Third Novartis Phase III trial shows Kisqali® combination therapy significantly improves PFS in HR+/HER2- advanced breast cancer

- Kisqali plus fulvestrant demonstrated superior efficacy, with a median PFS of 20.5 months vs. 12.8 months for fulvestrant alone, among overall study population of first- and second-line postmenopausal patients with HR+/HER2- advanced breast cancer

- In the subgroup of patients taking Kisqali plus fulvestrant in the first-line setting, median PFS was not reached and 70% were estimated to remain progression-free at median follow-up of 16.5 months

- MONALEESA-3 is the only randomized Phase III trial to study a CDK4/6 inhibitor plus fulvestrant in the first-line setting showing efficacy in patients with de novo advanced breast cancer and those who had not received adjuvant therapy in more than a year

- Data presented today at the 54th Annual Meeting of the American Society of Clinical Oncology (ASCO) in Chicago and published simultaneously in the Journal of Clinical Oncology

Basel, June 3, 2018 – Novartis today announced positive results from the third Phase III trial of Kisqali® (ribociclib) in advanced or metastatic breast cancer. MONALEESA-3 showed Kisqali plus fulvestrant significantly prolonged progression-free survival (PFS) compared to fulvestrant alone in postmenopausal women with hormone-receptor positive, human epidermal growth factor receptor-2 negative (HR+/HER2-) advanced breast cancer. MONALEESA-3 is the largest phase III trial to evaluate efficacy and safety of a CDK4/6 inhibitor plus fulvestrant in multiple advanced breast cancer patient populations – first-line and second-line settings. These data will be presented today as an oral presentation at the 54th Annual Meeting of the American Society of Clinical Oncology (ASCO) in Chicago (Abstract #1000) and published simultaneously in the Journal of Clinical Oncology.

Kisqali in combination with fulvestrant demonstrated a median PFS of 20.5 months (95% CI: 18.5-23.5 months) compared to 12.8 months (95% CI: 10.9-16.3 months) for fulvestrant alone (HR=0.593; 95% CI: 0.480-0.732; p=.00000041) across both treatment arms. The median PFS for the subgroup of patients receiving Kisqali plus fulvestrant in the first-line setting, including only de novo patients and those whose disease relapsed >12 months since end of neo(adjuvant) endocrine therapy, was not reached compared to 18.3 months for fulvestrant alone (HR=0.577; 95% CI: 0.415-0.802). In patients receiving treatment in the second-line setting, or those who relapsed <12 months since end of neo(adjuvant) endocrine therapy, the median PFS was 14.6 months compared to 9.1 months for fulvestrant alone (HR=0.565; 95% CI: 0.428-0.744).

“The MONALEESA-3 results in patients treated in this first-line setting were particularly significant. Nearly 70% of women who received ribociclib plus fulvestrant in this setting were estimated to remain progression-free at the median follow-up of 16.5 months,” said Dennis J. Slamon, MD, Director of Clinical/Translational Research, University of California, Los Angeles Jonsson Comprehensive Cancer Center. “In the advanced breast cancer setting, it is
important to ensure we provide patients with treatment options that increase time to disease progression while also maintaining quality of life."

Fifty percent of the women in MONALEESA-3 had lung and/or liver metastases and showed a consistent treatment benefit compared with the overall population. Follow-up to measure overall survival is ongoing as these data remain immature. “MONALEESA-3 data add to the robust body of evidence demonstrating the broad potential of Kisqali to treat pre- and postmenopausal women living with advanced breast cancer in various endocrine combinations and multiple lines of therapy,” said Samit Hirawat, MD, Head, Novartis Oncology Global Drug Development. “These results along with the other MONALEESA studies build a compelling case that Kisqali combination therapy should be a cornerstone of first-line treatment of HR+/HER2- advanced breast cancer.”

No new safety signals were observed in the MONALEESA-3 trial; adverse events were generally consistent with those observed in MONALEESA-2. The discontinuation rate due to adverse events was 8.5% for Kisqali plus fulvestrant compared to 4.1% for fulvestrant alone. The most common (≥5%) grade 3/4 adverse events in patients receiving Kisqali plus fulvestrant compared to fulvestrant alone were neutropenia (53.4% vs 0%) and leukopenia (14.1% vs 0%).

Additional Kisqali data are being presented at the 2018 ASCO Annual Meeting. Further results from MONALEESA-7 showed consistent treatment benefit among premenopausal women with HR+/HER2- advanced breast cancer regardless of prior chemotherapy treatment in the advanced setting (Abstract #1047). Initial safety data from the CompLEEment-1 trial demonstrated a consistent safety profile for Kisqali in a patient population more reflective of those seen in a real-world setting (Abstract #1056). Lastly, biomarker data from MONALEESA-2 showed that clinical benefit of Kisqali was consistent across gene expression subgroups with a trend toward greater Kisqali benefit in the high versus low ESR1 expression and low versus high RTK expression subgroups (Abstract #1022).

Novartis is in discussion with the US Food and Drug Administration (FDA) with respect to a supplemental New Drug Application (sNDA), seeking approval of Kisqali plus fulvestrant for the treatment of postmenopausal women with HR+/HER2- advanced breast cancer.

**About MONALEESA-3**
MONALEESA-3 is a Phase III randomized, double-blind, placebo-controlled study evaluating Kisqali in combination with fulvestrant compared to fulvestrant alone for the treatment of postmenopausal women with HR+/HER2- advanced breast cancer who received no prior or only one line of prior endocrine therapy for advanced disease. A total of 726 people were randomized in the trial, including first-line patients comprised of 367 women who were treatment-naïve and 345 who had received up to one line of prior endocrine therapy for advanced disease. Patients were randomized (2:1) to receive Kisqali plus fulvestrant or fulvestrant alone. Randomization was stratified by the presence or absence of lung or liver metastases and prior endocrine therapy (first-line versus second-line).

