Biomarker studies with negative results can be just as important to publish as those with positive results if the study had sufficient power to exclude a positive interaction because clinging to a long-favored but incorrect hypothesis in the face of negative evidence impedes scientific and clinical progress. The study by Viale et al. (1) in this issue of the Journal is a case in point. The investigators studied tumor tissue samples accrued from two large randomized trials that compared endocrine therapy vs cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) chemotherapy followed by endocrine therapy among breast cancer patients with node-negative hormone receptor–positive disease (International Breast Cancer Study Group Trials VIII and IX). In contrast to their expectations, Viale et al. (1) found that tumor Ki-67 labeling index (a measure of the percentage of tumors cells that express the cell proliferation antigen Ki-67 and are therefore in an active phase of the cell cycle) provided information on prognosis but did not predict which patients would benefit from adding CMF to endocrine therapy. This result is striking because it indicates that patients with aggressive node-negative, hormone receptor–positive breast tumors that have a high growth fraction—the patients most in need of additional therapy—obtain no extra benefit from the addition of CMF to their endocrine regimen when compared with patients with lower risk disease. At the most basic level, this study supports the long-held position of the American Society of Clinical Oncology Tumor Markers Expert Panel that measurements of the cell cycle (ie, S phase fraction or Ki-67 labeling index) should not be used for chemotherapy decision making (2). When compared with the positive results obtained by Paik et al. (3) with the 21-gene recurrence score assay, which was able to identify a group of high-risk, node-negative, hormone receptor–positive patients who differentially experienced benefit from CMF, the results reported by Viale et al. (1)

Affiliation of author: Department of Medicine, Division of Oncology, Siteman Cancer Center, Washington University in St Louis, St Louis, MO.
Correspondence to: Matthew J. Ellis, MB, PhD, FRCP, Department of Medicine, Division of Oncology, Siteman Cancer Center, Washington University in St Louis, Campus Box 8056, 660 South Euclid Ave, St Louis, MO 63110 (e-mail: mellis@wustl.edu).
DOI: 10.1093/jnci/djm325
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serve to emphasize the point that predicting chemotherapy sensitivity in the hormone receptor–positive subgroup requires an assay that integrates more biologic parameters than just the baseline rate of cell cycle progression.

The absence of an interaction between growth fraction and chemotherapy benefit also fuels the historic and increasingly vigorous debate regarding the role of chemotherapy for estrogen receptor (ER)–positive, HER2-negative disease. For example, data from a randomized study (Cancer and Leukemia Group B 9344) investigating the benefits of adjuvant paclitaxel suggest that patients with this breast cancer subtype have derived considerably less benefit from paclitaxel treatment than patients with ER-negative or HER2-positive disease (4). Furthermore, a recent meeting report on a subpopulation of tumor specimens from patients with node-positive and hormone receptor–positive breast cancer who were treated in a randomized trial of cyclophosphamide, doxorubicin, and fluorouracil (CAF) followed by tamoxifen vs tamoxifen therapy alone (Southwest Oncology Group 8814) suggests that the 21-gene recurrence score may identify a population of patients for whom CAF is ineffective despite having a 10-year relapse risk of 40% (5). Sadly, there are many patients with high-risk ER-positive, HER2-negative disease for whom neither chemotherapy nor endocrine therapy is an effective treatment. Because ER-positive disease is three to four times more common than ER-negative disease, the majority of deaths from breast cancer still occur among women who have an ER-positive tumor.

So what sources of data can we examine to shed light on the mechanisms of treatment resistance that is exhibited by high-risk ER-positive disease? Increasingly, we are looking to the results of neoadjuvant endocrine therapy studies to unravel the biology of ER+ breast cancer. Two such studies (6,7) have shown that aromatase inhibitors and tamoxifen dramatically decrease Ki-67 labeling index indicating that endocrine treatment exerts its therapeutic effects through the induction of cell cycle arrest. Indeed, on-treatment levels of tumor Ki-67 (ie, the level of Ki-67 measured in a tumor biopsy taken 2 weeks after the initiation of endocrine treatment), as opposed to the baseline level of Ki-67, looks to be a very promising method for predicting relapse, a result that breathes new life into the potential value of Ki-67 as a breast cancer biomarker (8). Curiously, one study of markers of benefit in neoadjuvant endocrine therapy of breast cancer found that apoptosis rates (detected with the terminal deoxynucleotidyltransferase-mediated UTP end-labeling [TUNEL] assay) were also decreased by endocrine therapy (9). This counterintuitive result suggests that the permanent breast cancer remissions induced by 5 years of tamoxifen (10) may involve alternative mechanisms of cellular attrition within tumors that are, perhaps, linked to cell cycle arrest (11). However, it is also readily evident from a study of late adjuvant therapy (the National Cancer Institute of Canada MA.17 trial) that for many patients, endocrine therapy does not produce permanent tumor regression but functions as maintenance therapy, preventing metastatic disease from becoming clinically evident (12). Clearly, an entirely new pharmacology to promote cell cycle arrest and cell death in ER-positive breast cancer will be required if we are going to make progress in both improving outcomes and reducing the amount of time that patients have to be exposed to estrogen deprivation and/or tamoxifen, given the attendant toxic effects and adverse effects of these treatments on quality of life.

To begin to design new treatment strategies, we must understand the genomic landscape of ER-positive breast cancer. Experiments are underway to sequence entire breast cancer genomes, and, at first glance, the data seem overwhelming, with hundreds of cancer-specific abnormalities to follow up for clinical correlations (13). However, a closer look suggests that these mutations often occur within well-studied pathways that are the focus of active drug development programs. The American College of Surgeons Oncology Group (ACOSOG) and the Central Clinical Trials Support Unit are currently accruing postmenopausal patients with ER-positive clinical stage 2 and 3 breast cancer to a neoadjuvant aromatase inhibitor study that is comparing the three approved aromatase inhibitors (ACOSOG Z1031). Participants are being asked to provide written informed consent for studies that include gene sequencing, expression profiling, and array comparative hybridization. Through this study, and others like it, we may be able to move toward a functionally annotated genome atlas for ER-positive breast cancer that will provide the roadmap for progress in this common and still often fatal disease (14).

References


