Latest analysis of Novartis NATALEE study shows Kisqali® reduces risk of cancer recurrence for early breast cancer patients with high-risk node-negative disease

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- *Addition of Kisqali® (ribociclib) to endocrine therapy (ET) demonstrated a 28% risk reduction in invasive disease-free survival (iDFS) in subgroup of patients with node-negative (N0) disease at high risk of recurrence*[1]
- *Patients with N0 disease are currently ineligible to receive CDK4/6 inhibitor (CDK4/6i) treatment to manage risk of recurrence; treatment with ET alone leaves them with significant unmet need*[2,3]
- *Efficacy, safety and tolerability profile observed in N0 disease subgroup are consistent with the overall NATALEE study population*[1,2,4,5,6]
- *Based on NATALEE data, the number of patients that could potentially benefit from CDK4/6i treatment to reduce their chances of cancer coming back could double; Novartis has submitted these results to FDA and EMA*[1,2]

East Hanover, May 31, 2024 – Novartis is announcing results from a subgroup analysis of patients with high-risk, node-negative (N0) hormone receptor-positive/human epidermal growth factor receptor 2-negative (HR+/HER2-) early breast cancer (EBC) from the Phase III NATALEE trial. The latest analysis demonstrated that Kisqali® (ribociclib) plus endocrine therapy (ET), compared to ET alone, showed an improvement in rates of invasive disease-free survival (iDFS), distant recurrence-free survival (DRFS), and distant disease-free survival (DDFS) in high-risk EBC patients with N0 disease[1,2]. These data are being presented at the 2024 American Society of Clinical Oncology (ASCO) Annual Meeting today and are consistent with the significant benefits observed in the broad population of patients with stage II and III HR+/HER2- EBC in the pivotal NATALEE trial, initially presented at ASCO 2023[1,2,5].

Kisqali iDFS, DRFS and DDFS rates in key pre-specified subgroup[1,2]:

Subgroup	3-year iDFS rate, %	3-year DRFS rate, %	3-year DDFS rate, %
High-risk node-negative (N0)	Kisqali + ET: 93.2 ET alone: 90.6 (HR=0.72; 95% CI: 0.41, 1.27)	Kisqali + ET: 96.3 ET alone: 92.5 (HR=0.58; 95% CI: 0.29, 1.17)	Kisqali + ET: 94.3 ET alone: 91.5 (HR=0.70; 95% CI: 0.38, 1.29)

“More than 1 in 3 patients diagnosed with early-stage breast cancer, regardless of nodal involvement, are at risk of experiencing recurrent disease despite treatment with standard chemotherapy and/or endocrine therapy,” said Denise A. Yardley, MD, Associate Director, Breast Cancer Research; Executive Member, Breast Cancer Research

Executive Committee, Sarah Cannon Research Institute; and Principal Investigator of the NATALEE clinical trial. “Notably, the NATALEE trial has shed light on the node-negative patient population, an important at-risk subgroup that could benefit from more options to reduce their risk of their cancer returning. The findings from this trial underscore the efficacy of ribociclib in early-stage node-negative breast cancer, highlighting its role as a viable and well-tolerated treatment intervention that could significantly diminish the recurrence risk for this particular group.”

The safety profile of Kisqali at the 400 mg dose in the high-risk, N0 subgroup remains consistent with the well-tolerated profile previously demonstrated in the intent-to-treat population with generally low-grade adverse events (AEs), other than laboratory findings. In the N0 subgroup, the rate of discontinuation due to all grade AEs was 24% vs 8% with Kisqali plus ET vs ET alone[1,2]. No new safety signals were identified[1,2].

“Currently available targeted therapies are approved only for a small proportion of patients, leaving a large number of people diagnosed with HR+/HER2- early breast cancer at risk of cancer returning, particularly those with high-risk N0 tumors,” said Jeff Legos, Executive Vice President, Global Head of Oncology Development, Novartis. “Our robust body of data continues to support the potential for Kisqali to benefit many more patients as they seek to reduce the likelihood of their cancer coming back with the addition of a CDK4/6 inhibitor to their endocrine treatment.”

Novartis submitted NATALEE data to the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) in 2023, and further submissions to global authorities are ongoing.

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[5]. The adjuvant ET in both treatment arms was a non-steroidal aromatase inhibitor (NSAI; anastrozole or letrozole) and goserelin if applicable[5]. The primary endpoint of NATALEE is iDFS as defined by the Standardized Definitions for Efficacy End Points (STEEP) criteria[5]. A total of 5,101 adult patients with HR+/HER2- EBC across 20 countries were randomized in the trial[5].

Results previously announced at the San Antonio Breast Cancer Symposium (SABCS) in December 2023 showed Kisqali plus ET, compared to ET alone, lowered the risk of cancer recurrence by 25.1% (HR=0.749; 95% CI: 0.628, 0.892; p=0.0006), along with consistent clinically meaningful iDFS benefit across key pre-specified subgroups[5].

NATALEE explored a lower starting dose (400 mg) of Kisqali than the dose approved for treatment in metastatic breast cancer (MBC) (600 mg) with the goal to minimize disruptions to patient quality of life without compromising efficacy. Compared to the 600 mg dose, the safety profile of Kisqali at 400 mg was observed to have lower rates of symptomatic AEs and less need for dose modifications when administered up to three years[5]. AEs of special interest (grade 3 or higher) are neutropenia (44.3%), liver-related AEs (e.g., elevated transaminases) (8.6%), and QT interval prolongation (1.0%)[1,5].

About Early Breast Cancer

More than 90% of patients diagnosed with breast cancer have EBC[7]. Despite adjuvant ET or being declared on remission, patients with EBC remain at risk for cancer recurrence, peaking within the first three years after initial diagnosis[1]. Patients with negative-node disease face a risk of recurrence up to 11% within the first three years after diagnosis, and 29% expect to recur within 20 years[8,9].

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.

In MBC, Kisqali has consistently demonstrated statistically significant OS benefit across three Phase III trials[10-21]. Updates to the NCCN Guidelines® for breast cancer, released in January 2023, recommend ribociclib (Kisqali) as the only Category 1 preferred CDK4/6 inhibitor for first-line treatment of patients with HR+/HER2- when combined with an aromatase inhibitor (AI), making Kisqali the preferred first-line treatment of choice for US prescribers in HR+/HER2- in MBC[22]. Additionally, Kisqali has the highest rating of any CDK4/6 inhibitor on the ESMO Magnitude of Clinical Benefit Scale, achieving a score of five out of five for first-line pre-menopausal patients with HR+/HER2- advanced breast cancer[23]. Further, Kisqali in combination with either letrozole or fulvestrant has uniquely, among other CDK4/6 inhibitors, received a score of four out of five for post-menopausal patients with HR+/HER2- advanced breast cancer treated in the first line[24].

Kisqali has been approved in 99 countries worldwide, including by the United States Food and Drug Administration (FDA) and the European Commission. In the U.S., Kisqali is approved for the treatment of adult patients 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. In the EU, Kisqali is approved for the treatment of women with HR+/HER2- advanced or MBC in combination with either an AI or fulvestrant as initial ET or following disease progression. In pre- or peri-menopausal women, the ET should be combined with a luteinizing hormone-releasing hormone agonist[25].

Kisqali was developed by the Novartis Institutes for BioMedical Research (NIBR) 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.

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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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