National Institute for Health and Care Excellence

Health Technology Evaluation

Ribociclib with an aromatase inhibitor for adjuvant treatment of hormone receptor-positive, HER2-negative early breast cancer [ID6153]

Response to stakeholder organisation comments on the draft remit and draft scope

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

Comment 1: the draft remit and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	Breast Cancer Now	We consider the single technology appraisal route to be appropriate.	Thank you for your comment. No action required.
	Novartis	It is appropriate for NICE to evaluate this topic and the single technology appraisal (STA) route is also considered appropriate.	Thank you for your comment. No action required.
	Astra Zeneca	No comments	No action required.
	Eli Lilly	N/A	No action required.
Wording	Breast Cancer Now	Yes the wording of the remit is appropriate.	Thank you for your comment. No action required.

Section	Stakeholder	Comments [sic]	Action
	Novartis	The wording of the remit is appropriate.	Thank you for your comment. No action required.
	Astra Zeneca	No comments	No action required.
	Eli Lilly	N/A	No action required.
Timing Issues	Breast Cancer Now	It is important this appraisal progresses 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 stress for both patients and their loved ones. This treatment could be an important step-forward in the treatment options for this group of patients. Interim findings have shown that this treatment could reduce the risk of recurrence, including in those patients with no nodal involvement. This would increase the patient population who could access a CDK 4/6 inhibitor in the adjuvant setting.	Thank you for your comments. NICE aims to provide draft guidance to the NHS within 6 months from the date when the marketing authorisation for a technology is granted.
	Novartis	No comment.	No action required.
	Astra Zeneca	No comments	No action required.
	Eli Lilly	N/A	No action required.
	Breast Cancer Now	None	No action required.

Section	Stakeholder	Comments [sic]	Action
Additional comments on the draft remit	Novartis	No additional comments.	No action required.
	Astra Zeneca	N/A	No action required.
	Eli Lilly	N/A	No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Breast Cancer Now	We consider to this to be accurate.	Thank you for your comment. No action required.
	Novartis	Novartis suggest the following updates are made to the background information to improve the clarity and accuracy of the content: • The definition of early breast cancer currently provided is unclear; the current wording implies that early breast cancer includes cancer that has spread near, but not infiltrated, the lymph nodes. Novartis suggest the wording is updated to "Breast cancer is described as 'early' if it is restricted to the breast or the breast and **nearby** lymph nodes, and has not spread to other parts of the body" to improve the clarity of this definition. • The draft scope notes that there were 45,908 new diagnoses of breast cancer in England in 2017, and of these, 36,601 (80%) were diagnoses of early breast cancer. While Novartis agrees that the data presented are accurate, Novartis request that these data are updated to reflect more recent data published by NHS Digital for 2020.[1] This source reports 39,730 new breast cancer cases in England in 2020, of	Thank you for your comments. The background section has been updated in line with the suggestions made. Estimates of BRCA mutations are based on published sources.

Section	Consultee/ Commentator	Comments [sic]	Action
		which 28,229 (71%) were diagnoses of early stage breast cancer.[1] • Novartis were unable to verify the reported statistics for hormone receptor positive (HR+) (80%) and oestrogen receptor positive (ER+) (two-thirds) using the provided source.[2] As an alternative, Novartis suggest that NICE replace these statistics to instead report the proportion of patients with HR+ and human epidermal growth factor receptor 2 negative (HER2−) breast cancer, to more closely align with the population relevant to this appraisal. This proportion was reported as 64.5% in the resource impact template for TA810 (abemaciclib in HR+/HER2−, node-positive, early breast cancer at high risk of occurrence), based on the midpoint of the values stated in Howlader *et al.* 2014 and DeKoven *et al.* 2012.[3, 4] • Finally, while Novartis disagree with the inclusion of olaparib as a relevant comparator (see Comparator Section), the incidence of BRCA1/2 mutations is currently not stated within the background information section. Novartis request that these data are included to highlight the low prevalence of these mutations, particularly within the population relevant to this appraisal. The ESMO clinical practice guidelines report that BRCA1 and BRCA2 mutation frequencies in breast cancer patients are <1–7% and 1–3%, respectively,[5] while a comprehensive meta-analysis estimates that 2.7% of HR+/HER2− breast cancer patients (i.e. the population relevant to this appraisal) have a germline BRCA1/2 mutation.[6] Similarly, the presence of a BRCA1/2 mutation should also be included as an additional factor that would influence the treatment decision, should olaparib be included in the final scope. 1. Digital N. Case-mix adjusted percentage of cancers diagnosed at stages 1 and 2 in England, 2020. Available from: https://digital.nhs.uk/data-	

