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External Assessment Group Report
Olaparib with abiraterone for untreated hormone-relapsed metastatic prostate cancer

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Date completed	28/06/2023

Source of funding

This report was commissioned by the NIHR Evidence Synthesis Programme as project number NIHR135998.

Declared competing interests of the authors

None

Acknowledgements

We would like to thank Dr Alastair Thomson, Consultant Clinical Oncologist, Royal Cornwall Hospitals NHS Trust, who provided expert clinical advice during the appraisal and commented on the draft report.

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.

This report should be referenced as follows:

Corbett M, Deng J, Uphoff E, Walton M, Lord J, Fulbright H, Dwan K, Hodgson R. Olaparib with abiraterone for untreated hormone-relapsed metastatic prostate cancer: A Single Technology Appraisal. CRD and CHE Technology Assessment Group, University of York, 2023.

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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Table of Contents

Table of Tables

Table of Figures

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 3.2.2.3.[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 3.2.2.3.[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 3.2.2.3.

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]

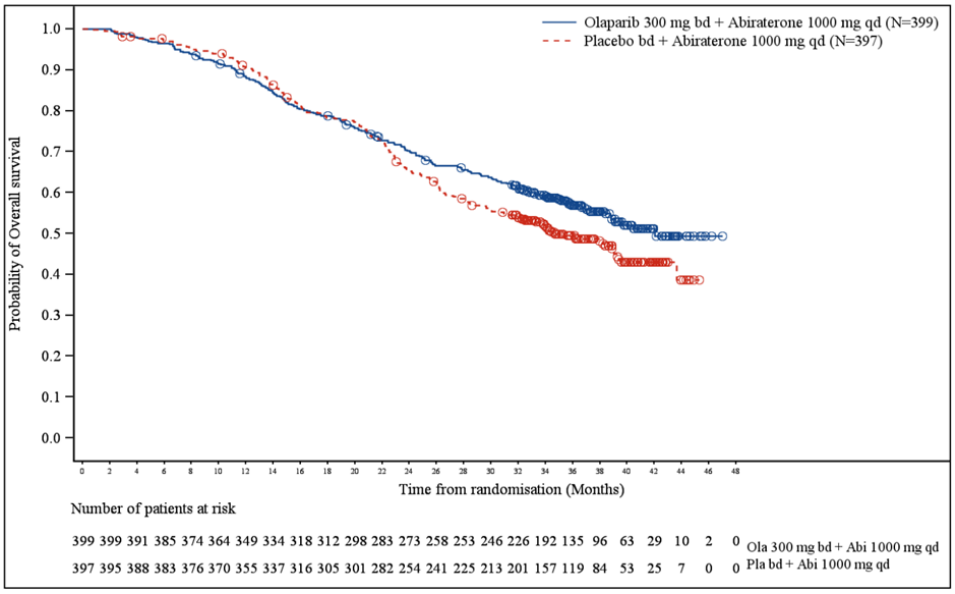
DCO data cut-off, HR Hazard Ratio, rPFS Radiological Progression-Free Survival

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.

