

inavolisib film-coated tablets (Itovebi®) Roche Products Ltd.

In Confidence

4 September 2026

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission assessed under the end of life and orphan equivalent medicine process

inavolisib (Itovebi®) is not recommended for use within NHSScotland.

Indication under review: 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.

In a randomised, double-blind, phase III study, inavolisib plus palbociclib and fulvestrant significantly improved progression-free and overall survival compared with placebo plus palbociclib and fulvestrant (a relevant comparator). Indirect evidence against the two other relevant comparators has limitations which raise uncertainty.

The submitting company's justification of the treatment's cost in relation to its health benefits was not sufficient and in addition the company did not present a sufficiently robust economic analysis to gain acceptance by SMC.

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

Advice must be treated in strict confidence until published on the [SMC website](https://www.scottishmedicines.org.uk) on **Monday 12 October 2026**.

Chair
Scottish Medicines Consortium

1. Clinical Context

1.1. Medicine background

Inavolisib is an inhibitor of the phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K) alpha isoform protein (p110 alpha), which is encoded by the *PIK3CA* gene. Patients with breast cancer whose cancer cells have a *PIK3CA* mutation produce abnormal forms of the PI3K enzyme, which causes the cancer cells to divide and grow uncontrollably. Inavolisib blocks the activity of the abnormal PI3K enzyme and promotes the degradation of mutated p110 alpha, thereby reducing cell growth and killing the *PIK3CA*-mutated breast cancer cells.¹⁻³

The recommended dose of inavolisib is 9 mg orally once daily with or without food. Inavolisib is administered as part of a 28-day cycle in combination with palbociclib (125 mg orally once daily on days 1 to 21) and fulvestrant (500 mg intramuscularly [IM] on days 1, 15 and 29, then monthly thereafter). Treatment with inavolisib should continue until disease progression or unacceptable toxicity. Treatment of pre- or perimenopausal women and men should also include a luteinising hormone-releasing hormone (LHRH) agonist in accordance with local clinical practice.³

1.2. Disease background

In Scotland, breast cancer is the second most common cancer overall with 5,536 diagnoses made in 2023; about 15% of these were either stage III (locally advanced) or IV (metastatic).⁴ Hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative disease is the most prevalent type, accounting for approximately 70% of all breast cancers.⁵ Locally advanced or metastatic breast cancer is an incurable disease, comprising a variety of subtypes defined by molecular markers. *PIK3CA* mutations are found in 35% to 40% of HR-positive, HER2-negative tumours⁶ and is associated with a worse prognosis.^{7,8}

1.3. Treatment pathway and relevant comparators

Systemic treatment for locally advanced or metastatic breast cancer aims to prolong survival, alleviate symptoms and maintain or improve quality of life.⁹ In this setting, for patients with HR-positive, HER2-negative disease whose advanced breast cancer has returned or progressed while receiving endocrine therapy or within 12 months of completing endocrine therapy, standard first-line therapy is cyclin-dependent kinase (CDK) 4/6 inhibitors plus fulvestrant.¹⁰ SMC has accepted the following CDK 4/6 inhibitors in combination with fulvestrant for use or restricted use within NHSScotland: abemaciclib (SMC2179), palbociclib (SMC2149) and ribociclib (SMC2198). NHSScotland Cancer Collaborative clinical management pathways, as well as clinical experts consulted by SMC, indicate that the relevant comparators are: ribociclib plus fulvestrant, abemaciclib plus fulvestrant and palbociclib plus fulvestrant.¹⁰ Data from the Cancer Medicines Outcome Programme-Public Health Scotland (CMOP-PHS) suggest that ribociclib is the most commonly used CDK 4/6 inhibitor for this indication, with abemaciclib and palbociclib used in a similar but smaller proportion.¹¹

1.4. Category for decision-making process

Eligibility for a PACE meeting

Inavolisib meets SMC end of life and orphan equivalent criteria for this indication.

2. Summary of Clinical Evidence

2.1. Evidence for the licensed indication under review

The evidence to support the use of inavolisib for this indication comes from the INAVO120 study. Details are summarised in Table 2.1

Table 2.1. Overview of relevant study.

