

## Hot Topics Scholarship Advocate Reports from the 2007 San Antonio Breast Cancer Symposium

Topic: Adjuvant chemotherapy

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The world-wide overview: New results for systemic adjuvant therapies.

Researchers carrying out clinical trials in different parts of the world have been sharing their data every 5 years since 1985 and this was an overview from the latest updated meta-analyses of trial results (2005-6).

World renowned oncology statistician Professor Richard Peto from the Clinical Trials Services Unit at Oxford, UK had an important message for all researchers, clinicians and patients on the importance of not dismissing slight improvements shown in many small trials. When these trial results are combined for assessment those small improvements or differences can become significant and it is actually by many moderate gains in the diagnosis and treatment of breast cancer that the UK/US breast cancer mortality rate at ages 35-69 years has almost halved. So that a woman born in the 1960's has half the risk of her mother born in the 1930's. Professor Peto said that further moderate improvements are still achievable and worthwhile and emphasised that it is not the one "BREAKTHROUGH" but lots of small gains in all areas of diagnosis and treatment that matters most. He gave examples in radiotherapy, chemotherapy and the use of both tamoxifen and aromatase inhibitors.

**Radiotherapy** There were 30,000 patients randomised in radiotherapy trials giving results which included the reducing the local recurrence rate by adding radiotherapy to mastectomy and axillary clearance with a 5 year gain from 2-8% in node negative patients to 22-3% in those with 4+ positive nodes. Mortality rates ranged from a loss of 0-6% at 15 years in node negative patients to a gain of 7-6% at 15 years for those with 1-3 positive nodes and 6-9% at 15 years for those with more than 4 positive nodes

**Tamoxifen** Trials of 5 year treatment with Tamoxifen in patients assessed by both estrogen ((ER) and progesterone (PR) status. In those who were ER- there was a slight 10 year loss if they were also PR- but a slight 10 year gain in those who were PR+, whereas in the ER+ patients there was a 10 year gain of 15.6% in the PR – and a gain of 13.4% in the PR+ patients. If the ER status only was used there was a recurrence rate 10 year loss of 0-3% for ER– and 10 year gain of 14.5% with a 15 year gain of 13.4% for ER+. Follow up continues for trials of 10 years versus 5 years of tamoxifen with 20,000 patients randomised in 3 separate trials.

Preliminary results from the largest one, the Adjuvant Tamoxifen: Longer against Shorter (ATLAS) trial were presented at a "Late-Breaking Session" the next evening ATLAS compared 10 with 5 years treatment with tamoxifen by randomising 11,500 patients at year 5 to continue

on tamoxifen to 10 years or stop at 5 years. Professor Peto explained some of the difficulties of analysing the data from this trial due to differences in how the ER status was tested. Meaning that only 59% were definitely ER+ and 41% were untested so the proportion of ER+ was about 90% and not 100%. Also, 2 years after randomisation, 83% were still on hormonal therapy treatment versus 4% so that the difference was 80% and not 100%. Therefore with about 90% ER+ and about 80% compliance, the ATLAS trial gets about 72% of the true effect of 5 extra years tamoxifen in ER+ disease and, if the true rate reduction is 0-80 (i.e. 20% reduction), ATLAS should get about 0-86 (14% reduction). In fact, the actual results so far shows that continuing tamoxifen more than 5 years confers approximately 12% reduction in the risk of breast cancer recurrence. A trend is starting to show a reduction in recurrence and in breast cancer mortality at 5+ years in those continuing to take tamoxifen for 10 years compared to the 5 year treatment group.

In 1996 the US NCI Clinical Alert advised that tamoxifen should be discontinued after 5 years saying that the results of trials showed that there was no advantage in continuing and it was unlikely to be of clinical benefit. The current NCI fact sheet states that taking tamoxifen for longer than 5 years is not more effective than 5 years of therapy. The 1995 interim results from 2 small trials suggested that continuing beyond 5 years actually increased the recurrence rate. However, the numbers were insufficient to justify dismissing the important question “when assessed long-term, could continuing tamoxifen therapy beyond 5 years moderately reduce the recurrence rate?” It is important to consider whether these recommendations were correct or are being proved to be premature. Professor Peto suggested that the 2002 NCI Factsheet stating that tamoxifen should be stopped at 5 years is wrong given the apparent 12% benefit, but questions remain to be answered on the long term side effect profile.

Efficacy of aromatase inhibitors vs. tamoxifen has been tested in different trials – the two major ones ATAC (anastrozole vs. tamoxifen) and BIG01-98/BCSG18-98 (letrozole vs. tamoxifen) showed a decrease of 3-5% in recurrences and 0-9% in breast cancer mortality in ER+ patients. Another large trial questioned using 2/3 years exemestane after 2/3 years tamoxifen and 3 smaller trials looked at a combination of tamoxifen then anastrozole. These trials showed there were 5 year gains in recurrence rate and mortality rate with aromatase inhibitors over tamoxifen. .

Chemotherapy trials were based on A) Chemotherapy (mostly CMF) vs. control, **B)**anthracycline vs. CMF, and C) Taxane vs. anthracycline. It was possible to combine the results of two or three of these trials to gain more results. New data shows that “polytherapy” is beneficial in reducing the recurrence rate in all age groups, but especially in the ER- patients aged over 70years. However, these analyses do not take into account the costs and side effects of taxanes and other chemotherapies, so no treatment recommendations are being made at present. Trials of myeloblastic chemotherapy vs. anthracycline-based control regimens of various strengths have not shown myeloblastic treatments to be of greater net benefit than the other, safer regimens. In summary, there have been successive improvements in early detection, local control, endocrine therapy (for ER+ breast cancer) and in chemotherapy. The effects of chemotherapy are proportional and independent of ER status. Myeloblastic therapy has not been shown to be better than other chemotherapy regimens studied. A longer mortality follow-up of more than 10 years is needed – particularly for radiotherapy, aromatase inhibitor, taxane and high-dose trials. One current international trial involving 38 countries started recruiting in 1996 and closed recruitment in March 2005 with 12,000 patients randomised. There are preliminary results on recurrence, but it is critical that all randomised patients are followed-up until at least 2010 and, preferably, beyond this so that clear information on its end-point of all cause mortality emerges and can be assessed. Ultimately, we need the reliable assessment of moderate differences in long-term survival with tens of thousands of patients randomised, which is provided by this 5 yearly world-wide overview, but this needs the input of all the main trial results to avoid an undue emphasis on particular studies and an unduly data-dependent emphasis on particular sub-groups.

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## Breast Cancer Stem Cells

A cell is an individual unit that, together with other cells, makes up the tissues of the body. A stem cell is one from which other cells develop. Stem cells, found in all multi-cellular organisms, have the ability to renew themselves through cell division, differentiating into a variety of specialized cell types.

The two broad types of stem cells are embryonic and adult. Embryonic stem cells are found in a blastocyst, an early stage of pregnancy in mammals. Adult stem cells are found in adult tissues. Embryonic stem cells can differentiate into all of the specialized tissues of the embryo. Adult stem cells, along with progenitor cells (more limited than stem cells, but possessing self-renewal and differentiation properties), serve as the body's repair system by replenishing specialized cells and maintaining the regular turnover of organs that regenerate (e.g., skin, intestinal tissues, and blood).

In recent years, it has been recognized that tumors are complex organs formed not only by neoplastic cells but also by supporting vasculature, immune cells and fibroblasts. This complexity of cancers has also extended to the neoplastic cells themselves. In an increasing number of cancers (most clearly in hematopoietic, central nervous system, and breast cancers), a restricted subset of tumor cells have been defined functionally as cancer stem cells through maintained self-renewal and *in vivo* tumorigenesis. Researchers have therefore posited that stem and progenitor cells play a role in initiating and sustaining malignant tumor growth. These cancer stem cells are believed to comprise less than 10 percent of breast cancer cells (Chang, 2007), perhaps only one in 100 (Pobojewski, 2003). Although aberrant, they do share self-renewal and differentiation properties with normal adult stem cells.

Cancer stem cells also are believed to be resistant to current therapies that target actively cycling cells. The number of these stem cells may be set during certain junctures of development including *in utero*, adolescence, pregnancy, lactation, and involution (Ginestier & Wicha, 2007; National Cancer Institute, 2004). Certain growth factors may play a role in determining the number of breast stem cells during these developmental times, possibly linking them to breast cancer risk.

Traditional breast cancer treatment aims to kill as many tumor cells as possible but often kills normal cells in the process as well. Targeting breast cancer stem cells could potentially

produce better results. Adherents to the breast cancer stem cell theory draw a parallel to a lawn filled with dandelions. Mowing makes the lawn appear weed free, but the roots remain and the dandelions grow back (Kolata, 2007). Similarly, chemotherapy and radiation can seemingly destroy the tumor, but the undetected breast cancer stem cells cause the tumor to regenerate.

