NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Olaparib for previously treated hormone-relapsed metastatic prostate cancer

Committee Papers

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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

Contents:

The following documents are made available to consultees and commentators:

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

Appraisal title

Single Technology Appraisal

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Type of stakeholder:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and Social Care and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal document (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health and Social Care, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
1	Patient organisation	Prostate Cancer UK	**We are concerned that docetaxel re-challenge is considered a suitable comparator for olaparib. This could result in some patients with metastatic hormone-refractory prostate cancer and BRCA1 and/or BRCA2 pathogenic variants being denied access to olaparib solely because they have not had prior docetaxel chemotherapy.** A significant proportion of patients will not be suitable for docetaxel treatment and therefore not suitable for re-challenge. These are patients who are likely to be of an advanced age, with comorbidities or a degree of frailty which excludes them from being treated with a taxane. In our previous ACD response we shared clinical opinion drawn from the British Uro-oncology Group outlining that very few men would tolerate the full 16 cycles of docetaxel due to dose limiting neurotoxicity[1].We still would like to reiterate this point. In normal practice patients would receive one round of chemo of 6-8 cycles but there is insufficient evidence that another round would be beneficial • In 2016 the 80+ age group accounted for 34% of all newly diagnosed metastatic prostate cancer population, >2000 patients[2]. • 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[2]. This represents a sizeable population of patients that, if identified as BRCA1 or BRCA2 mutated, could be denied olaparib. • 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. Those patients who are contra-indicated to chemotherapy, those of an older age, with poorer performance status, with comorbidities, or poor cognition could be indirectly discriminated against. This is troubling when the PROfound study shows clear evidence of benefit in the no-prior taxane population. To add to the above, clinical experts have also outlined	Thank you for your comments. The committee concluded that comparators are different for people who can and cannot have, or have already had, taxanes. Therefore, the committee concluded that the company's approach of considering these groups separately is acceptable (section 3.2). For the 'prior taxane' group, the committee concluded that cabazitaxel was the main comparator, but that radium 223 dichloride and retreatment with docetaxel are used in NHS practice (section 3.3). For the 'no prior taxane' group, the committee concluded that best supportive care and docetaxel are the most relevant comparators (section 3.4). The committee acknowledged that those who had not had previously had docetaxel were likely to be older, have poorer disease performance status, comorbidities, and poor cognition. (see section 3.2 and 3.27 of the guidance)

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			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 [3]	
2	Patient organisation	Prostate Cancer UK	**Statistically powered data for the prior and no prior taxane sub-groups is unlikely to ever be feasible in a clinical trial setting and they should be considered as one population.** Since the company has now provided exploratory analyses for people who have not had a taxane and this group is now considered a separate population we believe this will potentially discriminate against these patients, effectively penalising this group. BRCA1/2 patients only account for around 10% of the 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 and from those only 53 had not had a prior taxane[4]. These 53 patients were randomised across the olaparib and control arms. Given these circumstances and such low numbers of BRCA mutated patients, let alone the lower numbers of those who have a BRCA mutation and have not had a previous taxane, we feel that the decision by the company to no longer group the prior taxane and no prior taxane populations together, which originally mitigated the small patient numbers, is inappropriate as data on such a small number of patients is unfeasible. Greater flexibility with the patient sub-groups, by including them both in the indirect treatment comparison, should be considered. We recognise this may increase uncertainty of comparative effect, but we believe that the committee should rely on the evidence from PROfound that shows benefit of olaparib in both the prior and no-prior taxane sub-groups.	Thanks for your comment. The committee acknowledge the size of the 'no prior taxane' subgroup from the trial is a limitation and may contribute to the uncertainty related to that population (see section 3.7). However, the committee concluded that prior treatment does not appear to be affected by prior taxane use. Further, as noted in the guidance (section 3.2) the committee consider that since there are no common comparator treatments for the whole licensed population, it would be most appropriate to consider the groups separately in the analyses.
3	Patient organisation	Prostate Cancer UK	**We are concerned that prior taxane treatment is considered a modifier on the effectiveness of olaparib without sufficient justification. This could result in patients, who would benefit from this treatment, missing out. We believe the marginal decrease in certainty of the results is not sufficient enough to justify denying patients access to olaparib.** We recognise that the no prior taxane group represents a significant challenge for the appraisal process. This group is not well represented in clinical trials, not just in PROfound, but in other trials across metastatic patient pathway. However, as analysis of Public Health England data has shown[2] they represent a significant	Thank you for your comment. The committee concluded that the effectiveness of olaparib does not appear to be affected by prior taxane use (see section 3.7). However, as noted in the guidance (section 3.2) the committee consider that since there are no common comparator treatments for the whole licensed population, it would be most appropriate to consider the groups separately in the analyses.

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			proportion of the real-world patient population. There is also a potential equality issue, which the committee has recognised throughout, as many of the patients unable to tolerate chemotherapy are older patients. We are satisfied with the mitigation efforts made within the trial to reduce uncertainty by attempting to recruit patients who had not had prior chemotherapy. PROfound screened tissue from 4425 patients across 206 sites in 20 countries and still was not sufficiently powered to analyse by taxane use. The number of patients who are healthy enough for clinical trials, and who have eligible HRR mutations is small. This population included in the analyses was further restricted when the marketing authorisation was limited to BRCA1 and BRCA 2 patients only. We believe that to a large extent, the uncertainty of the analyses presented was unavoidable, given the challenges of recruiting patients with HRR mutations to a clinical trial. Again, we feel satisfied that the company has made sufficient effort to mitigate uncertainty wherever possible. To further mitigate the concerns of the committee, Prostate Cancer UK have surveyed UK based clinical experts to ascertain their views on the extent to which prior taxane use would modify treatment with olaparib. All clinical experts are clinical oncologists with a research interest in treatments for advanced prostate cancer. Clinicians were asked to score a set of statements on a scale of 1-9, 1 (very strongly disagree) through 5 (neutral) to 9 (very strongly agree). **Statement 1: There are plausible reasons to believe that prior use of a taxane would have a significant effect on the efficacy of olaparib.** • Clinical Expert 1 scored 3 • Clinical Expert 2 scored 3 • Clinical Expert 3 scored 6 • Clinical Expert 4 scored 3 **Statement 2: The same survival benefit would be expected from treatment with olaparib in patients previously treated with docetaxel and patients who have not been previously treated with docetaxel** • Clinical Expert 1 scored 7 • Clinical Expert 2 scored 8 • Clinical Expert 3 scored 3 • Clinical Expert 4 scored 7	

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			Statement 3: In the absence of robust data, it is reasonable to treat the cohort of men recruited to the PROfound trial with BRCA mutations as a single population for analysis. • Clinical Expert 1 scored 9 • Clinical Expert 2 scored 9 • Clinical Expert 3 scored 8 • Clinical Expert 4 scored 7 Three out of four clinical expert indicated that they did not agree that prior taxane use would have a significant effect on olaparib. They also answered that overall survival would be similar irrespective of prior use of a taxane. One was neutral (neutral is a score between 4 and 6) on whether prior use of a taxane may have a significant effect on the efficacy of olaparib but indicated overall survival may not be similar between prior taxane and no prior taxane groups. All clinical experts agreed that it was reasonable to treat the cohort of men in PROfound as a single population for analysis. We recognise the concerns the committee has highlighted over prior use of a taxane, and that this is a difference in the populations of the CARD and PROFOUND trials. However, we do not believe that the evidence supports denying patients in the no prior taxane group access to olaparib. Ideally, all BRCA patients would be analysed as a single group regardless of prior taxane, as we believe clinical opinion supports the theory that treatment with a taxane is unlikely to have significantly affected the results of the indirect treatment comparison. We appreciate the role of the NICE in reducing the uncertainty of analyses of cost effectiveness. However, in this instance, we do not believe that the marginal decrease in certainty of results warrants denying patients access to life extending treatment with olaparib. We are particularly concerned about this in regards to the patients who cannot tolerate chemotherapy, as they will likely only be left with palliative care as a treatment (see point 4 below).	
4	Patient organisation	Prostate Cancer UK	**Radium-223 is unlikely to be a comparator in patients who can't have chemotherapy. We are concerned that for patients who can't have chemotherapy, best supportive care is likely to be their only treatment option if olaparib is not approved.** Radium-223 dichloride is recommended as an option for treating adults with hormone-relapsed prostate cancer, symptomatic bone metastases and no known	Thank you for your comment. For the 'prior taxane' group, the committee concluded that cabazitaxel was the main comparator, but that radium 223 dichloride and retreatment with docetaxel are used in NHS practice (section 3.3). For the 'no prior taxane' group, the committee concluded that best supportive care and docetaxel are the most relevant comparators (section

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			visceral metastases. Within the PROfound study, only 35% of patients had bone metastases alone, 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[3] Due to the rarity of BRCA 1/2 mutations, and the rarity of only have bony metastases, it is very unlikely that many patients would ever be eligible for both olaparib and Radium-223. These treatments should not be viewed as comparators. It is vital that, for patients who can't have chemotherapy, both treatments are available to reduce the number of patients receiving best supportive care only. We do not believe the committee has adequately considered the implications of denying access to olaparib in this group. Denying these patients access to olaparib may deny them additional months of quality life. Olaparib can therefore meet an unmet need for some patients who cannot, or should not, have chemotherapy.	3.4).
5	Patient organisation	Prostate Cancer UK	**We are concerned that inclusion of the BRCA test cost in treatment costs will disadvantage olaparib as a first in class treatment and sets a precedent against other precision medicines.** The Cancer Drugs Fund clinical lead explained that the Genomic Test Directory includes testing for BRCA mutations. However, he said 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. In its response to consultation, the company agreed with the ERG's approach and included the cost of testing for BRCA mutations in its revised base case. The committee acknowledged that the revised company approach was appropriate. This seems like a decision that is punishing first in class drugs and rewarding drugs in the same class that come later (and therefore incur less risk to the company when funding trials). This could inadvertently give companies the incentive to hold back on releasing new drugs (so as not to be the first to do so and therefore penalised), and therefore have a huge impact on patients and their access to innovative medicine in the future.	Thank you for your comments. The NICE methods guide states: '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'.
6	Patient organisation	Prostate Cancer UK	**We strongly disagree with the assertion that olaparib is not innovative. We believe olaparib has innovation benefits not already captured in the model.**	Thank you for your comment. The committee concluded that olaparib is not innovative (section 3.28).

