Abstract: Given that KRAS mutant colorectal tumors do not respond to anti-EGFR monoclonal antibodies such as cetuximab or panitumumab, it is now standard that all patients with metastatic colorectal cancer who are candidates for these therapies undergo KRAS testing. BRAF encodes a protein kinase, which is involved in intracellular signaling and cell growth and is a principal downstream effector of KRAS. BRAF is now increasingly being investigated in metastatic colorectal carcinoma. BRAF mutations occur in less than 10–15% of tumors and appear to be poor prognostic markers. However the predictive nature of this biomarker is yet undefined. This article will review the evidence behind both KRAS and BRAF testing in metastatic colorectal cancer.

Introduction

The advent of target-specific cancer therapeutics has remarkably improved the outcomes of patients with metastatic colorectal cancer (mCRC). The 3 monoclonal antibodies that are approved in treatment of mCRC include cetuximab (Erbitux, ImClone) and panitumumab (Vectibix, Amgen), which are monoclonal antibodies against epidermal growth factor receptor (EGFR), and bevacizumab (Avastin, Genentech), which is a monoclonal antibody against vascular endothelial growth (VEGF) receptor. From recent trials, the predictive role of Kirsten rat sarcoma viral oncogene homolog (KRAS) has been well validated. It has been shown that patients with KRAS mutant tumors do not respond to cetuximab and panitumumab and, therefore, it is now recommended that all patients with mCRC who are candidates for anti-EGFR monoclonal antibody therapy have their tumors tested for KRAS mutation.1-3 However, even with KRAS mutational testing, there are still many patients with KRAS wild-type tumors that do not respond to treatment with cetuximab or panitumumab.1,3-5 This suggests that other factors such as alterations in other EGFR effectors, including members of the RAS-mitogen activated protein kinase (MAPK) or phosphoinositide 3-kinase (PI3K) pathways, could drive resistance to anti-EGFR therapy.6 V-raf murine sarcoma viral oncogene homolog B1 (BRAF) is a principle downstream effector of KRAS, but the relationship between BRAF and KRAS has not been completely
elucidated. The National Comprehensive Cancer Network (NCCN) has recently recommended consideration of BRAF testing for KRAS wild-type tumors, but the clinical utility of this information is still unknown. This article will discuss the data currently available on BRAF testing and how they apply to clinical practice.

**EGFR**

EGFR is a receptor tyrosine kinase and composed of an extracellular ligand binding domain, a lipophilic transmembrane domain, and an intracellular tyrosine kinase domain. EGFR is the link between the extracellular space and the intracellular signal transduction, which regulates nuclear process involved in cell growth, differentiation, survival, cell cycle progression, and angiogenesis. The EGFR signals through the MAPK pathway that regulates the G1 checkpoint and helps control cellular proliferation. MAPK activation is a common property of cancer, and often occurs due to activating mutations in the RAS and BRAF genes, which are downstream from EGFR.

Immunohistochemistry (IHC) of CRC tumors indicates that EGFR protein expression occurs in 60–80% of CRC. The BOND (Bowel Oncology with Cetuximab Antibody) study, which compared irinotecan plus cetuximab with cetuximab alone in irinotecan-refractory patients, showed response rates of 22.9% and 10.8% in the combination and monotherapy group, respectively. Entry criteria for this study required EGFR expression by IHC in the primary tumor or metastatic lesion. Data from the BOND study, however, showed that the degree of EGFR expression determined by staining intensity or percentage of staining cells did not correlate with response. In addition, other studies have shown a response rate of up to 25% in EGFR-negative CRC patients, indicating that analysis of IHC does not have predictive value. Thus, other markers for response to anti-EGFR therapy such as KRAS have been evaluated.

**KRAS**

KRAS protein is a GTPase and is involved in many signal transduction pathways. KRAS is part of the downstream signal transduction pathway of EGFR and acts as a molecular on/off switch. Once it is turned on, it recruits and activates proteins necessary for the propagation of growth factor and other receptor signals, such as c-Raf and PI3K. When the EGFR pathway is activated, small G-protein RASt, in concert with the protein kinase RAFt, activates the MAPK cascade. Mutations of KRAS suggest that tumors will not benefit from anti-EGFR agents because the activating mutation occurs downstream from the target of anti-EGFR therapy. The KRAS mutation occurs early in oncogenesis and seems to be preserved as the tumor progresses.