The breast cancer stem cell theory is enjoying increasing acceptance, with many laboratories focusing research in this area. According to the *New York Times*, the National Cancer Institute (NCI) is issuing a request for proposals that will result in \$5.4 million in grants to study breast cancer stem cells.

It is possible that the development of chemotherapy resistance selects for specific subpopulations of cancer stem cells, which are highly resistant to cytotoxic therapies through specific molecular mechanisms that may be targeted with novel therapies. Breast cancer stem cells can be identified through markers, such as aldehyde dehydrogenase (Wicha, 2007). These markers can set up tumor cells for selective targeting. One small study (Chang, 2007) targeting breast cancer stem cells was presented at the recent San Antonio Breast Cancer Symposium (SABCS). The research involved 30 women whose breast tumors highly expressed HER2, the protein made by the HER2/ gene. These women were given six weeks of Tykerb (lapatinib) to target the HER2/ gene, which has stem cell properties. Following six weeks of Tykerb, then other HER2 drugs including Herceptin (trastuzumab), surgery was performed. Breast tissue samples taken before and after Tykerb treatment showed that the number of stem cells in the tissue dropped from 11 percent to 5 percent. Following surgery, 63 percent showed no sign of cancer. Laino (2007) quotes a breast cancer physician as saying that this paper was one of the most significant at the 2007 SABCS.

Although the breast cancer stem cell theory may be controversial in some quarters, many believe that research in this area holds great promise. With the awarding of new money from the NCI, more research will test the theory and new knowledge will be gained. Resulting therapies will target breast cancer stem cells and provide more hope for the many women who develop breast cancer and who live with it. The true test of any newly developed therapy is patient survival, the ultimate end point for researchers. For those of us diagnosed with breast cancer, not only is survival a goal, but quality of life is as well. Targeting stem cells for therapy just might provide a giant step toward ensuring excellent quality of life.

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### References

- Chang, J. (2007, December 16). Decrease in tumorigenic breast cancer stem cells in primary breast cancers with neoadjuvant lapatinib. Paper presented at the meeting of the San Antonio Breast Cancer Symposium, San Antonio, TX.
- Ginestier, C. & Wicha, M. S. (2007). Mammary stem cell number as a determinate of breast cancer risk. *Breast Cancer Research*, 9, 109. Retrieved December 27, 2007 from <http://breast-cancer-research.com/content/9/4/109>.
- Kolata, G. (2007, December 21). Scientists weigh stem cells' role as cancer cause. *The New York Times*. Retrieved December 21, 2007 from <http://www.nytimes.com/2007/12/21/science/21stem.html?pagewanted=2&r=2&ref=us>.
- Laino, C. (2007, December 17). Tykerb targets cancer stem cells. Retrieved December 27, 2007 from [http://www.webmd.com/breast-cancer/news/20071217/tykerb-targets-cancer-stem-cells?ecd=wnl\\_brc\\_122007](http://www.webmd.com/breast-cancer/news/20071217/tykerb-targets-cancer-stem-cells?ecd=wnl_brc_122007).
- National Cancer Institute. (2004). Ongoing NCI research: Recent progress in breast cancer biology. Washington, DC: U.S. Government Printing Office.
- Pobojewski, S. (2003, February 24). U-M scientists find "stem cells" in human breast cancer. Retrieved December 27, 2007 from <http://www.cancer.med.umich.edu/news/stemcell.htm>.
- Wicha, M. (2007, December 13). Breast cancer stem cell: Targets for prevention and therapy. Paper presented at the meeting of the San Antonio Breast Cancer Symposium, San Antonio, TX.

## Who benefits from Adjuvant Chemotherapy?

Are our current standards of care and recommendations of adjuvant chemotherapy consistent with the fast changing pace of the science? Is our standard of care for adjuvant drug treatment appropriate for all women with hormone receptor positive breast cancer?

Moreover, what role do biomarkers and gene assays play in helping women and their physicians decide what adjuvant chemotherapy regime to choose? I hope to answer some of these questions in this article.

On December 13, 2007, Dr Don Berry Ph.D, Biostatistian at MD Anderson Cancer Center, in Houston Texas presented a meta-analysis (overview) of 15 randomized adjuvant clinical trials looking at high dose chemotherapy (HDC) with bone marrow transplant or autogolous stem cell support (SCT) vs. standard chemotherapy (SDC) for early stage breast cancer. These trials were compiled and presented because individual studies have limited statistical power (did not have enough participants within each individual study) to determine if high dose chemotherapy plus autogolous transplantation had any benefit in decreasing disease free survival and recurrence in high risk (patients with 10 or more cancerous axillary lymph nodes). The main questions addressed by this study were:

\*Is there an overall benefit in the adjuvant setting of high dose chemotherapy with stem cell support?

\*Are there subsets of patients who benefit from high dose chemotherapy?

The overall goal of this analysis was to determine (1) disease free survival (DFS), (2) Breast Cancer Specific Survival (time from surgery to death as a result of breast cancer treatment or related toxicities and (3) overall survival (the time from surgery to death)

### Methods Used

6,210 women participated in these combined clinical trials. 3,118 were randomized to high dose chemotherapy with stem cell support group and 3,092 were randomized to the standard dose chemotherapy group. Randomization means that every woman has an equal chance of receiving the new or experimental chemotherapy drug. The women were followed for an average of 6 years (range 0- 15.3 years). Forty eight percent (48%) of the women were estrogen receptor positive (ER+) and 23% were estrogen receptor negative (ER-). The remaining 29% of women

in the study had unclassified estrogen receptor status. (i.e. did not know if ER positive or negative)

## **Results**

Dr. Berry reported that there was no overall survival benefits for women who received high dose chemotherapy, however, over all survival was greater in the high dose treatment group if patients were pre- menopausal and had less than 10 positive lymph nodes. However, the relapse free survival (RFS) showed a modest but significant improvement in the HDC compared to standard chemotherapy. Although most of the women in the study were ER + and received tamoxifen, if the women was ER-, she had better survival outcomes as well. Women that were diagnosed Her2+, received no benefit from High Dose Chemotherapy. In addition, women with Her2- status received no benefits from either standard dose chemotherapy or high dose chemotherapy. When considering the original question posed by Dr Berry:

Is there an overall benefit in the adjuvant setting with high dose chemotherapy and stem cell support?

- Concluded that there was a modest benefit in relapse free survival
- Little or no benefit on overall survival

Are there any subsets who might benefit from high dose chemotherapy?

- There were none that could be identified so far.

During the Alamo Breast Cancer Foundation's mentoring session on Thursday evening, researchers on the panel noted that High Dose Chemotherapy with Stem Cell Transplantation was popular during the 1990's before clinical trials were done on this procedure. But were less favored after early results of trials began to become known as well as the potential side effects. Since that time, as a result of randomized clinical trials, researchers have been able to create more personalized, less toxic adjuvant treatment modalities that can be delivered safely at lower dosages.

Dr. Ragaz Spinelli presented data on December 13, 2007 on his meta-analysis of key randomized studies (MA-17, Big 1-98 trial, N9831, Fin Her Trial, BCIRG trial, Letrozole vs. Tamoxifen trial, Trastuzumab vs. Placebo trial) when they were first conducted in stage IV (metastatic breast, Her2 + cancer patients) and then compared the results obtained in trials conducted in the adjuvant setting after surgery was completed. It was postulated that for the majority of agents, any clinical effect in stage IV would predict and translate to higher sensitivity

in the adjuvant setting. Dr Spinelli noted that the earlier trials involving tamoxifen and or adjuvant chemotherapy (cytoxan, methotrexate and 5- Fluorouracil) were successful in treating metastatic disease and contributed to women having increased survival rates and longer periods of disease free survival.

Instead of focusing on adjuvant clinical trials, where there is a bottleneck with large numbers of agents competing for clinical trials, he presented data for a number of agents including tamoxifen, the taxanes and Herceptin, showing that clinical effect in state IV was a good surrogate for a greater effect in the adjuvant setting where the tumor burden is much lower and the disease is more sensitive to treatment.

In addition, he quoted from several sources and concluded that since 1985, tamoxifen may have saved worldwide over 20,000 breast cancer deaths per year with that one treatment alone. So we ask ourselves, how many more lives could have been saved if the guidelines had been implemented in 1980 instead of 1985 – i.e. a further 100,000 women. Similar calculations for the adoption of Herceptin in 2001 5 years earlier than the 2006 guidelines were also shown, where a further 50,000 women's lives could have been saved. Dr. Spinelli suggested that the focus be changed from the current way of getting new drugs approved through phase 3 clinical trials to a new paradigm. This new paradigm would consist of conducting studies that do not include placebo but using biomarkers and cohorts or comparative studies (studies of people with the same disease or problem) as an avenue for creating new drug therapies. Dr Spinelli further indicated that if his recommendations were adapted, newer drugs might get to the market sooner, and this new paradigm would save lives and be more cost-effective because early intervention with systemic may have a significant effect on mortality of breast cancer via a reduction in the risk of recurrence.

