NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

Ribociclib with an aromatase inhibitor for adjuvant treatment of hormone receptor-positive HER2-negative early breast cancer at high risk of recurrence

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using ribociclib plus an aromatase inhibitor in the NHS in England. The evaluation committee has considered the evidence submitted by the company and the views of non-company stakeholders, clinical experts and patient experts.

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

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

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

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

After consultation:

- The evaluation committee will meet again to consider the evidence, this evaluation consultation document and comments from the stakeholders.
- At that meeting, the committee will also consider comments made by people who are not stakeholders.

Issue date: April 2025

- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using ribociclib plus an aromatase inhibitor in the NHS in England.

For further details, see NICE's manual on health technology evaluation.

The key dates for this evaluation are:

- Closing date for comments: 15 May 2025
- Second evaluation committee meeting: 03 June 2025
- Details of membership of the evaluation committee are given in section 4.

1 Recommendations

1.1 Ribociclib with an aromatase inhibitor can be used as an option for the adjuvant treatment of hormone receptor-positive, HER2-negative, early breast cancer at high risk of recurrence in adults. It can only be used if the cancer is lymph-node positive and present in:

- at least 4 axillary lymph nodes, or
- 1 to 3 axillary lymph nodes and the cancer:
  - is grade 3, defined as at least 8 points on the modified Bloom–Richardson grading system or equivalent, or
  - has a primary tumour size of at least 5 cm.

It is recommended only if the company provides it according to the commercial arrangement (see section 2).

1.2 For women in pre- or perimenopause, and men, combine the aromatase inhibitor with a luteinising hormone-releasing hormone (LHRH) agonist

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

What this means in practice

Ribociclib with an aromatase inhibitor must be funded in the NHS in England for the adjuvant treatment of hormone receptor-positive, HER2-negative, early breast cancer at high risk of recurrence in adults, only if the cancer is lymph node positive and present in:

- at least 4 axillary lymph nodes, or

- 1 to 3 axillary lymph nodes and the cancer:
  - is grade 3, defined as at least 8 points on the modified Bloom–Richardson grading system or equivalent, or
  - has a primary tumour size of at least 5 cm.

It must be funded in England within 90 days of final publication of this guidance.

There is enough evidence to show that ribociclib with an aromatase inhibitor provides benefits and value for money, so it can be used routinely across the NHS in this population.

Why the committee made these recommendations

Adjuvant treatment aims to reduce the risk of cancer returning after surgery. Usual treatment for hormone receptor-positive, HER2-negative, early breast cancer at high risk of recurrence includes adjuvant endocrine treatment, such as aromatase inhibitors. Abemaciclib plus endocrine treatment is also an option if the cancer meets the criteria in section 1.1.

Results from a clinical trial suggest that, compared with an aromatase inhibitor alone, ribociclib plus an aromatase inhibitor may increase how long people have before their cancer returns. But this is uncertain. It is also unclear whether ribociclib plus an aromatase inhibitor increases how long people live, because the trial is ongoing.

Ribociclib plus an aromatase inhibitor has not been directly compared in a clinical trial with abemaciclib plus endocrine treatment. But results from an indirect comparison suggest that they work as well as each other.

When abemaciclib plus endocrine treatment is not an option, there is not enough evidence to show cost effectiveness of ribociclib plus an aromatase inhibitor compared with endocrine treatment alone. This is because there is no long-term evidence and there are uncertainties about some assumptions used in the economic model. So, ribociclib plus an aromatase inhibitor should not be used in this population.

When abemaciclib plus endocrine treatment is an option, the evidence shows ribociclib plus an aromatase inhibitor is a cost-effective use of NHS resources, compared with abemaciclib plus endocrine treatment or endocrine treatment alone. So ribociclib plus an aromatase inhibitor can be used in this population.

2 Information about ribociclib

Marketing authorisation indication

2.1 Ribociclib (Kisqali, Novartis) 'in combination with an aromatase inhibitor is indicated for the adjuvant treatment of patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative early breast cancer at high risk of recurrence. In pre- or perimenopausal women, or in men, the aromatase inhibitor should be combined with a luteinising hormone-releasing hormone (LHRH) agonist'.

Dosage in the marketing authorisation

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

Price

2.3 The list prices of ribociclib 200-mg tablets are:

- £983.33 per 21-pack
- £1,966.67 per 42-pack
- £2,950.00 per 63-pack

(excluding VAT; BNF online, accessed March 2025).

2.4 The company has a simple patient access scheme. This makes ribociclib available to the NHS with a discount. The size of the discount is commercial in confidence.

Carbon Reduction Plan

2.5 Information on the Carbon Reduction Plan for UK carbon emissions for Novartis will be included here when guidance is published.