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		and-information/publications/statistical/case-mix-adjusted-percentage-of-cancers-diagnosed-at-stages-1-and-2-in-england/2020. [Last accesssed: June 2023], 2022. 2. Dewis R GJ. Breast Cancer: Diagnosis and Treatment: An Assessment of Need. Cardiff (UK): National Collaborating Centre for Cancer (UK); (NICE Clinical Guidelines, No. 80-81S.) Available from: https://www.ncbi.nlm.nih.gov/books/NBK61907/. [Last accessed: June 2023]. 2009. 3. DeKoven M, Bonthapally V, Jiao X, et al. Treatment pattern by hormone receptors and HER2 status in patients with metastatic breast cancer in the UK, Germany, France, Spain and Italy (EU-5): results from a physician survey. J Comp Eff Res 2012;1:453-63. 4. Howlader N, Altekruse SF, Li CI, et al. US Incidence of Breast Cancer Subtypes Defined by Joint Hormone Receptor and HER2 Status. JNCI: Journal of the National Cancer Institute 2014;106. 5. Balmaña J, Díez O, Rubio IT, et al. BRCA in breast cancer: ESMO Clinical Practice Guidelines. Annals of Oncology 2011;22:vi31-vi34. 6. Shao C, Wan J, Tang H, et al. A comprehensive literature review and meta-analysis on prevalence of BRCAm, HRRm and HRD+ across tumor types. Journal of Clinical Oncology 2021;39:10589-10589.	
	Astra Zeneca	No comments	No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
	Eli Lilly	N/A	No action required.
Population *Is the population defined appropriately?*	Breast Cancer Now	Yes to the best of our knowledge.	No action required.
	Novartis	No comment.	No action required.
	Astra Zeneca	No comments	No action required.
	Eli Lilly	N/A	No action required.
Subgroups	Breast Cancer Now	We recognise that the node-positive and people with BRCA1/2 mutations have been pulled out as sub-groups in the scope, given the cost-effectiveness analysis may be different due to the different comparators for these groups. We note that from abstract recently published (2 June 2023), invasive disease free benefit in the ribociclib group was generally consistent across clinically relevant patient subgroups. We look forward to seeing further results from this study.	Thank you for your comment. No action required.
	Novartis	While Novartis disagree with the inclusion of olaparib as a relevant comparator (see Comparator section), the current wording for the subgroup relevant to olaparib does not accurately reflect the population in which olaparib received a positive recommendation in TA886 (olaparib in BRCA-positive, HER2–, high-risk early breast cancer after chemotherapy).[7] It is therefore requested that the following eligibility criteria are also stated within the final scope:[7] High-risk early breast cancer Previously received treatment with neoadjuvant or adjuvant chemotherapy Presence of germline BRCA1 or 2 mutations	See the comparator section for NICE's response to comparator comments. The scope is a brief document. This level of detail should be given during the submission stage of the appraisal.

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		Novartis would also like to highlight that there is no established or widely recognised definition for 'high-risk' breast cancer; multiple definitions exist within the literature and the definition varies between the trials conducted in this indication. In order to compare against abemaciclib, Novartis will endeavour to match the definition of 'high-risk' utilised in TA810, however, it should be noted that this definition may not match the broader literature. Any differences will be highlighted in the company submission. 7. National Institute for Health and Care Excellence (NICE). TA886: Olaparib for adjuvant treatment of BRCA mutation-positive HER2-negative high-risk early breast cancer after chemotherapy FAD. Available from: https://www.nice.org.uk/guidance/ta886/documents/final-appraisal-determination-document. [Last accessed: June 2023], 2023.	The appraisal committee can consider the definition of high-risk used in clinical practice during the appraisal.
	Astra Zeneca	See below comments on the "comparators" section, which also apply to the proposed subgroups.	See the comparator section for NICE's response
	Eli Lilly	Please note, extensive consideration was given to the definition of disease at high-risk of recurrence as part of NICE technology appraisal 810 for abemaciclib with endocrine therapy for adjuvant treatment of hormone receptor-positive, HER2-negative, node-positive early breast cancer at high risk of recurrence. In clinical practice, high risk of recurrence is defined based a combination of clinical and pathological features, such as the number of axillary lymph nodes that a breast cancer has spread to, tumours of T2 or greater (tumour size of 2 cm or greater), and high-grade disease.[1,2] Studies have shown that node involvement is a predictive factor for risk of recurrence, and therefore	Thank you for your comment. The appraisal committee can consider the definition of high-risk used in clinical practice during the appraisal. The additional subgroup of people with node

