National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

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

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Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness	AstraZeneca UK	We agree that it is appropriate that this topic undergoes a NICE appraisal given the prevalence of breast cancer in the UK, and the unmet need of patients with high-risk disease, as outlined below under the section on “timing issues”.	Thank you for your comment. No action required.
	Breast Cancer Now	Yes, it is appropriate.	Thank you for your comment. No action required.
Wording	AstraZeneca UK	We suggest that the remit wording should be aligned to the anticipated license (including ‘BRCA-mutated’ rather than ‘BRCA-positive’): [redacted]	Thank you for your comment. The wording of the draft remit is written as per the current NICE style to ensure consistency across all scopes and appraisals. No changes were made to the scope.

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	Breast Cancer Now	Please note that it is estimated that BRCA mutations are found in approximately 5% of breast cancer patients. BRCA mutations can be associated with more aggressive tumours, such as triple negative breast cancer that are more likely to recur.	Thank you for your comment. No action required.
Timing Issues	AstraZeneca UK	Breast cancer is **the most common cancer in the UK**, with around 55,900 new cases diagnosed every year, and accounting for 15% of all new cancer diagnoses (2016-2018 data). It causes 11,500 deaths every year, which equates to **32 deaths per day**(1). Around 87% of cases are diagnosed at an early stage of disease (stage I to III)(2). Early breast cancer (eBC) is therefore a significant cause of morbidity and mortality in the UK. Current treatment for eBC is determined by molecular sub-types linked to human epidermal growth factor receptor (HER2) and hormone receptor (HR) status amongst other factors. While patients with HER2+ disease have benefited from recent advances in immunotherapies, **those with HER2- disease have fewer treatment options and a lack of targeted therapies**; cytoreductive surgery and chemotherapy are the mainstay of treatment, with the addition of endocrine therapies in HR positive patients(3). With current therapy **recurrence is relatively common**; US studies have shown that for women diagnosed with stage I–III breast cancer, the overall cumulative incidence of developing distant metastases was shown to be 20%, 30% and 36% at 4, 8 and 12 years post-diagnosis(4), and that patients with high risk clinicopathologic features have worse prognosis(5). **Once distant metastases have developed the disease is generally considered incurable**, with 5-year survival rates of 26%(1), **and health-related quality of life** worsens compared with early disease(6).	Thank you for your comment. NICE aims to provide draft guidance to the NHS within 6 months from the date when the marketing authorisation for a technology is granted. NICE has scheduled this topic into its work programme.

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		There has been an increasing awareness in recent years of the role of genetic mutations such as BRCA1/2 genes in breast cancer, as well as in other tumour types. It is estimated that 15% to 20% of patients with triple negative breast cancer (TNBC), and 10-15% of patients with high-risk HR+, HER2- breast cancer will have a germline BRCA1/2 mutation(7); of those who test negative for a germline mutation, around 6% will have a somatic mutation(8). OlympiA is the **first Phase III clinical trial of a PARPi for use in early HER2- breast cancer patients with a germline BRCA mutation in the adjuvant setting**(9). Patients were eligible after completing definitive local treatment and neoadjuvant or adjuvant chemotherapy; this is representative of the UK eBC treatment pathway. Data from OlympiA were presented at the American Society of Clinical Oncology (ASCO) 2021 Annual Meeting. As such, we request that this appraisal be prioritised, to allow breast cancer patients to access olaparib aligned with its anticipated Medicines and Healthcare products Regulatory Agency (MHRA) Marketing Authorisation date, anticipated in [redacted]. (1) Cancer Research UK. Breast Cancer Statistics. [Internet]. [Cited 25/11/2021]. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer#heading-Two (2) Cancer Research UK. Early diagnosis. Proportion Diagnosed by Stage (stacked chart), England 2018 [Internet]. [Updated November 2021, cited	