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			Olaparib would be the first ever molecularly targeted treatment for prostate cancer. It is the drug that will open up the potential outlined in NHS Long Term Plan about genetic medicine for this cancer currently killing more than 11,500[6] men per year in the UK. In and of itself we believe that this should qualify olaparib for the more generous thresholds applied for "innovative" treatments. However, to illustrate further we are including just two of the unmodelled benefits of the change in practice that would happen should olaparib be approved: 1. Sequencing of prostate cancer tumours would become routine (probably at the point that they become metastatic, or possibly at the point that they become castration resistant and metastatic). This would increase very significantly the UK's speed and ability to recruit to modern clinical trials for advanced prostate cancer, many of which already rely on stratification on the basis of presence or absence of driver mutations. Faster recruitment to these globally competitive trials will increase immediate (free) access to other molecularly targeted treatments for prostate cancer through better recruitment in the UK, will increase UK plc's offer to pharma globally and will also ensure that the men recruited to those trials are more representative of the NHS-population. This benefit is articulated in the Genome UK report which states an aim to "*deliver[..] on the promise of genomic-enabled clinical trials, with more cancer patients than ever participating*[5]*.*" 2. Routine genetic testing of men eligible for olaparib (if approved) per the NHS test directory would identify about half of them carrying a BRCA mutation in their germline rather than somatically only. The sons and daughters (and future generations) of those men are at higher risk of multiple cancers as a result and for ovarian and breast cancer at least may benefit from risk reduction strategies thus reducing mortality and morbidity and saving long term costs to the NHS. Even for cancers where the risk is increased but where no preventative strategies are (yet) part of clinical practice those offspring would benefit from more intense screening and facilitated access to prevention and early diagnosis clinical trials. This also speaks to one of the key aims in the Genome UK report[5]: "***Targeted screening:*** *We aim to better use genomics to improve population health through improved disease prevention including better screening. This includes the use of personalised and risk stratified screening and testing of the family members of cancer patients to identify where they are at increased risk of cancer.*"	

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			Neither of these wider benefits are considered (or considerable) in the health economics model used to make the decision about this assessment. We therefore believe that olaparib does in fact meet both of criteria required to be considered as "innovative".	
7	Patient organisation	Prostate Cancer UK	**We are concerned that the committee has not considered temporary guidance which suggests alternatives to docetaxel chemotherapy during the pandemic.** During the COVID-19 pandemic enzalutamide was made available to metastatic hormone sensitive prostate cancer patients in place of docetaxel. This means, that since the start of the pandemic, the majority of patients will have not received docetaxel. For some patients, docetaxel still may not be an option due to the ongoing pandemic. Olaparib may be a more suitable option, as it can be taken orally at home, without the need to attend hospital. Therefore, it may be a more appropriate treatment for those needing to shield during the pandemic. For patients who would normally have received docetaxel during the pandemic, the committee should consider whether olaparib should be made available instead. In addition, for many of these patients, their condition may have now deteriorated to a point where they are unable to tolerate treatment with docetaxel at all. Denying them olaparib may further limit their treatment choices. We are concerned that making docetaxel a prerequisite for treatment with olaparib unfairly punishes patients who were advised not to have docetaxel during the pandemic and may now no longer able to tolerate treatment with docetaxel.	Thanks for your comment. The committee was unable to recommend olaparib in either population as it was not cost-effective.
8	Patient organisation	Tackle Prostate Cancer	Tackle Prostate Cancer is a patient-led Charity and as such does not have specific personnel with appropriate skills and training to adequately pass comments on many scientific and statistical arguments. Because of this, Tackle often work in close partnership with the Knowledge and Policy Teams at Prostate Cancer UK. However, the current patient representative for Tackle, [redacted], does some understanding that may be not possible for other patients.	Thanks for your comment.
9	Patient organisation	Tackle Prostate Cancer	Tackle have discussed this ACD with Prostate Cancer UK and we have similar opinions of how responses should be made on behalf of patients. Tackle are in complete agreement with the opinions of Prostate Cancer UK which are obviously more detailed that we can produce. Rather than make a lengthy duplicate submission we would ask that the Committee note the agreement of Tackle with Prostate Cancer UK. However, Tackle do have some points that we would like to strongly stress:	Thanks for your comment.

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10	Patient organisation	Tackle Prostate Cancer	We are very concerned at the possibility of inequality of care that may arise as a result of the potential restrictions that require patients to have been treated with taxane chemotherapy before being eligible to receive Olaparib. This will very effectively reduce the ability of clinicians to provide best possible therapy for many of their patients with advanced prostate cancer and co-existing BRCA 1 & 2 genetic abnormalities.	Thank you for your comments. The committee concluded that comparators are different for people who can and cannot have, or have already had, taxanes. Therefore, the committee concluded that the company's approach of considering these groups separately is acceptable (section 3.2). For the 'prior taxane' group, the committee concluded that cabazitaxel was the main comparator, but that radium 223 dichloride and retreatment with docetaxel are used in NHS practice (section 3.3). For the 'no prior taxane' group, the committee concluded that best supportive care and docetaxel are the most relevant comparators (section 3.4).
11	Patient organisation	Tackle Prostate Cancer	NICE, at other Appraisals related to prostate cancer, have already recognised a population of patients who are 'chemotherapy unsuitable'. This group of patients are unable to be given Olaparib even if they are clinically suitable for it.	Thank you for your comments. The committee concluded that comparators are different for people who can and cannot have, or have already had, taxanes. Therefore, the committee concluded that the company's approach of considering these groups separately is acceptable (section 3.2). For the 'prior taxane' group, the committee concluded that cabazitaxel was the main comparator, but that radium 223 dichloride and retreatment with docetaxel are used in NHS practice (section 3.3). For the 'no prior taxane' group, the committee concluded that best supportive care and docetaxel are the most relevant comparators (section 3.4). The committee acknowledged that those who had not had previously had docetaxel were likely to be older, have poorer disease performance status, comorbidities, and poor cognition. (see section 3.2 and 3.27 of the guidance)
12	Patient organisation	Tackle Prostate Cancer	In the future there will be a further group of patients who have not had taxane chemotherapy because, during the Covid pandemic, chemotherapy was not recommended and Novel Hormonal Agents (Enzalutamide or Abiraterone) were used as alternative additional therapy to ADT. Whilst these patients could still be eligible for chemotherapy, some may have already reached a stage clinically and physiologically where they could not adequately tolerate chemotherapy. They are at risk of being denied potentially life-extending with Olaparib treatment through no	Thanks for your comment. The committee was unable to recommend olaparib in either population as it was not cost-effective.

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			fault of their own. Whilst unfair may not be a word that is normally used in an appraisal, that to us is exactly what it seems like.	
13	Patient organisation	Tackle Prostate Cancer	We are not sufficiently qualified to make appropriate comments on treatments being used as comparators. However, we do understand that there is considerable differences of opinion concerning this. Of particular importance to use is the assumption that a second course of docetaxel is an alternative option for treatment. Such treatment is not one that we have heard of being utilised to any great extent and indeed we believe, was not one shared by clinical experts at the original appraisal. Also is there research-based evidence that states that this second course is effective? Could it be that the drug is licenced for up to 10 sessions but normally only 6 are used? This confusion was very graphically outlined by one patient who stated to our patient representative: "What's the point of having a second course of the same drug? Surely any cancer cells that could be killed by docetaxel should have been done so already? Am I not now just developing a breed of cancer cells that were resistant to this drug – just like we are getting bacteria resistant certain anti-biotics" In a disease that heavily relies on serial therapies, this is not an illogical statement and may well have truth in it?	Thanks for your comment. As noted in the guidance, the committee concluded that cabazitaxel is the most relevant comparator for people who have had a prior taxane; however, it heard that docetaxel re-challenge is used in the UK for some people who have previously had a taxane. As a result, it considered docetaxel re-challenge as a relevant comparator for this population. (see section 3.3)
14	Patient organisation	Tackle Prostate Cancer	Part of the job of a patient representative is to be able to adequately explain decisions made by NICE to our members. It is going to be extremely difficult to explain the inequality of treatment if the recommendations of the current ACD cannot be changed. Quite understandably, decisions made by NICE and the Scottish Medicines Consortium are made very independently of one another. However, the outcome of this current ACD will be even more difficult to explain to patients when the SMC have already approved the use of Olaparib using what seems (to the untrained eye, at least) to be the submission of similar evidence.	Thanks for your comment. NICE committees are independent and use their scientific and clinical judgement in deciding whether the available evidence is sufficient to provide a basis for recommending a treatment or not.
15	Company	Astra Zeneca UK	**Topic 1: Revised assumptions in the prior-taxane subgroup** **ACD Section 3.24:** "*…the committee noted the cost-effectiveness estimates for olaparib compared with cabazitaxel were higher than what NICE normally considers an acceptable use of NHS resources for people who have had treatment with a taxane. This was the case even when considering end of life criteria. The committee noted that olaparib was not cost effective even in the company's own base case.*" **Company Response:** • Olaparib requires commercial flexibility in order to be considered cost effective. Accordingly, [redacted]	Thanks for your comments. The committee have considered the updated analyses.

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			[redacted]. Taking this into account, we believe olaparib can be considered cost-effective in the No-Prior-Taxane subgroup, even when using the majority of the ERG-preferred assumptions in the economic modelling. Full results along with scenario analysis are presented in Appendix B.	
16	Company	Astra Zeneca UK	**Topic 2: Evidence in the population who have not taken docetaxel or cannot have it** **ACD Section 3.6:** "*The committee noted that subgroup analyses by prior taxane status for people who have BRCA mutations were not pre-specified in the clinical study protocol, and therefore constitute post-hoc analysis. It also noted the small size of the subgroup of people who had not had treatment with docetaxel, and the immaturity of overall survival data in this group. It concluded that these results were highly uncertain*" **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 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	Thanks for your comments. The committee have considered the updated analyses.
17	Company	Astra Zeneca UK	**Topic 3: Application of End-of-Life criteria to the No Prior-Taxane subgroup** **ACD Section 3.23:** "*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.	Thank you for your comment. The committee considered the company's comments alongside other comments from other stakeholders. They have subsequently agreed that olaparib likely meets end of life criteria for the no prior taxane population. The guidance has been amended accordingly.
18	Company	Astra Zeneca UK	**Topic 4: Choice of comparator** **ACD Section 3.3:** "*The committee concluded that cabazitaxel is likely to be the main, but not the only, comparator for olaparib in people who have had a taxane. It would have preferred to see exploratory analyses with radium-223 dichloride and*	The committee concluded that comparators are different for people who can and cannot have, or have already had, taxanes. Therefore, the committee concluded that the company's approach of considering these groups separately is acceptable (section 3.2). For the 'prior taxane' group, the committee concluded

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			retreatment with docetaxel because they are also relevant comparators" **Company Response:** • The company analyses vs docetaxel and cabazitaxel represent those most appropriate in the No Prior Taxane and Prior Taxane subgroups, respectively. Analyses against docetaxel rechallenge and radium-223 are do not reflect the patient populations, are compromised by feasibility concerns, and as a result would not be informative for decision-making.	that cabazitaxel was the main comparator, but that radium 223 dichloride and retreatment with docetaxel are used in NHS practice (section 3.3). For the 'no prior taxane' group, the committee concluded that best supportive care and docetaxel are the most relevant comparators (section 3.4).
19	Company	Astra Zeneca UK	Topic 5: Olaparib as an innovative medicine **ACD Section 3.27:** "*The committee understood that to consider a technology innovative, a substantial change in management of a condition and benefits not adequately captured in the economic analysis were both needed. It concluded olaparib is not innovative because it does not offer benefits not already included in the modelling*." **Company Response:** • The broader benefits of BRCA testing, currently not standard NHS practice, will enable wider benefits of earlier identification of *BRCA*m disease, and provide the opportunity for increased vigilance for patients with genetic considerations based on their heritable disease.	Thank you for your comment. The committee concluded that olaparib is not innovative (section 3.28).

