Optimizing Endocrine Therapies for the Individual Patient with Breast Cancer: Identifying Targets for Tailored Treatment

PROJECT SUMMARY AND PROGRESS REPORT

Approximately 60-65% of breast cancers have estrogen receptors inside the cancer cells. Estrogen promotes growth of these "estrogen receptor positive" (ER+) tumor cells. Therefore, targeted therapies that block estrogen or reduce estrogen levels, called endocrine therapy, are often effective treatments for ER+ breast cancer. Currently, there are two classes of endocrine therapeutics for breast cancer: selective estrogen receptor modulators (SERM), such as tamoxifen, and aromatase inhibitors, such as letrozole and exemestane. SERMs work by competing with estrogen to bind to the estrogen receptors in the breast cancer cells, and aromatase inhibitors work by interfering with the production of estrogen so that less estrogen is available in the body to reach the breast cancer cells. Patients with ER+ breast cancer who take tamoxifen or an aromatase inhibitor for five years have a reduced risk of disease recurrence. However, these drugs do not prevent recurrence in 15-30% of patients, and both classes of drugs come with significant side effects. Therefore, identifying features of the cancer cells that predict responsiveness to one or the other of these treatments would allow physicians to select the therapy most likely to prevent breast cancer recurrence so that ineffective therapies and unnecessary side effects are avoided and the risk of recurrence is minimized.

This **Susan G. Komen for the Cure Promise Grant** supports a 3-year, $3.9 million research project to discover biomarkers that could help identify pre- and post-menopausal women with breast cancer who would benefit most, with the fewest side effects, from different endocrine therapies.

RESEARCH TEAM

Giuseppe Viale, MD, is the chairman of the Central Pathology Office and the Biological Protocol Working Group of the International Breast Cancer Study Group (IBCSG) and and Lead Pathologist of the Breast International Group (BIG). He is also Professor of Pathology and Chairman at the University of Milan School of Medicine and Director of the Department of Pathology and Laboratory Medicine at the European Institute of Oncology in Milan, Italy.

Meredith Regan, ScD is the Group Statistician for the International Breast Cancer Study Group (IBCSG). She is also an Associated Professor of Medicine in the Department of Biostatistics and Computational Biology at the Dana-Farber Cancer Insitute and Harvard Medical School, Boston, MA.

Olivia Pagani, MD, is the study chair of the International Breast Cancer Study Group's TEXT trial and co-president of the breast cancer project group of the Swiss Group for Clinical Cancer Research and a Staff Oncologist in the Department of Medical Oncology at the Institute of Oncology of Southern Switzerland in Mendrisio, Switzerland.

The Co-Principal Investigators, Drs. Viale, Pagani, and Regan, have assembled a unique team of experienced investigators from around the world—medical and surgical oncologists, pathologists, basic researchers, and biostatisticians—who are working together with patient advocates to identify clinical biomarkers that will predict responsiveness to various endocrine therapies for breast cancer in order to maximize treatment efficacy while avoiding unnecessary side effects from these treatments. This multi-national team includes investigators from eight research institutions located in the US, Canada, Italy, and Switzerland as well as patient advocates from Europa Donna - The European Breast Cancer Coalition and the Associazione Salute Donna.

RESEARCH PROJECT AND PROGRESS

Through this Promise Grant, the investigators will study the biological characteristics of breast cancer in both pre- and post-menopausal patients, since the amount of estrogen in the body differs dramatically between these two groups. The team will look for changes in specific genes in the patients' cells and the tumor cells that may be used as biomarkers to predict response or resistance to tamoxifen or aromatase inhibitors. In addition, molecular markers of bone loss will be identified in pre-menopausal women since bone loss is a significant side effect of endocrine therapy in young women. Specifically, the project has three primary goals:

1. Investigate patient and tumor features in postmenopausal women with ER+ breast cancer who are enrolled in the BIG 1-98 trial, a large international Phase III study comparing different endocrine therapies in postmenopausal women. The team will analyze primary tumor samples for the presence or absence of specific biomarkers such as HER2 and the progesterone receptor. They will also analyze the variations in genes involved in hormone and/or drug metabolism and transport (how drugs move in and out of cells). These results will then be correlated with the outcomes of the BIG 1-98 trial to identify biomarkers that will predict responsiveness to tamoxifen or an aromatase inhibitor in postmenopausal women with ER+ breast cancer.