Section	Consultee/ Commentator	Comments [sic]	Action
		25/11/2021]. Available from: https://crukcancerintelligence.shinyapps.io/EarlyDiagnosis/ (3) National Institute for Health and Care Excellence. NICE guideline [NG101]. Early and locally advanced breast cancer: diagnosis and management. 18 July 2018. Available from: https://www.nice.org.uk/guidance/ng101 (4) Hess KR, Esteva FJ. Effect of HER2 status on distant recurrence in early stage breast cancer. Breast cancer research and treatment. 2013;137(2):449-455. doi:10.1007/s10549-012-2366-0 (5) Sheffield KM et al. Recurrence risk in early breast cancer as defined by clinicopathologic features. Journal of Clinical Oncology 39, no. 15_suppl. DOI: 10.1200/JCO.2021.39.15_suppl.e18581 (6) Lidgren M, Wilking N, Jönsson B, Rehnberg C. Health related quality of life in different states of breast cancer. Quality of life research. 2007;16(6):1073-1081. (7) Loibl S, Poortmans P, Morrow M, Denkert C, Curigliano G. Breast cancer [published correction appears in Lancet. 2021 May 8;397(10286):1710]. Lancet. 2021;397(10286):1750-1769. doi:10.1016/S0140-6736(20)32381-3 (8) O'Shaughnessy J, Brezden-Masley C, Cazzaniga M, et al. Prevalence of germline BRCA mutations in HER2-negative metastatic breast cancer: global results from the real-world, observational BREAKOUT study. Breast Cancer Res. 2020;22(1):114. Published 2020 Oct 27. doi:10.1186/s13058-020-01349-9 (9) Tutt ANJ, Garber JE, Kaufman B, et al. Adjuvant Olaparib for Patients with BRCA1- or BRCA2-Mutated Breast Cancer. N Engl J Med. 2021;384(25):2394-2405. doi:10.1056/NEJMoa2105215	

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	Breast Cancer Now	We would like to see this appraisal progress in a timely manner. A diagnosis of breast cancer causes considerable anxiety to the patient as well as their family and friends. The initial diagnosis can be shocking, and in the longer-term the fear of breast cancer returning or spreading to other parts of the body where it becomes incurable can cause considerable distress for both patients and their loved ones. New treatment options which can help to reduce the risk of the cancer returning are still needed.	Thank you for your comment. NICE aims to provide draft guidance to the NHS within 6 months from the date when the marketing authorisation for a technology is granted. NICE has scheduled this topic into its work programme.
Additional comments on the draft remit	AstraZeneca UK	No additional comments	Thank you. No action required.
	Breast Cancer Now	N/A	Thank you. No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	AstraZeneca UK	No comment	Thank you. No action required.
	Breast Cancer Now	To the best of our knowledge [the background section is accurate and complete].	Thank you for your comment. The statement about the proportion of people progressing to

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		We note the following reference which we haven't seen in previous NICE scopes. It should be noted that this is regional data which is nearly 30 years old. *Around 35% of people with early or locally advanced disease will progress to metastatic breast cancer.*	metastatic disease has been removed.
The technology/ intervention	AstraZeneca UK	Yes [the description of the technology is accurate].	Thank you for your comment. No action required.
	Breast Cancer Now	As far as we are aware. It is noted that olaparib is currently indicated for BRCA1 or BRCA2 positive, HER2 negative locally advanced or metastatic breast cancer after prior chemotherapy. It should be noted that whilst licensed the appraisal for this indication was recently suspended following non-submission by the company.	Thank you for your comment. No action required.
Population	AstraZeneca UK	The label [redacted]. AstraZeneca will keep NICE informed if this expectation changes throughout the course of the appraisal.	Thank you for your comment. The population section has been updated.
	Breast Cancer Now	Yes the population appears to be correct, although it might be helpful to include a mention of ER status. We aren't aware of any subgroups that need to be considered separately. Evidence from the OlympiA trial suggests no statistical heterogeneity in the treatment effect across sub-groups.	Thank you for your comment. Hormone receptor status has been included in the description of the population.