Criteria	INAVO120 study ^{8, 12}
Study design	International, randomised, double-blind, placebo-controlled, phase III study.
Eligible patients	• Women (with any menopausal status) and men (age ≥ 18 years) with PIK3CA-mutated, HR-positive, HER2-negative, locally advanced (inoperable) or metastatic breast cancer, and measurable disease per Response Evaluation Criteria in Solid Tumours (RECIST) v1.1. • Disease recurrence or progression during or within 12 months after completion of adjuvant endocrine therapy with an aromatase inhibitor or tamoxifen (endocrine resistant). • If a CDK 4/6 inhibitor was included as part of neoadjuvant or adjuvant therapy [that is (neo)adjuvant, therapy] the progression event had to be more than 12 months since completing the CDK 4/6 inhibitor portion. • No prior systemic therapy for locally advanced or metastatic disease. • No prior treatment with fulvestrant (except for patients that had received fulvestrant as part of neoadjuvant therapy only and the treatment duration was less than 6 months). • A fasting glucose of less than 126 mg/dL (7.0 mmol/L) and a glycated haemoglobin (HbA1c) level of less than 6.0%.
Treatments and Randomisation	Patients were randomised equally to receive (as part of a 28-day cycle): inavolisib 9 mg (n=161) or placebo (n=164) orally once daily, on days 1 to 28. All patients also received: palbociclib 125 mg orally once daily, on days 1 to 21; and fulvestrant 500 mg IM, on days 1 and 15 of cycle 1, and approximately every 4 weeks thereafter, until disease progression or unacceptable toxicity. Pre- or peri-menopausal women and men received luteinising hormone-releasing hormone (LHRH) agonists (for example, goserelin or leuprolide) concomitantly for the duration of the treatment. Patients at risk of developing hyperglycaemia^a could initiate treatment with metformin on day 1 of the study, where allowed by local regulations. Randomisation was stratified by: presence of visceral disease (yes or no), endocrine resistance (primary^b or secondary^c) and geographic region (North America and Western Europe, Asia or other).
Primary outcome	Investigator-assessed progression-free survival (PFS), defined as the time between date of randomisation to the date of first progression (using RECIST v1.1 criteria) or death from any cause, whichever occurred first.
Secondary outcomes	Overall survival (OS); objective response rate (ORR); best overall response (BOR); clinical benefit rate (CBR); and time to confirmed deterioration (TTCD) in: worst pain severity; physical functioning; role functioning; and global health status (GHS) or health-related quality of life (HRQoL).
Statistical analysis	Efficacy analyses were performed in the full analysis set (FAS) population, which included all randomised patients. A hierarchical statistical testing strategy was applied in the study with no formal testing of outcomes after the first non-significant outcome in the hierarchy. The type I error-controlled outcomes were tested in the order outlined above only if PFS was statistically significant (at the primary PFS analysis).

^a included patients with prediabetes, body mass index >30 kg/m², HbA1c $>5.7\%$, >45 years of age, family history of diabetes, history of gestational diabetes or any other factor that may lead to increased risk of developing hyperglycaemia, including certain ethnicities and inactive lifestyle.

^b relapse during the first 2 years of adjuvant endocrine therapy.

^c relapse whilst on adjuvant endocrine therapy after at least 2 years or within 12 months after completing adjuvant endocrine therapy.

At the September 2023 data cut (primary analysis for PFS), inavolisib plus palbociclib and fulvestrant (hereafter referred to as the inavolisib group) resulted in a statistically significant improvement in investigator-assessed PFS compared with placebo plus palbociclib and fulvestrant (hereafter referred to as the placebo group).¹² This was supported by consistent results from the blinded independent central review (BICR) assessment of PFS (September 2023 data cut)¹² and from the updated investigator-assessed PFS analysis (November 2024 data cut).⁸ At the November 2024 data cut (final analysis for OS), there was a statistically significant improvement in OS in the inavolisib group compared with the placebo group.⁸ The PFS and OS results from the November 2024 data cut were used to inform the economic analysis. Further details are presented in Table 2.2.