2. Identify genetic markers of bone loss in pre-menopausal women enrolled in the Tamoxifen and Exemestane Trial (TEXT), a large international Phase III study comparing different endocrine therapies in premenopausal women being treated with an ovarian suppressor. A subset of 200 of the newly enrolled patients will be included in a bone sub-study that will correlate genetic changes and bone mineral density measurements to identify biomarkers of bone loss.

Translational studies such as ours supported by the Promise Grant require the cooperation of many individuals and groups. They can only be accomplished through the efforts of thousands of people: the patients; the research teams at hundreds of participating trial sites who enroll patients, collect blood samples and ensure trial data quality; the cooperative groups and trial sponsors who facilitate the trials; the pathologists who prepare tissue specimens; the laboratory teams who prepare and analyze the tumor samples; and the IBCSG central offices.

—Meredith Reagan, Co-PI

3. Investigate patient and tumor features that may explain why effectiveness of and side effects from endocrine therapies vary among premenopausal women with ER+ breast cancer who are being treated with triptorelin (a drug used to shut down the ovaries). The team will analyze primary tumor samples from women enrolled in the TEXT trial for the presence or absence of specific biomarkers such as HER2 and the progesterone receptor. They also are collecting blood samples from all patients enrolled in the TEXT trial to expand the TEXT biospecimen bank to include DNA. Variations in genes involved in hormone and/or drug metabolism and transport will also be analyzed. These studies will help identify bio-

markers that will predict responsiveness to endocrine therapy in premenopausal women with ER+ breast cancer, and along with the bone sub-study, will help identify biomarkers that predict bone loss and other side effects from hormonal therapies.

During their first year of funding, the research team made significant progress towards two of their research goals. They have analyzed tissue samples from nearly 5,000 postmenopausal women with ER+ breast cancer who are enrolled in the BIG 1-98 trial. In one study to appear in the *Annals of Oncology*[*], the team determined that individually ER, PgR, HER2 status and Ki-67 do not significantly predict differential treatment effects among the treatment groups; however, a composite measure of risk informs treatment selection better than individual biomarkers and supports the choice of five years of letrozole for patients at highest risk for recurrence. A second study presented at the SABCS 2010 has ruled out CYP2D6—an important enzyme that helps the body metabolize drugs, including tamoxifen—as a biomarker of responsiveness to endocrine therapy. Previous data on CYP2D6 were conflicting, but suggested that CYP2D6 testing may identify patients for whom tamoxifen would not be effective. This study was designed to address the conflicts from the previous studies and provided strong evidence that mutations in CYP2D6 are not associated with response to tamoxifen.

In addition, the team has initiated a bone sub-study in a subset of premenopausal women with ER+ breast cancer who are enrolled in the TEXT trial to explore the potential of predicting bone loss in premenopausal women treated with endocrine therapy. Thus far, more than 60 patients have been enrolled in the bone sub-study. From among all TEXT trial patients, blood samples have been collected from approximately 1,400 patients for the studies of genes involved in hormone and/or drug metabolism and transport.

HOW WILL THIS RESEARCH BRING US CLOSER TO THE CURES?

It is estimated that 230,480 women in the U.S. will be diagnosed with breast cancer, and 39,520 women will die from this disease in 2011. Roughly 60-65% of breast cancers are estrogen receptor-positive (ER+). Endocrine therapies, including tamoxifen and aromatase inhibitors, are effective against ER+ breast cancer, but these drugs do not prevent recurrence in 15-30% of patients. Therefore, identifying which patients will respond to these drugs would optimize the use of endocrine therapies, alleviating unnecessary side effects while avoiding ineffective therapies.

The multidisciplinary research team funded by this Promise Grant is collectively focused on the goal of identifying markers that will predict which patients will respond to tamoxifen over aromatase inhibitors (or vice versa) so that the use of these therapies can be optimized. If successful, these studies will lead to a reduction in morbidity and mortality from ER+ breast cancer.

Susan G. Komen for the Cure® is proud to fund the quest for individualized therapy for estrogen receptor-positive breast cancer.

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*Viale, G., Regan, MM, Dell'orto, P., et al. (2011) Which patients benefit most from adjuvant aromatase inhibitors? Results using a composite measure of prognostic risk in the BIG 1-98 randomized trial. Ann Oncol ePub February 18, 2011.