Novartis Kisqali® shows deepening benefit in new analysis, reducing the risk of recurrence by 28.5% in a broad population of patients with early breast cancer

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- *Invasive disease-free survival benefit continued to increase after completion of the three-year treatment period across all patient subgroups, including those with node-negative disease*[1]
- *Results remain consistent across secondary endpoints, including distant disease-free survival, with a trend for improved overall survival**[1]
- *Safety is in line with previously reported results with generally low-grade symptomatic adverse events, reinforcing well-tolerated profile*[1]
- *People diagnosed with stage II or III HR+/HER2- early breast cancer, including those with node-negative disease, face a significant risk of recurrence despite being treated with adjuvant endocrine therapy*[2,3]
- *Late-breaking results to be presented at ESMO; regulatory reviews underway with FDA action expected in Q3*

East Hanover, September 16, 2024 – In an updated analysis from the pivotal Phase III NATALEE trial, investigational Kisqali® (ribociclib) added to endocrine therapy (ET) shows a deepening benefit beyond the three-year treatment period, reducing the risk of recurrence by 28.5% (HR=0.715; 95% CI 0.609–0.840; *P*<0.0001), compared to ET alone, in patients with stage II and III hormone receptor-positive/human epidermal growth factor receptor 2-negative (HR+/HER2-) early breast cancer (EBC)[1]. This invasive disease-free survival (iDFS) benefit was also consistent across all pre-specified patient subgroups, including those with node-negative disease[1]. Late-breaking data from this four-year post-hoc analysis will be presented today at the European Society for Medical Oncology (ESMO) Congress 2024[1].

iDFS benefit across pre-specified subgroups[1]:

Subgroup	4-year iDFS rate, %	4-year iDFS absolute benefit, %
Intention-To-Treat Population	Kisqali + ET: 88.5 ET alone: 83.6 (HR=0.715; 95% CI 0.609–0.840)	4.9
AJCC Tumor Stage II	Kisqali + ET: 93.9 ET alone: 89.6 (HR=0.644; 95% CI 0.468–0.887)	4.3

AJCC Tumor Stage III	Kisqali + ET: 84.3 ET alone: 78.4 (HR=0.737; 95% CI 0.611–0.888)	5.9
Node-negative disease	Kisqali + ET: 92.1 ET alone: 87.0 (HR=0.666; 95% CI 0.397–1.118)	5.1

Results were also consistent across secondary efficacy endpoints, including distant disease-free survival (HR=0.715; 95% CI 0.604–0.847; *P*<0.0001), with a trend for improvement in overall survival (HR=0.827; 95% CI 0.636–1.074; one-sided *P* value=0.0766)*[1].

“Clinicians are eager to address the substantial risk of cancer coming back as metastatic disease for patients diagnosed with HR+/HER2- early-stage breast cancer,” said Peter A. Fasching, M.D., Professor of Translational Medicine, University Hospital Erlangen and Comprehensive Cancer Center Erlangen-EMN and NATALEE trial investigator. “With longer follow-up, the clinically relevant benefit of adding ribociclib to endocrine therapy continues to improve, even after the end of ribociclib treatment, for both node-positive and node-negative patients. This is important because NATALEE includes a broad population of patients at risk of recurrence, including those diagnosed with high-risk, node-negative disease who deserve access to new treatment options to reduce that risk.”

Safety remains consistent with previously reported results with no new safety signals identified[1]. Adverse events (AEs) of special interest (grade 3 or higher) were neutropenia (44.4%), liver-related AEs (e.g., elevated transaminases) (8.6%), and QT interval prolongation (1.0%)[1].

“As we anticipate regulatory action from health authorities worldwide, we are highly encouraged by these longer-term results from NATALEE showing a deepening efficacy benefit for Kisqali,” said Shreeram Aradhye, M.D., President, Development and Chief Medical Officer, Novartis. “A large number of people diagnosed with HR+/HER2- early breast cancer remain at risk of recurrence, and these results add to the growing body of evidence supporting the potential of Kisqali to reduce this risk consistently across a broad population, including patients with node-negative disease who have few options beyond ET.”

Novartis submitted NATALEE data to the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) in 2023, and FDA regulatory action is expected in Q3.

