NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

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

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

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

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

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

Issue date: February 2021

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

After consultation:

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

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

The key dates for this appraisal are:

Closing date for comments: 26 March 2021

Second appraisal committee meeting: TBC

Details of membership of the appraisal committee are given in section 5

1 Recommendations

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

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

Why the committee made these recommendations

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

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

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

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

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

2 Information about olaparib

Marketing authorisation indication

2.1 Olaparib (Lynparza, AstraZeneca) is indicated 'as monotherapy for the treatment of adult patients with metastatic castration-resistant prostate cancer and BRCA1/2-mutations (germline and/or somatic) who have progressed following prior therapy that included a new hormonal agent'.

Dosage in the marketing authorisation

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

Price

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

3 Committee discussion

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

Treatment pathway

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

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

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

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

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

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

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

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

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

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

Clinical evidence

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Economic model

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

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

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

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

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

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

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

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

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

Treatment costs

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Utility values

The company's utility values based on PROfound are appropriate

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

End of life

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

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

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

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

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

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

Cost-effectiveness estimate

No analyses reflect the committee's preferred assumptions

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

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

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

Other considerations

Equalities

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

Innovation

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

4 Proposed date for review of guidance

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

Amanda Adler
Chair, appraisal committee
February 2021

5 Appraisal committee members and NICE project team

Appraisal committee members

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

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

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

NICE project team

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

Hannah Nicholas

Technical lead

Ewa Rupniewska

Technical adviser

Jeremy Powell

Project manager

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