NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final appraisal document

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

1 Recommendations

1.1 Ribociclib plus fulvestrant is recommended as an option for treating hormone receptor-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer in adults 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 company provides ribociclib according to the commercial arrangement (see section 2).

Why the committee made these recommendations

This appraisal reviews the additional evidence collected as part of the Cancer Drugs Fund managed access agreement for ribociclib plus fulvestrant for hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer in people who have had previous endocrine (hormone) therapy (NICE technology appraisal guidance 593).

The new evidence includes data from patients in clinical trials and from patients having treatment in the NHS, while this treatment was available in the Cancer Drugs Fund in England. It suggests that, compared with fulvestrant alone, people taking

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ribociclib plus fulvestrant have longer before their disease progresses and live longer.

Ribociclib is a CDK 4/6 inhibitor. Another treatment option is exemestane plus everolimus, which is a hormone therapy. There are no trials directly comparing ribociclib plus fulvestrant against exemestane plus everolimus. But an indirect comparison suggests that ribociclib plus fulvestrant may be the more effective option for people who have already had hormone therapy.

There are uncertainties about the economic modelling. But the base case results and most exploratory analyses suggest that ribociclib plus fulvestrant is a cost-effective alternative to exemestane plus everolimus. So, ribociclib plus fulvestrant is recommended only if exemestane plus everolimus is the most appropriate alternative to a CDK 4/6 inhibitor.

2 Information about ribociclib

Marketing authorisation indication

2.1 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 an aromatase inhibitor or 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 (LHRH) agonist.' NICE guidance recommends ribociclib with an aromatase inhibitor as initial endocrine-based therapy. The current appraisal covers only the combination of ribociclib with fulvestrant in people who have already had endocrine therapy.

Dosage in the marketing authorisation

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

Price

2.3 The list price for ribociclib is £2,950 for a 63 tablet pack of 200 mg tablets (excluding VAT; British national formulary online, accessed January 2021). The company has a commercial arrangement (simple discount patient access scheme). 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. The list price for fulvestrant is £522.41 per 2 x 250 mg/5 ml solution for injection. Fulvestrant is available to the NHS at contract prices negotiated through the Commercial Medicines Unit. These prices are lower than the list prices but are commercial in confidence.

3 Committee discussion

The appraisal committee considered evidence submitted by Novartis, a review of this submission by the evidence review group (ERG) and responses from stakeholders. See the committee papers for full details of the evidence.

Experience of people with advanced breast cancer

Advanced breast cancer affects all aspects of a person's life

3.1 Advanced breast cancer is an incurable condition. It can affect all aspects of life (physical, psychological, social and financial). Treatments that extend survival while improving quality of life are important to patients because they provide valuable extra time with families and friends.

Treatment pathway

Ribociclib would be a welcome treatment option for people who have already had endocrine therapy

3.2 First-line treatment for hormone receptor-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer is usually a CDK 4/6 inhibitor (abemaciclib, palbociclib or

ribociclib) with an aromatase inhibitor (letrozole or anastrozole). If symptoms are severe or the disease is progressing rapidly, then chemotherapy may also be needed first line. Tamoxifen can also be offered to some people in line with NICE's guideline on advanced breast cancer. NICE recommends everolimus plus exemestane at second line in postmenopausal women without symptomatic visceral disease that has recurred or progressed after a non-steroidal aromatase inhibitor (NICE technology appraisal 421). The patient and clinical experts explained that some people need second-line CDK 4/6 inhibitors. This includes people whose disease is progressing slowly. The experts also highlighted that during the COVID-19 pandemic, some people will have been started on endocrine therapy alone. They explained that the various CDK 4/6 inhibitors have a similar mode of action but have different side effect profiles. They are effective at increasing progression-free survival in clinical practice and are generally less toxic than the combination of exemestane and everolimus, or chemotherapy. The clinical expert explained that everolimus is associated with mouth ulcers and people report feeling ill while taking it. Therefore, patients would welcome the availability of CDK 4/6 inhibitors at second line in preference to everolimus and exemestane, and to delay the need for chemotherapy. Having a choice of CDK 4/6 inhibitors would also be welcome to allow switching if needed because of side effects. The committee concluded that a well-tolerated treatment that extends progression-free survival and delays the need for chemotherapy would be welcomed by people who have already had endocrine therapy.

