NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Olaparib for previously treated hormone-relapsed metastatic prostate cancer [ID1640]

Committee Papers

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Olaparib for previously treated hormone-relapsed metastatic prostate cancer [ID1640]

Contents:

The following documents are made available to consultees and commentators:

The **final scope and final stakeholder list** are available on the NICE website.

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Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Olaparib for previously treated hormone-relapsed metastatic prostate cancer [ID1640]

Document B

Company evidence submission

June 2020

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

The regulatory submission for the olaparib indication relevant to this appraisal was provided to the European Medicines Agency (EMA) on [redacted]. The anticipated marketing authorisation is aligned to the overall population of the pivotal Phase III PROfound study:

[redacted]

This section provides an overview of the health condition, the current clinical pathway of care, a description of olaparib (the technology being appraised), and the decision problem addressed in the company submission.

B.1.1 Overview of prostate cancer

Prostate cancer is the most common cancer in men in the UK[1] with a total of 42,668 people in England and Wales were diagnosed with prostate cancer between 2017 and 2018.[2] Although the majority of patients (83%) present with early stage disease at the time of diagnosis,[2] a substantial proportion of patients eventually develop resistance to therapy and progress to castration-resistant prostate cancer, or metastatic prostate cancer,[3] or (for ~40% of patients) metastatic castration-resistant prostate cancer (mCRPC).[4,5]

mCRPC - **the focus of this appraisal** - is associated with substantially increased symptom burden, deterioration in health-related quality of life (HRQoL), and increased mortality (with >3 higher risk of death) versus non-metastatic disease.[6-9] Almost all patients dying from prostate cancer have mCRPC,[10] and **fewer than half of patients with mCRPC in the UK survive for 5-years.**[11] Therefore, there is significant and urgent unmet clinical need for life-extending therapies for the treatment of mCRPC.

Approximately 20%−30% of patients with mCRPC have mutations in genes involved in the homologous recombination repair (HRR) pathway, such as *BRCA1, BRCA2, ATM*.[12,13] While not all HRR mutations (HRRm) are fully characterised, those patients with *BRCA2* and *CDK12*-mutations (two of the most well-characterised of the HRR mutations) have more aggressive disease, and worse prognosis, than those without.[14-26] Additionally, mutations in *BRCA-2* have been reported to lead a reduced response to taxane chemotherapy, highlighting the urgent need for new types of treatment in these patients.[27]

The presence HRRm render tumours sensitive to targeted therapy with poly(adenosine diphosphate)-ribose polymerase (PARP) inhibitors, such as olaparib, which specifically target and kill HRR-deficient tumour cells via a mechanism involving synthetic lethality (described in Section B.1.3).[28,29]

Olaparib is the only PARP inhibitor supported by Phase III trial data, demonstrating a statistically-significant extension in radiographic progression-free survival (rPFS), as well as a significant benefit overall survival (OS)[1], versus investigators' choice of NHA in patients with deleterious or suspected deleterious HRR mutations who have progressed after first-line treatment for mCRPC with an NHA,[30,31] and **provides a much-needed new therapeutic option to improve patient outcomes in this setting**.

B.1.2 Clinical pathway of care

The growth and survival of prostate tumours is dependent on androgens, particularly testosterone and dihydrotestosterone.[32] Due to the dependence of prostate tumours on androgen receptor signalling, all prostate cancers are treated with androgen deprivation therapy (ADT). However, eventually these tumours may develop resistance to ADT, characterised by increased levels of testosterone that drive cancer progression. Overall, around 40% of all patients with prostate cancer go on to develop metastatic castration-resistant disease (i.e. mCRPC),[4,5,33] which is an incurable form of cancer.[34]

[1] In patients with *BRCA1/2* and *ATM* mutations.

The use of docetaxel in the pre-mCRPC setting is increasing. In the 2019 National Prostrate Cancer (NPCA) Audit,[2] which used data from 2017−2018, docetaxel was used in the treatment of approximately 1 in 4 patients with metastatic hormone-sensitive prostate cancer (mHSPC). Since these data were collected, **NICE Guideline 131** (NG131, May 2019) for "Prostate Cancer: Diagnosis and Management" **recommended the addition of docetaxel to standard-of-care ADT for the treatment of patients with high-risk HSPC** (used synonymously with locally-advanced disease in NG131) **or mHSPC**, leading to a change in treatment paradigm and more patients receiving docetaxel in this setting. Six UK clinical experts were consulted by AstraZeneca to inform the company submission and highlighted that ~75% of patients currently receive docetaxel in the pre-mCRPC setting (AstraZeneca data on file). Data from the GETUG-AFU15 trial showed that, although the addition of docetaxel to ADT led to improved patient outcomes in this setting, prolonging median time to biochemical disease progression by ~11 months (versus ADT alone), the majority (50%) of patients still progressed within two years of starting therapy.[35]

Treatment with new hormonal agents (NHAs), specifically enzalutamide or abiraterone acetate, are the standard-of-care and recommended by NICE for patients with mCRPC.[36-38] With docetaxel moving earlier in the treatment pathway from May 2019 (per NG131),[36] most patients in England currently receive NHA as initial treatment for mCRPC after treatment with docetaxel and ADT for advanced HSPC. Although NHAs have substantially improved outcomes in patients with mCRPC, many (~60%) do not respond to these therapies and ~50% experience disease progression within 6–12 months of initiating therapy.[39,40]

Treatment options for mCRPC after NHA progression are limited. The six UK clinical experts consulted by AstraZeneca confirmed that **the standard-of-care for patients after disease progression on docetaxel and an NHA is cabazitaxel** (AstraZeneca data on file), which is recommended by NICE as a treatment option "in combination with prednisone or prednisolone for patients with metastatic hormone-relapsed prostate cancer whose disease has progressed during or after docetaxel chemotherapy".[41] Although NICE guidelines still recommend docetaxel post-NHA, in practice docetaxel is now predominantly used earlier in the treatment pathway (as

explained above); the 6 UK clinical experts consulted highlighted that re-treatment with docetaxel is not preferred in patients where cabazitaxel is a treatment option (AstraZeneca data on file).

Prognosis for patients with mCRPC who have progressed following treatment with NHA is extremely poor, with a median OS of just 13.6 months reported in the CARD study, the pivotal clinical trial for cabazitaxel in the post-NHA setting.[42]

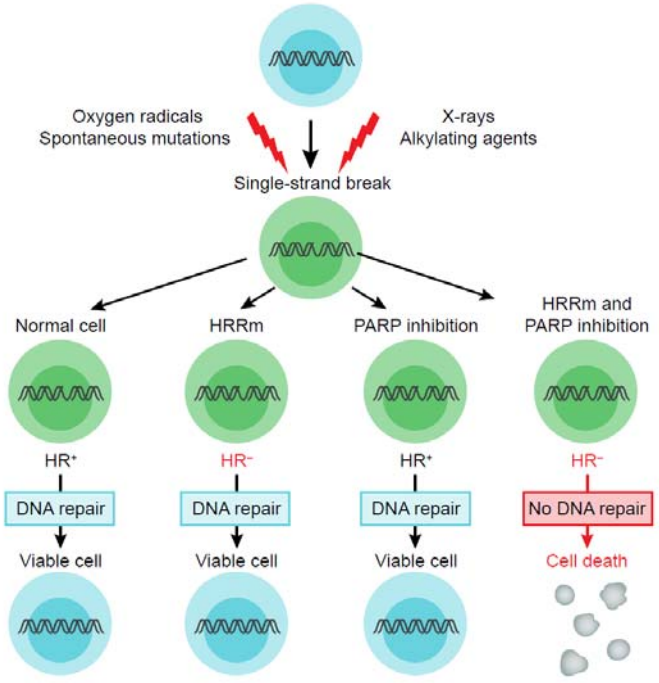
Treatment options are further limited once patients have exhausted cabazitaxel as a treatment option (i.e. patients have progressed on cabazitaxel or cannot receive it [e.g. due to frailty or contraindications]). Prostate cancer has a high propensity to metastasise to bone tissue. NICE guidelines recommend radium-223 dichloride (referred to radium-223 henceforth) as an option for treating patients with "hormone-relapsed prostate cancer, with symptomatic bone metastases and no known visceral metastases, only if they have already received docetaxel or docetaxel is contraindicated or is not suitable for them".[43] Although it is possible to use radium-223 dichloride instead of cabazitaxel, in those patients who have symptomatic bone metastases (and no known visceral metastases) and have received prior docetaxel for hormone-sensitive disease, **clinical expert opinion from 6 UK-based clinical experts indicates that in practice it is often reserved for later-lines of treatment, unless treatment with a taxane is not suitable** (AstraZeneca data on file).

Olaparib, the intervention relevant to this appraisal, offers a **new targeted treatment** option for those patients who have deleterious or suspected deleterious HRRm and whose disease has progressed after treatment with an NHA. **Based on the current clinical practice in England, where ~75% of patients receive docetaxel with ADT for metastatic HSPC (and radium-223 dichloride is reserved for later lines of treatment in eligible patients)** (AstraZeneca data on file),[44] **it is anticipated that olaparib will primarily displace treatment with cabazitaxel following disease progression after NHA.**

B.1.3 Description of the technology being appraised

The summary of product characteristics (SmPC) and European public assessment report (EPAR) can be found in Appendix C.

Table 1. Technology being appraised.

UK approved name and brand name	Olaparib (LYNPARZA®)
Mechanism of action	Olaparib inhibits poly(adenosine diphosphate)-ribose polymerase (PARP) proteins.[45] PARP enzymes are essential for repairing commonly-occurring DNA single-strand breaks (SSBs) in human cells. Olaparib works by trapping PARP enzymes at the site of SSBs, thereby preventing their repair. Persistent SSBs in the DNA are eventually converted into more harmful double-strand breaks (DSBs) during the process of DNA replication. Normal cells can repair DNA DSBs through the homologous recombination repair (HRR) pathway. However, cells with HRR defects/deficiencies are unable to accurately repair these breaks, leading to the accumulation of DNA damage and eventually cell death (or apoptosis).[46-48] **Mode of action of PARP inhibitors, including olaparib**  HR+, homologous repair positive; HR−, homologous repair negative; HRRm, mutation in the homologous recombination repair pathway; PARP, poly(adenosine diphosphate)-ribose polymerase. Source: Guha *et al*, 2011[46]

Marketing authorisation/CE mark status	A new marketing authorisation application for olaparib was submitted to the EMA on [redacted]. CHMP opinion is anticipated in [redacted], and marketing authorisation in [redacted].
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	***Indications*** For patients with mCRPC, it is anticipated that olaparib will be licensed [redacted], and will be one of several olaparib indications. Olaparib is also indicated as monotherapy in the following settings that are not covered by this submission. • Ovarian cancer[49] o Maintenance treatment of adult patients with advanced (FIGO stages III and IV) *BRCA1* or *BRCA2*-mutated (germline and/or somatic) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy. o Maintenance treatment of adult patients with platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy. • Breast cancer[49] o Treatment of adult patients with germline *BRCA1* or *BRCA2*-mutations, who have HER2-negative locally advanced or metastatic breast cancer. Patients should have previously been treated with an anthracycline and a taxane in the (neo)adjuvant or metastatic setting unless patients were not suitable for these treatments. o Patients with hormone receptor (HR)-positive breast cancer should also have progressed on or after prior endocrine therapy, or are considered unsuitable for endocrine therapy. In May 2020, the EMA Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion recommending a change to the olaparib marketing authorisation to include the following indication: • Adenocarcinoma of the pancreas[50] o Monotherapy for the maintenance treatment of adult patients with germline *BRCA1/2*-mutations who have metastatic adenocarcinoma of the pancreas and have not progressed after a minimum of 16 weeks of platinum treatment within a first-line chemotherapy regimen. ***Restrictions***[49] Olaparib is contraindicated for the following. • Patients with known hypersensitivity to the active substance or any of its excipients. • During breast feeding during treatment and for 1 month following receipt of the last dose. The safety and efficacy of olaparib in children and adolescents have not been established.

	Further details are provided in the SmPC, available here: https://www.ema.europa.eu/en/documents/product-information/lynparza-epar-product-information_en.pdf
Method of administration and dosage	Oral treatment Olaparib is available as 100 mg and 150 mg tablets. Olaparib is recommended at a dose of 300 mg (2 x 150 mg tablets) taken twice daily, equivalent to a total daily dose of 600 mg. Patients can continue treatment until radiological disease progression, unacceptable toxicity.
Additional tests or investigations	Patients must have confirmation of a deleterious or suspected deleterious HRR gene mutation (either germline or tumour) before olaparib treatment is initiated. HRR gene mutation status should be determined by an experienced laboratory using a validated test method. Note: genomic testing for cancer is provided by NHS England through a network of Genomic Laboratory Hubs (GLHs).[51] [redacted]
List price and average cost of a course of treatment	***List price per 28-tablet pack*** The list price for tablets is £2317.50 per 14-day pack; £4635.00 per 28-day cycle.
Patient access scheme (if applicable)	A confidential commercial access agreement is in place for olaparib; the net price of olaparib for NHS hospitals in England is £[redacted] per 14-day pack

ADP, adenosine diphosphate ribose; *ATM*, ataxia-telangiectasia mutated gene; *BRCA*, BReast CAncer gene; CHMP, Committee for Medicinal Products for Human Use; DSB, double stranded breaks; FIGO, Fédération Internationale de Gynécologie et d'Obstétrique [Federation of Gynaecology and Obstetrics]; HER2, human epidermal growth factor receptor 2; HRR, homologous recombination repair; PARP, poly (ADP-ribose) polymerase; SSB, single stranded breaks.

B.1.4 Decision problem

As highlighted above, the regulatory submission for the olaparib indication relevant to this appraisal was provided to the European Medicines Agency (EMA) on [redacted]. The anticipated marketing authorisation is aligned to the overall population of the pivotal Phase III PROfound study:

[redacted]

The overall population of patients included in the PROfound study had qualifying mutations in one or more of 15 HRR genes (*BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D, and RAD54L*).[30] Enrolment into the study was not restricted by prior taxane use (given the unmet clinical need for patients who had progressed after treatment with a NHA, regardless of whether they had received prior treatment with a taxane), or baseline metastases (bone, visceral, or other).[30] However, the clinical- and cost-effectiveness evidence presented in this submission focuses on the predefined subgroup of patients who had received prior treatment with a taxane and NHA, to align with the anticipated positioning of olaparib in the current clinical pathway of care in England (where the majority of patients receive a taxane [docetaxel] for non-metastatic or metastatic HSPC, before receiving NHA for mCRPC, as described in Section B.1.2).

The PROfound study assessed the efficacy and tolerability of olaparib versus investigators' choice of NHA, since re-treatment with NHA (i.e. enzalutamide after progression of abiraterone, and vice versa) are approved treatment options in this setting (by both the EMA[52,53] and the US FDA[54,55]) and is a standard-of-care in many countries where the PROfound study was conducted.[56] This strategy also ensured that patients for whom treatment with chemotherapy was unsuitable were not excluded from the study. Since re-treatment with NHA is not reimbursed in England,[57] an anchored Bucher indirect treatment comparison (ITC) was conducted versus cabazitaxel, the most-commonly used treatment option and current standard-of-care for patients whose disease has progressed after treatment with a taxane (i.e. docetaxel) and an NHA – the focus of the company submission.

The decision-problem specified by NICE for this appraisal also includes docetaxel and radium-223 dichloride as comparators of interest. These are discussed below.

- **Docetaxel:** As explained in Section B.1.2, since the publication of NG131 in May 2019,[36] the vast majority (~75%) of patients now receive docetaxel earlier in the treatment pathway (added to ADT, for HSPC; AstraZeneca data on file). Based on the opinion of 6 UK clinical experts, re-treatment with docetaxel for mCRPC is not routinely used in clinical practice, with patients receiving cabazitaxel following

disease progression after NHA (AstraZeneca data on file). Therefore, **treatment with docetaxel in the post-NHA setting, which is relevant to this appraisal, is only considered for the minority (~25%) of patients who have not previously received docetaxel for prostate cancer, and who are willing and able/fit enough to endure this treatment**. To fulfil the NICE scope, we investigated the feasibility of comparing olaparib to docetaxel in the subset of patients with previous NHA use via an indirect comparison; however, no suitable published randomised controlled trials (RCTs) for docetaxel in mCRPC after disease-progression on NHA were identified in the systematic literature review (SLR) conducted to inform this submission, thus limiting our ability to conduct any such analyses. Whilst we are unable to provide comparative evidence, it is worth highlighting that treatment with olaparib resulted in clinically-meaningful extensions to both rPFS and OS in the **overall study population** of PROfound, which included patients regardless of whether they had received prior treatment with a taxane (rPFS, HR, 0.39 [95% CI, 0.29–0.53] and 0.77 [95% CI, 0.50–1.22] in the “prior taxane” and “no prior taxane” subgroups , respectively; olaparib versus investigators’ choice of NHA). These data are further described in Section B.2.6 and Appendix E.

- **Radium-223:** As described in SectionB.1.2, radium-223 is recommended as a treatment option for patients with symptomatic bone metastases and no known visceral metastases, who have already received docetaxel treatment., However opinion from 6 UK-based clinical experts indicates that, in practice, **radium-223 is reserved for later-lines of treatment (i.e. after NHA and cabazitaxel), *unless* treatment with a taxane is not suitable** (AstraZeneca data on file).[58] Radium-223 is thus only an appropriate comparator for olaparib in the latter circumstance. This positioning is also supported by data from a recent UK national radium-223 audit, which also reported on its use in later lines of treatment.[59] Comparisons between olaparib and radium-223, in patients for whom treatment with docetaxel is unsuitable, is limited by two factors:
    1) There are no published RCTs for radium-223 dichloride for the treatment of patients whose disease has progressed after an NHA (section B.2.1.3).
    2) We would have to make the assumption that patients in PROfound who did not receive a taxane prior to NHA were “unsuitable” for treatment with

docetaxel, which may be inappropriate (since 19.5% of patients in the “no prior taxane” subgroup of PROfound did receive a taxane as subsequent treatment following disease progression on study treatment), and bias any analyses conducted.

Although a comparative analysis of olaparib versus radium-223 dichloride was not possible for this small group of patients due to these limitations, it is worth highlighting that data from PROfound show efficacy for olaparib in patients with baseline bone metastasis, with a HR of 0.57 (95% CI: 0.35–0.94) for rPFS versus investigators’ choice of NHA.

Given the limitations described above in addressing the relative clinical- and cost-effectiveness of olaparib versus docetaxel (in patients with no docetaxel use prior to NHA) and radium-223 dichloride (in patients who have bone metastases, no known visceral metastases, and in whom docetaxel is contraindicated), this submission focuses on the use of olaparib versus cabazitaxel in patients who have received a prior taxane and a NHA. The final scope issued by NICE and the decision-problem addressed in the company submission are detailed in Table 2.

Table 2. The decision problem.

	Final scope issued by NICE/reference case	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Patients with hormone-relapsed, metastatic prostate cancer with HRR gene alterations previously treated with hormonal therapy such as abiraterone or enzalutamide.	Patients with hormone-relapsed, metastatic prostate cancer with HRR gene alterations previously treated with a taxane (docetaxel) and hormonal therapy such as abiraterone or enzalutamide.	The vast majority (~75%) of patients have already received treatment with a taxane (docetaxel) prior to NHA in current clinical practice[58] Indirect treatment comparisons to docetaxel (for the minority of patients who have not receive a taxane prior to NHA) or radium-223 dichloride (for the small subset of patients who have bone metastases, no known visceral metastases, and for whom treatment with a taxane is unsuitable) was not possible due to limitations in published RCT evidence base
Intervention	Olaparib monotherapy	Olaparib monotherapy	N/A
Comparator(s)	Docetaxel Cabazitaxel Radium-223 dichloride (for people with bone metastases) The different positions that these comparators could be used in the treatment pathway will be considered in the appraisal.	Cabazitaxel	As mentioned above, indirect treatment comparisons to docetaxel and radium-223 dichloride were not feasible due to a lack of published RCT evidence on these treatments in the post-NHA setting.

Outcomes	The outcome measures to be considered include: progression-free survival time to pain progression skeletal-related events overall survival adverse effects of treatment health-related quality of life.	The following outcomes are presented: radiographic progression-free survival (rPFS) time to pain progression skeletal-related events overall survival second progression-free survival (PFS2) adverse effects of treatment health-related quality of life	PFS2 is an intermediate endpoint between PFS and OS and reflects real-life treatment decisions and patient experience. Its use is recommended by the EMA to capture potential negative impacts on next-line therapy and to demonstrate that any potential tolerability concerns are outweighed by treatment benefit[60]
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The economic modelling	Cost-effectiveness analysis of olaparib in the stated population of interest, in line with the NICE reference case.	N/A

	should include the cost associated with diagnostic testing in people with hormone-relapsed prostate cancer who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test.		
Subgroups to be considered	If the evidence allows the following subgroups will be considered: subgroups by HRR alterations, including BReast CAncer gene (*BRCA*) and ataxia-telangiectasia mutated (*ATM*) gene status.	In line with the anticipated marketing authorisation for olaparib, the company submission considers the treatment of patients with qualifying mutations in one or more of 15 HRR genes (i.e. the overall population of PROfound). rPFS data in the subgroup of patients who have mutations in *BRCA1, BRCA2, and ATM* genes (the primary endpoint in PROfound) are described in Section B.2.6.2.1; further analyses are available in the CSR (Section 11)	N/A
Special considerations including issues related to equity or equality	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.	Although this submission focuses on the subset of patients who have received treatment with a prior taxane and NHA, due to the demonstrated efficacy of olaparib in the overall study population of PROfound (and anticipated marketing authorisation), regardless of prior taxane use, we request that consideration is given to the small	

		group of patients who have not received a taxane prior to NHA under equality provisions	

ATM, ataxia-telangiectasia mutated; BRCA, BReast CAncer gene; CSR, clinical study report; EMA, European Medicines Agency; HRR, homologous recombination repair; NHA, new hormonal agent; NICE, National Institute of Health and Care Excellence; NHS, National Health Service; N/A, not applicable OS, overall survival; (r)PFS, radiographic progression-free survival; PFS2, second progression-free survival; RCT, randomised controlled trial.

B.1.5 Equality considerations

Although a formal comparative clinical and cost-effectiveness analysis versus docetaxel (for patients with no docetaxel use prior to NHA) and radium-223 (for patients with bone metastases and no known visceral metastases, in whom docetaxel was contraindicated) was not feasible due to the limited published RCT evidence identified (Section B.2.1), it is worth highlighting that **olaparib has shown efficacy in the overall HRRm population of the PROfound study, which included patients regardless of prior taxane use and baseline metastases** (bone, visceral, or other; Section B.2.6.2.3 and Section B.2.7).[30]

In addition to meaningfully extending survival and providing the hope of long-term response (for at least a small group of patients), olaparib also represents a more patient-centric treatment option than docetaxel and radium-223 dichloride, on account of its **oral administration** (negating the need for patients to travel to the hospital to receive treatment) and its **tolerability profile**, with most adverse events (AEs) being non-serious and manageable, without requiring discontinuation of treatment.[61]

Data from PROfound also showed no meaningful deterioration in patients' HRQoL over the course of olaparib treatment compared with investigator's choice of NHA; instead, patients benefitted from a reduced burden of pain as well as reduced incidence of symptomatic skeletal-related events, which are significant causes of morbidity in patients with mCRPC.[62,63] On account of these reasons, and given that many patients may not be able to access or wish to undergo treatment with docetaxel and/or radium-223 due to the factors described below,[37] we request that **NICE consider granting access to olaparib for those patients who have <u>not received a taxane</u> prior to NHA or for whom <u>treatment with a taxane is unsuitable</u>** under equality considerations.

- ~20% of men are considered clinically unsuitable for chemotherapy at diagnosis,
- Many others are simply unable to receive it for reasons beyond clinical factors, such as:

- The presence of a carer or loved one for support (both for attending hospital appointments for infusions and managing potential side effects),
- Proximity to treatment centres/access to public transport, regardless of whether they live alone or have a carer,
- The willingness and emotional endurance to tolerate the toxicity of chemotherapy, which is often underestimated, and
- Religious beliefs, for instance, due to the alcohol content present in docetaxel.

Collectively, these factors could prevent mCRPC patients from seeking treatment with docetaxel or radium-223 and thus compromise their prognosis in the absence of any alternative life-extending therapy.

B.2 Clinical effectiveness

B.2.1 Identification and selection of relevant studies

A systematic literature review (SLR) was conducted in January 2020 in order to identify published clinical evidence on the use of health technologies in patients with mCRPC whose disease had progressed following treatment with an NHA, irrespective of HRR mutation status. The scope of the SLR was broader than that of the decision-problem, and did not restrict inclusion by:

- Patients with mCRPC who had **HRR gene mutations**, to capture all studies in a post-NHA setting that could inform indirect comparisons with existing drugs that are not targeted to HRR mutations.
- The treatments and comparators specified in the final NICE scope, to ensure that no relevant studies were accidentally excluded.

Full details of the SLR methodology and results are provided in Appendix D.

The SLR identified 157 studies. Of these, a total of 14 studies, reported across 23 publications reported outcomes with olaparib,[64,65] cabazitaxel, [42,66-73] docetaxel[74-81] and radium-223[82-84] (i.e. the intervention and comparators specified in the NICE scope) in the population of interest.

Of the studies that reported on cabazitaxel, docetaxel, and radium-223 dichloride, the comparators of interest for this appraisal, just one (the CARD study of cabazitaxel versus NHA; described below), was appropriate for inclusion in the evidence base for this appraisal. Reasons for excluding the remaining studies are briefly described below and in further detail in Section B.2.9 (further details on all studies are provided in Appendix D).

B.2.1.1 Olaparib

The SLR identified three studies that assessed the efficacy and safety of olaparib in the population of interest for this appraisal (PROfound and TOPARP-A/B; three abstracts, two full text publications).[28,29,64,65,85] The TOPARP studies (comprising TOPARP-A and TOPARP-B) were Phase II single arm trials that evaluated the

300 mg and 400 mg dose of olaparib in patients who had received a prior taxane; enrolment was not restricted by whether patients had received a prior NHA. Given the availability of data from the much larger **Phase III**, PROfound **randomised-controlled trial in exact population and treatment setting relevant to this appraisal**, data from TOPARP were not included in the evidence synthesis.

B.2.1.2 Cabazitaxel

Eight publications that reported outcomes on cabazitaxel were identified by the SLR. Of these, only one study - CARD (NCT02485691) – was deemed relevant for an indirect treatment comparison with the PROfound trial (as described in Section B.2.9).[2] [42,67] CARD is an ongoing Phase IV RCT that assessed the efficacy and safety of cabazitaxel compared with an NHA (enzalutamide or abiraterone plus prednisolone) in patients with mCRPC, who had received previous treatment with docetaxel and an NHA.[66] As all patients enrolled in the CARD trial were required to have received previous docetaxel, the patient population is closely aligned with the prior-taxane subpopulation of the PROfound study, although not restricted to those patients who have mutations in HRR genes.[30] Detailed baseline characteristics in the PROfound and CARD studies is provided in Section B.2.3.7 and Appendix D (Section D.1.4), respectively.

The remaining six publications that reported outcomes in patients who received cabazitaxel were either small early phase or single-arm studies (often conducted in a single country or centre)[68-72] or cabazitaxel combination studies (with budesinone, prednisone, prednisolone, or abiraterone), or did not report on the outcomes of interest (split by those who had received a prior NHA, in case of a mixed population) and were therefore deemed unsuitable for inclusion in the evidence base for this appraisal, as described in Section B.2.9.[73]

[2] It is worth noting that the TROPIC study, the registrational clinical trial for cabazitaxel in mCRPC (which pre-dates CARD by nine years), did not evaluate its efficacy and safety in the post-NHA setting relevant to this appraisal. This study was thus not identified in the SLR or included in the evidence synthesis. As such, the CARD study provides a more relevant evidence base for comparative analysis versus olaparib due to 1) being more-recent, 2) being conducted in the post-NHA setting relevant to this appraisal, and 3) having an NHA comparator arm (like PROfound), thus making an anchored indirect treatment comparison versus olaparib possible.

B.2.1.3 Docetaxel

Although the SLR identified eight publications that included docetaxel, none of these studies were relevant to the decision-problem, since they: 1) they either did not include docetaxel as a monotherapy arm (four publications)[76-78], or 2) did not include patients based on progression on prior NHA therapy (a pre-requisite for randomisation in the PROfound study; three publications)[74,79] or 3) did not report appropriate data on the key survival outcomes of OS and rPFS results (three publications).[75,80,81] An overview of studies is presented in Appendix D. Radium-223

The SLR did not identify any studies that reported on outcomes after treatment with radium-223 dichloride monotherapy in mCRPC patients whose disease had progressed after treatment with an NHA. Of note, the SLR did identify the radium-223 international Early Access Program (iEAP; NCT01618370); however, this included patients regardless of whether they had received a prior NHA. Furthermore, only an abstract was available from the study at the time the SLR was conducted, providing insufficient evidence for further analysis and inclusion in the evidence base (as described in section B.2.9). An overview of the study is presented in Appendix D.

B.2.1.4 Summary

In line with the final NICE scope for this appraisal, evidence from studies of olaparib, cabazitaxel, docetaxel, and radium-223 were considered. The SLR identified two studies of interest: the PROfound trial, which compared olaparib against NHA re-challenge in a post-NHA setting in patients with one or more HRR mutations, and the CARD study, which compared cabazitaxel against NHA re-challenge in a post-NHA setting irrespective of HRR mutation status.[64,65,67] No suitable studies were identified which would facilitate robust indirect comparisons against either radium-223 or docetaxel. This is further discussed in Section B.2.9.

B.2.2 List of relevant clinical effectiveness evidence

Brief details of PROfound and CARD studies, the two clinical trials included in the evidence synthesis described in Section B.2.9 are presented in Table 3. Further details are on the PROfound study, the pivotal RCT for olaparib and the main source of data used in the economic analysis, are provided in Sections B.2.3 to B.2.7.

Details of the CARD study are provided in Appendix D (section D.1.4); comparative evidence of cabazitaxel versus olaparib is provided in Section B.2.9.

Table 3. Clinical effectiveness evidence overview of PROfound and CARD studies.

Study	PROfound (NCT02987543)[30,61,86]					CARD (NCT02485691)[67]				
Study design	Phase III, randomised, open-label, multicentre study					Randomised, open-label, multicentre, Phase IV post-marketing study				
Population	Patients with mCRPC and a deleterious or suspected deleterious genetic aberration in one or more of 15 HRR genes (assessed by prospective tissue testing) who experienced disease progression following NHA. Inclusion in the PROfound study was not restricted by prior taxane use (unlike CARD)					Patients with mCRPC and prior taxane therapy who experienced disease progression following NHA. Inclusion in the CARD study was **not restricted by biomarker status**; the study included patients regardless of whether they had HRR gene mutations (unlike PROfound)				
Intervention(s)	Olaparib 300 mg twice daily					Cabazitaxel 25 mg^2 /m body-surface area, intravenously q3w, plus oral prednisone 10 mg daily once daily.				
Premedication (for intervention arm)	None for olaparib					For cabazitaxel, premedication included an antihistamine, steroid, and H2 antagonist. Primary prophylactic G-CSF at each cycle was required for all patients.				
Comparator(s)	Investigators' choice of enzalutamide or abiraterone (hereafter referred to as "investigators' choice of NHA")					The other NHA (enzalutamide or abiraterone) versus the one a patient had previously progressed on.				
Primary endpoint	rPFS by blinded independent central review (BICR)					rPFS by investigator assessment				
Tumour assessment schedule	Every 8 weeks, per RECIST 1.1 and Prostate Cancer Working Group 3 (PCWG3) criteria					Every 12 weeks, per RECIST 1.1 and PCWG2				
Indicate if trial supports application for marketing authorisation	Yes	X	**Indicate if trial used in the economic model**	Yes	X	Yes		**Indicate if trial used in the economic model**	Yes	X
	No			No		No	X		No	

Rationale for use/non-use in the model	PROfound is the only Phase III RCT that provides clinical efficacy and safety outcomes **for olaparib** in patients with HRR gene mutations whose disease has progressed following an NHA, aligned with the intervention and population of interest for this appraisal.	CARD is the only trial that provides clinical efficacy and safety outcomes **for cabazitaxel, the main comparator for olaparib (per current clinical practice in England)** in patients whose disease has **progressed following a taxane and a NHA**, i.e. in the treatment setting relevant to this appraisal.
Reported outcomes specified in the decision problem	rPFS (by BICR), time-to-pain progression (TTPP), skeletal-related events (SRE), OS, AEs and HRQoL.	rPFS (investigator-assessed), SRE, OS.
All other reported outcomes	In company submission: ORR, PFS2 For a complete list of secondary and exploratory outcomes, please see the PROfound Clinical Study Report, version 1, 23 October 2019.[61]	In primary publication: PSA response, tumour response, pain response, ORR, AEs.[67]

AE, adverse event; CTC, circulating tumour cell; DoR, duration of response; G-CSF, granulocyte-colony stimulating factor; HRQoL, health-related quality of life; HRR, homologous recombination repair; mCRPC, metastatic castration-resistant prostate cancer; NHA, new hormonal agent; ORR, objective response rate; OS, overall survival; PFS2, second progression-free survival; PSA, prostate-specific antigen; q3w, every 3 weeks; rPFS, radiographic progression-free survival; SRE, skeletal-related events; TTPP, time to pain progression.
Source: PROfound Clinical Study Report, version 1, 23 October 2020,[61] de Bono *et al*, 2020[30] and de Wit *et al*, 2019.[67]

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

An overview of the PROfound study (the pivotal Phase III study for olaparib in the population of interest), including trial design, eligibility criteria, trial drugs and concomitant medications, primary and key secondary outcomes, and baseline characteristics is provided in the sections below (B.2.3.1−B.2.3.7). Further details are available in the Clinical Study Protocol and the Clinical Study Report (Sections 8−10).

Details of the CARD study (from which the efficacy data for cabazitaxel were derived and were used in the anchored ITC versus olaparib as described in Section B.2.9) are provided in Appendix D, section D.1.4.

B.2.3.1 *Trial design*

PROfound (NCT02987543) is a Phase III, randomised, open-label, multicentre study designed to assess the efficacy of olaparib compared with investigators' choice of enzalutamide or abiraterone (investigators' choice of NHA) in patients with mCRPC and had a confirmed HRR mutation, whose disease had progressed following an NHA (abiraterone or enzalutamide).[30,87] PROfound is the pivotal study investigating the efficacy and tolerability of olaparib in the population of patients relevant to this appraisal, and formed the basis of the EMA regulatory submission for olaparib in the mCRPC indication.

The PROfound study included multiple oral agents in the comparator arms. At the time of study design, it was believed that the differences in administration and safety profiles would enable investigators to differentiate between the different study treatments. Thus, PROfound was designed as an open-label study. The primary endpoint of rPFS was evaluated by BICR assessment, thus removing the risk of any investigator bias from the results.

Patients were randomised using an interactive voice response system/interactive web response system in a 2:1 ratio to receive either olaparib tablets, or investigators' choice of NHA. As highlighted in Section B.1.2, investigator's choice of NHA was

chosen as the comparator since treatment with NHA (i.e. enzalutamide after progression of abiraterone, or vice versa) is an approved treatment option (by both the EMA and the US FDA) and is a standard-of-care in many countries where the PROfound study was conducted.[88] This strategy also ensured that patients for whom treatment with chemotherapy was unsuitable were not excluded from the study.

The PROfound study did not restrict enrolment by prior taxane use (given the unmet clinical need for patients who had progressed after treatment with an NHA, regardless of whether they had received prior treatment with a taxane), or baseline metastases (bone, visceral, or other). Randomisation was stratified by previous taxane use (yes, no) and measurable disease at baseline (yes, no), to ensure that patients were well-balanced across treatment arms.

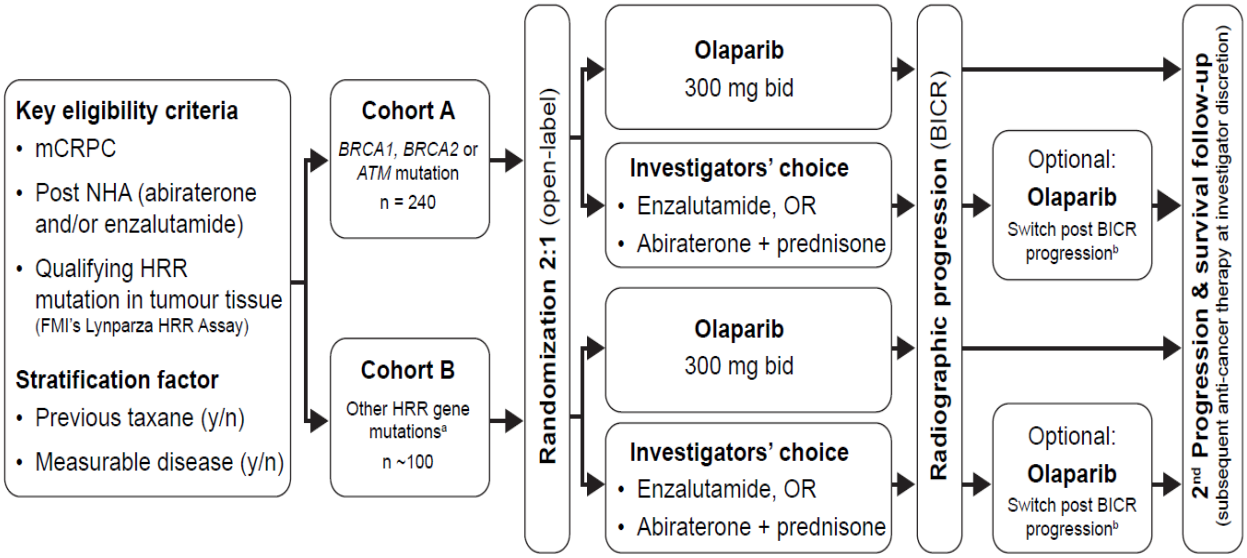
Based on the results of the Phase II TOPARP-A trial (which showed that patients with HRR gene mutations demonstrated notably higher response rates and marked improvements in rPFS and OS following olaparib treatment, when compared with patients without HRR gene mutations),[28] a decision was made to restrict enrolment to those mCRPC patients who had a qualifying tissue HRR gene mutations. The overall HRR-mutated (HRRm) population of PROfound included two Cohorts:

- *Cohort A: patients with at least one mutation in either BRCA1, BRCA2 or ATM genes.*
- *Cohort B: patients with mutations in BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D or RAD54L genes.*[87]

The primary endpoint of PROfound was rPFS (by BICR) for olaparib versus investigators' choice of NHA in Cohort A. The rationale for using only *BRCA1*, *BRCA2* and *ATM* tissue mutations (i.e. Cohort A) for the primary endpoint was based upon the prevalence of these mutations and/or how well mutations in these genes have been characterised to date.[61] It was expected that qualifying mutations would be detected in the tumour tissue of approximately 1 in 10 patients with mCRPC.

Treatment switching from investigators' choice of NHA to olaparib was permitted in the study following BICR-assessed radiographic disease progression. A summary of the study design is provided in Figure 1.

Figure 1. PROfound study design.



[a] Cohort B HRR pathway genes include *BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D* and *RAD54L*.
[b] Treatment switching was permitted post BICR-assessed radiographic disease progression and adjusted for using naïve and sophisticated adjustment methods (see section B.2.6.3.1).
ATM, gene for ataxia–telangiesctasia mutated; *BARD1*, gene for BRCA1 associated RING domain 1; BICR, blinded independent central review; bid, twice daily; *BRCA1*, gene for breast cancer type 1 susceptibility protein; *BRCA2*, gene for breast cancer type 2 susceptibility protein; *BRIP1*, gene for BRCA1 interacting protein C-terminal helicase 1; *CDK12*, gene for cyclin-dependent kinase 12; *CHEK1*, gene for checkpoint kinase 1; *CHEK2*, gene for checkpoint kinase 2; *FANCL*, gene for Fanconi anaemia, complementation group L; FMI, Foundation Medicine, Inc.; HRR, homologous recombination repair; mCRPC, metastatic hormone-resistant prostate cancer; NHA, new hormonal agent; *PALB2*, gene for partner and localiser of BRCA2; *PPP2R2A*, gene for protein phosphatase 2 regulatory subunit B alpha; *RAD51B*, *RAD51C*, *RAD51D*, genes for RAD51 paralogues B, C and D; *RAD54L*, gene for RAD54-like protein.
Source: PROfound CSP version 4, 7 March 2019.[87]

B.2.3.2 Eligibility criteria

Key eligibility criteria for the PROfound study are summarised in Table 4 with further details available in the PROfound Clinical Study Protocol, version 1, 23 October 2019 (section 3.1 and section 3.2). Following enrolment, all patients underwent central assessment to determine HRR pathway gene mutation status using a genetic assay, as described in Section B.2.3.6.[87]

Table 4. Key inclusion and exclusion criteria for the PROfound study.

PROfound (NCT02987543)[30,61,86]	
Inclusion criteria	**Exclusion criteria**

• Men aged ≥ 18 years with a histologically confirmed diagnosis of prostate cancer, ECOG PS 0–2, serum testosterone levels of ≤ 50 ng/dL for ≤ 28 days before randomisation, normal organ and bone marrow function measured ≤ 28 days prior to administration of study treatment and life expectancy ≥ 16 weeks • A qualifying HRRm in the tumour tissue • Eligible for enzalutamide or abiraterone treatment with documented current evidence of mCRPC and metastatic disease defined by at least one metastatic lesion diagnosed by either bone scan or CT/MRI scan • Progression as per local investigator following an NHA (e.g. abiraterone and/or enzalutamide) for the treatment of metastatic prostate cancer and/or HRPC • Patients without previous surgical castration must be currently taking and willing to continue taking LHRH analogue (agonist or antagonist) therapy for the duration of the study treatment • Radiographic disease progression as per local assessment at study entry while receiving ADT	• Previous treatment with a PARP inhibitor, receipt of any systematic anti-cancer therapy (except radiotherapy) within 3 weeks before study treatment or DNA-damaging cytotoxic chemotherapy, except if given for a non-prostate cancer indication and last dose > 5 years before randomisation. Previous estramustine is allowed. • Metastatic disease limited to regional pelvic lymph nodes of local recurrence (e.g. bladder, rectum), or spinal cord compression unless considered to have received definitive treatment and with evidence of clinically stable disease for 28 days • Patients with MDS or AML or other malignancy (including MDS and MGUS) within the last 5 years except adequately treated non-melanoma skin cancer or other solid tumours including lymphomas (without bone marrow involvement) curatively treated with no evidence of disease for ≥ 5 years • Patients ineligible for bone and soft tissue progression must meet the following criteria: a superscan showing intense symmetrical activity in the bones and no soft tissue lesion (measurable or non-measurable) that can be evaluated using RECIST. • Resting ECG indicating uncontrolled, potentially reversible cardiac conditions, as judged by the investigator, or patients with long QT syndrome

ADT, androgen deprivation therapy; AML, acute myeloid leukaemia; CT, computed tomography; ECG, electrocardiogram; ECOG PS, European Cooperative Oncology Group performance status; HRRm, homologous recombination repair pathway mutation; LHRH, leuteinising hormone-releasing hormone; (m)HRPC, (metastatic) hormone-resistant prostate cancer; MDS, myelodysplastic syndrome; MGUS, monoclonal gammopathy of unknown significance; MRI, magnetic resonance imaging; NHA, new hormonal agent; PARP, poly(adenosine diphosphate)-ribose polymerase; PSA, prostate specific antigen; RECIST, Response Evaluation Criteria in Solid Tumours.
Source: PROfound CSP version 4, 7 March 2019.[87]

B.2.3.3 Settings and locations where the data were collected

The PROfound study was conducted in 111 centres across: France, Japan, Canada, Turkey, Australia, South Korea, Netherlands, United states, Italy, Taiwan, Brazil, Argentina, Israel, Germany Spain, Sweden, **United Kingdom (five sites, four patients)**, Austria, Denmark and Norway.[30,87]

B.2.3.4 Trial drugs and concomitant medications

Patients in the PROfound study were randomised to receive either:

- **Olaparib tablets** (orally; 300 mg twice daily [bid]), or
- Investigators choice of NHA with either **enzalutamide** (160 mg orally once daily [od]) or **abiraterone acetate** (1000 mg orally od with prednisone 5 mg orally bid [prednisolone was permitted for use instead of prednisone, if necessary])

All study treatments were given continuously until BICR-assessed radiographic disease progression occurred, or until the patient discontinued treatment owing to AEs or consent was withdrawn.[87]

A list of permitted concomitant treatments is included in section 7.7 of the Clinical Study Protocol, version 4, 7 March 2019.[87] Overall, the concomitant treatments administered were generally representative of those commonly prescribed to manage side effects of olaparib or enzalutamide/abiraterone and were not considered to have impacted the study results.[61]

B.2.3.5 Outcomes used in the economic model or specified in the scope, including primary outcome

A full list of primary, secondary, and exploratory objectives of the PROfound study is available in the Clinical Study Report, version 1, 23 October 2019 (Table 2, page 51).[61] A brief description of the primary endpoint (rPFS by BICR in Cohort A) and key secondary endpoints (specified in the NICE scope and/or used in the economic model) is provided below.

B.2.3.5.1 Primary endpoint (Cohort A)

The primary endpoint in the PROfound study was rPFS, defined as time from randomisation until the date of objective disease progression (as assessed by BICR

using RECIST version 1.1 [for soft tissue disease] or Prostate Cancer Working Group 3 [PCWG3, for bone disease]) or death (by any cause in the absence of progression) regardless of whether the patient withdrew from randomised therapy or received another anti-cancer therapy prior to disease progression.[87]

B.2.3.5.2 Secondary outcomes

The secondary outcomes of PROfound that were used in the economic model and/or specified in the NICE scope (Table 2) are described below: [87]

- **BICR-assessed rPFS (in Cohort A+B)**: as described above.
- **Overall Survival (OS)**: time from randomisation to death from any cause regardless of whether the patient withdrew from randomised therapy or received another anti-cancer therapy.
- **Second progression-free survival (PFS2):** time from randomisation to the earliest investigator-assessed progression event subsequent to that used for the primary variable or death.
- **Time to pain progression (TTPP):** Time from randomisation to the time point at which worsening in pain was observed as assessed by BPI-SF item 3. This was assessed according to whether patients were symptomatic at baseline.
- **Time to first symptomatic skeletal-related event (SSRE):** time from randomisation to first SSRE was defined by the use of radiation therapy to prevent or relieve symptoms, occurrence of new radiologically confirmed symptomatic pathological bone fractures (vertebral or non-vertebral) or spinal compression, or surgical intervention for bone metastasis.
- **Objective response rate (ORR) by BICR**: for patients who had measurable disease at baseline determined by BICR, objective response rate assessed by BICR (RECIST 1.1 and PCWG3), is defined as the number (%) of patients with at least one visit response of complete (CR) or partial response (PR), in their soft tissue disease assessed by RECIST 1.1, in the absence of progression on bone scan assessed by PCWG3.

- **Health-related quality of life**: the patient-reported FACT-P will be used to assess health-related quality of life. The questionnaire was administered, at baseline, weeks 8, 16 and 24, and every 8 weeks thereafter to all patients who have not withdrawn consent. The following outcome measures were calculated from the FACT-P questionnaire; the resulting value is the total score for the associated questions or scaled scores:
    - Physical well-being subscale (PWB)
    - Social/family well-being subscale (SWB)
    - Emotional well-being subscale (EWB)
    - Functional well-being subscale (FWB)
    - Prostate cancer subscale (PCS)
    - Total Functional Assessment of Cancer Therapy- General (FACT-G) score, sum of PWB, SWB, EWB and FWB.
    - Trial Outcome Index (TOI), sum of PWB, FWB and PCS.
    - Functional Assessment of Prostate Cancer Symptoms Index 6 (FAPSI-6)
    - Total FACT-P score (sum of scores of all the sub-scales)
- **EQ-5D-5L**: The EQ-5D-5L index comprises 5 dimensions of health (mobility, self-care, usual activities, pain/discomfort and anxiety/depression). For each dimension, respondents select which statement best describes their health on that day from a possible 5 options of increasing levels of severity (no problems, slight problems, moderate problems, severe problems and unable to/extreme problems). A unique EQ-5D health state is referred to by a 5-digit code allowing for a total of 3,125 health states (for example, state 11111 indicates no problems on any of the 5 dimensions). These data were converted into a weighted health state index by applying scores from EQ-5D value sets elicited from general population samples (the base case was the UK valuation set).

B.2.3.6 Biomarker analyses

An investigational clinical trial assay, based on the FoundationOne CDx next-generation sequencing test and developed in partnership with Foundation Medicine, was used to prospectively identify patients with qualifying deleterious or suspected deleterious alterations in at least 1 of the 15 prespecified genes, selected for their direct or indirect role in HRR, namely: *BRCA1, BRCA2, ATM, BRIP1, BARD1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D*, and *RAD54L*. Tumour testing was conducted centrally with the use of archival or recent biopsy tissue from primary or metastatic disease. The presence of a deleterious or suspected deleterious alteration according to the central tumour test was required for inclusion in the study. Further details of HRRm testing are provided in section 5.7 of the Clinical Study Protocol, version 4, 7 March 2019.[87]

B.2.3.7 Baseline characteristics

Patient baseline characteristics are summarised Table 5 for:

- **Cohort A+B** (the overall population of PROfound, and the population of interest for this appraisal),
- **Cohort A** (the population that the primary endpoint of rPFS was analysed in) and,
- **Cohort A+B prior taxane subgroup** (on which the comparative clinical and cost-effectiveness evidence versus cabazitaxel in based on, which aligns with the anticipated positioning of olaparib in the current clinical pathway of care in England where the majority of patients receive a taxane [docetaxel] for HSPC, before receiving NHA for mCRPC).

Key baseline characteristics were largely well-balanced between treatment arms, and between the Cohort A+B, Cohort A, and the Cohort A+B prior taxane subgroup (Table 5).

Important prognostic variables, such as measurable disease at baseline and prior taxane use, were included as stratification factors to ensure balance across treatment arms (the size of the study did not allow for further stratification factors).

The primary endpoint in the study, rPFS (BICR), and the key secondary endpoint of OS were analysed with these stratification factors included in the model as covariates.

Minor discrepancies were observed in specific characteristics at baseline, such as ECOG status, and PSA. To assess if the results were impacted by these differences in key patient characteristics across the PROfound study treatment arms, a sensitivity analysis was performed which adjusted for [redacted]

Table 5. Patient characteristics for PROfound Cohort A+B, Cohort A, prior taxane subgroup

Baseline characteristics	Cohort A+B FAS		Primary study population: Cohort A FAS		Subgroup relevant for economic analysis: Prior taxane use[a] Cohort A+B	
	Olaparib 300 mg bid (n = 256)	Investigators' choice of NHA (n = 131)	Olaparib 300 mg bid (n = 162)	Investigators' choice of NHA (n = 83)	Olaparib 300 mg bid (n = 170)	Investigators' choice of NHA (n = 84)
Age	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (range)	69.0 (47–91)	69.0 (49–87)	68.0 (47–86)	67.0 (49–86)	[redacted]	[redacted]
< 65, n (%)	82 (32.0)	34 (26.0)	54 (33.3)	23 (27.7)	[redacted]	[redacted]
≥ 65, n (%)	174 (68.0)	85 (64.9)	108 (66.7)	60 (72.3)	[redacted]	[redacted]
≥ 75, n (%)	NR	NR	NR	NR	NR	NR
White	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Black or African American	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ethnic group, n (%)						
Hispanic or Latino	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Not Hispanic or Latino	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sites of disease at baseline, n (%)[b]						
Prostate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Locoregional lymph nodes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Distant lymph nodes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Respiratory	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Liver	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other distant metastases	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bone only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lymph node only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bone and lymph node only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ECOG performance status at baseline, n (%)						
0	131 (51.2)	55 (42.0)	84 (51.9)	34 (41.0)	[redacted]	[redacted]
1	112 (43.8)	71 (54.2)	67 (41.4)	46 (55.4)	[redacted]	[redacted]
2	13 (5.1)	4 (3.1)	11 (6.8)	3 (3.6)	[redacted]	[redacted]
Missing	0	1 (0.8)	0	0	[redacted]	[redacted]
Total Gleason index at baseline, n (%)						
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline pain score (BPI-SF worst pain [item 3]), n (%)						
0–< 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2–3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
> 3 ≥ 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline PSA (µg/L), n (%)						

Median, (range)	68.2 (0.2–7240.7)	106.5 (1.85–7115.0)	62.2 (0.20–7240.7)	112.9 (1.85–7115.0)	[redacted]	[redacted]
Measurable disease at baseline, n (%)[c]						
Yes	149 (58.2)	72 (55.0)	95 (58.6)	46 (55.4)	[redacted]	[redacted]
No	107 (41.8)	59 (45.0)	67 (41.4)	37 (44.6)	[redacted]	[redacted]
Missing	NR	NR	NR	NR	NR	NR
Previous taxane therapy at mCRPC, n (%)						
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Previous docetaxel only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Previous cabazitaxel only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Previous docetaxel and cabazitaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients with taxane treatment prior to randomisation, n (%)						
Yes	N/A	N/A	N/A	N/A	[redacted]	[redacted]
No	N/A	N/A	N/A	N/A	[redacted]	[redacted]
Previous docetaxel only	N/A	N/A	N/A	N/A	[redacted]	[redacted]
Previous cabazitaxel only	N/A	N/A	N/A	N/A	[redacted]	[redacted]
Previous docetaxel and cabazitaxel	N/A	N/A	N/A	N/A	[redacted]	[redacted]
Prior paclitaxel	N/A	N/A	N/A	N/A	[redacted]	[redacted]
Previous NHA use, n (%)						
Enzalutamide	103 (40.2)	54 (41.2)	67 (41.4)	40 (48.2)	[redacted]	[redacted]
Abiraterone	97 (37.9)	54 (41.2)	61 (37.7)	29 (34.9)	[redacted]	[redacted]
Enzalutamide and abiraterone	51 (19.9)	23 (17.6)	32 (19.8)	14 (16.9)	[redacted]	[redacted]
Missing	NR	NR	NR	NR	NR	NR
Single mutation status[d]						

BRCA1	8 (3.3)	5 (4.2)	8 (5.4)	5 (6.6)	[redacted]	[redacted]
BRCA2	81 (33.9)	47 (39.2)	80 (54.1)	47 (61.8)	[redacted]	[redacted]
ATM	62 (25.9)	24 (20.0)	60 (40.5)	24 (31.6)	[redacted]	[redacted]
BARD1	0	1 (0.8)	0	0	[redacted]	[redacted]
BRIP1	2 (0.8)	1 (0.8)	0	0	[redacted]	[redacted]
CDK12	61 (25.5)	28 (23.3)	0	0	[redacted]	[redacted]
CHEK1	1 (0.4)	1 (0.8)	0	0	[redacted]	[redacted]
CHEK2	7 (2.9)	5 (4.2)	0	0	[redacted]	[redacted]
FANCL	0	0	0	0	[redacted]	[redacted]
PALB2	3 (1.3)	1 (0.8)	0	0	[redacted]	[redacted]
PPP2R2A	6 (2.5)	4 (3.3)	0	0	[redacted]	[redacted]
RAD51B	4 (1.7)	1 (0.8)	0	0	[redacted]	[redacted]
RAD51C	0	0	0	0	[redacted]	[redacted]
RAD51D	1 (0.4)	0	0	0	[redacted]	[redacted]
RAD54L	3 (1.3)	2 (1.7)	0	0	[redacted]	[redacted]
Co-mutations[f]	17 (6.6)	11 (8.4)	14 (8.6)	7 (8.4)	[redacted]	[redacted]

[a] Subgroup adjusting for previous taxane (yes, no), collected via IVRS

[b] As per investigator assessment. Patients with multiple sites of disease within the same category of extent of disease are counted only once in that category.

[c] Derived from eCRF data.

[d] Proportions expressed as % of the total number of patients in the analysis set with single mutations: Cohort A+B (234 for olaparib and 118 for investigator's choice of NHA), Cohort A (148 for olaparib and 76 for investigator's choice of NHA), Cohort A+B prior taxane (163 for olaparib and 78 for investigator's choice of NHA). ATM ataxia telangiectasia mutated; BARD1 BRCA1 associated ring domain protein; bid twice daily; BRCA breast cancer susceptibility gene; BRIP1 BRCA1 interacting protein C-terminal helicase 1; CDK12 cyclin-dependent kinase 12; CHEK1 checkpoint kinase 1; CHEK2 checkpoint kinase 2; FANCL FA complementation group; FAS full analysis set; HRR homologous recombination repair; NHA new hormonal agent; PALB2 partner and localizer of BRCA2; PPP2R2A protein phosphatase 2 regulatory subunit B alpha; RAD51B RAD51 paralog B; RAD51C RAD51 paralog C; RAD51D RAD51 paralog D; RAD54L RAD54 like.

e Reported as a patient who received prior cisplatin and fluorouracil and paclitaxel.
[f] A detailed overview of co-mutations is given in Appendix M.
bid, twice daily; eCRF, electronic case report form; IVRS, interactive voice response system; NR, not reported; SD, standard deviation
Source: de Bono et al 2020,[30] Clinical Study Report Edition 1 – 23 October 2019[61] and de Wit 2019[67]

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

All analyses were performed in accordance with a comprehensive statistical analysis plan (SAP), which details the analyses to be conducted, summaries produced, and the analysis sets upon which they would be based (Sections 1-3 of the PROfound SAP).[89]

The main hypothesis evaluated in the PROfound study was that single agent **olaparib** at 300 mg bid has **superior efficacy and an acceptable tolerability profile as compared with enzalutamide or abiraterone** in mCRPC patients with deleterious or suspected deleterious HRR gene mutations and whose disease has progressed after treatment with an NHA such as enzalutamide or abiraterone.[87]

B.2.4.1 Analysis sets

The primary endpoint of the study was rPFS in Cohort A. The study planned to randomise approximately 240 patients (2:1 ratio of olaparib:investigators' choice of NHA), with the rPFS analysis occurring once approximately 143 rPFS events (confirmed by BICR) had occurred.[87]

It was expected that the targeted sample size of 240 patients in Cohort A with approximately 143 rPFS events (i.e. 60% maturity) would provide 95% power to demonstrate a statistically significant difference in rPFS at a 2-sided alpha level of 5%, assuming that true treatment effect was a HR of 0.53, translating an ~4.5-month improvement in median rPFS with olaparib, over an assumed 5-month median duration of rPFS on enzalutamide or abiraterone. The PROfound trial met its primary endpoint in Cohort A at DCO1 (4th June 2019), demonstrating a statistically-significant and clinically-meaningful rPFS benefit versus investigators' choice of NHA (HR, 0.34 [95% CI, 0.25–0.47], $p < 0.0001$).[87]

Cohort B of PROfound was an exploratory cohort and was designed to include ~100 patients with qualifying HRR gene mutations other than *BRCA1, BRCA2,* and *ATM*.[87]

Analysis of efficacy and patient-reported outcomes was conducted on the full analysis set (FAS) of Cohort A, Cohort B, Cohort A+B, whilst safety analyses were based on the safety analysis set (FAS) for each Cohort, as defined in Table 6.

Table 6. Definition of populations.

Population	Definition
Cohort A FAS	All patients randomised to receive olaparib or investigators' choice in Cohort A irrespective of whether treatment was received
Cohort B FAS	All patients randomised to receive olaparib or investigators' choice in Cohort B irrespective of whether treatment was received
Cohort A+B population FAS	All patients from the Cohort A FAS and Cohort B FAS
Safety analysis set	All patients randomised to receive study treatment and who received at least one dose of study treatment in Cohort A or in Cohort B were included. Data for patients who received investigators' choice and then switched treatment to olaparib following disease progression were summarised according to the treatment at the time of onset of the safety condition or laboratory result and were reported separately to the safety analysis, in a **safety switch analysis set**.

FAS, full analysis set; PRO, patient-reported outcome.
Source: PROfound CSP version 4, 7 March 2019.[87]

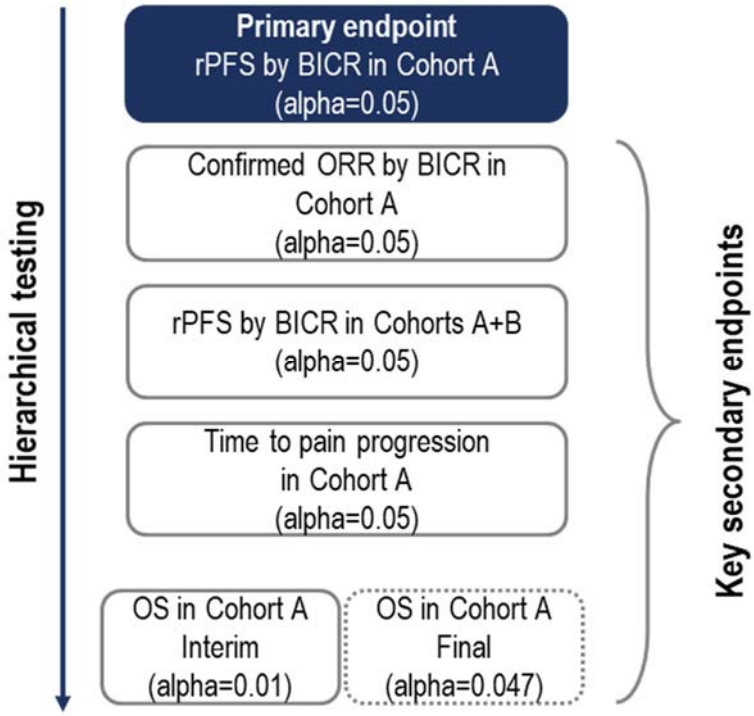
B.2.4.2 Outcome measures and statistical analysis

All calculations were performed with statistical analysis software (SAS®) Version 9.4 (SAS Institute, Inc, Cary, North Carolina, US), unless otherwise stated. Further information on sample size calculation and analysis of key outcome variables (including supporting sensitivity and subgroup analyses, and censoring) are described in detail in Section 9.8 of the PROfound Clinical Study Report, version 1, 23 October 2019.[61]

The PROfound study used a multiplicity strategy for statistical testing of primary endpoints and key secondary endpoints (Figure 2). Per study protocol, the primary analysis was performed when ~143 rPFS (60%) events in Cohort A had occurred, based on BICR assessment. Upon achieving statistical significance on the primary endpoint rPFS in Cohort A, testing of each of the secondary endpoints, i.e. ORR (Cohort A), rPFS (Cohort A + B), time to pain progression (Cohort A), and overall survival (Cohort A) was performed sequentially with the 2-sided 5% level of alpha recycled from the primary rPFS (Cohort A) endpoint (Figure 2). The data cut-off for the primary rPFS analysis (DCO1) occurred on 4th June 2019.[61]

Per the study protocol, the final analysis of OS was performed when ~146 (61%) OS events had occurred in Cohort A (DCO2, 20th March 2020). Safety summaries were also updated at the time of this analysis.[87] Top-line data from the final OS analysis are presented in Section B.2.6.3.1; further analyses are currently underway.[31] These will be provided to NICE as soon as possible.

Figure 2. Summary of the hierarchical testing structure for PROfound.



BICR, blinded independent central review; ORR, objective response rate; OS, overall survival; rPFS, radiographic progression-free survival
Source: Clinical Study Report, version 1, 23 October 2019.[87]

An overview of the analysis methods for key efficacy outcomes used in the economic model and/or included in the final NICE scope is provided in Table 7.

Table 7. Description of outcomes and methodology for statistical analysis.

Outcome & Cohort	Statistical analysis
rPFS (by BICR); Cohort A, Cohort B, Cohort A+B	• Stratified log-rank test: • Primary analysis (based on BICR [RECIST 1.1 and PCWG3] assessments and stratified in accordance with the pooling strategy[a] • Hazard ratio using Cox proportional hazards model (with ties=Efron and the stratification variables determined by the pooling strategy as covariates) • Plots and summaries of number (%) patients with progression or death events using Kaplan–Meier (KM) method. • Stratified log tank test and cox proportional hazards model will be repeated for confirmed FMI F1CDx patients and confirmed Myriad gBRCAm patients. KM plot will be produced for confirmed FMI F1CDx patients and confirmed Myriad gBRCAm patients. Sensitivity analyses and subgroup analyses conducted for rPFS by BICR are provided in Table 14 (Section 4.2) of the Statistical Analysis Plan (SAP)
OS	• Stratified log rank test stratified in accordance with the pooling strategy • Hazard ratio using a Cox proportional hazards model (with ties=Efron and the stratification variables determined by the pooling strategy as covariates) • Plots and summaries of number (%) patients with events using KM method. • Stratified log tank test and cox proportional hazards model will be repeated for confirmed FMI F1CDx patients and confirmed myriad gBRCAm patients.
Time from randomisation to second progression or death (PFS2); Cohort A, Cohort A+B	• Stratified log-rank test stratified in accordance with the pooling strategy • Hazard ratio using a Cox proportional hazards model (with ties=Efron and the stratification variables determined by the pooling strategy as covariates) • Plots and summaries of number (%) patients with events using KM method.

TTPP	• TTPP was analysed at the time of the primary rPFS analysis using the methods employed in the rPFS analysis. The *p* value was based on the stratified log-rank test using previous taxane treatment and measurable disease as strata, and HR and 95% CI based on the Cox model. A two-sided 5% alpha level was used to test TTPP based on the multiplicity strategy
Time to first SSRE; Cohort A, Cohort A+B	• Stratified log-rank test stratified in accordance with the pooling strategy • Hazard ratio using a Cox proportional hazards model (with ties=Efron and the stratification variables determined by the pooling strategy as covariates) • Plots and summaries of number (%) patients with events using KM method.
Time to deterioration in FACT-P (FACT-P total score, FACT-G total score, TOI, FAPSI-6, FWB, PWB, PCS); Cohort A, Cohort A+B	• Stratified log rank test stratified in accordance with the pooling strategy • Hazard ratio using a Cox proportional hazards model (with ties=Efron and the stratification variables determined by the pooling strategy as covariates) • Forest plot
FACT-P (FACT-P total score, FACT-G total score, TOI, FAPSI-6, FWB, PWB, PCS); Cohort A, Cohort A+B	• Summary statistics by treatment group • Change from baseline using a MMRM which includes treatment, visit and treatment by visit interaction as explanatory variables and the baseline FACT-P total score as a covariate, along with the baseline FACT-P total score by visit interaction and the stratification variables prior taxane and measurable disease as determined by the pooling strategy
FACT-P improvement rate (FACT-P total score, FACT-G total score, TOI, FAPSI-6, FWB, PWB, PCS); Cohort A, Cohort A+B	• Odds ratio using logistic regression adjusted for the stratification variables determined by the pooling strategy. If there are not at least 5 responses across both treatment groups then a Fisher's exact test using mid p-values will be used.

[a] Although it is expected that there will be enough rPFS events in each strata (where strata are defined as categories formed from – prior taxane * measurable disease * treatment) to allow a meaningful analysis, if any stratum for either treatment arm contains less than 5 events,

then a pooling strategy will be employed. The order of preference for pooling will be (prior taxane * treatment), (measurable disease * treatment), unstratified. In addition, for analyses on Cohort A+B, Cohort will be added as a stratification factor provided that the addition does not lead to <5 events in any strata. Prior taxane and measurable disease will use data collected via IVRS. The pooling strategy will be employed for Cohort A, Cohort B and Cohort A+B separately. All sensitivity analyses and secondary endpoints (except for ORR which only includes prior taxane) will use the same strata as the primary model, for that endpoint, unless there are <5 events per stratum and then an unadjusted model will be used.

BICR, blinded independent central review; BPI-SF, Brief Pain Inventory – Short Form; CI, confidence interval; FACT-G, Functional Assessment of Cancer Therapy – General; FACT-P, Functional Assessment of Cancer Therapy – Prostate; FAPSI-6, 6-item Functional Assessment of Cancer Therapy Advanced Prostate Symptom Index; FWB, functional wellbeing; g*BRCA*m, germline *BRCA* mutation; HR, hazard ratio; KM, Kaplan–Meier; OS, overall survival; PCWG2, Prostate Cancer Working Group 2; PCS, prostate cancer subscale; PFS2, second progression-free survival; PRO, patient-reported outcome; PWB, physical wellbeing; RECIST, Response Evaluation Criteria in Solid Tumours; rPFS, radiographic progression-free survival; SAP, statistical analysis plan; SSRE, symptomatic skeletal-related event; TOI, Trial Outcome Index; TTPP, time to pain progression.
Source: PROfound CSP version 4, 7 March 2019.[87]

B.2.5 Quality assessment of the relevant clinical effectiveness evidence

The PROfound study was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki[90] and that are consistent with International Council for Harmonisation (ICH)/Good Clinical Practice (GCP),[91] applicable regulatory requirements and the AstraZeneca policy on Bioethics.

A complete quality assessment in accordance with the NICE-recommended checklist for assessment of bias in RCTs is presented in Table 8 and Appendix D. **The risk of bias in the PROfound study is confirmed as being low.**

Table 8. Overview of quality assessments for the PROfound study

Study question	How was this question addressed in the PROfound study?	Risk of bias
Was randomisation carried out appropriately?	**Yes**. A central interactive voice-response or Web response system was used to randomly assign patients in a 2:1 ratio. Further details can be found in Sections 3.3 to 3.5 of the PROfound Clinical Study Protocol[87]	Low
Was the concealment of treatment allocation adequate?	**Not applicable** (PROfound was an open-label study). Radiographic disease progression was assessed by blinded central review by an independent third-party vendor to mitigate against risk of investigator bias	Low
Were the groups similar at the outset of the study in terms of prognostic factors?	**Yes**. A blocked randomisation list was generated to ensure an approximate balance between the olaparib and enzalutamide or abiraterone acetate arms in Cohorts A and B (2:1). The randomisation was stratified by previous taxane use (yes, no) and whether subject had measurable disease (yes, no). Minor imbalances were noted for some baseline characteristics; however, as described in 0, a sensitivity analysis which adjusted for prior taxane, measurable disease, and other important prognostic factors that appeared imbalanced across the treatment arms (including PSA, metastatic disease at diagnosis, and ECOG status [all as covariates]) showed that the impact on the hazard ratios for rPFS and OS compared with the primary and secondary analyses was minimal. The study results were thus robust,	Low

	and not impacted by minor differences in baseline characteristics across treatment arms.	
Were the care providers, participants and outcome assessors blind to treatment allocation?	**No**. This was an open label trial; however, radiographic disease progression was assessed by blinded central review by an independent third-party vendor and the study sponsors were blinded to actual treatment arm until the randomisation codes were received (29 July 2019)	Low
Were there any unexpected imbalances in drop-outs between groups?	**No**. Select minor imbalances were observed (see Section B.2.3.7), [redacted]	Low
Is there any evidence to suggest that the authors measured more outcomes than they reported?	**No**. Full documentation relating to the PROfound clinical trial methodology, analyses, and outcomes are included in the CSR, SAP and supporting references	Low
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	**Yes**. All efficacy and HRQoL data (except for ORR, DoR and BoR) were analysed using the full analysis set (FAS), which included all patients who were randomised in both Cohorts as part of the global enrolment regardless of the treatment actually received. ORR, DoR and BoR were analysed using the Evaluable for response (EFR) analysis set (a subset of the FAS, of patients who had measurable disease at baseline as per the RECIST 1.1 criteria). Standard censoring methods were used to account for missing data. Analysis sets and outcome variables are listed in Table 13 in the CSP. Further details can be found in Section 8.4 and Section 11 of the PROfound CSP and CSR respectively. Safety and tolerability assessments were based on the safety analysis set (SAS), which included all patients who were randomised as part of the global enrolment and received at least one dose of randomised study treatment in Cohort A or in Cohort B	Low

BoR, best objective response; CSP, Clinical Study Protocol; CSR, Clinical Study Report; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; EFR,evaluable for response;

FAS, full analysis set; ORR, objective response rate; OS, overall survival; PSA, prostate-specific androgen; RECIST, Response Evaluation Criteria In Solid Tumours; rPFS, radiographic progression-free survival; SAP, statistical analysis plan; SAS, safety analysis set
Source: PROfound Clinical Study report, version 1, 23 October 2019,[61] PROfound Clinical Study Protocol, version 4, 7 March 2019[87] and de Bono *et al*. 2020.[30]

B.2.6 Clinical effectiveness results of the relevant trials

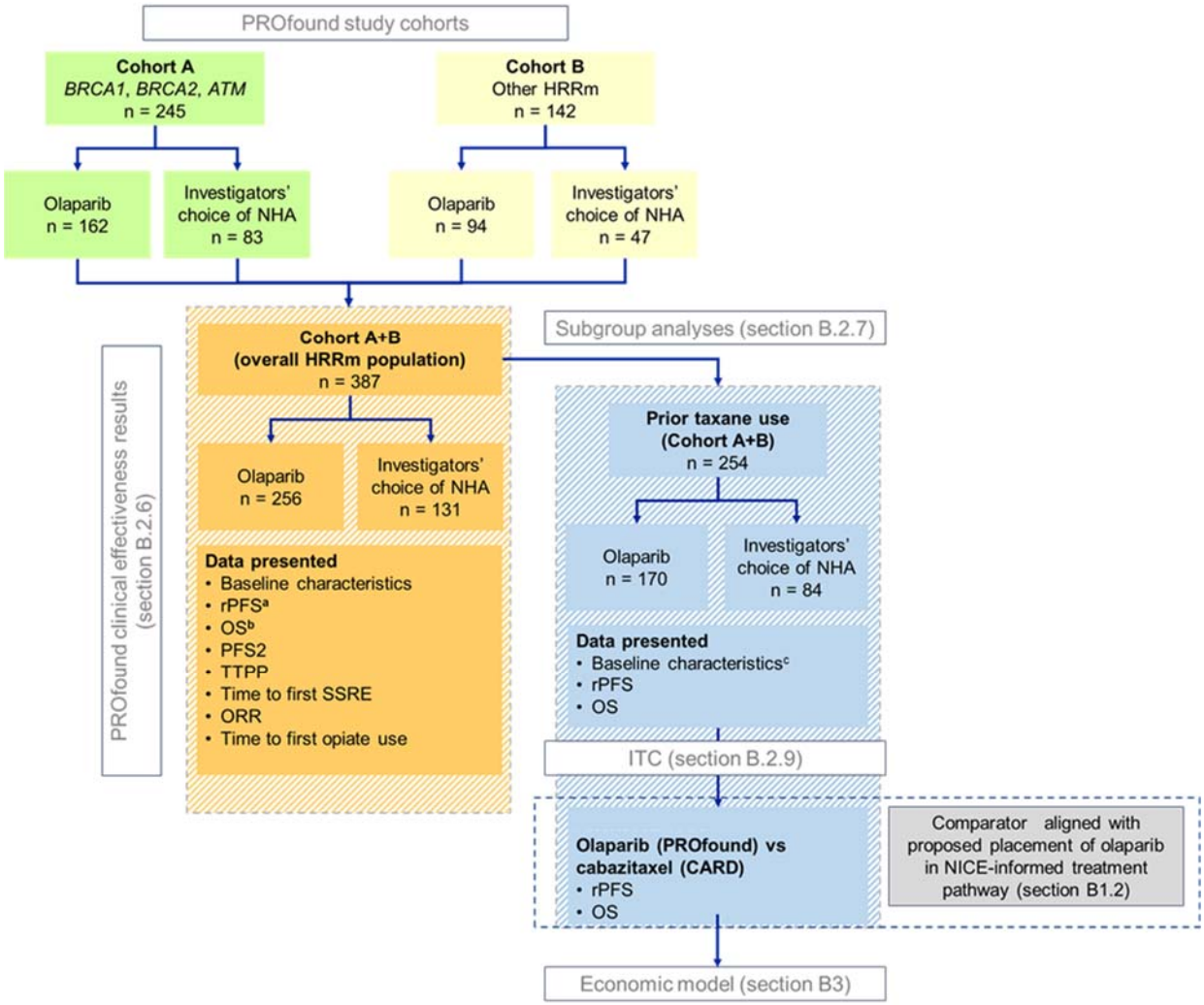
As discussed in section B.2.1, clinical effectiveness evidence on olaparib (the intervention of interest) and cabazitaxel (the main comparator of interest in current clinical practice in England) were derived from the PROfound[30,61] and CARD studies,[67] respectively. This section focuses on data on olaparib from the pivotal Phase III PROfound study. Key data on cabazitaxel from the CARD study are summarised in Appendix D, section D.1.4.; comparative analysis of olaparib versus cabazitaxel via an anchored indirect treatment comparison is described in section B.2.9.

B.2.6.1 PROfound: summary of clinical data

An overview of the data provided in Sections B.2.6 and B.2.7 is presented in Figure 3.

The key efficacy outcomes in Cohort A+B (the overall HRRm population in the PROfound study), Cohort A (wherein the primary endpoint of BICR rPFS was evaluated), and Cohort A+B prior taxane subgroup of PROfound (the main focus for comparative clinical- and cost-effectiveness analysis versus cabazitaxel, and the population reflective of the positioning of olaparib in clinical practice, where the majority of patients receive docetaxel [with ADT] for HSPC) are summarised in Table 9.

Figure 3. An overview of the PROfound trial and its placement in the current submission.



[a]Includes BICR-assessed rPFS (primary analysis) and investigator-assessed rPFS (sensitivity analysis)
[b]Includes unadjusted OS, and OS with treatment switching adjustment
[c]Baseline patient characteristics are presented in section B.2.3.7, not section B.2.7
ATM, gene for ataxia–telangiesctasia mutated; *BRCA1*, gene for breast cancer type 1 susceptibility protein; *BRCA2*, gene for breast cancer type 2 susceptibility protein; DoR, duration of response; HRRm, homologous recombination repair mutation; NICE, National Institute for Care and Health Excellence; ORR, objective response rate; OS, overall survival; PFS2, second progression-free survival; rPFS, radiographic progression-free survival; SSRE, symptomatic skeletal-related events; TTPP, time to pain progression.

Table 9. Key efficacy outcomes in Cohort A, Cohort A+B, Cohort A+B prior taxane subgroup (used in ITC analysis).

Endpoint	Cohort A		Cohort A+B		Cohort A+B prior taxane subgroup	
	Olaparib 300 mg bid (n = 162)	**Investigators' choice of NHA (n = 83)**	**Olaparib 300 mg bid (n = 256)**	**Investigators' choice of NHA (n = 131)**	**Olaparib 300 mg bid (n = 170)**	**Investigators' choice of NHA (n = 84)**
Median rPFS, months (95% CI) *DCO1: 14 June 2019*	**Primary outcome**		**Key secondary outcome**		**Key secondary outcome**	
	7.39 (6.24–9.33)	3.55 (1.91–3.71)	5.82 (5.52–7.36)	3.52 (2.20–3.65)	5.82 (5.39–7.36)	2.56 (1.84–3.52)
	HR, 0.34 (95% CI, 0.25–0.47) $p < 0.0001$		HR, 0.49 (95% CI, 0.38–0.63) $p < 0.0001$		HR, 0.39 (95% CI, 0.29–0.53)	
Median interim OS, months (95% CI) *DCO1: 14 June 2019*	**Key secondary outcome**		**Secondary outcome**		**Secondary outcome**	
	18.50 (17.22–NC)	15.11 (11.33–19.09)	17.51 (15.84–20.67)	14.26 (11.33–17.08)	15.84 (12.65–18.00)	11.37 (9.40–15.11)
	HR, 0.64 (95% CI, 0.43–0.97); $p = 0.0173$[a]		HR, 0.67 (95% CI, 0.49–0.93)		HR, 0.61 (95% CI, 0.43–0.88)	
Treatment switch-adjusted interim OS[b] (investigators' choice of NHA), months (95% CI); preferred analysis *DCO1: 14 June 2019* Note: HR reflects olaparib OS versus treatment switch adjusted OS on investigators' choice of NHA	**Additional analysis**		**Additional analysis**		**Additional analysis**	
	N/A	[redacted]	N/A	[redacted]	N/A	[redacted]
	[redacted]		[redacted]		[redacted]	

[a]Alpha spend was 0.01 at the interim analysis (DCO1); therefore, statistical significance was not reached.

[b]Results presented using RPSFTM method (Weibull, with no re-censoring). Other methods explored as per NICE DSU16 (Section A.7.2).[92]

bid, twice daily; CI, confidence interval; HR, hazard ratio; NC, not calculable; ORR, objective response rate; OS, overall survival; PFS2, second progression-free survival; rPFS, radiographic progression-free survival; RPSFTM: Rank Preserving Structural Failure Time Models; TTPP, time to pain progression.

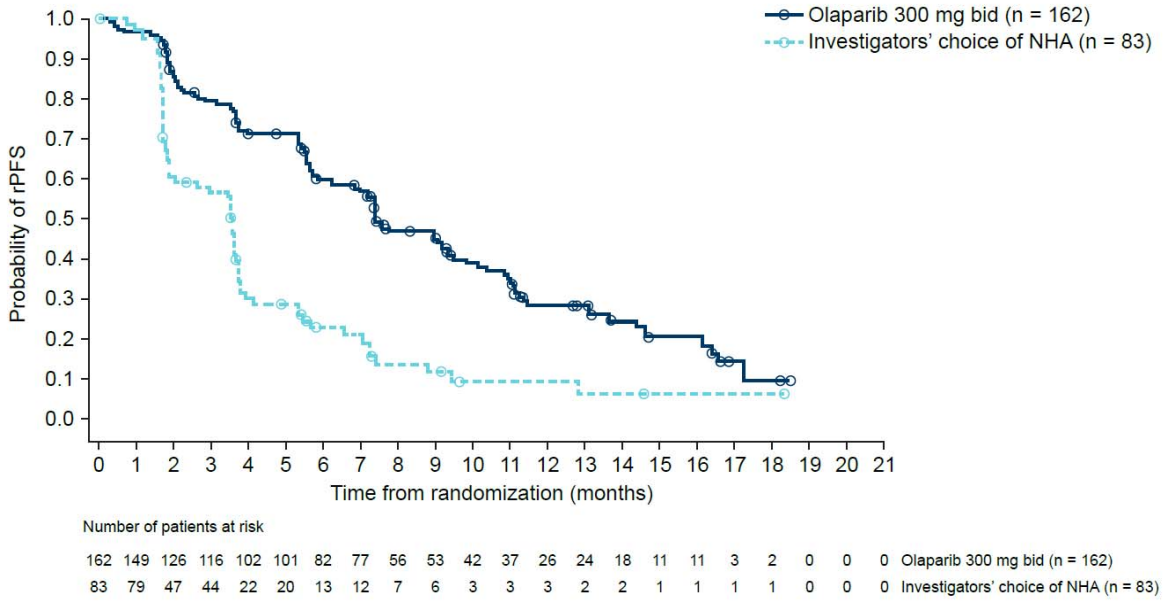
Source: de Bono et al 2020,[30] Clinical Study Report, version 1, 23 October 2019[61] and PROfound treatment switching analysis report.[93]

B.2.6.2 rPFS (BICR), DCO1 (4th June 2019)

B.2.6.2.1 Cohort A (primary endpoint)

The primary analysis of rPFS took place when 174 progression events had occurred (71% maturity) in Cohort A. The PROfound study met its primary endpoint at the time of this analysis, with olaparib treatment achieving a statistically-significant and clinically-meaningful improvement in median BICR rPFS compared with investigators' choice of NHA in Cohort A (7.39 months vs 3.55 months; HR, 0.34 [95% CI, 0.25–0.47]; $p < 0.0001$, Figure 4). There was clear separation of the Kaplan-Meier (KM) curves in favour of olaparib; this separation started at approximately 2 months (coinciding with the first planned tumour assessment) and was maintained throughout most of the study follow-up period. These data are supported by landmark rPFS assessments at 6- and 12-months, wherein ~60% and 28% of patients in the olaparib arms were alive and progression-free, respectively (versus, ~23% and 9% of patients in the investigators' choice of NHA arm).[30,61]

Figure 4. Primary outcome: Kaplan–Meier plot of BICR-assessed rPFS in Cohort A.



Primary outcome: BICR-assessed rPFS[a]	Olaparib 300 mg bid (n = 162)	Investigators' choice of NHA (N = 83)
Events, n (%)	106 (65.4)	68 (81.9)
Median rPFS, months (95% CI)	7.39 (6.24–9.33)	3.55 (1.91–3.71)

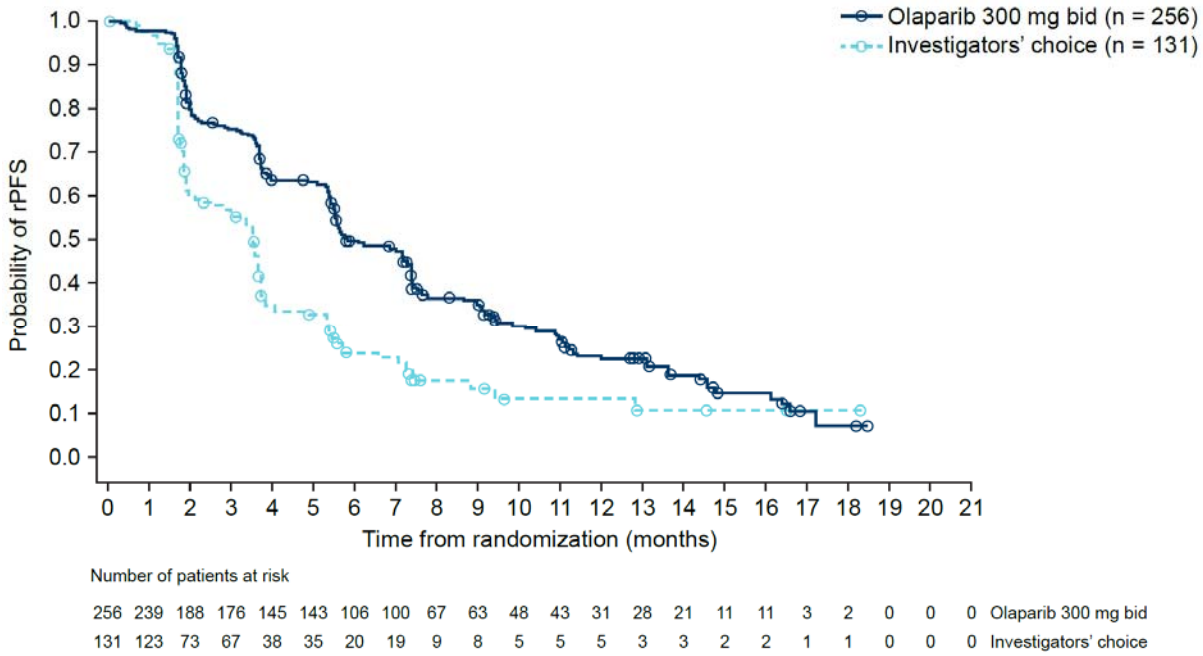
HR (95% CI)	0.34 (0.25–0.47)	
rPFS at 6 months, %	59.76	22.63
rPFS at 12 months, %	28.11	9.40

[a] Disease progression, as assessed by BICR and defined by RECIST version 1.1 and/or PCWG3 or death (by any cause in the absence of progression) regardless of whether the patient withdrew from randomised therapy or received another anti-cancer therapy before progression.
BICR, blinded independent central review; bid, twice daily; CI, confidence interval; HR, hazard ratio; PCWG3, Prostate Cancer Working Group 3; RECIST, Response Evaluation Criteria In Solid Tumours; rPFS, radiographic progression-free survival.
Source: de Bono et al 2020[30] and CSR edition 1, 23 October 2019.[61]

B.2.6.2.2 Cohort A+B (key secondary endpoint)

In the overall HRRm population (Cohort A+B), olaparib was associated with a statistically-significant and clinically-meaningful improvement in median BICR rPFS, versus investigators' choice of NHA (median rPFS, 5.82 months vs 3.52 months, respectively; HR, 0.49 [95% CI: 0.38–0.63; $p < 0.0001$]), as shown in Figure 5. As with Cohort A, there was clear separation of the Kaplan–Meier curves in favour of olaparib; this separation started at approximately 2 months (coinciding with the first planned tumour assessment), and was maintained for the majority of the study follow-up period. **~50% and ~25% of patients remained alive and progression-free in the olaparib arm at the time of 6-month and 12-month landmark rPFS assessments**, respectively (versus just 22% and 14% of patients in the investigators' choice of NHA arm), which is remarkable in this heavily pre-treated mCRPC population of patients.

Figure 5. Key secondary outcome: Kaplan–Meier plot of BICR-assessed rPFS in patients Cohort A+B



Key secondary outcome: BICR-assessed rPFS[a]	Olaparib 300 mg bid (n = 256)	Investigators' choice (N = 131)
Events, n (%)	180 (70.3)	99 (75.6)
Median rPFS, months (95% CI)	5.82 (5.52–7.36)	3.52 (2.20–3.65)
HR (95% CI)	0.49 (0.38–0.63); $p < 0.0001$	
rPFS at 6 months, %	49.66	23.67
rPFS at 12 months, %	22.13	13.47

[a] Disease progression, as assessed by BICR defined by RECIST version 1.1 and/or PCWG3 or death (by any cause in the absence of progression) regardless of whether the patient withdrew from randomised therapy or received another anti-cancer therapy before progression.
BICR, blinded independent central review; bid, twice daily; CI, confidence interval; HR, hazard ratio; PCWG3, Prostate Cancer Working Group 3; RECIST, Response Evaluation Criteria In Solid Tumours; rPFS, radiographic progression-free survival.
Source: de Bono et al 2020[30] and CSR edition 1, 23 October 2019.[61]

B.2.6.2.3 Pre-specified sensitivity and subgroup analyses

The rPFS benefit achieved with olaparib treatment was maintained in a range of pre-specified sensitivity and subgroup analysis (see sections 11.1.1. and 11.1.2.2. of the PROfound Clinical Study Report, version 1, 23 October 2020[61] and Appendix E), demonstrating a robust and consistent treatment effect across potential or expected prognostic factors. Subgroup analyses of eight pre-specified baseline characteristics (including the stratification factors of prior taxane [yes/no] and baseline metastases [yes/no]) showed clinically-meaningful reductions in the risk of radiological disease

progression or death in patients who received olaparib (ranging from 39% to 75% in Cohort A and from 23% to 88% in Cohort A+B). These data, as well as analyses by single HRRm status, are further described in Appendix E. The prior taxane subgroup of Cohort A+B – the focus of the comparative clinical- and cost-effectiveness evidence versus cabazitaxel, is further discussed in Section B.2.7.

B.2.6.2.4 Post-progression anticancer therapies (Cohort A + B), DCO1 (4th June 2019)

Subsequent anticancer therapies were received by a lower percentage of patients in the olaparib arm compared with the investigators' choice of NHA arm: 29.0% versus 68.7% in Cohort A, and 35.2% versus 63.4% in Cohort A+B (see Appendix M). Of these patients, treatment with a subsequent PARP inhibitor (olaparib) occurred in 1.9% (3/162) and 1.2% (3/256) of patients in the olaparib arm of Cohort A and Cohort A+B, respectively, versus, 61.4% (51/83) and 57.3% (75/131) of patients in the investigators' choice of NHA arm. The high percentage of patients in the investigators' choice of NHA arm who had treatment with a subsequent PARP inhibitor is consistent with the study design, which allowed patients to switch to olaparib treatment following BICR-assessed progression on investigators' choice of NHA. Other commonly reported subsequent treatments included hormonal therapy/taxane chemotherapy, which is consistent with clinical practice. A full list of subsequent therapies for Cohort A and Cohort A+B is provided in Appendix M.

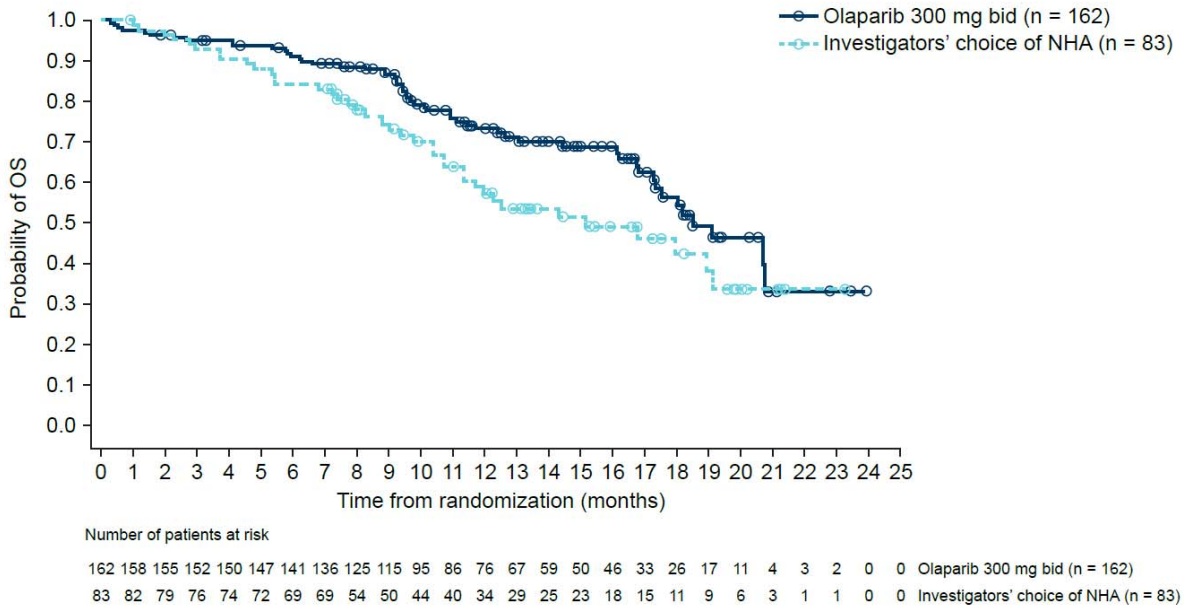
B.2.6.3 OS, DCO1 (4th June 2019)

At the 4th June 2019 data cut-off (DCO1), OS data were immature (Cohort A: 38% data maturity; Cohort A+B: 41% data maturity).

In Cohort A, 56.8% of patients in the olaparib arm and 48.2% of the investigators' choice of NHA arm were alive and in the survival follow-up. Olaparib was associated with a clinically-meaningful median OS benefit of 3.4 months compared with investigators' choice (median OS, 18.50 months versus 15.11 months; HR, 0.64 [95% CI, 0.43–0.97]; $p = 0.0173$). This benefit was observed despite most patients (61.4%) in the investigators' choice of NHA arm switching to olaparib treatment upon BICR-confirmed disease progression and confounding the OS analysis. The interim OS analysis was not statistically significant because the alpha spend at DCO1 was

0.01; however, a statistically significant survival benefit was achieved during the final OS analysis (DCO2), making olaparib the first and only PARP-inhibitor to show a significant OS benefit in mCRPC patients with a *BRCA1*, *BRCA2* and *ATM* gene mutations; these data are discussed in Section B.2.6.4.

Figure 6. Key secondary outcome: Kaplan–Meier plot of interim OS in patients in Cohort A.



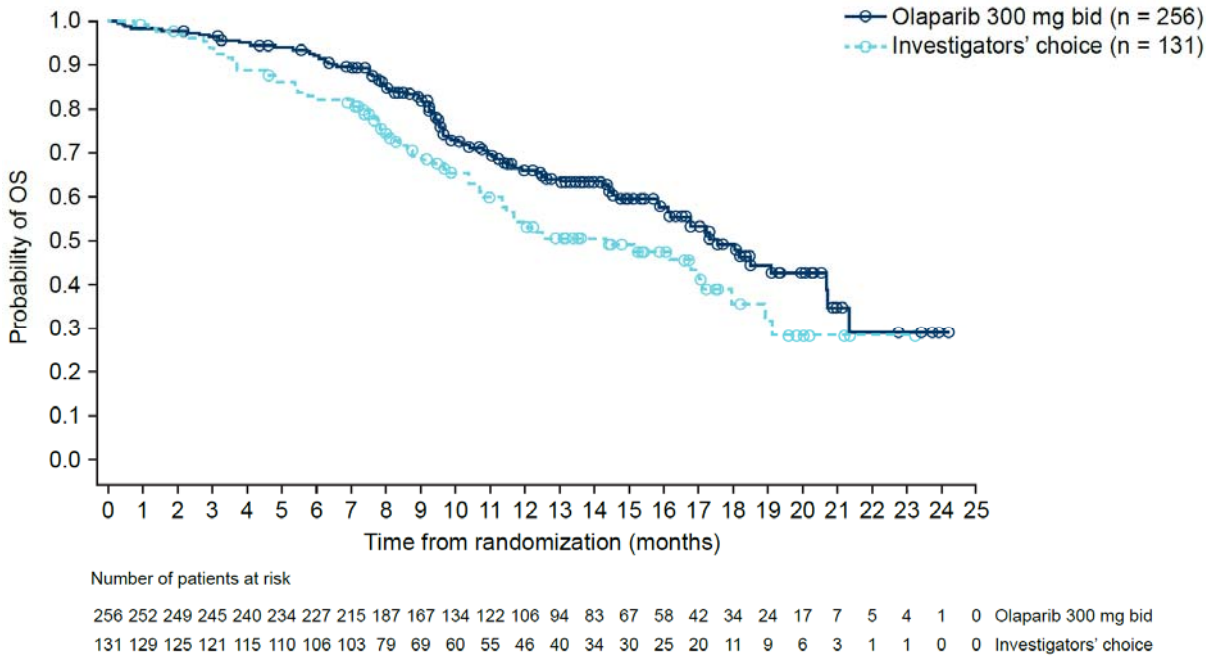
Key secondary outcome: interim OS	Olaparib 300 mg bid (n = 162)	Investigators' choice of NHA (n = 83)
Events, n (%)	54 (33.3)	39 (47.0)
Median OS,[a] months	18.50	15.11
HR (95% CI)	0.64 (0.43–0.97); *p* = 0.0173[b]	
OS at 6 months (%)[a]	91.20	84.15
OS at 12 months (%)[a]	73.07	56.94
OS at 18 months (%)[a]	56.30	42.13

[a]Alpha spend was 0.01 at the interim analysis; therefore, statistical significance was not reached.
[b]Calculated using the Kaplan–Meier method.
CI, confidence interval; HR, hazard ratio; OS, overall survival.
Source: Clinical Study Report Edition 1 – 23 October 2019.[61]

For the Cohort A+B, 53.9% of patients in the olaparib arm and 44.3% of patients in the investigators' choice of NHA arm were alive and in the survival follow-up at the time of DCO1. As in Cohort A, **treatment with olaparib was associated with a**

clinically-meaningful median OS benefit of 3.4 months in Cohort A+B compared with investigators' choice of NHA, despite most eligible patients (81.8%) in the investigators' choice of NHA arm switching to olaparib following BICR-assessed progression (median OS, 17.51 months versus 14.26 months, respectively; HR, 0.67 [95% CI, 0.49–0.93]; Figure 7). The Kaplan–Meier curves for olaparib and investigators' choice of NHA separated early (in favour of olaparib) and remained separated for the majority of the follow-up period (Figure 7).

Figure 7. Secondary outcome: Kaplan–Meier plot of interim OS in patients in Cohort A+B



Key secondary outcome: interim OS	Olaparib 300 mg bid (n = 256)	Investigators' choice of NHA (n = 131)
Events, n (%)	97 (37.9)	63 (48.1)
Median OS, months (95% CI)	17.51 (15.84–20.67)	14.26 (11.33–17.08)
HR (95% CI)	0.67 (0.49–0.93); *p* = 0.0063	
OS at 6 months, %[a]	92.07	82.92
OS at 12 months, %[a]	66.06	52.97

[a] Calculated using the Kaplan–Meier method.
bid, twice daily; CI, confidence interval; HR, hazard ratio; OS, overall survival.
Source: de Bono et al 2020[30] and Clinical Study Report Edition 1 – 23 October 2019.[61]

B.2.6.3.1 Treatment switching adjustment

As stated above, switching from investigators' choice of NHA to olaparib treatment was permitted upon BICR-confirmed radiographic progression up to DCO1, if deemed appropriate for the patient (see section B.2.3.1). Subsequently, a substantial number of patients in the investigators' choice of NHA arm switched treatment to olaparib (51/83 patients in Cohort A, and 75/131 patients in Cohort A+B), thus confounding the OS analysis. Given that olaparib is not currently approved or reimbursed in this treatment setting in the UK (i.e. after disease progression on two lines of NHA), treatment switch adjustment analyses were performed per NICE DSU TSD16 guidance,[92] to estimate the true OS benefit of olaparib compared with investigators' choice of NHA.

Multiple naïve and sophisticated adjustment methods were explored for the treatment switching analysis, in line with guidance from NICE DSU TSD16. The sophisticated methods included:

- Rank Preserving Structural Failure Time Model (RPSFTM)
- Inverse Probability of Censoring Weights (IPCW)
- Two-stage estimation (TSE).

The treatment switching analyses were performed using R (R Foundation). Detailed methodological considerations for the choice of adjustment method are provided in the technical report.[93] Of the aforementioned methods, the TSE approach was excluded, as an appropriate secondary baseline could not be identified, with the method considered to provide biased results. IPCW and RPSFTM methods were compared, with the **RPSFTM approach deemed the most appropriate** on the basis that it is not dependent on data, particularly time-varying data, to predict switching. The RPSFTM approach also utilises all data for switchers and non-switchers, compared with the IPCW approach, which involve analysis on reduced sample sizes. This issue of reduced sample size is particularly important in the case of the PROfound data, due to the relatively small sample size of the investigators' choice of NHA arm when divided into switchers/non-switchers.

In addition to this, the IPCW approach is also dependent on the 'no unmeasured confounders' assumption, i.e. that all baseline covariates and time-dependent confounders that predict switching and outcomes are included. This assumption may not hold when there is relatively little prognostic data collected post-randomisation, limiting the scope of time-varying covariables that can be included in an analysis, as is the case with the PROfound data. In contrast to the IPCW method, the RPSFTM approach does not rely on the 'no unmeasured confounders' assumption; however, it does rely on clinical and biological plausibility of the randomisation and common treatment effect assumptions, described in the technical report. The randomisation assumption was shown to hold in the analysis through plots comparing the counterfactual OS KM curves of the reference and comparator arms (see technical report for details). To investigate the common treatment effect assumption, a sensitivity analysis was included where a proportion of the olaparib treatment effect was applied to those switching to olaparib from investigators' choice of NHA. This showed that if the treatment effect were to decrease post-progression, it would still result in an overall benefit for the patients who switch, suggesting that the analysis is robust to changes in treatment effect over time.

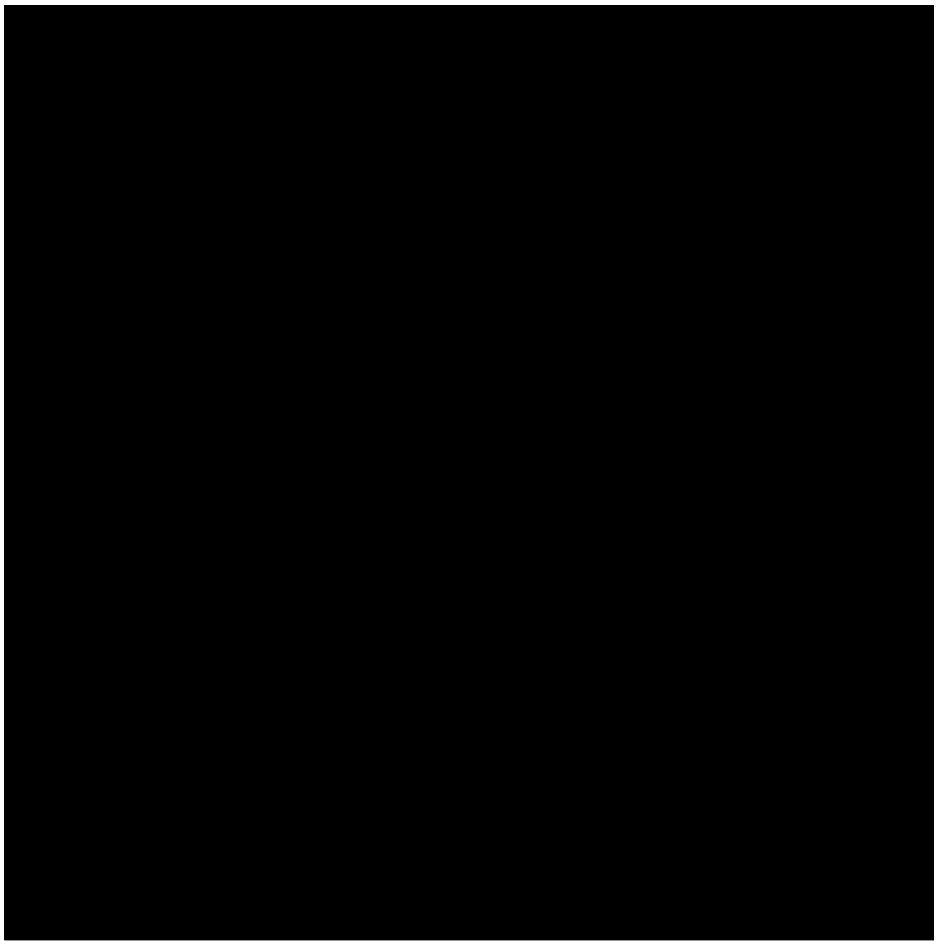
The choice of model used to calculate the acceleration factor for the RPSFTM is based on the plausibility of the assumptions each model makes and the analyst's preferences. For example, the log rank model gives equal weight to survival times, but a Weibull or Cox model may be preferred as they can include the trial stratification factors. The acceleration factor was consistent across each model; **the fully-parametric Weibull model was preferred**.

Re-censoring was performed to assess the impact of informative censoring on the results. In this analysis of the PROfound data, the results were consistent with and without re-censoring (Table 10). Therefore, to utilise the longer-term counterfactual data, **re-censoring was not considered in the preferred analysis.**

Using the RPSFTM method, the adjusted median OS for the investigators' choice of NHA arm ranged from [redacted] (according to test/censoring) in Cohort A+B; corresponding HRs for olaparib versus investigators' choice ranged from [redacted] in Cohort A+B. Results for these analyses are summarised in Figure 8, with the

preferred approach (RPSFTM Weibull model with no re-censoring) highlighted. Using this preferred approach, the OS gain demonstrated in with olaparib versus switch adjusted investigator's choice of NHA was [redacted] in Cohort A ([redacted]) and [redacted] **in Cohort A+B ([redacted],** see Figure 8). These results were highly consistent with the IPCW method, which produced an adjusted median OS of [redacted] in Cohort A ([redacted]) and [redacted] in Cohort A+B ([redacted]). This consistency of the IPCW method, which applies different assumptions to the RPSFTM method, supports the estimated 'true' OS difference for olaparib compared with investigators' choice of NHA.

Figure 8. Kaplan–Meier plot of counterfactual overall survival in Cohort A+B (RPSFTM Weibull method, no re-censoring).



Treatment-switching adjusted Kaplan–Meier curves for Cohort A are available upon request.
KM, Kaplan–Meier; RPSFTM, Rank Preserving Structural Failure Time Model.

Table 10. Median OS and HR for investigators' choice of NHA arm, adjusted for treatment switching; overall HRRm (Cohort A+B) and Cohort A

Test	Re-censoring	Cohort A+B		Cohort A	
		Median OS (months) for investigators choice of NHA adjusted for switching	OS HR (95% CI) olaparib[a] vs. investigators' choice of NHA	Median OS (months) for investigators choice of NHA adjusted for switching	OS HR (95% CI) olaparib[a] vs. investigators' choice of NHA
RPSFTM					
Log rank	Without	[redacted]	[redacted]	[redacted]	[redacted]
	With	[redacted]	[redacted]	[redacted]	[redacted]
Cox proportional hazards	Without	[redacted]	[redacted]	[redacted]	[redacted]
	With	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	Without	[redacted]	[redacted]	[redacted]	[redacted]
	With	[redacted]	[redacted]	[redacted]	[redacted]
IPCW					
Adjusted for switching using IPCW	N/A	[redacted]	[redacted]	[redacted]	[redacted]

[a] Median OS with olaparib was 17.51 months as presented in Section B.2.6.2.

Note: these data are used in the ITC comparison, section B.2.9.

CI, confidence interval; HR hazard ratio; IPCW, Inverse Probability of Censoring Weights; ITC, indirect treatment comparison; NHA, new hormonal agent; OS, overall survival; RPSFTM, rank preserving structural failure time model.

B.2.6.4 OS, DCO2 (20th March 2020)

A final analysis of OS was planned for Cohort A at approximately 61% maturity of the data (DCO2). At DCO2, the survival benefit of olaparib over investigators' choice was confirmed in the key secondary endpoint of OS in Cohort A (Figure 9). OS in Cohort A+B was a secondary endpoint, and at DCO2 again demonstrated a trend to survival benefit over investigators' choice of NHA (Figure 10). Notably, this trend in OS benefit was observed despite >80% of patients in the investigators' choice of NHA arm who were eligible to switch to olaparib in Cohort A+B receiving olaparib.

Figure 9. Secondary outcome: Kaplan–Meier plot of final OS in patients in Cohort A.

Key secondary outcome: final OS – Cohort A	Olaparib 300 mg bid (n = 162)	Investigators' choice of NHA (n = 83)
Events, n (%)	[redacted]	[redacted]
Median OS, months (95% CI)	[redacted]	[redacted]
HR (95% CI)	[redacted]	
OS at 6 months, %[a]	[redacted]	[redacted]
OS at 12 months, %[a]	[redacted]	[redacted]

*0.047 alpha spent at the final OS analysis. Maturity rate: 60%
bid, twice daily; CI, confidence interval; HR, hazard ratio; NHA, new hormonal agent; OS, overall survival.

Figure 10. Secondary outcome: Kaplan–Meier plot of interim OS in patients in Cohort A+B.

Key secondary outcome: final OS – Cohort A+B	Olaparib 300 mg bid (n = 256)	Investigators' choice of NHA (n = 131)
Events, n (%)	[redacted]	[redacted]
Median OS, months (95% CI)	[redacted]	[redacted]
HR (95% CI)	[redacted]	

bid, twice daily; CI, confidence interval; HR, hazard ratio; NHA, new hormonal agent; OS, overall survival.

Treatment switch analyses on data from DCO2 are currently in progress and will be supplied to NICE as soon as they become available.

B.2.6.5 Other key secondary endpoints

rPFS and OS data in the PROfound study were supported by a range of clinically-relevant secondary endpoints, including time from randomisation to second progression or death (PFS2), time to pain progression (TTPP), time to first symptomatic skeletal-related event (SSRE), and objective response rate, all of which showed meaningful improvements for olaparib versus investigators' choice of NHA. Collectively, these data highlight important patient benefits achieved with olaparib treatment, beyond extending survival, and are briefly summarised below. **The focus**

of discussion is the overall HRRm study population of PROfound, i.e. Cohort A+ B; further details on Cohort A are available in the Clinical Study Report, version 1, 23 October 2019, section 11.1. These data were not analysed in the prior taxane subgroup of Cohort A+B at the time of submission.[61]

B.2.6.5.1 PFS2, DCO1 (4th June 2019)

PFS2 is an intermediate endpoint between PFS and OS which reflects real-life treatment decisions and patient experience. Its use is recommended by the EMA to capture potential negative impacts on next-line therapy and to demonstrate that any potential tolerability concerns are outweighed by treatment benefit.[60] This is especially important in the heavily pre-treated mCRPC setting relevant to this appraisal, where even a small delay in disease progression and consequently overall survival is considered clinically meaningful.

Treatment with olaparib was associated with a [redacted]-month improvement in median PFS2 compared with investigators' choice of NHA in Cohort A+B ([redacted]; Figure 11). As with OS, this is a **remarkable benefit given that a high proportion of patients had switched to olaparib upon disease progression** (by BICR) on investigators' choice of NHA. Since olaparib is not available (approved or reimbursed) in England in this setting, this analysis underestimates the true PFS2 benefit of olaparib treatment and biases the results in favour of the control arm.

Figure 11. Secondary outcome: Kaplan–Meier plot of interim PFS2 by investigator assessment in patients in the overall HRRm population (Cohort A+B).

Key secondary outcome: PFS2	Olaparib 300 mg bid (n = 256)	Investigators' choice of NHA (N = 131)
Events, n (%)	[redacted]	[redacted]
Median PFS2, months (95% CI)[a]	[redacted]	[redacted]
HR (95% CI)	[redacted]	

[a] Calculated using the Kaplan–Meier technique.
CI, confidence interval; HR, hazard ratio; PFS2, second progression-free survival.
Source: CSR edition 1, 23 October 2019.[61]

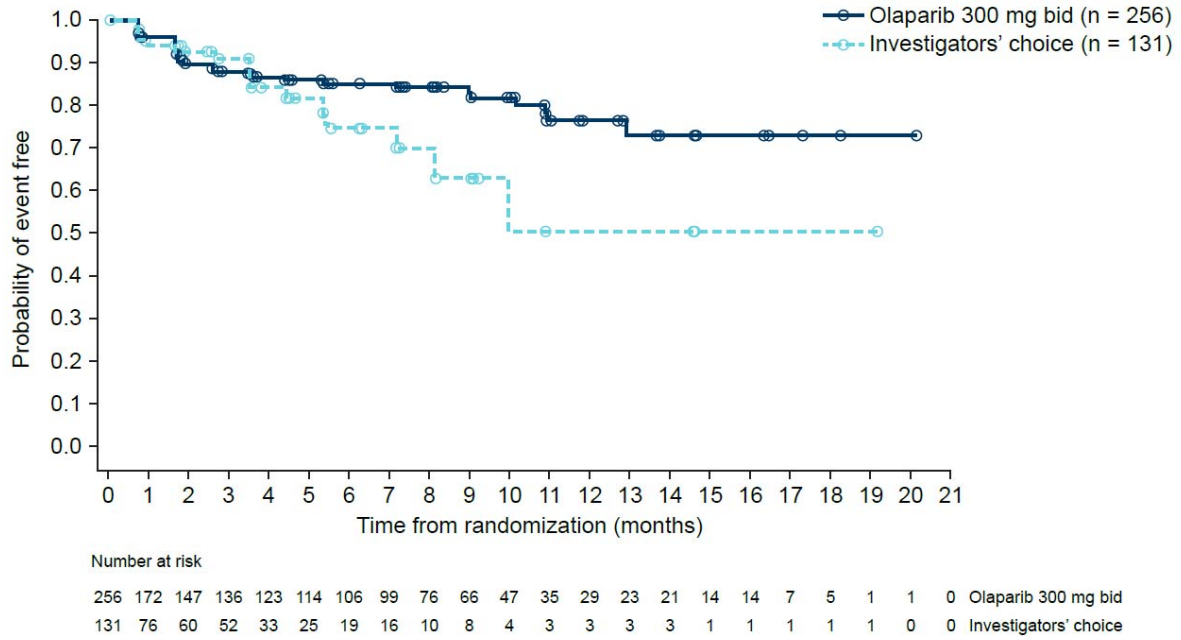
The PFS2 advantage with olaparib in Cohort A was broadly consistent with that observed in Cohort A+B (median PFS2 = [redacted]; see the Clinical Study Report, version 1, 23 October 2019, section 11.1.3.7.).

B.2.6.5.2 Time-to-pain progression, DCO1 (4th June 2019)

TTPP is a patient-relevant endpoint in mCRPC, with many patients experiencing substantial pain within bone tissue due to the location of their tumours (Section B.1.2). The Kaplan–Meier curves for TTPP in Cohort A+B (based on the Brief Pain Inventory - short form [BPI-SF] worst pain and opiate use items) separated from three months onwards and remained separated in favour of olaparib

for the duration of study follow-up. Median duration of TTPP was not reached in either arm at the time of DCO1 (HR, 0.64; 95% CI: 0.35–1.21; Figure 12). **At 12 months, over three-quarters of the patients in the olaparib arm had no pain progression (versus just 50% of patients in the investigator's choice of NHA arm).**

Figure 12. Secondary outcome: Kaplan–Meier plot of interim TTPP by investigator assessment in patients in overall HRRm population (Cohort A+B).



Key secondary outcome: TTPP	Olaparib 300 mg bid (n = 256)	Investigators' choice of NHA (n = 131)
Event, n (%)	32 (12.5)	16 (12.2)
Median TTPP, months	NR	NR
HR (95% CI)	0.64 (0.35–1.21)	
No pain progression at 6 months, %	85.22	74.74
No pain progression at 12 months, %	76.29	50.45

bid, twice daily; CI, confidence interval; HR, hazard ratio; NR, not reached; TTPP, time to pain progression.
Source: CSR edition 1, 23 October 2019.[61]

Treatment with olaparib was also associated with a statistically significant delay in TTPP compared with investigators' choice of NHA in Cohort A (median TTPP: not reached vs 9.92 months, respectively; HR, 0.44 [95% CI, 0.22–0.91];

p = 0.0192; see the Clinical Study Report, version 1, 23 October 2019, section 11.1.2).

B.2.6.5.3 Time to first symptomatic skeletal-related event, DCO1 (4th June 2019)

In mCRPC, the SSREs are a further indicator of worsening bone health due to tumour growth, and usually require further treatment. In the PROfound study, SSREs were defined as:

- Use of radiation therapy to prevent or relieve skeletal symptoms.
- Occurrence of new symptomatic pathological bone fractures (vertebral or non-vertebral) (radiologic documentation required).
- Occurrence of spinal cord compression (radiologic documentation required).
- Orthopaedic surgical intervention for bone metastasis.

The incidence of SSREs was lower in the olaparib arm than in the investigators' choice of NHA arm in Cohort A+B ([redacted];; Table 11), **highlighting an important benefit of olaparib treatment for patients in prolonging (potentially debilitating) and burdensome SSREs.**

Table 11. Time to first SSRE in patients in Cohort A+B.

Secondary outcome: time to first SSRE	Olaparib 300 mg bid (N = 256)	Investigators' choice of NHA (N = 131)
Events, n (%)	[redacted]	[redacted]
HR (95% CI)	[redacted]	
SSRE-free at 6 months	[redacted]	[redacted]
SSRE-free at 12 months	[redacted]	[redacted]

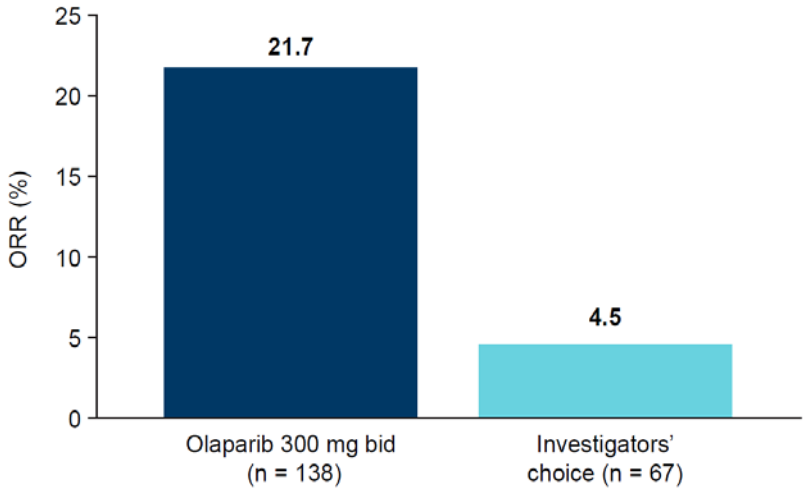
bid., twice daily; CI, confidence interval; HR, hazard ratio; SSRE, symptomatic skeletal-related event.
Source: CSR edition 1, 23 October 2019.[61]

A similar benefit was observed in Cohort A: 15.4% of patients in the olaparib arm and 22.9% of patients in the investigators' choice of NHA arm had experienced a first SSRE and the HR favoured olaparib (0.37; 95% CI: 0.20, 0.70). Further details are available in the CSR (Section 11.1.3.8.).

B.2.6.5.4 *Overall response rate, DCO1 (4th June 2019)*

Olaparib was associated with a clinically meaningful improvement in BICR confirmed ORR compared with investigators' choice of NHA in Cohort A+B (odds ratio [OR], 5.93 [95% CI, 2.01–25.40]; Figure 13). A total of 21.7% of patients in the olaparib arm achieved an objective response, compared with just three patients (4.5%) in the investigators' choice of NHA arm (Figure 13). These results were consistent with those observed for olaparib compared with investigators' choice of NHA in Cohort A (ORR, 33.3% vs 2.3%; OR, 20.86 [95% CI, 4.18–379.18]; $p < 0.0001$; see the Clinical Study Report, version 1, 23 October 2019, section 11.1.2.1)

Figure 13. Secondary outcome: confirmed BICR-assessed radiological ORR in Cohort A+B.



Key secondary outcome: ORR[a]	Olaparib 300 mg bid (n = 138)	Investigators' choice of NHA (n = 67)
Event, n (%) PR, n (%) CR, n (%)	30 (21.7) 29 (21.0) 1 (0.7)	3 (4.5) 0 (0.0) 3 (4.5)
OR (95% CI)	5.93 (2.01–25.40)	
Stable disease, %	60 (43.5)	29 (43.3)

[a] Radiological ORR based on BICR-assessed RECIST version 1.1 and bone scan data (using all scans regardless of whether they were scheduled or not) in patients with measurable disease.
BICR, blinded independent central review; bid, twice daily; CI, confidence interval; CR, complete response; OR, odds ratio; ORR, overall response rate; PR, partial response; RECIST, Response Evaluation Criteria In Solid Tumours.
Source: CSR edition 1, 23 October 2019.[61]

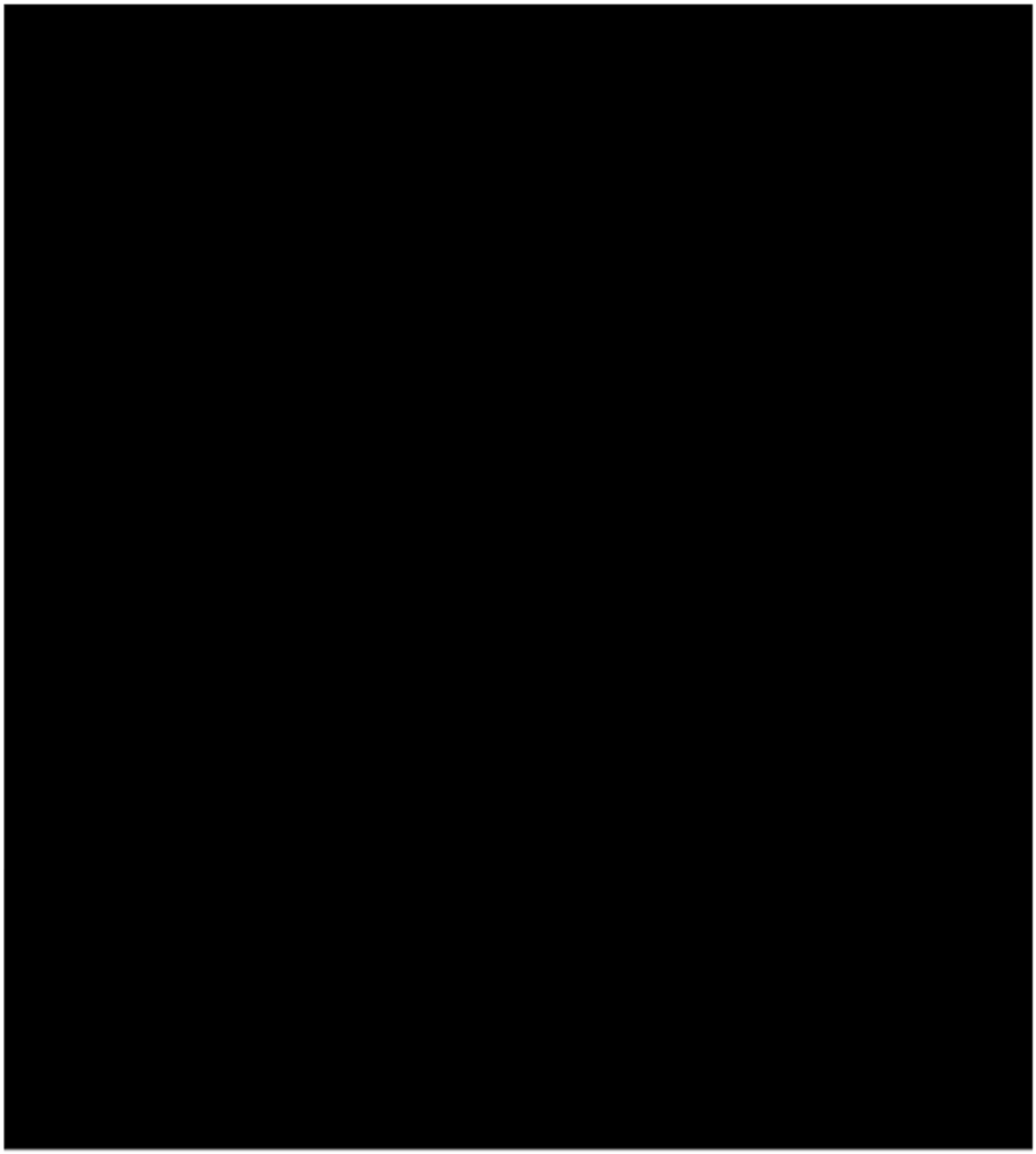
B.2.6.6 HRQoL, DCO1 (4th June 2019)

B.2.6.6.1 EQ-5D (predefined exploratory endpoint)

Baseline and overall compliance rates for the EQ-5D-5L were similar for the two treatment arms in Cohort A+B (baseline compliance: olaparib, [redacted]% vs investigators' choice of NHA, [redacted]%; overall compliance: [redacted]% vs investigators' choice of NHA, [redacted]%).

There was no meaningful change observed in the mean individual domain scores from baseline through to Week 64 across both treatment arms (Figure 14). Across both treatment arms, for patients who had evaluable assessments throughout the study period, their health state stayed the same. There was no change observed in the VAS from baseline to Week 64 across both treatment arms. Overall, the EQ-5D-5L data supported no worsening and no deterioration of individual domain scores or the VAS in the olaparib arm compared to the investigators' choice of NHA arm in Cohort A+B (Figure 14) or in Cohort A (data not shown; see Clinical Study Report, version 1, 23 October 2019, section 11.1.5.1).[61]

Figure 14. Mean change from baseline EQ-5D-5L scores up to week 64 (Cohort A+B).



bid, twice daily; EQ-5D, 5-dimension EuroQol questionnaire; SD, standard deviation; VAS, visual analogue scale.
Source: Clinical Study Report, version 1, 23 October 2019.[61]

B.2.6.6.2 FACT-P, DCO1 (4th June 2019)

Changes in Functional Assessment of Cancer Therapy – Prostate Cancer (FACT-P) total and subscale scores – a more-sensitive disease-specific PRO instrument - were

analysed using a mixed model repeated measures (MMRM) analysis of all of the post-baseline scores for each visit and were in favour of olaparib vs investigators' choice of NHA.

The time to deterioration in FACT-P Total and all subscale scores (with the exception of functional well-being, FWB) for Cohort A+B numerically favoured patients in the olaparib arm compared with investigators' choice of NHA arm, with HRs ranging from 0.68 to 0.94 (see Appendix M for details). For FWB, the HR suggested no detriment with olaparib treatment compared with investigators choice of NHA treatment.

Similar findings were observed in Cohort A, with time to deterioration in FACT-P Total and all subscale scores numerically favouring patients in the olaparib arm compared with the investigator's choice of NHA arm (with HRs ranging from 0.74 to 0.95); as described in the Clinical Study Report, version 1, 23 October 2019, section 11.1.4.6.[61]

Collectively, these data (in conjunction with other PRO data provided in the Clinical Study Report, version 1, 23 October 2019[61]) highlight that the efficacy of olaparib (for instance, in delaying radiographic disease progression, time to pain progression, and time to first symptomatic skeletal-related event) translates into meaningful improvements in patients' health-related quality-of-life and support a favourable risk: benefit profile for olaparib for the treatment of mCRPC patients with qualifying HRR gene mutations.

B.2.7 Subgroup analysis

In current clinical practice in England, the majority of mCRPC patients (~75%) have already received a treatment with a taxane (docetaxel; in combination with ADT for HSPC), prior to receiving treatment with NHA. The "prior taxane" subgroup of the PROfound study is thus most representative of the population of patients who would be eligible to receive treatment with olaparib in clinical practice in England. This population also forms the basis of the comparative clinical-effectiveness and cost-effectiveness analysis versus cabazitaxel, the most-commonly used treatment and standard-of-care in current practice, after disease progression on docetaxel and a NHA (presented in Section B.2.9 and Section B.3, respectively). This heavily pre-

treated population represents an area of significant unmet need, with median OS of just 13.6 months achieved in the CARD study (the largest RCT of cabazitaxel in the post-NHA setting).

In the PROfound study, 254 of 387 patients in the overall HRRm study population (Cohort A+B) had received prior treatment with a taxane: 170 patients in the olaparib arm and 84 patients in the investigators' choice of NHA arm. Randomisation in the study was **stratified by prior taxane use (yes/no), thus preserving balance amongst patients randomised to the treatment and control arm.** The majority of patients (173 of 254; 68%) had received docetaxel only (as would be expected in clinical practice). Some patients had received both docetaxel and cabazitaxel; however, proportions of these patients was well-balanced across olaparib and investigators' choice of NHA arms and is thus not expected to impact upon the study results/interpretation. Just 3 patients (of 254) had received cabazitaxel only. Detailed patient characteristics at baseline in the prior taxane group are shown in Section B.2.3.7, Table 5).

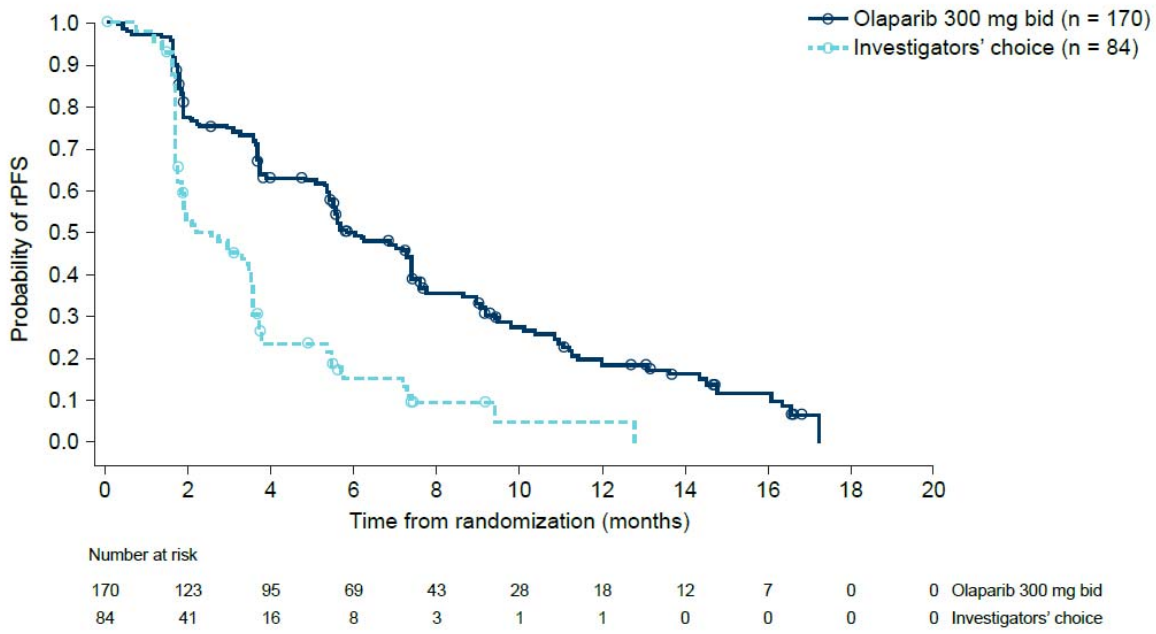
In this section, we describe key data (rPFS and OS) for olaparib versus investigators' choice of NHA in the prior taxane group. These data were used in comparative clinical- and cost-effectiveness for olaparib versus cabazitaxel described in Section B.2.9 and B.3, respectively). It is worth noting that although the prior taxane group is the focus of this submission, olaparib also achieved meaningful clinical benefit in those patients who had not received a taxane prior to randomisation in the study (rPFS HR, 0.77; 95% CI: 0.50–1.22, Cohort A+B), **highlighting an important benefit with olaparib treatment in this group of patients, who (if contraindicated or otherwise unsuitable for treatment with taxanes) have very limited treatment options**.

B.2.7.1 rPFS (BICR), DCO1 (4th June 2019)

At the time of the primary rPFS analysis (DCO1), 124 and 70 events, respectively, had occurred in the olaparib arm and the investigators' arm of the Cohort A+B prior taxane group. Treatment with olaparib resulted in a remarkable 69% reduction in the risk of radiographic disease progression in this subgroup versus investigators' choice of NHA (median rPFS, 5.82 months vs 2.56 months, respectively; HR; 0.39; 95% CI,

0.29–0.53; Figure 15). As with the overall Cohort A+B population, the KM-curves for olaparib and investigators' choice of NHA in the prior taxane group separated early, in favour of olaparib, and remained separated for entire the duration of the follow-up period, supporting a sustained rPFS benefit with olaparib treatment and addressing a key unmet need in this advanced and heavily pre-treated patient population.

Figure 15. Kaplan–Meier plot of BICR-assessed rPFS in Cohort A+B patients whom had prior taxane treatment



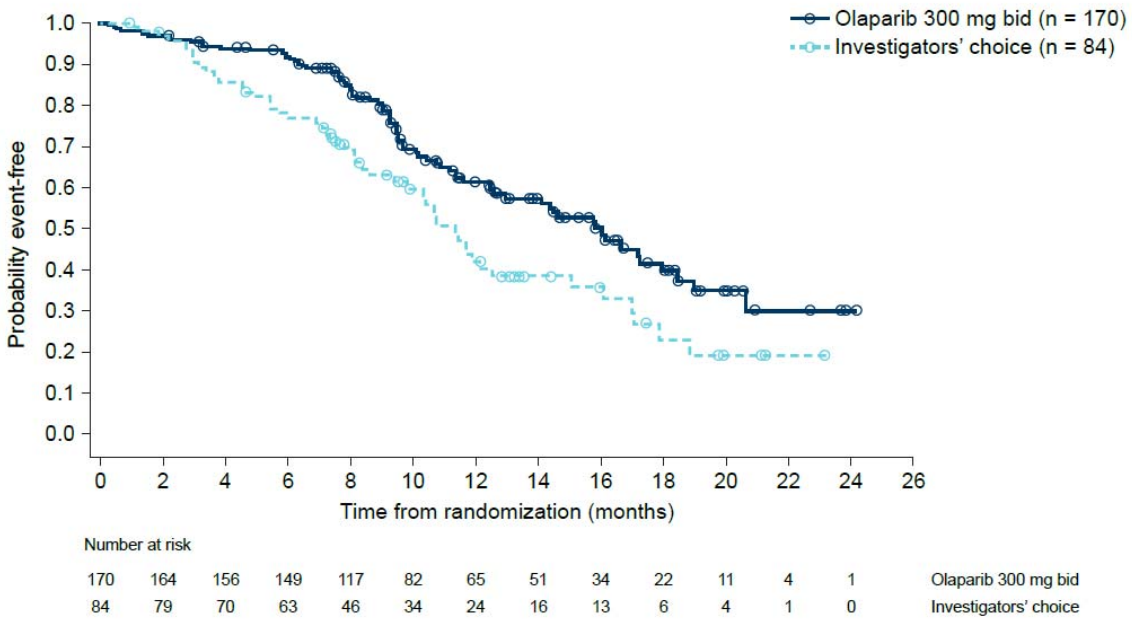
Primary outcome: BICR-assessed rPFS[a]	Olaparib 300 mg bid (n = 170)	Investigators' choice of NHA (n = 84)
Events, n (%)	124 (72.9)	70 (83.3)
Median rPFS, months (95% CI)	5.8 (5.4, 7.4)	2.6 (1.8, 3.5)
HR (95% CI)	0.39 (0.29–0.53)	

[a] Disease progression, as assessed by BICR defined by RECIST version 1.1 and/or PCWG3 or death (by any cause in the absence of progression) regardless of whether the patient withdrew from randomised therapy or received another anti-cancer therapy before progression.
BICR, blinded independent central review; bid, twice daily; CI, confidence interval; HR, hazard ratio; PCWG3, Prostate Cancer Working Group 3; RECIST, Response Evaluation Criteria In Solid Tumours; rPFS, radiographic progression-free survival.
Source: PROfound subgroup analyses, prior taxane Cohort A+B[94]

B.2.7.2 OS, DCO1 (4th June 2019)

At DCO1, 73 events (42.9%) had occurred in the olaparib arm and 49 events (58.3%) in the investigators' choice of NHA arm. Treatment with olaparib led to a 4.4-month median OS advantage compared with investigators' choice of NHA in the prior taxane subgroup of Cohort A+B, despite patients switching from investigators' choice of NHA to olaparib treatment upon BICR progression (median OS, 15.8 months vs 11.4 months; HR; 0.61 [95% CI, 0.43-0.88]; Figure 16). The OS Kaplan–Meier curves for olaparib and investigators' choice of NHA separated early and remained separated in favour of olaparib for the duration of follow-up period, a remarkable result, despite the level of switching (from investigators' choice of NHA to olaparib, upon disease progression, as noted above) and the advanced, heavily pre-treated stage of disease.

Figure 16. Kaplan–Meier plot of interim OS in patients whom had prior taxane treatment in Cohort A+B



Key secondary outcome: interim OS	Olaparib 300 mg bid (n = 170)	Investigators' choice of NHA (N = 84)
Events, n (%)	73	49
Median OS, months (95% CI)	15.8 (12.7, 18.0)	11.4 (9.4, 15.1)
HR (95% CI)	0.61 (0.43, 0.88)	

[a] Calculated using the Kaplan–Meier method.

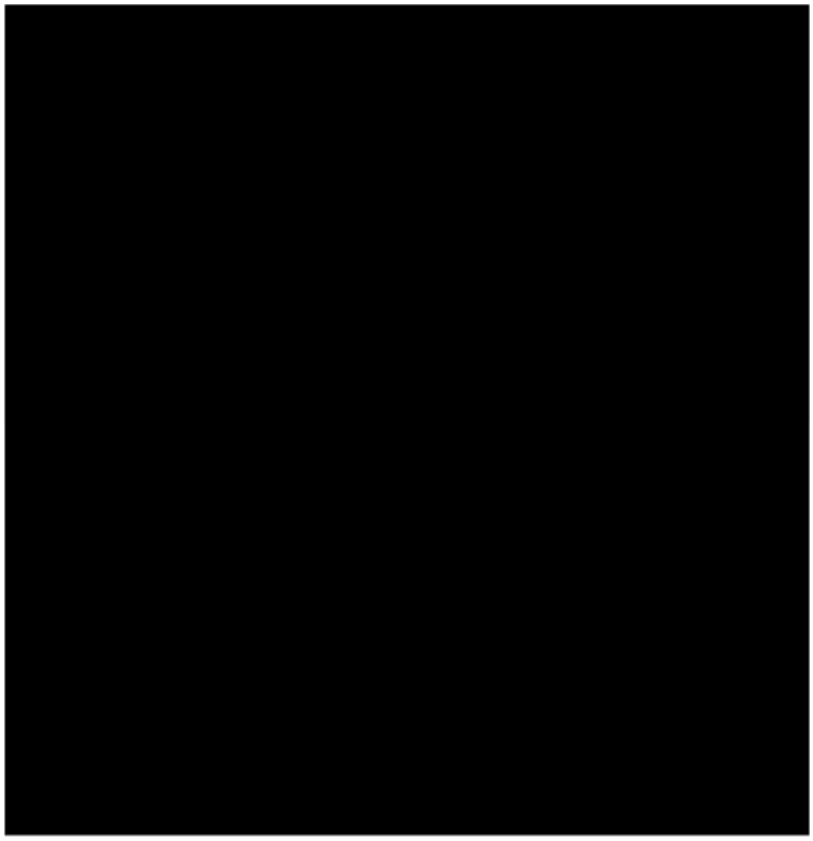
bid, twice daily; CI, confidence interval; HR, hazard ratio; OS, overall survival.
Source: PROfound subgroup analyses, prior taxane Cohort A+B[94]

Treatment switching from investigators' choice of NHA to olaparib post-disease progression confounds the OS analysis, as described in Section B.2.6.3.1, and underestimates the true OS benefit for olaparib versus investigators' choice of NHA. Since olaparib is not currently approved or reimbursed in England for mCRPC patients whose disease has progressed after NHA, treatment switching analyses were performed in line with NICE DSU TSD16 guidance,[92] to estimate the true OS benefit of olaparib more aligned to a setting where subsequent PARP-inhibitor treatment would not be available to patients whose disease had progressed after NHA.

