

New *in vitro* diagnostic product which can simultaneously detect multiple *RAS* gene mutations in colorectal cancer

*The IVD test kit created by National Cancer Center and G&G Science contributes to achieving more precise, individualized treatment by enabling clinicians to prescribe medications only for patients who really need them.*

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National Cancer Center  
G&G Science Co., Ltd.

#### Key points

- Anti-EGFR antibody treatment is ineffective for colorectal cancer with *KRAS* gene exon 2 mutation. Therefore, clinicians need to test for the presence of the mutation prior to administering anti-EGFR antibodies.
- Recently reported *RAS* gene mutations outside of *KRAS* exon 2 also correlate with poor therapeutic effects of anti-EGFR treatment. Existing *in vitro* diagnostics (IVDs) cannot detect those mutations.
- The new *in vitro* diagnostic product, MEBGEN™ RASKET KIT, is a simple and low-cost IVD test kit which simultaneously detects multiple *RAS* (*KRAS* and *NRAS*) gene mutations. It was developed through academic-industry partnership and obtained approval for the manufacture and sales in Japan by the Ministry of Health, Labour and Welfare of Japan on January 27, 2015, following CE mark approval in 2014.
- This IVD test kit enables more precise, individualized treatment by acquiring relevant genetic information of each colorectal cancer patient.

National Cancer Center (President: Tomomitsu Hotta, Head Quarters: Chuo-ku, Tokyo, hereinafter referred to as NCC) and G&G Science Co., Ltd. (President: Yukiko Abe, Head Quarters: Fukushima City, hereinafter referred to as G&G Science) successfully created MEBGEN™ RASKET KIT (RASKET KIT), a new IVD test kit to detect *RAS* gene mutations in unresectable advanced/recurrent colorectal cancer, prior to administering anti-epidermal growth factor receptor (EGFR) antibodies. RASKET KIT was commercialized by Medical & Biological Laboratories Co., Ltd. (President: Jun Sasaki, Head Quarters: Nagoya City, hereinafter referred to as MBL).

RASKET KIT is the Japan's first IVD test kit which can detect mutations in exon 2 (codon 12, 13), exon 3 (codon 59, 61), and exon 4 (codon 117,146) in both *KRAS* and *NRAS* genes in a single assay. MBL obtained CE mark approval in June, 2014 to market the product in Europe, and regulatory approval in Japan on January 27, 2015, as stated above.

The research group consisting of nine medical institutions in Japan carried out a comprehensive genetic analysis (BREAC trial) to identify potential new biomarkers of various mutations outside of *KRAS* exon 2 which correlate with poor therapeutic effects of anti-EGFR treatment on unresectable, advanced, recurrent colorectal cancer. Based on the results and findings from the BREAC trial and other studies, G&G Science and the multicenter study group led by Dr. Atsushi Ohtsu (Director of Exploratory Oncology Research & Clinical Trial Center), Dr. Katsuya Tsuchihara (Chief of Division of Translational Research, Exploratory Oncology Research & Clinical Trial Center), and Dr. Takayuki Yoshino (Chief of Department of Gastrointestinal Oncology, Hospital East) developed RASKET KIT which can simultaneously detect those newly found *RAS* mutations. The research and development was supported by strategic SME/venture development grant funding (2011) from the Japan Science and Technology Agency's A-STEP program.

“None of existing diagnostic kits could simultaneously detect multiple *RAS* gene mutations. RASKET KIT helps clinicians correctly select candidate patients for anti-EGFR antibody treatment and thus provide more appropriate and individualized treatments.” said Dr. Takayuki Yoshino, the principal investigator of the clinical evaluation trial for RASKET KIT.

## **Background**

It has been revealed that therapeutic effects of anti-EGFR antibodies were poor in patients with *KRAS* gene mutation in exon 2 (codons 12 and 13). Therefore, administration of anti-EGFR antibodies is not recommended for patients with the mutation. In addition, recently conducted retrospective *RAS* mutation analyses in several clinical trials indicated that existence of *KRAS* exon 3 or 4, or *NRAS* exon 2, 3, or 4 mutations also correlates with poor therapeutic effects of add-on treatment of panitumumab and cetuximab (both are anti-EGFR antibodies). Currently, it is a common view among colorectal cancer specialists that anti-EGFR antibodies should not be administered to patients with *RAS* gene mutations. However, there have been no IVD test kits until today to detect those *RAS* gene mutations in clinical practice. During this period, the research group for BREAC study identified that *RAS* gene mutations outside of *KRAS* exon 2 can work as predictive markers of therapeutic effects of anti-EGFR antibodies.

## **Research & development methodologies and results**

### **1) Collection of clinical specimens and search/identification of biomarkers (BREAC trial)**

In the BREAC trial, clinical specimens were collected at seven medical institutions in Japan from patients with unresectable advanced colorectal cancer who had received cetuximab, an anti-EGFR antibody. Eighty-six specimens in these were used for a comprehensive exon analysis to identify potential new target genes to test. Several new biomarker candidates were found and then validated with the specimens collected from other 150 cases. The research group confirmed that patients for whom anti-EGFR treatment was ineffective have *KRAS* exon 3 or 4, or *NRAS* exon 2, 3, or 4 mutations.

## **2) Development of RASKET KIT and conducting RAS KEy Testing (RASKET) study**

Based upon the results from BREAC trial, G&G Science started development of a new diagnostic kit by applying xMAP<sup>®</sup>-based PCR-rSSO method, and finally created RASKET KIT which is a simple and low-cost test kit to detect 48 types of *RAS* mutations using only 50 ng DNA.

The development was then handed over to MBL which performed a study at six medical institutions to clinically evaluate RASKET KIT (RAS KEy Testing (RASKET): UMIN ID UMIN000011784 – Clinical Evaluation of New Luminex<sup>®</sup>-Based *RAS* Gene Mutation Testing Reagent <http://www.umin.ac.jp/ctr/index.htm>). The study demonstrated that the test results of RASKET KIT were highly consistent with those of existing genetic assays including direct sequencing and scorpion-ARMS method. MBL applied approval of MEBGEN<sup>™</sup> RASKET KIT by the Ministry of Health, Labour and Welfare (MHLW) of Japan in January 2014, and acquired approval on January 27, 2015, following CE mark approval in 2014. This is the Japan's first IVD test kit to simultaneously detect exon 2, 3, and 4 mutations both in *KRAS* and *NRAS* genes. RASKET study data has been published in *EBioMedicine*, an Elsevier journal published with editorial support from Cell Press and The Lancet.

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