Clinical evidence

Sub-population B from MONALEESA-3 is relevant to NHS clinical practice

3.3 MONALEESA-3 is a multicentre, double-blind, randomised placebo-controlled trial comparing ribociclib plus fulvestrant against placebo plus

fulvestrant in 726 postmenopausal women with hormone receptor-positive, HER2-negative advanced breast cancer. The company submitted results for a subgroup of patients who had had previous endocrine therapy (n=346; referred to as sub-population B). The committee noted that MONALEESA-3 was not designed to have statistical power to detect treatment effects within subgroups and that this is a concern. However, it agreed that sub-population B is relevant to this appraisal and to NHS clinical practice.

Ribociclib plus fulvestrant improves progression-free survival and overall survival compared with fulvestrant alone

3.4 The primary outcome measure of MONALEESA-3 is investigator-assessed progression-free survival. During the appraisal for TA593, the committee was presented with a data cut from November 2017. This showed a clear progression-free survival benefit, but the results for overall survival were not statistically significant. Ribociclib was therefore recommended for use in the Cancer Drugs Fund while data was collected in MONALEESA-3. For the current appraisal, the company presented the latest data cut from June 2019. It noted that data collection for MONALEESA-3 has stopped, because it has met a pre-specified significance level for overall survival in the full population. After 46 months of follow up of patients who had had previous endocrine therapy (sub-population B), ribociclib plus fulvestrant increased median progression-free survival compared with placebo plus fulvestrant from 9.1 months to 14.6 months (hazard ratio [HR] 0.57; 95% confidence interval [CI] 0.43 to 0.74). Median overall survival increased from 32.5 months to 40.2 months (HR 0.73; 95% CI 0.53 to 1.00). The committee noted that the upper boundary of the confidence interval for overall survival included 1, and so could not be considered statistically significant. It agreed that any significance tests should be interpreted with caution because the study was not powered for this subgroup. But it noted that the confidence intervals have narrowed since the November 2017 data

cut, which suggests less uncertainty in the overall survival benefit. The committee concluded that ribociclib plus fulvestrant improves progression-free survival and overall survival, compared with placebo plus fulvestrant. However, it noted that the most relevant comparator is exemestane plus everolimus but this was not the comparator in the trial.

Ribociclib plus fulvestrant gives a numerical but not statistically significant benefit in overall survival

3.5 There is no trial directly comparing ribociclib plus fulvestrant against exemestane plus everolimus. So the company did network meta-analyses (NMAs) for sub-population B using overall-survival data from 4 trials and progression-free survival data from 5 trials. It connected the network to exemestane plus everolimus using data from the BOLERO-2 study. This is a phase 3 randomised controlled trial comparing exemestane plus everolimus with exemestane alone in 724 postmenopausal women with hormone receptor-positive locally advanced or metastatic breast cancer refractory to a nonsteroidal aromatase inhibitor. The company used a Bucher NMA for overall survival. This showed a numerical (but generally, not statistically significant) benefit in overall survival for ribociclib plus fulvestrant compared with the comparators (fulvestrant only, exemestane plus everolimus and exemestane only).

Ribociclib plus fulvestrant provide a numerical but not statistically significant benefit in progression-free survival

3.6 For progression-free survival, the ERG expressed concerns that the assumption of proportional hazards in BOLERO-2 appeared to have been violated. To address this, the company did a Bayesian NMA with hazards characterised by fractional polynomials (FP) to provide time-varying hazard ratios. The ERG noted that the company used data for fulvestrant 500 mg from MONALEESA-3 as the source of the informed priors. The ERG considered this approach to be inappropriate because it could lead to confirmation bias. It noted that the results of all the company's NMAs

