

Reimbursement Recommendation

Inavolisib (Itovebi)

Indication: Inavolisib in combination with palbociclib and fulvestrant is indicated for the treatment of adult patients with endocrine resistant, *PIK3CA*-mutated, hormone receptor–positive, human epidermal growth factor receptor 2–negative, locally advanced or metastatic breast cancer, following recurrence on or after completing adjuvant endocrine treatment.

Sponsor: Hoffmann-La Roche Limited

Final recommendation: Reimburse with conditions

Summary

What Is the Reimbursement Recommendation for Itovebi?

Canada's Drug Agency (CDA-AMC) recommends that Itovebi in combination with palbociclib (PAL) and fulvestrant (FUL) be reimbursed by public drug plans for the treatment of adult patients with endocrine-resistant, *PIK3CA*-mutated, hormone receptor–positive, HER2-negative, locally advanced or metastatic breast cancer, following recurrence on or after completing adjuvant endocrine treatment, only if certain conditions are met.

Which Patients Are Eligible for Coverage?

Itovebi in combination with PAL and FUL should only be covered to treat adults with hormone receptor–positive, HER2-negative breast cancer that has spread to nearby tissue or lymph nodes (locally advanced), or to other parts of the body (metastatic); has come back after hormone (endocrine) therapy; and has an abnormal *PIK3CA* gene. Patients should also have good performance status. Itovebi in combination with PAL and FUL should not be covered if the patient has been previously treated for hormone receptor–positive, HER2-negative metastatic breast cancer with mutations in the *PIK3CA* gene, or if they have uncontrolled diabetes.

What Are the Conditions for Reimbursement?

Itovebi in combination with PAL and FUL should be prescribed by, then managed under the care of, health care professionals with expertise in managing advanced or metastatic breast cancer. Reimbursement of Itovebi should be discontinued if the cancer becomes worse or there are unacceptable side effects. Price reductions exceeding 90% in the cost of Itovebi as part of the combination regimen with CDK4/6 inhibitor and FUL would be required to achieve an incremental cost-effectiveness ratio (ICER) below \$50,000 per quality-adjusted life-year (QALY) gained, relative to therapies currently in use.

Why Did CDA-AMC Make This Recommendation?

- Evidence from 1 clinical trial (INAVO120) demonstrated that Itovebi in combination with PAL and FUL delays cancer progression and likely results in patients living longer, compared to PAL plus FUL (PAL + FUL) alone.
- Based on the CDA-AMC assessment of the health economic evidence, Itovebi does not represent good value to the health care system at the public list price. A price reduction is therefore required. The pan-Canadian Oncology Drug Review Expert Review Committee (pERC)

Summary

indicated that Itovebi could be used in combination with a CDK4/6 inhibitor other than PAL, together with FUL. Price reduction analysis is based on the CDA-AMC base case with Itovebi in combination with a CDK4/6 inhibitor and FUL.

- Based on public list prices, Itovebi in combination with a CDK4/6 inhibitor and FUL is estimated to cost the public drug plans \$159 million over the next 3 years. The economic feasibility of adoption of Itovebi in combination with a CDK4/6 inhibitor and FUL must be addressed because at the submitted price, the incremental budget impact of Itovebi in combination with a CDK4/6 inhibitor and FUL is expected to be greater than \$40 million in years 2 and 3.

Additional Information

What is *PIK3CA*-Mutated, Hormone Receptor–Positive, HER2-Negative, Locally Advanced or Metastatic Breast Cancer?

Breast cancer is the most common cancer among females in Canada and remains a leading cause of cancer death worldwide. When it spreads beyond the breast or cannot be removed surgically, it is considered locally advanced or metastatic. The most common subtype of breast cancer is hormone receptor–positive, HER2-negative breast cancer, which represents 70% of cases. An estimated 40% of these patients have an abnormal *PIK3CA* gene which is associated with reduced response to endocrine therapy and worse prognosis.

Unmet Needs in *PIK3CA*-Mutated, Hormone Receptor–Positive, HER2-Negative, Locally Advanced or Metastatic Breast Cancer

There is an unmet need for targeted first-line treatment for patients with hormone receptor–positive, HER2-negative, locally advanced or metastatic breast cancer with an abnormal *PIK3CA* gene, that has returned after hormone (endocrine) therapy.

How Much Does Itovebi Cost?

Treatment with Itovebi in combination with a CDK4/6 inhibitor and FUL is expected to cost between \$19,806 and \$20,214 per patient, per 28-day cycle, assuming PAL is used as the CDK4/6 inhibitor.

Recommendation

pERC recommends that inavolisib (INA) in combination with PAL and FUL be reimbursed for the treatment of adult patients with endocrine-resistant, *PIK3CA*-mutated, hormone receptor–positive, HER2-negative, locally advanced or metastatic breast cancer, following recurrence on or after completing adjuvant endocrine treatment, only if the conditions listed in [Table 1](#) are met.

Rationale for the Recommendation

There is an unmet need for targeted first-line treatment for patients with hormone receptor–positive, HER2-negative, locally advanced or metastatic breast cancer with *PIK3CA* alteration and evidence of endocrine resistance. One phase III, randomized, double blind, placebo-controlled trial (INAVO120) (N = 325) demonstrated that treatment with INA plus PAL plus FUL (INA + PAL + FUL) demonstrated an added clinical benefit compared to placebo (PBO) plus PAL plus FUL (PBO + PAL + FUL) for patients with *PIK3CA*-mutated, hormone receptor–positive, HER2-negative, locally advanced or metastatic breast cancer who had shown evidence of endocrine resistance and had not received prior systemic therapy in the metastatic setting. After a median follow-up of 34.2 months, the final analysis showed that INA + PAL + FUL improved progression-free survival (PFS) compared to PBO + PAL + FUL (median PFS = 17.2 months versus 7.3 months; stratified hazard ratio [HR] = 0.42; 95% confidence interval [CI], 0.32 to 0.55) and likely improved overall survival (OS) (median OS = 34.0 months versus 27.0 months; stratified HR = 0.67; 95% CI, 0.48 to 0.94). pERC noted that the most common adverse events (AEs) in the trial were significant, but consistent with expectations for the class of drug under review and were generally considered manageable in clinical practice.

The sponsor-submitted network meta-analysis (NMA) suggested that INA + PAL + FUL may result in added clinical benefit for patients with previously untreated, hormone receptor–positive, HER2-negative, locally advanced or metastatic breast cancer in PFS, when compared to ribociclib (RIB) plus FUL (RIB + FUL). The NMA suggested that no treatment was favoured between INA + PAL + FUL and RIB + FUL in OS. The NMA is associated with considerable uncertainty due to clinical (differences in *PIK3CA* mutation, endocrine resistance, and menopausal status at baseline) and methodological heterogeneity across the included studies, which are also limitations to interpreting the comparisons for the indicated population with *PIK3CA* alteration and evidence of endocrine resistance.

Clinician groups noted that *PIK3CA* alterations are associated with endocrine resistance and poorer prognosis, and the clinical experts consulted by CDA-AMC for this review noted that disease relapse within 12 months of completing adjuvant endocrine therapy is a high-risk group. Treatment goals, identified by patients and clinicians, include prolonging survival, delaying disease progression, and maintaining acceptable quality of life (QoL). Based on the evidence reviewed, pERC concluded that INA + PAL + FUL met some of these treatment goals, representing a useful treatment option for patients with *PIK3CA*-mutated disease, as the treatment demonstrated meaningful clinical benefit in delaying disease progression and likely

improving survival, though the evidence for the treatment effect on health-related quality of life (HRQoL) is uncertain.

Using the sponsor-submitted price for INA and publicly listed prices for all other drug costs, the ICER for INA plus CDK4/6 inhibitors plus FUL (INA + CDK4/6 inhibitor + FUL) was \$713,555 per QALY gained compared with PAL + FUL and \$466,085 per QALY gained compared with RIB + FUL. At these ICERs, INA + CDK4/6 inhibitor + FUL is not cost-effective at a \$50,000 per QALY gained willingness to pay threshold for adult patients with endocrine-resistant, *PIK3CA*-mutated, hormone receptor–positive, HER2-negative, locally advanced or metastatic breast cancer, following recurrence on or after completing adjuvant endocrine treatment. A price reduction is required for the cost of INA as part of this regimen to be considered cost-effective at a \$50,000 per QALY threshold.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. INA + PAL + FUL should be reimbursed in adults aged 18 years or older who meet all of the following criteria: 1.1. documented diagnosis of hormone receptor–positive, HER2-negative, locally advanced or metastatic breast cancer 1.2. blood or tumour tissue documenting <i>PIK3CA</i>-mutated tumour status 1.3. evidence of endocrine-resistant disease defined by disease progression during or within 12 months of completing adjuvant endocrine therapy with an aromatase inhibitor or tamoxifen.	Based on the eligibility criteria from the INAVO120 trial, INA + PAL + FUL improved PFS and likely improved OS in patients with these characteristics.	<i>PIK3CA</i> alterations can be detected in tumour cells using genomic testing methods, such as NGS and PCR. Testing for <i>PIK3CA</i> alterations could be carried out at the time of new or recurrent metastatic breast cancer diagnosis. Tissue samples collected as part of routine diagnostic care (e.g., tissue biopsy, liquid biopsy) can be used for testing. pERC noted that it would be appropriate to align with the definitions for endocrine resistance used in the INAVO120 trial: • primary endocrine therapy resistance was defined as disease relapse while receiving the first 2 years of adjuvant endocrine therapy • secondary endocrine therapy resistance was defined as disease relapse while receiving adjuvant endocrine therapy but after the first 2 years, or disease relapse within 12 months of completing adjuvant endocrine therapy. These definitions were based on the fourth ESO-ESMO International Consensus Guidelines for Advanced Breast Cancer. pERC indicated that it would be reasonable to use INA in combination with an alternative CDK4/6 inhibitor and FUL, and that this helps support a patient-centred approach and optimized patient outcomes by addressing scenarios where 1 CDK4/6 inhibitor is preferred.
2. Patients must have a good performance status.	Patients with an ECOG PS score of 0 or 1 were included in the INAVO120 trial.	Patients with an ECOG PS score of 2 may be treated at the discretion of the health care professional.

