

Press Release

Initiation of the 4th-stage industry-academia collaborative Cancer Genome Screening Project for Individualized Medicine in Japan, "SCRUM-Japan"

Introducing latest analysis techniques that can shorten testing time, through promotion of a genetic screening of lung cancer in Asia
(LC-SCRUM-Asia)

Accelerating elucidation of the nature of cancer and development of new treatments, through multi-omics analysis using AI
(MONSTAR-SCREEN-2)

30 June 2021

National Cancer Center Japan

[Key points for presentation]

- The 4th-stage study of Japan's first industry-academia collaborative Cancer Genome Screening Project for Individualized Medicine, "SCRUM-Japan," was launched in June 2021, targeting a wide range of solid tumors.
- "LC-SCRUM-Asia" expands the screening platform for lung cancer to East Asia, and will realize individualized medicine by introducing the latest analysis techniques that shortens testing time.
- "MONSTAR-SCREEN-2" performs molecular profiling based on multi-omics analysis, including RNA and protein expression, to elucidate the nature of cancer and to promote the development of new treatments based on the findings.

The National Cancer Center Japan (President: Hitoshi Nakagama; Chuo-ku, Tokyo) launched in June 2021 the fourth-stage study of Japan's first Cancer Genome Screening Project for Individualized Medicine in advanced solid tumors, "SCRUM-Japan (Cancer Genome Screening Project for Individualized Medicine in Japan)" (project representative: Atsushi Ohtsu, Director of the National Cancer Center Hospital East). During the six years from its establishment in February 2015, more than 20,000 patients with advanced solid tumors have participated in the study. As a result, it has grown into the world's largest genomic screening platform. In addition, the genetic analysis results from patients with advanced solid tumors and their data including treatment courses have been shared among medical institutions and pharmaceutical companies nationwide under a secure environment. This project has also supported the acquisition of regulatory approval for 11 new drugs (13 indications) and 7 *in-vitro* diagnostics, contributing to the early delivery of effective therapeutic drugs and diagnostics to patients nationwide.

The third-stage study of SCRUM-Japan, which ended in March 2021, was conducted as two major projects: "LC-SCRUM-Asia" which aims to develop new drugs in East Asia, by conducting a

large-scale screening of lung cancer patients with rare genomic alterations with medical institutions in East Asia, and "MONSTAR-SCREEN," in which genetic analyses (liquid biopsy) using blood and gut microbiome analysis*¹ were performed, expanding the study population to a wide range of solid cancer patients, such as head and neck cancer, urological cancer, gynecological cancer, breast cancer and skin cancer, in addition to focusing on gastrointestinal cancer through to the second stage*².

In the 4th-stage SCRUM-Japan, "LC-SCRUM-Asia" aims to realize individualized medicine in East Asia, enhancing the international competitiveness of Asia with Southeast Asian countries, such as Thailand and Malaysia, expanding the international screening platform for lung cancer that has been developed in Japan and Taiwan since March 2019, and promoting the development of gene-targeting therapeutic drugs and diagnostics. In addition, "MONSTAR-SCREEN," newly named as "MONSTAR-SCREEN-2," will elucidate the nature of cancer and promote the development of new treatments based on the findings not only by evaluating gene aberrations using DNA analysis, but also by performing molecular profiling using multi-omics analysis*³, including RNA and protein expression.

"SCRUM-Japan" will continue to accelerate its activities to promptly deliver effective treatments to appropriate patients.

[Summary of the 4th-stage project]

◆ LC-SCRUM-Asia (Lung Cancer Genomic Screening Project for Individualized Medicine in Asia) (Former : LC-SCRUM-Japan)
Project representative: Koichi Goto, Chief of the Department of Thoracic Oncology, National Cancer Center Hospital East



① Expansion of the genetic screening platform to incorporate other Asian countries

In Japan, with the wide use of comprehensive genetic analysis using the next-generation sequencing (NGS)*⁴, individualized medicine has begun in earnest. However, individualized medicine in Asian countries is still in development. To advance the development of treatment for genomic alterations that occur frequently in Asians, it is necessary to build a screening platform for widely collecting gene analysis data from Asians. The 4th-stage LC-SCRUM-Asia will contribute to the realization of individualized medicine in Asia and to treatment development, by using the screening platform in which Taiwan participated during the third stage, and also by expanding it to incorporate Southeast Asian countries, such as Thailand and Malaysia.

