Reimbursement Review

Provisional Funding Algorithm

Indication: Hormone-receptor positive human epidermal growth factor receptor 2 negative breast cancer

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Publication date: March 2023

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

Key Messages

- For individuals with hormone-receptor positive (HR)+ human epidermal growth factor receptor 2 negative (HER2)– breast cancer who relapse within 6 months of completing or while on adjuvant abemaciclib, possible treatment options include endocrine therapy, other targeted therapies combined with hormone therapy and chemotherapy.
- For individuals with HR+ HER2)– breast cancer who relapse at or later than 6 months of completing adjuvant abemaciclib, possible treatment options include re-treatment with a different CDK4/6 inhibitor and endocrine therapy, other targeted therapies, and chemotherapy.
- Everolimus plus appropriate endocrine therapy may be a reasonable treatment option for individuals who progress on CDK4/6 inhibitor in the metastatic setting. However, this field is rapidly changing with new and emerging therapies on the horizon.

Background

The provisional funding algorithm process is used to provide advice when the drug programs have indicated that there is need to establish an appropriate place in therapy for the drug under review relative to alternative treatments that are currently reimbursed by the drug programs, including the impact on the appropriate sequencing of treatments for the purposes of reimbursement. The creation of a new provisional funding algorithm or update of an existing provisional funding algorithm is typically initiated following the issuance of a new pERC recommendation when there are potential implications regarding the funding sequence of drugs within a therapeutic area. CADTH will only initiate work on a provisional funding algorithm at the request of its Provincial Advisory Group.

The following items are considered by the expert panels when advising the jurisdictions on the provisional algorithm for the relevant indication:

- unmet therapeutic need for patients (particularly those in understudied populations)
- evidence supporting a particular sequence of therapies (if available)
- clinical experience and opinion that support a particular sequence of therapies
- clinical practice guidelines
- variability across jurisdictions regarding the reimbursement status of existing treatment options
- affordability and sustainability of the health care system
- implementation considerations at the jurisdictional level.

Note that provisional funding algorithms are not treatment algorithms; they are neither meant to detail the full clinical management of each patient nor the provision of each drug regimen. The diagrams may not contain a comprehensive list of all available treatments, and some drugs may not be funded in certain jurisdictions. Most drugs are subject to explicit funding criteria, which may also vary between jurisdictions. Readers

are invited to refer to the cited sources of information on the CADTH website for more details. Also note that as per process, implementation advice from panellists, and the resulting algorithms cannot contradict prior pERC recommendations or expand target populations beyond what was recommended.

Provisional funding algorithms delineate treatment sequences available to patients who were never treated for the condition of interest (i.e., incident population). Time-limited funding of new options for previously or currently treated patients (i.e., prevalent population) is not detailed in the algorithm.

Provisional funding algorithms may contain drugs that are under consideration for funding. Algorithms will not be dynamically updated by CADTH following changes to drug funding status. Revisions and updates will occur only upon request by jurisdictions.

Cancer drug programs from federal and provincial jurisdictions requested supplemental implementation advice along with a CADTH provisional funding algorithm on HR+ HER– breast cancer. Refer to Appendix 1 for a list of all past CADTH advice and recommendations relevant for this therapeutic area.

Implementation Issues

At the request of the participating drug programs, CADTH convened a panel of clinical experts from across Canada to provide advice for addressing the outstanding implementation issues as follows:

- selection guidance for treatment options in HR+ HER2– breast cancer
- re-treatment with a CDK4/6 inhibitor
- sequencing with everolimus and exemestane
- treatment interruption of CDK4/6 inhibitors within 2 years of adjuvant setting.

Consultation Process and Objectives

The implementation advice panel was comprised of 6 specialists in Canada with expertise in the diagnosis and management of patients with breast cancer, a representative from a public drug program, and a panel chair. The objective of the Panel was to provide advice to the participating drug programs regarding the implementation issues noted in the Background section. A consensus-based approach was used, and input from stakeholders was solicited using questionnaires. Stakeholders including patient and clinician groups and pharmaceutical manufacturers, and public drug programs were invited to provide input in advance of the meeting.

The advice presented in this report has been developed based on the experience and expertise of the implementation advice panel members and, as such, represents experience-informed opinion; it is not necessarily based on evidence.

