Single Technology Appraisal

Olaparib for adjuvant treatment of high-risk HER2-negative, BRCA-positive early breast cancer after chemotherapy [ID3893]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Olaparib for adjuvant treatment of high-risk HER2-negative, BRCA-positive early breast cancer after chemotherapy [ID3893]

Contents:

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Olaparib for adjuvant treatment of BRCA mutation-positive HER2-negative high-risk early breast cancer after chemotherapy

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

Definitions:

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

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

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

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

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

Comments received from consultees

Consultee	Comment [sic]	Response
AstraZeneca (manufacturer)	AstraZeneca welcomes the opportunity to comment on the preliminary recommendation made by the Appraisal Committee detailed in the Appraisal Consultation Document (ACD). Whilst we are disappointed with the Appraisal Committee's initial decision to not recommend olaparib for the adjuvant treatment of patients with human epidermal growth factor receptor 2 (HER2)-negative (HER2-), high-risk, early (Stage I–IIIA) breast cancer (eBC) which is associated with a germline mutation in the breast cancer susceptibility gene (g*BRCA*m), we were pleased to see that the External Assessment Group (EAG) and Appraisal Committee recognise the unmet need, as well as the benefit that olaparib offers, in this indication. We are committed to working with NICE to address the Appraisal Committee's remaining concerns outlined in the ACD. As outlined in the ACD, the Committee's concerns primarily relate to the utility values used in the cost-effectiveness model. Whilst AstraZeneca acknowledge these concerns, we firmly believe that the **OlympiA trial provides the set of utility values that is most relevant to the current decision problem and most appropriately reflects the utility experienced by patients in the OlympiA indication**, specifically those who are and remain progression-free. This position was also supported by clinical experts during the Appraisal Committee meeting, who emphasised that the OlympiA quality of life study was the most extensive and robust dataset for this specific group of patients, and that the Verrill et al. (2020) data were too pessimistic. We have briefly summarised our position on this topic, as previously detailed in our Technical Engagement Response: • **OlympiA health-related quality of life (HRQoL) data are relevant and appropriate** to this decision problem, and any **potential bias due to missing data is likely to be negligible** o The HRQoL response rate in OlympiA was in line with that expected in clinical trials in this setting, with response rates of [redacted] at baseline, dropping to only [redacted] at 24 months.[1] A certain level of missing data in HRQoL questionnaires is present in all clinical trials and does not directly infer that the data itself is biased.	Thank you for your comments. The committee noted the response rates to the HRQoL questionnaires in the OlympiA trial and agreed that these did not represent a major risk of bias. In the absence of other options (and better-quality evidence), the committee considered that the age-adjusted Verrill utility values presented by the EAG were the most suitable for decision making.

	○ The EORTC QLQ-C30 scores in OlympiA remain [redacted]; if the majority of missing observations were not random and attrition bias was present, the average utility score would be expected to increase over time as the remaining sample would consist of healthier patients. Therefore, even if some level of attrition bias occurred as a result of more severe patients not completing the questionnaires, evidence suggests that the magnitude of this potential bias on the HRQoL estimates is negligible. ○ In response to the EAG's critique of potential bias in the mapping algorithms, we demonstrated consistency between the values generated from applying different mapping algorithms, and showed that the choice of algorithm is not a key driver of the mapped utility estimates from OlympiA. Notably the mapped utility scores for the progression-free health state all fell significantly and meaningfully above (+~0.07) the utility scores from Verrill et al. (2020), the EAG's and Appraisal Committee's preferred source of utility values. • Verrill et al. (2020) is subject to **significant limitations**, and the differing age, selection bias from recruitment and the lack of g*BRCA*m and triple negative breast cancer (TNBC) patients in the study are likely to impart **bias in the utility results and limit its generalisability to OlympiA patients** ○ The population enrolled in Verrill et al. (2020) is not representative of a younger g*BRCA*m population, with the mean age in Group 2 (57.7 years) substantially higher than that reported in OlympiA (43.3 years);[1, 2] feedback from clinical experts indicates that the demographics of the patient population in OlympiA better align with the patient group anticipated to receive olaparib in clinical practice. ○ Almost half of the patients in Group 2 (48.1%) were unemployed and their questionnaires collected on average ~4 years after initial diagnosis, indicating a potential selection bias; at this point, patients with a 'normal' HRQoL are likely to have returned to work if they remain progression-free, have an improved quality of life, and are therefore unlikely to have completed the questionnaire in the study. The measured health utility of 0.732 from Verrill et al. (2020) for Group 2 is therefore likely to be negatively biased, and thus not applicable and relevant to the general demographics of the OlympiA patient population. ○ Although the EAG provided a sensitivity analysis to adjust for the older age of the Verrill et al. (2020) population, this did not adjust for other factors such as employment status as outlined above. Given that adjusting for age alone resulted in a significant ~0.04 change in the disease-free utility value, this emphasises the uncertainty which results from using a study with limited generalisability to the patient population who would receive olaparib in this setting. • Assigning a utility value of 0.732 (or 0.770 if considering the EAG age-adjusted sensitivity analysis) to a **young patient group who have early-stage, treatable breast cancer and are in remission lacks face validity**	

	○ There is no clear rationale as to why the utility value assigned to patients in the progression-free health state, who are in (potentially long-term) remission and not expected to experience any significant continuing breast cancer-related symptoms or adverse events from treatment, should be significantly lower than the values of the age-matched UK general population (0.877). This is especially true the longer that patients remain disease-free, as the anxiety relating to their condition and fear of potential recurrence fades with time. ○ Comparison of the different mapped OlympiA health state utilities and those from Verrill et al. (2020) with utility values in previous NICE appraisals in the eBC and metastatic breast cancer (mBC) settings and relevant empirical literature, demonstrated that there is no precedent of either accepting or concluding a <0.8 health state utility value for eBC patients who are in (long-term) remission. ○ Considering that patients with newly diagnosed mBC (which is generally considered to be incurable disease, with 5-year survival rates of only ~25%)[3] have been shown to have a utility value of ~0.73, it is highly unrealistic to assume that a similar utility value would also apply to patients with early-stage disease, particularly in individuals who remain progression-free for a long period of time and have significant potential for cure. ○ Interviews with UK clinical oncologists, who unanimously commented that the HRQoL of eBC patients will become similar to the age-matched general population over time, indicated that it is reasonable to assume that the 'true' health state utility value for (long-term) disease-free patients with g*BRCA*m, high-risk eBC ranges between 0.8–0.877. Consequently, we firmly believe that the **utility values applied in the company's base-case analysis represent a set of estimates that better reflect the HRQoL of patients for the specific indication addressed in this appraisal**; this was a position supported by clinical experts at the Appraisal Committee meeting. AstraZeneca believe that the Appraisal Committee's preferred values are too conservative, and are not reflective of the patients, or their experiences, under consideration in this appraisal. It should be noted that olaparib is the first and only approved medicine in Great Britain that targets germline *BRCA* mutations in patients with eBC (Stage I–IIIA) previously treated with neoadjuvant or adjuvant chemotherapy, and AstraZeneca remains committed to ensuring patients are able to access innovative, life-changing treatments, such as olaparib, in the NHS. However, there exists limitations and inflexibilities within the medicines access system in England that result in barriers to securing patient access to therapies that treat multiple types of cancer at potentially different stages of disease. We are committed to continuing discussions with NICE and NHS England, as well as clinical and patient group stakeholders, to explore routes to deliver patient access to olaparib in the UK, in all of its indications, including eBC. We will also continue collaborating more broadly on how medicines, such as olaparib,	