References provided by Prostate Cancer UK:

1. 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.
2. 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.
3. National Institute for health and Care Excellence, 2021. *Olaparib for previously treated hormone relapsed metastatic prostate cancer [ID1640] Committee Papers*. pp.555-572.
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. Supplementary Appendix for Olaparib for Metastatic Castration-Resistant Prostate Cancer. *New England Journal of Medicine*, 382(22)
5. GOV.UK. 2020. *Genome UK: the future of healthcare*. [online] Available at: <https://www.gov.uk/government/publications/genome-uk-the-future-of-healthcare/genome-uk-the-future-of-healthcare> [Accessed 25 January 2022].
6. Cancer Research UK. *Prostate cancer mortality statistics*. [online] Available at: <https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/prostate-cancer/mortality> [Accessed 20 January 2022].

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1. de Bono J, Mateo J, Fizazi K, et al. Olaparib for metastatic castration-resistant prostate cancer. N Engl J Med 2020;382:2091–102.
2. Hechmati G, Arellano J, Haynes I, Gunther O, Worsfold A, Rider A. Impact of bone metastases on quality of life in patients with castration-resistant prostate cancer (CRPC) at high risk for developing bone metastases. Value in health 2012;15:A277–A575.
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Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
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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 is 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.

Olaparib is an innovative and important new class therapy for patients with metastatic castration-resistant prostate cancer (mCRPC) and *BRCA1/2*-mutations (germline and/or somatic) who have progressed following prior therapy that included a new hormonal agent (NHA). It is the first targeted medicine in prostate cancer that offers men with *BRCA* mutations (*BRCA*m) the chance to live longer and better with their disease, through demonstrating unprecedented clinical efficacy in the mCRPC post-NHA setting for patients with *BRCA*m.[1] Olaparib has significantly improved outcomes for patients across a number of different indications, including ovarian, breast and pancreatic cancers, and has demonstrated the same long-term benefit for men with prostate cancer. The safety profile of olaparib is well-established and manageable and offers men an oral drug to allow them to live a 'normal' life.

There is a distinct unmet need for patients with mCRPC who have progressed on an NHA; mCRPC is associated with substantially increased symptom burden, deterioration in health-related quality of life (HRQoL), and increased mortality (with >3 higher risk of death) versus non-metastatic disease.[2-5] Almost all patients dying from prostate cancer have mCRPC,[6] and **fewer than half of patients with mCRPC in the UK survive for 5 years.**[7] As such there is substantial and urgent unmet clinical need for life-extending therapies for the treatment of mCRPC, of which patients with *BRCA*m make up a small subgroup with aggressive disease.

AstraZeneca remains committed to enabling access for this important new medicine and in our response, we aim to address the Committee concerns and help inform appropriate decision making in this population. Analyses presented in this ACD response are provided using the current approved commercial arrangement [redacted]

AstraZeneca remain committed to working with both NICE and NHS England to ensure access for patients given the high unmet need, as recognised by the Committee (ACD Section 3.1). We are confident that the [redacted], in conjunction with our ACD response, sufficiently demonstrates that olaparib does represent 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 an NHA.

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

Topic 1 Revised assumptions in the prior-taxane subgroup

ACD Section 3.24: "…*the committee noted the cost-effectiveness estimates for olaparib compared with cabazitaxel were higher than what NICE normally considers an acceptable use of NHS resources for people who have had treatment with a taxane. This was the case even when considering end of life criteria. The committee noted that olaparib was not cost effective even in the company's own base case.*"

Company Response:

- Olaparib requires commercial flexibility in order to be considered cost effective. Accordingly, [redacted] Taking this into account, we believe olaparib can be considered cost-effective in the No-Prior-Taxane subgroup, even when using the majority of the ERG-preferred assumptions in the economic modelling. Full results along with scenario analysis are presented in Appendix B.

The company welcome the opportunity to present additional analysis in consideration of the results in the Prior-Taxane subgroup, as discussed at the August 2021 committee meeting.

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 the company's base-case analysis. In order to guide decision making, the base case has been updated, incorporating some of the Committee's preferred assumptions (see **Error! Reference source not found.**). The corresponding analyses when taking in to account the [redacted] are also presented in Appendix B for consideration.

The company estimates largely reflect the ERG preferences with regards to the model assumptions. AstraZeneca would like to highlight that, by virtue of this approach, several conservative approaches to modelling have been incorporated into the analysis. Following the appraisal and initial consultation stage, the company have addressed a number of preferences noted by the Committee including:

- utilising the hazard ratio from the *BRCA*m prior-taxane subgroup to model the efficacy of cabazitaxel
- assuming only a proportion rather than 100% of people treated with cabazitaxel would be given prophylactic G-CSF for an average of 7 days
- using treatment discontinuation data (TDT) from PROfound to model treatment duration for olaparib, whilst using progression-free survival (PFS) data for cabazitaxel
- incorporating the costs of *BRCA*m testing for olaparib
- assuming cost of best supportive care (BSC) is the same irrespective of whether an active treatment was subsequently received
- assuming post-progression costs after olaparib or cabazitaxel do not include retreatment with abiraterone or enzalutamide

In addition to the above, the company in response to the first ACD, explored some of the Committee's preferences in scenario analyses which were recognised by the Committee to have a *"minor impact on cost-effectiveness estimates"*. These include:

- inclusion of the TROPIC study in the indirect treatment comparison (ITC)
- uncertainty around the effect of post-progression treatments on post-progression survival
- more flexible approaches for extrapolating overall survival (OS)
- uncertainty around dosing of olaparib
- uncertainty around the cost of post-progression treatments in the NHS

The company also acknowledge the Committee's preference of *"…using the ERG model, which applied the committee's preferences for other minor differences between the company's and the ERG's models, such as assumptions related to bone and CT scans while on treatment, or costs of ADT"* (ACD 2, Section 3.24). Accordingly, the updated cost-effectiveness results summarised incorporate the ERG's assumptions related to costs of ADT, bone and CT scans while on treatment. The impact on the cost-effectiveness results of applying these additional ERG assumptions to reflect the Committee's preference is shown in Table 8.

1.1 Extrapolation of overall survival in the olaparib arm

The company's original OS curve selection in the base case was updated to the exponential distribution (previously log-logistic) in response to Committee concerns. AstraZeneca agrees with the Committee's views that the *"Rayleigh, Weibull and exponential hazard function curves appeared reasonable although possibly pessimistic"* (Section 3.24). The company would like to highlight that among these choices, the Rayleigh distribution is the most pessimistic followed by the Weibull and exponential (see Table 2). We believe extrapolating with the Rayleigh distribution represents an overly pessimistic projection of the plausible overall survival and in effect provides a 'worst case' interpretation of the benefit of olaparib. Although the Weibull distribution was not considered at the Committee meeting, the June 2021 ERG report (*page 5*) indicated a preference for the Rayleigh or Weibull distributions given these curves *"…support proportional hazards, fit the KM data well, and seem not to generate unrealistic survival rates in extrapolation".* The company has therefore adopted the Weibull distribution in the revised base-case OS modelling of olaparib, with the Rayleigh regarded as the most pessimistic choice of the two curves. The impact of choosing the Rayleigh, Weibull and exponential distributions on the updated cost-effectiveness results is explored in Table 2. Given the incorporation of substantial conservative assumptions into the modelling, the company would encourage the Committee to consider the modelling results presented in Table 1 to represent a lower bound of uncertainty.

The individual impact of each change on the revised base case, relative to the previous base case presented in response to the first appraisal consultation document is shown in Table 8. As can be seen, most ERG-preferred inputs have already been adopted, making this a plausibly conservative estimate of the cost-effectiveness of olaparib in this population.

1.2 Summary of updated cost-effectiveness results in the base-case analysis

Please note, the cost-effectiveness results presented in this section and in Table 1 include [redacted]. The corresponding updated results including [redacted] are presented in Appendix B.

The updated cost-effectiveness results incorporating the changes highlighted in Table 1 demonstrate that **olaparib has the potential to be considered cost-effective compared with cabazitaxel** at an ICER of £[redacted] per QALY gained, and demonstrably so should [redacted]. As shown in Table 1, olaparib provides an additional [redacted] LYs and [redacted] QALYs at an incremental cost of £[redacted].

Based on the Committee's concern regarding the appropriate OS extrapolation curve choice, a list of scenarios is also provided to demonstrate the impact of various assumptions in order to guide decision making (Table 2**Error! Reference source not found.**) and show that the results are consistent with the base-case analysis in that olaparib is cost-effective (see Appendix A).

Table 1: Updated base-case results; *BRCAm Prior-Taxane subgroup* ([redacted])

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

1.3 Scenario analyses

Table 2: Cost-effectiveness scenario results; *BRCA*m, Prior-Taxane ([redacted])

Scenario	ICER (£/QALY)	Difference vs. updated base case
Updated base case	[redacted]	-
Explores alternative approaches for extrapolating overall survival		
Overall survival exponential distribution for olaparib	[redacted]	[redacted]
Overall survival Rayleigh distribution for olaparib	[redacted]	[redacted]
Overall survival splines model for olaparib	[redacted]	[redacted]
Explores consistent approach in modelling treatment duration for olaparib and cabazitaxel		
Uses rPFS to model treatment duration for olaparib and cabazitaxel	[redacted]	[redacted]

Topic 2 Evidence in the population who have not taken docetaxel or cannot have it

ACD Section 3.6: "*The committee noted that subgroup analyses by prior taxane status for people who have BRCA mutations were not pre-specified in the clinical study protocol, and therefore constitute post-hoc analysis. It also noted the small size of the subgroup of people who had not had treatment with docetaxel, and the immaturity of overall survival data in this group. It concluded that these results were highly uncertain*"

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 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

2.1 Addressing uncertainty in the available clinical evidence package

As has been stated in the previous company ACD response (April 2021), we acknowledge that there are some limitations to the available data in this small subgroup population. The PROfound study was originally powered to detect clinical efficacy of patients in the 'Cohort A' population, which contained patients with *BRCA1*, *BRCA2*, and *ATM* mutations and the appropriate comparator for the analysis in the BRCAm population differed depending on whether a prior taxane was received. Patients who were in the **'No Prior-Taxane'** population are expected to receive docetaxel or BSC, neither of which were comparators in the PROfound clinical trial, thus necessitating an indirect treatment comparison (ITC) to establish the clinical efficacy.

Nevertheless, the estimated benefit of olaparib based on the ITC analysis presented in our previous ACD response is remarkable and consistent with clinical expectation given the mechanism of action of PARP inhibitors. Moreover, the observed benefit in the No Prior-Taxane subgroup is consistent with results estimated in the Prior-Taxane subgroup. This is expected, given there is no biological rationale for the

relative efficacy of olaparib to vary based on prior use of taxane therapy use in persons with BRCA mutations (Table 3). The use of data from the entire *BRCA*m subgroup means that the analysis makes maximum use of the available data in *BRCA*m patients, thereby supporting decision making. The use of data from a small subgroup increases uncertainty and places the analysis at increased risk of erroneous findings.

Finally, it is worth noting that (as outlined in our previous ACD response) the approach taken to estimate the comparative efficacy in this population is arguably conservative. Analyses presented in the following section of this response demonstrate that olaparib remains plausibly cost-effective even when considering the upper bounds of uncertainty on key model parameters.