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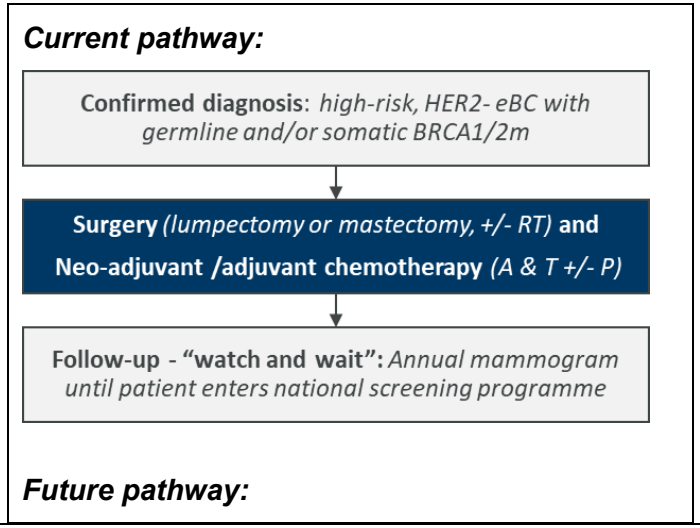
Comparators	AstraZeneca UK	The current treatment pathway for the relevant population is represented in Figure 1 (top panel), as well as the expected pathway with the addition of olaparib (bottom panel). Olaparib is positioned after existing "standard adjuvant therapy without olaparib", and as such would not displace them. The appropriate comparator for olaparib in this setting is 'watch and wait'/placebo. **Figure 1: Current and future expected treatment pathway in high-risk eBC BRCAm patients**  	Thank you for your comment. The comparators listed in the scope aims to be inclusive. A rationale should be provided for excluding any comparators from the evidence submission, which can be considered by the appraisal committee. The scope has been changed to expand from 'standard adjuvant therapy without olaparib' to 'established clinical management without olaparib'.

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		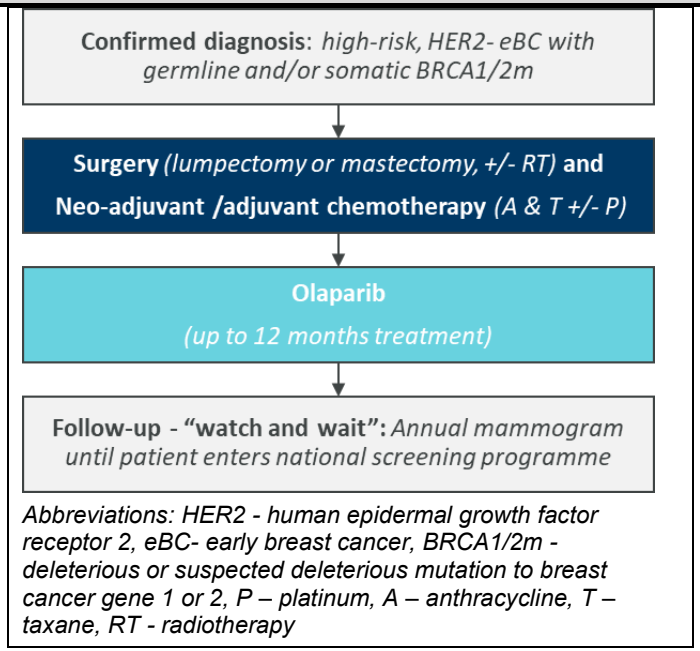 *Abbreviations: HER2 - human epidermal growth factor receptor 2, eBC- early breast cancer, BRCA1/2m - deleterious or suspected deleterious mutation to breast cancer gene 1 or 2, P – platinum, A – anthracycline, T – taxane, RT - radiotherapy* Treatment for eBC currently consists of chemotherapy and surgery (lumpectomy or mastectomy), with or without radiotherapy (RT). Patients receive either neoadjuvant chemotherapy then surgery (with or without RT), or surgery (with or without RT) followed by adjuvant chemotherapy. Physicians are guided by tumour characteristics such as size and nodal involvement to decide whether to use chemotherapy in the neo-adjuvant or adjuvant setting. For patients with TNBC the standard of care after initial treatment (surgery, chemotherapy, +/- radiotherapy) would be routine follow-up to monitor for disease recurrence. In patients with HR+ eBC extended endocrine therapy is	