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		mortality. In patients with HR+, HER2- early breast cancer, higher mortality rates are observed for patients with ≥4 positive lymph nodes, a Bloom-Richardson combined score grade 3 (well-differentiated), and greater tumour size. The effect on mortality may be compounded with a combination of these histopathologic characteristics.[3] In practice, clinicians will use validated risk prediction tools, such as the PREDICT breast cancer tool or the Nottingham Prognostic Index, as outlined in NICE Guideline NG101, to make an individualised assessment on a patient-by-patient basis about whether disease should be considered as high risk of recurrence.[3,4,5] For example, the PREDICT breast cancer tool takes into account a range of clinical and pathological features, including:[7] Tumour size Age at diagnosis Menopausal status Oestrogen receptor status Human epidermal growth factor receptor 2 (HER2) status Tumour grade Number of positive ALNs As well as node-positive patients the NATALEE trial included patients with node-negative disease. This may be a subgroup of interest to clinicians and may have lead to different conclusions on cost effectiveness.	negative disease has been added.

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		References 1. Cancer Research UK. TNM staging. Available at: https://www.cancerresearchuk.org/about-cancer/breast-cancer/stages-types-grades/tnm-staging. [Accessed: 03 December 2021]. 2. National Institute of Health and Care Excellence (NICE). Early and locally advanced breast cancer: diagnosis and management. Available at: https://www.nice.org.uk/guidance/ng101. [Accessed: 01 October 2021]. 3. Brown J, Method MW, Nelson DR. Abstract P5-08-18: Mortality rates associated with clinical and pathological characteristics of hormone receptor positive human epidermal growth factor receptor 2 negative early breast cancer: An analysis of the 2010-2016 surveillance, epidemiology, and end results data. 2019 San Antonio Breast Cancer Symposium; December 10-14. 4. National Health Service (NHS). PREDICT breast cancer. Available at: https://breast.predict.nhs.uk/tool. [Accessed: 08 December 2021]. 5. National Institute for Health and Care Excellence (NICE). Tumour profiling tests to guide adjuvant chemotherapy decisions in early breast cancer. Available at: https://www.nice.org.uk/guidance/dg34/resources/tumour-profiling-tests-to-guide-adjuvant-chemotherapy-decisions-in-early-breast-cancer-pdf-1053750722245. [Accessed: 03 December 2021].	
Comparators *Are the comparators listed considered to be the*	Breast Cancer Now	Yes, we consider the comparators listed to be appropriate. In 2022, abemaciclib (Verzenios) was approved for use on the NHS with endocrine therapy as an option for the adjuvant treatment of hormone receptor-positive, HER2-negative, node-positive early breast cancer in adults whose disease is at high risk of recurrence. Whilst in 2023, olaparib	Thank you for your comments. No action required.

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standard treatments currently used in the NHS with which the technology should be compared? Have all relevant comparators been included?		(Lynparza) was recommended as an adjuvant treatment for patients with germline BRCA1/2 mutations, who have HER2 negative high risk primary breast cancer which has been previously treated with neoadjuvant or adjuvant chemotherapy. However, there will be a group of patients from the NATALEE trial who may fall out of these two groups eligible for olaparib or abemaciclib, such as those who do not have a BRCA mutation and have no nodal involvement but could be eligible for adjuvant ribociclib. Currently, this group of patients would be receiving endocrine therapy. In line with the NICE early and locally advanced guideline, men and premenopausal women will be offered tamoxifen as an adjuvant endocrine therapy. Premenopausal women could also be offered an aromatase inhibitor with ovarian suppression. An aromatase inhibitor (letrozole, anastrozole or exemestane) will be offered as the initial adjuvant endocrine therapy for postmenopausal women with ER positive breast cancer who are at medium or high risk of disease recurrence. Extended therapy (total duration of endocrine therapy of more than 5 years) with an aromatase inhibitor will be offered for postmenopausal women who are at medium of high risk of disease recurrence and who have been taking tamoxifen for 2 to 5 years. Extending the duration of tamoxifen for longer than 5 years for both pre and post menopausal women with ER positive invasive breast cancer is also considered.	
	Novartis	Novartis disagree with the inclusion of olaparib as a relevant comparator to ribociclib.	NICE keeps the comparators list

