

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

Topic: Prediction of response to therapy / Prognostic assessment of patients with breast cancer

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SYMPTOM MANAGEMENT IN BREAST CANCER SURVIVORS

Dr. Charles Loprinzi addressed the **San Antonio Breast Cancer Symposium** audience of researchers and interested participants with the Plenary Lecture 5 addressing the five main symptoms that are experienced by breast cancer patients caused either by their cancer or their treatment. His research discussion included vaginal dryness, libido decline, fatigue, neuropathy and hot flashes. He explained that patients experience these symptoms in varying degrees depending on their personal biology reaction to the different therapies for treatment.

Clinical trials are needed to address these symptoms due to the increased number of survivors with early detection methods and the increased number of aged population.

With additional therapies now available, there are going to be more toxicities and biologic reactions that need further study to identify relief of these symptoms.

Vaginal Dryness is a common symptom reported in 36 – 71% of breast cancer patients in two studies evaluating menopausal symptoms. Estrogenic vaginal lubricant works well but should be considered only when their breast cancer tumor is estrogen negative.

Aromatase inhibitor therapy is known to decrease estrogen and therefore increase the probability of vaginal dryness. Two studies on non-estrogen vaginal lubricants indicated benefit while using the drugs. One of the drugs, Pilocarpine, while not studied for vaginal dryness, has had success with patients who use the drug for symptoms of dry mouth from other diseases and radiation therapy side effects. One benefit noted was improvement in vaginal dryness using 5 mg QID or BID. This drug is being currently studied for vaginal dryness and will hopefully show a benefit when the study concludes in 2009.

Libido problems are difficult for most clinicians to discuss with patients mainly because they feel inadequate to give advice since they lack appropriate education and resources. Referral to sex therapists would be beneficial when available in the patient's community. Early disappointing studies indicated using a testosterone trans-dermal preparation 10mg or a placebo showed similar results. One possible reason for the lack of improvement was that it appears that testosterone works better when it is used with estrogen and this study did not use estrogen. The Journal of Clinical Oncology, Jan. 05 reported beneficial results in the NCCTG NO2C3 trial

using estrogen cream for libido symptoms although not recommended for patients whose pathology results indicated an ER positive tumor. The estrogen in the cream can absorb and cross into the blood and organs and increase risk of developing another cancer.

Fatigue symptoms are common and may occur at any point of the disease. Fatigue may be improved dramatically with regular exercise. Exercise can decrease hormonal levels and reduce the risk of recurrence. Studies using the drugs modafinil and metyrosine have not proved beneficial for fatigue. The **Susan G. Komen for the Cure Brinker Award** lecture by Leslie Bernstein, PhD, confirmed the positive benefits of exercise. Dr. Loprinzi mentioned a quotation in his uncle's gym that he frequented as a child, "**He who could not make time for exercise, must take time for illness**".

A promising randomized study of American Ginseng 750 mg, 1000 mg, 2000mg or placebo showed improvement in 30% of participants using the ginseng. The results of this study will be compared with another trial that is about to complete from the Mayo Clinic.

Neuropathy induced by chemotherapy is another difficult to treat symptom. A trial of Gabapentin, 2700mg, daily for 2 to 6 weeks vs. placebo showed this drug was not helpful for pain caused by drug therapy. Additional studies using Vitamin E as a prevention of neuropathy could prove beneficial. One small study with 81 participants using 400 mg showed a reduction in neuropathy. However, due to side effects of Vitamin E, this is not a current recommendation. Vitamin E needs more study as it may interfere with other treatment drug therapies or radiation therapy. According to Dr. Loprinzi, a common misnomer for clinicians is that patients who experience immediate pain induced by Taxol therapy are experiencing joint or muscle related activity pain, however, he wanted participants to understand that the pain is actually directly caused by nerve injury proved by a marker in the blood results.

