NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

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

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using ribociclib with fulvestrant in the NHS in England. The appraisal committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts and patient experts.

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

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

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the 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 race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Issue date: April 2019

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 appraisal committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final appraisal document.
- Subject to any appeal by consultees, the final appraisal document may be used as the basis for NICE's guidance on using ribociclib with fulvestrant in the NHS in England.

For further details, see NICE's guide to the processes of technology appraisal.

The key dates for this appraisal are:

Closing date for comments: 9th May 2019

Second appraisal committee meeting: 16th May 2019

Details of membership of the appraisal committee are given in section 5.

1 Recommendations

1.1 Ribociclib with fulvestrant is not recommended, within its marketing authorisation, for treating hormone receptor-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer as initial endocrine-based therapy, or in people who have had previous endocrine therapy.

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 at or within 12 months after neoadjuvant endocrine therapy, and disease that has progressed after 1 line of endocrine therapy in an advanced setting and that the key comparator 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 with either untreated advanced disease or in those who have had a prior endocrine treatment. It is not known whether ribociclib increases the length of time people live because the final trial results are not available yet. An indirect comparison was conducted to compare ribociclib and fulvestrant with exemestane and everolimus.

The clinical effectiveness and cost-effectiveness estimates are highly uncertain. Also, the cost-effectiveness estimates are much higher than the range NICE normally considers an acceptable use of NHS resources.

Therefore, ribociclib with fulvestrant cannot be recommended for routine use in the NHS.

There are several uncertainties with the clinical trial evidence, which may be addressed if more data are collected. However, ribociclib with fulvestrant does not have plausible potential to be cost effective at the offered price. Therefore, ribociclib with fulvestrant cannot be recommended for use within the Cancer Drugs Fund.

2 Information about ribociclib

Marketing authorisation	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. In pre- or perimenopausal women, the endocrine therapy should be combined with a luteinising hormone-releasing hormone agonist.
Dosage in the marketing authorisation	The recommended dose is 600 mg (3 x 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. Management of severe or intolerable adverse drug reactions may need temporary dose interruption, reduction or discontinuation of Kisqali.
Price	£2,950 for a 63 tablet pack of 200 mg tablets (excluding VAT; British national formulary [BNF] online, accessed March 2019). The company has a commercial arrangement, which would apply if the technology had been recommended.

3 Committee discussion

The appraisal committee (section 5) 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. 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 page 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 patients 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 cyclin-dependent kinase 4 and 6 (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 clinical guideline on advanced breast cancer. The committee noted that since the CDK 4/6 inhibitors have been recommended, the number of people being offered an aromatase inhibitors alone is declining. However, there are patients 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 how long people live before their disease progresses 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, placebo-controlled, randomised 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 people 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 is 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, but that this approach was preferred to further splitting people into a subpopulation with a disease that has progressed at or within 12 months after neoadjuvant endocrine therapy, and a subpopulation with a disease that has progressed after 1 line of endocrine therapy in the advanced setting, that the company had initially suggested.

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. Treatment with 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 of people who 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.

Cyclin-dependent kinase 4 and 6 (CDK 4/6) inhibitors

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 exhibit similar clinical effectiveness and 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 they highlighted that their adverse effect profiles are different. Ribociclib is associated with an increased incidence of neutropenia and also needs regular electrocardiogram assessments and liver function tests 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 committee 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 was 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 and therefore using a hazard ratio that is 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 are highly uncertain. They further noted that the effect of this uncertainty on cost-effectiveness results is likely to be high, and that the direction of the effect is unknown.

Modelling of progression-free survival

Progression-free survival extrapolation is uncertain

3.6 After technical engagement, the company assumed a lognormal 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 also 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 patients who remain progression-free for longer than expected. The committee agreed that that the company's model is too optimistic, although the ERG's model could underestimate the number of people progression free at longer follow-up. They agreed that given the extent of the uncertainty in the clinical evidence, the ERG's extrapolation may be more appropriate, although if pessimistic it could overestimate the incremental cost-effectiveness ratios (ICERs). 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 ERG's unrestricted model is suitable for extrapolation

3.7 Because time on treatment was lower for ribociclib than it was for fulvestrant in the treatment arm, the company modelled time-to-treatment stopping for ribociclib and fulvestrant monotherapy (in the treatment arm) separately. They 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. They 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. The committee agreed with the ERG and concluded that unrestricted models were more suitable for the time-to-treatment stopping extrapolation for ribociclib with fulvestrant.

