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MEDIA & INVESTOR RELEASE

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

- *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*

Basel, 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 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[7]. In pre- or peri-menopausal women, the ET should be combined with a luteinizing hormone-releasing hormone agonist[6,7].

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 US prescribers in HR+/HER2- MBC[19]. 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[20]. 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[21].

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

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

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.

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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 US Securities and Exchange Commission. Novartis is providing the information in this media update as of this date and does not undertake any obligation to update any forward-looking statements contained in this media update 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.

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