3 Committee discussion

The evaluation committee considered evidence submitted by Novartis and a review of this submission by the external assessment group (EAG). See the committee papers for full details of the evidence.

The condition

Details of condition and unmet need

3.1 Breast cancer is the most common cancer in the UK. Hormone receptor-positive HER2-negative breast cancer is the most common subtype, accounting for about 68% of all breast cancers. The patient experts explained that hormone receptor-positive, HER2-negative early-stage breast cancer at high risk of recurrence has a considerable impact on quality of life. Initial diagnosis is distressing, and the fear of the cancer returning is a common cause of stress and anxiety for people and their families, affecting physical and psychological wellbeing, which can last many years. This is because of the need to have further treatment or the possibility of progression to incurable metastatic cancer. The clinical experts noted that early breast cancer relapses after initial treatment in about 30% of people. They noted that the risk of recurrence is higher with certain clinical and pathological risk factors such as a high number of positive lymph nodes, large tumour size, or high cellular proliferation measured by tumour grade or biomarkers. The patient and clinical experts agreed that a choice of targeted therapies that reduce the risk of recurrence would be valued. The committee concluded that people with hormone receptor-positive, HER2-negative, early breast cancer at high risk of recurrence, and their families, would welcome a new effective treatment option that reduces the risk of recurrence.

Unmet need

3.2 The patient and clinical experts explained that treatment for early breast cancer aims to cure it and reduce or delay the risk of recurrence, while providing a good quality of life. They explained that the treatment options are limited and have unpleasant side effects. The patient experts explained that people with a high risk of recurrence after surgery have a significant unmet need. They explained that this is because the treatment landscape has not changed over the last 30 years for people at high risk of recurrence who cannot have abemaciclib plus endocrine treatment. They explained that having different options is particularly important because people often choose treatments based on their side-effect profiles. The patient and clinical experts agreed that, because ribociclib is an oral treatment, it may be more convenient than other treatments, which may support adherence. The committee concluded that there is an unmet need for effective treatments and that people with the condition, particularly those who cannot have current treatments, and their families, would welcome an additional treatment option.

Clinical management

Treatment options and comparators

3.3 Adjuvant treatments after surgery of the primary breast cancer are prescribed based on prognostic factors as well as the risks and benefits of treatment. The clinical experts explained that most people whose cancer is at high risk of recurrence are first offered adjuvant chemotherapy. They explained that adjuvant endocrine treatment is then offered for 5 to 10 years based on menopausal status, risk of recurrence, and tolerance to medication. Some people may have tamoxifen, including women who have not reached menopause and men. Other people and women who have gone through menopause who are at medium or high risk of recurrence have aromatase inhibitors such as letrozole, anastrozole and exemestane. The clinical experts explained that bisphosphonates can

also be offered as an off-label add-on to adjuvant aromatase inhibitors for some women after menopause. Some people who have hormone receptor-positive, HER2-negative, lymph-node positive, early breast cancer at high risk of recurrence can have abemaciclib plus endocrine treatment (see NICE's technology appraisal guidance on abemaciclib with endocrine therapy). The clinical experts noted that in clinical practice, some people are at significant risk of recurrence and death but their cancer does not meet the eligibility criteria for abemaciclib plus endocrine treatment. So, their access to effective treatment is limited. But ribociclib plus an aromatase inhibitor may provide them with an alternative option. The committee noted that the choice of treatment is based on several factors. These factors include risk of recurrence, menopausal status, node involvement, the individual's health, and patient and clinician choice. The committee noted that standard care for hormone receptor-positive, HER2-negative early-stage breast cancer at high risk of recurrence is endocrine treatment and for some people whose cancer is lymph-node positive, abemaciclib plus endocrine treatment. It recognised that ribociclib plus an aromatase inhibitor may provide an additional choice for people with hormone receptor-positive, HER2-negative, early-stage breast cancer at high risk of recurrence, particularly for people whose cancer does not meet the eligibility criteria for abemaciclib plus endocrine treatment. The committee concluded that the appropriate comparators are endocrine treatment alone and, for some people whose cancer is lymph-node positive, abemaciclib plus endocrine treatment.

Clinical effectiveness

NATALEE results

3.4 NATALEE is an open-label, multicentre, randomised, phase 3 clinical trial comparing ribociclib plus an aromatase inhibitor with an aromatase inhibitor alone. The primary outcome is invasive disease-free survival (iDFS). Key secondary outcomes include recurrence-free survival, distant

