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Novartis Kisqali® Phase III NATALEE trial meets primary endpoint at interim analysis demonstrating clinically meaningful benefit in broad population of patients with early breast cancer

Kisqali plus endocrine therapy (ET) significantly reduced the risk of disease recurrence compared to standard ET alone in the adjuvant setting[1]

NATALEE is the first and only positive Phase III study of a CDK4/6 inhibitor demonstrating consistent benefit in a broad population of patients with stage II and III HR+/HER2- early breast cancer (EBC) at risk of recurrence, including those with no nodal involvement

Approximately 30-60% of people with HR+/HER2- stage II and III EBC treated with ET only remain at risk of breast cancer recurrence[2]

NATALEE results will be presented at an upcoming medical meeting and submitted to regulatory authorities worldwide

EAST HANOVER, N.J., March 27, 2023 -- Novartis today announced positive topline results from an interim analysis of NATALEE, a Phase III trial evaluating Kisqali® (ribociclib) plus endocrine therapy (ET) in a broad population of patients with hormone receptor-positive/human epidermal growth factor receptor 2-negative (HR+/HER2-) early breast cancer (EBC) at risk of recurrence[1]. The Independent Data Monitoring Committee recommended stopping the trial early as the primary endpoint of invasive disease-free survival (iDFS) has been met. Kisqali plus ET significantly reduced the risk of disease recurrence, compared to standard adjuvant ET alone, with consistent benefit in patients with stage II and stage III EBC regardless of nodal involvement[1].

"While most patients are diagnosed and treated early with the aim to cure breast cancer, the risk of cancer returning, often as metastatic disease, peaks within three years after diagnosis, but never goes away completely," said Dennis J. Slamon, MD, Director of Clinical/Translational Research, University of California, Los Angeles Jonsson Comprehensive Cancer Center and Chairman and Executive Director of Translational Research In Oncology (TRIO) and NATALEE trial lead investigator. "There is a critical need for new, well-tolerated options that keep patients cancer-free without disrupting quality of life. The NATALEE trial, where ribociclib was given for three years plus ET, was designed with these unmet needs in mind, and it is extremely encouraging that this study met its primary endpoint."

Per the NATALEE study protocol, patient follow-up will continue to evaluate long-term outcomes, including overall survival[1].

"The positive topline results from NATALEE represent a major milestone in our ambition to expand the benefits of Kisqali to patients with earlier stages of breast cancer, building on the heritage of this effective treatment in HR+/HER2- metastatic breast cancer," said Shreeram Aradhye, M.D., President, Global Drug Development and Chief Medical Officer, Novartis. "These data have the potential to be paradigm-shifting for patients at risk of recurrence, including those with no nodal involvement, who have limited well-tolerated options to prevent recurrence. Our teams are working on submissions to health authorities around the world with the hope to bring Kisqali to many more patients diagnosed with breast cancer."

These findings build on the legacy of Kisqali in metastatic breast cancer (MBC), where it has consistently demonstrated overall survival benefit while preserving or improving quality of life across three Phase III trials[3-14]. Updates to the NCCN Clinical Practice Guidelines in Oncology (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)[15].

About NATALEE
NATALEE is a global Phase III multi-center, randomized, open-label trial to evaluate the efficacy and safety of Kisqali with ET as adjuvant treatment versus ET alone in patients with HR+/HER2- EBC, being conducted in collaboration with Translational Research In Oncology (TRIO)[1]. The primary endpoint of NATALEE is iDFS as defined by the Standardized Definitions for Efficacy End Points (STEEP) criteria; secondary endpoints include safety, quality of life, and overall survival, among others. iDFS is a composite endpoint in EBC adjuvant trials, which incorporates locoregional relapse, ipsilateral and contralateral invasive breast cancer, distant recurrence, and types of new cancer events or death from any cause. Approximately 5,100 adult patients with HR+/HER2- EBC across 20 countries were randomized in the trial, including patients with tumor stages IIA (select patients), IIB or III, regardless of nodal involvement. NATALEE explored a lower starting dose (400 mg) of Kisqali than the dose approved for treatment in MBC (600 mg) with the goal to minimize disruptions to patient quality of life without compromising efficacy[1].