Advice on Funding Algorithm

Summary of Implementation Advice

Implementation advice regarding the optimal sequencing of treatments is summarized in Table 1. For each implementation issue, a summary of the relevant panel discussion is provided for additional context.

Table 1: Summary of Advice for Addressing Implementation Issues

Issue	Advice	Rationale
Selection guidance for treatment options in HR+ HER2– breast cancer	—	—
Treatment options for individuals who relapse within 6 months of completing adjuvant therapy.	The panel advises that for individuals who relapse within 6 months of completing adjuvant therapy with a CDK4/6 inhibitor, appropriate treatment options to consider include: • endocrine therapy • other targeted therapies combined with hormone therapy • chemotherapy.	In patients who relapse quickly (within 6 months) despite adjuvant treatment with CDK4/6 inhibitor, there is a lack of evidence or data to inform treatment choices. As such, treatment decisions should be individualized. If individuals are deemed to be still endocrine sensitive, it may be reasonable to make adjustment to the endocrine therapy. For example, if an individual progresses while on an aromatase inhibitor (e.g., letrozole, exemestane, anastrozole), then the treatment can be switched to an estrogen receptor antagonist (e.g., fulvestrant). Repeat treatment with a CDK4/6 inhibitor is not recommended. As such, other targeted therapy combined with hormone therapy would be reasonable, such as everolimus plus exemestane. Chemotherapy remains an option, especially if a visceral crisis is suspected.
Treatment guidance for individuals who relapse at or after 6 months when adjuvant therapy has been completed.	The panel advises that for individuals who relapse at or after 6 months when adjuvant therapy with a CDK4/6 inhibitor has been completed: • treatment with a CDK4/6 inhibitor and endocrine therapy is reasonable including ribociclib or palbociclib • if the relapse occurs while on an aromatase inhibitor as an endocrine therapy, switching to fulvestrant may also be an option.	In patients who relapse at or after 6 months despite adjuvant treatment with a CDK4/6 inhibitor, the Panel advises that treatment with a CDK4/6 inhibitor and hormone therapy.[1-3]
Re-treatment with CDK4/6 inhibitor	The Panel agreed that the 6-month time limit for allowing re-treatment with a CDK4/6 inhibitor was reasonable (as	The Panel recognizes that given the current landscape of CDK4/6 inhibitors, the only

Issue	Advice	Rationale
	advised by pERC) given the lack of evidence in this setting. Currently, CDK4/6 inhibitor options that are available in the metastatic setting only include ribociclib and palbociclib.	available CDK4/6 inhibitor in the adjuvant setting is abemaciclib.
Sequencing with everolimus with exemestane	The panel advises that everolimus plus appropriate endocrine therapy is reasonable to consider a post CDK4/6 inhibitor in metastatic setting of HR+ HER2– breast cancer.	The Panel discussed the lack of robust evidence to inform decision-making in this setting. There is, however, some limited real-world evidence that indicates prior exposure to CDK4/6 inhibitor therapy did not impact on reasonable clinical outcomes for patients taking everolimus plus exemestane.[4] The Panel recognizes that it is reasonable to consider everolimus with exemestane (or everolimus and fulvestrant) as an option posttherapy with CDK4/6 inhibitor as it is recognized in various international guidelines (e.g., ESMO).
Treatment interruption of CDK4/6 inhibitors during the 2 years of adjuvant setting	Treatment with a CDK4/6 inhibitor in the adjuvant setting should be completed for a total of 24 months within a 3-year period from beginning to completion, as long as there is no disease progression.	The Panel recognizes that patients may require a treatment interruption of a CDK4/6 inhibitor related to intolerance (e.g., diarrhea). The Panel has agreed that such treatment should be completed for a total of 24 months, allowing room for interruption due to intolerances or other reasons. However, the Panel agreed that, based on expert opinion, the total treatment duration from the beginning to completion should not exceed a 3-year period as this may impact on the effectiveness of treatment. In addition, there must be no disease progression during the treatment duration.

CDK4/6 inhibitor = cyclic-dependent kinase 4/6 inhibitor; HR = hormone-receptor; HER2 = human epidermal growth receptor 2; mTOR inhibitor = mechanistic target of rapamycin inhibitor; PIK3 = phosphatidylinositol-3 kinase; ECG = electrocardiogram.