disease-free survival (DDFS) and overall survival (OS). NATALEE enrolled 5,101 people with lymph-node negative or lymph-node positive, hormone receptor-positive, HER2-negative early breast cancer at high risk of recurrence. A total of 2,549 people had ribociclib plus an aromatase inhibitor and 2,552 had an aromatase inhibitor only. The results from the latest data cut in April 2024 showed a statistically significant improvement in iDFS in the ribociclib plus an aromatase inhibitor arm compared with the aromatase inhibitor-alone arm (hazard ratio [HR] 0.715, 95% confidence interval [CI] 0.609 to 0.840; p<0.0001). The results did not show a statistically significant difference in OS between the 2 arms (HR 0.827, 95% CI 0.636 to 1.074; p=0.0766). But the committee noted that at the April 2024 data cut, only 10.3% of iDFS events had occurred in the ribociclib plus an aromatase inhibitor arm and only 13.3% in the aromatase inhibitor arm. The committee concluded that because of the small number of events the clinical effectiveness results were highly uncertain, and this created further important uncertainties in the cost-effectiveness analyses. The committee acknowledged that the iDFS data was still relatively immature and that further follow up with more mature data was needed to fully assess the clinical benefits of ribociclib plus an aromatase inhibitor, including the predictions of longer-term outcomes.

Relevant population

3.5 The company's trial population (NATALEE) included people with hormone receptor-positive, HER2-negative early breast cancer at high risk of recurrence after primary breast tumour surgery. The committee noted that the company's trial population was in line with the marketing authorisation. But it included 5 subpopulations of people with hormone receptor-positive, HER2-negative early breast cancer at high risk of recurrence:

- population 1: people with lymph-node negative or lymph-node positive, hormone receptor-positive, HER2-negative early breast cancer at high risk of recurrence. This is the NATALEE ITT (intention-to-treat)

population and includes people with cancer for which abemaciclib plus endocrine treatment is an option and those for who it is not

- population 2: people with lymph-node positive cancer (which includes cancers for which abemaciclib plus endocrine treatment is an option and abemaciclib plus endocrine treatment is not an option)
- population 3: people with lymph-node negative cancer (for which abemaciclib plus endocrine treatment is not an option)
- population 4: people with cancer for which abemaciclib plus endocrine treatment is an option (which includes lymph-node positive cancer only)
- population 5: people with cancer for which abemaciclib plus endocrine treatment is not an option (which includes lymph-node negative or lymph-node positive cancer).

The committee noted that populations 1, 4, and 5 were most relevant for the evaluation. The EAG advised that focusing on the NATALEE ITT population (population 1) was challenging because NATALEE included people with cancer for which abemaciclib plus endocrine treatment was an option and also cancer for which it was not an option. But NATALEE only compared ribociclib plus an aromatase inhibitor with an aromatase inhibitor alone. The EAG explained most people in NHS clinical practice who are eligible for abemaciclib plus endocrine treatment would have it, instead of having endocrine treatment alone. The EAG advised that populations 4 and 5 were most representative of the NHS population because they included people with cancer for which abemaciclib plus endocrine treatment is an option (population 4) and was not an option (population 5). The committee noted that population 4 represented a population of people with cancer for which abemaciclib plus endocrine treatment is an option, as outlined in NICE Technology Appraisal Guidance TA810. That is, lymph-node positive with at least 4 axillary lymph nodes, or 1 to 3 axillary lymph nodes, and when there is grade 3 disease or a primary tumour size of at least 5 cm. The committee noted that population 5 includes all other people eligible for ribociclib plus an

aromatase inhibitor, excluding those in population 4. The EAG noted that the company provided the clinical evidence for all relevant populations, but did not provide the cost-effectiveness results for population 5. So, the EAG used the NATALEE ITT population (population 1) as a proxy to generate cost-effectiveness results for population 5. The committee questioned the face validity of using population 1 clinical data to produce cost-effectiveness results for population 5. The company explained that based on the NATALEE data, the efficacy of ribociclib plus an aromatase inhibitor compared with an aromatase inhibitor alone was the same irrespective of eligibility for abemaciclib plus endocrine treatment, and population 5 was not prespecified in NATALEE. The clinical experts highlighted the uncertainty of using one population's clinical evidence as a proxy for another. They questioned its relevance to hazard ratios, long-term outcomes and risk of recurrence. They explained that people with more node involvement have a higher risk of recurrence, while people with less node involvement tend to have a long-term reduced risk of recurrence. The committee noted that the outcomes may vary between populations in clinical practice. It agreed that people with cancer for which abemaciclib plus endocrine treatment is an option should be considered separately from people in which it is not an option. It concluded that it was necessary to see the cost-effectiveness results generated using population 5 data to inform decision making for people with cancer for which abemaciclib plus endocrine treatment is not an option.