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		As olaparib has only recently received a positive recommendation from NICE for the treatment HR+/HER2- early breast cancer, there is limited evidence on the use of olaparib in UK clinical practice. Novartis believe that patients with early breast cancer who test positive for a BRCA1/2 gene mutation are likely to receive targeted treatment with olaparib before ribociclib, with this view being validated through discussion with a UK clinical expert. Olaparib is therefore not regarded as a comparator, as a positive recommendation for ribociclib in HR+, HER2 early breast cancer after surgery of the primary breast tumour would not displace the use of olaparib in patients with BRCA mutation-positive HER2 high-risk early breast cancer after chemotherapy. Novartis therefore request that olaparib is removed as a relevant comparator from the NICE final scope for this evaluation.	inclusive. The most appropriate comparators will be discussed by the committee. In its evidence submission, the company should provide a clear rationale for excluding any comparators listed in the final scope.
	Astra Zeneca	AstraZeneca agree with the appropriateness of the proposed comparison versus standard endocrine therapy, and versus abemaciclib for the subgroup of patients with node positive disease at high risk of recurrence. However, we disagree that olaparib is a relevant comparator in this appraisal. Breast cancer patients who have BRCA1 or 2 mutations and a high risk of recurrence would be expected to receive treatment with a PARP inhibitor, as this is the only available treatment specifically designed to target the underlying genetic driver of their disease via synthetic lethality.(1) Based on insights from the clinical literature, as well as discussions with clinical experts, it is therefore not expected that CDK4/6 inhibitors would displace the use of PARP inhibitors in UK clinical practice;(2) such a comparison is therefore not relevant to the decision problem.	NICE keeps the comparators list inclusive. The most appropriate comparators will be discussed by the committee. In its evidence submission, the company should provide a clear rationale for excluding any comparators listed in the final scope.

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		Furthermore, if such a comparison were to be explored, due consideration would need to be given to important differences between the patient populations enrolled in the pivotal OlympiA and NATALEE trials, which may impact the feasibility and reliability of any such analyses. It would be important to consider: 1. Currently this comparison is proposed for patients with BRCA 1 or 2 mutations. However, olaparib is only approved for patients at high risk of recurrence,(3) therefore the only subgroup for which this comparison could be considered is “for people with BRCA1 or 2 mutations at high risk of recurrence”. 2. The recurrence risk profile of patients enrolled in the respective pivotal trials differed significant, with OlympiA exclusively enrolling high-risk patients,(4) while the NATALEE trial enrolled a broader population with a mixed risk profile.(5) The eligibility criteria for the OlympiA and NATALEE trials included different prognostic indicators and different thresholds by which to gauge recurrence risk, which would add complexity to any comparative analyses, and require significant adjustment for underlying patient characteristics. 3. It is unclear from publicly available data sources whether BRCA status was assessed as part of the NATALEE trial. BRCA mutation status can impact long-term prognosis and response to current treatment options,(6-8) and therefore ought to be considered as part of any comparative analyses. In conclusion, such a comparison is not relevant to this decision problem, and if explored, would likely be subject to significant methodological challenges which would create uncertainty and limit the reliability of any conclusions drawn on the relative efficacy of these therapies.	

