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Targeting *BRAF* Mutant Colorectal Cancer: Progress in Combination Strategies

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Summary

BRAF mutations in colorectal cancer portend a poor prognosis, with first-line treatment often involving triplet or quadruplet chemotherapy, and single agent targeted therapy with *BRAF* inhibitors failing to demonstrate clinical activity. Blockade of multiple critical nodes along the MAPK and other pathways may be necessary to improve response rates and survival.

Activating mutations in the *BRAF* oncogene are now well established as critical drivers of colorectal cancer (CRC) and other malignancies, and represent rational targets for the development of novel therapeutics. The most common *BRAF V600E* mutation activates the kinase domain and limits response to epidermal growth factor receptor (EGFR) inhibitors. While *BRAF* inhibitors have been shown to be effective in *BRAF* mutant melanoma where they are Food and Drug Administration (FDA) approved as monotherapy, they have failed to demonstrate single-agent clinical activity in *BRAF* mutant CRC (1). Similarly, vertical blockade strategies involving the MAPK pathway through the inhibition of *BRAF* and MEK inhibition failed to demonstrate meaningful activity in subsets of patients with advanced *BRAF* mutant CRC (2). This difference was shown by Prahallad and colleagues to be due to the minimal expression of EGFR in melanoma cells, which develop from the neural crest, in contrast to the rapid negative feedback upregulation and signaling of EGFR in CRC cells, which develop from epithelial cells that intrinsically express EGFR (3). Such rebound signaling following *BRAF* inhibition can be abrogated by the concomitant blockade of EGFR, as evidenced by *in vitro* and *in vivo* models, which demonstrated reduced ERK signaling when treated simultaneously with *BRAF* and EGFR inhibitors.

In the clinic, early signals of antitumor activity were observed in patients with advanced *BRAF* mutant CRC when treated with cetuximab and vemurafenib (4). These early data led to several dual combination trials involving *BRAF* inhibitors, such as vemurafenib or

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dabrafenib, and the EGFR inhibitors cetuximab or panitumumab, respectively. Preliminary results from these studies revealed modest increments in response and progression-free survival, and suggested that concurrent administration of multiple targeted therapies may be required for meaningful clinical benefit (Table 1). Novel triplet combinatorial approaches have now been pursued, including the triple blockade of EGFR, BRAF and MEK, targeted therapy and chemotherapy combinations (EGFR and BRAF inhibitors with irinotecan) (5), and cross-pathway blockade of EGFR, BRAF and phosphatidylinositol-3 kinase (PI3K) to minimize the development of signaling crosstalk. In this issue of *Cancer Discovery*, van Geel and colleagues describe a phase Ib dose-escalation trial involving the combination of cetuximab and the BRAF inhibitor encorafenib, with or without the PI3K alpha-specific inhibitor alpelisib in patients with advanced *BRAF* mutant CRC (6). The addition of a PI3K inhibitor is based on the hypothesis that activation of the PI3K/AKT pathway is an underlying mechanism of both innate and acquired resistance to BRAF inhibitors in *BRAF* mutant CRC (7).

One prominent issue in the development of novel targeted therapy combinatorial regimens is the inability to reach the single agent recommended phase 2 dose (RP2D) of each component drug, which has potential clinical implications of under-dosing patients. In this study, cetuximab was maintained at approved single-agent doses, while doses of encorafenib and alpelisib were escalated. The monotherapy maximum tolerated doses (MTDs) of both encorafenib and alpelisib were not reached in both doublet and triplet combinations. Encorafenib, currently with no approved indication, has a combination RP2D established in this study, which is less than half its monotherapy RP2D. In other similar doublet combination studies involving EGFR inhibitors with the FDA-approved BRAF inhibitors vemurafenib and dabrafenib, the combination doses of the BRAF inhibitors were largely established at monotherapy RP2Ds (Table 1). However, in this study, the authors elected to establish a lower combination RP2D of encorafenib, so as to enable a direct comparison of data with the triplet therapy arm. Interestingly, the study did include eight patients treated with the doublet combination of cetuximab and encorafenib at its monotherapy RP2D of 450mg daily, with the occurrence of only one dose limiting toxicity of QT prolongation, suggesting that such a dose was feasible. One thus wonders if higher doses of encorafenib should have been established in combination with cetuximab and if the true combination RP2D is closer to its monotherapy dose. Nevertheless, there is evidence that phase I studies underestimate toxicities when recommending doses of small molecule targeted agents based on modest numbers of patients. In a recent retrospective study, it was estimated that approximately 45% of patients in large phase III trials required dose modifications from doses/schedules established in phase I trials due to drug-related toxicities observed (8). Such issues will certainly come to the fore with the emergence of novel doublet and triplet combination regimens involving targeted agents.