In addition to the previously outlined advice, the Panel indicated that because an improvement in cost-effectiveness was a condition for reimbursement in each of the recommendations related to the drugs in scope, implementation of any advice herein should be contingent upon ensuring that the relevant treatments are affordable to public payers.

Panel Discussion

Selection Guidance for Treatment Options in HR+ HER2– Breast Cancer

Treatment Options for Individuals Who Relapse Within 6 Months of Completing Adjuvant Therapy

In patients who relapse quickly (within 6 months) despite adjuvant treatment with CDK4/6 inhibitor, treatment decisions need to be individualized given the lack of evidence or data to inform treatment choices. Endocrine therapy, alternative (non-CDK4/6 inhibitor) targeted therapies and chemotherapy are all potential options. If individuals are deemed to be still endocrine sensitive, it may be reasonable to make adjustment to the endocrine therapy by switching between aromatase inhibitors (nonsteroidal to steroidal) and estrogen receptor antagonists (e.g., fulvestrant). Clinicians may request testing for PI3K mutation status, in which case alpelisib may be deemed reasonable. It is noted that alpelisib has received a negative CADTH recommendation and thus is not considered in the funding algorithm. An mTOR inhibitor (everolimus), combined with endocrine therapy is also an option. It is noted that there may be jurisdictional differences with coverage and accessibility of different treatment options. Hence the guidance is designed to be general to allow for adaptation as warranted. The panel has also discussed that there is a potential role in the future to consider antibody-drug conjugates, such as trastuzumab deruxtecan or other new therapies; however, this is beyond the scope of the Panel discussion and may be revisited in the future, once CADTH has completed a formal reimbursement review of these emerging therapies.

Treatment Guidance for Individuals Who Relapse at or After 6 Months With Adjuvant Therapy Completed

In patients who relapse at or after 6 months, despite prior treatment with CDK4/6 inhibitors, the Panel advises that re-treatment with a CDK4/6 inhibitor is reasonable. Panellists have expressed their preference to ribociclib based on evidence of survival benefits in HR+ HER2– advanced breast cancer.[1] Ribociclib has also been evaluated in a sequential study via MAINTAIN[2]. In this study where patients have progression on a primary CDK4/6 inhibitor, ribociclib showed an improvement in progression-free survival in unresectable or metastatic HR+ HER2– breast cancer. Palbociclib was evaluated in PACE[3] which did not significantly improve progression-free survival. [1-3] the Panel has highlighted that the evidence may be conflicting in these studies and that some patients remained on the same CDK4/6 inhibitor throughout the study; while in practice, patients may be switched to a different CDK4/6 inhibitor. This is also an area where real-world evidence may help to support treatment decisions. The choice of CDK4/6 inhibitor may be impacted by different toxicity patterns. Switching endocrine therapy would be recommended as well depending on the individual patient circumstances and prior therapies.

In selecting CDK4/6 inhibitors in the metastatic setting, the Panel recognizes that all 3 CDK4/6 inhibitors (ribociclib, palbociclib, and abemaciclib) have received positive CADTH recommendations for use in HR+ HER2– metastatic breast cancer. However, each CDK4/6 inhibitor has a different toxicity profile. There may be contraindications, intolerance or other barriers (e.g., inability to obtain ECG monitoring) that may necessitate the use of an alternative CDK4/6 inhibitor At this time, abemaciclib is not considered in scope of this discussion, given the current unsuccessful pCPA negotiation.

Re-treatment With a CDK4/6 Inhibitor

The Panel recognizes that given the current landscape of CDK4/6 inhibitors, the only available CDK4/6 inhibitor in the adjuvant setting is abemaciclib. If re-treatment is indicated upon progression in the metastatic setting at or after 6 months, it would require changing to a different CDK4/6 inhibitor, which would be either ribociclib or palbociclib.