The treatment switching analyses were conducted on Cohort A+B first (as described previously in Section B.2.6.3.1) and then, for the purposes of the anchored ITC (discussed in Section B.2.9), the counterfactual data were subset by prior taxane use, to reflect the population of patients who would be likely to receive treatment with olaparib in real-world practice and the population of patients included in the CARD study, the main clinical trial for cabazitaxel in the post-NHA setting.

Since prior taxane use was a stratification factor in the PROfound study, the randomisation assumption of the RPSFTM method was considered to hold in this subgroup (see Table 5 for an overview of baseline characteristics across the study populations). The common treatment effect assumption was not considered to be impacted by subsetting to a stratified subgroup. The [redacted] adjusted overall survival in the investigator's choice of NHA arm to [redacted] months, and produced a hazard ratio [redacted] for olaparib versus treatment-switch adjusted investigators' choice of NHA (Figure 17), **thus demonstrating a substantial and clinically-meaningful survival benefit in favour of olaparib in patients with HRRm who have received a prior taxane and NHA**. These data were used to inform the anchored indirect treatment comparison of olaparib versus cabazitaxel, and are described in further detail in Section B.2.9.

Figure 17. Kaplan–Meier plot of counterfactual overall survival in patients who had prior taxane treatment in Cohort A+B (RPSFTM Weibull method, no re-censoring).



Treatment-switching adjusted KM- curves for Cohort A are available upon request.
RPSFTM, Rank Preserving Structural Failure Time Model

B.2.7.3 OS, DCO2 (20th March 2020)

The results of the final OS analysis in the prior taxane subgroup of Cohort A+B was consistent with those reported above (for the interim analysis, DCO1) and confirmed a substantial and clinically-meaningful median OS benefit for olaparib versus investigators' choice of NHA (median OS= [redacted] months and [redacted] months, respectively; [redacted],

Table 12). OS data were [redacted] mature at the time of this analysis. Treatment switching adjustment analyses on these data are currently underway and will be provided to NICE as soon as they become available.

Table 12. OS data in the prior taxane subgroup of PROfound at DCO2 (Cohort A+B)

Key secondary outcome: final OS	Olaparib 300 mg bid (n = 170)	Investigators' choice of NHA (N = 84)
Events, n (%)	[redacted]	[redacted]
Median OS, months (95% CI)	[redacted]	[redacted]
HR (95% CI)	[redacted]	

B.2.8 Meta-analysis

As described previously (in Section B.2.2.), the SLR identified three studies that assessed the efficacy and safety of olaparib in the population of interest for this appraisal (PROfound and TOPARP; three abstracts, two full text publications).[28,29,64,65,85]

The TOPARP studies were single-arm Phase II trials; TOPARP-A used the 400 mg dose of olaparib, and TOPARB-B included both 300 mg and 400 mg doses of olaparib. Neither study was explicitly set in a post-NHA population, although the majority of patients had received a prior NHA. Given the availability of data from the much larger **international, Phase III, PROfound randomised-controlled trial** in the population/treatment setting of interest for this appraisal, data from the TOPARP studies were not included in the evidence synthesis.

B.2.9 Indirect and mixed treatment comparisons

As discussed in Section B.2.1, an SLR was conducted in January 2020 in order to identify published clinical evidence on the use of health technologies in patients with mCRPC whose disease had progressed following treatment with an NHA, irrespective of HRR mutation status. The SLR 14 studies, reported across 23 publications, which reported on outcomes with olaparib,[64,65] cabazitaxel,[42,66-73] docetaxel[74-81] and radium-223[82-84] – the intervention and comparators specified in the final NICE scope - in the post-NHA setting. As described in Section B.2.1.3, the SLR did not identified any studies that reported outcomes on docetaxel or radium-223 dichloride in the population relevant to the decision problem, i.e. patients with mCRPC whose disease had progressed after treatment with a NHA.

The SLR identified eight publications that reported outcomes on cabazitaxel in the post-NHA setting. Of these, only one study - CARD (NCT02485691) – included a cabazitaxel arm as well as an NHA arm (as in PROfound), allowing for a comparative analysis between olaparib and cabazitaxel via an anchored indirect treatment comparison.

As described in Section B.2.3 and Appendix D (Section D.1.4.), CARD is an ongoing Phase IV RCT that assessed the efficacy and safety of cabazitaxel compared with an NHA (enzalutamide or abiraterone plus prednisolone) in patients with mCRPC, who had received previous treatment with docetaxel and an NHA.[66] As all patients enrolled in the CARD trial were required to have received previous docetaxel, the patient population is closely aligned with the prior-taxane subpopulation of the PROfound study, although there were some differences in distributions of prior treatments received and timing of disease progression on NHA in the two studies (see 0 and Appendix D for detailed baseline characteristics of PROfound and CARD). The CARD study was also not restricted to those patients who have mutations in HRR genes, which are associated with more aggressive disease and worse outcomes in mCRPC patients, as discussed in Section B.1.1.[30] The primary endpoint in CARD was rPFS (same as PROfound, although not assessed by BICR); OS was a secondary endpoint in both studies.[67] Collectively, this makes a comparison on outcomes relevant for an economic evaluation possible.

The remaining six publications identified in the SLR that reported outcomes in patients who received cabazitaxel were small single-arm studies (often conducted in a single country or centre; for example, Saad *et al.* 2014,[71] Saad *et al.* 2016,[70] Massard *et al.* 2017,[69] Louhanepessey *et al.* 2018,[68] and Shiota *et al*. 2020[12]) or cabazitaxel combination studies (with and without budesinone; van Soest *et al.* 2015[73]). In the absence of a common comparator with PROfound, only unanchored comparisons are feasible between these studies and the prior-taxane group of the PROfound trial. As indicated by the NICE DSU, unanchored comparisons should only be considered in the absence of anchored comparisons.[95] Since data from CARD provided the necessary evidence base for an anchored comparison; these studies were not considered relevant for evidence synthesis per NICE guidance.

Furthermore:

- Louhanepessey *et al.* 2018[68] and Massard *et al.* 2017[69] were abstract-only publications that only reported aggregate data with no associated Kaplan–Meier plots; no associated full text publications were identified.[68,69] Aggregate data are unsuitable for an ITC, particularly if no published Kaplan–Meier data are available.[68,69]

- Saad *et al.* 2016[70] and Saad *et al.* 2014[71] assessed outcomes from the Canadian cabazitaxel early access programme (NCT01254279), but did not report OS or rPFS, therefore, precluding an comparative analysis of these key endpoints.

In light of these factors, the CARD study was considered the most relevant source of evidence for cabazitaxel in the post-NHA setting and was used to inform the anchored ITC versus olaparib described below.

B.2.9.1 Indirect treatment comparison (ITC) approach

The PROfound and CARD studies share the same common comparator arm of investigator's choice of NHA, enabling the use of ITC methods to evaluate the relative efficacy of olaparib versus cabazitaxel.

Patient-level data were available for the pre-specified prior taxane subgroup of PROfound (Cohort A+B), which is similar to the population in the CARD study (i.e. post-taxane, post-NHA); while aggregate data were reported for the CARD study.

Given that there are some identified differences in the trial populations for PROfound and CARD (as noted above), the appropriateness for conducting an anchored PAIC was explored,[96] in line with the recommended process for selecting ITC approaches outlined in Appendix A of NICE DSU TSD 18. [95] This investigation was considered helpful in confirming whether any covariates available for matching in the PROfound and CARD studies could be plausibly considered an effect modifier (via statistical tests) and, if so, whether these might be imbalanced. This assessment determined

whether adjusting for differences could lead to more reliable estimates of relative efficacy between olaparib and cabazitaxel, as described below.

As noted previously, enrolment in the CARD study was not restricted by HRRm status (unlike PROfound) and as such, the HRRm status of patients in the study is not known. There is evidence to suggest that HRR mutations may be associated with worse outcomes on cabazitaxel treatment (relative to outcomes in those who do not carry these mutations). Although further research is needed to confirm this, it is thus possible that HRRm status is an effect modifier for cabazitaxel. If this is the case, then the inability to match PROfound and CARD populations by HRR mutations may bias the analysis in favour of cabazitaxel.

B.2.9.2 Indirect comparison methodology

The ITC was conducted in accordance with the NICE DSU TSD 18 guidance,[96] as detailed below.

B.2.9.2.1 Evidence base

The ITC was conducted on the prior taxane subgroup of the PROfound overall HRRm population (Cohort A+B). As described previously, this subgroup better matches the prior taxane-exposed population in the CARD study, and ensures alignment to the UK population of patients who currently receive cabazitaxel (i.e. after prior treatment with taxane and NHA) and who would be eligible to receive olaparib treatment, if it were to be recommended.

To inform the economic evaluation, the outcomes of interest for this analysis were OS and rPFS. OS was defined as time from randomisation to death due to any cause in both studies. The definitions of rPFS for the PROfound and CARD trials were as follows:

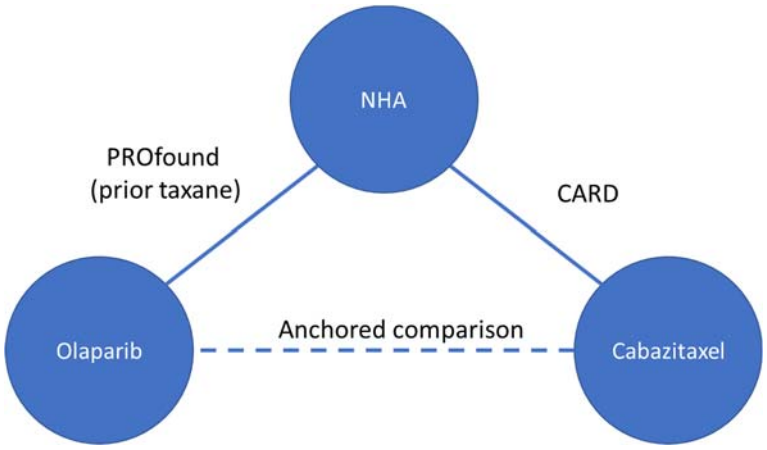
- **PROfound**: Time from randomisation until objective radiological disease progression (by RECIST 1.1 or prostate cancer working group 3 criteria or death)[97]

- **CARD**: Time from randomisation until objective tumour progression (RECIST 1.1 criteria), progression of bone lesions (according to prostate cancer working group 2 criteria) or death.[98]

Individual patient-level data (IPD) for rPFS were taken directly from the PROfound Cohort A+B prior taxane subgroup, whilst IPD for OS were derived from the RFPSTM treatment-switching analysis described in Section B.2.7.2. Aggregate data from the CARD study were sourced directly from the study publication.[67]

Following NICE DSU TSD 18 guidance, an anchored ITC was performed for the comparison of PROfound with CARD, since both studies include NHA as the comparator arm.[95] The specific evidence network for this analysis is shown in Figure 18.

Figure 18. Evidence network for the ITC (OS and rPFS)



B.2.9.2.2 Statistical methods

Following guidance from the NICE DSU TSD 18, the analysis was conducted in the following steps:

1. As described above, the prior taxane subgroup was derived from the Cohort A+B FAS of the PROfound study and used in the subsequent stages of the analysis:

    a. rPFS data for this subpopulation were used directly.

b. The counterfactual OS data were used after adjusting for treatment switching in the investigator's choice of NHA arm to olaparib. The counterfactual data was generated using the RPSFTM approach described in Section B.2.7.2. This adjustment was considered appropriate due to the high proportion of patients randomised to the investigators' choice of NHA arm of PROfound who switched to olaparib treatment after BICR-confirmed disease progression, as described previously.

2. Next, an assessment was conducted in the Cohort A+B prior taxane group to ascertain the extent to which the covariates available for matching were only prognostic, versus being *potential* effect modifiers for rPFS or OS, **and to guide the choice of ITC methodology** (i.e. unadjusted Bucher ITC or PAIC). This was conducted using multivariable cox regression with an interaction term between the randomised group and baseline variable to test for evidence of a statistically significant modification effect, with significance levels conservatively set at 80% so as not to exclude covariates that may be clinically important. The results of this analysis are described in Section and determined the next steps for the ITC.

All analyses were conducted using R® version 3.6.1.[99] Kaplan–Meier data in the CARD study were digitised using the methods of Guyot *et al*. 2012.[100]

B.2.9.2.3 Identification of effect modifiers

The full list of covariates published in the de Wit *et al*, 2019[67] publication (CARD) were considered for matching. The variables available in PROfound were assessed against this list to determine the comparability of the data and therefore the feasibility of matching. Factors available for matching were assessed for effect modification, as summarised in Table 13.

In accordance with NICE DSU TSD 18 guidance on anchored PAICs, only effect modifiers should be considered for adjustment; therefore, it was necessary to exclude any factors that were deemed to be prognostic only. The list of covariates (summarised in Table 13) was assessed by an AstraZeneca medical oncologist with experience in prostate cancer, who identified four factors that are prognostic factors

only (i.e. not effect modifiers), and thus should be excluded from consideration for the matching process, per NICE DSU guidance. This included neutrophil count per mm^3, haemoglobin (g/L), alkaline phosphatase (IU/L), lactate dehydrogenase (IU/L), previous NHA (abiraterone). the remaining list of covariates (age, ECOG score [0-2], presence of lung or liver metastases*, mean baseline PSA level [ng/ml], M1 disease at diagnosis and Gleason score [8-10]) were then tested for evidence of effect modification at the 80% significance level, focusing on OS.

- Effect modifiers for OS were tested in the analysis since it is the main endpoint routinely used to demonstrate superiority of antineoplastic therapies and the most-important driver of cost-effectiveness (over a lifetime horizon) in the advanced mCRPC setting. It would be expected that the findings for OS would also be applicable for rPFS.

- The significance level was set to 80% (rather than the conventional 95% level), to maximise chances of identifying any variables that could be *potentially* effect modifying.

Table 13. Summary of the covariates available for testing for effect modification

Variable available for matching	Considered for testing	Justification for exclusion (if appropriate)
Age	Yes	–
ECOG score (0-2)	Yes	–
Presence of visceral disease*	Yes	–
Mean baseline PSA level (ng/ml)	Yes	–
M1 disease at diagnosis	Yes	–
Gleason score (8-10)	Yes	–
Neutrophil count per mm^3	No	Identified as prognostic factor only (not effect modifier) by internal AstraZeneca Medical Oncologist, with experience in treating patients with mCRPC
Haemoglobin (g/L)	No	
Alkaline phosphatase (IU/L)	No	

Lactate dehydrogenase (IU/L)	No	
Previous NHA: abiraterone*	No	Due to differences in reported it was not possible to test or match on this variable (further clarification below)*

* Further details provided below.

Clarification around two variables (previous abiraterone treatment and visceral disease) noted in the Table above are as follows:

- Previous abiraterone treatment could not be tested appropriately as an effect modifier, due to differences in reporting across the PROfound and CARD trials. In the CARD study, data are only reported for the previous NHA treatment and separately for abiraterone and enzalutamide (it was not clear if one or more patients had received both NHAs). In contrast, in the PROfound study data were collected and reported for ≥1 prior treatment with abiraterone, enzalutamide, or abiraterone and enzalutamide.

- The reporting of visceral disease in both studies differed but was included for purposes of matching. In CARD, patients with visceral disease patients were categorised as follows: any patient with liver metastases was categorised as having liver metastases even if they had other metastatic sites; patients with lung metastases were denoted as having lung metastases, unless they also had liver metastases; and all other patients with visceral disease were categorized as having non-hepatic, non-pulmonary visceral metastases (such as adrenal, kidney, and others). In PROfound, visceral disease was not reported separately by liver, lung and other visceral metastases. Therefore, it was assumed all patients with visceral metastases in the CARD study had liver and/or lung metastases, and that it was appropriate to match with all visceral disease in the PROfound study. This assumption was considered reasonable by the AstraZeneca medical oncologist.

The results of the effect modifiers assessment for the treatment switching-adjusted OS endpoint are presented in Table 14 and show that:

- There are no significant effect modifiers for OS at the 80% significance threshold. Therefore, a Bucher **ITC,[101] unadjusted for variables**, is the most appropriate and reliable for estimating the relative efficacy of olaparib against cabazitaxel.

- Age and PSA could be considered a prognostic factor for OS based on statistical significance, but not an effect modifier as the interaction term was not significant at the 80% level.

In the absence of evidence to support effect modification, a PAIC is not expected to lead to a reduction in bias, and may only serve to introduce uncertainty via "over-matching" in the estimates of relative efficacy (as noted in the NICE DSU guidance).

Table 14. Assessment of effect modifiers for switching adjusted anchored analysis.

Covariate	Factor (OS switching-adjusted)	Interaction (OS switching-adjusted)
	** = statistically significant, may be interpreted as prognostic factor	** = statistically significant, may be interpreted as effect modifier
Age	[redacted]	[redacted]
Visceral disease	[redacted]	[redacted]
M1 disease at diagnosis	[redacted]	[redacted]
Gleason 8-10	[redacted]	[redacted]
ECOG 0-1	[redacted]	[redacted]
PSA*	[redacted]	[redacted]

*Binary covariate was used for modelling

**Covariate was significant at 80% level

B.2.9.3 Indirect comparison results

As outlined above, an **unadjusted ITC** is the most appropriate and reliable method for estimating the relative efficacy of olaparib against cabazitaxel, in the absence of any confirmed effect modifiers. The results of the unadjusted ITC show that olaparib is associated with rPFS and OS benefit versus cabazitaxel ([redacted]) and OS ([redacted] as described below.

B.2.9.3.1 rPFS

The proportional hazards assumption in the PROfound and CARD studies was assessed by visual inspection of the log-cumulative hazards plots and the Schoenfeld plots, and conducting Schoenfeld individual tests. Visual inspection of the log-cumulative hazards plots for rPFS indicates that proportional hazards assumption holds in both studies. This is further confirmed by the Schoenfeld individual tests, which resulted in p-values of 0.74 and 0.75 in the PROfound and CARD studies, respectively, indicating that there was no evidence against the null hypothesis of proportional hazards at the 95% significance level. Log-cumulative hazard plots and Schoenfeld plots for PROfound and CARD rPFS data are presented in Figure 19 and Figure 20, respectively.

Figure 19: PROfound rPFS: Schoenfeld (left) and log-cumulative hazards (right) plots

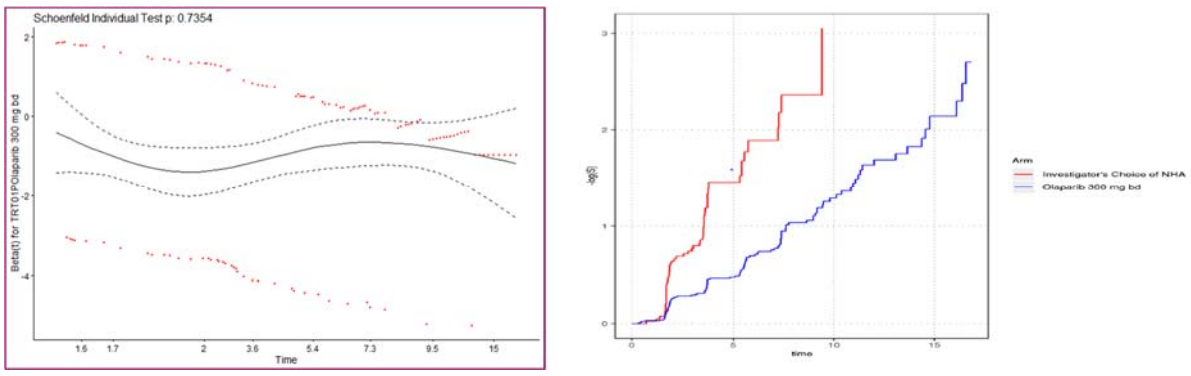
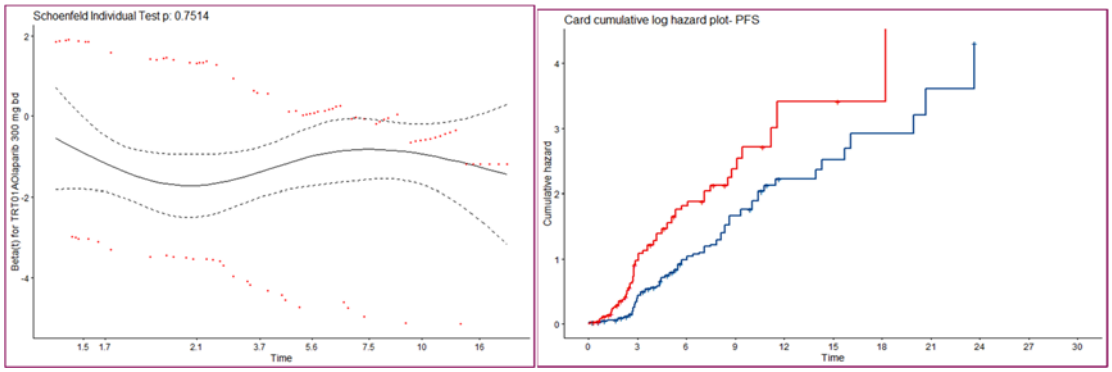


Figure 20: CARD rPFS: Schoenfeld (left) and log-cumulative hazards (right) plots



Since the proportional hazards assumption was determined to hold across both the PROfound and CARD trials, the Bucher *et al.* method[101] was considered appropriate for conducting the ITC.

The unadjusted ITC was conducted by calculating the hazard ratios from the PROfound prior-taxane IPD and the recreated IPD from the digitised Kaplan Meier data in CARD. In the ITC analysis for rPFS:

- The hazard ratio for olaparib versus investigator's choice of NHA in the PROfound Cohort A+B prior taxane subgroup was [redacted]
- The hazard ratio for cabazitaxel versus investigator's choice of NHA, generated from the recreated IPD data from the CARD study, was [redacted]
- The hazard ratio for **olaparib versus cabazitaxel was** [redacted] **for rPFS**.

B.2.9.3.2 OS

For OS, the proportional hazards assumption was assessed using the same approach as for rPFS. The log-cumulative hazards and Schoenfeld plots for the PROfound and CARD studies are presented in Figure 21 and Figure 22, respectively.

Visual inspection of the log-cumulative hazards plots for OS indicates that proportional hazards assumption holds in both studies. This is further confirmed by the Schoenfeld individual tests, which resulted in p-values of 0.27 and 0.94 in the PROfound and CARD studies, respectively, indicating that there was no evidence against the null hypothesis of proportional hazards at the 95% significance level. Therefore, the evidence of proportional hazards across both studies and rPFS/OS endpoints supports the use of constant hazard ratios to generate comparative evidence for olaparib and cabazitaxel.

Figure 21. PROfound OS: Schoenfeld (left) and log-cumulative hazards (right) plots

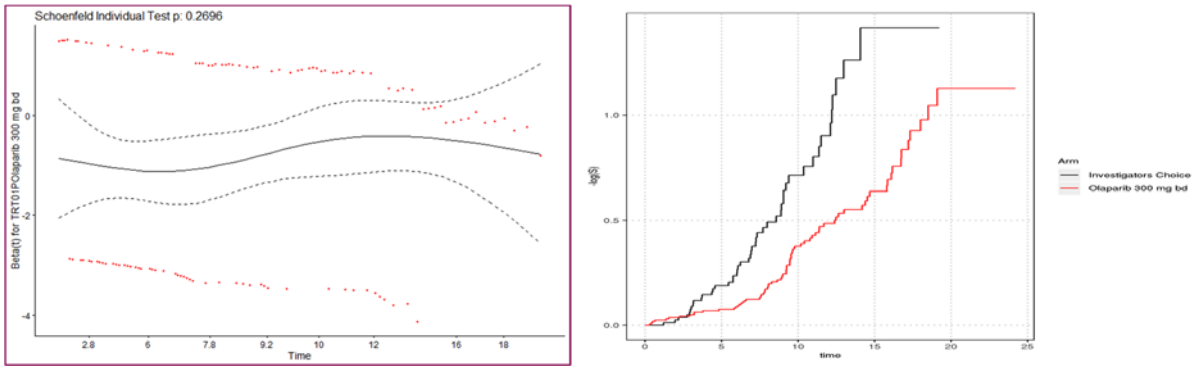
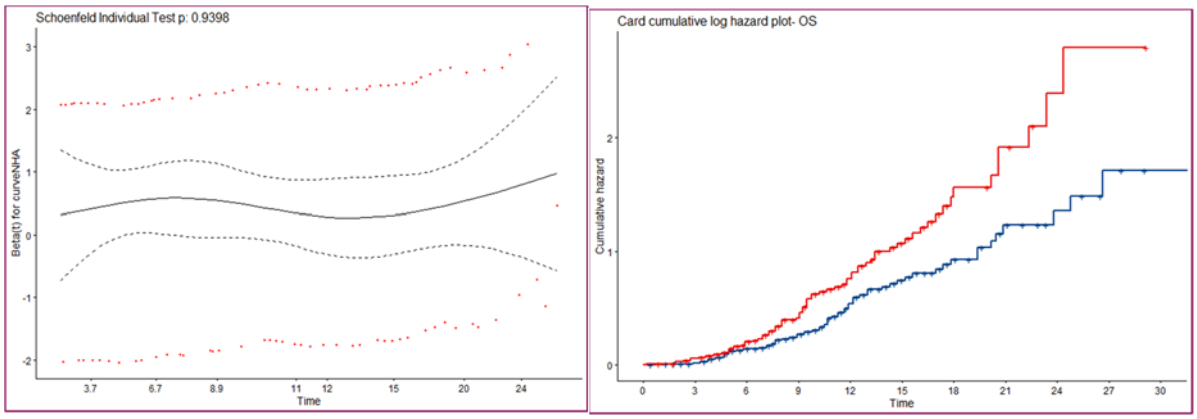


Figure 22. CARD OS: Schoenfeld (left) and log-cumulative hazards (right) plots



In the ITC analysis for OS:

- The hazard ratio for olaparib compared with investigator's choice of NHA in the PROfound Cohort A+B prior taxane subgroup was [redacted]..

- The hazard ratio for cabazitaxel versus investigator's choice of NHA, generated from the recreated IPD data from the CARD study, [redacted]

- The hazard ratio for **olaparib versus cabazitaxel was** [redacted]

B.2.9.3.3 Summary of results

The results of the unadjusted Bucher ITC are summarised in Table 15 and were used to inform the economic evaluation described in Section B.3. The use of constant hazard ratios was considered appropriate since the proportional hazards assumption was found to hold across both studies and no effect modifiers were identified. The results show that, in patients who have received prior taxane and progressed on NHA, **olaparib results in a** [redacted] **in disease progression, translating to a** [redacted] **in mortality compared with cabazitaxel**.

Table 15. Summary of results for rPFS and OS: Bucher anchored ITC olaparib versus cabazitaxel

	HR for rPFS (95% CI)	HR for OS (95% CI)
Bucher anchored ITC	[redacted]	[redacted]

CI, confidence interval; HR, hazard ratio; PFS, progression-free survival; OS, overall survival.

B.2.9.4 Strengths and limitations

The anchored Bucher ITC described in this section is the optimal methodology for comparison using the available data, i.e. patient-level data from the PROfound study and aggregate data from the primary publication of the CARD study. Since no treatment effect modifiers were identified in the analysis, an unadjusted ITC approach was deemed preferable to a PAIC and in accordance with NICE DSU guidance.

For OS, the unadjusted ITC approach represents the most parsimonious approach and closest to the pre-specified analyses from the original study and CSR, with no loss of precision/sample size; it would be expected that the same principles would

hold for rPFS. Additionally, for OS the unadjusted ITC approach accounts for treatment switching without explicit loss of precision/sample size. The ITC utilised the switching-adjusted (counterfactual) investigators' choice of NHA OS data from the prior taxane group of Cohort A+B of the PROfound study, which adjusted for the subsequent use of olaparib in the investigators' choice of NHA arm. These data were deemed necessary to use as there was a clear confounding impact of subsequent use of olaparib on OS in the NHA arm of PROfound. Additionally, olaparib is not licensed or reimbursed in this treatment setting in the UK; therefore, adjusting for treatment switching (to olaparib) is a necessary step to better reflect outcomes on clinical practice (unlike cabazitaxel, which is a reimbursed treatment). Without adjusting for treatment-switching, the ITC analysis would not be informative for decision making purposes.

B.2.10 Adverse reactions

All patients who were randomised to the PROfound study and received at least one dose of randomised study treatment in Cohort A or B were included in the **safety analysis set** (SAS) in their respective cohorts.[61] Safety data captured on patients receiving investigators' choice of NHA who subsequently switched to olaparib upon disease progression were summarised as per the treatment at the time of the onset of safety condition or lab result and reported in the **safety switch analysis set** (see Section 12, pages 237−280 of the PROfound Clinical Study Report, version 1, 23 October 2019).[61]

Overall, the safety and tolerability profile of olaparib in PROfound was consistent with the known safety and tolerability profile of olaparib and considered to be acceptable in this patient population. The most common AEs (reported by ≥20% of patients) in the olaparib arm (anaemia, nausea, decreased appetite, fatigue and diarrhoea) were known adverse drug reactions associated with olaparib and could generally be managed through dose modifications. No new safety signals were identified.

A summary of treatment exposure and adverse events reported in PROfound study is provided in the following sections; further details are available in the PROfound CSR (Section 12).[61] Collectively these data, in conjunction with the efficacy analysis

presented in Section B.2.6, support a positive benefit-risk profile for olaparib in patients with mCRPC who have failed prior treatment with an NHA and have HRR gene mutations. The safety profile in the subgroup of patients who had received treatment with a prior taxane was consistent with analyses in the Cohort A+B safety analysis set. This is as expected, since prior treatments received are not expected to impact upon a patient's tolerability of study treatments.

A limitation of the data summarised below is that they do not provide comparative evidence versus cabazitaxel, the standard-of-care in England in this treatment setting. Since the mechanisms of action of olaparib and cabazitaxel are different, such analyses may be unreliable and inappropriate for use in decision-making. The most appropriate methodology for conducting an ITC (unadjusted comparison versus PAIC) is also difficult to determine since standard matching variables (such as patients characteristics) may not be relevant to the occurrence of AEs and other unidentified potentially effect modifying factors may exist. Although a formal comparator safety analysis of olaparib versus cabazitaxel was not conducted due to these factors, 6 UK clinical experts consulted to inform the company submission highlighted that, in their experience, olaparib has a manageable tolerability profile; in a minority of experts who compared their experience of olaparib tolerability with cabazitaxel (2 clinical experts), both confirmed that olaparib had a more manageable tolerability profile in real-world clinical practice.[102]

B.2.10.1 Exposure to treatment, DCO1 (4th June 2019)

Exposure data reported in this section relates to length of time on treatment with the study drug (olaparib or investigators choice of NHA). In Cohort A+B, the median total duration of exposure to olaparib was ~1.9 times longer than in the investigators' choice of NHA arm (7.5 months versus 3.9 months), consistent with the delayed time to radiological disease progression in the olaparib arm. A total of 20.3% of patients remained on treatment in the olaparib arm at 12 months.[61]

Any deviation from the planned bid dosing was captured as a dose reduction or interruption and a reason assigned. Dose reductions/interruptions included missed or forgotten doses, or modifications in response to an AE. In both arms of Cohort A+B, AEs were the most-common reason for dose interruption (occurring in 90 patients

[35.2%] in the olaparib arm versus 11 [8.5%] patients in the investigators' choice of NHA arm). Median relative dose intensity and percentage intended dose were >98% in both treatment arms, indicating that dose intensity was not affected by dose modifications.

Dose interruptions, reductions, or modifications were not separately analysed for the prior taxane subgroup of Cohort A+B; the total and actual treatment duration in the subgroup was similar to the overall Cohort A+B population. These data are summarised in Table 16.

Table 16. Summary of treatment exposure, dose interruptions, and dose modifications: Cohort A + B SAS and prior taxane subgroup, DCO1 (4th June 2019)

	SAS		Prior taxane subgroup	
	Olaparib 300 mg bid (n = 256)	**Investigators' choice of NHA (n = 130)**	**Olaparib 300 mg bid (n = 170)**	**Investigators' choice of NHA (n = 83)**
Duration of treatment (days), median (range)				
Total treatment duration[a]	227.0 (1-692)	119.5 (17-596)	[redacted]	[redacted]
Actual treatment duration[b]	214.5 (1-589)	119.0 (17-596)	[redacted]	[redacted]
Patients, n (%)				
Dose interruptions	111 (43.4)	21 (16.2)	[redacted]	[redacted]
Dose reductions	63 (24.6)	7 (5.4)	[redacted]	[redacted]
Dose modifications	120 (46.9)	24 (18.5)	[redacted]	[redacted]

[a]Total treatment duration = (last dose date – first dose date +1). Median days

[b]Actual treatment duration = (last dose date – first dose date +1) excluding dose interruptions. Median days

Patient E7602055 (investigators choice of NHA) had treatment exposure 42 days longer than reported as discontinuation date was misreported. Due to this error, the dose durations are incorrectly derived. As this error was reported for only 1 patient, this would have had a very small impact on the calculations for dose durations; therefore, the reported dose durations are considered largely representative of their true values.

AE, adverse event; bid, twice daily; NHA new hormonal agent; SAS safety analysis set.[61]

B.2.10.2 Adverse events, DCO1 (4th June 2019)

The patients experiencing AEs in any category in Cohort A+B SAS and the prior taxane subgroup are summarised in Table 17. The majority of patients experienced 1 or more AEs during the course of the study. The incidence of AEs was similar in both treatment arms and across the full SAS and the prior taxane subgroup. The most common AEs in the olaparib arm (reported by ≥20% of patients) were anaemia, nausea, decreased appetite, fatigue and diarrhoea, which are known adverse drug reactions (ADRs) associated with olaparib treatment (data not shown; see Table 74 [Section 12.2.2.] of the CSR for details). These AEs were generally managed using olaparib dose modification; most AEs did not lead to treatment discontinuation (Table 17).

Further information on AEs leading to dose interruptions, reductions, or discontinuation of study treatment, AE of CTCAE Grade 3 or above, SAEs, and fatal AEs in the Cohort A+B SAS are provided in Section 12.2 of the PROfound CSR. Briefly:

- AEs leading to dose interruption occurred in 44.9% of olaparib-treated patients; the most common AEs leading to dose interruption in the olaparib arm (reported in ≥5% of patients) were anaemia (25.0%) and thrombocytopenia (5.5%). The majority of AEs of anaemia or thrombocytopenia were managed with dose reductions or temporary dose interruptions. Reported events of thrombocytopenia rarely led to permanent discontinuation of study treatment in the olaparib arm (2% of patients); AE of anaemia led to discontinuation of study treatment in 7% of patients in the olaparib arm.
- AEs of CTCAE Grade ≥ 3 were reported in 50.8% of olaparib-treated patients. Anaemia was the only AE of CTCAE Grade ≥ 3 reported in ≥ 5% of patients. Anaemia was also the most-common SAE in the olaparib arm, reported in 22 (8.6%) patients.
- Just 7 patients in the olaparib arm had Grade 4 AEs (lung infection and septic shock [both in 1 patient], pulmonary embolism [1 patient], respiratory failure and sepsis [both in 1 patient] and thrombocytopenia [4 patients]); two of the patients also had Grade 5 AEs.

- There were 15 fatal AEs (10 patients [3.9%] in the olaparib arm and 5 patients [3.8%] in the investigators' choice of NHA arm) during study treatment or 30-day follow-up. Two patients (1 patient in the olaparib arm [lung infection and neutropenia] and 1 in the investigators choice of NHA arm [pleural effusion]) had AEs with an outcome of death that were considered by the investigator to be causally related to study treatment.

The safety profiles of the prior taxane subgroup was comparable with the Cohort A+B SAS, with a similar proportion of Grade 3 and above AEs and SAEs in the two populations.

The frequency of AEs in the safety switch analysis set was similar to those randomised to receive olaparib (described above); these data are described in detail is Section 12.6 of the PROfound CSR.

Table 17. Adverse events in any category, DCO1 (4th June 2019) in Cohort A+B SAS/prior taxane subgroup.

	SAS		Prior taxane subgroup	
	Olaparib 300 mg bid (n = 256)	**Investigators' choice of NHA (n = 130)**	**Olaparib 300 mg bid (n = 170)**	**Investigators' choice of NHA (n = 83)**
Number (%) of patients[a]				
Any AE	244 (95.3)	114 (87.7)	[redacted]	[redacted]
Any AE, causally related to study treatment[b]	206 (80.5)	61 (46.9)	[redacted]	[redacted]
Any AE of CTCAE Grade 3 or higher	130 (50.8)	49 (37.7)	[redacted]	[redacted]
Any AE of CTCAE Grade 3 or higher, causally related to study treatment[b]	78 (30.5)	12 (9.2)	[redacted]	[redacted]
Any AE leading to death	10 (3.9)	5 (3.8)	[redacted]	[redacted]
Any SAE including those leading to death	91 (35.5)	36 (27.7)	[redacted]	[redacted]
Any AE leading to discontinuation	46 (18.0)	11 (8.5)	[redacted]	[redacted]
Any AE relating to dose reduction	57 (22.3)	5 (3.8)	[redacted]	[redacted]

Any AE relating to interruptions	115 (44.9)	24 (18.5)	[redacted]	[redacted]

[a] Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category were counted once in each of those categories.
[b] As assessed by the investigator.
Includes AEs with an onset date on or after the date of first dose and up to and including 30 days following discontinuation of randomised treatment or the day before switching to olaparib.
AE adverse event; bid twice daily; CTCAE Common Terminology Criteria for Adverse Events v4.03; DCO data cut-off; MedDRA Medical Dictionary for Regulatory Activities; NHA new hormonal agent; SAE serious adverse event; SAS safety analysis set.[61]

B.2.11 Ongoing studies

There are no ongoing studies relevant to the decision problem for this appraisal. The data cut-off for the final OS analysis of the PROfound study (DCO2) was on 20th March 2020. Top-line OS results from this data-cut are included in Sections B.2.6.3.1 and B.2.7.3;[31] further analyses including a treatment switch-adjusted analysis of OS and an anchored ITC versus cabazitaxel are currently underway and will be provided to NICE as soon as possible (as agreed during the decision-problem meeting on 17th March 2020).

B.2.12 Innovation

Olaparib is the only <u>targeted</u> therapy to have demonstrated a clinically-meaningful improvement in **both rPFS and OS in a Phase III RCT** versus investigators' choice of NHA, in mCRPC patients with qualifying HRR gene mutations, whose disease has progressed after treatment with an NHA.

Key data from the interim analysis of the PROfound study (which forms the basis of the company submission) were presented at the **Presidential Symposium** of the 2019 European Society of Medical Oncology (ESMO) Annual Congress (Barcelona, Spain).[64] Professor Maha Hussain, who presented these data referred to the "*significant effect [of olaparib] on disease progression and other clinically relevant effects such as pain progression and objective response rate*" as being a "***remarkable achievement in such heavily pre-treated patients with prostate cancer***". She added that "*prostate cancer has lagged behind all other common solid tumours in the use of molecularly targeted treatment*" and that it is "*very exciting that now we*

[clinicians] can personalise an individual's treatment based on specific genomic alterations in their cancer cells."

Results of the anchored Bucher ITC described in Section B.2.9 show that treatment with olaparib is associated with a [redacted] versus cabazitaxel, the current standard-of-care for patients with mCRPC who have received a prior taxane (for HSPC), and whose disease has progressed after treatment with an NHA ([redacted]; Section B.2.9.3.1). Treatment with olaparib was also associated [redacted] versus cabazitaxel ([redacted];Section □).

22.3% of patients in the olaparib arm of Cohort A+B were still on study treatment at the time of DCO1 (4th June 2019), providing hope for a sustained long-term response to treatment for at least a subset of patients, thus addressing a key unmet need in this setting.

In addition to extending survival, treatment with olaparib is associated with relevant and meaningful patient benefits, such as delayed time to pain progression, a significant cause of morbidity in patients with mCRPC (Section B.1). Olaparib also represents an alternative to cytotoxic chemotherapy with cabazitaxel, an important consideration since many men are unable to access chemotherapy and/or unwilling to undergo further chemotherapy at this stage of their lives.[103] Olaparib is also an oral treatment that can be taken at home, thus negating the need for patients to travel to hospitals for their infusion (as with cabazitaxel) and freeing capacity/resources for the NHS. These important benefits of olaparib represent further value to patients and the healthcare system beyond that which is captured in the QALY.

Finally, it is worth mentioning that a significant part of olaparib's clinical development programme was based in the UK and championed by UK scientists and clinicians. Phase II studies of olaparib in patients with mCRPC (TOPARP-A and TOPARP-B) were sponsored by The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust and funded by Cancer Research UK and AstraZeneca.

Professor Paul Workman, Chief Executive at The Institute of Cancer Research, said the following regarding results from the TOPARP-B study: "*Precision medicines targeted to specific genetic faults are transforming treatment for many different cancers, and with this new research it looks like we will soon be able to add prostate cancer to that list.* ***It's exciting to see a drug which the ICR helped pioneer having such widespread benefits for both women and men with cancer***".

Olaparib was granted **Breakthrough Therapy Designation** by the US Food and Drug Administration (FDA) in January 2019 for the treatment of *BRCA*1/2- or *ATM* gene-mutated mCRPC in patients who have received a prior taxane-based chemotherapy and at least one NHA (abiraterone or enzalutamide), based on the positive results of the TOPARP-A Phase II trial, which informed the PROfound trial. It was approved by the US FDA on the 19th of May 2020 as a treatment option "*for adult patients with deleterious or suspected deleterious germline or somatic HRR gene-mutated mCRPC, who have progressed following prior treatment with enzalutamide or abiraterone*" after being granted a priority review in January 2020.[104,105]

B.2.13 Interpretation of clinical effectiveness and safety evidence

B.2.13.1 Principle findings from the evidence base

B.2.13.1.1 Efficacy and HRQoL

The PROfound study met its primary endpoint in the interim analysis (DCO1, 4th June 2019), demonstrating a statistically-significant and clinically-meaningful improvement in rPFS (by BICR) for olaparib versus investigators' choice of NHA in patients with mCRPC and qualifying mutations in *BRCA1*, *BRCA2*, or *ATM* genes (Cohort A), who have who have failed prior treatment with an NHA (HR, 0.34, 95% CI, 0.25–0.47; $p < 0.0001$).

The study also met its secondary endpoint of rPFS (by BICR) in the overall population of patients with qualifying mutations in any of the 15 prespecified HRR genes (Cohort A+B), demonstrating a remarkable 51% reduction in the risk of radiological disease progression or death versus investigators' choice of NHA (HR, 0.49, 95% CI, 0.38–0.63; $p < 0.0001$). An rPFS benefit in favour of olaparib (versus investigators' choice of NHA) was observed across the pre-specified subgroup

analyses, which were conducted to assess the consistency of treatment effect across potential/expected prognostic baseline characteristics (such a previous taxane use or metastases at baseline [bone, visceral, other]), with olaparib treatment reducing the risk of radiological disease progression or death by 23% to 88% (Appendix E).

In the prior taxane subgroup, which is reflective of the real-world population of patients anticipated to receive olaparib in UK clinical practice,[c] olaparib reduced the risk of radiological disease progression or death by 61% compared with the investigators' choice of NHA (median rPFS, 5.8 months vs 2.6 months; Section B.2.7). Although the PROfound study was not powered to assess the efficacy of olaparib versus investigators' choice of NHA in this population, prior taxane use was a stratification factor in the study, ensuring balanced distribution of patients between olaparib and investigators' choice of NHA arms, and maintaining the robustness of this analysis.

rPFS data in the overall study population (Cohort A+B) and the prior taxane subgroup are also supported by the OS analysis, which showed a clinically meaningful reduction in the risk of death (HR, 0.67 [95% CI, 0.49–0.93) and HR, 0.61 [95% CI, 0.43-0.88], respectively), despite the majority of eligible patients (84.6% in Cohort A+B) crossing from investigators' choice of NHA to olaparib upon BICR-assessed rPFS progression (interim OS analysis; DCO1). The use of olaparib after investigators' choice of NHA confounds the OS analysis, biasing the results in favour of the comparator arm and underestimating the true OS benefit of olaparib treatment. A treatment-switching analyses using RPSFTMs were thus conducted in line with NICE DSU TSD 16 to adjust for treatment switching in Cohort A+B as well as the prior taxane subgroup. These analyses demonstrated an unprecedented OS benefit for olaparib versus investigators' choice of NHA in both populations (HR, [redacted] and [redacted], respectively).

The OS benefit was maintained in the final OS analysis (DCO2), with olaparib reducing the overall risk of death versus investigators' choice of NHA by [redacted]

[c] Since the majority (~75%) of patients receive docetaxel (a taxane) in combination with ADT for HSPC, prior to receiving an NHA for mCRPC.

[redacted] in the overall Cohort A+B population and the prior taxane subgroup, respectively [redacted] despite most patients in the investigators' choice of NHA arm switching to olaparib treatment after BICR-confirmed disease progression. Further analyses of these data are currently underway.

In the anchored Bucher ITC described in Section B.2.9, treatment with olaparib [redacted] versus cabazitaxel, the current standard-of-care for patients with mCRPC who have received a prior taxane (for HSPC), and whose disease has progressed after treatment with a NHA ([redacted], Section B.2.9.3.1). Treatment with olaparib was also associated [redacted] versus cabazitaxel ([redacted]; Section □), supporting its positioning as a new standard-of-care for patients with mCRPC and qualifying HRR gene mutations, whose disease has progressed after treatment with prior taxane and NHAd.

Importantly, [redacted]. Instead, treatment with olaparib resulted in meaningful benefits to patients (versus investigators' choice of NHA) in the form of delayed time to deterioration in FACT-P Total and all subscale scores in the overall study population (Cohort A+B), as well as delayed time to pain progression (HR, 0.64, 95% CI, 0.35–1.21), delayed time to first opiate use [redacted], and delayed time to first symptomatic skeletal-related event [redacted], which are significant causes of morbidity in patients with mCRPC. In the subgroup of patients with bone metastases only, olaparib reduced the risk of radiographic disease progression or death by 43% (see Appendix E for details).

[d] It is worth reiterating that while the prior taxane subgroup is the focus of this submission (aligned to the anticipated positioning of olaparib for the majority of mCRPC patients, who currently receive a taxane [docetaxel] earlier in the treatment pathway, prior to NHA), treatment with olaparib is also effective in those patients who have not received a prior taxane (rPFS HR = 0.77, 95% CI, 0.50-1.22 Cohort A+B).

B.2.13.1.2 Safety and tolerability

The median total duration of exposure to olaparib (7.5 months) was consistent with the median duration of BICR-assessed rPFS in the olaparib arm (Cohort A+B SAS). The high relative dose intensity and percentage intended dose of > 98% indicated that most patients were able to take the full dose of olaparib.

Overall, the safety and tolerability profile of olaparib in PROfound was consistent with the known safety and tolerability profile of olaparib. The most commonly-reported AEs in the olaparib arm (i.e. anaemia, nausea, decreased appetite, fatigue, and diarrhoea) were known ADRs for olaparib and could generally be managed through dose modifications. No new safety signals were identified.

Overall, the safety analyses showed that treatment with olaparib was well tolerated in patients with mCRPC. This is further corroborated by patient reported outcome (PRO) data, which show that treatment with olaparib had no detrimental impact on patients' HRQoL (relative to investigators' choice of NHA). Taken in the context of the substantial and sustained efficacy of olaparib in this setting, these data support a favourable risk-benefit profile for the use of olaparib in patients with mCRPC with qualifying HRR gene mutations, who have failed on previous NHA treatment.

B.2.13.2 Strengths and limitations of the evidence base

Strengths of the evidence base:

PROfound was a large, multicentre, randomised, prospective, Phase III, open-label study that provided comparative evidence for olaparib versus investigators' choice of NHA, in mCRPC patients with qualifying HRR gene mutations, who have previously failed treatment with NHA.[30]

The PROfound study was approved by the independent Institutional Review Board (IRB)/Independent Ethics Committee (IEC) associated with each study centre. It was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with International Council for Harmonisation (ICH)/Good Clinical Practice (GCP), applicable regulatory requirements, and the AstraZeneca policy on Bioethics. Quality of data was assured through monitoring of investigational sites, appropriate training for study personnel,

and use of data management procedures. In addition, an independent data monitoring committee was created to assess the safety of the study on a regular basis.

The **primary endpoint** of rPFS is widely-used in prostate cancer trials, and a clinically-relevant in prostate cancer. Owing to the open-label design of PROfound, rigorous methodology was employed to ensure robustness of the primary endpoint assessment, with the primary analysis of rPFS based on BICR-assessed of all radiological scans. The rPFS data are supported by a range of secondary endpoints, including PFS2 and OS, which consistently show a compelling clinical benefit in favour of olaparib (versus investigators' choice of NHA), despite the majority of patients switching over to olaparib after disease progression on NHA (see below).

Limitations of the evidence base:

In addition to the considerations involving comparators specified in the final NICE scope (Section B.1.4) and the need for treatment switching analysis (to adjust for patients switching from investigators' choice of NHA to olaparib confounding the OS analysis; Sections B.2.6.3.1 and B.2.7.2), the maturity of the interim OS analysis is also worth noting in relation to the clinical effectiveness evidence. At the time of the interim OS analysis (DCO1), OS data in the overall HRRm population of PROfound (i.e. Cohort A+B) was 41% mature. OS data maturity in the prior taxane subgroup was 48.0%.

The data-cut for the final OS analysis was on the 20 March 2020. OS data in the overall population (Cohort A+B) was 64% mature at the time of this analysis; further analyses of these data are currently underway and will be provided to NICE as soon as possible.

B.2.13.3 End of Life considerations

mCRPC represents an area of significant unmet need, with patients typically surviving less than two years from starting active treatment.

- In the COU-AA-301 study of abiraterone (plus prednisone) in patients with mCRPC whose disease had progressed after prior docetaxel treatment, a median OS of just 15.8 months was achieved with abiraterone treatment.[106]

- Similarly, in the AFFIRM trial of enzalutamide in mCRPC patients whose disease had progressed after prior docetaxel treatment, median OS of just 18.4 months was reported with enzalutamide treatment.[107]

The addition of cabazitaxel improved outcomes for those patients whose disease had progressed after receiving treatment with taxane and NHA (abiraterone, or enzalutamide), with a median OS of 13.6 months from the initiation of cabazitaxel treatment; however, life expectancy remains suboptimal with a need for new, life extending treatment options.

Data from the PROfound study directly show a clinically-meaningful OS benefit for olaparib versus investigators' choice of NHA, in mCRPC patients whose disease has progressed after treatment with a taxane and NHA, with a median [redacted] After adjusting for treatment switching, a survival gain of [redacted] was achieved for olaparib versus investigators' choice of NHA (using the RPSFTM preferred analysis).

In the anchored Bucher ITC versus cabazitaxel - the current standard-of-care in England and the relevant comparator for olaparib in mCRPC patients whose disease has progressed after treatment with taxane and NHA – olaparib was associated with [redacted]

In summary, treatment with olaparib offers a clinically-meaningful survival benefit (in excess of 3 months) versus the current standard-of-care, in a setting where usual life expectancy is less than 24 months or 2 years, thereby meeting the end-of-life criteria specified by NICE. These data are summarised in

Table 18 below.

Table 18. End-of-life criteria

Criterion	Data available
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	Median OS is just **13.6 months** after treatment with cabazitaxel, the most commonly-used treatment and current standard-of-care for mCRPC patients who have progressed after treatment with a taxane and NHA. [redacted]
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	Treatment with olaparib demonstrated a [redacted]

B.3 Cost effectiveness

B.3.1 Published cost-effectiveness studies

A total of four abstracts[108-111] were identified through systematic searching that reported on four independent cost-effectiveness analyses that estimated the relative cost of different sequences of taxanes and NHA in patients with mCRPC in Egypt,[108] Japan,[110] Russia[109] and Spain.[111] Full details of the SLR methodology and a summary of the literature identified are given in Appendix G.

Hand searches for previous HTAs and relevant economic assessments were also conducted. Based on a patient population with mCRPC who have experienced progression following an NHA no relevant evidence was identified. Despite this, previous NICE technology appraisals in the mCRPC indication were still considered, where relevant, to inform the approach taken in the cost-effectiveness analysis for olaparib. Based on the final NICE scope the following technology appraisals were considered potentially relevant (summarised in Table 20): TA391 (cabazitaxel),[41] TA412 and TA376 (radium-223 dichloride),[112] TA387[37] and TA259 (abiraterone),[113] TA377[38] and TA316 (enzalutamide),[114] TA101 (docetaxel).[115]

B.3.2 Economic analysis

As none of the publications identified by the SLR reported evidence specific to the UK, they were not considered relevant to this submission. Previous NICE technology appraisals in the broader mCRPC indication were still considered, where relevant, to inform the approach taken in the cost-effectiveness analysis for olaparib, even though they were not conducted specifically within the post-NHA setting.

B.3.2.1 Patient population

As described in section B.1.1, the anticipated EMA license for olaparib in this indication is [redacted]

In line with the decision problem and data limitations outlined in section 0 and section B.2, the cost-effectiveness analysis focused on the pre-specified prior taxane subgroup of the overall HRRm population (i.e., Cohort A+B) of PROfound. This subgroup aligns with the patient population with mCRPC who would be eligible to receive cabazitaxel in England and Wales, as cabazitaxel is only reimbursed for those patients whose disease has progressed during or after prior docetaxel treatment.[41] The prior taxane subgroup of PROfound included those patients who previously received at least one prior taxane-based treatment, and comprised approximately [redacted]% of the overall trial population. Prior taxane use (yes/no) was a stratification factor in the PROfound study, this ensuring balance between the treatment and comparator arms of the trial.

Table 19. Description of modelled patient population

Population	Description
HRRm (Cohort A+B) – Prior taxane	Patients with mCRPC and an HRR mutation whose disease progressed on an NHA (e.g. enzalutamide or abiraterone) and who, at baseline, had previously received at least one prior taxane-based treatment (docetaxel/cabazitaxel only) for prostate cancer Within the prior taxane subgroup of PROfound, the majority of patients ([redacted]) had received prior docetaxel only, [redacted] had received prior docetaxel and cabazitaxel. [redacted] of patients had

	received cabazitaxel only; this is not expected to have any impact on the analysis or the interpretation of the results. Further details are available in Section B.2.3.7.

HRR(m), homologous recombination repair (mutation); NHA, new hormonal agent; mCRPC, metastatic castration-resistant prostate cancer.

B.3.2.2 Model structure

A *de novo* economic model was developed in Microsoft Excel® to evaluate the cost-effectiveness of olaparib in the mCRPC setting. The cohort model follows a partitioned survival (or 'area-under the curve') approach with three health states (Figure 23):

- Stable disease (progression-free)
- Progressed disease
- Death

The partitioned survival model structure is a widely accepted approach that has been used in previous NICE health technology assessments across many oncology indications. The structure reflects the likely disease history of the patient population and is able to capture the key determinants of health and cost outcomes in a clear and simple manner. The model structure is flexible and is able to adequately quantify the primary objectives of treating patients with mCRPC: extending survival, delaying progression, and improving quality of life. The partitioned survival approach relies on the use of key endpoints (OS, rPFS) reported in clinical trials to estimate health and cost outcomes as described below.

Patients enter the model in the stable disease state and are assumed to be on treatment. At each model cycle, the number of patients in each independent and mutually exclusive health state is updated.

The stable disease state includes patients who are alive and whose disease has not yet progressed. Patients can either remain in the stable disease health state, progress, or die. At any model cycle the proportion of patients who are progression-free is represented directly from the rPFS curve for each intervention. Treatment-related costs, drug acquisition, drug administration and AE costs for each comparator are accrued based on the rPFS curve for each intervention (see Section

B.3.3.2 for further details). Monitoring costs associated with patients on treatment are also accrued.

The progressed disease state includes patients who are alive but whose disease has progressed. It is assumed that once patients have progressed they cannot return to the stable disease state; they can only transition into the death state. At any model cycle the proportion of patients with progressed disease is calculated as the difference between OS and rPFS (all patients who are alive who, but not progression-free). After progression, patients could receive subsequent treatment or best supportive care (BSC). These costs are accrued; however, no additional adjustment on survival is required as any impact of subsequent treatment is implicit in the OS data. Monitoring costs associated with patients who are alive but have discontinued treatment are accrued.

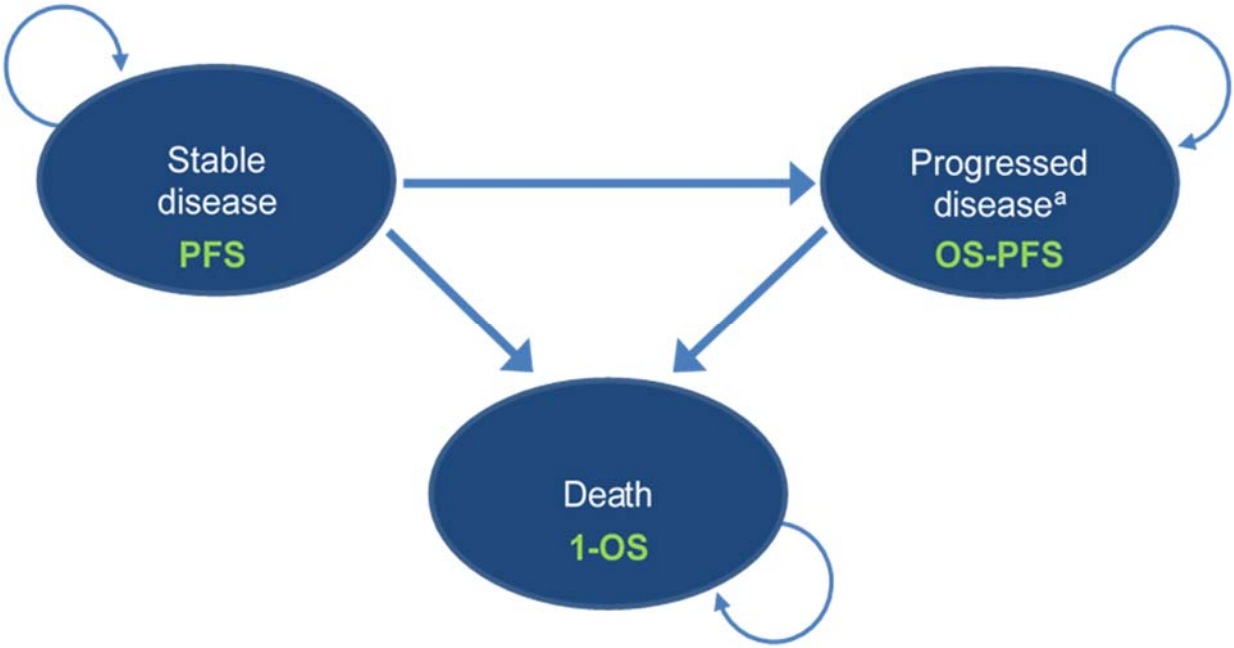
In the model, death is an absorbing state calculated as 1-OS; that is, all patients who are not alive. A one-off cost for end-of-life care is applied to patients who die at each model cycle.

Additionally, in line with standard practice for developing partitioned survival models in oncology, the following constraints are applied in the model to ensure logical patient flow at each cycle:

- The risk of death in the modelled population cannot be lower than the all-cause mortality of the UK general population at each model cycle, determined by published life tables.[116] This ensures that at any given cycle, the mortality risk of the modelled population is equal to or greater than that of the general population (matched on age [age at start of model equivalent to patients' mean age at baseline in the prior taxane subgroup of PROfound, 63.7 years] and gender).
- rPFS is constrained by OS, such that the number of patients who are progression-free cannot exceed the total number of patients alive.

Full details regarding modelling PFS, TTD and OS are presented in section B.3.3. Details regarding costs are described in section B.3.5.

Figure 23. Structure of the cost-effectiveness model



[a] Proportion of patients who have progressed calculated as the residual of OS and rPFS.
Health outcomes defined by rPFS and OS; in the base case analysis, cost outcomes are aligned with rPFS for patients who are on treatment and progression free, and PD (OS-rPFS) for patients who are alive but have progressed in the model.
1-OS, all patients that are not alive; OS, overall survival; rPFS, radiographic progression-free survival.

B.3.2.2.1 Justification of the chosen structure

The strengths of the partitioned survival approach are well-documented (NICE DSU TSD19).[117] As mentioned above, this approach is flexible, and is able to adequately quantify the primary objectives of treating patients with mCRPC, particularly as it is not necessary to model multiple lines of subsequent therapy given the limited treatment options for patients in the post-NHA setting. It directly uses trial-based time-to-event endpoints (OS, rPFS) and it is simple to incorporate indirect comparisons in the form of hazard ratios, where head-to-head trial data is not available.

The selected approach is consistent with previous appraisals relevant to this submission, as summarized in Table 20. The models developed in TA391 (cabazitaxel),[41] TA316[114] and TA377[38] (enzalutamide) and TA101 (docetaxel)[115] are believed to be incorrectly described as Markov models in the manufacturers' submissions; descriptions of the methods show that state occupancy in the

manufacturers' models were based on survival curves, following a partitioned survival model approach.[117]

Alternative model structures were considered; however, they were ultimately deemed less appropriate for addressing the decision problem, as discussed below:

- A patient-level discrete event simulation model may capture detailed changes along the clinical pathway more accurately (such as treatment pre- and post-docetaxel, and sequencing of subsequent lines of treatment), as in TA387 (abiraterone).[37] However, there were concerns with using the same model structure in the context of this appraisal. Patient-level simulations are more complex in nature and have additional data needs, often requiring access to individual patient-level data. Based on the limited amount of data available for the comparator, it would not be possible to simulate events other than first progression and death without introducing a significant amount of uncertainty into the model. Furthermore, no external data was identified to sufficiently validate patient-level model outcomes, other than rPFS/OS benefit, which are already modelled in a partitioned survival structure.
- Markov models require estimates of transition probabilities between health states. This process involves competing risks and multi-state modelling, consideration of selection effects and dependent censoring, and careful validation. In TA412[112] and TA376[118] (radium-223), the decision to develop a 5-health state Markov model was based on the need to explicitly model symptomatic skeletal-related event outcomes. This is an important measure for radium-223, due to the specific mechanism of action and population that radium-223 is indicated for (i.e. men with CRPC, symptomatic bone metastases and no known visceral metastases). Although the use of olaparib is not limited to patients with symptomatic bone metastases (efficacy has been observed regardless of the site of metastases at baseline), the importance of SREs for mCRPC patients with bone metastases in particular is acknowledged[119] and as discussed in section B.3.3.5. SREs can be considered in a partitioned survival structure in a clear and transparent way, without necessitating the use of a complex Markov structure.

B.3.2.3 Intervention technology and comparators

B.3.2.3.1 Intervention

The olaparib dosage is implemented in the economic analysis according to the anticipated European Marketing Authorisation for this indication, and the treatment regimen in the PROfound trial.[61]

The intervention is the tablet formulation of olaparib at the dose of 300 mg (2 x 150 mg tablets) taken twice daily, equivalent to a total daily dose of 600 mg, until disease progression or unacceptable toxicity (whichever occurred first).[61]

B.3.2.3.2 Comparators

In line with the decision problem stated in section 0 (Table 2), the most commonly-used and appropriate comparator for olaparib in current clinical practice (where the majority [~75%] of patients receive docetaxel with ADT for HSPC prior to an NHA, and radium-223 dichloride is received for later lines of treatment). This also aligns with where the evidence base allows for a robust ITC between the intervention and comparator of interest, thus minimising uncertainty and providing a meaningful analysis for decision-making purposes.

Cabazitaxel is administered at a licensed dose of 25 mg/m^2 every three weeks in combination with prednisolone 10 mg/day,[120] and for up to a maximum of 10 treatment cycles according to NICE guidelines (TA391).[41] The decision to limit treatment duration to a maximum of 10 cycles was based on the TROPIC study, a Phase III randomised open-label multicentre trial that compared cabazitaxel with mitoxantrone in men with mCRPC whose disease had progressed on or after treatment with docetaxel.

The key trial relevant to the current submission (i.e., in the post-NHA mCRPC setting) is the more recently conducted CARD study, which assessed cabazitaxel versus NHA after disease progression on NHA. It is worth noting that in CARD, cabazitaxel was administered until radiographic disease progression, unacceptable toxicity or patient's refusal of further study treatment. The range of treatment cycles received was 1 to 29 cycles, with a median of 7 cycles received.[67] The implications of various treatment duration assumptions is discussed further in Section B.3.3.3.

Cabazitaxel is administered with a specified premedication regimen per the SmPC. Clinical guidelines also recommend the concomitant use of primary prophylactic G-CSF to prevent neutropenia-related complications.[120] Cabazitaxel was administered in the CARD trial in accordance with this.

B.3.2.4 Perspective of the analysis

The economic evaluation takes an NHS/Personal Social Services (PSS) perspective, as per the NICE reference case. This includes drug acquisition and drug administration costs, costs associated with disease monitoring and resource use, adverse events, skeletal-related events, subsequent treatment and end-of-life care.

B.3.2.5 Time horizon

A lifetime horizon has been used, consistent with the NICE reference case. This is assumed to be 15 years given that the average age of patients in the prior taxane subgroup of PROfound was approximately 67 years at baseline,[61] (i.e. patients can live up to a maximum of 82 years of age). The time horizon is long enough to capture all important differences in costs or outcomes accrued over the lifetime of a patient with mCRPC while considering that a small minority of patients may respond exceptionally well to treatment in this setting, in line with clinical expert opinion (discussed in Section B.3.2.2).

B.3.2.6 Cycle length, half-cycle correction and discounting

The model cycle length is 1 month. This is short enough to accurately capture differences in cost or health effects between cycles. Half-cycle correction was applied to prevent under- or over-estimation of costs and quality-adjusted life years (QALYs). Half-cycle correction was not applied to direct drug acquisition and administration costs, since treatments are administered at the start of each cycle and costs would therefore be incurred at the start of each cycle regardless of the patient's movement thereafter, in line with previous submissions.[41]

The discount rate used for both costs and outcomes is 3.5% per annum, consistent with the NICE reference case.

Table 20. Features of the economic analysis

	Previous appraisals							Current appraisal	
Intervention	**Cab**	**Radium-223**	**Doc**	**Abiraterone**		**Enzalutamide**			
Factor	**TA391[121]**	**TA412/376[43]**	**TA101[115] [a]**	**TA387[37] Pre-ctx**	**TA259[113] Post-ctx**	**TA377[38] Pre-ctx**	**TA316[114] Post-ctx**	**Chosen values**	**Justification**
Model approach / structure	3 HS Markov cohort[b] (Partitioned survival)	5 HS Semi-Markov cohort	2 HS Markov cohort[b] (Partitioned survival)	Patient-level DES	3 HS Partitioned survival	3 HS Markov cohort[b] (Partitioned survival)	3 HS Markov cohort[b] (Partitioned survival)	3 HS Partitioned survival	Standard modelling approach and structure used widely in oncology. Flexible, and able to use key primary and secondary endpoints of the PROfound trial. Accepted in previous NICE technology appraisals for prostate cancer (TA259),[113] and appraisals for PARP inhibitors in other indications (ovarian cancer; TA620,[122] TA598[123]).
Time horizon	10 years	5 years (updated to 10 years)	15 years	Lifetime (up to age = 100 years)	10 years	10 years	10 years	15 years	To reflect all relevant costs and effects of treatment, believed to cover patients' lifetime.
Cycle length	3 weeks	1 week[c]	1 month	NA	3 weeks	1 week	3 weeks	1 month	Short enough to accurately capture differences in cost or health effects between cycles. The 1-month cycle length adequately reflects the duration of treatment cycles.
Half-cycle correction	Included	Excluded	NR	NA	Included	Included	Included	Included	Prevents under- or over-estimation of costs and QALYs.
Measure of progression	rPFS	PSA-PFS ALP-PFS[d]	N/A (not modelled)	TTD as proxy	TTD as proxy	TTD as proxy	TTD as proxy	rPFS	Primary outcome measure in PROfound and CARD, deemed most appropriate for patient population.

Treatment waning effect?	NA	NA	NA	NA	NA	NA	NA	NA	Consistent with other technology appraisals for prostate cancer, waning of treatment effect is not relevant when treating until progression.
Source of utilities	UK EAP for cab		Sandblom 2004 Volk 2004 Stewart 2005	UK mCRPC Patient utility study	COU-AA-301	AFFIRM	PREVAIL Sandblom 2004	PROfound	EQ-5D-5L data from the PROfound trial mapped to EQ-5D-3L utilities as recommended in the NICE reference case.
Source of costs	Standard UK databases (e.g., BNF, eMit, NHS schedule of reference costs, PSSRU)							Standard UK data bases	Best available sources relevant to the NHS setting in England; per the NICE reference case.

BNF, British National Formulary; Cab, cabazitaxel; Ctx, chemotherapy; DES, discrete event simulation; EAP, early access programme; ed, edition; EQ-5D, EuroQol 5-Dimension; eMIT, Drugs and pharmaceutical electronic market information tool; HS, health state; mCRPC, metastatic castration-resistant prostate cancer; PFS, progression-free survival; PPRS, PSA, prostate-specific antigen; PSSRU, Personal Social Services Research Unit; NA, not applicable; NICE, National Institute of Health and Care Excellence; NHS, National Health Service; NR, not reported; QALY, quality-adjusted life years; rPFS; radiologically confirmed progression-free survival; TTD, time to treatment discontinuation; UK, United Kingdom

[a] Based on the Assessment Group's report, as details of the manufacturer's submission are not available.[115]

[b] Incorrectly described as Markov models in the submission; the description of methods are actually consistent with a partitioned survival model approach.

[c] Assumed based on TA376 Committee Papers.[118]

[d] PFS as measured by PSA was also included however ALP- PFS was deemed the most appropriate measure of PFS for the decision problem.

B.3.3 Clinical parameters and variables

The clinical outcomes included in the economic analysis are listed below.

- Overall survival
- Radiographic progression-free survival
- Time to treatment discontinuation (scenario analysis only)
- Adverse events
- Skeletal-related events
- Health-related quality of life

B.3.3.1 Key efficacy data sources

A summary of the main efficacy data sources, analysed population and a description of assumptions needed to conduct the analysis is provided in Table 21. In general, safety outcomes were obtained from the same data source as the efficacy outcomes; however, in some cases (such as for specific AE- and SRE-inputs) it was necessary to obtain data from the literature. These are described in detail in the following sections of the submission.

B.3.3.1.1 Olaparib (PROfound)

The clinical outcomes used to inform the cost-effectiveness analysis were based on patient-level data from the Phase III pivotal study for olaparib, PROfound, at DCO1 (14th June 2019). The data used in the cost-effectiveness analysis for olaparib is based on the HRRm (Cohort A+B) prior taxane subgroup of PROfound as described in Section B.1.1, Section B.2.7 and Section B.3.2.1.

B.3.3.1.2 Cabazitaxel (CARD)

Clinical outcomes for cabazitaxel were based on published data as patient-level data from clinical trials were not available. The CARD[67] study was identified as the most relevant source of data for cabazitaxel, as discussed in section B.2.9. The efficacy outcomes (OS, rPFS) for cabazitaxel were estimated based on the anchored ITC results for olaparib versus cabazitaxel, in the absence of head-to-head trial data (as described in section B.2.9.). Safety outcomes were mainly sourced from the CARD study.[67,124]

Table 21. Summary of main clinical efficacy data sources for each intervention in the economic analysis.

Modelled population	Intervention	Key clinical data source	Trial population analysed	Rationale
mCRPC patients who have received prior treatment with a taxane and NHA	Olaparib	PROfound[61]	Prior taxane subgroup of overall HRRm population filtered (Cohort A+B)	• Pre-specified analysis subgroup in PROfound, and most relevant data for the decision problem and is aligned with the population of patients who would most likely receive olaparib in clinical practice in England based on the current treatment pathway in the UK.
	Cabazitaxel	CARD[67]	ITT; inclusion criteria required previous treatment with docetaxel	• Only source of evidence for efficacy and safety of olaparib in the post-NHA setting • Comparable to the PROfound study population (albeit not limited to patients with HRR gene mutations) • Included an NHA arm, allowing for an anchored ITC to be conducted on OS and rPFS as described in section B.2.9.

HRRm, homologous recombination repair mutation; ITC, indirect treatment comparison; ITT, intention-to-treat; mCRPC, metastatic castration-resistant prostate cancer; NHA, new hormonal agent; OS, overall survival; (r)PFS, (radiographic) progression-free survival.

B.3.3.2 Efficacy outcomes

Efficacy outcomes for olaparib were modelled based on time to event analysis of the patient level data from the PROfound trial. Outcomes for the cabazitaxel were modelled by applying the anchored ITC hazard ratios to the olaparib curves as the reference arm. Details regarding the ITC including an assessment of the proportional hazards assumptions are provided in section B.2.9 and Appendix D.

Methods for rPFS and OS are discussed first, followed by treatment duration (available for scenario analysis) in section B.3.3.2.

B.3.3.2.1 PROfound time to event analysis – olaparib

Given that the median duration of follow-up in the PROfound study was [redacted] months (olaparib arm)/[redacted] months (control arm),[61] and it is necessary to assess the cost-effectiveness of olaparib over a lifetime horizon, parametric survival analysis was

undertaken to extrapolate rPFS (section B.3.3.2.1.1), OS (section B.3.3.2.1.2) and TTD (scenario analysis; section B.3.3.3) to inform the cost-effectiveness model beyond the trial period. Outcomes were analysed based on patient-level data from the HRRm (Cohort A+B) prior taxane subgroup of PROfound.

Six standard parametric models were fitted to rPFS, OS and TTD data from PROfound (exponential, Weibull, log-normal, log-logistic, Gompertz, and generalised gamma).

The methods used to extrapolate outcomes followed the guidance outlined in NICE Decision Support Unit (DSU) Technical Support Documents (TSDs) 14[125] and 18.[96] However, the guidance focuses on situations where patient-level data are available for all interventions and economic analyses are undertaken on a single relevant trial. This is not applicable in this submission as the comparator arm of PROfound (NHA rechallenge) is not reflective of current UK practice for patients previously treated with NHA (Section 0) and was thus not included in this economic analysis.[114,126] Based on this, it is appropriate to extrapolate survival outcomes with olaparib based on the separately-fitted curves. The direct use of the separately-fitted curves to the olaparib arm data from PROfound represents the best use of the patient-level-data available for olaparib.

For each outcome, an assessment of the fitted models was conducted to determine which parametric survival models were most appropriate. The following factors were considered:

- Statistical goodness of fit (Akaike Information Criterion [AIC]/Bayesian Information Criterion [BIC])
  - The statistical fit of each curve was assessed by considering the total AIC and the BIC values.
- Visual fit to Kaplan–Meier plots
  - The goodness of fit of the parametric curves to the Kaplan–Meier data for olaparib was visually assessed, with consideration given to the entire trial period for which data were available.

- Clinical plausibility of model extrapolations for OS

  - External validation is greatly important in understanding the suitability of the extrapolated curves.[125] The plausibility of modelled overall survival estimates was validated against UK clinical expert opinion and published literature. This exercise was helpful for understanding the range of plausible outcomes that could be expected under the current standard of care (i.e. cabazitaxel), and to validate the survival extrapolations for olaparib.

Relevant and clinically plausible best fitting models were selected for the base case. Alternative models were considered in sensitivity analysis.

B.3.3.2.1.1 Radiographic progression-free survival (rPFS)

B.3.3.2.1.1.1 Olaparib (PROfound, DCO1 4th June 2019); HRRm (Cohort A+B) prior taxane subgroup

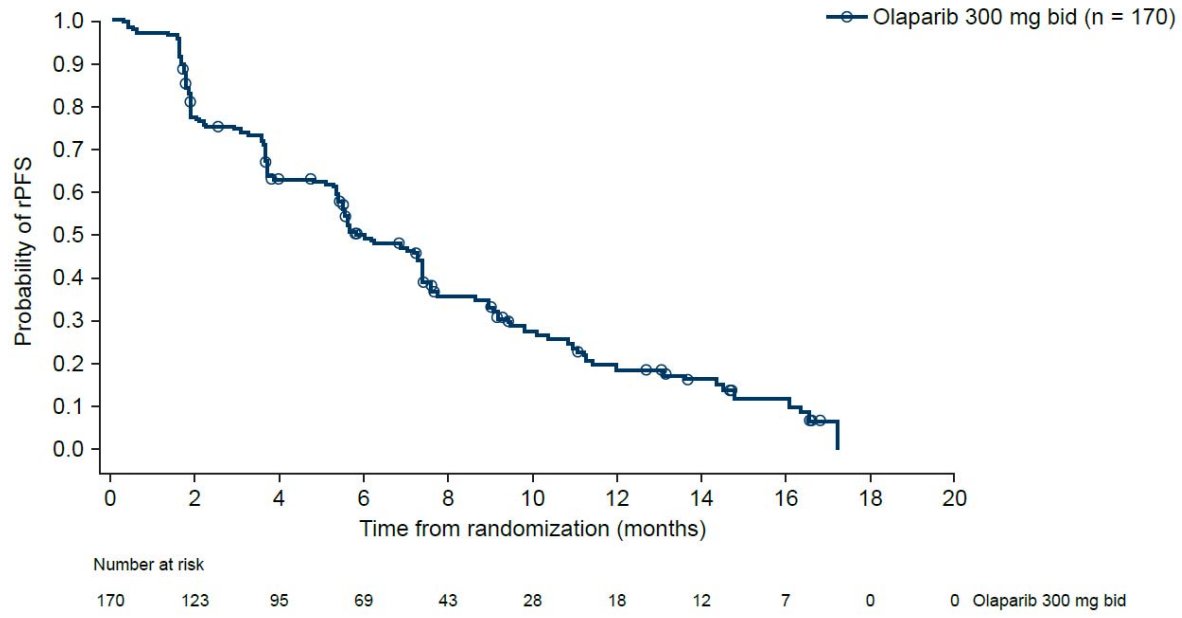
At DCO1, the rPFS data for the prior taxane subgroup of the overall HRRm (Cohort A+B) population in PROfound were relatively mature although not all patients had experienced an event (72.9% maturity, 124 events in 170 patients). These data are shown in Table 22.

Table 22. Number of events in the HRRm (Cohort A+B) prior taxane subgroup of PROfound.

Endpoint	Outcome	Olaparib 300 mg bid (n = 170)
rPFS	Events, n	124
	Maturity, %	72.9%

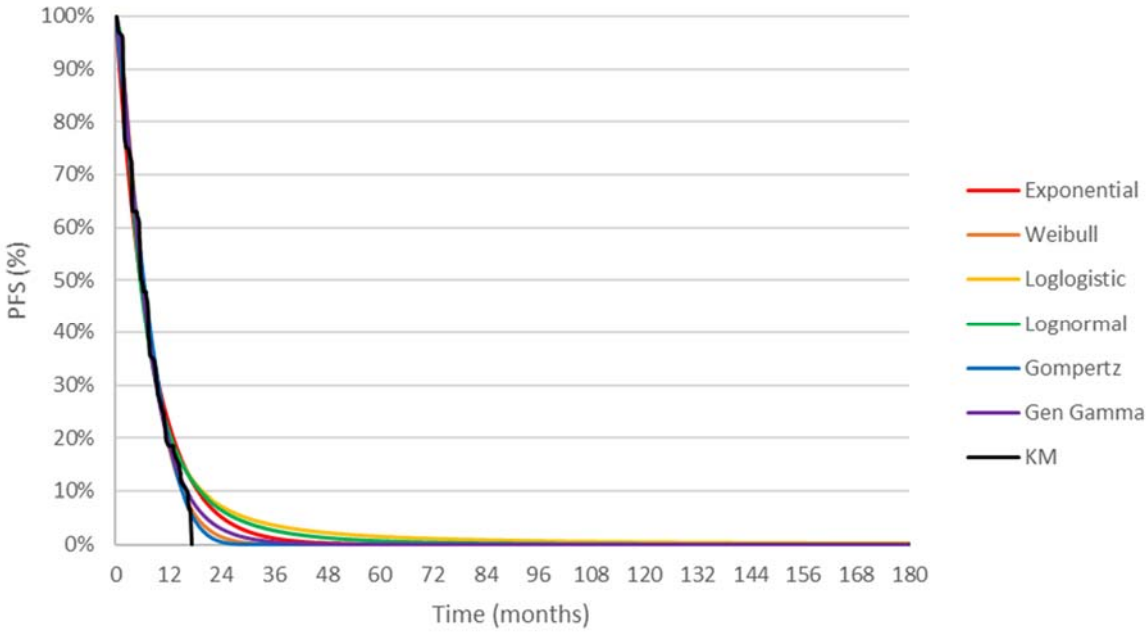
HRRm, homologous recombination repair; rPFS, radiographic progression-free survival.

Figure 24. Olaparib BICR rPFS, Kaplan–Meier plot (HRRm [Cohort A+B] – Prior taxane).



bid, twice daily NHA, new hormonal agent.

Figure 25. Modelled rPFS for olaparib based on PROfound (HRRm [Cohort A+B] – prior taxane).



Gen, generalised; KM, Kaplan–Meier; rPFS, radiographic progression-free survival.

The curves for the six parametric models fitted to the olaparib rPFS data (Cohort A+B, prior taxane subgroup) are shown in Figure 25. Based on a visual assessment of the separately-fitted parametric models, all distributions fitted reasonably well to the observed data, which is expected given the relative maturity of the Kaplan–Meier data for rPFS. Although there is some variation in the extrapolated outcomes, all distributions produced similar long-term outcomes for rPFS where <5% of patients are predicted to remain progression-free at 3 years.

According to the total AIC/BIC statistics (Table 23), the Weibull distribution was the best-fitting curve, and was thus used in the base case analysis. The generalised gamma distribution was the next best-fitting curve based on total AIC/BIC and was tested in scenario analysis.

Table 23. AIC and BIC values for parametric models for rPFS (HRRm [Cohort A+B] – prior taxane).

Distribution	AIC	BIC	Total
Exponential	768.5	771.6	1540.1
Weibull	756.3	762.6	1518.9
Loglogistic	760.2	766.5	1526.7
Lognormal	758.9	765.2	1524.1
Gompertz	761.3	767.6	1528.9
Gen gamma	756.7	766.1	1522.8

AIC, Akaike information criterion; BIC, Bayesian information criterion; bid, twice daily; Gen, generalised; HRRm, homologous recombination repair; rPFS, radiographic progression-free survival.

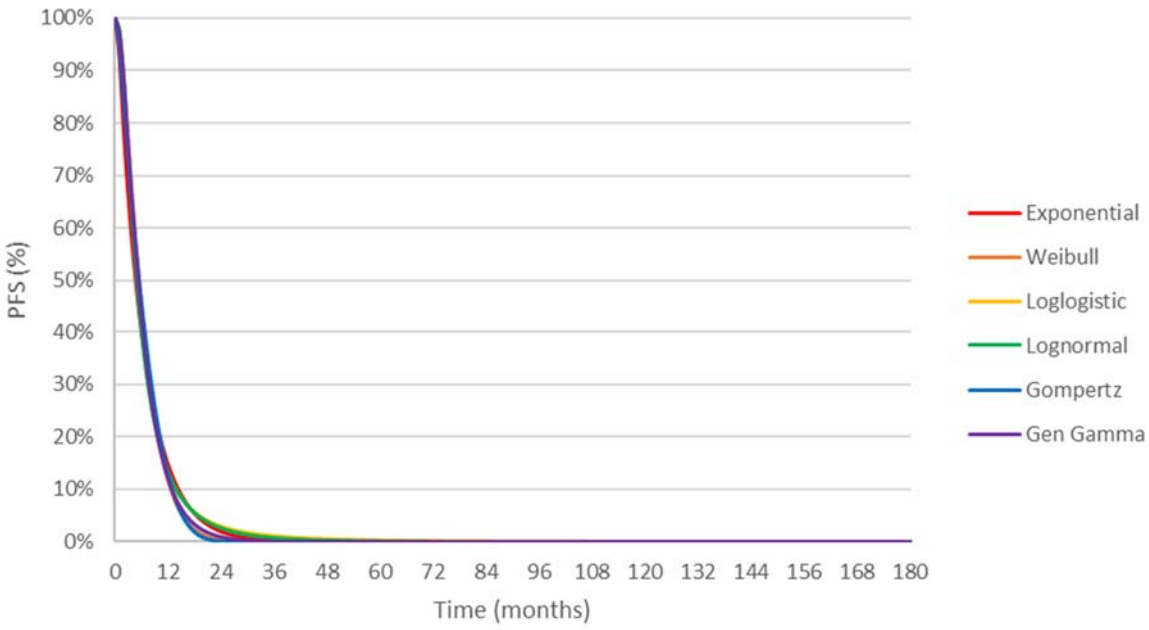
B.3.3.2.1.1.2 Cabazitaxel (anchored ITC HR applied to olaparib rPFS curve

In the absence of head-to-head trial data comparing olaparib with cabazitaxel, an anchored ITC was conducted to estimate the relative effectiveness of treatments (Section B.2.9 and Appendix D).

As described in Section B.2.9, treatment with olaparib reduced the risk of radiographic disease progression or death by [redacted]% versus cabazitaxel in the ITC analysis ([redacted]). rPFS in the cabazitaxel arm was modelled by applying the reciprocal of the estimates of relative effectiveness from the ITC to

the olaparib rPFS curve as the reference arm. The extrapolated curves for cabazitaxel are shown in Figure 26.

Figure 26. Modelled rPFS for cabazitaxel based on ITC HR vs olaparib as reference curve.



Gen, generalised; HR, hazard ratio; ITC, indirect treatment comparison; (r)PFS, radiographic progression-free survival.

B.3.3.2.1.2 Overall survival (OS)

B.3.3.2.1.2.1 Olaparib (PROfound, DCO1 4th June 2019); HRRm (Cohort A+B) prior taxane subgroup

Data presented in this section are based directly on the prior taxane subgroup of the PROfound study. At DCO1, OS data for olaparib in the prior taxane subgroup of the overall HRRm (Cohort A+B) population of PROfound were relatively immature (42.9% maturity, 73 events in 170 patients), Table 24. Median OS was 15.8 months in the olaparib arm.

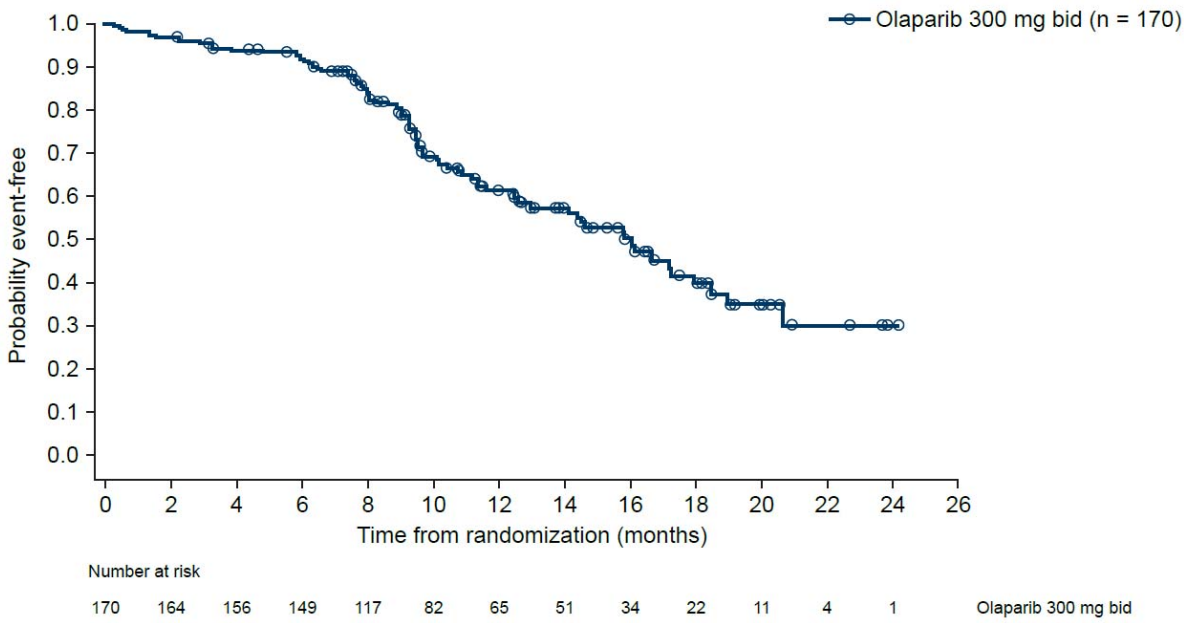
Figure 27 shows the Kaplan–Meier curves for the olaparib arm in the prior taxane subgroup of PROfound.[94] An overlay of Kaplan–Meier curves with parametric models fitted to the patient-level data are shown in Figure 28, with the respective AIC/BIC values for each parametric model presented in Table 25.

Table 24. Number of events in the HRRm (Cohort A+B) prior taxane subgroup of PROfound.

Endpoint	Outcome	Olaparib 300 mg bid (n = 170)
OS	Events, n	73
	Maturity, %	42.9

bid, twice daily; OS, overall survival.

Figure 27. OS Kaplan–Meier plot (HRRm [Cohort A+B] – prior taxane subgroup, olaparib)

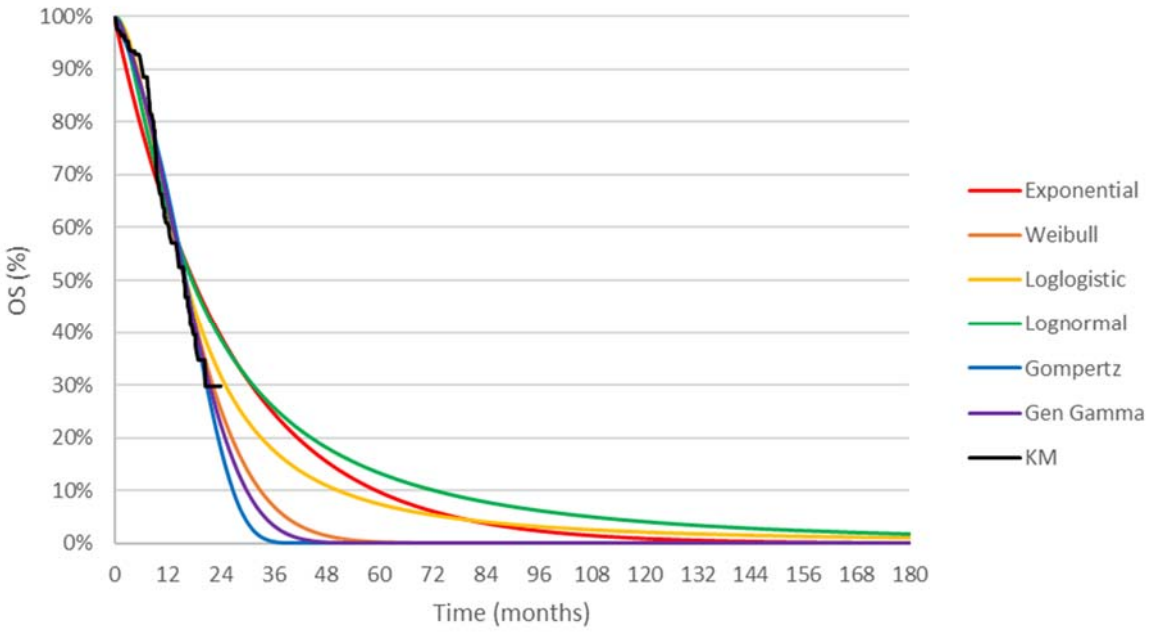


bid, twice daily; HRRm, homologous recombination repair mutation; OS, overall survival.

Based on a visual assessment of the separately-fitted parametric models for the olaparib arm (Figure 28), the exponential and log-normal distributions generated poor visual fits against the Kaplan–Meier curves for olaparib within the trial period. The Gompertz, generalised gamma and Weibull models were more pessimistic within the observed period, while the exponential and log-normal models were more optimistic. The log-logistic model produced extrapolations in between the optimistic and pessimistic curves.

The total AIC/BIC statistics were similar across distributions, except for the exponential and log-normal curves, which show poor statistical fit to the observed data (Table 25).

Figure 28. Modelled OS based on PROfound (HRRm [Cohort A+B] – prior taxane subgroup, olaparib).



KM, Kaplan–Meier; OLA, olaparib; OS, overall survival.

Table 25. AIC and BIC values for parametric models for OS (HRRm [Cohort A+B] – prior taxane, olaparib).

Distribution	AIC	BIC	Total
Exponential	622.5	625.7	1248.2
Weibull	604.5	610.8	1215.3
Loglogistic	608.1	614.4	1222.5
Lognormal	624.4	630.7	1255.1
Gompertz	604.1	610.3	1214.4
Generalised gamma	605.5	614.9	1220.4

AIC, Akaike information criteria; BIC, Bayesian information criteria; OS, overall survival.

PROfound is the first and only Phase III RCT to assess treatment of patients with mCRPC with HRRm whose disease has progressed after treatment with a taxane and NHA. All parametric models predicted a similar median OS estimate for olaparib compared with the observed median OS from PROfound at DCO1 (15.8 months).

Given the lack of other published data on long-term survival with PARP inhibitors in mCRPC, clinical experts experienced in using these treatments in mCRPC clinical

trials were consulted to understand which of the OS extrapolations best captured patient outcomes that could be realised in real-world clinical practice.

Based on UK clinical expert opinion,[58] long-term survival with olaparib is expected to be better than that achieved with the current standard-of-care in the real world setting, where a small number of patients remain alive 5 to 10 years after starting treatment in a post-NHA setting (described further in Section B.3.3.2.1.2.2). Based on an average of responses, approximately [redacted] of patients and [redacted] of patients who have previously received docetaxel and who have progressed on a prior NHA could remain alive 5 and 10 years after starting treatment with olaparib. Since the Weibull, Gompertz and generalised gamma distributions predicted no long-term survivorship at these timepoints for olaparib or with cabazitaxel (Section B.3.3.2.1.2.2), these distributions were considered clinically implausible and inappropriate to inform decision making.

The only remaining clinically plausible models are the exponential, lognormal and log-logistic curves. Of these curves, the lognormal and log-logistic distributions provided estimates of 5 and 10 year survival that were closest to those predicted by UK clinical experts. Although the exponential curve predicts a plausible OS rate at 5 years, it underestimates 10-year survivorship and showed poor visual fit to observed data, and was thus discarded as an option to model OS.

Of the lognormal and log-logistic distributions, the log-logistic model provided better statistical and visual fit to data. The log-logistic distribution was therefore used in the base-case analysis, despite producing more conservative estimates of long-term survival than that predicted by clinical experts. The lognormal distribution produced long-term survival estimates that most-closely reflected clinical-expert estimates, and was therefore tested in scenario analysis.

Table 26. OS estimates for olaparib (HRRm [Cohort A+B] - prior taxane, olaparib)

Olaparib	Median, months	1 year, %	3 years, %	5 years, %	10 years, %	Total AIC+BIC value	Statistical fit ranking (1 = lowest AIC+BIC)	Clinically plausible long-term survival estimates[a]
Observed (PROfound, prior taxane subgroup)								
Kaplan-Meier	15.8	[redacted]	-	-	-	-	-	-
Predicted by parametric models								
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1248.2	5	Yes
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1215.3	2	No
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**1222.5**	**4**	**Yes**
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1255.1	6	Yes
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1214.4	1	No
Gen gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1220.4	3	No
Potential OS from start of olaparib (after previous taxane and NHA, aligning with the modelled population)								
UK clinical expert opinion (average of responses)	–	–	[redacted]	[redacted]	[redacted]	=	=	–
OS from start of cabazitaxel (after previous NHA, aligning with the modelled population) – reference only (as in Table 27)								
UK clinical expert opinion (average of responses)			[redacted]	[redacted]	[redacted]	=	-	-

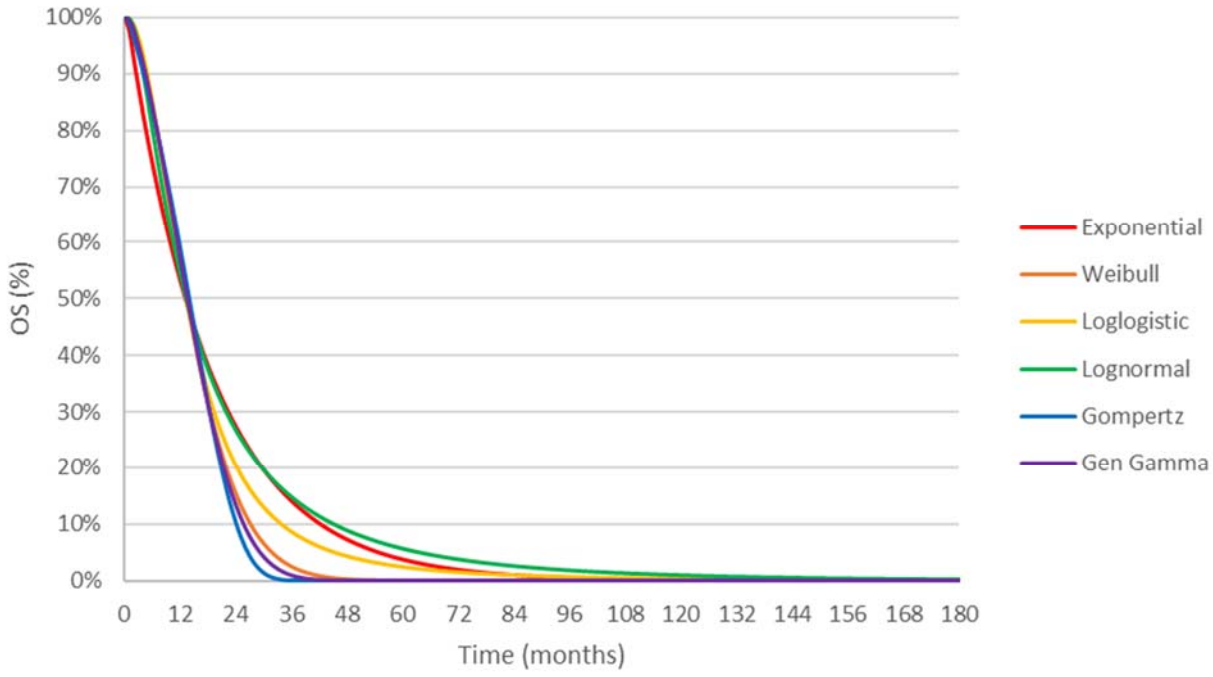
Gen, generalised; OS, overall survival.

[a] Yes = 5- and/or 10-year survival do not contradict estimates provided by clinical experts (i.e. long-term survivorship is non-zero); No = 5- and 10-year survival estimates contradict estimates provided by clinical experts.

B.3.3.2.1.2.2 Cabazitaxel (anchored ITC applied to olaparib OS curve)

As described in Section B.2.9, treatment with olaparib reduced the overall risk of death by [redacted]% versus cabazitaxel in the anchored ITC (OS HR, [redacted]), using data from the CARD[67] and PROfound studies.[30,61] The approach to modelling OS with cabazitaxel is the same as with rPFS, with the resulting curves shown in Figure 29.

Figure 29. Modelled OS for cabazitaxel based on ITC HR vs olaparib as reference curve.



Gen, generalised; HR, hazard ratio; ITC, indirect treatment comparison; OS, overall survival.

Median OS for cabazitaxel projected by all six distributions were similar to the median OS of 13.6 months observed in the cabazitaxel arm of the CARD trial.[67] In the absence of alternative sources of published literature on long-term survival outcomes achieved with cabazitaxel in a post-NHA setting (Section B.2), UK clinical expert opinion was sought to understand real-world survival outcomes on cabazitaxel and to validate the choice of distribution used in the base case analysis.

Based on UK clinical expert opinion, approximately [redacted] of patients could survive 5 years from the start of cabazitaxel in a post-NHA mCRPC (Table 27).[58] Clinicians

had experience with a small number of long-term survivors and all respondents expected some patients to survive 10 years from the start of treatment. In the average of responses, [redacted] of patients could survive 10 years from the start of cabazitaxel in the post-NHA mCRPC setting.

As with the comparison of survival estimates for olaparib, the Weibull, Gompertz and generalised gamma distributions drastically underestimated survival with cabazitaxel, and produce clinically implausible long-term OS outcomes that would not be appropriate to use for the purposes of decision making.

Of the remaining distributions, the log-logistic distribution produced the closest estimate for 3-year survival compared with the observed data at 2.8 years in the CARD study publication, and was clinically plausible albeit slightly conservative at 10 years, confirming that the use of the log-logistic distribution is appropriate and valid in terms of outcomes with cabazitaxel. The lognormal distribution produced long-term survival estimates for cabazitaxel that most closely matched estimates from UK clinician experts. There is consistency in the conclusions regarding the log-logistic and lognormal distributions for both cabazitaxel and olaparib, which provides support for validity of using these models in the base case and scenario analysis.

Table 27. OS for cabazitaxel (predicted via ITC)

	Predicted median, months	1 year, %	3 years, %	5 years, %	10 years, %	Clinically plausible long-term survival estimates[a]
Observed KM (CARD)[67]	13.6 CARD[67]	58.2	9.0 at 2.8 years*			
OS from start of cabazitaxel (predicted by ITC)						
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Yes
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	No
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Yes**
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Yes
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	No
Gen gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	No
OS from start of cabazitaxel (after previous NHA, aligning with the modelled population)						
UK clinical expert opinion (average of responses)[58]	–	–	[redacted]	[redacted]	[redacted]	–

Gen, generalised; ITC, indirect treatment comparison; OS, overall survival

* Last time point available based on data published by de Wit 2019.[67]

[a] Yes = 5- and/or 10-year survival do not contradict estimates provided by clinical experts (i.e. long-term survivorship is non-zero); No = 5- and 10-year survival estimates contradict estimates provided by clinical experts.

B.3.3.2.1.3 Summary of rPFS and OS distributions included in analysis

The choice of rPFS and OS curves used in the base case and sensitivity analyses is summarised in Table 28 along with a brief description of the rationale explained in Section B.3.3.2.1.1 and Section B.3.3.2.1.2. The base case rPFS and OS distributions for olaparib and cabazitaxel are shown in Figure 30 and Figure 31.

Table 28. Final rPFS and OS models selected for economic evaluation (HRRm [Cohort A+B] – prior taxane)

Analysis	rPFS	Justification	OS	Justification
Base case	Weibull	Best-fitting distribution based on statistical fit.	Log-logistic	Best-fitting distribution of the clinically plausible options, based on AIC/BIC.
OS scenario	Weibull	Best-fitting distribution based on statistical fit.	Lognormal	Best-fitting distribution of the clinically plausible options, based on 5- and 10-year modelled outcomes compared with UK clinical expert opinion.
rPFS scenario	Generalised gamma	Second-best-fitting distribution based on statistical fit.	Log-logistic	Best-fitting distribution of the clinically plausible options, based on AIC/BIC.

AIC, Akaike information criteria; BIC, Bayesian information criteria; HRRm, homologous recombination repair mutation; OS, overall survival; rPFS, radiographic progression-free survival.

Figure 30. Selected distribution for extrapolating OS for olaparib (PROfound, Kaplan–Meier estimate and loglogistic model; prior taxane subgroup) and cabazitaxel (via ITC).[a, b]

[a] Unadjusted Kaplan–Meier estimates, based on PROfound (prior taxane subgroup) for olaparib; anchored ITC HR (section B.2.9) for cabazitaxel vs olaparib applied to the modelled olaparib curve (half-cycle correction applied).
[b] Best fitting curve, log-logistic, based on combined assessment of visual and statistical fit to the Kaplan–Meier data, comparison of median OS estimates and clinical plausibility based on feedback from UK clinical experts.
HR, hazard ratio; KM, Kaplan–Meier; ITC, indirect treatment comparison; OS, overall survival.

Figure 31. Selected distribution for extrapolating rPFS for olaparib (PROfound, Kaplan–Meier estimate and Weibull model; prior taxane subgroup) and cabazitaxel (via ITC).[a,b]

[a] Unadjusted Kaplan–Meier estimates, based on PROfound for olaparib; anchored ITC HR for cabazitaxel vs olaparib applied to the modelled olaparib curve (half-cycle correction applied).
[b] Best fitting curve, Weibull, based on combined assessment of visual and statistical fit to the Kaplan–Meier data
HR, hazard ratio; KM, Kaplan–Meier; ITC, indirect treatment comparison; rPFS, radiographic progression-free survival.

B.3.3.3 Treatment duration

Treatment duration was explicitly modelled to accurately estimate treatment costs associated with each intervention. Several options were implemented to project a treatment duration curve over the time horizon, depending on the type of data that was available for each intervention, as outlined in Table 29.

Additionally, a maximum treatment duration of 10 treatment cycles was applied for cabazitaxel to ensure that costs reflected the duration of treatment administration in England, per NICE recommendations for cabazitaxel based on the TROPIC trial (TA391).[41] It should be noted that efficacy data from the CARD study, which was used in the ITC analysis to estimate the relative efficacy of olaparib versus cabazitaxel, reflects the administration of cabazitaxel until radiographic disease progression, unacceptable toxicity or patient's refusal of further study treatment

(median number of treatment cycles received, 7; range 1 to 29[67]). Therefore, the approach of restricting the costs of cabazitaxel to a maximum of 10 treatment cycles without adjusting the efficacy estimates for the duration of treatment may lead to conservative estimates of cost-effectiveness for olaparib versus cabazitaxel. The impact of removing the maximum treatment duration for cabazitaxel on the results is tested separately in a scenario.

Table 29. Summary of TTD approach selected for base case and scenario analysis

Analysis	Rationale
Base case • Treat to progression (rPFS curve) for all interventions	• Consistent approach used to determine treatment costs, assuming no early discontinuation of treatments for any interventions, but minimising potential bias due to implementing different methods. • Reflects treat to progression rule for olaparib per anticipated label and PROfound study design, and the administration of cabazitaxel in the CARD study (while capping costs to a maximum of 10 treatment cycles to align with NICE TA391 guidance; removal of treatment limit tested in scenario analysis).
Scenario 1 • Olaparib: Parametric TTD curve • Comparators: Median duration	• TTD approach for olaparib utilises the availability of patient-level data to reflect the expected duration of treatment (including any early discontinuation) using data from the PROfound study (Section B.3.3.3.3)[61] • Median duration approach for comparators reflects the potential early discontinuation of cabazitaxel in the CARD trial, in the absence of patient-level data or published TTD curves, although to align with the CARD trial the treatment limit of 10 cycles is removed in this scenario
Scenario 2 • Median duration for all interventions	• Consistent approach used to capure any early discontinuation of treatment for olaparib and cabazitaxel, and minimising potential bias that could be introduced by implementing different methods. To align with the CARD trial the treatment limit of 10 cycles is removed in this scenario for cabazitaxel.

TTD, time to treatment discontinuation.

B.3.3.3.1 Treat to progression (base case)

The treat to progression option assumes that patients receive treatment up until the point of progression, according to the rPFS curves defined in Section B.3.3.2.1.1.

This treatment duration rule accurately aligns with the expected use of olaparib based on its anticipated marketing authorisation for this indication, and the use of cabazitaxel (which is limited to a maximum of 10 treatment cycles by NICE).[41]

B.3.3.3.2 Median duration

The median duration of treatment is a commonly-reported outcome in clinical trials as a measure of the average time that patients received active treatment. As a median value was available for olaparib treatment in the PROfound study[61], and for cabazitaxel treatment in CARD,[67] it was possible to utilise this data as a common method of modelling treatment duration for each intervention ([redacted] and 5.1 months, respectively).

In the economic model, the median duration of time on treatment was used to predict the probability of treatment discontinuation at each model cycle using the exponential distribution:

Given the median treatment duration of X, the probability of remaining on on treatment at cycle *t* is:

$$\exp((\ln(0.5)/X)*t)$$

B.3.3.3.3 Parametric time to treatment discontinuation (TTD) curve

In this option, time on treatment was explicitly modelled using parametric curves fitted to time-to-treatment-discontinuation patient-level data following methods described in section B.3.3.2.1 and as described below. In the model, the TTD curves are constrained by rPFS to ensure logical patient flow according to the anticipated Marketing Authorisation for olaparib. That is, once a patient has confirmed evidence of progression, they are assumed to also discontinue treatment. This option was only available for olaparib as no other published time to treatment discontinuation data, either in the form of Kaplan–Meier data or parametric models, were available for cabazitaxel.

In the prior taxane subgroup of the overall HRRm (Cohort A+B) population of PROfound, [redacted] out of 170 patients had discontinued treatment in the olaparib arm; the median duration of treatment was [redacted] months (excluding dose interruptions).[61]

Figure 32 shows the Kaplan–Meier curves for time to treatment discontinuation, whilst Figure 33 shows an overlay of the Kaplan–Meier and modelled curves. As with rPFS and OS extrapolations, TTD was modelled based on separately-fitted parametric curves to the olaparib arm, since treatment with NHA (as the comparator arm of PROfound) is not a relevant comparator in this appraisal. Table 30 presents the AIC/BIC values for separately-fitted TTD curves to the olaparib data.

Based on an assessment of the visual and statistical fit of the curves to the Kaplan–Meier data, the Weibull was determined to be the best-fitting TTD curve and was used in a scenario analysis.

Figure 32. TTD, Kaplan–Meier plot (HRRm – prior taxane)

bid, twice daily; BICR, blinded independent committee review; HRRm, homologous recombination repair mutation; TTD, time to treatment discontinuation.

Figure 33. Modelled treatment duration based on PROfound (HRRm – prior taxane, olaparib).

Gen gamma, generalised gamma; HRRm, homologous recombination repair; KM, Kaplan–Meier; TTD, time to treatment discontinuation

Table 30. AIC and BIC values for parametric models for TTD (HRRm – prior taxane, olaparib)

Distribution	AIC	BIC	Total AIC+BIC
Exponential	890.2	893.4	1783.6
Weibull	876.2	882.5	1758.7
Loglogistic	888.7	895.0	1783.7
Lognormal	907.5	913.8	1821.3
Gompertz	877.5	883.8	1761.3
Generalised gamma	877.4	886.8	1764.2

AIC, Akaike information criterion; BIC, Bayesian information criterion; HRRm, homologous recombination repair; TTD, time to treatment discontinuation.

B.3.3.4 Adverse events

Adverse events have a quality of life and resource impact. There are clinically meaningful differences in the AE profiles for olaparib and cabazitaxel.

For each treatment, it was considered preferable to derive safety data from the same study that was used to determine relative efficacy. This ensures that the AEs

accurately reflect those that are relevant to the treatment, as observed in the safety and efficacy assessment in clinical trials. Furthermore, using the same data source for safety and efficacy inputs avoids introducing uncertainty related to cross-study differences (e.g. differences in trial populations or drug administration).

Treatment-related AE rates for olaparib were based on the PROfound trial.[61] AEs reported within the prior taxane subgroup of the overall HRRm population of PROfound were used in line with the modelled population. AE data for cabazitaxel were obtained from the CARD[67] study, with the exception of leukopenia and neutropenia, as described below:

- There is uncertainty around the AE incidence rates associated with cabazitaxel for leukopenia and neutropenia, since the de Wit *et al*, 2019 publication reported Grade 3 and above "laboratory abnormalities" in 32% and 45% of patients, respectively.[67] It was stated that these were based on systematic analysis of blood samples, which "may not have been reported as an AE". Clinical experts consulted by AstraZeneca on this topic confirmed that these are purely laboratory test results and would not necessarily reflect the actual incidence of complications causing a quality of life or resource use impact (such as infections and febrile neutropenia).
- To avoid overestimating the incidence of leukopenia and neutropenia associated with cabazitaxel treatment these data were obtained directly from UK clinical experts (the lowest of estimates from the responses were assumed: 5% leukopenia, 5% neutropenia), in the context of patients receiving primary prophylactic G-CSF with cabazitaxel (i.e., in line with the administration of cabazitaxel in the CARD study). This is an appropriate approach because it aligns with current expectations in clinical practice in England and Wales

The economic model included Grade 3 and above AEs occurring in at least 5% of patients in the olaparib arm of PROfound (prior taxane subgroup)[61] or cabazitaxel from CARD.[67] This is a commonly accepted approach as Grade 3 and above AEs reflect events that are likely to require hospitalization; therefore, having the greatest burden on resources and quality of life.

In addition, the following Grade 3 and above AEs were included, based on advice from UK clinical experts, even though they may occur in <5% of patients:

- Febrile neutropenia was included based on its relevance to this indication as a key concern with chemotherapy.
- Diarrhoea was also included due to the potential to lead to infections at the Grade 3 and above level.
- Fatigue/asthenia and musculoskeletal pain or discomfort was included due to the impact on quality of life, a particularly important consideration for patients on chemotherapy.
- Thrombocytopenia was included due to its severity and potential impact on resource use.

The AEs included in the economic model are summarised in Table 31. Based on a naïve side-by-side comparison, olaparib had a more tolerable and manageable safety profile compared with cabazitaxel, with either a lower of very similar incidence of Grade 3 or above AEs occurring in ≥5% of patients with the exception of anaemia.

Table 31. Grade 3 and above AEs affecting at least 5% of patients included in base case analysis.

	Olaparib	Cabazitaxel
Adverse event, %	**PROfound, HRRm – Prior taxane N = 170**	**CARD (N = 126)**
Anaemia	[redacted]	8.0[c]
Infection	[redacted]	7.9
Leukopenia	[redacted]	5.0 [b]
Neutropenia	[redacted]	5.0 [b]
Musculoskeletal pain or discomfort[a, e]	[redacted]	1.6
Thrombocytopenia[e]	[redacted]	3.2
Febrile neutropenia[e]	[redacted]	3.2
Diarrhoea[e]	[redacted]	3.2
Fatigue/asthenia[e]	[redacted]	4.0

[a] Described in de Wit *et al*. 2019[67] as including back pain, flank pain, musculoskeletal discomfort and/or pain, neck pain, or pain in extremities. No related events were reported in PROfound.
[b] Input values based on clinical expert advice on the incidence of leukopenia/neutropenia (Grade 3 and above) that would require hospitalisation (data on file).[102]

[c] Laboratory abnormalities reported in de Wit *et al*. 2019[67] may not have been reported as an adverse event in CARD although the values were used as clinical experts confirmed that this reflected what they would expect in clinical practice.[102]
[e] Occurred in fewer than 5% of patients in PROfound/CARD, but added to the list of AEs (validated by UK clinical experts).[61,67]

B.3.3.5 Skeletal-related events (SREs)

B.3.3.5.1 Overall occurrence of SREs

SREs are a key clinical aspect of mCRPC due to the high propensity for prostate cancer to metastasise to bone tissue. These events were therefore included in the economic model as a one-off cost and SRE-specific utility decrement for patients upon progression. The definition of SREs in the PROfound trial protocol[30,87] was consistent with the clinical literature and those used in other mCRPC trial protocols (for example, CARD [in the post-NHA mCRPC setting relevant to this appraisal],[67] and also ALSYMPCA [for radium-223 dichloride in patients with bone metastases only],[127] AFFIRM [for enzalutamide in a post-docetaxel population][107] and COU-AA-301 [abiraterone in a post-docetaxel population][128]). Based on data for the prior taxane subgroup of the overall HRRm population of PROfound, at least one SRE occurred in [redacted] of patients in the olaparib arm.[61] In the CARD study publication, SREs occurred in 18.6% of patients in the cabazitaxel arm, which is included in the analysis.[67]

B.3.3.5.2 Distribution of interventions used to manage SREs

In an attempt to more accurately capture the true impact of each SRE, following the approach used in previous NICE submissions in prostate cancer such as TA580,[57] TA316,[114] TA376,[118] and TA412,[43] the distribution of SRE therapies were incorporated into the economic model and used to weight SRE-related costs.

However, the distribution of each SRE was not analysed in PROfound and data were not available from the CARD study (as described above).[61,67] A targeted literature search was therefore conducted to identify relevant data that could inform the economic model.

The search identified a detailed breakdown of SREs from the ALSYMPCA (radium-223 dichloride versus placebo/best supportive care),[118] COU-AA-301 (abiraterone

plus prednisone versus placebo plus prednisone in a post-docetaxel setting) [129] and AFFIRM studies (enzalutamide versus placebo in a post-docetaxel setting).[63,114] The average value across trials was used in the economic model. The distribution of SRE therapies were assumed to be the same for olaparib and cabazitaxel, as presented in Table 32. UK clinical experts consulted by AstraZeneca confirmed that this is an appropriate method, and that the average values shown in Table 32 are generalisable to UK clinical practice in a post-NHA setting.

Table 32. Distribution of SREs identified from mCRPC clinical trials.

	ALSYMPCA TA376[118]	COU-AA-301 Logothetis 2012[129]	AFFIRM Saad 2017, TA316[63,114]	Calculated average
Spinal Cord Compression, %	7.7	19.1	19.7	15.5
Pathological Bone Fracture, %	12.1	15.3	11.2	12.9
Radiation to the Bone,[a] %	79.2	61.7	62.2[a]	67.7
Surgery to the Bone, %	1.0	4.3	7.0[a]	4.1

[a] AFFIRM pooled rates for radiation and surgery to the bone from Saad 2017[63] adjusted proportionally with ratio of events reported in NICE TA316 (AFFIRM interim analysis).[114]

The data used in the base case analysis are summarized in Table 33. The impact of uncertainty and various limitations of SRE assumptions in the economic model were tested extensively in scenario analyses and had minimal impact on the results compared with the base case analysis.

Table 33. Probability of SREs occurring with each intervention in the base case analysis.

	Overall probability of at least one SRE occurring (%)[a]	Distribution of SREs (%)

	Olaparib	Cabazitaxel	Assumed same for olaparib and cabazitaxel
	PROfound, HRRm prior taxane subgroup	CARD study[67]	Average of ALSYMPCA (TA376),[118] COU-AA-301[129] and AFFIRM[63,114,b]
Spinal Cord Compression, %	[redacted]	18.6	15.5
Pathological Bone Fracture, %			12.9
Radiation to the Bone, %[b]			67.7
Surgery to the Bone, %			4.1

[a] Reported as the number of patients experiencing at least one SRE.
[b] AFFIRM pooled rates for radiation and surgery to the bone from Saad 2017[63] adjusted proportionally with ratio of events reported in NICE TA316 (AFFIRM interim analysis).[114]

B.3.4 Measurement and valuation of health effects

The economic model uses HRQoL data collected from the PROfound study as detailed in the following sections (Section B.3.4.1 to Section B.3.4.3). Mean baseline health state utility values were analysed and applied to patients in the progression-free and progressed-disease health states in the model, assumed to be equal across interventions.

Additionally, the following adjustments were incorporated to capture important differences in the impact of treatment with olaparib versus cabazitaxel on patients' HRQoL; as the data required for these adjustments were not available from PROfound, inputs were sourced from previous NICE technology appraisals in prostate cancer and supplemented by targeted literature reviews:

- Utility decrements to AEs (Section B.3.4.4) due were incorporated to reflect differences in the safety profiles of olaparib and cabazitaxel (Section B.3.3.4);
- Utility decrements due to SREs (Section B.3.4.5) for the occurrence of SREs with olaparib and cabazitaxel (Section B.3.3.5);

- A modality-specific utility decrement was applied for the duration of treatment with cabazitaxel to reflect the negative impact of the intravenous administration of chemotherapy on patients' quality of life, and the benefit of olaparib taken orally (Section B.3.4.6).

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

To investigate the impact of treatment and the disease on patients' HRQoL, EQ-5D-5L data were collected in PROfound as a predefined exploratory endpoint. EQ-5D-5L assessments were carried out at baseline (day 1 on study treatment), and then every 8 weeks (+/- 7 days) until discontinuation of study treatment, and on the last dose of study drug (see section B.2.6.6 for details).[61] EQ-5D-5L was also collected every 8 weeks for up to 24 weeks after discontinuation of study treatment. EQ-5D data (to week 64) are presented in section B.2.6.4.2.

Patients were classified as being in the following health states:

- **Progressed disease (PD) state:** Any EQ-5D collected after the date of progression was classified as being observed while PD
- **Progression-free (PF) state:** Any EQ-5D collected prior to the date of progression or censoring for progression was classified as being observed while PF
- Any EQ-5D collected after the date of censoring for progression was classified as "PF/PD unknown."

Given the NICE position statement regarding the use of EQ-5D in technology appraisals,[130,131] the EQ-5D-5L measurements collected in the PROfound trial were analysed and mapped onto EQ-5D-3L, as described in section B.3.4.2.

B.3.4.2 Mapping

EQ-5D-5L measurements collected in the PROfound trial were mapped onto the EQ-5D-3L. HSUV were provided based on the societal preferences of the general population in the UK using the value sets developed (Dolan *et al*, 1993)[132] for the mapping ("crosswalk") approach to the three-level version of the EQ-5D (EQ-5D-3L) published by van Hout *et al*. 2012.[132]

Full details of the cross-walk methods and key model results are provided in Appendix H.

The impact of treatment (olaparib vs NHA) and disease progression (PF vs PD) on HSUVs were formally assessed using a linear mixed effects models fitted to observed data in the full analysis set of the HRRm population. These models give appropriate estimates of health state utility under the assumption that any missing data are missing at random. The best fitting model was chosen based on AIC/BIC criteria and the rest of the mixed effect modelling analysis was performed using that model. The regression showed a significant association between HSUV and progression and an improvement in EQ-5D-5L for olaparib vs NHA.

See Appendix H for more details of the outputs from these analyses.

The mean EQ-5D-3L HSUVs derived for PF and PD are shown in Table 34, and were assumed to be the same for olaparib and cabazitaxel.

Table 34. Mean (LSM) HSUV estimates by progression status (HRRm population)

Progression (BICR)	Estimate	SE	Lower CI	Upper CI	*p* value
PF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Note: These are the estimates for PF/PD for olaparib, if estimated by the model with treatment and progression as covariate. We have conservatively assumed the same utilities by treatment arm in the model (e.g. cabazitaxel and olaparib).
BICR, blinded independent central review; CI, confidence intervals; HRRm, homologous recombination repair mutation; LSM, least squares mean; PF, progression-free; PD, progressive disease; SE, standard error.

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

Appendix H provides details of the SLR search strategy for identifying health-related quality-of-life studies in the published literature. Two studies were identified specific to the patient population of interest in a post-NHA setting, however in both studies the size of the evaluated cohort was small (< 50 patients), and neither reported health state utility values. Therefore, the EQ-5D analysis from the PROfound study

was deemed to be the most relevant source of data for inclusion in the economic model.

Given the lack of published evidence in the post-NHA setting, a targeted literature review not restricted to post-NHA was conducted in an attempt to identify any studies that could be helpful for validating HSUV assumptions for olaparib or cabazitaxel in the appraisal (Table 35). Only one study was identified as appropriate: the UK early access programme (EAP) for cabazitaxel, which was an observational study conducted as part of an international phase IIIB/IV study within the bounds of clinical practice.[133] The primary objective of the early access programme was to allow early access to cabazitaxel for patients in clinical practice and similar to those evaluated in the TROPIC trial (i.e., patients with mCRPC who have received prior docetaxel); with the secondary objective being to document the safety of cabazitaxel in these patients.[133] [41], which is unique to the administration of cabazitaxel. The UK EAP included a total of 112 patients mCRPC with disease progression during or after docetaxel, across 12 UK cancer centres. Patients received cabazitaxel 25 mg/m^2 every 3 weeks with prednisolone 10 mg daily for up to 10 cycles in line with the SmPC. Full details are provided in Bahl 2015 and summarised in TA391.[41,133] The reported mean HSUV for PF was 0.7533 (Bahl, 2015)[133] or 0.7370 based on the weighted average of utility values across cycles (as reported in TA391), and 0.6266 for PD.[41,133] These values are similar to the EQ-5D analysis from PROfound, and were therefore tested in scenario analyses to understand the impact of utility assumptions on the results.

Table 35. Utility values based on targeted literature search in mCRPC setting (not specific to post-NHA population).

	Stable utility[a] (SD)	Progressed utility[a] (SD)	Comment
Bahl, 2015	Cycle / Stable disease 1 / 0.704 2 / 0.728 3 / 0.728 4 / 0.750 5 / 0.753 6 / 0.752 7 / 0.778 8 / 0.789 9 / 0.803 10 and thereafter / 0.819	0.6266 (0.298)	As reported in TA391: the UK EAP provides utility data for the stable disease state in a UK specific population treated with cabazitaxel, and for the progressive disease state recorded 30 days (last record) after the last cycle of treatment received for patients with evidence of progression.
TA391 (UK EAP)[41]	Mean: 0.7533 Weighted avg. of cycles: 0.7370		Additional values reported during clarification stage in TA391, based on analysis of the UK EAP data.
Loriot, 2015	0.85 (0.15)		Data collected in chemotherapy naïve patients in the PREVAIL study.
Diels, 2015	0.66 (0.02)	0.60 (0.03)	For the purposes of this table, the 'stable' state is assumed to be for patients undergoing chemotherapy and the progressed utility is assumed for patients characterised as 'post chemotherapy'.
Torvinen, 2013	0.74 (95% CI: 0.69–0.80)	0.59 (95% CI: 0.48–0.70)	For the purposes of this table, the 'stable' state is assumed to be for metastatic patients on active treatment and the progressed utility is assumed for patients characterised as receiving palliative care.

	Stable utility[a] (SD)	Progressed utility[a] (SD)	Comment
Wolff, 2012	Mean (SD) EQ-5D: 0.72 (0.30) No chemo: 0.81 (0.27) Post-chemo: 0.66 (0.30) Ongoing chemo: 0.64 (0.31)		Published in conference proceedings in German patients.
Diels, 2012	0.67		Updated above in Diels 2015. Mean utility for all patients recorded.
James, 2012	-	0.63 (0.26)	Published in conference proceedings only. Utility is for mCRPC patients progressed after docetaxel.
Sullivan, 2007	0.715	−0.07 decrement	Baseline utility recorded for the UK population studied with decrement for progression at −0.07
Sandblom, 2004	-	0.538 (0.077)	Utility value recorded in the last year before death in patients who died of prostate cancer
Murasawa, 2017	Localised prostate cancer: 0.86 (0.16) Advanced prostate cancer: 0.87 (0.14) CRPC: 0.80 (0.18)		Unclear whether the localised or advanced health states refer to hormone-sensitive and/or castrate-resistant prostate cancer. Health states not analysed by progression status.
Ghatnekar, 2014	0.688	0.603	Swedish tariffs.
Heidenreich, 2017	Enzalutamide: 0.81 (0.20) Bicalutamide: 0.83 (0.18)	Decrement from baseline at 61 weeks Enzalutamide: -0.11 (0.03) Biclutamide: -0.10 (0.04)	EQ-5D scores reported as adjusted mean changes from baseline at week 61 (not specifically due to progression).
Lloyd, 2015	*EORTC 8-D* Asymptomatic/mildly symptomatic before chemotherapy: 0.856 (0.089) Symptomatic before chemotherapy: 0.697 (0.118)		Health states aligned with movement through treatment pathway for patients with mCRPC and not analysed by progression status.

	Stable utility[a] (SD)	Progressed utility[a] (SD)	Comment
	Currently receiving chemotherapy: 0.750 (0.117) Post-chemotherapy: 0.753 (0.133) *EQ-5D-5L* Asymptomatic/mildly symptomatic before chemotherapy: 0.830 (0.126) Symptomatic before chemotherapy: 0.625 (0.173) Currently receiving chemotherapy: 0.692 (0.219) Post-chemotherapy: 0.700 (0.183)		

[a] Uncertainty is described as standard deviation unless otherwise note.

CI, confidence intervals; EAP, early access programme; EORTC-8D, European Organization of Randomised Controlled Trials 8 Dimension; EQ-5D(-5L), 5-dimension, (5-level) EuroQoL; (m)CRPC; metastatic castration-resistant prostate cancer; SD, standard deviation.

B.3.4.4 Adverse reactions

The occurrence of AEs have an impact on patients' HRQoL. To account for this in the economic model, treatment-specific AE rates (summarised in section B.3.3.4), mean utility decrements associated with AEs and the mean duration of each AE episode were used to calculate the total average QALY loss due to AEs for each treatment. For each treatment the total mean QALY loss associated with AEs was calculated as the sum of individual QALY loss associated with each AE. The total mean QALY loss due to AEs was applied once at the start of the model, assuming that AEs occurred soon after commencing each treatment. This approach is broadly consistent with previous NICE appraisals in prostate cancer,[41,134] and in other oncology indications.[135]

Utility decrements associated with AEs were not explicitly collected in PROfound, hence, these values were sourced from previous NICE appraisals in prostate cancer (TA391)[41] and the published literature (Table 36). Utility decrements were sourced from TA391, reflecting assumptions that have previously been accepted by NICE.[41] In TA391, due to a lack of data specific to prostate cancer, utility decrements in other indications were considered, including breast cancer (Lloyd 2006), non-small cell lung cancer indications (Nafees 2008 and Doyle 2008) were considered; where more than one value was identified, the average was used. Further details are available in NICE TA391.[41]

The duration of each AE episode was also not available from PROfound; therefore, the length of duration in days was assumed equal to that presented in TA391.[41] The duration of AEs were only required to transform mean utility decrements into a QALY loss.

A scenario analysis was tested, assuming that the impact of AEs on HRQoL would already be accounted for in the trial-based mean health state utility values and that AEs impact HRQoL equally, irrespective of treatment, and was shown to have minimal impact on the results.

Table 36. AE utility decrements and duration of AEs applied in the economic model

AE	Mean AE utility decrement	SE	Source as in TA391[41]	Mean AE duration (Days)	Source	Justification
Anaemia	0.1250	0.0217	Lloyd et al 2008	6.46	Duration not collected in PROfound; assumed equal to data reported in TA391 (TROPIC)[41]	Only available evidence
Infection	0.0900	0.0157	Assumed equal to neutropenia	7.00		Assumption required as no specific data available
Leukopenia	0.0900	0.0157	Assumed equal to leukopenia	4.65		Assumption required as no specific data available
Neutropenia	0.0900	0.0157	Nafees et al 2008	1.90		Only available evidence
Musculoskeletal pain or discomfort	0.0690	0.0120	Doyle et al 2008 (back pain)	9.55		Only available evidence
Thrombocytopenia	0.0900	0.0157	Assumed equal to neutropenia	5.88		Assumption required as no specific data available
Febrile neutropenia	0.1200	0.0209	Average of Lloyd et al 2006 and Nafees et al 2008	6.20		Average of studies available.
Diarrhoea	0.0470	0.0082	Nafees et al 2008	4.32		Only available evidence
Asthenia/fatigue	0.0940	0.0163	Average of Lloyd et al 2006 and Nafees et al 2008 (fatigue)	6.46		Average of studies available.

AE, adverse event; SE, standard error.

B.3.4.5 Skeletal related events

Similar to the above, and consistent with previous NICE appraisals in prostate cancer (TA259, TA316),[113,114] utility decrements for SREs were applied. As no utility decrements specific to a post-NHA setting were identified by the SLR, a targeted literature search was conducted, which identified one systematic literature review

study reporting on utility decrements associated with SREs in patients with castrate-resistant prostate cancer.[136] The duration of each SRE was derived from a previous NICE submission in mCRPC (TA316).[114,137]

The QALY loss associated with SREs was calculated using the same method applied for AEs; however, SRE decrements were applied as one-off decrement to the newly progressed cohort at each model cycle because SREs are often associated with disease progression, particularly for patients with bone metastases.[37,112,118]

The impact of excluding SREs from the analysis was tested in a scenario and had minimal impact on the results.

Table 37. SRE utility decrements and duration of SREs applied in the economic model

Skeletal related event therapy	Mean SRE utility decrement	Mean SRE duration (Days)	Source
Spinal Cord Compression	0.5550	30.44	Utility decrement based on Fassler 2011[136] Duration based on TA316
Pathological Bone Fracture	0.1300	30.44	
Radiation to the Bone	0.0700	30.44	
Surgery to the Bone	0.1300	30.44	Assumption: equal to pathological bone fracture as not reported in literature

SRE, skeletal-related event.

B.3.4.6 Modality-specific utility decrement

In previous NICE technology appraisals in prostate cancer, such as for abiraterone and enzalutamide (TA259, TA316),[113,114] it has been acknowledged that there is benefit related to drugs that can be conveniently taken orally. This benefit, even if it is small, is valued by patients with mCRPC.

Across disease areas, several studies have concluded that more convenient treatments can lead to greater utility values.[138-142] In a targeted literature search, one preference-based utility study was identified that estimated the impact of treatment

modalities regardless of differences in efficacy on health state preferences for cancer patients with bone metastases,[143] which is highly relevant to patients with mCRPC. The study included 121 participants from the UK general population who completed time trade-off interviews based on a series of sequential health state vignettes:

- Respondents first rated a basic health state representing cancer with bone metastases with no specified treatment.
- Treatments for bone metastases by mode of administration (i.e. injection or intravenous infusion) were then added to the basic health state vignette. The two treatment modalities were presented with and without chemotherapy (i.e. injection + chemotherapy), and infusion characteristics were also varied by the length of administration required.

The mean utility value in the 'basic' health state was analysed. Utility decrements associated with each subsequent health state differing by treatment modality were calculated. A summary of results from Matza *et al*, 2013 is included in Appendix H.3.[143]

The study concluded that respondents perceived an inconvenience with each type of treatment modality and that injections were preferred over intravenous infusions with and without receiving chemotherapy. Treatment modality can have a significant effect on health state utility and the study results could help to incorporate the value of different treatments for patients with bone metastases in cost-effectiveness models.

Based on Matza 2013,[143] the economic model incorporates a small modality-specific utility decrement associated with 30-minute IV infusion (health state C, -0.023) for cabazitaxel to account for the benefit associated with olaparib being an oral drug that can be taken by patients at home, since values for 1-hour IV infusion were not available. This is considered a conservative approach as the duration is shorter than the actual duration of infusion for cabazitaxel (1-hour intravenous infusion every 3 weeks, with specified premedication regimen and primary prophylactic G-CSF, and in combination with oral prednisone or prednisolone daily).

In the base case, the decrement was applied to the mean health state utility value (HSUV) based on the PROfound EQ-5D analysis for patients who remained on treatment with cabazitaxel at each cycle. The resulting utility value for progression-free patients on treatment with cabazitaxel was [redacted]. Upon discontinuing cabazitaxel it was assumed that the utility value for patients who remained progression-free would return to baseline as the IV administration no longer applies; i.e. the utility value for progression-free patients while off treatment with cabazitaxel was equal to [redacted], equivalent to the PF HSUV used for olaparib. The mean HSUV for patients who have progressed after initial treatment was [redacted].

Alternative HSUV values based on the UK EAP for cabazitaxel were tested in the scenario analyses (TA391; Bahl, 2015). In the UK EAP study, the HSUVs were obtained for patients already receiving IV treatment and it can be assumed that the mean PF HSUV value of 0.737 for patients treated with cabazitaxel is already inclusive of a utility decrement due to the intravenous administration of chemotherapy. Therefore, to maintain the same modality-specific difference in HRQoL between oral and IV drugs, the HSUV value for patients who are progression-free but have discontinued treatment with cabazitaxel was calculated by applying the value of 0.023 (Matza, 2013)[143] as an increment to the baseline PF HSUV. The resulting utility value for progression-free patients off treatment with cabazitaxel was equal to 0.7600, equivalent to the assumed PF HSUV used for olaparib. The mean HSUV for patients who have progressed after initial treatment was 0.6266.

Several scenarios were tested, each showing that these assupmtions had minimal impact on the results.

B.3.4.7 Health-related quality-of-life data used in the cost-effectiveness analysis

Table 38. Mean health state utility values used in the economic model (base case).[a]

Health state	Intervention	Mean utility value	SE	Reference in submission	Justification
Progression-free	Olaparib	[redacted]	[redacted]	B.3.4.2	Directly based on analysis of the PROfound data in which olaparib was assessed. The use of trial-based data from PROfound is preferred to allow for robust estimates of utility values in the specific HRRm population, and to match the data source relevant for efficacy and safety of olaparib in the economic analysis.
	Cabazitaxel: progression-free on treatment	[redacted] (after applying modality-specific decrement of -0.023 [Matza 2013,[143] C-A]) to PF)		B.3.4.6	Evidence to suggest that IV and injection mode of administration are associated with decrements to utility. Decrement associated with 30-minute IV infusion (health state C) considered a conservative approach as this is shorter than the actual duration of infusion for cabazitaxel and excludes any potential impact of receiving chemotherapy itself and/or the required premedication regimen.
	Cabazitaxel: progression-free off treatment	[redacted] (assumes modality-specific decrement no longer applies once discontinuing treatment with cabazitaxel and utility returns to baseline)		B.3.4.2	Once discontinuing treatment with cabazitaxel (e.g., patients who have progress or who have received the maximum of 10 treatment cycles) there should be no utility decrement due to the administration of intravenous drugs. The health state utility value is assumed to return to baseline.
Progressed disease	Olaparib and cabazitaxel	[redacted]	[redacted]	B.3.4.2	HSUVs expected to be different for patients who have evidence of progression compared with those who are considered progression-free. It is preferable to use the same data source as the progression-free utility values from PROfound.

[a] Before any adjustment due to AEs, SREs or mode of administration.

mCRPC, metastatic castration-resistant prostate cancer; HRRm, homologous recombination repair mutation; SE, standard error; SRE, skeletal related events.

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

An SLR was conducted in January 2020 to identify published literature on resource use and costs associated with the treatment/management of patients with mCRPC, whose disease has progressed after treatment with a taxane and NHA. Appendix G provides details full details. No recent and/or relevant data specific to England were identified.

Thus, it was more appropriate to source unit cost data were from standard UK cost tariffs and databases, where possible, in order to best reflect costs relevant to clinical practice in England, in line with the NICE reference case.

Drug costs for proprietary drugs were sourced from the British National Formulary (BNF), online.[144] The cost for generic drugs were sourced from the eMIT national database.[145] Unit costs associated with resource use were sourced from the NHS Schedule of Reference Costs[146] and Personal Social Services Research Unit (PSSRU) Unit Costs of Health and Social Care publication.[147] Where this was not possible, the model was supplemented with data obtained from previous technology appraisals or the published literature.

In line with the NICE reference case, the economic model considers all relevant costs, accrued over a lifetime horizon, as summarised below.

- Drug acquisition costs
- Drug administration costs
- Subsequent treatment costs
- Disease monitoring and patient follow-up costs
- Cost of AE management including SREs
- Other one-off costs (e.g., end of life care cost)

B.3.5.1 Intervention and comparators' costs and resource use

A summary of costs included in the economic analysis is provided in Table 39. A detailed description of each cost component is provided in the following sections.

Table 39. Summary of intervention and comparator costs included in the economic analysis (base case).