Another major challenge in the development of targeted drug combinations is determining if these combinations have true synergistic efficacy in early phase clinical trials, i.e. triplet versus doublet versus monotherapy strategies, so as to make 'go, no-go' decisions with increased confidence. The response rates of encorafenib and cetuximab doublet therapy in this study appear similar or marginally better than other BRAF/EGFR inhibitor combinations (Table 1). In this trial, the triplet arm expectedly had additional toxicities when

compared to the doublet combination, including those attributable to PI3K inhibition from alpelisib, such as hyperglycemia and diarrhea. While this trial was not designed for cross-arm comparison, the addition of alpelisib did not appear to improve response rates as predicted from preclinical studies. Although suitably powered, randomized studies are required to conclusively prove the efficacy of the triplet regimen versus doublet combination, considering the lack of greater patient benefit, coupled with the additional toxicity from PI3K inhibition, further development of this triplet combination is not justified. It is interesting to note that *BRAF* mutant CRC cell lines and murine samples (7), as well as tumor specimens from patients (2,5) treated with BRAF inhibitor-based therapies have failed to demonstrate recurrent acquired resistance alterations in PI3K, indicating that its role may be limited in driving associated resistant mechanisms. In this trial, while an *AKT* mutation and PTEN loss were detected in tumor biopsies obtained at disease progression in two responders, respectively, it is not clear if they were treated with the doublet or triplet combinations.

The detection of acquired mutations or amplification of *KRAS* in disease progression tumor biopsies in 4 of 6 responders is an important finding, and is consistent with drug resistance being driven through MAPK pathway reactivation in *BRAF* mutant CRC (1,7,9). Preliminary data from the SWOG S1406 randomized phase 2 trial of irinotecan and cetuximab, with or without vemurafenib, in *BRAF* mutant metastatic CRC reported an improvement in progression-free survival with the triplet combination, with toxicity rates similar to doublet regimens of irinotecan and cetuximab. These data suggest that vemurafenib sensitizes *BRAF* mutant CRC tumors to cetuximab and irinotecan, consistent with multiple preclinical studies (10). To further address the role of triplet versus doublet vertical blockade in *BRAF* mutant CRC, a three-arm randomized phase III clinical trial of the MEK inhibitor binimetinib, encorafenib and cetuximab versus encorafenib + cetuximab versus irinotecan or FOLFIRI + cetuximab is ongoing (BEACON CRC study, NCT02928224). The study is currently recruiting and is expected to readout in mid-2019, after including 645 patients with advanced *BRAF* mutant CRC. Triple inhibition of EGFR, BRAF and MEK has been shown to only partially overcome drug resistance driven through MAPK pathway reactivation in *BRAF* mutant CRC; the emergence of ERK inhibitors may now open the possibility for alternative combination strategies or even a quadruple inhibitor regimen for more complete pathway blockade. In addition, since *BRAF* mutant CRC is associated with microsatellite instability (MSI-H), and programmed death-1 (PD-1) inhibition has been shown to have significant benefit in mismatch-repair deficient CRC, the incorporation of immune checkpoint inhibitors into a combination regimen may be a logical next-step in the development of *BRAF*-mutant/MSI-H CRC therapy. Based on the preliminary patient benefit observed in this study, although patient numbers are small, *EGFR* amplification may also represent a promising predictive biomarker of response to EGFR/ BRAF inhibitor therapy and warrants further exploration in a larger cohort of patients in the future.

While it is rational to combine drugs to maximize antitumor efficacy by minimizing the development of drug resistance, the fiscal burden of treatment needs to be taken into consideration, especially in settings such as this where the monthly costs of a triplet combination regimen could easily exceed \$35,000. It is likely that the development of these

combinations will need to balance these costs with the overall benefit of such regimens. Regardless, these are exciting times in cancer medicine; we are now armed with a markedly improved understanding of the underlying biology of *BRAF* mutant CRC and a burgeoning armamentarium of novel antitumor molecularly targeted agents and immunotherapies for the development of rational combination therapies. This novel study has shown that it is safe to go beyond two targeted therapies in this disease. However, the key question that still remains is whether a triple combinatorial approach will ultimately lead to synergistic efficacy and an improvement in patient outcomes.

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Table 1

Combination targeted therapy with BRAF inhibitors in *BRAF*mutant CRC

Targets	BRAF + EGFR				BRAF + MEK	BRAF + MEK + EGFR	BRAF+ EGFR + PI3K	BRAF + EGFR + Chemo
	Venurafenib + Cetuximab	Venurafenib + Panitumumab	Dabrafenib + Panitumumab	Encorafenib + Cetuximab				
Drugs								
Reference	Hyman <i>et al</i> (4)	Yaeger <i>et al</i> (11)	Corcoran <i>et al</i> (12)	van Geel <i>et al</i> (6)	Corcoran <i>et al</i> (2)	Corcoran <i>et al</i> (12)	van Geel <i>et al</i> (6)	Hong <i>et al</i> (5)
n	27	15	20	26	43	91	28	19
Key Toxicities								
Fatigue	52%	34%	50%	50%	53%	49%	43%	89%
Diarrhea	44%	7%	45%	19%	35%	65%	54%	84%
Vomiting/nausea	26%	14%	50%	46%	63%	56%	50%	79%
Rash	74%	66%	60%	19%	NA	59%	36%	74%
Efficacy								
ORR	4%	13%	10%	19%	12%	21%	18%	35%
mPFS (months) (95% CI)	3.7 (1.8 to 5.1)	3.2 (1.6 to 5.3)	3.5(NA)	3.7 (2.8 to 12)	3.5 (3.4 to 4)	4.2 (4.1 to 5.6)	4.2 (4.1 to 5.4)	7.7 (3.1 to NA)
OS (months) (95% CI)	7.1 (4.4 to NR)	7.6 (2.1 to NR)	13.2 (NA)	NA	NA	9.1 (7.6 to 20)	NA	NA

ORR = objective response rate

mPFS = median progression free survival

mOS = median overall survival

NR = not reached

NA = not available

95% CI = 95% confidence interval