LETTER TO THE EDITOR

Have We Found the Key to Unravel Treatment Development Lags for Rare Cancers?: MASTER KEY Project

Hitomi S. Okuma[1] and Yasuhiro Fujiwara[1]

A recent study by Yamashita *et al.*[1] reported the critical delays of anticancer drug development in Japan compared with those in the United States. This so-called "lag" has diminished over time,[2,3] but a significant drug approval lag still exists for rare cancers (an annual incidence of less than 6 cases per 100,000 population). Furthermore, the review time lag by healthcare authorities was significantly shorter for rare cancer drugs, suggesting the main cause of persistent drug approval lag comes from developmental delays.[1]

Digging deeper into the matter of "developmental delays" as Yamashita *et al.* have pointed out, the following should be stated as main causes:

1. Few hospitals carry out precise diagnosis and treatment
2. Molecular background is not well investigated
3. Patient accrual takes time, with consequent high costs
4. Randomized trials are impracticable, making it difficult to set high success rates for approval
5. Industries are rarely interested in such a small market

As most are in the same boat when authors say a new approach for rare cancer is strongly needed, in May 2017, MASTER KEY Project: A Platform (basket/umbrella) Trial with a Registry Study for Rare Cancers,[4,5] was launched by National Cancer Center Hospital. The project is aimed at accelerating drug approval for rare cancers by conquering each of the above elements. It consists of two main parts, the prospective registry study part and the clinical trials part (**Figure 1**). The primary objective of the registry study is to collect consecutive data on biomarker, patient background, and prognosis to build a large-scale database highly reliable for use as historical control data in future clinical trials. Multiple clinical trials are placed under a "master protocol," allowing new trials to be added at any time.

As of February 2019, more than 500 of a planned 200 patients/year have been enrolled in the project. Cancer types include soft tissue sarcomas, tumors of the central nervous system, tumors of skin, salivary gland tumors, bone sarcomas, and others. There are eight ongoing clinical trials. Five are biomarker related, targeting BRAF, mismatch repair deficiency, human epidermal growth factor 2, anaplastic lymphoma kinase, and murine double minute 2. More trials are under planning.

MASTER KEY Project is the largest platform trial included with a registry study focused only on rare cancers. This is a continuous project aimed at accelerating treatment development for rare cancer patients, with clinical trials directed towards new drug approvals. It is important to note

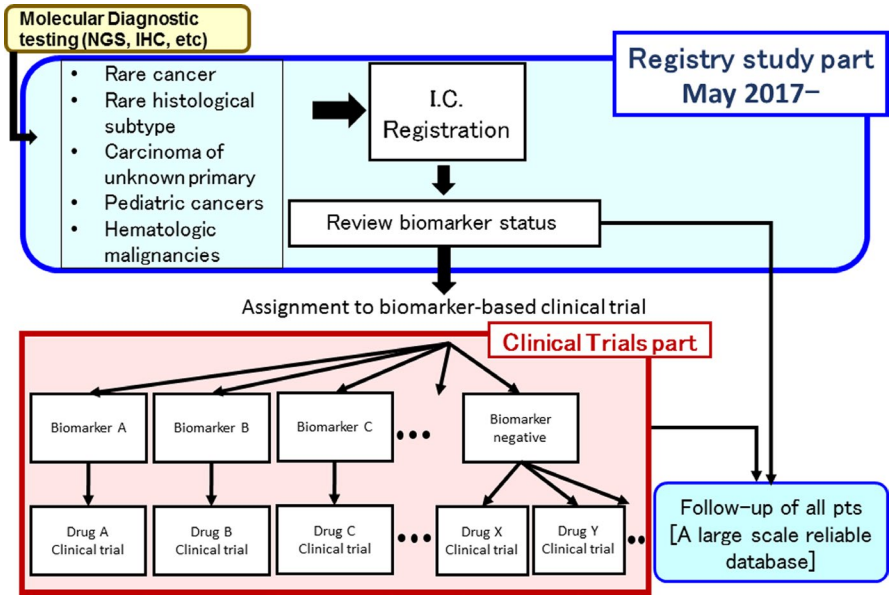

Figure 1 MASTER KEY Project at a glance. The trial is designed as a basket/umbrella trial. Patients with advanced rare cancers/cancers of unknown primary/rare tissue subtypes of common cancers undergoing a molecular diagnostic testing are enrolled into the registry study part. Multiple clinical trials are conducted simultaneously, and drugs are provided by various collaborating industries. Each clinical trial is ordinarily a single-arm study and will enroll 5–20 patients with the appropriate biomarker of interest (regardless of histopathologic cancer type) or appropriate cancer type. Typically, the primary endpoint is response rate (set according to each clinical trial), and a Bayesian method will be used. A biomarker-negative clinical trial will also be available so that all patients have a chance to be enrolled in a clinical trial. I.C., informed consent; IHC, immunohistochemistry; NGS, next-generation sequencing; pts, patients.

that great achievements cannot be reached without an academic industry collaboration approach alongside the sympathetic awareness from the regulatory authorities.

FUNDING
MASTER KEY Project is operated smoothly and fairly, in partnership with the following 11 companies conducting joint research, based on regulations for joint research designated in advance: Astellas Pharma Inc., Eisai Co., Ltd., Ono Pharmaceutical Co., Ltd., Kyorin Pharmaceutical Co., Ltd., Daiichi Sankyo Co., Ltd., Taiho Pharmaceutical Co., Ltd., Takeda Pharmaceutical Co., Ltd., Chugai Pharmaceutical Co., Ltd, Novartis Pharma K.K., Pfizer Inc., Bristol-Myers Squibb Co., Ltd., and Otsuka Pharmaceutical Co., Ltd.

CONFLICT OF INTEREST
Y.F. reports grants and other support from the Japan Agency for Medical Research and Development, grants and other support from the Ministry of Health Labor and Welfare, Japan, during the conduct of the study and other support from Astra Zeneca KK, Daiichi Sankyo Co., Ltd, Taiho Pharmaceutical Co., Ltd, Chugai Pharmaceutical Co., Ltd, Novartis Pharma KK, SRL Inc., and Bristol-Myers Squibb KK outside the submitted work. H.S.O. declared no competing interests for this work.

1. Yamashita, K., Kaneko, M. & Narukawa, M. A significant anticancer drug approval lag between Japan and the United States still exists for minor cancers. *Clin. Pharmacol. Ther.* **105**, 153–160 (2019).
2. Yonemori, K. *et al.* The notorious "drug lag" for oncology drugs in Japan. *Invest. New Drugs* **29**, 706–712 (2011).
3. Fujiwara, Y. & Ono, S. Regulatory review of new therapeutic agents. *N. Engl. J. Med.* **376**, 2598 (2017).
4. Okuma, H. *et al.* MASTER KEY project: a basket/umbrella trial for rare cancers in Japan. *J. Clin. Oncol.* **36** (suppl.), Poster: 165323, Abstract: TPS2598, (2018).
5. National Cancer Center Hospital Japan. Marker assisted selective therapy in rare cancers: knowledge database establishing registry project. <https://www.ncc.go.jp/jp/masterkeyproject/outline/overview/master_key_project_overview.html> (2017).

[1]Clinical Trial Management Section, National Cancer Center Hospital, Tokyo, Japan.
*Correspondence: Yasuhiro Fujiwara (yfujiwar@ncc.go.jp)

Received March 1, 2019; accepted March 5, 2019. doi:10.1002/cpt.1453