

**NATIONAL INSTITUTE FOR HEALTH AND CARE
EXCELLENCE**

Final appraisal document

**Ribociclib with fulvestrant for treating hormone
receptor-positive, HER2-negative, advanced
breast cancer**

1 Recommendations

1.1 Ribociclib with fulvestrant is recommended for use within the Cancer Drugs Fund as an option for treating hormone receptor-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer in people who have had previous endocrine therapy only if:

- exemestane plus everolimus is the most appropriate alternative to a cyclin-dependent kinase 4 and 6 (CDK 4/6) inhibitor and
- the conditions in the managed access agreement for ribociclib with fulvestrant are followed.

1.2 This recommendation is not intended to affect treatment with ribociclib with fulvestrant 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 clinician consider it appropriate to stop.

Why the committee made these recommendations

During technical engagement it was agreed that the appraisal will focus on people whose disease has progressed up to 12 months after neoadjuvant endocrine therapy

or after 1 line of endocrine therapy for advanced disease. The main alternative for this population is exemestane with everolimus.

Clinical trial evidence suggests that, compared with fulvestrant alone, ribociclib with fulvestrant increases the length of time before the disease progresses in people who have had previous endocrine treatment. It's not known whether ribociclib increases the length of time people live because the final trial results are not available yet. The results of an indirect comparison of ribociclib and fulvestrant with exemestane and everolimus are very uncertain.

The cost-effectiveness estimates are also very uncertain, and are above the range NICE normally considers an acceptable use of NHS resources. Therefore, ribociclib with fulvestrant cannot be recommended for routine use in the NHS.

Ribociclib with fulvestrant has the potential to be cost effective for the population considered in this appraisal, but more data are needed to resolve the uncertainties in the clinical evidence. Therefore, ribociclib with fulvestrant is recommended for this population in the Cancer Drugs Fund while these data are collected.

2 Information about ribociclib

Marketing authorisation	<p>Ribociclib (Kisqali, Novartis) is indicated for 'the treatment of women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer in combination with ... fulvestrant as initial endocrine-based therapy, or in women who have received prior endocrine therapy.</p> <p>In pre- or perimenopausal women, the endocrine therapy should be combined with a luteinising hormone-releasing hormone agonist'.</p>
Dosage in the marketing authorisation	<p>The recommended dose is 600 mg (3 × 200 mg), taken orally, once daily for 21 consecutive days, followed by 7 days off treatment (28-day cycle). Treatment should be continued as long as the patient is having clinical benefit from therapy or until unacceptable toxicity happens.</p> <p>Management of severe or intolerable adverse drug reactions may need temporary dose interruption, reduction or discontinuation of Kisqali.</p>
Price	<p>£2,950 for a 63-tablet pack of 200 mg tablets (excluding VAT; British national formulary online, accessed March 2019).</p> <p>The company has a commercial arrangement (managed access agreement including a patient access scheme and a commercial access agreement). This makes ribociclib available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.</p>

3 Committee discussion

The appraisal committee (section 6) considered evidence submitted by Novartis, a review of this submission by the evidence review group (ERG), and the technical report developed through engagement with stakeholders and comments received on the appraisal consultation document. See the [committee papers](#) for full details of the evidence.

The appraisal committee was aware that several issues were resolved during technical engagement, and agreed that:

- Ribociclib with fulvestrant is likely to be used in endocrine-resistant disease. This includes disease that has progressed at or within 12 months after neoadjuvant endocrine therapy and disease that has progressed after 1 line of endocrine therapy in an advanced setting (referred to as the company's combined population B). Following technical engagement, it was agreed that this was the key population in the appraisal (issues 1, 3 and 5; see technical report pages 7 to 9, 11 to 14 and 18 to 20).
- Exemestane with everolimus is the key comparator for population B (issue 2; see technical report pages 9 to 11).

It recognised that there were remaining areas of uncertainty associated with the analyses presented (see technical report table 2; pages 35 to 36) and took these into account in its decision making. It discussed the following issues, which were outstanding after technical engagement.

Treatment pathway

People with advanced breast cancer would welcome a new treatment option

3.1 Advanced breast cancer is an incurable condition. Patient experts explained that people value improvements in progression-free survival and want to delay chemotherapy for as long as possible. First-line treatment for hormone receptor-positive, human epidermal growth factor receptor (HER2)-negative locally advanced or metastatic breast cancer is usually a CDK 4/6 inhibitor (palbociclib, ribociclib or abemaciclib) with an aromatase inhibitor (letrozole or anastrozole). If symptoms are severe or the disease is rapidly progressive, then chemotherapy may be needed in the first instance, and tamoxifen can also be offered to some people in line with NICE's guideline on [advanced breast cancer](#). The committee noted that since CDK 4/6 inhibitors have been recommended, the number of people being offered an aromatase inhibitor alone has been declining. However, there are people who have only previously had an aromatase inhibitor and so could have a CDK 4/6 inhibitor with fulvestrant as a second-line treatment. The committee concluded that a treatment that

would extend progression-free survival and delay the need for chemotherapy would be welcomed by people who have already had endocrine therapy.