Sequencing With Everolimus With Exemestane

The Panel advises that everolimus plus appropriate endocrine therapy may be used post CDK4/6 inhibitor in metastatic setting of HR+ HER2– breast cancer. The panel has discussed the lack of robust evidence to inform decision-making in this setting. There is, however, some limited real-world evidence that indicates prior exposure to CDK4/6 inhibitor therapy does not appear to impact clinical outcomes for patients taking everolimus plus exemestane.[4] The Panel recognizes that it is reasonable to consider everolimus with exemestane (or fulvestrant) as an option posttherapy with a CDK4/6 inhibitor as it is already recognized in various international guidelines (e.g., ESMO). However, the field is rapidly changing where new data from other emerging therapies (e.g., antibody-drug conjugates) may also have a role in this evolving space.

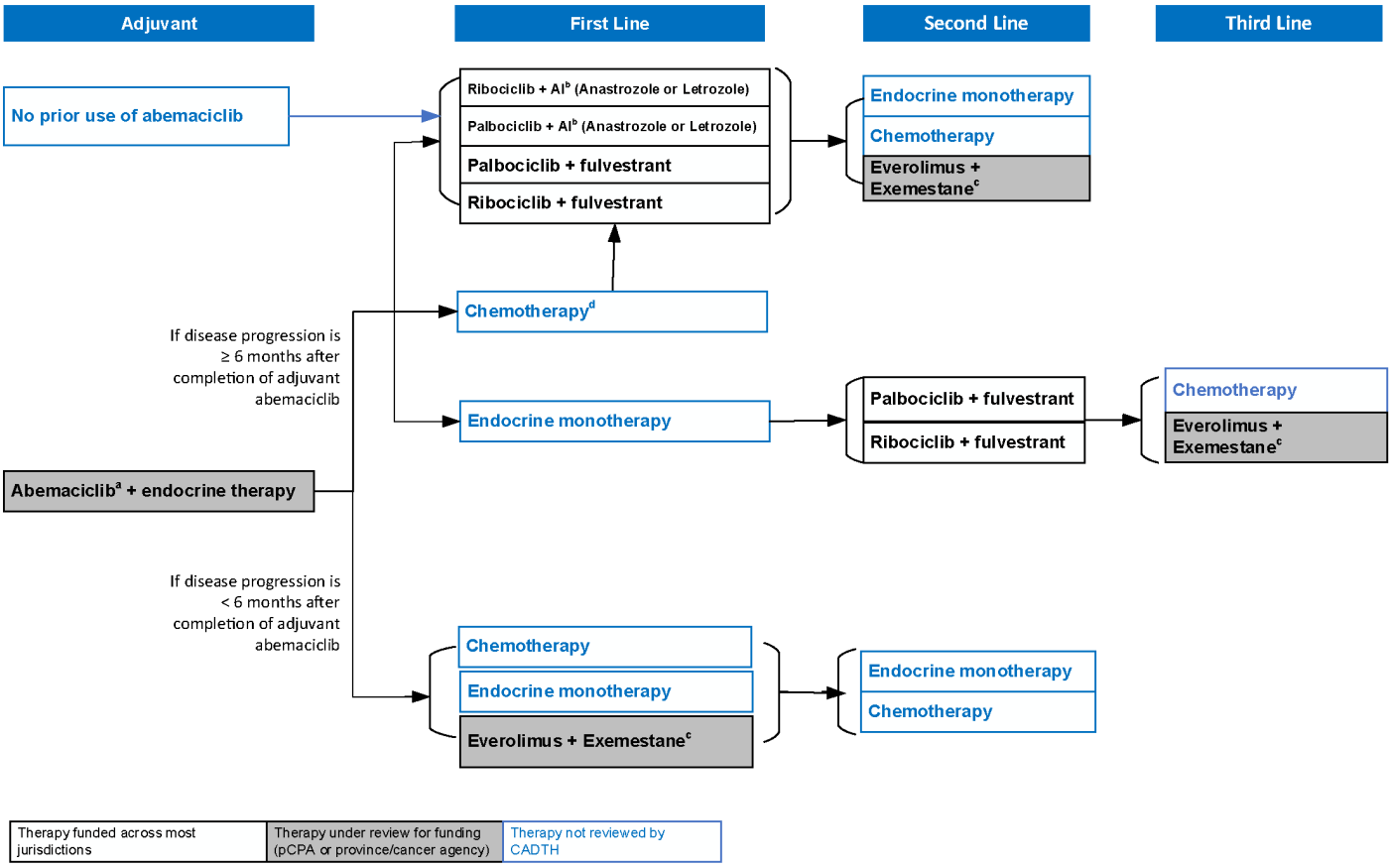
Treatment Interruption of CDK4/6 Inhibitors During the 2 Years of an Adjuvant Setting

