NICE National Institute for Health and Care Excellence

NICE guidance

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

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 are 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.

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 Recommendations

1.1 Abemaciclib 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 endocrine therapy only if:

- exemestane plus everolimus would be the most appropriate alternative and
- the conditions in the managed access agreement for abemaciclib with fulvestrant are followed.

1.2 This recommendation is not intended to affect treatment with abemaciclib 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

Current treatment for advanced hormone receptor-positive, HER2-negative breast cancer after endocrine therapy when chemotherapy is not needed immediately, is usually exemestane, tamoxifen, or exemestane plus everolimus. NICE does not recommend fulvestrant monotherapy.

Clinical trial evidence suggests that compared with fulvestrant alone, abemaciclib with fulvestrant increases the length of time before the disease progresses. However, it is uncertain whether people having abemaciclib with fulvestrant live longer, because people in the trial have not been followed-up for long enough. This uncertainty in the clinical benefit adds to the uncertainty about the cost-effectiveness estimates.

The cost-effectiveness estimates are based on an indirect comparison. Also, survival data are incomplete. Therefore the cost-effectiveness estimates are highly uncertain. Most of the plausible estimates are likely to be higher than what NICE normally considers an acceptable use of NHS resources, although the company's preferred estimate is lower. Therefore abemaciclib with fulvestrant is not recommended for routine commissioning in the NHS.

More evidence is needed to address clinical uncertainties. Longer follow-up data from the trial on how long people live are likely to reduce the uncertainty in the clinical- and cost-effectiveness results. Therefore abemaciclib with fulvestrant is recommended for use in the Cancer Drugs Fund,

while these data are collected.

2 Information about abemaciclib

Marketing authorisation	Abemaciclib (Verzenios, Eli Lilly) 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 … in women who have received prior endocrine therapy. In pre- or peri-menopausal women, the endocrine therapy should be combined with a luteinising hormone-releasing hormone (LHRH) agonist.'
Dosage in the marketing authorisation	The recommended dose of abemaciclib is 150 mg orally twice daily when used with endocrine therapy. Management of some adverse reactions may need dose interruption or dose reduction – see the summary of product characteristics. It should be taken continuously as long as the patient is deriving clinical benefit from therapy or until unacceptable toxicity occurs.
Price	£2,950 for 56 × 150 mg tablets (excluding VAT, British national formulary online [accessed March 2019]). The company has a commercial arrangement. This makes abemaciclib 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.

3 Committee discussion

The appraisal committee (section 5) considered evidence submitted by Eli Lilly and a review of this submission by the evidence review group (ERG). See the committee papers for full details of the evidence.

New treatment option

People with advanced breast cancer would welcome a new treatment option

3.1 Advanced breast cancer is an incurable condition. Patient experts explained that a diagnosis of advanced breast cancer affects both people's physical and mental health. They stated that the potential of abemaciclib plus fulvestrant to postpone or avoid the need for chemotherapy is important to patients who have previously had endocrine therapy, because chemotherapy has the potential to substantially reduce quality of life. They also highlighted the importance of people living for longer without the disease progressing, therefore in better health. Currently, the cyclin-dependent kinase (CDK4/6) inhibitors palbociclib and ribociclib together with aromatase inhibitors are the most commonly used first-line endocrine-based treatments for advanced breast cancer. The clinical experts explained that because of the potential for tumours becoming resistant, CDK4/6 inhibitors would not be used twice. Now that CDK4/6 inhibitors are recommended as first-line treatment, the number of people being offered aromatase inhibitors alone as first-line treatment may be expected to decline. However, the clinical experts noted that if a CDK4/6 inhibitor were available after endocrine therapy, they may offer patients whose disease is progressing slowly an aromatase inhibitor alone as the first treatment, reserving abemaciclib with fulvestrant for subsequent treatment. They stated that this may be preferable because some people, especially with a low tumour burden, have disease that responds well to endocrine therapy alone. People who would also potentially benefit from abemacicilb plus fulvestrant are those whose disease has progressed on or within 12 months of neoadjuvant or adjuvant endocrine therapy. These people are currently not eligible for a CDK4/6 inhibitor plus aromatase inhibitor in the NHS. 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 management