Table 2.2. Key efficacy results for INAVO120 in the Full Analysis Set (FAS) population.^{8, 12}

	Inavolisib + palbociclib + fulvestrant (n=161)	Placebo + palbociclib + fulvestrant (n=164)
Primary outcome: investigator-assessed PFS (data cut: September 2023)		
Median PFS follow-up	21.3 months	21.5 months
Events, n	82	113
Median PFS	15.0 months	7.3 months
Hazard ratio (95% CI), p-value	0.43 (0.32 to 0.59), p <0.001	
KM estimated event-free rate at 18 months	46%	21%
Primary outcome: investigator-assessed PFS (data cut: November 2024)		
Median PFS follow-up	34.2 months	32.3 months
Events, n	103	141
Median PFS	17.2 months	7.3 months
Hazard ratio (95% CI) ^a	0.42 (0.32 to 0.55)	
KM estimated event-free rate at 24 months	42%	17%
Secondary outcome: OS (data cut: November 2024)		
Median OS follow-up	34.2 months	32.3 months
Events, n	72	82
Median OS	34.0 months	27.0 months
Hazard ratio (95% CI), p-value	0.67 (0.48 to 0.94), p=0.02	
KM estimated event-free rate at 30 months	57%	46%

CI = confidence interval; FAS = full analysis set; KM = Kaplan-Meier; OS = overall survival; PFS = progression-free survival

^a descriptive only; not formally tested as reached statistical significance in the primary PFS analysis (September 2023 data cut)

The secondary outcomes, ORR, BOR and CBR, were hierarchically tested at the November 2024 data cut-off and these were all statistically significant, favouring the inavolisib group.¹

2.2. Health-related quality of life outcomes

Patient-reported outcomes were assessed as secondary outcomes in the hierarchical testing strategy, including TTCD in: worst pain severity (assessed on the Brief Pain Inventory-Short Form

(BPI-SF)), and physical functioning, role functioning, and GHS or HRQoL (assessed on the European Organisation for Research and Treatment of Cancer Quality of Life–Core 30 (EORTC QLQ-C30) questionnaire). TTCD in worst pain severity did not reach statistical significance and therefore subsequent patient-reported outcomes in the hierarchy were not formally tested. Overall, there was no difference in any of the patient-reported outcomes between the two treatment groups.¹

2.3. Indirect evidence to support clinical and cost-effectiveness comparisons

In the absence of direct evidence versus abemaciclib plus fulvestrant, and ribociclib plus fulvestrant, the submitting company provided a network meta-analysis (NMA). The results were applied in the economic base case. Further details are presented in Table 2.3.

Table 2.3: Summary of indirect treatment comparison

Criteria	Overview																				
Design	Bayesian NMA.																				
Population	Adults receiving first-line treatment for HR-positive, HER2-negative, locally advanced or metastatic breast cancer. Subgroup analyses were conducted according to endocrine sensitivity. A ‘mixed population’ NMA (including endocrine sensitive and endocrine resistant patients) informed the economic base case.																				
Comparators	Abemaciclib plus fulvestrant, ribociclib plus fulvestrant, and palbociclib plus fulvestrant (results not shown below as not included in the economic analysis). Capivasertib plus fulvestrant was also included in the NMA but is not considered a relevant comparator.																				
Studies included	Seven studies were included in the NMA: INAVO120 ^{8, 12} (for inavolisib plus palbociclib and fulvestrant; and, palbociclib plus fulvestrant); MONARCH-2 ¹³⁻¹⁵ (for abemaciclib plus fulvestrant); MONARCH plus cohort B (for abemaciclib plus fulvestrant); MONALEESA-3 ¹⁶⁻¹⁸ (for ribociclib plus fulvestrant); PALOMA-3 ¹⁹⁻²¹ (for palbociclib plus fulvestrant); FLIPPER ²² (for palbociclib plus fulvestrant); and CAPItello-291 ²³ (for capivasertib plus fulvestrant).																				
Outcomes	PFS and OS.																				
Results	The results in the mixed population suggest that inavolisib plus palbociclib and fulvestrant had superior efficacy compared to abemaciclib plus fulvestrant or ribociclib plus fulvestrant in terms of PFS; however, for OS the 95% CrI crossed one suggesting there was no evidence of a difference. In the endocrine resistant population, there was no evidence of a difference in PFS or OS when compared to abemaciclib plus fulvestrant (though the point estimates were similar to those in the mixed population); results for ribociclib plus fulvestrant were not available. Table 2.3.1 NMA results for inavolisib plus palbociclib and fulvestrant versus comparators <table><tr><th></th><th colspan="2">Mixed population</th><th colspan="2">Endocrine resistant</th></tr><tr><th>Comparator</th><th>PFS Hazard ratio (95% CrI)</th><th>OS Hazard ratio (95% CrI)</th><th>PFS Hazard ratio (95% CrI)</th><th>OS Hazard ratio (95% CrI)</th></tr><tr><td>Abemaciclib plus fulvestrant</td><td>0.42 (0.21 to 0.87)</td><td>0.58 (0.24 to 1.42)</td><td>0.46 (0.18 to 1.26)</td><td>0.52 (0.21 to 1.30)</td></tr><tr><td>Ribociclib plus fulvestrant</td><td>0.38 (0.18 to 0.81)</td><td>0.73 (0.30 to 1.80)</td><td colspan="2">NA</td></tr></table>		Mixed population		Endocrine resistant		Comparator	PFS Hazard ratio (95% CrI)	OS Hazard ratio (95% CrI)	PFS Hazard ratio (95% CrI)	OS Hazard ratio (95% CrI)	Abemaciclib plus fulvestrant	0.42 (0.21 to 0.87)	0.58 (0.24 to 1.42)	0.46 (0.18 to 1.26)	0.52 (0.21 to 1.30)	Ribociclib plus fulvestrant	0.38 (0.18 to 0.81)	0.73 (0.30 to 1.80)	NA	
	Mixed population		Endocrine resistant																		
Comparator	PFS Hazard ratio (95% CrI)	OS Hazard ratio (95% CrI)	PFS Hazard ratio (95% CrI)	OS Hazard ratio (95% CrI)																	
Abemaciclib plus fulvestrant	0.42 (0.21 to 0.87)	0.58 (0.24 to 1.42)	0.46 (0.18 to 1.26)	0.52 (0.21 to 1.30)																	
Ribociclib plus fulvestrant	0.38 (0.18 to 0.81)	0.73 (0.30 to 1.80)	NA																		