About Early Breast Cancer
More than 90% of patients diagnosed with breast cancer have EBC[2,16]. Approximately 30-60% of people with HR+/HER2-

stage II and III EBC treated with ET only remain at risk of breast cancer recurrence[2]. The risk of recurrence peaks within the first three years after initial diagnosis and continues over decades[2]. For many of these patients, there are currently no targeted therapeutic options outside of the standard chemotherapy and ET[17].

About Kisqali® (ribociclib)
Kisqali has consistently demonstrated overall survival benefit while preserving or improving quality of life across three Phase III trials[3-14]. Updates to the NCCN Guidelines® for breast cancer, released inJanuary 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 AI[15]. 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 premenopausal patients with HR+/HER2- advanced breast cancer[18]. 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 postmenopausal patients with HR+/HER2- advanced breast cancer treated in the first line[19].

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 metastatic breast cancer in combination with an AI as initial ET or fulvestrant as initial ET or following disease progression on ET in postmenopausal women or in men. In the EU, Kisqali is approved for the treatment of women with HR+/HER2- advanced or metastatic breast cancer in combination with either an AI or fulvestrant as initial ET or following disease progression. In pre- or perimenopausal women, the ET should be combined with a luteinizing hormone-releasing hormone agonist[14].

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 metastatic HR+/HER2-, HER2-enriched subtype[20], 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[21]. Novartis also plans to build on the findings from NATALEE with ADJUVANT WIDER, an open-label Phase IIIb trial evaluating Kisqali plus ET in a population of HR+/HER2- patients with stage II and III EBC that is closer to a real-world population.

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 atwww.Kisqali.com.

Indications

KISQALI® (ribociclib) is a prescription medicine used to treat adults with hormone receptor-positive, human epidermal growth factor receptor 2-negative (HR+/HER2–) 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 accompanying full Prescribing Information including Patient Information.

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 such as COVID-19; 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 US 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
Located in East Hanover, NJ Novartis Pharmaceuticals Corporation – an affiliate of Novartis – is reimagining medicine to improve and extend people's lives. We deliver high-value medicines that alleviate society's greatest disease burdens through technology leadership in R&D and novel access approaches. In our quest to find new medicines, we consistently rank among the world's top companies investing in research and development. Novartis employs nearly 14,500 people in the United States. For more information, please visit https://www.novartis.us

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References

- Novartis Data on File. Novartis Pharmaceuticals: 2022.
- Pan, H, Gray, R, Braybrooke, J, et al. 20-year risks of breast-cancer recurrence after stopping endocrine therapy at 5 years. *N Engl J Med.* Nov 2017;377(19):1836-1846. 10.1056/NEJMoa1701830
- Iqbal J, Ginsburg O, Rochon PA, Sun P, Narod SA. Differences in breast cancer stage at diagnosis and cancer-specific survival by race and ethnicity in the United States [published correction appears in *JAMA*. 2015 Jun 9;313(22):2287]. *JAMA*. 2015;313(2):165-173. doi:10.1001/jama.2014.17322
- Yardley DA, Yap YS, et al. Pooled exploratory analysis of survival in patients (pts) with HR+/HER2- advanced breast cancer (ABC) and visceral metastases (mets) treated with ribociclib (RIB) + endocrine therapy (ET) in the MONALEESA (ML) trials. Poster presented at the European Society of Medical Oncology Congress. September 9-13, 2022. Paris, France.
- Neven P, Fasching PA, et al. Updated overall survival (OS) results from the first-line (1L) population in the Phase III MONALEESA-3 trial of postmenopausal patients with HR+/HER2- advanced breast cancer (ABC) treated with ribociclib (RIB) + fulvestrant (FUL). Mini oral presented at the European Society for Medical Oncology Breast Cancer Congress. May 4, 2022. Patis, France.
- Hortobagyi GN, Stemmer SM, Burris HA, et al. Overall Survival with Ribociclib plus Letrozole in Advanced Breast Cancer.

