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**NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE**

**SINGLE TECHNOLOGY APPRAISAL**

**Olaparib for previously treated hormone-relapsed metastatic prostate cancer [ID1640]**
**Appraisal Committee Meeting – 4 August 2021**
***2nd Committee meeting***

The following documents are made available to the comittee:

1. **Appraisal Consultation Document (ACD)** as issued to consultees and commentators

2. **Comments on the Appraisal Consultation Document from Astrazeneca**

3. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   - Prostate Cancer UK

4. **Evidence Review Group critique of company comments on the ACD**

5. **Appraisal Committee Meeting presentation slides** – to follow

# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Appraisal consultation document

# Olaparib for previously treated BRCA-mutation positive hormone-relapsed metastatic prostate cancer

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using olaparib in the NHS in England. The appraisal committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts and patient experts.

**This document has been prepared for consultation with the consultees.** It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see the committee papers).

The appraisal committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?



Issue date: February 2021

**Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.**

After consultation:

- The appraisal committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final appraisal document.
- Subject to any appeal by consultees, the final appraisal document may be used as the basis for NICE's guidance on using olaparib in the NHS in England.

For further details, see NICE's guide to the processes of technology appraisal.

The key dates for this appraisal are:

Closing date for comments: [Day month year]

Second appraisal committee meeting: [Day month year]

Details of membership of the appraisal committee are given in section X

# 1 Recommendations

1.1 Olaparib is not recommended, within its marketing authorisation, for treating hormone-relapsed metastatic prostate cancer with BRCA1 or BRCA2 mutations that has progressed after abiraterone or enzalutamide in adults.

1.2 This recommendation is not intended to affect treatment with olaparib that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

**Why the committee made these recommendations**

Treatment for BRCA-mutation positive hormone-relapsed metastatic prostate cancer that has progressed after enzalutamide or abiraterone includes docetaxel, cabazitaxel, or radium-223. In its evidence submission, the company restricted the treatment population to people who have had docetaxel already. This is narrower than olaparib's marketing authorisation.

Clinical trial evidence shows that people taking olaparib have more time before their disease progresses, and live longer overall, than people having re-treatment with abiraterone or enzalutamide. However, this evidence is uncertain because re-treatment with abiraterone or enzalutamide is not considered effective and is not standard care in the NHS.

It is uncertain how effective olaparib is compared with cabazitaxel, radium-223 or docetaxel because there is no evidence directly comparing them. An indirect comparison suggests that olaparib increases how long people live compared with cabazitaxel, but this is uncertain.

The cost-effectiveness estimates are uncertain because of the limitations in the clinical evidence and economic model. They are higher than what NICE normally

considers an acceptable use of NHS resources. Therefore, olaparib is not recommended.

# 2 Information about olaparib

## Marketing authorisation indication

2.1 Olaparib (Lynparza, AstraZeneca) 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'.

## Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics.

## Price

2.3 The price for olaparib is £2,317.50 per pack of 56 tablets, each containing 100 mg or 150 mg of the active ingredient (excluding VAT; BNF online, February 2021). The company has a commercial arrangement. This makes olaparib available to the NHS with a discount and it would have also applied to this indication if the technology had been recommended. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

# 3 Committee discussion

The appraisal committee considered evidence submitted by AstraZeneca, a review of this submission by the evidence review group (ERG), NICE's technical report, and responses from stakeholders. See the committee papers for full details of the evidence.

## Treatment pathway

### There is an unmet need for new treatments for hormone-relapsed metastatic prostate cancer

3.1 People with newly diagnosed hormone sensitive metastatic prostate cancer are usually offered androgen deprivation therapy (ADT) alone or in combination with docetaxel. The NHS England interim guidance on treatment options during the COVID-19 pandemic currently allows use of new hormonal agents, which are abiraterone with prednisone or prednisolone (hereafter referred to as abiraterone) in combination with ADT, or enzalutamide in combination with ADT, although this guidance is temporary. When a person's disease progresses while taking ADT, their disease is then referred to as hormone-relapsed metastatic prostate cancer, also known as castration-resistant metastatic prostate cancer. Despite the cancer being hormone-relapsed, treatment with ADT continues. For people with hormone-relapsed metastatic prostate cancer for whom chemotherapy is not yet indicated, treatment options include abiraterone or enzalutamide if they have not had them before (see NICE's technology appraisal guidance 259, 316, 377, and 387), or 'watchful waiting'. Clinical experts confirmed that people would have either abiraterone or enzalutamide only once. So, people who had abiraterone or enzalutamide when their cancer was hormone sensitive would not have it again when their cancer was hormone relapsed. Thereafter, treatment options include:

- docetaxel
- re-treatment with docetaxel for people who had docetaxel when their disease was hormone sensitive
- cabazitaxel with prednisone or prednisolone (hereafter referred to as cabazitaxel) for people who have already had docetaxel and
- radium-223 for people with symptomatic bone metastases, no visceral metastases, and who have already had docetaxel or cannot have it.

Patient experts explained that hormone-relapsed metastatic prostate cancer affects all aspects of their lives and is difficult for them, their families, and their friends. They highlighted the need for treatments that can extend survival and help them maintain or improve their quality of life because there is no cure. Patient experts explained that they would like more options for treatment so they can delay chemotherapy (docetaxel and cabazitaxel) and its adverse effects. This is because the adverse effects of chemotherapy, especially docetaxel, can be debilitating, even up to 1 year after people have stopped taking it. The committee concluded that there is an unmet need for new treatments for hormone-relapsed metastatic prostate cancer.

## The company's population is narrower than the marketing authorisation and excludes people who have not taken docetaxel or cannot have it

3.2 The marketing authorisation from the European Medicines Agency states that olaparib is indicated 'as monotherapy for the treatment of adult patients with hormone-relapsed metastatic prostate cancer and BRCA1/2-mutations (germline and/or somatic) who have progressed following prior therapy that included a new hormonal agent'. The company further limited the population in its submission to NICE to people who have already had a taxane, such as docetaxel. The company explained that it did this because its clinical advisers suggested that in the NHS, around 75% of people have docetaxel earlier in the pathway, while their disease is in the hormone-sensitive stage. The ERG agreed that most people who ultimately get abiraterone or enzalutamide will have had treatment with docetaxel before, but that this proportion is likely to be less than 75%. The ERG also highlighted that the NHS England interim guidance on treatment options during the COVID-19 pandemic allows earlier use of enzalutamide and abiraterone in hormone-sensitive prostate cancer, before docetaxel. This means that the proportion of people who have had treatment with a taxane before will likely be lower during and after the COVID-19 pandemic. Clinical experts explained that having docetaxel before should not be a factor when deciding the population who would have olaparib in

NHS practice. The Cancer Drugs Fund clinical lead was disappointed with the company's decision to limit the population. He explained that many people who do not choose docetaxel early in the pathway might then be unable to take it after developing hormone-relapsed metastatic disease, for example, because they become too ill. At the company's proposed position, these people would never be eligible for olaparib. Clinical and patient experts explained that although they are keen to have olaparib available as early in the treatment pathway as possible, it was most important to have it available at some point. The committee appreciated that limiting the use of olaparib to people who had previously taken docetaxel would exclude people who could benefit from olaparib but cannot or should not have docetaxel. The committee was aware that these people are likely to be older (see NICE's technology appraisal guidance on abiraterone for treating newly diagnosed high-risk metastatic hormone-naive prostate cancer). But the committee agreed it could not consider the population who had not had a taxane because the company did not submit evidence for this group. The committee concluded that the company's proposed population for olaparib is narrower than the marketing authorisation and excludes people who have not taken docetaxel already or for whom it is not suitable.

## The company chose cabazitaxel as its comparator, but radium-223 and re-treatment with docetaxel are also relevant

3.3 The NICE scope lists docetaxel, cabazitaxel and radium-223 dichloride as comparators. The company included only cabazitaxel as a comparator in its submission. It explained that there is not enough evidence for both docetaxel and radium-223 in its chosen population. The company stated that its clinical advice suggested that radium-223 is often used later in the treatment pathway, once options such as cabazitaxel have been exhausted, whereas docetaxel is often used earlier. Therefore, the company argued that docetaxel and radium-223 were not relevant comparators. The ERG agreed that there is limited evidence for both docetaxel and radium-223 and that docetaxel would likely be used earlier

in the pathway. The committee was aware that re-treatment with docetaxel happens in NHS practice as documented in NICE's technology appraisal guidance on abiraterone and as noted by stakeholders in this appraisal (see section 3.1). The clinical experts at the meeting noted that people who had already had both docetaxel and abiraterone or enzalutamide may currently be offered docetaxel again or cabazitaxel. They may also be offered radium-223 if they have symptomatic bone metastases and no visceral metastases. The committee appreciated that, in the position chosen by the company, docetaxel re-treatment, cabazitaxel and radium-223 would all be options as alternatives to olaparib, and that patients together with their doctors would decide which treatment is best. The committee concluded that cabazitaxel is likely to be the main comparator for olaparib in the company's population, but radium-223 and re-treatment with docetaxel are also relevant.

## Clinical evidence

### The baseline characteristics of people in the PROfound trial are generalisable to NHS practice, but the comparator treatment is not

3.4 PROfound was a phase 3, randomised, open-label, multicentre trial of olaparib compared with investigator's choice of enzalutamide or abiraterone in people with hormone-relapsed metastatic prostate cancer that had progressed on abiraterone, enzalutamide or both. The trial enrolled people with homologous recombination repair gene mutations, including BRCA1, BRCA2, ataxia-telangiectasia mutation (ATM) and other mutations. It stratified them according to whether they had had taxane treatment before. The primary end point was time to disease progression determined radiographically. Overall survival was among the secondary end points. The company presented clinical evidence for the population who had BRCA mutations in line with the marketing authorisation (the licensed population) and for the subgroup of this population who had taxane treatment before (see section 3.2 from here onwards referred to as the 'BRCA-mutation prior-taxane population'). The committee was

satisfied that baseline characteristics from the BRCA-mutation prior-taxane population, including age, Eastern Cooperative Oncology Group performance status and prostate-specific antigen level are generalisable to the population in the NHS. However, it noted that some treatments that people had before entering the trial, such as having had both abiraterone and enzalutamide, did not reflect NHS practice. Clinical experts explained that re-treatment with abiraterone or enzalutamide would not happen in the NHS. They noted that some people had had both abiraterone and enzalutamide before the trial but explained that this would not be expected to modify the treatment effect of olaparib in the trial. The committee considered the generalisability of the control arm in the trial to the NHS given that re-treatment with abiraterone or enzalutamide is not standard practice and has no clinical benefit according to clinical experts, who advised that the comparator arm of PROfound could effectively be considered a placebo. The company acknowledged that the trial's comparator does not reflect current NHS practice. The committee concluded that baseline characteristics in the PROfound trial are generalisable to NHS practice with the exception of some people having had both enzalutamide and abiraterone before starting the trial. It further concluded that the comparator, re-treatment with abiraterone or enzalutamide, is not offered in the NHS.

## Olaparib is more effective than re-treatment with enzalutamide or abiraterone in PROfound, but results should be interpreted with caution

3.5 In the licensed population, the prior-taxane population, and the overall population of PROfound, olaparib increased both progression-free survival and overall survival compared with investigator's choice of abiraterone or enzalutamide. In the overall population, consisting of people with BRCA, ATM, or other homologous recombination repair gene mutations, the committee noted that olaparib appeared to increase progression-free survival in people who had had docetaxel before, compared with those who had not. The hazard ratios for progression or death were 0.39 (95% confidence interval 0.29 to 0.53) and 0.77 (95% confidence interval 0.50

to 1.22), respectively. However, the committee did not see any clinical results for people who had not had a taxane before in the population restricted to BRCA mutations only (subset of the licensed population). The committee recalled that re-treatment with abiraterone or enzalutamide is not expected to have clinical benefit (see section 3.4). Therefore, it was cautious when making conclusions about olaparib's wider benefits in the NHS, in which people have options of effective treatments. The committee concluded that olaparib was effective compared with enzalutamide or abiraterone in PROfound, but the results should be interpreted with caution. The committee also concluded that any comparison of olaparib with cabazitaxel or other relevant comparators (see section 3.3) would need to use other sources of data and an indirect treatment comparison.

### The company's method for adjusting for treatment switching in the PROfound trial is appropriate, including the use of recensoring

3.6 The company explained that in the PROfound trial, a large proportion of people switched from abiraterone or enzalutamide to olaparib after radiographic disease progression. The number of people who switched cannot be reported here because the company considers it confidential. The committee recognised that treatment switching confounded the treatment effect for overall survival. This was because people in the control arm who switched to olaparib may have benefitted from the treatment effect of olaparib and likely lived longer than if they had not switched. The company considered several different methods to adjust for treatment switching, including the rank preserving structural failure time model (RPSFTM), inverse probability of censoring weights and 2-stage estimation. The company chose the RPSFTM because it did not depend on time-varying covariates to predict switching, did not reduce the effective sample size, and did not assume that there are no unmeasured confounders. The ERG agreed that the RPSFTM was the most appropriate method. The company did sensitivity analyses to explore and validate the common treatment effect assumption in the overall trial population, but not the BRCA-mutation prior-taxane population. The

company further explained that it had applied recensoring to remove any censoring bias from the treatment switching-adjusted results. Recensoring involves censoring data before the end of the trial follow-up period to avoid informative censoring bias, related to the association between prognostic factors and treatment switching. Informative censoring can happen when adjusting survival times if some people who switched treatments did not die during the trial. The committee was aware that the main limitation of recensoring is losing longer-term survival information. The ERG preferred to consider results both with and without recensoring because both can bias results: one approach tends to overestimate the effect of treatment, and the other tends to underestimate it. The committee noted that towards the end of the trial follow-up period, there were very few patients contributing towards the overall survival estimates. Therefore, in this case, recensoring did not result in the loss of a large amount of data but avoided bias associated with informative censoring. The committee concluded that the company's method for adjusting for treatment switching is appropriate, including the use of recensoring.

## The indirect comparison of olaparib with cabazitaxel is uncertain because of differences between the PROfound and CARD trials

3.7 There was no direct clinical trial evidence comparing olaparib and cabazitaxel, so the company did an indirect treatment comparison to compare progression-free survival and overall survival. The company identified the CARD trial as a source of effectiveness evidence for cabazitaxel to use in its indirect treatment comparison. CARD was a phase 3, randomised, open-label, multicentre trial comparing cabazitaxel and prednisone with enzalutamide or abiraterone in people with hormone-relapsed metastatic prostate cancer. The primary endpoint was radiographic progression-free survival. Secondary endpoints included overall survival and skeletal-related events. All patients had previously had docetaxel and either enzalutamide or abiraterone. Clinical experts explained that the comparator in CARD was very similar to PROfound: people who already had abiraterone would be offered enzalutamide, and

vice versa. In the company's indirect treatment comparison, olaparib increased progression-free survival and overall survival compared with cabazitaxel. The results cannot be reported here because they are considered confidential by the company. The ERG highlighted several differences between the trials that may lead to uncertainty in interpreting the results of the company's indirect treatment comparison. It explained that all people in the BRCA-mutation prior-taxane population of PROfound had BRCA mutations by definition, whereas mutation status in CARD was unknown. In the BRCA-mutation prior-taxane population of PROfound, a proportion of people had previously had cabazitaxel (the company considers the proportion to be confidential so it cannot be reported). The ERG explained people in CARD had not had cabazitaxel before. It also noted that the trials were done in different locations, which might have limited generalisability of results to the NHS. Also, the trials assessed radiographic progression-free survival differently. Clinical experts explained that BRCA-mutation status does not affect how well cabazitaxel works. The expert also noted that prior cabazitaxel is unlikely to affect how well olaparib works, because its mode of action is different. However, the committee noted that this was not consistent with subgroup analyses from PROfound, in which prior treatment with a taxane seem to result in different estimates of effectiveness in the overall trial population (see section 3.5). In NICE's technology appraisal guidance on cabazitaxel for hormone-relapsed metastatic prostate cancer treated with docetaxel, the committee considered the TROPIC trial. This compared cabazitaxel plus prednisone with mitoxantrone plus prednisone in people with hormone-relapsed metastatic prostate cancer whose disease had progressed after docetaxel treatment and concluded that mitoxantrone plus prednisolone was unlikely to have clinical benefits. The committee considered that mitoxantrone was similar to the control arms of PROfound and CARD, and the company could explore whether TROPIC could be included in the indirect treatment comparison. The committee was aware that people enrolled in TROPIC did not have prior treatment with abiraterone or

enzalutamide, as in PROfound or CARD, and that the company should explore the effect of this difference in populations between the trials. The committee concluded that there were differences between the PROfound and CARD trials, which led to uncertainty in the company's indirect treatment comparison, and that the network may not include all relevant trials.

### Cabazitaxel's efficacy may be underestimated, and olaparib's overestimated, because the company did not adjust for treatment switching in CARD

3.8 The company did not adjust for treatment switching in CARD as it had done in PROfound. It explained this was because it did not have access to individual patient data from CARD. The committee considered that overall survival in the cabazitaxel arm in CARD may be underestimated because 33% of people in the abiraterone or enzalutamide arm switched to cabazitaxel after disease progression. Clinical experts explained that treatment switching was included in the trial protocol in PROfound, but not in CARD. The committee appreciated that this may explain why more people switched treatments in PROfound than in CARD but did not remove the risk of bias. The committee acknowledged that the company could not adjust for treatment switching in CARD using conventional methods without individual patient data. However, it noted that it could have attempted to gain access to the data or explore how the issue might affect results by doing a range of sensitivity analyses. It noted that patients in PROfound could also switch to cabazitaxel, but could do so in both arms, so it is not expected to have affected the results as much as in CARD. The committee concluded that cabazitaxel's efficacy is likely underestimated because the company did not adjust for treatment switching in CARD. This suggests that the relative efficacy of olaparib compared with cabazitaxel based upon the indirect comparison is likely overestimated.

## The company should have explored the effect of differences in post-progression treatments between the trials and those available in the NHS

3.9 The committee discussed treatments offered in the PROfound and CARD trials after disease progression. It noted these treatments did not reflect NHS practice, and that this would affect both costs of treatment (see section 3.16) and its outcomes (the company considers the distribution of post-progression treatments in PROfound confidential so it cannot be reported here). The committee noted that life-extending treatments could affect the hazard ratios for overall survival seen in the PROfound and CARD trials. Therefore, if these treatments were offered differently to how they are in the NHS, then the trial results (and costs) would not apply to the NHS. The committee considered that a large proportion of patients in PROfound and CARD had abiraterone or enzalutamide (of those people who had a post-progression treatment after cabazitaxel in CARD, 37% had abiraterone and 37% had enzalutamide). It recalled that these treatments would not offer any clinical benefit and would not be used in NHS practice (see section 3.4). Instead, people in the NHS would have access to life-extending treatments such as radium-223. The committee noted that use of radium-223 after disease progression on olaparib in PROfound was limited (the exact rate is considered confidential and cannot be reported here), while 15% of patients in CARD had it after disease progression on cabazitaxel. The committee noted that the differences in post-progression treatments between the 2 trials, and what treatments would be used in the NHS, further affected the reliability of company's indirect treatment comparison. This therefore affected the generalisability of trial results to NHS practice. The committee considered that the company should have explored the differences in post-progression treatments used in the different treatment arms in PROfound and CARD and should have compared the trials to each other and to NHS practice. The committee considered this would help it to understand if differences in post-progression treatments were likely to have affected the

relative treatment effect in the trials and in the indirect treatment comparison, and whether survival curves would be expected to be different if they had been based on post-progression treatments typically given in the NHS. The committee concluded that the company should explore whether adjusting for differences in life-extending post-progression treatments in the trials and in the NHS is likely to alter the estimates of how long people live after progression and the estimates of cost effectiveness.

## Economic model

### Hazard ratios from the prior-taxane population should be used to model survival on cabazitaxel

3.10 To estimate cost effectiveness of olaparib in its chosen population, the company used patient-level data from the BRCA-mutation prior-taxane subgroup of PROfound to model the absolute rates of progression-free survival and overall survival for people having olaparib. It then applied hazard ratios for progression-free survival and overall survival from the indirect treatment comparison to that data to model the efficacy for people taking cabazitaxel. However, it used hazard ratios from the licensed population, rather than from the prior-taxane subgroup. The company explained that it did this because olaparib's efficacy in the licensed population and prior-taxane populations were similar, and the former group had larger patient numbers. The committee disagreed with the company's approach, in comparing a subgroup to the whole group. The committee preferred using hazard ratios from the prior-taxane subgroup to model efficacy of cabazitaxel in the prior-taxane subgroup. The committee considered the company's approach to be inconsistent because the company had used data from the PROfound prior-taxane subgroup for other model inputs, for example olaparib survival, adverse events and baseline characteristics. The committee considered it appropriate to match data used in the model to the population under consideration where

possible. The committee concluded that hazard ratios from the prior-taxane population should be used to model survival on cabazitaxel.

## The clinical survey done by the company has limitations and should not inform the plausibility of survival extrapolations

3.11 The PROfound trial reported results based on a pre-specified analysis in June 2019 for the primary endpoint of radiological progression-free survival. At the latest data cut-off (March 2020) available for overall survival, the trial was still collecting data, as planned (exact number of events is considered confidential by the company and cannot be reported here). The company used parametric survival curves to fit the trial data and extrapolate them beyond the trial duration because the model uses a lifetime horizon. The company and the ERG both considered the Gompertz curve to be the most appropriate choice to extrapolate progression-free survival and time to treatment discontinuation. This was based on the best statistical fit to the olaparib PROfound observed data. To inform the clinical plausibility of long-term overall survival estimates the company surveyed 6 clinical experts from the NHS in England. The company selected the log-logistic curve to model overall survival because, it stated, it reflected clinical opinion from its survey. It explained that the exponential curve had the best overall fit to the observed data, but the estimates were too pessimistic compared with survey responses. The ERG highlighted concerns with the company's survey. It explained that olaparib's 3-year survival predicted by the surveyed experts was higher than the observed survival in PROfound at 2 years, which is unreasonable. The ERG also pointed out the highly varied responses between experts, indicating either problems with the survey, or that clinical experts had problems predicting survival with olaparib. The committee appreciated that because olaparib is not available in the NHS, clinicians will not have seen patients who are taking olaparib, making estimating their survival very difficult. The committee also had concerns about the company's use of survey results which lack face validity. It noted that survival for cabazitaxel predicted by the model chosen by the

company was much lower than the survival predictions for cabazitaxel suggested by the experts surveyed. The committee noted that the survey did not ask for survival predictions specifically for people with BRCA mutated disease. It noted that the company's survey of clinical experts was of limited value in terms of absolute estimates of survival, but that it may help to estimate the likely relative difference in survival between olaparib and cabazitaxel. The committee agreed that the log-logistic curve overestimated this relative difference in survival, compared with the survey results. Lastly, the committee recognised the challenges in asking clinicians to estimate survival for a drug they are not yet able to prescribe. The committee concluded that the survey had limitations and had limited value in informing long-term survival estimates.