CrI = credible interval; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; NA = not available; NMA = network meta-analysis; OS = overall survival; PFS = progression-free survival

3. Summary of Safety Evidence

In the INAVO120 study, inavolisib was compared with placebo when added to palbociclib and fulvestrant; palbociclib and fulvestrant is a relevant comparator for this indication. However, the company's NMA (section 2.3) did not compare safety outcomes with the other relevant comparators (abemaciclib plus fulvestrant and ribociclib plus fulvestrant).

In the INAVO120 safety analysis population at the November 2024 data cut-off, patients in the inavolisib group (n=161) received inavolisib for a median of 13.1 months, palbociclib for a median of 13.8 months, and fulvestrant for a median of 14.1 months. Patients in the placebo group (n=163) received placebo for a median of 7.5 months, palbociclib for a median of 7.2 months and fulvestrant for a median of 7.5 months. Patients in the inavolisib group had higher rates of adverse events (AEs) that were grade 3 or 4 (91% versus 85%), serious (27% versus 14%), led to dose interruptions of any study medicine (87% versus 77%) or discontinuation of treatment (6.8% versus 0.6%).⁸

Hyperglycaemia was commonly reported in patients receiving inavolisib (63% had any grade and 6.8% had grade 3⁸; this is an AE associated with PI3K inhibitors and constitutes a major safety issue during inavolisib treatment.¹ Relevant dose modifications and warnings are included in the Summary of Product Characteristics (SPC).³ In INAVO120, 74% of patients in the inavolisib group received hyperglycaemia treatment with an antidiabetic medicine (for example, metformin), with 6.8% receiving insulin for a median duration of 5 days (range: 1 to 539 days).¹ Although uncommon, two cases of diabetic ketoacidosis related to inavolisib have been reported in the postmarketing setting, including one fatal event, both occurred within one week of treatment initiation.¹

Overall, the (European) regulator noted that the substantial risk of hyperglycaemia could be managed in patients who are normoglycaemic at baseline with additional monitoring and risk minimisation measures required in patients with Type 1 and Type 2 diabetes mellitus. See the SPC for further information.¹

4. Summary of Clinical Effectiveness Considerations

4.1. Key strengths

- Inavolisib is the first treatment that specifically targets the *PIK3CA* mutation, for patients with locally advanced or metastatic breast cancer.³
- INAVO120 was a well-conducted, randomised, double-blind, phase III study, with stratification and well-balanced baseline characteristics between treatment groups. This means there is a low risk of bias and provides reassurance about the internal validity of the study.¹
- In INAVO120, treatment with inavolisib plus palbociclib and fulvestrant resulted in statistically significant and clinically meaningful improvements in median PFS and OS of approximately 7 to 10 months, compared with placebo plus palbociclib and fulvestrant (a relevant comparator).¹
- The inavolisib group also had statistically significant improvements in secondary outcomes, such as ORR, BOR and CBR, when compared with the placebo group.¹