Table 3: Overview of clinical efficacy of olaparib across Cohort A and *BRCA*m subgroups

	Primary study population: Cohort A		***BRCA*m**		***BRCA*m Prior Taxane**		***BRCA*m No Prior Taxane**	
	Olaparib 300 mg bid (n = 162)	**Investigators' choice of NHA (N = 83)**	**Olaparib 300 mg bid (n = 102)**	**Investigators' choice of NHA (n = 58)**	**Olaparib 300 mg bid (n = 72)**	**Investigators' choice of NHA (n = 35)**	**Olaparib 300 mg bid (n = 30**	**Investigators' choice of NHA (n = 23)**
Primary endpoint: BICR-assessed rPFS (DCO1) [a]								
Events, n (%)	106 (65.4)	68 (81.9)	62 (60.8)	51 (87.9)	48 (66.7)	34 (97.1)	14 (46.7)	17 (73.9)
Median rPFS, months (95% CI)	7.39 (6.24–9.33)	3.55 (1.91–3.71)	9.79 (7.62, 11.30)	2.96 (1.81, 3.55)	8.97 (7.36, 10.84)	1.91 (1.71, 3.52)	13.60 (7.38, NC)	3.71 (1.84, 6.57)
HR (95% CI)	**0.34 (0.25, 0.47); p < 0.0001**		**0.22 (0.15, 0.32)**		**0.19 (0.12, 0.32)**		**0.17 (0.08, 0.36)**	
Key secondary endpoint: final OS (DCO2) [b]								
Events, n (%)	91 (56.2)	57 (68.7)	53 (52.0)	41 (70.7)	41 (56.9)	27 (77.1)	12 (40.0)	14 (60.9)
Median OS, months (95% CI)	19.09	14.69	20.11 (17.35, 26.81)	14.44 (10.71, 18.89)	17.45 (13.0, 25.3)	11.93 (8.21, 15.15)	NR (NC, NC)	18.79 (11.33, NC)
HR (95% CI)	**0.69 (0.50, 0.97); p = 0.0175**		**0.60 (0.40, 0.91)**		[redacted]		[redacted]	
Median OS (switch-adjusted)	N/A		N/A	9.15	[redacted]		[redacted]	
HR* (95% CI)			**0.28 (0.10, 0.79)**		[redacted]		[redacted]	

* RPSFT with recensoring

2.2 Revised assumptions in the No Prior-Taxane subgroup

The ACD notes that the Committee did not consider the company analyses in this subgroup to be validated by the ERG and that the base-case analyses contained inappropriate assumptions, particularly with respect to the proportion and receipt of post-progression therapies in the economic model. (ACD Section 3.22).

The ERG did provide commentary on the key model parameters in this subgroup in their report dated June ’21 and ahead of the second ACM in August 21. Nevertheless, we acknowledge the Committee’s concerns and have presented a revised base case taking in to account the feedback received. Despite these amendments reflecting a conservative stance on plausible assumptions, we maintain that there remains a credible case for olaparib to be considered cost-effective in this subgroup, [redacted]

Original Base Case

The original base-case analysis for both docetaxel and BSC comparators are shown in

Table 4, below. In these analyses, olaparib represented a plausibly cost-effective use of NHS resources, with an ICER of [redacted] per QALY gained versus docetaxel for the taxane-suitable group, and [redacted] per QALY gained versus BSC in the taxane-unsuitable group. As described in our ACD response, the parameters and assumptions used to inform this analysis were derived from the best available evidence in these population as well as the previously accepted assumptions in the Prior-Taxane population.

Table 4 *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]	[redacted]
Patients who are unsuitable for treatment with docetaxel							
Best supportive care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Impact of post-progression therapies

The ACD identified two areas where the assumptions did not align with the Committee preferences:

1) *assuming that the same proportion of people whose disease progressed on olaparib or cabazitaxel would have an active treatment*

2) *adjusting for differences in post-progression treatments between PROfound and NHS practice*

As noted in our original submission (and reflected in the ACD) post-progression treatments were informed by the available data from the *BRCA*m subgroup populations in PROfound, adjusted to align with NHS practice by removing NHA re-challenge. Based on this data, a higher proportion of patients in the comparator arm (i.e., docetaxel) were observed to receive a subsequent treatment ([redacted]% and [redacted] for olaparib and docetaxel, respectively) which was applied in the original base-case analysis. An updated analysis has been provided aligning the subsequent treatment proportions across treatment arms, per the approach taken in the Prior-Taxane population (Table 5Table 5).

Table 5: *BRCA*m No Prior-Taxane results (costs and health outcomes discounted at 3.5%) – *same proportion of patients receiving active treatment*

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]	[redacted]
Patients who are unsuitable for treatment with docetaxel							
Best supportive care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Applying the same proportion to people receiving post-progression therapies results in a relatively small increase in the original base-case ICER from [redacted] to [redacted] in the docetaxel arm. As expected, no impact is observed in the BSC comparison as patients are assumed not to receive active treatment. Importantly, aligning with the Committee preferred assumptions with respective to post-progression therapy does not alter the conclusion that olaparib represents a plausibly cost-effective treatment option in this setting.

ERG Critique of Survival Analysis

The ERG provided a critique of the Company survival analysis with respect to the OS, PFS and TTD efficacy outcomes. It is not clear from the ACD whether the Committee considered these analyses or reached a preferred assumption at the 2nd ACD meeting – therefore, to support decision making we have provided an overview of the key considerations and impact on the cost-effectiveness results.

Overall Survival

As reported in our previous ACD response, the log-logistic model was selected as the base-case OS distribution for the docetaxel arm based on visual fit to the observed KM data, statistical performance, as well clinical and external validation of long-term projections. These selection criteria are consistent with recommendations in NICE DSU TSD 14. More complex 1-5 knot spline models were also explored but they failed to outperform the standard distributions (Exponential, Weibull, Log-logistic, Lognormal, Gompertz and Generalised Gamma) typically used to model long-term survival. The log-logistic distribution provided the best statistical fit to the observed data for docetaxel. Longer term OS projection for docetaxel produced by the log-logistic curve (mean [redacted] months; median [redacted] months) were also consistent with identified real-world evidence study results (mean, [redacted] months; median, [redacted] months).

The ERG noted that the log-logistic model may produce an overestimate of long-term survival and proposed to use a Rayleigh 1P distribution which resulted in an increase of the base-case ICERs to [redacted] versus docetaxel and BSC, respectively. We believe this may represent an overly pessimistic projection of plausible overall survival and in effect provides a ‘worst case’ interpretation of the

benefit of olaparib. As such we maintain the most appropriate base-case analysis would utilise the log-logistic distribution for OS.

Progression-free Survival

A similar validation approach that was taken for OS was also conducted for the PFS endpoint. Based on this, the lognormal distribution was selected as the base case survival curve for the PFS efficacy. This distribution provided the best statistical fit to the observed data and is supported by available RWE – the lognormal curve used in the analysis produced the closest estimates to the identified RWE results, compared with all other distributions. Modelled OS produced by the lognormal (mean [redacted] months; median [redacted] months) was highly consistent (mean [redacted] months; median [redacted] months).

Similar to the OS endpoint, the ERG preferred the Rayleigh 1P distribution to model long-term PFS outcomes – this distribution resulted in notably poorer long-term outcomes versus other distributions (see Figure 1) and can conceivably be considered a worst-case scenario. Applying the Rayleigh 1P distribution results in an increase in the ICER to [redacted] versus docetaxel and BSC, respectively.

Figure 1: ERG PFS distributions (replicated from ERG report)

Treatment Discontinuation

The ACD states the Committee preference to utilise TTD curves to model treatment duration for olaparib despite using the rPFS curves to model treatment duration for comparators. We have previously highlighted the inconsistency in this approach and the fact that it introduces bias in favour of the comparators. Nevertheless, we have applied the Committee's preferred approach in the base-case analysis for the no prior-taxane subgroup.

The parametric distribution selected for the base analysis to model olaparib TDT was the Weibull distribution – this reflected the best statistically fitting distribution to the available data. The ERG preferred to use the Rayleigh 1P distribution which resulted in a modest increase in the ICER to [redacted] and [redacted] versus docetaxel and BSC, respectively.

Revised Base Case Analysis

Consistent with the above, we propose to update the base-case analysis to take in to account the Committee feedback regarding post-progression treatment assumptions. Although we acknowledge the ERGs feedback on the survival analysis parameters, and the preferential use of the Rayleigh 1P distribution throughout, we believe this represent an overly pessimistic scenario which feasibly underestimates the benefit of olaparib in this population.

For completeness, the revised base-case analysis results are reported below (Table 6).

Table 6 *BRCA*m No Prior-Taxane results (costs and health outcomes discounted at 3.5%) – *revised base case analysis*

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]	[redacted]
Patients who are unsuitable for treatment with docetaxel							
Best supportive care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

We acknowledge the uncertainty inherent in this small, post-hoc subgroup population and the limitations of constructing this analysis based on the available data. However, it is worth noting that this analysis now reflects all preferred assumptions (where applicable) that were determined in the prior-taxane subgroup analyses, and as discussed in (Section 1.2 and 1.3), we maintain that these in themselves primarily reflect conservative interpretations of the plausible estimates.

Given this, we believe olaparib firmly represents a cost-effective treatment option to the NHS in this population, [redacted].

Topic 3 Application of End-of-Life criteria to the No Prior-Taxane subgroup

ACD Section 3.23: "*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.

As confirmed by the committee discussion (ACD Section 3.23), olaparib meets the end-of-life criteria in the Prior-Taxane subgroup. Given that olaparib in the No Prior-Taxane subgroup may be received at a different point in the treatment pathway, it is reasonable to examine the application of the end-of-life criteria separately for this population (per Section 3.23). However, we can consider that the criterion is still met in this population.

3.1 Consideration of the short life criterion

As stated above, olaparib may be received by a patient who is taxane-naïve in two settings: after an NHA received in the pre-mCRPC setting, and after an NHA received in the mCRPC setting. A 2019 survey of UK clinical experts (n=103) reported that, where NHAs would be available in UK practice in the mHSPC setting, proposed usage of docetaxel and NHA in patients with *BRCA*m disease would be roughly equal, with clinicians 'sometimes' using them in 35.8% vs 63.5% of cases respectively, and 'highly likely' to use them in 60.5% and 29.7% of cases, respectively.[8] From this we can infer that there is no clear preference for usage of NHA vs docetaxel in *BRCA*m patients in the mHSPC setting, and thus the split of olaparib usage in 1L mCRPC vs 2L mCRPC might be considered equivalent.

Data from a Canadian Registry have been submitted as part of the first Company ACD response (April 2021), and presented at the second NICE committee meeting for olaparib. Full details of the study can be found in the first company ACD response, but in brief this study detailed use of taxane therapy (docetaxel or

cabazitaxel) as the first treatment after an initial NHA received in the mCRPC setting. This aligns with UK clinical practice where NHA is received in the mCRPC setting and demonstrated that survival where in a subsequent line where docetaxel may be received is less than 24 months (mean [redacted] months, median [redacted] months), as shown in Table 7. These results are consistent with the modelled survival projections presented in our previous ACD response and reiterated in Section 2.2. Both external data and modelled survival clearly demonstrate that the prognosis in this population remains exceptionally poor and therefore qualifies for consideration of End-of-Life based on the short life expectancy criterion.