The most relevant comparator for this appraisal is exemestane with everolimus

3.2 Clinical experts explained that in England, advanced hormone receptor-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer that has progressed on endocrine therapy would be treated with either exemestane, tamoxifen, or exemestane plus everolimus. They noted that fulvestrant monotherapy was not recommended by NICE, and was available in some parts of the country but not others, so access is variable. They stated that chemotherapy would usually only be used after other less toxic options had been exhausted or if they were not suitable. The committee agreed that chemotherapy was not a relevant comparator. The committee noted that NICE's technology appraisal guidance on everolimus with exemestane for treating advanced breast cancer after endocrine therapy states this is the most clinically effective treatment after endocrine therapy and that it is the only other combination treatment option. The clinical experts explained that its use in clinical practice may be limited by adverse effects. The committee concluded that exemestane plus everolimus was the most relevant comparator for this appraisal. Exemestane or tamoxifen would be a relevant comparator for some people who cannot tolerate exemestane plus everolimus. Fulvestrant is not routinely commissioned but is sometimes used.

Clinical evidence

The clinical-effectiveness evidence is relevant to NHS clinical practice in England

3.3 The evidence for abemaciclib plus fulvestrant came from MONARCH 2. This was a multicentre, randomised, double-blind trial in women aged 18 or over with hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer which had progressed on or after endocrine therapy. All women enrolled were functionally menopausal. MONARCH 2 compared abemaciclib plus fulvestrant with placebo plus fulvestrant. There were no patients from the UK but the clinical experts confirmed that the population included in the trial was representative of people in England who would be eligible for treatment with abemaciclib plus fulvestrant. The committee concluded that the evidence from MONARCH 2 was relevant to NHS clinical practice in England.

Abemaciclib plus fulvestrant increases progression-free survival compared with

fulvestrant alone but the overall survival data are immature

3.4 The primary outcome measure of MONARCH 2 was investigator-assessed progression-free survival. Treatment with abemaciclib plus fulvestrant increased median progression-free survival compared with fulvestrant alone from 9.3 months to 16.4 months (hazard ratio 0.553; 95% confidence interval [CI] 0.449 to 0.681, p<0.001). Median overall survival had not been reached in either treatment group of MONARCH 2; 19.1% of patients in the abemaciclib plus fulvestrant group and 21.5% in the placebo plus fulvestrant group had died at the time of analysis. The committee agreed that the progression-free survival was promising but the benefit of abemaciclib plus fulvestrant on overall survival was unclear. The committee noted that the overall survival data came from a data cut in February 2017, but that an updated data cut was anticipated. The study is expected to complete in late 2021. The committee concluded that abemaciclib plus fulvestrant increased progression-free survival compared with fulvestrant alone but that the benefit in overall survival was at present unknown.

Adverse effects

The safety profile of abemaciclib plus fulvestrant is acceptable to patients

3.5 The committee noted that treatment discontinuations and dose reductions because of adverse events were more common in the abemaciclib plus fulvestrant group than in the placebo plus fulvestrant group. After the trial had started, the protocol was amended to reduce the starting dose of abemaciclib from 200 mg twice daily to 150 mg twice daily because of the number of adverse events. The patient experts explained that treatment with abemaciclib plus fulvestrant may delay or avoid the need for chemotherapy, which is likely to have worse adverse effects, so treatment with abemaciclib plus fulvestrant would be preferable for patients. The clinical experts explained that the adverse effects of abemaciclib would be manageable in clinical practice. The committee concluded on the basis of clinical and patient expert testimony that the safety profile of abemaciclib plus fulvestrant would be acceptable to patients.

