	-	-
Urinary tract obstruction	9 (1.0%)	9 (1.1%)	-	-	-	-	-	-
General disorders and administration site conditions	30 (5.5%)	33 (6.1%)	58 (6.7%)	49 (5.8%)	3 (1.5%)	7 (3.7%)	15 (3.8%)	11 (2.8%)
Fatigue	13 (2.4%)	10 (1.9%)	16 (1.8%)	16 (1.9%)	-	-	-	-
General physical health deterioration	6 (1.1%)	2 (0.4%)	18 (2.1%)	10 (1.2%)	-	-	-	-
Asthenia	1 (0.2%)	7 (1.3%)	11 (1.3%)	8 (0.9%)	-	-	5 (1.3%)	3 (0.8%)
Cardiac disorders	28 (5.2%)	13 (2.4%)	-	-	5 (2.5%)	3 (1.6%)	15 (3.8%)	10 (2.5%)
Atrial fibrillation	9 (1.7%)	5 (0.9%)	-	-			5 (1.3%)	3 (0.8%)
Gastrointestinal disorders	28 (5.2%)	25 (4.6%)	37 (4.2%)	25 (3.0%)	8 (4.0%)	4 (2.1%)	-	-
Diarrhoea	6 (1.1%)	5 (0.9%)	-	-			-	-
Abdominal pain	3 (0.6%)	9 (1.7%)	-	-			-	-
Nausea	-	-	9 (1.0%)	4 (0.5%)	1 (0.5%)	6 (3.2%)	-	-
Respiratory, thoracic and mediastinal disorders	28 (5.2%)	23 (4.3%)	-	-			31 (7.8%)	11 (2.8%)
Dyspnoea	14 (2.6%)	5 (0.9%)	-	-			-	-
Pulmonary embolism	11 (2.0%)	15 (2.8%)	-	-			26 (6.5%)	7 (1.8%)
Blood and lymphatic system disorders	21 (3.9%)	19 (3.5%)	37 (4.2%)	31 (3.7%)	4 (2.0%)	7 (3.7%)	67 (16.8%)	21 (5.3%)
Anaemia	13 (2.4%)	10 (1.9%)	29 (3.3%)	25 (3.0%)	3 (1.5%)	6 (3.2%)	60 (15.1%)	13 (3.3%)
Lymphopenia	-	-	-	-			7 (1.8%)	2 (0.5%)

Neoplasms benign, malignant and unspecified (including cysts and polyps)	20 (3.7%)	22 (4.1%)	52 (6.0%)	38 (4.5%)	1 (0.5%)	8 (4.2%)	-	-
Cancer pain	5 (0.9%)	9 (1.7%)	-	-	-	-	-	-
Metastatic pain	-	-	14 (1.6%)	16 (1.9%)	-	-	-	-
Eye disorders	-	-	14 (1.6%)	2 (0.2%)	-	-	-	-
Cataract	-	-	11 (1.3%)	1 (0.1%)	-	-	-	-
Injury, poisoning, and procedural complications	-	-	29 (3.3%)	19 (2.3%)	-	-	-	-
Fall	-	-	12 (1.4%)	6 (0.7%)	-	-	-	-

Abbreviations: - = not reported, ALP=- alkaline phosphatase, ALT = alanine aminotransferase, AST = Aspartate aminotransferase,

Sources:

COU-AA-302 TA387 NICE submission (unpublished CSR; COU-AA-302 study third interim analysis, 55% maturity data cut-off). *Incidence of grade 3 or 4 AEs occurring in ≥1% of patients across randomised groups*.

PREVAIL TA377 NICE submission (unpublished CSR; dated 13 February 2014). *Adverse events grade ≥3 reported in ≥1% of patients in either group by system organ class (Safety Set).*

PROpel CSR (Data Cut Off 1; 47.6% maturity) *Adverse Events of Common Terminology Criteria for Adverse Events Grade 3 or Higher by System Organ Class and Preferred Term (Frequency > 1% in either Treatment Arm) (Safety analysis set).*

PREVAIL Asia YS, Ahn H, Han W, Huang SP, Wu HC, Ma L, et al. Enzalutamide in Chemotherapy-Naïve Metastatic Castration-Resistant Prostate Cancer: *AEs of grade≥3 occurring in ≥2% of patients in either treatment group*. Adv Ther. 2022 Jun;39(6):2641–56.

A7. Priority Question: The submission states that real-world data and clinical expert opinion consistently indicate there is no difference in efficacy between abiraterone and enzalutamide in terms of rPFS or OS. The EAG notes that a large study by Schoen et al 2022 does not concur with this assumption of equivalence (https://www.nature.com/articles/s41391-022-00588-5). Please therefore demonstrate the robustness of this statement, with respect to the real-world data aspect. This can be done by describing how potentially relevant studies were first identified, and then selected, and by considering the quality of the relevant studies in terms of adjustment for potential confounders (e.g. using a Cox regression model or propensity scores).

The key objective of the Schoen et al study identified by the EAG was to assess how comorbidities interact with abiraterone and enzalutamide for mCRPC with respect to OS and treatment duration (rPFS was not evaluated) (6).

The target population (n=5,822) were exclusively veterans which was a purposeful treatment selection criterion because, as explained in the paper, many veterans with prostate cancer are high risk with multiple comorbidities. As noted by the authors, there is evidence that comorbid diseases and age can interact with treatments which affects survival (7–9) therefore the outcomes reported in the study should be interpreted within this context.

Although age is likely a prognostic factor, pre-existing conditions may also modify the outcomes of interest. Six clinical experts with significant experience in treating prostate cancer in the UK cautioned that abiraterone is not typically initiated in patients with cardiovascular disease or diabetes (reported in approximately 73% of the cohort in Schoen et al, 2022 (6)). Of note, the study highlighted that an important interaction was identified between veterans with mCRPC and cardiovascular disease or diabetes resulting in *"decreased survival with abiraterone, highlighting potential toxicity or decreased efficacy"* (6).

In the subgroup of patients without cardiovascular disease or diabetes (n=1,622) investigated in Schoen et al, 2022, the authors concluded that *"while there may be unknown biases in treatment selection, in patients without diabetes or cardiovascular disease [or who received two or more treatments] there were no differences in*

outcomes between the ARTAs, which supports the hypothesis that these medicines can be used interchangeably and have little differences in outcomes in fit patients." (6). The conclusion from the study with regards to the equivalence of abiraterone and enzalutamide in the subgroup unselected for high-risk comorbidities is fully aligned with the unanimous feedback from six prostate cancer clinical experts consulted by AstraZeneca.

In relation to how real-world studies cited in the company submission were identified, a systematic literature review, following the guidance of the Cochrane Collaboration and the Centre for Reviews and Dissemination (10,11) , was conducted. The searches were run on November 18, 2021, limited by date (2011 onwards) to cover the period after which NHAs were first approved for mCRPC and available in routine clinical practice. Please note the search date reflects the primary purpose of the real-world review which was for internal use to summarise available evidence on the real-world outcomes of abiraterone or enzalutamide in first line mCRPC. The search provided real-world resources cited in the submission. The study by Schoen et al, 2022 noted by the EAG was not identified in the company's literature review because the search was completed before the study in question was published in 2022. The quality of the studies in the review were assessed using the Cochrane ROBINS-I tool for non-randomised studies of interventions (12).

In summary, the review identified a number of studies reporting on the comparative effectiveness of abiraterone versus enzalutamide. The majority of included studies reported estimates of treatment effect without adjustment for differences in patient characteristics across groups, potentially leading to biased effect estimates. In accordance with best practice, we prioritised data from studies reporting adjusted analyses or those that were of prospective study design (13). Most studies were retrospective by design meaning that study authors had to rely on available data from registries, which may not capture all confounding factors between groups.

Only one comparative study by Chowdhury et al 2020 (14) reporting on both OS and PFS was prospectively designed. This reported no difference in outcomes between NHAs. The Chowdhury study is more informative due to its prospective study design and adjustment for confounders by propensity score matching. The study included 1,874 patients, of which 313 patients were from the UK. Potential confounders that

were adjusted included age, time from diagnosis to castration resistance, time from diagnosis to metastasis, time from metastasis to study start, alkaline phosphatase, prostate-specific antigen, haemoglobin, Gleason score, diabetes, use of analgesics, cardiovascular disease, ECOG status, prior radical prostatectomy, disease stage and bone lesions.

Based on the propensity score matched outputs, the study reported no evidence of difference in adjusted PFS (HR 1.040, 95% CI: 0.851-1.270, p=0.7000) and adjusted OS (HR 1.000, 95% CI 0.788 to 1.270, p=0.9986) (14). This is consistent with the output reported in the subgroup of patients without cardiovascular disease or diabetes in Schoen et al, 2022 (6).

Further details on the real-world review including the process of how studies were identified, selected and quality of the relevant studies based on the Cochrane ROBINS-I tool for non-randomised studies of interventions in terms of adjustment for potential confounders is provided in a separate summary report (see Appendix 1) of RWE to accompany this response.

In summary, the clinical expert opinion and the RWE we identified in our review, and the Schoen et al 2022 study identified by the EAG, support our conclusion that there is no meaningful difference in efficacy between abiraterone and enzalutamide in patients for whom abiraterone is clinically considered to be a treatment option.

Network meta-analysis and equivalence assumption

A8. Priority Question: The submission states (on p60) that "…the available evidence in the literature and clinical opinion suggests that it is plausible that treatment with prednisone may have a therapeutic effect on rPFS. To adopt the control arm of the COU-AA-302 study as a proxy for placebo in the network may therefore lead to underestimation of the treatment benefit of abiraterone in the network and may benefit enzalutamide over abiraterone in any comparison of rPFS". However, the treatment effect favouring enzalutamide in

the McCool et al NMA is large (HR 0.59). Is it clinically plausible that all this effect is due just to prednisone?

In the NMA conducted by McCool et al (15) it was assumed that the prednisone comparator arm of the COU-AA-302 study of abiraterone was equivalent to placebo to enable a trial network to be formed linking to the placebo arm of the PREVAIL trial of enzalutamide. The resulting rPFS hazard ratio for enzalutamide versus abiraterone was 0.59 (95%CI 0.48-0.72). This result is not aligned with expert opinion of 6 UK clinicians we consulted, who are experienced in the use of abiraterone and enzalutamide in the treatment of mCRPC; these clinicians unanimously agreed that abiraterone and enzalutamide are equivalent for rPFS (and OS). This rPFS result in the McCool NMA therefore appears to lack clinical face validity. McCool et al also noted that the result of their NMA should be interpreted with caution.

It is difficult to quantify the exact contribution of the assumption that prednisone is equivalent to placebo to the rPFS HR of 0.59 estimated by McCool et al. However, it is clear from the literature and clinical opinion that corticosteroid may have a therapeutic effect on rPFS, as discussed in section B.2.9.3.1 of our submission. It is also clear that an assumption of equivalence between prednisone and placebo would be required in order to conduct an NMA, and the resulting hazard ratio for rPFS estimated by McCool et al under this assumption is associated with a great deal of clinical uncertainty that is not adequately reflected in the 95% CI around the point estimate.

It was for this reason that we concluded that it would not be feasible to conduct a sufficiently robust NMA that has clinical face validity for rPFS.

A9. Priority Question: Section B.2.9 describes the important differences in trials contributing data to the NMA, please comment on:

a) **The validity of the network transitivity assumption.**

The validity of the network transitivity assumption was assessed by reviewing differences in trials contributing data to the NMA and assessing whether the distribution of treatment effect modifiers differed across sources of direct evidence. Due to the network geometry, and the absence of a closed loop, it was not feasible to test for transitivity in the form of inconsistency between direct and indirect evidence.

As noted in section B.2.9, there were some potentially important differences in baseline characteristics between trial populations:

- Gleason score
- Time since diagnosis
- Asymptomatic or mild pain versus symptomatic pain
- Visceral disease
- HRRm status (reported for PROpel only)

For the baseline variables of time since diagnosis, Gleason score, pain score and HRRm status, the impact of baseline status on treatment effect was not reported in at least one of the included studies; time since diagnosis was not assessed in any of the included studies whilst HRRm status was only assessed in PROpel. The prevalence of HRRm in PROpel was broadly consistent with prevalence identified in the phase 3 PROfound trial and The Cancer Genome Atlas (TCGA) datasets (16). As testing was not required for enrolment to PROpel, it is reasonable to assume that the HRRm prevalence in the intention to treat population of PROpel is also consistent with other studies in the NMA, where testing was also not a requirement for enrolment. The impact of time since diagnosis is unclear, however, there is no evidence to suggest that it modifies treatment effect.

The inclusion criteria for the COU-AA-302, PREVAIL and 9785-CL-0232 studies were restricted to asymptomatic or mildly symptomatic patients (4,5,17) , hence no data are available on the impact of symptomatic pain on the treatment effect of abiraterone or enzalutamide. At DCO3 of PROpel, there was no significant or meaningful difference in treatment effect for olaparib comparing subgroups with asymptomatic and mild pain versus moderate or severe pain at baseline.

Subgroup analyses based on Gleason score, which was higher for PROpel and 9785-CL-0232 than COU-AA-302 and PREVAIL, was assessed in PREVAIL only (17). In this study (PREVAIL), there was no evidence of a difference in treatment effect for enzalutamide versus placebo across subgroups with Gleason scores $\leq$7 or $\geq$8 . Other differences across studies that could theoretically invalidate the results of the OS NMA, include:

- Visceral disease, approximately 10-15% of patients in PROpel, 9785-CL-0232 and PREVAIL had liver or lung metastases at baseline versus 0% in COU-AA-302. In a prespecified subgroup analysis of PREVAIL (18), the treatment effect for enzalutamide on OS for patients with lung metastases (~8%) was similar to the overall effect observed in the study (i.e., the ITT population). For patients with liver metastases (~4%), the effect of enzalutamide did appear reduced; however, due to the small sample size of this subgroup, the reduced treatment effect in this population is unlikely to have impacted the overall study results used in the NMA. In PROpel, there was no evidence of an association between the presence of visceral metastases at baseline and treatment effect for olaparib and abiraterone. Hence, the different distribution of visceral disease across studies would not be expected to invalidate the transitivity assumption.
- Use of corticosteroids as background therapy, with 100% use in COU-AA-302 and PROpel (mandated by licence for abiraterone) versus 30% in the PREVAIL and 9785-CL-0232 studies of enzalutamide. As noted in section B.2.9.2 of our submission, there is a lack of evidence to suggest that corticosteroid use impacts OS. These findings are supported by the consistency in median OS when comparing the placebo control arms of COU-AA-302 (median 30.3 months, placebo + prednisone) and PREVAIL (median 31.3 months, placebo) (19,20). As noted above, the inclusion of patients with visceral disease in PREVAIL would not significantly bias the cross-trial comparison with COU-AA-302 given similarities in the median OS of patients with lung metastases (approximately two thirds of visceral metastases occurred in the lung) and the overall population of PREVAIL (18).
- Subsequent NHA use after progression, with 78% in the placebo arm of PREVAIL versus 54% in the placebo arm of COU-AA-302 (19,20). In both studies, the use of NHA in the placebo arm (‘naive to NHAs’) is expected to have improved OS outcomes for the control arms, thereby diluting the treatment effect in both studies. The greater use of NHAs in PREVAIL may have led to a greater dilution of effect for enzalutamide when compared with abiraterone in COU-AA-302. However, the degree to which this difference invalidates the transitivity assumption in the NMA is unclear. Ryan et al 2015 provides exploratory analyses of final OS data in COU-AA-302 that are adjusted for subsequent therapies (19), but the PREVAIL study

publications do not (20). However, the company submission for enzalutamide in TA377 includes indirect treatment comparisons of OS data for enzalutamide vs abiraterone, including analyses of enzalutamide OS data adjusted for subsequent therapies using IPCW vs unadjusted abiraterone OS data, and unadjusted enzalutamide OS data vs unadjusted abiraterone OS data. In both cases, there was no significant difference in OS for enzalutamide vs abiraterone (see section 6.7.7, page 109 of the enzalutamide company submission) (21). Assuming the IPCW adjustment for subsequent treatment in the PREVAIL trial data was robust, the fact there was no significant difference in OS for enzalutamide (when treatment effect is adjusted to remove the diluting effect of subsequent therapy in the placebo arm of PREVAIL) vs abiraterone (when the diluting effect of 54% subsequent use of NHAs in the placebo arm of the COU-AA-302 trial remained) is of note. Furthermore, despite the greater subsequent use of NHA in PREVAIL, there was no meaningful difference in the median OS of the placebo control arms (30-31 months) of PREVAIL and COU-AA-302 in their published final analyses. Additionally, there was no meaningful difference in median OS when comparing abiraterone in COU-AA-302 with enzalutamide in PREVAIL (34-36 months).

The definition of OS (time from randomisation to death from any cause) was consistent across studies. In summary, there was no evidence to suggest that the differences in trials contributing to the OS NMA would lead to a meaningful imbalance in the distribution of effect modifiers across studies. This assessment supports the assumption of transitivity which underpins the OS NMA. Noted differences in the presence of liver metastases (~4% in PREVAIL versus 0% for COU-AA-302) and the use of subsequent NHAs across studies are expected to have only negligible impact on study results. Therefore, these differences are not expected to alter the conclusions of the analysis in showing no significant or meaningful difference in OS across NHAs.

b) The reliability of the OS results used to justify the equivalence of abiraterone and enzalutamide.

The reliability of the NMA results for OS comparing abiraterone versus enzalutamide depends only on the studies contributing to this comparison, i.e., COU-AA-302, PREVAIL and 9785-CL-0232. The PROpel study comparing olaparib plus abiraterone versus placebo plus abiraterone has no impact on the comparison of abiraterone with

enzalutamide, and hence any differences involving this study are not considered. As noted in response to part a), there were no obvious differences in reported baseline characteristics that would invalidate the indirect comparison between abiraterone with enzalutamide. It is important to note that our NMA, which we acknowledged as exploratory in our submission, is only one source amongst other evidence supporting the conclusion that there are no clinically meaningful differences in OS (and rPFS) for enzalutamide and abiraterone. In addition the NMA, the weight of evidence across multiple sources clearly supports this conclusion:

- Expert opinion of 6 UK clinicians experienced in the use of both enzalutamide and abiraterone
- Prospective RWE by Chowdhury et al 2020
- RWE study by Schoen et al, 2022 identified by the EAG (see response to A7).
- Enzalutamide company submission for TA377, which reported an indirect treatment comparison and concluded there was no significant difference in OS for enzalutamide versus abiraterone, including when OS data from the PREVAIL trial of enzalutamide were adjusted for subsequent treatment.

A10. Priority Question: Please provide the statistical code used for the indirect and mixed treatment comparisons.

The statistical code used for the NMA has been provided as a separate attachment.

A11. Please provide the risk of bias assessments along with justifications for OS. Please also provide the justifications for risk of bias assessments relating to rPFS.

The SLR described in Appendix D of the submission identified the following studies as relevant to the decision problem and the indirect treatment comparison:

- PROpel trial for olaparib plus abiraterone versus abiraterone (1),
- COU-AA-302 trial of abiraterone (plus prednisone) versus placebo plus prednisone (4,19),
- PREVAIL trial of enzalutamide versus placebo (17,20),
- 9785-CL-0232 (‘PREVAIL Asia’) trial of enzalutamide versus placebo (5).

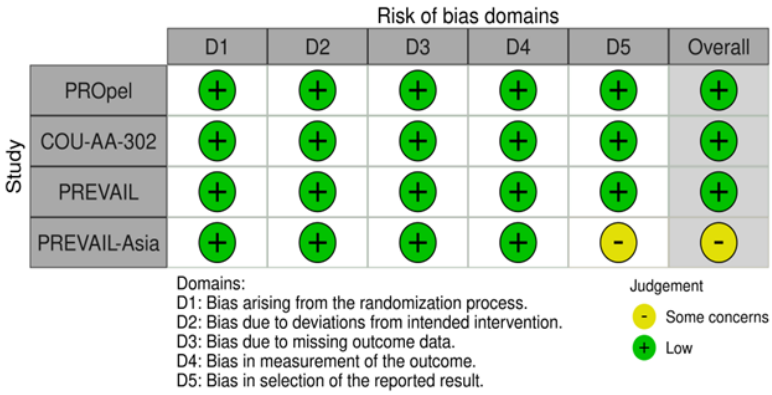
Risk of bias for each of these studies has been re-assessed for rPFS and OS using the Cochrane Risk of Bias 2 tool. Full results, with rationale for the ratings of each

domain of the RoB2 tool, are provided in the accompanying spreadsheet: 'ROB2_RCTS in NMA'.

Radiological progression-free survival

- The studies were generally at low risk of bias
- The PREVAIL-Asia trial of enzalutamide was judged to have some concerns due to uncertainty in whether the analyses conducted for rPFS were pre-specified

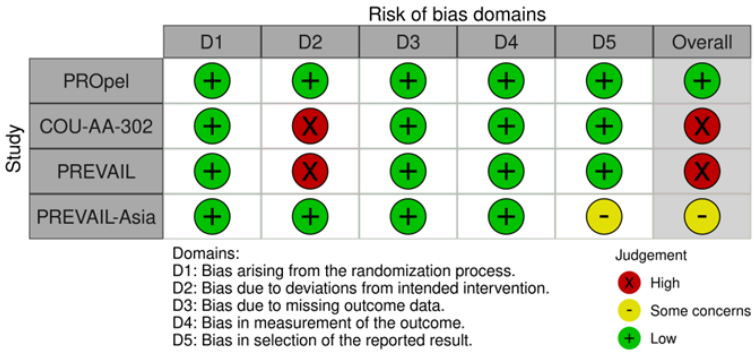
Figure 3: Risk of bias assessment for rPFS



Overall Survival

- The PROpel study was generally at low risk of bias
- The COU-AA-302 trial of abiraterone and PREVAIL trial of enzalutamide were judged to be at high risk of bias due to the occurrence of cross-over from the control to the intervention arm following disease progression, which may influence the OS results. The trials were otherwise at low risk of bias.
- The PREVAIL-Asia trial of enzalutamide was judged to have some concerns due to uncertainty in whether the analyses conducted for OS were pre-specified.

Figure 4: Risk of bias assessment for OS



Section B: Clarification on cost-effectiveness data

Comparators

B1. Priority Question: The EAG is concerned that the company's choice of enzalutamide as the primary comparator is based on trends which may be less relevant given the availability of cheap generic abiraterone.

c) Please present all model results in a fully incremental format and incorporate this functionality into the economic model. The EAG notes that this is stipulated in the NICE reference case.

The availability of generic abiraterone is not expected to impact clinical practice with respect to utilisation of abiraterone and enzalutamide because there are other reasons beyond acquisition costs such as patient characteristic and comorbidities which currently impact physician choice of treatment.

Clinical experts were specifically asked whether the availability of generic abiraterone would impact their choice of treatment. They explained that treatment choice between abiraterone and enzalutamide is currently generally guided by their administration and monitoring regimens, tolerability profiles, and interaction with other drugs. Given that current clinical practice is already guided by factors unrelated to drugs costs, it is unlikely that the availability of a cheaper generic version would result in abiraterone displacing current use of enzalutamide. This view is also reflected in the budget impact report for PROpel, which notes that olaparib in combination with abiraterone is expected to displace abiraterone and enzalutamide in equal proportions and that the current ratio of use for enzalutamide to abiraterone of 2:1 is unlikely to change (24).

At the request of the EAG, fully incremental results have been incorporated within the economic model and are presented in Table 6. Based on this analysis, it would be concluded academically that abiraterone extendedly dominates enzalutamide, which is unsurprising given the relatively lower acquisition costs of generic abiraterone. However, the results must be interpreted in the context of the current and future clinical need of patients. We consider that the fully incremental analysis is not informative in this case, given that enzalutamide could not be fully displaceable by abiraterone for the reasons described above.

Table 6: Incremental analysis on the base case analysis for olaparib versus enzalutamide and abiraterone in the ITT company base case

Regimen	Total costs	Total QALYs	Incremental cost	Incremental QALYs	Fully incremental ICER
Abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Enzalutamide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Olaparib + Abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The company has presented an alternative methodology in Table 7 based on the report by Murphy et al, 2020 (29), where a pooled weighted average ICER was considered. This method is advantageous because it considers both cost and QALY outcomes derived both enzalutamide and abiraterone weighted by their observed market share split to calculate a weighted outcome. The pooled ICER is derived by simply a weighted average of the incremental costs divided by a weighted average of the incremental QALYs, resulting in an ICER of [redacted] per QALY in the ITT base case analysis.

Table 7: Pooled ICER based on 2:1 ratio of enzalutamide to abiraterone in the ITT company base case

ITT population	Modelled outcomes			Weighted outcomes	
Regimen	ΔCost	ΔQALYs	Market share split	ΔCost	ΔQALYs
Enzalutamide	[redacted]	[redacted]	67%	[redacted]	[redacted]
Abiraterone	[redacted]	[redacted]	33%	[redacted]	[redacted]
			Sum	[redacted]	[redacted]
			Pooled ICER	[redacted]	

Treatment effectiveness and extrapolation

B2. Priority Question: Please comment on the clinical plausibility of OS estimates on abiraterone predicted by the generalised gamma curve (i.e. 2.6% at 10 years). Clinical advice to the EAG suggested OS of 8 – 10% at 10 years is expected using current care options. Please provide further justification for the use of the gen. gamma over the log-logistic which had a superior statistical fit in both treatment arms.

The generalised gamma curve extrapolation for OS was selected in the base case following diagnostic, visual, statistical fit and hazard function assessments, and clinical expert validation (see Section B.3.3.1 of the company submission).

Based on the AIC and BIC scores, it is reasonable to interpret the log-logistic and generalised gamma curves as comparable in terms of their statistical fit to the observed PROpel dataset. Although the scores for the log-logistic extrapolation are lower as noted by the EAG, the difference compared to the generalised gamma across both arms is less than 10.

Based on the latest available landmark at approximately 4 years for COU-AA-302 and PROpel, the generalised gamma and log logistic distributions were both assessed and concluded to provide reasonable predictions with slight underestimations across both treatment arms. However, the survival estimates predicted by the generalised gamma model were marginally more aligned to the predicted OS estimates versus both datasets and across both treatment arms (~33.8% vs. ~33.7% [COU-AA-302](19) and 38.7% [PROpel] for placebo plus abiraterone, and ~46.2% vs. 49.3% [PROpel] for the olaparib plus abiraterone at ~4 years (25)). The modelled median OS associated with the generalised gamma (and log logistic curve) was also highly consistent with the observed data from the PROpel study (42.1 vs. 43.0 months, respectively, for the olaparib combination, and 34.7 vs. 35.0 months for the placebo plus abiraterone arm).

The company is unable to comment on the expert opinion sought by the EAG but would like to highlight that clinical validation was also carried out by the company and the majority of clinical experts selected the generalised gamma curve as clinically plausible based on current care options. Additionally, a scenario analysis based on an alternative curve selection for OS using the log logistic curves has been presented in

the company evidence submission (see Table 55 in the company submission) to explore the uncertainty around the long-term OS extrapolation.

B3. Please use confidence intervals from an appropriate data source (e.g. Chowdhury *et al*. 2020) to model the uncertainty associated with the hazard ratio of 1.00 (OS and rPFS) between enzalutamide and abiraterone in the probabilistic sensitivity analysis.

Confidence intervals based on the Chowdhury et al. 2020 (14) findings for PFS and OS have been incorporated as requested by the EAG.

B4. Priority Question: There appears to be a significant divergence between the long-term prediction of time on treatment on olaparib compared to the selected extrapolation of PFS.

a) **Please provide clinical justification for the modelled numbers of patients who remain progression free, independent of treatment, for extended periods of time.**

Similar to the approach taken for OS, the generalised gamma curve was selected for PFS extrapolation in the base case following diagnostic, visual, statistical fit and clinical expert validation (see Section B.3.3.2 of the company submission).

In relation to the clinical justification for the modelled number of patients who remain progression-free, clinical expert viewpoint on progression-free survival was sought. As discussed in the company evidence submission, the lognormal and logistic model predictions were unanimously excluded by experts because they were highlighted to be potentially optimistic. Conversely, the Gompertz, exponential and Weibull distributions were excluded by most of the experts because these models predicted that almost no patients would remain in PFS, on the basis that these are too pessimistic to capture the minority of patients who are observed to respond well on treatment in the real world. On balance, the generalised gamma curve which predicted 3% of patients would be progression-free and alive by 10 years was selected as a reasonable estimate for abiraterone. To ensure the same functional form is maintained across both arms, the generalised gamma curve was also selected for olaparib plus abiraterone.

The Weibull distribution was applied in the base case for time on treatment because this ensured that time-on-treatment extrapolation did not exceed PFS over the time horizon particularly in the longer term. The summary of product characteristics for olaparib plus abiraterone state that treatment should be continued until either disease progression or toxicity therefore it was considered appropriate for time-on-treatment not to exceed PFS. The generalised gamma extrapolation of time on treatment curve which also remains below PFS was also provided in the company submission as a plausible option for modelling time on treatment.

b) Is the company suggesting that the benefit of treatment with olaparib will continue to persist long beyond the point of discontinuation?

Please see the company response in part a) regarding the justifications of the curve choices for progression-free survival and time on treatment.

The modelled time on treatment and rPFS was based on data from PROpel, where the median durations of rPFS and TDT for olaparib were [redacted] months (95% CI: [redacted]) and [redacted] months (95% CI[redacted]) months, respectively. As noted in response to A3 (reasons for discontinuation), patients may discontinue treatment for a number of reasons including radiological progression and tolerability. When the restricted mean survival times are considered based on a cut-off value of 44.3 months for PFS and 47.0 months for time on treatment, a similar trend is observed where PFS exceeds time on treatment for olaparib ([redacted] months [95% CI: [redacted]] vs. [redacted] months [95% CI: [redacted]], respectively) suggesting that the treatment benefit on olaparib does continue beyond the point of discontinuation.

c) Please provide further clinical justification for the use of divergent hazard functions to model TTD and PFS given their interdependence.

The generalised gamma was used to model PFS whereas the Weibull distribution was selected for the modelling of time on treatment in the company base case. Since the Weibull distribution is a special case of the generalised gamma, it was determined to be appropriate for modelling time on treatment.

For completion, the hazard functions were considered in the process of selecting the appropriate curve choice. However, the clinical plausibility of long-term extrapolations

was also considered in determining the appropriate curve choice for PFS and time on treatment.

A scenario analysis using the same functional form for PFS and TDT (i.e., generalised gamma distribution) was provided in section B.3.11 of the company evidence submission.

Subgroup analysis

B5. Priority Question: Results of the subgroup analysis of HRRm and non-HRRm patients suggests olaparib may be less effective in the non-HRRm subgroup. Consequently, whole-population effect estimates are likely to reduce the apparent cost-effectiveness of olaparib.

a) **Please provide a model scenario exploring the cost-effectiveness of olaparib + abiraterone in the non-HRRm population.**

Parameteric models of non-HRRm subgroup from PROpel has been incorporated into the updated model based on DCO3 dataset. Tthe non-HRRm population was defined as patients who were confirmed to be non-HRR-mutated and those whose HRR-mutation status is unknown. The cost-effectiveness results presented are based on the following:

1) Independent model were fitted for PFS and OS following assessment of proportional hazards undertaken using Schoenfeld residuals. The Schoenfeld residuals plot shows a non-linear and non-zero gradient for residuals against

time, indicating that an assumption of proportional hazards between the two trial arms may not hold.

Figure 5. Schoenfeld residuals plot for OS in non-HRRm subgroup

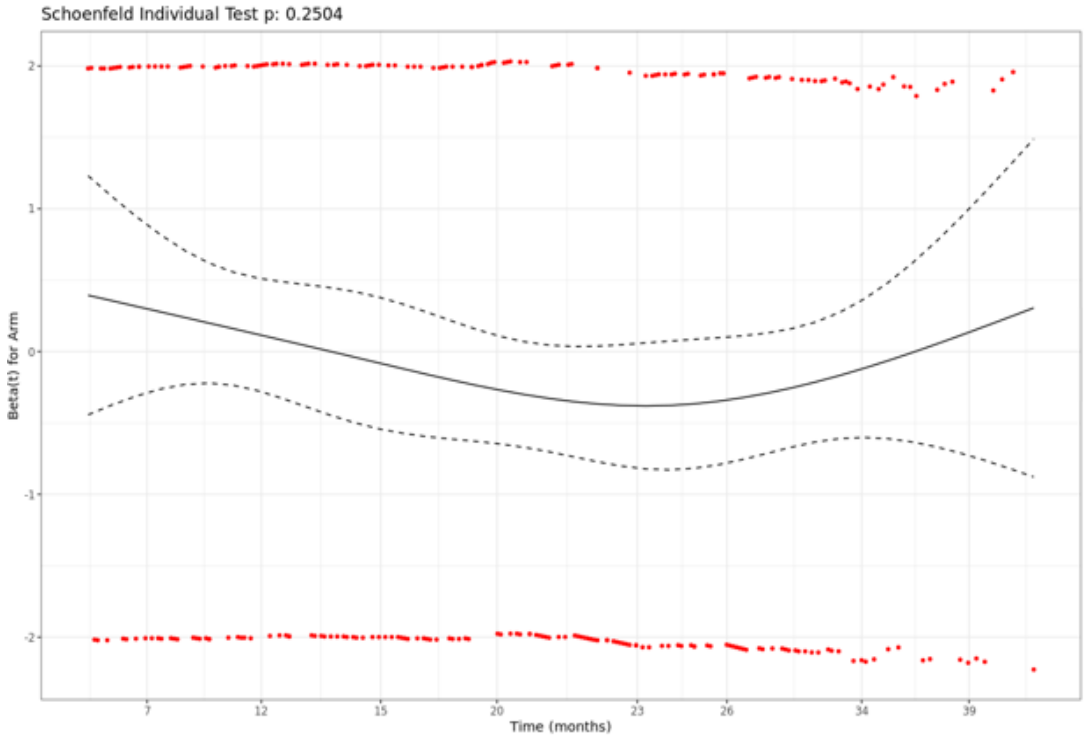
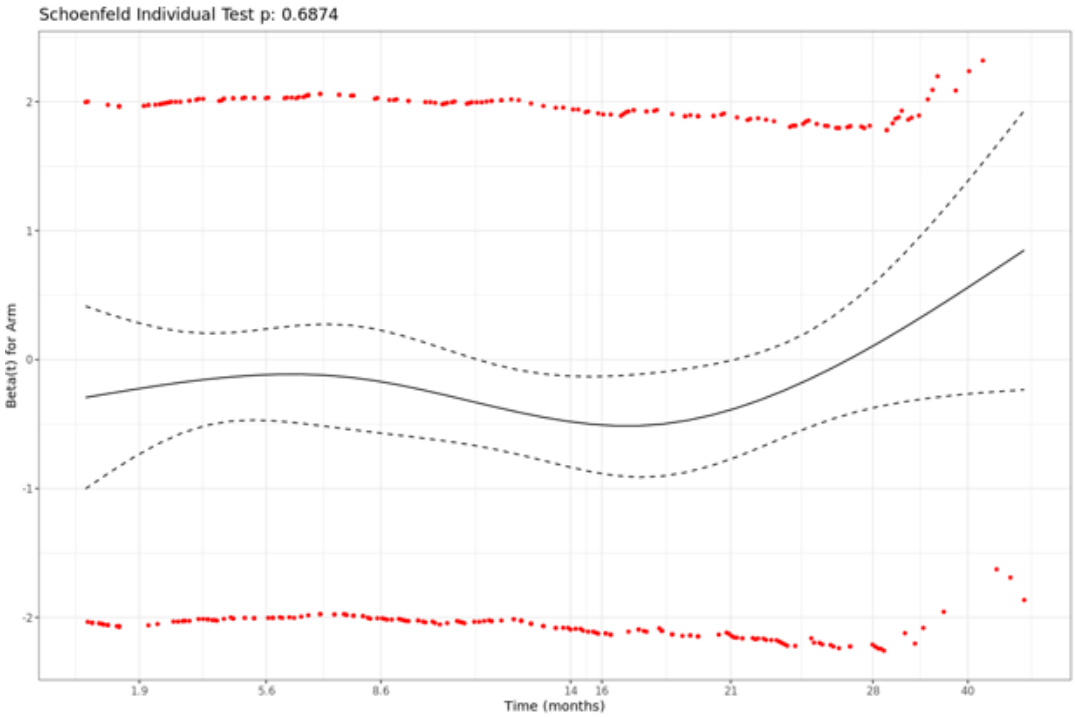


Figure 6: Schoenfeld residuals plot for PFS in non-HRRm subgroup



2) Lognormal curve for the extrapolation of OS, PFS and TDT – the models providing the best fit the data were selected in the scenario analysis requested. Due to time constraints, the company was unable to clinically validated the extrapolations for the non-HRRm subgroup.

Table 8. Goodness-of-fit test on OS parametric distributions of each treatment arm in non-HRRm

	Olaparib + Abiraterone				*Placebo + Abiraterone*			
	AIC	**BIC**	**AIC+BIC**	**Rank**	**AIC**	**BIC**	**AIC+BIC**	**Rank**
Exponential	1329	1333	1331	6	1386	1390	1388	6
Weibull	1312	1320	1316	4	1353	1360	1357	4
Lognormal	**1305**	**1312**	**1309**	**1**	**1343**	**1350**	**1347**	**1**
Log logistic	1308	1315	1312	2	1346	1354	1350	2
Gompertz	1322	1330	1326	5	1370	1377	1373	5
Generalised Gamma	1307	1318	1312	3	1345	1356	1350	3

Table 9. Goodness-of- fit test on PFS parametric distributions of each treatment arm in non-HRRm

	Olaparib + Abiraterone				*Placebo + Abiraterone*			
	AIC	**BIC**	**AIC+BIC**	**Rank**	**AIC**	**BIC**	**AIC+BIC**	**Rank**
Exponential	1447	1450	1449	5	1627	1630	1628	5
Weibull	1444	1452	1448	4	1624	1631	1628	4
Lognormal	**1438**	**1446**	**1442**	**1**	**1612**	**1620**	**1616**	**1**
Log logistic	1441	1448	1445	2	1614	1621	1617	2
Gompertz	1448	1455	1451	6	1629	1636	1632	6
Generalised Gamma	1440	1451	1446	3	1614	1625	1620	3

Table 10: Goodness-of- fit test on TTD parametric distributions of each treatment arm in non-HRRm

	Olaparib + Abiraterone (TTD OLA)				Olaparib + Abiraterone (TTD ABI)				Placebo + Abiraterone (TTDA)			
	AIC	BIC	AIC + BIC	Rank	AIC	BIC	AIC + BIC	Rank	AIC	BIC	AIC + BIC	Rank
Exponential	1852	1855	1853	4	1850	1854	1852	5	1837	1841	1839	5
Weibull	1852	1860	1856	5	1847	1854	1851	4	1832	1840	1836	4
Lognormal	**1842**	**1849**	**1846**	**1**	**1839**	**1846**	**1843**	**1**	**1814**	**1822**	**1818**	**1**
Log logistic	1847	1854	1851	3	1843	1850	1847	3	1817	1824	1820	2
Gompertz	1854	1861	1857	6	1851	1858	1855	6	1839	1846	1843	6
Generalised Gamma	1844	1855	1849	2	1841	1852	1846	2	1816	1827	1822	3

Table 11. Deterministic and probabilistic cost-effectiveness results in the non-HRRm subgroup

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental			ICER versus baseline (£/QALY)
				Costs (£)	LYG	QALYs	
Deterministic							
Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
versus Abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
versus Enzalutamide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Probabilistic							
Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
versus Abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
versus Enzalutamide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

b) Please provide a full probabilistic analysis of the HRRm subgroup.

Table 12. Probabilistic analysis in the HRRm subgroup

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental			ICER versus baseline (£/QALY)
				Costs (£)	LYG	QALYs	
Probabilistic							
Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
versus Abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
versus Enzalutamide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

B6. Priority Question: Please produce a scenario analysis incorporating the results from Question A3ii (i.e. the BRCA1/2 subgroup) analysis into the model.

Parameteric models of BRCA1/2 subgroup from PROpel has been incorporated into the updated model based on DCO3 dataset. The cost-effectiveness results presented below are based on the following:

1) Independent model were fitted for PFS and OS following assessment of proportional hazards undertaken using Schoenfeld residuals. The Schoenfeld residuals plot shows a non-linear and non-zero gradient for residuals against time, indicating that an assumption of proportional hazards between the two trial arms may not hold (Figure 7).

Figure 7: Schoenfeld residuals plot for OS in BRCAm subgroup

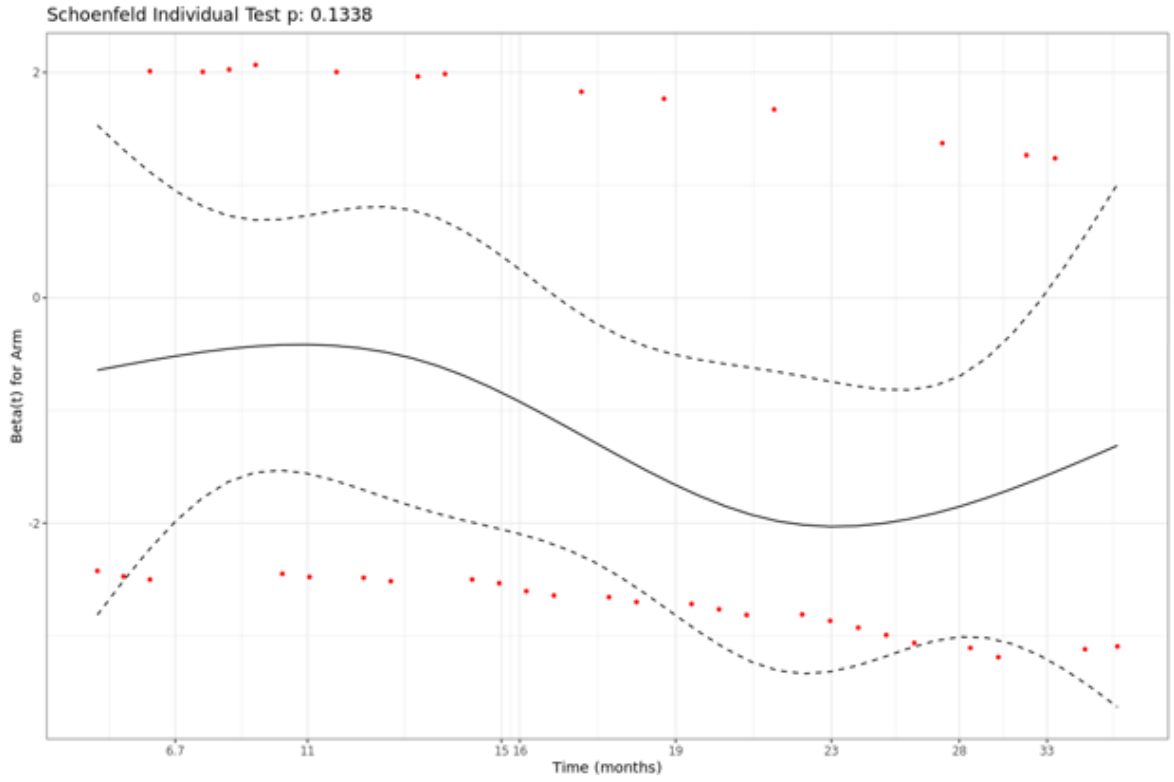
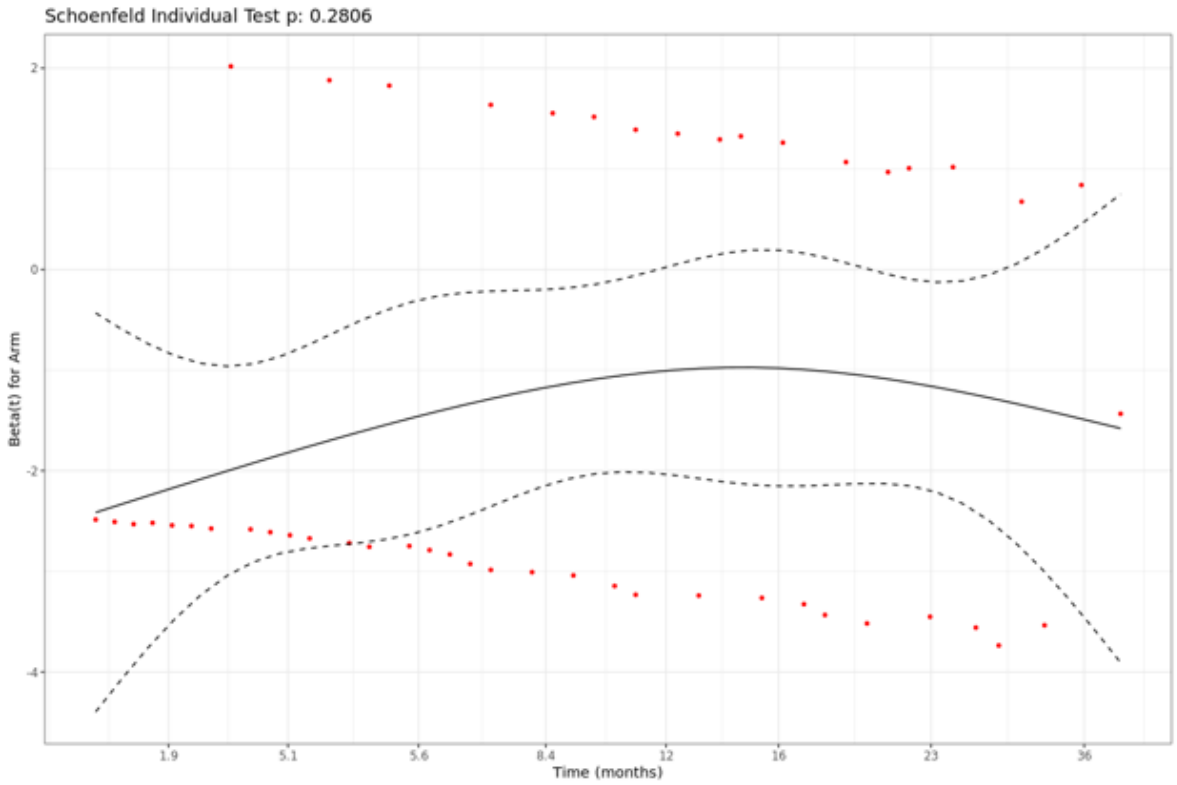


Figure 8. Schoenfeld residuals plot for PFS in BRCAm subgroup



2) Lognormal curve for the extrapolation of OS, PFS and TDT – the models providing the best fit the data across both arms were selected in the scenario analysis requested for the BRCAm subgroup. Due to time constraints, the company was unable to clinically validated the extrapolations for the BRCA1/2 subgroup.

Table 13 : Goodness-of- fit test on OS parametric distributions of each treatment arm in BRCAm

	Olaparib + abiraterone				***Placebo + abiraterone***			
	AIC	**BIC**	**AIC+BIC**	**Rank**	**AIC**	**BIC**	**AIC+BIC**	**Rank**
Exponential	151	153	152	1	230	232	231	5
Weibull	152	156	154	4	224	227	225	3
Lognormal	**150**	**154**	**152**	**2**	**223**	**227**	**225**	**2**
Log logistic	152	155	154	3	222	225	224	1
Gompertz	153	156	155	5	227	230	229	4
Generalised Gamma*	NA	NA	NA	NA	NA	NA	NA	NA

Table 14. Goodness-of- fit test on PFS parametric distributions of each treatment arm in BRCAm

	Olaparib + abiraterone				*Placebo + abiraterone*			
	AIC	**BIC**	**AIC+BIC**	**Rank**	**AIC**	**BIC**	**AIC+BIC**	**Rank**
Exponential	188	190	189	2	233	235	234	3
Weibull	189	193	191	5	235	239	237	6
Lognormal	**187**	**190**	**189**	**1**	**231**	**234**	**232**	**1**
Log logistic	188	192	190	3	232	235	233	2
Gompertz	190	194	192	6	235	238	237	5
Generalised Gamma	187	193	190	3	232	237	235	4

Table 15. Goodness-of- fit test on TTD parametric distributions of each treatment arm in BRCAm

	Olaparib + abiraterone (TTD OLA)				**Olaparib + abiraterone (TTD ABI)**				**Placebo + abiraterone (TTDA)**			
	AIC	**BIC**	**AIC + BIC**	**Rank**	**AIC**	**BIC**	**AIC + BIC**	**Rank**	**AIC**	**BIC**	**AIC + BIC**	**Rank**
Exponential	266	268	267	2	252	254	253	2	257	259	258	4
Weibull	267	271	269	5	254	258	256	5	257	260	259	5
Lognormal	**264**	**268**	**266**	**1**	**250**	**254**	**252**	**1**	253	256	254	2
Log logistic	266	269	267	3	252	256	254	4	**252**	**255**	**253**	**1**
Gompertz	268	272	270	6	254	258	256	5	259	262	261	6
Generalised Gamma	265	271	268	4	251	257	254	3	255	259	257	3

Table 16: Deterministic and probabilistic cost-effectiveness results in the BRCAm subgroup

Technologies	**Total costs (£)**	**Total LYG**	**Total QALYs**	**Incremental**			**ICER versus baseline (£/QALY)**
				Costs (£)	**LYG**	**QALYs**	
Deterministic							
Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
versus abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
versus enzalutamide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Probabilistic							
Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
versus abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
versus enzalutamide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Health-related quality of life

B7. Priority Question: The EAG is concerned that the high post-progression utility derived from PROpel may not appropriately capture the burden of progressed disease in this population.

The following response provides further information on the availability and missing data trends for health state utilities in the post progression period of PROpel. To

understand the extent to which the EQ-5D-5L data in PROpel captures the full burden of progressed disease, the following analyses were performed and are detailed in responses to part B to D:

(1) A summary of the ***time to progression*** (randomisation to progression) and the level of EQ-5D-5L missingness and utility score in the post-progression period. In this analysis, the time to progression was used as proxy for the overall prognosis, with early progression being indicative of worse outcomes, including quality of life.

(2) A summary of the ***time from progression*** to EQ-5D-5L measurement and the EQ-5D-5L missingness and utility score. The aim of this analysis was to assess the relationship between post-progression utility score and the timing of measurement relative to progression, i.e., was the post-progression analysis impacted by observations taken close to or at progression?

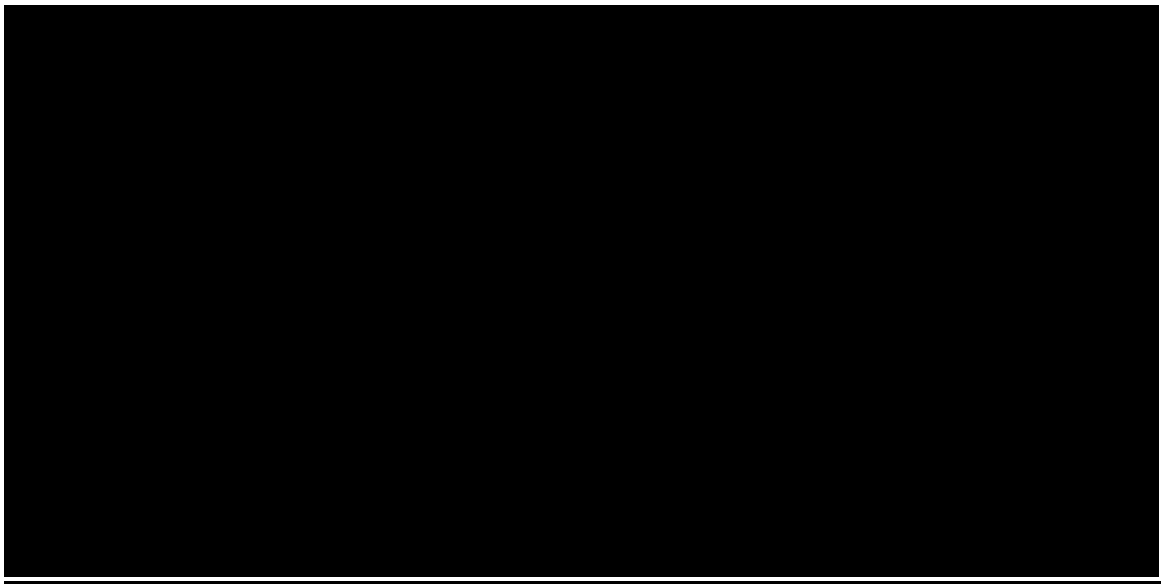
While requested, it was felt that the analysis of patient characteristics in those contributing EQ-5D-5L data over time may provide misleading conclusions on the impact of missing data on the post-progression health state utility in PROpel. This is because the 'baseline characteristics' of patients who completed the EQ-5D-5L over time can be influenced by factors other than failure to complete the EQ-5D-5L after progression, e.g., with 100% data collection, the characteristics of patients contributing data to the post-progression period would be expected to vary over time as those occupying the post-progression state in early phases of study follow-up would likely comprise patients with worse 'baseline' prognosis, and vice versa for later phases. Further, the association between 'baseline' and missingness at an on-study visit may be confounded by changes in the 'baseline' score or factor over time, which may not be available or collected at the same time as the missing EQ-5D-5L. For these reasons, the requested analyses were therefore not provided.