Table 7: Comparison of RWE results and modelled OS for docetaxel based on the TAX327 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]

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

For those patients who do receive an NHA in the pre-mCRPC setting, we acknowledge that there is a paucity of data on survival once patients have progressed – however, this is primarily due to this being a recent change to the UK clinical pathway.[9] As such, it is necessary to look to other sources of data to inform survival prognosis. It may be helpful to infer post-progression survival (PPS) as a naïve comparison of the reported OS and PFS from the clinical studies of these agents. While this could not be estimated from the relevant trials for enzalutamide in the mHSPC setting,[10,11] this is possible for the LATITUDE study which evaluated abiraterone acetate in this setting – in this trial, PPS can be inferred from the reported metastasis-free survival (33.9 months) and OS (53.3 months) at 19.4 months. It must be noted that such comparisons are limited by factors such as: confounding by comparators, the potential over-estimation of survival by virtue of the

clinical trial setting, and generalisability to of the trial to UK clinical practice. However, despite these limitations this method provides one possible source of overall survival expectation for patients' post-receipt of an NHA in the mHSPC setting.

3.2 Consideration of the extension to life criterion in the no prior taxane subgroup

The analyses presented for the no Prior-Taxane group demonstrate a clear extension to survival of at least three months. The mean modelled survival gain associated with olaparib compared with standard of care is much greater than 3 months using all parametric distributions. The mean incremental survival benefit of olaparib versus docetaxel from the model is shown to be between [redacted] months and [redacted] months, thereby meeting NICE's criteria for life-extending treatments at the end of life.

As has been detailed in a previous consultation response, there is strong clinical rationale that olaparib would extend life by at least 3 months in patients who had not received a prior taxane therapy:

- 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.

- Corresponding evidence on the potential for long-term OS benefit of olaparib come from a variety of tumour types. 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.[12] 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.

3.2.1 Summary

Data are inherently limited to evaluate survival in the post-NHA mCRPC setting where patients have not received a taxane, due to this clinical pathway being recently established. However, there is strong support from the economic modelling analyses and available RWE datasets, coupled with the known mechanism of action of olaparib and survival extension observed in other tumour types, that olaparib meets the end-of-life criteria in the No Prior-Taxane subgroup.

Topic 4 Choice of comparator

ACD Section 3.3: "*The committee concluded that cabazitaxel is likely to be the main, but not the only, comparator for olaparib in people who have had a taxane. It would have preferred to see exploratory analyses with radium-223 dichloride and retreatment with docetaxel because they are also relevant comparators*"

Company Response:

- The company analyses vs docetaxel and cabazitaxel represent those most appropriate in the No Prior Taxane and Prior Taxane subgroups, respectively. Analyses against docetaxel rechallenge and radium-223 are do not reflect the patient populations, are compromised by feasibility concerns, and as a result would not be informative for decision-making.

Cabazitaxel remains the overwhelming comparator of choice in the Prior Taxane population, a patient population implicitly suitable for taxane therapy by virtue of previous receipt of docetaxel. There remains no specific rationale that patients would be preferred for docetaxel treatment again, given concerns around docetaxel-resistance, which was the specific reason for the clinical development of cabazitaxel. The latest ERG report (June 2021) highlights that docetaxel re-treatment is used only in exceptional cases; it also notes that re-treatment is both hard to define, and explicitly not recommended in NICE guidelines in some cases.

As has been stated in a previous response, a robust comparison against radium-223 is not feasible. Given that only a small minority of patients will be eligible to receive radium-223, no cost-effectiveness analysis has been explored, with the company focus on docetaxel and BSC in patients who have not received a prior taxane, and cabazitaxel in those who have.

Topic 5 Olaparib as an innovative medicine

ACD Section 3.27: "*The committee understood that to consider a technology innovative, a substantial change in management of a condition and benefits not adequately captured in the economic analysis were both needed. It concluded olaparib is not innovative because it does not offer benefits not already included in the modelling*."

Company Response:

- The broader benefits of BRCA testing, currently not standard NHS practice, will enable wider benefits of earlier identification of *BRCA*m disease, and provide the opportunity for increased vigilance for patients with genetic considerations based on their heritable disease.

Olaparib is the first biomarker-targeted medicine available for patients with prostate cancer, and thus is inherently an innovative technology. The application of 'innovative' for the purposes of technology appraisal is such that additional benefits have not been captured in the modelling.

As discussed in Section 3.20 of the ACD, the cost of *BRCA* testing is included in the company modelling. Further benefits of BRCA testing, which until now are not considered standard of care (ACD Section 3.27: "*clinical advice suggested the NHS does not currently test for BRCA mutation*"). The introduction of BRCA testing will enable wider benefits of earlier identification of *BRCA*m disease and provide the opportunity for increased vigilance for patients with genetic considerations based in heritable disease. These benefits align with UK policy aims on the early identification of disease and have not been captured in the modelling.

Appendix A. Summary of changes incorporated into the updated base-case analysis; *BRCA*m, Prior-Taxane subgroup

Table 8. Summary of changes incorporated into the updated base-case analysis; *BRCA*m, Prior-Taxane subgroup

ACD Section	Model inputs (Olaparib vs Cabazitaxel)				Updated ICER (£ per QALY)	
	Original base case	Company ACD1 base case*	Updated base case	Input in the updated base case	Olaparib vs cabazitaxel	Impact vs company ACD1 base case*
3.24	Company assumptions on bone and CT scans, and costs of ADT	Company assumptions on bone and CT scans, and costs of ADT	ERG assumptions on bone and CT scans, and costs of ADT	ERG estimates; bone and CT scans, and costs of ADT	[redacted]	[redacted]
3.11	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	Unchanged	OS HR = [redacted] rPFS HR = [redacted]	[redacted]	[redacted]
3.12	Log-logistic distribution to model olaparib OS	Exponential distribution to model olaparib OS	Weibull distribution to model olaparib OS	Weibull	[redacted]	[redacted]
3.15	rPFS to model treatment duration for olaparib and cabazitaxel	TTD to model treatment duration for olaparib, and rPFS for cabazitaxel	Unchanged	TTD – olaparib; rPFS - cabazitaxel	[redacted]	[redacted]

3.17	Assumes that all patients receiving cabazitaxel have prophylactic G-CSF, in line with the CARD study protocol; for 14 days	Assumes only a proportion of people have prophylactic G-CSF, and have it on average for 7 days	Unchanged	79.5% uptake, based on UK EAP for cabazitaxel: 7 days	[redacted]	[redacted]
3.10	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)	Unchanged	Include subsequent treatments: docetaxel, cabazitaxel, radium-223	[redacted]	[redacted]
3.19	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	Unchanged	Apply BSC costs for all patients	[redacted]	[redacted]
3.20	Excludes the cost of testing for *BRCA* mutations	Includes the cost of testing for *BRCA* mutations	Unchanged	Same value as before £[redacted] per test, 9.7% prevalence	[redacted]	[redacted]
Updated base case ([redacted])					[redacted]	[redacted]

*Please note that "**ACD1 base case**" refers to the updated base case in the Company's response to the initial ACD

Appendix B: Cost-effectiveness results at (REDACTED)

As outlined in the Introduction to this ACD response, [redacted]

B.1 Cost-effectiveness results for the *BRCA*m Prior-Taxane subgroup

Consistent with the updates described in **Topic 1**, the cost-effectiveness results consider some of Committee's preferences. With regards to [redacted], the updated base case results are presented in Table 9 which demonstrate that **olaparib has the potential to be highly cost-effective compared with cabazitaxel** at an ICER of £[redacted] per QALY gained with an additional [redacted] and [redacted] LY and QALY gains.

Table 9: Cost-effectiveness results; *BRCAm Prior-Taxane subgroup* ([redacted])

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cabazitaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

Table 10: Cost-effectiveness scenario results; *BRCAm, Prior Taxane subgroup* ([redacted])

	Scenario	ICER (£/QALY)	Difference vs. proposed base case*
	Updated base case	[redacted]	-
	Explores alternative approaches for extrapolating overall survival		
	Overall survival exponential distribution for olaparib	[redacted]	[redacted]
	Overall survival Rayleigh distribution for olaparib	[redacted]	[redacted]
	Overall survival splines model for olaparib	[redacted]	[redacted]
	Explores consistent approach in modelling treatment duration for olaparib and cabazitaxel		
	Uses rPFS to model treatment duration for olaparib and cabazitaxel	[redacted]	[redacted]

*Please note that "**proposed base case**" refers to the cost-effectiveness results [redacted]

B.2 Cost-effectiveness results for the *BRCA*m No Prior-Taxane subgroup

Table 11. Cost-effectiveness results for the *BRCA*m No Prior-Taxane subgroup ([redacted])

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]	[redacted]
Patients who are unsuitable for treatment with docetaxel							
Best supportive care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

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Please clarify for the prior taxane modelling:

1. I*s the rate of bone and CT scans for olaparib the same as that for cabazitaxel while remaining on 1st line treatment, or only during the 1st 3 months of the modelling?*

Consistent with the Committee-preferred assumption, bone scans and CT scans for olaparib and cabazitaxel were equalised during the first 3 months; this assumption was introduced directly by the EAG in their revised base case analysis. ***This EAG update has been maintained in all subsequent Prior Taxane company generated base-case models and cost-effectiveness results to date.***

2. *Are ADT costs applied throughout the OS, are they applied equally in both arms and what is the cost per cycle.*

Consistent with the Committee-preferred assumption, the EAG in their original critique of the Prior Taxane company economic model removed ADT from BSC and applied this cost throughout the modelled OS to all patients. ***This EAG update has been replicated and maintained in all subsequent Prior Taxane company generated base case models and cost-effectiveness results to date.***

3. *In the olaparib arm what <u>cost</u> has been applied for active PPS treatment for those receiving active PPS treatment, how <u>long</u> is it assumed that this PPS treatment <u>lasts</u>, what <u>per cycle BSC costs</u> have been applied for these patients, thereafter, how does this compare to the per cycle BSC for those not receiving an active PPS treatment and is the approach in the cabazitaxel arm identical to that in the olaparib arm.*

In the olaparib arm, the PPS active treatments considered in the model are outlined in **Table 1** below along with the costs per cycle and the average duration. Following the initial ERG critique of the company submission, the EAG revised model:

- excluded NHAs namely enzalutamide and abiraterone from the active PPS treatments, therefore these are set at 0%.
- Equalised PPS active treatments for both olaparib and cabazitaxel, therefore the same costs and duration are assumed in the model.

In relation to the application of BSC, it is assumed that those who do not receive active PPS treatments would get BSC. In alignment with the ERG's approach and Committee-preferred assumption, the same best supportive care costs were incurred, regardless of whether an active treatment was received after disease progression. Similarly, across the olaparib and cabazitaxel arms, the same proportion receiving BSC, and associated costs are assumed in the model as per the ERG update.