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		used after completion of initial treatment (surgery, chemotherapy, with/without radiotherapy). Bisphosphonate therapy may also be used as adjuvant therapy in some postmenopausal breast cancer patients(3). (3) National Institute for Health and Care Excellence. NICE guideline [NG101]. Early and locally advanced breast cancer: diagnosis and management. 18 July 2018. Available from: https://www.nice.org.uk/guidance/ng101	
	Breast Cancer Now	No specific treatments have been listed in comparators – it currently just states “standard adjuvant therapy without olaparib”. For the eligible population group here, adjuvant treatment of high-risk HER2-negative, BRCA-positive early breast cancer after chemotherapy, the following treatments could currently be considered: <u>Hormone receptor positive, HER2 negative:</u> In line with the NICE early and locally advanced guideline, men and premenopausal women may be offered tamoxifen as an adjuvant endocrine therapy. Premenopausal women could also be offered an aromatase inhibitor with ovarian suppression. An aromatase inhibitor (letrozole, anastrazole, exemestane) may be offered as the initial endocrine therapy for postmenopausal women with ER positive breast cancer who are at high risk. Extended endocrine therapy (of over 5 years) may also be considered. <u>Triple negative breast cancer:</u> Patients may be offered a chemotherapy regimen that contains a taxane and an anthracycline. Chemotherapies may include paclitaxel, docetaxel and EC.	Thank you for your comment. The comparators listed in the scope aims to be inclusive. The scope has been changed to expand from ‘standard adjuvant therapy without olaparib’ to ‘established clinical management without olaparib’.

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Outcomes	AstraZeneca UK	Yes [the outcome measures capture the most important health related benefits (and harms) of the technology].	Thank you for your comment. No action required.
	Breast Cancer Now	They appear to be correct. The primary end point of the trial was invasive disease-free survival. Please note overall survival data is unlikely to be mature during this appraisal, however, the company will be best placed to answer this.	Thank you for your comment. No action required.
Economic analysis	AstraZeneca UK	The economic analysis will follow the NICE reference case. A lifetime time horizon is appropriate in this setting to capture all differences in costs or outcomes between the technologies being compared.	Thank you for your comment. No action required.
	Breast Cancer Now	N/A	Thank you. No action required.
Equality and Diversity	AstraZeneca UK	No equality considerations have been identified at this stage.	Thank you for your comment. No action required.
	Breast Cancer Now	The scope does not appear to promote discrimination.	Thank you for your comment. No action required.
Other considerations	AstraZeneca UK	The subgroups mentioned in the 'other considerations' were subgroups included in the OlympiA study (NCT02032823) relevant to this appraisal. It is expected that clinical and cost-effectiveness of olaparib will be consistent across these subgroups as the mechanism of action is applicable irrespective of subgroup type[10,11].	Thank you for your comment. No action required.

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		(10) Tutt A, Robson M, Garber JE, et al. Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and advanced breast cancer: a proof-of-concept trial. Lancet. 2010;376(9737):235-244. doi:10.1016/S0140-6736(10)60892-6 (11) Farmer H, McCabe N, Lord CJ, et al. Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. Nature. 2005;434(7035):917-921. doi:10.1038/nature03445	
	Breast Cancer Now	It is crucial that genetic testing pathway processes are in place to allow for streamlined genetic testing to identify patients in a timely manner for this treatment.	Thank you for your comment. Development of genetic testing pathway is not within the remit of this appraisal. However, any issues relating to the associated genetic testing and the implementation of necessary testing can be considered by the appraisal committee. No action required.
Innovation	AstraZeneca UK	Yes. Olaparib will be the first targeted treatment in early breast cancer in the HER2- population, and represents a step-change for patients with BRCA1/2 mutations. It will add a new class of therapy for a high-risk patient population where current treatment options are inadequate, resulting in a clinical unmet need for additional therapies that reduce the risk of disease recurrence and improve survival. Data from the OlympiA study show the substantial clinical benefit of olaparib in this population[(9)]:	Thank you for your comment. The innovative nature of olaparib will be considered by the NICE appraisal committee