② Search for comprehensive biomarkers that can be analyzed while keeping the turn-around time (TAT) short

The introduction of NGS has made it possible to analyze many genes at one time. However, the fact that TAT is 2 to three weeks under the current situation poses a barrier to linking the analysis results with treatment, especially the initial treatment. LC-SCRUM-Asia has introduced, since its

third stage, a next-generation sequencing analysis system "Ion Torrent™ Genexus™ System (Genexus) / Ion Torrent™ OncoPrint™ Precision Assay (OPA)," which can shorten the TAT to 3 to five days and detect 50 types of cancer genomic alterations. In addition, at the fourth stage, the project has introduced the "AmoyDx master panel® (AMP)," a large NGS panel that can even analyze gene expression. AMP targets 571 genes in analyses using DNA and 2,660 genes in analyses using RNA. AMP enables, in a short TAT, not only the comprehensive search for genomic alterations, which can serve as therapeutic targets, but also the analysis of biomarkers for predicting the therapeutic effects of immune checkpoint inhibitors. Analysis results are expected to contribute to the development of new treatments.

③ Introduction of a new NGS panel (Genexus/OPA Liquid System) using blood

Although remarkable advances have been made in genome analysis technology in recent years, one of the challenges in cancer genomic medicine is the physical and mental burden (invasion) imposed on patients during sample collection. Therefore, simpler and less invasive genetic testing using blood (liquid biopsy) has been developed recently. In the conventional liquid biopsy, genomic alterations occurring in tumors are detected by analyzing tumor-derived DNA present in the blood of cancer patients. However, the problem is that the detection sensitivity of fusion genes, which are usually tested using RNA, is extremely low. In addition, many liquid biopsy-based assays have been performed overseas and required complex logistics for transporting specimens, etc. To address this issue, LC-SCRUM-Asia has introduced "Genexus/OPA Liquid System," which allows to conclude the liquid biopsy assays in Japan, for the fourth stage. The Genexus/OPA Liquid System rapidly analyzes 50 cancer-related genes, using DNA and RNA in blood. It is expected to efficiently detect fusion genes, for which the sensitivity of the conventional blood gene analysis is low. By introducing this new blood analysis system, we aim to develop diagnostics of high analysis accuracy with reduced burden on patients.

④ Promotion of clinical studies by directly providing patients with genetic analysis results and clinical trial information

To date, more than 13,000 lung cancer patients have been enrolled in LC-SCRUM-Asia, and contributed to the development of therapeutic agents for various genomic alterations. Currently, however, the proportion of patients enrolled in an applicable clinical study is still as low as about 5% of those in whom genomic alterations are detected. At the fourth stage, we are planning to provide patients enrolled in LC-SCRUM-Asia with genetic analysis results and relevant clinical study information. We intend to promote the development of treatments and diagnostics, with the cooperation of patients, by raising their awareness about participation in clinical studies.

◆ MONSTAR-SCREEN-2 (Max Onco-Network with STARS-SCREEN-2, the world's largest cancer research network created with young physicians who will be the stars of future cancer treatments) (former: GI-SCREEN-Japan, MONSTAR-SCREEN)



Project representative: Takayuki Yoshino, Chief of the Department of Gastrointestinal Oncology, National Cancer Center Hospital East

① Elucidation of the nature of cancer by multi-omics analysis using AI (artificial intelligence)

Cancer cells are indicated to harbor various abnormalities that cannot be detected only from DNA changes. To elucidate the nature of cancer, molecular profiling is required using multi-omics analysis including not only the assessment of genomic alterations on a DNA level, but also RNA sequencing and proteomics.

