Novartis International AG
Novartis Global Communications
CH-4002 Basel
Switzerland

http://www.novartis.com

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Novartis investigational BYL719 (alpelisib) plus fulvestrant nearly doubles median PFS in patients with PIK3CA mutated HR+/HER2- advanced breast cancer compared to fulvestrant alone

- *In SOLAR-1 trial, BYL719 plus fulvestrant significantly improved PFS and ORR in these patients, following progression on or after an aromatase inhibitor with or without a CDK4/6 inhibitor, vs. fulvestrant alone*[1]
- *Approximately 40% of HR+ advanced breast cancer patients have a PIK3CA mutation which is associated with poor prognosis; currently there are no treatments that specifically target this mutation*[2]
- *BYL719 is first and only investigational alpha-specific PI3K inhibitor to show superior PFS and predictable, manageable tolerability in patients with PIK3CA mutated HR+/HER2- advanced breast cancer when added to fulvestrant*
- *Data presented today as a late-breaker during the ESMO 2018 Presidential Symposium will be basis of discussions with health authorities worldwide*

Basel, October 20, 2018 – Novartis today announced positive results from the global Phase III SOLAR-1 trial evaluating the investigational alpha-specific PI3K inhibitor BYL719 (alpelisib) in combination with fulvestrant. The trial evaluated the efficacy and safety of alpelisib in postmenopausal women with PIK3CA mutated hormone-receptor positive, human epidermal growth factor receptor-2 negative (HR+/HER2-) advanced or metastatic breast cancer that progressed on or after an aromatase inhibitor with or without a CDK4/6 inhibitor. These data will be presented today at the official press briefing at the European Society for Medical Oncology (ESMO) 2018 Congress and as a late-breaker during the Presidential Symposium (Abstract LBA3_PR).

In patients with PIK3CA mutated HR+/HER2- advanced breast cancer, BYL719 plus fulvestrant demonstrated a median progression-free survival (PFS) of 11 months (95% CI: 7.5-14.5 months) compared to 5.7 months (95% CI: 3.7-7.4 months) for fulvestrant alone. BYL719 plus fulvestrant reduced the risk of death or progression in those patients by an estimated 35% compared to fulvestrant alone (HR=0.65; 95% CI: 0.50-0.85; p<0.001). Overall response rate (ORR), indicating a reduction in tumor size of at least 30%, was more than doubled in patients with measurable disease who received BYL719 plus fulvestrant (36%) compared to those receiving fulvestrant alone (16%)[1].

“The results from SOLAR-1 are the most encouraging observed to date from a trial evaluating a PI3K inhibitor for patients with PIK3CA mutated HR+/HER2- advanced breast cancer,” said Fabrice André, MD, PhD, research director and head of INSERM Unit U981, and professor in the Department of Medical Oncology at Institut Gustave Roussy in Villejuif, France. “These data have the potential to allow physicians to address an unmet need in this patient population by using a biomarker-driven treatment to inform their sequencing decisions.”

PFS treatment effect was consistent across all subgroups, and regardless of whether aromatase inhibitor treatment was given, with or without a CDK4/6 inhibitor. The significant PFS improvement demonstrated with BYL719 plus fulvestrant in patients with a PIK3CA mutation was not observed for patients without the mutation[1].

“We are excited about the meaningful results seen in SOLAR-1 and about the possibility to reimagine what potential treatment options could look like for patients living with PIK3CA mutated HR+/HER2- advanced breast cancer – some of who were previously treated with a CDK4/6 inhibitor,” said Samit Hirawat, MD, Head, Novartis Oncology Global Drug Development. “We are actively engaging in discussions on these results with health authorities worldwide.”

Most adverse events were mild to moderate in severity and generally manageable through dose modifications and medical management. The discontinuation rate of BYL719 plus fulvestrant due to adverse events was 5% compared to 1% for fulvestrant alone. The most common all-grade adverse events (≥30%) were hyperglycemia (64% vs 10%), diarrhea (58% vs. 16%), nausea (45% vs. 22%), decreased appetite (36% vs. 11%) and rash (36% vs. 6%). Of these, the most common grade 3/4 events (≥5%) were hyperglycemia (37% vs. <1%), rash (10% vs. <1%), and diarrhea (7% vs. <1%)[1].

The SOLAR-1 trial is ongoing to evaluate secondary endpoints, including overall survival. Further analysis from SOLAR-1 will be presented and discussed at future medical congresses.

About PI3K inhibition in advanced breast cancer
Studies have established the role of PI3K signaling in several processes for cancer progression, including cell metabolism, growth, survival and motility[3]. Activation of the PI3K pathway in breast cancer is associated with resistance to endocrine therapy, disease progression and poorer prognosis[4,5].

Proteins in the PI3K pathway consist of four smaller parts called isoforms[6]. Approximately 40% of HR+ advanced breast cancer patients have genetic mutations that activate the alpha isoform, called PIK3CA mutations[2]. Mutations in the three other isoforms are typically not associated with advanced breast cancer[6].

Currently, there are no approved PI3K inhibitors for breast cancer.

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 the 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].

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[7].

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. Find out more at www.novartis.com.

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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
+1 862 579 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		