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Novartis investigational BYL719 (alpelisib) plus fulvestrant consistently improved PFS in patients with PIK3CA mutated HR+/HER2- advanced breast cancer in new SOLAR-1 analyses

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- - BYL719 plus fulvestrant meaningfully prolonged PFS vs fulvestrant alone in patients with PIK3CA mutated HR+/HER2- advanced breast cancer after progression on an aromatase inhibitor or after receiving up to one additional line of therapy1
- - SOLAR-1 is the first Phase III breast cancer trial to demonstrate potential viability of using liquid biopsy to select patients for targeted treatment1
- - Novartis continues to invest in flexible genomic profiling solutions to identify the approximately 40% of HR+ advanced breast cancer patients with a PIK3CA mutation who may benefit from targeted therapy2

EAST HANOVER, N.J., Dec. 6, 2018 /PRNewswire/ -- Novartis today announced additional analysis from the global Phase III SOLAR-1 trial investigating the alpha-specific PI3K inhibitor BYL719 (alpelisib) in combination with fulvestrant in men and postmenopausal women with PIK3CA mutated hormone receptor positive, human epidermal growth factor receptor-2 negative (HR+/HER2-) advanced or metastatic breast cancer.

In SOLAR-1, the addition of BYL719 to fulvestrant nearly doubled median progression-free survival (PFS) in patients with PIK3CA mutated HR+/HER2- advanced breast cancer who progressed on or after an aromatase inhibitor (AI) compared to fulvestrant alone. In this analysis, BYL719 plus fulvestrant also showed consistent clinically meaningful treatment benefit after progression on an AI or after receiving up to one additional line of therapy for advanced breast cancer[1]. These data will be presented today during an oral presentation at the 2018 San Antonio Breast Cancer Symposium (SABCS) (Abstract #GS3-08).

Approximately 40% of patients living with HR+ advanced breast cancer have a PIK3CA mutation, which over activates the PI3K pathway[2]. When activated, the PI3K pathway is associated with tumor growth, resistance to endocrine treatment and a poor overall prognosis[3,4]. Currently there are no approved treatments for breast cancer that specifically target this mutation.

"PIK3CA mutation is the most common actionable alteration in ER+ breast cancer, so it is encouraging to see a meaningfully prolonged PFS with BYL719 combination therapy in patients with PIK3CA mutated breast cancer who progressed on an aromatase inhibitor and who received up to one additional line of therapy prior to treatment with BYL719 plus fulvestrant," said Dejan Juric, MD, Director, Termeer Center for Targeted Therapies, Massachusetts General Hospital Cancer Center. "With the SOLAR-1 trial results, we can confidently say that identifying and targeting PIK3CA mutations is clinically important as we apply the precision oncology paradigm to breast cancer and continuously look for new treatment solutions to extend the lives of patients with this disease."

BYL719 in combination with fulvestrant consistently improved median PFS in patients with PIK3CA mutated HR+/HER2- advanced breast cancer who progressed within 12 months of AI treatment (mPFS: 11.0 months vs 6.8 months for fulvestrant alone) or received up to one additional line of therapy for advanced breast cancer

(mPFS: 10.9 months vs 3.7 months, respectively).

Most adverse events were mild to moderate in severity and generally manageable through dose interruption, dose reductions and medical management. Treatment discontinuation rate due to adverse events in those with a PIK3CA mutation receiving BYL719 plus fulvestrant was 3% compared to 2% for fulvestrant alone. The most frequent all-grade adverse events (≥40%) were hyperglycemia (65% vs 9%), diarrhea (54% vs 11%), nausea (46% vs 20%) and rash (40% vs 6%). The most common grade 3/4 events (≥10%) were hyperglycemia (37% vs <1%) and rash (13% vs <1%)[1].