Reimbursement condition	Reason	Implementation guidance
3. Patients should not be eligible if: 3.1. they have received prior systemic therapy in the metastatic setting 3.2. uncontrolled diabetes.	Patients who received any prior systemic therapy for metastatic breast cancer and patients with type 2 diabetes requiring ongoing systemic treatment or any history of type 1 diabetes were excluded from the INAVO120 trial.	pERC agreed with the clinical experts that patients presenting with well-controlled diabetes and recurrent endocrine-resistant breast cancer in practice can be considered for INA + PAL + FUL provided that these patients are closely monitored. For patients with uncontrolled diabetes, the committee agreed with the clinical experts that INA + PAL + FUL should not be considered.
Discontinuation		
4. Reimbursement of INA should be discontinued upon occurrence of any of the following: 4.1. disease progression 4.2. unacceptable toxicity.	These discontinuation criteria are consistent with the protocol of the INAVO120 trial and routine clinical practice.	pERC noted that evaluation of response to treatment should be based on standard clinical practice for metastatic breast cancer.
Prescribing		
5. INA + PAL + FUL should be initiated by, then managed under the care of health care professionals with expertise in managing advanced or metastatic breast cancer.	This is meant to ensure that INA + PAL + FUL is prescribed for appropriate patients and that adverse events are managed in an optimized and timely manner.	—
Pricing		
6. A reduction in price	The ICER for INA + CDK4/6 inhibitor + FUL is \$713,555 per QALY gained compared to PAL + FUL, and \$466,085 per QALY gained compared to RIB + FUL. Price reductions in excess of 90% will be required for the cost of INA as part of the INA + CDK4/6 inhibitor + FUL regimen to achieve an ICER below \$50,000 per QALY gained compared to therapies in current use.	—
Feasibility of adoption		
7. The economic feasibility of adoption of INA + CDK4/6 inhibitor + FUL must be addressed.	At the submitted price, the incremental budget impact of INA + CDK4/6 inhibitor + FUL is expected to be greater than \$40 million in years 2 and 3.	—
8. The organizational feasibility of conducting testing for <i>PIK3CA</i> alterations must be addressed.	Testing for <i>PIK3CA</i> alterations is required to determine eligibility for INA.	—

ECOG PS = Eastern Cooperative Oncology Group Performance Status; ESMO = European Society for Medical Oncology; ESO = European School of Oncology; FUL = fulvestrant; ICER = incremental cost-effectiveness ratio; INA = inavolisib; NGS = next-generation sequencing; OS = overall survival; PAL = palbociclib; PCR = polymerase chain reaction; pERC = pan-Canadian Oncology Drug Review Expert Review Committee; PFS = progression-free survival; QALY = quality-adjusted life-year; RIB = ribociclib.

Discussion Points

- Reimbursement request:** pERC reviewed the evidence from an interim safety analysis of the MORPHEUS-panBC trial, an ongoing, phase Ib/II, open-label, randomized umbrella trial evaluating the efficacy and safety of multiple treatment combinations in patients with locally advanced or metastatic breast cancer. pERC noted that the interim safety analysis was performed in 12 patients (INA plus abemaciclib [ABE] plus FUL group, n = 6 and INA plus RIB plus FUL [INA + RIB + FUL] group, n = 6) in the hormone receptor–positive cohort and that no efficacy result was available at the time of submission. Although this was considered insufficient evidence to support INA in combination with any CDK4/6 inhibitor (other than PAL) and FUL, pERC concluded that conducting additional clinical trials for INA in combination with other CDK4/6 inhibitors and FUL is unlikely to be feasible. pERC acknowledged that an approval for INA in combination with any CDK4/6 inhibitor and FUL would help to support a patient-centred approach and optimize patient outcomes by addressing scenarios where 1 CDK4/6 inhibitor is preferred based on the patient's individual circumstances and at the discretion of the health care professional.
- Unmet needs:** Patients and clinicians identified a clinical unmet need for targeted first-line treatment for patients with hormone receptor–positive, HER2-negative, locally advanced or metastatic breast cancer with *PIK3CA* alteration and evidence of endocrine resistance. pERC acknowledged input from the clinician groups that noted that *PIK3CA* alterations are associated with endocrine resistance and poorer prognosis, and input from the clinical experts consulted by CDA-AMC for this review that noted that disease relapse within 12 months of completing adjuvant endocrine therapy is a high-risk group. Additionally, patients and clinicians identified treatment goals, including improved survival, delayed disease progression, and maintenance of acceptable QoL. The committee concluded that INA + PAL + FUL meets some of these treatment goals, representing a useful treatment option for the patients with endocrine-resistant, *PIK3CA*-mutated disease, as the treatment demonstrated meaningful clinical benefit in delaying disease progression and likely improving survival, compared to PAL + FUL.
- Harms:** pERC discussed the evidence for harms observed with treatment with INA + PAL + FUL, which was only available for the comparison to PAL + FUL in the INAVO120 trial. No evidence for harms compared to other CDK4/6 inhibitors plus FUL was included in the submission. pERC considered the harms observed with treatment with INA + PAL + FUL within the context of a high-risk population with endocrine resistance and poorer prognosis. pERC acknowledged input from patients who indicated that hyperglycemia and diarrhea are acceptable AEs with standard management using oral antihyperglycemic and antidiarrheal drugs. pERC noted that the most common AEs observed in the trial were significant, but consistent with expectations for the drug class under review and were generally considered manageable in clinical practice.
- Indirect evidence:** Clinicians indicated that RIB is the most used CDK4/6 inhibitor in practice in Canada, while reassessment by CDA-AMC of ABE was under way at the time of this review. pERC reviewed the evidence from the sponsor-submitted NMA, comparing INA + PAL + FUL with CDK4/6 inhibitors — other than PAL — in patients with previously untreated, hormone

receptor–positive, HER2-negative, locally advanced or metastatic breast cancer. pERC noted that the NMA is associated with considerable uncertainty due to clinical (differences in *PIK3CA* mutation, endocrine resistance, and menopausal status at baseline) and methodological (differential follow-up) heterogeneity across the included studies, which are also limitations to interpreting the comparisons for the indicated population with *PIK3CA* alteration and evidence of endocrine resistance. Further, the proportional hazards assumption was violated for the OS and PFS data, and results from the interim analysis of OS in the INAVO120 trial may be considered premature to incorporate into an NMA. pERC also noted that the NMA did not evaluate HRQoL and safety outcomes. Therefore, pERC concluded that the clinical benefit of INA + PAL + FUL compared to RIB + FUL is less certain.

- **Remaining gaps and uncertainties regarding HRQoL:** pERC noted that the HRQoL benefit of INA + PAL + FUL in improving the probability of being without deterioration in HRQoL is less certain due to imprecision in the effect estimates, risk of bias due to informative censoring, and uncertainty in the clinical importance of the treatment difference. pERC also noted that although HRQoL appeared comparable between groups, these were not tested statistically, and between-group differences were not reported in the INAVO120 trial. Therefore, the committee could not draw a firm conclusion regarding the HRQoL benefit of INA + PAL + FUL for patients with endocrine-resistant, *PIK3CA*-mutated disease.
- **Remaining gaps and uncertainties regarding prior neoadjuvant and/or adjuvant CDK 4/6 inhibitor:** pERC acknowledged clinical expert input indicating that as CDK4/6 inhibitors become more widely available in the adjuvant setting, the number of patients without prior exposure to CDK4/6 inhibitors and whose disease relapses is expected to decline. Although the INAVO120 trial included patients who had an event (disease progression) more than 12 months since completion of the CDK4/6 inhibitor portion of neoadjuvant and/or adjuvant therapy, the committee agreed with clinician input that less than 5% of patients in the INAVO120 trial received CDK4/6 inhibitor in the adjuvant setting, thereby limiting the generalizability of the results to this group of patients. Therefore, the committee could not draw a firm conclusion regarding the benefit of INA + PAL + FUL for patients who have been exposed to CDK4/6 inhibitors in the adjuvant setting and experience disease relapse. However, consistent with previous guidance on the re-treatment with a CDK4/6 inhibitor through the associated Provisional Funding Algorithm, pERC agreed re-treatment was reasonable assuming relapse occurred at or after 6 months of adjuvant therapy completion.
- **Testing for *PIK3CA* alterations:** While *PIK3CA* mutations can be detected using next-generation sequencing (NGS) of tumour tissue sample, pERC noted that circulating tumour DNA, collected using a peripheral blood sample, can also be used to test for mutations as an alternative for patients in whom a traditional biopsy is contraindicated or challenging to perform. pERC noted that the availability and funding for testing for *PIK3CA* alterations in patients with relapsed hormone receptor–positive, HER2–negative, metastatic breast cancer is variable across Canada. While most provincial laboratories in Canada include *PIK3CA* on their NGS panels, funded testing options that target this mutation is available or is in the process of being available in some, but not all, jurisdictions. Similarly, circulating tumour DNA testing in this population is not funded in most, if not all, jurisdictions. pERC

also noted that the implementation of NGS testing for *PIK3CA* alterations may have a substantial health system impact on regions or centres without established *PIK3CA* testing (e.g., impact on personnel and currently available testing infrastructure). These issues may limit patients' access to testing in the short-term. However, according to the clinical experts, this will likely resolve over time since testing for *PIK3CA* mutations in breast cancer is expected to become standard of care in Canada.

- **Economic considerations:** pERC expressed concerns regarding the cost-effectiveness of INA + CDK4/6 inhibitor + FUL. CDA-AMC estimated ICERs of \$713,555 per QALY gained compared to PAL + FUL, and \$466,085 per QALY gained compared to RIB + FUL. These estimates were considered to be unreasonably high. These concerns also extended to the budget impact. The estimated incremental budget impact over the first 3 years of reimbursement is approximately \$139 million, with total spending on INA + CDK4/6 inhibitor + FUL projected to reach \$159 million over this period. This represents a substantial increase compared to current expenditures on available treatment options. pERC further acknowledged that the actual budget impact will depend on the size of the eligible population, treatment uptake, and whether clinicians prescribe RIB or PAL as the preferred CDK4/6 inhibitor in combination with INA. Uncertainty in these assumptions contributes to variability in the budget impact projections and may further influence the feasibility of adoption for public drug plans.

Background

Breast cancer is the most diagnosed cancer among females in Canada and remains a leading cause of cancer-related death worldwide. In 2024, more than 30,000 women in Canada were estimated to be diagnosed with breast cancer, and 5,000 were expected to die from the disease. Common symptoms include bloody or watery discharge and redness, scaling, or inflammation of the nipple. As the cancer progresses or metastasizes, patients may experience systemic symptoms including nausea, weight loss, muscle weakness, and bone pain. Hormone receptor–positive, HER2-negative breast cancer is the most prevalent subtype, accounting for 70% of all cases. The estimated 5-year survival rate in patients with hormone receptor–positive, HER2-negative metastatic breast cancer is 34%. An estimated 40% of these patients have mutations in the *PIK3CA* gene which are associated with reduced response to endocrine therapy and worse overall prognosis.

International guidelines are used in practice as there is no Canadian guideline specifying standard of care for patients with *PIK3CA*-mutated, hormone receptor–positive, HER2-negative breast cancer. The preferred first-line treatment option for this population, regardless of *PIK3CA*-mutation status, includes a CDK4/6 inhibitor combined with endocrine therapy (and a luteinizing hormone-releasing hormone agonist depending on menopausal status). Examples of CDK4/6 inhibitor include PAL and RIB; ABE does not have public funding. The December 2024 Provisional Funding Algorithm for hormone receptor–positive, HER2-negative breast cancer, including HER2-low, is available on the [project website](#). The clinical experts consulted for this review indicated that capivasertib (CAP) plus FUL could be considered in patients with exposure to CDK4/6

inhibitors in the adjuvant setting, depending on public funding. Further, this combination could be considered in patients with an *AKT*, *PTEN*, or *PI3KCA* mutation.

INA in combination with PAL and FUL has been approved by Health Canada for the treatment of adult patients with endocrine-resistant, *PIK3CA*-mutated, hormone receptor–positive, HER2-negative, locally advanced or metastatic breast cancer, following recurrence on or after completing adjuvant endocrine treatment. INA is a selective PI3K inhibitor. It is available as tablets and the dosage recommended in the product monograph is 9 mg taken orally once daily.

