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Chugai In-Licenses PI3K Inhibitor Inavolisib for Breast Cancer with a *PIK3CA* Mutation

- Chugai obtained exclusive development and marketing rights in Japan for PI3K inhibitor inavolisib, an investigational oral therapy for breast cancer with a *PIK3CA* mutation, from Roche.
- Inavolisib, in combination with palbociclib and fulvestrant, received Breakthrough Therapy Designation and Priority Review in the U.S. by the FDA based on positive data of the global phase III INAVO120 study for hormone receptor-positive, HER2-negative breast cancer.
- The inavolisib-based regimen is expected to be a new treatment option for patients with specific breast cancer subtypes

TOKYO, July 31, 2024 -- Chugai Pharmaceutical Co., Ltd. (TOKYO: 4519) announced today that it has concluded a license agreement with F. Hoffmann-La Roche Ltd (hereafter "Roche") [Head Office: Basel, Switzerland. Thomas Schinecker] for inavolisib, a PI3K alpha inhibitor, currently in development for advanced hormone receptor-positive, HER2-negative breast cancer with a *PIK3CA* mutation in combination with palbociclib and fulvestrant. Under the license agreement between Roche and Chugai, Chugai obtained exclusive rights for the development and marketing of inavolisib in Japan. Roche will receive an upfront fee and milestone payments.

"*PIK3CA* mutations are detected in approximately 40%[1] of patients with hormone receptor (HR)-positive breast cancer. Patients with *PIK3CA* mutated HR-positive, HER2 negative advanced BC have a poorer prognosis and thus there remains a significant unmet need for this patient group. Inavolisib, which has shown positive data in global clinical trials, is expected to be a new treatment option for patients with breast cancer. Chugai will work closely with Roche to conduct domestic development in order to bring inavolisib to patients with breast cancer as soon as possible," said Chugai's President and CEO, Dr. Osamu Okuda.

Inavolisib was discovered by Genentech, a member of the Roche Group, and is currently under development for two global Phase III clinical studies in patients with locally advanced or metastatic HR-positive/HER2-negative breast cancer with *PIK3CA* mutations (INAVO120 and INAVO121) and one global Phase III clinical study in patients with *PIK3CA* mutated HER2-positive breast cancer (INAVO122). The INAVO120 study demonstrated that the inavolisib-based regimen (in combination with palbociclib and fulvestrant) more than doubled progression-free survival, reducing the risk of disease worsening or death by 57% compared to palbociclib and fulvestrant alone (15.0 months vs. 7.3 months; hazard ratio [HR]=0.43, 95% CI: 0.32-0.59, $p<0.0001$) in the first-line setting. The inavolisib-based regimen has also been shown to be well tolerated with a manageable safety profile.

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Based on the positive results of the INAVO120 study, inavolisib has been granted Breakthrough Therapy Designation for the treatment of HR-positive, HER2-negative locally advanced or metastatic breast cancer with *PIK3CA* mutations in the first-line setting as well as Priority Review by the U.S. Food and Drug Administration (FDA) for the new drug application with a PDUFA date of November 27, 2024.

Chugai will continue to effectively utilize the research and development resources of the Roche Group to find innovative new drugs so as to satisfy unmet medical needs.

About inavolisib

Inavolisib is an investigational, oral targeted treatment that could provide well-tolerated, durable disease control and potentially improved outcomes for people with *PIK3CA*-mutated, hormone receptor-positive, human epidermal growth factor receptor 2-negative, locally advanced or metastatic breast cancer. Inavolisib has been designed to help minimize the overall burden and toxicity of treatment and is differentiated from other PI3K inhibitors due to its high potency and specificity for the PI3K alpha isoform versus other isoforms, and unique mechanism of action that facilitates the degradation of mutated PI3K alpha.

About the INAVO120 study

The INAVO120 study is a global Phase III, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of inavolisib in combination with palbociclib and fulvestrant versus placebo plus palbociclib and fulvestrant in people with *PIK3CA*-mutated, hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer whose disease progressed during treatment or within 12 months of completing adjuvant endocrine therapy and who have not received prior systemic therapy for metastatic disease.

The study included 325 patients. The primary endpoint is progression-free survival (PFS). Secondary endpoints include overall survival, objective response rate, and clinical benefit rate.

The INAVO120 study met its primary endpoint, extending PFS by 7.7 months compared to the control group, demonstrating the superiority of the combination of inavolisib, palbociclib and fulvestrant (hazard ratio, 0.43 [95% CI = 0.32, 0.59]; $p<0.0001$)[2]. Regarding safety, the incidence of hyperglycemia, diarrhea, stomatitis, nausea, and skin rash was higher in the inavolisib group compared to the control group, but most of these events were Grade 1-2 (incidence of Grade 3-4 events was hyperglycemia: 5.6%, stomatitis: 5.6%, diarrhea: 3.7%, nausea: 0.6%, and skin rash: 0%), confirming that the inavolisib was well tolerated and the safety profile was manageable.

About Hormone Receptor-Positive Breast Cancer

HR-positive breast cancer is the most prevalent type of all breast cancers, accounting for approximately 70%[3] of cases. A defining feature of HR-positive breast cancer is that its tumor cells have receptors that attach to one or both hormones – estrogen or progesterone – which can contribute to tumor growth. People diagnosed with HR-positive metastatic breast cancer often face the risk of disease progression and treatment side effects, creating a need for additional treatment options. The PI3K signaling pathway is

commonly dysregulated in HR-positive breast cancer, often due to activating *PIK3CA* mutations, which have been identified as a potential mechanism of intrinsic resistance to standard of care endocrine therapy in combination with cyclin-dependent kinase 4/6 inhibitors.

Sources

1. Mosele F, Stefanovska B, Lusque A, et al. Outcome and molecular landscape of patients with PIK3CA-mutated metastatic breast cancer. Ann Oncol. 2020;31(3):377-386. Available from: https://www.annalsofoncology.org/article/S0923-7534(19)39094-5/fulltext. Access date: July 2024
2. JhaveriKL, et al. SABCS 2023 (Abstract GS03-13).
3. National Cancer Institute: Surveillance, Epidemiology and Ends Result Program. Cancer Stat Facts: Female Breast Cancer Subtypes. Available from: https://seer.cancer.gov/statfacts/html/breast-subtypes.html. Access date: July 2024

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