Items	Olaparib	Reference in submission	Cabazitaxel	Reference in submission
Drug cost (unit), £	2317.50 per pack of 56 tablets at list [redacted] per pack of 56 tablets*	B.3.5.2	3696 per vial, no wastage	B.3.5.2
Premedication and concomitant medication costs (total per month), £	N/A	B.3.5.2	[redacted]	B.3.5.2
Administration cost (per administration), £	N/A	B.3.5.2	[redacted]	B.3.5.2
Adverse event costs (one-off total cost per intervention),[a] £	[redacted]	B.3.5.4	[redacted]	B.3.5.4
Skeletal-related event costs (one-off total cost per intervention),[a] £	[redacted]	B.3.5.4	[redacted]	B.3.5.4
PF disease monitoring costs (total per month), £	[redacted]	B.3.5.3	[redacted]	B.3.5.3
PD disease monitoring costs (total per month),[b] £	[redacted]	B.3.5.3	[redacted]	B.3.5.3
Subsequent treatment costs (total per month for PD receiving subsequent treatment), £	[redacted]	B.3.5.3	[redacted]	B.3.5.3
Best supportive care cost (total per month for PD receiving BSC),[b] £	[redacted]	B.3.5.3	[redacted]	B.3.5.3
End of life care (one-off cost), £	2060	B.3.5.5	2060	B.3.5.5

[a] Total one-off cost applied at start of model.

[b] Average cost applied at each model cycle for patients in PD health state in the model until death.

* Inclusive of confidential discount.

N/A, not applicable; PD, progressive disease; BSC, best supportive care; PF, progression-free.

B.3.5.2 Drug acquisition costs

B.3.5.2.1.1 Olaparib

Olaparib (Lynparza) is available in 150 mg and 100 mg film-coated tablet formulations and comes in pack sizes of 56 tablets or a multipack containing 112 film coated tablets (2 x 56 tablets). The full recommended dose of olaparib is 300 mg (2 x 150 mg tablets) taken twice daily, administered until disease progression or unacceptable toxicity (whichever occurred first). The 100 mg tablet is available for dose reduction.

The list price for olaparib is £2,317.50 per pack of 56 tablets.[148] A confidential patient access scheme (PAS) for olaparib is in place. The results presented in the economic analysis will be inclusive of the confidential PAS.

B.3.5.2.1.2 Cabazitaxel

Cabazitaxel (Jevtana) is indicated in combination with prednisone or prednisolone for the treatment of mCRPC for patients who have previously received treatment with docetaxel.[120] Cabazitaxel is available in 60mg/1.5ml concentrate and solvent for solution for infusion vials. The recommended dose of cabazitaxel is 25 mg/m^2 administered as a 1-hour intravenous infusion every 3 weeks. Dose modifications may be made for AEs (details available in the SmPC).[120] Oral prednisolone is available in a range of pack sizes; the pack size with the lowest cost per mg was used. Prednisolone is administered in combination with cabazitaxel throughout treatment, at a dose of 10mg daily.

There was uncertainty in the applicability of wastage assumptions based on TA391.[41] In the current appraisal, a conservative assumption was made that there is no wastage (i.e., vial sharing is allowed) in the NHS when preparing/administering cabazitaxel. If this were not the case, the costs associated with cabazitaxel could be underestimated compared with the true costs in real world practice, leading to conservative estimates of cost-effectiveness for olaparib versus cabazitaxel. A scenario was run where wastage occurred (i.e., no vial sharing) which showed that this led to higher costs for cabazitaxel.

The list price of cabazitaxel is £3,696.00 per vial (60mg/1.5ml).[121] There is an agreed confidential PAS in place for cabazitaxel, however the level of the discount is commercial in confidence. Therefore, the economic analysis assumes the list price for cabazitaxel. The price of prednisolone is £0.28 per pack of 28x5 mg tablets, based on the eMit database.

Cabazitaxel is administered with a specified premedication regimen per the SmPC to mitigate the risk and severity of hypersensitivity (consisting of antihistamine, corticosteroid and H2 antagonist),[120] and it is also recommended to administer primary prophylactic G-CSF concomitantly per clinical guidelines for the prevention neutropenia-related complications for patients receiving cytotoxic chemotherapy (Section B.3.5.2).).[41,149-151] The CARD study protocol was consistent with such recommendations.

The following subsections provide details of factors considered for drug cost calculations in the economic model.

B.3.5.2.1.3 Mean weight and BSA

Olaparib has a fixed dosing regimen, however, mean weight and body surface area (BSA) inputs were required for calculating the cost of other drugs with weight- or BSA-dependent dosing regimens. This includes the comparator, cabazitaxel, which has a BSA-dependent dose; concomitant G-CSF (weight-dependent) described in Section B.3.5.2.2.2; and subsequent treatments described in Section B.3.5.3.3.1 (docetaxel and radium-223 dichloride, dose dependent on BSA and weight, respectively).

Mean BSA was not available from CARD to inform the dosing of cabazitaxel treatment [61,67] Hence, the mean BSA value of 2.01 m^2 was assumed,[41,134] in line with the ERG's preferred assumption for estimating the cost of cabazitaxel in TA391 based on the TROPIC trial.[41]

Mean weight (kg) of olaparib was based on the prior taxane subgroup of PROfound ([redacted]).

B.3.5.2.1.4 Mean relative dose intensity

The mean relative dose intensity was included to reflect the dose administered in clinical trials, and the potential for dose reductions in real-world practice. In the economic model, the mean relative dose intensity was applied to the full dose required for each intervention. On average, patients in the PROfound trial received [redacted]% of the full recommended dose.[61] The mean relative dose intensity was not available from the CARD study;[67] however, in TA391 it was reported that patients in the TROPIC trial received 92.6% of the full dose.[41] This approach is consistent with feedback from clinical experts on the potential for dose reductions to manage AEs in current clinical practice and was used in the base case analysis. The mean relative does intensity for prednisolone was not identified and was assumed to be 100%. Given the low cost of prednisolone this is not expected to have any impact on the results. The impact of applying RDI was tested in a scenario analysis.

Table 40. Mean relative dose intensity

Intervention	Mean RDI (%)	Source
Olaparib	[redacted]	PROfound analysis,[61] Cohort A+B prior taxane subgroup
Cabazitaxel	92.6	TA391,[41] TROPIC (value not reported in CARD)[41]

NR, not reported; RDI, relative dose intensity.

B.3.5.2.2 Premedication costs

No additional medicinal products are required for olaparib, per the PROfound trial protocol, and per the SmPC for olaparib as a maintenance treatment in ovarian cancer.[49,61,65,87] There is a recommended premedication regimen for cabazitaxel, as detailed below.

B.3.5.2.2.1 Cabazitaxel: Premedication regimen

The economic model included the recommended premedication regimen for cabazitaxel, in line with the SmPC and CARD trial protocol, containing:[67,120]

- Antihistamine (dexchlorpheniramine 5 mg or diphenhydramine 25 mg or equivalent)

- Corticosteroid (dexamethasone 8 mg or equivalent)
- H2 antagonist (ranitidine or equivalent)

The recommended premedication regimen is used to mitigate the risk and severity of hypersensitivity, and should be performed at least 30 minutes prior to each administration of cabazitaxel. For each of the medications, the cheapest pack per mg of the oral medicinal formulation were assumed for the purposes of the economic model.

The approach to pre/concomitant medications was deemed to be conservative, potentially underestimating the costs associated with cabazitaxel. The model only considers concomitant medications that were mandated for all patients receiving cabazitaxel in the CARD trial protocol or the SmPC; therefore excluding the use of some medications that could potentially be administered in clinical practice, such as:

- Luteinising hormone-releasing hormone (LHRH) agonists (goserelin and leuprolelin) were excluded although in TA391 it was explained that LHRH agonists as administered concomitantly with cabazitaxel in 100% of patients in the TROPIC study. The CARD study protocol stated that LHRH treatment should be continued in patients who had previously received them but there was no data to understand how many patients this applied to. In contrast, few patients in the overall PROfound study population received goserelin/leuprolelin ([redacted]),[61] therefore, excluding the costs associated with LHRH could disproportionately underestimate the total costs of cabazitaxel[41,67]
- Anti-emetics supportive treatment to ameliorate gastrointestinal symptoms are recommended for treating nausea and vomiting with cabazitaxel. Anti-emetics were mandated for 100% of patients receiving cabazitaxel in the TROPIC trial protocol per TA391 (in line with ASCO guidelines).[41,149] They were recommended but not mandated in the CARD trial protocol,[67] and data on usage was not available. Fewer than [redacted]% of patients in the overall PROfound study population received a concomitant anti-emetic drug, again potentially underestimating the total costs associated with cabazitaxel.[61]

B.3.5.2.2.2 Cabazitaxel: Primary prophylactic G-CSF

Clinical experts in England and Wales generally follow clinical guidelines that currently recommend the administration of primary prophylactic G-CSF (SC injection or IV infusion) to reduce the risk of neutropenia complications (febrile neutropenia, prolonged neutropenia or neutropenic infection) before the occurrence of any clinical event when there is a high risk of febrile neutropenia with treatment with chemotherapy.[102,151-154] This is in line with the SmPC advice for cabazitaxel (based on evidence from clinical trials) and evidence from a large compassionate use programme and early access programme (CUP/EAP) for cabazitaxel that showed primary prophylactic G-CSF is an important consideration to improve the tolerability of cabazitaxel in the real world, and to limit the incidence and severity of neutropenia.[41,154]

In the CARD study, all patients were also mandated by protocol to receive prophylactic G-CSF at each treatment cycle to help prevent neutropenia-related complications. It was stated that commercially available products would be used, but that the choice of the product was left to the investigator's discretion.[67]

Consistent with current ESMO/ASCO clinical guidelines,[41,67,149-151] and the CARD study protocol, primary prophylactic G-CSF (filgrastim) was considered part of the premedication costs applied for the duration of treatment for cabazitaxel. The model assumes the cost of the cheapest pack for filgrastim listed in the BNF based on the cost per million units/ml of filgrastim (Neupogen®, £84.06 per 48million units/0.5ml solution for injection pre-filled syringes = £1.75 per 1million units/0.5ml).[155] According to the SmPC, filgrastim (Neupogen®) may be given as a daily subcutaneous injection or as a daily intravenous infusion diluted in 5% glucose solution given over 30 minutes, for up to 14 days per cycle of chemotherapy treatment (i.e., every 3 weeks for cabazitaxel).[156]

To ensure the economic analysis reflected current standard of care in England and Wales, clinical experts were consulted on the extent of use of G-CSF in patients who received cabazitaxel in a post-NHA setting. Clinicians stated a preference for administering G-CSF for all patients receiving cabazitaxel in real world practice, citing clinical guidelines and clinical trials for cabazitaxel that demonstrated the

importance of G-CSF for managing neutropenic sepsis (TROPIC, CARD).[41,67,149-151] Furthermore, it is easy for patients to self-administer filgrastim at home with the subcutaneous injection. In the base case analysis it was assumed that 100% of patients in the cabazitaxel arm received primary prophylactic G-CSF, in line with the CARD study protocol, advice from clinical experts based in England and Wales, and clinical guidelines.

For completeness, an alternative value of 79.5% was tested[154] based on the UK CUP/EAP study.[133] This is considered to be a conservative scenario based on advice from clinical experts in England and Wales and based on the mandatory administration of G-CSF in the CARD trial.[67] The impact of assuming a value in between the base case analysis and the value from the UK EAP study (90%) was tested in the scenario analyses.

Drug acquisition costs for olaparib and cabazitaxel (including pre- and concomitant medications) are summarised in Table 41 and Table 42 below.

Table 41. Unit cost per pack/vial for olaparib and comparators in the economic model

				Pack details			
Treatment	**Route of administration**	**Dosing**	**Vial sharing**	**Strength per unit**	**No. of units per pack**	**Cost of pack, £**	**Source**
Olaparib	Oral tablet	Oral tablets, at a dose of 300 mg twice daily	N/A	100 mg	56	2317.50 at list [redacted] (inclusive of PAS)	BNF February 2020 [148]
				150 mg	56	2317.50 at list [redacted] (inclusive of PAS)	
Cabazitaxel	IV infusion	Cabazitaxel administered at a dose of 25 mg/m^2 as a 1-hour intravenous infusion every 3 weeks in combination with prednisolone at a dose of 10 mg daily throughout treatment.	Yes	60 mg	1	3696.00	BNF February 2020 [121]
Prednisolone	Oral tablet		N/A	5 mg	28	0.28	eMIT[145]

BNF, British National Formulary; eMIT, drugs and pharmaceutical electronic market information tool; IV, intravenous; N/A, not applicable; PAS, patient access scheme.

* Price including confidential discount.

Table 42. Unit cost per pack/vial for premedication and concomitant medications in the economic model

Concomitant medication	Form: Route	Dosing	Vial sharing	Strength per Unit	No. units per pack	Cost of Pack, £	Source
Antihistamine (chlorphenamine)	Oral tablet	1 tablet (4 mg) every 4 to 6 hours. Maximum daily dose: 6 tablets (24 mg) in any 24 hours – for allergy relief.	N/A	4.0 mg	28	0.16	eMIT March 2020[145]
H2-antagonist (ranitidine)	Effervescent oral tablet Oral	150 mg twice daily, taken in the morning and evening.	N/A	150.0 mg	60	12.63	eMIT March 2020[145]
Corticosteroid (Dexamethasone)	Soluble oral tablet	Supportive treatment in malignant tumours: initially 8 (chosen)–16 mg/day, during longer lasting treatment 4–12 mg.	N/A	4.0 mg	50	12.23	eMIT March 2020[145]
G-CSF (filgrastim)	Infusion	Recommended dose of filgrastim is 0.5 million units (mu)/kg/day (5 micrograms/kg/day).	N/A	96.0 mu/ml	0.5 ml	84.06	BNF February 2020[155]

BNF, British National Formulary; eMIT, drugs and pharmaceutical electronic market information tool; G-CSF, granulocyte-colony stimulating factor; PDS, pre-filled, dual-chamber syringe; SC, subcutaneous.

Table 43. Proportion of patients in the cabazitaxel arm receiving each concomitant medication in the base case analysis

Concomitant medication with cabazitaxel	% Patients	Source/Justification
Antihistamine (chlorphenamine)	100	Recommended in SmPC, and included in the premedication regimen in the CARD protocol for all patients receiving cabazitaxel.[67,120]
H2-antagonist (ranitidine)	100	
Corticosteroid (Dexamethasone)	100	
G-CSF (filgrastim)	100	Recommended in current clinical guidelines for chemotherapies where there is a high risk of neutropenia-related complications,[41,149,150] recommended in SmPC for cabazitaxel, and mandated by the CARD protocol for all patients at every treatment cycle. Reflects actual use of G-CSF with cabazitaxel in NHS England as advised by clinical experts[67,102,120]

G-CSF, granulocyte-colony stimulating factor; LHRH, luteinizing hormone-releasing hormone; SmPC, Summary of Product Characteristics.

B.3.5.2.3 Drug administration costs

Relevant drug acquisition costs were applied at each model cycle for the duration of treatment as summarized in Table 44.

No administration costs are associated with olaparib, given that it is an oral treatment that can be administered at monthly clinical visits with no additional cost to the healthcare system.

The administration cost for cabazitaxel was derived from TA391.[41] This included the cost of delivering chemotherapy (NHS Schedule of Reference Costs 2018/2019[146]) and it was stated that the additional cost of 1 hour of pharmacist time was necessary (15 minutes required to order the appropriate dose of cabazitaxel and 45 minutes for preparation prior to the administration of chemotherapy).[41] The pharmacist costs were based on the PSSRU 2019 publication.[147] The total administration cost is assumed to also cover all three concomitant medications and prophylactic G-CSF described in section B.3.5.2.3. Overall, this is believed to be a slightly conservative approach to administration costs for cabazitaxel given the number and different types of concomitant medications.

Table 44. Administration costs applied for olaparib and cabazitaxel in the economic model.

Intervention	Description	Unit cost per administration, £	Source	Additional pharmacist costs per administration, £	Source
Olaparib (oral)	N/A	N/A	–	N/A	
Cabazitaxel (IV)	Deliver subsequent elements of a chemotherapy cycle	362	NHS Schedule of Reference Costs 2018/2019 (SB15Z)[146]; aligned with TA391	47	PSSRU Unit Costs of Health and Social Care 2019 (Hospital-based scientific and professional staff, Band 6)[147]; aligned with TA391

NHS, National Health Service; N/A, not applicable; NHS, National Health Service; PSSRU, Personal Social Services Research Unit.

B.3.5.3 Health-state unit costs and resource use

Costs related to ongoing disease monitoring/patient follow-up, including a range of nurse/consultant visits and diagnostic tests and procedures, were included in the analysis and are described in the sections below. The list of resources was validated by clinical experts,[157] who provided estimates of average frequency of resource use for mCRPC patients on treatment with cabazitaxel in the progression-free health state. The responses were based on their clinical experience with cabazitaxel in a post-NHA setting. Clinicians were also asked to provide estimates for olaparib, were this to become a treatment option for mCRPC patients in the future. The frequency of resource use was also elicited for patients who had discontinued treatment but remained alive (i.e, off treatment). The average of responses from the clinical experts was calculated and used in the model, representing the average monitoring / follow-up costs associated with current standard of care in England and Wales. The unit costs associated with ongoing disease monitoring over patients' lifetime were sourced from the NHS Schedule of Reference Costs 2018/2019.[146]

B.3.5.3.1 Monitoring resource use on treatment

The frequency of resource use on treatment was specific to each intervention, and costs were accrued for patients on treatment, at each model cycle. In general hospital visits would be required for patients treated with cabazitaxel at every treatment cycle (i.e., every 3 weeks). Clinical experts from England with experience in treating patients with PARP inhibitors within a clinical trial setting stated that their expectations for routine disease monitoring/follow-up in UK clinical practice would be similar to that of NHA, where patients would be seen on a monthly basis for the first 3-4 months, and less frequenctly after the first 3-4 months for patients in response to olaparib, leading to a reduction in overall resource use.[157] At this stage (i.e., after the first few months), given the tolerable safety profile of olaparib, it may even be possible for appointments to be non-face-to-face consultations (e.g. virtually; over the phone) although a conservative approach was taken and it was assumed that all consultations would be face-to-face.

B.3.5.3.2 Monitoring resource use off treatment

Monitoring costs for patients who had discontinued treatment were also included. It was assumed that the frequency of resource use did not depend on the initial treatment. Costs were accrued at each model cycle for the duration that patients were off treatment but remained alive.

B.3.5.3.3 Subsequent treatment & best supportive care

After progressing on their initial treatment, it is assumed that a proportion of patients will receive subsequent anti-cancer treatments while the remaining patients would only receive best supportive care, which is primarily aimed at symptom palliation.

B.3.5.3.3.1 Subsequent anti-cancer treatment

Subsequent treatment costs were applied as a total average cost for patients who progress at each cycle. The average cost was calculated using the proportion of patients receiving each subsequent treatment, based on the PROfound and CARD studies, and the average duration of each treatment which was obtained from the literature as this was not reported in the clinical trial publications (Table 45).

The proportion of patients receiving subsequent anti-cancer treatment after disease progression on initial treatment with olaparib and cabazitaxel were calculated as the ratio of the number of patients receiving subsequent treatment and the number of patients who had progressed as the denominator, as detailed in Table 45. At DCO1 in the olaparib arm of the prior taxane subgroup of the overall HRRm (Cohort A+B) population of PROfound, [redacted]% of patients who progressed went on to receive subsequent treatment ([redacted] patients out of 124 progression events). According to the de Wit publication,[67] 69 patients received subsequent treatment in the CARD study out of a total of 120 progression events. Therefore, 57.5% of patients progressed and received subsequent treatment.

The types of subsequent treatment were restricted to five active treatments approved by the EMA in the mCRPC setting and used in at least 2% of patients in either the olaparib arm of the PROfound study and the cabazitaxel arm in the CARD study (i.e. excluding investigational drugs or those that would be considered part of BSC): abiraterone, cabazitaxel, docetaxel, enzalutamide, and radium-223. This

appropriately aligns the cost of subsequent treatment with the use of anti-cancer treatments that could have affected efficacy outcomes from the clinical trials (implicit in the OS data used in the ITC). Re-challenge with abiraterone and enzalutamide is not reimbursed in England and does not reflect current standard of care;[114,126] therefore a scenario where subsequent treatments were adjusted and re-weighted to reflect no further NHA rechallenge, per current standard of care, was tested, which showed only a small impact on the results.

Table 45 provides a summary of the proportion of patients receiving subsequent treatment and the distribution of treatments in the economic model (values used in the base case and scenario shown for comparison). The data are consistent with the current clinical pathway for patients with mCRPC. The distribution of subsequent treatments received in the olaparib arm differed from that in the cabazitaxel arm, which is expected and does not lead to any bias since olaparib offers a new treatment option (as an alternative to cabazitaxel), extending the treatment pathway should it become available for the patient population. The distribution of subsequent treatment in the cabazitaxel arm reflects the use of radium-223 being reserved for later lines, as would be anticipated based on our understanding of the clinical pathway and advice from UK clinical experts.

B.3.5.3.3.2 Best supportive care (BSC)

The proportion of patients who did not receive any subsequent treatment were assumed to receive BSC (i.e. [redacted] of patients progressing on olaparib and 42.5% for cabazitaxel in the base case analysis). The list of therapies included in BSC in TA391 (analgesics, steroids, palliative radiotherapy, bisphosphonates and anti-androgens) were validated by six UK clinical experts consulted by AstraZeneca.[157] The following additional therapies were included based on their advice:

- Oestrogens
- Nurse specialist (hospital-based)
- Palliative nurse (community-based)
- Blood transfusion
- LHRH

The average proportion of patients receiving each type of therapy was elicited from each UK clinical expert,[157] with the average of responses used to inform the economic model; administration and dosing details were sourced from each SmPC where necessary. An average monthly cost of BSC (£[redacted]) was calculated and applied to the proportion of patients who have progressed and are receiving BSC at each model cycle.

Table 45. Data informing subsequent treatment costs applied in the economic analysis.

Subsequent treatment	Duration	Source / justification	% by initial treatment, as in trial (base case)		% by initial treatment, adjusted for NHA rechallenge (scenario)	
			Olaparib PROfound – HRRm prior taxane[87] (N = 170)	Cabazitaxel CARD[67] (N = 126)	Olaparib (adjusted)	Cabazitaxel (adjusted)
Overall % (n/N_p) receiving subsequent treatment[T]			[redacted]	57.5 (69/120)	[redacted]	57.5 (69/120) [67]
Total % receiving BSC only (remainder)			[redacted]	42.5	[redacted]	42.5
Of those receiving subsequent treatment, % receiving:						
Docetaxel	10 treatment cycles (30 weeks)	Maximum recommended duration in mCRPC setting[115]	[redacted]	4.7	[redacted]	14.7
Abiraterone	7.4 months	Median duration of exposure reported in COU-AA-301[106]	[redacted]	34.0	[redacted]	0
Enzalutamide	8.3 months	Median time on treatment reported in AFFIRM (interim analysis)[107]	[redacted]	34.0	[redacted]	0
Cabazitaxel	7 treatment cycles (22 weeks)	Median duration of exposure reported in CARD[67]	[redacted]	13.6	[redacted]	42.2
Radium-223	6 injections (24 weeks)	Median number of injections in ALSYMPCA[127,158] (>50% in interim analysis and >80% in safety update)	[redacted]	13.8	[redacted]	43.1

T n = number of patients receiving subsequent treatment reported in study; N_p = number of progression events reported in study

Table 46. Data informing Unit costs associated with subsequent treatment applied in the economic analysis

				Pack details			
Treatment	**Route of administration**	**Dosing**	**Vial sharing**	**Strength per unit**	**No. of units per pack**	**Cost of pack, £**	**Source**
Docetaxel	IV infusion	Administered at a dose of 75mg/m^2 as a 1-hour intravenous infusion every 3 weeks.	Yes	20 mg	1	4.61	eMIT[145]
Abiraterone	Oral tablet	The recommended dose is 1000 mg (2 X 500 mg tablets) as a single daily dose.	N/A	500 mg	56	2735.00	BNF[159]
Enzalutamide	Oral tablet	160 mg enzalutamide (four 40 mg soft capsules) as a single oral daily dose.	N/A	40 mg	112	2734.67	BNF[160]
Cabazitaxel	IV infusion	Cabazitaxel administered at a dose of 25 mg/m^2 as a 1-hour intravenous infusion every 3 weeks in combination with prednisolone at a dose of 10 mg daily throughout treatment.	Yes	60 mg	1	3696.00	BNF February 2020 [121]
Prednisolone	Oral tablet		N/A	5 mg	28	0.28	eMIT[145]
Radium-223	Injection	The dose regimen of Xofigo is an activity of 55 kBq per kg body weight, given at 4 week intervals for 6 injections.	Yes	6.6 MBq	1	4040.00	BNF[112]

BNF, British National Formulary; eMIT, Drugs and pharmaceutical electronic market information tool; IV, intravenous; N/A, not applicable.

Table 47. Unit costs associated with subsequent treatment applied in the economic analysis

			Pack details					Administration costs	
Treatment	**Route of administration**	**Dosing**	**Vial sharing**	**Strength per unit**	**No. of units per pack**	**Cost of pack, £**	**Source**	**Cost per administration**	**Source**

Docetaxel	IV infusion	Administered at a dose of 75mg/m^2 as a 1-hour intravenous infusion every 3 weeks.	Yes	20 mg	1	4.61	eMIT[145]	254	National Schedule of NHS Costs - Year 2018-19 SB12Z: Deliver simple parenteral chemotherapy at first attendance.
Abiraterone	Oral tablet	The recommended dose is 1000 mg (2 X 500 mg tablets) as a single daily dose.	N/A	500 mg	56	2735.00	BNF[159]	N/A	-
Enzalutamide	Oral tablet	160 mg enzalutamide (four 40 mg soft capsules) as a single oral daily dose.	N/A	40 mg	112	2734.67	BNF[160]	N/A	-
Cabazitaxel	IV infusion	Cabazitaxel administered at a dose of 25 mg/m^2 as a 1-hour intravenous infusion every 3 weeks in combination with prednisolone at a dose of 10 mg daily throughout treatment.	Yes	60 mg	1	3696.00	BNF February 2020[121]	362	National Schedule of NHS Costs - Year 2018-19 SB15Z: Deliver subsequent elements of a chemotherapy cycle.
Prednisolone	Oral tablet		N/A	5 mg	28	0.28	eMIT[145]	N/A	-
Radium-223	Injection	The dose regimen of Xofigo is an activity of 55 kBq per kg body weight, given at 4 week intervals for 6 injections.	Yes	6.6 MBq	1	4040.00	BNF[112]	254	National Schedule of NHS Costs - Year 2018-19 SB12Z: Deliver simple parenteral chemotherapy at first attendance.

eMIT, Drugs and pharmaceutical electronic market information tool; IV, intraveneous; N/A, not applicable.

Table 48. Proportion of patients receiving best supportive care after progressing on olaparib or cabazitaxel in the economic model (based on TA391 and clinical expert opinion).

Therapeutic class	Therapy	Receiving, %	Monthly cost, £	Source
Analgesics	Co-codamol	[redacted]	4.08	eMIT: Co-codamol 30mg / 500mg tablets / pack size 100, £1.70, regimen: 2 tablets 4 times a day
Steroids	Dexamethasone	[redacted]	13.06	eMIT: Dexamethasone 2mg tablets / Pack size 100, £8.58, regimen: max 10mg daily
Palliative radiotherapy	External beam RT	[redacted]	573.65	NHS ref cost 2018/2019,Weighted average of SC56Z:Other External Beam Radiotherapy Preparation (other, inpatient, outpatient, day case and Reg Day/Night)
Bisphosphonates	Zoledronic acid	[redacted]	2.93	eMIT:Zoledronic acid 4mg/100ml solution for infusion bags / pack size 1, £2.93,4 mg every 3–4 weeks, calcium 500 mg daily and vitamin D 400 units daily should also be taken
Anti-androgens	Bicalutamide	[redacted]	4.37	eMIT: Bicalutamide 150mg tablets / pack size 28, £4.02, 150mg (1 tablet) daily
Oestrogens	Diethylstilbestrol	[redacted]	377.28	BNF: Max dose of 3mg daily assumed, diethylstilbestrol 1 mg, 28 tabs/packet, £115.68
Nurse specialist	NHS	[redacted]	642.52	Band 6, Nurse specialist/team leader , Annual salary £33,411, Source: unit cost of health and social care 2019 Assumed average FTE 1 week per month in economic model
Palliative nurse	COMMUNITY	[redacted]	633.63	Mean basic salary for a community nurses, Annual salary £32,949, Source: unit cost of health and social care 2019 Assumed average FTE 1 week per month in economic model
Blood transfusion		[redacted]	521.00	NHS ref cost 2018/2019,SA38A,Single Plasma Exchange or Other Intravenous Blood Transfusion, 19 years and over

LHRH		[redacted]	75.24	BNF, Feb 2020: Leuprorelin: 11.25 mg presented as a three-month depot injection and administered as a single subcutaneous injection at intervals of three months / PDS: injection, £75.24 per 3.8mg unit

BNF, British National Formulary; eMIT, Drugs and pharmaceutical electronic market information tool; FTE, full-time employee; LHRH, luteinizing hormone-releasing hormone; NHS, National health Service; PDS, pre-filled dual chamber syringe.

Table 49. Summary of health-state unit costs for resource use

Resource type	Unit cost, £	National Schedule of NHS Costs 2018–2019: HRG code[146]
Outpatient visit consultant	244.84	WF01B-370: Medical Oncology - Non Admitted Face-to-Face, First
CT scan	105.37	RD22Z: Computerised Tomography Scan of One Area, with Pre- and Post-Contrast
Bone scan	263.59	RN15A: Nuclear Bone Scan of Two or Three Phases, 19 years and over
Full blood count	2.79	DAPS05: Haematology
Liver function test	1.10	DAPS04: Clinical Biochemistry
Kidney function test	1.10	DAPS04: Clinical Biochemistry
Prostate specific antigen (PSA)	1.10	DAPS04: Clinical Biochemistry
Chemistry panel	1.10	DAPS04: Clinical Biochemistry.
Non-consultant follow-up visit (e.g. nurse)	92.95	WF01A-101: Non-consultant led, Non-Admitted Face-to-Face Attendance, Follow-up (Urology)

CT, computed tomography; ECG, electrocardiogram; FDG, fluorodeoxyglucose; HRG, Healthcare Resource Group; MRI, magnetic resonance imaging; PET, positron emission tomography.

Table 50. Summary of health-state resource use frequency per month

On treatment, applied per cycle until treatment discontinuation	**Olaparib**	**Cabazitaxel**

Resource type	Frequency per month (first 3 months)	Frequency per month (month 4+)	Frequency per month
Outpatient visit consultant	[redacted]	[redacted]	[redacted]
CT scan	[redacted]	[redacted]	[redacted]
Bone scan	[redacted]	[redacted]	[redacted]
Full blood count	[redacted]	[redacted]	[redacted]
Liver function test	[redacted]	[redacted]	[redacted]
Kidney function test	[redacted]	[redacted]	[redacted]
Prostate specific antigen (PSA)	[redacted]	[redacted]	[redacted]
Chemistry panel	[redacted]	[redacted]	[redacted]
Non-consultant follow-up visit (e.g. nurse)	[redacted]	[redacted]	[redacted]
Off treatment, applied per cycle until transitioning to death	**Olaparib and cabazitaxel**		
Resource type	**Frequency per month**		
Outpatient visit consultant	[redacted]		
CT scan	[redacted]		
Full blood count	[redacted]		
Liver function test	[redacted]		
Kidney function test	[redacted]		
Prostate specific antigen (PSA)	[redacted]		
Non-consultant follow-up visit (e.g. nurse)	[redacted]		

CT, computed tomography.

B.3.5.4 Adverse reaction and skeletal-related events unit costs and resource use

The unit costs associated with the management of AEs occurring on treatment were sourced from the NHS Schedule of Reference Costs 2018/2019.[146]

Total average AE costs were calculated as the sum–product of the unit cost (Table 51) and treatment-specific probability of AEs occurring for each intervention (section B.3.3.4), applied as a one-off cost at the start of the model. SRE costs were calculated as a weighted average using the unit cost of each SRE (Table 51) and the distribution of SREs (Section B.3.3.5). The average SRE cost was applied to the proportion of patients experiencing SREs for each treatment (section B.3.3.5) as a one-off cost upon progression. A scenario was run where this was excluded from the analysis.

Table 51. Summary of AE and SRE unit costs

	Unit cost per event (£)	National Schedule of NHS Costs 2018-2019: HRG code
Adverse event, one-off cost applied to treatment-specific AE rate, at start of model[a]		
Anaemia	565	SA04G Iron Deficiency Anaemia with CC Score 14+
Infection	494	LA04 Kidney or Urinary Tract Infections
Leukopenia	431	SA08G-J Other Haematological or Splenic Disorders (weighted average)
Neutropenia	431	SA08G-J Other Haematological or Splenic Disorders (weighted average)
Musculoskeletal pain or discomfort	377	HC32G-K Lower Back Pain with Interventions with CC Score 0-6+ (weighted average)
Thrombocytopenia	545	SA12 G-K Thrombocytopenia with CC Score 0-8+ (weighted average)
Febrile neutropenia	997	PM45A-D Paediatric Febrile Neutropenia with Malignancy, with CC Score 0-6+ (weighted average)
Diarrhoea	446	FD10 Non-Malignant Gastrointestinal Tract Disorders
Fatigue/asthenia	337	FD10 Non-Malignant Gastrointestinal Tract Disorders AA31E Headache, Migraine or Cerebrospinal Fluid Leak, with CC Score 0-6; DZ38Z Oxygen Assessment and Monitoring
Skeletal related event, weighted average one-off cost applied to proportion of newly progressed patients experiencing one or more SREs[a]		
Spinal Cord Compression	6184	NEL HC28H-M Spinal Cord Conditions with and without Interventions (weighted average)
Pathological Bone Fracture	3752	NEL HD39D-H Pathological Fractures with CC Score 0-11+ (weighted average)
Radiation to the Bone	713	SC21Z-29Z Deliver a Fraction of Radiotherapy (weighted average) And SC56Z Other External Beam Radiotherapy Preparation
Surgery to the Bone	4196	NEL HD39D-E Pathological Fractures with CC Score 8-11+ (weighted average)
Total weighted average cost of SREs (one-off)	2055	Weighted by distribution of SREs in section B.3.4.5

[a] Treatment-specific AE and SRE rates reported in Table 31 and Table 32, respectively

AE, adverse event; HRG, Healthcare Resource Group; NHS, National Health Service; SRE, skeletal-related event.

B.3.5.5 Miscellaneous unit costs and resource use

B.3.5.5.1 End-of-life care

Typical costs associated with hospitalisation and palliative care towards the end of life were included based on the costs calculated in TA391 (inflated to 2020), and applied as a one-off cost for patients transitioning to death at each model cycle.[41]

The cost of end of life care in the economic analysis after adjusting for inflation was £2,059.91.[41] The original cost in TA391 was £1952.15 (assumed based on 2016 costs)[41]

B.3.5.5.2 Genetic mutation testing

Olaparib is specifically intended to be a treatment option for patients with one or more qualifying HRR gene mutations; patients must undergo genetic testing to determine their eligibility for treatment.

The cost of genetic testing was therefore considered, in line with the NICE reference case.

Olaparib is the first treatment for mCRPC patients with one or more qualifying HRR mutations. Patients must undergo genetic testing to determine suitability for treatment. As described in Section B.1.3, [redacted]. As such, no testing costs were included in the economic analysis. A conservative scenario has been included where a one-off cost of £[redacted] was applied to the olaparib arm, based on [redacted]. The inclusion of this one-off testing cost had minimal impact on the results.

B.3.6 Summary of base-case analysis inputs and assumptions

B.3.6.1 Summary of base-case analysis inputs

A summary of inputs used in the base case analysis, and those varied in DSA/PSA, is provided below.

Table 52. Summary of variables applied in the economic model (base case analysis)

Variable	Description / notes	Value	Measurement of uncertainty and distribution / 95% CI	Reference to section in submission
General model settings				
Cycle length		1 month	N/A	B.3.2.6
Time horizon		15 years	N/A	B.3.2.5
Discount rate: costs		3.5%	Scenario: 0%	B.3.2.6
Discount rate: health outcomes				
Patient characteristics				
Mean age		67.3 years	Normal, SE: 0.49	B.3.2.1
Mean BSA		2.01 m^2	Normal, SE: 0.01	
Mean weight		[redacted]	Normal, SE: [redacted]	
Survival parameters				
Olaparib – overall survival	Parametric analysis, loglogistic	Shape: Scale: [redacted]	Multivariate normal	B.3.3.2.1.2
Olaparib – progression-free survival	Parametric analysis, weibull	Shape: Scale: [redacted]	Multivariate normal	B.3.3.2.1.2
Cabazitaxel – overall survival	ITC HR vs olaparib	[redacted]	Lognormal CI: [redacted]	B.3.3.2.1.2

Cabazitaxel – progression-free survival	ITC HR vs olaparib	[redacted]	Lognormal, CI: [redacted]	B.3.3.2.1.1
Safety inputs				
Probability of AEs		Multiple values	Totals per treatment varied	B.3.3.4
Probability of SREs		Multiple values	Totals per treatment varied	B.3.3.5
Distribution of SREs		Multiple values	Totals per treatment varied	
Health-related quality-of-life				
PF mean utility value (baseline)	PROfound EQ-5D analysis	[redacted]	Beta, SE: [redacted]	B.3.4.2
PD mean utility value	PROfound EQ-5D analysis	[redacted]	Beta, SE: [redacted]	
PF – Modality-specific utility decrement (cabazitaxel only)	Intravenous infusion, decrement from literature	-0.023	Beta, SE: 0.0082	B.3.4.6
AE utility decrements	Each AE	Multiple values	Totals per treatment varied	B.3.4.4
SRE utility decrements	Each SRE	Multiple values	Totals per treatment varied	B.3.4.5
Total treatment-related costs				
Olaparib – drug costs	Per month	[redacted]	Beta, 10% around mean (max 100%)	B.3.5.2
IV/SC admin- first attendance	Unit cost	£254	Gamma, 10% around mean	
IV/SC admin- subsequent elements	Unit cost	£362	Gamma, 10% around mean	
Pharmacist – hourly cost	Cost per hour	£47	Gamma, 10% around mean	
Cabazitaxel – administration costs	Total per month	[redacted]	Gamma, 10% around mean	
Cabazitaxel – mean relative dose intensity		92.6%	Beta, 10% around mean (max 100%)	
Cabazitaxel – premedication costs	Each medication	Multiple values	N/A	
Cabazitaxel – % G-CSF		100%	N/A, scenarios only	

Prednisolone – mean relative dose intensity		100%	Beta, 10% around mean (max 100%)	
Olaparib – total drug acquisition and administration costs	Calculated total per month	[redacted]	N/A	
Olaparib – cost of AEs	Applied at start of model	[redacted]	Gamma, 10% around mean	B.3.5.4
Olaparib – cost of SREs	Applied at progression	[redacted]	Gamma, 10% around mean	
Cabazitaxel – total drug acquisition and administration costs (excl. premedications and G-CSF)	Calculated total per month	[redacted]	N/A	B.3.5.2
Cabazitaxel – total cost of premedications and G-CSF	Calculated total per month	[redacted]	Gamma, 10% around mean	
Cabazitaxel – cost of AEs	Applied at start of model	[redacted]	Gamma, 10% around mean	B.3.5.4
Cabazitaxel – cost of SREs	Applied at progression	[redacted]	Gamma, 10% around mean	
Health state resource use				
Olaparib, resource use unit costs – on treatment (first 3 months)	Each resource type	Multiple values	Totals per treatment varied	B.3.5.3
Olaparib, resource use frequency – on treatment (4+ months)	Each resource type	Multiple values	Totals per treatment varied	
Cabazitaxel, resource use unit costs – on treatment	Each resource type	Multiple values	Totals per treatment varied	
Resource use unit costs – off treatment	Each resource type	Multiple values	Totals per treatment varied	

Resource use frequency – off treatment	Each resource type	Multiple values	Totals per treatment varied	
Olaparib, proportion receiving subsequent treatment after progressing		[redacted]	N/A; Total cost varied	
Cabazitaxel, proportion receiving subsequent treatment after progressing		57.5%	N/A; Total cost varied	
Distribution of subsequent treatments by intervention	Each treatment	Multiple values	N/A; Total cost varied	
Average duration of subsequent treatment	Each treatment	Multiple values	N/A; Total cost varied	
Olaparib, total cost of subsequent treatment	Total calculated per month	[redacted]	Gamma, 10% around mean	
Cabazitaxel, total cost of subsequent treatment	Total calculated per month	[redacted]	Gamma, 10% around mean	
Olaparib, proportion receiving BSC after progressing	Patients not receiving subsequent treatment	[redacted]	N/A; Total cost varied	
Cabazitaxel, proportion receiving BSC after progressing	Patients not receiving subsequent treatment	42.5%	N/A; Total cost varied	
Total average cost of BSC	Calculated per month, applied to % on BSC in PD health state	[redacted]	Gamma, 10% around mean	
Other costs				
End-of-life care costs	One-off cost upon death	£2,060	Gamma, 10% around mean	B.3.5.5

AE, adverse event; BSC, best supportive care; G-CSF, granulocyte-colony stimulation factor; ITC, indirect treatment comparison; N/A, not applicable; PD, progressive disease; PF, progression-free; SE, standard error; SRE, skeletal related event.

B.3.6.2 Assumptions

Table 53. Assumptions applied in the economic analysis.

Assumption	Justification
Efficacy outcomes	
Olaparib: The prior taxane subgroup of the overall HRRm population of the PROfound trial[30,61] is reflective of the UK population of adult men with mCRPC and HRRm whose disease has progressed after following treatment with a taxane and an NHA (i.e. abiraterone or enzalutamide)	Olaparib is the only PARP inhibitor supported by Phase III trial data in patients with mCRPC with HRRm whose disease has progressed after treatment with a taxane and NHA, the focus of this economic analysis [30,61]
The CARD study is the most appropriate study to represent health outcomes associated with cabazitaxel in the economic analysis[67]	The CARD study was the only cabazitaxel study identified by the SLR (see section B.2.1). It is a large, multicentre, phase IV study, allowing an anchored comparison to be made with olaparib in PROfound.
Outcomes associated with cabazitaxel based on the CARD[67] study can be generalised to patients with mCRPC and an HRR mutation, and who have previously received docetaxel	Unlike PARP inhibitors, cabazitaxel does not target the HRRm pathway. Published evidence suggests that patient outcomes are likely to be worse at least for those who carry the more fully characterised HRR mutations (e.g. *BRCA2*). Therefore, our analysis is considered to present a conservative comparison for olaparib versus cabazitaxel, given that the HRRm status of patients in the CARD study is not known and (based on prevalence of these mutations) is expected to comprise a small proportion of the overall study population.
An unadjusted ITC approach is the most suitable method for comparing olaparib with cabazitaxel (anchored on re-challenge with NHA), extrapolating OS and rPFS assuming a constant HR	Guidelines recommend that an anchored approach is conducted when there is a common comparator arm across the included trials.[96] There was no evidence of effect modifiers that would justify adjusting for covariates in the ITC. Therefore, an unadjusted ITC using the prior

	taxane subgroup of PROfound is appropriate for estimating outcomes with cabazitaxel. Based on an assessment of the proportional hazards assumptions in the PROfound and CARD studies, the application of a constant HR is appropriate.
Treatment is administered until progression (according to the PFS curve) for olaparib and cabazitaxel (for up to a maximum of 10 treatment cycles).	This approach reflects the anticipated marketing authorisation of olaparib and its use in clinical practice. The maximum treatment duration for cabazitaxel is consistent with the NICE recommendations for cabazitaxel in TA391; however, it should be noted that cabazitaxel was administered until radiographic disease progression in the CARD study. The median number of cycles received in the CARD study was 7, ranging from 1 to 29.[67]
AEs and SREs	
The overall incidence of AEs and SREs are specific to each intervention	There are clinically meaningful differences in the AE and SRE profiles for olaparib and cabazitaxel that should be incorporated in the economic analysis
The grade ≥ 3 AE rates associated with cabazitaxel for neutropenia and leukopenia events are based on estimates adjusted for the use of primary prophylactic G-CSF in the UK, based on the opinion of UK clinical experts consulted to inform the company submission (n = 6)[102]	Approach reflects the expected resource impact on the NHS in the UK setting, based on the most conservative value provided by UK clinical expert opinion[102]
The distribution of SRE therapies is the same across interventions	As confirmed by clinical experts (n = 6),[102] there is no evidence suggesting that the distribution of SRE therapies would differ between olaparib and cabazitaxel
Utilities	
Patient HRQoL is affected by disease progression, and is adequately captured by EQ-5D data collected in PROfound	Trial-based data are preferred; analysis was conducted in line with the NICE reference case and position statement[130]. Clinically meaningful

	differences in AE and SRE profiles of olaparib and cabazitaxel are considered separately by applying utility decrements (below).
AEs and SREs have an impact on HRQoL, resulting in additional utility decrements	The EQ-5D data collected the PROfound study capture the HRQoL of patients randomised to receive olaparib or NHA. Differences in the quality of life impact of AEs and SREs for cabazitaxel would not be captured. A conservative approach was applied where utility decrements are applied to both the olaparib and cabazitaxel arms. Although this may lead to some double-counting (EQ-5D responses in PROfound may already include the impact of some AEs/SREs associated with olaparib), no bias, or minimal bias against olaparib, is expected.
The physical administration of cabazitaxel by intravenous (IV) infusion is associated with a small negative impact on quality of life for the duration of receiving treatment. If there is any impact associated with oral drugs, this is assumed to be already captured in the EQ-5D data collected in PROfound.	Evidence in the literature supports the view that the mode of administration can have an impact on patient HRQoL, suggesting a preference for drugs taken orally compared with IV infusion and injection administration. This has been acknowledged by the Committee and patient advocate groups in previous NICE submissions.[113,114] Patients in PROfound were randomised to receive oral drugs (olaparib, enzalutamide or abiraterone); it is an appropriate and unbiased approach to assume PROfound utility values already include any modality-specific impact of taking olaparib, and applying a utility decrement for cabazitaxel alone.
Costs and resource use	
The total cost of cabazitaxel includes the drug cost of the recommended premedication regimen plus concomitant medication (no additional administration costs are assumed)	Reflects current clinical guidance,[41,149,150] the SmPC for cabazitaxel, and the mandatory premedication regimen for the cabazitaxel arm in the CARD study.[67,120] There are no necessary premedication regimens for olaparib.[49,65]

The administration costs associated with cabazitaxel include pharmacists' time for ordering and preparing the drugs in addition to the normal nurse time required	Accurately reflects administration procedures and costs related to cabazitaxel in line TA391.
The costs to the NHS associated with subsequent treatments are based on the proportion of patients receiving subsequent anti-cancer treatment in clinical trials, adjusted for the UK setting	Subsequent treatment costs are explicitly accrued to align with the potential impact of subsequent anti-cancer treatment on overall long-term survival, which is implicit in the OS extrapolations based on trial data. Subsequent treatments were restricted to five active treatments approved by the EMA for mCRPC: abiraterone, cabazitaxel (after docetaxel), docetaxel, enzalutamide, and radium-223 dichloride (bone metastases, no visceral metastases, either after docetaxel or in patients who are unsuitable for treatment with docetaxel). Re-challenge with abiraterone and enzalutamide is not recommended by NICE after disease progression on NHA; however, these treatments have been included in the base case analysis to align costs with the anti-cancer treatments that could have affected efficacy outcomes from the clinical trials included in the economic analysis.

AE, adverse event; EMA, European Medicines Agency; IV, intravenous; G-CSF, granulocyte-colony stimulation factor; HR, hazard ratio; HRQoL, health-related quality of life; ITC, indirect treatment comparison; mCRPC, metastatic castration-resistant prostate cancer; NHA, new hormonal agent; OS, overall survival; SmPC, summary of product characteristics; SRE, skeletal-related event.

B.3.7 Base-case results

The cost-effectiveness results for olaparib versus cabazitaxel are presented in Table 54 (inclusive of the confidential PAS for olaparib and with cabazitaxel at list price).

The results show that **olaparib dominates cabazitaxel; therefore, at the cost-effectiveness threshold of £50,000/QALY for end-of-life medicines that is relevant to this appraisal, olaparib is expected to be a highly-cost effective use of NHS resources** in patients with mCRPC with HRRm and who have received a prior taxane and NHA. The analysis shows that olaparib provides an additional 0.55 LYs, and an additional 0.36 QALYs, at an incremental cost saving of £2,424 over patient's lifetime horizon, compared with cabazitaxel. The cost saving achieved with olaparib is driven by differences in resource use and subsequent treatment across the interventions, coupled with the costs incurred due to pre-/concomitant medications associated with cabazitaxel therapy.

Disaggregated cost-effectiveness results are presented in Appendix J.

B.3.7.1 Base-case incremental cost-effectiveness analysis results

Table 54. Base-case results (costs and health outcomes discounted at 3.5%).

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Olaparib	[redacted]	[redacted]	[redacted]	-£2,424	0.55	0.36	**Olaparib is dominant**	
Cabazitaxel	[redacted]	[redacted]	[redacted]					
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

B.3.8 Sensitivity analyses

Sensitivity analyses are important in understanding the impact of uncertainty on the estimated model outputs for each treatment. Structural and parameter uncertainty associated with model inputs was explored, in line with the NICE reference case:

- Probabilistic sensitivity analysis (PSA) was performed to account for joint uncertainties of key model inputs. The PSA simultaneously varied all parameters with uncertainty in the model according to their SD/SE where available (if not available, assumptions were made i.e., SD 10% around the mean), sampling various input parameters from appropriate probability distributions as listed in Table 52.
- One-way deterministic sensitivity analysis (DSA) was performed to test key model inputs for each treatment arm, which is useful for identifying key drivers of the model results and to examine individual areas of uncertainty.
- Scenario analyses were conducted to assess the impact of changes in model assumptions on the results. One or more model input(s) can be varied simultaneously.

The results are provided below.

B.3.8.1 Probabilistic sensitivity analysis

The results of the PSA based on 1,000 simulations are presented in Table 55, which shows consistency in the mean estimates, demonstrating the robustness of the base case results. The PSA simulations are also plotted in a scatterplot showing the cost and health outcomes for each run; the cost-effectiveness acceptability curve shows that when varying the cost-effectiveness threshold olaparib is consistently the most probable cost-effective option against cabazitaxel (Figure 34 and Figure 35).

Table 55. PSA results.

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Olaparib	[redacted]	[redacted]	[redacted]	-£2,597	0.50	0.33	**Olaparib is dominant**	
Cabazitaxel	[redacted]	[redacted]	[redacted]					
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

Figure 34. PSA results scatterplot, costs and QALYs for olaparib and cabazitaxel (1,000 simulations).

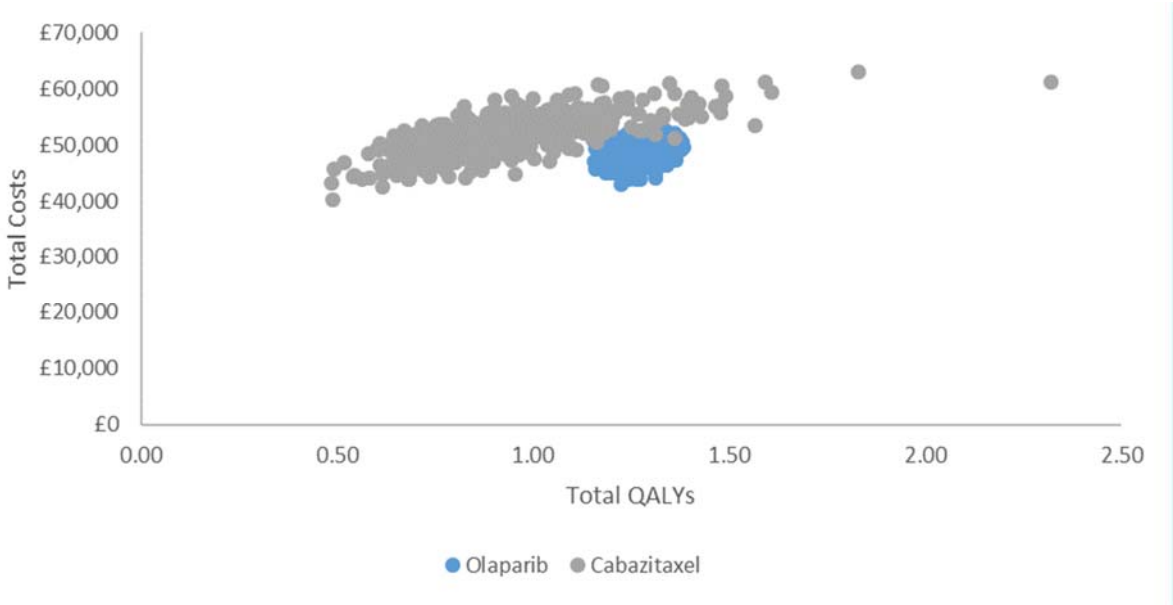
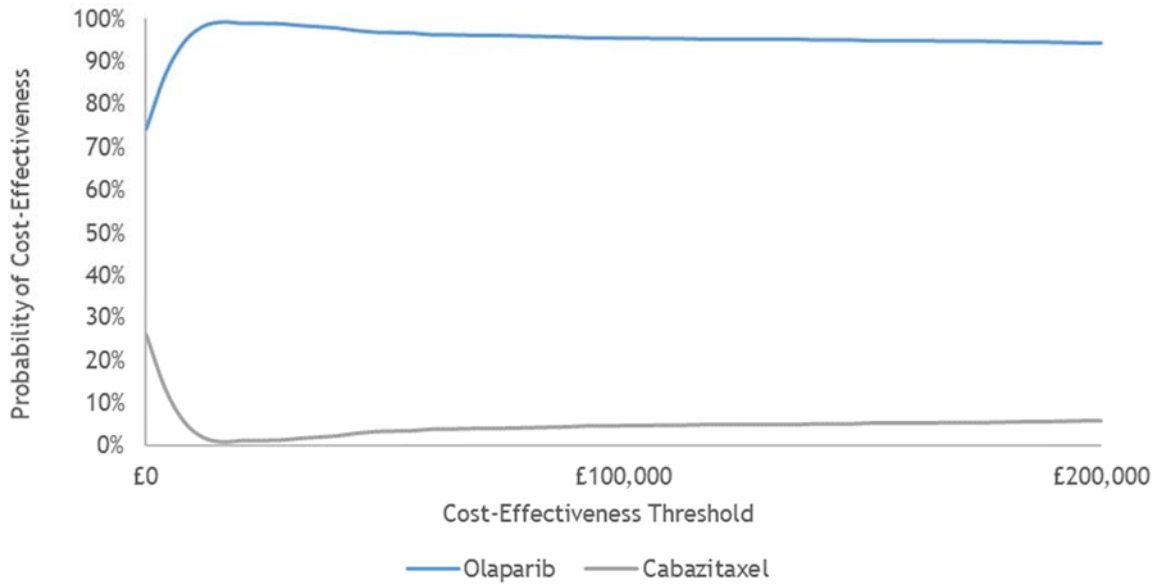


Figure 35. Cost-effectiveness acceptability curve (olaparib versus cabazitaxel).

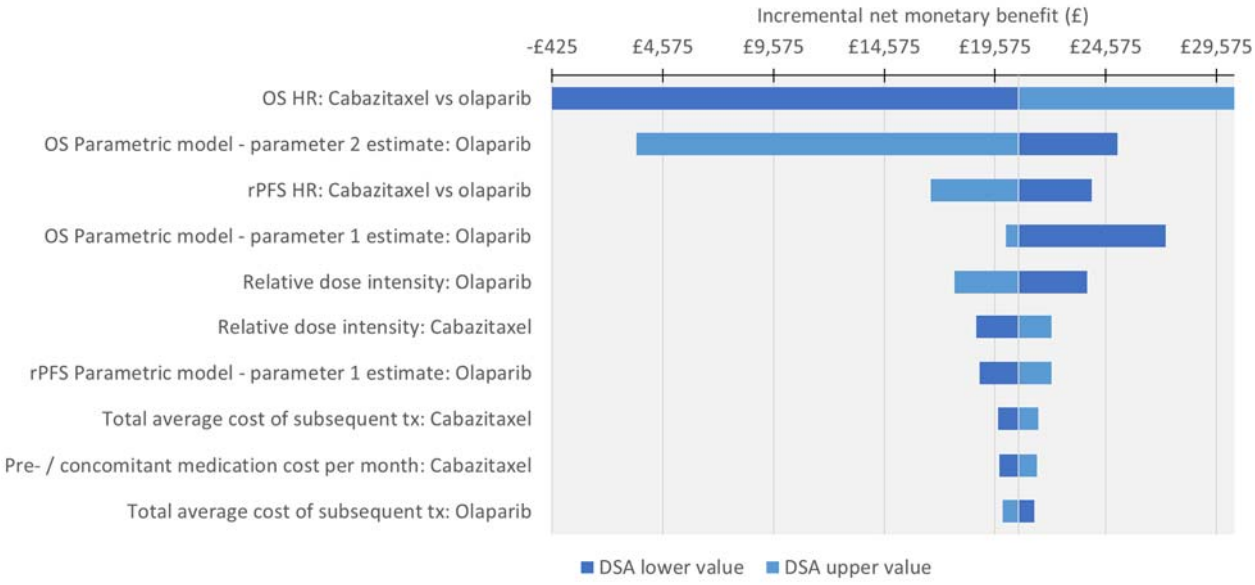


B.3.8.2 Deterministic sensitivity analysis

One-way sensitivity analyses were conducted by varying input values to their lower and upper values, to demonstrate the impact of changes in the model parameters on results. The inputs that had the most impact on the results in terms of incremental net monetary benefit (INMB) are displayed in Figure 36. As is usually the case in technology appraisals, varying inputs related to OS & PFS assumptions had the

most impact on the ICERs; this is to be expected, particularly when OS data are not fully mature (such as in this submission). The final OS update from the PROfound study will provide more certainty in this regard.

Figure 36. Tornado plot: 10 most influential inputs (DSA results).



B.3.8.3 Scenario analysis

An extensive list of scenarios were tested to provide a complete understanding of the impact of various assumptions on the model results. A brief description of each scenario and the results are presented in Table 56.

Olaparib remained dominant in each of the 17 scenarios tested, driven by the health benefits expected to be gained with olaparib treatment and the high costs associated with cabazitaxel.

Table 56. Scenario analyses

Scenario		Brief rationale	ICER (£ per QALY)
Base case			**Olaparib is dominant**
1	OS (Lognormal) distribution for olaparib	Explore the impact on the results when the lognormal distribution is selected for OS, which most closely reflected 5- and 10-year survival estimates from UK clinical experts.	**Olaparib is dominant**

2	rPFS (Generalised gamma) distribution for olaparib	Explore the impact on the results of using the next best-fitting distribution for rPFS.	**Olaparib is dominant**
3	Cost of cabazitaxel aligned with administration of cabazitaxel in the CARD study (allow treatment beyond 10 cycles)	The base case analysis is conservative because it restricts the cost of cabazitaxel to the reimbursable maximum of 10 treatment cycles (TA391) while efficacy from CARD is not adjusted for treatment duration. This scenario tests the impact on the results of aligning costs with the administration of the CARD study.	**Olaparib is dominant**
4	Treatment duration: medians reported for olaparib in PROfound, and cabazitaxel with no treatment cap based on CARD	Test alternative assumptions for treatment duration (consistent approach used for olaparib and cabazitaxel)	**Olaparib is dominant**
5	Treatment duration: TTD for olaparib (Weibull) based on PROfound, median for cabazitaxel with no treatment cap based on CARD	Test alternative assumptions for treatment duration (utilising patient-level data from PROfound, and the median reported in CARD)	**Olaparib is dominant**
6	G-CSF with cabazitaxel: 90%	Understand the impact of changing the % G-CSF use	**Olaparib is dominant**
7	G-CSF with cabazitaxel per UK EAP/CUP (Bahl 2015): 79.5%	Test the impact of using a different source for the % value of G-CSF use	**Olaparib is dominant**
8	Exclude modality-specific disutility due to IV administration (mean PF HSUV on treatment is the same for olaparib and cabazitaxel)	Test the impact of different assumptions; that the IV administration of cabazitaxel does not impact quality of life, therefore the PF utility while on treatment is the same across treatments.	**Olaparib is dominant**
9	Mean HSUV based on PROfound: Exclude AE & SRE disutility	Test alternative assumptions related to AE and SRE disutilities.	**Olaparib is dominant**
10	Mean HSUVs based on UK EAP in TA391 (PF: 0.737, PD: 0.627)	Understand the impact of different assumptions for the source/value of mean HSUVs; based on UK EAP for cabazitaxel (no modality-specific adjustment applied to cabazitaxel; modality-specific increment applied to olaparib instead).	**Olaparib is dominant**
11	Mean HSUVs based on UK EAP in TA391:	Test alternative assumptions related to HSUVs, AE and SRE disutilities.	**Olaparib is dominant**

	Exclude AE & SRE disutility		
12	Exclude SRE costs and SRE disutility	Understand the impact of removing SREs from the economic analysis (both costs and disutilities).	**Olaparib is dominant**
13	Assume 100% RDI for olaparib and cabazitaxel	Test impact of alternative assumption (dose reduction not allowed	**Olaparib is dominant**
14	Assume there is wastage (no vial sharing)	Understand the impact of alternative assumption due to uncertainty around the application of vial sharing in NHS practice (TA391).	**Olaparib is dominant**
15	Alternative subsequent treatment assumptions: exclude enza / abi and re-weight distribution	Explore alternative assumptions for the distribution of subsequent treatments (affects costs only; no adjustment for efficacy)	**Olaparib is dominant**
16	Include one-off cost of genetic testing (olaparib)	Included for completeness only as this does not reflect expectations; explore a scenario where genetic testing is not provided under the Genomic Test Directory.	**Olaparib is dominant**
17	Discount rates (costs and health outcomes): 1.5%	Understand the impact of discounting on the model results.	**Olaparib is dominant**

AE, adverse event; EAP, Expanded Access Program; G-CSF, granulocyte-colony stimulating factor; HSUV, health-state utility value; ICER, incremental cost-effectiveness ratio; IV, intravenous; NHS, National Health Service; OS, overall survival; PF, progression-free; QALY, quality-adjusted life year; rPFS, radiological progression-free survival; SRE, skeletal-related event.

B.3.8.4 Summary of sensitivity analyses results

The sensitivity analyses support the base case result that olaparib dominates cabazitaxel in this population, providing additional health benefits at a lower cost compared with cabazitaxel over the model time horizon (15 years).

At the cost-effectiveness threshold of £50,000/QALY for end-of-life medicines that is relevant to this appraisal, olaparib is therefore a highly cost-effective use of NHS resources. Olaparib remained dominant versus cabazitaxel in every scenario tested, driven by the health benefits associated with olaparib treatment and the high costs associated with cabazitaxel. The probabilistic analyses are consistent with the base case results, and predict that olaparib is the most probable cost-effective option versus cabazitaxel at any willingness-to-pay threshold ranging from £0 to £200,000/QALY.

B.3.9 Subgroup analysis

No additional subgroup analyses were conducted.

B.3.10 Validation

B.3.10.1 Validation of cost-effectiveness analysis

The modelling approach was determined by reviewing existing NICE technology appraisals in prostate cancer and considering the most appropriate methods for assessing the cost-effectiveness of olaparib in the population of interest. The strengths of the partitioned survival approach are well-documented (NICE DSU TSD19).[117] This approach is flexible, capturing clinically important aspects and quantifying the primary objectives of treating patients with mCRPC. It makes the best use of currently available evidence.

Before conducting the final analyses, a review of the cost-effectiveness model was performed by two internal health economists at AstraZeneca as well as an external health economist. The process involved a comprehensive and rigorous quality check, including validating the logical structure of the model, mathematical formulas, sequences of calculations, and the values of numbers supplied as model inputs. Technical validation was conducted by the external health economist, performing extreme-value sensitivity analyses, which sought to identify and correct potential inconsistencies in model behaviour. The process included checking the intermediate calculations for references (whether they are linked to correct cells, etc.), implementation (whether correct signs for the parameters are used, etc.), and evaluation of the face validity of predicted results. All Visual Basic for Applications (VBA) macros in the economic model were reviewed and validated. The appropriateness of distributions used in the probabilistic analysis of the model were also checked. Following the validation, corrections of any identified issues were incorporated into the final model used in this submission.

As outlined in the sections above, long-term model extrapolations were validated against key trial publications, and UK clinical expert opinion for each treatment in the

population of interest. Additionally, UK clinical experts consulted by AstraZeneca also validated the model approach or assumptions, provided advice from a clinical perspective, and/or directly provided model inputs related to: adverse events and skeletal-related events, primary prophylactic G-CSF with cabazitaxel, health state resource use for disease monitoring / follow-up and best supportive care.

All unit costs were obtained from sources relevant to the UK setting to ensure that the results of the economic analysis are appropriate for decision-making, in line with the NICE reference case. This included the most recent publications for the NHS Schedule of Reference Costs (2018-2019), PSSRU 2019, eMIT database, and BNF (online).

B.3.11 Interpretation and conclusions of economic evidence

The key data for olaparib are derived from the PROfound study, a large Phase III randomised clinical trial assessing the clinical efficacy and safety of olaparib versus investigator's choice of NHA in patients with mCRPC with HRR mutations, whose disease has progressed after treatment with an NHA. The analysis utilised the patient-level data from the prior taxane subgroup of the overall HRRm study population of PROfound (Cohort A+B), to reflect the population of patients who would be most-likely to receive treatment with olaparib in real-world practice (where the majority [~75%] of patients are treated with a taxane [docetaxel, with ADT] earlier in the clinical pathway, for HSPC]. A *de novo* cost-effectiveness model was developed in accordance with the NICE reference case to evaluate the cost-effectiveness of olaparib in this population of patients versus cabazitaxel, the current standard-of-care in this setting in England. The data for cabazitaxel was derived from the CARD study, the only source of clinical trial evidence for cabazitaxel in a post-NHA setting.[67] In the absence of head-to-head evidence comparing olaparib with cabazitaxel, an anchored ITC was conducted to estimate the relative effectiveness of treatments in accordance with NICE DSU TSD18, using the PROfound and CARD studies. Based on the ITC results, olaparib is expected to improve rPFS (HR[redacted]) and OS (HR,[redacted]) compared with cabazitaxel.

Extrapolation of time-to-event data was required to model health and cost outcomes associated with olaparib and cabazitaxel over a lifetime horizon. Parametric analyses

were conducted based on the prior taxane subgroup of the PROfound study, in line with NICE DSU TSD 14[125] (section B.3.3.2.1). Multiple alternative parametric functions were assessed according to best practice guidance to model outcomes with olaparib. Outcomes for cabazitaxel were modelled by applying the reciprocal of the ITC results to the parametric curve for olaparib as the reference arm.

Extrapolation of time-to-event data was required to model health and cost outcomes associated with olaparib and cabazitaxel over a lifetime horizon. Parametric analyses were conducted based on the prior taxane subgroup of Cohort A+B from the PROfound study, in line with NICE DSU TSD 14. Multiple alternative parametric functions were assessed according to best practice guidance to model outcomes with olaparib. Outcomes for cabazitaxel were modelled by applying the reciprocal of the ITC results to the parametric curve for olaparib as the reference arm.

At DCO1, the rPFS data within the prior taxane subgroup of PROfound were relatively mature and the parametric models were reasonable similar and consistent in terms of long-term outcomes; therefore, the selection of the most appropriate rPFS model was based on an assessment of the statistical goodness-of-fit (Weibull). The OS data were relatively immature (Section B.2.6), and thus the selection of OS distributions was determined by an assessment of the statistical goodness-of-fit of the parametric models, UK clinical expert advice on long-term outcomes on cabazitaxel in real-world clinical practice, as well as their expectations for olaparib based on experience in clinical trials and expectations based on the observed data from PROfound prior taxane subgroup. Of the six parametric distributions, the log-logistic model for OS was the only model that provided clinically-plausible (albeit, conservative) estimates of long-term survival for olaparib in conjunction with a reasonable statistical and visual fit to data. Outcomes predicted for cabazitaxel using each parametric distribution for olaparib were validated, and confirmed that it is most appropriate to use the log-logistic distribution. The lognormal distribution produced long-term survival estimates for olaparib and cabazitaxel that most closely matched estimates from UK clinician experts, therefore, this was tested in the scenario analysis.

The cost-effectiveness analysis presented in the submission is based on comparative evidence of olaparib versus cabazitaxel - the main treatment option and standard-of-care in the UK for the majority (~75%) of mCRPC patients who have received a prior taxane and NHA – and shows that **olaparib dominates cabazitaxel in this population, providing additional health benefits at a lower cost compared with cabazitaxel over the model time horizon. At the cost-effectiveness threshold of £50,000/QALY for end-of-life medicines that is relevant to this appraisal, olaparib is a highly cost-effective use of NHS resources**. The cost saving achieved with olaparib is driven by differences in resource use and subsequent treatment across the interventions, coupled with the costs incurred due to pre-/concomitant medications associated with cabazitaxel therapy. These results are seen *despite* a number of conservative assumptions applied in the model, that could have underestimated the cost of cabazitaxel compared with reality, including: assuming there is no wastage at all for cabazitaxel (i.e., vial sharing is allowed and applied routinely in practice across the UK), that the single administration cost of cabazitaxel at each model cycle covers a number of required premedications and prophylactic G-CSF with cabazitaxel, and that costs are only accrued for a maximum of 10 treatment cycles to reflect NICE recommendations despite modelling the efficacy of cabazitaxel using the CARD study, where this limitation was not imposed.

The sensitivity analyses supported the robustness of the base case results. **Olaparib remained dominant in every scenario tested, and in the probabilistic sensitivity analysis.** The PSA results were consistent with the base case analysis, with olaparib predicted to provide an additional 0.50 LYs and an additional 0.33 QALYs, and a cost saving of £2,597 compared with cabazitaxel. When varying the cost-effectiveness threshold from £0 to £200,000 per QALY gained, olaparib is consistently the most probable cost-effective option against cabazitaxel.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Olaparib for previously treated hormone-relapsed metastatic prostate cancer [ID1640]

Clarification questions - Response

July 2020

File name	Version	Contains confidential information	Date
ID1640_olaparib_ERG response_24July2020 [ACIC]	0.6	Yes	24 July 2020

Section A: Clarification on effectiveness data

A1. **Priority question:** Please clarify the definition of *suspected* deleterious mutation as used in Document B (e.g. page 36). Please complete the table below outlining how many participants had (1) deleterious mutations, and (2) suspected deleterious mutations in each trial arm (olaparib, investigators' choice of NHA) by each cohort.

Company response:

An investigational clinical trial assay, based on the FoundationOne CDx next-generation sequencing test developed in partnership with Foundation Medicine, was used to prospectively identify patients with qualifying deleterious or suspected deleterious alterations in at least 1 of the 15 prespecified genes. Qualifying HRR gene mutations included: *BRCA1*, *BRCA2* and *ATM* for Cohort A, and *BARD1*, *BRIP1, CDK12, CHEK1*, *CHEK2*, *FANCL*, PAL*B2, PPP2R2A, RAD51B, RAD51C, RAD51D* and *RAD54L* for Cohort B. All randomised patients in PROfound were categorised as having *deleterious* HRRm mutations.

A2. Please provide the definition of 'clinically meaningful', as used in document B, pages 70 (paragraph 1), 98 (paragraphs 2 and 3), 100 (paragraph 3), and 136 (paragraph 1).

Company response:

There is not an accepted or widely-recognised definition for what is considered to be a clinically meaningful benefit, and varies across cancer indications/endpoints; by an ASCO recommendation on metastatic solid tumours, a 20% improvement could be interpreted as ‘clinically meaningful’.(1) In the context of this submission, the term was used to highlight an important patient benefit versus the comparator or an existing standard of care

A3. Please provide the details of the studies for docetaxel in the same format as the studies for olaparib an cabazitaxel (that is, please provide table 14 appendix D in the same format as tables 12 and 13 in appendix D).

Company response:

The docetaxel studies identified by the SLR, with the same detail as presented in Tables 12 and 13 of Appendix D, are discussed in Table 1 below.

Table 1. Summary of identified publications reporting outcomes with docetaxel.

Publication	Trial ID	Intervention vs comparator	Prior therapies, n, (%)	Selected endpoints	Considered relevant to the decision problem:
Castellano *et al*, 2017(2)	NCT02036060	Stage II of study: Docetaxel (three-weekly, 75 mg/m^2 plus P 10 mg/d with (arm A) or without (arm B) AA 1000 mg daily	Stage I: abiraterone (1000 mg + prednisone 10 mg qd) until progressive disease	• rPFS	No: single-centre Japan study (no European patients). Abstract only: outcomes reported by response to prior NHA (hence different from the PROfound study population); no detailed information or KM available.
De Bono *et al,* 2017(3)	NCT00887198	Docetaxel	Placebo or abiraterone (1000 mg QD plus prednisone 5 mg BID	• ≥50% PSA decline • First subsequent therapy received	No: OS and PFS data not reported
Lewis *et al*, 2018(4)	NCT02494921	Ribociclib (escalating dose, starting at 200 mg daily + docetaxel 75 mg/m^2	Prior progression on abiraterone and/or enzalutamide	• RP2D • PSA50 response rate • ORR	No: no docetaxel monotherapy
Oudard *et al*, 2005(5)	NR	• Docetaxel (70 mg/m^2) and estramustine (280 mg PO tid) • Mitoxantrone 12 mg/m2 every 3 weeks (All patients received prednisone (10 mg daily).	N/A	• PSA response • Adverse events	No: no docetaxel monotherapy
Petrioli *et al*, 2015(6)	NR	Docetaxel 30 mg/m^2 iv + epirubicin 30 mg/m^2 iv	Docetaxel + abiraterone	• PSA response • Adverse events	No: no docetaxel monotherapy. Study included locally advanced (or metastatic) CRPC patients

Publication	Trial ID	Intervention vs comparator	Prior therapies, n, (%)	Selected endpoints	Considered relevant to the decision problem:
Pili *et al*, 2010(7)	NR	Docetaxel 75 mg/m^2 Vadimezan; 5,6-dimethylxanthenone-4-acetic acid 1,200 mg/m2) + docetaxel 75 mg/m^2	No previous chemotherapy	• PSA response • PFS • OS	No: not post-NHA.
Puente *et al*, 2018(8)}	NCT02036060	Stage II of study: Docetaxel (three-weekly, 75 mg/m^2 plus P 10 mg/d with (arm A) or without (arm B) AA 1000 mg daily	Stage I: abiraterone (1000 mg + prednisone 10 mg qd) until progressive disease	• Patient characteristics • Treatment dose intensity • Adverse events	No: no efficacy data
Sugiyama *et al*, 2018(9)	NR	Docetaxel 70 mg/m^2 every 3 weeks	Prior progression on abiraterone and/or enzalutamide (N=114)	• PSA response/PFS • OS	No: single-centre Japan study (no European patients). Abstract only. No detailed information or KM available

A4. Please provide the following outcomes for the TOPARP-B study 300mg BID arm in the format of the table below:

- OS KM data,
- rPFS KM data.

Please present the baseline characteristics of these patients, including prior treatments, and if possible, the subsequent treatments received, providing as much consistency with Table 5 (page 38, document B) as possible. If possible, please also provide this data restricted to patients with prior NHA experience.

Timepoint	N at risk	Event	Censored	S(t)
T=0	N=???	0	0	100%
T=???	N=???	N=???	N=???	???
T=???	N=???	N=???	N=???	???
Etc…	Etc…	Etc…	Etc…	Etc…

Company response:

The requested data are provided below to the best level of granularity available:

[Confidential file redacted]

The TOPARP-B study was an externally-sponsored study conducted by the Institute of Cancer Research (ICR). rPFS and OS KM plots from the study were included in the supplementary appendix of the primary publication (Mateo *et al*., 2020),(10) and are available in the public domain. All baseline features, including by dose group, can be found in the TOPARP-B study publication, and are available here:

- https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(19)30684-9/fulltext
- https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(19)30684-9/fulltext#supplementaryMaterial

A5. Please provide the PROfound CONSORT patient flow diagram for

- Cohort A
- Cohort A+B
- Cohort A+B prior taxane use.

Company response:

Please see Figure 2 of the CSR (p117) for a full flow diagram of patients across Cohort A and Cohort B (i.e. Cohort A+B). The patient flow for the Cohort A+B prior taxane subgroup is given in Table 2. Due to time constraints, we were unable to provide these in the form of a consort diagram; we would be happy to provide this at a later date, if helpful.

Table 2. Patient flow in PROfound Cohort A+B prior taxane subgroup

	Prior taxane subgroup[a]		
	Olaparib 300 mg bid	**Investigators' choice of NHA**	Total
Patients enrolled[b]	N/A	N/A	281
Patients randomized	170 (100.0)	84 (100.0)	254 (100.0)
Patients who were not randomized	N/A	N/A	27
Subject decision			2
HRRm eligibility criteria not fulfilled			1
Other eligibility criteria not fulfilled			24
Other			0
Full analysis set	170 (100.0)	84 (100.0)	254 (100.0)
Patients who did not receive treatment	0	1 (1.2)	1 (0.4)
Patients ongoing treatment at data cut-off[c]	34 (20.0)	6 (7.2)	40 (15.8)
Patients who discontinued treatment:[c]	136 (80.0)	77 (92.8)	213 (84.2)
Subject Decision	15 (8.8)	8 (9.6)	23 (9.1)
Adverse event	16 (9.4)	5 (6.0)	21 (8.3)
Severe Non-Compliance to Protocol	0	0	0
Objective radiographic progression	58 (34.1)	49 (59.0)	107 (42.3)
Unequivocal clinical progression	32 (18.8)	11 (13.3)	43 (17.0)
Development of study-specific discontinuation criteria	1 (0.6)	0	1 (0.4)
Other	14 (8.2)	4 (4.8)	18 (7.1)

Patients ongoing study at data cut off:	84 (49.4)	30 (35.7)	114 (44.9)
Patients who terminated study	86 (50.6)	54 (64.3)	140 (55.1)
Death	72 (42.4)	45 (53.6)	117 (46.1)
Screen failure	0	1 (1.2)	1 (0.4)
Withdrawal by subject	14 (8.2)	7 (8.3)	21 (8.3)
Other	0	1 (1.2)	1 (0.4)

[a] Subgroup adjusting for previous taxane (yes, no), collected via IVRS
[b] Informed consent received.
[c] Percentages are calculated from number of patients who received treatment. Treatment refers to study treatment and does not include treatment after switch to Olaparib.
Unless otherwise stated, percentages are calculated from the number of patients randomized.
Full analysis set - all randomized patients with treatment groups assigned in accordance with the randomization, regardless of the treatment actually received.
Blank cells indicate data not reported
NHA = New Hormonal Agent (abiraterone, enzalutamide).

A6. Please provide a version of Table 5 (page 38, document B) expanded to include time since diagnosis of prostate cancer and distribution of patients between countries. If possible, please also include time since diagnosis of metastatic prostate cancer and body surface area (BSA).

Company response:

The required additions to the table of patient baseline characteristics are given in below. Please note that patient height was not captured in PROfound; therefore, body surface area data cannot be provided. However, since olaparib has a fixed dose, this is not anticipated to have material impact on the appraisal.

Table 3. Baseline characteristics of patients in Cohort A+B, Cohort A, Cohort A+B prior taxane subgroup (expanded)

Baseline characteristics	Cohort A+B FAS		Primary study population: Cohort A FAS		Subgroup relevant for economic analysis: Prior taxane use[a] Cohort A+B	
	Olaparib 300 mg bid (n = 256)	Investigators' choice of NHA (n = 131)	Olaparib 300 mg bid (n = 162)	Investigators' choice of NHA (n = 83)	Olaparib 300 mg bid (n = 170)	Investigators' choice of NHA (n = 84)
Age Mean (SD) Median (range) < 65, n (%) ≥ 65, n (%) ≥ 75, n (%)	68.5 (8.44) 69.0 (47–91) 82 (32.0) 174 (68.0) NR	68.9 (7.58) 69.0 (49–87) 34 (26.0) 85 (64.9) NR	68.0 (8.23) 68.0 (47–86) 54 (33.3) 108 (66.7) NR	68.1 (7.36) 67.0 (49–86) 23 (27.7) 60 (72.3) NR	[redacted] NR	[redacted] NR
Time since diagnosis of prostate cancer (months) Mean (SD) Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time from mCRPC to randomisation (months) n Mean (SD) Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
White Black or African American Asian Other Missing	163 (63.7) 7 (2.7) 69 (27.0) 2 (0.8) 15 (5.9)	85 (64.9) 1 (0.8) 36 (27.5) 1 (0.8) 8 (6.1)	109 (67.3) 2 (1.2) 43 (26.5) 1 (0.6) 7 (4.3)	55 (66.3) 1 (1.2) 19 (22.9) 1 (1.2) 7 (8.4)	[redacted]	[redacted]
Ethnic group, n (%)						
Hispanic or Latino	17 (6.6)	12 (9.2)	12 (7.4)	9 (10.8)	[redacted]	[redacted]

Not Hispanic or Latino	228 (89.1)	112 (85.5)	145 (89.5)	69 (83.1)	[redacted]	[redacted]
Missing	15 (5.9)	8 (6.1)	5 (3.1)	5 (6.0)	[redacted]	[redacted]
Region, n (%)						
Asia	88 (34.4)	46 (35.1)	57 (35.2)	28 (33.7)	[redacted]	[redacted]
Europe	112 (43.8)	53 (40.5)	68 (42.0)	38 (45.8)		
N and S America	56 (21.9)	32 (24.4)	37 (22.8)	17 (20.5)		
Sites of disease at baseline, n (%)[b]						
Prostate	14 (5.5)	21 (16.0)	27 (16.7)	12 (14.5)	[redacted]	[redacted]
Locoregional lymph nodes	54 (21.1)	31 (23.7)	35 (21.6)	17 (20.5)	[redacted]	[redacted]
Distant lymph nodes	99 (38.7)	51 (38.9)	59 (36.4)	35 (42.2)	[redacted]	[redacted]
Bone	218 (85.2)	113 (86.3)	140 (86.4)	73 (88.0)	[redacted]	[redacted]
Respiratory	43 (16.8)	15 (11.5)	30 (18.5)	11 (13.3)		
Liver	25 (9.8)	18 (13.7)	18 (11.1)	13 (15.7)	[redacted]	[redacted]
Other distant metastases	57 (22.3)	31 (23.7)	34 (21.0)	15 (18.1)	[redacted]	[redacted]
Bone only	65 (25.4)	36 (27.5)	42 (25.9)	25 (30.1)	[redacted]	[redacted]
Lymph node only	18 (7.0)	9 (6.9)	13 (8.0)	5 (6.0)	[redacted]	[redacted]
Bone and lymph node only	46 (18.0)	19 (14.5)	26 (16.0)	14 (16.9)	[redacted]	[redacted]
ECOG performance status at baseline, n (%)						
0	131 (51.2)	55 (42.0)	84 (51.9)	34 (41.0)	[redacted]	[redacted]
1	112 (43.8)	71 (54.2)	67 (41.4)	46 (55.4)		
2	13 (5.1)	4 (3.1)	11 (6.8)	3 (3.6)	[redacted]	[redacted]
Missing	0	1 (0.8)	0	0	[redacted]	[redacted]
Total Gleason index at baseline, n (%)						
2	1 (0.4)	0	1 (0.6)	0	[redacted]	[redacted]
3	0	0	0	0		
4	2 (0.8)	0	2 (1.2)	0	[redacted]	[redacted]
5	2 (0.8)	1 (0.8)	2 (1.2)	1 (1.2)	[redacted]	[redacted]

6	6 (2.3)	4 (3.1)	6 (3.7)	3 (3.6)	[redacted]	[redacted]
7	57 (22.3)	27 (20.6)	41 (25.3)	22 (26.5)	[redacted]	[redacted]
8	61 (23.8)	28 (21.4)	36 (22.2)	12 (14.5)	[redacted]	[redacted]
9	101 (39.5)	56 (42.7)	59 (36.4)	35 (42.2)	[redacted]	[redacted]
10	21 (8.2)	11 (8.4)	10 (6.4)	7 (8.4)	[redacted]	[redacted]
Missing	5 (2.0)	4 (3.1)	5 (3.1)	3 (3.6)	[redacted]	[redacted]
Baseline pain score (BPI-SF worst pain [item 3]), n (%)						
0–< 2	125 (48.8)	57 (43.5)	83 (51.2)	37 (44.6)	[redacted]	[redacted]
2–3	31 (12.1)	13 (9.9)	17 (10.5)	9 (10.8)	[redacted]	[redacted]
> 3	93 (36.3)	56 (42.7)	56 (34.6)	34 (41.0)	[redacted]	[redacted]
≥ 4	NR	NR	NR	NR		
Missing	7 (2.7)	5 (3.8)	6 (3.7)	3 (3.6)	[redacted]	[redacted]
Baseline PSA (µg/L), n (%)						
Median, (range)	68.2 (0.2–7240.7)	106.5 (1.85–7115.0)	62.2 (0.20–7240.7)	112.9 (1.85–7115.0)	[redacted]	[redacted]
Measurable disease at baseline, n (%)[c]						
Yes	149 (58.2)	72 (55.0)	95 (58.6)	46 (55.4)	[redacted]	[redacted]
No	107 (41.8)	59 (45.0)	67 (41.4)	37 (44.6)	[redacted]	[redacted]
Missing	NR	NR	NR	NR	[redacted]	[redacted]
Patients with taxane treatment prior to randomisation, n (%)						
Yes	170 (66.4)	84 (64.1)	106 (65.4)	52 (62.7)	[redacted]	[redacted]
No	86 (33.6)	47 (35.9)	56 (34.6)	31 (37.3)	[redacted]	[redacted]
Previous docetaxel only	115 (44.9)	58 (44.3)	74 (45.7)	32 (38.6)	[redacted]	[redacted]
Previous cabazitaxel only	3 (1.2)	0	2 (1.2)	0	[redacted]	[redacted]
Previous docetaxel and cabazitaxel	51 (19.9)	26 (19.8)	29 (17.9)	20 (24.1)	[redacted]	[redacted]
Prior paclitaxel	1 (0.4)	0	1 (0.6)	0	[redacted]	[redacted]
Previous NHA use, n (%)						
Enzalutamide	103 (40.2)	54 (41.2)	67 (41.4)	40 (48.2)	[redacted]	[redacted]

Abiraterone	97 (37.9)	54 (41.2)	61 (37.7)	29 (34.9)	[redacted]	[redacted]
Enzalutamide and abiraterone	51 (19.9)	23 (17.6)	32 (19.8)	14 (16.9)	[redacted]	[redacted]
Missing	NR	NR	NR	NR	[redacted]	[redacted]
Single mutation status[d]						
BRCA1	8 (3.3)	5 (4.2)	8 (5.4)	5 (6.6)	[redacted]	[redacted]
BRCA2	81 (33.9)	47 (39.2)	80 (54.1)	47 (61.8)	[redacted]	[redacted]
ATM	62 (25.9)	24 (20.0)	60 (40.5)	24 (31.6)	[redacted]	[redacted]
BARD1	0	1 (0.8)	0	0	[redacted]	[redacted]
BRIP1	2 (0.8)	1 (0.8)	0	0	[redacted]	[redacted]
CDK12	61 (25.5)	28 (23.3)	0	0	[redacted]	[redacted]
CHEK1	1 (0.4)	1 (0.8)	0	0	[redacted]	[redacted]
CHEK2	7 (2.9)	5 (4.2)	0	0	[redacted]	[redacted]
FANCL	0	0	0	0	[redacted]	[redacted]
PALB2	3 (1.3)	1 (0.8)	0	0	[redacted]	[redacted]
PPP2R2A	6 (2.5)	4 (3.3)	0	0	[redacted]	[redacted]
RAD51B	4 (1.7)	1 (0.8)	0	0	[redacted]	[redacted]
RAD51C	0	0	0	0	[redacted]	[redacted]
RAD51D	1 (0.4)	0	0	0	[redacted]	[redacted]
RAD54L	3 (1.3)	2 (1.7)	0	0	[redacted]	[redacted]
Co-mutations[f]	17 (6.6)	11 (8.4)	14 (8.6)	7 (8.4)	[redacted]	[redacted]

[a] Subgroup adjusting for previous taxane (yes, no), collected via IVRS

[b] As per investigator assessment. Patients with multiple sites of disease within the same category of extent of disease are counted only once in that category. [c] Derived from eCRF data.

[d] Proportions expressed as % of the total number of patients in the analysis set with single mutations: Cohort A+B (234 for olaparib and 118 for investigator's choice of NHA), Cohort A (148 for olaparib and 76 for investigator's choice of NHA), Cohort A+B prior taxane (163 for olaparib and 78 for investigator's choice of NHA). ATM ataxia telangiectasia mutated; BARD1 BRCA1 associated ring domain protein; bid twice daily; BRCA breast cancer susceptibility gene; BRIP1 BRCA1 interacting protein

C-terminal helicase 1; CDK12 cyclin-dependent kinase 12; CHEK1 checkpoint kinase 1; CHEK2 checkpoint kinase 2; FANCL FA complementation group; FAS full analysis set; HRR homologous recombination repair; NHA new hormonal agent; PALB2 partner and localizer of BRCA2; PPP2R2A protein phosphatase 2 regulatory subunit B alpha; RAD51B RAD51 paralog B; RAD51C RAD51 paralog C; RAD51D RAD51 paralog D; RAD54L RAD54 like.

e Reported as a patient who received prior cisplatin and fluorouracil and paclitaxel.

[f] A detailed overview of co-mutations is given in Appendix M.

bid, twice daily; eCRF, electronic case report form; IVRS, interactive voice response system; NR, not reported; SD, standard deviation

Source: de Bono et al 2020,(11) Clinical Study Report Edition 1 – 23 October 2019(12) and de Wit 2019(13)

A7. Priority question: Radium-223 dichloride is recommended in NICE TA412 for treating hormone-relapsed prostate cancer with bone metastases and no known visceral metastases, and it is also considered a relevant comparator in TA391 for cabazitaxel. Please state if most patients' numbers under Other Distant Metastases: Bone Only of Table 5 (page 38, document B) would qualify for treatment with Radium-223 under current NICE guidelines. If most would not qualify, please explain why. If most would qualify please supply for this subgroup the following outcomes in each treatment arm in the format of the table below:

- OS KM data,
- rPFS KM data

Please provide this for Cohort A, Cohort A+B and Cohort A+B prior taxane use.

Timepoint	N at risk	Event	Censored	S(t)
T=0	N=???	0	0	100%
T=???	N=???	N=???	N=???	???
T=???	N=???	N=???	N=???	???
Etc…	Etc…	Etc…	Etc…	Etc…

Company response:

The NICE recommendation for radium-223 dichloride (TA412) is for patients with hormone-relapsed prostate cancer with bone metastases and no known visceral metastases who have already received treatment with docetaxel, or for whom docetaxel is contraindicated or is not suitable.

While it can be ascertained which of the patients in the bone metastases only subgroup had received prior docetaxel treatment, **it is likely that these patients would receive cabazitaxel after NHA in UK clinical practice, with radium-223 being reserved for later lines of treatment** (as explained in Section B.1.2 of Document B).

Moreover, in the prior taxane subgroup of Cohort A+B, 42 (24.7%) of patients in the olaparib arm and 19 (22.6%) patients in the investigators' choice of NHA arm had bone metastases only at study baseline. Given the small patient numbers, any analyses based on this dataset would be subject to substantial methodological issues associated with a small sample size and, as such, not provide a sufficiently

robust evidence base for decision-making. The ability to conduct an indirect treatment comparison between olaparib vs radium-223 using this dataset is also limited by a lack of published evidence on radium-223 in the post-NHA setting, as explained in Section B.2.1 and Section B.2.9.1 of Document B.

It is not possible to determine the group of patients with bone metastases only for whom treatment with docetaxel was contraindicated (or was not suitable), since this information was not collected. Furthermore, this population would fall outside the main subgroup of interest, which forms the basis of the company submission, i.e. patients who have received a prior taxane for their disease.

A8. Please provide the equivalent of Table 5 document B for the subset of patients in the control arm of:

- Cohort A **who did not cross over** to receive olaparib
- Cohort A+B **who did not cross over** to receive olaparib,
- Cohort A+B prior taxane use **who did not cross over** to receive olaparib.

Company response:

At DCO1, [redacted]%, [redacted]%, and [redacted]% of patients in the NHA arm of Cohort A, Cohort A+B, and Cohort A+B prior taxane subgroup, respectively, **did not cross over** to receive olaparib treatment after progression. Their baseline characteristics are provided in Table 4. Kindly note that information on regions and measurable disease at baseline are currently being analysed; we will follow-up with these data as soon as they become available.

Table 4. Baseline characteristics of patients in Cohort A+B, Cohort A, Cohort A+B prior taxane subgroup in the NHA arm who did not cross over to receive olaparib

	Cohort A+B FAS	Primary study population: Cohort A FAS	Subgroup relevant for economic analysis: Prior taxane use[a] Cohort A+B
	Investigators' choice of NHA (n = [redacted])	Investigators' choice of NHA (n = [redacted])	Investigators' choice of NHA (n = [redacted])
Age Mean (SD) Median (range) < 65, n (%) ≥ 65, n (%)	[redacted]	[redacted]	[redacted]
Time since diagnosis of prostate cancer (months) Mean (SD) Median (range)	[redacted]	[redacted]	[redacted]
Time from mCRPC to randomisation (months) Mean (SD) Median (range)	[redacted]	[redacted]	[redacted]
White Black or African American Asian Other Missing	[redacted]	[redacted]	[redacted]
Ethnic group, n (%)			
Hispanic or Latino	[redacted]	[redacted]	[redacted]

Not Hispanic or Latino	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]
Sites of disease at baseline, n (%)[b]			
Prostate	[redacted]	[redacted]	[redacted]
Locoregional lymph nodes	[redacted]	[redacted]	[redacted]
Distant lymph nodes	[redacted]	[redacted]	[redacted]
Bone	[redacted]	[redacted]	[redacted]
Respiratory	[redacted]	[redacted]	[redacted]
Liver	[redacted]	[redacted]	[redacted]
Other distant metastases	[redacted]	[redacted]	[redacted]
Bone only	[redacted]	[redacted]	[redacted]
Lymph node only	[redacted]	[redacted]	[redacted]
Bone and lymph node only	[redacted]	[redacted]	[redacted]
ECOG performance status at baseline, n (%)			
0	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]
Total Gleason index at baseline, n (%)			
2	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]

7	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]
Baseline pain score (BPI-SF worst pain [item 3]), n (%)			
0–< 2	[redacted]	[redacted]	[redacted]
2–3	[redacted]	[redacted]	[redacted]
> 3 ≥ 4	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]
Baseline PSA (µg/L), n (%)			
Median, (range)	[redacted]	[redacted]	[redacted]
Measurable disease at baseline, n (%)[c]			
Yes	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]
Patients with taxane treatment prior to randomisation, n (%)			
Yes	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]
Previous docetaxel only	[redacted]	[redacted]	[redacted]
Previous cabazitaxel only	[redacted]	[redacted]	[redacted]
Previous docetaxel and cabazitaxel	[redacted]	[redacted]	[redacted]
Previous NHA use, n (%)			
Enzalutamide	[redacted]	[redacted]	[redacted]
Abiraterone	[redacted]	[redacted]	[redacted]

Enzalutamide and abiraterone	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]
Single mutation status[d]			
BRCA1	[redacted]	[redacted]	[redacted]
BRCA2	[redacted]	[redacted]	[redacted]
ATM	[redacted]	[redacted]	[redacted]
BARD1	[redacted]	[redacted]	[redacted]
BRIP1	[redacted]	[redacted]	[redacted]
CDK12	[redacted]	[redacted]	[redacted]
CHEK1	[redacted]	[redacted]	[redacted]
CHEK2	[redacted]	[redacted]	[redacted]
FANCL	[redacted]	[redacted]	[redacted]
PALB2	[redacted]	[redacted]	[redacted]
PPP2R2A	[redacted]	[redacted]	[redacted]
RAD51B	[redacted]	[redacted]	[redacted]
RAD51C	[redacted]	[redacted]	[redacted]
RAD51D	[redacted]	[redacted]	[redacted]
RAD54L	[redacted]	[redacted]	[redacted]
Co-mutations[e]	[redacted]	[redacted]	[redacted]

[a] Subgroup adjusting for previous taxane (yes, no), collected via IVRS

[b] As per investigator assessment. Patients with multiple sites of disease within the same category of extent of disease are counted only once in that category. [c] Derived from eCRF data.

[d] Proportions expressed as % of the total number of patients in the analysis set with single mutations: Cohort A+B (234 for olaparib and 118 for investigator's choice of NHA), Cohort A (148 for olaparib and 76 for investigator's choice of NHA), Cohort A+B prior taxane (163 for olaparib and 78 for investigator's choice of NHA). ATM ataxia telangiectasia mutated; BARD1 BRCA1 associated ring domain protein; bid twice daily; BRCA breast cancer susceptibility gene; BRIP1 BRCA1 interacting protein C-terminal helicase 1; CDK12 cyclin-dependent kinase 12; CHEK1 checkpoint kinase 1; CHEK2 checkpoint kinase 2; FANCL FA complementation group; FAS full

analysis set; HRR homologous recombination repair; NHA new hormonal agent; PALB2 partner and localizer of BRCA2; PPP2R2A protein phosphatase 2 regulatory subunit B alpha; RAD51B RAD51 paralog B; RAD51C RAD51 paralog C; RAD51D RAD51 paralog D; RAD54L RAD54 like.

[e] A detailed overview of co-mutations is given in Appendix M.

bid, twice daily; eCRF, electronic case report form; IVRS, interactive voice response system; NR, not reported; SD, standard deviation

Source: de Bono et al 2020,(11) Clinical Study Report Edition 1 – 23 October 2019(12) and de Wit 2019(13)

A9. Please tabulate the post rPFS treatments (N? receiving each treatment out of N? patients) separately for:

- olaparib arm,
- comparator arm
- comparator arm without cross over to olaparib

Please provide this for Cohort A, Cohort A+B and Cohort A+B prior taxane use.

Company response:

Data on the subsequent anti-cancer treatments received post-discontinuation of study treatment (i.e., post-rPFS BICR) are given for both arms of PROfound in Table 5, below. Subsequent treatments received in comparator arm for patients who do not cross over to olaparib are also provided, per the request.

Table 5 Subsequent anti-cancer treatment received post-discontinuation of treatment study in PROfound (Cohort A, Cohort A+B, Cohort A+B Prior taxane)

	Cohort A			Cohort A+B			Cohort A+B Prior taxane		
	Olaparib 300mg bd	Investigators choice of NHA	Investigators choice of NHA Patients who do not switch to olaparib	Olaparib 300mg bd	Investigators choice of NHA	Investigators choice of NHA Patients who do not switch to olaparib	Olaparib 300mg bd	Investigators choice of NHA	Investigators choice of NHA Patients who do not switch to olaparib
	N = 162	N = 83	N = [redacted]	N = 256	N = 131	N = [redacted]	N = 170	N = 84	N = [redacted]
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Patients with any post-discontinuation anticancer therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abiraterone Acetate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Enzalutamide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ethinylestradiol	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Goserelin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Leuprorelin Acetate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cabazitaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Carboplatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Capecitabine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dexamethasone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Etoposide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Investigational Antineoplastic Drugs	[redacted]								
Investigational Drug	[redacted]								
Lutetium (Lu 177)	[redacted]								
Mitoxantrone	[redacted]								
Prednisolone	[redacted]								
Radium Ra 223 Dichloride	[redacted]								
Uftoral	[redacted]								
Various Therapeutic Radiopharmaceuticals	[redacted]								
Vinorelbine Tartrate	[redacted]								
Zoledronic Acid	[redacted]								
Cancer Vaccines	[redacted]								
Durvalumab	[redacted]								
Tremelimumab	[redacted]								
Tuberculin	[redacted]								
Goserelin Acetate	[redacted]								
Cisplatin	[redacted]								
Denosumab	[redacted]								
Estramustine Phosphate Sodium	[redacted]								
Vinorelbine Tartrate	[redacted]								

[a] Therapies post-discontinuation of study treatment. Patients can be counted in more than one anticancer therapy.(12)
[b] Off-label use of olaparib

A10. **Priority question:** Please provide the following, separately for each arm of PROfound, and for the subset of the PROfound control arm that did not cross over to receive olaparib. This should be based on DCO1 (4 June 2019) and also DCO2 (20 March 2020) where available:

- OS KM data,
- rPFS KM data
- TTD KM data,
- PFS2 KM data,

Please provide this disaggregated by events recorded (e.g. rPFS event, death, lost to follow-up, data cut-off date), flagging which events are treated as events and which as censoring, in the format of the table below. Please provide this separately for Cohort A, Cohort A+B and Cohort A+B prior taxane use. Please provide within Excel if possible.

Event type flag		Event/Censor	Event/Censor	Event/Censor	
Timepoint	N at risk	Event 1	Event 2	Etc…	S(t)
T=0	N=???	0	0	0	100%
T=???	N=???	N=???	N=???	N=???	???
T=???	N=???	N=???	N=???	N=???	???
Etc…	Etc…	Etc…	Etc…	Etc…	Etc…

Company response:

Please find the requested KM data for rPFS/OS/TTD endpoints in the specified populations in the Excel spreadsheets below. Please note that in the interest of time, and considering that PFS2 was neither included in the NICE final scope nor used in the economic modelling, these data have not been included.

[Confidential files redacted]

A11. **Priority question:** Table 5 has N/A for cells 'Patients with taxane treatment prior to randomisation' for Cohort A and for Cohort A+B and N/A for Previous taxane therapy at mCRPC for the target Cohort A+B prior taxane group.

- Please supply this data if available.
- Please clarify how previous taxane therapy at mCRPC differs from patients with taxane treatment prior to randomisation.
- The PROfound trial CSR p.90 has a stratification factor "previous taxane use (yes, no)". Of the above 2 descriptions of prior taxane use in table 5, please clarify which one most closely corresponds with this. Please state which definition corresponds to prior taxane use subgroup definition separately for (1) the cross over adjustment work, (2) the other inputs to the ITC and (3) the Kaplan Meier data used to estimate the parameterised curves of the economic model. If any of these taxane use definitions differs from the other(s) please provide the KM data corresponding to that requested under A10 above for the subgroup not addressed in the response to A10 above.

Company response:

Randomisation was stratified by previous taxane use (yes, no) and measurable disease at baseline (yes, no), to ensure that patients were well-balanced across treatment arms. All patients in the "prior taxane subgroup" of PROfound, and accordingly all analyses used in the submission which refer to this subgroup, received prior taxane therapy ***at any point*** prior to randomisation. Therefore, the prior taxane stratification factor in PROfound corresponds with the Cohort A+B prior taxane group of interest in the appraisal. The breakdown of patients for prior taxane experience has been completed for patients in Cohort A+B and Cohort A in Table 6.

Table 6. Prior taxane experience of patients in PROfound Cohort A+B, Cohort A, prior taxane subgroup

Baseline characteristics	Cohort A+B FAS		Primary study population: Cohort A FAS		Subgroup relevant for economic analysis: Prior taxane use[a] Cohort A+B	
	Olaparib 300 mg bid (n = 256)	Investigators' choice of NHA (n = 131)	Olaparib 300 mg bid (n = 162)	Investigators' choice of NHA (n = 83)	Olaparib 300 mg bid (n = 170)	Investigators' choice of NHA (n = 84)
Patients with taxane treatment prior to randomisation, n (%)						
Yes	170 (66.4)	84 (64.1)	106 (65.4)	52 (62.7)	[redacted]	[redacted]
No	86 (33.6)	47 (35.9)	56 (34.6)	31 (37.3)	[redacted]	[redacted]
Previous docetaxel only	115 (44.9)	58 (44.3)	74 (45.7)	32 (38.6)	[redacted]	[redacted]
Previous cabazitaxel only	3 (1.2)	0	2 (1.2)	0	[redacted]	[redacted]
Previous docetaxel and cabazitaxel	51 (19.9)	26 (19.8)	29 (17.9)	20 (24.1)	[redacted]	[redacted]
Prior paclitaxel	1 (0.4)	0	1 (0.6)	0	[redacted]	[redacted]
Previous taxane therapy for mCRPC, n (%)						
Yes	147 (57.4)	73 (55.7)	91 (65.2)	43 (51.8)	[redacted]	[redacted]
No	109 (42.6)	58 (44.3)	71 (43.8)	40 (48.1)	[redacted]	[redacted]
Previous docetaxel only	95 (37.1)	48 (36.6)	60 (37.0)	24 (28.9)	[redacted]	[redacted]
Previous cabazitaxel only	13 (5.1)	2 (1.5)	5 (3.1)	1 (1.2)	[redacted]	[redacted]
Previous docetaxel and cabazitaxel	39 (15.2)	23 (17.6)	26 (16.0)	18 (21.7)	[redacted]	[redacted]

A12. **Priority question**: Please provide the following outcomes, for the control arm of PROfound. This should be based on DCO1 (4 June 2019) and also DCO2 (20 March 2020) where available:

- **RPFST** OS KM data **Weibull without censoring**,
- **IPCW** OS KM data for the restricted variable analysis
- **IPCW** OS KM data for the all variable analysis.

Please provide this separately for Cohort A, Cohort A+B and Cohort A+B prior taxane use, in the format of the table below. Please provide within Excel if possible.

Timepoint	N at risk	Event	Censored	S(t)
T=0	N=???	0	0	100%
T=???	N=???	N=???	N=???	???
T=???	N=???	N=???	N=???	???
Etc…	Etc…	Etc…	Etc…	Etc…

Company response:

Please find the requested KM data attached in the Excel spreadsheet below.

[Confidential file redacted]

A13. Figure 8 (page 62, document B) and Figure 17 (page 78, document B) appear similar if not identical. Please provide in Excel the Weibull parameters underlying the smooth curves of the intended Figure 8 and Figure 17, and also implement these parameters within the Excel to derive the smooth curves of the figures. Please also provide the equivalent of this for Cohort A.

Company response:

We apologise for the duplication across Figure 8 / Figure 17 in the submission; please note that this occurs in the submission report only and does not affect any analysis used in the economic model.

The correct figures and parameter estimates implemented to produce the survival curve extrapolations are provided below for Cohort A+B, and Cohort A per the request.

Figure 1. Kaplan–Meier plot of counterfactual for overall survival in Cohort A+B (RPSFTM Weibull method, no re-censoring)

Table 7. Cohort A+B, Parameter estimates (Weibull distribution)

	Investigators' choice of NHA			Olaparib 300 mg bd		
Weibull	est	L95%	U95%	est	L95%	U95%
shape	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
scale	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Figure 2. Kaplan–Meier plot of counterfactual for overall survival in patients who had prior taxane treatment in Cohort A+B (RPSFTM Weibull method, no re-censoring)

Table 8. Cohort A+B Prior taxane, Parameter estimates (Weibull distribution)

	Investigators' choice of NHA			Olaparib 300 mg bd		
Weibull	est	L95%	U95%	est	L95%	U95%
shape	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
scale	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Figure 3. Kaplan–Meier plot of counterfactual for overall survival in Cohort A (RPSFTM Weibull method, no re-censoring)

Table 9. Cohort A, Parameter estimates (Weibull distribution)

	Investigators' choice of NHA			Olaparib 300 mg bd		
Weibull	est	L95%	U95%	est	L95%	U95%
shape	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
scale	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

A14. Please provide the equivalent of Table 10 document B for the target Cohort A+B prior taxane group, augmented with the equivalent of the additional IPCW analysis that was provided for Cohort A+B and Cohort A in the 23 March 2020 treatment switching report. Please state the justification for the company preferred treatment switching method for the Cohort A+B prior taxane group, and

for its preference between the two IPCW analyses for the Cohort A+B prior taxane group.

Company response:

The requested data are provided in Table 10 below. Following the treatment switching analysis framework discussed in NICE DSU TSD 16 and based on detailed assessment of the underlying assumptions across treatment switching methods in the Cohort A+B prior taxane subgroup, the preferred treatment switching method was deemed to be the RPSFTM approach for many of the same reasons outlined in Document B, Section B.2.6.3.2 as reiterated below.

First, the key assumptions associated with the RPSFTM method, as described in NICE DSU TSD 16, were shown to hold in the prior taxane subgroup of Cohort A+B; therefore, the RPSFTM analyses were deemed to be reliable:

- The randomisation (exclusion restriction) assumption has been shown to hold in the Cohort A+B prior taxane subgroup data through plots comparing the counterfactual OS KM curves of the reference and comparator arms.
- The common treatment effect assumption was tested through a sensitivity analysis where a proportion of the olaparib treatment effect was applied to those switching to olaparib from investigators' choice of NHA. This showed that if the treatment effect were to decrease post-progression, it would still result in an overall benefit for the patients who switch, indicating that the analysis is robust to changes in treatment effect over time.
- There was a high degree of consistency across the RPSFTM models that indicates the results are reliable and generally robust to structural assumptions (i.e., with and without re-censoring, and across the log rank, Cox PH and Weibull models).

Additionally, there are several limitations specific to the IPCW analyses, which do not affect the RPSFTM method, further supporting the preference for the RPSFTM approach:

- The IPCW approach is dependent on the 'no unmeasured confounders' assumption and on the availability of data, particularly time-varying data, to predict switching. This assumption may not hold when there is relatively little prognostic data collected post-randomisation, limiting the scope of time-varying covariables that can be included in an analysis, as is the case with the data for the prior taxane subgroup of Cohort A+B in PROfound. The RPSFTM approach is not subject to this limitation, and is therefore preferred to the IPCW method in this context.

- The IPCW analysis is reliant on a reduced sample size, and the method is prone to bias when there are relatively small patient numbers and a high degree of switching in the control arm. In the prior taxane subgroup of Cohort A+B, only [redacted] of 84 ([redacted]%) patients in the investigators choice of NHA arm did not switch to olaparib, and these patients form the basis of the IPCW investigators choice of NHA survival estimates. This small sample size increases the amount of uncertainty associated with the IPCW results. The RPSFTM is based on all data for switchers and non-switchers, and are therefore deemed to be more reliable than the IPCW results.

Table 10 Median OS and HR for investigators' choice of NHA arm, adjusted for treatment switching; Cohort A+B prior taxane group, Cohort A+B and Cohort A

Test	Re-censoring (RPSFTM) or All variables/ restricted variables (IPCW)	Cohort A		Cohort A+B		Cohort A+B prior taxane group	
		Median OS (months) for investigators choice of NHA adjusted for switching	OS HR (95% CI) olaparib[a] vs. investigators' choice of NHA	Median OS (months) for investigators choice of NHA adjusted for switching	OS HR (95% CI) olaparib[a] vs. investigators' choice of NHA	Median OS (months) for investigators choice of NHA adjusted for switching	OS HR (95% CI) olaparib[a] vs. investigators' choice of NHA
RPSFTM							
Log rank	Without	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	With	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cox proportional hazards	Without	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	With	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	Without	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	With	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IPCW							
Adjusted for switching using IPCW	Restricted	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted for switching using IPCW	All	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Median OS with olaparib was 17.51 months as presented in Document B, Section 2.6.

Note: these data are used in the ITC comparison, Document B, Section 2.9.

CI, confidence interval; HR hazard ratio; IPCW, Inverse Probability of Censoring Weights; ITC, indirect treatment comparison; NHA, new hormonal agent; OS, overall survival; RPSFTM, rank preserving structural failure time model.

A15. The 23 March 2020 treatment switching report states that “A final data cut will be provided to Visible Analytics at the end of April 2020, and an update to this report will be produced.” Please clarify if any DCO2 data has been supplied to Visible Analytics, and if it has, please provide a copy of the resulting report, even if only available in draft. If it is not available, please state when you anticipate it will be available. Please also supply any additional DCO2 treatment switching analyses for the Cohort A+B prior taxane group.

Company response:

While top-line analyses of OS were available (and included) at the point of submission in an effort to be fully transparent with the available data, further detailed analyses of these data are required and are currently underway. Once analyses have been performed, these data must also be quality-checked before they can be used. Currently the most likely date for availability of these materials is late July, although we will communicate any updates to NICE in the interim.

A16. **Priority question:** Please provide the PROfound EQ-5D data (mapped to UK social tariff) split by pre and post progression in the format of the table below for:

- Cohort A
- Cohort A+B
- Cohort A+B prior taxane use

Please provide this separately for the olaparib arm, the comparator arm and the comparator arm without cross over to olaparib. If it is felt that including PFS patients who were off treatment within this is misleading, please provide this data as well.

			EQ-5D	
PFS	N remaining	n reporting	Mean	s.d.
Baseline	N=?	n=?	μ=?	s.d.=?
8 weeks	N=?	n=?	μ=?	s.d.=?
16 weeks	N=?	n=?	μ=?	s.d.=?
24 weeks	N=?	n=?	μ=?	s.d.=?
Etc…				
PPS	N remaining	n reporting	Mean	s.d.
Last scheduled prior to progression	N=?	n=?	μ=?	s.d.=?
1st 8 week post progression	N=?	n=?	μ=?	s.d.=?
2nd 8 week post progression	N=?	n=?	μ=?	s.d.=?
3rd 8 week post progression	N=?	n=?	μ=?	s.d.=?
Additional	N remaining	n reporting	Mean	s.d.
Last day of study drug	N=?	n=?	μ=?	s.d.=?
30 days after last dose	N=?	n=?	μ=?	s.d.=?

Company response:

In response to this clarification question, further utility analyses have been performed. These are outlined below, with the results tables attached as a Word document at the end.

Analysis dataset

In accordance with earlier analyses, all results are based on the Cohort A+B FAS of the PROfound trial. Records with analysis flag (ANL01FL) set to “yes” were included in the analysis. Analysis record flag is equal to “Yes” for records where only one record qualifies for the corresponding scheduled visit. If more than 1 record qualified for the visit window then the closest to the planned study day value would be chosen, or the earlier in the event the values are equidistant from the planned study day.

Records with a missing response on any EQ-5D domains were removed from the analysis. Similarly, records with invalid responses were removed. Specifically, EQ-5D domain responses were required to be a number in the set (1, 2, 3, 4, 5), with a valid value for each of the five dimensions.

Health State Utility Values

Health state utility values (HSUVs) were calculated using the standard value set for EQ-5D-5L based on the societal preferences of the general population in the UK using the crosswalk algorithm from EQ-5D-3L.

Patient groupings

Patients were grouped according to cohort and prior taxane use, and also according to randomised treatment and crossover to olaparib. Results are presented separately for:

- Cohort A
- Cohort A+B
- Cohort A+B with prior taxane use

Prior taxane use is determined according to the recorded stratification variable ASTRAT1.

Both olaparib and investigator's choice treatment arms are reported, with those patients in the investigator's choice arm who did not crossover to olaparib also reported separately. Crossover in this group was determined by the presence of a crossover start date.

Visit schedule

Since not all patients contributed EQ-5D data at each scheduled visit, any missed visits (from baseline to end of study) were included with missing EQ-5D data. For missing visits, the visit window was recorded, and it was assumed that the patient attended at the target date, for the purposes of imputing the patient's expected attendance at these missing visits. E.g. if a patient's disease progression date fell after the target date of a missing visit, and the patient was still in the study at this target date, then this patient was classified as progression free at this particular visit.

Patients with imputed participation in the study but with missing data at any particular visit are included as ‘remaining’ at that visit but not ‘reporting’, and they do not contribute to the HSUV mean and standard deviation.

Least squares means

Least squared means according to heath state, whether progression free (PF) or progressive disease (PD), were estimated according to mixed effects models with a random patient-level intercept and a fixed effect of health state.

Progression free summaries

Progression free summaries for each scheduled visit were constructed as described above for all 8 week visits from Baseline to 88 weeks. Number remaining and number reporting were determined according to the definitions above.

Progressive disease summaries

For all patients whose disease progressed during the course of the study the date of progression was compared to actual visit dates, where available, or target visit dates, where visits were missed, to determine:

- The last scheduled visit prior to progression
- The first visit post progression
- The second visit post progression
- The third visit post progression

Where a visit was missed the patient counted towards number remaining, and where a visit was not missed, they also contributed towards number reporting and also to the HSUV mean and standard deviation (SD).

Additional end-of-treatment summaries

Very few patients attended a visit on their last day of treatment, and none attended a visit 30 days after their last day of treatment, as shown in Figure 4 and Figure 5. As a result, the provided summaries refer to:

- the last visit within 15 days of end of treatment but no later than last day of treatment

- the first visit after end of treatment

All patients who complete treatment are classified as ‘remaining’ but only those with visits classified as above are treated as ‘reporting’.

Figure 4: Histogram of time of last visit on or before end of treatment

Figure 5: Histogram of time of first visit after end of treatment

Outputs from the analyses are presented in the Word document attached below.

[Confidential file redacted]

A17. **Priority question:** In terms of patient recruitment to PROfound:

A17.1. Please state the total number N of possible recruits to PROfound who were screened using the FoundationOne® assay (or similar) to assess initial eligibility.

Company response:

Overall, 4,425 patients were enrolled for screening using the FoundationOne CDx next-generation sequencing test, which was developed in partnership with Foundation Medicine Inc.

A17.2. Please state the number, N_A, of those under bullet 1 above who were found to remain as possible recruits to PROfound Cohort A through the FoundationOne® assay (or similar). Of this N_A, please state the number n_A whose tumour testing found them to remain as possible recruits to PROfound Cohort A (and separately n_B as possible recruits to Cohort B if this applies). Please state the final number of N_A who were recruited to PROfound.

Company response:

In PROfound, 2,792 (69%) patients were successfully sequenced with a biomarker status outcome reported. 778 of these patients were found to have an alteration in ≥1 of 15 prespecified HRR genes, i.e. suitable for Cohort A or Cohort B. 391 of these patients were excluded, with the most common reasons being: did not have normal organ and bone marrow function (91), systemic anticancer therapy ≤ 3 weeks (49), not willing or able to comply with study protocol (33), had not experienced imaging-based progression (32), had ECOG>2 (26). Patients with co-mutations from both the Cohort A and Cohort B were included in Cohort A, with one exception of a patient with BRCA2 and CDK12 erroneously included in Cohort B (see Appendix M of Document B). Out of the 387 patients randomised in total, 245 patients were randomised to Cohort A and 142 patients were randomised to Cohort B.

A17.3. Please state the number, N_B, of those under bullet 1 above who were found to remain as possible recruits to PROfound Cohort B through the FoundationOne® assay (or similar). Of this N_B, please state the number n_B whose tumour testing found them to remain as possible recruits to PROfound Cohort B (and separately n_A as possible recruits to Cohort A if this applies). Please state the final number of N_B who were recruited to PROfound.

Company response:

The answer to A17.2 applies here also.

A17.4. Please state the total number N of possible recruits to PROfound who were not initially screened using the FoundationOne® (or similar). Of these, please state the number n_A whose tumour testing found them to remain as possible recruits to PROfound Cohort A, and the number n_B whose tumour testing found them to remain as possible recruits to PROfound Cohort B. Please state the final number of n_A and n_B who were recruited to PROfound

Company response:

All patients in PROfound were screened using the FoundationOne test.

A17.5. What are the procedures for sampling and undertaking the FoundationOne® assay (or similar), and what is the approximate cost of the FoundationOne® assay in £UK (please state original currency and exchange rate applied if no £UK cost is available)?

Company response:

The procedures for sampling and undertaking the FoundationOne® assay, as performed in the context of the PROfound study, are shown in Figure 6 and Figure 7. The test used formalin-fixed paraffin embedded tissue in the form of blocks or slides.

Please note that the sample requirements outlined in this response concern the test as performed during enrolment into PROfound study; therefore, minor discrepancies may exist compared with the current FoundationOne® assay procedure, as performed in commercial practice today. Details of the current FoundationOne® sample handling procedure can be found at https://www.foundationmedicine.co.uk/.

Figure 6. Sample acquisition and review process for the FoundationOne® test in PROfound

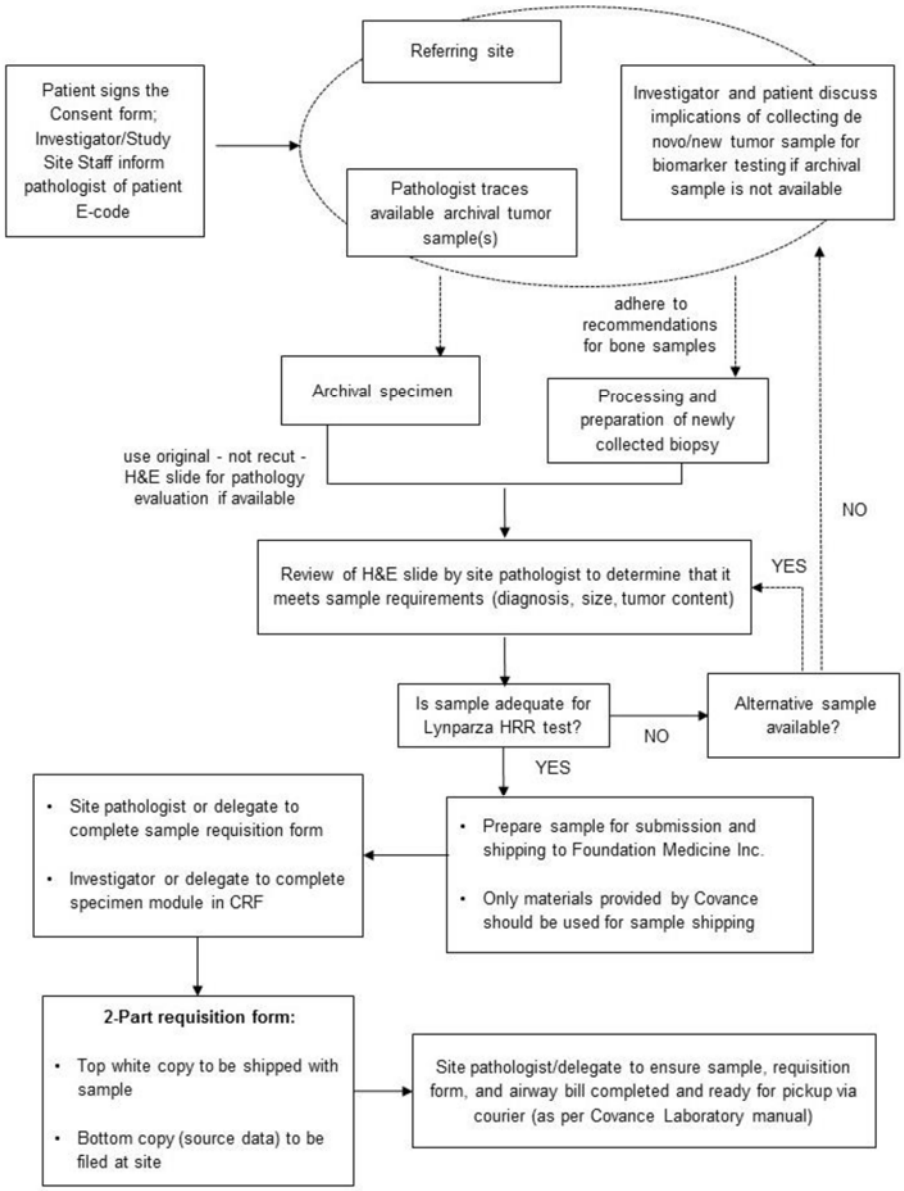
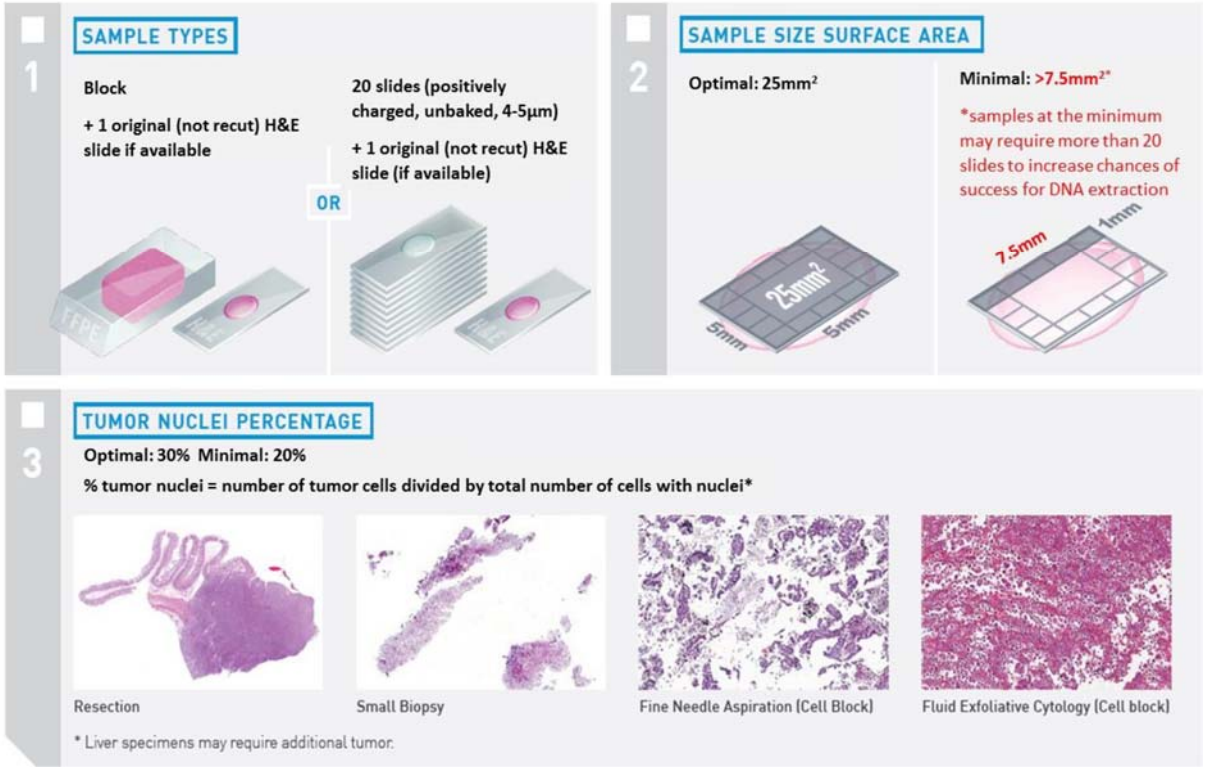


Figure 7. Sample requirements for the FoundationOne® test in PROfound



The anticipated cost of HRR testing in the UK, as part of the pan-cancer gene panel, is given as part of our answer to Question B10.

A18. Table 14 document B presents effect modifiers. Please tabulate the underlying values of the covariates for PROfound and for CARD that were inputted to the assessment of these effect modifiers. Please clarify if a similar analysis was undertaken for rPFS or if not please explain why this was not done (it is expected that this should have been possible given rPFS is the primary variable of both PROfound and CARD and that any rPFS analysis does not require the assumptions of the counterfactual OS data). If an rPFS analysis was performed please present its equivalent of Table 14 document B and the values

of the covariates for PROfound and for CARD that were inputted to the assessment of effect modifiers.

Company response:

An analysis was not initially considered necessary to test for rPFS effect modifiers, given the rationale outlined in Section B.2.9.2.3 of Document B. However, this has been conducted following the same methods that were used to test for effect modifiers on OS, as summarised below.

The potential effect modifiers for rPFS were assessed for the population of interest (Cohort A+B; prior taxane) using multivariable Cox regression analyses. The significance level was set to 20% (rather than the conventional 5% level), to maximise chances of identifying any variables that could be potentially effect modifying. The interpretation of a significant interaction result in this analysis would mean that the variable is more likely to be considered effect modifying.

As shown in Table 11, there are no significant effect modifiers for rPFS. The Bucher ITC, unadjusted for variables, as presented in the company submission therefore remains the most appropriate and reliable method for estimating the relative efficacy of olaparib versus cabazitaxel for both the rPFS and OS endpoints that is required to address the decision problem.

Table 11. Assessment of potential effect modifiers for rPFS

Covariate	rPFS - Effect modifier (coefficient (80% CI))
Age	[redacted]
Visceral disease	[redacted]
M1 disease	[redacted]
Gleason score 8-10	[redacted]
ECOG score	[redacted]
PSA*	[redacted]

	[redacted]

*Binary covariate was used for modelling

A19. If possible, please provide Table 16 durations augmented with means, and dose interruption augmented with duration range, median and mean. Please also explain why the paragraph prior to Table 16 suggests that the target group was not analysed for this data, yet it appears to be supplied in Table 16.

Company response:

The requested updates to Table 16 of Document B are presented in Table 12 below. With regard to the preceding paragraph stating that the analysis in the table is not included, this is an error based on the eventual last minute availability/insertion of the data in question. We apologise for the confusion.

Table 12. Summary of treatment exposure, dose interruptions, and dose modifications: Cohort A + B SAS and prior taxane subgroup, DCO1 (4th June 2019)

	SAS		Prior taxane subgroup	
	Olaparib 300 mg bid (n = 256)	Investigators' choice of NHA (n = 130)	Olaparib 300 mg bid (n = 170)	Investigators' choice of NHA (n = 83)
Duration of treatment (days),				
Total treatment duration[a], median (range)	[redacted]	[redacted]	[redacted]	[redacted]
Actual treatment duration[b], median (range)	[redacted]	[redacted]	[redacted]	[redacted]
Duration of treatment (days)				
Total treatment duration[a], mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Actual treatment duration[b], mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Patients, n (%)				
Dose interruptions	[redacted]	[redacted]	[redacted]	[redacted]
Dose reductions	[redacted]	[redacted]	[redacted]	[redacted]
Dose modifications	[redacted]	[redacted]	[redacted]	[redacted]
Dose interruption (days)				

Dose interruption duration, mean	[redacted]	[redacted]	[redacted]	[redacted]
Dose interruption duration, median (range)	[redacted]	[redacted]	[redacted]	[redacted]

SD = Standard deviation

A20. Please provide the min, max, median and mean DCO1 RDI separately for each arm for:

- Cohort A,
- Cohort A+B
- Cohort A+B prior taxane use.

Please also:

- state the total number of olaparib tablets taken to DCO1 and the total olaparib patient days on treatment to DCO1 for one of these patient groups, and if possible, for all three patient groups (cohort A, cohort A+B and cohort A+B prior taxane use). If this is available for DCO2 please also supply this.
- outline the arithmetic that would be used to calculate the mean olaparib RDI across two hypothetical patients: patient X who received a total of 2 packs of olaparib, took a total of 56 150mg tablets and ceased treatment on day 21 and patient Y who received a total of 4 packs of olaparib, took a total of 128 tablets and ceased treatment on day 42.
- clarify if the recorded treatment cessation dates were limited to assessment dates or could occur between assessment dates.

Company response:

Relative dose intensity (RDI) is expressed as the percentage of the actual dose delivered relative to the intended dose up to the point of treatment discontinuation.

- [redacted]

- [redacted]
- [redacted]

The requested data regarding the RDI of each arm of Cohort A, Cohort A+B and Cohort A+B prior taxane subgroup of the PROfound study are provided in Table 13. This includes the mean, median, min and max values for RDI for both arms of the PROfound study, as well as the number of days of treatment for olaparib which can be used to calculate the total number of tablets at DCO1 based on the recommended dose for olaparib..

Finally, recorded treatment cessation dates could occur between assessment dates. As is stated in the study protocol, the subject was free to discontinue treatment at any time, without prejudice to future treatment.

Table 13. Relative dose intensity across Cohorts of PROfound.

	Cohort A+B FAS		Primary study population: Cohort A FAS		Subgroup relevant for economic analysis: Prior taxane use Cohort A+B	
	Olaparib 300 mg bid (n = 256)	Investigators' choice of NHA (n = 131)	Olaparib 300 mg bid (n = 162)	Investigators' choice of NHA (n = 83)	Olaparib 300 mg bid (n = 170)	Investigators' choice of NHA (n = 84)
Relative dose intensity[a]						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Relative dose intensity (RDI) is the percentage of the actual dose delivered relative to the intended dose through to treatment discontinuation.

Table 14 Total number of days on treatment with olaparib across Cohorts of PROfound

	Cohort A+B FAS	Primary study population: Cohort A FAS	Subgroup relevant for economic analysis: Prior taxane use Cohort A+B
	Olaparib 300 mg bid (n = 256)	Olaparib 300 mg bid (n = 162)	Olaparib 300 mg bid (n = 170)
Total number of days on treatment[b]	[redacted]	[redacted]	[redacted]
Total number of days on treatment (actual, excluding dose interruptions)[c]	[redacted]	[redacted]	[redacted]

[a] Total treatment duration = (last dose date - first dose date +1)

[b] Actual treatment duration = (last dose date - first dose date +1) excluding dose interruptions.

Only includes data from the first treatment period.(12)

If the last dose date is unknown, the earliest available date where it is confirmed that no drug is being taken will be used instead.

Patient E7602055 had treatment exposure 42 days longer than reported as discontinuation date was misreported. Due to this error, the dose durations are incorrectly derived.

A21. **Priority question:** Please clarify if Table 17 NHA data is restricted to rPFS or may include olaparib related AEs among those who crossed over to olaparib. If the latter, please augment Table 17 with data for (1) SAS investigator choice NHA who did not cross over to olaparib, and (2) Prior taxane subgroup investigator choice NHA who did not cross over to olaparib.

Please also augment Table 17 with the individual SAEs causally related to treatment and the patients numbers experiencing these, and if the NHA data includes SAEs possibly related to olaparib cross-over also provide this for (1) SAS investigator choice NHA who did not cross over to olaparib, and (2) Prior taxane subgroup investigator choice NHA who did not cross over to olaparib.

Company response:

No AEs related to olaparib exposure were captured in the control arm of PROfound. All patients randomised to investigator choice, who received at least one dose of study treatment in Cohort A or in Cohort B, who subsequently switched to olaparib upon progression and received at least one dose of olaparib were included in the safety switch analysis set, and safety outcomes for these patients can be found in Section 12.6.2 of the CSR (p277).

As requested, Table 17 from Document B has been augmented below with SAEs causally related to treatment- these data can be found in Table 15 below.

Table 15. Adverse events in any category, DCO1 (4th June 2019) in Cohort A+B SAS/prior taxane subgroup.

	SAS		Prior taxane subgroup	
	Olaparib 300 mg bid (n = 256)	Investigators' choice of NHA (n = 130)	Olaparib 300 mg bid (n = 170)	Investigators' choice of NHA (n = 83)
Number (%) of patients[a]				
Any AE	244 (95.3)	114 (87.7)	[redacted]	[redacted]
Any AE, causally related to study treatment[b]	206 (80.5)	61 (46.9)	[redacted]	[redacted]
Any AE of CTCAE Grade 3 or higher	130 (50.8)	49 (37.7)	[redacted]	[redacted]
Any AE of CTCAE Grade 3 or higher, causally related to study treatment[b]	78 (30.5)	12 (9.2)	[redacted]	[redacted]

Any AE leading to death	10 (3.9)	5 (3.8)	[redacted]	[redacted]
Any SAE including those leading to death	91 (35.5)	36 (27.7)	[redacted]	[redacted]
Any AE leading to discontinuation	46 (18.0)	11 (8.5)	[redacted]	[redacted]
Any AE relating to dose reduction	57 (22.3)	5 (3.8)	[redacted]	[redacted]
Any AE relating to interruptions	115 (44.9)	24 (18.5)	[redacted]	[redacted]
SAEs causally related to treatment	**35 (13.7)**	**5 (3.8)**	[redacted]	[redacted]

[a] Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category were counted once in each of those categories.
[b] As assessed by the investigator.
Includes AEs with an onset date on or after the date of first dose and up to and including 30 days following discontinuation of randomised treatment or the day before switching to olaparib.
AE adverse event; bid twice daily; CTCAE Common Terminology Criteria for Adverse Events v4.03; DCO data cut-off; MedDRA Medical Dictionary for Regulatory Activities; NHA new hormonal agent; SAE serious adverse event; SAS safety analysis set.

A22. Please tabulate the number of PROfound patients experiencing 1st SSREs since baseline by arm, split by rPFS and PPS, if possible disaggregated by the type of SRE listed in the CSR section 8.4.2.4, including separate reporting of vertebral and non-vertebral fractures as available, for:

- Cohort A,
- Cohort A+B
- Cohort A+B prior taxane use.

Company response:

The requested data are provided in Table 16. Please note that it is not possible to separate out vertebral and non-vertebral fractures as this level of data was not collected in PROfound.

Table 16. Time to first Symptomatic Skeletal-related event, by prior/post rPFS and SSRE event type

	Cohort A+B FAS		Primary study population: Cohort A FAS		Subgroup relevant for economic analysis: Prior taxane use[a] Cohort A+B	
	Olaparib 300 mg bid (n = 256)	Investigators' choice of NHA (n = 131)	Olaparib 300 mg bid (n = 162)	Investigators' choice of NHA (n = 83)	Olaparib 300 mg bid (n = 170)	Investigators' choice of NHA (n = 84)
Prior to rPFS (BICR)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Use of radiation therapy to relieve or prevent skeletal symptoms	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Occurrence of new symptomatic bone fractures (vertebral or non-vertebral) deemed pathological (due to bone metastasis)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Occurrence of spinal cord compression deemed due to vertebral metastasis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Surgical intervention for bone metastasis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post rPFS (BICR)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Use of radiation therapy to relieve or prevent skeletal symptoms	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Occurrence of new symptomatic bone fractures (vertebral or non-vertebral) deemed pathological (due to bone metastasis)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Occurrence of spinal cord compression deemed due to vertebral metastasis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Surgical intervention for bone metastasis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Patients could have multiple SSRE events at the first SSRE date so can appear in multiple categories.
Patients with SSRE events on the same date as rPFS progression are counted in the post rPFS category.

A23. Please state when you anticipate the DCO2 results and the cross over analyses to be available.

Company response:

DCO2 for PROfound was in late March 2020. While top-line analyses of OS data from DCO2 were available (and included) at the point of submission in an effort to be fully transparent with NICE, further analyses of these data (i.e. the treatment switch analysis) are required before these data can be used in the cost-effectiveness analysis. Once the analyses have been performed, these data must also be quality-checked before they can be used. We anticipate that fully quality-checked final analyses will be available by the end of July; however, we will update NICE if these are available any sooner.

Section B: Clarification on cost-effectiveness data

B1. If the Model_Calcs worksheet is copied twice; once for olaparib with D4 set equal to 1, calling this Model_Calcs_OLAP, and once for cabazitaxel with D4 set equal to 2, calling this Model_Calcs_CABA, would the results of these two worksheet be exactly equivalent to those reported in the Results worksheet after running the Run_Deterministic VBA macro? If so, ignoring any effects upon running the DSA_Run, Tornado, PSA_Run and CEAC VBA macros, does having the Model_Calcs_OLAP worksheet and the Model_Calcs_CABA worksheet and taking results from these obviate the need for running the Run_Deterministic VBA macro?

Company response:

Yes, the worksheets may be copied as suggested and, ignoring any effects upon running the DSA_Run, Tornado, PSA_Run and CEAC VBA macros, would produce the same results without running the Run_Deterministic VBA macro. The VBA macros have been thoroughly validated by an external health economist, from a coding and implementation perspective.

B2. Given the graphed OS curves for olaparib in the OS_Graphs worksheet columns G:L, please provide an intuitive account of the need for and function of the adjustments made to the parameters in V14:V16 to arrive at the adjusted parameter values in V17:V19 for each of the possible values that the Distribution Index in V12 can take.

