NICE National Institute for Health and Care Excellence

NICE guidance

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

Technology appraisal guidance
Published: 26 October 2022

www.nice.org.uk/guidance/ta836

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

This guidance replaces TA619.

1 Recommendations

1.1 Palbociclib plus fulvestrant is recommended as an option for treating hormone receptor-positive, HER2-negative locally advanced or metastatic breast cancer in adults who have had endocrine therapy only if:

- exemestane plus everolimus is the most appropriate alternative to a cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor and
- the company provides it according to the commercial arrangement.

1.2 If patients and their clinicians consider palbociclib plus fulvestrant and abemaciclib plus fulvestrant or ribociclib plus fulvestrant to be suitable options, use the least expensive treatment. Take account of the monitoring and adverse event costs, dosage, price per dose and commercial arrangements.

Why the committee made these recommendations

This appraisal reviews the evidence for palbociclib plus fulvestrant for hormone receptor-positive, HER2-negative locally advanced or metastatic breast cancer after endocrine therapy (NICE technology appraisal guidance TA619). It also reviews new evidence from a clinical trial and data collected from people having treatment through the Cancer Drugs Fund managed access agreement.

Treatment for hormone receptor-positive, HER2-negative locally advanced or metastatic breast cancer after endocrine therapy includes exemestane plus everolimus, and the CDK4/6 inhibitors abemaciclib (plus fulvestrant) and ribociclib (plus fulvestrant) if exemestane plus everolimus is the most appropriate alternative. Palbociclib plus fulvestrant is another option that works in a similar way to abemaciclib and ribociclib.

The new evidence collected from people having treatment through the Cancer Drugs Fund shows that palbociclib plus fulvestrant is clinically effective. Additional clinical trial evidence shows that it increases how long people live compared with placebo plus

fulvestrant. Indirect comparisons suggest that it has similar clinical effectiveness to abemaciclib plus fulvestrant and ribociclib plus fulvestrant.

A cost comparison suggests palbociclib plus fulvestrant has similar costs to abemaciclib plus fulvestrant and ribociclib plus fulvestrant. So, palbociclib plus fulvestrant is recommended if it is used in the same population as abemaciclib and ribociclib.

2 Information about palbociclib

Marketing authorisation indication

2.1 Palbociclib (Ibrance, Pfizer) is indicated 'for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer:

- in combination with an aromatase inhibitor;
- in combination with fulvestrant in women who have received prior endocrine therapy.

  In pre- or perimenopausal women, the endocrine therapy should be combined with a luteinizing hormone-releasing hormone (LHRH) agonist'.

Dosage in the marketing authorisation

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

Price

2.3 The company's list price is £2,950 per 21-pack of 75 mg, 100 mg or 125 mg capsules (excluding VAT; BNF online, accessed July 2022). The average cost of a course of combination treatment at list price is £6,170.70 for the loading dose and £5,126.42 for the following cycles. The company has a commercial arrangement. This makes palbociclib 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 considered evidence submitted by Pfizer, a review of this submission by the external assessment group (EAG), and responses from stakeholders. See the committee papers for full details of the evidence.

Treatment pathway

People with advanced breast cancer value a choice of treatment options

3.1 People with advanced breast cancer who have had endocrine therapy are eligible for the cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors abemaciclib or ribociclib, in combination with fulvestrant, if exemestane plus everolimus is the most appropriate alternative (see NICE's technology appraisal guidance on abemaciclib and ribociclib). Patient experts said that these treatments can delay disease progression and delay or avoid the need for chemotherapy. Patient experts noted that they value a choice of treatment options because CDK4/6 inhibitors have different side effect profiles. Choice would give people the option to change to a different treatment if needed. Patient experts noted that the side effect profile of palbociclib is more similar to ribociclib than abemaciclib, but unlike ribociclib, palbociclib does not need any ECG monitoring. The committee concluded that having a choice of treatments is valued by people with advanced breast cancer.

Clinical evidence

PALOMA-3 is relevant to the NHS and has a long follow-up period

3.2 PALOMA-3 is a multicentre double-blind randomised placebo-controlled trial comparing palbociclib plus fulvestrant (n=347) with placebo plus fulvestrant (n=174) in adults with hormone receptor-positive, HER2-negative advanced breast cancer. An additional 28 months of

overall survival data were collected in the ongoing trial while palbociclib was also available to people through the Cancer Drugs Fund. After a median follow-up of 73.3 months in the trial, median overall survival was 6.8 months longer in people who had palbociclib plus fulvestrant compared with those who had placebo plus fulvestrant (median 34.8 months for palbociclib plus fulvestrant compared with 28.0 months for placebo plus fulvestrant [HR 0.81; 95% CI 0.65 to 0.99, p=0.02]). The committee noted that there was a relatively long follow-up period in PALOMA-3. The EAG noted that people in the trial may have had more previous treatments than people seen in NHS clinical practice, but considered that the results are generalisable to the NHS. The committee concluded that the results from PALOMA-3 are relevant to the NHS and the trial has a long follow-up period.