Hot Flashes have been treated successfully with anti-depressants such as SSRI's, including the drug Venlafaxine. A 40% reduction occurred by using 37.5 mg per day and 75 mg created a 60% reduction in hot flashes. Fluoxetine therapy has been studied with mixed results but not as helpful as Venlafaxine but better than the placebo according to studies. Paroxetine therapy has not proved as beneficial at either 50 mg and 100 mg per day according to 3 trials. Also noted,

earlier trials that were double blinded with placebo were flawed as they lacked baseline information including one that showed a 51% improvement using Venlafaxine therapy. The dates of hot flash diaries were not the same for the drug and the placebo. Extended release dosage of anti-depressants were most beneficial. Also showing great promise for hot flashes is Gabapentin- a non hormonal drug taken at 900 mg per day.

Dr. Loprinzi ended the presentation with a call to researchers to continue to explore resolution to these common symptoms in breast cancer patients because they can be debilitating in nature and decrease their quality of life significantly.

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The use of genomics in breast cancer sub-type identification, prognostic prediction and treatment optimization

Around the world, multiple research efforts are under way, using genomic approaches to increase our understanding of the biological characteristics of the various breast cancer sub-types. Researchers are using this new knowledge to develop targeted, highly specific breast cancer therapies designed to effectively treat each of the sub-types. This global research effort is leading us towards a new era of “personalised” cancer treatment based on our ever-increasing knowledge of the human genome and the various gene mutations and expression signatures associated with breast cancer. Scientific advances in this area are providing new and innovative treatment strategies that will lead us to a future where we can envisage breast cancer as a disease that we are capable of understanding and managing well enough to transform it from a deadly disease into a chronic or curable disorder. This report describes the results of two such studies, presented at the San Antonio Breast Cancer Symposium, 2007 (SABCS 2007).

A research group at UCSF, led by Dr Joe Gray, is using a genomic approach to study the response of a range of breast cancer sub-types to 26 approved or experimental cancer drugs. The researchers used 50 well-characterised breast cancer cell lines with distinct functional abnormalities in their studies. They are hopeful that these *in vitro* cultured cell lines will demonstrate sufficiently similar characteristics to *in vivo* breast cancer tumours to enable the reliable identification of clinically applicable molecular targets. This is a necessary first step in developing a laboratory system to predict individual tumour response and resistance to targeted therapies. The group is particularly interested in finding new treatment strategies for two breast cancer subtypes, the basal and luminal/amplifier, which tend to respond poorly to chemotherapy and have a greater likelihood of disease recurrence and progression. The research aims to identify the genetic drivers of these two types of cancer as a basis for developing rapid, reliable laboratory-based drug-screening methods so that therapeutic agents effective against these breast cancer subtypes can be identified. This kind of research is crucial for progress in drug selection, given the large number of potential candidates being developed worldwide. Currently there are 100 novel FDA-approved products, 400 more being tested in clinical trials, and many more in the pipeline.

In collaboration with pharmaceutical company GlaxoSmithKline, the research group used lapatinib, a dual function tyrosine kinase inhibitor effective in blocking some of the key receptors in the Her2 signalling pathway, to study the gene expression response of Her2 positive cell lines. Use of this targeted agent with known specificity to a cell line sub-type and with no activity in other (Her2 negative) breast cancer sub-types allowed assessment of the utility of markers identified using the *in vitro* screening system. This approach led to the identification of 155 genes whose expression was associated with response to lapatinib.

Branch capture assays were then used to undertake further transcriptional analysis to identify a subset of markers which were strongly predictive of the Her2 positive ErbB2 gene amplification, transcription, protein level and phosphorylation level, and which provided consistent results across a range of cell culture conditions. This screening identified six transcriptional markers (a six-gene expression profile) with high reproducibility. Dr Gray had previously reported to the conference that branch capture assay is an inexpensive technically sound technique with good reliability in measuring gene transcription level in both cell lines and tumours. Branch capture allows the expression of around 20 genes to be measured from a single 10m formalin-fixed paraffin embedded (FFPE) section. Branch capture has been found to have a high correlation to the more commonly used fluorescence in situ hybridisation (FISH) testing, and recent results have indicated that branch capture in combination with ErbB2 testing is a better predictor of survival in Her2 positive breast cancer than ErbB2 alone.