Company response:

We believe this question refers to the adjustment in the formulae in cells T13:16 and T17:19. The specific transformations identified in the clarification question are redundant and have no effect on the model results (no adjustment is ever made).

The formulae in cells T13:16 can be altered to simply replace the adjustment to set the rows to equal to 1, 2, 3 and 4, respectively, reflecting the 1st, 2nd, 3rd, 4th parameter estimates for the selected distribution. For example, the formula in cell T13 can be altered from *=INDEX(m.os.single.param,$B4+((T$11-1)*4))* to *=INDEX(m.os.single.param,1)* with no impact on the results.

The formulae in cells T17:19 be removed and set equal to cells T13:15. For example, the formula in cell T17 *=IFERROR(CHOOSE(T12,T13+T14,T13+T15,T13+T15,T13+T15,T13+T15,T13+T16),1)* can be replaced with *=T13* with no impact on the results.

B3. Within the *TTD_Graph* worksheet the relevant values are not drawn from the parameterised TTD curves but from the *PFS_Graph* worksheet parameterised curves when the *Efficacy* worksheet assumption for the discontinuation rule is to cap the TTDD by the PFS. This flows through to the *Model_Calcs* worksheet, but these values are subsequently restricted to be no more than the PFS values in cells P11:P251. Please provide the rationale for this model structure and comment upon the effect is has when changing the assumptions in the *Efficacy* worksheet around the discontinuation rule.

Addressing this may also raise concerns around the *Model_Calcs* worksheet AQ11:AQ251 calculation of the number of PFS patients off treatment. Does the model permit an exploration of the TTDD curve being applied, unconstrained by the PFS curve?

Company response:

The *TTD_Graph* worksheet chooses the correct curve depending on the selected treatment duration approach for each intervention in the model. The options available for olaparib and cabazitaxel are summarised in Table 17 below; full details for each method can be seen in Document B, Section B.3.3.3.2.

Table 17 Treatment duration options available in the economic model

***Efficacy* worksheet option (treatment duration rule)**	**Intervention / comparator, and data source**	***TTD_Graph* worksheet resulting range**
Treat to progression	• Olaparib (PROfound) • Cabazitaxel (ITC)	Parametrised rPFS curves (for both olaparib and cabazitaxel)
Treatment discontinuation curves	• Olaparib (PROfound) • Not available for cabazitaxel due to absence of published data	Parametrised TTD curves (olaparib only)

Median duration per trial	• Olaparib (PROfound) • Cabazitaxel (CARD)	Exponential TTD curve fitted to median value (for both olaparib and cabazitaxel)

The assumption that treatment duration is at most equal to the modelled rPFS curve is redundant and has no impact in the base case analysis when treating to progression. The model was therefore not set up to test the sole impact of removing the constraint on TTD. **Olaparib remains dominant to cabazitaxel when this constraint is removed in the base case and in the scenario analyses discussed in Table 18.**

As discussed in the company submission (Document B, Section B.3.3.3), the only approach that is deemed appropriate for decision-making purposes is that used in the base case analysis, where treatment duration is modelled by assuming a treat-to-progression rule for both olaparib and cabazitaxel (summarised in Table 18). This uses the same method and type of data for both olaparib and cabazitaxel, thus preventing the introduction of bias due to applying different methods for the intervention and the comparator. The treat to progression rule is also appropriately aligned with the study design of the PROfound and CARD clinical trials, uses the primary endpoint (rPFS) data from both studies, and is consistent with the anticipated Marketing Authorisation for olaparib, the intervention of interest for this appraisal. This rationale, as well as reasons for not utilising alternative approaches in the base case analysis, are summarised in Table 18.

Table 18 Base case and scenarios for treatment duration, including justification for approach

Analysis	Rationale
Base case • Olaparib and cabazitaxel: Treat to progression (rPFS curve)	• TTD data (either in the form of patient-level data or KM curves) are not available for cabazitaxel from the CARD study • Consistent approach, using rPFS being the primary endpoint in both PROfound and CARD clinical trials as a proxy for TTD, minimising potential bias due to implementing different methods between olaparib and cabazitaxel. • Reflects treat to progression rule for olaparib per anticipated EMA label and PROfound study design, and the administration of cabazitaxel in the CARD study (while capping costs to a maximum of 10 treatment cycles to align with NICE TA391 guidance). Note: the impact of removing the treatment limit for cabazitaxel was tested in scenario analyses.

Scenario 1 • Olaparib: Parametric TTD curve • Cabazitaxel: Median duration	• TTD approach for olaparib utilises patient-level data from the PROfound study to reflect the expected duration of olaparib treatment (including any early discontinuation; Document B, Section 3.3.3). Comparable published data are not available for cabazitaxel, either in the form of patient-level data or KM curves. • Median duration approach is utilised for cabazitaxel in the absence of published TTD data; however, this is an oversimplified approach that may not accurately reflect the duration of treatment or the shape of the treatment duration curve over time. The validity of the resulting curves as compared with actual treatment duration in clinical practice is also unclear. • Overall, this approach is not recommended for use in decision-making due to the data gaps and the inconsistency in modelling assumptions highlighted above. The use of different methods for olaparib and cabazitaxel may introduce an unquantifiable amount of bias into the model, which is unnecessary and avoidable.
Scenario 2 • Median duration for all interventions	• Not recommended for use in decision-making purposes, as modelling treatment duration based on the median exposure from trials is an over-simplified approach that uses a single summary statistic. This method may not accurately reflect the duration of treatment or the shape of the treatment duration curve over time for olaparib or cabazitaxel. The validity of the resulting curves with respect to actual clinical practice is also unclear. • Although this scenario allows the use of a consistent approach between olaparib and cabazitaxel to capture any early discontinuation of treatment, the base case approach (of treat to progression) is more appropriate, since it allows for a more detailed analysis that aligns with the primary endpoint and design of the PROfound and CARD clinical trials (as described above)

B4. The SSRE Quality of life effects and costs appear to be conditioned by the discounted sum of incident progressions, *c.inc.prog*. Please outline the rationale for this. If this is an error there is no need to submit amended results as the impact is likely to be minor.

Company response:

The range *c.inc.prog* represents the undiscounted half-cycle corrected incident progressions, this does not constitute an error. The occurrence of SSREs are a key clinical aspect of mCRPC due to the high propensity for prostate cancer to metastasise to bone tissue, with new symptomatic events often associated with disease progression.(14-16) The approach of applying SSRE quality of life effects and costs to the newly progressed patients at each model cycle (i.e., incident progressions) reflects this clinical feature.

B5. For DOF- GB-21957-MAY20 (ref#58) please clarify:

- how respondents were identified,
- the degree to which each had been involved in PARP treatment of mCRPC,
- whether conflicts of interests were recorded,
- whether they had any conflicts of interest prior to the survey,
- what if any remuneration was made,
- how the survey was carried out: questionnaire, telephone interview, group panel.

Please also supply the equivalent of Table 1 of ref#58 showing each respondent's response range (where this applies) rather than just their mid-point.

Company response:

All six respondents in the KEE study are leading UK clinical experts with at least 10 years' experience in the treatment of patients with prostate cancer, in particular mCRPC. In addition to their significant expertise in treating mCRPC, these clinicians were selected due to their experience in using PARP inhibitors (in a clinical trial setting).

The consultations took the format of questionnaires completed during one-hour teleconference interviews with two AstraZeneca employees, each with one clinician (i.e., six teleconferences in total), between 5th May and 15th May 2020. Conflicts of interest were not recorded prior to, or during, the consultations. Renumeration was in line with AZ honoraria for healthcare practitioners considered to be national experts[1] in their field.

We have provided the requested data, i.e., survival estimates for cabazitaxel and olaparib as presented in Table 26/Table 27 of Document B, showing the range of responses, for each respondent, in Table 19 below.

[1] National Expert: has specialist expertise in an area and is well-established as an expert within the UK. They may be key stakeholders in national guidelines or learned societies due to their research or expertise within a particular area. Taken from AZ UK Fair Market Value Table: Honoraria for Engagement of UK HCPs

Table 19 Expected survival from the point of progression on 1L mCRPC NHA, with subsequent treatment (range of responses)

	% patients alive at 3 years						% patients alive at 5 years						% patients alive at 10 years					
	#1	#2	#3	#4	#5	#6	#1	#2	#3	#4	#5	#6	#1	#2	#3	#4	#5	#6
Cabazitaxel	[redacted]																	
Olaparib	[redacted]																	

SoC = standard of care; NR = no response

B6. Please state the numbers of patients with leukopenia and neutropenia, and whether this information was communicated to the experts when consulting them about probable rates of leukopenia and neutropenia in the cabazitaxel arm of the CARD trial. Please also state how many experts were consulted, what question was put to them and provide each respondent's range for both leukopenia and neutropenia in a similar format to that requested under B6 above.

Company response:

The percentage of patients (not individual numbers of patients) with thrombocytopenia, anaemia, leukopenia and neutropenia based on the CARD study, as reported in the de Wit 2019 publication, were shown to six clinical experts (the same as described above in response to Question B5).

Each of the six participants were asked the following questions:

- "Which of the four laboratory abnormalities below (thrombocytopenia, anaemia, neutropenia and leukopenia) would be affected by G-CSF use?"
- "Based on your clinical experience, what is the actual expected Grade 3+ adverse event rates for patients treated with cabazitaxel in a post-NHA setting - please fill in the table considering patients with and without the use of primary prophylactic G-CSF separately".

All respondents confirmed that the incidence of thrombocytopenia and anaemia would not be expected to be affected by G-CSF use; therefore, only AE values for neutropenia and leukopenia were discussed and elicited. Please note that clinicians were not specifically asked for minimum or maximum values as part of this question. The ranges, where provided by each respondent, are as shown in DOF #21949, Table 2.

B7. Please outline the arithmetic required to derive the PFS on treatment cabazitaxel quality of life value.

Company response:

The utility value for cabazitaxel in the PFS "on treatment" state is applied to the proportion of patients remaining on treatment with cabazitaxel at each model cycle, and is calculated as follows:

$U_{CabazitaxelPFOnTx} = U_{BaselinePF} - U_{IVdecrement}$ = [redacted] - 0.0230 = [redacted]

The PFS baseline value of [redacted] ([redacted] rounded to 4 d.p. for reporting purposes only) is based on the PROfound EQ-5D cross-walk analysis presented in Section B.3.4 of the submission. A modality-specific decrement was applied to account for the benefit associated with olaparib being an oral drug that can be taken by patients at home (Section B.3.4.6 of the submission). The modality-specific utility decrement of 0.0230 is the utility decrement associated with the *30-minute* IV infusion vignette as reported in the Matza 2013 publication, since values for *1-hour* IV infusion (per the duration of infusion of cabazitaxel) were not available. This is deemed to be a conservative approach.

B8. Please clarify if Table 45 document B reports only the 1st subsequent treatment received during PROfound, or all subsequent treatments. If the former, please state the mean number of subsequent treatments. Please also provide for Cohort A, A+B and A+B prior taxane use:

- the Table 45 unadjusted olaparib arm data.
- DCO2 PROfound olaparib arm (1) number of progression events, (2) number of patients receiving subsequent treatments (3) mean number of subsequent treatments for

Company response:

Table 45 is based on the PROfound data for patients in the olaparib arm who received any subsequent treatment, restricted to the five active treatments that are approved by the EMA in the mCRPC setting and used in at least 2% of patients in either the olaparib arm of the PROfound study or the cabazitaxel arm in the CARD study (Section B.3.5.3.3.1).

Details of subsequent treatments received by patients in the PROfound study, including less-commonly used, unapproved and investigational drugs, were provided in response to CQ A9 (Table 5), which covers this request.

B9. Given the severity of spinal cord compression, please provide a more detailed rationale for assuming its effects only last for one month.

Company response:

Data on the duration of SREs was not available from the PROfound study; therefore, it was necessary to make an assumption in order to assess the quality of life effects of SREs in the economic model. In a previous technology appraisal in prostate cancer, TA316 (enzalutamide), a one month duration of SREs was considered reasonable based on a review of the literature. According to TA316, clinical experts acknowledged that some variation in the duration of each SRE would be expected, but confirmed the one-month assumption as being reasonable.

It is expected that this assumption would have minimal impact on the model results, as the duration of SREs only affects the calculated quality of life decrements associated with SREs in the model, and the duration of SREs are assumed to be equivalent across the intervention and comparator arms.

B10. **Priority question:** Please provide the arithmetic underlying the cost estimate for genetic mutation testing given in section B.3.5.5.2, outlining any sequencing of testing that has been assumed, the assumed prevalence of the genetic mutations of Cohort A in the patient group being tested, the assumed prevalence of the genetic mutations of Cohort B in the patient group being tested, the test unit cost, etc.. Please also provide a citation or reference for the test unit cost.

Company response:

The prevalence of HRR mutations amongst mCRPC patients has been assumed to be in line with the recent poster from De Bono *et al*., which reported on the prevalence of HRR gene alteration during recruitment into the PROfound study.(17) Of 4,425 patients who entered screening for PROfound, HRR gene profiles were obtained for 2,792 patients with a positive test in 27.9% of these patients. A co-

occurring qualifying HRR gene alteration in ≥1 gene was detected in 59 patients (7.6%). Of all randomised patients, 42.6% were European.

It is expected that patients would be screened for HRR mutations while receiving their initial therapy for mCRPC, assumed to be NHA aligned to the PROfound study and the anticipated use of olaparib in clinical practice. It is assumed that patients who have received a prior taxane will be screened, aligned to the focus of the company submission and the treatment pathway for the majority of prostate cancer patients in the UK. Given the prevalence HRR mutations (27.9%), it is anticipated that approximately four will need to be tested in order to identify one patient suitable for olaparib therapy (i.e. 100% / 27.9% = 3.58)

As stated in Document B (Section B.1.3), genomic testing for cancer is provided by NHS England through a network of Genomic Laboratory Hubs (GLHs). [redacted]. Thus, no barriers are anticipated to identifying patients eligible for olaparib treatment in routine clinical practice in England. Nonetheless, an estimate of the cost of genetic testing was included as a scenario analysis.

The figure of £[redacted] was considered a representative estimate for the HRR test, based on the costs of the tumour BRCA (tBRCA) testing service for ovarian cancer that AstraZeneca are currently funding, until the National Genomic Testing Directory for Cancer goes live. The costs for HRR testing are anticipated to be similar to tBRCA testing costs for the following reasons:

- There is no change or additional burden with respect to sample collection and preparation of tumour tissue, as the procedure is expected to be the same.
- The majority of labs already use hybrid capture next-generation sequencing (NGS) large gene panels, which already include the 15 HRR genes from Cohort A and Cohort B of PROfound. Therefore, the only additional requirement is the assessment of these additional gene regions and reporting, which is expected to incur no-minimal cost impact.

Section C: Textual clarification and additional points

C1. **Priority question:** Please provide reference 94: AstraZeneca. Sibyl parametric extrapolation report, PROfound Cohort A+B by subgroup of prior taxane use. January 2020.

Company response:

We apologise for the error in not including this in the initial submission. Accordingly, please find the report attached as a Word document below.

[Confidential file redacted]

C2. **Priority question:** Please provide reference 26: AstraZeneca. Matching adjusted indirect comparison to assess the efficacy of olaparib vs cabazitaxel and radium. Version 1.0. [Data on file].

Company response:

The reference 'AstraZeneca. Matching adjusted indirect comparison to assess the efficacy of olaparib vs cabazitaxel and radium. Version 1.0. [Data on file].' is erroneous in its title; this is due to it being a carry-over of an early citation in Endnote being included with the submission by mistake. The correctly-titled reference (Indirect treatment comparison to assess the efficacy of olaparib vs cabazitaxel) is attached, with further context provided below.

[Confidential file redacted]

Early in dossier development, AstraZeneca assessed the feasibility of an ITC of olaparib against cabazitaxel and radium-223 in the population relevant to the decision problem, as described in Document B Section 2.1.3 and Section 2.9. The feasibility assessment showed that it was only possible to conduct an ITC against cabazitaxel due to lack of appropriate data for radium-223.

The appropriateness of conducting an unadjusted Bucher ITC versus PAIC for estimating the relative efficacy of olaparib against cabazitaxel was considered, as discussed in Document B Section 2.9. A Bucher ITC, unadjusted for variables, was deemed the most appropriate method since no effect modifiers were identified. Therefore, no PAIC was ultimately conducted for the purposes of the NICE appraisal.

C3. In the file AZ mCRPC treatment flow research in the reference pack suggests interviews were conducted with 25 different UK specialists. Were these the same interviews in which data are reported from the 6 clinicians and if so, is there data available on the responses from the remaining 19 specialists?

Company response:

The mCRPC treatment flow research with 25 UK specialists was conducted by an external vendor; therefore, the identify of participants who took part in this research is not known to AstraZeneca. For this reason we are unable to comment on any overlap with the six UK clinical experts interviews cited elsewhere in the submission (please see response to B5 for the format of these interviews).

Participants in the treatment flow research were asked a distinct set of questions relative to the six expert interviews; the same information is therefore unavailable for the larger (n=25) dataset.

C4. The base case anticipates that the large majority of OS gain occurs after progression and treatment with olaparib has ceased. Please provide the biologic rationale that underlies this model output or suggests the model output is likely to be realised in practice.

Company response:

The model outputs are supported by observed data from the PROfound study. At DCO1, in the prior taxane subgroup of Cohort A+B, median OS (15.8 months) for patients randomised to the olaparib arm was approximately 2.7 times greater than

median rPFS (5.8 months). The gain in median OS associated with ***olaparib versus NHA*** (before and after adjustment for treatment switching) was also consistently greater than the PFS gain across Cohort A, Cohort A+B and Cohort A+B prior taxane subgroup analyses, providing evidence for continued post-progression gains in survival after treatment with olaparib has ceased. Based on the median observed values, the gain in OS was more than two times greater than the gain in rPFS across Cohort A (3.2), Cohort A+B (5.3), and the Cohort A+B prior taxane subgroup (2.9), consistent with the interpretation of the modelled results that a substantial proportion of the OS gain associated with olaparib in the Cohort A+B prior taxane subgroup occurs after disease progression.

C5. **Priority question:** The company position appears to be that the genetic mutations of Cohort A and the genetic mutations of Cohort B adversely affect rPFS and OS under current treatments. Please outline the evidence base for this, with full referencing, separately for Cohort A and for Cohort B.

Company response:

While not comprehensive, available evidence in the literature suggests that genetic mutations of genes in Cohort A and Cohort B adversely affect outcomes for patients who receive treatment with a taxane for their mCRPC. These are listed below with the available data:

HRR mutations (grouped):

- A retrospective analysis of 319 patients in a liquid biopsy testing program with mCRPC showed attenuated time to PSA progression on 1L NHA and docetaxel in patients with metastatic prostate cancer and select HRR mutations (in *ATM*, *BRCA1/2*, *CDK12*, *ERCC2*, *FANCC*, *FANCF*, or *PALB2* genes), compared with patients without germline HRR mutations (NHA: 3.3 months [2.7-3.9, n=21] vs 6.2months [5.1-7.3, n=155], respectively [p=0.01]; docetaxel: 7.2 months [5.6-8.7, n=8] vs 8.0 [7.1-9.1, n=18], respectively [p<0.001]).(18)

BRCA2 mutations:

- Germline *BRCA2* mutations may have a negative impact on response to 1L taxanes in patients with mCRPC. The PROREPAIR-B study was a European prospective cohort study carried out at 38 sites to assess the impact of germline mutations on CSS from diagnosis of mCRPC.(19) Cause-specific survival (CSS) was significantly worse in g*BRCA2* carriers compared with g*BRCA*wt patients (17.4 v 33.2 months; P=0.027). g*BRCA2*m was found to be an independent prognostic factor for CSS (HR=2.11; P=0.033).

CDK12 mutations:

- A retrospective multicentre study of 60 patients (from nine centres) with *CDK12* mutations showed that they had a shorter response to first-line therapy for mCRPC,(20) whether this was taxane chemotherapy (3.8 months, n=22) or NHA (5.3 months, n=34), compared with literature values(21-23) cited by the study.

-

C6. Please clarify if the effects of SSREs (1) subsequent to rPFS and (2) subsequent to 1st SSRE are included in the economic model.

Company response:

The economic model is a standard cohort partitioned survival model that has three health states: progression-free disease, progressed disease, and death. State occupancy is derived from modelled rPFS and OS. The cost and quality of life effects of first SREs are incorporated for newly progressed patients at each model cycle, consistent with the approach taken in relevant previous NICE technology appraisals in prostate cancer, such as TA259 (abiraterone for mCRPC previously treated with a docetaxel-containing regimen) and TA316 (enzalutamide for mCRPC previously treated with a docetaxel-containing regimen).(24, 25)

In order to accurately incorporate any sequential effect of SREs implied in the question (i.e., first SRE, and subsequent SREs) in the current model structure, time-to-event data for the time from first to subsequent SREs for olaparib and cabazitaxel, as well as the duration of subsequent SREs, would be required. These data are not available from either the PROfound or CARD studies, therefore, an approach

explicitly modelling first and subsequent SREs would be based on assumptions and it would remain uncertain as to when these effects should be applied (and for what duration). Given the absence of data to inform a meaningful approach, the time from first to subsequent SREs was not included in the economic model.

We would also like to point out that the cost and quality of life impact of SREs in the submitted model are not a key driver of the results. As demonstrated in the scenario analyses in Section B.3.8.3 of the submission, olaparib remained dominant even when excluding the cost and quality of life effects of first SREs. Based on this, the inclusion of subsequent SREs is expected to have only a minimal impact on the results.

C7. Please clarify if within the parametric fits to the KM data, one month is four weeks, i.e. 28 days, or one month is one calendar month, i.e. 30.4 days. If the timepoints reported for the KM data requested in Section A above are months, please similarly clarify the duration of one month for this data.

Company response:

Throughout the economic model, KM data, and parametric fits, one month is one full calendar month (365.25/12 = 30.44 days).

C8. Please supply the input and output HRs for the Bucher ITCs conducted using at least 3 decimal places. The current submission only provides these to 2 decimal places (e.g. 0.44)

Company response:

The ITC results have been presented below to 3 decimal places. In the ITC analysis for rPFS:

- The hazard ratio for olaparib versus investigator's choice of NHA in the PROfound Cohort A+B prior taxane subgroup was [redacted].

- The hazard ratio for cabazitaxel versus investigator's choice of NHA, generated from the recreated IPD data from the CARD study, was [redacted].
- The hazard ration for olaparib versus cabazitaxel was [redacted].

In the ITC analysis for OS:

- The hazard ratio for olaparib versus investigator's choice of NHA in the PROfound Cohort A+B prior taxane subgroup was [redacted].
- The hazard ratio for cabazitaxel versus investigators' choice of NHA, generated from the recreated IPD data from the CARD study, was [redacted].
- The hazard ratio for olaparib versus cabazitaxel was [redacted].

C9. Please provide a key to all abbreviations / acronyms used in Doc B.

Company response:

Please find the list included in Appendix C9 of this document.

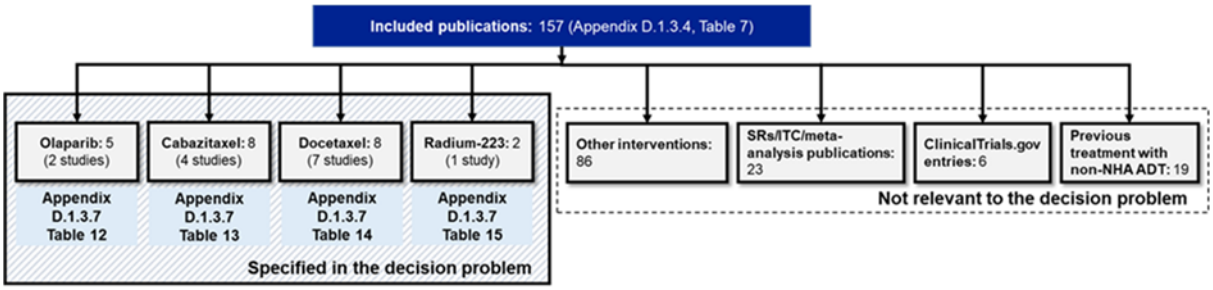
C10. Please supply reasons for exclusions for the publications in the clinical effectiveness excluded studies table (CS Appendix D, Table 8) and also for those initially included studies that were not in the final included set (see CS Appendix D, Table 7 and section D.1.3.7.)

Company response:

The 157 publications in the PRISMA diagram (Figure 1, Appendix D of Document B) were included based on the eligibility criteria provided in Section D.1.3.7, Table 7, which did not restrict results based on the interventions of interest to this appraisal.

Only those publications that reported outcomes on olaparib, cabazitaxel, docetaxel and radium-223, i.e. interventions relevant to the decision problem, are discussed in Appendix D.1.3.7. Figure 8 below outlines the initially included studies that were not included in the final set; these were excluded on the basis of not being relevant to the decision problem.

Figure 8. Breakdown of initially included studies in the clinical SLR



Details of the remaining studies that reported on olaparib, cabazitaxel, radium-223, and docetaxel (per Table 8 in Appendix D), with reasons for exclusion are provided in the Excel spreadsheet below.

[Confidential file redacted]

C11. Please clarify the number of conference abstracts included in the clinical effectiveness review, and specify which ones are included. There are variations in the number (CS Appendix D, Figure 1 'PRISMA flow diagram': 25 congress abstracts; CS Appendix D, section D.1.3.5 text says 29 unique abstracts; and CS Appendix D, Table 10 includes 26 that aren't highlighted in blue). In light of this, please also clarify the overall number of included studies.

Company response:

In total, 31 unique conference abstracts were included from electronic searches and hand searching, of which 25 unique publications were from hand searching of

congress abstracts. A summary of congress abstracts is provided in the Word document attached below.

[Confidential file redacted]

C12. Please supply a list of excluded studies with reasons for the cost-effectiveness reviews ((316 + 44) – 9 = 351 according to flow diagram in CS Appendix G, figure 6).

Company response:

The aim of the review was to identify published literature that reported economic, health state utility (HSU) and cost-of-illness evidence on the use of health technologies in patients with mCRPC who have experienced progression following treatment with a NHA including abiraterone and/or enzalutamide. The search strategy was broad (as detailed in Appendix G to Document B), and identified a large number of studies related to the clarification question; studies were then screened for inclusion/exclusion based on the specific eligibility criteria detailed in the submission. Given the large number of studies that were excluded (351), the list of excluded studies and primary reason for exclusion are provided in the Excel spreadsheet below.

[Confidential file redacted]

Appendices

C9: List of all abbreviations and acronyms used in ID1640 Document B

Acronym	Definition	Acronym	Definition
ADP	Adenosine diphosphate ribose	IV	Intravenous
ADT	Androgen deprivation therapy	IVRS	Interactive voice response system
AE	Adverse event	KM	Kaplan–Meier
AIC	Akaike Information Criterion	LHRH	Luteinising hormone-releasing hormone
ALP	Alkaline phosphatase	LSM	Least squares mean
AML	Acute myeloid leukaemia	LYG	Life years gained
ATM	Ataxia-Telangiectasia Mutated	mCRPC	Metastatic castration-resistant prostate cancer
BIC	Bayesian Information Criterion	MDS	Myelodysplastic syndrome
BICR	Blinded independent central review	MGUS	Monoclonal gammopathy of unknown significance
BNF	British National Formulary	mHSPC	Metastatic hormone-sensitive prostate cancer
BPI-SF	Brief Pain Inventory – Short Form	MMRM	Mixed model repeated measures
BRCA	BReast CAncer gene	MRI	Magnetic resonance imaging
BSA	Body surface area	NA	Not applicable
BSC	Best supportive care	NHA	New hormonal agent
CHMP	Committee for Medicinal Products for Human Use	NHS	National Health Service
CI	Confidence interval	NICE	The National Institute for Health and Care Excellence
CR	Complete response	NPCA	National Prostate Cancer Audit
CSP	Clinical study plan	NR	Not reported
CSR	Clinical study report	OR	Odds ratio
CT	Computed tomography;	ORR	Objective response rate
CTC	Circulating tumour count	OS	Overall survival
CTCAE	Common Terminology Criteria for Adverse Events v4.03	PAIC	Patient-adjusted indirect comparison
CUP	Compassionate use programme	PARP	Poly(adenosine diphosphate)-ribose polymerase
DCO	Data cut-off	PAS	Patient access scheme

DSA	Deterministic sensitivity analysis	PCWG2	Prostate Cancer Working Group 2
DSB	Double-strand breaks	PCS	Prostate cancer subscale
DSU	Decision Support Unit	PD	Progressive disease
EAP	Early access program	PDS	Pre-filled, dual-chamber syringe
ECG	Electrocardiogram	PET	Positron emission tomography
ECOG	European Cooperative Oncology Group performance status	PF	Progression-free
EFR	Evaluable for response	PFS	Progression-free survival
EMA	European Medicines Agency	PFS2	Second progression-free survival
eMIT	Drugs and pharmaceutical electronic market information tool	PR	Partial response
EORTC	European Organization of Randomised Controlled Trials 8 Dimension	PRO	Patient-reported outcome
EPAR	European public assessment report	PSA	Prostate-specific antigen
EQ-5D	Euroqol-5 Dimension	PSS	Personal Social Services
ESMO	European Society for Medical Oncology	PSSRU	Personal Social Services Research Unit
EWB	Emotional well-being subscale	PWB	Physical well-being
FACT-G	Functional Assessment of Cancer Therapy- General	QALY	Quality-adjusted life year
FACT-P	Functional Assessment of Cancer Therapy – Prostate	RCT	Randomised controlled trial
FANCL	Fanconi anaemia, complementation group L	RDI	Relative dose intensity
FAPSI-6	Functional Assessment of Prostate Cancer Symptoms Index 6	RECIST	Response Evaluation Criteria in Solid Tumours
FAS	Full analysis set	rPFS	Radiographic progression-free survival
FDA	U.S. Food and Drug Administration	RPSFTM	Rank Preserving Structural Failure Time Model
FDG	Fluorodeoxyglucose	SAE	Serious adverse event
FIGO	Fédération Internationale de Gynécologie et d'Obstétrique	SAP	Statistical analysis plan
FTE	Full-time employee	SAS	Safety analysis set
FWB	Functional well-being subscale	SC	Subcutaneous
G-CSF	Granulocyte-colony stimulating factor	SD	Standard deviation

GCP	Good Clinical Practice	SE	Standard error
HR	Hazard ratio	SF	Short form
HRG	Healthcare Resource Group	SLR	Systematic literature review
HRR	Homologous recombination repair	SRE	skeletal-related event
HSUV	Health state utility value	SSB	Single-strand breaks
ICER	Incremental cost-effectiveness ratio	SSRE	Symptomatic skeletal-related event
ICH	International Council for Harmonisation	SWB	Social/family well-being subscale
ICR	Institute of Cancer Research	TOI	Trial outcome index
IEC	Independent Ethics Committee	TSD	Technical Support Document
INMB	Incremental net monetary benefit	TSE	Two-stage estimation
IPCW	Inverse Probability of Censoring Weights	TTD	Time to discontinuation
IPD	Patient-level data	TTPP	Time to pain progression
IRB	Institutional Review Board	VAS	Visual analogue scale
ITC	Indirect treatment comparison	VBA	Visual Basic for Applications
ITT	Intention-to-treat		

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NICE National Institute for Health and Care Excellence

Patient organisation submission

Olaparib for previously treated, hormone-relapsed metastatic prostate cancer with homologous recombination repair gene mutations [ID1640]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	Prostate Cancer UK
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Prostate Cancer UK is the UK's leading charity for men with prostate cancer and prostate problems. We support men and provide information, find answers through funding research and lead change to raise awareness and improve care. The charity is committed to ensuring the voice of people affected by prostate disease is at the heart of all we do.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.]	We have a policy that our total income from pharmaceutical manufacturers must be below 1%. In the 2018/19 financial year, our total income from pharmaceutical companies was less than 0.004% of our total. We regularly speak with pharmaceutical companies, particularly those with prostate cancer products, to seek funding for specific projects. This includes; £37,000 from Janssen for learning and development for our specialist nurse helpline staff and a project targeting late stage prostate cancer diagnosis; and £35,500 from Astellas to fund our improvement programme and to support the activity of our nurse helpline. In addition, we have received £20,500 each from Bayer, Sanofi, BTG and Roche towards our improvement programme.

If so, please state the name of manufacturer, amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	None.
5. How did you gather information about the experiences of patients and carers to include in your submission?	Desk research and our own knowledge of the experiences of men. We have spoken with our specialist nurses about their experience of speaking with men in this indication. We have also engaged with the Chief Investigator of the TOPARP Study and other leading medical oncologists to better understand the operation of this treatment in this indication.
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Men with advanced disease can present with a number of different symptoms. Evidenced symptoms for advanced prostate cancer can include[i]: • Fatigue. • Pain, most commonly caused by prostate cancer that has spread to the bones. • Urinary problems, this includes problems emptying the bladder, incontinence, blood in urine and kidney problems. • Bowel problems including constipation, diarrhoea, faecal urgency, faecal incontinence, pain, bowel obstruction and flatulence. • Broken bones, fractures caused by bone thinning.

	• Sexual problems, including reduced libido and difficult getting or keeping an erection. • Lymphoedema, primarily around the legs. • Anaemia, caused by damage to bone marrow. • Metastatic spinal cord compression, as cancer cells grow in or near the spine, which evidence suggests can occur in 1 to 12% of patients[ii]. • Hypercalcaemia, caused by calcium leaking from the bones into the blood. • Eating problems Specfically men with advanced prostate cancer will inevitably progress to the metastatic castrate resistant stage of disease. At this point, a limited number of treatments are available to men, which aim to delay progression, reduce symptoms or improve quality of life. At this stage of disease, men may experience more significant symptoms due to the disease becoming more aggressive when hormone resistance occurs. Different symptoms (depending on where their cancer is) from their prostate cancer including those below: • Pain may develop and for some men with mCRPC this can be significant. Qualitative research from a study of 126 men with mCRPC found that 45% of men reported moderate to severe pain at treatment initiation (ref Jenkins et al: Treatment experiences, information needs, pain and quality of life in men with mCRPC) Clearly this is distressing for both men and their families as well as having an impact on quality of life. • Men with advanced prostate cancer who have bone metastasis, including in the spine, may develop spinal cord compression. These men require urgent treatment to prevent permanent nerve damage and potential paralysis. This can be a debilitating and life-changing problem. • Bone metastasis can also result in spontaneous fractures, without trauma and increased risk of fracture associated with trauma. • For men whose prostate cancer affects their bone marrow, they may become anaemic (so be more tired or become breathless) requiring blood transfusion, thrombocytopenic (be more prone to bruising and bleeding) and low white blood cell counts (making them more susceptible to infection).

	• Visceral metastases most commonly involve the liver and the lungs, causing considerable and intractable morbidity; Brain metastases commonly result in significant and distressing neurological deficits. • Weight loss and reduced appetite can often be a particular concern for carers. • If prostate cancer advances in the region around the prostate, men may experience urinary tract problems and renal problems. It is important to note that men are unlikely to experience all the above symptoms, as some will depend on the treatments received, while others will be the result of metastases and therefore dependent on their location. The severity of symptoms will also differ among men, while the likelihood of some of the most severe symptoms, for example Lymphoedema can be rare and vary between 1-20%[iii]. For some men, living with metastatic prostate cancer can be hard to deal with emotionally, especially as there are no current curative treatments for this stage of the disease. Symptoms and treatments can be draining and make men feel unwell. And some treatments, including hormone therapy, can make men feel more emotional and cause low moods. The pressure of advanced cancer can also put a strain on relationships. Metastatic prostate cancer and its treatments might mean that partners or family need to do more for patients, such as running the home or caring responsibilities. Additionally, the symptoms described for mCRPC and the side effects of treatments can make it difficult to work. a partner providing care might not be able to work as much either. Everyday tasks may become more difficult and respite care may be required to give carers a break. As the disease progresses, more palliative care and treatments will be offered. This includes palliative radiotherapy to ease bone pain, blood in urine and swollen lymph nodes.

Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Inevitably, men and their families express disappointment that there are no curative treatments for metastatic castrate-resistant prostate cancer. Many are interested in clinical trials with the hope of improving their life expectancy. There are two stages of metastatic prostate cancer, hormone-sensitive and castrate-resistant. The standard of care in the hormone-sensitive stage is docetaxel and hormone therapy (ADT). In the castrate-resistant setting men can receive docetaxel, abiraterone, enzalutamide, or cabazitaxel. Radium 223 is a further last line treatment. There are currently no precision treatments available for prostate cancer. Men will begin in the hormone-sensitive stage, where hormone therapy can prevent the growth of the prostate cancer. Eventually, hormone therapy will no longer prevent the growth of the cancer and the man will progress to the castrate-resistant stage of the disease. There are several treatments available in the metastatic castrate resistant setting, which are detailed below. However, there is a need for further treatments that offer good clinical benefit and improvement in the median overall survival, as this remains low past 18 months. Hormone therapy and docetaxel chemotherapy are also available in the hormone-sensitive setting. The treatments below are listed in what could roughly be considered the treatment pathway for metastatic disease. Despite **hormone therapy** no longer preventing the growth of the prostate cancer, it is likely still having an effect and so will continue to be taken at all stages of metastatic prostate cancer and with all other treatments. Hormone therapy causes side effects including hot flushes, reduced libido and erectile dysfunction, fatigue and mood swings which can have a huge impact on both a man and his family[iv]. Men living with long term hormone therapy frequently need to adapt their lives. Some express frustration at not being able to do what they used to do. For example, gardening, sport and domestic chores can become difficult. Some men express guilt at not being able to help partners with domestic chores and carers sometimes express feelings of helplessness as they feel unable to resolve their partners fatigue. Couples may also have to adapt to reduced capability for physical intimacy. It can be difficult for some partners

	who can find the loss of libido very hard whilst others express a changed but close intimacy. Single men can find it difficult to establish new relationships. Fatigue can lead to social withdrawal for some men. **Docetaxel chemotherapy** is only offered to those felt fit enough to receive it. It will be offered in the hormone-sensitive stage, but there is an opportunity for rechallenge or new administration in the castrate-resistant setting. Docetaxel offers a median survival benefit of 16 months if given first in the hormone-sensitive stage[v] and less than 3 months if given first in the castrate-resistant stage[vi]. While there are side-effects from chemotherapy, severe side effects are reported mostly during treatment and in the first 6 months after treatment. Adverse events include fatigue, alopecia, nausea/vomiting, diarrhea, nail changes and sensory neuropathy[vii] . Many men and their families are fearful of chemotherapy. Most men develop low blood counts making them vulnerable to infection, some of which are potentially life-threatening infections. Many men say that the taste changes that the chemotherapy can cause is extremely difficult to live with, adversely affecting their quality of life. Treatment means going into hospital, often to clinic on one day followed by chemotherapy the next day approximately every three weeks for 6 cycles of treatment. Some men travel long distances to receive their treatment. They are also required to self-monitor between visits, to be vigilant, recognise and to present back to hospital should any adverse reactions to treatment occur, for example, should they become febrile. Many men find this onerous and extremely anxiety provoking. **Abiraterone and enzalutamide** are both androgen receptor signalling inhibitors. Without a direct comparison, they offer similar survival benefit, 3 months for abiraterone[viii] and 5 months for enzalutamide[ix]. They are both available to patients in the metastatic castrate-resistant setting after docetaxel, or to patients who have not received docetaxel. Both treatments are currently being appraised by NICE in the metastatic hormone-sensitive setting. NHS England has a policy that no patient can receive both treatments, since there is no evidence of their efficacy in combination or in sequence. The treatments have different side-effect profiles. Adverse events for abiraterone include fatigue, back pain, nausea, constipation, bone pain, arthralgia and edema. Abiraterone is also associated with an elevation in aminotransferase levels which can lead to more frequent monitoring with liver-function tests during treatment[x]. Adverse events for enzalutamide include fatigue, back pain, constipation and athralgia[xi].

	We envisage **olaparib** would likely be prescribed after abiraterone or enzalutamide had failed, but before cabazitaxel was considered. **Cabazitaxel chemotherapy** is another taxane chemotherapy, available only in the castrate-resistant setting after administration of docetaxel[xii]. It is available as an alternative to abiraterone, enzalutamide or rechallenge with docetaxel. The standard of care globally only added cabazitaxel as an alternative choice following the publication of the CARD trial in December 2019, however in England and Wales cabazitaxel has been available as an alternative since 2016. It can be prescribed either before or after abiraterone or enzalutamide at this stage, however it is more frequently prescribed afterwards. It offers a similar survival benefit to docetaxel at this stage[xiii]. Evidence suggests it is more effective than enzalutamide or abiraterone following administration of docetaxel and an andogren signalling targeted inhibitor (enzalutamide or abiraterone)[xiv]. At this late stage of disease, many men will be too frail or have too many comorbidities to tolerate chemotherapy. It is not widely prescribed. Toxic side effects are most commonly haematological (neutropenia, leukopenia, anaemia). Other commonly reported side effects include diahorrea, fatigue, asthenia, nausea and constipation. These are similar to those for docetaxel. **Radium 223** is a treatment for men whose cancer has spread to the bones. It offers a median of just under 3 months of additional life[xv]. 70% of men also get some pain relief benefit from the treatment. Men receiving radium 223 report fewer adverse events that those receiving placebo[xvi]. However, the treatment is not offered at all hospitals because the treatment involves administration of a radioisotope.
8. Is there an unmet need for patients with this condition?	There is a need for further treatments that offer good clinical benefit and improvement in the median overall survival, as this remains low past 18 months.There are currently no precision treatments that target somatic genetic mutations for prostate cancer patients. There are numerous treatments available for prostate cancer in the metastatic castrate-resistant setting. However, there is uncertainty in how each patient will respond to any treatment. There are no specific treatments for men with the gene mutations identified in the PROFOUND and TOPARP trials. We know

	from these trials that men with these mutations are more likely to respond to olaparib and so it can be argued that for men with these gene mutations, there is an unmet need which olaparib addresses. 19.5% of patients in the olaparib arm of the trial and 13% of patients in the control arm received chemotherapy following discontinuation of the study treatment. This will likely be higher in the England and Wales given the subsequent treatment options available are fewer than in the trial. Receipt of olaparib for these men delays the points at which they will need further treatment with taxane chemotherapy, allowing them to delay the side-effects and impact on quality of life associated with taxane chemotherapy.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	There is currently no precision-medicine available that can respond specifically to mutations driving the growth of prostate cancer, olaparib is that medicine. Men with prostate cancer want more treatments to be available to them that work for them. This treatment offers more certainty for men with specific gene mutations that it will be effective in slowing the progress of their prostate cancer. There is a clear survival benefit from olaparib, though not yet statistically significant. In cohort A of the PROFOUND study the median overall survival benefit is 3.4 months, in the whole population the median overall survival benefit is 3.2 months. The survival benefit may have been obscured by the more than 80% crossover to olaparib among the patients in the control group whose disease had progressed. However, after performing a sensitivity analysis for those who crossed over to the Olaparib arm, a directional improvement in favour of Olaparib was seen in both cohorts, as well as the overall population. Progression free survival was statistically significant, showing 3.8 months in cohort A compared to 2.3 months in the whole population. As advanced prostate cancer progresses, symptoms are likely to become worse. In addition to delaying progression the study measured the delay to pain progression. In cohort A the median time to pain progression was 17.2 months compared to 5.5 months in the control arm. In cohort B this was 11.9 months compared to 6.9 months. Patients value any treatment that can delay the progrssion of symptoms.

	Compared to many other treatments for prostate cancer, there are comparatively fewer adverse events associated with olaparib. Particulary when balanced against the benefits of delayed symptoms from delayed progression, this targetted treatment offers improved survival without a reduction in quality of life.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	PROfound finds that anemia and nausea were the most common adverse events associated with olaparib. But this could in part be due to the fact that drug administration was nearly twice as long as in the olaparib group as the control group. The impact of these side-effects is also arguably outweighed by the delay to symptom of pain progression. There is concern in the data around pulmonary embolism, but this is not a recognised side-effect of olaparib.
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	The PROFOUND study was designed to investigate the benefit to patients with mutations in BRCA1 BRCA2 and ATM (making up cohort A in the study) and was able to show a benefit in terms of image based progression free survival for this cohort. There is uncertainty around precisely which gene mutations in cohort B are most responsive to olaparib, given the small numbers with some of the mutations. These mutations are BRIP1, BARD1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D, and RAD54L. Further research is needed to identify benefits for other mutations. Given the uncertainty inherent in precision medicines, we hope that data in the study is sufficient to allow the medicine to be approved and for further research to be reflected in future changes to the treatment criteria by NHS England.

Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	53.17% of men with metastatic prostate cancer are over the age of 75. 72.3% are over 70[xvii]. Men who have progressed from metastatic hormone-sensitive cancer to the metastatic castrate-resistant stage will be older. This treatment is largely for older men at the final stage of prostate cancer, it could be considered ageist to deny access to this treatment and olaparib should be considered an end-of-life treatment. It will only be patients with metastatic prostate cancer who will die from prostate cancer. Qualitative research in men with mCRPC has shown that men often attribute hip and back pain to 'old-age', suggesting that there may be a larger number of older men with inadquate pain control outside of a trial setting[xviii].
Other issues	
13. Are there any other issues that you would like the committee to consider?	It is important to note that patients in the control arm received a second AR inhibitor (either enzalutamide or abiraterone, whichever they hadn't previously received). While there is limited evidence on the efficacy of enzalutamide and abiraterone in sequence, it should be considered that compared to ADT alone the provision of a second AR inhibitor may make olaparib's clinical endpoint results weaker than they would have been. Consideration should be given as to whether patients who are unsuitable for abiraterone or enzalutamide should still be eligible to receive olaparib. We have been speaking with colleagues in NHS England and NHS Wales. In both diagnostic panel tests are either available or are being made available.
Key messages	
14. In up to 5 bullet points, please summarise the key messages of your submission:	

- There is no curative treatment available for men with metastatic prostate cancer. The best men can hope for is longer survival and fewer symptoms.
- Men with prostate cancer want more treatments to be available to them that work for them. This is the first treatment for prostate cancer that targets somatic genetic mutations responsible for the disease's progression and enables men who have reached the end of the prostate cancer pathway to gain additional months of life, with limited adverse events
- Olaparib will allow men to delay time to a second taxane, cabazitaxel, which evidence shows can have an impact on quality of life. Some men at this stage of the disease may also be unable to tolerate a taxane – either because of their age or because of the severity of their prostate cancer symptoms. Olaparib makes it possible for some these men [assuming they test positive for relevant genes to gain additional months of life in place of cabazitaxel.
- Data also shows a significant delay in the time to pain progression for patients who take olaparib compared to the control group.
- There is an equality issue in the provision of this treatment, it is likely to primarily benefit men over the age of 75 who make up more than 50% of this indication.

Thank you for your time.

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[i] References for each symptom available on request.

[ii] European Urology Volume 44 Issue 5 *Spinal Cord Compression in Metastatic Prostate Cancer* H Tazi et al. November 2003
[iii] Journal of Lymphoedoma Volume 5 Number 2 *Cancer-related lymphoedema in males: a literature review* Cosgriff & Gordon 2010
[iv] https://prostatecanceruk.org/prostate-information/treatments/hormone-therapy#-what-are-the-side-effects-of-hormone-therapy
[v] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6938598/
[vi] https://www.nejm.org/doi/full/10.1056/NEJMoa041318
[vii] New England Journal of Medicine *Docetaxel plus Prednisone or Mitoxantrone plus Prednisone for Advanced Prostate Cancer*. Tannock et al. October 2004
[viii] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3471149/
[ix] https://www.nejm.org/doi/full/10.1056/NEJMoa1207506
[x] https://www.nejm.org/doi/full/10.1056/NEJMoa1014618
[xi] https://www.nejm.org/doi/full/10.1056/NEJMoa1405095
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[xiii] De Bono J.S., Oudard, S., Ozguroglu, M., Hansen, S., Machiels, J., Kocak, I., Gravis, G., Bodrogi, I., … Sartor O. (2011). *Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial*. Lancet 376: 1147–54
[xiv] https://www.nejm.org/doi/full/10.1056/NEJMoa1911206
[xv] https://www.nejm.org/doi/full/10.1056/NEJMoa1213755
[xvi] https://www.nejm.org/doi/full/10.1056/NEJMoa1213755
[xvii] NCRAS/Get Data Out
[xviii] Jenkins, V., Solis-Trapala I., Payne, H., Mason, M., Fallowfield. L., May S., Matthews., Catt S. (2019). *Treatment Experiences, Information Needs, Pain and Quality of Life in Men with Metastatic Castrate-resistant Prostate Cancer: Results from the EXTREQOL Study. Clinical Oncology. 31:99-107*

NICE National Institute for Health and Care Excellence

Patient organisation submission

Olaparib for previously treated, hormone-relapsed metastatic prostate cancer with homologous recombination repair gene mutations [ID1640]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

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- Your response should not be longer than 10 pages.

About you

NICE National Institute for Health and Care Excellence

1.Your name	[redacted]
2. Name of organisation	TACKLE Prostate Cancer
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Tackle is a patient centred charitable organisation whose aims are to support men and their families whose lives are affected by prostate cancer. In addition we aim to represent the opinions of patients on any subject which is relevant to the diagnosis and treatment of prostate cancer. We also support local prostate cancer support groups around the UK. We represent 91 support groups in England and Wales and through them have 15,000 members - men and their families whose lives have been affected by prostate cancer.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.]	**NO**

If so, please state the name of manufacturer, amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**NO**
5. How did you gather information about the experiences of patients and carers to include in your submission?	Tackle gain regular feedback from our members via face to face contact at local and national meetings, from direct contact by telephone from individuals and from the questions and queries of patients on our patient helpline. We have a medical advisory board who advise when and where necessary. I do not have personal experience of being treated with Olaparib. The drug under discussion is not in current use for the treatment of prostate cancer and the clinical scenario where it is of potential benefit is restricted to a specific group of men that have been tested for genetic mutations. Thus no patient has direct experience of using it at this point in their treatment pathway apart from those patients involved in clinical trials. However, I have spoken with patients who are faced with the clinical scenario of advanced prostate cancer and who have metastatic disease now not responding to treatment. I can understand their needs and concerns. Tackle believe that it is appropriate for me to speak on their behalf.
Living with the condition	
6. What is it like to live with the condition? What do carers	Patients with advanced prostate cancer / metastatic prostate cancer will know that they have a limited life span. Many of these men will experience, or go on to experience, many side effects. Commonly these will be fatigue, chronic pain (often with exacerbations of acute pain), urinary and bowel problems, low

experience when caring for someone with the condition?	mood or frank depression. Metastases in bone can be particularly painful and can lead to pathological fractures sometimes requiring complex surgical intervention. Their quality of life may be very poor. A significant number will have already exhausted the currently approved therapy pathway of hormone treatment (e.g. Zoladex), chemotherapy and Abiraterone/Enzalutamide. For them there is no further approved treatment although newer therapies have been developed and may be available. The only course open to many will now be purely symptom relief and palliative care. They, and their family and carers, are often significantly distressed by physiological, psychological and social problems. A sub-set of patients has been identified within this group of men with advanced disease. These men have a genetic mutation which affects the mechanism of DNA repair within both normal and cancerous prostate cells. It is for this group that Olaparib is of potential great value in delaying progress of disease. There will always be some men who do not wish to have further treatment and will choose the option of palliative care and symptom relief but currently the opportunity to make a choice between that and further treatment and not simply does not exist. Patients, family and carers will all have experienced ups and downs during the treatment journey of prostate cancer. This new drug now offers some degree of hope for many who currently feel that the end of their life is now becoming a reality.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Most patients will have already exhausted the range of treatments currently available to them. For them, treatment will have simply just failed to work or will have produced intolerable side effects. They will not 'blame' the individual treatments for their failure but will obviously be distressed that available treatments have led to such a poor future outcome. For patients, the term 'current treatments' may well only refer to treatments that each individual patient has been offered by the clinicians. There may be regional variations in what is offered. A small number of patients may have experience of research / trial programs involving newer therapies, such as the drug under discussion. Some will have learned about newer therapies that are not available to them under the NHS and question why these are not available to them. Managing the expectations of patients with advanced disease can be as difficult as managing the current physical symptoms of that disease.

8. Is there an unmet need for patients with this condition?	There is, undoubtedly, an unmet need regarding the treatment of patients with advanced prostate cancer especially in the group of patients who have been identified as possessing genetic mutations – particularly the BRCA 1&2 and ATM mutations. Research has proven that such genetic mutations can be associated with advanced prostate cancer. Drugs which interfere with the DNA repair mechanism of cancer cells can lead to death of those cells and reduced progression of disease. There is a totally new an innovative ability to use this knowledge to provide targeted treatment for this specific group of patients. This so-called 'precision medicine' has never before been available to men with prostate cancer. However, women with advanced breast and ovarian cancers have this option now open to them using the same drug, Olaparib.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	Put simply, the advantages are the chance of slower progression of disease and a potential reduction in the onset of adverse events caused by the disease – if they are not present already. Patients know they are not curable – and will not expect it. They purely see this as a way of potentially achieving and increased quality of life for a longer period of time. What could be seen as a negative – i.e. a genetic mutation – could now become a positive as targeted therapy is now possible for them.

Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	Side effects of any treatment can be as bad as the disease itself. The aim of therapy must always be to produce the maximum benefit with the minimum side effects. Published research shows Olaparib to have a reasonable side effect profile. Patient will need regular monitoring. A major downside of the technology is the need for genetic testing to be performed to identify appropriate patients. Genetic screening is not a routine part of the management pathway for prostate cancer. There is no current guidance on this. A strong family history of breast cancer (possibly with known BRCA mutations) may encourage relevant testing. However, it would appear that such mutations may not always be inherited but occur spontaneously
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	This technology will only be of benefit to men who have been specifically identified as having the appropriate genetic mutation – currently BRCA 1&2, ATM being the most common. There is evidence that men with other genetic mutations may also benefit. Men with no such identifiable genetic defect will not benefit from this treatment.

Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	**NO**
Other issues	
13. Are there any other issues that you would like the committee to consider?	**NO**
Key messages	
14. In up to 5 bullet points, please summarise the key messages of your submission: • Most men with advanced prostate cancer will have exhausted all of the treatment options available to them • Genetic mutations have been identified in a sub-set of men with advanced prostate cancer • Treatment specifically targeted at this genetic mutation is now possible and provides an innovative way of treating men who, until now, have been untreatable.	

- Men with advanced prostate cancer know they are not curable. They merely wish for a better quality of life for a longer period of time.
- This new approach to targeted therapy could bring improvement in the physiological and psychological health of these men and their families.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Patient expert statement

Olaparib for previously treated hormone-relapsed metastatic prostate cancer [ID1640]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	**Peter Isard**
2. Are you (please tick all that apply):	**x** a patient with the condition? ☐ a carer of a patient with the condition? ☐ a patient organisation employee or volunteer?

	☐ other (please specify):
3. Name of your nominating organisation	Prostate Cancer UK
4. Did your nominating organisation submit a submission?	**x** yes, they did ☐ no, they didn't ☐ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	**x** yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. How did you gather the information included in your statement? (please tick all that apply)	**x** I have personal experience of the condition **x** I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: ☐ I am drawing on others' experiences. Please specify how this information was gathered:
Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	The three principal manifestations of advanced prostate cancer are weakness, fatigue and pain. The constant exposure to hormone therapy, to which the patient is introduced from the moment of diagnosis, means that muscles waste and bones become more fragile; strength is depleted. Tasks, which, historically, would have been easy, become either much harder or impossible: walking to the shops is exhausting, walking home is worse. This is inevitably draining. Imagine being ten to fifteen years older than your current age. This is the impact. Then, once the cancer has become embedded in the bone, pain management is the only route to any realistic quality of life. For the carer, the dependence of the patient becomes unavoidably greater as time passes. He is able to do less for himself until he is unable to get up from a chair or put himself to bed. Then the need for care becomes full time. It may not be 24 hours, but it is 7 days a week – no holidays, no social life, no respite.

Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and care available on the NHS?	Current treatments on the NHS for advanced prostate cancer are few, generic and follow a well-trodden path. Lack of response to any one of them simply moves the patient on to the next. The cause and nature of the cancer are not considered. By the time the patient reaches the final treatment option, Cabazitaxel, he is often too weak to tolerate it. For many, the preference is to decline the chemicals and their side effects and look to gentler final months through pain management. Olaparib could help some of these men.
10. Is there an unmet need for patients with this condition?	Yes, Olaparib is the first prostate cancer treatment that benefits specific genomic mutations – BRCA 1 and 2. Genetic defects are now increasingly becoming recognised as important factors in patients with aggressive and advancing prostate cancer. Olaparib also has the potential to fulfil an unmet need in patients with BRCA 1 and 2 mutations who are unsuitable for chemotherapy. It provides additional months of life to patients who would otherwise have no other treatment options. It is important that any patient who has been unable to have Docetaxel earlier in the treatment regime or who later cannot tolerate Cabazitaxel still has access to Olaparib.
Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	This treatment has given me a new lease of life. In February 2018, aged 57, I was told that I had between one and two years left to live. I was advised if there was anything that I wished to do before my death, I had better get on with it as it was likely that only half that life expectancy would be of reasonable quality. Three years later, I am still alive. Not only that, but my quality of life compares very favourably with anyone else of my own age. I am able to play tennis, run and practise karate. For all intents and purposes, my life is completely normal. That is all down to Olaparib: I take no other medication besides hormone therapy.

Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	Early on in the course of treatment, I did periodically experience some feelings of nausea. As my body became more accustomed to the drug, those bouts of nausea decreased to almost nothing; the only times of exception would occur after moments of intense physical activity. Otherwise, I have suffered no side effects from the drug.
Patient population	
13. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Olaparib benefits only those patients with defects in certain genes. Trial data shows that the benefits are derived regardless of whether a patient underwent earlier chemotherapy. Those who had undergone previous chemotherapy had slightly better outcomes than those who had not. However, it would not be right to deny an effective treatment to the latter because of their inability to tolerate an earlier more toxic regimen.
Equality	
14. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Conceivably, yes. As explained above, patients should have access to Olaparib irrespective of whether they have been previously treated with Docetaxel.

Other issues	
16. Are there any other issues that you would like the committee to consider?	I was diagnosed with advanced prostate cancer at the age of 56. Incidents of the cancer are occurring at increasingly younger ages; it is no longer just an old man's disease. I would be dead without Olaparib, but, instead, I am leading a high quality of life without debilitating side effects. But my treatment only came about through chance: I was lucky enough that my gene defect allowed me to gain the last UK place on the TOPARP B trial. There will have been others who have not been so lucky. There is clear value to genetic testing those who exhibit the disease at a younger age, because for those men there now exits an extremely successful treatment which can prolong their life and not just their existence.

Key messages

17. In up to 5 bullet points, please summarise the key messages of your statement:

- Without Olaparib, I would be dead
- I was diagnosed when young, totally unaware I had an aggressive germline cancer
- Because of Olaparib I have as high a quality of life as anyone who does not have my condition
- I was able to have this innovative drug therapy entirely by chance; there will be others who should have the same chance
- There is an opportunity to deliver an unmet need in patients who are unsuitable for chemotherapy, both Docetaxel and Cabazitaxel

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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Evidence Review Group's report t

Title: Olaparib for previously treated hormone-relapsed metastatic prostate cancer [ID1640]

Produced by *Warwick Evidence*

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Declared competing interests of the authors
None

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

Please note that: Sections highlighted in [redacted] are '[redacted]. Sections highlighted in [redacted]. Figures that are CIC have been bordered with blue. Depersonalised Data (DPD) is highlighted in pink.

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DEFINITION OF TERMS AND LIST OF ABBREVIATIONS

ADT	Androgen deprivation therapy
AE	Adverse events
AIC	Akaike information criterion
ATM	Ataxiatelangiectasia mutated gene
AUC	Area under curve
BARDI1	BRCA1 associated RING domain 1 gene
BIC	Bayesian information criterion
BICR	Blinded independent central review
BNF	British National Formulary
BoR	Best objective response
BPI-SF	Brief Pain Inventory – Short form
BRCA	Breast cancer gene
BSA	Body surface area
BSC	Best supporting care
Bt	Bathtub model
CDK12	Cyclin dependent kinase 12 gene
CEAC	Cost-effectiveness acceptability curve
CHEK1	Checkpoint Kinase-1 gene
CHEK2	Checkpoint Kinase-2 gene
CI	Confidence interval
CS	Company submission
CSP	Clinical study protocol
CSR	Clinical study report
CSS	Cause-specific survival
CT	Computerized Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DC01	First data cut-off
DC02	Second data cut-off
DNA	Deoxyribonucleic acid
DoR	Duration of response
DSB	Double-strand breaks
ECOG	Eastern Co-operative Oncology Group
EFR	Evaluable for response
EMs	Treatment effect modifiers
EMA	European Medicines Agency
EQ-5D	EuroQol five dimensions
ERG	Evidence review group
Ex	Exponential parametric model
FACT-P	Functional Assessment of Cancer Therapy – Prostate cancer
FANCL	Fanconi anemia complementation group gene
FAPSI-6	FACT Advanced Prostate Symptom Index (FAPSI) - 6
FAS	Full analysis set
FDA	Food and Drugs Agency
G-CSF	Granulocyte colony-stimulating factor
GG	Ggamma parametric model
GLH	Genomic Laboratory Hub
Go	Grompert 2 parametric model

HR	Hazard ratio
HRQoL	Health-related quality of life
HRR	Homologous recombination repair
HRRm	Mutation in the homologous recombination repair pathway
ICER	Incremental cost-effectiveness ratio
IP	Investigational product
IPCW	Inverse probability of censoring weights
IPD	Individual patient data
ITC	Indirect treatment comparison
ITT	Intention to treat
IVRS/IWRS	Interactive voice/web response system
KM	Kaplan-Meier
LHRH	Luteinizing hormone-releasing hormone
LL	Loglogistic parametric model
mCRPC	Metastatic castration-resistant prostate cancer
MDS/AML	Myelodysplastic syndrome/acute myeloid leukemia
mHSPC	Metastatic hormone-sensitive prostate cancer
MMRM	Mixed model repeated measure
MRI	Magnetic resonance imaging
NA	Not applicable
NC	Not calculable
NCI	National Cancer Institute
NCPC	Non-castrate prostate cancer
NHA	New hormonal therapy
NHS	National health system
NICE	The National Institute for Health and Care Excellence
NMA	Network meta-analysis
NR	Not reported
ORR	Objective response rate
OS	Overall survival
PAIC	Population-adjusted indirect comparison
PALB2	Partner and localizer of BRCA2 gene
PARP	Polyadenosine diphosphate-ribose polymerase
PC	Prostate Cancer
PCWG3	Prostate Cancer Working Group 3
PH	Proportional hazards
PFS	Progression free survival
PFS2	Second progression free survival
PICOS	Population, intervention, comparator, outcome, study design
PPS	Post progression survival
PP2R2A	Protein Phosphatase 2 Scaffold Subunit Abeta
PSA	Prostate-specific androgen
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PSS	Personal social service
QALYs	Quality adjusted life years
RA	Rayleigh model
RAD51C	RAD51 paralog C gene
RAD51D	RAD51 paralog D gene
RAD54L	RAD54 Like gene

RCT	Randomised controlled trial
RDI	Relative dose intensity
RECIST	Response Evaluation Criteria in Solid Tumour
RoB	Risk of bias
ROBIS	Risk of Bias in Systematic reviews tool
rPFS	Radiographic progression free survival
RPSFT	Rank preserving structural failure time models
RPSFTM	Rank preserving structural failure time
SAE	Serious adverse events
SAP	Statistical analysis plan
SAS	Statistical analysis set
SE	Standard error
SLR	Systematic literature review
SMPC	Summary of product characteristics
SoC	Standard of care
SRE	Skeletal-related events
SSBs	Single-strand breaks
SSREs	Symptomatic skeletal-related events
TEAE	Treatment emergent adverse event
TSE	Two stage estimation
TTD	Time to treatment discontinuation
TTPP/TPP	Time to pain progression
UK	United Kingdom
VAS	Visual analogue scale
VBA	Visual basic for applications
We	Weibull parametric model
WTP	Willingness-to-pay

1 EXECUTIVE SUMMARY

1.1 Critique of the decision problem in the company's submission

The company submission (CS) decision problem matches the intervention and outcomes described in the final NICE scope (Table 1).

Table 1 NICE final scope

Population	People with hormone-relapsed, metastatic prostate cancer with homologous recombination repair gene alterations previously treated with hormonal therapy (eg. abiraterone or enzalutamide)
Intervention	Olaparib
Comparator	- Docetaxel - Cabazitaxel - Radium-223 dichloride for people with bone metastases
Outcomes	- progression free survival - time to pain progression - skeletal related events - overall survival - adverse effects of treatment - health-related quality of life
Subgroups	HRR alterations, including BReast CAncer gene (BRCA) and ataxia-telangiectasia mutated (ATM) gene status

The CS decision problem varied from the decision problem as specified by NICE with regards to the population and comparator. The *population* in the CS decision problem narrowed this definition to only include those who had additionally received prior taxane treatment in addition to hormonal therapy. The ERG clinical advisors agreed with this rationale, citing two recent randomised controlled trials in which docetaxel was used early in the clinical pathway during the hormone sensitive stage prior to NHA use. [10, 21]. However, it was noted by the ERG's clinical advisors that in the wake of Covid-19 patients are being prescribed NHA's in the NHS to reduce patient risk. It is therefore likely that the number of patients taxane naïve will be increased going forward.

The CS limits the *comparators* to cabazitaxel alone. The rationale for the removal of docetaxel as a comparator is based upon the company's decision *to restrict the target population to only those with prior taxane use (such as docetaxel)*. No further RCT evidence was identified.

The *marketing authorisation* does not report on the prior use of taxane treatment. The CS have requested a change to the overall population to include prior taxane use but have also asked "*that consideration is given to the small group of patients who have not received a taxane prior to NHA under equality provisions*". However, in PROfound olaparib performs far less well in PFS in the "no-prior" than in the "prior" population.

1.2 Summary of the key issues in the clinical effectiveness evidence

1. The CS changed the scope of the STA by moving the positioning of docetaxel to make treatment with docetaxel an eligibility criterion for the population rather than for the comparator treatment. While the ERG think this change to scope is acceptable it does differ from the anticipated marketing authorisation currently in place for Olaparib in terms of the focus on prior use of taxane treatment.
2. The ERG considers that the CS systematic review is at high risk of bias due to unclear inclusion criteria, imprecision in specification of methods, and reliance on a single reviewer for final study selection and extraction.
3. There is a lack of RCT evidence around the comparator treatments (radium-223, cabitaxel and docetaxel) in people with mCRPC who have HRR gene alterations. It is unclear whether the comparator treatments interact in those with HRR gene alterations in the same way as Olaparib so it is hard to draw any conclusions on the effectiveness in this population.
4. Evidence for the clinical effectiveness of olaparib was presented from a single RCT (PROfound). The use of an open-label study design in PROfound is suboptimal, with the potential to introduce bias. No consideration is given to the different levels at which blinding can take place, or alternative study designs.
5. PROfound included Cohort A: comprising men with mutations (germline or somatic) to 3 HRR genes (ATM, BRCA1, BRCA2), and Cohort B: comprising men with mutations (germline or somatic) to 12 other HRR genes. However the company's *"target population"* was the prior taxane subgroup from cohort A+B. Overall, cohort A had better outcomes than cohort B (where presented). The choice of the "prior taxane, A+B" cohort as the target population appears to have been made " *to align with the anticipated positioning of olaparib in the current clinical pathway of care in England (where the majority of patients receive a taxane [docetaxel] for non-metastatic or metastatic HSPC, before receiving NHA for mCRPC [CS pg 14]*. Relative to the full A+B population the CS choice of prior taxane usage reduces the size of the olaparib-eligible population but tends to increase the apparent effectiveness of olaparib in terms of PFS.
6. Evidence of efficacy is limited to Cohort A, extrapolation from Cohort A to Cohort B is not supported by the presented evidence. Evidence of the efficacy of olaparib in cohort A+B is driven by the benefits seen in cohort A only.
7. The company requested a change to the decision problem so that the overall population should include prior taxane use but, notwithstanding this have also asked "that consideration is given to the small group of patients who have not received a taxane prior to NHA under equality provisions". However, in PROfound olaparib performs far less well in PFS in the

"no-prior" than in the "prior" population:

[redacted].

8. The ERG note that because of the very small and highly selected numbers of patients recruited in the UK the generalisability of the findings from the PROfound study to the UK setting may be compromised.
9. The choice of comparator in PROfound is inadequate and not applicable to clinical practice as people with mCRPC are neither limited to nor likely to be retreated with NHA on which they have previously failed.
10. Effectiveness and economic analyses in the CS are based on the comparison of olaparib versus cabazitaxel using data from the PROfound and the CARD trials in each of which all patients received prior taxane (docetaxel).
11. Network meta-analysis was inappropriate as the assumption of transitivity is likely to be violated by differences in HRR mutation status of samples in the two studies. The two trials differ noticeably in terms of geography. The PROfound trial was Asia, Europe and North and South America, whereas the CARD trial was conducted exclusively in Europe. These geographic differences may be the cause of some of the apparent differences in subsequent treatments.
12. In summary, due to the quality of the indirect treatment comparison, the ERG considers that these indirect comparisons are inadequate for providing meaningful, statistically significant information on the comparison of olaparib and cabazitaxel for either rPFS or OS. This is important for the cost effectiveness modelling because it contributes to the ERG cost effectiveness summary (please see 1.3).

1.3 Summary of the key issues in the cost effectiveness evidence

The key issues in the cost effectiveness evidence are:

1. **Model structure.** The model has an oddly convoluted structure which may have led to model errors. The ERG thinks there are a number of model errors, all of which bias the model in favour of olaparib. Is the submitted model structure correct (section 4.3.1.2)?
2. **The functional form for overall survival.** Should this be the Weibull, which has the lowest AIC+BIC, or the log-logistic (section 4.2.6.1 and section 4.2.6.5)? How should the company expert survey responses be viewed when deciding this (section 4.3.4.1)?
3. **Direct drug costs.** The olaparib relative dose intensity (RDI) is calculated from individual patient's time to treatment discontinuation (TTD) data. Given that olaparib is prescribed in packs should a tablet based RDI be applied (section 4.3.4.8)? Which RDI is the most

reasonable to apply: the mean, the median or 100% (section 4.3.4.8)? Should the RDI be applied to the rPFS curve or to the TTD curve (section 4.3.4.8)? Should a TTD curve be inferred for cabazitaxel (section 4.3.4.10)?

4. **G-CSF costs.** Do all cabazitaxel patients receive primary prophylaxis with G-CSF every cabazitaxel treatment cycle (section 4.3.4.11)? Do cabazitaxel patients who receive primary prophylaxis with G-CSF receive the maximum 14 days dose every cabazitaxel treatment cycle (section 4.3.4.11)?
5. **Post progression treatments.** Are the company calculated rates of post progression (PPS) drug treatments calculated on the same basis for cabazitaxel as for olaparib (section 4.3.2.1)? Would patients get another NHA during PPS (section 4.3.4.13)? May patients get more than one PPS drug treatment, will this differ by arm and is it linked to the duration of PPS (section 4.3.4.13)?
6. **rPFS and TTD curves.** Were events treated consistently when constructing the rPFS and the TTD KM curves (section 4.3.4.9)?
7. **Test costs.** Should genetic test costs be included as specified in the scope (section 4.3.4.18)? What is the prevalence of the HRR genetic mutations in the population that would be tested (section 4.3.4.18)?
8. **Cohort B.** Should genetic subgroups be analysed as specified in the scope (section 4.3.4.19)? What is the probable cost effectiveness of olaparib for Cohort B patients (section 5.4.3)?
9. **Prior taxane use.** The company cost effectiveness estimates exclude those with no prior taxane use, but the company argues that olaparib should be approved for these patients. Should the no prior taxane subgroup be analysed (section 4.3.4.19)? What is the probable cost effectiveness of olaparib for no prior taxane patients (section 5.4.3)?

Lesser issues that still have a cumulative effect upon the ICER are:

10. **ADT/LHRH**. Does the majority of mCRPC patients receive ADT/LHRH for the majority of their mCRPC (section 4.3.4.15)?
11. **Scans**. Do those receiving cabazitaxel require twice the rate of bone scans and CT scans of those receiving olaparib (section 4.3.4.16)?
12. **Wastage**. Are cabazitaxel vials routinely shared (section 4.3.4.17)? What wastage should be assumed for cabazitaxel (section 4.3.4.17)?

1.4 Summary of ERG's preferred assumptions and resulting ICER

The company base case is presented in Table 2 for ease of reference.

Table 2: Company base case results

Deterministic	Probabilistic

	Caba.	Olap.	net	Caba.	Olap.	net
Total QALYs	[redacted]	[redacted]	0.364	[redacted]	[redacted]	0.333
Total Costs	[redacted]	[redacted]	-£2,424	[redacted]	[redacted]	-£2,597
ICER			Dominant			Dominant

The ERG revised base case differs from the company in the following:

- ERG01: Apply the various ERG corrections to the model: G-CSF costing, BSC costing, cabazitaxel administration costs, olaparib monitoring costs, genetic test costs.
- ERG02: Apply the ERG Weibull curves for olaparib OS, PFS and TTD.
- ERG03: Cost drug use using the median RDI and the TTD curve.
- ERG04: Restrict primary prophylaxis G-CSF to 60% of patients and for only 7 days per cabazitaxel treatment cycle.
- ERG05: Exclude NHAs from the PPS treatments.
- ERG06: Applies the £79.90 drug tariff price for G-CSF.
- ERG07: ADT/LHRH throughout mCRPC.
- ERG08: Equal bone and CT scans while on treatment.
- ERG09: Cabazitaxel proportion getting PPS treatments and the balance between these.
- ERG10: Apply the ERG Cohort A+B prior taxane HRs.
- ERG11: It applies the company [redacted] test cost, conditioned by a 27.9% HRR prevalence.

Table 3: ERG's preferred model assumptions

Preferred assumption	Section	ΔCost	ΔQALY	ICER
Company base-case	..	-£2,424	0.364	Dom.
ERG01a: G-CSF costs correction	4.3.1.2	£4	0.364	£12
ERG01b: BSC costs correction	4.3.1.2	-£884	0.364	Dom.
ERG01c: cabazitaxel admin costs	4.3.1.2	-£2,003	0.364	Dom.
ERG01d: olaparib monitoring costs	4.3.1.2	-£2,320	0.364	Dom.
ERG02: ERG parameterised curves	3.6.1	-£3,190	0.188	Dom.
ERG03a: TTD costing	4.3.4.8	£3,068	0.364	£8,428
ERG03b: median RDI	4.3.4.8	£87	0.364	£240
ERG04: G-CSF use	4.3.4.11	[redacted]	[redacted]	[redacted]
ERG05: Exclude NHAs from PPS treatments	4.3.4.13	-£1,534	0.364	Dom.

ERG06: G-CSF tariff price	4.3.2.2	-£2,014	0.364	Dom.
ERG07: ADT/LHRH costs throughout	4.3.4.15	-£1,983	0.364	Dom.
ERG08: Equal On Tx bone and CT scans	4.3.4.16	-£1,596	0.364	Dom.
ERG09: Cabazitaxel PPS treatments	4.3.2.1	-£941	0.364	Dom.
ERG10: ERG ITC HRs	3.6.1.7	-£2,154	0.375	Dom.
ERG11: Test costs	4.3.4.18	[redacted]	[redacted]	[redacted]
Cumulative effect of ERG revisions	..	£18,397	0.194	£94,708

The ERG revised base case suggests quite considerable net costs and a much reduced QALY gain compared to the company base case. The main drivers of this are:

- ERG01a & ERG04: Modelling G-CSF costs
- ERG01b: Assuming BSC costs apply subsequent to PPS treatment
- ERG02: Using the OS Weibull rather than the OS log-logistic
- ERG03a: Costing using the TTD curve rather than the rPFS curve
- ERG03b: Costing using the median RDI rather than the mean RDI
- ERG05: Excluding NHAs from PPS treatments
- ERG09: Revising the proportion of cabazitaxel patients who get PPS treatments
- ERG11: Applying the genetic test cost estimate of the company

During the factual error check the company identified a number of ERG model revision errors:

- Conditioning the cabazitaxel non-G-CSF concomitant medication costs and ADT costs by the ERG revisions to the G-CSF costs.
- Dividing the company monthly ADT drug cost by 3.
- Incorrect cell referencing for olaparib PPS active treatments.
- Not applying the CABA TTD:PFS ratio to the concomitant medication costs for scenario SA05.

Correcting these errors reduced the net cost of the ERG revised base case by £521. The detail of the ERG revised base case is presented in Table 4.

Table 4: ERG base case results

	Deterministic			Probabilistic		
	Caba.	Olap.	net	Caba.	Olap.	net
Total QALYs	[redacted]	[redacted]	0.194	[redacted]	[redacted]	0.200
Total Costs	[redacted]	[redacted]	£17,876	[redacted]	[redacted]	£18,192
ICER			£92,026			£91,171

1.5 Summary of sensitivity analyses undertaken by the ERG

The ERG provides the following scenario analyses:

- SA01: For OS applying the ERG Rayleigh and log-logistic curves
- SA02: Applying the company curves, and for OS applying the Weibull and the log-logistic curves
- SA03: Applying PROfound olaparib 100%, mean and mean days RDIs
- SA04: Costing olaparib using the rPFS curve, and applying PROfound 100%, median and mean RDIs
- SA05: Inferring a TTD curve for cabazitaxel for costing purposes
- SA06: Increasing PPS treatment costs by 50% for olaparib
- SA07: Increasing the cabazitaxel on treatment disutility to 0.037
- SA08: TA377 QoL values
- SA09: Assuming no vial sharing and wastage for cabazitaxel.
- SA10: Revising the HRR prevalence to 17.6% and the HRR test cost to £0.

Table 5: ERG scenario analyses

	ΔCost	ΔQALY	ICER
ERG base-case	£17,876	0.194	£92,026
SA01a: OS ERG Rayleigh	£17,569	0.178	£98,713
SA01b: OS ERG log-logistic	£20,753	0.363	£57,134
SA02a: company curves, OS Weibull	£17,455	0.198	£88,015
SA02b: company curves, OS log-logistic	£20,437	0.375	£54,438
SA03a: olaparib 100% RDI	£18,316	0.194	£94,291
SA03b: olaparib mean RDI	£14,956	0.194	£76,995
SA03c: olaparib mean days RDI	£16,270	0.194	£83,759
SA04a: olaparib rPFS costing, 100% RDI	£12,727	0.194	£65,518
SA04b: olaparib rPFS costing, median RDI	£12,348	0.194	£63,565
SA04c: olaparib rPFS costing, mean RDI	£9,830	0.194	£50,603
SA05: cabazitaxel inferred TTD curve	£15,754	0.194	£81,103
SA06a: Same PPS treatments between arms	£17,846	0.194	£91,870
SA06b: Company cabazitaxel PPS treatments	£17,401	0.194	£89,581
SA06c: olaparib PPS costs 50% higher	£20,792	0.194	£107k
SA07: increased cabazitaxel disutility	£17,876	0.199	£89,816
SA08a: TA391 QoL values	£17,876	0.201	£88,827
SA08b: TA377 QoL values	£17,876	0.185	£96,571
SA09: no cabazitaxel vial sharing	£12,377	0.194	£63,715
SA10a: 17.6% HRR prevalence	[redacted]	0.194	[redacted]
SA10b: no genetic test cost	[redacted]	0.194	[redacted]
SA11a: No ADT/LHRH admin cost	£17,713	0.194	£91,184
SA11b: Monthly ADT/LHRH admin cost	£18,204	0.194	£93,712

ERG exploratory analyses by subgroup are presented below for the comparison of Cohort A with Cohort B and for the comparison of those with prior taxane use with those with no prior taxane use. These analyses are indicative and not definitive.

Table 6: ERG subgroup analyses: Cohort A+B, Cohort A and Cohort B

	Cohort A+B		Cohort A		Cohort B	
	QALY	Cost	QALY	Cost	QALY	Cost
Cabazitaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net	0.135	£17,755	0.263	£23,665	-0.086	£7,569
ICER		£132k		£90,078		Dominated

The above is not restricted to the prior taxane patient group, but it suggests that there may be relatively few patient benefits from treating Cohort B patients with olaparib. But there will still be quite considerable costs.

Table 7: ERG subgroup analyses: Cohort A+B by prior taxane use

	All patients		Prior taxane		No prior taxane	
	QALY	Cost	QALY	Cost	QALY	Cost
Cabazitaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net	0.135	£17,755	0.194	£17,876	0.020	£17,523
ICER		£132k		£92,026		£855k

Evidence Review Group Report

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

In 2018, prostate cancer was the most commonly diagnosed male cancer in the UK and between 2017 and 2018 42,668 people were diagnosed with prostate cancer in England and Wales.[1, 2] Age-period-cohort models based on 1979-2014 UK data have predicted the incidence of prostate cancer in the UK to increase over the next 15 years.[3] The CS describes the epidemiology, progression and current clinical pathway of care for homologous recombination repair gene mutation (HRRm) prostate cancer on p7-10 of Document B.

While most cases of prostate cancer have an early presentation, a proportion of patients will experience disease progression which may include the development metastatic castration-resistant prostate cancer (mCRPC) or metastatic hormone sensitive prostate cancer (mHSPC). Metastatic castration-resistant prostate cancer is an incurable form of the disease that does not respond to androgen deprivation therapy (ADT), and is usually preceded by hormone-sensitive disease.[4]

Page 7 of the CS states that "~40% of patients" with prostate cancer progress to mCRPC, referencing an editorial by Sciarra and Salciccia, and a letter which references the same article. Sciarra and Salciccia state that up to 40% of patients will develop metastatic disease but do not distinguish between mCRPC and mHSPC.[5]

The CS states that "fewer than half of patients with mCRPC in the UK survive for 5-years" and references the Cancer Research UK website which in turn references data from the Office for National Statistics.[6] These data show that in the UK, 49% of adults diagnosed with stage 4 prostate cancer in 2013 survived 5 years, although this group was not stratified by type of stage 4 prostate cancer (i.e. mCRPC or mHSPC).[7]

Hormone sensitive prostate cancer (also known as non-castrate prostate cancer, NCPC) is commonly treated with ADT, which can be used in combination with docetaxel, a taxane chemotherapy.[8] The CS states that "the addition of docetaxel to ADT led to improved patient outcomes" in the GETUG-AFU15 trial. The GETUG-AFU15 trial compared the survival of patients with mHSPC when treated with ADT vs ADT and docetaxel. While the trial demonstrated a trend towards improved survival in patients treated with ADT and docetaxel, this did not reach statistical significance overall, or in sub-group analyses of patients with high or low volume disease.[9]

However, the CHAARTED trial also compared survival of patients with mHSPC treated with ADT vs ADT and docetaxel, and demonstrated an increased overall survival in those treated with ADT and docetaxel (57.6 months vs. 44.0 months; hazard ratio for death in the ADT and docetaxel group, 0.61; 95% confidence interval, 0.47 to 0.80; P<0.001).[10] NICE Guideline 131 (NG131, May 2019)

recommends that docetaxel is considered in combination with ADT for locally advanced HSPC or mHSPC, and that docetaxel is offered for mCRPC when a patient's Karnofsky performance-status score is 60% or more.[11]

2.2 Background

Six UK clinical experts that were consulted by the company have "highlighted that ~75% of patients currently receive docetaxel" before the disease has progressed to mCRPC. The ERG clinical advisor confirmed that from 2016-2020 most patients will have received docetaxel prior to NHA. However, proportions are less than 75%. It is worth noting that since COVID-19 more patients are receiving NHA (Enzaluatmide predominantly in the NHS setting) instead of docetaxel to minimise patient risk of infection.

As the CS states, new hormonal agents (NHAs, e.g. abiraterone or enzalutamide) can be used as an option for the treatment of mCRPC following disease progression on docetaxel. Specifically, abiraterone with prednisolone, or prednisolone, or enzalutamide are recommended by NICE in these circumstances.[12, 13] Radium-223 dichloride can also be considered as a treatment for mCRPC where symptomatic bone metastases are present, without visceral metastases, and patients have already received docetaxel therapy, or docetaxel therapy is contraindicated.[14]

NICE also recommend "Cabazitaxel in combination with prednisone or prednisolone" as a treatment for mCRPC in people who have progressed during or after treatment with docetaxel, provided the person has an eastern cooperative oncology group (ECOG) performance status of 0 or 1, has had 225 mg/m^2 or more of docetaxel, and treatment with cabazitaxel is stopped when the disease progresses or after a maximum of 10 cycles (whichever happens first).[15] The CARD study compared cabazitaxel with abiraterone or enzalutamide in people with mCRPC who had previously received docetaxel and had disease progression on abiraterone or enzalutamide. The cabazitaxel group had significantly better outcomes than the new hormonal agent group, including overall survival (13.6 months vs 11.0 months; hazard ratio for death, 0.64; 95% confidence interval, 0.46 to 0.89; P=0.008).[16]

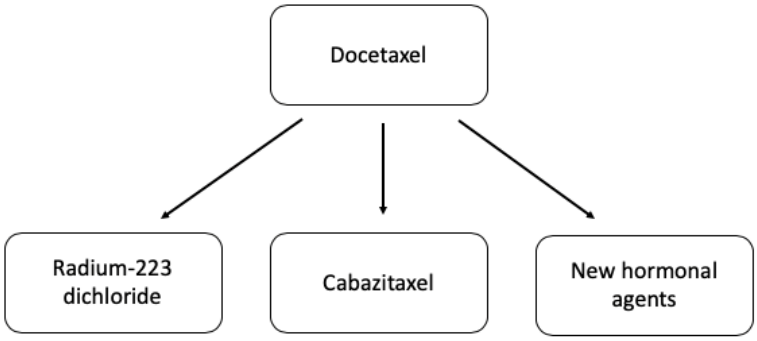


Figure 1. Treatment options for mCRPC recommended by NICE following progression on docetaxel.

Based on expert consultation, the CS describes the following typical UK treatment sequence for HRRm prostate cancer: docetaxel and ADT, followed by NHA, followed by cabazitaxel, with radium-223 dichloride typically reserved for later lines of treatment or instead of cabazitaxel when treatment with a taxane is not appropriate.

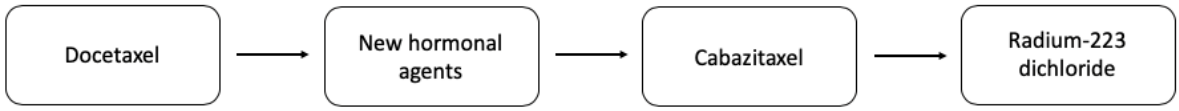


Figure 2. Typical UK treatment pathway for mCRPC.

As the CS explains, olaparib is a poly(adenosine diphosphate)-ribose polymerase (PARP) protein inhibitor and prevents the repair of DNA single-strand breaks (SSBs). These SSBs eventually convert to double-strand breaks (DSBs) which can be repaired in normal cells by HRR proteins. Cells with HRR gene mutations (e.g. HRRm prostate cancer cells) are unable to repair these DSBs, and instead undergo apoptosis.[17, 18]

The PROfound study found that in people with mCRPC who had progressed on abiraterone or enzalutamide, and had mutations in certain HRR genes, treatment with olaparib resulted in longer survival than treatment with abiraterone or enzalutamide (7.4 months vs. 3.6 months; hazard ratio for progression or death, 0.34; 95% confidence interval, 0.25 to 0.47; P<0.001).[19] In the CS, olaparib is proposed instead of cabazitaxel following progression after NHA treatment.

2.3 Critique of company's definition of decision problem

The ERG provide a comparison of the NICE final scope and CS decision problem in Table 8.

2.3.1 Population

The CS population (Document B, table 2, page 17) differs in part from the final NICE scope. The final scope defined the population as "*patients with hormone-relapsed, metastatic*

prostate cancer with HRR gene alterations previously treated with hormonal therapy such as abiraterone or enzalutamide". The population in the CS decision problem narrowed this definition to only include those who had additionally received prior taxane treatment in addition to hormonal therapy. The CS justify the rationale for restricting this patient group based upon testimony from three clinical advisors that around 75% of patients receive a taxane treatment such as docetaxel prior to new hormonal therapy (NHA) treatment in clinical practice.[20] **The ERG clinical advisors agreed with this rationale, citing two recent randomised controlled trials in which docetaxel was used early in the clinical pathway during the hormone sensitive stage prior to NHA use**. [10, 21]. However, it was noted by the ERG's clinical advisors that in the wake of Covid-19 patients are being prescribed NHA's in the NHS to reduce patient risk. It is therefore likely that the number of patients taxane naïve will be increased going forward.

2.3.2 Intervention

The intervention listed in the company decision problem matches that in the NICE final scope: olaparib.

2.3.3 Comparators

The comparators listed in the CS decision problem differ from the NICE final scope. The final NICE scope lists the comparators as:

(1) Docetaxel

(2) Cabazitaxel

(3) Radium-223 dicholoride (for people with bone metastases)

NICE scope also considers the potential differing positions that these comparators could be used in the treatment pathway.

The CS decision problem limits the comparators to cabazitaxel alone. The rationale for the removal of docetaxel as a comparator is based upon the company's decision to restrict the target population to only those with prior taxane use (such as docetaxel). The company justify this decision based upon the opinion of 6 UK clinical experts, that since the NG131 document was published in May 2019, 3 experts confirmed that around 75% of patients receive docetaxel prior to NHA treatment.[20] Additionally, the company investigated RCT evidence of docetaxel compared to Olaparib in those

with disease-progression on NHA, however, no evidence was identified in their systematic literature review (SLR). The ERG checked the studies reported in table 14 in the CS appendices (pages 30-31) as well as studies reporting on docetaxel in the title from the full excluded studies list provided by the company. The ERG agree that no trials reporting on NHA use prior to docetaxel treatment that include mutation analyses have been missed.

The CS also suggests the removal of radium-223 as a comparator. Differing from the NICE final scope, the CS indicates that clinicians reserve radium-223 for later in the treatment pathway following both NHA and cabazitaxel unless treatment with a taxane such as docetaxel is unsuitable.[20]. The ERG clinical advisor indicates that radium-223 is given to patients with no visceral metastasis or not eligible for docetaxel. The company suggest there is no suitable RCT evidence on radium-223 dichloride following disease progression on an NHA and that any evidence in which patients did not receive a taxane prior to NHA is because they were deemed unsuitable to receive this treatment.. The ERG checked the studies reported in table 15 in the CS appendices (page 32) as well as studies reporting on radium-223 in the title from the full excluded studies list provided by the company. The ERG agree that no trials reporting on NHA use prior to radium-223 treatment that include mutation analyses have been missed and so believe the removal of radium-223 as a comparator to be acceptable.

2.3.4 Outcomes

The NICE final scope outcomes including progression free survival, time to pain progression, skeletal related events, overall survival, adverse effects of treatment and health-related quality of life are addressed in the CS. The CS outlines the primary outcome of the PROfound study as radiographic progression-free survival (rPFS) by blinded independent central review (BICR). However, these outcomes are only reported for cohort A (with at least one mutation in either BRCA1, BRCA2 or ATM genes) and cohort A+B (several mutations) and the prior taxane A+B subgroup. This contrasts with the cost-effectiveness target group where these outcomes were only reported for the cohort A+B prior taxane subgroup. All other outcomes reported in the NICE final scope are reported as secondary outcomes in PROfound trial and were reported for cohort A+B prior taxane group.

2.3.5 Other relevant factors

The CS matches the NICE scope with regards to including a subgroup analysis by HRR gene alteration.

The NICE scope specifies that guidance will only be issued in accordance with the marketing authorisation. Food and Drugs Association (FDA) marketing authorisation was granted in 2014 and in the European Medicines Agency (EMA) on 22 November 2019 for the use of Olaparib (Lynparza) for several indications, including prostate cancer.[22, 23] The authorisation specifies "[redacted] However, the anticipated marketing authorisation does not report on the prior use of taxane treatment. The CS have requested a change to the overall population to include prior taxane use but have also asked "that consideration is given to the small group of patients who have not received a taxane prior to NHA under equality provisions". However, in PROfound olaparib performs far less well in PFS in the "no-prior" than in the "prior" population [redacted].

Table 8: Summary of decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
Population	People with hormone-relapsed, metastatic prostate cancer with homologous recombination repair gene alterations previously treated with hormonal therapy (eg. abiraterone or enzalutamide)	People with hormone-relapsed, metastatic prostate cancer with homologous recombination repair gene alterations previously treated with a taxane (docetaxel) and hormonal therapy (eg. abiraterone or enzalutamide)	• The vast majority (~75%) of patients have already received treatment with a taxane (docetaxel) prior to NHA in current clinical practice • Indirect treatment comparisons to docetaxel (for the minority of patients who have not receive a taxane prior to NHA) or radium-223 dichloride (for the small subset of patients who have bone metastases, no known visceral metastases, and for whom treatment with a taxane is unsuitable) was not possible due to limitations in published RCT evidence base	The population in the CS decision problem is restricted to people who have been treated with both a taxane as well as hormonal therapy. The opinion that ~75% of patients have already received treatment with a taxane prior to NHA treatment was deemed acceptable by our clinical advisors.
Intervention	Olaparib	Olaparib	N/A	The intervention in the CS matches the NICE final scope.
Comparator(s)	- Docetaxel - Cabazitaxel - Radium-223 dichloride for people with bone metastases The different positions that these comparators could be used in the treatment pathway will be considered in the appraisal	Cabazitaxel	As mentioned above, indirect treatment comparisons to docetaxel and radium-223 dichloride were not feasible due to a lack of published RCT evidence on these treatments in the post- NHA setting. PFS2 is an intermediate endpoint between PFS and OS and reflects real-life treatment decisions and patient experience. Its use is	The CS limited treatment comparisons to Cabazitaxel due to a lack of RCT evidence on Radium-223 dichloride and docetaxel following NHA treatment. NICE scope states that the different positions of the comparators in the pathway should be considered.

			recommended by the EMA to capture potential negative impacts on next-line therapy and to demonstrate that any potential tolerability concerns are outweighed by treatment benefit.	The ERG clinical advisors agree with the company clinical experts that in the majority of cases docetaxel is used earlier in the pathway. The ERG considers the removal of Docetaxel as a comparator, and it's inclusion within the population to be in line with current practice The ERG agrees there is a lack of trial evidence in the correct population on Radium 223-dichloride treatment.
Outcomes	- Progression free survival - time to pain progression - skeletal related events - overall survival - adverse effects of treatment - health-related quality of life	- Radiographic progression free survival - time to pain progression - skeletal related events - overall survival - second progression-free survival (PFS2) - adverse effects of treatment - health-related quality of life	PFS2 is an intermediate endpoint between PFS and OS and reflects real-life treatment decisions and patient experience. Its use is recommended by the EMA to capture potential negative impacts on next-line therapy and to demonstrate that any potential tolerability concerns are outweighed by treatment benefit.[24]	The outcomes in the CS match those in the NICE scope, except that not all outcomes are reported for the prior taxane A+B subgroup.
Economic analysis				
Subgroups	HRR alterations, including BReast CAncer gene (BRCA) and ataxia-telangiectasia mutated (ATM) gene status	*One or more of the 15 HRR genes.*	In line with the anticipated marketing authorisation for olaparib, the company submission considers the treatment of patients with qualifying mutations in one or more of 15 HRR genes (i.e. the overall population of PROfound). rPFS data in the	The subgroups reported in the CS match the NICE scope. Note: the chosen genes do not encompass all of the genes in the HHR pathway and CDK12 is not an HRR gene, but it's inactivation can have an impact

			subgroup of patients who have mutations in BRCA1, BRCA2, and ATM genes (the primary endpoint in PROfound) are described in Section A.7 and B.2.6.2.1; further analyses are available in the CSR (Section 11)	on HRR genes
Special considerations including issues related to equity or equality	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.	Although this submission focuses on the subset of patients who have received treatment with a prior taxane and NHA, due to the demonstrated efficacy of olaparib in the overall study population of PROfound (and anticipated marketing authorisation), regardless of prior taxane use, we request that consideration is given to the small group of patients who have not received a taxane prior to NHA under equality provisions	N/A	The CS changed the population from the NICE scope to include docetaxel as a prior treatment, which is not specified in the marketing authorisation.. However, based on the results of the PROfound trial the ERG feel the inclusion of docetaxel as a population to be appropriate. **However the ERG considers that the equality concern regarding those who have not been given a prior taxane as not appropriate since the the Olaparib group who had no prior taxane had poorer PFS than the prior taxane group.**

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

The CS includes a systematic review undertaken to identify "published clinical evidence on the use of health technologies in patients with metastatic castration-resistant prostate cancer (mCRPC) whose disease had progressed following treatment with a new hormonal agent (NHA; i.e. abiraterone or enzalutamide)" (CS Appendices, page 7).

The ERG critique of the SLR is provided below. The review processes were described for study selection (methods and number of reviewers), but not for data extraction. There was evidence that suboptimal processes were employed (e.g. single reviewer full text assessment), and that the methods described in the CS submission were not followed, e.g. exclusion criteria were applied that were not specified in the PICO. Table 9 provides the ERG quality assessment of the CS clinical effectiveness SLR.

Overall, the ERG considers the chance of systematic error in the clinical effectiveness SLR to be high. In particular, the ERG found the study selection criteria and process not to be well specified, and the submitted evidence to be inconsistent with both the company decision problem as defined in the CS (Doc B, page 17, Table 2) and the decision problem as described in the NICE scope.

Table 9. ERG assessment of risks of bias of the CS systematic review of clinical effectiveness

ROBIS domain, and signalling questions	ERG's assessment of whether criteria met, with comments
1: Study eligibility criteria	
1.1 Did the review adhere to pre-defined objectives and eligibility criteria?	**No**. No published protocol. Studies excluded for inconsistent reasons not specified in PICO (e.g. Mateo et al. 2015 excluded because of dose, but dose not an exclusion criteria).
1.2 Were the eligibility criteria appropriate for the review question?	**No**. Objective of the submission is to evaluate olaparib for people with hormone-relapsed, metastatic prostate cancer with homologous recombination repair (HRR) gene alterations previously treated with hormonal therapy such as abiraterone or enzalutamide. CS review does not consider HRR status and mixes those with/without mutated HHR genes in the network meta-analysis.
1.3 Were eligibility criteria unambiguous?	**No.** Study characteristics such as participant nationality, intervention doses and administration frequencies, and allowable

	concomitant treatments were not specified in the review criteria, but doses and participant nationality were subsequently used as exclusion criteria.
1.4 Were all restrictions in eligibility criteria based on study characteristics appropriate?	**Yes.** The only restrictions specified in the eligibility criteria were to exclude animal/in vitro studies, and reviews (after checking reference lists) and editorials. But, note, additional post hoc exclusion criteria were applied to search results.
1.5 Were any restrictions in eligibility criteria based on sources of information appropriate?	**No information**.
Domain 1 risk of bias	**High**
2: Identification and selection of studies	
2.1 Did the search include an appropriate range of databases/ electronic sources for published and unpublished reports?	**Yes**. Searches were conducted in an appropriate set of bibliographic databases (MEDLINE, MEDLINE In-Process, Embase, Cochrane Library).
2.2 Were methods additional to database searching used to identify relevant reports?	**Yes**. Supplementary searches of NICE technology appraisal documents, conferences and two clinical trial registers were conducted, and reference lists of relevant systematic reviews checked.
2.3 Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	**Probably yes**. Detailed search strategy provided (CS Appendices, Tables 1 – 3). Suitable terms were included and combined appropriately. Study type search filters for RCTs and SRs and Meta-Analyses were applied. This was appropriate for MEDLINE and Embase, but not for the Cochrane Library. Applying study type filters to databases such as CENTRAL and CDSR, which are specialist databases, may inadvertently cause some records not to be retrieved.
2.4 Were restrictions based on date, publication format, or language appropriate?	**No**. No restrictions on date or publication format, but limited to the English language. No justification for language restriction provided.
2.5 Were efforts made to minimise errors in selection of studies?	**No**. Appropriate assessment of titles and abstracts by two independent reviewers, with disputes between reviewers referred to a third reviewer. However, a single reviewer assessed full text papers. The PICO was poorly presented and reasons for exclusion were confusing.
Domain 2 risk of bias	**High**
3: Data collection and study appraisal	
3.1 Were efforts made to minimise error in data collection?	**No information**. The CS provided no information regarding the process of data extraction.
3.2 Were sufficient study characteristics	**No**. Extensive information present about two studies (PROfound,

available for both review authors and readers to be able to interpret the results?	and CARD) in the CS (Doc B, pages 23 – 105, Appendices, pages 36 – 41). Other studies that met the company inclusion criteria (e.g Mateo et al. 2015, Puente et al. 2018) were excluded so data were not extracted.
3.3 Were all relevant study results collected for use in the synthesis?	**No**. See box above.
3.4 Was risk of bias (or methodological quality) formally assessed using appropriate criteria?	**Probably no**. CS states "A complete quality assessment in accordance with the NICE-recommended checklist for assessment of bias in RCTs is presented." The tool used in the CS deviated considerably from the Cochrane Risk of Bias Tool, with many of the signalling questions not addressed, and the domain 'Measurement of outcomes' not assessed at all in the CS. In addition, signalling questions (rather than domains) were rated for risk of bias.
3.5 Were efforts made to minimise error in risk of bias assessment?	**No information**. CS documents do not report the process used for assessing risk of bias.
Domain 3 risk of bias	**High**
4: Synthesis and findings	
4.1 Did the synthesis include all studies that it should?	**No**. Exclusion criteria that were not pre-specified were applied to studies. For example, Sugiyama et al. (2018) excluded as no European patients, Louhanepessy et al. (2018) and Massard et al. (2017) excluded on the basis of sample size, and Mateo et al. (2015) excluded as intervention dose did not match dose used in PROfound trial. Further, results of studies on Olaparib only partially reported (i.e. PROfound included and described, while TOPARP-A/B was excluded despite meeting CS review inclusion criteria). Even if excluded from the network meta-analysis, these studies could have been described in the general clinical effectiveness section of the CS.
4.2 Were all predefined analyses followed or departures explained?	**No information.** CS documents do not report predefined analyses.
4.3 Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies?	**No.** One of the two studies (CARD) that the company included in the network meta-analysis was not applicable to the objective of the Single Technology Appraisal (STA). The population of interest to the STA was "Hormone-relapsed, metastatic prostate cancer with homologous recombination repair (HRR) gene alterations previously treated with hormonal therapy such as abiraterone or enzalutamide". The CARD study did not refer to the status of participant HRR genes. Second, (using the broader CS inclusion criteria) studies without a common comparator arm

	with PROfound, but that could potentially have added to the network, were excluded.
4.4 Was between-studies variation (heterogeneity) minimal or addressed in the synthesis?	**No**. Similarities in CARD and PROfound populations were partially addressed (Doc B, pages 82 – 85), but a critical difference (presence/absence of HRR mutations and their effect on treatment efficacy) was not addressed.
4.5 Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses?	**NA.** The NMA was inappropriate due to unknown status of HRR genes in the CARD trial.
Domain 4 risk of bias	**High**
Overall risk of bias in the review	**High**

- *Searches*

The company searched in an appropriate set of bibliographic databases were undertaken in January 2020 for records added since 1974. Suitable terms, including those for hormone-resistant prostate cancer, advanced disease, and relevant interventions, were included and combined appropriately. Study type search filters for RCTs and SRs and Meta-Analyses were applied. This was appropriate for MEDLINE and Embase, but not for the Cochrane Library. Applying study type filters to databases such as CENTRAL and CDSR, which are specialist databases, may inadvertently cause some records not to be retrieved. Some publication types were also excluded in the database searches, such as letters and abstract reports. No date limits were applied. In addition, the CS states that searches of NICE technology appraisal documents, relevant conference abstracts from 2017-2019, and two trial registers were undertaken.

- *Inclusion criteria*

The eligibility criteria for study inclusion and exclusion were defined according to patient, intervention, comparators, outcomes, and study design (PICOS) framework (CS Appendix D, Table 6, page 17).

Briefly, the inclusion criteria were English-language publications (full text or abstract) of many different kinds of study design (randomised controlled trials, single-arm studies, meta-analyses, systematic literature reviews, indirect treatment comparisons and human studies) in patients with mCRPC who have failed previous treatment with an NHA (such as abiraterone

and/or enzalutamide), or an agent that is androgen-blocking or androgen-depriving. The inclusion criteria did not limit by interventions/comparators nor the presence of HHR gene mutations, instead any paper at full text sorting reporting on an intervention not listed in the NICE scope was excluded unless they pertained information relevant to this review. The company do not report what information from papers including ineligible interventions/comparators might have been relevant. An eligible study had to report outcomes in the areas of:

- Time to pain progression
- Time to first symptomatic skeletal-related event
- Time to opiate use for cancer-related pain
- Time to radiographic progression
- Time to prostate-specific antigen progression
- PFS
- OS
- AEs of treatment
- Health-related quality of life

Full details of the study eligibility criteria are provided in CS Appendix D (Table 6, page 17). The ERG does not consider the inclusion criteria to be appropriate. In particular, the population as described in CS Appendix CS (Appendix G, Table 27) does not match either the population of interest as outlined in the NICE scope, nor other parts of the company's own submission (Doc B, Table 2, page 17) in relation to the presence of HRR gene mutations (see Table 10). The ERG considers removal of HRR gene status to be inappropriate as there is some evidence that outcomes and treatment responses might vary between those with/without HRR gene mutations.[25-27]

Table 10. Definition of population

Document	Definition
NICE scope	Hormone-relapsed, metastatic prostate cancer with homologous recombination repair gene alterations previously treated with hormonal therapy such as abiraterone or enzalutamide
CS Doc B	Patients with hormone-relapsed, metastatic prostate cancer with HRR gene alterations previously treated with a taxane (docetaxel) and hormonal therapy such as abiraterone or

	enzalutamide
CS Appendix G, Table 27	Patients with mCRPC who have failed prior treatment with a NHA such as abiraterone and/or enzalutamide or an agent that is androgen-blocking or androgen-depriving, regardless of HRR mutation status

Further, it is not standard systematic reviewing practice to combine the intervention and comparators under assessment domain. In not clearly defining the intervention and comparators, the review question has become very different to that of the NICE scope and studies will have been included comparing different comparators, rather than just studies comparing olaparib to a comparator. Also, the possibility of publication bias due to excluding studies in languages other than English is noted.

The study selection process was performed at abstract and full-text levels. Initially, two independent reviewers screened all the studies identified in the searches of bibliographic records at abstract level. Disagreements regarding inclusion/exclusion of any given abstract were discussed and reconciled between the two reviewers or with a help of a third reviewer. Full texts of all potentially eligible abstracts which passed to the second stage of screening were reviewed by one reviewer using the pre-specified eligibility criteria. The company provided a graphical display of the study selection process using a PRISMA study flow diagram (CS Appendix D, page 19). The ERG does not consider the study selection methodology and process to be acceptable. Full text assessment should be undertaken by two independent reviewers. There is a high risk of bias and of error when only one reviewer is involved in full text assessment.

From the PRISMA flow diagram (CS Appendix D, page 19) there appear to be 157 articles eligible for inclusion (including RCTs, single arm studies, systematic reviews, indirect treatment comparisons, meta-analysis publications, publications reporting previous treatment with a non-NHA ADT and ClinicalTrials.gov entries) yet within the appendices the company only report on 23 (CS Document B, B.2.1; Appendix D) or 21 (CS Document B, B.2.1.1 – B.2.1.3) publications meeting the inclusion criteria. The list of excluded studies (at full text review) were provided (CS Appendix D, embedded excel sheet, page 20). However, in the submission no reasons for exclusion were provided. Upon request the company provided this data. These 23 studies have then been discussed (appendix D,

tables 12-15, pages 23-32) and considered against the decision problem, with only 2 studies (PROfound and CARD trials, 4 papers) meeting the inclusion criteria. The ERG considers the reporting quality to be low. It is unclear of the exact process the company followed to determine their studies for inclusion, but there is a mismatch between the reporting in the PRISMA diagram from the reporting in the text and subsequently the reporting of the two studies finally included in the review. The company do not appear to have judged eligibility for inclusion from the PICOs reported. The company appear to have included further restrictions based upon the quality of evidence, size of studies, and comparability to the PROfound trial which were not reported in the inclusion criteria (appendix D, tables 12-15, pages 23-32). The ERG is unclear whether the company have combined their literature search to enable finding studies for the network meta-analysis together with the literature review, which may explain the differing criteria applied.

Overall, the ERG does not consider the method of study inclusion to be appropriate.

- *Critique of data extraction*

The CS does not report the method or process of data extraction, e.g. the number of reviewers who conducted extraction, whether extraction was checked for errors, how disagreements were managed. The ERG does not consider this systematic.

- *Quality assessment*

The company's assessment of study quality of the included studies (Table 8, p49 in the CS document B and section D.3, p42 CS appendices) are summarised in Table 11Table 12 together with the ERG's independent assessment. The company state they used the NICE recommended checklist to assess the RoB in the one included trial for Olaparib (PROfound), [19]and the one included trial for cabazitaxel (CARD) identified by the SLR.).[28] The latest NICE guidance recommends the Cochrane RoB tool as the preferred checklist, however domains from the checklist were missed and the tool was not used in the manner in which it was designed.[29] Two ERG reviewers independently assessed the RoB of both the PROfound trial and CARD trial using the Cochrane RoB as recommended by NICE. The domains and style have been changed in accordance with the checklist in table 8 below.

The PROfound trial was assessed across the domains of randomisation, blinding (participants, study personnel, and outcome assessors), similarity of groups at baseline and sample attrition/incomplete outcome data (Intention To Treat [ITT] analysis, sensitivity analysis).[19] The CS assessed all domains of the PROfound trial to be at low RoB, bar allocation concealment which was surprisingly deemed not applicable, although the company do not state if the RoB assessment was performed by two independent reviewers. The ERG partially agree with some of the RoB sub-domains assessed by the company. However, the ERG downgraded the quality of evidence in comparison to the company. Performance bias is at high risk due to the lack of blinding. It is unclear whether there is the potential for selection bias or attrition bias due to incomplete reporting of baseline characteristics, length of follow up and withdrawals.

Table 11. ERG assessment of PROfound trial quality

NICE checklist item	*CS judgement and rationale*	ERG judgement and rationale
Selection bias		
Was randomisation carried out appropriately?	*Yes* *Low RoB* "A central interactive voice-response or Web response system was used to randomly assign patients in a 2:1 ratio"	Yes De Bono et al 2020 reports a central interactive response technology for randomly assigning patients. [19]
Was the concealment of treatment allocation adequate?	*NA* *Low RoB* "PROfound was an open-label study. Radiographic disease progression was assessed by blinded central review by an independent third-party vendor to mitigate against risk of investigator bias"	No The study was open label meaning patients and investigators knew their allocated drug.
Were the groups similar at the outset of the study in terms of prognostic factors?	*Yes* *Low RoB* "A blocked randomisation list was generated to ensure an approximate balance between the olaparib and enzalutamide or abiraterone acetate arms in Cohorts A and B (2:1). The randomisation was stratified by previous taxane use (yes, no) and whether subject had measurable disease (yes, no). Minor imbalances were noted for some baseline characteristics; however, as described in , a sensitivity analysis which adjusted for prior taxane, measurable disease, and other important prognostic factors that appeared imbalanced across the treatment arms (including PSA, metastatic disease at diagnosis, and ECOG status [all as covariates]) showed that the impact on the hazard ratios for rPFS and OS compared with the primary and secondary analyses was minimal. The study results were thus robust, and not impacted by minor differences in baseline characteristics across treatment arms.	Unclear De Bono et al 2020 report an imbalance at baseline between groups. [19] With the control group having a higher percentage of patients with visceral metastates and higher median baseline PSA concentration. The Olaparib group had a higher proportion of patients with ATM alteration (Table 1, De Bono et al 2020).[19]. The company have undertaken statistical analyses to account for these differences however the results are not presented within their submission.
Overall rating of selection bias	*NR*	Unclear RoB Allocation was concealed until the point of enrolment but participants and investigators were aware of their treatment and there were notable differences at baseline between the treatment arms. The ERG cannot determine whether this was sufficiently accounted for within the analyses undertaken as these have not been presented.

Performance bias		
The comparison groups received the same care apart from the intervention(s) studied	*NR*	Unclear A range of concomitant medications was allowed in the study. However, no information is reported about whether these were balanced between the intervention and control arms. In addition, the majority of patients switched over to the Olaparib arms (81% reported in De Bono 2020)[19]
Participants receiving care were kept 'blind' to treatment allocation	*No* *Low RoB* This was an open label trial; however, radiographic disease progression was assessed by blinded central review by an independent third-party vendor and the study sponsors were blinded to actual treatment arm until the randomisation codes were received (29 July 2019)"	No Participants were not blinded to treatment allocation as this was an open label trial.
Individuals administering care were kept 'blind' to treatment allocation	*No* *Low RoB* This was an open label trial; however, radiographic disease progression was assessed by blinded central review by an independent third-party vendor and the study sponsors were blinded to actual treatment arm until the randomisation codes were received (29 July 2019)"	No This was an open-label trial. According to De Bono "The primary end point was imaging-based progression-free survival in cohort A" [19]. No information is provided in relation to blinding for all other outcomes.
Overall rating of performance bias	*NR*	High RoB Participants were aware of their assignment, this may have influenced self-reports of symptoms and the majority of patients received olaparib Assessors appears to have been aware of treatment allocation for all outcomes except radiographic disease progression.
Attrition bias		
All groups were followed up for an equal length of time (or analysis was adjusted to allow for differences in length of follow-up)	*NR*	No De Bono et al (2020) report a difference in follow up for overall survival between Olaparib and control arms, "median duration of follow-up for overall survival was 12.6 months and 13.2 months respectively". [19] In the CS this is reported to be 12.2 months and 12.1 months respectively.

The groups were comparable for treatment completion (that is, there were no important or systematic differences between groups in terms of those who did not complete treatment)	*No* *Low RoB* "Select minor imbalances were observed (see Section B.2.3.7), but were confirmed by multivariate modelling to have only minimal impact on the rPFS and OS hazard ratios"	Unclear Number of withdrawals is comparable across groups (23/256 olaparib [9%], 17/130 [13%]). No information is reported on the characteristics of those who withdrew from the study.
The groups were comparable with respect to the availability of outcome data (that is, there were no important or systematic differences between groups in terms of those for whom outcome data were not available).	*NR*	Unclear Outcome data was available for the majority of patients (256/256 in Olaparib treatment group and 130/131 in control group). No outcomes reported for those who withdrew.
Overall rating attrition bias	NR	Unclear RoB No clear information on withdrawals and median follow up time differs between the Olaparib and NHA arms
Detection bias		
The study had an appropriate length of follow-up	*NR*	Unclear Overall follow up is not reported. De Bono et al (2020) report a difference in follow up for overall survival between Olaparib and control arms, "median duration of follow-up for overall survival was 12.6 months and 13.2 months respectively".[19]
The study used a precise definition of outcome	*NR*	Yes All outcomes and their definitions are reported in the Clinical trial registry.

A valid and reliable method was used to determine the outcome	*NR*	Yes Objective disease progression (as assessed by BICR was measured using RECIST version 1.1 [for soft tissue disease] or Prostate Cancer Working Group 3 [PCWG3, for bone disease]) or death.
Investigators were kept 'blind' to participants' exposure to the intervention	*Yes.* *Low RoB* Radiographic disease progression was assessed by blinded central review by an independent third-party vendor and the study sponsors were blinded to actual treatment arm until the randomisation codes were received.	Yes Outcome assessors were blinded. De Bono 2020 reports primary and secondary endpoints were "assessed by an independent review committee".[19]
Investigators were kept 'blind' to other important confounding and prognostic factors	*NR*	Yes Radiographic disease progression was assessed by blinded central review by an independent third-party vendor and the study sponsors were blinded to actual treatment arm until the randomisation codes were received.
Overall rating detection bias	*NR*	Low RoB
Questions listed on the company submission not from the preferred NICE checklist		
Is there any evidence to suggest that the authors measured more outcomes than they reported?	*No* *Low RoB* "Full documentation relating to the PROfound clinical trial methodology, analyses, and outcomes are included in the CSR, SAP and supporting references"	No All outcomes stated in the clinical trial registry section were reported in the publication[30]).

Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	*Yes* *Low RoB* All efficacy and HRQoL data (except for ORR, DoR and BoR) were analysed using the full analysis set (FAS), which included all patients who were randomised in both Cohorts as part of the global enrolment regardless of the treatment actually received. ORR, DoR and BoR were analysed using the Evaluable for response (EFR) analysis set (a subset of the FAS, of patients who had measurable disease at baseline as per the RECIST 1.1 criteria). Standard censoring methods were used to account for missing data. Analysis sets and outcome variables are listed in Table 13 in the CSP. Further details can be found in Section 8.4 and Section 11 of the PROfound CSP and CSR respectively.	Yes ITT - De Bono et al 2020 report efficacy data were analyzed on an intention-to-treat basis, and safety data were reported for all the patients who received at least one dose of a trial drug. [19] No Missing data in section 8.4 of the CSP outlines that missing data will not be imputed. The ERG does not think this was appropriate.
BoR, best objective response; CSP, Clinical Study Protocol; CSR, Clinical Study Report; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; EFR,evaluable for response; FAS, full analysis set; ORR, objective response rate; OS, overall survival; PSA, prostate-specific androgen; RECIST, Response Evaluation Criteria In Solid Tumours; rPFS, radiographic progression-free survival; SAP, statistical analysis plan; SAS, safety analysis setN/A = not applicable; RoB = risk of bias.		
NICE checklist item	***CS judgement and rationale***	**ERG judgement and rationale**
Selection bias		
Was randomisation carried out appropriately?	*Yes* *Low RoB* "A central interactive voice-response or Web response system was used to randomly assign patients in a 2:1 ratio"	Yes De Bono et al 2020 reports a central interactive response technology for randomly assigning patients. [19]
Was the concealment of treatment allocation adequate?	*NA* *Low RoB* "PROfound was an open-label study. Radiographic disease progression was assessed by blinded central review by an independent third-party vendor to mitigate against risk of investigator bias"	**No** **The study was open label meaning patients and investigators knew their allocated drug.**

Were the groups similar at the outset of the study in terms of prognostic factors?	*Yes* *Low RoB* "A blocked randomisation list was generated to ensure an approximate balance between the olaparib and enzalutamide or abiraterone acetate arms in Cohorts A and B (2:1). The randomisation was stratified by previous taxane use (yes, no) and whether subject had measurable disease (yes, no). Minor imbalances were noted for some baseline characteristics; however, as described in , a sensitivity analysis which adjusted for prior taxane, measurable disease, and other important prognostic factors that appeared imbalanced across the treatment arms (including PSA, metastatic disease at diagnosis, and ECOG status [all as covariates]) showed that the impact on the hazard ratios for rPFS and OS compared with the primary and secondary analyses was minimal. The study results were thus robust, and not impacted by minor differences in baseline characteristics across treatment arms.	Unclear De Bono et al 2020 report an imbalance at baseline between groups. [19] With the control group having a higher percentage of patients with visceral metastates and higher median baseline PSA concentration. The Olaparib group had a higher proportion of patients with ATM alteration (Table 1, De Bono et al 2020).[19]. The company have undertaken statistical analyses to account for these differences however the results are not presented within their submission.
Overall rating of selection bias	*NR*	Unclear RoB **Allocation was concealed until the point of enrolment but participants and investigators were aware of their treatment and there were notable differences at baseline between the treatment arms. The ERG cannot determine whether this was sufficiently accounted for within the analyses undertaken as these have not been presented.**
Performance bias		
The comparison groups received the same care apart from the intervention(s) studied	*NR*	Unclear A range of concomitant medications was allowed in the study. However, no information is reported about whether these were balanced between the intervention and control arms. In addition, the majority of patients switched over to the Olaparib arms (81% reported in De Bono 2020)[19]
Participants receiving care were kept 'blind' to treatment allocation	*No* *Low RoB* This was an open label trial; however, radiographic disease progression was assessed by blinded central review by an independent third-party vendor and the study sponsors were blinded to actual treatment arm until the randomisation codes were received (29 July 2019)"	No Participants were not blinded to treatment allocation as this was an open label trial.

Individuals administering care were kept 'blind' to treatment allocation	*No* *Low RoB* This was an open label trial; however, radiographic disease progression was assessed by blinded central review by an independent third-party vendor and the study sponsors were blinded to actual treatment arm until the randomisation codes were received (29 July 2019)"	No This was an open-label trial. According to De Bono "The primary end point was imaging-based progression-free survival in cohort A" [19]. No information is provided in relation to blinding for all other outcomes.
Overall rating of performance bias	*NR*	High RoB Participants were aware of their assignment, this may have influenced self-reports of symptoms and the majority of patients received olaparib Assessors appears to have been aware of treatment allocation for all outcomes except radiographic disease progression.
Attrition bias		
All groups were followed up for an equal length of time (or analysis was adjusted to allow for differences in length of follow-up)	*NR*	No De Bono et al (2020) report a difference in follow up for overall survival between Olaparib and control arms, "median duration of follow-up for overall survival was 12.6 months and 13.2 months respectively". [19]
The groups were comparable for treatment completion (that is, there were no important or systematic differences between groups in terms of those who did not complete treatment)	*No* *Low RoB* "Select minor imbalances were observed (see Section B.2.3.7), but were confirmed by multivariate modelling to have only minimal impact on the rPFS and OS hazard ratios"	Unclear Number of withdrawals is comparable across groups (23/256 olaparib [9%], 17/130 [13%]). No information is reported on the characteristics of those who withdrew from the study.

The groups were comparable with respect to the availability of outcome data (that is, there were no important or systematic differences between groups in terms of those for whom outcome data were not available).	*NR*	Unclear Outcome data was available for the majority of patients (256/256 in Olaparib treatment group and 130/131 in control group). No outcomes reported for those who withdrew.
Overall rating attrition bias	NR	High RoB No clear information on withdrawals and median follow up time differs between the Olaparib and NHA arms
Detection bias		
The study had an appropriate length of follow-up	*NR*	Unclear Overall follow up is not reported. De Bono et al (2020) report a difference in follow up for overall survival between Olaparib and control arms, "median duration of follow-up for overall survival was 12.6 months and 13.2 months respectively".[19]
The study used a precise definition of outcome	*NR*	Yes All outcomes and their definitions are reported in the Clinical Study Report, version 1, 23 October 2019 (Table 2, page 51)
A valid and reliable method was used to determine the outcome	*NR*	Yes Objective disease progression (as assessed by BICR was measured using RECIST version 1.1 [for soft tissue disease] or Prostate Cancer Working Group 3 [PCWG3, for bone disease]) or death.

Investigators were kept 'blind' to participants' exposure to the intervention	*Yes.* *Low RoB* Radiographic disease progression was assessed by blinded central review by an independent third-party vendor and the study sponsors were blinded to actual treatment arm until the randomisation codes were received.	Yes Outcome assessors were blinded. De Bono 2020 reports primary and secondary endpoints were "assessed by an independent review committee".[19]
Investigators were kept 'blind' to other important confounding and prognostic factors	*NR*	Yes Radiographic disease progression was assessed by blinded central review by an independent third-party vendor and the study sponsors were blinded to actual treatment arm until the randomisation codes were received.
Overall rating detection bias	*NR*	Low RoB
Questions listed on the company submission not from the preferred NICE checklist		
Is there any evidence to suggest that the authors measured more outcomes than they reported?	*No* *Low RoB* "Full documentation relating to the PROfound clinical trial methodology, analyses, and outcomes are included in the CSR, SAP and supporting references"	No All outcomes stated in the clinical trial registry section were reported in the publication[30]).
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	*Yes* *Low RoB* All efficacy and HRQoL data (except for ORR, DoR and BoR) were analysed using the full analysis set (FAS), which included all patients who were randomised in both Cohorts as part of the global enrolment regardless of the treatment actually received. ORR, DoR and BoR were analysed using the Evaluable for response (EFR) analysis set (a subset of the FAS, of patients who had measurable disease at baseline as per the RECIST 1.1 criteria). Standard censoring methods were used to account for missing data. Analysis sets and outcome variables are listed in Table 13 in the CSP. Further details can be found in Section 8.4 and Section 11 of the PROfound CSP and CSR respectively.	Yes ITT - De Bono et al 2020 report efficacy data were analyzed on an intention-to-treat basis, and safety data were reported for all the patients who received at least one dose of a trial drug. [19] No Missing data in section 8.4 of the CSP outlines that missing data will not be imputed. The ERG does not think this was appropriate.
BoR, best objective response; CSP, Clinical Study Protocol; CSR, Clinical Study Report; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; EFR,evaluable for response; FAS, full analysis set; ORR, objective response rate; OS, overall survival; PSA, prostate-specific androgen; RECIST, Response Evaluation Criteria In Solid Tumours; rPFS, radiographic progression-free survival; SAP, statistical analysis plan; SAS, safety analysis setN/A = not applicable; RoB = risk of bias.		

The CARD trial was assessed (CS appendices, section D.3, page 42) across the domains of randomisation, blinding (participants, study personnel, and outcome assessors), similarity of groups at baseline and sample attrition/incomplete outcome data (Intention To Treat [ITT] analysis, sensitivity analysis).[28] The CS assessed all domains of the CARD trial as low risk of bias, except for allocation concealment for which the risk of bias was reported as not known. The ERG partially agrees with the company's assessment, however assessed performance bias and detection bias at high risk due to the lack of blinding.

Table 12: ERG assessment of CARD trial quality

NICE checklist item	*CS judgement and rationale*	ERG judgement and rationale
Selection bias		
Was randomisation carried out appropriately?	*Yes* *Low RoB* A central interactive voice-response or Web response system was used to randomly assign patients in a 1:1 ratio Randomisation was stratified by: ECOG performance status (0–1 vs 2), time from AR-targeted agent initiation to progression ([0; 6 months] vs [6; 12 months]),[a] timing of AR-targeted agent (before vs after docetaxel).	Yes De Wit 2019 paper and protocol report patients were randomly assigned to either arm A or B in a 1:1 proportion by using an Interactive Voice/Web Response System (IVRS/IWRS). [28]
Was the concealment of treatment allocation adequate?	*NA* Not applicable. The trial was open label. No blinded central review was performed; however, all the images (MRI, CT scan and bone scan) were archived centrally by the vendor in case of discrepancies	No The study was open label meaning patients and investigators knew their allocated drug. There was no treatment concealment
Were the groups similar at the outset of the study in terms of prognostic factors?	*Yes* *Low RoB* Patients were stratified at randomisation based on ECOG performance-status score (0 or 1 vs 2), time to disease progression (≤ 6 months vs >6–12 months), and timing of the previous alternative androgen-signaling–targeted inhibitor (before vs after docetaxel). Baseline characteristics appeared balanced overall between the cabazitaxel group and the androgen signaling-targeted inhibitor group (Table 1 and Supplementary table 1)	Yes Baselines characteristics were presented and appear balanced.[28]
Overall rating of selection bias	*NR*	Low RoB Although investigators and patients knew their drug choice, there was random allocation and the baseline characteristics appear balanced.
Performance bias		

The comparison groups received the same care apart from the intervention(s) studied	*NR*	Unclear A range of concomitant medications was allowed in the study. However, no information is reported about whether these were balanced between the intervention and control arms.
Participants receiving care were kept 'blind' to treatment allocation	*No* *Low RoB* This was an open label trial. No blinded central review was done; however, all the images (MRI, CT scan and bone scan) were archived centrally by the vendor in case of discrepancies. Details are available in the CARD Clinical Trial Protocol section 8.4.	**No** **Participants were not blinded to treatment allocation as this was an open label trial.**
Individuals administering care were kept 'blind' to treatment allocation	*No* *Low RoB* This was an open label trial. No blinded central review was done; however, all the images (MRI, CT scan and bone scan) were archived centrally by the vendor in case of discrepancies. Details are available in the CARD Clinical Trial Protocol section 8.4.	No Investigators and assessors were not blinded to treatment allocation.
Overall rating of performance bias	*NR*	High RoB High risk of bias because of the lack of blinding.
Attrition bias		
All groups were followed up for an equal length of time (or analysis was adjusted to allow for differences in length of follow-up)	*NR*	No De Wit et al (2019) study protocol states "Each patient will be treated until radiographic disease progression, unacceptable toxicity, or patient's refusal of further study treatment".[28]

The groups were comparable for treatment completion (that is, there were no important or systematic differences between groups in terms of those who did not complete treatment)	*NR* *Low RoB* No. There were no unexpected imbalances in dropouts between groups: Only 2 patients in the cabazitaxel group were lost to follow-up 12 patients (9.5%) in the cabazitaxel group and 4 patients (3.2%) in the androgen signalling targeted inhibitor group withdrew consent The principal reasons for the discontinuation of treatment with cabazitaxel or the androgen-signaling–targeted inhibitor were disease progression (in 43.7% and 71.0% of the patients, respectively) or an adverse event (in 19.8% and 8.9%) Further details are available in supplementary table 3	Yes There were similar rates of drop outs between the two groups and reasons for drop out were reported.
The groups were comparable with respect to the availability of outcome data (that is, there were no important or systematic differences between groups in terms of those for whom outcome data were not available).	*NR*	Unclear Outcome data available for the majority of patients (126/129 in treatment arm and 124/126 in control group). No outcomes reported for those who withdrew.
Overall rating attrition bias	*NR*	Unclear RoB
Detection bias		
The study had an appropriate length of follow-up	*NR*	Yes The study was event driven and ended after 197 disease progression events have occurred. De Wit et al (2019) report median follow up to be 9.2 months. However in the additional appendices the treatment arms reported a median length of treatment of 22.0 (3.0–88.0) weeks for cabazitaxel compared 12.5 (2.0–141.0) for controls (NHA alone).[28].
The study used a precise definition of outcome	*NR*	Yes Outcomes are defined in the study protocol. [28]

A valid and reliable method was used to determine the outcome	*NR*	Unclear Outcome measurement methods are reported in the study protocol. [28] All other outcomes use valid guidelines.
Investigators were kept 'blind' to participants' exposure to the intervention	*No* *Low RoB* This was an open label trial. No blinded central review was done; however, all the images (MRI, CT scan and bone scan) were archived centrally by the vendor in case of discrepancies	No There was no blinding.
Investigators were kept 'blind' to other important confounding and prognostic factors	*No* *Low RoB* This was an open label trial. No blinded central review was done; however, all the images (MRI, CT scan and bone scan) were archived centrally by the vendor in case of discrepancies	No There was no blinding.
Overall rating detection bias	*NR*	Unclear The ERG disagree and feel there is a high risk of bias due to the lack of blinding.
Questions listed on the company submission not from the preferred NICE checklist		
Is there any evidence to suggest that the authors measured more outcomes than they reported?	*No* *Low RoB* Documentation relating to the CARD clinical trial methodology, analyses, and outcomes are included in the Clinical Trial Protocol and supporting references	No "Health-related quality of life, biomarker analyses, and additional efficacy outcomes were assessed but are not reported here". reported in the paper by De Wit et al (2019) [28]

Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	*Yes* *Low RoB* The primary efficacy population is the Intent-To-Treat (ITT) population which includes all randomised patients. The health-related quality of life population is composed of patients who received at least one dose of the study drug and with an evaluable FACT-P questionnaire at baseline and at least one post baseline evaluable FACT-P. The health status population is composed of patients who received at least one dose of the study drug and with an evaluable EQ-5D-5L at baseline and with at least one post-baseline evaluableEQ-5D-5L. The safety population includes all patients who received at least one dose of the study drug. Standard censoring methods were used to account for missing data. Outcome variables are listed in section 5 of the Clinical Trial Protocol.	Yes De Wit et al (2019) undertook an ITT analysis including all randomised patients.[28]
BoR, best objective response; CSP, Clinical Study Protocol; CSR, Clinical Study Report; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; EFR,evaluable for response; FAS, full analysis set; ORR, objective response rate; OS, overall survival; PSA, prostate-specific androgen; RECIST, Response Evaluation Criteria In Solid Tumours; rPFS, radiographic progression-free survival; SAP, statistical analysis plan; SAS, safety analysis setN/A = not applicable; RoB = risk of bias.		
NICE checklist item	***CS judgement and rationale***	**ERG judgement and rationale**
Selection bias		
Was randomisation carried out appropriately?	*Yes* *Low RoB* A central interactive voice-response or Web response system was used to randomly assign patients in a 1:1 ratio Randomisation was stratified by: ECOG performance status (0–1 vs 2), time from AR-targeted agent initiation to progression ([0; 6 months] vs [6; 12 months]),[a] timing of AR-targeted agent (before vs after docetaxel).	Yes De Wit 2019 paper and protocol report patients were randomly assigned to either arm A or B in a 1:1 proportion by using an Interactive Voice/Web Response System (IVRS/IWRS). [28]
Was the concealment of treatment allocation adequate?	*NA* Not applicable. The trial was open label. No blinded central review was performed; however, all the images (MRI, CT scan and bone scan) were archived centrally by the vendor in case of discrepancies	No The study was open label meaning patients and investigators knew their allocated drug. There was no treatment concealment

Were the groups similar at the outset of the study in terms of prognostic factors?	*Yes* *Low RoB* Patients were stratified at randomisation based on ECOG performance-status score (0 or 1 vs 2), time to disease progression (≤ 6 months vs >6–12 months), and timing of the previous alternative androgen-signaling–targeted inhibitor (before vs after docetaxel). Baseline characteristics appeared balanced overall between the cabazitaxel group and the androgen signaling-targeted inhibitor group (Table 1 and Supplementary table 1)	Yes Baselines characteristics were presented and appear balanced.[28]
Overall rating of selection bias	*NR*	Low RoB Although investigators and patients knew their drug choice, there was random allocation and the baseline characteristics appear balanced.
Performance bias		
The comparison groups received the same care apart from the intervention(s) studied	*NR*	Unclear A range of concomitant medications was allowed in the study. However, no information is reported about whether these were balanced between the intervention and control arms.
Participants receiving care were kept 'blind' to treatment allocation	*No* *Low RoB* This was an open label trial. No blinded central review was done; however, all the images (MRI, CT scan and bone scan) were archived centrally by the vendor in case of discrepancies. Details are available in the CARD Clinical Trial Protocol section 8.4.	No Participants were not blinded to treatment allocation as this was an open label trial.
Individuals administering care were kept 'blind' to treatment allocation	*No* *Low RoB* This was an open label trial. No blinded central review was done; however, all the images (MRI, CT scan and bone scan) were archived centrally by the vendor in case of discrepancies. Details are available in the CARD Clinical Trial Protocol section 8.4.	No Investigators and assessors were not blinded to treatment allocation.
Overall rating of performance bias	*NR*	High RoB High risk of bias because of the lack of blinding.
Attrition bias		

All groups were followed up for an equal length of time (or analysis was adjusted to allow for differences in length of follow-up)	*NR*	No De Wit et al (2019) study protocol states "Each patient will be treated until radiographic disease progression, unacceptable toxicity, or patient's refusal of further study treatment".[28]
The groups were comparable for treatment completion (that is, there were no important or systematic differences between groups in terms of those who did not complete treatment)	*NR* *Low RoB* No. There were no unexpected imbalances in dropouts between groups: Only 2 patients in the cabazitaxel group were lost to follow-up 12 patients (9.5%) in the cabazitaxel group and 4 patients (3.2%) in the androgen signalling targeted inhibitor group withdrew consent The principal reasons for the discontinuation of treatment with cabazitaxel or the androgen-signaling–targeted inhibitor were disease progression (in 43.7% and 71.0% of the patients, respectively) or an adverse event (in 19.8% and 8.9%) Further details are available in supplementary table 3	Yes There were similar rates of drop outs between the two groups and reasons for drop out were reported.
The groups were comparable with respect to the availability of outcome data (that is, there were no important or systematic differences between groups in terms of those for whom outcome data were not available).	*NR*	Unclear Outcome data available for the majority of patients (126/129 in treatment arm and 124/126 in control group). No outcomes reported for those who withdrew.
Overall rating attrition bias	*NR*	Unclear RoB
Detection bias		
The study had an appropriate length of follow-up	*NR*	Yes The study was event driven and ended after 197 disease progression events have occurred. De Wit et al (2019) report median follow up to be 9.2 months. However in the additional appendices the treatment arms reported a median length of treatment of 22.0 (3.0–88.0) weeks for cabazitaxel compared 12.5 (2.0–141.0) for controls (NHA alone).[28].

The study used a precise definition of outcome	*NR*	Yes Outcomes are defined in the study protocol. [28]
A valid and reliable method was used to determine the outcome	*NR*	Unclear Outcome measurement methods are reported in the study protocol. [28] Non-radiographic measures have not been defined. All other outcomes use valid guidelines.
Investigators were kept 'blind' to participants' exposure to the intervention	*No* *Low RoB* This was an open label trial. No blinded central review was done; however, all the images (MRI, CT scan and bone scan) were archived centrally by the vendor in case of discrepancies	No There was no blinding.
Investigators were kept 'blind' to other important confounding and prognostic factors	*No* *Low RoB* This was an open label trial. No blinded central review was done; however, all the images (MRI, CT scan and bone scan) were archived centrally by the vendor in case of discrepancies	No There was no blinding.
Overall rating detection bias	*NR*	High The ERG disagree and feel there is a high risk of bias due to the lack of blinding.
Questions listed on the company submission not from the preferred NICE checklist		
Is there any evidence to suggest that the authors measured more outcomes than they reported?	*No* *Low RoB* Documentation relating to the CARD clinical trial methodology, analyses, and outcomes are included in the Clinical Trial Protocol and supporting references	No “Health-related quality of life, biomarker analyses, and additional efficacy outcomes were assessed but are not reported here”. reported in the paper by De Wit et al (2019) [28]

Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	*Yes* *Low RoB* The primary efficacy population is the Intent-To-Treat (ITT) population which includes all randomised patients. The health-related quality of life population is composed of patients who received at least one dose of the study drug and with an evaluable FACT-P questionnaire at baseline and at least one post baseline evaluable FACT-P. The health status population is composed of patients who received at least one dose of the study drug and with an evaluable EQ-5D-5L at baseline and with at least one post-baseline evaluableEQ-5D-5L. The safety population includes all patients who received at least one dose of the study drug. Standard censoring methods were used to account for missing data. Outcome variables are listed in section 5 of the Clinical Trial Protocol.	Yes De Wit et al (2019) undertook an ITT analysis including all randomised patients.[28]
BoR, best objective response; CSP, Clinical Study Protocol; CSR, Clinical Study Report; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; EFR,evaluable for response; FAS, full analysis set; ORR, objective response rate; OS, overall survival; PSA, prostate-specific androgen; RECIST, Response Evaluation Criteria In Solid Tumours; rPFS, radiographic progression-free survival; SAP, statistical analysis plan; SAS, safety analysis setN/A = not applicable; RoB = risk of bias.		

- *Evidence synthesis*

In the CS SLR review of clinical effectiveness, the number of publications meeting the review inclusion criteria is initially reported to be 23 (Document B, B.2.1). However, detailed information is presented in graphical, narrative, and tabular form for only two open-label RCTs: one comparing olaparib to abiraterone or enzalutamide (PROfound), [19] and one comparing cabazitaxel to abiraterone or enzalutamide (CARD).[28] As only a single RCT examining olaparib was included, direct treatment comparisons were not applicable. An indirect comparison of PROfound and CARD was provided in the CS. The ERG's critique of this is given in section 3.3.

3.2 Critique of trials of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)

Evidence for the clinical effectiveness of olaparib was presented from a single RCT (PROfound). [19] No further relevant trials were identified by the company and ERG.

