Innovation all for the patients

CHUGAI

Roche A member of the Roche group

Chugai Obtains Approval of FoundationOne CDx Cancer Genomic Profile as a Companion Diagnostic for Rozlytrek

- First approved next generation sequencing based pan-tumor companion diagnostic in Japan
- Enables physicians to identify patients who will likely benefit from Rozlytrek by detecting *NTRK* gene fusions
- Very rare occurrence of *NTRK* fusion in various adult and pediatric solid tumors and sarcomas

TOKYO, June 27, 2019 -- Chugai Pharmaceutical Co., Ltd. (TOKYO: 4519) announced that the Ministry of Health Labour and Welfare (MHLW) granted an additional approval for FoundationOne® CDx Cancer Genomic Profile as a companion diagnostic for Rozlytrek® (entrectinib) for the treatment of neurotrophic tyrosine receptor kinase (*NTRK*) fusion positive solid tumors on June 26, 2019. The approval enables FoundationOne CDx Cancer Genomic Profile to be used as a companion diagnostic for Rozlytrek by detecting *NTRK* fusion genes (fusion genes between *NTRK*1, *NTRK*2, *NTRK*3 and other genes). Rozlytrek is a ROS1/TRK inhibitor and was approved for the treatment of adult and pediatric patients with *NTRK* fusion positive advanced and recurrent solid tumors on June 18, 2019.

“The conventional concept of cancer treatment focuses on the site where the cancer started. However, it is drastically changing with the emergence of a completely new approach called tumor agnostic treatment; an approach which targets genomic mutations that drive cancers instead of the tumor location in the body. We are proud of the MHLW approval of FoundationOne CDx Cancer Genomic Profile as a companion diagnostic for Rozlytrek which represents this new tumor agnostic treatment approach,” said Dr. Minoru Watanabe, Chugai’s Vice President, Head of Foundation Medicine Unit. “A comprehensive genomic profiling test is especially beneficial in identifying rare gene mutations expressed in multiple cancer types, including *NTRK* gene fusions. Chugai will further strive to provide services to help physicians' swift and appropriate decision making in order to realize patient-centric healthcare.”

Developed by Foundation Medicine Inc., FoundationOne CDx Cancer Genomic Profile is a next-generation sequencing based *in vitro* diagnostic device for the detection and analysis of substitutions, insertion and deletion alterations, and copy number alterations in 324 genes and select gene rearrangements, as well as genomic signatures including microsatellite instability (MSI) and tumor mutational burden (TMB) using DNA isolated from patient’s tumor tissues. As a comprehensive companion diagnostic function, it can be also used as a companion diagnostic for certain molecular-targeted drugs approved in Japan.

As a leading company in the field of oncology, Chugai is committed to realize advanced personalized

CHUGAI PHARMACEUTICAL CO., LTD. Corporate Communications Dept.
1-1, Nihonbashi-Muromachi 2-chome, Chuo-ku Tokyo, 103-8324 Japan
Media Relations Group TEL:+81-(0)3-3273-0881 E-mail:pr@chugai-pharm.co.jp
Investor Relations Group TEL:+81-(0)3-3273-0554 E-mail:ir@chugai-pharm.co.jp

oncology care and contribute to patients and healthcare providers through comprehensive genomic profiling.

[Note]
A press release issued on June 18, 2019: Anti-Cancer Agent Rozlytrek, Approved for the Treatment of *NTRK* Fusion Gene Positive Advanced/Recurrent Solid Tumors
https://www.chugai-pharm.co.jp/english/news/detail/20190618150000_627.html

Approval information The underlined part has been newly added.

