Technology Guidance

Inavolisib

in combination with palbociclib and fulvestrant for *PIK3CA*-mutated, HR-positive, HER2-negative, locally advanced or metastatic breast cancer

Technology Guidance from the MOH Drug Advisory Committee

Guidance Recommendations

The Ministry of Health's Drug Advisory Committee has not recommended inavolisib, in combination with palbociclib and fulvestrant, for inclusion on the MOH List of Subsidised Drugs for *PIK3CA*-mutated, HR-positive, HER2-negative, locally advanced or metastatic breast cancer, following recurrence on or within 12 months of completing adjuvant endocrine therapy. The decision was based on the unfavourable cost effectiveness compared with palbociclib plus fulvestrant at the proposed price, and the unacceptable price-volume agreement proposed by the company.

Clinical indication, subsidy class and MediShield Life claim limit for inavolisib are provided in the Annex.

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Technology Evaluation

1.1. At the November 2025 meeting, the MOH Drug Advisory Committee ("the Committee") considered the technology evaluation of inavolisib, in combination with palbociclib and fulvestrant, for *PIK3CA*-mutated, hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer (LA/mBC), following recurrence on or within 12 months of completing adjuvant endocrine therapy (ET). The evaluation considered the company's evidence submission by Roche for inavolisib (Itovebi), and a review conducted by one of ACE's evidence review centres.

1.2. Expert opinion from clinicians at healthcare institutions, the MOH Cancer Drug Subcommittee, and patient experts from local patient and voluntary organisations helped ACE ascertain the clinical value of inavolisib.

1.3. The evidence was used to inform the Committee's deliberations around four core decision-making criteria:

- Clinical need of patients and nature of the condition;
- Clinical effectiveness and safety of the technology;
- Cost effectiveness (value for money) – the incremental benefit and cost of the technology compared to existing alternatives; and
- Estimated annual technology cost and the number of patients likely to benefit from the technology.

1.4. Additional factors, including social and value judgments, may also inform the Committee's funding considerations.

Clinical need

2.1. The Committee heard that *PIK3CA* mutations occur in approximately 35-40% of HR-positive breast cancer cases and are associated with endocrine resistance and poorer prognosis. Each year in Singapore, approximately 123 patients with HR-positive, HER2-negative breast cancer experience recurrence on or within 12 months of completing adjuvant ET. Inavolisib is a PI3K inhibitor that targets and degrades the mutated p110α subunit encoded by the *PIK3CA* gene, which drives cell growth and proliferation.

2.2. Currently, in local practice, first-line treatment for recurrence on or within 12 months of completing adjuvant ET, typically consists of a cyclin-dependent kinase 4/6 (CDK4/6) inhibitor combined with ET. All three locally available CDK4/6 inhibitors (palbociclib, abemaciclib, and ribociclib) are relevant treatment options. While international guidelines recommend fulvestrant as the preferred ET in this combination, local clinicians indicated that approximately 40% of patients may instead receive an aromatase inhibitor (AI) if they had previously received tamoxifen in the adjuvant setting. Inavolisib, in combination with palbociclib and fulvestrant, is therefore expected to replace regimens involving any of the three available CDK4/6

inhibitors given with either fulvestrant or an AI.

2.3. The Committee considered 20 testimonials from local patients about living with breast cancer and their experience with different treatments. They heard that the condition and treatment side effects negatively impacted patients' ability to perform daily activities and care for loved ones. The Committee also noted how their emotional and mental well-being were affected due to fears of disease progression and an uncertain future, as well as concerns with self-image and financial burden, resulting in a lower quality of life. While none of the patients were familiar with inavolisib, they valued new treatments that can prevent the cancer from spreading or worsening, have manageable side effects, are more affordable and prolong their time living with the condition.

Clinical effectiveness and safety

Inavolisib + palbociclib + fulvestrant versus palbociclib + fulvestrant

3.1. The Committee reviewed the clinical evidence from a phase III, randomised, double-blind, head-to-head trial (INAVO120) that investigated inavolisib + palbociclib + fulvestrant versus palbociclib + fulvestrant in *PIK3C*A-mutated, HR-positive, HER2-negative LA/mBC, following recurrence on or within 12 months of completing adjuvant ET, which was aligned with the approved HSA indication and the company's requested listing.

