

Comprehensive Biomarker Discovery Project for Bevacizumab in Breast Cancer

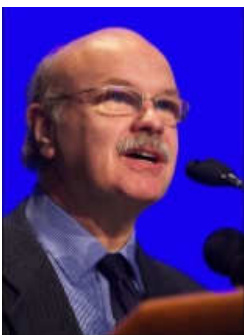
PROJECT SUMMARY AND PROGRESS REPORT

A Phase III clinical trial (called E2100) showed that adding bevacizumab (Avastin) to standard chemotherapy extended the median progression free survival for women with previously untreated metastatic breast cancer. (Bevacizumab is an anti-angiogenesis drug or anti-angiogenic therapy; it prevents tumors from forming their own blood vessels, a process called angiogenesis.) Based on the results of this trial, the Food and Drug Administration (FDA) gave accelerated approval for Avastin. Subsequent studies, however, did not show an improvement in overall survival, and many patients experienced significant side effects including high blood pressure, strokes, and life-threatening blood clots. As is the case for other anti-cancer therapies, it is likely that some patients gain considerable benefit from bevacizumab, and others gain little or no benefit while experiencing serious side effects. The ability to distinguish these patients would enable physicians to selectively prescribe anti-angiogenesis drugs to those most likely to respond while avoiding significant side effects.

This **Susan G. Komen for the Cure Promise Grant** supports a 5-year, \$5.8 million research project to discover biomarkers that will identify patients most likely to respond to anti-angiogenic therapy without experiencing significant side effects.

THE RESEARCH TEAM

Bryan Schneider, MD, is an Associate Professor of Medicine at the Indiana University Melvin and Bren Simon Cancer Center. Dr. Schneider holds appointments in the Divisions of Hematology/Oncology and Clinical Pharmacology in the Department of Medicine with a secondary appointment in the Department of Medical and Molecular Genetics.



David Flockhart, MD, PhD, is Director of the Division of Clinical Pharmacology at the Indiana University School of Medicine and Principal Investigator of the NIH Consortium on Breast Cancer Pharmacogenomics (COBRA).

Drs. Schneider and Flockhart, Promise Grant Co-Principal Investigators, have assembled a team of investigators from Indiana University, Dana Farber Cancer Institute, Massachusetts General Hospital, Research Advocacy Network, and the Eastern Cooperative Oncology Group with extensive experience in biomarker discovery and validation, pharmacogenetics, pathology, clinical oncology, bioinformatics, and psychosocial science. Working closely with patient advocates, the team is looking for biomarkers that can identify which women will benefit from treatment with bevacizumab and which women will experience toxicity without

benefit. Additionally, the patient advocates are developing an educational plan, which includes brochures and manuals, webinars, advocate mentor programs, and advocate grand rounds.

RESEARCH GOALS AND PROGRESS

Through this Promise Grant, the investigators will perform genome-wide association studies (GWAS, pronounced *gee-wahs*) to find biomarkers that predict response to bevacizumab with the least toxicity. GWAS involve rapidly scanning complete sets of DNA from a large group of people (or cohort). Therefore, these studies can detect important genetic associations that are often overlooked in biomarker discovery efforts. The team will also assess how biomarker information affects treatment decisions and physician recommendations regarding anti-angiogenic therapy, and create tools to aid patients and physicians with decision-making so that the results of this Promise Grant can be translated appropriately into patient care.

The project has two main goals:

1. Use GWAS to identify a molecular signature that predicts which patients will benefit most, with the fewest serious side effects, from bevacizumab. These studies will identify genetic variations in VEGF (vascular endothelial growth factors), the target for bevacizumab, as well as other, potentially unexpected genes that predict toxicity from and/or response to anti-angiogenic therapy. The most promising biomarkers will then be validated in a cohort of 2,450 patients enrolled in E5103, an ongoing clinical trial that is comparing standard chemotherapy to chemotherapy plus bevacizumab in the adjuvant setting.
2. Measure and compare quality of life and quality-adjusted life years of patients treated with bevacizumab to determine the degree to which a predictive biomarker might affect treatment decisions and physician recommendations regarding anti-angiogenic therapy. These surveys will assess the patients' perspective on how much of a benefit from bevacizumab is needed to outweigh its side effects and will be used to develop decision-making tools.

With their team, Drs. Schneider and Flockhart are leading the way to personalize medicine by discovering biomarkers for both the side effects and benefits of therapy. Not only is the scientific discovery important, but the researchers want to understand the clinical relevance of those discoveries in terms of patient decision-making and quality of life.

*Mary Lou Smith and Elda Railey
Patient Advocates, Promise Grant Team
Co-Founders, Research Advocacy Network*

During the first year of funding, the research team has made significant progress towards their research goals. They completed GWAS for 2,200 patients and identified molecular signatures that predict side effects from bevacizumab including hypertension and side effects from taxanes including peripheral neuropathy (a nerve problem that causes pain, numbness, tingling, burning, or muscle weakness in different parts of the body, most commonly the hands and feet). Bevacizumab-associated hypertension and neuropathy were found to occur more frequently in African Americans and older individuals. Ongoing studies are looking for biomarkers of efficacy as well as other side effects such as congestive heart failure and scarring of lung tissue.

