NICE National Institute for Health and Care Excellence

NICE guidance

Ribociclib with an aromatase inhibitor for previously untreated, hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer

Technology appraisal guidance
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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

1 Recommendation

1.1 Ribociclib, with an aromatase inhibitor, is recommended within its marketing authorisation, as an option for treating hormone receptor-positive, human epidermal growth factor receptor 2-negative, locally advanced or metastatic breast cancer as initial endocrine-based therapy in adults. Ribociclib is recommended only if the company provides it with the discount agreed in the patient access scheme.

Why the committee made this recommendation

Clinical trial evidence shows that ribociclib plus letrozole improves progression-free survival compared with letrozole alone. Although we do not know yet if this improvement leads to a survival benefit with ribociclib. But with the patient access scheme discount, ribociclib is a cost-effective use of NHS resources and it can be recommended.

2 The technology

Marketing authorisation

2.1 Ribociclib (Kisqali, Novartis) in combination with an aromatase inhibitor is indicated for the treatment of postmenopausal women with hormone receptor-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer as initial endocrine-based therapy.

Recommended dose and schedule

2.2 The recommended dose is 600 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 occurs. Ribociclib should be used together with 2.5 mg letrozole or another aromatase inhibitor. The aromatase inhibitor is taken orally, once daily, continuously throughout the 28-day cycle.

2.3 Some adverse reactions may need to be managed by temporary dose interruptions or delays, dose reductions, or permanently stopping the treatment. See the summary of product characteristics for further details.

Price

2.4 £2,950 for a 63-tablet pack of 200-mg tablets (excluding VAT; MIMS online, accessed November 2017). The company has agreed a patient access scheme with the Department of Health. This scheme provides a simple discount to the list price of ribociclib, with the discount applied at the point of purchase or invoice. The level of the discount is commercial in confidence. The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS.

3 Committee discussion

The appraisal committee (section 5) considered evidence submitted by Novartis, and reviews of this submission by the evidence review group (ERG) and the Decision Support Unit (DSU). See the committee papers for full details of the evidence.

Clinical management

Aromatase inhibitors are the appropriate comparator

3.1 The committee was aware that metastatic breast cancer is an incurable condition. NICE recommends endocrine therapy (such as aromatase inhibitors) as first-line treatment for people with metastatic hormone receptor-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer. But if symptoms are severe or the disease is rapidly progressive, people may need chemotherapy. The committee noted that in the clinical trial (MONALEESA-2) ribociclib was given in combination with letrozole (an aromatase inhibitor). The clinical experts explained that in clinical practice the available aromatase inhibitors (letrozole and anastrozole) are considered to be clinically equivalent, because they have similar clinical effectiveness and acquisition costs. The committee also heard that ribociclib plus an aromatase inhibitor would be used for people who have not had previous treatment for metastatic breast cancer, and who would otherwise be offered an aromatase inhibitor alone. It was aware of NICE's technology appraisal guidance on palbociclib for untreated HER-2 negative breast cancer, which is the same type of drug as ribociclib (a cyclin-dependent kinase 4 and 6 [CDK4/6] inhibitor). The committee noted that palbociclib is not a comparator for this appraisal because it is not established clinical practice in the NHS. The clinical expert explained that after disease progression most people would have several further lines of therapy, including chemotherapy. The committee concluded that the company had placed ribociclib appropriately in the treatment pathway, and that aromatase inhibitor therapy is the comparator.

Patients value improvements in progression-free survival

3.2 The patient expert stated that staying progression-free for as long as possible and being able to continue with normal activities, including working, is very highly valued by patients and their families. The clinical experts emphasised that ribociclib plus letrozole increased the progression-free survival of patients in MONALEESA-2. The patient and clinical experts explained that remaining progression-free delays the need for further treatments, including chemotherapy. Chemotherapy can be associated with significant side effects that reduce quality of life, and therefore delaying later-line treatments is considered very important to patients. The committee concluded that an increase in progression-free survival is highly valued by patients.

Clinical evidence

The clinical-effectiveness evidence is relevant to NHS practice

3.3 MONALEESA-2 was a double blind, placebo-controlled, randomised trial that included 668 postmenopausal women with hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer. It compared ribociclib combined with letrozole against placebo plus letrozole. The ERG noted that the proportion of people in the trial who presented with advanced or metastatic disease at the time of first diagnosis of breast cancer (34%) was higher than expected in the NHS (10%). But overall the trial population reflects patients seen in the NHS. The committee concluded that the MONALEESA-2 population is generalisable to NHS clinical practice.