Sources of Information Used by the Committee

To make its recommendation, the committee considered the following information:

- a review of 1 phase III, randomized controlled trial (RCT) in adults with endocrine-resistant, *PIK3CA*-mutated, hormone receptor–positive, HER2-negative, locally advanced or metastatic breast cancer, and who had not received any prior systemic therapy for metastatic breast cancer; 1 indirect treatment comparison (ITC); and 1 phase Ib/II, open-label randomized umbrella study
- patients' perspectives gathered by 3 patient groups: Breast Cancer Canada, Canadian Breast Cancer Network, and Rethink Breast Cancer
- input from public drug plans and cancer agencies that participate in the reimbursement review process
- 2 clinical specialists with expertise diagnosing and treating patients with breast cancer
- input from 2 clinician groups: Ontario Health (Cancer Care Ontario) Breast Cancer Drug Advisory Committee and the Research Excellence, Active Leadership Canadian Breast Cancer Alliance
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Perspectives of Patients, Clinicians, and Drug Programs

Patient Input

Input for this review was submitted by 3 patient groups: Breast Cancer Canada (BCC), Canadian Breast Cancer Network (CBCN), and Rethink Breast Cancer. BCC is a national organization that educates and advocates for precision oncology in breast cancer research. CBCN is a patient-directed national health charity aiming to improve care for individuals with breast cancer in Canada through education, advocacy, and informational resources. Rethink Breast Cancer is a national charity that educates, empowers, and advocates for system changes to improve the experience and outcomes of individuals with breast cancer. To gather information, BCC conducted 2 surveys: 1 from July 6 to 21, 2023 (171 responses), targeting patients with hormone receptor–positive, HER2-negative metastatic breast cancer and their caregivers; and the second from February 15 to 23, 2025 (169 responses, 54 patients receiving first-line treatment for hormone receptor–positive, HER2-negative metastatic disease). CBCN gathered information from medical literature,

past patient input submissions (e.g., alpelisib), and the 2022 Triple Negative Breast Cancer Patient Survey (981 responses, 30 patients receiving first-line treatment for metastatic hormone receptor–positive, HER2-negative breast cancer). Rethink Breast Cancer gathered information from patient meetings, a survey (2018 to 2019) of 78 patients with metastatic breast cancer, and a February 2025 interview with 1 patient with metastatic breast cancer who had experience receiving INA.

Patients with hormone receptor–positive, HER2-negative metastatic breast cancer experience a wide range of debilitating symptoms that vary based on site of metastasis, including fatigue, shortness of breath, nausea, pain, bone fractures, and reduced mobility, all of which greatly impact daily functioning. These physical challenges often restrict patients' ability to work, care for children, maintain relationships, and participate in their communities. Patients also report a profound emotional toll when faced with processing a life-limiting diagnosis, with fear of recurrence, financial insecurity, body image concerns, anxiety about the impact of their illness on their children, a sense of burdening caregivers, and isolation (common among patients). Rethink Breast Cancer noted that patients aged 20 to 40 years can face more aggressive breast cancer and experience additional challenges related to fertility, pregnancy, parenting, and career interruptions.

Treatment goals primarily involve delaying disease progression and improving QoL. The patient groups noted that treatment options and effectiveness vary based on the type and location of cancer, and degree of symptoms. For patients with hormone receptor–positive, HER2-negative metastatic breast cancer, current treatments, primarily endocrine therapy and CDK4/6 inhibitors, aim to maintain QoL as long as possible before switching to chemotherapy. The patient groups noted that chemotherapies are given sequentially and typically have diminishing PFS responses with later lines. The patient groups highlighted that there are currently no reimbursed treatments for those with hormone receptor–positive, HER2-negative metastatic breast cancer and a *PIK3CA* mutation who have experienced a recurrence within 12 months of being treated for early-stage breast cancer.

For patients with metastatic breast cancer, the primary improvement patients seek is extending their life without sacrificing QoL, and delay progression. Generally, patients value long-term health outcomes versus immediate concerns such as reducing symptoms or managing AEs. Even a few additional months is considered a meaningful improvement, with 1 patient noting “those months could be the difference that lets me see my son start kindergarten; they could be the ones that give me time to get him off diapers before it all falls on dad; Or they could be the first time he says I Love You. While a few months are short on time they are bursting with possibility.”

One patient, diagnosed with hormone receptor–positive, HER2-negative metastatic breast cancer in 2004 and having received 7 lines of treatment, had direct experience with INA for 18 months through a 2018 phase I clinical trial. The patient reported good energy levels while on treatment, which enabled them to continue working, and felt that the treatment addressed an unmet need for them. While they experienced hyperglycemia while receiving therapy, it was managed through metformin and a ketogenic diet.

Patient groups are in support of Canada providing *PIK3CA* genomic testing as standard of care for all hormone receptor–positive, HER2-negative breast cancer who may benefit from INA, provided that access is timely, equitable, and publicly funded.

Clinician Input

Input From Clinical Experts Consulted for This Review

When considering clinical unmet needs, the clinical experts highlighted the lack of evidence for first-line treatment in the subset of patients with *PIK3CA*-mutated disease, which, alongside endocrine resistance, are associated with poor breast cancer-related outcomes and limited duration of response. When considering nonclinical unmet needs, the clinical experts suggested that the once daily dosing of INA is more convenient for some patients compared with a twice daily dosing schedule and endocrine therapy requiring frequent monitoring and intramuscular injections. As testing for *PIK3CA* mutation is not yet standard across Canada, the clinical experts identified this as a barrier to access and delay in treatment given that this is a companion diagnostic required to assess suitability for the treatment. The clinical experts also indicated there is a challenge in diagnosing in a timely manner as symptoms of recurrent disease are not often recognized, leading to delays in treatment. However, the disease is usually slow-growing and therefore, underdiagnosis is not expected to be a major issue as per feedback from the clinical experts.

If INA + PAL + FUL is approved for public reimbursement, the clinical experts anticipated this would change the current treatment paradigm and would be considered in the first-line treatment setting in adults with endocrine-resistant, *PIK3CA*-mutated, hormone receptor–positive, HER2-negative, locally advanced or metastatic breast cancer. As response rate, duration of response, and duration of PFS become shorter with each subsequent line of therapy, the clinical experts indicated there would be an ethical concern if this therapy was used in later lines where it is likely less effective compared with the setting where it has been shown to be effective. Hence, the clinical experts indicated that the therapy under review would be offered before other treatments. Notably, the clinical experts indicated that if patients are treated with this combination, then subsequent therapy would not include a *PIK3CA* inhibitor (i.e., the clinical experts advised that there is currently no evidence for subsequently targeting similar pathways).

The clinical experts advised that the patient population that would be best suited for treatment with INA + PAL + FUL aligns with the unmet needs in the INAVO120 study population — adults with endocrine-resistant, *PIK3CA*-mutated, hormone receptor–positive, HER2-negative, locally advanced or metastatic breast cancer, and who had not received any prior systemic therapy for metastatic breast cancer. The clinical experts additionally highlighted that patients best suited for INA + PAL + FUL includes those who have not been exposed to CDK4/6 inhibitors in the adjuvant setting, who have a good Eastern Cooperative Oncology Group Performance Status (ECOG PS), and good renal and hepatic function.

The clinical experts noted ABE is the only CDK 4/6 inhibitor currently available for adjuvant treatment in the patient population considered high risk. Thus, the clinical experts anticipated that as CDK4/6 inhibitors become increasingly available in the adjuvant setting, those who have not been exposed to CDK4/6 inhibitors in the adjuvant setting and who experience disease relapse will decrease. Of note, the clinical

experts felt that prior exposure to CDK4/6 inhibitors should be clearly defined in possible reimbursement criteria because there are patients who do not tolerate adjuvant treatment. For example, if a patient experienced clinically significant AEs and did not have significant exposure to the CDK4/6 inhibitor, the clinical experts felt that they should have access to the treatment under review if they experience disease relapse.

The clinical experts indicated that a clinically meaningful response to treatment is improvement in cancer-related symptoms (e.g., improvement in pain control, breathing, nausea, or fatigue) and improvement in performance status. In terms of imaging (e.g., CT, PET, ultrasounds), the clinical experts referred to the Response Evaluation Criteria in Solid Tumours Version 1.1 (RECIST 1.1) criteria to determine a complete response (CR), partial response (PR), stable disease, or progressive disease. The clinical experts noted that clinical benefit for more than 6 months, which includes a CR, PR, and stable disease, often appears in breast cancer discussion. The clinical experts advised that bone scans are used after 4 to 6 months of starting treatment due to bone remodelling. For an individual patient, the clinical experts suggested that an improvement in symptoms and being able to stay on a treatment for a meaningful length of time are considered positive outcomes. The clinical experts also suggested that being able to avoid chemotherapy for a longer period is of importance to patients. As such, the clinical experts further suggested that minimal symptoms from cancer and from the treatment are meaningful to patients.

The clinical experts noted that there can be variation in the frequency of assessment depending on disease and patient factors. In general, the clinical experts indicated that tumour assessments are every 3 months initially and may be more frequent if symptomatic disease or rapidly growing disease or less frequent if the disease is responding to treatment or is stable. Notably, the clinical experts advised that the treatment under review requires close monitoring of fasting glucose to avoid severe hyperglycemia and other toxicities.

The clinical experts advised that the treatment under review should be continued until progression as per the INAVO120 trial in patients who are experiencing a response to treatment and tolerating the treatment. In addition to consideration for patient preference, the clinical experts advised to discontinue treatment if the therapy is not effective after 2 to 3 cycles, if there is toxicity despite supportive medications and dose adjustment, and/or if there is a negative impact on QoL.

The clinical experts advised that a medical oncologist should assess the patient, initiate the treatment under review, and provide follow-ups or may delegate trained family practice oncologists, nurse practitioners, or internal medicine specialists to deliver the treatment and/or provide follow-ups. The clinical experts noted that the prescribing oncologist should be available to help with toxicity management, dose changes, and treatment changes. The clinical experts advised that cancer clinics with medical oncology experts either at the site or overseeing the site are appropriate settings for treatment with INA + PAL + FUL.

Clinician Group Input

Input for this review was submitted by 2 clinician groups, the Ontario Health (Cancer Care Ontario) (OH [CCO]) Breast Cancer Drug Advisory Committee and the Research Excellence, Active Leadership (REAL) Canadian Breast Cancer Alliance. The OH (CCO) Breast Cancer Drug Advisory Committee provides timely evidence-based clinical and health system guidance on drug-related issues. REAL Canadian Breast Cancer

Alliance is a committee of multidisciplinary, clinical and academic oncologists across Canada and BCC, a patient organization, that publishes national clinical consensus recommendations. Information was gathered for the input through clinical expertise, review of published literature, global conferences, and virtual discussions.

The clinician groups highlighted the prevalence of hormone receptor–positive, HER2-negative metastatic breast cancer in Canada, noting that approximately 70% of breast cancer cases are in this population and up to 40% also have *PIK3CA* mutation. The groups noted that *PIK3CA* mutations are associated with endocrine resistance and poorer prognosis, and therefore *PIK3CA* is becoming recognized as an important target with unique prognostic and therapeutic implications. While targeted treatments do exist for the PI3K pathway (e.g., alpelisib and CAP), data supports their use in combination with endocrine therapy in the second-line setting only. The REAL Canadian Breast Cancer Alliance indicated that the availability of PI3K inhibitors in combination with CDK4/6 inhibitors and endocrine therapy in the first-line setting would improve PFS in this patient population; REAL Canadian Breast Cancer Alliance noted that because the OS benefit is challenging to demonstrate in the metastatic hormone receptor–positive population, PFS is considered globally recognized as a global end point for regulatory and funding decisions.