Including placebo data for ribociclib is not appropriate

3.8 The company based the extrapolation of time-to-treatment stopping for ribociclib in people who had ribociclib or placebo. The ERG noted that

given the lack of treatment effect, people may stop placebo earlier than ribociclib. The ERG explained that by including the placebo data the company was likely to overestimate rates of stopping compared with using only data from people having ribociclib. Unrealistic rates of stopping would underestimate the cost of ribociclib and the resulting ICERs. The committee agreed with the ERG and concluded that using placebo data for estimating time on treatment with ribociclib is not appropriate and could underestimate the ICER.

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 were higher on exemestane with everolimus than ribociclib with fulvestrant, this would reduce the relative overall survival gain for ribociclib with fulvestrant, and increase the ICER comparing ribociclib with fulvestrant with exemestane with everolimus. Conversely, if post-progression survival were lower 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 is uncertain.

Cost-effectiveness estimates

The most plausible ICERs for ribociclib with fulvestrant are uncertain, but are above the range considered to be a cost-effective use of NHS resources

3.10 The committee considered the cost effectiveness of ribociclib with fulvestrant in people who could have exemestane with everolimus. The committee recalled its preferred modelling assumptions:

- 3-knot spline models for progression-free survival extrapolation acknowledging that it may overestimate the ICER (see section 3.6),
- unrestricted models for time-to-treatment stopping extrapolation (see section 3.7), and
- the ERG's corrections and updated cost for electrocardiograms and end-of-life care, and removal of additional adverse events from the model (table 3 of the technical report).

The results all include the patient access schemes for ribociclib and everolimus. The company's base-case ICER compared with exemestane with everolimus was above £30,000 per quality-adjusted life year (QALY) gained, and the committees preferred base-case ICER was significantly above £30,000 per QALY gained. The exact ICERs are commercial-in-confidence and cannot be reported here. The committee recognised that there was a high level of uncertainty in the clinical evidence and that the direction of the effect on cost-effectiveness results is unknown (see section 3.5). It further noted that using the placebo data is likely to underestimate the ICER (see section 3.8). The committee also highlighted that the robustness of the ICER would need further exploration if equal post-progression survival were assumed (see section 3.9). The committee concluded that the most plausible ICERs for ribociclib with fulvestrant are uncertain, but above the range considered to be a cost-effective use of NHS resources.

Cancer Drugs Fund

Ribociclib with fulvestrant did not met the criteria to be considered for inclusion in the Cancer Drugs Fund

3.11 Having concluded that ribociclib with fulvestrant could not be recommended for routine use, the committee then considered if it could be recommended for treating hormone receptor-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer within the Cancer Drugs Fund. The committee 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 MONALEESA-3 was ongoing and that more data would be available. It agreed that there are several uncertainties:

- the ribociclib and fulvestrant results are based on a subgroup analysis of MONALEESA-3 trial (see section 3.2),
- the overall survival data included in the analysis are immature (see section 3.3),
- the results of the network meta-analyses are uncertain (see section 3.5),
- the extrapolation of progression-free survival is uncertain (see section 3.6),
- time-to-treatment stopping (see sections 3.7 and 3.8),
- post-progression survival (see section 3.9).

Some of these uncertainties could be resolved with further data collection. However, the committee was aware that ribociclib with fulvestrant does not have plausible potential to be cost effective at the offered price. The company presented a base-case ICER above £30,000 per QALY gained.

The committee's preferred adjustments resulted in an ICER significantly higher than £30,000 per QALY gained and still included substantial unresolved uncertainty. The committee concluded that because there was no plausible potential for this combination to be cost effective, ribociclib with fulvestrant did not met the criteria to be considered for inclusion in the Cancer Drugs Fund.

Conclusion

Ribociclib and fulvestrant is not recommended for use in the NHS

3.12 The committee recognised that there was a high level of uncertainty in the clinical evidence supporting the appraisal and the most plausible ICER was above the range that NICE normally considers an acceptable use of NHS resources. Because of this, the committee concluded that ribociclib with fulvestrant could not be recommended for routine commissioning use and did not meet the criteria to be considered for the Cancer Drugs Fund and therefore ribociclib and fulvestrant is not recommended as an option for people with hormone receptor-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer.

4 Proposed date for review of guidance

4.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Jane Adam
Chair, Appraisal Committee
April 2019

5 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.

Marcela Haasova
Technical Lead

Joanna Richardson
Technical Adviser

Gemma Barnacle
Project Manager

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