Ribociclib improves progression-free survival compared with letrozole alone

3.4 Progression-free survival in MONALEESA-2 was assessed both by the investigators and by independent review. The ERG raised concerns that the higher incidence of neutropenia with ribociclib could have resulted in some patients and investigators becoming unblinded to patient allocation, therefore the independent review is the more objective

outcome measure. The ERG noted that an independent progression-free assessment was not available for the most recent data cut-off (January 2017). At the independent review in June 2016 the median progression-free assessment had not been reached, but the hazard ratio was 0.597 (confidence interval 0.430 to 0.830). Using January 2017 data, investigator-assessed progression-free survival was 25.3 months for ribociclib and 16 months for letrozole (hazard ratio of 0.568, confidence interval 0.457 to 0.704). This suggests a statistically significant improvement in progression-free survival for ribociclib compared with letrozole. The committee concluded that ribociclib improves progression-free survival compared with letrozole alone.

It is not known whether ribociclib improves overall survival

3.5 The overall survival data from MONALEESA-2 are immature. Using January 2017 data, there were 50 (15%) and 65 (19.7%) deaths in the ribociclib and letrozole arms respectively. The median overall survival in MONALEESA-2 could not be estimated for ribociclib, and was 33 months for letrozole; the hazard ratio of 0.746 (confidence interval 0.517 to 1.078) is not statistically significant. The committee concluded that there are insufficient data to allow them to decide whether ribociclib, compared with letrozole alone, improves overall survival.

Adverse events

Ribociclib has an acceptable adverse effects profile

3.6 In MONALEESA-2 ribociclib was associated with an increased incidence of neutropenia in particular, but also other adverse events such as nausea and vomiting. The summary of product characteristics requires regular electrocardiogram assessments and liver function tests for people having ribociclib. The clinical experts explained that adverse events are more common when starting ribociclib treatment, and are usually resolved with dose reductions and interruptions. The committee acknowledged the risks associated with ribociclib and concluded that it has an acceptable adverse effects profile.

The company's economic model

The model uses a new approach in this disease area

3.7 The company's model is a patient-based state-transition model with 3 health states and death (an all-absorbing state):

- progression-free survival on first-line treatment (PFS1)
- progression-free survival on second-line treatment (PFS2)
- progression.

Because of the immaturity of the data, overall survival is modelled indirectly and is a function of the time spent in each state. The committee noted that this differs from many breast cancer economic models in NICE technology appraisals, which have used a partitioned survival approach, extrapolating progression-free survival and overall survival from clinical-trial data. It noted that the company's model uses a fixed post-progression state (PFS2), which is a new approach in this disease area. The committee acknowledged that the model may not be directly comparable with other breast cancer models.

The model structure is appropriate for decision-making

3.8 The committee noted that some of the model's results are counterintuitive (for example, decreasing incremental survival gain for ribociclib resulted in a decrease in the incremental cost-effectiveness ratio [ICER]). Therefore after the first committee meeting the DSU was asked to examine and comment on the model, and to assess the evidence supporting the key assumptions and inputs. The DSU did 'black-box' testing of the model and concluded that the model structure is acceptable, and does not contain hidden errors. The committee concluded that the model structure is appropriate for decision-making.

Progression-free survival state in second-line (PFS2)

BOLERO-2 data is representative of disease progressing on first-line therapy

3.9 Data from MONALEESA-2 were used to model survival in PFS1, but survival in PFS2 was modelled using data from the BOLERO-2 trial. BOLERO-2 was a placebo-controlled, randomised trial in 724 postmenopausal women with hormone receptor-positive, HER2-negative advanced breast cancer refractory to letrozole or anastrozole. It compared everolimus with exemestane against placebo with exemestane. The ERG and the DSU explained that a key assumption of the company's model is that patients in BOLERO-2 are representative of patients progressing in MONALEESA-2. The DSU noted that both studies have similar populations in terms of Eastern Cooperative Oncology Group (ECOG) status, previous neoadjuvant or adjuvant chemotherapy, number of metastatic sites and age. All the patients in BOLERO-2 had previous treatment with an aromatase inhibitor. The committee noted that patients in BOLERO-2 had not had previous treatment with a CDK4/6 inhibitor, and it is not known whether this would affect progression-free or overall survival. The ERG and DSU agreed that BOLERO-2 is broadly representative of patients with progressive disease in MONALEESA-2. The committee concluded that the use of BOLERO-2 data is appropriate.