The clinician groups agreed that INA would be used first line for all patients with hormone receptor–positive, HER2-negative metastatic or locally advanced breast cancer and a *PIK3CA* mutation following recurrence. The groups anticipate that the requested INA combination would displace second-line CAP in patients who did not receive an adjuvant CDK4/6 inhibitor and FUL with CDK4/6 inhibitors alone. OH (CCO) noted that the requested combination could also be an alternative to first-line CAP in those who received an adjuvant CDK4/6 inhibitor. According to clinician groups, patients best suited to INA are those with hormone receptor–positive, HER2-negative metastatic or locally advanced breast cancer and a *PIK3CA* mutation, who experience an early recurrence on endocrine therapy. Patients who are considered less suitable for treatment with INA are those without *PIK3CA* pathway abnormalities or those with contraindications to INA (e.g., severe, poorly controlled diabetes) or any of the drugs in the combination, type 1 diabetes, or patients who are unable to undergo appropriate monitoring. The groups noted that toxicity and clinical response should be reassessed using clinical assessments, blood tests, and restaging scans at standard frequencies. REAL Canadian Breast Cancer Alliance noted that patients with pre-existing type 2 diabetes or those at risk of glucose intolerance should have their blood sugar levels closely monitored during treatment. Discontinuation should be considered in the event of disease progression, refractory toxicity despite dose modifications, any grade 4 toxicity, or intolerance. The groups agreed that the treatment combination could be prescribed and monitored in the outpatient setting, by any oncologist with experience treating breast cancer.

OH (CCO) noted they do not support the requested removal of the phrase “within 12 months of completing adjuvant endocrine treatment” from eligibility criteria, as the most relevant patient population would be those who relapse early while on endocrine monotherapy. The group indicated that patients whose disease relapsed early while receiving CDK4/6 inhibitors should not receive the requested combination, as these patients made up less than 2% of the trial population. OH (CCO) also noted concerns regarding substantial toxicity associated with this regimen, noting that there were deaths due to toxicity, which is unusual for an

endocrine-based treatment. OH (CCO) also noted that while the INA trial was in combination with PAL, RIB is the most common CDK4/6 inhibitor used in practice. REAL Canadian Breast Cancer Alliance noted that while the INAVO120 study included a small sample size of male patients, both male and female patients should be eligible for INA triplet therapy in clinical practice.

Drug Program Input

Table 2: Responses to Questions from the Drug Programs

Drug program implementation questions	Response
Relevant comparators	
The comparator in the INAVO120 trial, PBO + PAL + FUL, is consistent with the current standard of care. The alternative treatment option is CDK4/6 inhibitor + aromatase inhibitor. RIB-containing regimens is also a reasonable standard of care. At the time of this review, CDA-AMC reassessment of ABE for hormone receptor–positive, HER2-negative advanced or metastatic breast cancer is under way. The reimbursement request is for INA in combination with any CDK4/6 inhibitor and FUL — is this a reasonable treatment option?	The committee agreed that an approval for INA in combination with any CDK4/6 inhibitor and FUL would help to support a patient-centred approach to address cases where 1 CDK4/6 inhibitor is preferred, based on the patient's individual circumstances and at the discretion of the health care professional. Note that ABE is under consideration for negotiation with pCPA.
Considerations for initiation of therapy	
Disease progression during adjuvant endocrine treatment or within 12 months of completing adjuvant endocrine therapy with an aromatase inhibitor or tamoxifen was an inclusion criterion in the INAVO120 trial. Should this timeline be maintained as eligibility for jurisdictional funding?	The committee referred to the definitions for primary and secondary endocrine resistance used in the INAVO120 trial: • primary endocrine therapy resistance was defined as disease relapse while receiving the first 2 years of adjuvant endocrine therapy • secondary endocrine therapy resistance was defined as disease relapse while receiving adjuvant endocrine therapy but after the first 2 years or disease relapse within 12 months of completing adjuvant endocrine therapy.
Patients with de novo metastatic breast cancer were excluded from the INAVO120 trial. Should they be excluded from funding?	pERC advised that reimbursement should align with the eligibility criteria used in the INAVO120 trial; that is, patients with de novo metastatic breast cancer and no evidence of endocrine resistance should not be eligible.
Fasting glucose < 7.0 mmol/L and hemoglobin A1C < 6.0% were inclusion criteria in the INAVO120 trial. Should these be maintained as eligibility for jurisdictional funding?	The committee acknowledged that the INAVO120 trial excluded patients with diabetes. The committee agreed that patients presenting with well-controlled diabetes and recurrent endocrine-resistant breast cancer in practice can be considered for INA + PAL + FUL provided that these patients are closely monitored. For patients with uncontrolled diabetes, the committee agreed that INA + PAL + FUL should not be considered.
Measurable disease per RECIST 1.1 was an inclusion criterion in the INAVO120 trial. Should this be maintained as eligibility for jurisdictional funding?	The committee advised to exclude this criterion for funding because it is relevant to end points in clinical trials but does not reflect clinical practice where many patients with breast

Drug program implementation questions	Response
	cancer have bone-only disease which is usually not considered measurable.
Considerations for prescribing of therapy	
There are scheduling differences between oral INA (continuous) and oral PAL (daily for 21 days, followed by 7 days off treatment). Proper counselling is required.	This is a comment from the drug plans to inform pERC deliberations.
Can INA be continued if PAL and/or FUL is discontinued?	pERC agreed with the clinical experts consulted by CDA-AMC for this review that this would be a rare scenario in clinical practice and advised that continuation of INA in this setting should be at the discretion of the health care professional.
Consistency with pre-existing recommendations for PAL or RIB + FUL and PAL or RIB + aromatase inhibitor.	This is a comment from the drug plans to inform pERC deliberations.
Generalizability	
Should the following patients be considered eligible for treatment: • patients with ECOG PS score > 1 • patients with CNS metastases • patients who receive initial chemotherapy due to visceral crisis.	pERC advised that patients with good performance status (up to ECOG PS score of 2) may be treated at the discretion of the health care professional. pERC agreed with the clinical experts consulted by CDA-AMC for this review that patients with CNS metastases and patients who receive initial chemotherapy due to visceral practice may also be considered for treatment at the discretion of the health care professional. The clinical experts highlighted the following factors that would be considered in clinical practice: • whether CNS metastasis is controlled or whether leptomeningeal disease is present • visceral crisis has been a poorly defined term and is a rare occurrence.
Should patients receiving existing treatments be switched to INA + PAL + FUL?	If the definition of existing treatment is CDK4/6 inhibitors plus endocrine, then the committee agreed with the experts that switching to INA + PAL + FUL can be considered in patients with less than 3 months of exposure to their existing therapy: • if the patient's <i>PIK3CA</i> status is pending • on a time-limited basis. The clinical experts consulted by CDA-AMC for this review indicated that the threshold of 3 months is associated with adequate exposure to observe benefit.
Funding algorithm	
Request to initiate a rapid provisional funding algorithm.	This is a comment from the drug plans to inform pERC deliberations.
Under what clinical circumstances would INA + PAL + FUL be preferred versus other existing treatments?	The committee advised to refer to the study population in the INAVO120 trial — adults with endocrine-resistant, <i>PIK3CA</i> -mutated, hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer, and who had not received any prior systemic therapy for metastatic breast cancer.

Drug program implementation questions	Response
Should patients who received prior adjuvant endocrine therapy, but whose disease progressed to greater than 12 months, be considered?	The committee indicated there is a lack of evidence for INA + PAL + FUL in this scenario.
Care provision issues	
Currently, all major breast cancer treatment guidelines recommend <i>PIK3CA</i> mutation testing in hormone receptor–positive metastatic breast cancer through PCR or NGS assays using tumour blood (to detect circulating tumour DNA) or tumour tissue. Recent reviews by CDA-AMC testing to identify <i>PIK3CA</i>, <i>AKT1</i>, or <i>PTEN</i> alterations noted a cost per test for NGS of \$750 (Reimbursement Recommendation, Capivasertib [Truqap] – Final Recommendation available on the project webpage). At the time of this review, funding for <i>PIK3CA</i> mutation testing is not uniform across the country.	This is a comment from the drug plans to inform pERC deliberations.

ABE = abemaciclib; CNS = central nervous system; CDA-AMC = Canada's Drug Agency; ECOG PS = Eastern Cooperative Oncology Group Performance Status; FUL = fulvestrant; INA = inavolisib; NGS = next-generation sequencing; PAL = palbociclib; pERC = pan-Canadian Oncology Drug Review Expert Review Committee; PBO = placebo; pCPA = pan-Canadian Pharmaceutical Alliance; PCR = polymerase chain reaction; RECIST = Response Evaluation Criteria in Solid Tumours Version 1.1; RIB = ribociclib.

Clinical Evidence

Systematic Review

Description of the Study

The INAVO120 study (N = 325) is an ongoing phase III, randomized, double blind, placebo-controlled, multicentre, global study evaluating the efficacy and safety of INA + PAL + FUL compared with PBO + PAL + FUL in adults with endocrine-resistant, *PIK3CA*-mutated, hormone receptor–positive, HER2-negative, locally advanced or metastatic breast cancer, and who had not received any prior systemic therapy for metastatic breast cancer. Notably, the trial population excluded patients with type 2 diabetes requiring ongoing systemic treatment at the time of study entry, or any history of type 1 diabetes, as well as patients with known and untreated, or active central nervous system metastases. The primary end point was investigator-assessed PFS, and a key secondary end point was OS.

The mean age of all patients randomized in the INAVO120 study was 54.0 years (standard deviation [SD] = 11.1 years; range, 27 years to 79 years). Most patients (63% of patients randomized) had an ECOG PS score of 0 and 36% of patients had an ECOG PS score of 1. Almost all patients (99%) had metastatic disease at study entry, while 1% of patients had locally advanced disease. Most patients (> 40%) had at least 1 lesion in the bone, lymph nodes, liver, or lung, while 20% of patients had at least 1 lesion in the pleura or peritoneum, or skin or soft tissue. Notably, less than 5% of patients had at least 1 lesion in the bone only or central nervous system. All patients had *PIK3CA* mutation and HER2-negative disease, and most patients had secondary endocrine-resistant (64%) and estrogen receptor–positive or progesterone receptor–positive (70%) disease. Most patients (83%) received prior neoadjuvant and/or adjuvant chemotherapy, 1% of

patients received prior neoadjuvant and/or adjuvant CDK4/6 inhibitor, and 99% of patients received prior neoadjuvant and/or adjuvant endocrine therapy.

Efficacy Results

At the primary analysis data cut-off date, the median duration of follow-up, defined as time from randomization to death for patients who had died at the clinical cut-off date, or the last known alive date for patients, was 21.3 months for all patients (INA + PAL + FUL group: 21.3 months; [REDACTED] and PBO + PAL + FUL group: 21.5 months; [REDACTED]). A summary of the key efficacy results at the primary analysis is presented in the Clinical Review report.