The analyses described above and provided in the below responses were felt to provide the best available evidence to assess potential bias in the post-progression utility score of PROpel.

a) Please provide further information on the patients contributing QoL data over time, including treatment arm, baseline characteristics, and number of observations included in the analysis at each time point. Please comment on any changing balance of patient characteristics due to attrition.

The EQ-5D-5L observations over the trial period are shown below. These data are also available in the CSR compliance tables (Table 14.2.13.3.2).

Figure 9: EQ-5D-5L observations over the trial period



The reasons for not performing an analysis of patient characteristics in those contributing EQ-5D-5L data over time has been described above. In place of this analysis, we provide an analysis of patient's post-progression utility, based on their time from randomisation to disease progression. A 6-monthly interval was used as per the CSR reporting of rPFS, and to ensure sufficient observations in each category.

Patients who completed the EQ-5D-5L having progressed within the first six months of the study had a lower post-progression health state utility than those who progressed after six months. This is likely because these are patients with a poor prognosis, which is likely correlated with lower utility. Amongst patients progressing at least 6 months after randomisation, there is no evidence to suggest that the time to disease progression is associated with utility. Importantly, there is no evidence to suggest that patients experiencing an early progression event had a lower EQ-5D-5L

completion rate. Instead, early progressors (within 6 months of randomisation), had the highest post-progression EQ-5D-5L completion rate, despite having the lowest mean utility. Overall, there is no evidence of a differential rate of EQ-5D-5L questionnaire completion amongst early vs. late progressors.

Table 17 . PROpel EQ-5D-5L data by time of progression

Time of prog.	Patients with PD, n	Patients with at least one EQ-5D-5L post-progression, n (%)	Mean	SD	Median	Q1	Q3	Min.	Max.
0-6 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6-12 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12-18 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18-24 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24-30 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30-36 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
36-42 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

a) Please present data on the timing of HRQoL collection relative to each patient's point of clinical progression in patients who contributed to the progressed disease utility value.

Summary statistics of EQ-5D-5L data collection following disease progression are shown in Table 18.

An exploratory analysis was performed to understand whether the mean utility in the post-progression health state differed based on the time from disease progression. The following analysis was performed at the intervals of 0-3, 3-6 and 6+ months, which was deemed appropriate based on the median and quantile times outlined above.

As shown in Table 18, there was no evidence of a meaningful difference in mean utility according to the time from disease progression to EQ-5D-5L.

Table 18 . PROpel EQ-5D-5L scores post progression

Time from progression to completion of EQ-5D-5L	Subjects, n	Observations, n	Mean	SD	Median	Q1	Q3	Min.	Max.
0-3 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3-6 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6+ months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

b) Please provide data on the number of missing observations in the HRQoL analyses at each time point. Please provide details on how missing observations were accounted for in the regression analysis.

Number of observations are available in the compliance tables of the CSR (Table 14.2.13.3.2). Further detail on the proportion of missing data after progression is provided in response to part b). The mixed model for repeated measures analysis (MMRM) was performed using all EQ-5D-5L data reported in PROpel. The results of the MMRM provides valid inferences on HRQoL under the missing at random assumption and conditional on the variables included (26).

c) If data allows, please provide an analysis of PD utilities which excludes data collected at (or close to) the point of clinical progression.

The data provided in responses to above indicate that the utility score in the post-progression period of PROpel was not affected by the timing of data collection relative to progression or that utilities were only available for those with a better prognosis (proxied by time of progression). Based on these analyses, excluding patients depending on their time since disease progression would not result in different post-progression utility values.

However, there remains the possibility that patients who did not complete the EQ-5D-5L did so because of declining health related quality of life, leading to bias in the estimated post-progression utility score. This is akin to data being missing not at random (MNAR).

To consider the impact of post-progression utility data that are MNAR, a simple sensitivity analysis was performed where patients who progressed without completing the EQ-5D-5L were assigned a range of plausible mean utility scores. The corresponding mean utility for all patients in the post-progression health state was thus estimated based on the weighted average of the observed mean utility for post-progression and the assumed mean utility for those with missing data. Figure 10 shows the change in the overall post-progression health state utility (for all patients) when assuming a differential utility amongst those with missing EQ-5D-5L responses in the post-progression period. Under the assumption that those patients with missing EQ-5D-5L values following progression have a lower utility than those completing the questionnaire, the overall utility in the post-progression period falls. When varying the utility values amongst those with missing data from [redacted], the utility in the overall post-progression population ranged from [redacted].

Figure 10: Overall post-progression health state utility (for all patients)

B8. Priority Question: Please provide the health state utilities generated in the PROfound study (as used in ID6224). These may be a useful alternative source to the PROpel trial.

As discussed with the EAG during the clarification teleconference, use of utility values from the PROfound study ([redacted] for progression-free and [redacted] for progressed disease in both treatment arms) as an alternative source for progressed disease utility values for the PROpel trial would not be appropriate due to differences in the populations between the two studies.

Patients in the PROfound study received olaparib monotherapy for treating mCRPC with BRCA1 or BRCA2 mutations that has progressed after abiraterone, or enzalutamide whilst they are in the metastatic or non-metastatic castration-resistant or in the metastatic hormone-sensitive stages. In contrast, patients in the PROpel study are naïve to treatment with a new hormonal agent and received this only in the first-line mCRPC setting, meaning that the two populations are not directly comparable in relation to their quality of life. Other notable differences include the presence of bone metastases, which are often associated with a decrease in quality of life, was 89% at baseline in PROfound versus 55% at baseline in PROpel (27).

The model includes the functionality to adopt the utility values accepted in the apprisals of abiraterone and enzaluatamide in mCRPC before chemotherapy was indicated. Given the population in PREVAIL and COU-AA-302 are all in first-line mCRPC these sources provide reasonable alternatives.

B9. Priority Question: Please clarify whether patients experiencing a dose interruption, reduction, or had discontinued treatment prior to progression contributed to HRQoL values. If not, please present a re-analysis of PROpel data including all patients.

Yes, patients experiencing a dose interruption, reduction, or had discontinued treatment prior to progression contributed to HRQoL values and the quality-of-life analysis presented by the company.

B10. Priority Question: Given the increased toxicity leading to dose reductions and discontinuation on olaparib, it may be inappropriate to apply the same utilities to both treatment arms.

a) **Please present the results of the health state utility MMRM 'Model 3', and generate treatment arm-specific health state utilities. Please ensure measurements from patients who had dose interruptions are included in this analysis.**

A summary of the parameter estimates of the mixed model for repeated measures (MMRM) 'Model 3', alongside the estimated marginal means for utility by treatment arm in the pre-progression and progressed disease states is presented below.

All the MMRM analyses were conducted on a dataset containing all completed EQ-5D-5L questionnaires in PROpel, including any observations obtained during dose interruption or modifications. The parameter estimates for MMRM 'Model 3' suggest there was no meaningful or statistically significant ($p>0.05$) difference in health state utility between randomised groups in PROpel.

In line with the base case, the only parameter significantly associated with utility scores was progression status. The small numerical difference in utility score across randomised groups of PROpel may be the result of differences in utility score at baseline (mean=0.81 [Standard Deviation {SD}=0.20] for olaparib versus mean=0.82 [SD=0.17] for placebo), which was of similar magnitude and direction (-0.01, olaparib versus placebo) to the between-arm differences estimated in the MMRM.

Whilst the impact of baseline imbalances could be mitigated through the inclusion of baseline utility score in the MMRM, the requirement for a completed baseline measure for inclusion in this analysis would have led to the loss of data from patients who completed the EQ-5D-5L during follow-up but did not complete a baseline measure in the study. To maximise the sample size in the analysis, the MMRM analyses were therefore performed without adjustment for baseline score.

Table 19: Summary of parameter estimates for MMRM 'Model 3' and estimated marginal means for utility by treatment arm in the progression-free state

Parameter	Estimate	Lower 95% confidence limit	Upper 95% confidence limit	p-value
Intercept	[redacted]	[redacted]	[redacted]	[redacted]
Randomised group (Olaparib versus placebo [reference])	[redacted]	[redacted]	[redacted]	[redacted]
Progression status (Progressed versus progression- free [reference]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated marginal means (least squares mean) for utility by treatment arm in the progression-free state (progressed disease)				
Placebo + abiraterone	[redacted]	[redacted]	[redacted]	[redacted]
Olaparib + abiraterone	[redacted]	[redacted]	[redacted]	[redacted]

As noted in Section B.3.4.1 of the company submission, several MMRM analyses were performed on the health state utility data from PROpel. This included models that adjusted for randomised group only, progression status only, and progression and randomised group both with and without interaction terms.

The aim of this analysis was to establish the key drivers of utility during the study, which was assessed on the goodness-of-fit and strength of associations across models. Across the MMRMs, progression status was the only parameter shown to be significantly associated with health state utility. When comparing statistical fit, the MMRM with progression only ('Model 2') provided the best fit to the utility data in PROpel. The MMRM 'Model 2' was therefore used to estimate the utility score in the company base case.

b) Please present a scenario analysis in the economic model using these health state utilities. Exclude separate consideration of AE-related disutilities in this analysis.

A scenario analysis has been conducted in the economic model using the treatment-specific health state utilities excluding separate consideration of AE-related disutilities in this analysis.

The health effects of treatment-emergent adverse events were captured separately as a one-off QALY adjustment at the start of the model time horizon (see Section B.3.4.4

of the company submission). These effects were modelled separately for each treatment arm and were based on the arm-specific prevalence, duration, and disutility of each individual event.

Table 20: Scenario analysis using treatment-specific health state utilities

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental			ICER versus baseline (£/QALY)
				Costs (£)	LYG	QALYs	
Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
versus Abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
versus Enzalutamide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

B11. Priority Question: Please amend the model to account for the effects of ageing upon HRQoL. Please use the EEPRU value set from the 2022 DSU Report – 'Estimating EQ-5D by age and sex for the UK'.

The model has been updated to account for the effects of ageing upon HRQoL using the EEPRU value set from the 2022 DSU Report – 'Estimating EQ-5D by age and sex for the UK'. This has a small impact on the base case results presented by the company.

Table 21: Scenario analysis accounting for the effects of ageing upon HRQoL

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental			ICER versus baseline (£/QALY)
				Costs (£)	LYG	QALYs	
Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
versus Abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
versus Enzalutamide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

B12. Priority Question: The model assumes that all adverse events persist for only 14 days.

a) Please comment on the face validity of this assumption.

Adverse event duration was assumed to last 14 days, this was a conservative estimate. Adverse event duration was not a large driver of the cost-effectivness results, we have provided a scenario analysis using AE duations from PROpel.

b) Please provide details of the durations of modelled AEs as observed in the PROpel study.

The durations of adverse events from PROpel are displayed in Table 22.

Table 22. Durations of adverse events from PROpel

Adverse Event (Grade 3+)	Duration of AEs observed in PROpel (days)
Anaemia	[redacted]
Leukopenia	[redacted]
Pneumonia	[redacted]
Pulmonary embolism	[redacted]
Hypertension	[redacted]
Myocardial infarction	[redacted]
Neutropenia	[redacted]
Nausea (all grades)*	[redacted]

**please note that only 1 patient in PROpel experienced G3+ nausea hence the data was run for all grades to derive a meaningful estimate of durarion for nausea*

c) Please include a scenario analysis in which the PROpel trial AE durations are used in the model.

Table 23: Scenario analysis incorporating PROpel trial AE durations

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental			ICER versus baseline (£/QALY)
				Costs (£)	LYG	QALYs	
Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
versus Abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
versus Enzalutamide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

B13. The EAG understands that nausea is a particularly important TRAE to these patients. Please explore the impact upon HRQoL of nausea and any management costs (e.g. anti-emetic drugs), using prevalence and duration data from the PROpel study.

Only 1 patient in each arm of PROpel experienced nausea as a Grade 3 or above adverse event. This was therefore not modelled in this original submission.

The model has now been amended to explore the affects of nausea as requested by the EAG. The unit cost for nausea was based on 10mg metoclopramide being taken 3 times day for 14 days.

The pack cost of metoclopramide is £0.97 per 28 pack of 10mg tablets and was sourced from the BNF. The adverse event disutility for nausea was sourced from Jung et al, 2010 (30).

The impact of including nausea events Grade 3 and above had a very limited impact on the results of the cost effectiveness analysis.

Table 24. Scenario analysis exploring impact of nausea and management costs

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental			ICER versus baseline (£/QALY)
				Costs (£)	LYG	QALYs	
Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
versus Abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
versus Enzalutamide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Resource use

B14. Please clarify why wastage was not accounted for on olaparib, enzalutamide, and abiraterone in the model. Please amend the model to include the impact of wastage on treatment acquisition costs.

Treatment acquisition costs are estimated directly from the time to treatment discontinuation (TDT) and time to discontinuation of abiraterone (TDA) data in PROpel.

In the model, the acquisition costs of olaparib, abiraterone and enzalutamide are applied to the proportion of patients “on drug” at the start of each cycle, as estimated from the TDT or TDA curves (with time to discontinuation of enzalutamide assumed equivalent to abiraterone monotherapy). This assumes that all patients who receive treatment at the start of each month will incur the full cost of one month’s treatment (broadly equivalent to an individual 28-day pack of olaparib, abiraterone or enzalutamide) irrespective of if they discontinue treatment at any point during that cycle. The model therefore considers the costs of unused tablets resulting from discontinuation of therapy.

The further incorporation of the costs from wasted medication will likely result in double-counting the wasted treatment.

B15. Priority Question: Please adjust treatment acquisition costs according to the observed relative dose intensities observed in the PROpel trial for olaparib and abiraterone, and a relevant source of RDI data for enzalutamide.

The relative dose intensity for olaparib and abiraterone derived from the latest data cut-off of the PROpel trial for olaparib and abiraterone have been applied to treatment acquisition costs in the model. The median relative dose intensity and percentage intended dose were high for olaparib and abiraterone, suggesting that the dose intensity was not affected by dose interruptions or reductions. Median relative dose intensity was 98.2%, and 100% for olaparib and abiraterone in both the olaparib combination arm and placebo plus abiraterone arms, respectively.

The relative dose intensity for enzalutamide was assumed to be equal to that of abiraterone observed in PROpel trial which was considered a reasonable assumption. Consequently, the application in the model resulted in a very small impact on the cost-effectiveness results.

Table 25: Scenario analysis adjusting acquisition costs according to observed RDIs

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental			ICER versus baseline (£/QALY)
				Costs (£)	LYG	QALYs	
Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
versus Abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
versus Enzalutamide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

B16. Priority Question: Please clarify the source of the data used to model PFS as a proportion of death. The model uses 18.7% and 11.9% for olaparib and abiraterone respectively, citing PROpel DCO3 Table 14.2.1.1.1. This table as provided in the reference pack suggests proportions of 10.3% and 8.3%, however.

The proportions shown in the CSR are from the total trial population 10.3% (41/399) and 8.3% (33/397). However, only 219 (55%) and 277 (70%) of olaparib in combination with abiraterone, and abiraterone patients experienced a progression event. The proportions used in the model are calculated as the number of fatal progression events divided by the number of progression events i.e., 41/219 (18.7%) and 33/277 (11.9%) for olaparib + abiraterone and abiraterone respectively.

B17. Priority Question: The company cites clinical opinion stating that testing for HRR mutations is not part of routine clinical practice but is likely to become part of NHS practice following the recent approval of olaparib monotherapy.

a) Please present a scenario analysis in which the cost of testing for HRRm status is included in the abiraterone/enzalutamide treatment arm following progression.

A scenario analysis incorporating testing costs for abiraterone, and enzalutamide has been included. Please note that diagnostic costs are applied as a one-off cost into the model therefore these have not been specifically applied to progressed disease state as requested by the EAG. This was considered to be a reasonable assumption given that the proportion of patients who are BRCA-mutated would not differ irrespective of whether an NHA was received prior to first-line mCRPC. The costs of biomarker testing would therefore be expected to remain consistent for those who received olaparib in combination with abiraterone as a first-line therapy or and olaparib monotherapy (PROfound) following NHA exposure.

The inclusion of testing costs for abiraterone and enzalutamide has a small impact on the cost-effectiveness analysis.

Table 26. Inclusion of biomarker testing costs in the abiraterone/enzalutamide arm

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental			ICER versus baseline (£/QALY)
				Costs (£)	LYG	QALYs	
Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
versus Abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
versus Enzalutamide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

b) Please also include these costs in a subgroup analysis in the HRRm subgroup of the PROpel trial to model the cost-effectiveness of olaparib plus abiraterone.

A scenario analysis applying testing costs for olaparib have been included as a one-off cost into the model. These were calculated by applying the unit costs per test derived from TA887 (28) to the number of tests per patient treated (estimated from

the prevalence of the HRR mutations). The inclusion of testing costs for olaparib has a small impact on the cost-effectiveness analysis.

Table 27: Inclusion of biomarker testing costs in the olaparib + abiraterone arm

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental			ICER versus baseline (£/QALY)
				Costs (£)	LYG	QALYs	
Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
versus Abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
versus Enzalutamide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

B18. The model only includes treatment toxicity monitoring costs in the first three months of treatment on olaparib and abiraterone. Please update the model to also include the treatment toxicity monitoring costs from four months onwards as per Table 46 of the submission.

The model has been updated to include the treatment toxicity monitoring costs from four months onwards however this has a very minimal impact on the cost-effectiveness analysis.

Table 28: Scenario analysis using four months treatment toxicity monitoring costs

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental			ICER versus baseline (£/QALY)
				Costs (£)	LYG	QALYs	
Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
versus Abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
versus Enzalutamide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Presentation of results

B19. Priority Question: Please present confidence intervals around probabilistic estimates of NHB in each analysis.

Table 29: Confidence intervals around probabilistic estimates of net health benefit

Technologies	NHB at £20,000 [95% CI]	NHB at £30,000 [95% CI]
Olaparib + Abiraterone	[redacted]	[redacted]
Enzalutamide	[redacted]	[redacted]
Abiraterone	[redacted]	[redacted]

B20. Priority Question: Please ensure all cost-effectiveness planes are presented with a line demarcating the WTP threshold.

The model has now been amended so that cost-effectiveness planes include a line to represent the WtP threshold as requested by the EAG.

Section C: Textual clarification and additional points

Search strategies

C1. Please provide the following search strategies, which were missing from the submission:

a) **Strategies of clinical trials registries (clinicaltrials.gov and WHO ICTRP registry) for the clinical evidence searches were not documented in 'Astrazeneca_Clinical Studies SLR-CONFIDENTIAL'.**

Specific strategies (supplementary searching) for the trial registries has been included in Appendix B (page 185) of the Clinical Studies SLR; red text outline the additions. This information was previously listed in 'other sources' therefore these totals have been reduced to align with above (p187).

b) **Strategies of supplementary sources for the cost-effectiveness searches were not documented in 'Astrazeneca_Economic Evaluations SLR-CONFIDENTIAL'.**

Handsearching tables have been added to the Economic Evaluations SLR in Appendix B (page 65).

c) **Strategies of supplementary sources for the health-related quality of life searches were not documented in 'Astrazeneca_HSUVs_SLR-CONFIDENTIAL'.**

Handsearching tables have been added to the HSUVs SLR in Appendix B (Page 64).

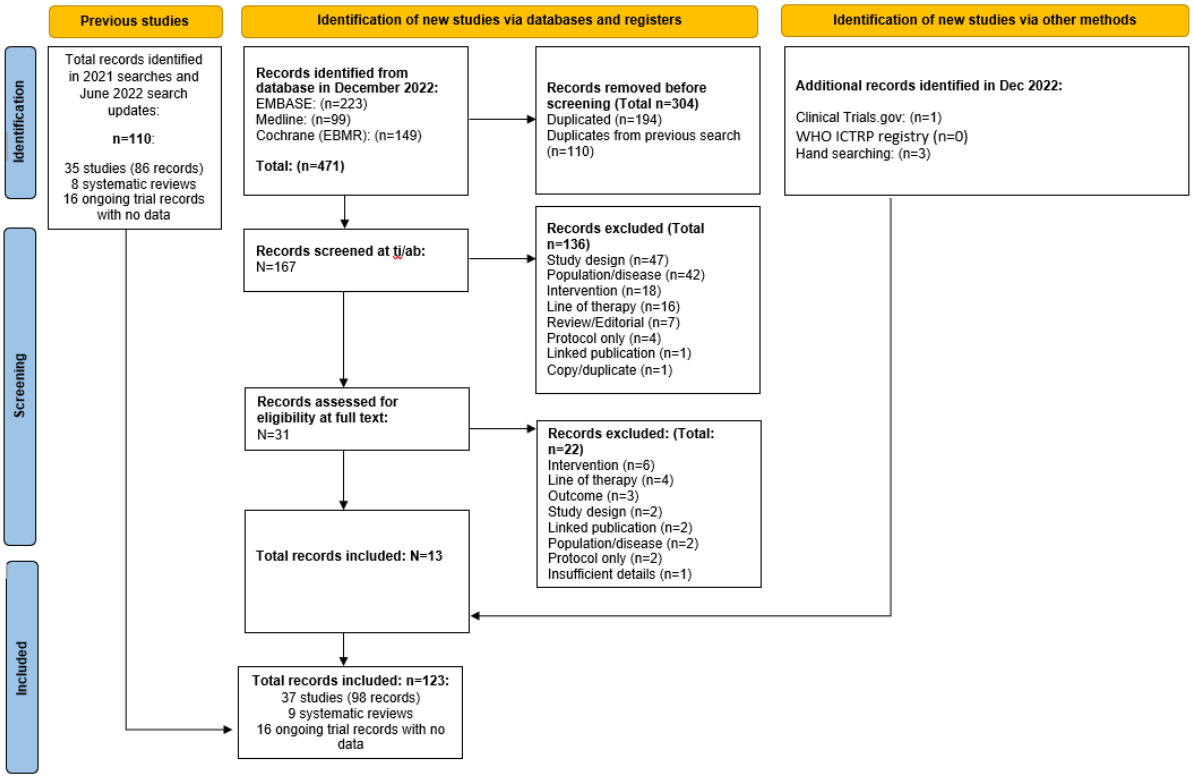
d) **Strategies of supplementary sources for the for cost and healthcare resource identification, measurement, and valuation searches were not documented in 'Astrazeneca_HCRU_Costs_SLR-CONFIDENTIAL'.**

Handsearching tables have been added to HCRU Costs SLR in Appendix B (Page 56).

C2. There are several ambiguities with the PRISMA diagrams in the submission:

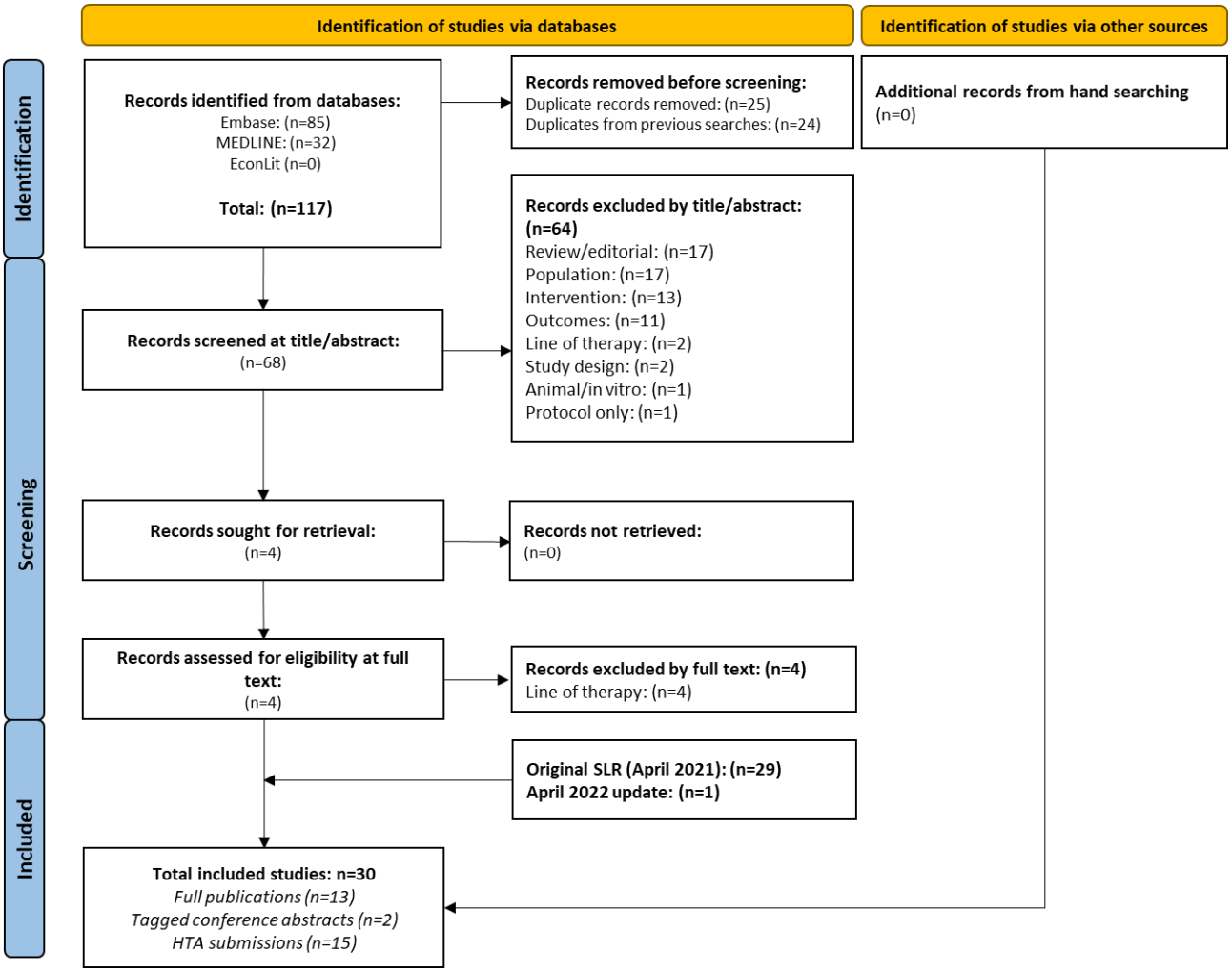
a) **For the clinical searches (in 'Astrazeneca_Clinical Studies SLR-CONFIDENTIAL'), the overall PRISMA flow chart (Figure 1, p. 31 of document 'Astrazeneca_Clinical Studies SLR-CONFIDENTIAL') is confusing as the hits from update 2 are not shown and only the includes from the original searches are represented.**

The text of the boxes in the PRISMA diagram in the Clinical Studies SLR (Figure 1, Page 31) has been updated to detail the search screening of the December 2022 combined update to clarify which searches inform the results. The previous PRISMA diagrams have been added to both Appendix P (PRISMA diagram from October 2023 report – Page 340) and Appendix Q (PRISMA diagram from July 2022 report – Page 341). All three PRISMA diagrams link together.



b) **For the cost-effectiveness searches (in 'Astrazeneca_Economic Evaluations SLR-CONFIDENTIAL'), the 'overall' PRISMA (p. 19) is just the results of the last update search, is this an error?**

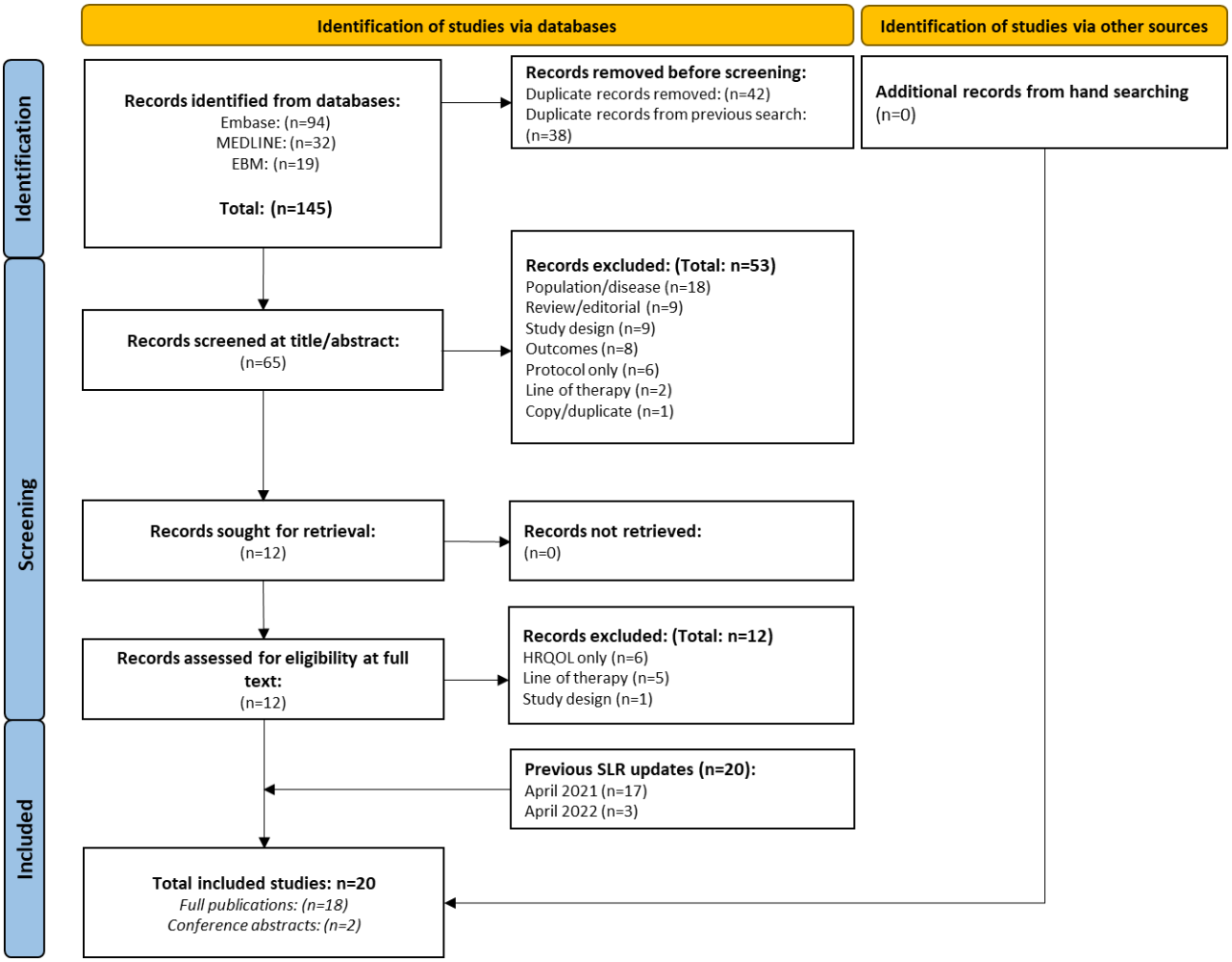
The overall PRISMA diagram in the Economic Evaluations SLR adds the total number of included studies. This is made up of the PRISMA diagram for the most recent SLR update, with an additional box detailing the total numbers from the original April 2021 and June 2022 update SLRs. The separate PRISMA diagrams for each SLR are provided in Appendix C (original review April 2021, updated review April 2022 and updated review December 2022 (combined) – Pages 73-75).



c) For the health-related quality of life searches (in 'Astrazeneca_HSUVs_SLR-CONFIDENTIAL'), the 'overall' PRISMA (p. 15) is just the results of the last update search, is this an error?

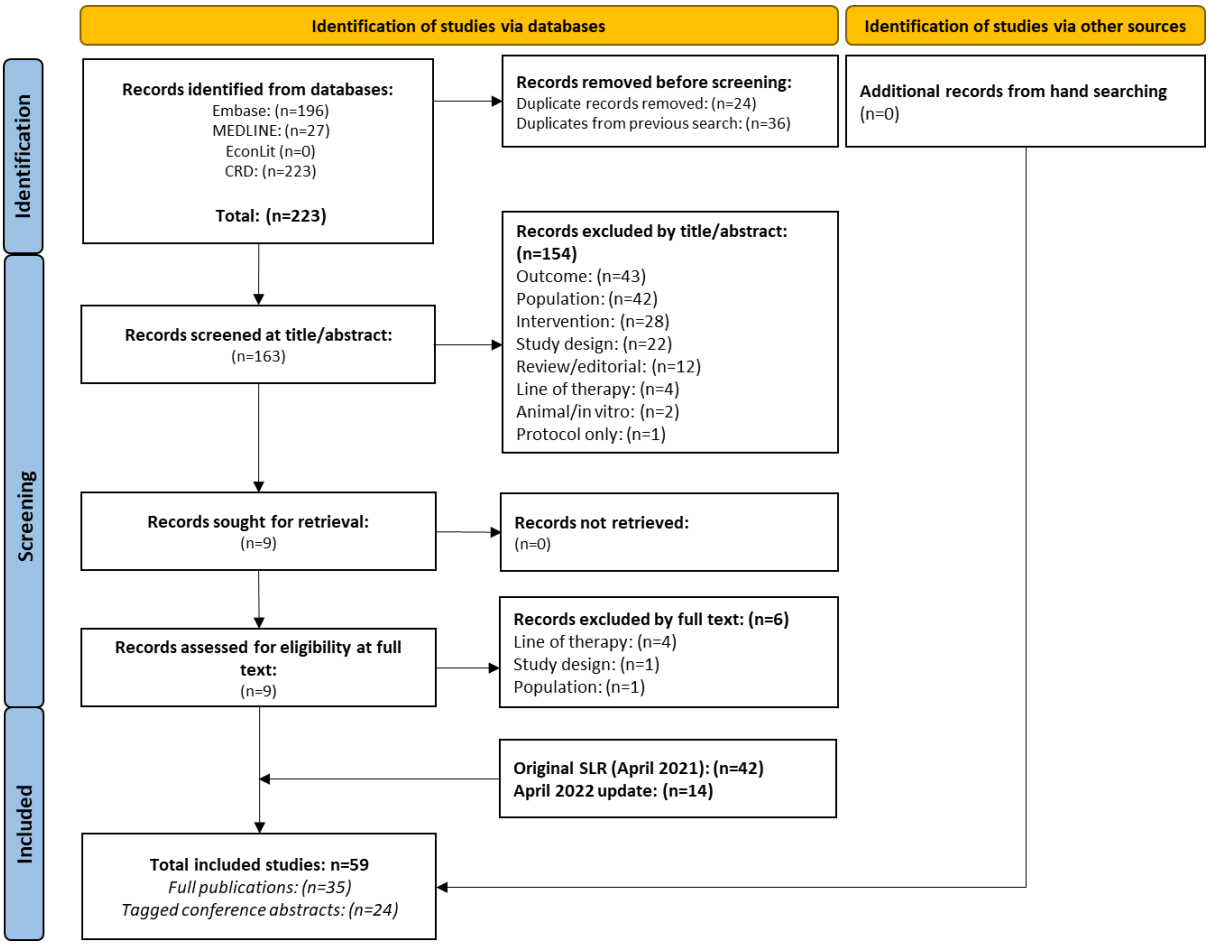
The overall PRISMA diagram in the HSUVs SLR adds the total number of included studies. This is made up of the PRISMA diagram for the most recent SLR update, with an additional box detailing the total numbers from the original April 2021 and June 2022 update SLRs. The separate PRISMA diagrams for each SLR are

provided in Appendix C (original review April 2021, updated review April 2022 and updated review December 2022 (combined) – Pages 72-74).



d) For the cost and healthcare resource identification, measurement, and valuation searches (in 'Astrazeneca_HCRU_Costs_SLR-CONFIDENTIAL'), the 'overall' PRISMA (p. 16) is just the results of the last update search, is this an error?

e) The overall PRISMA diagram in the HCRU Costs SLR adds the total number of included studies. This is made up of the PRISMA diagram for the most recent SLR update, with an additional box detailing the total numbers from the original April 2021 and June 2022 update SLRs. The separate PRISMA diagrams for each SLR are provided in Appendix C (original review April 2021, updated review April 2022 and updated review December 2022 (combined) – Pages 65-67).


Identification of studies via databases
Identification of studies via other sources
Identification
Screening
Included
Records identified from databases:
Embase: (n=196)
MEDLINE: (n=27)
EconLit (n=0)
CRD: (n=223)
Total: (n=223)
Records removed before screening:
Duplicate records removed: (n=24)
Duplicates from previous search: (n=36)
Additional records from hand searching
(n=0)
Records screened at title/abstract:
(n=163)
Records excluded by title/abstract:
(n=154)
Outcome: (n=43)
Population: (n=42)
Intervention: (n=28)
Study design: (n=22)
Review/editorial: (n=12)
Line of therapy: (n=4)
Animal/in vitro: (n=2)
Protocol only: (n=1)
Records sought for retrieval:
(n=9)
Records not retrieved:
(n=0)
Records assessed for eligibility at full text:
(n=9)
Records excluded by full text: (n=6)
Line of therapy: (n=4)
Study design: (n=1)
Population: (n=1)
Original SLR (April 2021): (n=42)
April 2022 update: (n=14)
Total included studies: n=59
Full publications: (n=35)
Tagged conference abstracts: (n=24)

References

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Olaparib with abiraterone for untreated hormone-relapsed metastatic prostate cancer [ID3920]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	Prostate Cancer UK
3. Job title or position	Senior Policy Officer
4a. Brief description of the organisation (including who funds it). How many members does it have?	Prostate Cancer UK is the UK's leading charity for men with prostate cancer and prostate problems. We support men and provide information, find answers through funding research and lead change to raise awareness and improve care. The charity is committed to ensuring the voice of people affected by prostate disease is at the heart of all we do.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	The total amount received in the year 22/23 from all companies totals £148,236 with the total from the submitting company coming to £10,350. This funding goes to projects such as our specialist nurses or our improvement programmes and accounts for 0.47% of our total annual income.
4c. Do you have any direct or indirect links	None.

with, or funding from, the tobacco industry?	
5. How did you gather information about the experiences of patients and carers to include in your submission?	Desk research and our own knowledge of the experiences of men. We have spoken with our specialist nurses about their experience of speaking with men in this indication.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Men with advanced disease can present with a number of different symptoms. Evidenced symptoms for advanced prostate cancer can include: • Fatigue. • Pain, most commonly caused by prostate cancer that has spread to the bones. • Urinary problems, this includes problems emptying the bladder, incontinence, blood in urine and kidney problems. • Bowel problems including constipation, diarrhoea, faecal urgency, faecal incontinence, pain, bowel obstruction and flatulence. • Broken bones, fractures caused by bone thinning. • Sexual problems, including reduced libido and difficultly getting or keeping an erection. • Lymphoedema, primarily around the legs. • Anaemia, caused by damage to bone marrow. • Metastatic spinal cord compression, as cancer cells grow in or near the spine, which evidence suggests can occur in 1 to 12% of patients[i]. • Hypercalcaemia, caused by calcium leaking from the bones into the blood. • Eating problems Men with hormone resistant metastatic prostate cancer (mCRPC) have a limited number of treatments available to them. At this stage of the disease, men may experience more significant symptoms due to the disease becoming more aggressive when hormone resistance occurs. Different symptoms from their prostate cancer (depending on where their cancer is) can include: • Pain may develop which for some men with mCRPC can be significant. • Men with advanced prostate cancer who have bone metastasis, including in the spine, may develop spinal cord compression. These men require urgent treatment to prevent permanent nerve damage and potential paralysis. This can be a debilitating and life-changing problem. • Bone metastasis can also result in spontaneous fractures, without trauma and increased risk of fracture associated with trauma.

	• For men whose prostate cancer affects their bone marrow, they may become anaemic (therefore becoming more tired or becoming breathless) requiring blood transfusions, thrombocytopenia (prone to bruising and bleeding), and develop low white blood cell counts (making them more susceptible to infection). • Visceral metastases can involve the liver and the lungs, causing considerable morbidity; brain metastases commonly result in significant and distressing neurological deficits. • Weight loss and reduced appetite can often be a particular concern for carers. • If prostate cancer advances in the region around the prostate, men may experience urinary tract problems and renal problems. It is important to note that men are unlikely to experience all the above symptoms, as some will depend on the treatments received, while others will be the result of metastases and therefore dependent on their location. The severity of symptoms will also differ among men. For some men, living with metastatic prostate cancer can be hard to deal with emotionally, especially as there are no current curative treatments for this stage of the disease. Symptoms and treatments can be draining and make men feel unwell. And some treatments, including hormone therapy, can make men feel more emotional and cause low moods. The pressure of advanced cancer can also put a strain on relationships. Metastatic prostate cancer and its treatments might mean that partners or family need to do more for patients, such as running the home or increasing caring responsibilities. Additionally, the symptoms described for mCRPC and the side effects of treatments can make it difficult to work. a partner providing care might not be able to work as much either. Everyday tasks may become more difficult and respite care may be required to give carers a break. As the disease progresses, more palliative care and treatments will be offered. This includes palliative radiotherapy to ease bone pain, blood in urine and swollen lymph nodes.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Inevitably, men and their families express disappointment that there are no curative treatments for metastatic hormone-resistant prostate cancer. Many are interested in clinical trials with the hope of improving their life expectancy. In the hormone-resistant setting men can receive docetaxel, abiraterone, enzalutamide, or cabazitaxel (if they have already had a previous round of docetaxel). Radium 223 is a further last line treatment. There is also Olaparib available for a small group of men who have been previously treated with an NHA and have a BRCA1 or 2 mutation. Docetaxel chemotherapy is only offered to those felt fit enough to receive it. It will be offered in the hormone-sensitive stage initially, but there is an opportunity for rechallenge or new administration in the castrate-resistant setting. While there are side-effects from chemotherapy, severe side effects are reported mostly during treatment and in the first 6 months after treatment. Adverse events include fatigue, alopecia, nausea/vomiting, diarrhoea, nail changes and sensory neuropathy[ii] . Many men and their families are fearful of chemotherapy. Most men develop low blood counts making them vulnerable to infection, some of which are potentially life-threatening infections. Many men say that the taste changes that the chemotherapy can cause is extremely difficult to live with, adversely affecting their quality of life. Treatment means going into hospital, often to clinic on one day followed by chemotherapy the next day approximately every three weeks for 6 cycles of treatment. Some men travel long distances to receive their treatment. They are also required to self-monitor between visits, to be vigilant, recognise and to present back to hospital should any adverse reactions to treatment occur, for example, should they become febrile. Many men find this onerous and extremely anxiety provoking. This treatment regimen and side effect profile are similar to that of cabazitaxel as well. Abiraterone and enzalutamide have different side-effect profiles. Adverse events for abiraterone include fatigue, back pain, nausea, constipation, bone pain, arthralgia and oedema. Abiraterone is also associated with an elevation in aminotransferase levels which can lead to more frequent monitoring with liver-function tests during treatment[iii]. Adverse events for enzalutamide include fatigue, back pain, constipation and athralgia[iv].

8. Is there an unmet need for patients with this condition?	Patient organisations and the patients themselves believe there is a strong need for further treatments that offer good clinical benefit and improvement in the median overall survival, as this remains low past 18 months - docetaxel offers a median survival benefit of less than 3 months if given first in the castrate-resistant stage[v], abiraterone and enzalutamide, without a direct comparison, offer similar survival benefit, 3 months for abiraterone[vi] and 5 months for enzalutamide[vii]. Radium 223 offers a median of just under 3 months of additional life[viii]. There are numerous treatments available for prostate cancer in the metastatic castrate-resistant setting. However, there is uncertainty in how each patient will respond to any treatment and so more treatments need to be made available to make sure every patient can have the best treatment that suits them and their cancer best.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	There are currently no combined therapies available for the mCRPC setting. Men with prostate cancer want more treatments to be available to them that work for them. This treatment combination offers them not only another treatment choice at this point in the pathway, but more certainty around surviving for longer – the PROpel trial showed a 7.4-month difference in median overall survival versus standard of care of abiraterone alone, thus highlighting the therapeutic potential of this treatment combination for men in this indication. We also know, from speaking with patients and carers about treatment options, that ease of administration is a key factor in choosing a treatment. Treatment with abiraterone and olaparib provides an option for patients to administer their treatment in the comfort of their own home as it is in pill form. This is in comparison to the administration of chemotherapy where a patient will need to travel into hospital multiple times over a few months and spend considerable time there for its administration. This combination therapy would be of benefit to those patients who are unable to have chemotherapy in this indication, perhaps due to frailty or other comorbidities, giving these patients a vital treatment choice in this part of the pathway.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	Unfortunately this treatment combination may not be the correct choice of treatment for some patients who may have other medical issues which could be exacerbated by the medication, or are more frail due to its side effect profile which includes anaemia, fatigue, nausea, back pain, and diarrhoea.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	As stated in section 9, this treatment could be of benefit for those patients who are unable to tolerate the effects of chemotherapy.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	n/a

Other issues

13. Are there any other issues that you would like the committee to consider?	n/a

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.	• Men in this indication need more treatment choice • There are few treatments for mHRPC which provide significant overall survival benefits past 18 months • Patients who cannot tolerate chemotherapy or who do not want chemotherapy would benefit most from this treatment • •

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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The information that you provide on this form will be used to contact you about the topic above.

Please select YES if you would like to receive information about other NICE topics - YES

For more information about how we process your personal data please see our privacy notice.

[i] European Urology Volume 44 Issue 5 *Spinal Cord Compression in Metastatic Prostate Cancer* H Tazi et al. November 2003
[ii] New England Journal of Medicine *Docetaxel plus Prednisone or Mitoxantrone plus Prednisone for Advanced Prostate Cancer*. Tannock et al. October 2004
[iii] https://www.nejm.org/doi/full/10.1056/NEJMoa1014618
[iv] https://www.nejm.org/doi/full/10.1056/NEJMoa1405095
[v] https://www.nejm.org/doi/full/10.1056/NEJMoa041318
[vi] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3471149/
[vii] https://www.nejm.org/doi/full/10.1056/NEJMoa1207506
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CONFIDENTIAL UNTIL PUBLISHED
External Assessment Group Report
Olaparib with abiraterone for untreated hormone-relapsed metastatic prostate cancer

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Declared competing interests of the authors

None

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

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Contributions of authors
Mark Corbett performed the critical appraisal of the clinical effectiveness evidence and contributed to the critique of the decision problem. Eleonora Uphoff wrote the critique of the decision problem and contributed to the critical appraisal of the clinical effectiveness evidence. Kerry Dwan contributed to the critical appraisal of the clinical effectiveness evidence. Helen Fulbright wrote the search strategy sections. Jasmine Deng, Joseph Lord and Matthew Walton wrote the critical appraisal of the cost-effectiveness analysis submitted by the company and implemented the additional economic analyses presented by the EAG. Robert Hodgson provided advice, commented on drafts and took overall responsibility for the report.

Note on the text
All commercial-in-confidence (CIC) data have been highlighted in blue and underlined, all academic-in-confidence (AIC) data are highlighted in yellow and underlined, all depersonalised data (DPD) are highlighted in pink and underlined.

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List of abbreviations

ADT	Androgen deprivation therapy
AE	Adverse event
AIC	Akaike Information Criterion
ATM	Ataxia-telangiectasia mutated
BIC	Bayesian Information Criterion
BICR	Blinded Independent Central Review
BNF	British National Formulary
BPI-SF	Brief Pain Inventory – Short form
BRCA	Breast cancer gene
BSA	Body surface area
CI	Confidence interval
CS	Company submission
CSR	Clinical study report
ctDNA	Circulating tumour DNA
DC01	First data cut-off
DC02	Second data cut-off
DC03	Third data cut-off
DSA	Deterministic sensitivity analysis
DSB	Double strand brakes
EAG	External Assessment Group
ECOG	Eastern Co-operative Oncology Group
EEPRU	Policy Research Unit in Economic Methods of Evaluation of Health and Social Care Interventions
EMA	European Medicines Agency
eMIT	Electronic market information tool
EQ-5D	EuroQol five dimensions
FDA	Food and Drug Administration
HR	Hazard ratio
HRQoL	Health-related quality of life
HRR	Homologous recombination repair
ICER	Incremental cost-effectiveness ratio
ITC	Indirect treatment comparison
ITT	Intention to treat
KM	Kaplan-Meier
mCRPC	Metastatic castration-resistant prostate cancer
MHRA	Medicines and Healthcare products Regulatory Agency

mHSPC	Metastatic hormone-sensitive prostate cancer
MMRM	Mixed-effects model for repeated measures
NHA	Novel hormonal agent
NHB	Net health benefit
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NR	Not reported
OADC	Oncologic Advisory Drug Committee
OS	Overall survival
PARP	Poly-ADP ribose polymerase
PAS	Patient Access Scheme
PCWG-3	Prostate Cancer Clinical Trials Working Group 3
PD	Progressed disease
PFC	Points for clarification
PFS	Progression free survival
rPFS	Radiological Progression free survival
PFS2	Time to second progression or death
PD	Progressed disease
PRO	Patient reported outcomes
PSA	Probabilistic sensitivity analysis
PSA	Prostate Specific Antigen
PSS	Personal social service
QALY	Quality adjusted life year
RCT	Randomised controlled trial
RDI	Relative dose intensity
RoB	Risk of bias
ROBINS-I	Risk Of Bias In Non-randomised Studies of Interventions
RWE	Real world evidence
SLR	Systematic literature review
SmPC	Summary of product characteristics
SSRE	Time to symptomatic l-related events
TA	Technical appraisal
TFST	Time to first subsequent therapy or death
TRAE	Treatment-related adverse event
TTD	Time to treatment discontinuation
TTDA	Time from randomisation to treatment discontinuation of abiraterone
TTPP	Time to pain progression

1 EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the external assessment group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.6 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main EAG report.

All issues identified represent the EAG's view, not the opinion of NICE.

1.1 Overview of the EAG's key issues

Table 1 Summary of EAG's key issues

ID	Summary of issue	Report sections
1.	Uncertainties in how the marketing authorisation for olaparib plus abiraterone should be interpretation and implications for the generalisability of PROpel.	2.2.3.3
2.	The survival benefits of olaparib plus abiraterone in the PROpel trial appear to be driven by the small subgroup of BRCA mutation patients. Substantial heterogeneity in cost-effectiveness should be explored in subgroup analysis.	3.2.2.3, 4.2.6
3.	Limited use of subsequent olaparib monotherapy in PROpel and inconsistency with current NHS practice.	4.2.6
4.	Assumption of efficacy equivalence between abiraterone and enzalutamide. The weight of real-world evidence suggests a statistically significant effect on OS in favour of enzalutamide.	3.4, 4.2.6
5.	The EAG identified a number of methodological issues in the company's model. Corrections were made, including age adjustment of utilities, implementation of the half-cycle correction, and the updating of outdated cost data)	5.4
6.	Uncertainties regarding the most appropriate OS extrapolation. The generalised gamma model preferred by the company may result in pessimistic extrapolations of comparator arm data. Alternative models produce more clinically plausible estimates of long-term OS and represent plausible alternatives. However, they result in substantial increases in the ICER for olaparib in the whole population.	4.2.6
7.	The use of the Weibull curve to extrapolate TTD where PFS is extrapolated using the generalised gamma may underrepresent treatment costs. Consistency in functional forms is preferred by the EAG, which significantly increases the ICER for olaparib.	4.2.6
8.	The company assumed adverse events persist for only 14 days, which may underestimate the impact of the additional burden of AEs on olaparib plus abiraterone. The EAG prefers AE duration to be based on that observed in the PROpel study.	4.2.6
9.	The health-state utilities used in the model appear to have been generated using a non-reference case approach. In order to meet the requirements of the NICE reference case, EQ-5D-5L trial data should be mapped to EQ-5D-3L.	4.2.7
10.	The company did not adjust treatment acquisition costs to account for observed relative dose intensity. Adjustment of acquisition costs using data from PROpel significantly reduces the ICER for olaparib against its comparators.	4.2.8
11.	The company's base case omitted the cost of testing for BRCA mutations where relevant. The EAG implemented testing costs as appropriate using a unit cost of £34.	4.2.8

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are:

- The EAG prefers to consider cost-effectiveness in the BRCA mutation subgroup separately.

