Cetuximab plus FOLFIRI in first-line treatment of *KRAS* mutation-negative, EGFR-positive metastatic colorectal cancer

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In July 2012, cetuximab was approved for use in combination with FOLFIRI (irinotecan, 5-fluorouracil, leucovorin) for first-line treatment of patients with *KRAS* mutation-negative (wild-type), EGFR-expressing metastatic colorectal cancer (mCRC) as determined by Food and Drug Administration-approved tests. A companion diagnostic, Therascreen KRAS RGQ PCR Kit for determining *KRAS* mutation status was approved concurrently with the cetuximab approval. The test is a real-time polymerase chain reaction assay that detects 7 mutations of the *KRAS* gene; tumors with none of these mutations are considered wild-type *KRAS* tumors.

The approval of cetuximab for this indication was based on retrospective analyses of outcomes according to tumor *KRAS* mutation status in the CRYSTAL trial and 2 supportive studies, the CA225025 study and the OPUS study.[1,2] Overall, these analyses showed that the addition of cetuximab to chemotherapy or best supportive care resulted in improved overall survival (OS), progression-free survival (PFS), and overall response rates (ORR) in patients with *KRAS* wild-type tumors, whereas no benefit, or even potential harm, was observed in patients with *KRAS* mutant tumors.

In the open-label CRYSTAL trial,[3] 1,217 patients with EGFR-expressing mCRC who had not received prior chemotherapy for metastatic disease were randomized to receive cetuximab plus FOLFIRI or FOLFIRI alone. In the total population, PFS (the primary end point) was significantly prolonged in the cetuximab group (median, 8.9 vs 8.1 months; hazard ratio [HR], 0.85; 95% CI, 0.74-0.99; $P = .036$). There were no differences between groups with regard to OS (the secondary end point) at the planned analysis (HR, 0.93; 95% CI, 0.82-1.07; $P = .327$, after 838 events) and a marginally significant improvement with cetuximab in an updated analysis (median, 19.6 vs 18.5 months; HR, 0.88; 95% CI, 0.78-1.00, after an additional 162 events).

Tumor tissue was evaluable for *KRAS* mutation status in 89% of the patients (1,079/1,217) in CRYSTAL; 676 patients (63%) had wild-type and 403 (37%) had mutant tumors. Among those with wild-type tumors, cetuximab patients had significantly prolonged OS (median, 23.5 vs 19.5 months for FOLFIRI alone; HR, 0.80; 95% CI, 0.67-0.94) and PFS (median, 9.5 vs 8.1 months; HR, 0.70; 95% CI, 0.57- 0.86) ORR was 57% with cetuximab plus FOLFIRI, compared with 39% with FOLFIRI alone. There were no improvements observed in cetuximab patients with *KRAS* mutant tumors in OS (median, 16.0 vs 16.7 months; HR, 1.04; 95% CI, 0.84-1.29), PFS (median, 7.5 vs 8.2 months; HR, 1.13; 95% CI, 0.88-1.46), or ORR (31% vs 35%) compared with FOLFIRI-alone patients with mutant tumors.

The CA225025 study[4] was an open-label, randomized trial that compared cetuximab plus best supportive care with best supportive care alone in 572 patients with previously treated EGFR-expressing mCRC. The study showed a statistically significant improvement in OS in the cetuximab arm and served as the basis for the approval of cetuximab in October 2007 as a single agent for treating EGFR-expressing mCRC after failure of both irinotecan- and oxaliplatin-based regimens or in patients who were intolerant to irinotecan-based regimens. For the retrospective analysis, tumor tissue was evaluable for *KRAS* mutation status in 79% of patients (453/572). Among patients with wild-type tumors, cetuximab treatment was associated with significantly prolonged OS (8.6 vs 5.0 months; HR, 0.63; 95% CI, 0.47-0.84) and PFS (median, 3.8 vs 1.9 months; HR, 0.42; 95% CI, 0.32-0.56) compared with best supportive care alone. Among patients with mutant *KRAS*, no improvements in OS or PFS were observed for the cetuximab group compared with the group receiving best supportive care alone.

The OPUS trial[5] was an open-label, randomized phase 2 study that compared cetuximab plus FOLFOX-4

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How I treat metastatic colon cancer

Although clinical trials test treatments in highly defined and selective populations of patients, in practice most of our patients would not necessarily be eligible for these studies, and we therefore need to extrapolate the results of experimental trials into more typical clinical situations. Let us consider 4 different patients who seek our advice. The first is a 74-year-old woman, 4 years out from stage II colon cancer (and without adjuvant therapy) who was found on a routine X-ray to have 7 < 1-cm asymptomatic pulmonary nodules. The second patient is 54 years old, asymptomatic, with 3 lesions in the right lobe of the liver, with a stage III colon cancer treated with adjuvant FOLFOX 3 years ago. Patient number 3 is 64 years old, and has mild fatigue and weight loss, and numerous liver and lung metastases. The fourth patient, aged 41 years, presents with a synchronous colon primary and multiple liver and peritoneal metastases and a PS of 2. Is it possible that a single regimen could meet the needs of each of these patients?