Dr. Dennis Slamon, MD, PhD, is a researcher in the Breast Cancer International Research Group (BCIRG), and like Dr Spinelli believes that genetic markers like topoisomerase 11a (Topo 11a), a gene which encodes an enzyme which is critical in DNA replication and function in the breast cancer cell and biomarkers, such as Her2, should be considered when making decisions regarding which adjuvant chemotherapy treatments to consider. The Topo 11a protein is a major target of the anthracyclines. Thus efficacy analyses may be determined by molecular

subtypes of the disease. To test this theory, in a 6 study meta-analysis of Her2 breast cancers, Dr. Slamon found that women who over-expressed HER2, and over-expressed the Topo 11a gene, benefited from anthracycline drug therapy. Anthracyclines are anti-cancer fighting drugs that prevent cancer cells from dividing and making copies of itself.

The women who have normal Topo 11a genes or who do not have the gene at all are not sensitive to adriamycin and cytoxan drug combinations or when adriamycin and Herceptin are given together. However, women who are Her2 negative do not receive benefit from taking adjuvant chemotherapy that includes anthracycline drugs such as Adriamycin. At the Alamo Breast Cancer Foundation's mentoring session on Thursday evening, the controversy among the panelists continued as to whether to expedite clinical trials and decide who benefits from adjuvant therapy. The biggest challenge or controversy for this group of researchers appeared to be how to address the fact that women are still being treated with adjuvant chemotherapy regimens based on retrospective studies that have been shown to be effective in phase 3 randomized clinical trials, yet sub groups of women are resistant, recurring or dying from breast cancer.

Dr Slamon suggested that not all patients need anthracyclines and researchers should be looking at the characteristics of tumors when conducting new studies. Dr. Radvin responded by saying that anthracyclines should continue as standard of care for node positive disease until further long term studies using genetic and biomarkers are analyzed.

The consensus of the majority of the panel was that anthracyclines do have known toxic side effects and new drugs are needed that are less toxic to the body. However, physicians on the panel as well as those in private practice are reluctant to let go of documented clinical research in favor of new and unproved treatment when making decisions about their patient's care.

After digesting the information at the San Antonio Breast Cancer Symposium, I have concluded that although standard of care guidelines are available to assist doctors and patients in planning care, there is no "one size fit all" treatment. Some ER, HER2+ women because of genetic predispositions are more sensitive to Tamoxifen and Herceptin than others.

Not every women needs anthracycline based chemotherapy. Long term studies need to done so that safety and efficacy of adjuvant drug treatments can be fully documented.

In the future, adjuvant chemotherapy treatment modalities have to be individualized by taking into consideration the women's cancer staging, tumor characteristics, genetic make-up, biomarkers, health history, as well as her life style.

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## Can a Battleship Be Turned?: The Role of Anthracyclines and Whom It Benefits

At the 2007 San Antonio Breast Cancer Research Symposium, findings were presented by two different researchers which may have a future significant affect on the current standard treatment of breast cancer.

According to a definition from the National Cancer Institute's online drug dictionary anthracyclines are "a type of antibiotic that comes from the fungus *Streptococcus peucetius*. Anthracyclines are used as treatments for cancer. Daunorubicin, doxorubicin, and epirubicin are anthracyclines."<sup>i</sup> The history of doxorubicin dates to the early part of the 20<sup>th</sup> century, when an [Italian](#) based pharmaceutical company investigated soil-based [microbes](#) as a possible treatment for cancer. Though the exact way that anthracyclines work is unclear, it is thought to interact with the DNA to prevent the progression of an enzyme, topoisomerase II. Doxorubicin first went into clinical trials in the 1960's.

Anthracyclines are now a standard form of treatment for breast cancer in a majority of breast cancer patients. However they do not come without a myriad of side effects. The prescribing information pamphlet, states that neutropenia, thrombocytopenia, anemia, fatigue, nausea and vomiting, diarrhea, constipation, and pyrexia are all common side-effects. The side effect that causes great concern though is the long-lasting affect on the heart, also known as its cardio-toxicity. Congestive heart failure and cardiomyopathy may manifest even years after treatment has finished. "The probability of developing impaired myocardial function... is estimated to be up to 20 percent at the highest doses. This toxicity may occur at lower cumulative doses in patients with prior mediastinal irradiation or on concurrent cyclophosphamide therapy or with pre-existing heart disease."<sup>ii</sup> Because of potential risks such as these, clinicians and patients are constantly in search of less toxic treatments with improved benefit.

Dr. Stephen Jones, Medical Director of US Oncology Research in Houston, presented an update of US oncology Trial 9735. This randomized trial compared four cycles of docetaxel (Taxotere) plus cyclophosphamide (TC) with four cycles of doxorubicin (Adriamycin) plus cyclophosphamide (AC). Results were first presented in 2005, and in 2007 an update with seven years of median follow-up is now available. Disease-free survival (DFS) for the TC arm was 81%, compared with 75% for the AC arm. Overall survival (OS) was 87% for TC, versus 82% for AC. TC showed a benefit for Her2+ and Her2- patients, though this aspect was difficult to

tease out.<sup>iii</sup> Additionally, outcomes by age and Her2 status were assessed. 16% of the subjects were 65 and older with a median age of 69, median age in the under 65 group was 50. More patients in the older age group had lymph node involvement. OS and S by age demonstrated that older patients had more deaths with out recurrence. Both age groups favored TC. Her2 was assessed in 170 pts (17%) through FISH with blocks obtained from those patients at Baylor, and patients who relapsed. Of the 170 assessed 27% Her2+, and 73% Her2-. These again showed DFS favoring the TC arm but Dr. Jones pointed out that the sample size was small.

The Cancer International Research Group, represented by Dennis Slamon, MD, Ph.D from the Santa Monica-UCLA Medical Center, presented further support for the discontinuation of anthracyclines. Using data from the registration trial for trastuzumab (Herceptin), this retrospective analysis showed that only patients who demonstrate amplification of both Her2 and Topo IIa benefit from anthracyclines. This would amount to around 8% of all breast cancers (35% Topo IIa+ of the 25% Her2+). Her2+ patients treated with AC with a normal or deleted Topo IIa gene had a median survival of just over 18 months. Patients with an amplified Topo IIa had a median survival of more than double that at 38.5 months. When Herceptin was added the difference disappeared.<sup>iv</sup>

In the meta-analysis presented of several other studies, patients who are Topo IIa and Her2 +, and therefore represent 8% of all breast cancers have an OS improvement of 30%. This, according to Dr. Slamon, “drags the whole group up and that was dictating treatment decisions for the last almost three decades.” In the most recent analysis of this study just looking at Her2- (or normal) patients, there is not a single case of Topo IIa also being amplified. With over 1600 patients, this supports Dr. Slamons findings that Topo IIa cannot occur without the patient also being Her+.

In the Alamo Breast Cancer Foundation Mentor sessions, this research was discussed extensively, with advocates asking why the threshold for the addition of a new drug is so low, and the removal of a treatment is so high. Dr. Slamon who was on the panel asked his fellow clinicians if they would continue to treat patients with a one-size-fits-all approach, particularly in light of the potential harmful effects of anthracyclines. Dr. Peter Ravdin discussed that in Dr. Jones’ trial both groups (Her2+ and Her2-) benefitted even if slightly, from anthracyclines. Dr. Ravdin also discussed how older trials did not collect tissue blocks and that newer trials are requiring this. He feels that this can add significantly to the ongoing study of therapies. Dr.

Slamon responded that the meta-analysis presented comprised almost 8,000 women including those before, as well as after, Herceptin was being tested. He feels that this provides basis for change in standard of care. Fran Visco of National Breast Cancer Coalition Fund added that perhaps newer clinical trials should include CMF and other treatments that may have been discontinued in the past as anthracyclines were added. Dr. Slamon finally asked what level of evidence is needed and how many women will suffer? Dr. Ravdin responded that guidelines will take time to change as they require “Level 1” evidence to change standard of care, and that some clinicians will change their practice based on what was presented. Most though, will not. In summary, to quote Dr.’s Jones and Slamons summations – TC seems to be an effective, less toxic, non anthracycline adjuvant chemotherapy regimen which could now be considered one of the standard regimens for early breast cancer and should now be considered for further testing in clinical trials. Furthermore, and to sum up advocates concerns, when will patients be treated based on individualized risk and benefit and not subjected to needless toxicities?