### The company's and ERG's approaches to extrapolating overall survival have limitations

3.12 The company selected the log-logistic curve to model overall survival for olaparib (see section 3.11). The ERG also emphasised that the company had applied a time-constant hazard ratio to the log-logistic model to estimate overall survival for cabazitaxel. It explained that it considered this approach to be inappropriate because log-logistic models do not support proportional hazards assumptions and the resulting estimates may overestimate survival gain for olaparib. The committee agreed with the ERG that the company had inappropriately applied a hazard ratio to a log-logistic model. The ERG explained that it had explored alternative models and had chosen the Rayleigh distribution for its base case, based on best statistical and visual fit. The committee noted that none of the parametric curves fitted the observed hazard rates from the trial well. It noted that Rayleigh, Weibull and exponential curves appeared reasonable although possibly pessimistic. The committee would have preferred for the company to have explored more flexible models that can better account for changes in the hazard rates, for example, one incorporating splines. The committee was also aware of the TROPIC trial (see section 3.7). It was aware that people enrolled in this trial did not have to have prior

treatment with abiraterone or enzalutamide, as in PROfound or CARD. But it considered that it could help validate survival extrapolations because of the maturity of the overall survival data. The committee concluded that the company should explore other parametric models as well as non-parametric modelling.

## Treatment costs

### The data on time to treatment discontinuation should be used to model olaparib treatment duration and costs

3.13 Olaparib has a confidential discount agreed between the NHS and the company. In its model, the company assumed people have olaparib until their disease progresses and used the progression-free survival data from PROfound to model olaparib costs, even though time to treatment discontinuation data were available. The company explained that it did this because only data on progression-free survival were available for cabazitaxel. The company further explained that the median progression-free survival and time to treatment discontinuation estimates from PROfound were similar. The committee noted that people may stop olaparib for reasons other than disease progression for example, adverse effects and personal choice. The ERG preferred to use the time to treatment discontinuation curve from PROfound. It explained that the curve for time to treatment discontinuation lies above the curve for progression-free survival, so the company may have underestimated olaparib's costs. The ERG also considered that using the curve for time to treatment discontinuation is aligned with the relative dose intensity calculation (see section 3.14). The ERG acknowledged that there are no data on time to treatment discontinuation available for cabazitaxel from the CARD trial. However, it explained that cabazitaxel is administered in hospital every 3 weeks rather than as a daily tablet like olaparib. Therefore, time to treatment discontinuation and progression-free survival are likely more aligned for cabazitaxel than for olaparib. Also, because cabazitaxel is less expensive than olaparib, the bias of using progression-

free survival to estimate its costs is lower than for olaparib. To explore this, the ERG did a scenario analysis in which it assumed that the cabazitaxel time to treatment discontinuation curve lies above the cabazitaxel progression-free survival curve by the same proportion as it does for olaparib. The committee concluded that time to treatment discontinuation was a better estimate of treatment duration and costs of olaparib than progression-free survival.

## The total cost of olaparib should be calculated using individual patient data from PROfound

3.14 To estimate the cost of olaparib in its original submission to NICE, the company used the mean relative dose intensity from PROfound. The relative dose intensity is the proportion of the planned dose of a drug a person takes over a given period of time. The ERG explained that the mean relative dose intensity did not account for patient exposure to treatment, and therefore did not result in an accurate estimate of the mean per-patient cost of olaparib during the trial and was also not suitable for extrapolation. The ERG preferred to use the median relative dose intensity. The company agreed with this approach during technical engagement. However, the committee was concerned with both the initial company approach and the ERG approach. It noted that generally the mean is the preferred metric to estimate costs but it agreed with ERG's concerns. The committee would have preferred for the company to calculate the costs of olaparib for each person based on their individual dose and treatment duration, and use these estimates to inform the mean per-patient cost of olaparib. The ERG clarified that unless the company provides it with the individual patients' data, it cannot calculate or validate these costs. The ERG suggested an alternative approach of presenting the mean monthly relative dose intensity over time for people remaining on treatment, and the number of observations for each time point. This would illustrate how the mean relative dose intensity changes throughout the model time horizon and how it affects model results. The ERG also questioned if the cost of olaparib in the model should be based on the

number of tablets consumed or the number of packs prescribed. This was because the NHS does not pay for individual tablets but pays for whole packs. It argued that if the cost was based on the number of packs prescribed, a relative dose intensity of 100% might be the most reasonable estimate. The Cancer Drugs Fund clinical lead explained that he expects minimal drug wastage with olaparib because clinicians often implement dose adjustments quickly when determining the right dose for an individual person. The committee was satisfied that it was appropriate for the company to have excluded drug wastage in its model. The committee concluded that the company should use individual patient data from PROfound to calculate the per-patient cost of olaparib in its base case. It also concluded that the company should present information on the mean monthly relative dose intensity over time for people remaining on treatment and the number of observations at each timepoint.

### The ERG's estimate of the costs of prophylactic granulocyte colony-stimulating factor in the cabazitaxel arm is appropriate

3.15 People taking cabazitaxel may take prophylactic granulocyte colony-stimulating factor (G-CSF) to prevent neutropenia. Therefore, the company and the ERG added the costs of G-CSF to the costs of taking cabazitaxel. The company assumed that all people taking cabazitaxel had prophylactic G-CSF for 14 days to align with the CARD study and with cabazitaxel's marketing authorisation, which recommends treatment with G-CSF 'usually for up to 14 days'. The ERG explained that the company's approach overestimated the use of G-CSF in people who take cabazitaxel. In its base case, the ERG assumed that a lower proportion of people have G-CSF, based on results of the company's survey with clinical experts (exact estimate is considered confidential by the company and cannot be reported here). It also assumed that treatment would typically last for 7 days, based on clinical opinion. Clinical experts and the Cancer Drugs Fund clinical lead explained that people would be unlikely to have G-CSF for more than 7 days and considered the ERG's estimate

to be reasonable. The committee concluded that the ERG's estimate of the costs of prophylactic G-CSF in the cabazitaxel arm was appropriate.

### The company's and ERG's estimates of post-progression treatment costs do not reflect NHS practice

3.16 Both the company and the ERG incorporated the costs of treatments after disease progression on olaparib and cabazitaxel. After technical engagement, both assumed that the same proportion of people whose disease progressed on olaparib or cabazitaxel would have an active treatment. The company considers the exact proportions of people having each treatment after disease progression on olaparib to be confidential and cannot be reported here. All remaining people would have best supportive care after progression. The company assumed that the treatments offered would differ depending on if the disease progressed on olaparib or cabazitaxel, and that disease could be re-treated with abiraterone or enzalutamide. The ERG acknowledged that in the NHS people are likely to have different treatments after progression, depending on their first treatment. However, it noted there were no reliable data to inform this. It reminded the committee that PROfound and CARD had important differences (see section 3.7) and using their proportion of post-progression treatments would not reflect NHS practice. The ERG again noted that re-treatment with abiraterone or enzalutamide would not happen in NHS practice. The company assumed that 7% of people in the cabazitaxel arm had re-treatment with cabazitaxel after disease progression on cabazitaxel, and the ERG assumed 27%. Clinical experts confirmed that in NHS practice, people would not have re-treatment with abiraterone, enzalutamide or cabazitaxel. They also considered that the company's estimate for the number of people having radium-223 in the olaparib arm was too low, while the ERG's estimate of 55% of people in both arms having radium-223 was too high. The committee therefore considered that both the company's and ERG's assumptions had limitations. Also, the company explained that its model allowed people to have only 1 active treatment after disease progression. The ERG noted

that people in PROfound had on average more than 1 active treatment after disease progression. Clinical experts confirmed that people can have multiple treatments after disease progression in NHS practice. The committee recalled its observation that life-extending treatments offered after disease progressed on olaparib were different in the PROfound trial compared with the NHS (see section 3.9). The committee concluded that the company's and ERG's estimates of post-progression treatment costs did not reflect NHS practice, and could affect cost-effectives estimates.

### The ERG's approach to costing best supportive care is appropriate

3.17 The company assumed that the costs of best supportive care differed for people who had had and stopped an active treatment after their disease had progressed on either olaparib or cabizitaxel, and those who did not have an active treatment after progression, that is, had best supportive care directly after olaparib or cabazitaxel. The company explained that this avoids double counting the costs of best supportive care, and that the model structure did not allow to estimate the costs of best supportive care after active treatment. The ERG disagreed with the company's approach and instead assumed the same best supportive care costs were incurred regardless of whether a person had an active treatment after disease progression. Clinical and patient experts explained that everyone would move to palliative care after active treatments had stopped, and that this would be the same for everyone. Therefore, the committee accepted the ERG's approach to costing best supportive care.

### All costs of testing for BRCA mutations should be included in the estimates of cost effectiveness

3.18 Before starting treatment with olaparib, people must have BRCA mutation (germline, somatic, or both) confirmed using a validated test method. The NICE methods guide states that 'if a diagnostic test to establish the presence or absence of this biomarker is carried out solely to support the treatment decision for the specific technology, the associated costs of the diagnostic test should be incorporated into the assessments of clinical and

cost effectiveness'. The company excluded the costs of testing for BRCA mutations in its base case, explaining that the NHS Genomic Test Directory already includes this test, so it is likely part of standard NHS practice. The company included the costs of testing in a scenario analysis, using costs from the testing service for ovarian cancer that the company currently funds (exact cost per test is confidential and cannot be reported here). The ERG included the testing costs in its base case because its clinical advice suggested the NHS does not currently test for BRCA mutation. One clinical expert noted that she did not routinely test for BRCA mutations other than for the small proportion of people who have a family history of BRCA mutations. Another clinical expert explained that he does genomic testing for all people with metastatic hormone-relapsed prostate cancer and that specialists in oncology have an increasing desire for testing in the NHS. The Cancer Drugs Fund clinical lead explained that the Genomic Test Directory includes testing for BRCA mutations, but that testing is not standard NHS care, and the cost of olaparib to the NHS should include testing costs. The ERG explained that it calculated the cost to identify 1 person with BRCA mutations by applying the company's cost per test to the expected prevalence of BRCA mutations in people with hormone-relapsed metastatic prostate cancer. This was based on the prevalence of BRCA mutations in people who entered screening for the PROfound trial (the company considers the exact value to be confidential and so it cannot be reported here). Clinical experts advised that the prevalence of BRCA mutations in people with hormone-relapsed metastatic prostate cancer in clinical practice is about 10%. The ERG advised that the cost of testing should include all costs of testing, including sample collection. The clinical experts advised that a diagnostic prostatic biopsy is usually, but not always, enough to test for BRCA mutations, and that a biopsy may need re-doing. The ERG noted that the company did not clarify which costs it included in its estimate of cost per test. The committee concluded that all costs of testing for BRCA mutations should be included in estimates of cost effectiveness.

## Utility values

### The company's utility values based on PROfound are appropriate

3.19 The company and the ERG used utility values from PROfound for the progression-free and post-progression health states. The utility values are considered confidential by the company so cannot be reported here. The company mapped EQ-5D-5L values from PROfound to generate EQ-5D-3L values. The company modelled worse quality of life while on cabazitaxel and prednisone than when on olaparib. While on treatment, cabazitaxel was associated with an additional decrement of -0.023 (Matza 2013) because it is administered intravenously. Once people stopped taking cabazitaxel, their utility reverted to the same as olaparib. The company sourced mean utility decrements associated with adverse events and the mean duration of adverse events from NICE's technology appraisal guidance on cabazitaxel for hormone-relapsed metastatic prostate cancer treated with docetaxel and the literature. The committee concluded that the company's utility values were appropriate.

## End of life

### It is unclear if olaparib meets NICE's criteria for life-extending treatments at the end of life

3.20 The committee considered the criteria for 'life-extending treatments at the end of life' outlined in NICE's guide to the methods of technology appraisal:

- 'a treatment must be indicated for patients with a short life expectancy, normally less than 24 months, and
- there must be sufficient evidence to indicate that treatment offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment.

In addition, the appraisal committees will need to be satisfied that:

- the estimates of the extension to life are sufficiently robust and can be shown or reasonably inferred from either progression-free survival or overall survival (taking account of trials in which crossover has occurred and been accounted for in the effectiveness review) and
- the assumptions used in the reference case economic modelling are plausible, objective and robust'.

The ERG explained that overall survival with cabazitaxel was less than an average of 24 months when using both the log-logistic curve (company base case) and Rayleigh curve (ERG base case) to extrapolate survival in the model. The company also presented results from other trials in hormone-relapsed metastatic prostate cancer, COU-AA-301 and AFFIRM, in which median overall survival ranged from 16 to 18 months with enzalutamide or abiraterone treatment. The committee was satisfied that olaparib is indicated for people with a short life expectancy. The committee acknowledged that that all parametric extrapolations of overall survival predicted at least 3 months of survival benefit for olaparib compared with cabazitaxel. However, it recalled these analyses were unlikely to be valid (see section 3.12). Therefore, the committee could not determine whether olaparib offers an extension to life of at least an additional 3 months compared with NHS standard care. The committee concluded that it is unclear whether olaparib meets NICE's criteria for life-extending treatments for people with a short life expectancy.

## Cost-effectiveness estimate

### No analyses reflect the committee's preferred assumptions

3.21 Because of confidential commercial arrangements for olaparib, cabazitaxel and other post-progression therapies, the cost-effectiveness estimates cannot be reported here. The committee noted that neither the company's nor the ERG's analyses fully reflected the committee's preferences. For the prior-taxane population chosen by the company, the committee would have preferred to see an analysis that:

- includes cabazitaxel, radium-223 and re-treatment with docetaxel as comparators (see section 3.3)
- explores if the TROPIC trial could be included in the indirect treatment comparison (see section 3.7)
- explores uncertainty around treatment switching in CARD (see section 3.8)
- explores uncertainty around the impact of post-progression treatments on post-progression survival (see section 3.9)
- uses the hazard ratios from the BRCA-mutation prior-taxane subgroup of PROfound to model the efficacy of cabazitaxel (see section 3.10)
- explores more flexible approaches for extrapolating survival (see section 3.12)
- uses long-term data from the TROPIC trial to validate extrapolation (see section 3.12)
- uses the time to treatment discontinuation data to model olaparib treatment duration and costs (see section 3.13)
- uses mean per-patient costs of olaparib, taking into account dose intensity and duration of treatment (see section 3.14)
- assumes only a proportion of people taking cabazitaxel have prophylactic G-CSF, and have it on average for 7 days (see section 3.15)
- accounts for costs of treatments used in NHS practice after disease progression on either olaparib or comparators; that is, does not include re-treatment with abiraterone or enzalutamide, or with cabazitaxel (after progressing on cabazitaxel), and includes radium-223 in the post-progression treatment costs (see section 3.16)
- assumes the cost of best supportive care is the same regardless of whether people had active treatment after progression (see section 3.17)
- includes the cost of testing for BRCA mutations on either olaparib or comparators (see section 3.18).

The committee considered results from a range of scenarios and concluded that, if its preferred assumptions were applied, the cost-effectiveness estimates for olaparib compared with cabazitaxel would be higher than what NICE normally considers an acceptable use of NHS resources.

## Other considerations

### Equalities

3.22 The committee recalled its recent appraisal of abiraterone for treating newly diagnosed high-risk metastatic hormone-sensitive prostate cancer (see NICE's appraisal consultation document on abiraterone). The committee noted that the company limited its submission to people who have already taken a taxane, which in the NHS would be docetaxel. It agreed that people who cannot or should not take docetaxel are likely to be older than those that can take docetaxel. The committee also noted that some people may not identify as men, but have a prostate. Age, sex, and gender reassignment are protected characteristics under the Equality Act 2010.

### Innovation

3.23 The Cancer Drugs Fund clinical lead explained that if recommended, olaparib would change the treatment pathway and may help to promote BRCA-mutation testing in prostate cancer in the NHS. The committee acknowledged these potential advantages. It also noted that treatment with corticosteroids at the same time as olaparib would not be needed. However, the committee noted that the company had modelled a relative increase in utility for treatment with olaparib compared with cabazitaxel, so did not consider there to be benefits not adequately captured in the economic analysis. The committee understood that both were needed to consider a technology innovative.

# 4 Proposed date for review of guidance

4.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Amanda Adler
Chair, appraisal committee
February 2021

# 5 Appraisal committee members and NICE project team

## Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee B.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

## NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

**Hannah Nicholas**

Technical lead

**Ewa Rupniewska**

Technical adviser

**Jeremy Powell**

Project manager

ISBN: [to be added at publication]

| | |
|---|---|
| **Organisation name – Stakeholder or respondent** (if you are responding as an individual rather than a registered stakeholder please leave blank): | AstraZeneca UK |
| **Disclosure**<br>Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry. | None |
| **Name of commentator person completing form:** | Janek Hendrich<br>HTA, Evidence and Reimbursement Manager<br>AstraZeneca UK Ltd. Horizon Place, Capability Green, Luton, Bedfordshire, LU1 3LU |



 

# AstraZeneca response to the Appraisal Consultation Document (ACD) for olaparib for previously treated, hormone-relapsed metastatic prostate cancer with homologous recombination repair gene mutations [ID1640]

AstraZeneca welcomes the opportunity to comment on the preliminary recommendation made by the Appraisal Committee detailed in the Appraisal Consultation Document (ACD). While we are disappointed the Appraisal Committee's preliminary decision not to recommended olaparib for previously treated, hormone-relapsed metastatic prostate cancer with homologous recombination repair gene mutations, we are committed to working with NICE to address the Committee's concerns outlined in the ACD. We are similarly committed to work with both NICE and NHS England to ensure access for patients given the high unmet need, as recognised by the Committee.

In responding to the ACD we have therefore looked to address the Committee comments and help inform appropriate treatment decision-making in this important patient population. In doing so we remain confident that olaparib is a cost-effective treatment option for patients with mCRPC and *BRCA1/2*-mutations (germline and/or somatic) who have progressed following prior therapy that included a new hormonal agent.



 

The key points covered in response to the ACD are as follows:





 

# Topic 1 Evidence in the population who have not taken docetaxel or cannot have it

**ACD Section 3.2:** "*The company's population is narrower than the marketing authorisation and excludes people who have not taken docetaxel or cannot have it*"

**Company Response:**

- Data solely in this population had not been provided previously due to limitations in the clinical evidence from PROfound
- To further support decision-making, we have provided additional evidence from the PROfound *BRCA*m no prior taxane subgroup, and we have provided additional exploratory cost-effectiveness analyses based on the no prior taxane subgroup.
- Despite these limitations, these analyses show that olaparib remains a cost-effective use of NHS resources.

## 1.1 Limitations of the available clinical evidence

AstraZeneca has submitted evidence from patients who were taxane-naïve previously as part of the Technical Engagement response, although this evidence was submitted as part of an overall *BRCA*m analysis. This presented the best available data for olaparib in the licensed population, which includes patients who may benefit from olaparib after progressing on a previous NHA with or without previous taxane-based treatment.

We recognise the desire by the Committee to review evidence specific to the *BRCA*m no prior taxane subgroup, where an appropriate treatment option for many patients may include docetaxel (see Section 1.3). We would like to reiterate that there are very limited data for docetaxel in this setting; as previously described, a systematic review of the evidence determined that docetaxel has not been assessed by a randomised clinical trial in a post-NHA mCRPC setting. Therefore:

- In the absence of clinical evidence for docetaxel in a comparable population to PROfound, a robust ITC is not feasible.
- Any comparative analysis is exploratory and must rely on a series of assumptions for clinical efficacy, as discussed later in this document (Appendix B).



 

Additionally, analyses specific to this subgroup of PROfound are more uncertain than in the prior taxane subgroup due to:

- Lower sample size
- High degree of treatment switch in the NHA arm of the PROfound study, which diluted the overall survival benefit
- Relatively immature data for overall survival in the olaparib arm

## 1.2 Summary of PROfound clinical efficacy in the no prior taxane subgroup

A summary of olaparib efficacy in the no prior taxane subgroup of PROfound is given in Appendix A, along with a comparison across *BRCA*m prior taxane, *BRCA*m no prior taxane subgroups and the overall *BRCA*m population (Table 15). Olaparib demonstrated remarkable efficacy in the *BRCA*m no prior taxane group, with an **83% reduction in the risk of radiographic progression** vs investigator's choice of NHA (median rPFS, [redacted] months vs [redacted] months, respectively; HR; [redacted]; 95% CI, [redacted], Figure 4). Median OS was not reached in the olaparib arm vs 18.79 months in the investigator's choice of NHA arm (HR; [redacted]; 95% CI, [redacted], Figure 5). The OS benefit of olaparib versus investigators' choice of NHA improved after adjusting for treatment switching in the *BRCA*m no prior taxane subgroup, with and OS HR of [redacted] (95% CI: [redacted]) using the RPSFT method with recensoring (Figure 6).

## 1.3 UK clinical pathway for patients with mCRPC who are taxane-naïve

Within the taxane-naïve population in the UK there are two distinct groups: patients who are taxane-suitable and those who are not.

### *1.3.1 Patients who are taxane-suitable:*

Docetaxel is the most appropriate treatment option for patients who are taxane-suitable; patients may also receive cabazitaxel after that. As described above, this population is analogous to the no prior taxane population from PROfound.

### *1.3.2 Patients who are taxane-unsuitable*

Patients may be unsuitable to receive docetaxel if they are contraindicated or are not able to tolerate it; NICE guidelines recommend its use in patients with Karnofsky



 

performance-status score of 60% or more.[1] As such, when patients are not considered fit enough to receive taxane chemotherapy docetaxel cannot be a treatment option. Accordingly, there is a substantial unmet need for new treatments for patients "*who could benefit from olaparib but cannot or should not have docetaxel*" (ACD, p7), as for the majority of these patients there are no life-extending treatment options. In UK clinical practice, after progression on an NHA, most patients would receive only best supportive care (BSC): therapies used to maintain or improve quality of life, with limited impact on duration of life.