For the first patient, who by some definition has lived with mCRC since her noncurative surgery 4 years previously, serendipitously found, is asymptomatic. Does she require treatment with a combination therapy and a biologic? An immediate and complete response is hardly necessary and single-agent capecitabine, with or without bevacizumab could be considered reserving other drugs for sequential use. For the second patient with potentially curative liver lesions, cetuximab-containing combination can be used, especially if the patient is considered to be "borderline resectable." The third patient is one who is representative of those patients who typically enter clinical trials, so that combination chemotherapy, with or without cetuximab or bevacizumab, should be considered, with various forms of "treatment holidays." The fourth patient is one in which an immediate and more complete response is required, to reverse a dire disease course, remembering that this patient may not have the ability to receive further lines of therapy. This is one scenario in which the choice of first-line cetuximab may be attractive, as achieving response is more important than prolonging response, although this considered a priority in responding patients. This raises the possibility of an individualized regimen, in which combination chemotherapy with cetuximab is given until a good response is achieved (typically 3-4 months), followed by chemotherapy (the same or different) and bevacizumab alone to help maintain the response, in the spirit of E3200 with bevacizumab or the VELOUR trial with aflibercept.

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(5-flourouracil, folinic acid, and oxaliplatin) versus FOLFOX-4 alone as first-line treatment in 337 patients with EGFR-expressing mCRC. ORR was the primary endpoint of the trial. For the retrospective analysis, tumor tissue was evaluable for *KRAS* mutation status in 93% of patients (315/337). Among patients with *KRAS* wild-type tumors, ORR was 57% in the cetuximab plus FOLFOX-4 arm compared with 34% with FOLFOX-4 alone, and improvements in PFS (median 8.3 vs 7.2 months, HR 0.57, 95% CI 0.38-0.86) and OS (median 22.8 vs 18.5 months, HR 0.86, 95% CI 0.60-1.22) were observed for the cetuximab group. Among patients with *KRAS* mutant tumors, no improvements in OS, PFS or ORR were observed with cetuximab plus FOLFOX-4 compared with FOLFOX-4 alone.

A safety analysis compared adverse events among wild-type *KRAS* patients receiving cetuximab plus FOLFIRI (317 patients) or FOLFIRI alone (350) in the CRYSTAL trial.[2] It should be noted that CRYSTAL used European Union (EU)-approved cetuximab; US-approved cetuximab produces approximately 22% greater drug exposure than EU-approved cetuximab. The most common adverse events in patients in the cetuximab group compared with the FOLFIRI-alone group were acne-like rash (86% vs 13%), diarrhea (66% vs 60%), neutropenia (49% vs 42%), stomatitis (31% vs 19%), and anorexia (30% vs 23%). Additional adverse events that were at least 10% more frequent with cetuximab, included pyrexia (26% vs 14%), paronychia (20% vs < 1%), palmar-plantar erythrodysesthesia syndrome (19% vs 4%), skin fissures (19% vs 1%), conjunctivitis (18% vs 3%), and infusion-related reactions (14% vs < 1%). The most common grade 3 or 4 adverse events in cetuximab patients were neutropenia (31% vs 24%), diarrhea (16% vs 10%), and acne-like rash (18% vs < 1%). Other grade 3 or 4 adverse events that were at least 2% more frequent in cetuximab patients included paronychia (4% vs 0%), palmar-plantar erythrodysesthesia syndrome (4% vs < 1%), stomatitis (3% vs 1%), infusion-related reactions (2% vs 0%), and skin fissures (2% vs 0%).

An additional safety analysis compared adverse events among wild-type *KRAS* patients receiving cetuximab plus best supportive care (118 patients) or best supportive care alone (124) in the CA225025 trial. The most common adverse events among the cetuximab patients compared with those receiving best supportive care alone were rash/desquamation (95% vs 21%), fatigue (91% vs 79%), nausea (64% vs 50%), pain-other (59% vs 37%), dry skin (57% vs 15%), and constipation (53% vs 38%). Additional adverse events that were at least 15% more frequent with cetuximab included pruritus (47% vs 11% with best supportive care alone), diarrhea (42% vs 23%), headache (38% vs 11%), infection without neutropenia (38% vs 11%), stomatitis (32% vs 10%), nail changes (31% vs 4%), and infusion-

related reactions (18% vs 0%). The most common grade 3 or 4 adverse events with cetuximab were fatigue (31% vs 29%), pain-other (18% vs 10%), dyspnea (16% vs 13%), rash/desquamation (16% vs 1%), gastrointestinal reactions-other (12% vs 5%), and infection without neutropenia (11% vs 5%). Other grade 3 or 4 adverse events that were at least 3% more frequent with cetuximab included confusion (6% vs 2%), dehydration (5% vs 0%), fever (3% vs 0%), infusion reactions (3% vs 0%), and arthralgia (3% vs 0%).

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