- The EAG prefers to maintain consistency in the parametric curves applied to estimate time on treatment and progression-free survival.
- The EAG prefers to use literature-derived hazard ratios to model the relative effectiveness of enzalutamide compared to abiraterone.
- The EAG has implement several corrections to the economic model these include: age adjustment of utilities, the inclusion of drug wastage (via a corrected half cycle correction), and the use of recent cost data.
- The EAG prefers the inclusion of genetic testing costs where treatment decisions are based on presence of specific prognostic markers.

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained compared to other treatment options.

Overall, the technology is modelled to affect QALYs by:

- Increasing progression-free survival;
- Increasing overall survival.

Overall, the technology is modelled to affect costs by:

- Higher first-line treatment costs;
- Lower subsequent treatment costs.

The modelling assumptions that have the greatest effect on the ICER are:

- The correction of methodological issues with the model;
- The population modelled, the benefits of olaparib with abiraterone increase substantially in the BRCA1/2 subgroup;
- The assumption of clinical equivalence between enzalutamide and abiraterone;
- The choice of parametric curve used to model OS;
- The choice of parametric curve used to model TTD.

1.3 The decision problem: summary of the EAG's key issues

Issue 1 Interpretation and implications of the wording of the marketing authorisation of olaparib plus abiraterone

Report section	2.2.3.3
Description of issue and why the EAG has identified it as important	The patient population indicated in the marketing authorisation for olaparib plus abiraterone are patients with mCRPC "*for whom chemotherapy is not clinically indicated"*. The company clarified that mCRPC patients may not be eligible for chemotherapy for three reasons: 1) they have received treatment at an earlier disease stage (i.e. chemotherapy retreatment not permitted); 2) they may not be fit enough to receive docetaxel; 3) docetaxel may be contraindicated. This interpretation of the marketing authorisation has implications both for the pathway positioning of olaparib plus abiraterone and the applicability of the PROpel trial results to the NHS population. Most patients in the PROpel cohort would not be eligible to receive olaparib plus abiraterone in NHS practice since the large chemotherapy-naïve subgroup, were fit enough (all were ECOG 0 or 1) to receive docetaxel; they should therefore receive docetaxel before they receive olaparib plus abiraterone (based on the license wording). The first-line use of abiraterone or enzalutamide is a much more plausible and likely scenario for these patients. This is at odds with the company anticipating that olaparib plus abiraterone will displace NHAs as a first-line therapy in mCRPC. Furthermore, patients not fit enough for chemotherapy, or contraindicated to chemotherapy, may have worse outcomes than the broader, fitter population recruited to PROpel.
What alternative approach has the EAG suggested?	N/A
What is the expected effect on the cost-effectiveness estimates?	The impact on cost-effectiveness is unknown.
What additional evidence or analyses might help to resolve this key issue?	Evidence in a population which more closely reflects the MA would help to resolve the issue, though such evidence does not currently exist.

1.4 The clinical effectiveness evidence: summary of the EAG's key issues

Issue 2 Efficacy of olaparib plus abiraterone in the PROpel trial driven by the small subgroup of BRCA mutation patients

Report section	3.2.2.3
Description of issue and why the EAG has identified it as important	Olaparib's established mechanism of action is conditional on the presence of BRCA1 and BRCA2 mutations. This is reflected in previous NICE recommendations for olaparib monotherapy which are all restricted to BRCA1/2 population. Moreover, the improvements in rPFS and OS observed in PROpel appear to be largely attributable to the subgroup of patients with BRCA mutations. There is limited evidence olaparib plus abiraterone provides benefit in non-BRCA 1/2 patients whilst posing an increased risk of SAEs (compared with abiraterone alone). The EAG considers that BRCA status is likely to be an important driver of cost-effectiveness as borne out by scenario analysis conducted by the company and that pooling these populations, as has been done in the company's base-case analysis, fails to recognise the potential for heterogeneity in cost-effectiveness estimates.
What alternative approach has the EAG suggested?	The EAG prefers to consider the cost-effectiveness of olaparib plus abiraterone in the BRCA mutation subgroup separately.
What is the expected effect on the cost-effectiveness estimates?	The ICER for olaparib plus abiraterone in the BRCA mutation population is reduced to [redacted] versus abiraterone, and to [redacted] versus enzalutamide in the EAG-corrected company base-case analysis. However, the present model structure is likely to underestimate the effectiveness of the comparator arm in this subgroup.
What additional evidence or analyses might help to resolve this key issue?	Clinical advice may help interpret the subgroup analysis of PROpel and justify whether it is appropriate to consider BRCA separately or as part of pooled population.

Issue 3 Limited use of subsequent olaparib monotherapy in PROpel

Report section	4.2.6
Description of issue and why the EAG has identified it as important	In the NHS, patients with a BRCA1 or BRCA2 mutation who have progressed after a NHA will be eligible for olaparib monotherapy. In PROpel, only [redacted] of patients in the abiraterone plus placebo (comparator) arm were treated with olaparib monotherapy following progression; around 10% of PROpel participants had a BRCA mutation. Observed OS in the comparator arm (placebo plus abiraterone of PROpel may therefore underestimate survival expected in an NHS cohort.
What alternative approach has the EAG suggested?	The EAG notes that an alternative model structure may be necessary to fully account for the treatment sequence used in this subgroup in NHS practice.
What is the expected effect on the cost-effectiveness estimates?	Incorporating PROfound data into an alternative model structure would increase QALY gain in the comparator arms, reducing the apparent cost-effectiveness of olaparib.
What additional evidence or analyses might help to resolve this key issue?	A state transition model in which post-progression survival in the comparator arm is informed using trial data from PROfound on olaparib monotherapy following an NHA.

Issue 4 Assumption of efficacy equivalence when comparing abiraterone and enzalutamide

Report sections	3.3 to 3.5
Description of issue and why the EAG has identified it as important	In the economic analysis the company assumed equivalent PFS and OS outcomes for patients receiving enzalutamide and abiraterone. This was justified on the basis of an 'exploratory' NMA of OS, clinical opinion, and a single prospective real-world study. No NMA was conducted for rPFS, due to trial heterogeneity. The EAG considers the company's NMA OS HR estimate to be unreliable due to important trial heterogeneity: primarily the imbalances in the proportion of participants crossing over to receive a subsequent NHA, but also differences in Prostate Specific Antigen (PSA) levels, and the exclusion of patients with visceral metastases in the abiraterone trial. The expected impact of this trial heterogeneity on the NMA result is that the HR estimate is likely to be biased in favour of abiraterone.
What alternative approach has the EAG suggested?	The EAG identified several recent studies in their updated evaluation of the real-world studies, and also performed a meta-analysis; the resulted in a HR of 0.84 (95% CI: 0.77 to 0.91), favouring enzalutamide. This supports the premise that the company's NMA result is not reliable and that there is uncertainty about the relative efficacy of enzalutamide and abiraterone. The EAG prefers the application of this HR to OS, PFS, and TTD to align treatment costs with prolonged expected effectiveness.
What is the expected effect on the cost-effectiveness estimates?	The application of a hazard ratio to adjust OS on enzalutamide versus enzalutamide increases the corrected company base-case ICER to [redacted]. Applying this hazard ratio to PFS and TTD increases the ICER versus enzalutamide to [redacted].
What additional evidence or analyses might help to resolve this key issue?	The EAG considers that all relevant evidence on the relative effectiveness enzalutamide and abiraterone has been identified. Ideally, this assumption would be informed by appropriate evidence from randomised controlled trial.

1.5 The cost-effectiveness evidence: summary of the EAG's key issues

Issue 5 Methodological corrections to the model

Report section	
Description of issue and why the EAG has identified it as important	The EAG identified a number of methodological issues in the company's model: the failure to adjust utilities over time as patients aged, the incorrect application of the half cycle correction to treatment acquisition costs, and the use of outdated NHS Reference Cost and eMIT cost data. The approach taken by the company on these issues all acted to reduce the incremental costs associated with olaparib plus abiraterone. Taken together the resolution of these issues led to a significant increase in the ICER for olaparib plus abiraterone. The company provided a scenario in which age adjustments were applied, but did not update their base-case analysis. The EAG did not consider these choices matters of judgement, and thus treated their resolution as model corrections.
What alternative approach has the EAG suggested?	The EAG prefers to adjust utilities over time as patients age in line with the NICE Reference Case. The EAG prefers to use current NHS Reference Cost and eMIT cost data. The EAG also prefers not to apply a half cycle correction to acquisition costs, which should be calculated as a function of the proportion of patients on treatment at the beginning of each model cycle.
What is the expected effect on the cost-effectiveness estimates?	These corrections increase the company's base-case ICER for olaparib plus abiraterone versus abiraterone alone by [redacted] to [redacted] per QALY gained, and versus enzalutamide by [redacted] to [redacted] per QALY gained.
What additional evidence or analyses might help to resolve this key issue?	The EAG has included these amendments in the base-case analysis and considers the issue resolved.

Issue 6 Equally plausible alternative OS extrapolations

Report section	4.2.6.3
Description of issue and why the EAG has identified it as important	The company used a generalised gamma distribution to extrapolate OS data from PROpel. This choice of parametric function predicts potentially optimistic long-term survival estimates on olaparib with abiraterone, while predicting more pessimistic long-term survival for patients receiving abiraterone and enzalutamide compared to observed data and other models with a superior statistical fit to the data. The log-logistic distribution produces clinically plausible long-term OS estimates across all treatment arms, and had a better statistical fit to trial data. However, it also under-predicted observed survival data for olaparib, and may therefore underestimate long-term survival. The log-logistic model may therefore present a similarly plausible counterbalance to the generalised gamma curve preferred by the company, in that the former offers more optimistic predictions for OS on current treatment options, while the latter is a more optimistic interpretation of available data for olaparib. The availability of olaparib monotherapy for a proportion of patients on the comparator arm may mean outcomes on the NHS are superior to those observed in the trial. It is therefore important to consider the log-logistic curve as a plausible alternative to the generalised gamma (Issue 3).
What alternative approach has the EAG suggested?	The EAG presents a scenario on the updated base-case analysis which explores the impact of applying the log-logistic curve to OS.
What is the expected effect on the cost-effectiveness estimates?	The use of a log-logistic curve to extrapolate OS on the corrected company base case increases the ICER by [redacted] to [redacted] versus abiraterone, and from [redacted] to [redacted] versus enzalutamide. The EAG base-case ICER increases from [redacted] using the gen gamma to [redacted] using the log-logistic curve.
What additional evidence or analyses might help to resolve this key issue?	Further expert input on the expected long-term survival on current treatment options would be informative. Is survival of 2.6% (gen gamma) or 8.4% (log-logistic) most likely on current treatment options?

Issue 7 Inconsistent time to discontinuation extrapolation

Report section	4.2.6.10 and 4.2.8
Description of issue and why the EAG has identified it as important	The company extrapolated time to discontinuation data using a different parametric function to that used to extrapolate PFS. This implied a rapid treatment discontinuation of treatment prior to progression. No evidence supporting diverging hazard functions for PFS and TTD was provided. The use of the company's preferred Weibull curve for TTD predicted the shortest mean time on treatment - [redacted]years vs [redacted]years using the generalised gamma, which had a superior statistical fit. This approach is likely to underestimate treatment costs on olaparib. The EAG considered the use of different functional forms to model PFS and TTD inappropriate, as it implicitly de-couples treatment discontinuation risk from its primary cause.
What alternative approach has the EAG suggested?	The EAG preferred the use of consistent functional forms to model time to discontinuation and PFS. This meant using a generalised gamma curve.
What is the expected effect on the cost-effectiveness estimates?	In the corrected company base-case analysis the use of a generalised gamma curve to model TTD increased the ICER from [redacted] to [redacted].
What additional evidence or analyses might help to resolve this key issue?	To justify the company's preferred distribution (Weibull) the company would need to demonstrate a significant divergence in the PFS and TTD including evidence of divergent hazard trends.

Issue 8 Modelling of adverse events using duration data from PROpel

Report section	4.2.7.5
Description of issue and why the EAG has identified it as important	The company assumed that all adverse events would last 14 days, despite the mostly much longer durations observed in the PROpel study. This impacted the time over which adverse event-related disutilities applied, and underestimated the impact of the AE-burden of olaparib plus abiraterone upon HRQoL.
What alternative approach has the EAG suggested?	The EAG preferred the use of observed durations in the PROpel study to model the impact of AEs on HRQoL.
What is the expected effect on the cost-effectiveness estimates?	This had a small impact on the cost-effectiveness of olaparib plus abiraterone, increasing the corrected company base-case ICER from [redacted] to [redacted] per QALY gained versus abiraterone, and from [redacted] to [redacted] versus enzalutamide.
What additional evidence or analyses might help to resolve this key issue?	None.

Issue 9 Health state utilities generated using non-reference case approach

Report section	
Description of issue and why the EAG has identified it as important	The company stated that EQ-5D-5L data collected in PROpel were cross-walked to EQ-5D-3L per the NICE reference case. However, there was no evidence of this process having been undertaken; all data derived from the trial and used in the regression models referred explicitly to EQ-5D-5L. The NICE reference case stipulates the use of the EQ-5D-3L value set, either directly from patients or mapped from other value sets if not available.
What alternative approach has the EAG suggested?	In order to meet the requirements of the NICE reference case, EQ-5D-5L data should be mapped to EQ-5D-3L in line with NICE methods guidance.
What is the expected effect on the cost-effectiveness estimates?	The impact upon cost-effectiveness estimates is unclear, but is likely to be small.
What additional evidence or analyses might help to resolve this key issue?	The company should map EQ-5D-5L to EQ-5D-3L using the Hernández Alava mapping algorithm or otherwise demonstrate that utilities were based on EQ-5D-3L values.

Issue 10 Dosing calculations

Report section	4.2.8
Description of issue and why the EAG has identified it as important	The company did not adjust treatment acquisition costs to account for the relative dose intensity in the trial. This means the model may not accurately reflect treatment costs in NHS practice, as missed doses, dose reductions, and dose interruptions lead to can less drug being used and dispensed.
What alternative approach has the EAG suggested?	The EAG suggest the observed relative dose intensity in the PROpel trial is used to adjust treatment acquisition costs. This approach assumes that all tablets not taken will result in cost savings, i.e. a new pack is not dispensed until the previous one has been used up.
What is the expected effect on the cost-effectiveness estimates?	Treatment costs are reduced across all interventions. The RDI for olaparib was lower than for abiraterone, which when applied in the model reduces the incremental costs associated with olaparib. The ICER for olaparib in the corrected company base-case analysis reduces from [redacted] to [redacted] for olaparib versus abiraterone, and [redacted] to [redacted] for enzalutamide.
What additional evidence or analyses might help to resolve this key issue?	The EAG consider this issue resolved.

Issue 11 Testing costs for BRCA1/2 mutations

Report section	
Description of issue and why the EAG has identified it as important	The company's base case omitted the cost of testing for BRCA1/2 mutations at the point of progression in the comparator arm, reflecting the availability of olaparib monotherapy following an NHA on the NHS. The company also use a unit cost of £400 per test, which is much higher than that applied in other appraisals. In the scenario presented in their PFC response, the company calculated and implemented genetic testing costs incorrectly, applying the unit cost of a test in the first cycle of the model, rather than the total cost of testing per patient identified at the point of progression. The company also incorrectly calculated BRCA1/2 testing costs in the subgroup analysis of BRCA mutation patients. For this subgroup, treatment decisions at the first line of treatment would be based on biomarker testing. This only affects total costs, as testing costs should be incurred in both treatment arms.
What alternative approach has the EAG suggested?	In the whole-population analysis, the EAG suggest testing costs are implemented at the point of progression in the comparator arm, and are calculated as the total cost of testing per actionable mutation identified. The unit cost of adding a gene to a NGS screening panel should be £34 in line with TA898. In the BRCA subgroup analysis, total per patient testing costs should be calculated as above, and applied to both arms in the first model cycle.
What is the expected effect on the cost-effectiveness estimates?	This had a small impact on the cost-effectiveness of olaparib plus abiraterone, increasing the corrected company base-case ICER from [redacted] to [redacted] per QALY gained versus abiraterone, and [redacted] to [redacted] versus enzalutamide.
What additional evidence or analyses might help to resolve this key issue?	Input from NHS England on appropriate unit cost for BRCA mutation testing in prostate cancer.

1.6 Summary of EAG's preferred assumptions and resulting ICER

Given the greater potential for cost-effective use of olaparib in the BRCA subgroup, the EAG presented two base-case analyses. The first is based on the whole population covered in the company's submission. The second is based on the BRCA subgroup analysis in PROpel. Note that the model structure as presented cannot fully capture the treatment effects of the comparator arm in this subpopulation, which comprises a sequence of treatments not used in the PROpel study. This analysis is therefore only illustrative of the potential cost-effectiveness of olaparib in this population.

For further details of the exploratory and sensitivity analyses done by the EAG, please refer to Section 6. Please note that the impact of a number of scenarios differs according the inclusion of other commercial arrangements not accounted for in the main EAG Report. For cost-effectiveness estimates considering all available commercial pricing arrangements, please refer to the confidential appendix to this report.

The results of the EAG's alternative base-case analyses are presented in Table 2 for the whole population, and Table 3 for the BRCA subpopulation. Equivalent probabilistic results are presented in

Table 4.

Table 2 Summary of EAG's preferred assumptions (whole population) - deterministic

Preferred assumption	Issue	Cum. ICER vs abiraterone	Cum. ICER vs enzalutamide
Corrections to company base case	*Key Issue 5*	[redacted]	[redacted]
Scenario 2b: RWE-derived hazard ratios used to estimate OS, PFS, and TTD for enzalutamide.	*Key Issue 4*	[redacted]	[redacted]
Scenario 4: Generalised gamma to model time to discontinuation	*Key Issue 6*	[redacted]	[redacted]
Scenario 6: Relative dose intensity used to adjust treatment acquisition costs	*Key Issue 10*	[redacted]	[redacted]
Scenario 7: Adverse event durations based on PROpel	*Key Issue 8*	[redacted]	[redacted]
Scenario 8: Testing costs for BRCA mutations	*Key Issue 11*	[redacted]	[redacted]

Table 3 Summary EAG's preferred assumptions (BRCA population) - deterministic

Preferred assumption	Issue	Cum. ICER vs abiraterone	Cum. ICER vs enzalutamide
Corrections to company base case (whole population)	*Key Issue 5*	[redacted]	[redacted]
Scenario 1: BRCAm subgroup (inclusive of biomarker testing costs for all arms).	*Key Issue 2*	[redacted]	[redacted]
Scenario 6: Relative dose intensity used to adjust treatment acquisition costs	*Key Issue 10*	[redacted]	[redacted]
Scenario 7: Adverse event durations based on PROpel	*Key Issue 8*	[redacted]	[redacted]

Table 4 EAG preferred model assumptions: pairwise probabilistic results

Scenario	Technology	Total		Incremental		ICER
		Costs	QALYs	Costs	QALYs	
EAG-corrected company base-case	Olaparib + Abiraterone vs	[redacted]	[redacted]			
	Abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Enzalutamide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG preferred assumptions: whole population	Olaparib + Abiraterone vs	[redacted]	[redacted]			
	Abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Enzalutamide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG preferred assumptions: BRCA population	Olaparib + Abiraterone vs	[redacted]	[redacted]			
	Abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Enzalutamide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

EXTERNAL ASSESSMENT GROUP REPORT

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

This report presents the EAG's critique of the company submission (CS) and executable economic model submitted by AstraZeneca to the National Institute for Health and Care Excellence (NICE). The CS reports on the clinical effectiveness and cost-effectiveness of olaparib in combination with abiraterone (and prednisone or prednisolone) for the treatment of metastatic castration resistant prostate cancer (mCRPC) in adult patients for whom chemotherapy is not clinically indicated.

In this section the EAG critiques the company's proposed positioning of olaparib plus abiraterone in the treatment pathway and its definition of the decision problem when compared with the NICE scope.

2.2 Background

2.2.1 Description of mCRPC

The company's description of the underlying health problem is broadly appropriate and relevant to the decision problem.

Prostate cancer is the most common form of cancer in the UK. An estimated 58,783 new cases of prostate cancer will be diagnosed in the UK in 2023. Incidence rates of prostate cancer increase with age such that prostate cancer mainly affects men aged over the age of 50. Lifetime risks of prostate cancer are higher in patients from a black-African family background (approximately 1 in 4), those with a family history of prostate cancer, and those who harbour specific homologous recombination repair mutations (HRR mutation).

The majority of prostate cancers are diagnosed at an early stage of the disease, before the cancer has spread beyond the area of the prostate gland. When diagnosed early treatment options are typically given with curative intent and may include surgery, radiotherapy, and hormone therapy.

Metastatic prostate cancer is more aggressive, and median overall survival rates reported in trials and registry data do not generally exceed 36 months.[1-4] In patients with metastatic castration-resistant prostate cancer (mCRPC), androgen deprivation therapy (ADT) no longer halts progression of the disease. mCRPC is also described as hormone-resistant or hormone-relapsed, though patients are still expected to derive some benefit from ADT and will generally continue to receive ADT. It is also

possible for non-metastatic prostate cancer to be castration resistant, which is not within the scope of the appraisal.

The company estimate in their submission that around 1,300 patients a year (CS p. 17-18) will receive a diagnosis of mCRPC in 2023, and incidence rates are expected to rise with the increase in older people in the UK population.

2.2.2 Description of olaparib plus abiraterone

Olaparib is a type of poly-ADP ribose polymerase (PARP) inhibitor, which kills cancer cells by manipulating the position of PARP enzymes, which play a crucial role in repairing DNA damage in cancer cells.[4] By preventing the detachment of PARP from DNA, olaparib prevents the subsequent action of base excision repair enzymes. As a result, when prostate cancer cells divide, DNA double strand breaks (DSBs) are formed, leading to cell death. In normal cells, a process called homologous recombination repair (HRR) effectively fixes DNA DSBs. However, in prostate cancer cells with HRR mutations, such as BRCA1 (Breast Cancer gene 1) and BRCA2 (Breast Cancer gene 2) mutations, these DNA DSBs cannot be adequately repaired.[4-6]

Reflecting this mode of action, olaparib has been used for the treatment of metastatic cancers such as ovarian cancer in women with harmful variants of BRCA1 and BRCA2.[7] NICE also recommends olaparib monotherapy for the treatment of mCRPC after abiraterone or enzalutamide in patients with BRCA1 and BRCA2 mutations.[8]

These previous indications considered olaparib as monotherapy only. This appraisal considers olaparib as part of a combination consisting of both olaparib and abiraterone. The CS outlines that pre-clinical studies have demonstrated that the addition of abiraterone leads olaparib to exert an anti-tumour effect in mCRPC irrespective of BRCA1 or 2 or other homologous recombination repair (HRR) mutations. This potentially represents a distinct and separate mode of action from the PARP/BRCA pathway described above.

The UK marketing authorisation, received from the UK Medicines and Healthcare products Regulatory Agency (MHRA) on the 15th March 2023, approved the use of olaparib in combination with abiraterone in a broad population of mCRPC patients (for whom chemotherapy is not clinically indicated) with and without a BRCA mutation. This reflects the European Medical Association approval which was obtained in December 2022. In the US however, the Oncologic Advisory Drug Committee (OADC) of the Food and Drug Administration (FDA) advised in April 2023 to restrict the use of olaparib plus abiraterone to mCRPC patients with breast cancer gene (BRCA) mutations. This is discussed further in Section 0.[9]

2.2.3 Position of olaparib plus abiraterone in the clinical pathway

Figure 1 in the CS (p. 21) shows the proposed positioning of olaparib plus abiraterone in the mCRPC treatment pathway. The company propose olaparib plus abiraterone as a first-line treatment for patients with mCRPC, alongside abiraterone monotherapy or enzalutamide, for patients in whom chemotherapy is not clinically indicated.

2.2.3.1 Novel hormonal agents

Novel hormonal agents (NHAs) are hormone therapies that may slow the spread of mCRPC in patients for whom the beneficial effects of ADTs have diminished. NHAs included as comparators in this appraisal are abiraterone and enzalutamide. Both therapies may precede or follow chemotherapy for people with no or mild symptoms. The EAG's clinical advisor indicated that 90-95% of NHS patients with mCRPC will receive an NHA (including bicalutamide) initially. The remainder receive chemotherapy.

2.2.3.2 Docetaxel

Chemotherapy, usually docetaxel, is recommended for patients scoring a Karnofsky performance status of 60 or higher, which corresponds with requiring only occasional assistance to perform daily activities.[10] Docetaxel can be given at an earlier stage of disease, usually at the mHRPC stage, in which case retreatment at mCRPC stage is not permitted.[11] In the pivotal PROpel trial, which compared olaparib plus abiraterone with placebo plus abiraterone, around 25% of patients had received docetaxel at an earlier stage of the disease (CS p. 29, 30). [redacted][12]

Patients may also receive docetaxel in combination with abiraterone or enzalutamide.

2.2.3.3 Olaparib in combination with abiraterone

The EAG sought clarification from the company on the meaning of the marketing authorisation i.e. for patients with mCRPC "*for whom chemotherapy is not clinically indicated*" noting that this wording contrasts with that used in the marketing authorisation for enzalutamide and abiraterone which are indicated for patients with mCRPC "*for whom chemotherapy is not **yet** clinically indicated*". The company response stated that mCRPC patients may not be eligible for chemotherapy for three reasons:

- Patients may have received treatment at an earlier disease stage, and retreatment is not permitted.
- Patients may not be fit enough to receive docetaxel.
- Docetaxel may be contraindicated for some patients.

In the PROpel trial, around 25% of patients received docetaxel in a disease stage prior to mCRPC, and therefore would be ineligible for retreatment with chemotherapy (CS, p. 29, 30). All PROpel participants had an ECOG status of 0 or 1, and therefore no participant would be ineligible to receive docetaxel because of a lack of fitness (CS, p. 30). Contraindications are likely to be uncommon. This implies that 75% of the PROpel trial population would be eligible to receive chemotherapy.

The EAG is concerned that the wording of the company's clarification is conflating the terms "clinically indicated" with "eligible to receive" but interpreted literally the company response implies that most patients in the PROpel cohort would not be eligible to receive olaparib plus abiraterone in NHS practice. The implications are that chemotherapy-naïve patients, who are fit enough (and not contraindicated) to receive docetaxel, should receive docetaxel before they receive olaparib plus abiraterone. However, the EAG is aware that this may not be the preferred option (for clinicians and patients) due to the intensity of chemotherapy and the severity and likelihood of side effects; first-line use of abiraterone or enzalutamide is a more plausible and likely scenario. This is at odds with the company anticipating that olaparib plus abiraterone will displace NHAs as a first-line therapy in mCRPC. Importantly, this may have implications for the applicability of the PROpel trial results to the NHS setting, since patients not fit enough for chemotherapy, or contraindicated to chemotherapy, may have worse outcomes than the broader, fitter population recruited to PROpel.

2.2.3.4 Other treatment options

The EAG's adviser stated that radium-223 radiotherapy would be a later-line therapy. As noted by the company, retreatment with enzalutamide or abiraterone in patients who have previously received either agent at an earlier stage or line of therapy is not recommended in guidelines and is not offered in the NHS.

2.2.4 BRCA mutation testing

Treatment specifically for mCRPC patients with BRCA mutations requires genetic testing. This may involve germline testing of blood or saliva, which detects inherited mutations in any cells of the body, or somatic tumour sequencing, which examines DNA within tumour cells to identify both inherited and newly acquired mutations.[4] In somatic tumour sequencing, either metastatic tissue or plasma circulating tumour DNA (ctDNA) are used. Tissue DNA testing for BRCA1 and BRCA2 is challenging and needs a fairly large tissue sample, because there are a large number of variants of BRCA1/2 mutations to detect and they are found on very different areas of the DNA.[13]

The recent NICE recommendations outlined in TA 887 position olaparib monotherapy as a second-line treatment for patients with BRCA mutation-positive mCRPC and established BRCA testing as part of NHS practice.[8] The introduction of olaparib combination treatment as a first-line treatment for all mCRPC patients would, however, remove the need for BRCA testing; use of olaparib in a first-line

setting prohibits use in subsequent lines of treatment and first-line treatment would not be conditional on mutation status. An Optimised recommendation (based on BRCA mutation status) for olaparib combination treatment in a first-line setting would, however, require retention of testing and may impact on current practice because testing would be brought forward to a first-line setting. The cost implications of testing and how this interacts with the target population are further discussed in Section 4.2.8.7.

2.3 Critique of the company's definition of the decision problem

In the sections below the EAG describes key issues relating to the company's definition of the decision problem. See Table 5 for a summary of the decision problem and critique by the EAG.

2.3.1 Population

As discussed above, most patients in the pivotal PROpel trial were eligible to receive chemotherapy. This potentially limits the applicability of PROpel's results to the NHS setting.

The PROpel trial only included patients who had not yet received treatment for mCRPC. Previous treatment with docetaxel was permitted only if used to treat localised prostate cancer or metastatic hormone-sensitive prostate cancer. Patients were excluded if they had received previous treatment with olaparib or abiraterone.

2.3.2 Intervention

The intervention, olaparib plus abiraterone and prednisone or prednisolone, matches the intervention described in the final scope by NICE.

2.3.3 Comparators

Of the two comparators listed in the final scope, the company chose enzalutamide as their main comparator, citing far greater and growing use of enzalutamide compared to abiraterone. Abiraterone is included as a secondary comparator.

The EAG's clinical advisor explained that enzalutamide and abiraterone are both used in UK clinical practice, and it is the EAG's understanding that many patients could receive either drug. There is likely to be variability in clinical decision-making regarding enzalutamide or abiraterone for mCRPC, depending on clinical experience and familiarity with the medications, as well as the consideration of side effects depending on individual patient characteristics. The clinical advisor considered the efficacy of enzalutamide and abiraterone to be similar. He noted that a limitation of abiraterone is that it needs to be given with prednisone or prednisolone. He indicated enzalutamide is not the preferred option for patients with a history of epilepsy due to a (low) risk of seizures. Abiraterone with

prednisone/ prednisolone can affect blood sugar levels, which can be problematic for patients with diabetes.[14]

The EAG considers enzalutamide and abiraterone to be equally relevant comparators for this appraisal and, notwithstanding the contraindications outline above, that the majority of patients are eligible to receive either treatment. A further exploration of the differences in efficacy between enzalutamide and abiraterone can be found in Section 3.5.

2.3.4 Outcomes

NICE specified five outcomes in the final scope: overall survival (OS), progression-free survival (PFS), response rate, adverse effects (AEs) of the treatment, and health-related quality of life. The company report data from the PROpel trial for all of the outcomes listed above, and additional outcomes. The primary outcome in PROpel was radiographic PFS (rPFS).

2.3.5 Subgroups to be considered

In the final scope, NICE asked the company to present evidence by HRR subgroup, including BRCA1, BRCA2, and ataxia-telangiectasia mutated (ATM) gene subgroups, if evidence was available. The company explained in the submission (Table 1, p.13) that enrolment into the PROpel trial was independent of HRR mutation status. Although pre-specified subgroup analyses based on HRR status (yes, no) were available, subgroup analyses based on BRCA and ATM mutations were not available due to small sample sizes of the subgroups.

The EAG believes that a thorough assessment of evidence on the efficacy and safety of olaparib plus abiraterone in mCRPC patients with and without BRCA mutations is crucial to this appraisal. In section 2.2.2 of this report we highlighted the role of BRCA genes in the working mechanism of PARP inhibitors, such as olaparib. In addition, there is growing evidence that olaparib may only be effective in patients with BRCA mutations. In April 2023, the FDA decided to restrict use of olaparib plus abiraterone to mCRPC patients with BRCA mutations because the available evidence and FDA-run subgroup analyses of the PROpel trial suggested that the efficacy shown in PROpel was driven by the subgroup of BRCA-positive patients, see Section 0.[9]

The EAG sought clarification from the company regarding the omission of BRCA subgroup analyses, and requested the results of subgroup analyses where available. The company provided some additional analyses which are discussed in Section 0.

2.3.6 Special considerations including issues related to equity or equality

NICE did not specify special considerations relating to issues of equity or equality in the final scope. The company highlight the increase risk of prostate cancer among black men and the increased

prevalence of BRCA gene mutations among people from Ashkenazi Jewish backgrounds. They also point out that transgender women can develop prostate cancer. The company does not discuss the implications for treatment with olaparib plus abiraterone in these subgroups of the population.

Table 5 Summary of decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
Population	Adults with hormone-relapsed metastatic prostate cancer for whom chemotherapy is not clinically indicated.	In line with scope and licensed indication		Most patients in the pivotal PROpel trial were eligible to receive chemotherapy. This potentially limits the applicability of PROpel's results to the NHS setting.
Intervention	Olaparib plus abiraterone (and prednisone or prednisolone)	Olaparib plus abiraterone (and prednisone or prednisolone)		Matches NICE final scope
Comparator(s)	Enzalutamide Abiraterone with prednisone or prednisolone	Main comparator: Enzalutamide Secondary comparator: Abiraterone with prednisone or prednisolone	Based on Blueteq requests in 2022 for their use in mCRPC before chemotherapy is indicated, enzalutamide accounts for twice as many initiations as abiraterone (67% vs 33%). Despite a 2-fold increase in total initiations of these therapies since 2020, abiraterone initiations have declined by 30% over the same period. Based on its far greater and growing use, enzalutamide is the main comparator for olaparib plus abiraterone, with abiraterone considered as a secondary comparator.	The EAG considers enzalutamide and abiraterone to be equally relevant comparators.
Outcomes	Overall survival Progression-free survival Response rate Adverse effects of treatment Health-related quality of life	Overall survival Progression-free survival (investigator-based & blinded independent central review) Response rate Adverse effects of treatment Health-related quality of life Time to first subsequent therapy or death (TFST) Time to second progression or death (PFS2) Time to pain progression (TTPP) and time to first opiate use	The PROpel trial assessed additional important outcomes that contribute to the evidence base for olaparib plus abiraterone and may be used in the economic model.	Outcomes listed in NICE final scope have been addressed.

		Time to symptomatic skeletal-related events (SSRE) Time to discontinuation of olaparib and abiraterone and time to discontinuation of abiraterone		
Subgroups	If the evidence allows, the following subgroup will be considered: -homologous recombination repair (HRR) status including: -breast cancer gene (BRCA1 and BRCA2) -ataxia-telangiectasia mutated (ATM) gene.	Pre-specified subgroup analyses based on HRR mutation status (yes, no) are provided to demonstrate the consistent efficacy of olaparib plus abiraterone across patients with or without HRR mutations.	Enrolment into the PROpel trial was for an 'all comer' population and independent of HRR mutation status. The intention-to-treat population of the PROpel trial is aligned with the licensed indication. The trial population was stratified by type of distant metastases, and prior use of docetaxel in metastatic hormone sensitive stage of disease. Analyses in the HRR-mutated (HRR mutation) subgroup were pre-specified, but determination of HRR mutation status in the PROpel trial was conducted after randomisation had occurred. ~ 28% of enrolled participants were found to have HRR mutations, which is generalisable to the UK population. Pre-specified subgroup analyses based on HRR mutation status (yes, no) are provided only to demonstrate the consistent efficacy of olaparib in combination with abiraterone across patients irrespective of HRR mutation status. BRCA1, BRCA2 or ATM mutations are specific types of HRR mutation that are included in the HRR mutation subgroup but were not pre-specified for analysis in the PROpel trial. Participants with each of these mutations represent <10% of the enrolled population. Subgroup analyses by these specific mutations are not provided.	The EAG considers patients with and without BRCA mutations to be key subgroups. There is a plausible biological mechanism to suggest the efficacy of olaparib (plus abiraterone) differs depending on BRCA status. Evidence suggests that olaparib may only be effective in patients with BRCA mutations.
Special considerations including issues		Not stated	Several potential equality issues relating to protected characteristics of age, sex and gender, race and religion require consideration:	The EAG acknowledge the inequalities in the prevalence of prostate cancer between subgroups of the UK

related to equity or equality			Around 1 in 6 men develop prostate cancer and this disproportionately affects men of black ethnicity – around 1 in 4 black men will develop prostate cancer. HRR mutations such as BRCA1 and BRCA2 increase the risk of developing prostate cancer and aggressive disease. Around 1 in 3-400 people in the population have a BRCA gene mutation, but people from Ashkenazi Jewish backgrounds have a 10-fold greater risk. People who have a prostate and do not identify as male (e.g., people who have or are undergoing gender reassignment, those who identify as non-binary people) can develop prostate cancer. Olaparib plus abiraterone was designated as an innovative medicine by the granting of an Innovation Passport in June 2022 as part of the MHRA-administered Innovative Licensing and Access Pathway.	population, along with the fact that all people with a prostate, regardless of gender, can develop prostate cancer. The company do not relate this information to potential implications for the treatment of mCRPC, and it is unclear how these inequalities would be addressed by the recommendation of olaparib plus abiraterone for mCRPC.

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

The company conducted a systematic literature review of randomised clinical trials (RCTs) of first line therapy for mCRPC. In the clarification response, the company also stated that a systematic review was performed to identify real-world evidence of studies comparing enzalutamide with abiraterone.

3.1.1 Systematic review of RCTs of first-line therapy for mCRPC

3.1.1.1 Searches

The original company submission included searches to identify clinical evidence for treating metastatic castration-resistant prostate cancer. A detailed description of the searches and most of the search strategies were included in the document 'Astrazeneca_Clinical Studies SLR-CONFIDENTIAL'.

In response to the EAG's PFCs (points for clarification), a further document was provided by the company, which included additional search strategies and corrections to errors identified by the EAG. Searches identified studies published up to 1 December 2022. The EAG's information specialist judged the search strategy to be appropriate (Table 6).

Table 6 EAG appraisal of evidence identification

TOPIC	EAG RESPONSE	NOTE
Is the report of the search clear and comprehensive?	YES	In the original company submission, the search strategies of clinical trials registries (clinicaltrials.gov and WHO ICTRP registry) were not documented. These were provided in the company's response to PFCs. In the original company submission, the overall PRISMA flow chart (Figure 1, p. 31 of document 'Astrazeneca_Clinical Studies SLR-CONFIDENTIAL') was confusing as the hits from update 2 were not shown and only the includes from the original searches were represented. This was corrected in the company's response to PFCs.
Were appropriate sources searched?	YES	A range of relevant databases, conference proceedings, and trials registry databases were searched.
Was the timespan of the searches appropriate?	YES	The searches were not limited by date in the strategy.
Were appropriate parts of the PICOS included in the search strategies?	YES	The searches combined the population with the intervention and the study type.
Were appropriate search terms used?	YES	Search terms were very comprehensive.
Were any search restrictions applied appropriate?	N/A	N/A
Were any search filters used validated and referenced?	YES	Search filters were used but not referenced.

EAG response = YES/NO/PARTLY/UNCLEAR/NOT APPLICABLE

3.1.1.2 Selection of evidence

Selection criteria were clearly stated and the company provided a table of excluded studies in the systematic literature review report. As stated above, the company provided an updated PRISMA flowchart in the clarification response.

3.1.1.3 Data extraction and risk of bias assessment

The EAG is satisfied that data were extracted appropriately. The Risk of Bias 2 tool was used to assess risk of bias for one outcome per study. Risk of bias was assessed for rPFS if available, or else for the primary trial outcome. The EAG's preference is for risk of bias to be assessed for key outcomes separately, since aspects of risk of bias such as bias in measurement of the outcome and selection of the reported result may differ between outcomes. The company provided a summary of risk of bias assessments for OS as part of the clarification response.

3.1.1.4 Evidence synthesis

Only one RCT of olaparib plus abiraterone was identified in the review so there was no pairwise meta-analysis of olaparib plus abiraterone studies. The evidence synthesis presented in the CS was an NMA. Details and further commentary on this analysis and the results are given in Sections 3.3 & 3.4.

3.1.2 Systematic review of real-world evidence for enzalutamide and abiraterone

The company cited a real-world study[15] as part of its assumption of efficacy equivalence when comparing enzalutamide with abiraterone; the EAG asked for clarification on how this study was identified and whether other relevant studies had been identified (see Section 3.5). This in the light of the EAG identifying a large study by Schoen et al 2022[16] which the company did not mention. In its clarification response, the company provided an appendix document describing how real-world studies were identified. This reported that searches were run on 18 November 2021, to identify real-world studies of enzalutamide and abiraterone for first-line treatment of mCRPC.

The company report the search strategy, selection criteria, and process for screening titles/ abstracts (in duplicate) and full-text reports (not in duplicate). A list of excluded studies was not provided.

Although 88 studies were included, only two studies were prioritised for data extraction because they were 1) prospectively conducted, 2) provided comparative PFS or OS data for abiraterone vs enzalutamide, and 3) adjusted for confounding factors. Results from another 11 studies were reported separately, because these provided comparative outcome data but were retrospective studies and/or did not adjusted for confounding factors. Studies which were included but not prioritised for data extraction were not listed. No study-specific details were provided of the risk of bias assessment results (using the ROBINS-I tool).

The EAG considered it important to further investigate the assumed equivalence of enzalutamide and abiraterone. The EAG undertook more up-to-date searches and identified additional studies not included in the company's systematic review; the results of this work are presented in Section 3.5.

3.2 Critique of trials of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)

The company's efficacy and safety data were based on the results of the PROpel placebo-controlled phase III trial, which randomised patients to either olaparib plus abiraterone or placebo plus abiraterone (clinicaltrials.gov identifier: NCT03732820).

3.2.1 Design and methods of the PROpel trial

The PROpel trial randomised 796 patients with mCRPC who were previously untreated for mCRPC (i.e. awaiting first-line treatment). The EAG's clinical adviser thought that the trial eligibility criteria (summarised in Table 5 of the CS) were reasonable in their recruitment restrictions and were therefore broadly applicable to the NHS setting. An exception was the restriction to including patients with an ECOG performance status (PS) of 0 or 1. The EAG's adviser estimated that in NHS practice around 10-20% of patients who were suitable for receiving olaparib plus abiraterone would have an ECOG

PS of 2, so the overall trial population is fitter than the population seen in the NHS. The trial was conducted across 17 countries (excluding a separate cohort from China), with 25% of participants enrolled in Asia, 44% in Europe, and 32% in North & South America). Forty-nine (6%) patients were enrolled in the UK.

Stratified randomisation was used to minimise treatment group differences in metastases type (bone only vs visceral vs other) and docetaxel treatment at mHSPC stage (yes vs no). The primary outcome was radiological PFS (rPFS) as assessed by the investigator using RECIST 1.1 (soft tissue) and the Prostate Cancer Clinical Trials Working Group 3 (PCWG-3) criteria (bone). The primary analysis was based on investigator assessed rPFS, with a sensitivity analysis conducted using blinded independent central review (BICR) assessment. Hazard ratios were calculated using a Cox proportional hazards model, adjusted for metastases site (bone only, visceral, other) and docetaxel treatment at mHSPC stage.

Participants randomised to receive placebo were not allowed to crossover to receive olaparib plus abiraterone. Further treatment following objective disease progression was provided at the investigator's discretion which included olaparib monotherapy

3.2.1.1 Critical appraisal of the PROpel trial

Risk of bias

The PROpel study was judged by the company to be at low overall risk of bias for both rPFS and for OS, which the EAG concurs with.

Applicability of subsequent therapies (following disease progression)

The EAG identified two issues on subsequent therapies, which may affect the applicability of the PROpel trial results to the NHS setting. Following disease progression, [redacted] received an NHA. Re-treatment with an NHA following disease progression is currently not permitted in the NHS. The EAG's clinical adviser thought that the clinical benefit of NHA re-treatment would be small and short-lived, though not negligible.

Also, in the NHS, patients with a BRCA1 or BRCA2 mutation who have progressed after a NHA will be eligible for olaparib monotherapy. In PROpel, [redacted] of patients in the abiraterone plus placebo arm were treated with olaparib monotherapy following progression; this is notably different to the proportion of patients who had a BRCA mutation (around 10%). Therefore, in PROpel, the OS results for the abiraterone arm may underestimate OS outcomes expected in an NHS cohort, where more patients would have gone on to receive olaparib monotherapy.

3.2.2 Results of the PROpel trial

3.2.2.1 Baseline characteristics

The baseline characteristics of participants recruited to the PROpel trial were reported in Table 6 of the CS and are reproduced here as Table 7.

Table 7 Baseline characteristics of PROpel trial participants (reproduced from the company submission)

Baseline characteristic		Olaparib + Abiraterone (n = 399)	Placebo + Abiraterone (n = 397)
Age, years, median (range)		69 (43–91)	70 (46–88)
< 65 years, n (%)		[redacted]	[redacted]
≥ 65 years, n (%)		[redacted]	[redacted]
Gleason score ≥8, n (%)		265 (66.4)	258 (65.0)
Median prostate-specific antigen, ug/L (min–max)		17.90 (0.07–1869.5)	16.81 (0.01–1888.0)
Median time from mCRPC to randomisation (range), months		[redacted]	[redacted]
Prior treatment with second-generation antiandrogen agents (NHA), n (%)			
Yes (Enzalutamide)		1 (0.3)	0
Prior docetaxel treatment, n (%)			
Yes		97 (24.3)	98 (24.7)
At mHSPC stage		90 (22.6)	89 (22.4)
ECOG performance status, n (%)			
0		286 (71.7)	272 (68.5)
1		112 (28.1)	124 (31.2)
HRR mutation status, n (%)			
HRR mutation		111 (27.8)	115 (29.0)
BRCA1		9 (2.3)	3 (0.8)
BRCA2		38 (9.5)	35 (8.8)
Non-HRR mutation		279 (69.9)	273 (68.8)
HRR mutation unknown		9 (2.3)	9 (2.3)
Baseline pain score (BPI-SF Item 3: worst pain in last 24 hrs), n (%)			
0 (no pain)		133 (33.3)	137 (34.5)
> 0 - < 4 (mild pain)		151 (37.8)	173 (43.6)
4 - < 6 (moderate pain)		53 (13.3)	36 (9.1)
≥ 6 (severe pain)		32 (8.0)	28 (7.1)
Missing		30 (7.5)	23 (5.8)
Site of metastases, n (%)			
Bone		349 (87.5)	339 (85.4)
Distant lymph nodes		113 (33.3)	119 (30.0)
Locoregional lymph nodes		82 (20.6)	89 (22.4)
Lung/Respiratory		40 (10.0)	42 (10.6)
Liver		15 (3.8)	18 (4.5)
Stratification factors at randomisation			
Site of distant metastases	**Docetaxel treatment at mHSPC stage**	**Number of patients, n (%)**	
		Olaparib + Abiraterone (n = 399)	**Placebo + Abiraterone (n = 397)**
As randomised (IWRS)			
Bone only	Yes	[redacted]	[redacted]
	No	[redacted]	[redacted]
Visceral	Yes	[redacted]	[redacted]
	No	[redacted]	[redacted]
Other	Yes	[redacted]	[redacted]
	No	[redacted]	[redacted]

Apart from the ECOG (0-1) eligibility criteria restriction, the EAG's adviser thought that the trial population was reasonably representative of the NHS population, although the trial population is younger (mean age, 69.1 years) than would be expected in an NHS cohort (the EAG's adviser estimated that the NHS population may be around 5 years older than the PROpel cohort). The EAG's clinical adviser considered that other prognostic factors were: disease site - patients with visceral metastases tend to have a worse prognosis than patients with bone-only metastases; time on previous treatment (shorter duration of response tends to be associated with worse prognosis); and level of pain. Time on previous treatment was not reported, but the other factors were balanced across trial treatment groups and similar to what would be seen in the NHS. The EAG notes (from CS Appendix Table 4) that only around 80% of patients in PROpel had received prior hormonal cancer therapy. This figure would be expected to be close to 100% in practice. Given these ECOG, age, and prior hormonal therapy data it may be that the PROpel cohort could achieve better outcomes than would have been seen had the trial be conducted in a cohort more representative of NHS practice.

3.2.2.2 Main efficacy results of the PROpel trial

The company reported clinical effectiveness results for the PROpel trial in Section B.2.6 of the submission.

Radiological progression-free survival

The primary outcome (rPFS) was formally analysed at two planned data cuts: on 30 July 2021 (DCO1) and 14 March 2022 (DCO2). OS was analysed at three planned data cuts, with the final data cut on 12 October 2022 (DCO3). An updated rPFS analysis was also performed at DCO3. The DCO3 rPFS results were used in the economic model, since these provided the longest available follow-up and were consist with the OS analyses (DCO3 OS data were also used in the model).

Treatment with olaparib plus abiraterone resulted in [redacted] (see Table 8, which is reproduced from CS Table 9, and Figure 1).

Table 8 rPFS results based on investigator assessment at different data cuts (reproduced from CS Table 9)

	Median rPFS, Months (95% CI) Olaparib + Abiraterone (n=399)	Median rPFS, Months (95% CI) Placebo + Abiraterone (n=397)	HR (95% CI)
DCO1 (Primary analysis, 30 July 2021)	24.84 (20.47–27.63)	16.59 (13.93–19.22)	0.66 (0.54–0.81) p<0.001
DCO2 (Final analysis,14 March 2022)	[redacted]	[redacted]	[redacted]
DCO3 (Updated analysis, 12 October 2022)	[redacted]	[redacted]	[redacted]

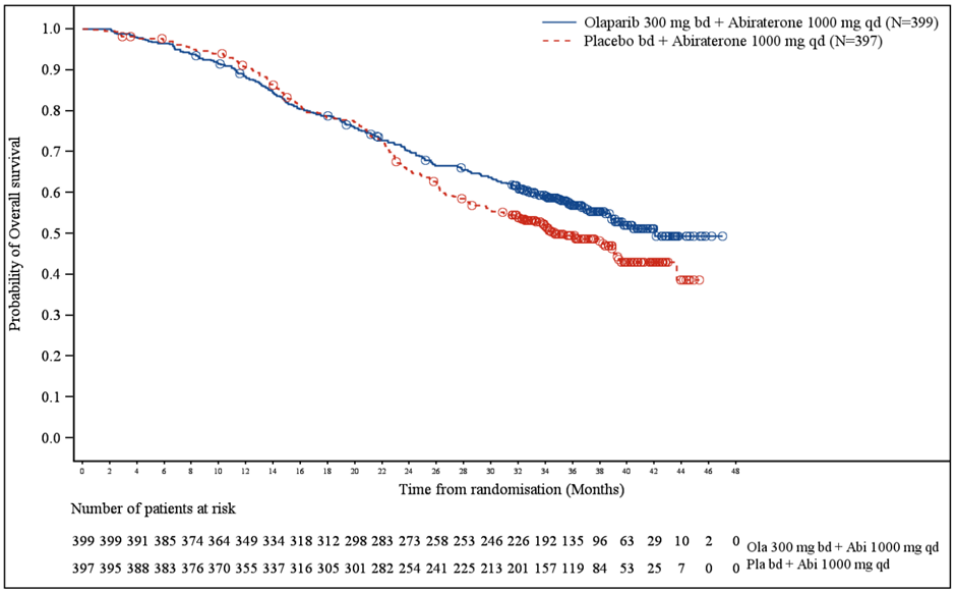
DCO data cut-off, HR Hazard Ratio, rPFS Radiological Progression-Free Survival

Figure 1 Radiological PFS based on investigator assessment for the latest data-cut off (DCO3). Reproduced from PROpel CSR Addendum 2

Overall survival

Analyses conducted at the three different data cut-offs showed a consistent trend, of improving OS (with olaparib plus abiraterone) as the data matured. At DCO1 the HR was 0.86 (95% CI: 0.66 to 1.12) with p=0.29; at DCO2 the HR was 0.83 (95% CI: 0.66 to 1.03) with p=0.11. At the latest data-cut (DCO3), olaparib plus abiraterone was associated with an improvement in median OS over placebo plus abiraterone of over 7 months. The HR was 0.81 (95% CI: 0.67 to 1.00) with the result not quite reaching statistical significance p=0.054. At 42 months median follow up, 51% of patients were still alive with olaparib plus abiraterone versus 43% with placebo plus abiraterone. The DC03 data are presented in Figure 2.