MONSTAR-SCREEN-2 has newly introduced a multi-omics assay from Caris Life Sciences, MI Profile that uses DNA and RNA extracted from tumor tissues, in order to perform whole exome sequencing (WES)^{*5} and whole transcriptome sequencing (WTS)^{*6}. Furthermore, immunohistochemistry (IHC)^{*7} is performed to evaluate protein expression and localization in clinical specimens. Thus, not only cancer cells, but also various cells and markers that make up the tumor immune microenvironment, are comprehensively analyzed. By introducing multi-omics analysis, which goes beyond the conventional genome analysis, we would like to deepen our understanding of highly diverse and complex cancers, aiming to elucidate the nature of cancer and to develop new treatments based on the obtained results.

In addition, we employ a multi-omics assay from Caris Life Sciences, MI Profile™ Blood," which analyzes circulating nucleic acids (cNA) extracted from blood. We will assess spatiotemporal heterogeneity by performing WES/WTS of circulating nucleic acids (cNA) before and after drug therapy, and also assess the mechanism of treatment resistance.

The multi-omics analysis produces enormous amounts of data. Therefore, AI-based analysis will be applied for information processing to handle a large amount/variety of data and extract the essence of the nature of cancer. By identifying biomarkers that more closely reflect the nature of cancer and therapeutic effects in a multi-layered manner, we will proceed with the study toward the realization of individualized medicine optimally tailored to each patient.

② International data integration for establishment of individual medicine

Since February 2021, "MONSTAR-SCREEN" has participated in the International Cancer Genome Consortium – Accelerating Research in Genomic Oncology "ICGC-ARGO"^{*8}. ICGC-ARGO is an international project to tackle important and unsolved issues for cancer eradication, by collecting genome sequencing data from 100,000 cancer patients and simultaneously analyzing them with abundant clinical information. The participation of MONSTAR-SCREEN in ICGC-ARGO is expected to accelerate the research on cancer etiology and cancer control and to contribute to

the development of cancer genomic medicine. Under the continued international cooperation, we aim to cooperate in the construction of a large database of genome analysis data combined with high quality clinical information, and also to develop new cancer diagnosis and treatment techniques at the world level by using the database.

[Achievements up to the third-stage project]

1) Achievements in company-sponsored or investigator-initiated clinical trials

Clinical and genomic data from more than 20,000 cancer patients were obtained. Of these patients, those with a rare frequency of genomic alterations were enrolled in investigator-initiated or company-sponsored clinical trials. Among 30 studies that reported the final results, we supported regulatory approval for 11 new drugs (13 indications). We also supported regulatory approval for 7 types of *in-vitro* diagnostics based on the gene analysis data collected by SCRUM-Japan.

2) Construction of a national network of investigator-initiated clinical trials and a clinical genome data sharing system across industry and academia

Currently, 21 investigator-initiated clinical trials using the SCRUM-Japan's genome screening platform are in progress at 9 institutions in Japan. Online clinical genome data are shared and secondarily used among 66 academic facilities and 17 pharmaceutical companies. The use of those data in research in participating medical institutions is being accelerated.

3) New drug discovery/clinical development through industry-academia sharing of clinical and genomic data

The use of the SCRUM-Japan database has led to the discovery of new resistance mechanisms and therapeutic targets, and the initiation of new investigator-initiated clinical trials. Company-sponsored clinical trials for new drug development are also in progress by domestic companies sharing the database.

4) Practical use of liquid biopsy

Since 2018, we have been working on the research of liquid biopsy to perform genetic screening of tumors using patients' blood. Compared with the conventional genetic screening using tumor tissues, the time to obtain test results has been shortened. This enables a greater number of patients to participate in company-sponsored or investigator-initiated clinical trials of new drugs. In addition, obtaining information on cancer genomic alterations in real time allows us to promote new studies and development of therapeutic drugs.