4.2. Key uncertainties

- It is uncertain if the patient population of the INAVO120 study is entirely reflective of patients who would be eligible for inavolisib in Scottish clinical practice because treatment options have evolved since the study was conducted. In INAVO120, only three patients (1.9%) had prior treatment in the (neo)adjuvant setting with a CDK 4/6 inhibitor, meaning there is limited data on patients being retreated with CDK 4/6 inhibitors (such as palbociclib). The regulator noted that the efficacy of inavolisib plus palbociclib, and fulvestrant may be lower in patients who previously received a CDK 4/6 inhibitor as part of (neo)adjuvant treatment.¹ However, recent European guidelines are supportive of CDK 4/6 inhibitor retreatment in certain circumstances (that is, after a treatment-free interval of more than 12 months), based on evidence regarding rechallenge with other therapies.⁹
- There is no direct evidence against the two other relevant comparators (abemaciclib plus fulvestrant, and ribociclib plus fulvestrant). The NMA presented by the submitting company is limited by the differences in *PIK3CA* mutation status and endocrine sensitivity status across the studies; the submitting company noted that patients with *PIK3CA* mutations have a poorer prognosis and therefore the efficacy of the comparators may be overestimated. A subgroup analysis was conducted in endocrine resistant patients, which is more relevant to this submission. However, no results were available for ribociclib plus fulvestrant and the results were inconsistent as there was no evidence of a difference in efficacy when compared with abemaciclib plus fulvestrant, although the point estimates were similar to those in the mixed population. The submitting company also noted that there was evidence of non-proportional hazards for some studies, however this could not be assessed across the whole network. The statistician consulted by SMC noted that this is a key limitation given that the duration of follow-up varied widely between the studies. Overall, the assessment team considered that the results of the NMA are uncertain. In addition, experts consulted by SMC stated their belief, that in clinical practice, palbociclib plus fulvestrant, abemaciclib plus fulvestrant and ribociclib plus fulvestrant were considered to have comparable efficacy.
- The substantial risk of hyperglycaemia is an important safety issue associated with inavolisib treatment. Since patients with Type 1 or Type 2 diabetes mellitus (who required ongoing anti-hyperglycaemic treatment) were excluded from the INAVO120 study, there is a lack of efficacy and safety data in these patients.¹ A post-authorisation safety study is included in the MHRA risk management plan.²
- The median age of patients in INAVO120 was 54 years (range: 27 to 79 years), with 82% younger than 65 years.¹ Subgroup analyses suggest less certainty in the OS benefit for older patients, however these are exploratory and cannot support definitive conclusions.⁸ CMOP-PHS data indicate that the median age of patients currently prescribed CDK 4/6 inhibitors in this setting is 64 years.¹¹

4.3. Clinical expert input

Experts contacted by SMC considered inavolisib to be a therapeutic advancement in this setting.

4.4. Service implications

This new medicine is oral and added to standard of care. However, the monitoring requirements (including HbA1c and fasting glucose) outlined in the SPC, and the potential need for new or intensified antihyperglycaemic treatment will likely have additional service implications.³

Diagnostic test required to identify patients eligible for treatment: contact local laboratory for information.

5. Patient and clinician engagement (PACE)

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of **inavolisib (Itovebi®)**, as an **orphan equivalent and end of life** medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- Advanced oestrogen receptor positive, HER2 negative breast cancer is an incurable, life-limiting condition that affects a large group of patients at a time in their life when they have a pivotal family role, caring for children, grandchildren, and elderly relatives and often still working. The diagnosis can be psychologically devastating and can have an emotional toll on patients who may feel fearful and anxious, as well as angry and alone. As the disease progresses, people can develop symptoms such as severe pain, breathlessness and fatigue. Increasingly those affected are unable to carry out normal day-to-day activities and there is an increased need for support from family and friends. Excluding external causes, secondary breast cancer is the leading cause of death in women aged 25 to 54 in Scotland, taking more lives in this age group than any other cancer.
- Currently there are no targeted treatments available in NHSScotland for patients with PIK3CA mutated breast cancer; patients with this mutation have a poorer prognosis. Many current treatments are administered parenterally and can involve hours in hospital treatment units. There is an unmet need for more effective therapies, including targeted treatments, with acceptable tolerability and administration schedules.
- Unlike existing treatments, inavolisib specifically targets the alpha isoform of PIK3CA. This treatment may give patients reassurance that they are receiving optimal treatment that is targeted to the specific mutation within their cancer. It may allow patients to plan and to spend time with family while they are well. It may give patients hope that their survival could be extended to a time when further treatments become available.
- When added onto current a standard of care option (fulvestrant and palbociclib), inavolisib significantly improved progression-free and overall survival. This would provide meaningful benefits to patients, with the potential to maintain physical health for longer by delaying the symptoms of disease. Inavolisib also offers a prolonged period of being free of chemotherapy; PACE participants highlighted the fatigue and toxicity (for example hair loss) associated with chemotherapy.
- Inavolisib is orally administered, therefore, patients only need to attend healthcare appointments to receive the fulvestrant (intramuscular injection) part of the regimen,