3.2. At median follow-up of 34.2 months (data cut-off November 2024), inavolisib + palbociclib + fulvestrant was associated with a statistically significant improvement in investigator-assessed progression-free survival (PFS) compared to palbociclib + fulvestrant (Table 1). However, there was uncertainty in the magnitude of PFS benefit due to discordance between investigator and blinded independent central review (BICR) assessment at the September 2023 data cut-off, with the latter showing less pronounced improvement. PFS concordance data and censoring information were not provided at the November 2024 cut-off, limiting further examination of this uncertainty.

3.3. Inavolisib + palbociclib + fulvestrant was also associated with a statistically significant improvement in overall survival (OS) compared to the palbociclib + fulvestrant arm (Table 1). However, it remains uncertain whether this OS benefit extends beyond the trial period.

3.4. In terms of safety, the Committee heard that inavolisib + palbociclib + fulvestrant was associated with a higher incidence of adverse events compared with palbociclib + fulvestrant, particularly hyperglycaemia (63.4% vs. 13.5%), stomatitis (35.4% vs. 18.4%), mucosal inflammation (20.5% vs. 11.7%) and diarrhoea (52.2% vs. 16.0%).

Table 1: Results of PFS and OS in INAVO120 trial

	Inavolisib + palbociclib + fulvestrant (N=161)	Palbociclib + fulvestrant (N=164)	Absolute difference	HR (95% CI), p value
PFS by investigator (primary analysis, DCO: Sept 2023)				
Patients with event, n (%)	82 (50.9)	113 (68.9)	-18.0%	-
Median PFS, months (95% CI)	15.0 (11.3 to 20.5)	7.3 (5.6 to 9.3)	7.7	0.43 (0.32 to 0.59), p<0.00001
PFS by blinded independent central review (primary analysis, DCO: Sept 2023)				
Patients with event, n (%)	77 (47.8)	98 (59.8)	-12.0%	-
Median PFS, months (95% CI)	16.4 (11.1 to 22.0)	7.4 (5.8 to 9.2)	9.0	0.50 (0.36 to 0.68), p<0.0001
PFS by investigator (updated analysis, DCO: Nov 2024)				
Patients with event, n (%)	103 (64.0)	141 (86.0)	-22.0%	-
Median PFS, months (95% CI)	17.2 (11.6 to 22.2)	7.3 (5.9 to 9.2)	9.9	0.42 (0.32 to 0.55), p<0.0001
OS (primary analysis, DCO: Nov 2024)				
Patients with event, n (%)	72 (44.7)	82 (50.0)	-5.3%	-
Median OS, months (95% CI)	34.0 (28.4 to 44.8)	27.0 (22.8 to 38.7)	7.0	0.67 (0.48 to 0.94), p=0.0190

Abbreviations: CI, confidence interval; DCO, data cut-off; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

3.5. Based on the available evidence, the Committee concluded that the submission's claim of superior efficacy for inavolisib + palbociclib + fulvestrant versus palbociclib + fulvestrant was reasonable, although the magnitude of PFS benefit and durability of OS benefit remain uncertain. The Committee considered the submission's claim of non-inferior safety to be inadequately supported. Given the higher incidence of adverse events in the inavolisib + palbociclib + fulvestrant arm, a conclusion of inferior safety was deemed more appropriate.

Inavolisib + palbociclib + fulvestrant versus other relevant comparators

3.6. The Committee heard that in the absence of direct evidence comparing inavolisib + palbociclib + fulvestrant with alternative CDK4/6 inhibitor combinations, the submission included a Bayesian network meta-analysis (NMA) with six additional trials. However, the NMA results should be interpreted with caution, as the selection of trials was not justified and led to exchangeability issues. The Committee noted that several included studies primarily enrolled patients receiving second or later lines of therapy, rather than the target first-line population, and the analysis also inappropriately included a capivasertib + fulvestrant study, which was not a relevant comparator.

