NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

Inavolisib with palbociclib and fulvestrant for treating recurrent oestrogen receptor-positive HER2-negative PIK3CA-mutated advanced breast cancer after adjuvant endocrine treatment

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

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

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

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Issue date: May 2026

Note that this document is not NICE's final guidance on these technologies. The recommendations in section 1 may change after consultation.

After consultation:

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- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using inavolisib with palbociclib and fulvestrant in the NHS in England.

For further details, see NICE's manual on health technology evaluation.

The key dates for this evaluation are:

- Closing date for comments: 18 June 2026
- Second evaluation committee meeting: 11 August 2026
- Details of the evaluation committee are given in section 4

Issue date: May 2026

1 Recommendations

1.1 Inavolisib plus palbociclib and fulvestrant should not be used to treat oestrogen receptor-positive, HER2-negative, PIK3CA-mutated locally advanced or metastatic breast cancer in adults when:

- the cancer has recurred during adjuvant endocrine treatment or within 12 months of completing it, and
- if neoadjuvant or adjuvant treatment included a cyclin-dependent kinase (CDK) 4 and 6 inhibitor, the cancer has recurred 12 months or more after stopping the CDK 4 and 6 inhibitor.

1.2 This recommendation is not intended to affect treatment with inavolisib plus palbociclib and 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 healthcare professional consider it appropriate to stop.

What this means in practice

These are NICE's draft recommendations. If these recommendations become final, inavolisib plus palbociclib and fulvestrant would not be required to be funded and should not be used routinely in the NHS in England for the condition and population in the recommendations.

This is because the available evidence does not suggest that inavolisib plus palbociclib and fulvestrant is value for money in this population.

Why the committee made these recommendations

Oestrogen receptor-positive, HER2-negative, PIK3CA-mutated, locally advanced or metastatic breast cancer can recur (come back) after adjuvant endocrine treatment

Issue date: May 2026

with or without a neoadjuvant or adjuvant CDK 4 and 6 inhibitor. After recurrence, usual treatment is a CDK 4 and 6 inhibitor (abemaciclib, palbociclib or ribociclib) plus fulvestrant.

Clinical trial evidence suggests that inavolisib plus palbociclib and fulvestrant increases how long people have before their condition gets worse compared with palbociclib plus fulvestrant. But this is uncertain because the trial population differs from the NHS population.

Even when considering the condition's severity, and its effect on quality and length of life, the most likely cost-effectiveness estimates are above the range that NICE considers an acceptable use of NHS resources. So, inavolisib plus palbociclib and fulvestrant should not be used.

2 Information about inavolisib plus palbociclib and fulvestrant

Marketing authorisation indication

2.1 Inavolisib (Itovebi, Roche) is indicated in combination with palbociclib and fulvestrant for 'the treatment of adult patients with PIK3CA-mutated, oestrogen receptor (ER)-positive, HER2-negative, locally advanced or metastatic breast cancer, following recurrence on or within 12 months of completing adjuvant endocrine treatment. Patients previously treated with a CDK 4/6 inhibitor in the (neo)adjuvant setting should have had an interval of at least 12 months between termination of CDK 4/6 inhibitor treatment and the detection of recurrence. In pre/perimenopausal women and in men, endocrine therapy should be combined with a luteinising hormone-releasing hormone (LHRH) agonist'.

Dosage in the marketing authorisation

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

Issue date: May 2026

Price

2.3 The list price of inavolisib is £5,418 per 28-pack of 3-mg tablets, and £10,836 per 28-pack of 9-mg tablets (excluding VAT; BNF online accessed May 2026).

2.4 Roche has a commercial arrangement for inavolisib, which would have applied if inavolisib with palbociclib and fulvestrant had been recommended.

2.5 Pfizer has a commercial arrangement for palbociclib. This makes palbociclib available to the NHS with a discount and it would have also applied to this indication if inavolisib with palbociclib and fulvestrant had been recommended. The size of the discount is commercial in confidence.

Sustainability

2.6 For information, Roche's Carbon Reduction Plan for UK carbon emissions is published on their webpage on sustainability.