which is given every 28 days.

- Whilst patients feel that taking inavolisib is tolerable, there is a greater risk of side effects (such as hyperglycaemia) when this treatment is added onto standard of care and there are increased monitoring requirements of blood glucose levels, and there will be a need to manage induced diabetes. However, PACE clinicians advised that these are considered to be reversible and manageable for most patients. Its less intensive administration schedule may be more tolerable than some chemotherapy regimens.
- Testing for PIK3CA mutations is not routinely available in Scotland which could have a significant service impact for laboratories

Additional Patient and Carer Involvement

We received patient group submissions from Breast Cancer Now, Make 2nds Count and METUP UK. All three organisations are registered charities. Breast Cancer Now has received 0.52% pharmaceutical company funding in the past two years, including from the submitting company. Make 2nds Count has received 17% pharmaceutical company funding in the past two years, including from the submitting company. METUP UK has not received any pharmaceutical company funding in the past two years. Representatives from all three patient groups participated in the PACE meeting. The key points of their submissions have been included in the full PACE statement considered by SMC.

6. Summary of Comparative Health Economic Evidence

6.1. Economic case

An economic case was presented and is summarised in Table 6.1.

Table 6.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost-utility analysis
Time horizon	40 years, with an assumed starting age of 54 years
Population	Adult patients with <i>PIK3CA</i> -mutated, ER+, HER2- locally advanced or metastatic breast cancer following recurrence on or within 12 months of completing adjuvant endocrine treatment.
Comparators	Palbociclib plus fulvestrant, abemaciclib plus fulvestrant, and ribociclib plus fulvestrant.
Model description	A cohort based partitioned survival model was used with four health states: progression-free (PF), first progressed disease (PD1), second progressed disease (PD2) and death. Occupancy of those states was defined by the area between the curves of time to first disease progression (PFS1), time to second disease progression (PFS2) and OS. The cycle length was 1-week.
Clinical data	Data for PFS1, OS, time to off treatment (TTOT) and AE rates for inavolisib plus palbociclib and fulvestrant and palbociclib plus fulvestrant were from the respective treatment arms of the INAVO120 study.^{8, 12} PFS2 was not directly observed and so modelled using the proxy of time to second subsequent treatment. The relative efficacy for abemaciclib plus fulvestrant and ribociclib plus fulvestrant compared to inavolisib plus palbociclib and fulvestrant was estimated using the hazard ratios (HRs) from the mixed population NMA (see Section 2.3 for further details). AEs for abemaciclib plus fulvestrant and ribociclib plus fulvestrant were from the MONARCH-2¹³ and MONALEESA-3¹⁷ studies, respectively.
Extrapolation	For patients receiving inavolisib plus palbociclib and fulvestrant and palbociclib plus fulvestrant, long-term OS, PFS1, PFS2 and TTOT data were extrapolated using parametric survival modelling. A piecewise

	approach was used, whereby the INAVO120 Kaplan-Meier (KM) data were used directly up to the timepoint where 20% of patients remained at risk and then a parametric applied thereafter. Curve selection was based on goodness of fit statistics, visual fit and clinical expert opinion. The curves selected in the base case were independently fitted KM plus log-normal for PFS1 and PFS2, KM plus Gamma for OS and KM plus Gamma for TTOT. The respective NMA mixed population hazard ratios were applied to the extrapolated inavolisib plus palbociclib and fulvestrant OS and PFS1 curves to estimate these outcomes for abemaciclib plus fulvestrant and ribociclib plus fulvestrant. To estimate PFS2 and TTOT for abemaciclib plus fulvestrant and ribociclib plus fulvestrant, the PFS1 hazard ratios from the NMA were applied to the respective inavolisib plus palbociclib and fulvestrant curves for these outcomes.
Quality of life	EQ-5D-5L data from the INAVO120 study were analysed to estimate health state utility values for the PF and PD1 health states. A value was sourced from the literature to estimate the health state utility value for the PD2 health state.²⁴ This resulted in health state utility values of 0.849 for PF, 0.777 for PD1 and 0.505 for PD2. Disutilities were included for AEs with values for these largely based on assumption.
Costs and resource use	Costs were included for testing, medicine acquisition and administration, subsequent treatments at first and second disease progression, healthcare resource use for disease management, management of AEs and end of life care.
PAS	A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a discount was offered on the list price for inavolisib. A PAS discount is in place for palbociclib, abemaciclib, ribociclib and trastuzumab, and a National Framework Contract Price was in place for fulvestrant, capecitabine and everolimus. These were included in the results used for decision-making by using estimates of the comparator, combination and subsequent treatment PAS and contract prices.

