NICE National Institute for Health and Care Excellence

NICE guidance

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

Technology appraisal guidance
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This guidance replaces TA831.

1 Recommendations

1.1 Olaparib is recommended, within its marketing authorisation, as an option for treating hormone-relapsed metastatic prostate cancer with BRCA1 or BRCA2 mutations that has progressed after a newer hormonal treatment (such as abiraterone or enzalutamide) in adults. Olaparib is only recommended if the company provides it according to the commercial arrangement.

Why the committee made these recommendations

This evaluation uses new cost-effectiveness estimates to update olaparib for previously treated BRCA mutation-positive hormone-relapsed metastatic prostate cancer (NICE technology appraisal guidance TA831). No new clinical evidence was reviewed.

Treatments for BRCA mutation-positive hormone-relapsed metastatic prostate cancer that has progressed after enzalutamide or abiraterone include taxanes (for example, docetaxel or cabazitaxel), radium-223 dichloride and best supportive care. The company provided evidence based on whether or not people had already had a taxane. This is because people have different treatments depending on whether they have had a taxane before.

Clinical trial evidence shows that people taking olaparib have more time before their cancer gets worse, and live longer overall, than people having retreatment with abiraterone or enzalutamide. However, this retreatment is not considered effective and is not standard care in the NHS.

For people who have had a taxane before, olaparib has not been directly compared with docetaxel, cabazitaxel or radium-223 dichloride. An indirect comparison suggests that olaparib increases how long people live compared with cabazitaxel.

For people who have not had a taxane before there is also no direct evidence comparing olaparib with docetaxel or best supportive care. But an exploratory indirect comparison suggests that olaparib may increase how long people live compared with both best supportive care and docetaxel.

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Olaparib likely meets NICE's criteria for a life-extending treatment at the end of life. When taking this into account, the most likely cost-effectiveness estimates are within what NICE considers an acceptable use of NHS resources. So olaparib is recommended.

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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 for olaparib.

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, March 2023). The company has a commercial arrangement. This makes olaparib available to the NHS with a discount. 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.

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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 non-metastatic prostate cancer are normally offered androgen deprivation therapy (ADT) or radical therapy such as surgery or radiotherapy. If the disease progresses with ADT, it is known as hormone-relapsed or castration-resistant prostate cancer. Treatment with ADT continues, either alone or with darolutamide or apalutamide. People with newly diagnosed hormone-sensitive metastatic prostate cancer are usually offered ADT alone, ADT with docetaxel with or without prednisolone (from now, referred to as docetaxel), ADT with enzalutamide (see NICE's technology appraisal guidance on enzalutamide for treating hormone-sensitive metastatic prostate cancer), or, if docetaxel is not suitable, ADT with apalutamide (see NICE's technology appraisal guidance on apalutamide for treating hormone-sensitive metastatic prostate cancer). For people with hormone-relapsed metastatic prostate cancer for which chemotherapy is not yet indicated, treatment options include abiraterone or enzalutamide if neither has been used before (see NICE's technology appraisal guidance on enzalutamide for treating metastatic hormone-relapsed prostate cancer before chemotherapy is indicated and abiraterone for treating metastatic hormone-relapsed prostate cancer before chemotherapy is indicated), or 'watchful waiting'. Darolutamide, enzalutamide, abiraterone and apalutamide are new hormonal agents. Olaparib is a poly-ADP-ribose polymerase (PARP) inhibitor, which works differently to hormonal agents. The clinical experts confirmed that people would have new hormonal agents only once. So, people who have

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had a new hormonal agent when their cancer was hormone sensitive or non-metastatic would not have it again when their cancer is hormone relapsed and metastatic. After this, treatment options include:

- docetaxel
- retreatment with docetaxel for people who had docetaxel when their disease was hormone sensitive
- cabazitaxel with prednisolone (from now, referred to as cabazitaxel) for people who have already had docetaxel
- radium-223 dichloride for people with symptomatic bone metastases and no metastases in the soft internal organs of the body (visceral metastases), and who have already had docetaxel or cannot have it.

The 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. They also explained that they would like more treatment options so they can delay chemotherapy (docetaxel and cabazitaxel) and its adverse effects. This is because the adverse effects, especially those of docetaxel, can be debilitating, even up to 1 year after people have stopped having it. The committee concluded that there is an unmet need for new treatments for hormone-relapsed metastatic prostate cancer.

The company's approach of considering people who have had or have not had a taxane separately is acceptable

3.2 The marketing authorisation for olaparib states that it is indicated 'as monotherapy for the treatment of adult patients with metastatic castration-resistant prostate cancer and BRCA1/2-mutations (germline and/or somatic) who have progressed following prior therapy that included a new hormonal agent'. The company limited the population in its initial submission to people who have already had a taxane (mainly docetaxel), from now referred to as the 'prior taxane' group. It chose cabazitaxel as the comparator (see section 3.3), which requires previous treatment with docetaxel. The company explained that it did this

