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CHUGAI
Roche Group

Translation

New Drug Application Filed for ALK Inhibitor "Alectinib Hydrochloride" for the Treatment of *ALK* Fusion Gene Positive Unresectable, Recurrent / Advanced Non-Small Cell Lung Cancer

October 8, 2013 (Tokyo) - Chugai Pharmaceutical Co., Ltd. [Main Office: Chuo-ku, Tokyo. Chairman & CEO: Osamu Nagayama (hereafter, "Chugai")] announced today that it has filed a new drug application to the Ministry of Health, Labour and Welfare (MHLW) on October 7, 2013, for ALK (Anaplastic Lymphoma Kinase) inhibitor "alectinib hydrochloride (Development code: AF802, Roche Development Code: RG7853, Compound number: CH5424802)" for the treatment of *ALK* fusion gene positive non-small cell lung cancer (NSCLC). On September 13, 2013, alectinib hydrochloride for the treatment of "*ALK* fusion gene positive unresectable, recurrent / advanced non-small cell lung cancer" was designated as orphan drug by MHLW.

Chugai filed the application with the MHLW based on the results from a Japanese phase I/II clinical trial, before the phase III clinical trial results will be available. The clinical trial was conducted at 13 medical institutions in Japan in *ALK* fusion gene positive lung cancer patients with a treatment history of chemotherapy. The clinical trial was conducted in two phases; the phase 1 portion was conducted to evaluate safety and to determine the recommended dose (24 patients), and the phase 2 portion was conducted to evaluate the efficacy and safety of the confirmed recommended dose (46 patients).

As a result, the recommended dose was determined to be 300 mg twice daily in phase 1. Phase 2 was conducted using the recommended dose, and as a result, tumor regression was observed in 43 (93.5%) out of 46 patients. Regarding safety, there were no treatment-related deaths and grade 4 or higher serious adverse reactions assessed according to CTCAE (Common Terminology Criteria for Adverse Events) defined by the Japan Clinical Oncology Group. The most frequently observed grade 3 or higher adverse reactions were neutropenia and increase in creatine phosphokinase (CPK). The incidence of both adverse events was 2 (4.3%) out of 46 patients*.

Based on the results of an American Phase I dose-escalation study of patients with *ALK* fusion gene positive NSCLC whose disease had progressed on crizotinib therapy, in addition to Japanese Phase I/II clinical trial results, alectinib hydrochloride was found to meet the criteria for Breakthrough Therapy Designation by U.S. Food and Drug Administration (FDA) on June 26, 2013. The results of the American study were presented as a late-breaker at the 2013 European Cancer Congress (ECC) in Amsterdam.

As the top pharmaceutical company in the field of oncology in Japan, Chugai will work for the approval to provide patients and medical professionals with new treatment options as soon as possible.

* Seto et al., Lancet Oncol. 14: 590-598 (2013)

About alectinib hydrochloride (AF802, CH5424802)

Alectinib hydrochloride is an oral ALK inhibitor created by Chugai Kamakura Research Laboratories. Alectinib hydrochloride is a drug candidate that matches with the PHC strategy that selects an appropriate drug for patients expected to obtain the therapeutic effect by using biomarkers and/or diagnostic tools. It has been reported that ALK fusion genes are expressed in two to five percent of the patients with NSCLC[1)]. It is considered that the ALK kinase activity is constantly increased in the cells with this fusion gene, and transforms the cells into tumor cells[2, 3)]. Alectinib hydrochloride demonstrates its anti-tumor effect by selectively inhibiting the kinase activity, and inhibiting the proliferation of tumor cells and inducing apoptosis[4)]. The rights to alectinib hydrochloride in overseas countries including Europe and the US have been licensed to F. Hoffmann-La Roche Ltd. [Head Office: Basel, Switzerland. CEO: Severin Schwan], and the clinical trials of alectinib hydrochloride (Roche Development Code: RG7853) are currently ongoing in the US, Europe and other countries.

1) Biomarker committee of The Japan Lung Cancer Society, Guidelines for ALK gene tests in lung cancer patients
2) Soda et al., Nature. 448: 561-566 (2007)
3) Takeuchi et al., Clin Cancer Res. 15: 3143-3149 (2009)
4) Sakamoto et al., Cancer Cell. 19: 679-690 (2011)

About Breakthrough Therapy Designation

Breakthrough Therapy designation is enacted as part of the FDA Safety and Innovation Act (FDASIA) signed into law in July, 2012. This programme is aimed to expedite the development and review of drugs for serious or life-threatening conditions. To be granted Breakthrough Therapy Designation, preliminary clinical evidence demonstrating that the drug may have substantial improvement on at least one clinically significant endpoint over available therapy is required. Although the Breakthrough Therapy Designation is distinct from the FDA's other programmes to expedite drug development and review, all the benefits of fast track designation are available to those who have received a Breakthrough Therapy Designation.