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<sup>1</sup> From the National Cancer Institute Dictionary of Cancer terms, retrieved January 10, 2008 from [http://www.cancer.gov/Templates/db\\_alpha.aspx?CdrID=44916](http://www.cancer.gov/Templates/db_alpha.aspx?CdrID=44916).

<sup>1</sup> From Doxil prescribing information pamphlet retrieved January 11, 2008 from [http://www.orthobiotech.com/common/prescribing\\_information/DOXIL/PDF/DOXIL\\_PI\\_Booklet.pdf](http://www.orthobiotech.com/common/prescribing_information/DOXIL/PDF/DOXIL_PI_Booklet.pdf)

<sup>1</sup> Notes from presentation of “Abstract #12 Extended follow-up and analysis by age of the US Oncology Adjuvant Trial 9735...” at 2007 SABCS on December 13, 2008.

<sup>1</sup> Notes from presentation of “Abstract #13 Role of anthracyclines-based therapy in the adjuvant treatment of breast cancer...” at 2007 SABCS on December 13, 2008.

## **Who Benefits from Adjuvant Chemotherapy? (Research into Predictive Factors)**

A major issue in planning the adjuvant therapy of breast cancer patients is to determine which patients will benefit from chemotherapy. Chemotherapy is offered to many women who might not benefit from it, while others who could benefit from it do not get chemotherapy.

Prognostic and predictive factors are aids in treatment decision-making for or against chemotherapy. Prognostic factors like pTNM-status and grading indicate the baseline risk, predictive factors indicate the benefit from a certain therapy. Predictive factors might help to reduce unnecessary use of chemotherapy, lowering adverse effects and cost on one hand, increasing patient confidence in their treatment selection on the other hand. Several lectures at the 2007 SABCS dealt with prognostic and predictive factors, some of them with the chance to predict who benefits from regimens based on anthracyclines.

Kathy Albain, MD reported about the “Prognostic and predictive value of the 21-gene recurrence score assay in postmenopausal, node-positive, ER-positive breast cancer”, showing for the first time the predictive value of the 21-gene Recurrence Score assay (RS) in node-positive breast cancer patients.

The 21-gene Recurrence Score assay (RS) is qualified as prognostic for women with node-negative, ER-positive breast cancer treated with tamoxifen alone. A high Recurrence Score assay predicts a large benefit from chemotherapy in node-negative disease but it predicts no benefit if the RS is low.

The study Dr. Albain presented used tissue blocks from The Breast Cancer Intergroup of North America trial conducted by the Southwest Oncology Group (SWOG 8814). This phase III trial randomised postmenopausal women with node-positive, ER + breast cancer in 5 years of tamoxifen alone, 6 x CAF ([cyclophosphamide](#), [doxorubicin](#), originally called Adriamycin®) and [fluorouracil](#), also known as 5FU) with concurrent tamoxifen and 6 x CAF and then tamoxifen. Interestingly, the later group had the superior disease free survival and overall survival over ten years.

The two primary objectives of the analysis of the material of the SWOG 8814 trial were to determine if the 21-gene Recurrence Score assay:

1. provides prognostic data for disease free survival for women with N+ disease in the tamoxifen alone control arm and
2. predicts a group that does not benefit from chemotherapy followed by tamoxifen, despite positive nodes.

The results showed that the 21-gene Recurrence Score assay is prognostic for disease free survival and overall survival of tamoxifen treated patients with positive nodes.

It is predictive of added CAF benefit in those patients whose tumors have a high 21-gene Recurrence Score assay.

There was no statistical significant benefit in patients with an intermediate RS.

Comparison of CAF followed by tamoxifen with tamoxifen alone showed no chemotherapy benefit for low RS.

There was no CAF benefit in disease free survival either early or late in RS low patients, but a stable impact over time when the RS was high.

The RS is also predictive for overall survival. The trial shows no benefit of CAF in low RS but a strong impact to overall survival in high RS.

A low 21-gene Recurrence Score assay (RS) may define a group of women with positive nodes who do not appear to benefit from anthracycline-based adjuvant chemotherapy.

Kathy Albain closed her presentation with the following perspectives on research:

- New strategies in endocrine/biologic therapy are needed for patients with low RS.
- Biology (not age) should drive treatment decisions, since for high RS chemotherapy is beneficial regardless of age.
- These data collectively challenge chemotherapy mandates for patients with node-positive, ER positive disease: not all benefit from chemotherapy, whereas others derive greater benefit than previously predicted
- SWOG 8814 joins a suite of studies that provide a consistent message regarding the value of the RS for individualized adjuvant therapy

- RS could be an aid in treatment decision-making for selected patients with node-positive, ER-positive breast cancer
- A prospective, randomized trial of chemotherapy plus endocrine therapy versus endocrine therapy alone should be a high priority in node-positive endocrine-responsive disease with low RS

Another approach to predicting sensitivity of breast tumours to specific chemotherapies which would allow clinicians to select the optimal therapy for individual patients was to identify a gene expression signature predicting for a pathological complete response to neo-adjuvant fluorouracil, epirubicin and cyclophosphamide (FEC) therapy in patients with large operable breast cancer. Pathological complete response is a surrogate for chemosensitivity.

The findings of Dr. Farmer and his colleagues identified a novel resistance mechanism of ER- breast cancer to FEC treatment which is stroma activation. These results should lead to trials combining anti-stromal agents with chemotherapy.

The clinical significance of MDR1/gp170 as a mechanism of multidrug resistance in breast cancer has not been established, despite the 2 leading classes of breast cancer drugs, anthracyclines and taxanes, both being substrates for this gene, Bruce Trock reported.

A meta-analysis of MDR1 and its clinical significance shows that MDR1 is expressed in approximately half of breast cancer patients, and is induced by chemotherapy. 56% of patients who express MDR1 after chemotherapy fail to achieve a clinical response. However, if MDR1 was measured prior to induction of chemotherapy it was no longer significantly associated with response. MDR1 seems not to be predictive of chemotherapy effect when measured prior to the therapy. Further follow-up is needed to determine the impact on survival, and multidrug reversing agents must be tested in more rigorously designed studies.

A number of biologic and clinical clues suggest that not all patients derive the same degree of benefit from chemotherapy. Markers predicting the benefit of chemotherapy were subject of several lectures at the SABCS 2007. But as Kathy Albin closed her presentation about the 21-gene Recurrence Score assay, more prospective, randomized trials necessary in node positive

ER+ disease with a low RS to obtain the crucial information we need to find reliable predictive markers to select the optimal therapy for individual patients.

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[10] Prognostic and predictive value of the 21-gene recurrence score assay in postmenopausal, node-positive, ER-positive breast cancer (S8814,INT0100).

*Albain K, Barlow W, Shak S, Hortobagyi G, Livingston R, Yeh I, Ravdin P, Yoshizawa C, Baehner F, Davidson N, Sledge G, Winer E, Hudis C, Ingle J, Perez E, Pritchard K, Shepherd L, Allred C, Osborne K, Hayes D. Southwest Oncology Group and The Breast Cancer Intergroup of NA, San Antonio, TX*

[35] A stroma-related gene signature predicts resistance to epirubicin-containing neoadjuvant chemotherapy in breast cancer.

*Farmer P, Bonnefoi H, Anderle P, Cameron D, Wirapati P, Becette V, André S, Piccart M, Campone M, Tubiana-Hulin M, MacGrogan G, Petit T, Jassem J, Rouanet P, Blot E, Bogaerts J, Bergh J, Iggo R, Delorenzi M.. National Centre of Competence in Research (NCCR) Molecular Oncology, Swiss Institute for Experimental Cancer Research (ISREC), Epalinges, Switzerland; Swiss Institute of Bioinformatics (SIB), Lausanne, Switzerland; European Organisation for Research and Treatment of Cancer (EORTC), Breast Cancer Group, Brussels, Belgium; The Swiss Group for Clinical Cancer Research (SAKK), Bern, Switzerland; The Anglo-Celtic Cooperative Oncology Group (ACCOG), Edinburgh University, Edinburgh, United Kingdom; The Swedish Breast Cancer Group (SweBCG), Karolinska Institute, Stockholm, Sweden*

[37] Multidrug resistance and breast cancer: a meta-analysis of MDR1 and its clinical significance.

