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MEDIA UPDATE

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

- *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]
- *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]

Basel, 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].

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

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[2]. 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[2].

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[8-19]. 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[20].

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[21]. 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[22].

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[23].

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

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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 connect with us on **LinkedIn**, **Facebook**, **X/Twitter** and **Instagram**.

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