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because its clinical advisers suggested that in the NHS around 75% of people have docetaxel while their disease is hormone sensitive. The ERG agreed that most people who have abiraterone or enzalutamide will have already had treatment with docetaxel, but that this proportion is likely to be less than 75%. The clinical experts explained that having previous treatment with docetaxel is not specified in olaparib's marketing authorisation and should not be a factor when deciding who would have olaparib in NHS practice. The Cancer Drugs Fund clinical lead was disappointed with the company's initial decision to limit the population. The clinical lead explained that many people who do not choose docetaxel early in the pathway might then be unable to have it after developing hormone-relapsed metastatic disease, for example if they become too ill. At the company's initial proposed position, olaparib would never be suitable for them. The clinical and patient experts explained that they are keen to have olaparib available as early in the treatment pathway as possible, but to have it at some point is most important. The committee appreciated that limiting olaparib to people who had had docetaxel would exclude people who cannot or should not have docetaxel but who could benefit from olaparib. It was aware that these people are likely to be older and more likely to have a poorer disease performance status, comorbidities, peripheral sensory neuropathy, poor bone marrow function, poor cognition or chemotherapy contraindications (see NICE's technology appraisal guidance on abiraterone for treating newly diagnosed high-risk hormone-sensitive metastatic prostate cancer). The committee also noted that NICE's recent recommendations on darolutamide, enzalutamide and apalutamide mean that more people would choose a new hormonal agent before docetaxel (see NICE's technology appraisal guidance on darolutamide with androgen deprivation therapy for treating hormone-relapsed non-metastatic prostate cancer, enzalutamide for treating hormone-sensitive metastatic prostate cancer, apalutamide with androgen deprivation therapy for treating high-risk hormone-relapsed non-metastatic prostate cancer and apalutamide with androgen deprivation therapy for treating hormone-sensitive metastatic prostate cancer). In response to the first consultation, the company submitted clinical-effectiveness data and exploratory cost-effectiveness analyses for the population who had not had a taxane, from now referred to as the 'no prior taxane' group (see section 3.7, section 3.12 and section 3.23). NICE's process requires a

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committee to initially appraise a drug across its marketing authorisation rather than by subgroups. However, the committee noted that there are no common comparator treatments for the whole licensed population as comparators are different for people who can and cannot have, or have already had, taxanes (see section 3.3 and section 3.4). Therefore, the committee concluded that the company's approach of considering these groups separately is acceptable.

Comparators

In the prior taxane group, cabazitaxel, radium-223 dichloride, and retreatment with docetaxel are all relevant comparators

3.3 NICE's scope for this appraisal lists docetaxel, cabazitaxel and radium-223 dichloride as comparators. But the company included only cabazitaxel as a comparator for people who have had treatment with a taxane before. It considered that there was not enough evidence for docetaxel and radium-223 dichloride. The ERG agreed that there is limited evidence for both docetaxel and radium-223 dichloride. The company stated that its clinical advice and data from a recent UK national audit suggested that radium-223 dichloride is often used later in the treatment pathway, once options such as cabazitaxel have been used. The committee recognised that this would mean radium-223 dichloride was a relevant comparator because it could be used at the same position as olaparib for some people. The company highlighted that NICE's guideline on the diagnosis and management of prostate cancer does not recommend repeat cycles of treatment with docetaxel if the disease recurs after the planned course of chemotherapy is completed. It also pointed out that cabazitaxel is more likely to be used instead of docetaxel retreatment because response rates to docetaxel may decline over time. The committee was aware that retreatment 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 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 dichloride if they have symptomatic bone metastases and no

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visceral metastases. The committee appreciated that, in the prior taxane group, docetaxel retreatment, cabazitaxel and radium-223 dichloride would all be alternatives to olaparib. It noted that patients and their treating clinician would decide which treatment is best. 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.

In the no prior taxane group, docetaxel and best supportive care are the most relevant comparators

3.4 For people who have not had treatment with a taxane, the company chose the following comparators depending on the reason for them not having a taxane:

- docetaxel and best supportive care (ADT and monitoring) for the group of people who had not had docetaxel but for whom docetaxel is appropriate
- best supportive care only for the group who had not had docetaxel and for whom docetaxel is unsuitable.

The committee agreed that these comparators are broadly appropriate but noted that radium-223 dichloride is also a relevant comparator for some people for whom docetaxel is unsuitable. For radium-223 dichloride, the company considered that there was not enough evidence on its use, and that it would be limited to a small minority of people. It also stated that radium-223 is only recommended after docetaxel, so it could not be a comparator in this group. For cabazitaxel, the company stated that it is not an appropriate comparator because docetaxel was more appropriate, and that cabazitaxel can only be used after docetaxel, in line with its licence. The company considered best supportive care would only be suitable when taxanes are not appropriate. The ERG did not comment about the appropriateness of comparators in the no prior taxane group. The committee concluded that the company had used the most appropriate comparators.

Clinical evidence

In the PROfound trial, the baseline characteristics of people are

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generalisable to NHS practice, but the comparator treatment is not

3.5 PROfound was a phase 3, randomised, open-label, multicentre trial of olaparib compared with investigator's choice of enzalutamide or abiraterone in 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 and other mutations. It stratified people according to whether they had had taxane treatment before. The primary endpoint was time to disease progression determined radiographically. Overall survival was among the secondary endpoints. The company presented clinical evidence for the population who had BRCA mutations in line with the marketing authorisation (the licensed population). It also presented it for the subgroup of this population who had had taxane treatment before (see section 3.2; from now, referred to as the 'BRCA-mutation, prior taxane subgroup'). The committee was satisfied that baseline characteristics from the BRCA-mutation prior taxane subgroup, including age, Eastern Cooperative Oncology Group performance status and prostate-specific antigen level, are generalisable to people in the NHS. However, it noted that some treatment regimens that people had had before entering the trial, such as having had both abiraterone and enzalutamide, did not reflect NHS practice. The clinical experts did not expect this to modify the treatment effect of olaparib in the trial. Clinical experts explained that retreating with abiraterone or enzalutamide has no clinical benefit and could effectively be considered a placebo. The company acknowledged that the comparator in its trial does not reflect current NHS practice. The committee concluded that baseline characteristics in PROfound were generalisable to NHS practice except for some people having had both enzalutamide and abiraterone before starting the trial. It further concluded that the comparator, that is, retreating with abiraterone or enzalutamide, is not offered in the NHS.