For a small minority of taxane-naïve patients, radium-223 may be a treatment option. However, radium-223 is not an appropriate comparator for the majority of this population as it is only indicated for patients with symptomatic bone metastases and no visceral metastases. The number of patients in the UK who can receive radium-223 may be further restricted by accessibility, as not all centres are licensed to receive, store, use, transfer and dispose of radium-223.

### 1.4 Exploratory cost-effectiveness analyses in the no prior taxane subgroup

Taking these limitations into account, in order to support the decision making process an exploratory cost-effectiveness analysis was has been conducted in these groups of patients (see Appendix B for full details). This showed that olaparib represents a cost-effective use of NHS resources, with an ICER of £40,896 per QALY gained versus docetaxel for the taxane-suitable group, and £48,709 per QALY gained versus BSC in the taxane-unsuitable group (Table 1).



 

**Table 1 Cost-effectiveness results in the *BRCA*m no prior taxane subgroup (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) |
|---|---|---|---|---|---|---|---|
| Olaparib | [redacted] | [redacted] | [redacted] | - | - | - | |
| *Patients who are suitable for treatment with docetaxel* | | | | | | | |
| Docetaxel | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £40,896 |
| *Patients who are unsuitable for treatment with docetaxel* | | | | | | | |
| BSC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £48,709 |
| Abbreviations: BSC: Best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years | | | | | | | |

# Topic 2 Choice of comparators

**ACD Section 3.3:** "*The company chose cabazitaxel as its comparator, but radium-223 and re-treatment with docetaxel are also relevant*"

**Company Response:**

- We do not feel that either radium-223 or docetaxel re-treatment are appropriate comparators in this setting. Radium-223 and docetaxel re-treatment are used only in a small minority of patients, and due to the lack of comparable clinical trial evidence it is not feasible to conduct a comparison versus olaparib.

## 2.1 Consideration of docetaxel re-challenge as a comparator

No clinical evidence has been identified for docetaxel, whether as initial therapy or as re-challenge, in this setting (see company submission). Furthermore, docetaxel re-treatment was not included in the NICE final scope for the appraisal, and whilst we recognise the committee comments we do not believe that it is an appropriate comparator for this appraisal on the basis that:

i. **Docetaxel re-treatment is not recommended in the NICE prostate cancer guidelines**: whilst docetaxel may be offered for patients with mHSPC and mCRPC according to NG131, docetaxel re-treatment is not recommended. In fact, the guidance states the "*Repeat cycles of treatment with docetaxel are not recommended if the disease recurs after completion of the planned course of chemotherapy*."[1]

ii. **Development of docetaxel resistance:** docetaxel use is associated with the potential for developing resistance,[2] with response rates diminishing substantially over time.[3]

iii. **Lack of clinician support for its use**: The British Uro-oncology Group (BUG) discussed the low usage of docetaxel re-treatment in the abiraterone ID945 Appeal (Point 4.), which stated that "*it is inaccurate to suggest that people who have previously had docetaxel as first-line treatment in the hormone-sensitive setting can have docetaxel again (for up to an additional 10 cycles)*". In the original company submission, the use of docetaxel re-treatment was proactively mentioned by 50% of participants (3/6). None of them considered



 

the use of docetaxel re-challenge for their patients. Similarly, both clinical experts for this appraisal stated that they did not consider docetaxel re-treatment a suitable option in their opinion, with one expert citing a distinct lack of clinical evidence in support of it (Technical Engagement Response from Experts, Issue 1, Q3).

iv. **Use of cabazitaxel**: cabazitaxel was developed specifically to address docetaxel resistance, and as such demonstrates anti-tumour activity in models resistant to docetaxel.[4] Therefore, it can be considered a more intuitive treatment choice than docetaxel re-treatment for patients with mCRPC who had progressed after docetaxel-based chemotherapy.

In summary, no robust analysis of olaparib vs docetaxel re-treatment is feasible due to the lack of evidence, and docetaxel re-treatment is not an appropriate comparator for the vast majority of patients in this setting.

### 2.2 Consideration of radium-223 as a comparator

As stated in the initial company submission, there are no published RCTs assessing radium-223 for the treatment of patients whose disease has progressed after an NHA. This position was supported by the ERG in their initial report (p23: "*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*").

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 or where patients are unsuitable for docetaxel. 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.[5] Radium-223 is thus only an appropriate comparator for olaparib in the latter circumstance. This positioning is supported by data from a recent UK national radium-223 audit, which also reported on its use in later lines of treatment.[6]


 

Therefore, while radium-223 may be a *possible* comparator in this treatment line, it is used only in a small minority of patients. Furthermore, the lack of evidence against radium-223 in a post-NHA setting means that no robust comparison of olaparib versus radium-223 is feasible.



 

# Topic 3 The indirect comparison of olaparib with cabazitaxel

**ACD Section 3.7:** "*The indirect comparison of olaparib with cabazitaxel is uncertain because of differences between the PROfound and CARD trials*"

**Company Response:**

- The indirect comparison is based on the most robust evidence base, utilising data from high quality randomised clinical trials. It provides the best estimate of the relative effectiveness of olaparib versus cabazitaxel for people with mCRPC who have previously received an NHA.
- Inclusion of the TROPIC study into the network of evidence for cabazitaxel has minimal impact and improves the ICERs in favour of olaparib by £[redacted] per QALY. Despite this, the TROPIC study is not comparable in terms of the patient population and is not relevant to the decision problem.
- The CARD study is the only relevant study for cabazitaxel as it was conducted in a post-NHA setting. CARD is comparable with PROfound in several important ways, such as: broad study baseline characteristics, clinical endpoints of interest, and a common comparator arm

## 3.1 Comparability of the CARD study

The ITC was conducted based on the CARD study,[7] which provides the most robust evidence base for cabazitaxel:

- It was the only trial identified that reported outcomes with cabazitaxel in a post-NHA, mCRPC setting.
- As all patients enrolled in the CARD trial were required to have received previous docetaxel, and thus the patient population is closely aligned with the prior-taxane subpopulation of the PROfound study.
  The CARD trial was similar to PROfound based on broad baseline characteristics, clinical endpoints of interest, and sharing a common comparator arm;

Therefore, the CARD study provides the best evidence base on which to conduct an anchored ITC. Clinical experts nominated for the appraisal have also confirmed the applicability of CARD for an ITC in the Technical Engagement response (Technical Engagement Issue 5, Q14). Regarding the CARD ITC, the ERG's concerns summarised in the ACD are not expected to have a meaningful impact on the results, and would not affect decision making:



 

- During the committee meeting the clinical experts confirmed that *BRCA*m status does not affect how well cabazitaxel works. Therefore, *BRCA*m status would have no impact on the ITC results.

- Randomised clinical trials provide the highest quality evidence for the safety and effectiveness of treatments for health technology appraisals; large clinical trials are often multinational but this does not mean that the evidence would not be generalisable enough for decision making in the UK. Rather than geographical location, it is more important to consider clinically relevant factors such as indicative baseline characteristics which may have the potential to influence outcomes; as concluded by the committee, the *"baseline characteristics in the PROfound trial are generalisable to NHS practice"*

- The ERG noted that a proportion of people had previously had cabazitaxel in the PROfound study, while no patients previously had cabazitaxel in the CARD study; during the committee meeting, clinical experts stated that this issue would not have an impact on the comparative analysis. Furthermore, it is correct to include all patients who have previously received taxane-base treatment because they are part of the relevant for the population for olaparib in the UK, therefore, the ERG's point does not undermine the analysis. Finally, if this issue did have any impact it would suggest that the base case analysis is conservative and may underestimate the relative benefit of olaparib.

### 3.2 Feasibility assessment for including the TROPIC study

The committee suggested that the company should explore whether the TROPIC study results can be included in an indirect comparison. TROPIC, the registrational study for cabazitaxel, was a randomised, multicentre, multinational, Phase 3 trial assessing whether cabazitaxel plus prednisone improved overall survival compared with mitoxantrone plus prednisone.[8] This study was conducted from 2007 to 2009, before the availability of abiraterone, enzalutamide or radium-223. AstraZeneca maintain that it is inappropriate to include the TROPIC study because the trial population is outside the scope for this appraisal, and it is not comparable with the


 

PROfound study. In any case, such a comparison would have minimal impact on the results because the hazard ratios for cabazitaxel versus the comparator arm were worse than in the CARD study (HR of OS, 0.72 and 0.64, respectively). The ITC HR of OS for olaparib versus cabazitaxel would improve to [redacted] based on the TROPIC study, compared with [redacted] based on the CARD study results which is used in the current base case analysis. Using the ITC OS HR based on TROPIC would improve the ICER by £[redacted] per QALY in favour of olaparib.

Despite being favourable for olaparib, incorporating results from the TROPIC study does not lead to more robust estimates of relative efficacy. Its inclusion would not be consistent with guidance on conducting ITCs for the following reasons:[9]

- The relevance and generalisability of the TROPIC study to current UK practice is unclear because the treatment paradigm and standard of care for patients with mCRPC has changed substantially in the past decade. Since the publication of the TROPIC results, several life-extending treatments have been reimbursed for use in mCRPC (e.g., abiraterone, enzalutamide, and radium-223). Developments in general clinical practice (administration of treatments and disease monitoring) and knowledge and ongoing research (clinical trials) in prostate cancer may also serve to improve the survival landscape for patients compared with 10 or more years ago.

- Because no patients in the TROPIC study had received previous NHA, none of these patients would have been eligible to receive olaparib; therefore, inclusion of the TROPIC population is not appropriate for decision-making from this perspective.

- As the TROPIC study was conducted before the availability of NHAs, the study population is not comparable with those of either the CARD or PROfound studies, which is fundamental to a robust indirect comparison. This is an important difference in the inclusion criteria based on previous treatments that may affect the generalisability of the trial results.


 

- There is inconsistency in the comparator arms, between the TROPIC study (mitoxantrone) and the PROfound and CARD studies (NHA re-challenge), that undermines the appropriateness of an anchored ITC. Mitoxantrone is understood to reflect best supportive care, while NHA re-challenge may offer some survival benefit to patients, and is currently used across several countries in Europe.[10,11]



 

## Topic 4 Treatment switching in CARD

**ACD Section 3.8:** "*Cabazitaxel's efficacy may be underestimated, and olaparib's overestimated, because the company did not adjust for treatment switching in CARD*"

**Company Response:**

- The ITC does not underestimate the relative effectiveness of cabazitaxel versus olaparib, as treatment switching was incorporated correctly in the analysis.
- It is appropriate to adjust for the high degree of treatment switching to subsequent olaparib in the NHA arm of PROfound, as olaparib is not currently a treatment option in the UK.
- It is not necessary to make any adjustment for cabazitaxel in the NHA arm of the CARD study, as this is an important treatment option within UK standard of care for patients who have progressed on an NHA. Excluding the survival impact of cabazitaxel after NHA deviates from UK practice; excluding the impact in only the CARD study deviates from UK practice and causes an inappropriate imbalance in the NHA arms across CARD and PROfound.
- Exploratory scenarios which improve the HR of OS for cabazitaxel vs NHA in 2% increments up to 10% only increase the ICERs between £[redacted] to £[redacted], indicating that this issue is also not a key driver of the results (Table 2)

The Committee's conclusion with respect to the potential impact of cross-over adjustment on the ITC estimates of relative effectiveness of olaparib versus cabazitaxel is incorrect from an NHS and PPS decision making perspective. The ITC provides robust estimates of the relative effect of olaparib versus cabazitaxel that is aligned with UK standard of care.

In the PROfound trial protocol, patients enrolled in the NHA arm were permitted to switch to receive olaparib after disease progression. The purpose of treatment-switch adjustment was to estimate the true OS benefit of olaparib compared with investigators' choice of NHA, given that it occurred in ~[redacted]% of patients and olaparib is not currently approved or reimbursed in this treatment setting in the UK (i.e. after progression on NHA). Without adjustment, the OS results from PROfound are heavily diluted and would not reflect the true benefit of olaparib compared with standard of care.



 

Unlike olaparib, subsequent cabazitaxel use after progression on NHA and taxane-based treatment is a relevant and reimbursed option that is reflective of current UK standard of care (as received in the NHA arm of both the CARD and PROfound studies). Hence, for decision making, the impact of cabazitaxel use after NHA in the control arm of CARD should be included in the efficacy estimates, as should the use of cabazitaxel after NHA or olaparib in PROfound. To exclude the survival impact of cabazitaxel after NHA would be a substantial deviation away from UK practice, and is not appropriate from an NHS and PPS perspective. Excluding the impact of cabazitaxel after NHA in *only* the CARD study (as is suggested by the ACD) deviates from UK clinical practice and causes an inappropriate imbalance in the NHA arms across the CARD and PROfound studies which would undermine the anchored ITC analysis.

AstraZeneca do not have the patient level data from CARD required to adjust the impact of subsequent cabazitaxel in the NHA arm of the CARD study. Although it is inappropriate to conduct an adjustment for this appraisal, it is clear that the impact of any adjustment would be much smaller than as seen in the PROfound analysis because the adjustment affects a much smaller proportion of patients in CARD (33% received subsequent cabazitaxel in the NHA arm), compared with more than twice the proportion of patients receiving subsequent olaparib in PROfound ([redacted]% received subsequent olaparib in the NHA arm). A range of scenario analyses show that this issue does not constitute a key driver of the results. When arbitrarily improving the HR of OS for cabazitaxel vs NHA in 2% increments, up to 10%, the ICERs were increased by between £[redacted] to £[redacted] (Table 2).



 

**Table 2 Scenarios testing the impact of varying the OS HR for cabazitaxel vs NHA**

| OS HR (cabazitaxel vs NHA) | ITC estimate (olaparib vs cabazitaxel)* | ICER | Difference vs base case |
|---|---|---|---|
| Base case HR = 0.64 | [redacted] | £40,748 | - |
| Scenarios: assumed improvement to cabazitaxel's effectiveness | | | |
| 2% improvement | [redacted] | £41,119 | £372 |
| 4% improvement | [redacted] | £41,534 | £787 |
| 6% improvement | [redacted] | £41,987 | £1,240 |
| 8% improvement | [redacted] | £42,483 | £1,735 |
| 10% improvement | [redacted] | £43,027 | £2,279 |

* Calculated as the ratio of the OS HR of olaparib vs NHA ([redacted]) to OS HR of cabazitaxel vs NHA (0.64) adjusted by varying improvements; example: the ITC estimate after assuming a 5% improvement to the OS HR for cabazitaxel vs NHA = [redacted] / (0.95 * 0.64) = [redacted]



 

## Topic 5 Effect of differences in post-progression treatments between the trials and those available in the NHS

**ACD Section 3.9:** "*The company should have explored the effect of differences in post-progression treatments between the trials and those available in the NHS*"

**Company Response:**

- Based on the available data, it is not feasible to estimate the specific impact of post-progression treatments in PROfound or CARD. The sample size from PROfound is too small to conduct time-to-event analysis, and individual patient-level data are not available for CARD (nor any other published data on post-progression treatments).
- Any differences in post-progression treatments between the PROfound and CARD studies, and relative to treatments available in the NHS, would be expected to have a limited impact on the results given the limited treatment options in the late-line mCRPC setting.
- Ultimately, any impact on the incremental results would be realised through the OS HRs applied in the model. Based on additional scenarios, it was confirmed that varying the HRs by +/- 10% of the base case ITC results had minimal impact on the ICERs
- Scenario analyses demonstrated that the impact of subsequent treatment costs on the ICERs are minimal, from a decrease of £[redacted] to an increase of £[redacted] (further discussed in Topic 8)

The ACD states, "*The committee discussed treatments offered in the PROfound and CARD trials after disease progression. It noted these treatments did not reflect NHS practice, and that this would affect both costs of treatment*" (ACD, p14). When using data from large randomised clinical trials for health technology assessment, the incorporation of multinational study centres can inherently lead to some differences between the post-progression treatments received in the trials compared with standard practice in any single country, such as the UK. This is the case for both the PROfound and CARD studies.

In a patient population that has received docetaxel and NHA, and then progressed on either olaparib or cabazitaxel, treatment options are limited. For this reason the impact of survival of any differences in post-progression treatments between the PROfound and CARD studies, and relative to treatments available in the NHS, would be expected to be limited. As stated by the BUG representative in the ID945



 

appraisal of abiraterone (newly-diagnosed high risk metastatic hormone-naive prostate cancer): "*For each subsequent treatment there was less benefit. The number of treatment lines had little impact on overall survival*" (ID945 Appeal point 131). That patients in the olaparib arm can potentially receive cabazitaxel as a subsequent therapy, whereas patients progressing on cabazitaxel may have exhausted available life-extending treatment options, represents one major advantage olaparib would contribute to the treatment pathway for patients with mCRPC in the UK.

Based on the available data, it is not possible to reliably estimate the direction nor magnitude of impact of post-progression treatments on patient outcomes in either study. The number of patients receiving each post-progression therapy is too small to conduct an analysis based on the PROfound data. Neither are there any published data on post-progression survival or time from first to second subsequent treatment available from the CARD study. These data would be required in order to test the impact on the ICERs. A comprehensive analysis would also involve revising the economic model structure to assess the sequential impact of the time from progression to first subsequent treatment, first to second subsequent treatment, and so on. Again, such a model would have extensive data requirements for each comparator, which are not available, as described above.

The company's updated base case analysis therefore reflects the overall survival from the clinical trials, with the cost of post-progression treatments restricted to include only those reimbursed by the NHS. Any differences in post-progression treatments between the trials, and relative to treatments available in the NHS, would be expected to have a limited impact on the incremental results. Ultimately, any impact on the incremental results would be captured through varying the OS HRs. AstraZeneca conducted additional scenario analyses, which demonstrated that varying the HRs by +/- 10% of the base case ITC results had minimal impact on the ICERs (Table 3). Subsequent treatment costs were also varied to understand their impact on the results, and the impact was found to be minimal (see Table 3, also expanded on in Topic 8).



 

**Table 3. Scenario analysis varying olaparib versus cabazitaxel hazard ratio**

| Scenario | ICER | Difference vs. base case |
|---|---|---|
| Base case ITC OS HR (ola vs cab) = [redacted] | £40,748 | - |
| Scenarios exploring potential impact of post-progression treatment on relative effectiveness | | |
| Assume differences in post-progression treatments worsen HR (ola vs cab) by 5% | £41,756 | £1,008 |
| Assume differences in post-progression treatments worsen HR (ola vs cab) by 10% | £43,027 | £2,279 |
| Assume differences in post-progression treatments improve HR (ola vs cab) by 5% | £39,910 | -£838 |
| Assume differences in post-progression treatments improve HR (ola vs cab) by 10% | £39,227 | -£1,521 |
| Scenarios exploring potential impact of subsequent treatment costs | | |
| Exclude cabazitaxel re-challenge in the cabazitaxel arm only | £41,854 | £1,106 |
| Exclude all subsequent treatment costs in both arms | £41,641 | £893 |



 

## Topic 6 Extrapolation of overall survival

**ACD Section 3.12:** "*The company's and ERG's approaches to extrapolating overall survival have limitations*"

**Company Response:**

Olaparib

- AstraZeneca's extrapolations of overall survival based on the log-logistic and exponential curves are consistent with the mechanism of action of olaparib and data from other advanced, metastatic disease settings, where the long-term benefit on olaparib treatment in a proportion of *BRCA*m patients has been proven (Technical Engagement Response document, Section 3.3.2)
- The log-logistic model best-reflected the expected outcomes for olaparib and comparators based on clinical expert opinion. However, given the concern of applying a HR to a non-proportional hazards model, the updated base case analysis uses the exponential curve, which provided the best fit to the observed data albeit predicting conservative outcomes (Section 6.1)
- Additional non-parametric, flexible splines models were explored upon request by the committee, but the exponential distribution remained the statistically best-fitting curve (Section 6.1)

Cabazitaxel

- Given that the TROPIC study was not conducted in a comparable trial population to PROfound, e.g., due to differences in the number and type of previous treatments, it is not appropriate to use the TROPIC study to validate the modelled outcomes based on a naïve comparison of survival. Despite this, the relative effectiveness of cabazitaxel versus the comparator arm in the CARD study was slightly improved and consistent with that from TROPIC (HR of OS, 0.64 and 0.72, respectively) (Section 6.2)
- Two relevant real-world evidence studies were conducted by AstraZeneca to support validation exercises, in the absence of other published data from randomised clinical trials in a post-NHA mCRPC setting. The results strengthened the validity of applying the exponential distribution in the base case analysis:
    - Modelled mean and median estimates in the base case analysis were highly consistent with those from the Canadian real-world study (Section 6.2.1)
    - Modelled OS rates at 3, 6, 12 and 24 months for cabazitaxel based on the exponential curve almost exactly matched the results from the US real-world study ([redacted]%, [redacted]%, [redacted]% and [redacted]%, compared with [redacted]%, [redacted]%, [redacted]% and [redacted]%, respectively) (Section 6.2.2)



 

Summary

- In the absence of published data from randomised clinical trials in a post-NHA mCRPC setting, RWE is the best available source of evidence to validate the company OS extrapolations. Two relevant studies demonstrated that the extrapolations based on the log-logistic (initial submission base case) and exponential distributions (updated base case) reflect patient outcomes, and are therefore suitable for decision-making

Despite the challenges associated with long term extrapolation of survival data, we would reiterate that the company's predictions are consistent with the mechanism of action of olaparib and data from other advanced, metastatic disease settings, where the long-term benefit on olaparib treatment in a proportion of *BRCA*m patients has been proven (Technical Engagement Response document, Section 3.3.2).

Furthermore, as part of the Technical Engagement process, NICE independently engaged with two clinical experts. Both consultees possess world-class expertise in mCRPC, extensive experience treating patients as part of UK clinical practice, and also have long-term experience of treating patients with olaparib within a clinical trial setting. As such they can be considered the foremost source of knowledge on the management of disease and patient outcomes on olaparib, as well as current standard of care. As part of the Technical Engagement process, their responses supported the view that long-term survival with olaparib is plausible:

> *Respondent 1: "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."*
>
> *Respondent 2: "OS estimates of Weibull are more plausible at 10 years however OS estimates at 3 and 5 years seem very conservative."*

**It is worth noting that the Technical Engagement questions were focused on data from the original submission, using data from Cohort A+B of PROfound. The EMA licence was subsequently granted in the BRCAm population, where the best response to olaparib therapy was observed .*



 

### 6.1 Olaparib: Flexible splines models fitted to the observed data in PROfound

As stated in the ACD: "*The committee would have preferred for the company to have explored more flexible models that can better account for changes in the hazard rates, for example, one incorporating splines*" (ACD, p17). In response with the committee's request, we have conducted additional analyses to explore whether other survival models may support decision making.

