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Anti-Cancer Agent Rozlytrek, Approved for the Treatment of *NTRK* Fusion Gene Positive Advanced/Recurrent Solid Tumors

- Rozlytrek has been approved for the treatment of adult and pediatric patients with *NTRK* fusion gene positive advanced/recurrent solid tumors in Japan ahead of the rest of the world
- In the STARTRK-2 study, 29 out of 51 patients (56.9%) with *NTRK* fusion gene positive solid tumors across ten cancer types responded to Rozlytrek

TOKYO, June 18, 2019 -- Chugai Pharmaceutical Co., Ltd. (TOKYO: 4519) announced today that the new drug application was approved by the Ministry of Health, Labour and Welfare (MHLW) for a ROS1/TRK inhibitor, Rozlytrek® Capsules 100 mg and 200 mg (generic name: entrectinib) (hereafter, Rozlytrek) for the treatment of *NTRK* fusion gene positive advanced and recurrent solid tumors. Rozlytrek was granted both *Sakigake* and orphan drug designations.

“We are pleased that Rozlytrek has been approved in Japan ahead of the rest of the world for the treatment of patients with *NTRK* fusion gene positive solid tumors, an extremely rarely observed condition, to be used regardless of their age and cancer type. It is a milestone in our pursuit of personalized healthcare,” said Dr. Yasushi Ito, Chugai’s Executive Vice President, Co-Head of Project & Lifecycle Management Unit. “Chugai will promote proper use of Rozlytrek as the most advanced personalized medicine to contribute to the treatment of each patient according to genetic mutations.”

This approval is mainly based on the results from the open-label, multicenter, global phase II study (the STARTRK-2 study). Efficacy was evaluated in 51 adult patients with *NTRK* fusion gene positive solid tumors, as well as in five pediatric patients with *NTRK* fusion gene positive solid tumors enrolled in overseas phase I/Ib study (the STARTRK-NG study). In addition, safety was assessed in mainly 339 patients enrolled in three studies consisted of the STARTRK-2 study and two overseas phase I studies (the STARTRK-1 study and the ALKA study).

Efficacy Evaluation

- The response rate per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) estimated by the independent review committee was 56.9% (95%CI: 42.3-70.7%) in the STARTRK-2 study.
- Four out of five patients responded to the drug according to the attending investigator assessment per RECIST v1.1 and Response Assessment in Neuro-Oncology (RANO) criteria in the STARTRK-NG study.

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Age	Tumor type	Assessed by investigator
0	Infantile fibrosarcoma	stable disease
3	Epithelioid glioblastoma	complete response
4	High-grade glioma	partial response
4	Malignant melanoma	partial response
4	Infantile fibrosarcoma	partial response

Safety Summary

- The most commonly reported adverse reactions included fatigue, constipation, dysgeusia, edema, dizziness, diarrhea, nausea, dysesthesia, dyspnea, pain, anemia, cognitive disorders, weight increase, vomiting, cough, blood creatinine increase, joint pain, fever and muscle pain.

	STARTRK-2 (N=206)	STARTRK-1 (N=76)	ALKA (N=57)
All adverse events (AE)	205 (99.5)	75 (98.7)	57 (100)
AE of grade 3 or higher	131 (63.6)	51 (67.1)	27 (47.4)
AE leading to death	13 (6.3)	6 (7.9)	1 (1.8)
Serious AE	81 (39.3)	30 (39.5)	24 (42.1)
AE leading to discontinuation	21 (10.2)	6 (7.9)	2 (3.5)
AE leading to withdrawal	93 (45.1)	39 (51.3)	25 (43.9)
AE leading to dose reduction	72 (35.0)	19 (25.0)	5 (8.8)

[Reference information]

Media release issued by Chugai on December 19, 2018

Title: Chugai Files a New Drug Application for a ROS1/TRK Inhibitor Entrectinib for the Treatment of *NTRK* Fusion-Positive Solid Tumors

https://www.chugai-pharm.co.jp/english/news/detail/20181219170000_579.html

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.

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.

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