Figure 2 Final analysis of OS at DCO3 (reproduced from CS Figure 4)



Complete response rates were [redacted]

Results for other secondary endpoints were presented in Table 11 of the CS. Olaparib plus abiraterone was associated with a statistically significant improvement in time to first subsequent therapy (HR 0.76, 95% CI 0.64 to 0.90, p=0.003). [redacted]

Subgroup analyses

The company pre-specified eight different subgroup analyses in PROpel for rPFS and OS: Site of distant metastases, docetaxel treatment at mHSPC stage, HRR gene mutation status, ECOG performance status, age, region, race, and prostate-specific antigen. However, only results from a global interaction test were presented, the EAG therefore requested interaction test results for all the individual subgroup analyses at the clarification stage. Since olaparib monotherapy is only recommended in patients with BRCA 1 or 2 mutations, the EAG also requested subgroup results for these patients (clarification question A4). The PROFOUND trial, which underpinned the olaparib monotherapy recommendation, showed differences in imaging-based PFS by mutation status, for

example reporting a HR of 0.21 (95% CI: 0.13 to 0.32) for olaparib versus clinicians choice of enzalutamide or abiraterone in the BRCA2 subgroup and a HR of 1.04 (95% CI: 0.61 to 1.87) in the ATM (ataxia-telangiectasia mutated) subgroup.[17] A limitation of the PROpel trial was that mutation status was only obtained after randomisation, as such randomisation was not stratified by HRR or BRCA mutation status.

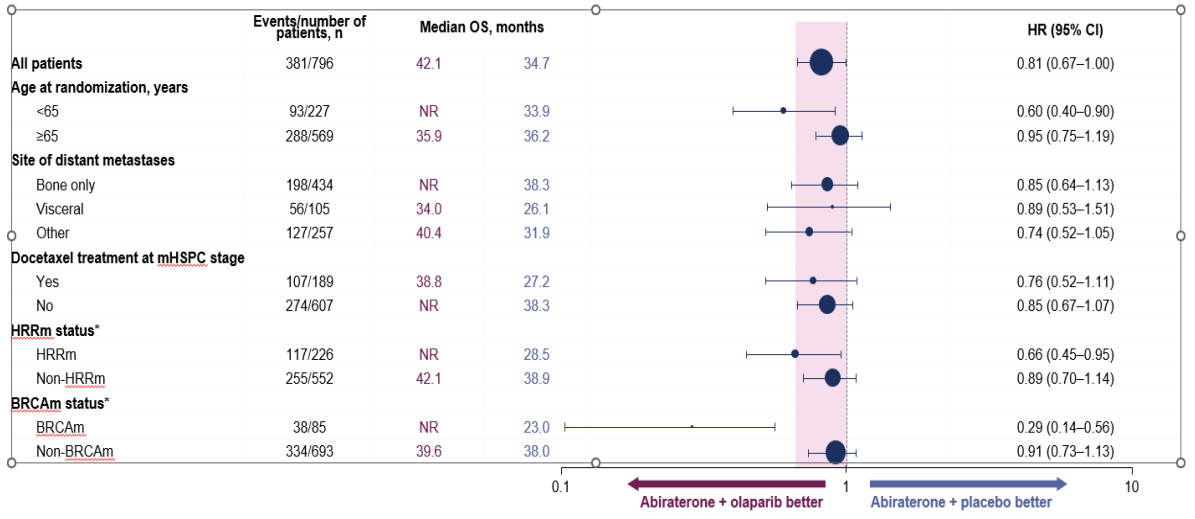
Pre-specified subgroup results

The subgroup results presented by the company showed [redacted]

Participants with BRCA 1 or 2 mutations

The company's clarification response provided results for patients with BRCA mutations [redacted] though not for patients without BRCA mutations. The EAG found the OS HR non-BRCA result in the Clarke ASCO[18] presentation supplied in the submission reference pack (Figure 3): HR 0.91 (95% CI: 0.73 to 1.13), indicating both a lack of a statistically significant treatment effect in the non-BRCA subgroup and a large difference in the relative treatment effect between the BRCA and non-BRCA subgroups.

Figure 3 PROpel subgroup analyses for OS (DCO3), reproduced from the Clarke ASCO presentation



More detailed BRCA subgroup results were recently published by the FDA.[9] Its Oncologic Drugs Advisory Committee recently advised restriction of the license for olaparib plus abiraterone in mCRPC to patients with BRCA positive tumours. The decision was based on concerns that efficacy

demonstrated in PROpel was largely attributable to patients with BRCA mutations, with modest benefit and possible harm for patients without BRCA mutations. The FDA considered that their post-hoc BRCA subgroup analyses were clinically relevant due to the strong and consistent predictive effect of BRCA mutation status for PARP inhibitors in prostate cancer and other cancers. In the FDA subgroup analyses, patients were divided into three groups based on tumour tissue and ctDNA testing results. Patients with positive results for BRCA by either tumour tissue or ctDNA testing were considered to have a BRCA mutation (11% of ITT. Patients those with negative results by both tests were considered to not have a mutation (54% of ITT), while patients with negative results by only one test or unknown results for both tests were considered to have undetermined BRCA status (35% of ITT).

The results reported in the FDA briefing document are replicated here in Table 9. The EAG concurs with the FDA's view that the analyses suggest that improvements in rPFS and OS in PROpel were heavily attributable to efficacy in the small BRCA mutation subgroup; there was no evidence of an effect on OS in the large non-BRCA mutation subgroup.

Table 9 PROpel results for rPFS and OS by BRCA mutation status* (reproduced from FDA briefing document)[9]

	IIT (N=796, 100%)		**BRCAm[1] (N=85, 11%)**		**Undetermined BRCA status[2] (N=284, 35%)**		**Non-BRCA[3] (N=427, 54%)**	
	Olaparib +AA/P	**Placebo + AA/P**	**Olaparib +AA/P**	**Placebo + AA/P**	**Olaparib +AA/P**	**Placebo + AA/P**	**Olaparib +AA/P**	**Placebo + AA/P**
rPFS (INV)								
Median in months (range)	25 (20, 28)	17 (14, 19)	NR (19, NR)	8 (6, 15)	NR (10, NR)	19 (14, 22)	22 (17, 25)	17 (14, 19)
HR (95%CI)	0.66 (0.54, 0.81)		0.24 (0.12, 0.46)		0.66 (0.46, 0.94)		0.85 (0.66, 1.11)	
rPFS (BICR)								
Median in months (range)	28 (20, NR)	16 (14, 19)	NR (NR, NR)	8 (4, 16)	NR (19, NR)	19 (14, 22)	20 (17, 28)	17 (14, 19)
HR (95%CI)	0.61 (0.49, 074)		0.19 (0.1, 0.37)		0.59 (0.41, 0.85)		0.82 (0.62, 1.08)	
OS								
Median in months (range)	42 (38, NC)	35 (31, 39)	NR (NR, NR)	23 (18, 34)	NR (40, NR)	38 (28, 39)	37 (33, NR)	38 (31, NR)
HR (95%CI)	0.81 (0.67, 1.00)		0.3 (0.15, 0.6)		0.73 (0.52, 1.03)		1.06 (0.81, 1.39)	

1 either ctDNA or tissue positive, 2 either ctDNA or tissue negative and other test unknown or both tests unknown, 3 both ctDNA and tissue tests negative

The FDA briefing document also commented on the PROpel trial design, stating that: "*Based on contemporary understanding of the importance of BRCA status as a predictive biomarker for PARP*

inhibitor efficacy, this trial design would be considered inappropriate today as the biomarker should have been prospectively evaluated." In summary, the FDA was concerned that, given the relatively long treatment duration, patients without BRCA mutations may receive ineffective treatment whilst being exposed to adverse events for a considerable amount of time.[9]

3.2.2.3 Adverse events

Safety results were reported in Section B.2.10.2 of the CS. The most frequently reported adverse events (AEs) of any grade were [redacted] in the olaparib plus abiraterone arm and [redacted] in the placebo plus abiraterone arm.

Treatment interruptions were more frequent with [redacted] more patients also required abiraterone interruptions in [redacted]. Dose reductions of olaparib were [redacted]. The occurrence of grade 3 or higher adverse events was greater with olaparib plus abiraterone (56%) than with placebo plus abiraterone (43%). Serious AEs were reported in [redacted] in the olaparib plus abiraterone arm and [redacted] in the placebo plus abiraterone arm.

3.3 Critique of trials identified and included in the indirect comparison

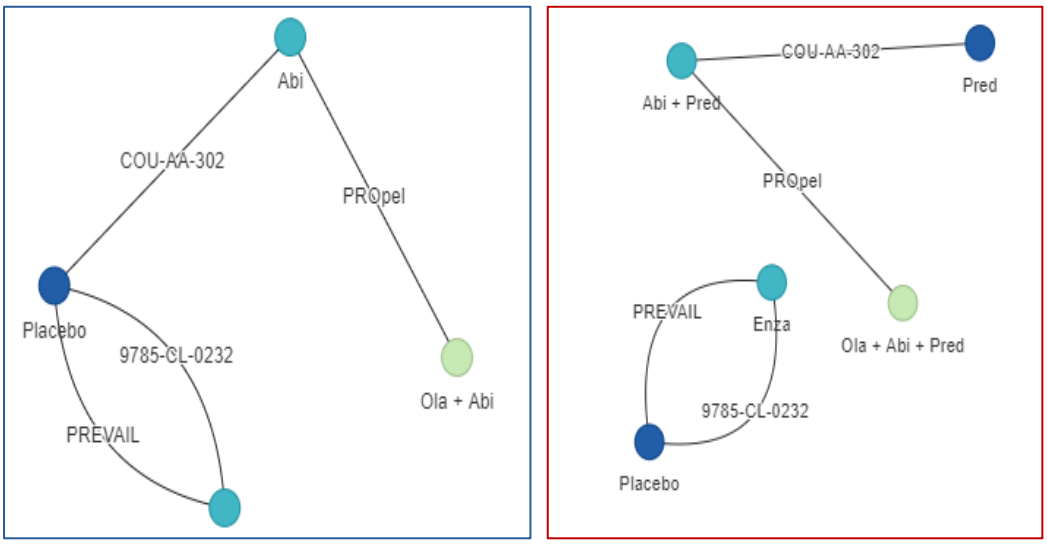
Company's approach to conducting network meta-analyses

Section B.2.9.1 of the CS with full details presented in Appendix D of the CS.

Four relevant RCTs were identified as relevant to the NMA: PROpel (which compared olaparib plus abiraterone vs placebo plus abiraterone), COU-AA-302 (abiraterone plus prednisone vs placebo plus prednisone), PREVAIL, and PREVAIL Asia (enzalutamide vs placebo). The network formed by the identified studies is depicted in Figure 9 of the CS and replicated here in Figure 4.

All patients in the placebo arms of COU-AA-302 and PROpel received corticosteroids (prednisone or prednisolone), which is expected, since abiraterone should be administered along with prednisone or prednisolone. However, this is higher than PREVAIL, where only 30% of the placebo group received corticosteroids. Although the comparator arms varied across these trials, the company considered it was reasonable to assume prednisone/prednisolone was equivalent to placebo for the purposes of OS comparisons. For rPFS, the company stated that the available evidence in the literature and clinical opinion suggested that it is plausible that treatment with prednisone may have a therapeutic effect. The company therefore thought that adoption of the control arm of the COU-AA-302 study as a proxy for placebo in a network may lead to underestimation of the treatment benefit of abiraterone and may benefit enzalutamide over abiraterone. Consequently, the company did not undertake an NMA for rPFS due to trial heterogeneity across the comparator arms.

Figure 4 Network of evidence for OS with (left) and without (right) the assumption that prednisone is equivalent to placebo (replicated from the CS, Figure 9)



Further trial heterogeneity

Table 4 in appendix D, section D1.1.2 of the CS presents the baseline data from the four identified trials. The submission notes some important differences in baseline characteristics including differences in Gleason score, median time since diagnosis, pain scores at baseline, and the presence of visceral metastases. HRR mutation was also not recorded in the abiraterone and enzalutamide trials, so the proportion of patients with HRR mutations is unknown in those trials. Gleason scores were a little higher in PROpel and PREVAIL Asia than in the COU-AA-302 and PREVAIL trials, with a higher proportion of patients scoring >8 at initial diagnosis (~66% for the former two studies vs ~52% for the latter two studies). The presence of visceral metastases was an exclusion criterion in COU-AA-302 but in the PREVAIL, PREVAIL Asia and PROpel studies patients with lung and/or liver metastases could be enrolled, with 10-15% of patients having visceral metastasis at baseline. Given that patients with visceral metastases tend to have a poorer prognosis than patients without visceral metastases, their exclusion from the COU-AA-302 trial may favour abiraterone in an NMA of OS. The CS also noted that the PROpel population was comprised of 19% of patients with moderate to severe pain scores (based on the brief pain inventory short form) at baseline, compared with 0-3% for the other trial populations. Finally, the CS noted that patients in the PROpel and PREVAIL Asia studies had lower median time since diagnosis (3 and 2.5 years, respectively) than patients in COU-AA-302 and PREVAIL (5.1 and 5.5 years).

The EAG notes further population heterogeneity across trials which may be important. There were differences in prostate-specific antigen levels, with PROpel (median PSA~17 ng/mL) and COU-AA-302 (median ~22 ng/mL) having notably lower prostate-specific antigen levels than PREVAIL (median ~50 ng/mL) and PREVAIL Asia (median ~60 ng/mL). Also, only around 80% of patients

had received prior hormonal cancer therapy in PROpel, compared to nearly all patients in PREVAIL and COU-AA-302 (data were not reported in PREVAIL Asia).

Other possible sources of heterogeneity between the studies were described in section B.2.9 of the CS. These included crossover/receipt of subsequent treatments following disease progression and differences in the definition of progression used across studies. There was a substantial difference in the proportion of patients crossing over to receive a subsequent NHA (i.e. abiraterone or enzalutamide) after progression, with 78% in the placebo arm of PREVAIL versus 54% in the placebo arm of COU-AA-302 receiving a subsequent NHA. The EAG considers this to be a particularly important heterogeneity issue, given that these patients were naïve to treatment with an NHA and are therefore likely to experience clinical benefit from subsequent treatment. This imbalance is very likely to bias survival estimates in favour of abiraterone over enzalutamide.

Trials were appraised using the Cochrane Risk of Bias tool (RoB 2). Both the COU-AA-302 trial of abiraterone and PREVAIL trial of enzalutamide were judged to be at high risk of bias due to the protocol permitting treatment crossover following disease progression.

3.4 Critique of the indirect comparison and/or multiple treatment comparison

The company undertook an indirect treatment comparison for overall survival between olaparib plus abiraterone with enzalutamide and abiraterone via the placebo/prednisone comparator. The OS network is depicted in Figure 4; results from the fixed-effect model is presented in Figure 10 of the CS with abiraterone as the reference treatment and replicated in Table 10 below. The results from the random effects model are consistent although the credible intervals are wide due to the influence of the vague prior for the between-study variance. The company, therefore, also implemented conducted a random effects model with an informative prior for the between-study heterogeneity which is presented in section D1.1.3 in Appendix D. The model fit summaries are presented in Table 20 of the CS and show the three models to be of similar fit. The indirect comparison was not directly used in the base-case economic model but was used to justify an assumption of a hazard ratio of 1 between enzalutamide and abiraterone (i.e. an assumption of efficacy equivalence).

Table 10: Company's NMA estimate for OS

Treatment comparison	Hazard ratio (95% credible interval)
Enzalutamide versus abiraterone	[redacted]
Olaparib plus abiraterone versus abiraterone	[redacted]
Placebo versus abiraterone	[redacted]

Points for critique

The EAG considers that the company has been inconsistent in its judgements on whether network transitivity assumptions are valid (i.e. whether the level of trial heterogeneity is low enough to justify running a NMA). On the one hand the transitivity assumption was judged not to be valid for rPFS (so no NMA was conducted) based on differences in corticosteroid use across placebo arms. Conversely, for OS, the transitivity assumption was judged to be valid, despite a considerable difference in subsequent NHA use across placebo arms. Given the clinical and methodological heterogeneity evident across several potentially important factors, the EAG considers that the transitivity assumptions have not been met, for both the rPFS and OS networks; the EAG therefore considers that the use of NMAs was not appropriate for deriving effect estimates for these comparisons.

As regards the company's OS NMA for enzalutamide versus abiraterone, although it is included as exploratory, it is nevertheless used by the company to justify using a hazard ratio of 1 in the economic model. The EAG considers this estimate to be unreliable due to the imbalance across the abiraterone and enzalutamide trials in the proportion of placebo participants receiving a subsequent NHA, differences in PSA levels, and the exclusion of patients with visceral metastases in the abiraterone trial (COU-AA-302). These differences mean that the estimate is likely to be biased in favour of abiraterone over enzalutamide. The EAG therefore anticipates that the HR result of [redacted] from the company's NMA would likely be <1 if this bias was absent. The EAG's evaluation of the real-world studies which compare enzalutamide with abiraterone broadly supports this observation (i.e. a HR<1, see Section 3.5 below), although uncertainty still remains.

3.5 Additional work on clinical effectiveness undertaken by the EAG

The company stated that real-world data and clinical expert opinion consistently indicate there is no difference in efficacy between abiraterone and enzalutamide in terms of rPFS or OS. In the absence of direct comparative RCT data, it therefore thought it reasonable to assume (within the economic analysis) that the relative efficacy estimates for the olaparib plus abiraterone versus abiraterone comparison observed in the PROpel trial could apply to a comparison of olaparib plus abiraterone versus enzalutamide.

Investigating the company's abiraterone versus enzalutamide equivalent efficacy assumption

The EAG identified a large study by Schoen et al 2022[16] which was at odds with the company's equivalent efficacy assumption. The EAG therefore asked the company (clarification question A7) how it identified the real-world evidence studies which compared abiraterone with enzalutamide. The company stated that it had conducted a systematic review, with searches run in November 2021 and studies critically appraised using the ROBINS-I tool. The review excluded patients who have previously received treatment for mCRPC. The ROBINS-I results were summarised in two lines, with

no further details provided; the extent of the biases affecting each of the studies could therefore not be appraised by the EAG.

The company's review identified three studies which reported OS hazard ratios which had been adjusted for possible confounders (Chowdhury et al,[15] Scailteux et al 2021 [19] and Tagawa et al[20]). The Chowdhury study, which was prospective, reported no significant difference between abiraterone and enzalutamide and the other two studies, which were retrospective, reported statistically significant differences favouring enzalutamide.

In their response to clarification A7, the company added that there is evidence that comorbid diseases and age can interact with treatments which affects survival, therefore the outcomes reported in the Schoen study (identified by the EAG) should be interpreted within this context. The company also stated that six clinical experts with significant experience in treating prostate cancer in the UK cautioned that abiraterone is not typically initiated in patients with cardiovascular disease or diabetes (reported in approximately 73% of the cohort in Schoen et al, 2022). With this in mind, the EAG notes that the Chowdhury et al study - which the company is partly basing its efficacy equivalence assumption on - is a similar cohort to the Schoen cohort in terms of comorbidity (65% cardiovascular disease, 17% diabetes) and age (both studies with mean ages in the abiraterone and enzalutamide groups of around 75 years). The EAG therefore considers the Schoen study to be equally relevant to the appraisal as the Chowdhury study.

Given the company's November 2021 search date, the EAG sought to update and broaden the company's review to identify peer-reviewed, published papers of non-randomised studies comparing abiraterone with enzalutamide in patients with mCRPC, regardless of the line of treatment. To be included in the EAG's review, studies had to report hazard ratios for OS and had to report using methods to adjust for possible confounding factors. Given the very limited time available, the EAG's searches were conducted via snowballing methods, beginning with the Chowdhury study (cited by the company). The EAG used Google Scholar's citation search facility and also scanned for relevant references in identified articles. Studies were evaluated if they were published between 2020-2023.

Nine studies (including the three identified in the company's review) were included in EAG's review (Table 11). Sample sizes ranged from 134 to 10,308 patients. All studies were retrospective, except for Chowdhury et al,[15] which recruited patients prospectively and consecutively from 199 centres across 16 countries. All studies adjusted their analyses for potential confounders by using multivariate Cox proportional hazards regression models and/or propensity score matching. Six of the nine studies reported statistically significant OS benefits favouring treatment with enzalutamide. One of these studies was funded by the manufacturer of enzalutamide.[20] Of the three studies which found no statistically significant difference in OS, one was funded and conducted by the manufacturer of

abiraterone (Chowdhury et al)[15] and the other two studies were the smallest studies identified and so may not have been adequately powered to detect significant difference.[21, 22]

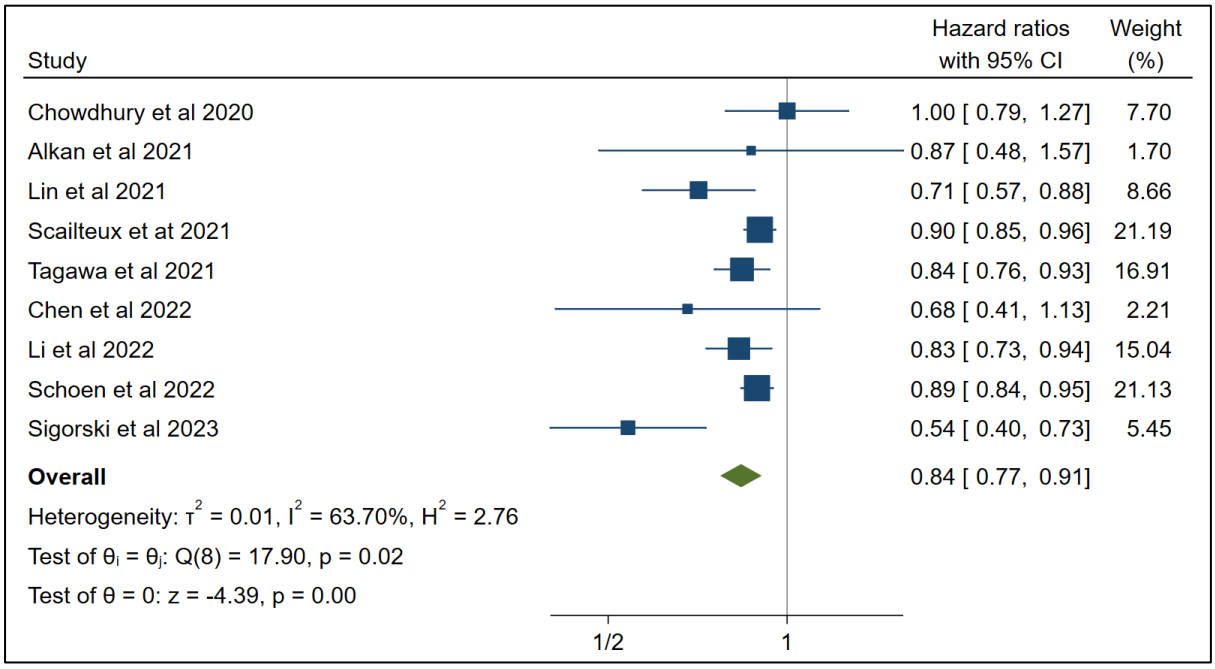
Table 11 Non-randomised studies comparing abiraterone with enzalutamide which report OS hazard ratios

Study	Funding	Study design	Setting and population	Sample Size		Confounder adjustment	OS HR (95% CI)
				Abir	Enza		
Sigorski et al 2023[23]	University	Retrospective	Poland. All post-chemotherapy	318	100	Multivariate Cox proportional hazards regression model	0.54 (0.40 to 0.73)
Li et al 2022[24]	University	Retrospective	Taiwan. Most had had prior chemotherapy. 24% diabetes, 15% CAD	1046	118	Propensity score matching. Multivariate Cox proportional hazards regression model	0.83 (0.73 to 0.94)
Schoen et al 2022[16]	Hospital	Retrospective	U.S. veterans. 26% previous docetaxel. 72% cardiovascular disease or diabetes.	3318	2504	Propensity score matching. Multivariate Cox proportional hazards regression model	0.89 (0.84 to 0.95)
Chen et al 2022[22]	Hospital	Retrospective	Taiwan. 16% diabetes, 8% Ischaemic heart disease	206	157	Multivariate Cox proportional hazards regression model	0.68 (0.41 to 1.14)
Lin et al 2021[25]	University	Retrospective	Taiwan. Chemotherapy naïve. 31% diabetes.	782	371	Propensity score matching. Multivariate Cox proportional hazard model	0.71 (0.57 to 0.88)
Tagawa et al 2021[20]	Pfizer & Astellas, conducted by STATinMED	Retrospective	U.S. veterans. All chemotherapy-naïve. ~31% diabetes	1945	1229	Multivariate Cox proportional hazards regression model	0.84 (0.76 to 0.94)
Alkan et al 2021[21]	No external funding	Retrospective	Turkey. All chemotherapy-naïve. Over 75s (median age 81). 19% Diabetes, 26% CAD. 46% ECOG 2-3	77	57	Multivariate Cox proportional hazards regression model	0.87 (0.48 to 1.56)
Chowdhury et al 2020[15]	Janssen, contributed to design, conduct and report writing	Prospective	Registry covering 16 countries. All chemotherapy-naïve. 65% cardiovascular disease, 17% diabetes	754	227	Propensity scores. Cox proportional hazards model with treatment as only predictor	1.00 (0.79 to 1.27)
Scailteux et at 2021[19]	French Drugs Agency	Retrospective	France. All chemotherapy-naïve. 17% diabetes, 11% ischaemic heart disease	6585	3723	Propensity scores as weights in Cox proportional hazards regression model	0.90 (0.85 to 0.96)

CI confidence intervals, Abir abiraterone, Enza enzalutamide, CAD Coronary artery disease, OS overall survival, HR hazards ratio

To synthesise the identified non-randomised studies the EAG conducted a pair-wise meta-analysis using random effects estimator, the results of which are reported in Figure 5. These results support an OS benefit in favour of enzalutamide; HR 0.84 (95% CI: 0.77 to 0.91).

Figure 5 Random-effects meta-analysis of OS



Overall, the EAG concludes that the results from these studies do not support the company's assumption that abiraterone and enzalutamide have equivalent efficacy. The EAG instead concludes that while there is uncertainty about the relative effectiveness of abiraterone and enzalutamide the balance of evidence indicates that enzalutamide is more efficacious. This is supported by both the randomised evidence accounting for the direction of the biases which will have affected the company's NMA (HR [redacted]) and the non-randomised evidence identified and synthesised in the EAG's meta-analysis (HR 0.84). To explore the impact of the company's equivalence assumption the EAG incorporates the results of the EAG's meta-analysis into the economic model, see Section 3.5 for further discussion.

3.6 Conclusions of the clinical effectiveness section

The evidence presented in the CS on the efficacy and safety of olaparib plus abiraterone is based on the results of the PROpel RCT, which has mature data on both rPFS and OS. The PROpel results showed that olaparib plus abiraterone produced a statistically significant improvement in rPFS when compared to abiraterone plus placebo. However, this did not quite translate into a statistically significant improvement in OS. Subgroup results raise concerns that the efficacy demonstrated in PROpel is largely driven by the effect seen in patients with BRCA mutations; there may be little benefit (rPFS) or even possibly no benefit (OS) in patients without BRCA mutations, together with

possible harm (in PROpel, grade ≥3 adverse event incidence was greater with olaparib plus abiraterone (56%) than with placebo plus abiraterone (43%)). Moreover, the PROpel trial may overestimate the relative survival benefits of olaparib plus abiraterone. Few patients in the PROpel trial ([redacted]) received subsequent treatment with olaparib monotherapy. Following TA887, olaparib monotherapy is standard of care on the NHS for patients with BRCA mutation which represented 11% of the PROpel trial population. A greater proportion of would therefore receive olaparib monotherapy in an NHS setting than observed in the PROpel trial with consequential impact on survival.

Clinical opinion, results from a real-world study, and results from the company's exploratory NMA of OS were all used by the company to justify an assumption that abiraterone and enzalutamide have equivalent efficacy in the economic modelling. No NMA was conducted for rPFS due to heterogeneity in trial populations including the greater use of corticosteroids in COU-AA-302 and PROpel compared with PREVAIL. Given the clinical and methodological heterogeneity evident across several potentially important factors, the EAG considers that the similarity (transitivity) assumptions were not met, for both the rPFS *and* OS networks; the EAG therefore considers that the use of NMAs of RCTs was not appropriate for deriving effect estimates for these outcomes.

The EAG also identified limitations in company's review of real-world (non-randomised) studies. The EAG therefore carried out additional work to expand and update the company's review, identifying nine studies in total. Meta-analysis of all identified evidence conducted by the EAG resulted in a statistically significant OS benefit favouring treatment with enzalutamide. The EAG considers that the results from the real-world (non-randomised) studies together with the NMA result of heterogeneous trials (which the EAG considers to be biased) do not support the company's assumption that abiraterone and enzalutamide have equivalent efficacy. The EAG instead concludes that, while uncertain, current evidence supports a survival benefit in favour of enzalutamide.

4 COST EFFECTIVENESS

4.1 EAG comment on company's review of cost-effectiveness evidence

The company undertook three systematic literature reviews (SLRs) to identify relevant economic evaluations, health-related quality of life (HRQoL), and cost and healthcare resource use measurement and valuation studies for patients with mCRPC in the first-line setting. These searches were conducted to 01 December 2022.

4.1.1 Search strategy

The original company submission included searches to identify cost-effectiveness studies for metastatic castration-resistant prostate cancer. The search strategies of supplementary sources were not documented in the original submission, but were supplied by the company upon request. The EAG were satisfied that the search strategy used was sufficient to identify existing cost-effectiveness, HRQoL, and cost and healthcare resource use studies.

4.1.2 Inclusion/exclusion criteria

Study eligibility criteria applied by the company were described in CS Appendix G for the review of economic evaluations, CS Appendix H for the quality-of-life studies, and CS Appendix I for the cost and healthcare resource use measurement and valuation studies. Full details of the eligibility criteria are included in the CS reference pack. In all cases, there was no language limit applied. Date limits were not applied except to exclude conference abstracts pre-2018. The characteristics of the population considered in all reviews were broadly similar to those in PROpel. At both the title/abstract review phase and the full publication review phase, studies were reviewed by two independent reviewers with discrepancies referred to a third analyst, where these were resolved by consensus.

The ERG considered the eligibility criteria and the company's assessment of identified studies against them to be generally appropriate.

4.1.3 Identified studies

The review of economic evaluations identified a total of 30 relevant studies for inclusion. These included 15 relevant published economic evaluations (13 full publications, 2 conference abstracts) and 15 HTA submissions. One of the publications was not extracted because it was an EAG perspective on TA387 – this was used to supplement the submission. This left 12 full publications that were extracted, three of which related to UK analyses. Of the 15 HTA submissions, 4 were NICE submissions.

The second review of HRQoL identified 30 relevant studies for inclusion. Two of these studies related to data specifically collected in the UK.

The third review of cost and resource use data identified 59 relevant publications for inclusion (35 full publications, conference abstracts). Of the full publications, one related to the UK (Scotland).

4.1.4 Interpretation of the review

The ERG considered the methods of the company's SLR sufficient to identify any existing cost-effectiveness analyses conducted in a relevant population and setting. As no relevant studies were identified by the review, the ERG is satisfied that the model presented by the company represents the most relevant analysis for decision making.

4.2 Summary and critique of the company's submitted economic evaluation by the EAG

4.2.1 NICE reference case checklist

Table 12 summarises the EAG's assessment of whether the company's economic evaluation meets the NICE reference case and other methodological recommendations.

Table 12 NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	QALY benefits for treated individuals were accounted for
Perspective on costs	NHS and PSS	An NHS and PSS perspective on costs was considered
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	A cost-utility analysis was implemented.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	The economic model adopted a 30-year (lifetime) time horizon. This suitably captured lifetime costs and benefits.
Synthesis of evidence on health effects	Based on systematic review	The company undertook a systematic review to identify relevant data sources. The company undertook an NMA of available trial evidence but this was not used in the model.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	Health effects were expressed in QALYs. Modelled health state utilities were based on EQ-5D-5L data were collected in the PROpel study. While the CS states EQ-5D-5L values were mapped to EQ-5D-3L, using the Hernández-Alava et al, this could not be confirmed by the EAG, and all further references made to HRQoL values used in the model refer to EQ-5D-5L values.

Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Reported directly from patients with mCRPC.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	HRQoL was not adjusted over time to reflect the impact of aging upon utility.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Costs based on UK sources including eMIT, BNF and NHS reference costs. Resource use based on previous appraisals and clinical advice.
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Costs and benefits were discounted at 3.5% per annum
PSS, personal social services; QALYs, quality-adjusted life years; EQ-5D, standardised instrument for use as a measure of health outcome.		

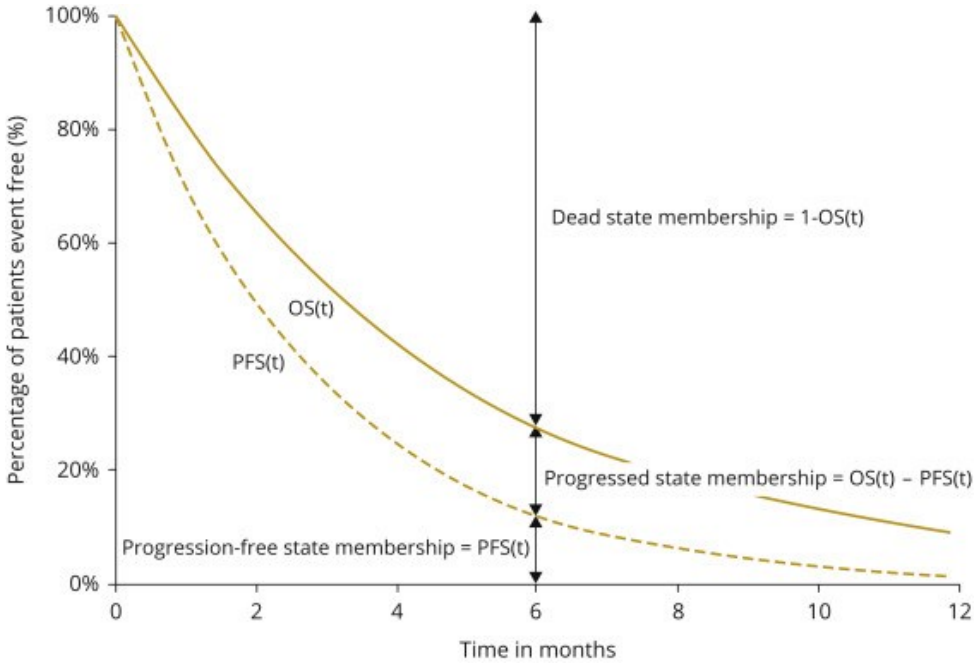
4.2.2 Model structure

The company submitted a partitioned survival model (PSM) to estimate the lifetime cost-effectiveness of olaparib in combination with abiraterone for the treatment of mCRPC. The PSM comprised three mutually exclusive health states: progression-free survival (PFS), progressed disease (PD), and Death. Modelled patients were allocated to receive either olaparib plus abiraterone, abiraterone, or enzalutamide. The model uses a cycle length of one month, and applies a half-cycle correction.

Patients enter the model in the PFS state and in each monthly cycle, patients can remain in this state, progress into PD, or progress to Death. Patients are not allowed to return to the PFS state once in the PD state. Transition probabilities were estimated from the trial outcomes of PFS and OS. Transition probabilities were estimated based on parametric models fitted to the observed PFS and OS data from the PROpel trial. Membership of the PD state was calculated as the difference between the proportion of patients in the PFS state and the Death state. Figure 6 provides a visual illustration of the calculation of model health state membership.

As stated in Section 3.5 the economic analysis assumed equivalence between abiraterone and enzalutamide, PFS and OS outcomes for patients receiving enzalutamide were therefore informed by parametric models fitted to the abiraterone arm of the PROpel trial. In the probabilistic analysis, the efficacy of enzalutamide is allowed to vary through the use of a hazard ratio centred at 1.0 versus abiraterone.

Figure 6 Partitioned survival model estimation of health state occupancy (CS Figure 14, Page 80)



Key: OS, overall survival; PFS, progression-free survival; (t), time

Points for critique

The EAG considers the three-state PSM structure adopted by the company to be appropriate for use in decision-making and is consistent with previous TA in this indication. The PSM structure, however, is limited by its capacity to represent the effectiveness of sequences of treatments not observed in the pivotal trial. As discussed in Section 3.2.1, the use of olaparib monotherapy in the comparator arm in only a very a small proportion of patients may underestimate its real-world effectiveness, and thus overestimate the cost-effectiveness of olaparib. While the impact of this issue may be small in the whole population (due to the relative rarity of BRCA mutation), it may render the current model structure entirely incapable of representing the cost-effectiveness of olaparib in mutation-driven subgroups, where it would be expected that the majority of patients would subsequently receive treatment with olaparib monotherapy. While precise figures for incremental QALY gain on olaparib monotherapy vs SoC in TA887 were redacted, estimates available in Committee papers range between 0.33 and 1.03. As a consequence, the present model structure may fail to capture QALY benefits of this magnitude on the comparator arm. If the Committee is to consider the BRCA subgroup analysis, an alternative model structure based on Markov model/state transition approach may be appropriate, as it would allow evidence on post-progression survival from PROfound trial to be incorporated, which may more fully represent outcomes following progression than PROpel.

4.2.3 Population

The modelled population is based upon the PROpel phase 3 trial data (n=796) and considers adult patients with mCRPC in whom chemotherapy is not clinically indicated. This population fully aligns with the marketing authorisation for olaparib in combination with abiraterone (and prednisone or prednisolone) and the NICE scope. The baseline characteristics of the modelled population are presented in Table 13, and include mean patient weight and BSA which were used to inform dosing associated with weight- and BSA-based therapies.

Table 13 Baseline patient characteristics of modelled population

Mean age	69.1
Mean weight	82.7 kg
Mean BSA	1.9m^2

The NICE scope listed several subgroup analyses that should be explored where evidence allows. This included subgroups based on HRR, BRCA1/2 and ATM gene mutations. The company included an exploratory analysis in the subgroup of patients with HRR mutation (28% of included patients) as requested in the NICE scope but did not include analysis by either BRCA or ATM gene mutation status. This was justified on the grounds that there was low prevalence of individual mutations in the PROpel trial. In response to a request from the EAG, the company provided a subgroup analysis in the BRCA sub-population, which comprised 10.7% of the PROpel population.

Points for critique

Eligible population

The licenced indication for olaparib plus abiraterone is adult patients with mCRPC in whom chemotherapy is "not clinically indicated". As discussed in Section 2.2.3, the EAG is unclear on how this should be interpreted and whether this matches exactly with the population recruited to the PROpel trial. In the company's clarification response, the company explained that this population consisted of multiple distinct groups, including patients in whom retreatment is not permitted following treatment at an earlier disease stage, patients who are not fit to receive docetaxel and patients in whom docetaxel is contraindicated. As previously discussed, this potentially rules out a substantive proportion of the population recruited to PROpel, as approximately 25% of the PROpel trial population meet these criteria. As such, it is unclear whether the modelled population is representative of patients who would be eligible for olaparib plus abiraterone in NHS practice.

Subgroup analysis

HRR-related mutations in prostate cancer, the most prevalent being BRCA mutation, have significant implications for treatment decisions due to affected tumours' sensitivity to PARP inhibitors such as

olaparib. The PROpel ITT population were not prospectively evaluated for, or stratified by, mutation subtype (including BRCA), which was instead determined following randomisation.

Pre-planned subgroup analysis on HRR mutation status indicated that olaparib may be less effective in the non-HRR mutation subgroup (OS HR 0.89, 95% CI 0.70 – 1.14), defined as patients confirmed to be non-HRR mutation and those with unknown HRR mutation status, compared to the HRR mutation subgroup (OS HR 0.66, 95% CI 0.45 -0.95). The EAG is concerned about the generalisability of the overall results of the PROpel trial in a heterogenous population with regards to the distribution oncogenic driver mutations, given that efficacy is likely largely attributable to a stronger treatment effect in a smaller biomarker subgroup. At the clarification stage the company provided a cost-effectiveness exploratory analysis of olaparib in patients in the non-HRR mutation subgroup. The model was updated to incorporate parametric models of PROpel non-HRR mutation subgroup based on the final data cut (DCO3). In the non-HRR mutation subgroup, olaparib plus abiraterone generated a QALY benefit of [redacted] at an ICER of [redacted] compared to abiraterone and [redacted] compared to enzalutamide. QALY gains were higher in the HRR mutation subgroup at [redacted] at an ICER of [redacted] compared to abiraterone and [redacted] compared to enzalutamide. Subgroup results are detailed further in Section 5.2.2.

The NICE scope also specified the patient population with BRCA mutations as a subgroup to be considered. As discussed in Section 0, BRCA mutation status is a key predictive biomarker for PARP inhibitor efficacy. This is evident in recommendations for olaparib monotherapy that advise treatment only in adult mCRPC patients with BRCA mutations who have progressed following prior therapy that included a new NHA (TA831). Furthermore, evidence from the PROfound trial which underpins this recommendation suggests that olaparib is more effective in patients with BRCA mutations compared to other subgroups. As discussed in Section 0 contrary to the PROfound trial, the PROpel population was not stratified based on BRCA status, which may highlight the clinical relevance of the BRCA subgroup analyses, stemming from the robust and consistent predictive impact of BRCA mutation status on PARP inhibitors. The company however provided post hoc analysis of OS and rPFS in the BRCA subgroup, and integrated these results into the model following clarification as discussed in Sections 4.2.6.2 and Section 0.

As of June 2023, olaparib plus abiraterone has received FDA approval for the treatment of mCRPC BRCA mutation-positive patients only. This is based on PROpel subgroup data which in exploratory analyses demonstrated that improvements in rPFS and OS in PROpel were heavily attributable to efficacy in the small BRCA mutation subgroup with little evidence of an effect on OS in the large non-BRCA mutation subgroup, see Section 0. Reflecting on this decision by the FDA, the EAG requested a further scenario analysis exploring cost-effectiveness specifically in the BRCA subgroup,

presented in Section 5.2.2. Parameterisation of BRCA subgroups in the company's updated model is explored further in Section 4.2.6.

The substantial heterogeneity in treatment effect within the whole population according to prospectively identifiable prognostic markers is an important signal that a recommendation on the basis of average cost-effectiveness (and indeed clinical effectiveness) presents a risk to patients. There is a clear clinical and biological rationale behind the expectation of superior effectiveness of olaparib in patients with BRCA mutations, and evidence suggestive of little to no additional benefit in patients without these gene alterations. The EAG therefore considers assessments of cost-effectiveness across the whole population to be potentially misleading, which instead should be assessed across individual sub-populations. As discussed in Section 0, the vastly differing risk/benefit profile and cost-effectiveness of olaparib on the basis of HRR mutation/BRCA mutation-status may mean it is unlikely that clinicians would be comfortable with using olaparib in this population without determining mutation status information beforehand through screening.

4.2.4 Interventions and comparators

In line with the PROpel trial, and as per the marketing authorisation granted on 15th March 2023, the modelled intervention is olaparib in combination with abiraterone (and prednisone or prednisolone). Dosing for the intervention was modelled in line with the relevant SmPCs, which is 300mg (2 x 150mg tablets) of olaparib taken twice daily, and 1000mg of abiraterone taken once daily with 5mg prednisone or prednisolone taken twice daily, all administered orally. When used in this combination, olaparib is to be continued until disease progression or unacceptable toxicity. Decisions regarding continuation of treatment for each component of this combination drug can be made independently, e.g., a patient may discontinue olaparib due to toxicity but continue taking abiraterone.

The NICE scope identifies enzalutamide and abiraterone with prednisone or prednisolone as relevant comparators. The company modelled enzalutamide as the primary comparator and abiraterone as the secondary comparator, reasoning that there is greater (and growing) use of enzalutamide in clinical practice. As justification, the company cited Blueteq requests in 2022 which indicated that enzalutamide accounted for 67% of total initiations compared to 33% for abiraterone. The comparators are also administered and dosed in line with their relevant SmPCs and are given until confirmed disease progression or unacceptable toxicity. No other stopping rules are applied in the model. The modelled dosing regimen for enzalutamide is 160mg (4 x 40mg soft capsules) as a single oral daily dose, and for abiraterone is 1000mg (2 x 500mg tablets) once daily without food, taken with prednisolone at 5mg twice daily, both administered orally.

Points for critique

Consideration of enzalutamide as primary comparator

The EAG does not consider it appropriate to designate a single primary comparator. As acknowledged in the CS, a substantive proportion of patients continue to receive abiraterone in NHS practice. Moreover, the Blueteq request data used to by the company to justify designating enzalutamide as the primary comparator on Blueteq request data drawn from a period which overlapped with the Covid-19 pandemic. During this period, NHS England revised its interim guidance on treatment options to focus on enzalutamide as initial therapy for newly diagnosed patients, suggesting a lower infection risk and thus reduced monitoring requirements. It is therefore unclear whether this pattern of prescribing will be reflective of future clinical practice.

Importantly, as discussed in Section 2.3.3 the EAG considers that the majority of patients are likely to be eligible for both treatment options with choice of one over the other largely determined by the preferences/experience of current the treating clinician. At the clarification step, the EAG therefore requested that the company present all comparators in a fully incremental format, per the NICE reference case. The company response updated the model to reflect fully incremental results which are presented in Section 5.2.2.

Availability of generic abiraterone

A licensed version of generic abiraterone for use in prostate cancer has been available on the NHS since late 2022, which costs significantly less than the proprietary product, and is a fraction of the cost of enzalutamide. In their clarification response, the company argues that this will likely not impact future trends in uptake of enzalutamide and abiraterone in clinical practice. Clinical advice to the EAG highlighted the relevance of cost in clinician choice between enzalutamide and abiraterone, which may influence ongoing trends in uptake which would not be captured in the Blueteq data obtained by the company. While transition of patients to the generic form may influence treatment decisions on an individual patient basis, the EAG also recognises that this may not be the key driver of prescribing trends in all patients, considering that treatment choice can be dependent on patient comorbidities or contraindications.

4.2.5 Perspective, time horizon and discounting

Consistent with the NICE methods guide,[26] the company's analysis adopted a NHS and Personal Social Services (NHS & PSS) perspective and discounted costs and benefits at a rate of 3.5% per annum. The impact of alternative discount rates was not explored in the analysis. Discounting was applied based on an annual discounting period, i.e. the discount factor was calculated according to the number of whole elapsed years, rather than being calculated on a continuous basis in each model cycle. This can potentially result in 'under-discounting' of costs and benefits and may skew the total apparent costs and benefits of interventions with different temporal distributions of cost accrual. The

EAG explored the impact of applying a continuously derived discount rate in the model with only minor differences noted compared with the company's analysis.

A lifetime horizon of 30 years was chosen for the base-case analysis. Scenario analysis explored the effects of using a shorter 20-year time horizon. Across all extrapolated parametric curves modelling OS, the model predicts ~0% survival at 30 years. Thus, the use of a lifetime horizon is considered appropriate by the EAG to account for the claimed impact of olaparib plus abiraterone on overall survival and progression free survival.

4.2.6 Treatment effectiveness and extrapolation

As discussed in detail in Section 4.2.2, the company used a PSM consisting of three health states: PFS, PD, and death. Consistent with this model structure, OS and PFS survival curves were used to calculate the health state membership based on observed OS and PFS data from the PROpel trial using data from the final data cut (DCO3, 12 October 2022). Due to a lack of appropriate data on the efficacy of enzalutamide, the analysis assumes that enzalutamide and abiraterone have equivalent efficacy.

To inform the model health state transitions, and cost and resource use, it was necessary to extrapolate the available PFS, OS, and TTD data observed in the trial (see Section 4.2.8). This was achieved using simple parametric models. The procedure for each extrapolation was similar for all three outcomes. The extrapolated survival curves inform patient membership of model health states, where membership of the Death and PFS states are informed by the survival curves themselves, and PD state membership is calculated as the difference between the proportion of patients in the PFS state and the Death state.

4.2.6.1 Clinical equivalence of abiraterone and enzalutamide

As described in Section 3.5, the company stated in their submission that 'all available evidence' indicates that enzalutamide and abiraterone are of equivalent efficacy. Further, the company implements a network meta-analysis of identified RCTs which suggest no meaningful numerical or statistically significant difference in efficacy between abiraterone and enzalutamide. In response to a clarification request by the EAG, the company provided a systematic literature review in support of this assumption. However, the company's focused upon a single real-world study (funded by the manufacturer of abiraterone) in support of this assumption, which suggested clinical equivalence of abiraterone and enzalutamide. Six clinicians consulted by the company agreed that in their practice they had observed no clinically meaningful differences with respect to efficacy between the two drugs.

Points for critique

As previously discussed in Section 3.5 the EAG carried out a rapid review comparing abiraterone and enzalutamide. This review identified several recent retrospective studies either not included in the company's systematic review or published after the date of the company's systematic searches (November 2021). These studies included several large European cohort studies recruiting several thousand patients or more. A meta-analysis of these studies (carried out by the EAG) indicated the existence of a statistically significant OS benefit in favour of enzalutamide; HR 0.84 (95% CI: 0.77 to 0.91).

Whilst the EAG acknowledges the lack of appropriate RCT evidence comparing abiraterone and enzalutamide and the clinical opinion received by the company with respect to the relative effectiveness of enzalutamide and abiraterone, the weight of real-world evidence suggests that enzalutamide is associated with a statistically significant survival benefit. And while it is important to acknowledge the limitations of these real word studies, taken at face value they indicate that the company's base-case assumption is inappropriate, and does not adequately reflect the balance of evidence. Given the importance of the efficacy of enzalutamide as a driver of the cost-effectiveness of olaparib, the EAG explores the uncertainty in the equivalence assumption and presents a scenario in Section 6 in which the results of the EAG's meta-analysis are incorporated into the economic model.

4.2.6.2 Treatment effectiveness in BRCA and HRR subgroups

The NICE scope highlighted BRCA mutation patients as a subgroup to be considered. The company reasoned in their submission that as specific mutation types were not pre-specified for analysis or prospectively tested for in the PROpel trial, this subgroup analysis should not be presented. The company also reasoned that the pre-specified subgroup analyses based on HRR mutation status were sufficient to demonstrate the consistent efficacy of olaparib plus abiraterone across patients with and without HRR mutations. In light of the recent recommendation of olaparib monotherapy only in BRCA patients, the FDA approval confined to this patient group (See Section 0), and the non-significant effect on OS observed in PROpel, the EAG requested that the company explore subgroup effects within the HRR mutation population itself, i.e. in patients with BRCA1 and 2 mutations. Whilst this was a non-stratified, *post hoc* analysis in a relatively small number of patients, in the BRCA subgroup, olaparib generated a large and significant treatment effect for OS (HR (HR 0.29 [95% CI 0.14 to 0.56]) and PFS (HR [redacted]The EAG also requested that these results be integrated into the economic model. The parameterisation of the BRCA subgroup results is discussed in further detail below.