The panel recognizes that patients may require occasional treatment interruption of adjuvant CDK4/6 inhibitor related to intolerance (e.g., diarrhea). However, additional implementation guidance is needed to support how such treatment should be funded and contract agreements be drafted with the potential for unpredictable treatment interruptions. The Panel has agreed that such treatment should be completed for a total of 24 months, allowing room for interruption due to intolerances or other reasons. However, based on expert opinion, the total treatment duration from beginning to completion should not exceed a 3-year period as this may have an impact on the effectiveness of treatment. In addition, there must be no disease progression during the treatment duration.

Provisional Funding Algorithm

Figure 1: Provisional Funding Algorithm Diagram for HR+ HER2– Breast Cancer

Hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative breast cancer



AC = Adriamycin-Cytoxan; AI = aromatase inhibitor; CDK4/6 inhibitor = cyclic-dependent kinase 4/6 inhibitor; CMF = Cyclophosphamide-Methotrexate-Fluorouracil; FEC = 5-Fluorouracil-epirubicin-cyclophosphamide; FAC = Fluorouracil-Adriamycin-Cytoxan; HR = hormone-receptor; HER2 = human epidermal growth factor receptor 2; LRHR = luteinizing hormone-releasing hormone agonists; pCPA = pan- Canadian Pharmaceutical Alliance.

Notes: Chemotherapy options: capecitabine, docetaxel, paclitaxel, nab-paclitaxel, doxorubicin, epirubicin, vinorelbine, gemcitabine, eribulin, FEC, FAC, AC, gemcitabine plus cisplatin, CMF.

Endocrine monotherapy options: anastrozole or letrozole, exemestane, tamoxifen, fulvestrant (re-treatment not funded if disease progression occurred during any prior fulvestrant therapy).

For premenopausal individuals, treatments would also include luteinizing hormone-release hormone agonists: goserelin, leuprolide, buserelin.

Breast cancer therapies are available for patients of all genders.

[a] Abemaciclib should be reimbursed for a maximum of 2 years (150 mg orally twice daily).

[b] In some jurisdictions, aromatase inhibitors may also include exemestane.

[c] Everolimus plus exemestane are under review for funding by province or cancer agency.

[d] Chemotherapy as first choice if visceral crisis is suspected and / or not endocrine responsive; after adequate response, consider other choices.

Figure 1 depicts the provisional funding algorithm proposed by the Panel. Note that this diagram is a summary representation of the drug funding options for the condition of interest. It is not a treatment algorithm; it is neither meant to detail the full clinical management of each patient nor the provision of each drug regimen. The diagram may not contain a comprehensive list of all available treatments, and some drugs may not be funded in certain provinces. All drugs are subject to explicit funding criteria, which may also vary between provinces. Readers are invited to refer to the individual drug entries on the CADTH website for more details.

Adjuvant Setting

Abemaciclib in combination with endocrine therapy is the only CDK4/6 inhibitor approved for use in the adjuvant setting.

First-Line Setting

For patients with no prior adjuvant use of abemaciclib, the first-line options include either ribociclib or palbociclib combined with an aromatase inhibitor or with fulvestrant. For patients with disease progression 6 months after completing adjuvant abemaciclib, the first-line options include either ribociclib or palbociclib combined with an aromatase inhibitor or with fulvestrant. Other options include chemotherapy and endocrine monotherapy. If chemotherapy is selected as first-line treatment to achieve initial adequate response due to suspected visceral crisis or when not endocrine responsive, additional maintenance options include ribociclib or palbociclib combined with an aromatase inhibitor or with fulvestrant.

For patients with disease progression within 6 months of completing adjuvant abemaciclib, available first-line options include chemotherapy, endocrine monotherapy, and non-CDK4/6 targeted therapies in combination with endocrine therapy which would be everolimus with exemestane.