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		• 3-year invasive disease–free survival (iDFS) of 85.9% in the olaparib group compared with 77.1% in the placebo group (hazard ratio [HR] 0.58; 99.5% CI, 0.41 to 0.82; P<0.001) ○ 3-year iDFS of 86.1% in the mature olaparib group (3.5+ years of follow-up) and 77.5% in the placebo group (HR 0.61; 99.5% CI, 0.39 to 0.95). • 3-year distant disease–free survival (dDFS) of 87.5% in the olaparib group and 80.4% in the placebo group (HR 0.57; 99.5% CI, 0.39 to 0.83; P<0.001). • Olaparib was associated with fewer deaths than placebo (59 and 86, respectively) (HR 0.68; 99% CI, 0.44 to 1.05; P = 0.02) (9) Tutt ANJ, Garber JE, Kaufman B, et al. Adjuvant Olaparib for Patients with BRCA1- or BRCA2-Mutated Breast Cancer. N Engl J Med. 2021;384(25):2394-2405. doi:10.1056/NEJMoa2105215	during the appraisal. No action required.
	Breast Cancer Now	We consider this treatment to be innovative and to have the potential to make a significant impact for patients and could be a step-change in the options available for this group of patients. The OlympiA trial showed that one year of adjuvant olaparib could reduce recurrence risk and the risk of progression to incurable secondary breast cancer. The trial showed that people who received olaparib had a 42% reduction in risk of breast cancer recurrence. 85.9% of those given olaparib for a year after treatment saw no return, relapse or spread of their breast cancer three years later, compared with 77.1% who were taking a placebo tablet.	Thank you for your comment. The innovative nature of olaparib will be considered by the NICE appraisal committee during the appraisal. No action required.

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Questions for consultation	AstraZeneca UK	**The majority of questions for consultation have been answered in the above sections, including those relating to:** • Comparators • Outcomes • Subgroups • Equality • Innovation • Benefits not captured in QALY calculations **The remaining questions for consultation are addressed below:** <u>How is high-risk, early or locally advanced breast cancer defined in clinical practice?</u> There is currently no specific definition of what constitutes a “high-risk” early breast cancer patient in UK clinical practice. From early consultation with UK clinicians, numerous factors may feed into an assessment of risk including tumour characteristics such as size, BRCA status, and nodal involvement. These factors can inform treatment decisions, such as whether to use chemotherapy in the neo-adjuvant or adjuvant setting, alongside other factors such as patient fitness. <u>Where do you consider olaparib will fit into the existing NICE pathway, early and locally advanced breast cancer?</u> In line with the proposed licence, olaparib therapy is proposed for the adjuvant treatment of [redacted]	Thank you for your comments. No further actions required.

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		[redacted]. Please see company response above for a diagram of the expected positioning of olaparib within the existing treatment pathway. To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly. Treatment with olaparib requires that a BRCA test is conducted to identify the patient as having a BRCA mutation.	
	Breast Cancer Now	**How is high-risk, early or locally advanced breast cancer defined in clinical practice?** The risk of recurrence is higher among patients with certain risk factors, such as large tumour size, higher number of positive lymph nodes. Research has shown that the risk of triple negative breast cancer coming back or spreading is higher than some types of breast cancer in the first few years. However, after around five years the risks are similar to, and may be lower than, other types of breast cancer.	
Additional comments on the draft scope	AstraZeneca UK	No additional comments	Thank you. No action required.
	Breast Cancer Now	N/A	Thank you. No action required.