Network meta-analysis

Both the company's and the ERG's network meta-analyses are associated with heterogeneity and uncertainty

3.6 Because there are no direct trials comparing abemaciclib plus fulvestrant with exemestane, exemestane plus everolimus or tamoxifen, the company presented a network meta-analysis. Both the company's and the ERG's preferred networks (which were not the same) included trials that had different eligibility criteria to MONARCH 2. In some trials in the networks, 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. The company's network meta-analyses to compare progression-free survival and overall survival across the treatments were based on hazard ratios. The ERG highlighted that for some of the studies included in the network, the proportional hazards assumption was not met. The ERG therefore presented a network meta-analysis that was based on a fractional polynomial method. The committee agreed that there was heterogeneity in both the company's and the ERG's network meta-analyses. The committee was reassured that both for progression-free survival and overall survival, the results showed that the ranking of treatment effectiveness (when the same treatments were included) was the same in the company's and the ERG's analyses. However, it noted that the analyses for overall survival were very uncertain because of the immaturity of the overall survival data from MONARCH 2. The committee was aware that there are several available methods that can be used if the proportional hazards assumption is not met and that there is no agreement about which is the best method. It agreed that if more complete overall survival data from MONARCH 2 were available, the current level of uncertainty would be reduced. The committee concluded that both the company's and the ERG's network meta-analyses were associated with heterogeneity because of the trials included and uncertainty because of the immature overall survival data from MONARCH 2.

The company's economic model

The model structure is appropriate for decision making but the overall survival data used in the model are immature

3.7 The company presented a partitioned survival model with 3 health states: progression-free survival, post-progression survival and death. The model had a

weekly cycle and a time horizon equivalent to a lifetime horizon. The company used parametric curves to model progression-free survival and overall survival. It fitted joint Weibull distributions for both abemaciclib plus fulvestrant and fulvestrant alone to the Kaplan–Meier data from MONARCH 2 for investigator-assessed progression-free survival and overall survival. The company applied hazard ratios from its preferred network meta-analysis to the fitted MONARCH 2 fulvestrant curves to estimate the survival curves for exemestane and everolimus plus exemestane. It did an adjusted indirect comparison with fulvestrant to estimate the relevant treatment effect of tamoxifen. The ERG used the survival curves derived from its fractional polynomial network meta-analysis in its base-case economic model. The committee was concerned that both the company's and the ERG's base-case models were based on the network meta-analyses that the committee had agreed contained heterogeneity and were uncertain because of the immaturity of the overall survival data in MONARCH 2 (see section 3.6). The committee concluded that the model structure was appropriate for decision making but that overall survival data used in the model were too immature to reliably predict the relative survival benefit of abemaciclib plus fulvestrant.

The company model underestimates the treatment duration and therefore costs of abemaciclib plus fulvestrant

3.8 In the model, the company estimated time to treatment discontinuation for abemaciclib plus fulvestrant and fulvestrant by jointly fitting Weibull curves to the time to treatment discontinuation data from the intention-to-treat population in MONARCH 2. To model time on treatment for the other comparators, the company calculated a hazard ratio from the median duration of therapy and the median progression-free survival statistics reported in the trial publications. It then applied this hazard ratio to the progression-free survival distribution in the model. The ERG considered joint curve fitting to be inappropriate because the proportional hazards assumption was not met. It preferred to use an alternative method using the progression-free survival curves from its fractional polynomial network meta-analysis. In the ERG's method, a hazard ratio was obtained from the median duration of therapy in the trial publications and the median progression-free survival in the model to estimate time on treatment for abemaciclib plus fulvestrant, fulvestrant, and exemestane plus everolimus. The ERG also highlighted the effect of the protocol amendment in MONARCH 2 (in which the starting dose of abemaciclib was

