ECOG-ACRIN Opens Trial E4112 Using Breast MRI and Genomics for Treatment Decision-Making in DCIS

A new cancer clinical trial by the ECOG-ACRIN Cancer Research Group addresses questions about the over-treatment of ductal carcinoma in situ (DCIS), a non-invasive, non-life-threatening breast cancer. Using personalized diagnostic tools may prevent unnecessary mastectomies and/or radiation for some women.

Philadelphia, Pa., February 5, 2015 – In direct response to recommendations made by a National Institutes of Health (NIH) scientific consensus panel, the ECOG-ACRIN Cancer Research Group announced today the opening of E4112, a clinical trial for women with newly diagnosed DCIS of the breast who, together with their doctors, will use the results of a magnetic resonance imaging (MRI) exam to determine whether to undergo a lumpectomy or a mastectomy. Following that decision, patients and their doctors will use the results of the Oncotype DX® genomic test for DCIS to decide whether to undergo radiation following lumpectomy.

“We believe we can apply combinations of advanced diagnostics to offer women with DCIS more targeted treatment options,” said radiologist and study chair Constance D. Lehman, MD, PhD, FACR, from the University of Washington and the Fred Hutchinson Cancer Research Center in Seattle. “Advanced imaging, advanced tissue diagnostics, and patient preferences guide this trial.”

The new study, funded by the National Cancer Institute (NCI), will recruit 350 women who are eligible for a lumpectomy, based on a mammogram and a tumor biopsy. The trial will require patients to have an MRI exam before surgery. The results of the MRI exam will be used to help determine the type of surgery they need.

“MRI is a useful diagnostic tool for surgical decision-making because it more accurately shows the extent of disease, compared to mammography or ultrasound,” said Dr. Lehman. “However, there are well-founded concerns that MRI, rather than guide more targeted treatments, may itself result in over-treatment, or in other words, unnecessary mastectomies, in women with DCIS.”

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Researchers do not know the full effects of using MRIs to make decisions about surgery for women with DCIS. Therefore, the primary goal of this trial is to find out how many women recommended for a lumpectomy instead undergo a mastectomy after the MRI results are considered.

**Use of MRI**

In this trial, women will undergo a bi-lateral (both breasts) MRI before surgery. Although prior studies have demonstrated the high accuracy of MRI compared to mammography and ultrasound (Berg, et al., *Radiology, 2004* and Lehman, et al., *NEJM, 2007*), the impact of MRI findings on mastectomy rates has not been carefully studied, particularly in women with DCIS.

Most often the decision to treat DCIS with either lumpectomy or mastectomy is based on the results from mammography alone. However, a previous trial showed that MRI sensitivity for detection of DCIS was 92 percent compared with only 56 percent by mammography (Kuhl, et al., *Lancet, 2007*).

Lehman and her colleagues are conducting this trial to clarify the number of women, diagnosed with DCIS by mammography, who have more extensive disease identified by MRI. They will also clarify the impact of the MRI findings on decisions regarding surgery.

“I have been diagnosed with DCIS twice, once over 25 years ago and again seven years ago, said breast cancer survivor Mary Lou Smith, JD, MBA, who helped design the study as a leader on the ECOG-ACRIN Cancer Research Advocates Committee. “I was young when first diagnosed. Even young women with this diagnosis may be willing to forego more aggressive treatment if the science can support it.”

Participating surgeons will complete a questionnaire after the MRI exam and after the patient/surgeon pre-surgical evaluation but before surgery. The questionnaire will query their decision-making process and their perceptions of the inclusion of the MRI.

**Standard Treatment**

In the U.S., surgery is recommended for all women with newly diagnosed DCIS: either lumpectomy or mastectomy. Lumpectomy is the removal of the portion of the breast that contains the DCIS tumor, but leaves the rest of the breast intact. Lumpectomy can be done if the DCIS tumor involves only a limited portion of the breast.

Mastectomy is a surgery that involves the removal of all the breast tissue. Mastectomy is done if the DCIS tumor is thought to be too large for lumpectomy. Mastectomy is also done if there is concern that the DCIS may involve other parts of the breast. In the U.S., about 75 percent of women with DCIS undergo a lumpectomy and 25 percent a mastectomy (Zujewski, et al., *Breast Cancer Res Treat, 2011*).
Over-Treatment with Radiation

An important aspect of this study is to provide each participant who undergoes a lumpectomy with their Oncotype DX DCIS Score to estimate their risk of recurrence so that they and their doctor can determine whether or not radiation therapy is required.

Genomic Health, Inc.’s (GHDX) Oncotype DX is a laboratory test that measures a group of cancer-related genes present in the patient’s tumor tissue to see how active (expressive) they are. The more active the cancer-related genes are, the more likely it is that the tumor will come back (recur) in the same breast within the next 10 years—either as DCIS or as invasive cancer.

Previous clinical trials have shown that radiation after lumpectomy reduces, by about 50 percent, the likelihood that the cancer will return in the same breast. (When mastectomy is performed radiation therapy is usually not needed.) Thus, about three out of four women treated with lumpectomy currently receive radiation therapy. However, the potential over-use of radiation in DCIS patients is a concern expressed by patient advocates and policymakers.