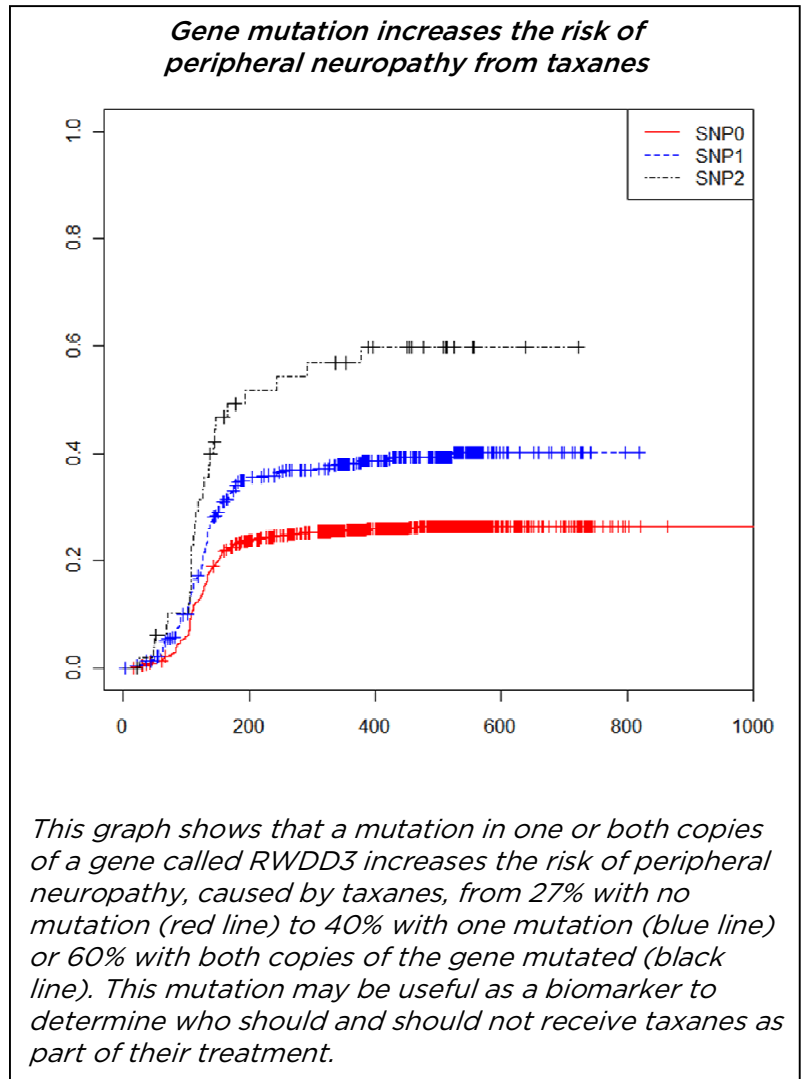
In addition, they are surveying the patients being treated with bevacizumab to assess their willingness to accept side effects compared to the perceived benefit (risk-to-benefit ratio). The investigators will create a decision tool based on this information to help physicians and patients determine whether to include anti-angiogenic therapy in their treatment plan.

They have also developed an 84-page tutorial entitled, *Biomarkers in Cancer: an Introductory Guide for Advocates*, to educate patient advocates about biomarkers. The patient advocates will also be disseminating information to the breast cancer community about the decision aid.

HOW WILL THIS RESEARCH BRING US CLOSER TO THE CURES?

Bevacizumab was originally approved for the treatment of HER2-negative, metastatic breast cancer. It is also being studied in women with earlier stage HER-2 negative breast cancer. However, not all eligible patients benefit from bevacizumab, and there are some substantial toxicities associated with its use, including stroke, blood clots, and high blood pressure. A test that could identify which patients will benefit from bevacizumab, and which will experience toxicity without benefit could have a positive impact on the treatment for Her2-negative, metastatic breast cancer. FDA recently reversed its approval of bevacizumab based on the marginal risk:benefit ratio. This controversy highlights the crucial need for biomarkers to select which patients will gain optimal benefit from this drug.

The multidisciplinary research team funded by this Promise Grant is collectively focused on the goal of identifying biomarkers that will predict both efficacy of and toxicity from bevacizumab. If successful, these studies will enable physicians to identify those patients most likely to reap the benefits of anti-angiogenic therapy and avoid the use of anti-angiogenics in those patients most likely to encounter serious side effects without benefit.



Susan G. Komen for the Cure® is proud to fund the quest for predictive biomarkers that will improve treatment efficacy while reducing toxicity.