Using the *in vitro* system, the 26 therapeutic agents were each screened at 9 concentrations for activity against the 50 cell lines, using an automated system to take multiple measurements (including gene copy number, gene expression, proteins and mutational status). Dose response was determined for each agent, measured by changes in viable cell numbers. Many of the drugs showed strong sub-type specificity. Markers predicting drug response were most accurate for the agents that showed the greatest variability of response among cell lines (the greater the specificity the more accurate the predictors). Drugs designed to specifically target particular genomic defects (e.g. trastuzumab against ErbB2 mutations) were found to be most effective against the cell lines expressing the target defects. The molecular predictors of response to lapatinib identified in these studies correlated closely with the results of clinical trials reported by

Di Leo et al, ECCO 2007, providing evidence for the utility of the *in vitro* screening system used here. However, given the small sample size in this study, further data will be needed to fully validate the method.

A second study investigated whether gene expression profiling could be used to better predict prognosis and response to endocrine therapy than standard clinical methods for defining estrogen and progesterone receptor status of breast cancers. This work represents collaboration among US and Netherlands-based researchers and Veridex LLC. The standard clinical techniques currently used to define estrogen and progesterone receptor status are immunohistochemistry (IHC) and biochemical assays. It is well established that patients with estrogen receptor positive (ER+) tumours respond well to endocrine therapy (e.g. tamoxifen and aromatase inhibitors). Those with estrogen and progesterone receptor positive (ER+/PR+) tumours are thought to have better prognosis than those with ER+/PR- tumours. A link has been established between PR-status and increased oncogenic growth factor pathway signalling. To gain a better understanding of the underlying biological basis of this difference, the researchers set out to determine the gene expression profiles of a large number of tumours for which ER and PR status had been defined in previous studies using standard clinical techniques. They hypothesised that ER+/PR- tumours would exhibit a profile distinct from both ER+/PR+ and ER-/PR- tumours and that the expression signature of this sub-type would predict a worse prognosis for ER+/PR- than ER+/PR+.

Two previously published gene expression profile datasets were used to identify genes that showed either notably high or low expression (RNA levels shown on microarray) in the 3 endocrine groups. The areas of intersection between these two datasets were then used to define expression profiles for each group. Both ER+/PR+ and ER-/PR- tumours demonstrated specific gene signatures, but the ER+/PR- group, as classified by standard clinical methods, proved to be a mixture of 3 different types, with signatures coinciding either with ER+/PR+ or ER-/PR-, or not coinciding with either but sharing some patterns with both. Tumours in this newly-defined “mixed signature” group constituted a distinctive ER+/PR- type at the gene expression (RNA transcription) level. Clinical data from previous studies showed that patients with ER+/PR- tumours with the distinctive mixed signature had a poorer outcome than those with either of the

other two transcription signatures. Standard clinical assays for assigning patients to ER/PR groups predicted a similar prognosis for ER+/PR+ and ER+/PR- and worse outcomes for ER-/PR- but when patients were reassigned on the basis of their tumours' gene expression profiles a more accurate prediction of outcomes was obtained.

Two features were noted for the distinctive ER+/PR- group. First, compared to the other two groups, these tumours exhibited a significantly greater alteration in gene copy number (greater genomic instability). Secondly, they had a higher transcriptional signature of the PI3K/Akt/mTOR oncogenic growth factors.

These results suggest that molecular profiling can distinguish among endocrine tumour types with different characteristics and prognostic outcomes more precisely than current standard clinical assays.

In summary, these two papers presented results demonstrating how scientific and technical advances in understanding genes and gene expression can be used to characterise breast cancer sub-types and to predict prognosis and identify optimal treatment strategies based on the molecular features of tumours.