	can be more effectively and flexibly assessed in order to prevent unnecessary delays to patient access. **References** 1. AstraZeneca Data on File. OlympiA Clinical Study Report. 2021. 2. Verrill M, Wardley AM, Retzler J, et al. Health-related quality of life and work productivity in UK patients with HER2-positive breast cancer: a cross-sectional study evaluating the relationships between disease and treatment stage. Health Qual Life Outcomes 2020;18:353. 3. Cancer Research UK. Survival. Available at: https://www.cancerresearchuk.org/about-cancer/breast-cancer/survival. (last accessed: November 2022)	
Breast Cancer Now	Breast Cancer Now welcomes the opportunity to respond to this Appraisal Consultation Document (ACD). We are incredibly disappointed that NICE has been provisionally unable to recommend olaparib for either routine use on the NHS, or for use on the Cancer Drugs Fund. Olaparib is a treatment that could save lives and we are urging AstraZeneca, NICE and NHS England to explore every possible solution to ensure this treatment can be recommended for use on the NHS, including AstraZeneca doing all it can to price the drug at a level that ultimately will ensure its availability. This is critical given it is noted in the ACD that in the company's analysis, olaparib was not cost-effective. The strength of feeling within the breast cancer community is clear, as of 1 December 2022 47,149 people have signed a petition calling for an urgent solution. Given the significance of this treatment for this group of patients, we urge NICE to invite patient and clinical experts back to the second committee meeting.	Thank you for your comments. Following an updated cost effectiveness analysis from the company, which adopted the committee's preferred assumptions and included a revised commercial arrangement, the committee is now able to recommend olaparib as a cost-effective use of NHS resources.
Breast Cancer Now	Are the provisional recommendations sound and a suitable basis for guidance to the NHS? The provisional recommendation to not recommend this treatment to eligible patients is not a sound or suitable basis for guidance for the NHS. The committee concluded that olaparib would be a welcome adjuvant treatment option to improve outcomes in this group of patients, as evidence has shown it can improve invasive disease-free survival, distant disease-free survival and overall survival compared to placebo. Olaparib represents a major advancement in the treatment options available and it could benefit hundreds of patients every year in England.	Thank you for your comment. Following an updated cost effectiveness analysis from the company, which adopted the committee's preferred assumptions and included a revised commercial arrangement,

	The potential long-term implications for this high-risk group need to be considered if this draft recommendation is not reconsidered, especially in light of limited treatment options and this being a high-risk population where prognosis remains poor. As discussed in our patient organisation submission and the committee meeting, olaparib is a treatment that could save lives and there is currently a clear unmet need in this group of patients. In the latest data available from OlympiA trial it shows that: - The percentage of patients alive at 4 years from randomization was 89.8% in the olaparib group and 86.4% in the placebo group, an absolute improvement in overall survival of 3.4%. - Invasive disease free survival at 4 years was 82.7% in the olaparib group and 75.4% in the placebo group – an absolute improvement of 7.3%. Distant disease free survival was 86.5% in the olaparib group and 79.1% in the placebo group – an absolute improvement of 7.4%. It is crucial that patients have access to the best possible treatment options to reduce the risk of recurrence or their breast cancer spreading so that they can continue living their lives to the fullest. If a patient progresses to incurable secondary (metastatic), it is a devastating diagnosis for both the patient and their loved ones. We know that the fear of recurrence and 'living under its shadow' can have a significant impact on the quality of lives of people after they finish their treatment for primary breast cancer. To have a new treatment option with olaparib, which is known to be generally well-tolerated, and could significantly reduce the risk of recurrence, including the risk of secondary breast cancer and the associated need for on-going and complex treatments could have a significantly positive impact on people's wellbeing and day-to-day lives. Someone with experience of olaparib told us: "I had the chance to watch my daughter grow up, and enjoyed every moment with her and my family. Without olaparib I believe she would have been left without a mother, and an incredible father left as a single parent. My husband and I are both full time back at work, contributing to society. Without olaparib, this wouldn't have been possible."	the committee is now able to recommend olaparib as a cost-effective use of NHS resources for routine commissioning.
Breast Cancer Now	<u>Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?</u> *Efficacy in subgroups* It is noted in the ACD that the additional data from the trial would provide further insight into the efficacy of olaparib in the subgroup with hormone receptor-positive HER2 negative breast cancer. Whilst clinical experts highlighted that they do not expect this subgroup to behave any differently, one option that should be considered is this subset being approved for use via the Cancer Drugs Fund whilst further	Thank you for your comments. Following an updated cost effectiveness analysis from the company, which adopted the committee's preferred assumptions outlined in the ACD and included a revised

	data is collected and the triple negative group being approved for routine use. The priority is ensuring that it's available for all eligible patients. *Discount rate* We would encourage the committee to explore further the cost-effectiveness results using both discount rates as part of the decision-making process. This transformative treatment can significantly reduce the risk of the cancer returning or spreading to become incurable secondary breast cancer. The latest data from the trial (published online in October 2022) has shown that all previous benefits have improved and that overall survival is statistically significant. We understand that NICE guidance outlines that the 1.5% rate may be considered when a treatment can result in substantial quality of life gains or life expectancy gains and olaparib is a treatment that could result in that benefit for patients. Without olaparib people could experience a recurrence or their disease could spread and devastatingly become incurable secondary breast cancer. The addition of olaparib to eligible patients for whom many will be in their 30s and 40s has the potential to restore them to full or near-full health and ultimately have benefits that are sustained over a very long period. We regularly hear from primary breast cancer patients who live day-to-day with the fear of their breast cancer returning or spreading to become incurable secondary breast cancer but patients who have received olaparib tell us it can lower the mental burden "It definitely has a big positive mental impact – I feel better knowing I'm having a treatment which shows positive survival results. It makes me feel more protected and makes a big difference to my life. An additional year of being on a treatment is worth it because looking at the statistics about the effectiveness of the treatment and knowing the benefits is so crucial for patients from a mental wellbeing perspective". Whilst we understand that the committee would need certainty in the data to enable a 1.5% discount rate and it has already highlighted immaturity of data regarding the hormone receptor subgroup, it is unclear from the ACD the specific concerns that remain regarding the triple negative population and why the 1.5% discount is not applicable to that specific group in light of the available evidence. We would welcome clarity on what further evidence would be required in this instance to meet the 1.5% discount rate. *Health-related quality of life* This treatment can help more people remain cancer free, survive breast cancer and ultimately enable them to live well. We believe this area should be revisited by the committee to see what flexibility there is regarding the use of both EAG and company estimates. We note the reference to the risk of bias because of low completion rates of the EORTC QLQ-C30 questionnaire. As per our technical engagement response, we feel the rates of completion are comparable to other studies and there will never be a complete response rate as it is dependent upon patients completing this.	commercial arrangement, the committee is now able to recommend olaparib as a cost-effective use of NHS resources for routine commissioning for both subgroups.

