# PREFERRED SPECIALTY MANAGEMENT POLICY

**POLICY:** Oncology – Cyclin Dependent Kinases 4, 6 Inhibitors Preferred Specialty Management Policy

- Ibrance® (palbociclib capsules and tablets – Pfizer)
- Kisqali® (ribociclib tablets – Novartis)
- Kisqali® Femara® Co-Pack (ribociclib tablets; letrozole tablets, co-packaged – Novartis)
- Verzenio® (abemaciclib tablets – Eli Lilly)

**REVIEW DATE:** 02/26/2025

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## OVERVIEW

Ibrance, Kisqali/Kisqali Femara Co-Pack, and Verzenio are cyclin-dependent kinase (CDK) 4, 6 inhibitors indicated for **hormone receptor (HR) positive (HR+), human epidermal growth factor receptor 2 (HER2)-negative breast cancer** in adults in the following settings:[1-4]

- For advanced or metastatic breast cancer, all three agents are indicated in combination with an aromatase inhibitor (AI) as initial endocrine-based therapy.
- For advanced or metastatic breast cancer, Ibrance and Verzenio are indicated in combination with fulvestrant for disease progression following endocrine therapy, while Kisqali in combination with fulvestrant is approved for use in postmenopausal women or men as initial endocrine based therapy or following disease progression on endocrine therapy.
- For early breast cancer, Verzenio is indicated for use in combination with endocrine therapy (tamoxifen or an AI) for the adjuvant treatment of node-positive disease at high risk of recurrence.
- For early breast cancer, Kisqali in combination with an aromatase inhibitor, and Kisqali Femara Co-Pack are indicated for the adjuvant treatment of Stage II and III breast cancer at high risk of recurrence.
- Verzenio is the only agent indicated for use as monotherapy for disease progression following endocrine therapy and prior chemotherapy in the metastatic setting.

**Table 1. FDA-Approved Indications for CDK 4, 6 Inhibitors in HR+, HER2-Negative Breast Cancer.[1-4]**

CDK 4, 6 – Cyclin-dependent kinase 4 and 6; HR+ – Hormone receptor positive; HER2 – Human epidermal growth factor receptor 2; AI – Aromatase inhibitor; [a] In combination with an aromatase inhibitor for the adjuvant treatment of HR+, HER2-negative stage II and stage III early breast cancer at high risk of recurrence; [b] For the adjuvant treatment of HR+, HER2-negative stage II and stage III early breast cancer at high risk of recurrence ; [c] For the adjuvant treatment of adult patients who have node-positive, early breast cancer at high risk of recurrence; √ – FDA-approved indication; [d] As initial endocrine-based therapy for the treatment of HR+, HER2-negative advanced or metastatic breast cancer; [e] For the treatment of HR+, HER2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy; [f] For the treatment of adult patients with HR+, HER2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy and prior chemotherapy in the metastatic setting.

Itovebi® (inavolisib tablets), a kinase inhibitor, is indicated in combination with Ibrance and fulvestrant for the treatment of HR+, HER2-negative, phosphatidylinositol-3-kinase (*PIK3CA*)-mutated, endocrine-resistant locally advanced or metastatic breast cancer, as detected by an FDA-approved test, following recurrence on or after completing adjuvant endocrine therapy.[5]

## Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines on breast cancer (version 1.2025 – January 31, 2025) make the following recommendations for recurrent unresectable (local or regional) or Stage IV HR+ and HER2-negative disease in postmenopausal or premenopausal women receiving ovarian ablation or suppression as "Preferred" regimens for first-line therapy: Kisqali + AI or fulvestrant (category 1); Verzenio + fulvestrant (category 1); Verzenio + AI (category 2A); Ibrance + AI or fulvestrant (category 2A).[6,7] The guidelines state in a footnote that there is controversy on the choice of CDK 4, 6 inhibitors as there are no direct comparative studies between the agents and there are some differences in the study populations in the Phase III randomized studies. The guidelines also state that in Phase III randomized controlled trials, Kisqali + endocrine therapy, Kisqali + fulvestrant, and Verzenio + fulvestrant have shown overall survival benefit in the first-line setting. CDK 4, 6 inhibitor + fulvestrant is recommended as a "Preferred" regimen for second- and subsequent-line therapy, if CDK 4, 6 inhibitor was not previously used (category 1). The guidelines state that if there is disease progression while on Ibrance, there are limited Phase II data to support the use of Kisqali in the second-line setting. In Phase III randomized controlled trials, fulvestrant in combination with a CDK 4, 6 inhibitor has shown overall survival benefit in the second-line setting. In this setting, single-agent Verzenio is recommended as a "Useful in Certain Circumstances" (for subsequent treatment) if there is progression on prior endocrine therapy and prior chemotherapy in the metastatic setting (category 2A). The guidelines also recommend Verzenio for 2 years as adjuvant therapy in combination with endocrine therapy in patients with HR+, HER2-negative, high risk (i.e., ≥ 4 positive lymph nodes, or 1 to 3 positive lymph nodes with one or more of the following: Grade 3 disease or tumor size ≥ 5 cm) disease as "preferred" therapy (category 1). The guidelines state to consider Kisqali for 3 years as adjuvant therapy in combination with an AI (anastrozole, letrozole, or exemestane) in postmenopausal or premenopausal women treated with ovarian ablation/suppression with HR+, HER2-negative disease with any lymph node involvement (excluding microscopic nodal involvement), or if no nodal involvement either tumor size > 5 cm, or if tumor size 2-5 cm, either Grade 2 (and high genomic risk or Ki-67 ≥ 20%), or Grade 3 as "Preferred" therapy (category 1). For HR+, HER2-negative disease with *PIK3CA*-activating mutations, the guidelines recommend Itovebi in combination with Ibrance and fulvestrant for first-line therapy as "Useful in Certain Circumstances" (category 1). For men with breast cancer, the compendium recommends that they be treated similarly to postmenopausal women, except that the use of an AI is ineffective without concomitant suppression of testicular steroidogenesis.[7]