3.7. Based on the random effects analysis, there were no clear differences in PFS, OS or all-cause discontinuations between inavolisib + palbociclib + fulvestrant and either ribociclib + fulvestrant or abemaciclib + fulvestrant, as the 95% credible intervals crossed the null.

3.8. Overall, the Committee concluded that the indirect evidence did not support the submission's claims of superior PFS for inavolisib + palbociclib + fulvestrant over these combinations. The Committee also noted that the submission did not provide comparisons with CDK4/6i + AI combinations, which were relevant comparators.

Cost effectiveness

4.1. The Committee considered the results of the submission's cost-utility analysis that compared inavolisib + palbociclib + fulvestrant with palbociclib + fulvestrant for *PIK3CA*-mutated, HR-positive, HER2-negative LA/mBC, based on the INAVO120 trial. Overall, the submission provided limited information on the methodology and conduct of the economic evaluation which impacted the credibility of the model and results presented. Key components of the base-case economic evaluation provided in the submission are summarised in Table 2.

Table 2: Key components of the company-submitted base-case economic evaluation

Component	Description
Type of analysis	Cost-utility analysis
Population	Patients with *PIK3CA*-mutated, HR-positive, HER2-negative locally advanced or metastatic breast cancer whose disease relapsed during treatment or ≤ 12 months after adjuvant endocrine therapy
Outcomes	Total and incremental direct medical costs; total and incremental LY gained; total and incremental QALYs; ICER
Perspective	Singapore healthcare system
Type of model	Partitioned survival model
Time horizon	47 years, based on a median follow-up of 34.2 months in the INAVO120 trial.
Health states	• Progression-free 1 (on first-line treatment) • Progression-free 2 (on second-line treatment) • Progressed disease (on chemotherapy) • Death • Long-term survival (explored in the scenario analysis)
Cycle length	One month
Extrapolation methods used to generate results	Transition probabilities from progression-free 1 to progression-free 2 and progression-free 1 to death were derived from the parametric extrapolation of OS and PFS curves from INAVO120 trial. Transition probabilities from progression-free 2 to progressed-disease and from progression-free 2 or progressed-disease to death were derived from the parametric extrapolation of OS and PFS curves from an external single-arm cohort study (Vasseur et al. 2024). The selection of parametric survival distributions was based on statistical and visual fit. <u>Inavolisib + palbociclib + fulvestrant</u> • progression-free 1 to progression-free 2: Log-logistic • progression-free 1 to death: Log-normal • progression-free 2 to progressed-disease: Log-normal • progression-free 2 to death: Gompertz • progressed-disease to death: Gompertz <u>Palbociclib + fulvestrant</u> • progression-free 1 to progression-free 2: Log-normal • progression-free 1 to death: Weibull

Component	Description
	• progression-free 2 to progressed-disease: Log-normal • progression-free 2 to death: Gompertz • progressed disease to death: Gompertz
Health-related quality of life	Utilities for progression-free health states were informed by EQ-5D data from INAVO120 trial. <u>Inavolisib + palbociclib + fulvestrant</u> • Progression-free 1: 0.835 • Progression-free 2: 0.771 <u>Palbociclib + fulvestrant</u> • Progression-free 1: 0.836 • Progression-free 2: 0.757 For progressed-disease health state, a utility of 0.505 was applied in both arms, sourced from external studies (Lloyd et al. 2006).
Types of healthcare resources included	• Drug and drug administration • Disease management cost • Healthcare resource use • Subsequent treatment costs • AE management costs

Abbreviations: AE, adverse event; HR+, hormone receptor-positive; HER2-, human epidermal growth factor receptor 2-negative; ICER, incremental cost-effectiveness ratio; LY, life years; OS, overall survival; PFS, progression-free survival; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha gene; QALY, quality-adjusted life year.

4.2. The base-case incremental cost effectiveness ratio (ICER) in the submission was between SG$165,000 and SG$205,000 per quality-adjusted life year (QALY) gained. However, the Committee considered the ICER to be highly uncertain and likely underestimated, given the following issues:

- The use of a four-state Markov model (comprising two progression-free health states, progressed-disease and death), added structural complexity that was not supported by INAVO120 trial data. The additional progression-free health state lacked clinical justification, and data for transitions from this health state were sourced from external studies that were not reflective of the intended population.