(Bucher and FP) suggest a numerical (but not statistically significant) benefit in progression-free survival for ribociclib plus fulvestrant over the comparators (fulvestrant only, exemestane plus everolimus and exemestane only). The ERG was therefore reasonably confident that there is a progression-free survival benefit for ribociclib plus fulvestrant compared with the comparators, but quantifying the exact level of this benefit is uncertain. The ERG noted that while the FP reduced the uncertainty related to proportional hazards, it increased the uncertainty overall. This is because it resulted in broader credible intervals and had used an informed prior from MONALEESA-3. Given the uncertainty, the ERG preferred to use the most conservative estimate in its base case, which uses results from the Bucher NMA. The committee agreed that the results from all the NMAs (Bucher and FP) for progression-free survival are highly uncertain. But it noted that the different NMAs had similar effects on the cost-effectiveness estimates. The committee concluded that the results of the NMAs suggest that ribociclib plus fulvestrant has a numerical (although not statistically significant) benefit in progression-free survival compared with fulvestrant only, exemestane plus everolimus and exemestane only.

Company's economic model

The partitioned survival model is preferred for decision making

3.7 The company submitted a semi-Markov state-transition model for the cost effectiveness of ribociclib plus fulvestrant compared with fulvestrant 500 mg and exemestane plus everolimus. It used data from MONALEESA-3 and the Bucher NMA to estimate progression-free survival. It used post-progression survival as a proxy for overall survival. The company assumed that post-progression survival was equal for all treatments. Overall-survival data became available in the latest June 2019 data cut for MONALEESA-3 and, in response to technical engagement, the company submitted a new partitioned survival model. This has 3 health states

(progression-free survival, post-progression survival and death), a 28-day model cycle, and a 40-year time horizon. All patients enter the model in the progression-free health state and start treatment. During each model cycle, patients in the progression-free health state can be on-treatment or off-treatment depending on if they experience unacceptable side effects. The proportion of patients who are progression-free and on-treatment is estimated using the time to stopping treatment. The proportion of patients in the post-progression health state is calculated as the difference between overall survival and progression-free survival per cycle. The ERG considered the structure of the company's model to be appropriate, capturing all relevant health states and clinically plausible transitions between health states. The committee agreed that it was preferable to use the model which best allows the use of actual survival data. Therefore, it concluded that the company's partitioned survival model is more appropriate for decision making.

Modelling overall survival

The overall-survival extrapolation is uncertain

3.8 The company fitted parametric survival distributions to the individual patient data from sub-population B of MONALEESA-3 to estimate overall survival for ribociclib plus fulvestrant and placebo plus fulvestrant. The company selected the Weibull-R distribution (R referring to a jointly fitted model) to extrapolate overall-survival data. It considered that the Weibull had the best statistical fit, excellent visual fit to the Kaplan-Meier data, projected overall survival consistent with clinical experts' expectations and met the proportional hazards assumptions. To produce the overall-survival curve for exemestane plus everolimus, the company applied the hazard ratio from the Bucher NMA to the Weibull-R distribution for overall survival for ribociclib plus fulvestrant. The ERG considered the Gompertz-R curve provided a better extrapolation, because it gave more plausible predictions according to its clinical expert (at least 90% of patients on

fulvestrant or exemestane plus everolimus would die by 5 years and at least 95% would die by 10 years). It also provided a better visual fit to the Kaplan-Meier data in the fulvestrant-only arm. The ERG noted that there is heavy censoring at the end of the Kaplan-Meier overall-survival curve for sub-population B of MONALEESA-3 from 34 months onward, so data beyond this point may be unreliable. The clinical expert at the appraisal meeting explained that it is possible for patients on ribociclib plus fulvestrant to survive for 10 years and some patients who were in the MONALEESA-3 trial are still alive 8 to 9 years later. The committee noted that the Weibull distribution estimated a 10-year survival of 5%, compared with 0% for the Gompertz distribution. It concluded that the most appropriate extrapolation of overall survival is uncertain but agreed that it is likely to lie between the Weibull curve and the Gompertz curve.

