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To the Press

World-first confirmation of standard treatment for RAS wild-type colorectal cancer

—Paper published in JAMA—

April 19, 2023

National Cancer Center

Yokohama City University

Highlights

- A prospective clinical trial[*1] demonstrated the statistically significant improvement of an anti-EGFR antibody (Panitumumab)[*2] in combination with mFOLFOX6 in patients with RAS wild-type[*3], and left-sided primary tumor (descending colon, sigmoid colon, rectosigmoid, rectum) and tumors throughout the entire colorectum (left-sided or right-sided [cecum, ascending colon, transverse colon]).
- Based on the results of this study, indicated that the use of the anti-EGFR antibody may be recommended as first-line therapy for patients with RAS wild-type metastatic colorectal cancer and left-sided primary tumors.
- The results of this study have been published in the high-impact peer-review scientific journal as *Journal of the American Medical Association* (JAMA).

Summary

The research group comprising the National Cancer Center (President: Hitoshi Nakagama, Chuo-ku, Tokyo); Hospital East (Director: Atsushi Ohtsu, Kashiwa-shi, Chiba); Deputy Director, Takayuki Yoshino, Yokohama City University (President: Michiko Aihara, Yokohama-shi, Kanagawa); Yokohama City University Medical Center (Director: Hideya Sakakibara, Yokohama-shi, Kanagawa); and Department of Surgery, Gastroenterological Center Associate Professor, Jun Watanabe; conducted a prospective, randomized, controlled PARADIGM trial[*4] to compare the efficacy and safety of mFOLFOX6 + anti-VEGF antibody (Bevacizumab) versus mFOLFOX6 + anti-EGFR antibody (Panitumumab) to verify standard treatment for chemotherapy-naïve patients with RAS wild-type, unresectable metastatic colorectal cancer.

The results demonstrated that mFOLFOX6 + anti-EGFR antibody produced a statistically significant improvement in overall survival (as the primary endpoint) in patients with metastatic colorectal cancer with both left-sided primary tumors and tumors throughout the entire colorectum, compared to mFOLFOX6 + anti-VEGF antibody.

This is the first time in the world that the superiority of anti-EGFR antibody treatment over anti-VEGF antibody treatment has been demonstrated in a prospective clinical trial for patients with

RAS wild-type, left-sided metastatic colorectal cancer. In Europe and the United States, this evidence was included in treatment guidelines for colorectal cancer in October 2022, and guidelines in Japan will also be updated; hence, it is anticipated that the precision medicine will be delivered to more patients with metastatic colorectal cancer.

The results of this study were reported in the plenary presentation of the 2022 American Society of Clinical Oncology (ASCO) annual meeting (5 June 2022; Chicago, IL; presenter: Takayuki Yoshino), and published in the scientific journal, *Journal of the American Medical Association* (JAMA) (19 April 2023; Japan time).

Background

Two large-scale, randomized, controlled clinical trials were conducted to compare anti-EGFR antibody and anti-VEGF antibody as molecularly-targeted drugs for first-line treatment for patients with unresectable metastatic colorectal cancer. However, the *post hoc* analysis results for RAS wild-type metastatic colorectal cancer were not consistent between the two trials, and no definitive conclusion was reached regarding which drug should be used. The results of subsequent post-analyses of several clinical trials suggested that anti-EGFR antibody may be effective for patients with RAS wild-type, left-sided, metastatic colorectal cancer. The PARADIGM study is the first prospective trial in the world to verify whether anti-EGFR antibody or anti-VEGF antibody is optimal as first-line therapy for patients with RAS wild-type, left-sided, metastatic colorectal cancer based on overall survival (a true endpoint) as the primary endpoint.

