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CHUGAI
Roche Group

Translation

An Anti-Cancer Agent, ALK Inhibitor "Alecensa®," Approved for the Treatment of *ALK* Fusion Gene Positive Unresectable, Recurrent / Advanced Non-Small Cell Lung Cancer

July 4, 2014 (Tokyo) - Chugai Pharmaceutical Co., Ltd. [Main Office: Chuo-ku, Tokyo. Chairman & CEO: Osamu Nagayama (hereafter, "Chugai")] announced today that it obtained approval by the Japanese Ministry of Health, Labour and Welfare (MHLW) on July 4, 2014, for "*ALK* fusion gene positive unresectable, recurrent / advanced non-small cell lung cancer," for the ALK inhibitor, "Alecensa® capsule 20 mg and 40 mg" [generic name: alectinib hydrochloride] (hereafter, "Alecensa®").
Alecensa® is a drug candidate that matches with the personalized healthcare (PHC) strategy proposed by Chugai and F. Hoffmann-La Roche Ltd. [Head Office: Basel, Switzerland. CEO: Severin Schwan] (hereafter, "Roche") that appropriate drugs for patients expected to obtain the therapeutic effect will be selected by using biomarkers and/or diagnostic tools.

On October 7, 2013, Chugai filed a new drug application for approval for *ALK* fusion gene positive unresectable, recurrent / advanced non-small cell lung cancer based on results from a Japanese phase I/II clinical trial (hearafter, "This trial"). The approval was obtained based on data from this trial.
On September 13, 2013, Alecensa® for *ALK* fusion gene positive unresectable, recurrent / advanced non-small cell lung cancer has been designated as orphan drug. Alecensa® was approved in about nine months from the new drug application.

This trial was conducted at 13 medical institutions in Japan in *ALK* fusion gene positive recurrent / advanced non-small cell lung cancer patients with a treatment history of one or more chemotherapy regimens. This trial was consisted of two phases. The phase 1 part was conducted to evaluate safety, tolerability and pharmacokinetic parameters and to determine the recommended dose (24 patients), and the phase 2 part was conducted to evaluate the efficacy and safety of the recommended dose (46 patients), setting the response rate as the primary endpoint.

As a result for the phase 1 part, the recommended dose was determined to be 300 mg twice daily, the maximum dose, since dose limiting toxicity was not observed. Phase 2 part was conducted using the recommended dose, and the response rate was 93.5% (95%CI: 82.1-98.6%).

Regarding safety, there were no treatment-related deaths and/or 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 reaction was neutropenia, and the incidence of the adverse event was 4 out of 58 patients (6.9%) who were treated twice daily 300 mg, the approved dose.

As the top pharmaceutical company in the field of oncology, Chugai is convinced that Alecensa® can contribute to the treatment of patients with *ALK* fusion gene positive unresectable, recurrent / advanced non-small cell lung cancer by providing a new therapeutic option.

About Alecensa® (alectinib hydrochloride)

Alecensa® is an oral ALK inhibitor created at Chugai Kamakura Research Laboratories. 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)]. Alecensa® demonstrates its anti-tumor effect by selectively inhibiting the kinase activity, through inhibition of the tumor cell proliferation and induction of apoptosis[4)].

The rights to Alecensa® in overseas countries including Europe and the US have been out-licensed to Roche, and the clinical trials of Alecensa® (Roche Development Code: RG7853) for the patients with non-small cell lung cancer who have *ALK* mutation and failed crizotinib treatment 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 conditions for approval of Alecensa®

The conditions for approval were given as: “Alecensa® will be handled by doctors, medical institutions and pharmacists, who have sufficient experience in diagnosis and chemotherapy in lung cancer and who can appropriately control risks associated with Alecensa®; a drug use surveillance of all patients who receive Alecensa® should be conducted until the data of a certain number of patients are accumulated.

About the drug use surveillance of Alecensa® (All-case registration surveillance)

For the first 1,000 patients who will receive Alecensa® treatment, data will be collected and analyzed to be reported to the authority. After collecting the data of 1,000 cases, a review and decision will be made to determine whether a new surveillance or further safety measures should be considered.

Results of this surveillance shall be reported to the public in future scientific meetings, as well as to the regulatory authorities.