<table>
<tr><td>Brand name</td><td>FoundationOne® CDx Cancer Genomic Profile</td></tr>
<tr><td>Nonproprietary name</td><td>・ Gene mutation analysis program (for use in cancer genome profiling)
・ Somatic gene mutation analysis program (for use in assessing anticancer drug indications)</td></tr>
<tr><td>Intended uses or indications</td><td>・ The Product is used for comprehensive genomic profiling of tumor tissues in patients with solid cancers.
・ The Product is used for detecting gene mutations and other alterations to support the assessment of drug indications listed in the table below.
<table>
<tr><th>Alterations</th><th>Cancer type</th><th>Relevant drugs</th></tr>
<tr><td>EGFR exon 19 deletions and EGFR exon 21 L858R alterations</td><td rowspan="3">Non-small cell lung cancer (NSCLC)</td><td>afatinib dimaleate, erlotinib hydrochloride, gefitinib, osimertinib mesylate</td></tr>
<tr><td>EGFR exon 20 T790M alterations</td><td>osimertinib mesylate</td></tr>
<tr><td>ALK fusion genes</td><td>alectinib hydrochloride, crizotinib, ceritinib</td></tr>
<tr><td>BRAF V600E and V600K alterations</td><td>Malignant melanoma</td><td>dabrafenib mesylate, trametinib dimethyl sulfoxide, vemurafenib</td></tr>
<tr><td>ERBB2 copy number alterations (HER2 gene amplification positive)</td><td>Breast cancer</td><td>trastuzumab (genetical recombination)</td></tr>
<tr><td>KRAS/NRAS wild-type</td><td>Colorectal cancer</td><td>cetuximab (genetical recombination), panitumumab (genetical recombination)</td></tr>
<tr><td><u>NTRK1/2/3 fusion gene</u></td><td><u>Solid tumors</u></td><td><u>entrectinib</u></td></tr>
</table></td></tr>
<tr><td>Conditions for approval</td><td>1. The necessary measures must be taken to ensure that the product is used by a physician with adequate knowledge and experience of cancer genomic medicine at a medical institution with a cancer genome profiling-based medical system pursuant to the “Guidelines for the Development of Core Hospitals and Other Facilities for Cancer Genomic Medicine,” and in compliance with the scope and timing of testing</td></tr>
</table>

	stipulated in the most recent guidelines, etc., of relevant academic societies. 2. Appropriate procedures and controls to protect personal information and up-to-date security and privacy protection measures to prevent unauthorized access must be implemented for tumor tissue specimens sent to the laboratory and for information obtained from these specimens. 3. Quality control of input data must be performed as described in the Remarks column of the attached Application Form. Any changes to the quality control of input data as described in the Remarks column of the Application Form (excluding minor changes specified by Order of the MHLW in Article 23-2-5, paragraph (11) of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices ["the Act"]) must be approved by the MHLW Minister pursuant to Article 23-2-5, paragraph (11) of the Act. Note that this approval applies *mutatis mutandis* to the provisions of Article 23-2-5 paragraph (13), Article 23-2-6, and Article 23-2-7 of the Act.

About Rozlytrek

Rozlytrek is an oral tyrosine kinase inhibitor that blocks ROS1 (c-ros oncogene 1) and TRK (neurotrophin receptors) family strongly and selectively. It blocks ROS1 and TRK kinase activity, and inhibits proliferation of cancer cells with *ROS1* or *NTRK* gene fusions. Rozlytrek has been granted Breakthrough Therapy Designation by the U.S. Food and Drug Administration and Priority Medicines designation by the European Medicines Agency for the treatment of *NTRK* fusion gene positive, locally advanced or metastatic solid tumors in adult and pediatric patients who have either progressed following prior therapies or have no acceptable standard therapies. FDA has granted priority review for Rozlytrek for the treatment of *NTRK* fusion-positive solid tumors and *ROS1* fusion-positive non-small cell lung cancer (NSCLC). In Japan, Chugai filed an application for approval of *ROS1* fusion gene positive NSCLC in March 2019.

About *NTRK* fusion gene positive cancer

NTRK fusion gene is an abnormal gene that can be formed by fusing the *NTRK* genes (*NTRK1*, *NTRK2*, *NTRK3* encode TRKA, TRKB, TRKC protein, respectively) and other genes (*ETV6*, *LMNA*, *TPM3*, etc.) as a result of chromosomal translocation[1-3]. The TRK fusion kinase made from *NTRK* fusion gene is thought to promote cancer cell proliferation. There is very rare expression of *NTRK* fusion but in various adult and pediatric solid tumors, including infantile fibrosarcoma, glioma, glioblastoma, diffuse intrinsic pontine glioma (DIPG), congenital mesoblastic nephroma, melanoma, inflammatory myofibroblastic tumor (IMT), uterus sarcoma, soft tissue tumor, gastrointestinal stromal tumor (GIST), secretory carcinoma of breast, secretory carcinoma of salivary gland, cancer of unknown primary, lung cancer, colorectal cancer, appendiceal cancer, breast cancer, gastric cancer, ovarian cancer, thyroid cancer, cholangiocarcinoma, pancreatic cancer, head and neck cancer, and various sarcomas.

[References]

1 Martin-Zanca D, Hughes SH, Barbacid M. A human oncogene formed by the fusion of truncated tropomyosin and protein tyrosine kinase sequences. Nature 1986; 319(6056): 743-8.

2 Martin-Zanca D, Oskam R, Mitra G, Copeland T, Barbacid M. Molecular and iochemical Characterization of the Human trk Proto-Oncogene. Molecular and Cellular Biology 1989; 9(1): 24-33.

3 Lange AM, Lo HW. Inhibiting TRK Proteins in Clinical Cancer Therapy. Cancers 2018; 10: 105.

###