Second-Line and Third-Line Settings

For patients with disease progression 6 months after completing adjuvant abemaciclib and who have received a CDK4/6 inhibitor plus an aromatase inhibitor or fulvestrant in the first-line setting, the second-line options include endocrine monotherapy, chemotherapy or everolimus with exemestane.

In patients who have received chemotherapy as first-line treatment followed by maintenance options of ribociclib or palbociclib combined with an aromatase inhibitor or with fulvestrant, their second-line options also include endocrine monotherapy, chemotherapy or everolimus with exemestane.

In patients who have received endocrine monotherapy in the first-line setting, their second-line options include palbociclib or ribociclib plus fulvestrant. Upon disease progression, their third-line options include chemotherapy and everolimus with exemestane.

In patients with disease progression within 6 months of adjuvant abemaciclib, their second-line options include endocrine monotherapy or chemotherapy.

Appendix 1: Past CADTH Advice and Recommendations

Note that this appendix has not been copy-edited.

Table 2: Relevant CADTH Recommendations

Generic name (brand name)	Date of recommendation	Recommendation

Abemaciclib (Verzenio)	October 18, 2022	The CADTH pCODR Expert Review Committee (pERC) recommends that abemaciclib (ABE) in combination with endocrine therapy (ET) be reimbursed for the adjuvant treatment of adult patients with hormone-receptor (HR)–positive, human epidermal growth factor receptor 2 negative (HER2)–, node-positive early breast cancer at high risk of disease recurrence based on clinicopathological features and a Ki-67 score of at least 20% only if the following conditions are met:
		Treatment with ABE-ET should be initiated in patients who have:
		• Confirmed HR-positive, HER2-negative, resected invasive early breast cancer without metastases
		• Ki-67 index score of ≥ 20%
		• Fulfill 1 of the following:
		  ○ Pathological tumour involvement in ≥4 ipsilateral axillary lymph nodes
		  ○ Or pathological tumour involvement in 1 to 3 ipsilateral axillary lymph node(s) AND at least 1 of the following criteria:
		  ▪ Grade 3 disease
		  ▪ Primary tumour size ≥ 5 cm
		• Undergone definitive surgery of primary breast tumour within 16 months of initiating treatment
		• Patients must not have any of the following:
		  ○ Metastatic disease
		  ○ Inflammatory breast cancer
		  ○ Prior treatment with a CDK4/6 inhibitor Abemaciclib, in combination with ET should be discontinued upon the occurrence of any of the following:
		  ○ Disease recurrence
		  ○ Unacceptable toxicity
		• Patients should be assessed for disease recurrence as per standard clinical practice.
		• Abemaciclib should be reimbursed for a maximum of 2 years (150mg orally twice daily).
		• ET can be continued beyond this time.
		• Treatment should be prescribed by clinicians with expertise and experience in treating early breast cancer. Treatment should be given in outpatient clinics by qualified practitioners with expertise in systemic therapy delivery.

Generic name (brand name)	Date of recommendation	Recommendation
		• Ongoing monitoring to assess patients for toxicity is required. • Abemaciclib with ET should only be reimbursed when administered in combination. • A reduction in price. • The feasibility of adoption of abemaciclib must be addressed.
Abemaciclib (Verzenio)	July 5, 2019	pERC issued separate recommendations for first-line systemic therapy/endocrine sensitive patients and for endocrine-resistant patients in the advanced or metastatic setting. **First-Line Systemic Therapy/Endocrine Sensitive (First-line systemic therapy or endocrine sensitive in the advanced or metastatic setting and at least 12 months since completing adjuvant hormone therapy)** pERC conditionally recommends the reimbursement of abemaciclib in combination with nonsteroidal aromatase inhibitor (NSAI) for the treatment of HR+, HER2- advanced or metastatic breast cancer in patients as initial endocrine-based therapy (i.e., who have not received any prior treatment for advanced or metastatic disease) if the following condition is met: • Cost-effectiveness being improved to an acceptable level. • The public drug plan cost of abemaciclib should not exceed the public drug plan cost of other available cyclic-dependent kinase (CDK) 4/6 inhibitors. **Endocrine-Resistant (progressive disease after prior ET in the metastatic setting)** pERC conditionally recommends the reimbursement of abemaciclib for the treatment of HR+, HER2- advanced or metastatic breast cancer, in combination with fulvestrant in patients with disease progression following ET if the following condition is met: • Cost-effectiveness being improved to an acceptable level.
Alpelisib (Piqray)	February 11, 2022	pERC recommends that alpelisib, in combination with fulvestrant, not be reimbursed for the treatment of postmenopausal women, and men, with hormone-receptor positive, human epidermal growth factor 2 (HER2)negative, PIK3CA-mutated advanced or metastatic breast cancer after disease progression following an endocrine-based regimen with a cyclin-dependent kinase 4 and 6 (CDK4/5) inhibitor.
Ribociclib (Kisqali)	June 4, 2020	pERC conditionally recommends reimbursement of ribociclib (Kisqali) in combination with a nonsteroidal AI (NSAI) and an luteinizing hormone-release hormone (LHRH) agonist as initial endocrine-based therapy in patients with pre- or perimenopausal HR-positive, HER2-negative advanced or metastatic breast cancer if the following conditions are met: • cost-effectiveness improved to an acceptable level • feasibility of adoption addressed (budget impact).