[Summary of the 4th-stage project]

- ◆ Planned period: June 2021 to March 31, 2024 (subject to changes)
- ◆ Study subjects: Advanced solid cancer patients with the following:

Lung cancer, colorectal cancer (including rectal and colon cancers), gastric cancer, esophageal cancer, hepatocellular carcinoma, biliary tract cancer (including gallbladder cancer and intrahepatic bile duct cancer), pancreatic cancer, small intestinal cancer (including duodenal cancer), appendiceal cancer, anal cancer, primary gastrointestinal neuroendocrine tumor or carcinoma, gastrointestinal stromal tumor (GIST), breast cancer, skin cancer (malignant melanoma, Merkel cell cancer), head and neck cancer, prostate cancer, renal pelvis cancer, urinary tract cancer, bladder cancer, renal cell cancer, ovarian cancer, fallopian tube cancer, peritoneal cancer, uterine body cancer, cervical cancer, malignant bone and soft tissue tumor, and cancer of unknown primary origin

◆ Planned sample size

LC-SCRUM-Asia: 5,000 patients with lung cancer

MONSTAR-SCREEN-2: 2,750 patients with advanced solid cancers other than lung cancer

◆ Participating companies (as of June 2021)

Amgen K.K., Medical & Biological Laboratories Co., Ltd., Eisai Co., Ltd., Ono Pharmaceutical Co., Ltd., Kyowa Kirin Co., Ltd., Daiichi Sankyo Co., Ltd., Sumitomo Dainippon Pharma Co., Ltd., Taiho Pharmaceutical Co., Ltd., Takeda Pharmaceutical Company Ltd., Chugai Pharmaceutical Co., Ltd., Nippon Boehringer Ingelheim Co., Ltd., Novartis Pharma K.K., Bayer Yakuhin Ltd. and Janssen Pharmaceutical K.K.

◆ Participating medical institutions (as of June 2021)

LC-SCRUM-Asia: 158, MONSTAR-SCREEN-2: 31

[Glossary]

*1 Gut microbiome

Hundreds of species of intestinal bacteria reside in the human large intestine, forming a population called the gut microbiome.

*2 Initiation of the 3rd-stage Cancer Genome Screening Project for Individualized Medicine in Japan, "SCRUM-Japan," September 12, 2019.

https://www.ncc.go.jp/jp/information/pr_release/2019/0912_1/index.html

*3 Multi-omics analysis

A method to perform all of the following analyses at one time: gene analysis (genomics), RNA analysis (transcriptomics), protein analysis (proteomics), etc. The term "mics (-omics)" means comprehensive analysis.

*4 Next Generation Sequencing (NGS)

An analyzer that reads a large amount of DNA (gene) base sequences at high speed.

*5 Whole exome sequencing (WES)

A method for comprehensively analyzing the exon regions (protein-coding regions) of all genes

(about 22,000 genes)

*6 Whole transcriptome sequencing (WTS)

A method for comprehensively analyzing RNAs transcribed from all genes (about 22,000 genes).

*7 Immunohistochemistry (IHC)

A method for detecting target antigens using specific antibodies, in order to visualize the presence and localization of target components in tissue sections under a microscope.

*8 Participation of MONSTAR-SCREEN in the International Cancer Genome Consortium (ICGC-ARGO) May 17, 2021.

https://www.ncc.go.jp/jp/information/pr_release/2021/0517/index.html

[Contact information]

◆ Inquiries from patients

SCRUM-Japan Office, National Cancer Center Hospital East

TEL: 04-7133-1111 E-mail: scrum_office@east.ncc.go.jp

How to participate: http://www.scrum-japan.ncc.go.jp/patient_participate/

◆ Media inquiries:

Office of Public Relations, Strategic Planning Bureau, National Cancer Center (Kashiwa Campus)

TEL: 04-7133-1111 FAX: 04-7130-0195 E-mail: ncc-admin@ncc.go.jp