3 Committee discussion

The evaluation committee considered evidence submitted by Roche, 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.

The condition

Details of the condition

3.1 Breast cancer has tumour subtypes that guide treatment. Oestrogen receptor-positive (often referred to as hormone receptor-positive), HER2-negative breast cancer is the most common subtype. PIK3CA gene mutations occur in around 30% to 40% of oestrogen receptor-positive, HER2-negative tumours. Breast cancer with a PIK3CA mutation is associated with a poorer prognosis than breast cancer without the mutation. A patient expert emphasised the importance of having targeted

treatment options available at earlier points of the treatment pathway. This is because targeted treatment may increase the time that the condition is relatively stable, delay the need for chemotherapy and allow people with the condition to continue their daily lives. A patient expert explained that people with metastatic breast cancer have repeated progression, which affects many aspects of life, with symptoms including fatigue, cognitive impacts, emotional burden, anxiety and cumulative side effects. They also reported patient perspectives on the importance of continuing stable first-line treatment for longer, and that targeted treatment gives people hope of living longer and having a better quality of life. The committee agreed that there is an unmet need for targeted treatments for oestrogen receptor-positive, HER2-negative, PIK3CA-mutated, metastatic breast cancer.

Clinical management

Treatment options and comparators

3.2 In advanced breast cancer:

- primary endocrine resistance is defined as:
  - relapse during the first 2 years of adjuvant endocrine treatment, or
  - progression within 6 months of starting endocrine treatment, for metastatic cancer.
- secondary endocrine resistance is defined as:
  - relapse after the first 2 years of adjuvant endocrine treatment, or
  - relapse within 12 months of completing adjuvant endocrine treatment, or
  - progression at least 6 months after starting endocrine treatment, for metastatic cancer.

Current treatment for oestrogen receptor-positive, HER2-negative, locally advanced or metastatic breast cancer that is endocrine treatment resistant is a cyclin-dependent kinase (CDK) 4 and 6 inhibitor plus fulvestrant. These are:

- abemaciclib plus fulvestrant, in line with NICE technology appraisal guidance TA725
- palbociclib plus fulvestrant, in line with NICE technology appraisal guidance TA836
- ribociclib plus fulvestrant, in line with NICE technology appraisal guidance TA687.

The company positioned inavolisib plus palbociclib and fulvestrant in line with its marketing authorisation, as an alternative to a CDK 4 and 6 inhibitor plus fulvestrant. The marketing authorisation for inavolisib specifies that if a CDK 4 and 6 inhibitor was used in the adjuvant or neoadjuvant setting, then a minimum interval of 12 months is needed between stopping treatment with CDK 4 and 6 inhibitor and detecting recurrence. The committee concluded that abemaciclib, palbociclib and ribociclib, each with fulvestrant, are the appropriate comparators for this evaluation.

Clinical effectiveness

INAVO120 trial and results

3.3 The clinical evidence for inavolisib plus palbociclib and fulvestrant came from INAVO120, a phase 3, multicentre, double-blind, randomised controlled trial. The trial included adults with PIK3CA-mutated, hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer that had progressed either on or within 12 months of completing adjuvant endocrine treatment. People were randomised to inavolisib plus palbociclib and fulvestrant (n=161) or placebo plus palbociclib and fulvestrant (n=164). People remained on treatment until disease progression, toxicity or loss of clinical benefit. The primary outcome was progression-free survival (PFS), and secondary outcomes included overall survival (OS), response rate, duration of response, time to off-treatment and adverse effects. At the PFS full-analysis set clinical cut-off date (September 2023), the mean PFS for inavolisib plus palbociclib and

fulvestrant was 15.0 months (95% confidence interval [CI] 11.3 to 20.5), compared with 7.3 months (95% CI 6.6 to 9.3) for placebo plus palbociclib and fulvestrant (hazard ratio [HR] 0.43; 95% CI 0.32 to 0.59; p<0.0001). At the OS clinical cut-off date (November 2024), the mean OS for inavolisib plus palbociclib and fulvestrant was 34.0 months (95% CI 28.4 to 44.8) compared with 27.0 months (95% CI 22.8 to 38.7) for placebo plus palbociclib and fulvestrant (HR 0.67; 95% CI 0.48 to 0.94; p=0.019). The committee noted the maturity of the trial data and concluded that the INAVO120 trial results showed that inavolisib plus palbociclib and fulvestrant statistically significantly increased PFS and OS compared with placebo plus palbociclib and fulvestrant.