Relationship between progression-free and overall survival

The size of the overall survival benefit is uncertain

3.10 The company's original base-case analysis assumed that the progression-free survival gain for ribociclib seen in MONALEESA-2 translates into an equivalent overall survival gain (full-OS surrogacy). The clinical experts stated that they would expect improved progression-free survival to result in a benefit in overall survival, but the precise

relationship between progression-free and overall survival is unknown. The ERG noted the interim survival analysis from the PALOMA-1 trial. This was an open-label trial of the CDK4/6 inhibitor palbociclib, given with letrozole, compared with letrozole alone in people with hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer. Only 38.5% of the progression-free survival gain for palbociclib was translated into an overall survival gain (partial-OS surrogacy). The ERG suggested that partial-OS surrogacy is more plausible than full-OS surrogacy. The DSU stated that progression-free survival gain is likely to result in an overall survival gain but there is no clear or predictable relationship between the two. The committee agreed that ribociclib improves progression-free survival, and it is likely that this would result in some improvement in overall survival, but the size of this benefit is uncertain. It noted that the partial-OS surrogacy assumption predicts an overall survival gain equal to 38.5% of the progression-free survival gain, based on interim survival results from PALOMA-1. But more recent data from the trial suggests that only 27.5% of progression-free survival gain translates into an overall survival gain. The assumption of full surrogacy was made by the company in the face of immaturity of the survival data from MONALEESA-2. The committee concluded that a degree of partial surrogacy is probably more likely than full surrogacy, however the magnitude of the relationship is highly uncertain.

Modelling of time to treatment discontinuation and progression-free survival

There is uncertainty about which extrapolations are the most appropriate

3.11 The company revised its base case in response to the DSU report and updated the extrapolation with the latest 2017 data for time to treatment discontinuation. The DSU noted the large difference between modelled progression-free survival and time to treatment discontinuation. The company stated that a difference was also observed between the Kaplan–Meier curves for progression-free survival and time to treatment discontinuation in MONALEESA-2, so this was a real finding in the trial. The company used an exponential distribution and explained that for

progression-free survival the exponential curve was the second best according to statistical goodness of fit, and that the choice of the curve was validated by clinical experts together with long-term validation using Kaplan–Meier curves for letrozole from the LEA, PALOMA-2 and ALLIANCE trials. The ERG critiqued the long-term validation and considered that the Weibull distribution is equally plausible for extrapolating progression-free survival in MONALEESA-2. The DSU noted that studies referenced in NICE's technology appraisal guidance on palbociclib for untreated HER-2 negative breast cancer (Paridaens et al., 2008; Bergh et al., 2012; and Moridsen et al., 2003) report lower median overall survival than the LEA and ALLIANCE trials, and that it is difficult to know which survival estimate is relevant for validation. The DSU suggested that overall, the Weibull distribution seems to be more appropriate for the extrapolation of time to treatment discontinuation and progression-free survival because it results in the difference between the modelled mean time to treatment discontinuation and mean progression-free survival being smaller than when the exponential distribution is used. The Cancer Drug Fund clinical lead noted that extrapolation using the exponential curve appeared to give clinically reasonable results for progression-free survival, and that there is some justification in using the Weibull curve to model time to treatment discontinuation. The committee agreed that there are a number of ways to extrapolate progression-free survival and time to treatment discontinuation in the model. It therefore concluded that there is uncertainty about which extrapolations are the most appropriate.

Utility values

The utility values are appropriate for decision-making

3.12 The company's original base case used EQ-5D 5-level data from MONALEESA-2 to inform PFS1; the BOLERO-2 adjusted value of 0.774 to inform PFS2; and the Lloyd et al. 2006 value of 0.505 for the progression state. The company's revised base case, in line with a recent EQ-5D-5L NICE position statement, mapped the 5-level EQ-5D data to 3-level values for the PFS1 state. Because the mapped 3-level utility is lower than the 5-level value, the utility in PFS2 has to be lower than the original

0.774. The clinical experts agreed that the utility for PFS2 is likely to be smaller than the utility for PFS1. The DSU suggested a value of 0.69 for PFS2. The company accepted this value and used it in their revised base case. The clinical and patient experts explained that people who are progression-free on ribociclib live a nearly normal life, and therefore the PFS1 utility value could be higher than that used in the model. The committee concluded that the utilities in the company's revised base case are appropriate for decision-making, but noted that the utilities used may undervalue the quality of life for patients in the progression-free health state.

Cost of subsequent therapies in the economic model

A range of estimates was considered by the committee

3.13 Therapies in the progression health state were not modelled directly. The clinical experts stated that post second-line several treatments are available. The company's original base case assumed a monthly cost of £2,000 based on clinical expert opinion. The ERG noted that details of how this was estimated were not provided and that an additional management cost is included in the model. It suggested an estimate of £1,140, based on NICE's technology appraisal guidance on fulvestrant for locally advanced or metastatic breast cancer and adjusting for inflation. The DSU stated that assuming that the mean time on third-line therapy is 6.1 months (Systemic Anti-Cancer Therapy chemotherapy dataset and Kurosky et al. 2016), based on time patients could be treated using some of the third-line available treatments, both the company and the ERG are likely to be overestimating the cost of third-line treatments. The company's revised base case assumed a monthly cost of £1,500, which is between its original value of £2,000 and the ERG's value of £1,140. The Cancer Drugs Fund clinical lead, together with experts in the Chemotherapy Clinical Reference Group, also estimated the cost of subsequent treatments. These estimates were presented as commercial in confidence because they included confidential pricing agreements and are therefore not presented here. The committee noted that in the ongoing appraisal of palbociclib, the ERG calculated the average cost of

subsequent therapies as £1,200 per month. It concluded that it would consider costs in the region of £1,140 to £1,200 in its decision-making.

