To the press

CLIP1-LTK fusion: A novel druggable gene fusion in NSCLC, identified using LC-SCRUM-Asia genomic screening platform ~A step further to precision medicine~

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National Cancer Center Japan
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Lung cancer is one of the most aggressive cancers causing an estimated 1.8 million deaths annually worldwide. Over the last two decades, targeted therapies stratified by oncogenic drivers has remarkably improved therapeutic outcomes in patients with non-small cell lung cancer (NSCLC). However, such oncogenic drivers are not found in 50-60% of NSCLC cases. Therefore, the identification of novel oncogenic kinase alterations should have immediate clinical applications for patients.

In a new publication appearing in *Nature*, a team of researchers and physicians at National Cancer Center Hospital East and Exploratory Oncology Research & Clinical Trial Center, led by Drs. Koichi Goto and Susumu S. Kobayashi, discovered a novel fusion gene "*CLIP1-LTK*" by whole-RNA sequencing using a multi-institutional lung cancer genome screening platform. This platform named LC-SCRUM-Asia was originally established in 2013 to identify patients with lung cancer harboring rare targetable oncogene drivers, and to develop effective molecular-targeted therapies. As of November 2021, more than 14,000 lung cancer patients were enrolled into LC-SCRUM-Asia, which has contributed to the clinical development of various targeted therapies, and corresponding companion diagnostics (CDx) for *ROS1*, *BRAF*, *NTRKs* and *RET*-altered NSCLCs. The *CLIP1-LTK* fusion was present in 0.4% of NSCLC patients in a mutually exclusive manner with other known oncogenic drivers. The team demonstrates that kinase activity of CLIP1-LTK fusion protein is constitutively activated and has transformation potential. In addition, they found that lorlatinib, an ALK inhibitor, inhibited CLIP1-LTK kinase activity, suppressed proliferation, and induced apoptosis in both cell line and murine models. Based on these preclinical findings, one NSCLC patient harboring the *CLIP1-LTK* fusion was treated with lorlatinib, and showed dramatic clinical response.

"This study not only shows that CLIP1-LTK is an oncogenic driver in NSCLC, but patients with CLIP1-LTK fusion can be treated by lorlatinib" said the co-leading author Dr. Hiroki Izumi, MD, PhD, National Cancer Center Hospital East. The other co-leading author Dr. Shingo Matsumoto, MD, PhD at the same institution added, "I believe that this oncogenic driver-targeted therapy will be

lined up in the molecularly-stratified precision medicine for NSCLC. To do so, urgent clinical development of CDx of *LTK* fusion and optimized molecular targeted agents are warranted".

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