A range of flexible spline-based models were fitted to the overall survival data from PROfound for olaparib arm of the *BRCA*m prior taxane and *BRCA*m no prior subgroups (described in Appendix B). The flexible spline-based models were assessed for the inclusion of 1 to 5 knots. Spline knot locations were chosen as equally-spaced quantiles of the uncensored survival times, and boundary knots were chosen as the minimum and maximum event times. The goodness-of-fit of each splines model was assessed according to the total AIC/BIC statistics. As shown in Table 4, the splines models with 5 knots had the best statistical fit to the observed data in the *BRCA*m prior taxane subgroup, compared with other splines models.

**Table 4 PROfound overall survival – comparison of 1-5 knot splines models separately fitted to the olaparib arm based on total AIC/BIC values**

| Spline (scale=hazard) Knots | *BRCA*m prior taxane Olaparib arm, n=72 |
|---|---|
| 1 | 710.4 |
| 2 | 715.4 |
| 3 | 721.4 |
| 4 | 716.4 |
| 5 | **706.2** |

Figure 1 shows an overlay of three plausible parametric curves and the flexible splines models.


 

**Figure 1 *BRCA*m prior taxane - parametric and flexible splines models for overall survival (olaparib)**

Based on an assessment of the AIC/BIC statistics associated with the six parametric distributions and flexible splines models, **the exponential remained the statistically best-fitting curve for olaparib in the prior taxane subgroup of *BRCA*m.** The 5-knot splines model was the second best-fitting curve, however the 5- and 10-year estimates fell below that predicted by the Weibull distribution, and were therefore deemed to provide a very conservative survival outlook (Table 5).

We maintain that the log-logistic model best-reflected the expected outcomes for olaparib and comparators based on feedback from its survey of clinical experts in the UK. However, given the concern of applying a HR to a non-proportional hazards model, the updated base case analysis uses the exponential curve. The exponential curve was accepted as plausible by the ACD, and provided the best fit to the observed data albeit predicting conservative outcomes. Figure 2 shows an overlay of the best-fitting curves, with olaparib displayed in the solid lines and comparators as dotted lines; OS estimates based on these extrapolations are given in Table 6.



 

**Table 5 PROfound overall survival – comparison of survival models separately fitted to the olaparib arm by AIC/BIC values**

| Model | 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 |
| G. Gamma | 353.2 | 360.0 | 713.2 |
| Splines | 345.1 | 361.1 | **706.2** |

Statistically best-fitting curve (used in model updated base-case)

Second best-fitting curve (used in scenario)

AIC, Akaike information criterion; BIC, Bayesian information criterion; G. Gamma, generalised gamma

**Figure 2 *BRCA*m prior taxane: best-fitting models for overall survival (olaparib, solid line; cabazitaxel, dotted line)**



 

**Table 6 OS estimates for olaparib (*BRCA*m, prior taxane)**

| Year | 1 | 3 | 5 | 10 | Total AIC+BIC | Ranking (1 = lowest AIC+BIC) | Clinically plausible long-term survival estimates |
|---|---|---|---|---|---|---|---|
| **Olaparib (PROfound, *BRCA*m prior taxane)** | | | | | | | **KEE survey[a]** |
| Exponential | [redacted] | [redacted] | [redacted] | [redacted] | **706.1** | 1 | No |
| Weibull | [redacted] | [redacted] | [redacted] | [redacted] | 728.7 | 7 | No |
| Loglogistic | [redacted] | [redacted] | [redacted] | [redacted] | 716.6 | 6 | Yes |
| Lognormal | [redacted] | [redacted] | [redacted] | [redacted] | 709.7 | 4 | Yes |
| Gompertz | [redacted] | [redacted] | [redacted] | [redacted] | 706.9 | 3 | No |
| Gen Gamma | [redacted] | [redacted] | [redacted] | [redacted] | 713.2 | 5 | No |
| Flexible splines (5 knots) | [redacted] | [redacted] | [redacted] | [redacted] | 706.2 | 2 | No |
| **Potential OS from start of olaparib (after previous taxane <u>and</u> NHA; as in initial submission for Cohort A+B, CS Document B)** | | | | | | | |
| UK clinical expert opinion (average of responses) | [redacted] | [redacted] | [redacted] | - | - | - | - |

[a] As in the Technical Engagement Response document; 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.

### 6.2 Cabazitaxel: Validation of the overall survival curves

As previously outlined in Section 3.2 above, the TROPIC trial population is not comparable with PROfound. Therefore it is inappropriate to validate the modelled survival outcomes of cabazitaxel using a naïve comparison of survival reported from TROPIC. The incremental benefit based on the longer-term TROPIC study is consistent with the CARD study; the relative benefit associated with cabazitaxel versus the comparator arm was consistent between the CARD and TROPIC studies, with a slight improvement demonstrated in the CARD study based on median gain (2.6 months and 2.4 months, respectively), and hazard ratios (0.64 and 0.72, respectively), which supports the use of the CARD study for this appraisal. Table 7 provides a summary of overall survival data published based on the CARD and TROPIC studies.

**Table 7. Overall survival from CARD and TROPIC studies**

| | **CARD, ITT[7] DCO: 27 March 2019** | | **TROPIC, ITT[4] DCO: 25 September 2009** | |
|---|---|---|---|---|
| | **Cabazitaxel** | **NHA rechallenge** | **Cabazitaxel** | **Mitoxantrone** |
| **n** | 129 | 126 | 378 | 377 |
| **Median OS, months** | 13.6 | 11 | 15.1 | 12.7 |
| **Median OS gain, months (cabazitaxel vs comparator)** | 2.6 | | 2.4 | |
| **HR, 95% CI (cabazitaxel vs comparator)** | 0.64 (0.46-0.89) | | 25 Sep 2009: 0.70 (0.59-0.83)[4]<br>10 Mar 2010: 0.72 (0.61–0.84)[12] | |

Since PROfound and CARD are the only randomised clinical trials assessing treatments in a post-NHA mCRPC setting that have published results, and the TROPIC study is not suitable for validating the survival curves. Therefore, we have explored real-world evidence data in recognition of the committee's desire to validate modelled outcomes with current standard of care.


 

### *6.2.1 Canadian RWE study conducted by AstraZeneca*

A retrospective longitudinal population study was conducted in Canada in patients diagnosed with prostate cancer between January 1, 2010 and December 31, 2018, using real-world, population-level data (*manuscript in preparation*). There were [redacted] records of prostate cancer found in Ontario between 2010 and 2018, with a total of [redacted] patients meeting the protocol defined criteria for mCRPC who received first-line treatment for mCRPC.

Despite not distinguishing between docetaxel from cabazitaxel (due to relatively small sample sizes), the study and its findings can be considered relevant: this is a recent study conducted on a large patient database, and also performed an appropriate stratification of patients aligning with the population for whom olaparib is indicated (previous NHA and previous taxane therapy). Furthermore, results are given from the start of first treatment for mCRPC after NHA and from the start of second treatment after NHA (results for these patients are based on relatively fewer patients). As expected, *BRCA*m status was not available.

#### 6.2.1.1 Results

The database allowed for an assessment of outcomes by first treatment after NHA and heavily pre-treated patients who received two prior treatments in the mCRPC setting, facilitating a comparison of patients that more closely align with the likely treatment pathway in the UK. Based on the RWE study, [redacted] of [redacted] patients ([redacted]%) received abiraterone, and [redacted] of [redacted] ([redacted] %) received enzalutamide as their initial treatment in the mCRPC setting while docetaxel was used in [redacted] patients ([redacted]%). For patients who started their first subsequent treatment after progressing on their initial NHA, there was no statistical difference in median OS in those that received therapy with a taxane or NHA re-challenge, although a numerical trend showed improved survival with taxanes. The majority of patients who had received two treatments in the mCRPC setting were NHA-experienced (i.e., treated with at least one NHA). In patients that failed two lines of treatment (at least one NHA), there was no statistical or clinically meaningful difference in overall survival between patients that received subsequent NHA re-challenge, taxane, or other therapy (predominantly radium-223).


 

There was high consistency in the mean and median OS estimates between this RWE study and modelled OS for cabazitaxel based on the CARD ITC. **The findings from the RWE study supported the validity of the modelled results using the log-logistic (initial submission base case) and exponential distributions (updated base case) as shown in Table 8.** The modelled OS produced by the loglogistic (mean [redacted] months; median [redacted] months) and exponential curve (mean [redacted] months; median [redacted] months) were highly consistent with the Canadian RWE study results (mean [redacted] months; median [redacted] months).

**Table 8 Comparison of RWE results and modelled OS for cabazitaxel based on CARD ITC**

| Survival from start of line to death | Treatment stratification | Mean | | Median | |
|---|---|---|---|---|---|
| | | Years | Months | Years | Months |
| **Canadian real-world evidence estimates** | | | | | |
| **First treatment after initial NHA in mCRPC** | **All post-NHA treatments** | [redacted] | [redacted] | [redacted] | [redacted] |
| | **Docetaxel or cabazitaxel** | [redacted] | [redacted] | [redacted] | [redacted] |
| **Second treatment after initial NHA in mCRPC** | **Docetaxel or cabazitaxel** | [redacted] | [redacted] | [redacted] | [redacted] |
| **Model – cabazitaxel based on CARD ITC (*BRCA*m after previous taxane and NHA)** | | | | | |
| **Exponential** | From start of cabazitaxel arm | [redacted] | [redacted] | [redacted] | [redacted] |
| Weibull | | [redacted] | [redacted] | [redacted] | [redacted] |
| Loglogistic | | [redacted] | [redacted] | [redacted] | [redacted] |
| Lognormal | | [redacted] | [redacted] | [redacted] | [redacted] |
| Gompertz | | [redacted] | [redacted] | [redacted] | [redacted] |
| Gen Gamma | | [redacted] | [redacted] | [redacted] | [redacted] |

Source: Ontario Cancer Registry, among those deceased prior to January, 1, 2020 (AstraZeneca Data on File)

### *6.2.2 US RWE study (FLATIRON) conducted by Merck;*

A separate RWE study was conducted on the FLATIRON database of US patients with mCRPC, diagnosed between January 1, 2013 and March 31, 2019. Of [redacted]



 

mCRPC patients in the FLATIRON database with at least three lines of therapy after mCRPC diagnosis, [redacted] ([redacted] %) had received an NHA as their first initial treatment, [redacted] ([redacted]%) were then treated with subsequent docetaxel, of which [redacted] ([redacted] %) were then treated with cabazitaxel. After excluding [redacted] patients with other primary cancers and those who participated in clinical trials, the final results were based on [redacted] patients who were treated with cabazitaxel.

#### 6.2.2.1 Results

Based on the KM data from the RWE study, OS rates at 3, 6, 12, and 24 months from the start of cabazitaxel were [redacted]%, [redacted]%, [redacted]%, and [redacted]%, respectively (Figure 3), which is very closely aligned with the modelled results based on the ITC for cabazitaxel with all distributions (Table 9). The extrapolations for cabazitaxel based on the exponential curve almost exactly aligned with the results based on the RWE study, supporting the validity of the exponential curve in the updated base case analysis. The modelled OS rates at 3, 6, 12 and 24 months were [redacted], [redacted], [redacted] and [redacted]%, respectively.

**Figure 3. Overall survival for patients with mCRPC treated with cabazitaxel after previous docetaxel and NHA therapy**



 

**Table 9 OS estimates for cabazitaxel (*BRCA*m, prior taxane; via ITC)**

| Month | | 3 | 6 | 12 | 24 |
|---|---|---|---|---|---|
| **US (FLATIRON) real-world evidence estimates** | | | | | |
| Treatment with cabazitaxel after NHA and docetaxel | | [redacted] | [redacted] | [redacted] | [redacted] |
| **Model – cabazitaxel based on CARD ITC (*BRCA*m after previous taxane and NHA)** | | | | | |
| **Exponential** | | [redacted] | [redacted] | [redacted] | [redacted] |
| Weibull | | [redacted] | [redacted] | [redacted] | [redacted] |
| Loglogistic | | [redacted] | [redacted] | [redacted] | [redacted] |
| Lognormal | | [redacted] | [redacted] | [redacted] | [redacted] |
| Gompertz | | [redacted] | [redacted] | [redacted] | [redacted] |
| Gen Gamma | | [redacted] | [redacted] | [redacted] | [redacted] |

### *6.2.3 Summary*

In the absence of published data from randomised clinical trials in a post-NHA mCRPC setting, RWE is the best available source of evidence to validate the company OS extrapolations. Two relevant studies demonstrated that the extrapolations based on the log-logistic (initial submission base case) and exponential distributions (updated base case) reflect patient outcomes, and are therefore suitable for decision-making.



 

## Topic 7 Incorporation of relative dose intensity

**ACD Section 3.14:** "*The total cost of olaparib should be calculated using individual patient data from PROfound*"

**Company Response:**

- The costs of olaparib are appropriately accrued in the model, based on the duration of treatment and dose received in PROfound
- The duration of treatment in the updated base case uses the treatment discontinuation curves derived from the individual patient-level data from the *BRCA*m prior subgroup of PROfound, per the committee's preferences (ACD Section 3.13)
- As previously demonstrated, dosing assumptions are not a key driver of the results and any impact is negligible. The median dose intensity applied in the base case analysis provides a good approximation for the actual dose received in the PROfound trial. When assuming that patients receive the full dose of 300mg bid for the duration of treatment, the ICERs improved by £[redacted] per QALY in favour of olaparib

The purpose of applying the relative dose intensity is to ensure that the costs applied in the economic model reflect the dose used in the clinical trial, and is relevant regardless of the method for modelling treatment duration. When the administered dose of the intervention is different to the full planned dose, a pragmatic approach is commonly applied and accepted in NICE technology appraisals, based on average summary values such as the mean or median values (as in NICE TA391 for cabazitaxel). The base-case analysis currently assumes the median RDI values of [redacted]% for olaparib and 96.1% for cabazitaxel, respectively.

Although further analysis of dosing at the individual patient level may provide a more accurate estimate of RDI, ultimately, the input value has minimal (almost negligible) impact on the results, as demonstrated by previous scenario analyses provided by AstraZeneca in the initial submission, Technical Engagement Response document, and in the updated scenario analyses prepared in response to the ACD (Section 10.3, Table 14). As RDI is not a key driver of the results, further analysis of the individual patient-level data has no impact on decision-making. AstraZeneca would also like to highlight that in terms of the ICERs, the company has accepted a conservative assumption in the base-case analysis. If the cost of interventions were



 

to reflect the full planned dose (i.e., RDI of 100%), this would only serve *improve* the ICER for olaparib versus cabazitaxel by £[redacted] (Section 10.3, Table 14).



 

## Topic 8 Post-progression treatment costs

**ACD Section 3.16:** "*The company's and ERG's estimates of post-progression treatment costs do not reflect NHS practice*"

**Company Response:**

- The post-progression treatment costs accrued in the updated base case analysis have been restricted to include only treatments reimbursed in NHS practice: docetaxel, cabazitaxel and radium-223
- The costs accrued in the updated model are therefore appropriately aligned with NHS practice, while based on the clinical trial data that is aligned with efficacy outcomes in the economic model
- Post-progression treatment costs have been investigated through scenario analyses, and have a minimal impact on the ICERs, increasing it between £893 and £1,106 (Table 10)
- The clinical trial data reflect that patients in the olaparib arm can potentially receive chemotherapy as a subsequent therapy, whereas patients progressing on cabazitaxel may have exhausted available life-extending treatment options. This aligns with feedback from the clinical experts, and is a major advantage that olaparib contributes to the treatment pathway for patients with mCRPC in the UK

The company's updated base case analysis already restricts the cost of post-progression treatments to include the specific treatments reimbursed by the NHS in the post-NHA mCRPC setting: docetaxel, cabazitaxel and radium-223. The impact of alternative post-progression treatment cost assumptions, such as excluding cabazitaxel re-challenge (although it would be reimbursed in the NHS), and excluding the cost of post-progression treatment costs altogether, was minimal (Table 10).

Despite this issue having little impact on the results, we would like to provide further clarity around the proportion of patients receiving cabazitaxel re-treatment radium-223 in the economic model. The ACD states that "*…the company assumed that 7% of people in the cabazitaxel arm had re-treatment with cabazitaxel after disease progression on cabazitaxel, and the ERG assumed 27%*". It also states that *"…the number of people having radium-223 in the olaparib arm was too low, while the ERG's estimate of 55% of people in both arms having radium-223 was too high"*. We believe that figures regarding post-progression treatments may have been reviewed


 

out of context; in fact, the figures are aligned with the treatment pathway for patients with mCRPC:

- The post-progression treatments applied in the model are linked to the clinical trial data from PROfound and CARD, which is appropriate for the purposes of the economic model. The data reflect that patients in the olaparib arm can potentially receive chemotherapy as a subsequent therapy before radium-223. Patients progressing on cabazitaxel may have exhausted available life-extending treatment options apart from radium-223, and therefore a higher proportion is likely, in line with the UK treatment pathway.

- The percentage of patients receiving post-progression cabazitaxel and radium-223 are reasonable. After restricting the cost of post-progression treatment to only those that are reimbursed in the NHS (i.e., excluding NHAs) per the ERG's and committee's feedback, of those who received a subsequent treatment after progression, cabazitaxel constituted [redacted]% of post-progression treatments in the olaparib arm and 27% in the cabazitaxel arm. Radium-223 constituted 55% of first post-progression treatment received after cabazitaxel. Based on the PROfound and CARD data, [redacted]% of patients who progressed in the intervention arm received subsequent treatment. Therefore, in the economic model, [redacted]% of patients progressing on olaparib received cabazitaxel; only [redacted]% of patients in the cabazitaxel arm actually accrue the cost of cabazitaxel re-treatment, and [redacted]% of patients accrue the cost of radium-223.

**Table 10 Scenarios exploring potential impact of subsequent treatment costs**

| Scenario | ICER | Difference vs base case |
|---|---|---|
| Base case | £40,748 | - |
| Scenarios exploring potential impact of subsequent treatment costs | | |
| Exclude cabazitaxel re-challenge | £41,854 | £1,106 |
| Exclude all subsequent treatment costs | £41,641 | £893 |



 

## Topic 9 End of life criteria

**ACD Section 3.20:** "*It is unclear if olaparib meets NICE's criteria for life-extending treatments at the end of life*"

**Company Response:**

- Olaparib offers an extension to life of at least an additional 3 months compared with current standard of care in the UK, as supported by the model results (based on survival extrapolations) and additional naïve comparisons of median overall survival reported in the literature for comparators

PARP inhibitors, such as olaparib, specifically target and kill homologous recombination repair (HRR)-deficient tumour cells via a mechanism involving synthetic lethality (described in the company submission, Document B, Section B.1.3). The mechanism of action of olaparib supports long-term survival benefit in patient with *BRCA*m disease; tumours specifically harbouring *BRCA1/2* mutations are most sensitive to olaparib monotherapy (relative to tumours with any of the other known HRR mutations). The incremental benefit of olaparib versus current standard of care for patients with *BRCA*-mutated disease is expected to be substantial, leading to an important change in the treatment pathway for mCRPC.

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.[13] 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.



 

The mean modelled survival gain associated with olaparib compared with standard of care is much greater than 3 months using all parametric distributions, including additional flexible spline models assessed at the request of the committee (Table 11). The incremental benefit of olaparib versus cabazitaxel is shown to be between [redacted] months and [redacted] months, thereby meeting NICE's criteria for life-extending treatments at the end of life.

Although simplistic, a naïve comparison of the median survival benefit of treatments across clinical trials is also supportive of the results. In the CARD study, cabazitaxel offered a 2.6 month extension to life versus NHA re-challenge. In the *BRCA*m prior taxane subgroup of PROfound, olaparib offered a [redacted] month gain versus NHA re-challenge despite high cross-over. After adjusting for cross-over the incremental benefit improved to [redacted] months.


 

**Table 11. Mean modelled survival gain (olaparib, PROfound *BRCA*m prior taxane; cabazitaxel via ITC)**

| | Mean overall survival predicted by the model | | | | | | |
|---|---|---|---|---|---|---|---|
| | **Exponential** | **Weibull** | **Loglogistic** | **Lognormal** | **Gompertz** | **Gen Gamma** | **Flexible splines** |
| **Olaparib** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Cabazitaxel (via ITC)** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Difference (months)** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

# Topic 10 Updated base case analysis

**ACD Section 3.21:** In the prior taxane analysis… "*the committee noted that neither the company's nor the ERG's analyses fully reflected the committee's preferences*."

**Company Response:**

- In order to guide decision making, several of the ERG's and Committee's concerns have been incorporated into the updated base case analysis, in this response to the preferences detailed in the ACD, as summarised inTable 12.

## 10.1 Issues addressed based on ACD feedback

Although we maintain that the rationale for the assumptions applied in the original base case are robust, AstraZeneca acknowledge that some of the Committee's preferences for model assumptions were not fully reflected in either the company's nor the ERG's base-case analyses (ACD Section 3.21). In order to guide decision making, the base case has been updated, incorporating some of the committee's preferred assumptions, these are summarised in Table 12.



 

**Table 12 Summary of changes incorporated into the updated base case analysis (ACD Section 3.21)**

| ACD reference | Committee's preferred analysis (ACD Section 3.21) | Company's response | |
|---|---|---|---|
| | | Reference in this document | Analysis provided |
| 3.3 | Includes cabazitaxel, radium-223 and re-treatment with docetaxel as comparators | Topic 2 | N/A (see Section Topic 2) |
| 3.7 | Explores if the TROPIC trial could be included in the indirect treatment comparison | Topic 3 | Scenario(s) |
| 3.8 | Explores uncertainty around treatment switching in CARD | Topic 4 | Scenario(s) |
| 3.9 | Explores uncertainty around the impact of post-progression treatments on post-progression survival | Topic 5 | Scenario(s) |
| 3.10 | Uses the hazard ratios from the BRCA-mutation prior-taxane subgroup of PROfound to model the efficacy of cabazitaxel | N/A | Incorporated in updated base case |
| 3.12 | Explores more flexible approaches for extrapolating survival | Topic 6 | Scenario(s) Exponential curve incorporated in updated base case |
| 3.12 | Uses long-term data from the TROPIC trial to validate extrapolation | Topic 6 | None needed |
| 3.13 | Uses the time to treatment discontinuation data to model olaparib treatment duration and costs | N/A | Incorporated in updated base case |
| 3.14 | Uses mean per-patient costs of olaparib, taking into account dose intensity and duration of treatment | Topic 7 | Scenario(s) |

| | | | |
|---|---|---|---|
| 3.15 | Assumes only a proportion of people taking cabazitaxel have prophylactic G-CSF, and have it on average for 7 days | N/A | Incorporated in updated base case |
| 3.16 | Accounts for costs of treatments used in NHS practice after disease progression on either olaparib or comparators; that is, does not include re-treatment with abiraterone or enzalutamide, or with cabazitaxel (after progressing on cabazitaxel), and includes radium-223 in the post-progression treatment costs | Topic 8 | Partially incorporated in updated base case and scenarios |
| 3.17 | Assumes the cost of best supportive care is the same regardless of whether people had active treatment after progression | N/A | Incorporated in updated base case |
| 3.18 | Includes the cost of testing for BRCA mutations on either olaparib or comparators | N/A | Incorporated in updated base case |


 

### 10.2 Summary of updated results in the base case analysis

The updated results, incorporating all changes, are presented in Table 13, which show that **olaparib remains highly cost-effective compared with cabazitaxel** with an ICER of £40,748 per QALY gained. Olaparib provided an additional [redacted] LYs and [redacted] QALYs at an incremental cost of £28,751. Based on the issues highlighted in the ACD, the list of scenarios have also been updated to understand the impact of various assumptions in order to guide decision making (Table 13), and show that the results are consistent with the base case analysis in that olaparib remains cost-effective.