NATALEE comparator data

3.6 The comparators in the NICE scope for people with hormone receptor-positive, HER2-negative early breast cancer were endocrine treatment alone and, for some people with lymph-node positive disease, abemaciclib plus endocrine treatment. The committee noted that the only endocrine treatments included as a comparator in NATALEE were the aromatase inhibitors, letrozole and anastrozole. The committee noted that in clinical practice, people with cancer for which abemaciclib plus

endocrine treatment is not an option have endocrine treatment alone. This includes anastrozole, letrozole, exemestane and tamoxifen. The clinical experts explained that letrozole and anastrozole are the most common aromatase inhibitors used in clinical practice. But when letrozole and anastrozole are not tolerated, exemestane is usually offered. Tamoxifen is generally used for people with a low risk of recurrence. They advised that letrozole, anastrozole and exemestane are clinically equivalent because they have similar clinical effectiveness, although they have different tolerability. The committee noted that letrozole and anastrozole are the most frequently used aromatase inhibitors in clinical practice. It concluded that the NATALEE comparator arm was generalisable to people having endocrine treatment in clinical practice.

Outcomes

3.7 The committee noted that iDFS was the primary endpoint of NATALEE and was used to inform the economic modelling. The company considered iDFS to be a clinically meaningful surrogate endpoint for OS because disease recurrence is associated with breast cancer mortality. It explained that any observed improvements in iDFS are anticipated, in the long term, to translate into improvements in OS. But the clinical advice to the EAG suggested that DDFS is a more appropriate proxy for OS than iDFS. The clinical experts advised that both iDFS and DDFS have limitations. They explained that iDFS includes any invasive recurrence, second primary cancers or deaths. iDFS tends to capture many different events, which can reduce the true treatment effect. While, DDFS focuses only on cancer spreading to distant parts of the body or death. These events are more likely to lead to death, making DDFS a good indicator of long-term outcome, but it may miss some local recurrences. The committee noted that both iDFS and DDFS have limitations, and it broadly accepted that evidence from iDFS was informative for decision making.

Indirect treatment comparison

3.8 There was no head-to-head data available that compared ribociclib plus an aromatase inhibitor with abemaciclib plus endocrine treatment. So, for people with hormone receptor-positive, lymph-node positive, HER2-negative, early breast cancer whose cancer is at high risk of recurrence and abemaciclib plus endocrine treatment is an option, the company did matching-adjusted indirect treatment comparisons (MAICs) comparing the clinical effectiveness of ribociclib plus an aromatase inhibitor with abemaciclib plus endocrine treatment and endocrine treatment alone. This was based on clinical effectiveness data from the monarchE trial, which compared abemaciclib plus endocrine treatment with endocrine treatment alone in people with cancer for which abemaciclib was an option. For the comparison of ribociclib plus an aromatase inhibitor with abemaciclib plus endocrine treatment, the company selected people in the NATALEE ribociclib plus an aromatase inhibitor and aromatase inhibitor-alone arms who met the monarchE inclusion criteria. It weighted the ribociclib plus an aromatase inhibitor individual patient data from NATALEE to match the monarchE abemaciclib plus endocrine treatment arm baseline characteristics. For the comparison of ribociclib plus an aromatase inhibitor with endocrine treatment alone, the company selected people in the NATALEE ribociclib plus an aromatase inhibitor and aromatase inhibitor-alone arms who met the monarchE inclusion criteria and then weighted them to match the monarchE abemaciclib plus endocrine treatment and endocrine treatment alone arms, respectively. The EAG explained that the comparison of ribociclib plus an aromatase inhibitor with endocrine treatment alone that the company did was not based on an indirect comparison, but instead a re-weighted NATALEE individual patient data analysis. The EAG explained that this is because it only uses outcome data from NATALEE. It also noted that reweighting the population reduced the effective sample size significantly. The EAG advised that the results of the company's MAIC were biased and uncertain. During clarification, at the EAG's request, the company provided simulated treatment comparisons for iDFS, DDFS and OS to

compare ribociclib plus an aromatase inhibitor with abemaciclib plus endocrine treatment. The committee noted that the company's iDFS simulated treatment comparison and MAIC results were consistent, but that the OS MAIC and simulated treatment comparisons provided inconsistent results. The simulated treatment comparison and MAIC results are confidential and cannot be reported here. The committee noted that, based on MAIC results, the company assumed equal efficacy between ribociclib plus an aromatase inhibitor and abemaciclib plus endocrine treatment. The clinical experts highlighted that both ribociclib and abemaciclib are available for metastatic breast cancer. They explained that in metastatic cancer, ribociclib and abemaciclib have similar efficacy in terms of response rates and progression-free survival (PFS) but have different side effects. They explained that they would also expect ribociclib and abemaciclib to be broadly equivalent in the adjuvant setting. The committee noted that the clinical experts broadly agreed with the company's equal-efficacy assumption. The committee concluded that ribociclib plus an aromatase inhibitor and abemaciclib plus endocrine treatment were likely to have similar efficacy in the adjuvant setting.

