Predictive Biomarkers for Response to Cetuximab in Colorectal Cancer: KRAS Marches On

In the parade of molecules that strives for validation as predictors of therapeutic activity, the oncogene KRAS seems to have found its place in front of the band. Bolstering this position are two studies that examined the utility of this marker in predicting response to cetuximab (CTX).

In the EVEREST study, presented by Sabine Tejpar, MD, PhD, University Hospital Gasthuisberg, Leuven, Belgium, patients with metastatic colorectal cancer (mCRC) were first treated with irinotecan, 180 mg/m2 q2w, plus a standard dose of CTX at 250 mg/day. After 22 days, patients with 0/1 skin toxicity were randomized to irinotecan plus standard or an escalated dose of CTX (up to 500 mg/day). For KRAS analysis, mutant (mt) versus wild-type (wt) genomic DNA was isolated from archived tissue samples, and KRAS status was then compared with treatment outcome.

Results for this study were mixed. While escalation of the CTX dose resulted in a non-significant trend toward higher response rates in KRAS-wt patients—42% versus 30% for the standard dose—there was a sharp distinction between outcomes according to KRAS status in both treatment arms. The progression-free survival (PFS) of KRAS-wt was 173 days versus 83 days for KRAS-mt ($p<0.0001$). The latter group was particularly resistant to response, as dose escalation of CTX showed no significant effect, and in fact, the rate of stable disease was lower for this group. Dr. Tejpar also presented data that suggested that skin toxicity is a biomarker for response that is independent of KRAS.

Discussing this study, and taking some issue with the conclusion regarding skin toxicity, was Mace L. Rothenberg, MD, Vanderbilt-Ingram Cancer Center, Nashville, TN. First addressing the study's main conclusion, Dr. Rothenberg agreed that KRAS-wt status was strongly associated with good response, as opposed to KRAS-mt. Dr. Rothenberg added, "Although skin toxicity in patients with KRAS mutant tumors tracked with progression-free survival, PFS was still quite short in these patients—and there were no objective responses in this group."

The second study, reported by C. Bokemeyer, MD, University Hospital, Hamburg, Germany, was a retrospective analysis of the OPUS investigation, first reported at the European oncology meeting ECCO in 2007. In this study, patients with mCRC were treated first-line with either FOLFOX alone (oxaliplatin 85 mg/m2 + 5-FU/FA every 2 weeks) or FOLFOX plus CTX (250 mg/m2 weekly; n=372). The results that were reported at that time showed trends toward, but no significant improvement in, PFS or overall survival (OS) in the CTX arm but showed a significant improvement in response rate. "The response rate was about 10% higher in patients who received cetuximab in addition to chemotherapy and 15% improved in patients who had good performance."

To tease out those patients who had the greatest response, Dr. Bokemeyer and colleagues set out to re-analyze the data relative to the patient's KRAS status. For this work, tissue samples from 233 patients were processed.

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The rate of KRAS mutations that was detected in these samples matched known values for colon cancer populations: 58% was KRAS-wt, and 42% KRAS-mt. Relating this proportion treatment efficacy, Dr. Bokemeyer stated that for KRAS-wt, "CTX/FOLFOX had a 61% overall rate of response, which was significantly improved over FOLFOX alone at 37%, with an odds ratio of 2.54 ($p=0.001$)." There was no improvement in efficacy in KRAS-mt patients, and in

fact, as in the EVEREST trial, these patients did worse on the combination. PFS for the combination versus FOLFOX alone was 7.7 versus 7.2 (p=0.016). The adverse events outcomes were as expected; the incidence of neutropenia and rash was higher in the combination arm but not considered significant.

Commenting on this study, Dr. Rothenberg expressed several concerns. Regarding the outcome for KRAS-mt patients on the combination, "Here we see the opposite, and possibly detrimental, effect on patient outcomes as compared with KRAS wild-type." Further, he took issue with the higher rates of grade 3/4 hematological and GI toxicities for the combination as compared with FOLFOX alone. "There's a difference in patterns of toxicity that are based on KRAS status – why?" He wondered if these observations would carry over to CTX combination with the FOLFIRI regimen and if the effect was limited to CTX or also would be seen with panitumumab. Dr. Rothenberg concluded, "Monoclonal antibodies against EGFR clearly are useful drugs in CRC, but we must learn how to use these drugs in a fashion that maximizes benefit and minimizes risk."