Clinical evidence

Population B from the company submission is relevant to NHS clinical practice

3.2 MONALEESA-3 is a multicentre double-blind randomised placebo-controlled trial comparing ribociclib and fulvestrant with placebo and fulvestrant in adults with hormone receptor-positive, HER2-negative advanced breast cancer. It enrolled 726 postmenopausal women, and results were presented separately for a subgroup of patients who had had previous endocrine therapy (n=345). This subgroup was considered in the company's submission as population B. The committee agreed that population B was relevant to this appraisal, but noted that the MONALEESA-3 trial was not designed to have statistical power to detect treatment effects within subgroups. The committee concluded that this was a concern. However, it preferred this approach rather than the company's initial suggestion of further splitting population B into 2 subpopulations: 1 with disease that has progressed at or within 12 months after neoadjuvant endocrine therapy, and another with disease that has progressed after 1 line of endocrine therapy in the advanced setting.

Ribociclib with fulvestrant increases progression-free survival compared with fulvestrant alone but overall survival data are immature

3.3 The primary outcome measure of MONALEESA-3 was investigator-assessed progression-free survival. In the whole population, which included patients who had not had previous endocrine therapy, ribociclib with fulvestrant increased median progression-free survival compared with fulvestrant alone from 12.8 months to 20.5 months (hazard ratio [HR] 0.593; 95% confidence interval [CI] 0.480 to 0.732). Similar results were found for the subgroup relevant to this appraisal who had had previous

endocrine therapy (population B; HR 0.565; 95% CI 0.428 to 0.802). At the time of the analysis, overall survival data were immature. The company provided interim overall survival data for the trial population (the data are confidential and cannot be presented here), but not for population B. The committee agreed that the progression-free survival benefit from ribociclib with fulvestrant was promising, but the benefit on overall survival was unknown. The committee noted that the results came from a data cut in November 2017, and that an updated analysis is expected after completion of the study in 2020. The committee concluded that ribociclib with fulvestrant increased progression-free survival compared with fulvestrant alone in people who had had previous endocrine therapy, but that the effect on overall survival was currently unknown.

CDK 4/6 inhibitors

A class effect for CDK 4/6 inhibitors with fulvestrant is possible

3.4 The company noted that ribociclib with fulvestrant and abemaciclib with fulvestrant may have similar clinical effectiveness, so suggested that a class effect for CDK 4/6 could be considered. The clinical experts explained that CDK 4/6 inhibitors have similar clinical effectiveness, but highlighted that their adverse effect profiles are different. Ribociclib is associated with an increased incidence of neutropenia. Also, regular electrocardiogram (ECG) assessments and liver function tests are needed during treatment. Abemaciclib is associated with an increased incidence of diarrhoea. The committee agreed with the experts that a class effect for CDK 4/6 inhibitors with fulvestrant is possible. The patient expert stated that, although abemaciclib with fulvestrant is an option within the Cancer Drugs Fund, given the different side effect profiles of these drugs, people would value a range of treatment options to be available to them. The committee noted that no indirect comparison had been done to compare ribociclib plus fulvestrant with abemaciclib plus fulvestrant. However, it

acknowledged that ribociclib is an additional treatment option that may be preferred by some people.

Network meta-analysis: progression-free survival

The results of the network meta-analysis are uncertain

3.5 Because there is no evidence directly comparing ribociclib and fulvestrant with exemestane and everolimus, a network-meta-analysis was done. After technical engagement, the ERG updated the company's network meta-analysis for population B. The meta-analysis included 6 studies comparing progression-free survival across the treatments to allow a comparison between ribociclib with fulvestrant and exemestane with everolimus. No results were presented for overall survival. There were substantial differences in the baseline characteristics of the patients included in the studies. In some trials, patients could have had previous chemotherapy, or more than 1 previous endocrine therapy in the advanced setting and not all the trials were specific to HER2-negative disease. Also, the ERG highlighted that the proportional hazards assumption had not been met in the MONALEESA-3 trial, so using a hazard ratio dependent on this trial is likely to be unreliable. The committee agreed with the ERG and concluded that the results of the network meta-analysis were highly uncertain. It further noted that the effect of this uncertainty on the cost-effectiveness results was likely to be high, and that the direction of the effect was unknown.