Points for critique

As discussed above, the BRCA subgroup was not prespecified in the PROpel trial. As a result, this was a non-stratified, *post hoc* analysis and contained a small number of patients. The EAG agree with

the FDA's assessment that this a flaw in the design of the PROpel trial, given the clinical and biological rationale for an enhanced treatment effect in this subgroup. Despite the limitations of PROpel, the large and significant treatment effect for OS and PFS means that the EAG consider this a relevant subgroup for the purpose of this analysis.

The CS states that pre-clinical studies have demonstrated that the addition of abiraterone leads olaparib to exert an anti-tumour effect in mCRPC irrespective of BRCA1/2 or other homologous recombination repair (HRR) mutations. This is, however, is not supported by trial evidence. Comparison of the OS HRs for olaparib plus abiraterone and placebo plus abiraterone in the BRCA and non-BRCA subgroups suggests that any treatment benefit in the whole population is largely driven by the effectiveness of olaparib in BRCA patients, with an HR of 0.24 (95% CI 0.12 to 0.46) compared to that in the non-BRCA patients of 0.85 (95% CI 0.0.66 to 1.11).

When substantial differences exist in treatment effectiveness between prospectively identifiable subgroups it is important to examine the cost-effectiveness of the intervention in both subgroups. The EAG considers that BRCA mutation status is likely to be an important driver of cost-effectiveness as borne out by scenario analysis conducted by the company (see Section5) and that pooling these populations, as has been done in the company's base-case analysis, fails to recognise the potential for heterogeneity in cost-effectiveness estimates across these two populations. The ERG considers that further efforts to explore this uncertainty are necessary to establish the cost-effectiveness of Olaparib combination treatment in both BRCA and non-BRCA patients.

4.2.6.3 Overall survival (OS) extrapolation

The observed OS data from the PROpel trial was obtained from the final data cut (DCO3, 12 October 2022) for a median follow-up of 36.5 months, where the OS data were 47.9% mature (381 events/796 patients). At DCO3, in the olaparib plus abiraterone arm, 44.1% of patients had died compared with 51.6% of patients in the placebo plus abiraterone arm. The OS KM data were then extrapolated using standard parametric models.

To extrapolate available OS data, the company fitted independent models to both arms independently following tests which established that the proportional hazards assumption may not hold. The company selected models on the basis of visual fit, statistical fit in terms of Akaike information criterion (AIC) and Bayesian information criterion (BIC), the desire for a common functional form of models to both arms, external validation against observed trial data, and clinical validation using experts.

The AIC and BIC for each of the models fitted to PROpel Kaplan-Meier (KM) curves for OS can be seen in Table 14 Goodness of fit (AIC + BIC) of parametric distributions for OS (CS Table 27, page

85). A comparison of each model against the underlying KM curve can be seen in Figure 7 and Figure 8.

Table 14 Goodness of fit (AIC + BIC) of parametric distributions for OS (CS Table 27, page 85)

	Olaparib + Abiraterone				Placebo + Abiraterone			
	AIC	BIC	AIC+BIC	Rank	AIC	BIC	AIC+BIC	Rank
Exponential	1828	1832	1830	6	2051	2055	2053	6
Weibull	1810	1818	1814	4	2003	2011	2007	2
Lognormal	1803	1811	1807	1	2012	2020	2016	4
Log logistic	1806	1814	1810	2	1999	2007	2003	1
Gompertz	1821	1829	1825	5	2020	2028	2024	5
Gen. Gamma	1805	1817	1811	3	2003	2015	2009	3

Figure 7 OS parametric extrapolation for olaparib plus abiraterone (CS Figure 17, Page 84)

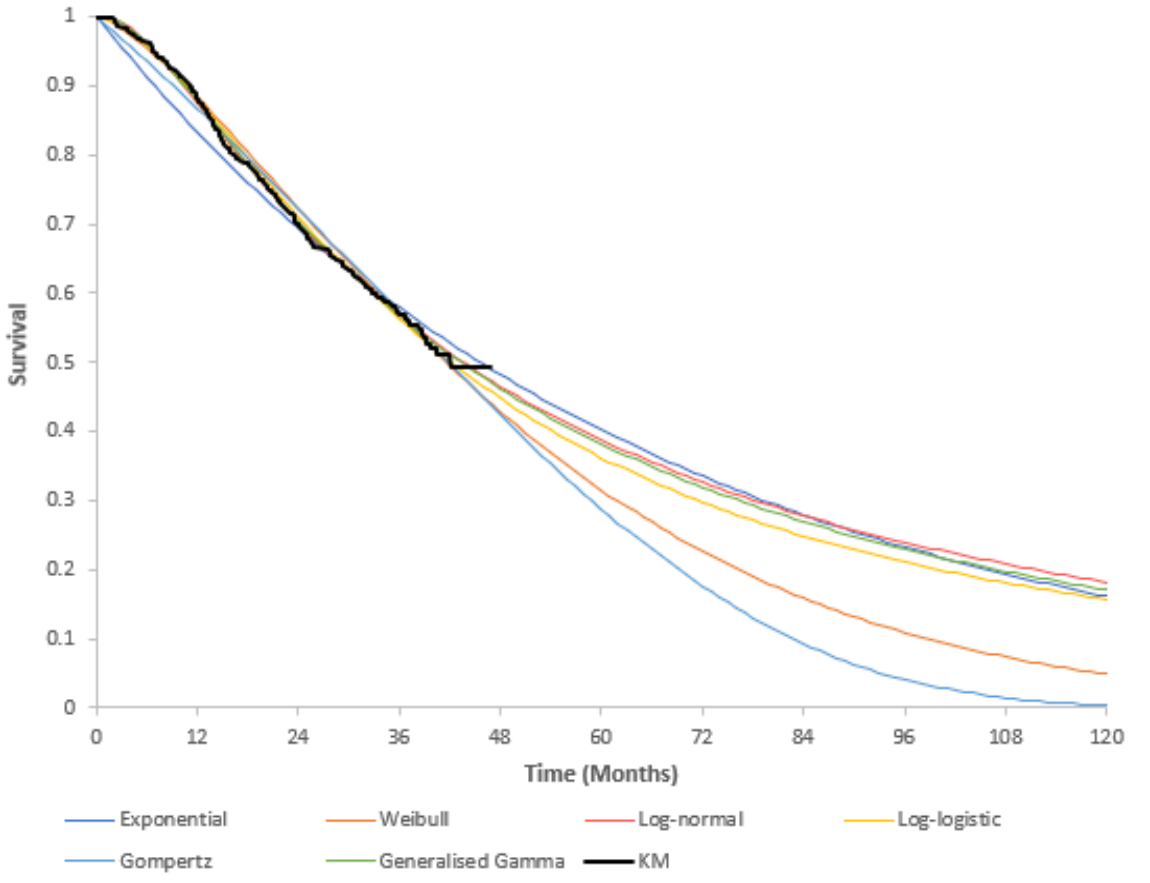
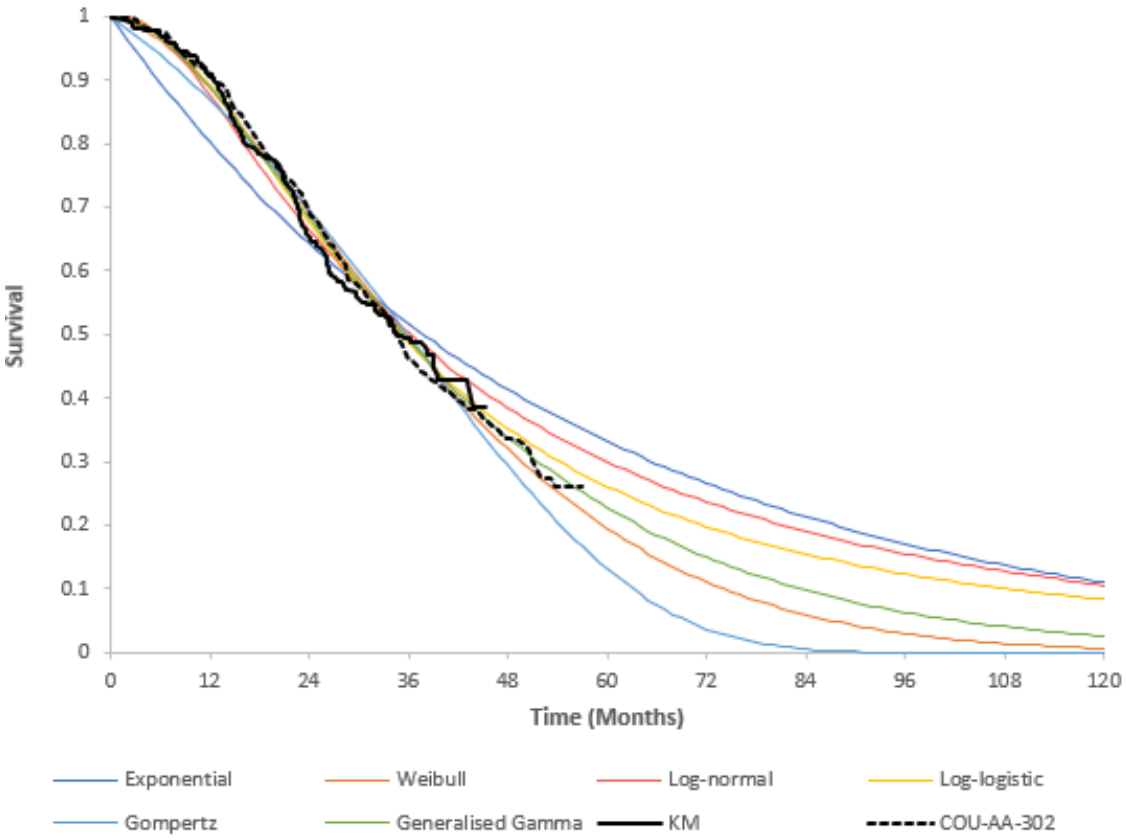
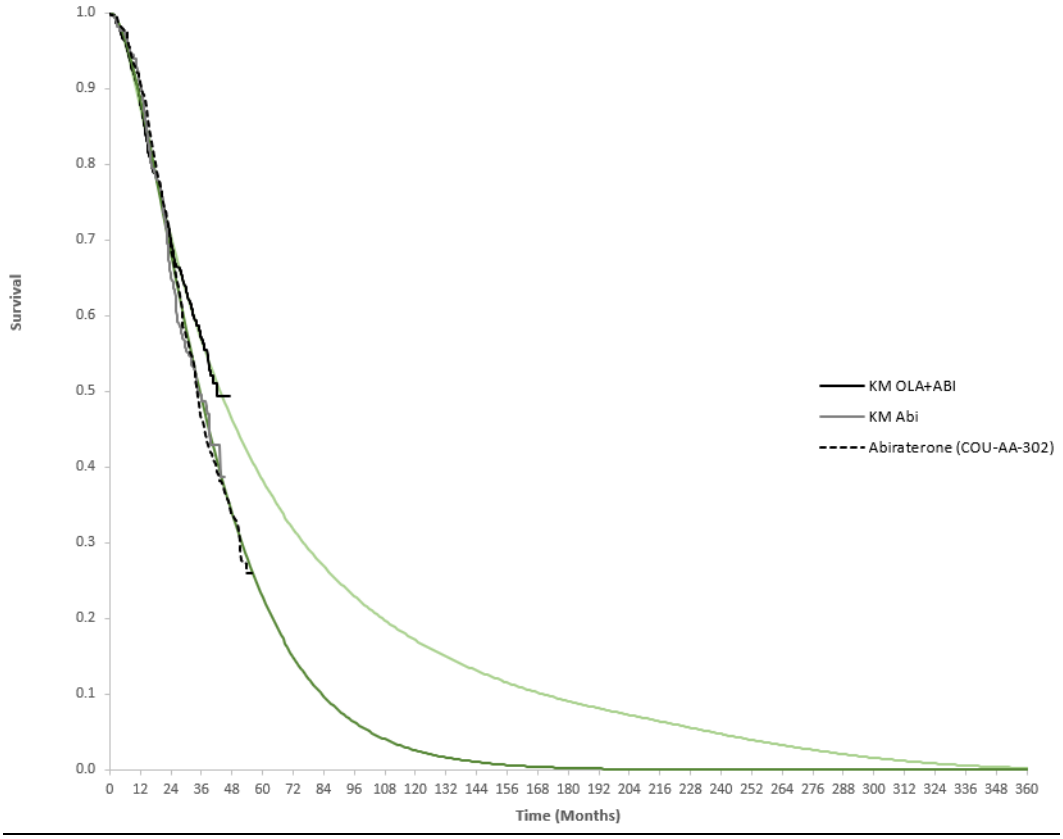


Figure 8 OS parametric extrapolation for abiraterone (CS Figure 18, Page 84)



The company selected the generalised gamma distribution for the base-case analysis (see Figure 9 for visual fit to KM data). Scenario analysis was also presented using the log-logistic distribution (considered the 2nd choice curve by the company). The log-logistic curve performed better than the generalised gamma curve in terms of statistical fit (AIC/BIC). In justifying the selection of the generalised gamma curve, the company cited the difference in the shape of hazards between the two arms along with the desire for a common distribution across both arms, and therefore the need for a functional form that allows for flexibility in the underlying pattern of hazards. The company also highlighted the superior fit to observed olaparib data at key time points of the generalised gamma compared to the log-logistic.

Figure 9 Modelled OS (base case analysis) for OLA+ABI and ABI (CS Figure 21, Page 89)



The company also compared the performance of each model fit against mortality milestones reported by the PROpel and COU-AA-302 trial (shown in

Table 15), as well as against the OS outcomes reported by the PREVAIL study which investigated enzalutamide versus placebo. The PREVAIL study had data available up to a ~6.5-year follow-up and at this landmark, showed 13.3% of patients were still alive in the enzalutamide arm. The company state that of the curves, the generalised gamma curve was most consistent with this landmark, predicting 11.9% of patients alive at 6.5 years.

They also sought clinical validation of 10-year estimates of OS where their clinical experts deemed the generalised gamma curve to produce the most reasonable 10-year estimates of OS for the abiraterone arm (~2-3% would be alive at 10 years).

Table 15 Comparison of OS predictions produced by alternative parametric models (CS Table 28, Page 86)

	Olaparib + Abiraterone					Placebo + Abiraterone				
	Year 1	Year 2	Year 4	Year 10	Median (mth)	Year 1	Year 2	Year 4	Year 10	Median (mth)
PROpel	88.2%	70.2%	49.3%	-	42.1	90.6%	65.5%	38.7%	-	34.7
COU-AA-302	-	-	-	-	-	91.3%	69.7%	33.7%	-	34.7
Exponential	83.3%	69.5%	48.2%	16.2%	45.0	80.2%	64.3%	41.4%	11.0%	37.0
Weibull	88.4%	72.4%	42.9%	4.9%	41.0	88.7%	69.2%	32.1%	0.6%	35.0
Lognormal	87.6%	70.4%	46.6%	18.2%	43.0	87.5%	66.6%	38.5%	10.6%	36.0
Log-logistic	88.3%	71.2%	44.8%	15.7%	42.0	89.0%	67.7%	35.3%	8.4%	35.0
Gompertz	86.8%	72.3%	42.4%	0.4%	41.0	86.8%	69.7%	29.4%	0.0%	35.0
Generalised Gamma	87.7%	70.5%	46.2%	17.1%	43.0	88.7%	68.3%	33.8%	2.6%	35.0

Points for critique

Choice of parametric extrapolation - OS

The EAG considered the company's choice of model for extrapolation of OS in the whole-population base case to be broadly appropriate, with some points noted. The generalised gamma curve was chosen by the company despite its inferior statistical fit compared with the log-logistic model, which performs marginally better in terms of AIC and BIC for both arms of the trial (see Table 14). The company's justification for selection of the generalised gamma curve was based on a desire for a common functional form between arms, and a flexible functional form that accounts for the different underlying pattern of hazards between treatment arms. In their clarification response, the company added that the estimates predicted by the generalised gamma were marginally better aligned to the observed data in PROpel for olaparib. The EAG considers this justification to be broadly appropriate, but notes that the generalised gamma curve under-predicts landmark OS on abiraterone in the PROpel study in a similar way to the under-prediction of olaparib OS using the log-logistic curve. In this manner it seems that both the log-logistic and generalised gamma curves are comparable statistically and visually, but the generalised gamma curve is a better (and more flattering) fit to olaparib, whilst the opposite may be said to be true for the log-logistic curve and abiraterone.

In addition, the EAG note that 10-year predictions from the model differ based on predictions from the generalised gamma and log-logistic models (2.6% vs 8.4%). Clinical advice sought by the company deemed these estimates to be reasonable predictions of long-term OS. The EAG's clinical advisor suggested 10-year survival estimates of between 8-10% are likely for current care options – an estimate more in line with the predictions generated by the log-logistic curve. The company noted only minor differences in the scenario analysis examining the impact of the log-logistic curve on cost-effectiveness. However, the EAG considers the log-logistic curve a plausible alternative to the generalised gamma, and therefore highlights this in a scenario analysis in Section 6.1. This issue may

require further clinical input to help inform the choice of survival curve in terms of long-term survival achieved on current care options.

4.2.6.4 Subsequent treatments

Due to the multinational design of PROpel trial, the distribution of subsequent therapies received post-progression by patients in the trial do not reflect clinical practice in the UK. This most notably includes retreatment with an NHA (or treatment with a different NHA) – with [redacted] of patients retreated with abiraterone, and [redacted] of patients treated with enzalutamide after progressing on olaparib and abiraterone. If these treatments are efficacious in improving post-progression survival, the OS outcomes reported in the trial might not reflect OS outcomes in the NHS population.

The company cite clinical expertise stating that retreatment with NHAs were unlikely to improve survival outcomes. However, the EAG received clinical advice which suggested there may be some clinical utility (albeit non-cost-effective) of NHAs in these patients.

Points for critique

As discussed in Section 3.4, the EAG had concerns regarding the applicability of the PROpel population in terms of the proportion of subsequent therapies they received following disease progression. Following disease progression, [redacted] received an NHA. The EAG's clinical advisor stated that the clinical benefit of NHA re-treatment is likely to be small and short-lived.

Furthermore, in the NHS population, patients with a BRCA1 or BRCA2 mutation who have progressed after a NHA are eligible for olaparib monotherapy. In PROpel, [redacted] of patients in the abiraterone plus placebo arm were treated with olaparib monotherapy following progression; this is notably different to the proportion of patients who had a BRCA mutation (around 10%). Therefore, in PROpel, the OS results for the abiraterone arm may underestimate that expected in the NHS cohort.

4.2.6.5 HRR mutation subgroup analysis - OS

The company presented a detailed description of the subgroup analysis conducted in the HRR-mutated population of the PROpel trial in Appendix E to the company submission. There was poor agreement between treatment arms in the statistical fit of each parametric model. The company again selected the generalised gamma curve to extrapolate OS in the HRR mutation subgroup, which was ranked sixth out of six curves for olaparib plus abiraterone, and third of six for the placebo plus abiraterone arm.

The EAG also requested that the company incorporate the non-HRR mutation subgroup analysis into the economic model, to explore the cost-effectiveness of olaparib in patients without HRR mutations at baseline. The lognormal curve had the best statistical fit to OS in both treatment arms, and was

therefore selected for use in this scenario analysis. As detailed in Section 5, olaparib plus abiraterone generated only [redacted] incremental QALYs in the company's preferred analysis of the non-HRR mutation subgroup, compared to [redacted] incremental QALYs in the HRR mutation population.

Points for critique

The EAG agrees on balance that the company's approach to extrapolation of OS in the two HRR mutation-based subgroups is reasonable.

4.2.6.6 BRCA1/2 subgroup analysis – OS

Since olaparib monotherapy is only recommended in patients with BRCA1 or 2 mutations, the EAG requested results for the subgroup (clarification question A4) (HR 0.29 [95% CI 0.14 to 0.56])). The EAG also requested a scenario analysis incorporating the results from the BRCA subgroup into the model (clarification question B6). In response, the company fitted parametric models to the observed Kaplan-Meier data for this subgroup using the same procedure as for the full population. The log-normal distribution was selected by the company based on statistical fit (AIC/BIC), as shown in Table 16.

Table 16 Goodness-of-fit (AIC/BIC) on OS parametric distributions of each treatment arm in BRCA subgroup (PFC Response Table 14)

	Olaparib + abiraterone				Placebo + abiraterone			
	AIC	**BIC**	**AIC+BIC**	**Rank**	**AIC**	**BIC**	**AIC+BIC**	**Rank**
Exponential	151	153	152	1	230	232	231	5
Weibull	152	156	154	4	224	227	225	3
Lognormal	150	154	152	2	223	227	225	2
Log-logistic	152	155	154	3	222	225	224	1
Gompertz	153	156	155	5	227	230	229	4
Generalised Gamma	NA	NA	NA	NA	NA	NA	NA	NA

The company did not perform external validation of these extrapolations, citing time constraints. The visual fit of the lognormal distribution to the underlying Kaplan-Meier data is shown in Figure 10. The company also did not provide corresponding analysis for the non-BRCA subgroup.

Figure 10 OS parametric extrapolation of OS for BRCA subgroup (adapted from company model)

Points for critique

The EAG considers the company's preferred extrapolations in the BRCA subgroup analysis to be appropriate.

4.2.6.7 Progression free survival (PFS) extrapolation

The observed PFS data from the PROpel trial was obtained from the final data cut (DCO3, 12 October 2022). The PFS data was then extrapolated using standard parametric models. Parametric models for PFS were fitted independently to both treatment arms from PROpel using the same procedure as for OS. The outcome used by the company was investigator-assessed PFS rather than PFS based on blinded independent review. The company justified this approach by stating investigator-assessed progression is more representative of how progression would be assessed in clinical practice. In addition, investigator-based assessment produces a less optimistic assessment of PFS. The EAG consider the company's reasoning to be appropriate.

The company concluded that all models had a good fit to the KM data (Figure 11 & Figure 12). The company identified the lognormal, generalised gamma, and log-logistic distributions as having the best fit across both treatment arms and disregarded the other distributions from consideration. The AIC and BIC for the models fitted to both arms of PROpel for OS can be seen in Table 17.

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Table 17 Goodness of fit (AIC + BIC) of parametric distributions for PFS (CS Table 29, Page 94)

	Olaparib + Abiraterone				Placebo + Abiraterone			
	AIC	**BIC**	**AIC+BIC**	**Rank**	**AIC**	**BIC**	**AIC+BIC**	**Rank**
Exponential	2008	2012	2010	4	2345	2349	2347	5
Weibull	2006	2014	2010	5	2342	2350	2346	4
Lognormal	1998	2006	2002	1	2331	2339	2335	1
Log logistic	2002	2010	2006	3	2332	2340	2336	2
Gompertz	2009	2017	2013	6	2347	2355	2351	6
Generalised Gamma	2000	2012	2006	2	2332	2344	2338	3

As discussed in Section 4.2.6.1, the company's base case considers abiraterone equivalent to enzalutamide with respect to PFS (i.e., a hazard ratio of 1.0 is applied to the abiraterone PFS curve). The company did not perform an NMA for the rPFS outcome, and as discussed above, did not systematically explore the implications of using PFS hazard ratios from alternative real-world data sources. The company implemented a single scenario analysis in which the impact of a hazard ratio of 0.962 from Chowdhury et al. was explored, which suggested a small benefit in PFS for enzalutamide compared with abiraterone. In response to a question from the EAG (clarification question B3), the company implemented the confidence intervals associated with the hazard ratios for OS and PFS Chowdhury et al. as a probabilistic scenario within the model.

Figure 11 PFS parametric extrapolation for olaparib plus abiraterone (CS Figure 25, Page 93)

Figure 12 PFS parametric extrapolation for abiraterone (CS Figure 26, Page 93)

Based on landmark estimates, the company considered there to be no clear preference between the lognormal, generalised gamma, and log-logistic curves. The company selected the generalised gamma curve for the base-case analysis as this model was marginally less optimistic than the other models. A scenario analysis using the lognormal and logistic curves for extrapolation of PFS was performed by the company.

Points for critique

Choice of extrapolation

The relative maturity of the PFS data meant the presented extrapolations were in relative agreement. The EAG note that the log-normal distribution had the superior statistical fit for both arms, however, differences in AIC/BIC scores were only small and therefore the EAG consider the company's choice of PFS extrapolation to be appropriate.

Assumption of equivalence between enzalutamide and abiraterone

As discussed elsewhere, given that PFS outcomes were not observed for enzalutamide in the PROpel trial, the company used the observed PFS outcomes for abiraterone, assuming equivalent efficacy between abiraterone and enzalutamide. Given the existence of evidence to suggest equivalent efficacy of enzalutamide over abiraterone (Chowdhury *et al*.), the company performed a deterministic scenario analysis using the hazard ratio from this paper, and implemented a probabilistic scenario incorporating the uncertainty surrounding this hazard ratio following a clarification question from the EAG.

4.2.6.8 HRR mutation subgroup analysis - PFS

The company presented a detailed description of the subgroup analysis conducted in the HRR-mutated population of the PROpel trial in Appendix E to the company submission. All parametric models were in relative agreement according to statistical fit. The company selected the lognormal distribution to represent both arms, which ranked second and third for the olaparib + abiraterone, and placebo + abiraterone arms, respectively.

Points for critique

The EAG agrees that the company's approach to extrapolation of PFS in the two HRR mutation-based subgroups is reasonable.

4.2.6.9 BRCA1/2 subgroup analysis – PFS

The company provided the results and model scenario for the BRCA1/2 subgroup following a clarification question from the EAG (Clarification Questions A4, B6) ([redacted]). In response, the company fitted a parametric model to the observed KM data for this subgroup using the same procedure as for the full population. The log-normal distribution was

selected by the company based on statistical fit (AIC/BIC), as shown in Table 18. The visual fit of the final curves is shown in Figure 13.

Table 18 Goodness-of-fit test on PFS parametric distributions of each treatment arm in BRCA subgroup (PFC Response Table 15)

	Olaparib + abiraterone				Placebo + abiraterone			
	AIC	BIC	AIC+BIC	Rank	AIC	BIC	AIC+BIC	Rank
Exponential	188	190	189	2	233	235	234	3
Weibull	189	193	191	5	235	239	237	6
Lognormal	**187**	**190**	**189**	**1**	**231**	**234**	**232**	**1**
Log logistic	188	192	190	3	232	235	233	2
Gompertz	190	194	192	6	235	238	237	5
Generalised Gamma	187	193	190	3	232	237	235	4

Figure 13 PFS parametric extrapolation of OS for BRCA1/2 subgroup (adapted from company model)

Points for critique

The EAG is satisfied that the company's preferred parametric extrapolation is the most appropriate in the BRCA subgroup.

4.2.6.10 Time to treatment discontinuation (TTD) extrapolation

Time on treatment for the olaparib plus abiraterone treatment arm was modelled independently for each component of this regimen using data from two endpoints from PROpel: time from randomisation to discontinuation of olaparib plus abiraterone (TTD) and time from randomisation to discontinuation of abiraterone (TTDA). The company's rationale for modelling these independently

was to ensure that the observed differences in treatment durations for both components of the combination regime were captured, thus allowing costs to be modelled more accurately. TTD and TTDA were extrapolated beyond the trial follow-up, following a similar process to that followed for OS and PFS.

The company deemed most models to fit the data well by visual inspection - the models overlaying Kaplan-Meier data are presented in Figure 14, Figure 15, and Figure 16. Citing the product characteristics of olaparib plus abiraterone, which recommend that treatment is continued until either disease progression, or unacceptable toxicity, the Weibull curve was selected for the base case as it does not exceed the PFS extrapolation at any point over the time horizon. The Weibull curve had the fifth-best statistical fit, and predicted the shortest mean time on treatment, at [redacted] years for olaparib (compared to mean PFS of [redacted] years). The company applied a cap in the model which ensured that time on treatment could not exceed PFS. The company also present a scenario analysis using the generalised gamma curve which provided a superior statistical fit than the Weibull curve (ranked second), and agreed with the functional form applied to PFS. The mean time on treatment for olaparib using the generalised gamma function was [redacted] years.

Figure 14 TTD parametric extrapolation for olaparib within the olaparib plus abiraterone arm (CS Figure 34, Page 102)

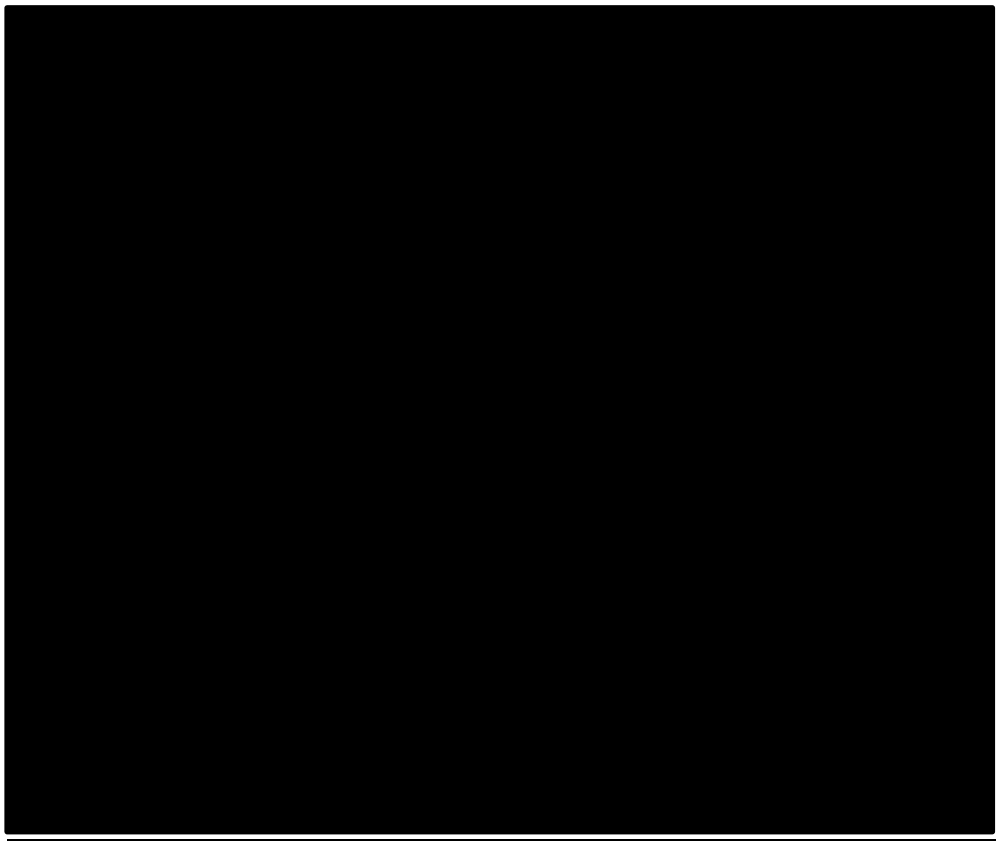

Figure 15 TTD parametric extrapolation for abiraterone within the olaparib + abiraterone arm (CS Figure 35, Page 102)

Figure 16 TTD parametric extrapolation for the abiraterone arm (CS Figure 36, Page 103)

Points for critique

Divergence of TTD from PFS

The EAG had concerns regarding the company's decision to extrapolate TTD and PFS using different functional forms, as this inherently leads to significant long-term divergence between predictions of time on treatment and progression-free survival, despite no statistical or clinical signal to support this assumption. Given that treatment discontinuation is most likely to occur at the point of disease progression, and no biological rationale or clinical evidence has been presented in support of a durable treatment effect off-treatment, the EAG consider it inappropriate to assume that patients remain progression free for extended periods off treatment. The approach adopted by the company is likely to underestimate treatment costs on olaparib, thereby inflating its relative cost-effectiveness.

The EAG note the company's justification for selection of the Weibull curve in order to prevent TTD exceeding PFS, but also note that the model is programmed to prevent this from happening. The EAG presents a scenario in Section 6 in which the same functional form is used for TTD as for PFS.

Assumption of equivalence between abiraterone and enzalutamide

Due to a lack of publicly available treatment discontinuation data for enzalutamide, the company assumed this to be equal to abiraterone. This is a reasonable approach in scenarios assuming equivalence in efficacy between abiraterone and enzalutamide, but as progression is the primary driver of discontinuation in this indication, TTD should be adjusted using the PFS hazard ratio where differences in efficacy are explored.

4.2.6.11 Adverse events

Adverse events included in the economic model were all-cause Grade ≥3 events experienced by ≥ 5% of patients receiving olaparib plus abiraterone or placebo plus abiraterone in the PROpel study, or enzalutamide in the PREVAIL trial. Adverse events were modelled to account for both the incidence and duration of events. To inform the disutilities and costs associated with each AE, event rates were estimated independently for each treatment arm, and were imposed as a one-off cost and QALY decrement in cycle 1 of the executable model (See Sections 4.2.8.5 and 4.2.7.5). Event rates were estimated as function of incidence. The incidence of each AE is summarised in Table 19.

Table 19 Adverse event rates included in the economic model (CS Table 34, Page 107)

Adverse Event	Olaparib + abiraterone	Abiraterone + placebo	Enzalutamide
Anaemia	[redacted]	[redacted]	3.3%
Leukopenia	[redacted]	[redacted]	0.0%
Pneumonia	[redacted]	[redacted]	1.3%
Pulmonary Embolism	[redacted]	[redacted]	0.0%
Hypertension	[redacted]	[redacted]	6.8%

Myocardial Infarction	[redacted]	[redacted]	0.0%
Neutropenia	[redacted]	[redacted]	0.0%
Nausea	[redacted]	[redacted]	1.0%

Points for critique

The EAG note that the inclusion of only Grade ≥3 nausea events may underestimate the impact of nausea on cost and health outcomes. While there is unlikely to be a material cost impact resulting from management of lower grade nausea events, these events can have a large impact on patient health-related quality of life - this was supported by advice obtained from the EAG's clinical advisor. The EAG note that grade 3 nausea events are likely to represent only a small proportion of overall nausea events. For example, in the olaparib plus abiraterone arm of PROpel, nausea AE rates of any grade were [redacted]

4.2.7 Health related quality of life

4.2.7.1 Collection of utility data from PROpel

Data were collected from participants in the PROpel trial using EQ-5D-5L questionnaires every 8 weeks, at week 52, upon treatment discontinuation, and until 12 weeks after disease progression. The company's PFC response noted that at each follow-up, a series of three patient reported outcomes (PRO) questionnaires was administered. The EQ-5D-5L was the third instrument to be completed at each PRO session, and thus had a substantially lower compliance rate than the first instrument, the BPI-SF, which had [redacted] and [redacted] compliance rates in the olaparib plus abiraterone and placebo plus abiraterone arms respectively. By comparison, compliance rates were [redacted] and [redacted] respectively for the EQ-5D-5L questionnaire.

The EAG requested further information on the collection of questionnaire responses from the PROpel study to assess whether attrition or non-completion were at random or may have otherwise failed to fully capture the HRQoL of patients involved in the PROpel trial. However, the company considered such an analysis was at risk of providing misleading conclusions on the impact of missing data on the post-progression health state utility. The company instead provided analysis of EQ-5D-5L according to the interval between randomisation and progression as a proxy for prognosis, and of EQ-5D-5L by timing of measurement relative to time of progression. These analyses were intended to assess how overall prognosis affected HRQoL, and whether the timing of observations may have generated a misleading impression of post-progression utility.

Points for critique

The MMRM approach described in Section 4.2.7.2 relies on the assumption that missing data occurs at random (i.e. not due to underlying characteristics or symptom severity) in order to generate internally valid inferences of patient HRQoL. Whilst there was no clear evidence that missingness

was not at random, the potential for disproportionate non-completion of questionnaires in patients with a higher symptom burden cannot be ruled out. The volume of PROs administered at each assessment may have exacerbated this effect, as it was much less likely that EQ-5D-5L was completed. As analyses of FACT-P and BPI-SF were not presented by health state, it was not possible to assess whether a larger difference was detected between health states with a higher PRO completion rate.

4.2.7.2 Health state utilities

The company stated that EQ-5D-5L data collected in PROpel were cross-walked to produce EQ-5D-3L utility values using the Hernández-Alava *et al*.[27] mapping algorithm. The company state that the economic model uses these mapped values to estimate health-state utilities. This, however, could not be confirmed by the EAG, and all further references made to HRQoL analysis in the company's PFC response were to EQ-5D-5L.

The EQ-5D-5L data were analysed using a mixed-effects model for repeated measures (MMRM), which aimed to determine the impact of treatment arm and progression state on utility. The model (Model 2) which considered only progression state as a predictor of utility was found to have the best fit in terms of AIC (see Table 20), and the utility values generated by Model 2 were applied in the cost-effectiveness model.

Table 20 Company EQ-5D-5L regression model fits (CS Table 32, Page 106)

Parameter	Model 1 (utility ~ treatment arm)	Model 2 (utility ~ health state)	Model 3 (utility ~ treatment arm + health state)	Model 4 (utility ~ treatment arm * health state + treatment arm + health state)
Intercept	[redacted]	[redacted]	[redacted]	[redacted]
Randomised treatment -Olaparib versus placebo	[redacted]		[redacted]	[redacted]
Progression state – PD vs PF		[redacted]	[redacted]	[redacted]
Interaction term (Olaparib and PD)				[redacted]
AIC score	[redacted]	[redacted]	[redacted]	[redacted]

The company found no significant difference in utility across treatment arms, and that they considered the results to indicate that there was no negative impact of the addition of olaparib to the abiraterone treatment regimen. The EAG requested the results of MMRM 'Model 3' in light of the potential effect of the increased toxicity of olaparib on HRQoL, which could mean the application of the same utility to each arm may overestimate QALY gain on olaparib. This model produced a small numerical difference in progression-free utility between treatment arms in favour of placebo plus abiraterone,

which was associated with a utility of [redacted], where this was [redacted] in the olaparib plus abiraterone arm.

The health state utilities applied in the company's base-case model based on MMRM Model 2 are presented in Table 21. The modelled utility associated with the progression-free health state is [redacted], whilst the impact of disease progression upon utility is [redacted], generating a progressed disease utility of [redacted].

Table 21 Utility values applied in company's base-case model (CS Table 33, Page 106)

Health state	Utility	Standard error	Lower 95%	Upper 95%
Progression-free	[redacted]	[redacted]	[redacted]	[redacted]
Progressed disease	[redacted]	[redacted]	[redacted]	[redacted]

Points for critique

Mapping of EQ-5D-5L to EQ-5D-3L

Whilst the company state that the Hernández Alava mapping algorithm was used to crosswalk EQ-5D-5L responses to EQ-5D-3L in line with NICE methods guidance (Section 4.3.16), no further reference was made in the submission or PFC response to EQ-5D-3L values. Instead, the MMRM analysis described appeared to be undertaken on EQ-5D-5L data, and the resulting utility values were implemented directly in the model. NICE reference case analyses are to use the 3L value set, and if these are unavailable, are to map from the 5L descriptive system data onto the 3L value set. The HRQoL value set used by the company therefore appears not to be consistent with the NICE reference case.

Progressed disease utility may not reflect real-world HRQoL

The EAG is also concerned that the utility associated with progressed disease does not adequately represent the burden of progressed disease. The utility derived from the PROpel trial remains very close to that used in the progression-free health state and is similar to that of the unaffected general population. An issue frequently observed in trial-derived utilities arises from the timing of data collection being too close to the point of progression to adequately characterise the impact of progressed disease upon a patient's quality of life. The company's response to clarification question B7a demonstrated that the average EQ-5D-5L response made within 3 months of progression was in fact numerically lower ([redacted]) than that between 3 and 6 months ([redacted]), and indeed any at any subsequent time thereafter ([redacted]). This analysis may suggest that the availability subsequent treatments upon which adequate symptom management can be achieved may decouple disease progression from any substantial impact on HRQoL in patients who survive for extended periods post-progression. However, the subsequent treatments given to patients in the PROpel study were

unrepresentative of those available on the NHS and may thus lead to overestimates of post-progression utility.

In light of the company's responses to clarification question B7, the EAG concludes that the utility score elicited from patients with progressed disease in the PROpel study was unlikely to have been affected by the timing of data collection. The possibility remains that sicker patients were less likely to complete questionnaire responses (particularly given the volume of PRO instruments administered), and thus biasing the responses to be more reflective of patients healthy enough complete all of the instruments presented to them. However, the EAG considers the company's exploratory approach to handling utility data missing not at random is too speculative for decision-making purposes, given the uncertain number and character of missing data, as it necessarily assumes all missing responses take a constant value.

The EAG highlights a comparison with utility values collected in the PROfound study, conducted in patients with mCRPC with a BRCA1/2 mutation. These patients had progressed following treatment with abiraterone at the point of entering the trial, and may therefore be broadly comparable to the progressed population considered in the present appraisal. The mean utility in this study amongst patients who were progression-free was [redacted] – markedly lower than the utility in the nominally equivalent population in PROpel. Due to the timing of trial enrolment relative to the point of radiological progression, this utility may better represent adequately controlled disease in patients who have failed an NHA. However, the EAG acknowledge that factors potentially impactful to HRQoL such as bone metastases were present at a higher frequency at baseline in PROfound than at baseline in PROpel. Patients in the PROfound study were also more heavily pre-treated than the progressed cohort of PROpel, with 55% having received a prior taxane in the former study, compared to 0% in the latter. In order to explore the impact of the use of a lower post-progression utility upon cost-effectiveness estimates, the EAG presents a scenario in Section 6 in which the progression-free utility from PROfound is used to represent post-progression HRQoL.

4.2.7.3 Comparison of utilities with previous appraisals

The company performed a systematic review to identify potential alternative HRQoL value sets in a first-line mCRPC setting, identifying only the PREVAIL trial for enzalutamide, and the COU-AA-302 trial for abiraterone. Available documents provided only progression-free health state utilities of 0.844 and 0.830 respectively. The company explored the use of these alternative values in scenario analyses.

The EAG requested that the company provide the utilities generated in the PROfound study (and used in TA887), as the PFS utility may represent a potentially informative alternative value to represent

post-progression utilities at an earlier line of therapy. The utility values from PROfound were [redacted] for progression-free, and [redacted] for progressed disease.

Points for critique

The EAG notes that the two alternative progression-free utility values identified by the company are higher than that of the general population at the modelled population age. The use of these alternative values has little impact upon cost-effectiveness.

As discussed previously, the EAG considered the progression-free arm of PROpel may present an alternative source for post-progression utility, given the lack of alternatives identified by the company. A scenario exploring the impact of using [redacted] as the progressed disease health-state utility is explored in Section 6.

4.2.7.4 Age-adjustment of utilities

In the original model submitted by the company, utilities were not adjusted to account for the impact of ageing on health-related quality of life. This meant that as the model progresses, the health state utility applied to a patient quickly exceeds that of an age-matched, unaffected member of the general population. The EAG requested at the clarification stage that the model be amended to adjust utilities over time using the EEPRU value set established by the NICE Decision Support Unit.[28]

In their clarification response, the company included a scenario in which utilities were adjusted over time as patients aged. This had the effect of reducing the incremental QALYs generated on olaparib in the company's base case (and thus increasing the ICER), as olaparib patients were modelled to survive for longer, and therefore the additional LYs gained at a more advanced age were subject to a larger quality-adjustment due the holistic effects of aging upon health. The company did not present an updated base-case analysis incorporating this scenario.

Points for critique

As stipulated in NICE Methods Guidance (Section 4.3.7), the adjustment of utility values in instances where baseline utility values derived from a trial are extrapolated over long time horizons is vital to ensure that modelled HRQoL does not exceed general population values at a given age. The utility applied in the progression-free survival health state ([redacted]) exceeds that seen in the general population less than two years into the modelled time horizon, and thus overestimates QALY gain in patients surviving beyond this point. This will disproportionately affect the treatment with the longest predicted OS, and indeed significantly increases the ICER for olaparib.

The EAG considers the inclusion of age adjustment methodologically fundamental and therefore treats this as a model correction in Section 5.3 and Section 6 as it affects the apparent impact of all other model scenarios.

4.2.7.5 Effect of adverse events on HRQoL

In recognition of the possibility of AEs occurring outside the scheduled collection of EQ-5D data in the PROpel trial, and thus the failure to capture their impact upon modelled health state utilities, and to reflect the distinct AE profile of olaparib, the model applies an independently derived set of disutilities to reflect the impact of AEs.

Disutilities associated with each type of AE were taken from Sullivan *et al*. 2011, reproduced below in Table 22, and were each multiplied by an assumed duration of 14 days. The EAG requested that the company produce a scenario in which the duration of modelled adverse events was equal to the mean duration observed in the PROpel study, as chronic (anaemia, hypertension) and acute (e.g. pneumonia, pulmonary embolism) events may vary vastly in duration.

Table 22 also presents the duration of AEs as observed in PROpel, which illustrates how the health effects of events such as hypertension and anaemia, whilst relatively minor, may be experienced over a long period. The company did not present data on AE duration by treatment arm.

Table 22 Adverse event disutilities applied in economic model (CS Table 35, Page 108)

Adverse event	Disutility	Modelled Duration (days)	Observed duration in PROpel
Anaemia	-0.020	14.00	[redacted]
Leukopenia	-0.020	14.00	[redacted]
Pneumonia	-0.079	14.00	[redacted]
Pulmonary embolism	-0.051	14.00	[redacted]
Hypertension	-0.037	14.00	[redacted]
Myocardial infarction	-0.056	14.00	[redacted]
Neutropenia	-0.020	14.00	[redacted]
Nausea	-0.04	-	[redacted]

The EAG received clinical advice suggesting that nausea is particularly important to these patients. Whilst this is typically of a lower grade, and thus would not meet the criteria for inclusion in the model, the EAG requested that a scenario be presented which explores the inclusion of a cost and disutility for nausea events of any grade.

The model also separately applied disutilities relating to skeletal-related events (SREs), reflecting the prevalence and severity of bone and spinal metastases following progression of mCRPC. Because these events are related to progression rather than prior treatment, SRE rates were assumed to be equivalent between treatment arms. The probability of experiencing an event was derived from the PROpel study, in which [redacted] of all patients experiencing non-fatal progression events also had an SRE. The types of SREs patients experienced, and their associated disutilities, were based on values previously used in TA831. Unlike for the treatment-related AEs above, disutilities associated with SREs were assumed to last for the whole cycle in which disease progression occurs (i.e. 30.44 days). The approach to modelling SREs is summarised in Table 23.

Table 23 Skeletal-related event occurrence and disutilities applied in company model

Skeletal-related event	Utility decrement	Duration of SRE (days)	Olaparib	Abiraterone	Enzalutamide
Probability of at least one SRE occurring			[redacted]	[redacted]	[redacted]
Spinal cord compression	-0.555	30.44	15.5%	15.5%	15.5%
Radiation to bone	-0.070	30.44	67.7%	67.7%	67.7%
Surgery to bone	-0.130	30.44	4.1%	4.1%	4.1%
Pathologic bone fractures	-0.130	30.44	12.9%	12.9%	12.9%
		Total disutility	[redacted]	[redacted]	[redacted]

Points for critique

The EAG could not validate the company's claim to have included consideration of the AE burden associated with subsequent therapies (i.e. docetaxel) in the model. This omission is unlikely to have a significant effect on QALY loss, and is likely to affect both treatment arms more or less equally. The EAG also notes that the AE-specific disutilities sourced by the company are very small. This may mean the model inadequately represents the impact of the differential toxicity profile of the alternative treatment options, particularly when combined with the 14-day assumed AE duration. The EAG prefers that AE durations are based on those observed in the PROpel trial, which in a number of cases are many times longer than the 14 days assumed in the company's base-case. This only has a minor impact on cost-effectiveness.

The EAG also notes that while the company attempt to separately account for the impact of skeletal-related events on HRQoL, this has only a very small effect upon QALYs accrued in this health state. This does not appear to align with the company's clarification response, in which they explain the substantially lower baseline utility observed in the PROfound study through the high rate SREs.

4.2.8 Resources and costs

The CS provided a description of resource use and costs applied in the model. This included drug acquisition costs, costs associated with management of adverse events, monitoring costs, costs of testing, acquisition and administration costs associated with subsequent treatments, and the costs of end-of-life care. No administration costs were applied for the intervention and comparator drugs, as all are administered orally.

The company carried out an SLR to identify relevant healthcare resource use and costs for therapies in the first-line mCRPC setting, but they experienced difficulty in translating these values to the UK setting. Therefore, the company adopted healthcare resource use from a previous appraisal of enzalutamide in this indication (TA377) and used NHS Reference Costs 2019-20, eMIT and the BNF to derive unit and drug cost values implemented in the model.

Points for critique

The EAG is satisfied that TA377 represents an appropriate source of resource use information. However, it was unclear why outdated NHS Reference Cost and eMIT data were used throughout the model. The EAG considers the use of consistent and up to date cost data a methodological issue, advice from NICE also supported the use of the latest cost data. The EAG therefore presents analysis using the latest NHS Reference Costs and eMIT drug cost data as a model correction (See Section 5.3). *Drug acquisition costs*

Dosing schedules and costs modelled for the intervention and comparators are summarised in Table 24

Table 24. Acquisition costs for olaparib plus abiraterone were based on their respective SmPCs. Patients on olaparib received300mg twice daily and 1000mg of abiraterone administered once daily, with prednisolone at 5mg twice daily. Patients in the abiraterone arm received the same dose of abiraterone and prednisolone.

All patients were assumed to receive 100% of their targeted dose for each comparator regimen. The cost per pack for olaparib at list price is £2,317.50 per 56-pack of 150mg tablets, and for abiraterone and prednisolone is £190 per 56-pack of 500mg tablets and £0.40 per 28-pack of 5mg tablets, respectively. A patient access scheme (PAS) is available for olaparib consisting of a simple discount of [redacted], reducing associated acquisition costs to [redacted] per 56-pack of 150mg tablets. [redacted] The modelled cost per pack for enzalutamide at list price is £2,734.67 per 112-pack of 40mg tablets. Enzalutamide and abiraterone are also subject to confidential commercial arrangements not included in the company's analysis or replicated in this report. Analyses inclusive of all confidential pricing arrangements are included in a confidential appendix to the EAG Report.

At the clarification stage, the company included a model scenario in which treatment acquisition costs were adjusted to reflect the observed relative dose intensity (RDI) in the PROpel trial in the olaparib plus abiraterone, and placebo plus abiraterone treatment arms. In the absence of equivalent data from PREVAIL, RDI for enzalutamide was assumed to be equal to that abiraterone observed in PROpel. The relative dose intensities applied in the model are presented in Table 24. Note that the company's written PFC response refers to median RDI rather than the mean RDI applied in the model, the figures report in Table 24 therefore do not match those supplied in the clarification response documentation.

Table 24 Drug dosing schedule and acquisition costs (CS Table 38 and company's economic model)

Regimen	Drug	Unit dose, mg	Dose per admin, mg	Admin per day	Cost per pack (£)	Unit per pack	Cost per cycle (£)	Relative dose intensity *
Olaparib + Abiraterone	Olaparib	150	300	2	2,317.50 With PAS: [redacted]	56.00	[redacted]	0.917
	Abiraterone	500	1,000	1	190.00	56.00	206.54	0.963
	Prednisolone	5	5	2	0.40	28.00	0.87	0.963
Abiraterone	Abiraterone	500	1000	1	190.00	56.00	206.54	0.972
	Prednisolone	5	5	2	0.40	28.00	0.87	0.972
Enzalutamide	Enzalutamide	40	160	1	2,734.67	112.00	2,972.73	0.972

* RDI adjustment not applied in company base case

The company did not explicitly account for drug wastage on olaparib, enzalutamide and abiraterone. The company reasons that the cost of unfinished packs is already considered, as drug acquisition costs were applied at the beginning of each cycle. Patients were therefore assumed to incur the full cost of treatment for each cycle notwithstanding treatment discontinuation at any point during the cycle. The company argues that further incorporation of wastage costs will result in double-counting.

Points for critique

The EAG is satisfied that the company's implementation of RDI-based adjustment to acquisition costs is reasonable, and notes this has a moderate impact on cost-effectiveness results as detailed in Section 6. A scenario examining the impact of inclusion of RDI on cost-effectiveness in the corrected model is examined in Section 6.