KRAS mutations are found in up to 40% of mCRC tumors. Point mutations of the KRAS gene have been identified most commonly in codons 12 and 13 and less commonly in codon 61. Randomized controlled trials of cetuximab or panitumumab with or without combination chemotherapy have evaluated outcomes for patients with mCRC harboring KRAS mutation (Table 1).1,5,9,19-22

The phase III CRYSTAL (Cetuximab Combined with Irinotecan in First Line Therapy for Metastatic Colorectal Cancer) trial evaluated the efficacy of an irinotecan-based regimen with or without cetuximab in first-line, advanced CRC. Overall, the results showed that cetuximab combined with 5-fluorouracil (5-FU), leucovorin, and irinotecan (FOLFIRI) had superior median progression-free survival (PFS) compared to FOLFIRI alone (8.9 vs 8 months; P=.0479). In patients with wild-type KRAS, the addition of cetuximab to FOLFIRI significantly improved the median PFS to 9.9 months (P=.017) as well as the objective response rate (ORR) to 59% (P=.0025). However, patients with mutant KRAS did not derive any clinical benefit from the addition of cetuximab.

Similarly, a first-line phase II study using an oxaliplatin-based regimen with or without cetuximab (OPUS study) showed that patients with mutant KRAS receiving cetuximab have a decreased median PFS compared to the control (5.5 vs 8.6 months; P=.0192), and a trend towards a decreased ORR (32.7% vs 48.9%; P=.106). In a phase III trial by Karapetis and colleagues, patients who were heavily pretreated were randomized to cetuximab alone or best supportive care. In this trial, 394 of 572 patients (68.9%) with CRC had KRAS mutational status analyzed. For patients with wild-type KRAS tumors, treatment with cetuximab as compared with supportive care alone significantly improved overall survival (OS, 9.5 vs 4.8 months; P<.001) and PFS (median, 3.7 vs 1.9 months; P<.001).

A phase III trial compared panitumumab to best supportive care in patients with mCRC who progressed after standard chemotherapy. In this trial, there was a PFS benefit (8 vs 7.3 weeks; P<.0001) in the panitumumab arm, but no difference in OS, as crossover was allowed in this study. Amado and colleagues also examined the KRAS status and the effectiveness of panitumumab. In the group of patients receiving panitumumab, benefit was seen only in patients with wild-type KRAS, shown by the increase in PFS (12.3 vs 7.3 weeks; P<.0001) and OS (8.1 vs 7 months).

Another similar study by Hecht and coworkers looked at the interaction of KRAS status and the efficacy of panitumumab in chemorefractory mCRC patients with low (1–9%) or negative (<1%) EGFR tumor cell
Table 1. Clinical Trial Evidence of the Response of Anti-EGFR Monoclonal Antibodies as Related to KRAS Mutational Status in Advanced Colorectal Carcinoma

<table>
<thead>
<tr>
<th>Author/Study</th>
<th>Treatment</th>
<th>KRAS Wild-type</th>
<th>KRAS Mutated</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Antibody Arm</td>
<td>Control Arm</td>
</tr>
<tr>
<td>Van Cutsem et al (CRYSTAL trial)</td>
<td>FOLFIRI ± cetuximab (First-line)</td>
<td>172</td>
<td>176</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RR, % 59.3</td>
<td>43.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Median PFS, mo 9.9</td>
<td>8.7</td>
</tr>
<tr>
<td>Bokemeyer et al (OPUS trial)</td>
<td>FOLFOX ± cetuximab (First-line)</td>
<td>61</td>
<td>73</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RR, % 61</td>
<td>37</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Median PFS, mo 7.7</td>
<td>7.2</td>
</tr>
<tr>
<td>Karapetis et al</td>
<td>Cetuximab vs supportive care (Chemo-refractory)</td>
<td>117</td>
<td>113</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RR, % 13</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Median PFS, mo 3.7</td>
<td>1.9</td>
</tr>
<tr>
<td>Amado et al</td>
<td>Panitumumab vs supportive care (Chemo-refractory)</td>
<td>124</td>
<td>119</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RR, % 17</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Median PFS, wk 12.3</td>
<td>7.3</td>
</tr>
<tr>
<td>Hecht et al</td>
<td>Panitumumab (Chemo-refractory)</td>
<td>94</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Median PFS, mo 15</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>OS, mo 54</td>
<td></td>
</tr>
<tr>
<td>Tol et al (CAIRO2 study)</td>
<td>Capecitabine, oxaliplatin, bevacizumab, ± cetuximab</td>
<td>RR, % 61.4</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Median PFS, mo 10.5</td>
<td>10.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Median OS, mo 21.8</td>
<td>22.4</td>
</tr>
<tr>
<td>Douillard et al (PRIME trial)</td>
<td>FOLFOX ± panitumumab (First-line)</td>
<td>No of patients 331</td>
<td>331</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Median PFS, mo 9.6</td>
<td>8</td>
</tr>
<tr>
<td>Peeters et al (181 study)</td>
<td>FOLFIRI ± panitumumab (First-line)</td>
<td>No of patients 303</td>
<td>294</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PFS, mo 5.9</td>
<td>3.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>OS, mo 14.5</td>
<td>12.5</td>
</tr>
</tbody>
</table>