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## **Preliminary results of the UK Taxotere as Adjuvant Chemotherapy (TACT) Trial.**

Previously reported Phase III adjuvant chemotherapy trials suggest a modest survival benefit favoring taxane containing regimens over anthracycline regimens. However, uncertainty remains with regard to the benefit of taxanes compared with anthracycline regimens of similar duration. The UK TACT Trial, a large multicenter Phase III randomized trial was developed to answer this question. This trial compared sequential FEC-Taxotere to standard UK anthracycline chemotherapy in an attempt to determine overall benefit as well as which sub-groups, if any, have more or less to gain from this intervention. It was hypothesized that a sequential docetaxel-containing chemotherapy regimen would result in improved outcomes when controlling for duration of therapy.

Between February 2001 and July 2003, 4162 women with operable early invasive breast cancers were recruited from 104 centers in the UK and Belgium. Centers chose 5FU, Epirubicin and Cyclophosphamide, (FEC) or Epirubicin followed by Cyclophosphamide, Methotrexate and 5FU, (E-CMF) as their control arm, representing standard UK practice. Patients were randomized to 5FU, Epirubicin, Cyclophosphamide followed by Taxotere, (FEC-T) or control. 2523 patients were randomized from centers using FEC and 1639 randomized from centers using E-CMF.

Tumor blocks were collected prospectively for Her2 testing, using a central testing lab, and creation of tumor microarrays. The primary endpoint was disease free survival (DFS) defined as time to loco-regional or distant relapse, contralateral invasive breast cancer or death prior to relapse. Secondary endpoints included overall survival (OS) tolerability of regimens and quality of life.

Dr. Ellis reported that by May, 2007, which represented a median follow up of 51.8 months, they were able to follow up with 97.3% of the patients originally recruited. The groups were well balanced with regard to age and disease histology. 20% of the patients were node negative. 23% of the patients were Her2 positive. 1/3 of the patients were given tamoxifen for 5 years, the other 2/3 were given an aromatase inhibitors for 5 years. 80% of the cohort was able to complete the 8

cycles of treatment. There was no difference in the dosage from institution to institution. The patients receiving the taxane had more toxicity than the control arm.

There was no difference in disease free survival (DFS) between the groups. There was no difference in overall survival (OS) between the groups. There was no additional benefit to the patients who were estrogen positive (ER+). Furthermore, and as expected in a trial that is negative overall, subgroup analyses by estrogen receptor (ER) and HER2 status revealed no benefit in favor of either regimen

The take home message from this study, according to the researchers, is that the addition of doxetacel to standard adjuvant chemotherapy does not seem to be beneficial to plus it has higher levels of stage 3 and stage 4 toxicities. The authors are not saying however, that taxanes are not good, they believe this study just points out that chemotherapy efficacy is important to the efficacy of taxanes and that further studies need to be done to determine how best they should be used in the adjuvant setting.

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## **Can Breast Cancer Tumor Response To Neoadjuvant Chemotherapy Be Assessed Using MRI And Biological Markers In Women With Locally Advanced Breast Cancer?**

Neoadjuvant therapy occurs when chemotherapy is administered before surgery and has traditionally been offered to patients with large tumors with the goal of achieving sufficient shrinkage thereby enabling patients to choose between breast conservation (lumpectomy) over mastectomy (removal). More recently, neoadjuvant therapy has been used as a way of determining the effectiveness of the treatments and adjusting the chemotherapy regime accordingly. Patients and the medical team want to know if the chemotherapy is having any effect on the breast cancer tumor. If so, to what extent?

Angela DeMichele presented preliminary results from the I-SPY Trial at the 2007 San Antonio Breast Cancer Symposium on Sunday 16<sup>th</sup> December. The I-SPY Trial is a unique ongoing multi-center study of nine institutions that uses both clinical biopsies and MRI imaging to assess clinical and pathological response of breast cancer to neoadjuvant chemotherapy. The investigators wanted to identify surrogate markers of response to neoadjuvant chemotherapy that are predictive of pathological remission and survival in women with stage II/III breast cancer. Specifically the investigators were interested in

1. non-invasive tools that can be used to approximate response to therapy
2. Improvements to surrogate endpoint of pathological Complete Response (pCR).

This was achieved by using serial biopsies and MRI images before, during at the end of neoadjuvant treatment.

Patients with confirmed primary breast cancer with tumors of at least 3 cm at diagnostic biopsy were eligible. The results presented were based on data from 222 patients. This group of women had the following characteristics: mean age 49 years (55% <50 years old) with a range of 27 – 69; racial distribution of 74% Caucasian, 19% African American, 4% Asian and 3% other; tumor size of 6 cm (0-25cm); and 70% had positive nodes; 54% were ER positive and 28% had Her2/neu over expression.

They were required to be initially treated with Anthracycline (AC) based neoadjuvant therapy; AC followed by T (91%), AC without T (6%); chemotherapy beyond AC +/- T (2%). Surgical treatment was individualized based on surgeon and patient. Serial MRI and core biopsies were performed at baseline (T1), after one cycle AC (T2), during treatment (T3) and pre-surgery (T4) to identify markers as predictors of tumor response.

Dr Nolan Hylton was responsible for the imaging component. Complete response, partial response and progressive disease were assessed by MRI using quantitative and serial measurements of the tumor by radiologists for the longest diameter (LD) and volume measurements were automated by the scan. Pathological Complete Response was defined as no invasive tumor in breast or lymph nodes (DCIS presence was considered as pathological complete response), as the primary endpoint occurred in 27% (56/211) and the imaging endpoint with pathological complete response in the breast occurred in 84% (46/67) node negative women while the node positive women achieved 16% (11/67) pathological complete response.

Endpoint analysis found that initial response of biomarkers after 1-4 days and MRI after one cycle of AC using longest diameter and volume was not as helpful as hoped. Immediately post treatment pathological response and MRI estimates showed changes in response to AC, T and AC without T. The final endpoint is survival defined as 3 year Disease Free Survival was not presented.

Imaging MRI showed five distinct patterns of breast cancer tumors from the most contained in type 1 to the most diffuse pattern correlating with inflammatory breast cancer as type 5. The distribution pattern in the patients were as follows; 1. Unicentric mass, well defined margins 17%, 2. Multi-lobulated mass, well defined margins (30%), 3. Area enhancement, irregular margins (nodules) 31%, 4. Area enhancement, irregular (no nodules), 5. Septal Spreading (9%). Patients previously ineligible for breast conservation based on types 1 & 2 MRI phenotypes were able to have breast conservation after chemotherapy. The percentage eligible for breast conservation post chemotherapy was 67% for this I-SPY trial, an improvement from an earlier similar study by Kaplan et al (47%) presented at SABCS in 2004.

Assays completed were Agilent array, DNA array, BAC array, MIP array, p53 array, Protein Lysate array and IHC. Distribution of the Luminal AB, Her-2, Basal Normal molecular subtypes showed that none of the Luminal A had pathological complete response while 45% of the Basal tumors had pathological complete response. Patients with Basal tumors that had good responses and did well, while patients whose tumors were poor responders fared badly.

Pathological complete response in those with HER2+/ER+ was 28%, HER2+/ER- 48% (without receiving Herceptin). In HER- patients, with ER+ and ER- pathological complete response was 9.6 % and 35.7% respectively. The effect of ER-/ER+ was 25.8% (p=0.0002) and the effect of HER2+/HER2- is 18.8% there was no interaction.

The study found several molecular predictors of which patients would achieve pathological complete response. These were NKI 70 genes, GHI Recurrence Score, T-FAC 30 gene set, TP53, Molecular subtypes, ER, Phospho ER, Her-2, Phospho Her-2 and MRI Volume. I-SPY investigators also tested Dr Frasier Symman's tool of Residual Cancer Burden (RCB), which integrates lymph node status, extent of tumor bed, and tumor size and tumor cellularity into a model. The output gives a continuous rather than a dichotomous measure of pathological response. Applying the Residual Cancer Burden to I-SPY provided a better separation than complete pathological response (pCR) of yes or no. It provided the investigators with confidence that the MRI data will show something similar.

The I-SPY Trial is continuing by adding the use of magnetic imaging spectroscopy (MRS) in place of the second biopsy in an addition 140 patients. Additional data will be collected on molecular markers.

The I-SPY Trial validated molecular predictors of response using surrogate markers of pathological complete response and RCB. New imaging measures of response were developed. Data suggest that changes in MRI volume are better than MRI Longest Diameter, clinical Long Diameter or mammography. The biology of this population is different from those that present for usual screening in that these patient have a poor prognosis being much younger with the

mean age of 47, with more ER+ (45%) and Her2+ (27%) with only 4 with GHI RS of 1 and 19% with Mammprint good prognosis. Nevertheless, neoadjuvant treatment was shown to be useful in optimizing regimes and to improve response.