The EAG does not agree with the company's reasoning that wastage is already inherently accounted for through the estimation of acquisition costs directly from the trial-derived TTD curves. The company applied a half-cycle correction to drug acquisition costs, this inherently assumes that the proportion of patients who discontinue part-way through the cycle do not incur these acquisition costs. This is contrary to the conceptual basis of the half-cycle correction, and to company's explanation that all patients on treatment at the beginning of a cycle incur the cost of a whole cycle's worth of treatment regardless of whether the model assumes they discontinue half way through the cycle. The EAG considers the exclusion of acquisition costs from the application of the half-cycle correction a methodological correction. This is discussed further in Section 5.3.

4.2.8.2 Subsequent treatments

The company applied a one-off cost associated with subsequent treatments at the point of disease progression on each of the initial treatments. The subsequent treatments modelled in the base case were elicited from clinical expert opinion which indicated that in the UK, docetaxel and cabazitaxel are the primary subsequent treatments administered after disease progression on an NHA. The company assumed that [redacted] of patients would receive a further line of therapy following progression, as observed across the full PROpel study population. The company also presented a scenario analysis which used the distribution of subsequent therapies observed in PROpel but noted that this commonly included retreatment with an NHA which is not permitted in the UK.

In addition, olaparib monotherapy is recommended following treatment with an NHA in patients with BRCA mutations, while radium-233 dichloride is recommended for those with symptomatic bone metastases following docetaxel failure. Again, the proportions of patients receiving each of these therapies was based on clinician elicitation.

Costing and duration of treatment for subsequent therapies were based on PROpel for olaparib plus abiraterone and abiraterone monotherapy, and on Leith 2022,[29] a real-world survey of mHSPC treatment patterns, for enzalutamide. Where treatment duration was not reported, the duration of the therapy considered to be the most similar was used. The model assumes that all subsequent PARP inhibitors are be olaparib monotherapy since it is presently the only approved therapy for mCRPC patients with specific genetic mutations, including BRCA[30].

Drug costs per cycle of subsequent therapies updated in the company's clarification response are summarised in Table 25. These costs were updated in EAG analyses to reflect the latest eMIT and BNF costs. Costs of treatments with weight- or BSA-based dosing were based on the PROpel trial and the cabazitaxel appraisal (TA255), respectively, in which mean body weight was 82.7kg and mean BSA was 1.90m^2. The number of vials required for each administration was estimated from the licensed dose. Drug wastage was included for intravenously administered subsequent therapies at the time of administration, based on the assumption that the contents of incompletely used vials would be discarded.

Table 25 Drug costs per cycle of subsequent therapies (Company's economic model, equivalent to CS Table 43)

Drug regimen	Drug	Unit Cost (Company) (£)	Total drug cost per cycle (£)	Cost Source	Unit Cost (EAG) (£)
Olaparib	Olaparib	[redacted]	[redacted]	BNF	[redacted]
Abiraterone	Abiraterone	190.00	207.41	BNF	190.00
	Prednisolone	0.40		eMIT	0.30
Docetaxel	Docetaxel	17.95	478.53	eMIT	15.67
	Prednisolone	0.40		eMIT	0.30
Enzalutamide	Enzalutamide	2,734.67	2,972.73	BNF	2,734.67
Cabazitaxel	Cabazitaxel	332.07	933.82	BNF	314.44
	Prednisolone	0.40		eMIT	0.30
Mitoxantrone	Mitoxantrone	61.67	631.28	eMIT	67.24
	Prednisolone	0.40		eMIT	0.30
Radium-233	Radium-233	4,606.19	5,345.91	NICE TA376	4040
Carboplatin	Carboplatin	24.11	391.15	eMIT	21.32

BNF: British National Formulary; eMIT: electronic market information tool; NICE: National Institute for Health and Care Excellence

Points for critique

The EAG agrees that it is appropriate to exclude retreatment with NHAs from the modelled cost calculations, and an approach based on an NHS-appropriate subsequent therapy distribution has been accepted in previous appraisals. However, this means that clinical and cost-data are not aligned in the model. The extent to which the reuse of NHAs in the trial will cause divergence in effectiveness estimates in the model and NHS practice are unclear.

A further potential issue is the availability of olaparib monotherapy to those with BRCA mutations following abiraterone and enzalutamide on the NHS, an option not available to patients in the PROpel trial. The costs of olaparib monotherapy were applied in the model, but any associated treatment benefits were not captured. This means the model may overestimate comparator arm costs and underestimate QALYs accrued, inflating the ICER for olaparib. As discussed previously, this is even more important in subgroup analyses where the primary comparator for olaparib is a sequence of abiraterone/enzalutamide followed by olaparib monotherapy in the majority of patients. Whilst the model accounts for the cost of subsequent olaparib use, there is no consideration of its effectiveness in terms of extending post-progression survival.

4.2.8.3 Treatment duration

The company modelled time on treatment using parametric distributions fitted to the time to treatment discontinuation data from PROpel for olaparib plus abiraterone, and abiraterone monotherapy. As described in Section 4.2.6.10, time to discontinuation for each component of the olaparib (TTD) plus abiraterone (TTDA) regimen was modelled independently to account for the proportion of patients who discontinue one component of the intervention but not the other.

Although the lognormal and log logistic distributions offered a better statistical fit, a Weibull distribution was used in the company base case for olaparib plus abiraterone and abiraterone monotherapy, as it did not exceed rPFS at any point. The company considered this appropriate on the basis of the olaparib and abiraterone SmPCs, which recommend treatment discontinuation at the point of disease progression, or unacceptable toxicity, thus avoiding the clinically inappropriate scenario of patients remaining on treatment beyond progression. The company also presented a scenario analysis using the generalised gamma curve, which offers a statistically superior fit for extrapolating treatment duration and is also consistent with the modelled extrapolations for PFS.

Due to lack of publicly available data on TTD for enzalutamide from RCTs identified in the SLR, TTD for enzalutamide was assumed to be equal to TTD for abiraterone. The company justified this assumption as an extension of the assumption of equal efficacy. That is, if the primary driver of discontinuation is progression, and the rate of progression is equal on enzalutamide, then TTD should follow a similar pattern.

Points for critique

As previously discussed in Section 4.2.6.10, the EAG considers the use of different functional forms to model PFS and TTD inappropriate, as it implicitly de-couples treatment discontinuation from its primary cause. As the company applied a cap to all TTD curves in the model to prevent time on treatment exceeding PFS, this should not be a factor influencing extrapolation choice.

The assumption of equivalence in TTD between abiraterone and enzalutamide is appropriate in the company's base-case, but due to the inherent link between PFS and TTD, any scenario exploring alternative PFS effects should apply the same hazard ratio to TTD as PFS as a proxy representation of this correlation of outcomes. This leads to underestimation of costs and overestimation of cost-effectiveness associated with olaparib plus abiraterone.

4.2.8.4 Health state unit costs and resource use

Healthcare resource use in the model was specific to the progression-free and post-progression health states and were modelled on a per-cycle basis. Resource use rates were based on TA377 and assumed to be equivalent by health-state between olaparib plus abiraterone and abiraterone monotherapy.

Enzalutamide was associated with a lower outpatient consultation frequency. During the initial three months of treatment, a higher weekly frequency use is implemented, which is subsequently reduced from four months onwards for olaparib, abiraterone, and enzalutamide. However, for docetaxel and secondary therapy, the reduction in frequency can occur at any time. Progression into the death state was associated with a one-off end-of-life cost sourced from TA391.

Unit costs relating to continuous disease monitoring over a patient's lifetime, summarised in Table 26, were sourced from NHS Schedule of Reference Costs 2019/20,[31] inflated to 2020/21 prices using the PSSRU 2022 inflation index.

Table 26 Monitoring costs per cycle (CS Table 46 and company's economic model)

Monitoring	Unit Cost (Inflation-Adjusted)	Olaparib + Abiraterone		Abiraterone		Enzalutamide		Subsequent Therapy
		First 3 Months	Months 4+	First 3 Months	Months 4+	First 3 Months	Months 4+	Any Time
Out-patient visit (consultation)	£156.00	£169.58	£84.79	£169.58	£84.79	£84.79	£42.40	£56.53
Out-patient visit (nurse)	£42.00	£45.66	£22.83	£45.66	£22.83	£22.83	£11.41	£15.22
CT scan	£120.57	£23.83	£23.83	£23.83	£23.83	£19.42	£19.42	£74.89
Bone scan	£316.49	£22.94	£22.94	£22.94	£22.94	£22.94	£22.94	£22.94
Full blood count	£2.58	£5.61	£2.80	£5.61	£2.80	£2.80	£1.40	£1.87
Liver function test	£6.09	£13.24	£6.62	£13.24	£6.62	£3.31	£1.66	£4.41
Kidney function test	£12.18	£26.48	£13.24	£26.48	£13.24	£13.24	£6.62	£8.83
Treatment toxicity monitoring	£2.58	£2.58	£2.58	£0.00	£0.00	£0.00	£0.00	£0.00
PSA test	£1.22	£2.65	£1.33	£2.65	£1.33	£1.33	£0.66	£0.88
	Total	**£309.99**	**£178.38**	**£309.99**	**£178.38**	**£170.65**	**£106.50**	**£185.57**

Points for critique

The EAG considered the resource use estimates used by the company reasonable. As described previously, the EAG does not consider the inflation of old NHS Reference Costs to the current cost year appropriate, given the existence of more recent cost collection data. The same applies for the eMIT costs used by the company, which were also outdated. The EAG applies current cost data as a model correction in Section 5.

4.2.8.5 Adverse reaction management costs

Costs associated with the management of treatment-related adverse events were based on Grade 3 or higher events occurring in more than 5% of patients in PROpel for olaparib plus abiraterone and placebo plus abiraterone, and PREVAIL for enzalutamide. Management costs were derived from the NHS Schedule of Reference Costs 2019/20 and inflation adjusted to 2020/21, unit costs and their respective sources can be found in Table 47 of the company submission (Page 121).

Total AE costs were applied as a one-time cost at the start of the model and were calculated as the sum-product of the unit costs and probability of AEs occurring specific to each intervention (see Table 47 of the CS and Table 19). The total costs of AEs by treatment regimen are summarised in Table 27. These costs were updated in EAG analyses to reflect the latest Schedule of Reference Costs 2021/22 and PSSRU 2022.[31, 32]

Table 27 Aggregate costs of adverse events by treatment regimen (CS Table 48, and company's economic model)

Treatment-emergent adverse events	Olaparib (£)	Abiraterone (£)	Enzalutamide (£)
Anaemia	[redacted]	[redacted]	49.42
Leukopenia	[redacted]	[redacted]	0.00
Pneumonia	[redacted]	[redacted]	25.57
Pulmonary embolism	[redacted]	[redacted]	0.00
Hypertension	[redacted]	[redacted]	44.76
Myocardial infarction	[redacted]	[redacted]	0.00
Neutropenia	[redacted]	[redacted]	0.00
Nausea*	[redacted]	[redacted]	0.01
Total (company base case) (£)	[redacted]	[redacted]	**119.74**
Total (EAG corrections) (£)	[redacted]	[redacted]	**151.54**

* not applied in company's base-case

Points for critique

Clinical advice to the EAG indicated that nausea is an important TRAE to patients. Nausea was also amongst the most common reported AEs ([redacted] in the PROpel olaparib plus abiraterone arm. The EAG requested a scenario which included management costs for nausea, which assumed 10mg metoclopramide taken three times daily based on a 14-day duration, rather than the AE duration observed in PROpel ([redacted]). The company concluded that as only one patient in each arm experienced Grade 3 or higher nausea, but observed duration data from PROpel included data for all severity grades, thus they did not model the observed duration of nausea. Management costs for nausea were only included if the event was Grade 3 or above. This accounts for a very small

proportion of nausea events in the PROpel study, and may underestimate the cost of management of this TRAE on the NHS. However, as metoclopramide is extremely cheap, the impact is likely to be extremely small.

4.2.8.6 End-of-life costs

The company applied a one-off cost of £2,170, derived from TA391 and uprated to 2016/17 using the PSSRU, at the time of mortality in the model. The EAG updated this cost in their corrections to 2020/21 using the PSSRU. This cost was lower than that used in TA387 and is generally lower than assumed terminal care costs in other oncology indications. However, as this cost applies to both treatment arms the effect on total costs is likely to be limited to the differential impact of discounting on later mortality events occurring on olaparib. As the impact on incremental costs is likely to be very small, the EAG did not explore the effect of alternative scenarios.

4.2.8.7 HRR mutation diagnostic testing costs

The company did not include diagnostic biomarker testing for HRR mutations in their base-case or original subgroup analyses, reasoning that testing is not a prerequisite for use of olaparib in the licensed indication. Further, the CS states this test is included in the NHS Genomic Test Directory and thus should be regarded as a standard component of the diagnostic evaluation for patients with mCRPC. Clinical opinion cited by the company suggests that, although screening for HRR mutations such as BRCA is not presently a standard procedure, biomarker testing will likely become a customary clinical practice following the approval of olaparib monotherapy for the BRCA-mutated population.

The company presented scenario analyses incorporating the cost of HRR mutation biomarker testing in the abiraterone and enzalutamide arms in order to screen for whether olaparib monotherapy is indicated as a subsequent therapy. The company assume a testing unit cost of £400, which is simply applied as a one-off cost in the first model cycle. This cost appears excessively high and was incorrectly applied in the model as a fixed unit cost rather than as a cost per patient, which does not consider the prevalence of the relevant HRR mutation in the population.

The company also presents a scenario in which testing costs are incurred for the full primary treatment population in the HRR mutation subgroup analysis. Detailed results of these scenarios are presented in Section 5, and the EAG explores the inclusion of biomarker testing in subgroup analyses presented in Section 6.

Points for critique

The EAG considers the inclusion of biomarker testing costs appropriate in the comparator arms in the whole-population analysis, given the availability of olaparib monotherapy at subsequent lines of

therapy, and the inclusion of testing costs in TA887. However, the company's calculation of the per patient testing cost, and application in the first model of the cycle, are incorrect. Per patient testing costs should be calculated as a function of the unit cost and the number of tests required to identify a single patient with the mutation. For example, assuming that the 10.7% of patients in the PROpel trial with a BRCA mutation is representative of the NHS population, 9.35 patients would need to be tested to identify one patient eligible for treatment, resulting in a testing cost of £3,738.32 per patient. In the scenario in which patients who progress on the comparator arm and become potentially eligible for treatment with olaparib monotherapy, the testing cost should be applied at the point of progression, rather than in the first treatment cycle as implemented by the company.

The EAG also notes that the cost of testing for BRCA mutations was included in TA887 of olaparib monotherapy for BRCA patients. The committee referenced the NICE methods guide in the Final Appraisal Document, stating that 'if a diagnostic test to establish the presence or absence of this biomarker is carried out solely to support the treatment decision for the specific technology, the associated costs of the diagnostic test should be incorporated into the assessments of clinical and cost-effectiveness'. On these grounds, the committee's preference was for the inclusion of testing costs. The EAG therefore includes the corrected cost of testing for BRCA mutations in the subgroup analysis presented in Section 6. The EAG also corrects the company's implementation of testing costs in the whole population. The EAG notes that the £400 unit cost per test may be too high, and highlights that the standard cost of adding a mutation onto a next-generation screening (NGS) panel was quoted by NHS England as £34 in TA898 of dabrafenib and trametinib in non-small cell lung cancer. The EAG therefore uses this value in the testing scenarios presented in Section 6.

4.2.8.8 Confidential pricing arrangements

The EAG notes that there are a number of confidential commercial arrangements in place for drugs comprising the comparator regimen, and for drugs currently in use as subsequent treatment options. The treatment acquisition costs used in the analyses presented in the company submission and the EAR (Section 6), include only the confidential pricing agreement for olaparib. Olaparib currently has a [redacted].

Table 28 presents details of which comparator and subsequent treatments have confidential prices which differ from the publicly available list prices used to generate the results in this report. These prices were made available to the EAG, and were used to replicate all analyses presented in the EAR for consideration by the Appraisal Committee. Details of all confidential pricing arrangements and all results inclusive of these arrangements are provided in the confidential appendix to this report. These prices were correct as of 9th June 2023

Table 28 Source of the confidential prices used in the confidential appendix

Treatment	Source of price/type of confidential arrangement
Olaparib	Simple PAS
Abiraterone	CMU
Prednisolone	eMIT price
Docetaxel	eMIT price
Enzalutamide	Simple PAS
Cabazitaxel	eMIT price
Mitoxantrone	eMIT price
Radium-233	Simple PAS
Carboplatin	eMIT price

5 COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

This section summarises the results of the company's updated base case as presented in the clarification response. The results presented in the following sections are inclusive only of the PAS discount for olaparib. [redacted]. Results inclusive of available commercial arrangements for the comparator treatments are provided in a confidential appendix to the EAG report.

5.1.1 Base-case results

The company presents in their submission a series of pairwise ICERs for all olaparib plus abiraterone compared with abiraterone alone, and enzalutamide. As discussed in Section 4.2.4, the company argued that enzalutamide should be designated the 'primary' comparator, and thus emphasised pairwise comparisons with enzalutamide in their submission.

The EAG requested that results be presented in a fully incremental format, as there was no clear justification for the preference of one comparator over the other in the majority of patients. The company argued that conducting a fully incremental analysis in this context lacks informative value, as it suggests that enzalutamide is fully displaceable by abiraterone. The company presented a pooled weighted average ICER as an alternative methodology, weighting results according to Blueteq requests in 2020 – 2022 (0.33:0.66 for abiraterone and enzalutamide respectively). The company cited Murphy *et al*.[33] as justification for this methodology, which does not support the use of pooled ICERs for multiple comparators. This report instead concludes that heterogeneity in cost-effectiveness results across sub-populations should be accounted for decision making and, where possible, should be presented transparently in a disaggregated manner to reduce decision uncertainty. The EAG also disagrees with the assertion that enzalutamide is not fully displaceable by abiraterone. The EAG considers that for the vast majority of patients this true and that fully incremental analysis which allows the evaluation of the incremental costs and benefits associated with each comparator in relation to the next best alternative is the most appropriate form in which to consider the results of the economic analysis. The EAG therefore reproduces all analyses in a fully incremental format in the following section.

The company base-case results updated to a fully incremental format are summarised in Table 29. Pairwise results are presented for comparison below in Table 30.

Compared with abiraterone, the results suggest that olaparib plus abiraterone is associated with increased costs (cost difference of [redacted]) but higher accrued QALYs (QALY difference of [redacted]

The company's base-case ICER comparing olaparib plus abiraterone with abiraterone only is [redacted] per QALY gained. In all scenarios, higher costs are primarily a result of the higher acquisition costs associated with olaparib.

Table 29 Fully incremental company base-case results (deterministic)

Technology	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
Abiraterone	[redacted]	[redacted]			
Enzalutamide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Olaparib + Abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 30 Pairwise company base-case results (deterministic)

Technology	Total costs	Total QALYs	Incremental costs (olaparib vs)	Incremental QALYs (olaparib vs)	ICER (olaparib vs)
Olaparib + Abiraterone	[redacted]	[redacted]			
Abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Enzalutamide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

5.2 Company's sensitivity analyses

5.2.1 Probabilistic sensitivity analyses

The EAG requested several updates to the company's economic model at the clarification stage. The EAG asked that the company update the model to incorporate confidence intervals around effect estimates based on evidence from an appropriate data source, Chowdhury *et al*., 2020, to model uncertainty associated with OS and PFS. The company also provided probabilistic results in the HRR and BRCA subgroups in their clarification response. The EAG noted that the PSA was set up to return parameter values to an independently established set of 'default inputs'. This meant that the PSA could not be easily run using the current model setup, and it was unclear whether the parameter values chosen elsewhere in the model carried through to the PSA results. To permit more transparent adjustment of the model, the PSA should be re-structured to run the selected model parameters, rather than an independently specified set of values. PSA results should also be presented in full in a table within the model. The appropriate exploration of confidence intervals (CIs) is also lacking in the PSA. This applies even to the company's scenario requested by the EAG, which ostensibly incorporates CIs from Chowdhury *et al*., 2020[15] to model uncertainty around the HRs between the two comparators,

but still uses a fixed 10% SE rather than allowing for variation within the CIs. Future model iterations should account for uncertainty by including ranges around observed data rather than a fixed SE assumption.

The company performed a probabilistic sensitivity analysis (PSA) on the base-case, running 1,000 model iterations (with a burn in of 220 iterations) for the pairwise comparisons, no further PSA was conducted. This appeared sufficient to achieve convergence in the company's base-case analysis. The mean probabilistic ICER for olaparib plus abiraterone compared to enzalutamide and abiraterone is presented in Table 31. The results of the PSA show that olaparib plus abiraterone had a [redacted] probability of being cost-effective at a threshold of £30,000 per QALY in comparison to enzalutamide, and [redacted] in comparison to abiraterone. Probabilistic analyses are presented in pairwise format due to the lack of model functionality to automatically generate these results and the limited time available to implement such functionality.

Table 31 Company base-case results: probabilistic pairwise analysis

Technology	Total		Incremental		ICER
	Costs	QALYs	Costs	QALYs	
Olaparib + abiraterone vs enzalutamide					
Olaparib + abiraterone	[redacted]	[redacted]			
Enzalutamide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Olaparib + abiraterone vs abiraterone					
Olaparib + abiraterone	[redacted]	[redacted]			
Abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Figure 17, Figure 18, and Figure 19 present the cost-effectiveness planes and the full cost-effectiveness acceptability curve from the base-case for both comparators.

Figure 17 Cost-effectiveness plane (versus enzalutamide) (from company model)

Figure 18 Cost-effectiveness plane (versus abiraterone) (from company model)

Figure 19 Cost-effectiveness acceptability curve (from company model)

5.2.2 Company additional scenario analyses

The company presented a range of scenario analyses in the original submission. The effect of these scenarios ranged between incremental costs of [redacted] and [redacted] in comparisons with enzalutamide, and [redacted] and [redacted] in comparisons with abiraterone. The incremental QALYs ranged between [redacted] and [redacted] in comparison to both comparators. These results are not replicated in this report but can be found in Table 55 and Table 56 of the CS. Pairwise results for the subgroup of patients with HRR mutations were also presented in the CS as requested in the NICE scope. These results have been replicated using the updated company model and presented as a fully incremental comparison as summarised in Table 32.

Table 32 Deterministic results in HRR mutation subgroup: fully incremental (from company model)

Technology	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
Abiraterone	[redacted]	[redacted]			
Enzalutamide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Olaparib + Abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

At the clarification stage, the EAG requested that the company present several scenario analyses to test the assumptions of the base case model. The results are presented in Table 33. The scenarios explored are as follows:

i. Deterministic and probabilistic results in the non-HRR mutation subgroup
ii. Probabilistic results in the HRR mutation subgroup
iii. Deterministic and probabilistic results in the BRCA subgroup
iv. Use of treatment-specific health state utilities, excluding separate consideration of AE-related disutilities
v. Accounting for the effects of ageing on HRQoL using the EEPRU value set from the 2022 DSU Report – 'Estimating EQ-5D by age and sex for the UK'
vi. Incorporating AE durations observed in the PROpel trial
vii. Exploring the impact of nausea, and management costs, on HRQoL using prevalence and duration data observed in the PROpel study
viii. Adjusting treatment acquisition costs according to RDIs observed in the PROpel trial
ix. Inclusion of the cost of testing for HRR mutation status in the comparator arms
x. Inclusion of the cost of testing for HRR mutation status in the olaparib plus abiraterone arm.

Table 33 Company's additional scenario analyses (Pairwise) - deterministic

Technology	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
non-HRR mutation subgroup					
Olaparib + Abiraterone	[redacted]	[redacted]			
Abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Enzalutamide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HRR mutation subgroup					
Olaparib + Abiraterone	[redacted]	[redacted]			
Abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Enzalutamide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BRCA mutation subgroup					
Olaparib + Abiraterone	[redacted]	[redacted]			
Abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Enzalutamide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment-specific health state utilities					
Olaparib + Abiraterone	[redacted]	[redacted]			
Abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Enzalutamide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Accounting for the effects of ageing upon HRQoL					
Olaparib + Abiraterone	[redacted]	[redacted]			
Abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Enzalutamide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incorporating PROpel trial AE durations					
Olaparib + Abiraterone	[redacted]	[redacted]			
Abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Enzalutamide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Impact of nausea and management costs					
Olaparib + Abiraterone	[redacted]	[redacted]			
Abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Enzalutamide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Acquisition costs according to observed RDIs					
Olaparib + Abiraterone	[redacted]	[redacted]			
Abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Enzalutamide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Including biomarker testing costs in the abiraterone/enzalutamide arm					
Olaparib + Abiraterone	[redacted]	[redacted]			
Abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Enzalutamide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Including biomarker testing costs in the olaparib + abiraterone arm					
Olaparib + Abiraterone	[redacted]	[redacted]			
Abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Enzalutamide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

5.2.3 Company's deterministic sensitivity analyses

The company performed a one-way deterministic sensitivity analysis (DSA) to identify variables with the greatest effects upon the ICER. The DSA for the pairwise comparison of olaparib plus abiraterone and enzalutamide, presented in Figure 20, suggests that the assumed HRs applied to enzalutamide OS and TTD outcomes were the most influential parameters. Results for pairwise comparison of olaparib plus abiraterone and abiraterone, presented in Figure 21, suggest pre-progression health state utility was the most influential parameter.

Figure 20 DSA tornado graph (versus enzalutamide) (from company model)

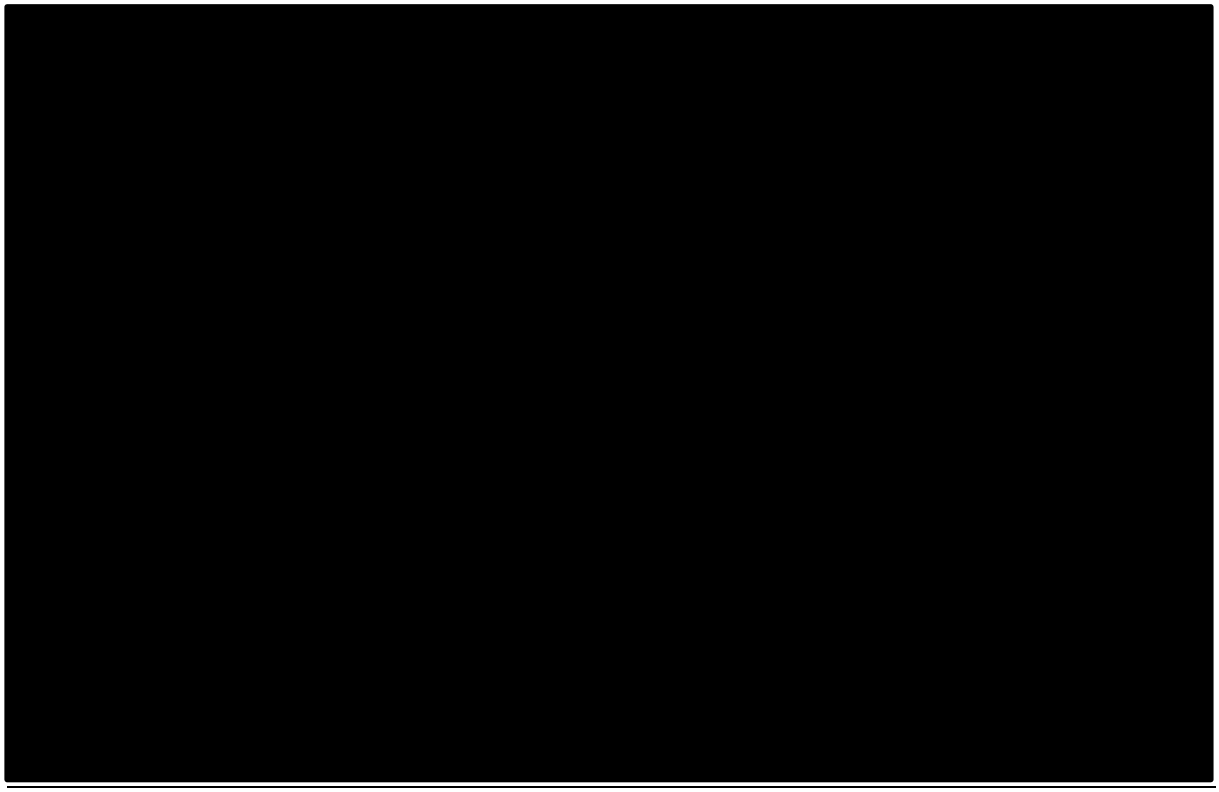

Figure 21 DSA tornado graph (versus abiraterone) (from company model)

5.3 Model validation and face validity check

As part of the EAG assessment of the economic analysis, the EAG checked the internal validity of the model and considered the face validity of the model's predictions. This included a series of model calculation checks, including pressure tests and formula auditing. Due to time constraints, only limited validation could be undertaken on the model scenarios presented by the company in their clarification response.

No significant structural errors were identified in the EAG's validation of the model, however, the EAG noted a number of methodological issues and outdated sources of cost data applied in the model. The methodological issues were namely the failure to apply age adjustment to utilities as patients aged, and an incorrect application of the half cycle correction to treatment acquisition costs. The EAG does not consider these issues matters of judgement; an analysis which omits age adjustment over a lifetime time horizon does not meet the NICE Reference Case. The company also used outdated NHS Reference Cost and eMIT cost data.

These issues are corrected in the analyses presented by the EAG in Section 6.

6 EXTERNAL ASSESSMENT GROUP'S ADDITIONAL ANALYSES

The EAG identified several limitations and areas of uncertainty in the cost-effectiveness analysis presented by the company, which are discussed in detail in Section 4.

The following section presents a number of alternative scenarios in which the EAG considers alternative approaches and assumptions. Given the high level of uncertainty associated with the effectiveness of olaparib plus abiraterone in patients without BRCA mutations, particular consideration has been given to this issue.

Descriptions of the EAG's exploratory analyses are provided in Section 6.1, and the degree of change on the ICERs and net health benefit compared to the company's base-case is explored in Section 6.2. As previously noted, there are a number of confidential commercial arrangements available for drugs comprising the comparator regimen, in addition to several subsequent therapies. These act in a number of different directions upon the cost-effectiveness outcomes presented at list price over the following sections, and thus the direction of change in costs between scenarios may not represent that presented in the confidential appendix to this report.

All results presented in Section 6.2 are replicated in the confidential appendix, inclusive of all confidential commercial arrangements available to NHS England.

6.1 Exploratory and sensitivity analyses undertaken by the EAG

The EAG conducted the following exploratory analyses after applying the corrections to the adjustment of utilities for age, the implementation of the half-cycle correction, and the use of the latest NHS Reference Costs and eMIT cost data. Each of the following analyses are based upon this 'corrected' version of the company's model.

The following scenarios include several of those already presented by the company in response to requests by the EAG. They are repeated in this section as they contribute the greatest uncertainty, and the associated cost-effectiveness are affected by the corrections described above.

1. Cost-effectiveness of olaparib plus abiraterone in the BRCA subgroup (inclusive of biomarker testing costs for all arms).

As described in Section 4.2.6.2, the EAG considered the clinical evidence from PROpel and broader clinical and regulatory context to support a case for the targeted use of olaparib in patients with BRCA1/2 mutations. This analysis replicates that presented by the company and is implemented in the corrected version of the model.

Significantly, this analysis cannot fully represent the effectiveness of the comparator arm for the BRCA subgroup, as it does not incorporate efficacy data on olaparib monotherapy received by most patients following progression on abiraterone and enzalutamide in current clinical practice. This may mean the model overestimates incremental QALYs on olaparib plus abiraterone. This analysis also incorporates the corrections to genetic testing cost calculation and implementation as described in Section 4.2.8, with all patients in both treatment arms incurring the full per-patient testing cost in the first cycle of the model.

2a. RWE-derived hazard ratios used to estimate OS for enzalutamide (whole population).

As described in Section 3.5 and Section 4.2.6.1, a rapid review conducted by the EAG identified a number of large retrospective studies which had not been considered by the company, suggesting superior OS outcomes on enzalutamide compared with abiraterone. The EAG presented the results of a meta-analysis of these studies in Section 3.5, which generated a hazard ratio of 0.84 in favour of enzalutamide. This scenario applies the hazard ratios for the meta-analysis to modelled OS projections adjusting the efficacy of enzalutamide relative to abiraterone.

2b. RWE-derived hazard ratios used to estimate OS, PFS, and TTD for enzalutamide.

This scenario represents an extension of Scenario 2a, in which the hazard ratio of 0.84 derived from the EAG's meta-analysis of RWE is also applied to PFS and TTD for enzalutamide. This is in recognition of the typical mechanism of extensions to OS as a result of a drug prolonging the progression-free period, and illustrates the effect of preserving a link between extension to PFS and OS. It is often the case that the effect of treatment on PFS is greater than upon OS in terms of hazard ratio, and thus transposing the OS HR to PFS and TTD may be a conservative assumption – particularly in light of the PFS HR of 0.59 generated in the McCool NMA.[34] The application of this HR for TTD also aligns treatment costs associated on enzalutamide with prolonged efficacy.

3. Log-logistic extrapolation used to model overall survival (whole population)

As noted in Section 4.2.6.3, the EAG considered the log-logistic curve to present a plausible alternative to the generalised gamma extrapolation of OS favoured by the company. The log-logistic curve had a marginally superior statistical fit to OS data from PROpel, and generated long-term OS estimates for abiraterone and enzalutamide that better aligned with clinical advice received by the EAG. This scenario extrapolates OS for olaparib plus abiraterone, and abiraterone/enzalutamide.

4. Generalised gamma extrapolation used to model time to discontinuation.

As discussed in Sections 4.2.6 and 4.2.8, the EAG was concerned that the use of different functional forms to extrapolate TTD and PFS was likely to underestimate treatment duration and thus acquisition

costs, given the close clinical linkage between these outcomes, and the assumption of an increasing discontinuation rate over time inherent to the Weibull distribution. This scenario applies the generalised gamma curve to TTD, in accordance with the company's preferred extrapolation of PFS.

5. Use of PROfound PFS utility to represent progressed disease.

As discussed in Section 4.2.7, the EAG was concerned that the utility data associated with progressed disease collected in the PROpel study may not adequately represent the burden of disease in these patients. The PROfound study recruited patients who had progressed following an NHA, who had a progression-free utility of [redacted] – significantly lower than those who had progressed following an NHA in the PROpel study. This scenario explores the impact of applying a utility of [redacted] to the post-progression health state in the model.

6. Relative dose intensity used to adjust treatment acquisition costs.

As discussed in Section 4.2.8, the EAG consider it appropriate to adjust treatment acquisition costs to account for the RDI observed in the PROpel study. This scenario applies the RDI values presented in the company's clarification response to the intervention and comparator drugs. This scenario assumes that all tablets not taken due to dose reductions or interruptions result in cost saving, i.e. a new pack is not dispensed until the previous one has been used up.

7. Adverse event durations based on PROpel study.

The EAG noted a substantial disparity between the assumed duration of AEs in the model, and the observed durations in the PROpel study. This scenario explores the impact of applying the AE durations observed in the PROpel study, which increases the total disutility associated with AEs.

8. Testing costs for BRCA mutations

As discussed in Sections 2.2.4 and 4.2.8.7, the EAG considered the inclusion of testing for BRCA1/2 mutations appropriate where treatment decisions are driven by the existence of these biomarkers. In the whole population, patients are tested for BRCA1/2 mutations following progression on abiraterone or enzalutamide. This scenario implements testing costs at the point of progression to the comparator arm. As in Scenario 1 above, per-patient testing costs should be calculated as a function of the unit cost of adding a gene to a NGS panel - £34 per NHS England, and the number of patients needed to be screened to identify one actionable mutation (9.35 using PROpel data, based on 10.7% prevalence)

6.2 Impact on the ICER of additional clinical and economic analyses undertaken by the EAG

The results of the scenario analyses described in Section 6.1 are presented in Table 34. These results include the PAS discount for olaparib only. The exploratory scenarios presented in Table 40 are conducted on the EAG-corrected company base-case analysis. Results inclusive of all available PAS discounts and other commercial arrangements are provided in the confidential appendix to this report.

Table 34 EAG Exploratory fully incremental scenario analyses (deterministic)

Scenario	Technology	Total		Incremental		ICER
		Costs	QALYs	Costs	QALYs	
EAG-corrected company base-case	Abiraterone	[redacted]	[redacted]			
	Enzalutamide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Olaparib + Abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1. BRCA subgroup (inclusive of biomarker testing costs for all arms)	Abiraterone	[redacted]	[redacted]			
	Enzalutamide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Olaparib + Abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2a. RWE-derived hazard ratio for OS used to estimate relative effectiveness of enzalutamide and abiraterone	Abiraterone	[redacted]	[redacted]			
	Enzalutamide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Olaparib + Abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2b. RWE-derived hazard ratios applied to OS, PFS and TTD	Abiraterone	[redacted]	[redacted]			
	Enzalutamide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Olaparib + Abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3. Log-logistic extrapolation used to model OS	Abiraterone	[redacted]	[redacted]			
	Enzalutamide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Olaparib + Abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4. Generalised gamma extrapolation used to model TTD	Abiraterone	[redacted]	[redacted]			
	Enzalutamide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Olaparib + Abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5. PROfound PFS utility to represent progressed disease	Abiraterone	[redacted]	[redacted]			
	Enzalutamide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Olaparib + Abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6. RDI used to adjust treatment acquisition costs.	Abiraterone	[redacted]	[redacted]			
	Enzalutamide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Olaparib + Abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7. AE durations based on PROpel study.	Abiraterone	[redacted]	[redacted]			
	Enzalutamide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Olaparib + Abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8. Testing costs for BRCA mutations	Abiraterone	[redacted]	[redacted]			
	Enzalutamide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Olaparib + Abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
*These represent marginal, but non-zero differences.						

6.3 EAG's preferred assumptions

The cumulative impact of the EAG's preferred assumptions on the whole-population base-case are presented in Table 35 below. Fully incremental probabilistic results are also presented below (Table 37). For reference, probabilistic results of the EAG-corrected company base case are presented in Table 36. The primary drivers of changes in the ICER compared to the original company base-case analysis are the corrections described in Section 5, the use of literature-derived hazard ratios to estimate the relative effectiveness of enzalutamide compared to abiraterone, the use of alternative extrapolations of OS, and the alignment of TTD and PFS extrapolations. Note that the following results are generally presented in a fully incremental format, reflecting the EAG's position that for the majority of patients treated on the NHS, there is unlikely to be a clear steer towards enzalutamide or abiraterone on the basis of efficacy or contraindications. The EAG also highlights that the results below are only inclusive of the PAS discount available for olaparib. There are commercial arrangements in place for the comparator treatments, which impact the magnitude and direction of the ICER effects across the scenario analyses below. Results inclusive of all available commercial arrangements are presented in the confidential appendix to this report.

The EAG whole-population base case adopts the following scenarios described in Section 6.1 on top of the corrections previously described:

Scenario 2b: RWE-derived hazard ratios used to estimate OS, PFS, and TTD for enzalutamide.
Scenario 4: Generalised gamma to model time to discontinuation
Scenario 6: Relative dose intensity used to adjust treatment acquisition costs
Scenario 7: Adverse event durations based on PROpel
Scenario 8: Testing costs for BRCA mutations

Table 35 EAG's preferred model assumptions (whole population) - deterministic

Preferred assumption	Section in EAG report	Cum. ICER vs abiraterone	Cum. ICER vs enzalutamide
Corrections to company base case	*4.2.7, 6.1*	[redacted]	[redacted]
Scenario 2b: RWE-derived hazard ratios used to estimate OS, PFS, and TTD for enzalutamide.	*4.2.6.1, 6.1*	[redacted]	[redacted]
Scenario 4: Generalised gamma to model time to discontinuation	*4.2.6.10, 6.1*	[redacted]	[redacted]
Scenario 6: Relative dose intensity used to adjust treatment acquisition costs	*4.2.8.1, 6.1*	[redacted]	[redacted]
Scenario 7: Adverse event durations based on PROpel	*4.2.7.5, 6.1*	[redacted]	[redacted]
Scenario 8: Testing costs for BRCA mutations	*4.2.8.8, 6.1*	[redacted]	[redacted]

Table 36 EAG-corrected company base case: probabilistic fully incremental results

Technology	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
Abiraterone	[redacted]	[redacted]			
Enzalutamide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Olaparib + Abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Indicates non-zero differences

Table 37 EAG's preferred model assumptions (whole population): fully incremental probabilistic results

Technology	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
Abiraterone	[redacted]	[redacted]			
Enzalutamide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Olaparib + Abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Given the greater potential for cost-effective use of olaparib in the BRCA subgroup, an alternative set of EAG preferred assumptions are presented in Table 38Table 3. Note that the EAG applies the lognormal extrapolations for OS, PFS, and TTD based on the company's implementation of the scenario. This approach aligns with the company's implementation of this scenario, in which projections of PFS and TTD adopted the same functional form. The EAG also reiterates that the model structure as presented cannot capture the full impact of the comparator arm on QALY gain, as

NHS practice comprises a sequence of treatments not used in the PROpel study. This analysis is therefore only illustrative of the potential cost-effectiveness of olaparib in this population, and is likely to over-estimate the real-world ICER. This analysis adopts the following assumptions:

Scenario 1: BRCA mutation subgroup (inclusive of biomarker testing costs for all arms).
Scenario 6: Relative dose intensity used to adjust treatment acquisition costs
Scenario 7: Adverse event durations based on PROpel

Table 38 EAG's preferred model assumptions (BRCA mutation population) (deterministic)

Preferred assumption	Section in EAG report	Cum. ICER vs abiraterone	Cum. ICER vs enzalutamide
Corrections to company base case (whole population)	*4.2.7, 6.1*	[redacted]	[redacted]
Scenario 1: BRCA subgroup (inclusive of biomarker testing costs for all arms).	*4.2.6.2, 6.1*	[redacted]	[redacted]
Scenario 6: Relative dose intensity used to adjust treatment acquisition costs	*4.2.8.1, 6.1*	[redacted]	[redacted]
Scenario 7: Adverse event durations based on PROpel	*4.2.7.5, 6.1*	[redacted]	[redacted]

The probabilistic results of the EAG's base-case analysis in the BRCA population are presented in fully incremental (Table 39) and pairwise (Table 40) format below. In this analysis, olaparib had a [redacted] probability of being the most cost-effective treatment option at a WTP threshold of £20,000 per QALY gained, and a [redacted] probability at £30,000. The cost-effectiveness plane for this analysis is presented in Figure 22.

Table 39 EAG's preferred model assumptions (BRCA mutation population): fully incremental probabilistic results

Technology	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
Abiraterone	[redacted]	[redacted]			
Enzalutamide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Olaparib + Abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Indicates non-zero differences

Table 40 EAG's preferred model assumptions (BRCA mutation population): pairwise probabilistic results

Technology	Total costs	Total QALYs	Incremental costs (olaparib vs)	Incremental QALYs (olaparib vs)	ICER (olaparib vs)
Olaparib + Abiraterone	[redacted]	[redacted]			
Abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Enzalutamide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Figure 22 Cost-effectiveness plane for EAG's alternative BRCA population base-case analysis (WTP threshold £30,000)

[redacted]

6.4 Conclusions of the cost effectiveness section

6.4.1 Summary of the company's cost-effectiveness analysis

The company submitted a *de novo* economic model to assess the cost-effectiveness of olaparib plus abiraterone in pairwise and fully incremental comparisons with abiraterone and enzalutamide for the treatment of untreated hormone-relapsed metastatic prostate cancer. In the absence of trial data comparing enzalutamide with olaparib plus abiraterone, it was assumed to be equally efficacious to abiraterone alone. The company's base-case analysis suggested that olaparib plus abiraterone was more costly and more effective than both abiraterone and enzalutamide. Olaparib plus abiraterone cost [redacted] and [redacted] more than abiraterone and enzalutamide respectively in the company's deterministic base-case analysis, but generated [redacted] incremental QALYs, with an ICER of [redacted] per QALY gained.

In the company's probabilistic base-case analysis, olaparib with abiraterone generated similar costs and QALYs, with a [redacted] probability of being the most cost-effective option at a willingness-to-pay threshold of £20,000 per QALY gained, and an [redacted] probability of at a willingness-to-pay threshold of £30,000 per QALY gained. Note that these results are based on the net price of olaparib inclusive of a patient access scheme, but are exclusive of confidential commercial arrangements for the comparator therapies.

6.4.2 Conclusions of the EAG's critique

The EAG considers the submitted evidence to broadly reflect the decision problem defined in the final scope, but note that the submitted analyses did not meet the requirements of the NICE reference case with regards to the use of unmapped EQ-5D-5L values derived from the PROpel trial directly in the model, and the failure to adjust utilities to reflect the impact of ageing. The EAG's review of the company submission identified several areas of uncertainty, and a number of significant methodological issues which the EAG has sought to address where possible in the presented corrections and revised base-case.

The EAG identified several uncertainties regarding the population eligible for treatment. It was not clear how the wording of the licenced indication, i.e. patients in whom chemotherapy is 'not clinically indicated' was to be interpreted with regards to the trial population, or how this corresponded to NHS practice. The company's description of this population appeared to rule out 25% of the PROpel trial population, and it was therefore unclear whether the trial data could adequately reflect the costs and outcomes associated with the use of olaparib on in NHS practice.

The EAG was also concerned that the heterogeneity of treatment effect according to presence of the BRCA1/2 biomarker was not reflected in the company's economic analysis. The EAG noted that the treatment effect observed in BRCAm patients may be driving clinical-effectiveness in the whole population, and olaparib combination treatment may have less potential for cost-effectiveness in patients without this mutation.

There were two primary issues identified with regards to the company's modelling of the comparators. Firstly, while it was argued by the company that the larger market share of enzalutamide justified its designation as 'primary comparator', the EAG disagreed that this was necessarily indicative of current and future NHS practice. This is because Blueteq data sourced in support of this assumption was drawn from a period in which interim Covid-19 guidance was in place in this indication. Furthermore, as generic abiraterone, costing a fraction of the price of the proprietary product, has been available since late-2022. This may influence uptake trends given the lack of a clear difference in efficacy between these treatments. The EAG considered these two treatments to be essentially clinically interchangeable for the majority of patients, and thus preferred to present cost-

effectiveness results in a fully incremental format, per the NICE reference case. The second issue relates to the mismatch between the trial and NHS practice with regards to the composition of the comparator arm. The availability of olaparib monotherapy following progression on an NHA on the NHS practice is likely to improve OS outcomes compared to the PROpel trial. This is especially the case in the BRCA subpopulation, in which the majority of patients are likely to receive effective treatment with olaparib. This is likely to mean the model underestimates OS outcomes in the abiraterone/enzalutamide treatment arm.

The EAG identified a number of issues that were considered to constitute methodological errors in the model. These comprised the failure to adjust utilities over time as patients aged, which resulted in patients having a HRQoL far above that of members of the unaffected general population, the application of a half cycle correction to acquisition costs incurred at the start of the month, and the use of outdated NHS Reference Costs and eMIT costs which were inflated to the current cost year, rather than using the latest data. These issues were included as model corrections, and resulted in a moderate increase to the ICER for olaparib with abiraterone.

The EAG considered the company to have overlooked a large body of real-world evidence, which taken as a whole suggested a small but significant benefit of enzalutamide over abiraterone. These studies indicated that the assumption of equivalence was not appropriate, or representative of the balance of evidence. The EAG undertook a rapid review and meta-analysis to produce alternative hazard ratios with which to model the relative effectiveness of enzalutamide.

The EAG noted that alternative parametric models generated clinically plausible long-term OS estimates and had a superior (if very similar) statistical fit to the generalised gamma curve chosen by the company. Alternative OS extrapolations may present equally plausible but less optimistic interpretations of data from the PROpel study; the EAG recognises that the log-logistic curve is an unflattering representation of observed data for olaparib plus abiraterone, despite producing a better fit to PROpel data on abiraterone alone.

The EAG had concerns regarding the company's extrapolation of TTD which predicted the shortest mean time on treatment and therefore much lower treatment costs than alternative extrapolations. The EAG further noted that this choice of extrapolation was inconsistent with the parametric function to that applied to PFS. This implied a divergence in TTP and PFS which assumes sustained PFS benefits after discontinuation of treatment. As the company did not provide evidence supportive of durable PFS benefits off-treatment, the EAG did not consider this assumption reasonable. The EAG prefers the use of consistent functional forms to model TTD and PFS reflecting the fact that these outcomes are likely to be strongly interlinked.

Finally, the EAG noted that genetic testing costs for BRCA1/2 mutations were not properly calculated or implemented correctly by the company. This affected the scenario in which testing costs were applied to all patients in the comparator arm, with the unit cost of a single test applied in the first model cycle rather than at the point of progression. It also affected the BRCA subgroup analysis, as again the cost of a single test was applied in the first cycle, rather than the total per cost of testing per eligible patient identified.

7 SEVERITY MODIFIER

The company has not made a case for the use of a severity modifier. The EAG agrees that the severity modifier would not apply for this population. Based on the company base-case analysis and modelled patient characteristics, absolute QALY shortfall is likely to be approximately [redacted] QALYs, or a proportional shortfall of [redacted]

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Single Technology Appraisal

Olaparib with abiraterone for untreated hormone-relapsed metastatic prostate cancer [ID3920]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by the end of **5 July** using the below comments table.

All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and separately highlight information that is submitted as 'commercial in confidence' in turquoise, all information submitted as 'academic in confidence' in yellow, and all information submitted as 'depersonalised data' in pink.

Issue 1 No evidence of mapping from EQ-5D-5L to EQ-5D-3L

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
"The company stated that EQ-5D-5L data collected in PROpel were cross-walked to EQ-5D-3L per the NICE reference case. However, there was no evidence of this process having been undertaken; all data derived from the trial and used in the regression models referred explicitly to EQ-5D-5L"	Amend the EAG report to reflect the company submission which states that *"In line with NICE methods guidance, the EQ-5D-5L responses collected in PROpel were 'cross walked' to produce EQ-5D-3L derived UK utility values using the Hernández Alava et al., 2017 algorithm"* or expand in the EAG report which specific analyses beyond what has been provided in the company evidence submission (see Section B.3.4.2) may be produced by the company to "demonstrate that utilities were based on EQ-5D-3L values."	In the company evidence submission Section B.3.4.2 titled "Mapping" - the company provided a description of the methods undertaken to map the EQ-5D-5L values collected in the PROpel submission to EQ-5D-3L. As summarised, the EQ-5D-5L responses collected in PROpel were 'cross walked' to produce EQ-5D-3L UK utility values using the Hernández Alava et al., 2017 algorithm as per the NICE reference case. The economic model uses these mapped EQ-5D-3L values to estimate the health state utility of patients in the progression-free and progressed disease states. There are no utility values reported using an EQ-5D-5L value set in any part of the company submission. Mixed models for repeated measures (MMRM) were used to estimate the statistical relationship between utilities and health state (e.g., defined by progression or treatment status) details of which is provided in Table 32 of the company evidence submission. The company would like to clarify that although the caption of Table 32 refers to EQ-5D-5L, this is only to reflect the fact that the HrQoL questionnaires administered in the PROpel study were based on the EQ-5D-5L instrument. Likewise any reference to EQ-5D-5L in the company's response to the EAG's	The EAG made this request in the EAR in light of the extent to which utility data was labelled as EQ-5D-5L throughout the company's clarification response. 'EQ-5D-5L scores' were explicitly presented and discussed in raw form in Fig 9, Table 18, and Table 19. The clarification response also states that 'the…(MMRM) was performed using all EQ-5D-5L data reported in PROpel'. No technical reference was made to mapping beyond the company submission. Evidence to demonstrate that mapping was undertaken includes the

		clarification questions seeks to highlight the underlying dataset from the clinical trial. This does not negate the company's evidence submission which clearly states, *"In line with NICE methods guidance, the EQ-5D-5L responses collected in PROpel were 'cross walked' to produce EQ-5D-3L derived UK utility values using the Hernández Alava et al., 2017 algorithm".* The EAG in their report have for the first time requested further evidence to demonstrate that mapping has indeed been conducted by the company. It is however not immediately clear to the company what more can provided beyond the information in the company evidence submission (see Section B.3.4.2) – therefore we welcome specific requests from the EAG or the NICE technical team to resolve this issue.	code used to implement the Hernández Alava algorithm, and a comparison of raw 5L utility values with their mapped 3L equivalents.