Mutation status of participants in SOLAR-1 was identified by a clinical trial assay developed by Qiagen*. A significant PFS benefit was observed for BYL719 plus fulvestrant in patients with a PIK3CA mutation regardless of whether the mutation was identified by a tumor tissue test or ctDNA test, suggesting the potential viability of using liquid biopsies to identify PIK3CA mutation status (tissue positive HR=0.65; mPFS 11.0 months; plasma positive HR=0.56; mPFS 10.9 months)[1].

Novartis has entered into agreements with both Qiagen and Foundation Medicine** to develop flexible companion diagnostic solutions for BYL719 that utilize both tumor tissue and plasma sample types.

"Our work to develop an effective PI3K inhibitor started more than two decades ago, and learning from multiple clinical trial experiences, we have been able to advance an investigational targeted therapy for patients with this specific breast cancer," said Samit Hirawat, MD, Head, Novartis Oncology Global Drug Development. "SOLAR-1 is the first breast cancer trial to show potential utility of liquid biopsies. We are excited to collaborate with Qiagen and Foundation Medicine on tissue and plasma tests that, if approved, may help oncologists identify patients who could benefit from BYL719 plus fulvestrant."

The SOLAR-1 trial is ongoing to evaluate secondary endpoints, including overall survival and will be presented and discussed in the future. Overall survival (OS) results were immature at the time of data cut-off after 52% of events (HR=0.73; 95% CI 0.48-1.10; p=0.06; median not estimable vs 26.9 months). The prespecified O'Brien-Fleming stopping boundary was not crossed. Discussions with health authorities regarding the SOLAR-1 data have begun.

About SOLAR-1
SOLAR-1 is a global, Phase III randomized, double-blind, placebo-controlled trial studying investigational BYL719 in combination with fulvestrant for postmenopausal women with PIK3CA-mutated HR+/HER2- advanced or metastatic breast cancer that progressed on or following aromatase inhibitor treatment with or without a CDK4/6 inhibitor[1].

The trial randomized 572 patients. Patients were allocated based on tumor tissue assessment to either a PIK3CA-mutated cohort or a PIK3CA non-mutated cohort. Within each cohort, patients were randomized in a 1:1 ratio to receive continuous oral treatment with BYL719 (300mg once daily) plus fulvestrant (500 mg every 28 days + Cycle 1 Day 15) or placebo plus fulvestrant. Stratification was based on visceral metastases and prior CDK4/6 inhibitor treatment[1].

The primary endpoint is local investigator assessed PFS using RECIST 1.1 for patients with a PIK3CA mutation. Secondary endpoints include but are not limited to overall survival, overall response rate, clinical benefit rate, health-related quality of life, efficacy in PIK3CA non-mutated cohort, safety and tolerability[1].

For the primary SOLAR-1 analysis, mutation status was determined by tumor tissue via polymerase chain reaction (PCR) analysis. Plasma ctDNA samples were also collected at baseline as a secondary endpoint. Plasma ctDNA mutation status of participants in SOLAR-1 was identified by an assay developed by Qiagen.

About BYL719 (alpelisib)

BYL719 is an investigational, orally bioavailable, alpha-specific PI3K inhibitor. In breast cancer cell lines harboring PIK3CA mutations, BYL719 has been shown to potentially inhibit the PI3K pathway and have antiproliferative effects. In addition, cancer cell lines with PIK3CA mutations were more sensitive to BYL719 than those without the mutation across a broad range of different cancers[5].

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.

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About Novartis

Novartis is reimagining medicine to improve and extend people's lives. As a leading global medicines company, we use innovative science and digital technologies to create transformative treatments in areas of great medical need. In our quest to find new medicines, we consistently rank among the world's top companies investing in research and development. Novartis products reach nearly 1 billion people globally and we are finding innovative ways to expand access to our latest treatments. About 125 000 people of more than 140 nationalities work at Novartis around the world. Novartis Pharmaceuticals Corporation, a US affiliate of Novartis, is located in East Hanover, NJ.

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