Breast Cancer Now	<u>Please tell us if the preliminary recommendations could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology</u> Triple negative breast cancer is more common in black women and women under 40. Therefore, a final negative recommendation would disproportionately impact certain groups.	Thank you for your comments. Please see the final draft guidance (FDG) - olaparib is now recommended following changes made by the company to its analysis and commercial arrangement.
Breast Cancer Now	<u>Has all of the relevant evidence been taken into account?</u> The breast cancer community is devastated about the prospect of this treatment not reaching the patients who need it. Women who have a) received olaparib either through the drug company early access scheme or private healthcare or b) who participated in the OlympiA trial have shared their views on the treatment and why they believe it's important that eligible women can access this treatment on the NHS. People explain the impact of a diagnosis of high-risk HER2-negative primary breast cancer with an altered BRCA gene: • "When you have triple negative breast cancer and a BRCA gene mutation, you know after surgery and chemotherapy there is nothing else. You know your risk of a recurrence is high and it's difficult to mentally process this information. I feel extremely privileged to have been able to take Olaparib. It makes you feel like you have a little army inside you fighting to keep you alive. Taking Olaparib has reduced my risk and has therefore, helped to reduce my anxiety about future breast cancer recurrences." • "Triple negative breast cancer is a very scary cancer because there was nothing on the market to stop it coming back (or lessen chances), unlike other breast cancers. It felt like a death sentence. I was pregnant at the time of by diagnosis and the baby had to be delivered at 32 weeks so chemotherapy could be started. My tumour had grown to 12cms so I had to deal with that too. My baby was in special care, it was such a stressful time for everyone but my family were amazing".	Thank you for your comments. Please see the FDG - olaparib is now recommended following changes made by the company to its analysis and commercial arrangement.

	• "I was 38 years old when diagnosed, wanting children and I thought I'd just been told I was going to die. I had stage 2, grade 2 breast cancer but was told it was treatable. While the blood drained out of my husband's face and he came numb, I thought – 'right well that's not the worst is it? Let's get on with the treatment then'. Tests confirmed that I had triple negative cancer and then genetic testing confirmed I carried the BRCA1 gene mutation. My family had to get tested too. We had to tell our extended family. There is a potential time bomb for some very young members of my family. I don't envy the day their parents have to sit them down to have that conversations. There is a sense of helplessness that comes from being a partner or family member of someone who has cancer. They take on a financial burden, do the housework, the cooking, the living when you are too chemo-sick and unable. What little energy they have is pushed into staying positive and supportive, all with the cold hard knowledge that they can't fix it - they can't make the person they love better. • "There is nothing worse than telling your husband, children and other family members that you have breast cancer. And then of course I found out I had the BRCA-1 gene mutation, and I felt even more guilty. Now I'm living with the fear that maybe one or both of my son's has it". • "I was diagnosed with triple negative breast cancer, aged 44, the same age as my grandmother had died from breast cancer. My son was age 15 exact same age my Dad was when his Mum was diagnosed. I didn't want history to repeat and I had heard there are a lot of new treatments for breast cancer now. However, we were shocked to find out after speaking to the oncologists that Triple Negative is not the same as other breast cancers and there are no other cures apart from Chemotherapy. Heart breaking to know I had already had a full hysterectomy and if I had found out about my BRCA2 before the cancer I could have also had a preventative double mastectomy too". • "I was diagnosed with triple negative breast cancer at 35. It was in my left breast and almost all of my lymph nodes in my armpit. I had a 5 week old baby and thought we were just starting our family. I naively asked if I was able to have fertility preserving chemotherapy. My oncologist was brilliant and clear - I was told that I would need life preserving chemo and it would be brutal. I should focus on surviving for my tiny daughter". • "It's daunting to know that your breast cancer is less common and more aggressive than other types of breast cancer, with a higher risk of returning in the years immediately following treatment – but at the same time there are fewer treatment options available to reduce that risk."	

	People who participated in the OlympiA trial explain why they got involved (please note this was a double-blinded trial): • "I found the trial, as I was researching my cancer - knowledge is power. I told my onco I wanted to get on the trial and he hadn't heard of it but he was able to find it with the info I gave him. The trial was brilliant, they really looked after me and still do as it's a 10-year trial. I am on year 8. I joined the trial because I wanted to increase my chances of survival, I have four kids and did not want them growing up without a Mother. It was a double blind trial, but looking at my side effects, I know I had olaparib. When a drug has been found to be successful, to save lives, to help families, why wouldn't it be put on the market? There is a drug that is the difference between someone dying or surviving." • "Triple negative breast cancer has a comparatively poor outcome to oestrogen or progesterone positive cancers, so participating on this trial, felt like I was being offered an extra safety net in terms of medical support, regardless if I was given the parp inhibitor or placebo. The ever prescient fact that I have two young family members who may also carry the BRCA1 gene mutation and have around an 80% chance of developing cancer. If there was something I could do to help develop smarter treatments and prevent them from having to endure the horror of standard cancer treatment, well, there was no need to ask twice. It became fairly apparent that I was not on the placebo as I did experience some wooziness with the parp inhibitor. So many of us have wanted to be able to carry on with life as normally as possible, go to work/college, look after family, enjoy life, but for many on chemo this is not possible. It's disruptive, can make you feel like crap, and accumulative poisoning slows you down. Mental health and finances suffer. Here is a drug that can be taken in tablet form, doesn't require as much hospital attendance, allowing some normalcy in life, and freeing up beds and chemo nurses to treat others who do need to go in for regular treatment. The current treatments do not cure at the same rate as olaparib. Reoccurrences are comparatively high. Here is a drug that has been proven to reduce reoccurrence and therefore cost". People with experience of olaparib in this indication (either through the drug company early access scheme or private healthcare) explain: • "I felt it important that I received this treatment to give me every possible chance of not having a recurrence or spread of my breast cancer. It also gives some peace of mind knowing all possible is being done, which is priceless at a stressful enough time. If you have gone through cancer you will know how important the emotional and mental side is, and how crucial a role that plays in recovery.	