Economic model

Company's modelling approach

3.9 The company presented a semi-Markov model with a partitioned-survival submodel for distant recurrence health states. The model comprised 6 mutually exclusive health states: iDFS, second primary malignancy (SPM), non-metastatic recurrence (NMR), remission, distant recurrence (DR), and death. The iDFS health state was split into 2 mutually exclusive sub-states: on-treatment and off-treatment. The DR health state was split into 2 mutually exclusive sub-states: endocrine treatment (ET)-resistant and ET-sensitive. The EAG explained that people enter the model in the iDFS state and may transition to the other states. Once in the SPM or death states, no further transitions occur. It explained that the company

model used a partitioned-survival submodel to estimate outcomes in the DR health state. It explained that because of the partitioned-survival submodel, it was unable to validate OS directly from the model, because a pay-off approach was used to calculate life years gained in the DR health state. People who have transitioned to the SPM health state exit the model without death, and so are not included in the life-years calculation. The clinical experts broadly agreed that the company's model structure appropriately captured all the relevant health states. The committee noted that the model assumed equal effectiveness of ribociclib plus an aromatase inhibitor and abemaciclib plus endocrine treatment except for adverse events, based on the indirect treatment comparison. It noted that the EAG considered that the model underestimated the cost of adverse events and preferred to use unit costs based on the severity of the grade 3 or greater adverse events, which the committee accepted. The committee concluded that the model structure was appropriate for decision making.

iDFS extrapolations

3.10 To estimate iDFS beyond the observed NATALEE data, the company explored various parametric distributions and applied them to the iDFS data from the NATALEE Kaplan–Meier curve. Based on appropriateness of visual and statistical goodness-of-fit, and clinical expert opinion, the company selected the exponential distribution for ribociclib plus an aromatase inhibitor, abemaciclib plus endocrine treatment and endocrine treatment alone. The company explained that all parametric distributions suggested comparable validity against Kaplan–Meier data, with similar AIC (Akaike Information Criterion) and BIC (Bayesian Information Criterion) values. But it explained that their long-term extrapolation varied substantially beyond the trial data. The EAG explained that to try and validate the extrapolations, it did a literature search and identified Martin et al. 2023. It noted that Martin et al. reported 5- and 10-year iDFS estimates for people who had endocrine treatment at 75.2% and 57.0%,

respectively. It explained that the company's estimates were similar. The committee acknowledged important limitations associated with long-term extrapolations, because only 10.3% of iDFS events were observed in the NATALEE ITT population (see section 3.4). It decided that all the extrapolations were highly uncertain because of the immaturity of the observed data. The committee noted it had not seen results exploring any alternative extrapolations. In the absence of other extrapolations, the committee considered the exponential extrapolation in its decision making, but the long-term iDFS extrapolation was highly uncertain. The committee decided that it needed to see more evidence exploring alternative iDFS extrapolations, including less optimistic ones. It noted that additional data collection is likely to be needed to address this uncertainty and inform the most appropriate extrapolation.

Treatment-effect waning

3.11 The committee noted that the company's model implemented a full treatment effect for ribociclib plus an aromatase inhibitor that is maintained for 8 years. It also noted that the company's model implemented a treatment-waning effect lasting until the point at which iDFS reaches general population mortality. The company explained this was based on carry-over benefit seen in the ATAC (arimidex, tamoxifen, alone or in combination) trial. The EAG advised that the company's treatment-effect waning assumption was arbitrary and not supported by the evidence. The EAG said that the ATAC trial suggested that the risk of recurrence continued to be lower for people who had anastrozole compared with people who had tamoxifen even after treatment had finished. But it clarified that the size of the benefit began to decrease by 8 years. It also explained that ATAC did not include outcomes specific to cyclin-dependent kinase (CDK) 4 and 6 inhibitors. The committee noted that the treatment effect was modelled so that the hazard of recurrence for ribociclib plus an aromatase inhibitor in iDFS gradually and linearly converged with that of endocrine treatment alone over a specified waning

period. The committee noted that both the company and the EAG explored waning assumptions in scenario analyses, noting that this was one of the key drivers for the cost-effectiveness analyses. The clinical experts explained that there is no data to inform treatment waning for ribociclib plus an aromatase inhibitor but they would not anticipate a waning of the treatment effect. The committee noted that the treatment-effect waning for ribociclib plus an aromatase inhibitor that would be seen in clinical practice is highly uncertain. It concluded it would consider the company's approach to treatment waning in its decision making but it would like to see a wider range of treatment-waning scenarios and their impact on modelled long-term outcomes, particularly in the DR health state.