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Presentations cited in this report:

[Abstract 31] **Genomic approaches to breast cancer subset identification and treatment.** *Albertson D, Chin K, Devries S, Feiler H, Pinkel D, Spellman P, Waldman F, Wang N, Hennessy B, Mills G, Barcellos Hoff MH, Bissell M, Guan Y, Hu Z, Kuo W-L, McCormick F, Neve R, Stampfer M, Wooster R, Yaswen P, Das D, Fridlyand J, Correll E, Jin J, Nordmeyer B, Sudar D, Chew K, Dairkee S, Ljung BM, Hwang S, Esserman L, Arbushites M, Benz C, Koehler M, Marks JD, Zhou Y, Park J, Weber B, Gray J.. University of California, San Francisco, CA; Lawrence Berkeley National Laboratory, Berkeley, CA; MD Anderson Cancer Center, Houston, TX; GlaxoSmithKline, King of Prussia, PA; California Pacific Medical Center, San Francisco, CA; Buck Institute for Age Research, Novato, CA; Genentech, South San Francisco, CA*

[Susan G. Komen for the Cure, Brinker Awards for Scientific Distinction Lectures] **“Omics” research in individualised breast cancer treatment – letting the tumours teach.** *Gray, J. Lawrence Berkley National Laboratory, Berkley, CA*

[Abstract 33] **Gene expression profiles of ER+/PR-breast cancer are associated with genomic instability and Akt/mTOR signaling, and predict poor patient outcome better than clinically assigned PR status.** *Creighton CJ, Osborne CK, van de Vijver M, Foekens JA, Wang Y, Zhang Y, Klijn JGM, Horlings HM, Hilsenbeck SG, Lee AV, Schiff R.. Baylor College of Medicine, Houston, TX; Netherlands Cancer Institute, Amsterdam, Netherlands; Erasmus MC-Daniel den Hoed, Rotterdam, Netherlands; Veridex LLC, a Johnson & Johnson Company, San Diego, CA*

Genomic Factors Predicting Breast Cancer Prognosis

One of the most fascinating areas of breast cancer research involves studying molecular biology. Molecular biology concerns itself with the various systems that exist within cells and how they interact. As knowledge of the human genome advances, scientists are discovering new and exciting ways to predict an individual patient's prognosis and best method of treatment.

Molecular Biology Basics

The basic control of the cell at the molecular level is the DNA. DNA is made up of genes, which are the source of genetic information that allows all the cells in our body to divide, grow and to combine with other cells to create organs and tissue. Cell type is determined by which genes are expressed.

A central question in molecular biology is what controls gene expression. Genes must be "turned on" at the correct time in the correct cell so the cells function normally. RNA plays an important role in translating genetic information from DNA to proteins. Proteins are essential to organisms, and are involved in all cellular processes. The study of gene expression analysis or gene expression signature (GES) involves determining which genes are expressed in sample cells.

Breast Cancer Subgroups

As the knowledge of breast cancer expands, so the number of ways scientists determine breast cancer prognosis grows. Breast cancer tumors have long been tested for nuclear grading scores. These scores indicate how aggressive the cancer is, how fast the cells in the tumor are dividing, and how different the tissue is from normal breast tissue. Size of the tumor, lymph node status and distant metastasis have also been standards for staging the prognosis of patients, and for determining their treatment. More recent consideration has been given to hormone receptor status (both estrogen and progesterone), and Her2 status which has greatly changed the treatment of breast cancer. Currently scientists are looking for new genomic indicators that will help provide better prognosis expectations and treatment options. Two such studies were presented at the San Antonio Breast Cancer Symposium in 2007.

Dr John Foekens presented the results of the study he and his associates have been working on in the Netherlands. The study combined the method of gene expression analysis and copy number analysis (CNAs). Gene expression analysis studies the expression levels of genes in RNA. It is also called gene expression signature (GES). In CNAs, DNA is studied to determine how the number of genes differs in various cell samples. The result of CNAs is a copy number signature (CNS).

One of the aims of this study was to show that combining conventional gene expression analysis with copy number alterations analysis using single nucleotide polymorphism (SNP) would improve the prediction of breast cancer recurrence. SNPs are a DNA sequence variation occurring when a single base differs between individuals. Secondly, the study sought to identify sub-groups of patients to improve determination of preferred treatment. Additionally, the scientists hoped to identify new genes that, when over expressed, cause breast cancer (oncogenes) and suppressor genes that can prevent breast cancer from forming. An oncogene is a gene that is capable of causing the transformation of normal cells into cancer cells.

