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

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- - 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[1]
- - 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[1]
- - 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[1]
- - 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

EAST HANOVER, N.J., June 3, 2018 /PRNewswire/ -- 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[1]. 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)[1].

"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[1].

"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[1]. The discontinuation rate due to adverse events was 8.5% for Kisqali plus fulvestrant compared to 4.1% for fulvestrant alone[1]. 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%)[1].

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)[2]. 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)[3]. 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)[4].

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.

Kisqali® (ribociclib) Important US Safety Information
Kisqali® (ribociclib) is a prescription medicine used in combination with an aromatase inhibitor as the first hormonal-based therapy to treat women who have gone through menopause with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer. It is not known if Kisqali is safe and effective in children. Kisqali can cause a heart problem known as QT prolongation. This condition can cause an abnormal heartbeat and may lead to death. Patients should tell their health care provider right away if they have a change in their heartbeat (a fast or irregular heartbeat), or if they feel dizzy or faint. Kisqali can cause serious liver problems. Patients should tell their health care provider right away if they get any of the following signs and symptoms of liver problems: yellowing of the skin or the whites of the eyes (jaundice), dark or brown (tea-colored) urine, feeling very tired, loss of appetite, pain on the upper right side of the stomach area (abdomen), and bleeding or bruising more easily than normal. Low white blood cell counts are very common when taking Kisqali and may result in infections that may be severe. Patients should tell their health care provider right away if they have signs and symptoms of low white blood cell counts or infections such as fever and chills. Before taking Kisqali, patients should tell their health care provider if they are pregnant, or plan to become pregnant as Kisqali can harm an unborn baby. 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. Do not breastfeed during treatment with Kisqali and for at least 3 weeks

after the last dose of Kisqali. Patients should tell their health care provider about all of the medicines they take, including prescription and over-the-counter medicines, vitamins, and herbal supplements since they may interact with Kisqali. Patients should avoid pomegranate or pomegranate juice, and grapefruit or grapefruit juice while taking Kisqali. The most common side effects (incidence ≥20%) of Kisqali when used with letrozole include white blood cell count decreases, nausea, tiredness, diarrhea, hair thinning or hair loss, vomiting, constipation, headache, and back pain. The most common grade 3/4 side effects in the Kisqali + letrozole arm (incidence >2%) were low neutrophils, low leukocytes, abnormal liver function tests, low lymphocytes, and vomiting. Abnormalities were observed in hematology and clinical chemistry laboratory tests.

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

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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," "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; our ability to obtain or maintain proprietary intellectual property protection; the particular prescribing preferences of physicians and patients; general political and economic conditions; safety, quality 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 is an affiliate of Novartis which 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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2. Hurvitz S, et al. Ribociclib (RIB) + tamoxifen (TAM) or a non-steroidal aromatase inhibitor (NSAI) in premenopausal women with hormone receptor-positive (HR+), HER2-negative (HER2-) advanced breast cancer (ABC) who received prior chemotherapy (CT): MONALEESA-7 subgroup analysis. Presented at the 54th Annual Meeting of the American Society of Clinical Oncology (ASCO), June 2, 2018, Chicago, Illinois (abstract #1047).

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).

4. Hortobagyi G, et al. First-line ribociclib (RIB) + letrozole (LET) in hormone receptor-positive (HR+), HER2-negative (HER2-) advanced breast cancer (ABC): MONALEESA-2 biomarker analysis. Presented at the 54th Annual Meeting of the American Society of Clinical Oncology (ASCO), June 2, 2018, Chicago, Illinois (abstract #1022).

Novartis Media Relations

Central media line: +41 61 324 2200

E-mail: media.relations@novartis.com

Eric Althoff
Novartis Global Media Relations
+41 61 324 7999 (direct)
+41 79 593 4202 (mobile)
eric.althoff@novartis.com

Julie Masow
Novartis Oncology Media Relations
+1 862 778 7220 (direct)
+1 862 579 8456 (mobile)
julie.masow@novartis.com

Novartis Investor Relations

Central investor relations line: +41 61 324 7944

E-mail: investor.relations@novartis.com

Central		North America	
Samir Shah	+41 61 324 7944	Richard Pulik	+1 212 830 2448
Pierre-Michel Bringer	+41 61 324 1065	Cory Twining	+1 212 830 2417
Thomas Hungerbuehler	+41 61 324 8425		
Isabella Zinck	+41 61 324 7188		

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