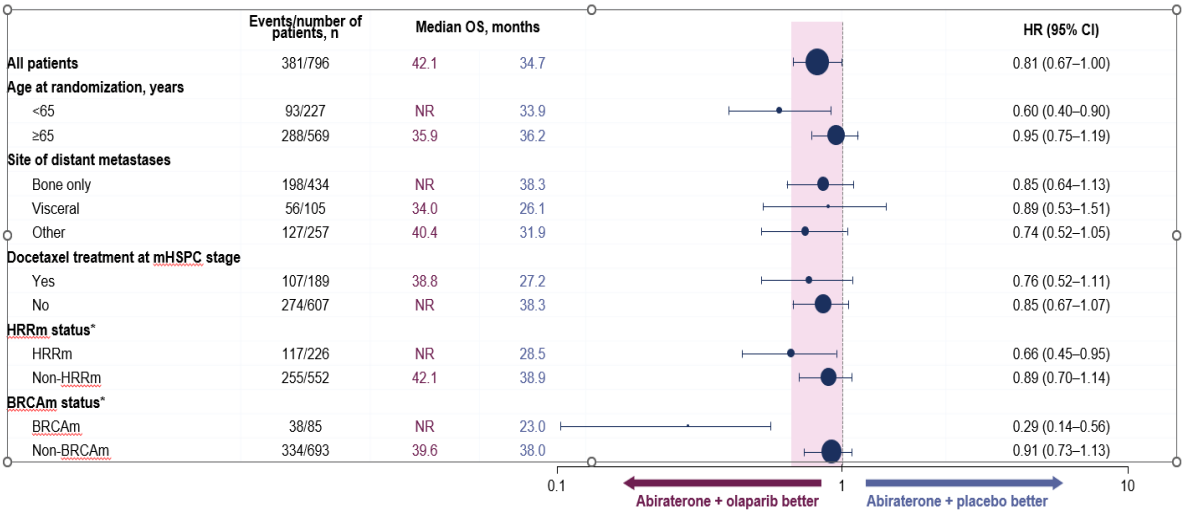
Pre-specified subgroup results

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]

	ITT (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

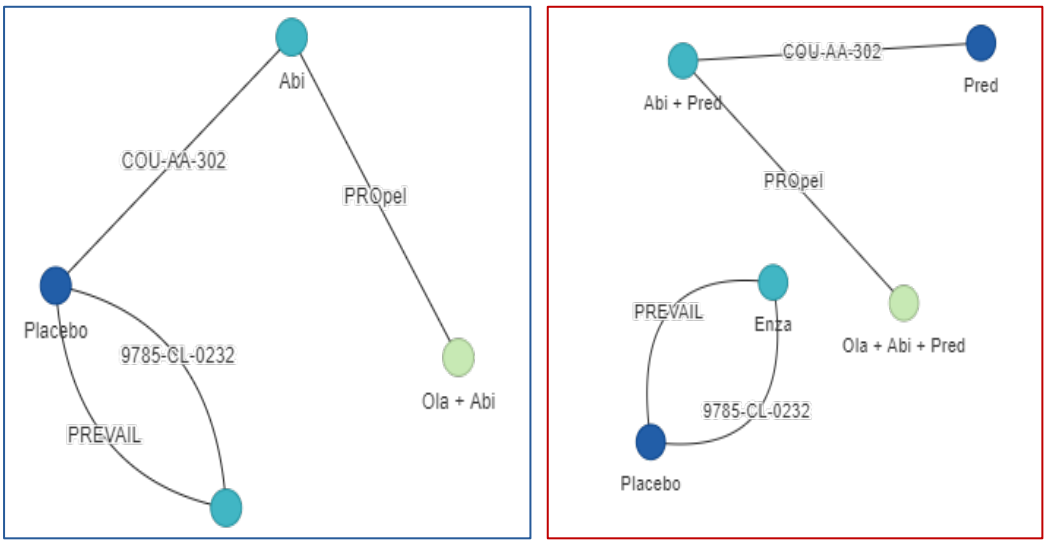
Company's approach to conducting network meta-analyses

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]