A large Systemic Anticancer Therapy (SACT) dataset supports the clinical effectiveness of palbociclib plus fulvestrant

3.3 Public Health England provided observational data from the SACT dataset for 1,140 people who had palbociclib plus fulvestrant through the Cancer Drugs Fund. Median follow-up was 10 months. Median treatment duration with palbociclib plus fulvestrant was 9.4 months and median overall survival was not yet reached. At 6 months, 88% of people taking palbociclib plus fulvestrant were alive; at 12 months, 75% were alive; and at 18 months, 63% were alive. The committee noted that equivalent overall survival rates were seen with abemaciclib plus fulvestrant at 6 and 12 months in SACT. It noted that the SACT dataset did not directly compare palbociclib plus fulvestrant with abemaciclib plus fulvestrant but the findings showing similar efficacy of the 2 treatments in NHS clinical practice were reassuring. The committee concluded that a large SACT dataset supports the clinical effectiveness of palbociclib plus fulvestrant.

Abemaciclib plus fulvestrant and ribociclib plus fulvestrant are appropriate comparators

3.4 Abemaciclib and ribociclib are CDK4/6 inhibitors recommended by NICE for treating hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy. Palbociclib is another CDK4/6 inhibitor

that works in a similar way to abemaciclib and ribociclib. The EAG's clinical advisers noted that the 3 drugs have the same primary mechanism although with some differences in individual inhibition of CDK4 and CDK6 in laboratory studies. They also noted differences in dosing schedules, serum concentration and toxicity. All 3 CDK4/6 inhibitors are administered orally. Palbociclib and ribociclib are given once daily for 21 days of a 28-day cycle. Abemaciclib is given twice daily for the whole cycle. All are combined with fulvestrant, which is given by intramuscular injection, twice in the first month, followed by once monthly. The committee concluded that abemaciclib plus fulvestrant and ribociclib plus fulvestrant are appropriate comparators for palbociclib plus fulvestrant.

MONARCH 2 and MONALEESA-3 can be compared with PALOMA-3, although there are some differences between the 3 trial populations

3.5 The pivotal clinical trials of abemaciclib plus fulvestrant and ribociclib plus fulvestrant are MONARCH 2 (n=669) and MONALEESA-3 (n=726). As in PALOMA-3 (see section 3.2), these trials compared a CDK4/6 inhibitor plus fulvestrant with placebo plus fulvestrant. All 3 trials had investigator-assessed progression-free survival as the primary endpoint. The committee considered that MONARCH 2 and MONALEESA-3 provided suitable clinical evidence for a comparison with PALOMA-3. People in PALOMA-3 and MONARCH 2 could be in any stage of menopause, while those in MONALEESA-3 were in postmenopause. However, in PALOMA-3 and MONARCH 2, people who were in premenopause or perimenopause had a luteinising hormone-releasing hormone agonist to make them functionally in postmenopause. The EAG noted that people in PALOMA-3 had more previous chemotherapy in the metastatic setting than the other 2 trials. The committee also noted that people in PALOMA-3 were younger (75% aged under 65 years) than those in MONARCH 2 (63% aged under 65 years) or MONALEESA-3 (53% aged under 65 years). The committee concluded that MONARCH 2 and MONALEESA-3 can be compared with PALOMA-3, although there are some differences between the 3 trial populations.

Clinical trials evidence suggests that palbociclib, abemaciclib and ribociclib are likely to provide similar health benefits

3.6 The results of PALOMA-3, MONARCH 2 and MONALEESA-3 show that palbociclib plus fulvestrant, abemaciclib plus fulvestrant and ribociclib plus fulvestrant improve progression-free survival and overall survival compared with placebo plus fulvestrant. The EAG stated that the hazard ratios for these outcomes were similar for the 3 treatments and the committee was aware that follow up was longer in the palbociclib trial than the others. Only PALOMA-3 and MONALEESA-3 collected data on subsequent therapy. This showed that most people had a follow-on therapy. The EAG stated that some people had a subsequent CDK4/6 inhibitor which is not standard NHS practice. However, the committee noted that this was more common in people who had placebo plus fulvestrant in the trial and had not had a CDK4/6 inhibitor before. The committee concluded that evidence from the 3 clinical trials suggests that palbociclib, abemaciclib and ribociclib, all in combination with fulvestrant, are likely to provide similar health benefits in terms of progression-free and overall survival.

