Targeting BRAF-Mutant Colorectal Cancer: Progress in Combination Strategies

Raghav Sundar1,2, David S. Hong3, Scott Kopetz3, and Timothy A. Yap3

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. Cancer Discov; 7(6): 558-60. © 2017 AACR.

See related article by van Geel et al., p. 610 (6).

Activating mutations in the BRAF oncogene are now well established as critical drivers of colorectal cancer and other malignancies and represent rational targets for the development of novel therapeutics. The most common BRAFV600E mutation activates the kinase domain and limits response to EGFR inhibitors. Although BRAF inhibitors have been shown to be effective in BRAF-mutant melanoma, where they are FDA approved as monotherapy, they have failed to demonstrate single-agent clinical activity in BRAF-mutant colorectal cancer (1). Similarly, vertical blockade strategies involving the MAPK pathway through the inhibition of BRAF and MEK failed to demonstrate meaningful activity in subsets of patients with advanced BRAF-mutant colorectal cancer (2). This difference was shown by Prabhallad 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 colorectal cancer 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 colorectal cancer when treated with cetuximab and vemurafenib (4). These early data led to several dual combination trials involving BRAF inhibitors, such as vemurafenib or 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; ref. 5); and cross-pathway blockade of EGFR, BRAF, and PI3K to minimize the development of signaling cross-talk. 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 PI3Kα-specific inhibitor alpelisib in patients with advanced BRAF-mutant colorectal cancer (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 colorectal cancer (7).

One prominent issue in the development of novel targeted therapy combinatorial regimens is the inability to reach the single-agent recommended phase II dose (RP2D) of each component drug, which has potential clinical implications of underdosing patients. In this study, cetuximab was maintained at approved single-agent doses, whereas doses of encorafenib and alpelisib were escalated. The monotherapy maximum tolerated doses (MTD) 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 450 mg 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 to 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. Although 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 colorectal cancer 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, although 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 colorectal cancer (1, 7, 9). Preliminary data from the SWOG S1406 randomized phase II trial of irinotecan and cetuximab, with or without vemurafenib, in BRAF-mutant metastatic colorectal cancer 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 colorectal cancer tumors to cetuximab and irinotecan, consistent with multiple preclinical studies (10).

Table 1. Combination targeted therapy with BRAF inhibitors in BRAF-mutant colorectal cancer

<table>
<thead>
<tr>
<th>Targets</th>
<th>Drugs</th>
<th>Vemurafenib + cetuximab</th>
<th>Vemurafenib + panitumumab</th>
<th>Dabrafenib + panitumumab</th>
<th>Encorafenib + cetuximab</th>
<th>Dabrafenib + trametinib</th>
<th>Dabrafenib + panitumumab + alpelisib</th>
<th>Encorafenib + cetuximab + panitumumab</th>
<th>Encorafenib + cetuximab + alpelisib</th>
<th>Vemurafenib + cetuximab + irinotecan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference</td>
<td>Hyman et al. (4)</td>
<td>Yaeger et al. (11)</td>
<td>Corcoran et al. (12)</td>
<td>van Geel et al. (6)</td>
<td>Corcoran et al. (2)</td>
<td>Corcoran et al. (12)</td>
<td>van Geel et al. (6)</td>
<td>Hong et al. (5)</td>
<td></td>
<td></td>
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<tr>
<td>N</td>
<td>27</td>
<td>15</td>
<td>20</td>
<td>26</td>
<td>43</td>
<td>91</td>
<td>28</td>
<td>19</td>
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<td>Key toxicities</td>
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</tr>
<tr>
<td>Fatigue</td>
<td>52%</td>
<td>34%</td>
<td>50%</td>
<td>50%</td>
<td>53%</td>
<td>49%</td>
<td>43%</td>
<td>89%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>44%</td>
<td>7%</td>
<td>45%</td>
<td>19%</td>
<td>35%</td>
<td>65%</td>
<td>54%</td>
<td>84%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vomiting/nausea</td>
<td>26%</td>
<td>7%</td>
<td>50%</td>
<td>46%</td>
<td>63%</td>
<td>56%</td>
<td>50%</td>
<td>79%</td>
<td></td>
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<tr>
<td>Rash</td>
<td>74%</td>
<td>66%</td>
<td>60%</td>
<td>19%</td>
<td>NA</td>
<td>59%</td>
<td>36%</td>
<td>74%</td>
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<tr>
<td>Efficacy</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>ORR</td>
<td>4%</td>
<td>13%</td>
<td>10%</td>
<td>19%</td>
<td>12%</td>
<td>21%</td>
<td>18%</td>
<td>35%</td>
<td></td>
<td></td>
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<tr>
<td>nPFS (months)</td>
<td>3.7 (1.8–5.1)</td>
<td>3.2 (1.6–5.3)</td>
<td>3.5 (NA)</td>
<td>3.7 (2.8–12)</td>
<td>3.5 (3.4–4)</td>
<td>4.2 (4.1–5.6)</td>
<td>4.2 (4.1–5.4)</td>
<td>7.7 (3.1–NR)</td>
<td></td>
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<td>OS (months)</td>
<td>7.1 (4.4–NR)</td>
<td>7.6 (2.1–NR)</td>
<td>13.2 (NA)</td>
<td>NA</td>
<td>NA</td>
<td>9.1 (7.6–20)</td>
<td>NA</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ORR, objective response rate; mPFS, median progression-free survival; mOS, median overall survival; NR, not reached; NA, not available; CI, confidence interval.
in BRAF-mutant colorectal cancer; 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, because BRAF-mutant colorectal cancer 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 colorectal cancer, the incorporation of immune checkpoint inhibitors into a combination regimen may be a logical next step in the development of BRAF-mutant/MSI-H colorectal cancer 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.

Although it is rational to combine drugs to maximize antitumor efficacy by minimizing the development of drug resistance, the fiscal burden of treatments 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 colorectal cancer 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.

Disclosure of Potential Conflicts of Interest

S. Kopetz is a consultant/advisory board member for Genentech, Array, Novartis, and Merck. T.A. Yap reports receiving commercial research grants from AstraZeneca, Roche, and Pfizer, is a consultant/advisory board member for Pfizer, Bristol-Myers Squibb, Ignyta, and Clovis Oncology, and has received travel support from Pfizer and Bristol-Myers Squibb. No potential conflicts of interest were disclosed by the other authors.

Grant Support

R. Sundar is supported by the National Medical Research Council (NMRC) research training fellowship, Singapore. D.S. Hong and S. Kopetz acknowledge funding from NIH R01 CA187238. T.A. Yap acknowledges funding from the Academy of Medical Sciences.

Published online June 2, 2017.

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*Cancer Discov* 2017;7:558-560.

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