News Release

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Sysmex Corporation

Sysmex Presents Academic Report Related to the Clinical Utility of RAS Gene Mutation Testing for Colorectal Cancer Using Liquid Biopsy

Details of Report on Clinical Utility of OncoBEAM™ RAS CRC Kit presented at the American Society of Clinical Oncology Gastrointestinal Cancers Symposium 2020 (ASCO-GI 2020)

Sysmex Corporation (HQ: Kobe, Japan; Chairman and CEO: Hisashi Ietsugu) provides notice that Dr. Yu Sunakawa, Associate Professor in the Department of Clinical Oncology at the St. Marianna University School of Medicine, presented his research findings at the American Society of Clinical Oncology Gastrointestinal Cancers Symposium 2020 (ASCO-GI 2020), held in San Francisco, California, the United States, from January 23 to 25, 2020. This research involved examining the utility of *RAS* gene[1] mutation testing for colorectal cancer with liquid biopsy[2] using BEAMing technology[3] (OncoBEAM™ RAS CRC Kit) to help guide treatment decisions for the re-challenge of anti-EGFR monoclonal antibody therapy in patients with metastatic colorectal cancer (mCRC).

This research involved collaborative biomarker studies (JACCRO CC-08[4] and CC-09AR[5]) conducted in cooperation with Sysmex and the Japan Clinical Cancer Research Organization (Location: Tokyo, Japan; Director: Dr. Fumimaro Takaku; “JACCRO”).

The overexpression of epidermal growth factor receptors (EGFR) on the surface of colorectal cancer cells is known to promote their cellular proliferation. Numerous studies have shown that anti-EGFR monoclonal antibody drugs are effective in preventing the proliferation of these cancer cells; however, this therapy is not effective in patients whose colorectal tumors harbor *RAS* mutations. Accordingly, decisions on the administration of anti-EGFR monoclonal antibody drugs are usually made by assessing *RAS* gene mutations using resected tissues.

In recent years, clinical studies have actively investigated re-challenge of mCRC patients with anti-EGFR therapy in an effort to improve the prognosis of patients who had previously responded to 1st-line anti-EGFR therapy treatment, but whose disease progressed during subsequent courses of therapy in which anti-EGFR drugs were eliminated. In the process, it was reported that no clinical benefit by the re-challenge of anti-EGFR monoclonal antibody drugs on patients determined to have wild-type *RAS* genes at the time of initial administration of anti-EGFR monoclonal antibody drugs might be due to the emergence of *RAS* mutations during anti-EGFR therapy (Source: *JAMA Oncol.* 2019;5(3):343-350).

Sysmex and JACCRO’s objective of this clinical research (JACCRO CC-08/09AR studies: retrospective[6] study), was to examine a possible relationship between clinical outcomes of the anti-EGFR re-challenge and the patient’s plasma *RAS* gene mutation status at the time of rechallenge. This analysis was accomplished via liquid biopsy using OncoBEAM™ RAS CRC Kit to determine the status of *RAS* gene mutations in circulating tumor DNA of mCRC patients prior to and during anti-EGFR therapy re-challenge. Results showed that the re-challenge of mCRC patients with anti-

EGFR monoclonal antibody drugs improved the prognosis (progression-free survival[7] and overall survival[8]) more for *RAS* wild-type patients than for *RAS* mutant patients. The results of this research, presented at ASCO-GI 2020, indicated the clinical utility of liquid biopsy for *RAS* gene mutation testing for colorectal cancer when deciding on the re-challenge of anti-EGFR monoclonal antibody drugs.

Since obtaining tumor tissue biopsy samples from metastatic sites place undue physical burden on patients, the liquid biopsy approach to determine *RAS* mutation status from blood samples is clearly a less invasive approach. Moreover, a liquid biopsy *RAS* mutation test gives the most timely *RAS* mutation result at the time of recurrence and anti-EGFR re-challenge, rather than relying on data obtained from testing archival tumor tissue samples. Going forward, progress on prospective[6] studies to verify the effectiveness of decisions to re-challenge mCRC patients with anti-EGFR monoclonal antibody drugs informed by OncoBEAM™ RAS CRC Kit for *RAS* gene mutation testing is expected to contribute to the clinical implementation and utility of this test in the re-challenge treatment of anti-EGFR monoclonal antibody drugs.