	"Olaparib is a clinically proven treatment which will ultimately reduce costs too - by reducing the numbers of those with the BRCA gene who have a recurrence or secondary cancer, and the knock on costs that has to the health service. And making Olaparib available more widely helps in pushing forward the development of personalised treatments to get the best outcomes for patients, and will in turn lead to further developments to combat cancer. The tablets and monthly blood tests are surely more cost-effective in the long run than more intensive treatments because of recurrence and spread? Not to mention the physical and emotional impacts on those who have the cancer gene". • "Olaparib for me is to prevent a dangerous aggressive Breast Cancer recur in my body. I am petrified of the cancer returning and being a secondary as this is not curable. I have a BRCA2 gene fault and the TNBC has already been in my body, this PARP inhibitor works by trying to fix the Gene Fault that causes Breast and Ovarian Cancer. I have had a full hysterectomy and a Double mastectomy. I am grateful there is also a medication that can also help to avoid a recurrence. The side effects are not pleasant however im sure they are far better than the effects the secondary breast cancer will be and it helps me to spend more time with my Children aged 12 and 16. As a family we were delighted to be offered this chance to help us avoid the aggressive cancer coming back. When treatments are found to help and work these should be made available for patients on the NHS for everyone with the BRCA1 and BRCA2 gene faults along with the preventative surgeries. There is no treatments for TNBC after chemo and for other breast cancers that are hormone related there are options to help. This needs to be available on the NHS like the hormone treatments are. I know research is being done constantly but when something is found that help it would be awful for secondaries to occur without trying to avoid them. Olaparib helps to avoid the recurrence. I have the BRCA2 gene fault which means my children have a 50/50 chance to also have this, I do hope when they are old enough the treatment is available for them should they also need it. I don't think it should be luck to receive treatment, everyone should be able to receive it when needed". • "As a mother, a wife, a daughter and a sister, Olaparib has hopefully bought me more precious time with my family - that is beyond priceless. I can't tell you what it feels like to wonder whether I must make this Christmas the best Christmas because I don't know if I'll be here for many more in the future. BRCA-1 triple negative breast cancer patients are living with the very real risks of our breast cancer coming back, Olaparib can reduce the risk and can help us sleep at night.	

	My oncologist has told me I should naturally live until I'm at least 80 years old and he wants me to survive my breast cancer diagnosis and live until I am at least 80 years old. That's why he wanted me to take Olaparib. It's about being here for more Christmases, to see your children graduate from university and start families of their own. It's about removing the worry of dying prematurely and it's about hope. I was quite tired when I started Olaparib after receiving 6 rounds of chemotherapy and a double DIEP mastectomy and I wasn't feeling my best. Having said that I would never have delayed the start of Olaparib - I couldn't wait to start the treatment. The side effects of Olaparib were quite tough although not as tough as chemotherapy treatment. You can experience fatigue and nausea alongside some other side effects, but I had a fantastic team who helped me through the treatment. . I had to take some time off work due to some of the side effects, but I would do it all again because for me it was worth every day of not feeling well. There is nothing more valuable than something that's trying to keep you alive.	

Comments received from clinical experts and patient experts

No comments received

Comments received from commentators

No comments received

Comments received from members of the public

No comments received

NICE National Institute for Health and Care Excellence

Olaparib for adjuvant treatment of high-risk HER2-negative, BRCA-positive early breast cancer after chemotherapy [ID3893]

Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	AstraZeneca UK
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

NICE National Institute for Health and Care Excellence

Olaparib for adjuvant treatment of high-risk HER2-negative, BRCA-positive early breast cancer after chemotherapy [ID3893]

Comment number	Comments
1	AstraZeneca welcomes the opportunity to comment on the preliminary recommendation made by the Appraisal Committee detailed in the Appraisal Consultation Document (ACD). Whilst we are disappointed with the Appraisal Committee's initial decision to not recommend olaparib for the adjuvant treatment of patients with human epidermal growth factor receptor 2 (HER2)-negative (HER2-), high-risk, early (Stage I–IIIA) breast cancer (eBC) which is associated with a germline mutation in the breast cancer susceptibility gene (g*BRCA*m), we were pleased to see that the External Assessment Group (EAG) and Appraisal Committee recognise the unmet need, as well as the benefit that olaparib offers, in this indication. We are committed to working with NICE to address the Appraisal Committee's remaining concerns outlined in the ACD. As outlined in the ACD, the Committee's concerns primarily relate to the utility values used in the cost-effectiveness model. Whilst AstraZeneca acknowledge these concerns, we firmly believe that the **OlympiA trial provides the set of utility values that is most relevant to the current decision problem and most appropriately reflects the utility experienced by patients in the OlympiA indication**, specifically those who are and remain progression-free. This position was also supported by clinical experts during the Appraisal Committee meeting, who emphasised that the OlympiA quality of life study was the most extensive and robust dataset for this specific group of patients, and that the Verrill et al. (2020) data were too pessimistic. We have briefly summarised our position on this topic, as previously detailed in our Technical Engagement Response: • **OlympiA health-related quality of life (HRQoL) data are relevant and appropriate** to this decision problem, and any **potential bias due to missing data is likely to be negligible** o The HRQoL response rate in OlympiA was in line with that expected in clinical trials in this setting, with response rates of [redacted] at baseline, dropping to only [redacted] at 24 months.[1] A certain level of missing data in HRQoL questionnaires is present in all clinical trials and does not directly infer that the data itself is biased. o The EORTC QLQ-C30 scores in OlympiA remain [redacted]; if the majority of missing observations were not random and attrition bias was present, the average utility score would be expected to increase over time as the remaining sample would consist of healthier patients. Therefore, even if some level of attrition bias occurred as a result of more severe patients not completing the questionnaires, evidence suggests that the magnitude of this potential bias on the HRQoL estimates is negligible. o In response to the EAG's critique of potential bias in the mapping algorithms, we demonstrated consistency between the values generated from applying different mapping algorithms, and showed that the choice of algorithm is not a key driver of the mapped utility estimates from OlympiA. Notably the mapped utility scores for the progression-free health state all fell significantly and meaningfully above (+~0.07) the utility scores from Verrill et al. (2020), the EAG's and Appraisal Committee's preferred source of utility values. • Verrill et al. (2020) is subject to **significant limitations**, and the differing age, selection bias from recruitment and the lack of g*BRCA*m and triple negative breast cancer (TNBC) patients in the study are likely to impart **bias in the utility results and limit its generalisability to OlympiA patients** o The population enrolled in Verrill et al. (2020) is not representative of a younger g*BRCA*m population, with the mean age in Group 2 (57.7 years) substantially higher than that reported in OlympiA (43.3 years);[1, 2] feedback from clinical experts indicates that the demographics of the patient population in OlympiA better align with the patient group anticipated to receive olaparib in clinical practice. o Almost half of the patients in Group 2 (48.1%) were unemployed and their questionnaires collected on average ~4 years after initial diagnosis, indicating a potential selection bias; at this point, patients with a 'normal' HRQoL are likely to have returned to work if they remain progression-free, have an improved quality of life, and