**About Kisqali® (ribociclib)**
Kisqali 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.

Kisqali was approved by the US Food and Drug Administration in March 2017 and by the European Commission in August 2017, as initial endocrine-based therapy for postmenopausal women with HR+/HER2- locally advanced or metastatic breast cancer in
combination with an aromatase inhibitor based on findings from the pivotal MONALEESA-2 trial. Kisqali is not currently approved for use in combination with fulvestrant or in premenopausal women.

Kisqali is approved for use in 59 countries around the world, including the United States and European Union member states. Kisqali was developed by the Novartis Institutes for BioMedical Research (NIBR) under a research collaboration with Astex Pharmaceuticals.

About the Kisqali Clinical Trial Program
With more than 2,000 patients enrolled in current trials, the MONALEESA program is the largest industry sponsored Phase III clinical program researching a CDK4/6 inhibitor in HR+/HER2- advanced breast cancer. In addition to MONALEESA-3, there are three other Phase III trials evaluating Kisqali combination therapy.

MONALEESA-7 is a Phase III randomized, double-blind, placebo-controlled trial investigating the efficacy and safety of Kisqali in combination with tamoxifen or a non-steroidal aromatase inhibitor plus goserelin versus tamoxifen or an aromatase inhibitor plus goserelin, in premenopausal or perimenopausal women with HR+/HER2- advanced breast cancer who had not previously received endocrine therapy for advanced disease.

MONALEESA-2 is a Phase III global registration trial evaluating Kisqali in combination with letrozole compared to letrozole alone in postmenopausal women with HR+/HER2- advanced breast cancer who received no prior therapy for their advanced breast cancer.

CompLEEment-1 is an open-label, multicenter, Phase IIIb study evaluating the safety and efficacy of Kisqali plus letrozole in pre- or postmenopausal women and men with HR+/HER2-advanced breast cancer who have not received prior hormonal therapy for advanced disease.

More information about these studies can be found at www.ClinicalTrials.gov.

About Novartis in Advanced Breast Cancer
For more than 30 years, Novartis has been tackling breast cancer with superior science, great collaboration and a passion for transforming patient care. With one of the most diverse breast cancer pipelines and one of the largest numbers of breast cancer compounds in development, Novartis leads the industry in discovery of new therapies and combinations, especially in HR+ advanced breast cancer, the most common form of the disease.

Important Safety Information from the Kisqali EU SmPC
The most common ADRs and the most common grade 3/4 ADRs (reported at a frequency ≥20% and ≥2% respectively) for which the frequency for Kisqali plus letrozole exceeds the frequency for placebo plus letrozole were blood and lymphatic system disorders (including abnormally low neutrophil and white blood cell count), headache, back pain, nausea, fatigue, diarrhea, vomiting, constipation, hair loss and rash and abnormally low levels of neutrophils or white blood cells, abnormal liver function tests (increased alanine and aspartate aminotransferase), abnormally low lymphocyte count, low levels of phosphate, vomiting, nausea, fatigue and back pain, respectively. Low levels of neutrophils was the most commonly seen severe adverse event; fever in addition to a low neutrophil count was reported in 1.5% of patients.

Kisqali can cause serious side effects such as a significant decrease in neutrophil count, abnormal liver function tests and may have an effect on the electrical activity of the heart known as QT/QTc interval prolongation, which could lead to disturbances in heart rhythm. As a precaution, patients should have complete blood counts, liver function, and serum electrolyte levels measured prior to starting treatment as well as during treatment with Kisqali. Patients should also have their heart activity checked before and monitored during treatment.
The efficacy and safety of ribociclib have not been studied in patients with critical visceral disease.

The use of Kisqali with medicinal products known to prolong QTc interval or strong CYP3A4 inhibitors should be avoided as this may lead to prolongation of the QT/QTc interval. If treatment with a strong CYP3A4 inhibitor cannot be avoided, the Kisqali dose should be reduced. Concomitant administration with other medicines that could affect cardiac repolarization or prolong the QT/QTc interval should be taken into account prior to and during treatment with Kisqali. Patients taking sensitive CYP3A4 substrates with narrow therapeutic index should use caution because of the increased risk of adverse events that may occur if these medications are co-administered with Kisqali.

Kisqali contains soya lecithin and therefore it should not be taken by patients who are allergic to peanut or soya.

Animal studies suggest that Kisqali may cause fetal harm in pregnant women. Therefore, as a precaution, women of childbearing potential should use effective contraception while receiving Kisqali during treatment and up to 21 days after stopping treatment. Women should not breast feed for at least 21 days after the last dose of Kisqali. Kisqali may affect fertility in males.


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About Novartis
Novartis provides innovative healthcare solutions that address the evolving needs of patients and societies. Headquartered in Basel, Switzerland, Novartis offers a diversified portfolio to
best meet these needs: innovative medicines, cost-saving generic and biosimilar pharmaceuticals and eye care. Novartis has leading positions globally in each of these areas. In 2017, the Group achieved net sales of USD 49.1 billion, while R&D throughout the Group amounted to approximately USD 9.0 billion. Novartis Group companies employ approximately 124,000 full-time-equivalent associates. Novartis products are sold in approximately 155 countries around the world. For more information, please visit http://www.novartis.com.

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3. De Laurentiis M, et al. Ribociclib (RIBO) + letrozole (LET) in patients (pts) with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) advanced breast cancer (ABC) with no prior endocrine therapy (ET) for ABC: Preliminary results from the phase 3b CompLEEment-1 trial. Presented at the 54th Annual Meeting of the American Society of Clinical Oncology (ASCO), June 2, 2018, Chicago, Illinois (abstract #1056).

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