There are some differences in low grade adverse events between palbociclib, abemaciclib and ribociclib that may impact treatment choice

3.7 The company noted that the 3 CDK4/6 inhibitors have a broadly similar profile of grade 3 or higher adverse events. But there are important differences in some low grade adverse events. Neutropenia is less common and lower grade with abemaciclib plus fulvestrant than with palbociclib plus fulvestrant or ribociclib plus fulvestrant. Any grade diarrhoea is more common with abemaciclib plus fulvestrant (87%) than with palbociclib plus fulvestrant or ribociclib plus fulvestrant (both less than 30%). The EAG noted that the lower rates of diarrhoea seen with palbociclib plus fulvestrant than with abemaciclib plus fulvestrant have the potential to improve health-related quality of life. The Cancer Drugs Fund clinical lead noted that diarrhoea has a direct impact on people having treatment. Neutropenia is a toxicity detected through regular blood testing but it may not affect the person having treatment or cause symptoms. The committee recalled that people with advanced breast

cancer value choice in treatments and the option to change to a different treatment if needed (see section 3.1). The committee concluded that there are some differences in low grade adverse events between palbociclib, abemaciclib and ribociclib that may impact treatment choice.

Indirect treatment comparisons

Well-designed indirect comparisons suggest that the clinical efficacy of palbociclib plus fulvestrant is similar to or better than the comparators

3.8 The company presented matching-adjusted indirect treatment comparisons (MAICs) of palbociclib plus fulvestrant compared with abemaciclib plus fulvestrant and ribociclib plus fulvestrant. These used latest survival data from the 3 pivotal trials (see section 3.6). In the MAICs, the PALOMA-3 population was statistically adjusted to resemble the MONARCH 2 and MONALEESA-3 populations. This was to predict the treatment effect if palbociclib plus fulvestrant had been evaluated in these populations. The EAG agreed with the company's approach to account for differences between the 3 trial populations (see section 3.5). It considered that the MAICs were well designed. The MAICs of palbociclib plus fulvestrant and abemaciclib plus fulvestrant included up to 12 potential treatment effect modifiers. The results suggested no statistically significant difference in progression-free survival or overall survival with palbociclib plus fulvestrant compared with abemaciclib plus fulvestrant. The committee noted that the MAICs suggest that the clinical efficacy of palbociclib plus fulvestrant is similar to abemaciclib plus fulvestrant. The MAICs of palbociclib plus fulvestrant and ribociclib plus fulvestrant included up to 13 potential treatment effect modifiers. The results suggested no statistically significant difference in overall survival with palbociclib plus fulvestrant compared with abemaciclib plus fulvestrant. However, some of the MAICs for progression-free survival, including when all effect modifiers were considered, suggested a statistically significant difference in favour of palbociclib plus fulvestrant. The committee noted that the MAICs suggest that the clinical efficacy of palbociclib plus fulvestrant is similar to or better than that of ribociclib plus fulvestrant. The committee concluded that the well-designed MAICs

suggest that palbociclib plus fulvestrant is similar to or better than the comparators.

Cost comparison

Palbociclib plus fulvestrant is likely to have similar costs to abemaciclib plus fulvestrant and ribociclib plus fulvestrant

3.9 The company presented a cost-comparison analysis that included the costs of drug acquisition, administration, monitoring and adverse events. The company base case assumed a 40-year time horizon. Adverse event rates were assumed to vary by treatment and were based on publicly available data. Monitoring differed by treatment, with:

- palbociclib needing a full blood count
- abemaciclib needing a full blood count and liver enzyme tests
- ribociclib needing a full blood count, ECG, serum electrolytes and a liver function test.

The EAG agreed the company's approach was reasonable. When taking account of the commercial arrangements for all treatments, the committee was satisfied that the total costs associated with palbociclib plus fulvestrant were likely to be similar to abemaciclib plus fulvestrant and ribociclib plus fulvestrant (the exact results are confidential and cannot be reported here). The committee therefore recommended palbociclib plus fulvestrant as an option for treating hormone receptor-positive, HER2-negative locally advanced or metastatic breast cancer in adults who have had endocrine therapy, only if exemestane plus everolimus is the most appropriate alternative to a CDK4/6 inhibitor.

Other factors

There are no equality issues relevant to the recommendations

3.10 The committee did not identify any equality issues.

4 Implementation

4.1 Section 7 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. Because palbociclib has been recommended through the fast track appraisal process, NHS England and commissioning groups have agreed to provide funding to implement this guidance 30 days after 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 advanced breast cancer and the doctor

responsible for their care thinks that palbociclib with fulvestrant is the right treatment, it should be available for use, in line with NICE's recommendations.

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.

Chair

Jane Adam
Chair, Technology appraisal evaluation committee A

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.

Catherine Spanswick and Sana Khan
Technical leads

Rufaro Kausi
Technical adviser

Thomas Feist

Project manager

ISBN: 978-1-4731-4787-4