Generic name (brand name)	Date of recommendation	Recommendation
Ribociclib (Kisqali)	April 22, 2020	pERC conditionally recommends the reimbursement of ribociclib (Kisqali) in combination with fulvestrant as initial therapy or following disease progression in patients with HR-positive, HER2-negative advanced breast cancers if the following conditions are met: • Cost-effectiveness improved to an acceptable level • Feasibility of adoption addressed (budget impact) Eligible patients include men and postmenopausal women who have not received any prior treatment for ABC or have received up to one line of treatment for ABC. Premenopausal or perimenopausal women rendered postmenopausal, either chemically or surgically, are eligible, and should be treated with a LHRH agonist or bilateral salpingo-oophorectomy.
Palbociclib (Ibrance)	May 3, 2019	pERC recommends reimbursement of Palbociclib (Ibrance) in combination with fulvestrant only if the following conditions are met: • cost-effectiveness is improved to an acceptable level • feasibility of adoption (budget impact) is addressed. Reimbursement should be in combination with fulvestrant for the treatment of patients with HR-positive, HER2-negative locally (ABC) or metastatic breast cancer (mBC) whose disease has progressed after prior ET. Patients should have good performance status and can be of any menopausal status (Perimenopausal and premenopausal women must be treated with an LHRH agonist). Treatment should continue until unacceptable toxicity or disease progression.
Ribociclib (Kisqali)	April 18, 2018	pERC conditionally recommends reimbursement of ribociclib (Kisqali) in combination with letrozole for the treatment of postmenopausal women with hormone-receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer who have not received any prior treatment for advanced or metastatic disease, only if the following conditions are met: • cost-effectiveness being improved to an acceptable level • feasibility of adoption (budget impact) being addressed.
Palbociclib (Ibrance)	November 21, 2016	pERC recommends reimbursement of palbociclib (Ibrance) conditional on the cost-effectiveness being improved to an acceptable level. Reimbursement should be in combination with letrozole, for the treatment of postmenopausal women with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer who have not received any prior treatment for metastatic disease. Treatment should continue until unacceptable toxicity or disease progression. Patients should have good performance status and neither be resistant to prior (neo)adjuvant aromatase inhibitor therapy, nor have active or uncontrolled metastases to the central nervous system.

Generic name (brand name)	Date of recommendation	Recommendation
Everolimus (Afinitor)	March 25, 2013	pERC recommends funding everolimus (Afinitor) in combination with exemestane, conditional on the cost-effectiveness of everolimus being improved to an acceptable level. Everolimus should be funded for the treatment of hormone-receptor positive, HER2 negative advanced breast cancer, in postmenopausal women with Eastern Cooperative Oncology Group Performance Status (ECOG) performance status ≤ 2 after recurrence or progression following a nonsteroidal aromatase inhibitor (NSAI), if the treating oncologist would consider using exemestane, pERC made this recommendation because it was satisfied that there is an overall clinical benefit of everolimus. However, the Committee noted that everolimus could not be considered cost-effective at the submitted price and the Economic Guidance Panel's estimates of the range of incremental cost-effectiveness ratios.

[a] Refer to published recommendation reports for full details including conditions and criteria.

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