Issue 2 Lack of critical analysis of the EAG's non-randomised study

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Section 3.5 in the EAR, a summary of non-randomised evidence identified and synthesised in a meta-analysis conducted by the EAG resulted in a HR 0.84 in favour of enzalutamide as compared to abiraterone	The description of the EAG's meta-analysis should be presented along with the strengths and uncertainties to allow fair and balanced assessment of whether it is appropriate to adopt the results in any base case analysis.	There is insufficient assessment of the evidence and a lack of commentary in the EAR with regards to: • the appropriateness of pooling the observational evidence identified by the EAG with respect to comparability of the	Not a factual inaccuracy. Although the evidence available is insufficient to justify stating that there is a clear difference in efficacy between abiraterone and enzalutamide, it nevertheless indicates that

leading to the EAG concluding on Page 51 that *"while there is uncertainty about the relative effectiveness of abiraterone and enzalutamide the balance of evidence indicates that enzalutamide is more efficacious."* The EAR however goes on to provide a contradictory conclusion on Page 112 where the EAG states "*Furthermore, as generic abiraterone, costing a fraction of the price of the proprietary product, has been available since late-2022. This may influence uptake trends given the lack of a clear difference in efficacy between these treatments. The EAG considered these two treatments to be essentially clinically interchangeable for the majority of patients, and thus preferred to present cost-effectiveness results in a fully incremental	For balance, the EAG summary should also acknowledge that the only study which included UK patients was Chowdhury et al. All other studies reflect a highly heterogeneous mix of patients from many different geographic regions across different lines of therapy which is not aligned with the population under consideration for the appraisal. The EAR should also provide further clarity on why in some instances the EAG considers abiraterone and enzalutamide as clinically interchangeable with no clear difference in efficacy, but in their NMA results, a benefit in favour of enzalutamide is supported for the base case.	baseline characteristics and the quality of the studies • the assumptions underpinning the meta-analysis, and • the strengths and limitations of such analyses. The company is particularly concerned that the meta-analysis included studies - as indicated in Table 11 of the EAR - with populations who were pre-treated for mCRPC with docetaxel. This is not aligned with the relevant positioning of the appraisal which is in first line use in adult patients who have not yet received treatment for mCRPC. This population is distinct from those enrolled in the PROpel study which included patients who received prior docetaxel in the neoadjuvant or adjuvant treatment for localised prostate cancer and metastatic hormone-sensitive prostate cancer (mHSPC). The company considers the pooling of studies across different lines of treatment in mCRPC as inappropriate and biased due to the differing risk profiles between the two groups of patients since those who are more heavily pre-treated for mCPRC are likely to have worse prognosis. Furthermore, the EAG's meta-analysis weights are linked to variance of studies rather than the	enzalutamide is more efficacious.

format, per the NICE reference case."		quality or risk of bias of the study design, or the generalisability of the study to a UK population. Despite the EAG concluding that the balance of evidence indicates that enzalutamide is more efficacious on Page 51 of the EAR, this is at odds with the clinical feedback received by the EAG (and the company) which highlighted *"The clinical advisor considered the efficacy of enzalutamide and abiraterone to be similar."* Further clarity should be provided on the clinical validity of the results from the EAG's meta-analysis.	

Issue 3 Prior docetaxel use in the PROpel study as justifcation for broadening EAG evidence reveiw

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
On Page 48 of the EAR, the EAG state *"Given the company's November 2021 search date, the EAG sought to update and broaden the company's review to identify peer-reviewed, published papers of non-randomised studies comparing abiraterone with enzalutamide in patients with mCRPC, regardless of the line of treatment (given*	Reference to the inclusion of patients who received docetaxel in the PROpel study should be revised to reflect that this was received in the earlier disease setting for localised prostate cancer and metastatic hormone-sensitive prostate cancer (mHSPC) not mCRPC.	Olaparib has another indication based on the pivotal trial named "PROfound" which includes patients in later lines of mCRPC who had progressed following treatment an NHA and potentially docetaxel. This population is distinct from the indication in consideration for this appraisal based on the PROpel study where those enrolled included patients who received prior docetaxel but in the neoadjuvant or adjuvant treatment for localised prostate cancer and metastatic hormone-sensitive prostate cancer (mHSPC) not mCRPC as suggested by the EAG. As stated in the NEJM evidence paper for PROpel: "*With the exception*	Thank you for pointing out the prior docetaxel for mCRPC issue in PROpel. The text "(given that nearly a quarter of the PROpel cohort had received prior docetaxel for mCRPC)." has now been deleted. Most of the studies included in the EAG's meta-analysis were in chemotherapy-naïve cohorts. The EAG also considered it reasonable

that nearly a quarter of the PROpel cohort had received prior docetaxel for mCRPC).” This misunderstanding is used as the primary justification to extend the scope of the EAG’s evidence review to include studies with pre-treated patients in their meta-analysis.		*of androgen depletion therapy and first-generation antiandrogen agents with a 4-week washout period, prior systemic treatment in the mCRPC first-line setting was not allowed. Docetaxel during neoadjuvant/adjuvant treatment for localized prostate cancer and metastatic hormone-sensitive prostate cancer (mHSPC) was permitted.”* It should be noted that these two groups have distinct profiles which is evident in the differences seen in the PFS and OS outcomes from PROpel clinical trial versus the PROfound study. This impacts on the relevance of the EAG’s expanded including both pre- and post-chemotherapy studies and the results of the associated meta-analysis.	to maximise the evidence-base (by including cohorts with patients who had previously received chemotherapy) given that studies adjusted for docetaxel use and that we were not aware of any reason to suspect that the use of prior chemotherapy for mCRPC would modify the relative OS effect seen when comparing abiraterone with enzalutamide.

Issue 4 Use of utility values from PROfound in the PROpel population

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
On Page 80, the EAR states with regards to the PROfound trial *“These patients had progressed following treatment with abiraterone at the point of entering the trial and may therefore be broadly comparable to the*	To acknowledge that the full PROfound data may not be generalisable to the PROpel population due to the differences in prior treatments received by patients.	The PROfound study cohort comprised patients who had progressed during treatment with a previous NHA for metastatic or non-metastatic castration-resistant prostate cancer or for mHSPC. The utilities from this cohort are not generalisable to the progressed patients in PROpel as approximately 55% of patients in PROfound had	Amendment made as suggested to existing caveats on Page 80/81 on EAR. Note that this is an exploratory scenario

progressed population considered in the present appraisal."		previous treatment with a taxane for mCRPC before entry to the study. The overall PROfound cohort is therefore more heavily pre-treated than the progressed cohort of PROpel; none of whom had received a taxane for mCRPC at the point of progression.	analysis, and does not affect the EAG base case. An additional correction to the discussion of baseline bone metastases with regards to the two trials has also been made.

Issue 5 Impact of olaparib monotherapy on costs and outcomes

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
On Page 113, *"The availability of olaparib monotherapy following progression on an NHA on the NHS practice is likely to improve OS outcomes compared to the PROpel trial. This is especially the case in the BRCA subpopulation, in which the majority of patients are likely to receive effective treatment with olaparib. This is likely to mean the model underestimates OS outcomes in the*	To revise text to fully reflect the fact that the model may underestimate both the costs and OS.	The statement does not fully reflect the impact of increasing the use of olaparib monotherapy in the control arm on the cost-effectiveness result, e.g., that the model may underestimate both the OS outcomes and costs in the abiraterone and enzalutamide treatment arms. The current EAG report speculates that the introduction of olaparib monotherapy would have a significant bearing on the ICER, when this is yet to be proven given that both costs and OS would be impacted by any change to the choice of subsequent treatment.	The company's model explicitly includes the cost of olaparib monotherapy for 14.9% of patients following progression on abiraterone and enzalutamide. This is discussed briefly in the EAR. This already represents the majority of secondary therapy costs on the comparators, and may in fact overestimate costs if BRCAm prevalence is

abiraterone/enzalutamide treatment arm."			below 14.9% in this population.

Issue 6 Clarity on whether the EAG-preferred base case includes HR for PFS, TTD and OS

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Page 16, the EAR states under the summary of Issue *4 "The EAG prefers the application of this HR to OS, PFS, and TTD to align treatment costs with prolonged expected effectiveness."* Page 108*, "The EAG whole-population base case adopts the following scenarios described in Section 6.1 on top of the corrections previously described: Scenario 2b: RWE-derived hazard ratios used to estimate OS, PFS, and TTD for enzalutamide."* However, in the EAG revised cost-effectiveness model, only the HR for OS is	Propose revising the EAR to clarify whether the EAG base case includes the application of a HR of 0.84 for abiraterone versus enzalutamide to PFS, OS and TTD, or justification for why this is applied to OS alone.	Alignment of the EAR with the EAG-revised cost-effectiveness model.	The company refers to a mistake in the default settings in the version of the model sent to the company. All results in the EAR were generated using the combination of scenarios described in the report itself.

included in the EAG base case. For PFS and TTD, a HR of 1.0 is assumed suggesting equivalent efficacy for abiraterone versus enzalutamide but a clinical benefit in favor of enzalutamide for OS alone.			

Issue 7 Upper confidence interval for results of the fixed effects NMA for abiraterone vs olaparib for OS

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**EAG Response**
The Company evidence submission, Page 57, erroneously reports the upper credible interval of the NMA results for olaparib plus abiraterone compared to abiraterone as HR of [redacted]. The company's error has been carried through to the EAR, Page 46, Table 10.	The upper CrI as indicated in Figure 10 should be revised to [redacted] as per Figure 10 in the company evidence submission.	To accurately reflect the upper credible interval of the NMA results for olaparib plus abiraterone compared to abiraterone.	Amendment made as suggested.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Olaparib with abiraterone for untreated hormone-relapsed metastatic prostate cancer [ID3920]

Technical engagement response form

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this evaluation.

Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAR that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

The deadline for comments is **5pm** on **17th August.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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About you

Table 1: About You

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	AstraZeneca UK
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	N/A
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	N/A

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Key Issues for Engagement

Table 2: Key Issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Issue 1 Interpretation and implications of the wording of the marketing authorisation of olaparib plus abiraterone	No	The wording of the marketing authorisation as defined by the MHRA (and the EMA) for olaparib plus abiraterone is reflective of the trial population and evidence base for the regulatory submissions. The PROpel study enrolled and stratified patients who were both docetaxel naïve (75%) and exposed (25%) in the pre-mCRPC setting; this is generalisable to the UK treatment pathway for prostate cancer where, if deemed suitable for their disease management, some patients may receive treatment with docetaxel. The NICE guidance [NG131][1] recommended docetaxel as the standard of care (SoC) for treating mHSPC (metastatic hormone sensitive prostate cancer). Nevertheless, the findings from the 2019 Annual Prostate Cancer Report[2] noted that, docetaxel uptake in the UK 'seemed low' at only 27% - this is aligned with the 25% docetaxel exposure observed in the PROpel study. Following this, the interim COVID-19 guidance [NG161][3] in 2020 recommended the use of enzalutamide plus ADT (androgen deprivation therapy) in mHSPC patients instead of docetaxel to reduce toxicity and potential for admission. As a result, the use of docetaxel in chemotherapy-naïve patients remained low, whilst the use of enzalutamide increased. Currently, in the UK the following NHAs can be initiated instead of docetaxel in the pre-mCRPC setting - apalutamide [TA741][4] and enzalutamide [TA712][5] which are available in mHSPC, and in non-metastatic castrate resistant prostate cancer (nmCRPC), apalutamide [TA740][6] and darolutamide [TA660][7] are also recommended. Docetaxel is therefore no longer considered the SoC in chemotherapy- and NHA-naïve patients, hence the proportion of patients who are both exposed to docetaxel (25% in the PROpel study) and are also NHA naïve (a pre-requisite for inclusion in the PROpel study) in the pre-mCRPC stages are in the minority. This is unsurprising as UK prostate cancer clinical experts consulted by the company have highlighted that NHAs are more efficacious, tolerable, and less toxic than docetaxel, and therefore even if a patient was historically 'fit' enough for chemotherapy, they would still mostly treat them with an NHA. Due to the historical placement of chemotherapy in the treatment pathway, the regulatory (and NICE) recommendations for enzalutamide *[TA377][8]* and abiraterone *[TA387][9]* in mCRPC (which followed that of docetaxel in the UK) were formulated to consider whether the evidence base for these NHAs supported use in those who received prior docetaxel. Their respective label wording for first line mCRPC includes the statement *"in whom chemotherapy is not **yet** clinically indicated"* to reflect the trial population (i.e., PREVAIL[10] and COU-

Key issue	Does this response contain new evidence, data or analyses?	Response
		AA-302[11]) who were mostly docetaxel naïve, hence would potentially be eligible for chemotherapy in the future. In contrast, the olaparib label - "*in whom chemotherapy is not clinically indicated*" - was amended slightly by the regulators to exclude the wording ***yet*** with the intent of differentiating the more contemporary PROpel trial which included patients who were both docetaxel naïve and exposed given the shift in clinical practice. The EAG is concerned that based on the license wording of olaparib plus abiraterone (i.e., for first line use in patients with mCRPC for whom chemotherapy is not clinically indicated), *"most patients in the PROpel cohort would not be eligible to receive olaparib plus abiraterone in NHS practice since the large chemotherapy-naïve subgroup, were fit enough (all were ECOG 0 or 1) to receive docetaxel; they should therefore receive docetaxel before they receive olaparib plus abiraterone"*. Whilst it is theoretically possible for the PROpel cohort to receive docetaxel on account of their performance status and lack of exposure to chemotherapy, eligibility for docetaxel does not preclude the use of NHAs (alone or in combination with a PARP inhibitor) in current day NHS clinical practice. Clinical practice and the evolving UK pathway does not necessitate the use of docetaxel before NHAs, and is instead guided by clinical judgment, eligibility and/or most importantly, patient choice in deciding whether chemotherapy is an appropriate treatment choice. The wording of the marketing authorisation for olaparib is therefore reflective of the PROpel study design where both docetaxel-naïve (~75%) and docetaxel-experienced (~25%) patients were enrolled in first-line mCRPC to reflect the changing landscape where docetaxel is no longer more commonly used before NHAs in the pre-mCRPC setting.

Key issue	Does this response contain new evidence, data or analyses?	Response
Issue 2 Efficacy of olaparib plus abiraterone in the PROpel trial driven by the small subgroup of BRCA mutation patients	No	The scope of the appraisal as defined by NICE is in '*adults with hormone-relapsed metastatic prostate cancer for whom chemotherapy is not clinically indicated'* which complements the MHRA (and EMA) license. On this basis, AstraZeneca would like to highlight that the totality of the evidence in relation to the intention-to-treat (ITT) and subgroup populations should be considered in the appraisal of the evidence base. To this end, we have provided a range of clinical and economic evidence to the committee for consideration, including the following analyses from the latest data cut of the PROpel study: 1. ITT including the following subgroups: a. Confirmed HRR (homologous recombination repair) mutation which is inclusive of those who are BRCA-mutation (BReast CAncer gene) (*requested at NICE scoping*), b. Confirmed BRCA mutation and finally (*requested at EAG CQs*), c. non-HRR mutation which includes those who are HRRm-unknown (*requested at EAG CQs*). In response to whether the efficacy of olaparib plus abiraterone is driven by those with a BRCA-mutation, the company would like to highlight the following considerations when interpreting the evidence: • The PROpel study was powered to demonstrate efficacy and safety in an ITT population, regardless of biomarker status. The presence of a biomarker was also retrospectively assessed, and HRR-mutation status (inclusive of BRCA-mutated subgroup) was only determined after randomisation. The analyses of the biomarker subgroups are therefore non-stratified and post-hoc, hence the results should be interpreted with caution. • Those with an HRR-mutation made up 25% of the trial population with the further subset of those who are BRCA-mutated subgroup comprising of 11% of the intention-to-treat population. It is therefore unlikely that the clinical benefit observed in the PROpel study is entirely driven by the BRCA-mutated subgroup who make up a relatively small proportion of the trial population. Furthermore, the analysis presented by the company in Section 2.7.2 of the dossier for the broader HRRm subgroup also demonstrated clinically meaningful benefit in favour of olaparib: ○ Median PFS was [redacted] months for olaparib plus abiraterone vs. [redacted] months for placebo plus abiraterone (HR=[redacted])

Key issue	Does this response contain new evidence, data or analyses?	Response
		○ Median OS was [redacted] for olaparib plus abiraterone vs. [redacted] months for placebo plus abiraterone (HR=[redacted]) • Although the benefit in the HRRm population including the BRCA-mutated subgroup is more pronounced, the data in the non-HRR-mutated subgroup also supports some benefit for olaparib plus abiraterone in those who do not carry an HRR-mutation (includes those without BRCAm): ○ The post-hoc analysis in non-HRRm demonstrates that olaparib is associated with a median PFS of [redacted] months vs. [redacted] months for placebo plus abiraterone (HR=[redacted], p=[redacted] ○ For OS, the median for olaparib was [redacted] months vs. [redacted] months for placebo (HR=[redacted]), p=[redacted]. These outcomes are noteworthy given olaparib was compared against an active treatment, abiraterone. By contrast, the studies for the current standard of care in the UK - PREVAIL for enzalutamide and COU-AA-302 for abiraterone – were compared against placebo and prednisone, respectively. Despite this, olaparib demonstrated clinical benefit in the ITT and subgroup populations when compared to the current approved treatment options in the UK. The assessment of the clinical value of olaparib in this indication should therefore be considered against the strength of the evidence base relative to the currently approved treatment options in the UK. Finally, the EAG cited olaparib's demonstrated efficacy in the BRCA-mutated population from previous NICE recommendations for olaparib monotherapy [TA887]. The company would like to highlight that the evidence base for PROpel should be considered on its own merits, hence conclusions in relation to prior investigations of olaparib monotherapy in an NHA-exposed population (PROfound study) are not applicable to this appraisal. The PROpel study is the first confirmatory study for olaparib plus abiraterone that validates the **combined** inhibition of PARP (poly-ADP ribose polymerase) and AR (androgen receptor) pathways in first-line mCRPC. It is therefore the combination of olaparib with abiraterone that results in increased DNA damage, leading to an improved anti-tumour effect that also demonstrates some efficacy in the non-HRRm population.

Key issue	Does this response contain new evidence, data or analyses?	Response
Issue 3 Limited use of subsequent olaparib monotherapy in PROpel	No	The EAG is concerned that only 1.6% of patients received subsequent olaparib monotherapy in the comparator arm, when <10% of the enrolled population were BRCA positive and would therefore be eligible for the olaparib monotherapy as per the PROfound trial following disease progression. However, it is worth noting that approximately 50% of patients with mCRPC will only receive one line of therapy and therefore will not progress to receive a subsequent treatment[12-14]. Additionally, there are various other factors that affects the choice of subsequent therapy including physician choice, contraindications, and patient fitness. Prostate cancer clinical experts consulted by the company also highlighted that there are barriers to accessing olaparib monotherapy for NHA-exposed patients in the UK mainly due to challenges in the uptake, feasibility and/or failure rate of deriving BRCA mutation testing. For this reason, not all patients in the UK who have a BRCA-mutation would be identified and eligible to receive olaparib monotherapy following disease progression on an NHA. Therefore, the EAG's assumption that ~10% patients who have a BRCA mutation should have received subsequent olaparib monotherapy is an overestimation of the expected NHS cohort. The budget impact assessment of olaparib monotherapy estimated that by 2023 approximately [redacted] patients would be eligible for olaparib as per the PROfound indication. This would mean on average, there should be about [redacted] new patients per month who may be eligible for olaparib monotherapy following progression on an NHA. [redacted]

Key issue	Does this response contain new evidence, data or analyses?	Response
Issue 4 Assumption of efficacy equivalence when comparing abiraterone and enzalutamide	Yes	Due to the lack of head-to-head studies comparing olaparib plus abiraterone to the primary comparator, enzalutamide, indirect methods were required to assess relative efficacy. A rigorous feasibility assessment of conducting a network meta-analysis (NMA) was undertaken which included a detailed qualitative evaluation of the included studies based on the study designs, baseline characteristics, prognostic factors and treatment effect modifiers (see Section B.2.9 in the company evidence submission). Due to distinct differences in the comparator arms between the relevant randomised trials for olaparib plus abiraterone (i.e., placebo + prednisone), abiraterone (i.e., prednisone) and enzalutamide (i.e., placebo) monotherapies, a strong network could not be established. However, a network for enzalutamide could be established via abiraterone by the grouping of placebo and prednisone and assuming these regimens have equivalent effect. This was reliant on the extent to which prednisone and placebo may be considered clinically equivalent and interchangeable. Overall, the available evidence in the literature and expert clinical opinion suggested that prednisone may have a therapeutic effect on rPFS (but not OS) therefore an NMA on PFS is likely to be biased. For this reason, the company concluded that it may be reasonable to assume prednisone was equivalent to placebo for the purposes of building a network of evidence for OS, but not necessarily for PFS. The results of the exploratory fixed effect NMA for OS (based on the pivotal randomised studies) presented in Section B.2.9.2.4 in the company submission suggested there were no meaningful differences in OS between enzalutamide and abiraterone (HR=[redacted], 95% CrI[redacted]. This was further supported and validated by evidence from six clinical experts interviewed by the company, all of whom explained that abiraterone and enzalutamide are clinically equivalent in terms of PFS and OS. The EAG considered the company's NMA OS HR based on randomised studies to be unreliable due to important trial heterogeneity which was likely to be biased in favour of abiraterone. The EAG's view is aligned with the company's qualitative feasibility assessment of the studies included in the NMA (see Section B.2.9.1 of the company evidence submission). The EAG identified further non-randomised studies and conducted a pair-wise

Key issue	Does this response contain new evidence, data or analyses?	Response
		meta-analysis using random effects estimator, the results of which support an OS benefit in favour of enzalutamide; HR 0.84 (95% CI: 0.77 to 0.91). This analysis was conducted for OS only and not for PFS. The company would like to highlight that the issues identified by the company and noted by the EAG with regards to heterogeneity in the company's NMA for OS are equally applicable to the EAG's analysis. Indeed, the pooling of non-randomised studies may be more prone to bias and confounding due to the fact that observational studies are a lower standard of evidence (when compared to the pooling of randomised studies). The company is also concerned with the lack of commentary in the EAG's report with regards to: • the appropriateness of pooling the observational evidence identified by the EAG with respect to comparability of the baseline characteristics and the quality of the studies, • the assumptions underpinning the meta-analysis, and • the strengths and limitations of such analyses The company is particularly concerned that the meta-analysis included studies - as indicated in Table 11 of the EAR - with populations who were pre-treated for mCRPC with docetaxel. This is not aligned with the relevant positioning of the appraisal which is in first line use in adult patients who have not yet received treatment for mCRPC. This population has a different risk profile from those enrolled in the PROpel study which included patients who received prior docetaxel in the neoadjuvant or adjuvant treatment for localised prostate cancer and metastatic hormone-sensitive prostate cancer (mHSPC). Furthermore, the EAG's meta-analysis weights are linked to a variance of studies rather than the quality or risk of bias of the study design, or the generalisability of the study to a UK population. Despite the EAG's conclusion that the balance of their evidence indicates that enzalutamide is more efficacious, this is at odds with the clinical feedback received by the EAG (and the company) which highlighted *"The clinical advisor considered the efficacy of enzalutamide and abiraterone to be similar."* Further clarity should be provided on the clinical and face validity of the results from the EAG's meta-analysis.

Key issue	Does this response contain new evidence, data or analyses?	Response
		Likewise, when considering other real-world evidence, only one comparative study by Chowdhury et al 2020 reporting on both OS and PFS was prospectively designed. Unlike the EAG's conclusion, this study reported no difference in outcomes between NHAs. The Chowdhury study is more informative due to its prospective study design and adjustment for confounders by propensity score matching. The study included 1,874 patients, of which 313 patients were from the UK. Potential confounders that were adjusted included age, time from diagnosis to castration resistance, time from diagnosis to metastasis, time from metastasis to study start, alkaline phosphatase, prostate-specific antigen, haemoglobin, Gleason score, diabetes, use of analgesics, cardiovascular disease, ECOG status, prior radical prostatectomy, disease stage and bone lesions. Based on the propensity score matched outputs, the study reported no evidence of difference in adjusted PFS (HR 1.040, 95% CI: 0.851-1.270, p=0.7000) and adjusted OS (HR 1.000, 95% CI 0.788 to 1.270, p=0.9986). This is consistent with the company's analysis for OS and clinical feedback in relation to the efficacy of abiraterone and enzalutamide. Further clarity should therefore be provided on the clinical and face validity of the results from the EAG's meta-analysis.

Key issue	Does this response contain new evidence, data or analyses?	Response
Issue 5 Methodological corrections to the model	No	AstraZeneca accepts the following EAG methodological corrections: • Application of age-adjustment to the utilities • No half-cycle correction to treatment acquisition cost • Use of the latest NHS Reference and eMIT cost data. This has been adopted in the updated economic model and company base case - these corrections have a combined minimal impact on the cost-effectiveness results.

Key issue	Does this response contain new evidence, data or analyses?	Response
Issue 6 Equally plausible alternative OS extrapolations	No	The generalised gamma curve extrapolation for OS was selected in the base case following diagnostic, visual, statistical fit and hazard function assessments, and clinical expert validation (see Section B.3.3.1 of the company submission). Based on the AIC and BIC scores, it is reasonable to interpret the log-logistic and generalised gamma curves as comparable in terms of their statistical fit to the observed PROpel dataset. Although the scores for the log-logistic extrapolation are lower as noted by the EAG, the difference compared to the generalised gamma across both arms is less than 10. Based on the latest available landmark at approximately 4 years for COU-AA-302 and PROpel, the generalised gamma and log logistic distributions were both assessed and concluded to provide reasonable predictions with slight underestimations across both treatment arms. However, the survival estimates predicted by the generalised gamma model were marginally more aligned to the predicted OS estimates versus both datasets and across both treatment arms (~[redacted] vs. [redacted] [COU-AA-302] and [redacted] [PROpel] for placebo plus abiraterone, and ~[redacted] % vs[redacted] % [PROpel] for the olaparib plus abiraterone at ~4 years. The modelled median OS associated with the generalised gamma (and log logistic curve) was also highly consistent with the observed data from the PROpel study [redacted] vs [redacted] months, respectively, for the olaparib combination, and [redacted] vs. [redacted] months for the placebo plus abiraterone arm). The company would also like to highlight that clinical validation was carried out and the majority of clinical experts selected the generalised gamma curve as the most clinically plausible based on current care options. Additionally, a scenario analysis based on an alternative curve selection for OS using the log logistic curves has been presented in Table 55 of the company submission to explore the uncertainty around the long-term OS extrapolation.

Key issue	Does this response contain new evidence, data or analyses?	Response
Issue 7 Inconsistent time to discontinuation extrapolation	No	AstraZeneca accepts the EAG's preference of using consistent functional forms to model time to discontinuation and PFS based on the generalised gamma curve. The summary of product characteristics for olaparib plus abiraterone states that treatment should be continued until either disease progression or toxicity therefore it was considered appropriate for time-on-treatment not to exceed PFS[15]. The EAG's preferred generalised gamma extrapolation of time on treatment curve which also remains below PFS was provided in the company submission as a plausible alternative (vs. the company's Weibull extrapolation at submission) for modelling time on treatment therefore this has been included in the update company base case.

Key issue	Does this response contain new evidence, data or analyses?	Response
Issue 8 Modelling of adverse events using duration data from PROpel	No	AstraZeneca accepts the EAG's preferred assumption to use observed duration of AEs in the PROpel study to model the impact on HRQoL. This has been adopted in our economic model, as shown by the new cost estimate in our revised base-case outlined in the *Summary of changes to the company's cost-effectiveness estimate(s)* section below. It is worth noting that this was not a large driver of cost effectiveness and therefore has a minimal impact on the ICER.

Key issue	Does this response contain new evidence, data or analyses?	Response
Issue 9 Health state utilities generated using non-reference case approach.	No	The company has provided *Appendix 1*: Health Utility Mapping outlines the process undertaken by the company to map EQ-5D-5L to EQ-5D-3L using the Hernández Alava mapping algorithm.

Key issue	Does this response contain new evidence, data or analyses?	Response
Issue 10 Dosing calculations	No	AstraZeneca accepts the EAGs request to use observed relative dose intensity to adjust treatment acquisition costs in the trial. This has been adopted in our economic model, as shown by the new cost estimate in our revised base-case outlined in the *Summary of changes to the company's cost-effectiveness estimate(s)* section below. The relative dose intensity for olaparib and abiraterone derived from the latest data cut-off of the PROpel trial for olaparib and abiraterone have been applied to treatment acquisition costs in the model. The median relative dose intensity and percentage intended dose were high for olaparib and abiraterone, suggesting that the dose intensity was not affected by dose interruptions or reductions. Median relative dose intensity was 98.2%, and 100% for olaparib and abiraterone in both the olaparib combination arm and placebo plus abiraterone arms, respectively. The relative dose intensity for enzalutamide was assumed to be equal to that of abiraterone observed in PROpel trial which was considered a reasonable assumption. Consequently, the application in the model resulted in a very small impact on the cost-effectiveness results.

Key issue	Does this response contain new evidence, data or analyses?	Response
Issue 11 Testing costs for BRCA1/2 mutations	No	In the ITT population, patients would be eligible for the combination therapy regardless of their biomarker status, therefore no specific genetic testing is required. For the biomarker subgroup analysis, AstraZeneca would welcome input from NHS England on the appropriate unit cost for HRRm/BRCA mutation testing in prostate cancer. The unit costs adopted by the company at present is derived from the olaparib monotherapy appraisal [TA887] for previously treated BRCA-mutation positive mCRPC.

Summary of changes to the company's cost-effectiveness estimate(s)

Table 3: Changes to the company's cost-effectiveness estimate

Changes to cost-effectiveness estimate	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Methodological corrections to the model	• Utilities have been adjusted over time as patients age • Half cycle correction to treatment acquisition costs not applied • Latest NHS Reference Cost and eMIT Cost Data used • Please note that the updated base-case has been run on the latest PAS price for olaparib of [redacted]	The company accepts the methodological changes presented by the EAG. This sets the company's base-case ICER for olaparib versus abiraterone at [redacted] per QALY gained, and versus enzalutamide to [redacted].
Modelling of adverse events using duration data from PROpel	• Duration of AEs amended from 14 days to those seen in the trial when modelling the impact on HRQoL	This increases the company's base-case ICER for olaparib plus abiraterone vs abiraterone to [redacted] per QALY gained, and vs enzalutamide to £[redacted] per QALY gained.
Dosing calculations	• Observed relative dose intensity used to adjust treatment acquisition costs	This reduces the company's base-case ICER for olaparib plus abiraterone vs abiraterone to [redacted] per QALY gained, and vs enzalutamide to [redacted] per QALY gained.
BRCA testing	• The base case has been updated to include BRCA testing costs upon progression in the abiraterone and enzalutamide arms	This reduces the company's base-case ICER for olaparib plus abiraterone vs abiraterone to [redacted] per QALY gained, and vs enzalutamide to [redacted] per QALY gained.
Testing unit cost	• A unit cost for BRCA testing of £400 has been used in the updated base case	This reduces the company's base-case ICER for olaparib plus abiraterone vs abiraterone to [redacted] per QALY gained, and vs enzalutamide to [redacted] per QALY gained.
TTD curve	• The company accepts the use of a generalised gamma distribution for the extrapolation of the TTD curve	This increases the company's base-case ICER for olaparib plus abiraterone vs abiraterone to [redacted] per QALY gained, and vs enzalutamide to [redacted] per QALY gained.
[redacted]	[redacted]	[redacted]

Updated Base Case

The ICER is presented at the updated base case as probabilistic as per NICE guidance. All key parameters were assigned appropriate probability distributions, point estimates were derived using Monte Carlo simulation techniques. In the base-case analysis 1000 iterations were run.

Olaparib plus abiraterone is associated with an incremental QALY gain of 1.17 and an incremental cost of [redacted], when compared to enzalutamide. This translates to an incremental cost per QALY of [redacted]. When compared to abiraterone, olaparib plus abiraterone is associated with an incremental QALY gain of 1.17 and an incremental cost of [redacted].. This represents an incremental cost per QALY gained of [redacted].

A pooled average weighted ICER for the updated base case is also presented in Table 4: Updated Base case results. This method is advantageous because it considers both cost and QALY outcomes derived both enzalutamide and abiraterone weighted by their observed market share split to calculate a weighted outcome, therefore aligning with UK clinical practice. The pooled ICER is derived by simply a weighted average of the incremental costs divided by a weighted average of the incremental QALYs, resulting in an ICER of [redacted]. per QALY in the ITT base case analysis. Please refer to

Appendix 2: NHSE data on the use of for further information on the use of enzalutamide and abiraterone in NHSE.

Table 4: Updated Base case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER for Olaparib + Abiraterone vs comparator (£/QALY)	Market Share	Weighted ICER
Olaparib + abiraterone	[redacted]	4.90	3.79	-	-	-	-	-	[redacted]
Enzalutamide	[redacted]	3.34	2.63	[redacted]	1.55	1.17	[redacted]	67%	
Abiraterone	[redacted]	3.34	2.63	[redacted]	1.55	1.17	[redacted]	33%	

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Sensitivity analyses around the revised base case

As the base case presented is probabilistic no further PSA was conducted. The cost-effectiveness plane from the updated base case for both comparators is presented below.

Figure 1: Enzalutamide cost-effectiveness plane

Figure 2: Abiraterone cost-effectiveness plane

Deterministic sensitivity analysis

To identify key model drivers around the updated base-case, one-way deterministic sensitivity analysis (DSA) was conducted.

Figure 3: Enzalutamide tornado plot

Figure 4: Abiraterone tornado plot

Scenario analysis

A wide range of scenario analyses were explored to test the assumptions of the updated base case model. A summary of all scenario analyses is provided in Table 5 and

Table 6.

Table 5: Abiraterone scenario analysis

Scenario		Cost	QALYs	Cost	QALYs	Inc Costs	Inc QALYs	Estimated ICER
Base case		[redacted]	**3.77**	**25,197**	**2.60**	[redacted]	**1.17**	[redacted]
Time horizon	20 years	[redacted]	3.71	25,194	2.60	[redacted]	1.11	[redacted]
NMA	Abi vs. Enza HR for PFS, Chowdury et al	[redacted]	3.77	25,197	2.60	[redacted]	1.17	[redacted]
	Abi vs. Enza NMA, OS fixed effects	[redacted]	3.77	25,197	2.60	[redacted]	1.17	[redacted]
	Abi vs. Enza NMA, OS random effects (informative priors)	[redacted]	3.77	25,197	2.60	[redacted]	1.17	[redacted]
OS extrapolation (olaparib+abiraterone arm)	Parametric: Log Normal	[redacted]	3.85	25,197	2.60	[redacted]	1.25	[redacted]
	Parametric: Log Logistic	[redacted]	3.68	25,197	2.60	[redacted]	1.08	[redacted]
PFS extrapolation (olaparib+abiraterone arm)	Parametric: Log Normal	[redacted]	3.77	25,197	2.60	[redacted]	1.17	[redacted]
	Parametric: Log Logistic	[redacted]	3.77	25,197	2.60	[redacted]	1.17	[redacted]
OS extrapolation (abiraterone arm)	Parametric: Log Normal	[redacted]	3.77	26,954	3.13	[redacted]	0.63	[redacted]
	Parametric: Log Logistic	[redacted]	3.77	26,415	2.96	[redacted]	0.80	[redacted]
PFS extrapolation (abiraterone arm)	Parametric: Log Normal	[redacted]	3.77	25,173	2.60	[redacted]	1.17	[redacted]
	Parametric: Log Logistic	[redacted]	3.77	25,174	2.60	[redacted]	1.17	[redacted]
TTD extrapolation	Parametric: Gen Gamma	[redacted]	3.77	25,197	2.60	[redacted]	1.17	[redacted]
Cost inclusion	Administration cost excluded	[redacted]	3.77	23,236	2.60	[redacted]	1.17	[redacted]
	Secondary therapy cost excluded	[redacted]	3.77	18,434	2.60	[redacted]	1.17	[redacted]

	Routine medical care costs excluded	[redacted]	3.77	17,227	2.60	119,210	1.17	[redacted]
	Adverse event costs excluded	[redacted]	3.77	25,009	2.60	122,485	1.17	[redacted]
	Mortality costs excluded	[redacted]	3.77	25,197	2.60	122,882	1.17	[redacted]
	Wastage excluded	[redacted]	3.77	24,420	2.60	122,851	1.17	[redacted]
Utility	Disutility excluded (all)	[redacted]	3.77	25,197	2.60	122,882	1.17	[redacted]
	AE disutility excluded	[redacted]	3.77	25,197	2.60	122,882	1.17	[redacted]
	SRE disutility excluded	[redacted]	3.77	25,197	2.60	122,882	1.17	[redacted]
	COU-AA-302	[redacted]	3.82	25,197	2.63	122,882	1.19	[redacted]
	PREVAIL	[redacted]	3.82	25197	2.63	122,881	1.19	[redacted]

Table 6: Enzalutamide scenario analysis

Scenario		Cost	QALYs	Cost	QALYs	Inc Costs	Inc QALYs	Estimated ICER
Base case		[redacted]	**3.77**	**89,624**	**2.60**	[redacted]	**1.17**	[redacted]
Time horizon	20 years	[redacted]	3.71	89,613	[redacted]	[redacted]	1.11	[redacted]
NMA	Abi vs. Enza HR for PFS, Chowdury et al	[redacted]	3.77	89,624	2.60	[redacted]	1.17	[redacted]
	Abi vs. Enza NMA, OS fixed effects	[redacted]	3.77	89,624	2.60	[redacted]	1.17	[redacted]
	Abi vs. Enza NMA, OS random effects (informative priors)	[redacted]	3.77	89,624	2.60	[redacted]	1.17	[redacted]
OS extrapolation (olaparib+abiraterone arm)	Parametric: Log Normal	[redacted]	3.85	89,624	2.60	[redacted]	1.25	[redacted]
	Parametric: Log Logistic	[redacted]	3.68	89,624	2.60	[redacted]	1.08	[redacted]
PFS extrapolation (olaparib+abiraterone arm)	Parametric: Log Normal	[redacted]	3.77	89,624	2.60	[redacted]	1.18	[redacted]
	Parametric: Log Logistic	[redacted]	3.77	89,624	2.60	[redacted]	1.18	[redacted]
OS extrapolation (abiraterone arm)	Parametric: Log Normal	[redacted]	3.77	92,030	3.13	[redacted]	0.64	[redacted]
	Parametric: Log Logistic	[redacted]	3.77	91,491	2.96	[redacted]	0.81	[redacted]
PFS extrapolation (abiraterone arm)	Parametric: Log Normal	[redacted]	3.77	89,596	2.60	[redacted]	1.17	[redacted]
	Parametric: Log Logistic	[redacted]	3.77	89,593	2.60	[redacted]	1.17	[redacted]

TTD extrapolation	Parametric: Gen Gamma	[redacted]	3.77	89,624	2.60	[redacted]	1.17	[redacted]
Cost inclusion	Administration cost excluded	[redacted]	3.77	87,663	2.60	[redacted]	1.17	[redacted]
	Secondary therapy cost excluded	[redacted]	3.77	82,862	2.60	[redacted]	1.17	[redacted]
	Routine medical care costs excluded	[redacted]	3.77	83,649	2.60	[redacted]	1.17	[redacted]
	Adverse event costs excluded	[redacted]	3.77	89,472	2.60	[redacted]	1.17	[redacted]
	Mortality costs excluded	[redacted]	3.77	89,624	2.60	[redacted]	1.17	[redacted]
	Wastage excluded	[redacted]	3.77	88,847	2.60	[redacted]	1.17	[redacted]
Utility	Disutility excluded (all)	[redacted]	3.77	89,624	2.60	[redacted]	1.17	[redacted]
	AE disutility excluded	[redacted]	3.77	89,624	2.60	[redacted]	1.17	[redacted]
	SRE disutility excluded	[redacted]	3.77	89,624	2.60	[redacted]	1.17	[redacted]
	COU-AA-302	[redacted]	3.82	89,624	2.63	[redacted]	1.19	[redacted]
	PREVAIL	[redacted]	3.82	89624	2.63	[redacted]	1.19	[redacted]

Subgroup analysis

Deterministic results for the subgroups of patients between mutation statuses are shown in the tables below.

Table 7: BRCAm subgroup results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER for Olaparib + Abiraterone vs comparator (£/QALY)	Market Share	Weighted ICER
Olaparib + abiraterone	[redacted]	7.31	5.61	-	-	-	-	-	[redacted]
Enzalutamide	[redacted]	2.61	2.04	[redacted]	1.55	3.56	[redacted]	67%	
Abiraterone	[redacted]	2.61	2.04	[redacted]	1.55	3.56	[redacted]	33%	

Table 8: HRRm subgroup results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER for Olaparib + Abiraterone vs comparator (£/QALY)	Market Share	Weighted ICER
Olaparib + abiraterone	[redacted]	5.10	3.96	-	-	-	-	-	[redacted]
Enzalutamide	[redacted]	2.63	2.07	[redacted]	2.47	1.89	[redacted]	67%	
Abiraterone	[redacted]	2.63	2.07	[redacted]	2.47	1.89	[redacted]	33%	

Table 9: Non-HRRm subgroup results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER for Olaparib + Abiraterone vs comparator (£/QALY)	Market Share	Weighted ICER
Olaparib + abiraterone	[redacted]	4.76	3.69	-	-	-	-	-	[redacted]
Enzalutamide	[redacted]	4.04	3.15	[redacted]	0.72	0.54	[redacted]	67%	
Abiraterone	[redacted]	4.04	3.15	[redacted]	0.72	0.54	[redacted]	33%	

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Appendices

Appendix 1: Health Utility Mapping Methodology

Evidence to demonstrate that mapping was undertaken includes the code used to implement the Hernández Alava algorithm, and a comparison of raw 5L utility values with their mapped 3L equivalents.

Hernandez value set – R code

The analysis was performed in R using the 'eq5d' package. As per the NICE reference case, utility values were estimated by mapping responses to the EQ-5D-5L descriptive system onto the 3L value set using the decision support unit (DSU) mapping function (Hernandez Alava et al, 2017), using the 'EEPRU dataset'. For each EQ-5D-5L measure collected in PROpel, utility values were estimated using the 'eq5d()' function, with the following arguments:

- The EQ-5D-5L profile derived from the individual patient data.
- The version is '5L'.
- The type is 'DSU'.
- The country is 'UK'.
- Age is derived from individual patient data.
- Sex is derived from individual patient data.

The method is comparable to that described in the following vignette - https://cran.r-project.org/web/packages/eq5d/vignettes/eq5d_nice_dsu.html

The relevant segment of the R code to estimate the utility at each visit is shown below:

```
data %>% mutate(target_var = pmap_dbl(list(Profile, Age, Sex),
                                       ~eq5d(scores = ..1,
                                             version = params$eq5d_level,
                                            type = params$eq5d_type,
                                             country = params$country,
                                             age = ..2,
                                            sex = ..3)))
```

Where ..1 is the 5L profile (e.g. 11111), ..2 is the age, and …3 is the sex column of the individual patient data file, and *params$eq5d_level* is '5L', *params$eq5d_type* is 'DSU', and *params$country* is 'UK'.

Comparison of raw EQ-5D-5L profiles, and the corresponding mapped EQ-5D-3L utility value using the Hernandez value set - Example

A comparison of EQ-5D-5L profiles and mapped EQ-5D-3L utility values for the five most frequently reported profiles in PROpel is provided in Table 10. For each profile, we report the mapped EQ-5D-3L utility values based on the NICE DSU value set (Hernandez et al 2017) according to hypothetical age groups.

This will allow the EAG to validate the mapped EQ-5D-3L utility values that have been used in the economic analysis.

Table 10: EQ-5D-5L profiles and mapped EQ-5D-3L utility values

Profile	EQ-5D-5L profile	Sex	Age group	EQ-5D-3L utility value (Hernandez et al 2017 value set)
1	11111	M	35 <= age < 45	0.987
	11111	M	45 <= age < 55	0.987
	11111	M	55 <= age < 65	0.987
	11111	M	65 <= age < 100	0.989
2	11121	M	35 <= age < 45	0.873
	11121	M	45 <= age < 55	0.864
	11121	M	55 <= age < 65	0.86
	11121	M	65 <= age < 100	0.868
3	11112	M	35 <= age < 45	0.892
	11112	M	45 <= age < 55	0.891
	11112	M	55 <= age < 65	0.891
	11112	M	65 <= age < 100	0.893
4	21111	M	35 <= age < 45	0.933
	21111	M	45 <= age < 55	0.928
	21111	M	55 <= age < 65	0.914
	21111	M	65 <= age < 100	0.909
5	21221	M	35 <= age < 45	0.734
	21221	M	45 <= age < 55	0.736
	21221	M	55 <= age < 65	0.736
	21221	M	65 <= age < 100	0.753

Comparison of NICE DSU value set (Hernandez) vs alternative value sets

We also report the PROpel utility values according to the Van Hout et al 5L to 3L cross-walk (https://www.sciencedirect.com/science/article/pii/S1098301512000587?via%3Dihub), and the 5L utilities from the Devlin et al value set for England (https://onlinelibrary.wiley.com/doi/full/10.1002/hec.3564).
These were produced by the same 'eq5d()' R function described above, using the following options within the function:

Van hout: eq5d(… version = '5L', country = 'UK', type = 'CW')

Devlin: eq5d(… version = '5L', country = 'England', type = 'VT')

The pre- and post-progression utility values using the NICE DSU (Hernandez), Van Hout and Devlin value sets are shown in Table X below.

The DSU and Van Hout crosswalk algorithms yield similar estimates of mean EQ-5D-3L utility score by progression-free and progressed disease state. The mean EQ-5D-5L utility scores derived using Devlin et al are noticeably higher than the crosswalk 3L values generated using either the DSU or Van Hout algorithms. This is in line with previous research that showed higher mean utilities with the EQ-5D-5L value set for England than for the 3L crosswalk algorithm, across a range of health conditions : (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5954043/).

Table 11: Utility values across different methodologies

Health state	NICE DSU, Hernandez (base case)	Van Hout	Devlin
Pre-progression	0.814 (0.801, 0.828)	0.813 (0.800, 0.827)	0.868 (0.857, 0.879)
Post-progression	0.775 (0.753, 0.798)	0.777 (0.755, 0.799)	0.836 (0.816, 0.855)

Appendix 2: NHSE data on the use of abiraterone and enzalutamide

AstraZeneca filed a freedom of information request from NHS England, as highlighted in the NICE Technical Engagement New Evidence Form.

As per Figure 5, the primary use of enzalutamide and secondary use of abiraterone in 1L mCRPC has remained constant since the introduction of generic abiraterone in October 2022. Over this 9 month period, enzalutamide and abiraterone 1L mCRPC NHA market share has ranged from [redacted] and [redacted] respectively.

Figure 5: 1L mCRPC NHA market share

Subgroup analysis for non-BRCAm

a) Could you integrate non-BRCA results into the model and produce cost-effectiveness analyses for this subgroup population?

Data from the latest data cut of patients confirmed as **not** harbouring a BRCA mutation in the PROpel trial have been integrated into the model as requested. The PROpel trial enrolled patients irrespective of mutation status and determined mutation status after randomisation. The subgroup analysis of the non-BRCAm subgroup is therefore a non-stratified, post-hoc analysis hence the results presented should be interpreted with caution.

In summary, in the non-BRCA mutated subgroup:

- Median PFS was [redacted] months for olaparib plus abiraterone vs. [redacted] months for placebo plus abiraterone (HR=[redacted] ([redacted]-[redacted], p=[redacted])
- Median OS was 39.6 months for olaparib plus abiraterone vs. 37.9 months for placebo plus abiraterone (HR=0.909 (0.734-1.127, p=0.386)

The post-hoc exploratory assessment in HRRm (see Appendices to company submission), non-HRRm, BRCAm (see company responses to CQs), and non-BRCAm subgroups, demonstrated trends in favour of olaparib plus abiraterone.

Economic analysis

*Independent models were fitted for OS (***Figure 1***) and PFS (*

Figure 2) following assessment of proportional hazards undertaken using Schoenfeld residuals. The Schoenfeld residuals plot shows a non-linear and non-zero gradient for residuals against time, indicating that an assumption of proportional hazards between the two trial arms may not hold.

Figure 1: Schoenfeld residuals plot for OS in the non-BRCAm subgroup

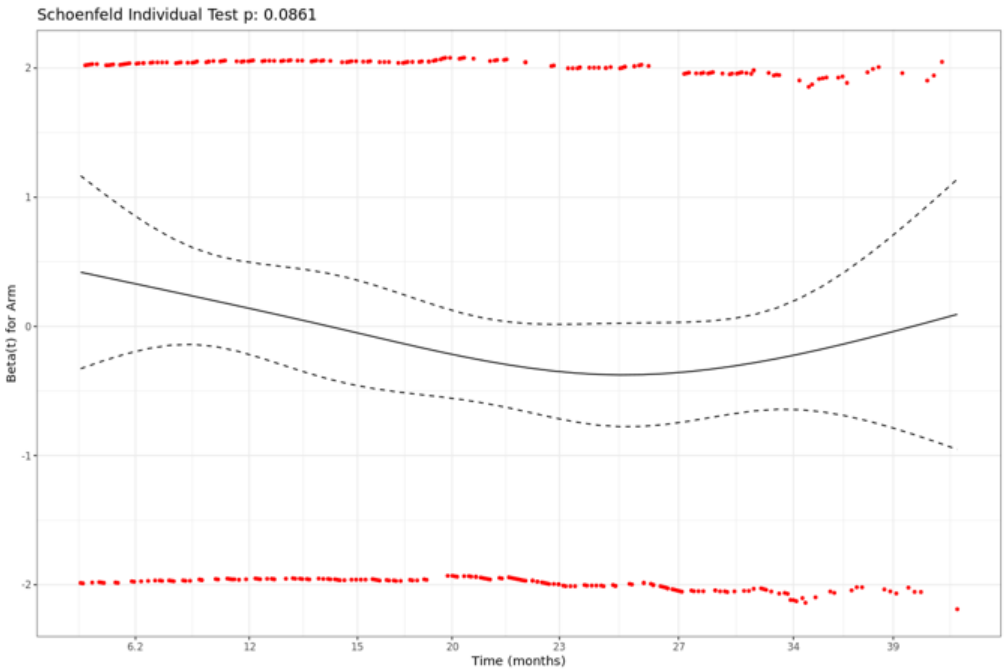
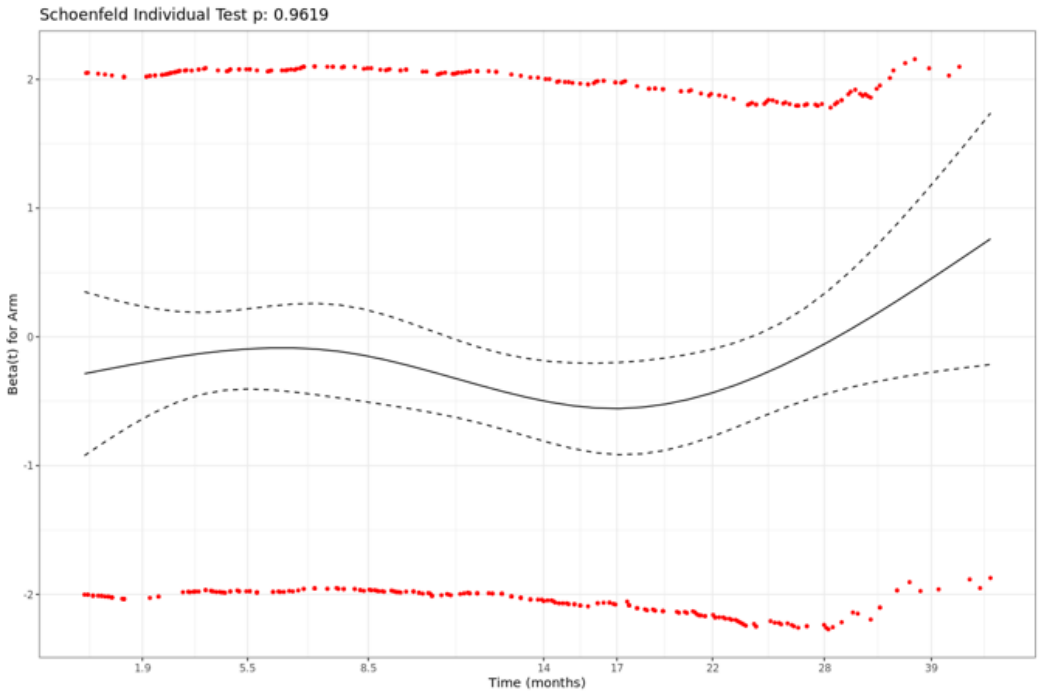


Figure 2: Schoenfeld residuals plot for PFS in the non-BRCAm subgroup



The statistical fit of each distribution was assessed using both the Akaike information criterion (AIC) and the Bayesian information criterion (BIC) goodness-of-fit statistics, with the results summarised below. The best statistical fits are distributions with the

lowest values indicating the most parsimonious fit to the data. For OS, PFS and OS across both treatment arms, the lognormal, log logistic, generalised gamma were the best fitting curves with a difference between scores of 10 or less.