The study population was made up of 313 breast cancer patients who were lymph node negative, none of whom had received adjuvant systemic therapy. The clinical target of the trial was distant metastasis-free survival (DMFS). 200 (133 ER+, 67 ER-) of the tumor samples were used to determine which chromosome regions had prognostic copy number signatures (CNS). Forty-five regions (consisting of 2,833 mapped genes) were discovered for the ER+ tumors and Fifty-six (consisting of 3,656 mapped genes) in the ER- cases. An 81 gene copy number signature was created, made up of 53 genes for ER+ and 28 genes for ER- tumors.

Using only CNAs, 113 patients (66 ER+, 47 ER-) were successfully separated into a groups with good outcome (98) and poor outcome (15). When the combination of GES and CNAs was used to test the data, the patients were separated into 3 distinct groups. The group of 98 with good outcome were split between 38 patients with a 90% 5 year MFS, and 60 patients with a 63% 5 year MFS. This is quite a significant indicator of patient prognosis that was shown to be statistically independent of other risk factors.

Studies by Hess and Potti that were completed in 2006 were used with the combination GES and CNAs results to consider treatment options. The poor prognosis group defined in the current

study was shown to be more sensitive to the chemotherapy agents Adriamycin, topotecan, and etoposide and less responsive to cyclophosphamide and to a lesser extent paclitaxel and 5-FU.

The conclusions that can be drawn from this study are the following:

1. CNAs can be used to indicate breast cancer prognosis
2. Copy number signature combined with GES provides additional information about breast cancer prognosis
3. Groups defined by combined testing with GES and CNS may be sensitive to certain chemotherapy agents while resistant to others.

The expression of alphavbeta6 (avb6) in breast cancer cells was discussed by Dr L. Jones from the United Kingdom. The design of the study hoped to establish a relationship between avb6 and breast cancer. First, the study considered whether avb6 was a mediating variable in breast cancer cell invasion. Next, the researchers looked at whether avb6 was useful to predict breast cancer prognosis. After proving these assumptions the scientists sought to show that avb6 was a new way to sub-classify breast cancer.

When avb6 is present, it acts as cell surface receptor that mediates intracellular communication that regulates cellular shape, mobility and the cell cycle. In normal tissue, avb6 is not present. In other types of cancer (oral, skin and lung) avb6 has been shown to be up regulated, or increased in the cell. Using three breast cancer cell lines (BT20, MDA MB468 and CA1a) the researchers showed that blocking the amount of avb6 in cells significantly inhibited the invasion of breast cancer.

Using two independent cohort studies with data available on breast cancer staging, tumor samples were stained for avb6. Each cohort group was then segmented by the level of expression of avb6 into Neg/Weak (<2.5), Moderate (>2.5 <5.5), or Strong (>5.5). These groups were then combined with the information on clinical pathological features such as size, hormone receptor status, Her2 status, lymph node status and distant metastasis. The level of expression of avb6 was consistent with the breast cancer stages 1-3 for both cohorts.

Next, the avb6 groups were compared for 10 year survival. As predicted by the study proposal, the group with the highest expression of avb6 had the lowest 10 year survival. This result was independent of tumor grade, size and lymph node status. Avb6 was then studied in relation to the several established molecular breast cancer sub-types, basal, Her2 positive, and luminal. The tumor cells were stratified by hormone receptor status, basal type, Her2 expression and avb6 expression. Avb6 created a new classification method that was more discerning than other types of molecular classification.

Using this new breast cancer sub-type allowed researchers to better predict poor prognosis than basal type or Her2 over expression. For tumors that were both avb6 and Her2 positive, the 10 year survival rate was 34%, while tumors with avb6 negative that were Her2 positive the 10 year survival rate was significantly better, at 52%. Considering tumors with basal type avb6 expression again showed a remarkable survival difference. Avb6 positive tumors had a 10 year survival rate of 55%, versus 70% for the avb6 negative group.

The conclusions drawn from this study were that avb6 is a promoter of breast cancer cell invasion, that its presence predicts poor prognosis without regard to tumor size, grade and lymph node status, and that using avb6 allows scientists to establish a new breast cancer sub-type. This new sub-type avb6 positive as a subset of basal and Her2 positive tumors predicted a worse prognosis.

