Novartis LEE011 (ribociclib) plus letrozole analyses show superior PFS across broad spectrum of patients in first-line HR+/HER2-advanced breast cancer versus letrozole

- **MONALEESA-2 analyses demonstrate superior PFS with LEE011 plus letrozole in pre-defined patient subgroups – from de novo to bone, liver and lung metastases – compared to letrozole alone**

- **LEE011 plus letrozole reduced risk of progression or death by 55% over letrozole alone in de novo patients, and by 54% in patients with three or more metastases – the most aggressive form of the disease**

- **Consistent with overall study population, most adverse events were mild to moderate, identified early through routine monitoring, and generally managed through dose interruption and reduction**

- **FDA granted LEE011 Breakthrough Therapy designation and Priority Review, which may lead to faster access for US patients**

**Basel, December 9, 2016** – Novartis announced today additional analyses from the Phase III MONALEESA-2 study that show LEE011 (ribociclib) plus letrozole significantly prolonged progression-free survival (PFS) across pre-planned patient subgroups with hormone receptor positive, human epidermal growth factor receptor-2 negative (HR+/HER2-) advanced or metastatic breast cancer, including post-menopausal women diagnosed de novo, those with visceral liver and lung metastases, and those with bone-only disease.\(^1\,^2\).

These findings demonstrate the strength of LEE011 plus letrozole in the first-line setting, showing that treatment benefit was evident across all patient subgroups regardless of their disease burden or tumor location, including those patients with aggressive disease. Data will be presented today at the San Antonio Breast Cancer Symposium (SABCS) (Abstracts P4-22-05 and P4-22-16).

“Results from the de novo subgroup of women in the MONALEESA-2 trial establish ribociclib in combination with letrozole as a meaningful treatment option in the first-line setting for this patient population,” said Joyce O’Shaughnessy, MD, Co-Chair, Breast Cancer Research, Texas Oncology-Baylor Charles A. Sammons Cancer Center. “These de novo patients are often diagnosed initially with advanced breast cancer that has already metastasized, so it is critical to start them with treatments that extend time until disease progression.”

“Breast cancer that has metastasized to areas such as the liver or lungs can often be more challenging to effectively treat with current standards of care,” said Howard A. Burris, MD, President, Clinical Operations and Chief Medical Officer, Sarach Cannon. “We have been encouraged by the MONALEESA-2 results because treatment benefit was observed regardless of the number of metastatic sites and was maintained across all subgroups taking ribociclib plus letrozole. Our observations indicate that this novel therapy may be a promising treatment option for many patients living with advanced forms of breast cancer.”
First-line ribociclib + letrozole in patients with de novo HR+, HER2− advanced breast cancer: A subgroup analysis of the MONALEESA-2 trial (Abstract P4-22-05)

A predefined subgroup analysis of the MONALEESA-2 trial evaluated the safety and efficacy of LEE011 plus letrozole versus letrozole alone in 227 patients with de novo advanced breast cancer, defined as disease found to be metastatic at the time of first diagnosis1. Because de novo disease has not been previously treated with systemic treatment for early-stage breast cancer, tumors may exhibit a different disease biology, which could result in varied responses compared to patients who experienced recurrence2. In patients with de novo advanced breast cancer, LEE011 plus letrozole reduced the risk of disease progression or death by 55% over letrozole alone (HR=0.448 [95% CI: 0.267–0.750])1. The 12-month PFS rate was 82% in the LEE011 plus letrozole arm compared to 66% with letrozole alone.

Consistent with the overall study population, most adverse events were mild to moderate in severity, identified early through routine monitoring, and generally managed through dose interruption and reduction1. The most common grade 3/4 adverse events (≥15% of patients with de novo advanced breast cancer; LEE011 plus letrozole vs. letrozole alone) were neutropenia (55.3% vs. 0.9%) and leukopenia (21.1% vs. 0%)1.