reduced, see section 3.5) on the Kaplan–Meier curves. More people who started on the 200 mg dose of abemaciclib stopped treatment early than people who started on the 150 mg dose. Therefore, time to treatment discontinuation was shorter with a bigger difference between the progression-free survival and time to treatment discontinuation curves in the intention-to-treat population. The ERG therefore considered that estimating time to treatment discontinuation using the intention-to-treat population underestimated the time on treatment, and therefore the costs of abemaciclib in the company's model. In the absence of time to discontinuation data for people who started on 150 mg twice daily abemaciclib, the ERG provided exploratory scenario analyses that reduced the hazard ratio between time to treatment discontinuation and progression-free survival in its base case by 5% and by 10%. It also presented a scenario where time to treatment discontinuation was the same as progression-free survival (hazard ratio of 1), which had a big effect on the cost-effectiveness results. The ERG scenarios projected longer time on treatment with higher associated costs, but no change in the projected benefit. The committee considered that a hazard ratio of 1 was highly unlikely because in practice, some people would stop treatment before progression. The committee agreed that the time to treatment discontinuation was uncertain, but likely to be underestimated in the company model.

Utility values in the economic model

The utility value for post-progression survival does not have a big effect on the cost-effectiveness results compared with exemestane plus everolimus

3.9 The company used EQ-5D data from MONARCH 2 to derive a utility value for the pre-progression health state in its base case. For post-progression survival in its base case, the company used a utility value of 0.505, taken from a study by Lloyd et al. (2006). This utility value was used in NICE's technology appraisal guidance on everolimus with exemestane for treating advanced breast cancer after endocrine therapy, which included a similar population. The committee was aware that using data from Lloyd et al. was not in line with NICE's reference case, because it used the standard gamble method to estimate the utility values. The ERG did scenario analyses with 2 different utility values for the post-progression health state. In 1 scenario, the ERG used the utility value derived from the EQ-5D data from MONARCH 2. In the other analysis, the ERG used a utility value derived from EQ-5D data from a study by Mitra et al. (2016), which

included patients with hormone receptor-positive, HER2-negative breast cancer. The committee concluded that changing the utility value for post-progression survival did not have a big effect on the cost-effectiveness results for abemaciclib plus fulvestrant compared with exemestane plus everolimus. The utility value from MONARCH 2, or the value derived from Mitra et al. and used in the ERG's base case were methodologically preferable to the value from Lloyd et al. because they used EQ-5D to measure health-related quality of life in people with breast cancer. However, the committee acknowledged that the Lloyd et al. data had been accepted in previous appraisals.

Subsequent treatments in the economic model

The ERG's changes to modelling of subsequent treatments are plausible

3.10 The ERG made some changes to the company's modelling of subsequent treatments, based on clinical opinion. It increased the use of paclitaxel, included tamoxifen, and removed bevacizumab, which is not available in the NHS. The company's model assumed that patients would stay on subsequent treatment for 37% of their time in the post-progression survival health state. The ERG amended this so that patients stayed on subsequent treatment for all but the last 3 months of their life. The ERG's scenario analyses also limited the amount of time that patients could have the most expensive subsequent treatments (fulvestrant and exemestane plus everolimus). The committee noted that when the ERG reduced the exposure to the most expensive subsequent treatments in the model, the incremental cost-effectiveness ratio (ICER) for abemaciclib plus fulvestrant compared with exemestane plus everolimus decreased, but the decrease was small. The committee concluded that the ERG's changes to the company's model were plausible but the exact treatments that people would have after abemacicilb plus fulvestrant were uncertain.

Cost-effectiveness results

The ICERs compared with exemestane plus everolimus are uncertain

3.11 The committee considered the cost effectiveness of abemaciclib plus fulvestrant in people who could have exemestane plus everolimus. The company's base case included the confidential commercial arrangement for abemaciclib but not the discount for everolimus (which reduces the costs of exemestane plus everolimus). Without this reduction included, abemaciclib plus

fulvestrant dominated exemestane plus everolimus (that is, was both cheaper and more effective). The ERG made some changes to the company's model in its preferred base case, including:

- correcting errors in the company's model, particularly related to the costs of subsequent treatment
- using curves for progression-free and overall survival derived from the ERG's fractional polynomial network meta-analysis, and the ERG's estimated time to treatment discontinuation curves (see sections 3.6 and 3.7)
- using the post-progression survival utility value derived from Mitra et al. (2016) (see section 3.9)
- including the ERG's changes to subsequent treatment modelling (see section 3.10).