Modelling of progression-free survival

Progression-free survival extrapolation is uncertain

3.6 After technical engagement, the company's original base case assumed a log-normal distribution for time to progression to extrapolate ribociclib and fulvestrant progression-free survival for population B. The ERG explained that the company's curves had potentially implausible extrapolations and suggested that a 3-knot spline had a better fit to the observed data and

more plausible extrapolation. The clinical experts acknowledged that the company's long-term extrapolation of progression-free survival seemed to be optimistic (results are confidential and cannot be presented here). However, they also acknowledged that there are some people who remain progression-free for longer than expected. The committee agreed that the company's model was too optimistic, although the ERG's model could have underestimated the number of people with progression-free disease at longer follow up. It agreed that, given the extent of the uncertainty in the clinical evidence, the ERG's extrapolation may have been more appropriate but, if pessimistic, may have overestimated the incremental cost-effectiveness ratios (ICERs). In its response to consultation, the company chose to use the ERG's 3-knot spline to extrapolate progression-free survival in its revised base case. The committee concluded that, unless further long-term data were available, the most appropriate extrapolation of progression-free survival was uncertain.

Modelling of time-to-treatment stopping

The unrestricted model is suitable for extrapolation

3.7 Because time on treatment was shorter for ribociclib than it was for fulvestrant in the treatment arm, the company originally modelled time-to-treatment stopping for ribociclib and fulvestrant monotherapy (in the treatment arm) separately in its base case. It used restricted models to extrapolate ribociclib and fulvestrant (in the treatment arm). The ERG explained that restricted models assume a common shape parameter across different treatment groups. It further explained that unrestricted models, determined only by the treatment group in which the curves are applied, were a more appropriate method to use in this instance. In response to consultation, the company used the unrestricted models for the time-to-treatment stopping extrapolation. The committee concluded that unrestricted models were more suitable for the time-to-treatment stopping extrapolation for ribociclib with fulvestrant.

ECG costs

Resting ECG costs are the most appropriate to be used in the model

3.8 In response to consultation, the company suggested that the cost of an ECG is not as high as suggested by the ERG (which was included in the committee's preferred base case). The ERG had used a cost of £256 and noted that this included resting 24-hour and 48-hour ECG monitoring, ambulatory ECG monitoring and exercise ECG monitoring. The company stated that the ECG would be a simple resting ECG and should be about £50. Committee members and the clinical expert explained that, when checking for QT-interval prolongation (the potential issue with ribociclib), a simple resting ECG would be appropriate, and the cost would be nearer the company's figure. The committee concluded that resting ECG costs are the most appropriate for the model.

Post-progression survival assumption

Assuming the same post-progression survival is not supported

3.9 The company used data from the MONALEESA-3 trial to estimate post-progression survival for ribociclib and fulvestrant. Because no exemestane with everolimus post-progression survival data were available, the company assumed that post-progression survival for exemestane with everolimus was the same as it was for ribociclib and fulvestrant. However, the ERG noted that, if post-progression survival was longer on exemestane with everolimus than on ribociclib with fulvestrant, the relative overall survival gain for ribociclib with fulvestrant would be reduced and the ICER comparing ribociclib with fulvestrant with exemestane with everolimus would increase. Conversely, if post-progression survival was shorter on exemestane with everolimus than on ribociclib with fulvestrant, the overall survival gain for ribociclib with fulvestrant would increase and the ICER would be reduced. The committee concluded that no evidence had been presented to support the assumption that post-progression survival was the same for exemestane

with everolimus and ribociclib with fulvestrant, and that the effect of this assumption on the cost-effectiveness results was uncertain.

The company's revised base case

All the committee's preferences are included in the revised base case

3.10 The company's revised base case included the following updates:

- the 3-knot spline models for extrapolating progression-free survival
- unrestricted models for time to stopping treatment
- the ERG's model corrections
- an updated cost for end-of-life care
- removal of additional adverse events
- an updated cost for ECGs (£52.09)
- an additional proposed discount for ribociclib, valid for this indication only (commercial access arrangement).

The committee concluded that the company's revised base case included its preferred assumptions as stated in the appraisal consultation document.