**Results based on overall survival analysis at time of 4-year post-hoc analysis; additional follow-up is planned to obtain more mature OS data.*

About NATALEE

NATALEE is a global Phase III multi-center, randomized, open-label trial to evaluate the efficacy and safety of Kisqali® (ribociclib) with ET as an investigational adjuvant treatment versus ET alone in patients with stage II and III HR+/HER2- EBC, being conducted in collaboration with TRIO[4,5]. The adjuvant ET in both treatment arms was a non-steroidal aromatase inhibitor (NSAI; anastrozole or letrozole) and goserelin if applicable[4,5]. The primary endpoint of NATALEE is invasive disease-free survival (iDFS) as defined by the Standardized Definitions for Efficacy End Points (STEEP) criteria[4,5]. A total of 5,101 adult patients with HR+/HER2- EBC across 20 countries were randomized in the trial[4,5].

About Kisqali® (ribociclib)

Kisqali® (ribociclib) is a selective cyclin-dependent kinase inhibitor, a class of drugs that help slow the progression of cancer by inhibiting two proteins called cyclin-dependent kinase 4 and 6 (CDK4/6). These proteins, when over-activated, can enable cancer cells to grow and divide too quickly. Targeting CDK4/6 with enhanced precision may play a role in ensuring that cancer cells do not continue to replicate uncontrollably.

Regulatory reviews for Kisqali as an EBC treatment are ongoing worldwide, including in the U.S., EU and China.

Kisqali has been approved as a treatment for metastatic breast cancer (MBC) patients in 99 countries worldwide, including by the U.S. FDA and the European Commission[6,7]. In the U.S., Kisqali is indicated for the treatment of adults with HR+/HER2- advanced or MBC in combination with an AI as initial ET or fulvestrant as initial ET or following disease progression on ET in post-menopausal women or in men[6].

In MBC, Kisqali has consistently demonstrated statistically significant overall survival benefit across three Phase III trials[8-18]. The NCCN Guidelines® for breast cancer recommend ribociclib (Kisqali) as the only Category 1 preferred CDK4/6 inhibitor for first-line treatment of people living with HR+/HER2- when combined with an AI, making Kisqali the preferred first-line treatment of choice for U.S. prescribers in HR+/HER2- MBC[19].

Kisqali was developed by Novartis under a research collaboration with Astex Pharmaceuticals.

Please see full Prescribing Information for Kisqali, available at www.Kisqali.com

Indications

KISQALI is a prescription medicine used to treat adults with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer that has gotten worse or has spread to other parts of the body (metastatic), in combination with:

- an aromatase inhibitor as the first endocrine-based therapy; or
- fulvestrant as the first endocrine-based therapy or following disease progression on endocrine therapy in postmenopausal women or in men.

It is not known if KISQALI is safe and effective in children.

IMPORTANT SAFETY INFORMATION

What is the most important information I should know about KISQALI?

KISQALI may cause serious side effects, including:

Lung problems. KISQALI may cause severe or life-threatening inflammation of the lungs during treatment that may lead to death. Tell your health care provider right away if you have any new or worsening symptoms, including:

- trouble breathing or shortness of breath
- cough with or without mucus
- chest pain

Severe skin reactions. Tell your health care provider or get medical help right away if you get severe rash or rash that keeps getting worse; reddened skin; flu-like symptoms; skin pain/burning; blistering of the lips, eyes, or mouth; or blisters on the skin or skin peeling, with or without fever.

Heart rhythm problems (QT prolongation). KISQALI can cause a heart problem known as QT prolongation. This condition can cause an abnormal heartbeat and may lead to death. Your health care provider should check your

heart and do blood tests before and during treatment with KISQALI. Tell your health care provider right away if you have a change in your heartbeat (a fast or irregular heartbeat), or if you feel dizzy or faint.

Liver problems (hepatobiliary toxicity). KISQALI can cause serious liver problems. Your health care provider should do blood tests to check your liver before and during treatment with KISQALI. Tell your health care provider right away if you get any of the following signs and symptoms of liver problems:

- yellowing of your skin or the whites of your eyes (jaundice)
- dark or brown (tea-colored) urine
- feeling very tired
- loss of appetite
- pain on the right side of your stomach area (abdomen)
- bleeding or bruising more easily than normal

Low white blood cell counts (neutropenia). Low white blood cell counts are very common during treatment with KISQALI and may result in infections that may be severe. Your health care provider should check your white blood cell counts before and during treatment with KISQALI. Tell your health care provider right away if you have signs and symptoms of low white blood cell counts or infections such as fever and chills.

Your health care provider may tell you to decrease your dose, temporarily stop, or completely stop taking KISQALI if you develop certain serious side effects during treatment with KISQALI.

What should I tell my health care provider before taking KISQALI?