Table 1: Goodness-of-fit test for OS in non-BRCAm subgroup

	Olaparib + Abiraterone		***Placebo + Abiraterone***	
	AIC	**BIC**	**AIC**	**BIC**
Exponential	1624.6	1628.5	1776.1	1779.9
Weibull	1608.1	1615.8	1736.5	1744.3
Lognormal	**1603.8**	1611.5	1746.5	1754.2
Log logistic	1604.8	1612.5	**1733.8**	1741.6
Gompertz	1617.2	1624.9	1749.2	1756.9
Generalised Gamma	1605.5	1617.0	1737.5	1749.1

Table 2 : Goodness-of- fit test for PFS in non-BRCAm subgroup

	Olaparib + Abiraterone		***Placebo + Abiraterone***	
	AIC	**BIC**	**AIC**	**BIC**
Exponential	1754.9	1758.7	2055.9	2059.8
Weibull	1753.6	1761.2	2052.2	2059.9
Lognormal	1748.7	1756.3	2045.7	2053.5
Log logistic	1752.3	1760.0	2045.0	2052.7
Gompertz	1756.0	1763.7	2057.4	2065.1
Generalised Gamma	1750.2	1761.7	2045.9	2057.4

Table 3: Goodness-of- fit test on TTD in non-BRCAm subgroup

	Olaparib + Abiraterone (TTD OLA)		**Olaparib + Abiraterone (TTD ABI)**		**Placebo + Abiraterone (TTDA)**	
	AIC	**BIC**	**AIC**	**BIC**	**AIC**	**BIC**
Exponential	2211.6	2215.5	2209.7	2213.5	2314.7	2318.6
Weibull	2213.2	2220.8	2207.2	2214.8	2309.5	2317.3
Lognormal	2202.2	2209.9	2197.5	2205.2	2298.0	2305.7
Log logistic	2208.0	2215.7	2203.0	2210.7	2297.2	2304.9
Gompertz	2213.4	2221.1	2211.0	2218.6	2316.3	2324.0
Generalised Gamma	2203.9	2215.4	2199.1	2210.6	2298.4	2310.0

Due to the timing of the request, the company was unable to clinically validated the extrapolations for the non-BRCAm subgroup. However, data from the PROpel study showed those who were BRCA-mutated performed better than those without a BRCA-mutation in the olaparib plus abiraterone arm. At the end of the follow-up period for OS (i.e., ~Year 3.5), ~71% of patients with a BRCA mutation were alive versus ~47% in the non-BRCA-mutated subgroup (48% vs. 26% for PFS, respectively). By contrast, patients with a BRCA-mutation treated with abiraterone at a similar landmark, had relatively worse outcomes compared to the group who did not have a BRCA mutation (OS; ~28% vs. ~44% respectively and for PFS; ~11% vs. ~17%, respectively).

Nevertheless, across both the BRCA-and non-BRCA-mutated subgroups, there was a trend in favour of olaparib plus abiraterone compared to abiraterone demonstrating efficacy irrespective of mutation status. The trend observed in the PROpel study was taken into consideration for selecting the appropriate extrapolation for OS and PFS in the long term for the non-BRCAm subgroup.

Among the standard parametric curves fitted to the OS data, the log logistic and generalised gamma curves offered the best combined fit to the observed olaparib and the abiraterone arms (as opposed to the lognormal and Weibull curves which only fit one treatment arm well). The exponential and Gompertz were the worse fitting models and were excluded in the first instance as a preferred curve choice for OS.

In terms of the long-term predictions of 10-year survival in non-BRCAm for the current care options, the generalised gamma predicted ~3% patients remained alive, whereas the log logistic predicted ~ 9% alive by Year 10. Comparing this to the ITT which includes the mutated subgroups, the experts consulted by the company with experience in using abiraterone in all patient groups predicted about 2-3% would remain alive. In the subset of patients without a BRCA mutation, considering the trend observed in the PROpel study, it is anticipated that the non-mutated patients treated with abiraterone would likely perform better than the ITT group, therefore the generalised gamma curve was considered to be pessimistic. The remaining log logistic curve which provides a reasonable balance between statistical fit and a reasonable estimate of long-term extrapolation predicting relatively better outcomes in the abiraterone arm, but poorer OS outcomes for olaparib plus abiraterone was selected to maintain consistency with the dataset across both the BRCA- and non-BRCA mutated subgroups.

For PFS, with the exception of Gompertz and exponential curves, most of the curves offered a reasonable fit the observed data in both treatment arms. The log normal, log logistic and generalised gamma predicted [redacted] of patients remained progression-free at the 10-year landmark with the current care options curves. Both curves were thought to be optimistic given the median PFS estimates observed in the trial and were excluded as the preferred extrapolation for PFS. The Weibull curve which predicted that nearly [redacted] would have experienced disease progression by 10 years in both arms was selected in the base case extrapolation for PFS.

In alignment with the summary of product characteristics for olaparib plus abiraterone, and abiraterone plus prednisone which recommend that treatment is continued until either disease progression or due to toxicity, the Weibull distribution for treatment discontinuation, which is aligned but does not exceed rPFS extrapolation over the time horizon, was deemed appropriate to use in the base case extrapolation for time on treatment in both arms.

The deterministic cost-effectiveness results for the non-BRCAm subgroup are presented in Table 4 below. To summarise, the log logistic curve was selected for the extrapolation of OS in both arms, whereas the Weibull curve was selected for PFS and time on treatment. With the exception of the individual parametric curve selections, the cost-effectiveness results incorporate all the EAG model updates and changes accepted for the ITT population following technical engagement namely:

- EAG's methodological corrections to the model
- Treatment toxicity monitoring for olaparib beyond 12 months.
- Modelling of adverse events using duration data from PROpel
- Mean dose intensity for olaparib, abiraterone and enzalutamide
- Inclusion of mutation testing at a unit cost of £34

Table 4: Cost-effectiveness results in the non-BRCAm subgroup *(including confidential discount for olaparib and list price for comparators and subsequent treatment)*

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER for Olaparib + Abiraterone vs comparator (£/QALY)	Market Share	Weighted ICER
Olaparib + abiraterone	[redacted]	4.57	3.52	-	-	-	-	-	[redacted]
Enzalutamide	[redacted]	3.95	3.06	[redacted]	0.62	0.47	[redacted]	67%	
Abiraterone	[redacted]	3.95	3.06	[redacted]	0.62	0.46	[redacted]	33%	

Issue 1.

The timing of NHAs in regard to docetaxel was an important question several years ago, but is now largely redundant. In the current clinical pathway, almost all clinicians would choose to use NHA before docetaxel for almost all patients.

Issue 2.

There are clear biological rationales for why the mechanism of action of olaparib is different when combined with NHAs than when used alone. Clearly the effect on BRCA 1&2 mutation tumours is largest but there is preclinical evidence demonstrating interactions with androgen receptor pathway and DNA repair pathway so that NHA may enhance the effect of olaparib in non-BRCA tumours and olaparib may augment the effectiveness of NHA. This is borne out in the sub-group analyses of the PROPEL trial, especially when considering rPFS in the non-BRCA group and non-HRR groups, where the results favour abiraterone + olaparib compared with olaparib (HR, 0.78 p=0.01) for non-BRCA patients. The HR for OS was 0.9, at the very least showing no-detriment to the use of the combination.

Issue 3.

10% of patients may be BRCA positive but of those only a proportion would get olaparib following NHA in the real world. Around 50% are unlikely to be fit for olaparib after abiraterone. Of those that are, in the region of 50% would not be tested or would fail testing, so it is likely that only around 2.5% of the 'control arm' real world patients would get olaparib. This is not too different from the 1.6% that got it in PROPEL.

Real world testing is a significant issue that takes time – to request, to retrieve the tumour block, perform the test, disseminate results. In our centre, around 50% of cases are not interpretable due to the tumour tissue being too old or there being too little tumour. Circulating tumour DNA tests are not available. A repeat biopsy of metastatic disease is burdensome for the patient and we have limited capacity in a busy NHS hospital.

Issue 4.

- The meta-analysis is almost fully comprised of retrospective studies that are prone to biases, many of which are unknown. The relative efficacy of abiraterone and enzalutamide have been discussed for many years at many, many meetings. The Conclusion is always that these drugs are considered equivalent with regard to efficacy. It may be that for some patients clinicians choose one over the other (eg. Diabetes, seizures etc.) but I have never heard anyone argue that the OS benefit of enzalutamide compared to abiraterone has a HR of 0.84. The best comparative evidence comes from a Canadian prospective study, in which, these drugs were directly compared in a randomised controlled trial. The conclusion was that there is no significant benefit to one compared with the other in terms of efficacy (Khalaf et al. PMID 31727538)

Issue 6.

A live expectancy of 8.4% at 10 years in patients with metastatic castrate resistant prostate cancer seems highly improbable to me. As stated in the submission document, median survival in mCRPC is around 36 months. These patients largely have advanced, widespread disease that has already become resistant to standard hormone therapy (eg. LHRH agonists). We treat many of these patients in our clinics and I would believe that 2-3% 10 year survival was much more realistic.

NICE National Institute for Health and Care Excellence

Patient expert statement

Olaparib with abiraterone for untreated hormone-relapsed metastatic prostate cancer [ID3920]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	**David Kinsey**
2. Are you (please tick all that	☒ a patient with the condition? ☐ a carer of a patient with the condition?

apply):	☐ a patient organisation employee or volunteer? ☐ other (please specify):
3. Name of your nominating organisation	Prostate Cancer UK
4. Did your nominating organisation submit a submission?	☒ yes, they did ☐ no, they didn't ☐ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐
7. How did you gather the information included in your statement? (please tick all that apply)	☒ I have personal experience of the condition ☒ I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: ☐ I am drawing on others' experiences. Please specify how this information was gathered:
Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	I was diagnosed with metastatic prostate cancer with cancer in my prostate and lymph nodes in my neck, chest and groin in February 2016 following referral by my GP. I had urinary problems with frequency, low flow and dribble after urinating causing embarrassment with wet patches on my trousers. I can still suffer from that problem occasionally. My diagnosis of incurable metastatic cancer was devastating and at the time my prognosis was two to three years. I joined the latest arm of the Stampede trial and had the then standard treatment of chemotherapy and hormone therapy from March 2016. Only the trial group had the follow up radiotherapy which was disappointing. The chemotherapy left me with peripheral neuropathy in my feet and fingers. The hormone therapy gives me angry and depressing mood swings and emotional changes such as crying at funerals which I never did before. My memory has suffered and my wife finds my sudden mood swings and lack of motivation annoying.

	Two and a half years after chemotherapy my psa started to rise then double. I was still being monitored under the Stampede trial and was put forward by my oncologist to join the Propel clinical trial which I did in February 2019. Assessment scans found an additional metastasis on my dorsal spine. I stayed on Prostap and was prescribed abiraterone and the trial drug olaparib. My psa has been <0.1 since three months into the trial but I live with the frustrating side effects of the medications. I have lost considerable muscle mass, more since taking abiraterone and olaparib. After chemotherapy and when only on Prostap hormone therapy I regained my fitness and cycled long distances with the Cycle Touring Club, I hardly cycle at all now due to lack of stamina, fatigue and loss of motivation. I have put on a lot of weight round my midriff and get breathless much sooner than I used to do. The extra weight is very hard to shift. My well being was monitored every three months by questionnaire reporting on a handheld electronic device and has changed little since about three months after starting taking the combination medication. I have no libido or desire which affects my relations with my wife. My blood counts are lower than the expected standard limits leading my GP to suggest that I'm anaemic. I asked my consultant and it seems the low blood counts are one of the expected side effects of the olaparib medication. I suffer from fatigue intermittently and some days can feel like sleeping all day. Motivation for completing projects has disappeared. I get frequent colds and throat infections. One of my 3 monthly scans found pulmonary embolisms and I am now on anticoagulants and have to be extra careful with DIY and sharps. My bones are weakened and since cracking first three then two more ribs with little trauma I take alendronic acid and calcium and vitamin D3 tablets to slow down the bone thinning. My final CT and bone scans in May 2023 showed no sign of active cancer which is very encouraging. I am aware of others that have tried abiraterone and it has stopped working for them, as has enzalutamide. There is always the worry for me and my wife that having started to come back after chemo therapy and initial hormone therapy then my cancer could return again and not be able to be controlled. There is also the concern that using the medications long term may bring on problems with my liver and heart but I will continue with them for as long as they work or until a better treatment becomes available. I live in hope.

Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and care available on the NHS?	We don't feel that hormone therapy and chemotherapy should always be the first treatment for my condition. The side effects, some short and some long term, should be avoided where possible. I am lucky to be on a trial which adds olaparib to abiraterone and my standard Prostap3 injections as this is not generally available elsewhere. I see that immunotherapy is available in some Trusts as a cure and this should be made more available to suitable patients. With regard to prostate cancer treatments geography is particularly important and the lack of opportunity for advanced treatments and trials away from major cities is very frustrating for patients and carers.
10. Is there an unmet need for patients with this condition?	Yes, for metastatic prostate cancer patients abiraterone or enzalutamide or equivalent possibly with the addition of olaparib should be available as a first line treatment instead of chemotherapy if the patient has no conflicting health conditions to prevent this. It would seem from results and reports in my support groups that immunotherapy can provide a cure and this should be pursued for all patients with metastatic prostate cancer.
Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	Olaparib added to hormone therapy and abiraterone seems to have been effective in controlling the growth and spread of my cancer. My wife is happy that the treatments that I have received and continue to receive have given her and me more time to look after our families.
Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	The combination of hormone therapy, abiraterone and olaparib has resulted in my having a lack of energy and enthusiasm for things that I used to enjoy such as long distance cycling. My blood counts are below the normal range and I seem more susceptible to catching colds and minor infections. The lack of libido and desire have dramatically changed my married life and I don't feel like a proper man, which can be very depressing. My wife has noticed a change for the worse in my moods, concentration and motivation.

Patient population	
13. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	The treatment that I receive consists of a hormone injection every three months and tablets for the abiraterone and olaparib and other oral medications to deal with the side effects of these drugs. This could mean that a patient would not need to attend a chemotherapy department, possibly some distance away from home, as I did initially. Patients with mobility issues or living in relatively remote areas could benefit from not having to travel for treatment.
Equality	
14. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	An oral treatment regime can be more acceptable to people with dementia or learning difficulties than an invasive treatment like chemotherapy. The medications can be supplied in the post to those unable to travel to get treatment.
Other issues	
15. Are there any other issues that you would like the committee to consider?	

Topic-specific questions	
16. [To be added by technical team if required, after receiving the company submission. For example, if the company has deviated from the scope (particularly with respect to comparators) – check whether this is appropriate. Ask specific, targeted questions such as “Is comparator X [excluded from company submission] considered to be established clinical practice in the NHS for treating [condition Y]?”] **if not delete highlighted rows and renumber below**	

Key messages
17. In up to 5 bullet points, please summarise the key messages of your statement: • Living with treatment for metastatic prostate cancer is not easy and can affect relationships and well being. • Any treatment that proves effective in extending life is worthy of consideration even with associated side effects. • Since starting on the combination of prostap, abiraterone and olaparib my psa has stayed virtually undetectable. • A patient starting on the same combination of medications as me needs to be prepared live with the side effects. •

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

Key issue	Does this response contain new evidence, data or analyses?	Response
Interpretation and implications of the wording of the marketing authorisation of olaparib plus abiraterone	No	Prostate Cancer UK agree with the NICE EAG that the marketing authorisation doesn't match the trial population. We are concerned that this marketing authorisation may exclude patients who may benefit from olaparib and abiraterone. We are also concerned that there is a lack of adverse event data for this treatment combination for patients who are unsuitable for docetaxel because either 1) they may not be fit enough to receive docetaxel, or 2) docetaxel may be contraindicated. These patients were unlikely to have been recruited to the PROpel trial due to poor health status, and generally patients who are recruited to clinical trials need to be of ECOG 0 or 1 to be able to participate. We would also note that ECOG scores may be subjective, and ask that a definition of the "chemo unsuitable"/ "untreated" group be established, as has been done in previous prostate cancer appraisals such as radium-223[TA412] It is worth highlighting however that our previous analysis in the abiraterone appraisal showed that patients who are not suitable for docetaxel are likely to be significantly older that other patients, thus this treatment option could provide this group of patients with another much needed treatment choice in this part of the pathway.
Efficacy of olaparib plus abiraterone in the PROpel trial driven by the small subgroup of BRCA mutation patients	No	Olaparib's mechanism of action is reliant on the presence of HRR mutations, including but not necessarily limited to BRCA 1 or BRCA 2. The PROfound trial previously showed that whilst treatment with olaparib was most beneficial inpatients with BRCA mutations, sub group analyses (although not powered) showed benefit in other HRR mutations. For

		olaparib in combination with abiraterone, it is likely that patients with non-BRCA HRR mutations may also benefit. For this reason, we would like to see the BRCA sub group analysed separately. We would also like to see non-BRCA HRR variant patients analysed separately, to determine if there is meaningful clinical benefit of treatment with abiraterone and olaparib in this patient cohort. We believe more data should be collected via registries to better identify which HRR mutations benefit from olaparib combination therapy.
Limited use of subsequent olaparib monotherapy in PROpel	No	Although the percentage of patients receiving subsequent olaparib monotherapy in the comparator arm was lower than the theoretical maximum of 10% (the proportion that had a BRCA mutation), we would not expect all patients with a BRCA mutation to necessarily receive olaparib monotherapy in practice. Clinical expert opinion should be sought to understand a realistic estimate of olaparib monotherapy subsequent therapy.
Assumption of efficacy equivalence when comparing abiraterone and enzalutamide	Yes/No	
Methodological corrections to the model	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses
Equally plausible alternative OS extrapolations	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses
Inconsistent time to discontinuation extrapolation	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses
Modelling of adverse events using duration data from PROpel	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses

Health state utilities generated using non-reference case approach	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses
Dosing calculations	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses
Testing costs for BRCA1/2 mutations	Yes/No	

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Olaparib with abiraterone for untreated hormone-relapsed metastatic prostate cancer [ID3920]

Technical engagement response form

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this evaluation.

Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAR that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

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Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

The deadline for comments is **5pm** on **<insert deadline>**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Technical engagement response form

About you

Table 1 About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Astellas Pharma Ltd.
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Interpretation and implications of the wording of the marketing authorisation of olaparib plus abiraterone	Yes/No	No response
Efficacy of olaparib plus abiraterone in the PROpel trial driven by the small subgroup of BRCA mutation patients	Yes/No	No response
Limited use of subsequent olaparib monotherapy in PROpel	Yes/No	No response
Assumption of efficacy equivalence when comparing abiraterone and enzalutamide	Yes	**Astellas Pharma agrees with the EAG that (1) enzalutamide has better effectiveness than abiraterone and that (2) the company's network meta-analysis is flawed.** (1) We are not aware of additional studies that report hazard ratios for overall survival (OS) and used methods to adjust for possible confounding factors beyond those identified by the EAG. **There are additional studies that offer supportive evidence that enzalutamide achieves better outcomes compared to abiraterone**, such as fewer cardiovascular event

		rates (Hu et al, 2022; Kulkarni et al, 2021; and hospitalisations (Hu et al, 2022; Riekhof et al, 2023; Schultz et al, 2018), in specific patient populations (Deol et al, 2023; Marar et al, 2022), and in terms of unadjusted hazard ratios (López-Campos et al, 2021); this is consistent with the findings of a scoping review (Shah et al, 2022) – see summary below. (2) **Astellas Pharma agrees that the company's network meta-analysis is flawed**. In addition to the issues identified by the EAG, the placebo arm in the COU-AA-302 trial cannot be interpreted as equivalent to the placebo arm in the PREVAIL trial. This is because the placebo arm in the COU-AA-302 trial includes prednisolone, which can affect patient outcomes (Schultz et al, 2019; Schultz et al, 2020), while the placebo arm in PREVAIL trial does not. The relevant comparators include abiraterone as well as enzalutamide, given that both are recommended by NICE. **Additional supportive evidence that enzalutamide achieves better outcomes:** • Deol et al, 2023: In frail patients, and following propensity score matching, the adjusted hazard ratio (HR) for overall survival for enzalutamide vs abiraterone was 0.86 (95% CI 0.78-0.94). • Hu et al, 2023: Patients treated with abiraterone were at "*greater risk of cardiovascular-related hospitalization compared to the ENZ group (IPTW [inverse probability of treatment weighting]-hazard ratio (HR) 1.82; 95% confidence interval (95%CI) 1.09-3.05). The risk of hospitalization for heart failure was greater in ABI (IPTW-HR 2.88; 95%CI 1.09-7.63)*." • Kulkarni et al, 2021: In patients with metastatic prostate cancer, the adjusted HR for cardiovascular events for abiraterone vs enzalutamide was 1.31 (95% CI 1.05-1.63).

		• López-Campos et al, 2021: Overall survival was longer in patients with mCRPC who were chemotherapy naïve treated with enzalutamide than in those treated with abiraterone (38.1 vs 29m; HR 1.4; p=0.027). • Marar et al, 2022: In patients with mCRPC, "*first-line abiraterone was associated with decreased median overall survival relative to first-line enzalutamide among non-Hispanic White patients (17 months [IQR, 9-32 months] vs 20 months [IQR, 10-36 months], respectively; inverse probability of treatment weighting hazard ratio, 1.21; 95% CI, 1.06-1.38).*" • Riekhof et al, 2023: In patients with advanced or metastatic prostate cancer, patients treated with enzalutamide experienced smaller increase in hospitalisation rates comparing post-treatment to pre-treatment period than patients treated with abiraterone. • Schultz et al, 2018: In patients with mCRPC and who were chemotherapy-naïve, in an adjusted analysis, enzalutamide was associated with fewer all-cause inpatient admissions [adjusted incidence rate ratio (95% CI 0.87 (0.76, 0.99)], days of hospitalization [0.84 95% CI (0.70, 1.02)], and outpatient visits [0.94 (0.90, 0.98)], and fewer prostate cancer-related outpatient visits [0.92 95% CI (0.87, 0.96)] compared with abiraterone. • Shah et al, 2022: This scoping review concluded: "*Existing data suggest that AA [abiraterone] and ENZ [enzalutamide] have important differences in outcomes including toxicities, response, disease progression, and survival. Additionally, adherence, healthcare utilization, and costs differ*." **References** • Deol ES, Sanfilippo KM, Luo S, Fiala MA, Wildes T, Mian H, Schoen MW. 2023. Frailty and survival among veterans treated with abiraterone or enzalutamide for metastatic castration-resistant prostate cancer. *Journal of Geriatric Oncology*. https://doi.org/10.1016/j.jgo.2023.101520 • Hu J, Aprikian AG, Vanhuyse M, Dragomir A. 2022. Comparative cardiovascular safety of novel hormonal agents in metastatic castration-

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		Cancer: An Administrative Claims Analysis. J Manag Care Spec Pharm. https://www.jmcp.org/doi/full/10.18553/jmcp.2019.19109 • Schultz NM, Penson DF, Wilson S, Song Y, Yang H, Ramaswamy K, Lowentritt B. 2020. Adverse Events Associated with Cumulative Corticosteroid Use in Patients with Castration-Resistant Prostate Cancer: An Administrative Claims Analysis. Drug Saf. https://link.springer.com/article/10.1007/s40264-019-00867-6 • Shah YB, Shaver AL, Beiriger J, Mehta S, Nikita N, Kelly WK, Freedland SJ, Lu-Yao G. 2022. Outcomes following abiraterone versus enzalutamide for prostate cancer: a scoping review. Cancers. https://doi.org//10.3390/cancers14153773
Methodological corrections to the model	Yes/No	No response
Equally plausible alternative OS extrapolations	Yes/No	No response
Inconsistent time to discontinuation extrapolation	Yes/No	No response
Modelling of adverse events using duration data from PROpel	Yes/No	No response
Health state utilities generated using non-reference case approach	Yes/No	No response
Dosing calculations	Yes/No	No response
Testing costs for BRCA1/2 mutations	Yes/No	No response

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the EAR that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Insert key issue number and title as described in the EAR	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the EAR	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER.
Insert key issue number and title as described in the EAR	…	…	[INSERT / DELETE ROWS AS REQUIRED]
Company's base case following technical engagement (or revised base case)	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Please provide company revised base-case ICER

Sensitivity analyses around revised base case
PLEASE DESCRIBE HERE

Single Technology Appraisal (STA)

Olaparib with abiraterone for untreated hormone-relapsed metastatic prostate cancer [ID3920]

EAG addendum: review of company's response to technical engagement

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None

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

Note on the text

All commercial-in-confidence (CIC) data have been highlighted in blue and underlined, all depersonalised data (DPD) are highlighted in pink and underlined.

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1 OVERVIEW

This addendum to the External Assessment Report (EAR) report presents the External Assessment Group's (EAG) critique of the additional evidence provided by the company in their response to a number of key issues that were raised by the EAG in its report, which were discussed at technical engagement.

The technical engagement covered 11 key issues for consideration. The company's response to technical engagement included further information which resolves issue 9. The company has also made several revisions to the economic analysis aligning with the EAG preferred assumptions. These revisions resolve issues 5, 7, and 8. A summary of the issues the EAG considers to be resolved, partly resolved or unresolved is provided in **Error! Reference source not found.**.

Table 1: Summary of the key issues

Issue		**Resolved?**
1	Interpretation and implications of the wording of the marketing authorisation of olaparib plus abiraterone	Partly (uncertainty remains)
2	Efficacy of olaparib plus abiraterone in the PROpel trial driven by the small subgroup of BRCA mutation patients	No
3	Limited use of subsequent olaparib monotherapy in PROpel	No
4	Assumption of efficacy equivalence when comparing abiraterone and enzalutamide	No
5	Methodological corrections to the model	Yes
6	Equally plausible alternative OS extrapolations	No (Uncertainty remains)
7	Inconsistent time to discontinuation extrapolation	Yes
8	Modelling of adverse events using duration data from PROpel	Yes
9	Health state utilities generated using a non-reference case approach	Yes
10	Dosing calculations	Partly (incorrectly implemented)
11	Testing costs for BRCA1/2 mutations	No

2 DESCRIPTION AND CRITIQUE OF ADDITIONAL EVIDENCE

2.1 Issue 1: Interpretation and implications of the wording of the marketing authorisation of olaparib plus abiraterone

The company proposed an explanation for the wording of the marketing authorisation, stating that due to the historical placement of chemotherapy in the treatment pathway, the regulatory (and NICE) recommendations for enzalutamide [TA377] and abiraterone [TA387] in mCRPC (which followed that of docetaxel in the UK) were formulated to consider whether the evidence-base for these NHAs

supported use in those who received prior docetaxel. Their respective label wording for first-line mCRPC includes the statement "*in whom chemotherapy is not **yet** clinically indicated*" to reflect the trial populations, who were mostly docetaxel-naïve, hence would potentially be eligible for chemotherapy in the future. The company stated that in contrast, the olaparib label - "*in whom chemotherapy is not clinically indicated*" - was amended slightly by the regulators to exclude the wording **yet** with the intent of differentiating the more contemporary PROpel trial which included patients who were both docetaxel-naïve and -exposed given the shift in clinical practice.

The EAG's response

The EAG maintains their opinion that the olaparib plus abiraterone marketing authorisation wording is somewhat ambiguous and difficult to interpret; this may have implications both for the pathway positioning of olaparib plus abiraterone and the applicability of the PROpel trial results to the NHS population.

In their TE response, the company stated that "eligibility for docetaxel does not preclude the use of NHAs (alone or in combination with a PARP inhibitor) in current day NHS clinical practice." The EAG concludes that 'eligible' does not equal 'clinically indicated' and mCRPC patients could receive docetaxel in the first-line if this is thought to be an appropriate treatment based on clinical judgement and patient preference. Based on current UK clinical practice, the company assumes that docetaxel will usually not be the most appropriate treatment, and in these cases docetaxel will be considered 'not clinically indicated', despite patients technically being eligible to receive it.

However, it remains confusing that the marketing authorisation specifically states that olaparib plus abiraterone is for use in first-line mCRPC patients for whom chemotherapy is not clinically indicated, since this implies that there are patients for whom chemotherapy (docetaxel) *is* clinically indicated. The size of this patient group in the NHS is unknown, as is how well it was represented in the PROpel trial cohort. This uncertainty may limit the applicability of the PROpel trial results to the NHS setting. Without knowing the proportion of patients for whom chemotherapy would be 'clinically indicated', it is also difficult to determine for certain that docetaxel is not a relevant comparator for olaparib plus abiraterone in first-line mCRPC.

The EAG considers this issue partly resolved. The issue can be resolved if the committee are confident that: 1) the wording of the marketing authorisation will be interpreted in practice without confusion, 2) docetaxel is not considered a relevant comparator in current NHS practice and 3) the subgroup of patients for whom chemotherapy is 'clinically indicated' (i.e. deemed preferable before an NHA) is very small in practice, or, those patients are unlikely to have different outcomes on olaparib plus abiraterone when compared to patients who are not given chemotherapy at first-line (despite being eligible).

2.2 Issue 2: Efficacy of olaparib plus abiraterone in the PROpel trial driven by the small subgroup of BRCA mutation patients

In the TE response, the company draws attention to the clinical benefits of olaparib plus abiraterone in the full ITT sample and in the HRRm and non-HRRm subgroups of the PROpel trial. The company does not consider evidence on the efficacy of olaparib monotherapy [TA887] to be applicable to this appraisal, given that the anti-tumour effects of olaparib and abiraterone combined are thought to lead to efficacy in the non-HRRm population.

The EAG's response

Whilst the EAG does not suggest that the efficacy of olaparib plus abiraterone in PROpel is proven to be driven entirely by the efficacy in the BRCA mutation subgroup, only that the data strongly suggest that the benefits of the treatment for rPFS and OS are larger for the BRCA mutation subgroup. Clearly, the distinction between BRCA-mutated and non-mutated patients is more informative than the difference between HRR and non-HRR mutations.

The relative difference in the rate of overall survival between patients with BRCA mutations (OS HR 0.29, 95% CI 0.14 to 0.56) and without BRCA mutations (OS HR 0.91, 95% CI 0.73 to 1.13) has significant implications for the cost-effectiveness of olaparib plus abiraterone and the EAG notes that the company have not provided cost-effectiveness analysis in a non-BRCA population. The EAG consider this an important omission, and is important that the committee are able to consider heterogeneity in cost-effectiveness estimates. It is probable that ICERS for a non-BRCA population are higher than those for both the BRCA and whole populations and may indicate that optimised recommendation is the most appropriate. In addition, the relative difference in the rate of overall survival between patients with and without BRCA mutations, has serious implications for patient safety and exposure to adverse events were highlighted by the Oncologic Drugs Advisory Committee in their advice to restrict the FDA license for olaparib plus abiraterone in mCRPC to patients with BRCA mutations.

The EAG acknowledges the company's word of caution regarding evidence on olaparib monotherapy [TA887], and recognises that the biological mechanisms of action of olaparib monotherapy in relation to BRCA mutations may differ from the working mechanisms of the olaparib plus abiraterone combination.

In summary, the EAG agrees with the company on the need for caution when interpreting evidence of olaparib monotherapy, but the issue of a potentially large difference in the relative efficacy of olaparib plus abiraterone between BRCA mutation and non-mutation subgroups remains.

2.3 Issue 3: Limited use of subsequent olaparib monotherapy in PROpel

In the PROpel trial only [redacted] of patients received olaparib monotherapy following progression on abiraterone plus placebo. This is significantly lower than the proportion of patients with a BRCA1 or BRCA2 mutation who would be eligible for olaparib monotherapy on the NHS.

The company response outlined that many patients will not proceed to receive subsequent treatment and that several factors may determine the choice of subsequent therapy including physician choice, contraindications, and patient fitness. The company also provided evidence from [redacted]

The company consider the EAG's assumption that all patients with BRCA mutation would receive subsequent olaparib monotherapy an overestimation.

The EAG's response

The acknowledges the points raised by the company and concurs that not all patients with BRCA mutation will necessarily go on to receive subsequent olaparib monotherapy. The EAG, however, maintains that the use of olaparib monotherapy in PROpel trial is likely to be less than in the NHS. As such, the PROpel trial may underestimate survival expected in an NHS cohort. Further clinical input on the utilisation of olaparib monotherapy may help resolve this uncertainty. The EAG notes that this issue is likely to be of greater significance in the BRCA subgroup analysis where all patients in the NHA arms would be eligible for olaparib monotherapy upon disease progression.

2.4 Issue 4: Assumption of efficacy equivalence when comparing abiraterone and enzalutamide

The company's base case economic analysis assumes equivalent PFS and OS outcomes for patients receiving enzalutamide and abiraterone. This was justified on the basis of an 'exploratory' NMA of OS, clinical opinion, and a single prospective real-world study. The EAG considers the company's NMA OS HR estimate to be unreliable due to important differences between the trials included in the network. To explore the relative effectiveness of enzalutamide and abiraterone the EAG conducted a pairwise meta-analysis of non-randomised studies identified in rapid review of the literature conducted by the EAG.

The company response expresses concern about the validity of the EAG meta-analysis, the reliability of the included studies and the appropriateness of pooling the data. The company specifically highlights that they are concerned that the meta-analysis included some studies where patients were pre-treated for mCRPC with docetaxel. They also considered that heterogeneity issues undermining

the company's NMA are applicable to the EAG's meta-analysis due to the potential for confounding bias in non-randomised studies.

The EAG's response

The EAG recognises the limitations and uncertainty associated with the pairwise meta-analysis and these are acknowledged in the EAR. However, the EAG considers that it is appropriate to both conduct a broader search for non-randomised evidence and to pool the identified studies; the EAG considers that this approach is no less valid than the NMA presented by the company. There is no significant evidence of heterogeneity in the included studies, as indicated by the presented forest plot and statistics. Further, the EAG has opted to present a random effects analysis to capture uncertainty resulting from heterogeneity among studies.

With respect to the company's concerns about the prior use of docetaxel, the EAG notes that most of the included studies were in chemotherapy-naïve cohorts and considers it reasonable to maximise the evidence base (by including studies which included patients who had previously received chemotherapy) given that studies adjusted for previous use of docetaxel. Moreover, the EAG are not aware of any reason to suspect that the use of prior docetaxel for mCRPC would represent a treatment effect modifier. The company are correct in highlighting the limitations of non-randomised studies, but the EAG notes that all studies included in the meta-analysis implemented methods to adjust for confounding.

The EAG disagrees that the limitations associated with the company's NMA are comparable to those associated with the EAG's meta-analysis. The assumptions made by the NMA are fundamentally different to those made in the pairwise meta-analysis. Specifically, violations of the transitivity assumptions outlined in the EAR are not relevant to a pairwise meta-analysis. The EAG also notes the TE response from Astellas Pharma Ltd, which both agrees with the EAG's conclusions regarding the adequacy of the NMA and outlines several further studies that support the superiority of enzalutamide. The EAG maintains that while uncertain, the balance of evidence supports a survival benefit in favour of enzalutamide.

Issue 5: Methodological corrections to the model

The company's updated economic analysis and revised base case implements several methodological corrects identified by the EAG. These relate to the following:

- Application of age-adjustment to the utilities
- No half-cycle correction to treatment acquisition cost
- Use of the latest NHS Reference and eMIT cost data.

The EAG's response

The EAG confirms these corrections have been appropriately implemented in the executable model and considers this issue resolved.

2.5 Issue 6: Equally plausible alternative OS extrapolations

The company's original analysis used a generalised gamma distribution to extrapolate OS data from PROpel. The EAG noted in the EAR that the log-logistic distribution also produced clinically plausible long-term OS estimates across all treatment arms and had a better statistical fit to trial data. The EAG considered the log-logistic model to be equally clinically plausible to the generalised gamma curve preferred by the company.

In response to a critique by the EAG, the company reiterated their arguments for the selection of the generalised gamma and outline that this was supported by clinical expert advice received by the company. The company acknowledged the lower AIC/BIC scores associated with the log-logistic curve but noted that these differences were small and do not support the selection of one curve over another. The company's base case retains the generalised gamma curve, scenario analysis was also presented using the log-logistic curve.

The EAG's response

The EAG consider that uncertainty remains with respect to the choice of distribution for extrapolating OS and considers both the log-logistic and generalised gamma curves equally plausible. This issue remains unresolved.

2.6 Issue 7: Inconsistent time to discontinuation extrapolation

The company's original analysis used different parametric functions to model discontinuation and PFS. This implied a rapid treatment discontinuation of treatment prior to progression which the EAG felt was not supported by appropriate evidence on hazard trends.

The company's response outlined summary of product characteristics (SMPC) for olaparib plus abiraterone states that treatment should be continued until either disease progression or toxicity and therefore that it was considered appropriate for time-on-treatment not to exceed PFS. The company confirmed that both the EAG-preferred generalised gamma extrapolation and the Weibull extrapolation (applied in the company's submission) are consistent with the SMPC and result in the time on the treatment curve remaining below PFS. The company considers the generalised gamma curve (preferred by the EAG) a plausible alternative to the Weibull curve and updated its economic analysis and revised base case to align with the EAG's preferred assumptions.

The EAG's response

The company accepted the EAG's approach to modelling time on treatment and included this in their revised base-case analysis. The EAG considers this issue is now resolved.

2.7 Issue 8: Modelling of adverse events using duration data from PROpel

The company assumed that all adverse events would last 14 days, despite the mostly much longer durations observed in the PROpel study. The EAG considered this approach underestimated the impact of the AE-burden of olaparib plus abiraterone upon HRQoL.

The company economic analysis and revised base case has been updated to align with EAG's preferred assumptions.

The EAG's response

The EAG confirms that the company has implemented the necessary updates to their economic analysis and considers this matter resolved.

2.8 Issue 9: Health state utilities generated using a non-reference case approach.

The EAG raised concerns that the mixed-effects model for repeated measures used estimate the utilities applied in the economic analysis was based on EQ-5D-5L value set. This would be inconsistent with NICE reference case which requires that EQ-5D-3L is used. The company's response confirmed that EQ-5D-5L data collected in PROpel were cross-walked to produce EQ-5D-3L utility values using the Hernández-Alava *et al,*[27] as per the NICE reference case. The company response further confirms that appropriate mapping was undertaken and outlines the process undertaken by the company.

The EAG's response

The EAG considers that this issue is likely to be a simple misunderstanding based on how input parameters in the company submission and clarification response were presented. The EAG acknowledges that the company have now provided the code used to generate the utility values used in the economic analysis along with a comparison of the NICE DSU (Hernandez) value set vs alternative value sets. The EAG is satisfied that the value set used in the company economic analysis is consistent with the NICE reference case and considers this issue to be resolved.

2.9 Issue 10: Dosing calculations

In the original analysis, the company did not adjust treatment acquisition costs to account for the relative dose intensity observed in the trial. As a result, this may not reflect the treatment costs observed in NHS practice, as missed doses, dose reductions, and dose interruptions can lead to less drug being dispensed. The EAG suggested that mean observed relative dose intensity from PROpel

should be used to adjust treatment acquisition costs. This approach assumes that all tablets not taken will result in cost savings i.e., a new pack is not dispensed until the previous one has been used up.

In response to the critique, the company accepted that their base-case should include the observed relative dose intensity from PROpel. However, the company argued that median values were more appropriate (as supposed to the mean values preferred by the EAG) and as a result included these in their revised base-case. The company described how median relative dose intensity in PROpel was high, at 98.2% in the olaparib combination arm, and 100% in the placebo plus abiraterone arm. The company assumed that the relative dose intensity for enzalutamide was equal to that of abiraterone.

The EAG's response

The company has accepted the EAG's approach to treatment acquisition costs adjusted for relative dose intensity and included this in their revised base-case analysis. However, the company used median values from PROpel which differ from the EAG preferred mean values. Medians should not be used to represent average dose intensity, as all a median of 100% says is that >50% of patients did not have a dose reduction. It says nothing about the total resource use. As a result, the EAG consider this issue partly resolved and note the minor impact on cost-effectiveness results.

2.10 Issue 11: Testing costs for BRCA1/2 mutations

The EAG had three concerns with the company's application of testing costs in the original analysis.

Firstly, the company's base case omitted the cost of testing for BRCA mutations at the point of progression in the comparator arm, reflecting the availability of olaparib monotherapy following an NHA on the NHS. Following a PFC response, the company incorrectly implemented these costs, applying them to the first model cycle rather than at the point of progression. Secondly, in the BRCA mutation subgroup, testing costs were implemented incorrectly. Treatment decisions at the first line would be based on biomarker testing. This only affects total costs as costs should be incurred in both treatment arms. The cost should be calculated as cost per *actionable mutation identified*. Finally, the EAG also argued that testing costs should be based on the unit cost of adding a gene to an NHS screening panel - £34 in line with TA898. This contrasts with the unit costs used in the company base-case of £400 based on TA887 for previously treated BRCA-mutation positive mCRPC.

The EAG's response

In response to the critique points raised by the EAG, the company described how, in the full population, patients would be eligible for the combination therapy regardless of biomarker status, and therefore no testing would be required. This is an apparent misunderstanding of the EAG's position that testing costs should be applied at the point of progression in the comparator arm. On the issue of

the appropriate testing cost, the company welcomed the input of NHS England. The company did not provide a response on the issue surrounding the calculation of testing costs in the BRCA subgroup.

As a result, the EAG consider this issue unaddressed and note the difference between the EAG and company-preferred base case. The EAG would welcome the input of NHS England to inform the correct unit costs for testing.

3 UPDATED MODELLING ASSUMPTIONS

In response to the issues noted in the EAR, and following the additional analyses undertaken by the company, an updated base-case cost-effectiveness model was presented.

The following EAG-preferred assumptions are incorporated within the company's revised model:

- Issue 5: Methodological corrections to the model
- Issue 7: Inconsistent time to discontinuation extrapolation
- Issue 8: Modelling of adverse events using duration data from PROpel
- Issue 9: Health state utilities generated using a non-reference case approach
- Issue 10: Adjustment of treatment acquisition costs for relative dosing intensity

In addition, the following issues have been partially accommodated in the company's revised model:

- Issue 6: Uncertainty over equally plausible alternative OS extrapolations

The company maintain their original position on the following assumptions:

- Issue 4: Equivalent PFS and OS outcomes for enzalutamide and abiraterone
- Issue 11: Testing costs for BRCA1/2 mutations

3.1 Results

The results of the company's updated base case are summarised in Table 2 below. These results are inclusive of the approved PAS discounts for olaparib plus abiraterone, and a updated discount for olaparib monotherapy but are exclusive of confidential PAS discounts for comparator and subsequent treatments. Results with PAS discounts for all comparators and subsequent treatments are provided in a confidential appendix separate to this document.

In the company's revised base case, the results indicate that olaparib plus abiraterone is associated with increased costs (cost difference of [redacted]) but higher accrued QALYs (QALY difference of [redacted]). The company's base-case ICER comparing olaparib plus abiraterone with abiraterone only is [redacted] per QALY gained.

Table 2 Fully incremental company base case results (whole population) – deterministic

Technology	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
Abiraterone	[redacted]	[redacted]	-	-	-
Enzalutamide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Olaparib + Abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Indicates non-zero differences

The corresponding pairwise results are shown in Table 3 below.

Table 3 Pairwise company base-case results – deterministic (whole population)

Technology	Total costs	Total QALYs	Incremental costs (olaparib vs)	Incremental QALYs (olaparib vs)	ICER (olaparib vs)
Olaparib + Abiraterone	[redacted]	[redacted]			
Abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Enzalutamide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The EAG also performed additional scenario analyses on the company's base case, as shown in Table 4 below.

Table 4 Company's additional scenario analyses (Pairwise) - deterministic

Technology	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
Scenario 1: BRCA subgroup (inclusive of EAG-preferred biomarker testing costs)					
Olaparib + Abiraterone	[redacted]	[redacted]			
Abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Enzalutamide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 2b: RWE-derived hazard ratios used to estimate OS, PFS, and TTD for enzalutamide					
Olaparib + Abiraterone	[redacted]	[redacted]			
Abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Enzalutamide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 3: Log-logistic extrapolation used to model OS					
Olaparib + Abiraterone	[redacted]	[redacted]			
Abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Enzalutamide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 8: Testing costs for BRCA mutations					

Olaparib + Abiraterone	[redacted]	[redacted]			
Abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Enzalutamide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

3.2 Updated EAG base-case analysis

The EAG performed two base case analyses, one in the whole population and one in the BRCA mutation subgroup. The EAG's base case analysis are unchanged from those presented in the EAR Results for the whole population base-case is shown in Table 5 below and incorporates the following assumptions:

Scenario 2b: RWE-derived hazard ratios used to estimate OS, PFS, and TTD for enzalutamide.
Scenario 4: Generalised gamma to model time to discontinuation
Scenario 6: Relative dose intensity used to adjust treatment acquisition costs
Scenario 7: Adverse event durations based on PROpel
Scenario 8: Testing costs for BRCA mutations

As noted above, results are inclusive of an updated PAS discount for olaparib monotherapy and therefore differ to those presented in the EAR.

Table 5 EAG's preferred model assumptions (whole population): fully incremental probabilistic results

Technology	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
Abiraterone	[redacted]	[redacted]	-	-	-
Enzalutamide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Olaparib + Abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The EAG's base-case for the BRCA mutation subgroup is shown in Table 6 below. The scenarios incorporated in the BRCA subpopulation include:

Scenario 1: BRCA mutation subgroup (inclusive of biomarker testing costs for all arms).
Scenario 6: Relative dose intensity used to adjust treatment acquisition costs
Scenario 7: Adverse event durations based on PROpel

Table 6 EAG's preferred model assumptions (BRCA mutation population): fully incremental probabilistic results

Technology	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
Abiraterone	[redacted]	[redacted]	-	-	-
Enzalutamide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Olaparib + Abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 1 Fully incremental company base case results (whole population) – probabilistic

Technology	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
Abiraterone	[redacted]	[redacted]			
Enzalutamide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Olaparib + Abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 2 Pairwise company base-case results (whole population) – probabilistic

Technology	Total costs	Total QALYs	Incremental costs (olaparib vs)	Incremental QALYs (olaparib vs)	ICER (olaparib vs)
Olaparib + Abiraterone	[redacted]	[redacted]			
Abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Enzalutamide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 3 Company's additional scenario analyses (fully incremental) - deterministic

Technology	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
Scenario 1: BRCA subgroup (inclusive of EAG-preferred biomarker testing costs)					
Abiraterone	[redacted]	[redacted]			
Enzalutamide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Olaparib + Abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 2b: RWE-derived hazard ratios used to estimate OS, PFS, and TTD for enzalutamide					
Abiraterone	[redacted]	[redacted]			
Enzalutamide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Olaparib + Abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 3: Log-logistic extrapolation used to model OS					
Abiraterone	[redacted]	[redacted]			
Enzalutamide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Olaparib + Abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 8: Testing costs for BRCA mutations					
Abiraterone	[redacted]	[redacted]			
Enzalutamide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Olaparib + Abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Scenario: company base case using mean RDI (EAG preferred method)					
Abiraterone	[redacted]	[redacted]			
Enzalutamide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Olaparib + Abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

1.1 EAG analyses (lead team requests)

Table 4 Scenarios on EAG base case (whole population): fully incremental deterministic results

Technology	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
Scenario: EAG base case using log logistic OS extrapolation					
Abiraterone	[redacted]	[redacted]			
Enzalutamide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Olaparib + Abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario: EAG base case using company's enzalutamide vs abiraterone HR of 1.01					
Abiraterone	[redacted]	[redacted]			
Enzalutamide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Olaparib + Abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

1. **The diagram doesn't show any subsequent treatments after olaparib + abiraterone. What subsequent treatments are permitted after olaparib + abiraterone, if any?**

Docetaxel is permitted for some patients after olaparib + abiraterone. In the PROpel trial, 60% of patients received docetaxel after trial discontinuation (EAG report section 2.2.3.2, p. 26). The company may not have included this option in their treatment pathway diagram because after olaparib + abiraterone followed by docetaxel, patients would not be eligible to receive retreatment with abiraterone within an NHS setting. Patients who received first-line abiraterone or enzalutamide followed by docetaxel would not be eligible to receive retreatment with abiraterone or enzalutamide (EAG report section 2.2.3.4, p. 27). Radium and best supportive care may follow olaparib + abiraterone and docetaxel and cabazitaxel.

2. **Are there specific treatments included within best supportive care e.g., radium?**

The EAG's clinical adviser considered radium-223 an option for later-line therapy (EAG report section 2.2.3.4, p. 27). The EAG would consider this separately from 'best supportive care', in line with TA887 for olaparib monotherapy. Best supportive care would be the continuation of androgen deprivation therapy (ADT) and monitoring. ADT is no longer able to stop progression of disease in mCRPC, but the EAG's clinical adviser explained that patients are still expected to derive some benefit from it (EAG report section 2.2.1, p. 24).

3. **Olaparib monotherapy isn't included – presumably because this pathway is not specific to people with BRCA mutations. If included, how would this be placed into this diagram (would include a note to say BRCA mutation only).**

Olaparib monotherapy is indicated for patients with BRCA mutations and mCRPC in the second line, after unsuccessful treatment with a new hormonal agent (abiraterone or enzalutamide). Retreatment with olaparib is not permitted (EAG report section 2.2.4, p. 27-28). Patients with BRCA mutations and mCRPC who receive olaparib + abiraterone in the first line would therefore not be eligible for olaparib monotherapy at a later stage. If olaparib + abiraterone were to become available for patients with BRCA mutations only in the NHS, olaparib monotherapy could not be given after olaparib + abiraterone.

4. **Docetaxel here does not look as though it can be given as a first line treatment, only after enza and abira. Is it possible to receive docetaxel first line?**

Our response to company queries regarding key issue 1 at technical engagement might be helpful here. It is the EAG's understanding that docetaxel can be

received for first line mCRPC, if it has not been received at an earlier disease stage (usually mHRPC). In the PROpel trial, 75% of patients had not received docetaxel in an earlier stage and would therefore be eligible for treatment with docetaxel in first line mCRPC (EAG report section 2.2.3.3, p. 26-27). The company appears to be arguing that, even though most of these patients may be eligible, docetaxel is usually not considered ‘clinically indicated’ at this stage. The company figure of the treatment pathway reflects this position. We do not know for what proportion of patients docetaxel may be clinically indicated in first-line mCRPC, although our adviser estimated that it might be in the region of 5-10% of patients.

Figure 1 OS extrapolations: Gen gamma vs log logistic