Study objectives

The objectives of the study are reported in the CSR (section 8, Table 2, page 51) as follows:

> The primary objective of the PROfound trial was to compare olaparib and enzalutamide/abirateron in terms of radiographic progression-free survival (rPFS) in people with metastatic Castration-Resistant Prostate Cancer and deleterious or suspected deleterious mutations in ATM, BRCA1, and BRCA2 genes.
>
> Secondary objectives included the following: overall response rate, pain (time to progression, interference, severity, change in pain, and duration), overall survival, quality of life (Cohort A - ATM, BRCA1, or BRCA2 gene mutations); rPFS, overall response rate, pain progression, overall survival (Cohort B - BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D or RAD54L gene mutations); rPFS, overall response rate, pain (time to progression, interference, severity, overall survival, change in pain and duration), health-related quality of life (Cohorts A+B).
>
> Exploratory objectives included the following: patient-reported treatment tolerability and overall health status (Cohort unspecified), rPFS in people who had previously received taxane therapy (cohort A), rPFS in people with qualifying tumour gene mutations detected

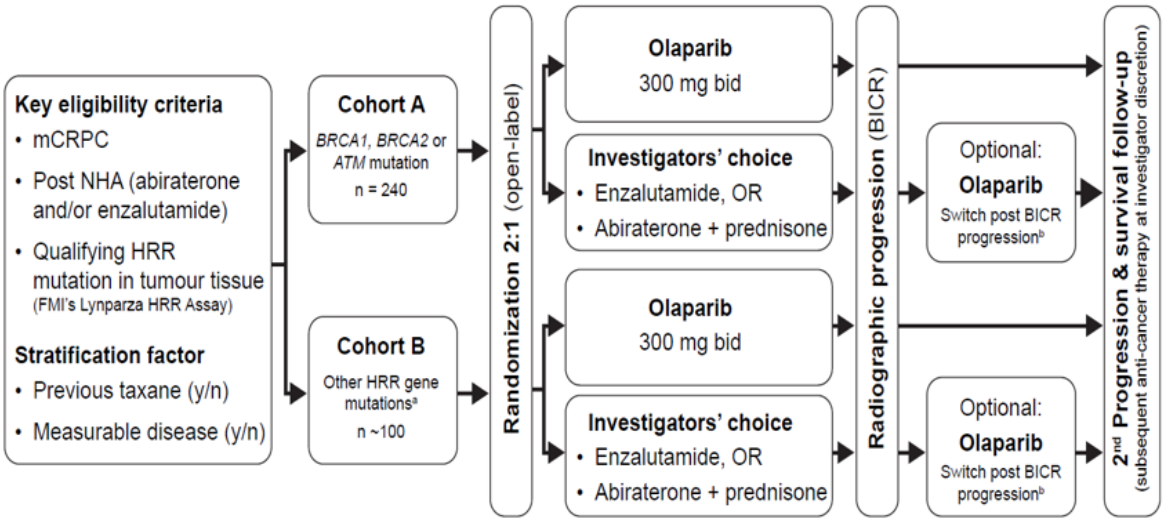
by ctDNA analysis (cohort A, cohort A+B).

The objectives of the CS differ somewhat from the PROfound trial in that the focus of the CS is the "target population," (people with mCRPC and deleterious or suspected deleterious mutations in HRR genes who have previously had taxane chemotherapy). This represents a different population to the one detailed in the NICE scope.

Study design and treatment

PROfound (NCT02987543) was an international, multi-centre, randomised, open-label phase, phase 3 trial, supported by AstraZeneca and Merck Sharp & Dohme (a subsidiary of Merck). The trial is described in the CS (Doc B, B.2.1, page 29) and CSR. The overall trial design is shown in Figure 1.

Figure 1. PROfound trial design



[a] Cohort B HRR pathway genes include *BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D* and *RAD54L*.
[b] Treatment switching was permitted post BICR-assessed radiographic disease progression and adjusted for using naïve and sophisticated adjustment methods (see section B.2.6.3.1).

Source: CS (Doc B, Figure 1, page 310)

Olaparib is anticipated to be licensed [redacted].

The trial included two cohorts**:**

Cohort A: comprising men with mutations to 3 HRR genes (ATM, BRCA1, BRCA2), and

Cohort B: comprising men with mutations to 12 other HRR genes (BARD1, BRIP1,

CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D, RAD54L). The CS states that the 15 genes were "selected for their direct or indirect role in HRR" (Doc B, B.2.3.6, page 36). No evidence is provided in the CS to support this statement or justify the exclusion of other genes in the HRR pathway.

The trial was conducted in two parts:

- Part 1, study participants received either (1) 300mg olaparib tablets twice daily, or (2) the physician's choice of abiraterone (1000mg once daily) with prednisone (5mg twice daily) or enzalutamide (160mg once daily). Concomitant medications were allowed in both trial arms, in accordance with the study protocol (CSR, section 9.4.4). Few instances in disallowed medications were reported for cohorts A and B (CSR, Tables 14 and 15). Participants were assessed every 4 weeks for 24 weeks, then every 8 weeks until blinded independent central review-assessed radiographic disease progression, at which point treatment with olaparib was stopped. Participants no longer on study treatments (either due to disease progression or withdrawal) were then followed up for 30 days (for safety assessment), every 8 weeks (for assessment of BICR radiographic disease progression for participants who withdrew only), and every 12 weeks for second disease progression and survival).
- Part 2 (treatment switching), participants in the abiraterone/enzalutamide arm were invited to switch to olaparib following (1) blinded independent central review-assessed radiographic disease progression, or (2) discontinuation of abiraterone/enzalutamide. The assessment schedule for this group then followed the olaparib group (see Part 1). The company's submission focusses on part 1.

The trial was relevant to the company's decision problem in terms of population, intervention, comparator, and outcomes, but differed from the NICE scope in relation to

(1) the population, as the majority of participants in the PROfound trial had received prior taxane therapy, and

(2) the comparators, as treatment with docetaxel was moved from being a comparator to being one of the defining characteristics of the population of interest. A detailed comparison to the NICE decision problem is provided in section 2.3 of the ERG report.

Comparator

In the PROfound trial, olaparib efficacy and safety was compared to 'investigator's choice of NHA' on the basis that "*re-treatment with NHA (i.e. enzalutamide after progression of abiraterone, and vice versa) are approved treatment options in this setting (by both the EMA [31, 32] and the US FDA [33, 34]) and is a standard-of-care in many countries where the PROfound study was conducted." (*CS Doc B, page 14). **The ERG does not agree that (1) physician's choice of NHA limited only to abiraterone or enzalutamide is an appropriate comparator nor that (2) retreatment with NHA represents standard of care**.

Abiraterone and enzalutamide

In the PROfound trial, all study participants had disease progression following treatment with abiraterone, enzalutamide, or both abiraterone and enzalutamide (see Table 13). This presents two key issues. First, neither the published trial nor the CS state whether participants in the control arm were being re-treated with a drug on which they had already failed. As [redacted] of the control arm participants had previously failed on both abiraterone and enzalutamide, a minimum of [redacted] of the control group received a drug for which there can be no expectation of a benefit. The maximum number of participants who were being re-treated cannot be established from the data presented in the CS/published trial. Second, data on treatment of mCRPC with abiraterone followed by enzalutamide (and vice versa) has suggested that the majority of participants do not benefit from subsequent NHA treatment.[35-39]The ERG could not find any reference to re-treatment with NHA in the EMA references provided by the company.

Table 13. Breakdown of prior NHA use

Previous NHA use	Cohorts A+B Full analysis set		Cohorts A+B prior taxane use	
	Olaparib	Physician's choice of NHA	Olaparib	Physican's choice of NHA
Enzaluatamide	103 (40.2%)	54 (41.2%)	[redacted]	[redacted]
Abiraterone	97 (37.9%)	54 (41.2%)	[redacted]	[redacted]
Abiraterone and enzalutamide	51 (19.9%)	23 (17.6%)	[redacted]	[redacted]

Instead of retreatment with a drug that has previously failed, there is a range of other treatment options which are more likely to be used in clinical practice, e.g. cabazitaxel, mitoxantrone, paclitaxel that could have been used as comparators. . Data from Table 5 (CS Doc B, page 40, reproduced in Table below) indicated that only between 20-23% of participants in the PROfound trial had previously received cabazitaxel and very few (less than 1% had received paclitaxel. These are two treatments would therefore be more likely to reflect physicians' choices for treatment in real-world settings.

Previous taxane use	Cohorts A+B FAS		Cohorts A+B prior taxane use	
	Olaparib	Physician's choice of NHA	Olaparib	Physican's choice of NHA
Cabazitaxel	54 (21.1%)	26 (19.9%)	[redacted]	[redacted]
Paclitaxel	1 (0.4%)	0 (0%)	[redacted]	[redacted]

Locations

Participants were enrolled from 206 study centres in 20 countries. Five sites were in the UK, from which only 4 participants were recruited (Doc B, B.2.3.3, page 33). The CS does not state if any of the 4 participants were included in their subgroup analyses. **The ERG note that because of the very small and highly selected numbers of patients recruited in the UK the generalisability of the findings from the PROfound study to the UK setting may be compromised.** The RG also note that the number of centres that were reported to provide data for PROfound varied from 111 (Doc B, B.2.3.3, page 33) to 139 (CSR, page 121). The number in Doc B appears to refer to Cohort A only. Further, countries in which recruitment was conducted are listed as in Asia, Australia, Europe, North America, and South America in the CSR (page 2) but Australia was omitted in the de Bono publication (figure 2, page 8) and clarification response (v0.1 02.07.20, Table 3, page 9). Overall, the conduct of the trial was fairly described in the CS.

Selection of participants

The CS reported the key eligibility criteria for the PROfound trial in Table 4 (Doc B, pages 31 – 32). Key inclusion criteria were: (1) men (≥ 18 years) with prostate cancer (histologically confirmed) that had metastasised (diagnosed by bone scan or CT/MRI scan) and was castration-resistant (serum testosterone levels of ≤ 50 ng/dL), (2) an ECOG grade of 0–2 (indicating no restrictions to daily living skills to capable of all self-case but unable to carry out work activities), (3) normal organ and bone marrow function measured ≤ 28 days before study treatment, (4) life expectancy ≥ 16 weeks, (5) qualifying HRR gene mutation in tumour tissue, and (6) radiographic disease following treatment with abiraterone and/or enzalutamide. Key exclusion criteria were: (1) prior treatment with PARP inhibitors, recent systematic anti-cancer therapy (excluding radiotherapy) or DNA-damaging cytotoxic, (2) metastatic disease limited to regional pelvic lymph nodes of local recurrence (e.g. bladder, rectum), or unstable spinal cord compression, (3) acute myeloid leukaemia, myelodysplastic syndrome, or other malignancies not curatively treated, and (4) uncontrolled cardiac conditions or long QT syndrome. Numerous other inclusion and exclusion criteria were reported in the study protocol. Overall, the inclusion/exclusion criteria map onto those in the NICE scope.

In its submission, the company defined qualifying HRR gene mutation in tumour tissue as 'deleterious or suspected deleterious alterations in at least 1 of the 15 pre-specified genes, selected for their direct or indirect role in HRR, namely: BRCA1, BRCA2, ATM, BRIP1, BARD1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D, and RAD54L' (Document B, B.2.3.6, page 36). No definition of 'deleterious or suspected deleterious' are provided in the CS. In response to clarification question A1 (definition of suspected deleterious mutation, and breakdown of the numbers of people with deleterious/suspected deleterious mutations), the CS did not provided a definition of suspected deleterious and stated that "All randomised patients in PROfound were categorised as having deleterious HRRm mutations".

Randomisation

Randomisation was conducted using a central interactive voice response or web-response system, with participants randomised in a 2:1 ratio (olaparib:control). Randomisation was

stratified on the basis of prior use of taxane chemotherapy (yes/no) and presence of measureable disease at baseline (yes/no), according to the Response Evaluation Criteria in Solid Tumors, version 1 (yes/no). It is unclear how stratified randomisation was performed. Participants are reported to have been enrolled from 6th February 2017 – 18th September 2018 (CSR, page 1).

In addition, the ERG notes that it is typical in multicentre trials to stratify randomisation by centre, to control for between-centre differences in participants demographics, and environmental, social, and disease management factors. This was not conducted in the PROfound trial.

Blinding

PROfound was reported as an open-label trial, but with assessment of the primary outcome (radiographic progression-free survival) conducted by blinded independent central review (BICR) of all scans. The rationale for conducting an open-label study was 'At the time of study design, it was believed that the differences in administration and safety profiles would enable investigators to differentiate between the different study treatments." The ERG disagrees with this statement as a justification for lack of blinding. Blinding can take place at various levels of a study: participants, clinicians, data collectors, outcome assessors, and data analysts. With the possible exception of clinicians, blinding could have been conducted at every level of the trial. For example, a double dummy design could have been employed to blind participants. The use of independent data collectors, outcome assessors, and data analysts who are not otherwise employed in the trial is also possible. **The ERG considers the overall lack of blinding in the trial to be suboptimal, with the potential to introduce bias, particularly in relation to self-reported outcomes such as adverse events, pain, and quality of life.**

Population "target group"

The target patients chosen by the company for olaparib treatment carry a HRRm defect and have previously been treated with docetaxel (the " HRRm [Cohort A+B] – Prior taxane " population). Evidence for olaparib effectiveness in this subgroup comes from the PROfound study in which docetaxel pre-treatment was a stratification factor at randomisation. The CS target population differs from that in the NICE scope which does not specify docetaxel pre-treatment. The CS states that their target "aligns" with the treatment pathway recommended

by NICE (NG131, May 2019) and as practised for the majority of mHRPC patients in England according to opinion of six questioned specialists.

The choice of a "prior taxane" population is based on poorer PFS performance in no-prior taxane patients relative to prior taxane patients seen especially in BRCA2 positive populations and to lesser extent in other HHRm positive populations[27, 40]. Relative to the full A+B population the CS choice of prior taxane usage reduces the size of the olaparib-eligible population but tends to increase the effectiveness of olaparib in PFS (Table 14).

Table 14. PFS HR (olaparib vs. NHA) according to cohort and prior or no-prior taxane use

PFS	Cohort A	Cohort A+B	Cohort prior taxane A+B	
	Figure 2 in de Bono		CS pg 72	pg 87
Hazard ratio (olaparib vs. NHA) by subgroup	0.34 (0.25–0.47)	0.49 (0.38–0.63)	0.39 (0.29–0.53)	[redacted]
prior taxane yes	0.28 (0.19–0.41)	0.39 (0.29–0.53)	0.39(0.29–0.53)	[redacted]
prior taxane no	0.55 0.55 (0.32–0.97)	0.77 (0.50–1.22)	NA	NA

In contrast, subgroup analyses conducted in PROfound [19] indicate a relatively poor response to olaparib in cohort B patients and strong response in cohort A patients, so that the choice of patients from both A and B cohorts for the target population would be expected to increase the size of the olaparib-eligible population but decrease the effectiveness of olaparib.

Since available evidence suggests that olaparib effectiveness is greatest in patients carrying BRCA2 and CDK12 mutations and relatively marginal in carriers of other HRR mutations [19] [41], the use of olaparib in a "BRCA2 / CDK12" target population would be expected to be more cost effective than its use in the CS selected population. The CS target population appears to include a substantial proportion of patients (Cohort B) who would be expected to experience relatively marginal benefit. Screening would be simplified for a BRCA2/CDK12 population. Further research seems necessary to determine if carriers of other HRR mutations benefit from olaparib.

Overall survival data (summarised in Table 15, CS pg 62, 75 and CS Table 10 Weibull RPSFTm without censoring) shows that median survival with olaparib is less in the "target population" than in the whole A+B cohort, but that relative to the NHA arm, the target population outperforms both cohorts A and A+B in "gain" in both median OS and in HR. This difference mainly results from notably poor survival in the target population NHA arm after RPSFT adjustment for cross over.

Table 15. Overall survival according to subgroup and prior taxane use *(months)*

	Cohort A	Cohort A+B	Cohort prior taxane A+B
Median RPSFTM adjusted NHA arm	[redacted]	[redacted]	[redacted]
Median olaparib arm	[redacted]	[redacted]	[redacted]
difference in medians ("gain")	[redacted]	[redacted]	[redacted]
Hazard ratio	[redacted]	[redacted]	[redacted]

In both trial arms the proportion of deaths reported in the CS target population is greater than that in the full A+B population, indicating that the full A+B population rather than prior taxane A+B population might represent a superior target for olaparib (Table 16, CS Figures 6,7,13, CS Table 9). A lack of prior taxane use appears to modify response to NHA to a greater extent than to olaparib.

Table 16. Number of deaths according to cohort and prior taxane use

	olaparib arm				NHA arm unadjusted for cross over			
Cohort	N	n deaths	% deaths	Median survival	N	n deaths	% deaths	Median survival
Prior taxane A + B	170	[redacted]	[redacted]	[redacted]	84	[redacted]	[redacted]	[redacted]
All A + B	256	[redacted]	[redacted]	[redacted]	131	[redacted]	[redacted]	[redacted]
A	162	[redacted]	[redacted]	[redacted]	83	[redacted]	[redacted]	[redacted]
B*	94	[redacted]	[redacted]	[redacted]	48	[redacted]	[redacted]	[redacted]
* deaths calculated by difference A+B - A								

Non-prior taxane A+B population

The CS requests "*that consideration is given to the small group of patients who have not received a taxane prior to NHA under equality provisions*". The no prior-taxane treatment population represents about 42% of those recruited in PROfound (CS Table 5); effectiveness and economic analyses in the CS are based on the comparison of olaparib versus cabazitaxel using data from PROfound and CARD trials in each of which all patients received prior taxane (docetaxel). No analysis of olaparib versus cabazitaxel was undertaken in the CS for a

no-prior taxane subgroup; in PROfound olaparib performs far less well in PFS in the "no-prior" than in the "prior" population and therefore **the ERG considers that the economic analyses submitted are not appropriate for decisions about the no-prior taxane population.**

Non-RCT

The CS does not include any non-RCTs.

Ongoing studies

The CS states that there are no ongoing studies relevant to the decision problem for the appraisal of olaparib in previously treated hormone-relapsed mCRPC. The ERG did not identify any further studies.

Description and critique of the company's outcome selection

The NICE scope lists the specified outcomes as:

- Progression-free survival (PFS)
- Time to pain progression (TPP)
- Skeletal related events (SRE)
- Overall survival (OS)
- Adverse effects (AE) of treatment
- Health-related quality of life (HRQoL)

In PROfound, radiographic PFS (rPFS) as assessed by blinded independent central review (BICR-assessed rPFS) was the primary endpoint and defined as time from randomisation until the date of objective disease progression or death, regardless of whether the patient withdrew from randomised therapy or received another anti-cancer therapy prior to disease progression.

The BICR-assessed rPFS used RECIST version 1.1 (for soft tissue disease) or Prostate Cancer Working Group 3 (PCWG3, for bone disease) or death, thus minimizing the risk of investigator bias from an open-label trial.

The company also included PFS2, an intermediary endpoint between PFS and OS, which was defined as time from randomisation to the earliest investigator-assessed progression event subsequent to that used for rPFS or death; this was included as a secondary outcome.

OS was defined as the time from randomisation to death from any cause regardless of whether the patient withdrew from allocated therapy or received another anti-cancer therapy prior to disease progression.

TTD was defined as time from randomisation to the time point at which worsening in pain was observed as assessed by BPI-SF item 3. This was assessed according to whether patients were symptomatic at baseline.

Time to first symptomatic SRE was defined by the use of radiation therapy to prevent or relieve symptoms, occurrence of new radiologically confirmed symptomatic pathological bone fractures (vertebral or non-vertebral) or spinal compression, or surgical intervention for bone metastasis.

To measure HRQoL, the patient-reported FACT-P was administered at baseline and every 8 weeks thereafter to all consenting patients. The EQ-5D-5L, also administered at every 8 weeks, responses were converted into a weighted health state index by applying sores from the EQ-5D value elicited from general population samples. In the economic model, the utility scores from the EQ-5D-5L was mapped to the EQ-5D-£L, as recommended in the NICE reference case.

Adverse events were graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.03. Safety outcomes were reported in the CS, and summarised in table

Overall, the outcomes selected in the CS were consistent with that of the NICE scope. Where additional outcomes were included, a clear justification was provided.

Summary and critique of the company's approach to statistical analysis and results

3.2.1.1 Company submission

The company provided data to the ERG in the following 6 submissions:

- The original CS (version 0.1) and CSR dated 01 June 2020: data cut 04 June 2019 ([redacted] (ola)/[redacted] (NHA) months median follow-up)
- An updated CS (version 0.2) dated 11 June 2020 with updated OS analyses at data cut 20 March 2020

- The clarification responses (version 0.1) dated 02 July 2020
- Additional clarification responses (version 0.3) dated 07 July 2020: the company provided quarterly cuts of Kaplan-Meier data, relevant to question A4, A10 and A12.
- Additional clarification responses (version 0.4) dated 13 July 2020: the company provided monthly cuts of Kaplan-Meier data.
- Additional clarification responses (version 0.5) dated 16 July 2020: the company provided more detail to some of the ERG clarification questions.
- Additional clarification responses (version 0.6) dates 24 July 2020: the company provided more detail on one of the ERG clarification questions and refused to supply full KM data.

3.2.1.2 Summary of trial statistics

The company's approach to trial statistics is presented in CS section B.2.4. Time to event outcomes were analysed using stratified log-rank tests and hazard ratios were calculated using Cox proportional hazards (PH) models. The assumption of PH was tested for rPFS and OS using Schoenfeld residuals.

The ERG reproduced a similar sample size calculation to that presented by the company using the 'power logrank' command in StataSE 16 (64-bit), and are satisfied that the PROfound trial was suitably powered to detect the specified difference in the primary outcome (HR of 0.53 in rPFS). The primary analysis took place after 174 (71% maturity) progression events had occurred in Cohort A, at the first data cut off (DCO1).

Figure 2 of the CS (page 45) details the hierarchical testing structure of the primary outcome (rPFS) and key secondary outcomes of PROfound. BICR- assessed rPFS in Cohort A was tested at the 5% level, as was ORR (Cohort A), rPFS (Cohort A+B) and TPP (Cohort A). OS at DCO1 was tested at alpha = 0.01 and at DCO2 at alpha = 0.047. The log-rank tests were stratified in accordance with the pooling strategy (previous taxane use and measurable disease at baseline).

In the CS and PROfound protocol, the company states that analyses would be stratified in accordance with the pooling strategy; prior taxane use and measurable disease at baseline.

Overall, the trial was suitably powered in terms of sample size.

Results for prior taxane subgroup, which is the focus of this submission, comes from subgroup analyses of the primary outcome, rPFS, and a key secondary outcome, OS. No

adjustment for the significance level for testing of subgroups was made in PROfound according to the protocol (section 8.5.4). Therefore, any results are purely exploratory and should only be used in support of rPFS results.

3.2.2 Summary of trial results

A summary of key outcomes from DCO1 are presented in Table 17. All results presented are as of DCO1 unless otherwise stated.

Table 17: A summary of the primary and key secondary outcomes for Cohort A, Cohort B and Cohort A+B in PROfound

	Cohort A		Cohort A+B		Cohort B	
	Olaparib	**NHA**	**Olaparib**	**NHA**	**Olaparib**	**NHA**
Number of patients	162	83	256	131	94	48
Median follow-up (days) (range)	[redacted]	[redacted]	227 (1-692)	119.5 (17-596)	[redacted]	[redacted]
Actual treatment duration	[redacted]	[redacted]	214.5 (1-589)	119 (17-596)	[redacted]	[redacted]
Primary outcome: BICR-assessed rPFS at DCO1						
Number of radiographic progressions or deaths	106 (65.4%)	68 (81.9%)	[redacted]	[redacted]	[redacted]	[redacted]
Median rPFS (months)	7.39 (6.24, 9.33)	3.55 (1.91 3.71)	[redacted]	[redacted]	[redacted]	[redacted]
HR (95% CI)	0.34 (0.25, 0.47)		0.49 (0.38, 0.63)		[redacted]	
p	< 0.0001		< 0.0001		[redacted]	
Progression-free rates (%) (95% CI)						
At 6 months	59.76	22.63	[redacted]	[redacted]	[redacted]	[redacted]
At 12 months	28.1	9.4	[redacted]	[redacted]	[redacted]	[redacted]
Secondary outcomes (at DCO1 unless otherwise stated):						
OS						

Number of deaths (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median OS (months) (95% CI)	18.5	15.11	[redacted]	[redacted]	[redacted]	[redacted]
HR (95% CI)	0.64 (0.43, 0.97)		0.67 (0.49, 0.93)		[redacted]	
P	[redacted]		0.0063		[redacted]	
OS rates (%) (95% CI)						
At 6 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
At 12 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
At 18 months	[redacted]	[redacted]			NR	NR
At 24 months					NR	NR
OS (DCO2)						
Number of deaths	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median OS (months) (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HR (95% CI)	[redacted]		[redacted]		[redacted]	
P	[redacted]		[redacted]		[redacted]	
OS rates (%) (95% CI)						
At 6 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

At 12 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
rPFS2						
Number of second radiographic progressions or deaths	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median rPFS2 (months)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HR (95% CI)	[redacted]		[redacted]		[redacted]	
P	[redacted]		[redacted]		[redacted]	
TTPP						
Event, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median TTPP, months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HR (95% CI)	[redacted]		[redacted]		[redacted]	
P	[redacted]		[redacted]		[redacted]	
No pain progression rates (%)						
At 6 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
At 12 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time to first symptomatic SRE						

Event, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HR (95% CI)	[redacted]		[redacted]		[redacted]	
P	[redacted]		[redacted]		[redacted]	
SRE-free rates, %						
At 6 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
At 12 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ORR						
Event, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Partial response, n (%)			[redacted]	[redacted]	[redacted]	[redacted]
Complete response, n (%)			[redacted]	[redacted]	[redacted]	[redacted]
OR (95% CI)	[redacted]		[redacted]		[redacted]	
P	[redacted]		[redacted]		[redacted]	
NC = not calculable, NR = not reported						

3.2.2.1 BICR-assessed rPFS

The primary outcome of PROfound was BICR-assessed radiographic progression-free survival (rPFS). At DCO1 olaparib demonstrated superior efficacy on this outcome for the Cohort A, with a hazard ratio of 0.34 (95% CI: 0.25 to 0.47).

The company does not present an analysis of whether the hazard ratio, which assumes proportionality of the hazard ratio between the two trial arms, is a suitable outcome when reporting this result for Cohort A. However, in section B.2.9.3 (page 86), detailing the results of the company's indirect treatment comparison results, the company presents log-cumulative hazard and Schoenfeld residuals vs time plots to assess the assumption of proportional hazards for rPFS and OS for PROfound and CARD. In both cases, the assumption of proportional hazards holds for both endpoints.

These tests for the assumption for PH were done on the prior-taxane subgroup of PROfound.

3.2.2.2 Overall Survival (OS)

Cohort A+B

The risk of death was decreased in the olaparib arm compared to the NHA arm in Cohort A+B (HR: 0.67; 95% CI: 0.49 to 0.93; p = 0.0063).

Cohort A

The risk of death was decreased in the olaparib arm compared to the NHA arm (HR: 0.64; 95% CI: 0.43 to 0.97; p = [redacted]) in Cohort A. However, as the significance level of OS at DCO1 was 1%, statistical significance was not reached.

As stated above, the company presented PH tests in the ITC section of the CS, section B.2.9.3.2 for the prior-taxane use subgroup. Again, no analyses were presented of the test of PH assumption for Cohort A.

Cohort B

There was [redacted] in risk of death between the olaparib and NHA arms in Cohort B [redacted]

3.2.2.2.1 OS at DCO2

The company state that a statistically significant survival benefit was achieved during the final OS analysis (DCO2; 20 March 2020) in Cohort A. These results were not presented as part of the original CS but were included as part of an updated submission (version 0.2; dated 11 June 2020).

The data for both cohorts A and A+B were more mature at DOC2 (≈60% and ≈64% maturity, respectively). According to Figure 2 of CS, the significance level of OS at DCO2 was alpha = 0.047.

Cohort A+B

In Cohort A+B, the risk of death was decreased in olaparib by 21% (HR=0.79; 95% CI: 0.61, 1.03; p = 0.0515). However, as p > 0.047, this HR was not statistically significant.

No tests for the assumption of proportional hazards were presented for any of the cohorts for OS at DCO2.

Cohort A

The risk of death in Cohort A was decreased, resulting in a HR of 0.69 (95% CI: 0.50, 0.97; *p* = 0.0175). The HR was slightly less favourable for olaparib compared to the HR at DCO1.

Cohort B

Results were not reported for Cohort B.

3.2.2.2.2 Adjustment for treatment switching

In Cohort A, 51/83 patients switched from NHA to olaparib, and 75/131 in Cohort A+B switched to olaparib. Treatment-switching adjustment analyses were undertaken to estimate the true OS benefit for olaparib compared to NHA as the switching would otherwise confound the original OS results.

The company chose the rank preserving structural failure time models (RPSFTM) approach to adjust for treatment switching instead of inverse probability of censoring weights (IPCW) or a two-stage estimation (TSE).

The TSE was excluded by the company as an appropriate secondary baseline could not be identified that would not bias the results, and as the IPCW method is dependent on the 'no

unmeasured confounders' assumption and involved the analysis of reduced sample sizes, the RPSFTM method was favoured.

RPSFT models that are used to calculate the acceleration factor are based on assumptions made by each of the models, and the company also included the analyst's preferred model into the decision making. These models were the log-rank, Weibull and Cox.

The acceleration factor, $\exp(\psi)$, is key in formulating RPSFT models. The log-rank method using the z-test statistic of ψ so that $Z(\psi) = 0$ for optimal values of ψ. This is also the case for the Weibull method, and for the Cox model $Z(\psi)$ should cross 0.[42] Moreover, the Weibull and Cox models are parametric in nature, and may be stratified.

Re-censoring was performed by the company? to assess the impact of informative censoring on the results, and then comparing those results to when re-censoring was not performed. On the event time scale, censoring may be informative on the treatment group, thus the counter-factual event times are re-censored at the minimum possible censoring time. As the results when re-censoring were consistent with the results when not re-censoring, it was not considered in the company's analysis.

The company performed the IPCW and compared those results to that of the without re-censoring Weibull RPSFT model, results show in

Table 18. Using the company's preferred approach, the OS gain demonstrated was [redacted] months in Cohort A and [redacted] months in Cohort A+B for olaparib versus NHA. These results, as well as the hazard ratios, were consistent across all models of the RPSFTMs and of the IPCW, see Table 10 of CS (page 62).

Adjustment of analyses for treatment switching were performed using R foundation.

Results of the treatment switching analysis are presented in

Table 18. As of CS version 0.2, analyses for treatment switching at DCO2 have not yet been reported.

Table 18. Results of the Weibull RPSFTM without any re-censoring and using the IPCW method to adjust for treatment switching for OS at DCO1

	Cohort A		Cohort A+B	
	Mean OS (months) of NHA adjusted for switching	**OS HR (95% CI)**	**Mean OS (months) of NHA adjusted for switching**	**OS HR (95% CI)**
RPSFTM Weibull No re-censoring	[redacted]	[redacted]	[redacted]	[redacted]
IPCW	[redacted]	[redacted]	[redacted]	[redacted]

For the remaining secondary outcomes, the company focused on the results for Cohort A+B. The results of Cohort A are presented in the CSR but the following outcomes were not analysed for the key subgroup, i.e. prior taxane use, which was the focus of the economic model in this submission.

3.2.2.3 Progression-free survival 2 (PFS2)

Cohort A+B

Treatment with olaparib was associated with a [redacted] in PFS2 compared to NHA in Cohort A+B [redacted]. Figure 8 of the CS shows the Kaplan-Meier plot of PFS2 at DCO1 for Cohort A+B. Whilst there was no clear separation of both curves for the first 3 months of follow-up, the curves did separate in favour of olaparib until about months 18 and 19.

Cohort A

Treatment with olaparib was associated with a [redacted] in median PFS2 compared with NHA in Cohort A, resulting in a statistically significant hazard ratio ([redacted]). These results were consistent with the results of Cohort A+B.

Cohort B

Results were not reported for Cohort B.

3.2.2.4 Time to pain progression (TTPP)

TTPP was based on responses of the Brief Pain Inventory – short form (BPI-SF) worst pain and opiate use items.

Cohort A+B

The company reported a hazard ratio [redacted] in Cohort A+B, at DCO1, suggesting that olaparib was associated with a [redacted] in pain progression, although the [redacted]. There is a clear separation of curves in the corresponding Kaplan-Meier plot after three months in favour of olaparib.

Cohort A

Treatment with olaparib, in Cohort A, was [redacted]). Median TTPP was not reached in the olaparib group but was reached in the NHA arm ([redacted]).

Cohort B

There was [redacted] in risk of pain progression between the olaparib and NHA arms in Cohort B [redacted]

3.2.2.5 Time to first symptomatic skeletal-related event (SSRE)

SSREs are an indicator of worsening bone health. In PROfound, they were defined as:

- Use of radiation therapy to prevent or relieve skeletal symptoms
- Occurrence of new symptomatic pathological bone fractures
- Occurrence of spinal cord compression
- Orthopaedic surgical intervention for bone metastasis

Cohort A+B

In Cohort A+B, the incidence of SSREs were [redacted].

Cohort A

The results were similar for Cohort A, resulting in a [redacted].

Cohort B

Results were not reported for Cohort B.

3.2.2.6 Overall response rate (ORR)

Cohort A+B

Olaparib was associated with [redacted]. In the olaparib arm, [redacted]

Cohort A

There were [redacted] in ORR for Cohort A [redacted].

Cohort B

There was [redacted] difference in BICR-confirmed ORR between the olaparib and NHA arms [redacted]

3.2.2.7 Patient-reported outcomes

The company utilised the following questionnaires to capture patient-reported HRQoL. These were:

- EQ-5D-5L
- FACT-P

3.2.2.7.1 EQ-5D-5L

Cohort A+B

Figure 11 of the CS (page 70) shows the mean change from baseline of the EQ-5D-5L domain and VAS scores. Baseline and overall compliance rates were [redacted]. There [redacted] (mobility, self-care, usual activities, pain/discomfort, anxiety/depression, VAS) from baseline to Week 64 across both treatment arms in Cohort A+B.

Cohort A

Section 11.1.5.1 of the CSR (page 234) indicated that there were [redacted].

Cohort B

Results were not reported for Cohort B

3.2.2.7.2 FACT-P

A mixed model repeated measure (MMRM) was used to analyse changes in Functional Assessment of Cancer Therapy – Prostate Cancer total and subscale scores. The full results of these are presented in the company appendices M.3.

Cohort A+B

The difference in least squares mean and time to deterioration for each of the FACT-P domains are as follows:

	Olaparib 300 mg bid	**Investigators' choice of NHA**
	(n = 162)	**(n = 74)**
FACT-Prostate total		
Difference in LS mean		
Time to deterioration		
Number of events, %		
Median (95% CI)		
HR olaparib versus NHA (95% CI)		
p		
FACT-General total		
Difference in LS mean		
Time to deterioration		
Number of events, %		
Median (95% CI)		
HR olaparib versus NHA (95% CI)		
p		
Trial Outcome Index		
Difference in LS mean		
Time to deterioration		
Number of events, %		
Median (95% CI)		
HR olaparib versus NHA (95% CI)		
p		
Physical wellbeing		
Difference in LS mean		

Time to deterioration		
Number of events, %	[redacted]	[redacted]
Median (95% CI)	[redacted]	[redacted]
HR olaparib versus NHA (95% CI)	[redacted]	
p	[redacted]	
Functional wellbeing		
Difference in LS mean	[redacted]	
Time to deterioration		
Number of events, %	[redacted]	[redacted]
Median (95% CI)	[redacted]	[redacted]
HR olaparib versus NHA (95% CI)	[redacted]	
p	[redacted]	
Prostate cancer subscale		
Difference in LS mean	[redacted]	
Time to deterioration		
Number of events, %	[redacted]	[redacted]
Median (95% CI)	[redacted]	[redacted]
HR olaparib versus NHA (95% CI)	[redacted]	
p	[redacted]	
6-item Functional Assessment of Cancer Therapy Advanced Prostate Symptom Index		
Difference in LS mean	[redacted]	
Time to deterioration		
Number of events, %	[redacted]	[redacted]
Median (95% CI)	[redacted]	[redacted]

HR olaparib versus NHA (95% CI)	[redacted]
p	[redacted]

[redacted]

Cohort A

Results were not reported for Cohort A.

Cohort B

Results were not reported for Cohort B.

3.2.2.8 Subgroup analyses

The company presents results of pre-specified subgroup analyses on BICR-assessed rPFS for 8 pre-specified subgroups in Cohort A and for 9 pre-specified subgroups in Cohort A+B. The results of these analyses are presented in company appendices E.

Additionally, the CS presents results of rPFS and OS for the prior-taxane subgroup, which was the focus of the submission. Results for rPFS were based on data from DCO1 and results of OS were based on data from DCO1 and DCO2.

Figure 4 of appendix E.1 presents the forest plot for rFPS by subgroup for Cohort A at DCO1. Overall, the benefit of olaparib was maintained across all of the 8 pre-defined subgroups.

Figure 5 of appendix E.1.2 presents the forest plot for rFPS by subgroup for Cohort A+B at DCO1. Of particular relevance to the CS are the results of the subgroup analyses of the 7 gene alterations with at least five disease progressions/deaths (BRCA1, BRCA2, ATM, CDK12, CHEK2, PPP2R2A, RAD54L). The risk of disease progression/death was decreased in the olaparib arm compared to the NHA arm for people with the BRCA2 mutation (HR: 0.21, 95% CI: 0.13 to 0.32), and increased in the olaparib arm compared to the NHA arm for people with the PPP2R2A mutation (HR: 6.61; 95% CI: 1.41 to 46.41). There was no

difference in risk of disease progression/death between the two treatment groups for people with BRCA1, ATM, CDK12, CHEK2, or RAD54L mutations.

3.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

3.3.1 Olaparib comparator studies

The company identified three studies where olaparib was assessed in the population of interest (PROfound, TOPARP-A,[27] TOPARP-B [43]).

The company lists the following reasons as to why the two TOPARP studies were excluded from the ITC:

- Neither study was explicitly set in the post-NHA era
- As both studies were Phase II in nature, only assessing olaparib at 400 mg (TOPARP-A) and at 300mg or 400 mg (TOPARP-B) with no NHA comparator, the company felt that data from the PROfound RCT, would be more suitable.

Briefly, TOPARP-B was a randomised, open-label, multicentre, phase II UK trial in patients with mCRPC who have received prior docetaxel treatment regardless of exposure to NHAs. Patients with DDR gene aberrations were randomised, 1:1, to receive either Olaparib (300mg; twice a day) or Olaparib (400 mg; twice a day).

3.3.2 Comparator studies

The company SLR, conducted in January 2020, identified 14 studies which reported on outcomes with treatments identified within the NICE scope: olaparib, cabazitaxel, docetaxel, and radium-223.

However, the company excluded the publications assessing docetaxel and radium-223 as they were not relevant to the decision problem.

The SLR identified eight publications on cabazitaxel that were potentially relevant to the decision problem – patients with mCRPC in the post-NHA setting. Only one of these studies, CARD, included an NHA arm which allowed for an anchored ITC to compare olaparib with cabazitaxel.

3.3.2.1 Cabazitaxel

Cabazitaxel was evaluated in TA391, where a phase III randomised open label multi-centre trial compared cabazitaxel with mitoxantrone in men with mCRPC previously treated with a docetaxel-containing regimen. Key areas of uncertainty included:

- Absence of any head-to-head RCTs comparing cabazitaxel with other second-line agents for the population of interest
- Uncertainty over the optimal dose and frequency of cabazitaxel
- Differences in patient populations used in the ITC
- Choice of parametric curve used in the economic analysis.

3.3.2.2 CARD

CARD[28] was a randomised, open-label, multicentre, phase IV post-marketing study in patients with mCRPC in the post-NHA setting who had received a prior taxane. Patients were randomised, 1:1, to receive either:

- Cabazitaxel (25 mg/m^2 of BSA; Q3W) + prednisone (BD) + granulocyte colony-stimulating factor
- Abiraterone (100 mg; BD) + prednisone (BD) OR enzalutamide (160 mg; BD)

Randomisation was stratified according to ECOG performance-status score (0 vs 1 vs 2), time to disease progression (≤ 6 months vs >6 or 12 months), and timing of the previous alternative androgen-signalling-target inhibitor (before vs after decotaxel).

Table 16 in the CS appendices D.1.4.2 gives details and full inclusion and exclusion criteria of CARD. Key inclusion criteria included histologically confirmed metastatic PC, measurable disease progression, prior docetaxel use, ECOG score of 0 to 2 and serum testosterone of < 0.5 ng/mL.

A full breakdown of baseline characteristics of CARD participants by treatment group is presented in Table 17 in the company appendices D.4.1.6.

The primary endpoint of CARD was imaging-based progression-free survival, or radiographic progression-free survival but the assessment included non-radiographic measures. This was defined as time from randomisation until objective tumour progression (according to RECIST v1.1), progression of bone lesions (according to Prostate Cancer

Working Group 2 criteria), or death. Secondary end points included OS, PFS, PSA response, tumour and pain responses, first symptomatic SRE, safety and HRQoL.

3.3.2.3 Company's feasibility assessment

The company conducted a feasibility assessment to determine the suitability of the available data for conducting a population-adjusted indirect comparison (PAIC) through the identification of treatment effect modifiers (EMs).

Treatment effect modifiers are variables where the magnitude of the effect of the primary exposure on an outcome differs depending on the level of an effect modifier. To identify effect modifiers, the company assessed the covariates in PROfound against those found in the CARD study at the 80% significance level. The results of these are presented in the CS Table 13 and 14 (pages 83 and 85, respectively).

The company concluded it was not necessary to conduct a PAIC because no effect modifiers were identified in the assessment of covariates in the PROfound and CARD datasets.

3.3.2.4 ERG summary

The ERG agrees that the common comparator of NHA between CARD and PROfound facilitates an anchored comparison. The ERG also agrees with the company's conclusions regarding a lack of EMs, and thus an anchored Bucher ITC is appropriate in this scenario.

Table 19 compares the study designs of PROfound and CARD.

Table 19. Study design of PROfound and CARD

	PROfound	**CARD**
Design	Randomised, open-label, multicentre, phase III	Randomised, open-label, multicentre, phase IV
Treatment groups	Olaparib (300 mg; twice a day) Enzalutamide or abiraterone	Cabatizaxel Enzalutamide or abiraterone
Eligibility criteria	Age >= 18 years Histologically confirmed PC ECOG 0-2 Serum testosterone <= 50 ng/dL for <= 28 days before randomisation Life expectancy >= 16 weeks Qualifying HRRm in the tumour tissue	Histologically confirmed PC ECOG <= 1 (ECOG=2 allowed is related to PC) Serum testosterone < 0.5 ng/mL Metastatic disease Disease progression and/or

	Eligible for treatment with NHA Progression following an NHA Radiographic disease progression at study entry while receiving ADT	appearance of >=2 new bone lesions and/or rising PSA Received prior docetaxel for at least 3 cycles Progression within 12 months of treatment with a prioer androgen-signalling-trargeted inhibitor PSA >= 2 ng/mL at study entry Prior androgen-signalling-targeted inhibitor must be stgopped at least 2 weeks before study treatment
Relevant subgroup	Prior taxane use	Intention-to-treat

Despite the apparent similarity of the two trial there were some concerns around this:

Primary endpoint blinding:

Both studies defined the primary outcome as imaging-based progression-free survival. However, no blinding of central review of imaging was conducted in CARD. This introduces a bias as the blinding of outcome adjudicators is crucial to ensure unbiased ascertainment of outcomes.

Genetic mutations were unknown in CARD: Unknown HRRm carrier status in CARD is likely to compromise the reliability of comparisons between CARD and all HRRm defined PROfound subgroups (i.e. pior taxane A+B, cohortA+B, and cohort A)

3.4 Critique of the indirect comparison and/or multiple treatment comparison

In the absence of direct evidence, the company sought to perform an indirect comparison of olaparib, from PROfound, with cabazitaxel, from CARD. As both trials had a common comparator, NHA, an anchored Bucher ITC was performed for rPFS and OS.

Table 20 presents the outcomes of rPFS and OS for PROfound and CARD, and the results for the indirect comparison between the olaparib and cabazitaxel (reference treatment). [redacted]

Table 20: Results of the anchored ITC for rPFS and OS

	PROfound		CARD		ITC results
	Prior-taxane (A+B)		Full		
	Olaparib (n=170)	NHA (n=84)	Cabazitaxel (n=129)	NHA (n=126)	Olaparib vs cabazitaxel (ref)
rPFS					
Events, n (%)	[redacted]	[redacted]	95 (73.6)	101 (80.2)	
Median rPFS (months)	[redacted]	[redacted]	8.0 (5.7, 9.2)	3.7 (2.8,5 5.1)	
HR (95% CI)	[redacted][+]		0.52 (0.40, 0.68)		[redacted]
P			<0.001		
OS					
Events, n (%)	[redacted]	[redacted]	70 (54.3)	83 (65.9)	
Median OS (months)	15.8 (12.7, 18.0)	11.4 (9.4, 15.1)	13.6 (11.5, 17.5)	11.0 (9.2, 12.9)	
HR (95% CI)	0.44 (0.31, 0.64) *		0.64 (0.46, 0.89)		[redacted]
P			0.008		

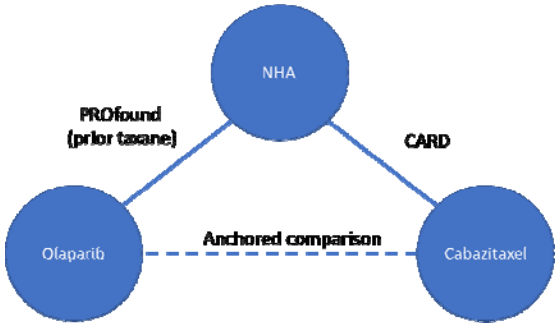
[+] company used this HR as stated on page 87, but reported 0.39 (0.29, 0.53) on page 73 of CS version 0.1 and in de Bono 2020

* after adjustment for treatment switching

3.4.1 Overall Survival

The ERG focusses on the NMA for overall survival. Using data from the CARD trial to obtain a HR of 0.64 for the comparison cabazitaxel versus NHA (new hormonal agent, abiraterone or enzalutamide) and a HR of [redacted] for the comparison of olaparib versus NHA, the CS estimated a Butcher ITC (unadjusted for variables) HR of [redacted] for the comparison olaparib versus cabazitaxel (or [redacted] for cabazitaxel versus olaparib as applied in the economic model).

The structure of the NMA (MS Figure 15) is shown below.



The ERG have identified the following potential limitations in the MS ITC:

The assumption of transitivity (i.e. that the RCTs included in the ITC are similar in all respects other than the intervention received) may be threatened because the populations almost certainly differ with respect to the proportions of their participants who have HRRms (homologous recombinant repair gene mutations). In PROfound, tumours in all participants had mutations in HRR genes, whereas this is extremely unlikely to be the case for the CARD trial.

When referring to HRR mutations in men who have mCRPC, the CS varyingly states that "*Approximately 20%−30% of patients with mCRPC have mutations in genes involved in the homologous recombination repair (HRR) pathway*"

According to the CS (**section B1.1**) there is evidence that the presence of HRRm is associated with more aggressive disease; however, no robust evidence has demonstrated a lack of concordance.

The PROfound trial and the CARD trial differ noticeably in terms of geography. The PROfound trial was 35% Asia, 43% Europe and 23% North and South America[1], whereas the CARD trial was conducted exclusively in Europe. These geographic differences may be the cause of some of the apparent differences in subsequent treatments

In CARD pre-randomisation treatment with cabazitaxel was unlikely since the publication states that "prior chemotherapy other than docetaxel for prostate cancer, except estramustine and except adjuvant/neoadjuvant treatment completed > 3 years ago" was not allowed. According to the CS Table 5, about 30% of the target PROfound population had received cabazitaxel prior to randomisation (olaparib arm 30% and comparator arm 31%). Further difference between populations may involve the timing of previous use of NHAs with respect to docetaxel treatment (before, after, concurrent). CARD patients had all previously received NHA therapy.

A further potential limitation is that the PROfound NHA was modelled using correction for the pronounced cross over [redacted] to olaparib upon progression.

[1] The percentages for the prior taxane subgroup broadly conforms with these percentages.

The trial result is thus strictly no longer a randomised result. It is uncertain that the true OS with NHAs in the absence of crossover would conform to a proportional hazards assumption.

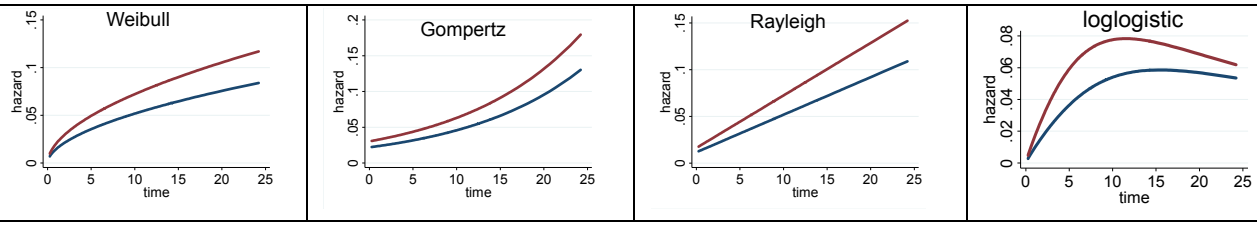
A further cause of serious concern is the inconsistent use of methods to determine HR inputs for the NMA and the subsequent use of the NHA output with a selected loglogistic model.

The HR input from PROfound (NHA vs. olaparib) was derived under a proportional hazards (PH) assumption using a Weibull distribution, while the CARD input (NHA vs. cabazitaxel) appears to derive from Cox PH model (treatment as the only variable) undetermined by any parametric distribution. In the base case economic model, the NHA output HR (olaparib vs. cabazitaxel = [redacted]) is applied to a loglogistic model of olaparib survival in PROfound. Loglogistic models do not conform to a PH assumption (i.e. the ratio of hazards varies with time) and the application to an HR invariant through time appears inappropriate. For consistency the input HRs from PROfound and CARD trials should be obtained from the same PH parametric distribution; the NMA output should similarly be applied to a parametric model with PH property. These inconsistencies threaten the reliability of the NMA.

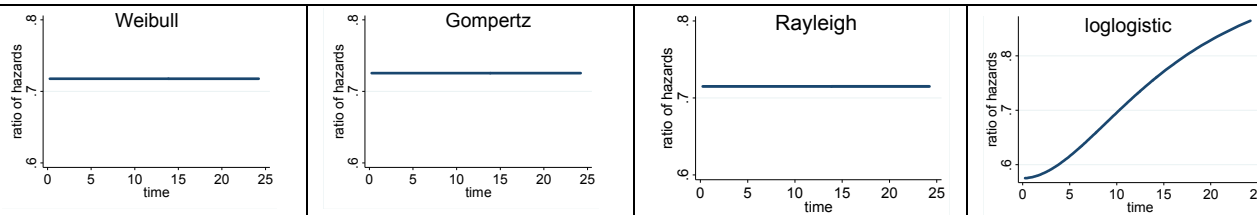
The ERG looked at the influence of parametric distribution on the hazards and ratio of hazards (HR) with a specimen data set. Weibull, Gompertz, Rayleigh, and loglogistic models were employed with treatment as covariate Table 21 shows the results: [a] hazard in treatment arms varies through time in all models; [b] with Weibull, Gompertz, and Rayleigh distributions the HR, although slightly differing between distributions, is constant through time so that hazard in one arm can be obtained exactly from the other arm by applying the appropriate HR; [c] the loglogistic distribution HR changes through time so that hazard one arm cannot be obtained by applying a time invariant HR to the other arm.

Table 21. Illustrative hazards and ratio of hazards according to different parametric distributions

Hazard according to treatment arm and parametric model



Ratio of hazards in treatment arms according to parametric model



3.4.2 Radiographic progression-free survival

There were 124 (72.9%) rPFS events in the olaparib arm of PROfound, which was a similar proportion of rPFS events as in CARD for the cabazitaxel arm. Using data from the CARD trial to obtain a HR of 0.54 for the comparison of cabazitaxel versus NHA (new hormonal agent, abiraterone or enzalutamide) and a HR of [redacted] for the comparison of olaparib versus NHA, the MS estimated a Butcher ITC (unadjusted for variables) HR of [redacted] for the comparison olaparib versus cabazitaxel (or [redacted] for cabazitaxel versus olaparib as applied in the economic model).

To calculate the HR for CARD, the company generated a HR from recreated IPD data by digitising the Kaplan-Meier plots for rPFS, which yielded a HR of [redacted], slightly different to the published HR of 0.54 (0.40, 0.73).

The hazard ratios and associated 95% confidence intervals for CARD were estimated using a stratified Cox PH model [according to de Wit 2019]. However, digitising the Kaplan-Meier curves and producing HRs using the IPD would produce unstratified results. As the PROfound protocol states (section 8.5.4; page 122), "*HRs for radiological progression by BICR (olaparib: investigator choice) and associated 2-sided CIs will be calculated from a Cox proportional hazards model (ties = Efron) that contains the treatment term, factor and treatment-by-factor interaction term*." Since the HRs for the prior taxane subgroup were unstratified, the ERG agrees that calculating unstratified HRs for rPFS in CARD is appropriate and provides a more suitable comparison. Furthermore, the ERG agrees the method the Efron approximation of tied survival times to be appropriate.

In addition to the concerns regarding transitivity, the ERG had a concern regarding the hazard ratios inputted into the ITC for rPFS. There was a discrepancy, albeit slight, between the hazard ratio of olaparib vs NHA reported in section B.2.7.1 (page 73) (HR:0.39; 95% CI: 0.29 to 0.53) of the CS (version 0.1) compared to the HR stated in section B.2.9.3.1 of the CS (page 87) (HR:0.38; 95% CI: 0.28 to 0.52). This is also the case for version 0.2 of the CS (date: 01 June 2020).

Table 22 presents the differences in the indirect comparison HR between olaparib and cabazitaxel (reference) when considering the two different hazard ratios reported in the CS. Results differ slightly due to rounding errors.

Table 22. Anchored Bucher ITC results using the two different HRs; olaparib vs NHA in Cohort A+B prior taxane use subgroup (PROfound), and cabazitaxel vs NHA (CARD), for rPFS presented in the CS

PROfound		**CARD HR** digitised; unstratified
Source	HR	[redacted]
Page 72 (published)	0.39	[redacted]
Page 87	**0.38**	[redacted]

Results in **bold** denotes company's choice of HR and results

3.4.3 Summary of the company ITC

In summary, due to the quality of the ITC, the ERG considers that these indirect comparisons are inadequate for providing meaningful, statistically significant information on the comparison of olaparib and cabazitaxel for either rPFS or OS.

3.5 Adverse events

The safety-evaluable population was used for the safety analysis, the safety analysis set (SAS). This population was defined as participants who received at least one dose of their randomised study treatment in Cohort A or B. There was a total of 386 patients in the safety analysis population for PROfound, 256 in the olaparib arm and 130 in the investigators' choice of NHA arm.

As stated in the PROfound protocol section 8.4.4.1, adverse events were to be grouped separately as AE onset before and after first dose of study drug. Any AE commencing or

worsening on the same day as the first dose of study treatment will be assumed to occur after the study treatment has been administered.

A treatment emergent AE (TEAE) was defined as an AE with the start date on or after the first dose date, and up to and including the 30-day (±7 days) follow-up visit after discontinuation of study treatment, until the time of the final analysis (rPFS).

Treatment exposure rates were presented in CS Table 16 (page 94) in section B.2.10.1. Data were available for the Cohort A+B SAS and for the prior taxane subgroup. In the SAS, median total treatment duration in the olaparib arm was 227 days, compared to 119.5 days in the NHA group. Median actual treatment duration was similar, 214.5 days in the olaparib arm and 119.0 days in the NHA arm. Dose interruptions, reductions and modifications were at a much higher rate in the olaparib arm compared to the NHA arm.

Results of treatment exposure were similar for the prior taxane subgroup. However, dose modifications was reported as not-applicable for this subgroup.

All AE data were as of DCO1.

3.5.1 Overview of adverse events

An adverse event as defined in the PROfound protocol "*is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, where or not considered causally related to the product*."

Table 23 (from Table 17 of CS) provides a summary of adverse events in PROfound, experienced by patients in the SAS and prior taxane subgroup, and are described in more detail below.

Table 23. Adverse events in any category, DCO1 in Cohort A+B SAS/prior taxane subgroup

	SAS		Prior taxane subgroup	
	Olaparib 300 mg bid (n = 256)	**Investigators' choice of NHA (n = 130)**	**Olaparib 300 mg bid (n = 170)**	**Investigators' choice of NHA (n = 83)**
Number (%) of patients				
Any AE	244 (95.3)	114 (87.7)	[redacted]	[redacted]

Any AE, causally related to study treatment	206 (80.5)	61 (46.9)	[redacted]	[redacted]
Any AE leading to death	10 (3.9)	5 (3.8)	[redacted]	[redacted]
Any AE leading to discontinuation	46 (18.0)	11 (8.5)	[redacted]	[redacted]
Any AE relating to dose reduction	57 (22.3)	5 (3.8)	[redacted]	[redacted]
Any AE relating to interruptions	115 (44.9)	24 (18.5)	[redacted]	[redacted]

AEs were experienced by 95.3% of patients in the olaparib arm and 87.7% in the NHA arm of the SAS. There was a big difference in AEs related to study treatment (80.5% in olaparib; 46.9% in NHA), AE leading to discontinuation ([redacted] in olaparib; [redacted] in NHA), AE relating to dose reduction (22.3 in olaparib; 3.8% in NHA) and AE relating to interruptions (44.9% in olaparib; 18.5% in NHA). AEs leading to death were similar across groups. [redacted]

3.5.2 Grade 3-4 adverse events

Common Terminology Criteria for Adverse Events (CTCAE) grade 3 or higher adverse events are presented in Table 24. The olaparib arm of the SAS had a higher proportion of patients with any AE grade 3 or higher, and AE grade 3 or higher related to treatment compared to the NHA arm. [redacted]

Table 24. Patients in the SAS or prior taxane subgroup in PROfound with grade 3-4 adverse events

	SAS		**Prior taxane subgroup**	
	Olaparib 300 mg bid (n = 256)	**Investigators' choice of NHA (n = 130)**	**Olaparib 300 mg bid (n = 170)**	**Investigators' choice of NHA (n = 83)**
Number (%) of patients				

Any AE of CTCAE Grade 3 or higher	130 (50.8)	49 (37.7)	[redacted]	[redacted]
Any AE of CTCAE Grade 3 or higher, causally related to study treatment	78 (30.5)	12 (9.2)	[redacted]	[redacted]

Table 25 below (adapted from Table 31 of the CS), lists the grade 3 and above AEs that affected 5% or more patients in the prior-taxane subgroup of PROfound that were included in the company base case economic model.

Table 25. Incidence of the most common grade 3-4 AEs that were included in the company economic model

Adverse event, %	**Olaparib; PROfound, HRRm – Prior taxane N = 170**
Anaemia	[redacted]
Infection	[redacted]
Leukopenia	[redacted]
Neutropenia	[redacted]
Musculoskeletal pain or discomfort	[redacted]
Thrombocytopenia	[redacted]
Febrile neutropenia	[redacted]
Diarrhoea	[redacted]
Fatigue/asthenia	[redacted]

Individual grade 3 or higher AEs are presented in section 12.2.2.3 in the CSR.

3.5.3 Serious adverse events (SAEs)

SAEs were defined as an AE during any study phase that fulfils one or more of the following:

- Results in death
- Is immediately life threatening
- Required in-subject hospitalisation or prolongation of exiting hospitalisation

- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the subject or may require medical intervention to prevent one of the outcomes

As seen in Table 26, SAEs were experienced in a higher percentage of participants (35.5%) in the olaparib arm than in the NHA arm (27.7%) at DCO1. Similarly, for the prior taxane subgroup ([redacted] vs [redacted]).

Table 26. Incidence of SAEs reported for the SAS and prior taxane subgroup of PROfound

	SAS		**Prior taxane subgroup**	
	Olaparib 300 mg bid (n = 256)	**Investigators' choice of NHA (n = 130)**	**Olaparib 300 mg bid (n = 170)**	**Investigators' choice of NHA (n = 83)**
Number (%) of patients				
Any SAE including those leading to death	91 (35.5)	36 (27.7)	[redacted]	[redacted]

A full breakdown of SAEs experienced by more than 2 patients by system organ class is presented in Table 84 of the PROfound CSR section 12.3.2. SAEs experienced by 10 or more participants in either treatment group is presented in Table 27. Differences between groups of >5% are presented in bold.

Table 27. Incidence of the most frequent* SAEs

SAEs, number (%)	Olaparib (n=256)	Investigators choice of NHA (n=130)
Patient with any SAE	**91 (35.5)**	**36 (27.7)**
Blood and lymphatic system disorders	**28 (10.9)**	**1 (0.8)**
Anaemia	**22 (8.6)**	**0**
Infections and infestations	22 (8.6)	11 (8.5)
Respiratory, thoracic and mediastinal disorders	**17 (6.6)**	**2 (1.5)**
Gastrointestinal disorders	13 (5.1)	3 (2.3)

General disorders and administration site conditions	11 (4.3)	5 (3.8)
Injury, poisoning and procedural complications	11 (4.3)	3 (2.3)
Renal and urinary disorders	10 (3.9)	6 (4.6)
**Frequent: experienced by 10 or more participants in either group*		

3.5.4 Common adverse events of any grade

Table 28 (adapted from CRS Table 74; DOC1) provides a summary of specific adverse events with ≥10 incidence in either treatment group. Events with a 5% or greater difference between groups are in bold.

Table 28. Incidence of common AEs in the SAS of PROfound

Adverse event, n (%)	Olaparib 300 mg bd (n=256)	Investigators' choice of NHA (n=130)
Patients with any AE	244 (95.3)	114 (87.7)
Anaemia	**118 (46.1)**	**20 (15.4)**
Nausea	**106 (41.4)**	**25 (19.2)**
Decreases appetite	**77 (30.1)**	**23 (17.7)**
Fatigue	**67 (26.2)**	**27 (20.8)**
Diarrhoea	**54 (21.1)**	**9 (6.9)**
Vomiting	**47 (18.4)**	**16 (12.3)**
Constipation	45 (17.6)	19 (14.6)
Asthenia	40 (15.6)	18 (13.8)
Back pain	35 (13.7)	15 (11.5)
Oedema peripheral	32 (12.5)	10 (7.7)
Cough	**28 (10.9)**	**3 (2.3)**
Dyspnoea	**26 (10.2)**	**4 (3.1)**
Arthralgia	24 (9.4)	14 (10.8)
Thrombocytopaenia	**22 (8.6)**	**2 (1.5)**
Weight decreased	21 (8.2)	7 (5.4)
Urinary tract infection	18 (7.0)	15 (11.5)

Dyspepsia	18 (7.0)	3 (2.3)
Musculoskeletal pain	17 (6.6)	6 (4.6)
Dizziness	17 (6.6)	5 (3.8)
Dysgeusia	**17 (6.6)**	**2 (1.5)**
Pyrexia	16 (6.3)	6 (4.6)
Neutropenia	**16 (6.3)**	**0**
Headache	15 (5.9)	2 (1.5)
Musculoskeletal chest pain	14 (5.5)	6 (4.6)
Insomnia	14 (5.5)	4 (3.1)
Lymphopenia	13 (5.1)	1 (0.8)

3.5.5 Skeletal related events (SREs)

Symptomatic SREs are a key clinical aspect of mCRPC due to the high propensity for prostate cancer to metastasise to bone tissue and were included in the company economic model as a one-off cost. They were defined in the protocol as "*use of radiation therapy to bone in order to prevent or relieve skeletal complications, occurrence of new symptomatic pathological bone fractures (vertebral or non-vertebral, resulting from minimal or no trauma), occurrence of spinal cord compression, or a tumour related orthopaedic surgical intervention.*"

At least one SRE occurred in [redacted] of patients in the olaparib arm of the prior-taxane subgroup.

3.6 Additional work on clinical effectiveness undertaken by the ERG

3.6.1 Parametric modelling of OS in the subgroup populations of PROfound

In clarification the ERG requested the underlying KM OS data so as to facilitate confirmation of the CS models and the exploration of alternative avenues of analysis. Unusually this request was refused, the company stating that they would be happy to undertake any analyses the ERG might request. Because of time constraints and anticipated delay in the company responding to NICE's second request for KM data, the ERG pursued the less satisfactory route of reconstructing IPD from digitised KM plots using the method of Guyot et al.[44], The reliability of reconstruction was tested by comparing reconstructed Weibull models with those available from the CS and clarification documents.

3.6.1.1 Prior taxane A+B cohort (target population)

In clarification the company kindly supplied a corrected version of CS Figure 14 that showed the KM plot for olaparib and RPSFTm NHA arms and Weibull modelling parameters. The graph is shown in Table 29(left). The number of patients in the NHA and olaparib arms is shown as 83 and 167 which is slightly different to the figures of 84 and 170 provided in CS Tables 5 and 9 and CS Figure 13.

Clarification and ERG Weibull models are shown for olaparib and for the CS RPSFTm NHA arm. The differences between reconstructed and CS models were judged sufficiently small for reconstructed models to be employed for further analysis.

Table 29. KM plot for olaparib and RPSFTm NHA

NHA arm data supplied in clarification	CS and ERG Weibull models of OS
[redacted]	

The CS explored six "standard" parametric models (exponential (EX), Weibull (We), Gompertz (GO), lognormal (LN), loglogistic (LL) and ggamma (GG)) to explore OS. Information criteria IC for the fitted models are presented in the Sibyl parametrics doc kindly supplied on clarification. The ERG similarly explored these models and additionally Rayleigh (RA) and bathtub (bt) models. Analyses were done with Stata version 15 software. The IC scores for the models are summarised in Table 30 and compared with the values available in the Sibyl doc (CS ref 94). The ERG IC scores for these six stratify in the same order as the Sibyl doc. with the GO model providing the lowest score and LN the highest. Of the models tested by the ERG the RA model provides the lowest IC sum by a substantial margin and represents the best fit of the olaparib OS models tested. Table 30 also shows IC scores for models of the NHA RFSFTm arm.

Table 30. IC scores for the models

	Sibyl doc. IC data olaparib			**ERG IC olaparib arm**			**ERG IC RPSFTm NHA arm**			**Sum of**
Model	AIC	BIC	Sum	AIC	BIC	Sum	AIC	BIC	sum	sums
GO	[redacted]	[redacted]	[redacted]	304.42	310.69	615.11	162.62	167.46	330.08	945.19
We	[redacted]	[redacted]	[redacted]	304.48	310.75	615.22	158.74	163.57	322.31	937.53
GG	[redacted]	[redacted]	[redacted]	305.57	314.98	620.55	159.81	167.06	326.87	947.42
LL	[redacted]	[redacted]	[redacted]	307.97	314.24	622.21	157.63	162.47	320.10	942.31
EX	[redacted]	[redacted]	[redacted]	324.29	327.42	651.71	165.56	167.98	333.55	985.26
LN	[redacted]	[redacted]	[redacted]	324.66	330.93	655.58	158.27	163.11	321.38	976.96
RA				301.55	307.82	609.38	160.26	165.10	325.36	934.74
bt				303.55	312.96	616.51	162.26	169.52	331.78	948.29
n.b. The Sibyl doc IC values for the PROfound NHA arm were for unadjusted for cross over NHA and not relevant.										

Summed across both arms the model with lowest score was Rayleigh followed in order by Weibull and loglogistic. These survival models are shown with extrapolation to 10 years in Figure 2.

[redacted]

Figure 2. Rayleigh Weibull and loglogistic models and reconstructed KM for PROfound prior taxane A+B population

Mean survival over the 15 year time horizon for each model is summarised in Table 31 with models arranged left to right according to ascending order of IC score.

Table 31. Target population 15 year mean survival according to treatment arm and model

population	intervention	parametric model						
		Rayleigh	Weibull	loglogistic	GGAMMA	Gompertz	exponential	lognormal
prior Taxane A+B	olaparib	17.49	18.08	24.49	17.29	16.50	26.21	30.06
prior Taxane A+B	RPSFTm NHA	14.07	14.75	19.76	16.93	13.86	20.50	20.38
	gain	*3.42*	*3.33*	*4.73*	*0.36*	*2.64*	*5.71*	*9.68*

For each arm, Rayleigh and Weibull models generate very similar survival while loglogistic models generate appreciably more favourable survival especially for the olaparib arm. Since Rayleigh and Weibull models support a lower IC sum across arms, the ERG favours these over the loglogistic model. The AUC difference to the model time horizon of 15 years between olaparib and RPSFTm arms was : 3.33, 3.42, and 4.73 months for Weibull, Rayleigh and loglogistic models. These three models were explored to see how well parametric modelled cumulative hazard corresponded to reconstructed (KM) cumulative hazard; the results are summarised in APPENDIX 1. Compared to the other models the loglogistic model as used in the company submission provides a relatively poor fit at early times and also from about 16 months onward.

The graph below takes data in the economic model for KM estimates (aggregated to one-month intervals) and the company loglogistic model (Fig 27 in the CS is nearest to this, but the extended time axis tends to mask the poor fit). Figure 3 shows the company logistic fit and KM plot (from data in the company economic model) together with CS Figure 27.

Figure 3. Company logistic fit and KM plot (from data in the company economic model) together with CS Figure 27

CS economic model KM estimate (aggregated to one-month intervals) and CS loglogistic model.	CS Figure 27
[redacted]	

3.6.1.2 PROfound Cohort A

In clarification the company kindly supplied a KM plot for olaparib and RPSFTm NHA arms together with Weibull model parameters for Cohort A. The graph is shown in Table 32 (left). The number of patients in each arm corresponded to the CS. The ERG used the same methods as described above for the prior taxane A+B population to analyse OS in cohort A. Company and ERG Weibull models showed concordance (Table 32).

Table 32. KM plot for olaparib and RPSFTm NHA arms Cohort A

RPSFTm NHA arm supplied in clarification	CS and ERG Weibull models of OS
[redacted]	

According to summed IC scores across both arms the best fit parametric model was the Rayleigh model followed by Gompetz, Weibull, bathtub (Table 33).

Table 33. Best fit parametric model Cohort A

	Olaparib				RPSFTm NHA					
Model	Obs	AIC	BIC	sum	Obs	AIC	BIC	sum	sum of sums	rank
Gompertz	162	264.16	270.34	534.50	83	168.79	173.63	342.42	876.92	2
bathtub	162	265.76	275.03	540.79	83	168.28	175.53	343.81	884.60	4
Rayleigh	162	266.48	272.66	539.14	83	166.28	171.12	337.39	876.53	1
ggamma	162	268.87	278.13	547.00	83	165.73	172.98	338.71	885.71	5
Weibull	162	270.41	276.59	547.00	83	164.70	169.53	334.23	881.23	3
loglogistic	162	274.56	280.74	555.30	83	164.25	169.09	333.35	888.65	6
exponential	162	285.28	291.46	576.74	83	171.81	174.23	346.04	922.78	7
lognormal	162	278.97	282.05	561.02	83	163.43	168.27	331.70	892.72	8

As for the prior taxane A+B cohort, Rayleigh and Weibull models delivered modest gains in mean survival relative to loglogistic. Relative to the target population olaparib delivered superior mean survival for cohort A.

Table 34. Cohort A: 15 year mean survival according to treatment arm and model

POPULATION	INTERVENTION	parametric model						
		Rayleigh	Gompertz	Weibull	GGAMMA	loglogistic	exponential	lognormal
Cohort A	olaparib	21.85	19.11	23.72	19.28	35.86	36.06	46.99
Cohort A	RPSFTm NHA	14.27	14.07	14.94	17.02	19.89	20.48	20.49
	gain	*7.58*	*5.04*	*8.78*	*2.26*	*15.97*	*15.57*	*26.51*

3.6.1.3 PROfound cohort A+B

In clarification the company kindly supplied a KM plot for olaparib and RPSFTm NHA arms together with Weibull model parameters for Cohort A+B. The graph is shown in Table 35 (left). The number of patients in each arm corresponded to the CS. The ERG used the same methods as described above for the prior taxane A+B population to analyse OS in cohort A+B. Company and ERG Weibull models showed concordance (Table 35).

Table 35. KM plot for olaparib and RPSFTm NHA arms Cohort A+B

RPSFTm NHA arm supplied in clarification	CS and ERG Weibull models of OS
[redacted]	[redacted]

IC scores for the parametric models shown in Table 36 indicate that across both arms Rayleigh and Weibull models provide the best fits.

Table 36. Best fit parametric model Cohort A+B

	Olaparib				RPSFTm NHA					
Model	Obs	AIC	BIC	sum	Obs	AIC	BIC	sum	sum of sums	rank
ggamma	256	422.05	432.69	854.74	131	267.35	275.98	543.33	1398.06	5
exponential	256	452.42	455.96	908.38	131	280.07	282.95	563.02	1471.40	8
Weibull	256	421.16	428.25	849.42	131	266.93	272.68	539.60	1389.02	2
Gompertz	256	420.91	428.00	848.91	131	273.88	279.63	553.51	1402.42	6
lognormal	256	448.11	455.20	903.31	131	266.88	272.63	539.50	1442.81	7
loglogistic	256	424.93	432.02	856.95	131	264.50	270.25	534.76	1391.71	3
bt	256	416.28	426.91	843.19	131	271.57	280.19	551.76	1394.95	4
Rayleigh	256	417.29	424.38	841.67	131	269.57	275.32	544.89	1386.55	1

Table 37. Cohort A+B: 15 year mean survival according to treatment arm and model

POPULATION	INTERVENTION	parametric model						
		Rayleigh	Weibull	loglogistic	GGAMMA	Gompertz	lognormal	exponential
Cohort A+B	olaparib	19.05	19.60	26.57	18.54	17.56	33.70	30.72
Cohort A+B	RPSFTm NHA	13.64	14.23	18.68	15.75	13.50	19.20	18.95
	gain	*5.41*	*5.37*	*7.89*	*2.79*	*4.06*	*14.50*	*11.76*

Mean survival with olaparib for Cohort A+B is less than for Cohort A. Loglogistic models result in greater benefit relative to NHA than is seen for Rayleigh and Weibull models.

3.6.1.4 CARD trial (cabazitaxel vs. NHA) population received prior taxane

The same methods as above were employed for the CARD trial OS.

	Cabazitaxel arm			CARD NHA arm			Sum of sums	
	AIC	BIC	sum	AIC	BIC	sum		rank
loglogistic	235.02	240.74	475.76	244.55	250.22	494.77	970.53	1
Weibull	237.68	243.40	481.09	244.46	250.13	494.58	975.67	2
ggamma	237.90	246.47	484.37	245.28	253.79	499.07	983.44	3
Rayleigh	239.90	245.62	485.51	246.72	252.40	499.12	984.64	4
lognormal	240.53	246.25	486.78	248.40	254.08	502.48	989.26	5
bt	241.90	250.48	492.37	248.72	257.23	505.96	998.33	6
Gompertz	247.78	253.50	501.27	255.30	260.97	516.27	1017.54	7
exponential	259.94	262.80	522.74	273.02	275.85	548.87	1071.61	8

Rayleigh, Weibull and loglogistic models for each arm are shown in Figure 4. Loglogistic models provide more optimistic survival for both arms.

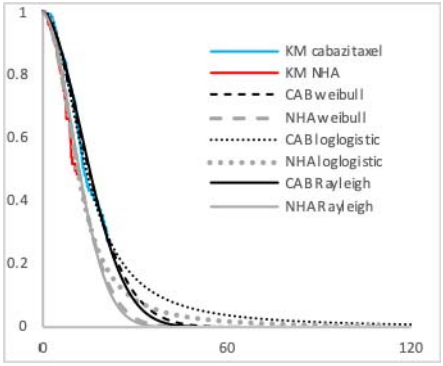


Figure 4. Rayleigh Weibull amd loglogistic models

The gain in mean survival from cabazitaxel over NHA is also greater for loglogistic models

	Weibull	loglog	Rayleigh
Gain cabazitaxel vs NHA	3.81	4.72	3.61

The difference in gain over NHA for olaparib in the PROfound target poplation relative to cabazitaxel in CARD was more than double for loglogistic models than for either Weibull or Rayleigh models.

15 yr gain in months	Weibull	loglog	Rayleigh
Gain olaparib vs cabazitaxel	2.48	5.79	2.25

Across all four arms Schoenfeld residual analysis yielded similar P values to those reported in the CS.

Proportion hazards plot showed that the plot for the olaparib arm crossed the plot for each of the other three arms at least once (Figure 5) with poorer PH correspondence at early times.

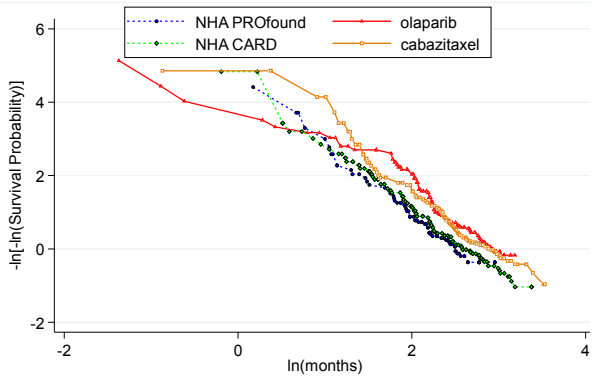


Figure 5. Proportion hazards plot
Cumulative hazard plots are shown in Appendix 1.

Table 38 summarises mean survival over a 15 year time horizon according to model and population

Table 38. Mean survival over a 15 year time horizon according to model and population

POPULATION	INTERVENTION	parametric model						
		lognormal	Weibull	loglogistic	Gompertz	exponential	Rayleigh	GGAMMA
prior Taxane A+B	olaparib	30.06	18.08	24.49	16.50	26.21	17.49	17.29
prior Taxane A+B	RPSFTm NHA	20.38	14.75	19.76	13.86	20.50	14.07	16.93
	gain	*9.68*	*3.33*	*4.73*	*2.64*	*5.71*	*3.42*	*0.36*
Cohort A + B	olaparib	33.70	19.60	26.57	17.56	30.72	19.05	18.54
Cohort A + B	RPSFTm NHA	19.20	14.23	18.68	13.50	18.95	13.64	15.75
	gain	*14.50*	*5.37*	*7.89*	*4.06*	*11.76*	*5.41*	*2.79*
Cohort A	olaparib	46.99	23.72	35.86	19.11	36.06	21.85	19.28
Cohort A	RPSFTm NHA	20.49	14.94	19.89	14.07	20.48	14.27	17.02
	gain	*26.51*	*8.78*	*15.97*	*5.04*	*15.57*	*7.58*	*2.26*
CARD	cabazitaxel	20.46	17.03	20.08	16.81	21.69	16.76	17.61
CARD	NHA	14.98	13.21	15.36	13.09	15.74	13.15	13.41
	gain	*5.48*	*3.81*	*4.72*	*3.72*	*5.95*	*3.61*	*4.19*
Parker	Ra 223	22.19	17.79	22.52	17.21	22.56	17.29	19.71

3.6.1.5 KM data for OS, PFS and TTD

In a second clarification response from the company (received 15 07 20) KM data for OS , PFS and TTD were provided aggregated to monthly intervals for cohorts A, A+B , and prior taxane A+B cohorts of PROfound. The ERG is uncertain of any merit in aggregating the data to monthly intervals. The ERG used this data to model PFS and TTD with parametric distributions. Model fit was assessed according to information criteria; models are presented in the ERG economic section and summarised in APPENDIX 3.

3.6.1.6 Cohort B

Because the clarification document supplied the number of censorings and events at each month for cohort A+B and for cohort A it was possible by subtraction to derive these event and censoring values for cohort B; this was done for PFS. The derived numbers correspond to those expected from data presented in CS Figures 6. PFS models (APPENDIX 4) suggest zero or very meagre advantage for olaparib vs. NHA for this primary outcome in cohort B.

3.6.1.7 CS modelling of OS for olaparib and cabazitaxel

To obtain a model for survival with cabazitaxel treatment, the CS applied an ITC derived HR of 1/0.7 to a loglog model of olaparib survival in the prior taxane A+B subgroup from PROfound. From the economic model this appears to have been implemented as : $S_{cab} = (S_{olap})^{\wedge HR}$; the HR used being 1/0.7. The ERG suggest this procedure is questionable; firstly applying a time invariant HR to a loglog model is not appropriate and as applied seems liable to produce erroneous results. To test the reasonableness of the method the ERG examined data for the subgroups of PROfound and CARD for which the CS has supplied HRs for olaparib and cabazitaxel vs. NHA or RPSFT NHA (summarised in Table 39). If the CS method is valid then applying the appropriate HR to one loglog model should generate the comparator arm loglog model.

Table 39. Hazard ratios reported in the CS

Cohort	CS HR olaparib vs. RPSFT NHA
Prior taxane A+B	[redacted]
A+B	[redacted]
A	[redacted]
	CS HR cabazitaxel vs. NHA
CARD trial	[redacted]

Figure 6. Hazards for loglog models of each arm in the prior taxane A+B cohort

[redacted]

Figure 7. Prior taxane A+B cohort. Loglogistic models were fit with treatment as covariate. Time invariant HR was applied to each loglog model.

The ERG analysis demonstrates that the hazards for loglog models of each arm in the prior taxane A+B cohort vary through time, as also does the ratio of the loglog model hazards (Figure 6 right). If the time invariant CS HR of 0.444 is applied to the loglog model for the NHA arm, the resulting model does not tally with the loglog model for the comparator (Figure 6 left) and over estimates survival. When the reverse procedure is undertaken (Figure 6 centre) the result underestimates the survival for the NHA arm. Changing the HR (from 0.444 to 0.647) minimises the difference between model and HR-adjusted model but fails to provide good fit (middle lower row Figure 7.). Time invariant HRs for cohorts A+B and for A produce similar results (**APPENDIX 5**).

Loglogistic models provide a good fit to reconstructed OS KM for both arms from CARD (cabazitaxel vs. NHA). Again however the loglog model hazards and the ratio of hazards vary through time and application of a time constant HR does not generate the appropriate loglogistic survival models. See the right hand diagram in Figure 8.

Figure 8. Application of time invariable HR to loglogistic models of CARD arms

On the basis of these results it seems unlikely that applying the ITC HR of 0.7 (prior taxane A+B cohort vs. cabazitaxel) to the loglog model for the olaparib arm will generate a reliable or meaningful loglog model for survival with cabazitaxel.

In contrast to the loglog model HR adjustment, when this procedure is applied to models that have a proportional hazards property (e.g. Weibull exponential and Rayleigh) the HR adjusted models conform to the appropriate comparator as would be expected. (Weibull models of OS in olaparib and NHA arms of the prior taxane A+B cohort are shown in APPENDIX 4).

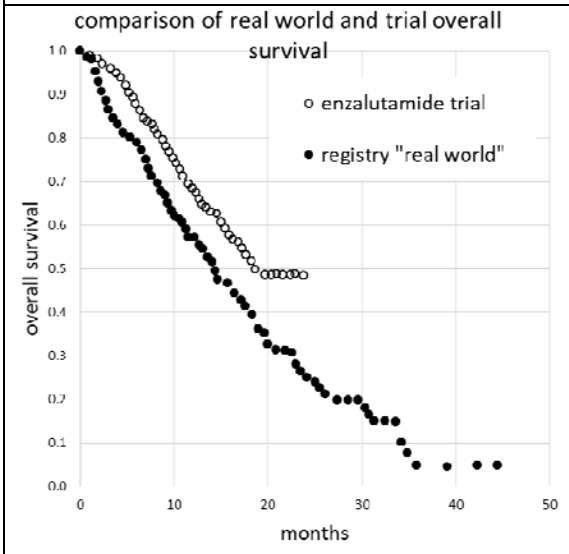
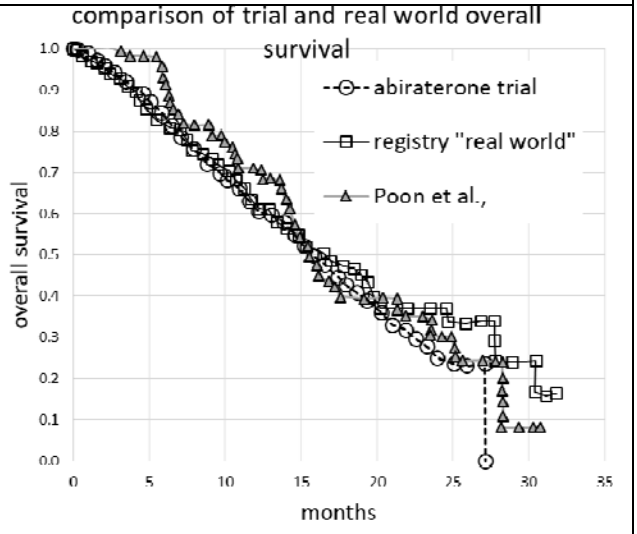
3.6.1.8 CS selection of loglogistic models of OS for the economic modelling

The CS explored survival in the olaparib arm of the prior taxane A+B subgroup by generating parametric fits to the PROfound trial data and then selecting the fit judged most near to clinicians' averaged survival predictions of 35% at 3 years, 21% at five year and 6% at 10 years. A loglogistic model was thereby selected and interpreted to reflect likely "real world" performance of olaparib; this model provided a poor fit to the trial data and scored poorly by AIC and BIC scores; the model departs from trial data after about 14 months. It should be borne in mind that the CS did not present published evidence to support these predictions. The methods used to obtain these averaged clinician predictions are discussed in detail in the

ERG cost effectiveness section. Median survival in the trial was 15.8 months (CS Figure 13) whereas that predicted by clinicians' predictions was approximately 58% greater (24.9 months).

The credibility of the clinicians' predictions might be enhanced should there be evidence of superior survival in a real world setting versus the clinical trial setting for post chemotherapy treatment(s) in mCRPC. A search for NHA treatments yielded three full publications presenting overall survival Kaplan-Meier plots that specifically compared real world and trial OS; the ERG digitised these and the results are summarised in Table 40.

Table 40. Real world vs. trial OS in post chemotherapy mHRPC treated with NHAs.

Alghazali et al., 2019	Svensson et al., 2016 and Poon et al., 2016
	

Alghazali et al., 2019 [45] compared trial and real world Swedish registry data and found that enzalutamide performed less well in the real world setting (median survival 14.3 months,) than in the clinical trial (median 18.4 months). Similarly, no superiority was seen for real world abiraterone treatment relative to clinical trial in a Swedish Registry study (Svensson et al., 2016 [46]) or a study of Hong Kong patients (Poon et al., 2016 [47]) Table 41.

Table 41. Median OS reported in post chemotherapy "real world" studies

Study	drug	Real world median OS vs. trial median	Mean age
Alghazali et al., 2019	enzalutamide	14.3 [11.00–18.20] vs. 18.4*	72 vs. 69
Svensson et al.,	abiraterone	16.6 vs. 15.8 [14.8 – 17.0]**	70.9 vs. 69
Poon et al.,	abiraterone	15.5 [13.8 – 23.6] vs. 15.8 [14.8 – 17.0]**	66 vs. 69

* Scher et al., 2012 [48] ** Fizzazi et al., 2012 [49]

Several Jansen sponsored abstracts reported real-world median survival for abiraterone, however no Kaplan-Meier plots were identified in these abstracts. The largest study [50] (N =553; median age 71 years) reported median OS of 18.2 (5% CI: 15.4 – 20.6) months, an improvement of 15.2% over the clinical trial median (15.8 months).

3.6.1.9 Summary of CS base case modelling of OS

The CS modelling of OS is questionable in that it has poor fit to the observed data, its selection is founded on a clinical opinion exercise that does not appear robust, and its implementation required application of a time constant HR to a loglogistic model that does not support proportional hazards. Other parametric models lacking these disadvantages such as Weibull and Rayleigh appear more appropriate. Rayleigh model parameters are summarised in Appendix 6.

3.7 Conclusions of the clinical effectiveness section

The CS changed the scope of the STA by moving the positioning of docetaxel to make treatment with docetaxel an eligibility criterion for the population rather than for the comparator treatment. While the ERG think this change to scope is acceptable it does differ from the marketing authorisation currently in place for Olaparib in terms of the focus on prior use of taxane treatment.

The ERG considers that the CS systematic review is at high risk of bias due to unclear inclusion criteria, imprecision in specification of methods, and reliance on a single reviewer for final study selection and extraction.

There is a lack of RCT evidence around the comparator treatments (radium-223, cabitaxel and docetaxel) in people with mCRPC who have HRR gene alterations. It is unclear whether the comparator treatments interact in those with HRR gene alterations in the same way as Olaparib so it is hard to draw any conclusions on the effectiveness in this population.

Evidence for the clinical effectiveness of olaparib was presented from a single RCT (PROfound). The use of an open-label study design in PROfound is suboptimal, with the potential to introduce bias. No consideration is given to the different levels at which blinding can take place, or alternative study designs.

PROfound included Cohort A: comprising men with mutations (germline or somatic) to 3 HRR genes (ATM, BRCA1, BRCA2), and Cohort B: comprising men with mutations (germline or somatic) to 12 other HRR genes. However the company's *"target population"* was the prior taxane subgroup from cohort A+B. Overall, cohort A had better outcomes than cohort B (where presented). The choice of the "prior taxane, A+B" cohort as the target population appears to have been made " *to align with the anticipated positioning of olaparib in the current clinical pathway of care in England (where the majority of patients receive a taxane [docetaxel] for non-metastatic or metastatic HSPC, before receiving NHA for mCRPC [CS pg 14]*. Relative to the full A+B population the CS choice of prior taxane usage reduces the size of the olaparib-eligible population but tends to increase the apparent effectiveness of olaparib in terms of PFS.

Evidence of efficacy is limited to Cohort A, extrapolation from Cohort A to Cohort B is not supported by the presented evidence. Evidence of the efficacy of olaparib in cohort A+B is driven by the benefits seen in cohort A only.

The company requested a change to the decision problem so that the overall population should include prior taxane use but, notwithstanding this have also asked "that consideration is given to the small group of patients who have not received a taxane prior to NHA under equality provisions".

However, in PROfound olaparib performs far less well in PFS in the "no-prior" than in the "prior" population:

[redacted].

The ERG note that because of the very small and highly selected numbers of patients recruited in the UK the generalisability of the findings from the PROfound study to the UK setting may be compromised.

The choice of comparator in PROfound is inadequate and not applicable to clinical practice as people with mCRPC are neither limited to nor likely to be retreated with NHA on which they have previously failed.

Effectiveness and economic analyses in the CS are based on the comparison of olaparib versus cabazitaxel using data from the PROfound and the CARD trials in each of which all patients received prior taxane (docetaxel).

Network meta-analysis was inappropriate as the assumption of transitivity is likely to be violated by differences in HRR mutation status of samples in the two studies. The two trials differ noticeably in terms of geography. The PROfound trial was Asia, Europe and North and South America, whereas the CARD trial was conducted exclusively in Europe. These geographic differences may be the cause of some of the apparent differences in subsequent treatments.

In summary, due to the quality of the indirect treatment comparison, the ERG considers that these indirect comparisons are inadequate for providing meaningful, statistically significant information on the comparison of olaparib and cabazitaxel for either rPFS or OS. This is important for the cost effectiveness modelling because it contributes to the ERG cost effectiveness.

4 COST EFFECTIVENESS

4.1 ERG comment on company's review of cost-effectiveness evidence

The company did not find any published UK cost effectiveness studies, but states that it did consider previous NICE mCRPC assessments to inform its modelling. The ERG thinks this is reasonable, particularly in the light of most of the identified cost effectiveness studies being of NHAs.

4.2 Summary of the company's submitted economic evaluation

4.2.1 NICE reference case checklist

Table 42: NICE reference case checklist

Element of health technology assessment	Reference case	ERG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Yes. No carer health effects are included.
Perspective on costs	NHS and PSS	Yes.
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Yes.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	[redacted] years. Very few patients are modelled as surviving to [redacted] years.
Synthesis of evidence on health effects	Based on systematic review	The company does not include consideration of the TOPARP-B 300mg arm. The OS and PFS curves for olaparib are based upon the olaparib arm of the PROfound study. The company ITC as summarised in the clinical effectiveness chapter provides OS and PFS hazard ratios for olaparib compared to cabazitaxel.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related	Yes. The pivotal trial's EQ-5D-5L data is cross walked to the UK social tariff

	quality of life in adults.	in the standard manner.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Yes.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Yes.
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	Yes.
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Yes.
PSS, personal social services; QALYs, quality-adjusted life years; EQ-5D, standardised instrument for use as a measure of health outcome.		

The company submission relies a lot upon the four company surveys of 6 UK experts. It is unclear whether the same experts were used for each telephone questionnaire, and whether all surveys were conducted during a single telephone questionnaire with each respondent or were conducted separately. The ERG will refer to each of these four surveys as:

- Company OS survey [51]
- Company G-CFS survey [52]
- Company resource use survey [53]
- Company mCRPC treatment survey [20]

4.2.2 Model structure

The company model is a partitioned survival analysis with a monthly cycle, and the usual three health states of:

- Progression free survival (PFS), in this case rPFS,
- Post progression survival (PPS)
- Dead

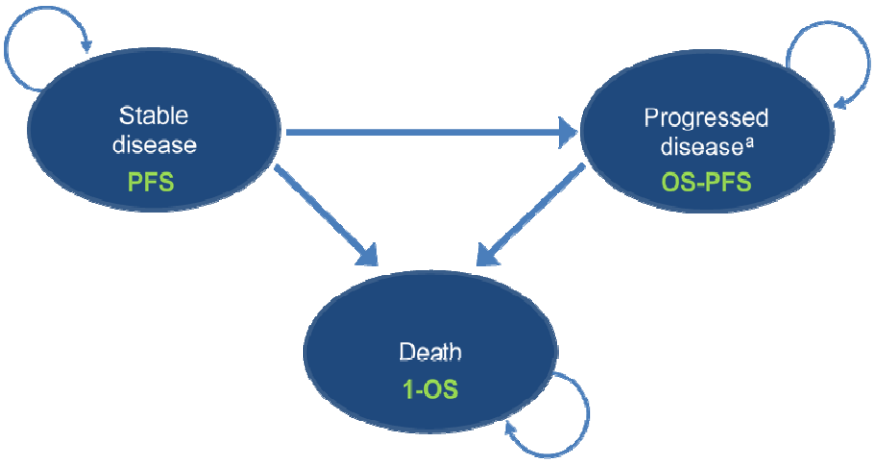


Figure 9: Company OS curves

The company model contains time to treatment discontinuation (TTD) curves which are not used for costing purposes for the company base case. The company base case assumes treatment is stopped at measured rPFS.

4.2.3 Population

The anticipated EMA license for olaparib is [redacted]

The company models a subgroup of the PROfound trial population: Cohort A+B with prior taxane use. The company argues that this is aligned with the patient population in England and Wales who would be eligible to receive cabazitaxel.

For the economic model the relevant patient baseline characteristics are: 67 years of age, [redacted] weight and 2.01m^2 body surface area (BSA).

4.2.4 Interventions and comparators

Olaparib is compared with cabazitaxel.

4.2.5 Perspective, time horizon and discounting

The perspective and discounting are as per the NICE methods guide. The time horizon is [redacted] years. In the company base case by [redacted] years [redacted] survive in the olaparib arm and [redacted] survive in the cabazitaxel arm.

4.2.6 Treatment effectiveness and extrapolation

4.2.6.1 Treatment effectiveness and extrapolation: OS olaparib

The ITC that provides the hazard ratios for cabazitaxel relies upon the PROfound trial Kaplan Meier (KM) data, adjusted for cross-over. This analysis fitted Weibull curves simultaneously to the olaparib arm and the control arm, assuming proportionate hazards. The company argues that for cost effectiveness modelling of the olaparib arm this proportionate hazards Weibull analysis is not relevant and that the olaparib arm should be viewed in isolation. As a consequence, the company fits the usual set of parameterised curves to the PROfound olaparib arm Cohort A+B OS KM data.

Figure 10: Company olaparib OS KM data and OS curves over 2 years

To help judge between the above curves the company conducted a telephone questionnaire survey of 6 English experts who were asked about the proportions of mCRPC patients previously treated with NHA that are likely to survive at 3, 5 and 10 years when treated with (a) standard of care (SoC), (b) radium-223, (c) cabazitaxel and (d) olaparib. The PROfound olaparib Cohort A+B prior taxane subgroup OS KM curve was presented during this exercise. The average of the respondents' midpoints for olaparib at 3, 5 and 10 years (4, 3 and 3 respondents respectively) were [redacted] respectively.

The parameterised curves extrapolated over the [redacted] year time horizon are shown in [redacted] below.

Figure 11: Company olaparib OS curves extrapolated to 15 years

The average of the parameterised curves' OS at 3, 5 and 10 years is presented in Table 43 below alongside the average of the respondents' midpoints, coupled with the AIC+BIC information criteria total.

Table 43: OS fitted curves' OS and AIC+BIC: Olaparib arm: Cohort A+B prior taxane

Curve	3 year	5 year	10 year	AIC+BIC[2]
Exponential	[redacted]	[redacted]	[redacted]	1248.2
Weibull	[redacted]	[redacted]	[redacted]	1215.3
Log-logistic	[redacted]	[redacted]	[redacted]	1222.5
Log-normal	[redacted]	[redacted]	[redacted]	1255.1
Gompertz	[redacted]	[redacted]	[redacted]	1214.4
Generalised gamma	[redacted]	[redacted]	[redacted]	1220.4
Respondent midpoint average	[redacted]	[redacted]	[redacted]	..

The Weibull and the Gompertz have the lowest total AIC+BIC. The generalised gamma has the next highest total AIC+BIC. The company rejects these due to their 3, 5 and 10 year survival estimates not corresponding with the respondents' midpoints' average. Of the three remaining curves with the

[2] Separate AIC and BIC not given due to reasons of space. See CS Doc B page 122 Table 25 for values.

highest total AIC+BIC, the total AIC+BIC is lowest for the log-logistic. The company selects the independently fitting olaparib log-logistic OS curve for its base case.

4.2.6.2 Treatment effectiveness and extrapolation: OS cabazitaxel

The company applies the ITC OS HR of [redacted], the reciprocal of [redacted], to the olaparib log-logistic OS curve to derive the cabazitaxel OS curve: OS $S(t)_{CABA}$=OS $S(t)_{OLAP}$^[redacted].

4.2.6.3 Treatment effectiveness and extrapolation: PFS olaparib

In common with the OS curve, the company fits the usual set of curves to the rPFS Kaplan Meier curves as shown below.

Figure 12: Company olaparib rPFS KM data and rPFS curves over 2 years

These have the following AIC and BIC.

Curve	AIC	BIC	AIC+BIC
Exponential	768.5	771.6	1540.1
Weibull	756.3	762.6	1518.9
Log-logistic	760.2	766.5	1526.7
Log-normal	758.9	765.2	1524.1
Gompertz	761.3	767.6	1528.9
Generalised gamma	756.7	766.1	1522.8

The company chooses the Weibull for its base case, because it has the lowest total AIC+BIC. The curves extrapolated to 5 years are shown below, there being little point showing the extrapolation beyond this to the [redacted] year time horizon.

[redacted]Figure 13: Company olaparib rPFS curves extrapolated to 5 years

As in the OS analysis, the Weibull largely lies below the log-logistic, with the separation for PFS occurring a little before the 1 year point.

4.2.6.4 Treatment effectiveness and extrapolation: rPFS cabazitaxel

The company applies the ITC PFS HR of [redacted], the reciprocal of [redacted], to the olaparib Weibull rPFS curve to derive the cabazitaxel PFS curve: rPFS $S(t)_{CABA}$=rPFS $S(t)_{OLAP}$^[redacted].

4.2.6.5 Treatment effectiveness and extrapolation: Base case curves

The extrapolation of the olaparib OS log-logistic and the olaparib PFS Weibull to [redacted] years, coupled with the [redacted] OS HR and [redacted] rPFS HR for cabazitaxel results in the following base case curves. It shows that there is some separation between the modelled rPFS curves, and a much larger separation between the modelled OS curves.

Figure 14: Company base case OS and PFS curves

These result in the following base case undiscounted PFS, PPS and OS months' survival[3].

Table 44: Company base case curves: Undiscounted months survival

	PFS	PPS	Total
Cabazitaxel	[redacted]	[redacted]	[redacted]
Olaparib	[redacted]	[redacted]	[redacted]
Net gain	[redacted]	[redacted]	[redacted]
As % total net gain	20%	80%	

The company base case anticipates that olaparib will result in an additional [redacted] month total overall survival. Relatively little of the gain occurs when patients are in rPFS and being treated with olaparib: only [redacted] months or 20%. The vast majority of the modelled gain, [redacted] months or 80%, is realised due to increase survival after progression when treatment with olaparib has stopped.

[3] Note that these differ from those reported in the *Results* worksheet, and are taken from the *Model_Calcs* worksheetEE13:EE14 multiplied by 12.

4.2.6.6 Olaparib time to treatment discontinuation

The company base case assumes that rPFS is synonymous with treatment duration. The company provides a scenario analysis that estimates parameterised TTD curves from the PROfound KM data for the olaparib arm.

Figure 15: Company olaparib TTD KM data and TTD curves over 2 years

These have the following AIC and BIC.

Table 45: Company scenario TTD curves' information criteria

Curve	AIC	BIC	AIC+BIC
Exponential	890.2	893.4	1783.6
Weibull	876.2	882.5	1758.7
Log-logistic	888.7	895.0	1783.7
Log-normal	907.5	913.8	1821.3
Gompertz	877.5	883.8	1761.3
Generalised gamma	877.4	886.8	1764.2

The company chooses the Weibull for its scenario analysis, because it has the lowest total AIC+BIC. As shown in Figure 16 below, the Weibull, gamma and Gompertz lie some way below and so result in lower treatment costs than the exponential, log-normal and log-logisitic.

Figure 16: Company olaparib TTD curves extrapolated to 5 years

The TTD Weibull can be compared with the PFS Weibull, as in

Figure 17 below.

Figure 17: Company olaparib Weibull PFS and Weibull TTD curves extrapolated to 5 years

In common with the Kaplan Meier data (not shown), the TTD Weibull lies a reasonable distance above the PFS Weibull. Using the PFS curve for costing rather than the TTD curve reduces costs in the olaparib arm.

There are no corresponding cabazitaxel TTD curves within the company model.

4.2.7 Health related quality of life

4.2.7.1 Health related quality of life: main health states

The quality of life values for the main health states in the olaparib arm are taken from the PROfound trial. It appears that the values used are not specific to the olaparib arm or to the Cohort A+B prior taxane target group.

PROfound collected EQ-5D-5L data, and this was mapped to the EQ-5D-3L using the standard cross walk approach, and valued using the standard UK social tariff. A linear mixed effects model was used to estimate mean values for PFS and PPS.

The economics model includes a quality of life decrement for ongoing treatment with cabazitaxel to account for the disutility of intravenous administration. This is taken from Matza et al[4] [54] who conducted a time trade off study among 121 members of the UK general population.

This results in the following main quality of life values:

- [redacted] for PFS;
- [redacted] for PPS; and,
- A decrement of -0.023 for ongoing treatment with cabazitaxel.

Both the PFS quality of life and the PPS quality of life are constant over the model time horizon.

4.2.7.2 Health related quality of life and cost: adverse events

For reasons of space the quality of life impacts and costs of adverse events are presented together. Adverse event rates were taken from the PROfound olaparib arm Cohort A+B prior taxane use patients, and from CARD for cabazitaxel. The QoL decrements and durations of events were taken from a variety of sources in the literature. Unit costs were largely based upon NHS reference costs.

Table 46: Adverse event rates, disutilities and costs

AEs	Olaparib	Cabazitaxel	QoL	Days	Cost
Anaemia	[redacted]	8.0%	-0.125	6.46	£565
Infection	[redacted]	7.9%	-0.090	7.00	£494
Leukopenia	[redacted]	5.0%	-0.090	4.65	£431

[4] Sponsored by Amgen

Neutropenia	[redacted]	5.0%	-0.090	1.90	£431
Musculoskeletal pain/discomfort	[redacted]	1.6%	-0.069	9.55	£377
Thrombocytopenia	[redacted]	3.2%	-0.090	5.88	£545
Febrile neutropenia	[redacted]	3.2%	-0.120	6.20	£997
Diarrhoea	[redacted]	3.2%	-0.047	4.32	£446
Fatigue/asthenia	[redacted]	4.0%	-0.094	6.46	£337
Total QALYs lost	[redacted]	-0.00062			
Total AE Cost	[redacted]	£210			

As shown in Table 46, adverse events have minimal effect upon the net QALYs and the net costs of the company base case.

4.2.7.1 Health related quality of life and cost: SSREs

For reasons of space the quality of life impacts and costs of SSREs are presented together. The rates of 1st SSREs was taken were taken from the PROfound olaparib arm Cohort A+B prior taxane use patients, and from CARD for cabazitaxel. The company submission states "*the distribution of each SSRE was not analysed in PROfound*", so the distribution of these events between the type of SSRE was based upon applying the means of the proportions reported during the abiraterone COU-AA-301 trial and the enzalutamide AFFRIM trial. Quality of life decrements were taken from the literature. Events were assumed to last for one month and were valued using NHS reference costs.

Table 47: SSRE rates, disutilities and costs

		Olaparib	Cabazitaxel			
Proportion	Dist\rate	[redacted]	18.6%	QoL	Days	Cost
Spinal Cord Compression	15.5%	[redacted]	2.9%	-0.555	30.44	£6,184
Pathological Bone Fracture	12.9%	[redacted]	2.4%	-0.130	30.44	£3,752
Radiation to the Bone	70.5%	[redacted]	13.1%	-0.070	30.44	£713
Surgery to the Bone	2.7%	[redacted]	0.5%	-0.130	30.44	£4,196
Total QALYs lost		[redacted]	-0.0137			
Total SSRE Cost		[redacted]	£382			

As shown in Table 47, SSREs have minimal effect upon the net QALYs and the net costs of the company base case.

4.2.8 Resources and costs

4.2.8.1 Direct drug and concomitant medication costs

Olaparib has a list price of £2,317.50 per 56 tablet pack. With a daily dose of 4 tablets this results in a 4 weekly cost of £4,365 and an annual cost of £60,462.

Cabazitaxel is BSA dependent, 25mgm^{-2} and G-CSF is weight dependent; 0.5mukg^{-1} respectively, with a mean patient weight of [redacted]. The company base case assumed no wastage of cabazitaxel due to vial sharing.

For the base case each cabazitaxel administration is assumed to require 14 days treatment with G-CSF as primary prophylaxis for neutropenia, with 100% of patients requiring this based upon the CARD protocol and clinical expert opinion. The proportion requiring G-CSF is varied in sensitivity analyses to 79.5% based upon the UK EAP study. G-CSF is assumed to have a 100% relative dose intensity (RDI).

This results in the following costs per treatment cycle, taken to be 4 weeks for olaparib and 3 weeks for cabazitaxel per patient receiving a full dose.

Table 48: Direct drug costs per treatment cycle per full dose

	Weeks	Dose/cycle	Pack	Units	units/kg	unit/dose	Cost/cycle
Olaparib	4	56	£2,317	56	..	2	£4,635
Cabazitaxel	3	1	£3,696	60	25	50	£3,095
G-CSF	3	14	£84	48	0.5	40	[redacted]
Cabazitaxel total							[redacted]

In common with the other resource use estimates, the company conducted a telephone questionnaire of 6 UK respondents regarding cabazitaxel dosing and G-CSF use [52]. 5 respondents provided estimates, with 2 (40%) respondents suggest that cabazitaxel would be at a reduced dose of 20mgm^{-2}, with another respondent (20%) suggesting that this dose might be used to lower the risk of neutropenia. 2 respondents (40%) stated that they did not use G-CSF: one due to applying the lower 20mgm^{-2} cabazitaxel dose and one due to budgetary restrictions. The company model does not apply these.

Both olaparib and cabazitaxel are associated with RDIs which reduce the drug use and costs: [redacted] for olaparib taken from the PROfound Cohort A+B prior taxane group, and 92.6% for cabazitaxel based upon TA391 and the TROPIC trial. The RDI for G-CSF was assumed to be 100%.

There is a [redacted] olaparib PAS, which reduces the annual cost to [redacted]. Cabazitaxel and other treatments within the model such as radium-223 also have PASs. This document only applies the

cabazitaxel PAS and costs all other treatments at list prices. The ERG provides a confidential cPAS appendix that applies all the relevant price discounts.

Table 49: Direct drug costs per model cycle and per year

	Cost/cycle	RDI	PAS	Cost/cycle	Cost/mth	Cost/year
Olaparib	£4,635	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cabazataxil	£3,095	92.6%	..	£2,866	£4,154	
G-CSF	[redacted]	100%	..	[redacted]	[redacted]	
Cabazitaxel total	[redacted]			[redacted]	[redacted]	

Cabazitaxel is limited to a maximum of ten 3 week treatment cycles, the model containing an adjustment which allows for this duration not corresponding with a whole number of the model's monthly treatment cycles.

There are additional concomitant medications costs for cabazitaxel related to antihistamine, H2-antagonist, anti-emetic and corticosteroid. These are minor, do not materially affect results and are not itemised here[5].

4.2.8.2 PFS administration and monitoring costs

PFS administration and monitoring costs were based upon the company resource use telephone questionnaire survey of 6 UK experts [53]. It is unclear whether these were the same 6 expert respondents who participated in the OS elicitation telephone questionnaire survey [51], but this seems likely to be the case.

Respondents were presented with a list of resource use by treatment; olaparib on treatment 1st 3 months, olaparib on treatment thereafter, cabazitaxel on treatment, off treatment and best supporting care (BSC) though this latter may also have been presented as palliative care. Respondents could add to the company list as they felt it necessary, but it appears that none did. It is unclear what information was provided with regards olaparib, why the 3 month breakpoint was chosen or if respondents were provided with a draft olaparib SmPC. Respondent's estimates were averaged, 4 providing estimates for olaparib and 5 for cabazitaxel. Resource use was largely valued using NHS reference costs, resulting in the following means and total monthly costs.

Table 50: Administration and monitoring resource use and monthly costs

	Olaparib				
Monitoring Costs	1st 3mth	Mth 4+	Caba. OnTx	Off Tx	Cost
Outpatient visit consultant	[redacted]	[redacted]	[redacted]	[redacted]	£244.84
Non-consultant follow-up visit	[redacted]	[redacted]	[redacted]	[redacted]	£92.95

[5] See CS Doc B Table 42 page 163 and

CT scan	[redacted]	[redacted]	[redacted]	[redacted]	£105.37
Bone scan	[redacted]	[redacted]	[redacted]	[redacted]	£263.59
Full blood count	[redacted]	[redacted]	[redacted]	[redacted]	£2.79
Liver function test	[redacted]	[redacted]	[redacted]	[redacted]	£1.10
Kidney function test	[redacted]	[redacted]	[redacted]	[redacted]	£1.10
Prostate specific antigen (PSA)	[redacted]	[redacted]	[redacted]	[redacted]	£1.10
Chemistry panel	[redacted]	[redacted]	[redacted]	[redacted]	£1.10
Monthly cost	[redacted]	[redacted]	[redacted]	[redacted]	

Note that the company table did not ask about concomitant G-CSF use with cabazitaxel, as this was covered by the separate telephone questionnaire mentioned in section 4.2.8.1 above.

On treatment monitoring costs for cabazitaxel are somewhat higher than those of olaparib mainly due to an increased visit frequency and a need for more CT scans and bone scans.

The model applies an administration cost per cabazitaxel administration of £362, based upon the NHS reference cost SB15Z: Deliver subsequent elements of a chemotherapy cycle. No administration costs are included for olaparib.

4.2.8.3 PPS costs: Active treatments and Best Supportive / Palliative Care

The distribution of active treatments received after progression was taken from the PROfound and CARD trials. The average duration of each treatment was taken from the literature. This results in the following mean costs among patients receiving an active treatment upon progression.

Table 51: PPS active treatment costs

	Monthly	Months	Cost	Olaparib	Cabazitaxel
Cabazitaxel	£4,747	5.06	£24,020	[redacted]	[redacted]
Docetaxel	£419	6.90	£2,887	[redacted]	[redacted]
Abiraterone	£2,973	7.40	£22,001	[redacted]	[redacted]
Enzalutamide	£2,973	8.30	£24,674	[redacted]	[redacted]
R223	£3,171	5.52	£17,502	[redacted]	[redacted]
Total				[redacted]	[redacted]
Total excluding NHAs				[redacted]	[redacted]

The company base case includes NHA post progression, despite the company noting that these are "*not reimbursed in England and does not reflect current standard of care*". A sensitivity analysis

which excludes PPS NHA use and increases the other treatments pro-rata results in the net savings from olaparib falling by roughly £400.

Based upon the resource use telephone questionnaire survey of 6 UK experts [53] the proportion of patients requiring the various resource use elements for best supportive care (BSC) or palliative care was as below.

Table 52: BSC/palliative care resource use and monthly costs

	Monthly	Proportion
Analgesics (co-codamol)	£4.08	[redacted]
Steroids (detamethasone)	£13.06	[redacted]
Palliative radiotherapy (external beam RT)	£573.65	[redacted]
Bisphosphonates (zoledronic acid)	£2.93	[redacted]
Anti-androgens (bicalutamide)	£4.37	[redacted]
Oestrogens (diethylstilbestrol)	£377.28	[redacted]
Advanced prostate cancer nurse specialist (NHS)	£642.52	[redacted]
Palliative nurse (Community)	£633.63	[redacted]
Blood transfusion	£521.00	[redacted]
ADT/LHRH	£75.24	[redacted]
Monthly BSC cost	[redacted]	

Active treatment was treated as a fixed cost, while total BSC costs were proportionate to the time spent in PPS. Both costs were conditioned by the proportion of those who progressed who received subsequent treatment. This was differentiated by arm based upon for PROfound for olaparib, [redacted], and CARD for cabazitaxel, 58%. So, among those modelled as surviving progression, if the total months PPS is T_O for olaparib and T_C for cabazitaxel, the total PPS costs are:

[redacted]

For the company base case the model estimates broadly the same proportion of patients, roughly 75%, surviving progression and incurring these costs. As a consequence, cabazitaxel incurs somewhat higher PPS active treatment costs, around £2k more than those incurred in the olaparib arm. The considerably longer time spent in PPS with olaparib, $T_O > T_C$, means that the BSC or palliative care costs in the olaparib arm are around £3k higher than those in the cabazitaxel arm.

4.2.8.4 Terminal care costs

One off terminal care costs of £2,060 are applied, based upon the TA391 cost uprated for inflation. These costs have minimal effect upon results.

4.3 ERG critique of the company's submitted economic evaluation

4.3.1 ERG cross check of submitted model structure

4.3.1.1 ERG model rebuild results

The ERG has rebuilt the company deterministic model using the company preferred set of assumptions, and gets a good agreement with the company results when the model errors summarised in section 4.3.1.2 below are applied in the ERG model rebuild: olaparib is estimated to result in QALY gains and cost savings, so dominates cabazitaxel.

Table 53: ERG cross check model rebuild

	Company model		ERG model rebuild	
	Costs	QALYs	Costs	QALYs
Cabazitaxel	[redacted]	[redacted]	[redacted]	[redacted]
Olaparib	[redacted]	[redacted]	[redacted]	[redacted]
Net	[redacted]	[redacted]	[redacted]	[redacted]
NHB at £30k/QALY	[redacted]		[redacted]	

4.3.1.2 Model errors

The company model is unusual. It has only a single Excel worksheet to model the patient cohort flow and distribution between the various health states for a single treatment. A Visual Basic for Applications (VBA) engine is then used to sequentially apply the comparator specific inputs to the patient cohort flow worksheet and then copy and paste the results as pure number to the results worksheet. This model structure requires extensive indirect indexing of model inputs through complicated formulae. There is no obvious reason to adopt this model structure in preference to the more usual, simple and transparent approach of having a cohort flow worksheet for each comparator that is being modelled. The model structure has also considerably complicated reliably revising it. The ERG urges the company to cross check the ERG revisions.

The lack of transparency may have contributed to the following errors.

- The olaparib monitoring costs incorrectly implement the higher monitoring cost during the first 3 months of treatment. Correcting this increases the on treatment monitoring costs in the olaparib arm from £1,343 to £1,767, so reduces the net savings by £425.

- Cabazitaxel has quite considerable concomitant medication costs due to G-CSF prophylaxis use to avoid neutropenia. These costs are not restricted to the ten 3 week cabazitaxel treatment cycles, but are applied to all patients who remain in PFS. Correcting this reduces the cabazitaxel concomitant medication costs from £8,376 to £5,944, so reduces the net savings by £2,432.
- BSC costs are conditioned by the arm specific proportion not receiving a subsequent treatment. The proportion receiving a subsequent treatment are modelled as receiving only one subsequent treatment and this is time limited, it is not for their entire post progression survival. These PPS active treatment costs also only include the direct drug and administration costs. Not including BSC subsequent to post progression treatment appears to be an error. Correcting this[6] reduces the net savings by £1,544.
- The NICE scope specifies: "*The economic modelling should include the cost associated with diagnostic testing in people with hormone-relapsed prostate cancer who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test*". The company includes a scenario analysis of a [redacted] test cost, which it states are "*the costs of the tumour BRCA (tBRCA) testing service for ovarian cancer that AstraZeneca are currently funding*". Within the model structure the test cost is added to the total costs in the olaparib arm for the company scenario analysis. This is an error because it does not take into account the prevalence of the relevant HRR genes in the population being tested; e.g. a prevalence of 27.9% and a test cost of [redacted] would imply an additional cost per olaparib patient of [redacted].
- Cabazitaxel administration costs do not take into account the lower 1st administration NHS reference cost, despite this being within the model. Correcting this reduces costs in the cabazitaxel arm by £108, so reduces the net savings by the same amount.
- The scenario analyses of costing olaparib based upon the time to treatment discontinuation (TTD) curve rather than the rPFS curve does not appear to work within the submitted model due to the model always taking the minimum value of the rPFS or the TTD curve[7]. This assumption is a key determinant of model outputs: applying the rPFS curve results in the olaparib drug costs of the company base case of [redacted] compared to [redacted] when the TTD curve is used: a net increase of [redacted].

[6] This subtracts the mean durations of PPS active drug treatments from the PPS.

[7] The ERG did query the implementation of this scenario analysis during clarification with the company suggesting that it still viewed the submitted model as being correct. Within the submitted model changing the dropdown in cell F38 of the *Efficacy* worksheet does alter the TTD curve values of column Q of the *Model Calcs* worksheet. But the direct drug costs are unaffected by this due to them being based upon column R of the *Model Calcs* worksheet which, being the minimum of the rPFS curve of column P and the TTD curve of column Q, is effectively equal to the rPFS curve of column P. For the TTD costing analysis the ERG removes the assumption of the TTD curve of column R being the minimum of rPFS and TTD, and sets it equal to the TTD curve. This also require the olaparib PFS QALYs to be based upon the PFS survival in BD13 and BE13.

Applying all the above corrections, bearing in mind that the TTD curves are not applied in the company base case, results in a net cost of [redacted], hence an ICER of [redacted] per QALY. Excluding the test costs from the corrections results in a net cost of [redacted], so an ICER of [redacted] per QALY.

4.3.2 Correspondence of written submission with cited references

4.3.2.1 PPS active drug treatments

The supplementary information to De Wit [28] reports that within CARD of the 129 patients randomised to cabazitaxel, 120 patients discontinued treatment. It also shows that of the 69 patients receiving a subsequent anticancer therapy 19 patients received palliative radiotherapy. Within the model palliative radiotherapy is accounted for under BSC costs. It can also be noted that in the olaparib Cohort A+B prior taxane group the 61 patients reported as receiving subsequent anti-cancer active treatment only covered active drug treatment.

Consequently, the ERG thinks that the appropriate numerator for calculating the proportion of cabazitaxel patients who receive drug treatments subsequent to progression is 50, hence 41.6%, rather than the company estimate of 57.5%. Correcting this reduces costs in the cabazitaxel arm from £9,106 to £6,599, and so increases the overall net costs by £2,508.

The ERG has also not managed to replicate the company balance between PPS treatments for cabazitaxel using the supplementary information to De Wit [28]. But applying the ERG estimates of the balance has relatively little effect upon costs.

4.3.2.2 G-CSF cost

The £84.06 cost of G-CSF is based upon the BNF list price for 48MU Neupogen. The drug tariff cost for 48MU is £79.90[8].

4.3.3 Correspondence of written submission with electronic model

The written submission generally provides a reasonable account of the electronic model, though the model errors should be borne in mind.

4.3.4 ERG commentary on company model, assumptions and inputs

4.3.4.1 Company expert survey: anticipated survival

The company surveyed six English experts through questionnaire teleconferences, with respondents being paid "*a fair market value*". They were asked about OS survival proportions at 3, 5 and 10 years among mCRPC NHA patients for treatment with 2nd line (a) standard of care, (b) cabazitaxel, (c) radium-223 and (d) olaparib:

[redacted]

[8] BNF NICE accessed 15 July 2020.

[redacted]

An obvious problem with the above question is that there is no mention of the genetic mutations of Cohort A or of the genetic mutations of Cohort B. It is unclear from the company cited reference [51] quite what was and was not communicated to respondents during the telephone questionnaire. The cited reference does not mention genetic mutation, with one of its conclusions being "[redacted]". As a consequence, it is unclear whether respondents answered the question above, or interpreted the question as being restricted to patients with the genetic mutations of Cohort A, the genetic mutations of Cohort B, prior taxane use, or a combination of all, some or none of the preceding characteristics. If any respondents did not implicitly include these characteristics, their responses may overestimate the OS proportions for the company target group: Cohort A+B prior taxane use.

To help inform respondents, they were shown the PROfound olaparib arm OS KM curve for the Cohort A+B prior taxane group, which showed [redacted] surviving at 12 months and [redacted] surviving at 24 months. Their responses are shown in Table 54 below. The company asserts that the respondents' midpoints are the most appropriate data to use and averages these to arrive at the pooled estimates.

Table 54: Company experts' OS midpoint estimates at 3, 5 and 10 years

Respondent	1	2	3	4	5	6	Mean
3 year OS							
SoC	[redacted]						
cabazitaxel	[redacted]						
radium-223	[redacted]						
olaparib	[redacted]						
5 year OS							
SoC	[redacted]						
cabazitaxel	[redacted]						
radium-223	[redacted]						
olaparib	[redacted]						
10 year OS							
SoC	[redacted]						
cabazitaxel	[redacted]						
radium-223	[redacted]						
olaparib	[redacted]						

An initial point to note is that only respondent 2, respondent 3 and respondent 4 provided a 5 year estimate and a 10 year estimate for olaparib. The individual responses for olaparib are graphed alongside the PROfound olaparib OS KM data and the parameterised curves that the company estimates using the PROfound olaparib OS KM data in

Figure 18 below.

Figure 18: Olaparib OS: company experts' predictions vs company parameterised curves

It is very difficult to understand how respondent 4 predicted a [redacted] survival at 3 years, given that the KM curve has already fallen to [redacted] by 1 year. The reasoning underlying the responses given by Respondent 2 are also difficult to understand.

The individual responses for cabazitaxel are graphed alongside the parameterised curves that the company estimates using the PROfound olaparib OS KM data, conditioned by the company [redacted] OS HR for cabazitaxel, in [redacted] below.

[redacted] Figure 19: Cabazitaxel OS: company experts' predictions vs company model

Due to cabazitaxel being currently widely used, it might be anticipated that respondents would be able to make better estimates of long term survival. The above shows that the company experts predict considerably higher survival with cabazitaxel than the company model predicts. This is particularly the case for respondent 4 throughout, with respondent 2 and respondent 5 also being somewhat above all the parameterised curves throughout.

It is invalid to concentrate upon the company experts' responses for olaparib, which by definition is conjecture, without simultaneously considering the company experts' responses for cabazitaxel. The majority of respondents suggest considerably greater survival with cabazitaxel than is modelled by the company preferred log-logistic curve. The ERG questions the reliability of respondent 2, respondent 4 and respondent 5. If these respondents are removed from the survey results, there is very little left.

The reasons for the apparent bias, or at a minimum lack of understanding, of respondent 2, respondent 4 and respondent 5 are unknown. It is possible that reasons for this bias or lack of understanding may have been inherent in the survey and that they have also affected the few remaining respondents, even if only to a lesser extent.

It can also be noted that SoC is estimated to be superior to both cabazitaxel and radium-223, when viewed according to the company preferred respondents' midpoints' average. SoC is also estimated to be roughly as good as olaparib at 3 years and at 5 years. The company experts appear to estimate that olaparib yields few if any survival benefits compared to SoC prior to year 5. This suggests that the company expert survey of anticipated survival is inaccurate, or olaparib confers few if any benefits relative to the current standard of care.

Given the above, the ERG thinks that the "*clinically plausible long term survival estimates*" of Document B Table 26 (page 124) and Table 27 (page 127) that the company uses to justify its preference for the log-logistic OS curve are difficult to credit.

It should be reiterated that the Weibull has a superior information criteria total of 1215.3 compared to the total for the log-logistic of 1222.5. A reasonably common situation in STAs is for one of the log distributions to have a superior internal fit to the KM data but for the AC to deem it to have an implausibly long tail when extrapolated over the model time horizon, and so for the AC to prefer the Weibull. The company base case reverses this, preferring one of the log distributions because of its long extrapolated tail, despite it having a worse internal fit to the KM data than the Weibull.

4.3.4.2 Probability of dying: log-logistic, Weibull and general population

The monthly olaparib probability of dying for the log-logistic and the Weibull as a multiple of that of the age matched male general population probability of death is presented in *[9].

[redacted]

[9] Note that due to the general population probability of death only being available on an annual basis, the ERG has derived monthly values by linearly smoothing the 11 values between the year end values.

Figure 20: Olaparib: Monthly probability of death relative to general population

Both the log-logistic and the Weibull suggest that the probability of death relative to that of the general population increases steeply during the 1st year. After the 1st year it continues to increase for the Weibull, until around year 6 when the general population probability of death starts to climb so reducing the ratio. The picture is very different for the log-logistic, with the probability of death relative to the general population peaking at the end of the 1st year, and declining steeply thereafter. By year 15, the monthly probability of death for the log-logistic has fallen to only [redacted] compared to 0.56% for the general population.

4.3.4.3 Choice of PFS and OS curves' functional forms

It is worth bearing in mind that within a partitioned survival analysis changing the PFS curve has no effect upon the OS curve. As a consequence, a shorter PFS can reduce drug costs without affecting overall survival and so not particularly affecting the total QALYs. For instance, the company base case applies Weibull PFS curves and log-logistic OS curves which results in a net monetary benefit at a willingness to pay of £30k/QALY of [redacted]. If the PFS curves are changed to be log-logistic the net monetary benefit roughly halves to [redacted].

4.3.4.4 PFS and PPS quality of life values: PROfound

From the information available, the ERG thinks that the most appropriate quality of life values are those of the company's mixed effects modelling analysis of the PROfound EQ-5D data. It is unclear whether this was a repeated measures analysis but the ERG assumes this to be the case.

4.3.4.5 PFS and PPS quality of life values: previous assessments

The ERG has reviewed the company submissions and ERG reports of previous STAs, and for those not available on the NICE website has sourced them through the NIHR website. TA412, TA376, TA387, TA259 and TA391 have had their quality of life values redacted. The TA316 original company submission and ERG report do not appear to be available on either the NICE website or the NIHR HTA website. As a consequence, it is not possible to assess whether the quality of life values of the current assessment are aligned these STAs.

The TA377 model structure for enzalutamide for mCRPC not previously treated with chemotherapy modelled post progression, PP1, and a progression after PP1, PP2. The quality of life value for PFS, 0.844, was taken from the PREVAIL trial, while those for PP1, 0.658, and PP2, 0.612, and palliative care, 0.500, were taken from the literature. Given the position sought, the PP1 and PP2 values are more relevant to the current assessment. They are both noticeably lower than the values of the current submission company base case. These values were drawn from Wolff et al [55] and Diels et al [56], and are summarised in the current company quality of life SLR, as per table 35 of the company submission. The ERG will supply a scenario analysis that applies these values, PP1 to the current model PFS health state and PP2 to the current model PPS health state.

If the lower quality of life for palliative care is applied in the current model it will reduce the total QALYs in both arms. Provided that the time spent in palliative care is similar in both arms this seems unlikely to affect the net QALYs.

The ERG report for TA391, cabazitaxel for mCRPC patients treated with docetaxel, notes "*The MS suggests that this result indicates that cabazitaxel therapy is not associated with a significant negative effect on utility, and may even improve it*". This appears to be based upon an analysis of EQ-5D data from the pivotal trial.

4.3.4.6 Cabazitaxel on treatment disutility

The disutility for those on cabazitaxel treatment, drawn from the time trade off study of Matza et al [54] of -0.023 is for an infusion of "at least" 30 minutes. Another estimate of -0.037 is provided for an infusion of 2 hours. The cabazitaxel SmPC specifies a 1 hour infusion for cabazitaxel. Given the health state descriptors the ERG thinks that the company chosen decrement is the most appropriate. The ERG will present a scenario analysis that increases the disutility for ongoing cabazitaxel treatment to -0.037.

4.3.4.7 Spinal cord compression ongoing QoL and cost

The company base case assumes that spinal cord compression only lasts one month. There is an argument that the QoL effects of SSREs during PROfound will have been captured in the EQ-5D data and as a consequence do not need to be separately accounted for. But it remains a concern that spinal cord compression may endure considerably longer than one month, with an ongoing QoL decrement

and large ongoing costs. Vertebral fractures may also be markers for some future spinal cord compressions. Since the company base case models a somewhat longer PPS for olaparib compared to cabazitaxel, not accounting for ongoing and increasing rates of spinal cord compression may bias the analysis in favour of olaparib.

4.3.4.8 Olaparib RDI and TTD curves

The company base case costs olaparib based upon the rPFS curve rather than the TTD curve. It also applies the mean olaparib RDI of [redacted] throughout the rPFS curve.

Each patient's RDI is calculated as the number of tablets consumed up to treatment discontinuation divided by the number of tablets that would be consumed at full dose, 4 per day, multiplied by the number of days to treatment discontinuation; i.e. it is based upon the individual's Time to Treatment Discontinuation (TTD). It seems logically inconsistent to apply RDI estimates that are based upon individual's TTDs to the rPFS curve. The ERG thinks that it is only reasonable to apply RDI estimates to the TTD curve.

There is also the concern that the clinical effectiveness data is based upon the observed treatment durations as per the TTD curve and not upon treatment durations equal to the PFS curve.

An alternative RDI measure is to ignore the individual patient data and estimate over the whole of the PROfound olaparib arm the total days on treatment excluding treatment holidays divided by the total days on treatment including treatment holidays, again based upon the TTD KM data. If this estimate is applied, the ERG thinks that it can only sensibly be applied to the TTD curve.

A further concern is that while treatment holidays and temporary dose adjustments will affect the number of olaparib tablets consumed, it will affect the number of olaparib packs that are dispensed considerably less and possibly not at all. There is an argument for applying an olaparib RDI of 100%.

Table 55: Olaparib RDI values

	Cohort A+B	Cohort A+B prior taxane
Minimum	[redacted]	[redacted]
Median	[redacted]	[redacted]
Maximum	[redacted]	[redacted]
Mean	[redacted]	[redacted]
Days	[redacted]	[redacted]

The company base case applies the Cohort A+B mean value. The company clarification response also notes that "[redacted]". It is not known

whether this affects the mean value in Table 55 for patients in the target Cohort A+B target population, but any impact seems likely to be minor and not to affect the median.

Based upon the 4th iteration of the company clarification response dated 24 July 2020, the mean RDI is a simple unweighted average across patients; i.e. a patient on treatment for 1 month with an RDI of 50% and a patient on treatment for 24 months with an RDI of 100% would be combined to yield a mean RDI of 75%. Weighting by exposure across these two patients would result in a mean RDI of 98%. The ERG thinks that it is more appropriate to weight patient RDIs by their exposure when calculating a mean RDI for use in the economic modelling.

Table 55 shows that there is considerable skew in the distribution of individual patient's RDIs. The median is considerably higher than the mean. The reasons for this cannot be confirmed without consideration of a scatterplot of individual patient's RDI against their treatment duration. But the ERG thinks it likely that patients who do badly and have a short time on treatment will tend to be those with a low RDI. As a consequence, applying the mean RDI to the modelled treatment duration curve will understate olaparib use during PROfound. The ERG thinks that the median RDI is a better measure of the typical patient experience over the period of the trial than the mean RDI.

The ERG base case will cost olaparib use using the median RDI and the TTD curve. The ERG will also present scenario analyses of separately applying: 100% RDI; the mean RDI; and, the mean days on treatment to the olaparib TTD curve. Additional scenario analyses applying: 100% RDI; the median RDI; and, the mean RDI to the olaparib PFS curve will also be provided. The values applied will be those of the Cohort A+B prior taxane group.

4.3.4.9 PROfound rPFS and TTD curves

The company provided monthly data cuts of the KM rPFS and TTD data are presented below for the Cohort A+B prior taxane group[10].

[redacted]

[10] The company clarification response of 02 July 2020 declined to provide any KM data. The company clarification response of 07 July 2020 provided 3 monthly data cuts of the KM data. The company response of 13 July 2020 provided monthly data cuts of the KM data. As of 21 July 2020 that ERG has not received the KM data requested at clarification and can only present the monthly amounts.

[redacted]

[redacted] Figure 21: rPFS and TTD curves

The TTD curve for both the olaparib arm of PROfound and the NHA arm of PROfound lie consistently above the corresponding rPFS curve. A similar pattern holds for Cohort A+B and for Cohort A. The PROfound study protocol[19] states that "*subjects may be discontinued from investigational product (IP) in the following situations: subject decision…, adverse event, severe non-compliance with the study protocol, bone marrow findings consistent with…MDS/AML, objective radiographic progression by …BICR, unequivocal clinical progression…, initiation of restricted anticancer therapy*". This appears to mean that patients were not obliged to cease treatment upon progression. No draft SmPC has been supplied but it is possible that it will not specify rPFS for olaparib treatment cessation. It may be relevant that the only references to discontinuation that the ERG can find in the abiraterone and enzalutamide SmPCs relate to adverse events. Other measures of progression may be used in clinical practice when treating patients with open ended oral therapies, particularly if clinical practice does not frequently scan for rPFS on a routine basis.

Bearing in mind that the clinical effectiveness estimates derive from the olaparib use depicted by the TTD curve and also that any RDI analyses are based upon the TTD curves, the ERG will apply the TTD curves for costing purposes.

It can also be noted that it is not uncommon for events to be treated differently in the rPFS KM S(t) curve construction than in the TTD KM S(t) curve construction. For instance, withdrawal of consent is often treated as censoring within the rPFS curve but as an event within the TTD curve. If this applies, withdrawal of consent events have no effect upon the position of the rPFS curve, but they will cause the TTD curve to fall. Treating events differently during the construction of the rPFS KM curve compared to the construction of the TTD KM curve can artificially reduce the TTD curve relative to the position of the rPFS curve. There is an argument for treating such events consistently between the rPFS curve and the TTD. The ERG clarification questions asked the company to itemise the different KM events and outline their treatment when constructing the rPFS curve and the TTD curve. The company declined to provide this. As a consequence, the ERG cannot state whether and to what degree these considerations apply. This may be a major consideration and uncertainty.

4.3.4.10 CARD cabazitaxel rPFS and TTD curves

The submitted company model does not have the facility to apply a TTD curve to cabazitaxel and no cabazitaxel TTD curves are presented in de Wit et al [28]. The ERG will explore this by costing

cabazitaxel based upon an ERG inferred TTD curve that lies above the cabazitaxel PFS curve by the same proportion that the olaparib TTD curve lies above the olaparib PFS curve.

4.3.4.11 Company expert survey: G-CSF use: cabazitaxel dose & G-CSF use

[redacted]

The company has chosen to rely upon its expert survey for most resource use estimates, but ignores these results. The reasons for this are unclear. The ERG thinks that if the company has confidence in its resource use survey the company base case should assume that [redacted] of cabazitaxel treatments are dosed at 20mgm^{-2}, and also do not receive G-CSF.

The company survey did not ask about the G-CSF duration of treatment per cabazitaxel treatment cycle. The model assumes that all those receiving G-CSF are prescribed the maximum 14 day G-CSF treatment per cabazitaxel treatment cycle.

ERG expert opinion suggests that primary prophylaxis with G-CSF is not standard practice, but that it may be provided as secondary prophylaxis following a neutropenia episode among those whose cabazitaxel dose is not reduced to 20mgm^{-2}. ERG expert opinion also suggests that up to a third of patients have their cabazitaxel dose reduced to 20mgm^{-2} at some point during their treatment. ERG expert opinion further suggests that G-CSF duration is more typically 5-7 days, and not the maximum 14 days, though clinicians may prefer pegylated G-CSF as it is a one off injection.

Implementing changes to the cabazitaxel dose requires consideration of the cabazitaxel 93% RDI that is applied in the model. If [redacted] of cabazitaxel treatments are dosed at 20mgm^{-2} this in itself would reduce the average cabazitaxel dose to [redacted] of 25mgm^{-2}. In the light of this, the ERG will not vary the cabazitaxel dose though this will may to overstate cabazitaxel costs. But the ERG will assume that only [redacted] of patients will receive G-CSF and for only 7 days rather than 14 days. The ERG will provide scenario analyses of 100% receiving cabazitaxel at 25mgm^{-2} and 100% receiving G-CSF for 14 days per cabazitaxel treatment cycle.

4.3.4.12 Company expert survey: G-CSF use: SSRE rates with cabazitaxel

The respondents were asked "*Please look at the table below and state whether the calculated average column reflects your expectations for patients with mCRPC currently receiving standard of care in a post-NHA setting".* From the responses it appears that the table may have been framed around a [redacted] estimate. The responses range from no difference to [redacted] There may be concerns around anchoring effects, and that any dissent from this was to suggest a lower estimate than that proffered by the

company. Any effects of this upon costs effectiveness are likely to be small, unless spinal cord compression is assumed to have long term cost and QoL effects.

4.3.4.13 PPS treatment rates and treatments

Among patients who progress, the company derives the proportions who receive a subsequent active drug treatment from PROfound for olaparib and from CARD for cabazitaxel. It might be anticipated that the rate of subsequent treatment might be in part dependent upon the duration of PFS and PPS, or OS.

Data supplied by the company at clarification indicates that among Cohort A+B prior taxane olaparib patients [redacted] were recorded receiving a subsequent anti-cancer drug, with a total of [redacted] treatments being received among these patients. This may suggest increasing the PPS drug costs in the olaparib arm by [redacted]. It would be informative to know how these numbers changed between DCO1 and DCO2.

The supplementary material to de Wit [28] only provides data on the 1st subsequent anti-cancer treatment, so there may also be some underestimation of the PPS drug costs in the cabazitaxel arm.

The company base case estimates [redacted] longer PPS for olaparib compared to cabazitaxel. The number of PPS drug therapies may be related to the duration of PPS. It also seems more likely that cabazitaxel could be used during PPS in the olaparib arm, so expanding the PPS treatment options and possible PPS treatment sequences compared to those available in the cabazitaxel arm.

The PPS treatment rates and durations drawn from may CARD also be overestimates if either are in part driven by OS duration. Figure 22 shows the ERG reconstructed CARD trial cabazitaxel OS KM curve, alongside the cabazitaxel OS curves generated by the company model for the Weibull and the log-logistic.