The PALOMA-2 study failed to show an overall survival benefit when Ibrance was combined with letrozole compared with placebo + letrozole in the first-line setting for postmenopausal patients with HR+, HER2-negative advanced breast cancer.[8] Based on an intention-to-treat analysis, the median overall survival was 53.9 months in the Ibrance plus letrozole arm and 51.2 months in the placebo plus letrozole arm; the difference between the arms was not statistically significant. PALOMA-2 met its primary endpoint of improving progression-free survival, but not the secondary endpoint of overall survival.

The MONALEESA-2 study demonstrated a significant overall survival benefit when Kisqali was combined with letrozole in first-line setting compared with placebo + letrozole (median, 63.9 vs. 51.4 months) in postmenopausal patients with HR+, HER2-negative advanced breast cancer.[9] The MONALEESA-7 study also demonstrated a significant overall survival benefit when Kisqali was combined with endocrine therapy in first-line setting compared with placebo + endocrine therapy (median, 58.7 vs. 48.0 months) in pre/perimenopausal patients with HR+, HER2-negative advanced breast cancer.[10]

**POLICY STATEMENT**

This Preferred Specialty Management program has been developed to encourage the use of Preferred Products. For all medications (Preferred and Non-Preferred), the patient is required to meet the respective standard *Prior Authorization Policy* criteria. The program also directs the patient to try one of the Preferred Products prior to the approval of a Non-Preferred Product. Requests for Non-Preferred Product will also be reviewed using the exception criteria (below). If the patient meets the standard Prior Authorization Policy criteria for Ibrance but has not tried a Preferred Product, a review will be offered for the Preferred Products using the respective standard *Prior Authorization Policy* criteria. All approvals are provided for the duration noted below.

**Automation:** None.

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| **Preferred:** | Kisqali, Kisqali Femara Co-Pack, Verzenio |
| **Non-Preferred:** | Ibrance |

## REFERENCES

1. Ibrance® capsules and tablets [prescribing information]. New York, NY: Pfizer; December 2024.
2. Kisqali® tablets [prescribing information]. East Hanover, NJ: Novartis; September 2024.
3. Kisqali® Femara® Co-Pack tablets [prescribing information]. East Hanover, NJ: Novartis; September 2024.
4. Verzenio® tablets [prescribing information]. Indianapolis, IN: Eli Lilly; November 2024.
5. Itovebi™ tablets [prescribing information]. South San Francisco, CA: Genentech;January 2025.
6. The NCCN Breast Cancer Clinical Practice Guidelines in Oncology (version 1.2025 – January 31, 2025). © 2025 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on February 21, 2025
7. The NCCN Drugs and Biologics Compendium. © 2025 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Search term: ribociclib. Accessed on February 21, 2025.
8. Slamon DJ, Dieras V, Rugo HS et al. Overall survival with palbociclib plus letrozole in advanced breast cancer. *J Clin Oncol.* 2024; 42;994-1000.
9. Hortobagyi GN, Stemmer SM, Burris HA, et al. Overall survival with ribociclib plus letrozole in advanced breast cancer. *N Eng J Med*. 2022;386:942-950.
10. Lu Y, Im S, Colleoni M, et al. Updated overall survival of ribociclib plus endocrine therapy versus endocrine therapy alone in pre-and perimenopausal patients with HR+/HER2- advanced breast cancer in MONALEESA-7: a phase III randomized clinical trial. *Clin Cancer Res*. 2022;28(5):851-859.