At the final OS analysis data cut-off date, the median duration of follow-up was 34.2 months for all patients (INA + PAL + FUL group: 34.2 months; [REDACTED] and PBO + PAL + FUL group: 32.3 months; [REDACTED]). A summary of the key efficacy results at the final OS analysis is presented in the Clinical Review report.

The following summary is focused on the results from the final OS analysis with the exception of PFS which includes a summary of the primary (final for PFS) analysis results.

Progression-Free Survival

PFS was defined as the time from randomization to the first occurrence of disease progression, as determined by the investigator according to RECIST 1.1, or death from any cause, whichever occurred first.

Primary analysis results: At the time of the primary analysis, which included the final analysis of the primary efficacy end point of investigator-assessed PFS, 50.9% of patients (82 of 161 patients) in the INA + PAL + FUL group and 68.9% of patients (113 of 164 patients) in the PBO + PAL + FUL group had an event (the first occurrence of disease progression or death). The median PFS was 15.0 months (95% CI, 11.3 months to 20.5 months) in the INA + PAL + FUL group and 7.3 months (95% CI, 5.6 months to 9.3 months) in the PBO + PAL + FUL group. INA + PAL + FUL was favoured over PBO + PAL + FUL (stratified HR = 0.43; 95% CI, 0.32 to 0.59; log-rank P value < 0.0001); this result was consistent with the results from the unstratified analysis and other sensitivity and supplemental analyses (data are presented in the Clinical Review report).

The treatment difference in PFS rates at 6 months, 12 months, and 18 months were 27.01% (95% CI, 16.87% to 37.15%), 23.28% (95% CI, 11.59% to 34.97%), and 25.14% (95% CI, 13.52% to 36.76%), respectively.

Updated results at the final OS analysis: At the time of the final OS analysis, which included descriptive results of the primary end point of investigator-assessed PFS, 64% of patients (103 patients) in the INA + PAL + FUL group and 86% of patients (141 patients) in the PBO + PAL + FUL group had an event (the first occurrence of disease progression or death). The median PFS was 17.2 months (95% CI, 11.6 months to 22.2) months in the INA + PAL + FUL group and 7.3 months (95% CI, 5.9 months to 9.2 months) in the PBO

+ PAL + FUL group. The stratified HR was 0.42 (95% CI, 0.32 to 0.55) following treatment with INA + PAL + FUL versus PBO + PAL + FUL.

The treatment difference in PFS rates at 6 months, 12 months, 18 months, and 24 months were [REDACTED], [REDACTED], [REDACTED], respectively. The Kaplan-Meier (KM) plot for investigator-assessed PFS is presented in the Clinical Review report.

A forest plot of HR for PFS in key subgroups by baseline characteristics is presented in the Clinical Review report to provide descriptive information on the consistency of the primary end point results across these baseline characteristics. The estimated effects in most prespecified subgroups were consistent with the main analysis. However, for patients aged 65 years or older, those not previously treated with neoadjuvant and/or adjuvant chemotherapy, and those previously treated with an aromatase inhibitor and tamoxifen, the point estimates suggested a smaller benefit, with wide 95% CIs spanning the null.

Overall Survival

OS was defined as the time from randomization to death from any cause.

At the time of the final OS analysis, 44.7% of patients (72 patients) in the INA + PAL + FUL group and 50% of patients (82 patients) in the PBO + PAL + FUL group had an event (death). The median OS was 34.0 months (95% CI, 28.4 months to 44.8 months) in the INA + PBO + PAL group and 27.0 months (95% CI, 22.8 months to 38.7 months) in the PBO + PAL + FUL group. INA + PAL + FUL was favoured over PBO + PAL + FUL (stratified HR = 0.67; 95% CI, 0.48 to 0.94; log-rank P value 0.0190); the prespecified statistical significance boundary was 0.0469.

The treatment difference in OS rates at 6 months, 12 months, 18 months, 24 months, and 36 months were 6.73% (95% CI, 1.38% to 12.08%), 10.27% (95% CI, 1.80% to 18.73%), 7.15% (95% CI, -3.11% to 17.40%), 9.52% (95% CI, -1.89% to 20.93%), and 10.25% (95% CI, -2.09% to 22.59%), respectively. The KM plot for OS is presented in the Clinical Review report.

Objective Response Rate

Objective response rate was defined as the proportion of patients with a CR or PR on 2 consecutive occasions at least 4 weeks apart, as determined by the investigator according to RECIST 1.1.

As the final OS analysis crossed the statistical significance boundary, other key secondary end points were tested hierarchically according to the prespecified, fixed order per the statistical analysis plan.

At the time of the final OS analysis, 62.7% of patients (101 patients) in the INA + PAL + PBO group and 28.0% of patients (46 patients) in the PBO + PAL + FUL group had a confirmed objective response (CR or PR). INA + PAL + FUL was favoured over PBO + PAL + FUL; the treatment difference in response rate was 34.7% (95% CI, 24.5% to 44.8%; Cochran-Mantel-Haenszel test P value < 0.0001). A total of [REDACTED] of patients ([REDACTED] patients) in the INA + PAL + FUL group and [REDACTED] of patients ([REDACTED] patients) in the PBO + PAL + FUL group had missing data and were classified as having not responded.

Duration of Response

Duration of response was defined as the time from the first occurrence of a CR or PR to the first occurrence of disease progression, as determined by the investigator according to RECIST 1.1, or death from any cause, whichever occurred first.

In accordance with the statistical analysis plan, formal hypothesis testing was not performed for this outcome given that the determination of duration of response is based on a nonrandomized subset of patients.

At the time of the final OS analysis, 57.4% of patients (58 of 101 patients with a confirmed objective response) in the INA + PAL + FUL group and 71.7% (33 of 46 patients with a confirmed objective response) in the PBO + PAL + FUL group had a subsequent event (the first occurrence of disease progression or death). The median duration of response was 19.2 months (95% CI, 14.7 months to 28.3 months) in the INA + PAL + FUL group and 11.1 months (95% CI, 8.5 months to 20.2 months) in the PBO + PAL + FUL group. The stratified HR was 0.60 (95% CI, 0.37 to 0.97) following treatment with INA + PAL + FUL versus PBO + PAL + FUL.

Time to Confirmed Deterioration in HRQoL

Time to confirmed deterioration in HRQoL was defined as the time from randomization to the first documentation of a 10-point or greater decrease from baseline in the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) global health status scale and quality of life scale (a 7-point Likert scale with higher scores indicating better global health status and quality of life) held for at least 2 consecutive cycles, or an initial decrease followed by death or treatment discontinuation within 3 weeks from the last assessment. The investigator referenced the study by Osoba et al., stating that a clinically meaningful difference in all EORTC QLQ-C30 scales is defined as a 10-point (or greater) change.

The time to confirmed deterioration in the worst pain severity end point was formally included in the testing hierarchy for the final analysis but did not reach statistical significance, thereby ending sequential testing of time to confirmed deterioration in physical functioning, role functioning, and HRQoL end points.

At the time of the final OS analysis, 36.6% of patients (59 patients) in the INA + PAL + FUL group and 34.1% of patients (56 patients) in the PBO + PAL + FUL group had an event (confirmed deterioration in global health status scale and quality of life scale measured by EORTC QLQ-C30). The median time to confirmed deterioration in HRQoL was 31.1 months (95% CI, 25.7 months to 40.3 months) in the INA + PAL + FUL group and 19.4 months (95% CI, 15.0 months to not estimable) in the PBO + PAL + FUL group. The stratified HR was 0.81 (95% CI, 0.56 to 1.19) following treatment with INA + PAL + FUL versus PBO + PAL + FUL.

The treatment difference in event-free rate at 6 months, 12 months, 18 months, and 24 months were

respectively. The KM plot for time to confirmed deterioration in the EORTC QLQ-C30 global health status scale and quality of life scale is presented in the Clinical Review report.



Time to End of Next-Line Treatment

The primary analysis results of time to end of next-line treatment (proxy for time to second objective disease progression) were used to inform the accompanying pharmacoeconomic analysis. A summary of the updated results at the final OS analysis are presented in the Clinical Review report. At the time of the final OS analysis, the stratified HR was 0.51 (95% CI, 0.38 to 0.68).

Harms Results

The following summary is based on the clinical cut-off date of November 15, 2024, at the final OS analysis.

Adverse Events

All patients in the study experienced at least 1 AE. The most common AEs ($\geq 15\%$ in any group) are summarized in the Clinical Review report, with neutropenia being the most common AE reported in both treatment groups (55% of patients).

Serious AEs

A total of 27.3% of patients (44 of 161 patients) in the INA + PAL + FUL group and 13.5% of patients (22 of 163 patients) in the PBO + PAL + FUL group experienced at least 1 serious adverse event (SAE); no single SAE was reported in more than 2.5% of patients in either group.

Withdrawals Due to AEs

A total of 8.7% of patients (14 patients) in the INA + PAL + FUL group and 0.6% (1 patient) in the PBO + PAL + FUL group withdrew from any study treatment component due to any AE; no single AE led to discontinuation among more than 1% of patients in either group.

Mortality

Six patients (3.7%) in the INA + PAL + FUL group and 2 patients (1.2%) in the PBO + PAL + FUL group were reported with an AE that led to a fatal outcome; no single AE led to a fatal outcome among more than 0.6% of patients in either group.

Notable Harms

Refer to withdrawals due to AEs in the previous subsection.

Critical Appraisal

Internal Validity

The INAVO120 trial was appropriately designed and powered to evaluate the efficacy of INA + PAL + FUL compared with PBO + PAL + FUL. There was adequate control for type I errors across the interim and final analyses, the interim analyses were undertaken by an external independent data monitoring committee, and the trial continued to its final analysis without early stopping. Known potential prognostic factors were balanced between groups based on baseline characteristics. As such, the methods used to achieve randomization and allocation concealment are appropriate and the risk of bias arising from the randomization process is low.

Discontinuation from all study treatment was high, although primarily due to progressive disease which is expected in oncology trials and incorporated in the PFS end point. There was an imbalance in the known AEs associated with INA + PAL + FUL observed between groups (i.e., hyperglycemia, stomatitis, and gastrointestinal AEs) as well as withdrawal from any study treatment due to AEs. As such, there is a potential for patients to infer treatment assignment, thereby potentially influencing the patient-reported outcomes.

The reasons for censoring in the analysis of all time to event end points provided by the sponsor did not enumerate the proportion of patients censored by reason; however, there was no major concern indicative of informative censoring. An assessment of the proportional hazards assumption assessment was not reported in the Clinical Study Report for the trial. A visual inspection of the KM plots for OS, duration of response, time to deterioration in HRQoL, and time to end of next-line treatment suggested some concerns for possible deviations from the proportional hazards assumption, thereby affecting the interpretation of the HRs. The interpretation of the between-group differences in KM-estimated probabilities at clinically relevant time points (used to assess the certainty of evidence for OS and time to deterioration in HRQoL) would not be affected by this limitation.