[redacted]

Figure 22: Cabazitaxel: CARD OS KM versus model curves

The CARD trial cabazitaxel OS KM curve lies everywhere above both the model Weibull and the model log-logistic curves, with the model anticipating that the HRR genes will adversely affect survival compared to the CARD trial. As a consequence, the CARD trial proportion of cabazitaxel patients receiving subsequent drug treatment may be an overestimate of that which would occur among the target population. The assumed PPS treatment durations in the cabazitaxel arm may be further curtailed by this consideration.

The PROfound trial and the CARD trial differ noticeably in terms of geography. The PROfound trial was 35% Asia, 43% Europe and 23% North and South America[11], whereas the CARD trial was conducted exclusively in Europe. These geographic differences may be the cause of some of the apparent differences in subsequent treatments.

As noted by the company, use of a second NHA is not reimbursed in the NHS. Consequently, the ERG revised base case will remove NHAs from the PPS treatments, in line with the company scenario analysis.

In the light of the above, the ERG will conduct a scenario analysis that increases the PPS drug costs by [redacted] in the olaparib arm. ERG expert opinion notes that there are few treatment options for patients who have failed cabazitaxel, and thinks it unlikely that more cabazitaxel patients would receive an active drug treatment during their PPS than would olaparib patients during their PPS. The ERG will provide a scenario analysis that equalises PPS treatment rates between the arms.

4.3.4.14 SSRE costs

The company submission states that data on the different types of SSREs was not analysed during PROfound. The company has provided this data at clarification. It suggests somewhat higher rates of surgery to the bone for the olaparib target group, which would increase the mean olaparib cost per SSRE from [redacted] to [redacted] among the target group. If the olaparib balance is assumed for cabazitaxel, the mean cost per SSRE increases from [redacted] to [redacted] among the target group. This will have no material effect upon results.

4.3.4.15 ADT/LHRH costs

The model includes ADT/LHRH costs as a part of BSC. Within this only [redacted] are assumed to receive this each month, equivalent to [redacted] of patients being on it given the 3 monthly dosing schedule. Within the company base case only around [redacted] of patients have these BSC costs applied, hence only around [redacted] are assumed to be receiving ADT/LHRH and even then only during PPS as far as the ERG can ascertain.

[11] The percentages for the prior taxane subgroup broadly conforms with these percentages.

In line with the treatment pathway of the company DPM pro-forma, ERG expert opinion suggests that the vast majority of patients will receive ADT/LHRH throughout their OS. No administration costs are directly associated with ADT/LHRH. It is a moot point whether the company resource survey responses will have considered this, given that ADT/LHRH was only identified as a part of BSC.

The ERG removes ADT/LHRH from BSC and applies this cost throughout the modelled OS to all patients. The ERG also includes an additional three monthly nurse led outpatient appointment for this at a three monthly cost of £147[12].

4.3.4.16 Bone scans and CT scans

The company resource use survey estimates that bone scans and CT scans will be roughly twice as frequent for patients being treated with cabazitaxel as for patients being treated with olaparib. No rationale for this is given.

ERG expert opinion suggests that due to cabazitaxel being a fixed duration regime, provided that the patient is tolerating treatment and having a PSA response, a bone scan and a CT scan would not be undertaken until the end of the course of treatment. But because the oral therapies have no pre-defined treatment cessation point bone scans and CT scans are likely to be more necessary with olaparib than with cabazitaxel, in part to assess continuance of treatment.

For its revised base case the ERG will equalise the cabazitaxel bone scan and CT scan rates with those of olaparib. It will provide scenario analyses of the company estimates, and of a single CT and single bone scan for cabazitaxel patients on treatment.

4.3.4.17 Cabazitaxel wastage

The company base case assumes that there will be cabazitaxel vial sharing and no wastage. The ERG agrees with this for the base case analysis. But vial sharing will be less than perfect and will depend upon clinic throughput. There will be some cabazitaxel wastage, even if only minor wastage.

4.3.4.18 Test panel and testing costs

The current GLH Test Directory does not include prostate cancer. The NICE scope specifies: "*The economic modelling should include the cost associated with diagnostic testing in people with hormone-relapsed prostate cancer who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test*".

The current Genomic Laboratory Hub (GLH) Test Directory does not cover mCRPC HRR testing. The company asserts that the 2021 GLH Test Directory will include prostate cancer under Core commissioning, stating "[redacted]". No

[12] 2018-19 NHS reference costs: WF01A, non-consultant led, non-admitted, face to face, medical oncology

further details are provided. The company provides a scenario analysis of test costs: "*a one-off cost of £[redacted] was applied to the olaparib arm, based on an average of the proposals received as part of the pan cancer panel*."

The ERG made enquiries with each of the 7 GLHs, asking:

- if they had the ability to panel test for (A) the Cohort A HRR genes and (B) the Cohort B HRR genes, and;
- if they were aware of or had an opinion about prostate cancer and the HRR genes being added to the 2021 GLH Test Directory, and as Core commissioning.

To date, the ERG has received responses from only 2 of the GLHs. Both have the ability to panel test for the Cohort A and the Cohort B HRR genes. Neither knows whether HRR genes will be specified as part of prostate cancer panel testing under Core commissioning. It is consequently unclear where the AstraZeneca Diagnostics team gets its information from.

The ERG asked the company to supply data on the number of patients screened and tested who remained eligible for PROfound, separately for Cohort A and for Cohort B. The company response pooled the data for Cohort A and Cohort B. For PROfound 4,425 patients were initially screened using the Foundation One sequencing test. For PROfound 2,792 were successfully sequenced, with 778 of these patients having Cohort A genes, Cohort B genes or both. As a consequence, it is unclear whether the prevalence of Cohort A+B HRR genes is 17.6% or 27.9% or somewhere between these two values.

For its revised base case the ERG will apply the company [redacted] test cost and an HRR prevalence among those being tested of 27.9%, also supplying a scenario analysis of a prevalence of 17.6% and a scenario analysis of £0 test cost. Note that there may be additional ancillary costs to this testing, such as sample preparation and dispatch, communication of results and counselling.

4.3.4.19 Subgroup analyses

The NICE scope specifies that "*if the evidence allows the following subgroups will be considered: subgroups by HRR alterations, including Breast Cancer gene (BRCA) and ataxia-telangiectasia mutated (ATM) gene status*". The PROfound trial was designed with pre-specified genetic mutations in mind, the primary efficacy variable being rPFS assessed by BICR in Cohort A: BRCA1/2 + ATM patients. The CSR forest plots also extensively analyse the different genetic mutation groupings.

There are reasons to think that the effect of olaparib is greater among those with BRCA1 and/or BRCA2, the CSR showing a statistically significantly lower rPFS BICR HR among these patients than across all Cohort A+B patients. Cohort A patients also have a lower rPFS BICR HR central estimate, though this is not statistically significantly different than that across all Cohort A+B patients.

The ERG thinks that there is a strong argument for examining the cost effectiveness of olaparib in Cohort A against that in Cohort B. The ERG considers Cohort A versus Cohort B by estimating for both Cohort A and for Cohort A+B OS, rPFS and TTD curves from the monthly KM data supplied at clarification, and hazard ratios for the comparison with cabazitaxel to estimate the cost effectiveness for Cohort A and for Cohort A+B. The cost, QALY and ICER estimates for Cohort B are inferred from these and the proportion of Cohort A+B that was Cohort B. While this analysis is not restricted to the prior taxane subgroup, it may give a general indication of the possible costs and benefits by subgroup.

The company base case is for the target subgroup of Cohort A+B prior taxane use. But the company submission also suggests that those without prior taxane use should also be allowed to receive olaparib "*under equality provisions*". This is confused. The ERG thinks that this argues for estimating the cost effectiveness of olaparib for all in Cohort A+B, and by implication the cost effectiveness of olaparib in Cohort A+B no prior taxane use.

Neither of these modelling exercises will be quite correct. But they should give an indication of the possible differences in costs effectiveness between Group A and Group B and between those with prior taxane use and those without prior taxane use.

5 COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

The company base case anticipates the following undiscounted patient survival.

Table 56: Company base case results: Undiscounted survival

	Cabazitaxel	Olaparib	Net gain	% total gain
PFS total	[redacted]	[redacted]	0.125	20%
PPS	[redacted]	[redacted]	0.499	80%
Total OS	[redacted]	[redacted]	0.625	

The company base case models the following QALYs.

Table 57: Company base case results: Discounted QALYs

	Cabazitaxel	Olaparib	Net gain	% total gain
AEs	[redacted]	[redacted]	0.000	0%
SSREs	[redacted]	[redacted]	0.001	0%
PFS	[redacted]	[redacted]	0.095	26%
PPS	[redacted]	[redacted]	0.268	74%
Total QALYS	[redacted]	[redacted]	0.364	

The company base case includes the olaparib PAS, but not the cabazitaxel PAS. Any PASs associated with the 2nd line treatments are also excluded.

Table 58: Company base case results: Discounted Costs

	Cabazitaxel	Olaparib	Net
Drug costs: Treatment	[redacted]	[redacted]	[redacted]
Admin costs: Treatment	[redacted]	[redacted]	[redacted]
Concomitant medication costs	[redacted]	[redacted]	[redacted]
AE management costs	[redacted]	[redacted]	[redacted]
SSRE management costs*	[redacted]	[redacted]	[redacted]
Disease management costs: On treatment	[redacted]	[redacted]	[redacted]
Disease management costs: Off treatment	[redacted]	[redacted]	[redacted]
Best supportive care (no sub tx)	[redacted]	[redacted]	[redacted]
Subsequent treatment costs	[redacted]	[redacted]	[redacted]
End of life care costs	[redacted]	[redacted]	[redacted]
Total cost	[redacted]	[redacted]	-£2,424
*Note that these differ from those of Table 47 due to being conditioned by the sum of the incidence of subsequent treatment.			

The company deterministic base case and associated probabilistic central results are presented in Table 59[13].

Table 59: Company base case results: Summary

	Deterministic			Probabilistic		
	Caba.	Olap.	net	Caba.	Olap.	net
Total QALYs	[redacted]	[redacted]	0.364	[redacted]	[redacted]	0.333
Total Costs	[redacted]	[redacted]	-£2,424	[redacted]	[redacted]	-£2,597
ICER			Dominant			Dominant
NHB @ WTP £20k/QALY			£9,705			£9,247
NHB @ WTP £30k/QALY			£13,346			£12,572

[13] Given dominance, results can be presented as the net health benefits for a given willingness to pay rather than as an ICER. This values the net QALY gain at the willingness to pay; e.g. [redacted] and adds the [redacted] net savings to this since both are benefits within the health system. For a given willingness to pay, a positive NHB suggests the technology is cost effective and the larger the positive NHS the better. A negative NHB suggests the technology is not cost effective.

NHB @ WTP £50k/QALY		£20,628		£19,222

The CEAC underlying the company base case probabilistic modelling is presented below.

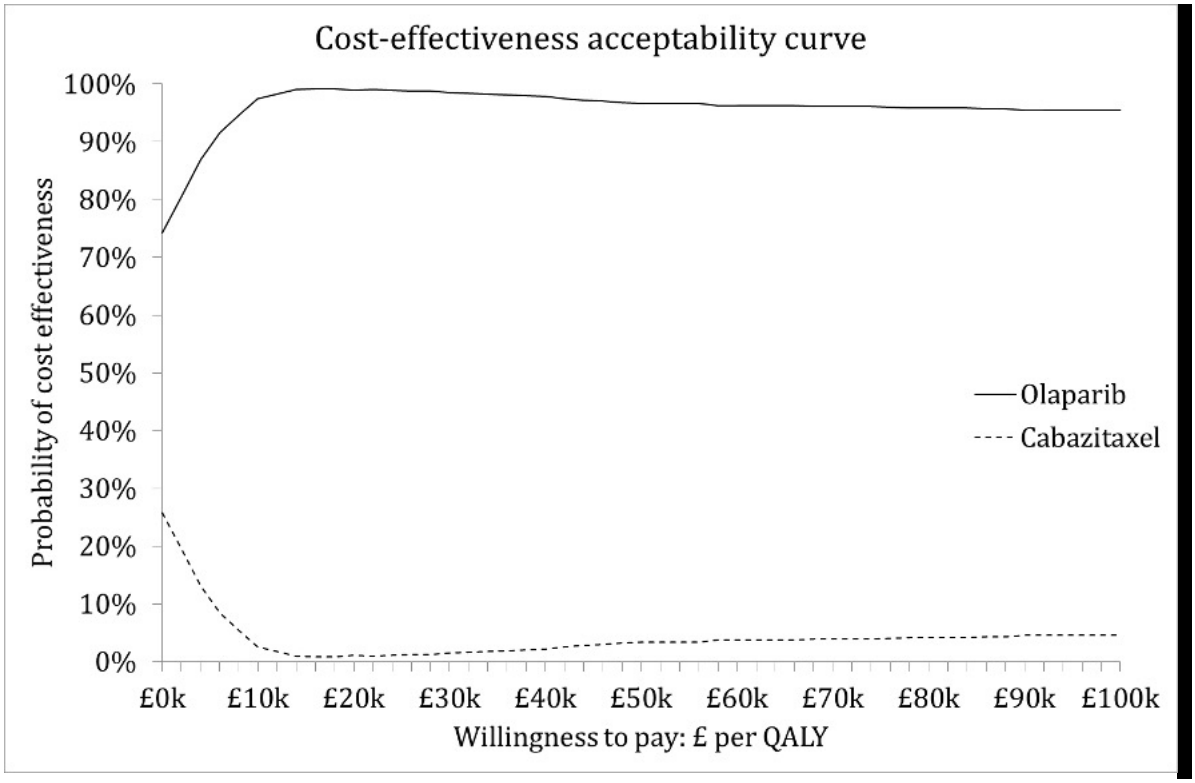


Figure 23: Company base case CEAC

5.2 Company's sensitivity analyses

For its univariate deterministic sensitivity analyses the company presents the net health benefits of the 10 most influential variables at a willingness to pay of £50k/QALY in the CS Doc B Figure 33 on page 190. Table 60 below presents the results for the 16 most influential, reported as ICERs as it has not been confirmed whether olaparib will qualify for end of life.

Table 60: Company univariate sensitivity analyses

	Low parameter value analysis				High parameter value analysis			
	Param	QALYs	Cost	ICER	Param	QALYs	Cost	ICER
OS HR: cabazitaxel vs olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OS - param 2: olaparib	[redacted]	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	[redacted]	Dominant
rPFS HR: cabazitaxel vs olaparib	[redacted]	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	[redacted]	[redacted]
OS - param 1: olaparib	[redacted]	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	[redacted]	Dominant
RDI: olaparib	[redacted]	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	[redacted]	[redacted]
RDI: cabazitaxel	[redacted]	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	[redacted]	Dominant
rPFS - param 1: olaparib	[redacted]	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	[redacted]	Dominant
Cost of subsequent tx: cabazitaxel	[redacted]	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	[redacted]	Dominant
Concomitant med monthly £: cabazitaxel	[redacted]	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	[redacted]	Dominant
Cost of subsequent tx: olaparib	[redacted]	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	[redacted]	Dominant
QoL: PPS	[redacted]	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	[redacted]	Dominant
QoL: olaparib (PFS) & cabazitaxel (PFS OffTx)	[redacted]	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	[redacted]	Dominant
QoL: cabazitaxel (PFS OnTx)	[redacted]	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	[redacted]	Dominant
BSC cost per month: olaparib	[redacted]	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	[redacted]	Dominant
Monitoring cost - OnTx: cabazitaxel	[redacted]	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	[redacted]	Dominant
rPFS Parametric - param 2 : olaparib	[redacted]	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	[redacted]	Dominant

The company also presents a range of scenario analyses, throughout which olaparib remained dominant over cabazitaxel[14]. This explored alternative functional forms for the OS curve and the rPFS curve, removing the 10 cycle cap for cabazitaxel, applying the TTD curve for olaparib coupled with there being no treatment cap for cabazitaxel, only 80% G-CSF use, various scenarios around utility values, 100% RDIs for both olaparib and cabazitaxel, and no wastage.

5.3 Model validation and face validity check

Retaining the PFS Weibull throughout, varying the OS functional form to apply some of the curves that are available results in the following undiscounted months of rPFS, PPS and OS, the last two columns reporting the proportion of the net gain in OS that is modelled as occurring during PFS and that is modelled as occurring during PPS.

Table 61: Company and ERG curves' undiscounted months PFS, PPS and OS

	PFS			PPS			OS				
	CABA	OLAP	net	CABA	OLAP	net	CABA	OLAP	net	PFS	PPS
Comp. Log-L	[redacted]									20%	80%
Comp. Weib.	[redacted]									43%	57%
ERG Log-L	[redacted]									23%	77%
ERG Weib.	[redacted]									49%	51%
ERG Rayleigh	[redacted]									54%	46%

The modelling that applies the ERG log-logistic OS curve shows a good correspondence with that which applies the company log-logistic OS curve, as does the ERG OS Weibull with the company OS Weibull.

The log-logistic OS modelling predicts [redacted] months additional OS, roughly double the [redacted] months additional OS of the Weibull modelling. For the log-logistic OS modelling 77% to 80% of the net OS gain occurs during PPS. For the Weibull OS modelling the net OS gain is roughly equally split between PFS gains and PPS gains.

In this context, it should be recalled that a short PFS for a given OS tends to improve the cost effectiveness estimate due to it having only a limited effect lowering the quality of life but a rather larger effect on lowering the direct drug costs.

It should also be recalled that for the company base case patients are assumed to remain on treatment throughout PFS but stop treatment immediately upon measured radiographic progression. For the revised ERG base case, as in PROfound, patients can remain on treatment beyond progression. Their treatment is determined by the PROfound time to treatment discontinuation (TTD) curve, in part due

[14] See CS Doc B table 56, page 190 for details.

to the application of a TTD based RDI. The Weibull TTS curve suggests an additional average [redacted] months on treatment in the olaparib arm in addition to the [redacted] months PFS; i.e. an average [redacted] months on treatment.

Given the similarity of the ERG log-logistic and Weibull with those of the company the ERG presents the proportions surviving at various points for the ERG curves.

Table 62: ERG curves' OS proportions by timepoint

	Cohort A+B prior taxane						
	Log-logistic		Weibull		Rayleigh		CARD
	CABA	OLAP	CABA	OLAP	CABA	OLAP	CABA
3 mth	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	98%
6 mth	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	87%
1 year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	57%
2 year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	22%
3 year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	..
5 year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	..
10 year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	..

The log-logistic suggests that a reasonable proportion, [redacted], will survive to 3 years with cabazitaxel and that this will be [redacted] with olaparib. 3 year cabazitaxel survival is lower with both the Weibull and the Rayleigh, only [redacted] and [redacted] respectively, with olaparib use boosting these to [redacted] and [redacted] respectively.

5 year survival for olaparib is [redacted] with the log-logistic, but effectively none with both the Weibull and the Rayleigh.

For the target group on cabazitaxel the model suggests median OS of between [redacted] months for all the curves, due to their internal similarity with their divergence mainly occurring during extrapolation. For the CARD trial the median OS was 13.6 months in the cabazitaxel arm. Caution must be exercised in interpreting the CARD trial 2 year OS for cabazitaxel of 22% in the light of only 6% of patients remaining at risk at this point. It is subject to a reasonable degree of uncertainty. Bearing this in mind, the ratio of the CARD trial cabazitaxel OS to that modelled is little different to 1 year when using the log-logistic, Weibull or Rayleigh: around [redacted] at 3 months, 6 months and 1 year respectively. The ratios only diverge at the 2 year point: [redacted] for the log-logistic, Weibull and Rayleigh respectively which on the basis of $S_{target\ group}(2year)=S_{CARD}(2year)^{HR}$ would crudely suggest an HR for the target group compared to the CARD patient group of [redacted] for the log-logistic, Weibull and Rayleigh respectively.

Data on the effect of mutations is sparse.

- Annala et al [57] found that in mCRPC patients up to 25% of patients harbour a deleterious germline or somatic mutation in BRCA1, BRCA2, ATM or other DRR gene. Among 319 patients that has targeted germline sequencing 22 patients had genes linked to homologous recombination while 113 did not. Median survival from mCRPC was 29.7 months for those with genetic mutations compared to 34.1 for those without.
- Castro et al [40] tried to evaluate the prevalence and effect of germline DDR (gDDR) mutations on metastatic castration-resistance prostate cancer (mCRPC) outcome. This study looked at ATM/BRCA1/BRCA2/PALB2 germline mutations on cause-specific survival (CSS) from diagnosis of mCRPC (n = 419). Median CSS after 2st taxane therapy was:
    - 16.9 (10.5-23.2) months vs 23.2 (19.6-26.7) months for patients with any of BRCA1/ BRCA2/ ATM/ PALB2
    - 12.8 (9.4 to 16.3) months vs 23.2 (19.6 to 26.7) months for patients with BRCA2
    - 24.0 (20.5 to 27.5) months vs 26.3 (23.7 to 28.8) months for patients with gDDR

The differences in median survival of both Annala et an and Castro et al, while restricted to germline mutations, may suggest that a reasonable difference in median survival should be anticipated between the target group and the CARD trial population when treated with cabazitaxel. The median cabazitaxel OS for the curves of the model are all quite similar. But the log-logistic appears to model much the same proportions surviving as in CARD, suggesting that the genetic mutations have little to no effect upon OS.

If HRR mutations have a detrimental effect upon OS the similarity of the log-logistic modelled cabazitaxel OS to that of CARD may be an argument against applying the log-logistic curve in the modelling.

5.4 EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

5.4.1 ERG exploratory analysis: Company target group

The ERG revised base case differs from the company in the following[15]:

- ERG01: Apply the various corrections to the model: G-CSF costing, BSC costing, cabazitaxel administration costs, olaparib monitoring costs, genetic test costs.
- ERG02: Apply the ERG Weibull curves for olaparib OS, PFS and TTD.
- ERG03: Cost drug use using the median RDI and the TTD curve.

[15] Note that within the ERG revised model the uncorrected company base case now suggests a saving of -£2,428. Either the ERG revisions have introduced a small error or there are some differences due to Excel rounding. The difference is inconsequential.

- ERG04: Restrict primary prophylaxis G-CSF to 60% of patients and for only 7 days per cabazitaxel treatment cycle.
- ERG05: Exclude NHAs from the PPS treatments.
- ERG06: Applies the £79.90 drug tariff price for G-CSF.
- ERG07: ADT/LHRH throughout mCRPC.
- ERG08: Equal bone and CT scans while on treatment.
- ERG09: Cabazitaxel proportion getting PPS treatments and the balance between these.
- ERG10: Apply the ERG Cohort A+B prior taxane HRs.
- ERG11: It applies the company [redacted] test cost, conditioned by a 27.9% HRR prevalence.

Table 63: ERG's preferred model assumptions

Preferred assumption	Section	ΔCost	ΔQALY	ICER
Company base-case	..	-£2,424	0.364	Dom.
ERG01a: G-CSF costs correction	4.3.1.2	£4	0.364	£12
ERG01b: BSC costs correction	4.3.1.2	-£884	0.364	Dom.
ERG01c: cabazitaxel admin costs	4.3.1.2	-£2,003	0.364	Dom.
ERG01d: olaparib monitoring costs	4.3.1.2	-£2,320	0.364	Dom.
ERG02: ERG parameterised curves	3.6.1	-£3,190	0.188	Dom.
ERG03a: TTD costing	4.3.4.8	£3,068	0.364	£8,428
ERG03b: median RDI	4.3.4.8	£87	0.364	£240
ERG04: G-CSF use	4.3.4.11	[redacted]	[redacted]	[redacted]
ERG05: Exclude NHAs from PPS treatments	4.3.4.13	-£1,534	0.364	Dom.
ERG06: G-CSF tariff price	4.3.2.2	-£2,014	0.364	Dom.
ERG07: ADT/LHRH costs throughout	4.3.4.15	-£1,983	0.364	Dom.
ERG08: Equal On Tx bone and CT scans	4.3.4.16	-£1,596	0.364	Dom.
ERG09: Cabazitaxel PPS treatments	4.3.2.1	-£941	0.364	Dom.
ERG10: ERG ITC HRs	3.6.1.7	-£2,154	0.375	Dom.
ERG11: Test costs	4.3.4.18	[redacted]	[redacted]	[redacted]
Cumulative effect of ERG revisions	..	£18,397	0.194	£94,708

The ERG revised base case suggests quite considerable net costs and a much reduced QALY gain compared to the company base case. The main drivers of this are:

- ERG01a & ERG04: Modelling G-CSF costs
- ERG01b: Assuming BSC costs apply subsequent to PPS treatment
- ERG02: Using the OS Weibull rather than the OS log-logistic
- ERG03a: Costing using the TTD curve rather than the rPFS curve
- ERG03b: Costing using the median RDI rather than the mean RDI
- ERG05: Excluding NHAs from PPS treatments
- ERG09: Revising the proportion of cabazitaxel patients who get PPS treatments
- ERG11: Applying the genetic test cost estimate of the company

The other ERG changes may appear less important, typically affecting the net costs to a lesser degree. But it should be borne in mind that their effect upon the ICER is based upon the company base case net QALY estimate. Their effects upon the ICER when the ERG revised base case net QALY estimate is applied will be proportionately greater. Individually they may still appear of lesser importance, but their effects are cumulative.

The ERG base case models the following undiscounted survival.

Table 64: ERG base case results: Undiscounted survival

	Cabazitaxel	Olaparib	Net gain	% total gain
PFS total	[redacted]	[redacted]	0.142	49%
PPS	[redacted]	[redacted]	0.149	51%
Total OS	[redacted]	[redacted]	0.291	

The ERG base case models the following QALYs.

Table 65: ERG base case results: Discounted QALYs

	Cabazitaxel	Olaparib	Net gain	% total gain
AEs	[redacted]	[redacted]	0.000	0%
SSREs	[redacted]	[redacted]	0.001	1%
PFS	[redacted]	[redacted]	0.106	54%
PPS	[redacted]	[redacted]	0.087	45%
Total QALYS	[redacted]	[redacted]	0.194	

The ERG base case includes the olaparib PAS, but not the cabazitaxel PAS. Any PASs associated with the 2nd line treatments are also excluded.

During the factual error check the company identified a number of ERG model revision errors:

- Conditioning the cabazitaxel non-G-CSF concomitant medication costs and ADT costs by the ERG revisions to the G-CSF costs.
- Dividing the company monthly ADT drug cost by 3.
- Incorrect cell referencing for olaparib PPS active treatments.
- Not applying the CABA TTD:PFS ratio to the concomitant medication costs for scenario SA05.

Correcting these errors reduced the net cost of the ERG revised base case by £521. These corrections are applied in all the following results, and account for the difference between the net cost of Table 63 and that of Table 66.

Table 66: ERG base case results: Discounted Costs

	Cabazitaxel	Olaparib	Net
Drug costs: Treatment	[redacted]	[redacted]	[redacted]
Admin costs: Treatment	[redacted]	[redacted]	[redacted]
Concomitant medication costs	[redacted]	[redacted]	[redacted]
AE management costs	[redacted]	[redacted]	[redacted]
SSRE management costs*	[redacted]	[redacted]	[redacted]
Disease management costs: On treatment	[redacted]	[redacted]	[redacted]
Disease management costs: Off treatment	[redacted]	[redacted]	[redacted]
Best supportive care (no sub tx)	[redacted]	[redacted]	[redacted]
Subsequent treatment costs	[redacted]	[redacted]	[redacted]
End of life care costs	[redacted]	[redacted]	[redacted]
Total cost	[redacted]	[redacted]	£17,876

The ERG deterministic base case and associated probabilistic central results are presented in Table 59.

Table 67: ERG base case results: Summary

	Deterministic			Probabilistic		
	Caba.	Olap.	net	Caba.	Olap.	net
Total QALYs	[redacted]	[redacted]	0.194	[redacted]	[redacted]	0.200
Total Costs	[redacted]	[redacted]	£17,876	[redacted]	[redacted]	£18,192
ICER			£92,026			£91,171

The probabilistic modelling has a similar central estimate to the deterministic modelling.

Figure 24: ERG base case CEAC

5.4.2 ERG scenario analyses: Company target group

The ERG provides the following scenario analyses:

- SA01: For OS applying the ERG Rayleigh and log-logistic curves
- SA02: Applying the company curves, and for OS applying the Weibull and the log-logistic curves
- SA03: Applying PROfound olaparib 100%, mean and mean days RDIs
- SA04: Costing olaparib using the rPFS curve, and applying PROfound 100%, median and mean RDIs
- SA05: Inferring a TTD curve for cabazitaxel for costing purposes
- SA06: Equalising the PPS treatments between the arms, applying the company cabazitaxel PPS balance between treatment estimates, and increasing PPS treatment costs by 50% for olaparib
- SA07: Increasing the cabazitaxel on treatment disutility to 0.037
- SA08: TA391 and TA377 QoL values

- SA09: Assuming no vial sharing and wastage for cabazitaxel.
- SA10: Revising the HRR prevalence to 17.6% and the HRR test cost to £0.
- SA11: Assuming no additional 3 monthly cost for ADT/LHRH administration, and assuming a monthly administration cost for ADT/LHRH.

Table 68: ERG scenario analyses

	ΔCost	ΔQALY	ICER
ERG base-case	£17,876	0.194	£92,026
SA01a: OS ERG Rayleigh	£17,569	0.178	£98,713
SA01b: OS ERG log-logistic	£20,753	0.363	£57,134
SA02a: company curves, OS Weibull	£17,455	0.198	£88,015
SA02b: company curves, OS log-logistic	£20,437	0.375	£54,438
SA03a: olaparib 100% RDI	£18,316	0.194	£94,291
SA03b: olaparib mean RDI	£14,956	0.194	£76,995
SA03c: olaparib mean days RDI	£16,270	0.194	£83,759
SA04a: olaparib rPFS costing, 100% RDI	£12,727	0.194	£65,518
SA04b: olaparib rPFS costing, median RDI	£12,348	0.194	£63,565
SA04c: olaparib rPFS costing, mean RDI	£9,830	0.194	£50,603
SA05: cabazitaxel inferred TTD curve	£15,754	0.194	£81,103
SA06a: Same PPS treatments between arms	£17,846	0.194	£91,870
SA06b: Company cabazitaxel PPS treatments	£17,401	0.194	£89,581
SA06c: olaparib PPS costs 50% higher	£20,792	0.194	£107k
SA07: increased cabazitaxel disutility	£17,876	0.199	£89,816
SA08a: TA391 QoL values	£17,876	0.201	£88,827
SA08b: TA377 QoL values	£17,876	0.185	£96,571
SA09: no cabazitaxel vial sharing	£12,377	0.194	£63,715
SA10a: 17.6% HRR prevalence	[redacted]	0.194	[redacted]
SA10b: no genetic test cost	[redacted]	0.194	[redacted]
SA11a: No ADT/LHRH admin cost	£17,713	0.194	£91,184
SA11b: Monthly ADT/LHRH admin cost	£18,204	0.194	£93,712

5.4.3 ERG subgroup analyses

As considered in more detail in section 4.3.4.19 of the previous chapter there are good arguments for considering the cost effectiveness of olaparib for Cohort A patients versus Cohort B patients, and for prior taxane use versus no prior taxane use. The modelling approaches of section 4.3.4.19 result in the following.

Table 69: ERG subgroup analyses: Cohort A+B, Cohort A and Cohort B

	Cohort A+B		Cohort A		Cohort B	
	QALY	Cost	QALY	Cost	QALY	Cost
Cabazitaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net	0.135	£17,755	0.263	£23,665	-0.086	£7,569
ICER		£132k		£90,078		Dominated

The above is not restricted to the prior taxane patient group, but it suggests that there may be relatively few patient benefits from treating Cohort B patients with olaparib. But there will still be quite considerable costs. While exploratory, the above suggests that it may not be cost effective to use olaparib among Cohort B patients.

Table 70: ERG subgroup analyses: Cohort A+B by prior taxane use

	All patients		Prior taxane		No prior taxane	
	QALY	Cost	QALY	Cost	QALY	Cost
Cabazitaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net	0.135	£17,755	0.194	£17,876	0.020	£17,523
ICER		£132k		£92,026		£855k

While exploratory, the above suggests that the cost effectiveness of olaparib is better in the Cohort A+B prior taxane patient group than the Cohort A+B no prior taxane patient group. Extending olaparib use to the Cohort A+B no prior taxane patient group may not be cost effective.

5.5 Conclusions of the cost effectiveness section

The company model structure is unusual and unnecessarily convoluted. This may have contributed to a number of errors. These errors all bias the company analysis in favour of olaparib. Correcting these errors results in the company base case no longer estimating olaparib to be cost saving.

Within oncology STAs is not unusual for the log-normal or the log-logistic to have a lower AIC and BIC than the Weibull, but for the AC to reject them for extrapolation due to their long tails. The current submission is unusual in reversing this. The Weibull OS curve has a lower AIC and BIC than the log-logistic, but the company prefers the log-logistic because of its long tail. The company cites its survey of 6 experts as the reason for preferring the log-logistic. The ERG thinks that many of the company experts' responses may not be applicable to the current assessment. They are certainly difficult to understand. This calls into question the company expert survey. The ERG prefers the Weibull or the Rayleigh for OS extrapolation.

The company applies the mean relative dose intensity (RDI) for olaparib, based upon individual patient's tablet consumption and time to treatment discontinuations (TTD). This data is highly skewed and the ERG thinks that the median is likely to be a better measure of the average experience over the period of PROfound. Olaparib is prescribed in packs. An RDI of less than 100% means that fewer tablets are consumed. But it does not mean that fewer packs will be prescribed. There is an argument for applying a 100% RDI for olaparib.

The company applies the RDI to the rPFS curve rather than the TTD curve. The ERG thinks that the RDI should be applied to the TTD curve. There is no TTD curve for cabazitaxel. This argues for inferring a TTD curve for cabazitaxel in order to treat both arms in a like manner.

The company has declined to supply some basic information on the types of events and their treatment within the construction of the rPFS KM curve and the TTD KM curve. If events have not been treated in a like manner during the construction of each curve it is possible that this has caused the TTD curve to be lower than it otherwise would be.

The proportion of cabazitaxel patients receiving a post progression drug treatment appears to have been estimated differently to that for olaparib, and is too high. The company base case includes NHAs as PPS treatments, despite these not being funded in the NHS. It also appears that olaparib patients tended to receive more than one post progression drug treatment. Given the modelled PPS gain, it might also be anticipated that olaparib patients would tend to receive more PPS treatments than cabazitaxel patients.

The company assumes that all cabazitaxel patients receive G-CSF as primary prophylaxis, at the maximum dose of 14 days per cabazitaxel treatment cycle. ERG expert opinion suggests that not all will receive it, and those that do will typically receive it for less than 14 days per cycle.

The base case does not include ADT/LHRH costs over the model time horizon. As per the company DPM pro-forma, the ERG thinks that the majority of patients will receive ADT/LHRH for most of their mCRPC.

The company anticipates that bone scans and CT scans will be roughly double for those receiving cabazitaxel compared to those receiving olaparib. ERG expert opinion suggests that this is unlikely to be the case. Cabazitaxel has a fixed treatment duration so may only require scans at the end of treatment. Olaparib may require more scans if these are going to be used to inform ongoing treatment.

The scope specifies that genetic subgroups should be examined if the data allows. The PROfound trial was built around the genetic subgroups of Cohort A and Cohort B. There is clinical evidence that the effectiveness of olaparib for Cohort B is worse than for Cohort A. Exploratory work by the ERG suggests that the cost effectiveness of olaparib for Cohort B is very much worse than that for Cohort A.

The company restricts the cost effectiveness analysis to those who have had a prior taxane, but also argues that olaparib should be approved for those without prior taxane use for reasons of equality. This seems incoherent. The ERG thinks that this argues for consideration of the cost effectiveness of olaparib among the subgroup without prior taxane use. Exploratory work by the ERG suggests that the cost effectiveness of olaparib for the subgroup without prior taxane use is very much worse than that for the company target group.

5.6 END OF LIFE

Table 61 in Section 5.3 above presents the undiscounted months survival and net months gain. The log-logistic, Weibull and ERG Rayleigh all predict an OS in the cabazitaxel arm of less than 24 months. The net OS gains are [redacted] months for the log-logistic OS curve, [redacted] months for the Weibull OS curve and [redacted] months for the ERG Rayleigh OS curve.

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APPENDICES TO ERG EXTRA WORK

APPENDIX 1. Comparison of cumulative hazard and parametric modelled cumulative hazard

A] PROfound Prior taxane A+B cohort

[redacted]

[redacted]

B] PROfound cohort A.

[redacted]

C] PROfound cohort A + B.

D] CARD trial cohort.

APPENDIX 2. Kaplan Meier plots for patient cohorts in PROfound and CARD

NHA arms PROfound and CARD

Intervention arms PROfound and CARD

The four NHA arms have similar trajectory however the prior taxane A+B cohort appears disadvantaged relative to the other three arms

The four intervention arms exhibit somewhat dissimilar trajectories particularly between 10 and 20 months of observation.

APPENDIX 3. Models of TTD olaparib and of PFS

TTD OLAPARIB

PFS olaparib arms	PFS NHA arms
[redacted]	

APPENDIX 4. Models of PFS in cohort B

Cohort B parametric models of PFS: dashed line NHA ; solid line olaparib

APPENDIX 5. Applying time invariant HRs to loglogistic models Cohorts A and A+B

Figure 25. Applying time invariant HRs to loglogistic models; Cohort A+B

Figure 26. Applying time invariant HRs to loglogistic models; Cohort A

Figure 27. Applying time invariant HRs to Weibull models; prior taxane A+B cohort

APPENDIX 6. Rayleigh model parameters of OS

The table below lists the lambda 1 and lambda 2 parameters for the Rayleigh models for OS; any desired HR can be applied to generate proportional hazards curves for other populations

COHORT	lambda 1	lambda 2
prior taxane A+B olaparib	[redacted]	[redacted]
prior taxane A+B RPSFT NHA	[redacted]	[redacted]
A+B olaparib	[redacted]	[redacted]
A+B RPSFT NHA	[redacted]	[redacted]
A olaparib	[redacted]	[redacted]
A RPSFT NHA	[redacted]	[redacted]
CARD cabazitaxel	[redacted]	[redacted]
CARD NHA	[redacted]	[redacted]

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

ERG report – factual accuracy check

Olaparib for previously treated hormone-relapsed metastatic prostate cancer [ID1640]

You are asked to check the ERG report to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies, you must inform NICE by the end of **11 August**. using the below comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

The factual accuracy check form should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Notes:

1. Minor typos and misspellings in the ERG report have not been corrected in this checklist.
2. We have categorised our response into four different tables, covering:
    - minor errors (e.g. in reproduction of trial data)
    - other errors, including those identified in the ERG rebuild model and relevant results produced in the report
    - misleading statements, that have material impact on the interpretation and conclusions drawn from the evidence provided
    - further clarifications based on comments in the ERG report (in case useful to the ERG/NICE in preparation for technical consultation).

Minor errors (including typos and reproduction of trial data)

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Executive summary			
P11: "Comparator: - Docetaxel - Cabazitaxel - Radium-223 dichloride for people with bone metastases"	"- Docetaxel - Cabazitaxel - Radium-223 dichloride for people with bone metastases The different positions that these comparators could be used in the treatment pathway will be considered in the appraisal."	Incomplete listing of comparator field.	Added to the NICE scope
P12, p113 "MMR mutations"	We suggest the following revision: "HRR mutations"	The ERG report incorrectly refers to HRR mutations as MMR mutations in several places. Since HRR (i.e. homologous recombination repair) is not the same as MMR (i.e. mismatch repair), we request that this be corrected.	Thank you for identifying this. We agree, the report should refer to HRR mutations. This has been corrected.
Issue: Marketing authorisation for olaparib			
P12: While the ERG think this change to scope is acceptable it does differ from the marketing authorisation currently in place for Olaparib, in terms of the focus on prior use of taxane treatment.	"While the ERG think this change to scope is acceptable it does differ from the anticipated marketing authorisation ~~currently in place for~~ Olaparib in this indication, in terms of the focus on prior use of taxane treatment."	There is currently no EMA marketing authorisation for olaparib for the treatment of prostate cancer. [redacted]	Amended
P24: "Food and Drugs Association (FDA) marketing authorisation was granted in	It is unclear what these dates represent. Please see suggested edit and revise accordingly. "Food and Drugs Association		

2014 and in the European Medicines Agency (EMA) on 22 November 2019 for the use of Olaparib (Lynparza) for several indications, including prostate cancer."	(FDA) marketing authorisation for olaparib in ovarian cancer was granted in 2014 and by the European Medicines Agency (EMA) in December 2014. Olaparib (Lynparza) has EMA marketing authorisation for several indications, and is currently being reviewed for the treatment of prostate cancer by the EMA (marketing authorisation anticipated in [redacted]."		
P24: However, the marketing authorisation does not report on the prior use of taxane treatment.	However, the anticipated marketing authorisation does not report on the prior use of taxane treatment.		
Critique of company's definition of decision problem			
P22: "The CS justify the rationale for restricting this patient group based upon testimony from three clinical advisors that around 75% of patients receive a taxane treatment such as docetaxel prior to new hormonal therapy (NHA) treatment in clinical practice."	"The CS justify the rationale for restricting this patient group based upon testimony from six clinical advisors that around 75% of patients receive a taxane treatment such as docetaxel prior to new hormonal therapy (NHA) treatment in clinical practice."	Incorrect number of advisors.	This has been amended throughout the ERG report in line with the information presented in Table 1 of AstraZeneca. DOF-GB-21948 May 20. 26 May 2020. This now reads: The CS justify the rationale for restricting this patient group based upon testimony from five clinical advisors that 60 - 80% of patients receive a taxane treatment such as docetaxel prior to new hormonal therapy (NHA) treatment in clinical practice.

Summary of trial results			
P58, Table 13: 36 ([redacted]) patients in Cohort A+B prior taxane subgroup investigator's choice of NHA arm who received prior abiraterone only.	We suggest the following revision: 36 ([redacted])	Typo (see Table 5 of CS)	The number/percentages of people with previous NHA use was reversed for abiraterone and enzalutamide in the ERG report. These have been corrected.
P59 (table): [redacted] of patients in the Cohort A+B prior taxane subgroup olaparib arm who received prior cabazitaxel.	We suggest the following revision: [redacted]	Typo (see Table 5 of CS)	Table 5 (CS Doc B, page 40) indicates that for patients with taxane treatment prior to randomisation in the olaparib arm 3 (1.8%) had previous cabazitaxel only and 51 (31.0%) had previous docetaxel and cabazitaxel. Combining these gives the values (54, 31.8%) in the ERG report.
P71: OS (DCO2) median OS (months) (95% CI), Cohort A olaparib: [redacted]	OS (DCO2) median OS (months) (95% CI), Cohort A olaparib:[redacted]	Typos	Typo corrected

P69/70: OS (DCO2) OS rates (%) (95% CI), Cohort A+B [redacted]	These figures have not been reported in the company materials. Please could the ERG clarify the source they have used, or remove, as appropriate.		Extrapolated from the KM curves by digitising the curve Extrapolated from the KM curves by digitising the curve in Figure 6, and other curves where appropriate.
P71: SRE-free rates (%), Cohort A+B NHA at 12 months: [redacted]	SRE-free rates (%), Cohort A+B NHA at 12 months: [redacted]		Typo corrected
P72: "However, as the significance level of OS at DCO1 was 10%, statistical significance was not reached."	"However, as the significance level of OS at DCO1 was 1%, statistical significance was not reached."		Typo corrected
P73: These results were not presented as part of the original CS but were included as part of an updated submission (version 0.2; dated 01 June 2020).	These results were not presented as part of the original CS but were included as part of an updated submission (version 0.2; dated 11 June 2020).	Error in date.	Typo corrected
P79: 3.2.2.6 Overall relapse rate (ORR)	3.2.2.6 Overall response rate (ORR)	Wrong term used	Typo. Correct it to Overall response rate
Cost effectiveness			
P121: Figure 14	Please update the graph to add the missing label for Year 15.	Missing label on graph.	No factual error. No revision required. The missing "15" is an anomaly of Excel. It is perfectly

			clear that the figure extends to 15 years.
P148/149: Table 58	Please highlight all rows CIC, except total net cost cell (-£2,424)	Consistency with the company confidentiality markings.	Proposed revision accepted.
P157, Table 66	Please highlight all rows CIC, except total net cost cell (£18,397)		Proposed revision accepted.
P118: Figure 10 P119: Figure 11 P120: Figure 12 P121: Figure 13 P122: Figure 14 P123: Figure 15 P124: Figure 16 P124: Figure 17 P135: Figure 18 P136: Figure 19 P137: Figure 20 P141: Figure 21 P144: Figure 22	Please highlight the graphs AIC (currently, only the titles are marked)		Proposed revision accepted.
P132: "The company includes a scenario analysis of a £[redacted] test cost, which it states are "[redacted]	Please highlight the text CIC: "[redacted]"		Proposed revision accepted.

RDI value for olaparib: P127, Table 49	Please consistently highlight the RDI value of [redacted] as CIC.		Proposed revision accepted so as to be consistent with the company submission mark-up. Also applies to Table 49. It is unclear to the ERG why the RDI should be CIC and not AIC.
P127 P142 P143	Please highlight the specific results (e.g., [redacted]% of respondents) from the survey of clinical experts as AIC as these were not included in the CS.	Confidentiality marking for data not provided in the CS.	Proposed revision accepted.

Other errors

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Introduction and background			
p23: However, these outcomes are only reported for cohort A (with at least one mutation in either BRCA1, BRCA2 or ATM genes) and cohort A+B (several mutations) but not the prior taxane A+B subgroup	We suggest the following revision: "outcomes are reported for cohort A (with at least one mutation in either BRCA1, BRCA2 or ATM genes) and cohort A+B (several mutations), and also the prior taxane A+B subgroup"	The statement suggests that the ERG missed these outcomes for rPFS BICR, which are presented in Section B.2.7.1 of the CS.	Amended
Critique of the methods of review(s)			
P31: "Similarities in CARD and PROfound populations were partially addressed (Doc B, pages 82 – 85), but a critical difference (presence/absence of HRR	Differences between CARD and PROfound populations, including presence/absence of HRR mutations, were addressed in the CS (Doc B, pages 82 – 85).	Misrepresentation/omission of evidence provided in CS.	This is not a factual error. 1. Pages 82 – 85 (Doc B) of the CS do not refer to presence/absence of HRR mutations.

mutations and their effect on treatment efficacy) was not addressed."			2. CARD provides no information about the presence/absence of HRR mutations, Therefore it is not possible to examine similarities in HRR mutations between CARD and PROfound.
Discussion on the PROfound study			
P77: Whilst there was a clear separation of both curves for the first 3 months of follow-up, the curves did not separate in favour of olaparib until about months 18 and 19.	We propose revising the statement: "Whilst there was no clear separation of both curves for the first 3 months of follow-up, the curves did separate in favour of olaparib until about months 18 and 19."	The written description of the PFS2 curves does not match the KM data given in Figure 11 of the CS (11th June).	Amended
Issue: Mis-representation of the company model structure and/or justification underlying model assumptions in the CS			
P122: Table 44	Please could the ERG kindly correct the table headers to correctly reflect the model structure and data being presented, as follows: • Add a footnote to describe PPS: "Post-progression survival is not modelled explicitly in the economic model, but is shown in this table calculated as the	Clarity with respect to the model structure and data used in the cost-effectiveness analysis.	No factual error. But the ERG accepts that the table could be labelled "Company base case curves: Undiscounted mean months survival". Note that the net gain is as given as a percentage of the total net gain (as stated in table 44) so is not a % of olaparib.

	residual of the mean OS minus PFS." • Relabel "Total" column header to "OS" • Correct "Net gain" column header to "As % of olaparib" State whether these are median or mean modelled outcomes		
P160: "Within oncology STAs is not unusual for the log-normal or the log-logistic to have a lower AIC and BIC than the Weibull, but for the AC to reject them for extrapolation due to their long tails. The current submission is unusual in reversing this. The Weibull OS curve has a lower AIC and BIC than the log-logistic, but the company prefers the log-logistic because of its long tail. The company cites its survey of 6 experts as the reason for preferring the log-logistic. The ERG thinks that many of the company experts' responses may not be applicable to the current assessment. They are certainly difficult to understand. This calls into question the company expert survey. The ERG prefers the Weibull or the Rayleigh for OS extrapolation."	This narrative does not reflect the fundamental reason for why the Weibull curve was rejected in CS Section B.3.3.2.1.2 and B.3.3.2.1.3., i.e. due to the fact that it was not consistent with the clinical expectation that some patients will survive at 5- and 10- years from the start of treatment.	Omission of company evidence.	No factual error. No revision required. P160 is the ERG critique. The reasons for the company choice are given towards the end of section 4.2.6.1.

P138: “By year 15, the monthly probability of death for the log-logistic has fallen to only [redacted]% compared to 0.56% for the general population.”	Please could the ERG clarify the data source for these values. We believe [redacted]% is based on the ERG’s extrapolated curves (and not directly referenceable to Figure 20).	Clarity regarding data source.	No factual error. No revision required. The source is the company log-logistic: cell M190 of Model_Calcs of the company submitted model.
Issue: Omission of relevant details regarding G-CSF with cabazitaxel, and dosing details			
P127: “In common with the other resource use estimates, the company conducted a telephone questionnaire of 6 UK respondents regarding cabazitaxel dosing and G-CSF use. 5 respondents provided estimates, with [redacted]respondents suggest that cabazitaxel would be at a reduced dose of 20mgm-2, with [redacted] suggesting that this dose might be used to lower the risk of neutropenia. [redacted]stated that they did not use G-CSF: one due to applying the lower 20mgm-2 cabazitaxel dose and one due to budgetary restrictions.”	The discussion regarding G-CSF use has not taken into account the full body of evidence provided in CS Section 3.5.2.2.2, which also included: • Clinical guidelines on the use of G-CSF, and • UK EAP for cabazitaxel In addition, we request that the details of the questionnaire are described more accurately. The correct descriptions are provided below: • [redacted]_did not use G-CSF for any reason o [redacted] of these respondents only administered cabazitaxel at the unlicensed dose of 20 mg/m^2. o [redacted]of these respondents would like to administer G-CSF for all patients but was not	Omission of evidence submitted by the company. Misrepresentation of the company use of the clinical expert survey on G-CSF.	No factual error. No revision required.
P142: “The ERG thinks that if the company has confidence in its resource use survey the company base case should assume that [redacted]% of cabazitaxel treatments are dosed at 20mgm-2, and also do not receive G-CSF”			
P127: “For the base case each cabazitaxel administration is assumed to require 14 days treatment with G-CSF as			No factual error. No revision required.

primary prophylaxis for neutropenia, with 100% of patients requiring this based upon the CARD protocol and clinical expert opinion."	able to, due to budgetary restrictions. • [redacted] administered G-CSF for all of their patients o [redacted] of these respondents suggested that cabazitaxel may also be administered at the unlicensed reduced dose of 20 mg/m^2. Please could the ERG revise these sections accordingly.		
P143: "If [redacted]% of cabazitaxel treatments are dosed at 20mgm-2 this in itself would reduce the average cabazitaxel dose to 92% of 25mgm-2. In the light of this, the ERG will not vary the cabazitaxel dose though this will may to overstate cabazitaxel costs"	Please correct the statement: "If [redacted]% of cabazitaxel treatments are dosed at 20mgm-2 this in itself would reduce the average cabazitaxel dose to 93.3% of 25mgm-2. Since the model applies the mean RDI of 92.6% to patients in the cabazitaxel arm, a reduced dose is already in effect from a cost perspective for all patients."	Incorrect statement and omission of relevant application of RDI in company model.	No factual error. No revision required.
Issue: Clarity around drug costs			
P128: Table 49	Please could the ERG kindly check the calculated cost per cycle in this table. They seem to be slightly different to those in the models.	Reported drug costs do not match costs in the model.	The ERG has not identified an error. There may be minor discrepancies due to these values being separately calculated and not being taken from the model directly; e.g. using an RDI of [redacted] rather

			than [redacted] but these are inconsequential. Could the company please outline which costs are thought to be incorrect and the size (%) of the discrepancies please.
P128: “There are additional concomitant medications costs for cabazitaxel related to antihistamine, H2-antagonist, anti-emetic and corticosteroid. These are minor, do not materially affect results and are not itemised here”	Cabazitaxel is also administered with prednisolone, although these costs are minor.	Exclusion of drug cost relevant for cabazitaxel.	The ERG accepts the proposed revision and will change the text to: “There are additional concomitant medications costs for cabazitaxel related to antihistamine, H2-antagonist, anti-emetic, prednisolone and corticosteroid. These are minor, do not materially affect results and are not itemised here”
Issue: Omission of quality of life data available for cabazitaxel, highly relevant to the company submission			
P138: “TA412, TA376, TA387, TA259 and TA391 have had their quality of life values redacted”	Please correct the statement for TA391 as values have been published based on the UK EAP for cabazitaxel and are publicly available (see FAD and committee papers for TA391). As explained in CS Section B.3.4.3, these values were also tested in scenarios. We would suggest revising ERG report Section 4.3.4.5 accordingly.	Incorrect statement and omission of relevant study that undermines subsequent text in ERG report section 4.3.4.5.	The ERG accepts that TA391 QoL values of PFS 0.737 and PPS 0.627 are available within the TA391 AC1 committee papers. It will revise the first paragraph of 4.3.4.5 to: “The ERG has reviewed the company submissions and ERG reports of previous STAs, and for those not available on the NICE website has sourced

			them through the NIHR website. TA412, TA376, TA387 and TA259 have had their quality of life values redacted. The TA316 original company submission and ERG report do not appear to be available on either the NICE website or the NIHR HTA website. As a consequence, it is not possible to assess whether the quality of life values of the current assessment are aligned these STAs. The quality of life values of TA391, Cabazitaxel for hormone-relapsed metastatic prostate cancer treated with docetaxel, as taken from the cabazitaxel EAP study are available: 0.737 for PFS and 0.627 for PPS. These may be less relevant to the current submission due to position sought being for patients who are both taxane and NHA experienced, whereas the TROPIC trial patients, apparently similar to the cabazitaxel EAP study patients, were only required to be docetaxel experienced. The TA391 company submission notes 71% 1 prior, 21% 2 prior

			and 8% more than 2 prior chemotherapy regimens, but does not tabulate any prior NHA use.”.
Issue: Inappropriate suggestions regarding expected marketing authorization for olaparib			
P142: “The PROfound study protocol states that “*subjects may be discontinued from investigational product (IP) in the following situations: subject decision…, adverse event, severe non-compliance with the study protocol, bone marrow findings consistent with…MDS/AML, objective radiographic progression by …BICR, unequivocal clinical progression…, initiation of restricted anticancer therapy*”. This appears to mean that patients were not obliged to cease treatment upon progression. No draft SmPC has been supplied but it is possible that it will not specify rPFS for olaparib treatment cessation.”	As noted by the ERG, objective disease progression was included as a criteria for treatment discontinuation. Please could the ERG clarify the specific query. As highlighted in the CS (P7, P12), , the anticipated marketing authorisation for olaparib in mCRPC specifies treatment [redacted]. Further details on this can be provided at the technical engagement.	Clarity of text and anticipated marketing authorisation for olaparib in mCRPC.	No factual error. No revision required.
P141: “It may be relevant that the only references to discontinuation that the ERG can find in the abiraterone and enzalutamide SmPCs relate to adverse events”	We do not believe that discontinuation of abiraterone and enzalutamide are relevant in this context, and would suggest clarifying the reasoning or removing this statement.		No factual error. No revision required.
Issue: Omission of relevant related to treatment duration, RDI, and PFS/TTD for cabazitaxel throughout ERG report			

P125: “There are no corresponding cabazitaxel TTD curves within the company model”	Please could this be amended to acknowledge the lack of TTD data for cabazitaxel: “There are no corresponding cabazitaxel TTD curves within the company model due to lack of available data.”	The current statement is misleading – it implies these data were available but omitted.	No factual error. No revision required.
P128: “Cabazitaxel is limited to a maximum of ten 3 week treatment cycles”	Please could this sentence be clarified: “Cabazitaxel is limited to a maximum of ten 3 week treatment cycles per NICE guidance”	Clarity regarding the reimbursement status of cabazitaxel in the UK NHS. The marketing authorisation and SmPC for cabazitaxel do not impose on the limit on the duration of cabazitaxel treatment.	No factual error. No revision required.
P128: Table 49	We would suggest relabeling the RDI column to “Mean RDI”	Clarity of the data being presented.	No factual error. No revision required.
P139: “It seems logically inconsistent to apply RDI estimates that are based upon individual’s TTDs to the rPFS curve. The ERG thinks that it is only reasonable to apply RDI estimates to the TTD curve.”	For purposes of transparency, please could the ERG clarify their position and preferred assumptions for cabazitaxel with respect to RDI and treatment duration / clinical effectiveness using TTD or PFS, in the same way that has been done for olaparib. It appears that there is inconsistency in the ERG’s preferred assumptions for olaparib and cabazitaxel but this is not clear in the current structure of the report.	Transparency with respect to the differences in the ERG’s preferred approach to RDI and treatment duration (PFS or TTD) between olaparib and cabazitaxel.	No factual error. No revision required.
P139: “There is also the concern that the clinical effectiveness data is based upon the observed treatment durations as per the TTD curve and not upon treatment durations equal to the PFS curve.”			No factual error. No revision required.
P140: “The ERG base case will cost olaparib use using the median RDI and the TTD curve.”			No factual error. No revision required.

P142: “Bearing in mind that the clinical effectiveness estimates derive from the olaparib use depicted by the TTD curve and also that any RDI analyses are based upon the TTD curves, the ERG will apply the TTD curves for costing purposes.”			No factual error. No revision required.
P142: Section 4.3.4.10 CARD cabazitaxel rPFS and TTD curves “The submitted company model does not have the facility to apply a TTD curve to cabazitaxel and no cabazitaxel TTD curves are presented in de Wit et al. The ERG will explore this by costing cabazitaxel based upon an ERG inferred TTD curve that lies above the cabazitaxel PFS curve by the same proportion that the olaparib TTD curve lies above the olaparib PFS curve.”			No factual error. No revision required.
P160: “There is an argument for applying a 100% RDI for olaparib.”			No factual error. No revision required.
P161: “This argues for inferring a TTD curve for cabazitaxel in order to treat both arms in a like manner.”			No factual error. No revision required.
P142: “The ERG will explore this by costing cabazitaxel based upon an ERG inferred TTD curve that lies above the cabazitaxel PFS curve by the same	Please could the ERG include the ratio that was used.	Omission of details means that the company cannot validate or replicate the ERG’s result.	No factual error. No revision required. The ratio is available to the company in cell H4 of the *ERG curves* worksheet as the

proportion that the olaparib TTD curve lies above the olaparib PFS curve."			named variable ERG.CABA.TTD.to.PFS.Tx.Ratio, this relying upon the values in cells H11:H18.
Issue: Statements regarding cabazitaxel PAS and relevant results figures in the ERG report			
P127/128: "This document only applies the cabazitaxel PAS and costs all other treatments at list prices. The ERG provides a confidential cPAS appendix that applies all the relevant price discounts."	Please could the ERG kindly check the costs for cabazitaxel and clarify in the text, if/where necessary, which results in the ERG report include the cabazitaxel PAS and which do not. Table 19, for example, seems to present cabazitaxel costs at list price but the text suggests this includes the cabazitaxel PAS price.	Potentially incorrect statement and/or tables.	This is a typo and should read "This document only applies the olaparib PAS and costs all other treatments at list prices. The ERG provides a confidential cPAS appendix that applies all the relevant price discounts.".
Issue: Resource use			
P145/146: "The company resource use survey estimates that bone scans and CT scans will be roughly twice as frequent for patients being treated with cabazitaxel as for patients being treated with olaparib. No rationale for this is given. ERG expert opinion suggests that due to cabazitaxel being a fixed duration regime, provided that the patient is tolerating treatment and having a PSA response, a bone scan and a CT scan would not be undertaken until the end of the course of treatment. But because the oral therapies have no pre-defined treatment cessation point bone scans and CT scans are likely to be more necessary with olaparib than	As described in CS Section 3.5.3 the resource use estimates were based on an average of responses from the survey of clinical experts, as this was deemed to represent the average monitoring / follow-up costs associated with current standard of care in England and Wales. Pease could the text in the report be updated to reflect this rationale.	Omission of company evidence / incorrect reference to lack of rationale.	No factual error. No revision required.

with cabazitaxel, in part to assess continuance of treatment."			
Issue: Best supportive care and subsequent treatment			
P131: "BSC costs are conditioned by the arm specific proportion not receiving a subsequent treatment. The proportion receiving a subsequent treatment are modelled as receiving only one subsequent treatment and this is time limited, it is not for their entire post progression survival. These PPS active treatment costs also only include the direct drug and administration costs. Not including BSC subsequent to post progression treatment appears to be an error. Correcting this reduces the net savings by £1,544."	The partitioned survival model is not set up to meaningfully estimate sequential costs of BSC, because the duration of subsequent lines of treatment is not modelled as these data are not available from the PROfound study. This simplistic means-based assumption to BSC applied in the ERG model structure introduces additional uncertainty. This fundamentally assumes 4 health states and makes assumptions about time from first to second progression and beyond, which is not available from the PROfound study. In light of these factors, we do not consider the company approach to be an "error" as such, and request that the ERG capture this appropriately in the report.	Company model approach incorrectly described as an error in the report.	No factual error. No revision required.
Issue: ERG rebuild of model (Excel workbook)			
p131: "The ERG urges the company to cross check the ERG revisions."	Although the ERG has kindly marked changes to the individual cells in the model in a transparent manner, there are a substantial number of revisions that have been made to the model; some of these are structural in nature.		

	We are cross-checking the ERG revisions and have so far been able to replicate the exact results.		
Balance of PPS treatments 'Sub Tx' cell I31:36	The calculations for olaparib balance of treatments incorrectly reference cabazitaxel (Col G). Please correct the formula to reference Col H.	Incorrect calculation for subsequent treatment (olaparib balance) affecting ERG results.	The ERG accepts that the olaparib PPS cells reference some cabazitaxel PPS values.
Balance of PPS treatments 'Sub Tx' cell K31:36	The distribution of PPS treatments received after cabazitaxel should include patients who received 'taxane combined with platinum agents' within the subsequent cabazitaxel bucket (i.e., 6 patients in total costed for subsequent cabazitaxel = 3 who received cabazitaxel and 3 who received taxane combination.)	Difference in incorporating patients who received subsequent treatment with taxane combination.	There is insufficient detail provided to justify the proposed amendment. Given time constraints the ERG supplies a scenario analysis that applies the original company balance of PPS treatments for cabazitaxel.
Cabazitaxel TTD scenario 'ERG' cell B23	Please include the ratios used in the scenario; we believe this should have been calculated in 'ERG Curves' cell H4 however this is currently referencing curves for cabazitaxel.	Not clear if proportion of TTD relative to PFS has been included in the model; the results do not change when changing options.	H4 references the H11 to H18 cells for CABA. The H11 to H18 cells for CABA reference the D11 to E18 cells for OLAP in order to calculate the appropriate TTD:PFS ratio.
Application of TTD ratio for cabazitaxel 'Model Calcs CABA' cells BH13:BI14	In the current ERG rebuild model, the TTD scenario for cabazitaxel only affects the drug and administration cost of cabazitaxel. The following costs should also be adjusted to be based on the TTD curve: • Concomitant medications: BH15, BI15	TTD ratio for cabazitaxel only partially implemented.	The ERG accepts that the concomitant medication and administration costs should be similarly amended. The effect upon BSC and sub tx costs is more problematic to implement within the company model structure. The ERG thinks that not addressing these elements will slightly

	• Disease management costs: BH18, BI18, BH19, BH19 • BSC and sub tx: BH20, BI20, BH21, BI21 Without correcting these cells, these cost categories remain based on PFS, and the total costs associated with cabazitaxel would be underestimated.		bias the analysis in favour of olaparib. The ERG provides amended results which similarly increase concomitant medication costs and administration costs.
Lower 1st administration cost 'Model Calcs CABA' cell BH18, BI18	Although this does not result in an error to the total cost for cabazitaxel, we would recommend including the lower cost of 1st administration to the administration cost category cell rather than disease management/monitoring costs to report the results accurately. 1. Remove the adjustment within the management cost formula in 'Model Calcs CABA' cell BH18: =(SUMPRODUCT(c.ontx,c.time.hrzn)*(INDEX(m.ru.OnTx, CHOOSE(macro.tx.index,1,3))*c.OnTx.Monit.index+INDEX(m.ru.OnTx,CHOOSE(macro.tx.index,2,3))*(1-c.OnTx.Monit.index)))*m.sel.dir.mc.disease ~~+IF(ERG.Corr.CABA.Admin.Cost,ERG.Corr.CABA.Admin.Cost.Reduction,0)~~ 2. Edit the formula in cell BH14:	Calculation in the wrong cell resulting in misleading totals in cost categories.	No factual error. No revision required. Also note that the company proposed revision would be much clearer if it could amend the relevant cells in the Model_Calcs_CABA worksheet, and use direct cell/variable referencing rather than the now unnecessary indirect indexing.

	=IF(ERG.Assump.CABA.TTD="TTD",ERG.CABA.TTD.to.PFS.Tx.Ratio,1) *((SUMPRODUCT(c.ontx.nhc,c.time.hrzn,c.maint.dur.flag) *INDEX(m.admin.Tx.cost,macro.tx.index)-$AY$9 +IF(ERG.Corr.CABA.Admin.Cost,ERG.Corr.CABA.Admin.Cost.Reduction,0)) *m.sel.dir.mc.admin)		
Cost of ADT/LHRH 'Disease Mgmt Cost' cell H89	Please could the ERG check the monthly cost for leuprorelin in 'Disease Mgmt Cost' cell H89, which may have been underestimated in the ERG rebuild model. The calculated cost of £75.24 in 'Other Drug Cost' cell L64 represents the monthly cost of leuprorelin. Furthermore, an additional monthly ancillary cost is not required since the model already includes the cost of regular visits that are applied for the duration of the patient's lifetime (on treatment, and every 3 months ~~for patients~~ even for patients who are off treatment). The ERG's inclusion of an additional monthly ancillary cost leads to significant double counting. Therefore we recommend the following change to the formula:	Incorrect cost of ADT/LHRH affecting ERG results.	The ERG accepts that F89 should not be divided by 3. But as these ADT costs are not applied to BSC costs but throughout the patient OS and these have not been accounted for in the other resource use responses the ERG rejects the removal of the ADT administration costs, other than from the BSC costing.

	=(F89~~/3+ERG.Corr.ADT.Monthly.Ancillary.Cost~~)*ERG.Corr.ADT. Percentage.Receiving		
Concomitant medications 'Model Calcs CABA' and 'Model Calcs OLAP' cell BH15, BI15	There are two errors that lead to an underestimation of the total cost of concomitant medications for cabazitaxel: • The percentage of patients receiving G-CSF '*ERG.Assump.GCSF.Proportion*' is applied to <u>all</u> pre-medications instead of just to G-CSF. • The ratio of G-CSF duration (i.e., 7/15 days = 50% is applied to <u>all</u> pre-medications instead of just to G-CSF. We suggest three changes (all required together) to correct these issues while maintaining the ERG's functionality: 1. Edit the percentage of G-CSF uptake directly in the inputs sheet ''Disease Mgmt Cost' cell H127 Replace 100% with "=ERG.Assump.GCSF.Proportion" 2. Edit the duration of G-CSF directly in the inputs sheet 'Other Drug Cost' cell I61: Replace the value 14 with "=ERG.Assump.GCSF.Days"	Incorrect implementation of concomitant medications for cabazitaxel affecting ERG results.	The company correctly identifies that the concomitant medication costs for cabazitaxel are all treated in a like manner to G-CSF. The total cost per model cycle for the additional concomitant medication costs is £2.37: The 60%*50% amendment to these underestimates these costs by £1.66 per month. The error is inconsequential to irrelevant. Given the PFS curve the ERG will more simply add £1.66 to each the cabazitaxel on treatment proportions' model cycles to correct for this. But there is a more serious error in that the CABA ADT costs are also conditioned by the 60%*50% ERG G-CSF amendment.

	3. Correct the formula in 'Model Calcs CABA/OLAP' cell BH15 (similar change required for BI15) =~~ERG.Assump.GCSF.Proportion*(ERG.Assump.GCSF.Days/14)*~~ (IF(ERG.Corr.CABA.Concomittant.Costs,SUMPRODUCT (ERG.Flag.CABA.OnTx,c.ontx,c.time.hrzn),SUMPRODUCT(c.ontx,c.time.hrzn)) *INDEX(m.monit.cost,macro.tx.index)*m.sel.dir.mc.monitor+BD24)		
Error regarding on/off-treatment life years 'Model Calcs CABA' and 'Model Calcs OLAP' cells BD15:BE16 As reported in P156 Table 64 (first two rows)	These calculations do not currently consistently show the total LYs on treatment / off treatment. In the ERG's model: Total PFLYs = on tx LY + off tx LY The calculation should show: Total LYs = on tx LY + off tx LY Where 'off tx LYs' are the total life years accrued post treatment-discontinuation until death. Since there are no other calculations dependent on these results, we suggest removing them in the model and removing the corresponding results from the ERG report.		The ERG agrees that the first two rows of Table 56 and of Table 64 for On Tx and Off Tx should be deleted.
ERG rebuild model results that include the ERG's modifications and preferred assumptions	Results that include the errors above should be reproduced and corrected in the ERG report. The following tables include such results:		The ERG provides a set of revised analyses and updates it's cPAS appendix.

	Table 63 Table 157 Table 67 Table 68 Table 69 Table 70		

Misleading statements

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Executive summary			
P11: “it was noted by the ERG’s clinical advisors that in the wake of Covid-19 patients are being prescribed NHA’s in the NHS to reduce patient risk. It is therefore likely that the number of patients taxane naïve will be increased going forward.”	We request that the ERG clarify that this is interim guidance and does not reflect routine clinical practice and is unlikely to give negative NICE guidance in ID945.	Misleading statement; does not qualify deviation from routine clinical practice.	Not a factual error. This reflects current clinical practice in Covid-19 times which we are experiencing. This is a clinical advisor statement.
P12, (P62): “The choice of a “prior taxane, A+B” (the target population) population was based on poorer PFS performance in no-prior taxane patients relative to prior taxane patients seen especially in people with BRCA2 mutations and to lesser extent in populations with mutations to other HRR genes.”	The prior taxane subgroup was selected on the basis of representing the most cost-effective use of NHS resources, and not due to poorer PFS. This statement does not reflect rationale provided by the company. Please could the ERG clarify which perspective this statement represents.	Misrepresentation of CS.	Amended to The choice of the “prior taxane, A+B” cohort as the target population appears to have been made “ *to align with the anticipated positioning of olaparib in the current clinical pathway of care in England (where the majority of patients receive a*

			taxane [docetaxel] for non-metastatic or metastatic HSPC, before receiving NHA for mCRPC [CS pg 14]". The ERG have found no statement in the CS suggesting the choice was made on grounds of cost effectiveness. The fact that efficacy was far superior in cohort A vs. other cohorts suggests this would be the target on the basis of cost effectiveness.
Critique of PROfound trial			
P57: No evidence is provided in the CS to support this statement or justify the exclusion of other genes in the HRR pathway.	The inclusion of the selected HRR mutations is justified from the results of the TOPARP-A study. This rationale is presented on p30 of the CS. Please could the ERG revise their statement accordingly.	Omission of evidence provided in the CS	This is not a factual error. While there is some overlap in the genes of interest between PROFound and TOPARP-A there are considerable differences. For example, 1. In TOPARP-A, HDAC2, MLH3, ERC3, MRE11, and NBN were associated with response to olaparib, but are not included in PROFound.

			2. PROFound includes genes that do not appear in TOPARP-A, e.g. BARD1, BRIP1, CDK12, CHEK1, PPP2R2A, RAD54L. The ERG maintains that no evidence is presented in the CS to explain why the particular genes were included and why others were omitted
P58: The ERG does not agree that (1) physician's choice of NHA limited only to abiraterone or enzalutamide is an appropriate comparator nor that (2) retreatment with NHA represents standard of care.	We would propose revising the statement to reflect that the trial does not reflect **UK clinical practice**, as this is incorrect from a global perspective (at the time the PROfound study was conducted): The ERG does not agree that (1) physician's choice of NHA limited only to abiraterone or enzalutamide is an appropriate comparator nor that (2) retreatment with NHA represents standard of care in the UK.	Misleading statement, as perspective (UK vs Global) unclear.	This is not a factual error. The CS states "re-treatment with NHA (i.e. enzalutamide after progression of abiraterone, and vice versa) are approved treatment options in this setting (by both the EMA[52,53] and the US FDA[54,55]) and is a standard-of-care in many countries where the PROfound study was conducted.[56]" The EMA and USFDA references do not refer to re-treatment with NHA being approved treatment options.

			And the National Comprehensive Cancer Network. Prostate cancer. NCCN Guidelines Version 1 (2020) does not refer to re-treatment as being a standard of care. In reference to progression after enzalutamide or abiraterone, the NCCN Guidelines states “Patients with disease progression after enzalutamide or abiraterone have the following options: docetaxel (category 1), abiraterone if previously given enzalutamide therapy, enzalutamide if previously given abiraterone, radium-223 for bone-predominant disease without visceral metastases (category 1), sipuleucel-T if asymptomatic or minimally symptomatic and without visceral metastases, life expectancy >6 months, and ECOG score 0-1, pembrolizumab if MSI-H/dMMR (category 2B), clinical trial, or secondary hormone therapy.”

P62: “Screening would be simplified for a BRCA2/CDK12 population.”	The ERG do not give any evidence to suggest that screening for two HRR genes would be any simpler than screening for 15 HRR genes. We believe the processes would be almost identical, given that a pan-tumour screening panel is most likely to be used. Please could the ERG kindly clarify their rationale or revise this statement.	Misleading statement; source/rationale unclear.	Not a factual error. “Simple” means less complicated. Screening for two mutations is less complicated than screening for 11 mutations.
P72: “However, as the significance level of OS at DCO1 was 10%, statistical significance was not reached.”	“However, as the significance level of OS at DCO1 was 10%, statistical significance was not reached. Statistical significance was reached at DCO2 (p64 of CS).”	Potentially misleading statement; does not capture relevant evidence from DCO2.	No factual error. OS at DOC2 results are presented in section 3.2.2.2.1, on page 73, which concludes statistical significance was reached for Cohort A.
Indirect treatment comparison			
P86: “The company concluded that it would not be feasible to conduct a PAIC.”	We propose revising the statement as follows: "The company concluded it was not necessary to conduct a PAIC because no effect modifiers were identified in the assessment of covariates in the PROfound and CARD datasets"	Misrepresentation of the evidence in the CS.	Amended
P89: When referring to HRR mutations in men who have mCRPC, the CS varyingly states that “Approximately 20%−30% of patients with mCRPC have mutations in genes involved in the homologous recombination repair (HRR) pathway” and “It was expected that qualifying mutations	We propose revising the statement: “When referring to HRR mutations in men who have mCRPC, the CS states that ‘Approximately 20%−30% of patients with mCRPC have mutations in genes involved in the homologous recombination repair (HRR) pathway’. ~~and ‘It was expected that qualifying mutations would be detected in the tumour tissue of approximately 1 in 10 patients with mCRPC’~~.”	The statement highlighted refers to rationale used at the point of designing the PROfound study, and has been superseded by several studies reporting HRR prevalence, as per Section B.1.1 of the CS.	Amended However no factual errors here since these are direct quotes from the company submission.

would be detected in the tumour tissue of approximately 1 in 10 patients with mCRPC".			
P89: According to the CS (section B1.1) there is evidence that the presence of HRRm is associated with more aggressive disease; therefore this imbalance may lead to a lack of concordance in the NHA arms of the trials that were used to anchor the ITC.	We propose revising the statement along the lines of the following, as this does not reflect the company position/CS in its current form: "According to the CS (section B1.1) there is evidence that the presence of HRRm is associated with more aggressive disease; however, no robust evidence has demonstrated a lack of concordance."	Misrepresentation of the evidence in the CS. There is no robust evidence that HRRm status would be an effect modifier for NHA treatment.	Amended
Issue: Language regarding the company model			
P131: "The company model is unusual. It has only a single Excel worksheet to model the patient cohort flow and distribution between the various health states for a single treatment. A Visual Basic for Applications (VBA) engine is then used to sequentially apply the comparator specific inputs to the patient cohort flow worksheet and then copy and paste the results as pure number to the results worksheet. This model structure requires extensive indirect indexing of model inputs through complicated formulae. There is no obvious reason to adopt this model structure in preference to the more usual, simple and transparent approach	The company model is not "unusual" (similar structures have been previously used and accepted in NICE TAs); relevant benefits associated with this form of model implementation have also not been acknowledged.	Language regarding model implementation is potentially misleading	No factual error. No revision required. The company model is unusual, as described by the ERG. The company does not state what the "benefits" of its submitted model structure are.

of having a cohort flow worksheet for each comparator that is being modelled."			
P132: "The lack of transparency may have contributed to the following errors."	We acknowledge that there are several differences between the company and ERG's preferred assumptions, but not all of the issues listed here are errors or mistakes. We would be grateful if the ERG could revise this sentence accordingly.	Incorrect and misleading statement.	No factual error. No revision required.
Issue: Statements or data related to survival			
P118, Figure 10	The graphs in Figure 10 and Figure 12 currently includes survival curves with an overlaid series for the "KM N risk". This graphical representation could be misleading. Please could the ERG add clarity regarding the data plotted for the "KM N risk" series. Alternatively, it is possible to display data for the numbers of risk in the conventional way to avoid confusion?	Clarity around KM graphs and corresponding text, which are currently ambiguous and may be open to misinterpretation.	No factual error. No revision required. But see revisions below.
P120, Figure 12			No factual error. No revision required. But see revisions below.
P118: "As a consequence, the company fits the usual set of parameterised curves to the PROfound olaparib arm Cohort A+B OS KM data"	Please could the population (e.g. prior taxane) be clarified in the text		The ERG will revise the text to: "As a consequence, the company fits the usual set of parameterized curves to the PROfound olaparib arm Cohort A+B prior taxane OS KM data (n=170)"
P120: "In common with the OS curve, the company fits the usual			The ERG will revise the text to:

set of curves to the rPFS Kaplan Meier curves as shown below."			"In common with the OS curve, the company fits the usual set of curves to the Cohort A+B prior taxane rPFS KM data (n=170) as shown below."
P121: "The company chooses the Weibull for its base case, because it has the lowest total AIC+BIC. The curves extrapolated to 5 years are shown below, there being little point showing the extrapolation beyond this to the 15 year time horizon"	We suggest the following revision: "The company chooses the Weibull for its base case, because it has the lowest total AIC+BIC. The curves extrapolated to 5 years are shown below, since almost all patients are predicted to have progressed by this time under each of the extrapolations."	Ambiguous statement by the ERG.	No factual error. No revision required.
Issue: Misleading text regarding source of SSRE rates used in the economic model			
P143: Section 4.3.4.12 Company expert survey: G-CSF use: SSRE rates with cabazitaxel	Please correct the title to: 4.3.4.12 Company expert survey: ~~G-CSF use:~~ SSRE rates with cabazitaxel	Misleading title that incorrectly suggests G-CSF use was linked to SSREs.	No factual error. No revision required. See section 4.2.1
P143: Section 4.3.4.12 Company expert survey: G-CSF use: SSRE rates with cabazitaxel "The respondents were asked "Please look at the table below and state whether the calculated average column reflects your expectations for patients with mCRPC currently receiving standard of care in a post-NHA setting". From the responses it appears that the table may have been framed around a [redacted] estimate. The responses range	We would suggest that the ERG considers removing this section as the CS does not use the values elicited from the clinical expert interviews, instead using cabazitaxel SSRE rates from de Wit et al.	Misleading text, which gives the impression that KEE estimates were used to inform SSRE rates for cabazitaxel in the economic model.	The ERG accepts that this is misleading. Section 4.3.4.12 will be appended with "*But it should be noted that the company does not use these results from its expert survey, preferring instead to use the values of de Wit et al*"".

from no difference to [redacted] There may be concerns around anchoring effects, and that any dissent from this was to suggest a lower estimate than that proffered by the company. Any effects of this upon costs effectiveness are likely to be small, unless spinal cord compression is assumed to have long term cost and QoL effects."			
Issue: Clarity / presentation of the ERG analysis			
P131: "The ERG has rebuilt the company deterministic model using the company preferred set of assumptions, and gets a good agreement with the company results when the model errors summarised in section 4.3.1.2 below are applied in the ERG model rebuild: olaparib is estimated to result in QALY gains and cost savings, so dominates cabazitaxel."	We suggest the following amends: "The ERG has rebuilt the company deterministic model using the company preferred set of assumptions, and gets a good agreement with the company results when the model errors summarised in section 4.3.1.2 below are not corrected for ~~applied~~ in the ERG model rebuild: olaparib is estimated to result in QALY gains and cost savings, so dominates cabazitaxel."	Revised for clarity.	No factual error. No revision required.
P131, Table 53	Please could the ERG kindly check the results as we obtain marginally different results using the ERG rebuild model (e.g., NHB of £[redacted] instead of the reported £[redacted]).	Potential small inaccuracy in the results tables.	The ERG incorrectly reports the NHB: The company model NHB should be [redacted] and the ERG model rebuild should be [redacted]
P154:	We suggest amending these labels to provide complete transparency about the assumptions made:	Clarity around the assumptions and data preferred by the ERG.	No factual error. No revision required.

• ERG02: Apply the ERG Weibull curves for olaparib OS, PFS and TTD • ERG03: Cost drug use using the median RDI and the TTD curve	• ERG02: Apply the ERG Weibull curves for olaparib OS, PFS and TTD**;** and ERG HRs for cabazitaxel OS and PFS • ERG03: Cost drug use using the median RDI and the TTD curve for olaparib**;** and mean RDI and PFS for cabazitaxel		These are transparently described in the preceding text; the table labels are abbreviated for reasons of space.
P154, Table 63	We would similarly request that the scenario labels in the tables are updated for clarity: • ERG03a: TTD costing for olaparib only • ERG03b: median RDI for olaparib only		No factual error. No revision required. These are transparently described in the preceding text, and the Table labels are abbreviated for reasons of space.
P165: • ERG03a: Costing using the TTD curve rather than the rPFS curve • ERG03b: Costing using the median RDI rather than the mean RDI	We would similarly request that these labels are updated for clarity: • ERG03a: Costing olaparib using the TTD curve rather than the rPFS curve • ERG03b: Costing olaparib using the median RDI rather than the mean RDI		No factual error. No revision required. These are transparently described in the preceding text, and the Table labels are abbreviated for reasons of space.

Further clarifications from the company, based on ERG report

Description of problem	Clarification	ERG Response
Issue: Countries in which recruitment was conducted		

P59: Further, countries in which recruitment was conducted are listed as in Asia, Australia, Europe, North America, and South America in the CSR (page 2) but Australia was omitted in the de Bono publication (figure 2, page 8) and clarification response (v0.1 02.07.20, Table 3, page 9).	Australia is mentioned as one of the countries with study centres in the De Bono publication (supplementary appendix p4) p33 of the CS. This differs from mentions of "Region" across the submission materials, which was a subgroup of interest in PROfound (including: Asia, Europe, North and South America).	No revision required.
Issue: Critique of the methods of review		
P28: "Studies excluded for inconsistent reasons not specified in PICO (e.g. Mateo et al. 2015 excluded because of dose, but dose not an exclusion criteria)." P28: "doses and participant nationality were subsequently used as exclusion criteria." P28: "the ERG found the study selection criteria and process not to be well specified" P30: "Exclusion criteria that were not pre-specified were applied to studies."	We acknowledge and apologise for any confusion introduced by the final column of Tables 12-15 of the Appendices, which discuss feasibility for the indirect treatment comparison. We are examining the issues raised in the ERG report with regards to the clinical SLR in readiness for technical consultation and would be happy to provide further information at that stage or prior (if helpful).	No revision required.
Issue: Clinical expert study		
P116: "It is unclear whether the same experts were used for each telephone questionnaire, and whether all surveys were conducted during a single telephone questionnaire with each	We note the issues raised regarding aspects of the clinical survey, and will examine these further in preparation for the technical engagement.	No revision required.

respondent or were conducted separately." P128: "It is unclear whether these were the same 6 expert respondents who participated in the OS elicitation telephone questionnaire survey, but this seems likely to be the case." P136: "The majority of respondents suggest considerably greater survival with cabazitaxel than is modelled by the company preferred log-logistic curve. The ERG questions the reliability of respondent 2, respondent 4 and respondent 5. If these respondents are removed from the survey results, there is very little left." P136: The reasons for the apparent bias, or at a minimum lack of understanding, of respondent 2, respondent 4 and respondent 5 are unknown.		
Issue: Indirect treatment comparison		
P13. "Network meta-analysis was inappropriate as the assumption of transitivity is likely to be violated by differences in HRR mutation status of samples in the two studies."	The company submission discusses that, while HRR status cannot be ascertained in CARD, there is no robust evidence to suggest this would violate the transivity assumption (p82 of CS).	Not a factual error; rather this is a difference of opinions.

P89: “The PROfound trial and the CARD trial differ noticeably in terms of geography. The PROfound trial was 35% Asia, 43% Europe and 23% North and South America , whereas the CARD trial was conducted exclusively in Europe. These geographic differences may be the cause of some of the apparent differences in subsequent treatments”	The baseline characteristics of the PROfound study population show similarity to those of the UK-based TOPARP-A/B study populations, which were conducted in pre-treated mCRPC populations.”	Not a factual error.
Issue: HRR genetic testing		
P146: “The ERG made enquiries with each of the 7 GLHs, asking: if they had the ability to panel test for (A) the Cohort A HRR genes and (B) the Cohort B HRR genes, and; if they were aware of or had an opinion about prostate cancer and the HRR genes being added to the 2021 GLH Test Directory, and as Core commissioning. To date, the ERG has received responses from only 2 of the GLHs. Both have the ability to panel test for the Cohort A and the Cohort B HRR genes. Neither knows whether HRR genes will be specified as part of prostate cancer panel testing under Core commissioning. It is consequently unclear where the AstraZeneca Diagnostics team gets its information from.”	[redacted]	No factual error. No revision required.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technical report

Olaparib for previously treated hormone-relapsed metastatic prostate cancer [ID1640]

This document is the technical report for this appraisal. It has been prepared by the NICE technical team.

The technical report and stakeholder's responses to it are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the appraisal committee meeting.

This report is based on:

- the evidence and views submitted by the company, consultees and their nominated clinical experts and patient experts and
- the evidence review group (ERG) report.

The technical report should be read with the full supporting documents for this appraisal.

Key issues summary

Issue	Summary	Technical Team Preliminary Judgement
Clinical effectiveness issues		
Issue 1 - The population in the company's submission is narrower than the scope and clinical trial evidence	• The population in the scope is defined as 'people with hormone-relapsed, metastatic prostate cancer with homologous recombination repair gene alterations previously treated with hormonal therapy (e.g. abiraterone or enzalutamide)' (NICE final scope) • The population in the pivotal phase III PROfound trial is in line with the population of the scope • The company's submission focuses on a subgroup; people who have been treated with hormonal therapy and a taxane (CS page 17) (however, it argues that the population which has not received a taxane should be included within any committee recommendation, due to equality considerations). • The company states this is based on clinical experts' opinion that in the UK, around 75% of patients have already received treatment with a taxane prior to new hormonal agent (NHA) treatment (CS page 14). • ERG clinical advisor confirmed that most patients will have received docetaxel prior to progression to mCRPC, but the proportion is likely less than 75% (ERG report page 23) • Since COVID-19, more patients are receiving NHA instead of docetaxel to minimise the risk of infection. It is expected that the number of patients with no prior taxane use will increase going forward (ERG report page 23)	• The evidence submitted only covers a subgroup of the population defined in the scope and clinical trial evidence. • It is acceptable for the company to state that it considers the base case value proposition of olaparib to be narrower than the scope population. However, the company should consider presenting exploratory scenarios within the full scope population, which would allow the committee to consider making broader recommendations. • Clinical advice is needed on what proportion of patients would have already received docetaxel prior to NHA treatment.

Issue 2 - The company presents analyses from the PROfound trial which suggest differing clinical effectiveness within subgroups	Cost effectiveness of olaparib in cohort B subgroup • PROfound is a randomised controlled trial (RCT) comparing olaparib to NHA (i.e. abiraterone or enzalutamide). • The trial included 2 cohorts: cohort A is composed of patients with 3 HRR mutations (ATM, BRCA1 and BRCA2) and cohort B is composed of patients with 12 other HRR mutations (CS page 30). • The effect of olaparib seems greater in patients in cohort A than across all cohort A+B patients. Therefore, the ERG believes that the cost effectiveness of olaparib in cohort B should be compared with that in cohort A (ERG report page 148). Cost effectiveness of olaparib in the no prior taxane subgroup • The company's submission focused on cohorts A+B with prior taxane use (CS page 107). The ERG considers that this choice may be based on poorer PFS outcomes in the group with no-prior taxane compared with prior taxane (ERG report page 63). • This may increase the presumed clinical effectiveness of olaparib in terms of PFS (ERG report page 114). • The company's cost effectiveness estimates exclude those with no prior taxane use. Instead, the company argues that access to olaparib should be considered for these patients, under equality provisions (CS page 19 and 21).	Cost effectiveness of olaparib in cohort B subgroup • Exploratory analyses comparing the cost-effectiveness of cohort A compared with cohort B should be conducted. Cost effectiveness of olaparib in the no prior taxane subgroup • Prior taxane use is not specified in the scope. It is unclear whether the evidence in the prior taxane group can be extrapolated to the no prior taxane group, therefore exploratory analyses should be conducted to consider the impact of this uncertainty.

	• The ERG believes the selection of the 'prior taxane' population is not appropriate for decision making about the no-prior taxane population (in PROfound, 42% did not receive prior treatment with taxane) (ERG report page 65). • No evidence is presented for the no prior taxane use, so the cost effectiveness of olaparib in this group is uncertain. • In addition, the effectiveness (PFS) of olaparib is higher in the 'prior taxane' group (ERG report page 114).	
Issue 3 - The company has not provided analyses compared with all comparators in the scope	• Comparators in NICE scope included cabazitaxel, docetaxel and radium-223 dichloride for people with bone metastases. NICE scope states that the different positions of the comparators in the pathway should be considered (NICE final scope). • The company's submission only included cabazitaxel as a comparator, because of the lack of evidence on radium-223 and docetaxel following NHA treatment. • The company also stated that docetaxel was excluded because it is usually used earlier in the pathway and it would not be used again at this point. Clinical experts consulted by the company reported that radium-223 was used in later treatment lines (after NHA and cabazitaxel) unless treatment with a taxane was not suitable (CS page 14 and 15). • Both ERG's and company's clinical experts agree that docetaxel is used earlier in the treatment pathway. • The ERG considers the exclusion of docetaxel appropriate and agrees that there is a lack of randomised controlled trial evidence on radium-	• It is likely that the most relevant comparator is cabazitaxel. However, clinical advice is needed on whether it is appropriate to exclude docetaxel and radium-223 from the comparators.

	223 dichloride in the population of interest (ERG report page 24 and 27).	
Issue 4 - Generalisability of the trial to the UK population and NHS clinical practice	Population • The PROfound trial was conducted in Asia (35%), Europe (43%) and North and South America (23%). Only 4 patients were recruited in the UK (CS page 33). Comparators • In the PROfound trial, all patients had progressed following treatment with abiraterone, enzalutamide or both (CS page 32). • In the control arm of the trial, patients would receive physician's choice of NHA, that is, abiraterone or enzalutamide (CS page 33). • [redacted]% of the control arm had previously received both abiraterone and enzalutamide; the ERG considers this represents a minimum of [redacted]% of the control arm received a treatment for which no benefit can be expected as they already progressed on these treatments (ERG report page 59). • The ERG supports its statement with data of patients with mCRPC treated with abiraterone followed by enzalutamide (or vice versa) that suggested that the majority of patients do not benefit from subsequent NHA treatment (ERG report page 59). • The ERG believes that other treatments could have been used as trial comparators such as cabazitaxel or paclitaxel, which are more likely to be used in clinical practice. In addition, many patients in the trial had not previously received cabazitaxel or paclitaxel (ERG report page 60).	• It is unclear whether the clinical trial results are generalisable to the UK population (patients characteristics in PROfound are in appendix 1 of this report). • Clinical advice is needed on the comparability of patients included in the PROfound trial to UK patients. • Clinical advice is needed on whether a benefit can be expected from subsequent NHA treatment. • The company should explore a scenario excluding patients in the control arm who had previously received both abiraterone and enzalutamide.

	• The ERG believes the choice of comparator in PROfound is inadequate and not applicable to clinical practice (ERG report page 59). • The ERG is concerned that the generalisability of the PROfound trial to the UK setting may be limited (ERG report page 60).	
Issue 5 - Heterogeneity of the PROfound and CARD trials used to indirectly compare olaparib with cabazitaxel	• In the company's submission, olaparib is indirectly compared with cabazitaxel using data from the PROfound (olaparib vs NHA) and the CARD (cabazitaxel vs NHA) trials (CS page 81). However, there are a number of differences between the trials which may mean they are too heterogeneous for indirect comparison. • All patients in PROfound are known to have an HRR mutation, while gene mutation status is unknown in CARD. The presence of HRRm is associated with more aggressive disease, although no robust evidence has demonstrated that HRRm status would be an effect modifier for NHA (CS page 8 and 80). The ERG considers this imbalance may lead to discrepancies in the comparator arms (NHA) of the trials that are used to anchor the indirect treatment comparison (ITC) (ERG report page 90). • Both studies included radiological progression-free survival (rPFS) as the primary outcome (ERG report page 88). However, the central review of imaging in CARD was not blinded, which introduces a bias (ERG report page 88). • Previous treatment with cabazitaxel in the CARD trial was very unlikely, while about 30% of the target PROfound population had received cabazitaxel prior to randomisation (ERG report page 90).	• When conducting an ITC, it is assumed that the RCTs included in the comparison are similar in all respects other than the intervention received (transitivity assumption). Given the differences between the two trials, the transitivity assumption may not hold in this case (ERG report page 89). • The heterogeneity between the PROfound and CARD trials may bias results. The company should explore steps to mitigate this or describe the potential impact this might have on results.

	• The two trials differ in terms of location: the PROfound trial was conducted in Asia (35%), Europe (43%) and North and South America (23%) while the CARD trial was conducted in Europe exclusively. This may lead to differences in subsequent treatments (ERG report page 90).	
Issue 6 - The indirect treatment comparison (ITC) of olaparib vs cabazitaxel is uncertain	<u>Methods to derive Hazard Ratios (HR)</u> • Methods used to determine HR inputs for OS for the ITC are inconsistent (ERG report page 91): o the HR from PROfound was obtained using a Weibull distribution under the proportional hazard assumption o The HR from CARD was obtained from a Cox model under the proportional hazard assumption o ERG believes that the HRs from PROfound and CARD should have been derived from the same parametric distribution and that these inconsistencies weaken the reliability of the ITC. • For PFS, the ERG noticed a slight discrepancy between the HRs reported in the company's submission ([redacted] vs [redacted]) which was due to rounding errors (ERG report page 93). • Moreover, the ERG believes the systematic literature review is at high risk of bias (See other issues for information), which may impact the quality of the network. • Due to the quality of the ITC, the ERG considers that the ITC is not appropriate to provide any meaningful or statistically significant outcomes on the comparison of olaparib and cabazitaxel for either rPFS or OS (ERG report page 93).	• The indirect treatment comparison is associated with uncertainty. • Although the ERG conducted analyses with alternative HR which had only a minor impact on cost-effectiveness results, this may not fully address the uncertainty. This is because some of the limitations of the company's analyses cannot be lifted in the ERG's alternative analyses (e.g. transitivity assumption may not hold) and the alternative HR are similar to the company's HR. The company should attempt to explore this in more detail.
Cost effectiveness issues		

Issue 7 - Choice of distribution for overall survival extrapolation	• To model OS with olaparib over time, the company used the loglogistic distribution (CS page 125) and the HR of olaparib vs cabazitaxel that was derived from the indirect treatment comparison is then applied to the curve to derive cabazitaxel OS. • Curve choice was based on phone questionnaires with clinical experts in which they were asked what proportion of patients were likely to survive at 3, 5 and 10 years when treated with standard of care, radium-223, cabazitaxel or olaparib. • Clinical experts estimated an average survival of [redacted]% at 3 years, [redacted]% at 5 years and [redacted]% at 10 years. The company chose the loglogistic model as it provided the best fit to clinical experts estimates (CS page 125). • The ERG believes the choice of loglogistic is questionable for the following reasons (ERG report page 113): o Applying an HR to a loglogistic model is not appropriate, because the hazards in loglogistic vary over time and the proportional hazard (PH) assumption does not hold (ERG report section 3.6.1.7) o As a result, loglogistic is unlikely to produce a reliable model for survival with cabazitaxel (ERG report section 3.6.1.7.) o Moreover, gain in OS for olaparib vs cabazitaxel was more than double for loglogistic model than for either Weibull or Rayleigh models, so loglogistic may overestimate the OS gain (ERG report page 106). o The clinical experts' estimates were quite heterogeneous (ERG report section	• The estimates from the company's clinical experts are heterogeneous. • The Weibull distribution seems the most appropriate as it has the lowest Akaike information criterion and Bayesian information criterion (AIC+BIC), has a proportional hazard property and provides more conservative OS predictions.

	4.3.4.1), and there is no robust published evidence in the real world setting to confirm these estimates (ERG report section 3.6.1.8). • The ERG believes it is more appropriate to use survival models that have a proportional hazards property, such as Weibull or Rayleigh (ERG report page 111 and 113). • The ERG's preferred assumption is to use the Weibull distribution, as it has the lowest AIC+BIC	
Issue 8 - Discrepancies between progression-free survival and time to treatment discontinuation curves	• To model radiological progression-free survival (rPFS) of olaparib over time, the company used the Weibull distribution (CS page 121). • The company assumes that rPFS is equivalent to treatment duration (CS page 133). • However, the Kaplan-Meier rPFS and time to treatment discontinuation (TTD) data from PROfound show that the TTD curves lie above the corresponding rPFS for both olaparib and NHA arms (ERG report page 142), suggesting that people have radiological progression sooner than treatment is stopped. • In the PROfound protocol, the possible reasons for treatment discontinuation were reported. The ERG considers that the protocol suggests that patients did not have to stop treatment upon disease progression (ERG report section 4.3.4.9). • The ERG believes that a same event may not be treated consistently when constructing the TTD and rPFS curves, which may explain the differences between curves. For example, withdrawal of consent events is often treated as censoring within PFS curves but as an event within the TTD curve (ERG report page 143).	• There is uncertainty about how the TTD and PFS curves were constructed and whether patients had to stop treatment upon progression. The company should clarify this further. • This has implications on the calculation of treatment acquisition costs.

	• At clarification, the ERG requested the daily KM data to investigate how events were treated in the construction of rPFS and TTD curves. • However, the company could not supply these data and the ERG was not able to assess whether and to what degree these considerations apply. • The ERG believes it may be a major consideration and source of uncertainty in the evidence (ERG report page 143) • For cabazitaxel, no TTD curve is presented in the publication of CARD trial. The ERG provides a scenario where cabazitaxel TTD curve is assumed to be lying above the cabazitaxel PFS curve by the same proportion than between the olaparib TTD and PFS curves (ERG report page 143).	
Issue 9 - Olaparib acquisition costs and relative dose intensity calculation	• Olaparib acquisition cost is calculated based on the mean olaparib relative dose intensity (RDI) of [redacted]% from the PROfound trial (CS page 158) • At clarification, company specified that an unweighted mean is used to calculate RDI, and the exposure across patients is not accounted for (e.g. a patient on treatment for 1 month with 50% RDI and a patient on treatment for 24 months with 100% RDI would result in a mean RDI of 75%) (ERG report page 141). • As individual patients' RDI is skewed, and the median RDI is considerably higher than the mean, the ERG believes that the median RDI ([redacted]%) should be used instead of the mean (ERG report page 141). • Also, the company applies the mean RDI for olaparib to PFS curves in its submission. The ERG considers it is inappropriate because the	• The ERG's approach using the median RDI seems more appropriate, as the company's approach using an unweighted mean is likely to underestimate the RDI of olaparib. • The ERG's approach of applying the acquisition costs to TTD curve instead of rPFS is more appropriate because it reflects the time spent on treatment.

	RDI estimates are based upon individual's TTD curve and costs should instead be applied to the TTD curve (ERG report page 140). • The ERG's preferred assumption is to use the median RDI and to apply it to the TTD curve (ERG report page 141).	
Issue 10 - Post progression treatments costs calculation	<u>Proportion of patients receiving an active subsequent treatment in the model</u> • The proportion of patients receiving active treatment following progression in the model is based on the PROfound (for the modelled olaparib arm) and CARD (for the modelled cabazitaxel arm) trials: 49% in PROfound and 58% in CARD. The rest of the patients receive best supportive care (BSC) (CS page 167). • However, the ERG considers that the proportion of patients receiving active post progression treatment in CARD should be 42% instead of 58%. This is because out of the 120 patients who discontinued treatment in CARD, 69 patients received a subsequent anticancer therapy including 19 patients who received palliative radiotherapy, which is already accounted for in the BSC costs (ERG report page 134). • So only 50 patients in CARD should be considered as receiving active post progression treatment. • Moreover, ERG experts explained that for patients who failed cabazitaxel, there are few treatment options available so it is unlikely that cabazitaxel patients would receive more of an active drug after progression than would olaparib patients (ERG report page 146).	<u>Proportion of patients receiving an active subsequent treatment</u> • It may be a more accurate reflection of the CARD trial for the model to assume 42% of patients received subsequent treatments, rather than 58%. • Clinical advice is needed on the proportion of patients receiving an active subsequent treatment after progression on olaparib or cabazitaxel (same or different rates). • Clinical advice is needed on the distribution of each subsequent treatment and whether it would differ between olaparib and cabazitaxel.

	• As a result, ERG's preferred assumption is that treatment distributions in post progression are equalised between arms. <u>Treatments included in the model</u> • In the model, the active treatments received following progression included: cabazitaxel, docetaxel, abiraterone, enzalutamide and radium-223 (CS page 167). • The ERG considers that NHA (i.e. abiraterone and enzalutamide) should not be part of subsequent treatments in the model as the company noted that it is not reimbursed in England and does not reflect current standard of care. ERG's preferred assumption is to exclude them from post progression treatment costs (ERG report page 146). <u>ERG's scenario of a 50% increase in olaparib PPS costs</u> • Active treatment was treated as a fixed cost, while total BSC costs were proportionate to the time spent in post progression survival (PPS) • At clarification, the company provided the number of patients who received a subsequent treatment after olaparib in the Cohort A+B prior taxane group: [redacted] patients received a subsequent treatment and a total of [redacted] treatments were received among these patients (ERG report page 144). • This implies that patients received more than one subsequent treatment ([redacted] treatment on average) • Moreover, the company base case estimates [redacted] longer PPS for olaparib compared to cabazitaxel (ERG report page 144).	<u>Treatments included in the model</u> • The company should consider removing NHA (i.e. abiraterone and enzalutamide) as subsequent treatments in the model because it is not reimbursed in England and does not reflect current standard of care. • The company should consider equalising distributions across the treatment arms. • Clinical advice is needed on types of treatments received after progression and whether NHA would be used in clinical practice. <u>ERG's scenario of a 50% increase in olaparib PPS costs</u> • The ERG scenario of 50% additional PPS costs in the olaparib arm is helpful to explore the uncertainty in this area but is likely to be highly conservative because there is also likely underestimation of costs in the cabazitaxel arm.

	• The number of subsequent active drugs received may be related to the duration of PPS and the ERG considers that PPS treatment options and treatment sequences are broader after olaparib than cabazitaxel, because it seems more likely that cabazitaxel could be used in PPS in the olaparib arm. • The ERG therefore provided a scenario with a [redacted] increase in olaparib PPS costs (ERG report page 146). However, the ERG notes that the CARD publication only provides the first subsequent anticancer treatment, so there may also be some underestimation of the PPS drug costs in the cabazitaxel arm (ERG report page 144).	
Issue 11 – Granulocyte colony-stimulating factor (G-CSF) costs estimate	• The company assumed that all patients receiving cabazitaxel would receive prophylaxis with G-CSF to reduce the risk of neutropenia, and that the treatment duration would be 14 days for all patients (CS page 160). • The company states that this is in line with SmpC of cabazitaxel and CARD study (CS page 160). • However, different outcomes were reported in the experts' survey conducted by the company. [redacted]. (ERG report page 143) • ERG clinical expert stated that primary prophylaxis with G-CSF was not standard practice but may be used in secondary prophylaxis in case of neutropenia, and that treatment duration was usually 5 to 7 days (ERG report page 144).	• The ERG's approach seems more appropriate as it is more in line with clinical experts' estimates consulted by the company and the ERG clinical experts. • Clinical advice is needed on the duration of treatment with G-CSF.

	• The ERG considers that the company's assumption overestimates the costs associated with G-CSF (ERG report page 144). • Moreover, as the company used the expert survey for most resource use estimates, the ERG considers that it should also be used for G-CSF costs (ERG report page 143). • The ERG's preferred assumption is that only [redacted] of patients on cabazitaxel will receive G-CSF and for only 7 days instead of 14 days. (ERG report page 144).	
Issue 12 - HRR genes test costs	• The current Genomic Laboratory Hub (GLH) Test Directory does not cover HRR testing for metastatic castration resistant prostate cancer (mCRPC) (ERG report page 147). • The company provided a scenario analysis including test costs, applied as one-off cost of £[redacted] (CS page 178). • At clarification, the company provided the number of patients that had been screened and tested for HRR mutations in the PROfound trial and who had remained eligible for trial: 4,425 patients were initially screened and tested, 2,792 were successfully sequenced and 778 of these had cohort A genes, cohort B genes or both (Company clarification response page 39). • As a result, the prevalence of cohort A+B HRR genes is unclear. It could be 17.6%, 27.9% or a value between these two (ERG report page 148). • As stated by the company in their clarification response, it is anticipated that approximately four patients will need to be tested to identify one patient suitable for Olaparib (i.e. 100%/27.9% =3.58) (company clarification response page 61)	• The ERG's approach is more appropriate. Costs associated with HRR gene testing should take into account the HRR prevalence as more patients would need to be tested in order to identify the eligible patients for olaparib. The cost of gene testing should be applied to all patients that need to be tested. • NICE's methods guide of technology appraisal states that if the use of a technology is conditional on the presence or absence or a particular biomarker (for example a gene or a protein), the costs associated with the diagnostic test should be incorporated into the assessments of clinical and cost effectiveness. A sensitivity analysis should be provided without the cost of the diagnostic test. • The company should consider incorporating the gene test costs in its base case analysis and provide a scenario without the test costs.

	• As a result, the ERG believes that the test cost should account for the HRR prevalence and the number of patients that need to be tested • The ERG's preferred assumption is to apply the £[redacted] test cost in its base case conditioned by an HRR prevalence of 27.9% ([redacted]/27.9%=[redacted]) (ERG report page 148).	
Issue 13 - End-of-life criteria	• The company stated that olaparib qualifies for end-of-life medicines (CS page 187). • The end-of-life criteria are the following: o The treatment is indicated for patients with a short life expectancy, normally less than 24 months. o There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment. o The treatment is licensed or otherwise indicated for small patient populations. • The ERG highlighted that the log-logistic, Weibull and Rayleigh all predict an OS in the cabazitaxel arm of less than 24 months. • The net OS gains are [redacted] months for the log-logistic OS curve, [redacted] months for Weibull and [redacted] months for Rayleigh OS curve (ERG report page 163).	• The criterion on short life expectancy appears to be met. • However, the estimates of the extension to life are based on the indirect treatment comparison which is uncertain. • Clinical advice is needed on the size of the population eligible for treatment with olaparib.

Other issues for information

Issue	Explanation
The systematic literature review is at high risk of bias	ERG considers the systematic literature review (SLR) conducted by the company to be associated with high risk of error. This is due to the lack of details in the description of study selection criteria, in the methods specifications and the reliance on a single reviewer for final study selection and extraction (ERG report page 12). The ERG considers that final study selection should be conducted by 2 independent reviewers. ERG believes that some excluded studies could have potentially added to the network. (ERG report page 32). The ERG does not consider the inclusion criteria of the review to be appropriate, as the population defined in the SLR does not match the population of the NICE scope nor the company's submission regarding the status of HRR genes (ERG report page 34 and 35).
Company's model is unusual	ERG highlighted that the company's model is unusual, and a Visual Basic for Applications (VBA) engine is used to sequentially apply the comparator specific inputs to the patient cohort flow worksheet. This model requires extensive indirect indexing of model inputs through complicated formulae. The ERG considers that the model is not very transparent, and the structure has considerably complicated the conduct of a reliable review. The lack of transparency may have contributed to the errors described in the next issue.
ERG costs correction on 1. G-CSF costing 2. BSC costing, 3. cabazitaxel administration, 4. olaparib monitoring	1. Cabazitaxel is associated with a considerable concomitant cost due to G-CSF prophylaxis. However, this cost is applied to all patients who remain in PFS and is not limited to the ten 3-week cabazitaxel treatment cycles. Correcting this reduces the net saving by £2,432. 2. BSC costs are applied to the proportion of patients not receiving an active subsequent treatment in each arm. However, the patients receiving an active subsequent treatment are assumed to receive only one subsequent treatment and for a limited period of time, that is, not for the whole post progression survival. The ERG believes that once patients stop their active subsequent treatment, they would receive BSC. ERG applies BSC costs following progression on subsequent treatment. Correcting this reduces the net savings by £1,544. 3. Cabazitaxel administration cost does not take into account the lower NHS reference cost for the 1st administration. Correcting this reduces the net savings by £108. 4. The monitoring costs associated with olaparib are implemented incorrectly as the higher monitoring cost is applied during the first 3 months of treatment only. Correcting this reduces the net savings by £425.

Proportion receiving ADT/LHRH (androgen deprivation therapy/Luteinizing hormone-releasing hormone)	In the company's submission, around [redacted]% of patients are assumed to be receiving ADT/LHRH, as part of BSC costs during PPS. However, experts consulted by the ERG suggested that the majority of patients receive ADT/LHRH throughout treatment pathway. The ERG's preferred assumption is to remove ADT/LHR from BSC cost and to apply a monthly ADT/LHRH cost during OS to all patients. In addition, a 3-monthly nurse led outpatient appointment is applied.
Bone and CT scans	The company assumed that bone scans and CT scans are about twice as frequent for patients having cabazitaxel than with olaparib, based on their clinical expert survey. ERG expert opinion suggested that scans were likely to be more necessary with olaparib than cabazitaxel because oral therapies have no pre-defined treatment cessation point while with cabazitaxel, scans would not be needed until the end of treatment course. The ERG's preferred assumption it to make the bone scans and CT scans frequency equal between olaparib and cabazitaxel.
Cabazitaxel wastage	The company assumed that there will be vial sharing for cabazitaxel and no wastage. The ERG agrees with this for the base case analysis but includes a scenario analysis where there will be some wastage for cabazitaxel, as vial sharing is rarely perfect.
Lack of daily KM data	At clarification, the ERG requested the daily Kaplan Meier data in order to reconstruct survival curves and conduct exploratory analyses. The company was unable to provide these data. The ERG highlighted that the use of monthly data to analyse PFS, OS and TTD is sub optimal.

Questions for engagement

Issue 1 - The population in the company's submission narrower is than the scope and clinical trial evidence

1. What proportion of people would have already received docetaxel in the non-Covid-19 world?

2. Would this proportion be substantially impacted by Covid-19? If so, what would the proportion be and over what period would it be impacted?

3. Would docetaxel retreatment be an option after treatment with new hormonal therapy?

4. Is the evidence submitted and the cost effectiveness of olaparib in the prior taxane group generalisable to the no prior taxane use cohort?

Issue 2 - The company presents analyses from the PROfound trial which suggest differing clinical effectiveness within subgroups

5. Should genetic subgroups be analysed separately?

6. Should the ‘no prior taxane’ subgroup be analysed separately?

7. What is the probable cost effectiveness of the ‘no prior taxane’ patients group?

8. What is the proportion of patients likely to decline docetaxel because of alcohol content?

Issue 3 - The company has not provided analyses compared with all comparators in the scope

9. Is it reasonable to assume that patients will have received docetaxel prior to progression to mCRPC and docetaxel is not a comparator?

10. Is it reasonable to assume that radium-223 is used later in the treatment pathway and would not be a comparator to olaparib?

Issue 4 - Generalisability of the trial to the UK population and clinical practice

11. Is the PROfound trial representative of the UK population and clinical practice in terms of:

    a. Patients included? (see patients characteristics in Appendix 1)

    b. Comparators used?

12. Is the ERG’s assumption that no benefit can be expected from subsequent treatment with NHA in patients who already progressed on NHA plausible?

Issue 5 - Heterogeneity of the PROfound and CARD trials used to indirectly compare olaparib

13. Is HRRm associated with more aggressive disease?

14. Based on the different HRRm status between PROfound and CARD trials, are the NHA arms in the 2 trials comparable?

Issue 6 - The indirect treatment comparison (ITC) of olaparib vs cabazitaxel is uncertain

15. Are the PROfound and CARD trials similar enough for the transitivity assumption to hold (i.e. the RCTs included in the comparison are similar in all respect other than the intervention received)?

Issue 7 - Choice of distribution for overall survival extrapolation

16. The company used the loglogistic distribution to extrapolate OS and the ERG prefers the Weibull distribution. The OS estimates for olaparib with both curves are presented in the table below. What is the most plausible approach?

Curve	OS at 3 years	OS at 5 years	OS at 10 years	AIC+BIC
Weibull	[redacted]	[redacted]	[redacted]	1215.3
Log-logistic	[redacted]	[redacted]	[redacted]	1222.5

Issue 8 - Discrepancies between progression-free survival and time to treatment discontinuation curves

17. In the PROfound trial, were patients obliged to stop treatment upon progression?

18. Were events treated consistently when constructing the rPFS and TTD KM curves?

Issue 9 - Olaparib direct drug costs and relative dose intensity calculation

19. Which olaparib relative dose intensity (RDI) is the most appropriate to use (mean, median, 100%)?

20. Should the RDI be applied to rPFS or TTD curves?

21. Should a TTD curve be deduced for cabazitaxel?

Issue 10 - Post progression treatments costs calculation

22. Is the proportion of patients receiving active subsequent treatments expected to be the same between olaparib and cabazitaxel?

23. What subsequent treatments are used in routine NHS practice?

    a. Please provide details of which are most commonly used, e.g. Treatment 1: 60% of patients, Treatment 2: 10% of patients, Treatment 3: 20% of patients

    b. The company assumed that the distribution of subsequent treatments received would vary between olaparib and cabazitaxel, while the ERG assumed that it would be the same irrespective of previous treatment and that NHA would not be included. Which approach is more reflective of current NHS clinical practice? Please add any further comments e.g. about treatment percentages, missing treatments etc.

Treatments	Proportion of patients receiving this treatment after progression (%)			
	Company's approach		**ERG's approach**	Comments
	Olaparib (PROfound)	Cabazitaxel (CARD)	Same for both arms	
Cabazitaxel	[redacted]	[redacted]	27%	
Docetaxel	[redacted]	[redacted]	18%	
Abiraterone	[redacted]	[redacted]	0%	
Enzalutamide	[redacted]	[redacted]	0%	
Radium-223	[redacted]	[redacted]	55%	

    c. Would NHA drug (abiraterone or enzalutamide) be used as a subsequent treatment after progression on olaparib or cabazitaxel?

24. Would patients get more than one active subsequent treatment? If so, would it differ by treatment arm and is it linked to PPS duration?

25. Once patients stop their active subsequent treatments, do they receive best supportive care?

Issue 11 - G-CSF costs estimate

26. What is the proportion of patients on cabazitaxel who receive primary prophylaxis with G-CSF?

27. Do these patients receive the maximum 14 days dose with every cycle of cabazitaxel treatment? If not, what is the average treatment duration?

Issue 12 - HRR genes test costs

28. Should genetic test costs be included in the analyses, as specified in the scope?

29. What is the prevalence of the HRR genetic mutations in the population that would be tested?

Issue 13 - End-of-life criteria

30. What is the estimated life expectancy of people with mCRPC with homologous recombination repair gene alterations previously treated with hormonal therapy?

31. Is there sufficient evidence to indicate that olaparib offers an extension to life of at least an additional 3 months, compared with cabazitaxel?

32. What is the estimated size of the population that would be eligible for treatment with olaparib?

Other issue for information – SLR

33. Can the company provide additional information on their inclusion criteria and further clarification of their methods?

Appendix 1 – Patients characteristics in PROfound

Patient characteristics for PROfound Cohort A+B, Cohort A, prior taxane subgroup (CS Table 5 page 38)

Baseline characteristics	Cohort A+B FAS		Primary study population: Cohort A FAS		Subgroup relevant for economic analysis: Prior taxane use[a] Cohort A+B	
	Olaparib 300 mg bid (n = 256)	Investigators' choice of NHA (n = 131)	Olaparib 300 mg bid (n = 162)	Investigators' choice of NHA (n = 83)	Olaparib 300 mg bid (n = 170)	Investigators' choice of NHA (n = 84)
Age	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)						
Median (range)	69.0 (47–91)	69.0 (49–87)	68.0 (47–86)	67.0 (49–86)	[redacted]	[redacted]
< 65, n (%)	82 (32.0)	34 (26.0)	54 (33.3)	23 (27.7)	[redacted]	[redacted]
≥ 65, n (%)	174 (68.0)	85 (64.9)	108 (66.7)	60 (72.3)	[redacted]	[redacted]
≥ 75, n (%)	NR	NR	NR	NR	NR	NR
White	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Black or African American	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ethnic group, n (%)						
Hispanic or Latino	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Not Hispanic or Latino	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sites of disease at baseline, n (%)[b]						
Prostate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Locoregional lymph nodes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Distant lymph nodes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Liver	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other distant metastases	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bone only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lymph node only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bone and lymph node only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ECOG performance status at baseline, n (%)						
0	131 (51.2)	55 (42.0)	84 (51.9)	34 (41.0)	[redacted]	[redacted]
1	112 (43.8)	71 (54.2)	67 (41.4)	46 (55.4)	[redacted]	[redacted]
2	13 (5.1)	4 (3.1)	11 (6.8)	3 (3.6)	[redacted]	[redacted]
Missing	0	1 (0.8)	0	0	[redacted]	[redacted]
Total Gleason index at baseline, n (%)						
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline pain score (BPI-SF worst pain [item 3]), n (%)						
0–< 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2–3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
> 3 ≥ 4	[redacted]NR	[redacted]NR	[redacted]NR	[redacted]NR	[redacted]NR	[redacted]NR

Missing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline PSA (µg/L), n (%)						
Median, (range)	68.2 (0.2–7240.7)	106.5 (1.85–7115.0)	62.2 (0.20–7240.7)	112.9 (1.85–7115.0)	[redacted]	[redacted]
Measurable disease at baseline, n (%)[c]						
Yes	149 (58.2)	72 (55.0)	95 (58.6)	46 (55.4)	[redacted]	[redacted]
No	107 (41.8)	59 (45.0)	67 (41.4)	37 (44.6)	[redacted]	[redacted]
Missing	NR	NR	NR	NR	NR	NR
Previous taxane therapy at mCRPC, n (%)						
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Previous docetaxel only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Previous cabazitaxel only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Previous docetaxel and cabazitaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients with taxane treatment prior to randomisation, n (%)						
Yes	N/A	N/A	N/A	N/A	[redacted]	[redacted]
No	N/A	N/A	N/A	N/A	[redacted]	[redacted]
Previous docetaxel only	N/A	N/A	N/A	N/A	[redacted]	[redacted]
Previous cabazitaxel only	N/A	N/A	N/A	N/A	[redacted]	[redacted]
Previous docetaxel and cabazitaxel	N/A	N/A	N/A	N/A	[redacted]	[redacted]
Prior paclitaxel	N/A	N/A	N/A	N/A	[redacted]	[redacted]
Previous NHA use, n (%)						
Enzalutamide	103 (40.2)	54 (41.2)	67 (41.4)	40 (48.2)	[redacted]	[redacted]
Abiraterone	97 (37.9)	54 (41.2)	61 (37.7)	29 (34.9)	[redacted]	[redacted]
Enzalutamide and abiraterone	51 (19.9)	23 (17.6)	32 (19.8)	14 (16.9)	[redacted]	[redacted]

Missing	NR	NR	NR	NR	NR	NR
Single mutation status[d]						
BRCA1	8 (3.3)	5 (4.2)	8 (5.4)	5 (6.6)		
BRCA2	81 (33.9)	47 (39.2)	80 (54.1)	47 (61.8)		
ATM	62 (25.9)	24 (20.0)	60 (40.5)	24 (31.6)		
BARD1	0	1 (0.8)	0	0		
BRIP1	2 (0.8)	1 (0.8)	0	0		
CDK12	61 (25.5)	28 (23.3)	0	0		
CHEK1	1 (0.4)	1 (0.8)	0	0		
CHEK2	7 (2.9)	5 (4.2)	0	0		
FANCL	0	0	0	0		
PALB2	3 (1.3)	1 (0.8)	0	0		
PPP2R2A	6 (2.5)	4 (3.3)	0	0		
RAD51B	4 (1.7)	1 (0.8)	0	0		
RAD51C	0	0	0	0		
RAD51D	1 (0.4)	0	0	0		
RAD54L	3 (1.3)	2 (1.7)	0	0		
Co-mutations[f]	17 (6.6)	11 (8.4)	14 (8.6)	7 (8.4)		

NICE National Institute for Health and Care Excellence

Technical engagement response form

Olaparib for previously treated hormone-relapsed metastatic prostate cancer [ID1640]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments **12 October 2020**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential

information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	**Professor Johann de Bono**
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Stakeholder. PROfound trial chief investigator. Medical oncologist.**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**Trial CI. Advisor to AstraZeneca. On AstraZeneca advisory boards (paid). No relationship with the tobacco industry.**

Questions for engagement

Issue 1: The population in the company's submission narrower is than the scope and clinical trial evidence	
1. What proportion of people would have already received docetaxel in the non-Covid world?	**30-50% of all CRPC patients; for M1 at diagnosis this will be 75% or more in fitter patients.**
2. Would this proportion be substantially impacted by Covid? If so, what would the proportion be and over what period would it be impacted?	**Yes. This number will decrease**
3. Would docetaxel retreatment be an option after treatment with new hormonal therapy?	**No**
4. Is the evidence submitted and the cost effectiveness of olaparib in the prior taxane group generalisable to the no prior taxane use cohort?	**Yes**
Issue 2: The company presents analyses from the PROfound trial which suggest differing clinical effectiveness within subgroups	
5. Should genetic subgroups be analysed separately?	**This was not preplanned but the data clearly show antitumour activity that is durable in BRCA loss tumours.**
6. Should the 'no prior taxane' subgroup be analysed separately?	**No**
7.What is the probable cost effectiveness of the 'no prior taxane' patients group?	**There is likely to be more clinical benefit in this population. Later treatment imparts less benefit.**
8. What is the proportion of patients likely to decline docetaxel because of alcohol content?	**Small.**

Issue 3: The company has not provided analyses compared with all comparators in the scope	
9. Is it reasonable to assume that patients will have received docetaxel prior to progression to mCRPC and docetaxel is not a comparator?	**For some yes.**
10. Is it reasonable to assume that radium-223 is used later in the treatment pathway and would not be a comparator to olaparib?	**Yes; >50% of patients never receive radium-223.**
Issue 4: Generalisability of the trial to the UK population and clinical practice	
11. Is the PROfound trial representative of the UK population and clinical practice in terms of: a. Patients included? (see patients characteristics in Appendix 1 of technical report) b. Comparators used?	**Yes it is. The patient population is the same. A UK comparator would be best supportive care.**
12. Is the ERG's assumption that no benefit can be expected from subsequent treatment with NHA in patients who already progressed on NHA plausible?	**Probably little benefit.**
Issue 5: Heterogeneity of the PROfound and CARD trials used to indirectly compare olaparib	
13. Is HRRm associated with more aggressive disease?	**Yes (See Castro et al, JCO 2013)**

<table>
<tr><td>14. Based on the different HRRm status between PROfound and CARD trials, are the NHA arms in the 2 trials comparable?</td><td>Yes</td></tr>
<tr><td colspan="2">Issue 6: The indirect treatment comparison (ITC) of olaparib vs cabazitaxel is uncertain</td></tr>
<tr><td>15. Are the PROfound and CARD trials similar enough for the transitivity assumption to hold (i.e. the RCTs included in the comparison are similar in all respect other than the intervention received)?</td><td>Yes</td></tr>
<tr><td colspan="2">Issue 7: Choice of distribution for overall survival extrapolation</td></tr>
<tr><td>16. The company used the loglogistic distribution to extrapolate OS and the ERG prefers the Weibull distribution. The OS estimates for olaparib with both curves are presented in the table below. What is the most plausible approach?

<table>
<tr><th>Curve</th><th>OS at 3 years</th><th>OS at 5 years</th><th>OS at 10 years</th><th>AIC+ BIC</th></tr>
<tr><td>Weibull</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>1215.3</td></tr>
<tr><td>Log-logistic</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>1222.5</td></tr>
</table>
</td><td>I would not like to speculate but the Weibull distribution appears too conservative based on my experience with olaparib. I have seen BRCA mutated cancer patients on olaparib for more than 5-years and some more than 10-years.</td></tr>
<tr><td colspan="2">Issue 8: Discrepancies between progression-free survival and time to treatment discontinuation curves</td></tr>
<tr><td>17. In the PROfound trial, were patients obliged to stop treatment upon progression?</td><td>Yes</td></tr>
<tr><td>18. Were events treated consistently when constructing the rPFS and TTD KM curves?</td><td>Yes</td></tr>
</table>

Issue 9: Olaparib direct drug costs and relative dose intensity calculation	
19. Which olaparib relative dose intensity (RDI) is the most appropriate to use (mean, median, 100%)?	**60-70%**
20. Should the RDI be applied to rPFS or TTD curves?	**This is not my expertise**
21. Should a TTD curve be deduced for cabazitaxel?	**This is not my expertise**
Issue 10: Post progression treatments costs calculation	
22. Is the proportion of patients receiving active subsequent treatments expected to be the same between olaparib and cabazitaxel?	**It depends on how sick the patient is.**
23. What subsequent treatments are used in routine NHS practice? a. Please provide details of which are most commonly used, e.g. Treatment 1: 60% of patients, Treatment 2: 10% of patients, Treatment 3: 20% of patients b. The company assumed that the distribution of subsequent treatments received would vary between olaparib and cabazitaxel, while the ERG assumed that it would be the same irrespective of previous treatment and that NHA would not be included. Which approach is more reflective of current NHS clinical practice? Please add any further comments e.g. about treatment percentages, missing treatments etc.	**Docetaxel (if not yet received in first line setting 50-60%)** **Cabazitaxel (estimated 40-50%)** **Radium-223 (estimated 20%)** **b) This is hard to comment on without data but olaparib treatment may change the likelihood of patients being fir enough for other agents.** **c) Patients are unlikely to get an NHA again in the UK unless they have private insurance or funding unless they did not tolerate the first NGHA and then moved onto the second.**

Treatments	Proportion of patients receiving this treatment after progression (%)			
	Company's approach		**ERG's approach**	Comments
	Olaparib (PROfound)	Cabazitaxel (CARD)	Same for both arms	
Cabazitaxel	[redacted]	[redacted]	27%	
Docetaxel	[redacted]	[redacted]	18%	
Abiraterone	[redacted]	[redacted]	0%	
Enzalutamide	[redacted]	[redacted]	0%	
Radium-223	[redacted]	[redacted]	55%	

c. Would NHA drug (abiraterone or enzalutamide) be used as a subsequent treatment after progression on olaparib or cabazitaxel?

24. Would patients get more than one active subsequent treatment? If so, would it differ by treatment arm and is it linked to PPS (post progression survival) duration?	**Possibly**
25. Once patients stop their active subsequent treatments, do they receive best supportive care?	**Yes; some patients refuse chemotherapy.**
Issue 11: G-CSF costs estimate	
26. What is the proportion of patients on cabazitaxel who receive primary prophylaxis with G-CSF?	**Most patients**

27. Do these patients receive the maximum 14 days dose with every cycle of cabazitaxel treatment? If not, what is the average treatment duration?	**Yes. Likely.**
Issue 12: HRR genes test costs	
28. Should genetic test costs be included in the analyses, as specified in the scope?	**Yes; genomic testing necessary.**
29. What is the prevalence of the HRR genetic mutations in the population that would be tested?	**BRCA alteration ~10%**
Issue 13: End-of-life criteria	
30. What is the estimated life expectancy of people with mCRPC with homologous recombination repair gene alterations previously treated with hormonal therapy?	**Approximately 1 year**
31. Is there sufficient evidence to indicate that olaparib offers an extension to life of at least an additional 3 months, compared with cabazitaxel?	**Yes olaparib will add at least 3 months of OS benefit to the BRCA patients.**
32. What is the estimated size of the population that would be eligible for treatment with olaparib?	**The BRCA population is 10% of mCRPC patients.**

Other issue for information - SLR	
33. Can the company provide additional information on their inclusion criteria and further clarification of their methods?	

NICE National Institute for Health and Care Excellence

Technical engagement response form

Olaparib for previously treated hormone-relapsed metastatic prostate cancer [ID1640]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments **12 October 2020**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential

information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	**Sree Rodda**
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**St. James Institute of Oncology**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Questions for engagement

Issue 1: The population in the company's submission narrower is than the scope and clinical trial evidence	
1. What proportion of people would have already received docetaxel in the non-Covid world?	**About 60% of patients.**
2. Would this proportion be substantially impacted by Covid? If so, what would the proportion be and over what period would it be impacted?	**Yes , At present all patients with hormone sensitive metastatic prostate cancer receive Enzalutamide or Abiraterone if fit (60%-70%). This will be expected to continue during the Pandemic period.**
3. Would docetaxel retreatment be an option after treatment with new hormonal therapy?	**If the patients already had Docetaxel prior to Abi/Eza there no evidence to re treat with Docetaxel.**
4. Is the evidence submitted and the cost effectiveness of olaparib in the prior taxane group generalisable to the no prior taxane use cohort?	**Although the Trial showed a benefit in Olaparib group both in progression free survival and Overall survival in prior Taxane group. The results of this should be interpreted with caution as the trial was not powered to detect progression free or overall survival advantage in prior Taxane versus no Taxane group.**
Issue 2: The company presents analyses from the PROfound trial which suggest differing clinical effectiveness within subgroups	
5. Should genetic subgroups be analysed separately?	**The trial was powered to detect progression free survival in Cohort A . And hence it's reasonable to analyse Cohort A and B separately.** **It's interesting to look at efficacy of Olaparib on individual gene mutations. However the trial was not powered to look at the effectiveness of olaparib on individual gene mutations.**

6. Should the 'no prior taxane' subgroup be analysed separately?	**No**
7.What is the probable cost effectiveness of the 'no prior taxane' patients group?	
8. What is the proportion of patients likely to decline docetaxel because of alcohol content?	**I have not come across any patients who have refused Docetaxel due to alcohol content.**
Issue 3: The company has not provided analyses compared with all comparators in the scope	
9. Is it reasonable to assume that patients will have received docetaxel prior to progression to mCRPC and docetaxel is not a comparator?	**Yes**
10. Is it reasonable to assume that radium-223 is used later in the treatment pathway and would not be a comparator to olaparib?	**It depends, If a patient has bone only mets and if the patient is symptomatic Radium -223 could be considered prior to Olaparib. If the patients are asymptomatic with Bone mets then Radium -223 could be offered after Olaparib.** If the patients have Visceral metastasis they are not eligible to receive Radium -223 .
Issue 4: Generalisability of the trial to the UK population and clinical practice	
11. Is the PROfound trial representative of the UK population and clinical practice in terms of: a. Patients included? (see patients characteristics in Appendix 1 of technical report)	a.)Patient baseline characteristics are generalizable to UK population. However 4 patients recruited from within UK. B.) As there is no clinically meaningful response which can be achieved by treating a patient with NHA once they have progressed on NHA it's not a routine

b. Comparators used?	practice in UK. The comparator of the study can be regarded as best supportive care.
12. Is the ERG's assumption that no benefit can be expected from subsequent treatment with NHA in patients who already progressed on NHA plausible?	Yes there no evidence that a clinically meaningful response can be achieved on subsequent treatment with NHA.
Issue 5: Heterogeneity of the PROfound and CARD trials used to indirectly compare olaparib	
13. Is HRRm associated with more aggressive disease?	Yes , published literature suggests that it's associated with increase in local failure after primary treatment, lower metastasis free survival and low overall survival .
14. Based on the different HRRm status between PROfound and CARD trials, are the NHA arms in the 2 trials comparable?	Yes
Issue 6: The indirect treatment comparison (ITC) of olaparib vs cabazitaxel is uncertain	
15. Are the PROfound and CARD trials similar enough for the transitivity assumption to hold (i.e. the RCTs included in the comparison are similar in all respect other than the intervention received)?	Profound trial only included patients with HRR mutations and CARD included all patients regardless of HRR mutation status. None of the patients in CARD received Carbazetaxel whilst 30% of Patients within PROFOUND trial did receive Carbaxetaxel.

	Radiological progression was confirmed by Blinded central review in Profound but not CARD. Due to Heterogeneity between two trials, results based on comparisons between these two trails should be interpreted cautiously.
Issue 7: Choice of distribution for overall survival extrapolation	
16. The company used the loglogistic distribution to extrapolate OS and the ERG prefers the Weibull distribution. The OS estimates for olaparib with both curves are presented in the table below. What is the most plausible approach? Curve / OS at 3 years / OS at 5 years / OS at 10 years / AIC+ BIC Weibull / [redacted] / [redacted] / [redacted] / 1215.3 Log-logistic / [redacted] / [redacted] / [redacted] / 1222.5	OS estimates of Weibull are more plausible at 10 years however OS estimates at 3 and 5 years seem very conservative.
Issue 8: Discrepancies between progression-free survival and time to treatment discontinuation curves	
17. In the PROfound trial, were patients obliged to stop treatment upon progression?	Treatment was discontinued after Radiological evidence of disease progression.

18. Were events treated consistently when constructing the rPFS and TTD KM curves?	yes
Issue 9: Olaparib direct drug costs and relative dose intensity calculation	
19. Which olaparib relative dose intensity (RDI) is the most appropriate to use (mean, median, 100%)?	Relative Dose intensity generally described by means of descriptive Statistics
20. Should the RDI be applied to rPFS or TTD curves?	
21. Should a TTD curve be deduced for cabazitaxel?	
Issue 10: Post progression treatments costs calculation	
22. Is the proportion of patients receiving active subsequent treatments expected to be the same between olaparib and cabazitaxel?	All patients in who received Olaparib can be treated with Carbazetaxel and Radium -223 on progression . However all patients who progression Carbazetaxel and Radium -223 might not be eligible to receive Olaparib.
23. What subsequent treatments are used in routine NHS practice? a. Please provide details of which are most commonly used, e.g. Treatment 1: 60% of patients, Treatment 2: 10% of patients, Treatment 3: 20% of patients b. The company assumed that the distribution of subsequent treatments received would vary between olaparib and cabazitaxel, while the ERG assumed that it would be the same irrespective of previous treatment and that NHA would not be included. Which approach is more reflective of current NHS clinical practice? Please add any further	a.)Post progression Pre Covid Treatment 1: Carbazetaxel about 30%-40% Treatment 2: Radium223 -20% However in patients with Bone only disease and symptomatic Radium -223 is generally considered prior to Carbazetaxel.

comments e.g. about treatment percentages, missing treatments etc.

Treatments	Proportion of patients receiving this treatment after progression (%)			
	Company's approach		**ERG's approach**	Comments
	Olaparib (PROfound)	Cabazitaxel (CARD)	Same for both arms	
Cabazitaxel	[redacted]	[redacted]	27%	
Docetaxel	[redacted]	[redacted]	18%	
Abiraterone	[redacted]	[redacted]	0%	
Enzalutamide	[redacted]	[redacted]	0%	
Radium-223	[redacted]	[redacted]	55%	

c. Would NHA drug (abiraterone or enzalutamide) be used as a subsequent treatment after progression on olaparib or cabazitaxel?

B.) Subsequent therapies will be the same post progression on Olaparib or Carbazetaxel.

c.) No

24. Would patients get more than one active subsequent treatment? If so, would it differ by treatment arm and is it linked to PPS (post progression survival) duration?

Post progression on Olaparib: They can get Carbazetaxel or Radium -223 for Bone only mets.

Post progression on Carbzetaxel : They can get Olaparib if HRRm present or Radium -223 for bone only mets.

25. Once patients stop their active subsequent treatments, do they receive best supportive care?

Yes

Issue 11: G-CSF costs estimate	
26. What is the proportion of patients on cabazitaxel who receive primary prophylaxis with G-CSF?	50-60%
27. Do these patients receive the maximum 14 days dose with every cycle of cabazitaxel treatment? If not, what is the average treatment duration?	Variable between trusts. On an average 7days.
Issue 12: HRR genes test costs	
28. Should genetic test costs be included in the analyses, as specified in the scope?	Yes
29. What is the prevalence of the HRR genetic mutations in the population that would be tested?	20%-30%
Issue 13: End-of-life criteria	
30. What is the estimated life expectancy of people with mCRPC with homologous recombination repair gene alterations previously treated with hormonal therapy?	12- 18 months
31. Is there sufficient evidence to indicate that olaparib offers an extension to life of at least an additional 3 months, compared with cabazitaxel?	Yes there seems to be an Overall survival advantage with Olaparib . However it can't be compared with survival advantage of Carbazetaxel.

32. What is the estimated size of the population that would be eligible for treatment with olaparib?	About 10% of all Castrate resistant metastatic prostate cancer patients.
Other issue for information - SLR	
33. Can the company provide additional information on their inclusion criteria and further clarification of their methods?	

NICE National Institute for Health and Care Excellence

Technical engagement response form

Olaparib for previously treated hormone-relapsed metastatic prostate cancer [ID1640]

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Deadline for comments 12 October 2020

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- Do not use abbreviations.
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- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
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About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	Prostate Cancer UK
Disclosure **Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.**	N/A

Questions for engagement

Issue 1: The population in the company's submission narrower is than the scope and clinical trial evidence	
1. What proportion of people would have already received docetaxel in the non-Covid world?	Prostate Cancer UK analysed data to understand chemotherapy uptake in patient cohorts with newly diagnosed metastatic prostate cancer by age, focusing specifically on the latest available treatments data from 2016. The results showed significant disparity in access to chemotherapy by age. 63.6% of men with a new diagnosis of metastatic prostate cancer aged under 70 receive chemotherapy. This starkly decreases to 21.9% for men aged over 70 and drops further to 5.7% for men aged 80 and above. These data reveal a cohort of men who are not receiving chemotherapy, strongly correlated with their increasing age. It is very unlikely that the sharp decrease in uptake by age is explained purely by patient choice, but by clinical decision over the physical burden on the patient from the treatment. These men will only receive androgen deprivation therapy, until disease progression when an HNA will be available. It is then very unlikely, given their reasons for not receiving docetaxel that these men to go on to receive cabazitaxel. This means that they miss out on the life extension made possible by cabazitaxel at this end of life stage of their disease and would benefit from olaparib. If olaparib were unavailable to them because of their inability to access prior docetaxel and later stage cabazitaxel, there is potential for these men to experience an inequality of access to the additional months of life that patients able to have both taxanes will receive. Olaparib for these patients therefore delivers to an unmet need, especially as evidence from the PROfound study shows the grade ≥3 adverse events caused by olaparib to be less invasive than cabazitaxel (anaemia vs infection and peripheral neuropathy, respectively).

