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TRIDENTE: A phase II study of rechallenge with encorafenib (ENCO), binimetinib (BINI), and cetuximab (CET) in BRAF V600E-mutant metastatic colorectal cancer (mCRC)

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Background

The BEACON CRC and BREAKWATER trials established ENCO + CET-based therapy as a standard-of-care for *BRAF* V600-mutant mCRC. Based on the efficacy of *BRAF*/MEK inhibitor rechallenge in *BRAF* V600-mutant melanoma, TRIDENTE trial evaluated the clinical utility of rechallenge with ENCO + BINI + CET in patients with *BRAF* V600E mutant mCRC who previously responded and then progressed on ENCO + CET-based therapy.

Methods

TRIDENTE (jRCTs031210511) is a multicenter, single-arm, phase II study. Key eligibility criteria included: *RAS* WT/*BRAF* V600E-mutant mCRC; ECOG PS 0-1; refractory or intolerant to fluoropyrimidine-based regimens and anti-PD-1 therapy (if MSI-H); and history of prior ENCO + CET-based therapy with at least a partial response (PR) followed by disease progression. A ENCO-free interval of ≥ 4 months after the last ENCO dose was required. The primary endpoint was investigator-assessed objective response rate (ORR). With a threshold ORR of 3% and an expected ORR of 20%, 21 patients were required (one-sided $\alpha = 0.05$, power 80%). In exploratory analysis using circulating tumor DNA (ctDNA), resistance genomic alterations were defined as mutations in *KRAS*, *NRAS*, *MAP2K1*, *EGFR* or amplifications in *MET*, *BRAF*, *KRAS*.

Results

Between Jan 2022 and Apr 2025, 21 patients were enrolled across 12 institutions. Median age was 58 years; 17 patients (81%) had ECOG PS 0. The median number of prior lines was 3. Previous ENCO + CET-based regimens were ENCO + CET (62%) and ENCO + CET + BINI (38%). The primary endpoint was met; ORR was 19.0% (90%CI, 6.8–38.4%), including 4 PRs. Stable disease was observed in 12 patients, and tumor shrinkage occurred in 11 patients (52.4%). Median PFS and OS were 2.8 and 9.6 months, respectively. No unexpected adverse events were observed. Among 20 patients with baseline ctDNA results, the ORR was 25.0% (3/12) in those without genomic alterations versus 12.5% (1/8) in those with alterations.

Conclusions

Rechallenge with ENCO + BINI + CET demonstrated clinical activity and manageable safety profile in patients with *BRAF* V600E-mutant mCRC who were initially sensitive but subsequently progressed on ENCO + CET-based therapy.

Clinical trial identification

jRCTs031210511.

Legal entity responsible for the study

The authors.

Funding

Ono Pharmaceutical Co., Ltd.

Disclosure

D. Kotani: Financial Interests, Personal, Invited Speaker: Bristol Myers Squibb, Chugai, Daiichi Sankyo, Eli Lilly, MSD, Merck Biopharma, Ono Pharma, Pfizer, Taiho Pharma, Takeda, Sysmex, Nihonkayaku, Novartis, Guardant Health; Financial Interests, Personal, Advisory Board: Takeda; Financial Interests, Institutional, Local PI: Ono pharma, MSD, Servier, Novartis, Janssen Pharma, IQVIA, Syneos Health, CIMIC Shiftzero, CIMIC; Financial Interests, Institutional, Funding: Ono Pharma. K. Harada: Financial Interests, Personal, Invited Speaker: MSD K.K., Nippon Kayaku Co., Ltd., Ono Pharmaceutical Co., Ltd.), Taiho Pharmaceutical Co., Ltd., Bristol Myers Squibb, Servier, Daiichi Sankyo, INC., AstraZeneca K.K., Astellas, Kyowa Kirin, Merck Serono, Nipro Corporation, BeOne. E. Shinozaki: Financial Interests, Personal, Invited Speaker: Merck Biopharm Japan, Chugai Pharmaceutical, Takeda Pharmaceuticals, Daiichi Sankyo, Eli Lilly Japan, Taiho Pharmaceutical; Financial Interests, Institutional, Other, collaboration study: Toppan holdings. Y. Matsubara: Financial Interests, Personal, Invited Speaker: MSD; Financial Interests, Personal, Writing Engagement: Chugai. H. Bando: Financial Interests, Personal, Advisory Board: Guardant Health Japan; Financial Interests, Institutional, Research Grant: Ono Pharmaceutical; Other, Lecture fee: Ono pharmaceutical, Taiho pharmaceutical, Guardant Health Japan; Other, Consultant Fee: GxD. Y. Nakamura: Financial Interests, Personal, Invited Speaker: Chugai, Merck Biopharma, MSD K.K, Daiichi Sankyo Co., Ltd., Guardant Health Japan Corp.; Financial Interests, Personal, Advisory Board: Natera, Inc., Exact Sciences, Guardant Health Pte Ltd, Tempus AI, Pfizer, Shionogi. M. Wakabayashi: Financial Interests, Personal, Invited Speaker, honoraria: Kyowa Kirin Co., Ltd., Daiichi Sankyo Co., Ltd. Y. Kagawa: Financial Interests, Personal, Invited Speaker: Chugai, Ono, Lilly, Merck, Takeda. T. Yoshino: Financial Interests, Personal, Invited Speaker: Chugai Pharmaceutical Co., Ltd., Takeda Pharmaceutical Co., Ltd., Merck Biopharma Co., Ltd., Ono Pharmaceutical Co., Ltd.; Financial Interests, Personal, Other, Consulting Fee: Sumitomo Corp., Indivumed; Financial Interests, Institutional, Research Grant: Bristol Myers Squibb K.K., Caris MPI, Inc., Chugai Pharmaceutical Co., Ltd., Daiichi Sankyo Co., Ltd., Eisai Co., Ltd., Exact Sciences Corporation, FALCO Biosystems Ltd., Medical & Biological Laboratories Co., Ltd., Merus N.V., Miyarisan Pharmaceutical Co., Ltd., MSD K.K., Natera Inc., Nippon Boehringer Ingelheim Co., Ltd., Ono Pharmaceutical Co., Ltd., Pfizer Japan Inc., Sysmex Corp., Taiho Pharmaceutical Co., Ltd., Takeda Pharmaceutical Co., Ltd. All other authors have declared no conflicts of interest.