

Neoadjuvant aromatase inhibitor trial completed

by David M. Ota, MD, FACS; Heidi Nelson, MD, FACS; and Matthew Ellis, MB, BChir, PhD

The American College of Surgeons Oncology Group (ACOSOG) has reached another important milestone: ACOSOG Z1031 is a phase III neoadjuvant aromatase inhibitor trial for estrogen receptor-positive, stage II/III postmenopausal breast cancer patients. The trial was activated in June 2005, and in August 2009 it completed patient enrollment (sample size = 375). The top 10 enrolling sites are listed in the Figure on this page.

There were 100 enrolling sites in total, and each site should be congratulated for this accomplishment.

Z1031 is a significant milestone for many reasons. First,

this is the largest cooperative group neoadjuvant aromatase inhibitor trial to have been conducted to date. Second, and most importantly, the trial included a mandatory pretreatment research core needle biopsy of the primary tumor and peripheral blood collection. This required the surgeon to obtain informed consent for the trial treatment and for the research biopsy. Because patient eligibility criteria required a palpable stage II or III breast cancer, many of these biopsies were performed by surgeons. More than 95 percent of enrolled patients have a pretreatment tumor tissue stored in the ACOSOG central

tissue bank. These specimens will be crucial for conducting laboratory investigations.

An important therapeutic question to consider involves the question of why there is a 60 percent tumor response rate when estrogen receptor-positive breast cancers are treated with an aromatase inhibitor. Scientists now have the tissue to study mechanisms of resistance, and such discoveries could lead to new therapeutic options for estrogen receptor-positive breast cancer patients.

A good example of new therapeutic options is already being incorporated into an amended Z1031. Z1031 has been amended to enroll an additional 140 subjects. Ki67 is a biomarker for tumor proliferation, and laboratory studies have shown that if tumor Ki67 is >10 percent after two to four weeks of aromatase inhibitor (AI) therapy, the ER+ breast cancer is unlikely to respond well to endocrine treatment. The amended Z1031 protocol, therefore, requires a second research biopsy in the two to four week window to assess Ki67. The biomarker information will be returned to the treating oncologist, who can recommend switching to neoadjuvant chemotherapy or continued aromatase inhibitor treatment,

Figure	
Site	Number enrolled
MD Anderson Cancer Center, Houston, TX	57
Washington University, St. Louis, MO	50
Doctors Hospital of Laredo, TX	24
Duke University, Durham, NC	22
St. Elizabeth Medical Center, Cincinnati, OH	20
University of Texas Southwestern, Dallas, TX	14
Anne Arundel Medical Center, Annapolis, MD	9
Covenant Medical Center-Lakeside, FL	8
Kansas City CCOP, MO	8
Columbus Ohio CCOP, OH	8

depending on the Ki67 value.

The tissue specimens of Z1031 are annotated with clinical tumor response data in a very specific therapeutic trial. Further laboratory investigations are under way to identify the next generation of biomarkers that predict response to AI therapy. Whole genome DNA sequencing of 50 primary tumors from Z1031 is being planned. These could help us identify somatic tumor mutations or gene amplification associated with tumor resistance.

Z1031 has the potential to become the neoadjuvant therapy

model for future trial designs. Surgeons see patients with primary breast cancer, which is accessible to local biopsy. For a surgeon-oriented cooperative, ACOSOG is well-positioned to take advantage of neoadjuvant therapeutic trial designs that incorporate fresh tissue collection; this tissue collection would apply to many solid tumors that are accessible to outpatient biopsy.

The ACOSOG Central Specimen Bank is funded by a National Cancer Institute core grant, and is designed to store appropriately preserved specimens. If you have a trial idea

which requires multi-site participation and an associated specimen collection for your correlative science studies, you are welcome to contact ACOSOG (Dr. Ota or Dr. Nelson) at david.ota@duke.edu or nelsonh@mayo.edu. ACOSOG conducts therapeutic trials for breast, gastrointestinal, and thoracic malignancies.

Dr. Ota, of Durham, NC, and ***Dr. Nelson***, of Rochester, MN, are ACOSOG Co-Chairs.

Dr. Ellis, of St. Louis, MO, is Z1031 study chair.