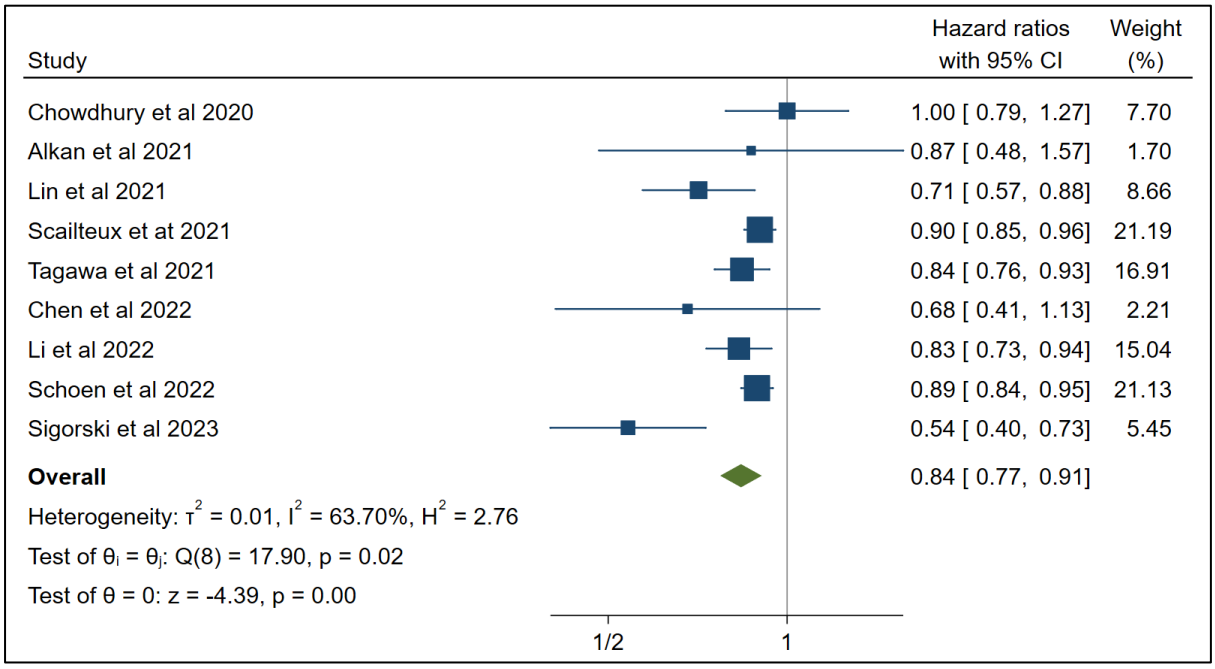
Table 11 Non-randomised studies comparing abiraterone with enzalutamide which report OS hazard ratios

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.		

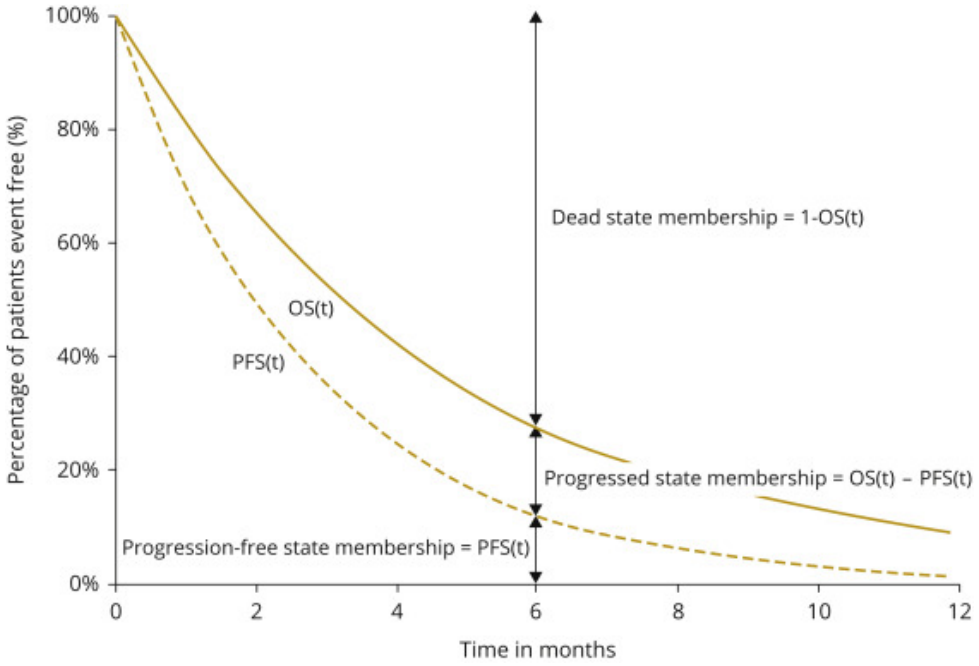
4.2.2 Model structure

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 3.2.2.3, 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 3.2.2.3 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 5.