Study method/results

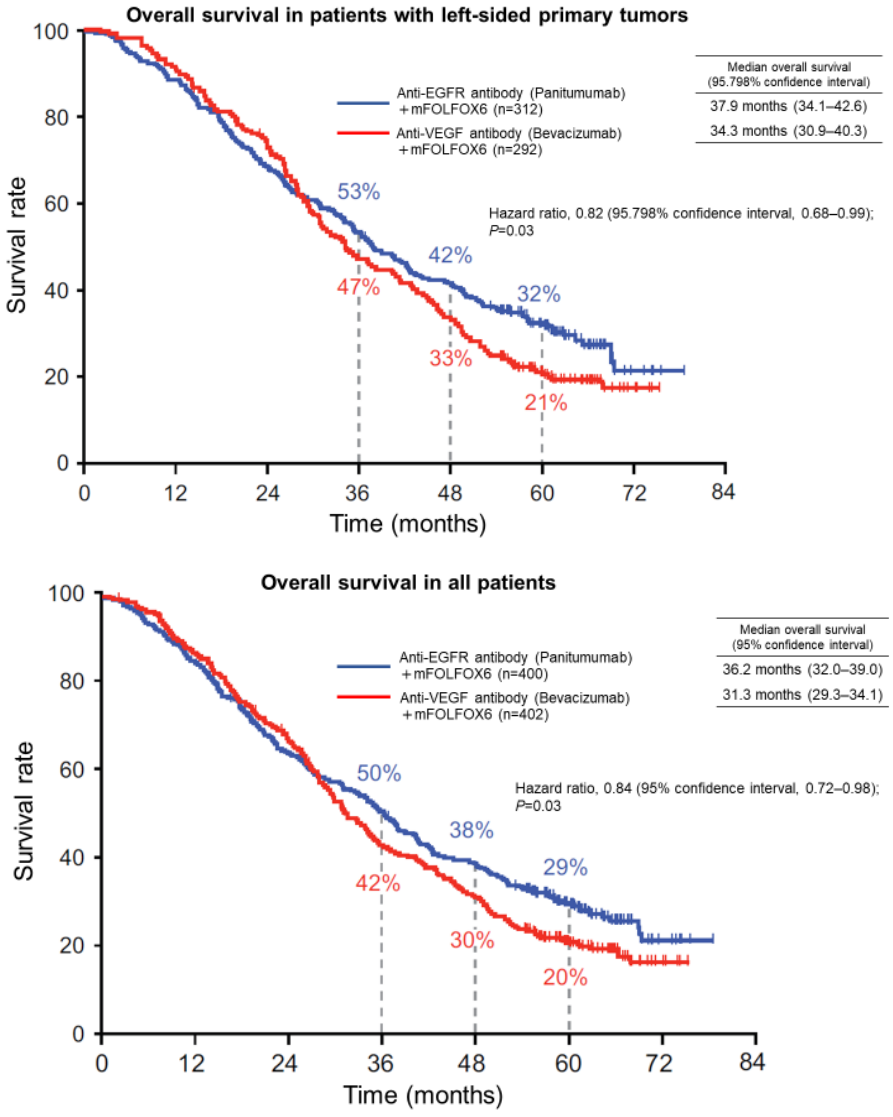
The PARADIGM trial was a multicenter, phase III, randomized, controlled study to verify the efficacy and safety of mFOLFOX6 + anti-VEGF antibody (Bevacizumab group) versus mFOLFOX6 + anti-EGFR antibody (Panitumumab group) in chemotherapy-naïve patients with RAS wild-type, unresectable metastatic colorectal cancer (NCT02394795). The concept and study plan were formulated jointly by researchers including Kei Muro, Deputy Director of the Aichi Cancer Center Hospital/Director of the Department of Clinical Oncology; Takayuki Yoshino, Deputy Director of the National Cancer Center Hospital East; and Associate Professor, Jun Watanabe, Department of Surgery, Gastroenterological Center, Yokohama City University. The study was conducted in cooperation with 197 study sites throughout Japan.