Modelling of time to stopping treatment

Time to stopping everolimus is likely to be between clinical opinion and the ERG's model using BOLERO-2 data

3.9 In its original model, the company assumed that everolimus is taken until the disease progresses. However, many people stop everolimus because of its toxicity. In response to technical engagement, the company used the ERG's clinical expert opinion to model time to stopping everolimus. In the company's updated model, 20% of patients stop everolimus at month 6, and 70% of patients who continue on everolimus will reduce their dose at month 6 from 10 mg daily to 5 mg daily. The ERG agreed that this is an acceptable and more realistic approach. However, it explained an alternative approach using summary data from BOLERO-2 to estimate the hazard ratios for stopping exemestane plus everolimus. The clinical expert considered the model based on clinical opinion to be more plausible. He explained that in clinical practice, and as seen in BOLERO-2, about 20% of patients cannot tolerate the side effects of everolimus and stop taking it within the first 2 to 3 months. Many patients who continue treatment do so

at a reduced dose (such as 5 mg). He noted that some patients experience later toxicities and then stop treatment. He explained that patients taking a reduced dose still have some benefit in terms of progression-free survival compared with those who stop completely. The Cancer Drugs Fund expert considered the ERG's model using BOLERO-2 data provides a smoother curve and is more plausible. The ERG highlighted that their extrapolation based on BOLERO-2 does not take into account the large proportion of patients stopping treatment early on, because it uses a summary statistic. The committee agreed that the time to stopping everolimus is likely to be between clinical opinion and the ERG's model using BOLERO-2 data.

The company's and ERG's base-case analyses

The committee took into account the results of the different base cases and scenarios in its decision making

3.10 The company's revised base case used:

- a partitioned survival model (see section 3.7)
- estimates from the second order fractional polynomial network meta-analysis for progression-free survival (see section 3.6)
- the Weibull curve to extrapolate overall survival (see section 3.8)
- the ERG's clinical expert opinion to model time to stopping everolimus (see section 3.9)
- an additional proposed discount for ribociclib, valid for this indication only (commercial access arrangement).

The ERG's analyses used the Bucher NMA for progression-free survival, and the Gompertz curve to extrapolate overall survival. The ERG provided 2 base cases using different approaches to stopping everolimus, using clinical expert opinion in its main base case and data from BOLERO-2 in its alternative base case. The committee agreed with using the partitioned survival model but noted uncertainty in which was the best assumption for

estimating progression-free survival (the FP NMA or the Bucher NMA), extrapolating overall survival (Weibull or Gompertz) and modelling time to stopping everolimus (clinical opinion or BOLERO-2 data). The committee noted that the Bucher NMA that the ERG had chosen for its base-case analyses provided a conservative estimate (see section 3.6), and that the ERG consider the true estimate to lie between its 2 base cases which differed in the approach used for modelling time to stopping everolimus (see section 3.9). The committee agreed that the true incremental cost-effectiveness ratio (ICER) is likely to be between the company's and ERG's base-case ICER. It therefore concluded that it would take into account the results of the different base-case analyses and scenarios in its decision making.

Cost-effectiveness estimates

The most plausible ICERs for ribociclib plus fulvestrant are within the range normally considered to be a cost-effective use of NHS resources

3.11 The committee considered the cost effectiveness of ribociclib plus fulvestrant in people who could have exemestane plus everolimus. It recognised that there is uncertainty about the most appropriate network meta-analysis to use for estimating progression-free survival (see section 3.6), the most appropriate parametric curve to extrapolate overall survival (see section 3.8) and the assumptions to use to model time to stopping everolimus (see section 3.9). It agreed that the most plausible assumptions lie between the base cases that the company and ERG have presented (see section 3.10). It noted that the company's revised base case, the ERG's main base case and most of the exploratory analyses resulted in ICERs that were within the range NICE normally considers to be a cost-effective use of NHS resources. These ICERs are presented as commercial in confidence to maintain the confidentiality of the patient access scheme for ribociclib and everolimus and the commercial arrangement for fulvestrant. Tgherefore, they cannot be reported here.

The committee concluded that it could recommend ribociclib with fulvestrant 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 CDK 4/6 inhibitor.

4 Implementation

4.1 Section 7(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months 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 fast track appraisal), at which point funding will switch to routine commissioning budgets. The NHS England and NHS Improvement 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 recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document.

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 advanced breast cancer and the doctor responsible for their care thinks that ribociclib with fulvestrant is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Review of guidance

5.1 The guidance on this technology will be considered for review 3 years after publication. 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
February 2021

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 a project manager.

Sharlene Ting
Technical lead

Carl Prescott
Technical adviser

Jeremy Powell
Project manager

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