FOLFIRI=fluorouracil, leucovorin, irinotecan; FOLFOX=fluorouracil, leucovorin, oxaliplatin; OS=overall survival; PFS=progression-free survival; RR=response rate.

expression by IHC. In this study, a response to panitumumab was observed in both the EGFR negative and EGFR low cohorts. When the KRAS analysis was examined, there was a clear advantage in patients with wild-type KRAS, as PFS (15 vs 7.1 months) and OS (54.0 vs 29.1 months) were both doubled compared to the KRAS mutant population.

The PRIME (Panitumumab Randomized Trial In Combination With Chemotherapy for Metastatic Colorectal Cancer to Determine Efficacy) trial is a
PTEN, hepatocyte growth factor, and insulin growth factor pathways, are being evaluated.28,29

Type patients did better overall in regard to PFS and OS for cetuximab monotherapy.5 Thus, other signal transduction pathways, which impact the efficacy of anti-EGFR therapy, such as BRAF, PI3KCA mutations, c-met, PSEN, hepatocyte growth factor, and insulin growth factor receptor pathways, are being evaluated.28,29

The 181 study is a randomized, multicenter, phase III study comparing FOLFIRI plus panitumumab to FOLFIRI alone as second-line therapy for mCRC.26,27 The study was amended to evaluate KRAS status. Correlating with previous studies, there was no difference in PFS, OS, or response rate among patients with KRAS mutant tumors. KRAS wild-type patients had a statistically significant median PFS of 5.9 months and 3.9 months for FOLFIRI plus panitumumab and FOLFIRI alone, respectively (HR 0.73; P=.004). The OS for this same group was not statistically significant (14.5 vs 12.5 months; P=.12). The improvement in PFS only in the KRAS wild-type group is yet more proof that KRAS is a predictive marker for response to anti-EGFR therapy.

KRAS testing has proven to be a breakthrough identification biomarker, which has been reproduced and validated by multiple clinical studies. However, KRAS is a negative predictive marker. When the previous studies were reviewed, the ORR for KRAS wild-type patients was only 17% (vs 0% in KRAS mutated patients) for panitumumab monotherapy1 and 12.8% (vs 1.2% in KRAS mutated patients) for cetuximab monotherapy.3 Thus, other signal transduction pathways, which impact the efficacy of anti-EGFR therapy, such as BRAF, PI3KCA mutations, c-met, PSEN, hepatocyte growth factor, and insulin growth factor receptor pathways, are being evaluated.28,29

The prognostic value of KRAS in mCRC is not yet established, as trials have conflicting results. In the phase III trial by Karapetis and colleagues, there was no difference in survival between KRAS wild-type and KRAS mutant patients who received supportive care.3 In the phase III trial by Hurwitz and associates evaluating irinotecan, fluorouracil, and leucovorin (IFL) with or without bevacizumab, KRAS analysis was performed in 230 patients.80,81 For patients treated with IFL plus placebo, the median PFS was 7.4 months for KRAS wild-type patients and 5.5 months for KRAS mutant patients (HR, 0.69; 95% confidence interval [CI], 0.44–1.08; P=.11) with OS of 17.6 months and 13.6 months, respectively. Although PFS and OS were longer in the KRAS wild-type group, these were not statistically significant. In the updated analysis of the CRYSTAL trial, the KRAS wild-type patients did better overall in regard to PFS and OS compared to the KRAS mutant patients.32 The OS in the control group was 20.0 versus 16.7 months for KRAS wild-type versus mutant patients, though the study was not statistically designed to show this difference. Thus, the prognostic value of KRAS in colon cancer is still uncertain and will need to be evaluated in future and ongoing studies.