Table 1: Active PPS treatment duration unit & total costs for olaparib & cabazitaxel

	Unit costs per model cycle	Average duration *olaparib & cabazitaxel*	Costs *olaparib & cabazitaxel*	% receiving *olaparib & cabazitaxel*
Cabazitaxel	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]
Abiraterone	[redacted]	[redacted]	[redacted]	[redacted]
Enzalutamide	[redacted]	[redacted]	[redacted]	[redacted]
Radium 223	[redacted]	[redacted]	[redacted]	[redacted]
Total costs olaparib & cabazitaxel			[redacted]	

Detailed costings of BSC are presented in the *'Disease Management and Model Calcs'* worksheets of the economic model and are consistent with the formulae the EAG used when rebuilding the Company deterministic model.

4. *Are there any other differences in modelling assumptions between olaparib and cabazitaxel, particularly in the light of ACD1 and ACD2.*

No, the modelling assumptions for olaparib and cabazitaxel following the initial ERG critique and technical engagement have been maintained and accounted for in subsequent updates. As previously communicated by the company, the most recent models provided following ACD2 replicate the ERG's base case assumptions and the agreed Committee assumptions for both the olaparib and cabazitaxel arms within the original model structure. The company latest ACD2 cost-effectiveness base case of [redacted] in effect incorporates most of the EAG-preferred assumptions and corrections, the exception being the use of the company OS functional forms and the assumption of 79.5% G-CSF uptake for a period of 7 days. For details on the exhaustive list of the ERG updates that were incorporated in the company prior taxane model, please see the recently provided model named **"ID1640 olaparib_CEM_1June2020_v1 ERG TE amended - 220121_ACD2update [ERG Model Update] _29Jun22",** sheet named ERG, and the company response to ***ACD2, Appendix 8, Table 8***.

5. *Which assumptions and associated model inputs differ for the no-prior taxane modelling compared to the prior taxane modelling, particularly in the light of ACD1 and ACD2 - please tabulate. The ERG has made an initial cursory check of possible modelling discrepancies, as per the attached. It would be helpful if these cell references could be worked into the tabulation.*

The company would like to emphasise that the *"discrepancies"* outlined by the EAG in their table below between no-prior and prior taxane models are to be expected, since the no-prior taxane model has not been fully critiqued or revised by the ERG to the same extent as the prior taxane model. Our understanding was that the primary purpose of progressing to an ACM3 was to enable this critique to take place. For ease, the company has outlined in **Table 2** below the key differences between both models, which we maintain are reasonable given relative differences between populations and comparators between the two models. The no prior taxane model also includes the functionality to adopt the ERG and Committee-preferred assumptions from the prior taxane model, if considered appropriate.

Table 2: No prior taxane vs. prior taxane model assumptions

Assumption	Olaparib_BRACm no prior tax_ERGCQs_ACD2_ACIC_v3_27Jun22	Olaparib+BRCAm prior tax_ERGCQs_ACD2_ACIC_v3_29Jun22
Extrapolation of overall survival	Log-logistic	Weibull
Extrapolation of progression-free survival	Lognormal	Gompertz
Treatment discontinuation rule based on: Olaparib Cabazitaxel Docetaxel	 Treat until progression NA Treat until progression	 Treatment discontinuation Treat until progression NA
Extrapolation of treatment discontinuation	Weibull	Gompertz
Concomitant medication costs in particular G-CSF costs	• Aligned with committee-preferred assumptions of 7 day-duration • Proportion consistent with original company assumption of 100% receiving ADT	Based on Committee-preferred assumption of a proportion receiving this over 7 days
Estimation of best supportive care > disease management costs> H41	ADT estimated as part of BSC, consistent with original company submission	Costs of ADT removed from BSC and applied to the modelled OS to for all patients.
Estimation of subsequent treatment >sub tx >E28:H39	• Different proportion of PPS active treatments between olaparib and docetaxel arms ***(scenario analysis equalising this presented in the***	• Same proportion of PPS active treatments between olaparib and cabazitaxel arms

	company response to ACD2, Appendix 8, Table 8) • Different proportion receiving BSC treatments between olaparib and docetaxel arms ***(scenario analysis equalising this presented in the company response to ACD2, Appendix 8, Table 8)*** • Removal of subsequent enzalutamide and abiraterone use from olaparib and docetaxel arms	• Same proportion receiving BSC treatments between olaparib and cabazitaxel arms • Removal of subsequent enzalutamide and abiraterone use from olaparib and cabazitaxel arms

NICE National Institute for Health and Care Excellence

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

Consultation on the appraisal consultation document – deadline for comments 5pm on 31 January 2022. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. 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 provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced.
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	**Prostate Cancer UK**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	Comments
	Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this

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	table.
Example 1	We are concerned that this recommendation may imply that ……..
1	**We are concerned that docetaxel re-challenge is considered a suitable comparator for olaparib. This could result in some patients with metastatic hormone-refractory prostate cancer and BRCA1 and/or BRCA2 pathogenic variants being denied access to olaparib solely because they have not had prior docetaxel chemotherapy.** A significant proportion of patients will not be suitable for docetaxel treatment and therefore not suitable for re-challenge. These are patients who are likely to be of an advanced age, with comorbidities or a degree of frailty which excludes them from being treated with a taxane. In our previous ACD response we shared clinical opinion drawn from the British Uro-oncology Group outlining that very few men would tolerate the full 16 cycles of docetaxel due to dose limiting neurotoxicity[1].We still would like to reiterate this point. In normal practice patients would receive one round of chemo of 6-8 cycles but there is insufficient evidence that another round would be beneficial • In 2016 the 80+ age group accounted for 34% of all newly diagnosed metastatic prostate cancer population, >2000 patients[2]. • 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[2]. This represents a sizeable population of patients that, if identified as BRCA1 or BRCA2 mutated, could be denied olaparib. • 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. Those patients who are contra-indicated to chemotherapy, those of an older age, with poorer performance status, with comorbidities, or poor cognition could be indirectly discriminated against. This is troubling when the PROfound study shows clear evidence of benefit in the no-prior taxane population. To add to the above, 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 [3]
2	**Statistically powered data for the prior and no prior taxane sub-groups is unlikely to ever be feasible in a clinical trial setting and they should be considered as one population.** Since the company has now provided exploratory analyses for people who have not had a taxane and this group is now considered a separate population we believe this will potentially discriminate against these patients, effectively penalising this group. BRCA1/2 patients only account for around 10% of the 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 and from those only 53 had not had a prior taxane[4]. These 53 patients were randomised across the olaparib and control arms. Given these circumstances and such low numbers of BRCA mutated patients, let alone the lower numbers of those who have a BRCA mutation and have not had a previous taxane, we feel that the decision by the company to no longer group the prior taxane and no prior taxane populations together, which originally mitigated the small patient numbers, is inappropriate as data on such a small number of patients is unfeasible. Greater flexibility with the patient sub-groups, by including them both in the indirect treatment comparison, should be considered. We recognise this may increase uncertainty of comparative effect, but we believe that the committee should rely on the evidence from PROfound that shows benefit of olaparib in both the prior and no-prior taxane sub-groups.
3	**We are concerned that prior taxane treatment is considered a modifier on the effectiveness of olaparib without sufficient justification. This could result in patients, who would benefit from this treatment, missing out. We believe the marginal decrease in certainty of the results is not sufficient enough to justify denying patients access to olaparib.** We recognise that the no prior taxane group represents a significant challenge for the appraisal process. This group is not well represented in clinical trials, not just in PROfound, but in other trials across metastatic patient pathway. However, as analysis of Public Health England data has shown[2] they represent a significant proportion of the real-world patient population. There is also a potential equality issue, which the committee has recognised throughout, as many of the patients unable to tolerate chemotherapy are older patients. We are satisfied with the mitigation efforts made within the trial to reduce uncertainty by attempting to recruit patients who had not had prior chemotherapy. PROfound screened tissue from 4425 patients across 206 sites in 20 countries and still was not sufficiently powered to analyse by taxane use. The number of patients who are healthy enough for clinical trials, and who have eligible HRR mutations is small. This population included in the analyses was further restricted when the marketing authorisation was limited to BRCA1 and BRCA 2 patients only. We believe that to a large extent, the uncertainty of the analyses presented was unavoidable, given the challenges of recruiting patients with HRR mutations to a clinical trial. Again, we feel satisfied that the company has made sufficient effort to mitigate uncertainty wherever possible. To further mitigate the concerns of the committee, Prostate Cancer UK have surveyed UK based clinical experts to ascertain their views on the extent to which prior taxane use would modify treatment with olaparib. All clinical experts are clinical oncologists with a research interest in treatments for advanced prostate cancer. Clinicians were asked to score a set of statements on a scale of 1-9, 1 (very strongly disagree) through 5 (neutral) to 9 (very strongly agree).

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

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	Statement 1: There are plausible reasons to believe that prior use of a taxane would have a significant effect on the efficacy of olaparib. • Clinical Expert 1 scored 3 • Clinical Expert 2 scored 3 • Clinical Expert 3 scored 6 • Clinical Expert 4 scored 3 **Statement 2: The same survival benefit would be expected from treatment with olaparib in patients previously treated with docetaxel and patients who have not been previously treated with docetaxel** • Clinical Expert 1 scored 7 • Clinical Expert 2 scored 8 • Clinical Expert 3 scored 3 • Clinical Expert 4 scored 7 **Statement 3: In the absence of robust data, it is reasonable to treat the cohort of men recruited to the PROfound trial with BRCA mutations as a single population for analysis.** • Clinical Expert 1 scored 9 • Clinical Expert 2 scored 9 • Clinical Expert 3 scored 8 • Clinical Expert 4 scored 7 Three out of four clinical expert indicated that they did not agree that prior taxane use would have a significant effect on olaparib. They also answered that overall survival would be similar irrespective of prior use of a taxane. One was neutral (neutral is a score between 4 and 6) on whether prior use of a taxane may have a significant effect on the efficacy of olaparib but indicated overall survival may not be similar between prior taxane and no prior taxane groups. All clinical experts agreed that it was reasonable to treat the cohort of men in PROfound as a single population for analysis. We recognise the concerns the committee has highlighted over prior use of a taxane, and that this is a difference in the populations of the CARD and PROFOUND trials. However, we do not believe that the evidence supports denying patients in the no prior taxane group access to olaparib. Ideally, all BRCA patients would be analysed as a single group regardless of prior taxane, as we believe clinical opinion supports the theory that treatment with a taxane is unlikely to have significantly affected the results of the indirect treatment comparison. We appreciate the role of the NICE in reducing the uncertainty of analyses of cost effectiveness. However, in this instance, we do not believe that the marginal decrease in certainty of results warrants denying patients access to life extending treatment with olaparib. We are particularly concerned about this in regards to the patients who cannot tolerate

	chemotherapy, as they will likely only be left with palliative care as a treatment (see point 4 below).
4	**Radium-223 is unlikely to be a comparator in patients who can't have chemotherapy. We are concerned that for patients who can't have chemotherapy, best supportive care is likely to be their only treatment option if olaparib is not approved.** 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 alone, 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[3] Due to the rarity of BRCA 1/2 mutations, and the rarity of only have bony metastases, it is very unlikely that many patients would ever be eligible for both olaparib and Radium-223. These treatments should not be viewed as comparators. It is vital that, for patients who can't have chemotherapy, both treatments are available to reduce the number of patients receiving best supportive care only. We do not believe the committee has adequately considered the implications of denying access to olaparib in this group. Denying these patients access to olaparib may deny them additional months of quality life. Olaparib can therefore meet an unmet need for some patients who cannot, or should not, have chemotherapy.
5	**We are concerned that inclusion of the BRCA test cost in treatment costs will disadvantage olaparib as a first in class treatment and sets a precedent against other precision medicines.** The Cancer Drugs Fund clinical lead explained that the Genomic Test Directory includes testing for BRCA mutations. However, he said 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. In its response to consultation, the company agreed with the ERG's approach and included the cost of testing for BRCA mutations in its revised base case. The committee acknowledged that the revised company approach was appropriate. This seems like a decision that is punishing first in class drugs and rewarding drugs in the same class that come later (and therefore incur less risk to the company when funding trials). This could inadvertently give companies the incentive to hold back on releasing new drugs