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 3.2.2.3. 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 3.2.2.3, 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 3.2.2.3), 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)

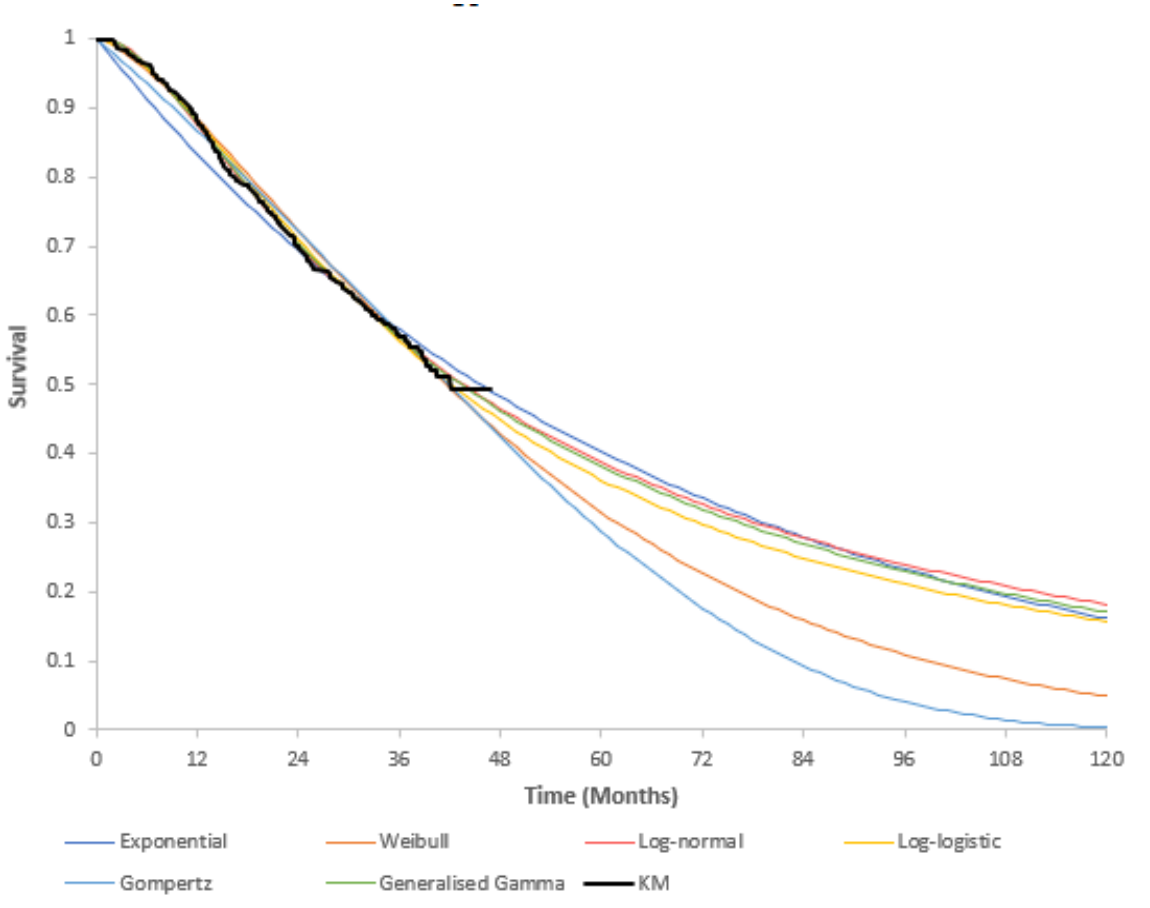
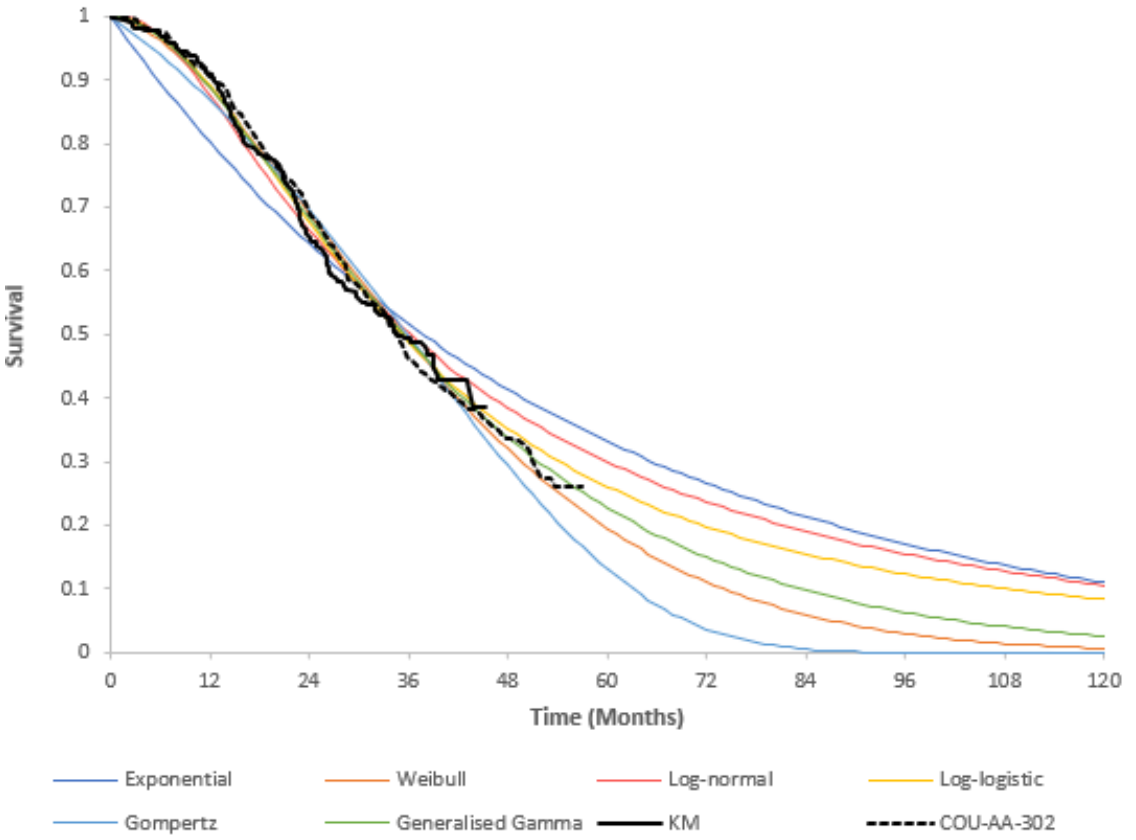
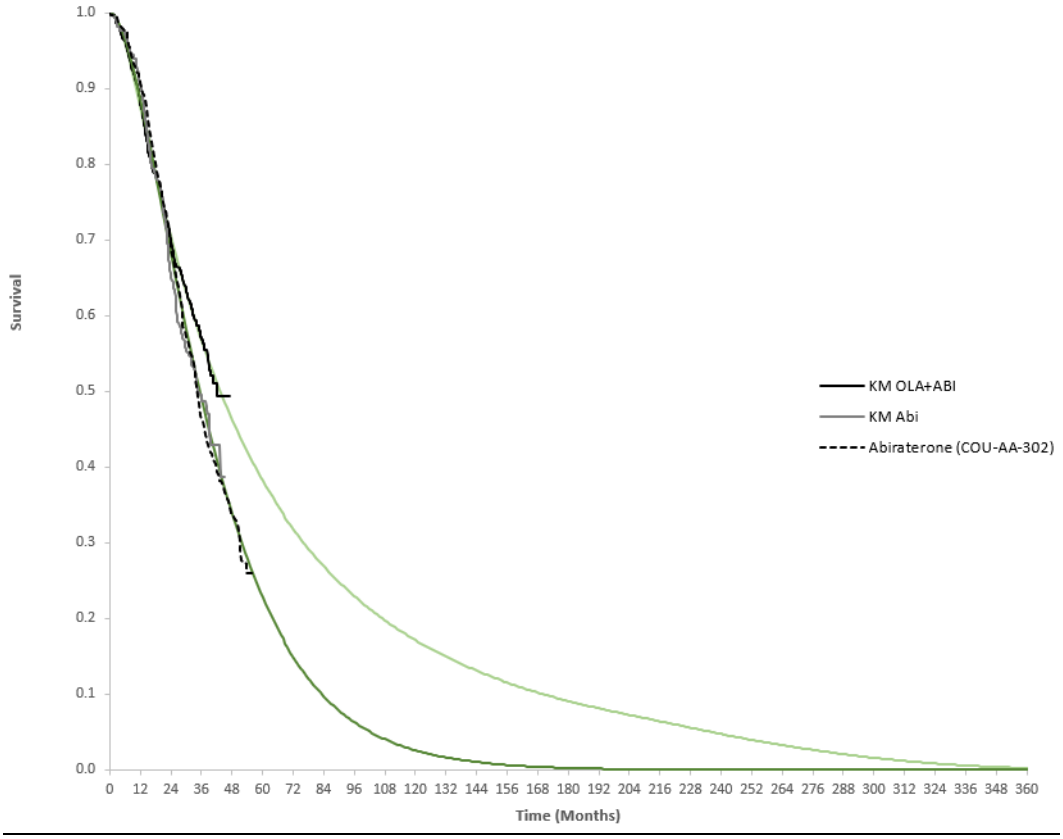