Before you take KISQALI, tell your health care provider if you:

- have any heart problems, including heart failure, irregular heartbeats, and QT prolongation
- have ever had a heart attack
- have a slow heartbeat (bradycardia)
- have problems with the amount of potassium, calcium, phosphorus, or magnesium in your blood
- have fever, chills, or any other signs or symptoms of infection
- have liver problems
- have any other medical conditions
- are pregnant, or plan to become pregnant. KISQALI can harm your unborn baby
    - If you are able to become pregnant, your health care provider should do a pregnancy test before you start treatment with KISQALI.
    - Females who are able to become pregnant and who take KISQALI should use effective birth control during treatment and for at least 3 weeks after the last dose of KISQALI.
    - Talk to your health care provider about birth control methods that may be right for you during this time.
    - If you become pregnant or think you are pregnant, tell your health care provider right away.
- are breastfeeding or plan to breastfeed. It is not known if KISQALI passes into your breast milk. Do not breastfeed during treatment with KISQALI and for at least 3 weeks after the last dose of KISQALI

Tell your health care provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. KISQALI and other medicines may affect each other, causing side effects. Know the medicines you take. Keep a list of them to show your health care provider or pharmacist when you get a new medicine.

What should I avoid while taking KISQALI?

Avoid eating grapefruit and avoid drinking grapefruit juice during treatment with KISQALI since these may increase the amount of KISQALI in your blood.

The most common side effects of KISQALI include:

- decreased white blood cell counts
- decreased red blood cell counts
- abnormal liver function tests
- infections
- nausea
- increased kidney function test
- tiredness
- decreased platelet counts
- diarrhea
- vomiting
- headache
- constipation
- hair loss
- cough
- rash
- back pain
- low blood sugar level

KISQALI may cause fertility problems if you are male and take KISQALI. This may affect your ability to father a child. Talk to your health care provider if this is a concern for you.

Tell your health care provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of KISQALI. For more information, ask your health care provider or pharmacist. Call your doctor for medical advice about side effects. You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

Please see full Prescribing Information including Patient Information.

About Novartis in Breast Cancer

For more than 30 years, Novartis has been at the forefront of driving scientific advancements for people touched by breast cancer and improving clinical practice in collaboration with the global community. With one of the most comprehensive breast cancer portfolios and pipeline, Novartis leads the industry in discovery of new therapies and combinations in HR+/HER2- breast cancer, the most common form of the disease.

Disclaimer

This press release contains forward-looking statements within the meaning of the United States Private Securities Litigation Reform Act of 1995. Forward-looking statements can generally be identified by words such as “potential,” “can,” “will,” “plan,” “may,” “could,” “would,” “expect,” “anticipate,” “look forward,” “believe,” “committed,” “investigational,” “pipeline,” “launch,” or similar terms, or by express or implied discussions regarding potential marketing approvals, new indications or labeling for the investigational or approved products described in this press release, or regarding potential future revenues from such products. You should not place undue reliance on these statements. Such forward-looking statements are based on our current beliefs and expectations regarding future events, and are subject to significant known and unknown risks and uncertainties. Should one or more of these risks or uncertainties materialize, or should underlying assumptions prove incorrect, actual results may vary materially from those set forth in the forward-looking statements. There can be no guarantee that the investigational or approved products described in this press release will be submitted or approved for sale or for any additional indications or labeling in any market, or at any particular time. Nor can there be any guarantee that such products will be commercially successful in the future. In particular, our expectations regarding such products could be affected by, among other things, the uncertainties inherent in research and development, including

clinical trial results and additional analysis of existing clinical data; regulatory actions or delays or government regulation generally; global trends toward health care cost containment, including government, payor and general public pricing and reimbursement pressures and requirements for increased pricing transparency; our ability to obtain or maintain proprietary intellectual property protection; the particular prescribing preferences of physicians and patients; general political, economic and business conditions, including the effects of and efforts to mitigate pandemic diseases; safety, quality, data integrity or manufacturing issues; potential or actual data security and data privacy breaches, or disruptions of our information technology systems, and other risks and factors referred to in Novartis AG's current Form 20-F on file with the U.S. Securities and Exchange Commission. Novartis is providing the information in this press release as of this date and does not undertake any obligation to update any forward-looking statements contained in this press release as a result of new information, future events or otherwise.

About Novartis

Novartis is an innovative medicines company. Every day, we work to reimagine medicine to improve and extend people's lives so that patients, healthcare professionals and societies are empowered in the face of serious disease. Our medicines reach more than 250 million people worldwide.

Reimagine medicine with us: Visit us at **https://www.novartis.com** and **https://www.novartis.us** and connect with us on **LinkedIn**, **LinkedIn US**, **Facebook**, **X/Twitter**, **X/Twitter US** and **Instagram**.

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