

A Multicenter Single-Arm Phase II Trial Evaluating the Safety and Efficacy of Panitumumab and Irinotecan in Patients with NeoRAS Wild-Type Metastatic Colorectal Cancer (C-PROWESS Trial)

Authors: *Hiroki Osumi,^{1,2} Kensei Yamaguchi,¹ Eiji Shinozaki¹

1. Department of Gastroenterological Oncology, The Cancer Institute Hospital of the Japanese Foundation for Cancer Research, Tokyo, Japan
2. Department of Gastroenterology, Kanagawa Cancer Center, Yokohama, Japan

*Correspondence to hiroki.osumi@jfcrr.or.jp

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BACKGROUND AND AIMS

Previous studies have demonstrated that patients with *RAS*-mutant metastatic colorectal cancer (mCRC) occasionally develop *RAS* wild-type (WT) status following systemic treatments, a phenomenon known

as NeoRAS WT.^{1,2} While anti-epidermal growth factor receptor (EGFR) monoclonal antibodies (mAb) are ineffective for *RAS*-mutant mCRC, recent advances in circulating tumor DNA (ctDNA) testing³ have enabled the detection of this conversion, suggesting that such patients might benefit from anti-EGFR therapy.⁴ Indeed, retrospective reports indicate favorable efficacy of anti-EGFR mAbs in patients with NeoRAS WT mCRC, achieving tumor shrinkage or long-term disease control.⁵ However, prospective efficacy and safety data for anti-EGFR-based treatments in this population remain limited. This multicenter, single-arm, Phase II trial (C-PROWESS) aimed to prospectively evaluate the efficacy and safety of panitumumab plus irinotecan in patients with NeoRAS WT mCRC.^{6,7}

MATERIALS AND METHODS

Patients with tissue-confirmed *RAS*-mutant mCRC who developed intolerance to or disease progression after fluoropyrimidine, oxaliplatin, and irinotecan were screened for *RAS* mutation status in ctDNA with the OncoBEAM™ *RAS* CRC assay (Sysmex, Kobe, Japan). Those without *RAS* mutations detected within 28 days before enrollment received panitumumab (6 mg/kg) and irinotecan (150 mg/m²) biweekly.

RESULTS

Among 404 patients screened for *RAS* status in ctDNA, conversion to NeoRAS WT was observed in 54 (13.3%), and 30 patients were enrolled. The response rate (RR) and disease control rate were 6.7% and 76.7%, respectively. With a median follow-up of 22.4

months, median progression-free survival (PFS) was 4.1 months, and median overall survival (OS) was 16.8 months. Grade 3 adverse events were observed in 14 patients (46.7%), with no Grade ≥ 4 adverse events. ctDNA next-generation sequencing results using Guardant360 were available for 27 patients. The RR for patients with none of the gene alterations related to anti-EGFR mAb resistance (negative hyper-selection cohort) was 16.7% (2/12), while no patient with any of these alterations achieved a response (0/15). Negative hyper-selection was associated with significantly longer PFS and OS (PFS: 6.1 versus 2.9 months; HR: 0.37; $p=0.018$; OS: 25.5 versus 13.1 months; HR: 0.34; $p=0.038$).

CONCLUSION

Anti-EGFR mAbs with chemotherapy may be effective for NeoRAS WT mCRC, especially for patients hyper-selected for the absence of gene mutations related to anti-EGFR mAb resistance detected by ctDNA next-generation sequencing.

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