iDFS event distribution

3.12 The company's model assumed that proportions of iDFS event types, such as death, SPM, NMR, or DR, differ for ribociclib plus an aromatase inhibitor and endocrine treatment alone. But it assumed abemaciclib plus endocrine treatment to be the same as ribociclib plus an aromatase inhibitor. The EAG noted that in the NATALEE ITT population for each health state, the 95% CI overlapped substantially, indicating insufficient statistical evidence of a difference between iDFS event distributions based on treatment. The EAG explained it would have preferred that the iDFS event distributions were pooled across treatments, so that they were equal for all treatments. In the absence of pooled iDFS event proportion estimates, the EAG preferred to use the iDFS event proportions for all treatments to equal those for ribociclib plus an aromatase inhibitor. The EAG noted that even when the iDFS event distributions were equal across treatments, the transition probabilities remained different, which aligned with clinical advice. The committee questioned if there is any reason to expect different event distributions between treatments. The clinical experts explained that there is no clear evidence suggesting a difference in event distributions between the treatment groups. The committee

concluded that, given the lack of data, it is appropriate to assume that iDFS event proportions for all treatments are equal to those for ribociclib plus an aromatase inhibitor.

PFS and OS in the ET-resistant and ET-sensitive DR sub-state

3.13 The committee noted that the company model used a weighted basket of treatments to estimate PFS and OS in ET-resistant and ET-sensitive DR sub-states. The proportion of each treatment included in the basket varies depending on the adjuvant treatment. The company estimated PFS and OS for the treatment baskets by fitting parametric lognormal PFS and log-logistic OS curves for ribociclib plus fulvestrant (ET-resistant DR sub-state) or ribociclib plus non-steroidal aromatase inhibitor (ET-sensitive DR sub-state) to individual patient data from the MONALEESA-2 and 3 trials. Outcomes for other treatments in the basket were estimated by applying HRs to the modelled curves. The EAG highlighted that varying PFS and OS for baskets of treatments in the ET-resistant and ET-sensitive DR sub-states has a substantial impact on cost-effectiveness results for ribociclib plus an aromatase inhibitor compared with endocrine treatment alone. It explained that applying HRs to log-logistic OS and lognormal PFS curves was not appropriate because they are accelerated failure time parametric curves. It also noted that the long-term proportional hazard assumptions were not justified for ribociclib plus an aromatase inhibitor compared with the basket of treatments. So, it used exponential PFS and gamma OS curves in ET-sensitive DR sub-states, and exponential PFS and Weibull OS curves in ET-resistant DR sub-states based on clinical advice. The company explained that for the ET-resistant DR sub-state, the EAG's chosen curves appeared pessimistic because of the absence of a long tail. (There were few people alive beyond 10 years). The company clarified that for ET-sensitive DR sub-states, the company curves may be optimistic, and the EAG's curves aligned more closely to the company's clinical expert opinion. The clinical experts noted that there is substantial uncertainty because of limited long-term data, and they could not

determine which curves are more appropriate. The committee concluded that both the company's and the EAG's PFS and OS were subject to significant uncertainty because of a lack of long-term data, but it preferred to use the EAG's chosen curves because they were more aligned with clinical expert opinion.

Treatment mix

3.14 In the company model, people with ET-resistant and ET-sensitive cancer who have previously had a CDK 4 and 6 inhibitor and are CDK 4 and 6 inhibitor-sensitive may go on to have subsequent treatment with CDK 4 and 6 inhibitors. The company assumed that 30% of people whose cancer is ET-resistant and CDK 4 and 6 inhibitor-sensitive would have subsequent CDK 4 and 6 inhibitor treatment. This was based on clinical opinion that a lower proportion would be retreated than those who had adjuvant endocrine treatment alone. The company made an assumption about people with ET-sensitive CDK 4 and 6 inhibitor-sensitive cancer who had previously had a CDK 4 and 6 inhibitor. It assumed that 45% would be retreated with a CDK 4 and 6 inhibitor when entering the ET-sensitive DR sub-state. This was compared with 90% of people who had adjuvant ET. The EAG thought that the proportions used by the company were not in line with the clinical advice it received. For the ET-resistant and ET-sensitive sub-states, the EAG preferred to assume that 90% of people who had a CDK 4 and 6 inhibitor and are CDK 4 and 6 inhibitor-sensitive are retreated with a CDK 4 and 6 inhibitor. The NHS England Cancer Drugs Fund clinical lead (from here, the Cancer Drugs Fund lead) explained that in clinical practice, retreatment is allowed in metastatic cancer. They clarified that currently, people with metastatic breast cancer can have CDK 4 and 6 inhibitor retreatment. But this is only if there has been a 12-month treatment break from CDK 4 and 6 inhibitors or if they have had 2 years of adjuvant CDK 4 and 6 inhibitor therapy without disease progression. The Cancer Drugs Fund lead also noted that adjuvant abemaciclib plus endocrine treatment has only been available for

a short time and so the retreatment rate with a CDK 4 and 6 inhibitor in clinical practice is not known. The committee noted that there is limited evidence of retreatment with CDK 4 and 6 inhibitors. But it preferred to assume that 90% of people would have retreatment with CDK 4 and 6 inhibitors in the ET-sensitive and ET-resistant DR sub-state.