Ribociclib dose

Assumptions about dose reduction over time are appropriate

3.14 Ribociclib is taken as three 200-mg tablets (600 mg dose) once daily, for 21 days of the 28-day cycle. A dose reduction of 400 mg to 200 mg is allowed for managing adverse events. The company assumed that patients who reduce their dose do not waste tablets. The clinical expert agreed that this would be the case in clinical practice. The ERG noted that wastage when treatment is stopped should be included, but that this has little impact on the cost effectiveness. The company incorporated wastage when treatment is stopped and explained that dose reductions based on individual participant data are more appropriate, because assuming a full dose does not reflect the MONALEESA-2 data. The committee concluded that dose reduction of ribociclib is an appropriate assumption in the model.

The company's revised base case

Does not include all the committee's preferences

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

- a patient access scheme
- partial-OS surrogacy
- exponential curves to extrapolate progression-free survival and time to treatment discontinuation
- January 2017 data for progression-free survival and time to treatment discontinuation
- cost of progression of £1,500

- updated utilities
- ribociclib dose reduction.

The company's revised base case resulted in an ICER of less than £30,000 per quality-adjusted life year (QALY) gained. These ICERs were presented as commercial in confidence to maintain the confidentiality around the patient access scheme and therefore cannot be reported here. The committee noted its earlier conclusions that the relationship between progression-free survival and overall survival is uncertain (see section 3.10), that there is uncertainty in how to extrapolate progression-free survival and time to treatment discontinuation (section 3.11), and that a range of subsequent therapies' costs should be considered in its decision-making (section 3.13). It concluded that the company's base case does not include all the committee's preferences, and that scenario analyses are needed for the committee's decision-making.

Cost-effectiveness estimate

The cost-effectiveness estimates are broadly within the range considered a cost-effective use of NHS resources

3.16 The committee considered the company's revised scenario analyses. It emphasised that the survival data for MONALEESA-2 are immature (see section 3.5), and that the relationship between progression-free survival and overall survival is unknown (see section 3.10). The committee agreed that the cost-effectiveness estimates are subject to high uncertainty given the assumptions about overall survival surrogacy (section 3.10), progression-free survival and time to treatment discontinuation extrapolation (section 3.11), and cost of subsequent treatments (section 3.13). It also noted that the company's model uses a new approach in this disease area (see section 3.7). The committee concluded that taking into account the uncertainties in the calculation of the cost-effectiveness estimates, it was persuaded that there were plausible cost-effectiveness estimates which were broadly in the range which could be considered a cost-effective use of NHS resources.

Innovation

There is a clinical need for better treatments for this patient group

3.17 The committee discussed the innovative nature of ribociclib. The clinical expert explained that CDK4/6 inhibitors offer a new effective treatment for people with this disease. The committee agreed that there is a clinical need for better treatments for this patient group. It noted that ribociclib prolongs progression-free survival, allowing people to live as near normal lives as possible and delaying chemotherapy. The committee recognised that no weight had been given in the cost-effectiveness analysis to the specific benefit of delaying chemotherapy with its attendant side effects, which patients consider important. The overall survival gain also remains an area of significant uncertainty, and this could be greater than that shown in PALOMA-1.

Conclusion

Ribociclib is recommended

3.18 The committee concluded that there are uncertainties in the modelling, but the most plausible ICERs for ribociclib compared with letrozole are broadly within the range normally considered a cost-effective use of NHS resources. It noted the innovative nature of ribociclib and the importance of progression-free survival to patients with this disease. The committee recommended ribociclib as a cost-effective use of NHS resources for treating hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer.

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 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 determination.

4.3 The Department of Health and Novartis have agreed that ribociclib will be available to the NHS with a patient access scheme which makes it available with a discount. The size of the discount is commercial in confidence. It is the responsibility of the company to communicate details of the discount to the relevant NHS organisations. Any enquiries from NHS organisations about the patient access scheme should be directed to the Novartis Commercial Operations team on 01276 698 717 or commercial.team@novartis.com.

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 a project manager.

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Accreditation