PFS and OS were identified as important outcomes in decision-making for the treatment of patients with breast cancer. As the primary analysis results of investigator-assessed PFS were consistent with the results from the sensitivity analysis of blinded independent central review-assessed PFS, there is a low risk of bias in the measurement of the outcome. There are concerns about the credibility of the results from the subgroup analysis of investigator-assessed PFS, due to the small sample size and lack of testing for treatment by subgroup interactions. Based on a study by Lux et al., only final OS results can confirm whether an intervention results in a clinically relevant difference in survival time versus a comparator in patients with hormone receptor-positive, HER2-negative metastatic breast cancer. More than 50% of patients received subsequent anticancer therapies, which were allowable per the protocol. As such, the effect estimated is that of INA + PAL + FUL versus PBO + PAL + FUL, followed by any other anticancer therapies provided postprogression.

Objective response rate and duration of response were identified as outcomes that would provide supportive information in decision-making. For objective response rate, the risk of bias due to missing outcome data were considered low because the proportion of patients with missing outcome data for this analysis were similar between groups and relatively small. However, there were concerns for risk of bias in the measurement of the outcome as this end point, as well as duration of response, were measured by the investigator and no sensitivity analysis was conducted. The analysis of duration of response included only a subset of patients with an objective response assessed by the investigator, and therefore, there is a risk of bias due to the likely loss of prognostic balance between groups. Importantly, this end point could not be formally interpreted for superiority as it was evaluated outside of the hierarchical analysis plan.

HRQoL was also identified as an important outcome in decision-making and was measured using the EORTC QLQ-C30 global health status scale and quality of life scale in the trial. There is evidence in the literature to support the validity and reliability of this scale in patients with breast cancer, but no literature was identified to inform its responsiveness in patients with breast cancer. Although there is evidence to suggest that a 10-point within-group deterioration in the EORTC QLQ-C30 global health status scale and quality of life scale score would be considered clinically important, there is no known threshold for a clinically important between-group difference in time to confirmed deterioration in HRQoL. There was a large amount of early censoring contributing to the risk of bias due to informative censoring. Further, less than 50% of patients remained after cycle 11 in the intervention group and after cycle 7 in the comparator group for the exploratory analysis of change from baseline in HRQoL.

Time to end of next-line treatment was a proxy for time to second objective disease progression. However, there is uncertain validity in this surrogate end point and is likely confounded by subsequent treatments. As such, there is considerable uncertainty in this exploratory analysis, thereby precluding any conclusions that can be made based on this outcome.

External Validity

The trial population aligned with the target population in the indication and in the clinical unmet need for a treatment with evidence for its use in the first-line setting in patients with endocrine-resistant, *PIK3CA*-mutated, hormone receptor–positive, HER2-negative, locally advanced or metastatic breast cancer. For specific subgroups where the treatment effect appeared smaller, credible effect modification cannot be inferred due to multiple limitations in these analyses, but there is uncertainty as to whether the results can be fully generalized to these subgroups. The clinical experts advised that there are no major concerns for the generalizability of results to male patients and adults aged 65 years or older, as — in their opinion — they are not expected to respond differently from their counterparts. Less than 5% of patients received a CDK4/6 inhibitor in the adjuvant setting, thereby limiting the generalizability of the results to this subset of patients.

The permitted therapies in trial are considered standard of care and reflective of clinical practice in managing the common AEs associated with the class of drug under review. The clinical experts also indicated that the list of subsequent anticancer therapies comprises of both commonly and uncommonly used treatments in practice, which may be due to the timing of the trial.

Lengthened OS with no worsening or improvement in QoL are the most important end points to patients with metastatic breast cancer. Additionally, time without disease progression with improvements in QoL and without added treatment toxicity are also meaningful to patients with metastatic breast cancer.

The clinical experts consulted for this review suggested that the reimbursement request for INA in combination with any CDK4/6 inhibitor and FUL can help address cases where 1 CDK4/6 inhibitor is preferred to optimize patient outcomes. However, there is a gap in the systematic review evidence for INA in combination with any CDK4/6 inhibitor (other than PAL) and FUL. Additionally, there remains a gap in the evidence for INA + PAL + FUL compared with other CDK4/6 inhibitors.

GRADE Summary of Findings and Certainty of the Evidence

Methods for Assessing the Certainty of the Evidence

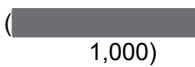
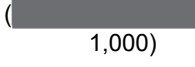
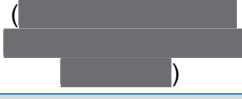
For pivotal studies and RCTs identified in the sponsor's systematic review, Grading of Recommendations Assessment, Development and Evaluation (GRADE) was used to assess the certainty of the evidence for outcomes considered most relevant to inform expert committee deliberations, and a final certainty rating was determined as outlined by the GRADE Working Group.

Following the GRADE approach, evidence from the RCT started as high-certainty evidence and could be rated down for concerns related to study limitations (which refers to internal validity or risk of bias), indirectness, imprecision of effects, and publication bias.

When possible, certainty was rated in the context of the presence of an important (nontrivial) treatment effect; if this was not possible, certainty was rated in the context of the presence of any treatment effect (i.e., the clinical importance is unclear). In all cases, the target of the certainty of evidence assessment was based on the point estimate and where it was located relative to the threshold for a clinically important effect (when a threshold was available) or to the null.

The reference points for the certainty of evidence assessment for PFS and OS were set according to the presence or absence of an important effect based on thresholds informed by the clinical experts consulted for this review. The reference points for the certainty of the evidence assessment for EORTC QLQ-C30 global health status scale and quality of life scale score and withdrawal of any treatment component due to AE were set according to the presence or absence of any effect based on the null.

Table 3: Summary of Findings for INA + PAL + FUL vs. PBO + PAL + FUL for Patients With Endocrine-Resistant, *PIK3CA*-Mutated, Hormone Receptor–Positive, HER2-Negative Locally Advanced or Metastatic Breast Cancer (Clinical Cut-Off Date of November 15, 2024)

Outcome and median follow-up	Patients (studies), N	Relative effect	Absolute effects (95% CI)			Certainty	What happens
			PBO + PAL + FUL	INA + PAL + FUL	Difference		
Investigator-assessed PFS							
KM estimates of the probability of being alive and without progression							
Probability of PFS at 6 months Median follow-up: 34.2 months	325 (1 RCT)	NR	579 per 1,000	834 per 1,000 ( per 1,000)	255 more per 1,000 ()	High ^a	INA + PAL + FUL results in an increase in the probability of being alive and without progression at 6 months and 18 months when compared with PBO + PAL + FUL.
Probability of PFS at 18 months Median follow-up: 34.2 months	325 (1 RCT)	NR	205 per 1,000	497 per 1,000 ( per 1,000)	292 more per 1,000 ()		
OS							
KM estimates of the probability of being alive							
Probability of OS at 12 months Median follow-up: 34.2 months	325 (1 RCT)	NR	767 per 1,000	870 per 1,000 (805 to 914 per 1,000)	103 more per 1,000 (18 more to 187 more per 1,000)	Moderate ^b	INA + PAL + FUL likely results in an increase in the probability of being alive at 12 months and 24 months when compared with PBO + PAL + FUL.
Probability of OS at 24 months Median follow-up: 34.2 months	325 (1 RCT)	NR	563 per 1,000	658 per 1,000 (573 to 730 per 1,000)	95 more per 1,000 (19 less to 209 more per 1,000)		

Outcome and median follow-up	Patients (studies), N	Relative effect	Absolute effects (95% CI)			Certainty	What happens
			PBO + PAL + FUL	INA + PAL + FUL	Difference		
HRQoL							
KM estimates of the probability of being without deterioration in HRQoL (defined as ≥ 10-point decrease from baseline in the EORTC QLQ-C30 global health status scale and quality of life scale held for at least 2 consecutive cycles, or an initial decrease followed by death or treatment discontinuation within 3 weeks from the last assessment)							
Probability of being without deterioration in HRQoL at 6 months Median follow-up: 34.2 months	325 (1 RCT)	NR				Low ^c	INA + PAL + FUL may result in an increase in the probability of being without deterioration in HRQoL at 6 months and 18 months when compared with PBO + PAL + FUL. The clinical importance of the increase is uncertain.
Probability of being without deterioration in HRQoL at 18 months Median follow-up: 34.2 months	325 (1 RCT)	NR					
Harms							
Withdrawal of any treatment component due to AE, n Median follow-up: 34.2 months	325 (1 RCT)	NR	6 per 1,000	87 per 1,000 (NR)	NR	Low ^d	INA + PAL + FUL may result in an increase in withdrawal of any treatment component due to AE when compared with PBO + PAL + FUL. The clinical importance of the increase is uncertain.

AE = adverse event; CI = confidence interval; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; FUL = fulvestrant; HRQoL = health-related quality of life; INA = inavolisib; KM = Kaplan-Meier; NR = not reported; OS = overall survival; PAL = palbociclib; PBO = placebo; PFS = progression-free survival; RCT = randomized controlled trial; vs. = versus.

Notes: Study limitations (which refer to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias were considered when assessing the certainty of the evidence. All serious concerns in these domains that led to the rating down of the level of certainty are documented in the table footnotes.

In consultation with 2 clinical experts consulted for this review, the thresholds of importance (i.e., a clinically meaningful difference) shown in the following footnotes were determined for the assessment of PFS and OS.

^aData from the INAVO120 trial show INA + PAL + FUL may provide a benefit based on a clinically meaningful difference of at least 50 more events per 1,000 patients.

^bRated down 1 level for serious imprecision. The 95% CI included the potential for little to no difference and potential for important benefit. Data from the INAVO120 trial show INA + PAL + FUL may provide a benefit based on a clinically meaningful difference of at least 50 more events per 1,000 patients.

^cRated down 1 level for serious study limitations. The censoring reasons provided by the sponsor did not enumerate the proportion of patients censored due to loss to follow-up. Based on the KM plot of time to deterioration in the EORTC QLQ-C30 global health status scale and quality of life scale, there was a large amount of early censoring contributing to the risk of bias due to informative censoring. Rated down 1 level for serious imprecision. The 95% CI included the possibility of both benefit and harm. There was no known threshold for a clinically important effect, and the clinical experts consulted for this review could not estimate the threshold of a clinically important difference. Hence, the target of the certainty of evidence assessment was based on the point estimate and where it was located relative to the null.

^dRated down 2 levels for very serious imprecision. Few events were observed to inform a higher certainty judgment. There was no known threshold for a clinically important effect, and the clinical experts consulted for this review could not estimate the threshold of a clinically important difference. Hence the target of the certainty of evidence assessment was based on the point estimate and where it was located relative to the null.

Source: Update Clinical Study Report of Study WO41554 (INAVO120).

Long-Term Extension Studies

The sponsor indicated that there is no long-term extension study planned. At the time of submission, the INAVO120 trial is ongoing, and the final analysis reached a clinical cut-off date of November 15, 2024. The total length of the study, from screening of the first patient to the end of the study, is expected to be 6 years.

Indirect Comparisons

Description of Network Meta-Analyses

The objective of the sponsor-submitted NMA was to compare INA + PAL + FUL and other CDK4/6 inhibitors to patients with previously untreated hormone receptor–positive, HER2-negative, locally advanced or metastatic breast cancer. Evidence from 6 studies were included in the NMA, and 2 networks of evidence were used to explore the potential intransitivity arising from differences across studies in endocrine resistance status. The INAVO120 study included patients with *PIK3CA*-mutated disease only, 3 of the included studies included patients with *PIK3CA*-mutated disease, and 2 of the included studies did not report this information. Importantly, the authors noted that the comparative evidence synthesized in the NMA may include patients regardless of their *PIK3CA* mutation status. The NMAs could only be conducted for PFS and OS due to the limited availability of outcomes data reported in the included studies. A subgroup analysis of patients who were postmenopausal was conducted due to observed differences in postmenopausal status at baseline between the INAVO120 study and the 5 other included studies (60% versus 79% to 100% of patients, respectively). The median follow-up duration ranged from 11.1 months to 80 months across the included trials.