Generalisability of INAVO120

3.4 In INAVO120, only 3 people (2 in the inavolisib plus palbociclib and fulvestrant arm; 1 in the placebo plus palbociclib and fulvestrant arm) had a CDK 4 and 6 inhibitor as part of adjuvant or neoadjuvant treatment. The EAG noted that, in NHS clinical practice, aromatase inhibitor monotherapies were used as adjuvant treatments for hormone receptor-positive, HER2-negative early breast cancer. NICE has since recommended abemaciclib plus an aromatase inhibitor (NICE technology appraisal guidance TA810, published in 2022) and ribociclib plus an aromatase inhibitor (NICE technology appraisal guidance TA1086; published in 2025) as adjuvant treatment options for early breast cancer at a high risk of recurrence. Because of this, the proportion of people with locally advanced or metastatic cancer who have adjuvant treatment with a CDK 4 and 6 inhibitor plus an aromatase inhibitor is expected to increase over time. So, the EAG noted it was unclear if the trial results were generalisable to the NHS. It also noted that it was unclear whether prior CDK 4 and 6 inhibitor plus aromatase inhibitor treatment affects the relative effectiveness of inavolisib plus palbociclib and fulvestrant, or a CDK 4 and 6 inhibitor plus fulvestrant. A clinical expert noted that, in the NHS, people can have retreatment with a CDK 4 and 6 inhibitor if there is

at least a 12-month interval between stopping CDK 4 and 6 inhibitor treatment and detecting recurrence. They noted that the same principle would be expected for inavolisib plus palbociclib and fulvestrant. The NHS England Cancer Drugs Fund clinical lead (from now, CDF clinical lead) added that around 7,500 people per year in England are starting adjuvant treatment with a CDK 4 and 6 inhibitor. A clinical expert noted that adjuvant CDK 4 and 6 inhibitor use is likely to reduce the number of recurrences by around a third. They noted that PIK3CA-mutated cancer is associated with a poorer prognosis and rapid progression. So, it is more likely to relapse within a year of treatment and would not be eligible for retreatment with a CDK 4 and 6 inhibitor. The EAG also highlighted that people in the trial were younger (with a mean age of 54 years), fitter (with a lower Eastern Cooperative Oncology Group [ECOG] performance status) and weighed less than the expected NHS population. Also, the trial included more people with Asian ethnicity and fewer people with Black or African American ethnicity than the expected NHS population. The committee noted that hyperglycaemia was apparent in 60% of people in the inavolisib plus palbociclib and fulvestrant arm of INAVO120, with 74% having treatment with an antidiabetic medicine. The clinical experts explained that people with insulin-dependent diabetes are unlikely to have inavolisib because of concerns with glycaemic control. Also, because hyperglycaemia is a reversible side effect, often happening early in treatment, preventive measures to control blood glucose or adjust dose can be implemented. They also noted that similar issues occur with alpelisib and capivasertib, which they already have experience with. So, the clinical experts did not think this would impact uptake of inavolisib plus palbociclib and fulvestrant. The CDF clinical lead added that real-world evidence for starting a CDK 4 and 6 inhibitor plus fulvestrant in England shows that:

- around 45% of people are prescribed palbociclib plus fulvestrant, with an average age of 73

- around 40% are prescribed ribociclib plus fulvestrant, with an average age of 63.

The clinical experts explained that palbociclib is favoured for people who are frailer and may be on multiple drugs. This is because it has fewer side effects than ribociclib and because ribociclib may not be suitable for some people, such as people with cardiac comorbidities. They also explained that a CDK 4 and 6 inhibitor can be used later in the treatment pathway as a rescue option, often in older people. As a result, people switching to a CDK 4 and 6 inhibitor plus fulvestrant may be older on average. Because inavolisib plus palbociclib and fulvestrant is a triplet treatment regimen for established endocrine resistance, the clinical experts expected it to be used by people who are sufficiently fit for triplet treatment. The committee noted the increasing number of people having adjuvant treatment with a CDK 4 and 6 inhibitor in the NHS compared with the trial. It also noted the large difference in age of people in the trial compared with people in the NHS having treatment with the comparators. It concluded that the generalisability of the trial population to the NHS population was uncertain.