Cost-effectiveness estimates

The most plausible ICERs for ribociclib with fulvestrant are uncertain with very small QALY gains

3.11 The committee considered the cost effectiveness of ribociclib with fulvestrant in people who could have exemestane with everolimus. The committee recognised that there was a high level of uncertainty in the clinical evidence and that the direction of the effect on the cost-effectiveness results was unknown (see section 3.5). It highlighted that the robustness of the ICER would need further exploration if equal post-progression survival was assumed (see section 3.9). The committee also noted the ERG's comment that the company's analysis was based on a very small increase in quality-adjusted life years (QALYs) for ribociclib, so

the resulting ICER was very unstable, and sensitive to even small changes in both costs and QALYs. The committee agreed this added to the uncertainty in the cost-effectiveness analysis. It noted that the company's revised base case resulted in an ICER of less than £30,000 per QALY gained. This ICER was presented as commercial in confidence to maintain the confidentiality of the proposed commercial access agreement for ribociclib and the patient access scheme for everolimus. Therefore, it cannot be reported here. However, the committee noted that the proposed commercial access agreement for ribociclib is only for this indication, so it could not take this price into account when considering ribociclib with fulvestrant for routine commissioning. The committee also noted that, when the current patient access scheme for ribociclib (which is the offered price for routine commissioning) was used in the cost-effectiveness analyses, the ICERs were all substantially above the range considered to be a cost-effective use of NHS resources. It therefore concluded that ribociclib with fulvestrant could not be recommended for routine commissioning.

Cancer Drugs Fund

Ribociclib plus fulvestrant is recommended for use in the Cancer Drugs Fund

3.12 Having concluded that ribociclib plus fulvestrant could not be recommended for routine use, the committee then considered whether it could be recommended for treating hormone receptor-positive, HER2-negative, advanced breast cancer after endocrine therapy within the Cancer Drugs Fund. It discussed the arrangements for the Cancer Drugs Fund agreed by NICE and NHS England in 2016, noting NICE's [Cancer Drugs Fund methods guide \(addendum\)](#). The committee was aware that more overall survival data from MONALEESA-3 will become available in 2020. The committee agreed that updated treatment-effectiveness data would make the results of the network meta-analysis, the extrapolation in the model and the cost-effectiveness results more reliable. It agreed that there were several uncertainties, including:

- the ribociclib and fulvestrant results because they are based on a subgroup analysis of MONALEESA-3 trial (see section 3.2)
- the results of the network meta-analysis (see section 3.5)
- the extrapolation of progression-free survival (see section 3.6)
- time-to-treatment stopping (see section 3.7)
- post-progression survival (see section 3.9).

Some of these uncertainties could be resolved with further data collection. The committee considered that, based on the cost-effectiveness analyses including the proposed commercial access agreement, there was plausible potential for ribociclib plus fulvestrant to be cost effective compared with exemestane plus everolimus, if subsequent data confirm the company's and committee's preferred assumptions. It therefore concluded that ribociclib plus fulvestrant met the criteria to be considered for inclusion in the Cancer Drugs Fund. It recommended ribociclib plus fulvestrant for use within the Cancer Drugs Fund as an option for people with hormone receptor-positive, HER2-negative, advanced breast cancer after endocrine therapy, only if:

- exemestane plus everolimus is the most appropriate alternative to a cyclin-dependent kinase 4 and 6 (CDK 4/6) inhibitor and
- if the conditions in the managed access agreement are followed.

4 Implementation

4.1 When NICE recommends a treatment as an option for use within the Cancer Drugs Fund, NHS England will make it available according to the conditions in the managed access agreement. This means that, if a patient with hormone receptor-positive, human epidermal growth factor receptor 2-negative, advanced breast cancer has had endocrine therapy, and the doctor responsible for their care thinks that ribociclib plus fulvestrant is the right treatment, it should be available for use, in line with NICE's recommendations and the Cancer Drugs Fund criteria in the managed access agreement. Further information can be found in NHS

England's [Appraisal and funding of cancer drugs from July 2016 \(including the new Cancer Drugs Fund\) – A new deal for patients, taxpayers and industry.](#)

- 4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance when the drug or treatment, or other technology, is approved for use within the Cancer Drugs Fund. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, for use within the Cancer Drugs Fund, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document or agreement of a managed access agreement by the NHS in Wales, whichever is the later.

5 Review of guidance

- 5.1 The data collection period is expected to end in December 2020, when enough data have been collected to address the clinical uncertainties highlighted by the committee. The process for exiting the Cancer Drugs Fund will begin at this point and the review of the NICE guidance will start.
- 5.2 As part of the managed access agreement, the technology will continue to be available through the Cancer Drugs Fund after the data collection period has ended and while the guidance is being reviewed. This assumes that the data collection period ends as planned and the review of guidance follows the standard timelines described in NICE's [Cancer Drugs Fund methods guide \(addendum\)](#).

Jane Adam
Chair, appraisal committee
June 2019

6 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by [committee A](#).

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

The [minutes](#) of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

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

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