	are therefore unlikely to have completed the questionnaire in the study. The measured health utility of 0.732 from Verrill et al. (2020) for Group 2 is therefore likely to be negatively biased, and thus not applicable and relevant to the general demographics of the OlympiA patient population. ○ Although the EAG provided a sensitivity analysis to adjust for the older age of the Verrill et al. (2020) population, this did not adjust for other factors such as employment status as outlined above. Given that adjusting for age alone resulted in a significant ~0.04 change in the disease-free utility value, this emphasises the uncertainty which results from using a study with limited generalisability to the patient population who would receive olaparib in this setting. • Assigning a utility value of 0.732 (or 0.770 if considering the EAG age-adjusted sensitivity analysis) to a **young patient group who have early-stage, treatable breast cancer and are in remission lacks face validity** ○ There is no clear rationale as to why the utility value assigned to patients in the progression-free health state, who are in (potentially long-term) remission and not expected to experience any significant continuing breast cancer-related symptoms or adverse events from treatment, should be significantly lower than the values of the age-matched UK general population (0.877). This is especially true the longer that patients remain disease-free, as the anxiety relating to their condition and fear of potential recurrence fades with time. ○ Comparison of the different mapped OlympiA health state utilities and those from Verrill et al. (2020) with utility values in previous NICE appraisals in the eBC and metastatic breast cancer (mBC) settings and relevant empirical literature, demonstrated that there is no precedent of either accepting or concluding a <0.8 health state utility value for eBC patients who are in (long-term) remission. ○ Considering that patients with newly diagnosed mBC (which is generally considered to be incurable disease, with 5-year survival rates of only ~25%)[3] have been shown to have a utility value of ~0.73, it is highly unrealistic to assume that a similar utility value would also apply to patients with early-stage disease, particularly in individuals who remain progression-free for a long period of time and have significant potential for cure. ○ Interviews with UK clinical oncologists, who unanimously commented that the HRQoL of eBC patients will become similar to the age-matched general population over time, indicated that it is reasonable to assume that the 'true' health state utility value for (long-term) disease-free patients with g*BRCA*m, high-risk eBC ranges between 0.8–0.877. Consequently, we firmly believe that the **utility values applied in the company's base-case analysis represent a set of estimates that better reflect the HRQoL of patients for the specific indication addressed in this appraisal**; this was a position supported by clinical experts at the Appraisal Committee meeting. AstraZeneca believe that the Appraisal Committee's preferred values are too conservative, and are not reflective of the patients, or their experiences, under consideration in this appraisal. It should be noted that olaparib is the first and only approved medicine in Great Britain that targets germline *BRCA* mutations in patients with eBC (Stage I–IIIA) previously treated with neoadjuvant or adjuvant chemotherapy, and AstraZeneca remains committed to ensuring patients are able to access innovative, life-changing treatments, such as olaparib, in the NHS. However, there exists limitations and inflexibilities within the medicines access system in England that result in barriers to securing patient access to therapies that treat multiple types of cancer at potentially different stages of disease. We are committed to continuing discussions with NICE and NHS England, as well as clinical and patient group stakeholders, to explore routes to deliver patient access to olaparib in the UK, in all of its indications, including eBC. We will also continue collaborating more broadly on how medicines, such as olaparib, can be more effectively and flexibly assessed in order to prevent unnecessary delays to patient access.

Olaparib for adjuvant treatment of high-risk HER2-negative, BRCA-positive early breast cancer after chemotherapy [ID3893]

References

1. AstraZeneca Data on File. OlympiA Clinical Study Report. 2021.
2. Verrill M, Wardley AM, Retzler J, et al. Health-related quality of life and work productivity in UK patients with HER2-positive breast cancer: a cross-sectional study evaluating the relationships between disease and treatment stage. Health Qual Life Outcomes 2020;18:353.
3. Cancer Research UK. Survival. Available at: https://www.cancerresearchuk.org/about-cancer/breast-cancer/survival. (last accessed: November 2022)

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Consultation on the draft guidance document – deadline for comments 5pm on Thursday 1 December 2022. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced.
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Breast Cancer Now
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**N/A**
Name of commentator person completing form:	[redacted]

Comment number	Comments

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	Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	Breast Cancer Now welcomes the opportunity to respond to this Appraisal Consultation Document (ACD). We are incredibly disappointed that NICE has been provisionally unable to recommend olaparib for either routine use on the NHS, or for use on the Cancer Drugs Fund. Olaparib is a treatment that could save lives and we are urging AstraZeneca, NICE and NHS England to explore every possible solution to ensure this treatment can be recommended for use on the NHS, including AstraZeneca doing all it can to price the drug at a level that ultimately will ensure its availability. This is critical given it is noted in the ACD that in the company's analysis, olaparib was not cost-effective. The strength of feeling within the breast cancer community is clear, as of 1 December 2022 **47,149** people have signed a petition calling for an urgent solution. Given the significance of this treatment for this group of patients, we urge NICE to invite patient and clinical experts back to the second committee meeting.
2	<u>Are the provisional recommendations sound and a suitable basis for guidance to the NHS?</u> The provisional recommendation to not recommend this treatment to eligible patients is not a sound or suitable basis for guidance for the NHS. The committee concluded that olaparib would be a welcome adjuvant treatment option to improve outcomes in this group of patients, as evidence has shown it can improve invasive disease-free survival, distant disease-free survival and overall survival compared to placebo. Olaparib represents a major advancement in the treatment options available and it could benefit hundreds of patients every year in England. The potential long-term implications for this high-risk group need to be considered if this draft recommendation is not reconsidered, especially in light of limited treatment options and this being a high-risk population where prognosis remains poor. As discussed in our patient organisation submission and the committee meeting, olaparib is a treatment that could save lives and there is currently a clear unmet need in this group of patients. In the latest data available from OlympiA trial it shows that: - The percentage of patients alive at 4 years from randomization was 89.8% in the olaparib group and 86.4% in the placebo group, an absolute improvement in overall survival of 3.4%. - Invasive disease free survival at 4 years was 82.7% in the olaparib group and 75.4% in the placebo group – an absolute improvement of 7.3%. Distant disease free survival was 86.5% in the olaparib group and 79.1% in the placebo group – an absolute improvement of 7.4%. It is crucial that patients have access to the best possible treatment options to reduce the risk of recurrence or their breast cancer spreading so that they can continue living their lives to the fullest. If a patient progresses to incurable secondary (metastatic), it is a devastating diagnosis for both the patient and their loved ones. We know that the fear of recurrence and 'living under its shadow' can have a significant impact on the quality of lives of people after they finish their treatment for primary breast cancer. To have a new treatment option with olaparib, which is known to be generally well-tolerated, and could significantly reduce the risk of recurrence, including the risk of secondary breast cancer and the associated need for on-going and complex treatments could have a significantly positive impact on people's wellbeing and day-to-day lives.