BRAF

BRAF encodes a protein kinase, which is involved in intracellular signaling and cell growth. The gene product is also a principal downstream effector of KRAS within the RAS/RAF/MAPK pathway.33 Activation of KRAS has been studied extensively, but BRAF has been only marginally investigated. BRAF mutations are seen most commonly in melanoma, but have also been detected in lung, thyroid, acute leukemias, lymphoma, and colon cancer.34–38

The high frequency of BRAF mutations in human cancer suggests that it may function as an oncogene, and plays an important role in both tumor initiation and maintenance of growth.39

The BRAF gene may be mutated anywhere along its sequence, but the most commonly tested areas include exon 11 codon 468, exon 15 codon 596, and exon 15 codon 600. Tumor DNA may be extracted from fresh, frozen, or paraffin-embedded tissue and amplified by polymerase chain reaction techniques. Sequence analysis of the above hot spots determines the presence of a mutation. More than 95% of BRAF mutations in CRC occur at exon 15 as a point mutation, V600E.21 This mutation results in constitutive activation of the BRAF kinase and promotes cell transformation.34,40

The incidence of BRAF mutations varies by the type of CRC. BRAF has been associated with mismatch repair deficient colon cancers, with approximately 40% of microsatellite instability (MSI)-high tumors having a BRAF mutation compared to nearly 5% of microsatellite stable tumors.41 BRAF mutations in rectal cancer are extremely rare, as was seen in a study by Kalady and colleagues; they found no mutation in 89 rectal cancer cases compared to a 17% incidence in 268 colon tumors.42 In fact, mutations in BRAF are found in less than 10–15% of mCRC cases.5,19,43,44 Mutations in KRAS and BRAF appear to be mutually exclusive. In a study of 113 patients with mCRC, KRAS mutation was detected in 30% of the patients. The BRAF V600E mutation was detected in 11 of 79 patients who had wild-type KRAS.19

Presence of BRAF mutation status in mCRC has been shown to impact the benefit to anti-EGFR antibodies (Table 2). Di Nicolantonio and coauthors looked retrospectively at 113 patients with mCRC who had received either cetuximab or panitumumab.19 None of the BRAF mutated patients responded to treatment, whereas none
of the responders carried BRAF mutations ($P=0.029$). In this study, BRAF mutation was a poor prognostic marker, as patients had shorter PFS and OS. Similar to this study, Loupakis and colleagues looked retrospectively at BRAF status in patients receiving irinotecan and cetuximab. Among the 87 patients in the study population, BRAF was mutated in 13 cases, and none of those patients responded to chemotherapy, compared to a 32% response rate in patients with wild-type BRAF. Once again, BRAF mutation was associated with a trend towards shorter PFS ($HR, 0.59; P=0.073$).

In the CAIRO 2 (Capecitabine, Irinotecan, Oxaliplatin, bevacizumab, ± cetuximab) study, 755 patients with mCRC were randomized to capecitabine, oxaliplatin, and bevacizumab, or the same regimen plus cetuximab. The cetuximab arm in this study had a shorter PFS and inferior quality of life. A retrospective analysis of BRAF V600E mutation was performed in 516 available tumors. BRAF mutations were found in 45 of these tumors (8.7%). Patients with BRAF mutations had a shorter median PFS and OS compared to wild-type BRAF tumors in both treatment groups. Also, subset analysis was done to determine outcome depending on KRAS status. Patients with wild-type KRAS had no difference in PFS or OS. However, patients with KRAS mutant tumors who received cetuximab had shorter median PFS (8.1 months) compared to patients who received no cetuximab (12.5 months; $P=0.003$). The authors concluded that BRAF mutation is a poor prognostic marker regardless of the treatment arm.

In a retrospective study of data from 2 institutions by Souglakos and coworkers, the prognostic and predictive value of KRAS, PIK3CA, and BRAF mutations for clinical outcomes in response to active agents in the treatment of mCRC was evaluated. Mutational status was determined in 168 patients; KRAS, BRAF, and PIK3CA mutations were present in $62$ (37%), $13$ (8%), and 26 (15%) patients, respectively. Multivariate analysis discovered BRAF mutation as an independent prognostic factor for decreased survival (HR 4.3; 95% CI, 2.1–7.6) and a lower PFS (HR, 4.0; 95% CI, 2.2–7.4). In this study, 92 patients were treated using chemotherapy and cetuximab. None of the 9 patients with BRAF mutations

