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: 02/21/2024; selected revision 12/11/2024

OVERVIEW

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

- All three agents are indicated in combination with an aromatase inhibitor (AI) as initial endocrine-based therapy.
- Ibrance and Verzenio are indicated in combination with fulvestrant for disease progression following endocrine therapy. 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.
- Verzenio is the only agent indicated for use as monotherapy for disease progression following endocrine therapy and prior chemotherapy in the metastatic setting.
- Verzenio is indicated for use in combination with endocrine therapy (tamoxifen or an AI) for the adjuvant treatment of node-positive, early breast cancer at high risk of recurrence.
- Kisqali, in combination with an aromatase inhibitor, and Kisqali Femara Co-Pack are indicated for the adjuvant treatment in HR+, HER2-negative Stage II and III early breast cancer at high risk of recurrence.

Table 1. FDA-Approved Indications for CDK 4, 6 Inhibitors in HR+, HER2-Negative Breast Cancer.[1-4]
Table 1 (continued). 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] For the adjuvant treatment of adults who have node-positive, early breast cancer at high risk of recurrence; √ – FDA-approved indication; [b] As initial endocrine-based therapy for the treatment of HR+, HER2-negative advanced or metastatic breast cancer; [c] For the treatment of HR+, HER2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy; [d] 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, following recurrence on or after completing adjuvant endocrine therapy.[10]

Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines on breast cancer (version 6.2024 – November 11, 2024) 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).[5,6] 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.[5] The guidelines state that 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). For HR+, HER2-negative disease with *PIK3CA*-activating mutations, the guidelines recommend Itovebi in combination with Ibrance and fulvestrant for first-line therapy (category 1) under "Useful in Certain Circumstances". For men with breast cancer, the compendium recommends they be treated similarly to postmenopausal women, except that the use of an AI is ineffective without concomitant suppression of testicular steroidogenesis.[6] 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 (category 2A).

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.[7] 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.[8] 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.[9]

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.

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

RECOMMENDED EXCEPTION CRITERIA

REFERENCES

1. Ibrance® capsules and tablets [prescribing information]. New York, NY: Pfizer; September 2023.
2. Kisqali® tablets [prescribing information]. East Hanover, NJ: Novartis; October 2022.
3. Kisqali® Femara® Co-Pack tablets [prescribing information]. East Hanover, NJ: Novartis; October 2022.
4. Verzenio® tablets [prescribing information]. Indianapolis, IN: Eli Lilly; March 2023.
5. The NCCN Breast Cancer Clinical Practice Guidelines in Oncology (version 6.2024 – November 11, 2024). © 2024 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on December 5, 2024.
6. The NCCN Drugs and Biologics Compendium. © 2024 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Search term: ribociclib. Accessed on February 19, 2024.
7. Finn RS, Rugo HS, Dieras V, et al. Overall survival (OS) with first-line palbociclib plus letrozole (PAL+LET) versus placebo plus letrozole (PBO+LET) in women with estrogen receptor–positive/human epidermal growth factor receptor 2–negative advanced breast cancer (ER+/HER2− ABC): analyses from PALOMA-2 [abstract LBA1003]. Presented at: American Society of Clinical Oncology (ASCO) 2022 Annual Meeting; Chicago, IL; June 3–7, 2022.
8. 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.
9. 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.
10. Itovebi™ tablets [prescribing information]. South San Francisco, CA: Genentech; October 2024.