Latest Novartis Kisqali® NATALEE analysis reinforces 25% reduction in risk of recurrence across broad population of patients with early breast cancer; supports regulatory submissions

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- With 5.6 months of additional follow-up and 78.3% of patients having completed Kisqali® (ribociclib) investigational treatment, the updated analysis shows sustained iDFS benefit and stability in secondary endpoints including overall survival (OS)[1,2]
- iDFS benefit remains consistent across key patient subgroups; among patients with stage II and stage III tumors, Kisqali lowered risk by 30% and 24.5%, respectively[1,2]
- Latest analysis continues to show a well-tolerated safety profile in line with previously reported results, and quality of life for Kisqali patients preserved vs. endocrine therapy (ET) alone[1,2,3]
- Risk of recurrence remains a short and long term concern; one in eight women treated with ET alone in NATALEE likely to experience invasive disease at 3 years[1,2]
- Kisqali is currently approved in the metastatic setting, where it has consistently demonstrated statistically significant OS benefit across three Phase III trials[4-15]; Novartis has filed NATALEE results with EMA and will submit these latest EBC data to the FDA by end of year

EAST HANOVER, N.J., Dec. 8, 2023 -- Novartis today announced results from an updated invasive disease-free survival (iDFS) analysis of the pivotal Phase III NATALEE trial, with a median follow-up of 33.3 months and following Kisqali® (ribociclib) treatment completion by 78.3% of patients. Results reinforce the benefit seen at the earlier interim analysis, with a 25.1% (HR=0.749; 95% CI: 0.628, 0.892; p=0.0006) reduction in risk of disease recurrence in patients with stage II and III hormone receptor-positive/human epidermal growth factor receptor 2-negative (HR+/HER2-) early breast cancer (EBC) treated with adjuvant Kisqali plus a non-steroidal aromatase inhibitor as standard endocrine therapy (ET) compared to ET alone[1,2]. Late-breaking data from this analysis will be presented today at the 2023 San Antonio Breast Cancer Symposium (SABCS) Annual Meeting.

Kisqali iDFS benefit across pre-specified subgroups[1]:

Subgroup	3-year iDFS rate, %	HR (95% CI)
ITT population	Kisqali + ET: 90.7 ET alone: 87.6	0.749 (0.628, 0.892)
AJCC Stage II	Kisqali + ET: 94.2 ET alone: 92.6	0.700 (0.496, 0.986)
AJCC Stage III	Kisqali + ET: 88.1 ET alone: 83.8	0.755 (0.616, 0.926)
Node-negative (N0)	Kisqali + AI: 93.2 ET alone: 90.6	0.723 (0.412, 1.268)

"As clinicians, we know that patients diagnosed with HR+/HER2- early breast cancer remain at risk of recurrence for decades, despite adjuvant endocrine therapy. Moreover, the real risk observed in this analysis in patients treated with endocrine therapy alone, including those with node-negative disease, highlights the need for effective and tolerable treatment options that can help keep patients cancer-free in the short and long term," said Gabriel N. Hortobagyi, MD, FACP, Professor of Breast Medical Oncology, The University of Texas MD Anderson Cancer Center. "The updated NATALEE results reinforce the potential of ribociclib to help address these needs for the broader at-risk population with no added disruptions to patients' quality of life compared to endocrine therapy alone."

Kisqali data across all secondary efficacy endpoints was also consistent, including distant disease-free survival (DDFS) (25.1% risk reduction) and recurrence-free survival (RFS) (27.3% risk reduction). With fewer than 4% of events in both treatment arms (3.3% in the Kisqali-ET arm and 3.4% in the ET only arm), overall survival (OS) results will continue to evolve in the longer term[1,2].

The safety profile of Kisqali at the 400 mg dose remained consistent with previously reported results, with generally low-grade adverse events (AEs), other than laboratory abnormalities. AEs of special interest (grade 3 or higher) were neutropenia (44.3%), liver-related AEs (e.g., elevated transaminases) (8.6%), and QT interval prolongation (1.0%)[1,2]. No new safety signals were identified[1,2].

"The final iDFS analysis of NATALEE represents a significant milestone, building upon the robust evidence supporting Kisqali as a potential new adjuvant treatment for a broad, clinically common and identifiable population of patients with stage II and III HR+/HER2- early breast cancer," said Jeff Legos, Executive Vice President, Global Head of Oncology Development at Novartis. "We are seeking approval for Kisqali in early breast cancer from health authorities worldwide, aspiring to more than double the number of at-risk patients who could potentially benefit from CDK4/6 inhibitor treatment in this setting."

Novartis submitted NATALEE data to the European Medicines Agency and plans to finalize submission to the U.S. Food and Drug Administration by end of year.

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[2]. The adjuvant ET in both treatment arms was a non-steroidal aromatase inhibitor (NSAI; anastrozole or letrozole) and goserelin if applicable[2]. The primary endpoint of NATALEE is iDFS as defined by the Standardized Definitions for Efficacy End Points (STEEP) criteria[2]. A total of 5,101 adult patients with HR+/HER2- EBC across 20 countries were randomized in the trial[2].

Results previously announced at the American Society of Clinical Oncology (ASCO) Annual Meeting 2023 showed Kisqali plus ET, compared to ET alone, lowered the risk of cancer recurrence by 25.2% (HR=0.748; 95% CI: 0.618, 0.906; p=0.0014), along with consistent clinically meaningful iDFS benefit across key pre-specified subgroups[2].

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[2]. 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%)[1,2].

About Early Breast Cancer

More than 90% of patients diagnosed with breast cancer have EBC[16]. Despite adjuvant ET, approximately one-third of those diagnosed with stage II and more than half of those diagnosed with stage III HR+/HER2- EBC experience cancer recurrence[17,18]. The risk of recurrence continues over decades with more than half of breast cancer recurrences occurring five or more years after diagnosis[17,19]. For many of these patients, there are currently no targeted therapeutic options outside of the standard chemotherapy and ET[20].

About Kisqali® (ribociclib)

Kisqali has consistently demonstrated OS benefit while preserving or improving quality of life across three Phase III trials in MBC[4-15]. 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- MBC when combined with an aromatase inhibitor (AI)[21]. 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[22]. 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[23].

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[20].

Novartis is committed to continuing to study Kisqali in breast cancer. Novartis is collaborating with SOLTI, which is leading the HARMONIA study to test whether Kisqali changes tumor biology to enable a better response to ET compared to Ibrance®* (palbociclib) for patients with HR+/HER2-, HER2-enriched subtype[24] MBC, and with the Akershus University Hospital in Norway on the NEOLETRIB trial, a neoadjuvant Phase II trial studying the effects of Kisqali in HR+/HER2- EBC to discover the potentially unique underlying mechanism of action[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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