The individual impact of each change in the base-case assumptions relative to the original base-case presented in the Technical Engagement Response document is shown in Appendix C.



 

**Table 13 Updated 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) |
|---|---|---|---|---|---|---|---|
| **Olaparib** | [redacted] | [redacted] | [redacted] | - | - | - | |
| **Cabazitaxel** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £40,748 |
| Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years | | | | | | | |

### 10.3 Scenario results

**Table 14 Scenario results (*BRCA*m, prior taxane)**

| | Scenario | ICER (£/QALY) | Difference vs. base case |
|---|---|---|---|
| | *Updated base case* | *£40,748* | - |
| 3.7 | Explores if the TROPIC trial could be included in the indirect treatment comparison | | |
| | ITC based on TROPIC | £38,929 | -£1,818 |
| 3.8 | Explores uncertainty around treatment switching in CARD | | |
| | Improve CARD HR by 2% | £41,119 | £372 |
| | Improve CARD HR by 4% | £41,534 | £787 |

| | | | |
|---|---|---|---|
| | Improve CARD HR by 6% | £41,987 | £1,240 |
| | Improve CARD HR by 8% | £42,483 | £1,735 |
| | Improve CARD HR by 10% | £43,027 | £2,279 |
| 3.9 | Explores uncertainty around the impact of post-progression treatments on post-progression survival | | |
| | Assume differences in post-progression treatments worsen HR (ola vs cab) by 5% | £41,756 | £1,008 |
| | Assume differences in post-progression treatments worsen HR (ola vs cab) by 10% | £43,027 | £2,279 |
| | Assume differences in post-progression treatments improve HR (ola vs cab) by 5% | £39,910 | -£838 |
| | Assume differences in post-progression treatments improve HR (ola vs cab) by 10% | £39,227 | -£1,521 |
| 3.12 | Explores more flexible approaches for extrapolating survival | | |
| | OS splines model for olaparib | £38,144 | -£2,604 |
| | OS (Loglogistic) distribution for olaparib | £32,963 | -£7,785 |
| 3.14 | Assume all patients receive the full dose of treatments | | |
| | Assume 100% RDI for olaparib and cabazitaxel | [redacted] | [redacted] |
| 3.16 | Different assumptions for costs of treatments used in NHS practice | | |
| | Subsequent treatment: exclude enza / abi and cabazi re-challenge | £41,854 | £1,106 |
| | No subsequent treatment costs | £41,641 | £893 |

# Appendix A. Data from PROfound no prior taxane subgroup

As part of the Technical Engagement response, clinical efficacy across the *BRCA*m population was given in addition to analyses in the *BRCA*m prior taxane population. Here we present data from the *BRCA*m no prior taxane subgroup, which confirm that olaparib clinical efficacy is maintained across prior and no prior taxane subgroups.

## A.1. Radiographic progression-free survival (DCO1, 4th June 2019)

In the subgroup of patients whom had received prior taxane therapy, treatment with olaparib was associated with an [redacted]% reduction in the risk of radiographic progression vs investigator's choice of NHA (median rPFS, [redacted] months vs [redacted] months, respectively; HR; [redacted]; 95% CI, [redacted]). Olaparib demonstrated similar efficacy in the *BRCA*m no prior taxane group, with an [redacted]**% reduction in the risk of radiographic progression** vs investigator's choice of NHA (median rPFS, [redacted] months vs [redacted] months, respectively; HR; [redacted]; 95% CI, [redacted], Figure 4).

**Figure 4. Kaplan–Meier plot of rPFS in patients with *BRCA*m with no prior taxane therapy**

[redacted]



 

| Outcome: BICR-assessed rPFS[a] | Olaparib 300 mg bid (n = 30) | Investigators' choice of NHA (n = 23) |
|---|---|---|
| Events, n (%) | [redacted] | [redacted] |
| Median rPFS, months (95% CI) | [redacted] | [redacted] |
| HR (95% CI) | [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: AstraZeneca Data on File

### A.2. Overall survival (DCO2, 20th March 2020)

As described in the Technical Engagement response, in the prior taxane subgroup of patients with *BRCA*m olaparib was associated with a remarkable [redacted]**% reduction in the risk of death** (median OS, [redacted] months vs [redacted] months, respectively; HR; [redacted]; 95% CI, [redacted]), again despite extensive treatment switch in the investigator's choice of NHA arm to olaparib upon progression. Treatment with olaparib in the no prior taxane group led to a [redacted]% reduction in the risk of death, with median OS not reached in the olaparib arm vs [redacted] months in the investigator's choice of NHA arm (HR; [redacted]; 95% CI, [redacted], Figure 5). These results confirm that the clinical efficacy of olaparib is maintained **regardless of prior taxane exposure**, again 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.


 

**Figure 5. Kaplan–Meier plot of final OS in patients with *BRCA*m with no prior taxane therapy**

| **Outcome: DCO2 OS, *BRCA*m no prior taxane** | **Olaparib 300 mg bid (n = 30)** | **Investigators' choice of NHA (n = 23)** |
|---|---|---|
| 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.

### A.2.1. Treatment switch analysis

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 [redacted]% of patients in both the no prior taxane ([redacted]) subgroup of *BRCA*m switching to olaparib treatment upon disease progression, thus confounding the OS analysis.

As in the initial submission and Technical Engagement response, treatment switch adjustment analyses were conducted to estimate the true OS benefit of olaparib compared with investigators' choice of NHA at the DCO2 analysis in the no prior



 

taxane population. Based on the methodology discussed at the NICE ID1640 committee meeting and subsequent ACD, the RPSFTM approach remained the most appropriate method for treatment switching adjustment, with recensoring applied.

The OS benefit of olaparib versus investigators' choice of NHA improved after adjusting for treatment switching in the *BRCA*m no prior taxane subgroup: OS HR [redacted] (95% CI: [redacted]), RPSFT with recensoring (Figure 6).

**Figure 6. Kaplan–Meier plot of counterfactual OS in the *BRCA*m no prior taxane subgroup (RPSFTM Cox PH, with recensoring), DCO2 (20th March 2020)**

### A.3. Summary of clinical evidence in the PROfound no prior taxane subgroup

In summary, olaparib demonstrates clinical efficacy in patient with *BRCA*m mCRPC, after progression on a prior NHA, regardless of prior taxane exposure. An overview of clinical efficacy in the no prior taxane subgroup compared with the prior taxane subgroup and overall *BRCA*m population is given in Table 15.



 

**Table 15. Summary table key endpoints from PROfound *BRCA*m population and *BRCA*m prior taxane/no prior taxane subgroups**

| | EMA label population: *BRCA*m | | Company base-case: *BRCA*m prior taxane | | *BRCA*m no 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) | Olaparib 300 mg bid (n = 30) | Investigators' choice of NHA (n = 23) |
| **Primary endpoint: BICR-assessed rPFS (DCO1)[a]** | | | | | | |
| Events, n (%) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Median rPFS, months (95% CI) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| HR (95% CI) | [redacted] | | [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) | [redacted] | | [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,[14] CSR edition 1, 23 October 2019,[15] PROfound CSR Addendum[16] PROfound analyses.[17]



 

# Appendix B. Exploratory analysis (*BRCA*m no prior taxane subgroup)

As stated in Topic 1, AstraZeneca recognise the desire by the Committee to review evidence specific to the *BRCA*m no prior taxane subgroup, within the context of:

- Absence of published randomised clinical trial data for docetaxel in the population of interest based on the literature (i.e., post-NHA mCRPC; please refer to Topic 1 and Topic 2).
- A relatively smaller sample size of the no prior taxane subgroup of *BRCA*m compared with the prior taxane subgroup, which was the initial rationale for presenting the *BRCA*m subgroup as a whole (including those with and without previous taxane-based treatment) in the company's Technical Engagement Response.

The exploratory cost-effectiveness analysis conducted for the *BRCA*m no prior taxane subgroup is outlined below. The analysis follows the UK clinical pathway for taxane-naïve patients, where:

- **Docetaxel is the appropriate comparator for patients for whom chemotherapy is suitable, but have not received it yet** (e.g., refused docetaxel, have not yet been indicated for docetaxel in their treatment pathway, or for whom docetaxel was not previously available)
- **Best supportive care (BSC) is the most appropriate comparator for patients who are unsuitable to receive docetaxel** either because they are contraindicated or because they are not able to tolerate it

## B.1. BRCAm no prior taxane economic model

### *B.1.1 Required changes to the economic model to incorporate docetaxel as a comparator (patients who are suitable for chemotherapy)*

In order to allow AstraZeneca to explore the *BRCA*m no prior taxane subgroup, it was necessary to revise the economic model. The *BRCA*m prior taxane model (Topic 10) was revised following the below steps:


 

- Docetaxel was fully implemented as an additional comparator per the availability of three vial options according to the eMit database, starting from the same model as outlined in Topic 10.
- Changes to the model were checked and validated by two health economists (one external health economist; and one from AstraZeneca). Results for the cabazitaxel comparison before and after the changes were almost the same, with the only difference being in total costs as a result of implementing the three vial options for docetaxel compared to the single vial in the previous model (ICER of £18,591/QALY and £18,660/QALY, respectively). This confirmed the use of the model for further adaptation to the *BRCA*m no prior taxane subgroups.
- A model version was created for the *BRCA*m no prior taxane subgroup by updating the clinical data for olaparib and docetaxel as summarised in Table 12 for clarity.

### *B.1.2 Required changes to the economic model to explore 'best supportive care' arm (patients who are unsuitable for chemotherapy)*

In UK clinical practice, after progression on an NHA BSC is the only option for patients who are unsuitable to receive docetaxel either because they are contraindicated or because they are not able to tolerate it. This therapy route was incorporated into the *BRCA*m no prior taxane model according to the following steps:

- Update necessary clinical inputs, incorporating the conservative assumption that outcomes with BSC may be proxied by the NHA re-challenge arm of PROfound (Section B.6.1)
- Update cost calculations in the 'Model Calcs' tab to reflect those incurred by patients receiving BSC for the lifetime horizon – this includes best supportive care and ongoing management costs for routine patient and disease monitoring (cells marked in red in the economic model)


 

**Table 16 Overview of key data sources used in the economic model**

| | PROfound – key data sources | | DCO, PROfound* |
|---|---|---|---|
| | ***BRCA*m prior taxane model** | ***BRCA*m no prior taxane model** | **Both models** |
| **Cross-reference in the ACD response document** | **Topic 10*** | **Appendix B** | **-** |
| Olaparib, OS | *BRCA*m prior taxane | *BRCA*m no prior taxane | DCO2 |
| Olaparib, rPFS | *BRCA*m prior taxane | *BRCA*m no prior taxane | DCO1 |
| Comparator, OS and rPFS | Cabazitaxel: ITC, CARD and PROfound (*BRCA*m prior taxane) | Docetaxel: Various scenarios<br>BSC: *BRCA*m no prior taxane, NHA arm | - |
| TTD (olaparib only) | *BRCA*m prior taxane | *BRCA*m no prior taxane | DCO1 |
| % Receiving subsequent treatment | *BRCA*m prior taxane | *BRCA*m no prior taxane | DCO1 |
| Distribution of subsequent treatments | *BRCA*m prior taxane | *BRCA*m no prior taxane | DCO2 (PROfound) |
| AEs (safety) | *BRCA*m prior taxane | *BRCA*m no prior taxane | DCO2 (PROfound) |
| SREs | *BRCA*m prior taxane | *BRCA*m no prior taxane | DCO1 |
| Age at baseline | *BRCA*m prior taxane | *BRCA*m no prior taxane | DCO1 |
| Weight at baseline | *BRCA*m prior taxane | *BRCA*m no prior taxane | DCO1 |

* The *BRCA*m prior taxane model has been previously described in the Document B of the initial submission, and in the Technical Engagement Response document. The ACD response document outlines any changes since then, including the exploratory analysis of olaparib versus docetaxel and versus best supportive care (Topic 10 and Appendix B) .

DCO: data cut-off

### B.2. Patient population, comparator and model structure

The exploratory cost-effectiveness analyses consider the two distinct groups of patients as follows:



 

- **Docetaxel is the appropriate comparator for patients for whom chemotherapy is suitable, but have not received it yet** (e.g., refused docetaxel, have not yet been indicated for docetaxel in their treatment pathway, or for whom docetaxel was not previously available)
- **Best supportive care is the only option for patients who are unsuitable to receive docetaxel** either because they are contraindicated or because they are not able to tolerate it

The model structure is the same as that for the *BRCA*m prior taxane analysis (Topic 10 and Appendix B.1).

### B.3. Patient characteristics

The mean baseline age and weight of patients in the *BRCA*m no prior taxane subgroup data from PROfound are provided in Table 17.

**Table 17. Mean age and weight, PROfound (*BRCA*m no prior taxane subgroup)**

| Characteristic | Mean (SD) |
|---|---|
| Age (years) | [redacted] |
| Weight (kg) | [redacted] |

### B.4. Efficacy outcomes

Extrapolation of time-to-event data was required to model health and cost outcomes associated with olaparib over a lifetime horizon; this was conducted based on the *BRCA*m no prior taxane subgroup of PROfound, using the same methods and software as previously described (see initial company submission, B.2.4.2). The distributions used to model rPFS and OS in this analysis were selected based on the best statistically fitting curves as indicated by the AIC/BIC values. rPFS and OS outcomes with docetaxel were estimated by applying HRs to the olaparib arm as the reference curve.


 

### B.4.1. Olaparib (PROfound, DCO2 20th March 2020); BRCAm no prior taxane subgroup

#### B.4.1.1. Overall survival

The data presented are based on the *BRCA*m no 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 no prior taxane subgroup were [redacted]% mature ([redacted] events in 30 patients; median not reached). The Kaplan-Meier plots and extrapolated curves for OS in the olaparib arm are shown in Figure 7 and Figure 8, respectively.

The AIC/BIC values for the parametric curves are provided in



 

Table 19, which includes the best-fitting splines model (one-knot spline model, based on assessment of AIC/BIC values in Table 18). The total AIC/BIC values for the distributions fitted to the observed data were similar. The log-logistic distribution providing the best statistical fit to the observed data, and was therefore used for the 'no prior taxane' subgroup analysis. The Weibull distribution was tested in the scenario analysis.

**Figure 7 OS, Kaplan–Meier plot (DCO2, *BRCA*m – no prior taxane)**

**Table 18 PROfound overall survival – comparison of 1-5 knot splines models separately fitted to the olaparib arm based on total AIC/BIC values**

| Spline (scale=hazard)<br>Knots | *BRCA*m prior taxane n=72 | *BRCA*m no prior taxane n=30 |
|---|---|---|
| 1 | 710.4 | **242.1** |
| 2 | 715.4 | 247.4 |
| 3 | 721.4 | 247.9 |
| 4 | 716.4 | 254.1 |
| 5 | **706.2** | 254.7 |



 

**Figure 8 *BRCA*m no prior taxane - parametric and flexible splines models for overall survival (olaparib)**



 

**Table 19 AIC and BIC values for parametric models for OS (DCO2, *BRCA*m no prior taxane)**

| Model | AIC | BIC | Total |
|---|---|---|---|
| Exponential | 119.8 | 121.2 | 241.1 |
| Weibull | 116.9 | 119.7 | 236.7 |
| Loglogistic | 116.9 | 119.7 | **236.6** |
| Lognormal | 117.1 | 119.9 | 237.1 |
| Gompertz | 117.9 | 120.7 | 238.5 |
| Gen Gamma | 118.9 | 123.1 | 242.0 |
| Splines | 118.9 | 123.1 | 242.1 |

AIC, Akaike information criterion; BIC, Bayesian information criterion; Gen, generalised; OS, overall survival.

#### B.4.1.2. Radiographic progression-free survival (rPFS)

At DCO1, the rPFS data for the *BRCA*m no prior taxane subgroup of the PROfound population were relatively mature, although not all patients had experienced an event ([redacted]% maturity, [redacted] events in 30 patients). The Kaplan-Meier plots and extrapolated curves for rPFS in the olaparib arm are shown in Figure 9 and Figure 10. AIC/BIC statistics for olaparib rPFS data are presented in Table 20. The lognormal distribution was the best fitting curve according to the AIC/BIC statistics and was therefore used to model rPFS in the base-case analysis.


 

**Figure 9 rPFS, Kaplan–Meier plot (DCO1, *BRCA*m no prior taxane)**

**Figure 10 Modelled rPFS for olaparib based on PROfound (DCO1, *BRCA*m – no prior taxane)**



 

**Table 20 AIC and BIC values for parametric models for rPFS (DCO1, *BRCA*m – no prior taxane)**

| Distribution | AIC | BIC | Total |
|---|---|---|---|
| Exponential | 116.0 | 117.4 | 233.4 |
| Weibull | 114.8 | 117.6 | 232.4 |
| Loglogistic | 114.7 | 117.5 | 232.2 |
| Lognormal | 114.6 | 117.4 | **232.0** |
| Gompertz | 115.9 | 118.7 | 234.5 |
| Gen Gamma | 116.5 | 120.8 | 237.3 |

AIC, Akaike information criterion; BIC, Bayesian information criterion; Gen, generalised; OS, overall survival.

### B.4.2. Docetaxel (HR applied to olaparib curve)

Based on the SLR, there were no published randomised clinical trials assessing docetaxel in a post-NHA mCRPC setting to inform a robust ITC in a comparator population to PROfound. As a further result of this, it is not feasible to validate the extrapolated curves for docetaxel. Findings from the wider evidence base are summarised below:

- The TAX327 registrational trial for docetaxel in the mCRPC setting.[8] The TAX327 study demonstrated that docetaxel monotherapy reduced the risk of death by 24% versus mitoxantrone (HR = 0.76, 95% CI 0.62 to 0.94; P=0.009); a comparable measure of PFS was not reported. Since TAX327 was conducted before the availability of NHAs the generalisability and applicability of this study to current standard of care is unclear.
- Based on the real-world evidence identified in an additional systematic literature review conducted by AstraZeneca, the relative effectiveness of docetaxel compared with NHAs in the post-NHA setting was inconclusive:
    - Three real-world evidence studies suggested that outcomes with docetaxel in a post-NHA mCRPC setting may be similar to NHA re-challenge.[18-20] However, the level of data reported were not sufficient for an ITC
    - Two studies based on patients in Japan suggested that docetaxel had improved efficacy compared with NHA re-challenge[21,22]


 

We do not believe there is one optimal approach to modelling outcomes with docetaxel because of the lack of evidence in a post-NHA setting. However, in order to undertake the analysis requested, given the TAX327 study is the registrational docetaxel and despite the age of the study and lack of a contemporary comparator, data from this study have been used for an ITC.

#### B.4.2.1. Exploratory indirect treatment comparison (PROfound vs TAX327, OS)

The exploratory ITC was helpful to inform a plausible estimate of relative efficacy on OS (rPFS was not reported in TAX327) and was used in the economic analysis. The ITC was conducted based on the following assumptions:

- The relative effectiveness of docetaxel (75 mg, 3-weekly regimen) versus mitoxantrone as assessed in TAX327 are generalisable to a post-NHA setting (OS HR = 0.76, 95% CI 0.62-0.94).
- An anchored ITC is possible using the comparator arms of PROfound and TAX327; however, it should be noted that this analysis is likely to underestimate the true benefit of olaparib versus docetaxel. The comparator arm in PROfound 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.[23] Mitoxantrone, the comparator arm in TAX327, offers no survival benefit and is not considered an active anti-cancer treatment for mCRPC. If the two comparator arms across studies were the same, the estimate of relative effectiveness for olaparib should be improved. Therefore, the analysis can be considered conservative in this regard.

The methods for the ITC based on TAX327 are consistent with those used when conducting the ITC based on CARD; further details are available for reference in Section 2.9 of the initial company submission and Appendix A.2. of the Technical Engagement response. Data sources are presented in Table 21.

- Aggregate data from TAX327 study were sourced directly from the study publication (OS HR = 0.76, 95% CI 0.62–0.94).[8]


 

- For olaparib, individual patient data (IPD) for OS were derived from the treatment-switching analysis based on the *BRCA*m no prior taxane subgroup of the PROfound population.

**Table 21. Summary of data sources for the exploratory ITC inputs (PROfound vs TAX327)**

| Treatment | Study details | OS |
|---|---|---|
| Olaparib | **PROfound** (olaparib vs NHA, mCRPC post-NHA) | *BRCA*m no prior taxane subgroup (derived from treatment-switching analysis) |
| Docetaxel | **TAX327** (docetaxel vs mitoxantrone, mCRPC) | HR reported in TAX327 |

The results of the exploratory ITC show that olaparib is associated with an OS benefit compared with docetaxel (Table 22). Proportional hazards assumptions between arms were tested within each trial. The proportional hazards assumption was assessed using the same approach as for PROfound and CARD. There was no evidence against the null hypothesis of proportional hazards at the 95% significance level (Schoenfeld p-value = 0.63 and 0.66 in the PROfound and TAX327 studies, respectively). As there was no clear violation, it was assumed that the use of constant hazard ratios to generate comparative evidence for olaparib and docetaxel is reasonable.