MRI is a promising non-invasive tool that can be used to approximate response to chemotherapy and several biomarkers were identified as surrogate endpoint of pathological Complete Response (pCR). The clinical application of this is that the type tumor pattern that presents in the breast (from MRI) can give the patient an expectation as to whether she is a candidate for breast conservation. It can also guide surgeons as to how much tissue to section in a diffuse tumor. In addition, biology of the tumor matters in pathological complete response, Dr DeMichele concluded that biology should be factored into treatment plans as well as comparing results of trials. She concluded that “one size does not fit all” and that “treatment must be tailored to maximize the outcome and minimize toxicity” particularly for non-responders.

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Abstract 80:  
Characterizing the biology and response of locally advanced breast cancer in women undergoing neoadjuvant therapy; preliminary results from the I-SPY trial. Nola Hylton, Lisa Carey, Angie DeMichele, Jeff Blume, Subha Madhava, Gloria Broadwater, Mark Rosen, Steve George, Laura Esserman and ISPY Clinical, Research, Pathology and Radiology Investigators.

## **Hot Topic Report: Two examples of research that may help to personalize treatment for breast cancer patients**

### **Introduction**

The huge impact of knowledge of the human genome is evident when a consumer is exposed to the vast array of research findings presented at the San Antonio Breast Cancer Symposium (2007). There is a strong focus on understanding the genetic make-up of the patient and the tumor, which leads to a personalized focus (Osborne, 2007a) and an aim to better understand the activity of and tumor response to significant drugs such as Herceptin and tamoxifen.

Rather than thinking about individual proteins and their activity, networks are considered as a whole, as was shown by Dr C. Kent Osborne who clearly displayed the HER signaling network and illustrated how, if only one component is blocked, ‘the tumor gets smart’ and becomes resistant – all pathways must be blocked completely. With HER-targeted therapy this could be done, he says, with the use of three drugs, such as Pertuzumab, Trastuzumab (Herceptin) and Gefitinib (Osborne, 2007b). HER2 over-expression leads to cancer cell proliferation and decreased likelihood of patients’ survival. At the symposium there were several poster reports of in vitro studies of relevance to this area (Harris 2007; Huang 2007; Thoms 2007; Tripathy 2007). These studies reinforced the variety of responses eg to Trastuzumab, explained by different characteristics of individual tumors, thus underlining the importance of ‘personalized’ treatment and the need for larger, double-blind, placebo-controlled in vivo studies.

This report will discuss new knowledge that helps to predict who will benefit from certain adjuvant therapies, in particular from the relatively new drug Pertuzumab and the long-time gold standard hormonal therapy Tamoxifen.

### **Pertuzumab**

Pertuzumab is an antibody known as a HER dimerization inhibitor (HDI). HDIs block the ability of the HER2 receptor to collaborate with other HER receptors. This should slow down tumor growth (Genentech). Indeed Pertuzumab inhibits both HER2 homodimerization (connecting with other HER2) and HER2 heterodimerization (connecting with other members of the HER signaling network – HER1, HER3 and HER4 (Fumoleau, 2007).

Trastuzumab (Herceptin) has had a dramatic effect for many breast cancer patients who have HER2 over-expression (Romond, 2005; Vogel 2002). But for some, their disease still progresses after treatment with Trastuzumab. Fumoleau et al. carried out a study to try to help such patients who have ‘high unmet needs’ (Fumoleau et al. 2007). The main purpose of this Phase II study was to check the safety of administering both Pertuzumab and Trastuzumab to such patients. The researchers were particularly keen to look at cardiac toxicity and a criterion for enrolment in the study was to have a Left Ventricular Ejection Fraction (LVEF) equal to or less than 55%, indicating satisfactory cardiac function. Firstly a small number of patients was tried on the combination of drugs to satisfy International Data Safety Monitoring Board standards. Having passed this hurdle, the study went on to complete recruitment by the end of July 2007.

Results for 61 patients were reported at the Symposium. The patients in the study had HER2 over-expressing metastatic breast cancer (but not to the brain) and their disease had progressed with Trastuzumab treatment – thus having ‘high unmet needs’ (see above). At San Antonio it

was reported that the main side effect from the drug combination using Pertuzumab was diarrhea, reported by 59% of the 61 participants. Only two of these patients had a severe occurrence of grade 3/ 4. Also, two patients had grade 3/ 4 skin rash and two had deep vein thrombosis. Other side effects reported (at grade 1/ 2 levels) were: rash 30%, skin problems (other than rash) 31%, nausea/ vomiting 36%, mucositis 33%, pain 43% and fatigue 28%. Whilst these side effects cause discomfort for the patients experiencing them, in the overall scheme they were considered acceptable.

As mentioned, the incidence of cardiac problems was a particular concern of the researchers. Two patients had a notable falling of LVEF during the study. One patient remained asymptomatic and the other withdrew from the study because of disease progression. However, out of 61 patients these events were not highly significant and the researchers were able to conclude that Pertuzumab and Trastuzumab are 'well-tolerated' by patients with HER2 positive breast cancer. The trial is ongoing, with an additional arm of Pertuzumab monotherapy.

In light of the Phase II study discussed above (indicating that Pertuzumab will be a relatively safe treatment) and knowledge of HER2 over-expression and knowledge (as described by Dr Osborne, see above) of the need to target the complete network of HER rather than HER2 individually, a key Phase III study will be one known as CLEOPATRA: A Study to Evaluate Pertuzumab + Trastuzumab + Docetaxel vs Placebo + Trastuzumab + Docetaxel in Previously Untreated HER2 Positive Metastatic Breast Cancer (Genentech, 2007b). The study, which aims to recruit 800 patients beginning in December 2007, will provide further evidence about the value of combining Pertuzumab with two recognised treatments for HER2 positive metastatic breast cancer.

### **Erythropoietin receptor expression**

Erythropoietin (EPO) is a hormone produced by the kidney that regulates red blood cell production. At the San Antonio Breast Cancer Symposium (2007), Larsson reported on a study of EPO receptor (EPOR) expression, particularly in relation to Tamoxifen response (Larsson 2007). Given the wide use of Tamoxifen as an adjuvant therapy in breast cancer treatment, it is important to be able to predict who may and who may not receive benefit from the drug. This study seems to provide important data that might ultimately be used for guidance in the prescription of Tamoxifen for premenopausal women. Larsson's study had two broad aims: firstly to evaluate EPO and EPOR expression in breast cancer and the possible effects of hypoxia and secondly to investigate possible correlations of EPOR expression and Tamoxifen response and survival.

Larsson examined EPOR expression in tumors of 564 premenopausal women who had Stage II breast cancer. EPOR could be detected through the C-20 antibody. In one arm of the study, the patients had been treated with Tamoxifen for 2 years and in the other arm, no adjuvant therapy was given for 2 years. Larsson wanted to measure EPOR expression, clinico pathological variables, Tamoxifen response and recurrence free survival. A total of 382 tumors were examined for EPOR expression. Of these, 212 had low expression and 170 had high expression. The study found that for those patients whose tumors had low EPOR expression, Tamoxifen had a significant effect on recurrence free survival whereas for those with high EPOR expression there appeared to be little difference in recurrence free survival between the Tamoxifen arm and

the control arm (with no Tamoxifen) in the study. This led Larsson to question whether there is a subgroup of patients with high EPOR expressing tumors for whom Tamoxifen treatment may have no effect. From the consumer point of view this study is important because these days 5 years of Tamoxifen continues to be treated as the gold standard adjuvant therapy. If clinicians can target women for whom Tamoxifen is likely to have little benefit, that group will be spared needlessly taking the drug. The study concludes that further research is necessary and it must be remembered that the study was confined to premenopausal women with Stage II breast cancer. It is, however, a further indication of ways that future treatment may be ‘personalized’.

Other studies concerning EPO and breast cancer seem to be concerned with EPO being an angiogenic signal which may herald progression to metastases (Eliopoulos 2004) or some potentially controversial use of synthetic EPO as a treatment for advanced breast cancer (Olsson 2002). The paper presented at San Antonio that reported on the possibility, through EPOR analysis, of predicting the usefulness of Tamoxifen for particular patients, appears to be groundbreaking.

### **Conclusion**

The two studies discussed above are important examples of how increased biochemical knowledge from the human genome is enabling researchers to target and personalize treatments. The papers discussed are concerned with two significant areas: women who have an over-expression of HER2 and whose breast cancer relapses after taking the relatively new ‘gold standard’ treatment Trastuzumab (Herceptin) and premenopausal women prescribed the ‘gold standard’ Tamoxifen as an adjuvant therapy. The first study suggests that a new drug (Pertuzumab) will be safe to take in conjunction with other drugs to combat HER2 dimerization and the second study suggests that it may be possible to predict who will and who will not receive benefit from Tamoxifen.