	Uptake of docetaxel has seen an overall increase of 10-15% year on year since 2017 (SACT data, 2019), however, it is not possible to know the distribution of docetaxel across age groups.
2. Would this proportion be substantially impacted by Covid? If so, what would the proportion be and over what period would it be impacted?	In its response to the COVID-19 pandemic, NICE recommended to give men with newly diagnosed metastatic prostate cancer enzalutamide in combination with androgen deprivation therapy in place of docetaxel chemotherapy. This was done to reduce the risk of COVID-19 infection that could result from docetaxel's immune system suppression as well as enabling patients to avoid hospital visits. For men who are intolerant of enzalutamide, abiraterone was made available. It is therefore certainly likely that fewer men have received docetaxel chemotherapy during the pandemic. 31-day treatment data from NHS England shows that the proportion of men receiving chemotherapy in April-June 2020 was significantly lower than the proportion receiving chemotherapy during the same period in 2019. Chemotherapy in April 2020 was 45% of April 2019 levels, 62% for May and 91% for June. It should be noted that NHS 31-day treatment data for chemotherapy includes enzalutamide and abiraterone, and we know that over 1000 men received NHAs between April to September 2020 but are included within the "chemotherapy" group. In addition, this data is only for all urological cancers, and is not specific to prostate cancer.
3. Would docetaxel retreatment be an option after treatment with new hormonal therapy?	It is not clear which stage of prostate cancer this question is referring to. Docetaxel became the standard of care in men with mHSPC in 2017 and it is unlikely that these men will have docetaxel again. Expert clinical opinion drawn

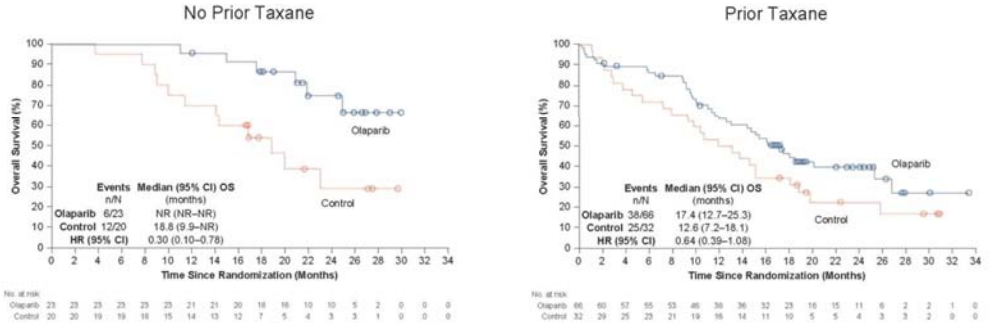
	from the British Uro-oncology Group outlines that very few men would tolerate the full 16 cycles of docetaxel due to dose limiting neurotoxicity. As it is challenging to disaggregate SACT data to know in which setting docetaxel is being used, it is not possible to know the extent of its use in the mCRPC setting. Expert clinical opinion must be sought if there is a need to establish the extent of its use in this population.
4. Is the evidence submitted and the cost effectiveness of olaparib in the prior taxane group generalisable to the no prior taxane use cohort?	Approximately 65% of men across both arms of the Profound Study (cohort A and B) received a prior taxane. When considered separately, patients with or without a prior taxane showed a favourable response to Olaparib, compared to the control arm, with greatest benefit being in the no prior taxane group. (*HR for rPFS: Cohort A prior taxane 0.28 (0.19-0.41), no prior taxane 0.55 (0.32-0.97); HR for OS: Cohort A prior taxane 0.57 (0.36-0.93), no prior taxane 0.84 (0.38-2.01)*). Although the greatest benefit appears to be in the prior taxane group, it is possible that this is driven not by a drop in effectiveness of olaparib, but by increased effectiveness of the control arm treatment in men not yet exposed to a taxane. **Table 2. Subgroup analyses of rPFS by prior taxane status in patients** **Table 3. Subgroup analyses of OS by prior taxane status in patients**

Table 2. Subgroup analyses of rPFS by prior taxane status in patients

	Prior taxane	Number of events, n (%)		Median rPFS, months		HR (95% CI)
		Olaparib	pcNHA	Olaparib	pcNHA	
Cohort A	Yes	72 (67.9)	47 (90.4)	7.4	1.9	0.28 (0.19, 0.41)
	No	34 (60.7)	21 (67.7)	7.4	4.1	0.55 (0.32, 0.97)

Table 3. Subgroup analyses of OS by prior taxane status in patients

	Prior taxane	Number of events, n (%)		Median OS, months		HR (95% CI)
		Olaparib	pcNHA	Olaparib	pcNHA	
Cohort A	Yes	39 (36.8)	30 (57.7)	17.3	11.7	0.57 (0.36, 0.93)
	No	15 (26.8)	9 (29.0)	20.7	19.1	0.84 (0.38, 2.01)

	Overall survival in patients with BRCA1/2 mutations were analysed by prior taxane status separately. As shown below OS benefit of olaparib over NHA was seen in both the prior taxane and no prior taxane groups. **Fig. S8. Kaplan-Meier Estimates of Overall Survival by Prior Taxane Status in Patients Harboring Alterations Only in *BRCA1* or *BRCA2* (A), *ATM* (B), or *CDK12* (C).*** **A. OS by Taxane Status: Patients with Alterations Only in *BRCA1* or *BRCA2***  This analysis is underpowered, but there is no evidence that either groups get no benefit from olaparib. Based on these data, we conclude that the benefit of olaparib over a novel hormonal agent re-challenge therapy is not dependent on previous taxane use, and therefore the evidence can be generalised between prior taxane status groups. We would be extremely concerned by a situation in which men were denied a clearly effective therapy based purely on their ability to tolerate another, unrelated and potentially more toxic drug earlier in the pathway. We have no comment on cost effectiveness.

Issue 2: The company presents analyses from the PROfound trial which suggest differing clinical effectiveness within subgroups	
5. Should genetic subgroups be analysed separately?	Genetic subgroup analyses offer insight, but are offset by too many confounding factors, primarily small sample size and subsequent low statistical power. Therefore, our preference would be that the various genetic mutations are grouped and analysed per the trial cohorts. However, given that the EMEA licence is likely to cover only BRCA1/2, and given the relatively large size of, and effect in, the sub-cohort with BRCA 1 or 2 mutated cancer in the trial it is relevant to consider BRCA1 and 2 mutations as a separate group for analysis.
6. Should the 'no prior taxane' subgroup be analysed separately?	See answer to Q4. Based on those data the no prior taxane group should not be analysed separately.
7. What is the probable cost effectiveness of the 'no prior taxane' patients group?	N/A
8. What is the proportion of patients likely to decline docetaxel because of alcohol content?	N/A
Issue 3: The company has not provided analyses compared with all comparators in the scope	
9. Is it reasonable to assume that patients will have received docetaxel prior to progression to mCRPC and docetaxel is not a comparator?	It is not reasonable to assume this because there is a significant disparity in access to chemotherapy by age. 63.6% of men with a new diagnosis of metastatic prostate cancer aged under 70 receive chemotherapy. This starkly decreases to 21.9% for men aged over 70 and drops further to 5.7% for men aged 80 and above. As these patients are then also very unlikely to receive docetaxel once they progress to mCRPC it cannot be used a comparator.

10. Is it reasonable to assume that radium-223 is used later in the treatment pathway and would not be a comparator to olaparib?	Radium-223 is used as a treatment in men with mCRPC who have symptomatic bone metastasis but no known visceral metastasis. It can only be administered if men have had prior treatment with docetaxel or if docetaxel is contraindicated and not suitable. Within the PROfound study, only 35% of patients had only bony metastases. Radium-223 delivers alpha radiation to bone metastases without affecting normal bone marrow. It reduces the risk of spinal cord compression. The patient populations are insufficiently similar for an indirect comparison and therefore Radium-223 shouldn't be used as a comparator.
Issue 4: Generalisability of the trial to the UK population and clinical practice	
11. Is the PROfound trial representative of the UK population and clinical practice in terms of: a. Patients included? (see patients characteristics in Appendix 1 of technical report) b. Comparators used?	Yes. While the PROFOUND study includes only four patients from the UK there is nothing to suggest that the patients were non-representative of the UK population. Indeed, the patient characteristics are very similar to the TOPARP trial - an academic-led Phase II study of Olaparib for men with advanced castrate-resistant prostate cancer in the UK. Recent evidence suggests that there is limited efficacy of NHA re-challenge. However, at the initiation of the PROfound trial, this was a suitable treatment comparator. This was also the control arm treatment selected for the CARD trial at a similar time. Loriot, Y., Bianchini, D., Ileana, E., Sandhu, S., Patrikidou, A., Pezaro, C., Albiges, L., Attard, G., Fizazi, K., De Bono, J. and Massard, C., 2013. Antitumour activity of abiraterone acetate

	against metastatic castration-resistant prostate cancer progressing after docetaxel and enzalutamide (MDV3100). *Annals of Oncology*, 24(7), pp.1807-1812. Khalaf, D., Annala, M., Taavitsainen, S., Finch, D., Oja, C., Vergidis, J., Zulfiqar, M., Sunderland, K., Azad, A., Kollmannsberger, C., Eigl, B., Noonan, K., Wadhwa, D., Attwell, A., Keith, B., Ellard, S., Le, L., Gleave, M., Wyatt, A. and Chi, K., 2019. Optimal sequencing of enzalutamide and abiraterone acetate plus prednisone in metastatic castration-resistant prostate cancer: a multicentre, randomised, open-label, phase 2, crossover trial. *The Lancet Oncology*, 20(12), pp.1730-1739. Maines, F., Caffo, O., Veccia, A., Trentin, C., Tortora, G., Galligioni, E. and Bria, E., 2015. Sequencing new agents after docetaxel in patients with metastatic castration-resistant prostate cancer. *Critical Reviews in Oncology/Hematology*, 96(3), pp.498-506.
12. Is the ERG's assumption that no benefit can be expected from subsequent treatment with NHA in patients who already progressed on NHA plausible?	A phase II study (Loriot et al., 2013) shows that there is a small benefit retreating men with NHA. However, we need to see the results from phase III to understand the full impact.
Issue 5: Heterogeneity of the PROfound and CARD trials used to indirectly compare olaparib	
13. Is HRRm associated with more aggressive disease?	There is evidence that a germline BRCA 1/2 mutation is associated with increased risk of metastasis at diagnosis, and poorer overall survival, compared to non- BRCA mutated PCa patients.

	However, the clinical relevance of HRRm at the mCRPC stage, following failure on a NHA is not well established. Mateo et al. found no difference in PFS on first-line NHA (8.3 months in both groups) between gDDR carriers (n = 330) and noncarriers (n = 60). It should be noted that these patients had germline, not somatic mutations, as is in PROfound. Annala et al showed that mCRPC patients with germline DNA repair defects exhibit attenuated responses to AR-targeted therapy, compared to non-carriers, though only a small number of patients (9 total) with BRCA/ATM mutations were included.
14. Based on the different HRRm status between PROfound and CARD trials, are the NHA arms in the 2 trials comparable?	While the trials are broadly comparable (see below), we do not know the HRRm status of patients in the CARD trial. We assume, given the number of men that needed to be screened in PROfound to obtain an entirely HRRm positive cohort (778 of 2792 patients for whom adequate sequencing was available had a HRRm mutation), and literature of the prevalence of HRRm in the population that the number of men with HRRm in the CARD trial is significantly lower than in the PROfound trial. We do not know what impact the differential HRRm status would have on the NHA arm between the two trials.

Issue 6: The indirect treatment comparison (ITC) of olaparib vs cabazitaxel is uncertain	
15. Are the PROfound and CARD trials similar enough for the transitivity assumption to hold (i.e. the RCTs included in the comparison are similar in all respect other than the intervention received)?	• Most patient characteristics between the two trials were similar, including age and cohort size. • A greater proportion of men in the PROfound Trial had Gleason Grade ≥8 compared to CARD (67% vs 56.6% respectively) • Both trials used the same control arm, though the proportion of men receiving a particular NHA before the trial varies between the two trials. • The number of men receiving a prior taxane varies between the two trials (100% CARD vs ~65% PROfound). • Median follow up is comparable between the two trials. • Treatment duration in both the control and treatment arms are comparable between treatments. The two studies are comparable in study population, study design, outcome measurements. There is a small variation in some treatment effect modifiers between the trials, such as prior taxane use and previous NHA received, though it is not possible to know what affect, if any, this would have on the outcome of the comparison. There was also a difference in treatment crossover between the two studies (30% in CARD and 80% in PROfound) that would need to be taken into account for an ITC.

<table>
<tr><td colspan="2">Issue 7: Choice of distribution for overall survival extrapolation</td></tr>
<tr><td>16. The company used the loglogistic distribution to extrapolate OS and the ERG prefers the Weibull distribution. The OS estimates for olaparib with both curves are presented in the table below. What is the most plausible approach?

<table>
<tr><td>Curve</td><td>OS at 3 years</td><td>OS at 5 years</td><td>OS at 10 years</td><td>AIC+ BIC</td></tr>
<tr><td>Weibull</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>1215.3</td></tr>
<tr><td>Log-logistic</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>1222.5</td></tr>
</table>
</td><td>N/A</td></tr>
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<tr><td colspan="2">Issue 9: Olaparib direct drug costs and relative dose intensity calculation</td></tr>
<tr><td>19. Which olaparib relative dose intensity (RDI) is the most appropriate to use (mean, median, 100%)?</td><td>N/A</td></tr>
<tr><td>20. Should the RDI be applied to rPFS or TTD curves?</td><td>N/A</td></tr>
<tr><td>21. Should a TTD curve be deduced for cabazitaxel?</td><td>N/A</td></tr>
<tr><td colspan="2">Issue 10: Post progression treatments costs calculation</td></tr>
</table>

<table>
<tr>
<td>22. Is the proportion of patients receiving active subsequent treatments expected to be the same between olaparib and cabazitaxel?</td>
<td>There is no evidence showing benefit from subsequent treatments after either olaparib or cabazitaxel in this setting, there is a very small population in the PROfound Study that received cabazitaxel prior to olaparib, but it is too small to determine whether this produced a beneficial effect.</td>
</tr>
<tr>
<td>23. What subsequent treatments are used in routine NHS practice?

c. Please provide details of which are most commonly used, e.g. Treatment 1: 60% of patients, Treatment 2: 10% of patients, Treatment 3: 20% of patients

d. The company assumed that the distribution of subsequent treatments received would vary between olaparib and cabazitaxel, while the ERG assumed that it would be the same irrespective of previous treatment and that NHA would not be included. Which approach is more reflective of current NHS clinical practice? Please add any further comments e.g. about treatment percentages, missing treatments etc.

<table>
<tr><td>Treatments</td><td colspan="4">Proportion of patients receiving this treatment after progression (%)</td></tr>
<tr><td></td><td colspan="2">Company’s approach</td><td>ERG’s approach</td><td>Comments</td></tr>
<tr><td></td><td>Olaparib (PROfound)</td><td>Cabazitaxel (CARD)</td><td>Same for both arms</td><td></td></tr>
<tr><td>Cabazitaxel</td><td>[redacted]</td><td>[redacted]</td><td>27%</td><td></td></tr>
<tr><td>Docetaxel</td><td>[redacted]</td><td>[redacted]</td><td>18%</td><td></td></tr>
<tr><td>Abiraterone</td><td>[redacted]</td><td>[redacted]</td><td>0%</td><td></td></tr>
</table>
</td>
<td>Expert clinical opinion should be sought to fully answer this question, especially in relation to treatment proportions.

On the NHS, the one novel treatment policy makes it impossible for patients to receive a second NHA. Radium 223 will only be available to patients that have received docetaxel, assuming they have bone metastases and no visceral metastases. As shown in question 1, only 21.9% men aged over 70 and 5.7% of men aged 80 and above received docetaxel in 2016. Given that age is also associated with a reduction in other physically burdensome treatments like surgery, it is unlikely that an older population would access cabazitaxel.</td>
</tr>
</table>

Enzalutamide	[redacted]	[redacted]	0%	
Radium-223	[redacted]	[redacted]	55%	

e. Would NHA drug (abiraterone or enzalutamide) be used as a subsequent treatment after progression on olaparib or cabazitaxel?

24. Would patients get more than one active subsequent treatment? If so, would it differ by treatment arm and is it linked to PPS (post progression survival) duration?	N/A
25. Once patients stop their active subsequent treatments, do they receive best supportive care?	The only patients to die from prostate cancer are those that reach mCRPC. It is therefore likely that those patients experiencing progression after receiving available and tolerated active treatments (see response to question 1), will receive palliation.
Issue 11: G-CSF costs estimate	
26. What is the proportion of patients on cabazitaxel who receive primary prophylaxis with G-CSF?	N/A
27. Do these patients receive the maximum 14 days dose with every cycle of cabazitaxel treatment? If not, what is the average treatment duration?	N/A
Issue 12: HRR genes test costs	

28. Should genetic test costs be included in the analyses, as specified in the scope?	The costs for genetic testing should not be included in the analysis as the NHS in England and Wales are commissioning and will reimburse for the necessary genomic testing when this drug is approved for use.
29. What is the prevalence of the HRR genetic mutations in the population that would be tested?	Based on the number needed to screen to find men with BRCA mutated cancers recruited into TOPARP and PROFOUND, we estimate the prevalence to be between 5.46% and 11.3% (respectively from each trial). The prevalence will be higher if other HRR mutations are included.
Issue 13: End-of-life criteria	
30. What is the estimated life expectancy of people with mCRPC with homologous recombination repair gene alterations previously treated with hormonal therapy?	N/A
31. Is there sufficient evidence to indicate that olaparib offers an extension to life of at least an additional 3 months, compared with cabazitaxel?	To our knowledge, there has not been a head to head phase 3 comparison between Olaparib and Cabazitaxel, and we have not seen the details of the ITC between the two treatments.
32. What is the estimated size of the population that would be eligible for treatment with olaparib?	Using data from the TOPARP B study, of the 592 men for whom genetic screening was successful, 5.46% had either a BRCA 1 or 2 mutation and were trial eligible. It should be noted that this may be an underestimation of the prevalence of BRCA 1 and 2 mutations in the UK mCRPC. This is because the exclusion criteria in TOPARP may not be completely reflective of the clinical use

	of Olaparib and trial ineligible men includes men who died before the start of the trial but were positive for a BRCA mutation after screening. The proportion of successfully sequenced men in PROfound with a BRCA1 or 2 mutation was around 11.3%, though we recognize only a minority of men in this group were from the UK, which may affect the prevalence of BRCA mutations. Data from Public Health England (Get Data Out) shows that 6017 men were diagnosed with metastatic disease in 2016. 24-month crude survival for these men was 59.5% (3580 patients). We have used 24-month crude survival as an approximate indicator of the number of men who would progress from metastatic to mCRPC and have received all treatments prior to Olaparib. Therefore, of the 3580 patients, we estimate approximately between 195- 405 patients would be have a BRCA 1/2 mutation and therefore be eligible for Olaparib, depending on whether the TOPARP B or PROfound BRCA 1/2 mutation prevalence proportion is used. We recognize that this is only an approximation, as we do not have data on the number of metastatic men who have survived after treatment with docetaxel (if suitable) and a novel hormonal agent.
Other issue for information – SLR	
33. Can the company provide additional information on their inclusion criteria and further clarification of their methods?	

NICE National Institute for Health and Care Excellence

Technical engagement response form

Olaparib for previously treated hormone-relapsed metastatic prostate cancer [ID1640]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments **12 October 2020**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential

information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Tackle Prostate Cancer**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**NIL**

Questions for engagement

Issue 1: The population in the company's submission narrower is than the scope and clinical trial evidence	
1. What proportion of people would have already received docetaxel in the non-Covid world?	This is difficult to say. Tackle do not have specific data, but Prostate Cancer UK may have. National Prostate Cancer Audit have published some figures. Our understanding is that this would be around 27%
2. Would this proportion be substantially impacted by Covid? If so, what would the proportion be and over what period would it be impacted?	Yes. The current temporary funding arrangements for abiraterone and enzalutamide will have reduced the use of docetaxel particularly in newly diagnosed metastatic disease. This funding was not in force when the olaparib trials under review in this appraisal were conducted.
3. Would docetaxel retreatment be an option after treatment with new hormonal therapy?	This may be an *option* but, in reality, may not be applicable to all patients. The use of docetaxel at any stage of disease will depend on the overall fitness / frailty of the patient and whether they can tolerate the drug at that stage of their disease.
4. Is the evidence submitted and the cost effectiveness of olaparib in the prior taxane group generalisable to the no prior taxane use cohort?	N/A
Issue 2: The company presents analyses from the PROfound trial which suggest differing clinical effectiveness within subgroups	
5. Should genetic subgroups be analysed separately?	N/A
6. Should the 'no prior taxane' subgroup be analysed separately?	N/A

7.What is the probable cost effectiveness of the 'no prior taxane' patients group?	N/A
8. What is the proportion of patients likely to decline docetaxel because of alcohol content?	All preparations of docetaxel contain a small amount of alcohol. Has this been an issue with certain patient groups? It is our understanding that medicines that contain alcohol are permitted within the Muslim faith and are thus not *'haraam'* but using alcohol itself is not permitted. This will apply particularly if there is no alternative drug preparation that does not contain alcohol.
Issue 3: The company has not provided analyses compared with all comparators in the scope	
9. Is it reasonable to assume that patients will have received docetaxel prior to progression to mCRPC and docetaxel is not a comparator?	This is a response for the clinical experts. Docetaxel may not have been used for a variety of clinical reasons. It may not always be a direct comparator.
10. Is it reasonable to assume that radium-223 is used later in the treatment pathway and would not be a comparator to olaparib?	No, this is not a reasonable assumption. Radium-223 is only of value in treating bone metastases. If it is to be used as a comparator is it logical only for this to be in a subgroup of the Olaparib patients that solely had bone metastases? Does such data sub-group analysis exist?
Issue 4: Generalisability of the trial to the UK population and clinical practice	
11. Is the PROfound trial representative of the UK population and clinical practice in terms of:	a) There is very low recruitment of patients from UK in PROfound trial but a large proportion from within Europe as a whole. Has this been a problem with interpreting other trials in the past?

a. Patients included? (see patients characteristics in Appendix 1 of technical report) b. Comparators used?	b) The ERG comment that other treatments such as cabazitaxel or paclitaxel could be used as comparators. Our experience suggests that very few patients are given cabazitaxel. We are unaware that paclitaxel has been approved by NICE for use in prostate cancer (although used in breast cancer).
12. Is the ERG's assumption that no benefit can be expected from subsequent treatment with NHA in patients who already progressed on NHA plausible?	This is for clinical experts to comment on.
Issue 5: Heterogeneity of the PROfound and CARD trials used to indirectly compare olaparib	
13. Is HRRm associated with more aggressive disease?	N/A
14. Based on the different HRRm status between PROfound and CARD trials, are the NHA arms in the 2 trials comparable?	N/A
Issue 6: The indirect treatment comparison (ITC) of olaparib vs cabazitaxel is uncertain	
15. Are the PROfound and CARD trials similar enough for the transitivity assumption to hold (i.e. the RCTs included in the comparison are similar in all respect other than the intervention received)?	N/A
Issue 7: Choice of distribution for overall survival extrapolation	
16. The company used the loglogistic distribution to extrapolate OS and the ERG prefers the Weibull distribution. The OS estimates for olaparib with both curves are presented in the table below. What is the most plausible approach?	We do not have the statistical expertise to give an opinion. However, experience of previous NICE appraisals suggests that NICE tend to favour stats that predict the worst outcome for the treatment concerned, but the pharma companies choose the most favourable! There is normally some sort of compromise made?

Curve	OS at 3 years	OS at 5 years	OS at 10 years	AIC+ BIC
Weibull	[redacted]	[redacted]	[redacted]	1215.3
Log-logistic	[redacted]	[redacted]	[redacted]	1222.5

Issue 8: Discrepancies between progression-free survival and time to treatment discontinuation curves	
17. In the PROfound trial, were patients obliged to stop treatment upon progression?	N/A
18. Were events treated consistently when constructing the rPFS and TTD KM curves?	N/A
Issue 9: Olaparib direct drug costs and relative dose intensity calculation	
19. Which olaparib relative dose intensity (RDI) is the most appropriate to use (mean, median, 100%)?	N/A
20. Should the RDI be applied to rPFS or TTD curves?	N/A
21. Should a TTD curve be deduced for cabazitaxel?	N/A
Issue 10: Post progression treatments costs calculation	
22. Is the proportion of patients receiving active subsequent treatments expected to be the same between olaparib and cabazitaxel?	N/A
23. What subsequent treatments are used in routine NHS practice?	This question is for the clinical experts to comment on. However, our impression from talking with patients in general is that few of them have experience of receiving either Radium-223 or cabazitaxel. Choice of subsequent treatment will

a. Please provide details of which are most commonly used, e.g. Treatment 1: 60% of patients, Treatment 2: 10% of patients, Treatment 3: 20% of patients

b. The company assumed that the distribution of subsequent treatments received would vary between olaparib and cabazitaxel, while the ERG assumed that it would be the same irrespective of previous treatment and that NHA would not be included. Which approach is more reflective of current NHS clinical practice? Please add any further comments e.g. about treatment percentages, missing treatments etc.

Treatments	Proportion of patients receiving this treatment after progression (%)			
	Company's approach		**ERG's approach**	Comments
	Olaparib (PROfound)	Cabazitaxel (CARD)	Same for both arms	
Cabazitaxel	[redacted]	[redacted]	27%	
Docetaxel	[redacted]	[redacted]	18%	
Abiraterone	[redacted]	[redacted]	0%	
Enzalutamide	[redacted]	[redacted]	0%	
Radium-223	[redacted]	[redacted]	55%	

c. Would NHA drug (abiraterone or enzalutamide) be used as a subsequent treatment after progression on olaparib or cabazitaxel?

depend on the fitness / frailty of the individual patient at that stage of their stage of disease progression and on the clinician responsible for their treatment.

24. Would patients get more than one active subsequent treatment? If so, would it differ by treatment arm and is it linked to PPS (post progression survival) duration?	N/A
25. Once patients stop their active subsequent treatments, do they receive best supportive care?	We assume this refers to 'palliative care' – which should be available on NHS to all patients. The degree of access to this and the level of care that is given will have considerable variations from one area of UK to another depending on local resources available.
Issue 11: G-CSF costs estimate	
26. What is the proportion of patients on cabazitaxel who receive primary prophylaxis with G-CSF?	N/A
27. Do these patients receive the maximum 14 days dose with every cycle of cabazitaxel treatment? If not, what is the average treatment duration?	N/A
Issue 12: HRR genes test costs	
28. Should genetic test costs be included in the analyses, as specified in the scope?	Logically costs of genetic testing should be included in overall cost analysis. BUT there is no current guidance concerning which patients with prostate cancer should be genetically tested and when in the course of their disease progression this should be performed. Our experience would suggest that genetic testing is rarely performed, and commonly instigated by the more knowledgeable patients who know about it.

29. What is the prevalence of the HRR genetic mutations in the population that would be tested?	Eles (2012) stated that 0.5 – 1% of all men newly diagnosed with PCa had genetic mutations De Bono (2015) stated that 19% men with hormone resistant PCa had BRCA or ATM mutation
Issue 13: End-of-life criteria	
30. What is the estimated life expectancy of people with mCRPC with homologous recombination repair gene alterations previously treated with hormonal therapy?	N/A
31. Is there sufficient evidence to indicate that olaparib offers an extension to life of at least an additional 3 months, compared with cabazitaxel?	For patients, *quality* of life is as important as *quantity* of life. If the life extension between two drugs is the same, then the *quality* of life during that period becomes an especially important factor in a decision process concerning treatment options. The side effects profile of olaparib is arguably better than cabazitaxel.
32. What is the estimated size of the population that would be eligible for treatment with olaparib?	Good Question!!!! There is currently no NICE guidance on genetic testing as to who should be tested and when.
Other issue for information - SLR	
33. Can the company provide additional information on their inclusion criteria and further clarification of their methods?	N/A

NICE National Institute for Health and Care Excellence

Technical engagement response form

Olaparib for previously treated hormone-relapsed metastatic prostate cancer [ID1640]

Questions for engagement

Note: The company would suggest that the Appendices of this document are reviewed prior to the responses given to the Questions for Engagement, as these provide additional context and clarity on the company responses.

Issue 1: The population in the company's submission narrower is than the scope and clinical trial evidence	
1. What proportion of people would have already received docetaxel in the non-Covid world?	As described in Document B, Section B.1.2., AstraZeneca consulted with UK clinical experts (n=6) to address this question in the company submission. **Estimates obtained from these experts highlight that the vast majority (~75%) of patients currently receive docetaxel in the pre-mCRPC setting** (AstraZeneca data on file), with tolerability concerns being the key factor limiting its use in these patients. This proportion is also consistent with feedback from clinical experts consulted by the ERG, as described in p25 of the ERG report: "*The opinion that ~75% of patients have already received treatment with a taxane prior to NHA treatment was deemed acceptable by our clinical advisors.*" Additionally, it is worth highlighting that NICE prostate cancer clinical guidance (NG131),(1) published in 2019, also recommend that docetaxel should be considered / offered to: • Patients who have newly-diagnosed high-risk non-metastatic prostate cancer, and • Patients with newly-diagnosed metastatic prostate cancer, lending further support to docetaxel use before patients develop **metastatic castration-resistant** disease.

2. Would this proportion be substantially impacted by Covid? If so, what would the proportion be and over what period would it be impacted?	The proportion of patients who receive docetaxel in the pre-mCRPC setting is likely to be impacted by interim guidance recommending the use of enzalutamide in the newly-diagnosed metastatic prostate cancer setting, alongside the option for switching patients who are intolerant to abiraterone treatment.(2) However, this guidance is ***temporary*** and was put in place in response to the exceptional circumstances resulting from the COVID-19 pandemic. As such, it does not constitute routine clinical practice in England. It is also worth noting that NICE has not recommended either enzalutamide (ID1605), or abiraterone (ID945), in the pre-mCRPC setting. Abiraterone with prednisone or prednisolone plus androgen deprivation therapy (ADT) was ***not recommended*** by NICE for treating newly diagnosed high-risk hormone-sensitive metastatic prostate cancer in ID945. The outcome of appraisal ID1605 is not known at present. **Therefore, these treatment options and any potential impact on the clinical pathway fall beyond the remit of this appraisal.**
3. Would docetaxel retreatment be an option after treatment with new hormonal therapy?	As described in the company submission (Document B, Section B.1.2.), "*the 6 UK clinical experts consulted (by AstraZeneca to inform the company submission) highlighted that re-treatment with docetaxel is not preferred in patients where cabazitaxel is a treatment option*".(3) This is also consistent with data from a retrospective analysis of 245 patients from the GETUG AFU-15 Phase III study, who received docetaxel re-challenge upon progression to mCRPC.(4) Docetaxel re-challenge showed activity in only a limited number of patients, with a PSA decline (>50%) observed in just 14% of patients.(4)
4. Is the evidence submitted and the cost effectiveness of olaparib in the prior taxane group generalisable to the no prior taxane use cohort?	The generalisability of 'prior taxane' vs 'no prior taxane' subgroups is supported by the clinical efficacy data in the prior taxane subgroup of *BRCA*m vs the overall *BRCA*m population of patients (which also included those who did not receive prior treatment with a taxane). Both the overall *BRCA*m population and *BRCA*m prior taxane subgroup show very similar OS benefit for olaparib vs investigators' choice of NHA, with consistent and stable OS HRs of [redacted] and [redacted], respectively (please see Appendix A.1 for further details).

	Cost-effectiveness analyses were conducted for both the prior taxane subgroup of *BRCA*m – the company's new base-case (Appendix A.3), as well as the suggested overall *BRCA*m scenario, per the ERG's request received on 6th October 2020 (Appendix A.4). For reference, these analyses include the final OS and safety data from the PROfound study (DCO2). The results show that olaparib is expected to be a highly-cost effective use of NHS resources compared with the current standard-of-care, cabazitaxel, in both the prior taxane subgroup of *BRCA*m as well as the overall *BRCA*m population, with an incremental cost-effectiveness ratio (ICER) of £18,596 /QALY and £20,176 /QALY, respectively. These results are as expected, given the similar and consistent clinical effectiveness of olaparib in the prior taxane subgroup of *BRCA*m and the overall *BRCA*m population, and (by implication) provide an indication of the cost-effectiveness of olaparib in the *BRCA*m 'no prior taxane' group of patients. Note: also see related responses to Questions 6 and 7 below.
A.1.1 Issue 2: The company presents analyses from the PROfound trial which suggest differing clinical effectiveness within subgroups	
5. Should genetic subgroups be analysed separately?	Not applicable. The recent positive CHMP opinion, released on 17th September, restricts the use of olaparib as monotherapy to adult patients with metastatic castration-resistant prostate cancer and ***BRCA1/2-mutations*** (germline and/or somatic) who have progressed following prior therapy that included a new hormonal agent.(5) In light of this opinion and the anticipated EMA marketing authorisation for olaparib in this indication, other genetic subgroups are no longer relevant.
6. Should the 'no prior taxane' subgroup be analysed separately?	As described above (in response to Issue 1, Q4), the clinical- and cost-effectiveness of olaparib in the prior taxane subgroup of *BRCA*m is similar to that in the overall *BRCA*m population, which also includes patients who had not received prior treatment with a taxane. Given this and the anticipated use of olaparib in routine clinical practice (where most patients will have received a

	taxane earlier in the treatment pathway), it is not deemed necessary to analyse the 'no prior taxane' subgroup of *BRCA*m separately. Furthermore, the small number of patients in the *BRCA*m no prior taxane subgroup (30 in the olaparib arm and 23 in the investigators' choice of NHA arm) are likely to make any specific analyses in this subgroup challenging.
7.What is the probable cost effectiveness of the 'no prior taxane' patients group?	As stated above (in response to Issue 1, Question 4), olaparib is expected to be a cost-effective use of NHS resources compared with current standard-of-care, cabazitaxel, in both the prior taxane subgroup of *BRCA*m and the overall *BRCA*m population (which includes both 'prior taxane' and 'no prior taxane' patients), with ICERs of £18,596 /QALY and £20,176, respectively. This approach is aligned to the request made by the ERG (email received 6th October, 2020), is consistent with their approach in the ERG report (Section 4.3.4, p147), and (by implication) provides an indication of the cost effectiveness of olaparib in the *BRCA*m 'no prior taxane' group of patients.
8. What is the proportion of patients likely to decline docetaxel because of alcohol content?	In the original company submission (Document B, Section B.1.5), religious beliefs were cited as a reason that may prevent some patients from accepting chemotherapy, due to the alcohol content present in docetaxel. The proportion of patients this may apply to is difficult to quantify accurately and is not available in the published literature; however, we would expect the proportion to be low, especially in the context of a *BRCA*m population that is relevant to this indication (20−30 patients in Year 1, based on calculations shown in response to Issue 13, Question 32). In a previous submission (NICE ID945), it was estimated that "*20% of men are considered clinically unsuitable for chemotherapy at diagnosis*," with the alcohol content in docetaxel cited as being one of several contributing factors. This figure is also consistent with the response to Issue 1, Question 1, where clinicians consulted by the company stated that ~25% of patients may not receive docetaxel treatment in the pre-mCRPC setting, for any reason.

A.1.2 Issue 3: ***The company has not provided analyses compared with all comparators in the scope***	
9. Is it reasonable to assume that patients will have received docetaxel prior to progression to mCRPC and docetaxel is not a comparator?	Please see response to Issue 1, Question 1. As described in Document B, Section B.1.2., UK clinical experts (n=6) consulted by the company stated **that the vast majority (~75%) of patients currently receive docetaxel in the pre-mCRPC setting.(3)** The experts also highlighted that re-treatment with docetaxel is not preferred in patients where cabazitaxel is a treatment option. This was also accepted by the ERG, who, in their report (p26) state that: "*The ERG clinical advisors agree with the company clinical experts that in the majority of cases docetaxel is used earlier in the pathway. The ERG considers the removal of docetaxel as a comparator, and it's inclusion within the population to be in line with current practice*." **In light of clinical expert evidence, we consider cabazitaxel, and not docetaxel, to be the appropriate comparator for olaparib in this patient population.** Furthermore, as described in Section B.2.1.3 of Document B, the clinical SLR conducted by the company did not identify any studies that reported outcomes on docetaxel in the population relevant to the decision problem, i.e. patients with mCRPC whose disease had progressed after treatment with a NHA, limiting our ability to conduct any comparative analyses of olaparib vs docetaxel in this setting.
10. Is it reasonable to assume that radium-223 is used later in the treatment pathway and would not be a comparator to olaparib?	As described in the company submission (Document B, Section B.1.2.), although it is possible to use radium-223 dichloride in those patients who have symptomatic bone metastases (and no known visceral metastases) and have received prior docetaxel for hormone-sensitive disease, clinical expert opinion from 6 UK-based clinical experts indicates that in practice it is often reserved for later-lines of treatment (once options such as cabazitaxel have been exhausted), unless treatment with a taxane is not suitable.(3). For these reasons, cabazitaxel is the most appropriate comparator for olaparib in this setting. Furthermore, as described in Section B.2.1.3 of Document B, the SLR did not identify any studies that reported outcomes on radium-223 dichloride in the population relevant to the decision

	problem, i.e. patients with mCRPC whose disease had progressed after treatment with a NHA, thus limiting our ability to conduct any comparative analyses. The ERG report (p26) "*agrees there is a lack of trial evidence in the correct population on radium 223-dichloride treatment*."
Issue 4: Generalisability of the trial to the UK population and clinical practice	
11. Is the PROfound trial representative of the UK population and clinical practice in terms of: a. Patients included? (see patients characteristics in Appendix 1 of technical report) b. Comparators used?	**a. Patients included** The baseline characteristics of patients in the PROfound trial (as stated in the technical team's question) and the *BRCA*m prior taxane subgroup (the company's new base-case; Appendix 1, Table 3), are largely reflective of the UK mCRPC patients, who may be eligible to receive olaparib treatment. For instance: • The mean age of all patients enrolled into PROfound was 68.1 years (67.1 years in patients with *BRCA*m [n=160]). This is consistent with Cancer Research UK data, which indicate a peak rate in cases between 65−69 years of age.(6) • Prior NHA therapy was a pre-requisite for entry into the PROfound study, and is specified in the anticipated EMA licence for the use of olaparib in *BRCA*m mCRPC.(5) This aligns with the use of NHA in clinical practice, with both abiraterone and enzalutamide recommended in by NICE and representing the standard of care in the first-line mCRPC setting.(7-10) • Finally, all patients in the prior taxane subgroup of *BRCA*m will have, by definition, received previous taxane therapy, which is consistent with the population of patients who currently receive cabazitaxel for mCRPC in clinical practice. **b. Comparators used** While some patients in UK clinical practice may receive abiraterone after enzalutamide, or vice versa, due to tolerability issues on the first NHA, we acknowledge that the comparator of

	investigators' choice of NHA in PROfound does not reflect the current standard-of-care in England. To address this, it was necessary to conduct an anchored indirect treatment comparison (ITC) vs cabazitaxel – the most relevant comparator in clinical practice within the NHS - using data from the CARD study.
12. Is the ERG's assumption that no benefit can be expected from subsequent treatment with NHA in patients who already progressed on NHA plausible?	This assumption has no impact on the comparative analysis presented in the company submission and the cost-effectiveness evidence for olaparib vs cabazitaxel. As discussed in Document B, Section B.2.2.1, investigators' choice of NHA was chosen as the comparator in the PROfound study since re-treatment with NHA (i.e. enzalutamide after progression of abiraterone, or vice versa) is an approved treatment option (by both the EMA and the US FDA) and, at the time of trial design, was standard-of-care in many countries where the PROfound study was conducted.(11) This approach also ensured that patients for whom treatment with chemotherapy was unsuitable were not excluded from the PROfound study. As noted in response to Question 11, the clinical and cost-effectiveness evidence presented in the company submission focus on a comparative analysis of olaparib vs cabazitaxel, taking into account the fact that NHA re-challenge is not standard clinical practice in England.
Issue 5: Heterogeneity of the PROfound and CARD trials used to indirectly compare olaparib	
13. Is HRRm associated with more aggressive disease?	Not applicable. As highlighted previously, the anticipated EMA marketing authorisation for olaparib in this indication restricts its use to those patients with *BRCA*m mCRPC, as opposed to HRRm mCRPC.(5)
14. Based on the different HRRm status between PROfound and CARD trials, are the NHA arms in the 2 trials comparable?	Not applicable. As highlighted above, the anticipated EMA marketing authorisation for olaparib in this indication restricts its use to those patients with *BRCA*m mCRPC, as opposed to HRRm mCRPC.(5) **There**

	is no evidence to suggest that *BRCA*m status is a treatment effect modifier for response to cabazitaxel or NHA treatment.
Issue 6: The indirect treatment comparison (ITC) of olaparib vs cabazitaxel is uncertain	
15. Are the PROfound and CARD trials similar enough for the transitivity assumption to hold (i.e. the RCTs included in the comparison are similar in all respect other than the intervention received)?	An ITC was necessary to address the scope of this appraisal and provide a comparative clinical and cost-effectiveness analysis of olaparib vs cabazitaxel, the standard-of-care for mCRPC patients in England who have received prior treatment with a taxane (docetaxel) and NHA. The CARD study was the only trial identified that reported on outcomes for cabazitaxel in the post-NHA setting that is relevant to this appraisal (Document B, Section B.2.8 to B.2.9).**The ITC leveraging data from PROfound and CARD studies provides the best estimate of the relative efficacy of olaparib compared with cabazitaxel, given the data that are currently available.** Importantly, • Both studies share the same common comparator arm of investigators' choice of NHA, enabling the use of an anchored ITC to evaluate the relative efficacy of olaparib versus cabazitaxel, • No evidence of effect modification for OS were identified at the 20% significance level in the initial company submission, consistent with there being no meaningful differences across the reported baseline characteristics for the two studies (Document B, Section B.2.9.2.3), and • There is no evidence to suggest that the relative effectiveness of cabazitaxel versus NHA would be any different in patients with *BRCA*m disease (relative to a biomarker unselected mCRPC population of patients).
Issue 7: Choice of distribution for overall survival extrapolation	

16. The company used the loglogistic distribution to extrapolate OS and the ERG prefers the Weibull distribution. The OS estimates for olaparib with both curves are presented in the table below. What is the most plausible approach?

Curve	OS at 3 years	OS at 5 years	OS at 10 years	AIC+ BIC
Weibull	[redacted]	[redacted]	[redacted]	1215.3
Log-logistic	[redacted]	[redacted]	[redacted]	1222.5

Not applicable.

As stated elsewhere, on 17th September 2020, the CHMP issued a positive opinion recommending the use of olaparib in adult patients with metastatic castration-resistant prostate cancer and *BRCA1/2* mutations (germline and/or somatic) who have progressed following prior therapy that included a new hormonal agent.(5)

As a result of this update, the economic model was updated to reflect the prior taxane subgroup of *BRCA*m, the new company base-case, as detailed in Appendix A.3. Briefly:

- Consistent with the approach taken in the initial submission (Document B, Section B.3.3), parametric analyses were conducted for the olaparib arm using final (DCO2) OS data for the *BRCA*m prior taxane subgroup of the PROfound trial.
- The ITC was updated to reflect the *BRCA*m population of PROfound, using the final (DCO2) OS data, after adjusting for treatment switching in the investigators' choice of NHA arm, and the published OS data from the CARD study (please see Appendix A.1.4.2.1 and Appendix A.2 for details).
- Outcomes for cabazitaxel were modelled by applying the reciprocal of the ITC results (olaparib vs cabazitaxel, OS HR [redacted]; rPFS HR [redacted]) to the parametric curve for olaparib as the reference arm.

The exponential distribution had the best statistical fit to observed data for the olaparib arm (based on combined AIC and BIC statistics); however, this distribution provided long-term survival estimates that were too pessimistic for patients with *BRCA*m disease, who are anticipated to derive the most clinical benefit from olaparib:

- Clinical experts previously consulted by AstraZeneca indicated that 5-year and 10-year OS rates of [redacted]% and [redacted]% were clinically-plausible for patients in the HRRm prior taxane population (Document B, Section B.3.3.2.1.2.1).

	• Based on observed data from the PROfound study, patients with *BRCA*m disease are anticipated to derive greater clinical benefit than the overall HRRm population of patients. • Therefore, 5-year and 10-year OS rates of at least (or in excess of) [redacted]% and [redacted]% would be expected for the *BRCA*m prior taxane subgroup of patients. • The exponential distribution, however, produced 5-year and 10-year estimates of just [redacted]% and [redacted]%. Of all the parametric survival extrapolations analysed, the log-logistic distribution most-closely reflected UK clinical expert opinion, and was used in the base-case analysis for the following reasons (please see Appendix A.3.3.2.2 for further details): 1. Survival estimates with the log-logistic distribution best reflected the observed OS KM data for the prior taxane subgroup of *BRCA*m within the trial follow-up period (with OS rates of [redacted]% and [redacted]% 1 and 3 years, respectively, vs [redacted]% and [redacted]% at 1 year and 33 months, respectively, in the observed data). 2. The log-logistic distribution provides the most clinically-plausible predictions for long-term OS rates at 5 and 10 years for patients in the prior taxane subgroup of *BRCA*m. • UK clinical experts stated that 5-year and 10-year OS rates of [redacted]% and [redacted]% would be plausible for HRRm patients who receive olaparib treatment • Based on observed data, the OS benefit achieved with olaparib in BRCAm patients would be expected to be better than that achieved in a HRRm population. • The modelled 5- and 10-year OS estimates for the *BRCA*m prior taxane analysis using the log-logistic distribution were [redacted]% and [redacted]%, respectively, which are similar to the estimates provided by clinical experts for the HRRm population. In contrast, the exponential distribution provided a severely pessimistic outlook for 5 and 10 year survival on olaparib ([redacted]% and [redacted]%, respectively (Appendix A.3.3.2.2, Table 14).

	Finally, a long-term survival benefit on olaparib treatment, in at least a proportion of *BRCA*m patients (evidenced by a survival "tail"), is consistent with its mechanism of action and long-term follow-up data from other advanced, metastatic disease settings (e.g. Study 19 in platinum-sensitive relapsed advanced ovarian cancer; as detailed in Appendix A.3.3.2.2). Please see Table 14 in Appendix A.3.3.2.2 for a detailed summary of the observed OS data from PROfound, extrapolated OS curves for olaparib, and the long-term survival estimates based on clinical experts' opinion discussed above. A scenario analysis was explored using the statistically best-fitting exponential distribution based on AIC/BIC values, as shown in Appendix A.3.7, Table 23. Olaparib remained a cost-effective treatment option even in this pessimistic analysis.
Issue 8: Discrepancies between progression-free survival and time to treatment discontinuation curves	
17. In the PROfound trial, were patients obliged to stop treatment upon progression?	Yes. Further information can be found in the PROfound CSR addendum, which states that "*Patients were to continue to receive study treatment **until objective radiological disease progression** as per Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 and Prostate Cancer Working Group 3 (PCWG-3), as assessed by blinded independent central view (BICR), or by investigator assessment (if after the DCO for the primary analysis), as long as they did not meet any other discontinuation criteria.*"(12) This is also consistent with the draft EMA SmPC for this indication, which *recommends that "treatment [with olaparib] be continued until progression of the underlying disease or unacceptable toxicity*."
18. Were events treated consistently when constructing the rPFS and TTD KM curves?	The events in the rPFS and TTD KM curves are treated according to the definition of each endpoint: • For rPFS, the events of interest are radiological disease progressions by BICR or death.

- For TTD, the events consist of treatment discontinuations and deaths, with the reasons for treatment discontinuation being as described in CSR TLF Table 14.1.1.1.1.

In any case, median rPFS was very similar to median TTD in the *BRCA*m population of patients ([redacted] months vs [redacted] months, respectively). An overlay of the KM data show substantial overlap, suggesting that there are no meaningful differences between these data (Figure 1). Median rPFS and TTD in the prior taxane subgroup of *BRCA*m were also similar ([redacted] months vs [redacted] months, respectively), with KM curves also following very similar trajectories (Figure 2).

As such, there is no evidence to suggest that using the rPFS curve to proxy treatment duration for olaparib would bias the cost-effectiveness analysis. This is supported by the scenario analysis results, where changing the modelling approach from rPFS to TTD (for olaparib) has a small impact on the cost-effectiveness results (Appendix 3.7, Table 23; please also see responses to Issue 9, Question 20 and Question 21).

Figure 1. PROfound – Monthly KM estimates for rPFS and TTD (*BRCA*m – olaparib arm, DCO1)

[redacted]

	Figure 2. PROfound – Monthly KM estimates for rPFS and TTD (*BRCA*m – prior taxane olaparib arm, DCO1) 
Issue 9: Olaparib direct drug costs and relative dose intensity calculation	
19. Which olaparib relative dose intensity (RDI) is the most appropriate to use (mean, median, 100%)?	We have updated the base-case analysis to use the median RDI values of [redacted]% and 96.1% for olaparib and cabazitaxel, respectively (Appendix A.3.5). The difference in the median RDI values between interventions remains small, and are both higher than their previously-used mean values of [redacted]% for olaparib and 92.6% for cabazitaxel. A scenario testing the impact of setting RDI to 100% for both interventions also shows that changing this assumption has minimal impact on the results (Appendix A.3.7, Table 23).
20. Should the RDI be applied to rPFS or TTD curves?	It is appropriate to apply the relative dose intensity (RDI) to the rPFS curve. This is confirmed by similarity in the median RDI through to treatment discontinuation and the median percentage intended dose through to progression ([redacted]% vs [redacted]%, respectively). As described in the company submission (Document B, Section B.3.3.3) and responses to the ERGs' clarification questions (CQ B3), **in the absence of observed TTD data for cabazitaxel,**

	using rPFS data to proxy treatment duration for both olaparib and cabazitaxel is the only robust and consistent way to model treatment duration for decision-making purposes. Furthermore, rPFS and TTD data are similar in the prior taxane subgroup of *BRCA*m (Issue 8, Question 18); changing the modelling approach from rPFS to TTD (for olaparib) has a small impact on the cost-effectiveness results (Appendix A.3.7, Table 23).
21. Should a TTD curve be deduced for cabazitaxel?	The clinical effectiveness data for olaparib and cabazitaxel are based upon treatment duration in the PROfound and CARD studies, respectively. As stated above, for decision-making purposes, it is appropriate to take a ***consistent*** approach to the type of data and methodology used for modelling treatment duration across interventions, using the best available evidence. **In the absence of observed TTD data for cabazitaxel, using rPFS data to proxy treatment duration for both olaparib and cabazitaxel represents the most robust and consistent approach**. • **Deducing a TTD curve for cabazitaxel unnecessarily introduces uncertainty into the analysis**, due to the inability to validate the approach or results in the absence of observed data. • In contrast, the approach of proxying treatment duration using rPFS data is directly based on the primary endpoints of the PROfound and CARD studies and does not require any additional assumptions or validation. Finally, the ERG has previously noted that efficacy data are linked to treatment duration (ERG Report Section 4.3.4.8, p139). By this same rationale, the incremental analyses provide a conservative estimate of the cost-effectiveness of olaparib vs cabazitaxel, regardless of the approach used for modelling treatment duration. This is because treatment costs for cabazitaxel are artificially restricted to a maximum of 10 treatment cycles **without any adjustments to efficacy in the base-case analysis.** Removing this constraint had a positive impact on the ICER, as detailed in Table 23 of Appendix A.3.

Issue 10: Post progression treatments costs calculation	
22. Is the proportion of patients receiving active subsequent treatments expected to be the same between olaparib and cabazitaxel?	There is no clinical reason to believe that the proportion of patients receiving active subsequent treatments would be different between olaparib and cabazitaxel. This input value is also not a driver of the cost-effectiveness analysis. In the primary rPFS analysis of the PROfound study (DCO1), [redacted]% of patients in the *BRCA*m prior taxane subgroup received any subsequent treatment ([redacted] patients out of 48 progression events). The same proportion of patients received subsequent treatment upon disease progression in the interim analysis of the CARD study, as calculated by the ERG (41.7%; 50 patients out of 120 events). Therefore, in the updated company base-case analyses, we apply an equal rate of [redacted]% for both arms, to reflect the proportions of patients who receive any post-progression anticancer therapy (Appendix A.3.3.5.1).
23. What subsequent treatments are used in routine NHS practice? a. Please provide details of which are most commonly used, e.g. Treatment 1: 60% of patients, Treatment 2: 10% of patients, Treatment 3: 20% of patients b. The company assumed that the distribution of subsequent treatments received would vary between olaparib and cabazitaxel, while the ERG assumed that it would be the same irrespective of previous treatment and that NHA would not be included. Which approach is more reflective of current NHS clinical practice? Please add any further comments e.g.	a) The distribution of subsequent treatments in the PROfound and CARD studies is provided in Table 1. Please see Part C. regarding how this relates to clinical practice. b) It is expected that the distribution of subsequent treatments will differ for patients progressing on olaparib, compared with patients progressing on cabazitaxel. As described in the company submission (Document B, Section B.1.2), the standard-of-care for patients after disease progression on docetaxel and an NHA is cabazitaxel. **Treatment options are limited in the next line of therapy, once patients have progressed on cabazitaxel**; a subset of patients with bone metastases and no visceral metastases may be eligible to receive radium-223. Re-treatment with a taxane is uncommon. **Olaparib offers a new targeted treatment option for patients** with *BRCA*m mCRPC, who have received prior treatment with a taxane and NHA. As described in the company submission, it is anticipated that olaparib will replace cabazitaxel in the treatment pathway (Document B, Section B.1.2). After disease progression on olaparib, it is expected that many patients will still be eligible to receive cabazitaxel as a next line therapy in clinical practice.

about treatment percentages, missing treatments etc. c. Would NHA drug (abiraterone or enzalutamide) be used as a subsequent treatment after progression on olaparib or cabazitaxel?	c) Although subsequent NHA use is not reflective of current practice in the NHS, these costs have been accounted for in the company base-case analysis to reflect the efficacy data from the PROfound and CARD studies, and the use of subsequent NHA in: • [redacted] out of 72 patients ([redacted]%) in the olaparib arm of the *BRCA*m prior taxane subgroup of PROfound, • 30 out of 129 patients (23.3%) in the cabazitaxel arm of the CARD study. Given the similar levels of subsequent NHA use in both PROfound and CARD studies, subsequent NHA costs are unlikely to have a meaningful impact on the incremental cost-effectiveness analysis. This was demonstrated in a scenario analysis where subsequent NHAs were excluded using the approach agreed with by the ERG (without adjusting for efficacy). The results of the scenario analysis show minimal impact on the ICER (Appendix 3.7, Table 23).

Table 1. Subsequent treatments for *BRCA*m prior taxane model (update provided by company; also described in Appendix 3.3.5.2)

Treatments	Proportion of patients receiving this treatment after progression (%)			
	Company's base-case (before adjusting for NHA)*		Company's scenario (after adjusting for NHA)*	
	Olaparib (PROfound)	Cabazitaxel (CARD)**	Olaparib (PROfound)	Cabazitaxel (CARD)**
Cabazitaxel	[redacted]	7%	[redacted]	27%
Docetaxel	[redacted]	5%	[redacted]	18%
Abiraterone	[redacted]	37%	[redacted]	0%
Enzalutamide	[redacted]	37%	[redacted]	0%
Radium-223	[redacted]	15%	[redacted]	55%

* Excluding investigational and treatments that have not been approved for use in mCRPC patients, adjusted to sum to 100%.

** Proportions suggested by the ERG (ERG Report, Section 4.3.2.1 with specific values sourced from electronic version of the ERG rebuild model)

24. Would patients get more than one active subsequent treatment? If so, would it differ by treatment arm and is it linked to PPS (post progression survival) duration?	Information on the proportions of patients who received more than one active subsequent treatment is not available for the *BRCA*m population of PROfound or the prior taxane subgroup of *BRCA*m. While the introduction of olaparib into the clinical pathway (replacing cabazitaxel) may facilitate cabazitaxel use post disease-progression on olaparib, it is unlikely that many patients will be fit

	enough to receive further active anticancer treatment (after already receiving docetaxel, NHA, olaparib, and cabazitaxel therapy). The costs and benefits of subsequent therapies used at any point in the PROfound and CARD studies have been accounted for in the base-case cost-effectiveness analysis (see Table 1 in the response to Q23); data from the PROfound and CARD studies do not allow us to further investigate the link between the number of active subsequent treatments received and any impact on PPS.
25. Once patients stop their active subsequent treatments, do they receive best supportive care?	In clinical practice, patients may receive best supportive care (BSC) and end-of-life care once anti-cancer treatment options have been exhausted, but this is likely to occur regardless of whether they receive olaparib or cabazitaxel in the post-NHA setting. **Because a number of post-progression costs are already accrued in the model, simply applying additional BSC costs after subsequent treatments is uninformative and introduces double-counting**, for example: • Ongoing post-progression resources (such as regular consultant and nurse visits, CT scans, and a range of other tests to monitor disease) that are likely to part of BSC, are already accounted for in the company's model. • Substantial end-of-life care costs are also already applied to all patients in the company's model. These costs are relevant for patients who would be considered to receive BSC (e.g. drugs administered for pain and hospice/palliative care). • **Furthermore the company's partitioned survival model is <u>not</u> set up to estimate sequential costs of BSC after subsequent treatment because of data limitations, which do not allow for the duration or cost of sequential lines of treatment or BSC to be modelled meaningfully**. The ERG's simplistic means-based approach to BSC fundamentally assumes 4 health states and makes strong assumptions about time from first to second progression and beyond, which may vary between interventions and lines of treatment. There are no data from the PROfound or CARD studies to support this

	approach. Ultimately, including these costs is not aligned to the PROfound or CARD studies and is likely to lead to additional uncertainty. In light of these issues, we have maintained our original approach in the revised base-case analysis.
Issue 11: G-CSF costs estimate	
26. What is the proportion of patients on cabazitaxel who receive primary prophylaxis with G-CSF?	Primary prophylaxis with G-CSF is clinically important to prevent neutropenic complications. The company base-case analysis assumes that all patients receive prophylactic G-CSF (see Document B, Section B.3.5.2.2.2, p160), based on the following rationale: The EMA licence for cabazitaxel recommends that patients treated with cabazitaxel may "*receive prophylactic G-CSF, as per American Society of Clinical Oncology (ASCO) guidelines and/or current institutional guidelines, to reduce the risk or manage neutropenia complications (febrile neutropenia, prolonged neutropenia or neutropenic infection).*"(13) Efficacy and safety outcomes for cabazitaxel are based on the CARD study, which required use of G-CSF in all patients (i.e. 100%), per the study protocol. The cost-effectiveness analysis was aligned to this, for consistency.
27. Do these patients receive the maximum 14 days dose with every cycle of cabazitaxel treatment? If not, what is the average treatment duration?	The company base-case analysis is informed by the EMA marketing authorisation for cabazitaxel, which recommends that "*treatment with G-CSF for the reduction in duration of neutropenia and incidence of febrile neutropenia (in cytotoxic chemotherapy for malignancy) is 5 µg/kg daily and should continue until the expected neutrophil nadir is passed and the neutrophil count has recovered to the normal range, usually for up to* ***14 days***".(14)
Issue 12: HRR genes test costs	
28. Should genetic test costs be included in the analyses, as specified in the scope?	HRRm testing costs (highlighted in the Issue title) are no longer applicable in light of the CHMP opinion recommending olaparib as a treatment option for patients with mCRPC and *BRCA*1/2-

	mutations (germline and/or somatic) who have progressed following prior therapy that included a new hormonal agent. *BRCA* testing costs are not included in the base-case cost-effectiveness analysis, as UK experts "believe men with advanced prostate cancer should [already] routinely have their tumours tested for DNA repair defects such as *BRCA* mutations", based on data from the TOPARP-B study.(15) Somatic testing is included on the NHS testing directory that was updated 17th September 2020,(16) although delays to implementation have occurred due to the COVID-19 pandemic. As such, *BRCA*m testing is likely to be part of clinical practice, regardless of the outcome of this appraisal. The inclusion of BRCA testing costs is explored in a scenario analysis ((Appendix A.3.7) assuming a unit cost of £[redacted] per test, and a prevalence rate of 9.7%.(17)
29. What is the prevalence of the HRR genetic mutations in the population that would be tested?	Not applicable. As mentioned above (in response to Question 28), based on the recent positive CHMP opinion,(5) only those patients with *BRCA1/2* mutations would be eligible to receive olaparib treatment. In a recent study of mutational status of patients enrolled in the PROfound study, patients with *BRCA1/2* mutations constituted 9.7% of the tested mCRPC population.(17)
Issue 13: End-of-life criteria	
30. What is the estimated life expectancy of people with mCRPC with homologous recombination repair gene alterations previously treated with hormonal therapy?	As detailed in Section B.2.13.3 of Document B, median OS on current UK standard-of-care in the treatment setting relevant to this appraisal is best demonstrated by patients receiving cabazitaxel in the CARD study. Here, patients who received cabazitaxel for mCRPC in a post-docetaxel and post-NHA setting and had a median OS of 13.6 months form the initiation of cabazitaxel therapy (18). The life expectancy criteria are met on this basis.
31. Is there sufficient evidence to indicate that olaparib offers an extension to life of at least an additional 3 months, compared with cabazitaxel?	In the updated indirect treatment comparison of olaparib vs cabazitaxel in the *BRCA*m population of patients (see Appendix 2 below), olaparib therapy was associated with [redacted]% reduction in the risk of death (HR: [redacted]). This translated to a modelled median OS benefit of [redacted] months for olaparib vs cabazitaxel treatment in the *BRCA*m prior taxane group of patients. Based

	on the undiscounted modelled results, treatment with olaparib resulted in a [redacted] month increase in mean OS vs cabazitaxel in the company's base-case analysis. Both the median and mean estimates are substantially greater than the 3 month extension to life required for the end-of-life (EoL) criterion to be met.
32. What is the estimated size of the population that would be eligible for treatment with olaparib?	It is unclear why this question is being asked in relation to the applicability of EoL criteria, given that the criterion "*the treatment is licensed or otherwise indicated for small patient populations*" no longer applies.(19) The company consider that the EoL criteria are satisfied as per the rationale given above (in response to Questions 30 and 31). Nonetheless, we anticipate the size of the eligible population to be small. In Document A (Section A.18) it was estimated that, in 2021 (Year 1), approximately [redacted] men with mCRPC and qualifying HRR gene mutations (whose disease has progressed after treatment with a taxane [docetaxel] and NHA) would receive treatment with olaparib, rising to [redacted] in Year 5 due to increasing market share versus cabazitaxel. In light of the restriction of the anticipated EMA marketing authorisation for olaparib to *BRCA*m patients, these numbers can be revised downward to [redacted] in Year 1 and rising to [redacted] in Year 5.
Other issue for information - SLR	
33. Can the company provide additional information on their inclusion criteria and further clarification of their methods?	Further information / context to address the ERG's questions / critique is provided below: • "*Description of the study selection criteria*" (p12 of ERG report) : the inclusion/exclusion criteria used to identify studies were specified in the initial submission. Appendix D.1.3.7 (Summary of relevant evidence identified, p22) includes a summary of the number of studies identified, using the inclusion criteria outlined in Appendix D.1.3, Table 6 (p17). However, we acknowledge that the criteria applied as part of the feasibility assessment for the ITC could have been labelled more clearly (labelled as 'Considered relevant to the decision problem' in Appendix D.1.3.7, Tables 12-15). This was previously clarified as part of company responses to the ERGs' questions (C12).

	• "*some excluded studies could have potentially added to the network*" (p16 of Technical Report): the ERG also noted that several publications identified in the SLR were not relevant to the decision problem (p84): "*the company excluded the publications assessing docetaxel and radium-223 as they were not relevant to the decision problem*". • Omission of HRR status from the list of inclusion criteria (ERG report p34-35): this was considered necessary in order to make the search as broad as possible so as not to miss any relevant or useful articles. Our expectation was that applying HRRm status to the SLR inclusion criteria would make the search highly restrictive and risk not identifying any relevant articles on comparator treatments, since olaparib is the first targeted treatment to have demonstrated efficacy in a Phase III trial in mCRPC patients who have received prior treatment with a taxane and NHA.

A.1 Appendix 1: PROfound trial, final analysis (20th March 2020)

A.1.1 Introduction and context

On 17th September, 2020, the CHMP issued a positive opinion for the PROfound indication of olaparib that is relevant to ID1640.(5) The indication wording is as follows:

"Lynparza is indicated as monotherapy for the treatment of adult patients with metastatic castration-resistant prostate cancer and BRCA1/2-mutations (germline and/or somatic) who have progressed following prior therapy that included a new hormonal agent".

This indication is narrower (i.e. more restrictive) than the patient population that was included in the PROfound study and that which the company's evidence submission to NICE for ID1640 was based on. This update was communicated to NICE on the same day, along with the AstraZeneca's intention to update the clinical- and cost-effectiveness evidence for olaparib in mCRPC – to align with the prior taxane subgroup of the population with *BRCA1/2* mutations (hereafter, ***BRCA*m**) - during the technical engagement stage.
This appendix provides an overview of key data in this subgroup, as well as the overall *BRCA*m population of patients.

A.1.2 PROfound: final OS analysis (20th March 2020 data cut-off)

Per the PROfound study protocol (and as described in Document B.2.4.2), the final analysis of OS was performed when ~146 (61%) OS events had occurred in Cohort A, the primary study population (data cut-off [DCO], 20th March 2020, hereafter referred to as DCO2).(20) Treatment with olaparib resulted in a statistically-significant and clinically-meaningful median OS benefit compared with investigators' choice of NHA in this Cohort of patients (median OS: 19.1 months vs 14.7 months, respectively; HR; 0.69; 95% CI, 0.50−0.97; P = 0.02). OS analyses from DCO2 are summarised below in Table 3 for:

- Cohort A (the primary study population),

- the *BRCA*m population of patients (aligned to anticipated EMA marketing authorisation for olaparib in this indication), and

- the prior taxane subgroup of *BRCA*m (which represents [redacted] of the *BRCA*m population and the company's proposed base-case).

In addition, we also provide rPFS analysis (by BICR) in the *BRCA*m population of patients, as well as the prior taxane subgroup of *BRCA*m, which informs the company's base-case. These analyses are based on DCO1 data, as further rPFS data were not collected after the PROfound study met its primary endpoint of rPFS in Cohort A in the first planned analysis (DCO1, 4th June 2019, Table 2).

Further details on these key efficacy endpoints as well as baseline characteristics and safety summaries in the *BRCA*m population (updated at DCO2) are provided in the following subsections (Section A.1.3 to Section A.1.5).

Table 2. Summary table key endpoints from PROfound (Cohort A, *BRCA*m, *BRCA*m prior taxane)

	Primary study population: Cohort A		EMA label population: *BRCA*m		Company base-case: *BRCA*m prior taxane	
	Olaparib 300 mg bid (n = 162)	Investigators' choice of NHA (N = 83)	Olaparib 300 mg bid (n = 102)	Investigators' choice of NHA (n = 58)	Olaparib 300 mg bid (n = 72)	Investigators' choice of NHA (n = 35)
Primary endpoint: BICR-assessed rPFS (DCO1)[a]						
Events, n (%)	106 (65.4)	68 (81.9)	[redacted]	[redacted]	[redacted]	[redacted]
Median rPFS, months (95% CI)	7.39 (6.24–9.33)	3.55 (1.91–3.71)	[redacted]	[redacted]	[redacted]	[redacted]
HR (95% CI)	**0.34 (0.25, 0.47); *p* < 0.0001**		[redacted]		[redacted]	
Key secondary endpoint: final OS (DCO2)[b]						
Events, n (%)	91 (56.2)	57 (68.7)	[redacted]	[redacted]	[redacted]	[redacted]
Median OS, months (95% CI)	19.09	14.69	[redacted]	[redacted]	[redacted]	[redacted]
HR (95% CI)	**0.69 (0.50, 0.97); *p* = 0.0175**		[redacted]		[redacted]	

[a] Disease progression, as assessed by BICR and defined by RECIST version 1.1 and/or PCWG3 or death (by any cause in the absence of progression) regardless of whether the patient withdrew from randomised therapy or received another anti-cancer therapy before progression.

[b] 0.047 alpha spent at the final OS analysis. Maturity rate: 60%

BICR, blinded independent central review; bid, twice daily; CI, confidence interval; HR, hazard ratio; OS, overall survival; PCWG3, Prostate Cancer Working Group 3; RECIST, Response Evaluation Criteria In Solid Tumours; rPFS, radiographic progression-free survival.

Source: de Bono et al 2020,(21) CSR edition 1, 23 October 2019,(12) PROfound CSR Addendum(22) PROfound analyses.(23)

A.1.3 Baseline characteristics (Cohort A, BRCAm, BRCAm prior taxane)

Baseline characteristics for Cohort A (the primary study population) were previously presented in Document B, Section B.2.3.7, Table 5. Here, we show these data, as well as baseline characteristics for the *BRCA*m population and the prior taxane subgroup of *BRCA*m (see Table 3 below). The baseline characteristics for the *BRCA*m population are consistent with and reflective of the primary study population, i.e. Cohort A.

Table 3. Patient characteristics for PROfound Cohort A, *BRCA*m, and *BRCA*m prior taxane subgroup

Baseline characteristics	Primary study population: Cohort A		EMA label population: *BRCA*m		Company base-case: *BRCA*m prior taxane	
	Olaparib 300 mg bid (n = 162)	Investigators' choice of NHA (n = 83)	Olaparib 300 mg bid (n = 102)	Investigators' choice of NHA (n = 58)	Olaparib 300 mg bid (n = 72)	Investigators' choice of NHA (n = 35)
Age						
Mean (SD)	68.0 (8.23)	68.1 (7.36)	[redacted]	[redacted]	[redacted]	[redacted]
Median (range)	68.0 (47–86)	67.0 (49–86)	[redacted]	[redacted]	[redacted]	[redacted]
< 65, n (%)	54 (33.3)	23 (27.7)	[redacted]	[redacted]	[redacted]	[redacted]
≥ 65, n (%)	108 (66.7)	60 (72.3)	[redacted]	[redacted]	[redacted]	[redacted]
White	109 (67.3)	55 (66.3)	[redacted]	[redacted]	[redacted]	[redacted]
Black or African American	2 (1.2)	1 (1.2)	[redacted]	[redacted]	[redacted]	[redacted]
Asian	43 (26.5)	19 (22.9)	[redacted]	[redacted]	[redacted]	[redacted]
Other	1 (0.6)	1 (1.2)	[redacted]	[redacted]	[redacted]	[redacted]
Missing	7 (4.3)	7 (8.4)	[redacted]	[redacted]	[redacted]	[redacted]
Ethnic group, n (%)						
Hispanic or Latino	12 (7.4)	9 (10.8)	[redacted]	[redacted]	[redacted]	[redacted]
Not Hispanic or Latino	145 (89.5)	69 (83.1)	[redacted]	[redacted]	[redacted]	[redacted]
Missing	5 (3.1)	5 (6.0)	[redacted]	[redacted]	[redacted]	[redacted]
Sites of disease at baseline, n (%)[a]						
Prostate	27 (16.7)	12 (14.5)	[redacted]	[redacted]	[redacted]	[redacted]
Locoregional lymph nodes	35 (21.6)	17 (20.5)	[redacted]	[redacted]	[redacted]	[redacted]

Baseline characteristics	Primary study population: Cohort A		EMA label population: *BRCA*m		Company base-case: *BRCA*m prior taxane	
	Olaparib 300 mg bid (n = 162)	Investigators' choice of NHA (n = 83)	Olaparib 300 mg bid (n = 102)	Investigators' choice of NHA (n = 58)	Olaparib 300 mg bid (n = 72)	Investigators' choice of NHA (n = 35)
Distant lymph nodes	59 (36.4)	35 (42.2)	[redacted]	[redacted]	[redacted]	[redacted]
Bone	140 (86.4)	73 (88.0)	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory	30 (18.5)	11 (13.3)	[redacted]	[redacted]	[redacted]	[redacted]
Liver	18 (11.1)	13 (15.7)	[redacted]	[redacted]	[redacted]	[redacted]
Other distant metastases	34 (21.0)	15 (18.1)	[redacted]	[redacted]	[redacted]	[redacted]
Bone only	42 (25.9)	25 (30.1)	[redacted]	[redacted]	[redacted]	[redacted]
Lymph node only	13 (8.0)	5 (6.0)	[redacted]	[redacted]	[redacted]	[redacted]
Bone and lymph node only	26 (16.0)	14 (16.9)	[redacted]	[redacted]	[redacted]	[redacted]
ECOG performance status at baseline, n (%)						
0	84 (51.9)	34 (41.0)	[redacted]	[redacted]	[redacted]	[redacted]
1	67 (41.4)	46 (55.4)	[redacted]	[redacted]	[redacted]	[redacted]
2	11 (6.8)	3 (3.6)	[redacted]	[redacted]	[redacted]	[redacted]
Missing	0	0	[redacted]	[redacted]	[redacted]	[redacted]
Total Gleason index at baseline, n (%)						
2	1 (0.6)	0	[redacted]	[redacted]	[redacted]	[redacted]
3	0	0	[redacted]	[redacted]	[redacted]	[redacted]
4	2 (1.2)	0	[redacted]	[redacted]	[redacted]	[redacted]
5	2 (1.2)	1 (1.2)	[redacted]	[redacted]	[redacted]	[redacted]

Baseline characteristics	Primary study population: Cohort A		EMA label population: *BRCA*m		Company base-case: *BRCA*m prior taxane	
	Olaparib 300 mg bid (n = 162)	Investigators' choice of NHA (n = 83)	Olaparib 300 mg bid (n = 102)	Investigators' choice of NHA (n = 58)	Olaparib 300 mg bid (n = 72)	Investigators' choice of NHA (n = 35)
6	6 (3.7)	3 (3.6)	[redacted]	[redacted]	[redacted]	[redacted]
7	41 (25.3)	22 (26.5)	[redacted]	[redacted]	[redacted]	[redacted]
8	36 (22.2)	12 (14.5)	[redacted]	[redacted]	[redacted]	[redacted]
9	59 (36.4)	35 (42.2)	[redacted]	[redacted]	[redacted]	[redacted]
10	10 (6.4)	7 (8.4)	[redacted]	[redacted]	[redacted]	[redacted]
Missing	5 (3.1)	3 (3.6)	[redacted]	[redacted]	[redacted]	[redacted]
Baseline pain score (BPI-SF worst pain [item 3]), n (%)						
0–< 2	83 (51.2)	37 (44.6)	[redacted]	[redacted]	[redacted]	[redacted]
2–3	17 (10.5)	9 (10.8)	[redacted]	[redacted]	[redacted]	[redacted]
> 3	56 (34.6)	34 (41.0)	[redacted]	[redacted]	[redacted]	[redacted]
Missing	6 (3.7)	3 (3.6)	[redacted]	[redacted]	[redacted]	[redacted]
Baseline PSA (µg/L), n (%)						
Median, (range)	62.2 (0.20–7240.7)	112.9 (1.85–7115.0)	[redacted]	[redacted]	[redacted]	[redacted]
Previous taxane therapy at mCRPC, n (%)						
Yes	91 (65.2)	43 (51.8)	[redacted]	[redacted]	[redacted]	[redacted]
Previous docetaxel only	60 (37.0)	24 (28.9)	[redacted]	[redacted]	[redacted]	[redacted]
Previous cabazitaxel only	5 (3.1)	1 (1.2)	[redacted]	[redacted]	[redacted]	[redacted]

Baseline characteristics	Primary study population: Cohort A		EMA label population: *BRCA*m		Company base-case: *BRCA*m prior taxane	
	Olaparib 300 mg bid (n = 162)	Investigators' choice of NHA (n = 83)	Olaparib 300 mg bid (n = 102)	Investigators' choice of NHA (n = 58)	Olaparib 300 mg bid (n = 72)	Investigators' choice of NHA (n = 35)
Previous docetaxel and cabazitaxel	26 (16.0)	18 (21.7)	[redacted]	[redacted]	[redacted]	[redacted]
No	71 (43.8)	40 (48.1)	[redacted]	[redacted]	[redacted]	[redacted]
Patients with taxane treatment prior to randomisation, n (%)						
Yes	NR	NR	[redacted]	[redacted]	[redacted]	[redacted]
Previous docetaxel only	NR	NR	[redacted]	[redacted]	[redacted]	[redacted]
Previous cabazitaxel only	NR	NR	[redacted]	[redacted]	[redacted]	[redacted]
Previous docetaxel and cabazitaxel	NR	NR	[redacted]	[redacted]	[redacted]	[redacted]
Prior Paclitaxel	NR	NR	[redacted]	[redacted]	[redacted]	[redacted]
No	NR	NR	[redacted]	[redacted]	[redacted]	[redacted]
Previous NHA use, n (%)						
Enzalutamide	67 (41.4)	40 (48.2)	[redacted]	[redacted]	[redacted]	[redacted]
Abiraterone	61 (37.7)	29 (34.9)	[redacted]	[redacted]	[redacted]	[redacted]
Enzalutamide and abiraterone	32 (19.8)	14 (16.9)	[redacted]	[redacted]	[redacted]	[redacted]
Missing	NR	NR	[redacted]	[redacted]	[redacted]	[redacted]
Single mutation status						
BRCA1	8 (5.4)	5 (6.6)	[redacted]	[redacted]	[redacted]	[redacted]
BRCA2	80 (54.1)	47 (61.8)	[redacted]	[redacted]	[redacted]	[redacted]

Baseline characteristics	Primary study population: Cohort A		EMA label population: *BRCA*m		Company base-case: *BRCA*m prior taxane	
	Olaparib 300 mg bid (n = 162)	Investigators' choice of NHA (n = 83)	Olaparib 300 mg bid (n = 102)	Investigators' choice of NHA (n = 58)	Olaparib 300 mg bid (n = 72)	Investigators' choice of NHA (n = 35)
ATM	60 (40.5)	24 (31.6)	[redacted]	[redacted]	[redacted]	[redacted]
BARD1	0	0	[redacted]	[redacted]	[redacted]	[redacted]
BRIP1	0	0	[redacted]	[redacted]	[redacted]	[redacted]
CDK12	0	0	[redacted]	[redacted]	[redacted]	[redacted]
CHEK1	0	0	[redacted]	[redacted]	[redacted]	[redacted]
CHEK2	0	0	[redacted]	[redacted]	[redacted]	[redacted]
FANCL	0	0	[redacted]	[redacted]	[redacted]	[redacted]
PALB2	0	0	[redacted]	[redacted]	[redacted]	[redacted]
PPP2R2A	0	0	[redacted]	[redacted]	[redacted]	[redacted]
RAD51B	0	0	[redacted]	[redacted]	[redacted]	[redacted]
RAD51C	0	0	[redacted]	[redacted]	[redacted]	[redacted]
RAD51D	0	0	[redacted]	[redacted]	[redacted]	[redacted]
RAD54L	0	0	[redacted]	[redacted]	[redacted]	[redacted]
Co-mutations[c]	14 (8.6)	7 (8.4)	[redacted]	[redacted]	[redacted]	[redacted]

[a] As per investigator assessment. Patients with multiple sites of disease within the same category of extent of disease are counted only once in that category.
[b] These patients received prior NHA, but data was not present in the eCRF at database lock.
[c] A detailed overview of co-mutations is given in Appendix M of Document B.
bid, twice daily; eCRF, electronic case report form; IVRS, interactive voice response system; NR, not reported; SD, standard deviation
Source: de Bono et al 2020,(21) Clinical Study Report Edition 1 – 23 October 2019,(12) PROfound analyses.(23)

A.1.4 Key efficacy analysis (BRCAm and BRCAm prior taxane)

A.1.4.1 rPFS-BICR, DCO1 (4th June 2019)

rPFS data from the primary analysis in Cohort A are described in Document B, Section B.2.6.2 and summarised in Table 2 above. Here, we present progression-free survival data for the *BRCA*m population of patients, aligned to the anticipated EMA marketing authorisation for olaparib in mCRPC patients who have received prior treatment with a NHA, and also for the prior taxane subgroup of the *BRCA*m population, aligned to the company's revised base-case and the anticipated positioning of olaparib in clinical practice within the NHS, as described in Document B, Section B.1.2. As mentioned above, rPFS data were not collected beyond the primary analysis; therefore, these data represent analyses from DCO1 (4th June 2019).

Treatment with olaparib resulted in a [redacted] **reduction in the risk of radiographic disease progression** or death vs investigators' choice of NHA in the *BRCA*m group of patients (median rPFS-BICR: [redacted] months vs [redacted] months, respectively; [redacted]; [redacted], Figure 3, Table 4).

Similar efficacy was observed in the prior taxane subgroup of *BRCA*m, where treatment with olaparib resulted in an [redacted]% reduction in the risk of radiographic disease progression or death vs investigator's choice of NHA (median rPFS: [redacted] months vs [redacted] months, respectively; [redacted], Figure 4, Table 4).

Figure 3. Kaplan–Meier plot of rPFS (BICR)[a] in the overall *BRCA*m population, DCO1 (4th June 2019)

[a] Disease progression, as assessed by BICR defined by RECIST version 1.1 and/or PCWG3 or death (by any cause in the absence of progression) regardless of whether the patient withdrew from randomised therapy or received another anti-cancer therapy before progression.
BICR, blinded independent central review; PCWG3, Prostate Cancer Working Group 3; RECIST, Response Evaluation Criteria In Solid Tumours; rPFS, radiographic progression-free survival.
Source: PROfound analyses.(23)

Figure 4. Kaplan–Meier plot of rPFS (BICR) in the *BRCA*m prior taxane subgroup, DCO1 (4th June 2019)

BICR, blinded independent central review; rPFS, radiographic progression-free survival.
Source: PROfound analyses.(23)

Table 4. Overview of rPFS (BICR) in the overall *BRCA*m population and *BRCA*m prior taxane subgroup, DCO1 (4th June 2019)

Outcome: BICR rPFS[a]	*BRCA*m		*BRCA*m prior taxane	
	Olaparib 300 mg bid (n = 102)	Investigators' choice of NHA (n = 58)	Olaparib 300 mg bid (n = 72)	Investigators' choice of NHA (n = 35)
Events, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Median rPFS, months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
HR (95% CI)	[redacted]		[redacted]	

[a] Disease progression, as assessed by BICR defined by RECIST version 1.1 and/or PCWG3 or death (by any cause in the absence of progression) regardless of whether the patient withdrew from randomised therapy or received another anti-cancer therapy before progression.
BICR, blinded independent central review; bid, twice daily; CI, confidence interval; HR, hazard ratio; NC, not calculable; PCWG3, Prostate Cancer Working Group 3; RECIST, Response Evaluation Criteria In Solid Tumours; rPFS, radiographic progression-free survival.
Source: PROfound analyses.(23)

A.1.4.2 OS, DCO2 (20th March 2020)

As described in Document B (Section B.2.6.4), the final analysis of OS was performed when ~146 (61%) events had occurred in Cohort A. These analyses are described in detail in Document B (Section B.2.6.4) and summarised in Table 2 above. Here, we present OS data for the *BRCA*m population of patients, and also for the prior taxane subgroup of *BRCA*m.

In the overall *BRCA*m population, treatment with olaparib resulted in a [redacted]**% reduction in the risk of death, with median OS gain of 5.67 months with olaparib** compared with investigators' choice of NHA (median OS, [redacted] months vs [redacted] months; HR, [redacted], Figure 4, Table 5). This OS benefit was observed despite >70% of all patients in the investigators' choice of NHA arm of the *BRCA*m population switching to olaparib treatment following disease progression on NHA**. A median OS of >20 months is unprecedented in this disease setting.**

A very similar OS benefit was observed for olaparib vs investigators' choice of NHA in the prior taxane subgroup of *BRCA*m, with the same hazard ratio of [redacted] (95% CI, [redacted]; median OS = [redacted] months for olaparib vs [redacted] months

for investigators' choice of NHA; Figure 6, Table 5), despite a substantial proportion of patients switching to olaparib upon disease progression in the comparator arm.

Figure 5. Kaplan–Meier plot of final OS in the overall *BRCA*m population, DCO2 (20th March 2020)

OS, overall survival.
Source: PROfound analyses.(23)

Figure 6. Kaplan–Meier plot of final OS in the *BRCA*m prior taxane subgroup, DCO2 (20th March 2020)

OS, overall survival.
Source: PROfound analyses.(23)

Table 5. Overview of OS in *BRCA*m and *BRCA*m prior taxane subgroup, DCO2 (20th March 2020)

Outcome: DCO2 OS	*BRCA*m		*BRCA*m prior taxane	
	Olaparib 300 mg bid (n = 102)	Investigators' choice of NHA (n = 58)	Olaparib 300 mg bid (n = 72)	Investigators' choice of NHA (n = 35)
Events, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Median OS, months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
HR (95% CI)	[redacted]		[redacted]	

bid, twice daily; CI, confidence interval; HR, hazard ratio; NHA, new hormonal agent; OS, overall survival.

A.1.4.2.1 Treatment switching adjustment

In total, there were 160 patients in the PROfound *BRCA*m population (102 patients in the olaparib arm, and 58 patients in the investigators' choice of NHA arm). The extent of treatment switching in the NHA arm at DCO2 was high, with more than 70% of all patients in both the *BRCA*m overall population and prior taxane subgroup of *BRCA*m switching to olaparib treatment upon disease progression, thus confounding the OS analysis.(24)

Table 6. Overview of the PROfound overall *BRCA*m population and the *BRCA*m prior taxane subgroup included in the treatment switching analyses

Population	N	Switchers	Unadjusted HR (95% CI)
*BRCA*m overall	N= 160 Olaparib arm: 102 NHA arm: 58	[redacted]	[redacted]
*BRCA*m prior taxane	N= 107 Olaparib arm: 72 NHA arm: 35	[redacted]	[redacted]

The treatment switch adjustment analyses were conducted to estimate the true OS benefit of olaparib compared with investigators' choice of NHA at the DCO2 analysis. Based on the updated analysis, the RPSFTM approach remained the most appropriate method for treatment switching adjustment, for the same reasons discussed in the

company submission and in response to the ERG clarification questions (please see Document B, Section B.2.6.3.1 for details). Briefly:

- RPSFTM is preferred on the basis that it is not dependent on time-varying data to predict switching.
- The RPSFTM approach also utilises all data for switchers and non-switchers, compared with other methods such as the IPCW approach, which involve analysis on reduced sample sizes. The issue of reduced sample size is pertinent in the case of the *BRCA*m analyses, due to the relatively small sample size of the investigators' choice of NHA arm.
- The RFSFTM approach does not depend on the 'no unmeasured confounders' assumption, which may not hold when there is relatively little prognostic data collected post-randomisation, thus limiting the scope of time-varying covariables that can be included in an analysis, as is the case here.

We note the ERG comments regarding the HR from CARD being obtained from a Cox PH model under the proportional hazard assumption; therefore, we have used a Cox PH model to derive the updated treatment switching analysis of the PROfound data. It is worth noting however, that HRs remain consistent between the Cox PH model and the Weibull model (which was used in the original company submission; data not shown), and do not meaningfully impact on the results obtained.

Models with and without recensoring were explored to understand the plausible range of results (counterfactual KM plots for the *BRCA*m and prior taxane subgroup of *BRCA*m presented in Figure 7 to Figure 10). The RPSFTM OS results with recensoring are preferred, since the results without recensoring consistently resulted in a long plateau after 15 months at/above ~[redacted]% survival in the investigators' choice of NHA arm, which was considered to be clinically-implausible in this setting (the RPSFT models without recensoring predicted long-term survival of [redacted]% after 15 months in the *BRCA*m population and [redacted]% after 15 months in the prior taxane subgroup of *BRCA*m; Figure 8 and Figure 10, respectively). Both sets of results (i.e. with and without recensoring) are shown below, for completeness.

The OS benefit of olaparib versus investigators' choice of NHA improved after adjusting for treatment switching in the overall *BRCA*m population and the *BRCA*m prior taxane subgroup (as shown in Figure 7 to Figure 10):

- *BRCA*m overall, RPSFT (with recensoring) OS HR [redacted] (95% [redacted])
- *BRCA*m overall, RPSFT (without recensoring) OS HR [redacted] (95% [redacted])
- *BRCA*m prior taxane, RPSFT (with recensoring) OS HR [redacted] (95% [redacted])
- *BRCA*m prior taxane, RPSFT (without recensoring) OS HR [redacted] (95% [redacted])

Figure 7. Kaplan–Meier plot of counterfactual OS in the overall BRCAm population (RPSFTM Cox PH, with recensoring), DCO2 (20th March 2020)

[redacted]

Figure 8. Kaplan–Meier plot of counterfactual OS in the overall BRCAm overall population (RPSFTM Cox PH, without recensoring), DCO2 (20th March 2020)

bd, twice daily

Figure 9. Kaplan–Meier plot of counterfactual OS in the BRCAm prior taxane subgroup (RPSFTM Cox PH, with recensoring), DCO2 (20th March 2020)

Figure 10. Kaplan–Meier plot of counterfactual OS in the BRCAm prior taxane subgroup (RPSFTM Cox PH, without recensoring), DCO2 (20th March 2020)

bd, twice daily

A.1.5 Safety analyses (treatment exposure and adverse event summaries), DCO2 (20th March 2020)

Safety data from the full safety analysis set (SAS) of the PROfound study were previously described in Document B, Section B.2.10. Here, we present updated safety analyses from DCO2 for the full SAS, the *BRCA*m population of patients (aligned to the anticipated EMA marketing authorisation for olaparib in the PROfound indication), and the prior taxane subgroup of *BRCA*m (Table 7, Table 8). These analyses are consistent with the data previously presented for the full SAS, as well as the known safety and tolerability profile of olaparib, and support a favourable risk-benefit profile for olaparib treatment. No new safety signals were identified in the DCO2 analysis.

Table 7. Summary of treatment exposure, dose interruptions, and dose modifications: SAS, *BRCA*m, *BRCA*m prior taxane subgroup DCO2 (20th March 2020)

	SAS		*BRCA*m		*BRCA*m prior taxane	
	Olaparib 300 mg bid (n = 256)	Investigators' choice of NHA (n = 130)	Olaparib 300 mg bid (n = 102)	Investigators' choice of NHA (n = 58)	Olaparib 300 mg bid (n = 72)	Investigators' choice of NHA (n = 35)
Duration of treatment (days), median (range)						
Total treatment duration[a]	277.3 (1–879)	159.3 (17–886)	[redacted]	[redacted]	[redacted]	[redacted]
Actual treatment duration[b]	263.3 (1–869)	156.4 (17–877)	[redacted]	[redacted]	[redacted]	[redacted]
Patients, n (%)						
Dose interruptions	111 (43.4)	21 (16.2)	[redacted]	[redacted]	[redacted]	[redacted]
Dose reductions	63 (24.6)	7 (5.4)	[redacted]	[redacted]	[redacted]	[redacted]
Dose modifications[c]	120 (46.9)	24 (18.5)	[redacted]	[redacted]	[redacted]	[redacted]

[a]Total treatment duration = (last dose date – first dose date +1). Median days

[b]Actual treatment duration = (last dose date – first dose date +1) excluding dose interruptions. Median days

[c] Number of patients with either an interruption and/or a dose reduction.

If patient was ongoing, data-cut-off has been used to calculate duration.

If the last dose date is unknown, the earliest available date where it was confirmed that no drug was being taken was used instead.

Only includes data from the first treatment period.

AE, adverse event; bid, twice daily; NHA new hormonal agent; SAS safety analysis set.

Source: PROfound CSR Addendum(22)

Table 8. Adverse events in any category, DCO2 (20th March 2020) in the SAS, *BRCA*m, *BRCA*m prior taxane subgroup .

	SAS		*BRCA*m		*BRCA*m prior taxane	
	Olaparib 300 mg bid (n = 256)	Investigators' choice of NHA (n = 130)	Olaparib 300 mg bid (n = 102)	Investigators' choice of NHA (n = 58)	Olaparib 300 mg bid (n = 72)	Investigators' choice of NHA (n = 35)
Number (%) of patients[a]						
Any AE	246 (96.1)	115 (88.5)	[redacted]	[redacted]	[redacted]	[redacted]
Any AE, causally related to study treatment[b]	210 (82.0)	63 (48.5)	[redacted]	[redacted]	[redacted]	[redacted]
Any AE of CTCAE Grade 3 or higher	133 (52.0)	52 (40.0)	[redacted]	[redacted]	[redacted]	[redacted]
Any AE of CTCAE Grade 3 or higher, causally related to study treatment[b]	83 (32.4)	12 (9.2)	[redacted]	[redacted]	[redacted]	[redacted]
Any AE leading to death	10 (3.9)	6 (4.6)	[redacted]	[redacted]	[redacted]	[redacted]
Any SAE including those leading to death	94 (36.7)	39 (30.0)	[redacted]	[redacted]	[redacted]	[redacted]
Any AE leading to discontinuation	51 (19.9)	11 (8.5)	[redacted]	[redacted]	[redacted]	[redacted]
Any AE relating to dose reduction	60 (23.4)	7 (5.4)	[redacted]	[redacted]	[redacted]	[redacted]
Any AE relating to interruptions	119 (46.5)	25 (19.2)	[redacted]	[redacted]	[redacted]	[redacted]

[a] Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category were counted once in each of those categories. [b] As assessed by the investigator. Includes AEs with an onset date on or after the date of first dose and up to and including 30 days following discontinuation of randomised treatment or the day before switching to olaparib.

AE adverse event; bid twice daily; CTCAE Common Terminology Criteria for Adverse Events v4.03; DCO data cut-off; MedDRA Medical Dictionary for Regulatory Activities; NHA new hormonal agent; SAE serious adverse event; SAS safety analysis set. Source: PROfound analyses,(23) PROfound CSR Addendum(22)

A.2 Appendix 2: Indirect treatment comparison, *BRCA*m population

An anchored indirect treatment comparison (ITC) was conducted in accordance with NICE DSU TSD 18 guidance, using the same methods as described in the company submission (Document B, Section B.2.9.1). The aim of the analysis was to estimate the relative effectiveness of olaparib versus cabazitaxel for patients with *BRCA*m mCRPC.

A.2.1 Evidence base

The evidence network for the ITC remains the same as in the company submission (Section B.2.9.1) i.e. using the PROfound and CARD studies.

Data for the overall *BRCA*m population of PROfound were used in the base-case analysis, as olaparib is similarly effective in the overall *BRCA*m population as in the prior taxane subgroup of *BRCA*m, the focus of the company's revised submission (Appendix A.1). **The overall *BRCA*m ITC facilitates the best use of the available data from the PROfound study, utilising the greater patient numbers in the whole *BRCA*m population and retaining as much statistical power as possible for the ITC**. The data included in the ITC are described below:

- **PROfound OS at DCO2**: Patient-level data based on the final OS analysis (DCO2) after treatment switching adjustment for mCRPC patients with *BRCA1/2* mutation(s), conducted using the *BRCA*m overall population.
- **PROfound rPFS (BICR) at DCO1**: Data were not collected for DCO2; therefore, patient-level data are based on rPFS at DCO1 and conducted using the *BRCA*m overall population.
- **CARD OS/rPFS data**: The OS and rPFS efficacy data reported in the CARD study publication were used;(18) no updated data were identified in the public domain since the initial company submission.

A.2.2 Statistical methods and assessment of effect modifiers

The *BRCA*m ITC was conducted using the same statistical methods as described in Section B.2.9.2.2 of the company submission; the only exception was that the reported HRs from the CARD study were used directly in the ITC to ensure an exact match with the cabazitaxel data, rather than the initial method of estimating the HRs through digitising the KM curves.

Based on statistical analyses from the company submission for Cohort A+B (DCO1), an unadjusted ITC was justified in the absence of confirmed effect modifiers (Section B.2.9.2.3). It was not deemed necessary or feasible to conduct a population-adjusted ITC within the *BRCA*m population, given the reduced sample size of patients with data available for matching. Therefore, an unadjusted ITC approach remained the most appropriate and reliable method for estimating the relative efficacy of olaparib vs cabazitaxel in the *BRCA*m population.

A.2.3 Indirect comparison results

A.2.3.1 rPFS

The proportional hazards assumption in the *BRCA*m subgroup of PROfound and the CARD studies was assessed by visual inspection of the log-cumulative hazards plots and the Schoenfeld plots, and conducting Schoenfeld individual tests. The results indicated that there was no evidence against the null hypothesis of proportional hazards at the 95% significance level (Shoenfeld p-value = 0.67 and 0.75 in the PROfound and CARD studies, respectively). Therefore the Bucher *et al.* method for the ITC was considered appropriate (25).

The ITC was conducted by calculating the hazard ratios from the PROfound *BRCA*m IPD and using the HR of rPFS as reported in the CARD study (de Wit 2019). In the ITC analysis for rPFS. The rPFS HR for olaparib versus cabazitaxel was [redacted], as shown in Table 9.

A.2.3.2 OS

For OS, the proportional hazards assumption was assessed using the same approach as for rPFS. There was no evidence against the null hypothesis of proportional

hazards at the 95% significance level (Shoenfeld p-value = 0.56 and 0.94 in the PROfound and CARD studies, respectively). This supports the use of constant hazard ratios to generate comparative evidence for olaparib and cabazitaxel. The OS HR for olaparib versus cabazitaxel was [redacted], as shown in Table 9.

Table 9. Summary of rPFS and OS ITC results for PROfound *BRCA*m population vs CARD

	PROfound	CARD
rPFS HR (95% CI), vs investigators' choice of NHA	[redacted]	0.54 (0.40 - 0.73)
ITC HR used in model **rPFS HR (95% CI), olaparib vs cabazitaxel**	[redacted]	
OS HR (95% CI), vs investigators' choice of NHA	[redacted]	0.64 (0.46-0.89)
ITC HR used in model **OS HR (95% CI), olaparib vs cabazitaxel**	[redacted]	

*. OS HR after treatment switching adjustment (RPSFT, with recensoring)

A.3 Appendix 3: Cost-effectiveness analyses in the prior taxane subgroup of *BRCA*m (revised company base-case)

A.3.1 Patient population / decision problem

As described in Appendix 1, the CHMP has issued a positive opinion for the PROfound indication of olaparib that is relevant to ID1640.(5) The indication wording is as follows:

"*Lynparza is indicated as monotherapy for the treatment of adult patients with metastatic castration-resistant prostate cancer and BRCA1/2-mutations (germline and/or somatic) who have progressed following prior therapy that included a new hormonal agent*".

In line with this regulatory update and the anticipated use of olaparib in clinical practice in the UK, this appendix presents new cost-effectiveness analyses of olaparib versus cabazitaxel, in the prior taxane subgroup of the *BRCA*m population.

A.3.2 Model structure

The cost-effectiveness analysis for the updated company base-case (i.e. the prior taxane subgroup of *BRCA*m) is based on the economic model previously described in the company submission (Document B, Section B.3). The model structure and general features of the economic analysis remain unchanged; updated model inputs are described in the following section.

A.3.3 Updated efficacy and safety inputs for the revised company base-case

The economic model assessing the cost-effectiveness of olaparib versus cabazitaxel uses the following inputs based on the PROfound ***BRCA*m prior taxane subgroup** of patients. The analysis makes use of the pre-specified final (DCO2) analysis of overall survival and safety endpoints,(26) whilst other inputs rely on DCO1 data (per the overview presented in Table 10). Key inputs that have been updated in the revised company base-case are described in the following sections (Section A.3.3.1 to Section

A.3.3.5 below); a detailed summary is provided towards the end of this Appendix in Table 19.

Table 10. Overview of clinical inputs used in the revised company base-case analysis

	Updated in the base-case analysis[Ŧ]	
	PROfound population	**DCO, PROfound***
OS (olaparib)	*BRCA*m Prior taxane	DCO2
ITC, OS (cabazitaxel)	*BRCA*m overall	DCO2 (PROfound)
rPFS (olaparib)	*BRCA*m Prior taxane	DCO1
ITC, rPFS (cabazitaxel)	*BRCA*m overall	DCO1 (PROfound)
TTD (scenario)	*BRCA*m Prior taxane	DCO1
% Receiving subsequent treatment	*BRCA*m Prior taxane	DCO1
Distribution of subsequent treatments	*BRCA*m Prior taxane	DCO2 (PROfound)
AEs (safety)	*BRCA*m Prior taxane	DCO2 (PROfound)
SREs	*BRCA*m Prior taxane	DCO1

AEs, adverse events; CS, company submission; DCO, data cut-off; ITC, indirect treatment comparison; OS, overall survival; rPFS, radiographic progression-free survival; SREs, skeletal-related events; TTD, time to treatment discontinuation

* *Note: DCO2 used if available, as specified; otherwise DCO1*. DCO1: data cut-off at primary rPFS analysis, 4th June 2019; DCO2: data cut-off at final OS analysis, 20th March 2020

Ŧ Inputs updated for the new base-case analysis; those not listed are the same as in the company submission (CS) Section B.3.

A.3.3.1 Patient characteristics

The mean baseline age and weight of patients in the *BRCA*m prior taxane subgroup data from PROfound are provided in Table 11.

Table 11. Mean age and weight, PROfound (*BRCA*m prior taxane subgroup)

Characteristic	**Mean (SD)**
Age (years)	[redacted]
Weight (kg)	[redacted]

SD, standard deviation

A.3.3.2 Efficacy outcomes

As in the original company submission, extrapolation of time-to-event data was required to model health and cost outcomes associated with olaparib and cabazitaxel over a lifetime horizon. The approach to modelling efficacy outcomes in this updated analysis for olaparib and cabazitaxel are consistent with the methods described in the initial submission (Document B, Section B.3.3). Briefly:

- Efficacy outcomes for olaparib were modelled based on time to event analysis of the patient-level data from the PROfound *BRCA*m prior taxane subgroup of patients, the population relevant to the revised company base-case.

- In the absence of head-to-head trial data comparing olaparib with cabazitaxel, outcomes for cabazitaxel were modelled by applying the reciprocal of the anchored ITC hazard ratios, to the olaparib curves as the reference arm. Given the similar efficacy observed in the overall PROfound *BRCA*m population and the prior taxane subgroup of *BRCA*m (OS HR of olaparib versus investigators' choice of NHA before adjustment for treatment switching = [redacted] and [redacted], respectively]; Appendix 2), the *BRCA*m ITC was deemed to represent the best estimate for the relative efficacy of olaparib versus cabazitaxel, by retaining as much statistical power as possible through patient numbers. Details regarding the ITC can be found in Appendix 2.

The distributions used to model rPFS and OS in the updated base-case analysis were selected following the same approach as outlined in the initial company submission (Document B, Section B.3.3), taking into account the statistical fit of the curves to the observed data as well as clinical plausibility of long-term survival estimates.

A.3.3.2.1 Radiographic progression-free survival (rPFS), DCO1

At DCO1, the rPFS data for the *BRCA*m prior taxane subgroup of the PROfound population were relatively mature, although not all patients had experienced an event ([redacted]% maturity, [redacted] events in 72 patients). The Kaplan-Meier plots and extrapolated curves for rPFS in the olaparib arm are shown in Figure 11 and Figure 12. AIC/BIC statistics for olaparib rPFS data are presented Table 12. The Gompertz distribution

was the best fitting curve according to the AIC/BIC statistics and was therefore used to model rPFS in the base-case analysis. The resulting curves for rPFS in the cabazitaxel arm after applying the reciprocal of the anchored ITC HR (olaparib vs cabazitaxel, [redacted]) are shown in Figure 13.

Figure 11. BICR rPFS, Kaplan–Meier plot (DCO1, *BRCA*m – prior taxane)

bd, twice daily

Figure 12. Modelled rPFS for olaparib based on PROfound (DCO1, *BRCA*m – prior taxane)

Table 12. AIC and BIC values for parametric models for rPFS (DCO1, *BRCA*m – prior taxane)

Distribution	AIC	BIC	Total
Exponential	329.7	332.0	661.7
Weibull	327.3	331.8	659.1
Loglogistic	334.5	339.1	673.6
Lognormal	338.6	343.2	681.8
Gompertz[a]	**324.0**	**328.6**	**652.6**
Generalised gamma	326.0	332.8	658.8

AIC, Akaike information criterion; BIC, Bayesian information criterion; Gen, generalised; HRRm, homologous recombination repair; rPFS, radiographic progression-free survival.
[a] The best fitting statistical model to the rPFS according to the AIC/BIC statistic is the Gompertz model and it has been used in the analysis.

Figure 13. Modelled rPFS for cabazitaxel based on *BRCA*m ITC HR vs olaparib as reference curve (DCO1)

A.3.3.2.2 Overall survival (OS), DCO2

Choice of extrapolated OS curve for olaparib in the base-case analysis:

The data presented are based on the *BRCA*m prior taxane subgroup of the PROfound study using the planned final analysis of OS (i.e. DCO2). OS data for the olaparib arm in the *BRCA*m prior taxane subgroup were [redacted]% mature ([redacted] events in 72 patients), with median OS of [redacted] months. The Kaplan-Meier plots and extrapolated curves for OS in the olaparib arm are shown in Figure 14 and Figure 15, respectively. The AIC/BIC values for the parametric curves are provided in Table 13.(24)

Figure 14. OS, Kaplan–Meier plot (DCO2, *BRCA*m – prior taxane)

bd, twice daily

Figure 15. Modelled OS for olaparib based on PROfound (DCO2, *BRCA*m – prior taxane)

Table 13. AIC and BIC values for parametric models for OS (DCO2, *BRCA*m – prior taxane)

Distribution	AIC	BIC	Total
Exponential	**351.9**	**354.2**	**706.1**
Weibull	352.6	357.1	709.7
Loglogistic	356.0	360.6	716.6
Lognormal	362.1	366.6	728.7
Gompertz	351.2	355.7	706.9
Generalised gamma	353.2	360.0	713.2

AIC, Akaike information criterion; BIC, Bayesian information criterion; Gen, generalised; OS, overall survival.

Following the same method as outlined in the initial submission (Document B, Section B.3.3), the OS distribution used to model survival for olaparib in the base-case analysis takes into account both the statistical fit of the curve to the observed data, as well as clinical plausibility of long-term survival estimates.

The total AIC/BIC values for the distributions fitted to the observed data were similar, with the exponential distribution providing the best statistical fit to the observed data (Table 13). However, this distribution provided long-term survival estimates that were too pessimistic for patients with *BRCA*m disease, who are anticipated to derive most benefit from olaparib. Clinical experts previously consulted by AstraZeneca indicated that 5-year and 10-year OS rates of [redacted]% and [redacted]% were clinically-plausible for HRRm patients. Based on observed data from the PROfound study, patients with *BRCA*m disease are anticipated to derive greater clinical benefit than the overall HRRm population of patients.(24) Therefore, 5-year and 10-year OS survival rates of at least (or in excess of) [redacted]% and [redacted]% would be expected for the *BRCA*m prior taxane subgroup of patients. The exponential distribution, however, produced 5-year and 10-year estimates of just [redacted]% and [redacted]%.

Of all the parametric survival extrapolations analysed, the log-logistic distribution most-closely reflected UK clinical expert opinion, and **was used in the base-case analysis for the following reasons**:

1. Survival estimates with the log-logistic distribution best reflected the observed OS KM data for the prior taxane subgroup of *BRCA*m

- Based on the observed OS KM data for the prior taxane subgroup of *BRCA*m, [redacted]% of patients were alive at 1 year and [redacted]% of patients were alive at the end of the follow-up period (approximately 33 months, close to 3 years). Of the six distributions, the log-logistic curve most closely reflected these observed figures ([redacted]% and [redacted]%, respectively; see Table 14). The statistically best-fitting exponential distribution was too conservative at 1 and 3 years compared with observed data from the PROfound trial.

2. As stated previously, the log-logistic distribution provides the most clinically-plausible predictions for long-term OS at 5 and 10 years for patients in the prior taxane subgroup of *BRCA*m

    - As demonstrated by the PROfound, TOPARP-A, and TOPARP-B studies, tumours harbouring *BRCA1/2* mutations are most sensitive to olaparib monotherapy (relative to tumours with any of the other known HRR mutations).(24, 27, 28) Therefore, it is expected that the 5- and 10-year survival estimates within the *BRCA*m prior taxane population would be *at least equal to or greater than* that predicted for the HRRm prior taxane population.

    - UK clinical experts consulted by the company for the initial submission for the HRRm (Cohort A+B) prior taxane population expected outcomes with olaparib to be better than that achieved with the current standard-of-care. Based on the average of responses, approximately [redacted]% of patients and [redacted]% of patients who have previously received docetaxel and who have progressed on a prior NHA were estimated to remain alive 5 and 10 years after starting treatment with olaparib (Document B, Section B.3.3.2.1.2).

      The modelled 5 and 10 year survival estimates for the *BRCA*m prior taxane analysis using the log-logistic distribution ([redacted]% and [redacted]%, respectively) were most similar to the clinicians' estimates for the HRRm prior taxane population, which can be considered to represent the lower

bound of plausible survival estimates for the *BRCA*m prior taxane population. In contrast, the exponential distribution provided a severely pessimistic outlook for 5 and 10 year survival on olaparib ([redacted]% and [redacted]%, respectively, as shown in Table 14).

3. Long-term benefit on olaparib treatment, in at least a proportion of *BRCA*m patients, is consistent with its mechanism of action of olaparib and data from other advanced, metastatic disease settings

    - As described in Document B, Section B.1.3, the presence of mutations in genes involved in the HRR pathway render tumours sensitive to targeted therapy with PARP inhibitors, such as olaparib, which specifically target and kill HRR-deficient tumour cells via a mechanism involving synthetic lethality (described in the company submission, Document B, Section B.1.3). *BRCA1/2* mutations are the best characterised amongst genes implicated in the HRR pathway; the sensitivity of *BRCA*m tumours to olaparib, with sustained clinical efficacy in at least a subset of patients, has been demonstrated in multiple studies, spanning not just prostate, but also ovarian, breast, and pancreatic indications.(29-31)

    - The long-term OS benefit of olaparib in a heavily pre-treated patient population is best evidenced in Study 19, a Phase 2 study of platinum-sensitive, recurrent high-grade serous ovarian cancer patients treated with maintenance olaparib.(29) The study examined OS in 265 patients who had received at least 2 platinum-based chemotherapy regimens (range 2 to ≥5) and were in complete or partial response to their most recent regimen; patients received either olaparib capsules (400 mg bid, n=136) or placebo (n=129). The trajectory of OS survival curves in *BRCA*m patients in Study 19 changed between 36 and 42 months from start of olaparib maintenance therapy, with the majority of patients alive at 3 years, also remaining alive at 5 years. Although in a different disease setting, these data are consistent with UK clinical expert opinion, which supports sustained OS in a proportion of patients who are still alive at

the end of the follow-up period in PROfound and the presence of a long-term OS tail, as predicted by the log-logistic extrapolation in this submission.

OS for cabazitaxel in the base-case analysis:

Survival outcomes for cabazitaxel were modelled by applying the reciprocal of the anchored ITC HR (olaparib vs cabazitaxel, [redacted] to the olaparib curve as the reference arm. The OS curves for cabazitaxel using each of the six distributions (Figure 16) show that most patients are expected to die by 5 years from the start of the model. In the base-case analysis, using the log-logistic distribution for olaparib, 5 and 10 year estimates for cabazitaxel were [redacted]% and [redacted]%, respectively, compared with [redacted]% and [redacted]% with the exponential distribution.

Figure 16. Modelled OS for cabazitaxel based on *BRCA*m ITC HR vs olaparib as reference curve (DCO2)

Table 14. OS estimates for olaparib (*BRCA*m - prior taxane, olaparib)

Olaparib	Median, months	1 year, %	3 years, %	5 years, %	10 years, %	Total AIC+BIC value	Statistical fit ranking (1 = lowest AIC+BIC)	Clinically plausible long-term survival estimates[a]
Observed (PROfound, *BRCA*m - prior taxane subgroup)								
Kaplan-Meier	[redacted]	[redacted]	[redacted]% at 2.8 years*	-	-	-	-	-
Predicted by parametric models								
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	706.1	1	No
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	709.7	3	No
Log-logistic (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**716.6**	**5**	**Yes**
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	728.7	6	Yes
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	706.9	2	No
Gen gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	713.2	4	No
Potential OS from start of olaparib (after previous taxane and NHA; as in initial submission for Cohort A+B, CS Document B)								
UK clinical expert opinion (average of responses)	–	–	[redacted]	[redacted]	[redacted]	=	=	–
OS from start of cabazitaxel (after previous NHA) – reference only (as in initial submission for Cohort A+B, CS Document B)								
UK clinical expert opinion (average of responses)			[redacted]	[redacted]	[redacted]	=	-	-

AIC, Akaike information criterion; BIC, Bayesian information criterion; CS, company submission; Gen, generalised; NHA, new hormonal agent; OS, overall survival.

[a] Yes = 5- and/or 10-year survival do not contradict estimates provided by clinical experts in the HRRm population (after NHA and taxane treatment); No = 5- and 10-year survival estimates contradict estimates provided by clinical experts.

* Last time point available in the prior taxane subgroup of *BRCA*m, PROfound.

A.3.3.3 Treatment duration

As described in the original submission (Document B, Section B.3.3.3), using the rPFS curves from PROfound (*BRCA*m prior taxane) and CARD studies, to model treatment duration was considered most robust and appropriate, for the following reasons:

- In the absence of observed TTD data for cabazitaxel, using rPFS to proxy treatment duration is the only consistent approach for modelling treatment duration for olaparib and cabazitaxel, making the best use of the available evidence for both interventions and minimising the amount of bias in the analysis.

- Assuming a treat-to-progression rule (i.e. proxying treatment duration based on the rPFS curve) is aligned to the expected real-world administration of both treatments. For olaparib, this reflects the anticipated EMA marketing authorisation and the administration of olaparib in the PROfound study.

The updated company model maintains flexibility to test scenarios using a treatment duration curve for olaparib, based on the parametric curves fitted to the patient-level data for TTD at DCO1 in the *BRCA*m prior taxane subgroup (TTD was not included as part of the planned analysis at DCO2). The analysis was conducted using the same methods as described in the company submission (Document B, Section B.3.3.3.3). The Kaplan-Meier plots and extrapolated curves for TTD in the olaparib arm are shown in Figure 17 and Figure 18; the Gompertz curve was selected for use in the scenario analysis as it was the statistically best-fitting curve based on AIC/BIC values (Table 15).

Figure 17. Olaparib TTD, Kaplan–Meier plot (DCO1, *BRCA*m – prior taxane)

bd, twice daily

Figure 18. Modelled TTD for olaparib based on PROfound (DCO1, *BRCA*m – prior taxane)

Table 15. AIC and BIC values for parametric models for TTD (DCO1, *BRCA*m – prior taxane)

Distribution	AIC	BIC	Total
Exponential	391.9	394.2	786.1
Weibull	389.7	394.2	783.9
Loglogistic	402.0	406.5	808.5
Lognormal	412.1	416.7	828.8
Gompertz	**383.7**	**388.2**	**771.9**
Generalised gamma	385.4	392.2	777.5

AIC, Akaike information criterion; BIC, Bayesian information criterion; Gen, generalised; TTD, time to treatment discontinuation.

The treatment costs associated with cabazitaxel are also capped to a maximum of 10 treatment cycles to align with NICE TA391 guidance; however, applying this restriction without adjusting efficacy estimates for the shorter duration of treatment is expected to lead to overall conservative estimates of cost-effectiveness for olaparib versus cabazitaxel. We have explored scenarios where the length of treatment with cabazitaxel was not limited to a maximum of 10 treatment cycles, allowing treatment costs to align with the efficacy data used in the ITC derived from the CARD study; this improved the cost-effectiveness of olaparib against cabazitaxel, as shown in Appendix 3.7, Table 23.

A.3.3.4 Adverse events and skeletal-related events

The updated values for treatment-related AE rates (occurring in at least 5% of patients) in the *BRCA*m prior taxane subgroup of PROfound are based on DCO2 data, whilst the overall occurrence of SREs are based on DCO1 data, as shown in Table 16.

No updates were applied to cabazitaxel data relative to the company submission (Document B, Section B.3.3.4 to B.3.3.5).

Table 16. Grade 3 and above AEs affecting at least 5% of patients, and probability of SREs occurring with each intervention, included in the base case analysis (olaparib, PROfound *BRCA*m – prior taxane; cabazitaxel, CARD)*

	Olaparib	Cabazitaxel
DCO2, Grade 3+ adverse event, %[Ŧ]	**PROfound *BRCA*m prior taxane (N = 72)**	**CARD (N = 126)**
Anaemia	[redacted]	8.0[c]
Infection	[redacted]	7.9
Leukopenia	[redacted]	5.0 [b]
Neutropenia	[redacted]	5.0 [b]
Musculoskeletal pain or discomfort[a, e]	[redacted]	1.6
Thrombocytopenia[e]	[redacted]	3.2
Febrile neutropenia[e]	[redacted]	3.2
Diarrhoea[e]	[redacted]	3.2
Fatigue/asthenia[e]	[redacted]	4.0
DCO1, Skeletal-related event, %[Ŧ]		
At least one SRE	[redacted]	18.6%

As described in the initial submission (Document B, Section B.3.3.4, Table 31):

[a] Described in de Wit *et al*. 2019 as including back pain, flank pain, musculoskeletal discomfort and/or pain, neck pain, or pain in extremities. No related events were reported in PROfound.

[b] Input values based on clinical expert advice on the incidence of leukopenia/neutropenia (Grade 3 and above) that would require hospitalisation (data on file).

[c] Laboratory abnormalities reported in de Wit *et al*. 2019 may not have been reported as an adverse event in CARD although the values were used as clinical experts confirmed that this reflected what they would expect in clinical practice.

[e] Occurred in fewer than 5% of patients in PROfound/CARD, but added to the list of AEs (validated by UK clinical experts).

* Produced for the *BRCA*m prior taxane analysis (initially presented in the company submission for Cohort A+B prior taxane population in Document B, Table 31).

[Ŧ] AEs were included part of the safety analyses from DCO2, which are consistent with the data previously presented in the initial company submission (Document B), as well as the known safety and tolerability profile of olaparib. No new safety signals were identified in the DCO2 analysis. Akeletal-related events were not included in the planned analysis for the DCO2 update.

A.3.3.5 Subsequent anti-cancer treatment

A.3.3.5.1 Proportion of patients receiving subsequent treatment

The number of patients who received subsequent treatment in the olaparib arm of the *BRCA*m prior taxane subgroup of the PROfound population at the time of the primary rPFS analysis (DCO1) is provided in Table 17.

Given the consistency in the figures between PROfound and CARD (Table 17), and that the input value is not a driver of the cost-effectiveness results, an equalised

proportion of [redacted]% of patients receiving any subsequent treatment after progression on olaparib and cabazitaxel is assumed in the updated base-case analysis.

Table 17. Summary of overall number of patients receiving subsequent treatment (olaparib, PROfound *BRCA*m prior taxane; cabazitaxel, CARD)*

		Olaparib	Cabazitaxel
Interim analysis	Number of patients receiving subsequent treatment (n)	[redacted]	50
	Number of progression events (N_p)	[redacted]	120
	% (n/N_p)	[redacted]	41.7%

n = number of patients receiving subsequent treatment reported in study; N_p = number of progression events reported in study, N = total number of patients in treatment arm.
* In PROfound, the numbers of progression events are only available at DCO1 (rPFS data were not collected beyond this) – therefore, it is not possible to update this figure based on DCO2 analyses. This input value is not a driver of the cost-effectiveness results.
No updated data from the CARD study were identified since the initial submission, and remain same as provided in Document B.

A.3.3.5.2 Distribution of subsequent treatments

The distribution of subsequent treatments received by patients after disease progression on olaparib and cabazitaxel therapy was derived using the same approach as described in the company submission (Document B, Section B.3.5.3.3).

The distribution of subsequent treatments in the olaparib arm is provided in Table 18, based on data for the *BRCA*m prior taxane subgroup of PROfound. The distribution of treatments received after disease progression on cabazitaxel reflects that calculated by the ERG (ERG Report Section 4.3.2.1), based on data from the CARD study.

As expected, the distribution of subsequent treatments differ for patients progressing on olaparib, compared with patients progressing on cabazitaxel. Next line treatment options are limited once patients have progressed on cabazitaxel – a subset of patients with bone metastases and no visceral metastases may be eligible to receive radium-223; re-treatment with a taxane is uncommon (Document B, Section B.1.2). Olaparib offers a new targeted treatment option for patients with *BRCA*m mCRPC, who have received prior treatment with a taxane and NHA. After disease progression

on olaparib, it is expected that many patients will still be eligible to receive cabazitaxel as a next-line therapy in clinical practice.

Although subsequent NHA use is not reflective of current clinical practice in the NHS, these costs have been accounted for in the company base-case analysis to align costs with the efficacy data from the PROfound and CARD clinical trials, where NHAs were a frequently-used subsequent treatment. In the scenario analysis, excluding subsequent NHAs had minimal impact on the results.

Table 18. Distribution of subsequent treatment applied in the economic analysis (olaparib, DCO2 PROfound *BRCA*m – prior taxane; cabazitaxel, CARD)*

	Olaparib			Cabazitaxel**		
	PROfound, *BRCA*m prior taxane (N=72)			CARD, All patients (N=129)		
Subsequent therapy	n	%	%, adjusted for NHA	n	%	%, adjusted for NHA
Cabazitaxel	[redacted]	[redacted]	[redacted]	3	7.3%	27.3%
Docetaxel	[redacted]	[redacted]	[redacted]	2	4.9%	18.2%
Abiraterone	[redacted]	[redacted]	[redacted]	15	36.6%	0.0%
Enzalutamide	[redacted]	[redacted]	[redacted]	15	36.6%	0.0%
Radium-223	[redacted]	[redacted]	[redacted]	6	14.6%	54.5%

NHA, new hormonal agent

* Excluding investigational and treatments that have not been approved for use in mCRPC patients, percentages adjusted to sum to 100%.

** Proportions suggested by the ERG (ERG Report, Section 4.3.2.1 with specific values sourced from electronic version of the ERG rebuild model).

A.3.4 Model revisions based on ERG review

In addition, the following revisions were applied in the updated version of the model, to reflect / account for the ERG's comments on the original company model for the Cohort A+B prior taxane group of patients (ERG Report, Section 4.3.1.2 and Section 5.4.1):

- ERG01a: Prophylactic G-CSF use costs are accrued until maximum treatment duration of cabazitaxel
- ERG01c: Cost of 1st administration of cabazitaxel reduced by £108
- ERG01d: Olaparib monitoring costs are revised to reflect the first 3 months of treatment

- ERG03b: Median RDI values are implemented for olaparib ([redacted]),(12) and cabazitaxel (0.961)(32)
- ERG06: The unit cost of G-CSF (previously £84.06) has been updated to £79.90 (£399.50 per 5 x 48million units) based on the NHS tariff cost proposed by the ERG(33)
- ERG09: Proportion and balance of patients receiving subsequent treatments and the cabazitaxel arm have been updated to match the ERG's calculated values.

Additionally, specific to the scenario analyses (Table 23), we have accounted for the ERG's comments as follows:

- Scenario 3: We have removed the model constraint on TTD that previously assumed TTD can be at most equal to rPFS
- Scenario 15: We have incorporated the prevalence of *BRCA*m gene mutations at a rate of 9.7% into the total cost of testing. Summary of key inputs in base case analysis

A.3.5 Summary of base-case analysis inputs

Key inputs used in the base case analysis are summarised in Table 19, including the parameters described in the previous sections (i.e. patient characteristics, efficacy safety, and subsequent treatment inputs). Inputs that have not been updated are marked as being the same as the company submission (CS) Section B.3.

Table 19. Summary of key features and assumptions in the revised base-case analysis [a]

	*BRCA*m – Prior taxane		Cross-reference to relevant section(s) in Appendix 3 (*BRCA*m – Prior taxane)	Cross-reference to relevant section(s) in Document B (Cohort A+B – Prior taxane)
Feature / assumption	**Base case**	**Key data source(s)**		
Modelled population	*BRCA*m prior taxane	PROfound trial	Section A.4.1	Section B.3.2
Baseline patient characteristics			Section A.4.1	Section B.3.2 / B.3.5
Mean age (SD)	[redacted]	PROfound, *BRCA*m prior taxane	Section A.4.3.1	Section B.3.2.2 Section B.3.5.2.1.3
Mean weight (SD)	[redacted]	PROfound, *BRCA*m prior taxane		
BSA	As in initial submission (Section B.3)		N/A	
Survival parameters			Section A.4.3.2	Section B.3.3
Olaparib rPFS distribution	Gompertz	PROfound, *BRCA*m prior taxane	Section A.4.3.2.1	Section B.3.3.2.1.1.1
Cabazitaxel rPFS ITC HR (95% CI)	[redacted]	*BRCA*m ITC		Section B.3.3.2.1.2.2
Olaparib OS distribution	Log-logistic	PROfound, *BRCA*m prior taxane	Section A.4.3.2.2	Section B.3.3.2.1.2.1
Cabazitaxel OS ITC HR (95% CI)	[redacted]	*BRCA*m ITC		Section B.3.3.2.1.1.2
Treatment costs			Section A.4.3.3 to A.4.3.5	Section B.3.3 / B.3.5
Treatment duration for olaparib and cabazitaxel	Until progression	-	Section A.4.3.3	Section B.3.3.3
RDI*	Median RDI olaparib: [redacted] Median TDI cabazitaxel: 0.961	** Changed to medians to account for ERG's comments;*	N/A	Section B.3.5.2.1.4

	*BRCA*m – Prior taxane		Cross-reference to relevant section(s) in Appendix 3 (*BRCA*m – Prior taxane)	Cross-reference to relevant section(s) in Document B (Cohort A+B – Prior taxane)
Feature / assumption	**Base case**	**Key data source(s)**		
		PROfound SAS TA391 (TROPIC)		
Safety inputs			Section A.4.3.4	Section B.3.3 / B.3.4
Probability of AEs	Olaparib: Multiple values updated Cabazitaxel: As in initial submission (Section B.3)	PROfound, *BRCA*m prior taxane De Wit 2019 (CARD); as in initial submission	Section A.4.3.4	Section B.3.3.4 Section B.3.4.4
Probability of SRE	Olaparib: [redacted]% Cabazitaxel: As in initial submission (Section B.3)	PROfound, *BRCA*m prior taxane De Wit 2019 (CARD); as in initial submission		Section B.3.3.5.1 Section B.3.4.5
Distribution of SREs	As in initial submission (Section B.3)		N/A	Section B.3.3.5.2
Health related quality of life			N/A	Section B.3.4
Mean health state utility values	As in initial submission (Section B.3)		N/A	Section B.3.4.1 Section B.3.4.2 Section B.3.4.7
IV decrement	As in initial submission (Section B.3)		N/A	Section B.3.4.6
AE utility decrements	As in initial submission (Section B.3)		N/A	Section B.3.4.4
SRE utility decrements	As in initial submission (Section B.3)		N/A	Section B.3.4.5
Other costs and resource use			N/A	Section B.3.5
% Receiving prophylactic G-CSF	As in initial submission (Section B.3)		N/A	Section B.3.5.2.2.2

	***BRCA*m – Prior taxane**		**Cross-reference to relevant section(s) in Appendix 3 (*BRCA*m – Prior taxane)**	**Cross-reference to relevant section(s) in Document B (Cohort A+B – Prior taxane)**
Feature / assumption	**Base case**	**Key data source(s)**		
Unit cost of G-CSF*	£79.90 per 48million units/0.5ml solution	** Changed to use NHS tariff cost (£399.50 per 5x48million units) to account for ERG's comments* NHS tariff cost, BNF online (accessed 10 Oct 2020)	N/A	
Duration of G-CSF	As in initial submission (Section B.3)		N/A	
All other unit costs and resource use frequencies	As in initial submission (Section B.3)		N/A	Section B.3.5

[a] Inputs which have not been updated are marked as being the same as the company submission (CS) Section B.3.

AE, adverse event; BSA, body surface area; G-CSF, granulocyte-colony stimulation factor; HR, hazard ratio; ITC, indirect treatment comparison; IV, intravenous; OS, overall survival; N/A, not applicable; rPFS, radiographic progression-free survival; RDI, relative dose intensity; SD, standard deviation; SRE, skeletal related event.

A.3.6 Base-case results

The cost-effectiveness results for olaparib versus cabazitaxel are presented in Table 20 (inclusive of the confidential PAS for olaparib and with cabazitaxel at list price). Disaggregated results for health and cost outcomes are provided in Table 21 and Table 22, respectively.

The results show that olaparib is expected to be a highly cost-effective use of NHS resources compared with current standard-of-care in patients with *BRCA*m mCRPC and who have received a prior taxane and NHA, with an incremental cost-effectiveness ratio of £18,596/QALY that lies below the cost-effectiveness threshold of £50,000/QALY for end-of-life medicines.

Table 20. Base-case results (costs and health outcomes discounted at 3.5%).

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Olaparib	[redacted]	[redacted]	[redacted]	£19,126	1.58	1.03	**£18,596**	
Cabazitaxel	[redacted]	[redacted]	[redacted]					
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

Table 21. Disaggregated base-case results: summary of QALY gain by health state (health outcomes discounted at 3.5%)

Health Benefits	Olaparib	Cabazitaxel	Increment
Total quality-adjusted life-years	[redacted]	[redacted]	[redacted]
Progression-free	[redacted]	[redacted]	[redacted]
Progressed	[redacted]	[redacted]	[redacted]
QALY loss: adverse events disutility	[redacted]	[redacted]	[redacted]
QALY loss: SSRE disutility	[redacted]	[redacted]	[redacted]

QALYs, quality-adjusted life years

Table 22. Disaggregated base-case results: summary of predicted resources use by category of cost (cost outcomes discounted at 3.5%)

Cost Outcomes	Olaparib, £	Cabazitaxel, £	Increment, £
Total costs	[redacted]	[redacted]	[redacted]
Drug costs: treatment	[redacted]	[redacted]	[redacted]
Admin costs: treatment	[redacted]	[redacted]	[redacted]
Concomitant medication costs	[redacted]	[redacted]	[redacted]
AE management costs	[redacted]	[redacted]	[redacted]
SRE management costs	[redacted]	[redacted]	[redacted]
Disease management costs: on treatment	[redacted]	[redacted]	[redacted]
Disease management costs: off treatment	[redacted]	[redacted]	[redacted]
Best supportive care (no subsequent treatment)	[redacted]	[redacted]	[redacted]
Subsequent treatment costs	[redacted]	[redacted]	[redacted]
End of life care costs, £	[redacted]	[redacted]	[redacted]

AE, adverse event; SRE, skeletal related event

A.3.7 Scenario analyses

An extensive list of scenarios were tested to provide a comprehensive understanding of the impact of various assumptions on the model results. A brief description of each scenario and the results are presented in Table 23. **Olaparib remained cost-effective against cabazitaxel in each of the 15 scenarios tested**.

Table 23. Scenario analyses

Scenario		Brief rationale	ICER (£ per QALY)
Base case			**£18,596**
Efficacy parameters			
1	OS (Exponential) distribution for olaparib	Explore the impact on the results when the distribution is changed for OS (exponential, statistically best-fitting distribution; lognormal, alternative plausible distribution).	£22,787
2	OS (Lognormal) distribution for olaparib		£17,646
3	rPFS (Generalised gamma) distribution for olaparib	Explore the impact on the results when the distribution is changed for rPFS.	£18,755
Treatment duration			
4	Treatment duration: Cost of cabazitaxel aligned with administration of cabazitaxel in the CARD study	Test the impact of different treatment duration assumptions. In these scenarios, cabazitaxel treatment costs are aligned	£11,623

Scenario		Brief rationale	ICER (£ per QALY)
5	Treatment duration: Olaparib TTD curve (Gompertz) and cabazitaxel rPFS	with the CARD study, which did not impose a maximum treatment duration.	£13,949
G-CSF use			
6	G-CSF with cabazitaxel: 79.5% based on UK EAP for cabazitaxel	Understand the impact of changing G-CSF assumptions	£19,667
Health-related quality of life, AEs and SRE parameters			
7	Exclude modality-specific disutility due to IV administration (mean PF HSUV on treatment is the same for olaparib and cabazitaxel)	Test the impact of different assumptions; assumes that the IV administration of cabazitaxel does not impact quality of life, therefore, the PF utility while on treatment is the same across treatments.	£18,735
8	Mean HSUV based on PROfound: Exclude AE & SRE disutility	Test alternative assumptions related to AE and SRE disutilities.	£18,633
9	Mean HSUVs based on UK EAP in TA391 (PF: 0.737, PD: 0.627)	Understand the impact of different assumptions for the source/value of mean HSUVs; based on UK EAP for cabazitaxel (no modality-specific adjustment applied to cabazitaxel; modality-specific increment applied to olaparib instead).	£18,340
10	Exclude SRE costs and SRE disutility	Understand the impact of removing SREs from the economic analysis (both costs and disutilities).	£18,692
Other cost and resource use assumptions			
11	Assume 100% RDI for olaparib and cabazitaxel	Test impact of alternative assumption for RDI (dose reduction not allowed).	£18,378
12	Assume there is wastage (no vial sharing)	Understand the impact of alternative assumption due to uncertainty around the application of vial sharing in NHS practice (TA391).	£12,829
13	Alternative subsequent treatment assumptions: exclude enza / abi and re-weight distribution	Explore alternative assumptions for the distribution of subsequent treatments (affects costs only; no adjustment for efficacy).	£18,350
14	Sequential BSC: Means-based 4-HS approach	Test impact of using the ERG's suggested means-based approach for including the sequential costs associated with best supportive care after subsequent treatment.	£22,465
15	Include one-off cost of genetic testing (olaparib)	Included for completeness only; scenario where genetic testing is not provided under the National Genomic Test Directory.	£22,606

Abbreviations: AE, adverse event; BSC, best supportive care; G-CSF, granulocyte-colony stimulation factor; HS, health-state; HSUV, health-state utility value; IV, intravenous; OS, overall survival; N/A, not applicable; rPFS, radiographic progression-free survival; RDI, relative dose intensity; SRE, skeletal related event; TTD, time to treatment discontinuation.

A.4 Appendix 4: Sensitivity analyses for the overall *BRCA*m population

During the NICE technical engagement teleconference on 30th September 2020, the ERG requested that the company provide an analysis of cost-effectiveness in the overall *BRCA*m population of patients.

To address this request, we have conducted a cost-effectiveness analysis with efficacy and safety inputs based on the **overall *BRCA*m population** of patients from PROfound. Note: Inputs are as per Table 10 in Appendix 3; however, overall *BRCA*m inputs have been used instead of the *BRCA*m prior taxane inputs (full details can be found in a version of the electronic model provided separately for the overall *BRCA*m population).

The results of this analysis are highly consistent with those presented for the *BRCA*m prior taxane subgroup (Table 24), with a difference in the ICER of just £1,580/QALY (ICERs= £20,176/QALY and £18,596/QALY, in the *BRCA*m overall population and prior taxane subgroup analyses, respectively).

Table 24. Base-case results (costs and health outcomes discounted at 3.5%).

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Olaparib	[redacted]	[redacted]	[redacted]	£21,808	1.65	1.08	**£20,176**	
Cabazitaxel	[redacted]	[redacted]	[redacted]					
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Olaparib for previously treated hormone-relapsed metastatic prostate cancer [ID1640]

Clarification questions

November 2020

File name	Version	Contains confidential information	Date
ID1640_olaparib_clarification question response 24Nov2020 [REDACTED]	2.0	Yes	24 November 2020

Section A: Clarification on effectiveness data

A1. Please tabulate the following data in sufficient detail to reproduce by arm the appendix Figures 3, 4, 5, 6, 7, 8, 9, 10, 17 (2 tables per Figure) of the AstraZeneca Technical Engagement response Appendix. Please provide Figure 1 of the TE response to Issue 18 at the same level of detail, including censoring, as the appendix Figures 3, 4, 5, 6, 7, 8, 9, 10, 17, and tabulate the TTD data in sufficient detail to reproduce the TTD KM curve of the revised Figure 1 (1 table).

	N at risk	Event	Censored	S(t)
T=0	N=???	N=???	N=???	S=???
T=???	N=???	N=???	N=???	S=???
T=???	N=???	N=???	N=???	S=???
Etc…				

Company response:

The requested data for the overall *BRCA*m population and prior taxane subgroup of *BRCA*m are provided in the embedded file below, as per the format used in the response to ERG CQ A10 (dated 24 July 2020).

Figure 1 of the Technical Engagement (TE) response (i.e. monthly KM estimates for rPFS and TTD in the *BRCA*m overall population; Issue 18) has been expanded below (in Figure 1 for rPFS and Figure 2 for TTD, respectively) to provide the same level of detail as other Figures in the TE response.

[Confidential file redacted]

Figure 1. rPFS-BICR, Kaplan–Meier plot (DCO1, *BRCA*m overall population)

Figure 2. Olaparib TTD, Kaplan–Meier plot (DCO1, *BRCA*m overall population)

A2. Please state which events were treated as censoring events for the construction of:

1. the OS KM curves, and provide the totals of each type of censoring event by arm
2. the PFS KM curves, and provide the totals of each type of censoring event by arm

3. the TTD KM curves, and provide the totals of each type of censoring event by arm

Company response:

The total numbers of censoring events are provided in Table 1; definitions are as follows:

- OS: Any patient not known to have died at the time of analysis was censored based on the last recorded date on which the patient was known to be alive.(1)
- rPFS: as stated in the TE response (to Question 18), the events of interest for the rPFS analysis were radiological disease progressions by BICR or death. Patients who had not progressed (defined as having either a complete response [CR], partial response [PR] or stable disease [SD] by RECIST 1.1 for soft tissue disease, or non-progressive disease [non-PD] for bone disease), or died at the time of analysis were censored at the time of the earliest date of their last evaluable RECIST 1.1 assessment (taking the latest target lesion, non-target lesion, or new lesion scan date) or bone scan assessment that showed non-PD. If performed at the same visit, then the latest of the previous RECIST 1.1 assessment or bone scan assessment was used.(1)
- TTD: Reasons for treatment discontinuation are provided in the CSR (Section 9.5.1), and included: patient decision, adverse event, severe non-compliance with the study protocol, bone marrow findings consistent with MDS/AML, objective radiological progression by BICR, unequivocal clinical progression, initiation of restricted anti-cancer therapy, development of study-specific discontinuation criteria, and other reasons.(1) Patients who had not discontinued treatment at the time of analysis were censored based on the last recorded date on which the patient was known to be alive.

Table 1. Total number of censored events in the overall *BRCA*m and *BRCA*m prior taxane populations in the PROfound study

Endpoint*	EMA label population: *BRCA*m	Company base-case: *BRCA*m prior taxane

	Olaparib 300 mg bid (n = 102)	Investigators' choice of NHA (n = 58)	Olaparib 300 mg bid (n = 72)	Investigators' choice of NHA (n = 35)
OS**	[redacted]	[redacted]	[redacted]	[redacted]
rPFS*	[redacted]	[redacted]	[redacted]	[redacted]
TTD*	[redacted]	[redacted]	[redacted]	[redacted]

* DCO1: data cut-off at primary rPFS analysis, 4th June 2019; ** DCO2: data cut-off at final OS analysis, 20th March 2020

A3. Please outline whether the RDI data of the TE response has been updated to relate to the BRCAm patient group for this analysis, and the BRCAm prior taxane patient group for this analysis. If it has not been updated to relate to the patient groups of interest please provide this.