First-line ribociclib + letrozole in patients with HR+, HER2− advanced breast cancer presenting with visceral metastases or bone-only disease: A subgroup analysis of the MONALEESA-2 trial (Abstract P4-22-16)

In separate predefined subgroups, 393 patients with advanced breast cancer with visceral metastases and 147 patients with bone-only disease were evaluated as part of the MONALEESA-2 trial. Those with visceral metastases have metastatic growth at the site of the lung or liver, and typically have a poorer prognosis than patients with non-visceral disease2. Results of these analyses show that first-line LEE011 plus letrozole was well tolerated and reduced the risk of disease progression or death by 47% (patients with visceral disease: HR=0.535 [95% CI: 0.385–0.742]) and by 31% (patients with bone-only disease: HR=0.690 [95% CI: 0.381–1.249]) respectively2. Treatment benefit with LEE011 in combination with letrozole was observed regardless of the number of metastatic sites and (HR=0.607 [95% CI: 0.437–0.845] among patients with less than 3 metastases; HR=0.456 [95% CI: 0.298–0.700] among patients with 3 or more metastases)2.

Among patients with visceral metastases the most frequent grade 3/4 adverse events (≥20% of patients; LEE011 plus letrozole vs. letrozole alone) were neutropenia (64.0% vs 1%) and leukopenia (20.8% vs 0.5%)2. Among patients with bone-only disease the most frequent grade 3/4 adverse events (≥20% of patients; LEE011 plus letrozole vs. letrozole alone) were neutropenia (53.6% vs 1.3%) and leukopenia (23.2% vs 1.3%)2.

“These additional results from the MONALEESA-2 study are very promising for women with HR+ advanced breast cancer,” said Bruno Strigini, CEO, Novartis Oncology. “We believe LEE011 could significantly benefit a broad range of women as an initial treatment for metastatic breast cancer and look forward to working with global health authorities to bring this new treatment to patients.”

The MONALEESA-2 study is ongoing to evaluate secondary endpoints, including overall survival. LEE011 received Breakthrough Therapy designation from the US Food and Drug Administration (FDA) in August 2016 and Priority Review in October 2016.

About LEE011 (ribociclib)

LEE011 (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 in a cell, can enable cancer cells to grow and divide too quickly. Targeting CDK4/6 with enhanced precision may play a role in ensuring cancer cells do not grow uncontrollably.
LEE011 is not approved for any indication in any market at this time. LEE011 was developed by the Novartis Institutes for BioMedical Research (NIBR) under a research collaboration with Astex Pharmaceuticals.

About the MONALEESA Clinical Trial Program
Novartis is continuing to assess LEE011 through the robust MONALEESA (Mammary ONcology Assessment of LEE011’s Efficacy and SAFety) clinical trial program, which includes MONALEESA-2, MONALEESA-3, and MONALEESA-7. These trials are evaluating LEE011 in multiple endocrine therapy combinations across a broad range of patients, including men and premenopausal women.

MONALEESA-2 is a Phase III randomized, double blind, placebo controlled, multicenter global registration trial to evaluate the safety and efficacy of LEE011 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.

The trial randomized 668 patients in a 1:1 ratio stratified by the presence of liver and/or lung metastases at 223 clinical trial sites globally. Patients received LEE011 600 mg/daily (three weeks on and one week off), or placebo, in combination with letrozole 2.5 mg/daily.

The primary endpoint of the trial was PFS. Secondary endpoints included: overall survival, overall response rate, clinical benefit rate, health-related quality of life, safety and tolerability.

In MONALEESA-2, the most common grade 3/4 (most severe) adverse events were as follows for LEE011 plus letrozole compared to letrozole alone: neutropenia (60% vs 1%), leukopenia (21% vs 1%), elevated alanine aminotransferase (9% vs 1%), lymphopenia (7% vs 1%) and elevated aspartate aminotransferase (6% vs 1%). The most common all-grade adverse events (≥35% of patients in either arm, regardless of relationship to study treatment) were as follows for LEE011 plus letrozole compared to letrozole alone: neutropenia (74% vs 5%), nausea (52% vs 29%), infections (50% vs 42%), fatigue (37% vs 30%), and diarrhea (35% vs 22%). Nausea, infections, fatigue, and diarrhea were mostly grade 1 or 2.

