

# CRC IN FOCUS

Current Developments in the Management of Colorectal Cancer

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## How Should *BRAF* V600E–Mutated Colorectal Cancer Be Treated?



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**H&O** How common is the *BRAF* V600E mutation in colorectal cancer (CRC), and how does it affect prognosis?

**SK** The *BRAF* V600E mutation is present in approximately 15% of patients with early-stage CRC and 6% of those with metastatic CRC. The prognosis of patients who have metastatic disease with the *BRAF* V600E mutation is very poor; the length of their survival is approximately half that of patients who have metastatic disease without the mutation.

In addition, approximately 1% of patients with metastatic CRC have a *BRAF* mutation other than V600E. The prognosis of these patients is better than that of the average person with metastatic CRC.

**H&O** How else does *BRAF* V600E–mutated CRC differ from CRC without the mutation?

**SK** The *BRAF* V600E mutation is slightly more common in patients who are older and female. The tumors are more likely to spread to distant lymph nodes and the peritoneum, and they are more likely to be poorly differentiated.

**H&O** What are the challenges in treating patients with *BRAF* V600E–mutated CRC?

**SK** The main difficulty is that the response of *BRAF* V600E–mutated CRC to standard chemotherapy

regimens is limited. The response rate is low, and the duration of the response is short. The disease tends to be aggressive, and patients are less likely to be able to tolerate subsequent lines of therapy.

**H&O** What is the current therapy for this type of CRC?

**SK** The standard chemotherapy regimens used for patients with *BRAF* V600E tumors reflect the aggressive nature of the disease. They usually consist of bevacizumab (Avastin, Genentech) plus either leucovorin/5-fluorouracil (5-FU)/oxaliplatin/irinotecan (FOLFOXIRI), if the patient can tolerate this regimen, or else leucovorin/5-FU/oxaliplatin (FOLFOX). When the disease progresses, the prognosis despite subsequent lines of therapy in these patients is very poor, with a progression-free survival (PFS) of approximately 2 months.

**H&O** What has been the experience with incorporating *BRAF* inhibitors into therapy?

**SK** When we administered *BRAF* inhibitors to these patients, either alone or in combination with MEK inhibitors, the response rates were low—in the single digits. The reason is that after treatment with *BRAF* inhibitors, feedback mechanisms reactivate the endothelial growth factor receptor (EGFR), among other receptor tyrosine kinases. The EGFR feedback reactivates signaling through the EGFR pathway, despite the inhibition.

The finding that these tumors do not respond to standard therapy with BRAF inhibitors suggested that the combination of a BRAF inhibitor and an EGFR inhibitor might be beneficial.

This hypothesis led to 2 recent randomized studies (Table)—Southwest Oncology Group S1406 (Phase II Study of Irinotecan and Cetuximab With or Without Vemurafenib in BRAF Mutant Metastatic Colorectal Cancer; NCT02164916) and BEACON CRC (Study of Encorafenib + Cetuximab Plus or Minus Binimetinib vs. Irinotecan/Cetuximab or Infusional FOLFIRI/Cetuximab With a Safety Lead-in of Encorafenib + Binimetinib + Cetuximab in Patients With BRAF V600E-mutant Metastatic Colorectal Cancer; NCT02928224).

I presented the results of SWOG S1406 at the 2017 American Society of Clinical Oncology (ASCO) Gastrointestinal Cancers Symposium. For this phase 2 study, we randomly assigned 106 patients with mutations in *BRAF* V600 and extended *RAS* wild-type metastatic CRC to either the standard of care with irinotecan/cetuximab (Eribitux, Lilly) or irinotecan/cetuximab plus the BRAF inhibitor vemurafenib (Zelboraf, Genentech/Daiichi Sankyo). We found that PFS was longer in the vemurafenib group than in the control group: 4.4 vs 2 months, respectively (hazard ratio [HR], 0.42;  $P=.0002$ ). However, even though the PFS was significantly longer with the addition of vemurafenib, opportunities for improvement remain. Based on these results, the combination was recently added to the National Comprehensive Cancer Network guidelines as a new standard-of-care option.

More recently, the results from the safety lead-in of the BEACON CRC trial were presented at the 2018 ASCO Gastrointestinal Cancers Symposium. The lead-in included 29 patients from the phase 2 BEACON study who had *BRAF* V600-mutant metastatic CRC that had progressed after 1 or 2 prior regimens. Patients received a combination of the BRAF inhibitor encorafenib, the anti-EGFR antibody cetuximab, and the MEK inhibitor binimetinib. The overall response rate was 48%, and the median PFS was 8 months. These results are substantially better than those seen historically in this population. The phase 3 portion of BEACON CRC is ongoing, with patients being randomly assigned either to encorafenib/cetuximab with or without binimetinib or to a standard-of-care arm.