Figure 8 OS parametric extrapolation for abiraterone (CS Figure 18, Page 84)



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)

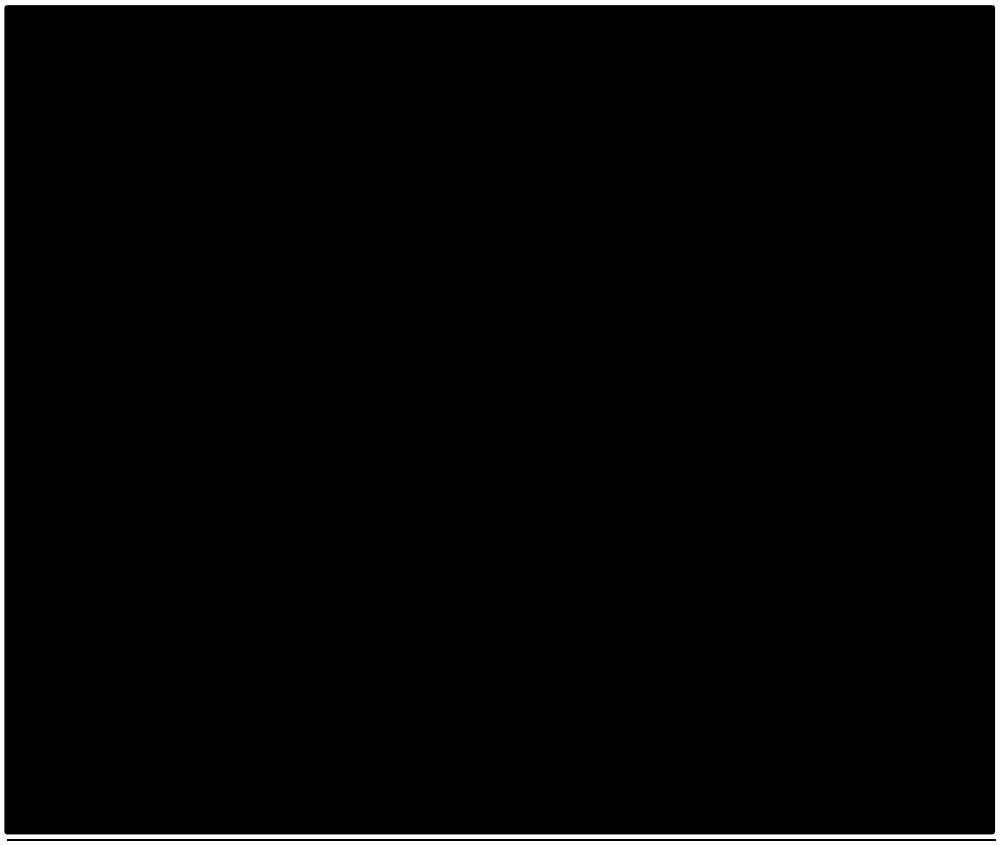

Figure 15 TTD parametric extrapolation for abiraterone within the olaparib + abiraterone arm (CS Figure 35, Page 102)