New England Journal of Medicine. 2022;386(10):942-950. doi:10.1056/NEJMoa2114663
- Hortobagyi, et al. Overall survival (OS) results from the phase III MONALEESA (ML)-2 trial of postmenopausal patients with hormone receptor positive/human epidermal growth factor receptor 2 negative (HR+/HER2–) advanced breast cancer (ABC) treated with endocrine therapy (ET) ± ribociclib. Proffered paper presented at the European Society of Medical Oncology Congress, September 16-21, 2021. Lugano, Switzerland.
- Im S-A, Lu Y-S, Bardia A, et al. Overall survival with ribociclib plus endocrine therapy in breast cancer.*New England Journal of Medicine*. 2019;381(4):307-316. doi:10.1056/nejmoa1903765
- Slamon DJ, Neven P, Chia S, et al. Overall Survival with Ribociclib plus Fulvestrant in Advanced Breast Cancer.*New England Journal of Medicine*. 2020;382(6):514-524. doi:10.1056/NEJMoa1911149
- Slamon, DJ, Neven P, Chia S, et al. Overall survival (OS) results of the Phase III MONALEESA-3 trial of postmenopausal patients (pts) with hormone receptor–positive (HR+), human epidermal growth factor 2–negative (HER2–) advanced breast cancer (ABC) treated with fulvestrant (FUL) ± ribociclib (RIB). Presented at the European Society of Medical Oncology Congress, September 29, 2019, Barcelona, Spain.
- Slamon D, Neven P, Chia S, et al. Updated overall survival (OS) results from the Phase III MONALEESA-3 trial of postmenopausal patients (pts) with HR+/HER2– advanced breast cancer (ABC) treated with fulvestrant (FUL) ± ribociclib (RIB. Presented at the American Society of Clinical Oncology Annual Meeting, June 5, 2021. Chicago, USA.
- Tripathy D, Im S-A, Colleoni M, et al. Updated overall survival (OS) results from the phase III MONALEESA-7 trial of pre- or perimenopausal patients with HR+/HER2– advanced breast cancer (ABC) treated with endocrine therapy (ET) ± ribociclib. Presented at the San Antonio Breast Cancer Symposium, December 9, 2020. Texas, USA.
- Yardley, D, Nusch A, Yap YS, et al. Overall survival (OS) in patients (pts) with advanced breast cancer (ABC) with visceral metastases (mets), including those with liver mets, treated with ribociclib (RIB) plus endocrine therapy (ET) in the MONALEESA (ML) -3 and -7 trials. Presented at the American Society of Clinical Oncology (ASCO) Annual Meeting. June 2020. Chicago, USA.
- O'Shaughnessy J, Stemmer SM, Burris HA, et al. Overall survival subgroup analysis by metastatic site from the Phase III MONALEESA-2 study of first-line ribociclib + letrozole in postmenopausal patients with HR+/HER2– advanced breast cancer. Presented at the San Antonio Breast Cancer Symposium, December 7-10, 2021. Texas, USA.
- Kisqali (ribociclib) Prescribing Information.
- NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) - Breast Cancer. NCCN Guidelines. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Published March 2023. Accessed March 7, 2023.
- American Cancer Society. Treatment of breast cancer stages I-III. Revised April 12, 2022. Accessed on September 15, 2022.https://www.cancer.org/cancer/breast-cancer/treatment/treatment-of-breast-cancer-by-stage/treatment-of-breast-cancer-stages-i-iii.html
- European Society for Medical Oncology – Magnitude of Clinical Benefit Scale Scorecard. https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-scorecards/scorecard-158-1. Published April 20, 2020. Updated August 21, 2020. Accessed September 9, 2020.
- European Society for Medical Oncology – Magnitude of Clinical Benefit Scale Scorecard. https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-scorecards/scorecard-9-1. Published March 29, 2022. Accessed April 1, 2022.
- Ribociclib vs. palbociclib in patients with advanced breast cancer within the HER2-enriched intrinsic subtype (HARMONIA). Identifier NCT05207709. Revised April 4, 2022. Accessed on February 6, 2022. https://clinicaltrials.gov/ct2/show/NCT05207709
- Novartis and Vestre Viken Hospital Trust (2022, April 1 – 2024, December 1). Neoadjuvant Treatment of Locally-advanced Breast Cancer Patients With Ribociclib and Letrozole (NEOLETRIB). Identifier NCT05163106. https://clinicaltrials.gov/ct2/show/NCT05163106

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Novartis Media Relations
E-mail: media.relations@novartis.com

North America
Julie Masow +1 862 579 8456
Michael Meo
Mary Carmichael +1 862 274 5414
Marlena +1 862 200 8344
Abdinoor +1 617 335 9525

Novartis Investor Relations
E-mail: investor.relations@novartis.com

North America +1 862 778
Sloan Simpson 5052

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