

Targeted therapy for *BRAF*-mutant colorectal cancer

Results from a new study suggest the benefit of a targeted therapy approach through combined blockade of *BRAF*, *MEK*, and *EGFR* in patients with metastatic colorectal cancer.

In the randomised, phase 3 BEACON CRC trial, Scott Kopetz (University of Texas MD Anderson Cancer Center, Houston, TX, USA) and colleagues randomly assigned (1:1:1) 665 patients with *BRAF*^{V600E}-mutant metastatic colorectal cancer who had progressed after previous chemotherapy to triplet (encorafenib 300 mg daily, binimetinib 45 mg twice daily, and cetuximab [initial dose 400 mg/m² body-surface area, then 250 mg/m² weekly], doublet (encorafenib and cetuximab), or control treatment (cetuximab plus irinotecan-based chemotherapy). The primary endpoints were overall survival in the triplet group versus the control group, and objective response in the triplet group versus the control group.

At the prespecified interim analysis, median follow-up was 7·8 months. Median overall survival was 9·0 months (95% CI 8·0–11·4) in the triplet group, 8·4 months (7·5–11·0) in the doublet group, and 5·4 months (4·8–6·6) in the control group (hazard ratio 0·52, 95% CI 0·39–0·70; *p*<0·001 for triplet vs control group). The proportion of patients achieving an objective response was 26% (95% CI 18–35) in the triplet group, 20% (13–29) in the doublet group, and 2% (0–7) in the control group (*p*<0·001 for triplet vs control). 128 (58%) patients in the triplet group, 108 (50%) in the doublet group, and 117 (61%) in the control group had a grade 3 or worse adverse event.

Kopetz commented, “it is encouraging to see a clear survival advantage for patients with an aggressive *BRAF*^{V600E}-mutant tumour” and is hopeful that the combination therapy will become standard of

care. Co-author Josep Tabernero (Vall d’Hebron Institute of Oncology, Barcelona, Spain) said, “by seeking out a novel combinatorial regimen we have potentiated *BRAF*-directed therapy”.

James McCracken (Austin Health, Melbourne, VIC, Australia) commented, “the authors are to be congratulated for offering a meaningful benefit to these patients”. Although not designed for such comparisons, he suggested that the similar outcomes between the triplet and doublet-therapy groups raised the question of the importance of *MEK* inhibition in this context. Tabernero added, “Future research will need to better define the benefits of the two combinatorial treatment groups as we pursue a potential paradigm shift in the treatment of this disease.”

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