Olaparib is more effective than retreating with enzalutamide or abiraterone but this comparison does not reflect NHS practice

3.6 In the licensed population and the BRCA-mutation prior taxane subgroup

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of PROfound, median progression-free survival was higher with olaparib (9.0 months, 95% confidence interval [CI] 7.4 to 10.8) compared with abiraterone or enzalutamide retreatment (1.9 months, 95% CI 1.7 to 3.5). Median overall survival was also higher with olaparib (17.5 months, 95% CI 13.0 to 25.3) than abiraterone or enzalutamide retreatment (11.9 months, 95% CI 8.2 to 15.2). The committee recalled that retreating with abiraterone or enzalutamide is not expected to have a clinical benefit (see section 3.5). The committee concluded that olaparib was effective compared with enzalutamide or abiraterone in PROfound. However, it thought that the results should be interpreted with caution because the comparator arm in the trial does not reflect NHS practice. 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.

Previous treatment with a taxane does not appear to affect the effectiveness of olaparib in PROfound

3.7 In its response to consultation, the company submitted results from PROfound for a subgroup of people who had not had treatment with docetaxel (see section 3.4 and section 3.12). The results in the no prior taxane group suggested that both progression-free and overall survival were higher with olaparib than with abiraterone or enzalutamide retreatment. The committee noted that, because of the inclusion and exclusion criteria in PROfound, the trial likely excluded many people who cannot or should not have docetaxel in NHS practice. The committee recalled that stratification in the trial was done on the basis of either mutation type or prior taxane, so there was no prespecified subgroup for those with a BRCA mutation who had had a taxane before. The company did provide analyses for those with BRCA mutations in the prior or no prior taxane subgroups. The committee noted this evidence but considered that, as it was not prespecified in the clinical trial protocol, it was a post-hoc analysis, which may introduce uncertainty. 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 subgroup. It concluded that these results were highly uncertain. The committee noted that it did not see any formal testing of interaction when this subgroup was compared with the subgroup who had had docetaxel. But it

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acknowledged that the clinical efficacy of olaparib in PROfound did not seem to have been affected by previous treatment with a taxane.

The company's method for adjusting for treatment switching in PROfound is appropriate, including using recensoring

3.8 The company explained that, in PROfound, most 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 biased the treatment effect for overall survival. This was because people in the control arm who switched to olaparib may have benefited 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. These included 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 assumption of a common treatment effect in the overall trial population, but not in the BRCA-mutation prior taxane subgroup. 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. This is to avoid informative censoring related to the association between prognostic factors and treatment switching. Informative censoring can happen when adjusting survival times if some people who switch treatments do 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 with and without recensoring because both can bias results. The recensoring approach tends to overestimate the effect of treatment, and the approach without recensoring tends to underestimate it. The committee noted that, towards the end of the trial follow-up period, data from very few people contributed towards the estimates of overall survival. Therefore, in this

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case, recensoring did not lose a large amount of data, but avoided informative censoring. The committee concluded that the company's method for adjusting for treatment switching was appropriate, including using recensoring.

The indirect comparison of olaparib with cabazitaxel for the prior taxane group is uncertain because of differences between PROfound and CARD

3.9 The company did not find direct clinical trial evidence comparing olaparib and cabazitaxel so it did indirect treatment comparisons for progression-free survival and overall survival. It used evidence from the CARD trial, a phase 3, randomised, open-label, multicentre trial. The trial compared cabazitaxel with enzalutamide or abiraterone in hormone-relapsed metastatic prostate cancer previously treated with docetaxel and either enzalutamide or abiraterone. The primary endpoint was radiographic progression-free survival. Secondary endpoints included overall survival and skeletal-related events. Clinical experts explained that the comparator in CARD was similar to that in PROfound, that is, people who had already had abiraterone were 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 the company considers them confidential. The ERG highlighted several differences between the trials. It explained that all people in the PROfound BRCA-mutation prior taxane subgroup had BRCA mutations, but mutation status in CARD was unknown. Some people in PROfound had had cabazitaxel (the company considers the proportion to be confidential so it cannot be reported). The ERG explained that people in CARD had not had cabazitaxel before. Also, the central review of radiographic disease progression imaging was blinded in PROfound, but open-label in CARD. The clinical experts explained that BRCA-mutation status does not affect how well cabazitaxel works. They also noted that previous cabazitaxel is unlikely to affect how well olaparib works because its mode of action is different. The ERG explained that some studies suggested BRCA-mutation status could modify treatment effect, and some suggested it does not. In NICE's technology appraisal guidance on cabazitaxel for hormone-relapsed metastatic prostate cancer treated with docetaxel, the committee