Utilities

3.15 In the company's model, health-related quality of life was accounted for by deriving utility values from EQ-5D-5L data collected in NATALEE. The company's model assumed equal progression-free utility values for ET-resistant and ET-sensitive DR sub-states but used lower utility values for ET-resistant progressed disease than ET-sensitive progressed disease. The company explained that ET-resistant disease is more aggressive than ET-sensitive, so a lower health-related quality of life would be expected for people with ET-resistant progressed disease. The utility values are considered confidential and cannot be reported here. The EAG explained that health-related quality of life differs between ET-resistant and ET-sensitive DR sub-states from the time of the disease relapse. So, it would expect a lower utility value for ET-resistant progression-free disease than ET-sensitive progression-free disease. So, the EAG preferred to use the NMR health-state utility value as the ET-sensitive progression-free utility value to differentiate between ET-sensitive and ET-resistant progression-free utilities. Progressed-disease utility values were calculated from MONALEESA-2 and 3 in the EAG base case. The clinical experts agreed that people with ET-resistant disease have much worse prognoses than ET-sensitive. The committee noted that the utility values used had a minimal impact on the cost-effectiveness results. It concluded that it was more appropriate to assume that ET-resistant progression-free disease would have a lower utility value than ET-sensitive. So, it concluded that the EAG's approach to estimating ET-sensitive progression-free utility value was more appropriate for decision making.

Severity

3.16 The company did not make a case to apply the severity modifier. NICE's methods on conditions with a high degree of severity did not apply.

Cost-effectiveness estimates

Acceptable ICER

3.17 NICE's manual on health technology evaluations notes that above a most plausible incremental cost-effectiveness ratio (ICER) of £20,000 per quality-adjusted life year (QALY) gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. But it will also take into account other aspects including uncaptured health benefits. The committee noted the high level of uncertainty associated with long-term iDFS and OS, treatment waning and retreatment with CDK 4 and 6 inhibitors. So, the committee concluded that an acceptable ICER would be around £20,000 per QALY gained.

Population for which abemaciclib is an option

3.18 The committee decided that it would consider people with cancer for which abemaciclib plus endocrine treatment is an option separately from people for which it is not (see section 3.5). For people with cancer for which abemaciclib plus endocrine therapy is an option, it considered the cost effectiveness of ribociclib plus an aromatase inhibitor compared with abemaciclib plus endocrine treatment and endocrine treatment alone. The exact results are commercial in confidence because they included confidential discounts for comparator or subsequent treatments. In both the company's and EAG's base case cost-effectiveness analyses, ribociclib plus an aromatase inhibitor was likely to be a cost-effective use of NHS resources compared with abemaciclib plus endocrine treatment. For the comparison of ribociclib plus an aromatase inhibitor with

endocrine treatment alone, deterministic and probabilistic ICERs were below £20,000 per QALY gained. The committee acknowledged important unresolved uncertainty, but taking into account the evidence and the nature of the population and comparators it decided that the level of uncertainty was manageable for this population. It concluded that the cost-effectiveness results were acceptable for decision making in people with cancer for which abemaciclib plus endocrine treatment is an option.

Population for which abemaciclib is not an option

3.19 The committee noted the company did not provide cost-effectiveness results for population 5, so the EAG used the NATALEE ITT population as a proxy to generate results for this population (see section 3.5). The committee noted that the company's and EAG's base-case ICERs for the comparison with endocrine treatment alone were within the range NICE normally considers a cost-effective use of NHS resources. But it also considered the important uncertainties affecting this population. In particular, it acknowledged the uncertainty associated with using a proxy population, and that the immaturity of the clinical evidence and associated uncertainties in the extrapolations were particularly important for this population and not fully explored by the company and the EAG. The committee concluded that the available cost-effectiveness estimates were not suitable for decision making in the context of a recommendation for routine use, because the clinical and economic evidence was too uncertain. So, ribociclib plus an aromatase inhibitor could not be recommended for routine use in the NHS for this population. The committee noted that managed access may provide the opportunity to collect additional data to address some uncertainties about the long-term clinical effectiveness of ribociclib plus an aromatase inhibitor (see section 3.24).

The committee's preferred assumptions

3.20 The committee's preferred assumptions were:

- CDK 4 and 6 inhibitor treatment effect is maintained for 8 years and treatment waning lasts until the point at which iDFS reaches general population mortality (see section 3.11)
- iDFS event distributions for endocrine treatment and abemaciclib plus endocrine treatment are equal to ribociclib plus an aromatase inhibitor (see section 3.12)
- exponential PFS and Gamma OS curves are used in ET-sensitive DR, and exponential PFS and Weibull OS curves are used in ET-resistant DR sub-states (see section 3.13)
- the proportion of people having retreatment with CDK 4 and 6 inhibitor therapy is 90% for both ET-sensitive and ET-resistant DR sub-states (see section 3.14)
- ET-sensitive progression-free utility values equal NMR utility values (see section 3.15)
- adverse events (grade ≥3) are graded according to severity (see section 3.9).