Indirect treatment comparison

3.5 There was no clinical trial directly comparing inavolisib plus palbociclib and fulvestrant with abemaciclib plus fulvestrant or ribociclib plus fulvestrant. So, the company used a network meta-analysis (NMA) to indirectly compare PFS and OS for abemaciclib plus fulvestrant and ribociclib plus fulvestrant with that for inavolisib plus palbociclib and fulvestrant. The company did an NMA with a population of mixed endocrine resistance using 7 randomised controlled trials: CAPItello-291, FLIPPER, INAVO120, MONALEESA-3, MONARCH-2, MONARCH plus and PALOMA-3. The results suggested an improvement in PFS (HR 0.42, 95% CI 0.21 to 0.87) and OS (HR 0.58, 95% CI 0.24 to 1.42) for inavolisib plus palbociclib and fulvestrant compared with abemaciclib plus

fulvestrant. The results also suggested an improvement in PFS (HR 0.38, 95% CI 0.18 to 0.81) and OS (HR 0.73, 95% CI 0.3 to 1.8) for inavolisib plus palbociclib and fulvestrant compared with ribociclib plus fulvestrant. The results imply that inavolisib plus palbociclib and fulvestrant is more effective compared with abemaciclib plus fulvestrant than with ribociclib plus fulvestrant. An NMA for only the endocrine-resistant population was also done, which excluded the FLIPPER and MONALEESA-3 trials. However, because ribociclib plus fulvestrant was only connected into the network through the MONALEESA-3 trial, the endocrine-resistant NMA does not have comparative efficacy results for ribociclib plus fulvestrant. The EAG noted that the endocrine-resistant NMA was more relevant to the scope population but having no results for ribociclib plus fulvestrant was an important limitation. The EAG also noted the heterogeneity between the baseline characteristics of the trials within the NMA which align with previously identified potential treatment effect modifiers of CDK 4 and 6 inhibitor regimens in this population. It highlighted that the PIK3CA mutation may also be a treatment effect modifier. The EAG considered clinical advice that the CDK 4 and 6 inhibitor plus fulvestrant regimens have similar efficacy and that TA836 concluded that palbociclib, abemaciclib and ribociclib, each with fulvestrant, were likely to provide similar health benefits for PFS and OS. The clinical experts agreed that, in clinical practice, the choice of CDK 4 and 6 inhibitor depends on comorbidities and side effect profiles, but it is assumed the treatment effects of all 3 are all similar. The company noted that because some trials in the NMA had unconfirmed PIK3CA mutation status, the clinical benefit of abemaciclib plus fulvestrant and ribociclib plus fulvestrant may be overestimated because of the poorer outcomes associated with having a PIK3CA mutation. A clinical expert noted that, although the overall outcomes with a PIK3CA mutation are worse, this does not impact the relative benefit of a CDK 4 and 6 inhibitor. They noted that the INAVO120 control arm is an appropriate reflection of what would be expected in clinical practice with a PIK3CA mutation. The committee noted the issues

with the NMA including the mixed endocrine-resistant population, as well as potential treatment effect modifiers highlighted by the EAG including PIK3CA mutation status. The committee noted the expert testimony and previous TA836 conclusion. It concluded that it was not appropriate to use the NMA results when comparing inavolisib plus palbociclib and fulvestrant with abemaciclib, palbociclib or ribociclib, each with fulvestrant. Instead, it was appropriate to assume similar treatment efficacy for the CDK 4 and 6 inhibitors plus fulvestrant combinations.