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considered the TROPIC trial. This compared cabazitaxel plus prednisone with mitoxantrone plus prednisone in hormone-relapsed metastatic prostate cancer that had progressed after docetaxel treatment. In that appraisal, the committee considered that mitoxantrone plus prednisolone was unlikely to have clinical benefits. Therefore, in this appraisal, the committee noted that mitoxantrone was similar to the control arms of PROfound and CARD. In response to consultation, the company explored if it could include TROPIC in its indirect treatment comparison. It argued that the population in TROPIC was not comparable to the population in PROfound. This was because people enrolled in TROPIC had not had treatment with abiraterone or enzalutamide, as in PROfound or CARD. It was also because there were differences in the inclusion and exclusion criteria, and the comparator arms, between TROPIC and PROfound. However, it did present a scenario analysis including TROPIC, which had a small effect on the cost-effectiveness estimates. The ERG agreed that TROPIC should be excluded from the indirect comparison. The committee concluded that there were differences between PROfound and CARD, which led to uncertainty in the company's indirect treatment comparison, and that the population in TROPIC was unlikely to reduce this uncertainty.

It is inappropriate to adjust for treatment switching in CARD

3.10 The company did not adjust for treatment switching in CARD as it did in PROfound. It explained that this was because it did not have access to individual patient data from CARD. In its first meeting, the committee considered that overall survival in the cabazitaxel arm in CARD may have been underestimated. This was because 33% of people in the abiraterone or enzalutamide arm switched to cabazitaxel after disease progression. The 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. In response to consultation, the company explained that cabazitaxel is available in the NHS and that it was inappropriate to adjust for treatment switching because the trial did not deviate from NHS practice. Adjusting would also cause an imbalance in the abiraterone or enzalutamide arms between CARD and PROfound, which would undermine the anchored

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indirect treatment comparison. The committee recognised that the need to adjust would also depend on whether the proportion of people switching treatment in the trial reflected NHS practice. It concluded that it was inappropriate to adjust for treatment switching in CARD. However, it acknowledged that there was still some uncertainty in the size of the effect estimate comparing olaparib with cabazitaxel.

Differences between NHS post-progression treatments and those in PROfound and CARD affect generalisability to NHS practice

3.11 The committee discussed treatments offered in PROfound and CARD after disease progression. It noted that these treatments did not reflect NHS practice, and that this would affect both costs of treatment and its outcomes (see section 3.19). The company considers that the distribution of post-progression treatments in PROfound is confidential so cannot be reported here. The committee noted that life-extending treatments could have affected the hazard ratios for overall survival seen in PROfound and CARD. 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 noted that most people 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 3.5). Instead, people in the NHS would have access to life-extending treatments such as radium-223 dichloride. The committee noted that using radium-223 dichloride after disease progression on olaparib in PROfound was limited (the proportion is considered confidential and cannot be reported here). However, 15% of people in CARD had radium-223 dichloride after disease progression on cabazitaxel. In response to consultation, the company excluded abiraterone and enzalutamide from post-progression treatments to align with NHS practice. The company stated that it could not adjust for differences in overall survival because it did not have the data. Instead, it did scenario analyses to explore the effect that differences in post-progression treatments may have had by improving or worsening the hazard ratio for overall survival for olaparib compared with cabazitaxel by 5% and 10%. The committee noted the differences in post-progression

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treatments between the 2 trials and the NHS. It concluded that this further affected the validity of the company's indirect treatment comparison and its generalisability to NHS practice.

Analyses comparing olaparib with docetaxel and best supportive care for the no prior taxane group are uncertain

3.12 The company believed that a robust indirect treatment comparison for olaparib compared with docetaxel in the no prior taxane group was not feasible. This was because of a lack of evidence for docetaxel in the relevant population. So the company did an exploratory indirect treatment comparison comparing olaparib with docetaxel using results from TAX327, a phase 3 randomised trial for docetaxel plus prednisone. The trial compared docetaxel plus prednisone with mitoxantrone plus prednisone, which the company considered not to be an active comparator. This mitoxantrone plus prednisone control arm was used as the anchor for the indirect treatment comparison, with the assumption that it is equivalent to the PROfound control arm of abiraterone or enzalutamide. The primary endpoint in TAX327 was overall survival. The trial did not report progression-free survival, so the company assumed that the size of relative treatment effect of docetaxel on progression-free survival would be the same as that on overall survival. The committee noted that several assumptions related to the TAX327 trial increased the uncertainty in the analyses. This included the generalisability of the trial, which was done before abiraterone or enzalutamide were available. To estimate the effect of olaparib compared with best supportive care, the company assumed the abiraterone or enzalutamide retreatment arms from PROfound could be used as a proxy for best supportive care. The results of the analyses cannot be reported here because the company considers them confidential. However, they showed that olaparib may increase overall survival compared with docetaxel, and may increase overall and progression-free survival compared with best supportive care. The committee noted the wide confidence intervals in the results for both comparisons, likely driven by the small size of the no prior taxane group in PROfound. The committee noted limitations in the olaparib arm, which included the small sample size of the no prior taxane group, treatment switching in the abiraterone or enzalutamide arm, immature overall survival data and lack of direct data to inform

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progression-free survival estimates. The committee considered that the results suggested that olaparib was more effective than docetaxel or best supportive care for people who had not had a prior taxane. However, given the issues with the analyses, the committee concluded that these results were uncertain.