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## References

Fumoleau, P. et al.: *Safety of Pertuzumab plus Trastuzumab in a Phase II trial of patients with HER2-overexpressing metastatic breast cancer which had progressed during Trastuzumab therapy*, paper presented at 30<sup>th</sup> Annual San Antonio Breast Cancer Symposium, 13 – 16 December, 2007, San Antonio, US.

Genentech (2007a): Genentech Press Release ([www.gene.com/gene/news/press-releases/display.do?method=detail&id=8431](http://www.gene.com/gene/news/press-releases/display.do?method=detail&id=8431)), May 15 2005.

Genentech (2007b): US National Institutes of Health, <http://clinicaltrials.gov/ct2/show/NCT00567190?term=cleopatra&rank=1>, January 1 2008.

Harris, L.N. et al. (2007) : *HER2 Tumors are Heterogeneous, Clinically, Molecularly, and in Response to Preoperative Trastuzumab: Pathway Analysis of Gene Expression Profiles from Three Breast Cancer Datasets*, poster 2009 presented at 30<sup>th</sup> Annual San Antonio Breast Cancer Symposium, 13 – 16 December, 2007, San Antonio, US.

Huang, W. et al. (2007): *Quantitative measurements of HER2 expression and HER2 : HER2 dimerization identity subgroups of HER2 positive metastatic breast cancer patients with different probabilities of response to Trastuzumab treatment*, poster 2007 presented at 30<sup>th</sup> Annual San Antonio Breast Cancer Symposium, 13 – 16 December, 2007, San Antonio, US.

Larsson, A-M, et al. (2007): *Erythropoietin Receptor Expression in Breast Cancer and Correlation to Tamoxifen Response*, paper presented at 30<sup>th</sup> Annual San Antonio Breast Cancer Symposium, 13 – 16 December, 2007, San Antonio, US.

Olsson, A-M, et al. (2002) : *Erythropoietin Treatment in Metastatic Breast Cancer*, Acta Oncologia, Vol. 41, No.6, 2002, 517

Osborne, C.K (2007a): Opening Remarks, 30<sup>th</sup> Annual San Antonio Breast Cancer Symposium, 13 – 16 December, 2007, San Antonio, US.

Osborne, C.K.(2007b): *Novel strategies for HER-targeted therapy and mechanisms of resistance*, paper presented at 30<sup>th</sup> Annual San Antonio Breast Cancer Symposium, 13 – 16 December, 2007, San Antonio, US.

Romond, E.H. et al. (2005): *Trastuzumab plus Adjuvant Chemotherapy for Operable HER2-Positive Breast Cancer*, New England Journal of Medicine, Vol. 353, No. 16, October 2005, 1673-1684.

Thoms, J. et al. (2007): *Beta 1 Integrin Overexpression is Associated with Decreased Survival and Trastuzumab Resistance in Metastatic Breast Cancer*, Poster 2023, presented at 30<sup>th</sup> Annual San Antonio Breast Cancer Symposium, 13 – 16 December, 2007, San Antonio, US.

Tripathy, D. et al. (2007): *Targeting the Chemokine Receptor CXCR4 in Acquired Trastuzumab Resistance*, Poster 306, presented at 30<sup>th</sup> Annual San Antonio Breast Cancer Symposium, 13 – 16 December, 2007, San Antonio, US.

Vogel, C.L. et al. (2002): *Efficacy and Safety of Trastuzumab as a Single Agent in First Line Treatment of HER2- Overexpressing Metastatic Breast Cancer*, *Journal of Clinical Oncology*, Vol. 20, No. 3, February 2002, 719-726.

## **ATLAS Study (Adjuvant Tamoxifen: Longer Against Shorter)**

The Adjuvant tamoxifen: Longer vs. Shorter (ATLAS) Study is an international randomized trial where tamoxifen was given beyond 5 years to women across the world. On Dec. 15, 2007, Dr. Richard Peto discussed the primary results of Christine Davies' extensive work on the world's largest tamoxifen. This particular study was designed and coordinated by the Clinical Trial Service Unit at Oxford, which included 11,500 women in 30 countries for 10 years versus 5 years of treatment. They found that there was a very significant improvement in 10-year survival rate in preventing or delaying recurrence by staying on tamoxifen beyond 5 years due to "the carry over effect."

Women can get a lower recurrence rate by continuing on tamoxifen past 5 years. This "carry-over effect" has an effect on breast cancer mortality when a patient goes from 5-10 years. The question is what were the risks and benefits in prolonging the duration of adjuvant tamoxifen beyond 5 years. How long can women be on tamoxifen (5 years, 10 years, and 15 years) and how long will "the carry over effect" help women to reduce mortality and morbidity? There are also side effects from tamoxifen that occur in a portion of the population and how would these be affected over the longer term?

The randomized ATLAS trial had 11,500 women patients participating were from 400 hospitals around the world to see if women who stayed on tamoxifen from 5-10 years had a better prognosis. Sir Richard Peto, preeminent well-known oncology statistician conveyed for Christine Davies the strengths and weak implications from the trials.

The ATLAS trial had 2 arms. One arm had women continue to take tamoxifen for 5 additional years. The second arm had women take aromatase inhibitors for an additional 5 years. These blinded arms were then compared to determine if they could tell which arm was best for the patient.

The results were interesting. There were not significant differences in mortality according to the ATLAS trial. There was no increase in non-breast cancer related death in the tamoxifen group. These study results were from data from years 6-10, but years 11-15 are still incomplete.

Other factors and interesting implications that Professor Peto mentioned were that women halved their recurrence rates the first 5 years and then 1/3 the second five years due to “the carry over effect.” He stated that more data is needed after 10 years. They do know that 83% of the patients continued the study for another five years, of which 80% were ER+.

Downfalls of the trial include women that were 59% ER positive and 41% were untested for ER. Due to the fact that the results came from 30 countries, as Professor Peto stated, “We are not getting real world facts.” Professor Peto told us that ER testing is not done in third world countries. Some feel that these untested populations need to be looked at further to determine real world results.

Women are managing better by staying on tamoxifen longer. There was a 12% reduction of breast cancer recurrence in years 5-9. At this point there is no significant reduction in years 10-14. Of the 48,000 women in the follow-up, 1500 women reported recurrences. There were 1300 recurrences in years 5-9 and 200 in years 10-14. In summary, the overall the recurrence rate is lower among those who continued on tamoxifen.

There are still the questions as to ethnic and geographic populations related to hormonal differences, genotype variants as Spanish American, Indians, and Chinese. Tamoxifen is a metabolizing enzyme that can have an effect on different genotypes, ethnic and geographic of people. We need to sort out the racial ancestry on this study and determine whether these influence the results.

The results indicate that tamoxifen is best for many parts of the world with a 3% hazard rate. It is also affordable. Sir Richard feels that limiting tamoxifen to only 5 years is based on a small amount of data from NSABP B-14 study that ended too abruptly, so those results may be premature. They are going to be watching and monitoring all the women in the study to get the answers they need.

The continuation of tamoxifen beyond 5 years will reduce recurrence over the next five to ten years due to “the carry over affect.” There needs to be further assessment to determine the long-term effects on recurrence and the side affects. Professor Peto told us that there is a 12% reduction in the risk of breast cancer recurrence by staying on tamoxifen. For the women on the second 5-year period there is an additional risk reduction of about 22% compared to women who were on the study for only 5 years. This is the largest tamoxifen study in the world!

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**Sources of Information:**

1. Notes and Tape by Margaret, Peggy Anderson, LEAD
2. San Antonio Breast Cancer Symposium Newsletter Issue 4, Dec. 16, 2007
3. Sir Richard Peto, Oxford University-ATLAS trial: Adjuvant Tamoxifen Longer Than Shorter, Breast Cancer Update, online
4. ATLAS abstract, SABCS, Result Content-#48
5. ATLAS Newsletter 10-January 2005, online
6. Adjuvant Tamoxifen-Longer Against Shorter-online
7. SABCS: Five-Year Cutoff on Tamoxifen Adjuvant Therapy Called Off Base Advice, Dec. 16, 2007- online

## **ATAC Trial Comparing Anastrozole over Tamoxifen**

Anastrozole, an aromatase inhibitor shows superior efficacy over tamoxifen according to Professor John Forbes, at the San Antonio Breast Cancer Symposium on Dec. 12, 2007. Professor Forbes was representing the ATAC Trialists Group. Anastrozole had an absolute advantage over tamoxifen for women with invasive breast cancer. Over a 5-year period there is an advantage of 2.8% in favor of anastrozole for hormone positive women compared to tamoxifen. There was a follow up study that showed an increase of 4.8% after 9 years that displayed a stronger carryover effect of the aromatase inhibitor.