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	Someone with experience of olaparib told us: "I had the chance to watch my daughter grow up, and enjoyed every moment with her and my family. Without olaparib I believe she would have been left without a mother, and an incredible father left as a single parent. My husband and I are both full time back at work, contributing to society. Without olaparib, this wouldn't have been possible."
3	<u>Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?</u> *Efficacy in subgroups* It is noted in the ACD that the additional data from the trial would provide further insight into the efficacy of olaparib in the subgroup with hormone receptor-positive HER2 negative breast cancer. Whilst clinical experts highlighted that they do not expect this subgroup to behave any differently, one option that should be considered is this subset being approved for use via the Cancer Drugs Fund whilst further data is collected and the triple negative group being approved for routine use. The priority is ensuring that it's available for all eligible patients. *Discount rate* We would encourage the committee to explore further the cost-effectiveness results using both discount rates as part of the decision-making process. This transformative treatment can significantly reduce the risk of the cancer returning or spreading to become incurable secondary breast cancer. The latest data from the trial (published online in October 2022) has shown that all previous benefits have improved and that overall survival is statistically significant. We understand that NICE guidance outlines that the 1.5% rate may be considered when a treatment can result in substantial quality of life gains or life expectancy gains and olaparib is a treatment that could result in that benefit for patients. Without olaparib people could experience a recurrence or their disease could spread and devastatingly become incurable secondary breast cancer. The addition of olaparib to eligible patients for whom many will be in their 30s and 40s has the potential to restore them to full or near-full health and ultimately have benefits that are sustained oer a very long period. We regularly hear from primary breast cancer patients who live day-to-day with the fear of their breast cancer returning or spreading to become incurable secondary breast cancer but patients who have received olaparib tell us it can lower the mental burden "It definitely has a big positive mental impact – I feel better knowing I'm having a treatment which shows positive survival results. It makes me feel more protected and makes a big difference to my life. An additional year of being on a treatment is worth it because looking at the statistics about the effectiveness of the treatment and knowing the benefits is so crucial for patients from a mental wellbeing perspective". Whilst we understand that the committee would need certainty in the data to enable a 1.5% discount rate and it has already highlighted immaturity of data regarding the hormone receptor subgroup, it is unclear from the ACD the specific concerns that remain regarding the triple negative population and why the 1.5% discount is not applicable to that specific group in light of the available evidence. We would welcome clarity on what further evidence would be required in this instance to meet the 1.5% discount rate. *Health-related quality of life* This treatment can help more people remain cancer free, survive breast cancer and ultimately enable them to live well. We believe this area should be revisited by the committee to see what flexibility there is regarding the use of both EAG and company estimates. We note the reference to the risk of bias because of low completion rates of the EORTC QLQ-C30 questionnaire. As per our technical engagement response, we feel the rates of completion are comparable to other studies and there will never be a complete response rate as it is dependent upon patients completing this.

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4	Please tell us if the preliminary recommendations could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology Triple negative breast cancer is more common in black women and women under 40. Therefore, a final negative recommendation would disproportionately impact certain groups.
5	Has all of the relevant evidence been taken into account? The breast cancer community is devastated about the prospect of this treatment not reaching the patients who need it. Women who have a) received olaparib either through the drug company early access scheme or private healthcare or b) who participated in the OlympiA trial have shared their views on the treatment and why they believe it's important that eligible women can access this treatment on the NHS. People explain the impact of a diagnosis of high-risk HER2-negative primary breast cancer with an altered BRCA gene: • "When you have triple negative breast cancer and a BRCA gene mutation, you know after surgery and chemotherapy there is nothing else. You know your risk of a recurrence is high and it's difficult to mentally process this information. I feel extremely privileged to have been able to take Olaparib. It makes you feel like you have a little army inside you fighting to keep you alive. Taking Olaparib has reduced my risk and has therefore, helped to reduce my anxiety about future breast cancer recurrences." • "Triple negative breast cancer is a very scary cancer because there was nothing on the market to stop it coming back (or lessen chances), unlike other breast cancers. It felt like a death sentence. I was pregnant at the time of by diagnosis and the baby had to be delivered at 32 weeks so chemotherapy could be started. My tumour had grown to 12cms so I had to deal with that too. My baby was in special care, it was such a stressful time for everyone but my family were amazing". • "I was 38 years old when diagnosed, wanting children and I thought I'd just been told I was going to die. I had stage 2, grade 2 breast cancer but was told it was treatable. While the blood drained out of my husband's face and he came numb, I thought – 'right well that's not the worst is it? Let's get on with the treatment then'. Tests confirmed that I had triple negative cancer and then genetic testing confirmed I carried the BRCA1 gene mutation. My family had to get tested too. We had to tell our extended family. There is a potential time bomb for some very young members of my family. I don't envy the day their parents have to sit them down to have that conversations. There is a sense of helplessness that comes from being a partner or family member of someone who has cancer. They take on a financial burden, do the housework, the cooking, the living when you are too chemo-sick and unable. What little energy they have is pushed into staying positive and supportive, all with the cold hard knowledge that they can't fix it - they can't make the person they love better. • "There is nothing worse than telling your husband, children and other family members that you have breast cancer. And then of course I found out I had the BRCA-1 gene mutation, and I felt even more guilty. Now I'm living with the fear that maybe one or both of my son's has it". • "I was diagnosed with triple negative breast cancer, aged 44, the same age as my

