

# ADVANCES IN ONCOLOGY

Current Developments in the Management of Solid Tumor Malignancies

Guest Section Editor: Axel Grothey, MD

## Colorectal Cancer in Focus

### Bevacizumab vs EGFR Antibodies in Metastatic Colorectal Cancer



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#### **H&O** What are the benefits and limitations of bevacizumab in metastatic colorectal cancer?

**AV** The angiogenesis inhibitor bevacizumab (Avastin, Genentech), which inhibits vascular endothelial growth factor A, has several benefits in metastatic colorectal cancer. It appears to confer a survival advantage, and depending on the study cited it also may add somewhat to response rate—although that depends on the agent it is paired with. Also, bevacizumab is generally well tolerated. The main limitations of bevacizumab are that it does not produce a large improvement in response rate or depth of response, and it bears a small risk—2% to 4%—of a major complication, such as stroke, heart attack, or bowel perforation.

#### **H&O** What are the benefits and limitations of epidermal growth factor receptor (EGFR) antibodies for metastatic colorectal cancer?

**AV** The EGFR antibodies cetuximab (Erbix, Bristol-Myers Squibb/Lilly) and panitumumab (Vectibix, Amgen) have an incremental effect on survival. They also appear to enhance the response rate, perhaps a bit more than bevacizumab does. We know that patients with a *RAS* mutation do not benefit from EGFR antibodies, but there is an opportunity for patients whose tumors do not have a *RAS* mutation to benefit. The main downside of these agents is that they can cause a severe acneiform rash.

#### **H&O** Which of these agents is more effective in metastatic colorectal cancer, bevacizumab or EGFR antibodies?

**AV** They are equally effective in my opinion, based on the

study I presented at the most recent annual meeting of the American Society of Clinical Oncology, CALGB (Cancer and Leukemia Group B)/SWOG 80405. In this study, patients with *KRAS* wild-type metastatic colorectal cancer who were receiving irinotecan/5-fluorouracil/leucovorin (FOLFIRI) or oxaliplatin/5-fluorouracil/leucovorin (mFOLFOX6) were randomly assigned to receive either bevacizumab or cetuximab. After a median follow-up of 24 months, overall survival was no different between the bevacizumab and cetuximab groups (see the Figure).

The FIRE-3 study from Europe, which looked at FOLFIRI in combination with either bevacizumab or cetuximab, produced a very different result: overall survival was longer with cetuximab. I do not believe that this shows the superiority of cetuximab over bevacizumab, however. The bevacizumab patients simply did poorly in this study. They did much worse than the patients in the CALGB/SWOG 80405 study; their average survival was 7 to 8 months shorter. Other unusual findings in FIRE-3 relate to the overall survival results. It is unprecedented in colorectal cancer for overall survival to differ when progression-free survival does not, and divergence of the survival curves at 18 months does not have a clear biological explanation.

#### **H&O** Does the choice of chemotherapy backbone matter when selecting the biologic agent?

**AV** The answer is that we do not know. In CALGB/SWOG 80405, more than two-thirds of the patients received FOLFOX as the backbone. We did not have enough patients on FOLFIRI to know whether the backbone made a significant difference. Also, we did not randomly assign patients to one or the other backbone therapy.

**H&O** Are either EGFR antibodies or bevacizumab preferred for a potentially curable situation, such as borderline resectable liver metastases?

**AV** The problem with bevacizumab in that setting is that you have to wait 6 to 8 weeks from the last dose of bevacizumab to perform surgery because of the potential surgical complications of bevacizumab, which can lead to postoperative bleeding. Aside from that one consideration, nearly all the data suggest that the choice does not matter. The one exception is a study that was published in *Lancet Oncology* in 2014 called New EPOC. This study looked at more than 250 people who were undergoing surgery for *KRAS* exon 2 wild-type colorectal cancer that had spread to the liver. The patients were randomly assigned to receive either chemotherapy alone or chemotherapy combined with cetuximab, which was administered for 12 weeks prior to surgery and again for 12 weeks after surgery. What was surprising was that after a median follow-up of 20.7 months, the average progression-free survival was lower in the group having chemotherapy and cetuximab (14.1 months) than in the group having chemotherapy alone (20.5 months); cetuximab appeared to be detrimental for these patients.

**H&O** What do you think made this study an outlier?

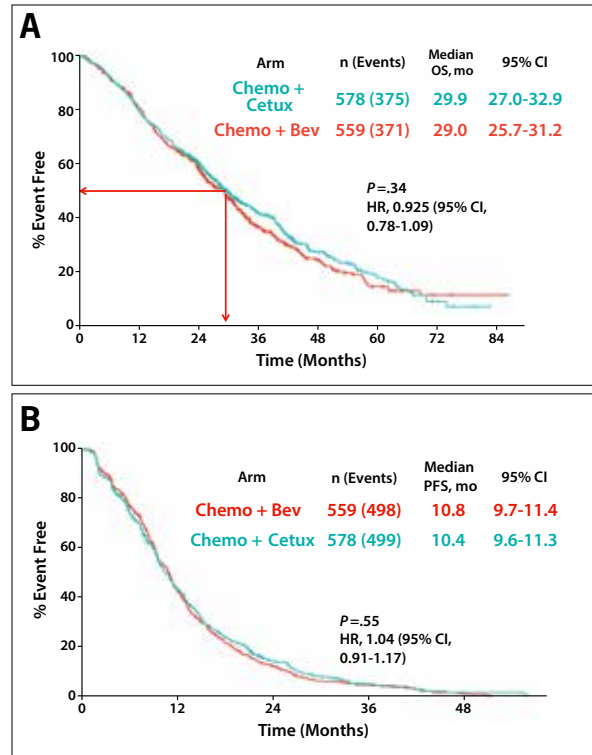
**AV** The reason is open to interpretation, but I believe there were issues with assuring the quality of the surgery. Furthermore, controlling for variables in the extent of liver involvement is a great challenge. In addition, many different chemotherapies were employed. Although I am skeptical about the results for these reasons, of course that does not mean the results are invalid.

