Researchers have temporarily halted accrual to a trial of bevacizumab (Avastin) and two chemotherapy regimens for early-stage colon cancer after they found an unexpected number of non-cancer-related deaths in one of the study arms. The data safety monitoring board (DSMB) recommended that enrollment be delayed until 60-day mortality data could be collected and reviewed for all patients currently in the study. Experts say that the imbalance in deaths is likely to be a statistical anomaly, but they agree that the safety committee acted appropriately.

Thus far, about 2,100 patients with stage II and III colon cancer have enrolled in the international phase III trial, which is run by Genentech, of South San Francisco, Calif., and Roche, in Basel, Switzerland. Called AV ANT, the trial is designed to compare disease recurrence rates in patients treated after surgery with one of three regimens: FOLFOX (oxaliplatin, leucovorin, and 5-fluorouracil), FOLFOX plus bevacizumab, or XELOX (capecitabine and oxaliplatin) plus bevacizumab.

Since the trial opened in December 2004, four (0.6%) patients have died of noncancer-related causes in the FOLFOX arm, three (0.4%) have died in the FOLFOX/bevacizumab arm, and seven (1.0%) in the XELOX/bevacizumab arm. Although the absolute number of deaths is small in all three arms, a substantial number of these patients may have already been cured of their disease by surgery and thus incurring unnecessary risk. Also, several of the deaths occurred in younger patients and some were due to cardiac problems, though further details have not been released.

The AV ANT DSMB recommended that accrual be suspended, “but the evidence is very weak that there is anything going on,” said Stephen L. George, Ph.D., professor of biostatistics at Duke University Medical Center in Durham, N.C., who is not affiliated with the trial. “I think their main concern is that there might be something, but that they don’t have the information yet.”

In addition to the twice-yearly meetings, which are typical for DSMBs, the AV ANT trial DSMB was scheduled to assess real-time safety data every 4 weeks until the first 300 patients had completed 6 weeks in the study. During the first face-to-face meeting of the
committee on Sept. 15, 2005, they reviewed data on those patients as well as for all of the 1,100 patients who began protocol treatment prior to September 14. The committee decided to continue monthly monitoring of the trial because 60-day all-cause mortality was uneven between the trial arms, with no deaths in the control arm, one death in the FOLFOX/bevacizumab arm, and three in the XELOX/bevacizumab arm.

When the committee met again in February and saw that the skewed 60-day mortality pattern remained, they asked for a hiatus in recruitment until they could look at 60-day mortality information on all patients enrolled. Patients who are currently enrolled in AVANT are continuing to receive treatment. The companies noted that part of the reason the DSMB requested the delay was that the trial was recruiting at an unusually fast pace, with more than 250 patients enrolling in January alone.

“The response is unusual,” said George, who is also director of the Cancer and Leukemia Group B Statistical Center. But given the remarkably rapid accrual, the DSMB’s decision to err on the side of caution rather than exposing more patients to potential harm was appropriate, he said.

A trial in a similar patient group comparing FOLFOX to FOLFOX plus bevacizumab is continuing as planned, although all patients have been informed about the events in the international trial. The similar trial, National Surgical Breast and Bowel Project (NSABP) C-08, does not include a capecitabine-containing regimen such as XELOX. However, upon hearing about the AVANT trial data, the NSABP administrators updated all their safety data to include even the most recently enrolled patients. They presented that information to both the chairman of their external DSMB and to the National Cancer Institute, the sponsor of C-08. Everyone agreed that no unusual safety signal was seen in the bevacizumab arm and that there was no reason to delay C-08.

“Early deaths or [gastrointestinal] perforations are very, very low [in AVANT] and are a small number of cases compared to the number of patients that have been entered on the trial,” said Michael O’Connell, M.D., director of the Allegheny Cancer Center and associate chairman of NSABP. “The fact that an increased safety signal has not been seen in advanced patients [in other trials] may be another argument that this is a statistical variation. I won’t be surprised if after the review of 60-day mortality data nothing comes of it.”

—Rabiya S. Tuma