The committee's additional requests

3.21 To address the substantial remaining uncertainty, the committee requested the following additional analyses:

- cost-effectiveness results generated using population 5 data
- a wider range of treatment-waning scenarios, including exploration of the impact of these scenarios on modelled long-term outcomes, particularly in the DR health state
- more evidence exploring alternative iDFS extrapolations, including less optimistic ones, to generate cost-effectiveness results using population 5 data and scenarios around treatment waning.

Equality

3.22 No equality issues were raised by the company, EAG or stakeholders. The committee did not identify any equality issues.

Uncaptured benefits

3.23 The committee considered whether there were any uncaptured benefits of ribociclib plus an aromatase inhibitor. It noted that the clinical experts had said that the indirect comparison and the QALY calculation may not capture the urgency of diarrhoea experienced by some people as a side effect of abemaciclib plus endocrine treatment. The committee noted that grade 3 or greater treatment emergent adverse events including diarrhoea were included in the model. It did not identify any additional benefits not captured in the economic modelling. So, the committee concluded that all benefits of ribociclib plus an aromatase inhibitor had already been taken into account.

Conclusion

Recommendation

3.24 The committee took into account its preferred assumptions and its acceptable ICER. For people with cancer for which abemaciclib plus endocrine treatment is an option (that is, lymph-node positive disease with at least 4 axillary lymph nodes, or 1 to 3 axillary lymph nodes and grade 3 disease or a primary tumour size of at least 5 cm), using the committee's preferred assumptions, ribociclib plus an aromatase inhibitor is likely to be a cost-effective use of NHS resources, compared with abemaciclib plus endocrine treatment or endocrine treatment alone. For people with cancer for which abemaciclib plus endocrine treatment is not an option, the committee concluded that the available cost-effectiveness estimates were not suitable for decision making in the context of a recommendation for routine use, because of important uncertainties in the evidence. It requested further evidence. The committee concluded that ribociclib plus an aromatase inhibitor can be used as an option for the adjuvant treatment of hormone receptor-positive, HER2-negative, early breast cancer at high risk of recurrence in adults only if the cancer is lymph-node

positive with at least 4 axillary lymph nodes, or 1 to 3 axillary lymph nodes and grade 3 disease or a primary tumour size of at least 5 cm.

Managed access

3.25 Having concluded that ribociclib plus an aromatase inhibitor could not be recommended for routine use in the NHS for people with cancer for which abemaciclib plus endocrine treatment is not an option, the committee considered whether it could be recommended with managed access. It decided that for this population, ribociclib plus an aromatase inhibitor could be a promising new medicine, with potential resolvable uncertainty, and may be a candidate for managed access. It noted that further evidence collection in NATALEE could have the potential to address the uncertainties associated with the immature data. But the committee understood that the company had not made a managed access proposal for ribociclib plus an aromatase inhibitor. The committee was unable to assess whether evidence that could be collected in managed access would resolve the uncertainties. So, the committee was unable to make a recommendation for managed access for this population.

4 Implementation

4.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 90 days of its date of publication.

4.2 Chapter 2 of Appraisal and funding of cancer drugs from July 2016 (including the new Cancer Drugs Fund) – A new deal for patients, taxpayers and industry states that for those drugs with a draft recommendation for routine commissioning, interim funding will be available (from the overall Cancer Drugs Fund budget) from the point of

marketing authorisation, or from release of positive draft guidance, whichever is later. Interim funding will end 90 days after positive final guidance is published (or 30 days in the case of drugs with an Early Access to Medicines Scheme designation or cost comparison evaluation), at which point funding will switch to routine commissioning budgets. The NHS England Cancer Drugs Fund list provides up-to-date information on all cancer treatments recommended by NICE since 2016. This includes whether they have received a marketing authorisation and been launched in the UK.

4.3 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 60 days of the first publication of the final draft guidance.

4.4 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has hormone receptor-positive, HER2-negative, early breast cancer at high risk of recurrence and the healthcare professional responsible for their care thinks that ribociclib is the right treatment, it should be available for use, in line with NICE's recommendations

5 Evaluation committee members and NICE project team

Evaluation committee members

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

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

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

Chair

Radha Todd

Chair, technology appraisal committee A

NICE project team

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

Harsimran Sarpal

Technical lead

Nigel Gumbleton

Technical adviser

Greg OToole

Project manager

Ian Watson

Associate director

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