Efficacy Results

The PFS and OS results from the base case using the fixed-effect model are presented in the Clinical Review report along with the sensitivity analyses using random-effects models for the endocrine-resistant and endocrine-sensitive network and for the endocrine-resistant network. The subgroup analysis of patients who were postmenopausal results from the endocrine-resistant and endocrine-sensitive network and from the endocrine-resistant network are also presented in the Clinical Review report.

Progression-Free Survival

Endocrine-resistant and endocrine-sensitive network: INA + PAL + FUL was favoured over FUL (HR = [redacted]; 95% credible interval [CrI], [redacted]), RIB + FUL (HR = [redacted]; 95% CrI, [redacted]), ABE plus FUL (ABE + FUL) (HR = [redacted]; 95% CrI, [redacted]), and PAL + FUL (HR = [redacted]; 95% CrI, [redacted]).

For the sensitivity analysis using random-effects model (half-normal [0.1] prior), though the point estimates for both comparisons with RIB + FUL and ABE + FUL favoured INA + PAL + FUL, the 95% CrIs crossed the null, suggesting the potential for little to no difference (HR = [redacted]; 95% CrI, [redacted] and HR = [redacted]; 95% CrI, [redacted], respectively).

Endocrine-resistant network: INA + PAL + FUL was favoured over FUL (HR = [redacted]; 95% CrI, [redacted]), ABE + FUL (HR = [redacted]; 95% CrI, [redacted]), and PAL + FUL (HR = [redacted]; 95% CrI, [redacted]).

In contrast to the base case results, the sensitivity analysis using either random-effects model (half-normal [0.1] prior and Turner prior) showed no treatment was favoured between INA + PAL + FUL and ABE + FUL (HR = [REDACTED]; 95% CrI, [REDACTED] and HR = [REDACTED]; 95% CrI, [REDACTED], respectively).

Overall Survival

Endocrine-resistant and endocrine-sensitive network: INA + PAL + FUL was favoured over FUL (HR = [REDACTED]; 95% CrI, [REDACTED]) and PAL + FUL (HR = [REDACTED]; 95% CrI, [REDACTED]). No treatment was favoured between INA + PAL + FUL and RIB + FUL (HR = [REDACTED]; 95% CrI, [REDACTED]). Though the point estimate for the comparison with ABE + FUL favoured INA + PAL + FUL, the 95% CrI crossed the null, suggesting the potential for little to no difference (HR = [REDACTED]; 95% CrI, [REDACTED]).

In contrast to the base-case results, the sensitivity analysis using either random-effects model showed no treatment was favoured between INA + PAL + FUL and any comparator. Though the point estimate for the comparison with FUL favoured INA + PAL + FUL (using the Turner prior), the 95% CrI included the null, suggesting the potential for little to no difference (HR = [REDACTED]; 95% CrI, [REDACTED]).

Endocrine-resistant network: INA + PAL + FUL was favoured over FUL (HR = [REDACTED]; 95% CrI, [REDACTED]), ABE + FUL (HR = [REDACTED]; 95% CrI, [REDACTED]), and PAL + FUL (HR = [REDACTED]; 95% CrI, [REDACTED]).

In contrast to the base case results, the sensitivity analysis using either random-effects model showed no treatment was favoured between INA + PAL + FUL and any comparator, except for the sensitivity analysis using random-effects model (Turner prior) in which INA + PAL + FUL was favoured over FUL (HR = [REDACTED]; 95% CrI, [REDACTED]).

Harms Results

Harms were not assessed in the NMA.

Critical Appraisal

The systematic literature review was conducted using standard methods with defined research questions and multiple databases were searched on March 6, 2024, and adapted in November 2024, for a supplemental systematic review as confirmed by the sponsor. The intervention and comparator were refined for the inclusion of studies in the NMA and are consistent with the objective and reflective of practice in the first-line treatment setting. The risk of bias of included studies was assessed using a relevant tool. Although the authors considered most included studies to be at low risk of bias, this was assessed at the study level, rather than at the level of the reported result, which ignores the fact that risk of bias can vary depending on the effect estimate being evaluated. As such, the risk of bias reported by the sponsor for each study may not universally apply to OS and PFS.

A separate Bayesian NMA was conducted for each end point and network and was reportedly consistent with the National Institute for Health and Care Excellence (NICE) Decision Support Unit technical support document. The networks were sparse, with just 1 or 2 studies contributing data to each node. Relevant

comparisons were informed entirely by indirect evidence, which adds uncertainty to the results for these comparisons.

The authors indicated that given the arbitrary nature of the informative priors and the limited data available to reliably estimate the random-effects variance, the results from the fixed-effect model were selected as the base case. A consequence of the fixed-effect model is that it is unlikely to adequately characterize the between-study heterogeneity. As such, the CrIs are narrower than with the random-effects model. The random-effects model accounts for within-study and between-study heterogeneity and is more likely to adequately express the uncertainty arising from this heterogeneity. Notably, many of the results with the fixed-effect model where the 95% CrI excluded the null were less precise in the sensitivity analyses using the random-effects models.

The sponsor indicated that the Turner priors were adopted because of their empirical basis, derived from a large compilation of meta-analyses, to provide a data-driven approach to setting priors for between-study heterogeneity. The sponsor indicated that the half-normal priors were included to align with new recommendations from the European Union health technology assessment and provide support for the robustness of the results by cross-validating with an alternative informative prior. Overall, the selected priors are acceptable given the sparse networks to inform the heterogeneity parameter.

The authors concluded that the proportional hazards assumption was violated for the OS data from the INAVO120 study and the PFS data from the MONARCH plus study (cohort B). However, the authors noted there was uncertainty in the power of the global Schoenfeld test and there was considerable loss to follow-up in later years resulting in heavy censoring for the OS data. Importantly, incorporating the OS data from an interim analysis in the INAVO120 study into an NMA may be considered premature.

The authors stated that the base case included the endocrine-resistant and endocrine-sensitive network to align with the overall populations evaluated in most of the included studies. Based on the authors' targeted search for prognostic factors and treatment effect modifiers, better response to previous endocrine therapy is associated with better outcomes with subsequent therapies while resistance to multiple lines of therapy is a poor prognostic factor. Though 2 networks of evidence were included to explore the potential bias due to intransitivity arising from differences across studies in endocrine resistance status, PFS and OS results comparing INA + PAL + FUL with RIB + FUL were not reported for the endocrine-resistant network.

While the INAVO120 study included patients with *PIK3CA*-mutated disease, the authors noted that the other studies included in the NMA included patients regardless of their *PIK3CA* mutation status. Based on the authors' targeted search for prognostic factors and treatment effect modifiers, *PIK3CA* mutation may be associated with worse clinical outcomes but better response to PI3K inhibitors. As such, heterogeneity in this patient baseline characteristic likely introduced bias in the NMA results. Further, including studies without the *PIK3CA* mutation is not reflective of the indication under review.

Due to observed differences in the postmenopausal status at baseline between the INAVO120 study and the other included studies, a subgroup analysis of patients who were postmenopausal was conducted. However, the MONARCH-2 and PALOMA-3 studies did not report HR data for the subgroup of patients who

were postmenopausal. Consequently, the HRs for the mixed population who were menopausal were used in the analysis. As such, the risk of bias in the NMA remains if menopausal status at baseline is a treatment effect modifier. The clinical experts consulted for this review advised that a part of the treatment is to induce menopause and as such, are of the opinion that any imbalance observed in this characteristic at baseline between groups would not be expected to influence the outcomes.

A targeted search was conducted to identify potential prognostic factors and treatment effect modifiers — site of metastasis, *PIK3CA* mutation, disease-free interval, prior treatment response, circulating tumour cells, ECOG PS, age, and race. However, the authors indicated that there was limited data reported in the included studies and as such, there was insufficient information to fully judge whether these patient characteristics were similar across the included studies.

The systematic literature review informing the NMA extracted outcome data exclusively for the first-line treatment setting. However, for the MONARCH plus study (cohort B), the authors considered this study in the first-line treatment setting because it included more than 75% of patients with disease that was previously untreated. Based on clinical expert input, response rate, duration of response, and duration of PFS become reduced with each subsequent line of therapy. Therefore, differences in this potential treatment effect modifier across the network likely introduced bias in the NMA results.

The median follow-up duration ranged from 11.1 months to 80 months across studies; the implications of including studies with differential follow-up in the NMA are unknown but likely introduced bias in the NMA as a source of methodological heterogeneity.

Although the NMAs address a gap in the systematic review evidence by providing evidence for INA + PAL + FUL compared with RIB + FUL, there remains a lack of evidence for the treatment effect of INA + PAL + FUL versus RIB + FUL on outcomes important to patients and clinicians, including HRQoL and harms. Further, there remains a gap in the evidence for INA in combination with any CDK4/6 inhibitor (other than PAL) and FUL.

Studies Addressing Gaps in the Evidence From the Systematic Review

Description of the Study

The MORPHEUS-panBC trial is an ongoing, phase Ib/II, open-label, multicentre, randomized umbrella study evaluating the efficacy and safety of multiple treatment combinations in patients with locally advanced or metastatic breast cancer; the estimated total enrolment is 580 patients. The hormone receptor–positive cohort (cohort 3) comprised of patients with locally advanced or metastatic hormone receptor–positive, HER2-negative disease with *PIK3CA* mutation who may or may not have had disease progression during or following previous lines of treatment for metastatic disease. An interim safety analysis of 12 patients in cohort 3 (INA plus ABE plus FUL [INA + ABE + FUL] group, n = 6 and INA + RIB + FUL group, n = 6) was submitted by the sponsor to inform on the combination of INA with other approved CDK4/6 inhibitors, including RIB and ABE. The median follow-up was approximately 6 months.

Efficacy Results

Efficacy results of the MORPHEUS-panBC trial were not submitted; only preliminary safety results and pharmacokinetic parameters were available in the interim analysis.

Harms Results

During the study, all patients in both groups experienced at least 1 AE. The most common AEs, occurring in at least 3 patients, in the INA + ABE + FUL group were hyperglycemia (100%), diarrhea (83%), nausea (83%), increased blood creatinine (50%), fatigue (50%), and decreased appetite (50%), and in the INA + RIB + FUL group, hyperglycemia (83%), diarrhea (67%), vomiting (67%), and headache (50%). There were no grade 4 or 5 AEs in either treatment group. Treatment-related AEs led to dose modification and/or interruption, most commonly due to hyperglycemia and diarrhea, in 6 patients (100%) in the INA + ABE + FUL group and 2 patients (33%) in the INA + RIB + FUL group. One patient in the INA + ABE + FUL group experienced an SAE, an upper respiratory tract infection that resulted in treatment discontinuation. No AEs resulted in study withdrawal in either treatment group.