Section	Consultee/ Commentator	Comments [sic]	Action
		1. Turk AA, Wisinski KB. PARP inhibitors in breast cancer: Bringing synthetic lethality to the bedside. Cancer. 2018 Jun 15;124(12):2498-2506. doi: 10.1002/cncr.31307. Epub 2018 Apr 16. PMID: 29660759; PMCID: PMC5990439. 2. Tung, N., Garber, J.E. PARP inhibition in breast cancer: progress made and future hopes. npj Breast Cancer 8, 47 (2022). https://doi.org/10.1038/s41523-022-00411-3 3. National Institute for Health and Care Excellence. TA886. Olaparib for adjuvant treatment of BRCA mutation-positive HER2-negative high-risk early breast cancer after chemotherapy. 10 May 2023. https://www.nice.org.uk/guidance/ta886 4. Tutt ANJ et al. Adjuvant Olaparib for Patients with BRCA1- or BRCA2-Mutated Breast Cancer. N Engl J Med. 2021 Jun 24;384(25):2394-2405. doi: 10.1056/NEJMoa2105215. Epub 2021 Jun 3. PMID: 34081848; PMCID: PMC9126186. 5. Slamon DJ et al. Rationale and trial design of NATALEE: a Phase III trial of adjuvant ribociclib + endocrine therapy versus endocrine therapy alone in patients with HR+/HER2- early breast cancer. Ther Adv Med Oncol. 2023 May 29;15:17588359231178125. doi: 10.1177/17588359231178125. PMID: 37275963; PMCID: PMC10233570. 6. Fasching PA. Breast cancer in young women: do BRCA1 or BRCA2 mutations matter? Lancet Oncol. 2018 Feb;19(2):150-151. doi:	

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		10.1016/S1470-2045(18)30008-1. Epub 2018 Jan 11. PMID: 29337093. 7. Mylavarapu S, Das A, Roy M. Role of BRCA Mutations in the Modulation of Response to Platinum Therapy. Front Oncol. 2018 Feb 5;8:16. doi: 10.3389/fonc.2018.00016. PMID: 29459887; PMCID: PMC5807680. 8. Song Y, Barry WT, Seah DS, Tung NM, Garber JE, Lin NU. Patterns of recurrence and metastasis in BRCA1/BRCA2-associated breast cancers. Cancer. 2020 Jan 15;126(2):271-280. doi: 10.1002/cncr.32540. Epub 2019 Oct 3. PMID: 31581314; PMCID: PMC7003745.	
	Eli Lilly	Comparators are appropriate. It is expected the definition of high-risk of disease recurrence is aligned to the recommendations made in NICE technology appraisal 810 for abemaciclib with endocrine therapy for adjuvant treatment of hormone receptor-positive, HER2-negative, node-positive early breast cancer at high risk of recurrence.	Thank you for your comment. The appraisal committee can consider the definition of high-risk used in clinical practice during the appraisal.
Outcomes	Breast Cancer Now	It is important to note that given this appraisal is looking at a treatment for early stage disease, as is common there is not currently mature overall survival data for this treatment.	Thank you for your comments. The appraisal committee will consider the maturity of the data and any associated uncertainties during the appraisal.

Section	Consultee/ Commentator	Comments [sic]	Action
	Novartis	The outcomes listed are considered appropriate.	Thank you for your comment. No action required.
	Astra Zeneca	No comments	No action required.
	Eli Lilly	N/A	No action required.
Equality	Breast Cancer Now	We have not identified any issues specific to this appraisal.	Thank you for your comment. No action required.
	Novartis	There are not considered to be any equality concerns related to this appraisal.	Thank you for your comment. No action required.
	Astra Zeneca	No comments	No action required.
	Eli Lilly	N/A	No action required.
Other considerations	Breast Cancer Now	N/A	No action required.
	Novartis	No comment.	No action required.
	Astra Zeneca	No comments	No action required.
	Eli Lilly	N/A	No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
Questions for consultation	Breast Cancer Now	N/A	No action required.
	Novartis	Have all relevant comparators for ribociclib been included in the scope? Please see previous comments in the Comparator section. Are the suggested subgroups appropriate for consideration? Please see previous comments in the Subgroup section. Would ribociclib be a candidate for managed access? Ribociclib may potentially be a candidate for managed access as later data cuts from the NATALEE trial are planned for 2025 and 2027. These later data cuts could reduce uncertainty in the decision problem by providing more mature data, particularly for invasive disease-free survival (iDFS).	See above responses. Comments on managed access noted; if appropriate the committee may consider the potential for managed access during the appraisal.
	Astra Zeneca	No comments	No action required.
	Eli Lilly	N/A	No action required.
Additional comments on the draft scope	Breast Cancer Now	None	No action required.
	Novartis	No further comments.	No action required.
	Astra Zeneca	N/A	No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
	Eli Lilly	N/A	No action required.

The following stakeholders indicated that they had no comments on the draft remit and/or the draft scope

N/A