A third study of interest is one that Dr Ryan Corcoran of Massachusetts General Hospital presented at the European Society for Medical Oncology (ESMO) annual meeting in 2016. This phase 1/2 study examined a combination of the BRAF inhibitor dabrafenib (Tafinlar, Novartis), the EGFR inhibitor panitumumab (Vectibix, Amgen), and the MEK inhibitor trametinib (Mekinist,

**Table.** Studies in Patients With *BRAF* V600E-Mutated Metastatic Colorectal Cancer

Regimen	Response Rate, % <sup>a</sup>	PFS, mo	Citation
<b>Single or doublet RAF/MEK inhibitors</b>			
Vemurafenib	5	2.1	Kopetz, 2015 ( <i>J Clin Oncol</i> )
Dabrafenib	11	NA	Falchook, 2012 ( <i>Lancet</i> )
Encorafenib	16	NA	Gomez-Roca, 2014 (ESMO, <i>Ann Oncol</i> )
Dabrafenib + trametinib	12	3.5	Corcoran, 2015 ( <i>J Clin Oncol</i> )
<b>Doublets with EGFR inhibitor</b>			
Vemurafenib + panitumumab	13	3.2	Yaeger, 2015 ( <i>Clin Cancer Res</i> )
Vemurafenib + cetuximab	4	3.7	Hyman, 2015 ( <i>NEJM</i> )
Encorafenib + cetuximab	19	3.7	Van Geel, 2017 ( <i>Canc Discov</i> )
Dabrafenib + panitumumab	10	3.4	Atreya, 2015 (ASCO, <i>J Clin Oncol</i> )
<b>Triplets with EGFR inhibitor</b>			
Vemurafenib + cetuximab + irinotecan	16	4.4	Kopetz, 2017 (ASCO GI, <i>J Clin Oncol</i> )
Dabrafenib + trametinib + panitumumab	32	4.2	Corcoran, 2016 (ESMO, <i>Ann Oncol</i> )
Encorafenib + cetuximab + alpelisib	18	4.2	Van Geel, 2017 ( <i>Canc Discov</i> )
Encorafenib + binimetinib + cetuximab	48	8.0	Van Cutsem, 2018 (ASCO GI, <i>J Clin Oncol</i> )

<sup>a</sup>Studies reported either a confirmed or an unconfirmed response.

ASCO, American Society of Clinical Oncology; ASCO GI, American Society of Clinical Oncology Gastrointestinal Cancers Symposium; EGFR, endothelial growth factor receptor; ESMO, European Society for Medical Oncology; mo, months; NA, not applicable; PFS, progression-free survival.

Novartis) in 35 patients with *BRAF* V600E-mutated metastatic CRC and found a response rate of 32%. In contrast, the response rate was just 10% among patients who received dabrafenib and panitumumab alone.

## H&O Does the addition of a phosphoinositide 3-kinase (PI3K) inhibitor improve outcomes?

**SK** A phase 1b study by van Geel and colleagues, which appeared in *Cancer Discovery* in 2017, did not find that adding the PI3K inhibitor alpelisib to treatment with encorafenib and cetuximab achieved a meaningful improvement in the response rate or durability. As a result, that combination is not being pursued further.

## H&O Does immunotherapy potentially play a role in patients with BRAF V600E-mutated CRC?

**SK** Approximately 20% of patients with BRAF V600E-mutated metastatic CRC also have microsatellite instability. Just like any other patients with microsatellite instability, these patients respond to checkpoint inhibitors such as nivolumab (Opdivo, Bristol-Myers Squibb) and pembrolizumab (Keytruda, Merck). The presence of the BRAF mutation does not appear to affect response to immunotherapy. Ongoing research is beginning to investigate combinations of immunotherapy and targeted therapy in patients with BRAF-mutated microsatellite-stable CRC.

## H&O What type of research is still needed?

**SK** One of the biggest problems we face is that even with combination therapies, acquired resistance develops in patients who have CRC. We need a better understanding of the mechanisms of resistance and of how tumors evade the current targeted therapies. At the same time, more research is needed to clarify the immune context of BRAF V600E-mutated CRC and to evaluate combinations of targeted therapies and immunotherapies.

BRAF V600E-mutated metastatic CRC is a very aggressive subset of colon cancer, and the standard-of-care options have been very limited. Fortunately, substantial activity is emerging from the current clinical trials. As a result, we hope to see a change in the standard-of-care options for these patients in the near future.

### Disclosure

Dr Kopetz has served on advisory boards for Genentech, Amgen, and EMD Serono.

## Suggested Readings

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