With future study avb6 may prove to be a therapeutic target for new treatments of breast cancer.

Conclusions

These two interesting genomic studies provide the basis for future research into new methods of discerning breast cancer prognosis which could help decide which patients to treat most aggressively. The study of avb6 also introduced a new sub-type of breast cancer and a potential target for therapy. I would like to see the GES, CNS study repeated with a larger patient population. I would also be very interested in seeing how the treatment of Her2 positive tumors with Herceptin might affect the 10 year survival rates in the avb6 study.

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Prognostic and Prediction Implications of Therapy in Breast Cancer Patients

In recent years, breast cancer research has made considerable advances in the areas of outcome prediction and treatment response based on traditional prognostic indicators such as pathological staging, nodal and hormonal status, biological tumor markers and gene expression in conjunction with newer diagnostic applications Oncotype DX, MammaPrint® and Adjuvant! Online. Additionally, endocrine therapies in both the adjuvant and neoadjuvant settings have evolved dramatically in the past decade and have played an integral role in treatment response and outcome prediction. Among the presentations from the 2007 San Antonio Breast Cancer Symposium were several studies aimed to assess the efficacy of these applications in terms of prognostic and predictive implications.

The first of these studies was outcome prediction for Clinical Stage II and III ER+ breast cancer based on treatment response, pathological stage, tumor grade, Ki-67 proliferation index, and estrogen receptor status after neoadjuvant endocrine therapy presented by MJ Ellis.

This study focused on a subset of the P024 trial, a multinational randomized phase III trial that showed the therapeutic superiority of letrozole to tamoxifen for the neoadjuvant management of breast cancer in ER+ postmenopausal women who were ineligible (too large) for breast-conserving surgery. The purpose of this study was to determine the relative efficacy of neoadjuvant endocrine therapy in predicting relapse risk in postmenopausal women with ER+ disease. To do so, clinical stage II or III patients were pooled from both the tamoxifen and letrozole arms and data on pathological stage, post treatment grade, response, adjuvant endocrine therapy and chemotherapy was collected prospectively.¹

A multivariate predictive model was used to correlate pre and post-treatment ER status and Ki67 proliferation index, pathological stage & grade and response to treatment. The model demonstrated that after 4 months of neoadjuvant endocrine therapy, patients with ER+ tumors who were downstaged to Stage 1 at surgery had 100% relapse free survival. The study further concluded that based on standard pathological factors, response data, and post treatment ER and

¹ MJ Ellis, SABSC 2007 General Session 6, Abstract #62

Ki67 status, a neoadjuvant endocrine risk algorithm is a promising new approach to predicting the course of ER+ breast cancer in postmenopausal women.²

The second of the presentations was prognostic utility of the 21-gene assay compared with Adjuvant! in hormone receptor positive operable breast cancer with 0-3 positive axillary nodes treated with adjuvant chemohormonal therapy (CHT). This study was an analysis of intergroup trial E2197.

This was a comparative study of diagnostic tests Adjuvant! Online and Oncotype DX for estimating outcomes at 5 years as opposed to the original design model of 10 years. Adjuvant! is an online tool that evaluates clinical data to aid physicians in determining risks and benefits of additional therapy after surgery. Oncotype DX analyzes the expression of a panel of 21 genes in a breast cancer tumor and quantifies the likelihood of disease recurrence, survival and response to chemotherapy in women with early-stage breast cancer. This study focused on a subgroup of trial E2197, a phase III Study comparing doxorubicin/docetaxel versus doxorubicin/cyclophosphamide as adjuvant treatment in women with node-positive or high-risk node negative patients.³ The results of this trial confirmed that no subset of patients derived an advantage when docetaxel replaced cyclophosphamide.