The results of the Oncotype DX test are reported as an individualized number between 0 and 100, called the DCIS Score™. The higher the DCIS Score, the more active are the cancer-related genes. In this trial, women with a score of less than 39 will be considered at low risk for recurrence and will forego radiation.

Because every person’s body and tumor are unique, obtaining a DCIS Score is important because the information it provides can be used along with traditional clinical and pathology assessments to make a more informed decision about whether or not to undergo radiation therapy, whose sole purpose in DCIS treatment is to prevent recurrence in the same breast.

The DCIS Score was validated in two recent clinical trials (Solin, et al., JNCI, 2013 and Rakovitch, et al., SABCS, 2014). However, what researchers don’t know about is women’s perceptions about a DCIS Score and the impact of the knowledge gained from that score.

"Adding radiation treatment after breast conserving surgery for DCIS improves the likelihood of local control in the breast, although survival is not changed,” said radiation oncologist Lawrence J Solin, MD, from the Einstein Healthcare Network in Philadelphia. “By combining the DCIS Score with sophisticated breast MRI imaging, this clinical study offers a potentially new approach to refine the treatment decision-making process and to better determine which patients might benefit from receiving radiation treatment."

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“This trial has the potential to give women diagnosed with DCIS individualized evidence-based options for treatment that they haven’t had in the past so they can make the best decisions for themselves,” said Ms. Smith.

**Patient-Reported Outcomes**

Patient-reported outcomes are an important aspect of this trial. Through questionnaires, researchers will evaluate the effects of the MRI and DCIS Score on study participants’ personal experience with the DCIS diagnosis and related decision-making process. Women will report their satisfaction with their treatment decision and whether they did or did not regret the one they chose. They will also be asked about quality of life issues including fear of the cancer returning and post-treatment concerns about such issues as radiation effects and body image.

These types of assessments have not been conducted previously in women with DCIS. In particular, researchers hope to learn whether the DCIS Score had an impact on women's perceptions of future cancer risk. Previous studies about providing tailored risk information in other disease contexts (colon cancer and diabetes) suggest that people may not fully understand risk information and may not accept that information as being a valid tool for making a treatment decision.

“The experience of being diagnosed with DCIS differs from being diagnosed with invasive breast cancer,” said Ms. Smith. “The medical community is relieved to find DCIS rather than invasive disease and yet the treatments are the same as for early stage invasive disease. This trial may shed light on how women are affected by this approach.”

"This trial begins and ends with our newly diagnosed DCIS patients, who struggle to balance concerns about their risk of recurrence with their equally legitimate concerns about the toxicities of therapy,” said medical oncologist and ECOG-ACRIN Breast Cancer Committee chair Kathy D. Miller, MD, from Indiana University and the Melvin and Bren Simon Cancer Center in Indianapolis. “This trial addresses those dual concerns head on, combining imaging and molecular tumor assessment to avoid over- and under-treatment."

**About this Trial**

This research is important because the frequency of DCIS diagnoses has increased seven-fold since mammography became routine and now accounts for one in five new cases annually in the U.S., or 64,640 cases in 2013, according to the American Cancer Society.

In 2009, the NIH State-of-the-Science Conference Statement on the Diagnosis and Management of DCIS concluded that current treatment—surgery and radiation—is producing excellent outcomes for women with DCIS, and that future research should focus not so much on developing new

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treatments, but on finding better methods to identify subsets of women who can receive less aggressive treatments. The panel also recommended research to evaluate women’s treatment decision-making preferences, and increase understanding of the impact of DCIS treatment decision on patients’ quality of life. Read the report at http://consensus.nih.gov/2009/dcisstatement.htm.

Lehman and her colleagues have designed a single clinical trial that responds fully to the NIH panel’s recommendations. The information obtained from trial E4112 will provide the foundation for a randomized phase III trial to evaluate the role of MRI in DCIS, similar to another ECOG-ACRIN trial that is ongoing in patients with invasive breast cancer (ACRIN 6694/A011104).

The formal name of this cancer clinical trial is E4112: Prospective Study of Magnetic Resonance Imaging and Multiparameter Gene Expression Assay in Ductal Carcinoma in Situ.

**Trial E4112 Availability**

Physicians and medical facilities across the U.S. are eligible to participate in this trial if they are associated with ECOG-ACRIN or the NCI through its National Clinical Trials Network (NCTN) or its NCI Community Oncology Research Program (NCORP). Information about trial E4112 is posted at http://ecog-acrin.org/clinical-trials/e4112-educational-materials and is continually updated.

**About the ECOG-ACRIN Cancer Research Group**

The ECOG-ACRIN Cancer Research Group is a membership-based scientific organization that designs and conducts cancer research involving adults who have or are at risk of developing cancer. ECOG-ACRIN comprises nearly 1100 member institutions in the United States and around the world. Approximately 12,000 physicians, translational scientists and associated research professionals from the member institutions are involved in Group research, which is organized into three scientific programs: Cancer Control and Outcomes, Therapeutic Studies and Biomarker Sciences. ECOG-ACRIN is supported primarily through National Cancer Institute research grant funding, but also receives funding from private sector organizations through philanthropy and collaborations. It is headquartered in Philadelphia, Pa. For more information, visit http://ecog-acrin.org or call 215.789.3631.

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