- The parametric functions selected for the long-term extrapolation of OS and PFS were optimistic for the inavolisib arm, potentially overestimating the incremental benefits over the time horizon. The long time horizon of 47 years used in the submission's base case was also optimistic and substantially exceeded the INAVO120 trial follow-up period.

- Treatment-specific utility weights were applied, which favoured the inavolisib arm. However, this was not supported by the health-related quality of life outcomes from the INAVO120 trial.

- The submission underestimated the costs of PIK3CA testing and adverse events management costs in the inavolisib arm.

4.3. The Committee considered the revised base case, which accounted for several uncertainties in the company's model. Key changes to the economic model included reducing the time horizon, using the same utility weights for both treatment arms, selecting alternative parametric functions for extrapolation and correcting the costs of testing and managing adverse events. These changes increased the ICER to more than SG$365,000 per QALY gained. Despite the revised base case assumptions, the Committee noted that issues with the model structure could not be resolved.

4.4. Overall, the Committee considered that inavolisib + palbociclib + fulvestrant did not represent a cost-effective use of healthcare resources for treating *PIK3CA*-mutated, HR-positive, HER2-negative, LA/mBC at the price proposed by the company.

Estimated annual technology cost

5.1. Using an epidemiological approach, the submission estimated that the annual cost impact to the public healthcare system would increase from between SG$3 million and SG$5 million in the first year, to between SG$5 million and SG$10 million in the fifth year of listing inavolisib on the MOH List of Subsidised Drugs for treating *PIK3CA*-mutated, HR-positive, HER2-negative LA/mBC.

5.2. The Committee considered that the company's financial estimates for inavolisib were high and uncertain due to the following: uncertainty in the proportion of patients who are endocrine-resistant and who will be tested for *PIK3CA* mutation; incorporation of prevalent patients which appears to be double counted; optimistic estimation of treatment duration based on PFS; and uncertainty in the uptake rate of inavolisib in clinical practice. The Committee also agreed that the price-volume agreement caps proposed by the company were unacceptably high and deviated from the company's budget impact analysis.

5.3. Based on the revised budget impact analysis, the annual cost to the public healthcare system was estimated to be less than SG$1 million in the first year, increasing to between SG$1 million and SG$3 million in the fifth year of listing.

Recommendations

6.1. Based on available evidence, the Committee recommended not listing inavolisib, in combination with palbociclib and fulvestrant, on the MOH List of Subsidised Drugs for treating *PIK3CA*-mutated, HR-positive, HER2-negative, LA/mBC, following recurrence on or within 12 months of completing adjuvant endocrine therapy. The decision was based on the unfavourable cost effectiveness compared with palbociclib plus fulvestrant at the proposed price, and the unacceptable price-volume agreement proposed by the company.

ANNEX

Recommendations by the MOH Drug Advisory Committee

Drug preparation	Company-proposed clinical indication	Subsidy class	MediShield Life claim limit per month
Inavolisib 3 mg and 9 mg capsules	Inavolisib, in combination with palbociclib and fulvestrant, for the treatment of adult patients with *PIK3CA*-mutated, HR-positive, HER2-negative, locally advanced or metastatic breast cancer, following recurrence on or within 12 months of completing adjuvant endocrine therapy	Not recommended for subsidy	Not recommended for MediShield Life claims

Agency for Care Effectiveness - ACE Agency for Care Effectiveness (ACE)

About the Agency

The Agency for Care Effectiveness (ACE) was established by the Ministry of Health (Singapore) to drive better decision-making in healthcare through health technology assessment (HTA), clinical guidance, and education.

As the national HTA agency, ACE conducts evaluations to inform government funding decisions for treatments, diagnostic tests and vaccines, and produces guidance for public hospitals and institutions in Singapore.

The guidance is not, and should not be regarded as, a substitute for professional or medical advice. Please seek the advice of a qualified healthcare professional about any medical condition. The responsibility for making decisions appropriate to the circumstances of the individual patient remains with the healthcare professional.

Find out more about ACE at www.ace-hta.gov.sg/about

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