Economic model

Hazard ratios from the BRCA-mutation prior taxane subgroup of PROfound should be used to model outcomes for cabazitaxel

3.13 In its initial submission, the company used patient-level data from the PROfound BRCA-mutation prior taxane subgroup 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 having 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 of comparing a subgroup with the whole group. The committee would have preferred the company to use hazard ratios from the BRCA-mutation prior taxane subgroup to model comparative effectiveness with cabazitaxel. The committee considered the company's approach to be inconsistent. This was because the company had used data from the BRCA-mutation prior taxane subgroup from PROfound for other model inputs, for example, survival, adverse events and baseline characteristics for olaparib. The committee considered it appropriate to match data used in the model to the population under consideration when possible. In its response to consultation, the company agreed with the committee and used the hazard ratios from the BRCA-mutation prior taxane subgroup to model survival on cabazitaxel in the prior taxane group. The committee concluded that the revised company approach was appropriate.

The company and ERG's approaches to extrapolating overall

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survival for both treatments in the prior taxane group appear plausible

3.14 PROfound reported results based on a prespecified 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 and, for the prior taxane group there had been 41 events (57%) with olaparib and 27 events (77%) with abiraterone or enzalutamide retreatment. The company used parametric survival curves to fit the trial data and extrapolate it beyond the trial duration because the model used a lifetime horizon. The company initially chose a log-logistic curve to model overall survival but then changed its preference after the first committee meeting. The company had explored more flexible models as requested by the committee but because of poorer statistical fit, the company chose the exponential model, noting it had the best fit. The ERG explained that it had explored other models and had chosen the Rayleigh distribution for treatment with olaparib for its base case, based on the best statistical and visual fit. The committee noted that none of the parametric curves fitted the observed hazard rates for the olaparib arm from the trial well. It noted that the Rayleigh, Weibull and exponential hazard function curves appeared reasonable although possibly pessimistic. The company agreed that these curves were all reasonable and possibly pessimistic but considered the Rayleigh to be the 'worst case' in terms of its predication of overall survival. As a result, the company chose the Weibull distribution. The ERG noted that this was its second preferred option and that there was no statistical or visual difference between this and the Rayleigh model. The ERG noted a considerable decline in the number of patients alive after 24 months and this led to uncertainty in the extrapolation. The committee noted that the cost-effectiveness results were sensitive to the change in distribution in the scenario analyses done by the company and ERG. It agreed that there was little difference in visual and statistical fit between the 2 curves, so deciding which curve was best would involve determining which curve had the most plausible long-term extrapolations. The committee concluded that both extrapolations may be pessimistic, and were equally uncertain and equally plausible. So it took both into account in its decision making.

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Both the company and ERG's approach to extrapolating overall survival for both treatments in the no prior taxane group are plausible

3.15 The company also extrapolated long-term overall survival in the no prior taxane group. The company selected the log-logistic distribution to extrapolate both arms in the comparisons of olaparib with docetaxel and best supportive care (see section 3.4). The ERG preferred the Rayleigh distribution to extrapolate both arms in both comparisons. The log-logistic and Rayleigh distributions had very similar extrapolations for the docetaxel arm and the best supportive care arms in the 2 different comparisons. However, there were some differences between the distributions in the olaparib arms in both comparisons. The company stated that, to extrapolate overall survival for olaparib, the log-logistic distribution had the best visual fit to the Kaplan–Meier data, the best statistical match and had been validated by clinical input. The ERG considered that the log-logistic model may overestimate long-term survival in the olaparib group in both comparisons and that the Rayleigh distribution provided more realistic extrapolations. The company considered that both the log-logistic and Rayleigh olaparib extrapolations were consistent with the 24-month Kaplan–Meier data. But it stated that the Rayleigh was overly pessimistic when extrapolating overall survival in the olaparib arm in both comparisons. The committee noted that the difference between the 2 extrapolations started at around 30 months. It predicted that overall survival after this point was substantially higher when the log-logistic distribution was used to extrapolate olaparib, for both comparisons. The committee concluded that both log-logistic and Rayleigh distributions showed a good visual and statistical fit, and had plausible long-term survival predictions, so it would take both into account in its decision making.

Treatment costs

Data on time to stopping treatment should be used to model olaparib treatment duration and costs

3.16 In its initial submission, the company assumed that people have olaparib

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until their disease progresses. It used time until disease progression in PROfound to model olaparib treatment duration and costs, even though there was data from PROfound on time to stopping treatment. It did this to be consistent with the cabazitaxel trial, which provided data on progression-free survival but not time to stopping treatment. The company explained that estimates of median progression-free survival and median time to stopping treatment from PROfound were similar. The committee noted, however, that people may stop olaparib for reasons other than disease progression, for example, adverse effects or personal choice. The ERG preferred to use the time to stopping treatment data from PROfound. It explained that the curve for time to stopping treatment was above the curve for progression-free survival, so the company may have underestimated olaparib's costs. The ERG considered that using the curve for time to stopping treatment aligned with the relative dose-intensity calculation (see section 3.17). The ERG explained that cabazitaxel is administered in hospital every 3 weeks. Therefore, time to stopping treatment and progression-free survival are likely more aligned for cabazitaxel than for olaparib, which is taken as a daily tablet. Also, because cabazitaxel is less expensive than olaparib, the bias of using progression-free survival to estimate its costs would be lower than for olaparib. In its response to the first consultation, the company agreed with the committee's conclusion, notably, that time to stopping treatment better estimates treatment duration and costs of olaparib than progression-free survival.