Economic model

Company's modelling approach

3.6 The company used a partitioned survival model with 4 mutually exclusive health states: PFS (the model entry), first progressive disease (PD1), second progressive disease (PD2), and death. At each model cycle, people can remain in the PFS health state or transition to the PD1 or death health state. Transition to the PD1 health state risks further progression to the PD2 or death health states. Those in the PD2 health state remain here until transitioning to the death health state. The model had 7-day cycles with a half-cycle correction to health outcomes and costs. It used a time horizon of 40 years, which was assumed to be a lifetime time horizon. The committee concluded that the model structure was appropriate for decision-making.

PFS extrapolation

3.7 To extrapolate PFS, the company did a piecewise approach using INAVO120 PFS Kaplan–Meier data, then applied a parametric extrapolation beyond the trial follow-up. Clinical advice to the company was that log-logistic or log-normal extrapolations are most clinically plausible because they estimate a 5% PFS at 10 years. The company preferred to fit a log-normal distribution to the entire dataset but only applied the log-normal distribution once 20% of people remained at risk, referencing recommendations from Pocock, Clayton and Altman (2002).

The company stated that this approach avoids under- or over-estimation that may occur when using parametric distributions from the start of the model. The EAG questioned the need for a piecewise approach since the parametric distributions had good visual fit to the Kaplan–Meier data in both arms. It found it unclear whether there were statistically and clinically significant turning points in the hazards. The EAG noted that the 20% patient-at-risk threshold is an arbitrary value and debatable, and cost-effectiveness results were sensitive to this assumption. It preferred to apply a log-logistic distribution from the start of the model because of its statistical and visual fit to the Kaplan–Meier data and clinical plausibility, and because it was appropriate for both treatment arms. The committee considered the different parametric distributions and concluded that the log-logistic distribution offered a good fit to the data. It agreed that using the 20% patient-at-risk threshold was arbitrary and added uncertainty to the modelling, so it preferred to apply the log-logistic distribution from the start of the model.

PFS and OS modelling

3.8 The company used the same approach as used for PFS to extrapolate OS, but instead used a gamma distribution and a 30% patient-at-risk threshold. The company explained that the higher threshold was because data is often more immature at this stage, and a higher threshold would mean the extrapolations were informed by a more robust dataset. To prevent illogical survival estimates, both the PFS1 and PFS2 curves were capped by OS. The EAG also used a gamma distribution to extrapolate OS but applied this from the start of the model. The EAG noted that applying a cap causes kinks in the curves which imply a sharp change in hazards, which may not be clinically plausible. It preferred to constrain PFS1 and PFS2 hazards so they cannot fall below the mortality hazard estimated from the OS curve, shifting the tail of the survival curves downwards. This ensured the extrapolations were logically consistent and clinically plausible. The committee noted that this issue was associated

with the limitations of partitioned survival models that independently model survival endpoints, especially when there is more than one progressed disease health state. It noted that it may be important to preserve information on PFS for longer in the model, rather than prematurely shifting down the curve before it crosses the OS curve. The committee preferred to apply the unconstrained log-logistic distribution from the start of the model for PFS (see section 3.7). For OS, it preferred to apply the gamma distribution from the start of the model, but to cap PFS by the absolute value of OS so that PFS cannot exceed mortality.

Treatment duration

3.9 The company used time-to-off-treatment data from INAVO120 to model treatment duration for both arms. It preferred to use a different parametric distribution than the log-normal distribution used for the PFS curves, stating that around 17% of people stopped treatment for reasons other than progression. To align with clinical expert opinion, it used a gamma distribution to extrapolate time to off-treatment at a 20% patient-at-risk threshold. The EAG noted that the separation between time to off-treatment and PFS curves was largely driven by discontinuation because of toxicity or adverse effects. The company's modelling implies that treatment discontinuation because of toxicity increases over time when in the progression-free health state because the time-to-off-treatment and PFS curves diverge. But clinical advice to the EAG was that most discontinuations because of toxicity occur early, and drug-associated adverse events can be well managed, so after 2 to 3 years the discontinuation rate is expected to be negligible. So, the EAG preferred to use the same distribution as for PFS (log-logistic), applied from the start of the model. The EAG modelling implies that the rate of treatment discontinuation because of toxicity decreases over time. The committee noted that a higher discontinuation rate would be expected earlier on, but people may also still discontinue treatment before their cancer progresses. The committee noted that when using the generalised

gamma approach, a higher discontinuation rate was seen earlier on as in the EAG's preferred distribution, but it maintained a separation of the treatment duration and PFS curves towards the end of treatment. The committee concluded that the generalised gamma distribution was the most appropriate to model treatment duration.