**Table 22 Summary of exploratory OS ITC results for PROfound *BRCA*m no prior taxane population vs TAX327**

| | PROfound | TAX327 |
|---|---|---|
| OS HR (95% CI), treatment vs comparator | [redacted] | 0.76 (0.62–0.94) |
| ITC HR used in model<br>OS HR (95% CI), olaparib vs comparator | [redacted] | [redacted] |

* OS HR after treatment switching adjustment (RPSFT, with recensoring).
CI, confidence interval; DCO2; data cut-off (20th March 2020). HR, hazard ratio; ITC, indirect treatment comparison; NHA, new hormonal agent; OS, overall survival

The exploratory analysis shows that treatment with olaparib results in an [redacted]% risk reduction in mortality compared with docetaxel (HR [redacted] (95% CI [redacted])). Due to the


 

mechanism of action of PARP inhibitors, the extent of benefit of olaparib versus docetaxel for patients with *BRCA*-mutated disease is expected to be large.

The resulting curves for OS after applying the reciprocal of the exploratory TAX327 ITC HR are shown in Figure 11. As it was not possible to conduct the ITC on rPFS, an assumption was made that the magnitude of relative effectiveness of docetaxel on overall survival would be the same as the magnitude of the relative effectiveness on progression-free survival. The HR of OS was applied to the rPFS curve for olaparib as the reference curve to model rPFS in the docetaxel arm (Figure 12).

**Figure 11 *BRCA*m no prior taxane – best-fitting models for overall survival (olaparib, solid; docetaxel, dotted)**



 

**Figure 12 *BRCA*m no prior taxane – best-fitting models for progression-free survival (olaparib, solid; docetaxel, dotted)**

### B.4.3. Best supportive care (HR applied to olaparib curve)

As previously described, there are no alternative treatments for the majority of patients who are unsuitable to receive docetaxel. Patients in this setting will typically receive only therapies to maintain/improve quality of life, with limited impact on duration of life. Although we would expect NHA re-treatment to offer more than minimal clinical efficacy, for the purposes of this analysis, the NHA re-challenge arm from PROfound was used to proxy outcomes associated with BSC. This represents a conservative analysis but facilitates a straightforward comparison to address this high unmet need patient population.

Olaparib demonstrated remarkable efficacy in the *BRCA*m no prior taxane group compared with NHA re-challenge (Section 1.2). Based on the results the PROfound study, olaparib reduced the risk of death compared with NHA re-challenge by [redacted]% after adjusting for cross-over (OS HR [redacted]; 95% CI, [redacted]), with a similar [redacted]% reduction in the risk of radiographic progression (rPFS HR [redacted]; 95% CI, [redacted]).



 

OS and rPFS associated with BSC was modelled in the same way as for docetaxel (by applying the reciprocal of the HRs to the olaparib curve as the reference arm). The resulting curves for BSC are shown in Figure 13 and Figure 14, respectively.

**Figure 13 *BRCA*m no prior taxane: best-fitting models for overall survival (olaparib, solid; BSC, dotted)**

**Figure 14 *BRCA*m no prior taxane: best-fitting models for progression-free survival (olaparib, solid; BSC, dotted)**



 

### B.4.4. Validation of efficacy outcomes

As outlined in Topic 1, there are no published randomised clinical trials assessing outcomes with current treatments in a post-NHA mCRPC setting (irrespective of *BRCA*m status). Therefore, survival outcomes were validated against a Canadian RWE study. The findings of the RWE study supported the validity of the modelled outcomes:

- **Docetaxel, *BRCA*m no prior taxane (Table 23):** The loglogistic curve used I the analysis produced the closest estimates to the RWE results, compared with all other distributions. Modelled OS produced by the loglogistic curve (mean [redacted] months; median [redacted] months) was consistent with the Canadian RWE study results (mean [redacted] months; median [redacted] months).

- **BSC, *BRCA*m no prior taxane (Table 24):** The loglogistic curve used in the analysis produced the closest estimates to the RWE results, compared with all other distributions. Modelled OS produced by the loglogistic curve (mean [redacted] months; median [redacted] months) was highly consistent with the Canadian RWE study results (mean [redacted] months; median [redacted] months).



 

**Table 23 Comparison of RWE results and modelled OS for docetaxel based on exploratory TAX327 ITC**

| Survival from start of line to death | Treatment stratification | Mean | | Median | |
|---|---|---|---|---|---|
| | | Years | Months | Years | Months |
| **Real-world evidence estimates** | | | | | |
| **First treatment after initial NHA in mCRPC** | **All post-NHA treatments** | [redacted] | [redacted] | [redacted] | [redacted] |
| | **Docetaxel or cabazitaxel** | [redacted] | [redacted] | [redacted] | [redacted] |
| **Second treatment after initial NHA in mCRPC** | **Docetaxel or cabazitaxel** | [redacted] | [redacted] | [redacted] | [redacted] |
| **Model – docetaxel based on exploratory TAX327 ITC** | | | | | |
| Exponential | *BRCA*m, post-NHA, from start of docetaxel | [redacted] | [redacted] | [redacted] | [redacted] |
| Weibull | | [redacted] | [redacted] | [redacted] | [redacted] |
| **Loglogistic** | | [redacted] | [redacted] | [redacted] | [redacted] |
| Lognormal | | [redacted] | [redacted] | [redacted] | [redacted] |
| Gompertz | | [redacted] | [redacted] | [redacted] | [redacted] |
| Gen Gamma | | [redacted] | [redacted] | [redacted] | [redacted] |

Source: Ontario Cancer Registry, among those deceased prior to January, 1, 2020 (AstraZeneca Data on File)



 

**Table 24 Comparison of RWE results and modelled OS for BSC (proxied by NHA re-challenge) based on the PROfound study**

| Survival from start of line to death | Treatment stratification | Mean | | Median | |
|---|---|---|---|---|---|
| | | Years | Months | Years | Months |
| **2L mCRPC (treated with NHA in 1L)** | **Abi/enza as 2L treatment** | [redacted] | [redacted] | [redacted] | [redacted] |
| **3L mCRPC (treated with NHA in 1/2L)** | **Abi/enza as 3L treatment** | [redacted] | [redacted] | [redacted] | [redacted] |
| **Model – NHA re-challenge based on PROfound (adjusted for cross-over)** | | | | | |
| Exponential | *BRCA*m, post-NHA, from start of NHA re-challenge | [redacted] | [redacted] | [redacted] | [redacted] |
| Weibull | | [redacted] | [redacted] | [redacted] | [redacted] |
| **Loglogistic** | | [redacted] | [redacted] | [redacted] | [redacted] |
| Lognormal | | [redacted] | [redacted] | [redacted] | [redacted] |
| Gompertz | | [redacted] | [redacted] | [redacted] | [redacted] |
| Gen Gamma | | [redacted] | [redacted] | [redacted] | [redacted] |

Source: Ontario Cancer Registry, among those deceased prior to January, 1, 2020 (AstraZeneca Data on File)

### B.5. Intervention and comparators' costs and resource use

As previously described in initial company submission Document B and the Technical Engagement response documents, all relevant costs over a lifetime horizon are considered, in line with the NICE reference case.

There were no changes to the unit costs of resource use values compared with those previously described, and they have not been replicated here. The only changes to costs are those directly related to the inclusion of docetaxel as a full comparator in the economic model as outlined in Table 25.



 

**Table 25 Summary of cost categories included in the *BRCA*m no prior taxane model**

| Cost category | Updates in the economic model | Impact |
|---|---|---|
| Drug acquisition costs | • Docetaxel 75mg/m$^2$ (21-week cycles), up to 10 treatment cycles<br>• Docetaxel incorporated per the availability of three vial options, according to the eMit database; previously, docetaxel was implemented based on a single vial (cheapest per mg)<br>• All other costs remain the same as in previous documents.<br>• No treatment costs required for BSC (which is costed separately) | Required to incorporate docetaxel as comparator |
| Drug administration unit costs | No change | - |
| Premedication and G-CSF unit costs | No change to unit costs – relevant treatments described below | |
| Subsequent treatment costs | Only docetaxel (see above) | Negligible |
| Disease monitoring resource use and patient follow-up unit costs | No change | - |
| Unit cost of AE management including distribution of SREs | No change | - |
| Other one-off costs (e.g., end of life care cost) | No change | - |

Abbreviations: AE: Adverse event; BSC: Best supportive care; SRE: Skeletal-related event

### B.5.1. Docetaxel: Premedication regimen

The economic model included the recommended premedication regimen for cabazitaxel, in line with the SmPC and administration of docetaxel in the TAX327 study, containing:

- Corticosteroid (dexamethasone 8 mg or equivalent)



 

### B.5.2. Docetaxel: Primary prophylactic G-CSF

Based on feedback from UK clinical experts, when there is a high risk of febrile neutropenia with treatment with docetaxel, primary prophylactic G-CSF may be administered to reduce the risk of neutropenia complications (febrile neutropenia, prolonged neutropenia or neutropenic infection). Clinical experts consulted for the initial company submission were asked "*In patients with mCRPC, treated with docetaxel after receipt of a new hormonal agent (abiraterone/enzalutamide), do you also use primary prophylactic G-CSF?*". Of the four clinicians that responded, usage varied from just a few patients to all patients. Distance from a hospital was cited as the main driver of use. On top of this, the current COVID-19 pandemic was cited as a factor driving usage further. In our analysis a value of [redacted] % has been assumed as a conservative representative national average for of patients receiving docetaxel in the post-NHA mCRPC setting who may receive primary prophylactic G-CSF. The economic model incorporates these costs.

## B.6. Treatment duration

The ACD suggests using TTD curves to model treatment duration for while using the rPFS curves to model treatment duration for comparators, despite this being an inconsistent approach. AstraZeneca has applied the committee's preferred approach in the base case analysis, but maintains that this inconsistency leads to an imbalanced analysis in favour of the comparators.

Data are presented based on the parametric curves fitted to the patient-level data for TTD at DCO1 in the *BRCA*m no prior taxane subgroup (TTD was not included as part of the planned analysis at DCO2). The analysis was conducted using the same methods as previously described. The Kaplan-Meier plots and extrapolated curves for TTD in the olaparib arm are shown in Figure 15 and Figure 16; the Weibull curve was selected as it was the statistically best-fitting curve based on AIC/BIC values (Table 26).



 

**Figure 15 TTD, Kaplan–Meier plot (DCO1, *BRCA*m – no prior taxane)**

**Figure 16. Modelled TTD for olaparib based on PROfound (DCO1, *BRCA*m no prior taxane)**



 

**Table 26 AIC and BIC values for parametric models for TTD (DCO1, *BRCA*m no prior taxane)**

| Distribution | AIC | BIC | Total |
|---|---|---|---|
| Exponential | 143.0 | 144.4 | 287.5 |
| **Weibull** | **132.9** | **135.7** | **268.6** |
| Loglogistic | 133.7 | 136.5 | 270.2 |
| Lognormal | 133.4 | 136.2 | 269.6 |
| Gompertz | 134.3 | 137.1 | 271.4 |
| Generalized Gamma | 134.9 | 139.1 | 274.0 |

### B.7. Relative dose intensity

The median RDI values were applied, as before, per Table 27 below. As previously discussed this is not a main driver of the cost-effectiveness results, with the impact of assuming 100% RDI being minimal.

**Table 27. Median RDI values used in the analysis**

| Intervention | RDI value (%) | Source / rationale |
|---|---|---|
| Olaparib | Median: [redacted] | PROfound |
| Docetaxel | Median: 96.1 | Assumption (based on cabazitaxel, TA391) |

### B.8. Measurement and valuation of health effects

There were no changes to the health state utility values used in the economic model. Mean health state utility values based on HRQoL data collected from the PROfound study have been previously detailed in Section B.3.4.1 to Section B.3.4.3 of the original submission for this appraisal.

### B.9. Adverse events (AEs) and skeletal-related events (SREs)

The updated values for treatment-related AE rates (occurring in at least 5% of patients) and SREs associated with olaparib in the *BRCA*m no prior taxane subgroup of PROfound are shown in Table 28.


 

For docetaxel, AE rates were taken from the TAX327 study, with the following exceptions:

- The rate for leukopenia was not reported, and the values for neutropenia (32%) and diarrhoea (32%) were not reported separately for Grade 3 and above AEs. For simplicity it is assumed that the rate of these AEs would be much lower, equivalent to that occurring with cabazitaxel (5%, 5% and 3.2%, respectively).
- Musculoskeletal pain or discomfort was not reported as an AE in TAX327 but UK clinical experts stated that this is a clinically important issue that would impact patients' quality of life. It is assumed that this would occur at the same rate as with cabazitaxel (1.6%).

SRE data were not reported in the TAX327 study, therefore, an assumption was made that these would occur at the same rate as observed in the NHA arm of the PROfound study ([redacted] %). The same rate was assumed for the BSC arm.

**Table 28 Grade 3 and above AEs affecting at least 5% of patients included in economic analysis.**

| | Olaparib | Docetaxel* | BSC |
|---|---|---|---|
| **Adverse event, DCO2 %** [a] | **PROfound, *BRCA*m – No prior taxane N = 30** | **TAX327 (N = 332)** | |
| Anaemia | [redacted] | 5.0 | N/A |
| Infection | [redacted] | 3.3 | N/A |
| Leukopenia | [redacted] | 5.0[b, c] | N/A |
| Neutropenia | [redacted] | 5.0[b] | N/A |
| Musculoskeletal pain or discomfort[d,e] | [redacted] | 1.6[b, c] | N/A |
| Thrombocytopenia[e] | [redacted] | 1.0 | N/A |
| Febrile neutropenia[e] | [redacted] | 3.0 | N/A |
| Diarrhoea[e] | [redacted] | 3.2 [b, c] | N/A |
| Fatigue/asthenia[e] | [redacted] | 5.0 | N/A |
| **Skeletal-related events, DCO1 %** [a] | | | |
| At least one event | [redacted] | Assumption: [redacted] | Assumption: [redacted] |



 

[a]AEs were included part of the safety analyses from PROfound at DCO2 (20th March 2020), which are consistent with the known safety and tolerability profile of olaparib; SREs were not part of the planned analysis and are therefore only available at DCO1 (4th June 2019)
[b]Assumed equivalent rate to cabazitaxel, as Grade 3+ AEs were not reported separately in the TAX327 study.
[c]Input values based on clinical expert advice on the incidence of leukopenia/neutropenia and diarrhoea (Grade 3 and above) that would require hospitalisation (data on file).
[d]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.
[e]Occurred in fewer than 5% of patients in clinical trials but added to the list of AEs based on impact on quality of life and/or resource use (validated by UK clinical experts).

## B.10. Subsequent anti-cancer treatment

### B.10.1. Proportion of patients receiving subsequent treatment

The number of patients who received subsequent treatment in the olaparib arm of the *BRCA*m no prior taxane subgroup of the PROfound population at DCO2 is provided in Table 29. Only [redacted] out of 30 ([redacted] %) of patients had received one or more subsequent treatments after progression on olaparib. The proportion of patients receiving subsequent treatment was not reported in the TAX327 study, therefore, this was assumed to be the same as those receiving subsequent treatment after NHA re-challenge in the *BRCA*m prior taxane subgroup of PROfound (i.e., active treatments received by patients with *BRCA*m mCRPC in the PROfound study who have already been treated with at least one taxane-based therapy, for whom the majority would have been docetaxel, and who have progressed on an NHA). In the NHA arm of the *BRCA*m prior taxane subgroup of PROfound, [redacted] out of 35 patients ([redacted] %) received subsequent treatment after disease progression.

It is assumed that patients in the BSC arm of the model do not receive any subsequent anti-cancer treatment as there are no treatment options available for the vast majority of patients.

### B.10.2. Distribution of subsequent treatments

The distribution of subsequent treatments was sourced from the PROfound trial for olaparib, based on the *BRCA*m no prior taxane subgroup of patients. As above, subsequent treatment data were not reported in the TAX327 study, therefore the distribution of treatments was again based on the NHA re-challenge arm of the


 

*BRCA*m prior taxane subgroup of PROfound. The distribution of treatments are summarised in Table 29.

**Table 29 Data informing subsequent treatment costs applied in the economic analysis (Olaparib, PROfound, *BRCA*m no prior taxane; Docetaxel assumed based on NHA arm of PROfound, *BRCA*m prior taxane)**

| Subsequent treatment | Duration | Source/justification | % by initial treatment, adjusted to exclude NHA re-challenge (updated base case) | |
|---|---|---|---|---|
| | | | Olaparib PROfound – *BRCA*m no prior taxane (N=30) | Docetaxel NHA re-challenge, PROfound – BRCAm prior taxane (N=35) |
| Overall % ($n/N_p$) receiving subsequent treatment[a] | | | [redacted] | [redacted] |
| **Of those receiving subsequent treatment, % receiving:** | | | | |
| Docetaxel | 10 treatment cycles (30 weeks) | Maximum recommended duration in mCRPC setting[24] | [redacted] | [redacted] |
| Cabazitaxel | 7 treatment cycles (22 weeks) | Median duration of exposure reported in CARD[7] | [redacted] | [redacted] |
| Radium-223 | 6 injections (24 weeks) | Median number of injections in ALSYMPCA[25] (>50% in interim analysis and >80% in safety update) | [redacted] | [redacted] |

[a]Excluding investigational and treatments that have not been approved for use in mCRPC patients, and subsequent NHA re-challenge; percentages re-adjusted to sum to 100%.
mCRPC, metastatic castration-resistant prostate cancer; NHA, new hormonal agent.

### B.11. Best supportive care

All patients are assumed to receive BSC; BSC costs were applied per the ERG's recommended calculations described in the ERG Report and Technical Engagement documents, over the lifetime horizon.


 

### B.12. Results

Olaparib represents a cost-effective use of NHS resources, with an ICER of £40,976 per QALY gained versus docetaxel for the taxane-suitable group, and £48,792 per QALY gained versus BSC in the taxane-unsuitable group (Table 30). Scenario analyses are presented in Table 31.

**Table 30 *BRCA*m no prior taxane 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) |
|---|---|---|---|---|---|---|---|
| Olaparib | [redacted] | [redacted] | [redacted] | - | - | - | |
| *Patients who are suitable for treatment with docetaxel* | | | | | | | |
| Docetaxel | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £40,976 |
| *Patients who are unsuitable for treatment with docetaxel* | | | | | | | |
| Best supportive care | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £48,792 |
| Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years | | | | | | | |

**Table 31 Scenario results for cost-effectiveness modelling olaparib versus either docetaxel or BSC**

| | | Docetaxel-suitable Olaparib vs docetaxel | | Docetaxel-unsuitable Olaparib vs BSC | |
|---|---|---|---|---|---|
| | **Scenario** | **ICER (£/QALY)** | **Difference** | **ICER (£/QALY)** | **Difference** |
| | Updated base case | £40,976 | - | £48,792 | - |
| 1 | Assume 100% RDI for olaparib and docetaxel | £41,280 | £305 | £49,342 | £550 |
| 2 | OS (Flexible splines) distribution for olaparib | £52,036 | £11,060 | £61,592 | £12,800 |
| 3 | OS (Weibull) distribution for olaparib | £52,009 | £11,034 | £61,565 | £12,773 |
| 4 | rPFS (Log-logistic) distribution for olaparib | £41,292 | £317 | £49,031 | £239 |
| 5 | rPFS (Weibull) distribution for olaparib | £45,269 | £4,293 | £52,917 | £4,125 |

# Appendix C. Description of changes and impact of the updated base case on the model results (*BRCA*m, prior taxane model)

The base case was updated to incorporate some of the ERG's and committee's preferred assumptions. The individual impact of updates to the inputs in the *BRCA*m prior taxane model is provided in Table 32 below.

**Table 32 Description of changes and impact of the updated base case on the model results***

| ACD Section | Model inputs | | | Updated ICER (£ per QALY) | |
|---|---|---|---|---|---|
| **3.21** | **Original base-case** | **Updated base-case** | **Input in the updated base-case** | **Olaparib vs cabazitaxel** | **Impact vs original base-case*** |
| 3.10 | ITC HRs based on *BRCA*m analysis of PROfound vs CARD | ITC HRs based on the *BRCA*m prior taxane subgroup of PROfound vs CARD | OS HR = [redacted]<br>rPFS HR = [redacted] | £19,785 | £1,193 |
| 3.12 | Log-logistic distribution to model olaparib OS | Exponential distribution to model olaparib OS | Exponential | £22,779 | £4,188 |
| 3.13 | Uses rPFS to model treatment duration for olaparib and cabazitaxel | Uses TTD to model treatment duration for olaparib, and rPFS for cabazitaxel | TTD – olaparib; rPFS - cabazitaxel | £20,923 | £2,331 |
| 3.15 | Assumes that all patients receiving cabazitaxel have prophylactic G-CSF, in line | Assumes only a proportion of people have prophylactic G- | 79.5% uptake, based on UK EAP for cabazitaxel; 7 days | £21,738 | £3,146 |

| | | | | | |
|---|---|---|---|---|---|
| | with the CARD study protocol; for 14 days | CSF, and have it on average for 7 days | | | |
| 3.16 | Accounts for costs of treatments used after disease progression on either olaparib or comparators, per the clinical trial studies (EMA-approved treatments) | Accounts for costs and treatments used in NHS practice, excluding re-treatment with abiraterone or enzalutamide (UK NHS treatments) | Include subsequent treatments: docetaxel, cabazitaxel, radium-223 | £18,345 | -£247 |
| 3.17 | The proportion of patients who don't receive subsequent treatment move on to receive best supportive care (BSC) | Applies the cost of BSC regardless of whether people had active treatment after progression | Apply BSC costs for all patients | £22,459 | £3,867 |
| 3.18 | Excludes the cost of testing for *BRCA* mutations | Includes the cost of testing for *BRCA* mutations | Same value as before £[redacted] per test, 9.7% prevalence | £22,600 | £4,008 |
| Updated base case | | | | £40,748 | £22,156 |

Abbreviations: *BRCA*: BReast CAncer gene; BSC: Best supportive care; G-CSF: Granulocyte colony-stimulating factor; HR: Hazard ratio; ITC: Indirect treatment comparison; OS: Overall survival; rPFS: Radiographic progression-free survival; TTD: Time to treatment discontinuation

* Additionally, one minor correction was made to cell 'Model Calcs'!$BE$18 which had negligible impact on the results (reduced the original base-case ICER by £5 per QALY).