6.2. Results

The base case economic analysis indicated that treatment with inavolisib was associated with better health outcomes against all comparators but also increased costs.

SMC considered results for decision-making that took into account all relevant PAS. SMC is unable to present these results due to competition law issues.

[Other data were also assessed but remain confidential.*](#)

6.3. Sensitivity analyses

A range of sensitivity and scenario analyses were considered, and descriptions of these key scenarios are provided in Table 6.2.

Table 6.2: Key scenario analysis results

#	Parameter	Base Case	Scenario
1	Time horizon (years)	40	10
2	Average age at start of treatment	54 years	65 years
3a	Survival modelling distributions applied to inavolisib + palbociclib & fulvestrant and	PFS = independently fitted KM + log-normal	PFS = independently fitted log-logistic
3b		PFS2 = independently fitted KM + log-normal	PFS2 = independently fitted log-logistic

3c	palbociclib + fulvestrant INAVO120 time-to-event data	OS = independently fitted KM + Gamma	OS = independently fitted Weibull (palbociclib + fulvestrant OS capped by inavolisib + palbociclib & fulvestrant OS)
3d		TTOT = independently fitted KM + Gamma	TTOT = independently fitted log-logistic
4	Estimated efficacy of abemaciclib + fulvestrant & ribociclib + fulvestrant arms	Point estimate from mixed population NMA applied to inavolisib + palbociclib & fulvestrant	Equal efficacy assumed to palbociclib + fulvestrant
5	Utilities	INAVO120 values for PFS and PD1, externals source for PD2	INAVO120 values for all states – value in PD2 state = 0.756
6	RDI for abemaciclib + fulvestrant and ribociclib + fulvestrant	100%	As per palbociclib and fulvestrant in palbociclib + fulvestrant arm of INAVO120
Combined scenarios			
C1	- Scenario 3a - PFS = independently fitted log-logistic - Scenario 3b - PFS2 = independently fitted log-logistic - Scenario 3d - TTOT = independently fitted log-logistic		
C2	- Scenario C1 - Scenario 4 - Equal efficacy assumed between abemaciclib + fulvestrant, ribociclib + fulvestrant and palbociclib + fulvestrant		
C3	- Scenario C3 - Scenario 5 - INAVO120 utility values for all states		

AE = adverse event; KM = Kaplan-Meier; NMA = network meta-analysis; OS = overall survival; PD1 = progressed disease 1; PD2 = progressed disease 2; PFS = progression-free survival; PFS2 = time to second disease progression; RDI = relative dose intensity; TTOT = time to off treatment.

6.4. Key strengths

- The INAVO120 study provided randomised evidence for inavolisib plus palbociclib and fulvestrant versus the relevant comparator palbociclib plus fulvestrant, which was utilised in the economic evaluation.
- A partitioned survival model was an appropriate choice for the economic model.
- The choice of comparators reflected Scottish clinical practice.

6.5. Key uncertainties

- The company used a piecewise approach to model each time-to-event outcome which involved using the INAVO120 study KM data directly up to the timepoint where 20% of patients remained at risk and then a parametric distribution applied thereafter. This may have led to statistical variation in the study KM data being carried into the economic analysis. While the submitting company provided some justification for that approach, full parametric extrapolations were explored in singular and combined scenarios.
- Some of the parametric distributions selected by the company for use in the survival analysis were seen as uncertain. While the log-normal curve was selected to extrapolate the PFS1 and PFS2 curves, the log-logistic distribution was a better statistical fit to the PFS1 KM data from the inavolisib arm of INAVO120 and to both arms PFS2 KM data. Clinical experts consulted by the company expressed a preference for either the log-normal or log-logistic curves for extrapolating PFS1 and PFS2 noting that the same distribution for both would be most likely.