Using relative dose intensity from PROfound to estimate the cost of olaparib is acceptable

3.17 To estimate the cost of olaparib in its original submission, 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 well for how much of a planned dose of a drug people had over time. So, it did not accurately estimate 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

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company's initial approach and the ERG's approach. It noted that generally the mean is the preferred metric to estimate costs, but agreed with the ERG's concerns. The committee would have preferred that the company had calculated the costs of olaparib for each person based on their individual dose and treatment duration, and used these estimates to inform the mean per-patient cost of olaparib. The ERG clarified that, unless the company provides it with the individual patient 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 the model results. In its response to consultation, the company argued that the costs of olaparib were appropriately reflected in the model because time to stopping treatment was based on individual patient data. It explained that it did not do an additional analysis based on individual dose because the model was not sensitive to relative dose intensity. It suggested that this was shown in its scenario analysis, in which assuming a full dose for the entire duration of treatment (that is, 100% relative dose intensity) had minimal effect on the cost-effectiveness estimates. The ERG questioned whether the cost of olaparib in the model should be based on the number of tablets consumed or the number of packs prescribed, because the NHS pays for whole packs, not individual tablets. It argued that, if the costs were based on the number of packs prescribed, a relative dose intensity of 100% might be the most reasonable estimate. The ERG highlighted that this concern would not apply to cabazitaxel because it is administered as an intravenous therapy in hospital. The Cancer Drugs Fund clinical lead explained that they expect minimal drug wastage with olaparib. This is because clinicians 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 exclude drug wastage in its model. It would have preferred the company to use individual patient data from PROfound to calculate the per-patient cost of olaparib, but acknowledged this was likely to have had a small effect on the cost-effectiveness results. It concluded that the company's approach is acceptable for decision making.

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

3.18 People having cabazitaxel may have prophylactic granulocyte colony-stimulating factor (G-CSF) to prevent neutropenia. The company and the ERG added the costs of G-CSF to the costs of having cabazitaxel. In its initial submission, the company assumed that all people having cabazitaxel had prophylactic G-CSF for 14 days. This was to align with CARD, and 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 its base case, the ERG assumed that a lower proportion of people have G-CSF, based on the results of the company's survey with clinical experts (the company considered the exact estimate confidential so it cannot be reported here). The ERG also assumed that treatment would typically last for 7 days, based on clinical opinion. The 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. In its response to consultation, the company agreed with the ERG's approach. The committee concluded that the ERG's estimate of the costs of prophylactic G-CSF in the cabazitaxel arm was appropriate. It also acknowledged that the company had followed this approach in its revised cost-effectiveness modelling.

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

3.19 Both the company and the ERG incorporated the costs of treatments after disease progression on olaparib and cabazitaxel. 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 more than 1 active treatment on average after disease progression. The clinical experts confirmed that people can have multiple treatments after disease progression in NHS practice. After technical engagement, both the company and the ERG 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

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confidential so they cannot be reported here. People who do not have active treatment would have best supportive care after progression. The company assumed that the treatments offered would differ depending on whether the disease progressed on olaparib or cabazitaxel, and that disease could be retreated 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 that there was no reliable data to inform this. It reminded the committee that PROfound and CARD had important differences (see section 3.9) and that using the trials' proportions of post-progression treatments does not reflect NHS practice. The committee again noted that retreatment with abiraterone or enzalutamide would not happen in NHS practice, which was confirmed by the clinical experts. They considered that the company's estimate for the number of people having radium-223 dichloride in the olaparib arm was too low. They also considered that the ERG's estimate that 55% of people in both arms would have radium-223 dichloride was too high. In its response to consultation, the company excluded abiraterone and enzalutamide from post-progression treatments. However, it continued to assume people would have different treatment after progression depending on whether they initially had olaparib or cabazitaxel. The company explained that this was because the proportions of post-progression treatments used in the model were based on the clinical trial data from PROfound and CARD. It claimed that the data reflects that people who take olaparib can then have chemotherapy as a subsequent therapy before radium-223 dichloride. It also claimed that the data reflects that people whose disease progresses on cabazitaxel may have exhausted their treatment options apart from radium-223 dichloride. So, a higher proportion of people having radium-223 dichloride than seen in the model is likely. The company highlighted that, after it excluded abiraterone and enzalutamide from its model, the proportion of other subsequent treatments in the model increased. The company provided 2 scenario analyses to explore the effect of the cost of post-progression treatment, in which it excluded:

- retreatment with cabazitaxel from post-progression treatment options

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- all costs related to post-progression treatments.

  Both had a minimal effect on the cost-effectiveness estimates. The committee agreed that both the company's and ERG's estimates of post-progression treatment costs did not reflect NHS practice. However, it acknowledged that adequate adjustment for these differences may not be possible, and that it was likely to have a minimal effect on the cost-effectiveness results. Therefore, it concluded that both approaches were not ideal, but were acceptable for decision making.

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

3.20 In its initial submission, 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 cabazitaxel
- did not have an active treatment after progression, that is, had best supportive care directly after olaparib or cabazitaxel.