By delivering new methods for diagnosing cancer to patients as quickly as possible, Sysmex is taking the lead in the global realization of personalized medicine and contributing to the enhancement of patients' quality of life and advances in healthcare.

Data Sheet

Presented at:	American Society of Clinical Oncology Gastrointestinal Cancers Symposium 2020 (ASCO-GI 2020)
Date:	January 23–25, 2020
Poster number:	166
Title:	*RAS* status in circulating-tumor DNA (ctDNA) and outcomes during rechallenge treatments with anti-EGFR antibodies in metastatic colorectal cancer (mCRC)

The study was performed on the association between the presence of *RAS* gene mutations (*RAS* wild-type patients (10 cases) and *RAS* mutant patients (6 cases)) and clinical outcome for patients receiving rechallenge with Cetuximab or Panitumumab (16 cases). Prior to re-challenge of anti-EGFR monoclonal antibody drugs, OncoBEAM™ RAS CRC Kit was used to measure *RAS* gene mutations in plasma samples.

The results showed significantly longer survival for *RAS* wild-type patients than for *RAS* mutant patients, both for progression-free survival (4.7 months for *RAS* wild-type patients and 2.3 months for *RAS* mutant patients) and overall survival (16.0 months for *RAS* wild-type patients and 3.8 months for *RAS* mutant patients). These results point to the clinical utility of *RAS* gene testing using liquid biopsy prior to re-challenge of anti-EGFR monoclonal antibody drugs and are expected to contribute to the determination of more appropriate treatment methods.

Terminology

1 *RAS* gene:
As the likelihood is high that patients with *RAS* gene (*KRAS*/*NRAS* gene) mutations will not benefit (prolongation of life, tumor reduction) from the administration of anti-EGFR drugs, companion diagnostics may be performed to treat the gene mutation first.

2 Liquid biopsy:
Similar in performance to a biopsy, which is carried out on a sample taken from tissue such as tumors, but which attempts to reduce the burden on the patient by using blood tests.

3 BEAMing technology:
This gene analysis method combines ultrahigh-sensitivity PCR and flow cytometry technologies. BEAMing technology is used to capture individual DNA molecules with magnetic particles in droplets measuring several microns in diameter and then detecting the amplification of the DNA molecules on the magnetic particles.
OncoBEAM RAS CRC Kit based on BEAMing technology is an in vitro diagnostic test (*in vitro* diagnostic medical device registration number: 30100EZX00010000, MHLW-approved on July 19, 2019, Manufactured and supplied by Sysmex) for detecting *RAS* mutations in ctDNA extracted from the plasma of colorectal cancer patients.

4 JACCRO CC-08AR test:
Biomarker research related to a Phase II clinical trial on the re-challenge of Cetuximab for tertiary treatment of *KRAS* gene wild-type unresectable, advanced, recurrent colorectal cancer to patients with a history of treatment with the anti-EGFR monoclonal antibody drug Cetuximab

5 JACCRO CC-09AR test:
Biomarker research related to a Phase II clinical trial on the re-challenge of Panitumumab for tertiary treatment of *KRAS* gene wild-type unresectable, advanced, recurrent colorectal cancer to patients with a history of treatment with the anti-EGFR monoclonal antibody drug Panitumumab

6 Prospective/retrospective:
A prospective (forward-looking) study refers to an epidemiological survey method indicating that information is to be gathered from the start of the survey forward into the future. By contrast, retrospective (backward-looking) studies indicate the gathering of patient information retroactive from the start of the study.

7 Progression-free survival:
The period during treatment (following treatment) when cancer is not progressing and the condition is stable.

8 Overall survival:
The period of a patient’s survival, beginning with the registration date of a clinical study.