<table>
<thead>
<tr>
<th>Author/Study</th>
<th>Treatment</th>
<th>Variable</th>
<th>BRAF Wild-type</th>
<th>BRAF Mutated</th>
<th>$P$ value/HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Di Nicolantonio et al$^{19}$</td>
<td>Panitumumab or cetuximab</td>
<td>No. of pts</td>
<td>68/79</td>
<td>11/79</td>
<td>$P=0.029$</td>
</tr>
<tr>
<td>Loupakis et al$^{53}$</td>
<td>Irinotecan + cetuximab</td>
<td>No. of pts</td>
<td>74/87</td>
<td>13/87</td>
<td>$P=0.016$</td>
</tr>
<tr>
<td>Tol et al$^{44,45}$ CAIRO2 trial</td>
<td>Capecitabine, oxaliplatin, bevacizumab, ± cetuximab</td>
<td>No. of pts (T)</td>
<td>231</td>
<td>28</td>
<td>$P=0.010$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No. of pts (C)</td>
<td>243</td>
<td>17</td>
<td>$P=0.003$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PFS, mo (T)</td>
<td>10.4</td>
<td>6.6</td>
<td>$P=0.010$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PFS, mo (C)</td>
<td>12.2</td>
<td>5.9</td>
<td>$P=0.003$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>OS, mo (T)</td>
<td>21.5</td>
<td>15.2</td>
<td>$P=0.001$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>OS, mo (C)</td>
<td>24.6</td>
<td>15</td>
<td>$P=0.002$</td>
</tr>
<tr>
<td>Van Cutsem et al$^{3,32}$ CRYSTAL trial</td>
<td>FOLFOX ± cetuximab</td>
<td>No. of pts (KRAS wt only)</td>
<td>566/625</td>
<td>59/625</td>
<td>$P=0.073$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PFS, mo, T/C</td>
<td>10.9/8.8 ($P=0.016$)</td>
<td>8/5.6 ($P=0.86$)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>OS, mo, T/C</td>
<td>25.1/21.6 ($P=0.0549$)</td>
<td>14.1/10.3 ($P=0.744$)</td>
<td></td>
</tr>
</tbody>
</table>

C=control arm; FOLFOX=fluorouracil, leucovorin, oxaliplatin; OS=overall survival; PFS=progression-free survival; RR=response rate; T=treatment arm; wt=wild-type.
responded to cetuximab, whereas 14 of the 83 BRAF wild-type patients responded. For those who received chemotherapy with or without bevacizumab, patients with BRAF mutations did poorly regardless of the type of chemotherapy they received. Overall, this study showed that BRAF mutations carry an especially poor prognosis regardless of treatment choice.

In a recent retrospective article by Sartore-Bianchi and associates, a comprehensive analysis of KRAS, BRAF, PIK3CA mutations, and PTEN expression in mCRC patients treated with cetuximab or panitumumab was conducted. Of all patients, 96 had wild-type KRAS and underwent testing for BRAF and PIK3CA mutations and PTEN expression. A multivariate analysis found that the loss of PTEN confirmed a significant association with lack of response (P<.001), whereas BRAF (P=.265) and PIK3CA (P=.075) were not significant. Survival analyses demonstrated that BRAF mutations (HR, 3.75; P=.015) and loss of PTEN (HR, 0.43; P=.009), but not PIK3CA mutations (HR, 1.20; P=.672), were significantly associated with decreased OS, whereas none of these alterations was significantly associated with PFS.

The previously described CRYSTAL trial randomized 1,198 patients with untreated mCRC to FOLFIRI with or without cetuximab. The benefit of cetuximab was limited to the wild-type KRAS patients. Recent analysis of the CRYSTAL trial, reported at the American Society of Clinical Oncology (ASCO) 2010 Gastrointestinal Cancers Symposium, evaluated the influence of KRAS and BRAF biomarkers on outcome. As expected, there was a statistically significant improvement in response rate and PFS for the KRAS wild-type/BRAF wild-type patients receiving cetuximab. As shown by several of the above reviewed trials, BRAF-mutant patients overall have a poor prognosis. Prior to this analysis, it was also believed that BRAF-mutant patients would be unlikely to respond to anti-EGFR therapy. Of the KRAS wild-type and BRAF mutant patients in the CRYSTAL trial, the OS for FOLFIRI plus cetuximab and FOLFIRI alone was 14.1 and 10.3 months, respectively (P=.7440). Although this was not statistically significant, there was an overall trend towards improved OS, PFS, and response, suggesting that KRAS wild-type/BRAF mutant patients may benefit from treatment with anti-EGFR therapy.

