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Circulating tumour (ct) DNA analysis of BRAF V600E dynamics and changes in genomic landscape in patients (pts) with first-line (1L) BRAF V600E-mutant metastatic colorectal cancer (mCRC) treated in BREAKWATER

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Background

The randomized phase III BREAKWATER study (NCT04607421) demonstrated statistically significant and clinically meaningful improvements in ORR with encorafenib + cetuximab (EC) + mFOLFOX6 vs chemotherapy ± bevacizumab (control) in 1L BRAF V600E-mutant mCRC (Kopetz et al 2025). Following FDA accelerated approval, EC+mFOLFOX6 is a new standard of care (SOC) for these pts.

Methods

The BREAKWATER study randomized pts with 1L BRAF V600E-mutant mCRC to receive EC, EC+mFOLFOX6, or control. Plasma samples were analyzed for ctDNA including at baseline (BL), Cycle 2 Day 15 (C2D15), and end of treatment (EOT) using the Guardant Infinity RUO assay. ctDNA and tissue concordance was analyzed with the QIAGEN Therascreen® BRAF V600E RGQ PCR Kit. Changes in genomic alterations from BL to EOT were evaluated. ORR and OS were assessed for BRAF V600E variant allele frequency (VAF)-high (≥median) and -low (<median) groups.

Results

BL plasma samples were analyzed for 494 of 514 (96%) pts; 86% (425/494) had BRAF V600E mutations detected in ctDNA with high concordance (87%) between ctDNA and tissue. ORR and OS benefits with EC+mFOLFOX6 were maintained independently of BL BRAF V600E VAF status (Table). Pts whose BRAF V600E status transitioned from BL detectable to undetectable (D/ND) at C2D15 had improved OS vs pts who remained detectable (HR: 0.30, 0.36, and 0.50 for EC+mFOLFOX6, EC, and control, respectively), with a higher percentage of D/ND pts in the EC+mFOLFOX6 (67%) vs EC (45%) and control (38%) arms. Previously described resistance mutations in KRAS, NRAS, and MAP2K1 were more frequently gained with EC vs EC+mFOLFOX6 (41% vs 16% NRAS; p ≤ 0.001) or control at EOT (241 paired plasma samples from BL).Table: 729MO

BRAF V600E VAF-high at BL			BRAF V600E VAF-low at BL		
EC (n=61)	EC + mFOLFOX6 (n=95)	Control (n=91)	EC (n=62)	EC + mFOLFOX6 (n=96)	Control (n=89)
ORR, % (95% CI) 49 (36, 62)	75 (65, 83)	42 (32, 53)	40 (28, 54)	63 (52, 72)	40 (30, 51)
OS HR (95% CI) 0.76 (0.52, 1.13)	0.50 (0.35, 0.73)	–	0.66 (0.41, 1.06)	0.39 (0.24, 0.64)	–

ORR, objective response rate; OS, overall survival.

Conclusions

Clinical benefit across BRAF V600E subgroups and differential patterns of acquired resistance mutations support EC+mFOLFOX6 as a SOC for pts with BRAF V600E-mutant mCRC.

Clinical trial identification

NCT04607421.

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Legal entity responsible for the study

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Disclosure

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