Critical Appraisal

The results of the MORPHEUS-panBC trial are based on an interim analysis with a small sample size (N = 12), which limits the certainty and generalizability of observed results. Only safety outcomes were reported, which limits the ability to determine whether the treatment combinations provide meaningful clinical benefit pertaining to outcomes outlined as important to patients, including OS, PFS, and HRQoL. Additionally, the median follow-up duration was short, at approximately 6 months in both groups, which may be insufficient to capture longer-term safety signals or delayed effects. As the study did not include a relevant comparator reflective of treatments used in clinical practice for the indication under review, it is not possible to assess relative safety or to infer causal effects. Finally, the absence of study sites in Canada may affect generalizability to patients living in Canada.

Testing Procedure Considerations

PIK3CA mutations are present in an estimated 40% of hormone receptor–positive, HER2-negative breast cancers and *PIK3CA*-mutated advanced breast cancer is associated with poorer outcomes, such as decreased OS, shorter PFS, and chemoresistance. *PIK3CA* mutations can be detected using NGS or polymerase chain reaction-based testing of the tumour tissue. Circulating tumour DNA, collected using a peripheral blood sample, can also be used to test for mutations as an alternative for patients in whom a traditional biopsy is contraindicated or challenging to perform. International guidelines recommend NGS testing of tumour tissue or plasma samples at the time of new or recurrent metastatic breast cancer diagnosis in patients with advanced hormone receptor–positive, HER2-negative breast cancer. Testing for *PIK3CA* mutations in breast cancer is not standard of care in Canada. The timing of *PIK3CA* mutation testing on primary or metastatic tumour tissue in current practice is variable and can depend on centre-specific protocols; however, it is mostly conducted at the time of metastatic diagnosis using NGS.

Key considerations and relevant information available from materials submitted by the sponsor, input from the clinical experts consulted by the review team, and sources from the literature were validated by the review team when possible are summarized in [Table 4](#).

Table 4: Considerations for NGS or PCR Testing for *PIK3CA* Mutations for Establishing Treatment Eligibility With Inavolisib in Hormone Receptor–Positive, HER2-Negative Locally Advanced or Metastatic Breast Cancer Following Recurrence on or After Completing Adjuvant Endocrine Treatment

Consideration	Criterion	Available information
Health system-related	Number of individuals in Canada expected to require the test (e.g., per year)	It was estimated that around 1,940 individuals with disease relapsed hormone receptor–positive, HER2-negative metastatic disease who have received chemotherapy and adjuvant endocrine therapy would be required to undergo testing. The clinical experts consulted for this review agreed with the sponsor’s assumption that 80% of those eligible for testing would receive testing.
	Availability and reimbursement status of the testing procedure in jurisdictions across Canada	The diagnostic capability to test for <i>PIK3CA</i> mutations using NGS exists across Canada; however, several jurisdictions send samples out of province for testing. Public funding for <i>PIK3CA</i> mutation testing in breast cancer may be available in some provinces. According to the clinical experts, funded <i>PIK3CA</i> testing using NGS is currently being set up in several other provinces. In jurisdictions where <i>PIK3CA</i> mutation testing is not publicly funded, patients may have to rely on other options, such as testing access programs, clinical trials, private insurance, or out-of-pocket payment. At present, <i>PIK3CA</i> testing using circulating tumour DNA is not publicly funded anywhere in Canada for breast cancer and the scope of its availability across the country is unclear.
	Testing procedure as part of routine care	At the time of this review, testing for <i>PIK3CA</i> mutations in breast cancer is not standard of care in Canada. According to the clinical experts, there is currently momentum to get <i>PIK3CA</i> mutation testing established as the standard of care in the population who has metastatic breast cancer, but this has yet to be fully realized.
	Repeat testing requirements	Because <i>PIK3CA</i> mutations tend to arise early in the tumorigenesis process and usually stay stable once they occur, testing does not need to be repeated.
	Impacts on human and other health care resources by provision of the testing procedure	Implementation of testing for <i>PIK3CA</i> mutations in individuals with hormone receptor–positive, HER2-negative locally advanced or metastatic breast cancer may have substantial resource and infrastructure impacts such as increased workloads for laboratory and clinical personnel, increased demand for genetic counselling services, and the need to upscale existing capacities and workflows to meet an increase in testing. Regions or centres without established <i>PIK3CA</i> testing will have to address these implementation challenges as the clinical landscape evolves.

Consideration	Criterion	Available information
Patient related	Accessibility of the testing procedure in jurisdictions across Canada	Previously, <i>PIK3CA</i> mutation testing for individuals with metastatic hormone receptor–positive, HER2-negative breast cancer was available through testing access programs or clinical trials; however, these are now being discontinued. Although there has been an increase in <i>PIK3CA</i> mutation testing uptake, access still varies between and within jurisdictions. Patients may experience access issues in the short-term while funding and infrastructure are established. However, this will likely resolve over time since testing for <i>PIK3CA</i> mutations in breast cancer is expected to become standard of care in Canada.
	Expected turnaround times for the testing procedure	The turnaround time for a comprehensive NGS panel or focused hotspot mutation testing is around 1 to 2 weeks.
	Burden associated with the testing procedure for patients, families, and/or caregivers	There could be psychological burdens on patients related to testing such as anxiety of waiting and possible distress if results were unfavourable; however, availability of a targeted treatment option may alleviate some of this burden.
Clinical	Clinical utility and validity of the testing procedure	The clinical experts acknowledged that using hotspot assays with partial gene coverage may miss some <i>PIK3CA</i> mutations. Patients who would otherwise be eligible for inavolisib, may not receive the drug if they have a <i>PIK3CA</i> variant not covered by the test. Conversely, more comprehensive NGS profiling can potentially identify <i>PIK3CA</i> mutations that were not specified in the INAVO120 trial. The clinical experts stated that they would consider any <i>PIK3CA</i> mutation actionable in clinical practice in the current absence of granular data for each variant. There is evidence supporting the clinical utility of using NGS testing to identify actionable mutations in breast cancer. ^a
	Risks of harm associated with the testing procedure	Because testing for <i>PIK3CA</i> alterations can be done using routinely collected tissue samples in most cases, there is no additional risk of harm associated with the testing as part of establishing treatment eligibility. Some patients may require an additional tumour biopsy in certain instances and could experience potential adverse events from the procedure, including pain or emotional distress, or they may face time or financial burden due to, for example, the need to take time off work or arrange travel to the clinical centre.
Cost	Projected cost of the testing procedure	Testing costs will depend on the type of testing used and can range from \$235 for a PCR-based assay covering 3 exons in the <i>PIK3CA</i> gene to \$750 per test for an NGS panel.

CDA-AMC = Canada's Drug Agency; NGS = next-generation sequencing; PCR = polymerase chain reaction.

^aCDA-AMC has not evaluated or critically appraised this evidence to determine its validity or reliability.

Economic Evidence

Economic Evaluation and Budget Impact

- INA is available as 3 mg and 9 mg tablets. At the submitted price of \$298.79 per 3 mg tablet and \$597.57 per 9 mg tablet, the cost of INA per 28-day cycle is expected to be \$16,732 per patient,

based on the Health Canada–recommended dosage. When INA is used in combination with PAL and FUL, the 28-day cycle cost is expected to range from \$19,806 to \$20,214 per patient.

- Clinical efficacy in the economic analysis was derived from the INAVO120 trial, which compared INA + PAL + FUL with PAL + FUL. Evidence from INAVO120 trial suggests that INA + PAL + FUL results in an increase in PFS and likely results in an increase in OS compared with PAL + FUL among patients with endocrine-resistant, hormone receptor–positive, HER2-negative, locally advanced or metastatic breast cancer with a *PIK3CA* mutation whose disease progressed on or following completion of adjuvant endocrine therapy and who had not received prior systemic therapy for locally advanced or metastatic breast cancer. For the comparison of INA + PAL + FUL with RIB + FUL and with ABE + FUL, clinical efficacy was informed by sponsor-submitted ITCs.⁴ The ITC results are based on interim OS data from the INAVO120 study, which have important implications on imprecision and preclude any definitive conclusions about the direction of the treatment effect.
- The results of the CDA-AMC base case suggest:
 - INA + PAL + FUL may be associated with higher costs to the health care system than PAL + FUL (incremental costs = \$394,507) and RIB + FUL (incremental costs = \$382,297), primarily driven by increased drug acquisition costs associated with INA.
 - INA + PAL + FUL may be associated with a gain of 0.60 life-years compared to PAL + FUL and 1.02 LYs compared to RIB + FUL. INA + PAL + FUL is anticipated to improve health-related QoL based on time in health states where it may result in a gain of 0.58 QALYs compared to PAL + FUL and 0.95 QALYs compared to RIB + FUL.
 - The ICER of INA + PAL + FUL compared to PAL + FUL is \$683,203 per QALY gained and \$400,783 per QALY gained compared to RIB + FUL. The estimated ICERs were highly sensitive to both the predicted OS benefit and the drug acquisition costs of INA. Notably, approximately 52% and 65% of the incremental benefit relative to PAL + FUL and RIB + FUL, respectively, was gained in the extrapolated period (i.e., after 34 months). In the absence of comparative evidence beyond this time point and uncertainty in the comparative clinical evidence, the QALYs gained for patients receiving INA + PAL + FUL predicted in the CDA-AMC base case are highly uncertain and may be overestimated. Additional price reductions may therefore be required.
- Estimates by CDA-AMC indicate that the budget impact of reimbursing INA + PAL + FUL for the treatment of adult patients with endocrine-resistant, *PIK3CA*-mutated, hormone receptor–positive, HER2-negative, locally advanced or metastatic breast cancer will be approximately \$120 million over the first 3 years of reimbursement compared to the amount currently spent on comparators, with an estimated expenditure of \$140 million on INA + PAL + FUL over this period. The actual budget impact will depend on the number of people eligible for treatment and its uptake.
- A scenario analysis conducted by CDA-AMC applied alternative CDK4/6 inhibitor distribution within the intervention group (16% PAL and 84% of RIB), reflecting the anticipated clinical practice as informed by expert consultation. In this analysis, the ICER for INA + CDK4/6 inhibitor + FUL is \$713,555 per QALY gained compared to PAL + FUL, and \$466,085 per QALY gained compared to RIB + FUL. Estimates by CDA-AMC indicate that the budget impact of reimbursing INA + CDK4/6

inhibitor + FUL for the treatment of adult patients with endocrine-resistant, PIK3CA-mutated, hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer will be approximately \$139 million over the first 3 years of reimbursement compared to the amount currently spent on comparators, with an estimated expenditure of \$159 million on INA + CDK4/6 inhibitor + FUL over this period.

pERC Information

Members of the Committee

Dr. Catherine Moltzan (Chair), Dr. Kelvin Chan (Vice Chair), Paul Agbulu, Dr. Phillip Blanchette, Dr. Matthew Cheung, Dr. Michael Crump, Annette Cyr, Dr. Jennifer Fishman, Dr. Jason Hart, Terry Hawrysh, Dr. Yoo-Joung Ko, Dr. Aly-Khan Lalani, Amy Peasgood, Dr. Anca Prica, Dr. Michael Raphael, Dr. Adam Raymakers, Dr. Patricia Tang, Dr. Pierre Villeneuve, and Danica Wasney.

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Regrets: None

Conflicts of interest: None



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