**H&O** Is there a particular reason to use one agent before the other one?

**AV** No, I would say that these are equal-opportunity drugs. Patients should have a choice because at the end of the day, you can mix and match and the patients will probably do just as well regardless of the combination you use first. In addition, the subsequent treatments that are used probably dilute the effect of the first-line treatment.

**H&O** How do you go about presenting the choice between bevacizumab and EGFR inhibitors to a patient?

**AV** In addition to presenting the risks and benefits, I explain that we do not need to use either agent as first-line therapy. We can begin with FOLFOX or FOLFIRI alone—I tend to use FOLFIRI most of the time—and begin using a biologic agent at a later point. We do not



**Figure.** Interim results of CALGB/SWOG 80405, presented at the 2014 American Society of Clinical Oncology annual meeting. **A**, Overall survival. **B**, Progression-free survival as determined by the investigators.

Bev, bevacizumab; CALGB, Cancer and Leukemia Group B; cetux, cetuximab; chemo, chemotherapy; HR, hazard ratio; mo, months; n, number of patients; OS, overall survival; PFS, progression-free survival.

know whether that is a superior approach, and it is not something that is easy to study, but most often I start patients on chemotherapy without a biologic as first-line therapy. Is that the right approach? If you have 5 experts, you will get 6 different opinions.

**H&O** Can bevacizumab and EGFR antibodies be combined with each other?

**AV** They were combined in the BOND-2 study by Saltz and colleagues, which was published in the *Journal of Clinical Oncology* in 2007. This phase 2 study showed that the combination of bevacizumab and cetuximab had highly substantial activity, even though the patients were not tested for *RAS* status back then. Among the 40 patients who were randomly assigned to bevacizumab and cetuximab alone, the time to progression was 4.9 months and the response rate was 20%. Among the 43 patients who were randomly assigned to bevacizumab and cetuximab in addition to irinotecan, the time to progression was 14.5 months and the response rate was 11.4%. Combining these agents did not lead to an excessive amount of toxicity, and the activity

against disease seemed to be favorable when compared with previous studies of cetuximab or cetuximab/irinotecan that did not include bevacizumab.

This led to a lot of excitement, but then the PACCE (Panitumumab Advanced Colorectal Cancer Evaluation) and CAIRO2 studies came out. Both of these showed that combining biologic agents was harmful, mostly because of toxicity. PACCE, which was published in the *Journal of Clinical Oncology* in 2009, included more than 1000 patients with metastatic colorectal cancer who were randomly assigned to receive panitumumab or not in combination with bevacizumab and oxaliplatin- or irinotecan-based chemotherapy. Panitumumab was discontinued after a planned interim analysis showed that it increased toxicity and decreased progression-free survival. Analysis of *KRAS* status showed that panitumumab was harmful for patients in both the wild-type and mutant groups. In CAIRO2, which was published in 2009 in the *New England Journal of Medicine*, 755 patients with previously untreated metastatic colorectal cancer were randomly assigned to capecitabine, oxaliplatin, and bevacizumab alone or in combination with cetuximab. The study found that the addition of cetuximab to chemotherapy shortened progression-free survival (from 10.7 to 9.4 months) and worsened quality of life.

The mistake, in my opinion, is that PACCE and CAIRO2 looked at combining biologic agents with chemotherapy as first-line therapy. I do think that combining biologic agents for second-line and third-line treatment without chemotherapy could be advantageous, and this is something worth pursuing in clinical trials but not recommended for the average off-study patient.

### Suggested Readings

Hecht JR, Mitchell E, Chidiac T, et al. A randomized phase IIIB trial of chemotherapy, bevacizumab, and panitumumab compared with chemotherapy and bevacizumab alone for metastatic colorectal cancer. *J Clin Oncol*. 2009;27(5):672-680.

Primrose J, Falk S, Finch-Jones M, et al. Systemic chemotherapy with or without cetuximab in patients with resectable colorectal liver metastasis: the New EPOC randomised controlled trial. *Lancet Oncol*. 2014;15(6):601-611.

Saltz LB, Lenz HJ, Kindler HL, et al. Randomized phase II trial of cetuximab, bevacizumab, and irinotecan compared with cetuximab and bevacizumab alone in irinotecan-refractory colorectal cancer: the BOND-2 study. *J Clin Oncol*. 2007;25(29):4557-4561.

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