Treatment efficacy of comparators

3.10 In the company model, treatment efficacy of abemaciclib plus fulvestrant and ribociclib plus fulvestrant was modelled by applying the PFS and OS hazard ratios from the mixed endocrine-resistant NMA to the PFS and OS curves for inavolisib plus palbociclib and fulvestrant. Treatment duration of abemaciclib plus fulvestrant and ribociclib plus fulvestrant was estimated by applying the PFS hazard ratios from the mixed endocrine-resistant NMA to the palbociclib plus fulvestrant time to off-treatment curves for inavolisib plus palbociclib and fulvestrant. In the company base case, the mean survival for abemaciclib plus fulvestrant was lower than that for palbociclib or ribociclib plus fulvestrant, reflecting the NMA results. The EAG preferred to assume equivalent efficacy of the CDK 4 and 6 inhibitors plus fulvestrant, so it modelled efficacy by matching PFS, OS and time to off-treatment with palbociclib plus fulvestrant using results from INAVO120. The committee had already concluded that all of the CDK 4 and 6 inhibitors have very similar efficacy (see section 3.5). It concluded that it preferred the EAG's approach to model the treatment efficacy of abemaciclib plus fulvestrant and ribociclib plus fulvestrant by matching PFS, PFS2, OS and time to off-treatment with palbociclib plus fulvestrant using the results from INAVO120.

Relative dose intensity

3.11 The company applied the following relative dose intensities in the model to account for the impact of dose reductions and interruptions on the costs of treatment:

- inavolisib plus palbociclib and fulvestrant: mean relative dose intensity from INAVO120
- palbociclib and fulvestrant: mean relative dose intensity from INAVO120
- abemaciclib plus fulvestrant: 100% relative dose intensity
- ribociclib plus fulvestrant: 100% relative dose intensity.

The company assumed a 100% relative dose intensity for abemaciclib plus fulvestrant, as assumed in TA725, but could not access the relative dose intensity used in TA687 to inform ribociclib plus fulvestrant.

The EAG preferred to assume:

- inavolisib: adjusted relative dose intensity from INAVO120 that excludes single-dose reductions from 9 mg to 6 mg inavolisib, because the doses cost the same
- palbociclib: adjusted relative dose intensity from INAVO120 that excludes all palbociclib dose reductions, because all doses have the same price
- abemaciclib plus fulvestrant: mean adjusted palbociclib relative dose intensity from INAVO120, where only dose interruptions or missed doses impact costs
- ribociclib plus fulvestrant: mean unadjusted palbociclib relative dose intensity from INAVO120, where all dose changes impact costs
- fulvestrant: mean fulvestrant relative dose intensity from INAVO120, from either the intervention or control arm where appropriate.

A clinical expert noted that abemaciclib, palbociclib and ribociclib all have different kinds of toxicities. But most side effects happen early on, allowing dose reductions or switching to a different CDK 4 and 6 inhibitor. So, the relative dose intensity is expected to be similar for each of the CDK 4 and 6 inhibitors. The committee concluded that assuming a 100% relative dose intensity for abemaciclib plus fulvestrant and ribociclib plus

Issue date: May 2026

fulvestrant was unlikely. It preferred to model relative dose intensity using adjusted values from INAVO120 in line with the EAG's approach.