Applying log-logistic curves for PFS1 and PFS2 generated higher estimates of the incremental cost-effectiveness ratio (see Table 6.3, Scenarios 3a and 3b). Additionally, the base case Gamma curve selected for TTOT was a poor fit to the observed data from INAVO120. The log-logistic distribution was the best statistical fit to the TTOT data and resulted in higher estimates of cost-effectiveness (Scenario 3d).

- The lack of direct comparable evidence against abemaciclib plus fulvestrant and ribociclib plus fulvestrant, which necessitated the use of an NMA, increased the uncertainty within the economics. The NMA also did not provide a comparison of PFS2 or TTOT which meant that the PFS1 hazards were used to estimate these outcomes relative to respective outcomes for inavolisib which added additional uncertainty. Given the concerns over NMA approach, its face validity, and how it had been applied in the economics, a scenario was explored which assumed equal outcomes (OS, PFS1, PFS2 and TTOT) between abemaciclib plus fulvestrant, ribociclib plus fulvestrant and palbociclib plus fulvestrant arms in the model. These analyses resulted in higher estimated incremental cost-effectiveness ratio (Scenario 4).
- Because of small patient numbers, the submitting company utilised an external source for the utility value in the PD2 health state, rather than a value estimated from the INAVO120 study. That external source had been used in other SMC submissions, but was limited by being published in 2006, which led to concerns that changes in clinical practice since then limited its applicability. Using the EQ-5D data to estimate PD2 health state resulted in a much higher estimate of cost-effectiveness relative to the company's base case (Scenario 5), although the submitting company noted that this measure may overestimate HRQoL at advanced stages of disease.
- The company's approach to relative dose intensity (RDI) for abemaciclib and ribociclib, and fulvestrant in the respective arms of the model, was to assume that these were 100%. This seemed likely to bias the results of the analysis in favour of inavolisib. As there was no reason to expect the RDI for either abemaciclib or ribociclib would be higher than that of palbociclib, a scenario was explored that used the RDI for palbociclib, and the RDI for fulvestrant, from the palbociclib plus fulvestrant arm of the INAVO120 study. This scenario resulted in modest upward pressure on the incremental cost-effectiveness ratio (Scenario 6).

7. Conclusion

The Committee considered the benefits of inavolisib in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that as inavolisib is an orphan equivalent medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, the Committee was unable to accept inavolisib for use in NHSScotland.

8. Guidelines and Protocols

In 2021, the European Society for Medical Oncology (ESMO) published ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer²⁵; these have been updated in 2026.⁹

9. Additional Information

9.1. Product availability date

13 February 2026

Table 9.1 List price of medicine under review

Medicine	Dose regimen	Cost per 28-day cycle (£)
Inavolisib + palbociclib + fulvestrant	9 mg orally once daily 125 mg orally once daily on days 1 to 21 of each 28-day cycle 500 mg IM once daily on days 1, 15, and 29, then monthly thereafter Treatment should continue until disease progression or unacceptable toxicity	Cycle 1: £14,831 Cycle 2 onwards: £14,308

Costs from BNF online on 19 May 2026. Costs calculated using the full cost of vials/ampoules assuming wastage. Costs do not take any patient access schemes into consideration.

10. Company Estimate of Eligible Population and Estimated Budget Impact

SMC is unable to publish the inavolisib budget impact due to commercial in confidence issues.

*Other data were also assessed but remain confidential.**

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This assessment is based on data submitted by the applicant company up to and including 17 July 2026.

*[*Agreement between the Association of the British Pharmaceutical Industry \(ABPI\) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:https://www.scottishmedicines.org.uk/about-us/policies-publications/](https://www.scottishmedicines.org.uk/about-us/policies-publications/)*

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC includes Scottish national contract prices in its decision-making. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document.

Patient Access Schemes (PAS): A PAS is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. The Patient Access Scheme Assessment Group (PASAG), established under the auspices of Public Services Delivery Scotland, reviews and advises NHS Scotland on the feasibility and acceptability on implementing proposed schemes. PASAG operates separately from SMC to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHS Scotland on the basis of a PAS that has been considered acceptable for implementation by PASAG, a set of guidance notes on the operation of the scheme will be circulated to health boards' Area Drugs and Therapeutics Committees prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.