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)

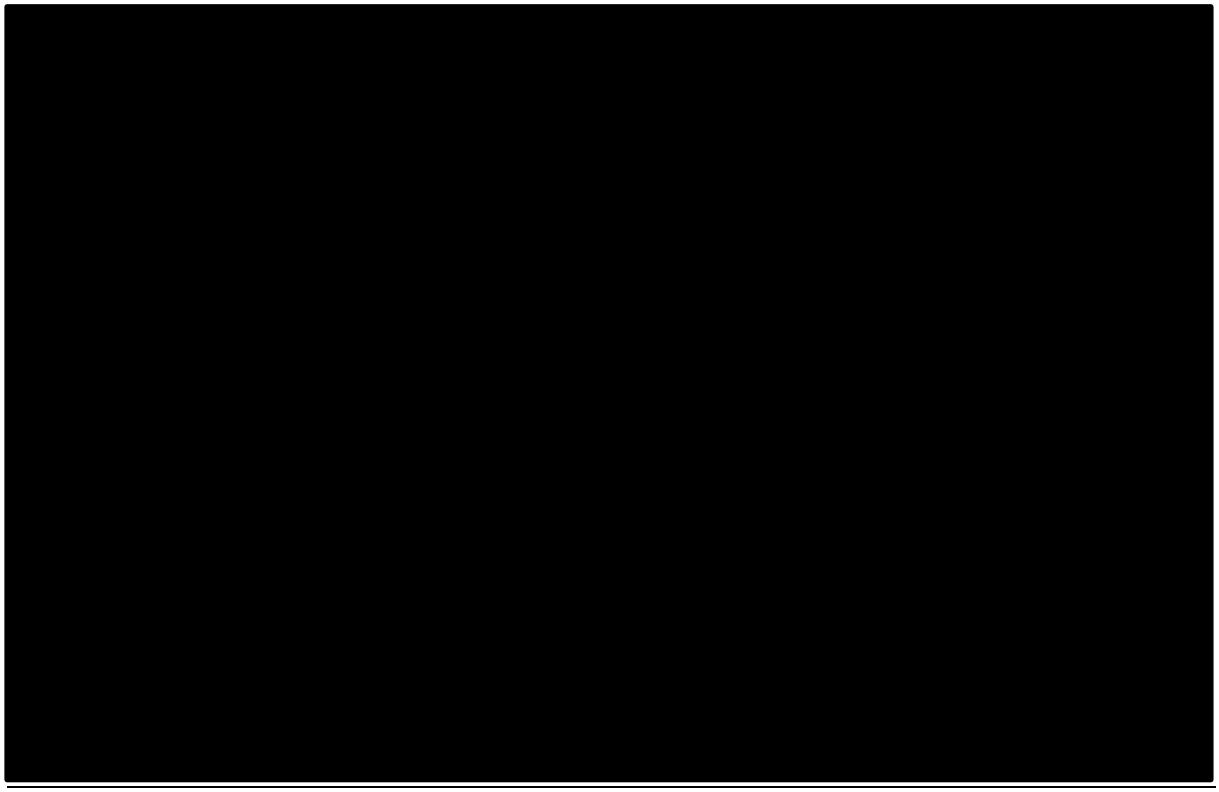

Figure 21 DSA tornado graph (versus abiraterone) (from company model)

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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