  The company explained that this avoided double counting the costs of best supportive care. It also explained that the model structure did not allow estimation of 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. The clinical and patient experts explained that everyone would start having palliative care after active treatments had stopped, and that this would be the same for everyone. In its response to consultation, the company agreed with the ERG's approach, and followed it in its revised cost-effectiveness modelling. The committee accepted this approach to costing best supportive care.

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

3.21 Before starting treatment with olaparib, people must have a BRCA mutation confirmed using a validated test. Section 5 in the NICE guide to

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the methods of technology appraisal 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 initial base case. It explained that this was because the NHS Genomic Test Directory 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 (the 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 mutations routinely. One clinical expert noted that they do not routinely test for BRCA mutations unless there is a family history. Another clinical expert explained that they do genomic testing for all people with hormone-relapsed metastatic prostate cancer, and that many oncologists want routine testing in the NHS. The Cancer Drugs Fund clinical lead explained that the NHS 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. It based this on the prevalence of BRCA mutations in people who entered screening for PROfound (the company considers the value to be confidential and so it cannot be reported here). The clinical experts advised that the prevalence of BRCA mutations in people with hormone-relapsed metastatic prostate cancer in clinical practice is about 10%. 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.

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Utility values

The company's utility values based on PROfound are appropriate

3.22 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 with cabazitaxel and prednisone than with olaparib. Cabazitaxel treatment was associated with an additional decrement of -0.023 (Matza et al. 2013) because it is administered intravenously. Once people stopped having cabazitaxel, their utility reverted to the same as that of 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.

Exploratory analyses

Exploratory analyses for people who have not had a taxane are highly uncertain

3.23 The company did exploratory cost-effectiveness analyses for people who had not had a taxane. The committee recalled its remit to look at a technology across the indication in its marketing authorisation. However, it appreciated that no single comparator would be relevant for people who had and who had not had treatment with docetaxel. It also recalled its concerns that people in PROfound who had not had treatment with a taxane were unlikely to represent people who cannot or should not have docetaxel in clinical practice. To compare olaparib with best supportive care, the company used the abiraterone or enzalutamide arm from PROfound as a proxy. At the second committee meeting, the committee noted that the company's exploratory analyses for the no prior taxane group did not mirror the committee's preferred assumptions for the prior

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taxane group, for example:

- assuming that the same proportion of people whose disease progressed on olaparib or cabazitaxel would have an active treatment (see section 3.19)
- adjusting for differences in post-progression treatments between PROfound and NHS practice.

  In response to the second consultation, the company updated its no prior taxane model to be consistent with the prior taxane model. The committee recalled that, while there may be a benefit for olaparib in overall and progression-free survival, there was substantial uncertainty in the effect estimates from the indirect treatment comparison for the no prior taxane subgroup (see section 3.12). It concluded that the company's exploratory analyses for people who have not had a taxane were uncertain and it would take this into account in its decision making.

End of life

Olaparib likely meets NICE's criteria for a life-extending treatment at the end of life for people who have and have not had a taxane

3.24 The committee considered the criteria for 'life-extending treatments at the end of life' outlined in Section 6 of NICE's guide to the methods of technology appraisal, that is:

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

  Also, the appraisal committees will need to be satisfied that:

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- 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, for the prior taxane group, overall survival with cabazitaxel was less than an average of 24 months when using both the Weibull curve (company updated base case) and Rayleigh curve (ERG's base case) to extrapolate overall 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 noted that, for the no prior taxane group, overall survival with cabazitaxel was also less than an average of 24 months when using both the log-logistic curve (company base case) and Rayleigh curve (ERG's base case) to extrapolate overall survival. The committee was satisfied that olaparib met the end of life criteria for both the prior taxane and no prior taxane groups. The committee acknowledged that both the company and ERG's preferred parametric extrapolations of overall survival predicted at least a 3-month survival benefit with olaparib compared with cabazitaxel in both the prior taxane and no prior taxane groups. The committee also noted that new hormonal agents are now available much earlier in the treatment pathway (see section 3.1). This would mean that olaparib, which is indicated for treatment if disease has progressed after a new hormonal agent, could also be offered earlier. This could mean a longer life expectancy than modelled by the company. However, according to the data currently presented, it was likely that the end of life criteria were met. The committee concluded that olaparib likely meets NICE's end of life criteria for people who have and have not had a taxane.

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Cost-effectiveness estimates

Olaparib is a cost-effective treatment option for people who have had a taxane at the price chosen by the company

3.25 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 the company addressed a number of its preferences from its first and second committee meetings, including by:

- using the hazard ratios from the BRCA-mutation prior taxane subgroup of PROfound to model the efficacy of cabazitaxel in the prior taxane group (see section 3.13)
- using the time to stopping treatment data to model olaparib treatment duration and costs (see section 3.16)
- assuming only a proportion of people having cabazitaxel have prophylactic G-CSF, and have it for an average of 7 days (see section 3.18)
- assuming treatments available to people after progression on olaparib or cabazitaxel do not include retreatment with abiraterone or enzalutamide (see section 3.19)
- assuming the cost of best supportive care is the same regardless of whether people had active treatment after progression (see section 3.20)
- including the cost of testing for BRCA mutations (see section 3.21)
- addressing other minor differences between the company's and the ERG's models, such as assumptions related to bone and CT scans while on treatment, and costs of ADT.