The MONALEESA-3 trial is a phase III trial evaluating LEE011 in combination with fulvestrant compared to fulvestrant alone in men and post-menopausal women with HR+/HER2- advanced breast cancer who have received no or a maximum of one prior endocrine therapy.

MONALEESA-7, the largest phase III trial of a CDK4/6 inhibitor in this patient population, is investigating LEE011 in combination with endocrine therapy and goserelin compared to endocrine therapy and goserelin alone in pre-menopausal women with HR+/HER2- advanced breast cancer who have not previously received endocrine therapy. Both MONALEESA-3 and MONALEESA-7 are fully enrolled.

About Advanced Breast Cancer
Up to one-third of patients with early-stage breast cancer will subsequently develop metastatic disease. Metastatic breast cancer is the most serious form of the disease and occurs when the cancer has spread to other parts of the body, such as the brain, bones or liver. Advanced breast cancer comprises metastatic breast cancer (stage 4) and locally advanced breast cancer (stage 3). Survival rates for women living with advanced breast cancer are lower than those for women with earlier stage disease. The 5-year relative survival rate for stage 3 breast cancer is approximately 72%, while metastatic (stage 4) breast cancer has a 5-year relative survival rate of approximately 22%.
About Novartis in advanced breast cancer
For more than 25 years, Novartis has been at the forefront of driving scientific advancements for breast cancer patients and improving clinical practice in collaboration with the global community. With one of the most diverse breast cancer pipelines and the largest number 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.

Disclaimer
The foregoing release contains forward-looking statements that can be identified by words such as "Breakthrough Therapy designation," "Priority Review," "may," "will," "exciting," "promising," "believe," "could," "look forward," "ongoing," "continuing," "evaluating," "investigating," "pipelines," "in development," or similar terms, or by express or implied discussions regarding potential marketing approvals for LEE011 or any other compound in the Novartis breast cancer pipeline, or regarding potential future revenues from LEE011 and the other compounds in the Novartis breast cancer pipeline. You should not place undue reliance on these statements. Such forward-looking statements are based on the current beliefs and expectations of management 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 LEE011 or any other compound in the Novartis breast cancer pipeline will be submitted or approved for sale in any market, or at any particular time. Nor can there be any guarantee that LEE011 or the other compound in the Novartis breast cancer pipeline will be commercially successful in the future. In particular, management's expectations regarding LEE011 and such other pipeline compounds could be affected by, among other things, the uncertainties inherent in research and development, including unexpected clinical trial results and additional analysis of existing clinical data; unexpected regulatory actions or delays or government regulation generally; the company's ability to obtain or maintain proprietary intellectual property protection; general economic and industry conditions; competition in general; global trends toward health care cost containment, including ongoing pricing pressures; unexpected safety, quality or manufacturing issues, 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
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, eye care and cost-saving generic pharmaceuticals. Novartis is the only global company with leading positions in these areas. In 2015, the Group achieved net sales of USD 49.4 billion, while R&D throughout the Group amounted to approximately USD 8.9 billion (USD 8.7 billion excluding impairment and amortization charges). Novartis Group companies employ approximately 118,000 full-time-equivalent associates. Novartis products are available in more than 180 countries around the world. For more information, please visit http://www.novartis.com.

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References


3. Hortobagyi G, Stemmer S, Burris H, et al. First-line ribociclib plus letrozole for postmenopausal women with HR+, HER2-, advanced breast cancer: First results from the Phase III MONALEESA-2 study. Presented at the European Society for Medical Oncology (ESMO) Congress, October 8, 2016, Copenhagen, Denmark (abstract # LBA1_PR)


7. Novartis Data on File

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