Please also provide the definition of the "median percentage intended dose through to progression", a clear outline of the arithmetic underlying its calculation and the N observations, mean, median, min and max for this for (1) the BRCAm patient group for this analysis, and (2) the BRCAm prior taxane patient group

Company response:

RDI analyses for the overall *BRCA*m population or the prior taxane subgroup of *BRCA*m are not available; however, there is no clinical reason why RDI in these populations would be any different to the observed data from Cohort A+B, which is used in the economic model, given that biomarker status is not anticipated to impact upon tolerability. Furthermore, as RDI is not a key driver of the cost-effectiveness analysis, these data are unlikely to have a significant impact on the results presented in the company's analysis.

The percentage intended dose (PDI) is not an input in the economic model. This value was provided in response to Issue 9, Question 20 of the TE response document, and is expressed as the percentage of the actual dose delivered relative to the intended dose, up to the point of BICR-assessed radiographic disease progression. The arithmetic follows the same logic as for RDI (previously outlined in response to ERG clarification question A20), but up to the point of progression. If the value for PDI were applied instead of RDI, this would slightly improve the ICER in favour of olaparib treatment.

A4. As per the discussion during the TE teleconference, please provide a scatterplot of patient RDI vs patient time to TTD event separately for the PROfound olaparib arm for:

1) the BRCAm patients and
(2) the BRCAm prior taxane patients.

It would be appreciated if this could be supplied
1) restricted to patients with discontinuation events, also stating N observations, mean, median, min and max RDI and TTD and
2) all patients treating censoring as a discontinuation event when calculating both the patient RDI and the patient TTD, also stating N observations, mean, median, min and max RDI and TTD.

If possible please provide this data for the DCO2, but if this is only possible for the DCO1 please outline why.

Note:

Subsequent ERG request (received 12th November 2020): "*If it is not possible to provide a scatter plot please divide patients into ordered TTD quintiles: 2 sets ordered min TTD to max TTD (1) dividing the TTD range into 5 equal time segments and (2) dividing the quintiles so as to have equal patient numbers in each quintile. For each quintile (2*5) please present (1) TTD min, max, median, mean (2) RDI min, max, median and mean (3) N observations. Please also provide the correlation coefficient and its standard error".*

Company response:

It is AstraZeneca company policy to not release patient-level data; therefore, we are unable to provide the scatterplot in the requested format. Further to the response to question A3 above, we reiterate that RDI is not a key driver of the cost-effectiveness

analysis, and as such the requested data would not have a substantial impact on the results presented in the company's analysis.

We also note the ERG's follow-on request. However, the small numbers of patients in each quintile make it impossible to produce an informative result. To provide a better understanding of the potential relationship between RDI and treatment duration, we have conducted the requested correlation analysis on the *BRCA*m overall population at DCO1. This analysis shows that there is no conclusive relationship between the two, evidenced by a Kendall's tau correlation coefficient of [redacted] (SE: [redacted]), with 95% CIs crossing zero [redacted]).

Section B: Clarification on cost-effectiveness data

B1. Please provide an account of all changes made to the electronic model for the modelling of the BRCAm patients compared to the original model (including any corrections), and for each change provide full cell referencing, the reason for the change and the rationale for the arithmetic of the change. Please provide an account of all differences between the BRCAm model and the BRCAm prior taxane model with full cell referencing and the rationale for each difference.

***Company* response:**

As described in Section A.3.4 of the TE response document, we made several revisions to account for the ERG's comments on the original company model for the Cohort A+B prior taxane group of patients (ERG Report, Section 4.3.1.2 and Section 5.4.1). For transparency, we have shaded the cells in the electronic model where any changes were made (**inputs** and calculations). In general, where a revision was made, the company attempted to apply the same method (or one that is as similar as possible) as in the ERG rebuild model, to help ease the ERG's review. It was not always possible to implement the revisions in exactly the same way due to the nature of some changes made in the ERG rebuild model, but the result would be the same (for example, the ERG rebuild model includes separate patient flow worksheets for olaparib and cabazitaxel while the company model uses one worksheet for both interventions).

We have detailed each revision in Table 2 and the cell references in the company model, as per the ERG's request. Please note that the revisions described below apply to both the overall *BRCA*m and the *BRCA*m prior-taxane models.

Table 2. Revisions made in the updated company model (applies to both models, for the *BRCA*m and *BRCA*m prior taxane population).

	Issue	ERG's correction in the rebuild model / preferred model assumption (Cohort A+B prior taxane)		Change(s) applied in the revised company model (*BRCA*m and *BRCA*m prior taxane)	Cell reference(s) in the revised company model (*BRCA*m and *BRCA*m prior taxane)
	Revisions affecting company base case and scenario results				
1	Formula revised Correction for G-CSF costs	ERG01a	Corrected to restrict G-CSF costs to the ten 3 week cabazitaxel treatment cycles.	Revision applied using the same formula and named range obtained from the ERG rebuild model.	Reference cell: 'Model Calcs'!$BH$15 'Model Calcs'!$BI$15 Relevant named range: ERG.Flag.CABA.OnTx
2	Formula revised Correction for the cost of 1st administration of cabazitaxel	ERG01c	Corrected to apply the cabazitaxel administration cost, taking into account the lower 1st administration NHS reference cost. This is applied by applying a single cost reduction in the administration costs by £108.	Revision applied by the same method of reducing the administration cost of cabazitaxel by £108. Note: As noted in the ERG report company factual accuracy check form (dated 24th August 2020), the cost reduction in the ERG rebuild model is applied to the disease management cost category. We have instead applied the cost reduction to the administration cost	Reference cell: 'Model Calcs'!$BH$14 Input value: 'Drug Cost'!$F$45

	Issue	ERG's correction in the rebuild model / preferred model assumption (Cohort A+B prior taxane)		Change(s) applied in the revised company model (*BRCA*m and *BRCA*m prior taxane)	Cell reference(s) in the revised company model (*BRCA*m and *BRCA*m prior taxane)
	Revisions affecting company base case and scenario results				
				category. This has no impact on the total costs.	
3	Formula revised Correction for monitoring costs with olaparib	ERG01d	The olaparib monitoring costs were corrected to implement the higher monitoring cost during the first 3 months of treatment.	Revision applied by editing the flag in model cycle 3, from 0 to 1.	Reference cell: 'Model Calcs'!$G$14 Relevant named range: ERG.OnTx.Monit.index
4	Values revised RDI input value	ERG03b	Applies the median RDI value for olaparib.	Input values revised to reflect the ERG's comments. Median RDI values are implemented for olaparib ([redacted]), and cabazitaxel (0.961).	Input values: 'Drug Cost'!$L$30 'Drug Cost'!$L$32
5	Value revised Unit cost of G-CSF	ERG06	Applies the £79.90 drug tariff price for G-CSF.	Input values revised to £79.90 reflect the ERG's comments.	Input value: 'Other Drug Cost'!$I$41
6	Values revised The proportion of patients receiving PPS treatments, and the balance of these, in the cabazitaxel arm	ERG09	The ERG thinks that the appropriate numerator for calculating the proportion of cabazitaxel patients who receive drug treatments subsequent to progression is 50, hence 41.6%, rather than the company estimate of 57.5%.	Input values revised to reflect the ERG's comments. Note: The ERG's suggested calculation of 50/126 results in 41.7% of patients receiving subsequent treatment, which has been implemented in the updated	Input values: 'Sub Tx'!$G$29 'Sub Tx'!$T$31:$W$36

	Issue	ERG's correction in the rebuild model / preferred model assumption (Cohort A+B prior taxane)		Change(s) applied in the revised company model (*BRCA*m and *BRCA*m prior taxane)	Cell reference(s) in the revised company model (*BRCA*m and *BRCA*m prior taxane)
	Revisions affecting company base case and scenario results				
			The ERG also updated the balance between PPS treatments for cabazitaxel using the supplementary information to De Wit.	company model. The balance of PPS treatments for the cabazitaxel arm was directly obtained from the ERG rebuild model.	
7	Value revised The proportion of patients receiving PPS treatments, in the olaparib arm	N/A	N/A	Input value revised to [redacted]% to reflect Issue 10 of the NICE Technical Report, as described in Issue 10, Question 22 of the TE response document. The same proportion of patients received subsequent treatment upon disease progression in the interim analysis of the CARD study, as in the interim analysis of the PROfound study. There is no clinical reason to believe that the proportion of patients receiving active subsequent treatments would be different between olaparib and cabazitaxel.	Input values: 'Sub Tx'!$F$29

	Issue	ERG's correction in the rebuild model / preferred model assumption (Cohort A+B prior taxane)		Change(s) applied in the revised company model (*BRCA*m and *BRCA*m prior taxane)	Cell reference(s) in the revised company model (*BRCA*m and *BRCA*m prior taxane)
	Revisions affecting company base case and scenario results				
	Revisions affecting company scenario results only				
7	Formula revised Constraining TTD by rPFS	N/A (ERG report, Section 4.3.1.2)	Affecting the company scenario analyses: the assumption that TTD always takes the minimum value of the rPFS or the TTD curve is removed.	Revision applied in the patient flow worksheet to reflect the ERG's comments.	Reference cell: 'Model Calcs'!$R$11:$R$251
8	Value revised Cost of testing for gene mutations	N/A (ERG report, Section 4.3.1.2)	Affecting the company scenario analyses: the cost of testing should take into account the prevalence of the relevant genes in the population being tested.	Tested scenario where the input value for the cost of testing accounts for the prevalence of *BRCA*m gene mutations implemented at a rate of 9.7%.	Input cell (for scenario): 'Drug Cost'!$E$7
9	Formula revised Incorporate ERG's BSC scenario	N/A (ERG report, Section 4.3.1.2)	Assume that BSC costs apply subsequent to PPS treatment. A means-based approach accrues an additional cost of BSC based on the difference between mean OS and the weighted average of mean duration of subsequent treatment.	Tested scenario using the ERG's means-based approach to best supportive care, using the same formulae and named ranges as obtained from the ERG rebuild model.	Reference cell: 'Model Calcs'!$BH$20:$BI$20 Input values: 'Sub Tx'!$F$58:$G$58
	No impact on results – miscellaneous/layout revisions undertaken by the company				

	Issue	ERG's correction in the rebuild model / preferred model assumption (Cohort A+B prior taxane)		Change(s) applied in the revised company model (*BRCA*m and *BRCA*m prior taxane)	Cell reference(s) in the revised company model (*BRCA*m and *BRCA*m prior taxane)
	Revisions affecting company base case and scenario results				
10	Formula revised to match ERG rebuild model	N/A	N/A	The formula cells were updated to match those in the ERG rebuild model.	'Model Calcs'!$BD$15:$BE$15 'Model Calcs'!$BD$18:$BE$18
11	Include toggle to change NHA assumption in PPS balance of treatments	N/A	N/A	Implemented to allow the user to quickly change between scenarios for subsequent treatment assumptions.	'Sub Tx'!$H$27 'Sub Tx'!$F$31:$G$36
12	Include toggle to change % G-CSF assumption	N/A	N/A	Implemented to allow the user to quickly change between scenarios for G-CSF assumptions.	'Disease Mgmt Cost'!$I$127 'Disease Mgmt Cost'!$I$128 'Disease Mgmt Cost'!$K$126:$L$127
13	Update KM graphs	N/A	N/A	Data used for graphs that include KM estimates from PROfound.	'Kaplan-Meier' worksheet

As described above and in Appendix A.4 of the TE response document, safety and efficacy input values were updated in the company model for the *BRCA*m and *BRCA*m prior taxane populations. Per the ERG's request, we have provided a list of any differences between the *BRCA*m model and the *BRCA*m prior taxane model, in Table 3 below (all else remains equivalent).

Table 3. Overview of clinical inputs used in the revised *BRCA*m and *BRCA*m prior taxane models.

	PROfound population-specific inputs, data source		DCO, PROfound*	Cell reference(s)
	***BRCA*m prior taxane model**	***BRCA*m overall model**	**Both models**	**Both models**
OS (olaparib)	*BRCA*m Prior taxane	*BRCA*m overall	DCO2	'OS Details Active'!$E$8:$N$32
ITC, OS (cabazitaxel)	*BRCA*m overall	*BRCA*m overall	DCO2 (PROfound)	'OS Details Active'!$E$39:$G$39
rPFS (olaparib)	*BRCA*m Prior taxane	*BRCA*m overall	DCO1	'PFS Details Active'!$E$8:$N$32
ITC, rPFS (cabazitaxel)	*BRCA*m overall	*BRCA*m overall	DCO1 (PROfound)	'PFS Details Active'!$E$38:$G$38
TTD (scenario)	*BRCA*m Prior taxane	*BRCA*m overall	DCO1	'TTD Details Active'!$E$8:$N$32
% Receiving subsequent treatment	*BRCA*m Prior taxane	*BRCA*m Prior taxane	DCO1	'Sub Tx'!$F$29:$G$30
Distribution of subsequent treatments	*BRCA*m Prior taxane	*BRCA*m overall	DCO2 (PROfound)	'Sub Tx'!$F$31:$G$36 'Sub Tx'!$T$31:$W$36
AEs (safety)	*BRCA*m Prior taxane	*BRCA*m overall	DCO2 (PROfound)	'AE Rates'!$D$7:$D$15
SREs	*BRCA*m Prior taxane	*BRCA*m overall	DCO1	'Event Mgmt Cost'!$G$38
Age at baseline	*BRCA*m Prior taxane	*BRCA*m overall	DCO1	'Characteristics RAW'!$E$11:$F$11
Weight at baseline	*BRCA*m Prior taxane	*BRCA*m overall	DCO1	'Characteristics RAW'!$H$18:$J$18

B2. To avoid any possible ambiguity please clarify for the revised company base case which of the ERG preferred model changes of the ERG report Table 63: ERG's preferred model assumptions have been:

1) Accepted in full,

2) Rejected in full, and

3) Partially accepted.

For those that have been partially accepted and applied in the company base case please provide an account of how the company revision differs from the ERG revision.

Company response:

We have expanded on Table 63 of the ERG report to provide a comparative overview of which of the ERG's preferred assumptions have been accepted in the revised company base-case for the *BRCA*m prior taxane and *BRCA*m overall subgroups (Table 4, below). Where possible, a cross-reference to the discussions in the TE response document is also provided.

As described above (in response to Question B1), where a revision was applied in the updated model, we attempted to utilise the same method (or one that is as similar as possible) as in the ERG rebuild model. Details of these changes are provided in Table 2 above. Further to this, although some of the ERG's preferred assumptions were rejected in the revised company base-case, we still conducted scenario analyses where deemed appropriate, to understand the impact of changing the assumptions.

Table 4. Comparison of ERG preferred model assumptions (based on initial submission, Cohort A+B prior taxane) and revised company base case (for the *BRCA*m and *BRCA*m prior taxane subgroups)

ERG Preferred assumption*	ERG Report Section*	Revised company base case	Cross-reference to further information / rationale
ERG01a: G-CSF costs correction	4.3.1.2	Accepted	For further details, please refer to: • Table 2 above.

ERG Preferred assumption*	ERG Report Section*	Revised company base case	Cross-reference to further information / rationale
			• Technical Engagement response document, Appendix A.3
ERG01b: BSC costs correction	4.3.1.2	Rejected	For further details, please refer to: • Technical Engagement response document, Issue 10, Question 25.
ERG01c: cabazitaxel admin costs	4.3.1.2	Accepted	For further details, please refer to: • Table 2 above. • Described in the Technical Engagement response document, Appendix A.3
ERG01d: olaparib monitoring costs	4.3.1.2	Accepted	For further details, please refer to: • Table 2 above. • Technical Engagement response document, Appendix A.3
ERG02: ERG parameterised curves	3.6.1	Rejected	The company's analyses are based directly on time-to-event analysis of the patient-level data from the PROfound trial.
ERG03a: TTD costing	4.3.4.8	Rejected	For further details, please refer to: • Technical Engagement response document, Issue 8 and Issue 9.
ERG03b: median RDI	4.3.4.8	Accepted	For further details, please refer to: • Table 2 above. • Technical Engagement response document, Issue 9.
ERG04: G-CSF use	4.3.4.11	Rejected	For further details, please refer to: • Technical Engagement response document, Issue 11.
ERG05: Exclude NHAs from PPS treatments	4.3.4.13	Rejected	For further details, please refer to: • Technical Engagement response document, Issue 10, Question 23.
ERG06: G-CSF tariff price	4.3.2.2	Accepted	For further details, please refer to: • Table 2 above.

ERG Preferred assumption*	ERG Report Section*	Revised company base case	Cross-reference to further information / rationale
			• Technical Engagement response document, Appendix A.3
ERG07: ADT/LHRH costs throughout	4.3.4.15	Rejected	N/A
ERG08: Equal On Tx bone and CT scans	4.3.4.16	Rejected	N/A
ERG09: Cabazitaxel PPS treatments	4.3.2.1	Accepted	For further details, please refer to: • Table 2 above. • Technical Engagement response document, Appendix A.3.
ERG10: ERG ITC HRs	3.6.1.7	Rejected	The ITC conducted by the company reflects the best available estimates of the comparative efficacy of olaparib (based on the PROfound data) and cabazitaxel (based on the CARD data in the De Wit et al, 2019 publication). Per the comments from the ERG, which are summarised in the NICE Technical Report (Issue 6, pg 7), the updated ITC analyses are based on the Cox PH model HRs for olaparib from the *BRCA*m subgroup of PROfound, and the HRs for cabazitaxel from the CARD study, as published in De Wit et al, 2019.
ERG11: Test costs	4.3.4.18	Rejected	For further details, please refer to: • Technical Engagement response document, Issue 12.

* As in Table 63 of the ERG Report.

B3. The two submitted electronic models contain the same hazard ratios in cells F17 and F33 of the Efficacy worksheet. Does this imply that the relative efficacy of olaparib compared to cabazitaxel is assumed to be the same for BRCAm patients as for the subgroup of BRCAm patients with prior taxane experience? If so, please provide the rationale for this assumption together with all supporting data, including any evidence of equivalent effect for cabazitaxel in the two groups. If not, please outline where the OS and PFS HRs can be found within the electronic models separately for

1) BRCAm patients and

2) the subgroup of BRCAm patients with prior taxane experience.

Company response:

In the absence of head-to-head RCT data comparing olaparib with cabazitaxel, an anchored indirect treatment comparison (ITC) was conducted in accordance with NICE DSU TSD 18 guidance, using the same methods as described in the company submission (Document B, Section B.2.9.1).

As explained in the TE response document (Appendix A.2 and Appendix A.3), it was deemed appropriate to utilise the data for the overall *BRCA*m population of PROfound in the ITC because:

- Olaparib has similar efficacy (in terms of rPFS and OS) in the overall *BRCA*m population (i.e., regardless of prior treatment with a taxane) as in the prior taxane subgroup of *BRCA*m. Please see Appendix A.1 of the TE response document for further details.

- Using the overall *BRCA*m population also facilitates the best use of the available data from the PROfound study, retaining greater patient numbers and as much statistical power as possible for the ITC (for further details, please see the TE response document, Appendix A.2).

- Finally, there is no clinical evidence to suggest that the relative efficacy of cabazitaxel would differ by prior treatment with a taxane, supporting the use of

the same hazard ratio (i.e. overall *BRCA*m) for the *BRCA*m prior taxane subgroup analyses.

B4. Please expand Table 17 and Table 18 of the TE response to provide the data for the olaparib BRCAm population.

Company response:

The requested data are presented in Table 5 and Table 6, below (based on Table 17 and Table 18 of the TE response document, respectively).

Table 5. Summary of overall number of patients receiving subsequent treatment (olaparib, PROfound *BRCA*m and *BRCA*m prior taxane; cabazitaxel, CARD)*, **

		Olaparib		Cabazitaxel
		PROfound, *BRCA*m prior taxane	PROfound, *BRCA*m	CARD(2)
Interim analysis	Number of patients receiving subsequent treatment (n)	[redacted]	[redacted]	50
	Number of progression events (N_p)	[redacted]	[redacted]	120
	% (n/N_p)	[redacted]	[redacted]	41.7%

n = number of patients receiving subsequent treatment reported in study; N_p = number of progression events reported in study, N = total number of patients in treatment arm.
* In PROfound, the numbers of progression events are only available at DCO1 (rPFS data were not collected beyond this) – therefore, it is not possible to update this figure based on DCO2 analyses. This input value is not a driver of the cost-effectiveness results.
No updated data from the CARD study were identified since the initial submission, and remain same as provided in Document B.
** Data table based on Table 17 of the Technical Engagement response document.

Table 6. Distribution of subsequent treatment applied in the economic analysis (olaparib, DCO2 PROfound *BRCA*m and *BRCA*m prior taxane; cabazitaxel, CARD)[*, *]**

	Olaparib						Cabazitaxel**		
	PROfound, *BRCA*m prior taxane (N=72)			PROfound, *BRCA*m (N=102)			CARD, All patients (N=129)(2)		
Subsequent therapy	**n**	**%**	**%, adjusted for NHA**	**n**	**%**	**%, adjusted for NHA**	**n**	**%**	**%, adjusted for NHA**
Cabazitaxel	[redacted]						3	7.3%	27.3%
Docetaxel							2	4.9%	18.2%
Abiraterone							15	36.6%	0.0%
Enzalutamide							15	36.6%	0.0%
Radium-223							6	14.6%	54.5%

NHA, new hormonal agent

* Excluding investigational and treatments that have not been approved for use in mCRPC patients, percentages adjusted to sum to 100%.

** Proportions suggested by the ERG (ERG Report, Section 4.3.2.1 with specific values sourced from electronic version of the ERG rebuild model).

** Data table based on Table 18 of the Technical Engagement response document.

B5. Given the net 1.081 QALY gain at a net cost of £21,808 for the BRCAm population and the net 1.028 QALY gain at a net cost of £19,126 for the BRCAm prior taxane subgroup, what are the implied net QALY gain, net cost and ICER for the no prior taxane BRCAm subgroup?

Company response:

The generalisability of the 'prior taxane' vs 'no prior taxane' subgroups is supported by the clinical efficacy data in the prior taxane subgroup of *BRCA*m vs the overall *BRCA*m population of patients (which also included those who did not receive prior treatment with a taxane) (see TE response Appendix A.1.4. for details). Both the overall *BRCA*m population and *BRCA*m prior taxane subgroup show very similar OS benefit for olaparib vs investigators' choice of NHA, with consistent and stable OS HRs of [redacted] and [redacted], respectively.

As described in the Technical Engagement response document (Issue 1, Question 4 and Issue 2, Question 6), olaparib is expected to be a highly-cost effective use of NHS resources compared with the current standard-of-care, cabazitaxel, in both the prior taxane subgroup of *BRCA*m as well as the overall *BRCA*m population, with an incremental cost-effectiveness ratio (ICER) of £18,596 /QALY and £20,176 /QALY, respectively. These results are as expected, given the similar and consistent clinical effectiveness of olaparib in the prior taxane subgroup of *BRCA*m and the overall *BRCA*m population (which also includes patients who did not receive prior treatment with a taxane).

Following the same logic as the ERG in their report (ERG Report, Section 4.3.4.19, page 148), this comparison provides an indication of the cost-effectiveness of olaparib in the *BRCA*m 'no prior taxane' group of patients, i.e. because the results in the overall *BRCA*m population (with includes patients both with and without prior taxane treatment) are similar to the *BRCA*m prior taxane subgroup, it is (by implication) reasonable to consider that the ICER in the *BRCA*m 'no prior taxane' subgroup would also fall within this range. Specifically, this implies that a ICER of around £20,176 /QALY is plausible in the no prior taxane *BRCA*m group of patients.

It should, however, be noted that an analysis of cost-effectiveness in the 'no prior taxane' group of *BRCA*m specifically has not been conducted at this stage, due to: 1)

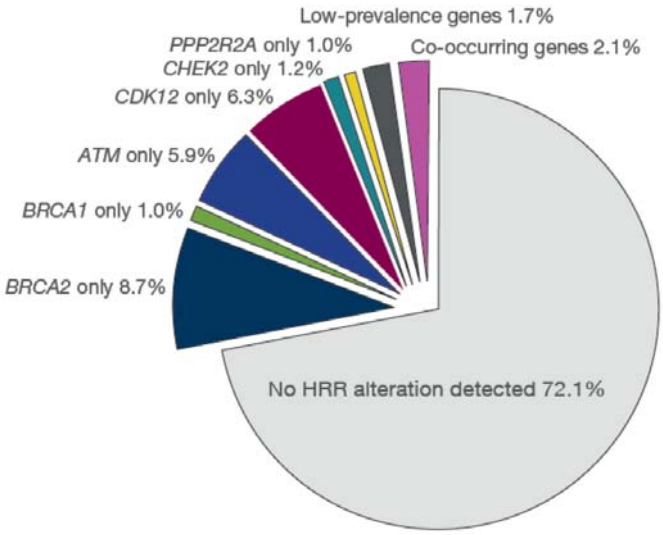
the small numbers of patients, and 2) provision of cost-effectiveness results in the overall BRCAm population, which includes these patients.

B6. Please outline the full data and arithmetic underlying the calculation of the 9.7% prevalence of BRCAm, with full referencing of the source data.

Company response:

Prevalence data were derived from the PROfound study and represents the proportion of patients who had a biomarker status reported (N=2,792) who had a *BRCA1/2* mutation (n=269, or 9.7%; see Figure 3).

Figure 3. Overview of HRR gene profile in patients screened for the PROfound study (n=2,792)



Source: (3)

B7. Please outline how to generate each of the scenario analyses of Table 23 of the TE response, together with any additional model copies that may be required.

Company response:

All of the scenarios analysed by the company can be generated with the electronic model that was provided during the TE process, that is, no additional model copies are required. We have expanded Table 23 of the Technical Engagement response

document to include instructions for how to replicate each of the scenarios (Table 7 below). It is also possible to reset all sheets to a selected scenario in the model, from the ‘Reset’ sheet, which will automatically enact the relevant change necessary, as described in Table 7. We would be happy to provide further assistance if there are any difficulties with generating the results.

Table 7. Scenario analyses as reported in Table 23 of the TE response document; expanded to include instructions for generating the results.

Scenario		Brief rationale	ICER (£ per QALY)	Company instructions for generating scenario analyses	
Base case			**£18,596**	N/A – the submitted model is already set to the base case	
Efficacy parameters				**Worksheet(s)**	**Instructions**
1	OS (Exponential) distribution for olaparib	Explore the impact on the results when the distribution is changed for OS (exponential, statistically best-fitting distribution; lognormal, alternative plausible distribution).	£22,787	• Efficacy	• Change the OS distribution using the dropdown list.
2	OS (Lognormal) distribution for olaparib		£17,646		• Change the OS distribution using the dropdown list.
3	rPFS (Generalised gamma) distribution for olaparib	Explore the impact on the results when the distribution is changed for rPFS.	£18,755		• Change the rPFS distribution using the dropdown list.
Treatment duration					
4	Treatment duration: Cost of cabazitaxel aligned with administration of cabazitaxel in the CARD study	Test the impact of different treatment duration assumptions. In these scenarios, cabazitaxel treatment costs are aligned with the CARD study, which did not impose a maximum treatment duration.	£11,623	• Drug Cost	• Delete the maximum number of treatment cycles for cabazitaxel (set cell to blank).
5	Treatment duration: Olaparib TTD curve (Gompertz) and cabazitaxel rPFS		£13,949	• Drug Cost, and; • Efficacy	• Delete the maximum number of treatment cycles for cabazitaxel (set cell to blank), and; • Change the discontinuation rule for olaparib to 'Treatment Discontinuation Curves', using the dropdown list.
G-CSF use					

Scenario		Brief rationale	ICER (£ per QALY)	Company instructions for generating scenario analyses	
6	G-CSF with cabazitaxel: 79.5% based on UK EAP for cabazitaxel	Understand the impact of changing G-CSF assumptions	£19,667	• Disease Mgmt Cost	• Change the G-CSF source to 'Cabazitaxel UK EAP', using the dropdown list.
Health-related quality of life, AEs and SRE parameters					
7	Exclude modality-specific disutility due to IV administration (mean PF HSUV on treatment is the same for olaparib and cabazitaxel)	Test the impact of different assumptions; assumes that the IV administration of cabazitaxel does not impact quality of life, therefore, the PF utility while on treatment is the same across treatments.	£18,735	• Utility	• Change the mode of administration disutility option to 'Exclude'
8	Mean HSUV based on PROfound: Exclude AE & SRE disutility	Test alternative assumptions related to AE and SRE disutilities.	£18,633		• Change the adverse event disutility and SSRE disutility options to 'Exclude'
9	Mean HSUVs based on UK EAP in TA391 (PF: 0.737, PD: 0.627)	Understand the impact of different assumptions for the source/value of mean HSUVs; based on UK EAP for cabazitaxel (no modality-specific adjustment applied to cabazitaxel; modality-specific increment applied to olaparib instead).	£18,340		• Change the utility data source option to 'Previous NICE Submissions'
10	Exclude SRE costs and SRE disutility	Understand the impact of removing SREs from the economic analysis (both costs and disutilities).	£18,692	• Utility, and; • Context	• Change the adverse event disutility and SSRE disutility options to 'Exclude', and; • Change the skeletal-related event management cost category to 'No'
Other cost and resource use assumptions					

Scenario		Brief rationale	ICER (£ per QALY)	Company instructions for generating scenario analyses	
11	Assume 100% RDI for olaparib and cabazitaxel	Test impact of alternative assumption for RDI (dose reduction not allowed).	£18,378	• Drug Cost	• Set the value of RDI for olaparib and cabazitaxel to 100%
12	Assume there is wastage (no vial sharing)	Understand the impact of alternative assumption due to uncertainty around the application of vial sharing in NHS practice (TA391).	£12,829		• Change the vial sharing option for cabazitaxel to 'No' using the dropdown list.
13	Alternative subsequent treatment assumptions: exclude enza / abi and re-weight distribution	Explore alternative assumptions for the distribution of subsequent treatments (affects costs only; no adjustment for efficacy).	£18,350	• Sub Tx	• Change the include NHA option to 'FALSE' using the dropdown list.
14	Sequential BSC: Means-based 4-HS approach	Test impact of using the ERG's suggested means-based approach for including the sequential costs associated with best supportive care after subsequent treatment.	£22,465	• Model Calcs	• Change the best supportive care option to 'ERG' using the dropdown list.
15	Include one-off cost of genetic testing (olaparib)	Included for completeness only; scenario where genetic testing is not provided under the National Genomic Test Directory.	£22,606	• Drug Cost	• Change the cost of gene mutation testing to 'Yes' using the dropdown list, and; • Set the value of the test cost to £[redacted] * (1/0.097) = £[redacted]

Abbreviations: AE, adverse event; BSC, best supportive care; G-CSF, granulocyte-colony stimulation factor; HS, health-state; HSUV, health-state utility value; IV, intravenous; OS, overall survival; N/A, not applicable; rPFS, radiographic progression-free survival; RDI, relative dose intensity; SRE, skeletal related event; TTD, time to treatment discontinuation.

References

1. AstraZeneca. Clinical Study Report PROfound, Version 1, 23 October 2019. 2019.
2. de Wit R, de Bono J, Sternberg CN, Fizazi K, Tombal B, Wülfing C, et al. Cabazitaxel versus Abiraterone or Enzalutamide in Metastatic Prostate Cancer. New England Journal of Medicine. 2019;381(26):2506-18.
3. de Bono JS, Fizazi K, Saad F, Shore N, Sandhu SK, Mehra N, et al. Central, prospective detection of homologous recombination repair gene mutations (HRRm) in tumour tissue from 4000 men with metastatic castration-resistant prostate cancer (mCRPC) screened for the PROfound study. Annals of Oncology. 2019;30(Supplement_5).

Evidence Review Group's report template

Title: Olaparib for previously treated hormone-relapsed metastatic prostate cancer [ID1640]

Technical engagement response

Produced by
Warwick Evidence

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None.

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Rider on responsibility for report
The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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Contributions of authors
Stinton, C. worked on the clinical effectiveness section of this appraisal; Patel, M. worked on the NMA and analysis of this appraisal; Connock, M. worked on the analysis of this appraisal; Fraser, H. supported the clinical effectiveness section; Harrison, C. supported the clinical effectiveness section; Court, R. supported the referencing and information specialist activities, Brown, A. supported the referencing and information specialist activities, Cummins, E. lead the economics of this appraisal, Johnston, R. supported the economics of this appraisal, Al-Khudairy, L lead this appraisal and provided clinical effectiveness support and oversight.

Please note that: Sections highlighted in yellow and underlined are 'academic in confidence' (AIC). Sections highlighted in aqua and underlined are 'commercial in confidence' (CIC). Figures that are CIC have been bordered with blue. Depersonalised Data (DPD) is highlighted in pink.

Table of Contents

1 EXECUTIVE SUMMARY

Issue	**Where discussed in ERG critique of company TE response document (section / page number)**	**Notes (if applicable, e.g. issue resolved)**
Clinical issues in original technical report		
The population in the company's submission is narrower than the scope and clinical trial evidence	Section 2.3, page 12	The revised submission restricts the population to the subgroup with BRCA1/2 mutations (BRCAm) following the issue of a positive CHMP opinion for the PROfound indication of Olaparib: "Lynparza is indicated as monotherapy for the treatment of adult patients with metastatic castration-resistant prostate cancer and BRCA1/2-mutations (germline and/or somatic) who have progressed following prior therapy that included a new hormonal agent"

The company presents analyses from the PROfound trial which suggest differing clinical effectiveness within subgroups	Section 3.1.2, page 19, Table 3	
The company has not provided analyses compared with all comparators in the scope		Similar to original submission. The CS limited treatment comparisons to Cabazitaxel due to a lack of RCT evidence on Radium-223 dichloride and docetaxel following NHA treatment. The ERG agrees there is a lack of trial evidence in the correct population on Radium 223-dichloride treatment.
Generalisability of the trial to the UK population and NHS clinical practice	Section 3.1.1, page 18	
Heterogeneity of the PROfound and CARD trials used to indirectly compare olaparib with cabazitaxel	Section 3.2, page 24	
The indirect treatment comparison (ITC) of olaparib vs cabazitaxel is uncertain	Section 25, page 25	
Cost: issues in original technical report		
Choice of distribution for overall survival extrapolation	Sections **Error! Reference source not found.**, **Error! Reference source not found.**, **Error! Reference source not found.** pages **Error!**	

	Bookmark not defined., **Error! Bookmark not defined.**, **Error! Bookmark not defined.**	
Discrepancies between progression-free survival and time to treatment discontinuation curves	Section **Error! Reference source not found.**, page **Error! Bookmark not defined.**	
Olaparib acquisition costs and relative dose intensity calculation	Company accepts median. Issue resolved.	
Post progression treatments costs calculation	Sections **Error! Reference source not found.**, 4.9, **Error! Reference source not found.** pages **Error! Bookmark not defined.**, 55, **Error! Bookmark not defined.**	
Granulocyte colony-stimulating factor (G-CSF) costs estimate	Section **Error! Reference source not found.** page **Error! Bookmark not defined.**	
HRR genes test costs	Issue unresolved. No change to issue other than prevalence of group being tested and no ERG comment.	
End-of-life criteria	No change to issue and no ERG comment.	
Clinical: new issues identified by ERG based on company's new evidence at TE		
RPSFTM adjustment: recensoring	Section 4.7 page 53	
Cost: new issues identified by ERG based on company's new evidence at TE		

None		

1.1 Critique of the decision problem in the company's submission

The revised submission population is narrower than the scope and was restricted to the subgroup with BRCA1/2 mutations (BRCAm) who have been previously treated with both a taxane as well as hormonal therapy.

1.2 Summary of the key issues in the clinical effectiveness evidence

- The trial result is thus no longer a randomised because of the cross-over from New Hormonal Therapy (NHA) to Olaparib upon progression and include a small subgroup. This presents problems for the randomisation, and thus, due the cross-over, the results from the trial cannot strictly be considered to have come from a fully randomised trial
- The very small and highly selected (BRCA1/2) numbers of patients recruited from the UK compromise generalisability of the findings from the PROfound study to UK settings.
- Indirect comparison of PROfound (Olaparib) and CARD (cabazitaxel) was provided. The ERG considers that these indirect comparisons are inadequate for providing meaningful, and in the case of Overall Survival (OS), statistically significant information on the comparison of olaparib and cabazitaxel.
- The trajectory of the Kaplan-Meier (KM) plot of overall survival for the prior taxane BRCAm population follows a changing trajectory at several time points, possibly partly due to the small subgroup of PROfound patients included.
- For overall survival of olaparib group the company have selected poor a fitting loglogistic model mainly informed by their clinical experts.

1.3 Summary of the key issues in the cost effectiveness evidence

The cost effectiveness modelling has a high degree of structural uncertainty. Rather than trying to arrive at a single set of structural assumptions and a single cost effectiveness estimate, it may be more appropriate for the Appraisal Committee (AC) to identify the main structural uncertainties that concern it, identify plausible ranges for each of these inputs and review the range of cost effectiveness estimates that result. This does not imply that the AC need be equipoise between the plausible ranges of each structural uncertainty.

The revised license causes the company to model the BRCAm prior taxane patients as its new target group, meaning that the OS, Progression Free Survival (PFS) and Time to Treatment Discontinuation (TTD) curves have to be revised, as well as the OS and PFS HRs for the

comparison with cabazitaxel. The OS elements have also been updated for the new data cut. Any cost of genetic testing is qualified by the lower [redacted] BRCAm prevalence.

Other than this, the company largely reiterates the arguments of its original submission and retains its approach. Thus the critique of the original ERG report still largely applies, and the ERG remains largely of its original opinion.

Some issues have come more to the fore during technical engagement and the updated data cut. These, with the company preference (A) followed by the ERG preference (B), are:

- When modelling BRCAm prior taxane patients should (A) the PROfound BRCAm all patients' HRs or (B) the BRCAm prior taxane patients' HRs be used in the ITC?
- Some patients receive a post progression course of chemo therapy, others do not. Once all active treatment has ceased for both groups would their ongoing monthly costs (A) remain very different or (B) tend to converge?
- Should (A) only the Cox model Rank preserving structural failure time models (RPSFTM) adjusted NHA OS data and resulting HRs be presented or (B) as per the original company submission, should the Log rank, Weibull and Cox models be presented?
- When RPSFTM adjusting the NHA arm OS data for cross over to olaparib, should (A) the with recensoring values be used and the without recensoring values be entirely rejected, or (B) the with recensoring values and the without recensoring values provide the plausible bounds for these inputs?
- Should (A) the deterministic cost effectiveness estimate or (B) the probabilistic cost effectiveness estimate be the basis for decision making?

The main ERG critique of the company Technical Engagement (TE) response is presented in Section 4. Given the brevity of this document, the cost effectiveness estimates are not summarised here and are only presented in Sections 5 and 6 in the cost effectiveness section. These estimates include the olaparib PAS but not the cabazitaxel cPAS, or the cPASs of the post progression treatments. A confidential appendix presents the cPAS inclusive cost effectiveness estimates.

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

Please refer to the original ERG ID1640 report dates 31/07/2020

2.2 Background

Please refer to the original ERG ID1640 report dates 31/07/2020

2.3 Critique of company's definition of decision problem

The company decision problem (Table 1) is similar to the original submission in terms of intervention, comparator and outcomes. The revised submission restricts the population to the subgroup with BRCA1/2 mutations (BRCAm) following the issue of a positive CHMP opinion for the PROfound indication of Olaparib:

"Lynparza is indicated as monotherapy for the treatment of adult patients with metastatic castration-resistant prostate cancer and BRCA1/2-mutations (germline and/or somatic) who have progressed following prior therapy that included a new hormonal agent".

Table 1: Summary of decision problem

	Final scope issued by NICE	Decision problem addressed in the original company submission	Decision problem addressed in the revised technical engagement report	Rationale if different from the final NICE scope	ERG comment
Population	People with hormone-relapsed, metastatic prostate cancer with homologous recombination repair gene alterations previously treated with hormonal therapy (eg. abiraterone or enzalutamide)	People with hormone-relapsed, metastatic prostate cancer with homologous recombination repair gene alterations previously treated with a taxane (docetaxel) and hormonal therapy (eg. abiraterone or enzalutamide)	People with hormone-relapsed, metastatic prostate cancer with BRCA1/2 mutations (BRCAm) previously treated with a taxane (docetaxel) and hormonal therapy (eg. abiraterone or enzalutamide)	• The vast majority (~75%) of patients have already received treatment with a taxane (docetaxel) prior to NHA in current clinical practice • Indirect treatment comparisons to docetaxel (for the minority of patients who have not receive a taxane prior to NHA) or radium-223 dichloride (for the small subset of patients who have bone metastases, no known visceral metastases, and for whom treatment with a taxane is unsuitable) was not	The population in the revised CS decision problem is restricted to people who have been treated with both a taxane as well as hormonal therapy with a BRCA1/2 mutation. The opinion that ~75% of patients have already received treatment with a taxane prior to NHA treatment was deemed acceptable by our clinical advisors.

				possible due to limitations in published RCT evidence base	
Intervention	Olaparib	Olaparib	Similar to original submission.	N/A	Similar to original submission. The intervention in the CS matches the NICE final scope.
Comparator(s)	- Docetaxel - Cabazitaxel - Radium-223 dichloride for people with bone metastases	Cabazitaxel	Similar to original submission.	As mentioned above, indirect treatment comparisons to docetaxel and radium-223 dichloride were not feasible due to a lack of published RCT evidence on these treatments in the post-NHA setting. PFS2 is an intermediate endpoint between PFS and OS and reflects real-life treatment decisions and patient experience. Its use is recommended by the EMA to capture potential negative impacts on next-line therapy and to demonstrate that any	Similar to original submission. The CS limited treatment comparisons to Cabazitaxel due to a lack of RCT evidence on Radium-223 dichloride and docetaxel following NHA treatment. NICE scope states that the different positions of the comparators in the pathway should be considered. The ERG clinical advisors agree with the company clinical experts that in the majority of cases docetaxel is used earlier in the pathway. The ERG considers the removal of Docetaxel as a comparator, and it's inclusion

				potential tolerability concerns are outweighed by treatment benefit.	within the population to be in line with current practice The ERG agrees there is a lack of trial evidence in the correct population on Radium 223-dichloride treatment.
Outcomes	**- Progression free survival** **- time to pain progression** **- skeletal related events** **- overall survival** **- adverse effects of treatment** - health-related quality of life	- radiographic progression free survival - time to pain progression - skeletal related events - overall survival - second progression-free survival (PFS2) - adverse effects of treatment - health-related quality of life	- radiographic progression free survival - skeletal related events - overall survival	PFS2 is an intermediate endpoint between PFS and OS and reflects real-life treatment decisions and patient experience. Its use is recommended by the EMA to capture potential negative impacts on next-line therapy and to demonstrate that any potential tolerability concerns are outweighed by treatment benefit.[1]	The outcomes in the CS match those in the NICE scope.
Economic analysis					

Subgroups	HRR alterations, including Breast Cancer gene (BRCA) and ataxia-telangiectasia mutated (ATM) gene status	One or more of the 15 HRR genes.	BRCA1/2 mutations	In line with the anticipated marketing authorisation for olaparib, the company submission considers the treatment of patients with qualifying mutations in one or more of 15 HRR genes (i.e. the overall population of PROfound). rPFS data in the subgroup of patients who have mutations in BRCA1, BRCA2, and ATM genes (the primary endpoint in PROfound) are described in Section A.7 and B.2.6.2.1; further analyses are available in the CSR (Section 11)	The subgroup is restricted to BRCA 1/2 mutations.
Special considerations including issues related	Guidance will only be issued in accordance with the marketing authorisation. Where the	Although this submission focuses on the subset of patients who have received treatment with a		N/A	The CS changed the population from the NICE scope to include docetaxel as a prior treatment and BRCA 1/2 mutation.

to equity or equality	wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.	prior taxane and NHA, due to the demonstrated efficacy of olaparib in the overall study population of PROfound (and anticipated marketing authorisation), regardless of prior taxane use, we request that consideration is given to the small group of patients who have not received a taxane prior to NHA under equality provisions

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

Please refer to the original ERG ID1640 report dates 31/07/2020.

The evidence is from two open-label RCTs: one comparing olaparib to abiraterone or enzalutamide (PROfound), and one comparing cabazitaxel to abiraterone or enzalutamide (CARD). As only a single RCT examining olaparib was included, direct treatment comparisons were not applicable. An indirect comparison of PROfound and CARD was provided in the CS. It should be noted that the current population of PROfound (BRAC1/2) are a sub-group of the PROfound study population, thus the randomisation and sample size calculations presented in the original paper are no longer applicable.

3.1 Critique of trials of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)

The company provided analyses based on the licensed indication of olaparib: "as monotherapy for the treatment of adult patients with metastatic castration-resistant prostate cancer and BRCA1/2-mutations (germline and/or somatic) who have progressed following prior therapy that included a new hormonal agent".

3.1.1 Population

Participants were enrolled from 206 study centres in 20 countries (Asia, Europe, North and South America). Five sites were in the UK, from which only four participants were recruited (Doc B, B.2.3.3, page 33). The CS does not state if any of the four participants were included in their subgroup analyses. The ERG note that because of the very small and highly selected numbers of patients recruited in main study, the UK the generalisability of the findings from the PROfound study to the UK setting may be compromised. Consistent with our previous report, the ERG reiterates that physician's choice of NHA limited only to abiraterone or enzalutamide is an inappropriate comparator. It is acknowledge by the company (TE response, page 6) that "the comparator of investigators' choice of NHA in PROfound does not reflect the current standard-of-care in England."

In the CS, all study participants had disease progression following treatment with abiraterone, enzalutamide, or both abiraterone and enzalutamide (see Table 2). The CS does not state whether participants in the control arm were being re-treated with a drug on which they had

already failed. [redacted] of participants from the BRCA mutation cohort control arm and [redacted]% of participants from the BRCA mutation plus prior taxane cohort control arm participants had previously failed on both abiraterone and enzalutamide. These are the minimum proportions of participants in the control group who received a drug for which there can be no expectation of a benefit. The maximum number of participants who were being re-treated cannot be established from the data presented in the CS, and the company did not provide this information. Data on treatment of mCRPC with abiraterone followed by enzalutamide (and vice versa) has suggested that the majority of participants do not benefit from subsequent NHA treatment.[2-5]

Table 2. Breakdown of prior NHA use

Previous NHA use	Cohort A		BRCA mutation		BRCA mutation plus prior taxane	
	Olaparib	Physician's choice of NHA	Olaparib	Physician's choice of NHA	Olaparib	Physican's choice of NHA
Abiraterone	67 (41.4%)	40 (48.2%)	[redacted]	[redacted]	[redacted]	[redacted]
Enzaluatamide	61 (37.7%)	29 (34.9%)	[redacted]	[redacted]	[redacted]	[redacted]
Abiraterone & enzalutamide	32 (19.8%)	14 (16.9%)	[redacted]	[redacted]	[redacted]	[redacted]

3.1.2 Summary of trial results

A summary of the key outcomes from PROfound were presented in Table 2 of the company's technical engagement response and shown in Table 3. For both outcomes, rPFS and OS, results were given for

1) Cohort A: the primary study population of PROfound;

2) the EMA label population: BRACm patients, and

3) the company base-case: BRCAm prior taxane subgroup.

The primary endpoint of PROfound was rPFS measured at DCO1 (04 June 2019). In the BRCAm population, which was aligned to the anticipated EMA marketing authorisation of olaparib, olaparib was associated with a [redacted] ([redacted] 95% CI: [redacted], [redacted]) of disease progression compared to patients in the NHA arm.

In the BRCAm prior taxane subgroup, olaparib was associated with an [redacted] ([redacted], 95% CI: [redacted], [redacted]) of disease progression compared to patients in the NHA arm of PROfound.

The key secondary endpoint of PROfound was OS measured at DCO2 (20 March 2020). In the BRCAm population, which was aligned to the anticipated EMA marketing authorisation of olaparib, olaparib was associated with a [redacted] (95% CI: [redacted], [redacted]) of death compared to patients in the NHA arm of PROfound.

In the BRCAm prior taxane subgroup, olaparib was associated with a [redacted] (95% CI: [redacted], [redacted]) of disease progression compared to patients in the NHA arm of PROfound, however this HR was not statistically significant at the 5% level. OS is an important outcome for people who have prostate cancer.

3.1.3 Treatment switching analysis of OS

Section A.1.4.2.1 of the company's TE responses details the adjustment for treatment switching for the 1) BRCAm and 2) BRCAm prior taxane arms of PROfound, where the company concluded that the RPSFTM approach was the most suitable for these analyses, the method used in the original CS. The ERG agrees with the justification for using the RPSFTMs as listed in the company's TE responses page 37.

The company used the ERG's recommendation of using a Cox PH model to derive the switching-adjusted HR, to keep it consistent with the model used in the CARD study and fit a Weibull to test the sensitivity of these results. The results were found to be consistent. The company explored models with and without re-censoring and concluded that models without re-censoring resulted in implausible long-term survival estimates.

Results of the treatment-switching analyses are shown in Table 4.

Across both the 1) BRCAm and 2) BRCAm prior taxane arms of PROfound, [redacted] of patients switched from NHA to olaparib. After adjusting for switching, treatment with olaparib resulted in a [redacted] reduction in the risk of death in the overall BRCAm population of PROfound, and a [redacted] reduction in the risk of death in the BRCAm prior taxane subgroup. The HR for BRCAm overall with Rank preserving structural failure time (RPSFT) with re-censoring was brought forward into the ITC analyses, presented in section 3.3.2.

Table 3: Summary of key endpoints from PROfound taken from Table 2 of company's TE responses

	Primary study population: Cohort A		EMA label population: BRCAm		Company base-case: BRCAm prior taxane	
	Olaparib 300 mg bid (n = 162)	**Investigators' choice of NHA (N = 83)**	**Olaparib 300 mg bid (n = 102)**	**Investigators' choice of NHA (n = 58)**	**Olaparib 300 mg bid (n = 72)**	**Investigators' choice of NHA (n = 35)**
Primary endpoint: BICR-assessed rPFS (DCO1)[a]						
Events, n (%)	106 (65.4)	68 (81.9)	[redacted]	[redacted]	[redacted]	[redacted]
Median rPFS, months (95% CI)	7.39 (6.24–9.33)	3.55 (1.91–3.71)	[redacted]	[redacted]	[redacted]	[redacted]
HR (95% CI)	**0.34 (0.25, 0.47); p < 0.0001**		[redacted]		[redacted]	
Key secondary endpoint: final OS (DCO2)[b]						
Events, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Median OS, months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HR (95% CI)	**0.69 (0.50, 0.97); p = 0.0175**		[redacted]		[redacted]	

Table 4: Results of the OS treatment-switching adjustments at DCO2 for the BRCAm arms of PROfound

	N	Arms, N (%)	Switched	Unadjusted	RPSFTM	
					With re-censoring	Without re-censoring
BRCAm overall	160	Olaparib: 102 (63.75%) NHA: 58 (36.25%)	[redacted]	[redacted]	[redacted]	[redacted]
BRCAm prior taxane	107	Olaparib: 72 (67.29%) NHA: 35 (32.71%)	[redacted]	[redacted]	[redacted]	[redacted]

3.2 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

In the original ERG report we identified that the assumption of transitivity in the indirect comparison is threatened because the study populations in CARD and PROFound are likely to differ in terms of genetic mutations. The company's response to this was "There is no evidence to suggest that BRCAm status is a treatment effect modifier for response to cabazitaxel or NHA treatment." (TE response, page 7 - 8) This assertion is incorrect. For example, several recent studies have suggested shorter PFS for participants receiving NHA who have BRCA1 or BRCA2 mutations compared to those without these mutations: 3.3 months (95% CI 2.7, 3.9) vs. 6.2 months (95% CI 5.1, 7.3),[6] and 4.3 months (95% CI 1.0, 7.6) vs. 9.2 months (95% CI 8.1, 10.3).[7, 8] This suggests that BRCAm status is a potential treatment effect modifier for NHA treatment. The ERG maintains that given the unknown HRRm carrier status in CARD, the reliability of comparisons between CARD and PROfound subgroups is uncertain.

3.2.1 Olaparib comparator studies

This was the same as in the original company submission. rPFS results were taken from PROfound at DCO1 (04 June 2019) and OS results were taken from PROfound at DCO2 (20 March 2020). The population of interest was the overall BRCAm population as this utilised greater patient numbers compared to using the BRCAm prior taxane subgroup.

3.2.2 Comparator studies

This was the same as in the original company submission. The published HRs for OS and PFS were taken from the CARD study to be included in the company's ITC analyses, as opposed to estimating the HR by digitising the published KM curves as to what was carried out the original CS. The ERG agrees with this approach since the HR used in the original submission was inconsistent.

3.3 Critique of the indirect comparison and/or multiple treatment comparison

Table 9 of the company's TE responses presented the inputs and results of the company's ITC analyses for both rPFS and OS.

3.3.1 Radiographic progression-free survival

Using data from the CARD trial to obtain a HR of 0.54 for the comparison cabazitaxel versus NHA (new hormonal agent, abiraterone or enzalutamide) and a HR of [redacted] for the comparison of olaparib versus NHA, the CS estimated a Butcher ITC (unadjusted for

variables) HR of [redacted] for the comparison olaparib versus cabazitaxel (or [redacted] for cabazitaxel versus olaparib as applied in the economic model).

3.3.2 Overall Survival

Using data from the CARD trial to obtain a HR of 0.64 for the comparison cabazitaxel versus NHA (new hormonal agent, abiraterone or enzalutamide) and a HR of [redacted] for the treatment switching-adjusted comparison of olaparib versus NHA in the BRCAm population, the CS estimated a Butcher ITC (unadjusted for variables) HR of [redacted] for the comparison olaparib versus cabazitaxel (or [redacted] for cabazitaxel versus olaparib as applied in the economic model).

3.3.3 Summary of the company ITC

The ERG replicated the ITC analyses and reproduced the same figures as the company.

As was the case in the original CS, the ITC has many potential difficulties which are detailed in sections 3.4.1-3 in the ERG orginal report.

As mentioned earlier, the assumption of transitivity may be threatened as the populations in PROfound and CARD are likely to differ with respect to the proportions of patients who have HRRms. In PROfound, tumours had mutations in the HRR genes, but this was not reported in CARD.

There were population differences between PROfound and CARD. The PROfound study took place in Asia, Europe, North and South America, whereas CARD was conducted exclusively in Europe.

In CARD, pre-randomisation treatment with cabazitaxel was unlikely, whereas about 30% of the target PROfound population had received cabazitaxel prior to randomisation.

A further potential limitation is that the PROfound NHA was modelled using correction for the pronounced cross over [redacted] to olaparib upon progression. The trial result is thus strictly no longer a randomised result. It is uncertain that the true OS with NHAs in the absence of crossover would conform to a proportional hazards assumption.

In summary, similar issues that arose when critiquing the ITC for the Cohort A+B prior taxane in the original submission also applied to the revised submission on the BRCAm population. Therefore, the ERG considers that these indirect comparisons are inadequate for providing meaningful, and in the case of OS, statistically significant information on the comparison of olaparib and cabazitaxel.

3.3.4 Adverse Events

The company presented safety data from the safety analysis set (SAS) of PROfound from DCO2 for the following populations: the updated full SAS from DCO2, the BRCAm population and the BRCAm prior taxane subgroup. These results were presented in Table 7 and Table 8 of the company's TE responses.

Across both the BRCAm and BRCAm prior taxane subgroups, the olaparib arm had [redacted] median total treatment and actual treatment durations. Furthermore, the olaparib arms had significantly [redacted] of patients experiencing either dose interruptions, dose reductions or dose modifications.

AEs were experienced by 96.1% of patients in the olaparib arm and 88.5% in the NHA arm of the updated SAS at DCO2. There was a big difference in AEs related to study treatment (82.0% in olaparib; 48.5% in NHA), AE leading to discontinuation (19.9% in olaparib; 8.5% in NHA), AE relating to dose reduction (23.4% in olaparib; 5.4% in NHA) and AE relating to interruptions (46.5% in olaparib; 5.4% in NHA). AEs leading to death were similar across groups. [redacted]. There were no [redacted] of the BRCAm subgroups, and the proportion of patients who experienced any AE leading to death was higher in the NHA arm of the BRCAm prior taxane subgroup compared to the olaparib arm ([redacted]% vs [redacted]%).

3.4 Additional work on clinical effectiveness undertaken by the ERG

3.4.1 Overall Survival target population (prior taxane BRCAm population)

As in the previous submission the company has selected a "prior taxane" subgroup as target population. This choice was justified as placing olaparib in the correct patient pathway within UK clinical practice. The restriction of olaparib to only *BRCAm* positive patients has reduced the number of *prior taxane BRCAm* patients from PROFOUND trial to N=72. In the company submission Figures 6 and 14 depict the OS KM for the *prior taxane BRCAm* population. The trajectory of the plot exhibits multiple phases and does not follow an internally consistent path, possibly due to the small subgroup of patients. As previously the company selected a loglogistic model to describe OS and justified this mainly on the basis of expert opinion; a critique of the expert opinion panel predictions is available in the ERG report. The ERG reconstructed the OS KM for the prior taxane olaparib arm. The resulting KM is shown in Figure 1 and information criteria scores for parametric models are summarised in Table 5.

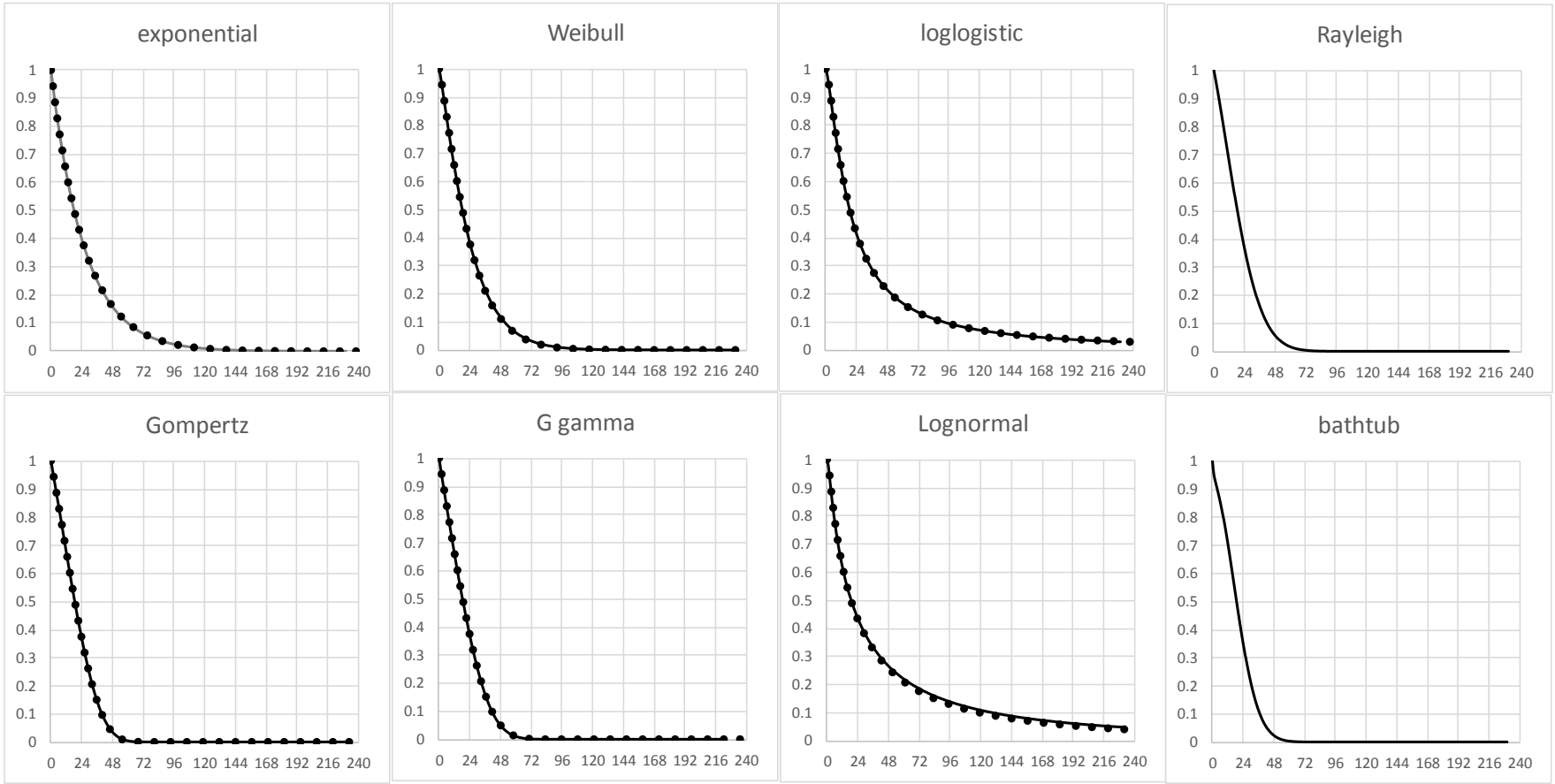
Figure 1. Reconstructed KM plot of overall survival of the prior taxane BRCAm population

Table 5. Information criteria scores for parametric models: prior taxane BRCAm population OS

rank	model	AIC	BIC	AIC+BIC
1	bathtub	181.6	188.4	**370.0**
2	exponential	183.9	186.2	**370.2**
3	Rayleigh	183.1	187.6	**370.7**
4	Gompertz	183.3	187.9	**371.2**
5	Weibull	184.9	189.4	**374.3**
6	ggamma	185.3	192.1	**377.5**
7	loglogistic	188.6	193.1	**381.7**
8	lognormal	195.1	199.6	**394.7**

ERG reconstructed parametric curves and those in the CS economic model were essentially identical (Figure 2). Of 8 models the loglogistic model ranks 7th according to information criteria score.

Figure 2. Comparison of ERG parametric models (solid line) with CS models (dots), Prior taxane BRCAm population



The company states that: *"survival estimates with the loglogistic distribution best reflected the observed OS KM data for the prior taxane subgroup BRCAm"*. Visual inspection does not seem to support this statement. Visual fits are shown in ***[redacted]3. The loglogistic model departs notably from the KM plot from about 17 months onwards (before median survival is reached). Both Rayleigh and bathtub models appear to have better visual fit than either loglogistic or exponential models. Rayleigh and bathtub models were obtained using the *stgenreg* package in Stata.[9] Rayleigh models are sometimes used to model survival of cancer patients[10] and have the expression

$$S(t) = \exp\left[-(\lambda_0 t + \lambda_1 t^2)\right]$$

[redacted]3

loglogistic

bathtub

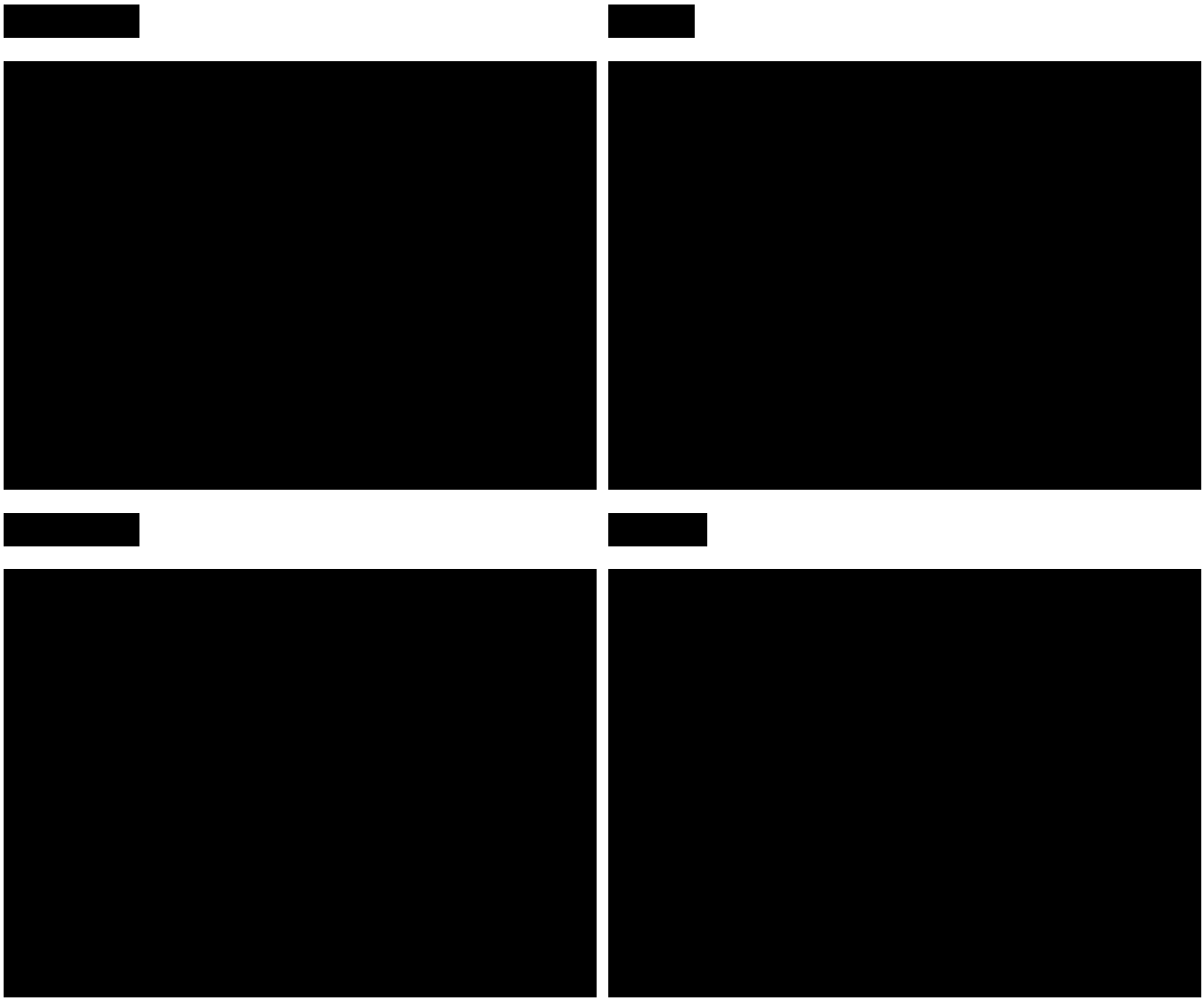
Rayleigh

exponential

The company justify a preference for the logistic model by selecting 12 months, and 33 month time points on the KM plot (observed survival) and finding that of the six company submission

models these values are most closely approached by the loglogistic model (stating: "*Of the six distributions the loglogistic most closely reflected these figures, (62.4%, and 27.8%) ; see Table 14*.") . The choice of these two time points must be considered both arbitrary and post hoc. Furthermore, the emphasis on the last observation at 33 months where uncertainty is at its greatest and where only one patient remains at risk is perhaps unusual. A more generally utilised method of looking at correspondence between model and observed survival involves comparison across the whole data span by comparing log observed cumulative hazard (i.e. KM estimated CH) with modelled log cumulative hazard. The relevant models for this comparison are shown in *** 4.

4



No model provides a good fit across the whole time span, however Rayleigh and bathtub models better conform to the observed log cumulative hazard. An additional comparison test (Hosmer and Lemeshow) plots log observed (KM) cumulative hazard versus log modelled cumulative

hazard, so that the forty-five degree equivalence line indicates a perfect fit between observed and modelled log cumulative hazards. The results from this plot are shown in Figure 5 in which the solid line reprents the line of perfect fit, the circles represent the modelled cumulative hazard data values and the dashed lines represent linear regression of the modelled cumulative hazard data. Over the observed time scale (33 months) the modelled log cumulative hazard for loglogistic and exponential models deviate from the observed log cumulative hazard to a greater extent than is the case for the bathtub and Rayleigh models and this is reflected in the liear regression lines coinciding less with the equivalence line.

Figure 5. Hosmer Lemeshow plots for observed versus modelled log cumulative hazard

The above analyses (visual fit, log cumulative hazard vs. log time, and observed vs. modelled log cumulative hazard) all tend to favour Rayleigh and bathtub models over exponential and loglogistic. The bathtub model predicts time dependent increase in increasing hazard beyond the observed data and may be over pessimistic in extrapolation. On this basis the Rayleigh model appears to represent the most reasonable choice for base case. Additionally, it would be reasonable to explore bathtub and other parametric models in sensitivity analysis. The company submission's choice of loglogistic model appears to be mainly supported by clinical opinion elicited by the company for the original submission. These do not appear to have been modified in the light of the substantially different populations specified.

The ERG explored eight models that are summaried in Figure 6. It should be noted that four models (Rayleigh, bathtub, Gompertz, ggamma) are very similar and predict very few survivors beyond 5 years. In contrast lognormal and loglogistic models predict more than 16% survivors at 5 years with further extrapolation yielding appreciable survivors after 20 years and appear optimistic by comparison.

Figure 6. Parametric models of OS for the prior taxane BRCAm population

To arive at an OS model for the comparator arm (cabazitaxel treated prior taxane population) the CS apply a HR (derived from the CS ITC analysis) to their loglogistic model for the olaparib arm, implemented as : $S_{cab} = (S_{olap})^{\wedge HR}$. In the base case economic model, the ITC output HR for the *all BRCAm population* (olaparib vs. cabazitaxel) is applied to the loglogistic model of olaparib survival for the *prior taxane BRCAm* population, which seems inappropriate. Furthermore, loglogistic models do not conform to a proportional hazards assumption (i.e. the ratio of hazards varies with time) and the application to an HR invariant through time is inappropriate. The ERG tested the validity of this method and concluded that it was innappropriate, see Appendix 1.

3.4.2Overall survival; *all BRCAm* population olaparib arm

The revised company submission has presented OS results for the whole BRCAm olaparib arm population (N=102). Since most of these patients (72%) are identical to those in the prior taxane BRCAm population it may be expected OS results are similar. The ERG reconstructed the OS KM for the olaparib arm (new company Figure 7). The reconstructed KM plot is shown in *** [redacted] and information criteria scores for parametric models are summarised in Table 6.

[redacted]

Table 6. Information criteria scores for parametric models: all BRCAm population overall survival

Rank	model	AIC	BIC	AIC+BIC
1	Rayleigh	238.3	243.6	481.9
2	Gompertz	238.8	244.1	482.9
3	bathtub	238.1	245.9	484.0
4	exponential	241.6	244.3	485.9
5	Weibull	240.3	245.6	485.9
6	ggamma	241.1	249.0	490.1
7	loglogistic	243.5	248.8	492.3
8	lognormal	251.9	257.2	509.1

The ERG reconstructed parametric curves and those in the company submission economic model were essentially identical as demonstrated in Figure 9. Models for the *prior taxane BRCAm* and *all BRCAm* populations are almost the same with slight superiority for the *all BRCAm* group (Figure 9).

Figure 9. Comparison of ERG parametric models (solid line) and CS models (dots); all BRCAm population N=102)

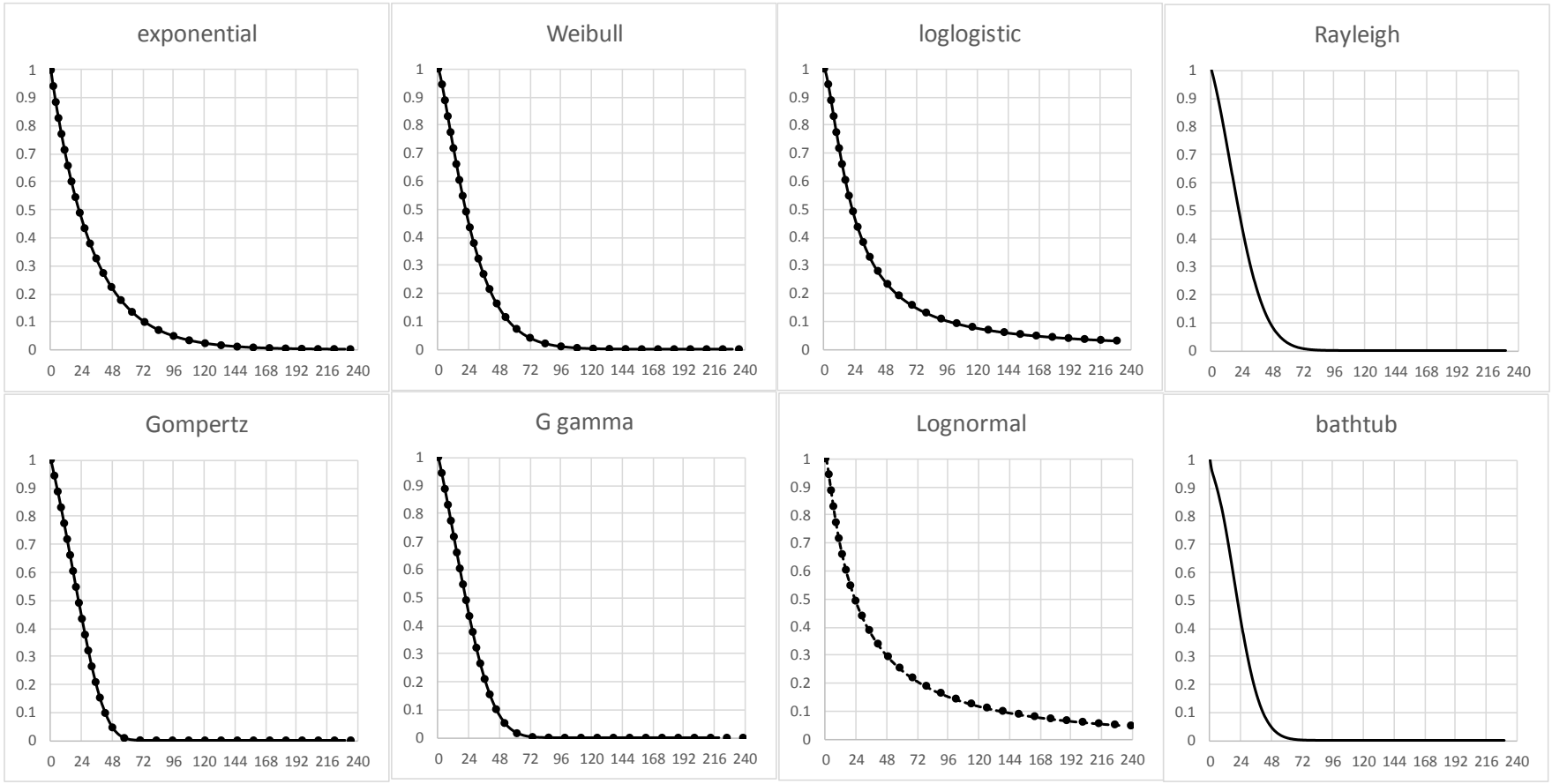
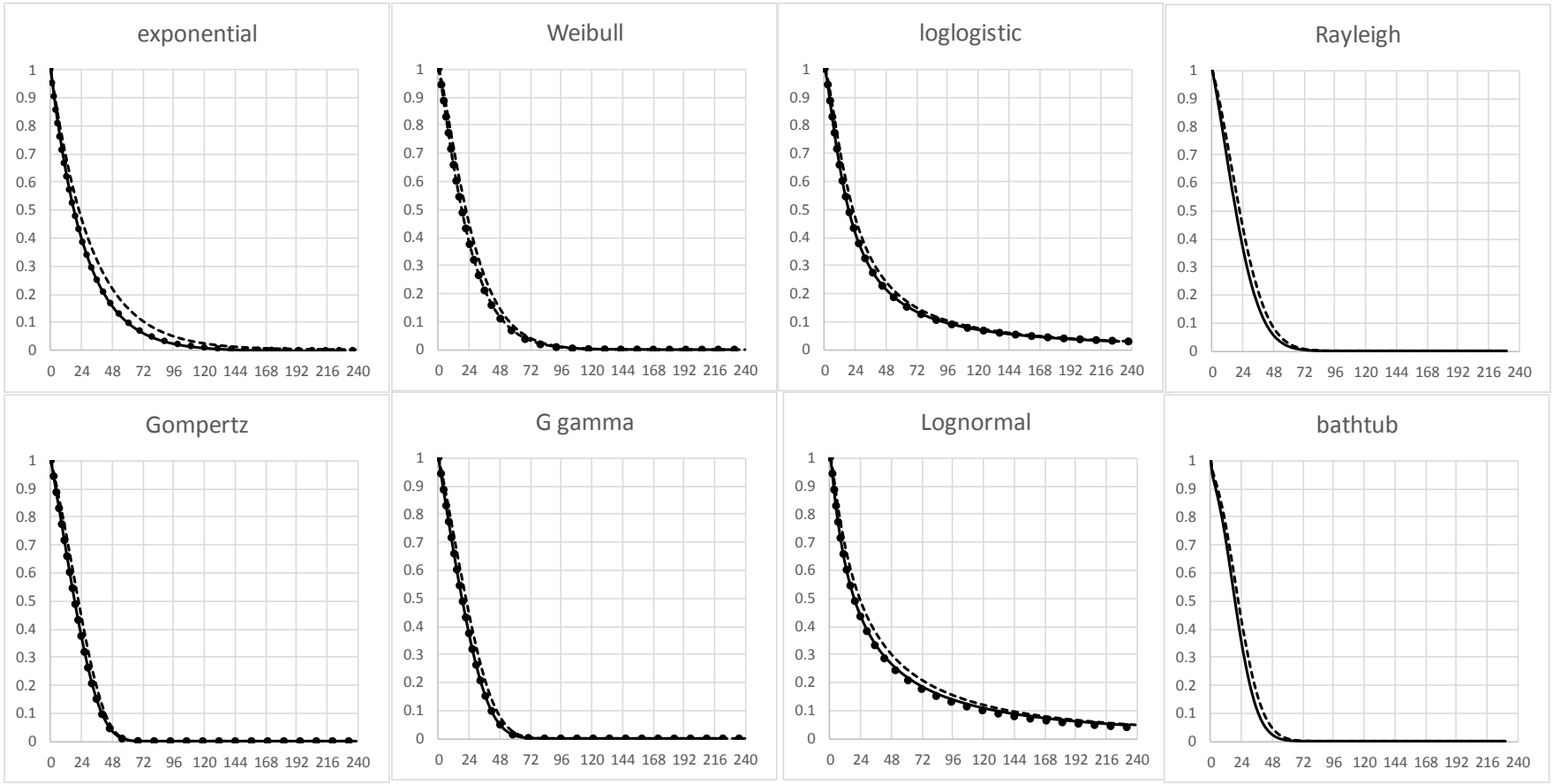


Figure 10. ERG (solid line) and CS (dots) models for prior taxane BRCAm population vs. ERG models all BRCAm population (dashed lines)



Of 8 parametric models for overall survival of all BRCAm in receipt of olaparib the loglogistic model ranked 7th according to information criteria score. ***[redacted]11 compares the visual fit generated by the loglogistic model with that for three alternatives models with lowest information criteria scores. In line with the information criteria scores for different models the Rayleigh, Gompertz and bathtub models present better visual fit to the observed overall survival than does the loglogistic model.

[redacted]11[redacted]

[redacted]

The company's choice of loglogistic model appears to be only supported by clinical opinions elicited by the company for the original submission. These do not appear to have been modified in the light of the substantially different populations specified by EMA.

In Figure 12 we summarise the eight models of overall survival in the BRCAm olaparib arm explored by the ERG. It should be noted that four models (Rayleigh, bathtub, Gompertz,

ggamma) are very similar and predict very few survivors beyond 5 years. In contrast lognormal, loglogistic and exponential models predict more than 16% survivors at 5 years with further extrapolation of the the loglositic model yielding appreciable survivors after 20 years and well beyond, and appears somewhat optimistic by comparison.

Figure 12. Parametric models of OS for the BRCAm population

3.4.3 Radiological progression free survival olaparib arm *prior taxane BRCAm* population

The company submission economic model only contained KM data for the olaparib arm; this was aggregated to monthly intervals 0 to 16 months; the observed data extends beyond 16 months to 16.85 months with events after 16 months. Therefore, the ERG reconstructed IPD for each arm using Figure 4 information in the company submission. The ERG reconstructed KM plot for the olparib arm is shown in Figure 12 together with ERG and company's Gompertz models.

Figure 13. Reconstructed KM of rPFS and Gompertz models for the prior taxane BRCAm population

Information criteria scores for the ERG parametric models of reconstructed rPFS KM for the olaparib arm are summarised in table below (

Table 7).

Table 7. Information criteria scores for parametric models: prior taxane BRCAm population rPFS

rank	Model	AIC	BIC	total
1	Gompertz	173.8	178.4	352.2

2	Rayleigh	174.6	179.2	353.8
3	bathtub	175.1	181.9	356.9
4	Weibull	176.9	181.4	358.3
5	ggamma	175.8	182.6	358.5
6	exponential	179.4	181.7	361.0
7	loglogistic	184.0	188.5	372.5
8	lognormal	188.1	192.6	380.7

As in the company submission (CS Table 12) the Gompertz model generated the lowest composite information criteria score. The low information criteria score models (Gompertz, Rayleigh, bathtub) were very similar and the ERG and company's Gompertz models were almost identical. It would be reasonable to use the company's Gompertz model (Figure 14).

Figure 14. ERG parametric models of rPFS prior taxane BRCAm population

3.4.4 Radiological progression free survival olaparib arm all BRCAm population

The company's economic model only contained KM data for the olaparib arm; this was aggregated to monthly intervals. Therefore, the ERG reconstructed IPD using KM information

in the CS Figure 4. The ERG reconstructed KM plot for the olparib arm of the *all BRCAm* population is shown in Figure 15 together with ERG and the company's Gompertz models which closely coincided.

Figure 15. Reconstructed KM and Gompertz models for rPFS of the all BRCAm population

Information criteria scores for ERG models are summarised in

Table 8.

Table 8. Information criteria scores for parametric models: all BRCAm population rPFS

Rank	Model	AIC	BIC	AIC+BIC
1	Gompertz	231.7	236.9	468.6
2	Rayleigh	231.7	236.9	468.6
3	Weibull	233.0	238.3	471.3
4	bathtub	233.2	241.1	474.2
5	ggamma	233.5	241.4	475.0
6	exponential	239.1	241.7	480.8
7	loglogistic	238.5	243.8	482.3

8	lognormal	243.9	249.2	493.1

For the all *BRCAm* population (as was the case for the prior taxane *BRCAm* population) the Gompertz model was best performing model according to IC but was equalled by the Rayleigh model. The ERG were unable to find information criteria scores of company's models of the all *BRCAm* population in the submission. The ERG Gompertz and Rayleigh models were very similar and it seems reasonable to employ the company's Gompertz model. The ERG models are summarised in Figure 16.

Figure 16. ERG parametric models of rPFS all taxane BRCAm population

3.4.5 TTD olaparib *prior taxane BRCAm* population

The company's economic model contained KM data for the olaparib arm that was aggregated to monthly intervals 0 to 16 months, however the observed data extends beyond 16 months to about 24 months. Therefore, the ERG digitised the KM plot from Figure 17 in the submission. The ERG reconstructed KM plot for the olparib arm of the *prior taxane BRCAm* population and are shown in Figure 16 together with ERG and CS Gompertz models which closely coincided.

Reconstructed KM plot: *prior taxane BRCAm* TTD	CS and ERG Gompertz parametric models
[redacted]	[redacted]

[redacted]

Information criteria scores for parametric models are summarised in Table 9. Gompertz and bathtub composite scores were almost equal.

Table 9. Table 5 Information criteria scores for models of TTD; prior taxane BRCAm population

Rank	Model	AIC	BIC	AIC+BIC
1	bathtub	355.5	364.4	719.9
2	Gompertz	357.1	363.0	720.1
3	Rayleigh	359.6	365.6	725.2
4	ggamma	358.8	367.7	726.5
5	Weibull	367.6	373.5	741.1
6	exponential	376.3	379.2	755.5

7	loglogistic	389.2	395.1	784.3
8	lognormal	403.7	409.7	813.4

The company selected their Gompertz model which ranked first according to company's information criteria scores (CS Table 15).

For those models common to both CS and ERG, the ranking of models according to information criteria scores. ERG models are summarised in ***[redacted]21; the ERG bathtub model was very similar to the Gompertz model and it seems reasonable to employ the CS Gompertz model.

[redacted]21

[redacted]

3.4.6 TTD olaparib all *BRCAm* population

The company did not include a KM plot for TTD olaparib for the *all BRCAm* population. This was supplied in response to an ERG clarification request together with underlying KM data aggregated to monthly intervals. The ERG used the former to develop parametric models; the resulting information criteria scores are shown in Table 10. Bathtub and Gompertz models generated the lowest composite information criteria scores. The reconstructed KM plot and the company's and ERG Gompertz models are shown in ***[redacted]22. The ERG and company's Gompertz models were almost identical (***[redacted]22).

Table 10. Information criteria scores for models of TTD; all BRCAm population

rank	Model	AIC	BIC	AIC+BIC
1	bathtub	249.2	257.1	506.3
2	Gompertz	251.1	256.4	507.5
3	Rayleigh	251.8	257.0	508.8
4	ggamma	254.0	261.9	515.8
5	Weibull	257.7	262.9	520.6
6	exponential	266.5	269.1	535.6
7	loglogistic	270.6	275.9	546.5
8	lognormal	287.1	292.3	579.4

[redacted]

[redacted]

[redacted]

[redacted]

[redacted] 22

On the basis of information criteria scores Gompertz, Rayleigh and bathtub models represent reasonable candidates for describing TTD in the *all BRCAm* population. ***[redacted] 23 summarises the ERG models of TTD olaparib in the *all BRCAm* population.

[redacted] 23

[redacted]

Summary

For modelling overall survival of olaparib group the company have selected poor fitting loglogistic models mainly on the grounds that these most closely conform to clinical opinion expressed in an elicitation exercise described in the previous submission (critiqued in the original ERG report). Superior fit models are provided by Rayleigh distributions for both *pior taxane BRCAm* and *all BRCAm* populations and these appear more appropriate.

To obtain models of overall survival for the comparator (cabazitaxel), the company have applied a time invariant HR to their loglogistic models for olaparib. The ERG doubt the validity of this procedure because loglogistic models do not support proportional hazards and the ratio of hazards between two loglogistic models is not time invariant but varies through time. The ITC HR for the comparison olaparib vs cabazitaxel *all BRCAm* population was applied for the comparison olaparib vs cabazitaxel *prior taxane BRCAm* population which seems an unnecessary action in view of the very close similarity of overall survival in the *prior taxane BRCAm* and *all BRCAm* populations. A better approach would be to use the ITC HR for the *prior taxane BRCAm* population.

In conclusion, because of the choice of parametric models for overall survival and the application of time invariant HR to logistic models, the ERG has concerns about the reliability of the comparison between olaparib and cabazitaxel used in the company's economic modelling.

The CS economic model has proposed Gompertz models to describe both rPFS and TTD olaparib; ERG reconstructions and modelling tend to support the use of Gompertz models.

4 COST EFFECTIVENESS

4.1 Should the no prior taxane subgroup be analysed separately

The company target group is the BRCAm prior taxane subgroup of the trial. The company argues that it is inappropriate to analyse the BRCAm no prior taxane subgroup separately due to small patient numbers: [redacted] for olaparib arm and [redacted] for the NHA arm.

The company presents cost effectiveness estimates for the BRCAm all patient group. The company argument is that the cost effectiveness in this group is not much worse than that of the target group, and so if olaparib is approved for the prior taxane group it should be approved for all patients.

The ERG still disagrees with this and thinks that it is legitimate for the company to specify BRCAm prior taxane patients as the target group, but to justify expanding olaparib use to all BRCAm patients the company should either:

- Perform an incremental analysis estimating the cost effectiveness of expanding use from the target group to all patients.
- Infer a cost effectiveness for the no prior taxane patients from the prior taxane and all patient cost effectiveness estimates.

These approaches should be result in broadly similar results. The ERG adopts the latter, time constraints limiting what is possible.

4.2 Which OS functional form should be used to extrapolate olaparib OS

The company reiterates its reliance upon its expert survey of the DCO1 data to justify its choice of the log-logistic. This is despite the log-logistic along with the log-normal having the worst information criteria as outlined below, with its AIC being 4.1 points worse and its BIC being 6.4 points worse than those of the exponential.

Table 11: Olaparib arm OS functional forms' information criteria

Form	AIC	BIC	Total
Exponential	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]
Loglogistic	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]

Section 4.3.4.1 of the original ERG report outlines why the ERG thinks that the company expert opinion on this is unreliable and biased in favour of olaparib. These arguments are unchanged. As presented in more detail above in the ERG review of clinical effectiveness, the ERG thinks that the Rayleigh curve is the best fit for the data and the most reasonable to apply in the cost effectiveness modelling.

The ERG will apply the olaparib Rayleigh OS curve in its revised base case, and will explore other functional forms as scenario analyses.

4.3 Should olaparib be costed using the TTD curve or the rPFS curve

The company states that using the TTD curve to cost olaparib has a small impact upon the cost effectiveness analysis. The ERG remains of the opinion that olaparib should be costed using the TTD curve. This has the additional benefit of being logically consistent with the application of an RDI, the calculation of which is based upon the TTD curve.

It should also be borne in mind that olaparib is dispensed in packs. The TTD curve may not entirely reflect this, and it is possible that even the TTD curve coupled with an assumed 100% RDI may underestimate the amount of olaparib that was dispensed during PROfound and so underestimate the olaparib treatment costs.
It is the case that there is no TTD data for cabazitaxel. Cabazitaxel is administered in hospital ever three weeks, while olaparib is an ongoing oral tablet, so there may be an argument that measurement of progression and cessation of treatment may be more likely to align with cabazitaxel than with olaparib; i.e. the cabazitaxel TTD curve may be more closely aligned with its PFS curve.

There is no perfect, unbiased solution but what seems clear is that:

- Olaparib is somewhat more expensive than cabazitaxel, and is also estimated to have a somewhat superior PFS curve to that of cabazitaxel. Even if the TTD curve lies above the corresponding PFS curve by the same proportion for both drugs, PFS costing will bias the net cost estimate by a significant amount in favour of olaparib.
- Costing olaparib using the PFS curve rather than the TTD curve underestimates the cost of olaparib that was observed during PROfound.
- Applying an olaparib RDI based upon TTD data to the PFS curve is inconsistent.

The ERG will supply the same scenario analysis that was provided in the original ERG report.

4.4 PPS active treatment costs and BSC costs

The company suggests that a proportion of patients receive an active treatment upon progression, with the remainder of patients not getting any PPS active treatment and only getting BSC. The company introduces considerations such as double counting and end of life costs, more accurately described as the cost of dying given the model implementation, but these are not relevant to the argument.
The argument here is whether those who receive an active treatment upon progression would, once that active treatment has stopped, tend thereafter to incur the same ongoing monthly costs as those who did not receive an active treatment upon progression. The company position is that they would not. The ERG position is that since the post progression treatment is not with curative intent, once active treatment has stopped the ongoing monthly costs will tend to converge between groups. There is an argument that this might not happen immediately, and it is relatively easy to explore scenarios where the ongoing monthly costs converge 2, 4 and 6 months after any PPS active treatment has ceased.

The company argues that this cannot be sensibly implemented within its model implementation. There are a number of aspects within a partitioned survival model that cannot be implemented perfectly, such as the incidence of progression. But this is not a bar to making reasonable assumptions in order to model this, which is what the company model does.

For those not receiving a PPS active treatment the total cost of PPS BSC is the total discounted months PPS multiplied by the monthly BSC cost. A reasonable estimate for BSC after PPS active treatment has ceased can be arrived at by subtracting the total months spent in active PPS treatment[1] from the total discounted months PPS, and multiplying this by the monthly BSC cost. This will introduce some error due to the total months spent in active PPS treatment not being discounted. But the ERG thinks that this error is likely to be minor and that this error will tend to favour olaparib due to progression and its costs occurring later for olaparib, meaning that its PPS active treatment duration that should be subtracted from the total discounted months PPS would if correctly discounted be smaller than that of the comparator arm[2].

The ERG revised base case will retain the original ERG approach of assuming that ongoing monthly PPS costs will be the same for those who have finished their PPS active treatment as for those who never had a PPS active treatment. The ERG will also supply scenario analyses which assume that it takes 2, 4 and 6 months post PPS active treatment for these costs to converge, alongside a scenario analysis of the company base case of these costs never converging.

4.5 GCS-F use

As outlined in the original ERG report section 4.3.4.11 the company G-CSF use assumptions of 100% of patients receiving it for 14 days are despite the company's own expert opinion, rather than because of it.

The company TE response chooses to highlight from the cabazitaxel SmPC on G-CFS use "…*usually for up to* ***14 days***". The ERG prefers to highlight "…*usually for* ***up to 14 days***". The ERG thinks that this supports its position that not all patients receive the maximum of 14 days use.

The ERG thinks that the company TE response adds little to the arguments presented in section 4.3.4.11 of the original ERG report.

The ERG revised base case will retain its preference for an average of 7 days use per cabazitaxel cycle among [redacted] of patients. A scenario analysis of 100% of patients requiring 14 days use per cabazitaxel cycle will be explored.

[1] Plus any additional months before ongoing monthly costs for the two groups converge.

[2] This is slightly conditioned by the duration of PPS active treatment being different between the arms if the PPS active treatments that are received are differentiated by arm, but this has no bearing upon the current argument.

4.6 Which set of HRs to apply for the BRCAm prior taxane target group

The company applies the BRCAm all patient HRs when modelling the BRCAM prior taxane target group. The ERG thinks that when modelling the BRCAM prior taxane target group it is more appropriate to apply the BRCAM prior taxane target group HRs.

The ERG revised base case the models the BRCAM prior taxane group the BRCAM prior taxane target group HRs.

4.7 NHA RPSFTM adjustment: With and without recensoring

Section A.1.4.2.1 of the company TE response presents the effects of adjusting the trial NHA arm OS for cross over to olaparib, using the RPSFTM method, for the new data cut. The new data cut and analyses raise a new issue. The company TE response presents two Cox model analyses for the BRCAm prior taxane patients: with recensoring and without recensoring. The company states that "*models with and without recensoring were explored to understand the plausible range of results*". The ERG agrees with this approach.

The company declined to supply the full Kaplan Meier data, so the best that the ERG can do is to digitise the figures of the company TE response. [redacted] shows the resulting curves for overall survival for the RPSFTM adjusted NHA arm, with and without recensoring. But the figures may not correspond exactly with those of Figures 9 and 10 of the company TE response due to being based upon digitized data.

[redacted]

[redacted]24[redacted]

The two NHA RPSFTM adjusted curves are reasonably similar up to month 7, after which point they begin to diverge. Note that in ***[redacted]24 the tail of the with recensoring KM curve is not overwritten from 14 months by the without recensoring KM curve. The with recensoring KM curve ends at a little over 14 months, just prior to the downward step in the without recensoring KM curve at this point.

The company rejects the without recensoring adjusted curve for the BRCAm all patients data, and by implication also for the BRCAm prior taxane patients data, mainly because of "*a long plateau after 15 months at/above ≈[redacted] survival … which was considered to be clinically implausible… (…[redacted] after 15 months in the prior taxane subgroup of BRCAm)*". But the ERG notes that Figure 10 on page 40 of the company TE response states that by month 17 only [redacted] of the original [redacted] are modelled as remaining at risk, with Figure 10 further suggesting that by around month 19 this has fallen further to only [redacted] remaining at risk. Because of the small number of patients modelled as remaining at risk within the "plateau" after month 17 it seems reasonable to be not too concerned about the "plateau" after month 17 from a statistical point of view.

The ERG assumes that the assessment of "*clinical-implausibility*" was based upon company expert opinion. The ERG notes that, as reviewed in section 4.3.4.1 of the original ERG report, the company expert opinion for which any detail is available in some instances stretches credibility and has also tended to favour the company case. ERG expert opinion felt unable to conjecture concrete OS estimates for the NHA patients for the counterfactual of them not being permitted to cross over to olaparib, to the extent that the ERG cannot express a clear preference for one curve over the other.

In the light of the above, for the ERG there is no obvious reason to strongly prefer one RPSFTM adjusted curve and to wholly reject the other. The ERG prefers the original company approach of using the with recensoring and without recensoring curves to explore the plausible range of results.

The original submission presented the following hazard ratio central estimates for olaparib compared to the NHA control arm, once the NHA control arm had been RPSFTM adjusted for cross over to olaparib.

Table 12: OS HRs: DCO1: With and without recensoring

Test	Recensoring	Cohort A+B	Cohort A
Log rank	Without	[redacted]	[redacted]
Log rank	With	[redacted]	[redacted]

Cox	Without	[redacted]	[redacted]
Cox	With	[redacted]	[redacted]
Weibull	Without	[redacted]	[redacted]
Weibull	With	[redacted]	[redacted]

There were minimal differences between the Cox and the Weibull, with the original company submission preferring the Weibull. While there was some divergence between with and without recensoring it was not dramatic. The latter does not apply to the new data cut. The OS HRs that are derived by the company for the new data cut using the Cox model with and without recensoring differ quite noticeably: for the BRCAm prior taxane target population [redacted] and [redacted] respectively, and for the BRCAm all patient population [redacted] and [redacted] respectively. Recensoring is much more of an issue than it was for the original company submission.

When the DCO2 Cox RPSFTM adjusted OS HRs inputted to the ITC they result in the following OS HRs for olaparib compared to cabazitaxel.

Table 13: ITC OS HRs: DCO2: Cox: With and without recensoring

Recensoring	BRCAm prior taxane	BRCAm all patients
With	[redacted]	[redacted]
Without	[redacted]	[redacted]

The ERG is also concerned that the company has not presented the DCO2 RPSFTM analyses for the Log rank and the Weibull, as there may be more divergences here too.

The ERG revised base case will present two full sets of analyses which apply (1) the prior taxane with recensoring OS HR and (2) the prior taxane without recensoring OS HR.

4.8 AEs and SREs

The adverse event and SRE rates for olaparib have been updated to reflect the BRCAm prior taxane group and the new data cut.

4.9 PPS subsequent treatment percentages

The company updates the proportion receiving PPS active treatment in the olaparib arm for the new data cut BRCAm prior taxane group to reflect the [redacted] patients who received subsequent treatment out of the number of progression events of [redacted], hence [redacted]. In contract to its original submission the company now simply assumes that the PPS active treatment percentage in the cabazitaxel arm is the same as in the olaparib arm. As per Section 4.3.2.1 of the original ERG

report the appropriate figure for cabazitaxel seems to be 41.7%, which is closely aligned with the company assumption.

As per Section 4.3.4.13 of the original ERG report, for the original data cut the number of PPS active treatments received was [redacted] higher than the number of patients receiving a PPS active treatment; i.e. many olaparib patients received more than one PPS active treatment. This may still be an issue.

4.10 PPS subsequent treatment by arm

The company revised base case assumes retains the assumption of PPS NHA use despite current UK guidelines. The company provides a scenario analysis that sets this to zero, and increases the other treatments pro rata.

Table 14: Distribution of PPS treatments by arm

	Company base case		Company scenario analysis	
PPS treatment	Olaparib	Cabazitaxel	Olaparib	Cabazitaxel
Cabazitaxel	[redacted]	7% (n=3)	[redacted]	27% (n=3)
Docetaxel	[redacted]	5% (n=2)	[redacted]	18% (n=2)
Abiraterone	[redacted]	37% (n=15)	[redacted]	..
Enzalutamide	[redacted]	37% (n=15)	[redacted]	..
Radium-223	[redacted]	15% (n=6)	[redacted]	55% (n=6)

As per the original ERG report there are concerns about the different geographic spread of patients in PROfound compared to CARD. These estimates are also based upon extremely small patient numbers. It may be reasonable to expect that more olaparib patients would receive PPS cabazitaxel, but as suggested in section 4.9 above this may also require [redacted] of olaparib patients to be modelled as receiving more than one PPS treatment.

In the light of the above, it may be most reasonable for the base case to assume the same proportion receiving and distribution of PPS treatments for each arm.

5 Company cost effectiveness estimates

5.1 Company TE base case: BRCAm prior taxane

The revised deterministic company base case estimates the following undiscounted years survival.

Table 15: Company TE base case BRCAm prior taxane: Survival

	Caba.	Olap	Net gain	As % total gain
PFS	[redacted]	[redacted]	[redacted]	[redacted]
PPS	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	1.833	

As in the original company base case, of the modelled total net survival gain from olaparib over cabazitaxel of 1.833 years, the vast majority, [redacted], is modelled as occurring after progression has occurred when patients will for the most part no longer be receiving olaparib.

The revised deterministic company base case estimates the following discounted QALYs.

Table 16: Company TE base case BRCAm prior taxane: QALYs

	Caba.	Olap	Net gain	As % total gain
PFS	[redacted]	[redacted]	[redacted]	[redacted]
PPS	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	1.026	

For the total discounted net 1.026 QALY gain the picture is similar to that of overall survival, the vast majority, [redacted], is modelled as occurring after progression has occurred when patients will for the most part no longer be receiving olaparib.

The revised deterministic company base case estimates the following discounted costs.

Table 17: Company TE base case BRCAm prior taxane: Costs

	Caba.	Olap	Net	As % total net
Tx: Drug cost	[redacted]	[redacted]	[redacted]	[redacted]
Tx: Admin	[redacted]	[redacted]	[redacted]	[redacted]
Concomitant Tx	[redacted]	[redacted]	[redacted]	[redacted]

AEs	[redacted]	[redacted]	[redacted]	[redacted]
SREs	[redacted]	[redacted]	[redacted]	[redacted]
On Tx management	[redacted]	[redacted]	[redacted]	[redacted]
Off Tx management	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent Tx	[redacted]	[redacted]	[redacted]	[redacted]
End of life	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	£19,126	

The direct drug costs of olaparib are offset by lower administration costs and concomitant medication costs. Due to the vast majority of the survival gain being modelled as occurring after progression, the ongoing PPS BSC costs for progressive disease are somewhat higher in the olaparib arm than in the cabazitaxel arm.

The company TE deterministic base case and associated probabilistic central results are presented in Table 18. Note that the model as submitted only permits a maximum of 1,000 PSA iterations. The PSA results are from an ERG run of the model as the company response does not appear to report the TE probabilistic base case results, despite the NICE methods guide. The worsening of the probabilistic ICER relative to the deterministic ICER by around 14% is due to higher total QALYs in the cabazitaxel arm resulting in a smaller net QALY gain[3].

Table 18: Company TE base case BRCAm prior taxane: Summary

	Deterministic			Probabilistic		
	Caba.	Olap.	net	Caba.	Olap.	net
Total QALYs	[redacted]	[redacted]	1.028	[redacted]	[redacted]	0.912
Total Costs	[redacted]	[redacted]	£19,126	[redacted]	[redacted]	£19,328
ICER			£18,596			£21,186

The CEAC underlying the company TE base case probabilistic modelling is presented in Figure 25.

[3] Note that other ERG runs have resulted in differences of, say, 17% suggesting that the model may not have completely converged after 1,000 iterations.

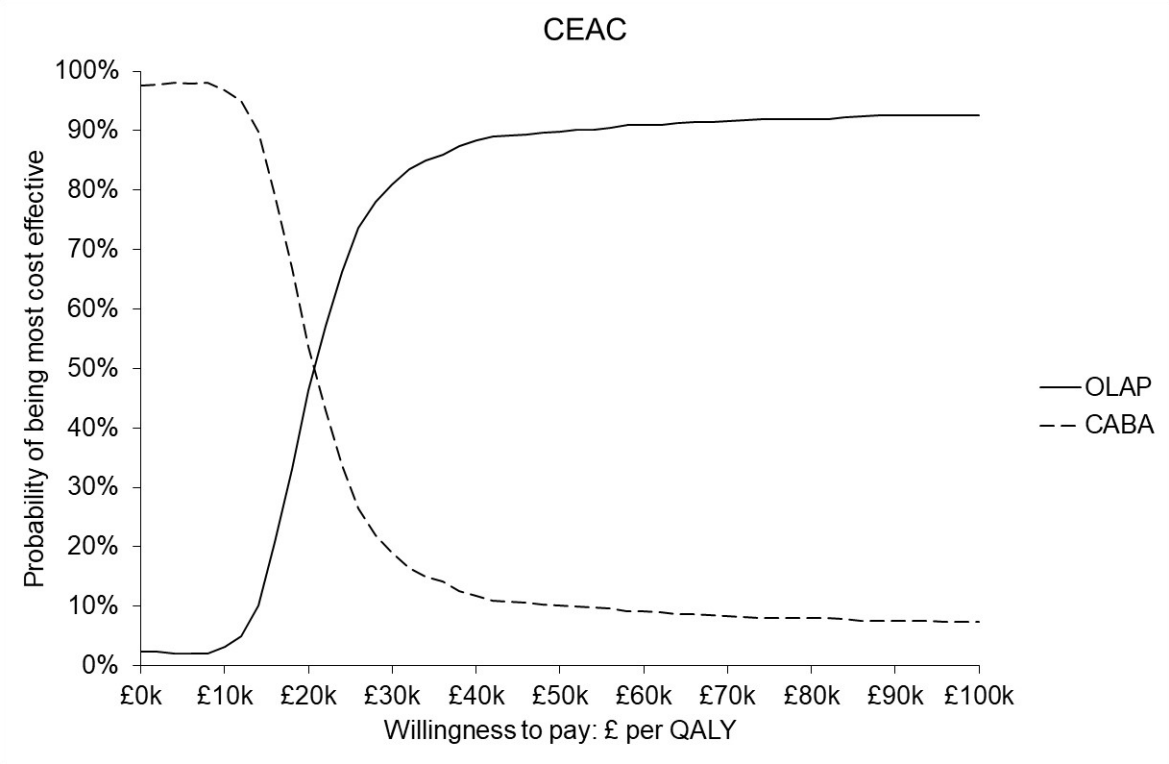


Figure 25: Company TE base case CEAC

5.2 Company TE sensitivity analyses

Table 19 below presents the results for the 16 most influential variables within the company base case. These are based upon an ERG model run of the company base case for the BRCAm prior taxane groups, applying the BRCAm all patient HRs within the ITC as per the company base case. The ERG has excluded the results for the OS – Param 1: olaparib and OS – Param 2: olaparib as something appears to have gone wrong within the model implementation of these univariate sensitivity analyses.

Table 19: Company TE univariate sensitivity analyses

	Low parameter value			High parameter value		
	ΔQALYs	ΔCost	ICER	ΔQALYs	ΔCost	ICER
OS HR: Caba vs Olap	-0.468	£2,601	Dom'ted	1.457	£28,029	£19,243
rPFS parameter 1: Olap	1.045	£34,109	£32,646	1.022	£13,211	£12,931
rPFS HR: Caba vs Olap	1.014	£16,117	£15,901	1.039	£23,307	£22,431
RDI: Olap	1.028	£14,971	£14,556	1.028	£19,673	£19,128
Mthly cost: PPS	0.991	£19,126	£19,300	1.066	£19,126	£17,942

RDI: Cabal	1.028	£21,027	£20,444	1.028	£18,355	£17,846
Mthly cost: PFS	1.012	£19,126	£18,901	1.045	£19,126	£18,301
Mthly BSC cost: Olap	1.028	£18,303	£17,796	1.028	£19,948	£19,396
Mthly other med. cost: Caba	1.028	£19,664	£19,119	1.028	£18,588	£18,073
Cost of subsequent Tx: Caba	1.028	£19,659	£19,115	1.028	£18,593	£18,078
Cost of subsequent Tx: Olap	1.028	£18,609	£18,094	1.028	£19,643	£19,099
Mean PFS cost: Caba on Tx	1.038	£19,126	£18,421	1.019	£19,126	£18,775
Monit. cost - OnTx: Caba	1.028	£19,484	£18,945	1.028	£18,768	£18,248
Monit. cost - OffTx: Olap	1.028	£18,833	£18,312	1.028	£19,419	£18,881
Mthly BSC cost: Caba	1.028	£19,401	£18,864	1.028	£18,851	£18,329
Mthly admin cost: Caba	1.028	£19,401	£18,863	1.028	£18,851	£18,329

The first scenario analysis around the OS HR is unusual in that the ICER for the lower value is dominance for cabazitaxel while the ICER for the higher value is not that much difference from the base case, suggesting a strong non-linearity in the OS HR. Further exploration of this by the ERG suggests that from the lower CI of the OS HR of [redacted] to an OS HR of marginally less than unity cabazitaxel dominates olaparib. The relationship thereafter is strongly non-linear thereafter, as shown in ***[redacted] **26**.

[redacted]

[redacted]26[redacted]

Despite the distribution for the OS HR also being skewed to the right, [redacted], the above may account for some or even most of the non-linearity of model results. This may be why the probabilistic ICER is higher than the deterministic ICER. Section 5.8.7 of the NICE methods guide[4] states that "*In non-linear decision models, probabilistic methods provide the best estimates of mean costs and outcomes*". Given this, the ERG thinks that olaparib should be evaluated using the probabilistic estimates.

[4] https://www.nice.org.uk/process/pmg9/chapter/foreword

5.3 Company TE BRCAm prior taxane: Applying target group HRs

The company base case is for the BRCAm prior taxane group but it inputs the BRCAm all patient group rPFS and OS HRs to the ITC. The ERG thinks that for the BRCAm prior taxane group the company should have inputted the BRCAm prior taxane group OS and rPFS HRs to the ITC, resulting in HRs relative to cabazitaxel of [redacted] and [redacted]. The deterministic results and associated probabilistic central results are presented in Table 20.

Table 20: Company TE base case results: Applying target group HRs: Summary

	Deterministic			Probabilistic		
	Caba.	Olap.	net	Caba.	Olap.	net
Total QALYs	[redacted]	[redacted]	0.980	[redacted]	[redacted]	0.746
Total Costs	[redacted]	[redacted]	£19,600	[redacted]	[redacted]	£19,154
ICER			£20,005			£25,679

Applying the no prior taxane specific HRs within the ITC worsens the costs effectiveness estimates by a reasonable margin: 8% for the deterministic analysis and 18% for the probabilistic analysis. The CEAC underlying the probabilistic modelling is presented below.

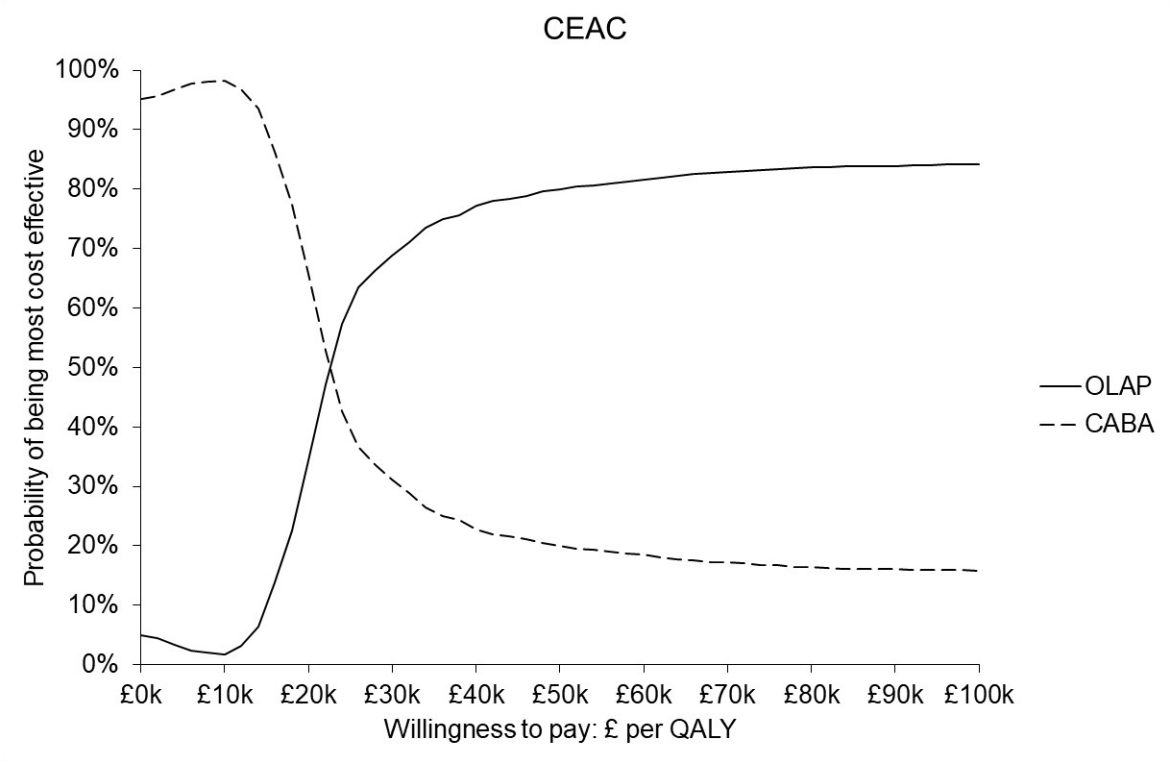


Figure 27: Company TE base case CEAC: Applying target group HRs

5.4 Company TE BRCAm all patients analysis

The company presents deterministic results for the BRCAm all patients group. This is relevant due to the company arguing for olaparib use across the BRCAm all patients group, as reviewed in Section 4.1 above. Note that this analysis applies the BRCAm all patients group rPFS and OS HRs.

Table 21: Company TE base case BRCAm all patients: Summary

	Deterministic			Probabilistic		
	Caba.	Olap.	net	Caba.	Olap.	net
Total QALYs	[redacted]	[redacted]	1.081	[redacted]	[redacted]	0.908
Total Costs	[redacted]	[redacted]	£21,808	[redacted]	[redacted]	£21,964
ICER			£20,176			£24,183

5.5 Implied company TE BRCAm no prior taxane patients

The results of Table 18 and Table 21, coupled with patient numbers of [redacted] and [redacted] respectively, imply the following estimated for BRCAm no prior taxane patients.

Table 22: Company TE BRCAm no prior taxane: BRCAm all patient HRs: Summary

	Deterministic			Probabilistic		
	Caba.	Olap.	net	Caba.	Olap.	net
Total QALYs	[redacted]	[redacted]	1.207	[redacted]	[redacted]	0.899
Total Costs	[redacted]	[redacted]	£28,244	[redacted]	[redacted]	£28,292
ICER			£23,410			£31,485

The results of Table 20 and Table 21, coupled with patient numbers of [redacted] and [redacted] respectively, imply the following estimated for BRCAm no prior taxane patients.

Table 23: Company TE BRCAm no prior taxane: BRCAm subgroup HRs: Summary

	Deterministic			Probabilistic		
	Caba.	Olap.	net	Caba.	Olap.	net
Total QALYs	[redacted]	[redacted]	1.323	[redacted]	[redacted]	1.298

Total Costs	[redacted]	[redacted]	£27,106	[redacted]	£28,708
ICER			£20,481		£22,121

6 ERG revised base case analyses

The ERG largely retains the assumptions of Section 5.4 of the original ERG report. For its modelling the ERG amends the post FAC ERG amended model to be aligned with the company TE supplied DCO2 BRCAm data as summarised in Table 19 of the company TE response:

- Apply the new data cut baseline age and weight, olaparib parameterised curves, ITC HRs, olaparib AEs, and olaparib SREs probability, with it being possible to specify these for either the BRCAm prior taxane target group or the BRCAm all patient group.
- Apply the percentage receiving PPS treatment and the distribution of PPS treatments for olaparib.
- Apply the median RDIs for olaparib and cabazitaxel.

With regards the HR estimates that are available, these are presented in Table 24 and Table 25.

Table 24: Alternative OS HRs: Olaparib vs cabazitaxel

ITC HR inputs source	BRCAm group	Censoring	HR	LCI	UCI
Company	Prior taxane	With	[redacted]	[redacted]	[redacted]
Company	Prior taxane	Without	[redacted]	[redacted]	[redacted]
Company	All patients	With	[redacted]	[redacted]	[redacted]
Company	All patients	Without	[redacted]	[redacted]	[redacted]
ERG digitised	Prior taxane	With	[redacted]	[redacted]	[redacted]
ERG digitised	All patients	With	[redacted]	[redacted]	[redacted]

The ERG HRs derived from ERG digitised Kaplan Meier data are applied as exploratory scenario analyses for the probabilistic modelling, due to the apparent non-linearity of the model and their narrower confidence intervals. But due to company declining to supply the Kaplan Meier data at clarification they should not be relied upon for decision making.

Table 25: Alternative PFS HRs: Olaparib vs cabazitaxel

ITC HR inputs source	BRCAm group	HR	LCI	UCI
Company	Prior taxane	[redacted]	[redacted]	[redacted]
Company	All	[redacted]	[redacted]	[redacted]

As reviewed in Section 4.7, the ERG presents two sets of estimates, (1) those that apply the RPSFTM adjusted values with recensoring, and (2) those that apply the RPSFTM adjusted values without recensoring.

The ERG revised base case also:

- Applies the BRCAm prior taxane curves and HRs when modelling the BRCAm prior taxane target group.
- Applies the ERG Rayleigh OS curve, while retaining the company Gompertz for PFS and TTD.
- Assumes the same PPS treatment distribution for both arms, applying the cabazitaxel PPS treatment distribution.
- Applies the olaparib PAS but does not apply the cabazitaxel PAS, or any of the PPS treatment PASs.

ERG revisions to the model implementation mean that the probabilistic modelling can be run over more than 1,000 iterations. For the ERG revised base cases the probabilistic modelling is run over 5,000 iterations. The exploratory probabilistic modelling is only run over 1,000 iterations due to time constraints.

For the probabilistic modelling the sampling of the company olaparib TTD Gompertz results in errors. Due to time constraints the ERG has not managed to correct this error, so for the probabilistic modelling has simply turned off sampling of the company olaparib TTD Gompertz. This is unsatisfactory for two reasons:

- It means that the model uncertainty will be incorrectly characterised.
- It may result in peculiar juxtapositions of the PFS curve and the TTD curve.

6.1 ERG revised base case: OS HRs with recensoring

The ERG revised deterministic base case estimates the following undiscounted years survival.

Table 26: ERG base case BRCAm prior taxane: RPSFTM with recensoring: Survival

	Caba.	Olap	Net gain	As % total gain
PFS	[redacted]	[redacted]	[redacted]	[redacted]
PPS	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	0.729	

The BRCAm prior taxane cost effectiveness estimates are presented in Table 27.

Table 27: ERG base case BRCAm prior taxane: RPSFTM with recensoring

	Deterministic			Probabilistic		
	Caba.	Olap.	net	Caba.	Olap.	net
Total QALYs	[redacted]	[redacted]	0.476	[redacted]	[redacted]	0.438
Total Costs	[redacted]	[redacted]	£28,380	[redacted]	[redacted]	£28,069
ICER			£59,670			£64,087

The associated CEAC is shown in Figure 28.

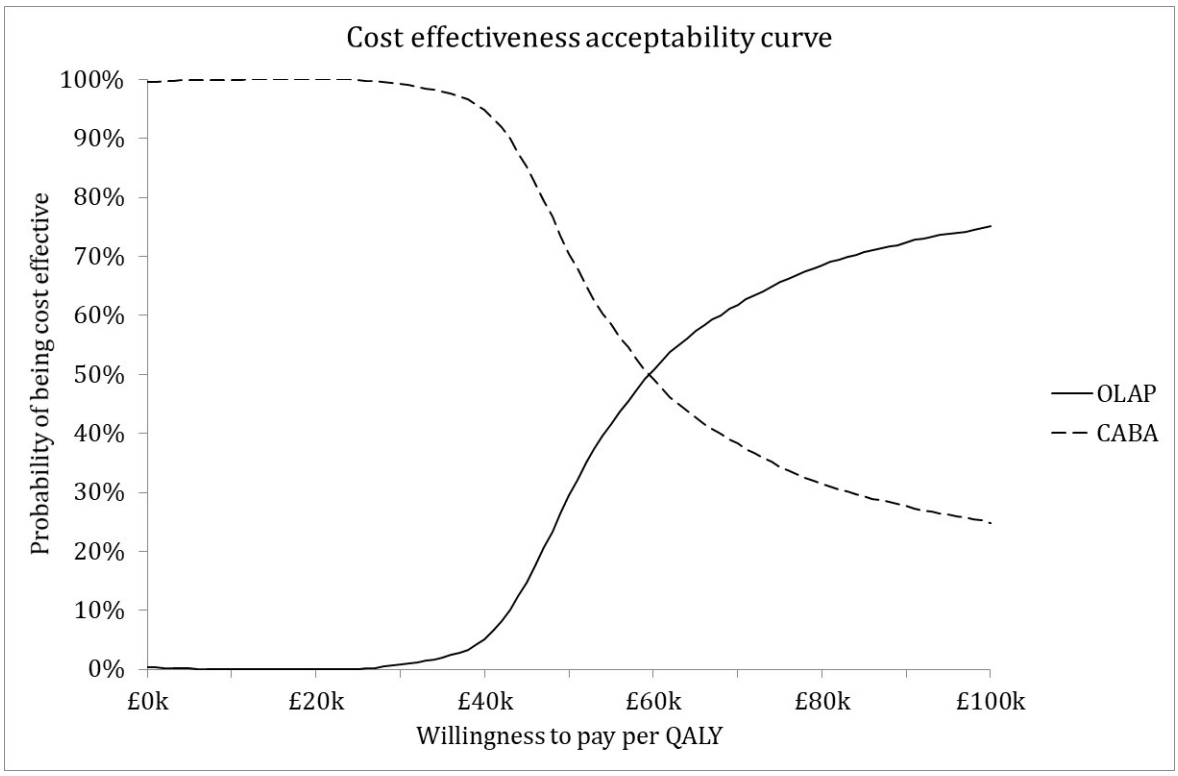


Figure 28: ERG base case BRCAm prior taxane: RPSFTM with recensoring: CEAC

The BRCAm all patient estimates are presented in Table 28.

Table 28: ERG base case BRCAm all patients: RPSFTM with recensoring

	Deterministic			Probabilistic		
	Caba.	Olap.	net	Caba.	Olap.	net
Total QALYs	[redacted]	[redacted]	0.541	[redacted]	[redacted]	0.491
Total Costs	[redacted]	[redacted]	£30,568	[redacted]	[redacted]	£29,867
ICER			£56,475			£60,786

The implied BRCAm no prior taxane estimates are presented in Table 29.

Table 29: ERG base case BRCAm no prior taxane: RPSFTM with recensoring

	Deterministic			Probabilistic		
	Caba.	Olap.	net	Caba.	Olap.	net
Total QALYs	[redacted]	[redacted]	0.699	[redacted]	[redacted]	0.619
Total Costs	[redacted]	[redacted]	£35,819	[redacted]	[redacted]	£34,179
ICER			£51,256			£55,183

6.2 ERG revised base case: OS HRs without recensoring

The ERG revised deterministic base case estimates the following undiscounted years survival.

Table 30: ERG base case BRCAm prior taxane: RPSFTM without recensoring: Survival

	Caba.	Olap	Net gain	As % total gain
PFS	[redacted]	[redacted]	[redacted]	[redacted]
PPS	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	0.543	

The BRCAm prior taxane estimates are presented in Table 31.

Table 31: ERG base case BRCAm prior taxane: RPSFTM without recensoring

	Deterministic			Probabilistic		
	Caba.	Olap.	net	Caba.	Olap.	net
Total QALYs	[redacted]	[redacted]	0.364	[redacted]	[redacted]	0.344
Total Costs	[redacted]	[redacted]	£26,053	[redacted]	[redacted]	£25,903
ICER			£71,516			£75,364

The associated CEAC is shown in Figure 29.

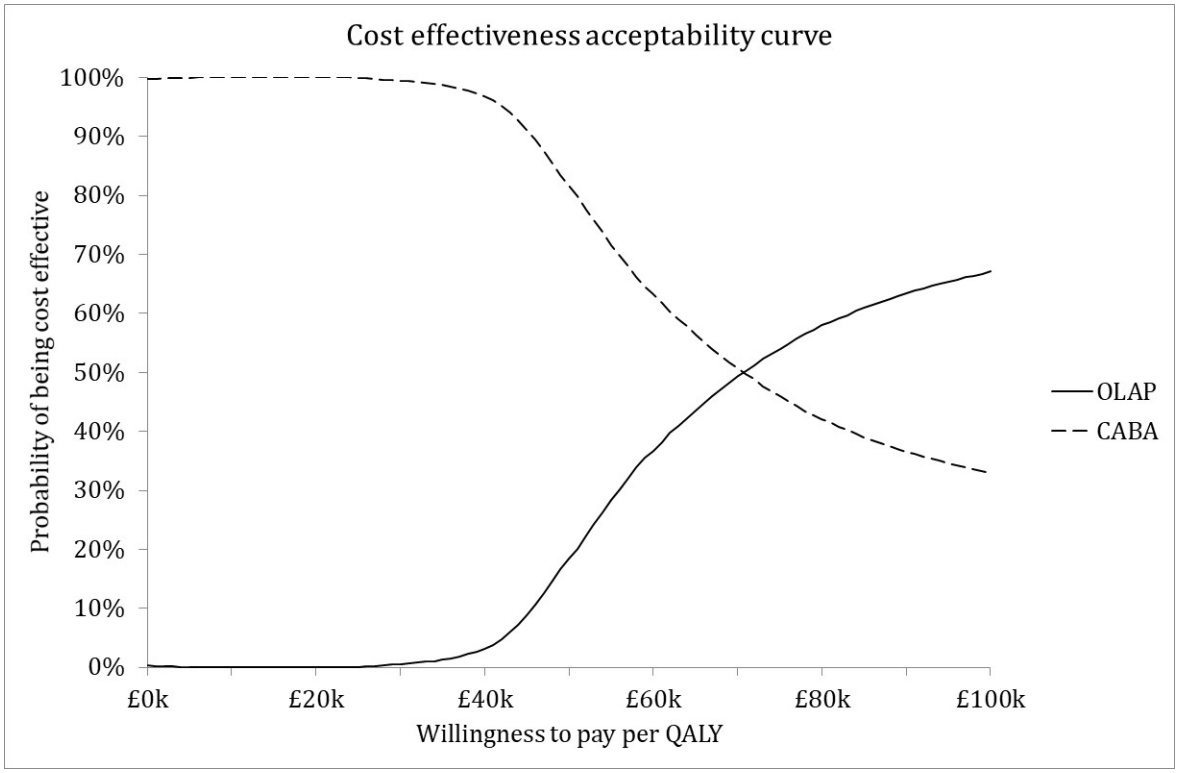


Figure 29: ERG base case BRCAm prior taxane: RPSFTM without recensoring: CEAC

The BRCAm all patient estimates are presented in Table 32.

Table 32: ERG base case BRCAm all patients: RPSFTM without recensoring

	Deterministic			Probabilistic		
	Caba.	Olap.	net	Caba.	Olap.	net
Total QALYs	[redacted]	[redacted]	0.395	[redacted]	[redacted]	0.356
Total Costs	[redacted]	[redacted]	£27,504	[redacted]	[redacted]	£26,981
ICER			£69,664			£75,798

The implied BRCAm no prior taxane estimates are presented in Table 33.

Table 33: ERG base case BRCAm no prior taxane: RPSFTM without recensoring

	Deterministic			Probabilistic		
	Caba.	Olap.	net	Caba.	Olap.	net
Total QALYs	[redacted]	[redacted]	0.468	[redacted]	[redacted]	0.385
Total Costs	[redacted]	[redacted]	£30,985	[redacted]	[redacted]	£29,568
ICER			£66,205			£76,727

6.3 ERG scenario analyses

The ERG provides the following scenario analyses:

- SA01: Applying the company OS curves for olaparib.
- SA02: Applying the BRCAm all patient HRs in the ITC.
- SA03: Assuming the time to convergence of PPS ongoing monthly costs between those who did and did not receive a PPS active treatment after cessation of all active treatments is 2, 4 and 6 months and never.
- SA04: Cost olaparib based upon the PFS curve.
- SA05: Infer a TTD curve for cabazitaxel on the basis of it lying above the cabazitaxel PFS curve by the same proportion as the olaparib TTD curve lies above the olaparib PFS curve.
- SA06: Assumes no vial sharing for cabazitaxel.
- SA07: 100% G-CSF use for 14 days for each cabazitaxel treatment cycle.
- SA08: Exclude the cost of genetic testing.

Table 34: ERG scenario analyses: Deterministic modelling

	RPSFTM with recensoring			RPSFTM without recensoring		
	ΔQALYs	ΔCost	ICER	ΔQALYs	ΔCost	ICER
ERG revised base case	0.476	£28,380	£59,670	0.364	£26,053	£71,516
SA01a: Exponential	0.705	£32,558	£46,200	0.550	£29,386	£53,386
SA01b: Gompertz	0.452	£28,047	£62,037	0.344	£25,755	£74,975
SA01c: Weibull	0.581	£30,191	£52,009	0.451	£27,518	£61,081
SA01d: Gen. Gamma	0.476	£28,495	£59,901	0.363	£26,105	£71,958
SA01e: Log-logistic	0.980	£36,760	£37,519	0.779	£32,926	£42,262
SA01f: Log-normal	1.149	£39,891	£34,711	0.905	£35,221	£38,922
SA02: BRCAm all patient HRs	0.504	£28,218	£55,938	0.370	£25,282	£68,390
SA03a: Converge 2 months	0.476	£28,312	£59,526	0.364	£26,053	£71,516
SA03b: Converge 4 months	0.476	£27,795	£58,438	0.364	£26,020	£71,426
SA03c: Converge 6 months	0.476	£27,428	£57,667	0.364	£25,654	£70,419
SA03d: Converge never	0.476	£27,428	£57,667	0.364	£25,654	£70,419
SA04: Olap. PFS costing	0.476	£25,982	£54,627	0.364	£23,655	£64,932
SA05: Caba. TTD inferred	0.477	£26,984	£56,583	0.366	£24,657	£67,448
SA06: Caba. No vial sharing	0.476	£22,466	£47,236	0.364	£20,090	£55,148
SA07: 100% 14 days G-CSF	0.476	£24,834	£52,213	0.364	£21,929	£60,196
SA08: No genetic test cost	0.476	£24,257	£51,000	0.364	£21,929	£60,196

The ERG also explores the use of the effect of using the ERG digitised HRs. For the with recensoring analysis they suggest a deterministic estimate of £60,784 per QALY, slightly worse than the company deterministic estimate, and a probabilistic central estimate of £58,682 per QALY, a reasonable amount better than both the deterministic estimate using the ERG digitised HRs and the central probabilistic estimate using company HRs.

Due to time constraints the ERG has not been able to produce the corresponding analyses for the without recensoring modelling.

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APPENDIX 1.

To obtain a model for survival with cabazitaxel treatment, the CS applied an ITC derived HR to a loglog model of survival in the olaparib arm of various subgroup cohorts from PROFOUND. The ERG question the reliability of this procedure because, unlike some other models such as Weibull, loglog models do not conform to a proportional hazards assumption and so the ratio of hazards of two loglog models varies through time. From the economic model it is evident that CS implements the HR adjustment using the form: $S_{cab} = (S_{olap})^{\wedge HR}$. Thus the HR applied is invariant through time. To test the reasonableness of the company method the ERG examined loglogistic models of survival in the olararib and the NHA RPSFTm arms of the prior taxane *BRCAm* population. Loglogistic models were generated using treatment as covariate. A time constant HR (olaparib vs. NHA RPSFTm) was obtained using Cox proportional hazards. If the CS procedure is reliable then loglogistic models for compared arms should have a ratio of hazards that is constant through time, and applying an appropriate time constant HR to one loglog model should generate the comparator arm loglog model.

The figure below summarises the application of this procedure. Figure A indicates that applying the Cox proportional hazards HR to one arm does not generate the model for the loglogistic model for the other arm. Figure B indicates that the hazard of loglogistic models in both arms varies through time as also does the ratio of these hazards.

In summary : a] The loglog hazard for each arm varies through time; b] The ratio of the loglog hazards varies through time; c] Applying a time constant HR to the loglog survival model of one arm does not generate the loglog model of survival for the other arm; a model is generated but the population for which it is appropriate is difficult to define.

The figure below summarises the application of this procedure using Weibull models for olararib and the NHA RPSFTm arms of the prior taxane *BRCAm* population.

The Weibull hazard for each arm varies through time but the ratio of these hazards is constant through time.

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

ERG critique – factual accuracy check
Olaparib for previously treated hormone-relapsed metastatic prostate cancer [ID1640]

You are asked to check the ERG critique to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies, you must inform NICE by **5pm on 7 January 2021** using the below comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

The factual accuracy check form should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Company notes:

We have categorised our response into three tables, covering:

- minor errors (e.g. in reproduction of trial data)
- other errors, including those identified in the ERG results produced in the report
- misleading statements, that have material impact on the interpretation and conclusions drawn from the evidence provided

Please note that the company have not received a copy of the post-FAC, post-TE ERG rebuild model. We have not been able to complete the factual accuracy check for specific issues requiring this.

Issue 1 **Minor errors (including typos and reproduction of trial data)**

Description of problem	Description of proposed amendment	Justification for amendment	ERG Comment
P21: "Results were similar in the BRCAm and BRCAM prior taxane subgroups." P25. "The company states that: "*survival estimates with the loglogistic distribution best reflected the observed OS KM data for the prior taxane subgroup BRCSm*"." P16: "In the BRACm population, which was aligned to the anticipated EMA marketing authorisation of olaparib"	Please amend to *BRCA*m.	Typographical change.	Proposed revision accepted
P25, Figure 3 P26, Figure 4 P31, Figure 8 P35, Figure 11 P41, Figure 17 P42, Figure 18 P43, Figure 19 P44, Figure 20	We would request that the ERG please mark these figures as AIC.	Confidentiality marking.	Proposed revision accepted
P49, Figure 21 P55, Figure 22	Please could the ERG check the highlighting is applied - we believe these figures are intended to be marked as AIC.	Confidentiality marking.	Figure 21 and Figure 23 are correctly marked as AIC.

			Figure 22 is the CEAC and is correctly not marked as AIC.

Issue 2 Other errors

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
P49, Figure 21	Please could the ERG check the legend labels for the 'with' and 'without' recensoring data series. We believe these should be swapped.	Incorrect labels.	Proposed revision accepted.
P51: "As per Section 4.3.2.1 of the original ERG report the appropriate figure for cabazitaxel seems to be 41.6%, which is closely aligned with the company assumption."	This is a rounding error by the ERG, in Section 4.3.2.1 of the first ERG report. The correct figure is reported in the Technical Engagement response document, based on the ERG's preferred calculation for the proportion of patients receiving subsequent treatment after cabazitaxel as 50 out of 120 patients = 41.7% to one decimal place.	Rounding error.	Proposed revision accepted.
P51: "As per Section 4.3.4.13 of the original ERG report, for the original data cut the number of PPS active treatments received was [redacted]% higher than the number of patients receiving a PPS active treatment; i.e. many olaparib patients received more than one PPS active treatment. This may still be an issue."	It is not possible to further investigate subsequent treatment based on the trial data, nor make inference to efficacy or cost outcomes. We request that a statement is included to reflect this, as this statement otherwise encourages a misinterpretation of the trial data from PROfound.	Incorrect statement.	No factual error. No revision required.

P22, Table 5 Figure 6 P31, Table 6 Figure 12	We have the following concerns regarding the ERG parametric analyses of the data from PROfound: • Reporting of the methods used by the ERG seems incomplete in the report. Of particular concern is a lack of information around the ERG Rayleigh and bathtub models, which are not endorsed by the NICE DSU for decision making. In an attempt to understand the reliability of these models for decision making, we were unable to identify any other TAs in oncology mentioning these models. • Only a selection of models appear to have been investigated by the ERG, which is a concern if the assessment is incomplete. For example, in Figure 6, there are extrapolations that fall between the selection of models extensively assessed. • The set of AIC/BIC values produced by the ERG are very different to those produced by the AZ estimates based on patient level data. Please note the company have not received a copy of the post-FAC, post-TE ERG rebuild model. We have not been able to complete the factual accuracy check for specific issues requiring this.	Misrepresentation/omission of evidence of ERG analyses.	1. Rayleigh and bathtub models were obtained using the *stgenreg* package in Stata. [*Crowther,M, Lambert,P. stgenreg: A Stata Package for general parametric Survival Analysis. Journal of Statistical Software.2013; 53 ('12)*] Rayleigh models are sometimes used to model survival of cancer patients and have the expression $S(t) = \exp [-(\lambda_0 t + \lambda_1 t^2)]$ See: [*Design and analysis of clinical trials with time-to-event endpoints.* CRC Press.2009 Editor K.E.Peace. *Chapter 3 Overview of Time-to-Event parametric models.*] Point 1 (above) added to the report As far as we are aware NICE DSU does not exclude use of any particular parametric models. Bathtub models have been used in previous NICE appraisals e.g.*Total hip replacement and surface replacement for the treatment of pain and disability resulting from end stage arthritis of the hip (Review of technology appraisal guidance 2 and 44).*

			Other models were obtained using the *streg* command in Stata. 2. This is a comment rather than a factual error. In fact the ERG used a wider selection of parametric models (8) than did the company (6) 3. This is a comment rather than a factual error. It is true that ERG and the company obtained different AIC/BIC values. The reason for this is probably that the ERG analysed each arm separately. It should be noted that for the 6 models employed by the company, the hierarchy of ERG's AIC/BIC scores was the same as obtained by the company.

Issue 3 Misleading statements

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
P20: " In the original ERG report we identified that the assumption of transitivity in the indirect comparison is threatened because the study populations in CARD and PROfound are likely	Remove or revise paragraph. There is no robust evidence to suggest that *BRCA*m status is a treatment effect modifier for cabazitaxel versus NHA. The data presented are from small non-RCT studies exploring *BRCA*m status as a potential prognostic factor	Misrepresentation of available data.	This is the ERG opinion, no factual error. The studies presented by the ERG suggest that men with BRCA1 or 2 mutations who are treated with NHA might have worse outcomes than those treated

to differ in terms of genetic mutations. The company's response to this was "There is no evidence to suggest that *BRCA*m status is a treatment effect modifier for response to cabazitaxel or NHA treatment." (TE response, page 7 - 8) This assertion is incorrect. For example, several recent studies have suggested shorter PFS for participants receiving NHA who have *BRCA1* or *BRCA2* mutations compared to those without these mutations: 3.3 months (95% CI 2.7, 3.9) vs. 6.2 months (95% CI 5.1, 7.3),[6] and 4.3 months (95% CI 1.0, 7.6) vs. 9.2 months (95% CI 8.1, 10.3).[7, 8] This suggests that *BRCA*m status is a potential treatment effect modifier for NHA treatment."	for patients treated with NHA. The studies themselves suggest that further confirmatory work is required in order for any such association to be made.		with NHA who do not have these mutations. We agree that additional work will improve our understanding of the impact of BRCA1/2 mutations.
P45: "The company argues that it is inappropriate to analyse the *BRCA*m no prior taxane subgroup separately due to small patient numbers: n=30 for olaparib arm and n=23 for the NHA arm."	We request that the ERG clarify that the company did not deem it necessary to analyse the 'no prior taxane' subgroup of *BRCA*m separately because the clinical- and cost-effectiveness of olaparib in the prior taxane subgroup of *BRCA*m is similar to that in the overall *BRCA*m population, per Technical Engagement response document, P3-4. Further to the above point, the small patient numbers are likely to make any specific	Misrepresentation of company Technical Engagement response document.	No factual error. No revision required. The company makes the same argument in its comment here as that on page 3 of its TE response and on page 45 of the ERG TE report. The argument made here is consequently not furthermore to the previous paragraph.

	analyses to the ‘no prior taxane’ subgroup particularly subgroup challenging.		
P51: “In contract to its original submission the company now simply assumes that the PPS active treatment percentage in the cabazitaxel arm is the same as in the olaparib arm.”	We request clarification that the company implemented this change in light of Issue 10 of the Technical Report, as explained in Question 22 of the Technical Engagement response document.	Misrepresentation of CS.	This is correct and the issue has been resolved with NICE prior to the PMB and ACM.