The primary endpoint was set as overall survival in patients with left-sided primary tumors, and the study was designed with the statistical procedure that overall survival in all patients would only be tested if overall survival in left-sided patients was significant. The main inclusion criteria were: 20–79 years of age; diagnosed with radically unresectable, RAS wild-type, metastatic colorectal cancer; no prior chemotherapy for colorectal cancer; good performance status (Eastern Cooperative Oncology Group PS = 0 or 1); and a sufficient organ function.

The 823 patients enrolled in the study from May 2015 to June 2017 were assigned at a 1 : 1 ratio

to either Bevacizumab group, or Panitumumab group. Among those the 823 patients, efficacy analysis set (Panitumumab group/Bevacizumab group) comprised 312/292 patients with left-sided primary tumors, and 400/402 of all patients, respectively.

The primary endpoint of overall survival during the median follow-up period of 5.1 years in patients with left-sided primary tumors was 37.9 months in the Panitumumab group and 34.3 months in the Bevacizumab group (hazard ratio[*5]: 0.82 (95.798% confidence interval: 0.68–0.99, *P* = 0.03), demonstrating a statistically significant improvement in overall survival in the Panitumumab group. The gap also widened from approximately 28 months after randomization, with the survival rate of the Panitumumab group exceeding that of the Bevacizumab group (Panitumumab group/Bevacizumab group, 3-year survival rate: 53%/47%, 4-year survival rate: 42%/33%, 5-year survival rate: 32%/21%, respectively). Furthermore, the median overall survival in all patients in the Panitumumab group was: 36.2 months and in the Bevacizumab group was 31.3 months (hazard ratio: 0.84 (95% confidence interval: 0.72–0.98; *P* = 0.03), demonstrating a statistically significant improvement in overall survival in the Panitumumab group.



There were no new safety concerns in either treatment group. In the Panitumumab group, 71.8% of patients experienced grade 3 or higher adverse events, compared to 64.9% of patients in the Bevacizumab group. Commonly observed adverse events in the Panitumumab group included acneiform dermatitis, paronychia, dry skin, and hypomagnesemia.

Outlook

This study demonstrates the feasibility of recommending the use of the anti-EGFR antibody as the first-line primary treatment for patients with RAS wild-type, left-sided, metastatic colorectal cancer. The world's first clear evidence from Japan will be included in guidelines for treatment of colorectal cancer both in Japan and overseas, with the expectation of providing an appropriate primary treatment to patients with RAS wild-type metastatic colorectal cancer.
In addition to this study, the PARADIGM biomarker trial (NCT02394834) is currently in progress, which aims to identify therapeutic response predictors and resistance mechanisms. Analysis linking biomarkers with the clinical data of approximately 800 Japanese patients with colorectal cancer obtained from the PARADIGM trial is expected to lead to further improvements in treatment outcomes for colorectal cancer and possible drug development.

We would like to express our sincere gratitude to the patients and their families for their cooperation in this study.

Publication

Journal: *Journal of the American Medical Association* (JAMA)
Title: Panitumumab vs Bevacizumab Added to Standard First-line Chemotherapy and Overall Survival Among Patients With *RAS* Wild-type, Left-sided, Metastatic Colorectal Cancer A Randomized Clinical Trial
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Date: April 19, 2023
DOI: 10.1001/jama.2023.4428

Glossary

*1 Prospective clinical trial
Research that collects new data and samples with the cooperation of patients and verifies the results

*2 Anti-EGFR antibody drugs

A type of molecular-targeted therapy used to treat cancer. These drugs inhibit the growth of cancer cells by binding with the Epidermal Growth Factor Receptors (EGFR) involved in proliferation of cancer cells, thereby inhibiting the action of these receptors.

*3 RAS wild-type

Refers to patients without RAS gene mutations. RAS is one of the proteins involved in cell proliferation; there are three types of RAS proteins: KRAS, NRAS, and HRAS.

*4 Randomized controlled trial

Research that randomly assigns the enrolled patients to each treatment group and compares treatment outcomes.

*5 Hazard ratio

Indication of the risk of death over a unit of time.

Enquiries

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