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	grandmother had died from breast cancer. My son was age 15 exact same age my Dad was when his Mum was diagnosed. I didn't want history to repeat and I had heard there are a lot of new treatments for breast cancer now. However, we were shocked to find out after speaking to the oncologists that Triple Negative is not the same as other breast cancers and there are no other cures apart from Chemotherapy. Heart breaking to know I had already had a full hysterectomy and if I had found out about my BRCA2 before the cancer I could have also had a preventative double mastectomy too". • "I was diagnosed with triple negative breast cancer at 35. It was in my left breast and almost all of my lymph nodes in my armpit. I had a 5 week old baby and thought we were just starting our family. I naively asked if I was able to have fertility preserving chemotherapy. My oncologist was brilliant and clear - I was told that I would need life preserving chemo and it would be brutal. I should focus on surviving for my tiny daughter". • "It's daunting to know that your breast cancer is less common and more aggressive than other types of breast cancer, with a higher risk of returning in the years immediately following treatment – but at the same time there are fewer treatment options available to reduce that risk." People who participated in the OlympiA trial explain why they got involved (please note this was a double-blinded trial): • "I found the trial, as I was researching my cancer - knowledge is power. I told my onco I wanted to get on the trial and he hadn't heard of it but he was able to find it with the info I gave him. The trial was brilliant, they really looked after me and still do as it's a 10-year trial. I am on year 8. I joined the trial because I wanted to increase my chances of survival, I have four kids and did not want them growing up without a Mother. It was a double blind trial, but looking at my side effects, I know I had olaparib. When a drug has been found to be successful, to save lives, to help families, why wouldn't it be put on the market? There is a drug that is the difference between someone dying or surviving." • "Triple negative breast cancer has a comparatively poor outcome to oestrogen or progesterone positive cancers, so participating on this trial, felt like I was being offered an extra safety net in terms of medical support, regardless if I was given the parp inhibitor or placebo. The ever prescient fact that I have two young family members who may also carry the BRCA1 gene mutation and have around an 80% chance of developing cancer. If there was something I could do to help develop smarter treatments and prevent them from having to endure the horror of standard cancer treatment, well, there was no need to ask twice. It became fairly apparent that I was not on the placebo as I did experience some wooziness with the parp inhibitor. So many of us have wanted to be able to carry on with life as normally as possible, go to work/college, look after family, enjoy life, but for many on chemo this is not possible. It's disruptive, can make you feel like crap, and accumulative poisoning slows you down. Mental health and finances suffer. Here is a drug that can be taken in tablet form, doesn't require as much hospital attendance, allowing some normalcy in life, and freeing up beds and chemo nurses to treat others who do need to go in for regular treatment. The current treatments do not cure at the same rate as olaparib. Reoccurrences are comparatively high. Here is a drug that has been proven to reduce reoccurrence and therefore cost". People with experience of olaparib in this indication (either through the drug company early access scheme or private healthcare) explain: • "I felt it important that I received this treatment to give me every possible chance of not

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	having a recurrence or spread of my breast cancer. It also gives some peace of mind knowing all possible is being done, which is priceless at a stressful enough time. If you have gone through cancer you will know how important the emotional and mental side is, and how crucial a role that plays in recovery. "Olaparib is a clinically proven treatment which will ultimately reduce costs too - by reducing the numbers of those with the BRCA gene who have a recurrence or secondary cancer, and the knock on costs that has to the health service. And making Olaparib available more widely helps in pushing forward the development of personalised treatments to get the best outcomes for patients, and will in turn lead to further developments to combat cancer. The tablets and monthly blood tests are surely more cost-effective in the long run than more intensive treatments because of recurrence and spread? Not to mention the physical and emotional impacts on those who have the cancer gene". • "Olaparib for me is to prevent a dangerous aggressive Breast Cancer recur in my body. I am petrified of the cancer returning and being a secondary as this is not curable. I have a BRCA2 gene fault and the TNBC has already been in my body, this PARP inhibitor works by trying to fix the Gene Fault that causes Breast and Ovarian Cancer. I have had a full hysterectomy and a Double mastectomy. I am grateful there is also a medication that can also help to avoid a recurrence. The side effects are not pleasant however im sure they are far better than the effects the secondary breast cancer will be and it helps me to spend more time with my Children aged 12 and 16. As a family we were delighted to be offered this chance to help us avoid the aggressive cancer coming back. When treatments are found to help and work these should be made available for patients on the NHS for everyone with the BRCA1 and BRCA2 gene faults along with the preventative surgeries. There is no treatments for TNBC after chemo and for other breast cancers that are hormone related there are options to help. This needs to be available on the NHS like the hormone treatments are. I know research is being done constantly but when something is found that help it would be awful for secondaries to occur without trying to avoid them. Olaparib helps to avoid the recurrence. I have the BRCA2 gene fault which means my children have a 50/50 chance to also have this, I do hope when they are old enough the treatment is available for them should they also need it. I don't think it should be luck to receive treatment, everyone should be able to receive it when needed". • "As a mother, a wife, a daughter and a sister, Olaparib has hopefully bought me more precious time with my family - that is beyond priceless. I can't tell you what it feels like to wonder whether I must make this Christmas the best Christmas because I don't know if I'll be here for many more in the future. BRCA-1 triple negative breast cancer patients are living with the very real risks of our breast cancer coming back, Olaparib can reduce the risk and can help us sleep at night. My oncologist has told me I should naturally live until I'm at least 80 years old and he wants me to survive my breast cancer diagnosis and live until I am at least 80 years old. That's why he wanted me to take Olaparib. It's about being here for more Christmases, to see your children graduate from university and start families of their own. It's about removing the worry of dying prematurely and it's about hope. I was quite tired when I started Olaparib after receiving 6 rounds of chemotherapy and a double DIEP mastectomy and I wasn't feeling my best. Having said that I would never have delayed the start of Olaparib - I couldn't wait to start the treatment. The side effects of Olaparib were quite tough although not as tough as chemotherapy treatment. You can

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	experience fatigue and nausea alongside some other side effects, but I had a fantastic team who helped me through the treatment. . I had to take some time off work due to some of the side effects, but I would do it all again because for me it was worth every day of not feeling well. There is nothing more valuable than something that's trying to keep you alive.

Insert extra rows as needed

Checklist for submitting comments

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- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
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- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the process manual for more information.
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- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