There were 6,241 women involved in the study that included 21 countries, and 24% of the women were from the United States. This study was conducted by Professor John S. Forbes from the University of New Castle at Calvary Matter Hospital in Australia. There was a 100-month median follow up study that showed the superior efficacy and no excess fracture risk for anastrozole compared with tamoxifen after the five-year treatment was complete. There have been previous reports of 33 and 68 months follow up showing studies of anastrozole is more effective and has fewer side effects than tamoxifen. It is better tolerated than Tamoxifen during treatment.

This study shows time to distant recurrence. It did not show a significant difference between the aromatase inhibitor and tamoxifen after 5 years but did show a 2.8 over the aromatase inhibitor. An important point in comparing apples to oranges is that there is no excessive fracture rate for anastrozole compared with tamoxifen after completion of treatment for 5 years. Another important fact is that contra lateral breast cancer showed only a 0.8% negligible difference in 5 years in favor of anastrozole with a 1.7 absolute advantage. There was no new mortality or morbidity related to this treatment.

Anastrozole is significantly superior to tamoxifen in prevention of breast cancer recurrences. Recurrence rates are lower with anastrozole after treatment is complete. The absolute difference in recurrence increased from 2.8% after 5 years to 4.8% after 9 years. Anastrozole shows a carry over effect similar to tamoxifen. As to the safety after 5 years, there was no excessive fracture or no new morbidity or mortality concerns. The incident in fractures was 30% higher in treatment with the two different arms. We now know the treatment will have a long term carry over effect

and there are no longer long-term effects. This trial gave us more treatment options, (but no toxicity concerns were measured), and they saw good safety efficacy for reducing risk of relapse. This study had several end points: disease free survivor, time to recurrence, contralateral breast cancer, time to distant recurrence and death. They all favored anastrozole.

After the 5-year study of anastrozole, there was no excess fracture rate, no new morbidity or mortality concerns. Anastrozole is advanced in preventing breast cancer recurrences; the absolute difference in recurrence rates had a carry over effect with anastrozole.

Patients who worried about going on aromatase inhibitors because of bone loss and risk of fractures no longer have to worry. More important is the fact that anastrozole may be more useful in preventing breast cancer recurrences in contralateral breast cancer, after 5 years with a 1.7% difference.

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**Sources of Information:**

- 1.AstraZeneca: ATAC 100 Months Dec. 2007 For US Media Only Trial Backgrounder
- 2.“Data Shows Armidex (Anastrozole) Continues To Be Superior To Tamoxifen in Helping Reduce The Risk of Recurrence In Patients with Early Stage Breast Cancer” by Laura Casaday, Media Report
- 3.Notes: Margaret or Peggy Anderson, Duluth, MN
- 4.San Antonio Breast Cancer Conference Slides-#41
- 5.San Antonio Breast Cancer Symposium Newsletter, Issue 3, Dec. 15, 2007
- 6.ATAC Trial: Anastrozole and Early Breast Cancer, Cancer Research UK, online
- 7.ATAC Trial: Findings at 68 Months, Breast Cancer Update, online
- 8.ATAC Trial, Armidex vs Tamoxifen vs Combination, Breast Cancer Update, online

## **Efficacy analysis of Capecitabine**

Integration of new cytotoxic agents is possible by either simultaneous or sequential addition to established regimens. This was a three-arm neoadjuvant study, designed to address the question of whether there would be benefit in adding capecitabine (X) to docetaxel (D) after pretreatment with epirubicin/cyclophosphamide (EC).

Patients were eligible in whom adjuvant chemotherapy would be considered otherwise.

Therefore, either large operable (T3) and locally advanced (T4) or estrogen (ER) and progesterone (PR) negative receptor status, or ER/PR positive tumors but clinically node positive disease were recruited in 115 German centers. Node status was not taken into account. Patients were randomized to receive 4 cycles of Epirubicin/cyclophosphamide (EC) and then randomized to either 4 cycles of docetaxel or 4 cycles of docetaxel and capecitabine (DX), or 4 cycles of docetaxel followed by 4 cycles of capecitabine (D-X). Patients with Her2 + tumors received trastuzumab concomitantly with all regimens. The primary endpoints were pathological complete response (CR) at surgery.

Between August 2005 and December 2006, 1512 patients entered and after receiving 4 cycles of EC, 1421 patients were randomized to D (471) and DX (471) and D-X (479).

9% of the D patients discontinued treatment due to toxicity. 12% of the DX patients discontinued treatment due to toxicity and 26% of the D-X arm discontinued due to progressive disease. The average tumor size was 4cm. 65% of patients were able to have lumpectomies despite the large tumor sizes. Neurological issues were much higher in the EC-DX arm. There were no high cardiac events.

22.1% of the patients in the EC-D arm achieved CR, 18.3% in the EC-DX arm and 21.7% in the EC-D-X arm. The researchers concluded that adding capecitabine appeared to be less effective in small tumors and more effective in large tumors and perhaps it would be better to reduce the dosage due to the negative impact of adding this drug and the overall negative response.

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## **Prediction of who benefits from Adjuvant Chemotherapy? Clinical Trials Attempting to Improve Upon Adjuvant Chemotherapy, Neoadjuvant Chemotherapy, and Hormonal Therapy**

Having just attended the 2007 San Antonio Breast Cancer Symposium (SABCS), I am impressed with the progress that has been made in the diagnosis and treatment of breast cancer, but equally overwhelmed that it is still not enough. The complexity of the disease is more apparent with each new advancement. As the saying goes “one step forward, two steps back”. More progress is certainly not due to a lack of dedication and passion on the parts of the clinicians and scientists.

Two of the main themes running through the conference were the questions: “Who will benefit and who will not”? and “Is there a way to pin point the benefactors”?

A very interesting study conducted by COBRA, the consortium on breast cancer pharmacogenomics was supported by NIH, “Cytochrome P450 2D6 Activity Predicts Adherence to Tamoxifen Therapy” (abstract 77) begins to answer the question of who would benefit the most. The study focused on how an individual metabolizes tamoxifen based on the presence of activity of CYP2D alleles. The higher the activity level, the more likely these women were to discontinue tamoxifen because of treatment related side effects. Ironically these were the women who would most likely benefit from continuing the drug. So, with genetic testing to identify these women before treatment started, co-medications could be used to alleviate the side effects of tamoxifen. This could increase compliance and thus potentially improve the long-term survival of the patient.

It is clear to me that this type of genomic research is key to the future of breast cancer treatments as researchers look at “tried and true” drugs and how to increase their efficacy. Another prime example is anthracycline, an old timer in the treatment of breast cancer. The 21-gene Recurrence Score assay looks at the prediction of those women who are node positive, and have a high RS and therefore are likely to benefit from anthracycline based chemotherapy, while those with a low RS score may not benefit. So, are we over treating? I think yes until more research suggests otherwise.

Another means of predicting “who will benefit and who will not”? is to look at the neoadjuvant world of research. Researchers again looked at a drug that has been used for quite awhile. Fulvestrant is an estrogen receptor antagonist used in the treatment of postmenopausal women with advanced breast cancer (Abstract 23). Altering the dose by comparing the approved dose (AD) vs. high dose (HD) of this drug and examining its effect on biomarkers may suggest a dose dependent downregulation on estrogen, and Ki67 LI. The results, which looked at baseline, 4 weeks and at surgery (16 weeks), showed a favorable response to the high dose regimen. So is it ready for the adjuvant setting? At this time more studies need to be done on its safety and efficacy.

The neoadjuvant setting does have its benefits with a faster turn around time for results. I certainly resonated with Dr. Spinelli’s “avant garde” view on expediting clinical trials through to the adjuvant setting. But how would this impact the patient? We wait and see.

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<sup>i</sup> From the National Cancer Institute Dictionary of Cancer terms, retrieved January 10, 2008 from [http://www.cancer.gov/Templates/db\\_alpha.aspx?CdrID=44916](http://www.cancer.gov/Templates/db_alpha.aspx?CdrID=44916).

<sup>ii</sup> From Doxil prescribing information pamphlet retrieved January 11, 2008 from [http://www.orthobiotech.com/common/prescribing\\_information/DOXIL/PDF/DOXIL\\_PI\\_Booklet.pdf](http://www.orthobiotech.com/common/prescribing_information/DOXIL/PDF/DOXIL_PI_Booklet.pdf)

<sup>iii</sup> Notes from presentation of “Abstract #12 Extended follow-up and analysis by age of the US Oncology Adjuvant Trial 9735...” at 2007 SABCS on December 13, 2008.

<sup>iv</sup> Notes from presentation of “Abstract #13 Role of anthracyclines-based therapy in the adjuvant treatment of breast cancer...” at 2007 SABCS on December 13, 2008.