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NICE National Institute for Health and Care Excellence

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

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| **Disclosure** Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry. | **We have no links to, or funding from, the tobacco industry** |
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| | table. |
| Example 1 | We are concerned that this recommendation may imply that …….. |
| 1 | **We are concerned that the need to compare olaparib to cabazitaxel has narrowed the patient population for olaparib (section 3.2) and could result in some patients with metastatic hormone-refractory prostate cancer and BRCA1 and BRCA2 pathogenic variants being denied access to Olaparib solely because they have not had prior docetaxel chemotherapy.**<br><br>We believe this could result in discrimination of patients by age, poorer performance status, co-morbidities, and poor cognition, as well as those with chemotherapy contra-indications. This is especially worrying when the PROfound study shows clear evidence of benefit in the no-prior taxane population.<br><br>• In 2016 the 80+ age group accounted for 34% of all newly diagnosed metastatic prostate cancer population, >2000 patients[1].<br>• Analysis of Public Health England data showed that in 2016 94% of newly diagnosed metastatic prostate cancer patients aged 80 or over did not receive chemotherapy[1]. This represents a sizeable population of patients that, if identified as BRCA1 or BRCA2 positive, could be denied olaparib.<br>• Despite growth in uptake in younger age groups between 2013-16, uptake of chemotherapy only slightly increased in the 80+ age group during the same time period (3.97% to 5.70%). This continues to suggest that there is a large group of patients, unlikely to ever be suitable for chemotherapy due to their age who could also miss out on olaparib.<br><br>In a recent Appraisal Consultation Document (ACD)[2], broader criteria than just age were provided for docetaxel chemotherapy unsuitability. They are as follows:<br>• Have a contraindication to docetaxel as listed in the summary of product characteristics for docetaxel and NHS England's clinical commissioning policy for docetaxel in combination with ADT.<br>• People with poor performance status, which is a measure of fitness (WHO or ECOG performance status 3 or 4, and may include people with performance status 2 because docetaxel is used with caution in this group).<br>• People with significant comorbidity such that prostate cancer is not likely to be the only life-limiting illness for the patient.<br>• People with peripheral sensory neuropathy or poor bone marrow function.<br>• People with poor cognition or social support, which results in an inability to understand treatment options or make a decision.<br><br>Patients with any of these criteria and/or older patients that progress to hormone-refractory prostate cancer, after treatment with a novel hormonal agent, seem likely to be denied access to Olaparib simply because of their unsuitability for a prior taxane. This is especially the case for patients with peripheral neuropathy or performance status, as the European Medicine's Agency product information for olaparib does not consider these to be factors that make patients unsuitable for it[3].<br><br>It is also very likely that these patients will be unsuitable for cabazitaxel chemotherapy and only those with bone and no visceral metastases will be able to access radium 223. Their treatment options will therefore be very limited, and they stand to lose out on additional months of life.<br><br>NICE cannot allow its processes, which require treatments to be compared to determine whether a new treatment can be considered clinically and cost-effective in comparison to the standard of care, to exclude a sub-population of patients from accessing a new treatment. This approach can only result in all patients needing to be suitable for taxanes if they are to gain additional months of life, leaving those patients unsuitable for taxanes with a clear unmet need and inequity of outcomes. This |

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|---|---|
| | is made worse by their being clear evidence of olaparib providing clinical benefit in the sub-population without prior taxane use in the PROfound study[4].<br><br>**NICE and the company must explore ways in which whole population evidence for olaparib can be used, while the Committee must be clear and transparent about the level of clinical benefit uncertainty in comparison to cabazitaxel that it is willing to accept.** |
| 2 | **We are concerned that excluding the use of olaparib in patients with no prior taxane use risks making olaparib unavailable to all future hormone -refractory metastatic prostate cancer patients, should cost-effective alternatives to docetaxel become available when patients are hormone-sensitive. NICE must not predicate all future treatment options on docetaxel use, especially when there is clear evidence of the clinical benefit from olaparib in the no-prior taxane sub-group.**<br><br>Prostate cancer treatments are continuing to evolve, with many last line treatments being trialled earlier in the prostate cancer pathway. Should these prove clinically and cost-effective in the hormone sensitive metastatic prostate cancer setting, they may reposition docetaxel, either providing an alternative option or significantly reducing its use as standard of care.<br><br>We are deeply concerned that this could result in patients missing out on Olaparib, without sufficient justification. This is not the case earlier in the hormone-refractory metastatic prostate cancer pathway when patients can have a novel hormonal therapy before or after docetaxel. This appraisal should not be requiring this specific prior treatment when there is evidence of clinical benefit from olaparib in both the no-prior and prior taxane groups.<br><br>**We want the NICE committee to have greater flexibility on the patient sub-groups included in the indirect treatment comparison, recognising this will increase uncertainty of comparative effect. We also want NICE to consider the evidence from PROfound that shows benefit of Olaparib in both the prior and no-prior taxane sub-groups.** |
| 3 | **We are concerned that NICE processes, which requires a comparator, is flawed on this occasion and inadvertently penalising a patient sub-group**. This is because:<br><br>Cabazitaxel, the comparator for olaparib, was not routinely available when the PROfound study started in 2016. This has required the company to conduct an indirect treatment comparison to compare the outcomes of olaparib to cabaztaxel using data from the PROfound and CARD trials, respectively.<br><br>The indirect treatment comparison has aimed to draw on the similarities between the two trials, however, the trials differ regarding the proportion of the population that have received prior chemotherapy. Patients from PROfound who have not received prior chemotherapy have therefore been removed from the comparison (section 3.10).<br><br>This results in a no-win situation where including the whole population from PROfound will draw criticism of a lack of similarity with the CARD trial and effect the ability to determine clinical cost-effectiveness. Excluding a sub-group to achieve greater similarity between the two trials, provides what is needed for clinical cost-effectiveness assessment, but places this sub-group at a disadvantage and denies them clinical benefit.<br><br>This cannot be an effective way to appraise a treatment trialled when a different standard of care was available. The result is to exclude a patient sub-group for whom PROfound trial evidence shows a clinical benefit.<br><br>This comparison is made more challenging by the different populations these treatments are intended to benefit, with cabazitaxel being whole population based[5] and olaparib specific to small |

| | |
|---|---|
| | sub-groups of patients with specific genomic variants. This means that the sub-group outside of the indirect treatment comparison is underpowered to demonstrate statistically significant outcomes and cannot be appraised it in its own right, as it less likely that clinical cost-effectiveness can be established.<br><br>**We want the NICE committee to have greater flexibility with the patient sub-groups included in the indirect treatment comparison, recognising this may increase uncertainty of comparative effect, but relying on the evidence from PROfound that shows benefit of olaparib in both the prior and no-prior taxane sub-groups.** |
| 4 | **Statistically powered data for the prior and no prior taxane sub-groups is unlikely to be feasible in a clinical trial setting and they should be considered as one population.**<br><br>Patients with a BRCA 1/2 pathogenic variant are a very specific subset (~10%) of the whole metastatic hormone refractory prostate cancer population. Over 4000 patients were screened as part of the PROfound trial. After eligibility criteria, sequencing failure and qualifying alterations were taken into account, only 387 patients underwent randomization. Of these, only 141 have a BRCA 1 or 2 pathogenic variant[6].<br><br>Given these circumstances we feel that the decision by the company to group the no prior taxane and prior taxane groups together to mitigate small patient numbers is an appropriate and reasonable decision. Our preference for this appraisal is for greater flexibility with the patient sub-groups included in the indirect treatment comparison, recognising this may increase uncertainty of comparative effect, but relying on the evidence from PROfound that shows benefit of olaparib in both the prior and no-prior taxane sub-groups.<br><br>**However, if for any reason this does not happen,** we want NICE and the company to discuss whether it is possible to use real world data from a managed access scheme to assess the effectiveness of Olaparib in the no prior taxane group within England, Wales and Northern Ireland. |
| 5 | **The committee is overestimating the role of prior taxane as a modifier of the effectiveness of Olaparib, despite the benefit of olaparib in the no prior taxane group.**<br><br>Although it was not feasible to generate sufficiently powered data, PROfound shows clinical benefit in cohort A patients regardless of prior taxane status.<br><br>There is no clear evidence available to show that prior docetaxel is a treatment effect modifier for olaparib. As such, we do not consider there to be sufficient justification for removal of the no prior taxane patients from the indirect treatment comparison.<br><br>Limiting the population in the indirect treatment comparison to prior taxane patients only, may increase similarity between the olaparib and cabazitaxel populations. However, on balance, the marginal increase in certainty of the results does not justify denying patients access to olaparib.<br><br>We consider the scenario presented by the company in the original indirect treatment comparison plausible and can ensure equitable access to olaparib and urge NICE to revisit this, recognising this may increase uncertainty of comparative effect and have implications for cost-effectiveness. |

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

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| 6 | **We fundamentally disagree with the assertion that radium-223 dichloride is a suitable comparator for Olaparib (section 3.3)**<br><br>Radium-223 dichloride is recommended as an option for treating adults with hormone-relapsed prostate cancer, symptomatic bone metastases and no known visceral metastases. Within the PROfound study, only 35% of patients had bone metastases, suggesting the treatment is not suitable for all patients that could receive olaparib. In addition to this, clinical experts have suggested a similar proportion of patients in U.K practice do not receive radium-223 dichloride[7].<br><br>Given the limited populations for both treatments and the differences in patient types it would not be feasible to compare them without removing 65% of the olaparib population. This will lead to a similar scenario to the one resulting from the cabazitaxel indirect treatment comparison, but would this time exclude patients with visceral metastases from accessing olaparib.<br><br>In addition to this, there is insufficient available evidence to know the sequence of treatments in the hormone-refractory metastatic prostate cancer setting to be certain that radium 223 is made available when olaparib is. As it is specifically indicated after docetaxel, clinicians could make it available before or after abiraterone or enzalutamide. Without clarity on the exact place on the pathway radium 223 is prescribed, it cannot be considered a comparator to olaparib. |
| 7 | **We fundamentally disagree with the assertion that docetaxel re-challenge is a suitable comparator for Olaparib (section 3.3)**<br><br>We reiterate that a significant proportion of patients, who are likely to be of advanced age, will not be suitable for docetaxel treatment and therefore not suitable for re-challenge. 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[8].<br><br>Clinical experts have also outlined that docetaxel re-challenge after treatment with a novel hormonal treatment is not an evidenced treatment option and is unlikely to occur regularly in practice [7]. |
| References | 1. Data in this analysis is based on patient-level information collected by the NHS, as part of the care and support of cancer patients. The data is collated, maintained and quality assured by the National Cancer Registration and Analysis Service, which is part of Public Health England (PHE). The data is taken from the Get Data Out tables.<br>2. National Institute for health and Care Excellence (NICE), 2021. *Abiraterone for newly diagnosed high-risk hormone-sensitive metastatic prostate cancer*.<br>3. European Medicines Agency, 2020. *Summary of Product Characteristics (Lynparza)*.<br>4. de Bono, J., Mateo, J., Fizazi, K., Saad, F., Shore, N., Sandhu, S., Chi, K., Sartor, O., Agarwal, N., Olmos, D., Thiery-Vuillemin, A., Twardowski, P., Mehra, N., Goessl, C., Kang, J., Burgents, J., Wu, W., Kohlmann, A., Adelman, C. and Hussain, M., 2020. Olaparib for Metastatic Castration-Resistant Prostate Cancer. *New England Journal of Medicine*, 382(22), pp.2091-2102.<br>5. de Wit, R., de Bono, J., Sternberg, C., Fizazi, K., Tombal, B., Wülfing, C., Kramer, G., Eymard, J., Bamias, A., Carles, J., Iacovelli, R., Melichar, B., Sverrisdóttir, Á., Theodore, C., Feyerabend, S., Helissey, C., Ozatilgan, A., Geffriaud-Ricouard, C. and Castellano, D., 2019. Cabazitaxel versus Abiraterone or Enzalutamide in Metastatic Prostate Cancer. *New England Journal of Medicine*, 381(26), pp.2506-2518.<br>6. de Bono, J., Mateo, J., Fizazi, K., Saad, F., Shore, N., Sandhu, S., Chi, K., Sartor, O., |

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

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| | Agarwal, N., Olmos, D., Thiery-Vuillemin, A., Twardowski, P., Mehra, N., Goessl, C., Kang, J., Burgents, J., Wu, W., Kohlmann, A., Adelman, C. and Hussain, M., 2020. Supplementary Appendix for Olaparib for Metastatic Castration-Resistant Prostate Cancer. *New England Journal of Medicine*, 382(22)<br>7. National Institute for health and Care Excellence, 2021. *Olaparib for previously treated hormone relapsed metastatic prostate cancer [ID1640] Committee Papers*. pp.555-572.<br>8. National Institute for health and Care Excellence, 2020. *Abiraterone for treating newly diagnosed high risk metastatic hormone-naive prostate cancer [ID945], BUG: Appeal Letter*. p.3. |
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Insert extra rows as needed

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# Appraisal Consultation Document (ACD) for olaparib for previously treated, hormone-relapsed metastatic prostate cancer with homologous recombination repair gene mutations [ID1640]

## Evidence Review Group's report summary

**Produced by:** Warwick Evidence

**Date completed** 09.07.2021

**Declared competing interests of the authors:** none

**Table of Contents**

## Topic 1 Evidence in the population who have not taken docetaxel or cannot have it

The company supplies cost effectiveness estimates compared to docetaxel of £40,896 per QALY for the taxane suitable group and £38,929 per QALY for those not suitable for taxane and so relative to BSC.

## Appendix B Exploratory analysis (*BRCA*m no prior taxane subgroup)

Section B.4.2.1 of appendix B of the ACD company response presents the results of the indirect treatment comparison of overall survival (OS) between olaparib (from PROfound study) and docetaxel (from TAX327).

The estimates from PROfound study are derived from olaparib vs NHA OS treatment switching-adjusted hazard ratio (HR) for the BRCAm no prior taxane subgroup. The method used for the treatment switching-adjustment is detailed in section A.2.1 of the company response. Patients ([redacted]%) in the prior taxane NHA group switched to olaparib upon disease progression, at DCO2.

The company applied the same methodology that was discussed at AC1 and subsequent ACD – a rank-preserving structural failure time model with re-censoring. The corresponding hazard ratios are presented in Table 1.

**Table 1. Treatment switching-adjusted OS HR**

| OS at DCO2 | No adjustment for switching | Switching-adjusted |
|---|---|---|
| BRCAm prior taxane subgroup | [redacted] | [redacted] |

As expected, the switching-adjusted OS HR results in a greater OS benefit for olaparib over NHA, however this also resulted in wider confidence intervals and the HR remained statistically insignificant.

The comparator HR is taken from TAX327 for docetaxel in the mCRPC setting. In this study, docetaxel monotherapy reduced the risk of death by 24% versus mitoxantrone (HR = 0.76; 95% CI 0.62 to 0.94).

The ERG agrees with the company's concerns regarding the comparator trial. TAX327 was conducted before the availability of NHAs, therefore comparability to PROfound is uncertain.

Table 22 of the ACD company responses presents the results of the indirect treatment comparison between olaparib and docetaxel: ITC HR = [redacted], an [redacted]% risk reduction of death for olaparib in comparison to docetaxel.

TAX327 did not report the rPFS outcome, therefore an ITC between olaparib and docetaxel was not possible. The company applied the ITC OS HR to the rPFS curve for olaparib under the assumption that the magnitude of relative effectiveness of docetaxel on OS would be the same as that on rPFS.

**Modelling OS**

ERG confirm the company's finding that spline models fail to generate superior AIC/BIC scores relative to other parametric models and that the differences between models' IC values is trivial (CS Table 20). The ERG reconstructed OS IC values that are summarised in Table 2. While reconstructing the OS KM (CS Figure 7) the ERG identified 12 events and believes that the 14 events quoted in CS page 55 section B 4.1.1 can be a typological error.

**Table 2. IC values for parametric models of OS**

| Model | AIC | BIC | aggregate |
|---|---|---|---|
| R1P | 52.6 | 54.0 | 106.6 |
| loglogistic | 54.5 | 57.3 | 111.8 |
| weibull | 54.6 | 57.4 | 112.0 |
| R2P | 54.6 | 57.4 | 112.1 |
| lognormal | 54.7 | 57.5 | 112.2 |
| gompertz | 55.6 | 58.4 | 114.0 |
| exponential | 57.4 | 58.8 | 116.1 |
| ggamma | 56.5 | 60.7 | 117.2 |

The company selected the loglogistic model based on AIC BIC values. However, this model is likely to be overgenerous for survival in extrapolation (Figure 1 left) (with survivors beyond 20 years) and does not support proportional hazards. Therefore, that application of a HR to obtain comparator survival would be inappropriate. The ERG prefers the Weibull or R1P/R2P models. Such models support proportional hazards, fit the KM data well, and seem not to generate unrealistic survival rates in extrapolation. The hazard for all three models is almost identical over the observed

phase of about 30 months. However, the loglogistic model hazard decreases and becomes fairly flat after 120 months (low probability of death with increasing age) that indicates survivors into the long term.

**Figure 1. OS and hazard predicted by loglogistic R2P and Weibull models**

**Modelling rPFS**

ERG reconstructed rPFS IC values are summarised in Table 3.

**Table 3. IC values for parametric models of rPFS**

| Model | AIC | BIC | aggregate |
|---|---|---|---|
| R1P | 61.5 | 62.9 | 124.5 |
| lognormal | 61.4 | 64.2 | 125.6 |
| loglogistic | 61.6 | 64.4 | 126.1 |
| exponential | 62.4 | 63.8 | 126.2 |
| Weibull | 62.0 | 64.8 | 126.8 |
| R2P | 62.7 | 65.5 | 128.1 |
| Gompertz | 63.1 | 66.0 | 129.1 |
| ggamma | 63.4 | 67.6 | 130.9 |
| bathtub | 64.7 | 68.9 | 133.5 |

The values are in line with the CS in terms of hierarchy of IC values. The company selected the lognormal model on the basis of low aggregate IC value. The lognormal does not support proportional hazards, therefore the application of a HR to obtain comparator survival would be inappropriate. The ERG prefers an alternative model that performs well on IC and generates a good visual fit. The Weibull, Rayleigh 1P, and exponential models support proportional hazards and perform well on IC. However, the exponential model has a poor visual fit relative to Weibull and R1P.

The R1P has the lowest IC aggregate value; therefore R1P represents the ERG preferred option and Weibull ranks second.

The relevant ERG reconstructed parametric curves are shown in Figure 2; exponential, lognormal and Weibull are essentially the same as the CS models (CS Figure 10).

**Figure 2. Parametric models of time to radiological progression**

## TTD modelling

ERG reconstructed rPFS IC values are summarised in Table 4.

**Table 4. Reconstructed rPFS IC values**

| Model | AIC | BIC | Aggregate |
|---|---|---|---|
| R1P | 52.8 | 54.2 | 106.9 |
| Weibull | 54.6 | 57.4 | 111.9 |
| R2P | 54.8 | 57.6 | 112.3 |
| lognormal | 54.8 | 57.6 | 112.4 |
| gompertz | 55.8 | 58.6 | 114.5 |
| loglogistic | 55.2 | 58.0 | 113.3 |
| ggamma | 56.5 | 60.7 | 117.2 |
| exponential | 63.3 | 64.7 | 128.0 |

The values are in line with the company in terms of hierarchy of IC values. The company selected the Weibull model on basis of low aggregate IC value. The R1P model provides a good visual fit (Figure 3) and provides a superior aggregate IC score relative to Weibull. Therefore, the ERG prefers the R1P model and Weibull as a second preference. The ERG reconstructed parametric curves are shown in Figure 3; the Weibull are essentially the same as the CS models (Figure 3).

**Figure 3. Parametric models of time to treatment discontinuation**

To model OS and PFS for docetaxel (comparator), the company apply a HR of [redacted] (reciprocal [redacted]) to their selected parametric model (loglogistic for OS and lognormal for PFS). The original ERG report highlights that those models do not support proportional hazards and therefore the method is inappropriate. The ERG has therefore applied the company's reciprocal HR to better fit models that support proportional hazard assumptions. In both cases, the best fit model by AIC/BIC aggregate value was the R1P model. Therefore, OS and PFS are generated from the R1P parameter of [redacted] for OS and [redacted] for PFS. The comparator docetaxel was generated for the expression:

$$S_{doc} = \exp(-\text{R1Pparameter} * HR * \text{time}^2)$$

The comparator BSC was generated using HRs of [redacted] and [redacted] for OS and rPFS respectively, and by applying these to the olaparib R1P models of OS and rPFS.

## Topic 2 Choice of comparators

### Comparators of cabazitaxel, radium-223 and re-treatment with docetaxel

The company reiterates the work provided it in the original submission. In the ERG report we state that the company 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.

NICE guidance (NG131, 2019) state that treatment with docetaxel should be stopped at the completion of 10 cycles. The ERG clinical advisor states that treatment cycles vary in practice (a ceiling of 10 cycles) and re-treatment may occasionally occur in exceptional cases (young patients, patients responding well to treatment, patient that will not benefit from other treatments). NICE guidance state "*Repeat cycles of treatment with docetaxel are not recommended if the disease recurs after completion of the planned course of chemotherapy, 2008*". However, the planned course of docetaxel can vary from 6 to 10 cycles in clinical practice which makes the precise definition of re-treatment clinically challenging. The evidence highlights some docetaxel treatment limitations such as intrinsic or acquired treatment resistance[1]. Although studies[2,3] have found reversal agents for docetaxel resistance, current clinical guidance is not clear.

## Topic 3 The indirect comparison of Olaparib with cabazitaxel

### The indirect comparison of olaparib with cabazitaxel

The ERG's reiterates previous concerns regarding the ITC:

Transitivity assumption: In PROfound, tumours in all participants had mutations in HRR genes. This is unlikely to be the case in CARD.

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 *BRCA*m status is a treatment effect modifier for response to cabazitaxel or NHA treatment." Several recent studies have suggested shorter PFS for men 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)[4], and 4.3 months (95% CI 1.0, 7.6) vs. 9.2 months (95% CI 8.1, 10.3)[5,6]. These studies suggest that men with BRCA1 or 2 mutations who are treated with NHA might have worse outcomes than those treated with NHA who do not have these mutations. Therefore, BRCAm status is a *potential* treatment effect modifier for NHA treatment.

There are similar types of evidence (i.e., retrospective cohort studies) that suggest BRCA mutations are not associated with treatment effect. The ERG believes that it is unclear if the assumption of transitivity has been violated, therefore we have uncertainty. The ERG agree with the company that additional work will improve our understanding of the impact of BRCA1/2 mutations.