	(so as not to be the first to do so and therefore penalised), and therefore have a huge impact on patients and their access to innovative medicine in the future.
6	**We strongly disagree with the assertion that olaparib is not innovative. We believe olaparib has innovation benefits not already captured in the model.** Olaparib would be the first ever molecularly targeted treatment for prostate cancer. It is the drug that will open up the potential outlined in NHS Long Term Plan about genetic medicine for this cancer currently killing more than 11,500[6] men per year in the UK. In and of itself we believe that this should qualify olaparib for the more generous thresholds applied for "innovative" treatments. However, to illustrate further we are including just two of the unmodelled benefits of the change in practice that would happen should olaparib be approved: 1. Sequencing of prostate cancer tumours would become routine (probably at the point that they become metastatic, or possibly at the point that they become castration resistant and metastatic). This would increase very significantly the UK's speed and ability to recruit to modern clinical trials for advanced prostate cancer, many of which already rely on stratification on the basis of presence or absence of driver mutations. Faster recruitment to these globally competitive trials will increase immediate (free) access to other molecularly targeted treatments for prostate cancer through better recruitment in the UK, will increase UK plc's offer to pharma globally and will also ensure that the men recruited to those trials are more representative of the NHS-population. This benefit is articulated in the Genome UK report which states an aim to "*deliver[..] on the promise of genomic-enabled clinical trials, with more cancer patients than ever participating*[5]*.*" 2. Routine genetic testing of men eligible for olaparib (if approved) per the NHS test directory would identify about half of them carrying a BRCA mutation in their germline rather than somatically only. The sons and daughters (and future generations) of those men are at higher risk of multiple cancers as a result and for ovarian and breast cancer at least may benefit from risk reduction strategies thus reducing mortality and morbidity and saving long term costs to the NHS. Even for cancers where the risk is increased but where no preventative strategies are (yet) part of clinical practice those offspring would benefit from more intense screening and facilitated access to prevention and early diagnosis clinical trials. This also speaks to one of the key aims in the Genome UK report[5]: **"*Targeted screening:*** *We aim to better use genomics to improve population health through improved disease prevention including better screening. This includes the use of personalised and risk stratified screening and testing of the family members of cancer patients to identify where they are at increased risk of cancer.*" Neither of these wider benefits are considered (or considerable) in the health economics model used to make the decision about this assessment. We therefore believe that olaparib does in fact meet both of criteria required to be considered as "innovative".
7	**We are concerned that the committee has not considered temporary guidance which**

	suggests alternatives to docetaxel chemotherapy during the pandemic. During the COVID-19 pandemic enzalutamide was made available to metastatic hormone sensitive prostate cancer patients in place of docetaxel. This means, that since the start of the pandemic, the majority of patients will have not received docetaxel. For some patients, docetaxel still may not be an option due to the ongoing pandemic. Olaparib may be a more suitable option, as it can be taken orally at home, without the need to attend hospital. Therefore, it may be a more appropriate treatment for those needing to shield during the pandemic. For patients who would normally have received docetaxel during the pandemic, the committee should consider whether olaparib should be made available instead. In addition, for many of these patients, their condition may have now deteriorated to a point where they are unable to tolerate treatment with docetaxel at all. Denying them olaparib may further limit their treatment choices. We are concerned that making docetaxel a prerequisite for treatment with olaparib unfairly punishes patients who were advised not to have docetaxel during the pandemic and may now no longer able to tolerate treatment with docetaxel.
References	1. 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. 2. 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. 3. National Institute for health and Care Excellence, 2021. *Olaparib for previously treated hormone relapsed metastatic prostate cancer [ID1640] Committee Papers*. pp.555-572. 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. Supplementary Appendix for Olaparib for Metastatic Castration-Resistant Prostate Cancer. *New England Journal of Medicine*, 382(22) 5. GOV.UK. 2020. *Genome UK: the future of healthcare*. [online] Available at: <https://www.gov.uk/government/publications/genome-uk-the-future-of-healthcare/genome-uk-the-future-of-healthcare> [Accessed 25 January 2022]. 6. Cancer Research UK. *Prostate cancer mortality statistics*. [online] Available at: <https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/prostate-cancer/mortality> [Accessed 20 January 2022].

Insert extra rows as needed

Checklist for submitting comments

NICE National Institute for Health and Care Excellence

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

Consultation on the appraisal consultation document – deadline for comments 5pm on 31 January 2022. Please submit via NICE Docs.

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. 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 provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	**Tackle Prostate Cancer**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**NO Disclosure to make**
Name of commentator person completing form:	[redacted]**, Tackle Prostate Cancer**

Comment number	**Comments** Insert each comment in a new row.

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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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	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	Tackle Prostate Cancer is a patient-led Charity and as such does not have specific personnel with appropriate skills and training to adequately pass comments on many scientific and statistical arguments. Because of this, Tackle often work in close partnership with the Knowledge and Policy Teams at Prostate Cancer UK. However, the current patient representative for Tackle, Dr Steve Allen, does some understanding that may be not possible for other patients.
2	Tackle have discussed this ACD with Prostate Cancer UK and we have similar opinions of how responses should be made on behalf of patients. Tackle are in complete agreement with the opinions of Prostate Cancer UK which are obviously more detailed that we can produce. Rather than make a lengthy duplicate submission we would ask that the Committee note the agreement of Tackle with Prostate Cancer UK. However, Tackle do have some points that we would like to strongly stress:
3	We are very concerned at the possibility of inequality of care that may arise as a result of the potential restrictions that require patients to have been treated with taxane chemotherapy before being eligible to receive Olaparib. This will very effectively reduce the ability of clinicians to provide best possible therapy for many of their patients with advanced prostate cancer and co-existing BRCA 1 & 2 genetic abnormalities.
4	NICE, at other Appraisals related to prostate cancer, have already recognised a population of patients who are 'chemotherapy unsuitable'. This group of patients are unable to be given Olaparib even if they are clinically suitable for it.
5	In the future there will be a further group of patients who have not had taxane chemotherapy because, during the Covid pandemic, chemotherapy was not recommended and Novel Hormonal Agents (Enzalutamide or Abiraterone) were used as alternative additional therapy to ADT. Whilst these patients could still be eligible for chemotherapy, some may have already reached a stage clinically and physiologically where they could not adequately tolerate chemotherapy. They are at risk of being denied potentially life-extending with Olaparib treatment through no fault of their own. Whilst *unfair* may not be a word that is normally used in an appraisal, that to us is exactly what it seems like.
6	We are not sufficiently qualified to make appropriate comments on treatments being used as comparators. However, we do understand that there is considerable differences of opinion concerning this. Of particular importance to use is the assumption that a second course of docetaxel is an alternative option for treatment. Such treatment is not one that we have heard of being utilised to any great extent and indeed we believe, was not one shared by clinical experts at the original appraisal. Also is there research-based evidence

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

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	that states that this second course is effective? Could it be that the drug is licenced for up to 10 sessions but normally only 6 are used? This confusion was very graphically outlined by one patient who stated to our patient representative: *"What's the point of having a second course of the same drug? Surely any cancer cells that could be killed by docetaxel should have been done so already? Am I not now just developing a breed of cancer cells that were resistant to this drug – just like we are getting bacteria resistant certain anti-biotics"* In a disease that heavily relies on serial therapies, this is not an illogical statement and may well have truth in it?
7	Part of the job of a patient representative is to be able to adequately explain decisions made by NICE to our members. It is going to be extremely difficult to explain the inequality of treatment if the recommendations of the current ACD cannot be changed. Quite understandably, decisions made by NICE and the Scottish Medicines Consortium are made very independently of one another. However, the outcome of this current ACD will be even more difficult to explain to patients when the SMC have already approved the use of Olaparib using what seems (to the untrained eye, at least) to be the submission of similar evidence.

Insert extra rows as needed

Checklist for submitting comments

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- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
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1 Company revised cost effectiveness estimates

1.1 Company June 2022 base case: BRCAm prior taxane

The original ERG report and ERG TE response noted the following differences. The ERG updates these for the company June 2022 ACD response, based upon Table 8 of the June 2022 company response. The ERG has not checked the implementation of these changes in the company submitted model.

- **ERG01**: Apply the various corrections to the model: G-CSF costing, BSC costing, cabazitaxel administration costs, olaparib monitoring costs, genetic test costs. **Company TE clarification response:** G-CSF costing, cabazitaxel administration costs and olaparib monitoring costs corrected. BSC costs post PPS explored as a scenario analysis. The ERG retains its preferences. **Company June 2022 ACD response:** BSC costs post PPS for all patients, though the ERG notes that this has no effect upon the ICER.
- **ERG02**: Apply the ERG Weibull curves for olaparib OS, PFS and TTD. **Company TE clarification response:** Not applicable DCO2. Company prefers DCO2 log-logistic OS curve, whereas ERG prefers DCO2 Rayleigh OS curve. **Company June 2022 ACD response:** Weibull distribution for OS.
- **ERG03**: Cost drug use using the median RDI and the TTD curve. **Company TE clarification response:** Median RDI but costed using the PFS curve. ERG prefers median RDI and costed using TTD curve. **Company June 2022 ACD response:** Cost using the TTD curve with the median RDI.
- **ERG04**: Restrict primary prophylaxis G-CSF to 60% of patients and for only 7 days per cabazitaxel treatment cycle. **Company TE clarification response:** Rejected. But ERG retains its preference. **Company June 2022 ACD response:** 80% of patients, based upon UK EAP analysis, receive 7 days G-CSF.
- **ERG05**: Exclude NHAs from the PPS treatments. **Company TE clarification response:** Rejected. The ERG retains its preference. **Company June 2022 ACD response:** NHAs removed from subsequent treatments.
- **ERG06**: Applies the £79.90 drug tariff price for G-CSF. **Company TE clarification response:** Accepted. **Company June 2022 ACD response:** No change.
- **ERG07**: ADT/LHRH throughout mCRPC. **Company TE clarification response:** Rejected. The ERG retains its preference. **Company June 2022 ACD response:** ???