A sample of 465 patients with hormone positive breast cancer who did not have a recurrence were assessed by both Adjuvant! Online and Oncotype DX Recurrence Score (RS). Tumor grade, nodal status, ER/PR and HER2 expression were compared in a series of multivariate analyses and yielded several results. An initial conclusion is that Oncotype DX RS has, overall, much greater prognostic power than Adjuvant! and is a highly significant predictor of recurrence in both node-negative disease (p=0.0007) and node-positive disease (p=0.0004).⁴ The study further revealed that there is relatively poor correlation between the two tests and confirmed their independence. However, when the researchers looked at using both Oncotype DX and

² Ellis MJ, SABCS 2007, Abstract #62

³ www.nci.nih.gov/clinicaltrials

⁴ Goldstein L., et. al. 2007 SABCS, General Session 6, Abstract #63

Adjuvant!, they found that RS provided additional prognostic information in hormone-positive breast cancer treated with adjuvant chemohormonal therapy.

"This study shows the significant added benefit of genomic analysis with Oncotype DX, when used in conjunction with the traditional clinical variables as measured by Adjuvant Online," said Steven Shak, M.D., chief medical officer of Genomic Health. "These results, combined with updated ASCO treatment guidelines now recommending Oncotype DX, clearly demonstrate that Oncotype DX provides critical information for breast cancer treatment planning that is not apparent by examination of clinical variables alone."⁵

There are some interesting implications of this study, the most striking being that, used together, these tools can help guide the patient and physician to the most effective individualized breast cancer treatment and in many cases, opt for a shorter and perhaps less aggressive regimen of chemotherapy. Given that this model was adjusted to 5 years and both Adjuvant! and RS are optimized for 10 years, these results are still considered exploratory and while promising, they certainly warrant further research.

The third presentation was the value of centrally-assessed Ki-67 labeling index as a marker of prognosis and predictor of response to adjuvant endocrine therapy in the BIG 1-98 trial of postmenopausal women with estrogen receptor positive breast cancer.

Expression of the Ki-67 protein has been widely used to assess the cell proliferation of a breast cancer tumor and has proven an effective prognostic marker for postmenopausal women with ER+ disease. Studies have shown a significant correlation between high Ki-67 proliferation rates and shorter disease free and overall survival. The aim of this study was to determine whether Ki-67 is predictive of efficacy of endocrine therapy in the post-operative adjuvant setting. In doing so, researchers would learn whether Ki-67 could serve as an indicator of which women will do better with adjuvant letrozole treatment than with tamoxifen.

⁵ Genomic Health Inc. , December 17, 2007

The BIG 1-98 trial randomized 8,010 postmenopausal women with early stage endocrine-responsive breast cancer to receive either the aromatase inhibitor letrozole or estrogen receptor modulator tamoxifen. The study showed that letrozole had a greater effect on disease free survival compared to tamoxifen.

This study was limited to a subset of 2,685 patients from the monotherapy arms of the BIG 1-98 Trial who were randomized to receive either letrozole or tamoxifen for 5 years. The women were divided into two groups based upon Ki-67 labeling index scores – those below 11% (n=1433) and those above 11% (n=1252), the latter being designated as high expressors of the protein.

Overall, pooling the two treatment arms, higher Ki-67 was confirmed to be a highly significant adverse prognostic factor for disease free survival in these patients, all of whom received some adjuvant endocrine therapy. In an analysis by treatment group, the poorest DFS were those patients with hi Ki-67 who were treated with tamoxifen.

A further STEPP analysis showed that, for subpopulations with higher Ki-67, there is a consistent benefit of letrozole over tamoxifen yet there was no clear benefit in the subgroup of women with low or median Ki-67.⁶

This study concluded that the hazard of experiencing a disease-free survival event with letrozole was half the hazard with tamoxifen. In post-menopausal women with ER+ disease, Ki67 is confirmed as a prognostic factor and may identify those patients who would benefit significantly from letrozole adjuvant therapy.

Overall, these three studies presented some interesting and provocative research in the areas of prognostic implication and prediction outcome. Much can be gleaned from these and the myriad other presentations from the 2007 San Antonio Breast Cancer Symposium that may benefit translational medicine and aid in the clinical application of more targeted and individualized therapies for women fighting breast cancer in the near future.

⁶ Viale G, 2007 SABCS, General Session 6, Abstract #64

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