**Exploration of including TROPIC in the indirect comparison**

The ERG agree with the company's assessment of inclusion of CARD in the ITC analyses and the exclusion of TROPIC[7]. Given the timeframe of when the TROPIC trial was conducted and the changes in treatment and standard of care since then, no patients in TROPIC received previous NHA so none would be eligible to receive olaparib. In addition, there are inconsistencies between comparative groups.

The company supplies a scenario analysis based upon the TROPIC study that sees the OS hazard ratio improve from its base case estimate of [redacted] to [redacted]. This improves the company revised base case cost effectiveness estimate for olaparib compared to cabazitaxel from £40,748 per QALY to £38,929 per QALY. The company has not supplied the model underlying these estimates, so the ERG cannot cross check these estimates or take them through to the cPAS appendix.

## Topic 4 Treatment switching in CARD

**Explore treatment switching within CARD**

The company explain adjusting for the impact of subsequent cabazitaxel deviates from standard of care for patients who progress on an NHA and causes an imbalance across the NHA arm in CARD and PROfound, if the adjustment is only applied to the CARD study. Although it is inappropriate to adjust for the impact of subsequent cabazitaxel in the CARD study, scenario analyses that arbitrarily

improve the performance of cabazitaxel compared to the comparator arm in CARD, suggesting that this has only a limited effect upon the cost effectiveness estimate. However, the ERG agree with the company that, while adjusting for treatment-switching should be applied for CARD, the company are unable to do so because of lack of individual patient level data.

The ERG exploratory analyses that suggests that accounting for treatment switching during CARD could worsen the OS hazard ratio for the prior taxane group to [redacted] will be incorporated in a full set of analyses and scenario analyses. This estimate was based on the assumption that the effect of switching on the hazard ratio is constant across trials.

- The ERG recreated both the PROfound OS adjusted and unadjusted datasets and matched them – patients who did not switch to either cabazitaxel or olaparib after progression on NHA should appear in both datasets.
- To estimate the effect of treatment switching the ERG applied a naïve simplifying assumption that the impact of patients receiving subsequent cabazitaxel in the NHA arm of CARD is equivalent to the impact of olaparib after NHA in PROfound. .The ERG picked 33% of patients (number of switchers in CARD) to switch now in PROfound (instead of the original [redacted] in PROfound). The ERG applied the derived adjustment factor to the CARD OS HR 0.64 (0.49, 0.89) to produce the CARD treatment adjusted OS HR [redacted].
- Finally, we applied the new CARD adjusted-HR to the ITC with the adjusted-HR from PROfound to get the estimate above.

**Topic 5 Effect of differences in post-progression treatments between the trials and those available in the NHS**

**Explore** the **impact of post-progression treatments on post progression survival**

The ERG agree with the company's statistical approach.

## Topic 6 Extrapolation of overall survival

### Explore more flexible approaches to extrapolating survival

The ERG confirm that spline models generate relatively poor AIC/BIC scores relative to at least five alternative parametric models (exponential, Rayleigh, bathtub, Gompertz, Weibull). Furthermore the spline models predict decreasing hazard (instantaneous risk of death) up to and beyond 20 years as the population ages (

**Figure 4**), whereas human populations generally experience increasing hazard with increasing age. The ERG consider these models a poor fit and implausible in extrapolation (please see Figure 5)

**Figure 4. Example of spline model hazard extrapolated to 20 years**

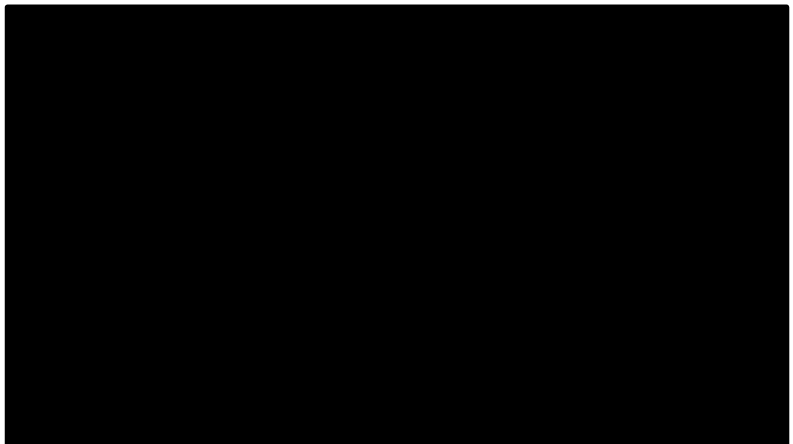

**Figure 5. Spline and exponential models extrapolated beyond 20 years (240 months)**

On AIC/BIC criteria the company have selected the exponential model for their new base case analysis. However, the company did not explore several additional models previously investigated by the ERG (original ERG report). In particular, the Rayleigh two parameter model provides IC values as good as those for the exponential, and therefore on the basis of IC offers an alternative to the exponential as presented in Table 5.

**Table 5. AIC/BIC values for parametric models of OS in olaparib arm**

| N | Model | AIC | BIC | **sum** | Rank on IC sum | df |
|---|---|---|---|---|---|---|
| 72 | exponential | 182.1116 | 184.3882 | **366.4998** | 1 | 1 |
| 72 | Rayleigh 2P | 181.0996 | 185.653 | **366.7526** | 2 | 2 |
| 72 | bathtub | 180.4766 | 187.3066 | **367.7832** | 3 | 3 |
| 72 | Gompertz | 181.3902 | 185.9435 | **367.3337** | 4 | 2 |
| 72 | Weibull | 182.6728 | 187.2261 | **369.8989** | 5 | 2 |
| 72 | ggamma | 183.4267 | 190.2567 | **373.6834** | 6 | 3 |
| 72 | loglogistic | 185.969 | 190.5223 | **376.4913** | 7 | 2 |
| 72 | lognormal | 191.8139 | 196.3672 | **388.1811** | 8 | 2 |
| 72 | Rayleigh 1P | 197.8901 | 200.1668 | **398.0569** | 9 | 1 |
| 72 | cubic spline models | 181.39 | 190.5 | **371.89** | >5 | 4 |
| 72 | cubic spline models | 183.23 | 194.61 | **377.84** | >5 | 5 |
| 72 | cubic spline models | 185.36 | 199.02 | **384.38** | >5 | 6 |

Discussion at the previous AC meeting suggested that the Rayleigh two parameter (R2P) model is a particular case of the Weibull model The ERG wishes to point out

that this is not the case. In the same way that the exponential model is a Weibull with shape = 1, R2P models are not just particular cases of Weibull modelling. Rather in effect two special cases of the Weibull model that fortuitously have shape = 1 or shape = 2 will be virtually equivalent to the corresponding R2P models.

Rayleigh 2 parameter (R2P) models predict a linear hazard that increases through time with slope that depends on λ1 and intercept depending on λ0; predicted survival and hazard are described[8]:

$$S_{(t)} = (\exp(-\lambda_0 t + \lambda_1 t^2))$$

$$h_{(t)} = \lambda_0 + 2\lambda_1 t$$

where $\lambda_0 > 0$ and $\lambda_1 \geq 0$

Alternative parameterisations termed Rayleigh can be found in the literature that have a single parameter (R1P) and generate linear hazard with slope depending on the magnitude of the parameter and intercept zero. R2P and R1P are compared with exponential and Weibull presented Table 6 below.

**Table 6. Models, hazard, and survival functions**

| Name | Hazard Function | Survival Function |
|---|---|---|
| Exponential | $\lambda_0$ | $e^{-\lambda_0 t}$ |
| Weibull | $\lambda_1 \gamma t^{\gamma-1}$ | $e^{-\lambda_1 t^{\gamma}}$ |
| R2P[8] | $\lambda_0 + 2\lambda_1 t$ | $e^{-(\lambda_0 t+\lambda_1 t^2)}$ |
| R1P[9] | $2\lambda_1 t$ | $e^{-\lambda_1 t^2}$ |

As it is well known a Weibull model has a single scale parameter (λ1) that multiplies with time raised to the power of the shape parameter (γ) that may take a variety of values resulting in monotonically increasing (shape >1) or decreasing hazard (shape <1) trajectories. In the particular case of Weibull shape parameter = 1 the hazard is constant through time and predictions are the same as those of an exponential model and of the R2P model where $\lambda_1$ will be very close to zero and the R2P $\lambda_0$ parameter will be almost the same as the Weibull scale parameter. In another Weibull special case of shape = 2 the resulting Weibull hazard increases linearly as also does the hazard for the R2P model and the R2P parameter $\lambda_0$ will be very close

to zero while the R2P $\lambda_1$ parameter will be almost identical to the Weibull scale parameter.

To support the clinical plausibility of long-term survival outcomes, and by the extension, the selection of the exponential and Weibull models, the company recall responses of clinical experts in the field of prostate cancer (as previously submitted in the CS plus two experts consulted by NICE the technical engagement process) and real world evidence. Clinical opinion of two newly involved experts is reported in the CS (page 22) giving opinions regarding Weibull modelling). They suggest that it is plausible that some patients would survive beyond 10 years (120 months). The company select the exponential model despite CS Table 6 depicting its long term survival estimates as clinically implausible while in the same Table the loglog and lognormal models are depicted as clinically plausible in extrapolation (CS Table 6). These models predict decreasing hazard (risk of death) with increasing time, and to

**Figure 6. Clinicians' predictions of percentages surviving at 3, 5 and 10 years with estimated binomial 95% confidence intervals**

The company's judgement of clinical plausibility of models in extrapolation (CS Table 6) is based on a survey that presented a range of clinicians' estimates of proportions alive at 3, 5, and 10 years. It is difficult to gauge the uncertainty associated with these estimates. Since the values are predicted proportions of survival for 72 patients, the ERG has attached binomial 95% CIs; Figure 6 provides an approximation of uncertainty associated with these predictions. Clearly the range of estimates from lowest 95% CI to highest 95% CI is wide (e.g. 8% to 75% at 3 years). Potential respondents one and six provided no estimates while one other only

provided data for 3 years. A full critique of the survey was included in the earlier ERG report.

The company presents the OS KM for the real-world FLATIRON study and compares KM data at time points with the exponentially modelled OS for cabazitaxel in the present submission (CS Figure 2). This applies an ITC HR of [redacted] to the olaparib exponential model under the assumption that proportional hazards hold. The ERG believes that the more appropriate comparison should be between exponential models (i.e. that for FLATIRON vs. that modelled for cabazitaxel) taking into account the uncertaintly associated with such small sample sizes (PROfound N = 72, FLATIRON N =[redacted]). Figure 7 indicates that the cabazitaxel OS derived from both Rayleigh and exponential olaparib OS models lies much closer to the FLATIRON KM plot and well within the 95% CI ranges for the FLATIRON exponential model (shaded area).

**Figure 7. Comparison of models for OS for Olaparib and cabazitaxel using different source data and methods showing FLATIRON KM data with 95% confidence intervals.**

The company provide Canadian real-world evidence for the proportions surviving on cabazitaxel and docetaxel after an NHA, and US real world evidence for the proportions surviving after docetaxel and an NHA. The ERG presents the values for the various curves and the undiscounted life years, for the scenarios of not adjusting

the CARD HR (Table 7) for cross over and adjusting the CARD HR for cross over (Table 8).

**Table 7. Cabazitaxel: proportions surviving and mean LY: Unadjusted HR**

| [redacted] | | | | | | | |
|---|---|---|---|---|---|---|---|
| [redacted] | | | | | | | |
| [redacted] | | | | | | | |
| [redacted] | | | | | | | |
| [redacted] | | | | | | | |
| [redacted] | | | | | | | |

**Table 8. Cabazitaxel: proportions surviving and mean LY: Adjusted HR**

| [redacted] | | | | | | | |
|---|---|---|---|---|---|---|---|
| [redacted] | | | | | | | |
| [redacted] | | | | | | | |
| [redacted] | | | | | | | |
| [redacted] | | | | | | | |
| [redacted] | | | | | | | |

**Topic 7 Incorporation of relative dose intensity**

Use mean per patient costs of olaparib taking into account dose intensity and duration of treatment

The company ACD response retains the median RDI as the best estimate and suggests that the RDI has little impact upon the ICER.

The company argues that a 100% RDI would improve the ICER due to the median olaparib RDI being less than the median cabazitaxel RDI. But this ignores the argument for assuming a 100% RDI which is that the olaparib RDI is based upon tablets consumed but if based upon pack prescribed, a 100% RDI may be more reasonable. This argument does not apply to cabazitaxel.

At technical engagement the company and the ERG agreed that, given data availability the median RDI was the most reasonable of the available estimates to apply. The ERG revised base case will retain the median RDI due to the concerns outlined in Section 4.3.4.8 of the original ERG report.

### Topic 8 Post-progression treatment costs

Account for NHS post progression costs of treatment that do not include abiraterone, enzalutamide or cabazitaxel after cabazitaxel, but include radium-223

The company outlines that varying the post progression treatment balance has minimal effect upon costs. The ERG agrees with this and retains its concerns about the geographic differences between PROfound and CARD and hence the desirability of differentiating post progression treatment costs based upon their treatment distributions, excluding the NHAs. The ERG will supply a scenario analysis that sets PPS cabazitaxel use in the comparator arm to zero, but notes that this results in roughly three quarters of PPS active treatment being R-223 and the remainder being docetaxel in the comparator arm.

### Additional ACD references and committee preferred analysis

### ACD reference 3.10. Use hazard ratios from the BRCA-mutation prior-taxane subgroup of PROfound for the indirect comparison

Table 12 of the company ACD response states that the hazard ratios from the prior taxane group have been applied. The ERG preferred base case and scenario analyses also applies the hazard ratios derived from the prior taxane group.

### ACD reference 3.13. Use the time to treatment curve for olaparib treatment duration

Table 12 of the company AC response states that its company model applies the Committee preference. The preferred ERG base case will do likewise.

**ACD reference 3.15. Assume only a proportion of patients get G-CSF, for a mean of 7 days**

The company revises the proportion receiving GCS-F, to 79.5% in its ACD response Table 12, and reduces the mean duration to 7 days. The ERG preferred base case will apply the Committee preference for the previous ERG assumptions.

**ACD reference 3.17. Assumes the same post progression best supportive care (BSC) care costs regardless of whether patients have active treatment after progression**

Table 12 of the company ACD response states that it implements the Committee preference. The ERG revised base case will apply the Committee preference.

**ACD reference 3.18. Includes the costs of testing for BRCA mutations**

During AC1, one of the clinical experts noted that BRCA testing could use diagnostic biopsies but that these would not be viable in perhaps 15-20% of patients, although maybe undertaken in perhaps as many as 35%. Coupling a 20% repeat biopsy with the 2018-19 NHS reference cost LB76Z Transrectal ultrasound guided biopsy of the prostate weighted day case and outpatient average cost of £492 suggests a mean repeat biopsy cost of £98, while a 35% repeat rate suggests a cost of £172.

NICE received a cost per test estimate from NHSE of [redacted], though it is not entirely clear quite what this cost covers.

Together these suggest a cost per test of [redacted] for the 20% repeat biopsy rate and [redacted] for the 35% repeat biopsy rate, both somewhat less than the company estimate of [redacted]. The ERG base case will retain the company estimate. The ERG will supply

scenarios that apply the other test cost estimates and that excludes the cost of testing.

**Revised company cost effectiveness estimates**

The revised company base case cost effectiveness estimates are presented below, including the probabilistic results (Table 9).

**Table 9. Company ACD base case BRCAm prior taxane: Summary**

| | Deterministic | | | Probabilistic | | |
|---|---|---|---|---|---|---|
| | Caba. | Olap. | net | Caba. | Olap. | net |
| Total QALYs | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Total Costs | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| ICER | | | £40,748 | | | £46,648 |

**Table 10. Company ACD base case BRCAm prior taxane: BSC: Summary**

| | Deterministic | | | Probabilistic | | |
|---|---|---|---|---|---|---|
| | BSC | Olap. | net | Caba. | Olap. | net |
| Total QALYs | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Total Costs | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| ICER | | | £48,792 | | | £53,327 |

**Table 11. Company ACD base case BRCAm no-prior taxane: Docetaxel: Summary**

| | Deterministic | | | Probabilistic | | |
|---|---|---|---|---|---|---|
| | Doc. | Olap. | net | Caba. | Olap. | net |
| Total QALYs | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Total Costs | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| ICER | | | £40,976 | | | £47,144 |

**Scenario analyses around extrapolation curves: comparison with cabazitaxel**

The ERG clinical review suggests that of the company curves the Weibull may be the most appropriate for extrapolating OS, PFS and ToT, though ToT might be better extrapolated using the spline model with a single knot. Unfortunately, it appears that the company prior taxane model only contains the 5 knot OS spline model and none of the other spline models. Given time constraints the ERG is restricted to only modelling the company Weibulls.

**Table 12: Company ACD BRCAm prior taxane: Weibulls throughout**

| | Deterministic | | | Probabilistic | | |
|---|---|---|---|---|---|---|
| | Caba. | Olap. | net | Caba. | Olap. | net |
| Total QALYs | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Total Costs | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| ICER | | | £48,169 | | | £55,331 |

**Scenario analyses around extrapolation curves: comparison with docetaxel and BSC**

The ERG clinical review suggests that spline models may be most appropriate. The company no prior taxane model only appears to contain the OS 1 knot spline model, and none that of the other curves. As a consequence, and given time constraints, the ERG has not been able to take this work forward.

**Revised ERG cost effectiveness estimates**

The ERG preferred base case that applies hazard ratios that do not adjust for treatment switching during CARD is as per its TE report.

**Table 13: ERG ACD base case BRCAm prior taxane: CARD OS HR unadjusted**

| | Deterministic | | | Probabilistic | | |
|---|---|---|---|---|---|---|
| | Caba. | Olap. | net | Caba. | Olap. | net |
| Total QALYs | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Total Costs | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| ICER | | | £59,670 | | | £64,087 |

The ERG preferred base case that applies hazard ratios that adjust for treatment switching during CARD is presented below in

Table 14.

**Table 14. ERG ACD base case BRCAm prior taxane: CARD OS HR cross over adjusted**

| | Deterministic | | | Probabilistic | | |
|---|---|---|---|---|---|---|
| | Caba. | Olap. | net | Caba. | Olap. | net |
| Total QALYs | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Total Costs | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| ICER | | | £71,516 | | | £82,231 |

**The ERG provides the following scenario analyses using the deterministic model**

- SA01: Applying the company OS curves for olaparib.
- SA02: 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.
- SA03: Assumes no vial sharing for cabazitaxel.
- SA04: Varying the cost of genetic testing.
- SA05: Assuming no PPS cabazitaxel use in the comparator arm.

It should be borne in mind that the NICE preferred probabilistic modelling consistently results in somewhat worse cost effectiveness estimates than the deterministic modelling.

**Table 15: ERG ACD BRCAm prior taxane: Scenario analyses: Deterministic**

| | CARD no HR adjustment | | | CARD HR adjustment | | |
|---|---|---|---|---|---|---|
| | ΔQALY | ΔCost | ICER | ΔQALY | ΔCost | ICER |
| ERG revised base case | [redacted] | [redacted] | £59,670 | [redacted] | [redacted] | £71,516 |
| SA01a: Exponential | [redacted] | [redacted] | £46,200 | [redacted] | [redacted] | £53,386 |
| SA01b: Gompertz | [redacted] | [redacted] | £62,037 | [redacted] | [redacted] | £74,975 |
| SA01c: Weibull | [redacted] | [redacted] | £52,009 | [redacted] | [redacted] | £61,081 |
| SA01d: Gen. Gamma | [redacted] | [redacted] | £59,901 | [redacted] | [redacted] | £71,958 |
| SA01e: Log-logistic | [redacted] | [redacted] | £37,519 | [redacted] | [redacted] | £42,262 |

| | | | | | | |
|---|---|---|---|---|---|---|
| SA01f: Log-normal | [redacted] | [redacted] | £34,711 | [redacted] | [redacted] | £38,922 |
| SA02: Caba. TTD inferred | [redacted] | [redacted] | £56,583 | [redacted] | [redacted] | £67,448 |
| SA03: Caba. No vial sharing | [redacted] | [redacted] | £47,236 | [redacted] | [redacted] | £55,148 |
| SA04a: [redacted] test cost | [redacted] | [redacted] | £53,861 | [redacted] | [redacted] | £63,931 |
| SA04b: [redacted] test cost | [redacted] | [redacted] | £55,465 | [redacted] | [redacted] | £66,026 |
| SA04c: No genetic test cost | [redacted] | [redacted] | £51,000 | [redacted] | [redacted] | £60,196 |
| SA05: PPS Tx costs | [redacted] | [redacted] | £61,561 | [redacted] | [redacted] | £74,197 |

**OS in the no-Taxane subgroup (CS Appendix A)**

The previous ERG report compared OS for the prior taxane BRCAm group (N=72) with that for the whole BRCAm group (N=102) using eight parametric models (Figure 8). This indicated very slight superior survival for the group that included the 32 no-taxane subgroup. The ERG conclude that the no-taxane subgroup has OS no worse than that of the prior taxane population and therefore agree with the analysis presented in the CS, while acknowledging the considerable uncertainty associated with the small number(N=32) of patients.

**Figure 8. ERG (solid line) and CS (dots) models for OS in months for the prior taxane BRCAm population vs. ERG models all BRCAm population (dashed lines)**

## References


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## Evidence Review Group's report summary: Addendum

**Produced by:** Warwick Evidence

**Date completed** 09.07.2021

**Declared competing interests of the authors:** none

**Scenario analyses around extrapolation curves: comparison with docetaxel and BSC**

The Appraisal Committee suggested that spline models may be most appropriate. Applying the ERG Rayleigh R1P curves within the company submitted model results in the following estimates. Note that unlike the main ERG analyses which are based upon the original company corrected by the ERG these estimates are based upon inserting the ERG curves into the ACD company model. The ERG has not rebuilt or cross checked the implementation of the ACD company model due to time constraints, which may be a concern given the convoluted company implementation and the range of errors identified in the original model.

**Table 1: ERG Scenario *BRCA*m no-prior taxane: BSC: Summary (company model)**

| | Deterministic | | | Probabilistic | | |
|---|---|---|---|---|---|---|
| | BSC | Olap. | net | BSC | Olap. | net |
| Total QALYs | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Total Costs | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| ICER | | | £71,249 | | | £79,035 |

**Table 2: ERG Scenario *BRCA*m no-prior taxane: Docetaxel: Summary (company model)**

| | Deterministic | | | Probabilistic | | |
|---|---|---|---|---|---|---|
| | Doc. | Olap. | net | Doc. | Olap. | net |
| Total QALYs | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Total Costs | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| ICER | | | £61,950 | | | £71,767 |