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

AZ comments

Comments	EAG Response
As outlined in the ACD, the Committee's concerns primarily relate to the utility values used in the cost-effectiveness model. Whilst AstraZeneca acknowledge these concerns, we firmly believe that the **OlympiA trial provides the set of utility values that is most relevant to the current decision problem and most appropriately reflects the utility experienced by patients in the OlympiA indication**, specifically those who are and remain progression-free. This position was also supported by clinical experts during the Appraisal Committee meeting, who emphasised that the OlympiA quality of life study was the most extensive and robust dataset for this specific group of patients, and that the Verrill et al. (2020) data were too pessimistic. We have briefly summarised our position on this topic, as previously detailed in our Technical Engagement Response: • **OlympiA health-related quality of life (HRQoL) data are relevant and appropriate** to this decision problem, and any **potential bias due to missing data is likely to be negligible** o The HRQoL response rate in OlympiA was in line with that expected in clinical trials in this setting, with response rates of [redacted] at baseline, dropping to only [redacted] at 24 months.[1] A certain level of missing data in HRQoL questionnaires is present in all clinical trials and does not directly infer that the data itself is biased. o The EORTC QLQ-C30 scores in OlympiA remain [redacted]; if the majority of missing observations were not random and attrition bias was present, the average utility score would be expected to increase over time as the remaining sample would consist of healthier patients. Therefore, even if some level of attrition bias occurred as a result of more severe patients not completing the questionnaires, evidence suggests that the magnitude of this potential bias on the HRQoL estimates is negligible. o In response to the EAG's critique of potential bias in the mapping algorithms, we demonstrated consistency between the values generated from applying different mapping algorithms, and showed that the choice of algorithm is not a key driver of the mapped utility estimates from OlympiA. Notably the mapped utility scores for the progression-free health state all fell significantly and meaningfully above (+~0.07) the utility scores from Verrill et al. (2020), the EAG's and Appraisal Committee's preferred source of utility values. • Verrill et al. (2020) is subject to **significant limitations**, and the differing age, selection bias from recruitment and the lack of g*BRCA*m and triple negative breast cancer (TNBC) patients in the study are likely to impart **bias in the utility results and limit its generalisability to OlympiA patients** o The population enrolled in Verrill et al. (2020) is not representative of a younger g*BRCA*m population, with the mean age in Group 2 (57.7 years) substantially higher than that reported in OlympiA (43.3	The EAG notes that the Committee's draft guidance was based on the cost-effectiveness estimates for olaparib being above what NICE considers to be an acceptable use of resources. That is the case irrespective of the choice for utility value in the economic model. Even when using the company's preferred utility values, the company's base case ICER is still above £20,000 - £30,000. We have previously addressed the issue of utility values in detail. To summarize, the utility estimates used in the company's base case are derived from the responses to the EORTC-QLC-c30 data from the OlympiA trial, which are prone to bias due to missing data. We acknowledge that other trials also have missing data for QoL; this means that these are also at risk of bias not that the OlympiA values are reliable. The committee acknowledges that the resulting mapped utilities are "unrealistically high because the disease-free value was only slightly lower than that of the age-matched people in the general population (0.877)". Our second point is that the company applies a mapping algorithm by Crott&Briggs which has been shown to produce biased estimates. In fact, all sensitivity analyses performed by the company using different

Comments	EAG Response
years);[1, 2] feedback from clinical experts indicates that the demographics of the patient population in OlympiA better align with the patient group anticipated to receive olaparib in clinical practice. ○ Almost half of the patients in Group 2 (48.1%) were unemployed and their questionnaires collected on average ~4 years after initial diagnosis, indicating a potential selection bias; at this point, patients with a 'normal' HRQoL are likely to have returned to work if they remain progression-free, have an improved quality of life, and are therefore unlikely to have completed the questionnaire in the study. The measured health utility of 0.732 from Verrill et al. (2020) for Group 2 is therefore likely to be negatively biased, and thus not applicable and relevant to the general demographics of the OlympiA patient population. ○ Although the EAG provided a sensitivity analysis to adjust for the older age of the Verrill et al. (2020) population, this did not adjust for other factors such as employment status as outlined above. Given that adjusting for age alone resulted in a significant ~0.04 change in the disease-free utility value, this emphasises the uncertainty which results from using a study with limited generalisability to the patient population who would receive olaparib in this setting. • Assigning a utility value of 0.732 (or 0.770 if considering the EAG age-adjusted sensitivity analysis) to a **young patient group who have early-stage, treatable breast cancer and are in remission lacks face validity** ○ There is no clear rationale as to why the utility value assigned to patients in the progression-free health state, who are in (potentially long-term) remission and not expected to experience any significant continuing breast cancer-related symptoms or adverse events from treatment, should be significantly lower than the values of the age-matched UK general population (0.877). This is especially true the longer that patients remain disease-free, as the anxiety relating to their condition and fear of potential recurrence fades with time. ○ Comparison of the different mapped OlympiA health state utilities and those from Verrill et al. (2020) with utility values in previous NICE appraisals in the eBC and metastatic breast cancer (mBC) settings and relevant empirical literature, demonstrated that there is no precedent of either accepting or concluding a <0.8 health state utility value for eBC patients who are in (long-term) remission. ○ Considering that patients with newly diagnosed mBC (which is generally considered to be incurable disease, with 5-year survival rates of only ~25%)[3] have been shown to have a utility value of ~0.73, it is highly unrealistic to assume that a similar utility value would also apply to patients with early-stage disease, particularly in individuals who remain progression-free for a long period of time and have significant potential for cure. ○ Interviews with UK clinical oncologists, who unanimously commented that the HRQoL of eBC patients will become similar to the age-matched general population over time, indicated that it is reasonable to assume that the 'true' health state utility value for (long-term) disease-free patients with g*BRCA*m, high-risk eBC ranges between 0.8–0.877.	mapping algorithms have considerably lowered the utility values estimated. We acknowledge that the clinical expert supported the company's position. However, our independent clinical experts supported the view of the EAG that the utility values used in the company's model were not the most appropriate values to have used (see previous critique). It is unclear how the company has assigned face validity to any of the utility estimates proposed. Previous appraisals have focused on different populations or research problems and there are conflicting opinions among UK clinical oncologists in what is the "true" health state utility value. In fact, the committee also concluded that "the utility values from the EAG's age-adjusted estimates using Verrill et al were the most appropriate of the ones presented by the company and the EAG".

Comments	EAG Response
Consequently, we firmly believe that the **utility values applied in the company's base-case analysis represent a set of estimates that better reflect the HRQoL of patients for the specific indication addressed in this appraisal**; this was a position supported by clinical experts at the Appraisal Committee meeting. AstraZeneca believe that the Appraisal Committee's preferred values are too conservative, and are not reflective of the patients, or their experiences, under consideration in this appraisal. It should be noted that olaparib is the first and only approved medicine in Great Britain that targets germline *BRCA* mutations in patients with eBC (Stage I–IIIA) previously treated with neoadjuvant or adjuvant chemotherapy, and AstraZeneca remains committed to ensuring patients are able to access innovative, life-changing treatments, such as olaparib, in the NHS. However, there exists limitations and inflexibilities within the medicines access system in England that result in barriers to securing patient access to therapies that treat multiple types of cancer at potentially different stages of disease. We are committed to continuing discussions with NICE and NHS England, as well as clinical and patient group stakeholders, to explore routes to deliver patient access to olaparib in the UK, in all of its indications, including eBC. We will also continue collaborating more broadly on how medicines, such as olaparib, can be more effectively and flexibly assessed in order to prevent unnecessary delays to patient access.	

Breast Cancer Now Comments that relate to the evidence

Comment	EAG response
Health-related quality of life This treatment can help more people remain cancer free, survive breast cancer and ultimately enable them to live well. We believe this area should be revisited by the committee to see what flexibility there is regarding the use of both EAG and company estimates. We note the reference to the risk of bias because of low completion rates of the EORTC QLQ-C30 questionnaire. As per our technical engagement response, we feel the rates of completion are comparable to other studies and there will never be a complete response rate as it is dependent upon patients completing this.	See response to same point raised by AZ