  The committee also acknowledged that the company explored some of its preferences from its first meeting in scenario analyses, and that they had a minor impact on cost-effectiveness estimates. Namely, the company explored:

- whether TROPIC could be included in the indirect treatment comparison (see section 3.9)

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- uncertainty around the effect of post-progression treatments on post-progression survival (see section 3.19)
- more flexible approaches for extrapolating survival (see section 3.14)
- uncertainty around dosing of olaparib (see section 3.17)
- uncertainty around the cost of post-progression treatments in the NHS (see section 3.19).

NICE's guide to the methods of technology appraisal notes that above a most plausible incremental cost-effectiveness ratio (ICER) of £20,000 per quality-adjusted life year (QALY) gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER and whether the technology meets the criteria for consideration as a 'life-extending treatment at the end of life'. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. The committee noted that the end of life criteria were met for olaparib, which means that a maximum acceptable ICER of £50,000 per quality-adjusted life year (QALY) gained applies. However, given that there was significant uncertainty around the network meta-analyses informing the clinical-effectiveness estimates for this appraisal, the committee considered the maximum acceptable ICER would be below this, and it agreed that the probabilistic ICER would better capture the uncertainty associated with the analyses. Applying confidential discounts for cabazitaxel, radium-223 dichloride, filgrastim and leuprorelin (which are subsequent treatments), and considering its preferences, the committee noted the cost-effectiveness estimates using its preferred assumptions for olaparib compared with cabazitaxel were within the range that NICE normally considers an acceptable use of NHS resources for people who have had treatment with a taxane. This was the case when considering both Weibull and Rayleigh curves for extrapolating overall survival, and the higher threshold for end of life criteria. So, the committee could recommend olaparib for use in the NHS for treating hormone-relapsed metastatic prostate cancer with BRCA1 or BRCA2 mutations that has progressed after abiraterone or enzalutamide in adults who have had treatment with a taxane.

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The cost-effectiveness estimates for people who have not had a taxane are uncertain but suggest olaparib is cost effective

3.26 The committee recalled high uncertainty in the results from the company's cost-effectiveness modelling for the group of people who have not had treatment with a taxane (see section 3.23). It noted that it had seen no modelling specifically for the group of people who cannot or should not have a taxane in NHS practice. As with the 'prior taxane' group, because of the uncertainties with the evidence, the committee agreed that the maximum acceptable ICER should be below the end of life threshold. The committee agreed that the probabilistic incremental cost-effectiveness ratio (ICER) would better capture the uncertainty associated with the analyses. Because of confidential discounts for cabazitaxel, radium-223 dichloride, filgrastim and leuprorelin, the cost-effectiveness results cannot be reported here. Most of the probabilistic ICERs were within the range NICE normally considers an acceptable use of NHS resources when considering the higher threshold for meeting end of life criteria. So the committee could recommend olaparib for use in the NHS for people who have not had a taxane, whether they cannot, should not, or choose not to have it.

Other considerations

There are some equalities considerations

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

Olaparib is not innovative because it does not offer benefits not

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already included in the modelling

3.28 The company considered olaparib to be inherently innovative because it was the first drug for metastatic hormone-relapsed prostate cancer with a specific biomarker. It also stated that the need to test for the BRCA mutation before using olaparib may encourage earlier diagnosis and lead to cost savings in the NHS. The company also stated that there would be wider benefits of earlier identification of BRCA mutations particularly if the mutation is heritable. However, the committee heard that, in the NHS the BRCA mutation testing that would be used would consist of testing the tumour. So, many of the mutations detected would be somatic mutations (mutations in the tumour cells) and not heritable germline mutations (mutations in the normal cells of the body). 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 corticosteroids given with cabazitaxel have associated adverse effects and that this could possibly be delayed. However, the committee noted that the company had modelled a relative increase in utility for treatment with olaparib compared with cabazitaxel, so it considered that these benefits had been adequately captured in the economic modelling. 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 the modelling had captured all the relevant benefits of olaparib.

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4 Implementation

4.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

4.2 Chapter 2 of Appraisal and funding of cancer drugs from July 2016 (including the new Cancer Drugs Fund) – A new deal for patients, taxpayers and industry states that for those drugs with a draft recommendation for routine commissioning, interim funding will be available (from the overall Cancer Drugs Fund budget) from the point of marketing authorisation, or from release of positive draft guidance, whichever is later. Interim funding will end 90 days after positive final guidance is published (or 30 days in the case of drugs with an Early Access to Medicines Scheme designation or fast track appraisal), at which point funding will switch to routine commissioning budgets. The NHS England and NHS Improvement Cancer Drugs Fund list provides up-to-date information on all cancer treatments recommended by NICE since 2016. This includes whether they have received a marketing authorisation and been launched in the UK.

4.3 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document.

4.4 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has hormone-relapsed metastatic prostate cancer with BRCA1 or BRCA2 mutations that has progressed after a newer hormonal treatment (such as abiraterone or enzalutamide) and the doctor responsible for their care thinks that olaparib is the right

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treatment, it should be available for use, in line with NICE's recommendations.

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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.

Heather Stegenga, Samuel Slayen, Rebecca Thomas and Hannah Nicholas
Technical leads

Carl Prescott and Ewa Rupniewska
Technical advisers

Shonagh D'Sylva and Jeremy Powell
Project managers

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