Subsequent treatment modelling

3.12 The subsequent treatment options for the PD1 and PD2 health states in the model were capecitabine, elacestrant (for cancer with an ESR1 mutation), everolimus plus exemestane, paclitaxel and best supportive care (for PD2 only). In the company's model, the proportion of people that had each subsequent treatment option in the PD1 and PD2 health states was informed by healthcare professionals from the company's clinical advisory board meeting. The company assumed that fewer people have elacestrant after inavolisib plus palbociclib and fulvestrant than after a CDK 4 and 6 inhibitor plus fulvestrant. The company also assumed that fewer people would have everolimus plus exemestane after inavolisib plus palbociclib and fulvestrant than after a CDK 4 and 6 inhibitor. This is because less benefit was assumed from having further endocrine-based treatment after inavolisib plus palbociclib and fulvestrant. The EAG instead assumed that the distributions for elacestrant and everolimus plus exemestane would only differ if progression was before or after 12 months (applies to only PD1 for everolimus plus exemestane). The clinical experts noted that more people may be eligible for elacestrant after inavolisib plus palbociclib and fulvestrant because survival on this treatment would be improved, and a minimum of 12 months treatment with a CDK 4 and 6 inhibitor is needed before elacestrant eligibility. However, healthcare professionals may not choose elacestrant when there is also a PIK3CA mutation, so uptake may be low. Healthcare professionals may also be cautious of using everolimus plus exemestane after a treatment that targets the same signalling pathway. The committee agreed that, based on the clinical experts' testimony, it was appropriate to model subsequent treatment distributions using the proportions informed by the company's clinical advisory board meeting.

PIK3CA testing costs

3.13 The company and EAG did not include the cost of PIK3CA testing in their economic models because the National Genomics Test Directory includes this testing. The clinical experts explained that PIK3CA mutations often occur early in the condition, so it is appropriate to test for the mutation at diagnosis of the metastatic stage of the condition. However, because PIK3CA-mutation testing is usually done at a later stage of treatment, together with ESR1-mutation testing, an additional step for testing would need to be implemented. The EAG reported that, for inavolisib plus palbociclib and fulvestrant, PIK3CA testing would need to happen earlier in the treatment pathway. The additional cost is uncertain because it is unknown how many people would have testing for other gene mutations in the second-line setting. It included a scenario in the economic model that included PIK3CA testing costs. However, the committee concluded that PIK3CA testing costs had been accounted for in the economic modelling, because it is already funded by its inclusion in the National Genomics Test Directory.

Severity

3.14 The committee considered the severity of the condition (the future health lost by people living with the condition and having standard care in the NHS). The committee may apply a greater weight to quality-adjusted life years (QALYs; a severity modifier) if technologies are indicated for conditions with a high degree of severity. The company provided absolute and proportional QALY shortfall estimates in line with NICE's technology appraisal and highly specialised technologies guidance manual. The general population QALYs were informed by the baseline characteristics from INAVO120, with a mean age of 54 years. The EAG noted that the QALY shortfall estimates were most sensitive to the comparator efficacies, health state utility estimates, and the starting age. The EAG report that the median age for first-line palbociclib plus fulvestrant in TA836 was 66 years, and the median age for ribociclib plus fulvestrant in

TA687 was 64 years. But, the EAG thought it appropriate to use the mean age from INAVO120 in its model because the treatment efficacies were all from INAVO120, resulting in a 1.2 severity weighting. Although the company's model used the NMA to inform treatment efficacy of the comparators, it also used the mean age from INAVO120, resulting in a 1.2 severity weighting. The committee noted that the mean age from INAVO120 may be 10 years younger than the age of people seen in clinical practice. However, it recalled the clinical expert comments on the possible explanations of why the trial population was younger than what is seen in clinical practice for CDK 4 and 6 inhibitors plus fulvestrant. But it noted that this difference was still substantially large. In the absence of the exact age that people may have this treatment in clinical practice, the committee agreed that using the mean age from the trial was acceptable. So, the committee concluded that the severity weight of 1.2 applied to the QALYs was appropriate, but noted the uncertainty associated with this assumption.

Other issues with impacts on cost effectiveness

3.15 In addition to the key issues discussed in sections 3.4 to 3.14, the EAG also made minor changes to the company's base-case modelling approaches and assumptions (see the EAG report in the committee papers). The additional changes were considered by committee. These were to:

- use the eMIT price rather than list prices for generic drugs
- use amended drug administration costs for subsequent fulvestrant doses and use the SB14Z NHS reference cost for the first attendance applied for subsequent treatment with paclitaxel
- use costs for inavolisib, palbociclib, abemaciclib and ribociclib in each weekly model cycle rather than each 28-day cycle
- amend the sampling method for log-logistic distribution

- apply mapped EQ-5D-3L utility values rather than EQ-5D-5L values, in line with the NICE reference case.