Initial Safety Data of Bevacizumab as Adjuvant Therapy for Colorectal Cancer

The results of a National Surgical Adjuvant Breast and Bowel Project (NSABP) (NCT00096278) trial indicate that bevacizumab is safe when it is given as postoperative adjuvant therapy (in conjunction with conventional chemotherapy) to patients with stage II or stage III colorectal cancer. The efficacy data from the study are not yet available, but the safety data were reported first because of the potential effect on ongoing or planned investigations that involve bevacizumab and other antiangiogenic agents.

Carmen J. Allegra, MD, University of Florida, Gainesville, FL, reported the initial safety data from NSABP C-08. This randomized phase 3 trial was designed to compare modified FOLFOX6 (5-FU/leucovorin plus oxaliplatin) with and without bevacizumab. The primary endpoint was disease-free survival. One of the most important findings of the safety analysis, said Dr. Allegra, is that bevacizumab is safe in the postoperative period in the patient population that is eligible for C-08. It is not clear how far the data can or should be extrapolated beyond the eligible population. "The fear has been that, as an antiangiogenic agent, bevacizumab could have serious toxicity for postoperative patients. This was not borne out in the study," he said.

The trial enrolled 2710 patients who were randomly assigned to either FOLFOX6 every 2 weeks for 12 doses or the same chemotherapy regimen with bevacizumab given every 2 weeks for 26 doses. Patients were assigned to a treatment group after Day 29 and before Day 50 postoperatively. The data that were presented by Dr. Allegra represented findings for 1321 patients who were treated with FOLFOX6 alone and 1326 who were treated with FOLFOX6 plus bevacizumab. The mean duration of follow-up was 28.5 months.

The addition of bevacizumab did not adversely affect the dose intensity of FOLFOX6. Dr. Allegra noted that the median dose intensity was 40.6 mg/m2/wk for FOLFOX6 alone and 41.6 mg/m2/wk for FOLFOX6 plus bevacizumab (p=0.13). A significantly greater percentage of patients who were treated with FOLFOX6 plus bevacizumab received at least 10 of the 12 doses of 5-FU (85% vs 80%; p<0.01) and oxaliplatin (78% vs 73%; p<0.01).

Dr. Allegra reported that bevacizumab was not associated with a significant increase in several toxicities that have been found in other studies of advanced disease, such as cardiac, central nervous system, or peripheral arterial ischemia; gastrointestinal perforation; or hemorrhage. Bevacizumab was associated with significantly fewer occurrences of thrombocytopenia (1.4% vs 3.4% for FOLFOX6 alone; p<0.001) and allergic reaction (3.1% vs 4.7%; p=0.03).

There was no difference between the early mortality in each group. Within 6 months of random assignment, the mortality rate was 0.96% for FOLFOX6 alone and 0.90% for FOLFOX6 plus bevacizumab (p=1.0). At 18 months, the corresponding mortality rates were 1.33% and 1.35% (p=1.0).

Most of the adverse events were grade 3, and these events occurred in significantly more patients in the FOLFOX6 plus bevacizumab group (p=0.0006). All of the adverse events were manageable, added Dr. Allegra. To isolate the effects of bevacizumab, the researchers evaluated adverse events that occurred in the 12 months that followed the completion of chemotherapy (Table 1). Focusing on wound complications, Dr. Allegra noted that all such complications were grade 3 and that they resulted in surgical intervention in all but one case and in discontinuation of bevacizumab in half of the cases. Most of the wound complications (63%) were symptomatic abdominal incisional hernias, and 37% was dehiscence, infection, or inflammation at the site of the infusion port. The median time to occurrence of the wound complications was 5 months for hernias and 2 months for the infusion port-related complications.