- **ERG08**: Equal bone and CT scans while on treatment. **Company TE clarification response:** Rejected. The ERG retains its preference. **Company June 2022 ACD response:** Apply the ERG preference.
- **ERG09**: Cabazitaxel proportion getting PPS treatments and the balance between these. **Company TE clarification response:** Rejected. The ERG retains its preference, but draws attention to the scenario analyses presented as requested by NICE. **Company June 2022 ACD response:** The same proportion of patients receiving the same balance of PPS treatments of cabazitaxel, docetaxel and R-223 in each arm.
- **ERG10**: Apply the ERG Cohort A+B prior taxane HRs. **Company TE clarification response:** Not applicable to DCO2. But the company applies DCO2 BRCAm all patient HRs when modelling DCO2 BRCAm prior taxane group. ERG prefers to apply group specific prior taxane HRs. **Company June 2022 ACD response:** HRs from BRCAm prior taxane subgroup.
- **ERG11**: It applies the company [redacted] test cost, conditioned by a 27.9% HRR prevalence. **Company TE clarification response:** Not applied for the base case but explored in a scenario analysis, using the 9.7% BRCAm prevalence. The ERG applies this in its base case, as per the scope, also applying the 9.7% BRCAm prevalence. **Company June 2022 ACD response:** Test costs with 9.7% prevalence applied in the base case.

There remain some concerns around the company June 2022 submission and its alignment with Committee preferences. For instance, it appears that bone and CT scans for olaparib may only be equalised with those of cabazitaxel for the 1st three months, with olaparib having fewer bone and CT scans thereafter[1]. The wording of the treatment of PPS BSC costs is also ambiguous, it not being clear whether the company implementation applies the BSC PPS cost to all those ceasing active PPS treatment and on what basis as well as to those who do not receive an active PPS treatment.

IMPORTANT NICE TECHNICAL TEAM NOTE: The company requested to increase its PAS from [redacted] to [redacted], and all ICERs in this document are inclusive of results using the [redacted] PAS discount. However, this PAS increase has not been accepted, therefore the PAS remains

[1] Cells H33 and H34 of *Disease_Mgmt_Cost*

[redacted]. The ICERs in this report should be interpreted only as showing the relative impact of different assumptions. Please see the cPAS appendix for decision-making ICERs inclusive of the current PAS discount of [redacted].

Table 1: Company June 2022 base case BRCAm prior taxane

	Deterministic			Probabilistic		
	Caba.	Olap.	net	Caba.	Olap.	net
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER			[redacted]			[redacted]

Note that the company submission did not submit probabilistic modelling. The ERG generates these results from the company submitted model. The central probabilistic cost effectiveness estimate is around 8% worse than the deterministic estimate.

1.2 Company June 2022 base case: BRCAm prior taxane: sensitivity analyses

The company also submits sensitivity analyses that explore the OS functional forms and using the PFS curve for costing of olpaparib.

- OS exponential distribution ICER: [redacted]
- OS Rayleigh distribution ICER: [redacted]
- OS splines distribution ICER: [redacted]
- rPFS costing of olaparib use ICER: [redacted]

1.3 Company June 2022 base case: BRCAm no prior taxane

The company provides an analysis that equalises the proportion of patients receiving subsequent PPS active treatments between those receiving olaparib and docetaxel during PFS.

- The log-logistic is retained by the company for OS, in contrast to the ERG preference for the Rayleigh 1P distribution.
- The log-normal is retained by the company for PFS, in contrast to the ERG preference for the Rayleigh 1P distribution.
- The company uses the TTD curve to cost olaparib, selecting the Weibull distribution in contrast to the ERG preferred Rayleigh 1P distribution.

Unfortunately, the company does not provide the equivalent of Section 2.2 and Table 8 of its June 2022 response which outline how its prior taxane modelling assumptions are aligned with those of the Committee. The no prior taxane modelling assumptions may not be aligned with the preferences of Committee. For instance, it appears that even during the 1st 3 months of the model Olaparib is assumed to require fewer bone and CT scans than both BSC and docetaxel, with this disparity increasing after the 1st 3 months. LHRH costs appear to be treated differently than in the prior taxane model. There may be other discrepancies between the prior taxane modelling and the no prior taxane modelling. This is a major concern. The ERG thinks that the company should be asked to tabulate where the no prior taxane assumptions are aligned with those of the prior taxane modelling and where they differ.

The company submitted June 2022 model results in the following cost effectiveness estimates, when the revised olaparib PAS is applied.

Table 2: Company June 2022 base case BRCAm prior taxane: vs Docetaxel

	Deterministic			Probabilistic		
	Doc.	Olap.	net	Doc.	Olap.	net
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER			[redacted]			[redacted]

Table 3: Company June 2022 base case BRCAm prior taxane: vs BSC

	Deterministic			Probabilistic		
	BSC	Olap.	net	BSC	Olap.	net
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER			[redacted]			[redacted]

The probabilistic cost effectiveness estimates are around 11% higher for the comparison with docetaxel and 6% higher for the comparison with BSC.

2 ERG revised base case analyses

As per the ERG TE response the ERG largely retains the assumptions of Section 5.4 of the original ERG report. For its modelling the ERG amends the post FAC ERG amended model to be aligned with the company TE supplied DCO2 BRCAm data as summarised in Table 19 of the company TE response:

- Apply the new data cut baseline age and weight, olaparib parameterised curves, ITC HRs, olaparib AEs, and olaparib SREs probability, with it being possible to specify these for either the BRCAm prior taxane target group or the BRCAm all patient group.
- Apply the percentage receiving PPS treatment and the distribution of PPS treatments for olaparib.
- Apply the median RDIs for olaparib and cabazitaxel.

The ERG revised base case:

- Applies the BRCAm prior taxane curves and HRs when modelling the BRCAm prior taxane target group.
- Applies the ERG Rayleigh OS curve, while retaining the company Gompertz for PFS and TTD.
- Assumes the same PPS treatment distribution for both arms, applying the cabazitaxel PPS treatment distribution.
- Applies the olaparib PAS but does not apply the cabazitaxel PAS, or any of the PPS treatment PASs.

IMPORTANT NICE TECHNICAL TEAM NOTE: The company requested to increase its PAS from [redacted] to [redacted], and all ICERs in this document are inclusive of results using the [redacted] PAS discount. However, this PAS increase has not been accepted, therefore the PAS remains [redacted]. The ICERs in this report should be interpreted only as showing the relative impact of different assumptions. Please see the cPAS appendix for decision-making ICERs inclusive of the current PAS discount of [redacted].

ERG revisions to the model implementation mean that the probabilistic modelling can be run over more than 1,000 iterations. For the ERG revised base cases the probabilistic modelling is run over 5,000 iterations.

For the probabilistic modelling the sampling of the company olaparib TTD Gompertz results in errors. Due to time constraints the ERG has not managed to correct this error, so for the probabilistic modelling has simply turned off sampling of the company olaparib TTD Gompertz. This is unsatisfactory for two reasons:

- It means that the model uncertainty will be incorrectly characterised.
- It may result in peculiar juxtapositions of the PFS curve and the TTD curve.

2.1 ERG revised base case: OS HRs with recensoring

The ERG revised deterministic base case estimates the following undiscounted years survival.

Table 4: ERG base case BRCAm prior taxane: Survival

	Caba.	Olap	Net gain	As % total gain
PFS	[redacted]	[redacted]	[redacted]	[redacted]
PPS	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	

The BRCAm prior taxane cost effectiveness estimates are presented in Table 5.

Table 5: ERG base case BRCAm prior taxane

	Deterministic			Probabilistic		
	Caba.	Olap.	net	Caba.	Olap.	net
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER			[redacted]			[redacted]

The probabilistic central estimate of cost effectiveness is around 7% worse than the deterministic estimate of cost effectiveness.

The associated CEAC is shown in **Error! Reference source not found.**.

[redacted]

There remains some ambiguity as to whether the 2nd ACD confirms olaparib as meeting the end of life criteria. Consequently, the ERG presents the probabilities of olaparib being cost effective at the unadjusted NICE WTP thresholds of £20,000 per QALY and £30,000 per QALY, and the corresponding thresholds with the end of life 1.7 QALY multiplier applied of £35,000 per QALY and £50,000 per QALY.

Table 6: ERG base case BRCAm prior taxane: probabilities of cost effectiveness

	Standard WTP		End of life WTP	
	WTP	Prob c/e	WTP	Prob c/e
NICE Lower WTP	£20,000	[redacted]	£35,000	[redacted]
NICE upper WTP	£30,000	[redacted]	£50,000	[redacted]

2.2 ERG scenario analyses

The ERG provides the following scenario analyses:

- SA01: Applying the company OS curves for olaparib.
- SA02: Applying the BRCAm all patient HRs in the ITC.

- SA03: Assuming the time to convergence of PPS ongoing monthly costs between those who did and did not receive a PPS active treatment after cessation of all active treatments is 2, 4 and 6 months and never.
- SA04: Cost olaparib based upon the PFS curve.
- SA05: Infer a TTD curve for cabazitaxel on the basis of it lying above the cabazitaxel PFS curve by the same proportion as the olaparib TTD curve lies above the olaparib PFS curve.
- SA06: Assumes no vial sharing for cabazitaxel.
- SA07: 100% G-CSF use for 14 days for each cabazitaxel treatment cycle.
- SA08: Exclude the cost of genetic testing, and assuming a test cost of only 10% of the base case value.

Table 7: ERG scenario analyses: Deterministic modelling

	Δ QALYs	Δ Cost	ICER
ERG revised base case	[redacted]	[redacted]	[redacted]
SA01a: Exponential	[redacted]	[redacted]	[redacted]
SA01b: Gompertz	[redacted]	[redacted]	[redacted]
SA01c: Weibull	[redacted]	[redacted]	[redacted]
SA01d: Gen. Gamma	[redacted]	[redacted]	[redacted]
SA01e: Log-logistic	[redacted]	[redacted]	[redacted]
SA01f: Log-normal	[redacted]	[redacted]	[redacted]
SA02: BRCAm all patient HRs	[redacted]	[redacted]	[redacted]
SA03a: Converge 2 months	[redacted]	[redacted]	[redacted]
SA03b: Converge 4 months	[redacted]	[redacted]	[redacted]
SA03c: Converge 6 months	[redacted]	[redacted]	[redacted]
SA03d: Converge never	[redacted]	[redacted]	[redacted]
SA04: Olap. PFS costing	[redacted]	[redacted]	[redacted]
SA05: Caba. TTD inferred	[redacted]	[redacted]	[redacted]
SA06: Caba. No vial sharing	[redacted]	[redacted]	[redacted]
SA07: 100% 14 days G-CSF	[redacted]	[redacted]	[redacted]
SA08a: No genetic test cost	[redacted]	[redacted]	[redacted]
SA08b: 10% genetic test cost	[redacted]	[redacted]	[redacted]

2.3 ERG base case: BRCAm no prior taxane

Applying the Rayleigh 1P distributions for OS, PFS and TTD results in the following.

Table 8: ERG base case BRCAm prior taxane: vs Docetaxel

	Deterministic			Probabilistic		
	Doc.	Olap.	net	Doc.	Olap.	net
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER			[redacted]			[redacted]

Table 9: ERG base case BRCAm prior taxane: vs BSC

	Deterministic			Probabilistic		
	BSC	Olap.	net	BSC	Olap.	net
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER			[redacted]			[redacted]

Note that this modelling is based upon the company submitted June 2022 model and so is subject to the concerns of Section 1.3 above. The base case assumptions of this model may not be aligned with Committee preferences.