The committee concluded that the EAG's additional changes were appropriate.

Cost-effectiveness estimates

Acceptable ICER

3.16 NICE's technology appraisal and highly specialised technologies guidance manual notes that, above a most plausible incremental cost-effectiveness ratio (ICER) of £25,000 per QALY gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. But it will also take into account other aspects including uncaptured health benefits. The committee noted the uncertainty associated with the generalisability of the trial to the NHS, including the age of the population. It also noted that the outcomes from the trial were mature and includes a direct comparison of inavolisib plus palbociclib and fulvestrant with palbociclib plus fulvestrant. So, the committee concluded that an acceptable ICER would be towards the upper end of the range NICE considers an effective use of NHS resources (£25,000 to £35,000 per QALY gained).

Company and EAG cost-effectiveness estimates

3.17 The company's corrected base-case deterministic and probabilistic ICERs were above the range normally considered an acceptable use of NHS resources. In the EAG's base case, the ICERs were substantially above the range normally considered an acceptable use of NHS resources. The exact ICERs cannot be reported here because of confidential commercial discounts.

Committee preferred assumptions

3.18 The committee's preferred assumptions were to:

- apply log-logistic distribution from the start of the model time horizon to model PFS and cap these by the absolute value of OS (see sections 3.7 and 3.8)
- apply a generalised gamma distribution to model treatment duration (see section 3.9)
- assume equal treatment efficacy of abemaciclib plus fulvestrant, palbociclib plus fulvestrant and ribociclib plus fulvestrant in the model, and match efficacy results to INAVO120 (see section 3.10)
- use adjusted INAVO120 relative dose intensity values that exclude the effect of dose reductions for inavolisib and palbociclib, as well as INAVO120 relative dose intensities applied to abemaciclib, ribociclib and fulvestrant (see section 3.11)
- model subsequent treatments assuming that a lower proportion of people would have elacestrant and everolimus plus exemestane as a subsequent treatment after inavolisib plus palbociclib and fulvestrant than after a CDK 4 and 6 inhibitor plus fulvestrant (see section 3.12)
- exclude additional PIK3CA-mutation testing costs (see section 3.13)
- apply a severity weight of 1.2 to the QALYs (see section 3.14)
- apply the EAG's additional model changes (see section 3.15).

Taking into account the committee's preferred assumptions, the ICER was higher than the committee's preferred threshold for an acceptable ICER.

Other factors

Equality

3.19 No equality issues were raised by the company, EAG or stakeholders. The committee did not identify any equality issues.

Uncaptured benefits

3.20 The committee considered whether there were any uncaptured benefits of inavolisib plus palbociclib and fulvestrant. It did not identify any additional benefits of inavolisib plus palbociclib and fulvestrant not already captured in the economic modelling. So, the committee concluded that all additional benefits of inavolisib plus palbociclib and fulvestrant had been taken into account.

Conclusion

Recommendation

3.21 The committee considered that inavolisib plus palbociclib and fulvestrant is an effective treatment in terms of PFS and OS compared with standard care. But, when applying its preferred assumptions, the cost-effectiveness estimates for inavolisib plus palbociclib and fulvestrant were above the range that NICE considers an effective use of NHS resources. So, inavolisib plus palbociclib and fulvestrant should not be used to treat recurrent oestrogen receptor-positive, HER2-negative, PIK3CA-mutated advanced breast cancer after adjuvant endocrine treatment.

4 Evaluation committee members and NICE project team

Evaluation 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 technologies being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Chair

Dr Radha Todd

Chair, technology appraisal committee A

NICE project team

Each evaluation is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the evaluation), a technical adviser, a project manager, and an associate director or principal technical adviser.

Summaya Mohammad

Technical lead

Joanna Richardson

Technical adviser

Jennifer Upton

Project manager

Ian Watson

Associate director

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