The committee noted that the effect on the cost-effectiveness results of using the ERG's fractional polynomial network meta-analysis was unclear because the scenario presented was combined with other changes to the model (including time to discontinuation). In the ERG's base-case results, abemaciclib plus fulvestrant still dominated exemestane plus everolimus based on the confidential discount of abemaciclib but not everolimus. When the confidential discount for everolimus was included, the company's base-case ICER compared with exemestane plus everolimus was below £30,000 per quality-adjusted life year (QALY) gained, and the ERG's base-case ICER was above £30,000 per QALY gained. The exact ICERs are commercial in confidence and cannot be reported here. Different sources of utility values and limiting the use of expensive subsequent treatments had little effect on the ICER compared with exemestane plus everolimus. The committee noted that the ERG's base-case ICER compared with exemestane plus everolimus increased further when the ERG matched the time on treatment to progression-free survival. The committee agreed that the time on treatment may have been underestimated in the company base case (see section 3.8). The committee agreed that the ICERs for abemaciclib plus fulvestrant were uncertain. Further trial data would be available within 2 years, which would give further information on overall survival and time on treatment which could reduce this uncertainty, but at present the committee concluded that it could not be confident enough that abemaciclib plus fulvestrant was a cost-effective use of NHS resources to recommend it for routine commissioning in the NHS in England.

Abemaciclib is not cost effective compared with treatments other than exemestane plus everolimus

3.12 The committee considered the cost effectiveness of abemaciclib plus fulvestrant compared with the other comparator treatments, based on the confidential commercial arrangement for abemaciclib but not the discount for everolimus. The committee did not consider chemotherapy to be a relevant comparator (see section 3.2). It noted that abemaciclib plus fulvestrant was not cost effective in people who would otherwise have treatments other than exemestane plus everolimus. The company's base-case ICERs (including the ERG corrections for the cost of subsequent treatment) and the ERG's base-case ICERs were £50,687 and £70,634 per QALY gained compared with fulvestrant, £57,247 and £63,436 per QALY gained compared with exemestane and the company's base-case ICER was £82,621 compared with tamoxifen. Exemestane plus everolimus was included in the model as a subsequent treatment. The committee noted that when the confidential discount for everolimus was included with the ERG's model corrections, the ICERs for abemaciclib plus fulvestrant compared with each of the above comparators were substantially above what could be considered a cost-effective use of NHS resources. Abemeciclib could therefore not be recommended in people for whom exemestane plus everolimus was not appropriate.

Cancer Drugs Fund

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

3.13 Having concluded that abemaciclib plus fulvestrant could not be recommended for routine use, the committee then considered if it could be recommended for treating advanced hormone receptor-positive, HER2-negative breast cancer after endocrine therapy 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 more overall survival data from MONARCH 2 will become available in 2019. The estimated study completion date is in 2021. The committee agreed that:

- further data on overall survival would likely reduce the uncertainty in the long-term benefit of abemaciclib plus fulvestrant

- further data may make it clearer which method is the most appropriate for doing the network meta-analysis
- more data may be able to be collected on time on treatment
- 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.

The committee considered that on the basis of the cost-effectiveness analyses including all commercial discounts, there was plausible potential that abemaciclib plus fulvestrant would be cost effective compared with exemestane plus everolimus if subsequent data confirm the company's preferred assumptions. It therefore concluded that abemaciclib plus fulvestrant met the criteria to be considered for inclusion in the Cancer Drugs Fund. It recommended abemaciclib plus fulvestrant for use within the Cancer Drugs Fund as an option for people with advanced hormone receptor-positive, HER2-negative breast cancer after endocrine therapy, 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 has advanced hormone receptor-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer, has had endocrine therapy, and the doctor responsible for their care thinks that abemaciclib 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 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.

Kirsty Pitt
Technical lead

Eleanor Donegan
Technical adviser

Gemma Barnacle
Project manager

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Accreditation