Also at the recent ASCO Gastrointestinal Cancers Symposium, a meta-analysis of the CRYSTAL and OPUS trials evaluated OS, PFS, and overall response with respect to KRAS and BRAF tumor mutation status. The results showed that the addition of cetuximab to chemotherapy for KRAS wild-type tumors (845 patients) produced a reduced risk of disease progression and increased overall response and OS (HR, 0.81; 95% CI, 0.69–0.9; P<.0001) compared to chemotherapy alone, which coincides with results from previous studies. The final analysis of BRAF mutational status is still pending.

The role of BRAF as a prognostic marker for early stage colorectal cancer is less studied. PETAACC-3 (The Pan-European Trials in Adjuvant Colon Cancer) was a large, randomized phase III trial, which assessed the role of irinotecan added to fluorouracil/leucovorin as adjuvant treatment for stage II and III colon cancer. The resection specimens of 1,564 patients were prospectively collected. These were analyzed for KRAS and BRAF mutations. BRAF mutations were significantly associated with right-sided tumors, older age, high grade, and MSI-high tumors. BRAF was a prognostic marker for OS in MSI-low and MSI-stable tumors, though KRAS was not. Another study, which retrospectively tested 649 colon cancers (stage I–IV), evaluated BRAF, KRAS, MSI, and CpG island methylator phenotype (CIMP). Colon cancers that exhibit widespread promoter methylation, also referred to as CIMP, have been associated with MSI and BRAF mutations. As previously seen, BRAF mutation in this study was associated with high mortality. CIMP-high was an independent predictor of low colon cancer-specific mortality. For patients who had a BRAF mutation and CIMP-high, the adverse influence of BRAF seemed to be overridden by the good prognosis of CIMP-high.

A potential problem faced by oncologists is turnaround time, as it may take weeks to obtain final test results or KRAS and BRAF tests. Currently, there are commercial kits in development that will test for KRAS and automatically test for BRAF if patients harbor wild-type KRAS.

Conclusion

KRAS testing highlights the importance of further development of diagnostic markers to predict response to targeted therapy. KRAS testing has been an important step forward in the management of mCRC, and it is clear that only patients with KRAS wild-type tumors should be considered for anti-EGFR therapy. Currently, commercial tests for BRAF are available; however, there is no standardized kit approved by the US Food and Drug Administration to test for BRAF mutation. NCCN guidelines recommend that patients with metastatic colorectal disease have BRAF gene status determined as part of their workup when the KRAS gene is not mutated. The guidelines also state that patients with a known V600E BRAF mutation should not be treated with anti-EGFR monoclonal antibodies.

The available data for BRAF mutations predicting response to anti-EGFR therapy are limited by retrospective analysis and small numbers of patients with BRAF mutations. However, it seems clear that this mutation is
a poor prognostic marker, as it is associated with shorter PFS and OS regardless of treatment. Given the recent results of the retrospective analysis of the CRYSTAL trial, it cannot be assumed that BRAF mutational status is predictive for response to anti-EGFR therapy. On the contrary, the CRYSTAL data suggest that KRAS wild-type/BRAF mutant patients may actually respond to anti-EGFR therapy.

Thus, based on the available data, BRAF testing should not routinely be performed outside of a clinical trial. With the evidence we currently have, it is unclear how we can apply the results of BRAF testing to the treatment of advanced CRC. Although patients with BRAF mutations have a poor prognosis, more information is necessary to determine the ability of BRAF testing to predict response to anti-EGFR therapy. It seems impractical to suggest that we need prospective studies evaluating BRAF mutational testing with anti-EGFR therapies prior to recommending its use in clinical practice, given that it occurs in less than 10–15% of patients. It may be reasonable to proceed with a meta-analysis of the current anti-EGFR therapy trials to evaluate BRAF mutations.

In conclusion, BRAF mutation is a negative prognostic marker in patients with mCRC and is associated with a shorter PFS and OS. In the future, comprehensive diagnosis of the EGFR signaling pathways may be needed to select mCRC patients who will respond to cetuximab- or panitumumab-based therapies.

References

27. Peeters M, Price T, Horko Y, et al. Randomized phase III study of panitumumab (pmab) with FOLFI versus FOLFI alone as second-line treatment (as) in patients (ps) with metastatic colorectal cancer (mCRC); patient-reported outcomes (PRO). Paper presented at: American Society of Clinical Oncology 2010 Gastrointestinal Cancers Symposium (GCS); January 22-24, 2010; Orlando, FL.